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Problems of Drug Dependence, 1985

Proceedings of the 47th Annual Scientific Meeting

The Committee on Problems of Drug Dependence, Inc.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

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Proceedings of the 47th Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc.

Editor: Louis S. Harris, Ph.D.

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Foreword

The National Institute on Drug Abuse (NIDA) is pleased to publish Problems of Dru De endence 1985, the proceedings of the 47th Annual Scientific meeting of the Committee on Problems of Drug Dependence, Inc. (CPDD). This. meeting was held in Baltimore, Maryland, in June 1985 to commemorate the 50th anniversary of NIDA's intramural research program, the Addiction Research Center (ARC). The ARC is a unique institution seeking to develop a fundamental understanding of drug addiction through multidisciplinary research. The ARC has made significant contributions in basic and clinical pharmacology and the behavioral and neurosciences and continues to provide new insights into the problems of addictive behavior. A symposium entitled "ARC Today" was held in which scientists from the ARC reported their latest findings. Papers from the symposium are included in this monograph.

The CPDD is an independent organization of internationally recognized experts in a variety of disciplines related to drug addiction. NIDA and the CPDD share many interests and concerns in developing knowledge that will reduce the destructive effects of abused drugs on the individual and society. The CPDD is unique in bringing together annually at a single scientific meeting an outstanding group of basic and clinical investigators working in the field of drug dependence. This year, as usual, the monograph presents an excellent collection of papers. It also contains progress reports of the abuse liability testing program funded by NIDA and carried out in conjunction with the CPDD. This testing program represents an example of a highly successful government/ private sector cooperative effort.

I am sure that members of the scientific community and other interested readers will find this volume to be a valuable "state-of-the-art" summary of the latest research into understanding of the biological, behavioral, and chemical bases of drug abuse.

Charles R. Schuster, Ph.D.
Director
National Institute on Drug Abuse

The papers in this monograph were presented or read by title at the 47th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., in Baltimdre, Maryland, June 10-12, 1985. The CPDD, an independent, nonprofit organization, conducts drug testing and evaluations for academic institutions, government, and industry. Louis S. Harris, the editor of the monograph, is chairman of the Department of Pharmacology, Medical College of Virginia, Richmond, Virginia.

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Introduction of Nathan B. Eddy Memorial Award Recipient–1985

William L. Dewey

It is indeed a pleasure for me to present the 1985 Nathan B. Eddy Award. The recipient of this award, Dr. Louis S. Harris, has been a personal friend for the past 25 years. Lou's first association with Pharmacolgy began in the late 1940's and early 50's when he was diener of the Pharmacology Department at Harvard. The chairman of that department at that time was Professor Otto Krayer. Lou tells many fine stories of his days in that most prestigious department. In the early 50's, Lou went to undergraduate school and then graduate school at Harvard, and took his Ph.D. in Pharmacology in 1958. From there, he went to the Sterling-Winthrop Research Institute in Rensselaer, New York. In the early 1960's, Dr. Harris, along with Sid Archer and Noel Albertson from Chemistry, and Anne Pierson in the Pharmacology Department, was very instrumental in bringing to the clinic the first narcotic antagonist analgesic to be marketed in this country. What you might not know is that these were very exciting times at Sterling-Winthrop. At one time, there were as many as 12 compounds in clinical trials that had come through the CNS division of the Institute, the division of which Lou was in charge. Lou's diverse knowledge of all aspects of Pharmacology allowed him to have significant input into the toxicological and clinical testing as well as the ability to lead the work going on in the basic pharmacology laboratory.

In early 1966, Lou opted for a major change in his career. He accepted the position of Associate Professor and Head of the CNS Division of the Department of Pharmacology at the University of North Carolina Medical School. During the late 1960's and early 70's at North Carolina, Lou had a grant to continue his studies on the narcotic antagonist analgesics and another grant, one of the first to be funded, to study the active constituents of marijuana. It was during these years that Don McMillan and Lou first described the pronounced tolerance that develops to Δ^9-THC and other constituents of marijuana. In further studies, evidence was generated which showed that, in fact, the tolerance

was a true pharmacodynamic effect and not due to an alteration in the metabolic handling of Δ^9-THC.

In 1972, Lou accepted the position of Professor and Chairman, Department of Pharmacology, at the Medical College of Virginia, Virginia Commonwealth University. Lou has established an outstanding Department of Pharmacology at M.C.V. There are 22 full-time faculty members in the department, and not surprisingly, one of the largest groups of faculty study the interactions of drugs and the central nervous system. A few years after arriving in Virginia, C.P.D.D. established the second morphine-dependent rhesus monkey colony in the United States at M.C.V. This colony, which is run by Dr. Mario Aceto, has been screening compounds for the committee for the past 10 years. Lou Harris also has made other very significant contributions to the Committee on Problems of Drug Dependence during this time by acting as chairman of the Program Committee. His contributions in this area have extended beyond programming the scientific sessions to the point where he is the caretaker of all aspects of the meeting.

Lou Harris has been a consistent consultant to the World Health Organization and to a number of pharmaceutical firms. He, Drs. Raj Razdan, Harry Pars and John Sheehan established a partnership to produce cannabinoids for therapeutic use. Although Lou has continued to be interested in the pharmacological effects of the opiates, narcotic antagonist analgesics and the active ingredients of marijuana, one of the major areas of his research effort in- recent years has been in defining the antitussive effects of a number of interesting compounds. He has also investigated the effects of various isomers of opiates on this system. One of the objectives of this line of research is to determine if, in fact, there is an antitussive receptor which is distinct from the various subclasses of opiate receptors which have been proposed. In this project, as well as in all of the projects throughout his career, he has utilized a broad range of levels of investigation going all of the way from organic chemistry through classical in vivo and in vitro pharmacological techniques and, ultimately, to clinical testing in man.

Dr. Harris has won a number of awards for his contributions in science over the years. In 1977, he was awarded the American Pharmaceutical Association Award of Achievement for distinguished service in Pharmacology. In 1981, he was chosen as the Hartung Lecturer at the University of North Carolina, and just this past year, he received the Virginia Commonwealth University Award of Excellence for superior contributions in the areas of teaching, research and service at the University. To this date, only three of the nearly 2,000 faculty of the University have 'been so honored.

Although, in our society one does not win an award for these types of things, I save the characteristics of Lou Harris which are most important until last. Lou, as many of you know, is

truly a very fine human being. He cares a great deal for his fellow workers and is a true and valued friend. I would be very remiss if I did not tell you that throughout Lou's career he has enjoyed the love, support, and companionship of his wife, Ruth, who is here today.

As I said in the beginning, I am privileged and pleased to have the opportunity to present the Nathan B. Eddy Award to my good friend, Dr. Louis S. Harris.

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Nathan B. Eddy Memorial Award Lecture

Louis S. Harris

As is the prerogative of the Eddy Award recipient, I can talk about anything I choose. My choice is to try to relate to you some of the excitement and romance of a particular era of drug development of which I was a part--that is, the agonist-antagonist analgesics. I think this is important to do since this flavor of drug development seems to be becoming extinct in the "modern" era.

Late in 1960, Dr. Leonard Grumbach, who was in charge of the analgesic program at the Sterling-Winthrop Research Institute, announced that he was leaving to return to academia. I was asked to take over this project. I was left with the legacy of a highly competent technical staff, namely Ann Pierson and Hatty Lawyer, some highly honed techniques and a huge amount of data. The objective of the analgesic program was the development of an analgesic with the efficacy of morphine but having little or no abuse liability. Indeed, these were the very ideals which inspired the original creation of the Committee on Drug Addiction (1) which has evolved into the current Committee on Problems of Drug Dependence.

Well, what had been going on at Sterling? First, techniques had been utilized to accurately quantitate the antinociceptive activity of potential drugs. For instance, the hot-plate procedure of Eddy and Leimbach (2) and the tail-flick test of D'Amour and Smith (3) had been modified to allow accurate, reproducible potency estimates. These methods were so good that one could predict with a high degree of accuracy that a drug would be an analgesic in man and even get a good approximation of the dose needed to produce this effect. The chemists at Sterling were making large numbers of derivatives of meperidine (several thousand), submitting them for pharmacological evaluation and most were found to have analgesic activity. Many were sent out for clinical trial and found to be efficacious. This was a very self-satisfying project for both the chemists and the pharmacologists. However, the only gain was the production of more and more potent narcotics which had the same potential for

abuse. To illustrate the situation we had reached, I put together information available at that time for seven drugs on which we had excellent quantitative analgesic data from animals and man and dependence data in man (4). The results are shown in Table 1. As I indicated before there was an excellent correlation between the animal antinociceptive data and the an-

TABLE 1

RANK-ORDER CORRELATION OF SEVEN WELL KNOWN ANALGESICS

COMPOUND	1 HOT-PLATE RANK	2 TAIL-FLICK RANK	3 ANALGESIC EFFECTIVENESS	4 ADDICTION LIABILITY
METHADONE	1	2	2	1
ISOMETHADONE	4	3	4	4
MEPERIDINE	5	5	5	5
KETOBEMIDONE	2	1	1	2
CODEINE	7	7	6	6
MORPHINE	3	4	3	3
D-PROPOXYPHENE	6	6	7	7

SPEARMAN RANK-ORDER COEFFICIENTS

1 vs. 2-0.93	1 vs. 3-0.93	1 vs. 4-0.9	2 vs. 3-0.93	2 vs. 4-0.89

algesic activity obtained in man. What was more interesting was the high correlation between the animal tests and dependence liability. What this indicated to me was that, while the animal antinociception tests were excellent for predicting analgesia, they were equally good in predicting dependence liability. Thus, if the drug development project continued along the same lines, its ability to meet the objective of developing a non-addicting analgesic was doomed to failure. Indeed, things looked so bleak at that time that Dr. Schauman, the developer of meperidine and methadone, was prompted to write, "It is, therefore, not correct to say that the depression of respiration and the constipating effects of the analgesics are side effects. They are inseparable from their analgesic activity. This is, unfortunately, also true for the liability to cause addiction. It will, therefore, not be possible to find morphine-like analgesics without the undesirable addiction and, in fact, all efforts in this direction have been unsuccessful" (5). Things, however, were not so bleak.

On the basis of some laboratory data which indicated that certain mixtures of nalorphine and morphine could produce analgesia without respiratory depression, Dr. Eddy asked Dr. Henry Beecher to evaluate these mixtures in man. The task was assigned to Dr. Louis Lasagna and their results were published in 1954 (6). As to the hypothesis tested, they found that nalorphine antagonized morphine's analgesic activity to the same degree as it antagonized its respiratory depressant effects. A surprising finding came from their use of nalorphine alone as a

control. They found nalorphine to be a potent analgesic. This was surprising since nalorphine had little or no analgesic activity in our standard animal test procedures. They reported a high incidence of dysphoric side-effects and, despite the fact that their analgesic data were fully confirmed and extended by Keats (7), this finding was not actively pursued as a drug development lead.

The problem we faced was how to break out of the traditional mold. What we decided to do first was to develop a new series of narcotic antagonists and secondly to drop from further consideration compounds which were active in our antinociceptive tests. We also had to develop a quantitative assay of antagonistic activity. We chose to use antagonism of analgesia in the tail-flick test (8). This procedure gave good dose-response relationships and there was a high correlation in the ability to antagonize opioid analgesics of different potencies and classes, Table 2 (9).

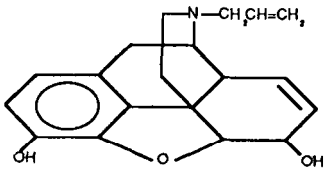
Table 2
A Rank Order Correlation Of Various Antagonists
Against The Analgesic Action Of Three Narcotics

A vs. Meperidine		B vs. Morphine		C vs. Phenazocine	
Rank	AD_{50} mg/kg s.c.	Rank	AD_{50} mg/kg s. c.	Rank	AD_{50} mg/kg s.c.
1	0.0135	1	0.018	1	0.019
2	0.018	7	0.048	5	0.033
3	0.019	2	0.029	2	0.028
4	0.019	3	0.030	3	0.029
5	0.024	6	0.046	7	0.048
6	0.034	4	0.038	8	0.054
7	0.046	8	0.057	9	0.09
8	0.049	5	0.044	4	0.030
9	0.052	9	0.058	6	0.046
10	0.092	12	0.26	12	0.2
11	0.094	11	0.19	13	0.37
12	0.134	10	0.130	10	0.098
13	0.146	13	0.46	11	0.19
14	0.37	14	0.60	14	0.40
15	0.45	15	0.63	15	1.0
16	0.66	16	2.2	16	1.4
17	3.9	17	9.0	17	6.3
18	10.9	18	11.6	18	11.0
19	14.5	19	18	19	29
20	48	20	50	20	70

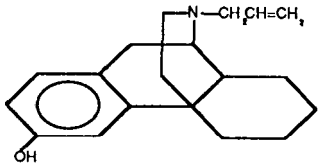
Rank Order Correlation Coefficietnts
A vs. B = 0.962
A vs. B = 0.952
B vs. C = 0.970

As to the direction of the chemical program, we knew that [Figure 1] replacement of the N-methyl group of the five-ring structure morphine resulted in an antagonist (nalorphine) as did the same replacement in the four-ring morphinan structure (levallorphan). We also knew from our own and others' work that replacement of the N-methvl by allyl in the two-ring meperidine series did not produce an antagonist. For a number of reasons Drs. Archer and Albertson turned to the three-ring benzomorphan series which had recently been introduced by Drs. May and Eddy (10).

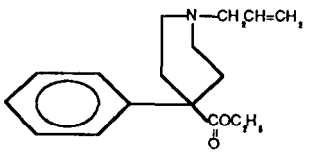
Figure 1



Nalorphine

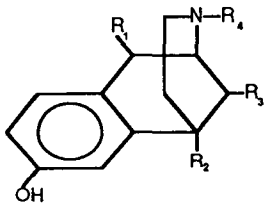


Levallorphan



They had found that phenazocine (Figure 2A) had good analgesic activity in animals and man and was less potent in monkey dependence studies than one would expect based on the analgesic data.

Figure 2



	R_1	R_2	R_3	R_4
A	-H	$-CH_3$	$-CH_3$	$-CH_2CH_2$ 
B	-H	$-C_2H_5$	$-CH_3$	$-CH_2CH=CH_2$
C	-H	$-CH_3$	$-CH_3$	$-CH_2CH=CH_2$
D	-H	$-CH_3$	$-CH_3$	$-CH_2CH=C(CH_3)_2$
E	-H	$-CH_3$	$-CH_3$	$-CH_2$ 
F	=O	$-CH_3$	$-CH_3$	$-CH_2$ 

Up to this point, antagonists in this series had not been reported. The first compound we seriously considered was the N-allyl compound in the 5-ethyl series (WIN 19362, NIH 7957, Figure 2B). Many of you will recognize this as a close analog of SKF-10,047, (Figure 2C) which we had also prepared and evaluated. NIH 7957 was inactive in the antinociceptive tests but was a potent antagonist. It reversed the respiratory and cardiovascular depression produced by morphine and had little CNS depressant activity. The compound was sent to Arthur Keats for analgesic evaluation in man. It should be noted that we had no evidence for efficacy as an analgesic in our animal studies. Dr. Keats reported that the compound produced analgesia with a potency greater than morphine. However, the nalorphine-like side-effects were so severe they precluded further work with this compound (10).

The second compound chosen for clinical trial was the dimethyl-allyl derivative (WIN-20228 or NIH 7958) (Figure 2D). Again, this compound had little or no activity in our antinociceptive tests and was a weak narcotic antagonist. Its pharmacology is summarized in Table 3. When NIH 7958 was evaluated by Keats as an analgesic in man he reported it to be a potent analgesia (10). No nalorphine-like side effects were seen. When the drug was tested in the morphine-dependent monkey at University of Michigan it was found not to support dependence. It was then studied at Lexington by Frank Fraser and his colleagues. They reported (11) that the drug produced considerably less opiate-like subjective effects than morphine and compared well to d-propoxyphene. When substituted for morphine in morphine-dependent subjects the drug was indistinguishable from saline. These very encouraging results led to the commercial development of this drug which you all know as pentazocine. As future events have demonstrated, the drug is not the perfect non-addicting substitute for morphine and our search for this ideal is still continuing.

Let me now continue with the historical description of the drug development project at the Sterling-Winthrop Research Institute. The next compound which aroused intense interest was the N-cyclopropylmethyl derivative NIH 7981, WIN 20740 (Figure 2E). This compound was inactive in the tail-flick test but was active in the hot-plate where it was noted that the animals appeared to be highly tranquilized. The compound was a potent analgesic antagonist and also antagonized opiate-induced respiratory and cardiovascular depression in the dog. A summary of the pharmacological properties is shown in Table 4. Of particular note is the polysynaptic blocking activity of the compound. The analgesic activity of this compound, which we know as cyclazocine, was evaluated by Lasagna (12) and proved to be 40 x morphine. However, nalorphine-like side effects were noted at the higher doses in this study. Later work indicated that these side effects occur at doses from 0.5-2.0 mg. When studied in the dependent monkey at UM, the compound did not substitute for

Table 3
Summary of the Pharmacological Properties of
NIH 7958

TEST	RESULT
1) Antagonism of morphine and meperidine in the rat tail flick	AD_{50} vs morphine = 9.0 mg/kg SC AD_{50} vs meperidine = 3.9 mg/kg SC
2) Rat tail flick	Inactive at 30, 60, and 120 mg/kg SC
3) Hot plate	ED_{50} > 200 mg/kg SC
4) Dog overt behavior	Marked effects at 5-10 mg/kg IM
5) Respiratory and cardiovascular depression in the anesthetized dog	Moderate at 10 mg/kg IM
6) Normalization of morphine- or meperidine-induced behavior in dogs	Poor to fair: 0.5 - 2.0 mg/kg IV
7) Reversal of morphine- or meperidine-induced respiratory and circulatory depression in the anesthetized dog	Poor: 1- 10 mg/kg IV
8) Monkey overt behavior	Slight depression at 10 mg/kg IM

Table 4
Summary of the Pharmacological Properties of
NIH 7981

1)	Antagonism of morphine and meperidine in the'rat tail flick	AD_{50} vs morphine = 0.029 mg/kg SC AD_{50} vs meperidine = 0.019 mg/kg SC
2)	Rat tail flick	Inactive at 60 and 120 mg/kg SC
3)	Hot plate	ED_{50} = 19 mg/kg SC
4)	Dog overt behavior	Marked effects at 0.031 - 2.5 mg/kg IM
5)	Respiratory and cardiovascular depression in the anesthetized dog	Moderate depression at 2.5 - 10 mg/kg IM
6)	Normalization of morphine- or meperidine-induced behavior in dogs	Good at 0.0075 - 0.015 mg/kg IV
7)	Reversal of morphine- or meperidine-induced respiratory and circulatory depression in the anesthetized dog	Fair to good at 0.015 - 0.030 mg/kg IV
8)	Monkey overt behavior	Slight effects at 0.125 mg/kg IM Moderate effects at 0.25 - 0.50 mg/kg IM Marked effects at 1.25 - 2.50 mg/kg IM
9)	Inclined screen	ED_{50} = 2.75 mg/kg SC
10)	Inhibition of polyneuronal reflex in the anesthetized cat	Linguomandibular reflex nearly abolished at 2.0 mg/kg IV
11)	Anticonvulsant activity	ED_{50} vs MES = 13.7 mg/kg IP ED_{50} vs Metrazol = 4.4 mg/kg IP

morphine. Indeed, it precipitated abstinence. Essentially, the same picture was found when the compound was evaluated by Fraser for dependence liability in man (13). The drug did not substitute for morphine but precipitated withdrawal. Further studies by Bill Martin revealed its excellent and long-lasting antagonistic activity. This, coupled with good oral activity, prompted him to suggest that cyclazocine be used as a blocking agent in the treatment of post-dependent narcotic addicts (14).

One final compound from this program must be mentioned, although its development came after I returned to academia. This compound is NIH 8847 or ketocyclazocine (Figure 2F). It was of great interest because, despite the N-cyclopropylmethyl group, it was not an antagonist. It was a potent analgesic. In the monkey, (15) it did not substitute for morphine nor did it precipitate withdrawal. When Bill Martin studied this compound in his animal test procedures he noted its atypical behavior. It was on the basis of his study of these and other diverse compounds that he put forth his brilliant hypothesis of multiple opiate receptors which has been the key to the recent discovery of endogenous opiates and search for receptor sites (16).

I trust this highly personal account of a specific drug development program has given some insight into how this work provided the ground work for a major development in our understanding of the physiological and biochemical substrates of pain. I feel strongly that this odyssey would have received the approbation of Dr. Eddy, whose encouragement, advice and guidance were instrumental in its successful completion.

References

1. Eddy, N.B., The National Research Council Involvement in the Opiate Problem, 1928-1971. National Academy of Sciences, Washington, D.C., 1973.
2. Eddy, N.B. and Leimbach, D., J Pharmacol Exp Ther 107, 385-393 (1953).
3. D'Amour, F.E., and Smith, D.L., J Pharmacol Exp Ther 72, 74-79 (1941).
4. Archer, S. and Harris, L.S., Progress in Drug Research, Vol. 8, Ed. E. Tucker, Birkhäuser Verlag, Basel, 1965.
5. Schaumann, O., Brit Med J, 1091 (1956).
6. Lasagna, L. and Beecher, H.K., J Pharmacol Exp Ther 112, 356 (1954).
7. Keats, A.S. and Telford, J., J Pharmacol Exp Ther 117, 190 (1956).
8. Harris, L.S. and Pierson, A.K., Minutes of the 24th Meeting of the Committee on Drug Addiction and Narcotics, 1962, Addendum 1, pp 3076-3085.

9. Harris, L.S., Archer, S., Pierson, A.K., Albertson, N.F., and Tullar, B.F., Minutes of the 25th Meeting of the Committee on Drug Addiction and Narcotics, 1963, App. 25, pp 3499-3507
10. Keats, A.S., Telford, J. and Papadopoulos, C N., Minutes of the 24th Meeting of the Committee on Drug Addiction and Narcotics.
11. Fraser, H.F. and Rosenberg, D.E., J Pharmacol Exp Ther 143, 149-156 (1964).
12. Lasagna, L., DeKornfeld, T.J. and Pearson, J .W., Minutes of the 25th Meeting of the Committee on Drug Addiction and Narcotics 1963, Appendix 9, pp 3250-3263.
13. Fraser, H.F. and Rosenberg, D.E., Ibid 1983, Appendix 8, pp 3237-3249.
14. Martin, W.R., Gorodetzky, C.W. and McClane, T.K., Ibid, 1965, Appendix 25, pp 4289-4301.
15. Swain, H.H and Seevers, M.H., Ibid, 1974, Addendum 1, pp 1168-1195.
16. Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E. and Gilbert, P.E., J Pharmacol Exp Ther 197, 517-532 (1976).

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Introductory Remarks

Carlton E. Turner

Thank you for your kind introduction. It's a pleasure for me to be among my fellow scientists again. As a scientist performing a public policy role at the White House, I spend my days coping with bureaucratic jargon. Bureaucrats love words like "optimize," "prioritize," and "interface." You can well imagine what a relief it is for me to hear words I can understand -- like benzodiazepine antagonists, kappa agonists, pharmacokinetics, and pentazocine.

All kidding side, I frequently find that I miss the challenges and the intellectual excitement of scientific research. My sense of deprivation has been considerably eased this morning by seeing my old friends and meeting some new ones. I intend to make the most of my opportunity to speak to you today. I will not simply congratulate the Addiction Research Center on its 50th anniversary, and extol its long list of accomplishments. Dr. Jerome Jaffe is eminently more qualified to do so, and will certainly do a better job than I could. Yet, I would like to say this much: those of you in the audience who have not become familiar with the life and work of Nathan B. Eddy would be immensely rewarded by doing so. This is especially true for those of you who are here for the first time. It, would give you a historical perspective as to why the ARC means so much to those of us who had the privilege of working with some of the pioneers in narcotics research.

I have been accorded carte blanche as to the substance of my remarks. Bill Dewey said I did not have to conform to any scientific protocol, or to any preconceived idea that he or I might have had. Accordingly, I would like to share with you some personal observations about the toils and tribulations of the research scientist today, when so much of the work being done is paid for directly or indirectly by the taxpayer. I would like to do this in the context of my own field of drug abuse policy.

Drug abuse affects every American citizen in some way, just as it affects the world community as a whole. There is no escaping

this problem. It acknowledges no geographic or economic boundary, and it makes no distinctions regarding class, race, or creed. It is perhaps the most democratic of all afflictions.

Yet, we in the scientific community have not been able to persuade our fellow citizens as to the true extent and severity of this problem. This may be because of the very nature of the scientific process, or to our inability to communicate with lay people in their own language, or to our mistrust of the media, or to the rapidly changing nature of society in which science and the nation seem to react only if there is a crisis.

Consider the media for a moment. In reporting what we do, the journalists are bound by what I call the "B-B approach" -- bucks and bodies. If there are no new bucks being thrown at the problem or bodies lying in the street, drug abuse is not something that makes headlines. If it is a slow, insidious process that destroys young people and families, it is not considered exciting enough for the front page of the morning edition or terse bulletins on the nightly news.

Scientists have special problems in communicating with the media and with the public. I have seen this sort of thing happen all too often: scientists come together for a meeting on a major national problem like drug abuse. During the meeting, they talk to each other as scientist to scientist. Then, when they try to share the results of their deliberations with the public, they still talk as if they were attempting to communicate with other scientists.

We have other problems as well. If I am a scientist with a liberal view that allows me to expound upon all theoretical possibilities, I will probably make some very dramatic ments. If I do, I can become the darling of the media while still retaining the respect of my scientific colleagues. But if I am a scientist who takes a conservative view, and will not advance any new proposition without a sound factual basis, then I will not play well before the television cameras, and my colleagues may shun me as a dullard. Yet, which approach best serves the public interest?

We don't allow the Food and Drug Administration and the Environmental Protection Agency to take a very liberal view. These agencies are charged with protecting the health and safety of the public. We <u>expect</u> them to be prudent where our interests are at stake -- and we have every right to so expect. Yet, for many years we have not demanded the same conservative, protective approach in the area of drug abuse.

If you think about it not as a scientist but as a member of the public, I think you will begin to realize that we must change our method of dealing with the drug issue. When we communicate to the public on drug abuse, we must state what we know in unequivocal terms. We must not allow ourselves to be coaxed

into careless speculation. We must be straightforward and we must speak plainly. We must not couch what we know in scientific language, such as, "the data seem to indicate that there is a theoretical possibility that on rare occasions this might be the case." We must call a spade a spade.

I'll give you an example of what I mean. Not long ago, I had the privilege of attending a celebration honoring Jacques Cousteau on his 75th birthday. As you know, the Cousteau Foundation has been concerned with the problem of environmental pollutants for many years. Recently, Cousteau and his son, Jean Michele, went to the Amazon River Basin to investigate the exploitation of the natives by cocaine growers.

Not only did the Cousteau group do their usual program, they also produced a documentary called "Snowstorm in the Jungle," which was aired twice on CNN, aired on French television, and is now being distributed worldwide. It is a gripping documentary that at one point recalls what a British diplomat said about the so-called "Opium War" of the last century: "Britain gave opium to the Chinese, and China went to sleep for a hundred years." Cousteau wonders if we are not seeing a modern-day "Opium War" in the distribution and abuse of cocaine. He asks: "Are we witnessing the decline of Western Civilization as we know it because of cocaine use?"

This documentary has provoked intense discussion about cocaine. Many scientists have said that cocaine is not an addictive drug. Amazingly, quite a few of these scientists are psychiatrists and psychologists. I am frightened that these modern-day followers of Freud should be seemingly unaware of their leader's extensive experiments with cocaine. We don't need massive new research programs to give us the facts on this drug. We need only consult Freud to be fully apprised of its horrors. We need only look at some of the early animal experiments done in Michigan to understand that we are dealing with a product so reinforcing that it will. inevitably do grave harm to any user. We need only look at the problems created by the widespread. use of cocaine between 1880 and the First World War to realize the social consequences that would follow if the drug were ever freely available again.

During the previous administration, one White House spokesman on drug abuse said that cocaine was so expensive only the wealthy could afford it, and they would know how to use it for recreational purposes without being irresponsible. I could forgive that person if he were a layman whose knowledge of cocaine was limited to a hurried briefing before he met with reporters, but I cannot forgive a purported expert for being ignorant of history.

The whole scientific community suffers when one of our members makes such an inexcusable gaffe. We lose credibility. We

shouldn't wonder when a skeptical public balks at spending more money on scientific research.

We must be willing to accept that drug abuse is not limited to heroin addiction. Heroin addicts are a small percentage of our population compared with other drug abusers, yet for years drug abuse was synonymous with heroin abuse. We must broaden that definition to include all drug abuse, whether the particular drug is licit or illicit. Why are we uneasy about being frank? Why do we call an addict a "substance abuser"? Why are we reluctant to include alcohol in our public discussions of abusive drugs? Why do we hesitate to apply the term "drug abuse" to the whole gamut of dangerous narcotics? When we are needlessly technical, we destroy our ability to communicate with the mass of people who need to hear us. We may say that information is available because we've published our various scientific papers. But is that information readily available to the public? If it isn't, we have a duty to communicate what we know to the American people in language they can understand.

We must take that duty seriously. We don't live on the 51st floor of a building that has only 50 stories. We live in the real world. The future of scientific research in this country depends to no small extent on the good opinion of our fellow citizens. Stating the facts on drug abuse candidly and fearlessly will do more than win praise for the CPDD and the Addiction Research Center; it will enhance the prestige of science in the United States.

Thank you.

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Studies of Kappa Agonist

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It is accepted that there is a group of chemical compounds, having vastly different pharmacologic activities and different structures, that are classified as opioid drugs (Goldstein and James 1984, Martin 1981). The agonist drugs, though very different from one another, share one common property; that their pharmacologic activity is specifically antagonized by naloxone. This property has become the definition of an opioid agonist.

The receptor subtypes that have been defined thus far are the mu, kappa, sigma, and delta opiate receptors (Iwamoto and Martin 1981; Wood et al. 1980; Miller 1982). Presumably, drugs that are active on the opiate system bind to these receptors causing pharmacologic activity. Yet, the drugs that we use as ligands in the laboratory have complex actions. Important variables that determine the specific action of a drug must perforce include what receptor or receptors bind the drug, whether the drug acts as agonist or antagonist at these sites, and the animal species to which the drug is given. Thus, just to begin an investigation there are many undefined variables with which to contend; four receptor subtypes; agonist or antagonist activity; and a minimum of seven animal species: mouse, rat, guinea pig, pigeon, dog, squirrel monkey, and man, that have been extensively studied. Each animal demonstrates unique profiles of responses to opioid compounds (Iwamoto and Martin 1981; Woolverton and Schuster 1983). Furthermore, the particular test used may have a unique opioid profile with respect to other tests even within the same species (Porreca et al., 1982). Despite all these efforts, it is not certain what are the exact boundaries of the pharmacologic effects of any of the receptor subtypes, though mu activity is probably best described.

The ARC has evolved a program to examine the problem of defining which action is coupled to which receptor subtype. The first efforts are being directed toward the mu receptor and the kappa receptor. Our investigations of kappa type opioid drugs are quite varied and involve a number of scientists using different methodologies. The work is organized, however, into three categories of research interests. The plan is to: 1) charac-

terize the effects of drugs believed to be relatively selective; 2) study the interaction of opioid antagonist with kappa agonists; and 3) develop *in vivo* models of the activity of the opiate system.

The first drug selected for study in man was ketocyclazocine. The drug possesses properties differing from morphine in animals and binds most specifically to kappa receptors *in vitro.* The drug was studied in a classical drug-abuse psychopharmacologic experiment in which morphine and cyclazocine serve as positive controls and placebo as the negative one. Subject mood states are measured using questionnaires, and vital signs are measured to determine physiologic responses.

In our initial studies of ketocyclazocine the drug had several qualities which, considered together, are distinctive among opioid drugs (Kumor *et al.*, 1984). Ketocyclazocine is not an euphoriant but generally causes dysphoria with distortions of perception. Thus, the MBG Scale scores did not increase on administration of the drug but the LSD Scale scores and Perception Scale scores did increase. Ketocyclazocine is clearly very different from morphine and subjects have little difficulty making a distinction. Among physiologic measures ketocyclazocine was not very active. It did cause increases in the blood pressure but little else. It is notable that there was only minimal miosis and respiratory rate depression caused by this drug in man.

At the maximal doses of ketocyclazocine and cyclazocine studied, 1.2 and 1.0 mg respectively, the drugs had many qualities in common. They shared the ability to cause elevations in the scores for the LSD and Perception Scale and they lacked the ability to cause elevations in the MBG Scale scores. However, at lower doses of ketocyclazocine (0.6 mg) and cyclazocine (0.5 mg) the two drugs were less similiar and cyclazocine appeared to have more in common with morphine than in the higher dose range.

One physiologic that might prove useful in studying kappa agonist properties is urinary flow rate. In animals, kappa selective drugs cause an increase in the urinary flow rate (Rathbun *et al.* 1983; Slizig and Ludens 1982). This property has value in monitoring drug action, especially in animals where subtle psychoactive changes are difficult to measure.

Morphine 30 mg and ketocyclazocine 1.2 mg are equivalent doses as measured on the "Feel Drug" scale. A comparison was made between the scores after ketocyclazocine (1.2 mg) alone and ketocyclazocine in combination with the dose of naloxone necessary to block morphine (30 mg) for that individual subject. Blockade of morphine was judged to be present if the combination of naloxone with morphine caused the subject to identify the drug as having no effect. The combination of this morphine blocking dose of naloxone with ketocyclazocine caused a significant decrease in the "Feel Drug" scale scores as compared with

the scores after ketocyclazocine alone. Furthermore, the scores after the combination are not different from placebo. Scales measuring responses more specific to ketocyclazocine also demonstrate a decline of drug effect with the addition of these doses of naloxone. The same pattern of reversal of psychopharmacologic effect is seen on the LSD Scale and the Perception Scale. The Perception Scale was a scale we developed during our first study of ketocyclazocine. It is the most sensitive scale we have for measuring the effects of ketocyclazocine. (Kumor et al., 1984).

Our preliminary conclusions, based on the completion of five subjects out of an anticipated 12 subjects, are that the psychopharmacologic activity of ketocyclazocine is blocked by naloxone and that ketocyclazocine blockade occurs at naloxone doses that are similiar to doses required to block an equally intense dose of morphine.

The puzzling aspect of these initial observations is that the doses required to block the effects of ketocyclazocine are much less than expected in a relative sense. Usually, the ratio of the amount of antagonist drug necessary to block kappa effects is 10-30 times the dose necessary to block morphine (Goldstein and James 1984; Kosterlitz et al., 1974; Schaffer and Holtzman, 1978). Our experiments do not demonstrate clearly this same separation of receptor subclass by naloxone sensitivity. It is worth observing, however, that we have obtained very large differences between subjects in regard to naloxone blockade of 1.2 mg of ketocyclazocine.

A study of schedule-controlled responding in squirrel monkeys has yielded results, possibly related results. (Katz and Goldberg, 1984). In that study, key-pressing behavior of squirrel monkeys was maintained either by food or electric-shock presentation. Both morphine and ethylketazocine decreased rates of responding maintained by food presentation and increased rates of responding maintained by shock.

Therefore, we set about to measure the urinary composition and flow rates after administration of ketocyclazocine, morphine and placebo. Urine was collected for a three-hour period after drug administration. The average urine volume decreases as a consequence of morphine administration and increases as a consequence of ketocyclazocine administration ($p<.05$). We see the same pattern of results for the milliosmol excretion but not for sodium excretion in which the amount of sodium excreted after ketocyclazocine was not different from placebo. The measures of urine volume and milliosmol excretion during morphine and ketocyclazocine differ significantly ($p<.05$) from placebo. Morphine differs from placebo for sodium excretion as well but ketocyclazocine did not.

This pattern is consistent with observations of urinary output in animals administered kappa agonists (Rathbun et al., 1983; Slizgi and Ludens 1982). It is an observation which has import-

ance because it is consistent with expectations that a kappa agonist should increase urine flow.

The evidence supports the idea that the activity of ketocyclazocine in man operates through a different mechanism from that of morphine; the drug has physiologic properties and subjective effects that are distinct from morphine and the drug causes an increase in urine flow.

Another property of interest is the interaction of naloxone with ketocyclazocine in human subjects. This experiment is of interest because in most research systems the dose of naloxone necessary to block the activity of drugs presumed to be kappa agonists is greater than the dose necessary to block morphine (Goldstein and James 1984; Kosterlitz et al., 1974; Schaeffer and Holtzman 1978). Subjects were given a randomized set of drug injections. The set included ketocyclazocine 1.2 mg, morphine 30 mg or placebo. These doses were also given simultaneously with varying doses of naloxone. Our studies are incomplete but several conclusions can be drawn.

Combinations of ketocyclazocine with naloxone result in diminution of drug effect. Contrary to general speculation, and contrary to our own expectations, significant ($p<.05$) blockade occurs at doses which are approximately the same as the doses of naloxone necessary to block morphine effects.

This blockade is demonstrated most clearly on the "Feel the Drug" scale results for the first five subjects presentation. Each of these drug effects was antagonized by naloxone at a dose of 0.1 mg/kg. Further the shifts in dose-effect curves for the two agonists were of comparable magnitude, and of a magnitude similar to that obtained in previous studies of antagonism of the effects of mu agonists (Goldberg et al., 1981). These studies indicate that there are some important similarities in the behavioral effects of morphine and ethylketazocine in the squirrel monkey.

It appears that the relative dose of antagonist necessary to block mu and kappa agonist may depend on the animal species or on the research methodology employed. (Porreca et al., 1982; Rathbun et al., 1983; Kosterlitz et al., 1974; Leander 1983; Tortella et al., 1980). In either case, these observations are of interest in developing an understanding of what constitutes the intrinsic features of kappa receptor agonism and what features are permissive.

Another focus of interest of the ARC concerns itself with another drug, BW942C, which proved to be very interesting to the study of the characteristics of kappa opiate agonists. While BW942C was incompletely studied at the time of the ARC studies, certain properties were known. It had a pentapeptide structure and opioid agonist activity that supported its development by Burroughs Wellcome Co. as an antidiarrheal agent for oral use. Some psychoactive effects had been observed in the phase I trials. Receptor binding studies were not available.

The ARC studies found that this drug has weak psychoactivity. The drug does not elevate scores on the MBG or liking scales but there are responses on the Feel Drug scale, PCAG and LSD scales of the ARCI. The PCAG and LSD scale score elevations occur only at the 2 mg dose, which was the highest dose used, whereas, increased scores on the "Feel Drug" scale occurred all three doses 0.5, 1.0, and 2.0 mg. There were no significant physiologic effects of the drug except that some individuals experienced increases in the blood pressure.

These findings can be summarized as follows: 1) BW942C is psychoactive when given parenterally; 2) it does not cause morphine-like subjective effects or euphoria; 3) increases in the LSD and PCAG scale scores suggest a qualitative similarity to ketocyclazocine; 4) and minimal miosis without additional physiologic effects suggests a qualitative similarity to ketocyclazocine (Johnson and Jasinski 1985). That is, there were elevations on the LSD, PCAG and Feel Drug Scales without other changes. However, though the profile of subjective scale scores is similiar qualitatively to ketocyclazocine, the scores were lower, and, therefore, less distinct, making conclusions tenuous.

Some light was shed on this by additional studies. During the-initial evaluations in human subjects, one of them remarked that the drug he received caused him to urinate a lot. Investigation into this phenomenon was undertaken using the rat.

The urine output after the Burroughs Wellcome drug was measured and compared to the urine output after two kappa agonist compounds, bremazocine and U 50488H, an Upjohn compound. These compounds are accepted as being kappa agonists, on the basis of their binding characteristics, diuretic activity and relative sensitivity to naloxone (Iwamoto and Martin 1981; Leander 1983; Romer et al., 1980). The urinary flow accumulated over a five-hour period was measured after increasing doses of these kappa opioid compounds given subcutaneously to rats.

U50488H and bremazocine cause linear increases in urine flow rate in response to increasing doses of drug. BW942C, in contrast, produces an inverted U-shaped curve having a lower peak elevation of urine flow rate than either U50488H or bremazocine. Another set of experiments investigated the urinary activity of the BW compound as a function of naltrexone doses (0.01 to 1.0 mg/kg). In these experiments, low doses of naltrexone reversed the antidiuretic effect of the high, 3 mg/kg dose of BW942C, to reveal a diuretic effect. Higher doses of naltrexone were needed to antagonize the diuretic effect of 0.3 mg/kg of BW942C.

The interaction of the BW drug with kappa agonists was also studied. The diuretic effects of intermediate doses of bremazocine and U50488H were antagonized by the BW compound in a dose related fashion. The results of these studies are interpreted as consistent with the pattern of a partial kappa agonist (Vaupel et al., 1985).

These results raised questions about the binding characteristics of BW942C. Dr. Chang at Burroughs Wellcome has studied BW942C and found that it is a potent ligand for mu and delta receptors in the rat (Chang 1985). He did not assay the binding of this compound to kappa receptors. At the ARC Tsung-Ping Su has examined the effect of BWO42C at mu, delta, kappa, and sigma binding sites derived from guinea pig brain tissue (Table 1.)

Table 1

DISSOCIATION CONSTANTS (K_i) of BW942C TOWARD MULTIPLE OPIOID RECEPTORS IN GUINEA-PIG BRAIN

MU	DELTA	KAPPA	SIGMA
[^{3}H] Naloxone	[^{3}H] DADLE	[^{3}H] EKC	[^{3}H] SKF
K_i(nM) 1.0	1.8	412	27% at 100,000 nM

$$*Ki = \frac{IC50}{1 + [^3H]/K_d}$$

Dr. Su has found that the BW drug binds with high affinity to delta and mu receptors as found by Dr. Chang. However, his results show that this drug also binds kappa receptors with moderate affinity. The dissociation constants of the drug at kappa receptors from the guinea pig are only 412 nM. Although this does not indicate a high degree of affinity for the kappa receptor, it is likely that the kappa receptor is involved in the activity of this drug. The sigma site is of some interest because activity at the sigma site may also cause an increase in urination (Leander 1983). However, BW942C does not appear to have sigma activity.

Further studies are needed which concentrate on examining the relationship between opiate binding sites and the pharmcologic activity, since there appears to be a dissociation between the results of these two experiments.

It is hoped that studies of kappa agonists like ketocyclazocine, ethylketazocine and explorations of interesting drugs like BW942C will allow us to arrive at a model of drug action that will account for the paradoxes that have been observed with kappa agonists. All of this work, studying the binding characteristics, psychoactivity, behavioral, and physiologic effects of agonist drugs or drugs which might be kappa agonists, in man and animals, focuses on attempting to define what effects of these agonists are the precise effects resulting from the interaction of the drug with subtype of receptor.

By studying these compounds alone and in the presence of antagonists, it should be possible to arrive at the fundamental profile of kappa agonism. It will be those clusters of effects which cannot be further split or subdivided in the presence of antagonists. Our outlook is cautiously optimistic because the tools needed for dissection of opioid pharmacological effects are being assembled. There are now antagonist drugs which appear to have selective antagonist action for the kappa receptor (Portoghese and Takemori 1984). Such drugs will allow further dissection of opioid activity and the achievement of defining the basic pharmacologic units of drug activity.

Our studies also make conspicuous the fact that the choice of animal species is very important and that studies involving the participation of human subjects are indispensable. Our studies also force the reexamination of the criteria we use to determine the labeling of drugs as agonists of receptor subclasses.

REFERENCES

Dr. Chang, personal communication, 1985.

Goldberg, S.R., Morse, W.H. and Goldberg D.M: Acute and chronic effects of naltrexone and naloxone on schedule-controlled behavior of squirrel monkeys and pigeons. J. Pharmacol. Exp. Ther. 216: 500-509, 1981.

Goldstein, A. and James, Lain F. Multiple opioid receptors, criteria for identification and classification. Trends in Pharmacological Sciences Vol 5. No. 12 503-505, 1984.

Iwamoto, E.T. and Martin, W.R. Multiple opioid receptors. Medicinal Research Reviews 1:411-440, 1981.

Johnson, R.E. and Jasinski, D.R., personal communication, 1985.

Katz, J.L. and Goldberg, S.R.: Comparison of effects of ethylketazocine and morphine on behavior controlled by noxious stimuli and food reinforcement in monkeys. Abstracts of the Ninth International Congress of Pharmacology 274, 1984.

Kosterlitz, H.W., Waterfield, A.A., and Berthoud, V. Assessment of the agonist and antagonist properties of narcotics analgesic drug by their actions on the morphine receptor in the guinea-pig ileum. In Narcotic Antagonists. Advances in Biochemical Psychopharmacology. Vo. 8. ed. Braude, M.C. Harris, L.S., May., E.L. Smith, J.P. and Villareal, J.E. 319-334. New York: Raven Press 1974

Kumor, K., Johnson, R.E., Jasinski, D. and Kocher, T. Comparative profile of the pharmacological activities of ketocyclazocine (K), morphine (M), cyclazocine (C) and placebo (P) in man. The Pharmacologist 26: 189 (p 162) 1984.

Leander, J.D. Further study of kappa opioids on increased urination. JPET 227:35-41, 1983.

Leander, J.D. A kappa opioid effect: increased urination in the rat. JPET 224:89-94, 1983.

Martin, W.R., Mini-symposium II. Multiple opioid receptors. Life Sciences 28:1547-1554, 1981.

Miller, R.J. Multiple opiate receptors for multiple opioid peptides. Medical Biology 60:1-6, 1982.

Porreca, F. et al. Tolerance and cross-tolerance studies with morphine and ethylketocyclazocine. J. Pharm. Pharmacol 34:666-667, 1982.
Portoahese, P.S. and Takemori, A.E. TENA, a selective kappa opioid receptor antagonist. Life Sci. 36:801-805, 1984.
Rathbun, R.C., Kattau, R.V. and Leander, J.D. Effects of mu- and kappa-opioid receptor agonists on urinary output in mice. Pharm. Biochemistry and Behavior 19:863-866, 1983.
Romer, D., Busches, H., R.C. Maurer, R., Petcher, T.J., Welle, H.B.A., Bakel, H.C.-C.K. and Akkermann, A.M. Bremazocine: A potent long-acting opiate kappa agonist. Life Sci 27:971-978, 1980.
Schaffer, G.J. and Holtzman, S.G. Discrimination effects of cyclazocine in the squirrel monkey. JPET 205:291-301, 1978.
Slizgi, G.R. and Ludens, J.H. Studies on the nature and mechanism of the diuretic activity of the opioid analgesic ethylketocyclazocine. JPET 220:558-591, 1982.
Tortella, F.C., Cowan, A. and Adler, M.W. EEG and behavioral effects of ethylketocyclazocine, morphine and cvclazocine in rats: differential sensitivities towards naloxone. Neuropharmacology 19: 845-950, 1980.
Vaupel, D.B., Cone, E.J. and Johnson, R.E. An enkephalin-like pentapeptide (BW942C) with partial kappa agonist activity. Abstract Soc for Neuroscience 1985.
Wood, P.L. et al. Actions of mu, kappa, sigma, delta and agonist-antagonist opiates on striatal dopaminergic function. JPET 215:697-703, 1980.
Woolverton, W.L. and Schuster, C.R. Behavioral and pharmacological aspects of opioid dependencies: mixed agonist-antagonists. Pharm Reviews 35:33-52, 1983.

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Metabolic Mapping of the Cerebral Effects of Abused Drugs

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INTRODUCTION

Interest in elucidating the anatomical sites which mediate the behavioral effects of pharmacological and physiological perturbations has led to the popularity of autoradiographic techniques to map the rates of cerebral blood flow and metabolism and the distributions of binding sites for drugs and neurotransmitters (Sakurada et al. 1978; Smith et al. 1980; Wamsley and Palacios 1983). The autoradiographic 2-deoxy-D-1-[^{14}C] glucose ([^{14}C]-DG) method is a functional mapping technique to measure local rates of glucose utilization throughout the central nervous system (Sokoloff et al. 1977). Glucose is almost the sole substrate for oxidative metabolism in the adult brain, and its utilization by the brain is stoich ometrically related to oxygen consumption Sokoloff 1972; Siesjö 1978). Therefore, rates of local cerebral glucose utilization (LCGU) can be used as indices of local energy metabolism and functional activity.

Animals subjected to the [^{14}C]DG procedure are injected intravenously with the radiotracer, and timed arterial blood samples are collected over a period of about 45 min. Pate of LCGU are calculated from concentrations of glucose and [^{14}C]DG in the arterial plasma and the radioactivity in the brain, measured by quantitative autoradiography. The [^{14}C]DG method has been used to map the *in vivo* distributions of action of various drugs, in-eluding muscurinic (Weinberger et al. 1979; Dow-Edwards et al. 1981; Dam et al. 1982; Dam and London 1983, 1984), dopaminergic (McCulloch et al. 1982 a,b) and γ-aminobutyric acid (GABA)-ergic agonists and antagonists (Palacios et al. 1982), noradrenergic antagonists (Sokoloff et al. 1978), and anesthetics (Nelson et al. 1980; Herkenham, 1981; Young et al. 1984).

Several studies related to drug abuse have utilized the [^{14}C]DG technique. In a study of phencyclidine's effects, autoradiograms demonstrated a drug-induced increase in the incorporation of the radiotracer in limbic areas, including the hippocampus, subiculm and cingulate cortex (Meibach et al. 1979). Acute treatment with

d-amphetamine stimulated LCGU in the extrapyramidal motor system, but not in mesolimbic dopaminergic areas (Wechsler et al. 1979; Orzi et al. 1983), which have been implicated in the rewarding properties of psychomotor stimulants (Wise 1983). In contrast, subchronic amphetamine treatment (1-2 weeks) significantly increased LCGU in the nucleus accumbens (Orzi et al. 1983). In a study of morphine-dependent rats, naloxone produced relative increases in [^{14}C]DG incorporation in the central nucleus of the amygdala, mammillary body, and medial septal nucleus (Wooten et al. 1982), consistent with a functional role of these brain areas in themorphine abstinence syndrome.

The pu pose of this paper is to present findings from our studies using [^{14}C]DG to map the in vivo cerebral distributions of action of several commonly abused drugs (i.e. nicotine, diazepam and phencyclidfne). Preliminary results on LCGU are presented in the context of how they relate to information pertaining to the relevant specific binding sites of these drugs.

CEREBRAL DISRIBUTIONS OF THE ACTIONS OF NICOTIIVE, DIAZEPAM AND PHENCYCLIDINE

Autoradiographic studies of receptors as well as metabolic mapping have been used to delineate the cerebral sites which mediate the various effects of nicotine (Clarke et al. 1984; London et al. 1985 a, b). Ligand binding studies, performed with slide-mounted sections of rat brain incubated with D,L-[^{3}H]-nicotine, have demonstrated heterogeneous, specific binding of the ligand, with dense labelling in the interpeduncular nucleus, medial habenula, thalamic nuclei, sensory areas, and the cerebral cortex (Clarke et al. 1984; London et al. 1985 b).

The distribution of nicotine's effects on LOGU generally correlates well with densities of [^{3}H]nicotine binding sites, supporting the view that nicotine binding sites visualized autoradiographically are functional receptors (Table 1). Brain regions such as the periaqductal gray matter and the CA_1 region of the hippocampus, which lack specific binding, show no metabolic response to the agonist. In addition, areas such as the caudate-putamen, dorsal nucleus of the lateral geniculate body, and subiculum, which have relatively low densities of binding sites, have either no metabolic response or a small enhancement of LCGU after the nicotine treatment. Although the ventral posterior nucleus of the thalarms, which has a moderate density of binding sites, shows no significant LCGU response, the superficial layers of the superior colliculus, which also have a moderate density, show an LOCU increase of 50 to 100% over control, and the interpeduncular nucleus and medial habenula, which have high densities of binding sites, show LCGD increases of at least 50%. Despite the apparent correlation between binding sites and the LOGU response to nicotine in the superior colliculus, acute unilateral enucleation blocks the increase in LCGD in the contralateral superior colliculus (Dam et al. 1985).

This observation suggests that [^{3}H]nicotine binding sites in the superior colliculus are not important to the nicotine-induced stimulation of LCGU in that brain region, and that the LCGU response in the superior colliculus is secondary to a retinal effect. Although the peripherally active antinicotinic agent hexamethonium had no effect on nicotine's stimulation of LCGU, nicotine's effect was antagonized by 2.5 mg/kg of mecamylamine, indicating a specific action (London et al. 1985 a).

TABLE 1. NICOTINE BINDING AND EFFECTS ON GLUCOSE UTILIZATION IN SELECTED REGIONS OF THE RAT BAIN

Brain Region	Binding Site Density [a]	LCGU Activation [b]
Caudate-putamen	+	-
Thalamus, ventral posterior n.	++	-
Lateral geniculate body, dorsal n.	+	+
Superior colliculus	++	++
Interpeduncular n.	+++	++
Medialhabenula	+++	+++
Hippocampus, CA_1	-	-
Subiculum	+	-
Periaqueductal grey matter	-	-

[a] Specific binding of 50 nM [^{3}H]D,L-nicotine was determined autoradiographically in 10 um slide-mounted brain sections. Data are from London et al. (1985 b). Specific binding <1 fmol/mg tissue, -; 1-10 fmol/ulg, +; 10-20 fmol/mg, ++; > 20 fmol/mg, +++.

[b] Local cerebral glucose utilization (LCGU) was determined as described previously (Sokoloff et al. 1977) 2 min after the subcutaneous injection of 0.9% NaCl (control) or 1 mg/kg D,L-nicotine (free base). No significant difference from control, -; increase of 20-50%, +; 50-100%, ++; 100%, +++.

The fact that metabolic maps may elucidate entire pathways or functional circuits activated by an agonist is illustrated by the effect of nicotine on LOGU in the habenulo-interpeduncular pathway (fig. 1). Nicotine stimulates LOGU in the medial habenula as well as the fasciculus retroflexus and interpeduncular nucleus, the fiber pathway and terminal field of the medial habenula, respectively. Studies in rats have demonstrated that stimulation of the habenular complex is rewarding (Sutherland and Nakajima 1981). Taken together, these findings implicate the habenular complex in the reinforcing effects of nicotine.

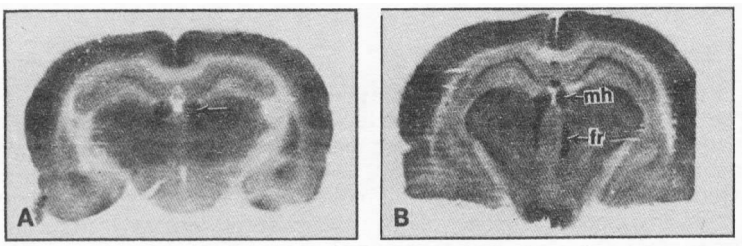

FIGURE 1. Effect of subcutaneous D,L-nicotine (1 mg/kg, 2 min before [^{14}C]DG) on autoradiographic grain densities, representing glucose utilization in the rat brain. These are photographs of x-ray film exposed to 20- µm brain sections from a control rat (A) injected with 0.9% NaCl (1 ml/kg), and another rat (B) injected with nicotine. Note the increased density in the medial habenula (mh) and fasciculus retroflexus (fr) after nicotine treatment.

A unique and completely different LCGU pattern is obtained in rats treated with phencyclidine (fig. 2). PFhencyclidine markedly alters LCGU throughout the neocortex, where alternating columns of higher and lower metabolic activity are apparent. Marked relative increases in LCGU are seen in the medial cortex, entorhinal cortex and subicular area. These findings are an extension of earlier observations (Meibach et al. 1979) and are consistent with observations on [^{3}H]phencyclidine binding in slide-mounted sections (Quirion et al. 1981) and whole homogenates of rat brain (Zukin et al. 1983). The highest levels of specific binding have been obtained in the subiculum and hippocampus, with moderate densities in the frontal cortex, striatum and hypothalamus. The apparent deregulation of cortical and limbic function, as indicated by LCGU, may help explain the severe emotional disorders in people who have self-administered phencyclidine (Pradhan 1984).

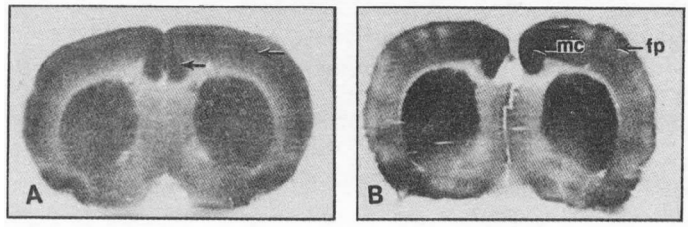

FIGURE 2. Effect of intravenous phencyclidine (1 mg/kg, 2 min before [^{14}C]DG) on autoradiographic grain densities, representing glucose utilization in the rat brain. These are photographs of x-ray film exposed to 20-μ m brain sections from a control rat (A) injected with 0.9% NaCl (1 ml/kg), and another rat (B) injected with phencyclidine. Note alternating columns of higher and lower LCGU in the frontoparietal cortex (fp) and a marked increase in the medial cortex mc) after phencyclidine treatment.

Despite the good correlations between densities of [^{3}H]nicotine and [^{3}H]phencyclidine binding sites and the distributions of the cerebral metabolic responses to these drugs, no simple relationships have been observed between markers for dopsminergic, muscarinic cholinergic and GABA-ergic systems and LCGU responses to the relevant agonists and antagonists (Dow-Edwards et al. 1981, McCulloch et al. 1982 a; Palacios et al. 1982). For example, the GABA-mimetic agents muscimol and 4,5,6,7-tetrahydroisoxazolo-[5,4-C]pyridin-3-ol (THIP) generally reduce LCGU (Palacios et al. 1982); whereas, areas such as the cerebellum and thalamus, which have high densities of GABA receptors, as measured by high affinity [^{3}H]muscimol binding, do not show greater LCGU depressions than does the striatum, which has a lower receptor density (Palacios et al. 1981). It should be noted, however, that autoradiographic studies of high affinity muscimol binding sites do not reveal all potential GABA receptors (Enna and Snyder 1975; Guidotti et al. 1979; Bowery et al. 1980; Tallman et al. 1980; Unnerstall et al. 1981).

It is now believed that the postsynaptic apparatus with which GABA combines to produce its characteristic responses is an oligomeric complex which bears the GABA receptor as well as a benzodiazepine binding site (Ticku 1983). This model for the benzodiazepine GABA receptor-ionophore complex is consistent with the positive reciprocal interactions observed between 1,4-benzodiazepines and GABA behaviorally as well as at cellular and molecular levels (Choi et al. 1978; Gallager 1978; Arnt et al. 1979; Guidotti et al. 1979). Despite the close association

between GABA-ergic neuronal systems and the actions of benzodiazepines, the LCGU pattern produced by diazepam differs from the metabolic responses to muscimol and THIP. Unlike diazepam, the GABA agonists produce a relative activation of the red nucleus and other components of the extrapyramidal motor system (Palacios et al., 1982). This effect may relate to the epileptic-like EEG effects of muscimol and THIP which have been observed in primates (Scotti de Carolis et al. 1969; Shoulson et al. 1978; Tamminga et al. 1979; Meldrum and Horton 1980). Another brain area which shows a relative LCGU activation after diazepam but not muscimol or THIP is the superior colliculus (fig. 3) where high densities of specific binding sites for [^{3}H]GABA (Bowery et al. 1984) and [^{3}H]flunitrazepam (Young and Kuhar 1979) have been observed. This discrepancy between the effects of diazepam as compared with the GABA agonists illustrates the fact that interactions at GABA and benzodiazepine recognition sites may have different physiological consequences.

In summary, <u>in vivo</u> metabolic mapping with [^{14}C]DG can provide a useful adjunct to receptor binding studies in elucidating the cerebral distrubutions of action of abused drugs. LCGU maps obtained in rats treated with nicotine or phencyclidine have provided results which generally are consistent with receptor binding studies. However, studies with diazepam manifest differences in LCGU effects as compared with those of GABA agonists, suggesting a dissociation between the actions of benzodiazepines and the function of GABA-ergic neuronal systems. Findings such as these, obtained by metabolic mapping, can provide information beyond that which is available from receptor binding assays, and can be useful in directing further studies on the anatomical substrates of the effects of psychotropic drugs.

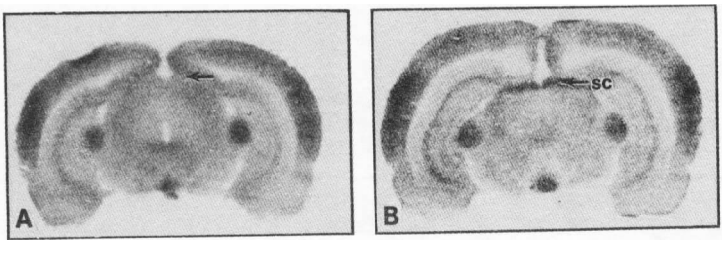

FIGURE 3. Effect of intravenous diazepam (2.5 mg/kg, 2 min before [^{14}C]DG) on autoradiographic grain densities, representing glucose utilization in the rat brain. These are photographs of x-ray film exposed to 20- µm brain sections from a control rat (A) injected with 0.9% NaCl (1 ml/kg) and another rat (B) injected with diazepam. Note enhanced [^{14}C]DG incorporation in the superior colliculus (SC) after diazepam treatment.

REFERENCES

Arnt, J., Christensen, A.V., and Scheel-Krüger, J. Benzodiazepines potentiate GABA-dopamine stereotyped dependent gnawing in mice. J Pharm Pharmacol 31:56-58, 1979.

Bowery, N.G., Hill, D.R., Hudson, A.L., Doble, A., Middlemiss, D. N., Shaw, J., and Turnbull, M. (-)Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. Nature 283:92-94, 1980.

Bowery, N.G., Price, G.W., Hudson, A.L., Hill, D.R., Wilkin, G.P., and Turnbull, M.J. GABA receptor multiplicity. Visualization of different receptor subtypes in the mammalian CNS. Neuropharmacology 23:219-231, 1984.

Choi, D.W., Farb, D.H., and Fischbach, G.D. Chlordiazepoxide selectively augments GABA action in spinal cord cell cultures. Nature 271:342-344, 1978.

Clarke, P.B.S., Pert, C.B., and Pert, A. Autoradiographic distribution of nicotine receptors in rat brain. Brain Res 323: 390-395, 1984.

Dam, M. and London, E.D. Effects of cholinomimetics on glucose utilization in rat brain optic systems. Eur J Pharmacol 87:137-140, 1983.

Dam, M. and London, E.D. Glucose utilization in The Papez circuit: Effects of oxotremorine and scopolamine. Brain Res 295:137-144, 1984.

Dam, M., Connolly, R., Wilkerson, G., and London, E.D. Effects of nicotine on glucose utilization in the rat brain visual system. Abst Soc Neurosci 11: in press, 1985.

Dam, M., Wamsley, J.K., Rapoport, S.I., and London, E.D. Effect of oxotremorine on local glucose utilization in the rat cerebral cortex. J Neurosci 2:1072-1078, 1982.

Dow-Edwards, D., Dam, M., Peterson, J.M., Rapopoti, S.I., and London, E.D. Effect of oxotremorine on local cerebral glucose utilization in motor system regions of the rat brain. Brain Res 226:281-289, 1981.

Enna, S.J. and Snyder , S.H. Properties of gamma-aminobutyric acid (GABA) receptor binding in rat brain synaptic membrane fractions. Brain Res 100:81-97, 1975.

Gallager, D.W. Benzodiazepines: Potentiation of a GABA inhibitory response in dorsal raphe nucleus. Eur J Pharmacol 49: 133-143, 1978.

Guidotti, A., Baraldi, M., Schwartz, J.P., and Costa, E. Molecular mechanisms regulating the interactions between the benzodiazepines and GABA receptors in the central nervous system. Pharmacol Biochem Behav 10:803-807, 1979.

Guidotti, A., Gale, K., Suria, A., Toffano, G. Biochemical evidence for two classes of GABA receptors in rat brain. Brain Res 172:566-571, 1979.

Herkenham, M. Anesthetics and the habenulo-interpeduncular system: Selective sparing of metabolic activity. Brain Res 210: 461-466, 1981.

London, E.D., Connolly, R.J., Szikszay, M., and Wamsley, J.K. Distribution of cerebral metabolic effects of nicotine in the rat. Eur J Pharmacol 110:391-392, 1985 a.

London, E.D., Waller, S.B, and Wamsley, J.K. Autoradiographic localization of [^{3}H]nicotine binding sites in the rat brain. Neurosci Letts 53:179-184, 1985 b.

McCulloch, J., Savaki, H.E., McCulloch, M.C., Jehle, J., and Sokoloff, L. The distribution of alterations in energy metabolism in the rat brain produced by apomorphine. Brain Res 243:67-80, 1982 a.

McCulloch, J., Savaki, H.E., and Sokoloff, L. Distribution of effects of halopetidol on energy metabolism in the rat brain. Brain Res 243:81-90, 1982 b.

Meibach, R.C, Glick S.D., Cox, R., and Maayani, S. Localisation of phencyclidine-induced changes in brain energy metabolism. Nature 282:625-626, 1979.

Meldrum, B. and Horton, R. Effects of the bicyclic GABA agonist, THIP, on myoclonic and seizure responses in mice and baboons with reflex epilepsy. Eur J Pharmacol 61:231-237, 1980.

Nelson, S.R., Howard, R.B., Cross, R.S., and Samson, F. Ketamine-induced changes in regional glucose utilization in the rat brain. Anesthesiology 52:330-334, 1980.

Orzi, f., Dow-Edwards, D., Jehle, J., Kennedy, C., and Sokoloff, L. Comparative effects of acute and chroic administration of amphetamine on local cerebral glucose utilization in the conscious rat. J Cereb Blood Flow Metab 3:154-160, 1983.

Palacios, J.M., Kuhar, M.J., Rapoport, S.I., and London, E.D. Increases and decreases in local cerebral glucose utilization in response to GABA agonists. Eur J Pharmacol 71:333-336, 1981.

Palacios, J.M., Kuhar, M.J., Rapoport, S.I., and London, E.D. Effects of γ-aminobutyric acid agonist and antagonist drugs on local cerebral glucose utilization. J Neurosci 2:853-860, 1982.

Pradhan, S.N. Phencyclidine (PCP): Some human studies. Neurosci Biobehav Rev 8:493-501, 1984.

Quirion, R., Hammer, R.P., Herkenham M., and Pert, C.B. phencyclidine (angel dust) "opiate" receptor: Visualization by tritium-sensitive film. Proc Natl Acad Sci USA 78:5881-5885, 1981.

Sakurada, O., Kennedy, C., Jehle, J. Brown, J.D., Carbin, G.L., and Sokoloff, L. Measurement of local cerebral blood flow with iodo(^{14}C)antipyrine. Am J Physiol 234:H59-H66, 1978.

Savaki, H.E., Kadekaro, M., Jehle, J., an Sokoloff, L. α -and β -adrenoreceptor blockers have opposite effects on energy metabolism of the central auditory system. Nature 276: 521-523, 1978.

Scotti de Carolis, A., Lipparini, F., and Longo, V.G. Neuropharmacological investigations on muscimol, a psychotropic drug extracted from Amanita muscaria. Psychopharmacologia 15:186 195, 1969.

Shoulson, I., Goldblatt, D., Charlton, M., and Joynt, R.J. Huntington's disease: Treatment with muscimol, a GABA-mimetic drug, Ann Neurol 4:279-284, 1978.

Siesjö, B.K. Brain Energy Metabolism John Wiley and Sons, Chichester, 1978. 607 pp.

Smith, C.B., Davidsen, L., Diebler, G., Patlak, C., Pettigrew, K., and Sokoloff, L. A method for the determination of local rates of protein synthesis in brain. Trans Am Soc Neurochem 11:94,1980.

Sokoloff, L. Circulation and energy metabolism of the brain. In: Siegel, G.J., Albers, R.W., Katzman, R., and Agranoff, B.W., Basic Neurochemistry 2nd Edition. Boston: Little Brown and Co., 1972. pp. 338-413.

Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M.H., Patlak, C.S., Pettigrew, K.D., Sakurada, O., and Shinohara, M. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 28:897-916, 1977.

Sutherland, R.J. and Nakajima, S. Self-stimulation of the habenular complex in the rat. J Comp Physiol Psychol 95:781-791, 1981.

Tallman, J.F., Paul, S.M., Skolnick, P., and Gallager, D.W. Receptors for the age of anxiety: Pharmacology of the benzodiazepines. Science 207:274-281, 1980.

Tamminga, C.A., Crayton, J.N., and Chase, T.N. Improvement in tardive dyskinesia after muscimol therapy. Arch Gen Psychiatry 36:595-598, 1979.

Ticku, M.K. Benzodiapine-GABA receptor-ionophore complex. Current Concepts. Neurophamacol 22:1459-1470, 1983.

Unnerstall, J.R., Kuhar, M.J., Niehoff, D.L., and Palacios, J.M. Benzodiazepine receptors are coupled to a subpopulation of ϒ-aminobutyric acid (GABA) receptors: Evidence from a quantitative autoradiographic study. J Pharmacol Exp Ther 218: 797-804, 1981.

Wamsley, J.K., and Palacios, J.M. Apposition techniques of autoradiography for microscopic receptor localization. In: Barker, S.K. and McKelvy, J.F., eds. Current Methods in Cellular Neurobiology. Vol. I. New York: John Wiley and sons, 1983. pp 241-268.

Wechsler, L.R., Savaki, H.E., and Sokoloff, L. Effects of d- and 1-amphetamine on local cerebral glucose utilization in the conscious rat. J Neurochem 32:15-22, 1979.

Weinberger, J. Greenberg, J.H., Waldman, M.T.G., Sylvestro, A., and Reivich, M.: The effect of scopolamine on local glucose metabolism in rat brain. Brain Res 177:337-345, 1979.

Wise, R.A. Brain neuronal systems mediating reward processes. In: Smith, J.E. and lane, J.D., eds. The Neurobiology of Opiate Reward Processes. New York: Elsevier Biomedical Press, 1983. pp. 405-437.

Wooten, G.F., DiStefano, P., and Collins, R.C. Regional cerebral glucose utilization during morphine withdrawal in the rat. Proc Natl Acad Sci USA 79:3360-3364, 1982.

Young, M.L., Smith. D.S., Greenberg, J., Reivich, M., and Harp, J.R. Effects of sufentanil on regional cerebral glucose utilization in rats. Anesthesiology 61:564-568, 1984.

Young III, W.S. and Kuhar, M.J. Autoradiographic localisation of benzodiazepine receptors in the brains of humans and animals. Nature 280:393-394, 1979.

Zukin, S.R., Fitz-Syage, M.L., Nichtenhauser, R., and Zukin, R.S. Specific binding of [^{3}H]phencyclidine in rat central nervous tissue: Further characterization and technical considerations. Brain Res 258:277-284, 1983.

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Behavioral Pharmacology of Licit Drugs in Experimental Animals

Steven R. Goldberg, Jonathan L. Katz, and Marcus E. Risner

Nicotine and caffeine are the two drugs used most frequently by man. While the bebavioral and clinical pharmacology of other psychoactive drugs have been extensively studied at the Addiction Research Center, studies of the behavioral and clinical pharmacology of nicotine and caffeine have only been initiated on a larger scale in the last few years. The relative lack of experimental studies with these drugs is probably related to the widespread acceptance of their use and to their less obvious toxicologic consequences compared to other drugs of abuse.

The present paper describes some effects of nicotine and sane nicotine metabolites. Additionally, the effects of caffeine are described when administered alone and when administered in the presence of an adenosine analog. All of the studies involve schedule-controlled behavior maintained by food presentation in rats, dogs, or squirrel monkeys. Experimental sessions lasting about one hour were conducted daily. During the sessions subjects were placed in isolation chambers that were equipped with a response manipulandum, various stimulus lights, and a food dispenser. The subjects were trained to press the response key under a multiple schedule consisting of fixed-interval and fixed-ratio components of food presentation. During the fixed-interval components, which were signalled by a distinctive visual stimulus, the first lever- or pedal-press response that occurred after the lapse of 5 minutes produced a food pellet and ended the component. During fixed-ratio components, which were signalled by a different visual stimulus, 30 responses were required to produce food and end the component. Fixed-interval and fixed-ratio components alternated until 10 componets of each type were completed and the session ended.

Drug experiments begain after responding stabilized. All drugs were given intramuscularly (monkeys, dogs) or intraperioneally (rats) before an experimental session and drugs were given no more frequently than twice weekly with either saline injections

or no injections given on other control days. Further details of methods can be found in Risner et al. (1985) and Goldberg et. al. (1985).

EFFECTS OF NICOTINE AND ITS METABOLITES

Figure 1 shows representative performances of a monkey responding under the multiple schedule of food presentation following injection of saline, l-nicotine, or the nicotine metabolites, l-cotinine or dl-nornicotine. After saline injection, responding during fixed-interval components

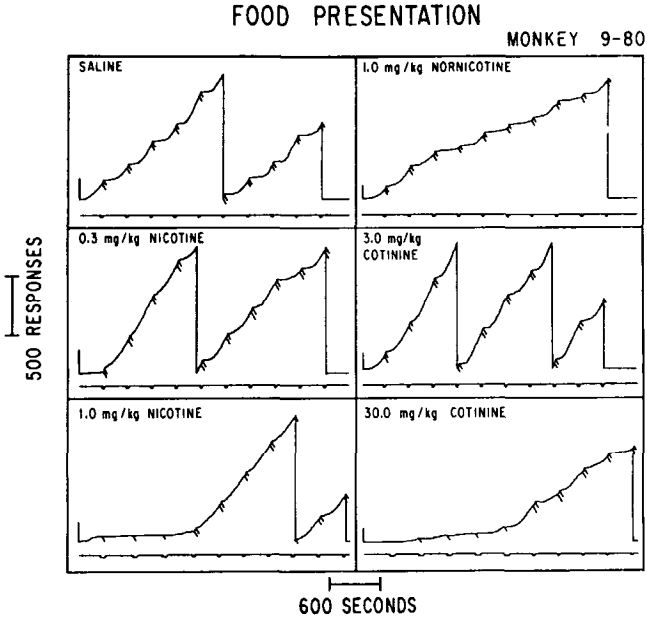

FIGURE 1 Representative cumulative-response records from monkey 9-80 showing behavior under the multiple fixed-interval five-min, fixed-ratio 30-response schedule of food presentation. Ordinates: cumulative lever-pressing responses; abscissae: time. Presentations of food are denoted by a slash on the curve. The fixed-ratio component is denoted by an offset of the horizontal line below the cumulative-response curve. The upper tracing reset to base after each 1100 responses and at the end of the experimental session. Entire sessions are shown.

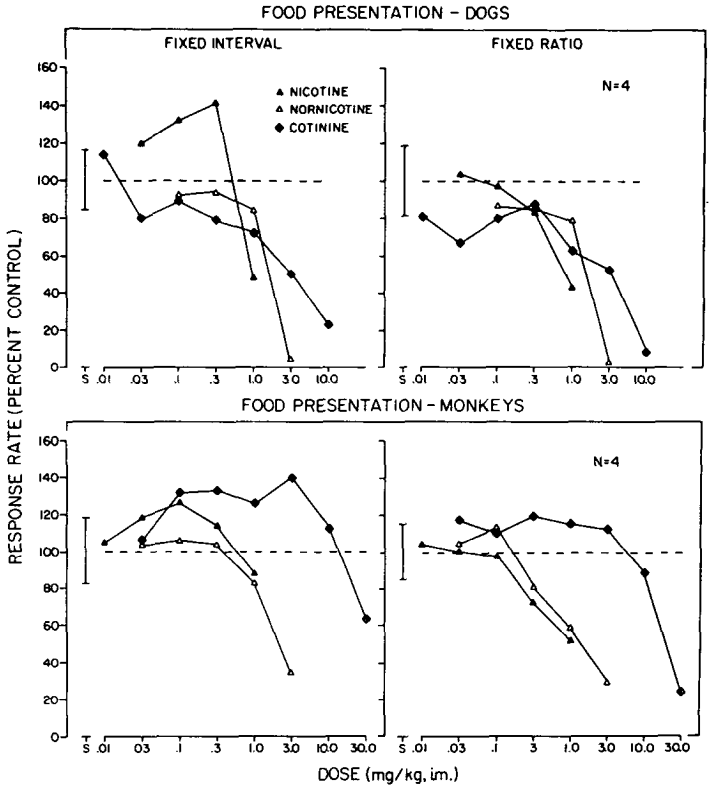

FIGURE 2 Effects of nicotine, nornicotine and cotinine on responding by beagle dogs (top panel) and squirrel monkeys (bottom panels) under the multiple fixed-interval five-min, fixed-ratio 30-response schedule of food presentation. Abscissae: dose, log scale; ordinates: overall response rate during FI components (left panels), or during FR components (right panels), expressed as a percentage of the mean saline-injection control rate. The dashed horizontal lines show the mean saline-injection control values, 100%; brackets at S represent ± S.D. Each point represents the mean of data obtained from four dogs or four monkeys.

gradually accelerated as the 5-minute interval progressed and overall rates of responding averaged 0.5 responses per second; during fixed-ratio components there was a brief pause followed by a constant high rate of responding and overall rates responding averaged 2.5 responses per second. Thus, overall rates of responding were much higher during the fixed-ratio components. Intermediate doses of both nicotine and cotinine increased fixed-interval responding, primarily by increasing response rates early in the fixed interval. Higher doses decreased both fixed-interval and fixed-ratio responding. In contrast, no dose of nornicotine increased rates of fixed-interval responding.

Effects of nicotine, cotinine and nornicotine expressed as a percentage of the control rate of responding in each component of the multiple schedule are summarized in figure 2. Each point is the mean of results from four monkeys or four dogs. Note that the effects of nicotine were the same in monkeys and dogs. Nicotine increased rates of fixed-interval responding at doses of 0.1 and 0.3 mg/kg; rates of both fixed-interval and fixed-ratio responding were decreased at a higher dose. Across the range of doses studied, nornicotine only produced dose-related decreases in both fixed-interval and fixed-ratio responding. Cotinine produced different effects in dogs and monkeys. Dogs showed only dose-related decreases in rates of responding; in monkeys, however, cotinine increased fixed-interval response rates across a much wider range of doses than nicotine. Cotinine was about 30-fold less potent than nicotine in decreasing rates of responding under the fixed-ratio schedule.

The effects of nornicotine, the N-demethylated metabolite of nicotine, were the same in the two species tested in the present experiments but were different from those of its parent compound, nicotine. In other paradigms, however, the pharmacologic profiles of nicotine and nornicotine may overlap, although nornicotine is typically less potent than nicotine. For example, nornicotine partially generalizes to the discriminative stimulus properties of nicotine, but is about 1/20th as potent as nicotine in this paradigm (Rosecrans 1979). Thus, nornicotine may have a role in the behavioral actions of nicotine. because nornicotine is also present as a naturally occurring alkaloid in tobacco plants (Piade and Hoffmann 1980), some of the behavioral and pharmacological effects of tobacco self-administration via smoking may be attributable to nornicotine.

In contrast to nicotine and nornicotine, the effects of cotinine on schedule-controlled responding were not the same In the two species tested in the present study. In the squirrel monkey but not the dog, cotinine increased rates of responding during fixed-interval components of the multiple schedule. Although cotinine is the principal metabolite of nicotine, its contribution to the effects of tobacco smoking

have typically been considered to be minimal. Cotinine is extremely weak in producing cardiovascular and respiratory effects. Furthermore, it is almost without effect in inhibiting nicotine binding (Abood et al. 1981), and has been reported not to generalize to the discriminative stimulus properties of nicotine (Rosecrans 1979). Thus, it is surprising to find cotinine producing psychomotor stimulant effects in the squirrel monkey.

EFFECTS OF CAFFEINE AND AN ADENOSINE ANALOG

Another behaviorally active, licit drug that is in widespread use is caffeine, which has effects that are similar in some respects to those of nicotine. For example, figure 3 shows an increase in rate of fixed-interval responding in a rat produced by presession injection of caffeine. Higher doses of caffeine decreased response rates under both fixed-interval and fixed-ratio schedules. Since in vitro studies have shown that caffeine has antagonist actions adenosine receptors in the central nervous system (Sattin and Rall 1970), the behavioral effects of combinations of caffeine and adenosine analogs have been studied recently. Several studies have confirmed that the behavioral effects of (-)-N^6-(phenylisopropyl)-adenosine (PIA), an adenosine analog, were antagonized by caffeine in a dose-related manner (Coffin and Carney 1983; Sirochmen and Carney 1981; Snyder et al., 1981). Results of those and previous in vitro studies have led to the suggestion that the psychomotorstimulant effects of caffeine may be due to its adenosine-antagonist actions.

In a recent study with rats as subjects (Goldberg et al. 1985). a high dose of caffeine, when administered alone, increased response rates and disrupted the temporal patterns of responding (Figure 3). When that dose was given in combination with (-)-PIA, the effects of (-)-PIA were antagonized, however, the temporal patterns of responding remained disrupted. If the changes in the patterns of responding were due to adenosine-receptor antagonist actions of caffeine, then those effects should have been diminished when the adenosine-receptor agonist was also administered. Thus, the results of that study suggested that the psychomotor stimulant effects of caffeine might involve effects not related to its antagonist actions at adenosine receptors.

A subsequent study in squirrel monkeys had related results. In that study, monkeys responded under a multiple fixed-interval, fixed-ratio schedule and caffeine increased response rates under the fixed-interval schedule at a dose of 30.0 umol/kg (Figure 4). The adenosine analog (-)-PIA produced dose-related decreases in response rates under both schedules. Caffeine was also administered with a dose of (-)-PIA that was inactive alone (0.1 umol/kg) and a dose that decreased response

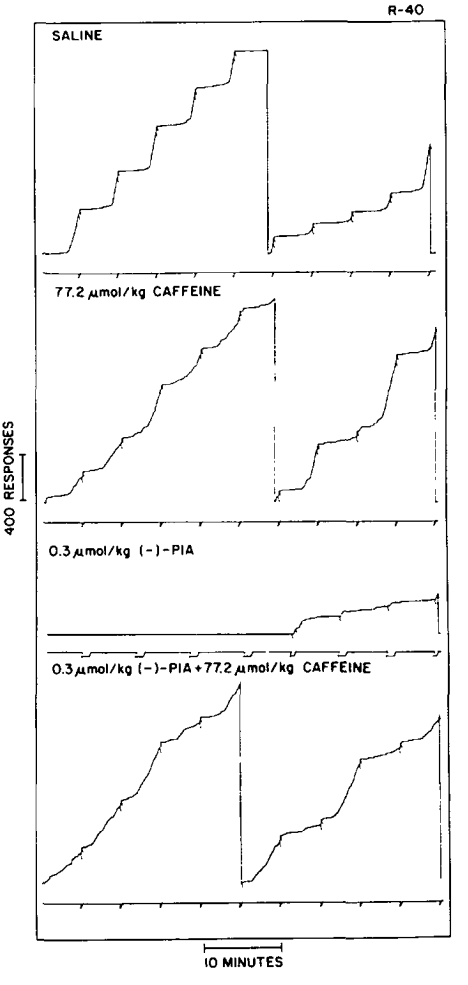

FIGURE 3 Control performances and effects of selected doses of caffeine and (-)-PIA on rat R-40 under the multiple fixed-interval five-min, fixed-ratio 30-response schedule of food presentation. Recordings as in figure 1.

rates under either schedule (0.3 umol/kg) by about 20 per cent (Figure 4). The increases in response rates produced by caffeine were unaltered by the concurrent administration of 0.1 umol/kg of (-)-PIA. The 0.3 umol/kg dose of (-)-PIA attenuated the increases in response rates produced by caffeine. However, the attenuation of the effect of caffeine was about the same as the effect of (-)-PIA alone. Caffeine

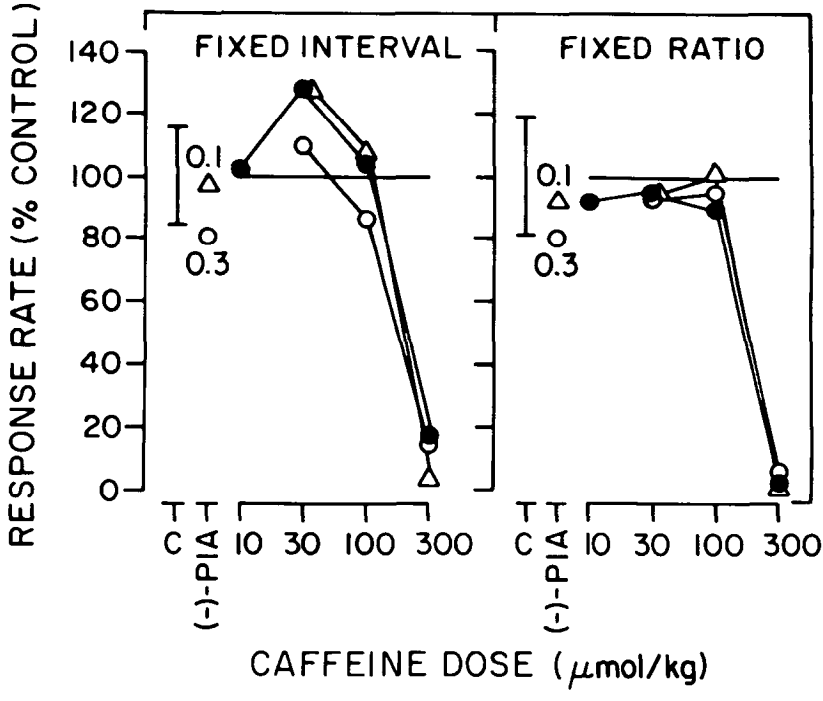

FIGURE 4 Effects of caffeine on average rates of responding of squirrel monkeys under the multiple fixed-interval five-min, fixed-ratio 30-response schedule of food presentation. Ordinates: average response rates expressed as a percentage of control response rates ; abscissae: dose of caffeine in umol/kg, log scale. Filled circles show effects of caffeine alone. Open triangles and circles show response rates after 0.1 or 0.3 umol/kg (-)-PIA, respectively, either alone (unconnected points at left) or in combination with caffeine (connected points). Vertical bars above C show ± 1 S.D. of control values.

alone increased response rates at 30.0 umol/kg to a rate of about 130 per cent of control. In combination with a dose of (-)-PIA that alone decreased response rates by 20 per cent, 30.0 ml/kg of caffeine produced a rate that was about 20 per cent less than the rate following caffeine alone. Although at some dose (-)-PIA attenuated the increases in response rate produced by caffeine, the attenuation occurred only at a dose of (-)-PIA that had effects of its own. Similarly, the decreases in response rates produced by caffeine were not appreciably altered by concurrent administration of (-)-PIA.

If the effects of response rates produced by caffeine were due to its antagonist actions at adenosine receptors, then those effects should be diminished in the presence of the adenosine agonist (-)-PIA. However, neither the increases in response rates under the fixed-interval schedule, nor the decreases in response rates under either schedule were altered by (-)-PIA, except at doses of (-)-PIA that had effects of its own. Thus, it appears that the psychomotor stimulant effects of caffeine may be due to some extent to actions apart from its adenosine-antagonist actions.

Since in the natural situation, licit drugs are often taken together, further studies will examine the effects of combinations of nicotine and caffeine. Additionally, licit drugs are often taken repeatedly and subsequent studies will examine the behavioral effects of chronic administration of these compounds. Finally, an important aspect of nicotine and caffeine is that they are widely self-administered by humans. Self-administration of nicotine has already been studied in squirrel monkeys (Goldberg et al. 1981). Subsequent studies will examine the effects of one drug on the self administration of the other. With the above experiments we hope to develop a better understanding of the behavioral pharmacology of licit drugs and the environmental conditions that contribute to persistent drug-seeking and drug-taking behavior.

REFERENCES

Abood, L.G., Reynolds, D.T., Booth, H. and Bidlack, J.M. Sites and mechanisms for nicotine's action in the brain. Neurosci Biobehav Rev 5 : 479-486, 1981.

Coffin, V.L. and Carney, J.M. Behavioral pharmacology of adenosine analogs. In: J.W. Daly, Y. Kuroda, J.W. Phillis, H. Shimizu and M. Ui, eds Physiology and Pharmacology of Adenosine. New York: Raven Press, 1983, pp

Goldberg, S. R., Prada, J.A. and Katz, J. L. Stereoselective behavioral effects of N^6-phenylisopropyl-adenosine and antagonism by caffeine. Psychopharmacology 87: 272-277, 1985.

Piade, J.J. and Hoffman, D. Chemical studies on tobacco smoke. LXVII. Quantitative determination of alkaloids in tobacco by liquid chromatography. J Liq Chromatogr 3: 1505-1515, 1980.

Risner, M.E., Goldberg, S.R., Prada, J.A. and Cone, E.J. Effects of nicotine, cocaine and sane of their metabolites on schedule-controlled responding by beagle dogs and squirrel monkeys. J Pharmacol Exp Ther 234: 113-119, 1985.

Rosecrans, J.A. Nicotine as a discriminative stimulus to behavior: Its characterization and relevance to smoking behavior. In: Cigarette Smoking as a Dependence Processs, National Institute on Drug Abuse Research Monograph 23. DHEW Pub. No (ADM) 79-800 Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1979, pp. 58-69.

Sattin, A. and Rail, T.W. The effect of adenosine and adenine nucleotides on the cyclic adenosine 3',5'-phosphate content of guinea pig cerebral cortex slices. Mol Pharmacol 6:13-23, 1970.

Sirochman, V. and Carney, J. Behavioral pharmacology of adenosine analogs. Fed Proc 40: 294, 1981.

Snyder, S.H., Katims, J.J., Annau, Z., Bruns, R.F. and Daly, J.W. Adenosine receptors and behavioral actions of methylxanthines. Proc Natl Acad Sci 78: 3260-3264, 1981.

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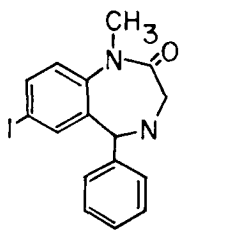
Pharmacology of Benzodiazepine Antagonists

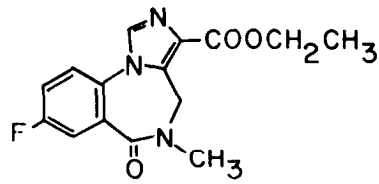
Harlan E. Shannon

The demonstration of specific receptor sites for benzodiazepines in 1977 by Squires and Braestrup as well as Mohler and Okada, and others, set the stage for the search for selective antagonists and endogenous ligands. Although the search for endogenous ligands has not yet been fruitful, the discovery and development of benzodiazepine antagonists has led to an exciting and challenging arena of pharmacologic research. The first report of an antagonist, BCCE (fig. 1), in 1980 was a direct result of the search for an endogenous ligand (Braestrup et al., 1980; Nielsen and Braestrup, 1980). Subsequently, in 1981, scientists at Hoffmann-LaRoche announced an imidazodiazepine antagonist flumazepil (Ro15-1788) which antagonized the behavioral, electrophysiological and biochemical actions of benzodiazepines and appeared to be relatively devoid of intrinsic activity (Hunkeler et al. 1981). Also in 1981, scientists at CIBA/GEIGY announced the pyrazoloquinolinone antagonists CGS 8216 and CGS 9895 (Bernard et al., 1981). These latter antagonists, however, were not without pharmacologic activity. Thus, very early studies indicated that benzodiazepine antagonists had very different pharmacologies, and that the pharmacologic story was complex and interesting.

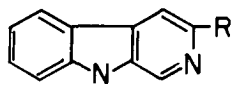
Initial studies in our laboratories with B-carbolines confirmed revious reports that BCCM was convulsant in its own right (fig. 2), and that other B-carbolines such as BCCE and 3HMC potentiated the convulsant effects of pentylenetetrazole (PTZ). Investigators in other laboratories demonstrated that these convulsant and proconvulsant effects were blocked by flumazepil and CGS 8216 (e.g., Schweri et al., 1982; Nutt et al., 1982). Similarly, CGS 8216 potentiated the convulsant effects of PTZ, and these proconvulsant effects were blocked by Ro15-1788 (File, 1983). Thus, the intriguing situation occurred of antagonists blocking antagonists even though all of these compounds appeared to be acting through a common

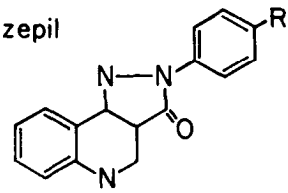


Diazepam



Flumazepil





βCCtB	t-Butyl ester	CGS 8216	H
βCCP	Propyl ester	CGS 9895	OMe
βCCE	Ethyl ester	CGS 9896	Cl
βCCM	Methyl ester		

FIGURE 1. Structures of benzodiazepine antagonists.

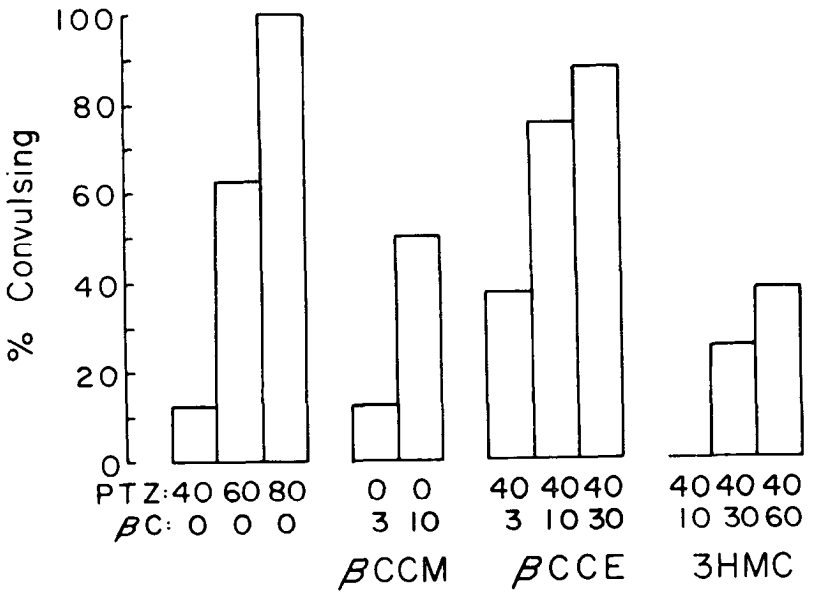


FIGURE 2. Convulsant effects of PTZ and BCCM, and pro-convulsant effects of BCCE and 3HMC in mice. Each bar represents the % of 8 mice exhibiting seizures.

receptor mechanism. These findings were interpreted by several investigators, including Polc et al. (1982), as indicating that certain B-carbolines as well as CGS 8216 were compounds with negative intrinsic activity, or inverse agonists.

B-carbolines and the pyrazoloquinolinone compounds also exhibited unusual receptor binding properties and thus were instrumental in the development of the concept that there may exist more than one type of benzodiazepine receptor. BCCE was found to have a Hill coefficient of less than 1.0, and had a higher affinity for benzodiazepine receptors in the cerebullum than in the hippocampus (Nielsen and Braestrup, 1980; Braestrup et al., 1980). These findings were reminiscent of earlier data for the triazolopyridazine C1218,872 which had a Hill coefficient of less than 1.0 and higher affinity for receptors in the cerebellum than in the hippocampus (e.g., Klepner et al., 1979). Early data suggested that CL218,872 was anticonvulsant but relatively less sedating than diazepam; and thus, it was hypothesized that the anticonvulsant and anxiolytic effects of benzodiazepines were mediated through a subpopulation of benzodiazepine receptors, termed Type I or BZ_1 and which were abundant in the cerebellum, whereas, the Sedative and muscle relaxant properties of benzodiazepines were mediated by a different subpopulation, termed Type II or BZ_2 and which were relatively more abundant in the hippocampus. Although subsequent studies demonstrated that the in vivo pharmacology of CL218,872 was qualitatively similar to diazepam (Oakley et al., 1984), the concept of BZ and BZ receptors has remained a dominant, though controversial (Polc et al., 1982; Martin et al., 1983), theme in research on benzodiazepine ligands. Evidence that other benzodiazepine receptor ligands may produce anticonvulsant activity without sedation or muscle relaxation also has been presented (e.g., Sieghart, 1983; Klockgether et al., 1985). Clarification of whether there is a single benzodiazepine receptor which exists in multiple states (Polc et al., 1982) or there are multiple benzodiazepine receptor subtypes, requires the delineation of antagonists selective for the anticonvulsant, muscle relaxant, or other effects of benzodiazepines, such as diazepam.

We have previously reported (Shannon et al., 1984) on a B-carboline which appears to be a selective antagonist of the anticonvulsant and anxiolytic but not the ataxic effects of diazepam: B-carboline-3-carboxylate-t-butyl ester (BCCtB). In mice, BCCtB neither blocked nor potentiated the convulsant effects of PTZ. However, at doses of 3 and 10 mg/kg, BCCtB produced a dose-related antagonism of the anticonvulsant effects of diazepam against PTZ (80 mg/kg). Further, BCCtB (30 mg/kg) did not antagonize the ataxic effects of diazepam in an inverted screen test in mice. The anxiolytic effects of diazepam were evaluated in rats responding under

a multiple schedule where in one component every twentieth response (FR 20) resulted in water presentation (unpunished component) and in another component every twentieth response (FR 20) resulted in both shock and water presentation (punished component). Diazepam p.o. first increased and then decreased rates in the punished component but only decreased rates in the unpunished component. BCCtB had no effect on response rates when administered alone, but antagonized the rate-increasing effects of diazepam in the punished component. BCCtB did not alter the rate-decreasing effects of diazepam in either component. Thus, BCCtB selectively antagonized the response rate-increasing effects of diazepam on punished behavior as well as the anticonvulsant effects of diazepam, but failed to antagonize the rate-decreasing and ataxic effects of diazepam. These results are consistent with the interpretation that BCCtB is a selective BZ_1 benzodiazepine receptor antagonist.

The parazoloquinolinone benzodiazepine receptor ligand CGS 9895 produced a somewhat different profile of antagonist activity in that it blocked the anticonvulsant and ataxic, but not the anxiolytic, effects of diazepam (Katzman and Shannon, 1985). Administered alone, the ED_{50} of diazepam in blocking the convulsant effects of 80 mg/kg of PTZ in mice was 0.69 mg/kg. The ED_{50} of diazepam was increased to 1.3 mg/kg at a dose of 1.0 mg/kg of CGS 9895, and to 6.1 mg/kg by a dose of 3.0 mg/kg of CGS 9895. CGS 9895 neither blocked nor potentiated the convulsant effects of PTZ. The ataxic effects of diazepam as measured on the Rotarod in rats was also antagonized very effectively by CGS 9895. Administered alone, the EC_{50} of diazepam was approximately 5.0 mg/kg p.o. In the presence of 1.0 and 3.0 mg/kg of CGS 9895, the ED_{50} for diazepam was increased to approximately 21 mg/kg and 134 mg/kg, respectively. In contrast, the response-rate increasing effects of diazepam in rats responding under the punishment schedule described above were unaltered by a dose of 3.0 mg/kg of CGS 9895. These results are consistent with the interpretation that CGS 9895 is a relatively selective BZ_2 benzodiazepine receptor antagonist.

CGS 8216, another pyrazoloquinolinone benzodiazepine receptor ligand, antagonized the anticonvulsant, ataxic and anxiolytic effects of diazepam, but had prominent effects in its own right. In mice, CGS 8216 produced a dose-related increase in the number of mice exhibiting clonic seizures after a dose of 40 mg/kg of PTZ, a dose which is nonconvulsant when administered alone (fig. 2). These effects are blocked by flumazepil (File, 1983). The anticonvulsant effects of diazepam in mice administered 8 mg/kg of PTZ were antagonized in a dose-related manner by CGS 8216. Doses of 1.0 and 3.0 mg/kg of the latter drug increased the ED_{50} of diazepam by approximately 10- and 43-fold, respectively- The ataxic effects of diazepam on the Rotarod were also antagonized by CGS 8216. Doses of 1.0 and 3.0 mg/kg

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produced shifts in the diazepam ED_{50} of approximately 13- and 206-fold, respectively. However, CGS 8216 did not produce parallel shifts in the diazepam dose-effect curve on the Rotarod, but rather appeared to produce an uncompetitive blockade. A dose of 100 mg/kg of diazepam failed to surmount the antagonism produced by 3.0 mg/kg of CGS 8216. In rats responding under the punishment schedule, CGS 8216 administered alone produced dose-related decreases in rates of responding and was approximately 10-fold more potent in decreasing rates under the punishment component as compared with the unpunished component. The rate-decreasing effects of CGS 8216 were antagonized by 30 mg/kg of Ro15-1788. When administered concomitantly with diazepam, doses of CGS 8216 as low as 0.1 and 0.3 mg/kg blocked the rate-increasing effects of diazepam, but this dose of CGS 8216 decreased rates to approximately 40% of control when administered alone. However, the rate-decreasing effects of 10 mg/kg of diazepam were not attenuated by any dose of CGS 8216.

The observations that CGS 8216 produces effects in its own right which are opposite in direction to diazepam and which are blocked by Ro15-1788 have led to the suggestion that it is an inverse agonist at benzodiazepine receptors (e.g., Polc et al., 1982). On the other hand, the interactions between CGS 8216 and diazepam might represent functional interactions or the algebraic summation of pharmacologically opposed actions. To determine between the two alternatives, theoretical dose-effect curves were constructed based on the equations presented by Ariens et al. (1964) for the interaction between two drugs at one receptor. Figure 3 presents the theoretical dose-effect curves for the interaction between an agonist with an intrinsic activity (alpha) of +1.0 and a K_a of 100, and an antagonist (drug B) with an intrinsic activity (beta) of -1.0 and a K_b of 10. When the concentration of drug 8 is 0, the agonist produces the familiar sigmoidal shaped curve. The dose-effect curve for the agonist is shifted to the right by increasing concentrations of drug B, but not in a parallel manner. As the dose of drug B is increased, the minima of the dose-effect curves for the two drugs given concomitantly decreases, asymptoting at -100%, consistent with the intrinsic activity (-1.0) of drug B. Although the theoretical curves are not precisely parallel, the curves in the presence of the antagonist becoming progressively steeper, it is doubtful that the small change in slope would be detectable experimentally. The experimental results described above for the interaction between diazepam and CGS 8216 are reasonably consistent with these theoretical dose-effect curves, supporting the hypothesis that CGS 8216 is an inverse agonist at benzodiazepine receptors.

In summary, the findings described above demonstrate that BCCE, CGS 9895 and CGS 8216 each have unique pharmacologic

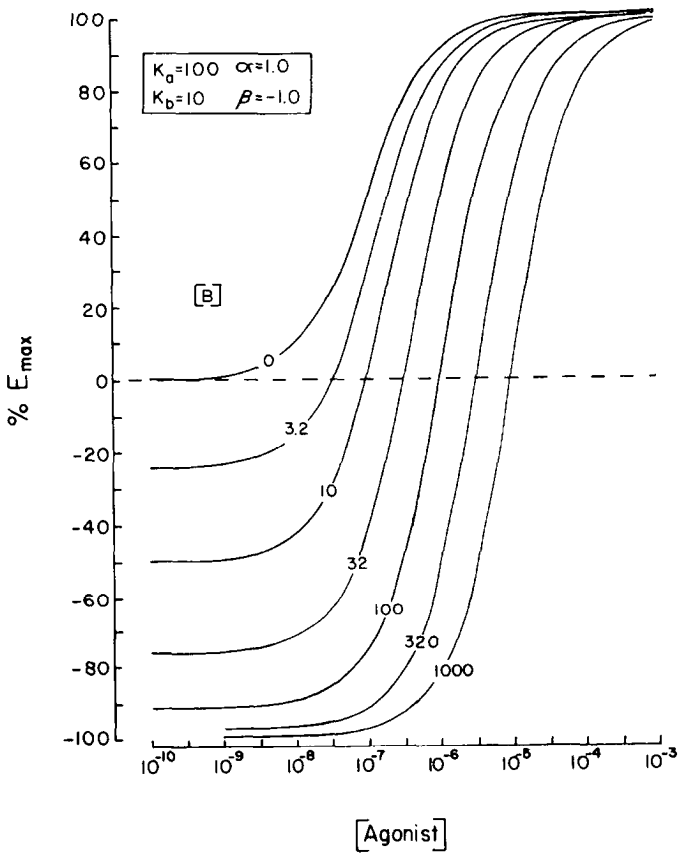

FIGURE 3. Theoretical concentration-effect curves for the interaction between an agonist with intrinsic activity of +1.0 and an inverse agonist (Drug B) with an intrinsic activity of -1.0.

properties and differ in their effectiveness in antagonizing the pharmacologic effects of diazepam (Table 1). All three benzodiazepine antagonists blocked the anticonvulsant effects

TABLE 1

Effect	BCCtB	CGS 9895	CBS 8216	Ro 15-1788
Anti-PTZ	Antagonist	Antagonist	Inv. Agonist	Antagonist
Ataxia	0	Antagonist	Antagonist	Antagonist
Punishment	Antagonist	0	Inv. Agonist	Antagonist

of diazepam as measured by the effectiveness of diazepam to block clonic seizures induced by 80 mg/kg of PTZ. The ataxic effects of diazepam as measured in an inverted screen test in mice or on the Rotarod in rats were not blocked by the B-carboline BCCtB. Moreover, the pyrazoloquinolinone CGS 9895 failed to block the anxiolytic effects of diazepam as measured by increased rates of responding under a punishment schedule in rats. In contrast, CGS 8216, like Ro15-1788, blocked all 3 effects of diazepam. However, CGS 8216, unlike Ro15-1788, appears to be an inverse agonist. These results are not inconsistent with the interpretation that there exists multiple benzodiazepine receptor subtypes. In fact, the data seem to suggest that there may exist at least three subpopulations of receptors. However, this inference is based not on selective antagonists for each of the three effects, but rather that ataxia and punishment are not blocked by unique antagonist.

Further delineation of the mechanisms of action of benzodiazepines by the use of selective antagonists should lead to a better understanding of the neurobiological substrates of anxiety and sedation and the possible role these effects might play in the etiology of drug abuse behavior.

REFERENCES

Ariens, E.J.; Simonis, A.M.; and van Rossum, J.M. Drug-receptor interaction: Interaction of one or more drugs with different receptor systems. In: Molecular Pharmacology Vol. I, ed. by E.J. Ariens, pp. 287-393. Academic Press: New York, 1964.

Bernard, P.; Berger, K.; Sobiski, R.; and Robson, R.D. CGS 8216 (2-phenylpyrazolo[4,3-c]quinolin-3(5H)-one), an orally effective benzodiazepine antagonist. The Pharmacologist 23:150, 1981.

Braestrup, C.; Nielsen, M.; and Olsen, C.E. Urinary and brain B-carboline-3-carboxylates as potent inhibitors of brain benzodiazepine receptors. Proc Natl Acad Sci U.S.A. 77:2288-2292, 1980.

File, S.E. Proconvulsant action of CGS 8216. Neurosci Lett 35:317-320, 1983.
Hunkeler, W.; Mohler, H.; Pieri, L.; Pole, P., Bonetti, E.P.; Cumin, R.; Schaffner, R.; and Haefely, W. Selective antagonists of benzodiazepines. Nature 290:514-516, 1981.
Katzman, N.J. and Shannon, H.E. Differential diazepam-antagonist effects of the benzodiazepine receptor ligand CGS 9895 in rodents. J Pharmacol Exp Ther, in press, 1985.
Klepner, C.A.; Lippa, A.S.; Benson, D.I.; Sano, M.C.; and Beer, B. Resolution of two biochemically and pharmacologically distinct benzodiazepine receptors. Pharmacol Biochem Behav 11:831-343, 1979.
Klockgether, T.; Schwarz, M.; Turski, L.; and Sontag, K.-H. ZK91296, an anticonvulsant B-carboline which lacks muscle relaxant properties. Eur J Pharmacol 110:309-315, 1985.
Martin, I.L.; Brown, C.L.; and Doble, A. Multiple benzodiazepine receptors: Structures in the brain or structures in the mind. A critical review. Life Sci 32:1925-1933, 1983.
Mohler, H. and Okada, T. Benzodiazepine receptor: Demonstration in the central nervous system. Science 198:849-851, 1977.
Nielsen, M. and Braestrup, C. Ethyl-B-carboline-3-carboxylate shows differential benzodiazepine receptor interaction. Nature 286:606-607, 1980.
Oakley, N.R.; Jones, B.J.; and Straughan, D.W. The benzodiazepine ligand CL218,872 has both anxiolytic and sedative properties in rodents. Neuropharmacology 23:797-802, 1984.
Polc, P.; Bonetti, E.P.; Schaffner, R.; and Haefely, W. A three-state model of the benzodiazepine receptor explains the interactions between the benzodiazepine antagonist Ro15-1788, benzodiazepine tranquilizers, B-carbolines, and phenobarbitone. Nauyn-Schmiedeberg's Arch Pharmacol 321:260-264, 1982.
Schweri, M.; Caine, M.; Cook, J.; Paul, S.; and Skolnick, P. Blockade of 3Ocarbomethoxy-B-carboline induced seizures by diazepam and the benzodiazepine'antagonists, Fo15-1788 and CGS 8216. Pharmacol Biochem Behav 17:457-460, 1982.
Shannon, H.E.; Guzman,F.; and Cook, J.M. B-Carboline-3-carboxy-t-butul ester: A selective BZ_1 benzodiazepine antagonist. Life Sci. 35:2227-2236, 1984.
Sieghart, W. Several new benzodiazepines selectively interact with a benzodiazepine receptor subtype. Neurosci Lett 38:73-78, 1983.
Squires, R.F. and Braestrup, C. Benzodiazepine receptors in rat brain. Nature 266:732-734, 1977.

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Human Studies of the Behavioral Pharmacological Determinants of Nicotine Dependence

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The National Institute on Drug Abuse (NIDA) initiated support of tobacco dependence research in the mid 1970's through its extramural funding mechanisms. Overviews of this research effort are summarized in prior NIDA Research Monographs (Research Monograph No.s 17, 23, 26, 37, and 48). By the late 1970's, NIDA's intramural program of research at the Addiction Research Center (ARC), under the general direction of Dr. Donald R. Jasinski, also began a systematic series of studies on the behavioral and pharmacological basis of tobacco dependence. These studies began as a collaborative effort by Dr. Goldberg, at the ARC, and Dr. Spealman, at Harvard University. Their preclinical investigations focused on the reinforcing and punishing properties of nicotine in animals (Goldberg, Spealman and Goldberg, 1981; Goldberg and Spealaman, 1982). Additional preclinical studies of tobacco dependence were being conducted at the ARC in Lexington, Kentucky under the direction of Drs. Goldberg and Risner (Risner and Goldberg, 1983). In 1980, the clinical laboratory of the ARC initiated a series of studies on tobacco dependence. The present paper will provide a brief overview of some of the progress of this clinical program of research in furthering the understanding of the behavioral and pharmacological determinants of nicotine dependence.

In brief, the studies conducted by the clinical pharmacology laboratory of the ARC confirmed that compulsive tobacco use is appropriately categorized as a form of drug dependence that is functionally equivalent to more commonly studied forms of drug dependence. Basic research strategies which had evolved primarily through earlier studies of opioids were then applied to the study of nicotine. These studies confimed that the role of nicotine in tobacco dependence is similar to the roles of morphine and cocaine in morphine dependence and cocaine dependence, respectively. Additionally, these studies provided a

rational basis for the phamacologic treatment of tobacco dependence, including substitution and blockade approaches. Most recently, studies have shown that nicotine, like other dependence producing substances, produces a variety of "therapeutic" effects which probably contribute to the strength of the dependence that often develops to tobacco.

ABUSE LIABILITY OF NICOTINE AND EQUIVALENCE TO TOBACCO SMOKE

The main purpose of these studies was to assess the equivalence of intravenous nicotine to tobacco smoke, and to determine if nicotine produced effects characteristic of those of other drugs of abuse. The methods were essentially those which have been developed at the ARC and other laboratories to quantitate the abuse liability of substances in humans (Jasinski, 1976; Jasinski, Johnson and Henningfield, 1984). In the first study, a range of doses of nicotine was givin to eight volunteers under placebo-controlled, double-blind conditions (Henningfield, Miyasato and Jasinski, 1985). The subjects were heavy cigarette smokers with histories of drug abuse. Nicotine and placebo were given in the form of research cigarettes (IH) and as intravenous injections (IV). Each of four doses (IV or IH) were presented on each test day at one hour intervals, following 9 hours of tobacco deprivation. A variety of self-reported, observer-reported, and physiologic measures were collected before, during, and after drug administration.

Similar responses to nicotine, whether given IV or IH, confirmed that nicotine was the critical determinant of some of the effects of tobacco smoke. For instance, self-reported "desire to smoke" decreased and "Liking" scores increased as a direct function of nicotine dose level. Certain quantitative differences in responses to nicotine, as a function of route of administration, may help explain why nicotine has not gained wide acceptance as a dependence producing drug. As shown in Figure 1, nicotine given via both routes of administration produced changes in mood, feelings, and observed behavior, that suggest that nicotine is a psychoactive substance. However, as shown in the figure, dose response functions were less pronounced when nicotine was given in the form of tobacco smoke. Furthermore, observable responses to nicotine were only marked at the highest doses. These findings distinguish nicotine from many other drugs of abuse in which observable responses much more closely parallel self-reported responses (e.g., Henningfield, Chait and Griffiths 1983). This same study showed that hallmark indicators of abuse liability in human studies were also produced by nicotine given by both routes of administration. Specifically, scores on the Morphine Benzadrine Group (MBG) scale of the Addiction Research Center Inventory (ARCI), as well as scores on the Liking scale of the Single Bose Questionnaire were elevated by nicotine. In addition, nicotine injections were identified as cocaine on the Single Hose Questionnaire by subjects with histories of cocaine abuse. The

temporal patterns of nicotine's subjective effects were also comparable irrespective of route of administration. Effects were observed within seconds of administration of the nicotine dose and diminished within a few minutes and were directly related in magnitude and duration to the nicotine dose. Two caveats regarding comparisons of dose effect functions across the two routes of administration were: (1) doses delivered by tobacco smoke were given during approximately five minutes of controlled smoking, whereas the injections were given in 10 seconds; (2) the indicated IH doses are the values obtained when cigarettes were machine-smoked according to the Federal Trade Commission method and may not reflect actual delivered doses of nicotine.

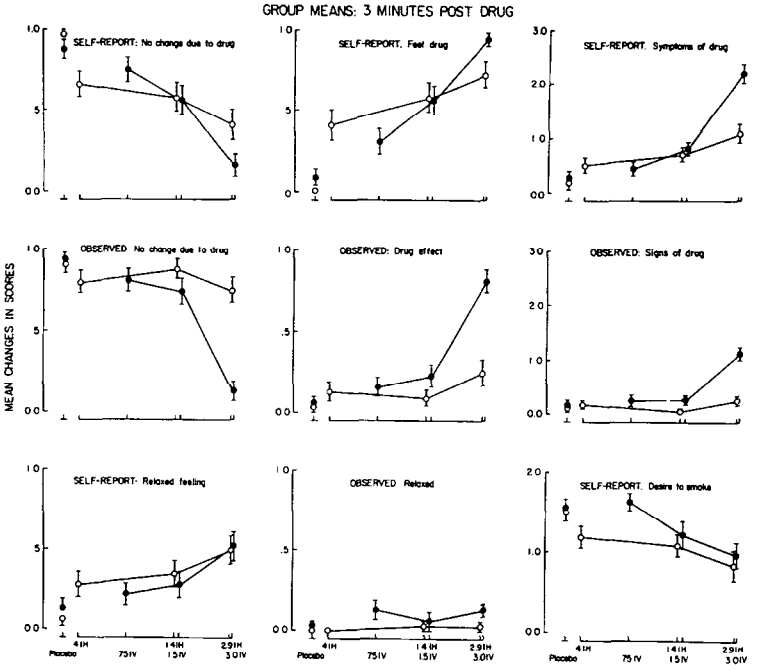

Figure 1. Summary of change-from-baseline scores on instruments for measuring self-reported and observer-reported changes. Measures were taken immmdiately before and about 3 minutes following drug administration (n=32, 8 subjects x 4 sessions). Open circles = inhaled (IH) nicotine, closed circles = intravenous (IV) nicotine. (Henningfield, Miyaseto and Jasinski, 1985)

MECAMYLAMIN EFFECTS ON RESPONSES TO NICOTINE

In a subsequent study, 4 subjects were each given 4 intravenous injections of either nicotine (.75, 1.5, 3mg) or placebo, at one hour intervals, on each of 4 test days (Henningfield, Miyasato, Johnson and Jasinski, 1984). One hour before each session, subjects were given either, the ganglionic blocker, mecamylamine HCl (2.5, 5, 10mg) or placebo. Several physiologic and subjective measures were collected. Mecamylamine produced a dose-related attenuation in nicotine-induced peripheral hypothermia (measured by finger-tip temperature), and reduced the pupilary constriction response to 3 mg of nicotine that normally occurred about 1 minute follwing injections. Self-reported nicotine dose strength estimates, normally a direct function of dose, were attenuated by mecamylamine pretreatment. These effects of mecamylamine, to partially block responses to iv nicotine, occurred at dose levels of mecamylamine that were without adverse physiologic effect.

Another study, conducted in collaboration with Dr. Rose (University of California, Los Angeles) and Ms. Sampson, evaluated mecamylamine's effects on discriminability and preference for inhaled nicotine (Rose, Sampson and Henningfield, 1985). Eight cigarette smokers were given either mecamylamine (2.5, 10, 20 mg) or placebo one hour before sessions. During tests, a smoke mixing device was used to blend the smoke from high and low nicotine yielding cigarettes (two identical cigarettes with nicotine base added to one were used during each test). This device permitted the experimenter to vary the nicotine concentration of the smoke and also permitted the subject to adjust the concentration to a preferred level. Mecamylamine reduced the overall satisfaction normally obtained by smoking the cigarettes, reduced strength and harshness ratings of the smoke, and produced dose-related increases in preferred nicotine concentration of smoke. These results are consistent with those obtained in other collaborative studies between the ARC and The Johns Hopkins University School of Medicine (e.g., Nemeth-Coslett, Heningfield, O'Keeffe and Griffiths, 1985). The results suggested that both central and peripheral nicotinic receptors determine responsestoniwtine.

EEG CORRELATES OF NICOTINE-INDUCED EUPHORIA

A study, conducted primarily by Dr. Lukas, examined the relationship between the time course of nicotine induced changes in EEG activity and self-reported euphoria (Lukas and Jasinski, 1983; Lukas and Henningfield, 1983). Subjects sat in a reclining chair with their eyes closed while EEG and physical activity were recorded. Subjects were instructed to indicate the onset and offset of drug-induced euphoria by moving a handheld lever switch (Mendelson, Lukas, Benedikt and Jones, this volume). Intravenous injections of nicotine (0.75 to 3.0mg) produced dose-related decreases in alpha EEG activity. In

addition, multiple, short episodes of euphoria appeared within 30 seconds of the injection. Effects of muscle tension and heart rate were biphasic--initial increases were followed by decreases. These EEG and behavioral effects subsided within 3-5 minutes.

EEG EFFECTS OF NICOTINE GUM ADMINISTRATION

A study conducted primarily by Dr. Pickworth, tested the effects of nicotine containing chewing gum on EEG parameters of tobacco deprived (12h), heavy cigarette smokers after a placebo or mecamylamine capsule. Scalp EEG'S were recorded from 10 subjects during an eyes-closed relaxed state (3 min) and an eyes-open, math task (3 mm). The algorithm output was the peak frequency and power estimates for each of the usual EEG frequency bands: delta, theta, alpha and beta. Recordings were taken before and after chewing gum containing 0, 4 or 8mg of nicotine at 1h intervals beginning 1h after a capsule (10mg) mecamylamine or placebo. The gum was given in a balanced randomized order.

Analysis of the nicotine content of the chewed gum indicated that about half the nicotine was extracted. Generally, the subjects did not equate the gum with the subjective qualities of cigarette smoking, nor did it reduce the desire to smoke. However, significant EEG effects were evident. The nicotine gun nicotine increased alpha frequency and alpha power; beta frequency was increased in the frontal leads only. Mecamylamine prevented some oftheniwtine-Induced EEG changes. These results suggest that gum-delivered nicotine has EEM: effects like those of smoked cigarettes. because mecamylamine attenuated only some of the nicotine's effects, several brain pathways appear to be involved in the complex actions of nicotine.

NICOTINE GUM EFFECTS ON STIMULUS PROCESSING

A study, conducted primarily by Dr. Herning, investigated the commonly described phenomenon whereby cigarette smokers report that smoking improves their ability to concentrate. The effects of nicotine on auditory information processing was evaluated by adminstration of nicotine gum in the presence or absence of mecamylamine. Eight cigarette smokers participated in a two day study. In a double-blind, counterbalanced order, a subject received 10 mg of mecamylamine or placebo after 12 hours of tobacco deprivation. After the mecamylamine or placebo administration, the subject received 0, 4, and 8mg doses of nicotine gum at hourly intervals in a counterbalanced order. The auditory oddball task was performed before and after the gum. The oddball task was comprised of 180-190 tones; approximately 20% (rare) of the tones were lower in pitch. The tone intensity was 60dB. The subject counted the rare tones in two noise conditions: 40dB and 60dB continuous white noise. In

this task, a P300 wave is generated to the rare tones. The latency of the P300 reflects the time it takes for the subject to evaluate the stimulus. The EEG was recorded from Fz, Cz, P_z, C_3 and C_4 for rare and frequent tones in each noise condition.

In general, the 6OdB background noise produced longer latency N100's and P300's than the 40dB background noise. Stimulus evaluation time increased with the high background noise. However, the 8 mg nicotine gum reduced the latency of P300 during the 60dB noise condition to that of the 40dB noise condition. Mecamylamine did not block the nicotine effect on P3OO latency. Thus, nicotine helps deprived smokers process stimuli particularly When the stimuli occur in a noisy environment.

EFFECTS OF NICOTINE DEPRIVATION AND ADMINISTRATION ON COGNITIVE PERFORMANCE

A new computerized cognitive performance assessment battery (PAB) was developed to measure subtle changes in behavioral performance that may occur as a function of pharmacologic interventions (Snyder and Henningfield, 1985). The PAB is a 5-task battery that requires about 20 minutes to complete. Tasks were selected, in part, on their sensitivity to cognitive and behavioral changes considered to be relevant to the demands of many kinds of occupational activities. Six cigarette-smoking volunteers, with moderate or no histories of substance abuse, were trained during daily sessions while they resided at the Clinical Pharmacology Research Laboratory of the Addiction Research Center. About 12 sessions were required for performance to become stable (baseline). The subjects were deprived of tobacco for 12 hours before experimental sessions. Thirty minutes before sessions, subjects were given one piece of nicotine containing gum to chew. The gum contained 0, 2 or 4mg nicotine.

The main findings were as follows: (a) 12 hour tobacco deprivation (placebo gum) significantly impaired performance (relative to baseline) as measured by both rate and accuracy measures on the PAB; (b) 2 mg of nicotine restored performance to baseline levels: (c) 4 mg of nicotine enhanced performance (relative to baseline) on some measures. This study confirmed observations by others that nicotine deprivation and administration my impair and enhance performance, respectively (Wesnes and Warburton, 1984), and extended these observations to show that cognitive performance was responsive to clinically relevant changes in nicotine abstinence and administration.

REDUCTION OF CIGARETTE SMOKING BY NICOTINE GUM ADMINISTRATION

In a study conducted in collaboration with Dr. Nemeth-Coslett, volunteer cigarette smokers, who expressed no intent to alter

their cigarette smoking behavior were studied while they resided on a clinical pharmacology research unit (Nemeth-Coslett and Henningfield, 1985). Multiple measures of cigarette smoking and nicotine effects were obtained including cigarette and puff counts, self-report measures, and cardiovascular measures. Each subject was studied during 9 daily 12-hour sessions in which nicotine gum was administered under staff observation every 2 hours (7 doses). Dose levels were, 0, 2 and 4mg nicotine. Each dose, and placebo, was given for 3 sessions in a randomized block sequence. Total number of puffs per day was significantly decreased at both the 2 and 4mg dose levels when compared to placebo, and total number of cigarettes per day was decreased at the 4mg dose level when compared to placebo. Whereas ratings of desire to smoke tended to be inversely related to nicotine dose, subject variability attenuated statistically significant effects. Drug strength ratings were directly related to dose level, but ARCI MBG scale and Single Dose Questionnaire Liking scale scores (indices of abuse liability) were not statistically altered by does. The low degree of abuse liability of the gum, compared with that produced by IV and inhaled nicotine, suggests that a challenge for treatment program is the maintenance of therapeutic compliance with adequate nicotine dose administration.

CONTROL OF OPERANT BEHAVIOR BY INTRAVENOUSLY ADMINISTERED NICOTINE

As discussed above, studies from the preclinical laboratory of the ARC, as well as other laboratories, showed that nicotine injections could serve to strengthen, weaken, or evoke operant behavior: Control of behavior has been demonstrated in several species of animals in which nicotine was found to serve as a positive reinforcer, a negative reinforcer, a punisher, and a discriminative stimulus (Henningfield and Goldberg, 1983a; Henningfield and Goldberg, 1985). A series of analogous studies was conducted using the human intravenous self-administration paradigm.

Subjects were male cigarette smokers; most bad histories of drug abuse. Three-hour sessions were run three days per week, during the six to twelve-week stay of subjects. An operant test panel with two levers and attendant stimulus lights were located near the subject's reclining chair. Before a session, the subject was catheterized in a forearm vein using a standard intravenous infusion set. Injections were delivered using automatically activated syringe pumps. Drug dose volume was lml and injection duration was 9.2 sec. Under concurrent schedules, two pumps were available to give drug and saline injections. To ensure that all drugs delivered reached the vein immediately following the operation of one of these pumps, a third pump delivred 0.5 ml of saline over 4.8 seconds. Cigarette smoking was not pemitted for 1 hour prior to or during sessions.

Self-Administration of Nicotine. Six subjects were studied under a simple schedule of nicotine or saline availability whereby ten-responses on one lever produced an injection of nicotine or saline (FR 10); responding on the other lever (activity lever) had no programmed consequence (Henningfield, Miyasato and Jasinski, 1983). Subjects self-administered both nicotine and saline; however, nicotine injections occurred in regular patterns whereas saline injections occurred with wide variability in pattern and frequency both within and across subjects. Patterns of nicotine self-administration were similar to those of humans smoking cigarettes and to animals self-administering psychomotor stimulants; i.e., monotonic patterns with fairly regular spacing within sessions. Nicotine produced dose-related increases in scores on a drug liking scale, and was identified as cocaine in subjects with histories of cocaine abuse. Nicotine also produced noxious effects including nausea, feelings of fear, coughing, and pain at the injection site. These effects occurred regardless of whether nicotine appeared to be maintaining or suppressing behavior.

Mecamylamine effects on nicotine self-administration. The effects of mecamylamine treatment on nicotine self-administration by human subjects was evaluated in a preliminary fashion by giving one subject either 10 mg of mecamylamine or placebo one hour before sessions (Henningfield and Goldberg, 1983b). Nicotine and saline were concurrently available under fixed ratio 10 schedules, and the nicotine-delivering lever was alternated each day. During each of the four consecutive sessions following mecamylamine pretreatments, number of saline injections equalled number of nicotine injections (mean=4.3, range=4-5, for both nicotine and saline), and scores on both the positive and negative visual line analogue scales were zero (neutral). When mecamylamine was replaced with placebo for two sessions, number of nicotine injections increased, exceeding number of saline injections (nicotine, mean=5.0; saline, mean = 3.5). Both negatix and positive visual line analogue scale scores increased to the levels at which they had been at before mecamylamine was given.

Concurrent saline versus multiple doses of nicotine in human volunteers and squirrel monkeys. A subsequent study examined the effects of systematic, within-subject, manipulations of nicotine dose in human and squirrel monkey subjects in which when ten lever presses were required to produce each intravenous injection of nicotine or saline (Goldberg and Henningfield, 1985). With the human subjects, nicotine and saline were presented concurrently, within sessions; with the animal subjects, saline and nicotine were presented sequentially, across sessions. A one-minute timeout followed each injection, and each session lasted 100 minutes (monkeys) or 180 minutes (humans). The results were similar in both species. All subjects self-administered both nicotine and saline. Number of nicotine injections exceeded number of saline injections in three of the four humans and three of the four monkeys tested,

indicating that nicotine was sending as a positive reinforcer for these subjects. With the human subjects, as injection dose increased from 0.75 to 1.5 mg, there was little change in number of injections taken per session. However, when dose was increased to 3.0mg, number of injections per session decreased. This is interesting since studies of the effects of nicotine field in cigarettes on cigarette smoking behavior have shown little effect on rate of cigarette consumption except when nicotine yield of the cigarettes exdeeded 2mg per cigarette. Nicotine self-administration rates were also inversely related to dose for the squirrel monkeys.

Avoidance of programmed nicotine injections. In subsequent studies, subjects who did not self-administer nicotine during initial sessions were tested under a concurrent schedule of nicotine avoidance and nicotine self-administration Henningfield and Goldberg, 1983b). Injections were scheduled to occur at predetermined intervals (30 min for 2 subjects and 15 min for 1 subject). Pressing the left lever ten times before an injection was programmed to occur, turned off the left lever light and avoided the next injection. Pressing the right lever ten times produced an injection. Thus, it was possible for a subject to avoid programmed injections of nicotine, to self-administer nicotine, or any combination thereof. A single injection of the dose to be studied was given to the subject 15 minutes before the start of a session.

In one subject, when 1.5 mg per injection of nicotine was given before sessions and programmed to be given at 15 minute intervals during the 3 hour sessions, 11 of the 12 programmed nicotine injections were consistently avoided by pressing on the left lever. Responding on the right lever, which would have produced nicotine injections, never occurred. When saline was substituted for nicotine, lever pressing declined until the third day when 11 programmed injections occurred. When nicotine was reinstated on the following day, responding increased and all 12 programmed injections were avoided. Scores on the negative effect visual line analogue scale corresponded with the lever-pressing behavior of the subject: scores were higher in the presence of nicotine and declined to zero when saline was substituted for nicotine.

Two additional subjects were presented with a range of doses, each given four times in a randomized block sequence. Doses were programmed to occur at 30 minute intervals. Rates of avoidance responding were directly related to nicotine dose level. Neither subject completed ths ten-responses on the alternate lever required to self-administer a nicotine or saline injection. Also, as with the previous subject, scores on the negative visual line analogue scale were also directly related to nicotine dose.

FUTURE DIRECTIONS AND CONCLUSIONS

These studies, completed and ongoing, have furthered the understanding of the behavioral and pharmacological determinants of tobacco dependence. It must also be noted that many of cur observations were not fundamentally new but were hopefully useful systematic extentions of previously reported observations (see reviews by Russell, 1976; Gritz, 1980, and Henningfeld, 1984). We are also hopeful that some of the strategies employed will be of use in the investigations of the behavioral pharmacology of drugs other than nicotine. For instance, the merging of self-administration techniques with self-report measures (a continuation of pioneering work by Fischman et al., and by Johanson et al. at Chicago), are helping to assess the complex relationship between the behavior of compulsive drug taking and the subjective effects produced by drugs. Similarly, the comparative animal-human studies are helping to better assess biologically common aspects of drug dependence.

This overview also serves as a summary of a research program that has largely achieved its initial goals, as originally proposed by Dr. Jasinski in the late 1970s; namely, to apply the opioid model of drug dependence in investigations of nicotine's role in tobacco dependence, and to provide a rational basis for the pharmacologic treatment of tobacco dependence, also based upon the opioid model (Jasinski, internal ARC memoranda). Studies conducted by ARC staff, as well as in collaboration with others such as Drs. Griffiths, Stitzer and Bigelow at Johns Hopkins, Dr. Kozlowski at the Addiction Research Foundation, Dr. Rose (Los Angeles), and Drs. Benowitz and Hall (San Francisco), have confirmed that many of tha fundamental behavioral and phamacologic determinants of dependence to known substances of abuse (e.g., opioids), also characterize nicotine dependence; for instance, (a) the finding that nicotine is discriminated from placebo in a dose-related manner and that such discriminations can be attentuated by pretreatment with an antagonist; (b) that the interoceptive effects of nicotine share commonalities with other known drugs of abuse (most notably, psychomotor stimulants); (c) nicotine can serve as both a positive reinforcer and an aversive stimulus (as does cocaine and other drugs) and thereby can either strengthen or weaken operant behavior according to the conditions of its presentation; (d) the finding that rates of tobacco and nicotine self-administration are related to nicotine dose per delivery and that these rates can be modified by pretreatment with an agonist or antagonist; (e) most recently, we have begun to quantitate the cognitive and electrophysiologic effects of tobacco abstinence and have confirmed that many of these effects may be reversed by nicotine administration; (f) and finally, exploratory treatment-related studies have confirmed that strategies for the treatment of tobacco dependence may profitably gain from earlier findings in the treatment of other forms of drug dependence; namely, that pharmacologic based treatments utilizing agonists and antagonists are rationally based.

REFERENCES

Goldberg, S.R., and Henningfield, J.E. Intravenous nicotine self-administration by squirrel monkeys and human volunteers: Manuscript in Preparation.

Goldberg, S.R., Spealman, R.D., and Goldberg, D.M. Persistent high-rate behavior maintained by intravenous self-administration of nicotine: Science, 214: 573-575, 1981.

Gritz, E.R. Smoking behavior and tobacco abuse. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Greenwich, CT: Jai Press, 1980, pp. 91-158.

Henningfield, J.E. and Goldberg, S.R. Stimulus properties of nicotine in animals and human volunteers: A review. In: Seiden, L.S. and Balster, R.L. eds. Behavioral Pharmacology: The Current status. New York: Alan R. Liss, 1984, pp. 433-449

Henningfield, J.E., Miyasato, K. and Jasinski, D.R. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp There, 234: 1-12, 1985.

Henningfield, J.E.; Miyasato, K.; Johnson, R.E. and Jasinski, D.R. Rapid physiologic effects of nicotine in humans and selective blockade of behavioral effects by mecamylamine. In: Harris, L.S., ed, Problems of Drug Dependence 1982, National Institute on Drug Abuse Research Monograph, No. 43 Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1983, pp. 259-265.

Henningfield, J.E.; Miyasato, K.; and Jasinski, D.R. Cigarette smokers self-administer intravenous nicotine. Pharm Biochem Behav, 19: 887-890, 1983.

Henningfield, J.E., and Goldberg, S.R. Nicotine as a reinforcer in human subjects and laboratory animals. Pharm Biochem Behav, 19: 989-992, 1983a.

Henningfield, J.E., and Goldberg, S.R. Control of behavior by intravenous nicotine injections in human subjects. Pharm Biochem Behav, 19: 1021-1026, 1983b.

Jasinski, D.R.; Johnson, R.E.; and Henningfield, J.E. Abuse liability assessment in human subjects. Trends Pharmacol Sci, 5: 196-200, 1984.

Lukas, S.E. and Jasinski, D.R. EEG power spectral effects of intravenous nicotine administration in humans. Fed Proc, 42:-1018, 1983.

Lukas, S.E. and Henningfield, J.E. EEG correlates of physiological and behavioral effects of intravenous nicotine in humans. Presented to the II World Conference on Clinical Pharmacology and Therapeutics, Washington, D.C., 1983.

Lukas, S.E., Mendelson, J.H., Benedikt, R.A. and Jones, B. EEG, physiologic and behavioral effects of ethanol administration, this volume.

Naneth-Coslett, R. and Henningfield, J.E. Effects of nicotine chewing gum on cigarette smoking and subjective and physiologic effect. Submitted for publication to Clin Pharm Ther, 1985.

Nemeth-Coslett, R., Henningfield, J.E., O'Keeffe, M.K. and Griffiths, R.R. Effects of mecamylamine on cigarette smoking and subjective ratings. Psychopharmacology, in press, 1985.

Snyder, F.R. and Henningfield, J.E. Cognitive effects of nicotine deprivation/administration. Paper presented at the annual meeting of the Behavioral Pharmacology Society, Wilmington, DE, 1985.

Spealman, R. D., and Goldberg, S.R. Maintenance of schedule-controlled behavior by intravenous injections nicotine in squirrel monkeys. J Pharmacol Exp Ther, 223: 402-408, 1982.

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Naltrexone Hydrochloride (Trexan): A Review of Serum Transaminase Elevations at High Dosage

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INTRODUCTION:

This paper reviews information about elevations of serum transaminase values derived from studies employing higher dosages of naltrexone (Trexan) than recommended for addiction. It is hoped this information will clarify questions which have been raised about the safe use of this drug in treating opioid addicts.

Naltrexone was approved by the Food and Drug Administration in November of 1984 as a pharmacologic adjunct to maintain the opioid-free state in detoxified formerly opioid-dependent individuals. The evidence that it is safe for this indication was based on experience in over 2,000 individuals who received at least one dose of the drug during eight years of clinical evaluations. This evidence is reassuring in spite of some missing data points resulting from high patient dropout rates, and minor abnormalities typically seen in a patient population of addicts. None of the adverse signs, symptoms or abnormal laboratory findings, including transaminase elevations which occurred with detoxified opioid addicts, displayed a sequence or pattern which implicated naltrexone as the cause.

After the New Drug Application was filed in December 1982, Du Pont evaluated naltrexone for several indications other than addiction. Conditions were selected for study in which it was postulated elevated levels of endogenous opioids were involved in the pathogenesis, and opioid blockade by naltrexone might have a beneficial effect. Du Pont sponsored studies to determine if naltrexone helps obese individuals lose weight and it provided supplies of naltrexone to an independent investigator who evaluated whether naltrexone improves mental function in patients with senile dementia. As a result of three studies of obesity and this study of senile dementia, a pattern of abnormal serum transaminase values emerged when naltrexone was used in 300 mg daily dosages. This is six times the recommended daily dosage for opioid addiction. Because of these

findings, these clinical trials were terminated. To minimize the possibility of hepatic injury in patients subsequently using naltrexone. the package insert warns of the potential for hepatotoxicity, contraindicates the use of naltrexone in patients with acute hepatitis or liver failure, and makes recommendations for the selection and subsequent monitoring of patients to receive naltrexone.

STUDY DESIGNS, SUBJECTS AND METHODS

The three trials of naltrexone in obese subjects were eight-week, parallel, randomized, double-blind, placebo controlled studies of the effects of naltrexone on body weight in outpatient males or nonfertile females. Participants weighed 30 to 100% above ideal body weight and were 18 to 63 years of age. Studies were conducted in a classical dose tolerance sequence. The first evaluated dosages of naltrexone of 50 and 100 mg per day; the next 200 mg per day; and the last 300 mg per day. Subjects were evaluated at two-week intervals. Safety assessment, at a minimum in each study, included a series of laboratory tests performed at baseline and at the end of the study. These included a complete blood count with differential, blood chemistry, urinalysis and electrocardiogram.

The six-week open dementia study measured effects of naltrexone on mental function. Ten males and females aged 67 to 73 years with the diagnosis of primary degenerative dementia participated. Subjects received naltrexone 50 mg per day during the first two weeks, 150 mg per day during the next two weeks, and 300 mg per day during the final two weeks. Safety assessment included performance at the beginning of the study and at two-week intervals of a complete blood count, blood chemistry, and an electrocardiogram. SGOT was the only liver function test obtained routinely.

For the purpose of this analysis, which follows one prepared by the FDA for the Summary Basis of Approval,(1) elevations of serum transaminase were considered significant if the following criteria were satisfied:

1. SGPT activity during treatment exceeded 100 units per liter. Levels of SGPT generally were elevated more than levels of SGOT. Where SGPT exceeded 100 units, SGOT was also elevated, however, in three subjects it was less than twice the upper normal limit.

2. A subject had essentially normal liver function tests at baselne. Subjects with trivial baseline elevations, that is five to ten units above the upper limit of normal, were included in the analysis but those with substantial SGOT or SGPT elevations at baseline were not. One subject was excluded on this basis. His SGPT was three times upper normal at baseline, rose to four times that limit at the end of the study and remained elevated near baseline levels eight months later.

RESULTS (OBESITY STUDIES)

Table 1 displays data on subjects with both baseline and treatment laboratory values from three obesity studies. The distribution of subjects by the dosage of naltrexone taken daily and the percentage, of those at risk at each dosage who developed transaminase elevations is provided. Statistical significance is achieved only between the placebo and 300 mg dosage groups.

TABLE 1
Obesity Studies

Subjects with clinically significant elevations of transaminase values

Medication	Subjects Affected/Exposed	P-Value*
Naltrexone (mg/day)	8/85 (9%)	-
50	0/17 (0%)	NS
100	1/20 (5%)	MS
200	2/24 (8%)	NS
300	5/24 (21%)	.01
Placebo	1/65 (2%)	

*Compared with placebo group by two-tailed fisher exact test.
NS = Not significant

Figure 1 describes laboratory results of a male age 50 who took naltrexone 300 mg a day. His peak SGPT value is the highest in the obesity studies. The lines at the bottom of the graph represent the upper limits of normal values; 36 units per liter for SGOT and 26 units per liter for SGPT. The highest value of SGPT. 532 units, occurred at Day 33 of the study after which naltrexone was discontinued. This subject was typical in that with discontinuation of naltrexone, transaminase values returned rapidly to or near normal values. He did experience mild nausea at the time of these elevations. Five other subjects with transaminase elevations reported no symptoms. The remaining two experienced some symptoms, including mild abdominal cramps, nausea, myalgia or fatigue some time during the administration of naltrexone. Some of these symptoms may have resulted from intercurrent viral infections.

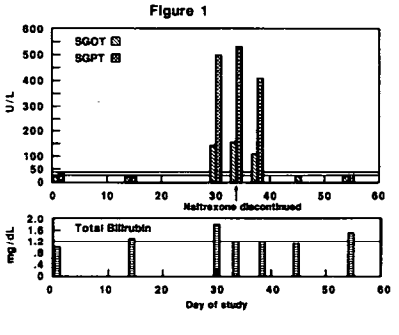


Figure 1

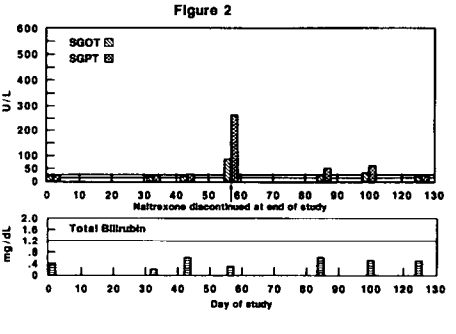


Figure 2

As one of two subjects with any elevation of serum bilirubin, this subject is unusual. His peak total bilirubin was 1.8 mg per deciliter; it was 1.3 mg per deciliter for the other subject. (Upper limit of normal = 1.2 mg/dl.) Alkaline phosphotase (not shown) was not elevated in any subjects in the obesity studies.

Figure 2 represents a more typical case. This subject was a male age 35 who took 300 mg of naltrexone per day for the entire 57 days of the study before routine laboratory values showed elevations of transaminase levels. Bilirubin remained normal. This subject reported no symptoms.

RESULTS (DEMENTIA STUDY)

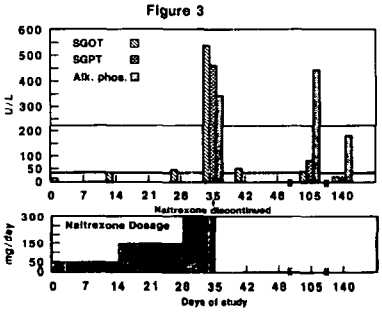
Table 2 shows data from the dementia study. Since only SGOT was monitored routinely, the criteria applied to the obesity trials are not applicable. Ten subjects received naltrexone at the 50 and 150 mg per day dosages. Nine continued to the 300 mg per day dosage phase. The tenth discontinued naltrexone after the fourth week when it was decided to stop the study before exposing this subject to the 300 mg dosage.

TABLE 2
Dementia Study

Subjects with clinically significant transaminase elevations

Study Period	Naltrexone Dosage (mg/day)	Subjects Affected/Exposed
Weeks 1 & 2	50	0/10
Weeks 3 & 4	150	0/10
Weeks 5 & 6	300	3/9

Figure 3



Three subjects who took 300 mg per day of naltrexone developed clinically significant elevations of SGOT. In two, elevations were first detected at the sixth week, when for the subject with the greater elevatlon, SGOT was 804 units. Laboratory values for the third subject are shown illustrated in figure 3. Slight elevations of SGOT at the second and fourth weeks lead to earlier retesting at the fifth week when a level of 540 units was detected. Values for SGPT, bilirubin and alkaline phosphotase were also obtained at this visit. SGPT was 462 units, total billrubin (not shown) was normal, and alkaline phosphotase was 345 units per liter (upper limit of normal = 220 u/1). One week later, after discontinuation of naltrexone, SGOT was 51 units per liter. Other values were not obtained at that visit. Subsequently, all values returned to within normal

limits. Follow-up enzyme determinations, not available in the other two subjects until eight and ten weeks after the peak values, were normal.

As in the obesity studies, symptoms were not typically associated with elevations of transaminase levels. Only one subject was thought to have had symptoms, which consisted of mild intermittent abdominal cramps.

CONSULTANT EVALUATIONS

In both the obesity and dementia studies, two experienced gastroenterologists served as independent consultants in the evaluation of subjects with elevated transaminase values. They and the investigators looked for explanations other than naltrexone for these findings. In the obesity studies, with the exception of infrequently used aspirin or acetaminophen. and in one subject a vitamin supplement, there was no history of use of concomitant medications. Two subjects during the dementia study took a diuretic (Dyazide) containing triamterene and hydrochlorothiazide. There was no history of industrial exposure to hepatotoxins nor with possibly one exception, more than social use of alcohol. Serology for hepatitis B surface antigen (five subjects) and mononucleosis (four subjects) was nonreactive. No evidence for hypersensitivity (rash, fever or eosinophilia) existed. Weight changes of subjects with elevated values of transamoinase in the obesity studies ranged from a gain of 0.7 kg to a loss of 12.7 kg. (Mean loss = 5.1 kg). This was not substantially different from subjects without elevated transaminase values.

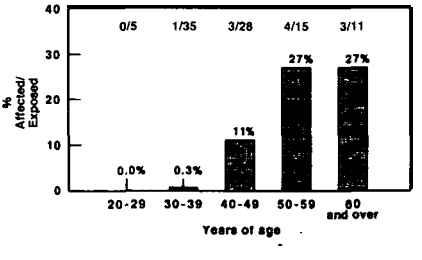
DISCUSSION

Figure 4 shows for obesity and dementia studies combined, ages of subjects who received naltrexone and those who developed elevations of transaminase values. Of subjects exposed to naltrexone who developed elevations of transaminase levels, only one was under age 40. This was a 35 year-old subject who took the 300 mg dosage of naltrexone for 57 days before this abnormality was detected.

Figure 4

Combined Obesity and Dematia Studies

Age distribution of those who recieved naltrexone and those who developed elevations of trasemineso



Chi-Square analysis across five age groups was not statistically significant. When subjects 20 to 39 years of age were compared to those 40 years or over, statistical significance was detected. Table 3 shows that in subjects 40 years or over who took the 300 mg dosage of naltrexone, the incidence of transamlnase elevations was 39%. In this same population, if the dosage of naltrexone is limited to 200 mg, the incidence of transaminase elevations falls to 8%. Below age 40, if the daily dosage of naltrexone is again limited to 200 mg, no elevations of transaminase values occurred.

TABLE 3

Combined Obesity and Dementia Studies

Relationship of elevated transaminase values to age and naltrexone dosage

Dosage (mg/day)	Age (years) 20-39	Age (years) 40 and over
50-200	0/25 (0%)	3/36 (8%)
300	1/15 (7%)	7/18 (39%)

Since in the 1976 NIDA study[2] of 1,005 addicts, 95% of participants were 40 years of age or younger and most were younger than 30 years, this relationship seems important for the safe use of naltrexone in detoxified opioid addicts. This population is both younger and will receive a lower dosage of naltrexone than the subjects in these studies who developed abnormal transaminase values.

SUMMARY

- In summary, evidence is presented associating typically asymptomatic and reverslble elevations of serum transaminase values with high daily dosages of naltrexone.
- Statistical significance was found only between placebo and the 300 mg dosage.
- Subjects aged 40 years and over were significantly more likely to develop this finding than younger subjects.
- All subjects with significant elevations of transamlnase values in these studies took daily naltrexone dosages higher than recommended for opioid addiction.
- The dally dosage of naltrexone recommended for oploid addiction did not cause abnormalities of serum transamlnase values in these studies.

REFERENCES

[1]Bradford, H.A., Kaim, S.C. FINAL REPORT: National Institute on Drug Abuse Studies Evaluating the Safety of the Narcotic Antagonist Naltrexone. BRI-NIDA-T/55-5/77. May 26, 1977.

[2]FDA "Summary Basis of Approval for Du Pont TREXAN"

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Naltrexone (Trexan): A Review of Hepatotoxicity Issues

Karl G. Verebey and S. Joseph Mulé

INTRODUCTION

Naltrexone (NT) is a narcotic antagonist recently released by the FDA as a new drug for the treatment of ex-opiate addicts. The package insert carries a "black box" warning of possible hepatotoxicity with NT therapy. The data supporting cautious use of NT comes mainly from two types of studies, one involving obese subjects and the other Alzheimers patients. In both of these groups at dose levels of 300 mg/day some liver function tests, mainly SGOT and/or SGPT, were elevated to abnormal levels (for details see the report of Pfohl (et al. in these proceedings). Based on this data the issue of hepatotoxicity of NT was widely publicized. Opposite views were expressed by clinicians who treated ex-opiate addicts with NT over 10 years (1) and did not observe hepatotoxicity. In fact, patients with abnormal enzyme (SGOT) levels when treated with NT did not deteriorate (2). Results from a study using up to 800 mg NT daily indicated that NT was not toxic even at high doses. Unfortunately, liver function tests were not specifically performed on this population (3).

The purpose of this review is to investigate and elucidate this dicotomy of opinions based on the scientific evidence from published literature. The following issues will be examined: (a) human and animal studies, which describe hepatic enzyme elevations caused by the opiate class of drugs; (b) The specificity of hepatic enzyme changes as a test identifying liver damage; (c) identification of other drugs which interfere with liver function tests; (d) review articles which describe the effects of opiate antagonists on the plasma level of the liver enzymes, and lastly (e) a mechanism which may be responsible for the observed NT effects on the hepatic enzymes as observed in the obese and Alzheimer studies.

OPIATE EFFECT ON HEPATIC ENZYMES - The literature describes fully the potential for opiate agonists to raise hepatic enzymes to abnormal levels in plasma. Both human studies (4 through 10) and

animal experiments (11 through 19) confirm this observation. Many questions are raised as to the meaning of elevated enzyme levels. Does it represent hepatocellular damage? Is the effect transient or does tolerance develop to hepatic enzyme elevations, just as tolerance develops to many other effects of opiates? The observation in an opiate addict is especially important. Are all the abnormal liver function test results related to previously acquired hepatitis? (8,9,20 through 26) or do some of the opiates have potentially hepatotoxic effects (12-17, 27, 28) or does concomitant alcohol use play a role in hepatic disease (29,30)?

Larsen and Schmidt (5) as early as 1967 described a diagnostic test to help determine whether or not an operation was necessary in postcholecystectomy syndrome. They called it the "Morphine Test." It involved the injection of 15mg morphine followed by determination of SGPT and LDH, 3hr, 6hr, and 24hr after morphine. A rise in serum enzymes as high as 30 times above control values was found with a peak at 6hr. In one case, a patient pre-operatively had a 15-fold increase in SGPT in responses to a morphine injection. In the same patient after choledochoduodenostomy the morphine test was negative. This finding indicated to the investigators that the opiate-related enzyme elevations are due to the stimulation of the bile duct system rather than to direct hepatocellular damage. Since not all patients had hepatic enzyme elevations after morphine, the phenomenon may be an individual characteristic of the patient's bile duct system, healthy or diseased. Apparently, if bile flow is not seriously obstructed, no changes in SGOT or SGPT levels are seen after morphine injections.

Faulk and Fleisher (4) studied the effect of codeine on patients with biliary dyskinesia. Maximal enzyme elevations were 5 to 10 times the control value of SGOT. In one patient the value was 85 times above control. An *in vitro* study of codeine on the enzyme test was negative. These authors as well as Larsen and Schmidt (5) considered the possibility that transaminase elevations reflected acute hepatocellular damage, which was the usual interpretation for abnormal SGOT and SGPT tests. Yet they felt that it was unlikely that high levels of transaminase seen in some patients after codeine were the results of hepatocyte necrosis. The patients were asymptomatic 4hr after codeine at the highest SGOT levels and jaundice was not evident clinically in any of the patients. Thus, the question was raised, is an increase in SGOT levels indicative of extensive hepatocellular necrosis? These investigators felt that opiate-related duodenal spasms and a concomitant rise in biliary tract pressure result in enzymes leading out of the hepatocytes into the general circulation without serious liver damage. These clinical reports raise two important questions: a) In the absence of physical signs, how specific are the transaminase elevations in the diagnosis of hepatotoxicity from drugs? and b) are there examples of other drugs or chemicals known to raise these enzyme levels in plasma without apparent physical liver damage?

DRUG INTERFERENCES WITH TRANSAMINASES

Drug interference with blood chemistry determinations is a well-known phenomenon (6,7,31). Drugs by various mechanisms produce changes in the body which may interfere with clinical laboratory tests. These include direct interference with the test, diet and other laboratory artifacts (6). Although liver enzyme elevations in plasma are routinely used to assess liver damage, these enzymes are not, by themselves, reliable indicators of liver function (32). Elevation may reflect only increased permeability to the hepatocyte plasma membranes, enzyme induction or reversible acute hepatocellular damage (31). Certain drugs may cause elevated enzyme levels without concomitant liver injury and other drugs may interfere with the determination of plasma enzyme measurement, while others may, in fact, cause injury to hepatocytes (7).

Aspirin, a non-prescription drug, has been reported to elevate both SGOT and SGPT to abnormal levels (33,34). *In vitro* studies ruled out direct interference with the test while another report indicates that the *in vitro* effect of salicylates on transaminases is inhibitory rather stimulatory (33). In these cases not all patients had elevated enzymes after salicylates and the elevated enzyme levels returned to normal after therapy was discontinued. The mechanism of enzyme elevations was not identified (33,34).

There is considerable evidence that Vitamin B_6 or pyridoxine derivatives serve as co-enzymes for transamition reaction (35,35) and thus cause increased enzyme activity in plasma both *in vivo* and *in vitro*, when present in increased quantities. Liver enzyme elevations in subjects taking Vitamin B_6 do not cause hepatocellular damage. The interference in this case is at the test level.

A "false elevation" of SGOT levels was reported after the administration of erythromycin (35). The interference by erythromycin was traced to the calorimetric assay procedure using dinitrophenylhydrazine. When other analytical test procedures were used, they were not affected by erythromycin. The authors suggest that inquiry should be made into the method by which SGOT was determined. Also, that an isolated SGOT elevation should not be taken as evidence of hepatocellular damage in patients receiving erythromycin without clinical signs of illness (37).

Zetler et al. reported SGPT elevation in patients receiving iproniazid (38). The authors conclude that the SGPT abnormalities were not associated with clinical evidence or other laboratory data of liver damage, in spite of continued administration of iproniazid. The above examples bring into focus that often transaminase elevations do not mean "impending diseaster" (38). Nonetheless, elevated hepatic enzyme levels are appropriate warning signs for liver problems and patients with elevated SGOT and SGPT should be followed carefully both clinically and by laboratory tests. This caution is also suggested on the basis of

recent animal data for drugs of abuse including the opiates which have the potential to elevate hepatic enzymes to abnormal levels.

Needham et al. (15) reports liver damage from narcotics in mice. Single and multiple injections of morphine, dihydromorphinone or methadone into mice produced fatty infiltration of the liver and increases of up to 10-fold in the level of SGOT. In a structural-activity comparison the levo-isomer of levorphanol caused similar SGOT elevations as morphine, while the inactive dextroisomer, dextrorphan, and the narcotic antagonist naloxone did not elevate SGOT levels (8). The authors reported less liver damage in animals pretreated with reserpine and propranolol (β-blocker) but not by dibenzyline (α-blocker) (15). Strain and sex differences were observed for both susceptibility to liver damage and SGOT elevations. Strain CXBK had the smallest response to SGOT increases after morphine. This strain also had the smallest number of opiate receptors in their brain as compared to other strains (15). It is quite possible that the differences in human subject response to elevated SGOT levels after morphine are related to individual differences in the numbers of opiate receptors.

Other opiates potentially hepatotoxic in animals are numerous (11, 12, 13, 14, 17, 19, 28). Chang and Ho (16) in an earlier study showed elevations in SGOT and SGPT levels after acute and continuous morphine administration. Elevations of SGOT and SGPT were prevented completely by hypophysectomy and partially by adrenalectomy. The authors conclude that the morphine-related changes in hepatic function are mediated through the CNS, especially the pituitary. Another school of thought entertains the possibility of local, direct hepatotoxic effects caused by morphine and other opiates (11, 12, 13, 14). Correia et al. (11) suggested that morphine rapidly depletes hepatic glutathione (GSH). GSH is known to detoxify reactive electrophilic metabolites in the liver. In the absence of GSH these reactive substances, that are a result of opiate or other drug metabolism, attack hepatocytes causing direct damage to the liver cells. The authors suggest that metabolic activation of morphine and other opiates, especially after large doses, could contribute in part, if not fully, to opiate-induced hepatic injury in rats.

Some of the studies show histopathologic changes in the liver after opiate administration in animals as well as in human subjects (12, 15, 27, 28). Thus, in these studies not only are elevations of SGOT and SGPT levels demonstrated but actual morphological and pathological changes as well, indicating that the opiate-related elevation of SGOT and SGPT may be a serious cause of liver problems.

THE ROLE OF NARCOTIC ANTAGONISTS - The narcotic antagonists, when used to pretreat animals prior to opiate administration, prevented the opiate-induced elevation of hepatic enzymes and concomitant hepatocellular injury (11, 14, 15, 16). Chang and Ho (16) administered 40 mg/kg of naloxone HCl at 8hr intervals to mice

implanted with morphine pellets. At 24hrs the naloxone-treated group's SGOT/SGPT levels were higher than control but greatly attentuated as compared with the morphine-implanted animals. A possible explanation for the lack of complete prevention of enzyme elevation by naloxone in this study was due to the short time action of naloxone and its sporadic administration (8hr apart). This schedule covered only short periods of opiate antagonism, while the implanted pellets were continuously releasing morphine. This hypothesis was confirmed by the studies of Needham et al. (15) who showed that the most effective time of total prevention of SGOT elevation by naloxone was when it was given 5 min before morphine. Sixty minutes prior to morphine was less effective and so was 30, 60 and 120 minutes after morphine. Correia et al. (11) have compared the structure-activity of the various morphine-like compounds and their N-ally-derived antagonists. Their results indicate that both nalorphine and naloxone by themselves do not induce elevated SGOT and SGPT levels, as the inactive d-isomer of levorphanol, dextrorphan, did not (11). Naloxone was used in similiar experiments with similiar results by James et al. (14). Naltrexone pretreatment antagonized the l-α-acetylmethadol-induced depletion of glutathione and the concomitant elevation of SGPT levels (14). The available studies and observations where opiate antagonists were used indicate prevention of hepatotoxicity and/or prevention of elevated hepatic enzymes.

There is a possible mechanism by which naltrexone-induced increases of SGOT & SGPT in the obesity and Alzheimer studies may be explained. Naltrexone is an N-cyclopropylmethyl derivative of noroxymorphone which is as potent an opiate agonist as morphine. When large doses of naltrexone are administered, it is possible that more N-delakylation takes place, producing noroxymorphone in the liver. Thus, an agonist metabolite of naltrexone is possibly involved in the observed SGOT-elevating effect of naltrexone, especially when given at high doses. Small amounts of noroxymorphone were identified in the urine of human subjects taking naltrexone (39). Thus, it is an established minor pathway of naltrexone biotransformation. In addition, a weak agonist effect of naltrexone which causes pupillary constriction has been reported (40,41). It is difficult to assess the role that Alzheimer's disease or obesity may play in addition to the effect of naltrexone on hepatic enzymes.

CONCLUSIONS

Several studies indicate that opiate antagonists block the hepatic enzyme-elevating effects of opiates as well as most of their other pharmacological effects. A review of the literature clearly indicates that it is the opiate agonists rather than the antagonists which are primarily responsible for the elevation of the hepatic enzymes. For this reason, it is somewhat illogical for the "black box" warning on the label of possible hepatotoxicity following naltrexone administration. The literature is not clear whether the enzyme elevations after opiate agonists

are, in fact, the result of hepatocellular damage or just temporary enzyme leakage into the circulation. Some studies indicate that tolerance does develop to hepatic enzyme elevations following chronic treatment with opiate agonists (23,24,28).

The major indictment of naltrexone appears to be the studies on the obese and the elderly suffering from Alzheimer's disease. The alteration in hepatic enzymes in these abnormal models may be due to predisposition aggravated by an agonist metabolite of naltrexone. Furthermore, no physical, clinical evidence of hepatotoxicity has been reported following long-term treatment with naltrexone. Any further studies concerning liver function should be fully controlled and directed toward the ex-opiate dependent population being maintained on naltrexone.

REFERENCES

1. Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. Clinical Evaluation of Naltrexone Treatment of Opiate-Dependent Individuals. Arch Gen Psychiat 35: 335-340, 1978.

2. Personal Communication Drs. Leonard Brahen, Richard Resnick and Jan Volavka.

3. Verebey, K. and Mule', S.J.: Naltrexone and β-naltrexol plasma levels in schizophrenic oatients after large oral doses of naltrexone. Res Comm Psychol Psych Behavior 4: 311-317, 1979.

4. Faulk, W.J. and Fleisher, G.A.: Effects of opiates on activity of serum transaminase. Proc Staff Meet Mayo. Clin. 32: 405, 1957.

5 Larsen, T. and Schmidt, A.: Increase in serum-GPT and serum-LDH after administration of morphine to oatients suffering from bile duct dyskinesia. Scand J Clin Lab Invest 18: suppl. 92): 175-177, 1967.

6. Christian, D.G.: Drug interference with laboratory blood chemistry determinations. Am J Clin Path 54: 118-142, 1970.

7. McNeely, M.D.D.: Drug interference with laboratory tests: Serum transaminases (SGOT,SGPT), Drug Therapy (Hosp) 79-84 Oct. 1978.

8. Wilson, B.K.; Elms, R.R.; and Thomson, C.P.: Outpatient vs Hospital methadone detoxification. Internat J Addict 10: 13-21, 1975.

9. Schussler, G.C.; Stimmel, B.; and Korn, F.: Increased serum thyroid binding in narcotic addicts is due to liver disease.
Am J Drug Alcohol Abuse 7: 379-387, 1980.

10. Cherubin, C.E.; Kane, S.; Weinberger, D.R.; Wolfe, E.; McGinn, T.: Persistence of transaminase abnormalities in former drug addicts. Ann Int Med 76: 385-389, 1972.

11. Correia, M.A.; Wong, J.S.; and Soliven, E.: Morphine metabolism revisited: Metabolic activation of morphine to reactive species in rats. Chem Biol Interactions, 49: 255-268, 1984.

12. James, R.C.; Freemand, R.W.; and Harbison, R.D.: ℓ-α-acetyl-methadol-induced tissue alterations in mice. Drug Chem Toxicol 7: 91-112, 1984.

13. James, R.C. and Harbison, R.D.: Hepatic glutathione and hepatotoxicity. Biochem Pharmacol 31: 1928-1835, 1982.

14. James, R.C., Goodman, D.R. and Harbison, R.D.: Hepatic glutathione and hepatotoxicity: Changes induced by selected narcotics. J Pharmacol Exp Ther 221: 708-714, 1982.

15. Needjam, W.P.; Schuster, L.; Kanel, G. and Thompson, M.L.: Liver damage from narcotics in mice. Toxicol Appl Pharmacol 58: 157-170, 1981.

16. Chang, Y.Y.H. and Ho, I.K.: Effect of acute and continuous morphine administration on SGOT and SGPT activities in the mouse.
Biochem Pharmacol 28: 1373-1377, 1979.

17. Page, J.G.; Sullivan, H.R.; Due, S.L. and Slater, I.H.: Plasma concentrations and electrocardiographic alterations after repetitive administration of propoxyphene to dogs.
Toxicol Appl Pharmacol 50: 505-514, 1979.

18. Hurwitz, A.: Narcotic effects on anionic dye disposition in mice.
Gastroenterol 76: 1285, 1979.

19. Vonen, 8. and Morland, J.: Isolated rat hepatocytes in suspension:
Arch Toxicol 56: 33-37, 1984.

20. Edland, J.F.: Liver disease in herion addicts. Human Pathol 3: 75-84, 1972.

21. Norris, R.F. and Potten, H.P.: Hepatic inflammation in narcotic addicts. Arch Environ Health 11: 662-668, 1965.

22. Jersild, T.; Johansen, C.; Balslov, J.T.; Hojggard, K.; Johansen, A. and Ott, C.: Hepatitisin young drug users. Scand J. Gastroent 7: Suppl. 79-83, 1970.

23. Gorodetsky, C.W.; Sapira, J.D.; Jasinski, D.R. and Martin, W.R.: Liver disease in narcotic addicts: I. The role of the drug.
Clin Pharmacol Ther 9: 720-724, 1968.

24. Sapira, J.D.; Jasinski, D.R.; and Gorodetsky, C.W.: Liver disease in narcotic addicts: II The role of the needle.
Clin Pharmacol Ther 9: 725-739, 1968.

25. Kreek, M.J.: Medical complications in methadone patients.
Ann NY Acad Sci 311: 110-134, 1978.

26. Bastomsky, C.H.; Dent, R.R.M. and Tolis, G.: Elevated serum concentration of Thyroxine binding globulin and caerulophasmin in methadone-maintained patients. Clin Biochem 10: 124-126, 1977.

27. Lee, T.H. and Press, P.J.: Hepatotoxicity of dextropropoxyphene.
Br Med J 296-297, July, 1977.

28. Thureson-Klein, A.; Wang-Yang, J. and Ho, I.K.: Lipid accumulation in mouse hepatocytes after morphine exposure. Experientia 34: 773, 1978.

29. Shaw, S.; Korts, D. and Stimmel, B.: Abnormal liver function tests as biological markers for alcoholism in narcotic addicts.
Am J Drug Alcohol Abuse 9: 345-354, 1983.

30. Charuvastra, C.V.; Panell, J.; Hopper, M.; Erhmann, M.; Blakis, M. and Ling, W.: The medical safety of combined usage of disulfiram and methadone. Arch Gen Psychiat 33: 391-393, 1979.

31. Burke, M.D.: Hepatic function testing. Postgrad Med 64: 177-185, 1978.

32. Hutchinson, D.R.; Smith, M.G. and Parke, D.V.: Prealbumin as an index of liver function after acute paracetamol poisoning.
Lancet 2: (8186): 121-123, July 19, 1980.

33. Russell, A.S.; Struge, R.A. and Smith, M.A.: Serum transaminases during salicylate therapy.
Br Med J: 428-429, May 22, 1971.

34. Manso, C.; Taranta, A. and Nydick, I.: Effect of Aspirin administration on serum glutamic oxaloacetic and glutamic pyruvic transaminases in children. Proc Sec Exp Biol Med 93: 84-88, 1956.

35. Marsh, E.M.; Greenberg, L.D. and Rinehart, J.F.: The relationship between pyridoxine ingestion and transaminase activity. J Nutrition 56: 115-127, 1956.

36. Glendening, M.B.; Cohen, A.M. and Page, E.W.: Influence of pyridoxine on transaminase activity in human placenta, maternal and fetal blood. Proc Soc Exp Biol Med 90: 25-28, 1955.

37. Sabath, L.D.; Gerstein, D.A. and Finland, M.: Serum glutamic oxalacetic transaminase: false elevation during administration of erythromycin. New Eng J Med 279: 1137-1139, 1968.

38. Zetler, L.; Kaplan, H. and Dussik, K.T.: liver function test in patients receiving iproniazid Am J Dig Dis 4: 1027-1033, 1959.

39. Cone, E.J. and Gorodetsky, C.W.: Metabolism of naltrexone and naloxone. In National Research Council. Committee on Problems of Drug Dependence. Problems of Drug Dependence 1975; proceedings of the 37th Annual Dependence Meeting, Washington D.C. May 19-21, 1975 Wash. D.C., National Academy of Sciences, 1975.

40. Martin, W.R.; Jasinski, D.R. and Mansky, P.A.: Naltrexone an antagonist for the treatment of heroin dependence. Arch Gen Psychiat 28: 784-791, 1973.

41. Verebey, K.; Volvaka, J.; Mule', S.J. and Resnick, R.B.: Naltrexone: Disposition, metabolism and effects after acute and chronic dosing. Clin Pharmacol Ther 20: 315-328, 1976.

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Progress Report from the Medical College of Virginia: Abused Solvents

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The voluntary inhalation of volatile chemicals remains one of the least understood substance abuse phenomena. The research literature (see Cohen 1981 and Glowa 1985 for reviews) concerned with this public health problem is minuscule compared to that published on more widely studied groups of abused substances such as alcohol, marijuana, narcotics, stimulants, and hallucinogens. Does this reflect the relatively minor scope of the drug abuse problem associated with solvents? Was solvent use a passing fad that no longer requires systematic scientific investigation? Some answers to these questions can be found in the epidemiology of solvent use in the United States.

The National Institute on Drug Abuse (NIDA) has two major national surveys conducted periodically to evaluate overall prevalence of use of various categories of drugs. The National Survey on Drug Abuse samples the U.S. population every three years with over 5000 respondents. Data from the 1979 survey (Miller and Cisin 1980) indicate that lifetime prevalence of inhalant use was 10% in 12-17 year olds and 17% in 18-25 year olds: These prevalence rates for inhalants are greater than those for cocaine, hallucinogens, heroin or phencyclidine for all age groups and rank just behind marijuana, alcohol and tobacco in terms of incidence of use. About 1% of the 12-17 age group had used inhalants within the month before the survey. The corresponding figure for the 18-25 group was about 0.5%. Thus, over 2 million 12-17 year olds and 1.5 million young adults were currently using inhalants in 1979. Unfortunately, the subsequent 1982 National Survey did not include inhalants in its reporting; the 1985 Survey currently being conducted will again include them.

For more recent information on national use patterns we must turn to the High School Senior Survey conducted annually since 1975 (Johnston et al. 1984). The samples for these surveys are over 15,000 high school seniors from both public and private schools throughout the U.S. For 1983, the lifetime prevalence for inhalants was 18.8%. This figure is higher than the corresponding figure for cocaine (16.2%), hallucinogens, including PCP (14.7%), sedatives (14.4%), and heroin (1.2%). The prevalence of inhalant use has not changed consistently from 1979-1983, ranging from 17.4% in 1981 to the 18.8% in 1983. Early reports from the 1984 survey show this value to be up to 19.0% (HHS News). Throughout the period of these surveys, 2.3-3.1% of

these high school seniors report having used an inhalant within the past 30 days.

This high incidence of reported inhalant use from both national surveys suggests that the inhalant abuse problem is not small nor was it a fad. In terms of incidence, inhalant abuse consistently ranks above or comparable to the much more widely studied drugs of abuse such as heroin, cocaine, and PCP. In spite of this, research on abused solvents has not kept pace with that on these other drugs of abuse. Some evidence for this is the lack of any papers specifically related to inhalant abuse research having been presented at this meeting for at least the last four years. We feel there is a need for additional efforts in this area.

We began a project to study the behavioral pharmacology of abused inhalants about five years ago. We focused most of our attention on research designed to characterize the acute behavioral effects of abused solvents. Our major tool for these studies was the schedule-controlled behavior of mice, although we have used various unconditioned behaviors as well. The rationale for this choice of measures was that acute behavioral effects in animals could reasonably be assumed to be a model of solvent intoxication. We were initially interested in quantitating behavioral effects of abused solvents with respect to concentration and duration of exposure, studying the time course of solvent effects, and comparing the effects of representative solvents. In other studies we have investigated interactions of an abused solvent with alcohol, possible tolerance to the effects of solvents, and comparisons of behavioral effects to acute toxicity for a variety of solvents. Space does not allow a complete review of this research, so I will use examples to illustrate the approaches we have used and the types of questions we have asked.

INHALATION METHODOLOGY

A factor which undoubtedly contributes to the relative lack of research on inhalants is the difficulty in controlling the critical parameters of the independent variable. Although dosage is difficult to establish, concentration and duration of exposure can be manipulated with considerable accuracy. Consequently, most studies of solvents take this approach, although a long-term goal of research in this field should be to correlate these parameters with dosages received by the subjects and with concentrations of the active materials in blood and at sites of action.

Static exposures. One relatively easy method of conducting inhalation studies is to use static exposures. Our static exposure chamber is illustrated in figure 1. It consists of a 29-liter glass jar with a plexiglas cover which can be bolted tight onto the top. A fan motor and injection and sampling ports are mounted in the cover. Suspended below the fan blade is a wire mesh basket which can contain a piece of filter paper.

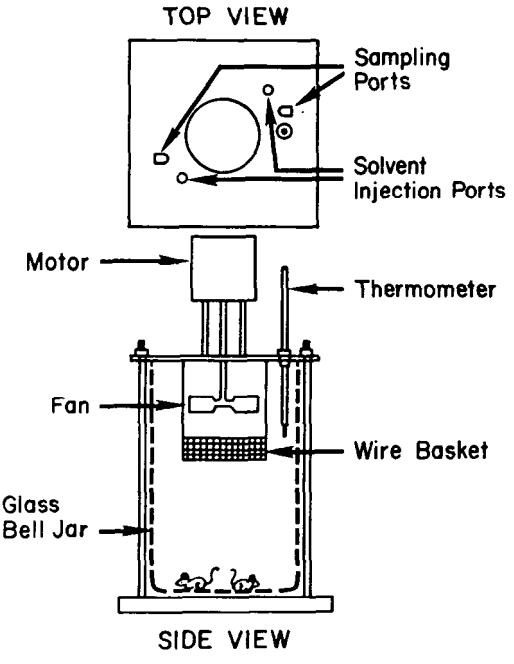

FIG. 1. Diagram of static exposure chamber for mice

Mice are placed in the tank, the cover bolted on, the solvent injected onto the filter paper, and the fan started to hasten volatilization and distribute the vapors evenly. The nominal chamber concentration of the vapor can be calculated from the gas laws assuming complete volatilization, a reasonable assumption when working with small liquid volumes of highly volatile solvents. We can also monitor the chamber concentration by using the sampling ports and a closed loop pumping system. The chamber atmosphere is pumped through the cell on a Miran 1A (Foxboro Analytical) infra-red spectrophotometer. By monitoring absorbence at a single wavelength, one can measure chamber concentration on-line.

Once the parameters have been established, exposures are highly accurate and reproducible using this exposure method. The time for volatilization is a function of the liquid volume injected and its volatility. A behaviorally active range of concentrations of nearly all the solvents we have studied can be easily achieved in this chamber with complete volatilization within a few minutes. To limit the accumulation of waste gases, we generally confine our exposure duration for six mice in this chamber to 60 minutes or less, with most of our exposures being 20-30 minutes.

One problem with our approach to static exposures is that in these closed systems behavioral testing of the subjects during exposures is difficult. Consequently, our studies using static exposures have utilized testing after removal from the chamber. The problem with this is that the subjects very rapidly recover. Figure 2 shows the effects of toluene on lever-pressing under a differential-reinforcement-of-low-rate (DRL) 10 second schedule (Moser and Balster 1981).

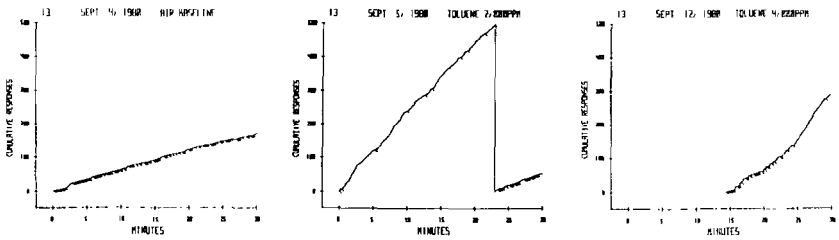

FIG. 2. Effects of toluene on DRL performance of a mouse. Responses are recorded cumulatively; the pen resets after 500 responses. Diagonal marks indicate delivery of the milk reinforcer. The left panel shows control performance with air only. The middle panel shows the effects of 2000 ppm and the right panel the effects of 4000 ppm.

The operant session began within one minute of the termination of the exposure. The middle panel shows that the response rate increasing effects of 2000 ppm are evident immediately but dissipate after 20 minutes. Similarly, the response rate decreasing effects of 4000 ppm recover by 15 minutes.

Another approach to studying solvent effects immediately after inhalation has been to use a simple test of motor performance similar to the rotarod (Balster 1980). One min post-exposure, mice are placed upon a horizontal wire mesh screen, the screen inverted, and the number of mice climbing to the top within one minute used as a measure of motor performance disruption. Animals can be repeatedly tested to measure recovery. Some results using this procedure will be shown later.

Dynamic exposures. We have also developed an approach to conducting tests of operant behavior during inhalant exposure (Balster et al. 1982). In order to have the greatest flexibility in arranging the vapor exposures, vapors are continuously generated and passed through the behavioral test chamber. Our exposure system is designed to allow a rapid adjustment of the chamber concentration. The chamber concentration can also be monitored on-line using IR

spectrometry, as described above. An example of the use of this approach is shown in Figure 3.

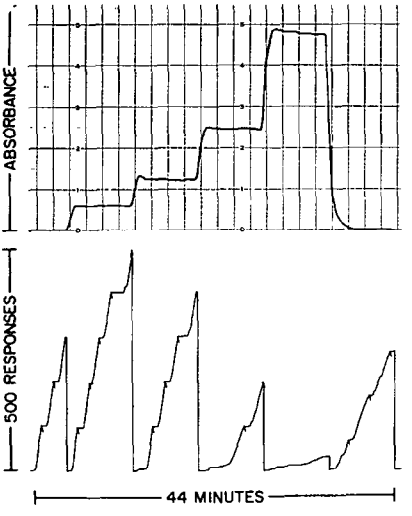

FIG. 3 Effects of dynamic exposure to 1,1,1-trichloroethane on responding under a fixed-ratio 100 schedule in a mouse. The upper panel shows infra-red absorbence corresponding to increases in concentration from 0 to 1000, 2000, 4000 and 8000 and returning to 0 ppm. The lower panel is the cumulative response record for that exposure session. The cumulative response pen was reset with each change in concentration. Diagonal marks indicate delivery of the water reinforcer (used with permission from Moser et al. 1985; copyright 1985 by Intox Press, Inc.).

The ability to rapidly change chamber concentration and concurrently monitor the vapor level and schedule-controlled behavior allowed us to obtain concentration-response data within a single test session. The session began with 5 minutes exposure to air (0 ppm). During subsequent 8-minute segments of the session, the mice were exposed to 1000, 2000, 4000, and 8000 ppm 1,1,1-trichloroethane, in an ascending order. The rapid changes in chamber concentrations are illustrated in the upper panel of the figure. The lower panel shows the cumulative response record for that test session. Concentration-related decreases in response rate were observed until at 8000 ppm the subject failed to emit the 100 responses required for reinforcement. When the chamber was purged, the animal rapidly resumed responding.

This approach is particularly valuable for examining the temporal relationship between introduction of solvent vapors and behavioral effects. Solvents differ in the degree to which chamber concentrations and behavioral effects are temporally correlated. 1,1,1-Trichloroethane is an example of one where changes in concentration are rapidly reflected in behavior (Balster et al. 1982; Moser and Balster 1985b; Moser et al. 1985).

EFFECTS OF CONCENTRATION AND EXPOSURE DURATION

All of our studies have examined concentration-effect curves for a variety of measures. As an example, figure 4 shows the effects of 30-minute exposure to 1,1,2-trichloroethane (Balster and Woolverton 1980). It illustrates a number of important

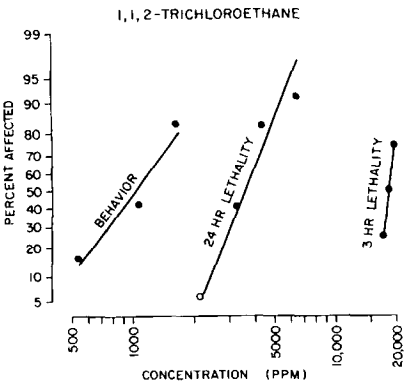

FIG. 4. Effects of 1,1,2-trichloroethane on the inverted screen test and lethality in mice. For the behavioral measure, the percentage of animals failing to climb on top of an inverted screen is shown. The lethality curves are for deaths occurring within 3 hour or 24 hours of exposure. N = 12 for each point.

points. The first point to notice is the relative steepness of the concentration-effect curves. For example, the complete concentration-effect curve for 3-hour lethality occurs between 16,000 and 20,000 ppm. At 17,500 ppm, 25% of the subjects died; at 19,500 ppm, 75% died. Thus, a change of about 10% in the exposure concentration resulted in significantly different toxicity. Similar, though less extreme, effects of concentration are seen on behavior. The steepness of these curves contrasts with those for systemic administration of most drugs of abuse, where doses over at least a 10-fold range typically comprise the dose-effect curve. The steepness of these curves also illustrates the need for accurate quantification of chamber concentration.

Another interesting point about the data in figure 4 concerns the issue of delayed effects evident in the lethality curves. The 3-hour curve reflects acute overdose deaths. At these high concentrations of 1,1,2-trichloroethane, subjects evidenced anesthetic effects and usually died during the exposure or shortly thereafter from respiratory failure. Notice the good safety mar in for behavioral effects and this type of acute lethality (a 17.6-fold difference in the EC50's). Animals who survived the acute intoxication generally recovered within a few minutes; however, over the next few hours their health would decline, often resulting in death within 24 hours. Thus, the 24-hour lethality curve is substantially to the left of the

3-hour curve and the safety margin for behavioral effects is much less (a 3.4-fold difference in the EC50's). These delayed deaths probably are due to nephrotic or hepatic damage caused by this agent. Delayed toxicity only occurs with some of the abused solvents we have tested (1,2-dichloroethane and 1,1,2-trichloroethane). Other inhalants such as dichloroethylene, 1,2-dichloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethylene, toluene, halothane, isoamyl nitrite, isobutyl nitrite, and n-butyl nitrite (Balster and Woolverton 1980; Moser and Balster 1985a; Rees et al. 1985b) do not show delayed lethal effects under these test conditions. Assuming that the behavioral effects we are measuring bear some relationship to the intoxication abusers experience with these materials, then on the basis of these data we would expect considerable differences among solvents in their potential for toxicity to abusers. Those without delayed toxicity and with the widest separation of behavioral and toxic effects would be the least dangerous. More research needs to be done relating the behavioral effects to toxic effects of abused solvents, particularly using more sensitive measures of toxicity than lethality. From research of this type should emerge a better idea of the relative risks associated with specific solvents.

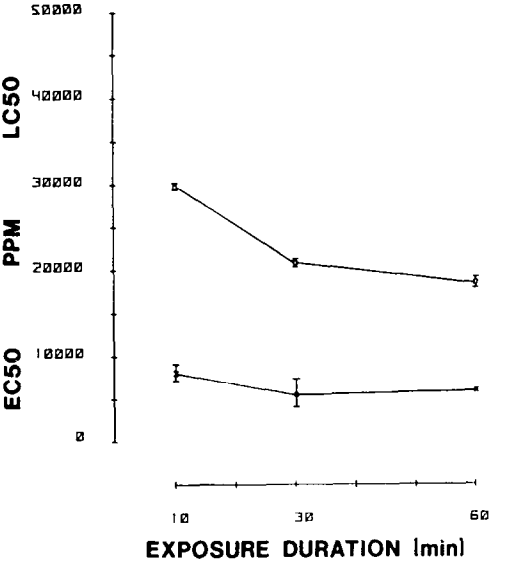

FIG. 5. Effects of exposure duration on the behavioral and lethal effects of 1,1,1-trichloroethane in mice. Shown are the LC50's (±95% confidence limits) for lethality in the upper curve and EC50's (±95% confidence limits) for the inverted screen test in the lower curve.

Exposure duration is also a determinant of inhalant effects (Moser and Balster 1985a, 1985b). Figure 5 shows the effects of exposure durations of 10, 30 or 60 minutes on the effects of 1,1,1-trichloroethane on the inverted screen test and 2-hour lethality. Exposures were conducted in the static chamber and behavior was measured 1 minute after removal. Increases in exposure duration from 10 to 30 minutes and from 30 to 60 minutes were associated with increased lethality (LC_{50}'s of 29,492, 20,616 and 18,358 ppm, respectively). For behavioral effects, the increase in exposure duration from 10 to 30 minutes increased the sensitivity of the animals, but a further increase to 60 minutes did not result in an additional increase in sensitivity. These results raise at least two interesting points. Since behavioral and lethal effects were not similarly modified by changing exposure duration, these effects may have different determinants. Also, the ratio of concentrations required for lethal vs. behavioral effects decreased with increasing exposure duration. Thus, with increasing exposure the safety margin for this solvent decreases, resulting in a greater probability of achieving toxic concentrations at intoxicating concentrations. This was not true for all solvents tested, For example, for toluene the safety margin was relatively unaffected by exposure duration. These differences are probably due to differences in blood:air Partition coefficients and consequent differences in equilibration rates. One goal of our research program is to better establish the power of these physical chemical properties to predict *in vivo* effects of abused inhalants.

INTERACTIONS WITH ALCOHOL

Alcohol is an abused solvent. For many reasons, concurrent use of oral alcohol and inhaled solvents might be expected to interact. A major reason for this prediction is that at least some abused solvents may have pharmacological properties similar to classic CNS depressants such as the barbiturates and alcohol. The toxicity of combined use of CNS depressants is well known. We studied the lethal and behavioral effects of oral ethanol in combination with inhaled 1,1,1-trichloroethane in mice (Woolverton and Balster 1981). For lethality, supra-additive effects were obtained at lower doses of ethanol (0.125-1.0 g/kg). At higher doses of ethanol the interaction was quantitatively less, but the concentration-effect curves for 1,1,1-trichloroethane were still substantially shifted to the left. Behavioral effects were measured using the inverted screen test. Most doses of ethanol shifted the concentration-effect curve for 1,1,1-trichloroethane to the left; and, with the exception of 0.25 g/kg, ethanol generally resulted in either an additive or supra-additive interaction with this solvent. These data further demonstrate the CNS depressant properties of 1,1,1-trichloroethane and also suggest that alcohol beverage consumption may increase the sensitivity of users to both the intoxicating and toxic effects of this solvent. The generality of this finding to other abused inhalants has not as yet been investigated.

TOLERANCE

Although tolerance has been said to occur in some of the clinical literature on abused solvents, we have not found much evidence for significant tolerance to the behavioral effects of either 1,1,1-trichloroethane (Moser et al. 1985) or toluene (Moser and Balster 1981). Both studies used schedule-controlled behavior of mice. After obtaining an initial concentration-effort curve, the subjects were given daily exposures prior to or during behavioral test sessions for periods of 15-50 days. Subsequent concentration-effect curves were not shifted to the right. On the other hand, with 1,1,1-trichloroethane there was some evidence for more rapid recovery from behaviorally active concentrations after repeated administration. The possibility of tolerance and/or dependence with abused solvents awaits further investigation.

SIMILARITIES WITH CNS DEPRESSANTS

One of the questions that has most interested us concerns the nature of the acute intoxications produced by abused inhalants. It is not clear whether all inhalants produce qualitatively similar intoxication, nor what these intoxications are like. There is some reason to believe that at least some solvent intoxication is similar to that which occurs with CNS depressants such as alcohol and the barbiturates. Various solvents share a number of behavioral and pharmacological effects with these depressants. I have already shown how a measure of motor performance similar to the rotarod is readily disrupted by a number of abused solvents. Motor coordination effects are common with depressants. Nitrous oxide and toluene have been shown to have anticonvulsant effects (Wood et al. 1982). Chloroform has been shown to suppress withdrawal signs in barbital-dependent monkeys (Yanagita and Takahashi 1973). We have shown an interaction between ethanol and 1,1,1-trichloroethane (Woolverton and Balster 1981) which is similar to the interactions among CNS depressants. Toluene has even been recently shown to have antipunishment effects similar to depressants (Wood et al. 1982). Much of our research on the effects of solvents on operant behavior found generally similar effects to those produced by inhaled ethanol and halothane (e.g. Moser and Balster, 1985b).

This leads to the hypothesis that the abuse potential of at least some inhalants is related to their ability to produce an intoxication similar to alcohol and barbiturates. Recently, we have begun to evaluate this hypothesis more directly by studying the discriminative stimulus effects of abused solvents. Drug discrimination is considered by many to be a model of subjective drug effects. We have taken two general approaches to comparing the discriminative stimulus effects of solvents to those of classic CNS depressants.

The first approach uses animals trained to discriminate a prototypic depressant, pentobarbital, from saline in a two-lever

operant task. Mice so trained will generalize to ethanol and other barbiturates, but not to chlorpromazine nor morphine (Moser et al. 1984). We have recently found that most of these animals also generalize to toluene (Rees et al. 1985a). We have preliminary data also showing generalization to 1,1,1-trichloroethane and halothane, but not to isoamyl nitrite.

Our other approach has been to train mice to discriminate injections of toluene from vehicle (Rees and Balster 1985). Although this has proven to be a difficult discrimination to train, we have a number of animals who have acquired it. Preliminary results from these animals indicate that they generalize to inhaled toluene and an injected barbiturate. Thus, taken together, these results provide additional evidence that at least toluene produces a CNS-depressant-like intoxication. It is unclear how many other abused solvents produce CNS depressant stimulus effects as well. The use of this model should help address this question. It is possible that classes of solvents and other volatile chemicals may differ with respect to their ability to produce depressant-like stimulus effects, and thus may differ in abuse potential as well.

REFERENCES

Balster, R.L. The effects of phencyclidine and three analogues on motor performance in mice. Pharmacology 20:46-51, 1980.

Balster, R.L.; Moser, V.C.; and Woolverton, W.L. Concurrent measurement of solvent vapor concentrations and effects on operant behavior using a dynamic exposure system. J Pharmacological Methods 8:299-309, 1982.

Balster, R.L., and Woolverton, W.L. Acute behavioral and lethal effects of several inhaled chlorinated hydrocarbon solvents in mice. Pharmacologist 22:169, 1980.

Cohen, S. The intentional inhalation of volatile substances. In: Mello, N.K., ed. Advances in Substance Abuse, Vol. 2. Greenwich, CT: JAI Press, 1981. pp. 123-143

Glowa, J.R. Behavioral effects of volatile organic solvents. In: Seiden, L.S., and Balster, R.L., eds. Behavioral Pharmacology: The Current Status. New York: Alan R. Liss, 1985. pp. 537-552

Johnston, L.D.; O'Malley, P.M.; and Bachman, J.G. Highlights from Drugs and American High School Students 1975-1983. National Institute on Drug Abuse. DHEW Pub. No. (ADM) 84-1317. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1984. 135 pp.

Miller, J.D., and Cisin, I.H. Highlights from the National Survey on Drug Abuse 1979. National Institute on Drug Abuse. DHHS Pub. No. (ADM) 80-1632. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1980. 34 pp.

Moser, V.C., and Balster, R.L. The effects of acute and repeated toluene exposure on operant behavior in mice. Neurobehav Toxicol Teratol 3:471-475, 1981.

Moser, V.C., and Balster, R.L. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. Toxicol Appl Pharmacol 77:285-291, 1985a.

Moser, V.C., and Balster, R.L. Effects of toluene, halothane and ethanol vapor on fixed-ratio performance in mice. Pharmacol Biochem Behav 22:797-802, 1985b.
Moser, V.C.; Coggeshall, E.M.; and Balster, R.L. Pentobarbital discrimination in mice. Fed Proc 43:947, 1984.
Moser, V.C.; Scimeca, J.A.;and Balster, R.L. Minimal tolerance to the effects of 1,1,1-trichloroethane on fixed-ratio responding in mice. NeuroToxicol 6:35-42, 1985.
Rees, D.C.; and Balster, R.L. Discriminative stimulus properties of injected toluene in mice. Toxicologist 5:24, 1985.
Rees, D.C.; Coggeshall, E.; and Balster, R.L. Inhaled toluene produces pentobarbital-like discriminative stimulus effects in mice. Life Sciences, in press, 1985a.
Rees, D.C.; Coggeshall, E.M.; Dragan, Y; Breen, T. J.; and Balster, R.L. Acute effects of some volatile nitrites on motor performance and lethality in mice. Neurobehav Toxicol Teratol, in press, 1985b.
Wood, R.W.; Coleman, J.B.; Schuler, R.; and Cox, C. Anticonvulsant and antipunishment effects of toluene. J Pharmacol Exp Ther 230:407-412, 1985.
Woolverton, W.L., and Balster, R.L. Behavioral and lethal effects of combinations of oral ethanol and inhaled 1,1,1-trichloroethane in mice. Toxicol Appl Pharmacol 59:1-7, 1981.
Yanagita, T., and Takahashi, S. Dependence liability of several sedative-hypnotic agents evaluated in monkeys. J Pharmacol Exp Ther 185:307-316, 1973.

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Progress Report From the Division of Behavioral Biology, The Johns Hopkins University School of Medicine

Roland R. Griffiths, Joseph V. Brady, Nancy A. Ator, Richard Lamb, George E. Bigelow, and John D. Roache

The Division of Behavioral Biology is the site of a group of infrahuman and human research projects dealing with the behavioral pharmacology of substance abuse. The general aim of this program of research is to promote a fuller understanding of addictive disorders and of their behavioral and biomedical foundations; in particular, the laboratory focuses upon determinants of drug self-administration and determinants of adverse drug effects. This aim is pursued via systematic experimental study of the contributory roles of both behavioral and pharmacological factors. A primary objective of this year's progress report is to provide a novel perspective on the breadth of research conducted at the Johns Hopkins laboratories by summarizing multidimensional abuse liability evaluations focusing on a single compound, triazolam, which is a representative of the benzodiazepine anxiolytic/hypnotic class of compounds that has been a major focus of research this last year.

Triazolam is a triazolobenzodiazepine which is marketed as an ultrashort-acting hypnotic (mean half-life 2 - 3 hr) under the product name Halcion. Of all the marketed benzodiazepine anxiolytics and hypnotics, triazolam has been the most controversial with respect to physical dependency potential and other adverse effects. The present set of multidisciplinary studies concerning the abuse liability of triazolam was undertaken, in part, to help resolve some of this controversy.

For purposes of this report, the term abuse liability will be used to refer to: (1) the liability <u>for</u> abuse (i.e., the likelihood that a drug will be abused) and/or (2) the liability of abuse (i.e., the untoward effects of abusing the drug). These two senses of abuse liability correspond directly to two major characteristics of drugs of abuse: (1) they have <u>reinforcing properties</u> (they have the capacity to maintain drug self-administration) and (2) they produce <u>adverse effects</u> (they have the capacity to harm the individual and/or society). The presence of both characteristics is necessary to define a drug of abuse.

1. Intravenous Drug Self-Injection in Baboons -- Triazolam (0.0001 - 0.32 mg/kg) was evaluated in our standard drug self-injection substitution paradigm in which each drug dose was substituted for cocaine (0.32 mg/kg) for 15 days under a continuously available fixed-ratio (FR 160) schedule with a 3-hr timeout following each injection. Comparing peak rates of self-injection (i.e., inj/day), triazolam maintained lower rates of self-injection than those maintained by the barbiturates amobarbital, pentobarbital and secobarbital, but consistently higher rates than those maintained by benzodiazepines which are slowly eliminated or have active metabolites which are slowly eliminated (e.g., diazepam and flurazepa). It is possible that elimination rate is a determinant of self-injection rate under this paradigm. However, the possibility remains that triazolam is a more efficacious reinforcer than other bentodiazepines.

2. Oral Drug Self-Administration in Baboons -- Triazolam (0.01 to 1.28 mg/ml) was studied under conditions in which drug and/or vehicle suspensions were available to baboons for oral consumption during daily 3-hr sessions. The baboons consumed behaviorally active amounts of drug with peak intake exceeding 10 mg/kg for all baboons. Animals had free access to water except during daily sessions. At each of a wide range of drug concentrations, a two-bottle choice condition was conducted in which the baboon had simultaneous access to vehicle and drug suspensions, with side positions of vehicle and drug alternating daily. In contrast to methohexital, triazolam and diazepam generally were not preferred to vehicle. Thus, under these conditions, triazolam is less efficacious as a reinforcer than methohexital, but indistinguishable from diazepam.

3. Drug Discrimination in Baboons -- Triazolam (0.0032 to 0.32 mg/kg, p.o.) was evaluated in baboons trained to discriminate lorazepam (1.0 mg/kg) in a two-lever drug vs. no drug food reinforcement drug discrimination procedure. In contrast to pentobarbital and methaqualone, triazolam and a variety of other benzodiazepines (alprazolam, bromazepam, diazepam, halazepam, temazepam) occasioned drug lever responding. These data suggest that the abuse liability of triazolam may be similar to other benzodiazepines and dissimilar to classic abused sedatives such as pentobarbital.

4. Physical Dependence in Baboons -- The physical dependence-producing properties of triazolam were evaluated in three different procedures. In the substitution procedure, baboons are maintained on pentobarbital via a continuous intragastric infusion. Twenty-four hour substitution of vehicle in baboons that have been maintained on 100 mg/kg/day pentobarbital results in suppressed food intake, while a similar vehicle substitution for 180-200/mg/kg/day results in suppressed food intake, tremor and convulsion. Triazolam, lorazepam and pentobarbital attenuated the suppression of food intake at the 100 mg/kg/day pentobarbital dose in contrast to chlorpromazine which did not. Triazolam has not yet been evaluated at the

high pentobarbital dose.

A second procedure for providing information about the physical dependence-producing capabilities of benzodiazepine-like compounds is to administer a test drug chronically and determine presence and extent of precipitated withdrawal signs (e.g., scratching, nose-rubbing, vomiting, tremor) upon administration of a benzodiazepine antagonist (i.e., precipitated withdrawal test). Baboons chronically exposed to triazolam (3.0 - 8.9 mg/kg/day) or diazepam (2.6 - 20.0 mg/kg/day) received intramuscular injections of the benzodiazepine antagonist Ro 15-1788 (5.0 mg/kg). The profile and severity of withdrawal signs at these somewhat arbitrary but high doses of triazolam and diazepam were identical.

Some limited observations of spontaneous withdrawal have been made by observing baboons for withdrawal signs after abruptly terminating drug after a period of chronic administration. After terminating triazolam (2.7 - 21.8 mg/kg/day), tremor and scratching/nose-rubbing increased over previous baseline levels and returned to those baseline levels when triazolam was reinstated. These relatively mild withdrawal signs were similar to those observed in baboons undergoing diazepam spontaneous withdrawal and contrast with the severe signs (e.g., convulsion) observed during spontaneous withdrawal from 200 mg/kg/day pentobarbital. As would be expected on the basis of the known pharmacokinetic differences between triazolam and diazepam in humans, onset of spontaneous withdrawal signs after triazolam tended to occur sooner than that after diazepam.

5. Comparison of Acute Effects of Triazolam and Pentobarbital in Drug Abusers -- The acute effects and time course of oral doses of placebo, triazolam (0.5 - 3.0 mg), and pentobarbital (100 - 600 mg) were examined using a within-subject, double-blind design in male volunteers with hi stories of drug abuse who resided in a research ward. Triazolam and pentobarbital produced comparable dose-related impairment on staff-rated and objective performance measures. With these measures, triazolam was 159 to 274 times more potent than pentobarbital. With subject-rated measures of drug effect, sleepiness, and drunkenness, in contrast, triazolam produced smaller effects than pentobarbital or was only 135 to 163 times more potent than pentobarbital. Similarly, with subject ratings of drug liking and estimated street value, triazolam produced smaller effects than pentobarbital and was only 91 to 122 times more potent than pentobarbital. Thus, these data indicate that at triazolam and pentobarbital doses which produced similar degrees of impairment, triazolam was less well liked than pentobarbital. Other results showed that higher doses of triazolam were categorized by the subjects as being predominantely benzodiazepine-like in contrast to higher doses of pentobarbital which were categorized as being predominantely barbiturate-like. Triazolam produced greater amnestic effects than pentobarbital on both immediate and delayed item recognition tasks. When subjects were required to rate how

well they thought they had done on two performance tasks, subjects under the influence of triazolam more consistently underestimated the degree of their impairment. Overall, these results suggest that triazolam has a lower liability for abuse (likelihood) than pentobarbital, but a greater liability of abuse (hazard) with regard to performance impairment on certain kinds of tasks.

6. Tolerance Development to Triazolam and Diazepam in Drug Abusers -- The effects of repeated administration of triazolam and diazepam on psychomotor performance and subject-rated liking were studied under double-blind conditions in male volunteers with histories of drug abuse who resided in a research ward. Six subjects received triazolam (2.0 or 3.0 mg) every second day (4 subjects) or every third day (2 subjects) for a total of 3 - 5 dosing occasions, and six subjects received 80 mg diazepam every third day (3 subjects) or every sixth day (3 subjects) for a total of 3 - 6 dosing occasions. The results showed that on the first dose occasion, the two drugs produced generally similar degrees of psychomotor impairment and subject-rated drug liking. Following the first diazepam dose, subsequent doses produced less of an effect (i.e., single-dose tolerance). Across at least the first three dose occasions, progressive tolerance development was observed with diazepam but no tolerance was observed with triazolam. It is possible that pharmacokinetic differences between diazepam and triazolam may account for the difference in the development of tolerance.

The implication of these results for the relative abuse liability of triazolam and diazepam is unclear. It could be suggested that the development of tolerance to diazepam but not triazolam may indicate a greater propensity for diazepam to produce dose-escalation and physical dependence. On the other hand, it could be suggested that tolerance to subject-rated drug liking with diazepam but not triazolam may make triazolam the preferred drug of abuse.

7. Self-Administration of Triazolam and Diazepam in Drug Abusers -- Oral self-administration of triazolam (1.0 or 2.0 mg), diazepam (40 or 80 mg) and placebo was studied under double-blind conditions in each of eight male subjects with histories of drug abuse who resided in a research ward. Each drug condition (triazolam, diazepam, and placebo) lasted a week. On the first day of a condition, the drug dose or placebo was administered. On each of the six following days, the same drug dose (or placebo) was available for self-administration once daily. In order to receive the drug on self-administration days, subjects were required to ride a stationary exercise bicycle; the riding requirement was progressively increased across the six days (from 0.5 to 3 hrs). In order to minimize carryover effects between the two active drug conditions, these were scheduled in counterbalanced order with three weeks between the end of one and the beginning of the other; the placebo condition was scheduled during the

middle week of the three-week period. The results showed that triazolam and diazepam were self-administered more frequently than placebo, but there were no meaningful differences between the compounds in self-administration. Subjects tended to cite reduced/weak effects and drug-produced sluggishness as being undesirable attributes of the diazepam condition, while subjects did not cite such effects for the triazolam condition. Subjects tended to cite memory impairment as an adverse effect of the triazolam condition and indicated that this effect would make the drug undesirable for street use. Subjects tended not to make such comments for diazepam.

CONCLUSION

Based on the studies of baboon intravenous and oral drug self-administration, baboon drug discrimination, baboon spontaneous drug withdrawal, and human acute dosing, it is concluded that triazolam has less abuse liability than barbiturates such as pentobarbital which are generally considered to have significant abuse liability. However, the relatively greater impairments of memory and judgement with triazolam compared to pentobarbital, which were demonstrated in the human acute effects study, represent domains of concern that warrant future research.

Based on studies of baboon intravenous and oral drug self-administration, baboon drug discrimination, baboon physical dependence (substitution, precipitated withdrawal, and spontaneous withdrawal), and human drug self-administration, the abuse liability of triazolam appears to be quite comparable to that of diazepam, the prototypic benzodiazepine. Limited data from the human drug self-administration study suggest that memory impairment may be greater with triazolam than with diazepam and underscore the need for future research concerning this potential adverse effect of triazolam.

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Stimulant Depressant Report

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The research group that has been developing a program to assess the dependence potential of drugs with stimulant, hypnotic or anxiolytic. properties has been in existence for almost three years. This group includes investigators from The University of Chicago (UC: Johanson, Schuster), Medical College of Virginia (MCV: Harris, Patrick, Yutrzenka), Johns Hopkins University (JH: Brady, Griffiths, Ator, Lamb) and the National Institute of Health (NIH: Jacobson). This group has been guided and chaired by Jim Woods from the University of Michigan. The purpose of our activities has been to develop a set of experimental procedures in animals capable of classifying compounds in terms of their stimulant and depressant properties and more importantly to evaluate their dependence potential. The goal is to be able to compare a new compound that is suspected to have stimulant or depressant properties to prototypes (e.g. amphetamine, pentobarbital, diazepam). Before beginning to use these procedures with new drugs, it was felt necessary to first evaluate the capability of the selected procedures using known drugs. Drs. Woods and Jacobson selected 10 drugs representing a range of pharmacological classes to be tested in a blind fashion by the various laboratories using procedures that this group believed capable of predicting dependence potential as well as differentiating between drug classes.

This report is divided into two parts. In the first part, the procedures that were used are described and the results from 10 compounds that have been evaluated up to this time presented in summary form. In the second part of this report, the results that have been obtained are critically evaluated in terms of their predictiveness, reliability and validity.

I. PROCEDURES AND RESULTS

A. Overview of the Procedures

Each of the participating laboratories selected procedures which the entire group believed were useful in assessing the stimulant

and depressant properties of drugs and/or which were useful in evaluating dependence potential.

1. Inverted Screen Test (MCV): This procedure was used to determine whether compound had effects on muscular function that were depressant-like. The time course of a drug's actions and its potency relative to pentobarbital were determined. This potency comparison was useful for all the investigators for selecting the initial dose for further testing of individual compounds.

2. Locomotor Activity (MCV): This procedure is useful for measuring both increases and decreases in activity produced by stimulant and depressant drugs. As with the inverted screen test, both time course and potency relative to either pentobarbital or amphetamine can be determined.

3. Barbiturate Physical Dependence (MCV): This procedure is being developed to determine whether compounds can substitute for pentobarbital in supporting barbiturate physical dependence. It is analogous to the single dose suppression test used with opiates. While other methods exist, a new method was considered necessary that was relatively inexpensive (using rodents) and required a relatively brief period of drug exposure to develop dependence.

4. Food Intake (UC, JH): For stimulant-like drugs, a decrease in food intake provides an indication of their anorectic properties. In addition, both barbiturates and benzodiazepines increase food intake so this procedure can also be used with sedatives.

5. Drug Discrimination (UC, JH): Drug discrimination techniques provide a behavioral means of classifying unknown compounds in terms of their discriminative stimulus properties compared to any selected prototype. The discriminative stimulus properties of the unknown compounds were compared to a prototypic stimulant, amphetamine, a prototypic barbiturate, pentobarbital, and/or a benzodiazepine. Drug discrimination studies were conducted with four species (pigeon, rat, rhesus monkey and baboon) using a variety of routes of administration. In addition, both food-reinforced and shock avoidance procedures were used. Such systematic replication allowed a good opportunity to assess reliability.

6. Self-Administration (UC, JH): Although the results from the other procedures can indirectly evaluate dependence potential by comparing the spectrum of action of an unknown compound to those of prototypic drugs of abuse, the only direct measure attempting to predict the dependence potential of the unknown drugs were the self-administration procedures. To the extent that reinforcing properties are directly correlated to dependence potential (a validity issue), this type of study is essential.

B. Results

1. Benzodiazepines and Sedatives

Five of the test compounds were benzodiazepines or sedatives (diazepam, bromazepam, temazepam, halazepam, methaqualone). All five produced a positive effect on the inverted screen test and decreased locomotor activity. Diazepam (DZ), bromazepam (BR) and temazepam (TE) suppressed signs of barbiturate withdrawal, methaqualone (MQ) partially substituted and halazepam (HA) did not substitute, most likely due to solubility problems. DZ and BR were tested on food intake and increased the amount consumed. The effects of DZ and BR but not pentobarbital on food intake were antagonized by Ro 15-1788.

In general, the drug discrimination results with DZ, BR and TE were similar. All three compounds substituted for benzodiazepines regardless of species or laboratory and where tested also substituted for pentobarbital. The results with HA and MQ differed somewhat across laboratories. In rhesus monkeys, HA substituted for pentobarbital but this drug was not evaluated in other species trained to discriminate pentobarbital from vehicle. In pigeons, this drug substituted for oxazepam, only partially substituted for lorazepam in baboons and only substituted for lorazepam in rats trained with the lower dose. MQ substituted for pentobarbital in rhesus monkeys and rats but not in baboons. In animals trained to discriminate a benzodiazepine, there was only a tendency for MQ to substitute.

The self-administration results indicate that the abuse liability of MQ is high. This is based upon the fact that all monkeys self-administered the drug regardless of whether they were on a pentobarbital or cocaine baseline. A similar conclusion could be made for HA. In contrast, the remaining anxiolytics were only self-administered when substituted for pentobarbital but not when substituted for cocaine. The limited range of conditions under which these drugs are self-administered suggest that these drugs possess less dependence potential than pentobarbital or MQ.

2. Psychomotor Stimulants

Three of the compounds (mazindol, fenetylline and mefenorex) had stimulant properties but only mazindol (MZ) was tested in the inverted screen test, locomotor activity test and pentobarbital substitution test. This compound was not positive on the inverted screen test, increased locomotor activity and exacerbated pentobarbital withdrawal signs and weight loss. All three compounds decreased food intake but the effects were erratic with MZ.

Both mefenorex (MX) and MZ reliably substituted for amphetamine but only one in four pigeons or monkeys tested generalized to

amphetamine when given fenetylline (FE). Order of potency was MZ, FE and MX.

MZ was clearly able to maintain responding in all of the monkeys tested regardless of whether it was substituted for pentobarbital or cocaine. In some cases responding was very high and the effects observed were similar to those of amphetamine or cocaine. The potency of this compound was similar to amphetamine. FE and MX were clearly self-administered by only 2 of 5 monkeys tested, both of which were maintained on a pentobarbital baseline. Both of these compounds were less potent than amphetamine.

3. Antidepressants

Two of the compounds (bupropion and nortriptaline) were antidepressants. The results from the inverted screen, locomotor activity and barbiturate dependence tests indicated that nortriptaline (NT) had some depressant properties but they were not barbiturate-like. Bupropion (BU) had some stimulant properties but they were modest compared to amphetamine. BU had modest effects on food intake whereas NT had no effect. BU substituted for amphetamine in pigeons and rhesus monkeys and NT only substituted for amphetamine in 50% of the pigeons and one of the four monkeys tested. Neither of these drugs substituted for oxazepam in pigeons or lorazepam in rats. Finally, BU was clearly self-administered whereas NT was not.

II. PREDICTIVENESS OF THE RESULTS

In this part of the report, the results which have been reviewed are evaluated in terms of reliability and validity. More specifically, the following questions are addressed:

1. Are the results that were obtained on a blind basis from the participating laboratories similar to each other and to results obtained with the test compounds in previous experiments using the same or similar procedures?

2. Were the compounds correctly classified in terms of their stimulant and depressant properties? A related validity question is whether the dependence potential of each of the compounds would have been correctly predicted? This question can only be partially answered. First of all, the prediction is restricted to dependence potential. Many factors (e.g. availability, side effects, availability of alternative drugs) influence actual abuse and their influence is difficult to assess. Second, our information concerning actual abuse is fragmentary and for some of the compounds little information is available.

Physical Dependence: Five of the compounds (DZ, BR, TE, MQ, BU) substituted to some degree for pentobarbital in suppressing overt signs and weight loss. DZ, BR and TE substituted most completely. These results are consistent with other studies

demonstrating that DZ at least partially substitutes for pentobarbital in rats (Martin et al. 1982), phenobarbital in rats (Tagashira et al. 1983), and barbital in rhesus monkeys (Yanagita and Takahashi, 1973). Precipitated withdrawal has also been recently demonstrated in baboons exposed to chronic BR. While TE also produced barbiturate-like physical dependence in these studies, additional studies are not available for comparison. MQ also substituted for pentobarbital although the substitution was not complete. In contrast, Jones et al. (1976) showed complete substitution for pentobarbital with MQ in the dog. Likewise, Tagashira et al. (1983) showed that MQ almost completely substituted for phenobarbital in rats. The other drug that partially suppressed pentobarbital withdrawal was BU. However, additional observations of the rats indicated that this suppression was due to motor impairment.

Two of the compounds tested, NT and HA, did not suppress pentobarbital withdrawal. This is not surprising for the antidepressant but the HA results are somewhat puzzling. However, since other studies on physical dependence with HA are not available, additional. studies seem required. The last compound tested in this procedure was MZ, which exacerbated pentobarbital withdrawal.

In summary, the results with the barbiturate physical dependence procedure seem to accurately predict the compounds that are capable of producing physical dependence.

Drug Discrimination: Many of the test compounds were tested in drug discrimination paradigms in several species, a form of systematic replication. In general, all five sedative compounds substituted for a depressant. The results were somewhat different across laboratories for HA. MQ clearly substituted for pentobarbital in rhesus monkeys and rats but not in baboons. MQ showed partial or no substitution in benzodiazepine-trained animals (pigeons trained on midazolam, rats and baboons trained on lorazepam). Despite some difference, in general the results across laboratories replicate well. In addition, the results correspond to those obtained by other investigators. For instance, several studies have shown that DZ substitutes for other anxiolytics and pentobarbital (Colpaert et al. 1976; Winger and Herling 1982) as a discriminative stimulus, BR has been shown to substitute for other benzodiazepines in rats (Colpaert et al. 1976; Shannon and Herling, 1983).

The remaining five compounds (MZ, FE, MX, BU, NT) were all tested in both pigeons and rhesus monkeys trained to discriminate d-amphetamine from saline. Despite differences in procedures, MZ, MX and BU reliably substituted for amphetamine in both species. In both species FE and NT showed only partial substitution. MZ was the most potent, FE was next, MX and NT were similar in potency and BU was the least potent. To my knowledge, MZ, FE and MX have not been tested in previous drug

discrimination studies. BU has been shown to function as a discriminative stimulus in rats and when amphetamine was substituted, it occasioned BU-lever responding (Jones et al. 1980). Jones et al. (1980) also tested several tricyclic antidepressants in m-trained rats. While in general, none of these compounds (imipramine, amitriptyline and desipramine) substituted, NT did substitute for bupropion in about 50% of the animals tested. This suggests that NT has some amphetamine-like stimulant properties.

In summary, the results of the drug discrimination studies demonstrate the reliability of the results obtained when benzodiazepines, sedatives, stimulants and antidepressants were tested. The results across species, procedures and laboratories correspond well. In addition, when data are available from previous studies, the results appear similar.

In addition to these results being reliable, the drug discrimination results correctly identified the unknown compounds in terms of their stimulant and depressant properties. Bearing in mind that the compounds tested in the present studies were unknown, drugs known to possess sedative properties, namely DZ, BR, TE, HA and MQ, were generally classified as having discriminative stimulus properties like sedatives. On the other hand, none of these compounds generalized to amphetamine, indicating drug class specificity. Drugs such as MZ and BU, which are known to possess psychomotor stimulant properties, were also correctly classified. That is, they reliably substituted for drug in amphetamine-trained animals but not in sedative-trained animals. While little is known about FE and MX, both of these drugs are metabolized to some extent into amphetamine-like compounds. While the degree of their stimulant effects may differ (FE only partially substituted), neither of these drugs substituted in sedative-trained animals.

Self-administration: MQ and HA were self-administered in rhesus monkeys regardless of whether they were substituted for pentobarbital or cocaine. In previous studies, MQ has been shown to be a robust reinforcer (Woods, CPDD report; Brady et al. 1975). HA, however, has not been shown to be a robust reinforcer in other studies. For instance, Yanagita (1983) showed that HA was not self-administered intragastrically. The JH group has also tested HA in baboons under non-blind conditions and found only modest rates of self-administration.

In rhesus monkeys and baboons, the remaining anxiolytics (DZ, BR, TE) were only self-administered when substituted for pentobarbital (UC) and not cocaine (UC, JH).

The remaining compounds were only tested in self-administration studies in the rhesus monkey. However, MZ had previously been tested both at Chicago and Hopkins and found to maintain responding when substituted for cocaine (Woolverton et al. in

press; Brady, p.c.). BU has also been shown to function as a positive reinforcer in previous studies (J.H.Woods). While NT itself has not been evaluated in self-administration studies, related antidepressants have not been shown to maintain responding (Johanson and Balster, 1978).

In summary, the self-administration data, while not as extensive, also appear to replicate across laboratories and species, and the results obtained, with the possible exception of halazepam, correspond well to published results.

Based upon the self-administration results, the tested drugs can be grouped into three categories in terms of dependence potential. The most robust reinforcing properties were seen with MQ, HA, MZ and BU. MQ is a well-known drug of abuse so these results are not surprising. Since BU or related drugs (nomifensine) are new drugs, it is not possible to compare the predictions to their abuse patterns. The results with HA and MZ are difficult to assess. Despite mazindol's known psychomotor stimulant properties this drug does not appear to be abused. However, the results from the present studies are not aberrant since previous studies have shown similar self-administration results. In human self-administration studies using the oral route, MZ was not self-administered (Chait et al. 1985). On the other hand, in human drug discrimination studies, MZ substituted for amphetamine (Schuster and Johanson, 1985). While this drug may have potential for abuse, other factors, e.g., an unpleasant side effect and the availability of similar stimulant drugs without this side effect, may alter that potential. The results with HA are more difficult to explain. In previous self-administration studies, this compound has not been shown to be a robust reinforcer. The self-administration results seen in rhesus monkeys in the present study demand further investigation.

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REFERENCES

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A Theory on the Nature of Physiologic Opiate Dependence: A Formal Statement

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INTRODUCTION

In a preliminary communication, we reported that in opiate-dependent preparations opiate antagonists have distinct dual actions and distinct dual receptor systems that correspond to their two main specific effects: 1) the cancellation of opiate neurodepression, and 2) the precipitation of abstinence (Villarreal et al. 1985). The receptor systems identified as dual are so not because their receptor sites have necessarily different recognition structures for ligands but because they are coupled to their respective effector mechanisms in the neuron through very different coupling systems. One of the two receptor systems operates in what may be called an "occupation" mode of drug-receptor interaction because its behavior shows the features that characterize systems described by "occupation theories" of drug action. The cancellation of opiate neurodepression is mediated by a receptor system that operates in occupation mode, by a system designated as O-coupled (Fig. 1). The other receptor system operates in what may be tailed a "rate" mode of drug-receptor interaction because its behavior shows the features that characterize systems described by "rate theories" of drug action. Opiate abstinence is mediated by a receptor system that operates in rate mode, by a system designated as R-coupled (Fig. 2).

The two receptor systems differ markedly with regard to their involvement in the process of opiate dependence. The O-coupled system of opiate neurodepression does not participate in the genesis of the abstinence response nor does it appear to participate with an immediate controlling role in the process of dependence itself. When the O-coupled system is separately manipulated by slow infusions of antagonists, what is obtained is simply the cancellation of opiate neurodepression, at the same concentrations of antagonist that are required to cancel neurodepression in non-dependent preparations. Afterwards, further slow additions of antagonists are totally devoid of further effects and abstinence as a possible rebound from neurodepression does not at all arise.

Abstinence was shown to result, instead, from the operation of a different receptor system, a system that operates in rate mode, a system that appears to show activation not in proportion to the number of receptors occupied but in proportion to the rate at which new occupation contacts are made between antagonist

molecules and receptors and in proportion to the duration of the excitatory microevents that the onsets of such antagonist-receptor contacts precipitate.

The R-coupled system undergoes a marked hypertrophy as a consequence of sustained exposure to dependence-producing opiates. The hypertrophy of the R-coupled system that mediates abstinence is manifested in the three most basic defining phenomenologic characteristics of opiate dependence: 1) the emergence of the capacity of the organism that becomes opiatedependent to respond with opiate abstinence syndromes; 2) the progressive increase in severity and duration of the abstinence syndromes that can be precipitated by antagonists in the progressive course of dependence; 3) the progressive sensitization to precipitation of abstinence by progressively lower doses of antagonists.

In short, opiate dependence was found to consist in a selective hypertrophy of the rate-coupled opiate receptor system that mediates abstinence. The purpose of the present paper is to examine the nature of this hypertrophy, and in so doing to present a concise statement of the theory of opiate dependence that the above findings have caused.

The evidence indicates that macroscopic opiate abstinence is an effect produced by the summation of small localized neuronal excitatory microevents designated as Elementary Abstinence Events (EAEs) which are transient, additive, and non-propagated and which are triggered by the onset of antagonist occupation of its receptors in the rate-coupled opiate receptor system. Opiate abstinence is produced not when some absolute number of receptors are occupied by antagonist. Opiate abstinence is produced when the EAEs are triggered at a sufficiently high rate to undergo temporal summation within the opiate-dependent neuron and thus attain neuronal threshold levels for the firing of fully propagated action potentials. Two types of factors can contribute to make the rate of EAE production sufficiently high to attain suprathreshold firing levels: 1) factors leading to a high rate of new chemical associations between antagonist molecules and their receptors, and 2) a sufficiently long duration of the EAEs to allow the temporal overlap necessary for the attainment of their suprathreshold summation at whatever rate of new chemical associations between antagonists and receptors is prevailing. Factors that will determine the rate of new chemical occupations of receptors are: 1) the dose of antagonist; 2) the chemical association rate constant between antagonists and their receptors; 3) the rate at which receptors previously occupied by antagonist molecules become free and thus available for new contacts with antagonist molecules; i.e., the chemical dissociation constant of the antagonist; 4) when the antagonist is given in a slow infusion, the rate at which the concentration of antagonist increases in the medium.

Several independent items of evidence imply that the key changing variable in dependence is the duration of the EAEs, that the hypertrophy of the R-coupled system resides in an increased half-life of the excitatory microevents triggered by the onset of antagonist occupation of its receptors.

The abstinence syndromes that result from the simple withdrawal of opiate administration in opiate-dependent organisms are presumed to result from the operation of a mechanism entirely analogous to that mediating antagonist-precipitated

abstinence. However, since the rate of change of receptor status must be much slower in opiate withdrawal than in antagonist-precipitated abstinence, the EAEs of the opiate-dependent neuron need to be correspondingly much longer for abstinence responses to be produced by simple opiate withdrawal.

Opiate dependence can now be understood as an opiate-induced increase in the average duration (half life) of the local non-propagated microevents designated as Elementary Abstinence Events. Further, it will be seen that the relative increase in EAE half-life which is the new defining feature of opiate dependence can be experimentally measured through the dose-ratio of concentrations of antagonist required to precipitate equal abstinence responses under conditions of different levels of dependence.

METHODS

We used the preparation for early opiate dependence *in vitro* in the isolated guinea pig ileum (Villarreal et al. 1977). Segments of ileum from guinea pigs receiving chronic morphine *in vivo* were also employed.

Additionally, we studied computer-produced solutions of conventional differential equations of drug-receptor kinetics (Gosselin 1977) applied to the opiate abstinence response. Analytic integrations and the techniques called "numerical methods" were used.

RESULTS

The basic findings in the opiatedependent guinea pig ileum have been summarized before (Villarreal et al. 1985). Here we will deal mainly with the abstinence response, with the R-coupled opiate receptor system. The abstinence response is characterized by the following features that may be said to typify rate-coupled modes of responding (Fig. 2): 1) the abstinence response is transient and fades away despite the continued presence of antagonist; 2) the response and its magnitude are conditioned by the rate at which the antagonist is administered, so that the abstinence response will become smaller and may even disappear altogether when antagonists are added at sufficiently slow rates; 3) successive administrations of one or more opiate antagonists produce either self-blockade or specific cross-blockade among antagonists for the response of precipitated abstinence.

The experimental evidence that macroscopic abstinence results from the summation of small subthreshold excitatory Elementary Abstinence Events comes from two sources; 1) the marked sensitivity of the abstinence response to the rate of antagonist administration coupled with the fact of specific self-and cross-blockade of the abstinence-precipitating effects of opiate antagonists, specially when these facts are examined in terms of their implications in the model of drug-receptor interaction that figure 2 presents; 2) reproduction at the macroscopic level of what is thought to occur at the molecular level by giving opiate-dependent segments of ileum series of multiple antagonist administrations in doses low enough to fail individually to produce observable responses. These series of administration add up and precipitate abstinence only if the intervals bet-

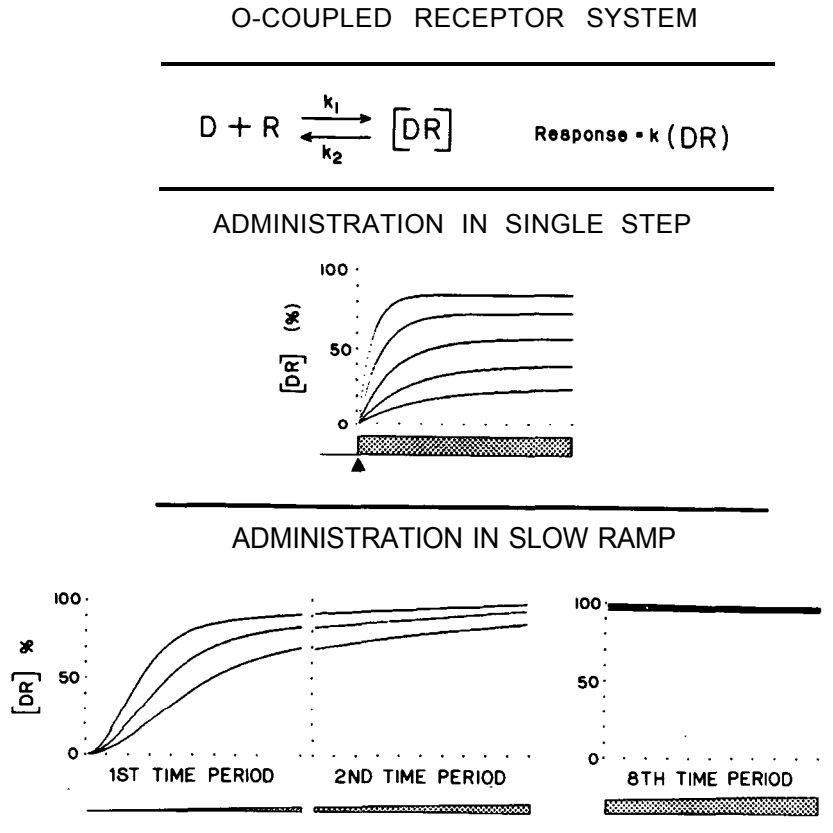

FIGURE 1. Computer-produced simulations of pharmacologic responses of an occupation eoupled receptor system. Note that the maximum effect of each dose is achieved monotonically and persists as long as the drug is present, and that the same maximum is reached regardless of the rate of drug administration. The shade area represents the drug administered.

ween the doses are sufficiently short; otherwise, the antagonists thus administered only block abstinence. As dependence is made to develop further, abstinence responses can be produced by the summation of the effects of smaller doses of antagonists given at longer intervals or by slower infusions of these compounds. This evidence provides very strong support for the view that the key changing variable in opiate dependence is an increased duration of the EAEs.

The R-coupled abstinence response showed an increase in sensitivity to naloxone of about 300-fold when comparing preparations exposed to morphine for only one hour with those obtained from animals treated with morphine around the clock for three days. This finding also requires the proposition of increased duration of the EAE since there are no changes in the chemical affinity of receptors for antagonists in opiate dependence (see below).

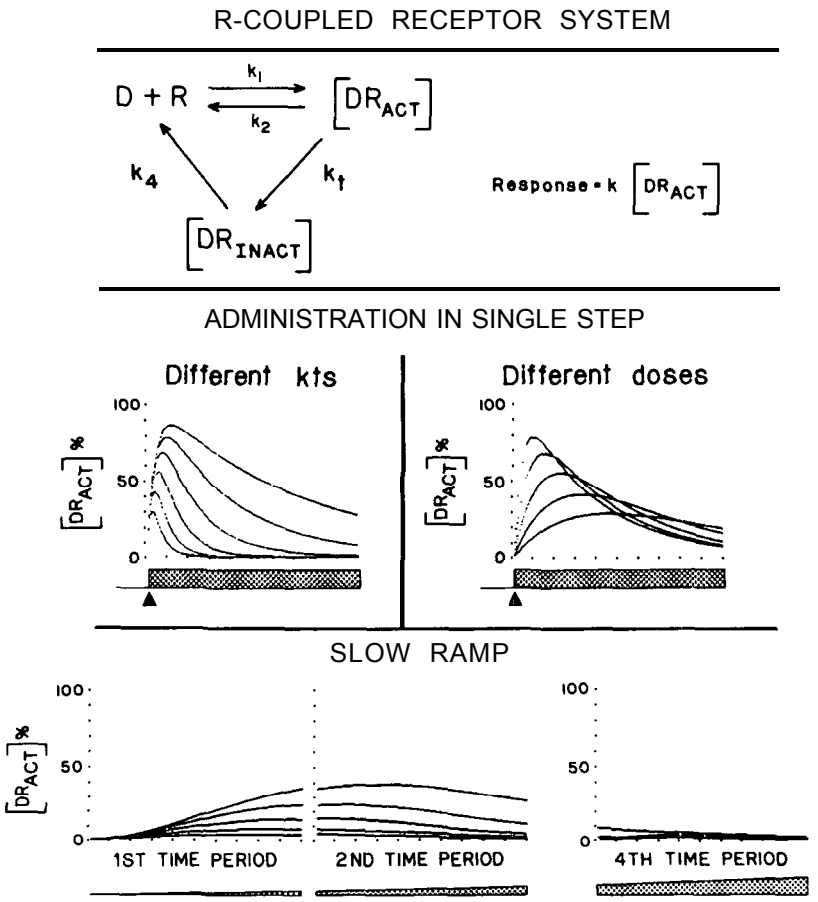

FIGURE 2. Computer-produced simulations of pharmacologic responses of a rate-coupled receptor system. Note that the maximum effect quickly fades away, and that the magnitude of the drug effect depends critically on the rate of drug administration. In the example shown, the rate of chemical dissociation between drug and receptor is much slower than the rate for association.

The response of antagonist-precipitated abstinence was simulated mathematically with the system of differential equations employed by Gosselin (1977) for drug-receptor systems operating in what is here designated as rate mode. Complete series of simulated responses to different numerical values of the dose parameter were produced under each tested set of conditions of the system. Dose-response curves were then obtained where the response taken was the peak quantity of receptors in the active state generated by each dose, the peak number of DRact of Fig. 2.

The overall morphology of all the types of experimental responses obtained in the ileum was reproduced by the mathematical behavior of the system of differential equations of the rate-coupled system. When the half-life of the EAEs was systematically prolonged, by introducing reductions in the rate of decay (kt) of the receptors in the active state, the simulated abstinence response to any given dose increased correspondingly in magnitude and duration up to a maximum, and there was a parallel increase in sensitivity to the abstinence-precipitating actions of progressively lower doses of antagonists. The simulated increase in EAE duration also reproduced the changes in response to multiple administrations and slow infusions of antagonists that are observed experimentally with the progression of dependence. In addition, dose-response curves for the simulated antagonist-precipitated abstinence responses obtained for conditions under which the duration of the EAEs was systematically increased showed increased sensitivity to antagonists in the form of parallel shifts to the left in the position of the dose-response curves for precipitated abstinence. It must be noted that this increased sensitivity was produced by the sole increase in EAE duration without modification either in the chemical affinity or in the number of receptors for antagonists. The effective dose 50 for precipitation of abstinence was found to be a linear function of the decay rate constant of the active state (the kt of Fig. 2), except in the extreme condition when the duration of the EAEs approaches that of the chemical occupation of receptor by antagonist and the behavior of the system approaches the behavior of occupation-coupled systems. The relative change in half-life of the EAEs can be algebraically derived from the change in the estimated relative kt. Therefore, the relative increases in EAE half-life can be measured through the dose-ratio (i.e., the proportion of change in dose) of antagonist required to precipitate equal abstinence responses for different levels of dependence.

DISCUSSION

Opiate dependence is the hypertrophy of the rate-coupled receptor system whose operation produces opiate abstinence. The hypertrophy is selective to the R-coupled opiate receptor system because opiate dependent neurons and organisms are highly supersensitive at all times only to the abstinence-precipitating effects of opiate antagonists (Villarreal and Castro 1978; Herz et al. 1978a).

Let us turn to an analysis of the site of such hypertrophy. Rate-coupled receptor systems consist of at least 3 components or 3 states of the receptor (Fig 2): free receptors, occupied active receptors, and occupied but inactive receptors. These components are linked by the rate constants for their chemical association (k1) and dissociation (k2 and K4) with antagonists and by the rate constant for the decay of the active state (kt) of the active receptors.. There is solid experimental evidence that in opiate dependence there is no increase in the number of receptors that bind opiate antagonists nor an increase in receptor chemical affinity for these drugs (Herz et al. 1978b and other work cited therein). Therefore, the hypertrophy of the R-coupled opiate receptor system that constitutes opiate dependence must consist in a magnification of the excitatory microevents (the EAEs) triggered by the onsets of the contacts of antagonist with its receptor. The evidence already available strongly indicates that such magnification of EAEs

has to involve increases in their duration. In conclusion, the most distinctive classical features of opiate dependence have been briefly summarized. A complete formal theory of physiologic opiate dependence is described with propositions that are both necessary and sufficient to account for all the experimental features of opiate dependence reviewed.

REFERENCES

Gosselin, R.E. Drug-receptor inactivation: A new kinetic model. In: van Rossum, J.M., ed. Handbook of Experimental Pharmacology. Vol. 47. Kinetics of Drug Action. New York: Springer-Verlag. 1977.

Herz, A.; Schulz, R.; Bläsig, J. Changes in neuronal sensitivity in opiate tolerance/dependence. In: Beers, R.F., and Bassett, E.G., eds. Mechanisms of Pain and Analgesic Compounds. Eleventh Miles International Symposium. New York: Raven Press. 1978a. pp. 383-397.

Herz, A.; Bläsig, J.; Fry, J.P.; Höllt, V.; Meyer, G.; and Przewlocki, R. Opiate receptors, their endogenous ligands and the development of tolerance/dependence. In: Boissier, J.R.; Lechat, P.; and Fichelle, J., eds. Advances in Pharmacology and Therapeutics: Jacob, J. ed. Receptors. Paris: IUPHAR. 1978b. pp. 47-56.

Villarreal, J.E., and Castro, A. A reformulation of the dual-action model of opioid dependence: Opioid-specific neuronal kindling. In: Beers, R.F., and Bassett, E.G., eds. Mechanisms of Pain and Analgesic Compounds. Eleventh Miles International Symposium. New York: Raven Press, 1978. pp. 407-428.

Villarreal, J.E.; Martinez, J.N.; and Castro, A. Validation of a new procedure to study narcotic dependence in the isolated quinea pig ileum. In: Report of the 39th Meeting of the Committee on Problems of Drug Dependence. Washington, 1977, pp, 305-314.

Villarreal, J.E.; Herrera, J.E.; and Salazar, L.A. The nature of opiate dependence. Proc West Pharmacol Soc 28:43-46, 1985.

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Endogenous Opioid Modulation of Luteinizing Hormone, Prolactin, and Estradiol in Women: Interactions with Ethanol

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In 1976, we reported that administration of the opiate antagonist, naltrexone, increased luteinizing hormone (LN) (mean plasma and pulse frequency) levels in abstinent heroin-dependent men (Mirin et al. 1976). Naltrexone-induced stimulation of plasma LH in normal men was subsequently reported by our laboratory (Mendelson et al. 1979). These data were consistent with observations of opiate antagonist stimulation of plasma LH in experimental animals (Bruni et al. 1977).

Administration of opiate antagonists also stimulates increased levels of plasma LH in women (Quigley and Yen 1980). The LH response to opiate antagonist stimulation appears to be dependent upon menstrual cycle phase (Ropert et al. 1981; Grossman et al. 1981; Blankstein et al. 1981) and is probably related to the influence of ovarian steroid hormone modulation of secretion of luteinizing hormone releasing hormone (LHRH) from the hypothalamus. Opioid antagonists have been shown to stimulate gonadotropin releasing hormone (GnRH) from human hypothalamic tissue in vitro (Rasmussen et al. 1983) and these data support the hypothesis that opioid antagonist stimulation of gonadotropins in intact men and women is a consequence of the drug effect at a hypothalamic site of action. The purpose of this study was to determine if alcohol attenuated naloxone-induced stimulation of pituitary and gonadal hormones in women. Although there have been numerous reports of adverse effects of chronic ethanol abuse on reproductive function in women (Hugues et al. 1980; Moskovic 1975; Valimaki and Ylikahri 1981), the site of alcohol's disruptive effects remains to be determined. This report is one of a series of studies designed to determine if alcohol disrupts hormonal secretion activity at the level of the hypothalamus, the pituitary, the ovary, or at all three sites in combination.

METHODS

Four healthy adult women with a mean age of 28.6 years (range 24 to 34 years) provided informed consent for participation in this study. All subjects had normal physical and mental status examinations as well as normal blood chemistry, hemogram and urinalysis studies. Subjects were not pregnant and none had any past history

of substance abuse or dependence. Each subject served as her own control in studies designed to assess the effects of acute alcohol administration on naloxone-induced stimulation of pituitary and gonadal hormones. All studies were carried out during the mid-luteal phase of the menstrual cycle. Menstrual cycle phase was determined by use of daily diary questionnaires and confirmed by plasma progesterone level determinations. Subjects were studied on two separate occasions, two days apart. The mean progesterone level for each study day was 14 + 1.2 (S.E.) ng/ml. Studies were carried out with a counterbalanced order of ethanol or placebo administration under double blind conditions. Two subjects received ethanol on the first study day and two subjects received placebo on the first study day. Subjects reported to the research facility at approximately 10:00 a.m. on each day following a 12-h fast. On arrival at the laboratory, subjects voided and a urine screen was forwarded for drug screen analysis. No positive drug screens were reported for any subjects. An intravenous catheter was inserted into the subjects' antecubital vein and connected to a slow infusion of 0.9% saline. During the study, subjects remained recumbent and could watch television or read magazines or books. They were not permitted to smoke or consume food but they could drink caffeine-free noncarbonated beverages or fruit juice. Baseline blood samples were collected every 30 min for 2-h. At 0 time, 5 mg of naloxone diluted in 8.6 ml of saline was administered intravenously at the rate of 1 ml/min. At 0 time, the subjects also began drinking either ethanol or ethanol placebo. The ethanol solution consisted of 2 ml of 43% alcohol per kg of body weight to which fruit juice was added for a total volume of 10 oz. This ethanol placebo consisted of 10 oz of fruit juice plus 10 ml of alcohol "floated" on the surface of the fruit juice. Subjects consumed the ethanol solution or the placebo within 15 min following initiation of drinking. Blood samples were collected at 15,20, 25,30,45,60,90,120,150, and 180 min following concurrent naloxone administration and initiation of drinking. Blood plasma samples were frozen at -70° C for subsequent analysis of luteinizing hormone, prolactin, and estradiol.

RESULTS

Figure 1 shows plasma LH levels in 4 women prior to and following naloxone plus ethanol or naloxone plus ethanol placebo administration at 0 time. Naloxone administration was followed by a prompt increase in LH levels ranging from 100 to 400% of baseline values ($p < .001$). All subjects showed at least 1 LH surge after naloxone administration and concurrent ingestion of placebo or alcohol. Two distinct LH surges following naloxone administration were measured in 2 women who received alcohol (right panel, fig. 1).

Figure 2 shows plasma prolactin levels prior to and following naloxone administration and concurrent ethanol or placebo intake. A prompt and significant increase in plasma prolactin levels ($p < .001$) was observed for all subjects following naloxone administration. The naloxone-induced stimulation of prolactin was remarkably concordant with the LH response. Two subjects (left panel fig. 2) had one prolactin surge whereas 2 subjects (right panel,

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FIGURE 1

PLASMA LH

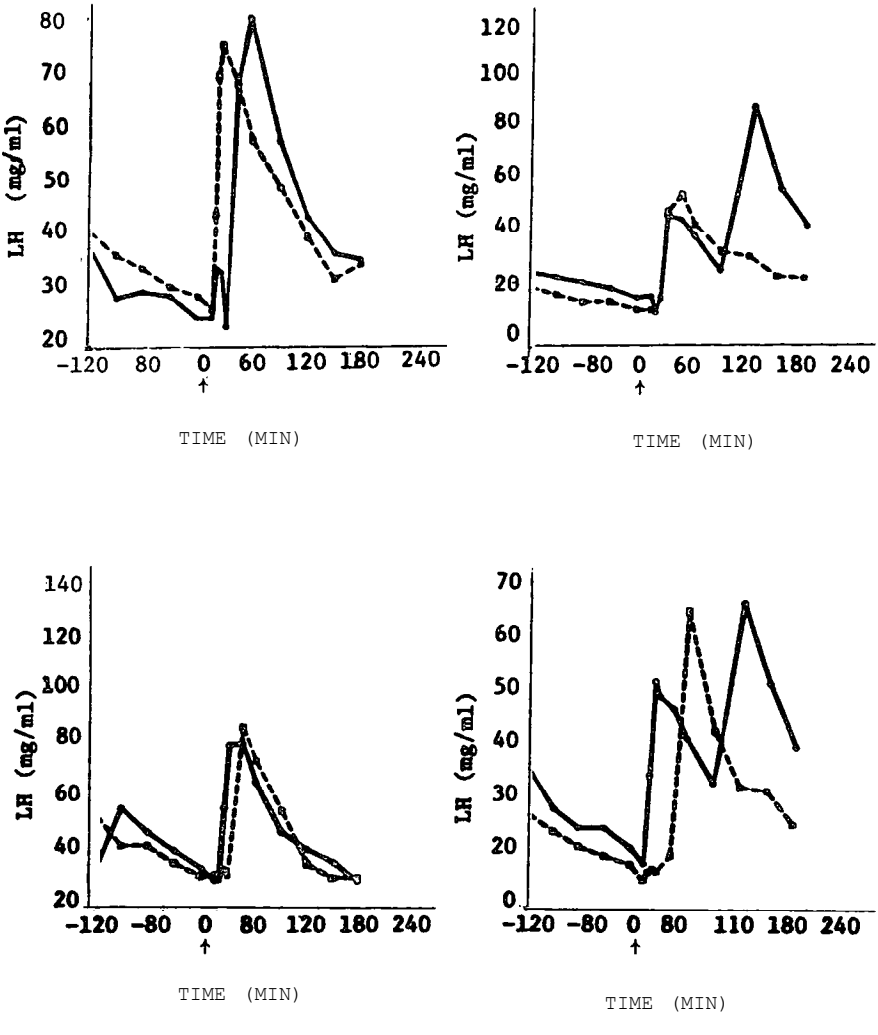


FIGURE 2

PLASMA PROLACTIN

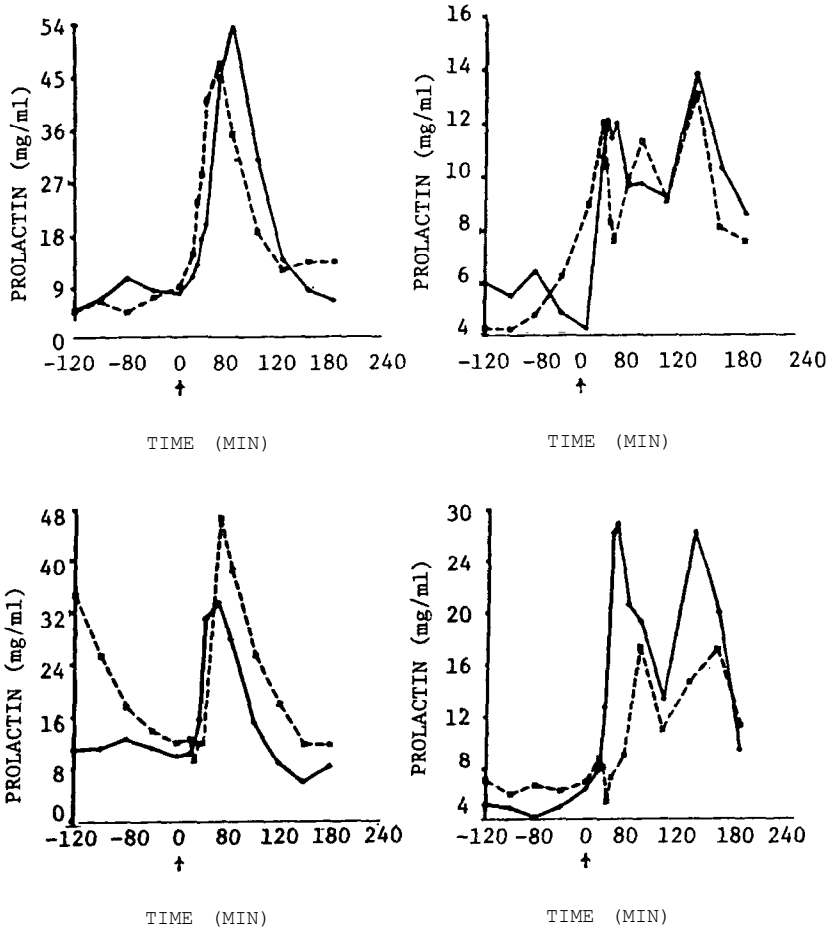


fig. 2) had a multiple pulse prolactin surge profile. Alcohol administration had no consistent effect on naloxone-stimulated plasma prolactin levels.

Figure 3 shows plasma estradiol levels prior to and following naloxone administration and concurrent placebo or ethanol intake. A significant increase ($p < .001$) in plasma estradiol levels following concurrent naloxone administration and alcohol was measured in all 4 subjects. However, no consistent changes in estradiol levels were observed following naloxone plus placebo.

DISCUSSION

The naloxone-induced stimulation of plasma LH levels found in this study (fig. 1) are consistent with other reports of significant opioid antagonist stimulation of LH during the midluteal phase of the menstrual cycle in normal women. Our observation of naloxone-induced stimulation of plasma prolactin levels is also consistent with recent reports of opiate antagonist stimulation of prolactin in women during the midluteal phase of the menstrual cycle (Snowden et al. 1984).

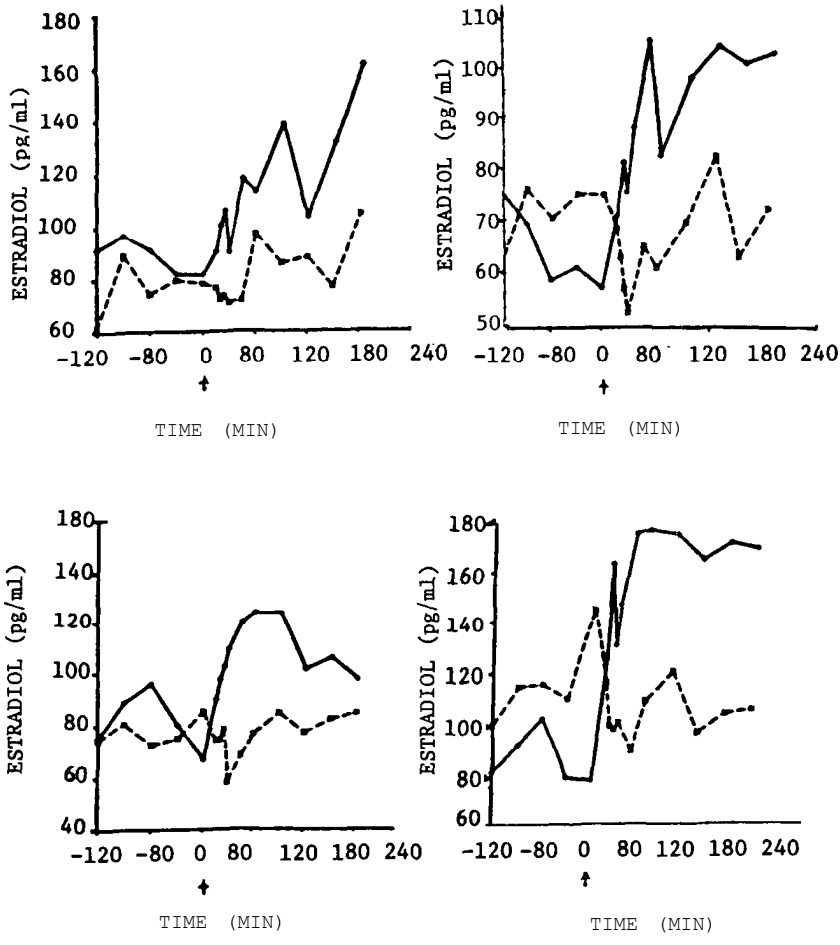
Our observations that alcohol caused a significant increment in plasma estradiol levels following naloxone administration was surprising. Acute administration of ethanol alone in doses analogous to those employed in this study did not produce any significant changes in plasma estradiol levels in either women or female rhesus monkeys studied during the follicular or midluteal phase of the menstrual cycle (Mello et al. 1983; Mendelson et al. 1981; Valimaki et al. 1983). We have been unable to locate any reports of opiate antagonist effects on plasma estradiol levels in female experimental animals or women. However, previous studies have shown that a single dose of synthetic GnRH sufficient to stimulate an eight to tenfold increase in plasma LH levels did not induce enhanced ovarian secretion of estradiol in normal women studied during the follicular phase of the menstrual cycle (Kletzky et al. 1982). Plasma estradiol levels rapidly increased following naloxone perturbation of LH and concurrent ethanol intake, a phenomena which suggests an increase in estradiol production rather than a decrease in estradiol clearance.

It is known that alcohol may affect enzyme systems which regulate steroid hormone synthesis and metabolism. However, studies which have demonstrated an alcohol effect on pyrimidine nucleotide cofactors (Veech et al. 1972; Ellingboe and Varanelli 1979), 5 alpha-A-ring reductase (Rubin et al. 1976; Gordon et al. 1976), aromatase (Gordon et al. 1979), cytochrome P 450 (Ishii et al. 1973), and 17-β hydroxy-steroid oxidoreductase (Cicero and Bell 1980) were all carried out with male experimental animals.

The possibility that gender differences may be of great importance for ethanol effects on gonadal steroids is highlighted by data reported in studies with gonadotropin receptors. Male rats administered ethanol in dosage of 3.6 gm/kg for 7 days had a 35% decrease

FIGURE 3

PLASMA ESTRADIOL



in testicular gonadotropin receptor concentration (Bhalla et al. 1979). In contrast, ethanol treatment of female simian luteal membranes in vitro caused an increase in LH recoptors (Cameron and Stouffer 1982). However, it would be difficult to explain the rapid increase in estradiol levels following concurrent naloxone and ethanol administration in this study as a consequence of rapid receptor induction produced by a single acute dose of alcohol. Further studies are clearly necessary to explain the processes underlying ethanol-related stimulation of plasma estradiol levels following naloxone perturbation of LH in women.

ACKNOWLEDGMENTS

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REFERENCES

References are available from Jack H. Mendelson, M.D., at the address listed below.

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Discriminative and Aversive Stimulus Effects of *b*-Carboline Ethyl Ester in Rhesus Monkeys

Kohji Takada, Gail D. Winger, J. Cook, P. Larscheid, and James H. Woods

β-Carboline-3-carboxylic acid ethyl ester (BCCE) binds exclusively to brain benzodiazepine receptors with high affinity, reverses the effects of benzodiazepines,and in contrast to the more recently developed benzodiazepine antagonists (e.g. Ro15-1788), has actions of its own which are in many instances opposite to those of anxiolytic benzodiazepines. For example, when given intravenously to rhesus monkeys, BCCE has been reported to produce apparant anxiety-like effects which were prevented by the administration of Ro15-1788 (Ninan et al., 1982). Studies in man showed that FG7142, the ethylamide congener of BCCE, induced panic anxiety (Dorowet al., 1983) These characteristics of BCCE and related compounds have led to a novel classification of drugs that act on benzodiazepine receptors and delineate a new functional aspect of the benzodiaze receptor complex, which may mediate and/or modulate some aspects of anxiety (for recent reviews, see Biggio and Costa, 1983, Richards and Mohler, 1984, and Braestrup et al., 1984).

The purpose of the present experiments was to determine whether the behavioral effects of BCCE in the rhesus monkeys are consistent with the conceptualization of this drugs as an inverse agonist at the benzodiazepine receptor. That is, does BCCE produce effects that are distinct and opposite from those of the anxiolytic benzodiazepines, and does it do so by acting at the same receptor?

METHODS

Discriminative Stimulus Effects Four rhesus monkeys were trained to disriminate 1 mg/kg BCCE from vehicle. The monkeys were trained to make thirty consecutive responses (FR30) on the rightmost of the two levers and receive a 300 mg Noyes banana-flavored pellet if they had received 1 mg/kg BCCE, 30 min earlier. If the injection had been a vehicle, responses on the leftmost lever were reinforced on the same schedule. A daily session lasted for 20 min or until 50 food pellets had been delivered. During test sessions, the FR30 response requirement could be met on either of the two levers. A separate group of four monkeys was trained to discriminate the effects of 10 mg/kg methohexital, an untra-short acting barbiturate, under a

multiple-trial procedure which has been described elsewhere (Bertalmio et al., 1982).

Reinforcing Effects To evaluate negatively reinforcing effects, three rhesus monkeys were prepared with intravenous catheters. During two daily sessions separated at least three hours, they were trained firsttopress a lever in the presence of a stimulus light andreceive intravenous infusions of cocaine, then to press the lever and turn off infusions of 7 ug/kg/sec histamine. A single response was necessary to terminate the infusion for two of the monkeys while five responses wererequired for the third monkey. Twenty infusions were initiated during each session. An unterminated infusion lasted for 15 sec; terminated and unterminated Infusions were followed by a five-min light-off period. During particular sessions, saline, the hydrochloride salt of BCCE, or midazolam was infused instead of histamine.

A separate group of monkeys in the same experimental setting were trained to respond to receive intravenous injections of methohexital under a previously described procedure (Woods, 1980). The capacity of midazolam to maintain self-injection responding was observed in these monkeys.

Drugs BCCE and Ro15-1788 were suspended in Emulphor, 95% ethanol, an water in a ratio of 1:1:8. Doses are expressed as the free base. Midazolam maleate was dissolved in water with a few drops of lactic acid added. Methohexital and the hydrochloride salt of BCCE were dissolved in water. The doses of these drugs are expressed as the salts. All drugs were administered subcutaneously in the study on the discriminative stimulus effects.

RESULTS

Discriminative Effects The effects of BCCE and midazolam, and these drugs in combination with Rol5-1788 in monkeys trained to dicriminate the effects of either BCCE(BCCE-trained monkeys) or methohexital (MIX-trainedmonkeys), respectively, are shown in Fig. 1. BCCE produced dose-related increases in drug-appropriate responding in the BCCE-trained monkeys, but not in the MTX-trained monkeys. In contrast, the short-acting benzodiazepine midazolam produced drug-appropriate responding in the MTX-trained monkeys but not in the BCCE-trained monkeys.

Midazolam (0.32 mg/kg, given 10 min before the session) completely prevented the effects of 1 mg/kg BCCE in two BCCE-trained monkeys tested (not shown). Ro15-1788 (1 mg/kg, given 10 min before the session) competitively antagonized both the effects of BCCE in BCCE-trained monkeys and those of midazolam in MTX-trained monkeys (Fig. 1, left and right panels).

Ro15-1788 produced dose-related increases in drug-appropriate responding in BCCE-trained monkeys at doses higher than the dose which antagonized the effects of BCCE (Fig. 2).

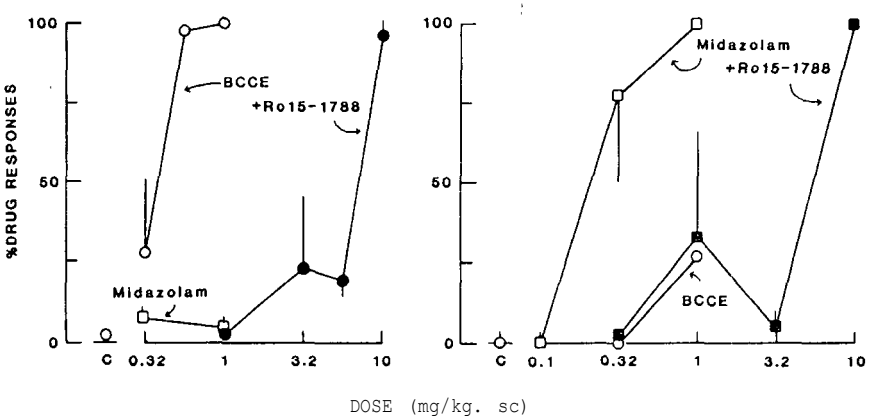

Fig. 1 Effects of BCCE (0) and midaszolam(□) in monkeys trained to discriminate either BCCE (left panel) or methohexital (right panel). The effects of Ro15-1788 in combination with BCCE (●) and midazolam (■) are also shown. Points at "C" represent the values after the control injections. Abscissae: dose in mg/kg, log scale. Ordinates: percent drug-appropriate responding. The vertical line at each point represent + S.E.

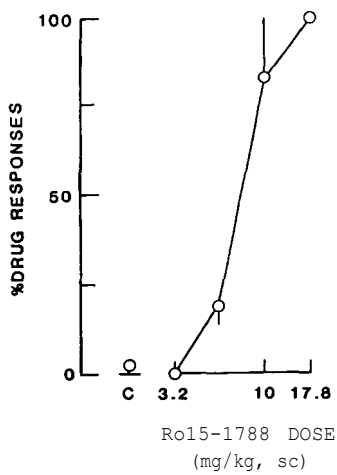

Fig. 2 Effects of Ro15-1788 given 30 min before the session in monkeys trained to discriminate BCCE. For other details, see the legend for Fig. 1.

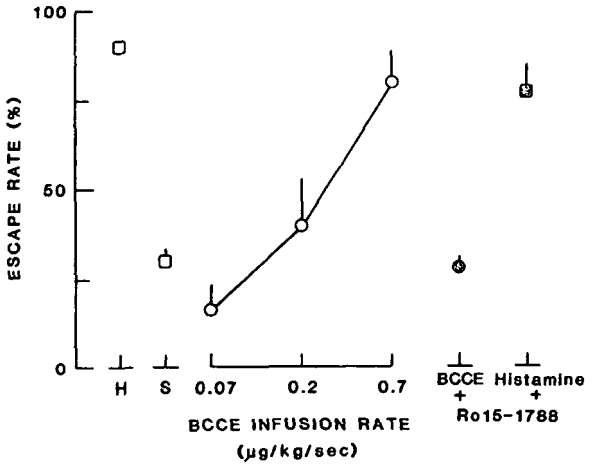

Fig. 3 Effects of 7 ug/kg/sec histamine, saline,various infusion rates of BCCE, and 0.7 ug/kg/sec BCCE or 7 ug/kg/sec histamine in combination with Ro15-1788 (shown on abscissa, respectively from left to right), on behavior maintained by the termination of intravenous infusions of these drugs. Ordinate: the percentage of trials during which the monkey responded to terminate the infusion. The vertical lines at each point are ± S.E.

Reinforcing Effects As shown in Fig. 3, BCCE maintained escape responding in a dose-related manner. Midazolam at infusion rates of 2 or 7 ug/kg/sec failed to maintain more escape behavior than that maintained by saline in two monkeys tested (not shown). Rol5-1788 (1 mg/kg given subcutaneously 10 min before the session) reduced BCCE-maintained escape responding but did not greatly affect the responding maintained by histamine.

In monkeys trained to self-administer intravenous infusions of methohexital, the substitution of 0.1 mg/kg/inj midazolam resulted in rates of responding that were 30% of those produced by 1 mg/kg/inf methohexital and 10 times greater than those maintained by saline.

DISCUSSION

The present results on the discriminative effects of BCCE and midazolam and the capacity of Ro15-1788 to reverse the effects of these two drugs, demonstrate that BCCE, as well as midazolam, have stimulus properties that are mediated through the benzodiazepine receptor. The discriminative stimulus effects of the two drugs are, however, distinct.

Rol5-1788, when given alone, in doses higher than those necessary to antagonize BCCE or midazolam produced BCCE-appropriate responding. Ro15-1788 has been reported to have either benzodiazepine-like agonist effects (e.g., Dantzer and Perio, 1982) or inverse agonist-like effects (File et al., 1982; see also review by Pellow & File, 1984). Partial generalization to the discriminative effects of a convulsant β -carboline has also been reported (Nielsen et al., 1985). In addition to these, the present results suggest that Ro15-1788 may act as a full inverse agonist at higher doses. Thus, although the dose, the experimental situation, and/or the species of animals used differed, the same compound has been shown to act as an agonist, an antagonist, as well as an Inverse agonist.

In the experiments to study the reinforcing effects, BCCE but not middazolam clearly maintained escape responding, which was prevented by Ro15-1788 at the same dose which antagonized the discriminative effects. Midazolam was shown to have a moderate capacity to maintain responding to receive the injection, as has been demonstrated in baboons (Griffiths et al., 1981). Thus, in the rhesus monkey, BCCE was a negatively reinforcing stimulus while midazolam was a positively reinforcing stimulus.

The experiments described demonstrate that although both the discriminative and reinforcing properties of BCCE are mediated through the benzodiazepine receptor, they are distinct and in the opposite direction from those effects of some benzodiazepines. These behavioral studies may be very useful in studying the pharmacological factors modifying anxiety, as well as studying similarity among substances related to anxiety, both those with exogenous and those with endogenous origins.

REFERENCES

Bertalmio, A.J., Herling, S., Hampton, R.Y., Winger, G.D., & Woods, J.H. A procedure for rapid evaluation of the discriminative stimulus effects of drugs. J Phancol Methods, 7: 289-299, 1982

Biggio, G. & Costa, E. (eds.) Benzodiazepine recognition site ligands: Biochemistry and pharmacology. Adv Biochem Psychopharmacol, 38, New York: Raven Press, 1983

Braestrup, C., Honore, T., Nielsen, M., Petersen, E.N., & Jensen, L.H. Ligands for benzodiazepine receptors with positive and negative efficacy. Biochem Pharmacol, 33, 859-862, 1984

Dorow, R., Horowski, R., Paschelke, G., Amin, M., & Braestrup, C. Severe anxiety induced by FG7142, a -carboline ligand for benzodiazpine receptors. Lancet, Jul 9: 98-99, 183

Griffiths, R.R., Lukas, S.E., Bradford, L.D., Brady, J.V., & Snell, J.D. Self-injection of barbiturates and benzodiazepines in baboons. Psychopharmacology, 75: 101-109, 1981

Nielsen, E.B., Jenson, S.A., Nielsen, M., & Braestrup, C. Discriminative stimulus properties of methyl 6,7-dimethoxy-4-ethyl-B-carboline-3-carboxylate (DMCM), an inverse agonist at benzodiazepine receptors. Life Sci, 36: 15-23, 1985

Ninan, P.T., Insel, T.M., Cohen, R.M., Cook, J.M., Skolnick, P., & Paul, S.M. Benzodiazepine receptor-mediated anxiety in primates. Science, 218: 1332-1334, 1983

Pellow, S. & File, S.E. Multiple sites of action for anxiogenic drugs: Behavioral, electrophysiological and biochemical correlations. Psychopharmacology, 83: 304-315, 1984

Richards, J.G. & Mohler, H. Benzodiazepine receptors. Neuropharmacol, 23: 233-242, 1984

Woods, J.H. Narcotic-reinforced responding: A rapid evaluation procedure. Drug Alc Depend , 5: 223-230, 1980

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Alcohol Effects on LHRH-Stimulated LH in Female Rhesus Monkeys

Nancy K. Mello, Jack H. Mendelson, Mark P. Bree, and Alice S. T. Skupny

INTRODUCTION

Chronic alcohol dependence is associated with several abnormalities of the menstrual cycle in women and in a female rhesus monkey model of alcoholism. Persistent amenorrhea, anovulation and luteal phase defects as well as pathological changes in the ovaries have been observed clinically (Hugues et al. 1980; Moskovic 1975; Ryback 1977; Jung and Russfield 1972), and in alcohol-dependent primates (Mello et al. 1983). However, it is not known if the toxic effects of chronic alcohol dependence occur primarily at the level of the hypothalamus, the pituitary or the ovary, or if alcohol simultaneously disrupts each component of the hypothalamic-pituitary-gonadal axis (see Cicero 1980; Van Thiel and Gavaler 1982 for review).

In an effort to identify the site or sites of alcohol-induced derangements of the menstrual cycle, the acute effects of alcohol on pituitary function were evaluated using synthetic LHRH stimulation. If alcohol significantly suppressed LHRH-stimulated pituitary release of LH and FSH, this would suggest that alcohol suppresses normal anterior pituitary function. Alternatively, if alcohol had no effect on LHRH-stimulated pituitary secretory activity, this could mean that alcohol's primary effects are exerted on the hypothalamus or the ovary.

METHODS

Six sexually mature female rhesus monkeys (4.7 to 9.4 kg) with normal ovulatory menstrual cycles were studied. Five monkeys were alcohol-naive and one monkey had a history of alcohol self-administration but had been alcohol-free for over one year. Vaginal swabs were done daily to determine the onset and duration of menstrual bleeding. Monkeys were maintained on ad lib food and water; monkey chow was supplemented daily with fresh fruit, vegetables and multiple vitamins. A 12-h light-dark cycle (7 a.m. to 7 p.m.) was in effect.

Animal maintenance and research was conducted in accordance with the guidelines provided by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facility is licensed by the U. S. Department of Agriculture. The health of the monkeys was periodically monitored by a consultant veterinarian from the New England Regional Primate Research Center.

The acute effects of alcohol and sucrose control solutions on LHRH-stimulated LH were evaluated in the same six female monkeys under identical conditions. Monkeys were studied during the follicular phase of the menstrual cycle. An acute venous catheterization procedure for collection of integrated blood samples was used and each sample reflected the true mean of LH during the collection period (Bree et al. 1982). Basal levels of LH were measured for 80 minutes before alcohol or sucrose was administered. LH was measured for an additional 120 minutes before LHRH was administered, and for 180 minutes after LHRH administration. Samples were collected at 20 minute intervals except during the first hour after LHRH administration when 15 minute intervals were used to more accurately follow the time-course of LHRH-stimulated LH activity. Samples were centrifuged, aliquots of plasma were withdrawn and frozen at -20°. Data were analyzed with ANOVA and LSD followup tests.

Alcohol (2.5 and 3.5 g/kg), prepared in a 25 percent solution, was administered through a pediatric grade nasogastric tube. Alcohol effects were compared with a sucrose control solution, isocalorically equivalent to 2.5 g/kg alcohol. Monkeys were fasted for 18 to 20 hours to insure uniform absorption of alcohol from the small intestine.

Synthetic LHRH (Gonadorelin hydrochloride; Factrel) (100 mcg i.v.) was administered 120 minutes after alcohol administration, during the ascending phase of the blood alcohol curve, to insure that the maximal effects of LHRH stimulation occurred at blood alcohol levels above 150 mg/dl (Mello et al. 1984b).

LH levels were determined in duplicate 0.100 ml plasma samples using a double antibody RIA procedure and materials supplied by the Contraceptive Development Branch, Center for Population Research, National Institute for Child Health and Human Development. The assay is based upon a method described by Monroe and co-workers (1970). Purified cynomolgus pituitary LH was radioiodinated using the Chloramine-T method and rabbit antiserum to human chorionic gonadotropin (hCG), (R 13, Pool D) was employed as the first antibody. The standard used for these assays was NICHD-rh LH, also known as WP-XV-20. Results are reported as mg NICHD-rh LH/ml plasma. The assay sensitivity was 7.0 ng/ml and the intra- and interassay CVs were 6.1% and 10.9% respectively.

Levels of alcohol in plasma were measured in duplicate in 20-microliter plasma samples using a dye-coupled colormetric micro-

method, based on enzymic oxidation of ethanol to acetylaldehyde (Léric et al. 1970). Assay sensitivity was 20 mg/dl. Intra- and interassay CVs were 3.0 and 4.5 respectively.

RESULTS AND DISCUSSION

LHRH Stimulation of LH Under Sucrose Control Conditions

LH levels were equivalent prior to and following administration of a sucrose control solution. LH averaged 19 (±0.8) ng/ml during the pre-sucrose baseline (samples 1-4) and 16 (+0.8) ng/ml during the 120 minutes following sucrose administration (samples 5-10).

Synthetic LHRH administration increased LH levels significantly ($p < .001$) as evaluated by ANOVA. LH increased within 30 minutes after LHRH administration and remained elevated over baseline throughout the sampling period (Figure 1). LHRH stimulation of a significant increase in LH within 30 minutes is consistent with previous observations in Macaque female monkeys (Ferin et al. 1974; Hamada and Suginami 1983; Krey et al. 1973).

Alcohol (2.5 and 3.5 g/kg) Effects on LH

Monkeys appeared intoxicated within 1 hour after alcohol administration. The average peak blood alcohol level after administration of 2.5 g/kg of alcohol was 201 (+14.5) mg/dl. The average peak blood alcohol level after administration of 3.5 g/kg was 272 (+7.7) mg/dl. The time-course and peak blood alcohol levels during the early follicular phase were comparable to our previous observations in female rhesus monkeys (Mello et al. 1984b).

The pre-alcohol baseline values of LH were equivalent in the two alcohol groups and averaged 24 (±0.47) ng/ml and 23 (±1.9) ng/ml respectively. Alcohol administration did not significantly alter LH levels. After administration of 2.5 g/kg alcohol, LH levels averaged 24 (±0.4) ng/ml. After administration of 3.5 g/kg of alcohol, LH values averaged 23 (±1.5) ng/ml. LH levels (samples 5-10) were significantly higher ($p < .001$) after alcohol (2.5 and 3.5 g/kg) administration than after sucrose control administration.

The lack of acute alcohol effects on LH is consistent with previous studies of acute alcohol effects in female Macaque monkeys (Mello et al. 1984a) and human females (Mendelson et al. 1981; McNamee et al. 1979; Välimäki et al. 1983) under non-stimulated conditions.

LHRH Stimulation of LH After Alcohol Administration

Alcohol also failed to delay or attenuate the LHRH-stimulated increase in LH. LHRH stimulated a significant increase in LH

(p < .001) after administration of both 2.5 and 3.5 g/kg of alcohol. LH increased within 30 minutes after LHRH administration when blood alcohol levels averaged 185 (±12) and 239 (±6) mg/dl (figure 1).

The magnitude of the LHRH-stiimulated increase in LH differed significantly between the alcohol and control conditions. The LH increase was significantly greater after administration of both 2.5 g/kg alcohol (p < .01) and 3.5 g/kg alcohol (p < .-001) than after sucrose control administration. The post-LHRH increase in LH also was greater after 3.5 g/kg alcohol than after 2.5 g/kg alcohol, but these differences were not statistically significant.

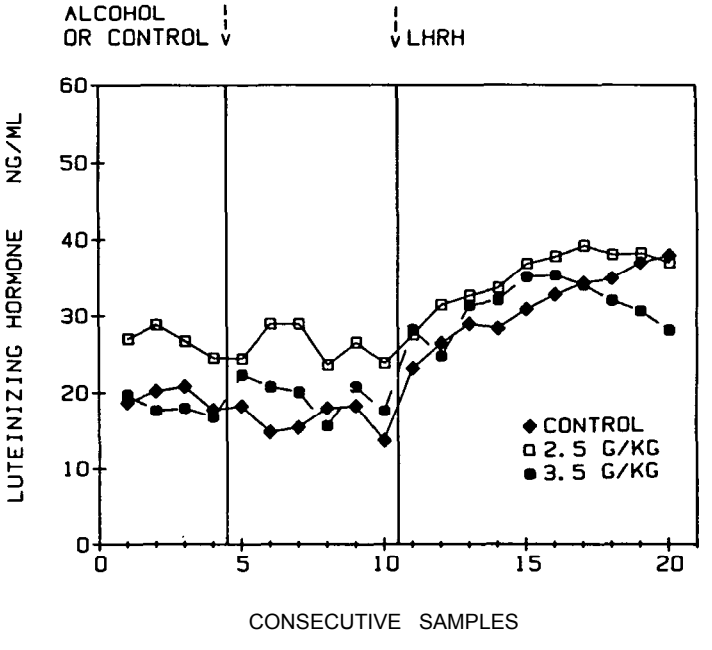

Figure 1: The effects of sucrose and alcohol on LHRH-stimulated LH (ng/ml). Data from a representative individual monkey are shown. Integrated plasma sample values for LH (ng/ml) are shown for four consecutive 20 minute samples prior to alcohol or sucrose administration; for six consecutive 20 minute samples following alcohol or sucrose and prior to LHRH administration (samples 5-10); and for 10 samples following LHRH administration. Samples 11 through 14 were collected at 15 minute intervals. Samples 15 through 20 were collected at 20 minute intervals.

It was surprising that alcohol administration was associated with a significantly higher LH response to LHRH stimulation than sucrose administration. The apparent stimulatory effect of alcohol on LH is difficult to explain since basal LH levels were significantly lower in the sucrose control group than in the 2.5 alcohol group ($p < .05$), but not in the 3.5 alcohol group. No comparable studies of acute alcohol effects on LHRH-stimulated LH in normal women or rhesus females are available for comparison. However, two studies of LHRH stimulation in alcoholic women during a period of sobriety reported that LH responses were comparable to non-alcoholic controls. (Hugues et al. 1980; Valimaki et al. 1984). Acute alcohol administration also had no suppressive effect on LHRH-stimulated LH in normal men (Ylikahri et al. 1978) and male rodents (Cicero et al. 1978).

These data suggest that a single high dose of alcohol does not reduce pituitary responsivity to synthetic LHRH stimulation in female rhesus monkey. These studies of acute alcohol effects on pituitary gonadotropins are discordant with studies of chronic alcohol effects where suppression of LH has been observed in female monkeys (Mello et al. 1983) and alcoholic women (Hugues et al. 1980; Moskovic 1975; Vilimski and Ylikahri 1981). This suggests that repeated or sustained episodes of alcohol intoxication are required to suppress pituitary secretory activity in females. We are unaware of any studies of LHRH stimulation of pituitary gonadotropins in females during chronic alcohol intoxication.

In summary, acute alcohol administration does not suppress LHRH-stimulated LH in female rhesus monkeys. Further studies will be necessary to evaluate the reliability of the apparent enhancement of stimulated LH activity after acute alcohol administration. At present, there is no obvious or simple explanation for the profound disruption of hypothalamic-pituitary-gonadal function that accompanies chronic alcohol intoxication.

REFERENCES

Bree, M.P.; Mello, N.K.; Harvey, K.L.; and Webb, S.A. Acute venous catheterization for integrated plasma sample collection in monkey. Pharmacol Biochem Behav 16: 521-523, 1982.

Cicero, T.J. Common mechanisms underlying the effects of ethanol and the narcotics on neuroendocrine function. In: Mello, N.K., ed. Advances in Substance Abuse: Behavioral and Biological Research. Vol. I. Greenwich: JAI Press, Inc., 1980. pp. 201-254.

Cicero, T.J.; Bernstein, D.; and Badger, T.M. Effects of acute alcohol administration on reproductive endocrinology in the male rat. Alcoholism: Clin Exp Res 2: 249-254, 1978.

Ferin, M.; Warren, M.; Dyrenfurth, I.; Vande Wiele, R.L.; and White, W.F. Response of rhesus monkeys to LHRH throughout the ovarian cycle. J Clin Endocrinol Metab 38: 231-237, 1974.

Hamada, K., and Suginami, H. Qualitative and quantitative changes in plasma luteinizing hormone (LH) under stimulation by intravenous infusion of synthetic luteinizing hormone-releasing hormone (LHRH) in Japanese monkeys (Macaca fuscata) as assessed by electrofocusing. Endocrinol Japan 30()1): 101-111, 1983.

Hugues, J.N.; Cofte, T.; Perret, G.; Jayle, M.S.; Sebaoun, J.; and Modigliani, E. Hypothalamo-pituitary ovarian function in 31 women with chronic alcoholism. Clin Endocrinol 12: 543-551, 1980.

Jung, Y., and Russfield, A.B. Prolactin cells in the hypophysis of cirrhotic patients. Arch Path 94: 265-269, 1972.

Krey, L.C.; Butler, W.R.; Weiss, G.; Weick, R.F.; Dierschke, D.J.; and Knobil, E. Influences of endogenous and exogenous gonadal steroids on the actions of synthetic LRF in the rhesus monkey. Excerpta Med Int Congr Ser 263: 39-47, 1973.

Léric, H.; Kaplan, J-C; and Broun, G. Dosage enzymatique de l'alcool sanguin par micromethode colorimetrique. Clin Chim Acta 29: 523-528, 1970.

McNamee, B.; Grant, J.; Ratcliffe, J.; Ratcliffe, W.; and Oliver, J. Lack of effect of alcohol on pituitary-gonadal hormones in women. Br J Addict 74: 316-317, 1979.

Mello, N.K.; Bree, M.P.; Mendelson, J.H.; and Ellingboe, J. Alcohol self-administration disrupts reproductive function in female Macaque monkeys. Science 221: 677-679, 1983.

Mello, N.K.; Bree, M.P.; Ellingboe, J.; Mendelson, J.H.; and Harvey, K.L. Lack of acute alcohol effects on estradiol and luteinizing hormone in female Macaque monkey. Pharmacol Biochem Behav 20(2): 293-299, 1984a.

Mello, N.K.; Bree, M.P.; Skupny, A.S.T.; and Mendelson, J.H. Blood alcohol levels as a function of menstrual cycle phase in female Macaque monkeys. Alcohol 27-31, 1984b.

Mandelson, J.H.; Mello, N.K.; and Ellingboe, J. Acute alcohol intake and pituitary gonadal hormones in normal human females. J Pharmacol Exp Ther 218: 23-26, 1981.

Monroe, S.E.; Peckham, W.D.; Neill, J.D.; and Knobil, E. A radioimmunoassay for rhesus monkey luteinizing hormone (RHLH). Endocrinology 86: 1012-1018, 1970.

Moskovic, S.: Effect of chronic alcohol intoxication on ovarian dysfunction. In: Srpski Arhiv za Celokupno Lekarstvo, V. 103, No. 9., 1975. pp. 751-758.

Ryback, R.S. Chronic alcohol consumption and menstruation. J Am Med Assoc 238: 2143, 1977.

Valimaki, M., and Ylikahri, R. Alcohol and sex hormones. Scan J Clin Lab Invest 41: 99-105, 1981.

Valimaki, M.; Harkonen, M.; and Ylikahri. R. Acute effects of alcohol on female sex hormones. Alcoholism: Clin Exp Res 7(3): 289-293, 1983.

Valimaki, M.; Pelkonen, R.; Salasporo, M.; Harkonen, M.; Hirvonen, E.; and Ylikahri, R. Sex hormones in amenorrheic women with alcoholic liver disease. J Clin Endocrinol Metab 59(1): 133-138, 1984.

Van Thiel, D.H., and Gavaler, J.S. The adverse effects of ethanol upon hypothalamic-pituitary-gonadal function in males and females compared and contrasted. Alcoholism: Clin Exp Res 6(2): 179-185, 1982.

Ylikahri, R.H.; Huttunen, MO.O; Harkonen, M.: Leino, T.; Helenius, T.; Liewendahl, K.; and Karonen, S-L. Acute effects of alcohol on anterior pituitary secretion of the tropic hormones. J Clin Endocrinol Metab 46(4): 715-720, 1978.

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Central Infusion of Rats With Agents Selective for Different Types of Opioid Receptor

A. Cowan, X. Z. Zhu, H. I. Mosberg, and F. Porreca

INTRODUCTION

The objective of this study was to describe, quantitate and compare naloxone-induced abstinence syndromes in rats associated with the central infusion of compounds that are claimed to be selective agonists at mu, kappa or delta opioid receptors. [D-Ala^2, MePhe^4, Gly-ol^5]enkephalin (GLYOL) (Handa et al. 1981) and the benzeneacetamide, U-50,488H (Vonvoigtlander et al. 1983), served as selective ligands at mu and delta receptors, respectively. [D-Pen^2, D-Pen^5) enkephalin (DPDPE), which is probably the most selective agonist at delta receptors that is currently available (Mosberg et al. 1983), was tested for the first time in a physical dependence paradigm. In addition, the following agents were included in the study for comparative purposes: morphine (mu-directed ligand), dynorphin A (endogenous ligand at kappa receptors) (James et al. 1982), and ethylketazocine (Martin et al. 1978) and xorphanol (Howes et al. 1985) (both kappa-preferring ligands).

MATERIALS AND METHODS

Animals

Male Sprague Dawley albino rats (180-200 g initially: Zivic-Miller) were used.

Procedure

Test compounds were infused centrally (at 1 ul/hr) to the caudal region of the Sylvian aqueduct of rats from subcutaneously implanted osmotic minipumps (Alzet 2001) as described in detail by Wei (1981). For GLYOL, U-50,488H, DPDPE and dynorphin A, the amount initially infused was 24.2 times the ED 50 value (i.c.v., nmol) reported in rat hot plate (Galligan et a1.1984) or paw pressure (Hayes et al. 1983) tests. This is equivalent to 49 nmo1/70 hr of morphine sulfate, an amount associated with marked physical dependence in rats (Chang et al. 1983). Ethylketazocine is not very active when given i.c.v. in standard rat antinociceptive tests. The amount infused was 24.2 times the dose (i.c.v., nmol) causing diuresis (4 ml in 2 hr) in normally hydrated rats (Khunawat and Cowan, unpublished results). Xorphanol has not previously been

tested i.c.v.; this morphinan derivative was therefore infused at 49 nmol/70 hr i.e. just like morphine.

Each rat lived in a Plexiglas observation box (26 cm long; 20 cm wide: 30 cm high). Animals were tested (while still in their boxes) in a constant environment room (Hotpack: 20±0.5°C) at +70 hr and again at +168 hr. Signs of abstinence were monitored for 0.5 hr before, and 0.5 hr after, naloxone (3 mg/kg, s.c.). Rats showing signs of abstinence during the control period were discarded.

Quatition of abstinence

Severity of abstinence was assessed by a point-scoring technique (Frederickson and Smits 1973) modified by weighting the signs (Frederickson et al. 1976). The signs scored, with the maximum possible score for each sign, are shown in table 1. The scoring between zero and maximum was not continuous but discrete with the following steps: 0,2,4,6,8,12,18,24 and 36. The scores for each of the signs were summed to give a grand total (maximum=150) which represented the severity of the abstinence syndrome precipitated by naloxone.

TABLE 1 *Abstinence Signs monitored and Maximum Possible Score for each Sign*

Sign	Score
Jumping (escape attempts)	36
Exploratory rearing	18
Wet-dog shakes	12
Head shakes	12
Yawning	12
Weight loss in 1 hr (>3 g)	18
Rectal hypothermia in 1 hr (>0.5°C)	18
Digging (manifestation of arousal/restless activity)	4
Excessive scratching (>6 episodes)	4
Flat posture	4
Ptosis	4
Licking penis (>3 times)	4
Forepaw tremor (>3 tines)	4

Compounds

The following test agents were kindly donated by the companies indicated: ethylketazocine methanesulfonate (Sterling Winthrop), naloxone hydrochloride (Endo) , xorphanol mesylate (Pars) and trans-(±)-3,4-dichloro-N-methyl-N-[1-pyrrolidinyl)cyclohexyl]-benzeneacetamide methanesulfonate (Upjohn). Dynorphin A (Peninsula), GLYOL (Peninsula) and morphine sulfate (Mallinckrodt) were purchased and DPDPE was synthesized as previously described (Mosberg et al. 1983).

RESULTS

Abstinence scores for each compound are listed in table 2.

At +70 hr, three levels of abstinence were associated with the injection of naloxone (3 mg/kg, s.c.). (a) Negligible syndromes (scores of <17) were precipitated by naloxone in rats on water, U-50,488H, dynorphin A and xorphanol. (b) A low-to-moderate abstinence score (26-37) was obtained with rats on DPDPE and ethylketazccine. (c) A high abstinence score (62-78) was obtained with rats on morphine and GLYOL.

At +168 hr, naloxone precipitated marked abstinence only in rats receiving GLYOL (score of 80.5) and morphine (score of 41.6).

Jumping and excessive scratching were only associated with GLYOL (especially) and morphine (to a lesser extent); weight loss was also only associated with these two mu-directed opioids. Hypothermia was only associated with U-50,488H and ethylketazocine while weight loss was never linked to either of these kappa-preferring agents. Abstinence from DPDPE was mainly characterized by the mu-like signs: head shakes, wet-dog shakes and rearing.

DISCUSSION

Bioassay and receptor binding studies point to GLYOL, DPDPE and U-50,488 being the most selective ligands at mu, delta and kappa receptors, respectively, that are currently available. Central infusion of comparable (antinociceptive) doses of these agents leads to three levels of physical dependence in rats as revealed by naloxone-precipitated abstinence syndromes: GLYOL (high)>>DPDPE (low)>U-50,488 (negligible). Additional studies showed that high and moderate abstinence syndromes are associated with morphine and ethylketazocine, respectively, while marked abstinence is not linked to either xorphanol or dynorphin A.

Under our conditions, jumping, excessive scratching and weight loss (but not hypothermia) seem to predominantly reflect abstinence at mu receptors in rats. In contrast, hypothermia (but not jumping, scratching and weight loss) accompanies abstinence at binding sites that recognize ethylketazocine and U-50,488. The abstinence scores associated with U-50,488 at +70 hr and +168 hr are essentially made up of points obtained from hypothermia.

Abstinence from DPDPE was mainly characterized by the morphine-like signs: head shakes, wet-dog shakes and rearing. Is this syndrome a consequence of DPDPE, when continuously infused, losing its selective action at delta receptors and cross-reacting with mu binding sites? This is a possibility. Note, however, that i.c.v. infusion of a large amount of U-50,488 does not elicit cross-reactions between kappa and mu binding sites, at least under the conditions of our test. Similarly, rats infused i.v. with a large dose of U-50,488 for 2 weeks display no overt evidence of precipitated abstinence when challenged with 3 mg/kg of naloxone (Tang and Collins 1985).

TABLE 2 *Abstinence precipitated by Naloxonea in Rats receiving Test Agent centrally for 70 hr, and 168 hr, from a subcutaneously implanted Minipump*

Test agent	Dose (nmol/70 or 168 hr)	N	Abstinence score (mean ± s.e.)
A. 70 hr			
GLYOL	3.4	5	78.4 ± 10.8**
Morphine	49	7	62.0 ± 9.5**
Ethylketazocine	3063	6	37.3 ± 6.1**
DPDPE	859	6	26.0 ± 6.3**
Xorphanol	49	4	16.4 ± 6.3
Dynorphin A	114	4	12.5 ± 4.0
U-50,488H	2923	4	8.5 ± 4.0
Distilled water		6	8.7 ± 1.3
B. 168 hr			
GLYOL	8.2	4	80.5 ± 16.4**
Morphine	118	5	41.6 ± 12.0*
Ethylketazocine	7351	6	39.0 ± 8.4
DPDPE	2062	2	29.0
Xorphanol	118	4	23.0 ± 5.8
U-50,488H	7015	4	21.5 ± 7.7
Distilled water		4	9.3 ± 1.7

[a]Naloxone (3 mg/kg, s.c.)
*P<0.05 and **P<0.01 (Mann-Whitney U test) in relation to distilled water

Results in vitro with DPDPE unequivocally indicate that this pentapeptide possesses unprecedented selectivity for delta opioid receptors. The present results in vivo are also unequivocal. Central infusion of DPDPE to rats is associated with the development of physical dependence. The implication is quite clear: in developing new analgesics, high selectivity for delta opioid receptors does not, in itself, guarantee freedom from physical dependence.

REFERENCES

Chang, K.-J.; Wei, E.T.; Killian, A.; and Chang, J.-K. Potent norphiceptin analogs: structure activity relationships and morphine-like activities. J Pharmacol Exp Ther 227:403-408, 1983.

Frederickson, R.C.A., and Smits, S.E. Time course of dependence and tolerance development in rats treated with 'slow release' morphine suspensions. Res Comm Chem Path Pharmacol 5:867-870, 1973.

Frederickson, R.C.A.; Hewes, C.R.; and Aiken, J.W. Correlation between the in vivo and in vitro expression of opiate withdrawal precipitated by naloxone: their antagonism by ℓ-(-)-Δ^9-tetrahydrocannabinol. J Pharmacol Exp Ther 199:375-384, 1976.

Galligan, J.J.; Mosberg, H.I.; Hurst, R.; Hruby,V.J.; and Burks, T.F. Cerebral delta opioid receptors mediate analgesia but not the intestinal motility effects of intracerebroventricularly administered opioids. J Pharmacol Exp Ther 229:641-648, 1984.

Handa, B.K.; Lane, A.C.; Lord, J.A.H.; Morgan, B.A.; Rance, M.J.; and Smith, C.F.C. Analogues of beta-LPH(61-64) possessiny selective agonist activity at μ-opiate receptors. Eur J Pharmacol 70:531-540, 1981.

Hayes, A.G.; Skingle, M.; and Tyers, M.B. Antinociceptive profile of dynorphin in the rat. Life Sci 33 (Suppl. I):657-660, 1983.

Howes, J.F.; Villarreal, J.E.; Harris, L.S.; Essigmann, E.M.; and Cowan, A. Xorphanol. Drug Alc Dep 14:373-380, 1985.

James, I.F.; Chavkin, C.; and Goldstein, A. Preparation of brain membranes containing a single type of opioid receptor highly selective for dynorphin. Proc Natl Acad Sci 79:7570-7574, 1982.

Martin, W.R.; Gilbert, P.e.; Thompson, J.A.; and Jessee, C.A. Use of the chronic spinal dog for the assessment of the abuse potential and utility of narcotic analgesics and narcotic antagonists. Drug Alc Dep 3:23-34, 1978.

Mosberg, H.I.; Hurst, R.; Hruby, V.J.; Gee, K.; Yamaura, H.I.; Galligan, J.J.; and Burks, T.F. Bis-penicillamine enkephalins possess highly improved specificity toward delta opioid receptors. Proc Natl Acad Sci 80:5871-5874, 1983.

Tang, A.H., and Collins, R.J. Behavioral effects of a novel kappa opioid analgesic, U-50488, in rats and rhesus monkeys. Psychopharmacology 85:309-314, 1985.

VonVoigtlander, P.F.; Lahti, R.A.; and Ludens, J.H. U-50,488: A selective and structurally novel non-mu (kappa) opioid agonist. J Pharmacol Exp Ther 224:7-12, 1983.

Wei, E.T. Enkephalin analogs and physical dependence. J Pharmacol Exp Ther 216:12-18, 1981.

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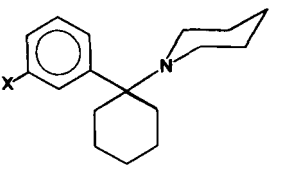
Electrophilic Affinity Ligands for the Phencyclidine (PCP) Receptor

Ralph A. Lessor, Mariena V. Mattson, Kenner C. Rice, and Arthur E. Jacobson

PCP abuse has become a major problem in the United States. The drug often induces violently aggressive behavior, and, in some oases, long-lasting psychosis. The mechanism of action of PCP is under Investigation in many laboratories. The existence of high-affinity receptors for phencyclidine in the central nervous system has been demonstrated (Zukin et al. 1983; Vincent et al. 1979; Rafferty et al. 1985). The first specific electrophilic affinity ligand for the PCP receptor was synthesized at NIADDK, NIH, and has been given the name metaphit (1-(1-(3-isothiocyanato) phenyl)cyclohexyl)piperidine, 2, figure 1) (Rafferty et al. 1985).



1. X=H (PCP)
2. X=NCS (METAPHIT)

FIGURE 1 - Structure of PCP and metaphit.

The utility of affinity ligands in the characterization of CNS receptors has been demonstrated in the past. In the opioid receptor system, for example, two groups have reported the isolation of receptor components labeled covalently by radiolabeled affinity ligands (Klee et al. 1982; Newman and Barnard 1984; Simonds et al. 1985). Metaphit has already proven to be of considerable value in the characterization of phencyclidine reoeptors. In the hippocampus and the striatum, about 50% of the PCP receptors were irreversibly inactivated by inoubation with 10 uM metaphit (Rafferty et al. 1985). In the Purkinje cells in the cerebellum, eleotrophysiological experiments Indicate that essentially all of the PCP receptors were inactivated using 10 uM metaphit (Wang et al. 1985). We have now found that higher concentrations of metaphit can completely inactivate PCP reaeptors in the rat hippocampus and striatum, as well as whole brain minus cerebellum, in a dose-related manner. The specificity of the irreversible interaction of metaphit with phencyclidine receptors

has also been demonstrated. No irreversible interaction with opioid, benzodiazepine, or muscarinic receptors was observed (Rafferty et al. 1985).

We now wish to report the synthesis and bioohemioal characterization of three new irreversible ligands for the phencyclidine receptor. These affinity ligands were prepared from analogs of PCP with known high affinities for the receptor in an attempt to identify affinity ligands which might be more potent than metaphit as irreversible ligands for the PCP reoeptors. PCE (1-phenylcyclohexylethylamine, 3a, figure 2), PCI (1-phenylcyclohexylisopropylamine, 4a, figure 3), and TCP 1-(1-(2-thienyl)cyclohexyl)piperidine, 5a, figure 4) are analogs of PCP which have greater affinities than PCP itself for the receptor system. We have prepared the corresponding isothiooyanates 3b, 4b, and 5b (figures 2, 3, and 4, respectively), and we have found that they interact in an irreversible manner with the PCP receptor system in vitro in rat brain preparations.

CHEMISTRY

The synthetic routes to 3b, 4b, and 5b all involve nitration of the aromatic nucleus as the key step in functionalization. Thus, nitration of PCE (3a) afforded meta-nitro PCE (3c) as the major product (figure 2). Reduotion with hydrogen over palladium afforded the amino compound 3d, which was converted to the isothiocyanate 3b by treatment with thiophosgene in a two-phase system of aqueous sodium bicarbonate and chloroform.

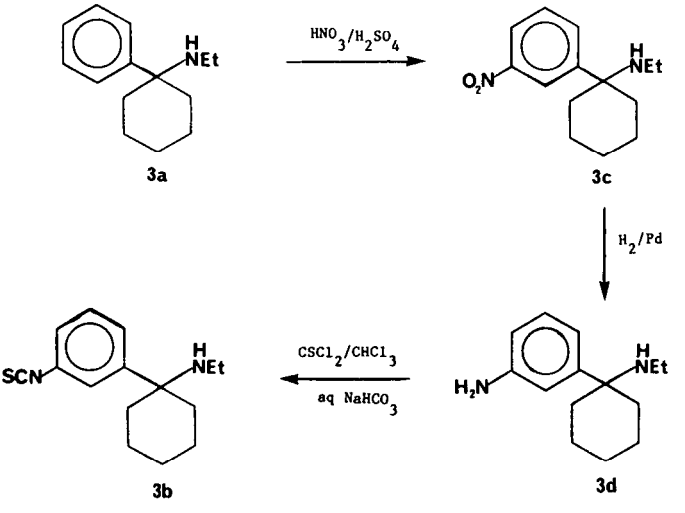


FIGURE 2 - Synthesis of ethylphit.

Nitration of PCI under similar conditions gave an inseparable mixture of meta- and para-nitro isomers 4c and 4d (figure 3). Hydrogenation of this mixture gave the meta-amino compound 4e.

Presumably, the transiently-formed para-amino compound 4f deaomposes in situ via a pathway such as that shown in figure 3. This is in accord with the reported instability of para-amino PCP (Johnson et al. 1981). Conversion of 4e to the corresponding isothiooyanate was achieved in the same manner as for 3b. It should be noted that 3b and 4b, containing both isothiocyanate and secondary amine functionalities, have the potential for self-condensation. These compounds, however were found to be stable both in solution and in the solid state, an expected result based on a preliminary experiment in which metaphit (2) failed to react to any detectable extent with PCE over a period of 24 hours. Apparently, the seoondary amine is sufficiently hindered sterically to preclude condensation with the aromatic isothiocyanate moiety.

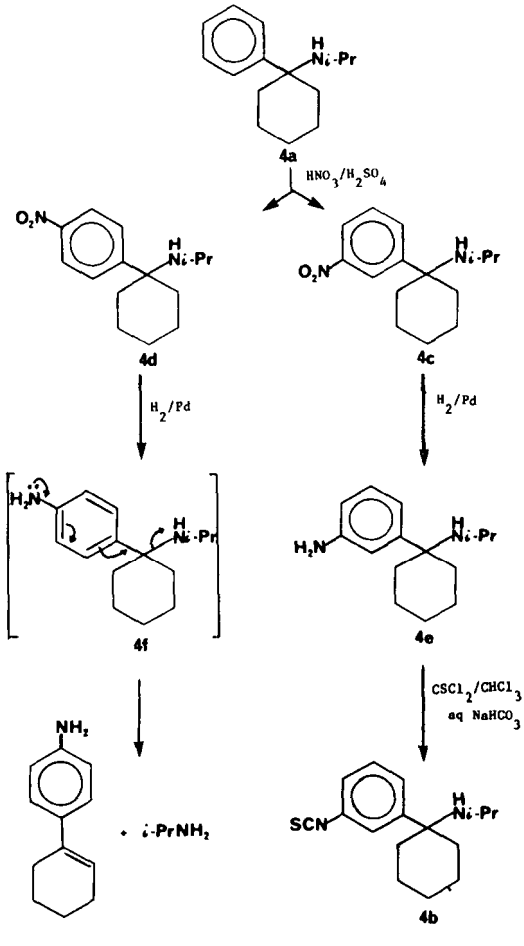


FIGURE 3 - Synthesis of isopropylphit.

Nitration of TCP (Kalir et al. 1969) afforded primarily the 5-nitrothienylcyclohexylpiperidine 5c, along with about 15% of the 4-nitro compound 5d (figure 4). All attempts to reduce 5c led

to decomposition, presumably involving loss of piperidine via a meohanism similar to that proposed for the deoomposition of para-amino PCI (figure 3). Bromination of TCP in hot glacial acetic acid afforded the 5-bromo TCP (5e). Nitration of this compound afforded a single product, which was assigned structure 5f on the basis of further transformations (vide infra). Catalytic reduction of 5f afforded the air-sensitive 4-amino TCP (5g), which was not isolated, but was converted directly to the isothiocyanate 5b as before. Proton NMR studies of this compound confirmed the position of the isothiocyanate group, with the coupling constant between the 3-and 5- protons of the thiophene ring being less than 1 Hertz, while in the parent TCP 5a the observed ortho coupling was about 4 Hertz between H-4 and both H-3 and H-5. All new compounds were fully characterized by C, H, and N combustion analyses, NMR, mass and infrared speotroscopy.

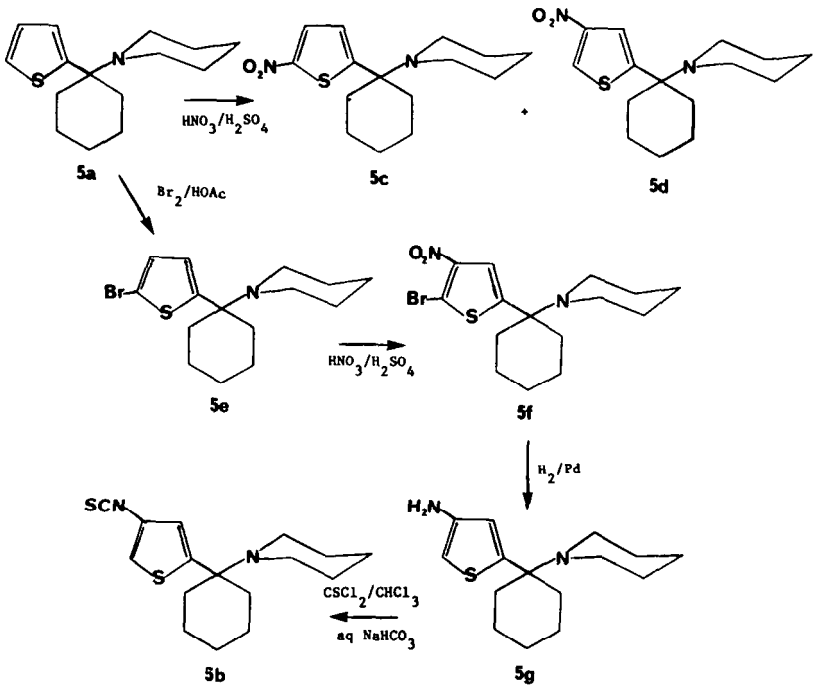


FIGURE 4 - Synthesis of thiophit.

BIOCHEMICAL PROCEDURE

Our in vitro assay procedure is adapted from Zukin et al.(1983), and uses adult male Sprague-Dawley rats (Taconia Farms, Germantown, NY). It has been described previously (Rafferty et al. 1985), using 8 nM [3H]-PCP as the radioligand, and homogenates from rat striatum and/or hippocampus. The assay we now utilize uses 5 nM [3H]-TCP (New England Nuclear, 55.3 Ci/mmol). The displacement

assays are carried out using whole rat brain homogenate (minus oerebellum and brain stem). Non-specific binding is estimated using 10 uM unlabelled TCP.

RESULTS AND DISCUSSION

We have found, as have others (Contreras et al. 1985; Vignon et al. 1983), that [3H]-TCP, rather than [3H]-PCP, is preferable as the radioligand in the PCP assay. TCP has considerably higher affinity for the PCP receptor than PCP. Non-specific binding decreased from 30% of the total binding with [3H]-PCP to 10% using [3H]-TCP. The decrease in non-speaifio binding enabled us to simplify the tissue preparation and use brain homogenate (minus the cerebellum and brain stem), rather than striatum and hippocampus.

Starting materials and target compounds were evaluated for their affinity for phenoyclidine receptors by displacement assays. The apparent IC50 for PCP (1) and PCE (3a) were similar (150 nM for PCP and 240 nM for PCE), using 8 nM [3H]-PCP as the radioligand in rat striatum and hippocampus homogenate. PCI (4a) had an apparent IC50 of 50 nM in that assay, and TCP (5 a) was twice as potent as PCI.

The affinities of the potential affinity ligands are all somewhat reduced oompared to the parent compounds, but were sufficiently high to warrant their further testing as irreversible ligands. Of the three new compounds (3b, 4b, and 5b), the thienyl oompound 5b displays considerably higher affinity for the PCP receptor (table 1). It should be noted that determination of a true IC50 for these affinity ligands is not possible due to their rapid and irreversible interaction with some of the receptor population under the assay conditions.

TABLE 1. Affinity of ligands for the phenoyclidine receptor in rat brain homogenate.

Compound	Apparent IC50, nM
PCP (1)	70
Metaphit (2)	2800
Ethylphit (3b)	3840
Isopropylphit (4b)	2700
TCP (5a)	20
Thiophit (5b)	900

The ability of the potential affinity ligands 3b, 4b, and 5b to interact irreversibly with the phencylidine receptor was explored at two concentrations. Briefly, the tissue homogenate was incubated with the test drug (10 uM and 100 uM concentration) for 10 minutes, then washed several times and evaluated by displacement of tritiated TCP with unlabeled TCP. Under these conditions, 2 uM TCP or 10 uM PCP, alone, were completely washed out of the homogenate. With the affinity ligands, a significant loss of binding sites was observed. All of the four affinity ligands completely inhibited the PCP reaeptors at a concentration of 100 uM.

At 10 uM, both metaphit and thiophit inhibited about 50 to 56% of the receptor population, irreversibly. Isopropylphit and ethylphit appeared to be somewhat more effective, irreversibly interacting with about 62 to 67% of the PCP receptors at the 10 uM concentration. There did not appear to be a significantly larger proportion of the PCP receptors inaotivated with isopropylphit or ethyphit to warrant testing these ligands further; thiophit had a much higher affinity for the PCP receptors, in displacement assays, than either of the other two affinity ligands.

The irreversible interaotion of thiophit on PCP receptors was further examined to see whether it interacted with the same set of PCP receptors as metaphit. Scatchard analyses were obtained in the presence and absence of 10 uM thiophit and metaphit, using various concentrations of [3H]-TCP (1.0 to 150 nM). The data, analyzed by least squares linear regression, revealed a significant loss of binding sites in the tissues treated with the affinity ligands, with no significant alteration in the affinity of the remaining sites (Kd for control, 0.015 uM, Kd for metaphit-treated tissue 0.021 uM, Kd for thiophit-treated tissue 0.027 uM; Bmax for control, 1000 fmol/mg protein, Bmax for metaphit- or thiophit-treated tissue 700 fmol/mg protein). Thus, about a 30% reduction was seen in Bmax for either thiophit or metaphit treated homogenate. These data indicated that thiophit and metaphit exerted similar effects, and probably interacted irreversibly with the same population of PCP receptors.

In conclusion, we have synthesized three new eleotrophilic affinity ligands for the PCP receptor, thiophit (5b), ethylphit (3b), and isopropylphit (4b), each of which are quite effective irreversible inhibitors. Thiophit has oonsiderably higher affinity for the PCP receptor than either of the other two affinity ligands, and is three times as potent as metaphit at the PCP receptor in displacement assays. However, thiophit does not appear to be any more efficacious than metaphit at irreversibly inactivating the PCP receptors. Since thiophit is more difficult to synthesize and purify than metaphit, it would appear to have no advantage over metaphit as an affinity ligand.

REFERENCES

Contreras, P.C.; Johnson, S.; Freedman, R.; Hoffer, B.; Olsen, K.; Rafferty, M.F.; Lessor, R.A.; Rice, K.C.; Jacobson, A.E.; and O'Donohue. T.L. Characterization of in vivo actions of metaphit. an acylating ligand for phencyclidine receptors. J Pharmacol Exp Ther, in review, 1985.

Johnson, P.Y.; Pan, R.; Wen, J.Q.; and Halfman, C.J. Synthesis of amine derivatives of phenoyclidine. J Org Chem 46:2049-2054, 1981.

Kalir, A.; Edery, H.; Pelah, Z.; Balderman, D.; and Porath, G. 1-Phenylcycloalkylamine derivatives. II. Synthesis and pharmacological activity. J Med Chem 12:473-477, 1969.

Klee, W.A.; Simonds, W.F.; Sweat,. F.W.; Burke, Jr., T.R.; Jaoobson, A.E.; and Rice, K.C. Identification of a Mr 58,000 glycoprotein subunit of the opiate receptor. FEBS Lett 150:125-128, 1982.

Newman, E.L. and Barnard, E.A. Identification of an opioid receptor subunit carrying the mu binding site. Biochemistry 23:5385-5389, 1984.

Rafferty, M.F.; Mattson, M.; Jacobson, A.E.; and Rice, K.C. A specific acylating agent for the [3H]phencyclidine receptors in rat brain. FEBS Lett 181:318-322, 1985.

Simonds, W.F.; Burke, Jr., T.R.; Rice, K.C.; Jacobson, A.E.; and Klee, W.A. Purification of the opiate receptor of NG108-15 neuroblastoma x glioma hybrid ceils. Proc Nat Acad Sci USA 82:4974-4978, 1985.

Vignon, J.; Chicheportiche, R.; Chicheportiche, M.; Kamenka, J.-M.; Geneste, P.; and Lazdunski, M. [3H]TCP: a new tool with high affinity for the PCP receptor in rat brain. Brain Res 280:194-197, 1983.

Vincent, J. P.; Kartalovski, B.; Geneste, P.; Kamenka, J. M.; and Lazdunski, M. Interactions of phencyclidine ("angel dust") with a specific reaeptor in rat brain membranes. Proc Natl Acad Sci USA 76:4678-4682, 1979.

Wang, Y.; Palmer, M.; Freedman, R.; Hoffer, B.; Mattson, M.V.; Lessor, R.A.; Rice, K.C.; and Jacobson, A.E. Antagonism of phencyclidine action by metaphit in rat cerebellar Purkinje neurons: An electrophysiological and biochemical study. Proc Nat Acad Sci USA 1985, in press.

Zukin, S.R.; Fitz-Syage, M.L.; Nichtenhauser, R.; and Zukin, R.S. Specific binding of [3H]-phencyclidine in rat central nervous tissue: Further characterization and technical consideration. Brain Res 258:277-284, 1983.

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AUTHORS

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Nalbuphine, Pentazocine, and Butorphanol Interactions With Tripelennamine in Mice

William K. Schmidt, Maria E. Marynowski, and Christine Smith

ABSTRACT

Tripelennamine significantly potentiates nalbuphine, pentazocine, and butorphanol analgesic responses in the mouse antiphenylquinone writhing (PQW) test (maximum potentiation = 119%, 59%, and 21%, respectively; Loewe isobologram technique with drugs co-administered s.c.). Tripelennamine was marginally active by itself in the mouse PQW test (ED50 = 6.5 mg/kg s.c. at 10 min). Tripelennamine produced motor impairment in the mouse fore-limb lift/grip test at a 2.4x higher dose (ED50 = 17 mg/kg s.c.). Median doses potentiating nalbuphine, pentazocine, and butorphanol analgesic effects were not motor impairing (tripelennamine dose range = 0.46-6.0 mg/kg s.c.).

Tripelennamine (1.1 - 30 mg/kg s.c.) failed to potentiate nalbuphine's narcotic antagonist activity in the mouse anti-Straub tail test, a test wherein tripelennamine was inactive by itself. Likewise, nalbuphine failed to potentiate tripelennamine activity in the mouse tetrabenazine-antagonism test or the mouse pupil diameter test. These data suggest that nalbuphine/tripelennamine potentiation in the mouse PQW test is not due to a pharmacokinetic/metabolic interaction.

In partially withdrawn morphine-dependent mice (Single Dose Suppression test), a non-impairing dose of tripelennamine (6.5 mg/kg. s.c.) decreased nalbuphine's and butorphanol's partial withdrawal-suppressing activity but enhanced pentazocine's withdrawal-suppressing activity. Thus pentazocine/tripelennamine dose combinations. became more narcotic-like (withdrawal suppression at all doses) while nalbuphine/tripelennamine dose combinations strongly exacerbated the withdrawal response (no suppression; enhanced withdrawal).

In non-withdrawn morphine-dependent mice (Precipitated Abstinence test), tripelennamine had little or no effect on nalbuphine, pentazocine, or butorphanol-induced precipitated withdrawal activity. In a follow-up test, a pentazocine/naloxone dose combination (cf. Talwin-Nx) failed to substitute for morphine

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withdrawal at any dose and precipitated moderately strong withdrawal responses in non-withdrawn morphine-dependent mice.

In conclusion, tripelennamine potentiated the analgesic activity of nalbuphine, pentazocine, and butorphanol in the mouse PQW test, but enhanced only pentazocine's partial mu-agonist (narcotic-like) effects in the mouse SDS test. Naloxone, in the 1:100 dose ratio used in Talwin-Nx, completely blocked pentazocine's partial mu-agonist activity.

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Development of Cigarette Smoking in Rhesus Monkeys

Kiyoshi Ando, Naoyuki Hironaka, and Tomoji Yanagita

It is generally understood that nicotine plays an important role in maintaining human smoking behavior as indicated by the smoker's lack of satisfaction with low - nicotine or nicotine-free cigarettes. Furthermore, the reinforcing effect of nicotine has been demonstrated by intravenous self-administration experiments in rhesus monkeys (Deneau and Inoki, 1967; Yanagita et al.,1974). Although intravenous nicotine self-administration behavior is easily developed in monkeys and smoking behavior is a widespread phenomenon and persistently maintainable in humans, monkeys do not readily develop cigarette smoking behavior. Several methods exist to shape smoking behavior in monkeys (Jarvik, 1967). A method we used previously was to reinforce smoking behavior with sweetened solution (Ando and Yanagita, 1981). Smoking a cigarette through a metal pipe was intermittently reinforced with the solution delivered from a nozzle located beside the pipe. After a long period of maintaining smoking behavior under this condition, the solution was removed. At this point, only 2 out of 14 monkeys continued to smoke cigarettes. Since the success rate was low in this method, other approaches to develop smoking behavior were attempted.

The present study was intended to investigate the development of cigarette smoking behavior in rhesus monkeys by manipulating environmental factors in 2 ways differing fran the earlier approach (Ando and Yanagita, 1981).

Experiment 1 SMOKING BEHAVIOR MAINTAINED BY NOZZLE LICKING REINFORCED WITH SUGAR SOLUTION

Methods

Subjects: Two male rhesus monkeys (5.7 and 8.2 kg) were used. Each was housed individually in a living cage.

Apparatus: The experimental sessions were conducted in the living cages. A panel of transparent plastic was mounted on the front of the cage, on which were attached a metal pipe (0.5 cm diameter) and a nozzle regulated by solenoid valve for dispensing sugar solution (5 cm to the left of the pipe). The pipe was connected to automatic cigarette dispenser which automatically lit a cigarette by the monkey's initial sucking at the pipe. When a switch detected that the cigarette had burned down, a new cigarette was shifted into place and lit as before. Electrochemical contact sensors connected to the nozzle detected licking responses. The cigarettes used were of the filtered "Peace" brand commercially available from Japan Tobacco Inc., and officially reported to contain 1.9 mg nicotine and 23 mg tar per cigarette.

Procedure: The training procedure for sucking at the pipe was described elsewhere in detail (Ando and Yanagita, 1981). In the reinforced smoking sessions, smoking through the pips for a critical duration of 0.1 s or longer was reinforced with about 0.5 ml of sugar solution delivered from the nozzle. The critical duration for reinforcement was gradually prolonged from 0.1 s by increasing the critical duration 0.1 s every time that 3 consecutive smoking responses had been reinforced (i.e. whenever the duration of 3 consecutive smoking responses met or exceeded the current critical duration). In the event that 7 consecutive smoking responses failed to be reinforced, the critical duration was decreased by 0.1 s. After the critical duration exceeded 0.5 s, the initial duration of each following session was set to 0.5 s.

When smoking responses under the above schedule stabilized, the response reinforcement contingency was changed. In reinforced licking sessions, licking the nozzle which dispensed sugar solution was reinforced with the solution under a random interval 30 s (RI-30 s) schedule where the first licking after a random interval (average 30 s) was reinforced. Smoking responses were no longer reinforced with the solution in this condition, although the monkey could smoke a cigarette any time during the session. The smoking and nozzle licking responses were observed in the conditions of reinforced licking under RI-30 s, RI-150 s, RI-750 s, and RI-1500 s, each observed for more than 10 sessions. Each session was given for 1 h every day except Saturday and holidays in all above schedules.

Results

A high rate of smoking responses was observed in 2 monkeys during 1- h sessions when smoking responses were reinforced with sugar solution as shown in figure 1. The number of nozzle lickings not reinforced with sugar solution in these sessions was close to the number of smoking responses. The number of cigarettes consumed during each session was stable across sessions(13-15 cigarettes). When nozzle licking responses were reinforced with sugar solution

under the RI-30 s schedule and smoking responses were no longer reinforced with the solution, the nozzle lickings did not decrease as much as the smoking responses did. The number of smoking responses in monkey No.865 decreased as the reinforced licking sessions under the RI-30 s schedules proceeded, while the number in the same condition did not decrease as the sessions proceeded in monkey No. 995. By increasing the schedule values to 150 s, 750 s, or 1500s for the reinforced lickings, the numbers of smoking responses, nozzle lickings, and cigarettes consumed decreased. When the schedule values were decreased, relatively higher rates of smoking responses in comparison with the previous schedules were observed with the reinstatement of the RI-150 s schedule in both monkeys although the number of smoking responses did not increase with the reinstatement of the RI-30 s schedule in monkey No. 865.

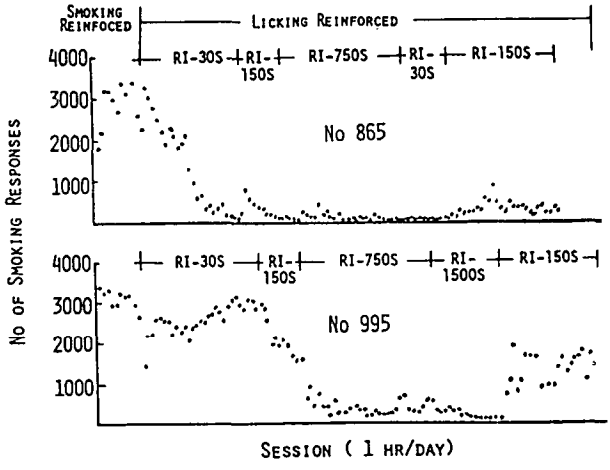

FIGURE 1. Smoking behavior in rhesus monkeys. First, smoking responses through a pipe were reinforced intermittently with sugar solution delivered from a separate nozzle. Then, lickings at the nozzle were reinforced with the solution under random interval (RI) schedules with the values described above while smoke was available from the pipe without sugar solution reinforcement.

EXPERIMENT 2. SMOKING BEHAVIOR DEVELOPED IN AN AVOIDANCE PROCEDURE

METHODS

Subjects: Four male rhesus monkeys (6.8-8.0 kg) were used. Each was housed and maintained in the same manner as in Experiment 1.

Apparatus: The experimental sessions were conducted in an experimental box where each monkey was restrained in a primate chair. A panel of transparent plastic similar to that in Experiment 1 was mounted in front of the seated monkey. The panel array, the automatic cigarette dispenser, and the brand of cigarettes used were the same as in Experiment 1. The same type of contact sensors as in Experiment 1 were used only in the early sessions for shaping avoidance responses.

Procedure: Monkeys were first trained to suck through a pipe for their daily water in the cages as in Experiment 1. Then, air-sucking responses and smoking responses at the pipe were trained by reinforcing with sugar solution as in Experiment 1, except that each monkey was restrained in a primate chair in the box and smoking responses with a puff duration of 0.2 s or longer were reinforced with the solution under the RI-30 s schedule. After stable smoking responses reinforced with sugar solution under the RI-30 s schedule were observed, the avoidance procedure was begun. In this procedure, smoking responses were no longer reinforced with the solution, but instead, either a smoking response through the pipe or a response of the monkey's face touching the pipe (connected to the contact sensor) could delay for 10 s or terminate delivery of an electric shock (2.5-6.3 mA) given to the monkey's tail. With no response, a shock of 10 or 30 s in duration was delivered after 10 s. This procedure could be described as a Sidman avoidance schedule with escapable longer shock durations (response- shock or shock-shock interval: 10 s; shock duration: 10 or 30 s). When smoking or touching avoidance responses were observed at higher rates, then only the smoking responses were allowed to be effective. When a stable and high rate of smoking responses was observed and the number of shocks delivered to the monkey per session became less than 10 for 5 consecutive sessions, the shock was no longer given to the monkeys and smoking responses were observed thereafter under the extinction condition of the avoidance procedure. The sessions in this experiment were given every day except Saturdays and holidays. Sessions ended after either 3 cigarettes were consumed or 30 m had elapsed, whichever came first. The blood nicotine levels after smoking were measured by gas chromatography method.

Results

The development of smoking behavior under the avoidance procedure was basically similar in all 4 monkeys. The number of avoidance responses by either smoking or touching increased over sessions. When touching responses became ineffective in avoiding or escaping shock, the number of avoidance response by smoking decreased at the beginning but then increased again over the sessions.

Table 1 summarizes the number of sessions required to establish smoking responses under the avoidance procedure (less than 10 shocks per session for 5 consecutive sessions) in 4 monkeys. The mean numbers of smoking responses and shocks per sessions averaged

over the 5 sessions are also shown in the same table. The sessions to the established smoking responses under the avoidance procedure varied depending on the monkeys. However, stable and high rates of smoking responses were observed in all 4 monkeys. The blood nicotine levels in the monkeys after smoking 3 cigarettes in the present avoidance procedure ranged between 31 and 59 ng/ml across monkeys.

TABLE 1. Establishment of Smoking Behavior under the Sidman Avoidance Procedure*

Monkey No.	Sessions Meeting Criterion	No. of Smoking Responses	No. of Shocks Delivered
828	166 - 170	1000.6+210.1	5.6+2.4
938	18 - 22	680.3+103.3	1.4+0.6
1004	28 - 32	364.0+ 73.1	3.8+2.6
1025	98 - 102	585.8+ 59.0	3.8+3.0

*The sessions which met the criterion of the establishment are shown for each monkey along with the means and standard deviations of smoking responses and of shocks per session. A session lasted for the time it took to consume 3 cigarettes. For the criterion, see the text.

When smoking responses were observed under the condition of extinction of the avoidance response, the smoking responses decreased within 6-11 sessions in monkey No.828, and within 11-15 sessions in monkey No.938. The mean numbers of smoking responses with standard deviation in above sessions were 0 in the former monkey and 42.8+17.4 in the latter monkey. Although smoking responses decreased over sessions in the other 2 monkeys as well, relatively high rates of the responses were still observed in sessions 46-50 in monkey No.1004 (102.8+26.8) and in sessions 76-80 in monkey No.1025 (128.6+36.8).

DISCUSSION

In rhesus monkeys, contrary to the case of intravenous nicotine self-administration behavior, cigarette smoking behavior was not so readily developed. This may be due to the aversive characteristic of cigarette smoke, the insufficient absorption of nicotine from the smoke through the buccal mucous membrane, and the fact that smoking covers more complex behavioral topography (including inhalation of the optimal amount of cigarette smoke into the lungs, etc.) than does simple pressing of a lever in a self-administration experiment. Thus, wnditioning processes with environmental factors may also play important roles in developing

smoking behavior with rhesus monkeys.

The results of Experiment 1 indicated that smoking behavior was induced by nozzle licking behavior that had in turn been reinforced by sugar solution. This phenomenon is analogous to the schedule-induced polydipsia originally reported by Falk (1961) in which water drinking was induced in rats by delivery of food pellets. The present phenomenon observed in monkeys also resembles the situation in human smoking behavior where smoking is induced or accelerated by other behaviors such as alcohol drinking, coffee drinking, and so on.

In Experiment 2, smoking behavior was developed and maintained under a negative reinforcement procedure. Comparing the present results with those reported earlier by Ando and Yanagita (1981), smoking behavior developed under the present negative reinforcement procedure seems to be more persistently maintained than that developed using a positive reinforcement procedure. The results obtained in this experiment suggest that in cases where a negative reinforcement mechanisn is involved in developing and maintaining smoking behavior, the behavior thus maintained will tend to be more persistent.

The present study may suggest that environmental factors play the primary role in developing smoking behavior, while nicotine plays a primary role in maintaining established smoking behavior.

REFERENCES

Ando, K., and Yanagita, T. Cigarette smoking in rhesus monkeys. Psychopharmacology 72:117-123, 1981.

Deneau, G.A., and Inoki, R. Nicotine self-administration in rhesus monkeys. Ann. N.Y. Acad. Sci. 142:4277-4279, 1967.

Falk, J.L. Production of polydipsia in normal rats by an intermittent food schedule. Science 133:195-196, 1961.

Jarvik, M.E. Tobacco smoking in monkeys. Ann. N.Y. Acad. Sci. 142: 280-294, 1976.

Yanagita, T., Ando, K., Oinuma, N., and Ishida, K. Intravenous self- administration of nicotine and an attempt to produce smoking behavior in monkeys. Proceedingsof the 36th Annual Scientific Meeting. Committee on Problems of Drug Dependence, National Academy of Science, Washington DC, 1974, pp.567.

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Substitution and Cross-Tolerance Profiles of Phenmetrazine and Diethylpropion in Rats Trained to Detect the Stimulus Properties of Cocaine

M. W. Emmett-Oglesby and D. M. Wood

Drugs with appetite-suppressing properties frequently have abuse potential of the amphetamine type. The abuse potential of these compounds is usually assessed through self-administration and drug preference studies, but these techniques have had limited applications in trying to predict degree of abuse potential between various compounds. In an attempt to provide a comprehensive evaluation of anorectic drugs, Schuster and Johanson (1985) have tested anorectic drugs across species for their ability to suppress food intake and to substitute for the stimulus properties of d-amphetamine. In their study, only fenfluramine and phenylpropanolamine could be differentiated from other anorectic drugs such as phenmetrazine and diethylpropion. Although diethylpropion is regarded as having less abuse potential than phenmetrazine (Cohen,1980; Hoekenga et al. 1978), these two compounds could not be differentiated with regards to their efficacy as discriminative stimuli substituting for d-amphetamine.

Our laboratory has been investigating the abuse potential of CNS stimulants using drug discrimination methodology, with special attention to the phenanenon of tolerance to the discriminative stimulus properties of cocaine. When subjects trained to detect cocaine are withheld from training and injected with cocaine every 8 hours, their ability to detect the cocaine training stimulus diminishes progressively over approximately 7 days (Wood et al., 1984) and then remains stable for at least another week of chronic injection (Wood and Emmett-Oglesby, 1985). When chronic injection is terminated, sensitivity to the training stimulus spontaneously recovers (Wood et al. 1984; Wood and Emmett-Oglesby, 1985). Based on these data, we have proposed that tolerance to the discriminative stimulus properties of cocaine may provide a model for tolerance to the subjective effects of CNS stimulants. In support of this hypothesis, we found that tolerance to the discriminative stimulus properties of cocaine wnfers cross-tolerance to the discriminative stimulus properties of methamphetamine (Wood et al., 1984).

In the present study, phenmetxazine and diethylpropion were evaluated in rats trained to detect the discriminative stimulus properties of cocaine. Tests were conducted to determine the substitution of these drugs for the cocaine training stimulus both prior to and during tolerance to cocaine. The drugs were clearly differentiated with respect to their cross-tolerance profiles.

METHODS

Subjects. Twenty-four male Long-Evans hooded rats (Charles River Breeding Laboratories, Willmington, MA) were housed individually in a large room of constant temperature (21 ± 1 °C). Body weights were maintained at 320 ± 10g by limiting daily access to food; water was freely available.

Apparatus. Discrimination training was conducted in standard operant chambers (Coulbourn Instruments, Columbus, OH). Each chamber was housed in a light and sound attenuating box that was fan ventilated. On one wall of the chamber a houselight was mounted centrally above a food cup, which was located between two response levers. Food reward (45 mg pellets, BioServ, Frenchtown, NJ) was delivered by a pellet dispenser. Recording of lever responses and scheduling of reinforcement contingencies was performed through TRS-80 Model-III microcomputers and printers (Radio Shack, Fort Worth, TX) connected to the chambers through LVB interfaces (Med Associates, East Fairfield, VT) using a program developed in this laboratory (Emmett-Oglesby et al. 1982; Spencer and Emmett-Oglesby, 1985).

Discrimination Training. Using food as a reinforcer, subjects were trained to press a lever, and their behavior was shaped progressively until 10 bar-press responses (FR10) were required to obtain reinforcement. Subjects were then trained to press one of the levers following cocaine injection and the other lever following saline injection. For this training, saline or 10.0 mg/kg cocaine was injected i.p., 15 min prior to each 10 min session. Following cocaine injection, only FR10 responses on one of the levers (the cocaine lever) were reinforced; responses on the saline lever were recorded but not reinforced. Similarly, following injection of saline, only FR10 responses on the saline lever were reinforced, and responses on the cocaine lever were recorded but not reinforced. Cocaine and saline injections were given in an irregular sequence, and no cue other than the effect of the drug was available to guide appropriate lever selection.

Only responses emitted prior to obtaining the first reinforcement were used to determine which lever was selected, and the first lever on which 10 responses occurred was considered the selected lever. Discriminative control was defined as 10 successive sessions of correct lever selection (saline following saline injection or cocaine following cocaine injection). Once this criterion had been achieved, tests were conducted whenever the correct lever was selected for four consecutive sessions.

Discrimination Testing. The testing procedure was identical to the training procedure, except that 10 responses on either lever produced food reinforcement, and sessions were conducted only until one reinforcement was obtained or 10 min had elapsed. For all test sessions, drugs were injected 15 min pretest, and the lever on which 10 responses were first emitted was recorded as the selected lever.

Procedure. Rats were assigned to three subgroups of 8 subjects each. Using one subgroup for each drug, initial dose-effect data were obtained for the generalization of cocaine (2.5, 5.0, and 10.0 mg/kg) and the substitution of phenmetrazine (0.64, 1.25, 5.0 and 10.0 mg/kg) and diethylpropion (0.32, 0.64, 1.25 and 2.5 mg/kg) to the cocaine training stimulus. Subsequently, training was halted, and all rats were injected with cocaine, 20.0 mg/kg, every 8 hours. On days 7-9, generalization and substitution data were re-determined for cocaine (5.0, 10.0 and 20.0 mg/kg), phenmetrazine (5.0, 10.0 and 20.0 mg/kg) and diethylpropion (1.25, 2.5 and 5.0 mg/kg). During generalization and substitution testing, a dose of one of the drugs was substituted for a regularly scheduled injection of 20.0 mg/kg of cocaine, and subjects were tested 15 minutes later. Otherwise, the rats continued to receive the 20.0 mg/kg dose of cocaine every 8 hours during these tests. After dose-effect curves were re-determined, chronic injections of cocaine were halted, and subjects were not trained or tested for at least 14 days. Stimulus control was demonstrated by testing for discrimination of the training dose (10.0 mg/kg of cocaine).

RESULTS

The subjects took approximately 60 sessions of training to discriminate cocaine, 10.0 mg/kg, from saline and to meet the criterion of selecting the correct lever on ten consecutive sessions. The animals were trained for another 30 sessions, and by the onset of the experiment, the discrimination of 10.0 mg/kg of cocaine fluctuated between 90 and 100%.

Prior to chronic administration of cocaine, the discriminative stimulus produced by cocaine was dose-dependent with an an approximate ED_{50} of 4 mg/kg (fig. 1). After 7 days of chronic administration, the dose-effect curve for the detection of cocaine shifted approximately 2-fold to the right (fig. 1). Chi-square analysis performed on the two overlapping doses (5.0 and 10.0 mg/kg) showed a significant effect of the chronic treatment with cocaine ($X^2 = 6.3$; $df = 1$; $P < 0.01$).

Prior to chronic administration of cocaine, phenmetrazine and diethylpropion were generalized to the cocaine stimulus, with approximate ED_{50}s of 3 and 0.64 mg/kg, respectively (Figs. 2 and 3). After 7 days of chronic cocaine administration, the dose effect curve for the detection of phenmetrazine had shifted approximately 2-fold to the right (fig. 2). Chi-square analysis on the two overlapping doses (5.0 and 10.0 mg/kg) showed a

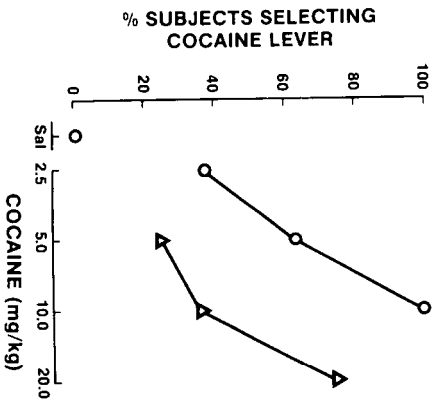

FIGURE 1. Generalization of cocaine to the cocaine training stimulus before and during chronic administration of cocaine. Ordinate: percentage of rats completing the first ten responses on the cocaine-lever. Data show selection of cocaine-lever before (0) and during (Δ) chronic treatment with 20 mg/kg/8-hr of cocaine. N=8 at all determinations.

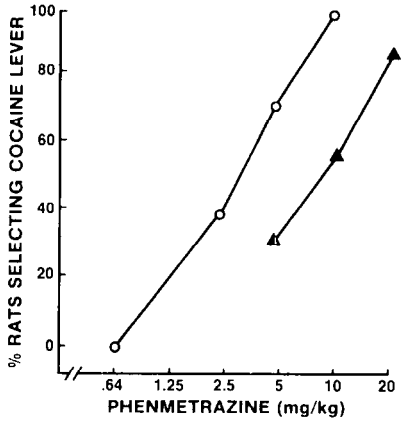

FIGURE 2. Substitution of phenmetrazine for the cocaine training stimulus before and during chronic administration of cocaine. Abscissa: dose of phenmetrazine. Ordinate: see Figure 1. Symbols and explanations are the same as Figure 1.

significant effect of chronic treatment with cocaine (X^2 = 8.5: df = 1; p< 0.01). Tolerance to cocaine also conferred cross-tolerance to diethylpropion (fig. 3), but the magnitude of the shift of the dose-effect curve was at least 4-fold. Prior to chronic cocaine administration, 88% of subjects detected a 1.25 mg/kg dose of diethylpropion as cocaine-like when given acutely. In wntrast, during chronic cocaine administration, all subjects selected the saline lever when retested at this dose. Chi-square analysis on the two overlapping doses (1.25 and 2.5 mg/kg) showed a significant effect of chronic treatment with cocaine (x^2 = 32.0; df = 1; p< 0.01). Tolerance to the stimulus properties of diethylpropion did not confer the same magnitude of tolerance to the behaviorally disruptive effects of this drug: lever responding was disrupted at 10.0 mg/kg.

CONCLUSIONS

Tolerance developed to the discriminative stimulus properties of cocaine after six days of injections with cocaine, 20.0 mg/kg/8-hr. These data agree with previous findings (McKenna and Ho, 1977; Wood et al. 1984; Wood and Emmett-Oglesby, 1985) both in terms of the time to achie#ve tolerance (6 days) as well as the magnitude of the tolerance obtained (an approximate 2-fold shift

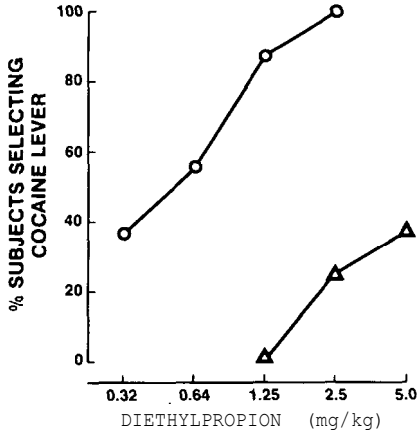

FIGURE 3. Substitution of phenmetrazine for the cocaine training stimulus before and during chronic administration of cocaine. Abscissa: dose of diethylpropion. Ordinate: see Figure 1. Symbols and explanations are the same as Figure 1.

to the right of the dose-effect curve).

Prior to chronic administration of cocaine, phenmetrazine and diethylpropion substituted for the cocaine training stimulus in a dose-dependent manner, and diethylpropion was approximately five times more potent than phenmetrazine. The present results can be contrasted with those obtained by Schuster and Johanson (1985) in Which phenmetrazine was more potent than diethylpropion in both pigeons and monkeys trained to detect the stimulus properties of d-amphetamine. This discrepancy may be due to species differences; for example, in drug preference tests in humans, these two compounds have been found to be approximately equally potent (Chait et al., 1984; Johanson and Uhlenhuth, 1978). Alternately, it may be possible that the stimulus properties of d-amphetamine and cocaine are not canpletely interchangeable, and the difference in potencies across studies may reflect different patterns of substitution for the two drugs used as training stimuli.

Tolerance to cocaine conferred cross-tolerance to phenmetrazine and to diethylpropion. The curve for the substitution of phenmetrazine for the cocaine training stimulus shifted approximately 2-fold to the right, Which is of the same magnitude as the shift for the detection of cocaine. However, the ability of diethylpropion to substitute for the cocaine training stimulus was reduced to a much greater extent. The magnitude of this cross-tolerance was such that diethylpropion did not completely substitute for the cocaine training stimulus. We previously reported that tolerance to cocaine's discriminative stimulus properties did not confer tolerance to its behavioral disrupting properties (Wood et al. 1984). This finding appears to also be true for drugs exhibiting cross-tolerance to the cocaine training stimulus: doses above 5.0 mg/kg of diethylpropion resulted in behavioral disruption such that no lever selection Was made during the 10 minute test period.

Cross-tolerance in the drug discrimination paradigm appears to be confined to drugs having stimulus properties similar to the training drug (Wood and Emmett-Oglesby, 1985). The present results are in agreement with this conclusion, and they also

suggest that within the category of drugs. that display cross-tolerance, it may be possible to differentiate them based on the magnitude of this cross-tolerance. In this regard, cocaine, methamphetamine and phenmetrazine are all Schedule II drugs, and the degree of shift in their dose effect-curves is comparable. In contrast, diethylpropion is a Schedule IV substance, is generally considered to have less abuse potential then the drugs described above (Cohen, 1980; Hcekenga et al. 1978), and shows a different profile in the test for cross-tolerance to the cocaine stimulus. These findings suggest that tolerance in the drug discrimination procedure may have potential for establishing a comprehensive evaluation of the dependence liability of CNS stimulants.

REFERENCES

Chait, L.D.; Uhlenhuth, E.H.; and Johanson, C.-E. Drug preference and mood in humans: effects of phenmetrazine. Fed Proc 43:570, 1984.

Cohen, S. Diethylpropion (Tenuate): update on abuse data. Drug Abuse Alcohol Rev 3:1-5, 1980.

Griffiths, R.R.; Brady, J.V.; and Bigelw, G.E. Predicting the dependence Liability of stimulant drugs. NIDA Res Monogr Ser 37: 182-196, 1981.

Emmett-Oglesby, M.W.; Spencer, D.G., Jr.; and Arnoult, D.E. A TRS-80-based system for the control of behavioral experiments. Pharmac Biochem Behav 17:583-587, 1980.

Hoekenga, M.T.; Dillon, R.H.; and Leyland, H.M. A comprehensive review of diethylpropion hydrochloride. In Central Mechanisms of Anorectic Drugs, S. Garattini and R. Samanin, eds., pp. 391-404, Raven Press, New York, 1978.

Johanson, C.-E. and Uhlenhuth, E.H. Drug self-administration in humans. In NIDA Res Monogr Ser 20:68-85, 1978.

McKenna, M. and Ho, B. Induced tolerance to the discriminative stimulus properties of cocaine. Pharmac Biochem Behav 7:273-276, 1977.

Schuster, C. R. and Johanson, C.-E.: Efficacy, dependence potential, and neurotoxicity of anorectic drugs. In Behavioral Pharmacology: The Current Status, L. S. Seiden and R. L. Balster, eds., pp. 263-279, Alan R. Liss, Inc., New York, 1985.

Spencer, D.G., Jr. and Emmett-Oglesby, M.W. Parallel processing strategies in the application of microcomputers to the behavioral laboratory. Beh Res Meth Inst 17:294-300, 1985.

Wood, D.M. and Emmett-oglesby, M.W. Characteristics of tolerance, recovery from tolerance, and cross-tolerance to cocaine used as a discriminative stimulus. J Pharmacol Exp Ther 1985 (In Press).

Wood, D.M.; Lal, H.; and Emmett-Oglesby, M.W. Aquisition and recovery of tolerance to the discriminative stimulus properties of cocaine. Neuropharmacol 23:1419-1423, 1984.

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Human Drug Discrimination: d-Amphetamine and Other Anorectics

L. D. Chait, E. H. Uhlenhuth, and C. E. Johanson

INTRODUCTION

An important pharmacological property of many drugs of abuse is their ability to serve as discriminative stimuli. Over the last 20 years researchers have developed and refined experimental procedures for studying the discriminative stimulus (DS) properties of drugs in laboratory animals. Typically animals are trained to emit one response (e.g. a right-lever press) after receiving a dose of drug and another response (a left-lever press) after receiving vehicle. Trained animals are then tested with other drugs to determine whether these drugs share DS properties with the training drug. Such drug discrimination (DD) studies have generally shown that drugs from different pharmacological classes do not possess similar DS properties (Schuster and Balster 1977). Furthermore, drugs that do share DS properties in laboratory animals often produce similar subjective effects in humans, a finding that has led researchers to adopt DD paradigms for studying the "subjective effects" of drugs in laboratory animals (Schuster et al. 1981).

Despite the wide use of DD procedures in other species, only a few attempts have been made to develop a comparable procedure for studying the DS properties of drugs directly in humans. The reason for this apparent lack of interest may lie in the fact that the subjective effects of drugs can be determined in humans directly by means of verbal reports (questionnaires). The Addiction Research Center Inventory (ARCI), for example, has proved to be a useful tool for classifying drugs according to their subjective effects. The Single Dose Questionnaire (SDQ), also developed at the Addiction Research Center, represents another means of studying the DS properties of drugs in humans. Although these questionnaires have yielded much useful data, their use is limited. For instance, the SDQ can be used effectively only with subjects who have taken a wide variety of commonly abused drugs, and does not provide a quantitative measure of DS effects. The ARCI does provide a quantitative measure of drug-induced changes in subjective states. However, specific scales have not been developed for all classes of psychoactive drugs, and the development and validation of such scales can be costly and time-consuming. More importantly, present methods of measuring DS effects of drugs in humans are not analogous to methods used with other species, making cross-species comparisons more difficult. Human DD studies could serve as a "missing link" between animal DD studies and studies employing conventional methods of measuring subjective effects.

We have recently developed an experimental protocol for studying the DS properties of drugs directly. in normal human. volunteers (Chait et al. 1984, 1985). To date, all subjects have been trained to discriminate 10 mg d-amphetamine (AMP) from placebo (P). AMP was chosen as the training drug because its DS properties have been widely studied in laboratory animals, and because of our experience in measuring the subjective effects of AMP in humans (e.g. Johanson and Uhlenhuth 1980). The protocol was designed, to parallel typical animal DD protocols with the substitution of a telephone verbal response for the usual lever-press or key-peck response. Subjects who reliably learned the AMP-P discrimination were then tested with other doses of AMP or with other drugs. In order to determine the relationship between the DS and subjective effects of these drugs, we also had subjects fill out subjective effects questionnaires at the same times that they made drug discrimination responses.

METHODS

Subjects

Thirty-five males and 29 females have participated to date. Each subject participated in only one study (Study 1: N=17, Study 2: N=27, Study 3: N=20). They were selected from a group of healthy adults, aged 21-35, recruited from the local university community via newspaper or bulletin board advertisements. Prior to participation potential subjects underwent a physical examination and psychiatric interview. Volunteers with histories of drug abuse or significant psychiatric or other medical disorders were not accepted. Subjects were paid a base wage at the end of each phase of the study. Informed consent was obtained.

Procedure

Subjects were told that their job was to learn to discriminate between two different drugs, "Drug A" and "Drug B," based on the effects produced by each. They were told that they could receive either appetite suppressants, sedatives or placebos. They were further informed that Drug A and Drug B would be different types. Subjects were not told that'they would be learning to discriminate an active drug from placebo. Subjects were given no other information as to what specific drugs they might receive, or what types of effects to use as "cues." Subjects reported to the laboratory between 9 and 11 a.m. three days per week (Monday-Friday) throughout the study. Upon arrival, subjects completed three subjective effects questionnaires (Profile of Mood States, a short version of the ARCI, visual analog scales). After filling these out (which took about 5 min) subjects received a capsule, which they ingested under observation of the experimenter. Subjects were then free to leave for the day, taking three additional sets of questionnaires to fill out 1, 3, and 6 hr later. They were instructed to leave the forms blank if they did not fill them out within 15 min of the scheduled time.

The protocol described here was used for the second and third studies. The protocol of the first study (Chait et al. 1984, 1985) was slightly different. Each of the studies consisted of three distinct phases:

1. Sampling/Training phase (Days 1-4). On the first and third day all subjects received Drug A, and it was identified to them as such at the

time of ingestion. All subjects received Drug B on the second and fourth day, and it was also identified to them as such. For half the subjects, Drug A was placebo and Drug B was 10 mg AMP. The assignments were reversed for the other subjects.

2. Training/Assessment phase (Days 5-11). The purpose of this phase of the study was to establish that the subjects had reliably learned the discrimination, and to provide additional exposure to the drugs for subjects who did not adequately learn the discrimination after the first four (sampling) days. On these seven (training) days, subjects received Drug A three times and Drug B four times (or vice versa), in a mixed order, with the restriction that the same drug could not be scheduled more than two days in succession. The order was different for different subjects. On these days, subjects were not told which drug they received when they ingested the capsule. At 1, 3 and 6 hr after capsule ingestion, in addition to the mood questionnaires described above, subjects filled out a form on which they identified (as Drug A or Drug B) the drug they believed they had received, and indicated on a 100-mm visual analog scale how certain they were that their identification was correct [0 = "NO IDEA (JUST GUESSING)"; 100 = "POSITIVE (ABSOLUTELY SURE)"]. Subjects were told that they were free to change their identification from hour to hour, based on what they believed at the time. There were no consequences attached to the 1- and 3-hr identifications, but the 6-hr identification was differentially reinforced as follows: After subjects filled out the final (6-hr) set of forms, they telephoned the experimenter, identified themselves, and reported their final drug identification (Drug A or Drug B). If their response was correct, they were told so and received $3.00 when they returned to the laboratory for the next session. If their response was incorrect, they were so informed and received no money at the next session. We decided that a subject had learned the discrimination if the 6-hr identification was correct either 5 days in a row, or on 6 of the 7 training days.

3. Test phase (Days 12-end). Subjects who successfully met one of the training criteria then entered the test phase. Subjects who did not were paid for their participation and debriefed. The purpose of the test phase was to determine whether the DS properties of AMP would generalize to those of other doses of AMP and other drugs. The test phase consisted of "test days" intermixed with additional training days. On test days subjects received other doses of AMP or other drugs (diazepam, phenmetrazine, mazindol, fenfluramine, phenylpropanolamine). Test days were exactly the same as training days except subjects were not informed when they telephoned whether or not their response was correct -- they were simply told that it was a "test day" and that they would receive $3.00 at the next session. Thus, on test days both responses were equally reinforced, and subjects received no feedback as to which drug they had received. Subjects were not told the purpose of test days, nor did they know when test days were scheduled until after they had reported their final drug identification. The order of treatments varied across subjects. Additional training days were interspersed over the course of the test phase in order to determine whether (and attempt to ensure that) subjects maintained the discrimination. These training days were exactly like the training days during the training/assessment phase. Training days were interspersed among the test days in an unsystematic fashion, with the restriction

that no more than two test or training days occurred in succession. The order varied across subjects.

After completing the study, subjects returned to the laboratory for a debriefing session. After the subjects filled out several personality questionnaires the experimenter questioned the subjects about their reactions to the study, described the exact nature and purpose of the study, and answered any remaining questions.

Doses of drugs were selected to be within the daily therapeutic range. All drugs were administered in 00-sized opaque gelatin capsules. The color of the capsules varied across subjects, but each subject always received the same color capsule. Drug capsules contained drug tablets plus dextrose powder; placebo capsules contained dextrose only. Placebo and drug capsules were identical in appearance.

RESULTS

Of the 64 subjects trained to discriminate AMP from P, 33 (52%) met one of the training criteria, and will be designated as "discriminators." Discriminators could reliably discriminate AMP from P by one hour after drug ingestion, and the accuracy of the discrimination increased as a function of hour. The 31 "nondiscriminators" could not discriminate as well, and their discrimination accuracy did not change as a function of hour. Subjects' ratings of how certain they were that their drug identification was correct increased as a linear function of hour, and certainty ratings of discriminators were generally higher than those of nondiscriminators, especially by hr 6.

For the subjects as a whole (N=64), AMP produced significant subjective effects (relative to P) on every subjective effects scale (10 Profile of Mood State scales, 5 ARCI scales and 6 visual analog scales). For 15 of these 21 scales, discriminators were affected significantly more than nondiscriminators. On most scales the peak effect of AMP was observed 3 hours after drug ingestion. In general, discriminators and nondiscriminators did not differ in their mood states in the absence of drug (i.e. on P days).

The results of the generalization testing are summarized in Figure 1. The DS effects of AMP were dose-related, with 2.5 mg resulting in primarily P-appropriate responding, and 5 mg intermediate (chance-level) responding. Both doses of phenmetrazine (PMT), and the high dose of mazindol (MAZ) and phenylpropanolamine (PPA) substituted for AMP. The high dose of fenfluramine (FFL) and the low dose of MAZ produced intermediate levels. of drug-appropriate responding, which reflected both between- and withinsubject variablity. Diazepam (DZ), and the low dose of PFL and PPA, produced primarily P-appropriate responding.

The subjective effects of the drugs given to discriminators on test days during the final phase of the studies are shown in Table 1. AMP produced dose-related changes in mood similar to those obtained during the earlier phases of the studies. PMT produced a profile of dose-related changes in mood very similar to that of AMP. MAZ produced dose-related increases in anxiety and LSD scores and decreases in hunger, whereas FFL (not shown in table) produced only a slight increase in "high" ratings. DZ resulted in a profile of subjective effects typical for

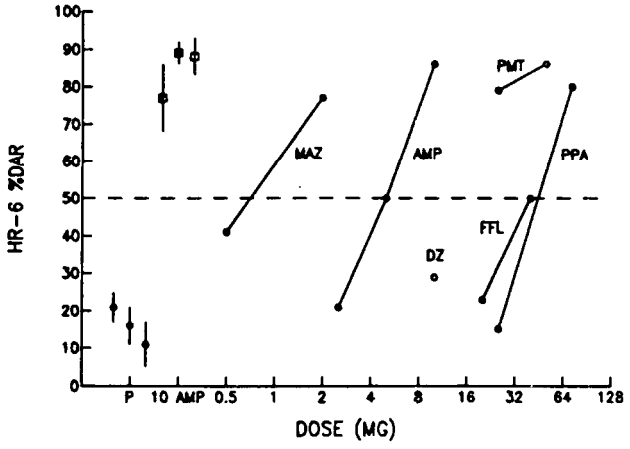

FIG 1. Group mean hour-6 percent drug-appropriate responding for the drugs tested for their ability to substitute for amphetamine. The two sets of points to the left show the data from training days (with placebo end 10 mg d-amphetamine) scheduled during the test phase of the studies. The three points in each set (from left to right) show the mean (± S.E.) % DAR from the first, second and third studies, respectively.

TABLE 1. Significant subjective effects of test drugs

	AMP	PMT	MAZ	PPA	DZ
POMS					
ANXIETY		+	+		
VIGOR	+	+		- +	
FATIGUE	-	-		+ -	+
FRIENDLINESS				-	
ELATION				-	
AROUSAL	+	+		- +	-
POSITIVE MOOD				-	
ARCI					
PCAG	-	-		+ -	+
BG		+			-
LSD	+	+	+	+ +	+
MBG	+	+			-
A		+		+	
VAS					
STIMULATED		+		+	
HIGH	+	+		+	
ANXIOUS		+	+	+	-
SEDATED	-			+	+
HUNGRY	-	-	-		

Symbols (+ and -) indicate the overall direction of change (relative to placebo) for each mood scale. Because most of the effects of PPA differed for the two doses tested, each dose was analyzed separately - the symbols on the left show the effects of 25 mg, those on the right the effects of 75 mg. Four mood scales, unaffected by any drug, are not shown. Number of subjects ranges from 7 (DZ) to 14 (PMT).

a benzodiazepine. The subjective effects obtained after PPA were particularly intriguing. It is often reported that this drug does not produce reliable subjective effects in humans at therapeutic doses. In our study, numerous subjective effects scales were affected by PPA, and the effect of the low dose (25 mg) was generally opposite to that of the high dose (75 mg). The low dose produced a profile of subjective effects similar to that of DZ, whereas the profile of effects after the high dose was more like those obtained with AMP and PMT (Table 1).

DISCUSSION

These studies demonstrate. that our experimental protocol offers a relatively simple and practical means of studying the DS effects of drugs in human volunteers. The parameters of the procedure could be easily adapted to accommodate other training drugs (with different time courses) and different routes of administration. The procedure requires no special apparatus or setting, and does not require that subjects remain in the laboratory after drug ingestion. In addition, the protocol does not require that subjects have a history of drug use. Although only slightly more than half of the subjects studied met our (rather stringent) training criteria, the proportion of subjects who learn a particular discrimination could probably be increased by increasing the dose of the training drug. As a group, our AMP nondiscriminators were generally less sensitive to the subjective effects of AMP than the discriminators. Presumably, some of these nondiscriminators would have met the training criteria if a higher training dose (15 or 20 mg) had been used.

Simultaneous measurement of DS and subjective effects allowed us to examine the relationship between these two distinct properties of drugs. Not unexpectedly, the two were closely related. Those subjects who learned the discrimination were those who were most sensitive to the mood-altering effects of AMP. The two variables also showed similar time courses and dose-related effects. There were notable dissociations between DS and subjective effects, however. For example, in two subjects DZ substituted for AMP, despite the fact that DZ did not produce AMP-like changes in mood in these subjects. The high dose of MAZ also substituted for AMP in most subjects, despite the fact that the profile of subjective effects produced by MAZ was qualitatively dissimilar to that of AMP. During the debriefing, some subjects reported using observations of their own behavior (e.g. skipping lunch, increased talking) as "cues" in making their drug discrimination responses. It may be possible for a drug to produce measurable, significant effects on mood without producing reliable DS effects. Conversely, it may be possible for a drug to produce reliable DS effects by means other than mood alteration.

The results of the generalization testing agree well with those obtained from laboratory animals trained to discriminate between AMP and vehicle (Schuster and Johanson 1985). However, more research with a variety of training and test drugs will be necessary to determine whether human DD studies will provide the same degree of drug-class specificity as animal studies. The DS properties of drugs are believed to be closely related to their dependence potential. Human drug discrimination studies may provide important information that cannot be obtained from studies which employ only questionnaires that measure specific mood states.

REFERENCES

Chait, L.D.; Uhlenhuth, E.H.; and Johanson, C.E. An experimental paradigm for studying the discriminative stimulus properties of drugs in humans. Psychopharmacology 82: 272-274, 1984.

Chait, L.D.; Uhlenhuth, E.H.; and Johanson, C.E. The discriminative stimulus and subjective effects of d-amphetamine in humans. Psychopharmacology 86: 307-312, 1985.

Johanson, C.E., and Uhlenhuth, E.H. Drug preference and mood in humans: d-Amphetamine. Psychopharmacology 71: 275-279, 1980.

Schuster, C.R., and Balster, R.L. The discriminative stimulus properties of drugs. In: Thompson, T., and Dews, P.B., eds. Advances in Behavioral Pharmacology. Vol. 1. New York: Academic, 1977. pp. 85-138.

Schuster, C.R.; Fischman, M.W.; and Johanson, C.E. Internal stimulus control and subjective effects of drugs. In: Thompson, T., and Johanson, C.E., - eds. Behavioral Pharmacology of - Human Drug Dependence. National Institute on Drug Abuse Research Monograph Dependence. National Institute on Drug Abuse ResearchWashington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981. pp. 116-129.

Schuster, C.R., and Johanson, C.E. Efficacy, dependence potential and neurotoxieity of anorectic drugs. In: Seiden, L.S., and Balster, R.L., eds. Behavioral Pharmacology: The Current Status. New York: Alan R. Liss, 1985. pp. 263-279.

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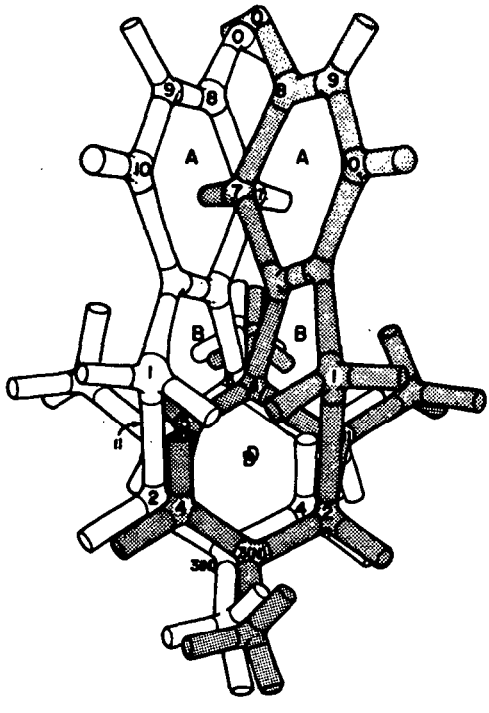
Proposal Regarding Opioid Anomalies: Preliminary Report

Mario D. Aceto and Paul C. Zenk

Studies of the optical isomers of metatocine and homologs revealed that (+)-isomers with ethyl or propyl groups at carbon 6 substituted for morphine in addicted monkeys (Ager et al., J. Med. Chem. 12, 288, 1969). Opioid activity associated with the (+)-isomer of a structurally rigid molecule such as 3-benzazocine (6,7-benzomorphan) is considered abnormal. Dreiding models of the antipodes of metazocine were constructed and it was determined that the piperidine rings could be superimposed and that the main difference was the orientation of the 11-substituent (Fig. 1).



Drieding models of (+)- and (-)-morphine were also constructed and the piperidine rings were also superimposed. The main difference was the orientation of rings C. The Drieding models were compared, and it was observed that the substituent on carbon 6 and 11 of these homologs of metazocine could impinge on the area occupied by ring C of natural morphine. Since (+)-morphine has little physical dependence liability, ring C of (-)-morphine or ring fragments of the metazocine homologs (6-ethyl or propyl of the benzormophan series) appear to be associated with mu activity.

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Differential Cross-Tolerance Among Morphine, Methadone, and Ethylketocyclazocine—EEG and Behavior

Oksoon Hong, Gerald Young, and Naim Khazan

In previous publications from this laboratory, using EEG and behavioral parameters, it has been shown that morphine-tolerant rats were not cross-tolerant to methadone or ethylketocyclazocine (EKC), but methadone- and EKC-tolerant rats were cross-tolerant to morphine (Meltzer et al. 1978; Young and Khazan 1984). Using mouse locomotor activity, Gwynn and Domino (1984) have recently demonstrated that unidirectional cross-tolerance develops between morphine and EKC. Also, the unidirectional cross-tolerance between morphine -and -methadone has been found in other studies (Brown and Garrett 1972; McMillan et al. 1980; Lange et al. 1983). Moreover, Paktor and Vaught (1984) reported differential analgesic cross-tolerance to morphine between lipophilic and hydrophilic opioid agonists. The purpose of the present study was to test for the presence of cross-tolerance between methadone, annu agonist, and EKC, a kappa agonist (Martin et al. 1976; Gilbert and Martin 1976), both of which are found to be very lipophilic with close partition coefficient values in comparison to morphine (Kaufman et al. 1975/76). (The partition coefficient value for EKC was determined in our laboratory.) Surprisingly, we found that methadone- and EKC-tolerant rats were bidirectionally cross-tolerant in spite of these opioids being mu and kappa agonists, respectively. Thus, while morphine and methadone, and morphine and EKC did not demonstrate bidirectional cross-tolerance, methadone and EKC did. It is, therefore, concluded that the phenomenon of opioid cross-tolerance does not appear to be a suitable index for delineating opioid receptor heterogeneity.

METHODS

Subjects. Female adult Sprague-Dawley rats (250 - 300 g) were used. They were anesthetized with ketamine hydrochloride (100 mg/kg, i.p.) and prepared with chronic cerebrocortical and temporalis muscle electrodes to record the electroencephalogram (EEG) and electromyogram (EMG), respectively (Khazan 1975).

Bipolar EEG electrodes were placed epidurally over the cortex, 2 mm anterior to bregma and 2 mm lateral to the midline, and ipsilaterally 3 mm posterior to bregma and 2 mm lateral to the midline. Each rat was also prepared with a chronic silicone rubber cannula inserted into the jugular vein for drug administration (Weeks 1972). After recovery from surgery, the rats were housed in individual cages with food and water available *ad libitum* and were connected to a Grass Model 7 polygraph by a flexible EEG cable (Khazan et al. 1967). A mercury pool swivel (Sutton and Miller 1963) provided a noise-free contact between the recording cable and the polygraph and permitted relatively unrestrained movement of the rats. Saline and drug injections were administered through the swivel via a feed-through cannula using a Harvard infusion pump controlled by solid state (BRS/LVE, Beltsville, MD) programing equipment. An alternate light-dark cycle was maintained with illumination from 6:00 A.M. to 10:00 P.M.

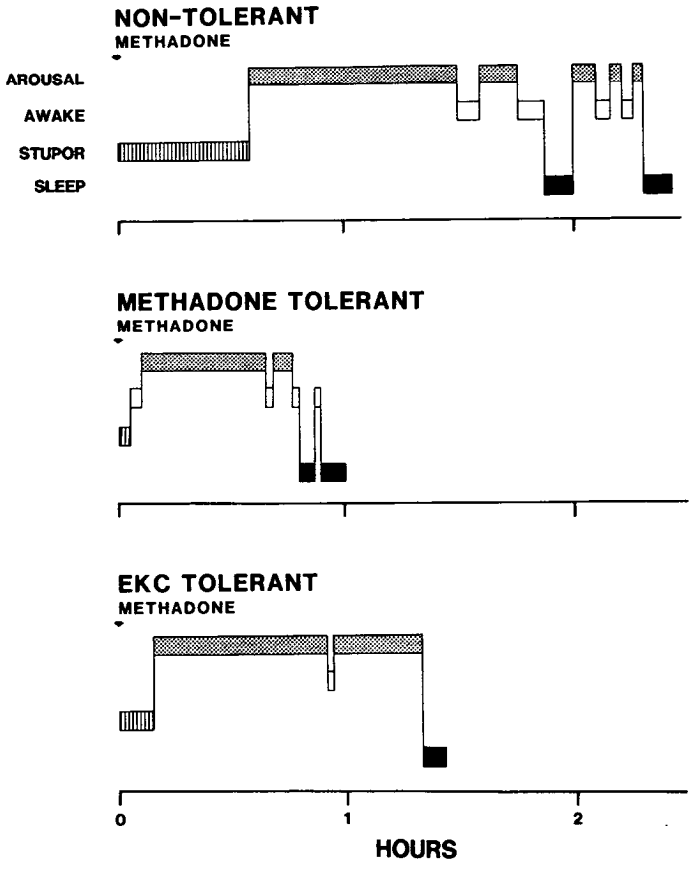
Procedure. Intravenous challenge doses of methadone hydrochloride (2 mg/kg. i.v.) or ethylketocyclazocine mathanesulfonate (4 mg/kg, i.v.) were administered in a randomized fashion to two groups of six naive rats each. An additional two groups of six rats each were made tolerant to and physically dependent on either methadone or EKC by a series of automatic i.v. injections. Methadone was initially administered at 0.25 mg/kg/2 hr for two days and increased to 0.5, 1.0 and 2.0 mg/kg/2 hr and 2.0 mg/kg/1.5 hr every other day. EKC was initially administered at 0.5 mg/kg/2 hr for two days and increased to 1.0, 2.0 and 4.0 mg/kg/2 hr and 4.0 mg/kg/1 hr every other day. At the end of the maintenance periods for methadone and EKC, tolerance and cross-tolerance to methadone (2 mg/kg, i.v.) and EKC (4 mg/kg, i.v.) were determined.

EEG and EMG activities were collected 24 hr per day on a Grass Model 7 polygraph for each rat. Drug-induced behavioral changes were observed and noted below the corresponding EEG tracings. The direct EEG, integrated EMG and behavior of the rats were used to distinguish among the behavioral states of stupor or catalepsy, arousal, quiet awake and slow-wave sleep (SWS) (Khazan et al. 1967). The durations of SWS suppression after drug administration were determined and the average values were calculated.

Drugs. Methadone hydrochloride (Merck and Co., Inc.) was dissolved in physiological saline and ethylketoeyclazocine methanesulfonate (Sterling-Winthrop Research Institute) was dissolved in physiological saline along with ermulsifying agent (Emulphor) and ethanol (18:1:1). All injections were administered i.v. in a volume of between 0.05 and 0.4 ml/rat.

Statistics. Data were analyzed by analyses of variance followed by Least Significant Difference tests for significant differences between means.

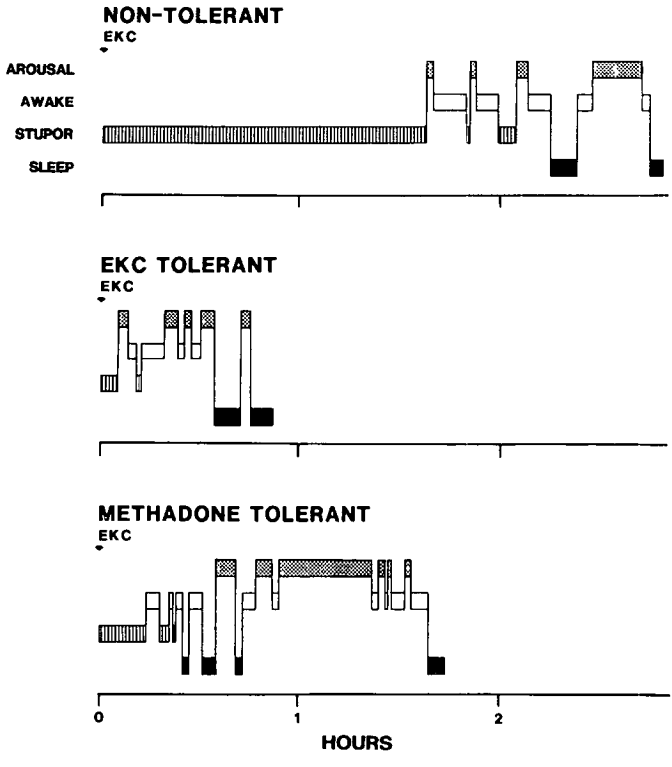
FIGURE 1.



RESULTS

Representative behavioral changes produced by the administration of methadone (2 mg/kg, i.v.) in non-tolerant, methadone-tolerant and EKC-tolerant rats are shown in Figure 1. In non-tolerant rats, methadone produced behavioral stupor accompanied by high-voltage slow-frequency EEG bursts for about 30 - 60 min which was followed by behavioral arousal associated with low-voltage desynchronized EEG for about 30 - 60 min. In methadone-tolerant rats, methadone produced less severe stupor lasting for a much shorter period of tine, which was followed by arousal lasting for a shorter period of time. Also, EKC-tolerant rats showed cross-tolerance to methadone as reflected by a reduced duration of stupor and, to a less extent, of arousal (Fig. 1; bottom).

FIGURE 2



Representative effects produced by the administration of EKC (4 mg/kg, i.v.) on ERG and behavior in non-tolerant, EKC-tolerant and methadone-tolerant rats are depicted in Figure 2. In non-tolerant rats, EKC produced a similar biphasic EEG and behavioral response consisting of about 30-60 min of behavioral stupor and associated high-voltage EEG bursts followed by up to 60 min of arousal and associated low-voltage desynchronized EEG. After chronic treatment with EKC, a significant degree of tolerance developed to the behavioral effects of EKC, as reflected in a reduced duration of stupor and arousal phases. Methadone-tolerant rats also showed a high degree of cross-tolerance to the EEG and behavioral effects of EKC (Fig. 2; bottom).

Since the administration of opioids disrupts the sleep-awake cycle and suppresses slow-wave sleep, (SWS), the latencies to

first occurrence of SWS was also used to measure the degree of tolerance and cross-tolerance. After methadone (2 mg/kg, i.v.) injections in non-tolerant rats, the first occurrence of SWS emerged at 144.5 ± 13.8 min (mean ± S.E.M.). However, in methadone-tolerant and EKC-tolerant rats, SWS appeared at 49.9 ± 3.8 and 69.0 ± 5.3 min, respectively. These values in the tolerant animals are significantly different from those in the non-tolerant animals ($p < 0.001$). Also, the latencies to the first episode of SWS after EKC (4 mg/kg, i.v.) administration in EKC-tolerant (36.8 ± 6.5 min) and methadone-tolerant (37.4 ± 2.5 min) rats were decreased in comparison to those in non-tolerant rats (115.0 ± 6.9 min), indicating significant tolerance and cross-tolerance ($p < 0.001$).

DISCUSSION

Earlier, we found that morphine-tolerant rats were not cross-tolerant to the EEG and behavioral effects of methadone, but, on the other hand, methadone-tolerant rats were cross-tolerant to morphine (Meltzer et al. 1978). Also, morphine-tolerant rats were not cross-tolerant to the effects of EKC on EEG and behavior, but EKC-tolerant rats were cross-tolerant to the effects of morphine (Young and Khazan 1984). Unidirectional cross-tolerances between morphine and methadone and between morphine and EKC have also been reported by others using different experimental protocols (Lange et al. 1983; McMillan et al. 1980; Gwynn and Domino 1984). The present study demonstrates bidirectional cross-tolerance between methadone and EKC.

It was shown in an *in vitro* study that selective mu, kappa and delta opioid agonists differentially protect receptor binding sites from deactiviation by N-ethylmaleimide (Wood and Charleson 1982). Furthermore, it has been reported with the guinea pig ileum preparation that tolerance developed to the inhibitory effects of selective mu and kappa opioid agonists on electrically-induced muscle twitches (Schulz et al. 1981). In this latter study, cross-tolerance among the selective mu agonists was found as well as among the selective kappa agonists; however, cross-tolerance between the mu and kappa agonists was not found. This led the authors to conclude that separate populations of mu and kappa receptors exist in the guinea pig ileum. Based upon cross-tolerance data with mu and delta agonists, Yaksh (1983) suggested that once animals are made tolerant to one opioid agonist, selective cross-tolerance develops such that they are cross-tolerant only to other opioids which activate the same opioid receptor subtype. However, our present data suggest that the phenomenon of cross-tolerance among opioid agonists may not be suitable as an index for defining multiple opioid receptor populations. Other experimental parameters are better suited to define opioid receptor subtypes; e.g., protection studies using receptor binding techniques.

Many investigators have tried to explain differential cross-tolerance of opioids on the basis of lipid solubility (Neil

1982; Lange et al. 1983; Paktor and Vaught 1984). For example, relative lipid solubility may influence the abilities of agonists to cross the blood-brain barrier (Paktor and Vaught 1984) or the accessibilities of different opioids to receptors at the cellular level (Neil 1982; Slotkin et al. 1980). Interestingly , morphine has a very low partition coefficient (1.42 at pH 7.4 and 37°C) (Kaufman et al. 1975/76), while methadone (Kaufman et al. 1975/76) and EKC (unpublished data from our laboratory) have very high partition coefficients; 116.33 and 112.4, respectively.

Altered pharmacological characteristics of the opioid receptors upon tolerance development may be involved in differential cross-tolerance. It was found that the endogenous opioid peptide dynorphin, a kappa opioid agonist (Chavkin et al., 1982; Oka et al., 1982; Yoshirmura et al., 1982; Corbett et al. 1982; James et al. 1982), antagonizes morphine-induced analgesia in non-tolerant mice (Tulunay et al. 1981). In contrast, dynorphin was found to augment morphine-induced analgesia in morphine-tolerant mice (Tulunay et al. 1981). Also, dynorphin has been reported to suppress withdrawal symptoms in heroin-dependent humans (Wen and Ho 1982) as well as in morphine-dependent monkeys (Aceto et al. 1982) and rats (Calligaro et al. 1983). Further-sore, in self-administration studies, we found that dynorphin, ketocyclazccine and EKC substituted for morphine in dependent rats self-administering morphine and sustained a state of dependence (Khazan et al. 1983; Young and Khazan 1983). Thus, kappa agonists appear to antagonize morphine effects in naive subjects; however, kappa agonists substitute for morphine or heroin in dependent subjects. These data suggest that critical changes may have occurred in receptor properties during the development of tolerance. These changes in receptor properties may also play a major role in defining emerging uni- or bidirectional cross-tolerance.

In conclusion, the phenomena of cross-tolerance to opioids appear to involve multidimensional factors which may include receptor heterogeneity, lipid solubility and/or changes in receptor characteristics associated with the development of tolerance.

ACKNOWLEDGMENT

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REFERENCES

References will be furnished upon request.

AUTHORS

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Three-Way Drug Discrimination in Post-Addict Volunteers: Hydromorphone, Pentazocine, and Saline

Warren K. Bickel, Kenzie L. Preston, George E. Bigelow, and Ira A. Liebson

Distinguishing different drugs on the basis of their interoceptive stimulus effects has been made possible by the development of experimental drug discrimination procedures (Overton, 1964). Drug discrimination procedures entail training subjects to emit one response after administration of one drug and to emit another response after administration of some other drug or vehicle. Similarities and differences between novel compounds and the training drugs can then be assessed by examining the extent and type of responding that occurs after the administration of the novel compound. One application of the drug discrimination procedure has been in the differentiation of drugs acting at the various opioid receptors. Studies of this type have shown that a variety of animals can distinguish between opioid drugs acting at different receptor subtypes (Herling & Woods, 1981).

Within opioid compounds, the mixed agonist-antagonist opioids are particularly interesting with respect to drug discrimination procedures because these drugs can function as agonists or antagonists. For example, the benzomorphan mixed agonist-antagonist pentazocine has been shown to share discriminative properties with the agonist morphine and the antagonist cyclazotine. Pentazocine's discriminative profile may be determined in part by the dose (Herling & Woods, 1981). Lower doses of pentazocine appear to be more similar to morphine than higher pentazotine doses. These results are consistent with the subjective effects profile of pentazocine in man in which low doses produce morphine-like subjective effects and higher doses (60 mg and above) result in a profile distinctly different from that of morphine (Jasinski et. al., 1970). This mixed action of pentazocine could make training a discrimination between pentazocine and morphine-like opioids difficult.

The purpose of the present study was to establish in man a discrimination between pentazocine, the morphine-like drug hydromorphone, and saline using a three-choice drug discrimination procedure. In this procedure a discrimination is trained between the three drugs instead of the typical two-drug discrimi-

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nation (White & Holtzman, 1981). Included in our adapted three-drug discrimination procedure are not only the operant discriminative performance, but other measures of discriminative performance, as well as subjective effect measures that have proven useful in describing the effects of the different drug classes. When combined with the traditional subjective measures, the drug discrimination procedure may result in finer and more complete descriptions of the interoceptive effects of psychoactive drugs.

METHODS

Subjects: The participants were four adult male post-addicts who gave written informed consent and were paid for their participation. The subjects reported prior narcotic use and participation in methadone maintenance and methadone detoxification programs. The subjects reported continuing sporadic opioid use, but were not physically dependent at the time of this study. The subjects lived on an eight-bed inpatient research unit throughout their participation in the study which was approximately eight weeks.

Drugs: The training drugs were saline, hydromorphone HCl 3 mg/70 kg of body weight and pentazocine 45 mg/70 kg of body weight. Hydromorphone was tested at 0.35, 0.75, 1.5, 3.0, and 4.0 mg/70 kg of body weight and pentazocine was tested at 11.25, 22.5, 45, and 60 mg/70 kg of body weight. Commercially obtained hydromorphone and pentazocine solution were diluted with bacteriostatic saline to the desired concentrations. Doses were administered intramuscularly under double-blind conditions in a constant volume of 2.5 ml/70 kg of body weight. Training drugs were identified to the subjects only by arbitrary letter codes. These drug letters remained unchanged throughout each subject's participation but were different for different subjects.

General Methods: The study proceeded in three phases: Training/Acquisition, Test of Acquisition and Test Drug Discrimination. Discrimination training was conducted on sessions 1-6, during which the subject received in a random block order, two sessions of exposure to each of the three training drugs (saline, hydromorphone and pentazocine). During these training exposures each drug was identified to the subject by the letter code prior to drug administration. The subject was instructed to attend carefully to the drug effects and try to discriminate precisely among them. In addition, the subject was informed that in each session he would be able to earn money by correctly identifying the administered drug by letter code. In sessions 7-12, acquisition of the discrimination was tested by exposing the subject in randomized block order to the training doses of each of the three training compounds to determine whether the subject could correctly identify them by letter code. During these and all subsequent exposures to test-of-acquisition sessions, the subject received feedback about the code of the administered training drug after the session. This test-of-

acquisition procedure was interpolated among test sessions during the subsequent testing phase to insure continued correct discrimination. Beginning with session 13, a series of test sessions was conducted. During this testing phase four doses of pentazocine and five doses of hydromorphone (including the training doses) and saline were tested one time in a randomized order. Following each test session, the subject did not receive feedback as to the correct drug identification. The subject was informed only that it was a test day and that he earned an amount of money (which was approximately the average amount earned over the last six test-of-acquisition sessions). Three of the four subject completed the test sessions.

Experimental Session: A microcomputer was programmed to present all questionnaires and performance tests in a prearranged and timed sequence. The subject indicated his responses on manipulanda which consisted of a numeric pad and three telegraph keys. Daily sessions began at 11:00 a.m. beginning with the measurement of respiration, heart rate, temperature, blood pressure, and pupil diameter. The subject then completed baseline subjective report forms and the psychomotor task in the experimental room. The scheduled drug was then given by i.m. injection. During the initial training sessions the subject was informed of the drug's identifying letter code at the time of injection. The subject remained under observation for the next ten minutes, and then returned to the experimental room to complete the post-drug discrimination, subjective effect, and performance testing. Post-drug testing lasted for 40 minutes and consisted of two reporting 20 min cycles. Each cycle contained assessments of drug discrimination, subjective effects, and psychomotor performance. At the end of the session the subject again completed the tasks obtained for the baseline measures and the staff again recorded the physiological measures. A sealed envelope was then opened, and the staff informed the patient of the letter code identity of the administered drug or that the session had been a test session, and the amount earned.

Discrimination Procedures: Drug discrimination data were collected via three procedures. In each of these only correct responses were converted to monetary reinforcement- for the subject. As one component of each assessment cycle, the subject made a discrete choice, naming by letter code (A, B, or C) the drug he thought he received. To gain quantitative information concerning the degree of stimulus similarity or the subject's confidence in his discrete choice, in a second component the subject distributed 50 points between one or more of the three drug alternatives, depending upon how certain he was of the identity of the administered drug. In a third component, the subject responded on a fixed interval, 1 sec schedule on telegraph keys designated with letter codes to earn points. During each 8.5 minute operant responding component, points could be earned for each of the three choice drugs by pressing the key corresponding to that drug; however, a 10 sec change over delay occurred whenever the subject switched from one key to another.

Subjective Effect Measures: The subjective effect measures included: (1) the 49-item Addiction Research Center Inventory (ARCI) short form, which contains the MGB scale ("euphoria"), the LSD scale ("dysphoria"); (2) a 32 item adjective rating scale containing an opioid agonist scale (to detect opioid agonist effects), an antagonist scale (to detect opioid withdrawal effects), and a scale composed of side-effects reported for the mixed agonist-antagonist opioids (kappa/sigma-receptor agonists), which the subject rated on a five point scale from 0 (no effect) to 4 (maximum effect); (3) 100-point quantitative visual analog scale to indicate the degree of drug effects, drug liking, "good" and "bad" effects, and a subjective "high" scale from "not at all" to "extremely".

Data Analysis: The results of the discrimination acquisition training are reported as mean percent correct identification for four subjects from sessions 7-12. The results of the subjective effect measures are reported as the mean of the overall scores (average from four exposures to each drug in sessions 1-12). Mean change from pre-drug scores are reported for ARCI scales and adjective checklist scales. Results of the dose response determinations are reported as the mean of the three subjects' single exposure at each dose level.

RESULTS

The results from the discrimination training and test of acquisition trials for the four subjects enrolled in this portion of the study are shown in Table 1 and 2. The discrimination between the three training drugs was readily learned, and few errors were made in identifying the training doses during the test of acquisition sessions (7-12). Table 1 shows drug-appropriate responding on each of the three drug levers for the operant responses as a function of the three drugs. Pentazocine was correctly identified at each presentation. The percent correct identification for hydromorphone and saline was 87.5. The other measures of discriminative performance paralleled the results of the operant measure.

Table 1
Percent of the Responding to the Three Drug Levers as a Function of the Drug Condition (Test of Acquisition Trials)

	Hydromorphone	Pentazocine	Saline
Hydromorphone Lever	87.5	0	
Pentazocine Lever	12.5	100	12.5
Saline Lever 0	0	87.5	

N = 4.

The subjective effects results produced by the training drugs in sessions 1-12 are shown in Table 2. The results of the drug "effect," drug "liking" and subject rated "good effects" ques-

tions of the quantitative visual analog scales show that qualitatively similar effects were produced on these three scales by both pentazocine and hydromorphone, with the hydromorphone effect being somewhat greater. The "bad effects" scale, on the other hand, shows a contrasting effect with pentazocine showing an increase and hydromorphone and saline showing almost no effect. The agonist adjective rating scale and the MBG scale of the ARCI show effects similar to the drug effect analog scale question with hydromorphone producing the largest increase, followed by pentazocine, and with saline showing little or no effect. The mixed agonist antagonist adjective rating scale and the LSD scale of the ARCI show an effect similar to that seen with the bad effects analog scale; namely, pentazocine increased these scales while the other two drugs had little or no effect.

Table 2

Results of Subjective Effect Measures from Training and Test of Acquisition Trials

	Hydromorphone	Pentazocine	Saline
Visual Analog Scales			
Drug Effect	45.7(13.4)	28.4(9.5)	3.6(3.0)
Drug Liking	38.3(10.7)	31.3(7.8)	3.2(2.6)
Good Effects	42.8(13.5)	32.5(10.6)	3.5(3.1)
Bad Effects	0.9 (0.5)	19.1(14.8)	0.4(0.1)
Adjective Rating Scales			
Agonist Scale	7.4(2.2)	4.1(2.5)	0.8(0.4)
Mixed Scale	1.1(0.7)	1.4(0.8)	0.1(0.2)
Addiction Research Inventory			
MBG	8.5(2.8)	2.1(1.8)	-0.1(0.5)
LSD	0.4(2.0)	1.1(0.6)	-0.2(0.6)

Standard errors are given in the parentheses. N = 4.

Dose effect functions for hydromorphone and pentazocine on the operant discrimination measure and subjective effect measures are presented in Figure 1. Orderly dose-response functions for the discrimination of both hydromorphone and pentazocine resulted with all three discrimination performance measures, although only the operant measure is graphed. Saline was correctly identified in all test sessions. Hydromorphone 0.35 mg was not correctly identified, whereas hydromorphone 0.75 and 1.5 mg produced 33% and 83% correct identifications, respectively. The training dose (3 mg) and 4 mg produced 100% correct identifications. Some of the responding at the lower doses of hydromorphone was made to the pentazocine lever (0.35 mg 33%, 0.75 mg 33%, 1.5 mg 17% responding to the pentazocine lever). Pentazocine 11.25 mg was identified as saline in each presentation, while pentazocine 20.5 mg and the training dose (45 mg) produced 100% correct identifications. The highest dose of pentazocine (60 mg) produced 83% correct identifications with the remaining 17% of responding

allocated to the hydromorphone lever. The two active test drugs also produced similar (but complementary and contrasting) orderly dose-dependent effects upon the various subjective effect measures. The results agree with those found in the discrimination training and test of acquisition sessions reported above. Both hydromorphone and pentazocine produced dose-related increases in ratings of "good effects" and the agonist scale. In contrast, only pentazocine produced dose-related increases on the ratings of the "bad effects" and the mixed agonist-antagonist scale.

DISCUSSION

The results of this study show that a discrimination between pentazocine, hydromorphone and saline can be trained in man. The three-way opioid drug discrimination was rapidly learned by post-addict volunteer subjects, and orderly dose-effect relationships were observed in this human opioid drug discrimination testing. A number of different measures of drug discrimination appear to be effective, including a "percent of drug lever" operant response measures, which is commonly used in animals studies.

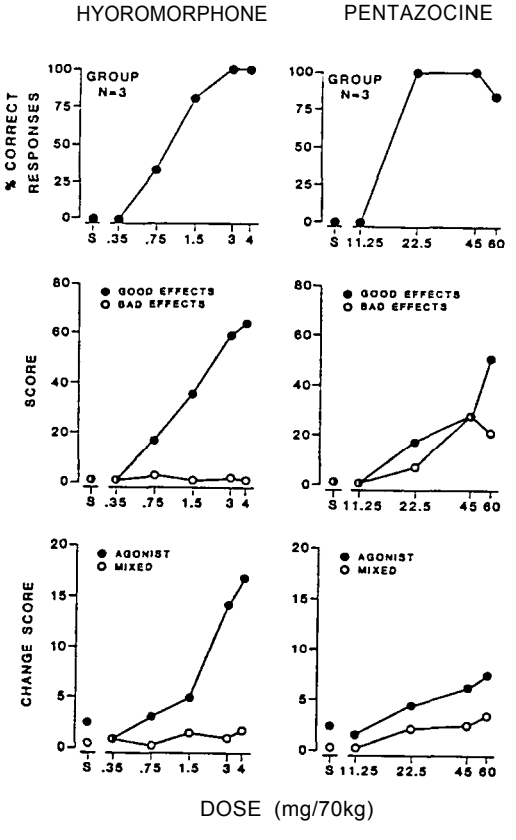

Figure 1. The left panels show the hydramorphone dose-effect functions and the right panel shows the pentazocine dose effect function from three subjects. The top two panels show the percent of drug appropriate responding from the operant measure as a function of dose. Subject rated "good" (open circles) and "bad" (closed circles) questions from the visual analog scale are present in the middle the panels. The agonist (filled circles) and mixed agonist-antagonist (open circles) from the opiate adjective checklist. Saline is indicated by S.

Some of the lower doses of hydromorphone were found to set the occasion for pentazocine responding. This finding could result from an intensity of effect discrimination between the drugs, but this explanation seems unlikely since the drugs produced a different profile of subjective effects. A more plausible explanation, which is consistent with previous findings, is that these drugs share discriminative properties and this commonality of stimulus effect may be most pronounced at low doses. This commonality might be lessened, and consequently the between-drug discriminability increased, at higher doses of pentazocine.

REFERENCES

Herling, S., & Woods, J.H. (1981). Discriminative stimulus effects of narcotics: Evidence for receptor-mediated actions. Life Sciences, 28, 1571-1584.

Jasinski, D.R., Martin, W.R., Hoeldtke, R.D. (1970). Effects of short- and long-term administration of pentazocine in man. Clinical Pharmacology and therapeutics, 11, 385-403.

Overton, D.A. (1964). State-dependent or "dissociated" learning produced with pentobarbital. Journal of Comparative and Physiological Psychology, 201, 67-75.

White, J.M., & Holtzman, S.G. (1981). Three-choice drug discrimination in the rat. Journal of Pharmacology and Experimental Therapeutics, 217, 254-262.

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Behavioral Contingencies and d-Amphetamine Effects on Human Aggressive and Non-Aggressive Responding

D. R. Cherek, T. H. Kelly, and J. L. Steinberg

Animal studies have reported biphasic effects of d-amphetamine on aggressive behavior, with low doses increasing and high doses decreasing aggressive behavior (Miczek, 1979; Smith and Byrd, 1984). Consumption of high doses of d-amphetamine has been consistently linked with the occurrence of human aggressive behavior (e.g., Cherek and Steinberg, 1985). This study examined the effects of low doses of d-amphetamine on human aggressive responding maintained at different rates by either avoidance of or escape from scheduled provocations in a laboratory setting (Cherek, 1981).

METHOD

Subjects:

Twelve males participated after giving their informed consent. Research subjects were recruited through advertisements soliciting participation in behavioral research projects. The advertisement and consent form did not mention aggressive behavior, since we did not want to imply that the research subjects must respond aggressively to participate in the experiment or to earn monetary reinforcements. All subjects were given a physical exam, including an EKG and structured psychiatric examination (Schedule for Affective Disorders and Schizophrenia-Lifetime Version--SADS-L), prior to drug administration. To avoid problems associated with drug usage by our subjects, daily breath alcohol measures were taken and urine samples were subjected to complete drug screen analysis.

PROCEDURE

Subjects were told that they would be randomly paired with another person participating in the research project at the same time, but in a different location. The situation was described as one in which they could influence the amount of money earned by another person by subtracting money from them. Subjects were told that the person with whom they were paired could choose to

subtract money from them at any time during the experimental session.

All subjects came to the medical center for daily 50-min sessions, 5 days per week. Four subjects participated in only behavioral studies to determine the effects of experimental parameters on aggressive responding. The remaining subjects participated in drug studies and were required to drink 6 oz of grape juice containing d-amphetamine elixir or wine 30 minutes prior to the session. The d-amphetamine was administered in doses of 5, 10, and 20 mg per 70 kg of body weight. The placebo consisted of grape juice and 10 ml of wine since the d-amphetamine elixir is a wine base. Successive drug doses were separated by at least 48 hours and were administered if preceding placebo session responses were within variability ranges established prior to drug administration.

The response console contained two response manipulanda (i.e., response button A and B). Pressing button A was maintained by a fixed ratio (FR) 100 schedule of point presentation. Each point delivery was indicated by increments of a counter mounted directly adjacent to button A. Subjects were paid ten cents for each point at the end of every session. Pressing button B ostensibly delivered an aversive stimulus to another person and was defined as aggressive. The completion of each fixed ratio (FR) 10 on button B resulted in the ostensible subtraction of one point, i.e., ten cents, from the other person. These two responses were concurrently available on a non-reversible option. The first response on either button activated and illuminated the button pressed and inactivated the other button. Upon completion of the ratio appropriate for the response button selected, both response options became available.

Aggressive responding was elicited by subtracting money from the subjects, which was attributed to the other person. Point subtractions were scheduled to occur at random time points throughout the session. In the absence of aggressive responses, subjects were scheduled to receive 40 provocations (point subtractions) per session. In addition to ostensibly subtracting a point from the partner, ten responses on button B initiated a provocation-free interval (PFI) during which point subtractions were not presented. PFI durations were either 125 or 500 seconds. When the PFI had elapsed, point subtractions were again scheduled to occur at random time points, Subjects were assigned to either an avoidance or an escape contingency. Under the escape contingency, at least one point subtraction (provocation) must be presented to the subjects before their aggressive responses will result in the initiation of a provocation-free interval. Therefore, in the escape contingency, regardless of the number of the subject's aggressive responses, at least five (5) point subtractions will be presented when the PFI is 500 sec and approximately 20 point subtractions will be presented when the PFI is 125 sec.

In the avoidance contingency, the situation differs in that aggressive responses prior to any provocation or during a PFI result in the initiation of a new PFI. In the avoidance condition, it is possible for the subjects to avoid all scheduled provocations.

Subjects were not actually paired with another person during the experiment, and they were debriefed and informed of this at the end of the experiment.

RESULTS

Aggressive responding usually occurred immediately following the subtraction of money from the subjects. Four subjects participated in a study of the effects of provocation-free interval (PFI) duration on the frequency of aggressive responses. Two subjects were assigned to an avoidance contingency and two subjects to an escape contingency. These subjects were exposed to the following sequence of PFI values over successive sessions: 500, 250, 125, 250, 125 and 500 seconds. PFI values were changed when the S.D. was less than 10 percent of the mean number of aggressive responses for the last three sessions. This experiment indicated that both the avoidance and escape contingency maintained a stable rate of aggressive responses over sessions. Manipulations of the PFI duration demonstrated an orderly inverse relationship between number of aggressive responses and PFI duration.

Subjects scheduled to receive d-amphetamine were assigned to either an escape or avoidance contingency for aggressive responses and to a provocation-free interval (PFI) of either 125 or 500 seconds. If possible, subjects were studied under both PFI durations.

The effects of placebo and the three doses of d-amphetamine on the number of aggressive responses per session (response button B) are shown in Figures 1 and 2 for the avoidance and escape contingencies, respectively. Dose-response curves at PFI values of 500 seconds are shown in the top half of the figures, and those at PFI values of 125 seconds are shown in the bottom half. The dose-response curves are expressed as percent changes from placebo baseline set at zero, in order to compare effects upon vastly different frequencies of aggressive responses. D-amphetamine either had no effect or increased aggressive responding at 10 mg/70 kg dose maintained by avoidance contingency. D-amphetamine resulted in decreases in aggressive responding maintained by an escape contingency in most subjects. Another subject (S-177) again evidenced an inverted U-shaped curve with aggressive responses increasing following administration of 10 mg/70 kg dose.

D-amphetamine generally resulted in dose-dependent increases in non-aggressive monetary reinforced responding. No inverted

U-shaped relationship between non-aggressive responding and d-amphetamine dose was observed.

DISCUSSION

The initial behavioral study indicated that both escape and avoidance contingencies maintained stable aggressive responding over sessions, and that the rate of aggressive responding changed in an orderly fashion when PFI durations were changed.

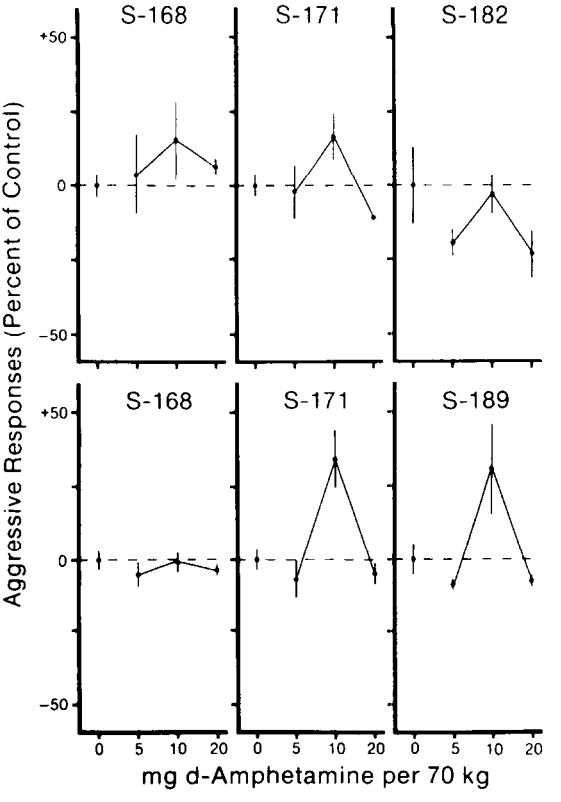

FIGURE 1. The effect of placebo (0) and three doses of d-amphatamine (5, 10 and 20 mg/70 kg) on aggressive responses which ostensibly subtracted points exchageable for money from a fictitious partner and which were maintained by initiation of provocation-free intervals of 500 seconds (top half of figure) or 125 seconds (bottom half of figure) during which no provoking point subtractions were presented. For these subjects, and avoidance cotingency was stipulated between aggressive responses and PFI. Data are expressed as percentage changes from placebo sesssions set at zero. Drug data points represent the mean of 3 different sessions. Vertical lines at all data points represent ± SEM.

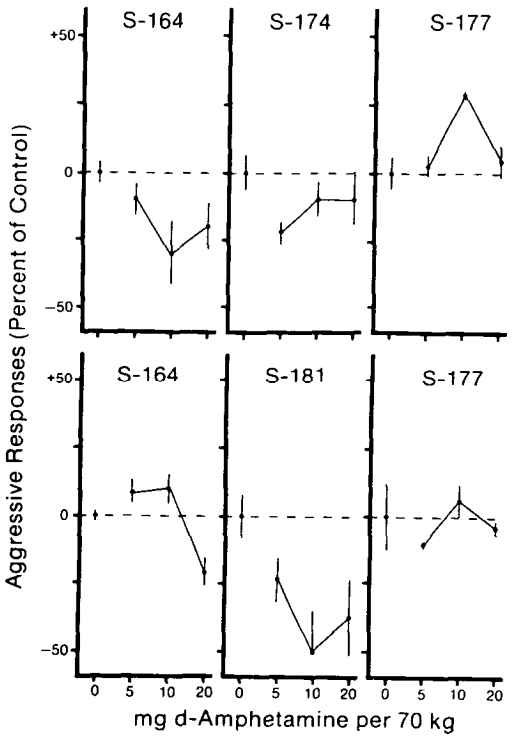

FIGURE 2. The effect of placebo (0) and three doses of d-amphetamine (5, 10 and 20 mg/70 kg) on aggressive responses which ostensibly subtrated points exchangeable for money from a fictitious partner and which were maintained by initiation of provocation-free intervals of 500 seconds (top half of figure) or 125 seconds [bottom half of figure during which no provoking point subtractions were presented. For these subjects, an escape contingency was stipulated between aggressive responses and PFI. Data are expreaed as peacentage changes from placebo sessions set at zero. Drug data points represent the mean of 3 different sessions. Vertical lines at all data points represent ± SEM.

D-amphetamine increased non-aggressive monetary reinforced responses in most subjects. Dose-response curves for aggressive responses were frequently biphasic with increases observed at 10/70kg doses and decreases observed at higher doses. Similar biphasic effects of d-amphetamine on animal aggressive behavior have been reported. Smith and Byrd (1984) have reported similar inverted-U-shaped functions of the effects of d-amphetamine on aggressive and threat behaviors in male stumptail macaque monkeys, and Emley and Hutchinson (1983) have reported similar effects of d-amphetamine on shock-elicited biting in squirrel monkeys.

Many subjects decreased aggressive responses to near or below placebo levels following the administration of the highest d-amphetamine dose (20mg/70kg). This effect was not observed on the number of monetary reinforced responses, which remained elevated or increased following the 20mg/70kg dose. This indicates that the decrease in aggressive responses observed at the highest dose was not due to an increase in behavior incompatible with button pressing.

Preliminary results indicate that the contingency relationship between aggressive responses and subsequent provocation (avoidance vs. escape) may alter the behavioral effects of d-amphetamine on aggressive responses.

REFERENCES

Cherek, D.R.: Effects of smoking different doses of nicotine on human aggressive behavior. Psychopharmacology 75:339-345, 1981.

Cherek, D.R. and Steinberg, J.L.: Effects of drugs on human aggressive behavior. In: G.D. Burrows and J.S. Werry (Eds.), Advances in Human Psychopharmacology. Vol. IV, JAI Press, Greenwich, CN, 1985 (in press).

Emley, G.S. and Hutchinson, R.R.: Unique influences of ten drugs upon post-shock biting attack and pre-shock manual responding. Pharmacol Biochem Behav 19:5-12, 1983.

Miczek, K.A.: A new test for aggression in rats without aversive stimulation: Differential effects of d-amphetamine and cocaine. Psychopharmacology 60:253-259, 1979.

Smith, E.O. and Byrd, L.D. Contrasting effects of d-amphetamine on affiliation and aggression in monkeys. Pharmacol Biochem Behav 20:255-260, 1984.

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Involvement of the Ventral Tegmental Dopamine System in Opioid and Psychomotor Stimulant Reinforcement

Michael A. Bozarth and Roy A. Wise

We have previously reported evidence that opioid reinforcement is dependent on action in the ventral tegmental area. Rats will self-administer morphine directly into the ventral tegmental area (Bozarth and Wise, 1981a), and the approximate anatomical boundaries of these reward-relevant opiate receptors correspond to the location of the dopamine-containing cell bodies in the ventral tegmentum (Bozarth, 1982; Bozarth and Wise, 1982). This reinforcing action of morphine is anatomically dissociable from physical dependence mechanisms (Bozarth and Wise, 1983a, 1984), and reward from systemically administered heroin is blocked by the administration of dopamine-receptor blockers (Bozarth and Wise, 1981b; Phillips et al., 1982).

The reinforcing action of psychomotor stimulants is also attenuated by dopamine-receptor blocking drugs (Yokel and Wise, 1975, 1976). Lesions of the dopamine-terminal field in the nucleus accumbens disrupt intravenous stimulant self-administration (Lyness et al., 1979; Roberts et al., 1977, 1980), and amphetamine has been shown to be self-administered directly into this brain site (Hoebel et al., 1983).

These data suggest that the reinforcing actions of both opioids and psychomotor stimulants are mediated by the ventral tegmental dopamine system. This has led to speculation that a common reward substrate may be involved in the rewarding effects of these two pharmacologically distinct classes of drugs (Bozarth and Wise, 1983b; Wise and Bozarth, 1981, 1982).

Experiment I: Effect of Ventral Tegmental Lesions on Intravenous Heroin Self-Administration

The ventral tegmental dopamine system has terminals in several brain regions including the frontal cortex and amygdala, but most work regarding the effects of lesions on drug self-administration has focused on the terminal field located in the nucleus accumbens. Dopamine-depleting lesions of this site attenuate psychomotor stimulant self-administration (Lyness et al., 1979; Roberts et al., 1977, 1980). Recently, it has been reported

that similar lesions fail to modify heroin intake (Petitt et al., 1984; also Bozarth and Wise, unpublished observation). This finding has been interpreted by some to suggest that opioid reinforcement involves mechanisms other than those mediating psychomotor stimulant reinforcement (e.g., Koob, 1985). This conclusion, however, neglects evidence that psychomotor stimulant reinforcement may also involve projections of this system outside of the nucleus accumbens; (a) psychomotor stimulants are self-administered directly into the frontal cortical projections of this system (Goeders and Smith, 1983; Phillips et al., 1981), and (b) some residual responding for intravenous stimulant drugs is present even after lesions of the nucleus accumbens (Roberts et al., 1980). Thus, other terminal projects of this system maybe-involved in reward from psychomotor stimulants. Another approach to assessing the importance of the ventral tegmental dopamine system in reinforcement from systemic opioid injections is to lesion the cell bodies of this system (viz., directly at the ventral tegmentum) and simultaneously deplete all of the terminal projections of this system. Previous work has shown that dopamine-depleting lesions at the ventral tegmentum effectively disrupt psychomotor stimulant self-administration (Bozarth and Wise, unpublished observation; Roberts and Koob, 1982).

METHODS

Rats were stereotaxically microinjected with 6-OHDA (8 µg/2 µl) into the ventral tegmentum and received intravenous catheters. Some subjects were pretreated with pargyline (50 mg/kg, i.p.) and desmethylimipramine (25 mg/kg, i.p.) to selectively destroy dopamine-containing neurons (n=15), while others received 6-OHDA alone which depletes both dopamine and norepinephrine (n=13). After 7 to 10 days recovery from the surgical procedure, the subjects were tested for the acquisition of a lever-pressing response to self-administer heroin (0.1 mg/kg/infusion) during 2-hour daily sessions. Testing continued for a total of 20 days. Other unlesioned subjects were tested for heroin (n=14) and saline (n=7) self-administration. Data from the second hour of testing were used to minimize the effects of session duration on mean hourly response levels (Bozarth, unpublished observation).

RESULTS

Figure 1 shows the mean levels of drug intake across the 20 days of testing for the 6-OHDA lesioned group (subjects not pretreated with pargyline and desmethylimipramine), for the unlesioned group, and for control animals tested for saline self-administration. Unlesioned subjects learned to self-administer heroin while those injected with 6-OHDA showed responding similar to saline control animals. Figure 2 compares the effects of 6-OHDA only (dopamine and norepinephrine depletions) and 6-OHDA plus pargyline and desmethylimipramine (dopamine-specific

depletions); the fact that similar effects on behavior were produced by both treatments suggests that the lesion effect was due to dopamine depletions and that noradrenergic systems are not involved. The level of drug intake was also shown to be related to the extent of lesioning (see Figure 2).

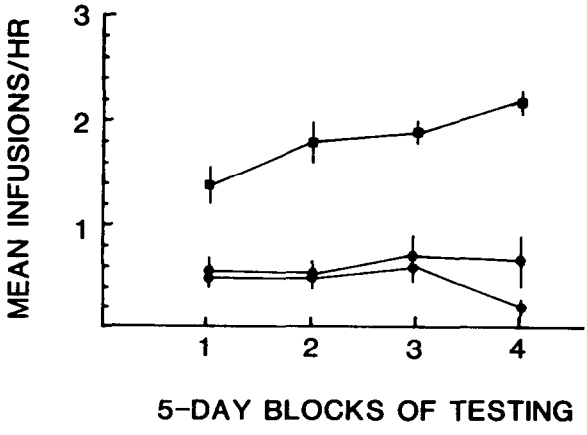

FIGURE 1: The effect of 6-OHDA lesions on intravenous heroin self-administration. ◆ 6 -OHDA lesioned; ■ heroin control; ● saline control. The data depict the means and SEMSs of 5-day blocks of testing.

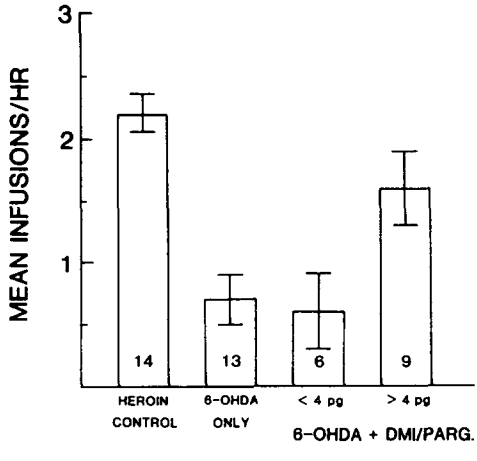

FIGURE 2: The effects of 6-OHDA lesions on intravenous heroin self-administration. Data represent the last 5-day block of testing. Numeric values inside the bars indicate the numbers of animals tested in each condition; numeric values below the bars depict the level of dopamine remaining after lesioning. Control Dopamine levels in the ventral tegmentum were 11.09 ± 2.33 pg/µg.

To determine if nonspecific effects on motor activity could account for the effect of these dopamine-depleting lesions in heroin intake, a separate group of rats was tested for the acquisition of a lever-pressing response to receive food. Rats with ventral tegmental lesions and food-deprived to 80% of their ad libitum weight learned to lever-press for food at rates comparable to unoperated control subjects (means = 94 ± 18 and 103 ± 19/20 minutes, respectively; n=11/group). This rules out any possible effect of these lesions on general motor activity and suggests that the effect of these lesions is specific to drug-reinforced responding.

Experiment II: Effect of Ventral Tegmental Morphine Injections on Intravenous Cocaine Self-Administration

The results from Experiment I appear to confirm the hypothesis that opioid and psychomotor stimulant reinforcement involve a common neural substrate. If both classes of drugs derive their reinforcing actions by the activation of this ventral tegmental system, then the activation by one of these drugs should render activation by the other redundant. That is, the opioid action in the ventral tegmental area should be equivalent to psychomotor stimulant activation in the terminal fields of this system.

Animals given noncontingent injections of a drug while intravenously self-administering that compound show a pause in their responding for drug. This is probably related to the subjects' attempt to maintain a constant level of rewarding drug action (Wise, 1985; Yokel, 1985). If opioids are rewarding because of their action at the ventral tegmental dopamine-containing cell bodies and psychomotor stimulants are rewarding because of their action in the dopamine-terminal fields of the same system, then opioid activation at the ventral tegmentum should cause a significant change in the intravenous self-administration of psychomotor stimulant.

METHOD

Rats were stereotaxically implanted with unilateral cannulae in the ventral tegmental area and received intravenous catheters. After 5 to 7 days recovery from the surgical procedure, they were trained to intravenously self-administer cocaine (1 mg/kg/infusion) during daily 6-hour test sessions. Once patterns of responding for cocaine stabilized (usually within 10 to 15 days of testing), the subjects were unilaterally microinjected with drug vehicle (i.e., Ringer's solution) into the ventral tegmental area. Next, a series of central morphine injections (0.3 to 10.0 µg/0.5 µl Ringer's solution) were begun with microinjection challenges occurring on every third day of testing. After the completion of this phase of testing, the central morphine challenge of intravenous cocaine self-administration was repeated but with narcotic antagonist injections 20 minutes prior to testing (naltrexone hydrochloride, 3 mg/kg, i.p.). This latter test should determine if the effect of

central morphine injections is due to a specific opiate-receptor mediated action or is the result of some nonspecific physico-chemical interaction.

RESULTS

Changes in cocaine intake after morphine microinjections are shown in Figure 3. There was a dose-dependent decrease in responding for intravenous cocaine, and the time-course of this effect corresponds to the time-course of other morphine effects from central injections (Bozarth, unpublished observation). Pretreatment with naltrexone had no effect on control levels of responding for cocaine but did antagonize the effect of central morphine on cocaine intake (see Figure 4). These data indicate that central morphine injections can cross-substitute for systemic cocaine reinforcement and that this is due to a specific effect mediated by opiate receptors.

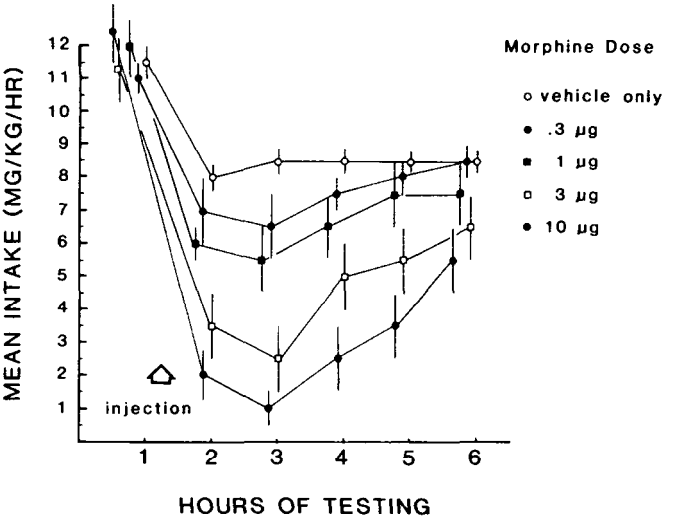

FIGURE 3: The effect of noncontingent ventral tegmetal morphine injections on intravenous cocaine self-administration. All microinjections were unilateral in 0.5µl Ringer's solution. Ventral tegmental injections were given 1 hours into the test session.

There are two points that deserve special mention regarding the effect of ventral tegmental morphine on responding for intravenous cocaine injections. First, morphine microinjections produce a response slowing and not a true response pause. This would be expected from unilateral activation of a reward substrate that is bilaterally activated by systemic cocaine injections: the intravenous cocaine effect produced on the side

contralateral to the morphine injection should continue to contribute to the net reinforcing impact of this experimental condition. Second, an examination of the individual data records reveals that the inter-response times for cocaine self-administration are increased following ventral tegmental morphine injections and gradually return to baseline values in an orderly fashion. If the effect of these microinjections on cocaine intake were the result of some nonspecific effect on general motor activity, such orderly data would not be expected. Also, these morphine microinjections have been reported to increase (not decrease) locomotor activity (Joyce and Iversen, 1979), and several subjects increased responding on an "inactive" lever while they decreased lever pressing on the cocaine associated lever; thus, these microinjections might increase lever pressing in nonspecific fashion, but they would be unlikely to produce a nonspecific decrease in drug intake.

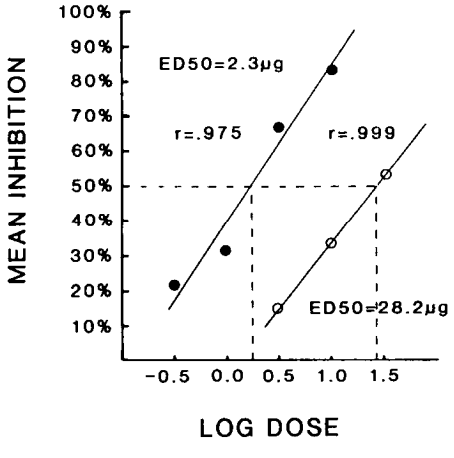

FIGURE 4: Dose-response analysis illustrating the effect of noncontingent ventral tegmental morphine injections on responding for intravenous cocaine. Data represent the percent inhibition of normal drug intake during the time of peak drug action (i.e., 7 and 2 hours after microinjections). The dose-response curve was shifted to the right by systemic naltrexone injections 20 minutes prior to testing.

DISCUSSION

The experiments reported in this paper confirm the importance of the ventral tegmental dopamine system in opioid reinforcement and strengthen the notion that opioid and psychomotor stimulant reinforcement may involve the activation of a common reward

substrate. Although dopamine-depleting lesions of the nucleus accumbens produce different effects on heroin and cocaine self-administration (Bozarth and Wise, unpublished observation; Pettit et. al., 1984), depletions at the level of the dopamine-containing cell bodies of the ventral tegmentum produce similar effects on the intravenous self-administration of both classes of compounds. Furthermore, the demonstration that morphine microinjected into the ventral tegmental area results in a dose-dependent attenuation in responding for intravenous cocaine provides direct support for the hypothesis that opioids activate the same rewarding neural pathway as psychomotor stimulants.

The notion that opioids and psychomotor stimulants may activate the same reward pathway is consistent with their well documented effects on brain stimulation reward (e.g., Esposito and Kornetsky, 1978). These and other addictive drugs lower thresholds (Esposito and Kornetsky, 1978) and increase rates of lever pressing (Reid and Bozarth, 1978) for brain stimulation reward. The important role of dopamine in the rewarding effects of electrical brain stimulation (Fibiger, 1978; Wise, 1978) and its apparent role in psychomotor stimulant and opioid reinforcement have prompted speculation about a common neural circuit underlying these rewarding events (Wise and Bozarth, 1984). Whether additional mechanisms are involved in the long-term maintenance of heroin self-administration remains to be determined.

ACKNOWLEDGMENTS

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Acute Chlordiazepoxide Dependence in the Rat: Comparisons to Chronic

Norman R. Boisse, Rani M. Periana, John J. Guarino, and Howard S. Kruger

Benzodiazepines are one of the most widely prescribed drug classes in the practice of medicine. Diazepam, chlordiazepoxide and all other congeners currently available in the U.S. are CNS depressants that are capable of producing physical dependence characterized by a depressant type withdrawal syndrome with few distinctions from and many similarities to barbiturate withdrawal (Ryan and Boisse 1983; Gay et al. 1983).

Experimental benzodiazepine dependence has been produced in the mouse, rat, cat, dog, monkey and baboon (Ryan and Boisse 1983; c f Brady and Lukas 1984) and with several different drugs including diazepam, chlordiazepoxide and flurazepam. The severity of the withdrawal syndrome has been shown to increase with dose and duration of chronic treatment (Boisse et al. 1982; Lukas and Griffiths 1982). Interestingly, Lukas and Griffiths (1984) have reported consistent withdrawal reactions from only 3 days of exposure but not at 1 day or 1 hour of diazepam infusion in drug-naive baboons. However, more information is needed regarding the minimal dose-duration requirements for other ligands and other species.

This report describes such a study for acute chlordiazepoxide dependence in the rat. Over the past several years our laboratory has accumulated dose-duration data for chronic chlordiazepoxide dependence which provides an appropriate group for comparison. Dependence is revealed by precipitation with the benzodiazepine receptor antagonist Ro 15-1788.

METHODS

Male Sprague-Dawley rats (375-500 gms, Charles River Breeding Laboratories, Wilmington, MA) were used and housed two per cage in our environmentally controlled animal facility. All drug solutions were freshly prepared. Chlordiazepoxide HCl was administered intragastrically by gavage. Ro 15-1788 was suspended in 10% acacia and injected i.p. Concurrent controls received

isovolumic water or vehicle.

Initial acute exploratory studies utilized the initial loading dose (450 mg/kg) for the induction of severe dependence In the chronically equivalent maximally tolerable (CEMT) model for chlordiazepoxide in the rat (Ryan and Boisse 1983). Ro 15-1788 (25 mg/kg) was injected at 4 and subsequent 24 hour intervals in separate groups of animals. Once acute dependence was revealed, Ro 15-1788 dose was optimized for the pretreatment time that gave maximal dependence. Subsequently, lower doses of chlordiaze-poxide--10, 20, 40, 75 and 150 mg/kg--were evaluated for Ro 15-1788 challenge at t = 4 hours.

Chronic chlordiazepoxide or water treatments were all twice daily (8 A.M. and 6 P.M.) for 5 weeks. Chronic doses were 5, 10, 20, 40, 75, 150 mg/kg (Boisse et al. 1982) or CEMT (Ryan and Boisse 1983). The principal chronic comparison group was 75 mg/kg which gave the maximum Ro 15-1788 precipitated withdrawal. The Ro 15-1788 challenge was given 4 hours after the last chlordiazepoxide dose.

The method of withdrawal evaluation including operational definitions for signs and each of their grades has been reported (Ryan and Boisse 1983). Three or four independent trained observers rated signs just prior to (t = 0) and at t = 5, 15, 30 and 60 minutes after Ro 15-1788. All raters but one were blind to the treatment. The intensity of individual signs two) and of the syndrome (total WD) was estimated from the average rating of all co-observers. To compensate for initial baseline differences in total WD score and more sensitively quantify the reaction to Ro 15-1788 challenge, the initial WD score was subtracted from the WD score obtained after Ro 15-1788 and is called the delta (Δ) WD score.

Gross neurological testing included 5 different ladder and open-field tests with operationally defined grades (Ryan and Boisse 1983) which detected CNS depression. All grade points accrued for these tests were pooled to give a TDP or "total depression point" score. Inter-observer reliability for both withdrawal and depression tests is high and has been reported (Ryan and Boisse 1983).

RESULTS

Acute dependence was maximally developed 76 hours after a maximally tolerable dose of chlordiazepoxide. The withdrawal reaction was rapid in onset and fully developed by 5 minutes after Ro 15-1788. Recovery from withdrawal was usually complete by 2 hours.

Acute dependence began to emerge as soon as 28 hours, was well developed from 52-100 hours and was lost by 124 hours after chlordiazepoxide 450 mg/kg. At all observation times that dependence was detectable, rats showed some CNS depression (TDP

criterion) before Ro 15-1788 that was reversed by Ro 15-1788. At 4 hours, Ro 15-1788 failed to completely reverse residual TDP; while at 124 hours, chlordiazepoxids no longer produced discernible CNS depression.

The acute and chronic dose-response curves for precipitated withdrawal (Δ WD criterion) were parallel (acute below chronic) and both peaked at 75 mg/kg. However, although the withdrawal precipitated 4 hours after the low acute dose (75 mg/kg) was just as severe as that for the acute high dose (450 mg/kg) at 76 hours, it was less reliable. Therefore, the acute syndrome for 450 mg/kg was selected for detailed comparison to the most severe chronic syndrome (75 mg/kg dose).

For the total WD score criterion, net withdrawal (test-control) was 9.2 for chronic and 3.1 for acute. Therefore, chronic dependence was 3 times more severe than acute dependence.

Sign by sign analysis of the withdrawal responses revealed substantial incidences for several signs in the control groups, usually for minimal grades. This fact complicated the direct comparison of acute and chronic dependence. Accordingly, the respective control groups were used to develop operational criterion for the occurrence of signs in the drug-treated groups. The true incidence due to dependence for each sign was estimated by defining the presence of the sign by a severity that exceeded the upper 95% confidence limit for that sign in the matched controls. All signs for acute dependence (except diarrhea, 18% incidence) were also seen in chronic dependence. Virtually all chronics exhibited struggle on handling and tremors while these were absent in acutes. Frequencies of signs were usually greater in chronic but several signs exhibited similar frequencies.

The mean intensities of individual signs during the peak of the syndrome were also analyzed. For acute dependence, these signs were significantly more severe than in controls by ordered Chi square contingency table analysis. These signs are tail erection, arched back and muscle hypertonus. For chronic dependence, twelve signs were significantly more intense than controls; these were struggle on handling, high step, tremors, salivation, arched back, irritability, reduced spontaneous motor activity, muscle hypertonus, increased startle (tactile evoked), curled claw, piloerection, and ear twitches. Major differences between acute and chronic were for struggle on handling, startle--tactile, salivation, irritability, and tremors, which were all more pronounced in the chronics.

DISCUSSION

This study demonstrates that physical dependence can be well developed following a single intoxicating benzodiazepine exposure. Moreover, a rat model for acute chlordiazepoxide dependence that produces reliable antagonist (Ro 15-1788) precipitated withdrawal has been achieved.

Measurement of CNS depression and of precipitated withdrawal signs over time following an acute chlordiazepoxide dose revealed that measurable CNS depression and its reversal are a necessary but not a sufficient precondition for antagonist efficacy in producing withdrawal. Clinical implications are that there may be a risk of iatrogenic withdrawal in reviving over-dosed patients. However, it is difficult to predict in man since the response to the antagonist in the rat varied with chlordiazepoxide and antagonist dose and their dose interval.

The minimal duration of acute exposure required by the brain to develop quantifiable dependence may be less than 4 hours since time must pass following intragastric injection for absorption to be complete. Intravenous acute chlordiazepoxide treatments will be needed to obtain an even more refined picture of the minimal dose-duration for the CNS to become dependent.

Acute and chronic chlordiazepoxide dependence in the rat have many points of similarity. All signs seen in acute are also seen in chronic. The chlordiazepoxide dose-response curves for acute and chronic dependence were parallel, supporting the hypothesis that precipitated withdrawal reflects a common mechanism. However, when maximal acute withdrawal is compared to maximal chronic withdrawal, the acute represents about one-third of chronic in terms of total WD score corrected by respective controls. These observations suggest that there may be two mechanisms for dependence induction, one which is very fast (4-76 hours) and one which is very slow (5 weeks) to develop and apparently contributes more to the final picture for chronic dependence.

The most parsimonious explanation for these similarities and differences between acute and chronic dependence is that they share a common mechanism at the level of the receptor for expression of withdrawal but differ in receptor-coupled counteradaptive mechanism.

REFERENCES

Boisse, N.R.; Gay, M.H.; Guarino, J.J.; Kruger, H.; and Ryan, G.P. Antagonist induced withdrawal following chronic chlordiazepoxide dosing in the rat. Neuroscience Abstracts 8:109.12, 1982.

Boisse, N.R.; Ryan, G.P.; and Guarino, J.J. Experimental induction of benzodiazepine physical dependence in rodents. In: Harris, L.S., ed. Proceedings of the 43rd Annual Scientific Meeting, Committee on Problems of Drug Dependence 1981. National Institute on Drug Abuse Research Monograph 41. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1982. pp. 191-199.

Brady, J.V., and Lukas, S.E. Testing Drugs for Physical Dependence Potential and liability. The Committee on Problems of Drug Dependence, Inc. National Institute on Drug Abuse Research Monograph 52. DHHS Pub. No. (ADM) 84-1332. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1984.

Gay, M.H.; Ryan, G.P.; Boisse, N.R.; and Guarino, J.J. Phenobarbital tolerance and physical dependence: chronically equivalent dosing model. Eur J Pharmacol 95:21-29, 1983.

Lukas, S.E., and Griffiths, R.R. Precipitated withdrawal by a benzodiazepine receptor antagonist (Ro 15-1788) after 7 days of diazepam. Science 217:1161-1163, 1982.

Lukas, S.E., and Griffiths, R.R. Precipitated diazepam withdrawal in baboons: effects of dose and duration of diazepam exposure. Eur J Pharmacol 100:163-171, 1984.

Ryan, G.P., and Boisse, N.R. Experimental induction of benzodiazepine tolerance and physical dependence. J Pharmacol Exp Ther 226:100-107, 1983.

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Physical Dependence of Benzodiazepines in the Rat and Dog

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The purpose of this paper is to summarize efforts to understand benzodiazepine dependence in the rat and dog. Although it is generally assumed that all benzodiazepines have an equal propensity to produce physical dependence, there are few well-controlled studies in the literature which have evaluated this issue. Studies herein reported compare the ability of diazepam and its two metabolites, nordiazepam and oxarepam to produce physical dependence. Most studies were conducted in rats and dogs prepared with a gastric fistula which facilitated chronic dosing with water insoluble drugs. All of the methodologies used in these experiments have been previously described (see Nozaki, et al., 1981; Martin, et al., 1982; McNicholas and Martin, 1982; McNicholas, et al., 1983) and will be only briefly described here. Rats and dogs were surgically prepared with a chronic gastric fistula. Diazepam, nordiazepam, oxazepam or lorazepam was diluted to appropriate concentrations with lactose and prepared for administration in #4 capsules which were administered via the gastric fistula 4 times daily, at 0700, 1300, 1900 and 2400 hours. Rats were made dependent on pentobarbital by feeding them ground Purina Rat Chow mixed with pentobarbital. Every 2 weeks rats dependent on nordiazepam or oxazepam were withdrawn for different time periods according to a replicate block Latin square cross-over design and observed for 8 hours for signs of abstinence. All rats were observed from zero hours of abstinence until the end of the abstinence syndrome. Diazepam (60 mg/kg/day) and lorazepam (100 mg/kg/day) dosed dogs were stabilized at the highest dose level that was consistent with maintaining appetite, body weight and general good health. The dogs maintained on nordiazepam were stabilized at a dose that produced plasma levels of nordiazepam, as measured by the method of Rao, et al. (1982), comparable to the plasma levels of nordiazepam diazepam-dependent dogs. The time course of abstinence was studied using a Latin square crossover design and 8-hour observation periods in which the dogs were withdrawn for varying times up to 72 hours. Suppression studies were carried out when dogs were maximally abstinent; from 64-72 hours for diazepam-dependent dogs and 40-48 hours for nordiazepam-dependent dogs using graded doses of diazepam and nordiazepam. Precipitation studies were conducted with graded doses of Ro15-1788 or

CGS-8216 administered 1 hour after a normal maintenance dose of the drug of dependence. The dogs were then observed for 4 hours.

Dependence Studies in the Rat: Rats were made dependent on pentobarbital (208 ± 5.4 mg/day self administered in food) or diazepam (133 mg/kg/day administered via the gastric fistula in 4 divided doses). Pentobarbital-dependent rats frequently dosed themselves until they became comatose. Diazepam-dependent rats showed some sedation and behavioral depression early in the addiction cycle. Tolerance developed to these effects. When the drug of dependence was abruptly withdrawn, abstinence syndromes emerged in both groups of rats. The pentobarbital abstinence syndrome emerged rapidly with signs of abstinence appearing within an hour after the last dose. The abstinence syndrome peaked by the 8th hour. The signs of diazepam abstinence on the other hand did not emerge until the 10th hour and did not peak until the 48th hour (Figure 1). Plasma levels of diazepam and its metabolites were determined in 4 rats at 6, 19, 30 and 54 hours after the last dose. Mean plasma levels in ng/ml and their SE's 6 hours after the last dose of diazepam were: diazepam - 512 ± 187; nordiazepam - 155 ± 82; oxazepam-175.2 ± 79; 3-OH diazepam-36 ± 36. By 19 hours plasma levels of diazepam and nordiazepam were less than 30 ng/ml and plasma levels of oxazepam and 3-OH diazepam were undetectable. Rats were also chronically intoxicated with oxazepam or nordiazepam (133 mg/kg/day) administered in four equally divided intragastrically. The dose of the drug of dependence was increased gradually over a 4 week period until the stabilization dose was achieved. The nordiazepam-dosed rats were not overtly sedated during any part of the addiction cycle nor was there any weight loss. Twenty-five percent of the animals died while stabilized on nordiazepam. The only pathologic change seen on post-mortem examination was impacted feces extending from the rectum to the transverse colon. It was more difficult to stabilize rats on oxazepam because of loss of appetite. About 50% of the rats who achieved the stabilization dose level died. Post-mortem examination of the dead rats revealed extensive mineralization and degeneration of renal tubules. The time courses of intensity of abstinence of rats dependent on and withdrawn from diazepam, nordiazepam and oxazepam are shown in Fig. 1. The nordiazepam abstinence syndrome may have had a slightly more rapid onset and may have been somewhat less intense than the diazepam abstinence syndrome. This decreased intensity was partly a consequence of the fact that head and body tremors, twitches and jerks and explosive awakenings were less common in the nordiazepam abstinence syndrome than in the diazepam abstinence syndrome. Hostility was more pronounced in the nordiazepam-dependent and abstinent rats than in the diazepam-dependent rats. The oxazepam-dependent rats also showed significantly fewer head and body tremors, and explosive awakenings, less food ingestion and hostility but more wet dog shakes than diazepam-dependent rats at the time of peak abstinence. Oxazepam-dependent rats had decreased food and water intake throughout the period of chronic intoxication which was further diminished when the drug was withdrawn. As can be seen from Figure 2 the oxazepam-dependent rats exhibit-

ed abstinence signs at the first hour of abstinence. These remained constant to the 40th hour of abstinence when they increased somewhat and then decreased. Plasma levels were only obtained at 6 and 30 hours after the last stabilization dose of nordiazepam in 3 or 2 rats. Only nordiazepam was detected in the plasma. The mean levels were 990 ± 10 and 617 ± 141 at 6 and 30 hours.

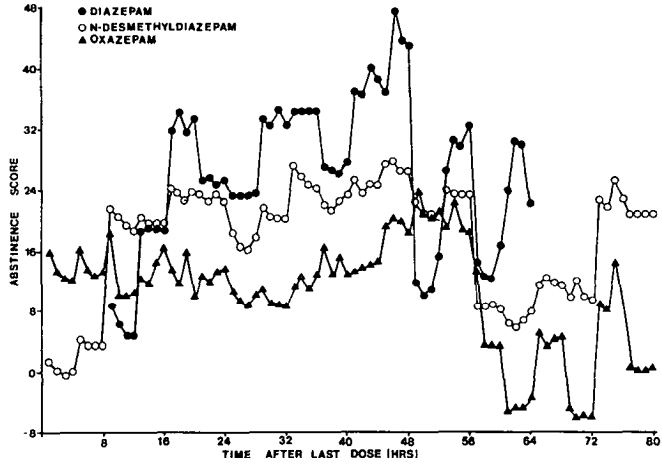

Fig. 1: The time course of the abstinence syndromes seen in benzodiazepine-dependent rats. The abstinence score was calculated for each hour using the weighting factors previously determined in the Diazepam Abstinence Scale (Martin, et al, 1982). Each abstinence score for nordiazepam (N-desmethyldiazepam) is the average of 7 rats; for oxazepam 5 rats were studied from 0 through 48 hours, and 3 of these rats from 48 through 80 hours.

Both Ro15-1788 and CGS-8216 precipitated abstinence in the diaze-Pam-dependent rat (McNicholas and Martin, 1982; McNicholas and Martin, in preparation). The precipitated abstinence syndrome was characterized by an increase in activity, wet dog and head shakes, poker tail and digging. Neither Ro15-1788 or CGS-8216 produced these signs of precipitated abstinence in rats who received single doses of diazepam. CGS-8216 produced a significant arousal response in untreated rats whereas Ro15-1788 did not. With both drugs the qualitative characteristics of the precipitated abstinence syndrome were similar. They were about equipotent and a peak abstinence syndrome was seen with a 15 mg/kg dose of Ro15-1788 and with 5 mg/kg of CGS-8216. Doses up to 8 times larger did not increase peak intensity of the precipitated abstinence but did prolong its duration. The precipitated abstinence syndrome was less intense than the withdrawal abstinence syndrome.

Dependence Studies in the Dog: Dogs have been made dependent on diazepam 60 mg/kg/day, nordiazepam (30 mg/kg/day) and lorazepam (100 mg/kg/day) (McNicholas, et al., 1983; McNicholas, et al., in preparation). During chronic intoxication none of the dogs were overtly sedated or ataxic. The diazepam and nordiazepam abstinence syndromes differed qualitatively. Food and water intake

of the diazepam-dependent dogs increased during the first 24 hours of abstinence and did not decline until the 32nd and 48th hour respectively. Dogs gained weight until the 40th hour of abstinence. Weight decreased thereafter. In contrast the nordiazepam dogs progressively lost weight throughout abstinence until the 64th hour at which time they gained weight. Their food and water intake decreased progressively until the third day of abstinence and at this time they consumed neither food nor water during the observation period. The second notable observation was that the lorazepam-dependent dogs did not have convulsions or myoclonic jerks. Three diazepam-dependent dogs died in withdrawal status epilepticus. Two other dogs lost weight rapidly and died while intoxicated. Post-mortem examination showed them to have an obstructive hepatitis. The diazepam and the nordiazepam abstinence syndrome differed in that tremors, twitches and jerks, hot foot walking, stiff legged walking and loss of body weight were either statistically significantly more common or more severe in the nordiazepam-dependent dogs than in the diazepam-dependent dogs. Marked cumulation of nordiazepam (11.5 ± 24 µg/ml) and oxazepam (1.8 ± 0.4 µg/kg) occurred in the diazepam-dependent dog. Stabilization plasma levels are presented in parenthesis. Plasma levels of nordiazepam and oxazepam decreased slowly. The peak withdrawal abstinence syndrome was observed when plasma levels had decreased to 10% of stabilization levels at about 40 hours. Stabilization plasma levels of diazepam were 0.42 ± 0.06 µg/ml and they fell rapidly, declining to 10% of the stabilization dose at about 19 hours. In the nordiazepam-dependent dogs stabilization plasma levels of nordiazepam were 12.7 ± 3.2 µg/ml and oxazepam 2.3 ± 0.2 µg/ml and reached 10% of stabilization level by about 56 hrs. Stabilization level of lorazepam in lorazepam-dependent dogs was 0.12 ± 0.06 µg/ml and it declined rapidly to 10% of the stabilization level in 8 hours. CGS-8216 precipitated abstinence in diazepam-dependent dogs but not in lorazepam-dependent dogs. The effects of graded doses Ro15-1788 and CGS-8216 (0.29, 0.87, 2.60, 8.00 and 25.0 mg/kg intragastrically) were studied in nordiazepam-dependent and stabilized dogs. Both drugs produce a dose-related increase in the incidence of gross tremors, respiratory rate, twitches and jerks and hot foot walking. Convulsions were observed in 3 of 5 dogs who received 8 mg/kg of Ro15-1788 and in 1 dog who received 8 mg/kg of CGS-8216. Convulsions were seen in only one dog who received 25 mg/kg of Ro15-1788 and CGS-8216. The convulsions came on from 30 minutes to 3 hours after antagonists were administered. The effects of Ro15-1788 and CGS-8216 on food and water intake and on body weight were erratic during the four hours after antagonist administration and no trend was observed. The precipitated abstinence syndrome produced by Ro15-1788 was well developed within an hour after administration whereas the abstinence syndrome produced by CGS-8216 did not appear until after the 1st hour following its administration. As can be seen from Figure 2, the Ro15-1788 precipitated abstinence dose response curve is steeper than the CGS-8216 dose response curve. It is also monophasic whereas the CGS-8216 dose response curve either plateaus or is biphasic. When comparisons of doses of Ro15-1788 and

CGS-8216 which produced precipitated abstinence syndrome of comparable intensities were made, Ro15-1788 was 8 times more potent than CGS-8216 in precipitating abstinence. Ro15-1788 also produced a dose-related increase in body temperature.

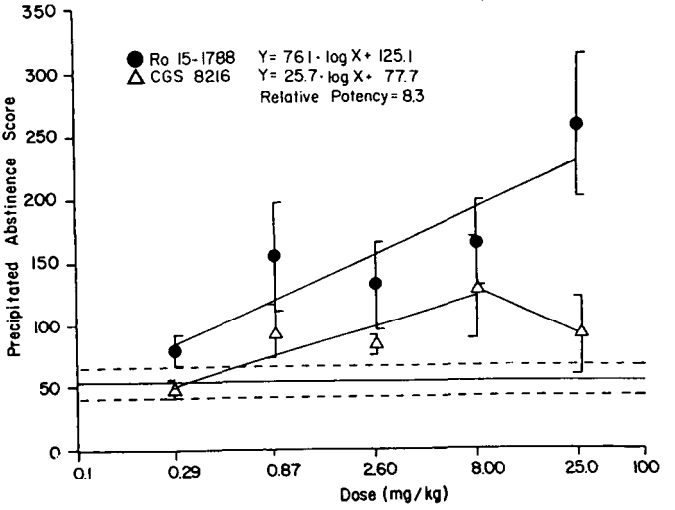

Fig. 2: Dose-response curves of abstinence precipitated by Ro15-1788 and CGS-8216 in 4 nordiazepam-dependent dogs. All dogs received all treatments. Each value is the mean ± SEM calculated using the Precipitated Abstinence Scale generated from Ro15-1788 data. Placebo response ± SEM is shown by the horizontal solid and dashed lines, respectively.

Figure 3 summarizes results obtained in suppression studies in dogs dependent on diazepam (60 mg/kg/day) and nordiazepam (32 mg/kg/day). The dogs were maximally abstinent at the time the suppression studies were conducted. In the diazepam-dependent dog some signs of abstinence were suppressed by diazepam in a dose-related manner including gross tremors, tonic-clonic seizures, stiff legged walking and loss of appetite and weight loss. In the abstinent nordiazepam-dependent dog, however, the effects of diazepam were more complex. The lowest dose (0.75 and 1.5 mg/kg) produced a modest suppression of abstinence. However, a 3.0 mg/kg dose level caused a worsening of abstinence which was a consequence of enhanced tremoring. The 6 mg/kg/dose suppressed all signs of abstinence. In contrast, the smallest dose (0.35 mg/kg) of nordiazepam worsened abstinence.

CONCLUSIONS: (1) These studies have shown that a high level of physical dependence can be produced in the dog by the chronic administration of doses of diazepam and nordiazepam which do not produce overt signs of sedation or ataxia. (2) These data indicate that the major signs of abstinence are a consequence of the dogs being dependent on nordiazepam. (3) This dependence may be a consequence of the accumulation of high plasma levels of nordiazepam and possibly oxazepam. (4) As have been shown by others, there were marked differences in the rate that the rat and dog metabolized diazepam. In dependent rats most of the diazepam and

its metabolites have been eliminated by 24 hours following the last dose. Nordiazepam and oxazepam accumulate in the dog and are eliminated more slowly. Differences in the rate of metabolism and excretion of metabolites may play a role in the differences in the propensity of benzodiazepine to produce physical dependence. (5) Several lines of evidence have been presented indicating that di-

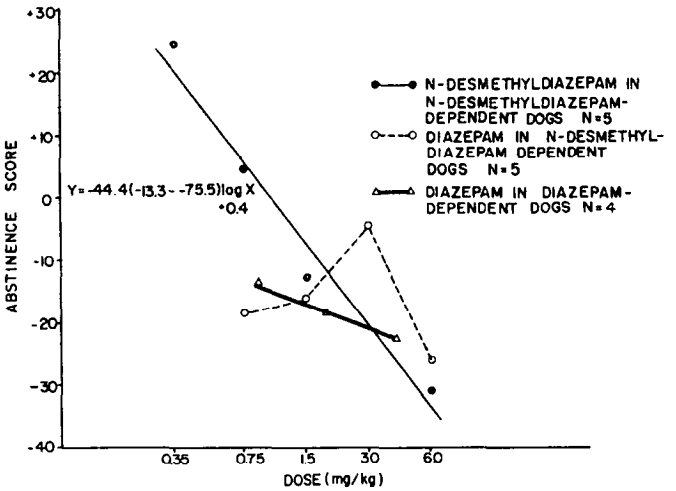

Fig. 3: Suppression of diazepam and nordiazepam abstinence by nordiazepam and diazepam. Each circle (filled and open) represents the mean response of 5 dogs calculated using the Diazepam Abstinence Scale (McNicholas, et al, 1983). The ability of diazepam to suppress diazepam abstinence is also shown.

azepam, nordiazepam andoxazepammay produce different types of physical dependence. Further, diazepam dependence in both the rat and dog is probably a mixed dependency. (6) There are differences between the rat and dog in the characteristics ofabstinence syndrome produced by diazepam and nordiazepam. Further, the effects of the benzodiazepine and antagonists Ro15-1788 and CGS-8216 are different in the rat and dog. These findings suggest that these species differ in their response to benzodiazepine agonists and antagonists.

Acknowledgment. This work was supported by National Institute of Drug Abuse Grant #DA02195.

References

Nozaki, M, Martin, W.R., Driver, M. B., Diringer, M, and Wu, K. M. Use of sedative hypnotic and antianxiety drugs. Drug Alc Depend 7:221-231, 1981.

Martin, W. R., McNicholas, L. F. and Cherian, S. Diazepam and pentobarbital dependence in the rat. Life Sci 31:721-730, 1982.

McNicholas, L. F. and Martin, W. R. The effect of a benzodiazepine antagonist, Ro15-1788, in diazepam dependent rats. Life Sci 32:731-737, 1980.

McNicholas, L. F., Martin, W. R. and Cherian, S. Physical dependence on diazepam and lorazepam in the dog. J. Pharmacol Exp Ther 226:783-789, 1983.

Rao, S. N., Dhar, K., Ku, H. H. and Okamoto, M. Determination of diazepam and its pharmacologically active metabolites in blood by Bond-Elut column extraction and reversed-phase high-performance liquid chromatography. J Chromatogr 231:341-348, 1982.

McNicholas, L. F., Martin, W. R. and Pruitt, T. A. N-Desmethyl-diazepam physical dependence in dogs. J. Pharmacol Exp. Ther. (In Press).

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EEG, Physiologic and Behavioral Effects of Ethanol Administration

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INTRODUCTION

Previous studies have measured the effects of acute ethanol administration using various electrophysiological and behavioral indices (Engel and Rosenbaum, 1944; Varga and Nagy, 1960; Begleiter and Platz, 1972). While it has been noted that feelings of well-being or euphoria ensue shortly after consuming ethanol, little is known of the time-course of this response or of its temporal relationship with other ethanol-induced effects. The electroencephalogram (EEG) is a sensitive measure of the brain's electrical activity which exhibits specific patterns during various behavioral states such as asleep, awake, alert, etc. Furthermore, discrete changes in EEG activity can be quantified using power spectral analysis. Using computerized analysis, psychoactive drugs have been found to induce characteristic changes in the EEG (Fink, 1969). However, attempts to determine if such alterations in EEG activity are correlated with behavioral changes have had limited success.

Most attempts to determine the effects of drugs on behavior have relied on data obtained from questionnaires. Since visual, motor and sometimes verbal activities are necessary to obtain responses to questionnaires, reliable drug-induced changes in EEG activity are unobtainable. The present study was designed to concomitantly measure EEG, physiologic and behavioral activity after acute ethanol administration. Behavioral measures were obtained using both a verbal questionnaire and an instrumental response.

METHODS

Subjects: Eighteen adult male volunteers between the ages of 21 and 35 years were recruited via newspaper advertisements and provided informed consent for participation in this study. Individuals with a past or current history of alcohol or drug abuse were excluded. All subjects had normal physical, blood chemistry, and urinalysis examinations.

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Experimental Design and Setting: The effects of a low and a high dose of ethanol were compared with placebo ethanol under controlled conditions. Subjects were prepared with scalp electrodes for recording the EEG, temporalis muscle electrodes for recording muscle tension, a thermocouple electrode (attached via a noseclip) for recording respiratory rate, and a photoelectric finger clip for recording pulse. EEG and physiologic measures were recorded on a Grass Model 78D polygraph. The EEG activity was also recorded on FM magnetic tape for subsequent computer analysis with a Pathfinder Signal Averager (Nicolet Instrument Co., Madison, WI).

Studies were conducted in an electrically shielded, sound-and-light-attenuated chamber. An intravenous catheter was inserted to collect integrated blood samples for analysis of plasma ethanol levels (Léric et al., 1970).

Six subjects received placebo (350 ml of concentrated pineapple juice), 6 subjects received low dose ethanol (1.1 ml/kg of 80 proof vodka in 350 ml of fruit juice--0.412 g/kg) and 6 subjects received high dose ethanol (2.2 ml/kg of 80 proof vodka in 350 ml of fruit juice--0.823 g/kg).

Behavioral Measures: Two different procedures were used for assessing behavioral measures of ethanol effects. The questionnaire was administered verbally every 15 minutes. The subject was asked to rate himself on a scale of 0 to 10 with 0 representing a completely sober state, 5 moderately intoxicated, and 10 extremely intoxicated. A joystick manipulandum was wired to an event pen on the polygraph. The joystick had 4 positions (forward, center, back, and side) and a button on the top (Fig. 1). The lower button was not used. Less than 1 N of force was required to move the joystick to one of the 3 positions and the excursion of the joystick was 2 cm. These specific characteristics for joystick deflection allowed the subjects to nonverbally communicate behavioral changes with a minimum of movement. Subjects were instructed to operate the joystick according to their subjective state as follows:

Forward	detect ethanol effect
Side	detect strong ethanol effect
Backward	ethanol effects disappeared
Button	detect a feeling of well being (e.s., euphoric)

Ethanol Administration: Drug solutions were placed in an inverted bottle and attached to a peristaltic pump. Tubing from the pump was directed through the wall of the chamber and terminated with a mouthpiece. A 10 ml reservoir between the pump and the subject's mouthpiece was filled with 3 ml of vodka and 7 ml of fruit juice to provide a strong initial taste of ethanol (Mendelson et al., 1984). The placebo solution only contained the small "priming" 3 ml of ethanol. Solutions were delivered to the subjects at a rate of 23 ml/min.

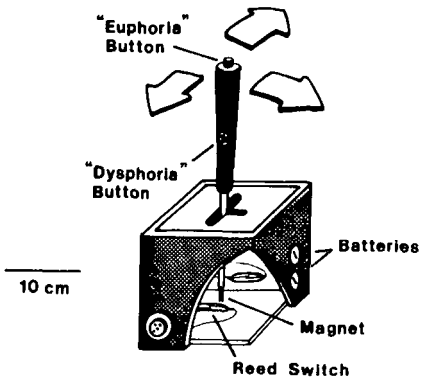

Figure 1: Joystick device used to record behavioral changes.

Procedure: Baseline EEG, physiologic and behavioral data were recorded during the first 30 minutes of the experiment. Joystick control responses were also recorded during this time. After the 30 minute baseline period, the subject was instructed to place the drinking tube mouthpiece in his mouth and the peristaltic pump was activated for 15 minutes. EEG, physiologic and behavioral measures were recorded continuously, and blood samples were drawn every 5 minutes for the next 2 hours.

RESULTS

Physiological Measures: Resting heart rates during baseline recording were 53-62 bpm for all three treatment groups. The placebo and low-dose treatments produced a mild tachycardia (10-12 bpm) during the drinking phase which subsided during the rest of the session. The high-dose ethanol elevated heartrates by 16-29 bpm during drinking and then returned to levels similar to the other two treatment groups. No consistent changes in muscle tension or respiratory rate were observed.

Behavioral Measures: The data from the self-rating questionnaire indicated that all three groups detected an ethanol effect. The placebo response was characterized by a delayed onset and shorter duration of "intoxication". Further, subjects' peak self-rating score was about 2.0 compared with 5.0 for both the low-dose and high-dose ethanol-treated groups. There was no difference between the two ethanol treatment groups in the time course of self-rating scores. In contrast, the data from, the joystick device revealed clear differences between all three groups. Also, 5 out of 6 subjects that received 0.823 g/kg of ethanol reported multiple episodes of euphoria each lasting approximately 3 minutes in duration. Table 1 shows the latency to detection of ethanol effects, the latency to euphoria, the duration of ethanol effects and the corresponding plasma ethanol levels (PEL).

Table 1

Treatment	Detect Latency (min)	PEL mg/dl	Euphoria Latency (min)	PEL mg/dl	Duration of Effect	PEL mg/dl
Placebo	38.75[a] 6.4	0	None	0	41.6± 8.8	0
0.412 g/kg Ethanol	14.2± 1.8	31.2± 5.0	29[b]	35.7	96.2± 15.5	44.7± 2.6
0.823 g/kg Ethanol	11.4± 5.5	31.7± 4.2	23.5± 6.1	44.4± 7.2	117.7± 2.0	75.2± 4.2

[a]Values represent means ± S.E. for six subjects

[b]Value is from one subject only

EEG Activity: The EEG effects of acute ethanol administration were dose-related and were selective for different frequency bands. The 0.412 g/kg dose of ethanol produced a clear increase theta power that appeared to follow plasma ethanol levels; alpha power was not affected. The high-dose ethanol increased alpha power which subsided by about 60 min after drinking. The increased alpha activity was accompanied by episodes of euphoria (r^2=0.89, correlation coefficient 0.95). Theta activity gradually increased during the session and paralleled the plasma ethanol curve (r^2= 0.93, correlation coefficient 0.97). No EEG changes occurred after placebo administration.

DISCUSSION

The results of this study provided information relating to the temporal relationship between ethanol-induced electrophysiological and behavioral effects. Further, a non-verbal instrumental response was found to be more sensitive than a verbal self-rating scale for assessing behavioral changes. This continuous measure of behavioral effects permitted direct comparisons with electrophysiological changes and plasma ethanol levels.

Our subjects reliably detected blood ethanol levels at about 30-34 mg/dl. This is a much lower blood ethanol level for detection than previously reported by Mirsky et al. (1941). These differences may be due to variations in drug dose, methods of drug administration, and behavioral responses for detection. The use of an instrumental response to measure changes in subjective states in the present study provided additional information relating to the reinforcing properties of ethanol. Subjects reliably indicated that they were experiencing a feeling of well being or high (i.e., euphoria) at blood ethanol levels of about 49 mg/dl after the high dose. Only 1 subject experienced euphoria after receiving the low ethanol dose. Since the blood ethanol levels of all subjects that received the low dose exceeded 50 mg/dl (data not shown) it is unlikely that absolute blood ethanol levels are re-

sponsible for euphoria. Alternatively, the appearance of euphoria after the 0.823 g/kg dose of ethanol may be due to the fact that plasma ethanol levels continued to rise during the recording session while the levels after the 0.412 g/kg dose had peaked. Thus, the rate of increase may be more important than absolute levels.

The present study found that high-dose ethanol increased alpha power in parietal recording sites. These results are in agreement with previous studies reporting that ethanol increases alpha activity (Davis et al., 1941; Engel and Rosenbaum, 1945; Docter et al., 1966; Begleiter and Platz, 1972). These EEG changes occurred at blood ethanol levels of 30-35 mg/dl which are in agreement with the study by Davis et al. (1941) showing that an increase in energy in the theta and alpha bands occurred at blood ethanol levels of about 35 mg/dl. In the present study, however, increased theta activity paralleled the increasing plasma ethanol levels while the increased alpha activity correlated with the episodes of euphoria.

In conclusion, the present study provides data suggesting that there is a direct relationship between EEG activity, detection of ethanol effects and plasma ethanol levels. These relationships, however, appear to exist only during the ascending limb of the blood ethanol curve. These data also demonstrate that the paroxysmal episodes of euphoria are correlated with transient changes in EEG activity. These discrete changes in electrophysiological activity may be related to the reinforcing properties of ethanol.

ACKNOWLEDGEMENTS

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REFERENCES

Begleiter, H., Platz, A.: The effects of alcohol on the central nervous system in humans. In: Kissin, B. and Begleiter, H., eds. The Biology of Alcoholism, Vol 2, pp. 293-343, Plenum Press, New York, 1972.

Davis, P.A., Gibbs, F.A., Davis, H., Jetter, W.W. and Trowbridge, L.S.: The effects of alcohol upon the electroencephalogram (brain waves). Quart. J. Stud. Alc. 1: 626-637, 1941.

Docter, R.F., Naitoh, P. and Smith, J.C.: Electroencephalographic changes and vigilance behavior during experimentally induced intoxication with alcoholic subjects. Psychosom. Med. 28: 605-615, 1966.

Engel, G.L. and Rosenbaum, M.: Delerium III. Electroencephalographic changes associated with acute alcohol intoxication. Arch. Neurol. Psychiat. 53: 44-65, 1945.

Fink, M.: EEG and human psychopharmacology. Ann. Rev. Pharmacol. 9: 241-258, 1969.

Lèric, H., Kaplan, J.-C. and Broun, G.: Dosage enzematic de l'alcool sanguin par microméthode colorimetrique. Clin. Chim. Acta 29: 523-528, 1970.

Mendelson, J.H., McGuire, M. and Mello, N.K.: A new device for administering placebo alcohol. Alcohol 1: 417-419, 1984.

Mirsky, I.A., Pikes, P., Rosenbaum, M. and Lederer, H.: "Adaption" of the central nervous system to varying concentrations of alcohol in the blood. Quart. J; Stud. Alcoh. 2: 35-45, 1941.

Varga, B. and Nagy, T.: Analysis of a rhythms in the electro-encephalogram of alcoholics. Electroenceph. Clin. Neurophysiol. 12: 933-946, 1960.

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Neurochemical and Pharmacologic Investigations of Punished Behavior

Steven I. Dworkin, Tatsuo Miyauchi, and James E. Smith

Research on the neurobiological mechanism of reinforcement has increased our understanding of the neurobiological components of drug abuse (see Smith and Lane 1983). Recent studies have implicated dopamine-containing neurons to be involved in the reinforcing effects of several different classes of abused drugs (Bozarth and Wise 1981; Wise 1980). Moreover, specific neuronal pathways activated by these drugs have been identified. However, there have been few investigations on the role of noxious or aversive environments in engendering or maintaining compulsive drug use. It has long been suggested that certain drug classes, including barbiturates and benzodiazepines, acquire their reinforcing effectiveness by attenuating the aversiveness of punitive environments (Davis et al. 1963). Therefore, a complete analysis of neurobiological mechanisms of compulsive drug use should include the neurobiological effects of punishment. Studies investigating the neurobiological consequences of punishment should control for response rate, reinforcement density and the direct effects of noxious stimulation. We used a behavioral procedure which results in similar rates of responding and inter-reinforcement intervals in punished and unpunished rats. The behavioral effects of pentobarbital and a neurobiological assessment of punishment were then determined using the behavioral procedure.

METHOD

Triads of-male Fischer F-344 littermates (3 months old at the start of the, experiment) were used. The three littermates were run simultaneously on a yoked-box procedure (Figure 1). The first two littermates were trained to respond on two different schedules of food presentation. For one littermate, a random ratio (5 resp min, 100 resp max) reinforcement schedule was arranged for lever pressing (RR); for the second littermate, reinforcement was arranged according to a random-interval schedule yoked directly to the inter-reinforcement intervals produced by the first littermate (yoked RI). The third littermate was placed on a response-independent food presentation schedule yoked to the RR rat (yoked-food). Daily session terminated after 90 min or 100 food presentations were delivered to the yoked random-interval rat.

After rates of responding of both RR and yoked RI rats had stabilized, a punishment contingency was added to the RR schedule.

A random ratio (25 resp min, 400 resp max) schedule of electric food shock (0.4 ma, 100 sec) was used. The same intensity and duration of shock was given to the yoked-food rats whenever the RR rats were delivered shock. This yoked group was used to control for the neurochemical effects of shock itself. Shock was never delivered to the rats on the RI schedule.

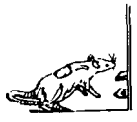

FIGURE 1. A diagram of the yoked-box procedure.

Once responding under this condition was stable the session length was decreased to 45 minutes for the rats tested with pentobarbital. Five pairs of rats were used to determine effects of the drug. Sodium pentobarbital was administered in a random series with a minimum of seven days between determinations. Each dose (3.0-17.0 mg/kg) was evaluated at least twice in each subject. Doses are presented in terms of total salt. Drug was administered to the punished and unpunished rats on different days.

Rats used for the neurochemical studies were implanted with chronic jugular catheters for pulse labelling neurotransmitters. At the beginning of the last session, radioactive precursors (0.2 mCj D-[U-^{14}C]-glucose, 0.5 mCi L-[G-^{3}H]-tryptophan 1.0 mCi L-[2,6-^{3}H]-tyrosine) were injected in 100 ul of saline through the jugular catheter of these rats. The three rats in each litter were sacrificed at 60 min or 90 min after the pulse labelling by immersion in liquid N_2 until totally frozen. The contents of biogenic monoamines and amino acids in 4 brain regions were determined by HPLC-ECD (Co et al. 1982) and HPLC-fluorometer methods, respectively. Radioactivity of each neurotransmitter was measured after collecting each peak. The turnover rates were calculated using a previously reported procedure (Lane et al. 1981).

RESULTS

The cumulative record in Figure 2 illustrates that the random-ratio schedule of food presentation initially engendered a high,

constant rate of responding while responding maintained by the yoked random-interval contingency occurred at a much lower rate. The addition of the shock contingency resulted in similar rates and patterns of punished (random-ratio subjects) and unpunished (yoked, random-interval subjects) responding. Extremely low rates of responding were elicited by the non-contingent presentation of food.

Figure 3 shows the dose-effect curve for pentobarbital which has been reported to selectively increase punished responding indicated by the closed circles (Branch et al. 1977). The pentobarbital dose of 5.6 mg/kg produced over a three-fold increase in responding. Unpunished responding, represented by open circles, was not affected at doses that increased punished responding. The largest dose investigated decreased both punished and unpunished responding.

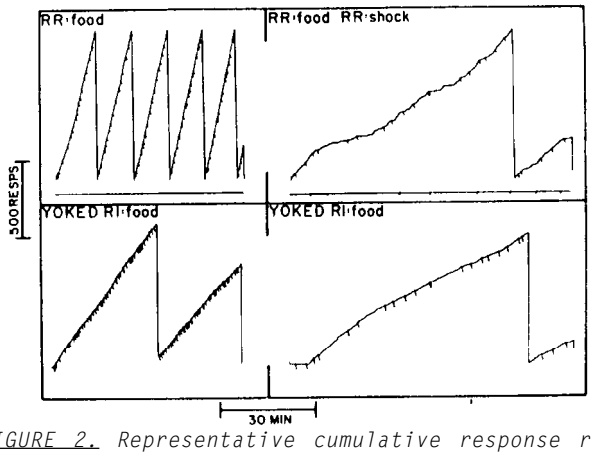

FIGURE 2. Representative cumulative response records from two littermates responding on the yoked schedule. The records on the left depict responding before the shock contingency was introduced. The records on the right show the effects of the shock contingency. Deflections of the bottom pen indicate shock presentations. Response rates as well as reinforcement density were comparable for the punished and unpunished subjects.

An additional group of subjects was trained on the schedule for the turnover rate studies. The content and turnover rates of dopamine, serotonin and GABA were evaluated in the prefrontal cortex, pyriform cortex, hippocampus and amygdala in order to determine specific neurotransmitter pathway systems involved in punished and unpunished responding. These regions were selected because they have been suggested to be involved in reinforced or punished responding.

Figure 4 shows the mean response rates and observed schedule values for the 8 littermate triads before and after the intro-

duction of the shock contingencies. The introduction of the shock contingency resulted in comparable rates of punished and unpunished responding. The subjects were implanted with chronic indwelling venous catheters after the 40th session.

The rats were then sacrificed during the 54th session after either 60 min or 90 min (4 littermate triads each) from the start of the session. Radioactive tyrosine, tryptophan and glucose were injected via the chronic indwelling catheters immediately before the session to determine neurotransmitter turnover.

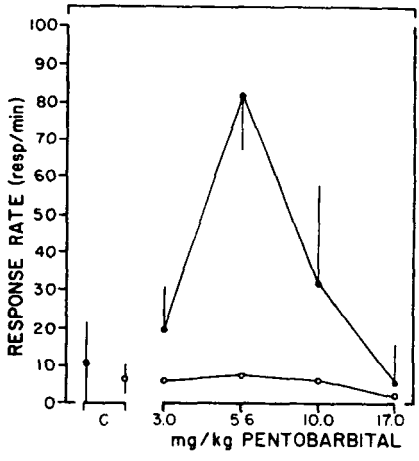

FIGURE 3. Dose effect curve for pentobarbital response rate plotted as percent control is displayed on the ordinate while dose is indicated on the abscissa. Points above "C" are means of data collected from days that immediately preceded drug injections and sessions following saline injections Vertical bars indicate ±SD

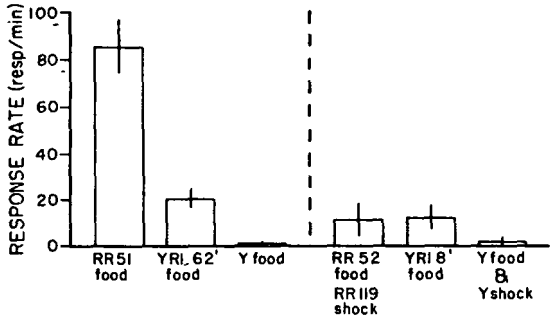

FIGURE 4. Obtained rates of responding and schedule values. The last five days of the non-shock and shock conditions were used to calculate these means. Vertical lines indicate 2 SEM.

Figure 5 shows turnover rate data for GABA in three brain regions. These data indicate that although GABA turnover was increased by shock, there was not a specific punishment effect. Thus, GABA turnover seems to be affected by noxious stimulation independent of the behavioral procedure studied. Since GABA neuronal systems are affected by pentobarbital, the specific effects of pentobarbital on punished responding may be the result of the different turnover rates in punished and unpunished subjects.

Turnover rates of the biogenic amines in two brain areas are shown in Figure 6. DA turnover rate was decreased while 5-HT was increased in the punished rat. These changes are in line with the reported effects of dopamine and 5-HT on motor activity and previous studies showing the involvement of the amygdala in punishment procedures.

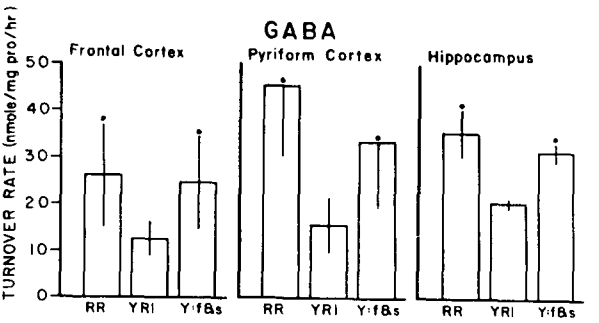

FIGURE 5. Changes in GABA turnover. The first bar indicates the utilization rate for the punished dub-ject. Data for the unpunished subject on the interval schedule and the yoked-response independent food and shock rate are indicated by the center and right bar, respectively. The vertical bars indicate ± 1SD. "8" indicate signicant differences $p < 0.5$.

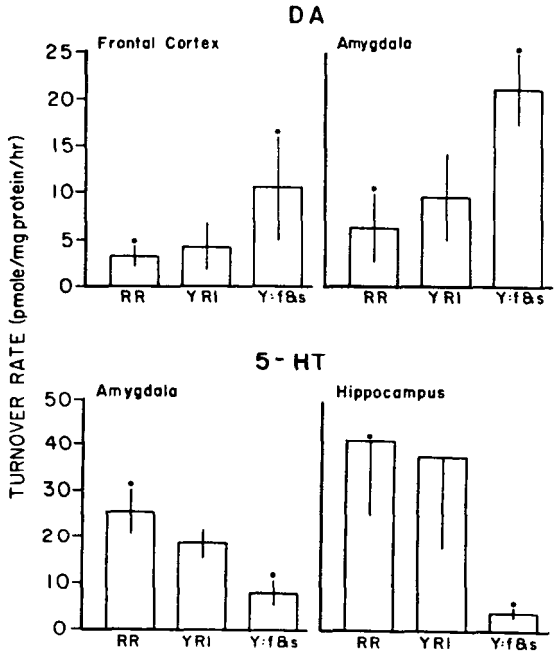

FIGURE 6. Turnover rates of the biogenic amines. Details are the same as in Figure 5.

CONCLUSION

The behavioral procedure used resulted in comparable rates of punished and unpunished responding. Pentobarbital selectively increased only the punished responding. Therefore, provided a pharmacological verification that we were investigating punished responding and provided data which suggests there would be neurobiological differences in the punished and unpunished rats.

The behavior procedure was then used to determine the neurobiological consequences of electric foot-shock punishment. For this determination, the neurobiological consequences of punished responding were compared to rats emitting comparable rates of unpunished responding. In addition, both subjects had nearly identical inter-reinforcement intervals and similar inter-response time distributions. The yoked response-independent food and shock group was added to determine the direct neurochemical effects of food and shock.

Preliminary data collected from 4 of 23 dissected brain areas indicate that turnover rates of the amino acid neurotransmitter are increased by noxious stimulation. Moreover, punished responding results in a decrease in turnover rates of dopamine

and a concomitant increase in 5-HT turnover. We are currently collecting data from the remaining brain areas and hope to be able to construct a pathway diagram for the neurotransmitters involved in punishment.

Additional studies will be attempted to verify these pathways using neurotoxin lesions and intracranial drug administration techniques.

REFERENCES

Bozarth, M.A. and Wise, R.A. Heroin reward is dependent on a dopaminergic substrate. Life Sci 29:1881-1886, 1981.

Branch, M.N., Nicholson, E. and Dworkin, S.I. Punishment-specific effect of pentobarbital: Dependence on the type of punisher. J Exptl Anal Behav 28:285-273, 1977.

Co, C.; Smith, J.E.; and Lane, J.D. Use of a single compartment LCEC cell in the determination of biogenic amine content and turnover. Pharmacol Biochem Behav 16:641-646, 1982.

Davis, J.D. and Miller, N.E. Fear and pain: Their effect on self-injection of amobarbital sodium by rats. Science 141:1286-1287, 1963.

Lane, J.D.; Sands, M.D.; Co, C.; Cherek, D.R.; and Smith, J.E. Biogenic monoamine turnover in discrete rat brain regions is correlated with conditioned emotional response and its conditioning history. Brain Res 240:99-108, 1985.

Smith, J.E. and Lane J.D. The Neurobiology of Opiate Reward Processes, Elsevier: New York, 1983.

Wise, R.A. Action of drugs of abuse on brain reward systems. Pharmacol Biochem Behav 13:Suppl 1, 213-223, 1980.

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The Central and Peripheral Effects of Delta-9-Tetrahydrdcannabinol on Gastrointestinal Transit in Mice

Jennifer E. Shook, William L. Dewey, and Thomas F. Burks

INTRODUCTION

Delta-9-tetrahydrocannabinol (THC) has been shown to be the major psychoactive constituent of marijuana (4). THC produces many diverse effects in addition to its psychoactive properties, including its remarkable effectiveness as an antiemetic for patients receiving cancer chemotherapy (7, 8). The mechanism(s) of this action in regulating gastrointestinal function is unknown.

Our goal in the present study was to characterize the effects of THC on gastric emptying and small intestinal transit in mice after central (intracerebroventricular) and peripheral (intravenous) administration. Due to the morphine-like nature of the effects of THC on transit noted during experimentation, we also tested for antagonism by naloxone.

METHODS

Fasted male ICR mice (18-23 grams) received injections of drug, vehicle or distilled water, followed by oral administration of ^{51}Cr as sodium chromate (0.5 uCi, 0.2 ml/mouse) 5 minutes later. Thirty-five minutes after administration of the radioactive marker, each animal was sacrificed by cervical dislocation and the stomach and small bowel were removed. The small intestine was placed on a ruled template and divided into ten equal segments. The stomach and intestinal segments were then placed into individual consecutive test tubes. Each tube was evaluated for gamma radiation by counting in a Tracor analytic gamma counter for 1.0 minutes.

The percent gastric emptying was determined as: % G.E. = 100 x (total counts - stomach counts)/(total counts). From this, the % inhibition of gastric emptying was calculated as:
% inhibition = 100 [(control % G.E.-Test % G.E.)/Control % G.E.)]

Small-intestinal transit was determined by the geometric center method (6) according to the following equation:
G.C. = Σ [(fractions of counts in each segment)(segment number)]

Using the G.C., the % inhibition of transit was calculated as follows:
% inhibition = 1OO[(test G.C.-control G.C.)/(1.O-control G.C.)]

The mean percent inhibition (± s.e.m.) was determined for each experimental condition, and linear regression analysis was performed in order to determine the A5O for inhibition of gastric emptying and small intestinal transit. Results were analyzed statistically using the t-test for grouped data.

Delta-9-tetrahydrocannabinol was prepared for injection by dissolving 1OO mg of THC in 1.O ml of a 1:1 mixture of emulphor (GAF Corporation, Linden, N.J.) and ethanol by sonication. This solution was then diluted with distilled water in order to obtain the appropriate concentrations for injection. Vehicle-control solutions containing the same concentrations of emulphor, ethanol and water as each THC dose used were also tested.

THC, vehicle and distilled water were injected either via the intracerebroventricular (i.c.v.) route in a total volume of 3.O ul or by the intravenous route (i.v.) in a dose volume of 10.O ml/kg body weight.

For the antagonism study, naloxone HCl (Sigma) was dissolved in distilled water and injected subcutaneously (s.c.) 15 minutes prior to i.v. injections in a dose volume of 10.0 mg/kg.

RESULTS

THC produced dose-dependent inhibition of small intestinal transit by both i.c.v. and i.v. routes of administration (Table 1). The A50 values for percent inhibition of transit for THC by i.c.v. and i.v. routes were 1.16 (0.75, 1.79) ug/g and 1.19 (1.04, 1.35) ug/g body weight, respectively. THC was thus equipotent in producing inhibition of small intestinal transit by the two different routes of administration.

As shown in Table 2, THC also produced inhibition of gastric emptying in a dose-dependent fashion by both i.v. and i.c.v. injection. The A50 values for percent inhibition of gastric emptying by THC were 3.27 (2.36, 4.54) ug/g after i.c.v. and 1.26 (1.01, 1.58) ug/g body weight after i.v. administration. The A50 values for the i.c.v. and i.v. routes of administration were significantly different ($p < 0.1$). The i.v. route of administration was marginally more potent than i.c.v. in the ability to inhibit gastric emptying.

The gastrointestinal transit values obtained in vehicle-treated animals were not different from those of animals injected with distilled water (data not shown).

The results presented in Table 3 demonstrate that the antitransit effects of THC were not altered by naloxone pretreatment. The gastrointestinal transit of naloxone-vehicle and naloxone-distilled water-treated mice were not different from mice injected with distilled water only (data not shown).

Table 1. The Effects of THC on % Inhibition of Small Intestinal Transit After i.c.v. and i.v. Administration

Dose of THC (ug/g i.v.)	n	G.C.	% Inhibition
0	7	5.3 ± 0.35	0
0.1	8	5.20 ± 0.29	2.4 ± 1.6
0.3	7	4.66 ± 0.26	27.5 ± 5.1
1.0	8	3.24 ± 0.20	55.2 ± 4.0
3.0	8	2.31 ± 0.29	64.8 ± 7.7
10.0	7	1.95 ± 1.8	83.0 ± 3.2

Dose of THC (ug. i.c.v.)	n	G.C.	%Inhibition
0	7	4.4 ± 0.19	0
1.0	7	4.2 ± 0.35	15.1 ± 7 2
10.0	8	2.97 ± 0.29	41.1 ± 8.7
100.0	8	2.14 ± 0.23	65.9 ± 7.1

Table 2. The Effects of THC on % Inhibition of Gastric Emptying in Mice After i.c.v. and i.v. Administration

THC (ug/g i.v.)	n	% Inhibition	THC (ug i.c.v.)	n	% Inhibition
0.1	8	4.6 ± 4.6	1.0	8	1.0 ± 0.8
0.3	7	33.4 ± 7.7	10.0	8	23.8 ± 6.3
1.0	8	55.1 ± 64.	100.0	8	56.8 ± 5.6
3.0	8	71.0 ± 4.6			
10.0	7	78.4 ± 4.0			

Table 3. The Effects of Naloxone Pretreatment on the Antitransit Effects of THC in Mice

	3.0 ug/g THC i.v.[a]	3.0 ug/g s.c. Naloxone plus 3.0 ug/g THC i.v.[a]
Small Intestinal Transit	69.8 ± 8.2	74.0 ± 1.9
Gastric Emptying	72.5 ± 3.0	66.0 ± 10.5

[a] mean % Inhibition, ± s.e.m., n = 6/group.

DISCUSSION

Although the therapeutic potential of the cannabinoids as antiemetic agents has been enthusiastically explored, the pharmacological activity of these compounds on gastrointestinal function has been largely neglected. Several investigators have shown that cannabinoids can slow the rate of passage of a charcoal meal through the small intestine of mice after s.c. (3) and oral (1, 2) administration, but are low in potency relative to morphine.

The results presented in this paper demonstrate that THC inhibits both gastric emptying and small intestinal transit in mice, and that i.c.v. and i.v. THC are equipotent in ability to inhibit small intestinal transit. THC was less potent in inhibiting gastric emptying after central administration. The extremely high doses of THC which are required to produce these effects after central administration suggest that THC is acting at a peripheral site in producing these effects. Another plausible explanation of these findings is that THC itself is not responsible for this effect, but one of its metabolites may be the causative agent. In either case, THC would have to be given at high doses after i.c.v. injection, so that it can cross outward through the blood brain barrier in significant amounts to cause its effects directly, or to be metabolized to the active form at the liver.

Interestingly, the potency of THC after i.c.v. and i.v. administration was found to be greater than that reported for s.c. and oral administration. These differences are probably due to differences in absorption and distribution of the drug. The potencies of i.c.v. and i.v. administration more closely approximate that of morphine than the oral and s.c. routes. The potency of THC in production of its effects on the gastrointestinal system is similar to its potency in producing analgesia (5).

The lack of antagonism of THC by naloxone suggests that the antitransit activities of THC are not opioid mediated.

Our findings support the work of Sridhar and co-workers who recently reported that orally administered THC results in significant decreases in gastric emptying in humans (9).

In summary, we have shown that THC inhibits gastric emptying as well as small intestinal transit in mice. These antitransit effects may be related to the antiemetic activity of THC, perhaps by diminishing gastrointestinal motility. Further characterization of the effects of the cannabinoids and their analogs on gastrointestinal function may aid in the search for more selective antiemetic drugs with less behavioral effects, and will determine their potential for use as antidiarrheal agents in the future.

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REFERENCES

Anderson, P.F.; Jackson, D.M.; and Chesher, G.B. Interaction of Delta-9-tetrahvdrocannabinol and cannabidiol on intestinal motility in mice. J Pharm Pharmacol. 26:136-137, 1974.

Chesher, G.B.; Dahl, C.J.; Everinqham. M.; Jackson. P.M.; Marchant-Williams, H.; and Starmer, G.A. The effects of cannabinoids on intestinal motility, and their antinociceptive effect in mice. Br J Pharmacol. 49:588-594, 1973.

Dewey, W.L.; Harris, L.S.; and Kennedy, J.S. Some pharmacological and toxicological effects of 1-trans-delta 8 and 1-trans-delta 9 - tetrahydrocannabinol in laboratory rodents. Arch Int Pharmacodyn. 196:133-145, 1972.

Gaoni; Y. and Mechoulam, R. Isolation, structure and partial synthesis of an active constituent of hashish. J American Chemical Society. 86:1646-1647, 1964.

Martin, B.R. Structural requirements for cannabinoid induced antinociceptive activity in mice. Life Sciences. 36:1523-1530, 1985.

Miller, M.S.; Galligan, J.J.; and Burks, T.F. Accurate measurement of intestinal transit in the rat. J Pharmacol Methods. 6:211-217, 1981.

Sallan, S.E.; Zinberg, N.E.; and Feei, E. III. In: Cohan S. and Stillman, R.C.; eds. The Therapeutic Potential of Marihuana, Plenum Publishing Corp., New York, 1976. pp. 329-335.

Sallan, S.E.; Cronin, C.; Zelen, M.; and Zinberg, W.E. Antiemetics in patients receiving chemotherapy for cancer. N Eng J Med. 302:135-138, 1980.
Sridhar, K.; Ricci, D.; Large, R.; and McCallum, R.W. Effect of tetrahydrocannabinol on gastric emptying of solids in humans. Gastroenterology. 86:1265, 1984.

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Morphine Potentiates Feeding via the Opiate Reinforcement Mechanism

Roy A. Wise, Francois Jenck, and Loucas Raptis

The direct reinforcing effects of opiates, their effects on pain and avoidance behavior, and their effects on feeding and drinking have led to an interest in the role of endogenous opioid peptides in control of motivated behavior. In the case of pain and aversion, the opioid systems are seen as part of centrifugal gating mechanisms for noxious input pathways; the opioid systems act to attenuate incoming pain signals. These systems are thus characterized as pain modulating systems, and this characterization is generally accepted.

In the case of positive motivational effects, initial speculation has been that one or more opioid peptide systems is involved in the central mechanisms of positive reinforcement. The fact that central injections of morphine facilitate reinforcing brain stimulation (Broekkamp et al. 1976) and have reinforcing effects of their own (Bozarth and Wise 1971; Phillips and LePiane 1980), and the fact that both effects are due to actions in the ventral tegmental area, fits with this characterization. The "positive reinforcement" mechanism through which opiates are thought to have their reinforcing action is a mechanism thought to synapse on ventral tegmental dopaminergic cells which project to the nucleus accunbens (Wise and Bozarth 1984); cocaine and amphetamine appear to activate the same reinforcement circuitry at the synapses of the dopaminergic projection to nucleus accumbens (and perhaps also the dopaminergic projection to the frontal cortex).

The first information on an endogenous positive reinforcement circuit in the brain came from studies of electrical brain stimulation. Such studies indicate a major set of so-called "first-stage" fibers which descend the medial forebrain bundle (Gallistel et al. 1981) and are thought to synapse on dopaminergic cells in the ventral tegmental area (Wise and Bozarth 1984). These fibers are not thought to be opioid-peptide containing. Both dynorphin-containing and enkephalin-containing terminals are found int he ventral tegmental area, however (Watson et al. 1982), so it is thought that one or both of these transmitters can interact with the reinforcement circuit at this point. This is the site where opiates are rewarding in their own right and where opiates facilitate brain stimulation reinforcement.

Brain stimulation studies have identified this mechanism with more than simple reinforcement function, however. The system has also been associated with motivational functions of "drive" and

"incentive motivation" (Glickman and Schiff 1967; Hoebe 1969; Trowill et al. 1969; Valenstein et al. 1970; Wise 1974). The drive effects are straightforward; stimulation at lateral hypothalamic reward sites causes sated animals to behave as if they were food- and water-deprived (Wise 1974). Such animals eat and drink and perform learned tasks reinforced by food and water, despite the fact that they are sated as reflected in tests immediately before and after the 20-sec stimulation tests. Thus motivational theorists have characterized this system as more than simply a positive reinforcement system.

While not agreed as to how, exactly, the system should be characterized, most brain stimulation specialists are agreed that activation of this system produces something more general than simply the arousal associated with positive reinforcement. The possibility exists that the motivational effects of opioids are also more general than simply the motivational arousal associated with the concept of reinforcement. Naloxone inhibits free-feeding and lever-pressing for food (McCarthy et al. 1981; Mello et al. 1981). and there is evidence to suggest that opiates facilitate these behaviors. Since the same mechanism is thought to mediate stimulation-induced feeding and brain stimulation reinforcement (Glickman and Schiff 1967; Hoebel 1969), it is possible that the same ventral tegmental morphine injections that are reinforcing and that facilitate brain stimulation reinforcement will also facilitate stimulation-induced and deprivation-induced feeding. The present experiments explore this possibility.

METHODS

Two procedures were followed; in the first, eating was induced by lateral hypothalamic electrical stimulation, and in the second eating was induced by 22h food deprivation. In each procedure morphine was injected into the ventral tegmental area through 30 gauge hypodermic cannulae inserted through chronically implanted 23 gauge guide cannulae. In the stimulation experiment, control injections were also tested in the periventricular gray substance, 2 mm dorsal to the ventral tegmental area.

In the stimulation-induced eating experiment the animals were tested several days before any drug injections were made. Stimulation intensity was adjusted to a level that produced eating at a mean latency of 10 sec at a stimulation frequency of 50 Hz (0.1 msec rectangular pulses) in sated animals. Stimulation was administered in 20 sec trains with a 20-sec inter-train interval. No eating was seen during the 20-sec no-stimulation periods, as the animals were allowed to satiate in the test box just prior to testing. Once the optimal stimulation intensity was established, each animal was tested at a number of stimulation frequencies, ranging from high frequencies that induced immediate eating to low frequencies that failed to induced eating within the 20 sec cutoff time. Latency to complete eating of three 45 mg food pellets was measured for each 20-sec train of stimulation. Four series of stimulation freqencies were tested each day: the first and third series were ascending frequencies and the second and fourth were

descending frequencies. The animals were tested daily in this fashion until their day-to-day frequency-latencyfunctions were stable (two to three weeks), and then drug testing began.

In the stimulation experiment, morphine was injected unilaterally into the ventral tegmental area in 0.25 ul of physiological saline, twenty minutes before testing; saline was given on test days between drug tests. Each animal was tested first with periaqueductal gray injections (0.5, 1.0, 2.5 and 5.0 ug); when dose-response data were complete the animal was then tested with ventral tegmental injections (0.1, 0.25, 0.5 and 1.0 ug) through a second cannula (the cannulaewere angled so as to avoid each other). Again, latency to complete eating of three 45 mg food pellets was measured at each stimulation frequency.

In the deprivation-induced eating experiment, two measures were taken. Meal segments of five 45 mg pellets each were introduced to the food cup at 72-sec intervals: each meal segment was left in the cage for 36 sec. Latency to make oral contact with the first pellet in each segment and time to complete the eating of each segment were taken. After responses stabilized, animals were tested following drug or saline injections on alternate days. Morphine (0.3 or 0.6 ug) was injected bilaterally in 0.5 ul of saline 10 min before drug tests: the lowest doses were tested first.

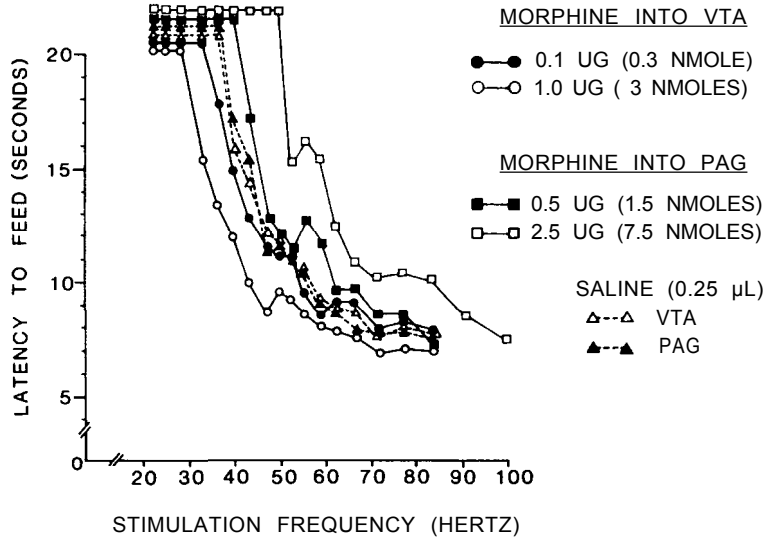

FIG 1. The effects of morphine injections into the ventral tegmental area (VTA) and the periaqueductal gray (PAG) on stimulation-induced eating latency. Latencies longer than 20 sec were not measured; off-scale latencies are represented merely to indicate the range of stimulation frequencies tested.

RESULTS

Low (1.0 ug) doses of ventral tegmental morphine decreased latencies in the stimulation-induced eating paradigm (Fig. 1); the results were dose-orderly and were seen across all frequencies of stimulation. While latency to make oral contact and time to consume were not separately measured, the two co-vary in this paradigm and both seemed to be affected. Morphine increased latencies when injected into the periaqueductal gray (Fig. 1); the effective doses were somewhat higher than for the ventral tegmental effects. Decreased latencies were seen in every animal having a cannula placement within the area of the ventral tegmental dopamine cell bodies; increased latencies were seen in every animal having a cannula placement within the periaqueductal gray.

In the deprivation-induced feeding paradigm, morphine decreased eating times but not eating latencies (Fig. 2). Latency scores were very short in this paradigm, and there was little room for improvement under morphine; this may explain the lack of latency effects. Morphine attenuated the response-slowing effects normally seen with satiety. The doses required to alter free-feeding were similar to those necessary to alter stimulation-induced feeding.

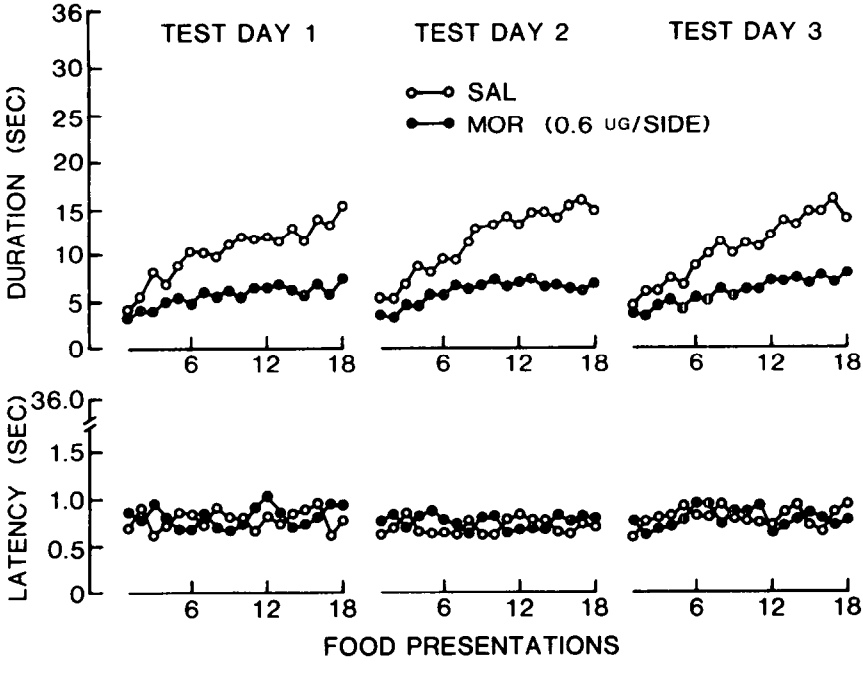

FIG 2. The effects of morphine injections (0.6 ug per side) on latency and duration scores in the free-feeding paradigm.

DISCUSSION

These experiments suggest that the effects of morphine on feeding are likely to be mediated by the same ventral tegmental opiate receptor population as is involved in the reinforcing effects of morphine and the facilitating effects of morphine on brain stimulation reward. The ventral tegmental area is the most sensitive reward site known for centrally injected morphine reinforcement (Bozarth and Wise 1982) and is also the most sensitive site for facilitation of brain stimulation reinforcement (Broekkamp et al. 1976); similar testing of other sites is important for experiments with the feedingparadigms, butitis not expected that lower doses will be effective at other sites.

Our data tend to support the view that hypothalamically induced feeding and hypothalamically induced brain stimulation reinforcement involve a common endogenous substrate, since both paradigms are sensitive to morphine injections at the same central site. It thus appears inappropriate to characterize this substrate as simply a reinforcement mechanism, although it would be equally misleading to characterize it as simply a hunger or feeding mechanism. In all probability the mechanism is involved in a wide range of positively motivated behaviors (Glickman and Schiff 1967); opiate effects seem to extend at least to drinking as well as eating (Ostrowski et al. 1981).

The most general and descriptive characterization of this mechanism is that it is a mechanism of "approach behaviors" (Glicknman and Schiff 1967). The two most general classes of behaviorally effective stimuli are the class of stimuli that elicits approach behaviors (this is a characteristic of positive reinforcers) and the class of stimuli which elicits withdrawal behaviors (punishers or negative reinforcers); opioids interact with each of these two classes, but separate mechanisms are involved. Painmessages are modulated by opioid actions in the periaqueductal gray and spinal cord (Basbaum and Fields 1978; Mayer and Price 1976).

The ventral tegmental actions of opiates are associated with approach behaviors. These injections induce forward locomotion in their own right (Joyce and Iversen 1979), and they facilitate the approach of food induced by deprivation and by hypothalamic stimulation. Approach is the universal unconditioned response to positive reinforcers, and is the commnon denominator of medial forebrain bundle motivational systems. The nornmal motivational function of ventral tegmental opioid effects might thus best be characterized as the amplification of effectiveness of approach-eliciting environmentalstimuli (much as the function of the peri-aqueductal gray injections is the attenuation of effectiveness of withdrawal-eliciting stimuli) rather than simply as a positive reinforcer. This more broad characterization captures characteristics of interest to students of Pavlov as well as those of interest to students of Skinner, and suggests a more general perspective on drug abuse than is offered by strict operant psychology.

REFERENCES

Basbaum, A.I., and Fields, H.L. Endogenous pain control mechanisms: Review and hypothesis. Ann Neurol, 4:451-462, 1978.

Bozarth, M.A. and Wise, R.A. Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sci 28:551-555, 1981.

Bozarth, M.A. and Wise, R.A. Localization of the r-d-relevant opiate receptors. In: Harris, L.S., ed. Problem of Drug Dependence 1981. National Institute on Drug Abuse Research Monograph 41. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1982. pp. 158-164.

Broekkamp, C.L.E.; Van den Boggard, J.H.: Heijnen, H.J.; Rops, R.H.; Cools, A.R. and Van Rossum, J.M. Separation of inhibiting and stimulating effects of morphine on self-stimulation behavior by intracerebral microinjections. Eur J Pharmacol 36:443-446, 1976.

Gallistel, C.R.; Shizgal, P.; and Yeanans, J. A portrait of the substrate for self-stimulation. Psychol Rev 88:228-273, 1981.

Glickman, S.E. and Schiff, B.B. A biological theory of reinforcement. Psychol Rev 74:81-109, 1967.

Hoebel, B.G. Feeding and self-stimulation. Ann NY Acad Sci 157:758-778, 1969.

Joyce, E.M. and Iversen, S.D. The effect of norphine applied locally to mesencephalic dopamine cell bodies on spontaneous motor activity in the rat. Neurosci Lett 14:207-212, 1979,

Mayer, D.J. and Price, D.D. Central nervous system mechanisms of analgesia. Pain 2:379-404, 1976.

McCarthy, P.S.; Dettmar, P.W.; Lynn, A.G.; and Sanger, D.J. Anorectic actions of the opiate antagonist naloxone. Neuropharmcol 20:1347-1349, 1981.

Mello, N.K.; Mendelson, J.H.; and Bree, M.P. Naltrexone effects on morphine and food self-administration in morphine-dependent rhesus monkeys. J Pharmcol Exper Ther 218:550-557, 1981.

Ostrowski, N.L.; Rowland, N.; Foley, T.L.; Nelson, J.L.; and Reid, L.D. Morphine antagonists and consummatory behaviors. Pharmacol Biochem Behav 14:549-559, 1981.

Phillips, A.G. and LePiane, F.G. Reinforcing effects of morphine microinjection into the ventral tegmental area. Pharmacol Biochem Behav 12:965-968, 1980.

Trowill, J.A.; Panksepp, J.; and Gandelman, R. An incentive model of rewarding brain stimulation. Psychol Rev 76:264-281, 1969.

Valenstein, E.S.; Cox, V.C.; and Kakolewski, J.W. Re-examination of the role of the hypothalamus in motivation. Psychol Rev 77:16-31, 1970.

Watson, S.J.; Khachaturian, H.; Akil, H.; Coy, D.H.; and Goldstein, A. Comparison of the distribution of dynorphin systems and enkephalin systems in brain. Science 218:1134-1136, 1982.

Wise, R.A. Lateral hypothalamic electrical stimulation: does it make animals hungry? Brain Res 67:187-209, 1974.

Wise, R.A. and Bozarth, M.A. Brain reward circuitry: Four circuit elements "wired" in apparent series. Brain Res Bull 12:203-208, 1984.

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Turning Behavior Induced by Phencyclidine: Relationship to Antagonism of N-Methyl-D-Aspartate in the Rat Striatum

Kenneth M. Johnson and Lawrence D. Snell

Structure-activity-relationship (SAP) studies over the last several years have shown a strong correlation between the discriminative stimulus properties of PCP-like drugs and their ability to displace ^{3}H-PCP from a membrane binding site found in brain tissue (Zukin and Zukin, 1981). This correlation extends beyond the arylcycloalkylamines to include certain substituted dioxolanes and psychotomimetic benzomorphans (Holztman, 1980; Brady et al., 1982; Hampton et al., 1982). These data suggest that the discriminative stimulus properties of these drugs may be related to an action at PCP/sigma receptors.

We recently postulated that PCP-like drugs may act through PCP/sigma receptors localized on dopamine (DA) containing neurons in the striatum to block reuptake, enhance release and/or to increase DA metabolism. SAR studies convinced us that the dopaminergic effects of PCP were not mediated via an action on these receptors, and, by extension, that the discriminative stimulus properties of PCP were not related to striatal dopaminergic mechanisms (Snell et al., 1984; Johnson and Snell, 1985). In spite of this, we found an apparent correlation between drug-induced turning behavior in rats with unilateral lesion of the substantia nigra and the affinity of these drugs for the PCP/sigma binding site in vitro (Johnson and Snell, 1985). Therefore, we focused our attention on striatal acetylcholine (ACh). Striatal cholinergic neurons are thought to receive excitatory input from the cortex, and because these neurons release ACh in response to glutamate (Lehmann and Scatton, 1982) it has been proposed that this amino acid may be the excitatory neurotransmitter in this pathway. It has been recently demonstrated that ketamine, a PCP derivative, stereoselectively inhibited the effects of excitatory amino acids on cat spinal neurons (Lodge et al., 1982). Interestingly, this effect appeared to be selective for the receptor subtype activated by N-methyl-D-aspartate (NMDA). In this paper, we describe the effects of several PCP-like drugs on NMDA - stimulated release of ACh and DA from striatal slices. In addition we show that antagonism of NMDA - induced ACh release is strongly correlated with ipsilateral turning in substantia nigra lesioned rats.

METHODS

Male Sprague-Dawley rats (200-300g) obtained from the Holtzman Co. were used in all studies. Unilateral destruction of the substantia nigra was accomplished as previously described (Snell, et al., 1984). Net ipsilateral rotations were counted in two successive fifteen minute bins. Because most of the drugs tested produced gross ataxia which at higher doses interfered with turning, inverted U shaped dose response curves were obtained. For this reason, in this paper we only report the turning produced by the most effective drug dose.

In separate experiments, DA and ACh release were estimated by measuring the radioactivity released from superfuse striatal slices (0.4mm) preincubated in the presence of 10nM ^{3}H-DA and 10µM pargyline or 50nM ^{3}H-choline and 10µM hemicholinuim-3, respectively. Details of these protocols are as previously described (Snell et al., 1984; Leventer and Johnson, 1984). Also, we estimated the affinity of several of the drugs studied here for the PCP/sigma site in cortical membranes as previously described (Snell et al., 1984).

RESULTS

2-Aminophosphonovalerate, a classic antagonist of electrophysiological responses to NMDA, shifted the NMDA dose response curve for stimulation of ACh release about ten-fold to the right in a parallel fashion. PCP (0.1µM), however produced a non-parallel shift to the right of about five-fold at the ED_{50} concentration of NMDA (figure 1). We found that etoxadrol, a substituted dioxolane with PCP-like behavioral properties, produced a similar non-parallel shift to the right of the NMDA dose-response curve for DA release (data not shown).

Representatives from three chemical classes known to have PCP-like discriminative stimulus properties were tested for their ability to inhibit NMDA-induced ACh and DA release from the rat striatum. These data are shown in table 1. PCP, etoxadrol, and (-) cyclazocine each inhibited the stimulated release of both neurotransmitters. These drugs were 2-7 fold more potent in inhibiting NMDA-induced ACh release than DA release. The effects of ethylketocyclazocine (EKC), N-allylnormetazocine (NANM), and morphine on NMDA-stimulated ACh release were compared to (-) cyclazocine (figure 2). The rank-order potency ((-) cyclazocine> NANM>EKC>>morphine) suggested that this effect may be mediated through the PCP/sigma site. Since dexoxadrol is more potent than its enantiomer, levoxadrol, in competing with ^{3}H-PCP for its binding site and in producing PCP-like behavior (Hampton et al., 1982; Shannon, 1983), we tested this pair's relative ability to inhibit NMDA-stimulated ACh release (table 2). For similar reasons we also compared the activities of 1-[1-(napthyl) cyclohexyl] piperidine HCl (m-amino-PCP) and 1-[-1-(m-nitrophenyl) cyclohexyl] piperidine HCl (m-nitro-PCP). In each

case, the more behaviorally active member of the pair produced significant inhibition of ACh release, while its counterpart did not (table 2). We also found that dexoxadrol and m-amino-PCP induced significant ipsilateral turning, while their counterparts, levoxadrol and m-nitro-PCP, were essentially void of

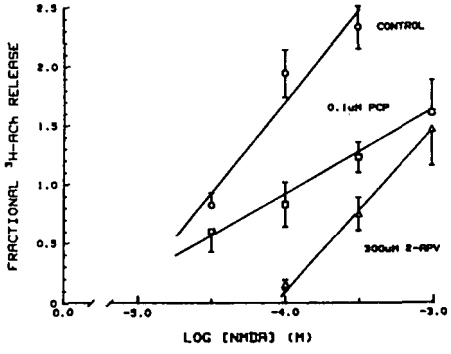

FIGURE 1. Stimulation of ACh release by NMDA in presence or absence of either PCP or 2-amino-4-phosphonovalerate (2-APV). Each data point represents the mean ± S.E. of 6-7 experiments.

TABLE 1. Effect of PCP, etoxadrol, and (-) cyclazocine on NMDA-induced striatal ACh and DA release

Drug	IC_{50}μM (95% Confidence Limits)	
	ACh Release	DA release
PCP	0.07(0.04-0.10)	0.38(0.17-0.83)
Etoxadrol	0.10(0.06-0.16)	0.75(0.31-1.7)
(-)Cyclazocine	0.12(0.08-0.18)	0.26(0.15-0.46)

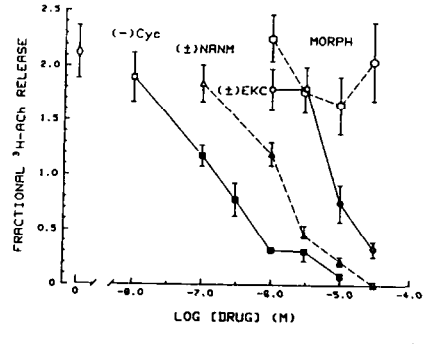

FIGURE 2. Effect of benzomorphans and morphine on NMDA-induced ACh release. Each data point respresents the mean ± S.E. of 5-7 experiments except for the control (open diamond) which is the mean ± S.E. of 15 experiments. The filled symbols are significantly different from control at P<0.05 (Student's t-test).

activity at the same dose (table 2). Of the other drugs utilized in this study, NANM, PCP, (-) cyclazocine, and etoxadrol produced significant ipsilateral turning during the first 15 min period following administration (table 3) while morphine and EKC did not.

TABLE 2. Effect of PCP-related drugs on turning behavior, NMDA-induced ACh Release, and ^{3}H-PCP binding

Drug	Net Ipsilateral Turns (0-15 min) after 10mg/kg	% Inhibition NMDA-induced ACh Released at 0.1µM	IC_{50}(µM) Inhibition of ^{3}H-PCP Binding (95% Confidence Limits)
Dexoxadrol	50.2±15.0*	42.5 + 9.4**	0.39(0.19- 0.82)
Levoxadrol	4.0± 1.0	16.0+14.0	19.00(7.50- 4.70)
m-Amino-PCP	67.2± 2.2*	50.5+ 6.6**	0.20(0.08- 0.47)
m-Nitro-PCP	8.0± 3.5	8.4±10.0	4.30(0.76-24.00)

*P<0.05 (Mann-Whitney U-test). **P<0.05 (Student's t-test).

TABLE 3. The effect of PCP and related compounds on turning behavior in rats with unilateral destruction of the substantia nigra

Drug (mg/kg)	Net ipsilateral turns	
	0-15 min	15-30 min
Saline[a]	3.7± 1.5	4.0± 2.6
Ethylketocyclazocine (10)	3.7± 2.7	1.72±1.7
Morphine (2)	10.32±5.5	10.72±8.2
N-Allylnormetazocine (10)	24.0± 5.6*	16.0± 7.5
Phencyclidine (10)	25.3± 1.2*	18.3± 1.9*
(-) Cyclazocine (5)	47.8±11.0*	11.0± 5.8
Etoxadrol (10)	50.7±17.0*	20.3±10.0
Amphetamine (5)	56.7± 1.9*	125.7±25.0*

[a] Saline (0.9% NaCl) and all other drugs were injected in a volume of lcc/kg (i.p.). Each drug was tested in 3-5 rats. * P<0.05 (Mann-Whitney U test).

DISCUSSION

Barring profound dispositional or metabolic differences between dexoxadrol and levoxadrol or m-amino-PCP and m-nitro-PCP, it is quite possible that these drugs induce ipsilateral turning by acting through a PCP/sigma receptor. This notion is strongly supported by the data in table 2. A comparison of the behavioral effects of (-) cyclazocine, NANM, and EKC with their affinity for the site labelled by ^{3}H-PCP (IC_{50} values: 1.0, 2.2, and > 30µM, respectively, Johnson and Snell, 1985) also lends support to this

possibility. Thus, it appears that turning behavior in rats with unilateral destruction of the subitantia nigra may be a useful model of PCP/sigma receptor activity in the whole animal.

In spite of several disadvantages of this behavior as a model of PCP action, it is a significant advantage that the neurochemical and neuroanatomical substrates mediating turning behavior are fairly well understood (particularly when compared to drug discrimination models). This makes it possible to investigate the effects of PCP-like drugs on a relatively well circumscribed set of neurotransmitters and neuronal pathways with some reasonable hope of establishing significant links between cause and effect.

In this context then, it is reasonable to ask how these PCP-like drugs induce turning. If the effect is mediated through PCP/sigma receptors as suggested, on what kinds of neurons are these receptors located? What is their function? We speculate that some of these receptors exist on the soma of striatal cholinergic interneurons and that they function to regulate the interaction between the cortico-striatal excitatory amino acid transmitter (perhaps glutamate) and one of its receptor subtypes, which, when stimulated, induces ACh release. Thus, these PCP/sigma drugs would be "anticholinergic" in that they inhibit stimulated ACh release. Although we know of no study reporting the effect of classic NMDA antagonists on turning behavior, it has been shown that anticholinergics like scopolamine induce weak ipsilateral turning similar to that reported here (Pycock, 1980).

Although it is possible that NMDA-type receptors mediate release from a site distant to either DA or ACh containing neurons, biochemical and anatomical data suggest that they are located on these neurons (Roberts and Anderson, 1979). The ability of NMDA to promote Ca^{++}-dependent, TTX sensitive ACh release in the striatum, but not in the hippocampus, prompted the proposal that these receptors were localized on the cell bodies rather than terminals of cholinergic neurons (Lehmann and Scatton, 1982). Thus it seems reasonable to propose that the PCP/sigma receptor is localized very near the NMDA receptor on cholinergic cell bodies in the striatum. That these receptors are probably not identical proteins is supported by the data in figure 1. That is, PCP is not a competitive inhibitor of the NMDA response. Thus, occupation of the PCP/sigma site appears to modulate the NMDA response mechanism rather than the recognition site itself. The nature of this mechanism is open to investigation.

The ability of PCP-like drugs to inhibit NMDA-induced DA and ACh release poses interesting questions concerning the relationship of these effects to those observed on turning. For example, since striatal DA release is known to inhibit ACh release, blockade of NMDA-stimulated release of DA might be expected to increase ACh release. However, it appears that the greater potency of PCP-like drugs in inhibiting ACh release (Table 1) relegates their ability to inhibit NMDA-induced DA release to a place of secondary importance. That is, even at concentrations

as high as 10 µM, PCP did not enhance NMDA-induced ACh release. A second question asks whether the ability of PCP-like drugs to enhance spontaneous DA efflux or to block DA reuptake might contribute to their ability to block NMDA-induced ACh release. Since our recent studies of DA release showed that drugs like cyclazocine, NANM, etoxadrol, and dexoxadrol do not evoke significant DA release at reasonable concentrations (Snell et al., 1984), spontaneous DA release is probably not a factor in this study. Also, the minimal concentration of PCP required to elicit spontaneous DA release (1-3µM, Snell et al., 1984) is 30-100 fold greater than that required to block NMDA-induced release. In this regard, this effect of PCP-like drugs is also mechanistically distinct from that which underlies the inhibition of K^+-stimulated ACh release as that required 3-10µm PCP before significant inhibition was observed and inhibition was produced by low concentrations (100nM) of EKC (Leventer and Johnson, 1983, 1984). Of all the biochemical effects of PCP, none except displacement of ^{3}H-PCP from its binding site occur at concentrations of PCP as low as those which affect NMDA-induced ACh release.

In summary, the similar structure-activity-relationships among the PCP-like drugs regarding inhibition of NMDA-induced ACh release and induction of ipsilateral turning suggest that the former mechanism may underlie the latter behavioral effect. Also, demonstration a direct antagonism of an NMDA (or glutamate) - induced behavior by PCP-like drugs is sorely needed to strengthen this argument. In addition, we feel like studies of the interaction between PCP and excitatory amino acids in other brain areas and in other neurotransmitter systems are needed to determine the importance of this phenomenon in other behavioral effects of PCP.

REFERENCES

Brady, K.T., Woolverton, W.L., and Balster, R.L. Discriminative stimulus and reinforcing properties of etoxadrol and dexoxadrol in monkeys. J Pharmacol Exp Ther 220: 56-62, 1982.

Hampton, R.Y., Medzihradsky, E., Woods, J.H., and Dahlstrom, R.J. Stereospecific binding of ^{3}H-phencyclidine in brain membranes. Life Sci 30: 2147-2154, 1982.

Holtzman, S.G. Phencyclidine-like discriminative effects of opioids in rat. J Pharmacol Exp Ther 214: 614-619, 1980.

Johnson, K.M., and Snell, L.D. Effects of phencyclidine (PCP)-Like drugs on turning behavior, ^{3}H-dopamine uptake, and ^{3}H-PCP binding. Pharmacol Biochem Behav 22: 731-735, 1985.

Lehmann, J. and Scatton, B. Characterization of the excitatory amino acid receptor-mediated release of ^{3}H-acetylcholine from rat striatal slices. Brain Res 252: 77-89, 1982.

Leventer, S.M. and Johnson, K.M. Effects of Phencyclidine on the release of radioactivity from rat striatal slices labeled with (^{3}H) choline. J Pharmacbl Exp Ther 225: 332-336, 1983.

Leventer. S.M. and Johnson, K.M. Phencyclidine-induced inhibition of strital acetylcholine release: comparisons with mu, kappa, and sigma opiate agonists. Life Sci 34: 793-801, 1984.

Lodge, D., Anis, N.A., and Burton, N.R. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurons by amino acids and acetylcholine. Neurosci Lett 29: 281-286, 1982.

Pycock, C.Y. Turning behavior in animals. Neurosci 5: 461-514, 1980.

Roberts, P.J., and Anderson, S.D. Stimulatory effect of L-glutamate and related amino acids on ^{3}H-dopamine release from rat striatum: an in vitro model for glutamate actions. J Neurochem 32: 1539-1545, 1979.

Shannon, H.E. Discriminative stimulus effects of phencyclidine: structure activity relationships. In: Kamenka, J.M., Domino, E.F., Geneste, P. eds. Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications, 1983. pp. 311-335.

Snell, L.D., Mueller, Z.L., Gannon, R.L., Silverman, P.B., and Johnson, K.M. A comparison between classes of drugs having phencyclidine-like behavioral properties on dopamine efflux in vitro and dopamine metabolism in vivo. J Pharmacol Exp Ther 231: 161-169, 1984.

Zukin, S.R., and Zukin, R.S. Identification and characterization of ^{3}H-phencyclidine binding to specific brain receptor sites. In: Domino, E.F. (ed.) PCP (Phencyclidine): Historical and Current Perspectives, 1981. pp. 105-130.

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The Reinforcing and Rate Effects of Intracranial Dopamine Administration

Steven I. Dworkin, Nick E. Goeders, and James E. Smith

Most substances with high abuse liability have at least three behavioral effects in common. These drugs are self-administered, they alter ongoing rates and temporal patterns of behavior and have stimulus properties that permit accurate detection of their administration. Central dopamine pathways have been suggested to be involved in all three effects.

Mesolimbic dopaminergic neurons are thought to have an important role in central drug reinforcement processes. The potential involvement of projections from this system to the ventral tegmental area (VTA), nucleus accumbens (NA) and medial prefrontal cortex (MPC) has been assessed using neurotoxin lesion and intracranial self-administration methodologies. 6-hydrodopamine (6-OHDA) lesions of the NA decrease intravenous amphetamine (Lyness et al. 1979) and cocaine (Roberts et al. 1977; 1980) self-admistration and either increase (Smith et al. 1985) or do not affect (Pettit et al. 1984) intravenous opiate self-administration. However, 6-OHDA lesions of the ventral mesencephalic tegmentum increase intravenous amphetamine (Deminere et al. 1984) and decrease intravenous cocaine self-administration (Roberts and Koob 1982). These data generally suggest dopamine (DA) releasing neurons to be involved in the mediation of the reinforcing neuronal activity that follows contingent presentation of opiate and stimulants.

The VTA supports intracranial self-administration of morphine (Bozarth and Wise, 1981) and neurotensin (Glimcher et al. 1983) while morphine (Olds 1982), met-enkephalin (Goeders et al. 1984), cholecystokinin (Hoebel and Aulisi 1984) and amphetamine (Hoebel et al. 1983) are self-administered into the NA and cocaine into the MPC (Goeders and Smith, 1983). It is generally assumed that this self-administration is the result of the reinforcing properties of these substances. However, intracranial administration could directly affect motor activity and/or schedule-controlled behavior. These studies were initiated to directly assess the reinforcing, rate-effects and stimulus properties of centrally administered dopamine. The first

experiment was designed to determine if DA itself has intrinsic reinforcing properties and will initiate reinforcing neuronal activity (support intracranial self-administration). The second study assessed the behavioral effects of intracranial administration of dopamine into rats responding on a fixed-interval schedule of food presentation. A third study in progress will evaluate the stimulus properties of centrally administered dopamine.

Experiment I

Male Fischer 344, 90-150 day old rats were implanted with unilateral injection cannula into one of three brain regions: nucleus accumbens (N=4), ventral tegmental area (N=4), or medial prefrontal cortex (N=4). The rats were allowed to intracranially self-administer picomolar doses of dopamine directly into these regions during three-hour sessions every third day using electrolytic microinfusion systems. Initially, each response resulted in a 5-second 100nl infusion paired with tone and light stimuli, followed by a 1-second time-out. As self-administration was acquired, the interval was increased to 1 minute (fixed interval 1-minute schedule). Responses made during the interval resulted in the brief presentation of stimuli paired with infusions while responses during infusions had no programmed consequence. After stable rates and patterns of dopamine administration were observed, the effects of substitution of vehicle were determined (extinction). After responding stabilized during the extinction phase, dopamine was again made available and reacquisition assessed.

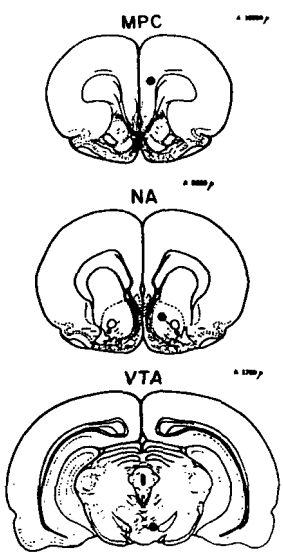

FIGURE 1. Regions of the medial prefrontal cortex, nucleus accumbens and ventral tegmental area where unilateral intracranial injetion guide cannulae were implanted.

Experiment II

Seventeen male Fischer rats were evaluated in the second study. Rats were implanted with bilateral intracranial injection cannulae into the nucleus accumbens (N=6) or with unilateral cannula into the medial prefrontal cortex (N=4) and subsequently trained to respond on a fixed-interval E-minute schedule of food presentation. When responding stabilized, the effects of response-independent microinfusion of dopamine (1000-1200 pm) or vehicle were determined. Intracranial infusion were presented at either 5 or lo-minute intervals and were paired with a light and tone stimulus complex. The infusion system was calibrated to deliver 100 nl over 5 seconds and infusion durations were varied from 5 to 25 seconds. The effects of systemic cocaine injection on FI responding were also assessed in these animals.

RESULTS

Experiment I

Rats with cannula implanted in the NA self-administered DA while those with cannula implanted into the VTA or MPC did not at the dose range investigated (25-3000 pm per infusion). Response-contingent presentations of DA (700-800 pmols per infusion) into the NA maintained stable rates of self-administration significantly above vehicle (Figure 2). Responding was well maintained by the FI 1-min schedule. However, the response patterns observed from one infusion to another were variable with typical scalloped patterns of fixed interval schedule-controlled behavior occasionally observed (Figure 3). Responding extinguished over several sessions when vehicle was substituted for DA but was subsequently reengendered during the first session that dopamine was again made available.

Experiment II

Response-independent intracranial infusions of DA did not significantly alter response rates or temporal patterns of responding maintained by the FI 2-min schedule with the doses investigated (Figure 4). However, systemic cocaine significantly affected these patterns, demonstrating that the cannulae implantation and intracranial infusions did not alter brain systems mediating these effects of the drug.

DISCUSSION

Dopamine was self-administered into the nucleus accumbens but not into the VTA or MPC of experimentally naive rats which suggests regional specificity in its ability to initiate reinforcing neuronal activity. Amphetamine (Hoebel et al. 1983), morphine (Olds 1982), methionine enkephalin (Goeders et al. 1984) and cholecystokinin (Hoebel and Aulisi 1984) are also self-administered into this region. Several of these substances are thought to produce reinforcing effects through action on

dopaminergic systems. Therefore, it is not surprising that DA is directly self-administered, suggesting endogenous release to be involved in the initiation of reinforcing neuronal activity in this structure. Since DA was not self-administered into the VTA or MPC by experimentally naive rats, DA innervations of these regions may not be involved in the direct initiation of reinforcing neuronal activity. However, behavioral history could modulate the sensitivity of neuronal systems. Neurotransmitters or drugs not self-administered into discrete brain regions in experimentally naive subjects may be after animals are trained with other reinforcers. If this is indeed true, then experimentally naive subjects should be used for determining the possible reinforcing effects of intracranially infused substances.

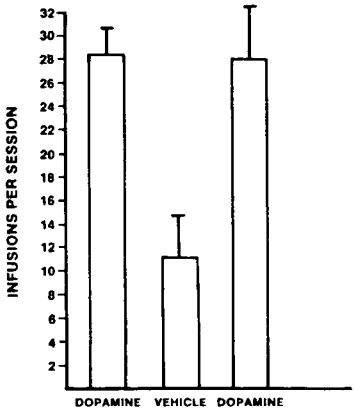

FIGURE 2. Intracranial infusions (means ± S.D.) of dopamine, vehicle and dopamine(redetermination) into the nucleus accumbens (N=4) during 3-hour bi-weekly self-administration sessions. Dopamine intake was significantly higher than vehicle.

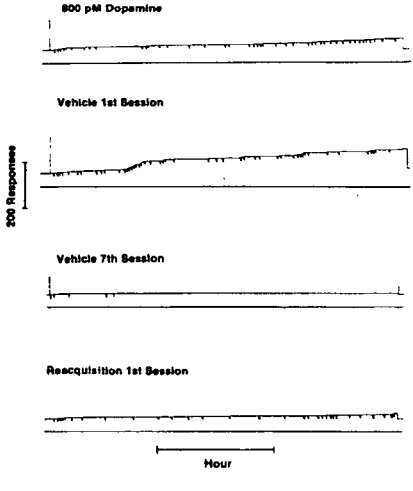

FIGURE 3. Cummulative response records for one rat responding on FI 1 - min schedules of dopamine or vehicle presentation into nucleus accumbens. lop panel represents responding and the pen deflections infusions when 800 pmoles of dopamine was available. The next two panels represent responding during the first and the seventh successive extinction sessions. The bottom panel shows responding in the next successive session when 800 pmoles of dopamine was again available

The number of sessions necessary for responding to extinguish following vehicle substitutions suggests that DA administered into the NA has potent reinforcing properties. The maintenance of responding with the fixed interval contingency may have contributed to the prolonged extinction effect. Fixed interval schedules engender responding that is more resistant to extinction than that maintained with the small fixed-ratio response requirements usually used with intracranial drug self-administration procedures. Moreover, the fixed-interval schedule was used to control for potential increases in locomotor behavior that have been observed after DA administration into the NA (Costall et al. 1982). An interval schedule minimizes the possibility that an injection will elicit lever pressing that results in another injection that elicits lever pressing, etc. The maintenance of responding under the fixed-interval schedule suggests that potential motoric effects of DA infusions did not confound assessment of the reinforcing properties of the neurotransmitter. The role of increased locomotor activity in this self-administration is unlikely since a single dose of DA that increases locomotor activity is 1000 times higher (Costall et al. 1982) than the total amount self-administered in a 3-hour session. The bi-weekly sessions (3 and 4 days apart) were used to avoid potential modification of receptor densities or affinities (which could result in sensitization or tolerance and thus, unstable behavioral data) which may also have contributed to the extended duration of extinction. Two-lever discrimination and receptor blockade experiments are currently in process.

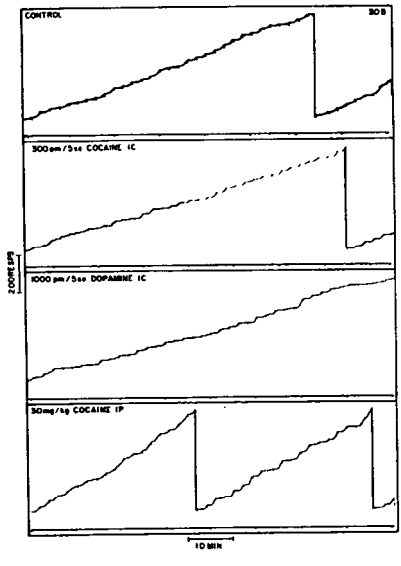

FIGURE 4. Effects of fixed-time 10-minute unilateral infusions into the medial prefrontal cortex. The top record shows control performance. The second and third panel, respectively, show the effect of intracranial infusion of 300 pmol of cocaine and 1000 pmol of dopamine. The 100 nanoliters infusions were delivered over 5 seconds. The lower record depicts the effects of an i.p. injection of 30 mg/kg of cocaine.

Data from the second study demonstrates that non-contingent infusions of dopamine into the same areas that support self-administration at doses that are self-administered do not disrupt responding maintained by a food schedule. Therefore, the reinforcing effects of the agents appear to be independent of the motoric or rate-altering effects. It may be necessary to simultaneously activate several areas of the dopaminergic system to alter responding maintained by schedules of food presentation. A second possibility is that discrete brain regions may be involved in the different behavioral effects of DA. A particular region that supports self-administration may not be involved in the stimulus properties or rate effects of a drug.

REFERENCES

Bozarth, M.A. and R.A. Wise. Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sci. 19:551-555, 1981.

Costall, B., A.M. Domeney and R.J. Naylor. Behavioural and biochemical consequences of persistent overstimulation of mesolimbic dopamine systems in the rat. Neuropharm. 21:327-335, 1982.

Deminere, J.M., H. Simon, J.P. Herman and M.LeMoal. 6-hydroxydopamine lesion of the dopamine mesocorticolimbic cell bodies increases (+)-amphetamine self-administration. Psychopharmacol. 82:281-284, 1984.

Glimcher, P.W., A.A. Giovino and B.G. Hoebel. Self-injection of neurotension into the ventral tegmental area (VTA). Neurosci Abst. 9:120, 1983.

Goeders, N.E., J.D. Lane and J.E. Smith. Intracranial self-administration of methionine enkephalin. Pharmacol Biochem Behav. 20:451-455, 1984.

Goeders, N.E. and J.E. Smith. Cortical dopaminergic involvement in cocaine reinforcement. Science 221:773-775, 1983.

Hoebel, B.G. and E. Aulisi. Cholecystokinin self-injection in the nucleus accumbens and block with proglumide. Neurosci Abst. 10:694, 1984.

Hoebel, B.G.; A.P. Monaco; L. Hernandez; E.F. Aulisi; B.G. Stanley and L. Lenard. Self-injection of amphetamine directly into the brain. Psychopharmacol. 81:158-163 1983.

Lyness, W.W.; N.M. Friedle and K.E. Moore. Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on d-amphetamine self-administration. Pharmacol Biochem Behav. 11:553-556, 1979.

Olds, M.E. Reinforcing effects of morphine in the nucleus accumbens. Brain Res. 237, 429-440, 1982.

Pettit, H.O.; A.Ettenberg; F.E. Bloom and G.F. Koob. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacol. 84:167-173, 1984

Roberts, D.C.S.; M.E. Corcoran and H.C. Fibiger. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol Biochem Behav. 6:615-520, 1977.

Roberts, D.C.S.; G.F. Koob; P. Klonoff and H.C. Fibiger. Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol Biochem Behav. 12:781-787, 1980.

Roberts, D.C.S. and Koob. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacol Biochem Behav. 17:901-904, 1982.

Smith, J.E.; F.G. Guerin; C. Co; T.S. Barr and J.D. Lane. Effects of 6-OHDA lesions of the central medial nucleus accumbens on rat intravenous morphine self-administration. Pharmacol Biochem Behav. In press, 1985.

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How Effective is LAAM Treatment? Clinical Comparison with Methadone

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INTRODUCTION

Levo-alpha Acetyl Methodol (LAAM) was developed in the early 1970's as a long acting (48-72 hours) synthetic opiate for use in the maintenance treatment of opiate addiction (1,2).

This paper reports the results of a clinical comparison of LAAM and methadone, the traditional maintenance treatment, with particular attention to the effects of greater treatment duration on patient and on patient reports of undesirable symptoms. These results suggest that even prolonged regimens of LAAM can be associated with annoying psychological symptoms in some patients. These results and our clinical experience with LAAM over the past nine years are discussed with regard to its role in the maintenance treatment of opiate addiction.

METHOD

LAAM Treatment Program - At the time of intake, informed consent and a history and physical, as well as a battery of tests are obtained.

Patients are initially started on a three day per week schedule, either Monday-Wednesday-Friday or Tuesday-Thursday-Saturday and the initial LAAM dose is determined from a conversion table if the patient is already on ethadone, or estimated if the patient is a new program intake using a low maximum dose for safety (i.e., 30, 30, 40). Subsequently, adjustments are made to the dosage in 10 mg. increments (eg., the above dose increased to Monday, 40, Wednesday 40, Friday, 50). Patients may require a week or two to adjust to LAAM and may initially report some mild withdrawal symptoms, which may disappear with no dose change.

During the course of treatment the patient is offered the full range of counseling, medical, and social work services available to the Methadone patients. All patients are assigned an

an individual counselor and are required to meet at least once per week for the first month of treatment and at least once per month thereafter. All patients are required to give supervised urine specimens on a randomized schedule, once per week.

Subjects - Subjects were all male veterans who applied for outpatient opiate abuse treatment at the Drug Dependence Treatment Center of the Philadelphia V.A. Medical Center. Approximately 90% of all subjects were Philadelphia residents. There were no eligibility criteria for substance abuse treatment at this center other than eligibility for veterans benefits. However, based on the results of the standard pre-treatment screening for LAAM, patients were excluded if they showed evidence of psychosis, life-threatening medical conditions, or other medical conditions requiring multiple medications.

Data Collection - The Addiction Severity Index (ASI) was administered at intake and six months after treatment admission by an independent research technician. The ASI is a structured, 40-minute, clinical research interview designed to assess problem severity in seven areas commonly affected by addiction: medical, legal, drug abuse, alcohol abuse, employment, family, and psychiatric. In each of the areas, objective questions are asked that measure the number, extent, and duration of problem symptoms in the patient's lifetime and in the past 30 days. The patient also supplies a subjective report of the recent (past 30 days) severity and importance of the problem area. In order to retain valid general measures of outcome in each of the problem areas, and to overcome the inherent unreliability of single-item criteria, we constructed criterion composites from sets of single items within each of the ASI problem areas. Scores on each composite were calculated for all patients at admission and follow-up, with higher scores indicating greater problem severity (6).

RESULTS

In a first step in our overall evaluation of LAAM we compared patients at the start of LAAM treatment with their status six months later to determine if greater benefits would be shown in patients who remained in treatment longer. When patients who remained in treatment less than six months (n=13) were compared to those who remained in treatment longer than 6 months (n=17) we found that the long term patients showed greater improvements and improvements in more areas than the short-term group.

Because these results indicate that LAAM is an effective treatment, we thought it would provide an additional, relevant perspective to compare the LT LAAM patients with a comparable group of opiate dependent patients who were treated on methadone maintenance within the same overall treatment program. To this end, the 17 LAAM patients who remained on the program more than six months were matched with patients from our methadone program on three ASI variables which have previously been predictive of

treatment outcome (7). These variables were the ASI severity scores on employment and psychiatric status, as well as years of opiate use. The patients were also matched on number of prior drug treatments and the presence of a profession, skill or trade. After the LAAM patients were matched with 17 methadone patients, a range of variables were examined to determine if any important background differences existed between the groups at intake. There were no statistically significant differences in any of the variables we examined, although there was a trend ($p<10$) toward a difference in age between the two groups, with the LAAM group being older; and trends toward differences ($p<10$) between the groups in years of education, years of alcohol abuse and years of stimulant abuse. None of the variables that indicate severity in medical, employment, legal, family or psychiatric status were significantly different between the two groups. Thus, the matching procedure appears to have produced groups that were quite similar across a range of variables which have typically been important in determining treatment outcome.

Pre-to-post treatment improvements were evaluated in both matched groups using the paired t-test on our battery of ASI variables. These comparisons are presented in Table 1. As can be seen, the two groups were similar with regard to the number and size of the improvements shown in most of the areas except psychiatric status. The improvements in the drug use composite and in "days of heroin use" were significant ($p<01$) for both groups. The methadone group also showed a significant decrease ($p<01$) in stimulant abuse. Legal status seemed to improve for each group, and this was especially evident in the LAAM group. The legal composite score improved significantly ($p<05$) for the LAAM group. and both "crime days" and illegal income appeared to decrease ($p<08$, $p<06$ respectively). Although similar improvements could be seen in the methadone group, only improvement in "crime days" was statistically significant ($p<05$). There was also a trend toward improvement ($p<08$) in the family composite for the LAAM group, but not in the methadone group. The LAAM group seemed to improve slightly in the employment area, although only "days worked in the past month" improved significantly ($p<05$). The ethadone group did not show this improvement. There was not much indication of change in alcohol use for either group, although the LAAM group showed significant ($p<05$) improvement in number of days intoxicated. Neither group showed significant change in medical status following treatment.

Although most of the changes from baseline to six months were not significant on the psychiatric measures, it should be noticed that the LAAM group seems to have worsened whereas the methadone group seems to have improved somewhat. "Days of psychiatric problems" decreased significantly ($p<05$) for the methadone group but actually increased in the LAAM group.

Given that the two groups showed a number of significant improvements following treatment, it became important to examine the relative efficacy of the two treatmentsthrough a

Table 1

COMPARISON OF SIX-MONTH OUTCOMES IN IN MATCHED DRUG ABUSE PATIENTS TREATED WITH LAAM OR METHADONE LONGER THAN SIX MONTHS

	N=17 LAAM PATIENTS ADMISSION		SIX-MO. FOLLOW - UP		N=17 METHADONE PATIENTS ADMISSION		SIX-MO. FOLLOW - UP	ANCOVA
MEDICAL FACTOR	228		170		179		46	N.S.
Days Medical Probs.	5		5		6		1	N.S.
EMPLOYMENT FACTOR	420		371		583		567	N.S.
Days Worked	10	*	16		14		12	N.S.
Money Earned	544		669		614		744	N.S.
ALCOHOL USE FACTOR	90		51		56		62	N.S.
Days Drinking	8		4		5		5	N.S.
Days Intoxicated	3	*	1		1		1	*
DRUG USE FACTOR	323	**	173		344	**	169	N.S.
Heroin Use Days	13	**	2		26	**	3	.09
Stimulant Use Days	3		2		4	**	1	.07
Depressant Use Days	7		9		2		2	N.S.
LEGAL FACTOR	108	*	13		165		85	N.S.
Crime Days	5	.08	0		8	*	1	N.S.
Illegal Income	237	.06	57		350		24	N.S.
FAMILY FACTOR	306	.08	209		279		238	N.S.
Days Family Prob.	2		2		2		1	N.S.
PSYCHIATRIC FACTOR	143		247		193		104	*
Days Psychiatric Problems	8		12		9*		3	**

All criteria were measured during the 30 days prior to treatment start and prior to six-month follow-up. Larger factor scores equal worse status (see 13).

*=p<.05
**=p<.01

comparison of the six-month follow-up results.

Differences in Outcome at Six-Month Follow-Up - An analysis of Covariance (ANCOVA) was performed to determine differences in outcome between the two groups. The pre-treatment score of each criterion variable was used as the covariate in these analyses. The results of these analyses are presented in the last column of Table 1. As can be seen, there were some significant differences between the two groups. As previously discussed, the LAAM group worsened psychiatrically, and the methadone group improved on this measure. The ANCOVA revealed a significant difference in both the psychiatric composite ($p<05$) and days of reported psychiatric problems ($p<01$) reported by the two groups at the six-month interval. There was also a significant ($p<05$) difference in ANCOVA for "days intoxicated", with the LAAM group showing improvement, while the methadone group stayed the same. Finally, there was also a trend toward a difference in the drug use area, with the methadone group showing better adjusted outcomes in heroin use days ($p<09$) and stimulant use days ($p<07$) than the LAAM group.

DISCUSSION

The present study evaluated the clinical efficacy of LAAM in comparison to methadone. First patients who had been stabilized on LAAM but had stayed in treatment less than six months were compared with those LAAM patients who remained in treatment for at least six months. The long-term and short-term LAAM groups were evaluated on seven areas of adjustment at the six-month follow-up and, though both groups showed improvements, the long-term groups showed greater changes in more problem areas, particularly drug use, alcohol use, employment, legal status and family relations. The only area in which these long-term patients did not show improvement was their general psychiatric status, with many patients reporting increases in anxiety and tension following six months of LAAM.

Because of these findings, it was important to determine if LAAM offered any clear advantages over the standard maintenance medication, ethadone. This evaluation was done by matching each of the long-term LAAM patients with a methadone-maintained patient who had the same background status at the start of treatment and who stayed on methadone for approximately the same duration. Although this matching procedure was done retrospectively, the resulting group of methadone patients were not significantly different from the LAAM patients across 28 pre-treatment status variables that were selected as being potentially important for treatment outcome. Again, these retrospective matching procedures may not be considered a definitive evaluation, but the resulting data do offer an additional perspective on the relative benefits of LAAM and methadone for those patients who showed evidence of long-term engagement in maintenance treatment. The results of these matched comparisons were similar in many ways to the results of

prior reports (1-5) showing very similar amounts and types of improvements in the two groups. While the results were comparable in most of the outcome areas evaluated, the two groups differed significantly in the area of general psychiatric status. The methadone group showed significant reductions in psychiatric symptoms during the six-month period, and we have seen this result in several prior evaluations of methadone (8, 9). In contrast, the LAAM patients showed increases (albeit not significant) in psychiatric problems during the six-month period of treatment, especially in the symptoms of anxiety and tension.

There had been some indication in the early LAAM literature of symptomatic increases in anxiety during the induction and early treatment phases (4, 5). In fact, we attributed the increases in psychiatric symptoms among our short-term patients to the often reported problems of induction and stabilization with LAAM. These adverse symptoms are often vague and it is not always possible to distinguish between withdrawal symptoms or medication side effects. Individuals vary in their initial adjustment to LAAM; some are comfortable with the first dose, while others drop out complaining of withdrawal symptoms. These symptoms are not clearly dose-related and seem to be the result of individual differences in the metabolism of LAAM.

Regardless of the reasons for increased psychiatric symptoms in the short-term patients, the increased symptoms seen in the long-term patients were reported well after the stabilization phase of LAAM by patients who had essentially accepted and adapted to the medication.

Crowley and his associates (10) have reported that LAAM produces generalized activation in patients, which persists well after the initial stabilization phase. Crowley has recorded this heightened activity using a movement detector placed on the patient's body for week-long periods. He reports that general bodily movement is greater than the pre-LAAM baseline at all points, even during sleeping hours. Given these data, we suspect that the increased reports of anxiety and tension seen in our patients may partially reflect this stimulation effect and the effects of mild withdrawal symptoms on the off-medication days.

Regardless of the potential reasons, it is now clear from several reports that LAAM is not as well tolerated or as acceptable to the patient population as methadone. We have made LAAM available in this clinic for the past six years. We have never had more than 25 maintenance patients on LAAM, in contrast to an average of 300 methadone maintenance patients. In fact, our experience has been that it is only when take-home doses of methadone are not available to a patient that the patient will even consider LAAM maintenance. Even under these conditions, the majority of patients who start LAAM do not stabilize and less than 30% of patients who take one dose of LAAM remain on the medication for 30 days.

There are several potential reasons for this lack of patient acceptance. First, the availability of methadone take-home medication, and the lack of LAAM take-home medication, make LAAM less attractive to the patient. Second, the investigational status of LAAM as well as the recent cancer scares, since proven false (11), have also prevented wider acceptance. Despite these environmental factors, it seems clear that physiological stabilization on LAAM is difficult for many patients and some side-effects such as hyperarrousal, mild withdrawal effects and possibly some symptoms of anxiety may persist for as long as six months during LAAM maintenance. However, we and others continue to find definite benefits associated with LAAM both for the treatment program and that segment of the patient population that can adjust to the LAAM maintenance regimen.

REFERENCES

Complete references will be supplied by the authors upon request.

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Major Patterns of Polydrug Abuse Among Heroin Addicts

John C. Ball, Eric Corty, Diane L. Erdlen, and David N. Nurco

The topic of polydrug abuse has received increased scientific and medical attention during the past decade in the United States (e.g., Johnson et al., 1985). This awakened interest in polydrug abuse, that is, the "simultaneous or sequential use of more than one psychoactive drug for nonmedical purposes" (Wesson and Smith, 1979, p. 151) has undoubtedly been influenced by the continuing spread of new patterns of drug abuse (e.g., PCP, cocaine) and concomitant recognition that multiple use of drugs is commonplace in many populations.

In studying the extent of polydrug abuse and its long-term dynamics, it is efficacious to focus research upon particular populations or specific samples of drug abusers. For the prevalence of drug abuse and polydrug abuse both vary widely in different populations. In this regard, it is especially meaningful to investigate patterns of polydrug use among designated populations of drug abusers. These subjects are already involved with at least one drug and, therefore, are likely to be at risk for abuse of others as well. The present paper investigates the patterns of polydrug abuse over the addiction careers of male heroin addicts. This approach makes it possible to investigate the specific impact of opiate addiction vs. non-addiction upon polydrug abuse.

The present study seeks answers to three questions. 1. What classes of non-opiate drugs are used by active heroin addicts? 2. Are there distinct patterns of polydrug abuse among heroin addicts? 3. How stable are patterns of polydrug abuse over subsequent non-addiction and addiction periods?

PROCEDURE

The sample consisted of 105 consecutive male admissions to a methadone maintenance program in Pennsylvania. Forty percent of the subjects were white and sixty percent black. The mean age at the time of interview was 34.1 years and all subjects were at least 25 years old. The mean time from onset of addiction to time of interview was 11.3 years.

The 105 addicts were interviewed during a nine-month period by two experienced and specially trained interviewers at the treatment program. The interviews were conducted in private and the data were kept confidential. The interview schedule included detailed questions about the frequency of specific types of drug use during each subject's addiction career.

As in our previous research (Ball et al., 1983), each subject's career since the onset of addiction was recounted with respect to successive periods of addiction, non-addiction, and incarceration. A person was considered as being in an addiction period if he reported at least 4 days of regular opiate use per week or at least 16 days per month. A person was considered as being in a non-addiction period if he reported less frequent use. All 105 subjects had a first addiction period. Only 86 of the subjects had a non-addiction period and data were also collected on that period. Ninety-six of the subjects had at least two addiction periods. For those with multiple addiction periods, data were collected on the longest subsequent addiction period.

RESULTS

The data here reported focus on five classes of non-opiate drugs. These are amphetamines, barbiturates, cocaine, Valium, and other non-opiates. Data on the use of marijuana and alcohol were also collected, but these data are reported separately in order to facilitate analysis.

1. The extent of polydrug abuse. The extent of polydrug abuse in the three different periods is shown in Table 1. In the first addiction period, some ten to 30 percent of the sample used each of the five classes of non-opiates. Amphetamines were used on a monthly basis by 29.5% of the addicts, cocaine by 21.9%, Valium by 18.1%, other non-opiates by 15.2%, and barbiturates by 10.5%. Turning to days per month of use for those who used each drug, amphetamines were used 10.8 days, cocaine 11.9 days, Valium 8.8 days, other non-opiates 8.7 days, and barbiturates 11.7 days.

During the first non-addiction period the overall prevalence of non-opiate use markedly decreased, but the frequency of use increased for four of the five classes. For these 86 subjects, the percent using each drug dropped to 19.8% for the amphetamines, 11.6% for cocaine, 9.3% for Valium, 7.0% for other non-opiates, and 3.5% for barbiturates. The mean days per month of use for those using was, respectively, 13.8, 9.1, 17.2, 18.7, and 12.7.

For the 96 subjects with subsequent addiction periods, there was a general increase from the non-addiction period in prevalence of non-opiate drug use: 22.9% used amphetamines, 21.9% cocaine, 11.5% Valium, 8.3% other non-opiates, and 2.1% barbiturates (this

last was a decrease). Days of use per months were, respectively, 11.5, 13.8, 12.4, 9.1, and 8.0. With respect to prevalence and frequency of use; the subsequent addiction period resembles the first addiction period.

Marijuana was the most prevalent non-opiate drug in all three addiction periods. It was used by 44.8%, 33.7%, and 30.2% of the samples in the first addiction, first non-addiction, and subsequent addiction periods, respectively. (Mean days of use per month were 22.0, 21.9, and 23.2, respectively.) Alcohol was used by 20.0%, 18.6%, and 11.5% during these periods and, respectively, for 16.8, 14.7, and 19.5 days per month. (See Table 1.)

TABLE 1. Number of addicts abusing specific classes of non-opiate drugs during addiction and non-addiction periods

Drugs Abused	1st Addiction Period (n=105)		1st non-addiction Period (n=86)		Subsequent Addiction Period (n=96)	
	n	days of use per mo. for users	n	days of use per mo. for users	n	days of use per mo. for users
• Heroin	104	25.8	41	6.7	91	23.8
• Other opiates	37	13.7	10	4.6	30	18.0
1. Cocaine	23	11.9	10	9.1	21	13.8
2. Amphetamines	31	10.8	17	13.8	22	11.5
3. Barbiturates	11	11.7	3	12.7	2	8.0
4. Valium	19	8.8	8	17.2	11	12.4
5. Other non-opiates	16	8.7	6	18.7	8	9.1
• Marijuana	47	22.0	29	21.9	29	23.2
• Alcohol	21	16.8	16	14.7	11	19.5

NOTE: Other opiates include illicit Methadone, Morphine, Dilaudid, etc. Liquid codeine, Demerol, Periodan, and Pantapon.
Other non-opiates include Talwin and Pyribenzamine, PCP, Quaalude and inhalants.

2. Patterns of drug abuse. Analysis of individual patterns of non-opiate drug use by these male addicts provides information about major lifetime patterns of drug use. Three major patterns of drug use were found during the first addiction period. These are shown in Table 2. (Again, marijuana and alcohol use were analyzed separately.) The first pattern consisted only of opiate use and this was found for 39% of the subjects. These subjects did not abuse any of the five classes of non-opiates on a regular monthly basis. The second pattern involved the monthly use of one non-opiate as well as opiates. We termed this pattern Polydrug I and found that 41% of the addicts ware so classified. The third pattern was termed Polydrug II. In this case there was monthly use of two or more of the five classes of non-opiates. The final 20% of the sample was so classified.

TABLE 2. Number of addicts classified as Opiates Only, Polydrug I, and Polydrug II abusers in addiction and non-addiction periods

Drug Abuse Classification	First Addiction Period	Non-Addiction Period	Subsequent Addiction Period
A. Opiates Only	41	22	52
B. Polydrug I	43	22	32
C. Polydrug II	21	9	12
D. No Abuse	--	33	--
TOTAL	105	86	96

In the first non-addiction period, 25.6% of the 86 subjects were classified as Opiates Only, 25.6% were classified as Polydrug I, 10.5% were classified as Polydrug II, and the remaining 38.4% were not regular users of any opiates or of the five non-opiates. In the subsequent addiction period, 54.2% of the 96 subjects were classified as Opiates Only, 33.3% as Polydrug I, and 12.5% as Polydrug II.

Before turning to a more detailed description of the two classifications of polydrug abusers, it is pertinent to comment on the use of marijuana and alcohol in this classification. In the first addiction period., 34.1% of the Opiates Only, 39.5% of the Polydrug I, and 76.2% of the Polydrug II subjects were regular marijuana users. Though there were differences among groups in the prevalence of marijuana use, in all groups the frequency of use for those who did use was high. Respectively, it was 23, 19, and 24 days per month. Alcohol use showed a similar picture. Only 10% of the Opiates Only group and only 14% of the Polydrug I group were regular users of alcohol while 52% of the Polydrug II group used alcohol regularly. Among those who did use it, alcohol was used 15.8 days per month in the Opiates Only group, 14.3 days per month in the Polydrug I group, and 18.5 days per month in the Polydrug II group.

Polydrug I Abusers. In the first addiction period there ware 43 Polydrug I abusers. The most common non-opiate drug abused in this group was amphetamines (37.2%), followed by cocaine (20.2%), Valium (16.3%), barbiturates (9.3), and other non-opiates (7.0%). Frequency of use, for those who used these drugs, was, respectively, 12.9, 12.8, 6.9, 9.2, and 6.7 days per month.

Polydrug I abuse markedly decreased during the first non-addiction period. For the 22 subjects so classified, 40.9% used amphetamines, 31.8% used cocaine, and 27.3% used Valium. The days of use per month did not decrease and were, respectively, 16.8, 10.4, and 20.8. Polydrug I abuse increased during the subsequent addiction period. For the 32 subjects so classified, 40.6% used amphetamines, 40.6% used cocaine, 15.6% used Valium, and 3.1% used other non-opiates. The days of use per month were, respectively, 16.5, 16.2, 6.8, and 10.0.

Polydrug II Abusers. In the first addiction period, 21 addicts were found to fit the Polydrug II classification. These addicts abused two or more non-opiates in addition to their use of opiates. (See Table 3.) Most common was amphetamines which were used by 71.4% of these subjects for an average of 8.7 days per month. Next in order were other non-opiates (61.9% and 9.2 days per month), Valium (57.) and 9.9 days per month), cocaine (38.1% and 13.1 days per month). Each subject used on a regular basis a mean of 3.14 of the non-opiates. Certain patterns were notable For example, the concurrent use of barbiturates and amphetamines was uncommon while the concurrent use of Valium and amphetamines was common.

TABLE 3. The Extent and Frequency of Drug Abuse Among 21 Polydrug II Abusers During Their First Addiction Period

ID#	Amphet.	Barbs.	Cocaine	Valium	Other Non-Opiates					Number of Different Drugs
					Quaal.	Other Hallu.	Talwin& Pyrib.	PCP	Inh.	
008		25		25	2		2			4
009	1			8						2
013	2		4							2
014	4			8		\				2
015	2					2				2
016	4	4		4	4		16	4	1	7
017	1					1				2
018	1		1	2	1					4
025	10		30	4	1	1				5
026		1	1							2
029	4	8			8		8			4
044		4		4	1	1		2		5
049			8		8	4				3
051		20	30	8	8	12		8		6
061	15	30								2
062	15				8					2
082	30			30						2
084	10			15	15					3
111	30		4							2
114			20	10						2
119	2			1	1					3
										Mean = 3.14
Number of Abusers = 15		7	8	12	11	6	3	3	1	
Mean Days/Month =	8.7	13.1	12.2	9.9	5.2	3.5	8.7	4.7	1.0	

3. The continuity of polydrug abuse. We next traced the continuity of the three major patterns of drug abuse. Overall, we found stability during successive addiction periods and a decrease in polydrug abuse during the non-addiction period.

With respect to continuity and change among the 34 Opiates Only subjects who had a non-addiction period, 29.4% of them continued to abuse only opiates. 44.1% shifted to a lesser pattern of abuse and did not regularly use any drugs. 23.5% became Polydrug I abusers and only 2.9% became Polydrug II abusers.

Of the 35 Polydrug I abusers who had a non-addiction period, 57.2% shifted to a lesser pattern of abuse during their first non-addiction period (22.9 became Opiates Only abusers and 34.3% abused no drugs), 34.3% remained Polydrug I abusers and 8.6% became Polydrug II abusers.

Of the 17 Polydrug II abusers who had a non-addiction period, 70.6% of these moved to less abusive patterns during their non-addiction period -- 23.5% to Opiates Only, 11.8% to Polydrug I, and 35.3% to no abuse. Only 29.4% remained as Polydrug II abusers.

Marked stability was seen from the first addiction to the subsequent addiction period. Thus, of the 39 Opiates Only addicts who had a subsequent addiction period, 87.2% of these remained as Opiates Only abusers (7.7% became Polydrug I and 5.1% became Polydrug II abusers). Of the 38 Polydrug I addicts who had a subsequent addiction period, 57.9% remained Polydrug I abusers; 36.8% became Opiates Only and 5.3% became Polydrug II abusers. Finally, of the 19 Polydrug II abusers who had a subsequent addiction period, 42.1% remained Polydrug II abusers, 21.1% became Opiates Only abusers, and 36.8% became Polydrug I abusers.

DISCUSSION

Investigation of the extent of polydrug abuse among 105 heroin addict admissions to a methadone maintenance program revealed that there were three distinct patterns of drug abuse within this population. First, it was found that some 39% of these addicts do not abuse non-opiate drugs (excluding marijuana and alcohol) on a regular basis. Second, it was observed that 41% are Polydrug I abusers who regularly use one non-opiate drug as well as opiates. And, third it was found that 20% of these addicts are Polydrug II abusers who regularly use two or more non-opiate drugs in addition to heroin.

Further analysis of drug abuse patterns within this sample during successive periods of addiction and non-addiction revealed that the extent of polydrug abuse markedly declines during the non-addiction period. At the same time it was found that the frequency of abuse, for those who continued their polydrug patterns of abuse, remained high.

It was also found that the three major patterns of drug abuse established in the years after onset of opiate addiction ware quite stable over the addicts' careers. Thus, each of these three drug abuse patterns continued over the years of addiction. When change occurred it was generally in the direction of a lesser degree of abuse.

REFERENCES

Ball, J. C., Shaffer, J. W., and Nurco, D. N. The day-to-day criminality of heroin addicts in Baltimore. Drug and Alcohol Dependence, 1983, 12, 119-142.

Johnson, B. D., Goldstein, P. J., Preble, E., Schmeidler, J., Lipton, D. S., Spunt, B., and Miller, T. Taking care of business: The economics of crime by heroin abusers. Lexington, MA: Lexington Books, 1985.

Wesson, D. R. and Smith, D. E. Treatment of the polydrug abuser. In: DuPont, R. L., Goldstein, A., and O'Donnell, J., eds. National Institute on Drug Abuse, Handbook on Drug Abuse. Washington, DC, supt. of Docs., U.S. Govt. Print. Off., 1979. pp 151-158.

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Treatment of Cocaine Abuse

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INTRODUCTION

Much has been written about the cocaine epidemic, but few articles have dealt with treatment approaches. This article addresses several of the most critical issues in the treatment of cocaine abusers and offers some guidelines and suggestions for determining specific treatment strategies. Much of the material in this article is based on the author's clinical experience with a wide variety of cocaine-abusing patients and a more detailed discussion of these clinical issues can be found in other publications (Washton et al. in press).

INDICATIONS FOR TREATMENT

Treatment is indicated when the cocaine user is unable to stop taking the drug in spite of physical, psychological, or social problems resulting from the drug use. It is important to emphasize that severe cocaine abuse can develop with any route of administration. Intranasal administration offers no protection against addiction or medical consequences (Washton et al. 1983), although problematic use may develop more rapidly with freebase smoking and intravenous administration. Some of the clinical characteristics of cocaine dependence are described in Table 1.

TABLE 1

Cocaine Dependence: Clinical Characteristics

1. Loss of control over use
   - inability to refuse the drug when offered
   - inability to limit amount of use
   - "binge" patterns of excessive use for 24 hrs or longer
   - unsuccessful attempts to stop usage for a significant time period
2. Drug compulsion
   - persistent or episodic cravings and compulsions
   - compulsive use despite absence of drug-induced euphoria
   - compulsions override desire to stop usage
   - fear of being without cocaine
   - compulsion to use other drugs in absence of cocaine

3. Continued use despite adverse consequences

   - medical complications: lethargy, insomnia, nasal or sinus problems, appetite disturbance, loss of sex drive, impotence
   - psychiatric complications: depression, irritability, anhedonia, paranoia, suicidal/homicidal ideation or gestures
   - social complications: financial, relationship, legal, or job problems; general deterioration in psychosocial functioning

4. Denial

   - denies that the problem exists
   - denies or downplays the seriousness of adverse effects
   - acts defensive in response to inquiries about the drug use

IS COCAINE ADDICTIVE?

The academic debate over "physical" vs. "psychological" addiction to cocaine focuses on issues of physiological tolerance and withdrawal, but from a purely clinical standpoint these may be largely irrelevant. The key issue is not physiologic dependence, but the recurrent compulsion to use the drug and a continuing pathologic pattern of use in the face of adverse consequences. The physiological component of cocaine dependence may lie in the drug's powerful effects on brain neurotransmitters such as norepinephrine and dopamine (Gold et al. in press). Tolerance to cocaine is evidenced by the increasing quantities of the drug required to achieve desired effects and the eventual failure to reproduce these effects despite further escalation of use. Although no dramatic withdrawal syndrome follows abrupt cessation of cocaine use, a number of post-cocaine symptoms may emerge in high-dose chronic users, especially in heavy freebase and i.v. users, including: depression, insomnia, irritability, appetite disturbance, and intense cravings for cocaine.

SEVERITY OF ABUSE

The severity of abuse can differ dramatically among those who seek treatment and is determined by at least several factors, including: dosage, frequency, and chronicity of use; degree of psychosocial disruption; strength of drug urges and cravings; extent of other drug and alcohol abuse; and, extent of drug-related medical and psychiatric complications. Treatment needs will vary according to the severity of abuse and other aspects of the patient's clinical status. Since cocaine abusers do not comprise a homogeneous group of patients, no single treatment approach will be optimal in all cases.

INPATIENT OR OUTPATIENT?

Hospitalization of the cocaine abuser is usually required only in severe cases and so most can be treated as outpatients. Unlike heroin or alcohol, cocaine can be stopped abruptly without medical

risk or a dramatic withdrawal syndrome and no substitute drugs or gradual weaning from cocaine are needed.

CRITERIA FOR HOSPITALIZATION

Inpatient treatment of the cocaine abuser is usually indicated for those with the following characteristics:

1. Heavy users whose drug compulsion is uncontrollable, especially heavy freebasers and i.v. users;
2. Those with physical dependency on other drugs or alcohol;
3. Those with severe medical or psychiatric complications;
4. Those with severe psychosocial impairment;
5. Those who have failed in outpatient treatment.

ROLE OF HOSPITALIZATION

The major objectives of inpatient treatment should be to break the cycle of compulsive drug use, address related and co-existing problems, and strengthen the patient's motivation and skills for maintaining abstinence following hospital discharge. Inpatient treatment should be seen as only the first step in a more comprehensive recovery plan that must include outpatient aftercare treatment. The critical task of recovery is to maintain a drug-free lifestyle without the artificial protection of the hospital environment. Permanent abstinence following inpatient treatment is highly unlikely and relapse rates following hospitalization will remain unacceptably high unless the discharge plan includes intensive aftercare treatment.

COMPLETE ABSTINENCE

From Cocaine

The treatment must require immediate and complete cessation of cocaine use. A treatment goal of returning to "occasional" use is not only unrealistic but potentially dangerous for anyone who has been dependent on the drug. Attempts to reduce rather than discontinue cocaine use may be temporarily successful in some cases, but usually lead back to heavy use and additional drug-related consequences that could have been avoided via complete abstinence.

From Other Drugs/Alcohol

Abstinence from all drugs of abuse, including marijuana and alcohol, is important in order to maximize the benefits of treatment and minimize the possibility of relapse. The major goals of treatment must be to develop a reasonably satisfying drug-free lifestyle and to develop ways of coping without resorting to mood-altering chemicals.

Many cocaine abusers resist the idea of giving up alcohol or marijuana stating that they have had no problem with these substances in the past and would like to continue "social" or "recreational" use. The clinician must emphasize that complete abstinence offers the widest margin of safety, as evidenced by the following considerations: (1) while staying away from cocaine, one is often more likely to switch to other substances for substitute "highs" even in the absence of previous problems with these substances;

(2) substances that have been used in conjunction with cocaine, such as alcohol and marijuana, acquire the capacity through associative conditioning to trigger intense urges and cravings. for cocaine; (3) even a single glass of wine or beer or a single marijuana cigarette may reduce one's ability to resist temptation for cocaine due to the "disinhibiting" effect of these substances; and, (4) a thorough evaluation of the patient's present and past use of various mood-altering substances often reveals more significant abuse patterns than previously recognized-- since alcohol and other drugs are often used to self-medicate cocaine side effects, rather than to get "high", the user is often unaware of having acquired a simultaneous dependency on other substances.

URINE TESTING

Urine testing is essential in order for treatment to be successful. Throughout the entire course of treatment, the patient's urine should be tested at least 2-3 times per week for cocaine and all other only abused drugs (e.g., opiates, barbiturates, benzodiazepines, amphetamines, marijuana, PCP, etc.). Despite mutual trust and a strong therapeutic alliance between patient and clinician, urine testing is necessary because of the re-emerging denial and self-deceipt that is characteristic of the chemical dependency problem. Clinicians who fail to take the necessary counteractive measures are likely to become enablers of the patient's continuing drug use. It must be emphasized that the purpose of urine testing is NOT to catch the patient in a lie Rather, urine testing is a valuable treatment tool that helps to break through denial, promote self-control over drug-use impulses, and provide an objective monitor of treatment progress. Consequences for drug-positive urines must be stipulated at the outset of treatment. Although a rare or infrequent "slip" might be expected-any emerging-pattern of regular or frequent drug use should lead to revision of-the treatment plan, including temporary hospitalization if other efforts fail.

TREATMENT CONTRACTING

A written treatment contract should be used to clarify and concretize treatment requirements. The contract should specify the following: (1) that the patient immsdiately discontinue all use of mood-altering substances; (2) that the patient remain in treatment for no less than 6-12 months since this is the minimum amount of time needed to begin a solid recovery and promote long-lasting changes in lifestyle and behavior; (3) that a urine sample be given whenever requested; (4) that a severe relapse may necessitate immediate hospitalization; and, (5) that designated family members and/or significant others can be contacted in the event of relapse, premature termination from treatment, or for discussion of treatment progress.

STAGES OF TREATMENT

In our outpatient Relapse Prevention and Recovery (RPR) program, treatment is roughly divided into four phases, each of which focuses on specific tasks in the recovery process. There are no rigid dividing lines between the successive phases and patients

progress through these stages at differing rates.

Phase I: Stopping All Drug Use

The immediate goal of treatment is to stop all drug use and to maintain total abstinence for an initial 30-day period. Patients are seen daily or every 2-3 days for abstinence training, supportive counseling, urine testing, and drug education meetings involving family members. Joining a self-help group such as Cocaine Anonymous (CA) is strongly encouraged and may be required in some cases. Abrupt cessation rather than gradual reduction of cocaine use is essential. The likelihood of early treatment failure is increased if there is a tapering-off period because any involvement with the drug at all only heightens the patient's ambivalence about stopping and saps their motivation to achieve total abstinence. Major tasks of this phase include: breaking through denial; discarding all drug supplies and paraphernalia; establishing a committment to total abstinence; breaking off relationships with drug dealers and users; anticipating and handling drug urges; and, forming an initial support network.

Phase II: Relapse Prevention and Lifestyle Change

This phase lasts for approximately 6-12 months and focuses on counteracting the most common and predictable factors that can lead to relapse. Patients attend twice weekly cocaine recovery groups in conjunction with individual or family sessions at least once a week. Critical issues in this phase include: recognizing the earliest warning signs of relapse combatting "euphoric recall"; overcoming the desire to test personal control over drug use; avoiding "high risk" situations; preventing "slips" from becoming full-blown relapses; learning how to cope with stress and how to have a good time without drugs; and, forming new social relationships.

Phase III: Preparing for Long-Term Abstinence

This phase usually lasts for an additional 6-12 months and focuses on issues that are crucial to maintaining long-term abstinence. Treatment consists of a once weekly "advanced" recovery group with other senior members of the program and/or individual psychotherapy based on individual clinical needs. Major issues include: enhancing personal relationships and feelings of self-esteem; counteracting "flare-up" periods, overconfidence and renewed denial; addressing issues of "arrested maturity"; strengthening the commitment to drug-free living; realizing plans, goals and aspirations.

Phase IV: Follow-Up

When the formal treatment phases have been completed, patients are followed on a reducing schedule of periodic visits at 3-6 month intervals. Returning for more frequent contact during high-stress or "flare-up" periods is strongly encouraged. Continued participation in CA or some other self-help recovery network may become increasingly important during this phase of recovery.

FAMILY INVOLVEMENT

Close family members and especially the spouse or parents of the cocaine abuser should be involved in the treatment for a number of reasons. Family members can provide additional information about the patient's drug use and other behavior. Well-intentioned family members often function as enablers by making excuses for the cocaine abuser, providing money for the drug, or otherwise trying to spare the patient from suffering the consequences of his/her behavior. Family members need instruction and guidance in how to deal with the cocaine abuser and how to provide the necessary support to foster the patient's recovery. They also need an opportunity to deal with their own feelings of anger, blame, guilt and victimization so as to minimize family stress and confusion which could itself lead to the patient's early relapse and treatment failure.

SELF-HELP GROUPS

Participation in a self-help group is essential to long-term recovery for many patients. These groups should be used in conjunction with a program of professional treatment and should also be used as a continuing support system after treatment has ended. Professionals who employ an abstinence-oriented treatment approach Will find that self-help groups enhance their therapeutic success and provide an invaluable source of information and emotional support for their patients. Cocaine Anonymous chapters are rapidly proliferating in many areas of the U.S. CA is modeled after Alcoholics Anonynmus (AA) and Narcotics Anonymous (NA), utilizing the same 12-steps of recovery Which include admitting one's powerlessness over drugs and the need for total abstinence to arrest the disease of chemical dependency. CA provides an intensive peer-support network that is immediately available at no wst to any newcomer Who wants to stop using cocaine. In places where CA chapters do not exist, patients should be encouraged to try AA or NA meetings.

PHARMACOLOGIC TREATMENT

There is no definitive evidence that antidepressants, lithium, amino acids, or other psychotropic agents block the cocaine euphoria, ameliorate post-cocaine symptoms, or eliminate craving for cocaine. There is no known cocaine antagonist and no medication that has been shown to prevent relapse, despite earlier claims Which have not been replicated. If such medications were found they might indeed be helpful, especially in extreme or intractable caseswherepsychological interventions alone have failed. Recent trials with bromcriptine (Dackis, Gold 1985), a dopamine agonist used in treating infertility, suggest the potential use of this drug in eliminating urges and cravings for cocaine during the immediate post-drug abstinence period. However, the clinical efficacy of bromocriptine in treating cocaine abusers remains to be determined by controlled systematic studies.

PSYCHIATRIC ISSUES

Cocaine-induced psychosis tends to be self-limiting with disappearance of psychotic symptoms usually within 2-5 days after cessation of drug use. Hospitalization and short-term use of neuroleptics or sedative-hypnotics may be needed to facilitate initial management of some patients, although others may require no psychotropic medication and show complete remission of symptoms within 24-28 hours.

Depression is a common side effect of chronic cocaine abuse and a common complaint during initial cocaine abstinence. symptoms mimicking bipolar disorders, attention deficit disorders, and anxiety disorders may also be generated by cocaine abuse. Therefore, it is essential to allow a sufficient post-cocaine recovery period before making a definitive psychiatric diagnosis or introducing psychotropic medication. In cases where there is a genuine dual diagnosis of psychiatric illness and chemical dependency, both problems must be treated. It is nonetheless imperative that the drug abuse problem be dealt with as a primary disorder and not merely as a symptom of the psychiatric illness. In order to avoid unrealistic or distorted expectations, patients who receive psychotropic medication should be informed that the medication is to treat their psychiatric disorder and not to prevent relapse to drug use. The medication cannot be a substitute for the lifestyle change and other treatment efforts that are essential to recovery.

OTHER INTERVENTIONS

In addition to formal treatment interventions, a regular schedule of exercise and planned leisure time activities is an important feature of many patients' recovery plan. These activities help not only to reduce stress but also to instill a feeling of greater control over one's life. Workaholism and lack of satisfying social or leisure time are often precursors to relapse.

SUCCESS RATES

Success rates will depend upon a variety of factors including the severity of abuse, the patient's motivation to be drug free, and the extent to which the treatment program meets certain clinical needs. In our highly structured and intensive RPR outpatient program, we have found that over 65% of patients complete the 6-12 month program and over 75% are still drug free at 1-2 year follow-up (Washton 1985). The highest success rates are found in those with a strong desire to stop using cocaine, a history of good functioning before cocaine, and a genuine acceptance that the chemical dependency problem exists.

REFERENCES

Dackis, C.A., and Cold, M.S. Bromocriptine as a treatment for cocaine abuse. Lancet II: 1151-1152, 1985.

Cold, M.S. 800-COCAINE. New York: Bantam, 1984.

Cold, M.S.; Washton, A.M.; Dackis, C.A. Cocaine abuse: neurochemistry, phenomenology, and treatment. National

Institute on Drug Abuse Research Monograph, in press.
Stone, N.S.; Fromme, M.; Kagan, D. Cocaine: Seduction and Solution. New York: Pinnacle, 1985.
Washton, A.M. Success rates in cocaine abuse treatment. ADAMHA Science press Seminar. April, 1985.
Washton, A.M. Treatment of Cocaine Abuse. Psychiatric Clinics of North America, in press.
Washton, A.M.; Gold. M.S.; Pottash, A.C. Cocaine abuse: techniques of assessment, diagnosis and treatment. Psychiatric Medicine, in press.
Washton, A.M.; Gold, M.S.; Pottash, A.C. Intranasal cocaine addiction. Lancet II: 1374, 1933.
Washton, A.M.; Gold, M.S.; Pottash, A.C. Survey of 500 callers to a national cocaine helpline. Psychosomatics 25: 771-775, 1934.

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Cocaine Treatment Outcome: Cocaine Use Following Inpatient, Outpatient, and No Treatment

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Recently a number of clinical researchers have presented some strategies for treating the cocaine user. Anker and Crowley (1981) were among the first of these investigators to design and implement a systematic treatment approach to this problem. Their evaluation of contingency contracting has supplied some useful data on one way of addressing this problem. Tennant and Rawson (1982) and more recently Gawin and Kleber (1983) and Resnick and Resnick (1984) have evaluated several pharmacotherapies as a first step in dealing with the symptoms experienced by cocaine users in acute cocaine withdrawal. Siegel (1984) has described treatment priorities for working with cocaine smokers. Washton, Gold and Pottash (in press) have presented what they feel are the critical issues in the assessment, diagnosis and treatment of cocaine dependency.

Recent review articles on cocaine treatment by Smith (1983), Kleber (1984) and Resnick and Resnick (1984) have reviewed a range of treatment strategies. The treatment techniques reviewed have ran ed from long distance running (Siegel) to methylphenidate (Kleber) to self-help groups (cocaine anonymous). Each of these reviews provides some guidelines for treatment considerations; however, little has been documented concerning treatment outcome.

In spite of this lack of empirical evidence concerning treatment efficacy, current advertising campaigns by a number of treatment organizations would suggest that there are highly effective treatments for cocaine dependence currently available.

This study has several purposes. First demographic and drug use descriptive data are presented on a group of 83 subjects who presented themselves for an information and education session regarding cocaine use. The second goal of the study is to provide a description of the course of cocaine use by a group of cocaine users who presented themselves for an education session, but decided not to enter treatment. Finally, the study provides a comparison of follow-up data on 2 groups of treated subjects. One group of these subjects was treated in a 28-day hospital inpatient program and a second group which was treated in a structured 6-month outpatient program.

METHOD

Subjects

Subjects were 83 cocaine users recruited from persons calling a 24-hour cocaine treatment and information hotline. Subjects interested in exploring treatment options came in for an initial 2-hour interview/education session. At the end of this session subjects were allowed to select inpatient hospital treatment, structured outpatient treatment, or participation in the cocaine anonymous self-help group, or no treatment. At the time of the initial session all subjects signed a consent form permitting a follow-up interview.

The limitations of this study as a result of patient self-selection to groups are evident. This type of study needs to be replicated with subjects randomly assigned to groups. However, considering the current lack of information on the course of cocaine and other drug/alcohol use among a self-identified group of problem cocaine users, the study provides some useful descriptive data. In addition, the data provide an indication of the impact of two current treatment methods in producing sustained periods of cocaine abstinence.

PROCEDURE

The content of the education/information session included:

INTERVIEW/EDUCATIONAL
SESSION CONTENT

A. Interview
    1. Completion of intake questionnaire.
    2. Review of current drug use and drug use history.
    3. Review of current medical/psychological issues.
    4. Perceived treatment need.
B. Education
    1. Education regarding cocaine medical/psychological effects.
    2. Education regarding addiction process.
    3. Neurochemical and behavioral effects.
    4. Review of treatment options.
C. Session Length: 2 hours
D. Cost: $100

The content of the 3 "programs" included in the following outlines.

PROGRAM CONTENT:
NO FORMAL TREATMENT

A. Program Orientation: Twelve-step Principles
B. Program Content
    1. AA, NA, CA Meetings plus Alanon

2. No Treatment

C. Recommended Program Duration: Open

D. Cost: None

PROGRAM CONTENT: OUTPATIENT

A. Program Orientation: Neurobehavioral Model

B. Program Content
   1. Individual directive sessions, professional staff
   2. Psychiatric evaluation
   3. Relapse prevention and education groups
   4. Family and conjoint counseling
   5. Urine testing

C. Recommended Program Duration: 6 Months

D. Cost: $600 Per Month

PROGRAM CONTENT: HOSPITAL

A. Program Orientation: Johnson Institute/Hazleden Model

B. Program Content
   1. Individual counseling, recovering staff
   2. Psychiatric medication and psychotherapy
   3. AA, CA, NA groups
   4. Movement therapy, reality therapy, assertive training, education (primarily alcohol) groups
   5. Two weekly aftercare groups for 6 months
   6. Recommended lifetime involvement in AA, CA, NA

C. Recommended Program Duration: 29 Days Plus Aftercare

D. Cost: $12,000-$15,000

Subjects were contacted by telephone for a follow-up interview approximately 8 months following the initial interview session (range 6-11 months). Contents of this interview and qualifications of the interviewer are included in the following outline:

FOLLOW-UP INTERVIEW PROCEDURES

A. Content of Structured Telephone Interview
   1. Account of cocaine use since initial interview
   2. Account of alcohol and other drug use since initial interview
   3. Rating of 8 areas of functioning
   4. Account of participation in treatment and self-help groups
   5. Rating of program helpfulness

B. Interviewer
   1. Experienced in hospital and outpatient drug abuse research
   2. Independent licensed social worker not affiliated with either program

C. Interview Duration: 15-30 minutes

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RESULTS AND DISCUSSION

Table 1 presents demographic and drug use characteristics of subjects in each of the 3 groups. As can be seen from this table there were no differences in subject characteristics prior to entering treatment. In addition, Ss did not differ in terms of amount of prior alcohol and other drug use, or type of employment.

TABLE 1
SUBJECT CHARACTERISTICS

	No Formal Treatment (n=30)	Outpatient (n=30)	Hospital (n=23)
Sex			
Male	73%	77%	65%
Female	27%	23%	25%
Mean Age	29 years	30 years	28 years
Mean Years of Education	13.1 years	12.4 years	13.0 years
Marital Status			
Single	40%	40%	35%
Married	54%	50%	52%
Divorced	6%	10%	13%
Mean Years of Cocaine Use	6.6 years	4.6 years	5.7 years
Mean Amount of Cocaine Use	7.1 grams/wk	7.0 grams/wk	8.6 grams/wk
Type of Use			
Intranasal	54%	57%	61%
Freebase	43%	40%	30%
Intravenous	3%	3%	9%

Table 2 summarizes the amount of treatment that subjects in each group received. Subjects who left the educational interview not committing to either of the formal treatment programs rarely went into any form of treatment, and only 20% ever attended more than one self-help group. Subjects in the outpatient group participated in this program for close to the recommended duration of 6 months (5.4 months). About one-third also attended self-help groups. Subjects in the hospital group nearly all completed the recommended 28-day hospital stay. Most (83%) went on to participate in the self-help program, but only 26% attended the hospital's aftercare programs.

TABLE 2
AMOUNT OF PROGRAM PARTICIPATION

No Formal Treatment		Hospital
a. 20% attended more than one CA or AA meeting.	a. Mean duration in treatment = 5.4 months	a. Mean number of hospital days = 26.5
b. 18% enrolled in other treatment	b. 30% attended more than one CA or AA meeting	b. 26% attended more than one aftercare meeting
		c. 83% attended more than one CA or AA meeting

Table 3 presents the percentage of Ss in each program who reported a return to monthly or more frequent use following the initial interview.

TABLE 3
COCAINE USE AT FOLLOW-UP INTERVIEW

		Program		
		No Formal Treatment	Outpatient	Hospital
Number of Ss Returning to Monthly or More Frequent Cocaine Use	Yes	14	4	10
	No	16	26	13
Percentage Returning to Monthly Cocaine Use		47%	13%	43%

$x^2 = 8.81$, $p < .05$

As indicated in this table, significantly fewer of the Ss in the outpatient group returned to monthly or more frequent cocaine use. Since follow-up interviews were conducted 8 months following the initial interview, most of the outpatients were only about 2 months out of treatment. It could be argued that the differential relapse rate was simply a function of time out of treatment since hospital subjects had been discharged 7 months earlier.

One issue which was of extreme importance to almost all Ss was the relationship between alcohol and/or marijuana use and the subsequent relapse to cocaine. All Ss entered the study for cocaine-related problems. Many did-not view their use of alcohol or marijuana as being a problem. At the educational interview it was stated there was no established relationship between marijuana or alcohol use and success in cocaine treatment. However, it was strongly recommended that six months of abstinence from all drugs and alcohol would be useful to

promote the necessary lifestyle changes needed for abstinence from cocaine. This was an issue discussed frequently among subject and the staffs of both treatment programs.

Tables 4 and 5 suggest that there is a relationship between alcohol/marijuana use and relapse to cocaine. As noted in these tables, a significantly lower proportion of those subjects not returning to alcohol or marijuana use did not relapse to cocaine use. Although not documented, the sequence of use would almost immediately start with a return to occasional alcohol/pot use, followed by resumed consumption of these substances and finally relapse to cocaine use. The need for total abstinence from alcohol and all druas as a part of the cocaine treatment is now a standard aspect of both treatment programs.

TABLE 4
COCAINE USE AT FOLLOW-UP INTERVIEW
Marijuana Use

		Number of Ss returning to monthly marijuana use	
		Yes	No
Number of Ss returning to monthly cocaine use	Yes	17	11
	No	12	43

Monthly marijuana use-return to cocaine use 59%

No marijuana use-return to cocaine use 20%

$x^2 = 10.7$, $p < .05$

Table 4 presents the percentage of Ss across all programs who returned to marijuana use and subsequently did or did not return to cocaine use.

TABLE 5
COCAINE USE AT FOLLOW-UP INTERVIEW
Alcohol

		Number of Ss returning to monthly or more frequent alcohol use	
		Yes	No
Number of Ss returning to monthly cocaine use	Yes	26	2
	No	26	29

Monthly alcohol use-return to cocaine use 50%

No alcohol use-return to cocaine use 6%

$x^2 = 14.59$, $p < .01$

Table 5 presents the percentage of Ss across all programs who returned to alcohol use and subsequently did or did not return to cocaine use.

SUMMARY

Based upon a sample of 83 cocaine users self-selected into one of 3 programs, several conclusions seem possible.

1. There seems to be little difference in Ss populations who choose hospital, outpatient or self-help/no treatment.
2. Current hospital aftercare programs may not be appropriately oriented for cocaine users. It appears the hospital program in this study retained fewer than 30% of the Ss in aftercare.
3. Outpatient treatment for cocaine dependency is a viable form of treatment which Ss will participate in for up to 6 months on a fee for service basis.
4. Only about 20% of the Ss who were referred to self-help groups attended more than one meeting.
5. Preliminary outcome data suggest that outpatient treatment may result in a lower relapse rate to cocaine than hospital or no treatment. However, this conclusion is extremely guarded due to a large number of methodological issues and the short follow-up period.
6. Relapse to cocaine use is higher among Ss who returned to alcohol or marijuana.

REFERENCES AVAILABLE UPON REQUEST

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Abuse of Cocaine With Opioids: Psychological Aspects of Treatment

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INTRODUCTION

Cocaine abuse has recently been increasing at an alarming rate among the general population, as well as among treated drug abusers. Past surveys have usually reported that some opiate addicts abuse cocaine. In 1969-71 about 17% of addicts a plying for treatment reported cocaine abuse (Simpson & Sells 1974). The rate of abuse for those already in treatment programs then was lower; however, in a study from New York City methadone programs the rate had more than tripled from 1974 to 1979 (Kaul & Davidow 1981). Older studies have described cocaine-abusing addicts as most often antisocial black males (Chambers et al. 1972), and the types of treatments currently being advocated for cocaine abuse might not be appropriate for this type of samples from 1979-80: 204 addicts applying for treatment and 120 ex-heroin addicts on methadone maintenance for at least three months.

METHODS

Information for psychiatric diagnoses was collected using the Schedule for Affective Disorders and Schizophrenia (SADS) to make Research Diagnostic Criteria (RDC) diagnoses. Two other assessments focused on the addicts' social adjustment and drug abuse: the Addiction Severity Index and the Social Adjustment Scale. The addiction severity index covers six problem areas: medical, employment, legal, family/social, substance abuse, and psychological. These areas are rated on nine point scales with larger numbers indicating more severe problems. The social adjustment scale covers six areas over the previous two weeks including relationships at work, during social leisure and within the extended family. Scoring ranges from 1 to 5 with lower scores indicating better adjustment.

RESULTS

To compare amounts of various drugs, the mean number of days each drug was used over the previous 30 days were compared for the

methadone and admission samples. The admission sample used significantly more heroin and cocaine than the methadone maintenance sample, but equivalent amounts of alcohol, prescription medication and marijuana. The admission sample reported an average of 9 (± 11) days of cocaine use out of the previous 30 days, and 74% reported some cocaine use over the previous month. Twenty percent of the methadone sample had used cocaine in the last month, and the mean number of days of abuse was 1.4 (+ 5) days.

Although current cocaine abuse was less in addicts on methadone, the lifetime amount of abuse was equivalent between the methadone maintained and admission samples. Overall, 69% of the addicts had abused cocaine during their lifetime, including 74% of the admission sample and 58% of the methadone sample.

Most addicts who had a lifetime history of cocaine abuse did not abuse other drugs, except marijuana. Only 49% of the cocaine abusing addicts reported abuse of marijuana in addition to heroin and cocaine. This was significantly less marijuana abuse than the 73% reported by the addicts who did not abuse cocaine. Similarly, only 18% of the cocaine abusers reported abuse of other drugs besides marijuana, which was less abuse than the 29% reported by those who did not abuse cocaine. In summary, most cocaine abusing addicts were not polydrug abusers and appeared to abuse fewer other drugs than did the rest of this sample.

The demographic characteristics of the cocaine abusers are compared to the non-abusers in this Table. The cocaine abusers were substantially more often black and unemployed.

DEMOGRAPHIC INDICES (N-324)

Index	Cocaine (n=175)	No Cocaine (n=149)	P
Age (years)	29.2	28.2	ns
Black Race	69%	38%	0.001
Male	72%	72%	ns
Married	36%	33%	ns
Lower Class	90%	87%	ns
Unemployed	52%	38%	0.01

An interesting difference in the rates of cocaine abuse during the previous 30 days was that methadone maintenance seemed to be associated with a substantial reduction in cocaine abuse by blacks, but with a lesser reduction by whites. For the admission sample there were significantly more black (89%) than white (59%) cocaine abusers. However, for the methadone sample there was no difference in the rates of current cocaine abuse between the two races (27% vs 22%). For both races, cocaine abuse appeared to decrease during methadone maintenance compared to admission.

Several indices of antisocial behavior and social impairment were associated with cocaine abuse. Among the blacks, the percentage of cocaine abusers was higher for the addicts with antisocial personalities. The rate of cocaine abuse was not higher for antisocial whites or for any other RDC diagnosis. Thus, as suggested by older studies, antisocial blacks appear to have higher rates of cocaine abuse. Arrest rates and illegal activities were consistent with this increased rate of antisocial personality. Although the cocaine abusers had no more drug-related crimes nor total arrests, the cocaine abusers spent more days during the last month in illegal activities (11 days) and committed more crimes against persons (0.6) than did the non-abusers (8.5 days and 0.3 crimes). This supports the increased rate of antisocial personality disorder among the cocaine abusers.

COCAINE ABUSE SEVERITY AND ANTISOCIAL INDICES

Index	Cocaine (n=175)	No Cocaine (n=149)	P	Corr (n=324)	P
ASI Problems					
Legal	3.8	3.1	.01	.17	.01
Family	3.5	3.2	.05	.13	.05
Drugs	5.5	5.4	ns	.13	.05
Employment	3.4	3.2	ns	.07	ns
Medical	1.9	1.7	ns	.03	ns
Psychology	3.3	3.2	ns	-06	ns
Social Adjustment					
Work	2.9	2.4	.001	.18	.001
Mean	2.3	2.1	.05	.12	.05

The six problem scales of the Addiction Severity Index (ASI) shown in this Table demonstrate that the cocaine abusers had more severe family and legal problems than did the non-abusers. Drug abuse, employment, medical and psychological problems were not significantly different between abusers and non-abusers. Cocaine abusers also had more severe employment problems as shown by the Social Adjustment Scale and their high rate of unemployment.

To relate cocaine abuse severity to antisocial indices, we correlated the cocaine abuse ratings from the ASI with the six problem rating scales of the ASI and with the Social Adjustment Scale. These correlations are also shown in the Table. Because the ratings were derived from duration, as well as frequency, of cocaine abuse, they had a significant correlation with age, and age adjusted partial correlations are presented. In general, the associations between the various indices of antisocial behavior and severity of cocaine abuse yielded results very similar to those obtained using the simple dichotomy of abusers and non-abusers. For the ASI scales of legal, family and drug problems and for the social adjustment scales of work and the overall mean, the correlations were significant and in the expected direction. More severe cocaine abuse was associated with more severe problems.

Because the rate of cocaine abuse differed. between whites and blacks, the analyses were also run within racial groups. The racially stratified results for the ASI indicated that the white cocaine abusers had more severe family problems, but the black cocaine abusers did not. The black cocaine abusers had more severe legal problems on the ASI, but the white cocaine abusers did not. The correlational analyses supported these racial differences. The severity of cocaine abuse among white addicts was most strongly associated with family problems ($r = 0.18$, $p<0.01$), while among black addicts, cocaine abuse severity was most strongly associated with legal proglems ($r = 0.18$, $p<0.01$).

DISCUSSION

To briefly summarize our findings: 1. Cocaine abuse is very common among opioid addicts. 2. Cocaine abusers are not simply multiple drug abusers, but use it preferentially and usually in combination with opioids (speedballs), 3. Antisocial blacks are disproportionately common among cocaine-abusing addicts.

These data were gathered before the prevalence curves for cocaine abuse in the country appear to have peaked and before the recent sharp downtown in cost and sharp increase in availability and quality of cocaine. Non-systematic data from our methadone program, as well as from other programs in the Northeast, suggest marked rises in the number of methadone maintenance patients using cocaine during the past four years. Thus, the cocaine abuse rates reported in this paper are probably lower than the current rates, and the need for active programmatic interventions is even more apparent.

One treatment implication of our findings might be a structured program for antisocial cocaine abusers in methadone maintenance programs. Recently, we have described an interpersonal technique for the outpatient psychotherapy of cocaine abusers (Rounsaville et al. in press), but this approach is generally lenient, with little emphasis on the strict adherence to the rules that characterize a methadone maintenance program and that may be needed to work with antisocial personality disorder (Sturup 1948; Wood et al. in press; Shamise 1981). Cocaine-abusing addicts without antisocial personality may respond to more traditional psychotherapy, but it will probably be unsuccessful in curbing cocaine abuse among the antisocial addicts and a clearly defined program structure may be needed (Woody et al. in press). The structure for this treatment might include a time limited weekly group of cocaine-abusing ex-addicts with the goal of three months abstinence from cocaine use. Psychiatric evaluation is important, because cocaine abusers with other concurrent disorders may remain abstinent when treated with specific medications. For example, some cocaine abusers have remained abstinent using lithium or desipramine (Gawin & Kleber 1984), and some addicts may self-medicate dysphoria or adult forms of attention deficit disorders with cocaine (Khatzian 1983). The decisions to use these medications are complex and need careful psychiatric evaluation. The

addict would then enter a group, whose focus would be to specifically identify stimuli that elicit craving for cocaine and to then learn ways to avoid these situations including behavioral techniques to reduce this craving. This special treatment program would include regular urine monitoring, but might also allow addicts who are abusing cocaine to have cocaine positive urines during the first three weeks of being in the group treatment. The time limitation of several weeks insures the administrative termination of antisocial addicts who may have no intention of stopping their cocaine abuse, while allowing time for treatment effects in addicts who seriously want to stop their cocaine use. The group itself may be limited to several months, because the available data suggests that abstinence from cocaine for about three months is associated with continued abstinence at a one-year follow-up (Gawin & Kleber 1984). For those addicts who continue to abuse cocaine beyond the initial few weeks, residential treatment might be considered. Ongoing studies at our methadone maintenance program are piloting this type of treatment group with some success.

REFERENCES

Available on request from the authors.

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Descriptive Epidemiology of Adult Cocaine Use In Four U.S. Communities

James C. Anthony, Christian J. Flitter, Michael R. Von Korff, Elsbeth M. Chee, and Morton Kramer

At prior meetings of the Comittee on Problems of Drug Dependence, the reported research on human cocaine use outside the laboratory setting has involved studies of help-seeking cocaine users (e.g., Helfrich et al., 1983; Washton et al., 1984). Important as it is, this perspective on cocaine use may give an inpressiom that most cocaine users report problem or need help. In contrast, this paper examines cocaine use and cocaine problem reported by adults in four U.S. community populations sampled without regard to help-seeking. It is based on standardized interviews with more than 15,000 adults in four coordinated, community-based probability sample surveys of the NIMH Epidmiologic Catchment Area (ECA) Program.

METHODS

Methods for the ECA surveys have been described in detail elsewhere (Eaton et al., 1984, Eaton and Kessler, 1985). A synopsis follows.

Communities Sampled. The populations under study were defined in terms of their residence inside the boundaries of mental health catchment areas in four U.S. communities: New Haven (Ct.), Baltimore City (Md.), St. Louis (Mo.), and Durham-Piedmont (N.C.). Except in New Haven, these Epidemiologic Catchment Areas were comprised of two or more mental health catchment areas.

Household and Institutional. A minimum of 3,000 household residents age 18 years and older were sampled in each ECA. In addition, because they were of special interest in this study of mental health and behavior, more than 400 adults residing in criminal justice facilities, nursing hares, and other institutional group quarters were included in each site's sample.

Methods of Sampling. Each sample was drawn as a multi-stage probability sample, sometimes with oversampling of individuals in special populations (e.g., the elderly). A roster of residents was obtained for each sampled household, and adult residents were drawn at random. No replacements or substitutions were permitted. In Baltimore,one adult age 18-64 was selected at random. In addition, all adults age 65 and older were selected.

Methods for sampling institutions were more complex (Eaton and Kessler, 1985). For present purposes, it will suffice to say that careful probability sampling

methods were used so that the ECA samples would represent the combined household and institutional populations of each epidemiologic catchment area.

Data Gathering. Cocaine experience and the other characteristics displayed in this paper's analyses were assessed by means of standardized face-to-face interviews, conducted privately with individual respondents. Each site hired and trained survey research interviewers for data gathering in the field. Training lasted 5 to 8 days, most of which was aimed toward development of competence in administering the NIMH Diagnostic Interview Schedule (DIS). The DIS touches on many issues that some respondents find sensitive, including non-medical and illegal drug use. For this reason, special attention was given to development of rapport and inteviewers' sensitivity to these issues. The data on cocaine experience are based upon replies to standardized DIS intewiew questions on non-medical drug experience that are asked some 20-30 minutes into the interview, following a series of questions on demographic, social, health, and mental health topics (Anthony et al., in preparation). Some of the detailed drug data are not available from the New Haven site, shown by "N/A" in the tables.

Follow-up Interviews. There was a follow-up interview with each participant 6 months and 1 year after the baseline DIS inteview. The 1-year follow-up was mainly a re-administration of the DIS. In this paper, follow-up data are presented for Baltimore only.

Data Gathering Periods. All ECA sampling and data gathering operations were completed during the period 1980-1934. The New Haven survey sample was drawn in 1980-81, the Baltimore and St. Louis samples in 1981, the Durham sample drawn in 1982-83.

RESULTS

Survey Response Pates and Samples Obtained. The response rate in the baseline household surveys has ranged from 75-80% and the institutional sample response has been higher. The follow-up household survey response rate in Baltimore was 82%.

There were 5,035 participants in the New Haven household suwev: 3,058 drawn for the basic ECA sample, and 1,977 elderly persons draw in an augmentation sample supported by the National Institute on Aging. There ware 3,481 participants in the Baltimore household survey, 3,004 participants in the St. Louis household survey, and 3,921 participants in the Durham household survey. Distribution of these samples by gender and by age is given in Table 1.

TABLE 1
Distribution of ECA Household Samples at Baseline By Gender and By Age

		New Haven	Baltimore	St. Louis	Durham
Gender:	Men	2,063	1,322	1,202	1,488
	Women	2,063	2,159	1,802	2,370
Age:	18-39	1,463	1,534	1,536	1,403
	40-59	763	762	702	805
	60+	2,809	1,185	766	1,712
All Persons:		5,035	3,481	3,004	3,921

Table 2 shows the composition of the household samples in relation to non-medical drug experience. In the New Haven sample of 5,035 adults, 875 reported a history of past or current non-medical drug use and 22 reported daily use of cocaine for two weeks or more. In the Baltimore household sample of 3,481 adults, 794 reported a history of past or current non-medical drug use, 108 reported cocaine use on six or more occasions, and 13 reported daily cocaine use for two weeks or more. In the St. Louis household sample of 3,004 adults, 762 reported past or current non-medical drug use, 99 reported cocaine use on six or more occasions, and 17 reported two weeks of daily cocaine use. The Durham-Piedmont household sample included 97 adults reporting a historyof cocaine use, 12 with a history of two weeks or more of daily use. Data (not tabled) from Baltimore and the Durham-Piedmont ECA surveys indicate a majority of the cocaine users (50-65%) reported cocaine use in the year prior to interview.

TABLE 2
Baseline History of Non-Medical Drug Use in the ECA Household Samples

	New Haven	Baltimore	St. Louis	Durham
All Persons	5,035	3,481	3,004	3,921
History of Non-Medical Drug Use				
No information	234	162	141	136
Never used	3,926	2,525	2,101	3,191
Yes, past and/or current	875	794	762	614
Cocaine used 6+ times	N/A	108	99	97
Cocaine used daily for two week or more	22	13	17	12

Table 3 shows the extent of cocaine use in relation to a history of marijuana use. In each sample at baseline, virtually all of those with a history of six or more occasions of cocaine use also reported six or more prior occasions of marijuana use.

TABLE 3
Relationship Between Baseline Histories of Cocaine and Marijuana Experience in the ECA Household Samples

	New Haven	Baltimore	St. Louis	Durham
History of Six or More Occasions of Non-Medical Use	637	583	628	422
Marijuana No, Cocaine No	N/A			
Marijuana Yes, Cocaine No		473	495	300
Marijuana Yes, Cocaine Yes		100	98	94
Marijuana No, Cocaine Yes		8	1	3

Table 4 extends the profile of adult subjects with cocaine experience, accounting for sampling weights and adjusting for survey non-responses. In Baltimore, St. Louis and Durham, an estimated 12 to 14 percent of adults who reported cocaine use on six or more occasions also reported daily cocaine use for two

weeks or more. In Baltimore, 15 percent reported a sense of tolerance, i.e., heeding larger amounts to achieve drug effects. The corresponding estimates for St. Louis and Durham were 19 percent and 14 percent.

TABLE 4
Profile of Adult Cocaine Users
in Relation to Selected Cocaine Problems

	New Haven	Baltimore	St. Louis	Durham
Number of subjects with a history of six or more occasions of cocaine use	N/A	108	59	97
Estimated proportion of such users with a history of:				
Two weeks daily cocaine use		12%	12%	14%
Perceived tolerance to cocaine		15	19	14
Feeling dependent on cocaine		1	2	3
Failed effort to reduce cocaine use		1	2	6
Cocaine withdrawal symptoms		0	2	4
Health problems due to cocaine		3	3	3
Social/job problem due to cocaine		1	2	<1
Psychlogical problems due to cocaine		2	9	1 1
Professional consultation about drugs		17	20	15

Health and social problem associated with cocaine use were reported less frequently. In Baltimore, social or occupational problem were attributed to cocaine use by an estimated two percent of those who had used cocaine on six or more occasions, and smaller proportions reported psychological or health problem due to cocaine use, cocaine withdrawal symtoms, or feeling dependent on cocaine. No one in the Baltimore sample reported a failed effort to cut down on cocaine use. In St. Louis and Durham, social or job problem ware attributed to cocaine use by an estimated 9% and 11% of those who had used cocaine on six or more occasions. In Baltimore, two percent of the cocaine users reported such problems.

Congruent with these results on health and social problems, the cocaine users sampled for the ECA suweys were not likely to report drug-related help-seeking. In Baltimore, St. Louis, and Durham, no more than one-fifth of the cocaine users reported that they had talked to a doctor or other professinal about any drug problem. In addition, reported involvement in self-help groups for drug or alcohol problem was extremely rare.

Table 5 gives estimates for lifetime prevalence of cocaine use (six or more occasions), with standard errors. At all three sites for which data are available, the prevalence values for men age 18-49 are close to nine percent and the female rates are near three percent. These are significant differences between the gender-specific rates. Further, age-specific differeces are present.

TABLE 5
Estimated Lifetime Prevalence of Cocaine Use in Three
ECA Household Populations by Age, Gender, and ECA Site (In Percent)
[SESUDAAN Standard Errors Inside Brackets]

All Men 18-49		8.7 [1.1]	9.3 [1.4]	9.4 [1.4]
All Women 18-49		3.0 [0.6]	3.1 [0.7]	3.6 [0.9]
Men	18-24	8.7 [2.0]	9.1 [2.7]	14.7 [3.2]
	25-29	15.4 [3.0]	13.1 [3.5]	17.8 [3.9]
	30-34	12.9 [3.0]	10.7 [2.6]	8.6 [2.8]
	35-39	0.6 [0.6]	3.2 [2.1]	3.0 [1.7]
	40-44	0.3 [2.0]	0.2 [0.2]	0.0 --
	45-49	0.3 [2.0]	0.6 [0.6]	0.0 --
Woman	18-24	5.7 [1.6]	3.8 [1.1]	5.8 [2.0]
	25-29	4.3 [1.2]	3.9 [1.4]	7.8 [2.8]
	30-34	1.4 [0.9]	3.4 [1.7]	1.8 [1.1]
	35-39	1.4 [0.1]	0.2 [1.7]	1.3 [1.2]
	40-44	0.0	0.0 --	0.6 [0.6]
	45-49	0.0	0.0 --	0.0

whereas Table 5 is concerned with a prior history of cocaine use at baseline, the estimates in Table 6 are transition-based incidence estimates. These estimates derive from follow-up reports of cocaine use by the men and women in the Baltimore household sample who reported no cocaine use at baseline. Among these groups, the proportion reporting mine involvment at follow-up serves to estimate the cumulative incidence of cocaine use in adulthood.

TABLE 6
Transition Into Increased Cocaine Use
in the Baltimore Household Follow-up Sample

	All Ages	18-24	25-34	35-44	45-49	60+
N of Men in Follow-up Sample Who at Baseline Reported Few or No Prior Occasions of Cocaine Use	931	155	204	120	158	294
Number reporting 6 or more occasions of cocaine use at follow-up	26	10	13	2	1	0
Cumulative incidence	2.8%	6.5%	6.4%	1.7%	0.6%	0.0%
N of Women in Follow-up Sample Who at Baseline Reported Few or No Prior Occasions of Cocaine Use	1673	242	394	223	279	535
Number reporting 6 or more occasions of cocaine use at follow-up	12	5	6	1	0	0
Cumulative incidence	0.7%	2.1%	1.5%	0.4%	0.0%	0.0%

As the data show, (a) men a pear to be at substantially greater risk of involvement in cocaine use, and (b) there is a negative association between age and the cumulative incidence rate. This method of estimating incidence of cocaine involvement has sane defects (discussed below), but the pattern of obsewed relationships with sex and age generally converges with the pattern of relationships in the data on lifetime prevalence of cocaine involvement.

Estimation of prevalence and incidence rates for the combined household and institutional populations at each site is underway. As might have been expected, most of the cocaine-experienced institutional residents were located in the criminal justice facility samples. Here, the data in Table 7 indicate that the institutional samples result in 30-60 percent increases over the number of household subjects with a lifetime history of cocaine use (on six or more occasions). However, after proper weighting to account for differences in probability of selection, inclusion of the institutional sample data leads to trivially small departures from the household prevalence values reported in Table 5.

TABLE 7

Age Distribution of ECA Household and Institutional Cocaine Users

		New Haven	Baltimore	St. Louis	Durham
Household	18-24	N/A	38	31	34
	25-29		39	36	39
	30-39		25	29	22
Institut.	18-24		29	18	14
	25-29		18	17	12
	30-39		19	10	4
Both Samples, 18-39			168	141	125

DISCUSSION

because there are early results, we hesitate to offer an extended discussion. However, we note a difference between the self-reprted health of cocaine users in this study as compared with results from prior studies of help-seeking cocaine users. Relatively few of the ECA cocaine users have reported cocaine-related problems in the areas of psychological, social, or occupational functioning; health; or cocaine dependence. A large majority of users reported no help-seeking for drug-related problem. This may be an artifact of the interview methods, but the ECA surveys' questions seem to be similar to the questions used in the prior studies. Another explanation may relate to differences in type or degree of cocaine involvement, with the help seekers being more intensively involved (e.g., using more hazardous mutes of administration). Parsimony may dictate a simple obsewation that compared with cocaine users in the community, a group of help-seeking cocaine users will be more likely to have problems and reed help. As prior epidemiologic research has shown, associations famd among patients who are seeking help can easily be biased because of self-selection and referral processes. These biases may not be readily apparent until community studies are done (Kleinbaum, Kupper and Morgenstern, 1982).

The prevalence and incidence estimates fron this study indicate clear differences in occurrence of cocaine use that are specific to age and gender. The

incidence estimates are unusual in that they are based upon a transition to six or more occasions of cocaine use. Though the observed incidence relationships mainly are congruent with those obsewed in the lifetime prevalence data, they might not pertain to occurrence of first cocaine use in the population. Further, compared to adults age 25-29 years, younger adults age 18-24 seemed to be at equal or higher risk of increased cocaine involvement during the follow-up period. This intriguing pattern was not present in the data on lifetime prevalence. These issues require further study, with analysis of sampling error.

The observed association between marijuana and cocaine use also is unresolved. This association has been found consistently in prior studies, but its causal significance remains uncertain (O'Malley et al., 1984; Kandel, Murphy, and Karus, 1984; Clayton, 1984).

Finally, we note that the ECA research strategy is not one of national sample *epidemiology,* and the ECA samples should not be, viewed as representative of the nation. Rather, the strategy is one of community epdemiology, allowing a look within and across communities for variation in the population experience with cocaine. Because of uniformity in methods, the ECA surveys offer a form of replication. However, in this case the replication does not fail if community variation is found. Instead, community variation suggests a need to search for the underlying factors that may have theoretical and empirical relevance to the occurrence of cocaine use in the population. This strength of the ECA Program will be an important focus for our future epidemiologic research on cocaine.

REFERENCES AVAILABLE UPON REQUEST

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Psychological Issues in the Treatment of Cocaine Abuse

Richard B. Resnick and Elaine Resnick

The psychological issues that will be addressed in this paper, while not all inclusive, are the most typical and central to patients. The items are presented in the order that they are usually approached in treatment: a)gaining control over cocaine use; b)conditioning and cognitive relabeling; c)family relationships; d)somatopsychic problems; e)psychodynamic issues and beyond psychopathology.

GAINING CONTROL OVER COCAINE USE

The first goal is to help the patient gain control over his/her use of cocaine. [Henceforth, references to "his" are intended to mean "his" or "her."] Unless cocaine use is stopped, any treatment will be ineffective, possibly even counterproductive. Unfortunately, many patients are seen in psychotherapy by therapists who do not realize their patients are using cocaine. We saw a patient for consultation who was in psychotherapy for three years, but never revealed that his cocaine dealer lived on the same block as the therapist's office and that whenever he left a session, he felt compelled to buy cocaine. Since the therapist was not aware of this crucial fact, therapy continued to be focused on obtaining useless insight, while the treatment itself became associated with cocaine use.

Complete abstinence from cocaine is difficult to attain, so the therapist should anticipate and be prepared to deal with relapses. Typically, when a patient has an episode of relapse, he will label himself and the treatment a failure. This type of self-denigrating response can be avoided when it is anticipated and discussed in advance. Each episode of drug use then becomes an opportunity to identify and explore its causes, an approach that helps the patient regain control.

It is frequently necessary to bolster the patient's limited internal control by including strategies of external controls such as contingency contracts, urinalysis, making money unavailable and changing the geographic environment. We rely heavily on these

methods and on working with family members. Hospitalization is sometimes the only way for the person to regain control, but generally is necessary only for those who lack close personal relationships or who have poor work histories.

We have found contingency contracts very valuable in helping patients deal with their ambivalence about giving up cocaine. While being on a contingency contract, cocaine users experience relief similar to how heroin addicts feel on naltrexone. Energy that was previously drained by ambivalence and guilt is restored and can be directed to more important aspects of treatment.

Checking urines several times a week is essential for a contingency contract, but urine screening is also an important component of treatment for patients who do not have a contract. When presented as a tool that helps undercut the denial that is endemic to drug users, patients generally appreciate the value of leaving urine samples and are more likely to discuss each instance of cocaine use. The patient's facade is disrupted by this strategy, exposing his vulnerability and need for help.

CONDITIONING

Conditioned abstinence has been well documented in both clinical and laboratory studies, but many therapists/counselors do not appreciate its pivotal role in producing cocaine craving and relapse. We wish to emphasize the importance of including it in treatment. When faced with craving caused by conditioned stimuli, an awareness of the specific cues that triggered it can be instrumental in enabling the patient to maintain control.

Conditioned abstinence can be elicited in the therapist's office by tetracaine powder, which simulates cocaine, and the patient taught behavioral techniques that promote deep relaxation. Practice sessions of this type, as Abe Wikler predicted, are very helpful in extinguishing the conditioned responses.

COGNITIVE RELABELING

Chronic cocaine users often complain that the effects from cocaine have changed and instead of producing euphoria, it primarily causes dysphoria. One might ask the question: Why would anyone persist in using a drug that, for the most part, makes them feel bad? In exploring this question, it becomes clear that they simply do not anticipate feeling bad. Memories of the dysphoric feelings produced by cocaine are not spontaneously recalled, either when anticipating its use or when asked to imagine using it and describe its effects. Helping the patient to integrate the memories of the dysphoria leads to a relabeling of cocaine use as a negative experience, so that anticipating using the drug becomes less desirable.

FAMILY RELATIONSHIPS

Serious unresolved issues of separation/individuation are ubiquitously present in the families. Family members often serve as primary enablers. They are unable to set appropriate limits or let the patient experience the consequences of his behavior. Families require a great deal of support and guidance for the painful task of letting go. Usually it is helpful, if not essential, to include relevant family members in the treatment process. Wives, husbands or parents may need to be referred to one of many groups organized for that purpose or for individual psychotherapy.

The patient's lack of internal controls can usually be traced to an absence of phase appropriate limit setting during early childhood and adolescence, when external controls form the basis for internalization and self-regulation. Instead of continuing to collude with the patient's psychopathology, family members in treatment often become instrumental in forcing the patient to stop denial and avoidance and begin facing the cocaine problem. Teaching families to identify characteristic signs of cocaine use can free them from being manipulated by the patient. Knowing that the patient's behavior is drug related enables them to respond appropriately.

SOMATOPSYCHIC PROBLEMS

Symptoms of depression that commonly emerge when chronic cocaine use is discontinued are dealt with primarily by appropriate psychotropic medications. Tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) help relieve the low energy, sleep disturbances, difficulty with concentration and other depressive symptoms commonly found in this group. If left untreated, these symptoms often lead to a resumption of cocaine use, which compromises the treatment process. Imipramine and norpramine are the TCAs most often used for this patient population, but our experience with the HAOI phenelzine (Nardil) has led us to prefer it.

We began using phenelzine because of reports of its special efficacy for atypical depression. Symptoms most responsive to phenelzine include anxiety, hypersomnia and hyperphagia, and its efficacy has been correlated with extreme sensitivity to rejection in relationships, feeling worse in the evening and having a history of positive response to self-administered amphetamine. These symptoms are also characteristic of cocaine abusers and, therefore, we speculated that they might be similarly responsive to phenelzine. Phenelzine also serves as a deterrant to cocaine usc, because it greatly intensifies the dysphoric effects of cocaine. Patients almost always discontinue phenelzine during periods of relapse and then go back on the medication when they regain control.

We offered phenelzine to 24 patients who requested treatment for cocaine abuse. One year after initial consultation, 18 of the 24 individuals were cocaine-free and all of them were continuing to take phenelzine. All 6 patients who were still using cocaine had either discontinued the medication (N=2) or refused to take it initially (N=4).

Blood pressure measurements after self-administered cocaine on 5 individuals taking phenelzine showed no unusual increase beyond what one would expect to find from cocaine in a person not taking an MAOI. However, the theoretical possibility that cocaine could precipitate a hypertensive crisis is of concern and all patients must be informed of this risk along with standard information on dietary restrictions.

PSYCHODYNAMIC ISSUES

Compulsive cocaine users usually have Axis II diagnoses of borderline or narcissistic personality disorders. These individuals have a fragile and fragmented sense of self and inadequate relationships with others, the etiology of which can be traced to the first 3 years of life, when the cohesion of internalized self and object representations normally occurs. Serious problems from unresolved separation-individuation cause personal relationships to be fraught with hostile dependence and primitive ambivalence. Self-soothing mechanisms are deficient and inner resources to cope with the vicissitudes of daily life are limited.

Although psychotropic medications reduce the amplitude of anxiety and other affects, the skilled use of the transference relationship is the framework within which the developmental problems that made these individuals vulnerable to cocaine abuse can be corrected. The patient must begin to turn to the therapist, instead of using cocaine to deal with intolerable internal states. The therapist's task is to help the patient recognize his cocaine use as an attempt to mask intense rage and despair stemming from unfulfilled developmental needs. Pre-oedipal needs that are mobilized in therapy can be worked through and resolved, particularly when they emerge in the transference.

BEYOND PSYCHOTHERAPY

These patients suffer from considerable internal tension, often experienced as a "knot" or "hole in the pit of the stomach." Cocaine offers rapid, but ephemeral relief from this state. The feeling of relaxation associated with its use is one of the major reinforcers for continuing to take the drug. Behavioral techniques that induce relaxation, such as imagery, breath exercises, biofeedback and self-hypnosis, have been shown to be highly beneficial in stress-related disorders. These techniques have potential value for use in substance abuse treatment.

We've been particularly impressed by the benefits of breath techniques and use them routinely in treatment. Most patients simply do not breathe properly and learning to do so provides many desirable effects for which cocaine was previously used - feeling more relaxed, more open and better able to connect with people in an intimate way. Cocaine loses its appeal when the patient discovers euphoria (well-being) in the warmth of human relationships.

REFERENCES

References are available from the senior author.

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Use of Nonnarcotic Drugs by Narcotic Addicts

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INTRODUCTION

Research on the life-styles of narcotic addicts tends to concentrate almost exclusively on their addiction because, as has been noted elsewhere (Nurco and Shaffer, 1982), the addiction is the organizing theme around which each addict's life is centered. What may be forgotten is that, although the narcotic addictive drugs clearly dominate the addict's behavior, very few addicts use narcotic drugs to the exclusion of other drugs; and, although no one would argue that the other drugs influence the addict as much as his narcotics, the fact remains that marijuana, cocaine, and other illicit substances are pervasive components of the addict's day-to-day life.

Apparently, nonnarcotic drugs fulfill two functions for narcotic addicts: (1) a complementary function, intensifying or prolonging the effect of the narcotic drugs during periods of addiction; and (2) a substitutive function, taking the place of narcotics both during periods of addiction and during periods of nonaddiction. Although there are large individual variations in drug preferences and in drug habits, it seems that different drugs may tend to be used for these two purposes; and, as has been noted before in other observations on addict life-styles (Nurco, Cisin, and Balter, 1981b; Waldorf, 1973), the pattern for white addicts is in some respects similar but is in most respects quite different from the pattern for black addicts.

These are the principal conclusions from an analysis of nonnarcotic drug use among narcotic addicts whose careers have been the subject of an intensive survey.

MATERIALS AND METHODS

Between July 1973 and January 1978, detailed confidential interviews were conducted with 354 male narcotic (principally heroin) addicts from the Baltimore metropolitan area. These 354 addicts represented a stratified random sample from a population

of 6,149 known narcotic users arrested (or identified) by the Baltimore police department between 1952 and 1976. The sample was stratified by race and year of police contact.Over 90% of the men selected were actually interviewed, usually at the offices of the research team. Subjects were paid $15.00 for their participation,and the confidentiality of all information obtained is protected by Maryland law. Of the 354 subjects, 195 were black and 159 were white. Mean age at interview was 34.1 years, with a standard deviation of 7.9 years.

To be eligible for inclusion in the study, subjects had to have used a narcotic addictive drugs on at least four separate days a week for a period of at least one month while at large in the community. Since a major purpose of the interview was to obtain detailed chronological information concerning concomitants of addiction from the time of first regular narcotic use to the time of interview, each subject was asked to describe in detail his periods of addiction, periods of nonaddiction in the community, and periods of incarceration, with the criteria for successive periods of addiction being the same as that for inclusion in the study. For this analysis, periods of incarceration were excluded.

RESULTS

As Table 1 indicates, four out of five narcotic addicts of both races reported some use of nonnarcotic drugs during their career.

TABLE 1

Percent Using Nonnarcotic Drugs During Periods of:

	Addiction		Nonaddiction[1]	
Drug[2]	Blacks	Whites	Blacks	Whites
	(N=195)	(N=159)	(N-165)	(N=154)
All Non-narcotics	87.7	83.7	66.1	81.2
Marijuana	59.0	41.5	56.4	63.0
Cocaine	66.2	54.7	23.7	20.8
Barbiturates	22.6	45.3	6.7	31.2
Amphetamines	7.2	31.5	6.1	25.3
Benzodiazepines	12.8	7.6	11.5	16.2
Hallucinogens	4.1	12.6	3,6	25.3
Quaaludes	2.6	3.1	4.2	10.4

[1]Thirty black addicts and five white addicts did not have any periods of nonaddiction while at large in the community.

[2]A number of other drugs were mentioned but not included in the table since there were no more than five users per cell.

Marijuana and cocaine were by far the most widely used drugs overall, while barbiturates were also popular, particularly among white addicts. Amphetamines and hallucinogens were also mentioned by at least one-fourth of the white addicts and much less frequently by blacks.

Different drugs apparently serve different functions for narcotic addicts. Thus, among addicts of both races, cocaine and barbiturates are much more prevalent during periods of narcotic addiction than they are during periods when the addict is free of his narcotic drugs. In contrast, among white addicts but not among blacks, marijuana, benzodiazepines, and hallucinogens are considerably more popular during nonaddictive periods than they are during periods of addiction. Quaaludes, which are used by relatively few addicts, seem more popular during periods of nonaddiction for both races, but the difference is far greater among white addicts.

As has been noted many times before, white addicts and black addicts display vivid differences in the details of their life styles (Nurco, Cisin, and Balter, 1981a, 1981b, 1981c; Nurco and Shaffer, 1982). Drug preferences among the nonnarcotic drugs are no exception to this rule. For example, barbiturates, amphetamines, and hallucinogens are much more popular among whites than they are among blacks, both during addictive periods and during periods of nonaddiction.

Another index of the importance of the nonnarcotic drugs in the lives of narcotic addicts lies in the answer to the question, How often are such drugs used? Table 2 shows, separately for black addicts and white addicts, and separately for periods of addiction and periods of nonaddiction, the number of times per week each nonnarcotic drug was used by addicts who used that drug.

TABLE 2

Frequency of Use of Nonnarcotic Drugs
(Average Number of times Per Week
Each Drug is Used by Those Who Use It)

	During Periods of:							
	Addiction				Nonaddiction			
	Blacks		Whites		Blacks		Whites	
Drug	N	Mean	N	Mean	N	Mean	N	Mean
All Non-narcotics	171	7.4	133	10.1	109	8.3	125	9.7
Marijuana	115	5.7	66	6.3	93	8.9	97	9.0
Cocaine	129	3.9	87	5.6	39	1.1	32	2.3
Barbiturates	44	1.3	72	3.6	11	1.5	48	1.6
Amphetamines	14	0.9	50	2.7	10	0.2	39	1.2
Benzodiazepines	25	1.0	12	2.5	19	0.6	25	2.1
Hallucinogens	8	0.4	20	0.3	6	0.1	39	0.8
Quaaludes	5	0.5	5	3.3	7	0.7	16	1.3

Non-users of each drug have been eliminated from the calculation. So, Table 1 reflected the number of narcotic addicts who had used each nonnarcotic drug; Table 2 reflects the intensity of use among the users. As might be expected, for both races under both conditions, marijuana users are the most frequent users. Cocaine use is almost as frequent as marijuana use during addiction periods (particularly among whites) but falls off dramatically during periods of nonaddiction.

A similar pattern (heavier use among whites. and .a marked fall off in use from addictive periods to nonaddictive periods) can be seen for amphetamines and less emphatically for benzodiazepines. Barbiturate use follows a quite different pattern: during addictive periods, white addicts who use barbiturates use them much more frequently than black addicts. Among whites, there is a considerable fall off in nonaddictive periods, but there is no similar fall off for black users. For Quaaludes and hallucinogens the small number of users in-each group makes the interpretation of the pattern of intensity of use hazardous.

DISCUSSION

The overall-picture that emerges from this consideration of the popularity and intensity of nonnarcotic-drug use among narcotic addicts confirms and amplifies inferences that could be drawn from earlier work of, for example, Inciardi (1981) and McGlothlin et al. (1977). Two conclusions seem justified: (1) For the great majority of narcotic addicts, their periods of addiction include the use of various nonnarcotic drugs, especially marijuana and cocaine, in quantities that are certainly not negligible. Thus, what appears to be the consequences of narcotic use may indeed be exacerbated by an interactive or catalytic effect of narcotic and nonnarcotic drugs; and (2) The great majority of narcotic addicts are seldom completely drug free. Even during periods when they are not addicted to narcotic drugs, their use of other drugs, especially marijuana, deserves careful attention by those responsible for maintenance of drug free states.

The problem for the therapist is not merely one of defining treatment goals for each addict; obviously, the primary goal must involve control of the narcotic addiction. Sometimes it may happen that control of the narcotic addiction will fortuitously be accompanied by or lead rapidly to control over other nonnarcotic drug habits. On the other hand, to the extent that the addict has learned to use such drugs as cocaine and marijuana as substitutes for the narcotics during periods of nonnaddiction, control of the narcotic addiction may indeed exacerbate the nonnarcotic drug habit. The therapist's dilemma may occur when he or she has achieved control over the narcotics and must choose whether or not to work toward a completely drug free state. Not only does this choice draw upon a philosophic stance with respect to what is desirable behavior for the addict, but it also involves a decision concerning the allocation of the therapist's time. Would that time be better

spent pursuing the nonnarcotic drug involvement of a "dry" addict or might it better be devoted to the narcotic problem of another patient? The eternal dilemma of this analog of triage imposes a requirement for thoughtful evaluation of ultimate objectives that may be difficult for even the most conscientious therapist to achieve.

FOOTNOTE

Narcotic addicts are here defined as persons who have used opium, its derivatives or synthetics for non-medical reasons, for four or more days per week for at least one month while at large in the community.

REFERENCES

Inciardi, J.A. The impact of drug use on street crime. Paper presented at the annual meeting of the American Society of Criminology, November. 1981.

McGlothlin, W.H.; Anglin, M.D.; and Wilson, B.D. An evaluation of the California Civil Addict Program. (NIDA Services Research Monograph Series). Rockville, Maryland: National Institute on Drug Abuse, 1977.

Nurco, D.N.; Cisin, I.H.; and Balter, M.B. Addict careers. I. A new typology. The International Journal of the Addictions, 1981, 16:1305-1325.

Nurco, D.N.; Cisin, I.H.; and Balter, M.B.: Addict careers. II. The first ten years. The International Journal of the Addictions, 1981, 16:1327-1356.

Nurco, D.N.; Cisin, I.H.; and Balter, M.B.: Addict careers. III. The first ten years. The International Journal of the Addictions, 1981, 16:1357-1372.

Nurco, D.N. and Shaffer, J.W. Types and characteristics of addicts in the community. Drug and Alcohol Dependence, 1982, 9:43-78.

Waldorf, D. Careers in dope. Englewood Cliffs, New Jersey: Prentice-Hall, 1973.

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Drug Dependence in Pregnancy: Intrapartum Course and Management

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INTRODUCTION

Psychotropic drug use and abuse in pregnant women is a health problem important to both the woman and her passively dependent offspring. It has been well documented in previous studies that drug dependent women experience an increased incidence of medical and obstetrical complications[1,2,4,6,8]. It is for this reason that drug dependent women must be considered high risk during labor and delivery. However, little information exists on the specifics of the intrapartum course of these patients.

At Family Center in Philadelphia, a clinical and research program within the Thomas Jefferson University Hospital (TJUH) providing comprehensive pre- and postnatal services for drug dependent women and their infants, an investigation was undertaken to study these women with respect to the intrapartum course and appropriate methods of management. The primary objective of this study was to determine whether drug dependent women experience normal or expected patterns of labor and if the use of standard intrapartum management for them is appropriate.

THE STUDY

Subjects for the study included 336 women who delivered between January 1982 and August 1984. Of these women, 112 were drug dependent before and during pregnancy, and were enrolled in Family Center where they were offered obstetrical, psychosocial and addiction services. The great majority of them were referred to Family Center from medical centers and services throughout the City of Philadelphia and surrounding areas. They were "hard-core" addicts with 72% on daily methadone maintenance. A group of 224 women of similar socio-economic status, parity, gravidity and delivery date that attended the same prenatal clinic were selected to serve as a comparison group.

METHOD

Upon presentation to the hospital, Family Center patients were admitted for a thorough evaluation of their medical and addiction status. After substantiation of addiction by urine toxicology and clinical signs of withdrawal, patients were stabilized on methadone if dependent on opiates. Those women dependent on either barbiturates or tranquilizers were admitted to a specialized detoxification unit. Following discharge, the women returned bi-monthly for prenatal care to a special clinic for high-risk pregnancies which was staffed by a perinatologist. Prenatal care included daily methadone administration, urine toxicologies repeated weekly, ultrasound examinations performed routinely, and antenatal testing utilized as indicated.

During labor, drug dependent women were managed by methods similar to those used for non-drug dependent women. However, certain considerations were necessary for the following reasons. Since it is not uncommon for drug dependent women to confuse the early signs of labor with signs of withdrawal, they may medicate themselves during the early hours of labor and arrive at the hospital with a high blood level of narcotics. It was therefore necessary to obtain a urine drug screen, and, when appropriate, methadone was administered promptly following admission to prevent withdrawal during labor and delivery. As with all patients, intravenous solutions were started prophylactically, and, due to the presence of sclerotic veins, many of the intravenous users required the insertion of a subclavian line.

The post-partum course was monitored by standard methods. For patients requiring subclavian lines, a chest radiograph was required to rule out complications such as pneumothorax. If labor and delivery were uncomplicated, patients were discharged from the hospital on the third or the fourth day. Methadone maintenance was continued during the post-partum period.

RESULTS

Table 1 presents antepartum data on all patients included in this study. There was a significantly greater portion of white patients in the Family Center group. This was related to the referral pattern which encompassed a less homogenous population then the comparison group, whose population is comprised by a predominantly black group of patients who live in the vicinity of TJUH. The patients also tended to be younger in the comparison group. In both the Family Center and comparison group, one-fifth were delivering their first child. Patients in the comparison group had adequate prenatal care significantly more often.

As in previous studies[4], rates of obstetrical and medical complications were significantly higher ($p<0.05$) in the drug dependent women. These included premature delivery with gestation less than 37 weeks, intrauterine growth retardation (IUGR), abruptio

placentae, hypertensive disorders, thrombophlebitis, cellulitis, abscesses and hepatitis. One maternal death occurred in the Family Center group secondary to post-partum hemorrhage.

TABLE 1: ANTEPARTUM CHARACTERISTICS

	Family Center (n=112)	Comparison Group (n=224)
Mean Age (Years)	28	24
Race (%): White	45	14
Black	48	84
Hispanic	7	2
Parity (%): Primiparas	20	20
Multiparas	80	80
Adequate Prenatal Care (≤ 4 visits)	65	85

In Table 2, although not statistically significant, medical induction of labor was required more frequently in the Family Center group. Indications. for labor induction tended to be markedly different. The most common indications for induction in the Family Center group were hypertensive disorders and IUGR, whereas in the comparison group the most common indication was postmaturity. Among patients who did not have an elective Cesarean section, there was a significantly lower ($p<0.03$) incidence in the Family Center group of secondary arrest of dilatation. This dysfunctional labor pattern is defined by Friedman as a cessation of progressive cervical dilatation in the active phase of labor prior to full dilatation for a period of at least two hours[5] Thus, the active phase of labor during which most of the cervical dilatation occurs was disrupted significantly less in the Family Center group.

TABLE 2: INTRAPARTUM PROFILE

	Family Center (n=112)	Comparison Group (n=224)	P
Onset of Labor (%):			
Spontaneous	68	78	NS
Medical Induction	15	9	NS
Elective Cesarean Section	17	13	NS
Method of Delivery (%):			
Spontaneous Vertex	56	71	NS
Low Forceps	19	9	<0.02
Mid Forceps	4	2	NS
Repeat Cesarean Section	11	9	NS
Primary Cesarean Section	11	8	NS
Required Subclavian Line (%)	23	0	

In Table 2 it was also demonstrated that there was a significant difference between the two groups with respect to delivery type. The use of low forceps was required more than twice as often for Family Center deliveries; 84% of these forceps deliveries occurred under epidural anesthesia. Cesarean section rates were similar in both groups.

Also in Table 2, it should be noted that almost one-fourth of the Family Center patients required the insertion of a subclavian intravenous line, with two of the patients, or 8%, developing pneumothorax as a complication. For both of these patients, insertion of a chest tube was necessary.

Table 3 demonstrates that the median duration of the first, second and third stages of labor was similar in both groups. The onset of labor was considered to have occurred when the patient began to have regular, perceivable contractions.

TABLE 3: MEDIAN LENGTH OF LABOR FOR VAGINAL DELIVERIES

	Stage of Labor		
	First (Hrs/Mins)	Second (Mins)	Third (Mins)
Family Center (n=88)	8/10	16	6
Comparison Group (n=184)	8/23	16	6

Narcotic agents used for systemic analgesia included meperidine (Demerol) and morphine. Butorphanol (Stadol) was also used, but only in the comparison group due to its antagonistic properties in the presence of other narcotic agents. Narcotic antagonists such as naloxone (Narcan) were not used except in emergency situations when the woman or infant was obtunded from a narcotic overdose. Referring to Table 4, almost equal numbers of patients in both groups received systemic analgesia. However, regional anesthesia, generally utilizing epidural or pudendal block, was provided significantly more often in the Family Center group. In particular, epidural anesthesia was utilized in 40% more patients.

TABLE 4: ANALGESIA AND ANESTHESIA ADMINISTERED DURING LABOR IN VAGINAL DELIVERIES

	Family Center (n=88)	Comparison Group (n=184)	P
Regional Anesthesia (%)	60	41	<0.005
Epidural	50	36	<0.03
Pudendal Block	11	5	NS
Spinal	1	1	NS
Systemic Analgesia (%)	36	38	NS
No Analgesia or Anesthesia (%)	26	35	NS

For purposes of this study, fetal distress was defined as a fetal scalp pH reading of 7.2 or less, or if one or more of the following patterns of fetal heart rate was present as interpreted from electronic monitor tracings: prolonged bradycardia, late decelerations, severe variable decelerations or variable decelerations with late components. In Table 5 it is noted that there was no significant difference in the incidence of fetal distress between the two groups. Likewise, meconium was not passed in the amniotic fluid more frequently in either group. Mean Apgar scores and perinatal mortality rates were also similar in both groups. In the Family Center group, significantly fewer infants were born after a gestational period of 37 weeks or more. Accordingly, infants born to the drug dependent women weighed 350 grams less on the average; however, the infants born in this group were mostly of normal weight for gestational age.

TABLE 5: PERINATAL OUTCOME FOR VIABLE DELIVERIES

	Family Center** (n=110)	Comparison Group (n=222)	P
Fetal Distress (%)	21	20	NS
Meconium Passed in Amniotic Fluid (%)	21	24	NS
Mean Apgar Scores			
At one minute	7.4	7.5	NS
At five minutes	8.6	8.6	NS
Perinatal Mortality (%)			
Intrauterine deaths	2.7	0.9	NS
Neonatal deaths	0.9	1.4	NS
Total perinatal deaths*	3.6	2.2	NS
Mean birth weight (grams)	2813	3163	(0.01
Gestational Age<37 wks.(%)	25	13	< 0.005

*Includes all subjects in study (Family Center: n=113; Comparison: n=224)
**Includes one set of twins born at 36 weeks gestation

In both groups, post-partum complications and complications related to the use of analgesia or anesthesia were rare and of similar incidence.

DISCUSSION

Despite continued improvements in care, substance abuse during pregnancy remains an extremely high risk condition for both mother and fetus. This population continues to have a high incidence of medical and obstetrical complications related to the drug dependent woman's erratic lifestyle, tendency to neglect health care, and continued use of illicit drugs during pregnancy even with the administration of methadone[4].

Excessive sedation is frequently avoided during the latent and active phases of labor because of potential prolongation. In contrast, sedation has been used to "rest" the uterus in abnormal labors. This has led to the suggestion that narcotics may have a tocolytic effect. From these data, and that reported by others, it is evident that the median duration of labor for drug dependent women is not significantly different from non-drug dependent women[6,8]. It has been our experience that women who excessively medicate themselves at the onset of labor may experience a prolonged latent phase and then progress on to have a normal active phase after the effects of the drugs have worn off.

The active phase of labor for Family Center women as compared to the control group was faster and more efficient. The incidence of secondary arrest of dilatation occurred in a significantly smaller portion of Family Center women. Friedman and co-workers have demonstrated an association between higher birth weights and an increased incidence of cephalopelvic disproportion and dysfunctional labor during the active phase[5]. The difference between the two study groups in the active phase of labor therefore, may be secondary to the decreased mean birth weight seen in drug dependent women.

Low forceps delivery occurred with more than twice the frequency in the Family Center group. Three reasons for this difference may be postulated. First, the 40% increased use of epidural anesthesia in the Family Center women may have led to an increased need for forceps. Epidurals are known to increase the duration of the second stage of labor, which may provoke operative interference prematurely[3]. In our study, and others[7], women with epidurals did have an increase in the average duration of the second stage of labor; however, this was expected and was not associated with any significant increase in maternal, fetal or neonatal morbidity. Epidurals may also decrease perineal sensation and thus decrease reflex maternal bearing down efforts during the second stage of labor[9]. Forceps may then be necessary for this latter reason. It should be remembered that 84% of the forceps deliveries in the Family Center group occurred under epidural anesthesia. Secondly, the high rate of premature deliveries may have prompted some elective forceps deliveries. This is a common practice to prevent trauma to the premature infant's fragile head. Finally, it has been our experience that patients in the Family Center group are generally less cooperative, sometimes leading to a prolonged and difficult second stage of labor.

Systemic analgesia was given to an equal number of patients in each group. It is often given to Family Center patients for relief of anxiety and uterine pain during the latent stage of labor. When Family Center patients are in the active phase of labor, epidural anesthesia may be initiated. The 40% increased use of anesthesia during labor in the Family Center group did not lead to an overall increased complication and morbidity rate as was indicated by similar incidences in both groups of puerperal morbidity, meconium staining, fetal distress and low Apgar scores.

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CONCLUSION

Drug dependent pregnant women: (1) are given epidural anesthesia more-frequently which is associated with an increased incidence of forceps delivery but not with an alteration in perinatal and puerperal outcome; (2) have a normal course of labor but a faster and more efficient active phase; and (3) have sclerotic veins, which often necessitates the insertion of subclavian IV lines and consequently predisposes the women to complications such as pneunothorax. These data continue to emphasize the fact that drug dependent women are in need of high risk prenatal and intrapartum management and that careful monitoring and utilization of epidural anesthesia during the intrapartum period can prevent possible untoward complications for mother and infant.

REFERENCES

1. Blinick, G., Wallach, R.C., Jerez, E., Ackerman, B.D, Drug Addiction in Pregnancy and the Neonate. Am J Obstet Gynecol 125:135-142, 1976.
2. Connaughton, J.F., Reeser, D., Schut, J., Finnegan, L.P. Perinatal Addiction: Outcome and Management. Am J Obstet Gynecol 129:676-686, 1977.
3. Doughty, A. Selective Epidural Analgesia and the Forceps Rate. Br J Anes 41:1058-62, 1969.
4. Finnegan, L.P. Drug Dependence in Pregnancy: Clinical Management of Mother and Child. National Institute on Drug Abuse Research Monograph, DHEW Pub. No. (ADM) 79-678. Washington, D.C.: Supt. of Docs., US Govt. Print. Off., 1979, pp 29-48.
5. Friedman, E.A. and Sachtleben, M.R. Dysfunctional Labor III. Secondary Arrest of Dilatation in the Nullipara. Obstet Gynecol 19:576-91, 1962.
6. Pelosi, et al. Pregnancy Complicated by Heroin Addiction. Obstet Gynecol 45:512-15, 1975.
7. Scanlon, J. Effects of Obstetrical Anesthesia and Analgesia on the Newborn: A Selected Annotated Bibliography for the Clinician. Clin Obstet Gynecol 24:264, 1981.
8. Stone, M.L., et al. Narcotic Addiction in Pregnancy. Am J Obstet Gynecol 109:716-20, 1971.
9. Walton, P. and Reynolds, F. Epidural Analgesia and Instrumental Delivery. Anesthesia 39:218-23, 1984.

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Long-Term Followup Studies of the Medical Status of Adolescent Former Heroin Addicts in Chronic Methadone Maintenance Treatment: Liver Disease and Immune Status

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In 1969, a research program was initiated to determine possible efficacy and also medical safety of short or long-term methadone maintenance treatment, with intervals of drug free treatment, in the management of adolescent hard-core heroin addicts, defined as young people between the ages of 14 and 19 years, with a history of two years or more of multiple dose daily use of heroin, with development of tolerance, dependence, and recidivism to heroin abuse following attempts at detoxification and drug-free treatment. This program began at The Rockefeller University Hospital and moved in 1970 to the Department of Public Health of the New York Hospital-Cornell Medical Center.

In previously reported prospective and retrospective studies of adult heroin addicts at time of entry and during long-term methadone treatment, it has been shown that chronic liver disease caused by hepatitis B virus, other viruses and alcohol abuse, is present in over 50% of patients. It has also been shown that methadone itself is not hepatotoxic, with no liver function test abnormalities appearing in the absence of viral or alcohol-induced injury. [1-5]

There are three study groups: 1) "Retrospective study group," all patients admitted to program between 1969 and 1971 and still in treatment at time of beginning of study in June 1971 (N=25); 2) "Prospective study group," all patients admitted to program between June 1971 and June 1973 with no exclusions (N=59); 3) "Post prospective study group," all patients admitted to program between June 1973 and September 1976 with no exclusions (N=34). Patients were evaluated at time of admission to program and prospectively from 1971 to 1976. All patients remaining in treatment, or being followed at clinic in 1984 were re-evaluated then (N=35, 30% of original 3 groups). Evaluation consisted of history, physical examination, urine monitoring for drugs of abuse and laboratory tests of routine and special types.

From time of admission, abnormal SGPT levels became normal in 25% of patients. Conversely, 15% of patients developed abnormal

SGOT values; in each case, clinical and laboratory evidence of hepatitis infection and/or chronic alcohol abuse was documented. Serum protein and immunoglobulin abnormalities improved with time in treatment.

Percentages of patients studied with abnormal (elevated) test results at admission and after 2 and 10 years of treatment:

	SGOT	SGPT	Total Protein	Albumin	Globulin	IgG	IgA	IgM	IgE
Adm.	65	56	69	23	89	60	5	31	-
2 yrs.	59	36	37	11	85	36	4	36	82
10 yrs.	80	31	19	13	38	0	0	19	27

Using both standard assays available at time of original testing and recently developed monoclonal antibody techniques for retesting of banked sera, it was shown that 29.7% of the original study group were hepatitis B surface antigen positive either at time of admission to or during early treatment (1969-1976). None of the patients re-evaluated in 1984 (30% of the entire original group) were HB_SAg positive; however, 82% had some marker of prior HBV infection (HB_SAb and/or HB_cAb).

In conclusion, after 10 years or more of treatment, abnormalities in liver function persist in a majority of adolescent-young patients and are primarily due to past infection with hepatitis B virus and also with delta virus, non A non B hepatitis virus (es) and chronic alcohol abuse.

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REFERENCES

Kreek, M.J.: Medical safety and side effects of methadone in tolerant individuals. JAMA 223:665-668, 1973.

Kreek, M.J.: Medical complications in methadone patients. Ann N.Y. Acad Sci. 311:110-134, 1978.

Kreek, M.J.: Metabolic interactions between opiates and alcohol Ann N.Y. Acad Sci 363:36-49, 1981.

Kreek, M.J.; Dodes, L.; Kane, S.; Knobler, J.; Martin, R.: Long-term methadone maintenance therapy: Effects on liver function Ann Intern Med 77:598-602, 1972.

Novick, D.M.; Gelb, A.M.; Stenger, R.J.; Yancovits, S.R.; Adelesberg G.; Chateau F.; Kreek, M.J.: Hepatitis B serologic studies in narcotic users with chronic liver disease Am J Gastroenterol 75:111-115, 1981.

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Double-Blind Comparison of Desipramine and Placebo for Treatment of Phencyclidine or Amphetamine Dependence

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ABSTRACT

Open clinical trials have suggested that desipramine may be an effective agent for treatment of phencyclidine (PCP) or amphetamine dependence. Four pairs (eight subjects) with PCP and two pairs (four subjects). with amphetamine dependence were studied. One subject in each pair was given desipramine or placebo under double-blind conditions. Although desipramine clearly was no more effective than placebo in treatment of PCP dependence, subjects with amphetamine dependence who received desipramine remained in treatment longer and submitted more urine samples absent of amphetamine than did subjects who received placebo.

INTRODUCTION

Dependence upon phencyclidine (PCP) is a relatively new problem to emerge in many communities of the United States.[1,2] Amphetamine dependence is a long-standing, endemic problem of low prevalence.[3,4] Both dependencies are similiar in that there is no recognized medical treatment for them. Based on non-blind observations, desipramine has appeared to be a useful treatment agent for PCP or amphetamine dependence.[3,6] The basis for initial use of desipramine in treatment of these dependencies is that one of its primary pharmacologic properties is blockage of the re-uptake of norepinephrine into neurons.[7] Chronic administration of PCP or amphetamine to laboratory animals and *in vitro* preparations have been reported to alter noradrenergic activity.[8,10] Due to a possible theoretical basis for use of desipramine plus suggestive non-blind trials, two double-blind, placebo-controlled clinical trials were done and are reported here. One trial was conducted with persons dependent upon PCP and the other with persons dependent upon amphetamines.

METHODS

Subjects for this study were admitted to a special drug-dependency research clinic located in Eastern Los Angeles County (West Covina), and were aware that they had a 50% chance of receiving placebo. All subjects gave a history of multiple, separate ingestions of either PCP or amphetamines each day for a minimum of 30 consecutive days just prior to admission. They perceived themselves to be so dependent that they could not cease drug use without medical assistance. All denied dependence upon any other drug, including marijuana or alcohol, and didn't regularly use any medication for a medical or psychiatric problem. Use of PCP or amphetamines was documented by urine analysis with thin-layer chromatography and enzyme immunoassay. Absence of other drug use was also documented by these same urine analysis techniques, and absence of alcohol in breath at the time of admission was documented by breath analyzer. Likely tolerance was suggested in each subject in that none exhibited dilated pupil, hypertension, hyperreflexia, nystagmus, sedation, or slurred speech at the time of admission. Subjects were admitted in pairs. Four pairs (eight subjects) were admitted to the PCP study, and two pairs (four subjects) were admitted to the amphetamine study.

Placebo and desipramine were both administered in identical, unmarked capsules. Each set of capsules was randomly assigned a number by a monitor who was not in direct contact with the clinical study so that no person who administered medication, examined, or collected data from subjects was aware of which subjects received desipramine or placebo. Each desipramine capsule contained 25 mg of active drug. Subjects were instructed on admission that they were to attend the clinic for five consecutive days, and this period was to be followed by twice-weekly clinic visits for a maximum of six weeks. They were informed that they could voluntarily drop out of the study at any time or that they could discontinue the study and obtain active desipramine at any time. The first day's dose of medication was one capsule of placebo or desipramine every six hours for a maximum of 100 mg of desipramine in a 24-hour period. Subjects were informed that they could increase the dosage on subsequent days to a maximum of six capsules for a maximum of 150 mg of desipramine in a 24-hour period.

On every day of clinic attendance, a specific set of data were collected on each subject. A withdrawal score was determined by assessing the following symptoms: anorexia, insomnia, agitation, apathy, anxiety, nausea, myalgia, diaphoresis, anergy, mental confusion, diarrhea, depression,

drug craving, and difficulty concentrating. Each withdrawal symptom was scored 0 for absent, 1 for mild, 2 for moderate, and 3 for severe. These symptoms were selected for assessment since persons dependent upon PCP had previously reported these to be common during withdrawal.[6] Subjects were asked the following during each visit: use of PCP or amphetamine within the previous 24 hours, effectiveness of the medication, and the ability of the medication to reduce drug craving, provide energy, prevent depression, and assist sleep. An inquiry was made to determine if the subject may have experienced any of the following side-effects: dry mouth, tremor, sedation, hallucinations, blurred vision, or dysphoria. A urine specimen was collected on each day of attendance which was analyzed for the presence of PCP or amphetamines by enzyme immunoassay. The following data were compared for each pair of subjects: days of retention in the study; conversion of urine containing PCP or amphetamine on admission to negative later in the study; mean withdrawal score for the first four days of drug administration; and the self-reports of subjects relative to drug effectiveness to reduce drug craving, provide sleep assistance, and prevent anergy and depression.

RESULTS

PCP subjects who received either desipramine or placebo appear ed similiar in that ages of the four who received desipramine ranged from 21 to 38 years (Mean 26.5) and those who received placebo ranged from 19 to 36 (Mean 25.3) (PNS). In addition, subjects in the desipramine group had used PCP for three to eight years (Mean 6.0) compared to the placebo group who used PCP for four to nine years (Mean 6.5) (PNS). There were two male and two female pairs. All eight subjects reported that they used PCP two to four separate times each day (Table One). In only one pair did desipramine appear superior to placebo. This subject remained in treatment 27 days although the maximum study period was 42 days. Retention in treatment, except for this one subject, was extremely poor. No subject in either study group remained over five days. In addition, this was the only subject of eight to convert urine from PCP positive on admission to PCP negative during the study. Mean daily withdrawal scores between the subjects in three pairs were not significantly different and are likely skewed since all but one subject continued PCP use during the study. Self-reports were almost identical in both groups. Three of four (75%) subjects in both groups reported that the drug they received was effective, reduced PCP craving, and provided energy. Three of four (75%) desipramine subjects compared to two of four (50%) placebo subjects reported sleep assistance (PNS). The reverse was true in prevention of depression in that three of four (75%) placebo compared to two of four desipramine subjects stated that their medication accomplished this.

The two subjects dependent upon amphetamines who received desipramine were males ages 28 and 23 years. They had used amphetamines for 55 and 33 months. Paired subjects who received placebo were 30 and 26 years of age and had used amphetamines for 20 and 75 months. All four subjects claimed to use one to one and one-half grams per day and took three to four separate ingestions per day. All subjects used by the oral and sniffing routes, although one subject who received desipramine also used intravenously. One subject, who was female, received placebo. The subjects in each pair who received desipramine remained considerably longer in treatment than did placebo subjects (Table Two). Subjects in both groups, however, reported that their respective medication was effective, reduced drug craving, prevented depression, and assisted sleep. Neither subject who received placebo, however, stated it provided energy; while one desipramine subject reported this. Mean daily withdrawal scores were not statistically different. Both subjects who received desipramine converted their urine from amphetamine positive on admission to amphetamine negative during the study. Only one placebo subject did this. Fifteen (15) of 20 (75.0%) urines submitted by desipramine subjects compared to four of seven (57.1%) submitted by placebo subjects were amphetamine negative, although this difference was not statistically significant (PNS). The one subject who completed the maximum study period of 42 days requested to continue desipramine on a non-blind basis after the study. This request was honored and he continued to take desipramine for approximately nine months, during which time there was no amphetamine use as determined by repeated urine tests.

Some side-effects, particularly dry mouth, were reported by subjects in desipramine and placebo groups. There was no consistent pattern of side-effects, and no subject ever stated they were severe enough to cause discontinuation of the study.

DISCUSSION

Initial open clinical trials with desipramine to medically assist withdrawal from PCP and amphetamine dependence were undertaken because this tricyclic antidepressant is a potent blocker of norepinephrine re-uptake into neurons.[7]

Some animal and *in vitro* studies show that PCP and amphetamines may affect central noradreneraic systems.[8,10] We initially believed that desipramine's capability of making more norepinephrine available to receptors might prove to be medically helpful in withdrawal from PCP and amphetamine dependence. Initial open clinical trials with desipramine suggested that this may be the case.[3,6]

The purpose of the two double-blind, placebo-controlled trials reported here was to take a small number of subjects who met very specific admission criterion and determine if desipramine should be further investigated as a medical treatment for either PCP or amphetamine dependence. If strict study criteria are established, subjects who meet them are difficult to identify and recruit. By use of paired subjects and the study methods used here, a small number of subjects can be used to determine if further study of a withdrawal treatment agent is warranted.

The best outcome measures for determining if a treatment agent may be effective for withdrawal from drug dependence in ambulatory patients are probably retention in treatment and conversion of admission urine from drug-positive to drug-negative after admission. Retention has been especially noted as a major criterion erion for effectiveness of treatment of drug dependence.[11] One subject in the amphetamine dependence group who received desipramine remained in treatment the entire 42 days of the study, and the other who received desipramine remained in treatment longer than the control subject. Both subjects who received desipramine converted their admission urine from amphetamine positive to amphetamine negative during the study. Only one subject who received placebo did this. Although more subjects in this trial may have statistically altered results, these observations are encouraging and should foster further investigation. Amphetamine dependence has been notoriously difficult to treat. [5,12] For example, Anderson et al. found treatment of amphetamine dependence to be so ineffective that none of 18 patients returned for even repeat clinic visits after being admitted to a structured treatment program.[12]

Some recent reports provide a theoretical explanation why desipramine might be effective in assisting medical withdrawal from amphetamine dependence, but not from PCP dependence. While some early reports in the 1950's and 60's suggest that PCP administration may deplete the central nervous system of norepinephrine, a new study by Wagner et al. shows that PCP tolerance is unrelated to the central norepinephrine or dopamine depletion. It is reasonably certain that amphetamine administration affects central noradrenergic activity and appears to block norepinephrine re-uptake in a manner similiar to desipramine.[8,10] Chronic amphetamine administration has also been shown to produce central nervous system dopamine depletion.[10] Since PCP does not appear to affect central nervous system catecholamines while amphetamine does, there is ample reason to expect desipramine to have a different effect in these two forms of drug dependence. Desipramine is likely to be effective in treating

amphetamine dependence due to its ability to either block re-uptake of catecholamines and make them more available to receptor sites and/or alter receptor site sensitivity. One amphetamine-dependent person who received desipramine in this study desired to continue taking desipramine for several months in a manner analogs to reports using this drug to treat cocaine dependence. This desire may be due to changes in receptor site sensitivity. It is possible that an anti-depressant agent other than desipramine might be effective in treating PCP dependence. Based on a successful non-blind trial with desipramine in withdrawal from amphetamine dependence, a theoretical, neurochemical rationale, and the indication of positive benefits in this study, we recommend that desipramine be further studied as a treatment for withdrawal from amphetamine dependence.

TABLE ONE

Major Outcome Measures In Eight Subjects With PCP Dependence

Pair	Days In Treatment		Urine Conversion To Negative	
	Desipramine	Placebo	Desipramine	Placebo
1	2	4	No	No
2	3	3	No	No
3	27	2	Yes	No
4	5	5	No	No

TABLE TWO

Major Outcome Measures In Four Subjects With Amphetamine Dependence

Pair	Days In Treatment		Urine Conversion To Negative	
	Desipramine	Placebo	Desipramine	Placebo
1	42	12	Yes	Yes
2	14	3	Yes	No

REFERENCES

1. McCarron, M.M., Schulze, B.W., Thompson, G.A., et al: Acute phencyclidine intoxication: clinical patterns. complications and treatment. Ann Emerg Med 1981; 10:290-247.

2. Rawson, R.A., Tennant, F.S., Jr., McCann, M.A.: Characteristics of 68 phencyclidine abusers who sought Treatment. Drug Alcoh Depend 1981; 8:223-227.

3. Tennant, F.S., Rawson, R.A.: Cocaine and amphetamine dependence treated with desipramine in Harris, L. (ed) Problems of Drug Dependence, 1982. NIDA Research Monograph-Series 43, National Institute on Drug Abuse, Rockville, Maryland, 1983; pp 351-355.

4. Kalant, O. J., Kalant, H.: Amphetamine and related drugs: clinical toxicity and dependence: a comprehensive bibliography of the international literature. Toronto, Addiction Research Foundation, 1974.

5. Tennant, F.S., Jr.: Treatment of dependence upon stimulants and hallucinogens. Drug Alcoh Depend 1983; 11:111-114.

6. Tennant, F.S., Rawson, R.A., McCann, M.: Withdrawal from chronic phencyclidine (PCP) dependence with desipramine. Am J Psychiatry 1981; 138:845-847.

7. Fawcett, J., Maas, J.W., Dekirmenjian, H.: Depression and MHPG excretion: response to dextroamphetamine and tricyclic antidepressants. Arch Gen Psychiat 26: 246-251, 1972.

8. Moore, K.E., Chiueh, C.C., Zeldes, G.: Release of neurotransmitters from the brain in vitro by amphetamines, methylphenidate, and cocaine, in Ellinwood EH and Kilbey M.M. (eds): Cocaine and Other Stimulants. New York, Plenum Press, 1977, pp. 143-160.

9. Tonge, S.R., Leonard, B.E.: Interaction of phencyclidine with drugs affecting noradrenadine metabolism in the rat brain. Psychopharmacologia 1972; 23:86-90.

10. Wagner, G.C., Seiden, L.S., Schuster, C.R.: Methamphetamine-induced changes in brain catacholamines in rats and guinea pigs. Drug Alcoh Depend 4:435-438, 1979.

11. Simpson, D.D.: The relation of time spent in drug abuse treatment to post-treatment outcome. Am J. Psychiatry 1979; 136: 1449-1453.

12. Anderson, W.H., O'Malley, J.E., Lazare, A.: Failure of outpatient treatment of drug abuse, II: Amphetamines, barbiturates, hallucinogens. Am J. Psychiatry 1972; 128:1572-1576.

13. Wagner, G.C., Gardner, J., Tsigas, D.J., et al: Tolerance following the repeated administration of high doses of phencyclidine: no relation to central catecholamine depletion. Drug Alcoh Depend 1984; 13:225-234.

14. Gavin, F.H., Kleber, H.N.: Cocaine abuse treatment: open pilot trial with desipramine and lithium carbonate. Arch Gen Psychiat 1984; 41:903-909.

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Abstract of Clinical Research Findings: Therapeutic and Historical Aspects

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Parenteral drug abusers are at high risk for acquired immune deficiency syndrome (AIDS), which is caused by the lymphadenopathy associated virus (LAV; also known as HTLV-III). The aims of this study are to determine when parenteral drug abusers began to be exposed to LAV and whether patients in methadone maintenance treatment have a lower prevalence of exposure to LAV. We tested fives of sera for antibody to LAV (anti-LAV) by ELISA at the Centers for Disease Control. Western blots were also used in groups 1-3 and in some patients from group 4. Group 1 includes sera collected in 1969 from 43 methadone maintenance patients. Group 2 consists of sera collected between 1971-74 from 66 methadone patients. Group 3 includes specimens collected in 1984 from 35 long-term methadone patients. Groups 4 and 5 were collected between 1978-83 during studies of chronic liver disease. Group 4 consists of 101 current or former parenteral heroin abusers, of whom 48 were receiving methadone maintenance when studied. Group 5 contains 17 alcohol abusers. All in groups 1-5 were in New York City treatment facilities and all males were heterosexual. RESULTS: All in groups 1-2 were negative for anti-LAV. Only 3/35 (9%) in group 3 had been exposed to LAV based on ELISA or Western blot. In group 4, 0/7 sera collected in 1978 were positive for anti-LAV; for 1979, 14/49 (29%); for 1980, 8/18 (44%); and for 1981-83, 14/27 (52%). Only 1/17 (6%) of group 5 had anti-LAV. An analysis of group 4 revealed that 11/48 (23%) methadone maintained patients had a positive anti-LAV compared with 25/35 (47%) not currently in treatment($p=0.01$). Anti-LAV was found in only 6/35 (17%) patients in treatment for 5 or more years, in 3/24 (12.5%) who reported no needle use since admission to treatment, and in 1/18 (6%) who met both of the above criteria. We conclude that methadone maintenance treatment can protect parenteral drug abusers against AIDS and that early implementation of such treatment on a large scale should be strongly considered for regions with large numbers of parenteral heroin abusers but low prevalences of anti-LAV.

DISCUSSION: ETHICAL ASPECTS OF LAV ANTIBODY TESTING IN PARENTERAL DRUG ABUSERS

Several ethical questions have arisen during the conduct of this and other studies of anti-LAV. First, can banked sera be studied for anti-LAV? Second, should attempts be made to identify, locate, and inform donors of banked sera of a positive anti-LAV? Third, when a study is clearly labelled as AIDS research, under what circumstances should patients be told of a positive test?

We consider that the answer to the first question is yes, and the second, no. Title 45, part 46 of the Code of Federal Regulations (45 CFR 46) specifically exempts existing pathological or diagnostic specimens from Health and Human Services (HHS) policies for the protection of human subjects, as long as the subjects who donated the specimens cannot be identified. Thus, pre-existing sera may be studied for anti-LAV or any other newly developed test, and attempts to identify the donors should not be made.

The third question pertains to prospective studies which are clearly labelled as AIDS research. There has been much debate as to whether subjects who donate blood for these studies should be told of a positive anti-LAV result. Beyond denoting exposure to LAV, the significance for the individual of a positive anti-LAV is unknown; it could mean infection, immunity, or neither one. Also, the rates of false-positive and false-negative anti-LAV tests are not known. Grave psychological damage may occur after an individual has been told that he or she is positive. Recently, the situation of persons who donate blood at blood banks and are found to be positive for anti-LAV has been reviewed (CDC,1985). Public Health Service recommendations therein state that such individuals should be told of their positive test and then receive counseling. This view also received support in a letter to physicians from the Commissioner of Food and Drugs (HHS, 1985) and an article in the "Law-Medicine Notes" section of the New England Journal of Medicine (Curran, 1985). We question whether this approach is appropiate for parenteral drug abusers, who are a known high risk group for AIDS and thus should be taking precautions anyway (Marmor et al. 1984). While we would not wish to interfere with a patient's right to know, we believe that his or her right not to know about a test result with uncertain implications for the individual should also be protected. We urge the medical community to consider whether our patients would be better served by giving them some input in the decision as to whether or not they should be told of a positive anti-LAV test. Such input should be considered both at the time of informed consent and at the time the test results become available. Finally, before anyone is told of a positive test, a repeat assay should be performed. In addition, efforts to maintain confidentiality must accompany all anti-LAV testing (Bayer et al. 1984).

REFERENCES

Bayer, R.; Levine, C.; and Murray, T.H. Guidelines for Confidentiality in Research on AIDS. IRB: A Review of Human Subjects Research 6(6): 1-7, 1984.

Centers for Disease Control (CDC). Provisional public health service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. Morbid Mortal Weekly Rep 34:1-4, 1985.

Code of Federal Regulations, 45 CFR 46, Revised as of March 8, 1983.

Curran, W.J. AIDS research and "the window of opportunity." N Engl J Med 312:903-904, 1985.

Health and Human Services (HHS), Food and Drug Administration. Important AIDS Information, 1985.

Marmor, M.; Des Jarlais, D.C.; Friedman, S.R.; Lyden, M.; and El-Sadr, W. The epidemic of acquired immunodeficiency syndrome (AIDS) and suggestions for its control in drug abuser J Substance Abuse Treat 1;237-247, 1984.

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The Effects of Cannabis Use on the Clinical Condition of Schizophrenics

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Some cannabinoids are known to exert marked changes in psychic function and it would seem logical to assume that such effects should aggravate the mental disturbances experienced by individuals who suffer from pre-existing psychoses. It has been reported, for example, that cannabis use interferes with the proper clinical identification of psychotic illness. Harding and Knight (1973) described the case of 4 individuals who were diagnosed as paranoid schizophrenics on admission, but presented a clear picture of hypomania 3 to 4 days later. The 4 were heavy users who had been smoking up until the time they entered hospital. The authors concluded that the thought disorder, echolalia, echopraxia and hallucinations, exhibited by these patients at first, were actually drug effects which masked the more specific manifestations of their affective disorder.

Schizophrenics who use cannabis have been observed to become unusually violent and destructive (Bernhardson and Gunne 1972); patients suffering from major affective disorders might react with severe dysphoria after the administration of cannabis (Ablon and Goodwin 1974), or exhibit paranoid and aggressive behaviour El-Guebaly (1975); and psychotics in general appear to display increased elation and psychomotor agitation subsequent to using the drug (Rottanburg et al. 1982).

More important perhaps than the mere distortion of symptoms, is the influence that the continuing use of cannabis could have on the clinical course of such psychotic disorders; on their therapeutic response; and on the long term residual deficit. Some case reports clearly indicate that cannabis is capable of interfering with the recovery of schizophrenics in treatment. Treffert (1978), for instance, observed four patients who tended to relapse each time they resumed the habit; and Davison and Wilson (1972) noted a weekly pattern of symptom reactivation in a young patient who was using the drug during week-end leaves. The significance of individual case observations, of course, must be tested through the study of larger patient populations;

this paper reports on one such attempt. It concerns a survey conducted at the Department of Psychiatry of the Montreal General Hospital, which had the following objectives:

a) to establish the prevalence of cannabis use in a population of schizophrenics in treatment, and to select subgroups on the basis of the cannabis use status; b) to assess the severity of their clinical condition through objective and quantifiable indicators; and c) to establish the variance of such measures of severity across the different subgroups.

METHOD

From the hospital's medical records, 260 patients were selected who had been receiving services for a minimum of 6 months. That is, those who had been seen regularly since, at least, January of the same year. A total of 137 were interviewed and provided a complete cannabis, alcohol and other drug usage history, as well as a urine sample to be tested for cannabinoids. It was not possible to obtain cannabis data from the remaining 123, as some of them refused to cooperate and the rest had moved outside the hospital's sector, could not be located, were deceased, or had spent time in hospital during the period surveyed.

The sample was selected from all patients who, as of the study period, had been given a working diagnosis of schizophrenia (all conditions classified as "schizophrenic psychoses" in the ICD-9) by their own treating psychiatrists, regardless of any other psychiatric diagnoses they may have had in the past. Their condition as schizophrenics was not independently confirmed; the diagnoses entered in the hospital chart were accepted as valid.

The urine sample obtained at the time of the interview was frozen and stored for a period of a few days to several weeks. Cannabinoids were then measured with "EMIT", a semiquantitative enzyme immunoassay kit. This method requires a minimum of 50 ml of urine and is capable of detecting Δ^9-THC urinary metabolites at a concentration of 20 ng/ml or more (O'Conner and Regent 1981). Only qualitative results were requested.

Three separate cannabis use categories were established on the basis of the information available in the medical record, the report given by the subjects during the interview, and the result of the urine screen: a) Active users: individuals who admitted to having consumed the drug during the previous 6 months, whose medical record contained references to usage during the same period, or whose urine was found positive for cannabinoids; b) Arrested users: all those who reported having used cannabis in the past, who denied any use over the last 6 months, and whose urine test proved negative; c) Never-users: the ones denying any previous experience and having a negative urine screen.

The following criteria were utilized to assess the subject's

clinical condition during the six-month study period:
a) Frequency of service contacts; as per the number of times seen at scheduled appointments or spontaneous visits (e.g. emergency room).
b) Degree of delusional activity; rated as absent (0) transient (1) or continuous (2) according to the number of visits at which the treating psychiatrists recorded observing any form of delusional thought disorder (i.e. ideas of reference or influence, depersonalization, delusional perception, delusions). Only patients whose files contained a minimum of three entries during the period were rated.
c) Degree of hallucinatory activity; (any form of hallucination or perceptual distortion)rated as absent (0) transient (1) or continuous (2) on the same basis as the delusional symptoms.

FINDINGS

This inquiry reveals that the percentage of cannabis users among schizophrenics in Montreal is similar to the one found in the general population of Canada (Health & Welfare Canada 1980). In fact, the rate is slightly higher among patients if the comparison is made between subjects aged 18 to 29 only. But this might be an artifact of sampling and methodology. The general population sample included respondents from rural communities and areas of the country where the use of cannabis is much less extensive than in Montreal; and the urinary screen performed on the schizophrenics may be a more reliable instrument of detection than the self-report questionnaire interview used in the Canadian survey. The comparison, nonetheless, strongly suggests that the use of cannabis is not less prevalent among psychotic patients in treatment than in the community at large. Our findings are in line with observations made on samples of psychiatric populations elsewhere in North America; as equally significant levels of use were found at an acute general hospital unit (Westermeyer and Walzer 1975) and at a psychiatric hospital for more chronic cases (Magliozzi et al. 1983). One interesting feature in the prevalence of THC use in this sample of schizophrenics is the marked drop in the number of current users among the older patients. In the age range 30 to 49, for example, a total of 64% reported having used the drug in the past, but only 6% were still doing it at the time of the study. None of the past-users aged 50 or more admitted to current use. This age-related decline is much steeper in the schizophrenics than in the community at large, and indicates a greater than expected rate of abandonment of the habit among the patients.

Cannabinoids were found in the urine of 17 patients; seven patients were included in the "active users" group on the basis of self-reported information alone, and an additional one because of notes found in the hospital file. It is relevant to point out that among the 25 cannabis-using schizophrenics, only two had any mention of such practice in their medical records.

Table I: Total Sample (N=260)

	Current use (N=25)	Past use (N=51)	No use (N=61)	Use unknown (N=123)
Mean Age	27.3	32.8	45.7	35.5
Sex				
M %	80	66	47.5	49.5
F %	20	34	52.5	50.5
Years in treatment (average)	6.1	9.3	12.9	9.0

Slightly over 18% of the subjects whose cannabis use status could ascertained fall in the category of current users; an additional 37.2% had used cannabis in the past but abandoned the habit prior to the last six months. It is clear that active users are to be found mostly among the younger schizophrenics; in that tendency, this sample of psychotics does not differ from the general population. It is also evident that schizophrenic males are overrepresented in the cannabis-using categories, this time in a higher ratio than could be expected (i.e. in the total sample males outnumber females 1.5 to one; among cannabis users the ratio is 2.7 to one).

Never-users are, in the average, more than 10 years older than the other two groups; factor that explains why they had been under psychiatric care for a longer time. Duration of treatment is defined here as the total number of calendar years elapsed from the time the patients were first seen at a psychiatric facility; regardless of the actual date of onset of their illness and of the periods of remission that might have existed since then.

Judging by the measures utilized in this study, the clinical condition of schizophrenics appears to vary in accordance with their cannabis use status. The active users' group presents the highest percentage of members who exhibited continuous delusional or hallucinatory activity during the study period. Not surprisingly, it is also the group which required the most intense therapeutic intervention, as suggested by a higher average number of hospital contacts over the same period.

Given the disparity in age, sex distribution and duration of illness, which separates active users from the rest, a number of questions come to mind with respect to these findings. Are cannabis users more symptomatic because of the effects of the drug,

or because of their being at an earlier stage in the course of schizophrenia? (Harrow et al. 1985) Wouldn't a group containing a disproportionately larger number of male schizophrenics score higher in severity of symptoms, regardless of cannabis use? Was there an inter-group difference in the level of pharmacotherapy administered during the study period? Couldn't the difference in severity of symptoms be explained also by an inter-group variance in the prevalence of other toxic habits, such as alcohol, hallucinogen and stimulant use?

An attempt was made at answering these questions by looking at the data from subjects aged 30 years or less only. This sub-sample of 52 schizophrenics contained 19 current cannabis users (au), 21 former users (pu) and 12 never-users (nu). There were no significant inter-group differences in mean age (au:24.6 ± 3.2, pu: 26.1 ± 3.0, nu:25.7 ± 4.1) or average duration of illness (au:4.3 ± 2.7, pu:5.9 ± 3.7, nu:5.1 ± 3.2). However, the variance in measures of severity of illness observed in the total sample, is still present in this group of younger schizophrenics. Both the rating on delusional symptoms (cu:1.36 ± .7, pu:0.85 ± .7, nu: 0.5 ± .6) and that on hallucinations (cu:0.89 ± .8, pu:0.57 ± .6, nu:0.25 ± .4) were significantly higher among patients who used cannabis during the study period (p = .0006 and .04 respectively).

Table 2: Factors accounting for the variance on each indicator; subsample of schizophrenics aged 30 or less (N=52)*

Source of Variance	Delusional Activity	Hallucinatory Activity	Dosage Medication	Number of visits
Age	.73	.73	.91	.84
Sex	.46	.04	.81	.04
Other Substances	.10	.95	.07 •••	.19
Years on treatment	.13	.53	.50	.61
Cannabis use	.03	.02	.15	.05

* Expressed as level of significance (PR >F) on each parameter after correcting for the contribution of the remaining four.

Younger patients, the ones at an early stage of the illness, and those who use other drugs are more frequently reported as being delusional. But the factor that correlates most significantly with delusional activity is the degree of cannabis involvement. This finding indicates that the records of current users contain more mentions of delusions, even when they are older and at a

more advanced phase of schizophrenia, or when they are exempt from other toxic effects.

Curiously, the frequency of hallucinations does not appear to be equally influenced by age, use of other drugs, or duration of illness. It does, however, correlate significantly with degree of cannabis involvement. It would seem also to be dependent on the patient's sex, as hallucinations have been recorded more often in the charts of female schizophrenics than their male counterparts. This finding is interesting in itself and calls for further exploration. (Table 2)

The average amount of neuroleptic medication prescribed during the six-month period did not differ significantly between the three groups (au:2.3 ± 3.0, pu:3.6 ± 3.0, nu:2.0 ± 2.2; these figures represent equivalent mg. of chlorpromazine per kg./body weight per day). But there is a tendency for schizophrenics who use other substances in addition to or instead of THC to be prescribed larger doses (see Table 2).

CONCLUSIONS

Assuming that these were, indeed, bona fide schizophrenics, the first finding is that the ones who reported having sometime used cannabis, tend to cease this practice more readily than users in the community at large. One possible reason is the negative reinforcement effect of experiencing a high frequency of untoward reactions. In our sample, all except 7 of the 76 subjects reporting previous cannabis experience answered affirmatively to a question on the occurence of adverse psychic effects. Another tentative explanation is the alleged existence of a process of progressive desensitization towards the mood altering action of the drug. This phenomenon - not to be mistaken for a build-up of tolerance - was observed by Schneider (1976) in a group of schizophrenics in Germany. Their increasing affective dullness make them lose the ability to experience euphoria. Such a response would greatly diminish the appeal of the drug. Yet another, more likely, explanation, is the fact that chronic schizophrenics tend to become socially withdrawn. Giving up the habit may be just one among the many adjustments imposed on them by an increasingly deprived existence.

Those schizophrenics who were using cannabis during the observation period appeared to display a more symptomatic clinical condition. But such association may simply indicate that the sicker patients are the ones who tend to use drugs in the first place. The design of this study does not permit to rule out such a possibility categorically. However, the fact that schizophrenics who abandon the habit show less psychotic activity than the ones who continue using the drug, suggests that selectiveness of users is certainly not the only factor at play. (see Table 3)

Table 3: Average values on each indicator according to cannabis use status, and corrected for other sources of variance.*

Cannabis Use Status	Delusional Activity	Hallucinatory Activity	Number of visits
Current users	1.51	0.99	8.9
Never users	0.75	0.24	4.6
Former users	1.15	0.68	6.0
	p = .0307	p = .0271	p = .0532

* Expressed as Least Squares means (SAS General Linear Models Procedure)

Three other major explanations may be proposed for the findings: a) Cannabis causes an actual worsening of schizophrenic symptoms due to its disorganizing effects on psychic function, b) Cannabis causes a toxic psychosis which blends with the schizophrenic symptomatology and makes it appear more pronounced, c) Cannabis neutralizes the therapeutic action of antipsychotic medication. Of course, these explanations are speculative and need to be properly tested. Nevertheless, they are consistent with the ones reported recently by Knudsen and Vilmar (1984). The use of cannabis does appear to adversely affect the clinical condition of schizophrenics. Psychiatric practitioners are alerted to the clinical importance of these findings.

REFERENCES (List available from senior author)

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A Stage Model of HTLV-III LAV Infection in Intravenous Drug Users

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INTRODUCTION

Intravenous (IV) drug users are the second largest group of persons who have contracted the acquired immunodeficiency syndrome (AIDS)(1). The virus believed to cause AIDS--human T-cell lympotropic virus type III/lymphadenopathy associated virus (HTLV-III/LAV)--has been isolated and tests for the presence of antibody to HTLV-III/LAV are now commercially available. Clinical interpretation of the "meaning" of HTLV-III/LAV seropositivity among IV drug users is complicated by scarcity both of longitudinal data on persons exposed to the virus and information about the hallmarks of the early stages of infection, the multiple effects of virus upon the imnme system, and immunologic change due to IV drug use in the absence of HTLV-III/LAV. (2-7).

We report here evidence for a cumulative order in lymphocyte abnormalities among persons with antibodies to HTLV-III/LAV. The abnormalities include a reversed T4/T8 ratio, and low counts of T4 (helper) cells, total lymphocytes and B cells. These abnormalities are cumlative in that a person who has any specific abnormality will typically have all of the preceding abnormalities in the order. The order generates a model for the stages of HTLV-III/LAV infection progression and provides a scale that is potentially useful for assessing the severity of infection at a single point in time.

METHODS

Subjects. Primary subjects were 270 IV drug users recruited with informed consent from drug detoxification and methadone maintenance programs in New York City during 1934. All had injected drugs (primarily heroin and cocaine) within the previous five years. At the time of entry into the study, none of the subjects had sought treatment for either AIM or AIDS related complex (ARC). They participated with informed consent and full assurances that participation or refusal to participate would not affect their status within the drug treatment program. Information on drug use and symtoms consistent with AIDS related complex (ARC) in the previous five years was gathered by interview. A 25 ml blood sample was also collected.

Twenty-nine IV drug users who met the Centers for Disease Control surveillance definition for AIDS and who were seen at our participating hospitals were used as additional subjects.

Laboratory Studies. Complete blood counts and determinations of lymphocyte subsets were done on 5 ml aliquots of whole blood at the New York City Department of Health laboratory within six hours of blood drawing. Lymphocyte subsets were determined using the tile blood method of Reinherz and Schlossman (8) with monoclonal antibodies OKT3 OKT4, OKT8 (Ortho) and B1 (Coulter) and a Coulter EPICS C flow cytometer.

Presence of antibody to HTLV-III/LAV (CDC 451) was treasured with an enzyme linked immmosorbent assay (ELISA) developed at the Centers for Disease Control. Immnoglobulins were quantitated at Beth Israel Medical Center with a rate nephelameter (Beckman) using anti-IgG, anti-IgA, and anti-IgM (Beckman). Serun beta-2 microglobulin was measured at the Manhattan Veteran's Administration Medical Center using a microtiter enzyme linked immunosorbent assay developed there (9).

RESULTS

Immulogic differences. Table 1 presents immmologic variables for the HTLV-III/LAV antibody seropositive and seronegative IV drug users and the IV drug using AIDS patients. The elevated lynphocyte counts and immunoglobulin levels in the seronegative IV drug users are consistent with findings for IV drug users prior to the AIDS epidemic (6,7).

Multiple statistically significant differences were found between the HTLV-III/W seronegative and seropositive groups. The seropositive group was intermediate between the seronegative group and the AIDS patients for T4/T8 ratio, T4 cells, total lymphocytes, B cells, and serum beta-2 microglobulin. The T8 cell count, however, was higher in the seropositive group than in either the seronegative group or the AIDS patients. These multiple differences led us to look for an underlying pattern that would organize the immunologic data of the seropositive IV drug users.

CUMULATIVE LYMPHOCYTE ABNORMALITIES-METHODS

To examine the possibility of an underlying pattern, we focused on the lymphocyte variables that appeared to decline monotonically from the seronegative to the seropositive to the drug using AIDS patients: T4/T8 ratio, total lymphocytes, T4 cells, and B cells.

We first dichotunized these variables into "normal" versus "abnormally low" values. A value of less than 1.0 for the T4/T8 ratio has been frequently used as abnormally low in AIDS research, and was used here. By this criterion, 23% of the semnegative IV drug users had an abnormally low ratio, presumbly due to factors other than HTLV-III/LAV infection.

There are no generally accepted definitions of abnormal values for IV drug users on the other lymphocyte variables. The elevated values in seronegative IV drug users indicated some provision for background drug injection would be needed in determining what should be considered "abnormal." We defined the bottom 5% of the semnegative IV drug users as being "abnormally low" for lymphocyte, T4 and B cell counts. By this criterion, absolute cell counts per microliter were categorized as abnormally low when equal to or below 1745 for total lymphocytes, 491 for T4 cells, and 73 for B cells.

Guttman scalogram analysis (10-12) was used to test for a cumulative order among these lymphocyte abnormalities in 123 IV drug users who were not heavy users of alcohol.[1]

CUMULATIVE LYMPHOCYTE ABNORMALITIES-RESULTS

Table 2 presents the sequential and cumulative immuologic abnormalities in order of frequency in the population, the number of scaling errors associated with each abnormality, and the percentages of persons with the different scale scores. (Scale scores 0 through 4 represent the number of cumulative abnomalities.)

The triangular pattern of positive signs seen in Table 2, representing sequential and cumulative abnormalities within a population, is the essential concept of Guttman scaling. Almost 90% (110/123) of the subjects conformed perfectly to this scale. The coefficients of reproducibility and scalability exceeded the conventional criteria (.90 and .60 respectively) for accepting the existence of a Guttman scale within a dataset. The scale scores are significantly related to each component abnormality, but are not determined by any single component. The highest correlation between the scale and any of its component variables was a correlation of -.75 with absolute T4 cell count. Thus, only 56% of the variance in the scale scores can be attributed to variation in the T4 cell count. This scale of cumulative immunologic abnormalities then represents the multiple abnormalities associated with HTLV-III/LAV infection rather than only a single effect. Approximately one third of the seropositive IV drug users had no lymphocyte abnormalities, another third had only a reversed T4/T8 ratio, and the final third had multiple lymphocyte abnormalities.

Table 3 presents the mean values for lymphocyte subsets, immunoglobulins and serum beta-2 microglobulin by the different scale scores for the 110 seropositive IV drug users who confomed perfectly to the Guttman scale. As expected, those in the first category of the scale (no lymphocyte abnormalities) do not differ significantly on any of the imnmologic variables from the seronegative IV drug users for whom data were presented in Table 1. The rise in T8 cell count that was inferred from the statistically significant differences in Table 1 contributes to the first lymphocyte abnormality (a T4/T8 ratio less than 1.0). T8 cell counts then decrease monotonically with additional abnormalities.

Serum IgG and serum beta-2 microglobulin increase markedly with the decrease of T4 cells to an abnormally low level. Since neither of these two variables was used in the Guttman scaling, we compared them across all levels of lymphocyte abnormalities. Duncan nultiple range tests showed the 0 and 1 abnormality groups to be significantly less than the 2,3 and 4 abnormality groups for IgG ($p<.001$), and the 0 abnormality group to be less than the 2,3 and 4 abnormality groups for serun beta-2 microglobulin ($p<.001$).

The presence of ARC symptoms was also significantly higher among the groups with 2 or more lymphocyte abnormalities ($p<.01$ by chi square). The seropositive groups with 0 and 1 abnormality did not differ from the seronegative IV drug users in frequency ARC symptoms, with 60% reporting at least one ARC symptom. Weight loss (of 10 lbs. or more) was the most common symptom, occurring in approximately 80% of the subjects with sympotoms in all groups.

We next applied the scaling technique to 29 IV drug users with AIDS from our participating hospitals. One of these drug users had Kaposi's sarcoma as the

initial AIDS diagnosis; the rest had opportunistic infections. The same order of abnormalities was found, and 26 of the 29 conformed perfectly to the scale.

We am currently prospectively following the sample of 123 IV drug users from Table 2. Within the first year, 2 of then were diagnosed with AIDS; both came from the group of subjects with scale scores of 4 at the time of the first blood sample.

DISCUSSION

The cumulative nature of the order and the relationship between increasing abnormalities and surveillance definition AIDS strongly suggests that the pattern is associated with increasing severity of HTLV-III/LAV infection. The appearance of the different lymphocyte abnormalities may be conceptualized in terms of different stages in progressive HTLV-III/LAV infection.

The first abnormality in the order, a reversed T4/T8 ratio, reflects changes in the relative distributions of lymphocyte's subsets without an overall loss of peripheral blood lymphocytes. The elevated T8 cell count associated with the reversed ratio is also seen in responses to other viruses, such as Epstein-Barr virus (13) and cytomegalovirus infections (14), and need not be considered as representing seriously impaired immune function.

The second abnormality, a low T4 count, is associated with reduction in all lymphocyte subsets, changes in serum IgG and beta-2 microglobulin, and a marked increase in symptoms consistent with AIDS related complex. These multiple changes suggest that the appearance of this abnormality reflects major deterioration in immune function.

The appearance of a low total lymphocyte count and a low 8 cell count am associated with further decreases in T4 cells and with increasing likelihood of opportunistic infections.

For seropositive persons who conform to the scale, the lymphocyte abnormality scale integrates the many immune system changes associated with HTLV-III/LAV into a single measure of severity that can be used to monitor change over time. Calculatiom of the scale score is a simple matter of counting the abnormalities and should be readily understood by patients. The scale can also be used in the interpretation of ARC symptoms among seropositive IV drug users. ARC symptoms in those with 0 or 1 abnormality very likely stem from causes other than HTLV-III/LAV infection, while symptoms in persons with 2 or more abnormalities are likely to be related to HTLV-III/LAV and deserve whatever aggressive treatment is available.

It should be emphasized that the scale measures HTLV-III/LAV infection severity at a single point in time; it does not imply that the disease will necessarily progress in any individual. Additional research is being conducted to determine transition probabilities and risk factors for movement between scale categories and to determine the probabilities of developing surveillance definition AIDS.

FOOTNOTE

[1]Heavy alcohol use appears to alter relationships among lymphocyte subsets in IV drug users with antibody HTLV-III/LAV, particularly the relationship between T4 cells and B cells. This alteration will be the subject of a separate report.

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REFERENCES:

1. Center for Disease Control. Personal communication, July 22, 1985.
2. Barre-Sinoussi, F., Chermann, J.C., Rey, F., et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983; 228:868-71.
3. Lane, C.H., Masur, H., Edgar, L.C., et al. Abnormalities of B cell activation and immunoregulation in patients with the acquired immuno-deficiency syndrome. N Eng J Med 1983; 309;453-458.
4. Ed Sadr, W., Stahl, R.E., Sidhu, G., Zolla-Pazner, S. The acquired immunodeficiency syndrome: laboratory findings, clinical features, and leading hypotheses. Diag Immunol 1984; 2:73-85.
5. Prince, H.E., Moody, D.J., Shubin, B.L., and Fahey, J.L. Defective monocyte function in AIDS: evidence form a monocyte-dependent T cell proliferative system. J. Clin Immunol 1985; 5:21-25.
6. Kreek, M.J., Dodes, L., Kane, S., et al. Long term methadone maintenace therapy: effects on liver function. Annals of Internal Medicine 1972; 77:598-602.
7. Cushman, P., Persistent increased immunoglobulin M in treated narcotic addiction. Journal of Clinical Immunology 1973 52:122-128.
8. Reinherz, E.L., Kunz, P.C., Goldstein. G., Schlossman, S.F. Separation of functional subsets of human T cells by monoclonal antibody. Proceedings of the National Academy of Sciences, 1979; 76: 4061-4065.
9. Zolla-Pazner, S., William, D., El-Sadr, W. et al. Quantitation of Beta-2 microglobulin and other immune characteristics in a prospective study of man at risk for AIDS. Journal of the American Medical Association 1984; 251:2951-2955.
10. The Statistical Analysis System (SAS), SAS Institute, Cary, N.C.
11. Guttman, L., 1974. The Basis for Scalogram Analysis, in Scaling: A Source Book for Behavioral Sciences, Chicago: Aldine, 142-171.

12. Menzel, H., A new coefficient for scalogram analysis. Public Opinion Quarterly 1953 17:268-280.
13. DeWaele, M., Thielemans, C., Van Camp, B. Characterization of immunogulatory T cells in EBV induced infectious mononucleosis by nonoclonal antibodies. New England Journal of Medicine 1981 304:460-462.
14. Hirsch, M.S., Feldenstein, D. Cytomegalo-virus induced immunosuppression. Annals of the New York Academy of Sciences 1984 437:8-15.

Table 1. Means for immunologic variables by HTLV-III/LAV antibodies among New York drug detoxification and methadone patients and AIDS IV.

	HTLV/III/LAV Antibody Negative	HTLV-III/LAV Antibody Positive	IV drug users with AIDS
Total Lymphocytes	2910	2617	942*
B Cells	314	225	32*
T4 (Helper Cells)	1099	790	59*
7% (Suppressor Cells)	890	1084	551*
T4/T8 ratio	1.39	0.87	.14*
IgG	1636	2175	2146*
IgG	247	269	456
IgM	327	369	266
Beta-2 microglobulin	2.79	3.59	6.11*
Approximate number of cases	110	160	29

Galls are in absolute nurbers per microliter, immunoglobulins in milligrams per 100 milliliters, and beta-2 microglobulin in milligrams per liter. Differences of means (t) test was used to test for significant differences between antibody negatives and antibody positives with probability level of .05; significant differences are indicated by an asterisk (*) in the column for HTLV-III/LAV antibody positive data. For beta-2 microglobulin, N=32 for antibody negatives and N=47 for antibody positives. N for the AIDS IV drug using cases is 23 for immunoglobulins and 13 for beta-2 microglobulin.

Table 2. Lymphocyte Abnormality Pattern
Among IV Drug Users with HTLV-III/LAV Antibody

Abnormality Present*					Distribution of	
T4/T8 Patio	T 4 cells	Total Lymphocytes	B cells	Scale Score**	Scale Number	Scores Percent
-	-	-	-	0	38	31%
+	-	-	-	1	40	33
+	+	-	-	2	20	16
+	+	+	-	3	14	11
+	+	+	+	4	11	9
Percent with Abnormality	66	31	24	16		
Scale Errors***	5	7	6	8		

*Abnomel values are T4/T8 ratio less than 1, T4 count less than 492 cells per microliter, total lymphocytes count less than 1746 cells per microliter, and B cell count less than 74 cells per microliter. See text for derivation.

**An individual's "scale score" is simply his or her number of abnormalities.

*** The "scale errors" associated with a given abnormality are the responses that do not conform to the triangular + pattern in the table. Them are a total of 123 responses for each item (1 per subject). Thus the responses of 5 subjects to the first abnormality would have to be changed to make all 123 subjects conform on this item.

Table 3. Means on Immunologic Variables by Cummulative Lymphocyte Abnormalities Among 110 HTLV-III/LAV Antibody IV Drug Users

	Number of Abnormalities				
	0	1	2	3	4
T4/T8 ratio	1.54	.59	.39	.54	.43
T4 cells	1.54	813	396	332	265
Lymphocytes	3048	3126	2178	1414	1256
B cells	346	255	202	135	48
T8 cells	854	1498	1081	696	670
IgG	1704	1847	2866	2882	2883
IgA	266	267	284	260	323
IgM	383	397	343	366	429
Beta-2 microglobulin	3.1	3.3	4.1	3.9	4.0
% with ARC symptom	63	58	92	86	90

Cells are in absolute numbers per microliter; immunoglobulins in milligrams per 100 milliliters; Beta-2 microglobulin in milligrams per liter.

Effects of Cocaine on Pregnancy Outcome

Ira J. Chasnoff, William J. Burns, Sidney H. Schnoll, and Kayreen A. Burns

In conjunction with the increased use of cocaine in the United States, there has been growing concern regarding potential efffects on pregnancy, the fetus and the newborn infant. The number of cocaine-using pregnant women presenting to the Perinatal Addiction Project of Northwestern Memorial Hospital has escalated dramatically in the last two years, providing an opportunity to evaluate the effects of cocaine on this population.

SUBJECTS AND METHODS

From January 1983 to September 1984, 23 infants were born to cocaine-using women enrolled in the Perinatal Addiction Project of Northwestern Memorial Hospital's Institute of Psychiatry and Prentice Women's Hospital and Maternity Center. All of the women were enrolled by the second trimester of pregnancy and completed a course of intensive prenatal care. Maternal urine samples and breathalyzer tests were obtained on a regular basis in order to screen for illicit drug and/or alcohol use. In order to specifically evaluate the effects of cocaine on pregnancy and the newborn, the cocaine-using women were divided into two groups based on concurrent use or nonuse of narcotics, and were compared to two control groups. One control group was selected from the population of the Perinatal Addiction Project representing methadone-maintained patients who did not abuse cocaine, and the other control group was selected from nonaddicted pregnant women presenting for prenatal care at the Prentice Ambulatory Care clinic. Both control groups were matched for maternal age, gravidity and cigarette and alcohol use.

Women in Group I (N=12) conceived while on cocaine. These women had no history or evidence of opiate use, but four women used alcohol at least twice monthly and six used marijuana at least three times monthly through the first two trimesters of pregnancy. Seven women smoked cigarettes throughout pregnancy. Women in Group II (N=11) conceived while using both cocaine and heroin. Two of these women used alcohol at least twice monthly and five used marijuana at least three times monthly through the first two

trimesters of pregnancy. Eight women smoked cigarettes throughout pregnancy. Upon admission to the project, each woman in Group II was placed on a regimen of low-dose methadone maintenance which, by the beginning of the third trimester, ranged from 5 to 45 mg per day (mean=21.8 mg). The methadone dose was held at the same level for the duration of the pregnancy. Approximately 60% of women in each of Groups I and II continued to use cocaine throughout pregnancy.

Women in Group III (N=15) were opiate-abusing women selected from the pool of women enrolled in the Perinatal Addiction Project; selection was based on the previously mentioned criteria (age, gravidity , cigarette, marijuana and alcohol use). Group III women conceived while addicted to heroin and were converted to methadone maintenance in the same manner as described for Group II women. The mean dose of methadone for these women was 17.3 mg per day, with a range from 5 to 40 mg per day. Three of these women used alcohol at least twice monthly and seven used marijuana at least three times monthly during the first two trimesters of pregnancy. Eleven women smoked cigarettes throughout pregnancy.

Group IV women (N=15) were a group of nonsubstance-abusing women selected from a population in a general prenatal care clinic. Despite their lack of involvement in the Perinatal Addiction Project, four of the women had evidence of alcohol use and two women used marijuana in the first two trimesters of pregnancy. Ten of these women smoked cigarettes throughout pregnancy.

Reproductive histories of all women were reviewed. The addicted women in Groups I, II and III had used drugs during all previous pregnancies. Analysis of variance and Chi-square analysis were utilized for statistical analysis of the maternal parameters which would affect neonatal outcome.

All neonates were examined at birth when weight, crown-to-heel length and fronto-occipital head circumference were recorded. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) (Brazelton 1968) was administered at three days of age by trained examiners who were blind to the infants' prenatal history. Neonatal data were analyzed utilizing a four-way analysis of variance. For those items which reached statistical significance ($P<.05$), the Multiple Range Test was utilized to identify differences between subsets.

RESULTS

There were no statistical differences between any of the four groups as to mean maternal age (25.4, 28.7, 25.4 and 26.1 years, respectively). Groups I (5 white, 5 black, 2 Hispanic), II (5 white, 6 black), III (11 white, 3 black, 1 Hispanic) and IV (4 white, 10 black, 1 Hispanic) were similar as to race (Chi-square analysis). The incidence and distribution of alcohol, marijuana and cigarette use in the four groups was statistically similar (Chi-square analysis), and there was no significant difference between Groups II and III in mean daily methadone dose in the third trimester.

All four groups of women were similar as to gravidity, with means of 2.6, 2.8, 3.0 and 2.5 pregnancies, respectively. However, there was a significantly increased rate of spontaneous abortions in previous pregnancies among the cocaine-using women (ANOVA, F=4.98, P<.005). Group I women had a spontaneous abortion rate of 37.6% (mean spontaneous abortions .98, S.D. 1.1); Group II women's rate was 46.4% (mean spontaneous abortions 1.3, S.D. 1.2) and Group III women's rate was 15.7% (mean spontaneous abortions .47, S.D. .9). There was no history of spontaneous abortions in Group IV women. In the present series of pregnancies under study, two women in Group I and two women in Group II had onset of labor with abruptio placentae in the third trimester, immediately following intravenous self-injection of cocaine,

All infants were delivered at term gestation as determined by the criteria of Ballard et al. (1977). All infants were singleton, and there was an even distribution of infants by sex in each group. Apgar scores in the four groups were similar. One infant with "prune belly syndrome" including major malformations of the genito-urinary tract, bilateral hydronephrosis and bilateral cryptorchidism was delivered to a woman in Group I who had used 4 to 5 grams of cocaine in a single day at 5 weeks gestation and had had no other cocaine use until the third trimester. No other congenital malformations occurred in any infants in any of the groups.

Although infants delivered to methadone-maintained women in Groups II and III tended to be smaller, there were no statistical differences in birth weights, lengths or head circumferences among infants in the four groups (Table 1).

TABLE 1. Growth Measurements of Newborns*

	I	II	III	IV
	Cocaine	Cocaine & Methadone	Methadone	Control
Weight (gm)	3168±508	3127±363	2977±715	3372±624
Length (cm)	49.8±1.9	49.4±2.2	48.6±3.1	50.8±2.9
Head circumference (cm)	33.4±1.9	33.3±1.3	32.9±2.2	34.5±1.7

*Values are mean±S.D.

On the BNBAS, using the a priori cluster method of Als (1978), the 47 scores of each infant's BNBAS were grouped into four dimensions, and ANOVA was used to compare mean differences in each dimension for the four groups of infants (Table 2). Significant differences were found in the interactive (F=3.6, P<.02) and state organization (F=4.4, P<.01) dimensions. Multiple internal comparisons revealed that methadone-exposed infants performed significantly worse on the interactive dimensions than did control infants (P<.05). Infants of cocaine-dependent mothers performed significantly worse on the state organization dimension than both methadone and control infants (P<.05).

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TABLE 2. Brazelton Dimensions

	I		II		III		IV	
	Cocaine		Cocaine I Methadone		Methadone		Control	
	X	S.D.	X	S.D.	X	S.D.	X	S.D.
Interactive	2.8	.4	2.5	.7	2.9*	.4	2.1	.9
Motoric	2.3	.5	2.4	.7	2.1	.3	1.9	.4
State Organization	2.4†	.5	2.1	.4	1.9	.3	2.0	.2
Physiological	1.0	0	1.0	0	1.0	0	1.0	0

ANOVA
Significant difference from Group IV (Multiple Range Test, $p<.02$)
Significant difference from Groups III and IV (Multiple Range Test, $p<.02$)
δAll physiologic cluster scores all within the normal range, and there was no variation.

By one month of age, two cocaine-exposed infants in Group I had died; the first infant died at two weeks of age with a diagnosis of Sudden Infant Death Syndrome and the second infant with meningitis which had its onset at approximately one week of age. There were no deaths during the neonatal period in any of the other groups.

DISCUSSION

With the growing use of cocaine in the United States, it can be assumed that a large number of women have used cocaine while pregnant. Although there are conflicting reports of cocaine's teratogenicity in animal studies (Mahalik et al. 1980; Fantel and Macphail 1982), the effects of cocaine on pregnancy in the human have not been previously studied.

The cocaine-using women in the present study had a higher rate of spontaneous abortions than even women who had used heroin during previous pregnancies. Cocaine acts peripherally to inhibit nerve conduction and prevent norepinephrine reuptake at the nerve terminals, producing increased norepinephrine levels with subsequent vasoconstriction, tachycardia and a concomitant acute rise in blood pressure (Ritchie and Greene 1980). Placental vasoconstriction also occurs (Sherman and Gautieri 1972), decreasing blood flow to the fetus. An increased frequency of uterine contractions in humans has been reported (Weiner 1980). The increased rate of spontaneous abortions found in cocaine-using women in Groups I and II would be consistent with these pharmacologic actions of cocaine.

In the third trimester of pregnancy, several women in Groups I and II reported feeling contractions and increased fetal activity within minutes of using cocaine. Four women in these two groups experienced onset of labor with abruptio placentae immediately following self-injection of cocaine. The hypertension and vasocon-

striction associated with cocaine use most likely induced the abruptio placentae, a predictable outcome given the association between acute hypertension and abruptio placentae (Pritchard et al. 1978).

The occurrence of prune belly syndrome in an infant whose mother used a heavy dose of cocaine at 5 week s gestation is consistent with the report of Mahalik et al. (1980), who found an increased incidence of cryptorchidism and hydronephrosis when cocaine was administered to gravid mice on any of days 7 to 11 of gestation. At 5 week s gestation, the urogenital system is forming in the human (Arev 1974), and a heavy dose of a teratogenic agent as reported by this woman could interrupt mesodermal development and produce the abnormalities noted (Petersen et al. 1972).

No interference with intrauterine growth was noted in either of the cocaine-exposed groups of infants. This is consistent with reported growth patterns of other nonopiate-exposed infants (Chasnoff et al. 1982; Chasnoff et al. 1983). The occurrence of Sudden Infant Death in one infant from Group I raises the question of increased risk of SIDS for infants exposed in utero to cocaine. Although an increased risk of SIDS has been reported for infants born to narcotic-addicted women (Chavez et al. 1979), larger numbers of cocaine-exposed infants will need to be followed before the risk of SIDS for this group can be ascertained.

Previous reports on differences in neurobehavior detected by the BNBAS between drug-free infants and infants delivered to methadone-maintained women (Chasnoff et al. 1982), women who used phencyclidine during pregnancy (Chasnoff et al. 1983) and women addicted to pentazocine and tripelennamine during pregnancy (Chasnoff et al. 1983) have shown consistent patterns of depressed interactive behavior and state control among the drug-exposed neonates. This was confirmed by the findings on the state organization cluster which showed significant impairment in organization abilities in infants whose mothers used cocaine as compared to control infants or to infants whose mothers used methadone. It is evident from this that cocaine exposure in utero significantly interferes with an infant's ability to maintain adequate state control in the neonatal period, a factor which places cocaine-exposed infants in a category of high risk similar to infants exposed to narcotics in utero.

Although the cocaine/methadone Group II infants showed weaker reflexes and poorer state control than the control infants in Group IV, they displayed no significant deficits in auditory or visual orientation. This lack of significant deficits in orientation responses among the Group II cocaine/methadone-exposed neonates is surprising. The use of ethanol, marijuana and nicotine was similar in all four groups and, therefore, probably does not account for these findings. It is possible to speculate that with the Group II infants being exposed to both a CNS depressant (methadone) and a CNS stimulant (cocaine) in utero, there was an interaction resulting in each of the drugs antagonizing the effects of the other. Whether or not these effects occur in the fetus or neonate is currently unknown. In addition, the dosages of the drugs used,

frequency of use, contaminants used to adulterate the street drugs abused and other factors may be significant in relation to their effects on fetal and neonatal development.

It is apparent from the present study that cocaine exerts an influence on pregnancy outcome as well as neonatal neurobehavior. There is also the possibility from the present data that cocaine-exposed infants are at risk for a higher rate of congenital malformations and perinatal mortality. Continuation of these studies is necessary to verify the current findings and to determine if there are other problems associated with cocaine use during pregnancy.

REFERENCES

Als, H. Assessing an assessment: conceptual considerations, methodological issues, and a perspective on the future of the neonatal behavioral assessment scale. In: Sameroff, 0., ed. Organization and Stability of Newborn Behavior: A Commentary on the BNBAS. Monographs of the Society for Research in Child Development. Vol. 43. Chicago: University of Chicago Press for the Society for Research in Child Development, 1978. pp. 14-28.

Arey, L.B. Developmental Anatomy: A Textbook and Laboratory Manual of Embryology. Ed. 7. Philadelphia: W. B . Saunders Co., 1974. pp. 295-313.

Ballard, J.L.; Dazmaier, K.; and Driver, M. A simplified assessment of gestational age. Pediatr Res 1:372, 1977.

Brazelton, T. B . Neonatal Behavioral Assessment Scale. Philadelphia : Spastics International Medical Publications, 1968. pp. 63-64.

Chasnoff, I.J.; Burns, W.J.; Hatcher, R.P.; and Burns, K.A. Phencyclidine: effects on the fetus and neonate. Dev Pharmacol Ther 6:404-408, 1983.

Chasnoff, I.J.; Hatcher, R.; and Burns, W.J. Polydrug- and methadone-addicted newborns: a continuum of impairment? Pediatrics 70:210-213. 1982.

Chasnoff, I.J.; Hatcher, R.; Burns, W.J.; and Schnoll, S.H. Pentazocine and tripelennamine: effects on the fetus and neonate. Dev Pharmacol Ther 6:162-169, 1983.

Chavez, C.J.; Ostrea, E.M., Jr.; Stryker, J.C.; and Smialek. Z. Sudden infants death syndrome among infants of drug dependent mothers. J Pediatr 95:407-409, 1979.

Fantel, A.G., and Macphail, B.J. The teratogenicity of cocaine. Teratology 26:17-19. 1982.

Mahalik, M.P.; Gautieri, R. F.; and Mann, D.E. Teratogenic potential of cocaine hydrochloride in CF-1 mice. J Pharm Sci 69:703-706, 1980.

Petersen, D.S.; Fish, L.; and Cass, A.S. Twins with congenital deficiency of abdominal musculature. J Urol 107:670-672. 1972.

Pritchard, J. A.; Mason, R.; Corley , M.; and Pritchhard, S. Genesis of severe placental abruption. Am J Obstet Gynecol 108:22-27, 1970.

Ritchie, J.M., and Greene, N.M. Local anesthesia. In Gilman, A.G.; Goodman, L. S. ; and Gilman, A., eds. The Pharmacological Basis of Therapeutics. Ed. 6. New York: Macmillan Publishing Co., Inc., 1980. pp. 300-320.

Sherman, W.T., and Gautieri, R.F. Effects of certain drugs on perfused human placenta X: norepinephrine release by bradykinin. J Pharm Sci 61:878-883, 1972.

Weiner, N. Norepinephrine, epinephrine, and the sympathomimetic amines. In Gilman, A.G., Goodman, L.S.; and Gilman, A., eds. The Pharamcological Basis of Therapeutics. Ed. 6. New York: Macmillan Publishing Co., Inc., 1980. pp. 138-175.

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Disparity in Hemispheric and Thalamic Growth in Infants Undergoing Abstinence

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INTRODUCTION

Infants exposed prenatally to narcotic agents become passively addicted in utero and usually undergo Neonatal Abstinence Syndrome (NAS). This syndrome is a generalized disorder characterized by signs and symptoms of central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress, and vague autonomic symptoms which include yawning, sneezing, mottling, and fever. The clinical evaluation and management of neonatal abstinence have been the subjects of several investigations.[1-8] Currently, many investigators are studying whether narcotics (including methadone) taken during gestation can cause irreversible, injurious effects upon the developing nervous system of the fetus and/or the neonate. Preliminary studies by Tenner have demonstrated some abnormalities in the gentricular system of infants born to drug-dependent women.[9] In an earlier cross-sectional study of 59 infants at birth and at one month of age,[10] no statistical differences between the intracranial hemidiameters of NAS infants versus controls were found.

Despite the fact that many investigators have reported that somaticgrowthis retarded in infants exposed to psychoactive drugs, no studies have evaluated rate of brain growth. Studies of brain growth within the first year of life in drug-exposed infants and control infants could provide basic and useful information regarding any possible effects on the brain. Ultrasound measures have been used in previous studies for the measurement of intracranial volume, ventricular size and volume, and cortical mantle thickness.[11-17] Serial ultrasound images of the brain permit the assessment of neonatal regional brain growth with a linear accuracy of 1 to 2mm.

The purpose of the present study was to evaluate brain growth in drug-exposed infants undergoing abstinence in comparison to a control group of non-drug-exposed infants.

MATERIALS AND METHODS

Ultrasound examinations were performed on 52 drug-exposed and 38 control infants. Only infants with repeated examinations at birth, and 1 and 6 months are reported here. They include 22 infants born to women maintained on methadone during

pregnancy and 15 control infants who were studied serially at similar intervals from their early neonatal course to age 6 months. The control infants were a healthy, symptom-free group of infants born to drug-free mothers enrolled in the hospital's regular prenatal clinic. The infants in both groups were full term and the mothers were comparable in age, race and relevant socio-econanic factors.

The mothers of the drug-exposed infants were enrolled in Family Center of the Thomas Jefferson University Hospital in Philadelphia. Family Center is a methadone maintenance program providing medical, psychiatric and social services for pregnant and post partum drug-dependent women and their children. Although the mothers of the study infants were on an average daily methadone maintenance dose of 40mg., almost all used various quantities of heroin, diazepam or amphetamines at least once during pregnancy. Both the study protocol and the consent forms are approved by the Investigational Review Board at Thomas Jefferson University. Informed consent was obtained from all mothers prior to examinations.

Using the Neonatal Abstinence Scoring System,[18] the drug-exposed infants were monitored shortly after birth for signs and symptoms of abstinence. Depending upon the score, pharmacotherapy was administered for treatment of NAS. Doses of medication were adjusted dependent on the severity of the NAS score and maintained until symptoms of abstinence subsided. Of the 22 drug-exposed infants, 17 showed symptoms severe enough to warrant pharmacotherapy. Of these, seven were treated with paregoric, four with phenobarbital and six with a combination of three of the following: paregoric, phenobarbital and diazepam.

PRODEDURE

Ultrasound examinations were scheduled for all infants at 24 and 72 hours following birth, and at 1 month and 6 months of age. Infants were examined by a real-time sector scanner (5MHz., Mark 100 sector scanner, Advanced Technology Laboratories, Bellevue, WA). The sole contact with the infants was the transducer applied lightly to the scalp with water soluble gel as an acoustical coupling agent. Transaxial (transverse) scans through the temporal bone enabled identification of the superior-lateral borders of the lateral ventricles, the intracranial hemidiameter (ICHD), and at a lower level, the thalami. The ICHD was defined as the maximum distance between the midline echo from the interhemispheric fissure and the first echo from the inner table of the parietal bone at the same level.

The maximal cross-sectional area of the left and right thalami were measured as study parameters for sub-hemispheric brain growth. At. 0.5cm. above the cantho-meatal line, the bodies of the thalami are outlined in cross section. For area measurements, areas were obtained by tracing the

outlines on a Graphics Analyzer (Numonics). Increases in the above parameters over the first 1-month and subsequent 5 month period served as indices of cerebral growth.

RESULTS

The drug-exposed infants and the control infants were found to be comparable on mean birth weight (drug-exposed = 2915g; controls = 3057g), length (drug-exposed = 48.5cm,; controls = 50.2cm.), gestational age (drug-exposed = 38.7 weeks; controls = 39.1 weeks), and head circumference (drug exposed = 33.8cm.; controls = 34.1cm.) The figures for the control infants were slightly, but not significantly higher on all four measures.

Comparisons of the thalamic areas (TA), ICHDs and HCs revealed no statistically significant differences between Family Center and control groups, with the exception of ICHD at one month; ICHDs of the controls were found to be greater ($p = < .01$) [see Table I]. These findings parallel the overall results when the two populations are analyzed in a cross-sectional manner, that is both groups of infants compared at each examination date.[10] Although statistical significance was not reached in the majority of measurements, the Family Center infants did show smaller brain growth measures both at birth and atonemonth. The HC and TAs were larger in Family Center infants by six months of age, whereas the ICHDs were not.

However, when actual growth patterns over the six-month period were analyzed longitudinally for each of the two groups of infants, significant differences in growth between Family Center and control infants became apparent. During the first month, contol infants had a greater rate of growth for both the right ($p = < .05$) and the left ($p = < .05$) TA and ICHDs ($p = < .05$), but not in HC [see Table II]. During the remaining five months, the Family Center infants showed greater growth of the thalami ($p = < .001$) and HC ($p = < .05$). Between one and six months of age, the rate of thalamic growth for drug exposed infants more than doubled that of the controls, resulting in larger thalami at six months, with HC also somewhat greater [see Tables].

When examining the general overall brain growth during the first six months of life, only the growth of the ICHD in drug exposed infants was not greater than in the controls. Measurements in the infants undergoing abstinence were smaller at birth and smaller in growth during the first month; however, there was then an exaggerated occurrence of growth of the TAs and HCs in drug-exposed infants by six months of age. The drug-exposed infants had caught up with, and in many cases, even surpassed the control group.

This is in direct contrast to the somatic growth pattern which was compared and analyzed longitudinally in both groups of infants. During the first month, the drug-exposed infants

(slightly smaller at birth) experienced more rapid growth in weight (664gms. vs. 353gms. - controls) and length (5.0cm. vs. 1.4cm. - controls). During the remaining 5 months, their growth then slowed considerably in both weight (3.73gms. vs. 4442gms. - controls) and length (7.5cm. vs. 9.5cm. controls). Mean weight gain in 6 months totaled 3837 grams for the drug-exposed infants and 4795 for the control infants; total mean gain in length was 12.5 and 11.1cm. respectively.

No increase in the incidence of hemorrhage, structural abnormalities or dampened arterial pulsations was noted. One infant in each of the groups was classified as intrauterine growth retarded (IUGR) by the Lubchenco newborn maturity and classification chart of birth weight versus gestational age.[19]

DISCUSSION

This study attempted to elucidate subtle effects of maternal opiate intake on the perinatal and neonatal brain. Though not statistically significant, all measurements studied were smaller for infants undergoing abstinence when measured at birth and at one month. A significant rebound effect has been shown in the measurements of the TA and the HC. Statistical significance was demonstrated when analyzing the degree of brain growth of the drug-exposed infants during the first month of life and in the following five months, and then comparing those figures to the growth of the controls during the same time. Family Center infants began life with smaller brain measurements, although not to a significant degree. Their brain growth was less during the first month (while undergoing abstinence); however, during the remaining five months they surpassed the control group in growth. It cannot be ascertained from the existing data exactly at what point in time this occurred, but by six months of age, this brain growth and change were evident. These findings suggest a depression of growth of the central nervous system in infants undergoing abstinence, possibly related to the maternal intake of opiates during gestation. Also, these changes in brain growth were independent of the accelerated (first month) and slowed (last five months) somatic growth pattern.

REFERENCES

1. Kandall, S.R., and Gartner, L.M. Late Presentation of Drug Withdrawl Symptoms in Newborns. Am J. Dis Child 127:58-61, 1972.

2. Rajegowda, B.K.; Glass, L.; Evans, H.E.; Maso, G.; Swartz, D.P.; and Colbanc, W. Methasone Withdrawl in Newborn Infants. J Pediatr 81:532-534, 1972.

3. Kron, R.E.,; Litt, M.; and Finnegan, L.P. Behavior of Infants Born to Narcotic Addicted Mothers. Pediatr Res

7, 1973.

4. Finnegan, L.P.; Emich, J.P.; and Connuauhton, J.F. Abstinence Score in the Treatment of the Infants of the Drug Dependent Mother. Int J Clin Pharm Thera Toxicol 10:139, 1974.

5. Kaplan, S.L.; Kron, R.E.; Phoenix, M.D.; Litt, M.; and Finnegan, L.P. Correlations Between Scores on the Brazelton Neonatal Assessment Scale: Measures of Newborn Sucking Behavior and Birth Weight in Infants Born to narcotic Addicted Mothers. Pediatr Res 8:344, 1974.

6. Kron, R.E.; Litt, M.; and Finnegan, L.P. Effect of maternal Narcotic Addiction on Sucking Behavior of Neonates. Pediatr Res 8:346, 1974.

7. Rosen, T.S., and Pippenger, C.E. Disposition of Methadone and its Relationship to Severity of Withdrawl in the Newborn. Presented at the NIDA Perinatal Research Conference, Nashville, Tennessee, September, 1974.

8. Kron, R.E.; Kaplan, S.L.; and Finnegan, L.P. The Assessment of Behavioral Change in Infants Undergoing Narcotic Withdrawl: Comparative Data From Clinical and Objective Methods. Addict Dis 2:257, 1975.

9. Tenner, M.S. Unpublished Data, 1976.

10. Pasto, M.E.; Graziani, L.J.; Leifer, B.; Tunis, S.L.; and Finnegan, L.P. Brain Growth in Infants Exposed to Psychoactive Drugs In Utero. Pediatr Res 17:1677, 1983.

11. Galentneky, C.L. and Kazner, E. Echoencephalography in the Diagnosis of Ventricular Dilatation. In: Proceedings in Echoencephalography, New York: Springer-Verlag, Berlin-Heidelberg.

12. Lombroso, C.T., and Erba, G. Two-Dimensional Ultrasonography For Visualization of Ventricular Landmarks. In: Proceedings Echoencephalography, New York: Springer-Verlag, Berlin-Heidelberg.

13. Kossoff, G.; Garrett, W.J.; and Radavonovich, G.; Ultrasonic Atlas of Normal Brain of Infant. Ultrasound in Med and Biol. 1:259-266,1974.

14. Leas, RF.; Harrison, R.B.; and Sims, T.L. Gray Scale Ultrasonography in the Evaluation of Hydrocephalus and Associated Abnormalities in Infants. Am J Dis Child 132:376-378, 1978.

15. Skolnick, M.L.; Rosenbaum, A.E.; Matzuk, T.; Guthkelch, A.N.; and Heinz ER: Detection of Dilated Cerebral Ventricles in Infants: Correlative Study Between Ultrasound and Computed

Tomography. Radiology 131:477, 1979.

16. Babcock, D.S.; Han, B.K.; and LeQuesne, G.W. B-Mode Gray Scale Ultrasound of the Head in the Newborn and Young Infant. AJR 134:457-468, 1980.

17. Dewbury K.C., and Aluwihare, A.P.R. The Anterior Fontanelle as an Ultrasound Window for Study of the Brain: A Preliminary Report. Brit J Radiology 53:81-84, 1980.

18. Finnegan, L.P. (ed.) Drug Dependence in Pregnancy: Clinical Management of Mother and Child. A Manual for Medical Professionals and Paraprofessionals Prepared for The National Instituteon Drug Abuse. Services Research Branch, Rockville, Maryland, US Government Printing Office, Washington, D.C., 1978.

19. Lubchenco, L.C.; Hansman, C.; and Boyd, E. Classification of Newborns Based on Maturity and Intrauterine Growth. Pediatr 37:403, 1966.

TABLE 1. *Family Center and control infants: brain scan measures at 24/72 hours, 1 month and 6 months*

Brain Measurements	Family Center (n=22)	Controls (n=15)	T-test p-value
R. Thal (mm^2)			
24/72 hrs	226.3	242.7	> .40
1 month	304.0	337.5	< .10
6 months	433.3	384.5	< .10
L. Thal (mm^2)			
24/72 hrs	230.7	238.8	>.20
1 month	304.0	329.3	.06
6 months	420.6	383.4	< .10
ICHD (mm)			
24/72 hrs	34.3	35.3	>.20
1 month	38.3	41.5	< .01*
6 months	46.9	49.0	< .10
HC (cm)			
24/12 hrs	33.8	34.1	>.30
1 month	36.4	37.2	>.20
6 months	42.9	42.1	>.20

*Significant at $p \leq .05$ on t-test for differences between means

TABLE 2. *Brain growth of Family Center and control infants between birth and six months of age*

Brain Measurements	Family Center (n=22)	Controls (n=15)	T-test p-value
R. Thal (mm^2)			
0-1 mos	77.7	94.8	< .05*
1-6 mos	129.3	47.0	<.001"
Total- 0-6 mos	207.0	141.8	< .01*
L. Thal (mm^2)			
0-1 mos	73.3	90.5	< .05*
1-6 mos	116.6	54.1	< .OO1*
Total - 0-6 mos	189.9	144.46	< .03*
ICHD (mm)			
0-1 mos	4.0	6.2	< .05*
1-6 mos	8.6	7.5	n.s. [1]
Total - 0-6 mos	12.6	13.7	n.s.[1]
HC (cm)			
0-1 mos	2.6	3.1	n.s.[1]
1-6 mos	6.5	4.9	< .05*
Total - 0-6 mos	9.1	8.0	n.s. 1

*Significant
[1]Not Significant

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Naloxone-Precipitated Withdrawal in Humans After Acute Morphine Administration

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Acute antagonist sensitivity, also known as acute physical dependence, refers to the precipitated opioid withdrawal symtoms (abstinence syndrome) that result from the administration of an opioid antagonist several hours after a single administration of an opioid agonist (Martin & Eades, 1961). This phenonanon is quite remarkable since the precipitated withdrawal response which characterizes physical dependence is generally thought to develop only after prolonged opioid agonist exposure. Animal laboratory studies have found that acute antagonist sensitivity is a measurable and robust phenomenon with dogs, monkeys, and rodents (Smitts, 1975; Martin & Eadas, 1964). Further, comparisons in the animal laboratory of acute and chronic physical dependence have found them both to be characterized by similar signs and symtoms (Martin & Eadas, 1964). This similarity suggests that acute and chronic opioid exposure may represent the beginning and ending points in the continuous process of physical dependence development.

There have been a few non-systematic demonstrations of acute antagonist sensitivity in man. For example, acute antagonist sensitivity was clearly documented in a study by Nutt and Jasinski (1974) in which postaddicts received methadone-naloxone mixtures given at weekly intervals. They found that-the second administration of the mixture significantly increased withdrawal scores. Jones (1979) also demonstrated the phenomenon when naloxone (.14 or .28 mg/kg, iv.) was administered to normal volunteers 24 hours after an injection of morphine (.14 mg/kg or .21 mg/kg, im.). Jonas reports that the symtoms following naloxona administration were qualitatively similar to those obtained in opioid-dependent individulas during withdrawal. Additional studies are needed to systematically characterize the pharmacology of acute antagonist sensitivity in man in order to understand it's relationship to chronic dependence. The present study is a beginning in that direction.

The purpose of the present study was to characterize the acute withdrawal symptoms, objective signs and physiological responses precipitated when non-dependent post-addicts receive naloxone six hours after an injection of morphine and to demonstrate a morphine dose-response function.

METHODS

Subjects: The participants were three adult male post addicts who reported prior narcotic addiction of 2 to 8 years, previous participation in methadone main-

tenance and detoxification programs, and continued sporadic use of opioids (twice a week or less), but who were not currently addicted. Subjects gave written informed consent, were paid for their participation and lived on a eight-ted inpatient research unit throughout the study. In order to verify the absence of current addiction the subjects were observed for withdrawal symptoms during the three days they lived on the ward prior to the start of the study.

Drugs: Morphine doses as salt were at 1, 3, 5.6, 10, and 17 mg, and the naloxone challenge dose was 10 mg. Doses were given under double-blind procedures in a constant volume of 1 ml subcutaneously in the right or left arm.

Procedures: In this study, subjects were exposed to six morphine doses in an ascending followed by a descending sequence. The ascending dose sequence was used in this pilot study because we were unsure of the severity of the withdrawal reaction. Subject safety was assured with the ascending dose sequence because marked withdrawl signs would result in the omission of scheduled higher doses.

Subjects participated in twelve sessions, each composed of two parts, a morning session (A.M. session) in which mophine or morphine placebo was administered and an afternoon session (P.M. session) in which naloxone was administered. Two or three sessions were conducted per week with a minimum of 48 hours intervening. Sessions began by connecting the subjects to a recording device and allowing the physiologic measures to stabilize for approximately 20 min. During this twenty-minute interval a baseline pupil photo was taken, subjective reports we completed, and objective signs of withdrawal were observed. Baseline measures were then recorded for the last 10 min. Approximately 30 min after starting the session the subject received a drug injection. During the morning sessions, physiologic measures were continuously monitored for 3 hours post injection with pupil photographs taken, subjective forms completed, and observations for objective signs of withdrawal made every thirty minutes. Completion of this cycle of measures took from five to seven minutes. At the conclusion of the three hours the subject was returned to the ward. Five and a half hours after the morphine or morphine-placebo injection, subjects were brought back to the experimental room, and baseline measures ware again obtained. Six hours after the morphine injection the subject received a 10 mg injection of naloxone and was monitored for the next 75 minutes. During the afternoon session, the measurement battery of pupil photographs, subjective reports, and observation of objective signs of withdrawal was administered every 15 min.

Measurement: Two physiologic measures were recorded continuously throughout each session: (1) skin temperature, by a thermister on the tip of the middle finger and (2) respiration, by a thermister held by a clip on the left nostril. Air moving across the thermister resulted in cooling, thereby activating a Schmitt trigger and recording a respiration. All signals were amplified on a Beckman polygraph and stored and summarized on a PDP 8 minicomputer. Pupil photographs were taken in ambient room lighting (approximately 1 foot candle) using a polaroid camera with a 3X magnification. At each measurement point, subjects filled out opioid symptom and withdrawal symptom questionnaires. Each of these was composed of twenty items which described typical opioid effects (e.g., nodding, skin itchy) and common withdrawal symptoms (e.g. painful joints, hot or cold flashes, irritable). Subjects marked on a ten point scale from 0 = not at all to 9 = extremely, the extent to which they currently experienced each symptom. Subjects also marked 5 visual analogue scales (10 am) to indicate drug effect,

drug liking, "good" drug effects and "bad" drug effects and subjective "high"; each line was anchored with "not at all" on one end and "extremely" on the other.

In order to quantify the presence of specific opioid withdrawal signs, observations of the subject were taken by a research technician who was continuously present in the experimental room. Observer ratings consisted of a modified Himmelsbach (1939) with each of six signs being rated by the observer on a 4 point scale (0 = absence of the sign, 1 = slight, 2 = moderate, and 3 = extreme). The following signs were observed: (1) lacrimation (tearing) was rated by inspecting the subject's eyes while moving the lower eyelid up and down; (2) rhinorrhea (runny nose) was rated by listening for fluid sounds while the subject blew out one nostril while blocking the other; (3) perspiration was rated by the amount of wetness when touching the subject's forehead, palms and armpits; (4) piloerection (gooseflesh) was rated by obsewing the skin reaction when the observer lightly dragged his or her finger across the inside of the subject's forearm and stomach; 5) yawning was rated by obsewing its presence or absence during the observation period; (6) restlessness was rated by visually obsewing the frequency of the seat movements. A composite score was calculated by adding together the scores obtained for the various signs.

Data analysis. Measures analyzed included pupil diameter, respirations per minute, skin temperature, total score on the opiate and withdrawal symptom questionnaires, visual analogue scale scores, and the composite score from the observer rating of withdrawal sings. Initial data analyses used average scores across two observations in each subject (ascending and descending function which did rot differ significantly). The last 10 min of data collected prior to drug administration sewed as the baseline for the two continuously monitored physiologic measures.

Dose-effect analysis used data from the first fifteen min post naloxone since this appeared to be peak effect for measures which showed time course, particularly obsewer ratings. A repeated measures analysis of variance (ANNA) was conducted to assess overalls significance. Effects were considered statistically significant at $P < 0.05$.

RESULTS

Although we were prepared to terminate subject's participation with the occurrence of, marked withdrawal signs, this proved to be unnecessary. All subjects were able to tolerate the naloxone effects. Figure 1 shows dose effect functions for selected physiological, subjective reports, and obsewer rating measures. Pre-naloxone pupil diameter (Figure 1, top panel) showed a dose related decrease at 6 hours after morphine with residual pupil constriction especially apparent after the 10 and 17 mg dose. Naloxone administration increased pupil diameter to placebo levels. A similar effect was seen with respiration. The middle panel of Figure 1 shows the effects of naloxone (as a function of morphine pre-treatment dose) on the withdrawal questionnaire. Withdrawal scores increased in an orderly dose-related fashion when naloxone was preceded by morphine doses from 3 to 17 mg. Significant treatment effects were obtained with the withdrawal questionnaire ($F = 4.08$; $df=5, 10$; $P < 0.05$). The bottan panel of Figure 1 shows the effect of naloxone (as a function of morphine pretreatment dose) on the composite observer rating score of objective withdrawal signs. The composite score shows orderly increases in obsewer rated signs related to the preceding morphine dose. Significant treatment effects were obtained with the composite score at 15 min

post naloxone (F - 8.1, df=5, 10; P < 0.01). Individual withdrawal signs that shared dose-related increases included lacrimation, perspiration and rhinorrhea.

DISCUSSION

This study showed that precipitated withdrawal sighs can be obtained in post-addict males following brief exposure to morphine and extends prior work by demonstrating dose-related effects. This finding suggests that precipitated withdrawal is specifically related to the presence of opioid agonists in the body. The signs and symptom appeared similar to those observed after chronic opioid exposure including subjective reports of discomfort and observable withdramwal signs. The physiologic measures, however, primarily showed reversal of the morphine effect with no apparent rebound above baseline levels. This may be a difference between withdrawal seen after brief and chronic opioid exposure (e.g., Martin & Eades, 1964).

Physical dependence is one factor which tends to Perpetuate compulsive drug use and addiction and is thus an important component of drug abuse liability (e.g., Dole & Nyswander, 1980). Physical dependence is revealed by the characteristic physiological and behavioral sighs that occur after the discontinuation of a chronically administered substance (Jasinski 1977; Martin & Eades, 1964). Illuminating the mechanisms of opioid physical dependence and the variables that modulate it may result in a better understanding of compulsive drug use and the design of better treatments. One approach to the study of physical dependence would be the examination of acute antagonist sensitivity reactions which may represent the incipient stages of opioid physical dependence.

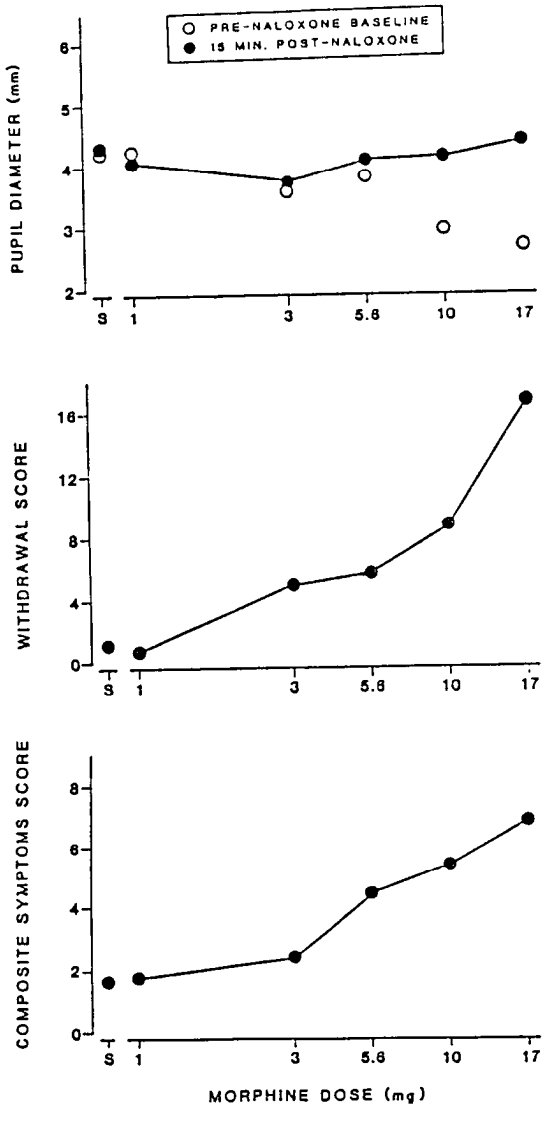

Figure 1. The effect of naloxone on pupil diameter (top panel), withdrawal symptom questionaire (middle panel), and observer rated withdrawal signs (bottom panel) as a function of morphine pretreatment dose. In the top panel the open circle with the horizontal line represents the P.M. (pre-naloxone) baseline and the closed circle represents the effect obtained 15 minutes post naloxone administration In the bottom two panels the data are taken from measures obtained 15 min post-naloxone administration. Saline is indicated by S.

REFERENCES

Dole, V.P. & Nysvander, M.D. (1980). Methadone maintenance: A theoretical perswrscective. In D.J. Lettieri, M. Savers, & H. Wallenstein- Pearson (Eds.). theories of drug abuse: Selected contemporary perspectives. NIDA Monograph 30. DHHS Publications No. (ADM) 80-907. Washington, D.C: Supt. of Doc., U.S. Govt. Print off. pp. 256-261.

Jasinski, D.R. (1977). Assesment of the abuse potential of morphine like drugs (methods used in man). In Martin, W.R. (Ed.). Drug addiction I. Handbook of experimental pharmacology, p. 197-258.

Jones, R.T. (1979). Depandence in non-addict humans after a single dose of morphine. In E. Leong Way (Ed.), Endogenous and exogenous opiate agonists and antagonists. New York: Pergamon Press, p. 557-560.

Martin, W.R., & Eades, D.G. (1964). A comparison between acute and chronic physical dependence in the chronic spinal dog. Journal of Pharmacology and Experimental Therapeutics, 146: 385-894.

Nutt, J.G. & Jasinski, D.R. (1973). Methadone-naloxone mixtures for the use in methadone maintenance programs. I. An evaluation of their pharmacological feasibility. II. Demonstration of acute physical dependence. Clinical Pharmacology and Therapeutics, 15: 156-166.

Smiths, S.E. (1974). Quantitation of physical dependence in mice by naloxone-precipitated jumping after single dose of morphine. Research Communications in Chemical Pathology and Phamacolocgy, 10: 651-661.

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Marijuana Effects and Behavioral Contingencies

Richard W. Foltin: Marian W. Fischman, Margaret J. Nellis, Daniel J. Bernstein, Maria R. Ruiz, and Joseph V. Brady

Kelatively few studies have manipulated any environmental features during periods of repeated daily marijuana smoking in a controlled laboratory. Some of these have shown that monetary contingencies maintain behavior well despite the intoxicating effects of tne drug (Mendelson et al., 1976; Miles et al., 1974). Although the use of money to maintain work performance approximates job conditions, this single powerful contingency may also override the potential sensitivity of other behavioral measures to drug effects.

The present research extends the study of the effects of marijuana intoxication to a residential setting that permits both controlled drug administration and measurement of a wide range of activities in a naturalistic setting. Specialized programming features of the laboratory permit the arrangement and systematic manipulation of relationships between subject behaviors and environmental resources. The interactions between smoked marijuana and performance of a number of structured tasks were studied in the presence and absence of behavioral contingency requirements. During the contingency periods, access to empirically determined high probability activities was contingent upon the performance of empirically determined low probability activities. Thus, high probability behavior was used to reinforce performance of low probability behavior. The effect of this contingency arrangement was determined under placebo, marijuana, and no smoking conditions.

METHOD:

Subjects. Nine healthy adult male volunteers ranging in age from 26 to 43 participated in three long-term residential experiments. Three of the subjects participated in Experiment 1 as "no-smoking" controls. Five of the six subjects in Experiments 2 and 3 (placebo and marijuana smoking) had histories of daily marijuana use, while the sixth smoked 2-3 times weekly. Subjects received extensive medical and psychiatric examinations prior to

research participation and signed consent forms which provided a detailed explanation of the experimental procedure.

Laboratory. The studies were conducted in a self-contained, human residential, programmed laboratory environment which has been previously described in detail (Brady et al., 1975). The three identical private rooms (2.5 x 3.4 x 2.4 m) are similar to small efficiency apartments containing kitchen and bathroom facilities, bed, desk, chair, and other furnishings. The social living area (4.3 x 6.7 x 2.7 m) is equipped with tables, chairs, sofa beds, and a complete kitchen facility. The workshop (2.6 x 4.1 x 2.7 m) contains an exercise area and a washer-dryer combination. A common bath serves the social living area and the workshop. Access to the exterior walls of the laboratory is provided by a corridor between the residential chambers and the external ouilding shell that permits transfer of supplies and materials through two-way storage facilities accessible from both sides.

One subject resided in each of the three efficiency apartments and all had access to other areas at programmed times. All subjects remained within the residential laboratory environment throughout the duration of the study. A networked computer system with terminals in each room provided all contact between subjects and experimenters. Subjects were monitored from an adjacent control room using an extensive video and audio monitoring system and a computerized behavioral observation program (Bernstein & Livington, 1982).

Standard day. The day consisted of three sections: a private work period, a performance test, and a period of social access. Subjects were awakened at 09:00, ate breakfast and had a work period from 10:00 to 14:30. During the work period subjects were required to remain in their private rooms and engage in one of the four performance tasks. These were a computerized vigilance task, a computerized digit-symbol substitution task, a manual latchet rug hooking task, and a manual word list alphabetizing task. Subjects were tested in a performance battery from 15:00 to 16:00 and had access to the social area for the remainder of the day. The day ended at 24:00.

Procedure. The design for the work period portion of each of the three experiments is presented in Table 1. All studies consisted of baseline and contingency periods, while Experiments 2 and 3 involved placebo and marijuana cigarette smoking superimposed on these conditions. During baseline conditions ("B" - Table 1), subjects-performed one-of-four work tasks in the absence of restrictions. Each behavioral activity was monitored continuously via the computerized observational system and time spent in each activity was recorded for each subject. The resultant time-based behavioral hierarchies determined the contingency conditions ("C" in Table 1) during which subjects had to spend time doing the least preferred work activity in their hierarchy in order to earn time to engage in their most preferred work activity. A contingency relationship was determined for

Table 1

EXPERIMENTAL DESIGNS

Experiment 1

Day	1 2 3 4 5	6 7	8 9 10 11	12 13 14
Condition	B_1	B	C	B

Experiment 2

Day	1	2 3 4 5 6	7 8 9 10 11 12	13 14 15
Drug	none	placebo	marijuana	placebo
Condition		B	C	B

Experiment 3

Day	1 2	3 4 5	6 7 8	9 10 11 12 13 14	15 16 17	18 19 20 21 22 23	24 25
Drug	none	placebo	marijuana	placebo	none	marijuana	none
Condition		B		C	B	C	B

B_1 = Work and individual activities until 16:30 : Individual and social activities PM (Baseline)

B = Work activities until 16:30 : Individual and social activities PM (Baseline)

C = Contingency

each subject using the response-probability procedure of Premack (1965). This required that subjects engage in four times the amount of their least preferred baseline activity (the instrumental activity) in order to maintain baseline levels of their most preferred activity (the contingent activity).

A ratio of time spent in the contingent activity (most preferred work activity) to time spent in the instrumental activity (least preferred work activity) was calculated. Thus, if during the baseline conditions a subject spent 30% of his time alphabetizing words and 5% of his time engaged in the vigilance task, the ratio would be 30:5. This baseline ratio was then multiplied by 1/4 to yield the contingency ratio - in this case 1.5. Thus, this subject would be required to engage in the instrumental (vigilance) task for one minute in order to earn a minute and a half on the contingent (word sorting) task. In order to regain the baseline amount of time for word sorting (30%), this subject would have to spend 20% of his time performing the vigilance task, i.e., four times the baseline amount.

During contingency periods, lack of availability of the contingent task was indicated by illumination of a red light in each subject's room. Time earned for the contingent task accumulated as time was spent performing the instrumental task. As long as there was time accumulated for the contingent task, each subject could use it as he chose. Time earned was carried over each day for the entire contingency period.

In Experiment 1 (no drugs) a two-day baseline (days 6 and 7) was followed by a four-day contingency and another three-day baseline. In Experiment 2, a five-day placebo baseline was

followed by a six-day marijuana/contingency period and another three-day placebo baseline. In Experiment 3, a three-day placebo baseline was followed by a three-day active drug baseline and two six-day contingency periods during which data were collected under both placebo and active drug conditions. These were separated by a three-day no-smoking baseline period.

Drug administration. Marijuana cigarettes with 0% (placebo) and 1.84% THC concentrations were provided by The National Institute on Drug Abuse. Cigarettes were smoked using an experimenter-controlled uniform puff procedure. After lighting the cigarette, subjects responded to colored stimulus lights signalling a five second "ready" period, a five second period for deep inhalation, a 10 second period to hold the smoke in their lungs, and a forty second period to exhale and await the next puff. Subjects were given three puffs/cigarette in Experiment 3 and five puffs/cigarette in Experiment 2. A cigarette was always smoked prior to the private work period at 10:00. In addition, a cigarette was smoked prior to the performance battery and a final cigarette was smoked during the social access period.

RESULTS

All subjects readily adapted to continuous residence in the programmed environment and followed the protocol accurately. Eight of the nine subjects remained in the programmed environment for the duration of their studies. S2, in Experiment 3, elected to leave on the evening of day 17.

The mean percent total time spent engaging in the instrumental and contingent activities before, during and after the contingency period for all subjects is presented in Table 2. The top three rows are the values derived during the six placebo or no-drug contingency periods and the bottom three rows present the values derived during the five active drug contingency periods.

Table 2

Mean percent total work period spent in instrumental and contingent activities for each subject in each experiment before, during and after placebo and drug contingencies

		#1						#2						#3					
		1		2		3		1		2		3		1		2		3	
		I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
No drug or Placebo	Before	.01	.50	.06	.53	.07	.58							.06	.27	.02	.18	.05	.20
	During	.00	.00	.17	.34	.28	.45							.17	.12	.09	.12	.11	.11
	After	.00	.56	.08	.08	.00	.66							.23	.15	.03	.30	.00	.10
	Before							.01	.60	.05	.52	.06	.36	.01	.15			.01	.24
	During							.48	.04	.16	.30	.14	.05	.13	.02			.05	.04
	After							.01	.42	.03	.43	.00	.28	.04	.18			.00	.00

I = Instrumental task

C = Contingent task

During the placebo and no-smoking baseline work periods all six subjects spent between 1% and 6% of that period engaged in the work task that was later to be designated the instrumental activity. In contrast, subjects spent between 18% and 58% of their work period under this baseline condition engaged in the activity that was to function as the contingent activity during the contingency period. When the contingency period was in effect and active drug was not administered, five of the six subjects increased the time spent engaged in the instrumental activity, resulting in mean instrumental activity levels greater than 3 times the baseline level. The remaining subject, S1 in Experiment 1, engaged in neither the instrumental nor contingent activity. The five subjects who made contact with the contingency all decreased the amount of time spent in the contingent activity, resulting in a mean decrease to three-fifths of baseline levels. When the contingency was no longer in effect, the amount of time spent in the instrumental activity was again at near zero levels for five out of the six subjects and the percentage of time spent in the contingent activity increased above the previous level in four out of six subjects.

When subjects smoked active marijuana during baseline periods, they spent between 1% and 6% of that time engaged in the work task that was later designated the instrumental activity and 15% to 60% of the time engaged in the activity that was to function as the contingent activity. These values are remarkably similar to those obtained during the no drug/placebo baseline periods. When contingency periods occurred after active marijuana was smoked, increases of up to 12 times the baseline instrumental level were observed. This effect is similar to that recorded during non-drug/placebo conditions. In contrast, although the amount of time spent engaged in the contingent activity under the active marijuana condition decreased below baseline in a manner similar to that observed under the no drug/placebo condition, the magnitude of that decrease to approximately one fifth of baseline levels is three times the decrease observed under the placebo/no drug contingency period. Thus, although the temporal distribution of instrumental and contingent activities were similar under drug and non-drug conditions in the absence of a contingency, when the contingency was introduced, the pattern changed. Time spent engaged in instrumental activities increased to a similar extent under both drug and non-drug conditions, but time spent in the contingent activity decreased substantially more after smoking active marijuana. Following the contingency, instrumental activity returned to baseline levels in all subjects, while contingent activity returned to baseline in four of the five subjects.

DISCUSSION

The results of these experiments show clearly that there are interactions between behavioral contingencies and the effects of smoked marijuana upon performance. Introduction of a contingency requiring subjects to increase the amount of time spent in a low probability work activity in order to earn time to engage in a

high probability work activity was effective in modifying patterns of work behavior. Compared to the no drug/placebo conditions, smoked marijuana was associated with a markedly yreater decrease in the use of time earned to perform high probability activities during contingency periods (i.e., reinforcement consumption). This was true despite the fact that the drug had no apparent effect on the time spent engaging in such high probability activities under non-contingent baseline conditions nor upon the increases in low probability activity which occurred under contingent conditions. These latter observations effectively control for nonspecific performance deficits.

Several clinical reports have suggested that chronic marijuana use results in the loss of desire to work and an "amotivational syndrome" (McGlothin & West, 1968; Smith, 1968). Although rndrijuana-intoxicated subjects tend to choose less active behaviors (Babor et al., 1976; Miles et al., 1974), there is little, if any, experimental support for decreased performance of an operant maintained by monetary gain (see review by Miles, 1975). The present findings also indicate that operant performance per se was not impaired by marijuana, although drug did alter the response to the contingency arrangement resulting in suboptimal use of resources. These selective changes in components of a behavioral contingency may be indicative of an "amotivational" effect resulting from repeated use of smoked marijuana, and suggest a possible experimental approach to investigating such drug effects.

Of methodological interest are the findings related to the experimental modifications in patterns of work in response to contingency manipulations. In addition to confirming the results of previous studies (Bernstein & Ebbesen, 1978; Danaher, 1974) which showed that components of a human behavioral repertoire can function to reinforce other components of that same repertoire, the results of the present study extend the generality of these findings beyond self-selected activity preferences to required work performances. The functional analysis of behavioral contingencies under conditions of repeated drug use within Premack's (1965) differential probability formulation could provide a valuable approach to characterizing the behavioral pharmacology of drugs of abuse.

REFERENCES

Bernstein, D.J., and Ebbesen, E.B. Reinforcement and substitution in humans: A multiple-response analysis. Journal of the Experimental Analysis of Behavior 30:243-253, 1978.

Bernstein, u., and Livingston, C. An interactive program for observation and analysis of human behavior in a long-term continuous laboratory. Behavior Research Methods and Instrumentation 14:231-235, 1982.

Brady, J.V., Bigelow, G.E., Emurian, H.H., and Williams D.M. Design of a oroqrammed environment for the experimental analysis of social behavior. In D.H. Carson (Ed.), Man-Environment Interactions: Evaluations and Applications. 7: Social Ecology, tnvironmental Design Research Associates, Inc., Milwaukee, WI, 1975, pp. 187-208.

Uanaher, B.G. Theoretical foundations and clinical applications of the Premack principle: Review and critique. Behavior Therapy 5:307-324, 1974.

Mendelson, J.H., Kuehnle, J.C., Greenberg, I., and Mello, N.K. The effects of marijuana use on human operant behavior: Individual data. In M.C. Braude and S. Szara (Eds.), Pharmacology of Marijuana, Vol. 2. New York: Raven Press, 1976, pp. 643-653.

Miles, C.G., Congreve, G.R.S., Gibbins, K.J., Marshman, J.A., Devenyi, P., and Hicks, R.C. An experimental study of the effects of daily cannabis smoking on behaviour patterns. Acta Pharmacologica et Toxicologia 34:1-44, 1974.

Premack, u. Reinforcement theory. In D. Levine (Ed.), Nebraska Symposium on Motivation. Lincoln: University of Nebraska Press, 1965, pp. 123-180.

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Chronic Naltrexone Effect on Cortisol

Thomas R. Kosten, Mary Jeanne Kreek, Jayanthi Ragunath, and Herbert D. Kleber

Cortisol rises following bolus injections of opioid antagonists (Volavka et. al., 1979; Naber et. al., 1981; Judd et. al., 1981) and falls following acute opioid administration (Cushman and Kreek, 1974). Because low cortisol levels go back up to normal during chronic methadone treatment (Kreek, 1978), we measured cortisol levels during chronic opioid antagonist treatment to assess whether they would remain persistently elevated.

METHODS

Twenty-one former opioid addicts in the Connecticut Mental Health Center Drug Dependence Unit had been taking naltrexone for at least 15 weeks after giving written informed consent (Kosten et al., 1983). They had morning and afternoon cortisol sampling during naltrexone maintenance, and seven had repeat sampling 22 weeks (mean) after stopping naltrexone. Subjects were maintained for a mean of 5.5 months on a three times per week dosing schedule of 100 mg on Monday and Wednesday and 150 mg on Friday. The normative criteria were that the morning cortisol levels should be below 25 µg/dl and that the PM or afternoon levels should be no more than 70% of the AM or morning levels. The 21 former addicts had a mean age of 30 (± 6.3) years, 76% were male and 71% were white. They had been using primarily heroin for a mean of 6.7 years. While taking naltrexone three patients with normal baseline SGOT levels developed elevations in serum SGOT - 69, 81, 89 (nl < 41) and 2 of 3 had SGOT elevations - 303, 305 (nl < 45). Before starting naltrexone two addicts had elevations in SGOTs of 56 and 69; during naltrexone treatment both dropped to normal.

RESULTS

Five of the 21 patients had cortisol levels above the upper limit of normal for our assay (25 µg/dl), although three patients were within the inter-assay coefficient of variation for the upper limit of normal. As a criterion for flattened diurnal variation, we used a difference of less than 30% between the AM

and PM cortisol levels (Doe et at., 1960; Krieger et al., 1971). Using this criterion four subjects had minimal diurnal variation, and their cortisol levels remained at or above 15 µg/dl. In contrast to these relative elevations, two subjects had unusually low cortisol levels, and one of the two also had minimal diurnal variation. For the entire study group the mean AM cortisol level was 20.5 µg/dl and the mean PM cortisol level was 11.1 µg/dl. Using the Critical Ratio Z Test with normative means from the literature (contact authors for references) of 14.4 µg/dl for AM level and 7.8 µg/dl for PM level, the cortisol levels for both AM ($Z=4.5$, $P>0.001$) and PM ($Z=3.2$, $p>0.01$) were significantly higher than normative values.

Five (71%) of the seven subjects who had cortisol levels determined both during and after naltrexone treatment had AM cortisol levels that dropped, and six (86%) of the seven had PM levels that dropped. For all 7 subjects the mean AM cortisol level was 13.7 µg/dl and the mean PM level was 7.5 µg/dl. These values are almost the same as the normals. For the AM cortisols the mean drop was 6.9 µg/dl ($t=1.82$, $p<0.06$), and for the PM cortisols the mean drop was 4.7µg/dl ($t=1.94$, $p<0.05$). The AM levels were positively correlated with the number of weeks since stopping naltrexone ($r=0.7$, $p<0.006$), but PM levels and the change in levels (during minus after naltrexone) were not significantly correlated with time since stopping. The duration of naltrexone treatment, the dosing interval while taking naltrexone, and demographic factors were also not related to cortisol levels.

DISCUSSION

The present study with patients maintained on naltrexone for at least 15 weeks has indicated that for many patients (43%) cortisol levels may be elevated or have relatively high, flattened diurnal variation during chronic naltrexone maintenance. Our mean AM cortisol level (20.5 µg/dl) was significantly above normative means and, interestingly, the same as that reported by Volavka et. al. (1979) in normals following 20 mg of I.V. naloxone (20.5 µg/dl). Four of our 21 subjects had flattened diurnal variation with cortisol levels remaining above 15µg/dl. These relatively high flat levels are similar to the well documented prodrome of Cushing's syndrome (Doe et al., 1960; Krieger et al., 1971; Weitzman et al., 1971) and further suggests that naltrexone may chronically elevate cortisol levels. We used a somewhat more stringent criterion than the usual clinical criterion of a 50% difference between AM and PM cortisol levels, because this clinical criterion was based on 15 to 18 hour differences between samples, and we used only 6 to 8 hours. The usual clinical criteria of 50% difference would have classified many of the subjects with relatively elevated cortisol levels as also having flattened diurnal variation and have increased the number of subjects with flattened patterns to ten.

In a subgroup of seven subjects, whom we were able to reassess after stopping the naltrexone, cortisol levels were significantly lower after it was stopped. Only one subject had flattened diurnal variation, and he was abusing alcohol at the naltrexone-free sampling. Thus, the rise in cortisol levels following acute bolus opioid antagonist administration may be sustained to some degree with chronically administered opioid antagonists.

Since alterations in liver function may alter steroid metabolism, liver enzyme levels were tested on all patients at the time of this endocrine testing. Three patients who had no abnormality before starting naltrexone and no clinical evidence of hepatitis or alcohol abuse developed elevations in their liver transaminases while taking naltrexone. While a higher dosage of naltrexone as used in obesity and Alzheimer studies (150 mg twice daily) has been associated with hepatotoxicity (Allen et al., 1985), and at least one other case of elevated liver enzymes at 50 mg daily has been reported (Rustgi et al., 1985), it is our hope that investigations into questions of dose-related hepatotoxicity can proceed without depriving appropriate patients of the opportunity to use the drug in a prudent and effectively monitored fashion.

REFERENCES

Allen, J.I.; Mitchell, J.; Knopman, D.; Levine, A.S.; and Morley, J.E.: High dose naltrexone and hepatic enzyme abnormalities. Gastroenterology 88, 1646, 1985.

Cushman, P., Jr. and Kreek, M.J.: Some endocrinological observations in narcotic addicts. In: Zimmerman E., and Hurgo, R., eds. Narcotics and the Hypothalamus. Raven Press, New York. 1984.

Doe,R.P., Vennes, J.A. and Flink, E.B.: Diurnal variation of 17-hydroxy-corticosteroids, sodium, potassium, magnesium and creatinine in normal subjects and in cases of treated adrenal insufficiency and Cushing's syndrome. Journal Clinical Endocrinology Metabolism 20, 253-264, 1960.

Judd L.L., Janowsky, D.S., Zettner, A., et. al.: Effects of naloxone-HCl on cortisol levels in patients with affective disorders and normal controls. Psychiatric Research 4, 277-283, 1981.

Kosten, T.R., Jalali B., Hogan I., Kleber, H.D.: Family denial as a prognostic factor in opiate addict treatment outcome. Journal Nervous Mental Disease 171, 611-615, 1983.

Kreek M.J.: Medical complications in methadone patients. Annals New York Academy of Science 23, 2777-2780, 1978.

Krieger, D.T.; Allen, W.; Rizzo, F.; and Krieger, H.P.: Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocr Metab 32, 266-284, 1971.

Naber, D., Pickar, D., Davis, G.C., et. al.: Naloxone effects on beta endorphin, cortisol, prolactin, growth hormone, NVA and MHPG in plasma of normal volunteers. Psychopharmacology 74, 125-128, 1981.

Nugent, C.A., Nichols, T., Tyler, F.H.: Diagnosis of Cushing's syndrome: single dose dexamethasone test. Arch Int Med 116, 172-176, 1965.

Rustgi, V.K.; MaGuire, M.; Wise, T.N.; and Cooper, J.N.: Naltrexone use in the irritable bowel syndrome. Gastroenterology 99, 1563, 1985.

Volavka, J.; Cho, D.; Mallya, A.; Bauman, J.: Naloxone increases ACTH and cortisol levels in man. New England Journal of Medicine, 300, 1056-1057, 1979.

Weitzman, E.D.; Fukushima, D.; Nogeire, C.; Roffwarg, H.; Gallagher, T.F.; and Hellman, L.: Twenty four hour pattern of the episodic secretion of cortisol in normal subjects. Journal Clinical Endocrinology Metabolism, 33, 14-22, 1971

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Nature and Incidence of Conditioned Responses in a Methadone Population: A Comparison of Laboratory, Clinic, and Naturalistic Settings

Anna Rose Childress, A. Thomas McLellan, and Charles P. O'Brien

INTRODUCTION

In the four decades since Wikler's (1948) original observations of opiate withdrawal-like responses in drug-free patients, there has been much study of conditioned withdrawal-like responses in both animals and humans (O'Brien, et al. 1985; Childress et al., 1984; Grabowski and O'Brien, 1980; Sideroff and Jarvik, 1980; Temes, et al., 1979; O'Brien et al., 1977; Teasdale et al., 1973). Given these findings, the existence of conditioned withdrawal-like responses is generally accepted, but the incidence and clinical importance of these conditioned phenomena remains quite controversial. In a recent test of Wikler's notions about the prevalence of these responses and their role in relapse, McAuliffe (1982) interviewed Baltimore street addicts concerning their past experiences with conditioned withdrawal. Of 40 addicts with at least one period of voluntary abstinence outside an institution, only 11 (27.5%) acknowledged an experience with conditioned withdrawal sickness. Even for those 11 patients the symptom were reported as mild and infrequent; only 2 episodes of opiate use and 1 relapse were attributed to symptoms of sickness associated with conditioned withdrawal. Thus, the McAuliffe interviews provide support for the existence of conditioned withdrawal-like symptoms (in some patients), but directly challenge Wikler's notions about their frequency and their importance in drug use/relapse.

Though interesting, the McAuliffe data are limited by their reliance upon the long-term memory and unverifiable self-reports of a population of active street addicts. Such data do, however, underscore the real need for more direct, reliable and controlled measures of these conditioned phenonena and their clinical inpact in a large population sample. To this end, cur research center has developed a set of procedures: 1) To determine the nature and incidence of conditioned phenomena (withdrawal-like, craving, and high-like responses) in opiate-dependent patients; 2) to attempt extinction of these responses; and 3) to examine their postulated role in clinical outcome, including relapse. The results of our early extinction attempts and their impact on clinical outcome are presented elsewhere in this volume (see McLellan et al., 1985). The current paper presents cur findings on the nature and incidence of conditioned opiate phenomena in a large sample of opiate-dependent patients. Measurements were taken from three different sources: 1) the research laboratory, 2) clinic extinction sessions, and 3) real life. These three settings allowed us to compare conditioned opiate phenomena across a wide range of eliciting conditions.

STUDY I - LABORATORY ASSESSMENT

Subject Selection

The subjects or this study ware 77 male patients from the Drug Dependence Treatment Center of the Philadelphia Veterans Administration Medical Center. For this study we selected patients who were either maintained on, or detoxifying from, methadone. Since our pilot work had shown that the presence of methadone (or any opiate) can generally attenuate the expression of conditioned withdrawal-like phenomena, we reasoned that the incidence and intensity of these responses in the methadone population would be a conservative estimate of the frequency of these responses in an abstinent population. Patient volunteers were recruited through contact or referral from their drug counselor. All patients were clinically screened to rule out diagnoses of major thought disorder (schizophrenia) or organic brain syndrome.

Procedures

Patients who met diagnostic criteria were eligible to enter a large scale treatnent-outcome study assessing the clinical impact of extinction on drug use/relapse (see McLellan et al., 1985). As part of the pre-treatnent assessnenteach patient was initially evaluated in a controlled laboratory setting. As our laboratory testing procedures have been detailed in previous Proceedings (Childress et al., 1983, 1984), they only will be summarized here in the interest of conserving space. Briefly, patients were given exposure to both neutral (video; activity) and drug-related (video; cook-up) ritual stimuli while we recorded both physiological and subjective responses. Physiological responses included GSR (an arousal index), peripheral skin temperature, heart rate and respiration. Subjective responses were obtained by asking the patient to rate the degree (on a four-point scale) of high, craving or withdrawal-like feelings experienced during several baseline, neutral and drug-related stimulus periods.

Results

Physiological Measures - Laboratory measures were completed for 65 of the 77 screening candidates. Analysis of variance performed upon the group data (n=65) showed no overall statistically significant effect of interval (neutral versus drug-related stimuli) for either respiration or heart rate. For both GSR (arousal) and skin temperature, however, there was a significant difference between the response to neutra and to drug-related stimuli ($p<.01$). The CGS arousal response to drug-related video was significantly greater than that seen in response to the neutral video ($p<.01$). The arousal response had a short latency of onset (2 to 5 seconds) and generally recovered in about 5 minutes. Skin temperature showed significantly greater reductions to drug-related than to neutral stimuli. The temperature response was longer in both latency and in duration than the GSR (arousal) response -- skin temperature would often begin to decline after a minute or so of the drug video and continue to fall throughout the cook-up ritual and for several minutes beyond. Recovery could take 10 to 15 minutes and for some patients, recovery to baseline had not occurred by the end of the session. Though the overall average decrease in skin temperature to drug-related stimuli was approximately 2.2 C°, this average reflects a wide range of response -- from 'non-responders' (no differential temperature drop) to patients with temperature decrements of 6.6 C° in response to drug-related (but not neutral) stimuli. As shown in Table 1, about 34% of the patients tested showed a greater (by at least 1.6 C°) reduction to drug-related as compared to neutral stimuli.

Approximately one-third of our patients were "non-responders" -- they showed neither a differential arousal nor a differential temperature response to the

standardized drug-related stimuli in our laboratory setting. None of the physiological responses were strongly correlated with each other or with the subjective measures of high, craving and withdrawal.

TABLE 1
INCIDENCE OF HIGH, CRAVING AND WITHDRAWAL-LIKE RESPONSES IN METHANE PATIENTS EXPOSED TO DRUG-RELATED STIMLI

	SUBJECTIVE RESPONSES*			PHYSIOLOGICAL RESPONSES * (Reduction In Skin Temperature)
	High	Craving	Withdrawal	
Laboratory Setting: Pretest (N=25)	.05	.48	.20	.34 (N=65)
Clinic Setting: Extinction Sessions (N = 17)	.32	.50	.41	(Not Measured)
Naturalistic Setting: Weekly Reports (N = 17)	.76	.94	.94	(Not Measured)

*Proportion of patients exhibiting the response.

Subjective Measures - Table 1 shows subjective responding to laboratory stimuli for patients tested (n=25) since our last report (Childress et al., 1984). About 48% of the patients reported increases craving to the standard drug-related stimuli, and 20% reported increased subjective withdrawl. Increased high-like feelings were rarely reported (5%). Correlations subjective reports of high-like, craving and withdrawal-like feelings were consistently low, e.g., patients who reported craving often reported no withdrawal and vice versa (multiple r-. 23).

STUDY II: WITHIN-TREATMENT (EXTINCTION) ASSESSMENT

Subject Selection

Patients who completed the laboratory assessnment and other screening procedures were eligible for random assignment into a treatment-outcome study featuring extinction (repeated exposure to drug-related stimuli) as a clinical intervention. One-third of the eligible patients (n=23) here assigned into extinction treatmerit packages, which were conducted on either an outpatient or an inpatient basis. For purposes of the following observations, we included four pilot patients who here treated in the sane manner as the randomly assigned patients (total n=27).

Procedures

The procedures for our extinction sessions have been fully described in previous Proceedings (Childress et al., 1983, 1984) and will therefore only be summarized here. Briefly, extinction patients were given several hour-long treatment sessions, each comprised of psychotherapy (30 min.), exposure to extinction stimuli (15 min), and finally, relaxation (15 min.). Extinction stimuli included verbal

imagery, tapes, color slide, video tapes, and the handling of drug objects in a cook-up ritual. A fixed trials procedure determined the number of exposures to each stimulus us category; number of sessions varied depending on the protocol (outpatient, 35 sessions; inpatient, 22 sessions) and, of course, the patients' attendance.

Measures - Data for the extinction trials was based on the Within-Session Rating Scale (1982) a quantified subjective report listing 24 withdrawal-like and 24 high-like symptoms. If a patient acknowledged feeling high, craving or withdrawal, the nature and intensity of these feelings were probed by use of the corresponding symptom list. The WSRS was administered at the beginning of the session (baseline), immediately after the presentation of the extinction stimuli (post-stimulus), and at the end of the session (post-relaxation).

Results

Of 27 patients given the extinction package (inpatient or outpatient), 22 patients completed 9 or more extinction trials. The data reported below are used on these 'treatment completers'.

Subjective Craving - As shown in Table 1, about 50% of the patients given extinction reported increases in subjective craving for at least 5 sessions. Since sane of these patients had up to 32 stimulus presentations, some increase in craving could conceivably have occurred by chance, and not due to the drug-related stimli. To examine this possibility, we compared reports of craving in the extinction group with reports of craving the other treatment groups at comparable tine points in the treatment session. The amount of craving experienced by the extinction patients was significantly greater ($p<.001$) than that reported in the other treatment groups who did hot receive exposure to drug related stimuli.

Subjective Withdrawal - Approximately 41% of the extinction patients experienced an increase in Subjective withdrawal-like symptoms for 5 or more extinction sessions. During sessions, patients in the extinction groups reported significantly more withdrawal-like symtoms than patients in treatment control groups who did not receive exposure to drug-related stimuli ($P<.001$). Interestingly, the evocative power of a given stimulus sometimes seemed to interact with the patient's mood and/or cognitive set. For example, patients often responded more strongly to the drug-related stimuli when they were in a negative affective state (anger, anxiety, depression, etc.). Conversely, a cognitive set such as "It's not real dope - I can't get high" tended to reduce craving and/or withdrawal.

Subjective High - Almost one-third of the extinction patients reported an increase in subjective high in response to drug-related extinction stimuli. These resonses were less commonly reported than craving and withdrawal, and they usually faded early in the series of extinction sessions.

STUDY III - NATURALISTIC ASSESSMENT

During thepast year, we have offered outpatient subjects the opportunity to systmatically report episodes of craving and/or withdrawal-like feelings which occurred during the course of their daily activities. Of 21 patients who entered the treabrent-outcm study in the past year, 17 chose to participate in the reports.

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Procedures

Reports of craving and withdrawal were obtained weekly by means of a brief (15 minute) strwtured interview. A trained interviewer documented, among much other information, the intensity of the episodes, the situation in which they cccurred, what the patient felt triggered the feelings, and what he did to cope with them (including drugs used, if any), etc. In a final section of the report, the interviewer and patient selected up to three "probable contributors" to the episode(s) of craving and withdrawal from a 40 factor list. This factor list was divided into four general categories of stimuli; 1) Internal, Non-Drug Related, (anger, etc.), 2) External, Non-Drug Related (fight with spouse, etc.), 3) Internal, Drug-Related (withdrawal, etc.), and 4) External, Drug-Related (sight of pusher, sight of drug paraphernalia, etc.). The patient and interviewer also documented any other contributors which did not fit easily into the four categories and these were noted as other. These same categories of information were obtained with regard to episodes of illicit opiate use. Each weekly interview could could document up to seven episodes of craving and/or withdrawal, and up to seven episodes of illicit opiate use.

Results

The described below are based on 17 patients who represent more than 165 total weeks of study participation. These patients gave weekly reports very regularly, enabling us to document more than 92% of the total tine period. The experiences reported by this group of patients fell into three distinct categories: 1) Episodes of drug craving, (defined as an increased desire to seek/use drugs), 2) episodes of withdrawal-like feelings; and 3) episodes in which craving and withdrawal occurred together. Episodes of high-like feelings (in the absence of actual drug use) were also recorded, but we did not document contributing factors for high-like episodes. These high-like episodes were less common (in total number) than episodes of craving or withdrawal, but the majority of our patients (76%) experienced at least one such episode during the study.

Drug Craving - Nearly all patients (16 out of 17, or 94%) reported episodes of drug craving, either alone or in conjunction with withdrawal-like feelings. More than 75% of the patients sampled reported episodes of drug craving without any withdrawal-like feelings. A total of 97 such craving-alone' episodes were documented, though almost half (48) of these here contributed by a single patient. Overall, the factors most associated with these craving-alone' episodes were the sight/presence of a drug-using friend (cited by 50% of the patients sampled); drug talk (44%); desire for euphoria (44%); the offer of drugs (38%); and depression (38%)

Withdrawal - Again, nearly all (16 of 17, or 94%) of the patients reported at least one episode of withdrawal-like feelings, either alone or in conjunction with craving. About 60% of the patients experienced withdrawal episodes without craving. The factors most frequently reported as contributors to these withdrawal-alone' episodes were physical discomfort, (cited by 38% of the patients), such as fatigue, flu, nausea, a severe cold, etc. and methadone dose 'not holding' (cited by 31%).

Interestingly, the physical illness factors (flu, etc.) often cited as 'contributors' to the 'withdrawal-alone' episodes have symptoms (watery eyes, stuffy nose, nausea, etc.) that resemble opiate withdrawal. For many of our patients, the distinction between opiate withdrawl and these physical illnesses has blurred, such that they mistakenly cross label' one for the other, or even attribute one

to the other, as in, "This flu is really knocking the methadone right out of my body -- I'm really sick..."

It is difficult to determine tither some of the naturally occurring withdrawal-like episodes may have been conditioned in origin. Since these patients we on methadone, 'dose-not-holding' was a ready attribution for any withdrawal discomfort, and may easily have masked the role of triggering stimuli.

Concurrent Craving and Withdraw1 - Ten of the 17 patients (59%) reported episodes in which craving and withdrawal occurred together. This type of experience was reported less frequently than either the 'craving-alone' or 'withdrawal-alone' episodes, totalling 37 episodes for the entire reporting period of 165 weeks. The factors cited for these 'craving-plus-withdrawal episodes were very similar to those reported for withdrawal-alone episodes, with physical discomfort (cited by 70% of the patients) and methadone dose 'not holding' (cited by 40%) heading the list.

Opiate Use - Only 7 of 17 (41%) patients reported episodes of illicit opiate use, totalling 27 episodes for the 165 weeks covered by these interviews. The factors most associated with these episodes of opiate use were drug craving , desire for euphoria, depression and anger. Interestingly, none of the patiesnts reported feelings of withdrawl as a contributor to their opiate use. Comparing the self-reports of opiate use with urinalysis records revealed that some patients had systmetically 'underestimated' their use of illicit opiates. Given the small subject sample and this reporting bias, the contributing factors documented for these episodes may not be generalizable to opiate use by different populations or in different circumstances.

SUMMARY AND DISCUSSION

In general, data from three different eliciting conditions has provided generous confirmation for the existence of conditioned opiate phenomena: 1) A sizeable proportion of our patients experience subjective craving, subjective withdrawal, and withdrawal-like changes in skin temperature, even to standard stimuli in the artificial conditions of a laboratory. 2) In extinction sessions, as stimulus opportunities become more varied and closer to those in the patient's own environment, a larger proportion of patients show increased subjective response. 3) Finally, our weekly report data indicate that conditioned craving is a nearly universal phenomenon in the lives of cur methadone patient population.

Conditioned Withdrawal

These data suggest that it is probably not very meaningful to speak about conditioned withdrawal in the sense of a unitary pattern of responses, both physiological and subjective, which reliably occur together in the same patient to a given set of stimuli. What we see, instead, are a number of different kinds of responses that can occur in different patients at different times to the same external stimuli. For example, one patient may exhibit a strong temperature decrease; another, increased arousal, and yet another, subjective withdrawal symptoms in response to the same set of stimuli. Moreover, with a change in state (mood or cognitive set) the expression,-direction and very nature of all these responses may change. Of course, the dynamic quality of these responses in no hey detracts from their potential significance, but it does suggest that studies addressing conditioned withdrawal employ multiple, and repeated, physiological and subjective measures. Reliance upon the long-term memory of

'untrained' reporters who nay be poor at recognizing/labeling internal states, as in the McAuliffe interviews, could result in an underestimate of the actual incidence of these responses.

Conditioned Craving and Conditioned Withdrawal

Perhaps one of the most infomative aspects of these data was the relative independence of craving and withdrawal. This independent relationship was evident in all three settings -- laboratory, clinic, and real life. Patients would sometimes report intense craving, but no withdrawal-like feelings - or withdrawal, but no craving. Craving seems to be a state of increased motivation or desire for specific drug reinforcer. This desire that may be triggered by withdrawl discomfort, but may just as frequently occur in the absence of any "deficiency" state. In this respect, drug craving seems similar to craving for other reinforcers such as food: we can experience intense desire for an eye-appealing dessert without being 'hungry' -- in fact, he may have just finished a large, satiating meal. Similarly, patients can report strong craving for opiates ('to get higher') even after a large dose of methadone.

It is important to note that just because craving and withdrawal often showed low correlations with our peripheral physiological treasures, this should not be taken to mean that these phenomena have no physiological correlates. On the contrary, there are undoubtedly a host of significant central nervous system events that occur in response to the presentation of our evocative stimuli, but most of these are not accessible to our gross autonomic measures.

Implications for an Abstinent Population

Our study of mehadone patients suggests that conditioned craving and withdrawal-like episodes are not at all uncommon, even in a population whose responses may be blunted or masked by the presence of a chronic opiate. These studies in methadone patients, however, do not permit the best assessment of the clinical significance of these responses, i.e., tither they can trigger relapse to drug use in an abstinent patient. To address this question, we have recenly begun to measure --and extinguish -- these responses in a population of abstinent opiate abusers. Our preliminary findings suggest that, if anything, the incidence of conditioned craving and withdrawl-like responses in abstinent patients is even greater than in the methadone population. Several abstinent patients who have come to our extinction program upon completion of a 30-day terapeurtic community are surprised at their vulnerability when viewing drug-related stimuli. A well-controlled outcome study of abstinent patients who received extinction, now in progress, will help determine the clinical significance of these pervasive conditioned phenomena.

REFERENCES

References are available from the first author on request.

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CSF Endorphins in Chronic Opioid-Dependent Humans

Charles P. O'Brien, Lars Y. Terenius, Fred Nyberg, and A. Thomas McLellan

INTRODUCTION

More than a decade ago, specific opioid receptors (Pert & Snyder, 1973; Simon et al, 1973; Terenius, 1973) and endogenous opioids (Hughes et al, 1975, Pasternak et al, 1975 and Terenius & Wahlstrom, 1975) were discovered. While there has been considerable progress in understanding their distribution, biosynthesis and role in various physiological systems, it is as yet unclear how, if at all, they are affected by opioid tolerance and dependence.

Several studies in human addicts have been conducted although the large number of variables and small sample sizes involved make interpretation of the data difficult. Emrich (Enrich et al, 1983) reported increased beta-endorphin immuno-reactivity in the plasma of addicts in withdrawal. Clement-Jones et al, (1979) found cerebrospinal fluid (CSF) and plasma beta-endorphin activity, but not met-enkephalin, to be elevated during mild withdrawal. In contrast, Ho and colleagues (Ho et al, 1980) found greatly decreased beta-endorphin-like immunoreactivity in plasma from 19 men with unspecified levels of dependence on heroin. Holmstrand et al, (1981) studied CSF of 17 formerly dependent subjects before and three weeks after beginning methadone maintenance. There was great variance in levels at the first tap and some of their subjects showed marked increases in CSF endorphins at the second examination despite their being on methadone.

The radio-receptor assay (RRA) was the assay method used by Holmstrand et al and it was also utilized in the present study and in a preliminary study (O'Brien et al, 1982). It has the potential for identifying all receptor-active material in the sample by measuring the degree to which the unknown endorphin material is active in a test sample of opioid receptors. The major disadvantage of the RRA method is that while total endorphin activity in the sample can be measured, the identity of the substance(s) producing the activity at the receptor is unknown.

METHODS

Subjects - Subjects were 57 male veterans in treatment at the Drug Dependence Treatment Center of the Philadelphia Veterans Administration Medical Center. Sixty percent were black with mean age 32.2, 11.8 years of opioid dependence, including 5.8 years on methadone, modal dose 35-45 mg.

A total of 98 spinal taps were performed on these 57 subjects while they were hospitalized. Subjects were encouraged to participate repeatedly, especially when they made the transition from one stage of addiction to another (e.g. methadone maintenance to detoxification). All subjects were required to provide an observed urine specimen for drug screening prior to the spinal tap. Six of these were positive for illicit drugs. In addition, six subjects who were anxious about the spinal tap procedure were given benzodiazepine medication the night prior to their spinal tap. Subsequently, we and others (Wuster et al, 1980) have seen systematic effects on endorphin levels in subjects receiving benzodiazepines. Therefore a total of 12 specimens were omitted due to pre-tap medication. The remaining 86 samples included in the present analyses were divided into four groups:

Methadone Maintenance (MM) N=29 Subjects were included in this group if the spinal tap had been performed within 30 hours since their last methadone dose and the dose had remained constant for at least one week.

Detoxification (D) N=22 Subjects were included in this group if they were in the process of detoxification and if there had been at least a 30% reduction from their stabilized methadone dose over the preceding week and they had received this reduced dose less than 96 hours prior their spinal tap.

Late Detoxification (LD) (LD) N=4 Four subjects were gradually detoxified and then kept in the hospital opioid free. A spinal tap was performed on the fifth day.

Drug Free - N=22 - Subjects were included in this group if the patient had been detoxified to zero dose and had ingested no methadone or other drug since detoxification. The verified drug-free period prior to the spinal tap averaged 95 days (±58) and a minimum of 31 days drug free.

Naltrexone (NT) N=9 Subjects included in this group had been on 350 mg per week of naltrexone for at least 2 weeks prior to the spinal tap.

Normal Controls (NL) N=38 The results of CSF endorphin analyses from 18 males and 20 females in Sweden were used in this study as a control group. These non-addict subjects were all white, with an average age of 26 and had no history of drug abuse nor any neurological or psychiatric condition.

Spinal Tap Procedure - CSF was obtained between the hours of 0830 and 0950 by lumbar puncture with the patient in the lateral decubitus position. A 22-gauge spinal needle was inserted into L3-L4 after local anesthesia with 2% lidocaine. Sixteen ml of CSF was collected in four tubes, centrifuged in a refrigerated centrifuge and the supernatant was frozen to -60°C.

Assay procedures - After thawing, a four ml portion of the CSF was extracted with methylene chloride to remove methadone and methadone metabolites if present. Samples from subjects receiving. naltrexone were extracted at room temperature because this has been found to be necessary to remove naltrexone metabolites which may interfere with the RRA. Next the extracted sample was separated on a Sephadex G10 column into two fractions (I, II) and then assayed in a mu receptor assay (Terenius 6 Wahlstrom, 1975). The receptor source was highly purified synaptic plasma membranes obtained by sucrose gradient centrifugation from rat brain minus cerebellum. The labeled ligand was ^{3}H-dihydromorphine. Incubations occurred at 25° for 20 minutes. At each experimental occasion, a standard curve with met-enkephalin was included.

RESULTS

Between-Group Comparisons - The mean values (+/- S.D.) for both fractions are presented for all groups in Table 1, with the results of the statistical analyses presented in the last column. Two findings were apparent. First, the three addict groups showed higher mean endorphin levels than the Normal Control group. In the case of Fraction I, all paired comparisons between the addict groups and Normal Controls reached statistical significance ($p<.05$). In the case of Fraction II, paired comparisons showed that the normal control sample differed significantly ($p<.05$) from the detoxification and the drug-free samples, but was not statistically different from the methadone maintenance group. The second finding was that there were no significant ($p>.10$) differences among the three main addict samples (MM, D, DF) for FI and for FII, MM was slightly lower than DF but within normal range. Thus there was no evidence for lowered endorphin levels in addicts as compared to normals; on the contrary, FI was elevated at all stages and FII was elevated in the DF and D stages.

Table II shows several significant correlations between FI values and clinical measures, particularly depressive symptoms. In contrast, no clinical measure correlated with FII.

The analysis of the relationship between the "hours since the last methadone dose" and the Fraction I levels in detoxifying subjects showed that a curvilinear function produced the best explanatory power. The U-shaped curvilinear function is shown in Figure 1 and indicates that the Fraction I values appear to

TABLE 1
Comparison of Endorphin Levels in Addicts and Normal Controls

	MM	D*	LD	DF	NT	NL	ANOVA[1**] (Paired) Comparisons
N=	28	21	4	22	9	38	p =
FI	1.7	2.0	1.8	1.4	1.4	1.1	.02 (NL MM=D=DF)
+/-S.D.	(1.7)	(1.9)		(0.7)		(0.5)	
FII	7.3	10.8	8.4	10.1	32.7	6.2	.04(NL=MM D=DF)
+/-S.D.	(5.8)	(10.7)			(9.4)	(5.1)	

*See Figure 1.

**One-way analysis of variance followed by Duncan's Multiple Range Test for paired comparisons. Late Detox and Naltrexone groups were not included due to small sample size.

Table II
Correlations Between Addiction Status Variables and Endorphin Levels

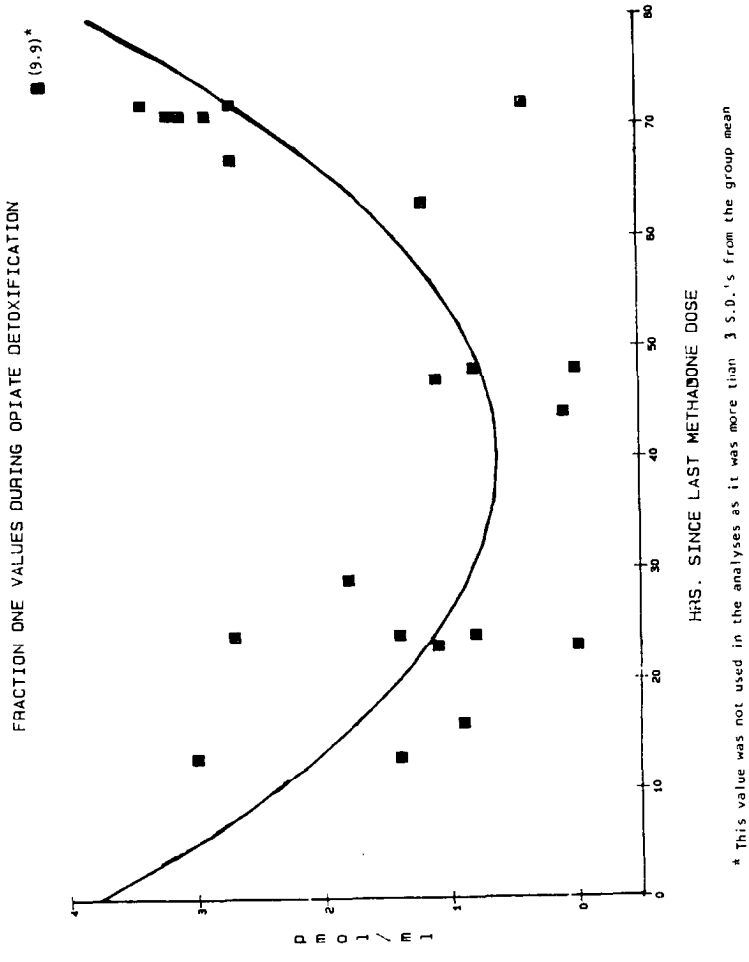
	MM N=29*		D N=22*		DF N=22	
VARIABLE	FI	FII	FI	FII	FI	FII
Age	.15	-.04	.09	-.07	.22	.-33
Race (0 = W, 1 = B)	.14	.06	.07	.20	.25	.07
Years Addicted	.11	.20	.38**	.03	.22	-.20
Mg. Last Meth. Dose	.28**	.20	.22	.05	.00	.04
Hrs. Since Last Meth.	.10	.11	.32**	.21	.01	-.02
Withdrawal responses	.14	.15	.33**	.21	.00	.02
Beck Dep. Inv.	.30**	.37*	.24	.21	.23	.23

*One patient not used because values were three S.D. above mean.

**p .05

drop during withdrawal to below the threshold of the assay (0.4pg/ml) at approximately 35-45 hours following the last dose of methadone. Further, the data indicate that these fraction values increase to a high of approximately 3.5pg/ml by 65-70 hours following the last methadone dose. The curvilinear equation accounts for approximately 43% of variance in the Fraction I values and suggests that time since last methadone dose may be among the most important contributors to the observed Fraction I values in detoxifying patients. It is noteworthy that this relationship was not seen for Fraction II data in this group, suggesting that the two fractions vary independently, during this period, and are likely affected by different variables.

Figure 1



DISCUSSION

This study is, to our knowledge, the largest series of human opioid addicts whose endorphin activity has been measured. In some aspects the results are suprising in that large changes in opioid intake (methadone maintenance state vs drug-free state) are reflected in relatively small changes in CSF endorphins. Clearly there is no evidence for general suppression of endogenous opioid activity as a result of large doses of exogenous opioids.

Of course, the assay method reported here involves total endorphin activity measured in an opioid receptor test system, and perhaps subsequent more specific immuno-assays will show that a specific sub-set of opioid peptides is suppressed by the

dependent state. Also, it is possible that variance will be reduced by examining a single specific endogenous opioid. We plan to perform RIA's for selected peptides in addicted patient CSF as the next phase of this project.

The assays performed on these 57 patients with a mean of more than eleven years of opioid dependence show significant differences from the 38 Swedish normals. The addict patients have small but significantly higher mean endorphin levels than the normals and there is strikingly increased variance in patient groups. The increased endorphin levels are present in drug-free as well as methadone maintained patients, but the large variance prevents a clear interpretation of this increase.

The FI findings in the detoxification group were particularly interesting. As shown in Figure 1, there is an initial decrease in FI endorphins during the first 35-40 hours of withdrawal with an apparent rebound over 40-75 hours. All four subjects studied at 4-5 davs (early drug free) showed values in the normal range suggesting a fall again after 75 hours. FI levels also correlated significantly with severity of withdrawal resnonses. a composite measure of signs and symptoms. These FI changes are unlikely to he a simple stress response because they were not found during alcohol withdrawal (Borg et al, 1982). FII endorphins while generally somewhat elevated did not show a systematic change during withdrawal.

Several interesting clinical correlations with endorphin levels were observed. For maintenance patients, there was a small but significant positive correlation between methadone dose and level of FI. In a feedback system, one would have predicted a negative correlation. Although none of the patients in this study met diagnostic criteria for clinical depression at the time of the spinal tap, the presence of depression in opioid addicts is well documented (O'Brien et al, 1984), and many patients had some depression symptoms. There was a consistent, if modest, relationship between both fraction I and II values and our composite measure of depression, across all addict stages. This was most profound in the methadone maintenance sample where both Fraction I (R=.30) and Fraction II (R=.37) were significantly related to our composite measure of depression symptoms. This correlation is consistent with findings of increased CSF FI in unipolar depressed non-addict patients (Agren & Terenius, 1984).

REFERENCES

Agren, H. and Terenius, L. Depression and CSF endorphins. Psychiat Res 10:303-311, 1984.

Beck, A.T. and Beamesderfer, A. Assessment of Depression. Vol. 7, 151-169. Ed. P. Pichot, Karger: Basel. 1974.

Borg, S., Kvande, H. Rydberg, U., Terenius, L. and Wahlstrom, A. Endorphin levels in human cerebrospinal fluid. Psychopharmacology 78:101-103, 1982.

Clement-Jones, V., L. McLaughlin, P.J. Lowry, G.M. Besser and L.H. Rees. Acupuncture in heroin addicts. Lancet ii: 380, 1979.

Dixon, W.V. and Brown, M.B.: BMDP-79: Biomedical Computer Programs. Los Angeles: University of California Press, 1979.

Emrich, H.M., Nusselt, L. Gramsch, C. John, S.: Heroin addiction: Beta Endorphin Immunoreactivity in plasma increases during withdrawal. Pharmakopsychiatria 16:93, 1983.

Ho, W.K.K., H.L. Wen & N. Ling. Beta endorphin-like immuno-activity in the plasma of heroin addicts and normal subjects. Neuropharmacology 19:117, 1980.

Haertzen, C.A. An Overview of Addiction Research Center Inventory Scales (ARCI). Rockville, MD: NIDA. 1974.

Holmstrand, J., L. M., Gunne, A. Wahlstrom and L. Terenius. CSF-endorphins in heroin addicts. Pharmacopsychiatria 14(4):126-128, 1981.

Hughes, J., T.W. Smith, H.W. Kosterlitz, L. Fothergill, B.A. Morgan & H.R., Morris. Identification of two related pentapeptides from the brain with potent opiate agonist activity. Nature 258:577-579, 1975.

O'Brien, C.P., Terenius, L., Wahlstrom, A., McLellan, A.T. and Krivoy, W.: Endorphin Levels in Opioid-Dependent Human Subjects. Annals NY Acad of Sci 398-378-387, 1982.

O'Brien, C.P., Woody, G.E., and McLellan, A.T.: Psychiatric Disorders in Opioid Dependent Patients. J of Clinical Psych 45(2):9-13, 1984.

Pasternak, G.W., R. Goodman & S.H. Snyder. An endogenous morphine-like factor in brain. Life Sci 16:1765, 1975.

Pert, C.B. and S.H. Snyder. Opiate receptor: Demonstration in nervous tissue. Science 179: 1011-1014, 1973.

Simon, E. J. , J.M. Hiller I. Edelman. Stereospecific binding of the potent narcotic analgesic ^{3}H-etorphine to rat brain homogenate. Proc Natl Acad Sci USA 70:1947, 1973.

Terenius, L. Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fractions from rat brain. Acta Pharmacol Toxicol 33:377-384, 1973.

Terenius, L. and A. Wahlstrom. Inhibitor(s) of narcotic receptor binding in brain extracts and in cerebrospinal fluid. Acta Pharmacol (Kbh.) (Suppl. 1), 33:55, 1974.

Terenius, L. and Wahlstrom, A. Morphine-like ligand for opiate receptors in human CSF. Life Sci 16:1759-1764, 1975.

Wuster, M., T.Duka and H. Herz. Diazepam-induced release of opioid activity in brain. Neurosci. Lett 16:335, 1980.

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Treatment Outcome in Cocaine Abusers

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INTRODUCTION

With the widespread proliferation of cocaine use in recent years, the number of users seeking treatment has increased dramatically. Unfortunately, little has been written about specific treatments for cocaine abuse and few reports of treatment outcome have appeared in the literature (Anker and Crowley, 1982; Kleber, 1984).

We now report treatment outcomes in 63 cocaine abusers who entered our specialized outpatient treatment program at Regent Hospital. The purpose of this study was to access the feasibility and effectiveness of our outpatient treatment model, the Relapse Prevention and Recovery Program (RPR) in a cohort of employed, middle-class cocaine abusers.

METHODS

Patients

The patients were 63 chronic cocaine abusers consecutively admitted to the outpatient RPR program during a 6-month period ending in December 1983. Most were white (94%) males (73%) between the ages of 24 and 40 years (mean 31.5 years) with an average of 15.5 years education. All were employed and most earned over $25,000 per year.

Forty-seven patients (75%) entered the outpatient program with no immediately preceding hospital stay. The remaining 16 patients completed 4-10 weeks of intensive inpatient treatment at Regent or Fair Oaks Hospitals before entering the program for aftercare treatment. Those who required initial hospitalization were typically the more severely impaired abusers with serious drug-related problems including polydrug dependence and medical/psychiatric complications.

Upon entering either inpatient or outpatient treatment, all patients met DSM-III criteria for cocaine abuse. They were using an average of 6.5 grams of cocaine per week (range 1-32 grams/week) resulting in significant disruption of physical, psychological, and social functioning. The preferred method of cocaine use was intranasal in 62% of the cases, freebase smoking in 33%, and intravenous injection in 5%. History of cocaine use ranged from 1-12 years (mean 4.7 years) with at least 6 months of compulsive use immediately

prior to treatment.

In addition to cocaine, 84% of the patients were using sedative-hypnotics, marijuana or alcohol to counteract the unpleasant stimulant effects of chronic cocaine use. No patients were physically dependent on these other substances or required medical detoxification. Forty-seven patients (75%) reported no history of severe chemical abuse or dependency before cocaine although all had at least experimented with marijuana and other drugs. Twelve patients had a history of alcohol or sedative-hypnotic dependency, 2 had a history of amphetamine dependency, and 2 had a history of opiate dependency.

Treatment

The RPR program, described in detail elsewhere (Washton et al. 1985), focused on drug abstinence and recovery. The initial goal was to achieve immediate abstinence from cocaine and all other mood-altering chemicals. Other goals were to improve personal functioning through continued abstinence, to reduce the potential for relapse, and to develop a more satisfying and responsible life without mood-altering drugs.

The program was fairly structured, but flexible enough to accommodate the individual needs of each patient. A variety of intervention procedures were utilized including: treatment contracting, drug education, urine monitoring, problem-oriented counseling, cocaine recovery groups led by a professional therapist, and individual psychotherapy mixed with couples and/or family sessions where indicated. Specific relapse prevention strategies (Washton 1985; Marlatt 1982) were used to modify addictive behaviors, enhance self-control, and promote long-term abstinence.

Initially, the program consisted of frequent supportive and educational sessions to facilitate early abstinence and separate the patient from drug-oriented environments and other high-risk situations. Subsequently, most patients participated in twice weekly cocaine recovery groups and at least once weekly individual therapy or counseling sessions. The group sessions focused primarily on abstinence and recovery issues including cocaine urges, addictive thinking, and precursors of relapse, as well as techniques for avoiding high-risk situations, reducing drug access, and coping with stressful situations or negative mood states that threaten abstinence. Individual sessions also focused on abstinence and recovery, but with a greater emphasis on personal problems related to drug use. Urine testing for cocaine and other drugs was conducted at least 2-3 times per week throughout the entire course of treatment. Upon entering the program, patients signed a treatment contract agreeing to stay in treatment for at least 6 months.

RESULTS

We evaluated treatment retention and drug free success rates 7-19 months after admission to the program. Follow-up status was determined using supervised urine testing combined with clinical assessment interviews. Of the original 63 patients, 59 (94%) completed at least 3 months of treatment, and 42 patients (67%) completed at least 6 months. The average retention time was 26.5

weeks with 49% of the original sample still continuing beyond 7 months of treatment at the time of the follow-up evaluation.

At 7-19 month follow-up, 51 (81%) of the original 63 patients were still abstinent and 12 patients had dropped out of treatment and relapsed to cocaine. Among the 51 who were still abstinent, approximately half had experienced one or two isolated "slips" to cocaine, but no major relapses during the course of treatment.

Success rates were directly related to the amount of time spent in treatment. Among those completing at least 6 months of treatment, 95% (40 of 42) were still drug free at follow-up. Similarly, among the 51 patients who were continuing to remain drug free at follow-up the average time spent in treatment up to that point was 37.5 weeks as contrasted with only 7.5 weeks for patients who had relapsed. No significant differences were found between previously hospitalized and non-hospitalized patients with regard to retention in the out-patient program or success rates at follow-up.

DISCUSSION

This preliminary report provides encouraging data on retention rates and clinical outcome in cocaine abusers treated as outpatients. The high success rates in our program can be attributed to certain characteristics of the patient sample and to certain aspects of our treatment approach.

Most patients were successfully employed in professional or highly skilled jobs, had a history of good functioning before cocaine and were willing to enter a program that required complete abstinence. They were motivated by a variety of internal and external factors, including the fear of losing a good job, career or relationship because of drug use. The program seemed to be especially well-suited to their clinical needs, since it addressed their drug abuse problem immediately and directly within the context of a fairly structured, high-expectation program with clearly defined performance requirements and a strong emphasis on abstinence, recovery, and relapse prevention.

To facilitate the-acceptability and effectiveness of the treatment program, a wide range of intervention-techniques were employed including cognitive, behavioral and supportive techniques. The use of cocaine recovery groups seemed to be especially helpful in promoting identification and early formation of a peer-support network and in counteracting feelings of uniqueness and isolation. Moreover, the use of frequent urine testing served as an objective monitor of patient progress and promoted self-control.

Our finding that success rates were approximately equal for hospitalized vs. nonhospitalized patients must be interpreted in light of the initial clinical differences between these two patient groups. The hospitalized patients were using larger doses of cocaine and were more likely to show medical and psychiatric complications related to the drug use. Without initial hospitalization, they probably would have had little change of succeeding in outpatient treatment. The fact that these otherwise poor-prognosis patients succeeded nearly as well in outpatient aftercare treatment as those who required no hospitalization at all suggests that the treatment

sequence of inpatient followed by outpatient treatment was an effective intervention strategy for this high-severity group.

It is likely that no single treatment modality will be optimal for all cocaine abusers. Systematic studies are needed to evaluate differing treatment methods and to identify the essential ingredients of the most effective approaches.

REFERENCES

Anker, A.L., and Crowley, T.J. Use of contingency contracts in specialty clinics for cocaine abuse. In: Harris, L.S. ed. Problem of Drug Dependence: 1981. National Institute on Drug Abuse Research Monograph 41. U.S. Govt. Print. Off., 1982. pp. 452-459.

Kleber, H.D., and Gawin, F.H. The spectrum of cocaine abuse and its treatment. Journal of Clinical Psychiatry 45: 18-34, 1984.

Marlatt, G.A. Relapse prevention: A self-control program for the treatment of addictive behaviors. In: Stuart, R.B., ed. Adherence, Compliance, and Generalization in Behavioral Medicine. New York: Brunner/Mazel, 1982. pp. 329-378.

Washton, A.M. Treatment of cocaine abuse. Psychiatric Clinics Of North America, in press. 1985.

Washton, A.M.; Gold, M.S.; Pottash, A.C. Cocaine abuse: Techniques of assessment, diagnosis and treatment. Psychiatric Medicine, in press. 1985.

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Biological Evaluation of Compounds for Their Physical Dependence Potential and Abuse Liability IX. Drug Testing Program of The Committee on Problems of Drug Dependence, Inc. (1985)

Arthur E. Jacobson

The Drug Testing Program of the Committee on Problems of Drug Dependence receives compounds from various sources (university laboratories and industry, both domestic and foreign, and U.S. Government laboratories) for evaluation of their potency as antinociceptives or narcotic antagonists, as well as of their dependence potential and abuse liability, as a public service. These compounds generally are of the opioid class. Methodology for the evaluation of the depressant and stimulant classes of compounds is being examined, and the compounds which were studied will also be discussed.

OPIOID TESTING LABORATORIES

Three groups continue to be concerned with the evaluation of compounds as opioids: the Medical College of Virginia (Drs. M.D. Aceto, L.S. Harris and E.L. May), the University of Michigan (Drs. J.H. Woods, F. Medzihradsky, C.B. Smith, G.D. Winger, and D.E. Gmerek), and NIADDK, NIH (Dr. A.E. Jacobson and M. Mattson). This paper serves as an introduction to the work, and summary of the results, of these workers so that the data which were obtained can be examined within the context of the particular opioid class. The complete work of the MCV and UM groups is published in this volume (Aceto et al. 1986; Woods et al. 1986), and should be consulted for the detailed examination of the evaluated compounds. I have classified the examined compounds in accord with the classical opioid structural types, so that the changes which are made in these classes can be more easily compared from year to year (Jacobson 1985).

CLASSES OF EXAMINED COMPOUNDS AND OPIOIDS OF SPECIAL INTEREST

The evaluated compounds can be seen in tables 1-8 under the general classification of 4,5-epoxymorphinans (tables 1 and 2), morphinans (table 3), 6,7-benzomorphans (table 4), phenylmorphans and phenylpiperidines (table 5), and a miscellaneous set of compounds which cannot be as conveniently categorized as the others (tables 6-8).

The 4,5-epoxymorphinans shown in table 1 and 2 are more numerous than all but the miscellaneous compounds. One of the interesting compounds in tables 1 and 2 is NIH 10001, a hydrazin-naloxone (spiro diaziridine) which was very potent on the mouse vas deferens, had high affinity for the opioid receptors in the rat brain homogenate (RBH) and was two times as potent as naloxone in the in vivo TFA assay (tail flick vs. morphine, in mice). Its effect on the vas deferens preparation was not antagonized by naltrexone and, thus, it was devoid of opioid agonist activity. It appears to be a pure narcotic antagonist in vitro and in vivo.

Further data on buprenorphine (NIH 8805) and nalmefene (NIH 10365) have been obtained and are shown in table 1. Buprenorphine is used clinically in Europe and displays analgesic activity after sublingual introduction, a novel and potentially very useful route of administration for analgesics. Nalmefene appears to be a potent naraotic antagonist. It does not substitute for-morphine in the single dose suppression (SDS) test in monkeys. Nalmefene has ten times the potency of naloxone in precipitating withdrawal in non-withdrawn (NW) monkeys and it was not self-administered (SA).

Table 2 shows 11 compounds which were prepared as potential affinity ligands, or their precursors, for specific opioid receptors. In order to see whether. those compounds would display narcotic antagonist activity in vivo, they were examined in the TFA assay by iv introduction. All of the compounds with the classical side-chains on nitrogen known to transform narcotic agonists to their antagonists did indeed display antagonist activity. Their in vivo potency ranged from one-eighth to four times that of nalorphine. Further data concerning these compounds is being published as a joint paper with several of the individuals in the Drug Testing Program (Lessor et al. 1986).

The (+)-enantiomer of N-4-methylpentylnormetazocine (NIH 10098, table 4) is distinctive in that it has considerably higher affinity for opioid receptors in the RBH assay than its (-)-enantiomer (NIH 10097). It is very unusual for a (+)-enantiomer in the opioid series to have higher affinity than its (-) enantiomer for the opioid receptors. It does not have opioid agonist activity in the vas deferens (it is not antagonized by naltrexone), unlike the (-) enantiomer, but is more potent on that preparation (and less efficacious) than the (-)-enantiomer. There would appear to be a considerable separation of in vitro agonist and antagonist activity in these enantiomers. The (+)-enantiomer does not suppress morphine withdrawal in SDS. It showed some antagonist aotivity in NW; a full withdrawal syndrome was not noted in that assay, however. In rodent assays, it had slight agonist activity in only the PPQ assay and did not show antagonist activity in the TFA assay. The (-)-enantiomer (NIH 10097) was, as expected, significantly more potent as an antinociceptive in vivo. A possible explanation for the difference in the in vivo and in vitro activities of these two enantiomers might lie in their differential metabolism in vivo. This (+)-enantiomer would have to be much more rapidly or effectively metabolized to inactive products than its (-) counterpart to account for the in vivo data.

A second (+)-enantiomer in the benzomorphan series, NIH 10019, (+)-N-propynylnormetazocine, appeared to act like a narcotic antagonist in the vas deferens preparation and was found to have very high affinity for the opioid receptors in RBH (table 4). Severe ataxia and catatonia were noted in the SDS assay, and it only partially suppressed the effects of morphine in that assay. The compound was tested in a phencyclidine displacement assay using 3H-PCP (Jacobson and Mattson 1986) and was found to be about 0.3 times as potent as PCP and, thus, can be said to have affinity for the PCP receptors comparable to (+)-SKF 10047 (racemic SKF 10047 is the prototypic sigma receptor ligand).

STATISTICS

A general discussion of the methodology used in the evaluation of opioids has been previously given (Jacobson 1980). The number of compounds received for evaluation and their source vary yearly. The mean of the number of compounds per year, over the past seven years, which were sent to the University of Michigan and the Medical College of Virginia is 93 (±30). The number sent this year is within that mean (87 compounds). The results of the evaluation of 43 compounds by MCV and 36 compounds by UM are compiled in this Monograph (Aceto et al. 1986; Woods et al. 1986). The mean of the number of evaluated compounds has been 95 (±20), thus the total of 79 compounds evaluated by the two groups this year is within the standard error limits of the mean. The numbers of these compounds obtained from our various, disparate, sources generally fall close to, or within the standard error limits of the mean for the past 7 years. Thus, 23% of the samples were obtained from industrial sources (mean = 29%), universities submitted 41% of the samples (mean = 44%), about 26% came from NIADDK, NIH (mean = 18% ±12), and the DEA submitted 3% of the samples.

STIMULANTS AND DEPRESSANTS

Five groups have been involved with the evaluation of the stimulant and depressant classes of compounds: the University of Chicago (Drs. C. Johanson and R. Schuster), the Medical College of Virginia (Drs. Patrick, Yutrzenka, and Harris), the Johns Hopkins University (Drs. R. Griffiths, N. Ator, R. Lamb, and J. Brady), NIADDK, NIH (Dr. A. Jacobson, M. Mattson), and NIDA (Dr. E. Cone), with Dr. J. Woods (University of Michigan) as Chairman. The assays, and parameters, examined have been the inverted screen test, locomotor activity, barbiturate physical dependence, food intake, drug discrimination and self-administration assays. Four anxiolytics have been examined (diazepam, bromazepam, temazepam and halazepam), as have two antidepressants (bupropion and nortryptyline), a sedative (methaqualone), a stimulant (fenetylline), and two anorectics (mazindol and mefenorex). A full report on the results obtained with these compounds will be published in this Monograph (Johanson 1986).

The program on the evaluation of stimulants and depressants will be continued, with emphasis being placed on methodology and validation of results, with a limited number of compounds. The question of

whether this consortium of laboratories should accept drugs in these classes from outside sources (universities or industry) for evaluation of their dependence potential, continues as a subject of discussion within the CPDD. Funding for this work has, thus far, come mostly from the CPDD itself.

ABBREVIATIONS USED IN TABLES 1 - 8.

Antinociceptive assay (ED50, sc injection except where noted, mice) [Confidence limits are listed in the MCV and UM reports (Aceto et al. 1986; Woods et al. 1986)]: HP = hot plate; N = Nilsen; PPQ = phenylquinone; TF = tail flick; TFA = tail flick antagonism vs. morphine. These assays are done at MCV, except for the HP and N which are done at NIADDK, NIH.

I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis.

EC50 Determinations:
These assays are done at UM. RBH = binding affinity, in the presence of 150mM NaCl, to rat cerebrum membrane preparations, in nM (parenthesized number is the +sodium/-sodium [+Na/-Na] ratio). EC50 was determined by displacement of 0.5nM 3H-etorphine. The EC50 of morphine, for comparison = 23.6 (1.69). NE = no effect. NOTE: The present EC50 data cannot be direotly compared with those from my previous reports (Jacobson 1983, and previous years) since I formerly quoted -Na values. However, the previously stated numbers can be recalculated for comparison with those which will be utilized this year and in the future, through the use of the +Na/-Na ratio.

GPI = electrically stimulated guinea pig ileum EC50, rounded to one significant figure, in nM except where noted. (E = exponential, e.g. 7E-9 M = 7 x 10-9 M, where -9 is an exponent [7E-2 M= 7 x 10-2 M = 0.07 M]) (parenthesized numbers are maximum percent inhibition at EC50); [bracketed letters: A = antagonized by 10-7M naltrexone; NA = not antagonized by naltrexone; SA = slight antagonism; NE = no effect on inhibition of twitch]. NOTE: The GPI assay has been phased out of the normal routine. These data will not be obtained as part of the general assays. The VD assay will continue.

VD = electrically stimulated mouse vas deferens EC50 values, rounded to one significant figure. Agonist activity stated as E = x10 M, thus: 7E-2 = 0.07 M (parenthesized numbers are maximum percent inhibition at EC50); [bracketed letters: A = antagonized by 10-7 M naltrexone; NA = not antagonized by naltrexone; NE = no effect on inhibition of twitch; SA = slight antagonism by naltrexonel. Compounds which suppress the twitch and are not antagonized by naltrexone (noted herein) or UM 979 [NIH 8859, (-)-5,9-alpha dimethyl-2-(3-furylmethyl)-2'-hydroxy-6,7-benzomorphan] are said to be non-opioid agonists (e.g. clonidine can suppress the twitch, but is not antagonized by naltrexone. It is a non-opioid agonist). (The effect of UM 979 is not noted in this report, but see the UM report (Woods et al. 1986) for these data). Compounds which bind with reasonable affinity in the rat brain homogenate assay, suppress the twitch in the VD, but are not blocked by narcotic antagonists may have antagonist properties,

also. This is experimentally determinable by observing their antagonism to morphine's suppression of the twitch in the VD preparation (for these data see Woods et al. 1986).

Data From Monkey Colonies:
These data are from either MCV or UM. SDS = single dose suppression: NS = no suppression; CS = complete suppression; PS = partial suppression. (Parenthesized numbers = dose range studied, in mg/kg; if CS, then dose at which CS was observed is noted in the parentheses). Potency comparison with morphine [M] may be stated, in brackets.
NW = studies in non-withdrawn monkeys: PW = precipitated withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N], in brackets; NP = no precipitation; SP = slight precipitation.

Other Studies:
RI = rat infusion (from MCV): NS q no suppression; CS = complete suppression; PS = partial suppression.
PPD = primary-physical dependence.
SA = self-administration (from UM): NE = no effect; High = codeine-like; IN = intermediate between saline and codeine; SE = slight effect.-
Normal monkeys: M-like = morphine-like effect.
DD = drug discrimination (from UM).

Previous Reports:
A new column has been added to the tables this year which relates the year in which previous work on a compound has been reported. These data are published in the annual compilations of "Problems of Drug Dependence".

NOTE: The numbers used in the tables may be rounded. For precise values, and details of the procedures, see the MCV and UM reports in these Proceedings (Aceto et al. 1986; Woods et al. 1986).

REFERENCES

Aceto, M.D.; Harris, L.S.; and May, E.L. Dependence studies of new compounds in the rhesus monkey, rat and mouse (1985). In: Harris, L.S. ed. Problems of Drug Dependence: 1985. National Institute on Drug Abuse Research Monograph. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1986, in press.

Jacobson, A. E. and Mattson, M. V., Unpublished results, 1986.

Jacobson, A.E. Biological evaluation of compounds for their dependence liability. VIII. Drug testing program of the Committee on Problems of Drug Dependence. Inc. (1984). In: Harris, L.S. ed. Problems of Drug Dependence: 1984. National Institute on Drug Abuse Research Monograph. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1985. pp. 298-308.

Jacobson, A. E. Biological evaluation of compounds for their dependence liability. VII. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1983). In: Harris, L.S. ed. Problems of Drug Dependence 1983. National Institute on Drug Abuse Research Monograph. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 352-360.

Jacobson, A.E. Biological evaluation of compounds for their dependence liability. IV. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1980). In: Harris, L.S. ed. Problaems of Drug Dependence: 1980. National Institute on Drug Abuse Research Monograph 34. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1981. pp. 287-296.

Johanson, C. Summary report of the CPDD stimulant/depressant groups. In: Harris, L.S. ed. Problems of Drug Dependence: 1985. National Institute on Drug Abuse Research Monograph. Washington, D.C.: supt. of Docs., U.S. Govt. Print. Off., 1986, in press.

Lessor, R.A.; Bajwa, B.S.; Rice, K.C.; Jacobson, A.E.; Streaty, R.A.; Klee, W.A.; Smith, C.B.; Aceto, M.D.; May, E.L.; and Harris, L.S. Probes for narcotic receptor mediated phenomena. 13. Potential irreversible narcotic antagonist-based ligands derived from 6,14-endoethenotetrahydrooripavine. Chemistry, biochemistry, and pharmacology. J. Med. Chem., in review, 1985.

Woods, J.H.; Medzihradsky, F.; Smith, C.B.; Winger, G.D.; and Gmerek,D.E. Evaluation of new oompounds for opioid activity. In: Harris, L.S. ed. Problems of Drug Dependence: 1985. National Institute on Drug Abuse Research Monograph. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1986, in press.

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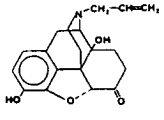
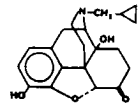
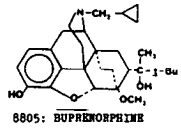
TABLE 1 - 4,5-EPOXYMORPHINANS[a]



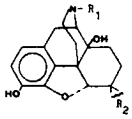
7890: NALOXONE



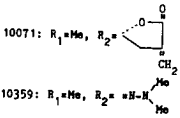
8503: NALTREXONE



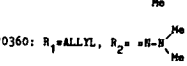
8805: BUPRENORPHINE



10001: R_1=ALLYL, R_2=

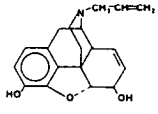


10071: R_1=Me, R_2=

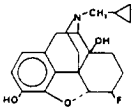


10359: R_1=Me, R_2= =N-Me(Me)

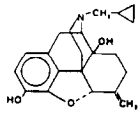
10360: R_1=ALLYL, R_2= =N-Me(Me)



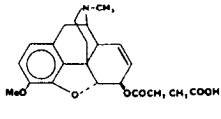
10124: NALORPHINE



10357



10365: NALMEFENE

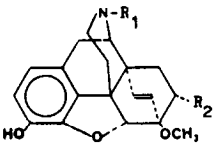


10384

NIH	MCV	UM	HP	M	PPQ	TF	TFA	RBH	VD	SDS	MW	Other	Previous Report
7890	4449	426	I	I	I	I	0.04	-	-	NS(0.05, 0.1)	PW(0.05)	-	1983
8503 9930	4002	1312	I	-	-	-	0.007	-	-	-	-	-	1970,1975 1982,1983
8805 10276	4387	952	0.035	0.04	0.016	0.14	1.0	-	-	PS(0.08-0.64)	PW(0.32)	RI-PPD	1974,1981
10001	4308	(10001)	1	I	-	-	-	4.	LE-11(88)[NA][b]	-	-	-	1982,1983
10071	4329	(10071)	2.6	-	-	-	-	35.	GE-6(88)[SA]	-	-	-	--
10124 2105	4336	1411	13.8	27.	I	I	0.5	-	-	NS(0.5,2.)	PW(0.1,0.5)	-	1953,1983
10357	4433	-	I	-	I	I	0.003	-	-	-	-	-	--
10359	4420	-	0.5	-	0.02	0.2	I	-	-	-	-	-	--
10360	4421	-	I	-	I	I	0.009	-	-	-	-	-	--
10365	4426	(10365)	I	-	I	I	0.001	-	$>10^{-5}$	NS(0.001-0.04)	PW(0.01) [10xH]	SA-ME; PPD-ME; DD-EXC-like	--
10384	4448	-	I	-	10.6	I	I	-	-	CS(12)	-	-	--

a) See text for explanation of abbreviations.
b) GPI = 5E-9(46)[A]

TABLE 2 - 4,5-EPOXYMORPHINANS (CONTINUED)[a]



10226: R_1=ALLYL, R_2= NH-C(=O)-C(H)=C(H)-COOMe

10227: R_1=ALLYL, R_2= $NHCOCH_2Br$

10228: R_1=ALLYL, R_2= N=C=S

10229: R_1=n-Pr, R_2= NH_2

10230: R_1=n-Pr, R_2= NH-C(=O)-C(H)=C(H)-COOMe

10231: R_1=n-Pr, R_2= $NHCOCH_2Br$

10232: R_1=n-Pr, R_2= N=C=S

10233: R_1=CPM, R_2= NH_2

10234: R_1=CPM, R_2= $NHCOCH_2Br$

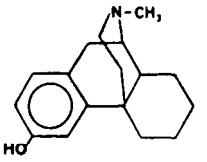
10235: R_1=CPM, R_2= N=C=S

10236: R_1=CPM, R_2= NH-C(=O)-C(H)=C(H)-COOMe

NIH	MCV	HP	TFA (i.v.)
10226	4471	I	6.3
10227	4439	I	2.1
10228	4440	I	0.6
10229	4441	I	I
10230	4472	I	1.8
10231	4442	I	0.6
10232	4443	I	0.7
10233	4444	I	I
10234	4445	I	0.4
10235	4446	I	0.2
10236	4447	I	1.5

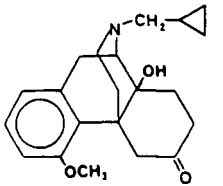
a) See text for explanation of abbreviations.

TABLE 3 - MORPHINANS[a]



4590: (-)-LEVORPHANOL

4591: (+)-DEXTRORPHAN

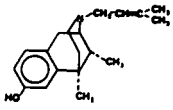


9977

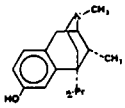
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	VD	SDS	NW	PPD	Previous Report
4590 } 10123	4474	510	0.2	0.2	0.03	0.4	-	-	-	-	-	-	1956,1964, 1983
4591	4473	106	30	-	24.	I	I	-	-	PS(0.25-0.4)	NP(1.-4.)	tolerance, dependence	1956,1981
9977	4298	(9977)	I	-	-	-	-	55.	7E-6(88)[NA]	-	-	-	1982

a) See text for explanation of abbreviations.

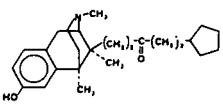
TABLE 4 - 6,7-BENZOMORPHANS[a]



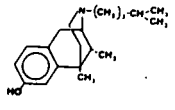
7958: PENTAZOCINE



8374

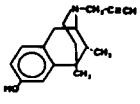


9752

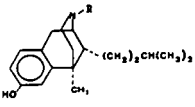


10097: (-)

10098: (+)



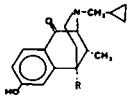
10019: (+)



10156: R=n-C_5H_{11}

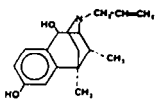
10157: R=$CH_2CH_2C_6H_5$

10160: R=CPM



10165: R=C_2H_5 (ETHYLKETOCYCLAZOCINE)

10346: R=CH_3 (KETOCYCLAZOCINE)

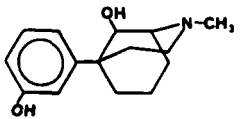


10178

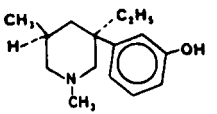
MIMe	MCVe	UMe	MP	M	PPQ	IP	IPA	RSH	VD	SDS	AM	Previous Report
7958	4268	381	7.6	6.5	1.8		1	I	-	MS(2.5-10)	PW(1.2-10.)-atypical	1962,1981, 1983
8374	4480	696	12.3	-	3.1	I	21.4	-	-	-	-	1968
9752	4203	1229	I	I	-	-	-	-	-	-	PW{0.01-0.3-s.c. 0.3-30-p.o.	1980
10019	4321	(10019)	-	-	-	-	-	1.0	3E-8(30)[NA]	-	-	1983
10097	4332	(10097)	3.1	-	-	-	-	195.	7E-8(91)[A]	-	-	1983
10098	4333	(10098)	I	-	-	-	-	10.	7E-9(20)[NA]	-	-	1983
10156	4345	(10156)	I	-	-	-	-	59.	1E-8(18)[A]	-	-	1984
10157	4349	(10157)	I	-	-	-	-	1230.	> 1E-5	-	-	1984
10160	4351	(10160)	I	-	-	-	-	-	2E-8(19)[NA]	-	-	1984
10165 8848	4348	975	0.09	-	0.04	0.4	I	-	-	PS (0.1)	NP(0.025,0.1)	1974,1983
10178	-	(10178)	-	-	-	-	-	32700.	9E-7(54)[NA]	-	-	-
10346 8847	4414	974	0.65	-	0.15	0.8	I	-	-	PS(0.2-0.8)	-	1974

a) See text for explanation of abbreviations.

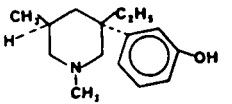
TABLE 5 - PHENYLMORPHAN AND PHENYLPIPERIDINES[a]



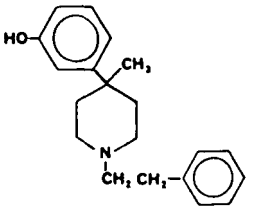
10154



10320



10321



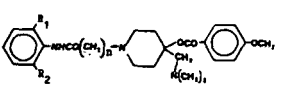
10344: R=CH_3

10345: R=n-C_3H_7

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	VD	SDS	NW	Previous Report
10154	4344	(10154)	I	-	-	-	-	7.5	7E-6(82)[SA]	-	-	1983
10320	4401	(10320)	6.9	-	I	I	0.95	40.	1E-8(22)[NA]	NS(0.03-2)	PW(2.,4.)	-
10321	4402	(10321)	2.0	-	0.4	2.3	I	62.	5E-7(52)[A][b]	CS(6.)	-	
10344	4412	-	I	-	0.2	I	5.8	-	-	NS(0.03-2.)	PW(0.03-4) [0.01xN]	-
10345	4413	-	1.8	-	0.4	2.1	I	-	-	CN(1.,4.)	-	-

a) See text for explanation of abbreviations.
b) "Non-competitive" antagonism

TABLE 6 - MISCELLANEOUS[a]



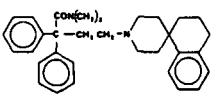
8627: R_1=R_2=Me, R_3=OMe, n=1

8630: R_1=R_2=Cl, R_3=OMe, n=1

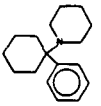
8631: R_1=Cl, R_2=Me, R_3=OMe, n=1

8632: R_1=R_2=Me, R_3=OMe, n=2

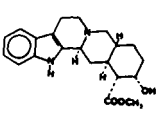
8633: R_1=R_2=Me, R_3=H, n=1



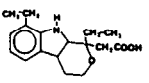
8634



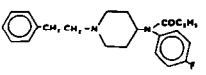
9580: PCP



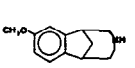
9689: YOHIMBINE



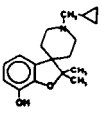
9918



10022



10036

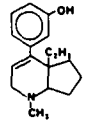


10150

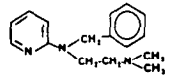
MIB#	MCV#	UN#	HP	H	FPQ	TF	TFA	RBH	VD	SDS	HN	Other	Previous Report
8627	-	851	0.4	-	-	-	-	-	-	CS(0.01)	-	-	-
8630	-	857	1.3	-	-	-	-	-	-	HS(7.-32.)	HP(8.)	-	-
8631	-	862	0.5	-	-	-	-	-	-	CS(0.05-0.2)	-	-	-
8632	-	863	10.5	-	-	-	-	-	-	CS(4.0)	-	-	-
8633	-	864	7.9	-	-	-	-	-	-	CS(16.)	-	-	-
8634	-	865	0.2	-	-	-	-	-	-	HS(0.1-0.4)	HP(0.2)	-	-
9580	4158	-	I	I	2.2	I	4.2	-	-	-	-	-	1979,1980, 1981
9689	4184	-	-	-	17.1	I	5.6	-	-	HS(0.06-4.)	HP(0.06-4.)	RI-RS	1979,1980
9918	4258	1319	1	I	12.9	I	I	-	3E-7(54)[HA] 3E-5(70)[SA]	HS(20,40.)	-	-	-
10022	4323	(10022)	0.015	-	-	-	-	200.	6E-8(93)[A]	-	-	-	1982
10036	-	1399	1.8	-	-	-	-	84,500	2E-5(38)[HA]	HS(1.,3.)	HP(1.9)	-	-
10150	4340	-	I	-	3.3	I	0.5	665	4E-7(58)[HA]	CS(0.4,0.8)	-	-	-

a) See text for explanation of abbreviations.

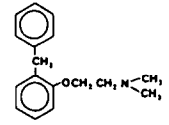
TABLE 7 - MISCELLANEOUS (CONTINUED)[a]



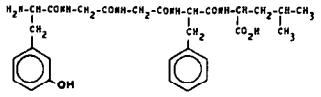
10153



10186: TRIPELENNAMINE

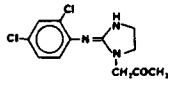


10197: PHENYLTOLOXAMINE

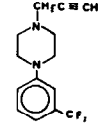


10270: N-(N-(N-L-*o*-HYDROXYPHENYLALANYLGLYCYL) GLYCYL)-L-PHENYLALANYL)-L-LEUCINE

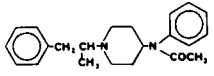
10271: N-(N-(N-D-*o*-HYDROXYPHENYLALANYLGLYCYL) GLYCYL)-L-PHENYLALANYL)-L-LEUCINE



10318



10319

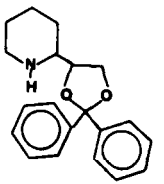


10354

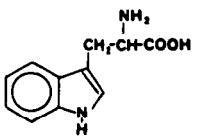
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	VD	SDS	MW	Previous Report
10153	4432	-	I	-	35.5	I	2.1	-	-	-	*PW*(1.6,6.4)	-
10186	4375	(10186)	3.9	-	-	-	-	10300	2E-7(25)[HA]			1983
10197 10121	4338	(10197)	41.	-	-	-	-	>6000	5E-8(13)[SA]	-	-	1982,1983
10270	4427	(10270)	I	-	I	I	I	10000	$>10^{-5}$	-	-	-
10271	4428	(10271)	I	-	I	I	I	5900	9E-6(76)[A]	-	-	-
10318	4399	(10318)	I	-	0.6	I	I	1050	4E-5(99)[HA]	NS(0.25-32.)	-	-
10319	-	(10319)	I	-	-	-	-	6000	$>10^{-4}$[HA]	-	-	-
10354	4416	-	0.17	-	0.09	0.3	I	-	-	CS(0.4)	-	-

a) See text for explanation of abbreviations.

TABLE 8 - MISCELLANEOUS (CONTINUED)[a]



10374: ALPHA (-) = LEVOXADROL
10375: ALPHA (+) = DEXOXADROL
10376: BETA RACEMATE = BETA DIOXADROL
10377: BETA (-)-DIOXADROL
10378: BETA (+)-DIOXADROL



10429: L-TRYPTOPHAN

NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	VD	SDS	NW	Previous Report
10374	4450	(10374)	I	-	I	I	I	>10000	$>10^{-5}$	NS(0.75-18.)	-	-
10375 8202	4451	(10375) 590	I	-	2.7	I	6.5	>10000	$>10^{-5}$	PS(1.,3)	-	1967
10376	4452	(10376)	I	-	I	I	I	>10000	$>10^{-5}$	NS(0.38,6.)	-	-
10377	4453	(10377)	I	-	I	I	I	7500	$>10^{-5}$	NS(1.5,6)	NP(1.5,6)	-
10378	4454	(10378)	I	-	I	I	I	>10000	$>10^{-5}$	PS(3.,12.)	-	-
10429	4475	-	-	-	-	-	I	-	-	NS(32.-128)	-	-

a) See text for explanation of abbreviations.

Dependence Studies of New Compounds in the Rhesus Monkey, Rat, and Mouse (1985)

M. D. Aceto, L. S. Harris, and E. L. May

All the drugs, except, dextrorphan, nalorphine, naloxone, naltrexone, pentazocine, tryptophan and yohimbine were supplied by Dr. Arthur Jacobson, Medicinal Chemistry Section, NIADDK under the auspices of the Committee on Problems of Drug Dependence, Inc. The chemical structures of the test compounds were unknown to us when they were originally submitted.

For the most part, the procedures described by Seevers and his colleagues (1936, 1963) and Deneau (1956) regarding the facilities and training of the monkeys were used and a brief description follows. The monkeys were injected with 3 mg/kg s.c. of morphine sulfate every 6 hr for at least 90 days before being used. This dose schedule was reported by Seevers and Deneau (1963) to produce maximal physical dependence.

This study was supported by a contract (#271-81-3830) from the National Institute on Drug Abuse, Dr. Khursheed Asghar, Contract Officer.

Modified procedures for the precipitated withdrawal (PPt-W) and single-dose suppression (SDS) tests were reported by Aceto and co-workers (1977 and 1978). The PPt-W test was initiated by the injection of a test drug 2½ hr after an injection of morphine and the animals were observed for signs of withdrawal. The SDS test was started approximately 15 hr after the last dose of morphine at which time the animals were showing withdrawal signs. The onset and duration of action of the test drug were noted. In both tests, a vehicle control and an appropriate positive control (naloxone, 0.05 mg/kg or morphine sulfate, 3.0 mg/kg) along with 3 different treatments (doses) of a test compound were randomly allocated to the 5 monkeys of a group. Occasionally 4 monkeys comprised a group and 2 doses of test compound were studied. Usually, 3 or 4 groups per compound were used. All drugs were given subcutaneously or (1 ml/kg) intravenously (1-2 ml) and the vehicle used is indicated for each compound. The observer was "blind" with regard to the treatment given. A minimum 2-week

washout and recuperation period between tests was allowed. In the primary physical dependence (PPD) tests, the animals of a group received the drug every 4-6 hr for 30-50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically, and were observed for signs of physical dependence. All potency estimates are rough approximations only.

The rat-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Semi-restrained male, Sprague-Dawley rats were medicated by continuous infusion through indwelling intraperitoneal cannula for 6 days with a drug. Rats were anesthetized and each was fitted with a specially prepared cannula which was passed subcutaneoulsy from the nape of the neck to the lateral side of the lower abdomen and then inserted in the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through, swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr.

In the substitution for morphine (SM) test, the animals first received morphine (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3-6). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for ½ hour at 24,48,72 and/or 96 hr after stopping the infusion of morphine.

In the primary physical dependence (PPD) study, the rats received test compound for 6 days and then were placed in abrupt withdrawal and observed as above. Occasionally a drug was given along with morphine.

Table 1

Comparative Data-ED 50 mg/kg s.c. (95% C.L.) of Selected Standards in 3 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick Test	Tail-Flick Antagonism Test	Phenylquinone Test
Pentazocine	15% at 10.0	18 (12.4-26)	1.65 (1.0-2.5)
Cyclazocine	17% at 1.0[a]	0.03 (0.02-.78)	0.011 (0.046-0.03)
Nalorphine ·HCl	None at 10.0	2.6 (0.69-9.75)	0.6 (0.025-1.44)
Naloxone l HCl	None at 10.0	0.035 (0.010-0.93)	No Activity
Naltrexone ·HCl	None at 10.0	0.007 (0.002-0.02)	No Activity
Morphine Sulfate	5.8 (5.7-5.9)	----	0.23 (0.20-0.25)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but no further increase in reaction time was seen.

Three mouse tests were used in our laboratory at the Medical College of Virginia to provide a preliminary estimate of the potency and profile of activity of each test compound. The tests were the tail-flick agonist (TF) and the morphine antagonist (TF vs M) tests and the phenylquinone (PPQ) test (Dewey et al., 1970; Dewey and Harris, 1971). Reference-standard data for these tests are shown in table 1. In addition, Dr. Jacobson provided us with estimated starting doses. These doses were based on results obtained from the mouse-hot plate (HP) (Eddy and Leimbach, 1953; Jacobson and May, 1965; Atwell and Jacobson, 1978) and Nilsen (N) (Perrine et al., 1972) tests from his laboratory. Reference data for these tests are shown in table 2.

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Table 2

Comparative Data (ED50 mg/kg/s.c) [95% S.E.] from the Hot Plate and Nilsen Test

Compound	Hot Plate Test Subcutaneous Oral	Nilsen Test Subcutaneous Oral
Morphine Sulfate	0.98(0.83-1.1) 6.3(4.7-8.3)	1.3(1.0-1.7) 8.3(6.0-11.4)
Codeine Phosphate	6.8(4.5-10.2) 13.5(9.7-18.7)	7.4(4.9-11.0) 14.7(9.2-23.3)
Levorphanol Tartrate	0.2(0.1-0.3) -	0.2(0.16-0.3) 2.5(1.7-3.7)
Meperidine·HCl	5.3(4.0-7.1) -	- -
(-)-Metazocine·HBr	0.6(0.5-0.9) 10.6(8.0-14.1)	0.5(0.3-0.7) 26.0(21.0-33.0)
Dihydromorphinone ·HCl	0.19(0.15-0.25) 0.9(0.7-1.2)	0.2(0.15-0.3) 1.8(1.5-2.1)
Nalorphine·HCl	9.9(5.7-2.1) -	23.0(16.2-32.7) -
Cyclazocine	1.5(1.1-2.1) -	0.1(0.07-0.16) -
Pentazocine	9.3(6.7-12.8) -	6.5(4.4-8.8) -
Chlorpromazine·HCl	1.1(0.9-1.5) -	- -

Naloxone·HCl and Naltrexone·HCl, no dose response.

Phenobarbital, Amobarbital, Valium, Oxazepam, Flurazepam, Mepromate and Mescaline are inactive on the hot plate test.

References

Aceto, M.D., Flora, R.E. and Harris, L.S. The effects of naloxone and nalorphine during the development of morphine dependence in rhesus monkeys. Pharmacol, 15:1-9, 1977.

Aceto, M.D., Flora, R.E. and Harris, L.S. Caffeine elicited withdrawal signs in morphine-dependent rhesus monkeys. Eur J. Pharmacol, 50:203-207, 1978.

Atwell, L. and Jacobson, A.E. The search for less harmful analgesics. Lab Animal, 7:42-47, 1978.

Deneau, G.A. An analysis of factors influencing the development of physical dependence to narcotic analgesics in the rhesus monkey with methods for predicting physical dependence liability in man. Doctoral Dissertation, University of Michigan, 1956.

Dewey, W.L., Harris, L.S., Howes, J.F. and Nuite, J.A. The effects of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. J. Pharmacol Exp Ther, 175:435-552, 1970.

Dewey, W.L. and Harris, L.S. Antinociceptive activity of the narcotic antagonists analogues and antagonistic activity of narcotic analgesics in rodents. J Pharmacol Exp Ther, 179:652-659, 1971.

Dewey, W.L. and Patrick, G.A. Narcotic antagonists in the rat infusion technique. Proc. from the 37th annual meeting, Committee on Problems of Drug Dependence, NRS-NAS, U.S.A. 64-73, 1975.

Jacobson, A.E. and May, E.L. Structures related to morphine, XXI, 2'-Substituted benzomorphans. J Med Chem, 8:563-566, 1965.

Perrine, T.D., Atwell, L., Tice, I.B., Jacobson, A.E. and May, E.L. Analgesic activity as determined by the Nilsen method. J Pharm Sci, 61:86-88, 1972.

Seevers, M.H. Opiate addiction in the monkey. I. Methods of study. J Pharmacol Exp Ther, 56:147-156, 1936.

Seevers, M.H. and Deneau, G.A. Physiological aspects of tolerance and physical dependence. In: Root, W.S. and Hofman, F.G., eds. Physiological Pharmacology, Vol. I. New York: Academic Press, 1963. pp. 565-670.

Tieger, D.G. Induction of physical dependence on morphine, codeine, and meperidine in the rat by continuous infusion, J Pharmacol Exp Ther, 190:408-415, 1974.

SUMMARY OF COMPOUNDS TESTED

COMPOUND #		CHEMICAL CLASS OR GENERIC NAME	MOUSE					RAT		MONKEY		
NIH	MCV		TF,	TFvsM,	PPQ,	HP,	N	SM,	PPD	SDS,	PPt-W,	PPD
4590	4474	Levorphanol	+		+	+	+					
4591	4473	Dextrorphan	+	+	+	+				+	+	+
7890	4449	Naloxone	+	+[a]	+	+	+			+	+	
7958	4268	Pentazocine	+	+	+	+	+			+	+	
8374	4480	6,7-Benzomorphan	+	+	+	+						
8503	4002	Naltrexone	+	+	+	+						
8805	4387	Buprenorphine	+	+	+	+	+	+[b]	+	+[c]	+	
8848	4348	Ethylketocyclazocine	+	+	+	+				+	+	
9580	4158	Phencyclidine (PCP)	+	+	+	+	+					
9689	4184	Yohimbine	+	+	+	+		+[d]		+	+	
9918	4258	Indole	+	+	+	+	+			+		
10124	4336	Nalorphine	+	+[e]	+	+	+			+	+	
10150	4340	Benzofuran	+	+	+	+				+	+	
10153	4432	Cyclopentanopyridine	+	+	+	+						
10226	4471	Endoetheno-oripavine		+[f]		+						
10227	4439	Endoetheno-oripavine		+[f]		+						
10228	4440	Endoetheno-oripavine		+[f,g]		+						
10229	4441	Endoetheno-oripavine		+[f]		+						

SUMMARY OF COMPOUNDS TESTED

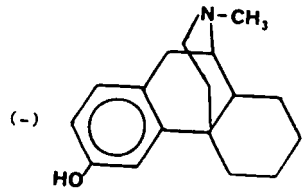
COMPOUND #		CHEMICAL CLASS OR GENERIC NAME	MOUSE				RAT	MONKEY	
NIH	MCV		TF,	TFvsM,	PPQ,	HP, N	SM, PPD	SDS,	PPt-W, PPD
10230	4472	Endoetheno-oripavine		+[f]		+			
10231	4442	Endoetheno-oripavine		+[f]		+			
10232	4443	Endoetheno-oripavine		+[f]		+			
10233	4444	Endoetheno-oripavine		+[f]		+			
10234	4445	Endoetheno-oripavine		+[f]		+			
10235	4446	Endoetheno-oripavine		+[f]		+			
10236	4447	Endoetheno-oripavine		+[f,g]		+			
10270	4427	Peptide	+	+	+	+			
10271	4328	Peptide	+	+	+	+			
10318	4399	Imidazolidine	+	+	+	+		+	
10320	4401	3-Phenylpiperidine	+	+	+	+		+	+
10321	4402	3-Phenylpiperidine	+	+	+	+		+	
10346	4414	Ketocyclazocine	+	+	+	+		+	
10354	4416	Piperidinoacetanilide	+	+	+	+		+	
10357	4433	14-Hydroxydihydromorphinone	+	+	+	+			
10359	4420	14-Hydroxydihydromorphinone	+	+	+	+			
10360	4421	14-Hydroxydihydromorphinone	+	+	+	+			
10365	4426	Nalmefene	+	+	+	+		+	+

SUMMARY OF COMPOUNDS TESTED

COMPOUND #		CHEMICAL CLASS OR GENERIC NAME	MOUSE				RAT	MONKEY	
NIH	MCV		TF	TFvsM	PPQ	HP, N	SM, PPD	SDS	PPt-W, PPD
10374	4450	1,3-Dioxolane							
10375	4451	1,3-Dioxolane	+	+	+	+		+	
10376	4452	1,3-Dioxolane	+	+	+	+		+	
10377	4453	1,3-Dioxolane	+	+	+	+		+	+
10378	4454	1,3-Dioxolane	+	+	+	+		+	
10384	4448	Codeine	+	+	+	+		+	
10425	4475	L-Tryptophan		+				+	

a) TFvsM-s.c., i.v., and i.v. time course study
b) Special Combination Study (Rat Infusion)
c) Regular 15-hour SDS and Special 9 and 19 hr SDS
d) Special infusion with morphine (Rat Infusion)
e) Regular s.c. and special i.v. (TFvsM)
f) Special i.v. (TFvsM)
g) Special i.v. time course study (TFvsM)

NIH 4590; 10123; MCV 4474; UM 510 (-)-3-Hydroxy-N-methylmorphinan·tartrate (Levorphanol)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 0.4 (0.3 - 0.6)

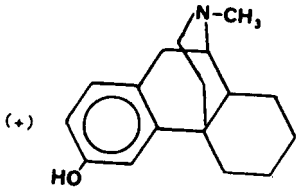
2) TF vs. M -

3) PPQ - 0.030 (0.008 - 0.100)

4) HP - 0.17 (0.14 - 0.21)

5) N - 0.22 (0.16 - 0.30)

NIH 4591; MCV 4473; UM 106 (+)-3-Hydroxy-N-methylmorphinan·tartrate (Dextrorphan)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 13% at 10.0, 30% at 30.0, 61% at 100.0

3) PPQ - 23.8 (12.3-46.0)[a]

4) HP - Approx. 30.0

[a] At 0.1 and 1.0 mg/kg naloxone partly antagonized this effect (35% maximal antagonism).

MONKEY DATA	# Animals	3	1	4	3
A) (SDS)	bose (mg/kg/s.c.)	4.0	1.5	1.0	0.25

$3H_2O$ 1 mg/kg

3(Morphine) 3.0

In the preliminary SDS study, a cumulative dose of 10.0 mg/kg in 30 min produced severe ataxia, slowing, body sag and partial eyelid ptosis. In the SDS study, the drug reduced the number of withdrawal signs (see figure) but this was accompanied by the dose-related side effects indicated above.

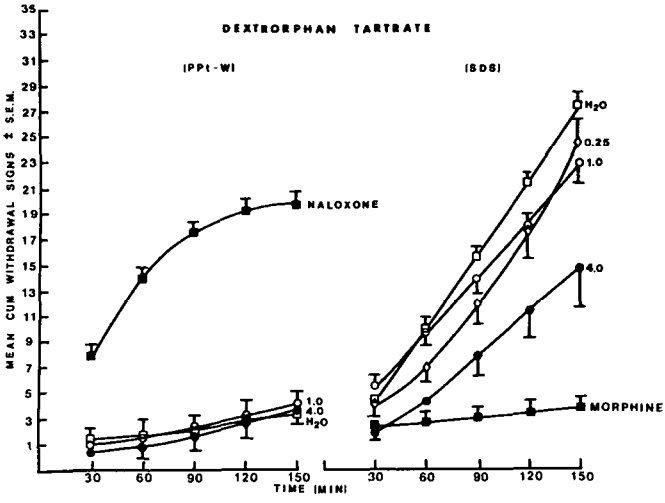
NIH 4591; MCV 4473; UM 106 (+)-3-Hydroxy-N-methylmorphinan·tartrate (Dextrorphan tartrate)

(continued)...

B) (PPt-W)

# Animals	3	3	3	3
Dose (mg/kg/s.c.)	4.0	1.0	H_2O 1mg/kg	Naloxone 0.05

Dextrorphan did not precipitate withdrawal in the dose range of 1.0-4.0 mg/kg s.c. (see figure). Dose-related side effects indicated above were observed.



C) (PPD)

The experimental details and summary are shown in the accompanying table. In brief, dextrorphan was given 4-6 times a day for 30 days. The dose range investigated was 3.0-13.0 mg/kg s.c. Ataxia and slowing (at times severe) and body sag were the main effects noted. Tolerance to these acute effects developed rapidly until a dose of 10.0 mg/kg was reached by day 10. At the end of day 30, the animals were placed in abrupt withdrawal. A syndrome characterized by the signs lying on side or abdomen, scratching, wet-dog shakes, fighting, pacing, frequent touching of genital area, and rubbing face against cage was observed.

Thirteen hours into withdrawal, the animals were challenged with a high dose of naltrexone (1.0 mg/kg/sc). The antagonist promptly exacerbated withdrawal. In addition, 2 of 3 animals retched and vomited. However, none of the animals ever showed rigid abdomens or vocalized when their abdomens were palpated, signs always observed in morphine-addicted monkeys either during abrupt or precipitated withdrawal. All the animals gained weight throughout the study.

Conclusion:

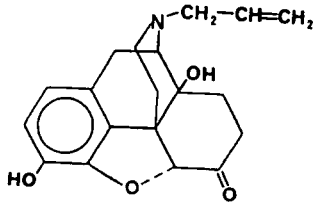
The rodent and monkey data suggest that dextrorphan may interact with an opioid receptor relatively insensitive to naloxone or naltrexone. It seems to have properties in common with both kappa and sigma (PCP) agonists.

Table 1

Summary of A Primary Physical Dependence Study With Dextrorphan Tartrate

Day	Dose mg/kg/s.c 4-6 times/day	Comments
1	3.0	The principal effects noted were ataxia and slowing, (at times severe), and body sag. Tolerance to these acute effects developed rapidly until a dose of 10 mg/kg was reached. This study was initiated with 4 monkeys, by day 15 one monkey was removed because he was overly aggressive with the other monkeys in the group. Drug was given six x day except on days 13, 14, 20 and 21 in which case it was given 4 x day.
2	5.0	
3-4	6.0	
5-7	7.0	
8	8.0	
9	9.0	
10-21	10.0	
22-28	11:o	
29-30	13.0	
31 A. Abrupt withdrawal (8-12 hours		At the end of day 30, the monkeys were placed in abrupt withdrawal. After 8-12 hours, a withdrawal syndrome was noted and recorded as follows: lying on side or abdomen (2/3); drowsiness (1/3); restless (3/3); repeated touching of genital area (2/3); rubbing face (2/3). (Ratios refer to number of animals for which the signs were observed over the number of animals observed).
31 B. Precipitated withdrawal (13 hrs) Naltrexone (1.0 mg/kg/s.c.)		Naltrexone promptly exacerbated withdrawal. In addition to the above, 2/3 retched and vomited. Withdrawal signs were no longer evident 18 hr after the beginning of withdrawal.

NIH 7890; MCV 4449; UM 426 Naloxone·HCl



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive

2) TF vs. M -
   a) 0.04 (0.01 - 0.10) s.c.
   b) 0.02 (0.01 - 0.03) i.v.

3) PPQ - Inactive

4) HP - Inactive

Special Intravenous Time Course

ED80 of Naloxone (0.1 mg/kg, i.v.) vs. Morphine ED80 s.c.

Time (min)	% Antagonism
30	75
60	49
90	22
120	0

MONKEY DATA # Animals / Dose (mg/kg/s.c.) 3 - 5/Dose, see figure

A) (PPt-W - 2 hr after morphine, nonwithdrawn animals)

B) (SDS - 15 hr after morphine withdrawal)

As shown in the figure, naloxone precipitated withdrawal; however, the same doses required to precipitate a full withdrawal syndrome also exacerbated abrupt withdrawal (SDS) and extended the duration of action when levels of morphine were quite low or falling. In this laboratory, blood levels of morphine measured fluorometrically in addicted rhesus monkeys 2 hr after morphine were found to be 110 ± 5.8 ng/g blood. During the period 15-16 hr after abrupt withdrawal, morphine was not detected. Although it is possible that small but undetected critical amounts might still be present especially in the brain, these results raise the possibility that naloxone may act noncompetitively in withdrawn addicts.

NIH 7890; MCV 4449; UM 426 Naloxone·HCl

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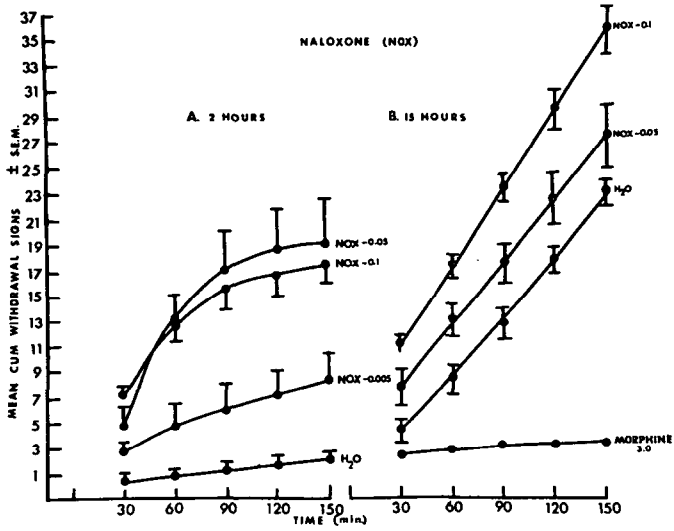
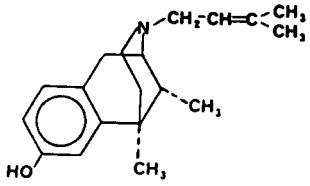


NIH 7958; MCV 4268; UM 381 2'Hydroxy-5,9α-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (Pentazocine lactate-Ampuls)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0 and 30.0

2) TF vs. M - 8.5 (3.3 - 21.5)

3) PPQ - 7.6 (5.5 - 10.7)

4) HP - 6.5 (4.8 - 8.8)

MONKEY DATA (SDS)

Animals
Dose (mg/kg/s.c.)

5 / 2.5, 3 / 5.0, 3 / 7.5, 3 / 10.0

5 (H_2O) 1 ml/kg

5(Morphine) 3.0

(continued)...

A) (SDS - 15 hr after morphine)

The results are illustrated in the accompanying figure. At the 2 higher doses pentazocine (base) produced convulsions which were terminated with injections of pentobarbital. Ataxia, myoclonic jerks, and slowing were also observed at these doses. The animals showing convulsions were removed from the study. Doses with an N of less than 3 were not plotted. At the next lower dose, pentazocine may have exacerbated withdrawal and did not substitute for morphine. The lowest dose produced effects similar to the vehicle and morphine substituted completely.

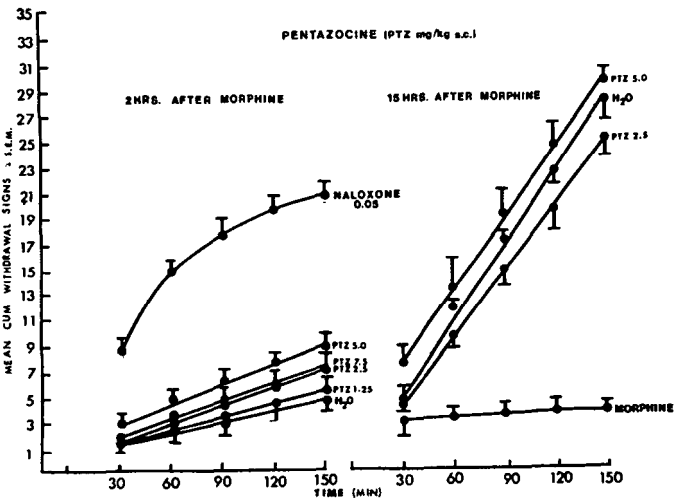
MONKEY DATA B) (PPt-W)	# Animals Dose (mg/kg/s.c.)	4 10.0	4 7.5	7 3.0
	3 1.25	8(H_2O) 1 ml/kg	9(Naloxone) 0.05	

B) (PPt-W - 2 hr after morphine; nonwithdrawn animals)

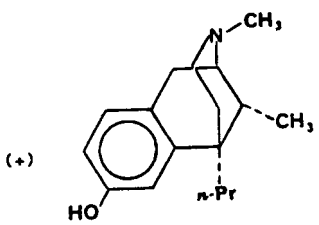
At the highest dose, pentazocine produced convulsions in 3 of 4 animals. Pentobarbital terminated these convulsions. At the 7.5 mg/kg dose, one animal convulsed and was similarly treated with pentobarbital. Ataxia, slowing and body sag was also noted in some of these animals. The data from the monkeys showing convulsions were not used in plotting the figures. Interestingly, only 4 animals in the entire study had rigid abdomens or vocalized when their abdomens were palpated. These 2 signs are usually noted in addicted monkeys receiving drugs with antagonist properties. In any case, even into the convulsive range (7.5 mg/kg) few withdrawal signs were elicited by pentazocine (see figure). In addition, the results were not dose-related. Pentazocine seems to be an atypical antagonist or partial antagonist.

NIH 7958; MCV 4268; UM 381 (Pentazocine lactate-Ampuls)

(continued)...



NIH 8374; MCV 4480; UN 696 (+)-2'-Hydroxy-2,9 α-dimethyl-5-propyl-6,7-benzomorphan·HCl



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

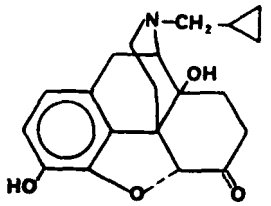
1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 21.4 (13.4 - 34.5)

3) PPQ - 3.1 (0.9 - 10.7)

4) HP - 12.3 (10.0 - 15.2)

NIH 8503; 9930; MCV 4002; UM 1312 Naltrexone hydrochloride



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

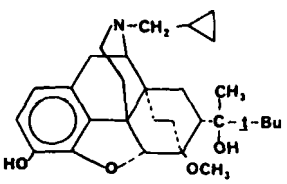
1) TF -

2) TF vs. M - 0.007 (0.003 - 0.020)

3) PPQ -

4) HP - Inactive

NIH 8805; 10276; MCV 4387; UM 952 21-Cyclopropylmethyl-7α-[(S)-1-hydroxy-1,2,2-trimethylproyl]6,14-endoethano-6,7,8,14-tetrahydrooripavine (Buprenorphine)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 0.14 (0.09 - 0.23)[a]

2) TF vs. M - 1.0 (0.3 - 3.3)

3) PPQ- 0.016 (0.005 - 0.042)[b]

4) HP - 0.035 (0.028 - 0.045)

5) N - 0.04 (0.03 - 0.06)

[a)]Biphasic Curve - 58% at 1.0; 30% at 10.0
[a)]Naloxone AD50 vs the TF-ED80 = 0.15 (0.06 - 0.36)
[b)]Naloxone AD50 vs PPQ ED80 = 0.060 (0.025 - 0.150)

MONKEY DATA
A) (SDS) Regular 15-hr withdrawal

# Animals	1	3	4	5	5	3	3	9(H_2O)	9(Morphine)
Dose (mg/kg/s.c.)	0.64	0.32	0.16	0.08	0.02	0.005	0.0016	1ml/kg	3.0

NIH 8805; 10276; MCV 4387; UM 952 Buprenorphine

(continued)...

In the dose range of 0.005 - 0.160 mg/kg, NIH 10276 significantly alleviated many withdrawal signs during the first hour. The drug significantly reduced the number of withdrawal signs at 0.02 and 0.005 mg/kg during the first 2½ hrs. In both cases, however, the drug did not completely substitute for morphine. (see figure)

MONKEY DATA
B) (SDS) Special 9-hr withdrawal

# Animals / Dose (mg/kg/s.c.)	3 / 0.32	3 / 0.08	3 / 0.002	3(H_2O), 1 mg/kg

3(Morphine)
3.0

NIH 8805 did not substitute for morphine at any of the doses tested.

MONKEY DATA
C) (SDS) Special 19-hr withdrawal

# Animals / Dose (mg/kg/s.c.)	3 / 0.32	3 / 0.08	3 / 0.02

NIH 8805 partially suppressed withdrawal at the 2 lower doses. In the 19 hr withdrawal test, even morphine did not alleviate the sign vocalizes when abdomen palpated and only partially reduced the incidence of many of the other signs.

MONKEY DATA	# Animals / Dose (mg/kg/s.c.)	3 / 0.32	3 / 0.08	3 / 0.02
D) (PPt-W)				

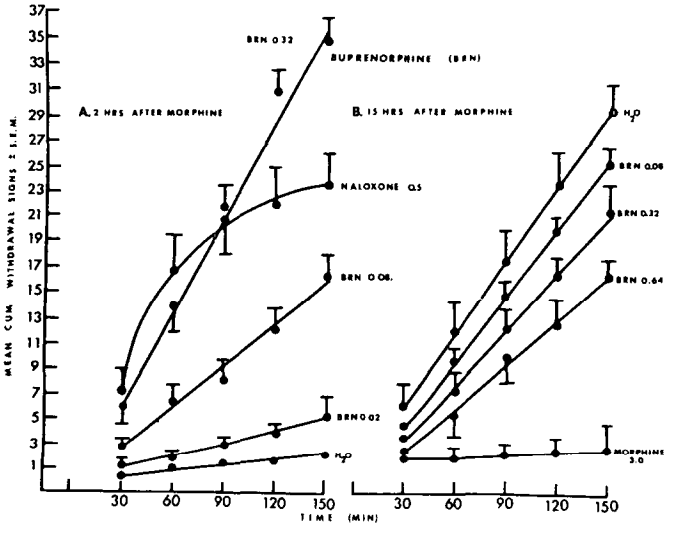
NIH 8805 precipitated withdrawal in a dose-related manner. Onset of action was prompt and duration of action was more than 2½ hr. Naloxone duration of action is about 1½ hr. At the 2 higher doses, some animals were still vocalizing after abdominal palpation (after morphine at noon and four hrs later). The drug appeared to be an irreversible antagonist. (see figure)

NIH 8805; 10276; MCV 4387; UM 952 Buprenorphine

(continued)...

Conclusion

Buprenorphine has been classified as a partial mu agonist. Accordingly, it would be expected to display competitive antagonist properties in nonwithdrawn subjects (PPt-W) and to fully or partly suppress abstinence in withdrawn subjects (SDS). The results in this laboratory and those of others in spinal dogs and mice are in accord.



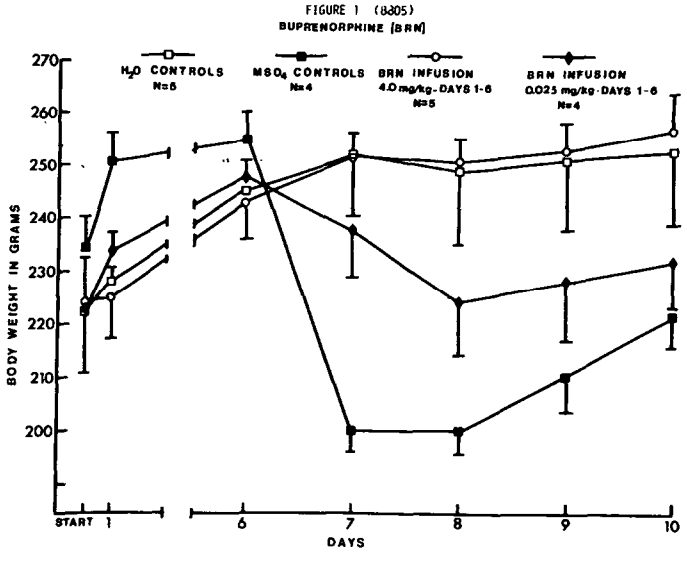
RAT INFUSION

1) PPD. When given continously for 6 days at 0.025 and 4.0 mg/kg, there is some indication at the low but not the high dose that NIH 8805 may produce physical de endence as evidenced by the modest weight loss (Figure 1) and behavioral withdrawal signs at 24 hr (Table 1).

2) Special Combination Study. When given in combination with morphine for 6 days at the low dose (0.025 mg/kg) NIH 8805 seems to increase the degree and duration of weight loss (Figure 2) but does not affect the behavioral withdrawal

syndrome (Table 2); at the high dose, NIH 8805 acts as an antagonist and interferes with the development of morphine physical dependence.

3) Special Combination Study. When given in combination with morphine at 0.006 mg/kg, NIH 8805 does not block the weight loss normally associated with morphine withdrawal (Figure 3) nor attenuate the behavioral withdrawal syndrome (Table 3).



NIH 8805; 10276; MCV 4387; UM 952 21-Cyclopropylmethyl-7-α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]6,14-endoethano-6,7,8,14-tetrahydrooripavine (Buprenorphine)

(continued)...

FIGURE 2 (8805)

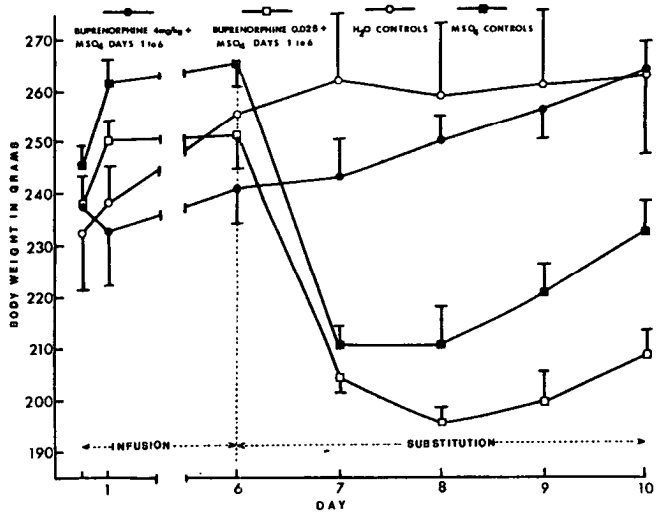


FIGURE 3 (8805)

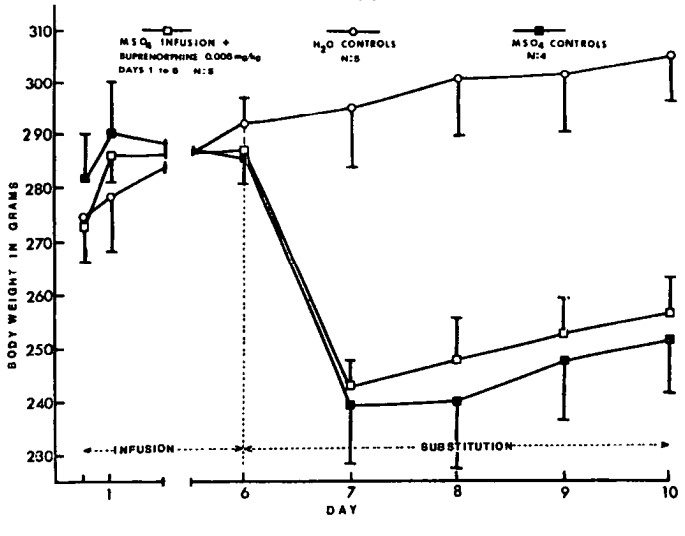


Table 1 (8805)

PRIMARY PHYSICAL DEPENDENCE STUDY IN CONTINUOUSLY-INFUSED RATS (BUPRENORPHINE)

TREATMENT		Hours in Withdrawal[1,2,3] (x = mean) 24 (Day 7)	48 (Day 8)	72 (Day 9)	96 (Day 10)
A. Water Controls N=5		x = 1.0	x = 1.8	x = 1.6	x = 0
B. Morphine Controls[3,4]		x = 10.2	x = 10.4	x = 7.4	x = 3.8
	p - vs. Water	0.004	0.022	0.048	0.075
C. Buprenorphine HCl[3,5] (high dose)		x = 0.6	x = 2.6	x = 1.6	x = 1.2
	p - vs. Water	0.383	0.540	0.383	0.345
	p - vs. Morphine	0.004	0.022	0.038	0.155
D. Buphrenor hine HC1[6] (low dose)		x q 5.5	x = 2.3	x = 2.0	x = 0.8
	p - vs. Water	0.032	0.452	0.365	0.322
	p - vs. Morphine	0.322	0.044	0.175	0.206

1)Hypertensitivity, squealing, aggression, wet-dog shakes, rubbing and chewing; 2)One-tailed test (Mann-Whitney U-Test), $p<0.05$; 3)Studies shown in Tables 1 and 2 (Buprenorphine) were done at same time. H_2O and morphine control scores included in each table; 4)50 mg/kg - day 1, 100 mg/kg - day 2, 200 mg/kg - days 3-6, N=5; 5)Buprenorphine - 4 mg/kg, Days 1-6, N=5; 6)Buprenorphine - 0.025 mg/kg, Days 1-6, N=4.

Table 2 (8805)

PRIMARY PHYSICAL DEPENDENCE STUDY IN CONTINUOUSLY-INFUSED RATS (BUPRENORPHINE)

TREATMENT	Hours in Withdrawal[1,2,3], (x = mean) 24 (Day 7)	48 (Day 8)	72 (Day 9)	96 (Day 10)
A. Water Controls N=5	x = 1.0	x = 1.8	x = 1.6	x = 0
B. Morphine Controls[3,4]	x = 10.2	x = 10.4	x = 7.4	x = 3.8
p - vs. Water	0.004	0.022	0.048	0.075
C. Buprenorphine HCl[3,5] (high dose)	x = 1.0	x = 1.6	x = 2.2	x = 1.2
p - vs. Water	0.579	0.540	0.461	0.345
p - vs. Morphine	0.004	0.016	0.111	0.155
D. Buphrenorphine HCl[6] (low dose)	x = 6.4	x = 16.4	x = 6.8	x = 4.2
p - vs. Water	0.028	0.004	0.274	0.183
p - vs. Morphine	0.093	0.111	0.345	0.421

1)Hypertensitivity, squealing, aggression, wet-dog shakes, rubbing and chewing; 2)One-tailed test (Mann-Whitney U-Test), $p<0.05$); 3)Studies shown in Tables 1 and 2 (Buprenorphine) were done at same time. H_2O and morphine control scores included in each table; 4) 50 mg/kg - day 1, 100 mg/kg - day 2, 200 mg/kg - days 3-6, N=5; 5) Buprenorphine - 4 mg/kg, Days 1-6, N=5; 6) Buprenorphine - 0.025 mg/kg, Days 1-6, N=4.

Table 3 (8805)

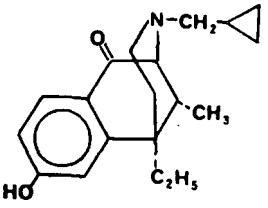
SPECIAL COMBINATION INFUSION STUDY (BUPRENORRHINE AND MORPHINE)

IN CONTINUOUSLY-INFUSED RATS

TREATMENT	Hours in Withdrawal[1,2] (x = mean) 24	48	72	96
A. Water Controls N=5	x = 0.8	x = 6.4	x = 6.2	x = 4.4
B. Morphine Infusion[3]	x = 9.3[2]	x = 12.3[2]	x = 5.0	x = 4.0
C. Morphine plus Buprenorphine Infusion[4]	x = 6.4[2]	x = 6.4	x = 6.2	x = 4.4

1)Hypertensitivity, squealing, aggression, wet-dog shakes, rubbing and chewing; 2)One-tailed test (Mann-Whitney U-Test), $p<0.05$ compared with water controls; 3) 50 mg/kg - day 1, 100 mg/kg - day 2, 200 mg/kg - days 3-6, N=4; 4)Morphine schedule plus buprenorphine (0.006 mg/kg - days 1-6).

NIH 8848; 10165; MCV 4348; UM 975 Ethylketocyclazocine, EKC



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 0.4 (0.1 - 1.0)

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 0.004 (0.002 - 0.100)

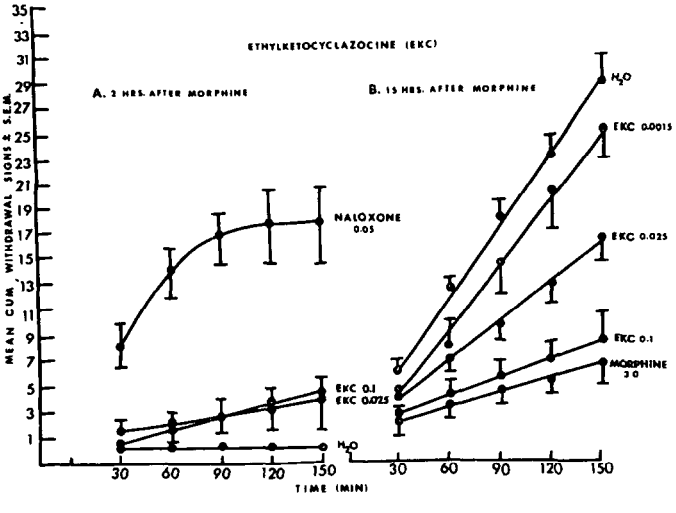
4) HP - 0.009 (0.007 - 0.120)

MONKEY DATA # Animals / Dose (mg/kg/s.c.) 3 - 5/Dose see figure

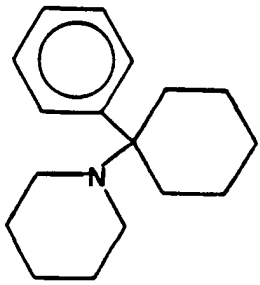
A) (PPt-W - 2 hr after morphine, nonwithdrawn animals)

B) (SDS - 15 hr after morphine)

In this laboratory EKC demonstrated no antagonist properties (see A in figure), but partly suppressed abstinence signs (see B in figure). The suppression was associated with severe side effects namely ataxia, body sag and slowing and may be a consequence of EKC's own agonist activity. Interestingly, these side effects are also seen after high doses of morphine especially in non-tolerant monkeys.



NIH 9580, MCV 4158, 1-(Phenylcyclohexyl)piperidine·HCl (Phencyclidine, PCP)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

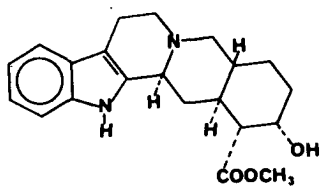
2) TF vs. M - 4.2 (1.7 - 10.2)

3) PPQ - 2.2 (1.0 - 4.6)

4) HP - Inactive at 1.0 and 20.0

5) N - Inactive at 1.0 and 5.0

NIH 9689, MCV 4184 (Yohimbine·HCl)



MOUSE DATA ED50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 3.0, 10.0 or 30.0

2) TF vs. M - 5.6 (2.7 - 11.5)

3) PPQ - 17.1 (6.6 - 44.1)

4) HP - N.T.

MONKEY DATA

A. SDS - # Animals / bose (mg/kg/s.c.) | 3 / 0.0625 | 3 / 0.25 | 4 / 4.0 | 4 (H_2O) / 1 ml/kg | 4Morphine) / 3.0

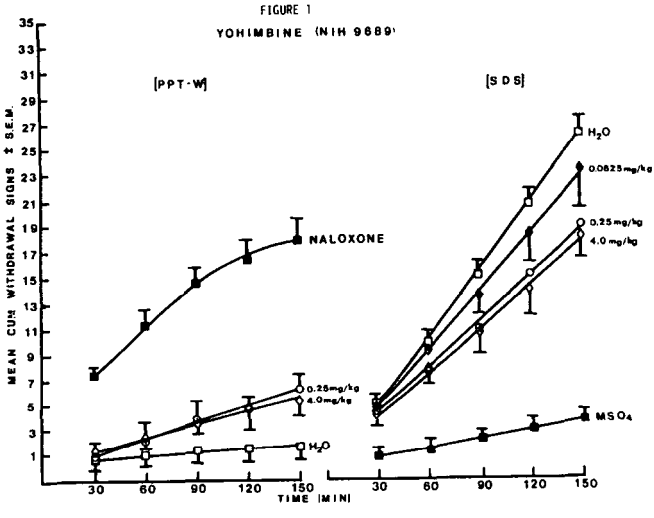
B. (PPt-W) - # Animals / Dose (mg/kg/s.c.) | 2 / 0.0625 | 3 / 0.25 | 4 / 4.0 | 4 (H_2O) / 1 ml/kg | 4(Naloxone) / 0.05

NIH 9689, MCV 4184 (Yohimbine·HCl)

(continued)...

Yohimbine (YOH) an $\alpha_{\gamma 2}$ antagonist, has been reported to produce a syndrome resembling spontaneous opiate withdrawal in nonhuman primates (Gold et al., Psychopharmacology of Clonidine, eds. Lal and Fielding, 1981) and to reverse morphine (M) antinociception in rodents (Aceto and Harris, op cit). Therefore, it was of considerable interest to us to study the action of YOH on M dependence. In maximally dependent nonwithdrawn rhesus monkeys, YOH in the dose range of 0.06 - 4.0 mg/kg/s.c. did not precipitate withdrawal. In withdrawn addicts, YOH neither substituted for M nor exacerbated withdrawal. YOH did suppress the signs fighting, avoids contact, and retching (see figure 1).

FIGURE 1
YOHIMBINE (NIH 9689)



RAT INFUSION

When given to rats in combination with M continuously for 6 days by intraperitoneal infusion at doses of 1.44 and 14.4 mg/kg/24 hr, as much weight loss was noted during withdrawal as that observed in the M controls (figure 2). In addition, the withdrawal syndromes (hypersensitivity, squealing, aggression, wet-dog shakes, rubbing and chewing) were similar. Interestingly, at 72 and 96 hrs, the YOH controls showed an increased incidence of wet-dog shakes compared with the H_2O controls (tables 1 and 2).

(continued)...

CONCLUSION

These results are not in accord with the hypothesis (Gold et al., op cit) that increased hyperactivity of the locus coeruleus mediates opiate withdrawal.

FIGURE 2
YOHIMBINE (YOH)

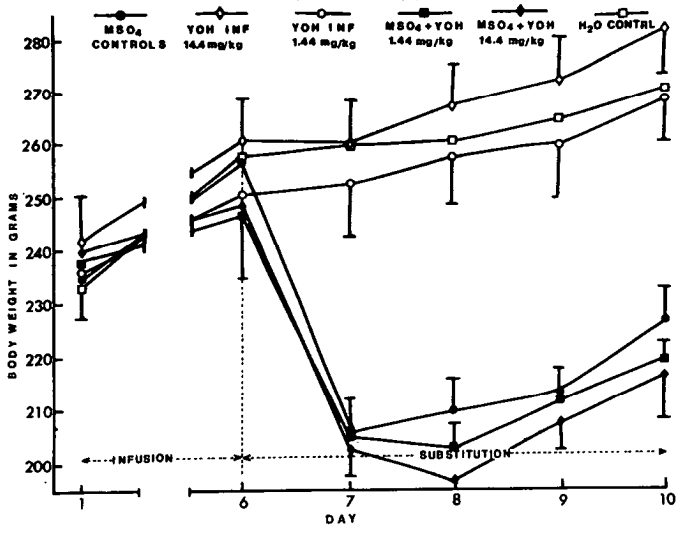


TABLE 1

SPECIAL COMBINATION INFUSION STUDY IN CONTINUOUSLY-INFUSED RATS (YOHIMBINE)

(COMPARED WITH WATER CONTROLS)

TREATMENT	Hours in Withdrawal[1,2] (x = mean) 24	48	72	96
A. Water Controls N=5	x = 1.8	x = 0.4	x = 1.0	x = 1.6
B. Morphine Sulfate Controls[3]	x = 12.4[2]	x = 9.2[2]	x = 9.8[2]	x = 6.0[2]
C. Morphine plus 9689 Infusion[3,4]	x = 21.3[2]	x = 9.5[2]	x = 4.3	x = 8.0
D. Morphine plus 9689 Infusion[3,5]	x = 16.6[2]	x = 4.0[2]	x = 9.5[2]	x = 9.5
E. 9689 Controls[6]	x = 2.2	x = 6.2[2]	x = 5.8[2]	x = 9.4[2]
F. 9689 Controls[7]	x = 2.2	x = 4.0[2]	x = 8.2[2]	x = 5.6

1) Hypersensitivity, squealing, aggression, wet-dog shakes, rubbing and chewing; 2) One-tailed test (Mann-Whitney U-Test, $p<0.05$, probability value vs water controls; 3) 50 mg/kg - day 1, 100 mg/kg - day 2, 200 mg/kg - days 3-6, N=5 from 24-48 hr and N=4 from 72-96 hr; 4) 1.44 mg/kg - days 1-6, N=4 from 24-48 hr and N=3 from 72-96 hr; 5) 14.4 mg/kg - days 1-6, N=5 from 24-48 hr and N=4 from 72-96 hr; 6)14.4 mg/kg - days 1-6, N=5; 7)14.4 mg/kg - days 1-6, N=5.

TABLE 2

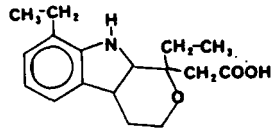
SPECIAL COMBINATION INFUSION STUDY IN CONTINUOUSLY-INFUSED RATS (YOHIMBINE)

(COMPARED WITH MORPHINE CONTROLS)

TREATMENT	Hours in Withdrawal[1,2] (x = mean) 24	48	72	96
A. Morphine Controls	x = 12.4	x = 9.2	x = 9.8	x = 6.0
B. Water Controls N=5	x = 1.8[2]	x = 0.4[2]	x = 1.0[2]	x = 1.6[2]
C. Morphine plus 9689 Infusion[3,4]	x = 21.3	x = 9.5	x = 4.3	x = 8.0
D. Morphine plus 9689 Infusion[3,5]	x = 16.6	x = 4.2	x = 9.5	x = 9.5
E. 9689 Infusion[6]	x = 2.2[2]	x = 6.2	x = 5.8	x = 9.4
F. 9689 Infusion[7]	x = 2.2[2]	x = 4.0	x = 8.2	x = 5.6

1)Hypersensitivity, squealing, aggression, wet-dog shakes, rubbing and chewing; 2) One-tailed test (Mann-Whitney U-Test), $p<0.05$, probability value vs morphine controls; 3)50 mg/kg - day 1, 100 mg/kg - day 2, 200 mg/kg - days 3-6, N=5 from 24-48 hr and N=4 from 72-96 hr; 4)1.44 mg/kg - days 1-6, N=4 from 24-48 hr and N=3 from 72-96 hr; 5)14.4 mg/kg - days 1-6, N=5 from 24-48 hr and N=4 from 72-96 hr; 6)14.4 mg/kg - days 1-6, N=5; 7) 14.4 mg/kg - days 1-6, N=5.

NIH 9918; MCV 4258; UM 1319 1,8-Diethyl-1,3,4,9-tetrahydro-pyrano[3,4-b]indole-1-acetic acid (Etodolac)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0 and 30.0

2) TF vs. M - Inactive at 1.0 and 30.0

3) PPQ - 12.9 (6.1 - 27.4)

4) HP - 10% at 20%, 20% at 50, 0% at 100

5) N - 12% at 100

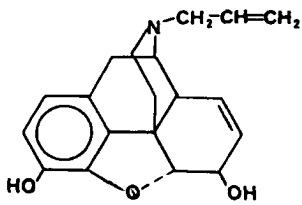
MONKEY DATA SDS

Animals / Dose (mg/kg/s.c.) 3 / 20.0, 3 / 40.0, 3(DMSO) / 1mg/kg

3(Morphine) / 3.0

At the doses tested, the drug did not substitute for morphine. The drug appeared to suppress the withdrawal signs retching and vomiting.

NIH 10124; MCV 4336; UM 1411 (Nalorphine·HCl)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/i.v.)

1) TF - 12% at 1.0, 19% at 10.0, and 12% at 30.0

2) TF vs. M
a) 0.5 (0.1 - 1.7) s.c.
b) 0.8 (0.3 - 1.0) i.v.

3) PPQ - 3% at 1.0, 49% at 3.0, 43% at 10.0 and 60% at 60.0

4) HP - 13.8 (9.0 - 21.3)

5) N - 27.0 (18.5 - 39.5)

NIH 10124; MCV 4336; UM 1411 (Nalorphine·HCl)

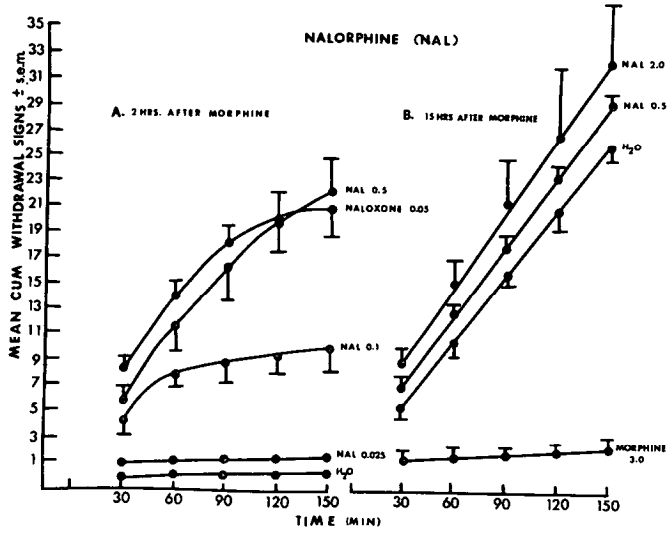
(continued)...

MONKEY DATA # Animals 3 - 5/Dose
bose (mg/kg/s.c.) see figure

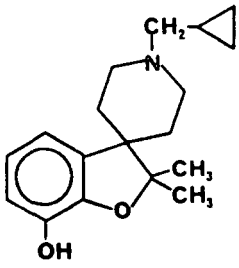
A) (PPt-W - 2 hr after morphine, nonwithdrawn animals)

B) (SDS - 15 hr after morphine, withdrawal)

Nalorphine's action was very similar to that of naloxone. However, it's potency was about 1/10 that of the reference compound. In morphine-addicted monkeys, nalorphine exhibits only mu antagonist properties. It does behave differently in nonwithdrawn and withdrawn animals supporting the speculation that nalorphine acts competitively in the nonwithdrawn state and noncompetitively in the withdrawn state. See discussion in naloxone report (NIH 7890).



NIH 10150, MCV 4340 (1'-cyclopropylmethyl-2,2-dimethyl-spiro[benzofuran-3(2H),4'piperidin-7-ol])



MOUSE DATA ED50 (95% C.L.) (mg/kg/s.c.)

1) TF - 6% at 1.0, 5% at 10.0 and 58% at 30.0

2) TF vs. M - 0.5 (0.009 - 2.5)

3) PPQ - 3.3 (1.3 - 8.3)

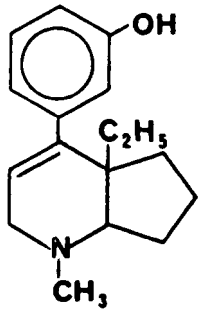
4) HP - 20% at 50 (No Dose Response)

MONKEY DATA (SDS)	# Animals / Dose (mg/kg/s.c.)	2 / 0.8	4 / 0.4	3 / 0.1

2 / 0.025	4(di1HCl + H_2O) / 1 ml/kg	4(Morphine) / 3.0

NIH 10150 substituted completely for morphine at the 2 higher doses. The action was prompt but brief (<90 min). The drug is estimated to be 4 times more potent then morphine at its peak effect.

NIH 10153, MCV 4432 (3-(4a-Ethyl-2,4a,5,6,7a-hexahydro-1-methyl-1H-1-pyridin-4-yl)phenol·HBr



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 2.1 (1.2 - 3.7)

3) PPQ - 35.5 (22.3 - 56.7)

4) HP - 40% at 50.0

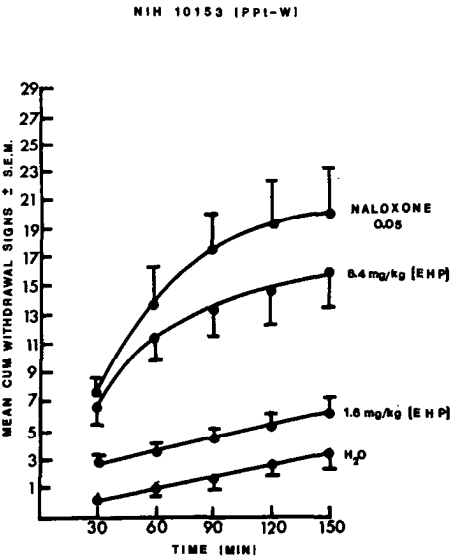
MONKEY DATA (PPt-W)	# Animals / Dose (mg/kg/s.c.)	3 / 6.4	3 / 1.6	3 / 0.4

NIH 10153, MCV 4432

(continued)...

4 (H_2O)	4 (Naloxone)
1 ml/kg	0.05

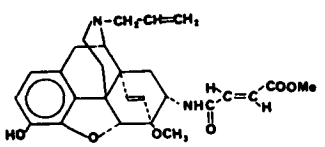
NIH 10153 promptly precipitated withdrawal as did naloxone and acted for a similar length of time (90 min). The drug is approximately 1/150 as potent as the reference compound. Data for the 2 lower doses was not plotted because n was less than 3.



NIH 10226, MCV 4471 N-Allyl-7α-methylfumaroylamino-6,14-endoethenotetrahydronororipavine oxalate

MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/i.v.)

Special Intravenous Study



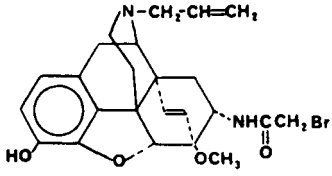
1) TF -

2) TF vs. M - 6.3 (5.1 - 7.8)i.v.

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10227, MCV 4439 N-Allyl-7α-bromoacetylamino-6,14-endoetheno-tetrahydronororipavine oxalate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.or i.v.)

1) TF -

2) TF vs. M - 2.1 (0.8 - 5.7) (i.v.)

3) PPQ -

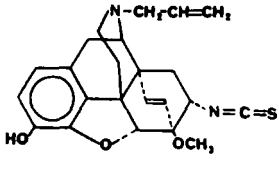
4) HP - Inactive (s.c.)

Duration Study i.v. (AD80 of NIH 10227) - (9.0 mg/kg) vs. ED80 of morphine SO4) s.c.

% Antagonism	Pretreatment Time (min)
86	30
74	120
43	240

Drug Supply Exhausted

NIH 10228, MCV 4440 N-Allyl-7α-isothiocyanato-6,14-endoethenote-trahydronororipavine oxalate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

1) TF -

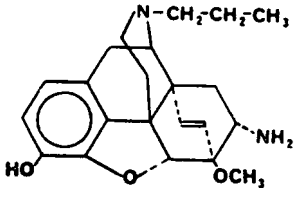
2) TF vs. M - 0.6 (0.3 - 1.1) i.v.

3) PPQ -

4) HP - Inactive (s.c.)

155-509 O - 86 - 15

NIH 10229, MCV 4441 7α-Amino-N-propyl-6,14-endoethenotetrahydronororipavine dioxalate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

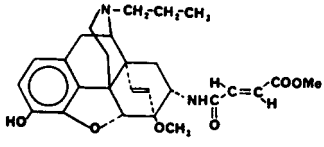
1) TF -

2) TF vs. M - Inactive at 0.1, 1.0 and 10.0 (i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10230, MCV 4472 7α-Methylfumaroylamino-N-propyl-6,14-endoethenotetrahydronororipavine



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

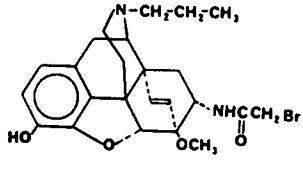
1) TF -

2) TF vs. M - 1.8 (0.9 - 3.6) (i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10231, MCV 4442 7α-Bromoacetylamino-N-propyl-6,14-endoethenotetrahydronororipavine



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

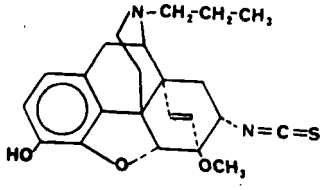
1) TF -

2) TF vs. M - 0.6 (0.3 - 1.2) (i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10232, MCV 4443 7α-Isothiocyanato-N-propyl-6,14-endoetheno-tetrahydronororipavine oxalate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

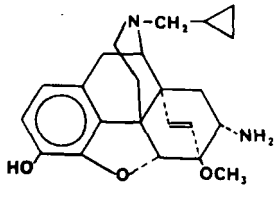
1) TF -

2) TF vs. M - 0.7 (0.3 - 1.5) (i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10233, MCV 4444 7α-Amino-N-cyclopropylmethyl-6,14-endoetheno-tetrahydronororipavine



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

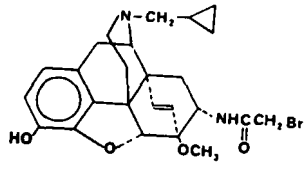
1) TF -

2) TF vs. M - 2% at 1.0, 5% at 3.0, 3% at 10.0, 52% at 30.0(i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10234, MCV 4445 7α-Bromoacetylamino-N-cyclopropylmethyl-6,14-endoethenotetrahydronororipavine



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

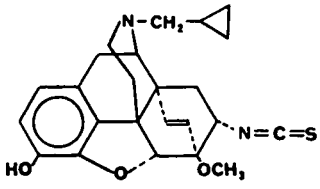
1) TF -

2) TF vs. M - 0.4 (0.2 - 0.9) (i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10235, MCV 4446 7α-Isothiocyanato-N-cyclopropylmethyl-6,14-endoethenotetrahydronororipavine oxalate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

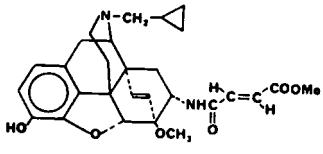
1) TF -

2) TF vs. M - 0.2 (0.1 - 0.4) (i.v.)

3) PPQ -

4) HP - Inactive (s.c.)

NIH 10236, MCV 4447 7α-Methylfumaroylamino-N-cyclopropylmethyl-6,14-endoethenotetrahydronororipavine



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c. or i.v.)

1) TF -

2) TF vs. M - 1.5 (0.6 - 3.8) (i.v.)

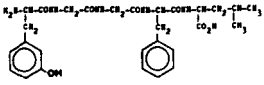
3) PPQ -

4) HP - Inactive (s.c.)

Special TFvsMorphine Duration Study

Pretreatment Time (min)	% Antagonism ± S.E.
30	90 ± 11
120	69 ± 13
180	82 ± 13
240	47 ± 9
800	32 ± 6
360	26 ± 5

NIH 10270, MCV 4427 N-(N-(N-L-m-Hydroxyphenylalanylglycyl)glycyl)-(L-phenylalanyl)-L-leucine acetate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

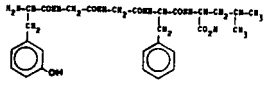
1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - Inactive at 1.0 and 10.0, 11% at 30.0

4) HP - Inactive at 50.0, 10% at 100.0

NIH 10271, MCV 4428 N-(N-(N-(D-m-Hydroxyphenylalanylglycyl)-glycyl)-L-phenylalanyl)-L-leucine acetate



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

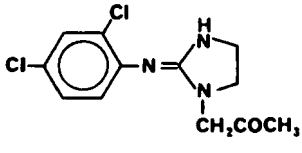
1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 0% at 1.0, 29% at 10.0 and 0% at 30.0

4) HP - Inactive at 100.0

NIH 10318, MCV 4399 1-Acetonyl-2-(2,4-dichlorophenyl)iminoimidazolidine·HCl



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0 and 10.0; 22% at 30.0

2) TF vs. M - 0% at 1.0; 18% at 10.0; 4% at 30.0

NIH 10318, MCV 4399 1-Acetonyl-2-(2,4-dichlorophenyl)iminoimidazolidine·HCl

(continued)...

3) PPQ - 0.6 (0.3 - 1.4)

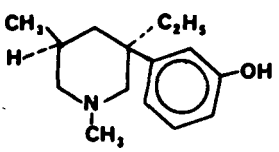
4) HP - 40% at 50; 10% at at 100.0

MONKEY DATA (SDS) # Animals Dose (mg/kg/s.c.) 1 / 32.0, 3 / 8.0, 2 / 4.0

2 / 0.25 4(H_2O) / 1ml/kg 4(Morphine) / 3.0

NIH 10318 did not substitute for morphine. One animal receiving 8.0 mg/kg was given 30.0 mg of pentobarbitol to alleviate severe tremors.

NIH 10320, MCV 4401 (3R,5R)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0 and 10.0; 20% at 30.0

2) TF vs. M - 0.95 (0.30 - 3.0)

3) PPQ - 34% at 30.0

4) HP - 10.0 (5.1 - 14.9)

MONKEY DATA A) (SDS) # Animals Dose (mg/kg/s.c.) 1 / 2.0, 3 / 0.5, 3 / 0.125

2 / 0.03 3(H_2O) / 1ml/kg 3(Morphine) / 3.0

In the dose range tested, NIH 10320 did not substitute for morphine and may have exacerbated withdrawal.

NIH 10320, MCV 4401 (3R,5R)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride

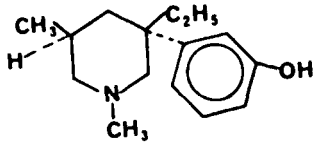
(continued)...

MONKEY DATA B) (PPt-W)	# Animals Dose (mg/kg/s.c.)	1 4.0	3 2.0	2 0.5

1 0.125	3(H_2O) 1 ml/kg	3(Naloxone) 0.05

NIH 10320 precipitated withdrawal at the two higher doses. A rapid onset of action and duration similar to that of naloxone was observed. The drug is about 1/80 as potent as naloxone.

NIH 10321, MCV 4402 (3R,5S)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 2.3 (0.9 - 6.2)

2) TF vs. M - Inactive at 1.0, 10.0 and 3.0

3) PPQ - 0.4 (0.1 - 1.1)[a]

4) HP - 2.0 (2.1 - 2.5)

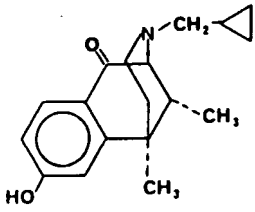
[a] Naloxone AD50 vs NIH 10321 ED80 in PPQ = 0.6 (0.1 - 3.2)

MONKEY DATA (SDS)	# Animals Dose (mg/kg/s.c.)	2 6.0	3 2.0	3 0.5

3 0.125	3(H_2O) 1 ml/kg	3(Morphine) 3.0

At the highest dose, NIH 10321 substituted completely for morphine. At the 2.0 and 0.5 mg/kg doses some suppression of withdrawal was also noted. The onset of action was prompt and the duration of action was approximately 1½ hr.

NIH 10346; 8847; MCV 4414; UM 974 Ketocyclazocine



MOUSE DATA ED50 (95% C.L.) (mg/kg/s.c.)

1) TF - 0.8 (0.4 - 1.5)[a]

2) TF vs. M - Inactive at 1.0, 10.0, and 30.0[a]

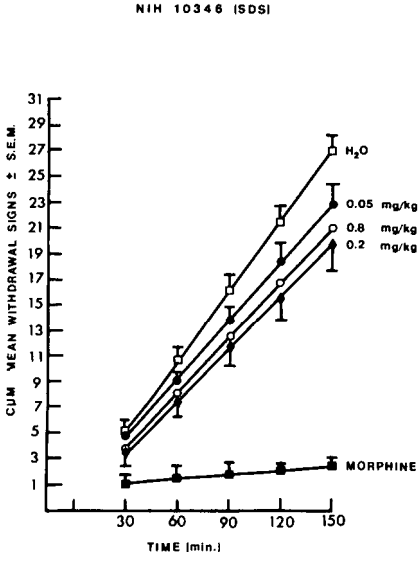
3) PPQ - 0.15 (0.1 - 0.2)[a]

4) HP - 0.7 (0.5 - 0.8)

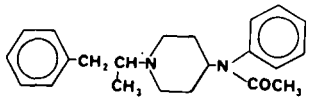
[a]Vehicle - Tween 80 H_2O

MONKEY DATA (SDS) # Animals / Dose (mg/kg/s.c.) 6 / 6.0, 4 / 0.4, 4 / 0.2, 5 / 0.5, 1 / 0.025, 3 (H_2O) / 1 ml/kg, 3 (Morphine) / 3.0

NIH 10346 produced dose-related side effects designated ataxia, body and jaw sag and slowing. The drug reduced the total number of withdrawal signs in the dose range which produced side effects but did not substitute completely as did morphine (see figure). The action of this drug is reminiscent of that of ethylketocyclazocine.



NIH 10354, MCV 4416 N-[1-(1-Methyl-2-phenethyl)-4-piperidyl]acetanilide



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 0.3 (0.2 - 0.5)

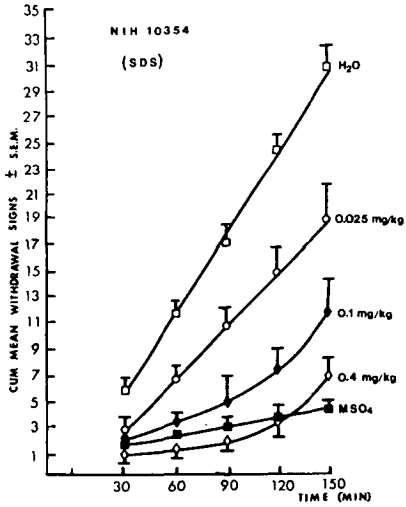
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 0.09 (0.03 - 0.24)

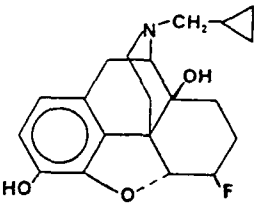
4) HP - 0.17 (0.12 - 0.23)

MONKEY DATA (SDS) # Animals Doses (mg/kg/s.c.) n = 3 or 4/dose see figure

NIH 10354 substituted completely for morphine. The onset of action was rapid but its duration of action may be shorter than that of morphine. The drug is approximately 10x as potent as morphine at peak effect (see figure).



NIH 10357, MCV 4433 17-Cyclopropylmethyl-3,14-dihydroxy-4,5α-epoxy-6ß-fluromorphinan·HCl



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

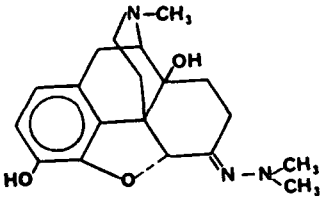
1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 0.003 (0.001 - 0.008)

3) PPQ - 16% at 0.4, 34% at 1.0, 61% at 10.0, 47% at 20.0 and 58% at 30.0

4) HP - Inactive

NIH 10359, MCV 4420 N,N-Dimethyloxymorphazone



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 0.2 (0.1 - 0.4)[a]

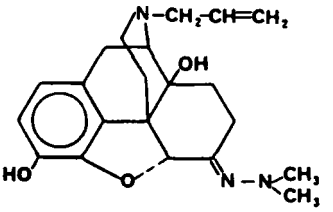
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 0.02 (0.01 - 0.06)[a]

4) HP - 0.5 (0.4 - 0.7)

[a]Vehicle - Tween 80 + H_2O

NIH 10360, MCV 4421 N,N-Dimethylnaloxazone



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0,[a] 10.0 and 30.0

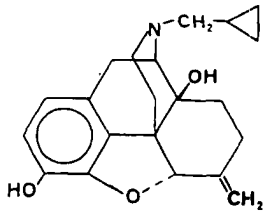
2) TF vs. M - 0.009 (0.004 - 0.020)[a]

3) PPQ - Inactive at 1.0, 10.0 and 30.0

4) HP - Inactive at 5.0 and 20.0

[a]Vehicle - Tween 80 + H_2O

NIH 10365, MCV 4426 17-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-7-methylenemorphinan·HCl (Nalmefene)



MOUSE DATA ED50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 0.001 (0.002 - 0.004)

3) PPQ - Inactive at 0.003, 0.03, 1.0, 10.0 and 30.0

4) HP - Inactive

MONKEY DATA	# Animals					
A) (SDS)	Dose (mg/kg/s.c.)	3, 0.04	3, 0.008	1, 0.001	3(H2O) 1 ml/kg	3(Morphine) 3.0

(SDS - 15 hr after morphine withdrawal)

As shown in the figure, NIH 10365 did not substitute for morphine. Instead, it exacebrated withdrawal at the 2 higher doses. Data for the lower dose was not illustrated because n = 1. The controls behaved as expected.

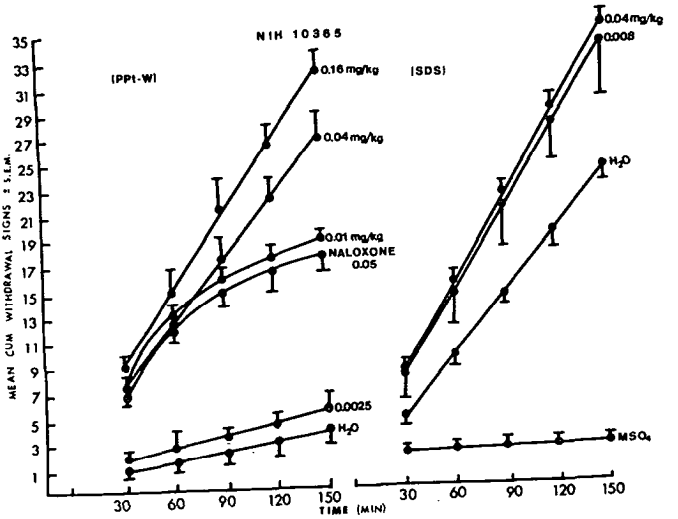
MONKEY DATA	# Animals					
B) (PPt-W)	bose (mg/kg/s.c.)	3, 0.16	4, 0.04	3, 0.01	2 0.025	5(H2O) 1 ml/kg	5(Naloxone) 0.005

B) (PPt-W - 2 hr after morphine, nonwithdrawn animals)

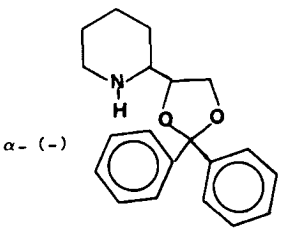
NIH 10365 promptly precipitated withdrawal. The drug is about 5-10x as potent as naloxone.

NIH 10365, MCV 4426 17-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-7-methylenemorphinan·HCl (Nalmefene)

(continued)...



NIH 10374, MCV 4450 α-(-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·Hcl (Levoxadrol·HCl) (R,R)-α-Racemate is dioxadrol.



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 26% at 30.0, 18% at 10.0 and 34% at 1.0

4) HP - Inactive at 5.0 and 20.0 mg/kg

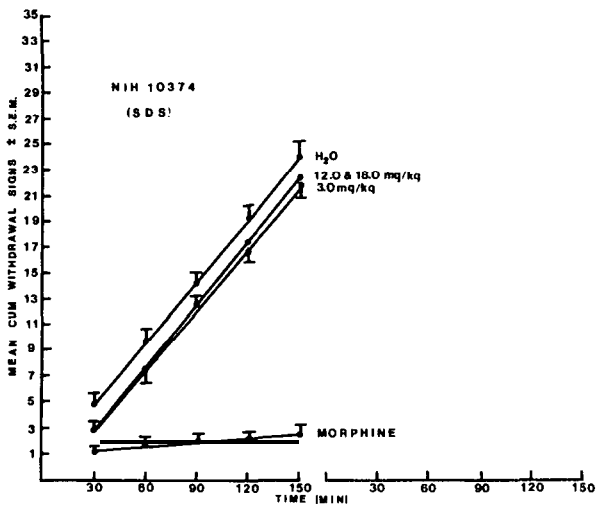
MONKEY DATA (SDS) # Animals / Dose (mg/kg/s.c.) 1 / 0.75, 4 / 3.0, 3 / 12.0

3 / 18.0 5(H_2O), 1 ml/kg 5(Morphine) / 3.0

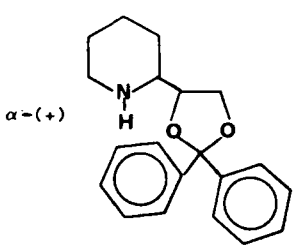
NIH 10374, MCV 4450 α-(-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl (Levoxadrol·HCl) (R,R)-α-Racemate is dioxadrol.

(continued)

In the dose range of 0.75 - 18 mg/kg, NIH 10374 did not substitute for morphine in withdrawn animals. At the highest does, convulsions were noted about 30 minutes after drug was given. In one of the animals, the convulsion had a very short duration. The results of the lowest dose were not plotted because n = 1 (see figure).



NIH 10375, MCV 4451 α-(+)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl (Dexoxadrol·HCl) (S,S)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 6.5 (3.8 - 11.1)

3) PPQ - 2.7 (1.1 - 6.3)

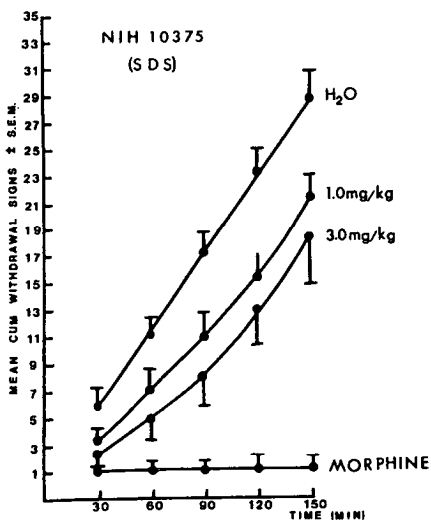
4) HP - Inactive at 5.0 and 20.0 mg/kg

NIH 10375, MCV 4451 α-(+)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl (Dexoxadrol·HCl) (S,S)

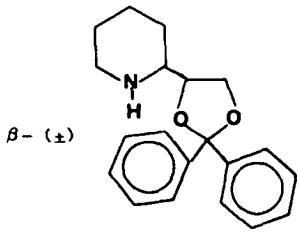
(continued)...

MONKEY DATA (SDS)	# Animals					
	Dose (mg/kg/s.c.)	1, 0.25	3, 1.0	3, 3.0	1, 9.0	3(H_2O), 1 ml/kg	3(Morphine), 3.0

As shown in the figure, a modest dose-related attenuation of withdrawal signs accompanied by side effects characterized NIH 10375. This action is remimiscent of that of ethylketocyclazocine. Dose-related slowing, and ataxia to the point of prostration was observed. At the highest dose, naloxone 0.05 mg/kg/s.c. reversed these effects. The data from the 0.25 and 9.0 mg/kg doses were not plotted because n = 1 for each dose.



NIH 10376, MCV 4452 ß-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl (ß Racemate of Dioxadrol)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

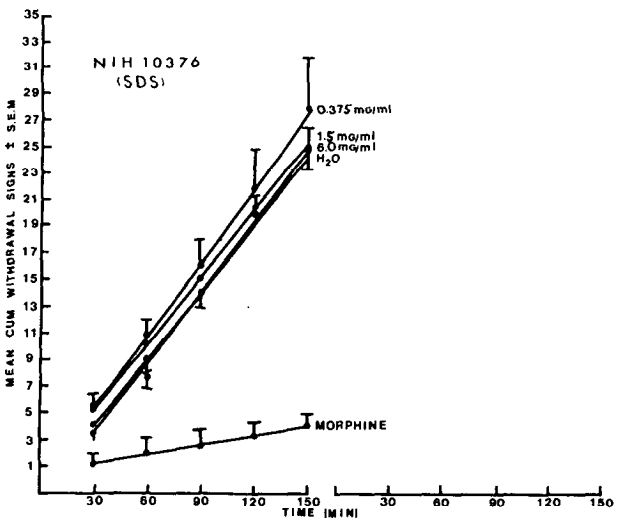
3) PPQ - Inactive at 10.0 and 5% at 30.0

4) HP - Inactive at 5.0 and 20.0 mg/kg

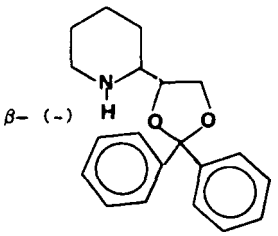
MONKEY DATA (SDS)	# Animals				
	Dose (mg/kg/s.c.)	3 / 6.0	3 / 1.5	2 [a] / 0.375,	
		3(H_2O) / 1 ml/kg		3(Morphine) / 3.0	

As shown in the figure, NIH 10376 neither substituted for morphine nor exacerbated withdrawal.

[a] Not plotted, N=2.



NIH 10377, MCV 4453 ß-(-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl [ß-(-)-Dioxadrol]



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - Inactive at 0.1 and 10.0, 14% at 1.0 and 10.0

3) PPQ - Inactive at 1.0 and 10.0

4) HP - 10% at 20.0

MONKEY DATA A. (SDS) # Animals / Dose (mg/kg/s.c.) 3 / 6.0, 3 / 1.5, 3(H_2O) / 1ml/kg

3(Morphine) / 3.0

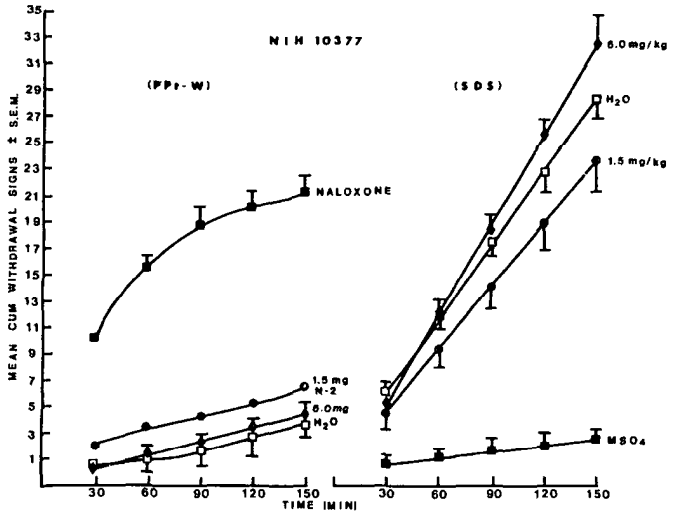
NIH 10377 did not substitute for morphine in the dose range 1.5 - 6.0 (see accompanying figure).

MONKEY DATA B) (PPt-W) # Animals / Doses (mg/kg/s.c.) 2 / 9.0, 3 / 6.0, 2 / 1.5

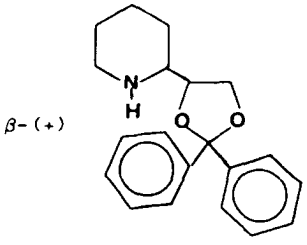
1 [a] / 0.375, 3(Naloxone), / 0.05, 3(H_2O) / 1ml/kg

This compound did not precipitate withdrawal in morphine-addicted monkeys. (see appropiate figure)

NIH 10377, MCV 4453 ß-(-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl [ß-(-)-Dioxadrol]



NIH 10378, MCV 4454 ß-(+)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl [ß-(+)-Dioxadrol]



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - Inactive at 1.0, 10.0 and 30.0

2) TF vs. M - 0% at 1.0, 12% at 10.0 and 43% at 30.0

3) PPQ - Inactive at 1.0 and 10.0 47% at 30.0

4) HP - Inactive at 5.0 and 20.0

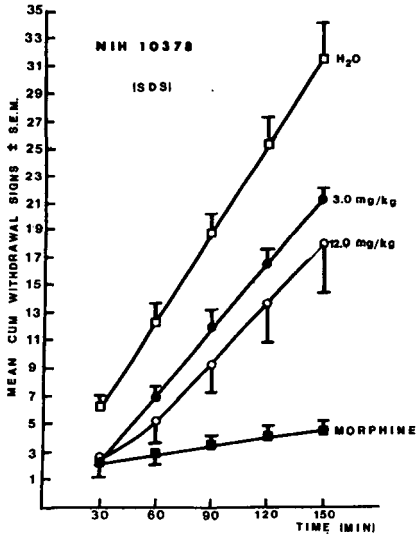
MONKEY DATA (SDS) # Animals bose (mg/kg/s.c.) 3/12.0, 3/3.0, 3(H_2O) 1ml/kg

3(Morphine) 3.0

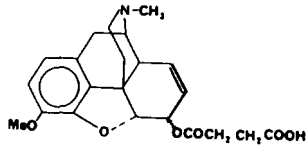
NIH 10378, MCV 4454 ß-(+)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine·HCl [ß-(+)-Dioxadrol]

(continued)...

As shown in the figure, NIH 10378 appeared to be substituting at least partly, in withdrawn addicts. Insufficient drug was provided for full evaluation.



NIH 10384, MCV 4448 6-Succinylcodeine



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF - 44% at 40.0, 14% at 10.0 and 0% at 1.0

2) TF vs. M - Inactive at 1.0, 10.0 and 30.0

3) PPQ - 10.6 (5.6 - 18.9)

4) HP - Inactive

NIH 10384, MCV 4448 6-Succinylcodeine

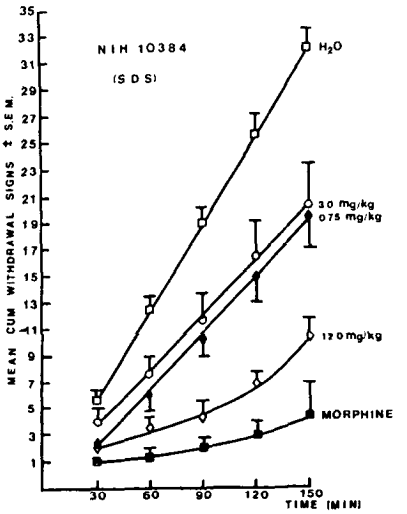
(continued)

MONKEY DATA (SDS)	# Animals	4	3	3
	Dose (mg/kg/s.c.)	12.0	3.0	0.75

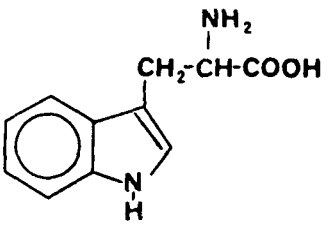
3(H_2O) 1mg/kg

3(Morphine) 3.0

As shown in the figure (NIH 10384) this compound substituted completely for morphine at the highest dose. Some alleviation of withdrawal was evident at the lower doses. The action is prompt and of shorter duration than that of morphine.



NIH 10429, MCV 4475 (L-Tryptophan tartrate)



MOUSE DATA ED or AD50 (95% C.L.) (mg/kg/s.c.)

1) TF -

2) TF vs. M - 0% at 1.0, 26% at 10.0 and 30.0, 6% at 40.0

NIH 10429, MCV 4475 (L-Tryptophan tartrate)

(continued)...

3) PPQ -

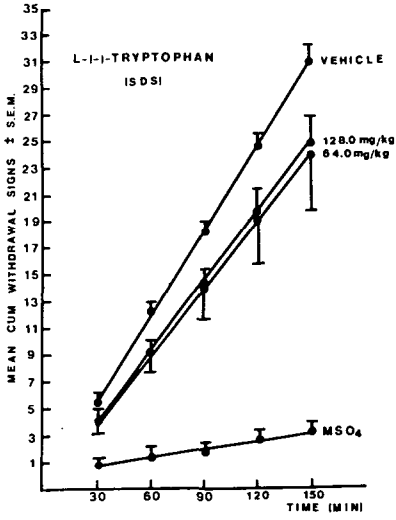
4) HP -

[a]Vehicle - Tween 80 + H_2O

MONKEY DATA (SDS)	# Animals / Dose (mg/kg/s.c.)	1 [a] / 32.0	3 / 64.0	3 / 128.0
		3(H_2O + Tween80) / 1ml/kg	3(Morphine) / 3.0	

As shown in the accompanying figure, tryptophan neither substituted for morphine nor exacerbated withdrawal.

[a] This dose not plotted, N=1.



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Evaluation of New Compounds for Opioid Activity (1985)

James H. Woods, Fedor Medzihradsky, Charles B. Smith, Gail D. Winger, and Debra E. Gmerek

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Medicinal Chemistry Section, NIAMDD, National Institutes of Health, Bethesda, MD. The drugs, which come originally from pharmaceutical companies, universities, and government laboratories, are submitted to Dr. Jacobson, who performs the MOUSE ANALGESIA tests. Values obtained in these tests for some representative opioid drugs are given in Table I.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. Only after the evaluation is complete and the report submitted back to Dr. Jacobson are the chemical structure and the mouse-analgesia data released to the evaluating laboratory.

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use two groups of monkeys to test the discriminative effects of submitted drugs. One of these groups, consisting of four monkeys, is trained to discriminate administration of the kappa agonist ethylketazocine (EKC). The other group is trained to discriminate the mu agonist, codeine. The procedures used with the EKC-trained monkeys have been described in Bertalmio, et al., 1982. The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in isolation chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the trial. The left lever is designated correct if they were given a sham injection before the start of the trial. Each trial lasts 15 min and

consists of an initial 10-min black-out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are earned before the 5-min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min trials. During a training session, if EKC is given, it is given on the penultimate trial of that session. Responding on the drug-appropriate lever is reinforced during that trial and on the subsequent, final trial of the day. These last two trials may be preceded by from zero to four sham trials on a training day. A training session of six sham trials is also scheduled from time to time.

With this type of multiple discrete trial training, the animals can be tested with a cumulative dosing procedure. On a test session, the first trial is preceded by an injection of saline, and prior to subsequent trials, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six trials are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each trial of a training session must be on the injection appropriate lever, either sham or EKC.

The procedure for the codeine-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-trial paradigm. The main difference between the codeine procedure and the EKC procedure is that the codeine monkeys are on a fixed-ratio, 20 schedule rather than a fixed-ratio, 100 schedule and they receive a single pellet for correct responses. They can earn as many as 10 pellets during the five minute, food-availability period of each trial, but each pellet is earned by making 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 40 total responses prior to earning the first food‘ pellet of each trial. Tests of the discriminative effects of submitted drugs in the codeine-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

DEPENDENCE EVALUATION IN RHESUS MONKEYS

The single-dose suppression (SOS) test determines the ability of a drug to suppress the signs of withdrawal in monkeys which have been made dependent by the chronic administration of morphine (3 mg/kg every six hours). Compounds suspected of having morphine-antagonist properties are tested for their ability to precipitate the withdrawal syndrome in nonwithdrawn (NW) morphine-dependent monkeys. Nondependent monkeys (Normals) are used to determine whether the acute effects of the test drug are reversible by nalorphine or naloxone. In a primary dependence (PDS) study, non-dependent monkeys receive the test drug every six hours for 30 days to determine whether withdrawal signs will appear when the animals are challenged with an antagonist or when drug administration is discontinued.

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting) by Deneau and Seevers (1963) and by Villarreal (1973).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys was studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior were produced by the compound.

The schedule of intravenous drug delivery was a fixed-ratio 30; when a light above a lever was illuminated, the 30th response produced a five-sec intravenous drug injection accompanied by another light that was illuminated during drug delivery. After each injection, a ten-min timeout condition was in effect during which responses had no scheduled consequence and neither light was illuminated. Each of the two daily sessions consisted of 13 injections or 130 min, whichever occurred first. Other details of the procedure and initial findings with a variety of narcotics are given in previous reports (Woods, 1977; 1980).

Doses of the drugs are typically described in terms of moles/kg/injection (inj), to facilitate direct comparisons among drugs. Duplicate observations of codeine (7.5×10^{-7} mol/kg/inj; 0.32 mg/kg/inj) and of saline were obtained for each monkey. A saline substitution was conducted before and after the series of observations on a test drug; the control rates of codeine-reinforced responding were obtained by a random sampling of two sessions interpolated between the drug-substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; each symbol is the mean of duplicate observations for a given dose in each monkey. The closed circles indicate the averaged data for

observations on the subset of monkeys used to study each drug under each of the experimental conditions. In all cases, the rates of responding given are those calculated during only the fixed-ratio portion of each session.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Details of the binding assay were described in the 1978 ANNUAL REPORT (Swain et al., 1978). Briefly, aliquots of a membrane preparation from rat cerebrum were incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of the drug under investigation. Stereospecific, i.e., opioid-receptor-related interaction of ^{3}H-etorphine was determined as the difference in binding obtained in the presence of an appropriate excess of dextrorphan and levorphanol, respectively. The potency of the drugs in inhibiting the stereospecific binding of ^{3}H-etorphine was determined from log-probit plots of the data It should be noted that since April 1982 the concentration of ^{3}H-etorphine in the binding assay was reduced from 3.0 nM to 0.5 nM, a concentration approaching the K_D of the radiolabeled opioid. This change was implemented in order to let the determined EC50 approximate the true K. of a given drug. However, due to the different concentrations of the radiolabeled ligand the EC50 determined since April, 1982 are lower than those obtained previously. For the purpose of reference, Table II contains EC50 values of representative opiates determined in binding assays using 0.5 nM ^{3}H-etorphine. Unless specifically noted in the Report, it should be assumed that 0.5 nM etorphine was used in the binding assays.

INHIBITION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA PIG ILEUM AND MOUSE VAS DEFERENS PREPARATIONS.

Submitted drugs are evaluated on two smooth muscle preparations, the details of which were described in the 1978 ANNUAL REPORT (Swain et al, 1978). Shown in the following pages are the EC50's for the tested drug alone, for the drug in the presence of naltrexone (a pure opioid antagonist which is more effective against 20-called "mu" agonists than against so-called "kappa" agonists), and for the drug in the presence of UM 979 (an antagonist which appears to be more effective against "kappa" than against "mu" drugs) (Smith, 1978). The maximum depression of the electrically induced twitch in each of the preparations is also indicated. The concentrations of both naltrexone and UM 979 used in tests of antagonism are for the guinea pig ileum always 10^{-7} M, and for the mouse vas deferens always 10^{-8} M.

TABLE I

MOUSE ANALGESIA. Before submission to The University of Michigan, all compounds are evaluated for analgesic activity by Dr. Arthur E. Jacobson. Shown below are comparative data (ED 50mg/kg) (95% Confidence Interval) from Hot Plate[a-c] and Nilsen assays. umol/kg

Compound	HOT PLATE (sc/mg/kg)	HOT PLATE (oral ,mg/kg)	NILSEN (sc, mg/kg)	NILSEN (oral, mg/kg)
NIH #	(sc, umol/kg)	(oral, umol/kg)	(sc. umol/kg),,	(oral, umol/kg)
Morphine sulfate	0.98 (0.83-1.1)	6.3 (4.7-8.3)	1.3 (1.0-1.7)	8.3 (6.0-11.4)
NIH 0001, 9929	2.9 (2.5-3.3)	18.9 (14.1-24.9)	3.9 (3.0-5.1)	24.9 (18.0-34.1)
Codeine phosphate	6.8 (4.5-10.2)	13.5 (9.7-18.7)	7.4 (4.9-11.0)	14.7 (9.2-23.3)
NIH 0002	17.1 (11.3-25.7)	34.0 (24.4-47.1)	18.6 (12.3-27.7)	37.0 (23.2-58.7)
Levorphanol tartrate	0.2 (0.1-0.3)	-	0.2 (0.16-0.3)	2.5 (1.7-3.7)
NIH 4590	0.5 (0.2-0.7)	-	0.5 (0.4-0.7)	6.2 (4.2-9.1)
Meperidine.HCl	5.3 (4.0-7.1)	-	-	-
NIH 5221	18.7 (14.1-25.0)	-	-	-
(-)-Metazocine.HBr	0.6 (0.5-0.9)	10.6 (8.0-14.1)	0.5 (0.3-0.7)	26.0 (21.0-33.0)
NIH 7569	1.9 (1.4-2.8)	34.1 (25.7-45.3)	1.6 (1.0-2.3)	83.6 (67.5-106.1)

TABLE I Continued

Dihydromorphinone.HCl NIH 0123	0.19 (0.15-0.25) 0.6 (0.5-0.8)	0.9 (0.7-1.2) 2.8 (2.2-3.7)	0.2 (0.15-0.3) 0.6 (0.5-0.9)	1.8 (1.5-2.1) 5.6 (4.7-6.5)
Nalorphine.HCl NIH 2105	9.9 (5.7-17.1) 28.4 (16.4-49.1)	- -	23.0 (16.2-32.7) 66.1 (46.6-94.0)	- -
Cyclazocine NIH 7981	1.5 (1.1-2.1) 5.5 (4.1-7.7)	- -	0.1 (0.07-0.16) 0.4 (0.3-0.6)	- -
Pentazocine NIH 7958	9.3 (6.7-12.8) 22.6 (23.5-44.9)	- -	6.5 (4.4-8.8) 22.8 (15.4-30.9)	- -
Naltrexone.HCl NIH 8503			No dose response	
Naloxone.HCl NIH 7890			No dose response	

No antinociceptive activity in hot plate assay: Phenobarbital, amobarbital, diazepam, meprobamate, mescaline, oxazepam, flurazepam.

Chloropromazine.HCl	1.1 (0.9-1.5) 3.2 (2.4-4.2)

a) Eddy and Leimbach (1953); b) Jacobson and May (1965); c) Atwell and Jacobson (1978); d) Perrine, Atwell, Tice, Jacobson and May (1972).

TABLE II

EC50 of representative opioids in displacing 0.5 nM ^{3}H-etorphine in a membrane preparation from rat cerebrum

Compound	EC50 (M) -NaCl	EC50 (M) +NaCl	+Na/-Na
UM 911	14.6	28.3	1.94
Morphine	14.0	23.6	1.69
Dextrorphan	6180	9820	1.59
UM 1071R	1.14	1.55	1.36
Ketazocine	10.7	14.1	1.32
Ethylketazocine	5.22	6.60	1.26
(-)SKF 10047	4.09	3.93	0.96
Etorphine	0.47	0.37	0.79
(-)Cyclazocine	0.85	0.53	0.63
Maltrexone	1.43	0.63	0.44

NOTE: Binding data for these and other compounds, determined in binding assays using 3.0 nM ^{3}H-etorphine, are included in the 1978 and 1981 ANNUAL REPORTS.

SUMMARY OF TESTS PERFORMED

The compounds which were evaluated at the University of Michigan during the past year and the individual tests which were performed are shown in Table III. Also shown are dates of Annual Reports in which results are reported of earlier tests on those compounds conducted at Michigan.

TABLE III

SUMMARY ON TESTS PREPARED

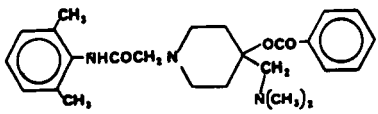
UM	NIH	CHEMICAL MCV	CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
0851	8627		Xylidide	+	-	-	-	-	-	-	-
0857	8630		Piperidineacetanilide	+	-	-	-	-	-	-	-
0862	8631		Toluidide	+	-	-	-	-	-	-	-
0863	8632		Xylidide	+	-	-	-	-	-	-	-
0864	8633		Xylidide	+	-	-	-	-	-	-	-
0865	8634		Diphenylnaphthalene	+	-	-	-	-	-	-	-
1229	9752	4203	Benzomorphan	-	+	-	-	1980	-	1980	-
1319	9918	4258	Morphinan	-	-	-	-	+	-	-	-
	9977	4298	Morphinan	-	-	-	-	-	+	+	-
	10001	4308	Hydrazinaloxone	-	-	-	-	+	+	+	-
1386	10019	4321	Benzomorphan	-	-	-	-	-	+	+	-
	10022	4323	Fentanyl	-	-	-	-	-	+	+	-
	10036		Benzazocine	1982	1982	-	-	-	+	+	-
	10071	4329	Morphanone	-	-	-	-	-	+	+	-
	10097	4332	Benzomorphan	-	-	-	-	-	+	+	-
	10098	4333	Benzomorphan	-	-	-	-	-	+	+	-
	10121	4338	Phenyltoloxamine	-	-	-	-	-	+	+	-
	10150	4340	Spiro-benzofuran	-	-	-	-	-	+	+	-
	10154	4344	Methylmorphan	-	-	-	-	-	+	+	-
	10156	4345	Benzomorphan	-	-	-	-	-	+	+	-
	10157	4349	Benzomorphan	1983	-	-	-	-	+	+	-
	10160	4351	Benzomorphan	1983	-	-	-	-	+	+	-

TABLE III Continued

UM	NIH	CHEMICAL MCV	CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS
	10178		Benzomorphan	-	-	-	-	-	+	+	-
	10186		Tripelennamine	-	-	-	-	-	+	+	-
	10270	4427	Peptide	-	-	-	-	-	+	+	-
	10271	4428	Peptide	-	-	-	-	-	+	+	-
	10318	4399	Imidazalidine	-	-	-	-	-	+	+	-
	10319		Phenylpiperazine	-	-	-	-	-	+	+	-
	10320	4401	Phenylpiperidine	-	-	-	-	-	+	+	-
	10321	4402	Phenylpiperidine	-	-	-	-	-	+	+	-
	10365*	4426	Nalmefene	-	+	-	+	-	+	+	-
	10374	4450	Levoxadral	-	-	-	-	-	+	+	-
	10375	4451	Dexoxadral	-	-	-	-	-	+	+	-
	10376	4452	Dioxadral	-	-	-	-	-	+	+	-
	10377	4453	Dioxadral	-	-	-	-	-	+	+	-
	10378	4454	Dioxadral	-	-	-	-	-	+	+	-

NIH 8627 4-(Dimethylaminomethyl)-4-hydroxy-1-piperidineaceto-2',6'-xylidide, p-anisate ester

MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: 0.44 (0.34 - 0.55)

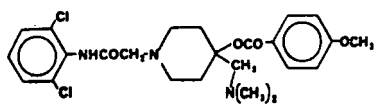


OBSERVATIONS ON THE MORPHINE-DEPENDENT RHESUS MONKEY

This compound was studied over a 0.0025 - 0.1 mg/kg range of doses under 14-hr withdrawn conditions; two monkeys per dose. Slight suppression of abstinence signs was observed at the lowest dose; complete suppression of abstinence signs was observed at 0.01 mg/kg. Duration of action of this drug was 6 hr at 0.1 mg/kg, and this dose was estimated to be equivalent to 3.0 mg/kg of morphine.

NIH 8630 2',6'-Dichloro-4-(dimethylaminomethyl)4-hydroxy-1-piperidineacetanilide, p-anisate ester

MOUSE ANALGESIA; ED50, (mg/kg)
Hot Plate: 1.3 (1.0-1.6)

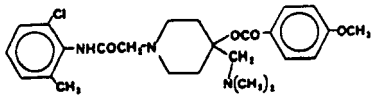


OBSERVATIONS ON THE MORPHINE-DEPENDENT RHESUS MONKEY

This compound was studied over a 2.0 - 32.0 mg/kg range of doses under 14-hr withdrawn conditions; two monkeys per dose. No suppression of abstinence signs was observed at the lowest dose; exacerbation of abstinence signs was observed at the higher doses.

NIH 8631 6'-Chloro-4-(dimethylaminomethyl)-4-hydroxy-1-piperidineaceto-o-anisate ester

MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: 0.53 (0.43 - 0.66)

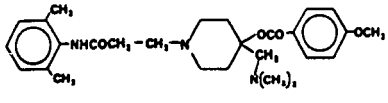


OBSERVATIONS ON THE MORPHINE-DEPENDENT RHESUS MONKEY

This compound was studied over a 0.025 - 0.2 mg/kg range of doses under 14-hr withdrawn animals, two monkeys per dose. Partial, transient suppression of abstinence signs was observed at the lowest dose. Suppression of abstinence signs was seen at 0.1 - 0.2 mg/kg. Suppression of abstinence was accompanied by signs of phenothiazine-like intoxication.

NIH 8632 4-(Dimethylaminomethyl)-4-hydroxy-1-piperidinepropiono-2',6'-xylidide, p-anisate ester

MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: 10.5 (8.3 - 13.2)

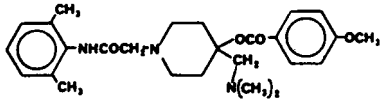


OBSERVATIONS ON THE MORPHINE-DEPENDENT RHESUS MONKEY

This compound was studied over a 1.0 - 4.0 mg/kg range of doses in 14-hr withdrawn animals; two monkeys per dose. No suppression of abstinence signs was observed at the lowest dose; complete suppression of abstinence signs, plus signs of CNS stimulation was observed at the highest dose. Dose estimated to be equivalent to 3.0 mg/kg of morphine was 4.0 mg/kg with a 4-5 hr duration of action at that dose.

NIH 8633 3-(Dimethylaminomethyl)-4-hydroxy-1-piperidineaceto-2',6'-xylidide,benzoate ester,dicyclohexane-sulfamate

MOUSE ANALGESIA; ED50, (mg/kg)
Hot Plate: 7.9 (6.3 - 10.0)

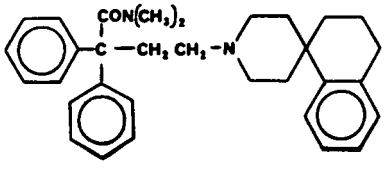


OBSERVATIONS ON THE MORPHINE-DEPENDENT RHESUS MONKEY

This compound was studied over a 4.0 - 16.0 mg/kg range of doses in 14-hr withdrawn animals, two monkeys per dose. Partial suppression of abstinence signs was observed at the lowest dose; Complete suppression of abstinence signs, preceded by preconvulsive signs, was observed at the highest dose. Dose estimated to be equivalent to 3.0 mg/kg of morphine was 16.0 mg/kg with a 4-hour duration of action at this dose.

NIH 8634 1,2,3,4-Tetrahydro-N,N-dimethyl-a,a-diphenylnaphthalene-1-spiro- 4'-piperidine-1'-butyramide hydrochloride

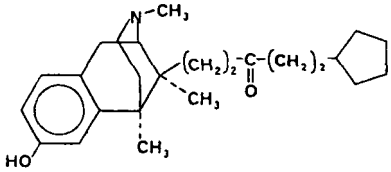
MOUSE ANALGESIA; ED50, (mg/kg)
Hot Plate: 0.21 (0.16 - 0.26)



OBSERVATIONS ON THE MORPHINE-DEPENDENT RHESUS MONKEY

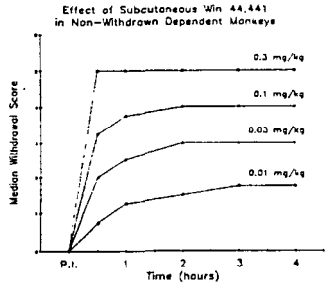
This compound was studied over a 0.1 - 0.4 mg/kg range of doses in 14-hour withdrawn animals; two monkeys per dose. No suppression of abstinence signs was observed at any dose; Slight sedation and ataxia was observed at the highest dose in withdrawn monkeys.

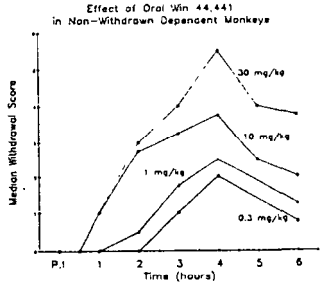
NIH 9752 (2α,6α,11S)-(-)-1-Cyclopentyl-5-(1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)-3-pentanone methanesulfonate

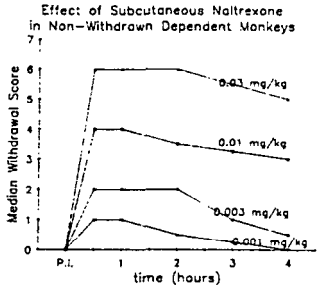


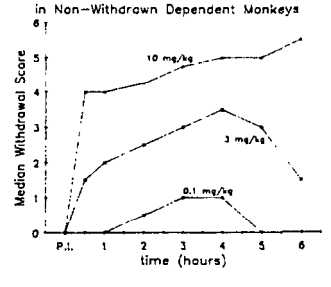
SINGLE DOSE PROCEDURE IN NON-WITHDRAWN MONKEYS

NIH 9752 was given by intranasal gastric intubation to non-withdrawn morphine-dependent rhesus monkeys (n= 3-6/dose) 1.5 - 2 hr after the last maintenance dose of morphine and approximately 0.5 hr after feeding the animals. Oral doses (1 ml/kg) of NIH 9752 (0.3, 1, 10 and 30 mg/kg) produced morphine withdrawal signs of increasing severity. The normal maintenance dose of morphine (3 mg/kg, s.c.) was given 4 hr after NIH 9752 administration. The peak effects occurred 4 hr after administration. Withdrawal lasted more than 6 hr. Orally administered NIH 9752 had a slower onset of action than s.c. NIH 9752. Orally administered NIH 9752 was approximately 100 times less potent than s.c. NIH 9752. In comparison, orally administered naltrexone was 1000 times less potent than s.c. naltrexone.



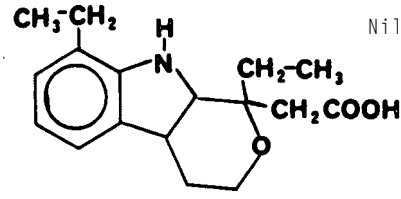






155-509 0 - 86 - 16

NIH 9918 1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (Etodolac)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 20% @ 50, 0% @ 100
Nilsen: 12% @ 100

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Not studied due to lack of solubility at appropriate concentrations.

INHIBITION OF TWITCH OF ELECTRICALLY STIMULATED GUINEA-PIG ILEUM

This drug caused only a slight inhibition of the twitch (less than 10%, n=6) which was completely antagonized by either naltrexone, 10^{-7} M, or UM 979, 10^{-7} M. In all preparations, this drug increased the magnitude of the twitch at concentrations of 10^{-4} and greater.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

High Affinity

	EC50 (M)	Maximum Response
Drug alone	3.47×10^{-7}	53.6 ± 7.4%
After naltrexone	8.63×10^{-8}	42.9 ± 17.5%

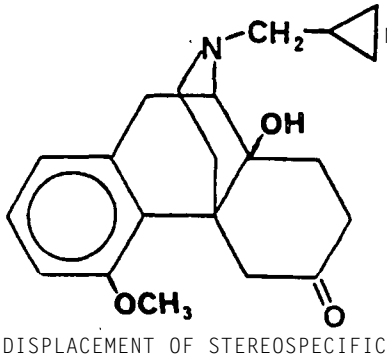
Low Affinity

	EC50 (M)	Maximum Response
Drug alone	2.58×10^{-5}	70.1 ± 5.5%
After naltrexone	4.48×10^{-4}	73.3 ± 6.8%

SUMMARY

NIH 9918 appears to have an opioid-like effect upon both preparations which occurs at high drug concentrations and which is antagonized more effectively by naltrexone than by UM 979. In addition, NIH 9918 has a marked inhibitory effect upon the mouse vas deferens which occurs at much lower concentrations and which is not blocked by either antagonist.

NIH 9977 (-)-N-Cyclopropylmethyl-14-hydroxy-4-methoxymorphinan-6-one



MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: 30% at 50

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 55 nM in presence of 150 nM NaCl

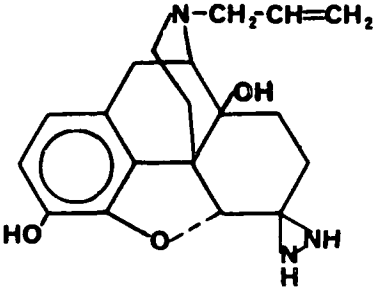
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	7.05×10^{-6}	87.5 ± 6.9%
After naltrexone	7.47×10^{-6}	78.0 ± 7.5%
With equimolar concentration of naltrexone	Very slight reversal	
Equimolar concentration with morphine	Very slight reversal	

SUMMARY

NIH 9977 was approximately equipotent to morphine in displacing ^{3}H-etorphine in rat brain membrane. NIH 9977 also appeared to be a mixed agonist-antagonist of low potency on the mouse vas deferens.

NIH 10001 6-Desoxy-6,6-hydrazinaloxone



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 3.65 nM in the presence of 150 mM NaCl

NIH 10001 6-Desoxy-6,6-hydrazinaloxone

(continued)...

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

The EC50 for NIH 10001 was 5.45 x 10^{-9} M + 5.11 M, with a 45.8 ± 6.3% inhibition of the twitch. Both naltrexone (10^{-7} M) and UM 979 (10^{-7} M) NIH 10001 continued completely blocked the inhibitory effect of this compound upon the preparation. In the presence of both naltrexone and UM 979, NIH 10001, in concentrations of 10^{-8} and higher, caused marked increases in the magnitude of the twitch. At the highest concentration,. NIH 10001 also caused contractions of the baseline.

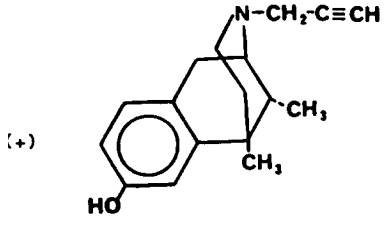
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	1.24 x 10^{-11}	87.5 ± 3.8%
After naltrexone	8.25 x 10^{-12}	78.6 ± 2.9%
After UM 979	9.91 x 10^{-12}	84.6 ± 2.4%

SUMMARY

On the guinea-pig-ileal preparation, NIH 10001 might have slight opioid activity which is blocked by both naltrexone and UM 979. However, one must keep in mind that upon this preparation, agents which are not opioid in nature but which suppress the twitch (e.g., mianserin) are also blocked by these two drugs. On the mouse vas deferens, NIH 10001 appears to be devoid of opioid agonist activity.

NIH 10019 (+)-5,9-Dimethyl-2'-hydroxy-2-propynyl-6,7-benzomorphan.HBr



MOUSE ANALGESIA, ED50, (mg/kg)
Hot plate: Inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 1.0 nM in the presence of 150 mM NaCl

NIH 10019 (+)-5,9-Dimethyl-2'-hydroxy-2-propynyl-6,7-benzomorphan.HBr

(continued) . . .

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

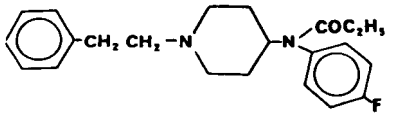
	EC50 (nM)	Maximum Response
Drug alone	25.6 ± 5.6	29.8 ± 1.8%
After naltrexone	21.9 ± 6.7	31.5 ± 1.8%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	Slight reversal	

SUMMARY

NIH 10019 is devoid of morphine-like agonistic activity upon the isolated mouse vas deferens preparation. The ability of this drug to slightly reverse the effects of morphine suggests that it might have slight antagonistic activity. It has a high affinity for the etorphine recognition site.

NIH 10022 p-Fluorofentanyl hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.015 (0.011-0.020)



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 200 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	62.0 nM ± 16.3	92.5 ± 9.4%
After naltrexone	4.33 µM ± 2.35	82.5 ± 3.2%
With equimolar concentration of na ltrexone	Complete reversal	
Equimolar concentration with morphine	No reversal	

NIH 10022 p-Fluorofentanyl hydrochloride

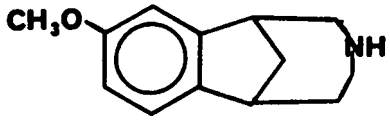
(continued) . . .

SUMMARY

Upon the mouse vas deferens preparation, NIH 10022 is a morphine-like agonist which is slightly more potent than morphine and equally efficacious. The binding data are in agreement in terms of potency estimate. The compound is more active on the hot plate than would be expected on the basis of in vitro studies.

NIH 10036 9-Methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine oxalate

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate 1.8 (1.1 - 2.7)



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 84.5 μM in the presence of NaCl

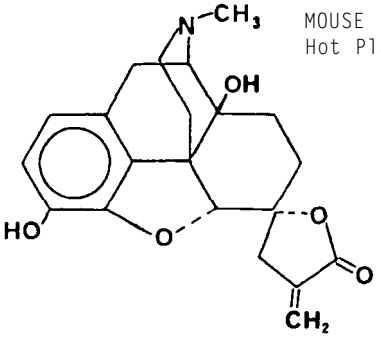
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	2.35×10^{-5}	38.1 ± 10.5%
With naltrexone	2.11×10^{-6}	21.8 ± 1.5%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10036 is devoid of opioid agonistic or antagonistic activity upon the isolated mouse vas deferens preparation; it displaces etorphine only at high concentrations.

NIH 10071 6ß-(ß-Carboxyallyl)-oxymorphon-6α-ol-δ-lactone acetic acid salt



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.6 (1.8 - 3.6)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 35 nM in presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

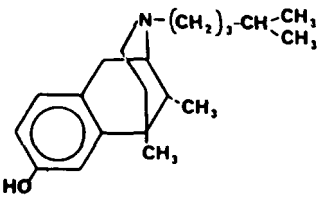
	EC50 (μN)	Maximum Response
Drug alone	5.74 ± 1.75	87.6 ± 3.0%
After naltrexone	20.4 ± 0.6	84.5 ± 2.8%
With equimolar concentration of naltrexone		No reversal
Equimolar concentration with morphine		Marked reversal

SUMMARY

NIH 10071 appears to be a morphine antagonist which has very slight morphine-like agonistic activity at high concentrations. It is as effective, but approximately 30 times less potent than morphine in suppressing the twitch of the mouse vas deferens preparation. Its potency at the etorphine binding site suggests a higher potency.

NIH 10097 α-(-)-N-4-Methylpentyl-N-normetazocine.HBr

(-)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 3.1 (2.4 - 4.1)

NIH 10097 α-(-)-N-4-Methylpentyl-N-normetazocine.HBr

(continued)....

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 195 nM in the presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

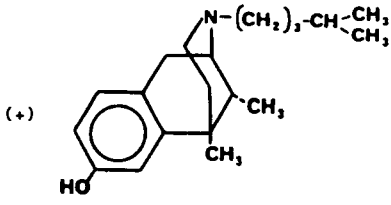
	EC50 (nM)	Maximum Response
Drug alone	70.6 ± 2.4	91.3 ± 3.0%
After naltrexone	706.1 ± 24.7	49.6 ± 2.9%
With equimolar concentration of naltrexone	Marked reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

Upon the mouse vas deferens preparation, NIH 10097 appears to be a morphine-like agonist. The binding data suggest a potency similar to morphine.

NIH 10098 α-(+)-N-4-Methylpentyl-N-normetazocine.HBr

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 30% at 50, 70% at 100



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 10 nM in the presence of 150 mM NaCl

NIH 10098 α-(t)-N-4-Methylpentyl-N-normetazocine.HBr

(continued) . . .

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

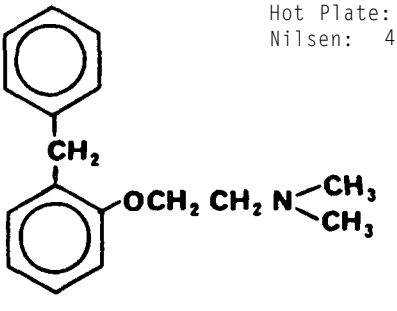
	EC50 (nM)	Maximum Response
Drug alone	7.6 ± 3.50	19.8 ± 2.6%
After naltrexone		No suppression
With equimolar concentration of naltrexone		No reversal
Equimolar concentration		Marked reversal

SUMMARY

NIH 10098 is an opioid antagonist upon the mouse vas deferens preparation. The binding data indicate a high affinity for the etorphine-recognition site.

NIH 10121, 10197 Phenyltoloxamine dihydrogen citrate

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 40.5 (27.5-59.6)
Nilsen: 40% at 80



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of >6000 nM in the presence of NaCl

NIH 10121, 10197 Phenyltoloxamine dihydrogen citrate

(continued)...

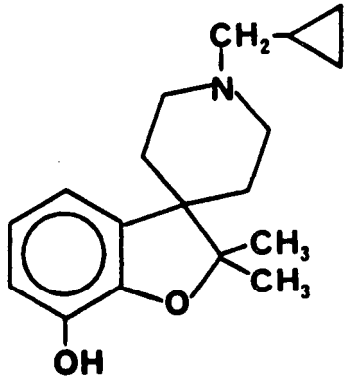
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	5.41×10^{-8}	12.5 ± 2.7%
After naltrexone	1.00×10^{-7}	15.5 ± 3.5%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10121 (10197) has no significant opioid activity on either preparation.

NIH 10150 1'-Cyclopropylmethyl-2,2-dimethyl-spiro[benzofuran-3(2H),4'piperidine-7-ol]



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 70% at 50
(No dose-response)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 665 nM in the presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	4.17×10^{-7}	58.2 ± 9.2%
After naltrexone	3.94×10^{-7}	31.4 ± 2.1%
With equimolar concentration of naltrexone	Reversal	
Equimolar concentration with morphine	Reversal	

NIH 10150 1'-Cyclopropylmethyl-2,2-dimethyl-spiro[benzofuran-3(2H),4'piperidine-7-ol]

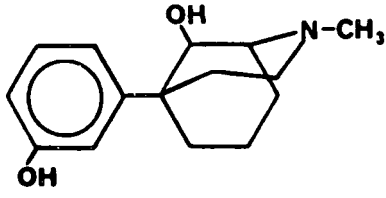
(continued)...

SUMMARY

NIH 10150 appears to be a mixed opioid agonist-antagonist upon the mouse vas deferens preparation. It was less potent in both preparations than a number of reference standards.

NIH 10154 9ß-Hydroxy-5-(m-hydroxyphenyl)-2-methylmorphan mandelate

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 30% at 100



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 7.5 nM in presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

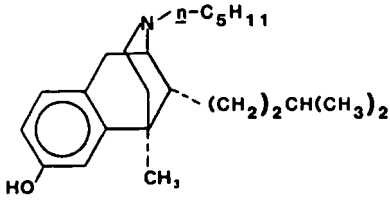
	EC50 (µM)	Maximum Response
Drug alone	7.31 ± 0.24	82.3 ± 4.8%
After naltrexone	14.6 ± 5.57	41.1 ± 2.2%
With equimolar concentration of naltrexone	Marked reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10154 is a morphine-like agonist upon the mouse vas deferens preparation. It is as efficacious, but less potent than morphine. It was considerably more potent in the binding assay.

NIH 10156 2'-Hydroxy-5-methyl-9α-(3-methyl)butyl-2-pentyl-6,7-benzomorphan

MOUSE ANALGESIA, ED50, (mg/kg)
Hot Plate: 30% at 100



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 58.5 nM in presence of NaCl

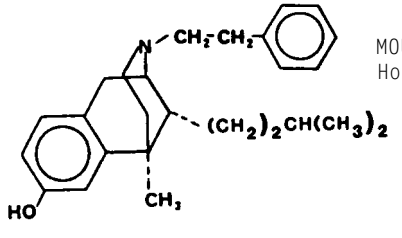
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	9.62×10^{-9}	18.2 ± 1.2%
After naltrexone	7.52×10^{-8}	16.7 ± 1.4%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10156 has a very slight inhibitory effect upon the mouse vas deferens preparation which does not seem to be morphine-like. This drug is also devoid of opioid antagonistic activity upon the isolated mouse vas deferens preparation. It was, however, quite potent in the binding assay.

NIH 10157 2'-Hydroxy-5-methyl-9 α-(3-methyl)butyl-2-phenethyl-6,7-benzomorphan oxalate



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 50% at 50

NIH 10157 2'-Hydroxy-5-methyl-9α-(3-methylbutyl-2$_T$phenethyl-6,7-benzomorphan oxalate

(continued)....

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 1230 nM in presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	Undeterminable	No inhibition

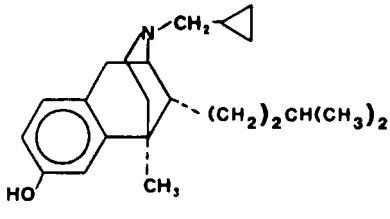
NIH 10157 did not inhibit the twitch at any concentration studied. At a concentration of 3 x 10^{-6}, NIH 10157 did cause a gradual reversal in the inhibitory action of an equimolar concentration of morphine. However, it was impossible to determine whether this represented a pharmacological action. NIH 10157 does not appear to have opioid agonist activity upon this preparation.

SUMMARY

NIH 10157 is devoid of opioid activity in the mouse vas deferens and is active in the binding assay at very high concentrations.

NIH 10160 2-Cyclopropylmethyl-2'-hydroxy-5-methyl-9α-(3-methylbutyl-6,7-benzomorphan oxalate

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 30% at 50



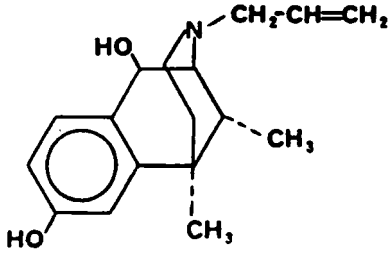
NIH 10160 2-Cyclopropylmethyl-2'-hydroxy-5-methyl-9α-(3-methyl) butyl-6,7-benzomorphan oxalate

(continued) . . . .

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	1.85×10^{-8}	18.6 ± 0.8%
After naltrexone	1.79×10^{-8}	14.7 ± 0.6%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No reversal	

NIH 10178 1,8-Dihydroxy-N-allylnormetazocine



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 32.70 μM in presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

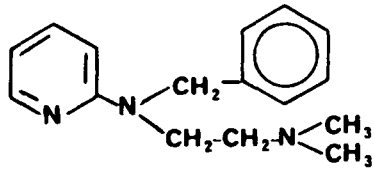
	EC50 (M)	Maximum Response
Drug alone	8.52×10^{-7}	54.4 ± 4.4%
After naltrexone	5.87×10^{-7}	50.9 ± 10.1%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10178 has no significant opioid activity in either preparation.

NIH 10186 N,N-Dimethyl-N'-2-pyridinyl-1,2-ethanediamine hydrochloride (Tripelennamine)

MOUSE ANALGESIA; ED50 (mg/kg)
Hot Plate: 3.9 (1.9-7.9)



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 10.3 μM in the presence of NaCl

INHIBITION OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

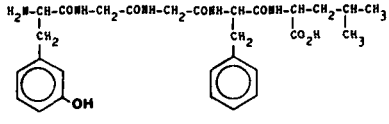
	EC50 (M)	Maximum Response
Drug alone	1.86×10^{-7}	25.4 ± 9.4%
After naltrexone	1.43×10^{-7}	29.1 ± 9.6%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No alteration of response	

SUMMARY

NIH 10186 has no opioid activity in either preparation.

NIH 10270 N-[(N-(N-L-m-Hydroxyphenylalanylglycyl)glycyl)]-L-phenylalanyl)-L-leucine acetate

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive



NIH 10270 N-[(N-(N-(L-m-Hydroxyphenylalanylglycyl)glycyl)]-L-phenylalanyl)-L-leucine acetate

(continued) . . .

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of >10 μM in the presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

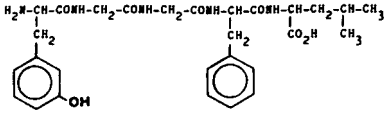
NIH 10270 did not suppress the twitch of the mouse vas deferens significantly at any concentration. In equimolar concentration, it did not reverse the inhibitory action of a maximally effective concentration of morphine (10 uM).

SUMMARY

NIH 10270 has no significant opioid action upon either preparation.

NIH 10271 N-[(N-(N-D-m-Hydroxyphenylalanylglycyl)glycyl)]-L-phenylalanyl)-L-leucine acetate

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 5.93 μM in the presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	9.13×10^{-6}	75.5 ± 5.3%
After naltrexone	2.16×10^{-5}	41.8 ± 5.3%
With equimolar concentration of naltrexone	Reversal	
Equimolar concentration with morphine	No reversal	

NIH 10271 N-[(N-(N-D-m-Hydroxyphenylalanylglycyl)glycyl)]-L-phenylalanyl)-L-leucine acetate

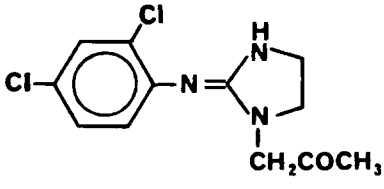
(continued) . . .

SUMMARY

NIH 10271 appears to be much less potent than morphine, but to possess opioid actions in both preparations.

NIH 10318 1-Acetonyl-2-(2,4-dichlorophenyl)iminoimidazolidine-

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 40% @ 50



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING (0.5 nM)

EC50 of 1.0 μM in presence of NaCl

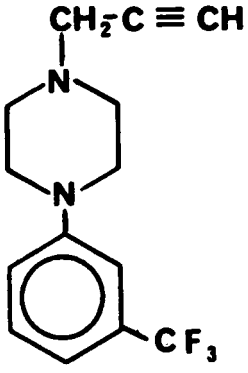
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	3.76×10^{-5}	98.5 ± 7.7%
With naltrexone	4.87×10^{-5}	97.7 ± 12.5%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10318 inhibits the twitch of the mouse vas deferens, but through a non-opioid action. It displaced etorphine with a low potency.

NIH 10319 N-Propargyl-N'-(3-trifluoromethylphenyl)piperazine-HCl



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 60% @ 100

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

NIH 10319 had an EC50 >6 μM

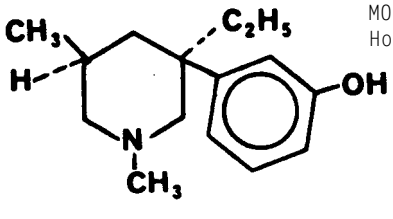
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

Only in a concentration of 10^{-4} did NIH 10319 cause a slight and transient' inhibition of the twitch. This activity was not altered in the presence of naltrexone. In an equimolar concentration, naltrexone did not reverse the slight inhibitory action of NIH 10319; NIH 10319 did not reverse the inhibitory action of a maximally effective concentration of morphine.

SUMMARY

NIH 10319 is devoid of significant opioid agonist or antagonist activity upon the isolated mouse vas deferens preparation or in the binding assay.

NIH 10320 (3R,5R)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride



MOUSE ANALGESIA; ED50 (mg/kg)
Hot Plate: 6.9 (4.0 - 12.0)

NIH 10320 (3R,5R)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride

(continued) . . .

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 40.0 nM in the presence of NaCl

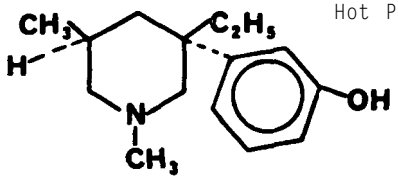
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	1.18×10^{-8}	22.4 ± 4.5%
With naltrexone	1.74×10^{-8}	23.7 ± 1.2%
With equimolar concentration of naltrexone	No reversal	
Equimolar concentration with morphine	Partial reversal	

SUMMARY

NIH 10320 is an opioid antagonist upon the isolated mouse vas deferens preparation. The binding assay confirms opioid activity with a correspondingly appropriate potency.

NIH 10321 (3R,5S)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 1.95 (1.2 - 2.5)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 62 nM in the presence of NaCl

NIH 10321 (3R,5S)-1,5-Dimethyl-3-ethyl-3-(3-hydroxyphenyl)piperidine hydrochloride

(continued)...

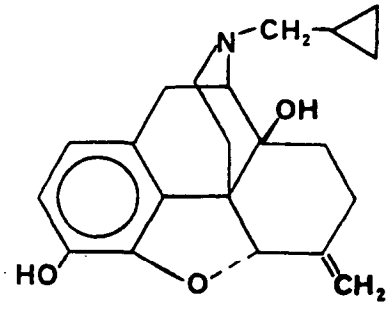
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50 (M)	Maximum Response
Drug alone	4.59×10^{-7}	52.1 ± 5.1%
With naltrexone	0.21×10^{-7}	26.4 ± 6.8%
With equimolar concentration of naltrexone	Marked reversal	
Equimolar concentration with morphine	No reversal	

SUMMARY

NIH 10321 appears to be an opioid agonist upon the isolated mouse vas deferens preparation; it is slightly less potent than morphine, also less efficacious. NIH 10321 was antagonized in what appears to be a non-competitive manner by naltrexone. Naltrexone also completely reverses the inhibition of the twitch produced by NIH 10321. The binding data correspond in potency to the potency in the smooth muscle preparation.

NIH 10365 17-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-7-methylenemorphinan.HCl (Nalmefene)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

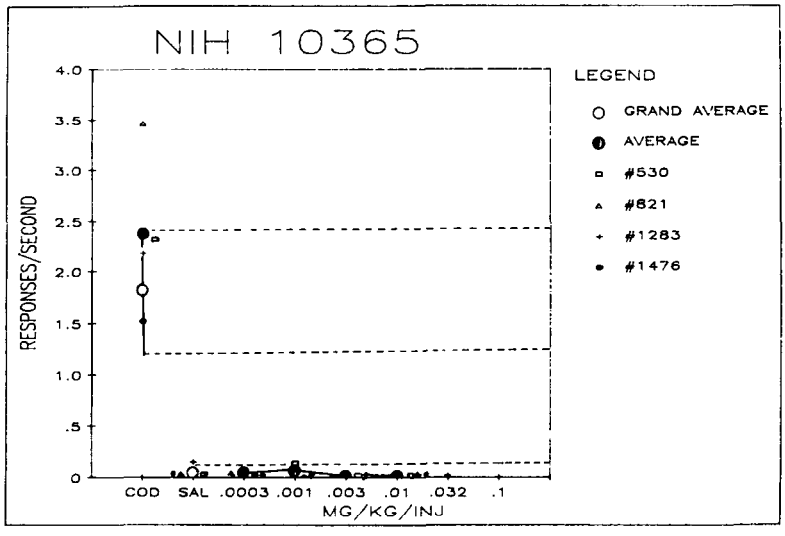
NIH 10365 was found to be inactive as an agonist in concentrations from 3×10^{-8} to 3×10^{-5} M. In equimolar concentrations, it completely reversed the inhibitory action of morphine (10 μM).

NIH 10365 17-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-7-methyl-enemorphinan.HCl (Nalmefene)

(continued)...

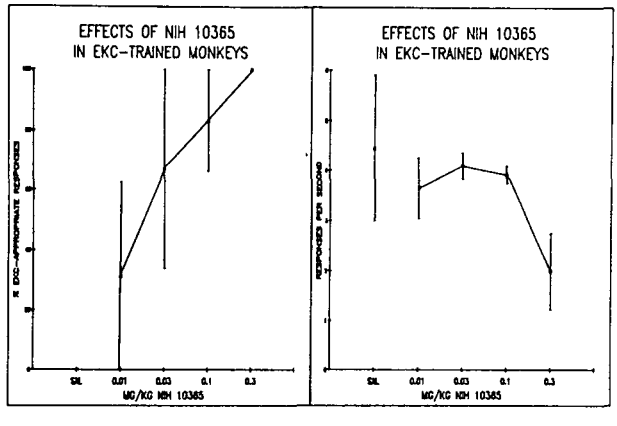
DRUG SELF-ADMINISTRATION IN RHESUS MONKEYS

NIH 10365 did not maintain rates of responding above those maintained by saline at any of the tested doses: 0.003 - 0.1 mg/kg/inj.



DRUG DISCRIMINATION IN RHESUS MONKEYS

NIH 10365 produced EKC-like discrimination in each of three monkeys. 100% EKC-appropriate responding occurred at a dose of 0.3 mg/kg.



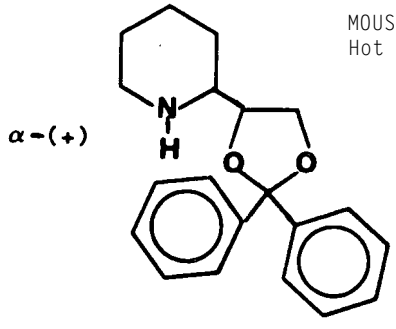
NIH 10365 17-Cyclopropylmethl-3,14-dihydroxy-4,5-epoxy-7-methylenemorphinan.HCl (Nalmefene)

(continued) . . .

SUMMARY

NIH 10365 had no narcotic agonist activity in the mouse vas deferens, but was an effective antagonist of morphine. It failed to maintain self-injection responding at rates above those of saline. It produced drug-appropriate responses in monkeys trained to discriminate ethylketazocine from saline. This suggests that NIH 10365 may have kappa-agonist activity in monkeys.

NIH 10374 (-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine.HCl (Levixadrol.HCl)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of >10 μM in the presence of NaCl

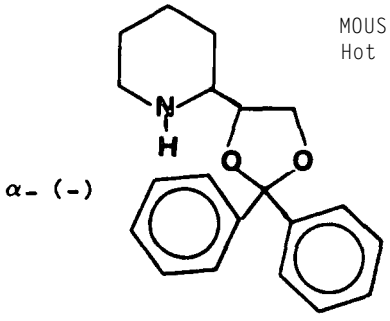
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10374 did not inhibit the twitch at any concentration and increased the twitch magnitude at concentrations above 3×10^{-6} M. It is devoid of opioid agonistic and antagonistic activity upon the mouse vas deferens preparation.

SUMMARY

NIH 10374 failed to display significant opioid activity in either preparation.

NIH 10375 (-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine.HCl (Dexoxadrol. HCl)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of >10 μM in presence of NaCl

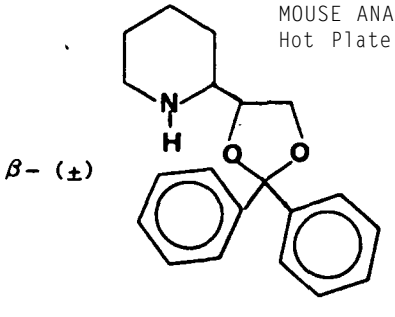
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At no concentration did UM 1275 inhibit the twitch of this preparation. At concentrations of 3 x 10^{-6} M and higher there were increases in the magnitude of the twitch. NIH 10375 is devoid of opioid agonistic and antagonistic activity upon this preparation.

SUMMARY

NIH 10375 failed to display significant opioid activity in either preparation.

NIH 10376 β-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine.HCl (β Racemate of Dioxadrol)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: No dose-response

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of >10 μM in the presence of NaCl

NIH 10376 β-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine,HCl (β Racemate of Oioxadrol)

(continued) . . .

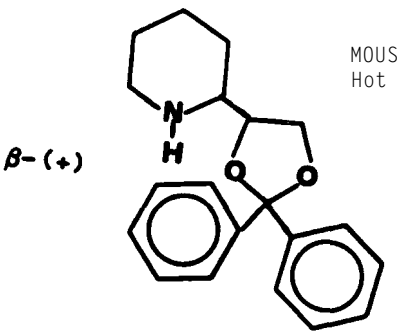
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At no concentration did NIH 10376 inhibit the twitch of this preparation. At concentrations of 3 x 10^{-6} M it increased the magnitude of the twitch. NIH 10376 did not block the inhibitory effect of morphine and thus is devoid of opioid agonistic and antagonistic activity upon this preparation.

SUMMARY

NIH 10376 failed to display significant opioid activity in either preparation.

NIH 10377 β-(-)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine-.HCl (β-(-)-Dioxadrol)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 7.47 μM in the presence of NaCl

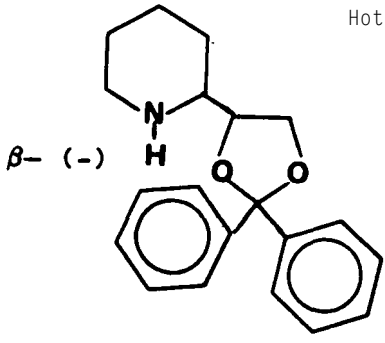
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10377 did not inhibit the twitch at any concentration and increased the twitch magnitude at concentrations above 3 x 10^{-6} M. It did not block the inhibitory effect of morphine, and is thus devoid of opioid agonistic and antagonistic activity upon this preparation.

SUMMARY

NIH 10377 failed to display significant opioid actions in either preparation.

NIH 10378 β-(+)-2-(2,2-Diphenyl-1,3-dioxolan-4-yl)piperidine-.HCl (β-(+)-Dioxadrol)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: Inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of >10 μM in the presence of NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10378 did not inhibit the twitch at any concentration and increased twitch magnitude at concentrations above 3 x 10^{-6} M. It did not block the inhibitory effect of morphine; thus, NIH 10378 is devoid of opioid agonistic and antagonistic activity upon this preparation.

SUMMARY

NIH 10378 failed to display significant opioid actions in either preparation.

ACKNOWLEDGEMENT

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Behavioral Extinction in the Treatment of Opiate Dependence

A. Thomas McLellan, Anna Rose Childress, and Charles P. O'Brien

Former opiate addicts (even those who have remained drug-free for several months) often report symptoms of opiate withdrawal (e.g. nausea, gooseflesh, etc.) and/or intense drug craving when exposed to stimuli previously associated with the act of drug injections. This phenomenon of learned or "conditioned" withdrawal/craving is widely reported and is potentially important in explaining relapse to drug use. However, no effective, clinically applicable intervention had been available to "extinguish" these conditioned phenomena. An ongoing project to develop such an intervention has revealed three findings.

1. CONDITIONED DRUG RESPONSES ARE PERVASIVE. Among methadone patients, presentation of stimuli previously associated with drug use in a laboratory setting. produced conditioned-physical signs of withdrawal in 34% of subjects tested, while 48% reported subjective symptoms of craving. This was true despite the fact that actual physical withdrawal was blocked by the methadone.

Among drug-free patients, presentation of stimuli previously associated with drug use in a laboratory setting produced conditioned-physical signs of withdrawal in 50% of subjects tested, while 88% reported subjective symptoms of craving. This was true despite the fact that these patients had been in an inpatient drug-free, Therapeutic Community Program for 30 days following detoxification.

2. EMOTIONAL STATES MAGNIFY CONDITIONED DRUG RESPONSES. Drug-related stimuli that had been extinguished under 'normal" conditions showed powerful conditioned withdrawal responses when the subject was angry. Emotional states of anger, depression and anxiety appear to be the most powerful enhancers of conditioned drug responses. Emotional states may elicit feelings of withdrawal and subjective reports of drug craving even without other drug-related stimuli. Emotional states may also become part of a conditioned stimulus complex (with other, tangible drug-related stimuli) to produce enhanced levels of conditioned withdrawal and conditioned craving.

3. CONDITIONED DRUG RESPONSES CAN BE EXTINGUISHED. An inpatient program of two, hour-long "extinction sessions" per day was employed over a 10-day period. Within each extinction session a 5-minute audio tape involving "drug-talk", and video presentation of a drug "buy" and injection, and a mock cook-up procedure were repeated three times. Each subject received 10 days of extinction training, with two sessions per day and three exposures to each of the three stimuli per session, for a total of 180 stimulus presentations. Significant reductions in both physical signs of conditioned withdrawal and subjective symptoms of craving were seen over the course of the extinction sessions. Generalization testing with different drug-related stimuli also showed significant reductions in physical reactivity and subjective reports of drug craving.

The authors discuss the problems associated with turning a laboratory-based procedure into a clinical intervention. Encouraging preliminary results from an integrated treatment "package" which includes extinction, relaxation training, education and professional psychotherapy are presented.

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Identifying Types of Drug Intoxication: A Laboratory Evaluation of Subject-Examination Procedures

George E. Bigelow, Warren K. Bickel, John D. Roache, Ira A. Liebson, and Pat Nowowieski

This study assessed a subject examination procedure developed and used by the Los Angeles Police Department for identifying and differentiating types of drug intoxication. Subjects were 80 normal, healthy, adult male volunteers. Raters were four experienced staff of the Los Angeles Police Department, who had been trained in a standardized examination procedure. Under double-blind conditions subjects received one of the following 8 treatments: Placebo, p.o., smoked; d-Amphetamine 15 mg, p.o.; d-Amphetamine 30 mg, p.o.; Oiazepam 15 mg, p.o.; Diazepam 30 mg, p.o.; Secobarbital 300 mg, p.o.; Marijuana 1.3% THC, smoked; Marijuana 2.8% THC, smoked. Subjects were then examined independently by each of the four raters, who attempted to identify the drug class producing any observed drug intoxication. Examinations consisted of: (a) Interview, to assess alertness, responsiveness, speech and conversation characteristics, mood and attitude; (b) Physiological signs, including pulse rate, blood pressure, oral temperature, pupil size, pupil response to light and dark, nystagmus, visual pursuit, perspiration, salivation; (c) Field sobriety test, including standing steadiness and time perception, one-foot balance, hand-to-nose test, walk-the-line test. Raters performed remarkably well in identifying the drug classes administered to subjects, and did so with a low rate of false positive errors. In 320 subject-examinations there were 157 judgements of drug intoxication. On 91.7% of those occasions the rater correctly identified the general drug class the subject had received (stimulant, depressant, marijuana). For all drug classes the sensitivity of drug recognition was dose-related, with higher doses being more likely to be correctly detected. For all drug classes, subjects judged to be intoxicated by a particular drug class were highly likely to have-received that drug class; accuracies of judgements of stimulant, marijuana, and depressant intoxication were 80%, 97.5%, and 92.7%, respectively. This combination of dose-related sensitivity and high accuracy argues for the validity of this assessment procedure.

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Sociopathy and Psychotherapy Outcome

George E. Woody, A. Thomas McLellan, Lester Luborsky, and Charles P. O'Brien

One hundred and ten nonpsychotic opiate addicts were randomly assigned to receive paraprofessional drug counseling alone or counseling plus professional psychotherapy. The outcomes of patients who received psychotherapy were examined in terms of their DSM III diagnoses. Four groups were compared: opiate dependence alone (N = 16), opiate dependence plus depression (N=16); opiate dependence plus depression plus antisocial personality disorder (N = 17); and opiate dependence plus antisocial personality disorder (N = 13).

Those with opiate dependence plus antisocial personality disorder alone improved only on ratings of drug use. Patients with opiate dependence alone or with opiate dependence plus depression improved significantly and in many areas. Opiate dependent patients with antisocial personality plus depression responded almost as well as those with only depression. Antisocial personality disorder alone is a negative predictor of psychotherapy outcome, but the presence of depression appears to be a condition that allows the patient to be amenable to psychotherapy, even though the behavioral manifestations of sociopathy are present.

AUTHORS

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Lowered Drug Abuse Recidivism Following Psychotropic Medication

David M. Ockert, Edgar E. Coons, Irl Extein, and Mark S. Gold

Drug use recidivism as a joint function of short-term psychotroic medication (primarily tricyclic antidepressants and lithium) and participation in an outpatient psychosocial treatment phase, post inpatient hospitalization, was studied in a population composed predominantly of white, high-economic status, detoxified, opioid and cocaine abusers. Both administration of psychotropic medication and participation in the outpatient phase significantly predicted a drug-free outcome at a 3½ month follow-up, approximately 1½ months after medication was discontinued. These effects were additive, not interactive. An inferred mode of protective action of the psychotropic drugs is to reduce hypersensitivity to the stress and low energy depression components of the protracted abstinence syndrome seen in detoxified drug abusers and, thereby, reduce their susceptibility to reinitiation of drug use during the critical time of re-entry into the community and beginning of treatment on an outpatient basis. The data do not support the assumption that non-addicting psychotropics interfere with recovery.

AUTHORS

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The Role of Early Classroom Environment in Predicting Marijuana Use in Late Adolescence

Sheppard G. Kellam, Ulder J. Tillman, and Paul S. Albert

Aggression in young male children is, except for sex, the strongest and most frequently replicated early predictor of later heavy drug use and delinquency. We examined whether the prediction from first grade aggressiveness to adolescent marijuana use is mediated by the level of aggression in the first grade classroom.

Our study population, the 1966-67 first grade cohort (N=1,242) of Woodlawn, a poor black Chicago community, had been rated by first grade teachers for aggression (fighting and breaking rules), shyness (sitting alone, not participating), underachievement, and inability to concentrate, and we followed up 10 years later, at ages 16 or 17, by reinterviewing 75% (N=939) of the mothers, and then, with parental permission, reinterviewing 75% (N=705; 344 boys, 361 girls) of the original students.

The first grade classroom environments of this cohort were studied in terms of the prevalence of aggression among classmates, and this was included in analyses along with the individual child's aggression rating in predicting marijuana use 10 years later. Similarly, we studied the influence of the level of aggression in first grade classrooms on males who were (a) shy, (b) shy and aggressive, and (c) neither shy nor aggressive. Females were not addressed because males and females differ in the predictive importance of early shy and/or aggressive behavior.

Our studies revealed that (1) nonshy, nonaggressive males in a first grade classroom with a high level of aggression were not likely to try marijuana 10 years later; (2) aggressive males who had been in classrooms with high a gression levels were more likely to try marijuana 10 years later; (3) level of aggression in first grade classroom did not influence trying marijuana later for shy males (including those who were shy and aggressive); and (4) first grade classroom environment as measured by level of aggression did not influence heavy drug use, but it did influence whether marijuana would be tried at least once by age 16 or 17. We concluded that children are particularly at risk and these appear to be the aggressive children observable as early as first grade. Those not at risk are also of great interest for research into vulnerability of substance abuse. Future studies should include analyses of the impact of classroom aggression as a potential mediating variable.

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Characteristics of Cocaine Users in Treatment

Sidney H. Schnoll, Amin N. Daghestani, Judy Karrigan, Sarah B. Kitchen, and Thomas Hansen

Retrospective chart review was performed on 172 patients admitted to a chemical dependence program over a 5-year period for the treatment of cocaine abuse. Information was obtained on patient demographics, route and amount of cocaine use, other drug and alcohol use, employment status, education, previous psychiatric and/or drug abuse treatment, legal history and medical and psychiatric diagnoses. Over the period studied, the percent of cocaine-related admissions increased from 0.6% to 51.8%. The patient population was predominantly male (69.2%) and had a mean age of 30.384 years. Over 83% of the patients were high school graduates, 63.4% were employed and over 50% were working in managerial, professional or skilled labor positions. Thirty-seven percent of the working patients were dealing cocaine. Forty-four percent were smoking cocaine free base, 34% snorting cocaine and 21.6% using intravenously. Fifty-six percent of the patients were taking cocaine daily, and the average weekly dose was 8 grams. Most patients used 1-3 grams each time they used. Over 50% of the cocaine users presented for treatment within 1 year of initiating use, and 37% used for less than 6 months. The patients viewed cocaine as the drug which caused them to seek treatment, although past and current use of other drugs, especially alcohol, was common. The other drugs were initially used to modify the effects of cocaine, usually to sedate or "bring down" the patient after a cocaine run. Of all the drugs on which information was available, alcohol was the most frequently used in conjunction with cocaine (89.4%). Marijuana was the next most commonly used drug, with 43% reporting using it on a daily basis. Thirty-three percent of the patients *were using* sedative-hypnotic medications daily to assist in sleeping after taking cocaine. Twenty-five percent of the patients were using heroin to modify the effects of cocaine. These were predominantly intravenous users of cocaine. Most of the cocaine users had used other drugs before using cocaine but few had received previous drug treatment or psychiatric treatment. The most common reason for seeking treatment related to financial difficulties related to the use of cocaine. The patients tended to

be cooperative, with less than 16% of the patients relapsing while in the chemical dependence program. They were receptive to follow-up care. The compliance with treatment may be related to the high degree of success this population has had in conforming to societal roles.

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Comparative Evaluation of Ciramadol, Morphine, and Pentazocine

Kenzie L. Preston, George E. Bigelow, and Ira A. Liebson

The subjective, physiological and behavioral effects of morphine, pentazocine, and ciramadol, an opioid agonist/antagonist, were studied in adult, male, non-dependent opioid abusers living on a clinical research ward. Fifteen subjects were randomly assigned to one of three groups. Each group received, by i.m. injection, placebo and three doses of one active drug, twice in randomized block order under double-blind conditions in 4.5-hour experimental sessions. Physiological measures did not differentiate between the three drugs. All three drugs decreased respiratory rate and pupil diameter and increased blood pressure. Morphine, ciramadol, and pentazocine produced different profiles on the subjective effect measures. All three drugs increased subject ratings of "liking," "good effects," "any effects," and "high" on visual analog scales. Pentazocine alone increased subject-rated "bad effects" and ARCI scales measuring dysphoria and sedation. Significant observer-rated drug effects were seen following administration of morphine and pentazocine, but not following ciramadol. Overall, the effects of morphine (7.5, 15, 30 mg) and pentazocine (22.5, 45, 90 mg) were dose related. The effects of ciramadol were not dose related, with all three doses (30, 60, 120 mg) producing effects approximately equivalent to morphine 15 mg. Thus, ciramadol exhibited a ceiling effect typical of the opioid partial agonists, but did not produce the dysphoria and sedation characteristic of pentazocine-like mixed agonist/antagonists.

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Distinguishing Opioid Agonists From Mixed Agonist-Antagonists Using a Novel Test for Analgesia in the Rat: Cold Water Tail-Flick

M. W. Adler, A. Cowan, E. B. Geller, R. Pizziketti, and N. Pressman

Although useful for evaluating standard opioid agonist analgesics in animals and for predicting efficacy in man, most models currently used require highly specialized procedures or adjustments in the noxious stimulus to differentiate opioid agonists from mixed agonist-antagonists. Furthermore, changes in the sensitivity of the test often result in positive responses being elicited with agents that are either not analgesics or only weak ones, at best. The technique described in this report uses cold water as a noxious stimulus in rats. Male S.D. rats (160-260 g) were injected SC and tested over 3 hours by dipping their tails in a 1:1 solution of ethylene glycol and water kept at -10°C by a cold water circulating bath. Latency to attempted tail removal was the endpoint, with 60 sec the cutoff. DR curves for morphine and methadone showed the expected 100% of maximal possible analgesia (MPA); at a dose of 10.0 mg/kg morphine and 2.5 mg/kg of l-methadone, all rats had this effect. Pentazocine, nalorphine, nalbuphine, and butorphanol all demonstrated a dose-related analgesia but did not reach 100% MPA. Naloxone (1 mg/kg) was able to block and antagonize the antimciceptive effects of both the agonists and the mixed agonist-antagonists. Chlorpromazine, diazepam, ethanol, amitriptyline, aspirin and acetaminophen failed to show antinociceptive activity, thus confirming the test's specificity. Recalculating the same datawitha 30-sec cutoff, it is possible to further differentiate among the mixed agonist-antagonist opioids.

The rat cold water tail flick test is simple to do and requires little specialized equipment or extensive training. The utility of the test lies in its ability to classify the antinociceptive effects of a given drug, without the need for stimulus modification, into one of three categories: narcotic agonist, mixed agonist-antagonist, or neither.

ACKNOWLEDGEMNTS

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Morphine Antinociception in Spinally Transected Rats

C. Advokat

Numerous studies have confirmed the analgesic efficacy of intrathecal and epidural opiates in a variety of acute and chronic pain states. Of particular significance are several reports which indicate that, under certain clinical and experimental conditions, tolerance to such analgesia may not develop when the spinal cord is chronically exposed to morphine. These results suggest that the spinal cord plays an important functional role in the mediation of opiate tolerance. To examine this role more fully, a series of investigations was initiated to assess opiate antinociception in spinally transected rats.

All subjects (male, albino rats, 250-350g) received a nociceptive assessment on the tail flick (TF) withdrawal test. On the next day the spinal cord of experimental rats was transected (T_6-T_{10}) under one of two anesthetic conditions, 1) ether or 2) Nembutal. Approximately 24 hrs after transection all rats were again tested on the TF, after which separate groups of animals received a single injection of either 0.75, 1.5, 2.25 or 3mg/kg, s.c. morphine, followed by a final test 3-35 min later. The same procedures were followed with additional groups of rats who were tolerant to the analgesic effect of morphine on the TF. Tolerance was induced by s.c. injections of 3mg/kg, 3x a week. Tolerant rats then received either 1) no surgery 2) sham surgery or 3) a spinal transection under either ether or Nembutal. Final TF assessments were performed 24 hrs later both before and 35 min after, a 3 mg/kg dose of morphine.

Regardless of which anesthetic was used, rats who sustained a spinal transection showed a significant drop in TF latency 24 hrs after surgery. Neither sham operated nor unoperated rats showed a change in latency. However, the

response to an acute morphine injection was affected by the anesthetic. The morphine dose response curve of rats previously given Nembutal was similiar to that of unoperated rats. The curve of rats given ether was shifted to the right. Spinal rats were less responsive to morphine if they had undergone surgery under ether rather than Nembutal on the previous day. In addition, rats who were tolerant prior to spinal transection remained tolerant. The latency increase to a 3 mg/kg dose of morphine was significantly less in tolerant than in nontolerant spinal rats regardless of the anesthetic used during surgery. These data confirm previous reports which demonstrated that spinal transection reduced the TF latency. The results further indicate that the antinociceptive effect of morphine may be potentiated in spinal rats if they received an anesthetic dose of pentobarbital within the preceding 24 hrs. However, such potentiation does not occur if rats are tolerant to morphine prior to spinalization. (Supported by PHS grant DA 02845-01)

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Prevalence of Tobacco Dependence and Withdrawal

Steven W. Gust, Terry F. Pechacek, and John R. Hughes

Over one-third of the approximately 54 million U.S. smokers try to quit each year, but only one in five is successful. The role of tobacco dependence and withdrawal in causing relapse to smoking has not been extensively studied. The purpose of the present study was to estimate the prevalence of tobacco withdrawal and dependence in a sample of 40-65 yr. old adult males, a population which has the highest lifetime smoking prevalence. Approximately 75% of U.S. middle-aged males were current or former smokers at the time of this survey.

A population-based sample of 1006 current and former smokers were surveyed in the fall of 1983 for tobacco dependence and withdrawal by both the Diagnostic and Statistical Manual of the American Psychiatric Association and the Fagerstrom Tolerance Questionnaire criteria. Ninety percent of the sample fulfilled DSM-III criteria for tobacco dependence; i.e., has smoked for at least 1 month and had at least one of the following: unsuccessful attempt to quit (61%), DSM-III defined tobacco withdrawal (21%), or tobacco use despite a disease worsened by smoking (23%). Sixty-four percent of the subjects fulfilled Fagerstrom's criteria for dependence; i.e., scored >7 on his tolerance scale. Twenty-one percent of the sample had to quit for at least 24 hours in the past and fulfilled DSM-III criteria for tobacco withdrawal; i.e., met tobacco use criteria and had at least 4 of the following: craving for tobacco (73%), restlessness (50%), irritability (42%), anxiety (44%) difficulty concentrating (22%), headache (3%), drowsiness (8%), or gastrointestinal disturbances (3%).

The prevalence of tobacco dependence was found to be from 64 to 90% in middle-aged male smokers. The lower prevalence of withdrawal (21%) may have occurred because the more heavily addicted smokers may not have been able to quit for at least 24 hours. The clinical relevance and validity of these dependence/withdrawal instruments needs to be determined, but the high prevalence rates observed provide support for the contention that tobacco is an addictive substance.

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Physical Dependence on Nicotine Gum: A Placebo Substitution Trial

John R. Hughes, Dorothy Hatsukami, and Kelli P. Skoog

Introduction: Many smokers and physicians are reluctant to use nicotine gum because they fear ex-smokers will become dependent on the gum. However, whether ex-smokers develop physical dependence on the gum has never been tested.

Methods: Five of the ten subjects (Ss) have been run. The Ss were women, used 4-13 pieces of gum/day and had used gum from 2-12 months. Week 1 was baseline. In Weeks 2 and 3 Ss received both placebo and nicotine gums in a crossover design. Week 4 was return to baseline. The Ss and research assistant were told that Ss had a 50/50 chance of receiving placebo at some point during the study. Ss and their observers rated withdrawal symptoms on 4 days of each week. Weight and heart rate were recorded at the end of each week. Ss were told to chew the same number of gums throughout the study.

Results: Drug returns, self-monitoring, and salivary cotinine indicated Ss did not change the number of gums chewed/day. Two Ss relapsed on the second day of placebo substitution, one to nicotine gum and one to smoking. Breath CO and observer reports confirmed none of the other 3 Ss smoked. The subject and observer withdrawal scores of these three subjects increased during the placebo period and returned to baseline on resumption of nicotine gum (see below). Weight and heart rate did not change with placebo. Anecdotally, subjects noted that during placebo substitution they experienced a craving that was specific for nicotine gum.

Conclusion: Our results indicate smokers can develop physical dependence upon nicotine gum.

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Reinforcing and Discriminative Stimulus Properties of Anorectics in Rhesus Monkeys

W. L. Woolverton, R. de la Garza, C. E. Johanson, and C. R. Schuster

Several anorectics are marketed in the U.S. but, with the exception of amphetamine (amph), little is known about their stimulus properties. In the present study the reinforcing and amph-like discriminative stimulus properties of several anorectics were evaluated in rhesus monkeys.

One group of monkeys was prepared with i.v. catheters and allowed to self-administer cocaine under a FR 10 schedule for 2 hrs/day. Saline and several doses of each anorectic were made available for 6-15 consecutive sessions with baseline conditions reinstated between doses. Another group was trained to discriminate d-amph (0.56 or 1.0 mg/kg) from saline in a signalled avoidance/escape trial paradigm. Responding on one lever avoided or escaped electric shock when drug was given. Responding on the other lever was correct when saline was given. Infusions were given nasogastrically 1 hr before the session (30 trials or 40 min). When the discrimination was acquired, doses of each anorectic were administered before test sessions in which responding on either lever avoided or escaped shock. A drug that produced responding comparable to that seen with amph (at least 90% on the drug lever) was considered to have substituted for amph.

The anorectics could be classified into 4 groups. One group (mazindol, phenmetrazine and benzphetamine) was self-administered by all monkeys and substituted for amph. The second (phentermine and phendimetrazine) was self-administered by 1 of 4 monkeys and substituted for amph. The third (clortermine and phenylpropanolamine) was not self-administered but substituted for amph in some monkeys. The fourth (chlorphentermine) was not self-administered and did not substitute for amph.

Based on these results, the first group would be predicted to have high dependence potential while chlorphentermine is likely to have low dependence potential. The others are predicted to have some amph-like subjective effects but low dependence potential. Surprisingly, some compounds substituted for amph but were not reliable positive reinforcers. Though amph-like discriminative stimulus effects are often presumed to predict dependence potential, these results suggest a separation between reinforcing and discriminative stimulus effects.

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Immunoregulatory T Cell Subsets in British Parenteral and Non-parenteral Heroin Abusers

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Parenteral drug abusers comprise the second largest group of patients with acquired immune deficiency syndrome (AIDS). The most characteristic immunologic abnormality in AIDS is a marked decrease in the ratio of T4-positive (helper/inducer) to T8-positive (suppressor/cytotoxic) lymphocytes in the peripheral blood resulting from a diminished number of T4-positive cells. Studies in homosexual men have indicated that abnormalities of T lymphocyte subsets may be seen in apparently healthy subjects: We studied T lymphocyte subsets in 14 parenteral and 10 non-parenteral heroin abusers at St. George's Hospital, London, during May-September 1984. These patients had no acute or chronic inflammatory disease other than minor liver transaminase elevations in five. Twelve of the 24 patients were receiving oral methadone maintenance treatment. At the Royal Free Hospital, London, T lymphocyte subsets were determined by indirect immunofluorescence using monoclonal antibodies OKT3, OKT4, and OKT8. No significant differences were found in T4/T8 ratios or in absolute numbers of T3 (total T cells), T4, or T&positive cells in the two groups. The mean T4/T8 ratios were similar to means obtained from normal subjects in two other studies from this laboratory. Two parenteral and two non-parenteral heroin abusers had T4/T8 ratios less than 1.2 which, in all cases, were due to an increased number of T8-positive cells. The essentially normal T4/T8 ratios in the patients we studied are consistent with the observation that AIDS had not been reported in any British heterosexual parenteral drug abusers at the time this study was completed. Also, in another study during 1983-84 (Lancet, 1984, 2, 477), only 1.5% of 269 drug abusers from London had antibody to HTLV-III. These data suggest that neither narcotic drugs nor repeated exposure to unsterile injectable substances are directly responsible for low T4/T8 ratios in parenteral drug abusers with AIDS.

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Possible Mechanisms Involved in the Use and Abuse of Amitriptyline in Methadone Patients

Shean-jang Liu and Richard I. H. Wang

Tricyclic antidepressants given to depressed patients in the methadone (MD)maintenance program have been shown to improve the therapeutic effects of MD, such as reduction in the need for MD and in the use of illicit drugs. In addition, it has been reported that amitriptyline (AT) is widely abused among drug patients. The present studies were designed to investigate the pharmacological basis for these clinically significant observations. Eight patients maintained on MD (20-60 mg/day) for at least 3 months were selected *as* inpatients to study the effect of acute AT intake on the plasma levels and urinary excretion of MD. On day 1, blood samples were drawn at 0,1,2,4,8 and 24 hr after their regular MD intake. On days 2 and 3, AT (50 mg) was given twice a day at 10-hr intervals in addition to MD. Blood samples were drawn on the same schedule as that of day 1. Total urine was collected in 0-12 and 12-24 hr periods for each day of the study. The plasma levels of MD and the urinary excretion of MD and EDDP (the major pyrrolidine metabolite of MD), expressed as MD:EDDP ratio was not significantly changed by acute AT intake. These results indicate that acute AT administration does not affect the metabolism of MD. In a study conducted in rats, it was found that acute administration of AT (20-30 mg/kg, ip) 1 hr before administration of ^{14}C-MD (4 mg/kg, SC) prolonged the duration of MD analgesia but did not significantly change the brain concentration of ^{14}C-MD and the percentages of total in liver or urine as watersoluble metabolites. These results suggest that AT treatment prolonged MD analgesia by increasing the sensitivity of central nervous system to MO rather than by changing MD metabolism. In a separate human subject study, a total of 1129 urine samples were collected for screening of drugs of abuse from 63 MD maintenance patients. The urine tests revealed that 35 urine samples representing 17 different patients were positive for both AT and benzodiazepine conjugate metabolites on the same urine samples. Identification of individual benzodiazepines could not be made from urine samples. It was found that all 7 patients chosen for blood tests were positive for chlordiazepoxide in their plasma

samples which were collected 1-2 days after their urine samples were found positive for both AT and benzodiazepine metabolites. The results indicate that MD maintenance patients might take AT together with a benzodiazepine rather than take AT alone. When confronted, all 7 patients admitted occasional abuse of Limbitrol which contains AT and chlordiazepoxide.

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Recent Drug Use in Male and Female Arrestees

Eric D. Wish, Elizabeth Brady, and Mary Cuadrado

This paper presents findings from a study of male and female arrestees processed in Manhattan Central Booking. Approximately 6400 males and 100 females were asked to be interviewed shortly after arrest, about their recent drug and alcohol use. Almost all (95%) of the persons approached participated in the interview, and 84% of these provided a urine specimen for analysis.

The finding indicate that: 1) 54% of all male arrestees charged with serious offenses (the majority were felony offenses) had a urine test positive for opiates, methadone, cocaine or PCP. Cocaine was the drug most likely to be found (in 41% of the males). 2) Estimates of drug use derived from thin layer chromatography were approximately two thirds below the estimates provided by EMIT urine tests. 3) The prevalence of cocaine in the urines of females charged with prostitution (or who reported having engaged in prostitution at some time in their lives) was almost twice as high as was found in the urines of the other females or of male arrestees.

The findings are contrasted with those from a comparable study of arrestees in Washington D.C. In addition, the implications of these findings for the drug abuse treatment needs of arrestees are presented.

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Behavioral Activity of Morphine and Naltrexone During Chronic Osmotic Infusion of Morphine in Rats

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Development of tolerance and dependence during chronic morphine infusion was examined in rats. Parallel experiments assessed the ability of morphine and naltrexone to alter rates of food-reinforced behavior before, during, and after a 2-week infusion regimen.

Rats lever pressed under a fixed-ratio 30 schedule of food delivery during sessions divided into six 5-min ratio components separated by 10-min timeout (TO) periods. Dose-response curves were obtained by injecting cumulative s.c. doses of morphine or naltrexone at the start of consecutive TO periods. Before chronic morphine infusion, morphine decreased response rates in 5 rats in a dose-dependent manner, abolishing responding at a dose of 5.6 or 10 mg/kg. In 6 other rats, naltrexone decreased response rates at a dose of 10 or 32 mg/kg. For chronic morphine administration, each rat was implanted s.c. with an osmotic pump (Alzet model 2ML2) that infused 10 mg/kg morphine per day for 2 weeks. Cumulative doses of morphine or naltrexone were tested on day 6 and day 12 of morphine infusion, and again on day 20, 6 days after morphine infusion ceased.

Response rates decreased 30 to 40% the day after pump implantation, and remained suppressed by 20% for the duration of morphine infusion. During chronic morphine infusion, the naltrexone dose to suppress response rates by 60% or more was decreased 320- or 1000-fold, to 0.032 or 0.1 mg/kg. The rate-decreasing effects of 0.032 or 0.1 mg/kg naltrexone were accompanied by a 6 to 17 g weight loss and were reversed by acute morphine doses of 3.2 to 32 mg/kg. Increased naltrexone sensitivity disappeared by 6 days after cessation of morphine infusion, when a dose of 10 or 32 mg/kg was again required to suppress behavior. Taken together, these data suggest that the 10 mg/kg/day morphine infusion induced and maintained dependence. In contrast, no tolerance developed during the infusion regimen. Similar acute doses of 5.6 or 10 mg/kg morphine abolished responding before, during, and after chronic infusion. Thus, chronic infusion of a low dose of morphine may yield dependence without concurrent behavioral tolerance.

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Ethylketocyclazocine: Evaluation of Supraspinal Analgesia and Abuse Liability

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Cur laboratory has previously reported that drugs with mu receptor activity raise the escape threshold in a model for supraspinal analgesia (Sasson, et al., Society for Neuroscience Abstracts 9:794, 1983) and lower the reward threshold in a mode? of drug-induced euphoria (Kornetsky, et al., Arch Gen Psychiat 38:289-292, 1979) suggesting both analgesic potency and abuse liability. The present study examines the effect of ethylketocyclazocine (EKC), a putative kappa agonist, in these two models. Kappa receptor agonists are believed to produce spinally mediated analgesia and have little or no abuse potential. If EKC raises the escape threshold for supraspinally mediated pain, then either the kappa agonists have supraspinal analgesic activity or EKC is also active at mu receptors. In one group of rats electrodes were stereotaxically implanted in the midbrain reticular formation and escape behavior was maintained by electrical stimulation to this site. An escape threshold was determined by varying the current intensity according to a modification of the psychophysical method of limits. A second group of rats had electrodes implanted in the medial forebrain bundle at the level of the lateral hypothalamus and reward thresholds were determined using a similar psychophysical procedure.

Results indicate that subcutaneous administration of EKC (0.06-1.0 mg/kg) increased escape threshold in a dose-dependent manner while having no effect on reward threshold. Since opiates with mu receptor activity raise the escape threshold and lower the threshold for rewarding brain stimulation, these data suggest that the increase in escape threshold by EKC is mediated supraspinally by kappa receptors and that this drug probably has no abuse potential.

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Neonatal Abstinence, Pharmacotherapy, and Developmental Outcome

Karol Kaltenbach and Loretta P. Finnegan

The majority of infants born to drug-dependent women undergo Neonatal Abstinence Syndrome (NAS) and often require pharmacology for the treatment of withdrawal symptoms. Phenobarbital, Paregoric, and Diazepam have been recommended for the treatment of the syndrome. While some investigators have examined the efficacy of these agents in treating NAS there are no data regarding the use of specific pharmacologic agents and developmental outcome. This study evaluated 85 infants born to drug-dependent women who were maintained on methadone during pregnancy. Severity of infant withdrawal was assessed with a neonatal abstinence scoring system. Infants who required pharmacotherapy were randomly assigned to one of four treatment regiments: Paregoric, Phenobarbital (titration), Phenobarbital (loading), and Diazepam. When treatment was not successful with the assigned agent, one of the other agent(s) was used. At 6 months of age, the developmental status of infants was assessed with the Bayley Scales of Mental Development. Based on NAS treatment, four groups were defined: I) Paregoric (n=21); II) Phenobarbital (n=17); III) More than one agent (n=31); and (V) No treatment (n=16). Data for the Phenobarbital loading and titration groups were combined since analysis revealed no differences between groups. All infants who initially received Diazepam were included in group III since Diazepam as a single agent was not successful. Results of one *way* analysis of variance revealed no differences in developmental status between groups (P=<.10, F=.25). Scores for all groups were well within the normal range of development. Implications of these findings include: 1) the severity of withdrawal is not related to developmental outcome when appropriately managed with pharmacotherapy, and 2) the use of pharmacotherapy does not adversely affect developmental outcome and may help ameloriate the consequences of NAS.

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Individual Differences in Alcohol Preference in Humans

Harriet de Wit, Joseph Pierri, Eberhard H. Uhlenhuth, and Chris E. Johanson

The reinforcing properties and subjective effects of alcohol (0.5 g/kg) were measured in 29 normal adults using a 7-session choice procedure. On the first 4 sessions, subjects sampled two color-coded drinks containing alcohol or placebo. On the next 3 sessions they chose whichever drink they preferred. Sessions were conducted Monday, Wednesday and Friday evenings in a recreational environment with groups of 4 subjects. Subjects completed self-report mood questionnaires before and several times after consuming the drink. The questionnaires were the Profile of Mood States (POMS), a short version of the Addiction Research Center Inventory (ARCI), visual analog scales (VAS), and a drug liking questionnaire.

As many subjects chose the alcohol-containing drink 3 times (N=9) as chose it 0 times (N=9) or 1 or 2 times (N=11). Data from all 29 subjects taken together showed no systematic pattern of preference or mood effects. However, when subjects were grouped according to their frequency of alcohol choices (0, 1 or 2, or 3 choices) clear individual differences emerged. On the POMS, alcohol increased scores on Vigor and Elation subscales in the 3-time choosers while it decreased Vigor in the O-time choosers. Alcohol also increased Confusion (POMS) and "Dysphoria" (LSD Scale; ARCI) in the 0-time chasers. Frequency of alcohol choice was also related to subjects' drug use histories: 3-time alcohol choosers reported higher alcohol and marijuana use outside the laboratory than 0-time choosers. One- and 2-time choosers reported intermediate subjective effects and intermediate drug use histories. The 1- or 2-time choosers were much more likely to choose alcohol on sessions conducted on Friday evenings than on Mondays and Wednesdays. Thus, alcohol choice was related to drug use history, subjective response to the drug, and environmental influences such as day of the week.

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A Pharmacokinetic-Pharmacodynamic Model of Acute Tolerance to Cocaine

May J. Chow, John J. Ambre, Tsuen Ih Ruo, Arthur J. Atkinson, Jr., Dennis J. Bowsher, and Marian Fischman

The pharmacokinetics of cocaine were studied in five subjects with histories of drug abuse who were otherwise healthy. A two-compartment system was used to model the distribution kinetics of this drug. The steady state distribution volume averaged 131.8 L or 1.96 L/kg, elimination clearance 2.10 L/min, and elimination-phase half-life 48 min. Cocaine concentrations in a hypothetical biophase were estimated in order to correlate the chronotropic effects of this drug with its pharmacokinetics. The experimentally determined kinetic parameters indicate that the peak chronotropic effect would occur 7.3 min after intravenous bolus injection of cocaine, and that biophase cocaine concentrations would initially accelerate the heart rate by 0.3 bpm for each 1 ng/ml. The kinetic analysis also demonstrated that the chronotropic effects of cocaine decline more rapidly than either plasma levels or biophase concentrations. This progressive attenuation in intensity of the chronotropic effect of a given biophase cocaine concentration could be modeled as a first-order process and is compatible with either the intervention of homeostatic reflex mechanisms or the phenomenon of acute tolerance.

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Effects of the Optical Isomers of N-Allylnormetazocine on Electric Shock Titration

Barbara K. Slifer and Linda A. Dykstra

In the past few years an isomeric separation of effects between the stereoisomers of N-allylnormetazocine has been demonstrated. The (+)-isomer has been shown to have predominately sigma-agonist activity while the (-)-isomer has been reported to have effects that are mediated by the mu and/or kappa receptors, including antinociception in rodents. A measure of antinociception frequently used with primates is the shock titration procedure. In this procedure, drugs with analgesic effects increase the intensity at which monkeys maintain a shock. We used the shock titration procedure to evaluate the optical isomers of NANM in squirrel monkeys and compared these effects to those of phencyclidine (PCP) and morphine. Four squirrel monkeys (Samiri sciureus) were trained to respond (FR 5) to terminate (T.O. 15 s) and decrease the level of shock delivered to the tail. The shock level increased (0.02-5.6 mA in 30 steps) every 15 s if the animal failed to respond. Dose-effect curves were determined for (-)-NANM (0 -5.6 mg/kg), (+)-NANM (0 -10.0 mg/kg), PCP (0 -1.0 mg/kg) and morphine (0 -3.0 mg/kg) alone. Then (-)-NANM (0.01 -0.3 mg/kg) was tested in the presence of 3.0 mg/kg morphine.

Morphine (0.1-1.7mg/kg) produced dose-related increases in the levels at which shock was maintained, while the highest dose eliminated responding. The lower doses of (+)-NANM, PCP, and (-)-NANM resulted in either no change or modest decreases in shock levels. Higher doses of PCP (0.56-0.75 mg/kg) and (+)-NANM (1.7-3.0 mg/kg) suppressed responding in all but 1 or 2 animals, respectively. Shock level increases were seen in the remaining animals at the highest doses. The (-)-isomer produced only decreases in shock levels and suppressed responding at doses that did not produce shock level increases. When (-)-NANM was tested in the presence of a rate-suppressing dose of morphine, the effects of morphine were antagonized in a dose-related manner. In conclusion, differences between the optical isomers of NANM on median shock level are small and thus do not demonstrate stero-selectivity in the squirrel monkey shock titration procedure.

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A Comparative Study of Abrupt and Gradual Cessation of Long-Term Therapeutic Self-Administration of Benzodiazepines

Howard Cappell, Usoa Busto, Gloria Kay, Claudio Naranjo, Edward M. Sellers, and Martha Sanchez-Craig

Recent studies suggest that long-term use of benzodiazepines within the accepted theapeutic dose range may lead to physical dependence. The present study concentrated on two behavioral indices of benzodiazepine dependence: reluctance to continue with the medication (placebo vs. active diazepam) issued by the investigators and unauthorized self-administration during treatment. Forty volunteers interested in stopping chronic use of benzodiazepines met the inclusion/exclusion criteria and attended at least one treatment session after assessment. The mean daily dose was approximately 15 mg of diazepam or its equivalent. The mean duration of use was 86.7 months. Any use of another psychoactive drug during the previous six months with the exception of modest alcohol consumption ($\leq$30 g/day) was a criterion for exclusion. After a two-week baseline period during which patients recorded their use of benzodiazepines, they began individualized behavioral therapy emphasizing problem-solving and coping with abstinence. A gradual withdrawal regime was negotiated with each patient. In a double-blind design, patients were randomly assigned to receive placebo (n=19) or diazepam (n=21) during the withdrawal phase. Plasma benzodiazepine concentrations were determined from samples taken weekly. Eighty-four percent of patients in the placebo condition self-administered at least one unauthorized dose of a benzodiazepine, whereas only 33% of subjects in the diazepam condition did so ($p<.01$). Seven patients in the placebo condition spontaneously requested a switch from the medication that they were being issued and continued the withdrawal using their own prescribed supplies. Only one patient in the diazepam condition requested such a switch ($p<.05$). Withdrawal symptoms were more frequent and intense among patients in the placebo condition. The data on unauthorized self-administration suggest that even at apparently low doses in long-term users, some pharmacological action of diazepam is the basis for continued use, and that this is a bona fide form of drug dependence. These data also provide empirical support for the use of a tapered withdrawal regime in attempts to achieve abstinence.

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The Roles of D_1 and D_2 Receptors in Methamphetamine-Induced Changes in Transmitter Systems of the Basal Ganglia

J. W. Gibb, P. K. Sonsalla, C. J. Schmidt, and G. R. Hanson

Multiple and single administrations of high doses of the potent stimulant, methamphetamine (METH), cause prominent changes in monoamine and substance P (SP) transmitter systems associated with the basal ganglia. Thus, rats given 5 injections of METH (15 mg/kg/dose, I.P., every 6h) exhibit substantial decreases in the activity of synthesizing enzymes, transmitters and metabolites associated with the striatal dopamine (DA) and serotonin (5HT) systems. In addition, the same treatment protocol alters the activity of the SP striatonigral pathway resulting in significant increases in nigral SP concentrations. Although acute administration of METH does not cause detectable changes in the DA and SP parameters mentioned above, it does reduce the levels of striatal 5HT, 5-hydroxyindoleacetic acid and the activity of tryptophan hydroxylase (TPH).

We have previously reported data which demonstrate that METH-induced release of DA is likely responsible for all of the aforementioned acute and subacute changes in the basal ganglia transmitter systems. We now present evidence that D_1 and D_2 receptors have differential roles in mediating the transmitter changes caused by METH treatments. The data demonstrate that haloperidol (HA), a nonspecific D_1 and D_2 antagonist, significantly attenuates or blocks all of the previously described effects. In comparison, pretreatment with the D_2 antagonist, sulpiride, blocks the effects of multiple doses of METH on striatal tyrosine hydroxylase (METH alone = 64%; combination = 90%), DA concentrations (METH alone = 37%; combination = 95%), and nigral SP levels (METH alone = 144%; combination = 84%); however, unlike HA, sulpiride does not alter the effects of either single or multiple doses of METH on the 5HT system. Finally, the relatively specific D_1 antaoonist, SCH 22390, does attenuate striatal changes in TPH activity (METH alone = 7%; combination = 58%) and 5HT levels (METH alone = 18%; combination = 50%) caused by multiple doses of METH. These results suggest that both D_1 and D_2 receptors are involved in mediating METH-related effects on the basal ganglia; specifically, changes in DA and SP parameters are D_2-mediated whereas changes in the 5HT system are associated with D_1 receptors. (Supported by USPHS grants DA 00869, MH 39304, GM 07579, and MH 40175).

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Site(s) of Action of Delta-9-Tetrahydrocannabinol in a Drug Discrimination Paradigm

David J. Mokler, Margaret F. O'Neal, Louis S. Harris, and John A. Rosecrans

The purpose of the present experiment was to determine the areas of the brain involved in the discriminative stimulus properties of Δ^9-THC. Male Sprague-Dawley rats were trained on a fixed-ratio 10 operant paradigm to discriminate 3.0 mg/kg THC from its vehicle. THC or vehicle were administered ip 30 min prior to the start of a 10 min session; the vehicle was a 3% (v:v) solution of emulphor: ethanol (1.1) in saline. Following administration of THC, responses on one lever were rewarded with presentation of a dipper of sweetened milk, whereas responses on the opposite lever were reinforced following vehicle administration.

Once animals were able to discriminate THC from vehicle, cannulae were implanted aimed at either the prefrontal cortex or were A:3.6, L:-2.5, V:-0.5 from bregma; for the dorsal hippocampus the coordinates were A:-2.8, L:-2.2, V:-2.0 from bregma (Pellegrino, Pellegrino and Cushman, 1979). Following recovery from surgery to an accurate level of discrimination, animals were infused with sterile saline to accustom them to the procedure. All infusions were made by micro-syringe in a volume of 0.5 ul over 45 sec with a 60-sec waiting period following infusion before removal immediately following infusions.

When animals were accustomed to the procedure, 0.5 ul of a 10% emulphor:ethanol vehicle was administered intracranially (ic). All animals made 100% of their responses on the vehicle lever following this treatment. Administration of 5 or 10 ug THC into the prefrontal cortex produced 100% drug lever responding in 3 of 7 animals. Another 3 animals showed partial generalization to some dose of ic THC. Higher doses were not tested due to the solubility limits of THC in this vehicle.

Administration of 10 ug THC resulted in vehicle lever responding following infusion into the dorsal hippocampus, with the exception of one animal which generalized completely to 5 ug THC ic. Retest of this dose of THC verified these results. All animals showed appropriate lever responding following peripheral administration of either THC or vehicle.

These preliminary data suggest the involvement of the prefrontal cortex in the discriminative stimulus properties of THC. Further experiments are in progress to increase the number of animals tested with infusion of THC bilaterally into these brain areas.

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Effects of THC on Adult Frontal Cortex Dopamine Turnover in the Male Fischer-344 (CDF) Rat

John A. Rosecrans, Susan E. Robinson, J. H. Johnson, and David J. Mokler

Male CDF rats were administered 10 mg/kg of THC (s.c.) on 4,6 and 8 days of age. Rat litters were culled to 8 pups each; 4 males and 4 females. THC was dissolved in an emulfor/ alcohol (5% each) vehicle and 2 males in each litter were administered vehicle only or THC. At day 130, rats were conditioned to an 8-day foot shock-induced analgesia (FSIA) paradigm consisting of a daily 15-sec 1.5 mA scrambled foot-shock while being restrained. THC had few effects on the growth rate of the survivors (90%) of neonatal treatment. Rats in each TRT group were subdivided into two experimental groups; control and stressed. Analgesia was evaluated in each subject using time of tail-withdrawal from hot water (55 C). A cut off latency of 8-10 secs was utilized. Acute FSIA was evaluated on day 1 by measuring the tail-withdrawal response (TWR) before and after foot shock. The development of conditioned analgesia was evaluated by measuring the TWR prior to daily FSIA exposure (days 2-7). Control rats were handled as were stressed groups but were never shocked. All rats were sacrificed on day 8,15 min. after exposure to the shock environment only (Conditioned Response session); TWR's were also evaluated as before. Brain areas and plasma were removed and frozen for later brain amine (HPLC method) and neuoroendocrine (RIA methods) evaluation. The results of these studies indicated that rats can be conditioned behaviorally to FSIA, which can also be observed by an activation of the pituitary adrenal axis and an alteration of both brain area 5-HT (5HIAA/5HT) and DA (DOPAC/DA). THC did not significantly alter neuroendocrine function (plasma corticosterone or prolactin) nor acute and conditioned analgesia. 5-HT turnover was significantly altered in each brain area region (hypothalamus, hippocampus, frontal cortex) by FSIA; the effect, increases or decreases, were area specific. THC has no effect on either control or stress-induced alterations in 5-HT and/or 5-HIAA. THC, however, did significantly alter frontal cortex DA turnover. The effect was not seen as a reduction of the overall stress-induced increase in DOPAC, but a reduction of both DA and DOPAC suggesting that neuronal flow to the FC was slowed down in rats given THC 4 months prior to this evaluation.

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Buprenorphine: Effect on Brain-Stimulation Reward Threshold

Carol Hubner and Conan Kornetsky

The potential utility of the mixed agonist-antagonist buprenorphine hydrochloride in the treatment of opiate addiction has been suggested given this drug's ability to produce morphine-like euphoria (Jasinski, et al., Arch Gen Psychiat 35:501-516, 1978) without inducing significant physical dependence in animals (Rance, Brit J Clin Pharmacol 7:281S-286S, 1979) and man (Jasinski, et al., Arch Gen Psychiat 35:501-516, 1978). The purpose of the present study was to assess the reinforcing properties of buprenorphine by determining its effect on the threshold for rewarding brain stimulation in rats with electrodes stereotaxically implanted in the medial forebrain bundle-lateral hypothalamic region of the brain. Increased sensitivity for rewarding brain stimulation has been used as an animal model of drug-induced euphoria and is thought to be predictive of abuse liability in man. Morphine, in addition to other drugs of abuse, has been shown to lower reward thresholds. Buprenorphine administered subcutaneously produced a dose-dependent. lowering of the reward threshold. These results are consistent with its partial mu agonist activity. Of importance, however, is the finding that the minimum effective dose of buprenorphine that will lower the threshold for rewarding brain stimulation is between 0.008 and 0.015 mg/kg (sc). Relative to morphine on the same task, this makes buprenorphine approximately 200 times more potent, while it is reported to be only 25-40 times more potent than morphine as an analgesic in animals (Cowan, et al., Brit J Pharmacol 60:537-545, 1977).

ACKNOWLEDGEMENTS

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Pharmacologic Profiles of Phencyclidine (PCP) and PCP Analogues: Electroencephalographic, Behavioral, and Receptor Binding Studies

Antonia Mattia, Arthur P. Leccese, Karen L. Marquis, Esam E. El-Fakahany, and J. Edward Moreton

PCP is a widely abused substance which has a broad spectrum of activity, but a poorly understood mechanism of action. We are utilizing a comprehensive model and a series of PCP analogues to better define the pharmacology and structure-activity relationships of this unique class of drugs. The effects of PCP, several analogues (PCA, NMPCA, PCE, NsBPCA, PCPY, TPCY, TCP and Ketamine), and SKF 10,047 have been evaluated on the following parameters: (1) rotarod performance, loss of righting reflex, convulsant activity, and lethality after acute doses of 0.1 to 51.2 mg/kg administered on a cumulative iv schedule; (2) direct electroencephalogram (EEG) and EEG power spectra after acute doses from 0.1 to 12.8 mg/kg; (3) overt behavior scored using the procedure of Sturgeon et al. (1979) at doses used to obtain the EEG dose-response curves; (4) spontaneous locomotor activity (SLA) assessed in photocell activity cages over the complete range of behaviorally active doses; (5) analgesic activity assessed on the hot plate apparatus; (6) pro- and anticonvulsant activity assessed in the electroshock model at selected ip doses; and, (7) [^{3}H] PCP receptor binding. The rotarod test proved reliable in separating compounds with respect to potency, but measurements of righting reflex, convulsant activity and lethality were less discriminating. The characteristic EEG responses produced by PCP and related compounds were dose dependent. Typically, at lower doses, the EEG response consisted of low amplitude theta activity which developed into high amplitude, slower frequency EEG activity at higher doses. These EEG effects were correlated with dose-dependent increases in locomotion, sterotypy, and ataxia. With respect to increases in SLA, PCP was the most efficacious, while PCE was least efficacious. The remaining compounds differed mainly in potency, over a two- to four-fold range. All of the compounds, particularly PCA,

decreased the severity of electrically induced convulsions. Increasing doses of PCP and each compound tested led to increasing degrees of analgesia until non-specific drug effects prevented performance of the appropriate response. Binding constants from receptor displacement experiments were correlated with EEG and behavioral effects. This integrated approach utilizing EEG, behavioral and receptor binding methods should help to better define the agonist properties and mechanism of action of PCP-like compounds. This would facilitate the search for antagonists, potentially useful research tools, and therapeutic agents.

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A Reevaluation of Naltrexone Toxicity in Recovering Opiate Addicts

Isabelle O. Arndt, John S. Cacciola, A. Thomas McLellan and Charles P. O'Brien

In view of the finding that naltrexone leads to elevations of liver enzymes in obese patients at high doses, we have re-examined data from laboratory tests in opiate abuse patients being treated with naltrexone. Subjects were 25 opiate-dependent male veterans who applied for and stayed in naltrexone treatment at least one month between 1981 and 1984. The dose schedule was 100 mg Monday and Wednesday, 150 mg on Friday. The subjects were selected retrospectively with complete laboratory evaluation at baseline and one month being the only inclusion criterion. The lab tests we studied are as follows: CBC and differential, glucose, BUN, creatinine, uric acid, sodium, potassium, chloride, CO_2, phosphate, calcium, total protein, albumin, alkaline phosphatase, SGOT, LDH, bilirubin, cholesterol, urinalysis and urine specific gravity. There were no significant differences between mean laboratory values at baseline and at one month. In addition, there were no significant increases in the percentage of abnormal values for a n y specific test at baseline versus one month. Furthermore, the total number of abnormal values for all tests was the same at both evaluations (approximately 15%). Although the majority of changes seen in laboratory tests were in the direction of normalcy at one month, inspection of individual values showed three lab tests for which the number of changes from normal to abnormal exceeded the number of changes from abnormal to normal by more than one patient. For hematocrit and CO, , the magnitude of the changes was small and the direction of the changes inconsistent. For SGOT, eight cases became elevated from normal to abnormal, while only four cases went from abnormal to normal. The magnitude of the changes was small, the highest SGOT being 56 mu/ml (normal 8-40 mu/ml). There were no patterns of deterioration in other liver function tests, and we were impressed with the variability of transaminases at both time points. In summary, we found no systematic changes in laboratory values after one month of naltrexone treatment. However, we continue to require periodic evaluation of liver function tests, particularly in long-term naltrexone treatment.

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Violent Experiences as Precursors to Drug Abuse and Parenting Failures

Dianne O. Regan, Saundra M. Ehrlich, Robert H. Smith, and Loretta P. Finnegan

Because women traditionally serve as primary caretakers, dependency on drugs has serious consequences for their children. Drug dependent women generally attempt to be good mothers. However, the presence of drug dependence coupled with depression, a lowered self-esteem and occurrences of physical or sexual abuse place these women at high risk for parenting. The present study was initiated to explore maternal exposure to violence and *the* potential for subsequent abuse or neglect of one's own children. Family Center is a comprehensive program, providing obstetrical, psychosocial, and addictive services for pregnant drug-dependent women and their infants. Between 1979 and 1984, 248 women completed a violence questionnaire. The amount of violence/abuse experienced by 178 Family Center women far exceeded that reported by a control group of 70 drug-free women. Forty percent (68) of Family Center women had children in foster placement. Women who reported a history of sexual trauma, particularly if occurring in childhood or repeatedly, were more likely to have placed their children in foster care than women who were physically abused (without sexual trauma) as children and/or adults or women who were not abused at all (p=<.01).

	Family Center (n=178)		
	With Mother (n=110)	Foster Care (n=68)	Control (n=70)
	%	%	%
Beaten as child	19	19	16
*Beaten as adult	69	41	17
**Molested as child	28	54	7
**Raped as child	15	59	0
*Raped as adult	21	44	4
**Raped repeatedly	8	77	0

**p=<.01, *p=<.05

This study suggests that failure to resolve childhood sexual trauma or attempting to cope with the trauma by using illicit drugs, disrupts the ability of women to parent children. Sexual assault of women, particularly if occurring in childhood, may have subsequent and untoward effects upon their children.

AUTHORS

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Dependence Upon U-50,488 in Rhesus Monkeys

Debra E. Gmerek and James H. Woods

Six group-housed rhesus monkeys (4-5 kg) were given the kappa selective agonist U-50,488 (trans-3,4-dichloro-N-methyl-N-(2-(1-pyrrolidinyl)-cyclohexyl)-benzeneacetamide methanesulfonate hydrate) over a period of four months at maximally tolerable doses. Thus, as tolerance developed to U-50,488-induced stupor, muscle relaxation and convulsions, the doses were increased from 0.3 mg/kg/56 hrs to 17.5 mg/kg/4 hrs. Cross-tolerance to morphine induced picking at fingers and toes and excessive yawning associated with unusual tongue movements. These behaviors are not observed in deprived. morphine-dependent monkeys. The abdominal rigidity and defense associated with withdrawal from morphine was not detected during U-50,499 abstinence. Opioid agonists were administered to monkeys deprived of U-50,488 for nine hours. Behavior associated with U-50,488 withdrawal was suppressed in a dose-related manner by U-50,488, tifuladom, and in a stereoselective manner by ethylketazocine. Withdrawal from U-50, 488 was not suppressed by morphine. Opioid antagonists were administered beginning 1 hr after the last maintenance dose of U-50,488. Withdrawal behavior resembling that seen during deprivation from U-50,488 was precipitated in a dose-related fashion by buprenorphine, Mr 2266, nalorphine, naloxone, naltrexone and Win 44,441. The mu selective antagonist ß-funaltrexamine and bremazocine did not precipitate-any signs of withdrawal in the U-50,488-dependent monkeys at doses up to 10 mg/kg and 0.3 mg/kg, respectively. Dependence associated with chronic administration of U-50,488 was qualitatively and pharmacologically distinct from morphine dependence, and appears to be mediated by kappa receptors. Supported by USPHS Grant OA 00254.

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