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Behavioral Effects of Neonatal Cocaine Exposure Using a Rodent Model

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BARRON, S. AND J. IRVINE. *Behavioral effects of neonatal cocaine exposure using a rodent model.* PHARMACOL BIOCHEM BEHAV **50**(1) 107–114, 1995.—This study examined the effects of neonatal cocaine exposure on behavior using a rodent model. Rat pups were implanted with intragastric cannulas on postnatal day (PND) 4 and artificially reared (AR) from PND 4–10. The AR groups included two cocaine doses (20 mg/kg per day and 60 mg/kg per day) and an AR control. A sham surgery control group was also included that was reared naturally by its dam. Offspring from these neonatal treatment groups were examined for suckling performance (PND 13), passive avoidance learning (PND 23–24), activity (PND 18–21), or spontaneous alternation (PND 21). Neonatal cocaine exposure had no effect on suckling measures or passive avoidance learning. Activity was increased in the 60 mg/kg per day cocaine group relative to controls. In addition, spontaneous alternation was delayed in the 20 mg/kg per day cocaine-exposed females relative to all other groups. These data suggest that neonatal cocaine exposure may alter performance on some relatively simple tasks. More work is clearly warranted to look at the effects of neonatal cocaine exposure on more complex behaviors.

Neonatal exposure Prenatal cocaine effects Hyperactivity Behavior

THERE has been considerable concern and controversy regarding the severity of the effects associated with prenatal cocaine exposure (12). Cocaine-exposed infants have been reported to exhibit delayed growth as indicated by decreased head circumference (38) and reduced birth weights (27). Behavioral studies suggest that cocaine-exposed infants may perform more poorly on the Brazelton test(16). In particular, overreactivity to environmental stimuli and altered stress responses appear to be the more frequent behavioral characteristics displayed by infants with prenatal cocaine histories (2,9,16,29). A limited number of studies have also suggested that infants exposed to cocaine in utero displayed sucking deficits including poor and prolonged feeding, random sucking, and disorganized rooting and sucking when attempting to feed (28,31). It is important to note, however, that there are many inconsistencies within the clinical literature (see entire Neurotoxicol. Teratol. 15(5) for discussion; also 34).

Some of these discrepancies within the clinical literature could be due to such variables as maternal undernutrition, polydrug use, limited prenatal care, etc., which are difficult to control for in clinical populations. As a result of the inherent difficulties in studying clinical populations, a variety of animal models have been used to examine cocaine's teratogenic effects. The majority of animal studies that have focused on the behavioral teratogenic effects of prenatal cocaine exposure have been rodent models. From these rodent studies, prenatal cocaine exposure has been associated with a variety of behavioral alterations including learning deficits (18,20,21,42,44,45) and changes in activity (19,23,25) in rats. Prenatal cocaine exposure may also be associated with overreactivity, particularly in situations of stress (8). However, the rodent literature is also somewhat discrepant, and there are a number of studies that report little or no effect of prenatal cocaine exposure (17,36,37,43).

The current set of experiments administered cocaine neonatally to rat pups to model third-trimester human fetal exposure. In humans, the third trimester of pregnancy is associated with rapid CNS neuronal growth and proliferation, referred to as the "brain growth spurt." It has been suggested that this may be a sensitive period for the behavioral teratogenic effects of drugs. For rats, this period of brain growth occurs during the first weeks after birth (13); thus, to mimic this third-trimester exposure, drugs must be administered to the neonatal rat pup.

The available literature looking at cocaine exposure during this neonatal period in rats is limited. A number of alterations in the CNS have been reported, including reduced hippocam-

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pal volume (46), abnormalities in the visual system (41), reduced DNA synthesis (3) and increased metabolic activity in a variety of cortical regions in female rats tested as adults (14). However, West et al. found no cocaine-related effects on brain weight, although 80 mg/kg per day cocaine hydrochloride resulted in reduced survival and body weight (10). A limited number of behavioral studies suggest that neonatal cocaine exposure may also have behavioral teratogenic effects. In particular, deficits in balance and coordination (5) and an altered response to amphetamine challenge in adult female rats (22) have been reported, although there was little evidence of altered response to cocaine when rats were tested as preweanlings, weanlings, or adults (6,30). In addition, one study has assessed learning following neonatal cocaine exposure, and these researchers found deficits in passive avoidance learning in 13-day-old rat pups (33).

In the present study, the effects of neonatal cocaine exposure were examined on a variety of behaviors in young rats including suckling behavior, learning, and activity following neonatal cocaine exposure. The methodology used to administer cocaine to neonatal rat pups was an artificial rearing method whereby an intragastric cannula was surgically implanted and pups were artificially reared from postnatal day (PND) 4–10. Pups were fed using an infusion pump and timer, and the drug was added directly to the milk formula. One strong advantage of this technique is that control was maintained over the quantity of drug and the amount of food that each pup received.

METHOD

Mating Procedure

Parent animals were Sprague–Dawley rats obtained from Charles Rivers (Portage, MI). Females were individually placed with males each night, and the morning when a seminal plug was found was denoted as gestation day 0 (GD 0). At this time, pregnant females were individually housed in plastic breeding cages in a temperature- and humidity-controlled nursery with a 12 h : 12 h light–dark cycle. Twenty-four hours after parturition, litters were culled to 10, maintaining five males and five females whenever possible.

Artificial Rearing

On PND day 4, one male and one female pup from each litter was randomly assigned to one of four possible treatment groups: artificially reared (AR) that received 20 mg/kg per day cocaine hydrochloride, AR that received 60 mg/kg per day cocaine hydrochloride, an AR control group that received the stock milk solution, or a sham surgery control group that was reared by its natural dam.

Artificial rearing entailed the implantation of an intragastric cannula through which the pups were fed throughout the drug administration period. This surgical procedure has been described in previous papers and will only be briefly detailed here (see Samson and Diaz [39] for further details). Briefly, on PND 4, each AR pup was anesthetized with a halothane/compressed air mixture and implanted with an intragastric cannula that was made from polyethylene tubing (Clay Adams PE-10, Division of Bectin Dickinson, Parsippany, NJ). The sham control group underwent a similar surgical procedure, except that the gastrostomy tube was not implanted. Upon recovery, the AR pups were placed in the AR apparatus (described subsequently), and the sham surgery controls were returned to their dams.

The housing apparatus for the AR pups consisted of a plastic tank divided into separate compartments (approximately 12 × 10 cm for each pup). The walls of the compartment were made from netting and a roll of artificial fur that was attached along the lower portion of one of the walls for the pup to burrow underneath. The fur encased plastic tubing with hot water (60°C) pumped through it. This tubing/fur acted as a heat source for the pups, and the pups spent virtually all of their time rooting or sleeping under this fur. This apparatus was based on a model that decreased the isolation associated with artificial rearing, as described by S. Kelly et al. (personal communication).

The AR pups were fed a milk solution (49) for 20 min every 2 h with the aid of a timer and a multisyringe infusion pump (Harvard Apparatus no. 2265, S. Natick, MA), resulting in 12 daily feeds. For the cocaine-exposed pups, cocaine was added to the stock milk solution for four of the 12 daily feeds to mimic a "binge" model of cocaine abuse. During the remaining eight feeds, all AR pups received the stock milk formula. Because cocaine is photosensitive, the syringes were kept covered with aluminum foil. The amount of milk administered each day was equivalent to 33% of the average daily body weight of the AR pups. On each morning, pups were weighed and bathed in warm water, and their bladders were voided. The AR pups were maintained under these conditions from PND 4–9. On PND 10, all pups received the stock formula to allow the animals to recover from any acute effects of cocaine or cocaine withdrawal, and on PND 11, the pups were returned to their dams. It should be noted that withdrawal has never been observed by the experimenters.

The sham control pups were also weighed daily from PND 4–10. These pups were maintained with their natural dam with an additional eight surrogate pups that had been added to the litter, resulting in 10 pups per litter. These surrogate pups served to maintain the lactational performance of the dam until the AR pups were returned to their home cage.

On PND 11, the intragastric cannulas of the AR pups were cut close to the skin by the abdominal wall, and both the AR and sham pups were ear-punched for later identification. The surrogate pups were removed from the litter, and the AR and sham controls were bathed in a slurry of feces and water from the mother's home cage before return to their home cage. Litter sizes were maintained at eight pups per litter. There was virtually no pup mortality using this procedure.

Suckling Behavior

Subjects were individually tested for suckling behavior on PND 13. This age was chosen to ensure that all AR subjects had at least 48 h of contact time with their dam after artificial rearing and before the start of this experiment. Approximately 1 h before testing, the dam was removed from the experimental subject's cage. Each pup was tail-marked and kept with conspecifics in a cage kept warm by a heating pad until testing. The dams used for the suckling test were surrogate untreated lactating dams with similar aged pups. These dams were anesthetized with pentobarbital (80 mg/kg), which blocked milk letdown. The anesthetized dam was placed in a supine position in the center of a heated test cage (19 × 10 × 8 in.). Each pup was weighed immediately before testing and placed in the lower right corner of the test cage for a 1-h videotaped test session. After testing, the pup was weighed again to ensure that milk letdown had indeed been blocked, and the pup was inspected for eye opening.

The videotapes were scored by two experimenters blinded

as to treatment condition with a real-time event recorder. The dependent variables included latency to attach to the nipple, nipple shifting, and total time spent suckling. There were nine to 11 subjects per sex in each cell of this experiment. In this and all subsequent experiments, there was a maximum of one subject per sex and neonatal treatment from any given litter in each cell of the experimental design to control for possible litter effects (1).

Activity

Subjects were tested daily from PND 18–21. Subjects were individually removed from their home cage and placed in one of four automated activity monitors (Omnitech Instruments, Columbus, OH) for a 30-min test session. The activity monitors measured 39 × 39 cm and were lined with infrared photobeams. Each activity monitor was contained within a sound-attenuated box with red light illumination (5 W). Activity data were recorded in 5-min blocks, and the dependent measures included horizontal activity (as measured by photobeams crossed), total distance traveled, amount of time spent in stereotypic movements, and number of stereotypic movements. At the conclusion of each test session, the pup was removed from the chamber, tail-marked for later identification, and returned to its home cage. Subjects were tested daily at the same time. Body weights were recorded immediately after testing on PND 21. Approximately 11 to 15 per sex and neonatal treatment were included in this experiment.

Spontaneous Alternation

Subjects were tested for spontaneous alternation in a T maze at 21 days of age. The T maze was made of black Plexiglas and consisted of a 60-cm runway that lead to two arms, each 37 cm in length. The alley began with a start box (20 cm in length), and each arm ended with a goal box (19 cm in length). The start box and the goal boxes were separated from the rest of the maze by guillotine doors that prevented reentry. Subjects were taken from their home cage, individually placed in a holding cage, and brought into the sound-attenuated test room, which was lit only by red light. Once in the test room, each subject was kept in the holding cage for a 30-s habituation period. At this time, subjects were transferred to the start box facing the guillotine door. After 5 s, the guillotine door was raised and a timer started. The subject was allowed to explore the T maze until it entered either goal box with all four feet. At this time, the guillotine door was lowered, the latency and side preference were recorded, and the animal was returned to the holding cage for 15 s. The animal was then returned to the start box for a second trial. This procedure was repeated until the subject chose the opposite goal box from that selected on the first trial. All subjects were weighed at the conclusion of the experiment.

Passive Avoidance Testing

Subjects were tested at 23 days of age for passive avoidance learning and 24 h later for retention. The test apparatus consisted of a stainless-steel rectangular chamber (11 × 41 × 15 cm) divided into two equal compartments by a guillotine door. One of the compartments was painted black and the other white. Both compartments had grid floors made of stainless-steel bars (0.3 cm in diameter) that were spaced 1.5 cm apart. A light (28 V, 1.0 mean spherical candle power) was located at the far end of the white compartment. A Coulbourn Instruments (Allentown, PA) solid-state shock generator was employed to deliver a 0.5-mA pulse of distributed shock to the grid floor for 0.5 s. Testing was conducted under red light with white masking noise in the background.

Pups from each of the neonatal treatment groups were individually removed from their home cage and brought into the test room. Each pup was placed in the white compartment of the apparatus facing the unlit light. The guillotine door was raised, which activated a timer and turned on the 28-V light that signaled the start of the trial. When the subject crossed into the dark compartment with all four feet, the guillotine door was closed and a photocell beam was broken that activated the shock generator, turned off the light, and the latency to enter the black compartment was recorded. The subject was returned to its holding cage, and, after a 60-s intertrial interval, the subject was returned to the white compartment for an additional trial. This procedure was repeated until the animal reached the learning criterion, which was defined as remaining in the white compartment without crossing into the black for two consecutive 60-s trials. To test for retention of this learning task, the identical paradigm was repeated 24 h later.

General Statistical Procedures

In all of the experiments reported in this article, the data were analyzed by analysis of variance (ANOVA) with repeated measures when necessary unless otherwise indicated. Subsequent significant interactions were broken down by simple main effects analyses followed by post hoc Duncan tests. In all cases, the accepted significance level was $p < 0.05$ unless otherwise indicated. If sex did not contribute to a significant main effect or as part of an interaction, the data were collapsed across sex.

RESULTS

Suckling

There were no significant differences across the neonatal treatment groups in the percentage of subjects that did not attach to the nipple (15, 0, 20, and 10% for the 60 mg/kg, 20 mg/kg, stock, and sham groups, respectively). An ANOVA was conducted on the latency to attach to the nipple including only those subjects that displayed nipple attachment. There were no significant differences across neonatal treatment groups in either attachment latencies (Fig. 1a) or total time spent suckling (Fig. 1b) ($p > 0.20$ for each). There were significant differences across neonatal treatment groups in eye opening on the day of testing. A significantly greater number of pups in the AR groups had at least one eye partially open at the time of testing relative to the sham control groups (45, 55, 50, and 10% for the 60 mg/kg, 20 mg/kg, stock, and sham groups, respectively). A χ^2 analysis verified these differences: $\chi^2(4) = 10.38; p < 0.05$.

Activity

An ANOVA was conducted on horizontal activity and total distance traveled using both day and block as repeated measures. The analyses revealed main effects of neonatal treatment; however, this did not interact with day or block. Thus, for clarity, additional analyses were conducted in which an average activity measure for each day, collapsed across block, was calculated. These average daily activity measures were analyzed with ANOVA. These data are presented in Fig. 2 and 3. Similar results were obtained for both horizontal activity and distance traveled across the four test days. The ANOVA for horizontal activity revealed a significant main effect of

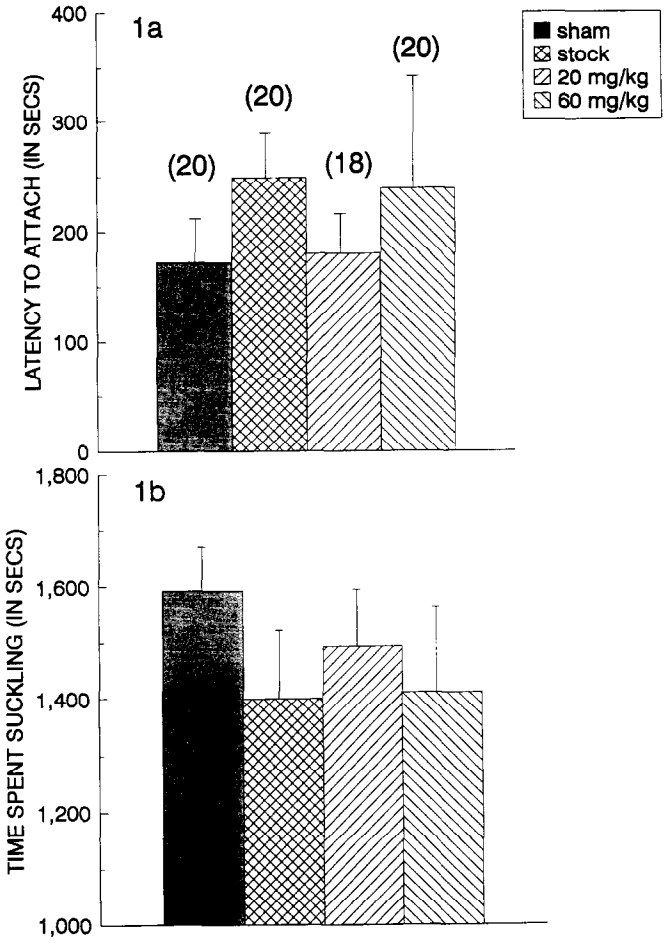

FIG. 1. (a). Average attachment latencies (SEM) collapsed across sex as a function of neonatal treatment. The number per group is presented above each bar. (b). Average time spent suckling (SEM) during the test session, collapsed across sex, as a function of neonatal treatment.

neonatal treatment: $F(3, 101) = 2.83$, $p < 0.05$. There was also a significant main effect of day because activity changed over the four test days; however, this did not interact with neonatal treatment. Planned comparisons revealed that the 60 mg/kg cocaine group displayed significantly greater horizontal activity than the two control groups: $F(1, 101) = 6.18$. The control groups did not differ from each other or the 20 mg/kg cocaine group.

The results for total distance traveled were comparable. The overall ANOVA on total distance traveled revealed a significant main effect of neonatal treatment, $F(3, 101) = 3.83$, with the 60 mg/kg group showing greater distance traveled over the four test days relative to controls, which did not differ from each other: $F(1, 101) = 9.38$. Again, the 20 mg/kg cocaine group did not differ from controls. There were no significant differences among neonatal treatment groups for either the number of stereotypic movements or total stereotypy time ($p > 0.10$ for each).

Spontaneous Alternation

The average number of trials observed before alternation are presented in Fig. 4. An ANOVA on these data revealed a significant neonatal treatment × sex interaction: $F(3, 84) = 3.22$; $p < 0.05$. Planned comparisons revealed that 20 mg/kg females required more trials to alternate than the control females, $F(1, 85) = 8.73$; $p < 0.01$), which did not differ from each other or from the 60 mg/kg females. Male performance was unaffected by neonatal treatment. There were no differences across neonatal treatment groups either in the speed to run down the runway on the first trial or in side preference.

Passive Avoidance

Figure 5 presents the number of trials to reach criterion on both the acquisition and retention day. There were no neonatal treatment effects on the number of trials for acquisition or retention of the passive avoidance learning task ($p > 0.10$). Similarly, the speed to cross into the dark compartment (the reciprocal of the latency score) on the first two trials during both the acquisition and retention test was unaffected by neonatal treatment (data not shown).

General Body Weight Data

The body weight data from these experiments are presented in Table 1. In all four experiments, there was a main effect of neonatal treatment that was due to the AR groups weighing less than the sham control. There were no differences between the AR groups. In addition, in all studies except the suckling experiment, there was a main effect of sex that was due to males weighing more than females.

DISCUSSION

This set of experiments used a behavioral screening approach to assess the effects of neonatal cocaine exposure in rats. The results from these experiments suggest that neonatal cocaine exposure alters performance on some relatively simple measures. Spontaneous alternation was delayed in 20 mg/kg female rats and a mild hyperactivity in an open field was displayed by both male and female rats exposed to 60 mg/kg cocaine. In contrast, there were no effects of neonatal cocaine exposure on either suckling behavior or passive avoidance learning. The AR subjects weighed less than the sham controls; however, body weight differences alone cannot explain the behavioral differences because there were no body weight differences among any of the AR groups.

The available literature on the effects of neonatal cocaine exposure on behavior are extremely limited. Contrasting the findings from the current study and those from the prenatal models must be done somewhat cautiously because there are marked differences in these models including exposure period and route of administration. To the best of our knowledge, suckling behavior in rodents has not been examined with rodent models looking at prenatal cocaine exposure. The current experiment suggested that there was no evidence of cocaine-related suckling deficits associated with neonatal cocaine exposure. However, these results are in contrast with more recent data collected by our laboratory that showed that cocaine-exposed offspring did display suckling deficits when more severely challenged. Cocaine-exposed pups that were food deprived for 24 h displayed a variety of suckling deficits when required to traverse a runway for access to a dam (Hansen, Segar, and Barron, manuscript in preparation). It is possible that the 1-h deprivation period used in the present study did not sufficiently challenge the cocaine-exposed pups, and

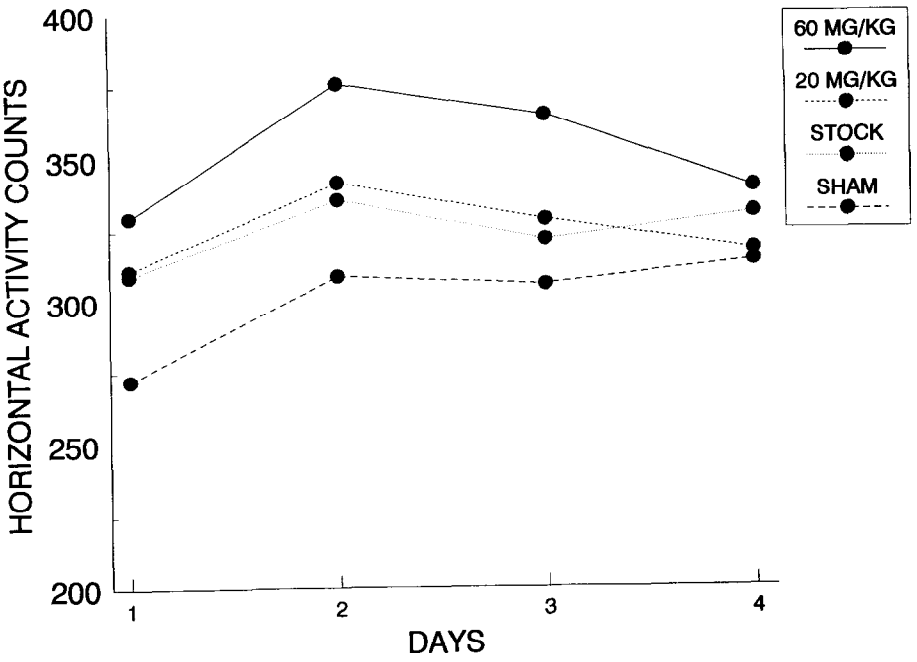

FIG. 2. Average horizontal activity (SEM) collapsed across sex and day as a function of neonatal treatment.

that a suitable challenge is required to see cocaine-related suckling deficits.

Eye opening was accelerated in all AR subjects, although this did not seem to have an effect on any of the suckling measures. This early eye opening associated with AR has been previously reported (24), and is most likely due to the increased handling experienced by the AR pups relative to the sham controls.

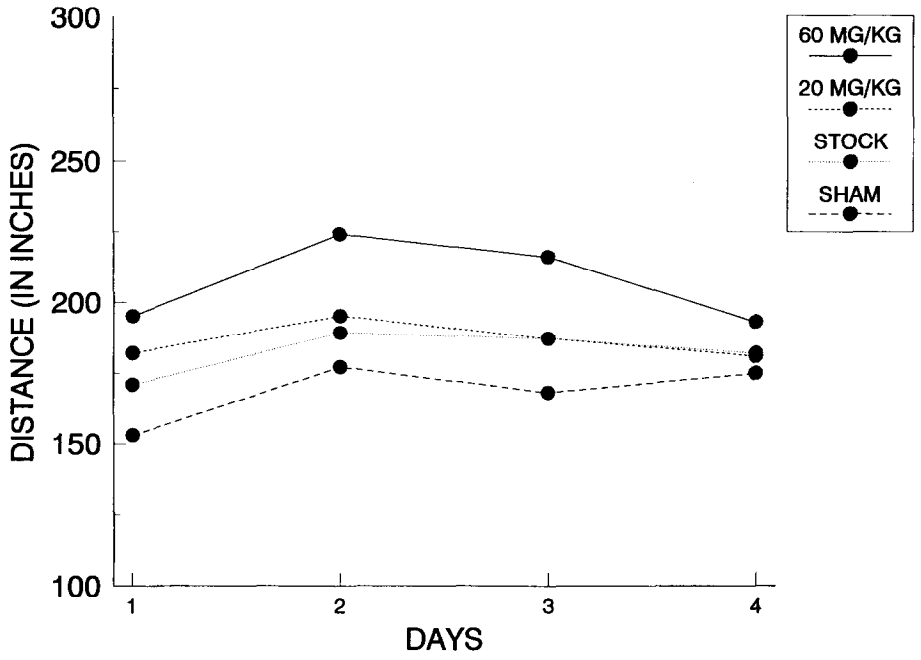

FIG. 3. Average total distance traveled (SEM) collapsed across sex and day as a function of neonatal treatment.

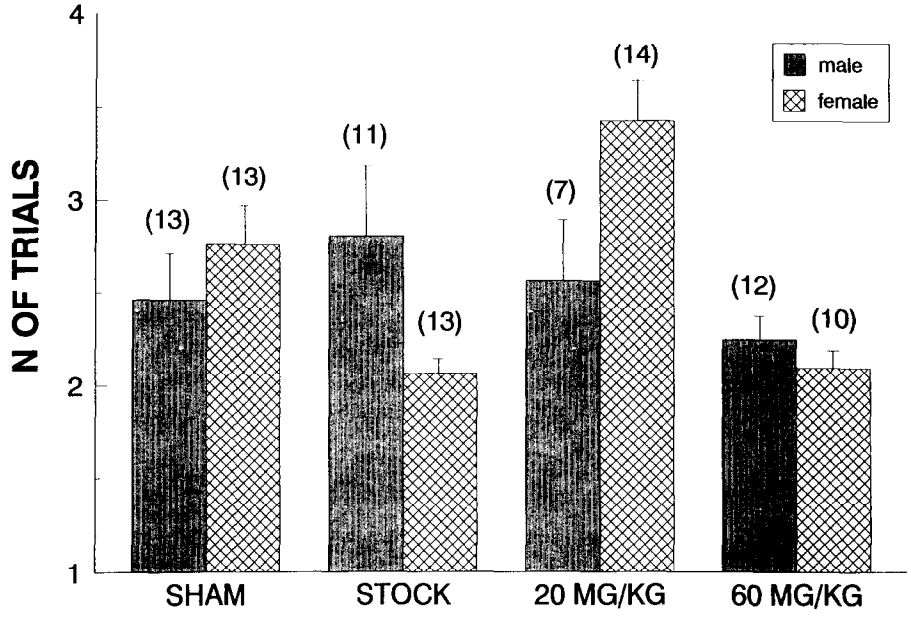

FIG. 4. The average number of trials to alternate spontaneously as a function of neonatal treatment and sex. The number per group is presented over each bar.

A moderate hyperactivity in the open field was observed in subjects exposed to the 60 mg/kg dose of cocaine. It should be noted that this effect was somewhat subtle. Previous data from this laboratory have reported that running wheel activity was unaffected in rats exposed to either 20 or 40 mg/kg cocaine tested for 30 min (6). The running wheel apparatus is typically used to measure locomotor activity, whereas the open-field paradigm measures a number of behaviors in addition to activity such as exploratory behavior and/or emotionality (4,48). Thus, it is possible that the alterations in activity as measured by the more traditional "open field" may be more indicative of changes in exploratory behavior or reactivity.

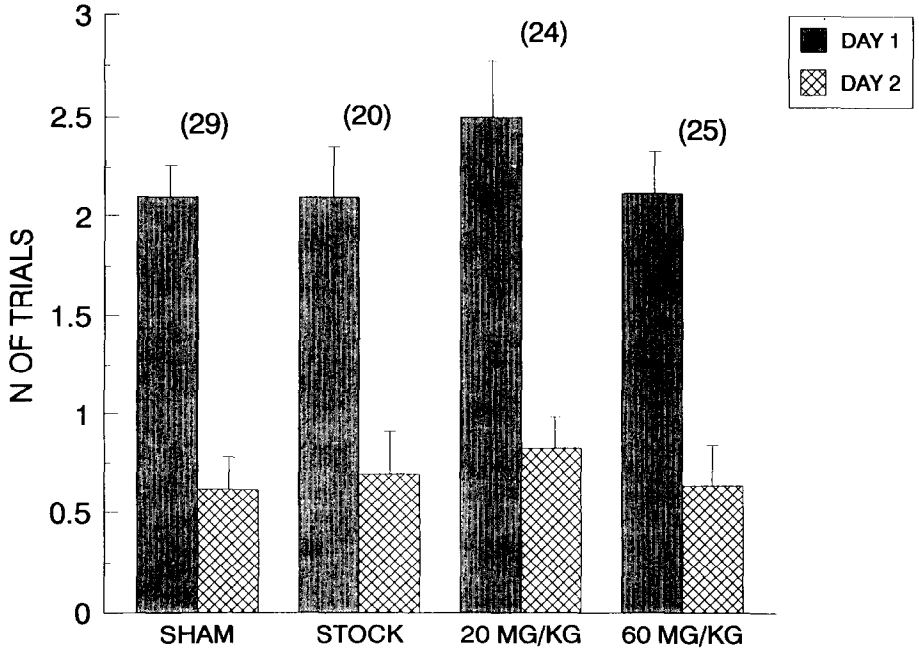

FIG. 5. The average number of trials to learn the passive avoidance task during acquisition and 24-h retention, collapsed across sex, as a function of neonatal treatment.

TABLE 1

BODY WEIGHTS (g) ± SEM

	Experiment 1	Experiment 2	Experiment 3	Experiment 4
60 mg/kg	20.7 ± 0.46	46.2 ± 1.6	40.6 ± 1.1	63.1 ± 1.9
20 mg/kg	22.1 ± 0.51	46.9 ± 1.5	43.5 ± 1.3	62.0 ± 4.9
Stock	22.1 ± 0.44	46.6 ± 1.4	42.8 ± 1.4	63.5 ± 2.7
Sham	31.1 ± 0.70*	60.1 ± 1.9*	54.1 ± 1.2*	79.2 ± 2.1*

*Differs from other same age neonatal treatment groups ($p < 0.01$).

This hypothesis is supported by data suggesting that prenatal/neonatal cocaine exposure may alter reactivity and/or stress responses. Alternatively, the effects of cocaine on activity may be dose dependent, with activity changes more likely at higher doses.

Spontaneous alternation typically emerges in rat pups between PND 18 and 22 (15). This behavior is thought to be the unlearned tendency to alternate responses in a T or Y maze in a situation in which neither arm provides extrinsic reward. It is readily apparent in rats, although animals with response inhibition deficits tend to perseverate and continue to return to the first unrewarded arm entered (35). The only group that showed a delay in spontaneous alternation was the 20 mg/kg females. These findings suggest that there may be a sex difference in the sensitivity to cocaines' effects on spontaneous alternation. There have been reports that prenatal cocaine exposure can have differential effects across the sexes. This has been demonstrated by sex differences in sensitivity to cocaine effects as well as by alterations in sexually dimorphic behaviors (26,32,47). Further work is clearly warranted to examine whether there is a sex difference in sensitivity to neonatal cocaine's effects, and to see whether sexual differentiation is affected.

The results from the spontaneous alternation study were also intriguing because they suggested a cocaine-related effect on spontaneous alternation that was limited to females exposed to the lower dose of cocaine. There have been a number of studies from the prenatal cocaine literature suggesting that certain behaviors may be more sensitive to cocaine's effects at lower doses (32). The mechanism underlying this hypothesis is based, in part, on data showing that exposure to low vs. high doses of cocaine exert different effects neurochemically. Consequently, these effects could potentially result in differential behavioral outcomes. It is possible that spontaneous alternation in females may be a behavior that is more susceptible to low-dose effects than high.

Our absence of cocaine-related effects on passive avoidance learning are comparable to the prenatal literature (37) with the exception of pups exposed prenatally to very high doses of cocaine (11). These results are in contrast, however, with the work of Alleva et al., who found that pups exposed to cocaine neonatally showed deficits in passive avoidance learning (33). The subjects from their study were tested at a very young age and required more trials than are typically reported for passive avoidance learning. The differences between the results from Experiment 1 and the data of Ricceri may be related, in part, to an interaction between age and neonatal cocaine exposure.

The model used in this set of experiments focused on a developmental period that encompassed the brain growth spurt. The findings suggest that the third trimester may indeed be a sensitive period for the effects of cocaine on the developing CNS. In rats, the CNS regions that undergo the most growth and development during this postnatal period include the hippocampus, cerebellum, and olfactory bulbs (7). Although West et al. found no weight differences in cerebellum, cortex, or whole brain (10), it is possible that subtle alterations within one or more of these late-developing regions may mediate the behavioral effects observed in the present study.

These data suggest that neonatal cocaine exposure does appear to have some behavioral teratogenic effects in rats. However, at least for the simple tasks examined in this set of experiments, these effects may be more subtle than observed with other known behavioral teratogens such as alcohol. Further work is clearly needed to better discern the extent of cocaine's effects on the developing offspring. In particular, studies that further challenge offspring may provide some important information regarding the behavioral teratogenic potential of this drug during the third trimester of pregnancy.

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REFERENCES

1. Abbey, H.; Howard, E. Statistical procedures in developmental studies on species with multiple offspring. Dev. Psychobiol. 6: 329–335; 1973.
2. Anday, E. K.; Cohen, M. E.; Kelley, N. E.; Leitner, D. S. Effect of in utero cocaine exposure on startle and its modification. Dev. Pharmacol. Ther. 12:137–145; 1989.
3. Anderson-Brown, T.; Slotkin, T. A.; Seidler, F. J. Cocaine acutely inhibits DNA synthesis in developing rat brain regions: Evidence for direct actions. Brain. Res. 537:197–202; 1990.
4. Archer, J. Tests for emotionality in rats and mice. A review. Animal Behav. 21:205–235; 1973.
5. Barron, S.; Irvine, J. The effects of neonatal cocaine exposure on two measures of balance and coordination. Neurotoxicol. Teratol. 16:89–94; 1994.
6. Barron, S.; Kaiser, D. H.; Hansen, L. S. Neonatal cocaine exposure, activity and responsivity to cocaine in a rodent model. Neurotoxicol Teratol. 16:401–409; 1994.
7. Bayer, S. A.; Altman, J.; Russo, R. J.; Zhang, X. Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. Neurotoxicol. 14:83–144; 1993.
8. Bilitzke, P. J.; Church, M. W. Prenatal cocaine and alcohol exposures affect rat behavior in a stress test (the Porsolt Swim Test). Neurotoxicol. Teratol. 14:359–364; 1992.
9. Chasnoff, I. J.; Lewis, D. E.; Griffith, D. R.; Willey, S. Cocaine and pregnancy: Clinical and toxicological implications for the neonate. Clin. Chem. 35:1276–1278; 1989.
10. Chen, W. A.; Andersen, K. H.; West, J. R. Cocaine exposure during the brain growth spurt: Studies of neonatal survival, somatic growth, and brain development. Neurotoxicol. Teratol. 15: 267–273; 1993.
11. Church, M. W.; Overbeck, G. W. Prenatal cocaine exposure in the Long-Evans rat: II. Dose-dependent effects on offspring behavior. Neurotoxicol. Teratol. 12:335–343; 1990.
12. Church, M. W.; Kaufmann, R. A.; Keenan, J. A.; Martier, S. S.;

Savoy-Moore, R. T.; Ostrea, E. M., Jr.; Subramanian, M. G.; Welch, R. A.; Zajac, C. S. Effects of prenatal cocaine exposure. In: Watson, R. R., ed. Biochemistry and physiology of substance abuse, vol. III. Boca Raton, FL: CRC Press, 1989: 179–204.
13. Dobbing, J.; Sands, J. Comparative aspects of the brain growth spurt. Early Hum. Dev. 3:79–83; 1979.
14. Dow-Edwards, D. L.; Freed, L. A.; Milhorat, T. H. Stimulation of brain metabolism by perinatal cocaine exposure. Dev. Brain Res. 42:137–141; 1988.
15. Egger, J.; Krsiak, M. Ontogenetic aspects of central cholinergic involvement in spontaneous alternation behavior. Dev. Psychobiol. 6:289–299; 1973.
16. Eisen, L. N.; Field, T. M.; Bandstra, E. S.; Roberts, J. P.; Morrow, C.; Larson, S. K.; Steele, B. M. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton Scale. Pediatrics 88:477–480; 1991.
17. Giordano, M.; Moody, C. A.; Zubrycki, E. M.; Dreshfield, L.; Norman, A. B.; Sanberg, P. R. Prenatal exposure to cocaine in rats: Lack of long-term effects on locomotion and stereotypy. Bull. Psychonom. Soc. 28:51–54; 1990.
18. Goodwin, G. A.; Heyser, C. J.; Moody, C. A.; Rajachandran, L.; Molina, V. A.; Arnold, H. M.; McKinzie, D. L.; Spear, N. E.; Spear, L. P. A fostering study of the effects of prenatal cocaine exposure: II. Offspring behavioral measures. Neurotoxicol. Teratol. 14:423–432; 1992.
19. Henderson, M. G.; McMillen, B. A. Effects of prenatal exposure to cocaine or related drugs on rat developmental and neurological indices. Brain Res. Bull. 24:207–212; 1990.
20. Heyser, C. J.; Chen, W. J.; Miller, J.; Spear, N. E.; Spear, L. Prenatal cocaine exposure induces deficits in Pavlovian conditioning and sensory preconditioning among infant rat pups. Behav. Neurosci. 104:955–963; 1990.
21. Heyser, C. J.; Goodwin, G. A.; Moody, C. A.; Spear, L. P. Prenatal cocaine exposure attenuates cocaine-induced odor preferences in infant rats. Pharmacol. Biochem. Behav. 42:169–173; 1992.
22. Hughes, H. E.; Pringle, G. F.; Scribani, L. A.; Dow-Edwards, D. L. Cocaine treatment in neonatal rats affects the adult behavioral response to amphetamine. Neurotoxicol. Teratol. 13:335–339; 1991.
23. 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.
24. Kelly, S. J.; Hulsether, S. A.; West, J. R. Alterations in sensorimotor development: Relationship to postnatal alcohol exposure. Neurotoxicol. Teratol. 9:243–251; 1987.
25. Johns, J. M.; Means, L. L.; Means, M. J.; McMillen, B. A. Prenatal exposure to cocaine II: Effects on open-field activity and cognitive behavior in Sprague–Dawley rats. Neurotoxicol. Teratol. 14:343–349; 1992.
26. Levin, E. D.; Seidler, F. J. Sex-related spatial learning differences after prenatal cocaine exposure in the young adult rat. Neurotoxicology 14:23–28; 1993.
27. MacGregor, S. N.; Keith, L. G.; Chasnoff, I. J.; Rosner, M. A.; Chisum, G. M.; Shaw, P.; Minogue, J. P. Cocaine use during pregnancy: Adverse perinatal outcome. Am. J. Obstet. Gynecol. 157:686–690; 1987.
28. Madden, J. D.; Payne, T. F.; Miller, S. Maternal cocaine abuse and effect on the newborn. Pediatrics 77:209–211; 1986.
29. Maone, T. R.; Mattes, R. D.; Beauchamp, G. K. Cocaine-exposed newborns show an exaggerated sucking response to sucrose. Physiol. Behav. 51:487–491; 1992.
30. Meyer, J. S.; Yacht, A. C. Lack of behavioral sensitization to repeated cocaine administration from postnatal days 1 to 10. Int. J. Neurosci. 72:107–113; 1993.
31. Oro, A. S.; Dixon, S. D. Perinatal cocaine and methamphetamine exposure: Maternal and neonatal correlates. J. Pediatr. 111:571–578; 1987.
32. Raum, W. J.; McGivern, R. F.; Peterson, M. A.; Shryne, J. H.; Gorski, R. A. Prenatal inhibition of hypothalamic sex steroid uptake by cocaine: Effects on neurobehavioral sexual differentiation in male rats. Dev. Brain Res. 53:230–236; 1990.
33. Ricceri, L.; Tirassa, P.; Aloe, L.; Alleva, E. Postnatal cocaine exposure affects neonatal passive avoidance performance and cholinergic development in rats. Pharmacol. Biochem. Behav. 45: 283–289; 1993.
34. Richardson, G. A.; Day, N. L. Detrimental effects of prenatal cocaine exposure: Illusion or reality? J. Am. Acad. Child Adolesc. Psychiatry 33:28–34; 1994.
35. Riley, E. P.; Lochry, E. A.; Shapiro, N. R.; Baldwin, J. Response perseveration in rats exposed to alcohol prenatally. Pharmacol. Biochem. Behav. 11:513–519; 1979.
36. Riley, E. P.; Foss, J. A. Exploratory behavior and locomotor activity: A failure to find effects in animals prenatally exposed to cocaine. Neurotoxicol. Teratol. 13:553–558; 1991.
37. Riley, E. P.; Foss, J. A. The acquisition of passive avoidance, active avoidance and spatial navigation tasks by animals prenatally exposed to cocaine. Neurotoxicol. Teratol. 13:553–558; 1991.
38. Ryan, L.; Ehrlich, S.; Finnegan, L. Cocaine abuse in pregnancy: Effects on the fetus and newborn. Neurotoxicol. Teratol. 9:295–299; 1987.
39. Samson, H. H.; Diaz, J. Effects of neonatal ethanol exposure on brain development in rodents. In: Abel, E. L., ed. Fetal alcohol syndrome, vol. 3: Animal studies. Boca Raton, FL: CRC Press; 1982:131–150.
40. Seliger, D. L. Effects of prenatal administration of d-amphetamine on rat offspring activity and passive avoidance learning. Physiol. Psychol. 1:273–280; 1987.
41. Silva-Araujo, A.; Salgado-Borges, J.; Cardoso, V.; Silva, M. C.; Castro-Correia, J.; Tavars, M. A. Changes in the retinal ganglion cell layer and optic nerve of rats exposed neonatally to cocaine. Exp. Eye Res. 56:199–206; 1993.
42. 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.
43. 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.
44. Spear, L. P.; Kirstein, C. L.; Frambes, N. A. Cocaine effects on the developing CNS: Behavioral, psychopharmacological and neurochemical studies. Ann. NY Acad. Sci. 562:290–307; 1989.
45. Spear, L. P.; Kirstein, C. L.; Bell, J.; Yootanasumpun, V.; Greenbaum, R.; O'Shea, J.; Hoffman, H.; Spear, N. E. Effects of prenatal cocaine exposure on behavior during the early postnatal period. Neurotoxicol. Teratol. 11:57–63; 1989.
46. Tavares, M. A.; Silva, M. C. Body weight gain and hippocampal volumes of rats exposed neonatally to psychostimulants. Brain Res. 619:137–145; 1993.
47. Vathy, I.; Katay, L.; Nunn Mini, K. Sexually dimorphic effects of prenatal cocaine on adult sexual behavior and brain catecholamines in rats. Dev. Brain Res. 73:115–122; 1993.
48. Walsh, N. R.; Cummins, R. A. The open-field test: A critical review. Psychol. Bull. 83:482–504; 1976.
49. West, J. R.; Hamre, K. M.; Pierce, D. R. Delay in brain growth induced by alcohol in artificially reared rat pups. Alcohol 1:213–222; 1984.