EFFECTS OF MESOLIMBIC DOPAMINE DEPLETION ON RESPONDING MAINTAINED BY COCAINE AND FOOD

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The hypothesis that mesolimbic dopamine is selectively involved in cocaine reinforcement was investigated in the rat. Animals were trained under a multiple schedule in which responding was reinforced by intravenous cocaine (0.75 mg/kg/injection) or food (45-mg pellets) under fixed-ratio 15 schedule requirements in alternate 30-min components of a 2-hr daily session. Infusion of the catecholaminergic neurotoxin 6-hydroxydopamine, but not the vehicle solution, into the region of the nucleus accumbens and olfactory tubercle produced selective reductions in cocaine self-administration without significantly altering responding maintained by food within the same sessions. This effect was reproduced in intact animals by substituting saline for cocaine in the self-administration component. These results support the hypothesis that the reinforcing effects of cocaine are dependent upon mesolimbic dopamine and demonstrate that cocaine self-administration can be disrupted in animals without altering behavior maintained by a nondrug reinforcer.

Key words: cocaine, self-administration, dopamine, 6-hydroxydopamine, nucleus accumbens, reinforcement, multiple schedule, lever press, rat

That the reinforcing properties of cocaine are critically dependent upon mesolimbic dopamine has been inferred from studies demonstrating that removal of dopamine from the nucleus accumbens using the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA) decreases or disrupts cocaine self-administration in rats (Petit, Ettenberg, Bloom, & Koob, 1984; Roberts, Corcoran, & Fibiger, 1977; Roberts, Koob, Klonoff, & Fibiger, 1979). Two alternative hypotheses to explain these results are that nucleus accumbens dopamine depletion may alter cocaine self-administration by a process that is independent of changes in the reinforcing properties of cocaine, or that nucleus accumbens dopamine depletion may alter general reinforcement processes that are not specific to cocaine.

These issues have been partially addressed by demonstrations that nucleus accumbens dopamine depletion only transiently alters operant responding for food (Roberts et al., 1977), yet produces long-lasting alterations in cocaine self-administration without altering apomor-

phine (Roberts et al., 1977, 1979) or heroin self-administration (Petit et al., 1984). In these studies, however, operant responding was maintained by food under different schedule conditions and in different animals than was cocaine self-administration. Moreover, the self-administration of apomorphine and heroin may be preserved in part as a result of their postsynaptic neurochemical properties that may to some degree overcome the neurochemical deficits produced by nucleus accumbens presynaptic lesions.

However, depletion of dopamine in the nucleus accumbens has been reported to attenuate high rates of responding under a fixed-interval schedule of food reinforcement (Robbins, Roberts, & Koob, 1983). Such lesions also decrease locomotor activity (Koob, Riley, Smith, & Robbins, 1978; Taghzouti, Simon, Louilot, Herman, & Le Moal, 1985) and adjunctive drinking (Robbins & Koob, 1980), suggesting reduced motivational excitement and reduced nonspecific excitement engendered by a motivational state. At the same time, these animals exhibit hyperphagia during restricted access to food, which may indicate an inability to express a change in motivational state by switching from one behavioral activity to another (Koob et al., 1978). Mesolimbic dopamine depletion also attenuates the expression of psychostimulant-conditioned hyperlocomotion (Gold, Swerdlow, & Koob, 1988), although operant responding maintained by conditioned reinforcers is preserved (Taylor &

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Robbins, 1984). It is unclear to what degree these effects of nucleus accumbens dopamine depletion may contribute to alterations in cocaine self-administration independent of changes in the reinforcing properties of cocaine.

Although mesolimbic dopamine is not necessary for the normal regulation of food and water intake (Koob et al., 1978; Le Moal et al., 1977), nucleus accumbens dopamine depletion does attenuate food hoarding (Kelley & Stinus, 1985; Koob et al., 1978). It has also been proposed that dopamine is critical for noncocaine reward (Wise, 1982), including food reward (Wise, Spindler, de Wit, & Gerber, 1978). However, attenuation of food reward has yet to be demonstrated using manipulations other than neuroleptic drugs, and these effects remain highly controversial (for reviews see Bozarth, 1991; Bradshaw & Szabadi, 1989; Ettenberg, 1989; Miller, Wickens, & Beninger, 1990; Wise, 1982). Thus, despite recent studies using elegant behavioral (Willner, 1991) and biochemical (Phillips, Pfaus, & Blaha, 1991) methods, the hypothesis that mesolimbic dopamine modulates food reward has yet to be demonstrated using the mesolimbic dopamine depletion procedure.

In order to examine further the hypothesis that cocaine reinforcement is critically and selectively dependent upon nucleus accumbens dopamine, we tested the effects of mesolimbic dopamine depletion on behavior maintained under a multiple schedule of cocaine and food reinforcement in the rat. Recent evidence from this laboratory indicates that 6-OHDA infusion into the olfactory tubercle in addition to the nucleus accumbens results in a more pronounced disruption of cocaine self-administration than do lesions of the nucleus accumbens alone (unpublished observations). Indeed, others have proposed an involvement of the olfactory tubercle in cocaine reinforcement (Kornetsky, Huston-Lyons, & Porrino, 1991). Therefore, in this study, lesions of the terminal fields of the mesolimbic dopamine projections were directed to the area of the olfactory tubercle in addition to the nucleus accumbens.

METHOD

Subjects

Male albino Wistar rats, weighing 220 to 260 g upon arrival, were habituated to the

animal colony for 1 week with food and water ad libitum and were handled daily. All animals were group-housed (2 or 3 per cage) throughout the study and were maintained on a 12:12-hr light/dark cycle (lights on at 5:00 a.m.). All behavioral procedures began shortly after the onset of the dark phase, and all procedures were carried out in accordance with the *Guide for the Care and Use of Laboratory Animals* endorsed by the National Institutes of Health.

Drugs

Cocaine HCl and 6-OHDA HBr were obtained from Sigma Chemical Co. Cocaine was dissolved in sterile physiological saline. 6-OHDA was dissolved in a vehicle of saline with 0.1 mg/mL ascorbate and kept in a light-safe ice-filled bucket until infusion.

Surgery

Rats were anesthetized with a halothane/oxygen vapor mixture and implanted with chronic intravenous jugular catheters as previously described (Caine, Lintz, & Koob, 1993). The catheters consisted of polyethylene tubing fit to a guide cannula bent at a right angle and encased in dental cement. The cannula was anchored subcutaneously on the animal's back with a durable mesh, and the tubing was passed subcutaneously to the external jugular vein. All animals were allowed to recover for a minimum of 4 days before self-administration training. The patency of each catheter was maintained by flushing daily with heparinized (30 USP units/mL) sterile physiological saline. The integrity of each catheter was tested periodically by infusing 0.1 mL of Brevital® sodium (1% methohexital sodium), which resulted in pronounced loss of muscle tone within 3 s of i.v. injection.

Mesolimbic dopamine depletions were achieved by anesthetizing the animal (see above) and placing the head in a Kopf stereotaxic instrument with the toothbar set at +5.0 mm. Bilateral 30-gauge injectors were lowered into the region of the olfactory tubercle (+3.2 mm anterior to bregma, ± 1.7 mm from midline, -9.0 mm from skull surface), and 4 μ L of 6-OHDA in a volume of 1 μ L was infused over a period of approximately 3 min through each injector; 1 min later the injectors were raised into the region of the nucleus accumbens (-7.8 mm from skull surface), and the procedure was repeated. Sham-operated animals

were processed similarly but were infused with the vehicle only.

Apparatus

Testing chambers consisted of a Plexiglas® enclosure with a white houselight and a single aluminum lever that extended approximately 2.5 cm into the chamber. A food hopper was located at the center of one wall of the chamber, immediately to the right of the lever. Food reinforcers (45-mg A/L formula Noyes rodent pellets) were delivered via a Coulbourn E14-12 pellet feeder. A white cue light was mounted above the lever and the houselight was located at the top of the enclosure. A polyethylene tube with steel coil wrapping was inserted into the chamber through a small hole in the roof and was attached to the animal's catheter via an internal cannula. The tube was attached above the chamber to a steel swivel apparatus connected to a Razel® Model A infusion pump. The sessions were controlled using a Spider® computer system programmed in BBC BASIC computer language.

Behavioral Procedures

After habituation and handling for 1 week, animals were restricted to 3 g of rat chow per animal per day for 48 hr and then 18 to 20 g daily thereafter. Under this regimen, weights dropped an average of 12% in the first 48 hr and then slowly increased over the course of the study: The subjects weighed 296.3 ± 3.9 g (mean $\pm$ SEM) at the start of training and 352.5 ± 9.2 g at the end of the study. Beginning on the 3rd day of this regimen, the animals were trained on a fixed-ratio (FR) schedule of food reinforcement. The delivery of each reinforcer initiated a timeout, during which responses were recorded but were without scheduled consequences. The FR was gradually increased to a value of 15, and the timeout was gradually lengthened to 2 min. The delivery of each reinforcer was paired with illumination of the white cue light above the lever; this light remained on for the duration of the timeout. After reliable responding was maintained under this schedule on a daily basis, the animals were catheterized as described above. Following a minimum of 4 days recovery from surgery, the animals were trained on a multiple FR 15 schedule with a 2-min timeout after each reinforcement. Each reinforcer during the first and third 30-min components of

the 2-hr session consisted of one 45-mg food pellet, and each reinforcer during the second and fourth 30-min components consisted of one i.v. injection of 0.25 mg cocaine dissolved in 0.1 mL saline infused by activation of the Razel® pump for 4 s. Illumination of the white houselight served as a discriminative stimulus for the cocaine-reinforcement components. Each subject was maintained on this schedule 6 days per week until a minimum of three consecutive sessions with less than 20% variation in the total number of reinforcers in both reinforcer categories (cocaine and food) was recorded. As the animals achieved this baseline criterion, they were alternately assigned to be administered 6-OHDA or vehicle as described above ($n = 6$ per group). Substitution of saline for cocaine in the self-administration syringe was tested in 4 intact animals.

Neurochemical Measurements

Following completion of behavioral testing, all 6-OHDA- and vehicle-treated subjects were decapitated, and the brains were dissected on dry ice. Unfortunately, these tissues were lost during relocation of the laboratory in January 1992. Therefore, 12 other animals were treated with 6-OHDA ($n = 6$) or vehicle ($n = 6$) in an identical manner, were maintained under identical housing and feeding conditions for 14 days, and were then sacrificed accordingly. The frontal cortex, amygdala, olfactory tubercle, nucleus accumbens, and caudate-putamen were removed from thick coronal slices and were stored at -70°C until they were assayed for dopamine and dihydroxyphenylacetic acid (DOPAC) using electrochemical detection after separation by high-pressure liquid chromatography (Felice, Felice, & Kissinger, 1978).

Data Analysis

Due to individual variability in the baseline values for cocaine or food reinforcers earned in a session, all data were calculated within-subject and were analyzed as the percentage of each animal's mean baseline values for the last three consecutive sessions prior to treatments (lesion, sham, or saline substitution). The data for cocaine self-administration or food reinforcers for 10 consecutive sessions (as shown in Figures 1 and 2) were each subjected to a two-factor analysis of variance (ANOVA) with Treatment (6-OHDA, sham, or saline substitution) as a between-subjects factor and

Fig. 1. The effects of 6-OHDA or vehicle infusion into the nucleus accumbens and olfactory tubercle, or substitution of saline for cocaine, on the number of self-injections (top panel) or food pellets (bottom panel) earned in daily multiple-schedule sessions. Values are the mean of the individual subjects' percentage of baseline (6-OHDA and sham, $n = 6$ per group; saline substitution, $n = 4$). Inset shows the average standard error of the mean (SEM) for the data points

6-OHDA **VEHICLE** **SALINE SUBSTITUTION**

Fig. 2. The effects of 6-OHDA (top panel) or vehicle (middle panel) infusion into the nucleus accumbens and olfactory tubercle, or substitution of saline for cocaine (bottom panel), on the number of reinforcers earned in the multiple schedule on the last session prior to treatment and on the seventh session posttreatment for 3 individual animals. Each mark on the time line indicates delivery of a reinforcer (45-mg food pellet or 0.25-mg cocaine i.v. injection).

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shown on each panel. Asterisks indicate values significantly different from the sham group as revealed by Newman-Keuls post-hoc comparisons following significant main effects of Session and Treatment $\times$ Session interaction (* $p < .05$ or ** $p < .01$).

Table 1
Cocaine and food reinforcers earned in daily sessions for individual subjects.

Subject	Cocaine (day)						Food (day)					
	-3	-2	-1	+5	+6	+7	-3	-2	-1	+5	+6	+7
6-OHDA												
1	20	21	21	10	13	11	27	27	26	26	25	26
2	11	13	14	2	7	2	27	28	26	21	28	28
4	9	9	9	4	5	6	25	25	25	14	22	23
8	20	21	20	8	3	3	22	24	26	19	18	21
9	18	19	18	13	12	11	25	24	26	25	22	24
11	17	21	15	9	3	1	22	23	24	26	22	17
Vehicle												
3	18	15	19	28	25	23	16	15	19	19	21	19
5	10	13	16	11	13	13	12	13	12	9	12	13
6	13	13	15	12	19	14	25	23	27	26	28	28
10	19	19	17	16	24	18	14	14	12	22	25	25
12	12	17	12	14	14	12	23	27	26	28	29	30
13	8	11	10	10	12	12	30	30	27	26	26	30
Saline substitution												
14	12	19	14	4	3	6	26	28	28	20	28	28
15	15	16	16	1	1	5	18	26	25	15	4	22
16	10	13	10	5	7	4	27	26	27	30	30	30
17	15	18	18	21	11	9	22	27	23	30	29	29

Session as a within-subject factor with repeated measures. Following a statistically significant main effect, interactions were explored by one-way ANOVA and Newman-Keuls a posteriori tests. The effects of 6-OHDA on regional dopamine concentrations were analyzed by one-way ANOVA, and a statistically significant main effect was followed by Newman-Keuls a posteriori tests for independent brain regions. Level of significance was set at $p < .05$.

RESULTS

The effects of 6-OHDA or vehicle infused into the nucleus accumbens and olfactory tubercle, or saline substitution for cocaine in the self-administration syringe, on the percentage of baseline self-administration or food-reinforced behavior maintained under the multiple schedule are shown in Figure 1. Total numbers of cocaine self-injections and food pellets earned daily by each individual subject during the course of the study are shown in Table 1. Mean and standard error values for cocaine self-injections and food pellets earned in daily sessions during the three sessions prior to treatments were 15.19 ± 0.9 and 23.33 ± 1.2 , respectively, for the 16 subjects. Mean and standard error postoperative values for the last three sessions for the 6 animals treated with

6-OHDA were 6.83 ± 1.5 cocaine self-injections and 22.63 ± 1.2 food reinforcers, and for the 6 vehicle-treated animals were 16.08 ± 2.2 cocaine self-injections and 23.10 ± 2.7 food reinforcers per 2-hr session. Mean and standard error values for the last three sessions for animals receiving saline substituted for cocaine were 6.42 ± 1.6 self-injections and 24.6 ± 2.3 food reinforcers per 2-hr session.

Two-factor ANOVA of the self-administration data shown in Figure 1 revealed a significant main effect of Session, $F(2, 9) = 6.98$, $p < .0001$, and a Session $\times$ Treatment interaction, $F(2, 18) = 2.02$, $p < .01$. One-way ANOVA indicated that the treatment significantly altered self-administration in posttreatment Sessions 6, $F(2, 13) = 8.66$, $p < .01$, and 7, $F(2, 13) = 23.90$, $p < .0001$. Newman-Keuls a posteriori tests indicated that behavior in posttreatment Sessions 6 and 7 of the lesion group and the saline-substitution group was each different from that of the sham group ($p < .05$ in each case), but these two groups were not different from each other ($p > .1$). There were no statistically significant main effects of Treatment, $F(2, 13) = 2.38$, NS, or Session, $F(2, 9) = 0.248$, NS, on food-reinforced behavior.

Selected event records of the effects of 6-OHDA treatment or saline substitution on self-injections and food reinforcers earned for

Table 2
Levels of DA ($\mu\text{g/g}$ wet weight) in 6-OHDA- and vehicle-treated animals.

Brain region	6-OHDA	Vehicle	% Alteration
Nucleus accumbens***	1.23 (0.24)	5.68 (0.76)	-78.35
Olfactory tubercle***	2.59 (0.37)	5.77 (0.51)	-55.11
Caudate-putamen	9.42 (0.68)	10.48 (0.86)	-10.11
Amygdala	0.37 (0.03)	0.27 (0.04)	+37.04
Frontal cortex	0.14 (0.01)	0.15 (0.03)	-6.7

Values represent the mean and standard error of the mean (in parentheses).

*** Significant effect of 6-OHDA treatment ($p < .001$, Newman-Keuls independent comparisons following significant overall main effect by ANOVA).

3 individual subjects are shown in Figure 2. By Session 7 posttreatment, the individual values for all of the 6-OHDA-treated animals were 6, 15, 23, 56, 60, and 73% of prelesion cocaine self-administration values and were 74, 88, 104, 76, 96, and 90% of prelesion food-reinforcer values for these same animals. The individual values for all of the vehicle-treated animals in posttreatment Session 7 were 77, 100, 102, 103, 110, and 133% of preoperative cocaine self-administration totals and were 135, 98, 111, 90, 104, and 114% of preoperative food-reinforcer totals for these animals. The individual values for all of the animals receiving saline substituted for cocaine for seven sessions were 32, 40, 46, and 53% of cocaine self-administration totals and 103, 96, 112, and 121% of presubstitution food-reinforcer totals.

Neurochemical analyses of discrete brain regions (see Table 2) indicated a statistically significant overall depletion of dopamine, $F(1, 10) = 13.23$, $p < .01$, in 6-OHDA-treated animals relative to vehicle-injected controls. Post-hoc individual comparisons revealed that the depletion of dopamine was selective for the regions of the nucleus accumbens, $F(1, 10) = 30.78$, $p < .001$, and olfactory tubercle, $F(1, 10) = 25.36$, $p < .001$. Unfortunately, due to a technical failure (see Method), it was not possible to compare the degree of dopamine depletion with the behavioral changes for individual subjects.

DISCUSSION

Rats trained to self-administer cocaine and to obtain food pellets under a multiple FR 15 FR 15 schedule of reinforcement significantly decreased their self-administration of cocaine without altering their food-reinforced behavior following depletion of dopamine from the region of the nucleus accumbens and olfactory

tubercle. These results are in agreement with previous studies showing that mesolimbic dopamine depletion disrupted cocaine self-administration in rats trained to self-administer cocaine, but only transiently altered responding for food in a separate group of rats trained to respond for food under different schedule requirements (Roberts et al., 1977). Moreover, the degree of dopaminergic depletion, the time course of extinction of cocaine self-administration, and the magnitude of the decrease in self-administration observed here were all similar to that previously reported (Roberts et al., 1977, 1979).

It is important to note that the disruption of cocaine self-administration by mesolimbic dopamine depletion observed here cannot be attributed to the previously documented effects of these lesions on operant performance (Robbins et al., 1983), behavioral activation (Koob et al., 1978; Taghzouti et al., 1985), or general motivational excitement (Robbins & Koob, 1980), because responding for food under identical schedule requirements and within the same sessions remained unaffected. Finally, these findings complement those of Petit et al. (1984), which demonstrated that mesolimbic dopamine depletion can produce selective disruption of cocaine self-administration without altering responding for another reinforcer (i.v. heroin). The present results support the hypotheses that mesolimbic dopamine depletion disrupts cocaine self-administration by reducing the reinforcing effectiveness of cocaine, and that depletion of mesolimbic dopamine sufficient to disrupt cocaine self-administration does not necessarily alter other reinforcement processes.

The lack of alterations in responding maintained by food following mesolimbic dopamine depletion is in agreement with other studies. Such lesions do not attenuate food or water

intake under other conditions (Koob et al., 1978; Le Moal et al., 1977), nor do such lesions alter responding for food in an auditory and visual discrimination task (Robbins & Everitt, 1987) or in a reaction time task (Amalric & Koob, 1987). In contrast, performance in all of these behavioral paradigms is altered by lesions of the nigrostriatal dopamine pathways (Amalric & Koob, 1987; Fibiger, Phillips, & Zis, 1974; Marshall, Richardson, & Teitelbaum, 1974; Robbins & Everitt, 1987; Ungerstedt, 1971). It is tempting, therefore, to speculate that the documented effects of systemic administration of dopamine receptor antagonists on food reinforcement (Beninger et al., 1987; Ettenberg & Camp, 1986; Horvitz & Ettenberg, 1988; Nakajima & Baker, 1989; Rolls et al., 1974; Willner, Phillips, Sampson, & Muscat, 1989; Tombaugh, Tombaugh, & Anisman, 1979; Wise & Schwartz, 1981; Wise et al., 1978) are mediated by blockade of nigrostriatal, but not mesolimbic, dopaminergic pathways. However, the present data do not preclude an involvement of mesolimbic dopaminergic activity in food-reinforced behavior; rather, they suggest that a mesolimbic dopamine depletion of sufficient magnitude to disrupt cocaine self-administration does not disrupt food-reinforced behavior under the conditions used here. Indeed, much evidence supports a role for mesolimbic dopamine in preparatory and anticipatory phases of ingestive behavior (Hernandez & Hoebel, 1988; Phillips et al., 1991). Moreover, the rats used in this study were food restricted; therefore, the neural substrates regulating food acquisition and consumption may be different than those in free-feeding animals.

An alternative interpretation of the present results may involve rate dependency and the different reinforcement rates produced by cocaine and food under this multiple schedule. Although rate differences were not explicitly controlled in the present experiment, a previous study of the effects of mesolimbic dopamine depletion on operant behavior reported a suppression of high rates of responding late in fixed intervals (Robbins et al., 1983). It is difficult to interpret the present results as a rate-dependency effect based on those findings, because the responding in this study was higher for food than for cocaine, yet a selective effect on responding for cocaine was observed. Nevertheless, further studies to evaluate the effects of mesolimbic dopaminergic depletion

on multiple schedules of food and cocaine, in which the rates of responding for both reinforcers are equivalent, would address this question.

In summary, the observation that mesolimbic dopamine depletion disrupted cocaine self-administration without altering responding for food under a multiple schedule of reinforcement supports the hypothesis that cocaine self-administration in the rat is critically and selectively dependent upon mesolimbic dopamine. This work follows more than two decades of research to develop complex behavioral schedules of drug reinforcement such that, as stated by Brady and colleagues, "the contribution of the present research lies in the development of adequate controls for many of the nonspecific behavioral effects of the compounds studied" (Griffiths, Wurster, & Brady, 1975, p. 364). Thus, future studies using similar behavioral paradigms may provide valuable information with regard to the specific modulation of cocaine's reinforcing properties.

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