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Behavioral responses to dopamine agonists in adult rats exposed to cocaine during the preweaning period

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Abstract

In order to determine whether developmental cocaine exposure altered the functional responses of dopamine systems, the behavioral responses to selective D1 or D2/D3 agonists were examined and compared to rats treated during the same period with a selective inhibitor of the dopamine transporter, GBR 12909. Sprague–Dawley rats were administered cocaine or GBR 12909 at 25 or 50 mg/kg/day during postnatal days (PND) 11–20. At 60+ days of age, rats were administered a challenge drug (either SKF 82958, a full D1 agonist, at 1.0 or 10 mg/kg, or quinpirole, a D2/D3 agonist, at 0.08 or 0.5 mg/kg, or saline) and subjected to 1 h of behavioral assessment. The cocaine or GBR treatments produced significant effects in three behavioral categories: distance traveled, sniffing, and rearing. For distance traveled, preweaning treatments interacted with sex since in the males, all cocaine- and GBR-treated groups showed relatively flat patterns of locomotor activity across time blocks, while in the treated females, locomotor activity typically increased across the time blocks. For other behaviors, the treatments generally produced enhanced responses to the challenge drugs. These results suggest that intermittent inhibition of the dopamine transporter with either cocaine or GBR during PND 11–20 produces long-term alterations in the functional responses of dopaminergic systems but that the neural substrates for these effects depend upon the sex of the animal.

Keywords: Substance abuse; Prenatal; SKF 82958; Quinpirole; Locomotion; GBR 12909

1. Introduction

Development of the forebrain dopaminergic systems occurs during both the pre and postnatal life in the rat. During postnatal life, dopaminergic neurons differentiate, a process characterized by axonal expansion and synapse formation. These processes are followed by axonal retraction and neuronal cell death. Substantial changes in DA receptors, second messenger systems, transporters, mRNAs, enzyme and neurotransmitter content, and electrophysiologic responses have been described in postnatal rat brain (Murrin and Zeng, 1986, 1989; Rao et al., 1991; Srivastava et al., 1992; Teicher et al., 1991; Wang and Pitts, 1994, 1995). The behavioral responses to dopamine agonists and cocaine also undergo maturation during the postnatal period (Moody and Spear, 1992; Spear and Brick, 1979; Ujike et al., 1990). Since systems are most vulnerable to environmental perturbation during periods of development, we hypothesized that function within forebrain dopamine systems, such as those that mediate specific behaviors like locomotion and sniffing and that undergo development during the postnatal period, would be permanently altered by cocaine exposure. Since inhibition of the DA transporter is central to many of cocaine's psychoactive effects, we also examined the effects of administration of 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine (GBR 12909), the selective inhibitor of the DA transporter (Andersen, 1989), during an equivalent period of development.

We utilized a challenge drug paradigm to investigate the functional responses of forebrain dopaminergic circuits. Adult rats of both sexes, which received injections of cocaine

Abbreviations: VEH, vehicle-treated; GBR-25, GBR 12909-injected group at 25 mg/kg; GBR-50, GBR 12909-injected group at 50 mg/kg; COC-25, cocaine HCl-injected group at 25 mg/kg; COC-50, cocaine HCl-injected group at 50 mg/kg; SKF, SKF 82958 challenge drug at 1.0 or 10 mg/kg; 5-HT, serotonin; DA, dopamine; NE, norepinephrine; sc, subcutaneous; ANOVA, analysis of variance; PND, postnatal day.

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or GBR during the preweaning period (PND 11–20), were administered either a specific D1 agonist, SKF 82958, or a nonspecific D2/D3 agonist, quinpirole (see Andersen et al., 1990 for review of receptor subtypes), and the resulting behaviors were recorded. Since others reported that ontogenic cocaine administration results in an uncoupling of the D1 receptor from its Gs protein (Wang et al., 1995) and since the D1 and D2 receptor systems reciprocally regulate behavior (Johansson et al., 1987), we expected to see a reduction in D1-mediated behavioral responses and a possible increase in D2-mediated behavioral responses associated with the circuits vulnerable to cocaine's effects during the period of drug administration.

2. Materials and methods

2.1. Dosing and subjects

All procedures were approved by SUNY's Institutional Animal Care and Use Committee. Adult female Sprague–Dawley rats (COBS, Charles River, Wilmington, ME) were mated in our AAALAC-accredited vivarium (20–22°C) with males of the same strain. Starting from the morning of a sperm-positive smear, referred to as gestation day 1 (G1), the females were housed individually with ad lib food and water and left undisturbed until day of birth in $44 \times 24 \times 20$ cm plastic cages with wood chip bedding. On the day of birth, the litter was culled to 10 pups maintaining equivalent sex representation, if possible, and the pups were toe-clipped for identification. Litters were randomly placed into one of five treatment groups: 25 or 50 mg/kg cocaine HCl (COC-25 or COC-50), 25 or 50 mg/kg GBR 12909 diHCl (GBR-25 or GBR-50), or vehicle (sterile water, 5 μl/g body weight) with all pups in a litter receiving the same treatment. Drugs were injected subcutaneously in dilute solutions (either 0.5% or 1.0%) with daily rotation of the injection site to minimize the possibility of skin necrosis. Equal doses (in mg/kg) of cocaine and GBR were administered because of the difficulties encountered when equating the action of these two drugs in vivo. For example, in vitro GBR has a higher affinity for the dopamine transporter than cocaine (Rothman et al., 1989). However, in vivo cocaine is about fourfold more potent in increasing the dopamine overflow as determined using cerebral microdialysis (Rothman et al., 1991). Subcutaneous injections were administered daily from days 11–20 except for GBR 12909 which, due to its longer half life, was only administered on "odd" days with vehicle on "even" days. This pattern of GBR administration was selected to produce a periodic rise and fall of the plasma drug concentrations as produced by daily cocaine administration. On day 21, the pups were weaned into same-sex cages, ear-clipped for identification, and weighed every 4 days thereafter until they were 60 days of age.

2.2. Behavioral measures

Beginning on day 56, the adult females underwent daily vaginal smears to determine the day of the estrous cycle. On the morning of the study (females in diestrus), each rat was removed from its cage, weighed, and drugs were injected subcutaneously with a randomly chosen challenge drug dose: saline (1.0 ml/kg body weight), (±)-SKF 82958 HBr at 1.0 or 10 mg/kg, or (−)-quinpirole HCl at 0.08 or 0.5 mg/kg, with no more than 1 subject/sex/litter receiving the same challenge drug dose. Immediately following injection, the rat was placed in the Digiscan Activity Monitor (model RXYZCM, Dreher and Jackson, 1989, Accuscan, Columbus, OH) for 60 min of observation. The inside of the laminate activity chamber measured $60 \times 60 \times 37$ cm and contained two 6-W light bulbs for illumination, a fan (model 30CFM), 48 infrared sensors spaced 2.5 cm apart with 16 along each side and 16 placed 10 cm from the floor of the chamber for sensing vertical activity, and a $42 \times 42 \times 30$ cm Plexiglas open box for the animal, which did not contain wood chip bedding. Each chamber was washed with soap and thoroughly rinsed between sessions. Although the Accuscan collects information in 21 behavioral categories, we analyzed only total distance traveled and margin time. Margin time or wall hugging was defined as the time spent within 2.5 cm of one of the walls of the chamber. Behaviors were collected in 1-min intervals and were subsequently collapsed (averaged) into 5-min blocks. Each session was videotaped using a Panasonic video camera through a one-way window measuring 30×30 cm and centered in the top of the laminate chamber. The videotapes were later analyzed using the Observer software (Noldus, The Netherlands) by an individual unaware of the sex, treatments, or challenge drug doses. Behaviors scored using the Observer were: sniffing (sniffing with subject on all four legs for ≥ 1 s), rearing (subject is standing on hindlegs with forelegs free in air or in contact with wall ≥ 1 s), grooming (grooming or scratching head or body ≥ 1 s), and quiet (subject not engaged in any behavior ≥ 2 s — may be asleep or awake). The time spent in each behavior was recorded in seconds for 1 out of every 10 min of the session, starting at 9 min.

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

2.3. Drugs

Cocaine HCl (Sigma, St. Louis, MO) dissolved in water (Baxter, 5 μl/g body weight), GBR 12909 (Research Biochemicals, Natick, MA) dissolved in warm water with

Table 1
Effects of cocaine or GBR 12909 injections on body weight (mean ± S.E.M., g)

	Vehicle	GBR-25	GBR-50	COC-25	COC-50
Males					
PND 11–20 weight difference	21.0 ± 0.4	19.4 ± 0.3*	19.7 ± 0.4	20.1 ± 0.4	17.7 ± 0.5*
Weight at day 60	352 .5± 4.7	350.4 ± 2.9	365.8 ± 3.1	365.6 ± 5.1	370.9 ± 3.7*
Females					
PND 11–20 weight difference	20.9 ± 0.4	18.2 ± 0.3*	20.0 ± 0.5	19.9 ± 0.3	17.7 ± 0.4*
Weight at day 60	231.4 ± 2.4	224.9 ± 2.5	231.1 ± 2.2	232.8 ± 2.9	226.6 ± 3.3

* Significant difference from same-sex vehicle-injected controls.

sonication, saline (Baxter, 1.0 ml/kg body weight), (±)-SKF 82958 HBr, and (−)-quinpirole HCl (LY-171555), both dissolved in saline and from Research Biochemicals.

2.4. Statistics

Body weights were analyzed by two-way analysis of variance (ANOVA) (Treatment × Sex) at each age. Data for each of the six behaviors were analyzed by four-way ANOVA with preweaning treatment (VEH, COC-25 or COC-50, GBR-25 or GBR-50), sex (male or female), and challenge drug dose (saline, SKF 82958 at 1 or 10 mg/kg or quinpirole at 0.08 or 0.5 mg/kg) as between subjects variables and the repeated measure, time block, as a within subjects variable using SYSTAT. Challenge drug responses within treatment groups or within specific time blocks were assessed using the Dunnett's test with the response to saline injection as the control. Data were expressed as means ± standard error and a P value of $\leq .05$ was considered statistically significant. All within subjects comparisons were adjusted using the Greenhouse–Gessier correction. In addition, for the distance traveled measure, the multiple three-way interactions prompted an in-depth examination of the responses to the challenge drugs within each treatment group and sex using ANOVA. In this case, since the four-way interaction was not significant, the Bonferroni correction was applied both at the ANOVA level and for the post hoc Dunnett's tests (e.g., for Fig. 2) such that a P value of .01 or less was required for significance.

3. Results

A total of 64 litters was prepared for this study: 15 vehicle, 12 COC-25, 12 COC-50, 13 GBR-25, and 12 GBR-50. Of the 10 pups in each litter, no more than 1 rat/sex received the same challenge drug dose. The final number of subjects within each cell was between 9 and 13 due to inequities in sex distribution within litters and technical problems with either the Digiscan equipment or the videotaping.

The effects of the postnatal treatments on body weights are given in Table 1. There were main effects of treatment on weight gained over the 10-day injection period with the GBR-25 and COC-50 groups gaining less weight than the vehicle-injected controls in both sexes. At 60 days, while there was a main effect of sex, there were no treatment effects among the females ($P = .121$). There were, however, treatment effects for the males ($P = .018$, ANOVA) with the COC-50 males weighing significantly more than the controls ($P = .003$, Dunnett's).

3.1. Distance traveled (Digiscan)

The ANOVA for distance traveled indicated that there were significant main effects of challenge drug dose [$F(4,514) = 31.606$, $P < .001$] and sex [$F(1,514) = 25.173$, $P < .001$] with no main effect of treatment [$F(4,514) = 1.694$, $P = .150$]. The interaction of challenge drug dose and time block was highly significant [$F(44,5654) = 36.879$, $P < .001$].

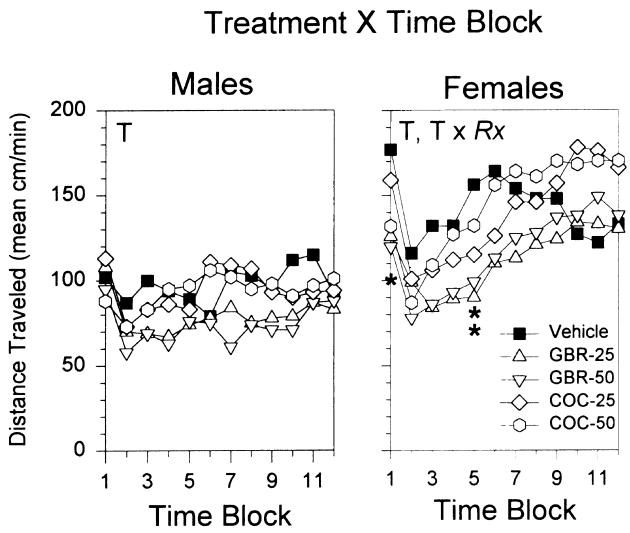

Fig. 1. Sex × Preweaning treatment group × Time block interaction for distance traveled collapsed across challenge drug dose. Since 4/5 subjects received a dose of a DA agonist just prior to being placed in the activity chamber, responses to these drugs are embedded in the overall treatment group differences. Significant time block (T) and preweaning treatment (Rx) effects appear in each panel ($P \leq .05$) determined by ANOVA. * Significant difference from the preweaning vehicle controls within a specific time block ($P < .05$, Dunnett's test).

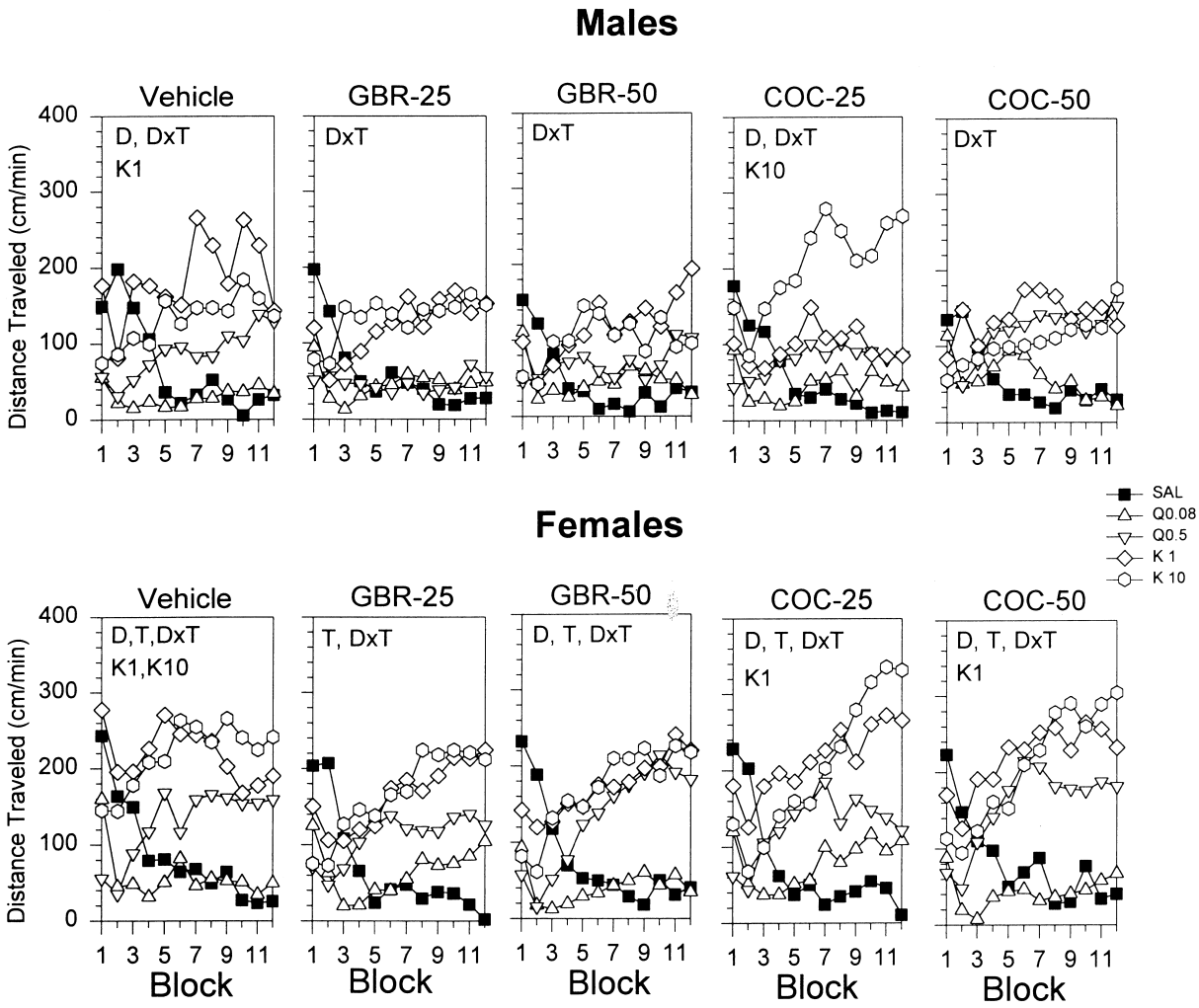

Fig. 2. Distance traveled across time blocks of 5 min each following challenge drug injection of SKF 82958 at 1.0 or 10.0 mg/kg (K1 or K10) or quinpirole at 0.08 or 0.5 mg/kg (Q0.08 or Q0.5) in adult rats exposed to cocaine, GBR 12909, or vehicle during PND 11–20. Each line represents 9–13 rats with rats receiving saline represented by filled symbols, quinpirole in triangles, and SKF in open squares and hexigons. The letters *D* (challenge drug dose), *T* (time), and $D \times T$ (Dose × Time interaction) refer to statistically significant effects using the Greenhouse–Geisser (G–G) correction ($P \leq .01$) determined by ANOVA using time as a repeated measure. When challenge drug dose was significant, the data were collapsed across time block and the Dunnett's post-hoc test was performed. Challenge drug doses, which produced responses significantly different from the saline responses, are indicated ($P < .01$).

Preweaning treatment interacted with sex and time block [$F(44,5654) = 1.748$, $P = .022$] with a medium-sized effect (Cohen, 1988). There also was a significant interaction between time, sex, and challenge drug dose ($P < .001$). The four-way interaction, however, was not significant. Females were more active and reactive both to the preweaning treatments and to the challenge drugs than males (Fig. 1). Within sex, ANOVA indicated that only the females showed a significant time block by preweaning treatment interaction ($P < .001$). Within the females, two time blocks, one and five, showed significant preweaning treatment effects by one-way ANOVA ($P < .05$) and within these, the GBR-50 females were significantly different from the vehicle-injected controls in the first time block and both GBR-treated groups were significantly different during time block 5 (Fig. 1).

The significant time block by preweaning treatment interaction in females, as well as the significant treatment by challenge Drug dose × Time block interaction, suggest that the treatments alter sensitivity to the DA agonists. To examine this possibility, ANOVA was conducted within each treatment group and sex to examine the response to each challenge drug dose over time. However, since the omnibus four-way interaction (between preweaning treatment, sex, challenge drug dose, and time block) was not significant, the Bonferroni correction was applied within each treatment group/sex and *P* values of $\leq .01$ were considered significant. The results of the ANOVA for each treatment group/sex are indicated in each panel in Fig. 2. For the males, challenge drug dose was significant only in the vehicle males and the COC-25 males ($P < .01$, ANOVA). Post-hoc analysis indicated that SKF at 1.0 mg/kg in the

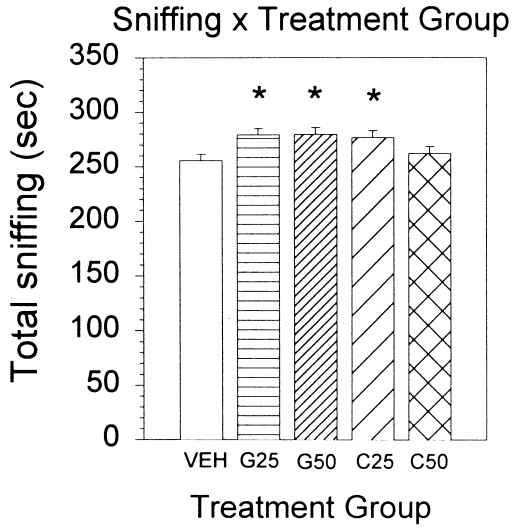

Fig. 3. Duration of sniffing (s) produced a significant main effect of treatment in adult rats which received a preweaning treatment of cocaine (COC-25 or COC-50), GBR (GBR-25 or GBR-50), or vehicle. Each bar was collapsed across sex and drug doses. Sniffing was assessed from video tape recordings of each rat during 1 of every 10 min (beginning at 9 min) in the activity chamber using the Noldus software. $N = 105-119$ for each preweaning treatment. * Significant difference from the vehicle controls by Dunnett's test ($P < .05$).

vehicle-treated males and SKF at 10.0 mg/kg in the COC-25 males significantly increased locomotion compared to the saline-injected control group ($P < .01$, Dunnett's). For both the GBR-25 and GBR-50 males and the COC-50 males, none of the challenge drugs significantly altered locomotor activity. Within the females, however, all groups responded similarly to the challenge drugs except the GBR-25 group, which did not show a significant challenge drug dose effect (Fig. 2). In the vehicle-treated females, both doses of SKF significantly increased locomotion while in the COC-25 and COC-50 females, only SKF at 1.0 mg/kg stimulated locomotor activity undoubtedly due to the greater variability in the response to SKF at 10 mg/kg. None of the groups showed significant alterations in distance traveled following quinpirole and there were no significant treatment-related differences in response to saline.

3.2. Margin time (Digiscan)

The analysis of variance for margin time (wall hugging) indicated that there was a significant main effect of sex [$F(1,514) = 10.167$, $P = .002$], with females showing a greater amount of time spent in the margin. A main effect of challenge drug dose [$F(4,514) = 10.298$, $P < .001$] was produced by a significant reduction in the time spent in the margin by rats challenged with SKF at 1 and 10 mg/kg and quinpirole at 0.5 mg/kg compared to the saline-injected rats ($P < .05$, Dunnett's). There was also a time block by challenge drug dose interaction ($P < .001$). Overall, there was no main effect of preweaning treatment [$F(4,514) = 2.262$, $P = .061$] and no significant interactions with treatment.

3.3. Sniffing (Observer)

For sniffing, treatment produced a main effect [$F(4,473) = 3.360$, $P = .01$], which was a small effect size (Cohen, 1988), with GBR-25, GBR-50, and COC-25 groups all showing a significant increase in sniffing compared to the preweaning vehicle control group ($P < .05$, Dunnett's test, Fig. 3). Sex was not significant ($P = .262$, ANOVA). Challenge drug dose produced a significant main effect ($P < .001$, ANOVA) with all doses except quinpirole at 0.08 mg/kg producing an increase in sniffing. There was also a significant three-way interaction between time block, sex, and challenge drug dose ($P = .001$, ANOVA, not shown). There were no significant treatment-related differences in response to saline.

3.4. Rearing (Observer)

The four-way analysis of variance indicated that there was a main effect of challenge drug dose ($P < .001$) since rearing was decreased by each of the challenge drug doses ($P < .05$, Dunnett's). There was also a significant treatment group by challenge drug dose interaction [$F(16,473) = 1.796$,

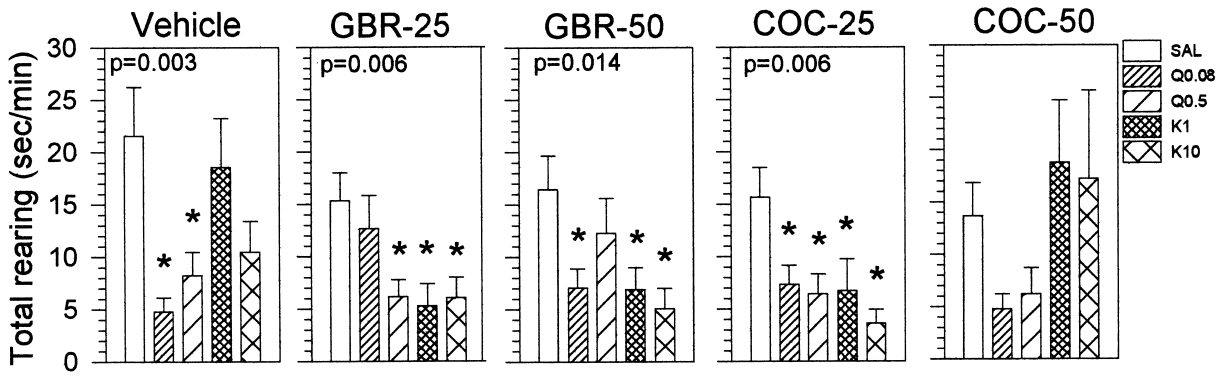

Fig. 4. Rearing produced a significant interaction between treatment group and challenge drug dose. Rearing is shown here collapsed across time block with P value for the challenge drug dose effect indicated in each panel. * Significant difference from the saline-injected control by Dunnett's test ($P < .05$).

$P = .029$], which was a large effect size (Cohen, 1988) (Fig. 4). Within the preweaning vehicle-treated group, rearing was decreased by both doses of quinpirole ($P < .05$, Dunnett's test). In the GBR-treated groups, a dampening of this response was seen since only one dose of quinpirole reduced rearing ($P < .05$). However, in these groups, both doses of SKF reduced rearing ($P < .05$). In the COC-25 group, rearing was decreased by all challenge drug doses and in the COC-50 group, there were no significant challenge drug dose effects (Fig. 4). Overall, sex was not significant ($P = .071$) nor did sex interact with any of the other variables. There were no significant treatment-related differences in response to saline.

3.5. Grooming (Observer)

The analysis of variance for grooming indicated that there were significant main effects for sex ($P < .001$) and challenge drug dose ($P < .001$) while preweaning treatment produced a $P = .124$. Females showed greater durations of grooming than males. Overall, both challenge drug doses reduced grooming compared to the saline-injected controls. There were also significant Sex × Challenge drug dose and Time × Challenge drug dose interactions but preweaning treatment did not interact with any of these variables (data not shown). There were no significant treatment-related differences in response to saline.

3.6. Quiet (Observer)

All challenge drug doses reduced the time scored as quiet except quinpirole at 0.08 mg/kg (data not shown). There were no significant treatment-related differences in response to saline.

4. Discussion

Cocaine and GBR 12909 administration during the preweaning period (PND 11–20) alters the adult behavioral responses to selective DA agonists. Four behaviors showed preweaning treatment-related effects with distance traveled (locomotion) showing a significant interaction between sex and preweaning treatment group. Males receiving either cocaine or GBR at 25 or 50 mg/kg during the preweaning period showed a dampening of the locomotor response to SKF 82958 as adults (Fig. 2). Females treated with GBR also showed a dampening of the locomotor responses while females treated with cocaine showed locomotor responses more like the controls. Other behaviors such as sniffing and rearing were affected by the cocaine and GBR treatments, but sex did not play a role in these effects. Interestingly, for sniffing the GBR-treated groups generally responded to the challenge drugs in the same way as the COC-25 group did. The COC-50 group, however, responded within normal or control limits suggesting that the non-DA actions of cocaine, such as those affecting the 5-HT and NE systems, may "normalize" the DA actions in those circuits mediating sniffing, resulting in a normal pattern of responses for the COC-50 group. While preweaning cocaine and GBR affected multiple behavioral responses to DA agonists, only locomotor activity exhibited sex-dependent effects. Other behaviors, such as sniffing, showed treatment-related effects, which did not depend on sex and yet revealed enhanced challenge drug responsiveness for all but the COC-50 group. While male and female pups metabolize cocaine similarly (unpublished data), it is possible that different metabolism of the challenge drugs in male and female adults may contribute to the sex differences observed.

While it is not possible to identify with certainty the brain regions, which mediate the behavioral changes observed in the current experiment, microinjection studies have enabled the identification of specific groups of neurons that are involved in the production of specific behaviors. For example, intrastriatal injections of SKF 38393, a D1 agonist, or quinpirole produce stereotyped sniffing and paw nibbling, but not locomotion (Bordi and Meller, 1989; Dreher and Jackson, 1989; Mogenson and Wu, 1991; Plaznik et al., 1989). Intra-accumbens injections of these same drugs produce locomotor and rearing behaviors (Delfs et al., 1993). Thus, changes in locomotion imply that distinct alterations are produced in the mesolimbic dopamine system by the preweaning treatments while effects on sniffing may be related to functional changes in circuits involving the dorsal striatum. While the preweaning treatments generally dampened the response of the mesolimbic dopamine system, these same treatments enhanced the responsiveness of the nigrostriatal system as evidenced by the treatment-related increases in sniffing responses to the dopamine agonists. Other data pertaining to this model support the neuroanatomical differences observed here (Dow-Edwards et al., 1993).

In general, cocaine does not produce a uniform effect on all dopaminergic regions. In the adult, many groups have found for example that the striatum and accumbens exhibit different neurochemical responses to cocaine (Goeders and Kuhar, 1987; Izenwasser et al., 1990; Missale et al., 1985). Some support for the differential vulnerability of dopaminergic regions can also be found in a study of similarly-treated pups examined shortly after subacute administration of cocaine or GBR (both at 25 mg/kg) at 21 days of age where cocaine stimulated glucose metabolism in the ventrolateral striatum, but not in the accumbens in females, while in males there was no effect in striatum and a reduction in nucleus accumbens (Frick and Dow-Edwards, 1995). Differential vulnerability of the DA terminal regions may also be related to the fact that each brain region matures at a slightly different rate. For example, it has been shown that the accumbens and striatum are in different states of maturation during the time of drug exposure (Hattori and McGeer, 1973). Maturation of latency and conduction velocities

occurs later in the mesoaccumbens neurons than in the nigrostriatal neurons (Wang and Pitts, 1994). In addition, differences in states of maturation across sexes during cocaine and GBR administration may contribute to the sex-related differences reported here.

The similarity in patterns of changes between cocaine and GBR indicate that inhibition of the DA transporter alone during the preweaning period is sufficient to produce the long-term alterations in the DA responses, which we observed. However, in females, non-DA effects of cocaine may play a significant role in regions, such as the mesoaccumbens system, since in females GBR administration reduced the locomotor response to the D1 agonist, while cocaine administration produced a more normal response profile. Apparently, the non-DA effects of cocaine (i.e., the 5-HT effects) block or prevent the DA effect particularly in this pathway. Serotonergic fibers have been shown to innervate dopaminergic forebrain regions and blockade of 5-HT synthesis or 5-HT receptors has been shown to enhance cocaine-induced locomotor activity (Mogilincka et al., 1977). Dopamine synthesis and release in forebrain is also regulated through 5-HT_{1A} and 5-HT_3 receptors (Ahlenius et al., 1990; Blandina et al., 1988; Chen et al., 1991). Although the interaction between DA and 5-HT is well established in the adult male, future studies should focus on this interaction in females, as well as how cocaine treatment may alter it.

D1 agonists systemically administered induce grooming, locomotion, sniffing, and oral movements in an open field (Arnt et al., 1987; Braun and Chase, 1986; Ellison et al., 1988; Molloy and Waddington, 1987; Rosengarten et al., 1983). Overall, the patterns of response to SKF 82958, the specific agonist used in the present study, resemble those described by Meyer and Shults (1993) using the same equipment and unhabituated Long–Evans rats of unspecified sex. For example, both studies showed increased locomotor activity to SKF, although we found an increase following 1.0 mg/kg while they did not. Both studies found a decrease in margin time and rearing following SKF. However, we found that SKF decreased grooming rather than increasing it as Molloy and Waddington (1987) have reported. While the reason for this difference is not clear, postnatal handling has been shown to alter grooming in the open field in mice (Clausing et al., 1997) and all of our groups received a significant amount of postnatal handling. Hypothetically, changes in the sensitivity of the pathways mediating grooming that are initiated during the preweaning period may persist into adulthood and alter the drug responsiveness of this system.

Across all treatment groups, quinpirole (and SKF) produced biphasic effects on locomotor activity particularly at the higher doses. That is, initially, quinpirole reduced locomotor activity and then later, activity increased. This biphasic response has been found by others and may be related to the decreased activity produced by quinpirole when baseline activity levels are high and vice versa when activity levels are low (Eilam and Szechtman, 1989; Van Hartesveldt et al., 1992; Wu et al., 1993). In unhabituated rats, such as those used in the current study, initial activity levels are high presumably due to exploratory activity. Later, when exploratory activity is low in the saline-injected animals, the 0.5 mg/kg dose of quinpirole stimulates locomotor activity. This pattern was seen in all groups of the current study, except the GBR-25 and GBR-50 males, where no subsequent increase was seen (Fig. 2). Therefore, in these groups of males, the effect on the D2 circuit appears late in the session when the normal exploratory behavior has subsided. Overall, injection of quinpirole reduced wall-hugging behavior, which was shown by others (Van Hartesveldt et al., 1992), and may be related to the anxiolytic effects of the drug (Treit and Fundytus, 1989).

In summary, administration of cocaine or GBR 12909 during the preweaning period, a time equivalent to third trimester human development (Bayer et al., 1993), produced sex-dependent effects on locomotor activity which may be mediated by the mesolimbic DA system. Preweaning treatment-induced alterations in other behaviors such as rearing and sniffing, which are presumably mediated by pathways other than the mesolimbic system, were not affected in a sex-specific manner. The effects on mesolimbic dopamine function may be related to the uncoupling of the D1 receptor from its Gs protein (Wang et al., 1995). Other behavioral changes associated with reduced D1 function have also been found in this model, such as the absence of sensitization following repeated apomorphine administration found in males exposed to PND 11–20 cocaine (Busidan and Dow-Edwards, 1999). PND 11–20 cocaine treatment also decreases preprodynorphin mRNA in accumbal neurons which are neurons bearing D1 receptors and comprising the descending component of the mesolimbic DA system (Dow-Edwards and Hurd, 1998). Since other DA-related behaviors such as reinforcement and conditioning are known to be mediated by the mesolimbic DA system, it is reasonable to conjecture that other DA-mediated behaviors may be affected as well. Although the mesolimbic dopamine system was less affected by cocaine in females than other forebrain dopamine systems, cocaine certainly affects dopamine function in females. Further work should be aimed at determining the basis for the sex differences in response to preweaning cocaine administration, as well as the effects of cocaine administration during other periods of development.

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