Enduring behavioral effects of weaning-through-puberty cocaine dosing in the rat

ROBERT F. SMITH, C. NANI MEDICI, and DANI K. RAAP

George Mason University, Fairfax, Virginia

To determine whether cocaine administration during a developmental period corresponding to middle and late childhood results in enduring changes in behavior, we injected rats with 5 or 20 mg/kg/d of cocaine s.c. from weaning (postnatal day 21; P21) through P60; controls included uninjected and vehicle-injected controls. The 20-mg/kg dose resulted in a transient, male-limited weight reduction for the last 10 days of dosing, which rapidly recovered to normal after dosing ceased. Approximately 5 months later, the subjects were given a brief battery of behavioral tests. Female 20-mg subjects received fewer reinforcements than control subjects in a DRL-20 task. Female subjects also displayed altered patterns of cocaine-stimulated changes in open-field activity. No significant lasting effects were seen in males. These data suggest that the central nervous system retains sufficient plasticity into later development to produce long-lasting functional changes in response to drug administration and that cocaine consumption during the rat equivalent of childhood produces very long lasting plastic changes in behavior.

Developmental exposure to a number of drugs, including alcohol (Driscoll, Streissguth, & Riley, 1990), opiates (Kaltenbach & Finnegan, 1989), and cocaine (Chasnoff, Burns, Schnoll, & Burns, 1985; Smith, Matran, Kurkjian, & Kurtz, 1989) has been investigated. For cocaine, most developmental studies in animals have focused on the effects of administration during the prenatal period. A few have included administration on postnatal days 1–10 (P1–P10; see, e.g., Barron & Irvine, 1994) or P11–20 (Dow-Edwards, Fried-Malen, & Hughes, 1993). Although many effects are not of large magnitude, developmental cocaine has been reported to produce effects on behavior (Heyser, Chen, Miller, Spear, & Spear, 1990; Johns, Means, Anderson, Means, & McMillen, 1992; Smith et al., 1989; Spear, Kirstein, & Frambes, 1989), cerebral metabolic rates (Dow-Edwards, Fried, & Fico, 1990; Dow-Edwards et al., 1993), and many physiological systems (Akbari, Kramer, Whittaker-Azmitia, Spear, & Azmitia, 1992; Goodwin, Moody, & Spear, 1993; Raum, McGivern, Peterson, Shryne, & Gorski, 1990; Smith, Royall, & Coss, 1995; Vathy, Katay, & Mini, 1993), as measured later in life.

In humans, exposure to cocaine during childhood and adolescence has been documented (e.g., Hicks, Morales, & Soldin, 1990; U.S. Department of Health and Human Services, 1991). Although lasting effects of cocaine administration as late as P11–20 have been reported in animal studies (Dow-Edwards et al., 1993), no studies to date

have investigated possible lasting effects of cocaine administered during a period corresponding to human childhood and early adolescence. The central nervous system (CNS) retains developmental plasticity during this period, however; many reports indicate that a well-studied manipulation, environmental enrichment, produces changes in fine neuromorphology (e.g., Greenough, 1987), especially of systems developing at the time of enrichment (Fernandez, Adaro, Sanhueza-Tsusumi, Inzunza, & Bravo, 1997). This continued plasticity is part of the rationale for Witt's (1994) recommendation of assessing an animal model of adolescent use of another addictive drug, alcohol. The present study was conducted as a preliminary assessment of whether pre- and periadolescent [PPA] cocaine usage in the rat induces lasting changes in behavior. We selected P21–P60 as dosing ages for two reasons: (1) It incorporates an age range previously uninvestigated, and (2) this work was intended to serve as a model for cocaine use in PPA children. Although it is difficult to establish exact age equivalencies between rats and humans, this time period begins 6–7 days before clear prepubertal changes in females and persists past sexual maturity in both males and females. Doses included a low dose (5 mg/kg) and a moderate dose (20 mg/kg, about 0.3 LD₅₀ for adult rats), as well as uninjected and vehicle-injected controls.

METHOD

Subjects

Forty (20 male and 20 female) Long-Evans hooded rats (LSD:blu) used as subjects were derived from litters bred in our laboratory and culled to 4 males and 4 females on the day of birth. Animals were weaned on the 1st day of administration and were housed individually in hanging wire cages. The subjects had ad-lib access to water and food, except when food deprivation was required for differential reinforcement of low rates of responding (DRL-20) testing. The

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animals were maintained on a 12:12-h light:dark schedule (0700–1900 on), in a colony maintained at 20–25.5°C. Cocaine injection occurred from 0900–1100, and behavioral testing from 1000–1700.

Drug Administration

Dose groups included 5 and 20 mg/kg/d of cocaine, a vehicle-injected control group, and an uninjected control group. The subjects were injected daily from P21 through P60. Cocaine hydrochloride (NIDA Drug Supply System) was mixed daily as a 10-mg/ml solution in sterile isotonic saline. Side of subcutaneous injection (chosen for slow absorption and a relatively long duration of action) to the flank was altered daily, and location on each side was varied. Minor necrosis occurred at the injection sites in 20-mg/kg subjects. Body weights were taken daily during the administration period.

Design

The study was designed to control for genetic components of variance. From each of the five litters, one male and one female were assigned to the 5-mg dose group, one sex pair to the 20-mg dose group, and one sex pair to each of the injected and uninjected control groups. No paired control was included, since previous work indicated that a reduction in food intake is not seen in pregnant females at doses as low as 20-mg/kg (e.g., Smith et al., 1989). Each animal was tested sequentially on each of the behavioral tests. Behavioral tests started at 215 days of age (155 days after dosing ended).

Open Field. Open field testing was chosen for its sensitivity both to cocaine administration earlier in life (see, e.g., Smith et al., 1989) and to juvenile manipulations such as enrichment (Morgan, 1973). A 76 × 76 cm box with four BRS/LVE infrared photosensors (two in each horizontal dimension) was used to record motor activity. The OPN software system (Spencer & Emmett-Oglesby, 1985), running on IBM PCs, segregated beam breaks into six consecutive 5-min periods.

DRL-20 Sec Acquisition

DRL responding was used to assess the ability of the animals to learn to pattern responses appropriately to the schedule. As with the open field, both cocaine administration earlier in development (Smith et al., 1989), and juvenile manipulations such as enrichment (Ough, Beatty, & Khalili, 1972) affect this measure. Gerbrands G7321 Skinner boxes were housed in BRS/LVE sound attenuation chambers and were controlled by the OPN software system. Beginning 5 days after open field testing, the subjects were food deprived to 80% of their ad-lib weight, shaped to barpress, and given 4 days of 30 min per day on a continuous reinforcement schedule. After pretraining, the subjects were shifted to a DRL-20-sec schedule for 30 min per day for 20 days.

Cocaine-Stimulated Activity

Five days after the completion of DRL training (and resumption of ad-lib feeding), the subjects were given an intraperitoneal injection of 5 mg/kg of cocaine 10 min prior to a 10-min session in the open field, using the apparatus described above. The intraperitoneal route was chosen for relatively rapid absorption, producing high serum levels and strong effects on activity.

Data Analysis

Because of the design of the study, a subject in each dose/gender combination was a littermate of 1 subject in each of the other dose/gender combinations. Since there are litter (genetic) contributions to some behaviors, the subjects within each gender/dose combination were not independent of the subjects in each other combination; their behavior was correlated by virtue of their genetic relationships. A traditional analysis of variance (ANOVA), treating dose and gender as between-subjects effects, would thus violate the assumption of independence of each data point. Thus, the analysis selected was to treat dose and gender as correlated measures in an ANOVA (see Kirk, 1982; Winer, 1971). Significant ANOVA effects were followed by Newman–Keuls post hoc tests.

RESULTS

An ANOVA of weekly body weights during cocaine administration indicated that there were significant drug × day [$F(12,138) = 2.67, p < .01$] and drug × sex × day [$F(12,138) = 2.39, p < .01$] interactions. As Table 1 indicates, 20-mg males, but not females, had reduced body weight gain from P50 through P60, as compared with saline-injected controls. At P60, 20-mg males weighed 7.3% less than control males. Following completion of administration, differences in body weights disappeared within 10 days (data not shown).

An ANOVA of activity counts during the 30-min open field testing revealed no group-related differences, although expected time period [$F(5,20) = 60.43, p < .001$] and sex [sex × trial interaction; $F(5,20) = 6.70, p < .001$] effects were observed. An ANOVA for the two 5-min periods of activity following cocaine administration revealed no significant drug-associated effects, although the drug × sex × time periods effect approached significance [$F(3,12) = 3.43, p < .06$]. To compare basal and cocaine-stimulated activity, an ANOVA was performed,

Table 1
Body Weights During Dosing

Dose Group	Age (in Days)													
	21		28		35		42		49		56		60	
	M	SEM	M	SEM	M	SEM	M	SEM	M	SEM	M	SEM	M	SEM
Males														
Saline	46.8	1.34	78.7	1.93	133.2	2.02	185.0	2.85	239.6	1.21	290.7	2.04	316.6	4.04
5 mg cocaine	44.7	1.83	81.3	2.83	133.4	4.90	187.3	6.46	238.1	7.91	288.3	7.95	311.1	9.51
20 mg cocaine	48.6	2.10	83.6	3.74	137.9	6.85	188.9	7.19	233.4	8.53	276.8*	8.98	294.0*	8.05
Females														
Saline	46.8	1.63	77.2	1.87	122.1	2.61	152.6	2.97	181.1	2.64	198.5	1.84	212.1	2.92
5 mg cocaine	45.0	1.44	73.7	1.91	115.6	2.57	150.6	3.57	178.8	4.64	202.2	5.14	211.7	5.48
20 mg cocaine	45.7	1.67	73.9	2.72	116.5	4.10	150.9	6.26	175.9	6.98	199.7	9.06	208.5	8.44

* $p < .05$; different from saline group.

comparing the two 5-min periods of cocaine-stimulated activity with the first two 5-min periods of basal activity. This ANOVA revealed a significant fourth-order interaction between periadolescent drug, gender, time period, and pretest cocaine dosing [$F(3,12) = 4.27, p < .05$; see Figure 1]. Newman-Keuls post hoc tests failed to determine specific group differences contributing to this interaction; Figure 1, which depicts cocaine-stimulated activity as percent change from basal level, suggests that it is attributable to time-period-specific changes in cocaine-stimulated activity, limited to female subjects. Females who were uninjected during the PPA period have a large increase in activity in response to cocaine during the first 5 min of activity, but a negligible increase during the second period. The first-period increase is muted in animals dosed with cocaine during the PPA period (especially in the 5-mg group), but the second-period change is larger in 20-mg animals than in controls.

An ANOVA on reinforcements received during the 20 days of DRL testing indicated significant drug $\times$ day [$F(57,228) = 2.52, p < .001$], drug $\times$ sex [$F(3,12) = 5.02, p < .05$], and drug $\times$ sex $\times$ day [$F(57,228) = 2.16, p < .001$] interactions. These were principally attributable to female 20-mg animals receiving fewer reinforcements than other groups on several days of testing (see Figure 2). Newman-Keuls post hoc tests indicated that the 20-mg females received significantly ($p < .05$) fewer reinforcements than did uninjected controls on Days 7, 9, 10, 12, 15, and 16. An analysis of males alone revealed smaller dose-related differences than those seen in females; these differences did not reach significance. DRL effects in females were not attributable to differences in response

rate. No significant dose-related differences were found in response rate.

DISCUSSION

Daily cocaine administration during the PPA period produced changes in behavior that were detectable about 6 months later. Cocaine effects included a reduction in reinforcements received in a difficult operant barpressing task and altered sensitivity to the motor activity effects of cocaine. Changes were seen at a dose of cocaine that resulted in minor, but significant, body weight reductions in males during the dosing period, but the observed behavioral effects were seen only in females, which had no significant cocaine-related changes in body weight.

Cocaine effects were seen in behaviors previously found to be disrupted by cocaine administration earlier in development. Prenatal cocaine alters cocaine-stimulated activity (see, e.g., Kunko, Wallace, & Robinson, 1996; Peris, Coleman-Hardee, & Millard, 1992), and alters DRL performance (Medici, Smith, & Raap, 1999; Smith et al., 1989; Smith, unpublished data). Thus, two behaviors sensitive to prenatal cocaine exposure continue to be sensitive to cocaine exposure much later in development.

As an initial report, the present study utilized several behavioral tests in the same animals. Since each animal was tested on each task, it is not possible to distinguish whether, for example, juvenile cocaine directly alters DRL performance or whether the observed differences on DRL are attributable to an interaction of juvenile dosing and the testing experiences in the open field. It is also

Figure 1. Cocaine-induced changes in activity in the open field. Data points represent percent change from basal (nondrugged) activity. Only two consecutive 5-min time periods were tested after 5-mg/kg cocaine injection, and those are compared with the first two 5-min periods of basal activity data. $N = 5/\text{group}$. F-PER 1, female, time period 1; F-PER 2, female, time period 2; M-PER 1, male, time period 1; M-PER 2, male, time period 2; SAL, saline-injected; UN, uninjected.

Figure 2. Differential reinforcement of low rates of responding for females. Data are averaged across 5-day blocks for clarity. $N = 5/\text{group}$.

possible that DRL carries over to cocaine-stimulated activity. At one level of analysis, this distinction lacks meaning, since our data indicate to an effect of cocaine; however, it is clearly of importance to determine whether cocaine directly affects substrates for a behavior or whether it affects how those substrates may be altered by experiences intervening between dosing and testing. We note that several reports have indicated that earlier (prenatal) cocaine administration may alter reactions to environmental events and, subsequently, alter behavior (Smith et al., 1989; Wood, Molina, Wagner, & Spear, 1995).

The present data suggest that PPA cocaine produced very long lasting changes in the CNS. Clearly, effects detected approximately 6 months after the end of cocaine administration cannot be attributed to residual cocaine. Although the developing CNS is subject to environmentally-induced structural changes at the ages at which administration occurred (Greenough, 1987; Juraska, Fitch, Henderson, & Rivers, 1985), there have been few studies of whether drug exposure at these ages produce lasting effects on behavior. We have found that PPA cocaine also produces lasting alterations in estrous cyclicity (Raap, Smith, & Medici, 1996) and in cocaine place preference (Smith, Morin, Raap, & Medici, 1996). Other studies of juvenile drug effects are beginning to emerge; Harrison, Connor, Nowak, and Melloni (1997) reported that chronic juvenile cocaine enhances intruder aggression in hamsters, tested shortly after administration ceased. Melloni, Connor, Nash, and Harrison (1997) also found that juvenile androgen increases aggression and hypothalamic arginine vasopressin in hamsters; as with the Harrison study, this effect was examined shortly

after the conclusion of drug administration. Shtieglman, King, and Ferris (1997) found a similar effect on aggression after juvenile alcohol. Siciliano, Smith, and Morin (1997) found that chronic alcohol during the PPA period produced later changes on DRL and the open field.

The mechanisms by which PPA drug exposure might produce long-lasting changes in behavior are poorly understood. We note, however, that increased excitatory neurotransmitter activity stimulates process outgrowth in neurons (Lipton & Kater, 1989). Enrichment effects on brain growth may be maximal in areas undergoing active growth at the time of enrichment (Fernandez et al., 1997). We hypothesize that synaptic activity stimulated by PPA cocaine may induce lasting neuromorphological changes, much as stimulation-induced activity appears to. Subsequently, these morphological changes may mediate lasting changes in behavior. However, possible similarities between mechanisms underlying enrichment and cocaine probably do not imply similar behavioral effects of the two; the stimulation produced by enrichment most affects particular sensory system(s) subject to stimulation, whereas the cocaine effects most affect particular neurotransmitter systems.

The analogy to the environmental enrichment literature offers a possible explanation for the gender-specific effects noted in the present study. Juraska et al. (1985) found that dendritic branching in response to enrichment is gender-specific, with female (i.e., nontestosterone-primed) CNS being less reactive to enrichment than is male (i.e., primed) CNS. Dow-Edwards et al. (1993) found a similar female-limited effect for cocaine dosing in the P11–P20 period; as measured later at P63, cocaine

dosing altered metabolic rates (2-DG uptake) only in females. Interestingly, we further analyzed Dow-Edwards et al.'s (1993) data and found that most cocaine effects in females were in brain areas with sexually differentiated metabolic rates and that cocaine shifted rates toward the male-typical values (unpublished; available from the authors by request). Thus, either developmental cocaine or environmental enrichment can interact with gender to affect aspects of CNS structure or function. An underlying mechanism for the gender differentiation in putative cocaine-induced CNS changes may be that neurons in females have greater morphological (growth) responses to cocaine-stimulated firing.

Endocrine disruption may also play a role in the effects of PPA cocaine. Although we did not measure steroid levels, cocaine in older rats produces multiple endocrine effects (King, Schenken, Kang, Javors, & Riehl, 1990). The male-limited body weight suppression we observed during administration may have been due to cocaine-induced reduction in testosterone and its subsequent anabolic effects (Li, George, Bianco, Lawrence, & Dhabu-wala, 1997). Raap et al. (1996) also found that PPA cocaine disrupts estrous cyclicity in females (both during and following dosing), likely reflecting underlying cocaine-induced hormonal effects. Further work will be required to determine whether disruption of endocrine control systems underlies the effects of PPA cocaine.

Although only 5 sex pairs of animals were tested per drug condition, PPA cocaine resulted in significant changes in behavior. Significance with these group sizes may be partly due to the sensitivity of the experimental design; since the design matched subjects for genetic and litter factors across dose groups, those components of variance did not contribute to the error variance. This resulted in relatively high power for a small subject size for detecting interactions, ranging from .724 for the triple interaction in cocaine-stimulated versus basal open field activity to 1.000 for the triple interaction in DRL reinforcements; power for group and sex main effects was much lower, in some cases less than .2. When its use is feasible, this design appears to be sensitive to interaction effects with relatively small sample sizes. Clearly, however, the results reported here require replication with larger sample sizes.

The present study included a restricted range of behavioral tests, but the effects warrant some concern. Our data on basal versus cocaine-stimulated open field activity imply that PPA cocaine may cause long-lasting changes in sensitivity to cocaine; if verified, this might affect later predisposition to self-administer cocaine. The DRL task is a relatively difficult operant task, and our changes in female performance on this task suggest that the neural systems mediating this type of cognitive learning may be altered by PPA cocaine, which suggests that similar types of cognitive learning may be altered by this dosing regimen.

Clearly, drug use of many types is detrimental to neural development when administration occurs during pre-

natal development, in both animals and humans. The present data contribute to a recent small body of data suggesting that the sensitivity of the developing CNS to drug-induced alterations continues into the approximate period of middle childhood through puberty. Since human use of addictive drugs is high during the PPA period, these data underscore the need to better understand the consequences of PPA cocaine.

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