Long-Term Effects of Developmental Exposure to Cocaine on Learned and Unlearned Behaviors

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INTRODUCTION

The purpose of this chapter is to review the effects of exposure to central nervous system (CNS) stimulants on the neurobehavioral development of experimental animals. The focus is on the effects of cocaine.

A search was made of the experimental literature on the effects of prenatal and/or early postnatal exposure to cocaine. The search encompassed the years 1982 to mid-1993. Only one selection criterion was imposed on the search: only articles reporting original experimental results were included. The search generated 57 relevant articles. A tabular summary of these, presented in chronological order, is provided in table 1. The table is structured with authors and date in the first column, with subsequent columns for dose (expressed as the hydrochloride unless specified as the free base), species and strain, dose rate expressed on a per diem basis, exposure period (embryonic or postnatal age given in days), route of drug administration, the concentration of the drug in solution, the major types of control groups used, principal variables investigated, and finally the major effects obtained (including negative findings).

DESIGN CONSIDERATIONS

Several points regarding design of developmental studies appropriate for cocaine are discussed in this chapter. Some of these arise from develop-mental considerations, some from the nature of cocaine's pharmacological effects, and some from considerations of experimental design logic.

The control groups used in studies of cocaine exposure are particularly important for several reasons. First, cocaine is a potent anorectic agent and therefore suppresses food consumption and

weight gain. This is obviously important during pregnancy in developmental studies, when weight gain is a normal process that accompanies embryonic develop-ment. While all experiments reviewed below included an ad libitum fed and saline-injected (or water-gavaged) control group (AL), only a subset of the experiments reviewed included nutritionally matched pair-fed (PF) controls (i.e., groups given diet in the amount equal to that consumed by yoked cocaine-treated animals on the same gestational day) (Vorhees 1986). Pair-fed controls in cocaine-exposure experiments, especially in prenatal studies, are one of the most important controls needed; their absence raises questions about the interpretation of the results obtained. An exception to this rule is when the dose given does not induce an alteration in food consumption or weight gain. As shown in table 1, several authors have reported data in which the dose and dosing regimen used did not significantly reduce maternal weight in either absolute terms or in terms of weight gain during gestation.

A second relevant control in prenatal studies arises from the potential for maternal carryover effects. In this situation, the use of surrogate or other fostering procedure is indicated. The purpose of these procedures is to remove the treated neonates from the influence of their treated (biological) dam. One approach is for treated and control neonates to be reared by untreated dams prepared separately and timed to deliver shortly before the experimental groups. Such offspring are said to be surrogate fostered. Another approach is when neonates are reared by dams of the opposite treatment group. Litters reared in this fashion are known as cross-fostered.

Finally, the converse of cross-fostering occurs when neonates are reared by dams from within the same treatment group but not by their biological dam. These offspring are known as fostered (Vorhees 1986). In table 1, surrogate fostering has been designated S-FOS, while cross-fostering or fostering has been designated FOS. Only a subset of the experiments reviewed in table 1 included either type of fostered rearing control.

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993.

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Fantel and MacPhail 1982	50 60 75 60	Rat:SD M:SW	1d 1/d	E8-12 E7-16	IP IP.	n.g. n.g.	AL PF	Visceral malformations	50:-- 60: resorp. fetal wt. 75: mat. leth. fetal edema m60: fetal wt
Church et al. 1988a	20 30 40	Rat:LE	2/d	E7-19	SC	20	AL	Preg. outcome	mat. leth.: 60-90 mat. wt. gain all grps. fetal. mort.: 70-90 fetal wt.: 90

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
DeVane et al. 1989	30 (base)	Rat:SD	1/d	E18 or 19	IP	30	None	T_	mat. 45' fetal 55'
Dow-Edwards et al. 1989	40,80 20,40	Rat:SD	1/d	E0-16	PO SC	26-32 20,40	AL	mat. wt. gain mat. peak	500ng/ml _ h 1,000 " _ hr.
Church et al. 1988b	20,25, 30,35, 40,45	Rat:LE	2/d	E7-19	SC	20	AL	Preg. outcome	Ibid
Dow-Edwards et al. 1988	25 50	Rat:SD	2/d 1/d	P1-2 P3-10	SC	n.g.	AL	2-DG	metab. act. in F in multiple cerebral areas

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Fung et al. 1989	30 (base)	Rat:SD	Con-tinuous	E2-birth	mini-pump	20	AL S-FOS	loco. ontogeny activity spiperone bind. DA turnover	-- -- -- -- -- --
Hutchings et al. 1989	3060 10	Rat:W	1/d	E7-21*	PO	6121 0	AL PF S-FOS	Mat. wt. gain activity	at 60 mg/kg on P20 and 23
Smith et al. 1989		Rat:LE	1/d	E3-17*	SC		AL	mat. wt. offspring wt. neg. geo. surf. rt. spont. alt.	-- -- -- -- in M

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Smith et al. (cont.)								open-field	in M
								DRL-20	response rate
								act. av.	--
								tail-flick	latencies
								T-water maze	lat. male earl trials only
								sleep time	--
								shock sensit.	
Spear et al. 1989a	40	Rat:SD	1/d	E7-19*	SC	13.3	AL PF	mat. wt.	--
								gest. length	--
								litter size	--
								offspring wt.	--
								eye opening	--
								lower incisors	--
								surf. rt.	--
								cliff avoid.	--
								horiz. screen	--
								vert. screen	--
								neg. geo.	--

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Spear et al. 1989a (cont.)								odor cond. shock-induced wall climbing and act. shock sensit.	--
Spear et al. 1989b	10,20,40	Rat:SD	1/d	E7-19*	SC	13.3	AL	coc. 2 hr. at 40 plasma mat. fetal brain mat. fetal	 2200 ng/ml 800 2900 2200
Wiggins et al. 1989	10,60	Rat:LE	1/d	E19 or 20	PO	n.g.	None	fetal: mat. brain fetal: mat. plasm	.7 at 1.5 h. at 60 mg/kg 1.5 ibid

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Church et al. 1990	20,30, 40,50	Rat:LE	2/d	E7-20	SC	20	AL PF	mat. wt. gain mat. mort. offspring wt. litter size offspring mort. pinna det. incisors fur dev. eye opening vag. patency	dose-dep. dose-dep. ≥40 dose-dep. ≥30 at 50 at 40 and 50 at 20, 40, 50 -- at 40 and 50 at 30, 40, 50 at 40 and 50
Church and Overbeck 1990a	20,30, 40,50	Rat:LE	2/d	E7-20	SC	20	AL PF	neg. geo. spont. alt. activity passive av. act. av.	-- -- (freq.) left bias -- vs. PF ret. lat. at 50 -- vs. PF

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Church and Overbeck 1990b	20,30, 40,50	Rat:LE	2/d	E7-20	SC	20	AL PF	BAEP	interpeak lat. at 50 mg/kg amplitude at 50 mg/kg
Dow-Edwards 1990	30,60	Rat:W	1/d	E7-21*	PO	n.g.	--	_ h. at 60: mat. plasma fetal plasma mat. brain fetal brain	 5400 ng/ml 3000 3500
Dow-Edwards et al. 1990	60	Rat:W	1/d	E7-20*	PO	12	PF S-FOS	2-DG	hypothal. nigrostriat. MFB hippo. septum amygdala

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Finnell et al. 1990	20,40,60	DBA/2J SWV	1/d	E6-8 E8-10	IP	n.g.	AL	stage effects implantations resorptions mat. wt. gain fetal wt. malform. (ntd and urinary)	-- -- -- -- -- 40,60,DBA all doses SW
Giordano et al. 19901	30	Rat:SD	1/d	E12-21	SC	30	AL	activity w/ d-A chall. coc. chall.	 -- --
Henderson and McMillen 1990	15 (base)	Rat:SD	2/d	E1-birth	SC	n.g.	AL S-FOS	birth wt. litter size surf. rt. eye opening act. P30 act. P60	 -- -- --

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Heyser et al. 1990	40	Rat:SD	1/d	E7-19*	SC		AL	mat. wt. gain	
								litter size	--
								birth wt.	--
								sens. precond.	at P8
									at P12
									-- at P21
								1st order cond.	at P8
									-- at P12
									-- at P21
Raum et al. 1990	10	Rat:SD	single	PO	SC	n.g.	AL	0.5 h.estradiol	
								0.5 h. testost.	
	10,30	Rat:SD	2/d	E15-20	SC	n.g.	AL	mat. wt. gain	at 30
								litter size	--
								offspring wt.	--
								anogenit. dist.	--
								scent marking	in males
								intromiss. lat.	
								plasma LH	
								plasma FSH	--

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Raum et al. (cont.)	3		2/d	E15-20 and P1-5			AL and S-FOS	testosterone organ wts. birth wt. P50 wt. scent marking	-- -- -- in males
Scalzo et al. 1990	40	Rat:SD	1/d	E7-19*	SC	13.3	AL	recept. bind. P2 striatum D1 striatum D2 n. accumb. D n. accumb. D	 -- -- --
Sobrien et al. 1990	40	Rat:SD	1/d	E14-20*	SC	n.g.	AL	mat. wt. gain litter size birth wt. offspring wt. pinna detach. incisor eruption eye opening	-- -- -- -- -- -- --

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Sobrien et al. 1990 (cont.)								neg. geo. surface rt. olfact. behav. cliff avoidance startle dev. air righting act. w/ d-A act w/ coc.	-- -- -- attenuated attenuated
Barron et al. 1991	60	Rat:LE	1/d	E13-20*	PO	13.3	AL	mat. wt. gain mat. plasma coc fetal wt. litter size umbilical lgth.	 430 ng/ml 5-50 -- --
Church et al. 1991	30	Rat:LE	2/d	E7-20	SC	20	AL PF S-FOS	mat. wt. gain birth wt. offspring mort.	 -- --

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Church et al. (cont.)								pinna detach. fur dev. eye opening vag. patency neg. geo. loco. act. pass. av. act. av.	-- -- -- -- -- -- --
Church and Overbeck 1991	30,40	Rat:LE	2/d	E7-20	SC	20	AL PF S-FOS	BAEP threshold latency	 at 40 at 40
Clow et al. 1991	10,20,40	Rat:SD	1/d	E7-19*	SC	3.33 6.66 13.3	AL PF S-FOS	mat. wt. gain 3H-naloxone autoradiog.	at 40 in med prefrontal rost. olf. tuber cingulate cx. hippo. CA1 DG mol layer motor cx. sensory cx. entorhinal cx.

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
El-Bizri et al. 1991	2.1, 4.2, 8.5,17, 34	Rat:SD	1/d	E0-19	IP SC	n.g.	AL	mat. wt. gain IP peak (5") T_ SC peak offspring wt. brain DA brain NE act. embryo culture	 510 ng/ml 21" 147 ng/ml -- -- -- -- development
Hughes et al. 1991	50	Rat:SD	1/d	P1-10 P11-20	SC		AL	act. w/ d-A .1 mg/kg .25 mg/kg	 early grp. late grp.
Rodriguez-Sanchez et al. 1991	40	Rat:W	1/d	E7-19 E7-P15 P0-15	SC	n.g.	AL some S-FOS	Somatostatin-IR front. cortex Hippocampus	 prenatal grps. prenatal grps. -- P0-15 grp.

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Rodriguez-Sanchez et al. (cont.)								SS receptors	no. in cortex affinity in ex.
Rodriguez-Sanchez and Arilla 1991	40	Rat:W	1/d	E7-19 E7-P15 P0-15	SC	n.g.	AL	Somatostatin-IR 125I-Tyr Somat. in striatum	-- all grps. receptors in E7-19 and E7-P affinity E7-19
Seifert and Church 1991	40,50	Rat:LE	2/d	E7-20	SC	n.g.	AL PF S-FOS	Offspring wt. femur dry wt. femur ash wt. femur organ. wt	at 50 mg/kg at 40 mg/kg at 40 mg/kg at 40 mg/kg

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Webster et al. 1991 (based on Webster and Brown-Woodman 1990)	70 60 50	Rat:SD	1/d 1/d 2/d	E16 only	IP	20	AL	Cx necrosis Cx cavitation BS cavitation Str. hemorrhage	
Foss and Riley 1991a	60 40	Rat:LE	1/d	E13-20* E7-20*	PO SC	13.3 13.3	AL PF	mat. wt. gain litter size offspring wt. acoustic startle startle habit. prepulse inhib.	-- both grps. -- both grps. -- both grps. -- both grps. -- both grps. -- both grps.
Foss and Riley 1991b	40	Rat:LE	1/d	E13-20*	SC	13.3	AL PF	mat. wt. gain startle w/ coc. open-field w/ coc. chall.	-- no pattern

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Riley and Foss 1991a	60 40	Rat:LE	1/d	E13-20* E7-20*	PO SC	13.3 13.3	Al PF	holeboard	-- both grps.
Riley and Foss 1991b	60	Rat:LE	1/d	E13-20*	PO	13.3	AL PF	pass. av. act, av, Morris maze	-- -- --
Akbari et al. 1992	40 40,10	Rat:SD	1/d	E13-22 E13-P5	SC	13.3	AL	3H-paroxetine 5HIR 3H-paroxetine	P1,7 pre grp. hipp., pre grp. -- or early in pre/post grp. P28 all Δ gone
Akbari and Azmitia 1992	40	Rat:SD	1/d	E13-22	SC	13.3	AL S-FOS	DA-IR	hippocampus ant. cingulate parietal cortex
Bilitzke and Church 1992	40	Rat:LE	2/d	E7-20	SC	20	AL PF S-FOS	mat. wt. gain resorptions offspring wt. pinna detech.	 (after birth) -- up to P120 --

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Bilitzke and Church (cont.)								fur dev. ear opening eye opening offspring mort. Porsolt test	-- -- -- -- immob. time
Church and Rauch 1992	50	Mouse: BALB/c xSJL	1/d	E7-18	SC	20	AL PF	mat. wt. gain water consump. food consump. resorptions birth wt. offspring wt. pinna detach. fur dev. ear opening eye opening	-- -- -- --

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Goodwin et al. (II) 1992	40	Rat:SD	1/d	E7-19*	SC	13.3	AL FOS	P7 cond odor avoid. P17: cond. aud. av. cond. odor av. shock aggr. intruder aggr.	C40-C40 on train. trls. 2-4 av FOS/C40 on train. trls. 2-3 -- -- ≈ lat C40-C40 C40-FOS grps. --
Heyser et al. (I) 1992c	40	Rat:SD	1/d	E7-19*	SC	13.3	AL FOS	mat. wt. gain litter size birth wt. pup retrieval mat. aggr. FOS/lc FOS/C40 lc/FOS lc-lc	 -- -- -- -- -- -- lat. to attack

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Heyser et al. (I) 1992c (cont.)								C40/FOS C40-C40	intruder freez -- attacks lat. to attack intruder submission
Heyser et al. 1992b	40	Rat:SD	1/d	E7-19*	SC	13.3	AL PF S-FOS	mat. wt. gain litter size offspring mort. offspring wt. cond. place pref cham. entries	-- -- --
Heyser et al. 1992a	40	Rat:SD	1/d	E7-19*	SC	13.3	AL cellulose control	Coc.-induced odor preference	Coc-induced odor pref at low dose only in prenatal coc grp.

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Johns et al. (I) 1992a	15	Rat:SD	2/d	E1-20 E2-3,8-9, 14-15,19-	SC	n.g.	PF S-FOS	mat. wt. gain litter size offspring wt. surface rt. eye opening act. P30, 15" Diurnal nocturnal act. P60, 15" diurnal nocturnal	coc-D grp. coc-I grp. -- both grps. -- both grps. -- both grps. coc-D grp. -- both grps. coc-I grp. -- both grps. -- both grps. -- both grps.
Johns et al. (II) 1992b	15	Rat:SD	2/d	E1-20 E2-3,8-9, 14-15,19-	SC	n.g.	PF S-FOS	spont. alt. open-field win-stay maze P30 and 60	-- both grps. non-entries coc-D entry coc-I -- (both ages)

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Meyer et al. 1992	20	Rat:SD	2/d	E10-19*	SC	6.6	AL PF S-FOS	P 11 Coc. chall. vocalizations digging time grooming time stationary time loco. time wall clim. time	 -- -- -- -- -- no in coc. offspring at mid low coc chall. do
Minabe et al. 1992	40	Rat:SD	1/d	E7-19*	SC	13.3	AL PF S-FOS	active cells in A9 and A10 nuclei	in A10 and A9 -- after apomorphine challenge

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Rodriguez-Sanchez and Arilla 1992	40	Rat:W	1/d	E7-19 E7-P15 P0-15	SC	n.g.	AL	somatostatin-IR 125I-Tyr Somat. in olfactory bul	E7-19 grp. E7-P15 grp. -- P0-15 grp. receptors and affinity E7-19 and P0-15 grps.
Tyrala et al. 1992	10	M:ICR	1/d	E6-14	IP	n.g.	AL	fetal brain cell culture AchE protein	 specific act.
Weaver et al. 1992	10,20	Rat:SD	1/d	E20	IP	n.g.	AL	c-FOS in SCN pre-trt. D1 ant. SCH-23390	 blocks
Dow-Edwards et al. 1993	50	Rat:SD	1/d	P11-20	SC	10	AL	2-DG males	 n. accumbens piriform cx. med. genicul. auditory cx.

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Dow-Edwards et al. 1993 (cont.)								females	5/6 mot. area 7/17 limbic 2/8 hypothal. 3/11 sensory 1/3 assoc.
Factor et al. 1993	10,40	Rat:SD	contin-uous	E8-22	mini-pump	NA	AL some S-FOS	PPT2 mRNA PPT TrpH act. subst. P in med. raphe n	-- all ages -- all ages -- all ages -- all ages
Seidler and Slotkin 1993	30,100	Rat:SD	3/d	E8-20 E18-20	SC	3.3 11.1	AL	ODC activity 3H-thymidine DNA content protein/DNA	ODC on P2, no change thereafter -- all other parameters

TABLE 1. Effects of prenatal and/or early postnatal exposure to cocaine on experimental animals: 1982-1993
(continued).

Authors	Dose	Species	Rate	Exposure	Route	Conc	Controls	Variable	Effect
Vathy et al. 1993	**10**	**Rat:SD**	**2/d**	**E11-18**	**SC**	**n.g.**	**AL** **1/2 FOS**	**surf. righting** **vaginal patency** **open field act.** **F lordoses after ovariectomy** **M No. mounts** **intromissions** **post-ejac. time** **preoptic n.**	**--** **--** **--** **NE** **DA**

*Adjusted for evidence of conception as embryonic day E0.

Symbols: --=no change; =significant increase; =significant decrease; E=embryonic day; PN=postnatal day; AL=ad lib fed control; PF=pair fed control;

S-FOS=surrogate fostered control; FOS=cross-fostered control; SD=Sprague-Dawley rat; LE=Long-Evans rat; W=Wistar rat; SC=subcutaneous;

IP=intraperitoneal; PO=per oral (gavage); M=mouse with specific strain noted; n.g.=concentration not given in article.

Doses are expressed in mg/kg. Except where noted, dose was expressed as the hydrochloride. Drug concentration is expressed as mg/ml of solution.

1This study contained only 2 litters per group.

2Preprotachykinin.

Overview of Design Features of the Current Literature on Cocaine

In order to provide a sense of the areas of investigation among the 57-reports reviewed here, table 2 provides a summary by focus area. Slightly more than 42 percent of the studies focused on behavioral effects, while 27 percent concentrated on neurochemical effects, nearly 16 percent on teratogenesis or early postnatal physical outcome (termed

TABLE 2. Summary of experiments on developmental exposure to cocaine, 1982 to 1993.

Area	No. of Articles*	Percent
Behavioral teratologic		
Pharmacokinetic		
Developmental toxicity/teratologic		
Neurochemical		
Neurophysiologic		
Total		

KEY: * =Some experiments were difficult to classify and were therefore divided and half placed in two separate categories.

"developmental toxicity" in table 2), nearly 10 percent on pharmaco-kinetics (although these studies are all very limited in scope), and about 5percent on neurophysiological measures.

Table 3 reveals the distribution of test species in the literature. No studies in monkeys were found. All the studies identified were conducted in rodents, and rat studies constituted better than 93 percent of the published literature. Of the 54 articles reporting results in rats, nearly 60 percent were conducted using the Sprague-Dawley (SD) strain, nearly 30 percent in Long-Evans (LE), and about 10 percent in Wistar (W) rats.

A further examination of table 1 reveals that about 50 percent of the published articles on developmental cocaine exposure have included

TABLE 3. Summary of experiments on developmental exposure to cocaine, 1982 to 1993.

			No.*		Percent
Species	Rat				93.1
	Mouse				6.9
Strain (rat)	SD				59.3
	LE				29.6
	W				11.1

KEY: SD = Sprague-Dawley; LE = Long-Evans; W = Wistar; * = total sums to more than 57 because some articles reported results from multiple experiments in two species.

pair-fed or similar nutritional controls. Of those studies reporting postnatal outcome measures, about 50 percent included some type of fostering controls, most being of the surrogate fostering type. The confluence of nutritional and fostering controls occurred in roughly 25percent of the prenatal exposure experiments that included postnatal outcome. Experiments without postnatal evaluation obviously do not need fostered controls; this category includes teratologic and fetal neurochemical experiments.

Table 4 shows the distribution of exposure periods. Interestingly, better than 83 percent of studies used only prenatal exposure, just under 8per-cent a combination of prenatal and postnatal exposure, and about 9per-cent early postnatal exposure only (prior to weaning). In light of the fact that early postnatal exposure in rodents is roughly analogous to late second and third trimester exposure in humans in terms of CNS development (Bayer et al. 1993), the relative neglect of this latter exposure period is unfortunate as it suggests that most of the experiments to date have modeled less than half of the early developmental stages that are critical to human intrauterine brain development.

Table 5 summarizes another aspect of the developmental cocaine literature. The top half of the table shows the dose rate schedules of cocaine administration. Although cocaine has a short biological half-life (0.3 hour after intravenous (IV) administration, 0.75 hour after intra-peritoneal (IP) administration, and 2 hours after subcutaneous (SC)

TABLE 4. Summary of experiments on developmental exposure to cocaine, 1982 to 1993.

Exposure Period	No.*	Percent
Prenatal		
Pre- and postnatal		
Postnatal		
Total		

KEY: * =Total number exceeds 57 because several experiments were reported in which there were multiple treatment regimens used (e.g., the articles by Rodriguez-Sanchez and colleagues included a prenatal only group, a pre- and postnatal group, and a postnatal only treated group). Each group was tallied separately.

TABLE 5. Summary of experiments on developmental exposure to cocaine, 1982 to 1993.

Dose Rate/Route	No.	Percent
Dose rate		
Once/day		68.4
Twice/day		26.3
Over twice/day		1.8
Continuous		3.5
Total		
Route of administration		
SC		70.0
IP		11.7
PO		15.0
IV		0
Infusion		3.3
Total		

NOTE: Total exceeds 57 because these articles report experiments using more than one route of administration.

KEY: SC = subcutaneous; IP = intraperitoneal; PO = per oral (gavage); IV = intravenous.

administration in rats (DeVane et al. 1989; Nayak et al. 1976)), over 68percent of the studies relied upon single daily dose administration regimens. About 26 percent used twice per day schedules, while only one experiment (1.8 percent) used more than twice per day administration. That experiment, by Seidler and Slotkin (1993), used thrice per day dosing. This chapter also summarizes preliminary data from an experi-ment conducted by the author using 5-times-a-day dosing of cocaine during gestation.

The bottom half of table 5 shows the routes of drug administration that have been employed. By a large margin (70 percent), experimenters have used SC administration. Slightly less than 12 percent used the IP route, and not one of these examined behavioral outcomes. The IP adminis-tration experiments are predominately teratologic, with a small number being pharmacokinetic or neurochemical. Interestingly, all of these studies, save the one that was exclusively pharmacokinetic, report finding cocaine-induced effects on the progeny. A similar minority (15percent) of the studies used an oral (PO) route of administration. None of the published studies used an IV route. Finally, 3.3 percent of the studies used infusion via subcutaneously implanted osmotic minipumps for cocaine delivery.

Deficiencies in the Current Literature on Cocaine

Having summarized the approaches reported in the developmental cocaine literature, it is germane to point out the gaps that exist. First, the rat, and primarily the SD rat, has been the dominant species and strain used. Since no single species provides an entirely adequate model of human disorders, there is a clear need to expand the range of models to other species. Among rats, the heavy reliance upon the SD rat, although understandable in terms of its broad scientific acceptance and use by regulatory agencies as a standard in investigations of developmental toxicity, may overly weight the findings towards this one strain. If the literature were replete with striking cocaine-related developmental effects, one would be less concerned about the possible limitations of the SD rat; but given that this is not the case (see below), exploration of other strains may prove fruitful.

Another shortcoming is the heavy focus on exposure during most of pregnancy. Two obvious gaps exist here: the first is the value of rodent postnatal exposure as a model of human late second and all of third trimester, and second is the value of investigating discrete exposure intervals. Of the published prenatal studies, almost all have

used exposure throughout most of pregnancy. The opportunity to find critical period effects is lost with this strategy, and thus important effects may exist that have yet to be uncovered.

Another area where gaps exist is in the dose-rate schedules that have been used. Heavy reliance upon once-a-day dosing may be insufficient. Again, if the existing literature supported the view that cocaine given once per day was inducing clear neurodevelopmental effects, there would be no compelling reason to question this approach. However, the contrary is the case, with few effects having been established with certainty. This situation, taken together with the fact that cocaine has a biological half- life in rodents of 0.3 to 2 hours depending on the route of administration, raises questions about what may be being missed by current models that administer the drug only once a day.

Finally, these studies have relied upon the SC route of administration to a great extent. Using the same logic as expressed above, no concern would exist had striking effects been reported using this route. As this is not the case, further exploration of other routes seems worthwhile. Among the other routes needing further attention are the IP and IV routes. Further work with PO administration may also prove useful and consideration should be given to inhalation exposure. Given the degree of sophisti-cation possible in facilities with equipment and expertise in inhalation toxicology, the technical barriers to this approach should not prevent this route from being investigated.

In toto, the current developmental cocaine experimental literature appears heavily weighted towards a limited range of experimental models that have produced mixed results. However, if one ignores for the moment the possible limitations of the models, the next pertinent question becomes, what effects related to cocaine exposure have been reported?

BEHAVIORAL EFFECTS OF DEVELOPMENTAL COCAINE EXPOSURE

Of the 57 experiments reviewed, 24 have been behavioral teratologic studies. Of these 24, 15 have reported finding cocaine-related effects (table 6). These 15 studies are individually reviewed below. However, itshould be noted that describing the results as positive in 15 of 24, or 62.5percent, of the studies overstates the apparent strength of the

TABLE 6. Summary of positive behavioral teratologic experiments on prenatal cocaine, 1982 to 1993.

Article	Route	Dose	Exp.	Effect
Hutchings et al. 1989	PO	30,60	7-21*	Loco. act. P20 and 23 only at 60 mg/kg
Smith et al. 1989	SC	10	3-17*	Spont. alt. freq. (males only)
				Open-field act. (males only)
				DRL-20 res. rate
				Tail-flick lat.
				T-water mz. lat. (M, early trls. only)
				Shock sensitivity
Spear et al. 1989a	SC	40	7-19*	Odor conditioning
				Shock-induced wall climbing
				Act. during shock-ind. wall climb.
Church/Overbeck 1990a	SC	20,30, 40,50	7-20	Left bias in spont. alt. (non-D-dep.)
				Pass. av. ret. at 50 mg/kg
Henderson/McMillen 1990	SC	15	1-birth	Surface righting dev.
Heyser et al. 1990				Loco. act. at P30; - at P60
	SC	40	7-19*	Sens. precond., P8, 12; not at P21
				1st order cond., P8; not at P12, 21
Raum et al. 1990				
	SC	10,30	15-20	Scent marking in males
Sobrien et al. 1990				Lat. to intromission
	SC	20	14-20*	Surface righting and cliff avoid. dev.
				Startle dev.
				Res. on loco. act. to d-A and coc.
Church et al. 1991				
Heyser et al. 1992b	SC	30	7-20	Loco. act.
	SC	40	7-19*	Cond. place preference
				No. chamber entries

TABLE 6. Summary of positive behavioral teratologic experiments on prenatal cocaine, 1982 to 1993 (continued).

Article	Route	Dose	Exp.	Effect
Johns et al. 1992a	SC		1-20 2-3, 8-9, 14-15, 19-20	Loco. act. P30 1st 15' (Coc-D grp.) Loco. act. P30. dark cycle (Coc-I grp.)
Johns et al. 1992b	SC		Ibid	Open-field non-entries (Coc-D grp.) Open-field act. (Coc-I grp.)
Bilitzke and Church 1992	SC		7-20	Immobil. time on Porsolt swim test
Goodwin et al. 1992	SC		7-19*	Odor cond. P7; coc-coc, 2-4 train. trls. FOS/coc 2 and 3 train. trials only - aud. cond. P17; - Odor cond. P17 Lat. to 1st attack shock- induc. aggr. in coc-coc and fos-coc grps.
Meyer et al. 1992	SC		10-19*	Effects tested using coc. challenge: wall climb. all ch. doses in AL and PF wall climb. high dose only in coc. grp.

NOTE: Papers are listed in chronological order. Two papers (Raum et al. 1990 and Vathy et al. 1993) reporting positive findings on sexual behaviors are not included in this table, but are shown in table 1.

KEY: * = Adjusted for evidence of conception as embryonic day E0.

findings since every report contained multiple behavioral and other measures. In most of the experiments with positive findings, there were as many (or in some cases, more) negative than positive findings.

Therefore, one should bear this in mind as the positive effects are discussed in greater detail.

Among the behavioral teratogenic studies, Hutchings and colleagues' (1989) is the only study with positive findings that used the oral route of administration. These authors reported that offspring exposed in utero to 60 milligrams per kilograms (mg/kg) of cocaine administered by gavage on embryonic days (E) 7 to 20 showed increased locomotor activity on days 20 and 23, but on surrounding test days cocaine-exposed offspring did not show similar effects. Progeny exposed by the same regimen to a lower dose of 30 mg/kg showed no changes in activity. While significant cocaine-related effects were found in this experiment, the small number of test days showing a change and their sporadic occurrence within a larger context of more numerous test days when no effects were obtained raise doubt as to the strength and reproducibility of these findings.

Among the studies administering cocaine by injection, Smith and colleagues (1989) reported decreased spontaneous alternation frequency and open-field activity only among males, increased responding on a differential reinforcement of low rate (DRL)-20 operant schedule, decreased tail-flick latencies, increased latencies to reach a goal in a water T-maze, and decreased footshock sensitivity in rats exposed in utero to 10mg/kg of cocaine administered once per day on E3 to 17. Superficially these results appear to support a large number of cocaine-related effects, but the findings are difficult to interpret. The effects reported stem from analysis of variance (ANOVA) interaction terms. The significant F-ratios obtained were small and significant only because of the large degrees of freedom. A concern is that the effects account for only a small percentage of the variance and may not prove to be meaningful or replicable. If the authors or others cannot replicate these effects, then they are not reliable indices of cocaine-induced developmental neurotoxicity. As discussed below, there is little indication in the literature that the findings reported in this article are seen by other investigators.

Spear and colleagues (1989a) administered SC cocaine to rats on days E7to19 and found that the offspring showed a decrease in odor condition-ing, a decrease in shock-induced wall climbing, and increased activity during the wall-climbing test. These findings may represent a promising lead because the authors have replicated at least portions of these findings (decreased odor conditioning). Moreover, they have extended the findings to other effects of prenatal cocaine exposure. Some of these other effects are similar to those reported in

this first experiment (Spear et al. 1989a) and some are quite different, but together they suggest that cocaine is capable of inducing developmental effects in progeny exposed in utero.

Among the positive behavioral effect studies is that published by Church and Overbeck (1990a). This report is part of a series published by the Church laboratory on prenatal cocaine exposure using a wide range of dependent variables. The authors reported finding two behavioral effects: an increase in left turning bias in animals tested on a spontaneous alterna-tion procedure with no cocaine-related effects on the primary response measured on this task (viz., alternation frequency) and a decrease in passive-avoidance retention times. Church and Overbeck (1990a) obtained these results in rats administered doses of cocaine ranging from 20 to 50mg/kg twice a day given to the dams on days E7to20. The principal difficulties in interpreting these findings are that the left turning bias is of unknown significance, the increase was not dose-dependent, and the behavior was not central to what the task was intended to measure. The passive-avoidance effect was found in the high-dose group, but no other cocaine-exposed group was affected on this measure. The high-dose group in this study received a dose that produced significant maternal and off-spring toxicity. Specifically, the 50-mg/kg dose increased maternal death and reduced maternal weight gain. In the offspring, this dose reduced litter sizes and increased neonatal mortality. Obviously, these types of toxicity are not trivial. In such a context, the passive-avoidance effect, while interesting, stands in pale contrast with death. This view might be altered if it could be shown that cocaine-exposed offspring have persistent and substantial memory impairments at lower doses, but converging evidence employing multiples tests of memory have yet to appear in the literature. At present, the passive-avoidance effect does not appear commensurate to the other effects of cocaine at very high doses.

Henderson and McMillen (1990) administered 15 mg/kg cocaine twice a day on E1 to 22 and found decreased surface righting development and increased locomotor activity at 30 days but not 60 days of age. A number of investigators have tested cocaine-exposed offspring for reflex ontogeny, including using tests of surface righting, but no such effects were obtained by others even at higher doses (Johns et al. 1992a; Spear et al. 1989a; Vathy et al. 1993). Thus, it is difficult to reconcile this finding with those of other investigators who have not found such effects. No published replication of the effect has yet appeared. The increase in day 30 activity is interesting and may be significant, but other laboratories

have reported opposite effects (Church et al. 1991; Smith et al. 1989). One similar effect on activity has been reported and is discussed below (Johns et al. 1992a).

Heyser and colleagues (1990) administered 40 mg/kg of SC cocaine on E7to19 and found decreased sensory preconditioning in offspring on postnatal days 8 and 12, but the effect was no longer present by day 21. Odor conditioning was also reduced in the cocaine-exposed progeny on day 8, but not on days 12 or 21. These data, although different in their details from previous work (Spear et al. 1989a), nevertheless represent apparently consistent findings. To the extent that these data converge, they signify the first instance in the experimental literature on prenatal cocaine of consistent evidence of behavioral effects. Note, however, that these are neonatal effects. These early effects tell little about whether cocaine is capable of inducing long-term effects, which is the principal concern about this drug when taken by women during pregnancy.

In another experiment, Raum and colleagues (1990) administered cocaine at doses of 10 or 30 mg/kg twice a day on E15to20 or 3 mg/kg twice a day on E15 to postnatal day (PN) 5 and found decreased scent marking in males at the two lower doses, but not at the higher dose. They also found decreased intromission latencies, increased plasma leutinizing hormone (LH) levels, and short-term decreases in estradiol and testosterone levels. These data may be important as they suggest that cocaine may have hor-monal effects during critical stages of sexually dimorphic CNS organi-zation. Such influences could lead to long-term alterations in sex-related behaviors such as scent marking. The observation of an apparent biphasic effect of cocaine dose, with effects seen at 3 and 10mg/kg but not at 30-mg/kg, is intriguing, but must be interpreted with caution until it can be replicated.

Sobrien and colleagues (1990) administered a dose of 20 mg/kg of SC cocaine on E14 to 20 and found increased surface righting, cliff avoidance, acoustic startle development, and an attenuated increase in locomotor activity after acute challenge doses of either d-amphetamine or cocaine. The surface righting findings are at variance with the other data for cocaine's effects on surface righting and are the opposite of Henderson and McMillen's (1990) findings mentioned above, who found decreased development of this reflex. It is not possible to resolve these discrepancies until more laboratories have examined the righting reflex of in utero cocaine-exposed offspring. However, with three studies reporting no effects, one an

increase, and one a decrease, it appears that cocaine has no major effect on the development of this reflex. As noted, Sobrien and colleagues also found accelerated cliff avoidance and startle development. Similar effects have not yet been reported by other laboratories. Diminished stimulant-induced locomotor activity could be a significant finding and should be further investigated.

Church and colleagues (1991) reported that 30 mg/kg SC cocaine twice a day on E7 to 20 induced reductions in locomotor activity in the exposed progeny at 20 days of age. Although direct comparisons are difficult because of methodological differences, this observation is certainly not consistent with that of Henderson and McMillen (1990), who reported increased cocaine-related activity at 30 days of age. Although the activity measuring devices were similar, length of testing (15 minutes versus 6hours) and age at testing (20 versus 30 days of age) differed between the two studies. How such discrepancies can be resolved is unclear given the general reluctance in this field for investigators to replicate each others' findings. Heyser and colleagues (1992b) have reported that progeny exposed to 40 mg/kg of SC cocaine administered to the dam on E7to19 exhibit decreased conditioned place preferences (CPP) measured as time spent in one of three chambers, and concomitantly display an increase in the number of chamber entries during testing. In other words, the cocaine-exposed progeny did not remain in the chamber previously associated with acute cocaine exposure as long as controls and moved between chambers more often, resulting in higher chamber entry counts. The place preference effect was complex; however, inasmuch as the effect occurred most clearly in comparison with ad libitum fed controls, a comparison may not be informative. The more important comparison, with pair-fed controls, was only significant under very specific circum-stances. The cocaine-exposed group differed from pair-fed controls only at a conditioning dose of 5 mg/kg of cocaine when a black test chamber was used, but a similar reduction occurred only at a conditioning dose of 2mg/kg of cocaine when a white chamber was used. The other groups, the 2 mg/kg black test chamber group and the 5 mg/kg white test chamber group, performed no differently from controls. This unusual conditioning-dose dependency by test chamber interaction is difficult to explain and raises questions about the robustness of the effect. Should others find the same effect, it may eventually prove to be important, but until then this effect should be viewed as preliminary.

Johns and colleagues (1992a, 1992b) reported that rats administered SC cocaine at a dose of 15 mg/kg twice a day on E1 to 20 (daily

group) or E2to3, 8to9, 14to15, and 19to20 (intermittent group) exhibited increased initial activity at 30 days of age (daily group), decreased nocturnal activity (intermittent group) during 24-hour testing, increased nonentries (daily group) (i.e., instances of not leaving the start chamber in a separate short-term open-field test), and increased section crossings (intermittent group) in the open field. The increased day 30 initial activity in the daily exposure group is consistent with the data of Henderson and McMillen (1990) and should be confirmed by further experiments. The change in nocturnal activity could have implications for a cocaine effect on the circadian clock. Weaver and colleagues (1992) have reported that cocaine can alter c-fos expression in the supra-chiasmatic nucleus after prenatal exposure. Moreover, this effect can be blocked by pretreatment with the dopamine (D) type 1 (D1) antagonist SCH-23390. If cocaine is capable of interfering with the biological clock by acting on dopamine receptors critical for early circadian entrainment, this could represent an important finding.

Bilitzke and Church (1992) reported that 40 mg/kg SC cocaine twice a day on E7 to 20 reduced swimming immobility time on a Porsolt swim test. The Porsolt swim test was developed as a screening procedure for drugs with potential antidepressant activity. Why prenatal cocaine might induce an effect consistent with the acute effects of antidepressants is not clear, but the effect appeared clear cut and represents a promising lead worthy of further investigation. If the underlying effect of prenatal cocaine exposure is to increase reactivity, then reduced immobility might be seen as a reflection of exaggerated responsiveness to stress.

Goodwin and colleagues (1992) reported that 40 mg/kg of cocaine administered SC to dams on E7 to 19 produced offspring showing decreased odor conditioning at 7 days of age, no changes in auditory or odor conditioning at 17 days, and decreased shock-induced aggression as adults. This experiment included a fostering/cross-fostering design intended to help factor out the direct effects of cocaine on the offspring from those occurring indirectly through changes in maternal rearing. One might suspect that maternal rearing could be altered by maternal exposure to a drug such as cocaine. When the maternal rearing variable was factored in, the findings on day 7 odor conditioning showed that cocaine-exposed offspring raised by cocaine-exposed dams showed no evidence of odor conditioning when given 2, 3, or 4 training trials. This finding was in contrast with controls that showed good conditioning under all three training trial conditions. Cocaine-exposed offspring raised by

untreated foster dams, however, did not show evidence of odor conditioning when given 2 or 3 training trials but did when given 4 trials, indicating that being raised by a control dam ameliorated the severity of the odor conditioning impairment. This finding raises the important point that studies which fail to control for maternal carryover effects from cocaine exposure may overestimate the drug's effects on the progeny.

However, it would be imprudent to extrapolate these data too far. First, this (Goodwin et al. 1992) is the only study reporting such a maternal modifying effect (and the only one that has systematically looked for one as well). The effect on odor conditioning was the only behavior on which a maternal-base modifying influence was found, and no other measured responses showed such modification. The magnitude of the maternal influence on odor conditioning was not great, and does not suggest a major interpretational problem exists due to maternal effects. While some effects, such as this one, may be exacerbated by allowing cocaine-exposed dams to rear their own offspring, other effects may go in the opposite direction. No conclusions concerning over- or underestima-tion are possible based on the limited data currently available. For shock-induced fighting, maternal rearing did not alter the outcome for in utero cocaine-exposed offspring; under both rearing conditions, cocaine-exposed offspring exhibited reduced aggression latency. Therefore, the effect on offspring aggression appeared to be a direct (maternally unmodified) effect. However, this effect was also not very large, being insignificant by standard ANOVA methods and only significant by reliance upon preplanned comparison tests. While the design of the experiment may imply a rationale for an a priori comparison test such as the one performed on these data, it is not clear whether this comparison was explicitly preplanned or merely deemed logical; the report does not discuss this point.

Meyer and colleagues (1992) reported that 20 mg/kg SC cocaine twice a day on E10to19 to dams induced a failure of the normal increase in wall climbing by the offspring caused by an acute dose of cocaine when given at 11 days of age. This effect occurred at mid and low cocaine challenge doses, but was not apparent at the higher dose tested. These results may bear some resemblance to Spear and colleagues' (1989a) finding of reduced shock-induced wall climbing in cocaine-exposed progeny, but with only two such studies published, comparisons are difficult. An idea raised by these data, however, is whether cocaine exposure leads to postnatal changes in the offspring's response to stimulation. Altered responsiveness may occur regardless

of whether the signal administered to the organism is a stimulant such as a cocaine challenge or an environ-mental stimulation such as shock. These two studies' data provide a hint that this may be the case, but the findings thus far are too limited to reach any conclusions.

Overview of Behavioral Findings

The positive behavioral teratologic experiments reviewed here provide little convergence of findings, but they provide leads worthy of further investigation. Areas that appear promising are cocaine's possible effects on critical organizing events of sexually dimorphic differentiation (Raum et al. 1990; Vathy et al. 1993), cocaine's possible effects on circadian clock entrainment (Weaver et al. 1992), cocaine's effects on early clas-sically conditioned odor learning (Goodwin et al. 1992), and cocaine's possible long-term effects on adult cognitive capacities (see below). These areas are especially relevant to the long-term effects of cocaine on offspring behavior and could have direct relevance to understanding the risks this drug poses to children exposed prenatally.

Another point revealed by the data summarized in tables 1 and 6 and the study reported below is the number of sex-specific effects reported in cocaine-exposed offspring. Future research in this area should evaluate and separately report findings in terms of male-female differences whenever differential effects are encountered, as this information may prove to be a crucial distinction for understanding cocaine's developmental neurotoxicity.

Clear deficiencies are evident in the existing literature. These gaps in knowledge need to be rectified by inclusion of better control groups, replication of findings within and across laboratories, greater scrutiny and diversity in the parameters of the models being testing (including dose, dose rate, route of administration, and pattern of internal dose), and exten-sion of the models to other species. Greater attention to these areas should permit the field to discern the correct relationship between prenatal cocaine exposure and possible long-term effects on the brain and behavioral development.

An Alternate Model

In order to illustrate one alternate approach to modeling the effects of prenatal cocaine exposure, the results of a preliminary experiment that has not been previously published are described (Vorhees et al., in press). Because of the short half-life of cocaine discussed earlier, the

author decided to administer cocaine 5 times per day at 2-hour intervals instead of once or twice a day as all of the models reviewed herein have done. SD rats were mated in the laboratory (plug day was considered E0) and assigned on a weight-matched basis to one of four treatment groups. Cocaine (20 mg/kg) was administered SC five times a day on days E7 to 12 or days E13 to 18. Controls were injected with vehicle on days E7 to 12 or days E13 to 18 and pair fed to one of the matched cocaine-exposed dams. The dose of cocaine was expressed as the free base and was dis-solved in a citrate buffer in a dosing volume of 6.67 mg per milliliter (mL) at pH 5.0 A stability test performed on this solution by gas chroma-tography mass spectrometry confirmed what the literature reported: cocaine is stable for more than 1 week in solution at a pH of 5.0. On the day of birth (P0), litters were randomly culled within sexes to 4 males and 4 females per litter when possible. Litters were weaned on P28.

On days P9, 11, and 13 all offspring were tested for olfactory orientation to their home cage bedding. On P10, 12, and 14 they were tested for early crawling and pivoting in a small photocell activity monitor designed for mice (1 minute a day). After weaning, 2 males and 2 females were retained. On P50 to 51, all remaining offspring per litter were tested for acoustic and tactile startle in a prepulse inhibition paradigm. The inter-stimulus interval (ISI) was 50 milliseconds (ms), the signal was 115deci-bels (A scaled) (dB(A)), and the signal duration was 20 ms. On P53 each rat received a single 30-minute test in a photocell activity monitor. On day 58 each rat was tested in a 150 centimeter (cm) straight swimming channel for swimming ability and motivation to escape from water. This swim test was followed by testing in a Morris hidden platform maze. Rats received 2 days of acquisition (8 trials/day) to find the hidden platform followed by 4 test trials on the third day to assess memory in the absence of the platform.

After the test trials were completed, the platform was replaced and 4-addi-tional reinstatement trials were given. On the fourth and fifth test days rats were given 8 trials per day with the platform shifted to the opposite quad-rant. Finally, 1 week after the completion of the Morris maze, rats received testing in the Cincinnati multiple-T water maze, 2trials per day in what is referred to as path B (the elective-choice path of the maze).

All the data in this experiment were analyzed using litter, not individual, offspring as the unit of analysis (litter mean stratified by sex, with sex used as a within-subjects factor) by analysis of variance. There were 12-

litters in each of the 2 cocaine-exposed groups and 8 each in the PF groups for a total of 40 litters in the experiment or approximately 320-offspring for the preweaning tests and 160 for the postweaning tests.

Two sets of results are discussed to illustrate those tests that showed cocaine exposure-related findings. First, regardless of exposure period, cocaine-exposed offspring exhibited delayed olfactory orientation as neonates compared to controls. The effect was not strictly significant, occurring at $p < 0.07$ (see figure 1). In the Morris maze, a significant effect of cocaine was found for the early treated group among females, with the cocaine-exposed animals having longer search latencies on the first 8 (day 1) of the 16 acquisition trials compared with PF controls. Why this effect was only seen among females is not yet known. The effect is illustrated in figure 2. A related effect was found on another maze test (not shown).

The effect of cocaine exposure on performance in the Morris maze, while not large, is nevertheless in contrast with the findings reported by Riley and Foss (1991b) who found no effect of prenatal cocaine exposure on Morris maze acquisition. What could account for this difference? Two possibilities worth considering are differences in dose rate and exposure period. Riley and Foss administered 60 mg/kg of cocaine once a day by gavage on days E13 to 20, whereas the author administered 20 mg/kg of cocaine 5 times per day on days E7 to 12 in the affected group. In the Riley and Foss study, cocaine exposure was during late embryogenesis and fetogenesis while exposure in the author's study was during organ-ogenesis. In Riley and Foss' study, the once a day exposure undoubtedly produced a single short-lived daily peak whereas the author's experiment produced 5 smaller peaks spread throughout the diurnal phase. The differ-ence in outcome may be due to differences in peak concentration, duration of exposure per day, or to the stage of development cocaine exposure occurred. Each of these factors is sufficiently important pharmacologically and embryologically to easily account for differences in outcome. This kind of alternative modeling that may prove beneficial to understanding cocaine's potential for inducing developmental neurotoxicity.

FUTURE DIRECTIONS

Although this chapter does not review postnatal cocaine exposure or tera-tological or neurochemical studies beyond what is shown in table 1, it should be stressed that many of these experiments have generated

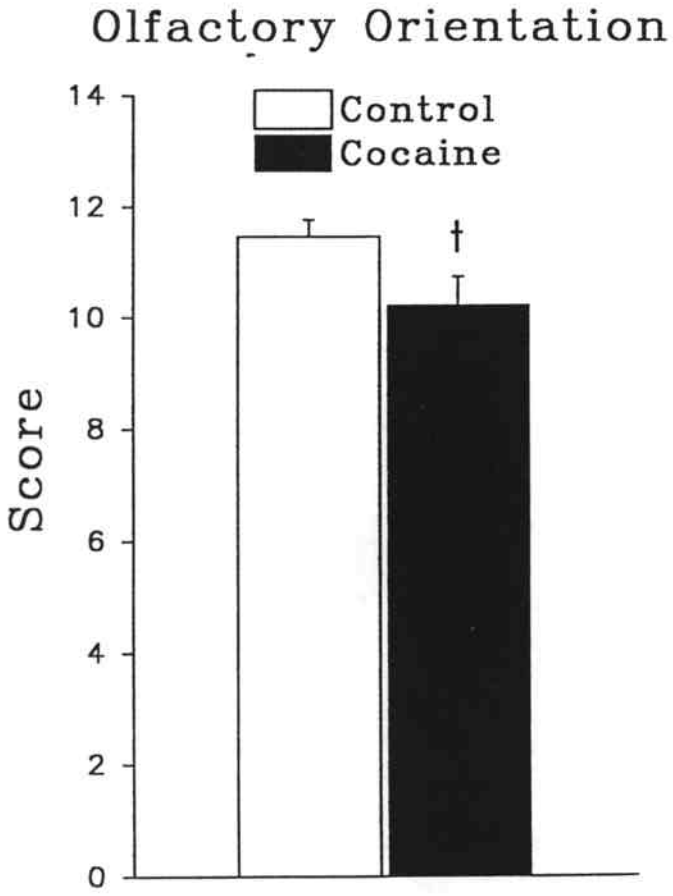

Figure 1. Effect of prenatal cocaine exposure (20 mg/kg five times a day) on olfactory orientation scores of offspring on days P9,11 and 13 in response to the scent of home cage versus clean bedding in a two-choice task. Analysis of variance showed a main effect of treatment with a probability of $p<0.07$. Exposure period (E7-12 or E13-18), sex and day of testing were not significant nor were the interactions between these terms. $p<0.07$ compared to control.

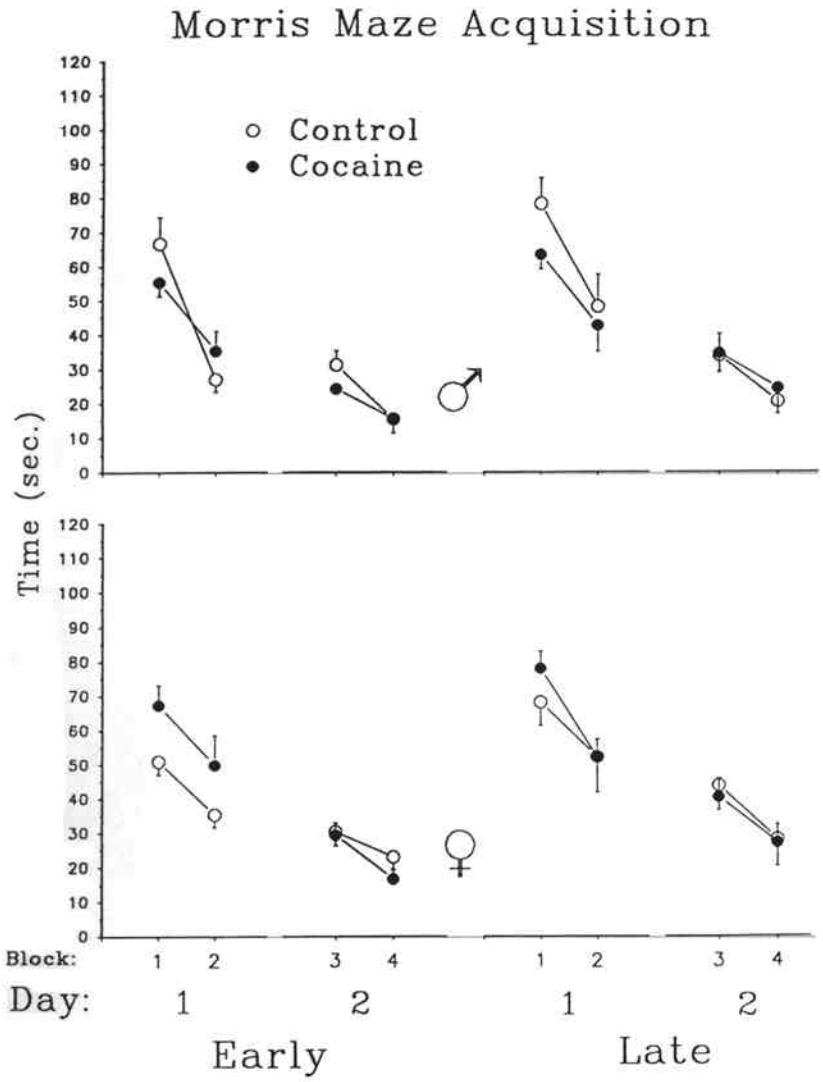

Figure 2. Effect of prenatal cocaine exposure compared to pair-fed controls on aquisition (latency by seconds) on the Morris hidden platform maze. A 2-between (treatment, exposure period), 3-within (day, trial, sex) ANOVA on latency data showed a significant main effect of exposure period ($p < 0.02$). As shown, the female cocaine-exposed group had longer latencies on day 1(particularly trials 2-8) than their pair fed controls. Data are plotted in blocks of 4 trials each.

interesting evidence of cocaine-related developmental effects. Of these studies, those producing the least evidence of major effects have been theteratological experiments. In general, the teratological experiments indicate that cocaine does not induce major dysmorphic effects in rodents. By contrast, some of the most promising data have been those (Dow-Edwards et al. 1989, 1993; Hughes et al. 1991) (table 1) showing that early postnatal exposure induces autoradiographic evidence of long-term changes in 2-deoxyglucose activity and concomitant changes in startle and locomotor activity. Perhaps more research should be directed towards late gestational events in the case of cocaine, since dopaminergic neurotransmitter release and postsynaptic receptor function are relatively late events in brain development. Given cocaine's known effects on dopaminergic systems, it is logical to believe that cocaine may have more pronounced effects on these systems during synaptogenesis (dendritic arborization and pruning) than during earlier stages when proliferation and migration are the dominant events. The early stages of ontogeny should not be neglected, but both logic and data now suggest that greater attention to later stages of development may be warranted.

In sum, although the experimental evidence of cocaine's effects on early CNS development remains unclear, there is gradually mounting evidence suggesting that some specific effects may exist. It appears that early investigations looking for gross dysmorphogenesis, increased rates of embryonic death, or severe behavioral impairments have not been borne out. However, as recent investigations have focused on specific systems that cocaine might be expected to affect such as dopamine receptors important in setting circadian rhythms or interactions with hormonal priming agents such as testosterone, it has become apparent that subtle but potentially important effects may in fact be present. These newer lines of research, along with better exposure models, should produce new insights into the developmental effects of cocaine.

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