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Behavioral Responses to a D_1 Dopamine Agonist in Weanling Rats Treated Neonatally with Cocaine and Δ^9-Tetrahydrocannabinol

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MEYER, J. S. AND R. KUNKLE. *Behavioral responses to a D_1 dopamine agonist in weanling rats treated neonatally with cocaine and Δ^9-tetrahydrocannabinol.* NEUROTOXICOL TERATOL **21**(4) 375–380, 1999.—We determined whether neonatal exposure to cocaine with or without Δ^9-tetrahydrocannabinol (THC) altered the behavioral responses of weanling rats to the full D_1 dopamine (DA) agonist SKF 81297. Rats were injected SC once daily from postnatal day (PD) 1 through 5 with cocaine (20 mg/kg), the same dose of cocaine plus THC (10 mg/kg), or drug vehicle. On PDs 24, 25, or 26, male and female littermates were administered 3 or 10 mg/kg of SKF 81297 or saline vehicle, and then tested 15 min later in an open-field apparatus. Neither neonatal drug treatment nor gender influenced the behavioral responses to SKF 81297. The drug challenge did, however, produce several dose-dependent behavioral effects, including increases in locomotor activity, line crossing, sniffing, and headshakes, and a decreased incidence of rearing, grooming, and stationary behavior. Furthermore, even though earlier administration of cocaine and THC failed to alter D_1 receptor sensitivity, animals in both neonatal treatment groups exhibited an overall increase in grooming behavior and a decrease in sniffing compared to controls when the results were combined across doses of SKF 81297. These findings indicate that early postnatal exposure to cocaine can alter certain behaviors independently of functional changes in the D_1 receptor system.

Cocaine Neonatal Dopamine D_1 receptors Behavior SKF 81297 Δ^9-Tetrahydrocannabinol Rat

MANY studies investigating the neurobehavioral consequences of developmental cocaine exposure have focused on the dopaminergic system. One putative mechanism by which cocaine alters dopaminergic development involves occupancy and blockade of plasma membrane dopamine (DA) transporters in the fetal brain (18). By inhibiting DA reuptake, cocaine might increase the activation of fetal DA receptors such as the D_1 receptor.

In the human fetal brain, D_1 receptor mRNA and receptor binding have been detected as early as the latter part of the first trimester (2,35). Receptor expression in the striatum is initially patchy, with a predominant localization to striosomes (6). By late fetal development, however, D_1 receptors display the more homogeneous distribution characteristic of the adult striatum. In fetal rats, polymerase chain reaction (PCR) enabled detection of D_1 receptor mRNA in the forebrain on gestational day (GD) 11, followed by a large increase in the hybridization signal at GD 18 (7). Despite this late gestational rise in D_1 receptor gene expression, striatal D_1 receptor binding is low at birth in rats and rises rapidly during the first 2–3 postnatal weeks (30,36). Interestingly, D_1 receptors in rats are preferentially localized to the striosomal compartment from birth until 10 days of age (23), suggesting that early postnatal development of this receptor subtype in rats corresponds to the late fetal period (third trimester) in humans. Consequently, neonatal cocaine treatment of rats may serve as a reasonable

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model of third trimester human exposure, at least with regard to potential effects on the developing dopaminergic system.

Several previous studies have examined the influence of neonatal cocaine administration on various aspects of DA function. Cocaine acutely inhibited DA turnover in the forebrain but not the brainstem when given as a single dose of 30 mg/kg to rat pups on postnatal day (PD) 1 or 7 (32). Chronic administration of cocaine to pups produced a variety of effects measured prior to or at weaning age, including reduced DA overflow and an altered striatal distribution of D_2 receptor-expressing cells (15), and a sensitization of certain behavioral responses to the D_1 agonist SKF 38393, the D_2 agonist quinpirole, or combinations of these compounds (5). Adult rats treated with cocaine neonatally were found to respond more strongly to a low dose of amphetamine (16), and to display reduced striatal D_1 receptor binding and impaired behavioral responsiveness to high doses of SKF 38393 (27). Although these disparate results, which may reflect significant differences in drug treatment regimens across studies, do not lend themselves to a simple interpretation, they do show that early postnatal administration of cocaine can produce both short- and long-term changes in the dopaminergic system.

Cocaine-using women almost always consume other substances as well, both licit (tobacco and alcohol) and illicit (marijuana and opiates). Such polydrug abuse may play an important role in the neurological and behavioral findings reported for cocaine-exposed infants (34). Indeed, a recent study found that maternal use of marijuana as well as cocaine was significantly related to elevated circulating norepinephrine concentrations in neonates (20). Other substances such as tobacco and alcohol have likewise been reported to influence the behavior of cocaine-exposed offspring on the Brazelton Neonatal Behavioral Assessment Scales (8). Unfortunately, polydrug abuse during pregnancy has received relatively little attention in the animal literature to date.

The purpose of the present study was to determine whether coadministration of Δ^9-tetrahydrocannabinol (THC), the principle active agent in marijuana, would alter the behavioral effects of neonatal treatment with cocaine. We were particularly interested in behavioral responses to D_1 receptor stimulation, given the probable colocalization of these receptors with cannabinoid receptors in a subset of projection neurons in the corpus striatum (13). D_1 receptors are positively coupled to adenylyl cyclase, whereas cannabinoid receptor activation leads to an inhibition of cyclase activity (10). As cocaine indirectly stimulates DA receptors due to its reuptake-blocking effects, we hypothesized that coadministration of THC might reduce cocaine's influence on the development of the dopaminergic system. We accordingly challenged weanling subjects with a selective D_1 receptor agonist, namely the full agonist SKF 81297 (1), rather than the partial agonist SKF 38393 that has been used in previous studies of cocaine-exposed animals.

METHOD

Animals

The animals were Sprague–Dawley rats derived from Charles River CD strain. Nulliparous females approximately 3 months of age were bred in the laboratory with stud males. Prior to delivery, the dams were transferred to standard plastic tubs with a bedding of pine shavings. They were given Formulab 5008 rodent diet (PMI Feeds, St. Louis, MO) and tap water ad lib, and they were maintained under a 14:10 light:dark cycle (lights on at 0600 h) at a temperature of approximately 22°C. Litters were culled to eight pups each (sex balanced when possible) on PD 1, and remained with their mothers until the day of behavioral testing.

Neonatal Drug Administration

Litters were randomly assigned to one of three treatment groups (n = 9 litters per group): cocaine only (COC), cocaine plus THC (COC-THC), and vehicle (VEH). We had initially planned to administer twice-daily injections of 20 mg/kg cocaine with or without 10 mg/kg THC for 10 days. During preliminary studies, however, these treatment regimens led to high rates of pup mortality, despite the fact that some other laboratories have reported successful use of even higher cocaine doses in neonatal rats (5,16). After testing several variations of dosing and length of treatment, we found satisfactory growth and survival of pups with the above-mentioned doses given once daily for 5 days. Consequently, the COC group received SC injections (0.05 ml/10 g body weight) of 20 mg/kg cocaine HCl in vehicle from PD 1 through PD 5, the COC-THC group received 20 mg/kg of cocaine HCl and 10 mg/kg of THC together in the same vehicle, and the VEH group received injections of vehicle only [5% absolute ethanol, 5% of the emulsifying agent Cremophor EL (BASF Corp., Mount Olive, NJ), and 90% physiological saline]. While away from the litter, pups were kept in an incubator maintained at approximately 33°C. All injections occurred between 0900 and 1100 h.

Behavioral Testing

Three male and three female pups from each litter were tested once on either PD 24, 25, or 26. The apparatus was a 30 × 30 × 33-cm open field with a glass floor and walls. The floor of the open field was marked with a grid of four 15 × 15 cm squares. On the day before testing, each animal was habituated to the test apparatus for 15 min.

On the day of testing, the animals received a SC injection of either saline, 3.0 mg/kg, or 10.0 mg/kg of SKF 81297 (2,3,4,5-tetrahydro-6-chloro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine HBr; Research Biochemicals Inc., Natick, MA) (0.8 ml/100 g body weight, dissolved in saline). These doses are based on a preliminary experiment performed with untreated weanlings, and they are within the upper range of doses used in previous studies of adult rats (9,14,31). Fifteen minutes after the injection, each animal was placed in the open field for a period of 10 min, during which time its behavior was videotaped from above. Behavioral testing was conducted between 0900 and 1400 h. All doses were tested in both genders from each litter.

The videotapes were scored by two trained raters who were blind to both the neonatal treatment and drug challenge status of the animals. One rater counted the absolute frequency of line crossings (defined as both front paws crossing a line) and head shakes during the entire 10-min test period. The second rater used a time-sampling procedure in which the following behaviors were scored for their presence or absence every 5 s: locomotion (ambulation), rearing, grooming, sniffing, and stationary behavior (absence of locomotion or any of the other behaviors listed). The choice of behaviors to be measured was based on several considerations. First, locomotor activity, grooming, and sniffing were previously shown to be increased in preweanling rats treated with the partial D_1 agonist SKF 38393 (17,22,33). Second, head shaking and rearing were included because these behaviors appeared to be altered in the preliminary dosing experiment mentioned above. Finally, we assessed stationary behavior in case any of our treatment groups displayed a generalized decrease in behav-

TABLE 1

OFFSPRING BODY WEIGHT GAIN DURING TREATMENT AND WEIGHT AT TIME OF TESTING

Group	Gender	Weight Gain From PD1-5 (g)	Weight at Testing (g)
Vehicle	M	6.4 ± 0.2	84.8 ± 3.4*
	F	6.0 ± 0.2	77.1 ± 2.5
Cocaine	M	5.6 ± 0.2	80.4 ± 2.6*
	F	5.7 ± 0.2	76.9 ± 2.0
Cocaine + THC	M	5.9 ± 0.2	81.1 ± 2.3*
	F	5.5 ± 0.2	75.2 ± 1.4

All males and females were averaged for each litter. Values shown represent mean ± SEM for $n = 9$ litters per group.

*Denotes a significant gender difference ($p < 0.001$).

ioral activity that might not be detected just from reduced locomotion. It should be noted that, taken together, these categories constitute all of the behavioral responses observed in the present subjects in the above-described test setting.

Statistical Analysis

All data were analyzed using two- and three-way analyses of variance (ANOVA) performed with the SYSTAT (SYSTAT, Inc., Evanston, IL) statistical software package. Neonatal treatment and challenge dose were between-subject variables, whereas gender was considered a within-subject variable to avoid litter effects. Post hoc analyses of treatment main effects were conducted by means of orthogonal contrasts using simple one-way ANOVAs. The two degrees of freedom available for these contrasts were used to compare the combined drug-exposed groups against the vehicle controls, and to compare one drug-exposed group against the other. Dose effects of SKF 81297 were analyzed using Tukey's post hoc tests.

RESULTS

Body weight gain of the animals between PD 1 and PD 5, and body weight at the time of drug challenge are shown in Table 1. There was a nonsignificant trend toward a treatment effect on weight gain, $F(2, 24) = 2.91$, $p = 0.07$, which was related to the fact that the COC and COC-THC litters both tended to gain less weight than VEH litters during the period of drug treatment. There was a similar nonsignificant trend for males to gain more weight than females during the treatment period, $F(1, 24) = 3.47$, $p = 0.07$. At PD 25 when the animals were tested, there was no influence of treatment on body weight; however, males weighed significantly more than females at this time, $F(1, 24) = 54.74$, $p < 0.001$.

There was no influence of either neonatal drug treatment or gender on behavioral responses to SKF 81297. There were

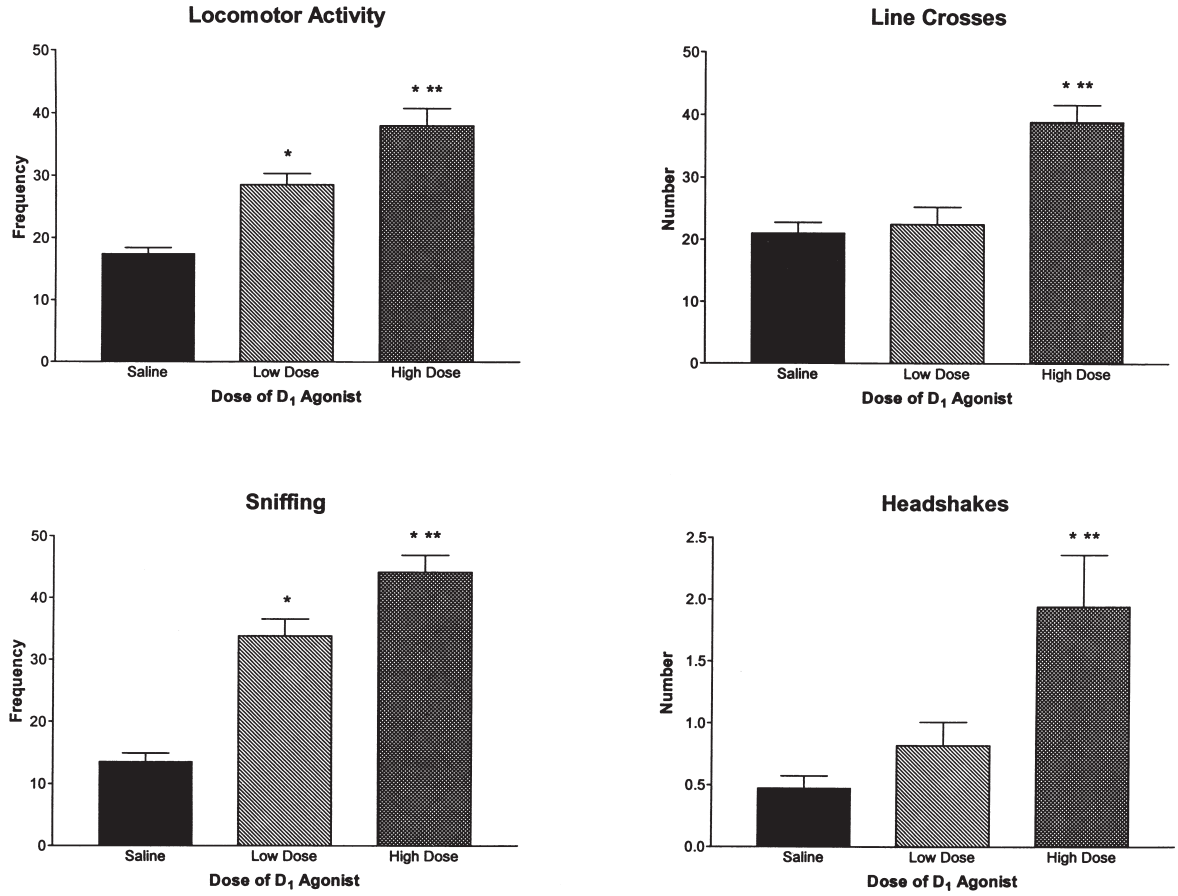

FIG. 1. Behaviors stimulated by low (3 mg/kg) and high (10 mg/kg) doses of the D_1 agonist SKF 81297. Data (mean ± SEM) are pooled across neonatal treatment and gender. *Significantly different from the saline control group (at least $p < 0.05$). **Significantly different from the low-dose group (at least $p < 0.05$).

clear dose-dependent effects, however, of this compound on weanling behavior. Behaviors stimulated by the D_1 agonist included locomotor activity, $F(2, 75) = 19.89$, $p < 0.001$, line crossing, $F(2, 75) = 5.87$, $p = 0.004$, sniffing, $F(2, 75) = 35.23$, $p < 0.001$, and head shakes, $F(2, 75) = 4.53$, $p = 0.014$ (see Fig. 1). This drug challenge also led to significant decreases in rearing, $F(2, 75) = 35.90$, $p < 0.001$, grooming, $F(2, 75) = 10.03$, $p < 0.001$, and stationary behavior, $F(2, 75) = 23.85$, $p < 0.001$ (Fig. 2).

Although administration of cocaine with or without THC failed to alter D_1 receptor sensitivity in the subjects, there were main effects of neonatal treatment on two behaviors, thereby indicating functional alterations that were manifested independently of test condition (that is, dose of SKF 81297). As shown in Fig. 3, the neonatal drug treatments led to increased grooming, $F(2, 75) = 3.09$, $p = 0.051$, and decreased sniffing, $F(2, 75) = 4.39$, $p = 0.016$. In both cases, post hoc testing using orthogonal contrasts showed that the combined COC and COC-THC groups differed significantly from the VEH control group but did not differ significantly from each other.

DISCUSSION

There were three main findings from this study. The first finding is that administration of the full D_1 receptor agonist SKF 81297 to weanling rats led to dose-dependent increases in locomotor activity, line crossing, sniffing, and head shakes, and decreases in rearing, grooming, and stationary behavior in an open-field test situation. The second finding is that 5 days of neonatal treatment with either cocaine alone or cocaine plus THC did not alter behavioral responsivity to the subsequent drug challenge. Third, although the neonatal drug treatments failed to influence D_1 receptor sensitivity, they did produce a generalized increase in grooming and a decrease in sniffing behavior when the data were collapsed across doses of the D_1 agonist. Because the results were similar for the two treatment groups, it appears that these effects were largely due to cocaine with little or no modification by concomitant THC administration.

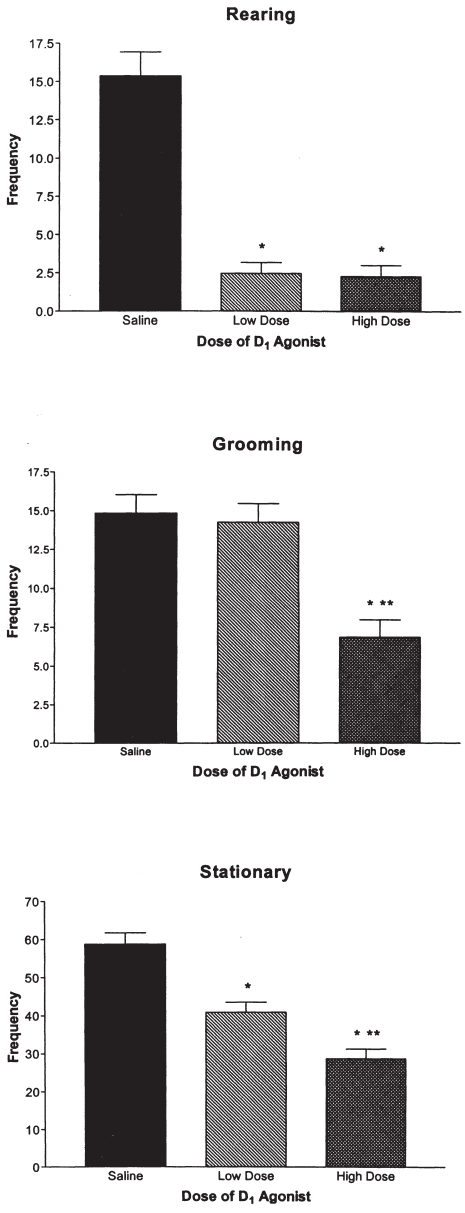

FIG. 2. Behaviors inhibited by low (3 mg/kg) and high (10 mg/kg) doses of the D_1 agonist SKF 81297. Data (mean ± SEM) are pooled across neonatal treatment and gender. *Significantly different from the saline control group (at least $p < 0.05$). **Significantly different from the low-dose group (at least $p < 0.05$).

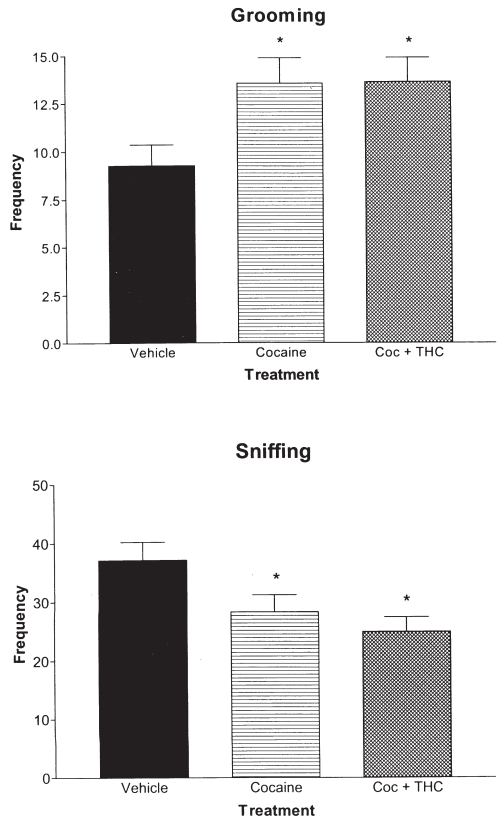

FIG. 3. Effects of neonatal treatment on behavior. Data (mean ± SEM) are pooled across dose of SKF 81297 and gender. *Combined COC and COC-THC groups are significantly different from the VEH controls (at least $p < 0.05$) but not from each other.

Administration of the partial D_1 agonist SKF 38393 has been found to stimulate locomotor activity and sniffing behavior in rat pups at PD 17 or 21 (17,22,33). The present results with SKF 81297 are consistent with these previous reports. However, there were two unexpected findings with the latter compound, namely the dose-related increase in head shakes and the significant decrease in grooming observed at the higher challenge dose. Head shaking is well known to be activated by serotonin 5-HT_2 receptors (26), and indeed, we only scored this behavior because we noticed its appearance during the collection of preliminary data. Interestingly, a recent study of adult rats found no head-shake response to either SKF 38393 (up to 40 mg/kg) or SKF 81297 (up to 10 mg/kg), although head shaking elicited by the 5-HT_2 agonist DOI was potently inhibited by D_1 receptor antagonists (31). The present results, therefore, suggest that D_1 receptor stimulation evokes this behavior in weanling animals, but the response is lost in adulthood. D_1 receptor mediation of the head shake response to SKF 81297 in weanlings could be tested by determining whether the response is blocked by pretreatment with a selective D_1 receptor antagonist. The SKF 81297-induced decrease in grooming was also surprising, because SKF 38393 was previously shown to stimulate grooming in both adult rats (21) and younger animals (17,22). The reason for the discrepant results with these two compounds is not clear at the present time.

Neonatal cocaine treatment failed to influence behavioral responsiveness to D_1 receptor activation at weaning age. It is unlikely that the 5-day treatment period was insufficient for a drug effect to occur, as Rock and Neal-Beliveau (27) found reduced sensitivity to a D_1 agonist following a mere 3 days of cocaine exposure (PD 0 to PD 2). Importantly, though, these investigators performed their behavioral testing when the subjects reached adulthood. Thus, certain DA-modulatory effects of neonatal cocaine administration may only emerge as the animals mature. In another recent study, Bowman et al. (5) showed that 5 days of cocaine treatment (30 mg/kg twice daily) from PD 14 to PD 18 resulted in sensitized responses to a low dose of SKF 38393 administered on PD 20. The cocaine dose used in the present study may have been too low to observe such sensitization, or more likely, the mechanisms underlying cocaine sensitization have not yet matured during the first week to 10 days postnatal [see (19)].

Addition of THC to the cocaine treatment likewise had no influence on the behavioral responses to SKF 81297. It is unlikely that this negative finding occurred because the dose of THC, 10 mg/kg, was too low. This dose is quite active behaviorally, and in adult rats repeated treatment with this dose leads to marked tolerance and reduced brain cannabinoid receptor binding (25). Fernández-Ruiz and co-workers have reported a number of effects of maternal THC or hashish administration on dopaminergic functioning of the offspring (4,11,12,24,28,29). These studies have typically involved relatively long-term cannabinoid treatment beginning early in gestation and continuing postnatally until weaning. Consequently, the negative results in the present study may be related more to the timing of the THC treatment than to the dose. Developmental effects of cannabinoids on the DA system may require a more extensive treatment period than used in the present study, or perhaps there is a critical period of pre- or postnatal development (other than PD 1–5) for cannabinoid modulation of dopaminergic function.

Despite their normal D_1 receptor sensitivity, the cocaine-exposed weanlings differed from controls in overall amounts of grooming and sniffing when the data were collapsed across doses of SKF 81297. To our knowledge, this is the first report of alterations in these behaviors following developmental cocaine administration. The nature of the mechanisms underlying these changes, and whether they will persist into adulthood, remain to be determined. Barron and Irvine (3) previously reported that a high dose of cocaine (60 mg/kg/day) given intragastrically from PD 4 to PD 9 led to elevated locomotor activity in both male and female rats at PD 18–21. The lack of a similar effect in the present study may reflect differences in treatment regimen and testing conditions compared to the experiment of Barron and Irvine.

In summary, neonatal rats were treated once daily for 5 days with either cocaine alone or cocaine plus THC, and then challenged with the full D_1 receptor agonist SKF 81297 at weaning age. The dopaminergic drug produced a number of behavioral effects; however, these effects were not modified by the earlier cocaine or THC administration. On the other hand, neonatal cocaine treatment was associated with several behavioral changes that have not been previously reported in cocaine-exposed offspring. These results suggest that early postnatal exposure to cocaine can lead to altered behavior patterns independently of functional changes in the D_1 receptor system.

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