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The Effects of Neonatal Cocaine Exposure on a Play-Rewarded Spatial Discrimination Task in Juvenile Rats

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WILLFORD, J. A., T. M. SEGAR, L. S. HANSEN-TRENCH AND S. BARRON. *The effects of neonatal cocaine exposure on a play-rewarded spatial discrimination task in juvenile rats.* PHARMACOL BIOCHEM BEHAV **62**(1) 137–143, 1999.—This study examined the effects of neonatal cocaine exposure on the rewarding properties of play in a modified T-maze. Animals were artificially reared from postnatal day (PND) 4–9 with drug concentrated in four daily feeds. There were four treatment groups, 40 mg/kg/day cocaine, 20 mg/kg/day cocaine, an artificially reared control and a surgery control. From PND 38–42, subjects were tested with a food reward (EXP 1) or a play reward (EXP 2). No deficits in learning were seen when the reward was food. The 20 mg/kg/day cocaine group, however, showed impaired learning and altered play behavior when the reward was access to a play partner. Neonatal cocaine exposure thus appears to differentially affect learning based on the type of reward presented. © 1998 Elsevier Science Inc.

Neonatal cocaine exposure Learning Play behavior Behavioral teratology

THE clinical literature reporting the effects of prenatal cocaine exposure has focused primarily on early postnatal and infant development. Recently, however, an increasing number of children prenatally exposed to cocaine have been assessed in the preschool and school age years. These reports suggest that children exposed to cocaine show behavioral disruption in attachment and play behavior relative to children not exposed prenatally to cocaine (18,31). One study examining cognitive development has demonstrated that prenatal exposure to cocaine can result in lower IQ scores and deficits in contexts of free play (2). Another study, however, reports no deficits related to intellectual ability or academic achievement in school-age children who had prenatal exposure to cocaine (30). Children exposed to cocaine during development are also at risk for other prenatal and postnatal variables such as lack of prenatal care, malnutrition, polydrug abuse, and poor parenting skills. These variables make the assessment of the effects of prenatal cocaine exposure difficult.

One way to better understand the effects of cocaine exposure on development is to use animal models. Models utilizing animal subjects allow for the control of amount and frequency of drug exposure as well as a number of biological and psychosocial factors. The data from rodent models also demonstrate particular behaviors that are sensitive to cocaine exposure during development. These include cognitive performance (41), social behavior (16,43,44) and responses to stress (7,20). Recently, studies have shown that rough-and-tumble play is affected on a number of measures as a result of prenatal cocaine exposure. For example, cocaine-exposed offspring show less pinning and play solicitation (43,44).

Play behavior is frequently displayed by young rats from approximately postnatal day (PND) 21 to the onset of puberty. Play behavior is characterized by chasing, pouncing, pinning, and rough-and-tumble activity. The purpose of play behavior may include increased physical fitness and the learning of competitive, social, predatory, and avoidance skills (26). Play also serves a role in the social development of rats. For example, social skills such as bonding, establishment of rank, learning of social communication, and resourceful skills may function in play (24,26).

Play is a very rewarding experience for young rats (9,38). As with other rewarding activities, the mesolimbic dopamine

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pathway may be involved with the reward associated with play behavior. Direct manipulations of the dopaminergic system do affect play behavior. For example, lisuride, a dopamine agonist, induces a significant increase in play behavior in juvenile rats (11). The role of dopaminergic manipulation on play behavior, however, appears complex with other dopaminergic agonists and antagonists decreasing play behavior (27,28). Cocaine also elicits its rewarding effects in the mesolimbic pathway. Many studies suggest that chronic treatment with cocaine during development may result in alterations of the dopamine system (33,35). Ultimately, these changes may be expressed in an altered response to play.

Given the recent reports on the possible effects of prenatal cocaine exposure on play behavior, the following experiments were designed to assess the effects of neonatal cocaine exposure on learning when access to play was the reinforcer. The neonatal model was employed to focus drug exposure on a period of development referred to as the "brain growth spurt" that is characterized by neuronal migration and synaptogenesis. This developmental stage is comparable to third trimester neurodevelopment in humans (5).

METHOD

Mating Procedure

Parent animals were Sprague–Dawley rats obtained from Harlan Laboratories (Indianapolis, IN). Rats were bred at the University of Kentucky. Pregnant females were placed in breeding cages with wood chip bedding and given ad lib food and water. These animals were housed in a temperature-controlled nursery with a 12 L:12 D cycle. Twenty-four hours following parturition litters were culled to 10 pups, maintaining five males and five females whenever possible.

Neonatal Surgery Procedure

On PND 4, pups were randomly assigned to one of four treatment groups; an artificially reared (AR) 40 mg/kg/day cocaine hydrochloride group, an AR 20 mg/kg/day cocaine hydrochloride group, an AR control group receiving a milk solution with no drug added (stock), or a surgery control group that was reared with a lactating dam (sham). Within each litter, only one female and one male were assigned to each of the four treatment groups to control for litter effects (1).

The surgery and artificial rearing procedures are routinely used in our lab and will only be briefly described here. Additional details of the surgery and artificial rearing procedures are presented in Samson and Diaz (32). Each pup was lightly anesthetized with halothane (50% halothane/50% compressed air) and an intragastric cannula was implanted into the stomach. The sham controls underwent a similar surgical procedure; however, the intragastric cannula was not implanted. Upon recovery from anesthesia, AR pups were housed in the AR apparatus and shams were returned to their home cage to be reared by lactating dams.

Artificial Rearing Procedure

AR pups were individually maintained in Styrofoam cups with wood chip bedding and a piece of artificial fur attached to the inside of the cup. The artificial fur served to help reduce the stress of maternal deprivation that can occur with AR (39). These cups floated in a stainless steel water bath. Using our established procedure, the water bath was maintained at 48°C until PND 7 and then gradually reduced across the remaining days for a final temperature of 42°C.

The feeding cannula was attached to Tygon tubing, which was connected to a syringe containing formula designed to mimic rat milk (42). The syringes were mounted on an infusion pump (Harvard Apparatus Model 2265) controlled by a timer programmed to infuse milk for 20 min every 2 h. As a result, pups received 12 daily feeds.

Each day the AR pups were weighed, their cannulas flushed with distilled water and their bladders voided. For the cocaine-exposed groups, drug was concentrated in four consecutive daily feeds to mimic a binge model of cocaine use. During the additional eight feeds all AR pups received the stock milk formula. The milk administered each day was equivalent to 30% of the average daily body weights of the AR pups. The AR pups were maintained under these conditions from PND 4–9. On PND 10, all AR pups received a 24-h drug-free period to allow for recovery from any effects of cocaine exposure. Although no systematic measurement has been taken, no obvious signs of cocaine withdrawal have ever been observed in this laboratory.

The sham control pups were also weighed daily from PND 4–10. These pups were housed with additional surrogate pups and a lactating dam maintaining 12 pups per litter when possible. Surrogate pups functioned to maintain lactation performance by the dams until the AR pups were returned to their home cages.

On PND 11 the intragastric cannulas of the AR pups were cut near the abdominal wall and both AR pups and sham controls were earmarked for later identification. The AR pups and sham controls were then bathed in a warm slurry of maternal feces and water and then returned to their home cage; a procedure that virtually eliminates pup mortality. Animals were weaned and housed with two to three same-sex conspecifics on PND 21.

Modified T-Maze Apparatus

The test apparatus used in this study was a modified T-maze adapted from Normansell and Panksepp (24). It was made of polyurethane-treated plywood. To maximize distinctive cues between the two arms of the maze, one arm was painted blue with a smooth floor texture and the other arm was painted white with a coarse floor texture. In addition, for Experiment 2, goal boxes were enlarged (40 × 40 cm) to allow for more room to play. Removable barriers were added to confine playmates within the goal box.

Behavioral Testing

For both experiments subjects were individually housed 5 days prior to testing. In Experiment 1 subjects were habituated on PND 35 to the test apparatus by allowing them to explore the maze until the animal ate a sweetened cereal (Froot Loop) reward placed in each goal box or until 5 min had elapsed. Subjects were then given additional exposure to the Froot Loop reward for two additional days in their home cages. The correct goal box was identified for each subject prior to beginning testing. The correct goal box for an individual subject remained the same for the duration of testing. Beginning on PND 38, each subject was given six trials per day for 5 consecutive days. A trial began when the rat was placed in the start box and ended when the rat chose the correct compartment, chose the incorrect compartment, or traversed the maze without choosing a compartment for 60 s. If a subject chose the correct compartment, it was confined to that compartment with a Froot Loop reward for 60 s or until the Froot

Loop was eaten. If a subject chose the incorrect compartment, it was confined in the incorrect compartment with no reward for 60 s. If the subject did not choose a compartment during the trial, it was returned to its home cage without reward. The intertrial interval was approximately 60 s. There were approximately 12–13 subjects/treatment/sex in Experiment 1. In addition, the correct compartment was counterbalanced across treatment group to control for side preferences. Experimenters were blind to treatment condition.

In Experiment 2, each subject was assigned to a same-sex playmate matched for body weight (using a ±5 g body weight criterion). For each cell of the experimental design, subjects from each neonatal treatment group were paired with three to five partners from each of the neonatal treatment groups. The number of subjects/treatment/sex was 17–22. The increased number of subjects in each cell of this experiment relative to Experiment 1 was to ensure adequate representation of play partners from all treatment groups.

The general testing procedure was similar to Experiment 1. On PND 35, subjects were habituated to the test apparatus. Beginning on PND 37, they were tested for 5 days. Immediately prior to the beginning of a trial, the same-sex weight matched playmate was placed in the correct compartment behind the barrier. When the subject chose the correct goal box, the barrier was removed to release the playmate, and the pair was allowed to play for 60 s. Each subject had the same playmate across all test sessions and test days.

The dependent variables examined in both experiments were the number of correct choices, latency for the animal to choose a side after being placed in the start box, and learning on the first day of testing. In addition, play behavior of the animals was monitored in Experiment 2 by measuring the frequency of pinning. Pinning is a reliable and easily quantified behavior that has been shown to correlate highly with other measures of play in rats (25). A pin was defined as the subject restraining the play partner on its dorsal side for at least 1 s. In addition, body weights were recorded for each experiment. In Experiment 1, body weights were recorded following habituation. In Experiment 2, body weights were recorded following days 1 and 5 of testing.

Data Analysis

On each of the measures investigated, the data were analyzed with planned comparisons. These tests were completed using a statistical program for univariate/multivariate analyses in which specific linear comparisons among cell means can be evaluated. Planned comparisons were performed based on a priori predictions that neonatal cocaine exposure would affect learning and play. There were three comparisons for each of the analyses. First, the stock and sham control groups were compared to each other and, if they did not differ, they were pooled together to provide greater power for statistical analyses. The drug groups were then compared to the pooled control groups. Measures were taken to control for family wise error rate on these analyses making the accepted level of significance, $p < 0.03$.

In preliminary analyses both day and trials within each day were examined. There were no trial × day × neonatal treatment interactions. Therefore, the data were examined by collapsing across trial within a given day and using these means in the analyses. For each of the analyses, sex was also analyzed as a variable. There were no sex differences on any of the measures; therefore, the data were collapsed across this variable as well.

RESULTS

Learning

Subjects that failed to choose the correct side were given a 60-s ceiling for those trials. In Experiment 1, the average latency to choose the correct side is presented in Fig. 1a. All treatment groups learned the task as shown by a reduction in the latency to choose the correct side across days of testing. The number of correct choices over days of testing is presented in Fig. 1b. The number of correct trials increased over days for all treatment groups. The 40 mg/kg/day cocaine-exposed group had significantly fewer correct choices than the control groups only on day 5, $F(1, 85) = 5.87$, $p < 0.02$. Examination of performance on day 1 showed that latencies decreased within the first day of testing, as shown by a main effect of trial, $F(5, 455) = 3.20$, $p < 0.01$, although there were no differences across prenatal treatment groups (data not shown).

In Experiment 2, all treatment groups showed a decrease in the latency to choose the correct side across days of testing. The 20 mg/kg/day cocaine-exposed group, however, took significantly longer to choose the correct side, $F(1, 150) = 5.15$, $p < 0.03$, and had fewer correct choices relative to controls, $F(1, 150) = 4.61$, $p = 0.03$ (see Fig. 2a and 2b). Examination of the latencies for acquisition of the task on day 1 suggested that the 20 mg/kg/day cocaine-exposed offspring did not show the same linear trend over the first test session as the other treatment groups. This effect was supported by a marginally significant linear neonatal treatment × trial interaction, $F(3, 150) = 2.54$, $p = 0.058$ (see Fig. 3).

To determine whether there were differences in the rate of acquisition across the two experiments, the slope of the acquisition curves was assessed using linear regression. The slope

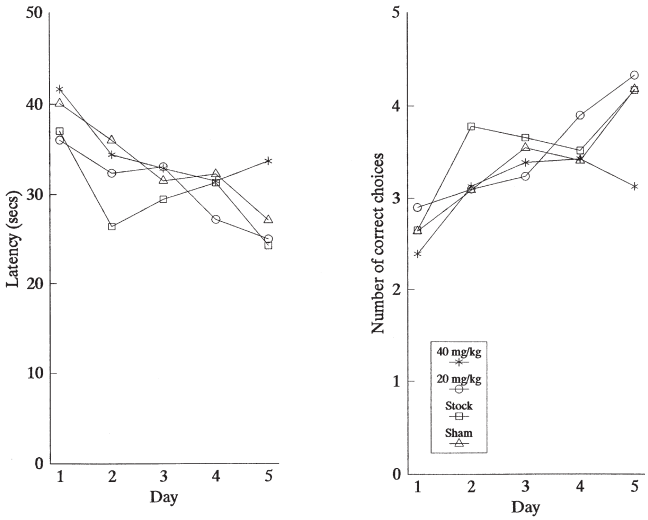

FIG. 1. (a) Average latency to choose the correct side for Experiment 1. Average SEM across the 5 days of testing for each treatment group are ±3 (40 mg/kg); ±3 (20 mg/kg); ±3 (stock); ±2 (sham). (b) Number of correct choices for Experiment 1. Average SEM across the 5 days of testing for each treatment group are ±0.4 (40 mg/kg); ±0.4 (20 mg/kg); ±0.4 (stock); ±0.3 (sham). Data presented are collapsed across sex and trial on each day of testing as a function of neonatal treatment group when access to a sweetened food was the reward.

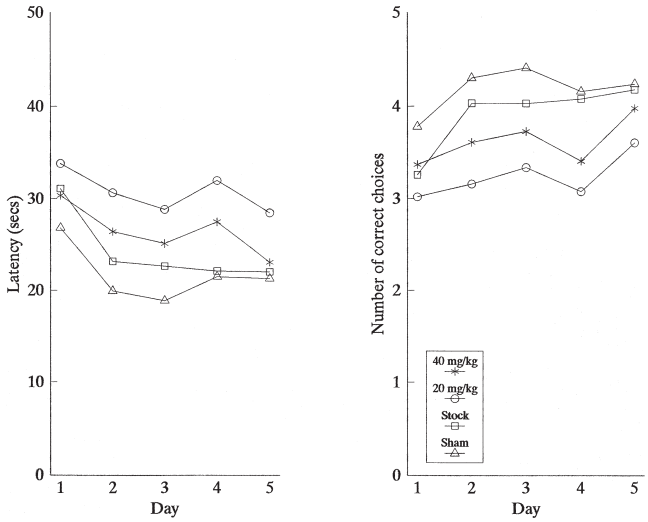

FIG. 2. (a) Average latency to choose the correct side for Experiment 2. Average SEM across the 5 days of testing for each treatment group are ±3 (40 mg/kg); ±4 (20 mg/kg); ±3 (stock); ±3 (sham). (b) Number of correct choices for Experiment 2. Average SEM across the 5 days of testing for each treatment group are ±0.4 (40 mg/kg); ±0.4 (20 mg/kg); ±.3 (stock); ±0.4 (sham). Data presented are collapsed across sex and trial on each day of testing as a function of neonatal treatment group when access to a play partner was the reward.

of the regression line for each treatment group was compared for Experiments 1 and 2 using a t-test. There were no differences between the slopes for any of the treatment groups.

Play Behavior

For each day the number of pins by each subject was divided by the number of correct trials. Because there were differences in the number of correct choices, this correction was done to control for the number of trials in which subjects had

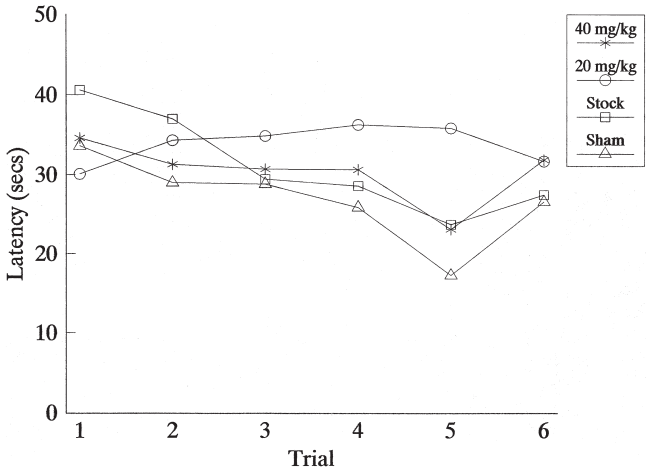

FIG. 3. The average latency to choose the correct side collapsed across sex on the first day of testing as a function of neonatal treatment group when access to a play partner was the reward. Average SEM across the 5 days of testing for each treatment group are ±4 (40 mg/kg); ±4 (20 mg/kg); ±4 (stock); ±4 (sham).

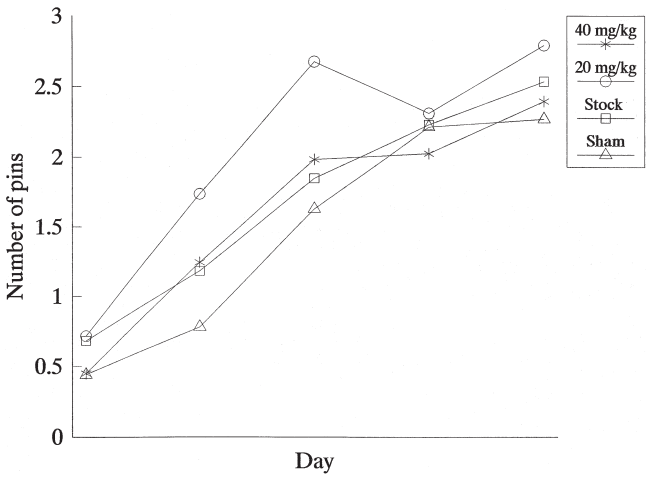

FIG. 4. The average number of pins collapsed across sex and trial for each day of testing as a function of neonatal treatment group. Average SEM across the 5 days of testing for each treatment group are ±0.2 (40 mg/kg); ±0.3 (20 mg/kg); ±0.2 (stock); ±0.2 (sham).

access to the playmate. For all subjects the average number of pins increased across days of testing and subjects in the 20 mg/kg/day cocaine-exposed group displayed more pins than controls on both days 2, $F(1, 101) = 6.95$, $p < 0.01$, and 3, $F(1, 101) = 6.26$, $p = 0.01$ (see Fig. 4).

Body Weights—Experiments 1 and 2

For Experiment 1, body weights were recorded after habituation (see Table 1). There was a treatment effect in Experiment 1, $F(3, 89) = 2.71$, $p = 0.04$. Post hoc Newman–Keuls test revealed that subjects exposed to the high dose of cocaine (40 mg/kg/day) weighed significantly less than sham controls. There were no other differences across the treatment groups in Experiment 1. For Experiment 2, body weights were recorded on days 1 and 5 of testing (see Table 2). No body weight differences were expected in Experiment 2 because subjects were bodyweight matched prior to the beginning of testing. As expected, there were no differences in body weights across neonatal treatment groups in Experiment 2. In Experiments 1 and 2 males weighed more than females, $F(1, 89) = 117.89$, $p < 0.00$; $F(1, 146) = 91.90$, $p < 0.001$, respectively.

DISCUSSION

A neonatal model was utilized to assess the effects of cocaine exposure during a period of CNS development that is

TABLE 1

EXPERIMENT 1—BODY WEIGHTS (IN g) ± SEM

Treatment Group	Male	Female
40 mg/kg cocaine	165 ± 3*	132 ± 3*
20 mg/kg cocaine	169 ± 4	139 ± 3
Stock	168 ± 4	136 ± 2
Sham	174 ± 5	145 ± 5

*Significantly different from the sham treatment group, $p = 0.05$.

TABLE 2
EXPERIMENT 2—BODY WEIGHTS (IN g) ± SEM

	Day 1		Day 5	
Treatment Group	Male	Female	Male	Female
40 mg/kg cocaine	171 ± 7	146 ± 4	198 ± 7	151 ± 3
20 mg/kg cocaine	169 ± 6	147 ± 3	198 ± 6	158 ± 3
Stock	174 ± 6	142 ± 4	203 ± 4	158 ± 3
Sham	176 ± 10	147 ± 5	204 ± 8	162 ± 4

similar to the third trimester in humans. This study shows that this period of development is sensitive to early cocaine exposure and its later effects on social behavior. Neonatal cocaine exposure resulted in learning deficits as well as altered play behavior in rats. The major findings from this study can be summarized as follows: 1) performance in a modified T-maze was not impaired with a Froot Loop reward, 2) neonatal exposure to 20 mg/kg/day cocaine resulted in learning deficits when access to play was the reward, and 3) neonatal exposure to 20 mg/kg/day cocaine also resulted in increased pinning behavior on certain days of testing.

The results from Experiment 1 showed that neonatal cocaine exposure had little effect on learning this spatial discrimination task for access to a Froot Loop reward. Although there was some evidence of impaired performance in the 40 mg/kg cocaine-exposed offspring on the last day of testing, all treatment groups showed learning across days, as evidenced by a decrease in the latency to choose the correct side and an increase in the number of correct trials. It is not clear whether extending the number of test days beyond 5 days would have revealed cocaine-related deficits for the high-dose cocaine group. These results provide further support for earlier findings from our laboratory suggesting that neonatal cocaine exposure has little effect on relatively simple forms of learning (4).

The results from Experiment 2 are particularly interesting in relation to the results from Experiment 1 in which the 20 mg/kg cocaine-exposed subjects showed no impairments on a similar learning task when the reward was food. There were no differences in the slopes of the regression lines for acquisition suggesting no differences in the rate of acquisition between the two experiments. These findings suggest that the deficits be seen in the 20 mg/kg treatment group in Experiment 2 may motivational rather than learning deficits. These results could be interpreted in a number of ways. First, these findings suggest that some aspect of the inherent rewarding properties of play may be altered for the 20 mg/kg cocaine-exposed offspring. A reduction in the rewarding aspects of play could result in poorer learning of the T-maze spatial task. Alternatively, if contact with the conspecific was qualitatively different for this group, the 20 mg/kg offspring could have learned equally well in this experiment, yet, chose to have contact with the conspecific less often. In other words, the deficit may not be in learning the task but rather, in the motivation or desire to gain access to a conspecific. Indeed, when the 20 mg/kg cocaine-exposed offspring engaged in play, they displayed more pinning behavior than controls suggesting that some aspect of their encounters are different.

These cocaine-related effects observed in Experiment 2 were limited to offspring exposed to the lower dose of cocaine. Pups exposed to the higher dose of cocaine showed no effects on either acquisition of the task or on play behavior. This unusual dose-dependent effect has been previously shown by others (29) as well as in our lab on dependent measures including activity response in a running wheel (3), learning in a T-maze, and novelty in an open field (manuscript in preparation). These studies demonstrate long-term behavioral differences between the low and high doses of cocaine. The mechanism underlying these long-term changes is not known. Raum and colleagues argue that the absence of a dose effect following prenatal cocaine exposure may be explained by differential pharmacological effects of low vs. high doses, particularly on the noradrenergic system, with lower doses enhancing activity and higher doses blocking transmission (15,17). Thus, it is not entirely surprising that effects on behavior in Experiment 2 were limited to the low-dose cocaine-exposed group.

Prenatal exposure to cocaine results in decreased pinning behavior and less solicitation of play (16,43,44). The findings from the current study suggest that neonatal cocaine exposure may not produce the same effects as those seen following prenatal cocaine exposure. It should also be noted that there were differences in the testing procedures. For example, there were differences in the length of play sessions with ours being shorter.

Although a number of studies have shown that a variety of prenatal or neonatal manipulations can reduce the amount of rough-and-tumble play as measured by pins (23,43), very few studies have reported perinatal manipulations that increase the number of pins. Two other substances that produce increased rough-and-tumble play include perinatal lead exposure (14) and neonatal cadmium exposure (13). Cadmium, lead, and cocaine all affect catecholamine activity, and consequently, may share underlying mechanisms of action.

As stated previously, the dopaminergic system is important in play behavior. Studies examining the effect of prenatal exposure to cocaine on dopaminergic function suggest dopamine systems may be altered, although the findings tend to be mixed. Recent work from our laboratory has shown that neonatal cocaine exposure had no effect on density of DA receptors in various brain regions; however, a reduced sensitivity to the activating effects of the D_2 agonist quinpirole was observed (manuscript in preparation). Other studies have reported decreased dopamine transporter binding as well as increased D_2 receptor binding (8,12,33), although these effects may depend on the age of testing (36,37). In addition, dopaminergic challenges by agonists or antagonists after prenatal cocaine exposure appears to have functional consequences with regard to behavior (21,22). It is conceivable that the effects displayed by the 20 mg/kg/day treatment group could be mediated through catecholaminergic systems.

A number of brain regions have also been implicated in play fighting or social behaviors, including the amygdala (19), the medial septal area (6), the prefrontal cortex (10), and the parafasicular nucleus in the thalamus (34). The prefrontal cortex and its connections with the amygdala undergo considerable postnatal development with adult patterns of projections not observed until approximately postnatal day 12 (40). Although it is not currently known whether neonatal cocaine exposure affects these circuits and/or structures, this circuit is still undergoing considerable differentiation during our neonatal drug administration period.

There were body weight differences in Experiment 1, with the 40 mg/kg/day treatment group weighing less than the sham group. This reduction in body weight did not appear to be significant with regard to the interpretation of the results from Experiment 1 because neonatal treatment had no effect

on any behavioral measures. In addition, neonatal treatment did produce alterations in behavior but not body weights in Experiment 2.

The results from this study show that neonatal cocaine exposure has behavioral teratogenic effects in offspring. As the current study shows, these effects were only apparent in certain reward conditions. Currently, there is a considerable amount of discrepancy regarding the severity of the effects of in utero cocaine exposure. We believe that aspects of the environment such as the type of reward or the amount of stress that can result in differences in behavioral outcome of cocaine-exposed offspring may contribute to these discrepancies. In future studies, it may be important to systematically vary the dimensions of a particular task to determine cocaine's effects.

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