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NATIONAL INSTITUTE
ON DRUG ABUSE

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News Scan
NIDA ADDICTION RESEARCH NEWS

NEWS UPDATE

Research News

Persistent Brain Changes in Response to Cocaine Depend on Expectation of Reward

Drug addiction dramatically shifts a person's attention, priorities, and behaviors toward a focus almost entirely on seeking out and taking drugs. An animal study funded by NIDA has identified some of the specific long-term adaptations in the brain's reward system that may contribute to this shift. Using an animal model of addiction, investigators were able to distinguish brain changes in rats trained to self-administer cocaine versus those that were trained to self-administer natural rewards such as food or sucrose for several weeks. The investigators also were able to look at how much the expectation of receiving the drug influenced those brain changes by comparing rats trained to self-administer the drug versus those that received the same amount of cocaine but received it passively by infusion (that is, they could not control their own drug taking by self-administration). In the normal processes of learning and memory formation, there is a well-documented strengthening of communication between brain cells, known as long-term potentiation (LTP). This study found that LTP was similar in the rats that had learned to self-administer cocaine, food, or sucrose; however, the increase in LTP due to cocaine persisted for up to 3 months of abstinence while the increase in response to natural rewards dissipated after only 3 weeks. Importantly, the nature of the cocaine experience had a strong effect on the outcome since rats exposed to cocaine when they did not expect it (passive infusions) did not display LTP. LTP in rats that self-administered cocaine persisted after they were trained to stop drug self-administration behaviors. This indicates that, once established, it is very difficult to reverse the "memory trace" associated with drug reward.

Chen BT, Bowers MS, Martin M, Hopf FW, Guillory AM, Carelli RM, Chou JK, Bonci A. Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron*. 2008;59(2):288–297.

Antibiotic Improves Efficacy of Morphine and Reduces Reward Response

Pain is one of the most common reasons people consult a physician. Morphine, an opioid analgesic that is often prescribed to manage pain symptoms or suppress pain, also activates a type of immune cell called microglia. Interestingly, the activation of microglia can in turn decrease morphine's ability to suppress pain. Therefore, suppressing the activation of microglia may improve the ability of morphine to reduce or suppress pain. Studies have shown that the antibiotic minocycline inhibits the activation of microglia and enhances the suppression of pain by morphine. However, scientists have been concerned that minocycline might also enhance morphine's rewarding properties, increasing the potential for addiction, as well as respiratory depression (inadequate breathing), a dangerous side effect that can lead to reduced consciousness and even death. To test whether the combination of morphine and minocycline produces these unwanted side effects, researchers funded in part by NIDA gave mice oral minocycline before a morphine injection. The researchers found that minocycline actually reduced the respiratory depression produced by the morphine injections, as well as behaviors associated with drug seeking in people. Researchers also confirmed that the combination of minocycline, when administered with morphine, produced increased suppression of pain compared to morphine injection alone. Whether or not minocycline would also improve the efficacy of morphine in a model of chronic pain would need to be studied, since the mice used in this study were free of chronic pain and associated inflammation.

Hutchinson MR, Northcutt AL, Chao LW, Kearney JJ, Zhang Y, Berkelhammer DL, Loram LC, Rozeske RR, Bland ST, Maier SF, Gleeson TT, Watkins LR. Minocycline suppresses morphine-induced respiratory depression, suppresses morphine-induced reward, and enhances systemic morphine-induced analgesia. *Brain Behav Immun*. 2008 Jul 31; [Epub ahead of print].

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New Analytic Method to Test Effectiveness of Open-Enrollment Group Interventions

Psychosocial interventions for alcoholism and drug abuse are most commonly delivered to patients in the context of group therapy. In groups with closed enrollment, once a group is formed new members cannot be added; conversely, in groups with open enrollment, members can join or leave the group at any time. Since open-enrollment groups have significant economic and clinical advantages, such as a reduced wait time for enrollment, it is the most common type of group used in community-based substance abuse treatment settings. However, constant turnover in the membership within open-enrollment groups presents a significant challenge for conventional statistical methods used to analyze treatment outcomes over time. In a new study funded in part by NIDA, investigators compared a method of analysis called latent class pattern mixture models (LCPMMs) with the more commonly used latent growth model (LGM) method—which cannot take changes in group membership into account—to examine outcomes of a clinical trial of two treatments for alcohol use disorder: Getting Along, a group intervention; and a standard individual-based treatment (IBT). While LGM found that group treatment was more effective than IBT, LCPMM was able to incorporate more information relative to group therapy (such as how differences in attendance are influenced by when in the year a patient joins a group) and found no significant difference in effectiveness between group therapy and IBT. The authors conclude that although larger numbers of clinical trial participants are needed to use the LCPMM method, results from this study indicate that LCPMM, compared with LGM, may provide a more accurate and conservative estimate of how well group therapy interventions work for patients.

Morgan-Lopez AA, Fals-Stewart W. Analytic methods for modeling longitudinal data from rolling therapy groups with membership turnover. *J Consult Clin Psychol*. 2007;75(4):580–593.

Middle School Interventions Reduce Nonmedical Use of Prescription Drugs

The rates of nonmedical use of prescription drugs among adolescents and young adults in the United States are alarmingly high. Researchers funded in part by NIDA examined whether several universal drug abuse preventive interventions for middle school-age youth could reduce their future nonmedical use of prescription drugs. The interventions, which were administered to both middle school-aged children and their families, were tested in two randomized, controlled studies conducted in the rural Midwest. The first study tested two different family-based interventions, the Preparing for the Drug Free Years (PDFY) program and the Iowa Strengthening Families Program (ISFP), which focus on teaching families about risk and protective factors for substance use. The second study compared the school-based Life Skills Training (LST) intervention program with the Strengthening Family Program for Parents and Youth 10–14 (SFP), a revised version of the family-based ISFP, plus the school-based LST programs. Both studies followed participants until the age of 21 and also included control groups of students that did not receive any of the interventions being tested. Beginning in the 9th or 10th grade, students were asked about prescription drug abuse. Results from both studies showed that teens and young adults who had received the interventions in middle school reported less prescription drug abuse compared with participants who had not received the interventions. The magnitude of the difference depended on the specific intervention received, with the ISFP (in study 1) and SFP programs (in study 2) producing significant decreases in rates of prescription drug abuse. Whether these results can be generalized to other populations (such as nonrural or international populations) and whether the effects of the interventions persist into emerging adulthood years will need to be examined in further studies.

Spoth R, Trudeau L, Shin C, Redmond C. Long-term effects of universal preventive interventions on prescription drug misuse. *Addiction*. 2008;103(7):1160–1168.

Stress Hormone Levels Altered in Maltreated Foster Children

Over 300,000 children enter foster care in the United States every year. These children have often experienced neglect, abuse, or both and are at high risk for later behavioral and social problems, including substance abuse. Scientists believe that a hormone system in the brain called the hypothalamic-pituitary-adrenocortical (HPA) system may play a role in how maltreatment influences later behavior. The HPA system produces a hormone called cortisol, which is involved in stress reactivity, sleep and eating cycles, and learning, as well as other processes. Researchers funded in part by NIDA examined whether maltreated foster children have different patterns of cortisol production compared with peers who have not been abused or neglected. The researchers studied 117 maltreated children aged 3 to 6, who were currently in foster care, as well as 60 low-income children who lived with their parents and had not experienced abuse or neglect. The researchers found that morning cortisol levels differed depending on the type of maltreatment the children experienced.

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For example, foster children who had experienced severe physical neglect were more likely to have low morning cortisol levels, and foster children who had experienced severe emotional maltreatment were more likely to have high levels of morning cortisol. Both abnormally low and high cortisol levels could affect later development, explain the authors. "Children with low morning cortisol levels might lack the needed resources to undertake the processes involved in learning and socialization…[, and] in contrast, elevated cortisol levels have been shown to impair cognitive processes, particularly vigilance and memory.…Thus, both low and high morning cortisol levels might be dysfunctional and might place foster children at risk for a host of difficulties," they conclude.

Bruce J, Fisher PA, Pears KC, Levine S. Morning cortisol levels in preschool-aged foster children: Differential effects of maltreatment type. *Dev Psychobiol*. 2009;51(1):14–23.

Deep Brain Stimulation Decreases Cocaine Seeking in Rats

Cocaine addiction is a significant problem in this country. While there are effective treatments, relapse continues to be a major barrier to long-term recovery. A surgical technique called deep brain stimulation (DBS), which uses permanently implanted electrodes to disrupt abnormal electrical activity in the brain, has shown promise as a treatment for some psychiatric disorders. To test the potential use of DBS as a treatment for cocaine addiction, researchers funded in part by NIDA implanted rats with DBS electrodes in the shell of the nucleus accumbens, an area of the brain thought to play a role in reinstatement of drug-seeking behavior. The researchers then taught the rats to self-administer either cocaine or food. After several weeks of self-administration, the rats went through a period of withdrawal followed by a reinstatement test, in which they are given either a cocaine injection or food pellets. The DBS electrodes were turned on during the reinstatement test, and reward-seeking behaviors in the rats receiving DBS were compared to a group of control rats that were taught to self-administer either cocaine or food but did not receive DBS. The researchers found that DBS in the nucleus accumbens shell significantly reduced the reinstatement of drug-seeking behavior but not food seeking, indicating that "DBS does not produce a generalized disruption of normal behavior," explain the authors. In another control experiment, DBS to a part of the brain called the dorsal striatum did not reduce the reinstatement of drug-seeking behavior after re-exposure to cocaine, indicating that the effect of DBS is anatomically specific. DBS may have potential as a treatment for cocaine addiction; however, the treatment would likely be reserved for severe (life-threatening) addiction cases since it involves invasive surgery.

Vassoler FM, Schmidt HD, Gerard ME, Famous KR, Ciraulo DA, Kornetsky C, Knapp CM, Pierce RC. Deep brain stimulation of the nucleus accumbens shell attenuates cocaine priming-induced reinstatement of drug seeking in rats. *J Neurosci*. 2008;28(35):8735–8739.

Immune System Proteins Interfere With Painkilling Effects of Opioids

Opioid drugs are commonly used medically because of their effective analgesic, or pain-relieving, properties. When used chronically, however, analgesic tolerance (loss of pain suppression following repeated opioid exposure) can occur. Tolerance to opioids has been thought to occur when brain neurons adapt to the presence of opioid drugs; however, investigators have recently proposed that the immune system, particularly an inflammation-promoting protein called IL-1, may also play a role. To test this hypothesis, investigators funded in part by NIDA administered morphine or methadone with or without proteins that inhibit the production of IL-1 and related molecules in a rat model of pain. The researchers found that blocking IL-1 significantly increased the duration of morphine- or methadone-induced analgesia (pain reduction) and that coadministration of morphine along with the IL-1 protein blocker increased the analgesic efficacy of morphine by almost eightfold. Furthermore, they showed that blocking the production of IL-1 reduced the development of tolerance to morphine as tested by exposure to heat, indicating that inflammation does play a role in the development of opioid tolerance. The researchers also found that several other inflammation-inducing proteins produced by a type of cell called microglia can block the painkilling effects of the opioids. When they blocked activity of the microglia, the researchers found that morphine-induced analgesia was increased. Finally, the researchers identified a set of inflammation-inducing proteins and gene products that likely contribute to some of the negative side effects of long-term opioid administration—including heightened sensitivity to painful stimuli, touch, and pressure. These results suggest that reducing inflammatory responses to opioids may have potential therapeutic uses.

Hutchinson MR, Coats BD, Lewis SS, Zhang Y, Sprunger DB, Rezvani N, Baker EM, Jekich BM, Wieseler JL, Somogyi AA, Martin D, Poole S, Judd CM, Maier SF, Watkins LR. Proinflammatory cytokines oppose opioid-induced acute and chronic analgesia. *Brain Behav Immun*. 2008 Jul 1; [Epub ahead of print].

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Functional Embryonic Stem Cells Isolated From Rats

The advent of a reliable approach to deleting, inserting, and modifying genes at will in a living organism has been a major advancement in biomedical research. The basic technique requires the modification of a gene of interest, which is then used to replace the normal gene in an embryonic stem (ES) cell line. The resulting genetically modified ES cell is then injected into an early-stage embryo of the laboratory animal to be studied, where the modified or deleted gene can become a heritable trait. One of the biggest obstacles for the generation of such genetically modified animals is the availability of ES cells in different animal systems. Previously, this technique had been conducted successfully in only a few inbred strains of mice. Now, researchers funded in part by NIDA have captured ES cells from rat blastocysts—very early embryos—using a special cell culture regimen designed to suppress proteins that cause stem cells to differentiate into other cell types. The resulting cultured ES cells possessed two important traits that are required for their use in genetic research: when injected into normal mouse embryos, they produced viable chimeric rats (rats possessing genetic material from both the original embryo and the injected ES cell); and male rats possessed genes from the ES cell in their sperm—thus, the traits can be passed on to their offspring. The ability to create rats in which any gene of interest can be reproducibly modified or deleted represents an important advance. The rat is a far easier organism for carrying out physiological and pharmacological studies, and a particularly more relevant model system to investigate complex mental disorders. Therefore, this breakthrough is poised to significantly enhance researchers' abilities to dissect the genetic components of substance use and other psychiatric disorders.

Buehr M, Meek S, Blair K, Yang J, Ure J, Silva J, McLay R, Hall J, Ying QL, Smith A. Capture of authentic embryonic stem cells from rat blastocysts. *Cell*. 2008;135(7):1287–1298.

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- Congressional staffers, call Geoffrey Laredo at 301-594-6852.

The National Institute on Drug Abuse (NIDA) is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports most of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. Fact sheets on the health effects of drugs of abuse and other topics are available in English and Spanish. These fact sheets and further information on NIDA research and other activities can be found on the NIDA home page at http://www.drugabuse.gov. To order publications in English or Spanish, call NIDA's new *DrugPubs* Research Dissemination center at 1-877-NIDA-NIH (1-877-643-2644) or 240-645-0228 (TDD), or fax or e-mail requests to 240-645-0227 or drugpubs@nida.nih.gov.

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