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Lesions of Central Serotonin Systems Affect Responding on a Progressive Ratio Schedule Reinforced Either by Intravenous Cocaine or by Food

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ROBERTS, D. C. S., E. A. LOH, G. B. BAKER AND G. VICKERS. *Lesions of central serotonin systems affect responding on a progressive ratio schedule reinforced either by intravenous cocaine or by food.* PHARMACOL BIOCHEM BEHAV **49**(1) 177–182, 1994.—The effect of intraventricular infusions of the serotonergic neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT), was examined in rats trained on a progressive ratio schedule for either IV cocaine or food reinforcement. Animals in the 5,7-DHT treatment group responded to significantly higher breaking points than vehicle-injected control animals, regardless of whether food or cocaine was used as the reinforcing stimulus. Analysis of the regional brain amines indicated that depletions of mesencephalic 5-HT correlated with postsurgical alterations in responding. These findings suggest that depletion of forebrain 5-HT produces a general effect on responding rather than a specific alteration in the reinforcing effects of psychomotor stimulant drugs.

Cocaine Self-administration Serotonin 5,7-Dihydroxytryptamine

COCAINE acts as an indirect agonist at dopamine (DA), 5-hydroxytryptamine (5-HT), and noradrenaline receptors (8). Because each of these transmitter systems has the potential to influence the reinforcing effects of cocaine, a substantial research effort has been directed to understanding their relative importance. Considerable evidence now indicates that the mesolimbic DA system plays a critical role in cocaine reinforcement [see (32) for review]. Pharmacological blockade of DA receptors attenuates the reinforcing effects of cocaine and amphetamine (3,6,7,11,29,39,43,45–47), and lesion experiments confirm that psychostimulant self-administration is disrupted by denervation of the DA input to the nucleus accumbens (19,25,34,46,47,49) or destruction of DA neurons in the ventral tegmental area (36). Further, binding studies have demonstrated a positive correlation between the reinforcing efficacy of cocaine analogs and their affinity for the DA transporter (30).

5-HT has also been implicated in the reinforcing effects of psychomotor stimulants, although its role is less clear. The rate of amphetamine or cocaine self-administration can be affected by a variety of 5-HT agonists and antagonists (16, 21,26,41,48). Interestingly, intracerebral infusions of 5,7-dihydroxytryptamine (5,7-DHT), a 5-HT neurotoxin, has been found to increase the rate of responding for psychostimulant drugs (16,20), although it is an open question whether such changes represent a diminution or an enhancement of the reinforcing effects.

Progressive ratio (PR) schedules have proved helpful in evaluating the effects of various pharmacological and neurotoxic treatments on cocaine self-administration (9,10,28). The dependent measure, breaking point, has been shown to be sensitive to dose (33,37), DA receptor blockade (37), and lesions to DA systems (13,31).

Using the PR schedule, we found that groups of animals

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that received 5,7-DHT infusions into the median forebrain bundle (MFB) or the amygdala responded to higher breaking points than did vehicle-injected controls (17). These data indicate that serotonin systems may play an inhibitory role in cocaine reinforcement because serotoninergic denervation appears to increase the motivation of animals to respond for intravenous cocaine. However, in our original study (17), considerable variability in the behavioral measure was noted within the 5,7-DHT-treated groups. Although some animals showed substantial increases in breaking points, other animals failed to show a change from baseline. This variability could not be accounted for by 5-HT depletions in any brain region examined. Furthermore, the possibility that the effect of 5,7-DHT treatments might produce a nonspecific effect on operant responding was not tested. In light of recent findings that lesions of 5-HT systems can significantly alter food reinforced behavior (44), it remains possible the observed increases in responding on the PR schedule might not be specific to cocaine.

The objectives of the present investigation were to replicate our previous observation of increased cocaine self-administration following 5,7-DHT lesions, to examine whether the behavioral measure correlates with the 5-HT depletions in specific anatomical regions, and to determine whether the 5-HT lesion effect is specific to cocaine or generalizes to food-reinforced responding.

METHOD

Subjects

Male Wistar rats were purchased from Charles River Farms (Quebec) at an initial weight of 275–300 g and following acclimatization, were maintained on a reversed 12-h day : night cycle for the duration of the experiment.

Cocaine Self-Administration Study

The rats were food deprived for 24 h, and trained to press a lever for food on an FR 1 schedule. Food was then available ad lib for the remainder of the study. Each rat was implanted with a chronically indwelling silastic jugular cannula that exited at the midscapular region [see (35) for details]. Following cannulation, the rats were housed singly in 50 cm × 50 cm × 40 cm testing chambers. Cannulae were mounted on counter balanced swivels, allowing free movement in the operant chamber.

Rats were allowed access to a lever for a 5-h period each day. Initially, each response on the lever activated a syringe driver that delivered 0.1 ml of saline solution containing 0.5 mg of cocaine HCl over a 5-s. period. This is roughly equivalent to a dose of 1.5 mg/kg/injection. Concurrent with the start of the injection, a stimulus light in the testing chamber was activated for 20 s. The light signalled a postinfusion time-out period when responses had no consequence. After subjects had developed a consistent pattern of responding (i.e., an injection every 7–10 min), a PR response schedule was initiated.

The PR schedule requires an increase in the number of responses to obtain each additional infusion of cocaine. At the start of each daily session the requirement was reset to 1. Responses for subsequent infusions increased according to the following progression: 2,4,6,9,12,15,20,25,32,40,50,62,77,95, 118,145,178,219,268,328,402,492,603.

This sequence is derived from the equation: ratio = $5 \times e^{(0.2 \times \text{infusion number})} - 5$ rounded to the nearest integer. See (38) for a discussion of exponential series in PR schedules. A rat was assumed to have reached the breaking point (BP) if it did not respond sufficiently to obtain an infusion for a 1-h period. BP was defined as the ordinal value of the last increment in the schedule completed. Typically, rats reach their BPs within the first 3 h of the session.

A stable baseline was defined as a period of 3 days in which responding did not vary by more than 4 BPs. The day after a stable baseline was established, each animal was prepared for stereotaxic surgery (see below). Following surgery, rats were allowed to recover for 1 day before being given access to cocaine. Rats were then permitted to self-administer cocaine on the PR schedule for 7 days.

Food Reinforcement Study

Two groups of rats (n = 12) were maintained on a food-restricted diet (12–15 g of Purina Rat Chow), which reduced weight gain to 1–2 g/day. Rats were individually housed in opaque plastic tubs except when being tested. The operant testing chambers used for this study were identical to those employed during the self-administration study. Rats were trained to press a lever for food using the same PR schedule described above. One 45 mg food pellet (Noyes Co., Lancaster, PA) was delivered upon completion of each ratio requirement of the schedule. A 5-s time-out period was signalled by the activation of a stimulus light. The breaking point was defined as the ordinal value of the final ratio achieved prior to either a 10-min period of nonresponding or failure to obtain a food pellet within 20 min.

After 5 days of stable responding had been established animals underwent stereotaxic surgery. After surgery, rats were allowed free access to food for a 24-h recovery period and were then reintroduced to the food-restricted diet and tested for a 10-day period. Rats were tested for an additional 4 days under extinction (nonreinforced) conditions. During these trials, responses sufficient to complete a ratio requirement turned on the stimulus light and activated the pellet dispenser, but no food pellets were presented.

Surgery

Thirty minutes prior to surgery animals were injected with desipramine (Sigma Chemicals, St. Louis, MO) 25 mg/kg IP, then anesthetized with halothane (Fluorothane, Ayerst, Montreal). Animals were given bilateral infusions (10 μg in 2 μl/2 min) of either 5,7-DHT (Sigma) or the ascorbic acid vehicle solution (0.2 mg/ml). Using a flat skull orientation (23) the 5,7-DHT and vehicle solutions were infused into the lateral ventricles via sterotaxically positioned 22 gauge cannulae (coordinates: AP −0.8, DV −3.2, ML ±1.3, relative to bregma). Once in position, a length of plastic tubing attached to the cannula was lifted above the level of the head of the animal. This allowed the solution to slowly drain into the ventricles. The amount of solution entering the ventricles was determined by the movement of a small air bubble positioned within the tubing. After the air bubble had moved a predetermined distance, indicating a 2 μl infusion, the tubing was then lowered to stop the infusion process. The cannula was left in place for approximately 1 min following each infusion.

Biochemical Analysis

Following behavioral testing, rats were decapitated and their brains were removed and quickly dissected on ice. Samples were then frozen in liquid nitrogen for subsequent bio-

chemical analysis. Six specific regions were dissected: cortex, caudate nucleus, nucleus accumbens septi, mesencephalon, amygdala, and hippocampus. A group of nonlesioned animals was also decapitated to serve as an additional comparison group. This group did not participate in the behavioral testing.

After homogenizing in ice-cold 0.1 N perchloric ascorbic acid (0.05 mM) and EDTA (10 mg%), samples were centrifuged to remove precipitating protein, and the supernatants were used for analysis of 5-HT and DA by high pressure liquid chromatography (HPLC) using a modification of the procedure described by Baker et al. (1). The HPLC system consisted of a solvent delivery system (Model 510, Waters Associates, Milford, MA, USA) coupled to an automatic injector (WISP, Waters Model 710B). Compounds of interest were separated on a Spherisorb 5 ODS (2) column (4.6 mm × 250 mm, 5 μm particle size, Phenomenex, Torrence CA) fitted with a precolumn (4.6 × 30 mm). Eluants from the column were detected by an electrochemical detector (Model 460, Waters) with applied potential set at 0.85 volt. Chromatographic peaks were recorded and integrated using a Model 740 integrator (Waters). The mobile phase for the HPLC system consisted of 55 mM $NaH_2PO_4 \cdot H_2O$, 0.73 mM octanesulfonic acid (sodium salt), 0.37 mM disodium EDTA, and 10% v/v acetonitrile; the pH value was adjusted to 3.0 with phosphoric acid.

RESULTS

Cocaine Self-Administration

Ten rats in the 5,7-DHT group and eight vehicle-treated rats completed the experiment. Figure 1 shows the average daily BP for each group before and after the lesion. Daily BPs of the groups were compared by a repeated measures ANOVA (SPSS-PC, Version 3.0). No significant difference was found between the groups on the three baseline days, $F(1, 16) = 1.74$, $p > 0.05$. Analysis of the postsurgical data revealed a significant group by day interaction, $F(6, 96) = 2.38$, $p < 0.05$. The 5,7-DHT-lesioned group demonstrated an average increase in BP of 33% on postsurgical testing days, although considerable variability was observed. In contrast, the overall performance of the rats that received the ascorbic acid infusions declined to 95% of control values.

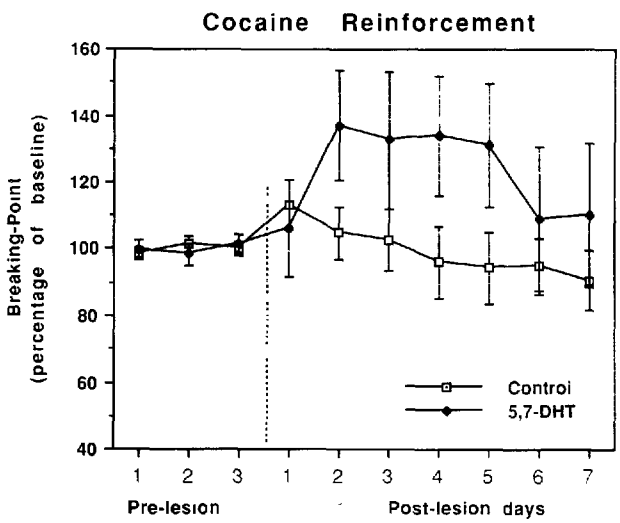

FIG. 1. The effect of 5,7-DHT lesions on breaking points established under a PR schedule for IV cocaine reinforcement. Each point represents the daily mean (±SEM) breaking point for groups of rats that received intraventricular infusions of either 5,7-DHT ($n = 10$) or vehicle ($n = 8$). Three baseline days are shown, followed by data from 7 consecutive postlesion days beginning 2 days after surgery.

Biochemical Results

Results of the HPLC analysis of tissue samples from the individual brain regions for both the 5,7-DHT and ascorbic acid vehicle groups are shown in Table 1. Because no significant differences were found between the data from five vehicle-injected animals and eight experimentally naive animals, the data were pooled to form a single control group. Concentrations of 5-HT in four out of the five brain regions from the 5,7-DHT group were significantly reduced compared with controls. The hippocampus showed the largest depletion (90%), while the remaining regions showed more modest reductions (range 14–34%). No significant difference between the 5,7-DHT and control groups was found in 5-HT levels in the amygdala or in the DA levels or the DA/DOPAC ratio in any brain region examined.

Food Reinforcement

Statistical comparison of the group receiving no surgery and the ascorbic acid vehicle group showed no significant difference in pre- or postsurgical BPs. Data from these two groups were combined to form a single control group. Repeated measures ANOVA reveal no statistically significant differences between the baseline BPs of the control and 5,7-DHT lesion groups. However, analysis of BPs on postsurgical days (1–10) demonstrated a significant group by day interaction, $F(9, 171) = 3.65$, $p < 0.001$. Postlesion BPs of all subjects were converted to percentage baseline scores. A subsequent Newman-Keuls comparison of groups for each postsurgical day revealed that the BPs of the lesioned group were significantly greater than controls on days 5, 6, and 8 ($p < 0.05$) (Fig. 2)

Repeated measures ANOVA of data from the 4 extinction days revealed a significant effect of day, $F(3, 57) = 20.47$, $p < 0.001$. Duncan's multiple range test revealed a significant difference between groups on day 4 ($p < 0.5$) (Fig. 3).

Biochemical Analyses

Student's *t*-test comparisons of the control and 5,7-DHT groups revealed significant reductions in 5-HT levels in all assayed brain regions of the lesioned group (Table 1). Three samples were unavailable for analysis—one each of nucleus accumbens septi and caudate of the lesion group, and one hippocampal sample of the control group. No statistically significant difference in DA content between the control and 5,7-DHT lesion groups was demonstrated in any of the brain regions analyzed.

Comparison of Behavioral and Neurochemical Results

To determine the relationship between the behavioral data and the effects of the 5,7-DHT infusions, the mean postsurgical percentage change in BP was compared with 5-HT content of each of the brain regions. In the cocaine reinforcement study, the only statistically significant correlation observed was between postsurgical increases in BP and the 5-HT content of mesencephalon ($r = -0.45$). In the food reward study, increase in BP were correlated with decreases in 5-HT content in the mesencephalon ($r = -0.49$), cortex ($r = -0.46$), and amygdala (-0.46).

TABLE 1
REGIONAL SEROTONIN CONTENT

	CTX	CAUD	NAS	MES	HIPPO	AMY
Cocaine Reinforcement						
Control	199.1	403.5	644.3	506.0	250.4	331.6
(SEM) n = 12	11.8	22.9	58.2	31.3	21.1	28.9
5,7-DHT	140.3	268.3	555.5	332.4	26.2	223.9
(SEM) n = 10	17.7	41.8	81.3	43.0	4.6	40.7
% control	70*	66*	86	65*	10*	71
Food reinforcement						
Control	205.2	506.0	593.4	514.5	154.4	539.2
(SEM) n = 12	10.6	31.6	36.6	25.9	11.9	39.0
5,7-DHT	38.4	177.2	252.4	316.5	1.6	81.9
(SEM) n = 9	7.0	33.3	45.9	20.2	1.2	20.0
% control	18*	35*	42*	61*	1*	15*

The Effect of intracerebral 5,7-DHT infusions on serotonin concentration (ng/g) in various brain regions. Abbreviations: cortex (CTX), caudate nucleus (CAUD), nucleus accumbens septi (NAS), mesencephalon (MES), hippocampus (HIP), and amygdala (AMY). Significant differences between lesion and control groups indicated by $*p > 0.05$.

DISCUSSION

In a previous study (17), we reported that groups of rats receiving 5,7-DHT infusions into either the MFB or the AMY responded on average to significantly higher BPs compared to controls. However, several aspects of our previous study suggested that further characterization of the phenomenon was necessary. Of particular concern was the large variability within the 5,7-DHT groups. Some of the rats showed dramatic increases in BP values after the lesion, although the others continued to respond at prelesion levels. Reductions in 5-HT content within the nucleus accumbens, amygdala, and cortex were observed, but the behavioral effect did not appear to correlate with 5-HT depletions in any of these areas. In the present study, we examined whether cocaine self-administration might be similarly affected by intracerebral infusions of 5-7,DHT, and if so, whether the behavioral effect could be linked to a pattern of 5-HT depletions. The results show that 5,7-DHT (ICV) produces increases in BPs on a PR schedule for cocaine reinforcement.

Again, the effect was not observed in all animals. Six of the 10 animals showed a clear increase, elevating their responding by up to seven BPs (corresponding to an increase in total responses ranging from 94 to 894 presses). An attempt was made to account for this variability by examining the neurochemical pattern of depletions produced by the neurotoxin. A small but significant correlation was found between depletions of 5-HT in the midbrain and increases in respond-

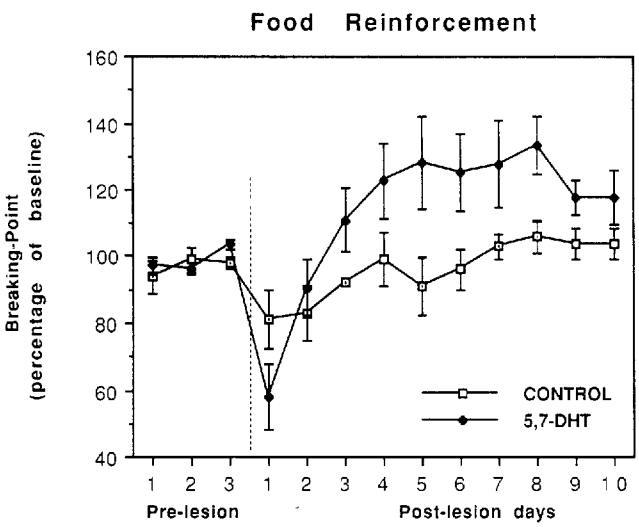

FIG. 2. The effect of 5,7-DHT lesions on breaking points established under a PR schedule for food reinforcement. Each point represents the daily mean (±SEM) breaking point for groups of rats (n = 12) that received intraventricular infusions of either 5,7-DHT or vehicle. Three baseline days are shown, followed by data from 10 consecutive postlesion days beginning 2 days after surgery.

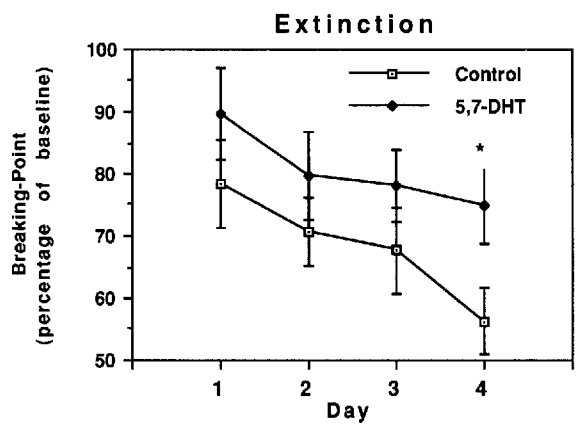

FIG. 3. The effect of 5,7-DHT lesions on responding during behavioral extinction. Animals were trained to respond on a PR schedule for food reinforcement. During extinction testing, the pellet dispenser discharged upon completion of each ratio of the PR sequence, although no pellet was delivered. Points represent the mean (±SEM) for groups of rats that received either 5,7-DHT or vehicle expressed as a percent of baseline responding. Asterisk indicates significant difference between groups.

ing. Depletions of 5-HT in the nucleus accumbens or amygdala did not correlate significantly with the behavioral data.

The present data are consistent with our previous report (17). One interpretation of the data is that the action of cocaine on 5-HT systems might be somehow aversive, with the result that the motivation to self-administer cocaine increases following removal of 5-HT systems. This suggestion is consistent with other 5-HT lesion studies that have reported increases in the rate of amphetamine intake following either intraventricular injections of 5,7-DHT (20) or 5,7-DHT lesions of the MFB (20). Conversely, the motivation to self-administer cocaine appears to diminish following stimulation of 5-HT receptors. Fluoxetine (27) and L-tryptophan (22) pretreatments significantly decrease the BP reached by rats self-administering cocaine on a PR schedule of reinforcement. In addition, a decrease in the rate of both cocaine and amphetamine intake have been reported following either fluoxetine (4,12,16,26,48) dietary L-tryptophan (5,41), systemic L-tryptophan, or quipazine pretreatments (18,20).

However, not all the data support the idea of a specific role for 5-HT in cocaine reinforcement. For example, it might be predicted that the blockade of 5-HT receptors would enhance the motivation to self-administer psychomotor stimulants by attenuating the hypothesized adverse effect. This prediction is not supported by experimental evidence. Lacosta and Roberts (14) have recently reported that cocaine self-administration on a PR schedule is unaffected by MDL 72222, ketanserin, or methysergide (5-HT_3, 5-HT_2, and nonspecific 5-HT antagonists, respectively). These findings are consistent with those of three other studies that report that ritanserin (a 5-HT_2 receptor antagonist) or GR23032F (a 5-HT_3 receptor antagonist) pretreatments fail to alter the rate of cocaine self-administration in rats (15,24).

To assess whether the increase in breaking points was due to a specific alteration in cocaine reinforcement, we examined the effect of 5,7-DHT lesions on responding for food reinforcement on a progressive ratio schedule. The postsurgical changes closely paralleled those observed in rats responding for cocaine reward (Fig. 2). This suggests that the lesion effect generalizes to a least one other reinforcer. Previous reports have shown that 5-HT depletion (42) or pharmacological blockade (2,40) causes perseveration. These data, together with the demonstration that the 5,7-DHT-lesioned animals showed elevated responding during extinction, indicates that they may have a general increase in motivation or an inability to withhold responding. It would appear that 5,7-DHT lesions produce a general alteration in behavior rather than a specific change in cocaine reinforcement mechanisms.

Finally, the 5-HT depletions produced by the neurotoxin deserve comment. 5,7-DHT caused dramatic reductions in 5-HT content in all animals from the food reinforcement study; however, the depletions from the animals in the cocaine self-adminstration experiment were less striking. Although the cocaine would have been cleared from the system by the time of the 5,7-DHT injections, it is likely that chronic cocaine treatment had an effect on transporter mechanisms, thus imparting a partial protective effect against the neurotoxin. We have observed this effect previously (unpublished observations) and it requires further study.

In summary, we have replicated earlier work showing 5-HT depletion causes increased BPs on a cocaine-maintained PR schedule and have extended this finding to a second reinforcer. The data show that support for a specific role for 5-HT in the reinforcing effect of cocaine is equivocal, and alternate explanations are becoming more attractive. Finally, correlational data indicate that the effect is most closely associated with depletion of mesencephalic 5-HT.

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REFERENCES

1. Baker, G. B.; Coutts, R. T.; Rao, T. S. Neuropharmacological and neurochemical properties of (N-(2-cyanoethyl)-2-phenylethylamine, a prodrug of 2-phenylethylamine. Br. J. Pharmacol. 92: 242-255; 1987.
2. Beninger, R. J.; Phillips, A. G. Possible involvement of serotonin in extinction. Pharmacol. Biochem. Behav. 10:37-41; 1979.
3. Bergman, J.; Kamien, J. B.; Spealman, R. D. Antagonism of cocaine self-administration by selective D_1 and D_2 antagonists. Behav. Pharmacol. 1:355-363; 1990.
4. Carroll, M. E.; Lac, S. T.; Asencio, M.; Kragh, R. Fluoxetine reduces intravenous cocaine self-administration in rats. Pharmacol. Biochem. Behav. 35:237-244; 1990.
5. Carroll, M. E.; Lac, S. T.; Asencio, M.; Kragh, R. Intravenous cocaine self-administration in rats is reduced by dietary L-tryptophan. Psychopharmacology (Berlin) 100:293-300; 1990.
6. Davis, W. M.; Smith, S. G. Positive reinforcing effects of apomorphine, *d*-amphetamine and morphine: Interaction with haloperidol. Pharmacologist 16:193; 1974.
7. De Wit, H.; Wise, R. A. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with noradrenergic blockers phentolamine and phenoxybenzamine. Can. J. Psychol. 31:195-203; 1977.
8. Galloway, M. P. Neurochemical modulation of monoamines by cocaine. In: Lakoski, J. M.; Galloway, M. P.; White, F. J., eds. Cocaine: Pharmacology, physiology, and clinical studies. Boca Raton, FL: CRC Press; 1992:163-190.
9. Hubner, C. B.; Koob, G. F. The ventral pallidum plays a role in mediating cocaine and heroin self-administration in the rat. Brain Res. 508:20-29; 1990.
10. Hubner, C.; Moreton, J. Effects of selective D_1 and D_2 dopamine antagonists on cocaine self-administration in the rat. Psychopharmacology (Berlin) 105:151-156; 1991.
11. Johanson, C.-E.; Kandel, D. A.; Bonese, K. F. The effects of perphenazine on self-administration behavior. Pharmacol. Biochem. Behav. 4:427-433; 1976.
12. Kleven, M. S.; Woolverton, W. L. Effects of three monoamine uptake inhibitors on behavior maintained by cocaine or food presentation in rhesus monkeys. Drug Alcohol Depend. 31:149-158; 1993.
13. Koob, G. F.; Vaccarino, F. J.; Amalric, M.; Bloom, F. E. Positive reinforcment properties of drugs: Search for neural substrates. In: Engel, J.; Oreland, L., eds. Brain reward systems and abuse. New York: Raven Press; 1987:35-50.
14. Lacosta, S.; Roberts, D. C. S. MDL 72222, ketanserin, and methysergide pretreatments fail to alter breaking points on a progressive ratio schedule reinforced by intravenous cocaine. Pharmacol. Biochem. Behav. 44:161-165; 1993.
15. Lane, J. D.; Pickering, C. L.; Hooper, M. L.; Fagan, K.; Tyers, M. B.; Emmett-Oglesby, M. W. Failure of ondansetron to block the discriminative or reinforcing stimulus effects of cocaine in the rat. Drug Alcohol Depend. 30:151-162; 1992.
16. Leccese, A. P.; Lyness, W. H. The effects of putative 5-hydroxytryptamine receptor active agents on *d*-amphetamine self-administration in controls and rats with 5,7-dihydroxytryptamine median forebrain bundle lesions. Brain Res. 303:153-162; 1984.

17. Loh, E. A.; Roberts, D. C. S. Break-points on a progressive ratio schedule reinforced by intravenous cocaine increase following depletion of forebrain serotonin. Psychopharmacology (Berlin) 101:262–266; 1990.
18. Lyness, W. H. Effect of L-tryptophan pretreatment on *d*-amphetamine self-administration. Subst. Alcohol. Action/Misuse 4:305–312; 1983.
19. Lyness, W. H.; Friedle, N. M.; Moore, K. E. Destruction of dopaminergic nerve terminals in nucleus accumbens: Effects of *d*-amphetamine self-administration. Pharmacol. Biochem. Behav. 11:553–556; 1979.
20. Lyness, W. H.; Friedle, N. M.; Moore, K. E. Increased self-administration of *d*-amphetamine after destruction of 5-hydroxytryptaminergic neurons. Pharmacol. Biochem. Behav. 12:937–941; 1980.
21. Lyness, W. H.; Moore, K. E. Increased self-administration of *d*-amphetamine by rats pretreated with metergoline. Pharmacol. Biochem. Behav. 18:721–724; 1983.
22. McGregor, A.; Lacosta, S.; Roberts, D. C. S. L-Tryptophan decreases the breaking point under a progressive ratio schedule of intravenous cocaine reinforcement in the rat. Pharmacol. Biochem. Behav. 44:651–655; 1993.
23. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. 2nd ed. Orlando, FL: Academic Press; 1986.
24. Peltier, R.; Schenk, S. GR38032F, a serotonin 5-HT_3 antagonist, fails to alter cocaine self-administration in rats. Pharmacol. Biochem. Behav. 39:133–136; 1991.
25. Pettit, H. O.; Ettenberg, A.; Bloom, F. E.; Koob, G. F. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berlin) 84:167–173; 1984.
26. Porrino, L. J.; Ritz, M. C.; Goodman, N. L.; Sharpe, L. G.; Kuhar, M. J.; Goldberg, S. R. Differential effects of the pharmacological manipulation of the serotonin system on cocaine and amphetamine self-administration. Life Sci. 45:1529–1536; 1989.
27. Richardson, N. R.; Roberts, D. C. S. Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. Life Sci. 49: 833–840; 1991.
28. Risner, M. E.; Cone, E. J. Intravenous self-administration of fencamfamine and cocaine by beagle dogs under fixed-ratio and progressive-ratio schedules of reinforcement. Drug Alcohol Depend. 17:93–102; 1986.
29. Risner, M. E.; Jones, B. E. Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacol. Biochem. Behav. 5:477–482; 1976.
30. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223; 1987.
31. Roberts, D. C. S. Breaking points on a progressive ratio schedule reinforced by intravenous apomorphine increase daily following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol. Biochem. Behav. 32:43–47; 1989.
32. Roberts, D. C. S. Neural substrates mediating cocaine reinforcement: The role of monoamine systems. In: Lakoski, J. M.; Galloway, M. P.; White, F. J., eds. Cocaine: Pharmacology, physiology and clinical strategies. Boca Raton, FL: CRC Press; 1992: 73–90.
33. Roberts, D. C. S. Self-administration of GBR 12909 on a fixed ratio and a progressive ratio schedule in rats. Psychopharmacology (Berlin) 111:202–206; 1993.
34. Roberts, D. C. S.; Corcoran, M. E.; Fibiger, H. C. On the role of ascending catecholamine systems in intravenous self-administration of cocaine. Pharmacol. Biochem. Behav. 6:615–620; 1977.
35. Roberts, D. C. S.; Goeders, N. E. Drug self-administration: Experimental methods and determinants. In: Boulton, A. A.; Baker, G. B.; Greenshaw, A. J., eds. Neuromethods, vol. 13th. Clifton, NJ: Humana Press; 1989:349–398.
36. Roberts, D. C. S.; Koob, G. F. Disruption of cocaine self-administration folowing 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacol. Biochem. Behav. 17:901–904; 1982.
37. Roberts, D. C. S.; Loh, E. A.; Vickers, G. J. Self-administration of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. Psychopharmacology (Berlin) 97:535–538; 1989.
38. Roberts, D. C. S.; Richardson, N. R. Self-administration of psychomotor stimulants using progressive ratio schedules of reinforcement. In: Wu, P.; Boulton, A.; Baker, G. B., eds. Neuromethods: Animal models of drug addiction, vol. 24. Clifton, NJ: Humana Press; 1992:263–269.
39. Roberts, D. C. S.; Vickers, G. J. Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioral screen for antipsychotic drug activity. Psychopharmacology (Berlin) 82:135–139; 1984.
40. Rosen, A. J.; Cohen, M. E. The effects of cinanserine, a potent serotonin antagonist, on acquisition of a runway response in the rat. Neuropharmacology 12:501–508; 1973.
41. Smith, F. L.; Yu, D. S. L.; Smith, D. G.; Leccese, A. P.; Lyness, W. H. Dietary tryptophan supplements attenuate amphetamine self-administration in the rat. Pharmacol. Biochem. Behav. 25: 849–854; 1986.
42. Srebro, B.; Lorens, S. A. Behavioral effects of selective midbrain raphe lesions in the rat. Brain Res. 89:303–325; 1975.
43. Wilson, M. C.; Schuster, C. R. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacology (Berlin) 26:115–126; 1972.
44. Wogar, M. A.; Bradshaw, C. M.; Szabadi, E. Evidence for an involvement of 5-hydroxytryptaminergic neurones in the maintenance of operant behaviour by positive reinforcement. Psychopharmacology (Berlin) 105:119–124; 1991.
45. Woolverton, W. L. Effects of a D_1 and D_2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol. Biochem. Behav. 24:531–535; 1986.
46. Yokel, R. A.; Wise, R. A. Increased lever pressing for amphetamine after pimozide in rats: Implication for a dopamine theory of reward. Science 187:547–549; 1975.
47. Yokel, R. A.; Wise, R. A. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology (Berlin) 48:311–318; 1976.
48. Yu, D. S. L.; Smith, F. L.; Smith, D. G.; Lyness, W. H. Fluoxetine-induced attenuation of amphetamine self-administration in rats. Life Sci. 39:1383–1388; 1990.
49. Zito, K. A.; Vickers, G. J.; Roberts, D. C. S. Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. Pharmacol. Biochem. Behav. 23: 1029–1036; 1985.