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Prenatal Cocaine Exposure Attenuates Cocaine-Induced Odor Preference in Infant Rats

CHARLES J. HEYSER, GREGORY A. GOODWIN, CAROLE A. MOODY AND LINDA PATIA SPEAR[1]

Department of Psychology and the Center for Developmental Psychobiology, State University of New York at Binghamton, Binghamton, NY 13902-6000

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HEYSER, C. J., G. A. GOODWIN, C. A. MOODY AND L. P. SPEAR. *Prenatal cocaine exposure attenuates cocaine-induced odor preference in infant rats.* PHARMACOL BIOCHEM BEHAV 42(1) 169–173, 1992.—In order to further examine whether prenatal cocaine exposure alters the later reward efficacy of cocaine, exposed offspring were tested for cocaine-induced odor preference early in life. Test offspring were derived from Sprague-Dawley dams that received daily SC injections of 40 mg/kg/3 cc cocaine hydrochloride (C40) from gestational day 8–20, nutritional control dams receiving daily SC saline injections (NC), and nontreated control dams (LC). At testing on postnatal day 8 (P8), both LC and NC offspring were observed to exhibit a preference for the odor that had been paired on P7 with 2.0, 5.0, or 10.0 mg/kg cocaine. In contrast, C40 offspring exhibited a significant odor preference only when the odor had been previously paired with 5.0 or 10.0 mg/kg cocaine. These results, combined with previous work from our laboratory showing that adult offspring exposed gestationally to cocaine did not exhibit a cocaine-induced conditioned place preference, provide evidence that offspring exposed prenatally to cocaine are less likely to develop a preference for stimuli associated with cocaine. Further studies are needed to determine whether these alterations in cocaine preference reflect a learning deficit, pharmacokinetics factors, or an attenuation in the rewarding properties of cocaine.

Cocaine Developmental toxicology Olfactory learning Drug abuse Reward

THE potential impact of in utero cocaine exposure is of substantial concern. A number of studies have indicated that the prevalence of cocaine use among pregnant women ranges from 8% to 13.5% (9,11,22). Cocaine use during pregnancy has been associated with a higher incidence of preterm delivery, premature rupture of placental membranes, microcephaly, and small-for-age infants (11,22) [for reviews see (10, 23)]. Neurobehavioral assessments of these infants have revealed a number of differences between cocaine-exposed and nondrug-exposed infants, including increased muscle tone, irritability, tremulousness, a depression of interactive behavior, and poor state organization [(2,3,6); see, however, (25)].

Animal models of gestational cocaine exposure were first used to examine its teratogenic effects (19,20). More recent studies have focused on neural and behavioral effects at nontoxic doses (for a review of clinical and animal findings, see 7). Behavioral assessments have revealed a number of consequences of gestational cocaine exposure, including alterations in the normal ontogenetic pattern of locomotor activity (15, 29) and deficits in classical conditioning (12,32,33) and sensory preconditioning (12) during the preweanling period. In adulthood, such offspring have been reported to exhibit alterations in DRL-20 acquisition and water maze performance (29).

A number of neural alterations have also been reported following gestational exposure to the dopamine (DA) uptake inhibitor cocaine. Neural regions affected include not only the DA system (8,27,32) but other neural systems as well (5,8). Exposed offspring also have been reported to exhibit an attenuated locomotor response to cocaine and *d*-amphetamine at 30 days of age (30), and to fail to exhibit cocaine-induced conditioned place preferences (CPP) in adulthood, conditioning that was evident in offspring of pair-fed and ad lib control dams (13). This lack of cocaine-induced CPP in adult offspring exposed gestationally to cocaine could potentially reflect an attenuated sensitivity to the rewarding properties of cocaine, perhaps due to long-term alterations in the functioning of the mesolimbic DA system, a region implicated in cocaine reward (1,16,18,37). Alternately, the lack of CPP in cocaine-exposed offspring may be the result of a learning defi-

[1] Requests for reprints should be addressed to Dr. Linda P. Spear, Department of Psychology, Box 6000, SUNY Binghamton, Binghamton, NY 13902-6000.

cit, with these animals unable to form the necessary associations for such conditioning to occur.

The purpose of the present study was to examine further the effects of gestational exposure to cocaine on the rewarding properties of cocaine by assessing whether the deficits in CPP seen in adult exposed offspring would also be evident early in life. Procedures were modified for testing in infancy by pairing cocaine with a novel odor rather than stimuli associated with a particular location (as in CPP). Odors are highly salient stimuli early in life and have previously been shown to support associative conditioning (17,26,34,36), including cocaine-induced olfactory preferences (28) in infant rat pups. The cocaine-induced odor preference procedure is analogous to the CPP paradigm. The acquisition phase can be thought of in terms of classical conditioning, with the drug serving as the unconditioned stimulus (US) and the odor as the conditioned stimulus (CS). After pairing the odor with the drug, the odor presumably becomes associated with the effects of the drug. A drug is considered to have rewarding properties if animals given a previous pairing of the odor and drug spend more time, during an odor preference test, in the presence of that odor than control animals that had not received such paired exposure. Conversely, a reduction in the time spent in the odor previously paired with the drug relative to control animals would presumably reflect its aversive qualities.

The model for gestational exposure used in the present study consisted of the SC administration of 40 mg/kg cocaine daily from gestational days 8–20. This procedure has been reported to produce maternal plasma cocaine levels in the range of or slightly above those reported in human cocaine users (31) and to induce neurobehavioral alterations in exposed offspring [e.g., (5,12,32)].

METHOD

Subjects, Breeding, and Chronic Drug Treatments

Offspring were generated from Sprague-Dawley rats purchased from Charles River laboratories (Wilmington, MA). Animals were housed in a temperature- and humidity-controlled colony room on a 12 L:12 D cycle with the lights on at 0700 h. All dams were housed in pairs and habituated to the colony room for 2 weeks after arrival. Prior to the onset of mating, dams were handled for 5 min daily for 5 days, with SC injections of 3 cc/kg 0.9% saline being given the last 3 days of handling. Dams were individually housed in hanging cages prior to mating, with an adult male being placed in each cage daily at 1700 h and removed the following morning at approximately 0900 h. Day 1 of gestation (E1) was defined as the day of detection of a copulatory plug. The dams were randomly assigned to three treatment groups and individually housed in Plexiglas breeding cages.

Dams assigned to the cocaine (C40) and lab chow (LC) treatment groups had ad lib food (powdered lab chow) and water available throughout the study. A cellulose nutritional control group (NC) was given ad lib exposure to a diet diluted with a nondigestible fiber, a procedure recently developed in our laboratory to match, without explicit food restriction, the transient reduction in chow intake typically associated with the onset of cocaine treatment [see (21) for further discussion]. Dams in this NC group received ad lib food (powdered lab chow) and water from E1 to E7. On E8, each dam in the NC group was placed on a diet consisting of 60% powdered lab chow and 40% cellulose, receiving ad lib access to this diet and water throughout the remaining gestational period. Preliminary work in our laboratory has shown that dams placed on a diet containing cellulose take 3–4 days to adjust their intake to counteract for the presence of this nondigestible fiber, matching the transient reduction in food intake at the onset of drug treatment typically observed in C40 dams (12,14). Dams were SC injected daily between 1000 and 1200 h with either 40 mg/kg/3 ml cocaine hydrochloride (C40) or an equal volume of 0.9% saline (NC) from E8–E20. Injections were made in a volume of 3 ml/kg in order to minimize cocaine-induced skin necrosis, and injection sites were varied daily [see (32)]. Dams in the LC control group were not injected. Daily weights and intake of food and water were recorded from E1–E22.

Gestational length was recorded for each gravid dam. On postnatal day 1 (P1), all pups were weighed and the total number of pups of each sex recorded. Each litter was culled to 8–10 pups and fostered to an untreated surrogate dam that had given birth to a litter within the preceding 24–72 h.

Procedure

A total of 115 animals (C40, $n = 40$; NC, $n = 40$; LC, $n = 35$) were used in this experiment, with 9–10 pups from each prenatal treatment group being tested in each of the four conditioning groups. Only one pup from each litter was assigned to any given conditioning group. Training and testing were conducted by different individuals; both individuals were unaware of prenatal history and conditioning group assignment.

Conditioning occurred in a plastic cylinder (10 cm in diameter) located in an incubator maintained at 34(±1)°C. On postnatal day 6 (P6), each pup was removed from the home cage and placed onto 250 ml of pine shavings scented with 1.0 cc orange odor (Spectrum Chemical, Gardena, CA). After a 5-min exposure to the odor, each pup was given an IP injection of 0.9% saline (5 cc/kg) and was placed immediately back onto the orange odor for 25 additional min. On P7, each pup was removed from the home cage, weighed, and placed onto 250 ml of pine shavings scented with 1.0 cc lemon odor (Humco Laboratory, Texarkana, TX). After a 5-min odor exposure, each pup was given an IP injection of 0 (saline), 2.0, 5.0, or 10.0 mg/kg/5 cc cocaine HCl and placed back in the lemon odor for an additional 25 min. Upon completion of the conditioning trial on each day, pups were placed in an odor-free holding incubator maintained at 34(±1)°C for 1 h to allow for dissipation of the conditioning odors prior to being returned to the home cage and colony room.

To avoid a potential confound of drug effects on performance, preference testing was conducted 24 h after the second day of conditioning, with all groups receiving the same odor preference test between lemon and orange on P8. Testing was conducted in a (20 × 10 × 9 cm) rectangular chamber, divided into two equal areas by a center line bisecting the long axis of the apparatus. Under the wire mesh floor on one side of the apparatus was placed 250 ml of pine shavings scented with 1 cc orange odor; under the wire mesh on the other side was placed the same amount of pine shavings scented with 1 cc lemon odor. Each pup was placed on the midline of the wire grating with the animal's head oriented directly away or toward the experimenter, with the orientation varying randomly among animals. The amount of time spent on the lemon side was recorded for a test duration of 6 min. Although previous work in our laboratory has shown that the two test odors are approximately equally preferred by infant rat pups with equivalent or no prior exposure to these odors,

the odor presentation-to-test interval varied for the two odors in this experiment (48 h for orange, 24 h for lemon) which could influence subsequent odor preference. Hence, saline-saline treated pups from each prenatal treatment group served as the baseline in the test for odor preference, with cocaine-induced odor preference being defined as a significant increase in the time spent in the presence of the odor previously paired with cocaine relative to baseline values provided by the saline-saline animals. Defining odor preference relative to the performance of control animals is a conservative procedure that has been frequently employed in ontogenetic classical conditioning studies using cocaine (28) and other stimuli [e.g., (34,35)] as unconditioned stimuli.

RESULTS

Maternal Data

An analysis of variance (ANOVA) performed on percentage body weight gain during pregnancy revealed no significant differences among the prenatal treatment groups (Table 1). ANOVA also revealed no significant differences in mean daily food or water intake among prenatal treatment groups (Table 1). Although there was a tendency for a slight reduction in maternal food intake for the first 2 days of treatment onset at E8 for C40 dams (mean ± SEM: 18.11 ± 1.4) and NC dams (17.98 ± 1.98) when compared with LC dams (24.63 ± 1.05), a 2 × 20 (Prenatal Treatment × Days) repeated measure ANOVA across day using a Geisser Greenhouse conservative F revealed only a significant main effect of Days for body weight gain, $F(19, 532) = 317.37$, $p < 0.01$ and food intake, $F(19, 532) = 230.91$, $p < 0.01$. Similarly, although there was a trend for an increase in water intake in NC dams relative to LC and C40 dams (see Table 1), the repeated measure ANOVA on these data revealed only a significant main effect for Days, $F(19, 532) = 79.52$, $p < 0.01$ (Table 1). As can be seen in Table 1, no differences were observed between the three prenatal treatment groups in gestational length.

TABLE 1

MATERNAL/LITTER SUMMARY DERIVED FROM LITTER MEANS

	C40	NC	LC
Percentage gestational weight gain	30.08 (1.77)	34.21 (2.23)	33.15 (2.00)
Food intake (g)	26.26 (1.53)	23.63 (1.03)	26.17 (0.80)
Water intake (ml)	55.28 (1.80)	61.23 (2.46)	54.29 (2.27)
Gestational length (days)	23.00 (0.00)	23.00 (0.13)	23.10 (0.10)
Litter size	15.80 (0.66)	15.36 (0.58)	14.10 (1.19)
Number of male pups in litter	8.20 (0.59)	8.18 (0.58)	7.00 (1.01)
Number of female pups in litter	7.60 (0.52)	7.00 (0.55)	7.10 (1.11)
Offspring body weights			
Postnatal Day 1 (g)			
Males	7.46 (0.12)	6.60 (0.22)	7.50 (0.13)
Females	6.94 (0.12)	6.20 (0.20)	7.05 (0.22)
Conditioning (P7)			
Males	18.10 (0.50)	18.07 (0.33)	18.35 (0.50)
Females	17.09 (0.33)	17.73 (0.30)	18.07 (0.42)

SEM indicated in parentheses.

Litter Size, Composition, and Offspring Body Weight

A 3 × 2 (Prenatal Treatment × Sex) ANOVA conducted on the number of male and female pups in each litter failed to reveal any significant differences (Table 1). However, a 3 × 2 (Prenatal Treatment × Sex) ANOVA performed on litter means of male and female body weight at P1 revealed a significant main effect of Sex, $F(1, 28) = 93.18$, $p < 0.01$, and Prenatal Treatment, $F(2, 28) = 8.18$, $p < 0.01$. Tukey's tests revealed that males weighed significantly more than females at P1, and NC offspring weighed significantly less than C40 and LC offspring, with the latter two groups not differing from each other (Table 1). A 3 × 2 (Prenatal Treatment × Sex) ANOVA conducted on male and female body weights at the time of conditioning (P7) revealed no significant differences (Table 1).

Conditioned Odor Preference

No sex differences were revealed in preliminary analysis of the preference data, so the data were collapsed across this variable prior to further analysis.

The amount of time spent in the lemon-scented compartment was used as the dependent measure in the analysis of conditioned odor preference. A 3 × 4 (Prenatal Treatment × Dose) ANOVA revealed a significant main effect of Prenatal Treatment, $F(2, 103) = 4.68$, $p < 0.05$, and Dose, $F(3, 103) = 36.86$, $p < 0.01$, along with a significant Prenatal Treatment × Dose interaction, $F(6, 103) = 3.01$, $p < 0.01$. Tukey's tests conducted comparing the saline-saline groups across prenatal treatment revealed no significant differences, indicating similar baseline preference for the odors among the prenatal treatment groups. Dunnett's tests were conducted comparing pups from each prenatal treatment group given the various conditioning doses of cocaine (2.0, 5.0, or 10.0 mg/kg) on P7 to those that received saline. As can be seen in Fig. 1, LC and NC offspring conditioned with doses of 2.0, 5.0, or 10.0 mg/kg cocaine spent significantly more time in the lemon odor than their saline-conditioned counterparts. In contrast, only C40 offspring conditioned with doses of 5.0 and 10.0 mg/kg cocaine spent significantly more time in the presence of the lemon odor than saline-conditioned C40 pups, with no significant difference observed between the C40 offspring that received 2.0 mg/kg cocaine and their saline controls (see Fig. 1).

DISCUSSION

Offspring exposed gestationally to cocaine exhibited a cocaine-induced odor preference when odors were paired with doses of 5.0 or 10.0 mg/kg cocaine, but not with a 2.0 mg/kg dose. In contrast, significant odor preferences were observed in both LC and NC control offspring at all doses examined. Thus, infant rats exposed gestationally to cocaine do not ex-

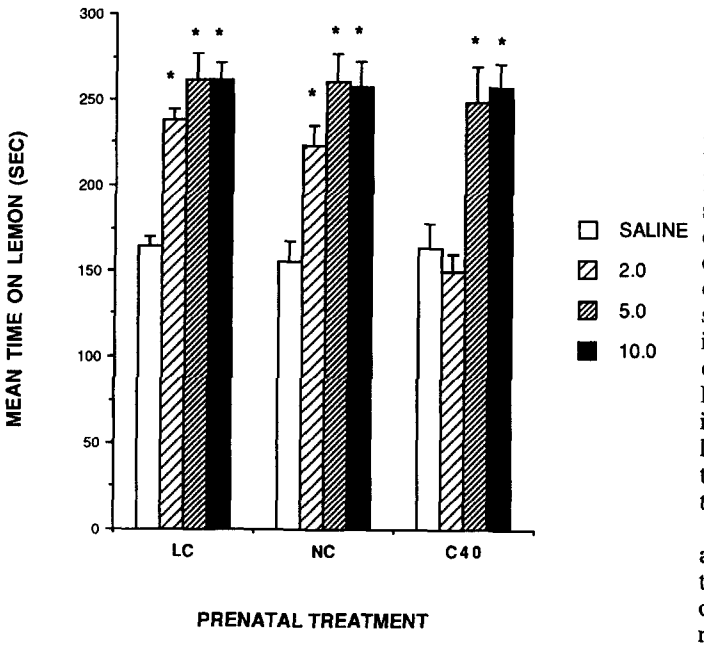

FIG. 1. Mean time (s) spent on the test day (postnatal day 8) by animals from each of the prenatal treatment groups in the presence of the lemon odor following the pairing of this odor with 0 (saline), 2.0, 5.0, and 10.0 mg/kg cocaine. Odor preference was defined as occurring if the animals conditioned with cocaine spent significantly more time in the drug-paired chamber than animals receiving saline (*$p <$ 0.05 for these comparisons). Error bars indicate SEMs LC = Nontreated control; NC = Nutritional control; C40 = Cocaine.

hibit a cocaine-induced odor preference at a dose sufficient to induce a preference in control offspring. This finding in infant rats is reminiscent of previous findings that adult offspring exposed gestationally to cocaine did not exhibit a CPP for cocaine (13).

The three most likely explanations for the lack of conditioned odor preference in C40 offspring following the 2.0 mg/kg training dose of cocaine are an attenuation in the reward efficacy of cocaine, a learning deficit, or an alteration in the pharmacokinetics of cocaine. Perhaps the most intriguing possibility is that early cocaine exposure may alter the development of brain reward systems, resulting in a reduction in the rewarding properties of cocaine. According to this explanation, C40 offspring may require higher doses to support a conditioned preference for cocaine than control offspring because cocaine is less effective as a reinforcer in these offspring. Given the proposed involvement of the mesolimbic DA system in the reward mechanisms of cocaine (16,18,37), it is possible that alterations in dopaminergic functioning induced by gestational exposure to cocaine (27,33) may attenuate the reward efficacy of cocaine in these offspring.

A second possibility is that the lack of observed odor preference may reflect a learning deficit in C40 offspring. Offspring exposed prenatally to cocaine have been observed to exhibit deficits in a number of conditioning tasks early in life, including deficits in appetitive (32) and aversive (12) classical conditioning at P7–P8, the same age examined in the present study. It could be argued that because C40 offspring exhibited significant conditioning at higher doses of cocaine (5.0 and 10.0 mg/kg), the lack of conditioning at the low dose (2.0 mg/kg) of cocaine is unlikely to reflect a simple conditioning deficit. Yet, the magnitude of conditioning reflects the amount of associative strength formed between the CS and US during conditioning, with the amount of associative strength being a function of US intensity (24). Hence, greater intensities of the US may increase the magnitude of the conditioning and could serve to overcome deficits in associative learning evident in C40 offspring at low US intensities. In this study, a variety of intensities of an appetitive US (i.e., different doses of cocaine) were used, whereas cocaine-exposed and control offspring received training with only a single intensity of an appetitive (milk) or aversive (footshock) US in previous studies (12,32). Consequently, it is not yet known whether an increase in US intensity might be sufficient for the expression of conditioning in C40 offspring using these other reinforcers. Because US intensity influences the magnitude of conditioning, it is difficult to rule out entirely that a general associative learning deficit may be responsible for the lack of a conditioned odor preference in C40 offspring following exposure to 2 mg/kg cocaine during conditioning.

It is also possible that the lack of odor preference in C40 animals conditioned with 2 mg/kg cocaine could be related to potential alterations in cocaine pharmacokinetics in these offspring. For instance, if C40 offspring metabolized cocaine more rapidly than control animals, higher delivered doses of cocaine might be necessary to support a cocaine-induced odor preference in these animals. Indeed, increased levels of the cocaine metabolite benzoylecgonine have been reported in offspring prenatally exposed to cocaine when acutely challenged with cocaine; yet, this effect was evident at P30, but not during the preweanling period (P15) (30). However, in previous work, C40 offspring that did not display cocaine-induced CPP in adulthood were nevertheless observed to exhibit an effect of cocaine during conditioning in one aspect of their test behavior (chamber entries); these data provide evidence against a simple pharmacokinetic explanation of the CPP deficit [see (13)]. To the extent that this CPP deficit for cocaine in adult C40 offspring reflects a similar phenomenon to the lack of olfactory conditioning with 2 mg/kg cocaine in infant C40 offspring, a pharmacokinetics explanation of the latter data would appear unlikely. Further work, however, is needed to clarify this issue.

Although there was a trend for a reduction in maternal food intake in C40 dams and their NC counterparts for several days at the onset of treatment on E8, no significant differences were found among the three prenatal treatment groups in maternal weight gain during pregnancy. A similar lack of a cocaine-induced alteration in weight gain has been occasionally observed using this cocaine treatment protocol (32), although more typically a slight reduction in maternal weight gain in cocaine-exposed pregnant dams has been seen using this (5,12,14) and other [e.g., (4)] cocaine treatment regimens. Thus, it would appear that this dosing regimen is about at threshold for the production of body weight reductions in the dams, although the factors leading to the presence or absence of such weight alterations in specific experiments remains to be clarified. Despite the lack of differences among the treatment groups in maternal weight gain, NC offspring exhibited significantly lower body weights than C40 and LC pups at P1, an effect that was no longer evident by P7. The mechanism underlying this transient reduction in neonatal body weights in NC dams whose food intake closely matched that of C40 dams is not clear. Such a reduction was not seen in our initial study using this NC group (21), and hence further work is needed to determine the reliability of this effect and to examine further the appropriateness of this novel nutritional con-

trol which matches chow intake (but perhaps not water intake) with that of cocaine-exposed dams without the explicit food restriction associated with pair-feeding.

Taken together with the lack of cocaine-induced CPP obtained in adult offspring gestationally exposed to cocaine (13), the results of the present study suggest that offspring exposed gestationally to cocaine are less likely to develop a preference for stimuli associated with cocaine. Further studies are needed to assess whether this lack of conditioning reflects a change in the rewarding properties of cocaine, a learning deficit, or pharmacokinetics factors.

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REFERENCES

1. Bozarth, M. A. New perspectives on cocaine addiction: Recent findings from animal research. Can. J. Physiol. Pharmacol. 67: 1158-1167; 1989.
2. Chasnoff, I. J.; Burns, W. J.; Schnoll, S. H.; Burns, K. A. Cocaine use in pregnancy. N. Engl. J. Med. 313:666-669; 1985.
3. Chasnoff, I. J.; Griffith, D. R.; MacGregor, S.; Dirkes, K.; Burns, K. A. Temporal patterns of cocaine use in pregnancy. JAMA 261:1741-1744; 1989.
4. Church, M. W.; Overbeck, G. W.; Andrzejczak, A. L. Prenatal cocaine exposure in the Long-Evans rat: I. Dose-dependent effects on gestation, mortality, and postnatal maturation. Neurotoxicol. Teratol. 12:327-334; 1990.
5. Clow, D. W.; Hammer, R. P.; Kirstein, C. L.; Spear, L. P. Gestational cocaine exposure increases opiate receptor binding in weanling offspring. Dev. Brain Res. 59:179-185; 1991.
6. Doberczak, T. M.; Shanzer, S. R.; Kandall, S. R. Neonatal effects of cocaine abuse in pregnancy. Pediatr. Res. 21:359A; 1987.
7. Dow-Edwards, D. L. Cocaine effects on fetal development: A comparison of clinical and animal research findings. Neurotoxicol. Teratol. 13:347-352; 1991.
8. Dow-Edwards, D. L.; Fico, T. A.; Hutchings, D. E. Functional effects of cocaine given during critical periods of development. Teratology 37:518; 1988.
9. Durand, D. J.; Espinoza, A. M.; Nickerson, B. G. Association between prenatal cocaine exposure and sudden infant death syndrome. J. Pediatr. 117:909-911; 1990.
10. Farrar, H. C.; Kearns, G. L. Cocaine: Clinical pharmacology and toxicology. J. Pediatr. 115:665-675; 1989.
11. Fulroth, R.; Phillips, B.; Durand, D. J. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. Am. J. Dis. Child. 143:905-910; 1989.
12. Heyser, C. J.; Chen, W. J.; Miller, J.; Spear, N. E.; Spear, L. P. Prenatal cocaine exposure induces deficits in Pavlovian conditioning and sensory preconditioning among infant rat pups. Behav. Neurosci. 104:955-963; 1990.
13. Heyser, C. J.; Miller, J. S.; Spear, N. E.; Spear, L. P. Prenatal exposure to cocaine disrupts cocaine-induced conditioned place preference in rats. Neurotoxicol. Teratol. (in press).
14. Heyser, C. J.; Spear, L. P. Effects of subcutaneous administration of cocaine during gestation on maternal and offspring body weights: Three years worth of data. Teratology 41:616; 1990.
15. Hutchings, D. E.; Fico, T. A.; Dow-Edwards, D. L. Prenatal cocaine: Maternal toxicity, fetal effects and locomotor activity in rat offspring. Neurotoxicol. Teratol. 11:65-69; 1989.
16. Johanson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41:3-52; 1989.
17. Johanson, I. B.; Hall, W. G. Appetitive conditioning in neonatal rats: Conditioned orientation to a novel odor. Dev. Psychobiol. 15:379-397; 1982.
18. Koob, G. F.; Goeders, N. E. Neuroanatomical substrates of drug self-administration. In Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological, basis of reward. New York: Oxford University Press; 1989:214-263.
19. Mahalik, M. P.; Gautieri, R. F.; Mann, D. E. Teratogenic potential of cocaine hydrochloric in CF-1 mice. J. Pharm. Sci. 69:703-706; 1980.
20. Mahalik, M. P.; Gautieri, R. F.; Mann, D. E. Mechanisms of cocaine-induced teratogenesis. Res. Commun. Sub. Abuse 5:279-302; 1984.
21. Moody, C. A.; Goodwin, G. A.; Heyser, C. J.; Spear, L. P. A novel nutritional control for transient drug-induced anorexia during pregnancy. Teratology 43:495-496; 1991.
22. Neerhof, M. G.; MacGregor, S. N.; Sullivan, T. P. Cocaine abuse during pregnancy: Peripartum prevalence and perinatal outcome. Am. J. Obstet. Gynecol. 161:633-638; 1989.
23. Plessinger, M. A.; Woods, J. R., Jr. The cardiovascular effects of cocaine use in pregnancy. Reprod. Toxicol. 5:99-113; 1991.
24. Rescorla, R. A.; Wagner, A. R. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In Black, A. H.; Prokasy, W. F., eds. Classical conditioning II: Current research and theory. New York: Appleton-Century-Crofts; 1972:64-99.
25. Richardson, G. A.; Day, N. L. Maternal and neonatal effects of moderate cocaine use during pregnancy. Neurotoxicol. Teratol. 13:445-460; 1991.
26. Rudy, J. W.; Cheatle, M. D. Odor-aversion learning in neonatal rats. Science 198:845-846; 1977.
27. Scalzo, F. M.; Ali, S. F.; Frambes, N. A.; Spear, L. P. Weanling rats exposed prenatally to cocaine exhibit an increase in striatal D2 binding associated with an increase in ligand affinity. Pharmacol. Biochem. Behav. 37:371-373; 1990.
28. Smith, C. A.; Holman, E. W. Rewarding and aversive effects of stimulant drugs in infant rats. Pharmacol. Biochem. Behav. 26: 211-215; 1987.
29. Smith, R. F.; Mattran, K. M.; Kurkjian, M. F.; Kurtz, S. L. Alterations in offspring behavior induced by chronic prenatal cocaine dosing. Neurotoxicol. Teratol. 11:35-38; 1989.
30. Sobrian, S. K.; Burton, L. E.; Robinson, N. L.; Ashe, W. K.; James, H.; Stokes, D. L.; Turner, L. M. Neurobehavioral and immunological effects of prenatal cocaine exposure in rat. Pharmacol. Biochem. Behav. 35:617-629; 1990.
31. Spear, L. P.; Frambes, N. A.; Kirstein, C. L. Fetal and maternal brain and plasma levels of cocaine and benzoylecgonine following chronic subcutaneous administration of cocaine during gestation in rats. Psychopharmacology 97:427-431; 1989.
32. Spear, L. P.; Kirstein, C. L.; Bell, J.; Yoottanasumpun, V.; Greenbaum, R.; O'Shea, J.; Hoffmann, H.; Spear, N. E. Effects of prenatal cocaine exposure on behavior during the early postnatal period. Neurotoxicol. Teratol. 11:57-63; 1989.
33. Spear, L. P.; Kirstein, C. L.; Frambes, N. A. Cocaine effects on the developing central nervous system: Behavioral, psychopharmacological, and neurochemical studies. Ann. N Y Acad. Sci. 526:290-307; 1989.
34. Spear, N. E.; Kurcharski, D. Ontogenetic differences in the processing of multi-element stimuli. In: Roitblat, H.; Terrace, H., eds. Animal cognition. Hillsdale, NJ: Erlbaum; 1984:545-567.
35. Spear, N. E.; Rudy, J. Tests of learning and memory in the developing rat. In: Shair, H. N.; Barr, G. A.; Hofer, M. A., eds. Developmental psychobiology: Current methodological and conceptual issues. New York: Oxford University Press; 1991:84-113.
36. Sullivan, R. M.; Wilson, D. A. Neural correlates of conditioned odor avoidance in infant rats. Behav. Neurosci. 105:307-312; 1991.
37. Wise, R. A. The role of reward pathways in the development of drug dependence. Pharmacol. Ther. 35:227-263; 1987.