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Differential behavioral responses to chronic amphetamine in adult male and female rats exposed to postnatal cocaine treatment

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Abstract

The impact of cocaine exposure during development on behavioral sensitization as measured by locomotor activity and stereotypy following repeated intermittent administration of amphetamine is examined. Male and female Sprague–Dawley rats were exposed to cocaine at 50 mg/kg/day during postnatal days (PND) 11–20 and, as adults (PND193–212), were administered seven daily injections of 2.0 mg/kg amphetamine. Both locomotor activity and stereotypic behavior were assessed following the first and seventh injections. Control males and females showed sensitized behavior following repeated amphetamine injections with females showing greater locomotion while males showed increased stereotypy. Male rats pretreated with cocaine failed to develop sensitized locomotor or stereotypic responses following repeated amphetamine injections consistent with dampened D_1 receptor activity. Females pretreated with cocaine did not show a sensitized locomotor response but did display sensitization of stereotypy following repeated amphetamine administration. Thus, it appears that postnatal cocaine treatment produces differential effects on the circuits mediating sensitization behavior in male and female rats.

Keywords: Behavioral sensitization; Stereotypy; Locomotor activity; Prenatal cocaine; Substance abuse

1. Introduction

The impact of cocaine during development on behavioral and neurochemical measures is important to examine. Events occurring in brain development during the third trimester of human gestation approximately correspond to events occurring during postnatal day (PND) 4 to 19 of the Sprague–Dawley laboratory rat (Bayer et al., 1993). Our laboratory has identified multiple behavioral and neurochemical alterations following daily cocaine treatment during PND11–20. This postnatal cocaine treatment prevented the development of sensitization to apomorphine, a direct D_1/D_2 dopamine (DA) agonist, in male adults (Busidan and Dow-Edwards, 1999; Seeman, 1995). In addition, the expression of prodynorphin mRNA, a marker sensitive to D_1 receptor stimulation, was decreased in the shell of the nucleus accumbens in adult cocaine-pretreated males (Dow-Edwards and Hurd, 1998). Males were also observed to display a reduced locomotor response to an SKF 82958 (D_1 agonist) challenge (Dow-Edwards and Busidan, 1998) while females showed a reduced locomotor response to acute amphetamine (Hughes et al., 1991). Alterations in glucose metabolism were also shown to depend upon gender. Adult females pretreated with cocaine showed increases in glucose metabolism in the caudate nucleus (Dow-Edwards et al., 1993; Frick and Dow-Edwards, 1995) while males pretreated with cocaine showed decreases in glucose utilization in the accumbens when compared with control animals (Dow-Edwards et al., 1993). While other groups have examined the effects of cocaine administration during PND11–20 and found no significant changes in exploratory activity under baseline conditions (Vorhees et al., 2000). No other groups have examined sensitized behavior following postnatal cocaine. Taken together, these data suggest that preweanling cocaine exposure alters functional development such that exposed adult males show reduced mesolimbic D_1 receptor-medi-

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ated responses while females displayed enhanced nigrostriatal activity.

The present study examined the behavioral responses following repeated D-amphetamine administration in male and female offspring treated with cocaine during PND11–20. Amphetamine is known to increase DA release from presynaptic terminals and inhibit the reuptake of DA from the synaptic cleft, thus indirectly increasing activity in DA circuits (Kuczenski, 1983). Repeated intermittent administration of amphetamine has been shown to result in an enhanced behavioral response (i.e., sensitization) as assessed by measuring either locomotor activity (e.g., Aizenstein et al., 1990; Cadoni et al., 2000; Camp and Robinson, 1988; Laudrup and Wallace, 1999; McNamara et al., 1993; Robinson and Becker, 1986; Segal and Kuczenski, 1987) associated with the mesolimbic DA system (e.g., Cador et al., 1995; Hitzemann et al., 1980; Kalivas and Weber, 1988; Paulson and Robinson, 1991) and/or stereotypic behavior (e.g., Aizenstein et al., 1990; Camp and Robinson, 1988; Huang et al., 1995; Richtand et al., 1997; Robinson and Becker, 1986; Segal and Kuczenski, 1987) related to nigrostriatal DA function (e.g., Asher and Aghajanian, 1974; Creese and Iversen, 1975; Hitzemann et al., 1980). It was hypothesized that the cocaine-pretreated males would not develop a sensitized locomotor response to amphetamine but that females pretreated with cocaine would show increased stereotypic responses following repeated amphetamine treatment.

2. Methods

2.1. Animals

Male and female offspring of Sprague–Dawley rats (VAF strain, Charles River Laboratories, Wilmington, MA) were housed in our AAALAC-approved vivarium (20–22°C, 12L/12D cycle). All subjects were administered 50 mg/kg/day cocaine HCl ($n=24$) or distilled water (10 ml/kg, $n=23$) subcutaneously from PND11–20. Cocaine HCl (NIDA, Research Triangle Park, NC) was dissolved in distilled water (5 mg/ml). This cocaine dose was found to produce clinically relevant blood cocaine levels in rats (Dow-Edwards, unpublished data). The subcutaneous route of administration has been used within this model for over 15 years and results in minor temporary reductions in body weight. Subjects came from a total of 16 litters where 8 litters were administered water while the other 8 litters were given cocaine. These treatments did not vary within litter.

Animals were weaned on PND21, housed in same-sex pairs in plastic tubs with wood chips, and allowed ad lib access to Purina Rat Chow and water. Rats were ear-clipped for identification purposes and weighed every 4 days until behavioral testing began. The animals were gentled prior to testing. All procedures were approved by the SUNY Institutional Animal Care and Use Committee.

2.2. Behavioral procedures

Beginning between PND193 and 212, animals were injected intraperitoneally with 2.0 mg/kg amphetamine or saline (1.0 ml/kg) for seven consecutive days. D-Amphetamine sulfate (Sigma, St. Louis, MO) was dissolved in physiological saline (0.9% sodium chloride, 2.0 mg/ml). This locomotor sensitizing amphetamine dose and injection regimen was adapted from Segal and Kuczenski (1987). Each subject was injected at approximately the same time each day. Locomotor activity was assessed beginning 60 min postinjection on Trials 1, 4, and 7. Animals were placed within one of three open Plexiglas bins ($42 \times 42 \times 30$ cm, with no wood-chip bedding). Each bin was surrounded by a Digiscan Activity Monitor (model RXYZCM, Accuscan, Columbus, OH) connected to a Digiscan Analyzer (model V6.1B) that was controlled by a Dell 450i computer with Digipro 1.5 software. Each Plexiglas bin and Digiscan Monitor was contained within an off-white laminate sound-attenuating chamber measuring $60 \times 60 \times 37$ cm inside equipped with two 4-W bulbs for illumination and a fan (model 30 CFM, Dayton). Each locomotor activity session was 60 min in duration where only total distance traveled (cm) was collected in twelve 5-min blocks (Busidan and Dow-Edwards, 1999).

To allow for blind behavioral observations, Trials 1 and 7 were videotaped using an RCA video camera through a one-way mirror measuring 30 cm^2 centered on top of the laminate chamber. S.M.M., unaware of the treatment conditions, analyzed the videotapes using Observer 3.0 (Noldus, The Netherlands). Each 60-min session was divided into six time blocks and the last 60 s of each time block was observed. Time (seconds) spent in each behavior included: nonstereotypic sniffing (≥ 1 s), grooming (scratching or licking head or body ≥ 1 s), rearing (standing on hind quarters with forelimbs free or in contact with the wall ≥ 1 s), locomotion (moving from 1 quadrant to another ≥ 2 s), and quiet (asleep or alert but not engaging any behavior ≥ 2 s). Stereotypy or purposeless repetitive movements of the head and body were separated into three categories of intensity: low (slight weaving of head beyond sniffing ≥ 2 s), medium (constant head weaving and slow patterned repetitive movements ≥ 2 s) and intense (swift vibration of head and/or the body ≥ 2 s). The total time spent in each behavior (maximum = 60 s) was summed for the each of the six observation periods and averaged within treatment groups.

Following Trials 1 and 4, each rat was returned to the homecage and the Plexiglas bin was thoroughly cleaned with diluted Joy antibacterial soap (1:10, soap/water) and rinsed. After injections on Days 2, 3, 5, and 6, rats were immediately returned to the homecage. Immediately follow-

Table 1
Body weights during PND11–20 and on first day of behavioral testing

	Water-female	Water-male	Cocaine-female	Cocaine-male
Day 11	28.2 ± 1	28.7 ± 1	27.2 ± 1	28.3 ± 1
Day 20	52.8 ± 2	54.9 ± 2	46.5 ± 2	48.1 ± 2
Test day	349.8 ± 11	628.9 ± 32	361.1 ± 10	610.3 ± 17

Weight in grams ± S.E.M. $n = 11–12$/group.

ing Trial 7, female rats were vaginally smeared and the experiment terminated.

2.3. Statistical analysis

Data from three subjects were incomplete due to videotaping malfunctions and were, therefore, not included in any of the behavioral analyses. Data collected from the Digiscan monitor was analyzed in four-way analysis of variance (ANOVA) with pretreatment (cocaine or water), drug (amphetamine or saline), gender (male or female) as between-subjects variables and the repeated measure, test trial (Trials 1 and 7) using SYSTAT. Trial 4 data were not included within these analyses since Trial 4 was not videotaped for stereotypy assessment. To assess changes in behavioral drug responses (i.e., sensitization) across the test trials within pretreatment and gender, amphetamine responses were compared to saline responses with t tests corrected for multiple comparisons (Bonferroni) within each pretreatment/gender group.

Behaviors observed on the videotapes (time spent in seconds) were analyzed in separate four-way ANOVAs with drug (amphetamine or saline), pretreatment (cocaine or water), gender as between-subjects variables, and trial (1 or 7) as a within-subjects variable. The Fisher's LSD post hoc comparison was used to reveal Trial 1 and 7 differences (i.e., sensitization) within the Pretreatment and Gender groups. The observer reliability Pearson correlation coefficient was found to be $r = .959$ when 10 sessions were rescored and correlated. Interobserver reliability was not an issue since only one observer scored the videotapes. Data were expressed as means ± S.E.M. and $P < .05$ was considered statistically significant.

3. Results

3.1. Mortality and body weight

A total of 3 out of 152 pups died during cocaine treatment (2 cocaine-males, 1 cocaine-female, and 0 vehicle-treated). Body weight was analyzed in a gender × pretreatment pretreatment ANOVA on PND11, 20, and the first amphetamine test day. No gender or pretreatment differences were found on PND11. Cocaine treated rats weighed less than vehicles controls on PND20 [$F(1,43) = 13.338$, $P < .002$] but by the first amphetamine test day this difference had disappeared. Males weighed more than females on the first amphetamine test day [$F(1,43) = 179.086$, $P < .001$]. Mean body weights for each Pretreatment and Gender group are presented in Table 1.

3.2. Total distance traveled (Digiscan)

The four-way ANOVA revealed a significant main effect of Drug [$F(1,36) = 51.445$, $P < .001$]. Amphetamine-injected rats traveled more distance than saline-injected animals. Further, a reliable interaction of Gender × Pre-Pretreatment × Trial was revealed [$F(1,36) = 5.804$, $P = .021$]. Total distance traveled is shown for each gender, pretreatment, and drug group during Trials 1 and 7 in Fig. 1. Since the omnibus four-way interaction was not significant, Bonferroni corrected t tests were used to determine the effect of amphetamine versus saline injections for each pretreatment/gender group. The water-pretreated females given amphetamine showed significantly higher total distance traveled than saline controls during Trial 7 [$t(5.4) = 4.233$, $P = .014$]. In contrast, cocaine-pretreated females injected with amphetamine displayed more distance traveled than the saline-injected animals only during Trial 1 [$t(5.2) = 3.476$, $P = .033$]. In Trial 7, a significantly

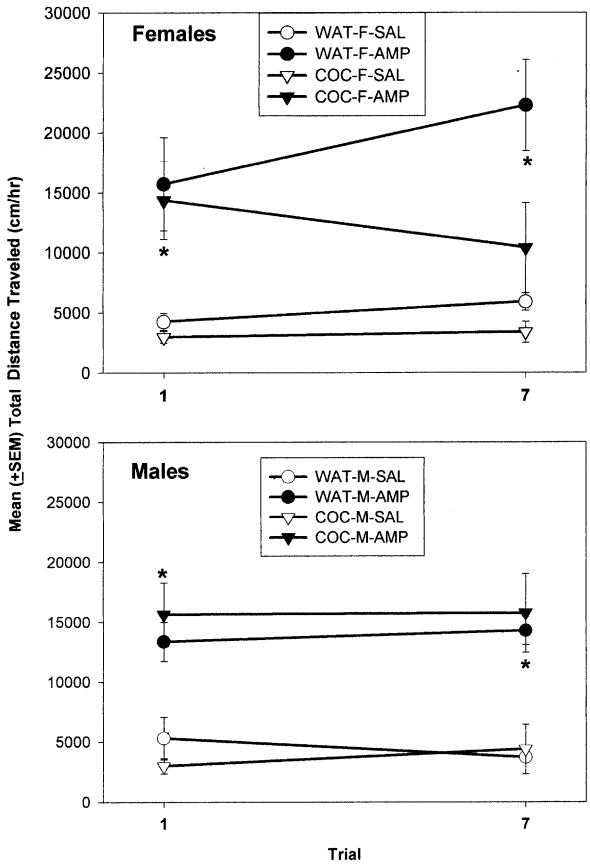

Fig. 1. The mean (± S.E.M.) total distance traveled (cm/h) during Trials 1 and 7 are shown for each Pretreatment and Gender group injected with either saline (SAL, $n = 5–6$) or amphetamine (AMP, $n = 5–6$). * Indicates significantly different from the saline group ($P < .034$, Bonferroni corrected t test).

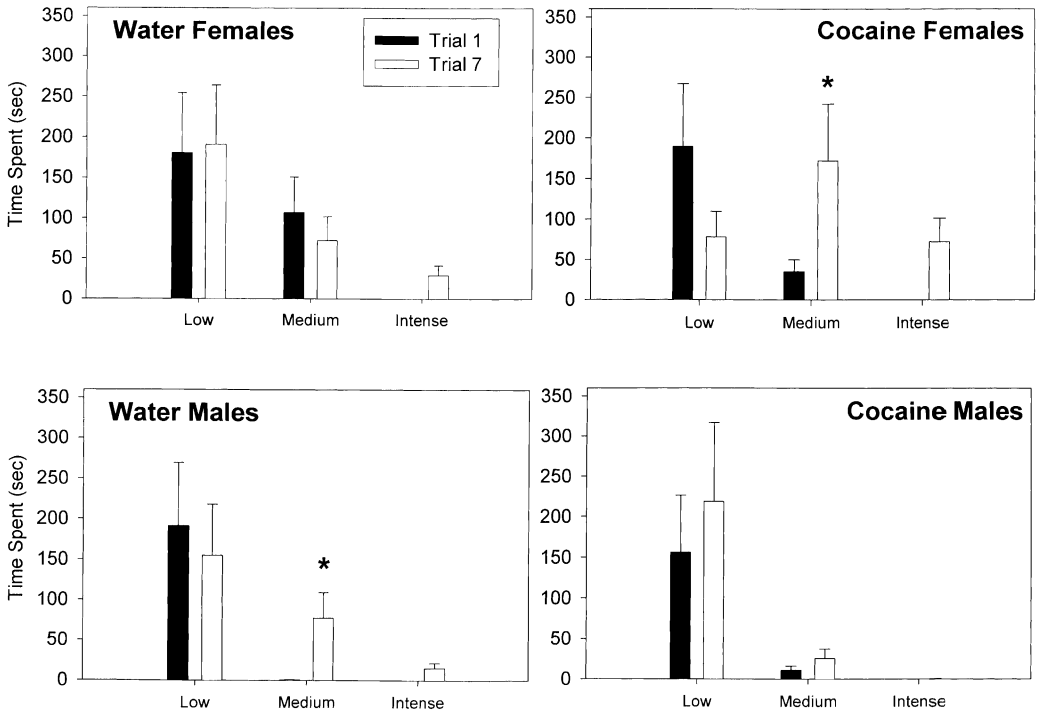

Fig. 2. The mean (±S.E.M.) time spent (seconds) in low, medium, and intense stereotypy are displayed for each Pretreatment and Gender group on Trials 1 and 7 following amphetamine administration. The cocaine-females and the water-males significantly increased medium stereotypy from Trial 1 to 7 (* $P<.05$, Fisher's LSD).

greater distance traveled under amphetamine conditions was seen for the male water-pretreated rats [$t(4.7)=9.268$, $P=.001$]. On the other hand, cocaine-pretreated males showed a significant increase following amphetamine injection compared to saline-injected rats only during Trial 1 [$t(5.8)=4.588$, $P=.008$] (Fig. 1).

3.3. Behavioral observations

Overall, amphetamine-injected rats spent significantly more time rearing ($P=.017$) and in locomotion ($P<.001$), but reliably less time in grooming ($P<.001$), quiet ($P<.001$), and nonstereotypic sniffing ($P<.001$) than saline-injected animals. In general, males groomed more than females ($P=.032$). Sniffing decreased from Trial 1 to 7 [$F(1,36)=6.360$, $P=.016$]. A reliable Pretreatment × Gender × Trial interaction was found for rearing [$F(1,36)=5.767$, $P=.022$] where cocaine-females and water-males showed decreased rearing across trials while water-females showed increased rearing across trials and cocaine-males maintained time spent rearing. Overall, however, relatively little rearing was seen (< 14 s of 360 total seconds) (data not shown).

Pretreatment significantly affected medium stereotypy as a significant four-way interaction was found [$F(1,36)=5.072$, $P=.031$] when analyzed in a Pretreatment × Gender × Drug × Trial ANOVA. Fisher's LSD post hoc comparisons revealed that the cocaine-pretreated females ($P<.002$) and water-pretreated males ($P<.049$) showed increased medium stereotypy from Trials 1 to 7 under amphetamine conditions. Cocaine-pretreated males showed only a slight increase in medium stereotypy with repeated amphetamine administration (Fig. 2).

4. Discussion

Only the water-pretreated female control group showed increased total distance traveled following repeated amphetamine administration consistent with the development of sensitization of locomotor activity (e.g., Cadoni et al., 2000; Laudrup and Wallace, 1999; Segal, 1975; Segal and Kuczenski, 1987). On the contrary, the water-pretreated males showed a development of sensitization as measured by stereotypy of medium intensity. Typically, females show more robust sensitization than males (Camp and Robinson, 1988; Robinson and Becker, 1986). Thus, while the present dose and injection regimen were not sufficient to induce locomotor sensitization in the male rats, sensitization of stereotypy was observed. The lack of consistent pairing of amphetamine with the locomotor chambers, use of a short observation period, and the lack of control for the female estrous cycle may account for the relatively small amount of sensitization.

Offspring pretreated with cocaine regardless of gender either showed no increase in distance traveled or reduced distance traveled with repeated amphetamine administration (Fig. 1). These results are similar to the finding that cocaine-

pretreated animals fail to develop a sensitized response following repeated apomorphine administration (Busidan and Dow-Edwards, 1999). In addition, seven daily injections of 1.5 mg/kg amphetamine did not produce locomotor sensitization in males regardless of prenatal cocaine treatment (Glatt et al., 2000). However, despite the experimental conditions used in the present study, cocaine-pretreated females developed a robust sensitization to amphetamine as measured by stereotypy of medium intensity.

The water-pretreated females and cocaine-pretreated males showed very little change in stereotyped behavior comparing the first and last test days following repeated amphetamine administration (Fig. 2). However, both the water-pretreated males and cocaine-pretreated females showed reliable increases in medium stereotypy time across trials indicative of the development of sensitization of stereotyped behavior. Others have found sensitization of stereotypic behaviors with repeated amphetamine injections in rats (e.g., Aizenstein et al., 1990; Camp and Robinson, 1988; Huang et al., 1995; Richtand et al., 1997; Robinson and Becker, 1986; Segal and Kuczenski, 1987), however, typically a longer span of observation has been employed. For example, 2, 3, or 4 h of observation reveals that immediately following an amphetamine injection is a period of hyperactivity which is followed by a phase of focused stereotypy and then another locomotor activity phase (Leith and Kuczenski, 1982; Robinson and Becker, 1986; Segal, 1975; Segal and Kuczenski, 1987). When amphetamine is repeatedly administered, the onset of the stereotypy phase appears earlier and the stereotypy is more intense while the poststereotypy locomotor activity phase becomes more intense as well (Leith and Kuczenski, 1982; Segal, 1975; Segal and Mandell, 1974). Thus, it is possible that the cocaine-pretreated females of the present study may have displayed a prolonged stereotypic phase during the time of observation (60–120 min following amphetamine injection) while the water-pretreated females had already progressed to the poststereotypy hyperactive phase. Clearly, a more prolonged assessment of the behavioral response is warranted. Following prenatal cocaine (20 mg/kg sc, twice/day, gestational days 15–21), male rats were found to increase stereotyped sniffing after repeated amphetamine administration (1.5 mg/kg ip × 7 days) (Glatt et al., 2000). While these data appear inconsistent with our own, different cocaine exposure times should affect different developmental events and thus manifest in different behavioral outcomes.

The present results are consistent with the findings of glucose metabolism studies previously reported by our laboratory. Females pretreated with cocaine during PND11–20 showed an increase in glucose metabolism in the caudate nucleus as compared with water-pretreated control females (Dow-Edwards et al., 1993; Frick and Dow-Edwards, 1995). This area and the associated nigrostriatal pathway has been shown through lesion and microinjection studies to mediate stereotypic behavior induced by amphetamine (e.g., Asher and Aghajanian, 1974; Creese and Iversen, 1975; Hitzemann et al., 1980). Thus, it is not surprising that the cocaine-pretreated females displayed an enhanced stereotypic response to repeated amphetamine since cocaine-pretreated females show increased functional activity in the caudate–putamen under baseline conditions well into adulthood.

Repeated amphetamine injections in the current study of males pretreated with cocaine during PND11–20 did not result in the enhancement of locomotion, stereotypy, or any observed behavior. Male rats pretreated with cocaine were previously reported to exhibit a dampened behavioral response to a D_1 selective agonist (Dow-Edwards and Busidan, 1998), a failure to develop a sensitized behavioral responses to apomorphine (Busidan and Dow-Edwards, 1999), a reduction in accumbens mRNA associated with D_1 receptors (Dow-Edwards and Hurd, 1998), and a decreased glucose metabolism in the nucleus accumbens (Dow-Edwards et al., 1993). The mesolimbic DA pathway has been implicated in the expression of amphetamine-induced locomotion (e.g., Cador et al., 1995; Hitzemann et al., 1980; Kalivas and Weber, 1988; Paulson and Robinson, 1991) and D_1 receptors have been shown to be necessary for the production of locomotor sensitization (Vezina, 1996). Thus, the present findings support an effect of PND11–20 cocaine in dampening D_1 responses of the mesolimbic system in male offspring.

These sex differences in behavior reported within the present study could be accounted for by a gender difference in sensitivity to the amphetamine regimen utilized. Control females increased locomotor activity while the control males increased medium stereotypy following the same dose, injection, and observational period. Again, the sampling of behaviors sooner after amphetamine injection may alter this conclusion. It is also possible that male and female rats may be undergoing different developmental changes during the cocaine administration. Differences in cocaine brain levels cannot account for the observed behavioral differences since cocaine brain concentrations did not vary with gender (unpublished data). However, gonadal steroids may influence the brain's response to cocaine (e.g., Sell et al., 2000; Sircar and Kim, 1999).

In summary, the present study found that female rats pretreated with cocaine during PND11–20 sensitized to amphetamine-induced stereotypy but not locomotor activity while male rats pretreated with cocaine did not develop sensitization of any behavioral category. Thus, postnatal cocaine exposure may differentially affect the nigrostriatal DA system and the mesolimbic DA pathway in male and female rats.

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