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Behavioral Sensitization to Apomorphine in Adult Rats Exposed to Cocaine During the Preweaning Period: A Preliminary Study

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BUSIDAN, Y. AND D. L. DOW-EDWARDS. *Behavioral sensitization to apomorphine in adult rats exposed to cocaine during the preweaning period: A preliminary study.* PHARMACOL BIOCHEM BEHAV **63**(3) 417–421, 1999.—Sixty-day-old rats treated with cocaine (50 mg/kg SC) during postnatal days (PND) 11–20 received daily injections of apomorphine (2.0 mg/kg SC) for 10 consecutive days to examine the development of sensitization to a direct dopamine agonist. Behavior was monitored on days 1, 5, and 10, using a photobeam system, and on day 10 using the videotape assessments as well. Locomotor sensitization to apomorphine developed in the preweaning vehicle-treated males only. Neither the cocaine-treated males nor any females exhibited locomotor sensitization to repeated apomorphine injections at 2 mg/kg. There were no other treatment-related effects except for grooming, which showed an interaction between treatment and gender. Overall, every behavior analyzed showed significant apomorphine effects, except rearing. Margin time (wall hugging), grooming, and quiet were significantly decreased by apomorphine, while locomotion and the duration of sniffing were increased. In summary, these data indicate that with respect to locomotor activity, the development of sensitization to apomorphine at 2.0 mg/kg is prevented by preweaning cocaine administration in males. These data further suggest that developmental cocaine exposure produces long-term alterations in DA D_1 receptor-mediated responses in male rats. © 1999 Elsevier Science Inc.

Apomorphine Cocaine Behavioral sensitization Distance traveled Dopamine Gender differences

THE human brain undergoes development throughout the prenatal period of gestation as well as during a substantial portion of childhood. Although the exact timing of events relative to birth is not known, the state of maturation of the human brain at 20 weeks gestation is relatively equivalent with that of the rat on the day of birth (2). Therefore, the postnatal period in the rat approximates the later half of prenatal development in humans. For the past several years, our lab has been studying cocaine's effects during multiple postnatal periods, and found that cocaine exposure during postnatal day (PND) 11–20 produces alterations in baseline glucose metabolism and in the behavioral responses to challenge drugs such as amphetamine and SKF 82958 in adult rats (5,6,10). Cocaine's effects are frequently dependent on the gender of the animal. For example, glucose metabolism is increased in multiple brain regions, including the nigrostriatal pathway, in females, and depressed in selected brain regions, including the mesolimbic system, in males (6). Males also show a depressed locomotor response to SKF 82958, a dopamine (DA) D_1 receptor agonist (5). Further studies have shown that cocaine-treated males exhibit long-term reductions in the expression of preprodynorphin mRNA, in the shell of the nucleus accumbens, an intracellular marker that is sensitive to D_1 stimulation (7). Together, these studies indicate that cocaine at 50 mg/kg during PND 11–20 enhances function in the nigrostriatal system in females, while in males it depresses D_1 responsiveness primarily in the mesolimbic DA system.

The current study examined the responses to a direct DA D_1:D_2 agonist, apomorphine (21), administered over a period of 10 days to adult rats exposed to cocaine during PND 11–20.

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Studies from other laboratories have shown that apomorphine progressively increases locomotor activity (sensitization) with repeated treatment, due to the stimulation of dopamine receptors (12–16). High doses of apomorphine (>1.0 mg/kg) act via the postsynaptic dopamine receptor to increase locomotor activity (12,13). Although the stimulation of dopamine D_2 receptors may enhance the development of sensitization to apomorphine, they are not sufficient because administration of a selective D_2 blocking agent such as sulpiride does not prevent the development of sensitization. The D_1-type receptors, however, are necessary because administration of a selective D_1 blocking agent such as SCH23390 prior to the apomorphine prevents the development of sensitization (16,17). Because D_1 receptor-mediated events are necessary for the development of behavioral sensitization to apomorphine, and there is a dampening of D_1 receptor-mediated responsivity following PND 11–20 cocaine administration in males, we hypothesized that preweaning cocaine would impair sensitization to repeated apomorphine administration in adulthood.

METHOD

Dosing and Subjects

SUNY Institutional Animal Care and Use Committee approved all procedures. Adult virgin female Sprague–Dawley rats (VAF strain, Charles River, Wilmington, ME) were mated in our AAALAC-approved vivarium (20–22°C; 12 L:12 D cycle, lights turned on at 0700 h) with males of the same strain. Upon detection of a sperm-positive smear on the following morning, referred to as gestation day 1 (G1), the females were weighed, housed individually, and left undisturbed until day of birth in 44 × 24 × 20-cm plastic cages containing wood chip bedding with ad lib food and water. On the day of birth, postnatal day 1 (PND1), the litter was culled to 10 pups, maintaining equal gender representation, if possible, and the pups were toe clipped for identification. From PND 11–20, all pups in a litter were administered daily subcutaneous (SC) injections of a randomly assigned treatment, 50 mg/kg cocaine HCl, or vehicle (sterile water, 5 μg/g body weight). On PND 21, the pups were weaned into same sex cages, ear clipped for identification and weighed every 4 days thereafter until 60 days of age.

Behavioral Measures

On day 60, each rat (females in a random phase of the estrous cycle) was subjected to the first of three behavioral studies, conducted on days 1, 5, and 10 of challenge drug injections. Between 1000–1400 h each rat was removed from its home cage, weighed (females subjected to vaginal smears before each behavioral study), injected subcutaneously with 2.0 mg/kg apomorphine HCl or saline (1.0 mg/kg body weight) and immediately placed in the open Plexiglas box (42 × 42 × 30 cm; with no wood chip bedding) of the Digiscan Activity Monitor [model RXYZCM (16), Accuscan, Columbus, OH] for 60 min of observation. The Digiscan Monitor has 48 infrared sensors spaced 2.5 cm apart, with 16 along each side for sensing horizontal activity and 16 sensors 10 cm from the floor of the box for sensing vertical activity. The Plexiglas box and Digiscan Monitor were within a white laminate chamber measuring 60 × 60 × 37 cm inside and containing two 6-watt light bulbs for illumination and a fan (model 30 CFM). Although the Digiscan Monitor collects information in 21 behavioral categories, we analyzed only distance traveled and margin time (defined as the time spent within 2.5 cm of the wall) because the other behavioral categories were either redundant (distance traveled equals horizontal activity), irrelevant (time in one corner vs another), or insensitive (stereotypy). Measures of rearing were not used, because data derived from direct observation using the videotapes are more accurate. Behaviors were collected in minute intervals and then subsequently collapsed into 5-min blocks to facilitate the analysis. Following the session, the rat was returned to its home cage and each box was washed with soap and thoroughly rinsed. Rats continued to receive daily subcutaneous injections of the same challenge drug (apomorphine or saline) for a total of 10 days while remaining in their home cages. On injection days 6–9, cage mates were separated into individual cages for 2–3 h following injection to avoid aggressive behavior, which developed following repeated apomorphine administration.

The behavioral sessions on day 10 were videotaped using a Panasonic video camera through a one-way window measuring 30 × 30 cm, and centered on the top of the laminate chamber. The videotapes were later analyzed using the Observer software (Noldus, The Netherlands) by an individual unaware of the gender, preweaning treatment, or challenge drug administered. The videotapes were scored by dividing the 60-min observation period into six 10-min time blocks and then viewing only the last minute of each time block. For each time block, the behaviors were scored in seconds, starting at minute 9, and included: sniffing (sniffing in one location on all fours for ⩾1 s; walking–sniffing (engaged in sniffing and walking simultaneously, ⩾2 s); rearing (subject is standing on hind legs with forelegs free in the air or in contact with a wall of the box, ⩾1 s), grooming (grooming or scratching head or body, ⩾1 s), rotation (circling in either direction ⩾2 360° circles); and quiet (subject not engaged in any behavior—may be asleep or awake ⩾2 s). The total duration of each behavior (maximum = 60 s) for each of the six time blocks was used to calculate group averages.

Prior to the data collection, the observer underwent training until there was less than a 5% difference in the behaviors scored on two sequential runs for 10 different sessions. Because a single observer examined all tapes, interobserver reliability was not a problem.

Drugs

Cocaine HCl (Sigma Chemical Co., St. Louis, MO) was dissolved in water (Baxter 5 μl/g body weight). Apomorphine HCl (Sigma Chemical Co.) dissolved in saline (Baxter, 1.0 ml/kg body weight) was stored in the freezer in vials wrapped in tin foil to minimize oxidation.

Statistics

Body weights were analyzed by a two-way analysis of variance (ANOVA) (gender by preweaning treatment) on postnatal days 11 and 20 and on the first day of challenge drug injection (day 60). Data for the behaviors collected on the 3 test days were analyzed by four-way ANOVA with preweaning treatment (50 mg/kg cocaine or vehicle), sex (m or f), and challenge drug (apomorphine or saline) as between-subject variables and the repeated measure, test day, as a within-subjects variable using SYSTAT. Challenge drug responses within treatment groups and genders were assessed using a *t*-test corrected for multiple comparisons (Bonferroni), with the response to saline serving as the control. Although the Digiscan monitor collected data during 60 1-min intervals,

TABLE 1
BODY WEIGHTS DURING PND 11–20 AND ON FIRST DAY OF BEHAVIORAL TESTING*

	VEH-m	VEH-f	COC-m	COC-f
Day 11	27.6 ± 1	26.5 ± 1	28.7 ± 1	28.4 ± 1
Day 20	49.8 ± 1	49.2 ± 1	52.0 ± 1	50.7 ± 1
Δ†	22.2 ± 1	22.8 ± 1	23.4 ± 1	22.3 ± 1
Day 60‡	389.7 ± 12	250.3 ± 6	422.0 ± 11	252.1 ± 9

*Weight in grams ± SEM.
†n = 17–21/group.
‡n = 10–13/group.

they were collapsed into 12 5-min blocks to simplify the analysis. These 12 blocks were subsequently collapsed to provide a single mean value for each behavior because there were no group-related differences within each session. The behaviors, which were collected only on the final day of testing from the videotape analysis, were analyzed using a three-way ANOVA for preweaning treatment (50 mg/kg cocaine or vehicle), challenge drug (apomorphine or saline), and gender. Data were expressed as mean ± standard error and a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Seven vehicle-treated litters and seven cocaine-treated litters were produced giving rise to 42 and 35 pups, respectively. The body weight differences of the animals in the cohort from which our subjects were drawn are shown in Table 1. Although the cocaine-treated males weighed slightly more than the control males at 60 days of age, this difference did not attain significance ($p = 0.053$). There were no significant main effects of preweaning treatment on body weights in the females.

Due to technical problems with the equipment, the data from only 48 subjects (10–13 rats/treatment group/gender) were available from the Digiscan Monitor. However, data from 70 rats (17–18 rats/ treatment group/gender) were included in the videotaped behavioral analysis.

Distance traveled (Digiscan Monitor)

The ANOVA for distance traveled produced a highly significant, $F(2, 80) = 4.943$, $p = 0.009$, four-way interaction between test day, gender, challenge drug, and preweaning treatment (Fig. 1). The vehicle-treated males showed an increase in distance traveled (sensitization) with repeated apomorphine administration across the 3 test days. Further analysis indicated that the apomorphine-injected vehicle-treated males showed significantly greater locomotor activity compared to their saline-injected controls on all of the days ($p < 0.0167$, t-test). Although the cocaine-treated males receiving apomorphine showed an increase in locomotor activity compared to the saline-injected males from the same preweaning treatment group on the first day of testing ($p < 0.0167$, t-test), this difference was not seen on subsequent test days. Neither the vehicle nor the cocaine-treated females receiving apomorphine displayed an increase of distance traveled across test days. In the vehicle-treated female group, apomorphine produced significantly greater locomotor activity than did saline on the first day of testing alone ($p < 0.0167$, t-test). This difference was not seen in the cocaine-treated females. There were no within-session treatment-related effects for distance traveled on any of the 3 test days (data not shown).

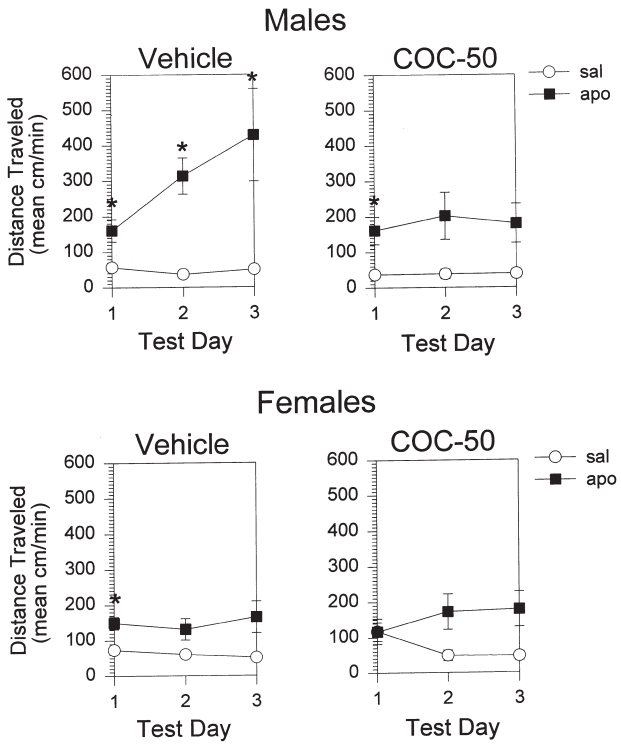

FIG. 1. Distance traveled (mean of 12 5-min blocks ± SEM, cm/min) during the three test days (injection days 1, 5, and 10) following an injection of 2.0 mg/kg of apomorphine or saline in adult rats treated with 50 mg/kg cocaine or vehicle during PND 11–20. Each line represents five to seven rats, with the saline-injected rats represented by open circles and the apomorphine-injected rats by filled squares. The * indicates a significant difference from the saline-injected rats of the same treatment/gender group ($p < 0.0167$, t-test).

In addition, there was a highly significant main effect of challenge drug, $F(1, 40) = 31.846$, $p < 0.001$, and an interaction between gender and challenge drug, $F(1, 40) = 4.973$, $p = 0.031$, with no main effect of preweaning treatment, $F(1, 40) = 1.255$, $p = 0.269$. There were also interactions between test day and gender, $F(2, 80) = 3.469$, $p = 0.036$, and test day and challenge drug, $F(2, 80) = 8.354$, $p = 0.001$.

Margin Time (Digiscan Monitor)

Margin time demonstrated a main effect of challenge drug, $F(1, 40) = 32.492$, $p < 0.001$, and test day, $F(2, 80) = 5.267$, $p = 0.007$. There was also a significant three-way interaction between test day, sex, and challenge drug, $F(2, 80) = 3.490$, $p = 0.035$. The apomorphine-injected rats show a decrease in margin time compared to the saline-injected control group. Although overall the males showed a lower margin time than the females on the first day of testing, this difference was not seen in subsequent test days (data not shown).

Observed Behaviors (on the Final Test Day)

To determine whether differences in locomotor behavior on the final day of testing may be due to the presence of com-

peting behaviors, such as stereotypic sniffing, the final test session was videotaped, and later the behaviors were scored. All of the behaviors scored from the videotapes showed highly significant ($p < 0.01$) main effects of challenge drug, except rearing. None of the behaviors produced significant main effects of preweaning treatment or gender. However, grooming produced a significant interaction between preweaning treatment and gender, $F(1, 62) = 5.345$, $p = 0.024$ (Fig. 2). Males that received preweaning cocaine showed greater amounts of grooming than the vehicle-treated males, while the vehicle-treated females showed greater amounts of grooming than the preweaning cocaine-treated females. Further analysis of treatment effects within genders did not attain significance. Overall, grooming was displayed for a significantly greater amount of time in saline-injected rats compared to the apomorphine-injected rats ($p < 0.001$) (Fig. 2).

Rotational behavior was seen predominantly in rats challenged with apomorphine and considerably more in females than in males (data not shown). For analysis purposes, sniffing was combined with walking–sniffing, because these can be considered one behavior (sniffing, which occurs with or without walking). While sniffing is substantially increased by apomorphine in both genders, there was no difference between the preweaning treatment groups (cocaine 50 mg/kg or vehicle) for total sniffing (data not shown). Apomorphine also reduced time spent in "quiet."

DISCUSSION

The results indicate that 50 mg/kg cocaine administered during PND 11–20 prevented the development of sensitization to the direct DA agonist, apomorphine, given repeatedly for a period of 10 days at 2 mg/kg to adult male rats (Fig. 1). An increase in distance traveled over the 3 test days (sensitization) was evident only in the male control group, which received vehicle injections during PND 11–20. Examination for possible appearance of competing behaviors also suggested that cocaine-treated males show no sensitization of any kind to repeated apomorphine. However, it is possible that examination of behaviors following other doses of apomorphine may reveal a different pattern of responses. The exact mechanism for apomorphine-induced sensitization is unknown at this time. Other studies have shown that although both the D_1 and D_2 DA receptors contribute, it is the D_1 receptor that is necessary for the development of sensitization (16,17). That is, concomitant administration of selective D_1 blocking agents along with apomorphine prevents the development of sensitization, while concomitant administration of D_2 blocking agents does not (16,17). We have previously shown that preweaning cocaine-treated male rats show a depressed locomotor response to a direct and selective DA D_1 receptor agonist, SKF 82958, when tested in adulthood (5). Furthermore, preprodynorphin mRNA, an intracellular marker that reflects stimulation of the D_1 receptor–effector complex, was reduced in males exposed to cocaine (7). This reduction was localized to the shell of the nucleus accumbens, which is the "limbic" portion of the nucleus, and an important striatal locus for the action of psychostimulants (20). Because cocaine-treated males showed impaired sensitization to apomorphine at 2.0 mg/kg and the D_1 receptor appears to be critical for this process, these data suggest that preweaning cocaine impairs D_1 receptor-mediated events that may involve neurons in the shell of the nucleus accumbens.

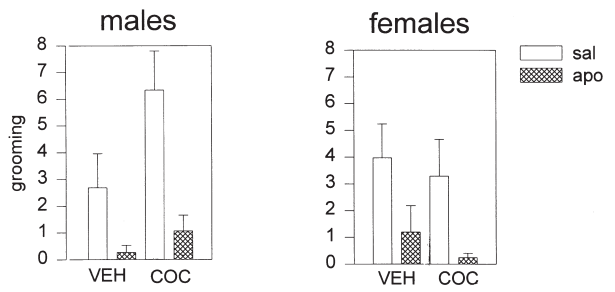

FIG. 2. Time spent grooming (mean ± SEM in s/min) in males and females that received either 50 mg/kg of cocaine or vehicle during the preweaning period. Grooming showed a significant interaction between preweaning treatment and gender. Data for apomorphine and saline-injected groups are shown because apomorphine significantly attenuated grooming behavior. Grooming was assessed from videotaped recordings for each rat during 1 out of every 10 min (beginning at minute 9) on the last day of testing (day 10) using the Noldus software. Each bar represents 7–11 rats.

Apomorphine, a direct D_1 and D_2 agonist (21), significantly increased the distance traveled and sniffing duration, and decreased the time spent grooming, quiet, and in the margin, in both genders. Apomorphine stimulates postsynaptic dopamine receptors, at the dose used in the current study (2.0 mg/kg), producing increased locomotion even in the first session (see Fig. 1). In other studies, it appears that even higher doses (e.g., 5 mg/kg) either reduce or increase locomotor activity during the initial session, although explicit statistical testing is often not performed (1,11,13). Also, others have shown that high doses of apomorphine produce stereotypic (or repeated) sniffing, licking, and gnawing on the initial exposure [e.g., (1,18,19)]. In our study, even after the 10th dose of apomorphine, no significant stereotypy, such as sniffing or locomotor activity, was seen. However, Mattingly et al. (13) rated stereotypy during repeated injections of 5 mg/kg apomorphine and found that some stereotypic behavior was evident following the first injection, but that it did not increase across subsequent days of exposure. Therefore, the responses of the control males in the present study are similar to those in the literature.

Many other investigators have also reported that apomorphine induces gnawing and licking responses (1,8,18,22) that were not observed in our experiments, perhaps for several reasons. First, we recorded behaviors by placing a video camera on top of the one-way mirror located above the activity box. From this angle it was impossible to score oral movements with any certainty. Secondly, the activity box did not include objects for the rat to gnaw. In other studies gnawing was observed when the rat chewed on the wire mesh of the activity chamber or on blocks that were placed in the chamber (18,22). Because our chamber lacked objects, and the videotapes could not assess oral movements, we cannot state with certainty whether oral behaviors were produced selectively in one or another preweaning treatment group.

All females in our study failed to develop sensitization to apomorphine at 2 mg/kg/day. On the other hand, other studies have shown that females sensitize more readily to indirect DA agonists, such as amphetamine (3). Apparently, estrogen attenuates apomorphine-induced stereotypy and decreases its effects on locomotor activity and circling (9). However, estrogens' interactions with the dopamine system are complex [see (4) for review]. Because other studies predominantly use male subjects to study sensitization to apomorphine, further study

will be necessary to understand why females do not show this response.

In conclusion, preweaning cocaine treatment impaired the development of sensitization to repeated apomorphine administered at 2 mg/kg to adult male rats, which was not due to an increase in competing (e.g., stereotypic) behaviors. Because the D_1 receptor is essential for the development of apomorphine-induced sensitization, these data suggest that preweaning cocaine produces a functional impairment in D_1-mediated effects. Other data in this model support an impairment of D_1-mediated responses involving the nucleus accumbens in males. In females, no sensitization was seen in any preweaning treatment group, suggesting that the mechanisms for the production of sensitization to direct vs. indirect agonists are quite different in males and females. In addition, in females, preweaning cocaine does not produce long-term alterations in the function of the circuits involved in the behavioral responses to repeated apomorphine administration.

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