Pharmacology Biochemistry and Behavior, Vol. 44, pp. 161–165, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

MDL 72222, Ketanserin, and Methysergide Pretreatments Fail to Alter Breaking Points on a Progressive Ratio Schedule Reinforced by Intravenous Cocaine

SUSAN LACOSTA AND DAVID C. S. ROBERTS[1]

Department of Psychology, Carleton University, Ottawa K1S 5B6, Canada

Received 27 January 1992

LACOSTA, S. AND D. C. S. ROBERTS. *MDL 72222, ketanserin, and methysergide pretreatments fail to alter breaking points on a progressive ratio schedule reinforced by intravenous cocaine.* PHARMACOL BIOCHEM BEHAV 44(1) 161–165, 1993.—The effects of three serotonin [5-hydroxytryptamine (5-HT)] receptor antagonists on cocaine self-administration behavior were investigated. Specifically, the effects of MDL 72222 (a specific 5-HT_3 receptor antagonist), ketanserin (a specific $5HT_2$ receptor antagonist), and methysergide (an aselective 5-HT_1/5-HT_2 receptor antagonist) on the breaking points reached by rats on a progressive ratio schedule for cocaine reinforcement were examined. Pretreatments with MDL 72222 (7.5–1,920 μg/kg, SC), ketanserin (0.4–6.4 mg/kg, IP), and methysergide (2.5–20 mg/kg, IP) failed to alter breaking points from baseline values. Although tested at twice the highest doses previously reported to have significant behavioral effects, the three 5-HT receptor antagonists were without effect. These data suggest that relatively specific blockade of 5-HT receptor subtypes does not influence the reinforcing effects of cocaine.

Cocaine Self-administration MDL 72222 Ketanserin Methysergide Serotonin 5-HT_1 5-HT_2 5-HT_3 Progressive ratio

THE importance of dopamine (DA) in the reinforcing effects of psychomotor stimulant drugs has been well established (24). More recently, studies have indicated that serotonin [5-hydroxytryptamine (5-HT)] may also play an important role in the reinforcing properties of both amphetamine and cocaine. Increases in the rate of amphetamine self-administration have been found in rats depleted of forebrain serotonin following either intraventricular injections of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) (16) or 5,7-DHT lesions of the median forebrain bundle (MFB) (14). Conversely, fluoxetine (a 5-HT reuptake inhibitor) (14,20,33), quipazine (a 5-HT receptor agonist) (14), and both systemic (14) and dietary (31) pretreatments of L-tryptophan (a 5-HT precursor) decreased the rate of amphetamine self-administration.

Fewer studies have examined the effects of serotonergic manipulations on cocaine self-administration although these data appear to be consistent with the amphetamine work. Specifically, both repeated (7) and acute (19) pretreatment with fluoxetine (7,19) or repeated administration of dietary tryptophan (8) significantly diminished the rate of cocaine self-administration.

Because agonist pretreatments decrease the rate of cocaine intake, one might predict an increase in the rate of cocaine self-administration following pretreatment with 5-HT antagonists. Unfortunately, the data do not support this hypothesis. Instead, pretreatment with cinanserin, ritanserin (both 5-HT_2 receptor antagonists), or GR23032F (a 5-HT_3 receptor antagonist) failed to alter the rate of cocaine self-administration (18–20).

In the above-mentioned studies, rate of drug intake was used as the dependent variable, which in many cases is difficult to interpret. For example, changes in the rate of drug intake have been depicted as reflecting both an increase and a decrease in drug reinforcement (32,34). Further, changes in an animal's motivation to self-administer a drug can be detected by alterations in breaking points obtained from a progressive ratio (PR) schedule even when no changes in rate are observed (15,23,25,27).

Our lab recently employed a PR schedule of reinforcement to better assess the role of 5-HT systems in cocaine self-administration. For example, an increase in breaking points was found following intracerebral infusions of 5,7-DHT into

[1] To whom requests for reprints should be addressed.

either the MFB or amygdala (15). These findings support the idea that the motivation to self-administer cocaine is increased following the removal of 5-HT systems.

Conversely, pretreatment with certain pharmacological agents has been found to significantly decrease the breaking points reached by rats self-administering cocaine on a PR schedule of reinforcement. Specifically, systemic pretreatment with either fluoxetine (a specific 5-HT reuptake inhibitor) (21) or L-tryptophan (a 5-HT precursor) (17) diminished breaking points for cocaine reinforcement.

The above studies using a PR schedule have shown that stimulation of 5-HT receptors decreases an animal's motivation to self-administer cocaine. As a result, it might be predicted that under a similar reinforcement schedule blockade of 5-HT receptors would diminish the inhibitory effect of these receptors, thereby increasing the reinforcing efficacy of cocaine.

The purpose of the present study was to examine the effects of three 5-HT receptor antagonists on cocaine self-administration behavior using a PR schedule of reinforcement. Specifically, the effects of MDL 72222 (a specific 5-HT_3 receptor antagonist), ketanserin (a specific 5-HT_2 receptor antagonist), and methysergide (an aselective 5-HT_1/5-HT_2 receptor antagonist) on breaking points established by rats on a PR schedule for cocaine reinforcement were investigated.

METHOD

Subjects

Male Wistar rats (Charles River Farms, Quebec, Canada) weighing approximately 275–300 g at the start of the experiments served as subjects. Rats were individually housed and maintained on a 12 D : 12 L reversed cycle (lights off 9:30 a.m.–9:30 p.m.). Food and water were freely available.

Apparatus

Plexiglas boxes (25 × 25 × 25 cm) served as both animal housing and testing chambers. Each box was equipped with a wire grid floor, a removable response lever mounted on one wall, a stimulus light placed to the left of the lever, and a water bottle. Rats were surgically implanted with chronically indwelling jugular cannulae. The cannulae were attached to tubing encased within a protective spring. The tubing, held in suspension above the cage by a counterbalance and swivel, extended to a 10-ml syringe. Infusions of cocaine HCl were delivered to animals by a Razel syringe driver fitted with a 5-RPM motor. The counterbalanced swivel allowed animals free movement in the testing chamber. Response monitoring, infusion delivery, and data recording were controlled by an IBM-compatible computer.

Procedure

Approximately 1 week following their arrival from the supplier, rats were food deprived for 24 h and then trained to press a lever for food reward (Noyes pellets) on a fixed ratio (FR) 1 schedule of reinforcement. Once animals exceeded 100 lever responses in each of two training sessions, they were anesthetized using sodium pentobarbitol (Somnotol, 60 mg/kg, IP) and surgically implanted with a chronically indwelling jugular cannula exiting from the animal's back at the midscapular region (26). Following cannulation, rats were singly housed in operant testing chambers.

Initially, rats were postoperatively trained to respond on a lever for cocaine infusions on an FR 1 schedule of reinforcement. Specifically, each lever response resulted in the delivery of a cocaine injection (0.6 mg/0.12 ml saline/injection over 5 s). Concurrent with the start of injection, a stimulus light was activated that signaled a 20-s postinfusion time-out period during which time responses produced no programmed consequence. Cocaine self-administration sessions took place for a 5-h period daily. Each session began with the introduction of the lever into the testing chamber and a "priming" injection.

After a rat achieved a constant rate of responding on an FR 1 schedule of reinforcement (a minimum of 3 consecutive days in which the total number of daily infusions varied no more than 10%), a PR schedule was imposed. In accordance with this schedule, the first lever response of the session resulted in a drug infusion while the response requirements required to obtain subsequent infusions were incremented following the progression: 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603. The initial ratio was reset to 1 at the beginning of each session.

Typically, rats will respond during the first 3 h of a session but fail to respond during the last 2 h, when the requirements imposed by the PR schedule become too demanding. A rat was assumed to have reached its breaking point if it failed to obtain an infusion for a 1-h period. In this case, the breaking point was defined as the last increment in the schedule completed prior to a 1-h period of nonreinforcement. This breaking point served as the dependent measure.

Pretreatments

Once a rat had established a consistent baseline level of responding on a PR schedule of reinforcement for 3 consecutive days, it was placed into one of three 5-HT receptor antagonist drug pretreatment experiments:

1. *MDL 72222:* (7.5, 15, 30, 60, 120, 960, or 1,920 μg/kg, SC) 30 min prior to testing.
2. *Ketanserin:* (0.4, 0.8, 1.6, 3.2, or 6.4 mg/kg, IP) 1 h prior to testing.
3. *Methysergide:* (vehicle, 2.5, 5, 10, or 20 mg/kg, IP) 1 h prior to testing.

In each experiment, five animals were tested at each dose. Animals were replaced in the event of illness or cannula failure. As a result, not all rats received all doses of drug. All drug doses were administered in a counterbalanced fashion. Animals in the methysergide study also received a vehicle injection of distilled water (1 ml/kg). Rats were required to reestablish a stable daily breaking point for 3 days before being given the next dose of drug.

Drugs

Cocaine HCl, supplied by NIDA (Bethesda, MD), was prepared in a vehicle solution of 0.9% saline. MDL 72222 [Research Biochemicals, Inc. (RBI), Natick, MA] was dissolved in one drop of glacial acetic acid and taken to volume with distilled water. The final solution was adjusted to a pH of 5–6 with 1 N NaOH. Ketanserin (RBI) was dissolved in 0.9% saline. Methysergide (Sandoz Canada, Inc., Dorval, Quebec, Canada) was dissolved in three to five drops of HCl and taken to volume with distilled water. The final solution was adjusted to a pH of 5–6 with 1 N NaOH. All three 5-HT receptor antagonists were injected in a volume of 1.0 ml/kg body weight.

Statistical Analyses

All analyses were performed on the breaking points. Mean breaking points established following drug pretreatment were compared with those established the day previous to testing using a two-way (treatment × dose) repeated-measures analysis of variance (ANOVA). Treatment served as the within-subjects measure and dose as the between-subjects measure.

RESULTS

Figures 1, 2, and 3 show the effects of MDL 72222, ketanserin, and methysergide, respectively, on the breaking points achieved by rats self-administering cocaine on a PR schedule of reinforcement. Analysis using a repeated two-way ANOVA revealed no significant main effects of treatment or dose and no significant treatment × dose interactions of either MDL 72222 [treatment, $F(1, 28) < 1$, NS, dose, $F(6, 28) < 1$, NS, treatment × dose, $F(6, 28) < 1$, NS] or methysergide [treatment, $F(1, 20) < 1$, NS, dose, $F(4, 20) < 1$, NS, treatment × dose, $F(4, 20) < 1$, NS]. Similar analysis revealed a significant main effect of treatment within animals for ketanserin, $F(1, 20) = 6.05$, $p < 0.05$. This significant treatment effect is probably not related to ketanserin but to the handling of animals because no main effect of dose, $F(4, 20) < 1$, NS, or treatment × dose interactions, $F(4, 20) < 1$, NS, were evident. In addition to breaking points, both the response rate and time of establishing breaking point remained unchanged following 5-HT antagonist pretreatments as compared to baseline values (data not shown).

DISCUSSION

Pretreatments with MDL 72222 (7.5–1,920 μg/kg, SC), ketanserin (0.4–6.4 mg/kg, IP), or methysergide (2.5–20 mg/kg, IP) failed to alter the breaking points reached by rats self-administering cocaine on a PR schedule of reinforcement from baseline values. These data suggest that the relatively specific blockade of 5-HT receptor subtypes does not influence the reinforcing effects of cocaine.

Several studies employing the PR schedule of reinforcement have demonstrated an important, albeit inhibitory, role for 5-HT in cocaine reinforcement. For example, increases in breaking points have resulted from bilateral 5,7-DHT lesions of both the MFB and amygdala (15). Thus, the motivation to

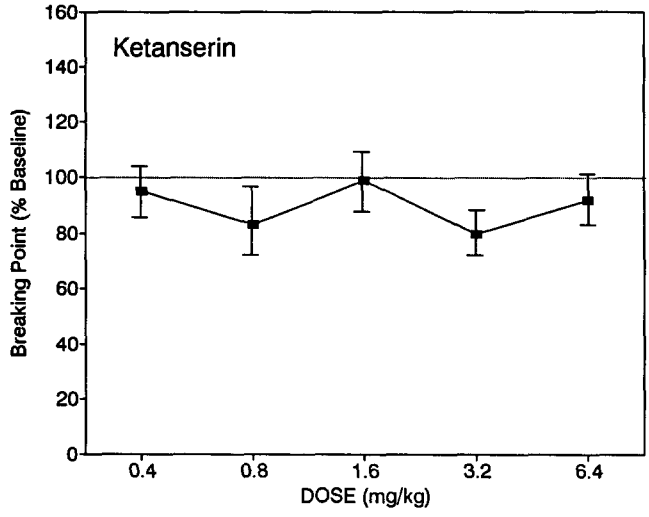

FIG. 2. Effect of ketanserin pretreatment on the breaking points reached by rats self-administering cocaine on a PR schedule of reinforcement. The mean (±SEM) breaking point values following pretreatment with ketanserin (0.4, 0.8, 1.6, 3.2, or 6.4 mg/kg, IP) are shown. Five rats were tested at each dose. All values are expressed in terms of percent of baseline performance. The SE bars refer to the mean SEMs for each dose group.

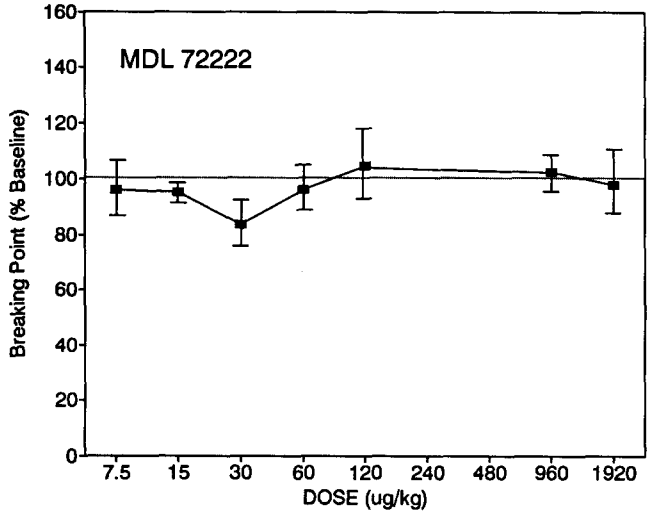

FIG. 1. Effect of MDL 72222 pretreatment on the breaking points reached by rats self-administering cocaine on a PR schedule of reinforcement. The mean (±SEM) breaking point values following pretreatment with MDL 72222 (7.5, 15, 30, 60, 120, 960, or 1,920 μg/kg, SC) are shown. Five rats were tested at each dose. All values are expressed in terms of percent of baseline performance. The SE bars refer to the mean SEMs for each dose group.

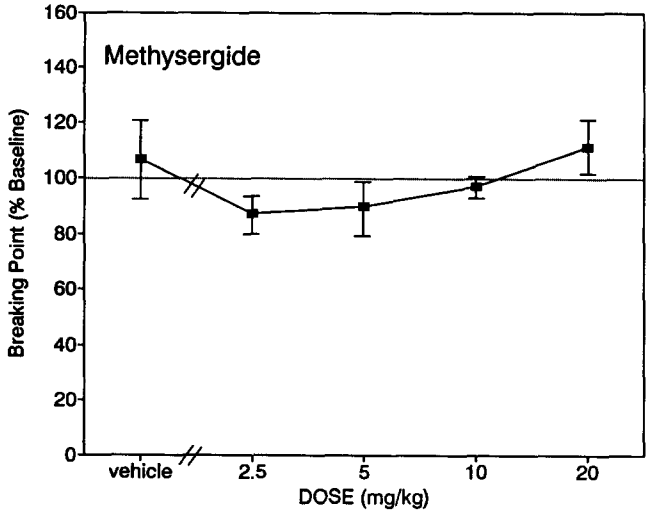

FIG. 3. Effect of methysergide pretreatment on the breaking points reached by rats self-administering cocaine on a PR schedule of reinforcement. The mean (±SEM) breaking point values following pretreatment with methysergide (2.5, 5, 10, or 20 mg/kg, IP) and vehicle (1 ml/kg) are shown. Five rats were tested at each dose. All values are expressed in terms of percent of baseline performance. The SE bars refer to the mean SEMs for each dose group.

self-administer cocaine appears to increase following removal of 5-HT systems. These findings are consistent with other 5-HT lesion studies, which have reported increases in the rate of amphetamine intake following either intraventricular injections of 5,7-DHT (16) or 5,7-DHT lesions of the MFB (14).

Conversely, the motivation to self-administer cocaine seems to diminish following stimulation of 5-HT receptors. Fluoxetine (21) and L-tryptophan (17) pretreatments significantly decrease the breaking points reached by rats self-administering cocaine on a PR schedule of reinforcement. These data are supported by studies reporting a decrease in the rate of both cocaine and amphetamine intake following either fluoxetine (7,19,20), dietary L-tryptophan (8,31), systemic L-tryptophan (14), or quipazine (14) pretreatments.

A significant role for 5-HT in cocaine reinforcement is also evident from the receptor binding studies of Ritz et al. (22). Specifically, these researchers revealed a negative relationship between the reinforcing efficacy of cocaine analogs in self-administration studies and their binding potencies at 5-HT reuptake sites.

In summary, the above data suggest that 5-HT plays an important, possibly inhibitory, role in cocaine reinforcement. As a result, it might be predicted that the blockade of 5-HT receptors would diminish the adverse effect of 5-HT, thereby increasing the reinforcing efficacy of cocaine. The findings of this study do not support this hypothesis because the relatively specific blockade of 5-HT receptor subtypes failed to alter cocaine's reinforcing properties. Our findings are consistent with those of three studies that report the inability of cinanserin (a 5-HT_2 receptor antagonist) (17), ritanserin (a 5-HT_2 receptor antagonist) (16), or GR23032F (a 5-HT_3 receptor antagonist) (15) pretreatments to alter the rate of cocaine self-administration in rats.

It might be argued that the PR schedule is insensitive to changes in drug reinforcement. However, the PR schedule used in this study has been shown to be sensitive to changes in drug dose and a variety of pharmacological manipulations and neurotoxic lesions (15,17,21,23,25,27).

There are several possible reasons why 5-HT lesions might increase the reinforcing effect of cocaine while 5-HT antagonists have no effect. First, 5-HT lesions and 5-HT antagonist pretreatments do not inhibit 5-HT function in either the same manner or extent. For example, while 5-HT lesions result in the chronic and nonspecific destruction of 5-HT functioning, the 5-HT antagonist pretreatments employed in this study were acute and relatively specific to the 5-HT receptor subtypes. As a result, possibly the chronic rather than acute blockade of 5-HT receptor subtypes is necessary to alter cocaine's reinforcing properties.

Second, evidence suggests that 5-HT lesions may result in compensatory changes in other neurotransmitter systems such as dopamine (30). It is possible, then, that increases in the motivation to self-administer cocaine following 5-HT lesions may be due to an indirect change in DA function and not the attenuation of 5-HT function.

Alternatively, it may be argued that the failure to find a significant effect of 5-HT antagonist pretreatments on cocaine self-administration behavior results from employing insufficient doses. This seems unlikely, however, because doses similar to those used in this study have been employed successfully in other behavioral studies (3,6,10,12,14,28,29).

Significant behavioral effects of MDL 72222 have been reported with doses as low as 30 μg/kg although other studies have used doses as high as 1 mg/kg (13). At a relatively low dose, MDL 72222 (30 μg/kg) has been effective in blocking morphine-, nicotine- (2,6), and MDMA-induced place preference (3) and reducing the effects of naloxone, picrotoxin, and phencyclidine (PCP) in drug-induced place aversion tests (1).

Ketanserin has been shown to produce significant behavioral effects at a dose of 3.2 mg/kg. Specifically, a significant reduction in lysergic acid diethylamide (LSD) self-administration behavior has been found following pretreatment with 3.2 mg/kg ketanserin while even lower doses of the drug (0.2–1.6 mg/kg), dose dependently reduced lever responding for LSD by blocking the LSD cue (10). Similar doses have also been found to attenuate the behavioral side effects induced by both L-5-HTP and 5-Me-ODMT pretreatments (28).

Studies have reported significant behavioral effects of methysergide at doses as low as 2.5–10 mg/kg. At this dose range, methysergide significantly augments MDMA-induced locomotor hyperactivity (12). Similarly, at a dose of 10 mg/kg methysergide significantly attenuates amphetamine self-administration (14) and potentiates the rate-increasing effect of amphetamine on self-stimulation behavior (29).

We examined the effects of MDL 72222, ketanserin, and methysergide at doses ranging from 15–1,920 μg/kg, 0.4–6.4 mg/kg, and 2.5–20 mg/kg, respectively. Although tested at twice the highest dose reported to have significant behavioral effects, each drug pretreatment failed to significantly alter cocaine reinforcement from baseline levels.

The inability to find a significant change in cocaine self-administration behavior following pretreatment with 5-HT antagonists may have resulted from using inappropriate drug pretreatment intervals. The injection times employed in this study have been based upon those used successfully in other behavioral studies (3,6,10,14). We acknowledge the fact that in our experiments the breaking point is not established for approximately 2 h into the self-administration session. Therefore, it is possible that the time course of drug actions for the three 5-HT antagonists tested were ineffective within this experimental paradigm.

In summary, it appears that relatively specific, acute blockade of 5-HT_3, 5-HT_2, and 5-HT_1 receptor subtypes does not influence the reinforcing effects of cocaine. Thus, possibly either the blockade of other 5-HT receptor subtypes, simultaneous blockade of all 5-HT subtypes, or chronic blockade of one or more 5-HT subtypes may be required to alter cocaine reinforcement.

ACKNOWLEDGEMENTS

The authors thank Sandoz Canada, Inc. (Dorval, Quebec), for their generous gift of methysergide used in this study. This research was funded by a grant from the M.R.C. (of Canada) and a contract from the National Institute on Drug Abuse (No. 271-90-7401).

REFERENCES

1. Acquas, E.; Carboni, E.; Garau, L.; Di Chiara, G. Blockade of acquisition of drug-conditioned place aversion by $5HT_3$ antagonists. Psychopharmacology (Berl.) 100:459–463; 1990.
2. Acquas, E.; Carboni, E.; Leone, P.; Di Chiara, G. 5-HT_3 receptor antagonists block morphine- and nicotine- but not amphetamine-induced place-preference conditioning. Pharmacol. Res. Comm. 20:1113–1114; 1988.
3. Bilsky, E. J.; Reid, L. D. MDL 72222, a serotonin 5-HT_3 receptor

antagonist, blocks MDMA's ability to establish a conditioned place preference. Pharmacol. Biochem. Behav. 39:509–512; 1991.
4. Blandina, P.; Goldfarb, J.; Craddock-Royal, B.; Green, J. P. Release of endogenous dopamine by stimulation of 5-hydroxytryptamine$_3$ receptors in rat striatum. J. Pharmacol. Exp. Ther. 251:803–809; 1989.
5. Blandina, P.; Goldfarb, J.; Green, J. Activation of a 5-HT$_3$ receptor releases dopamine from rat striatal slice. Eur. J. Pharmacol. 155:349–350; 1988.
6. Carboni, E.; Acquas, E.; Leone, P.; Di Chiara, G. 5-HT$_3$ receptor antagonists block morphine and nicotine but not amphetamine induced reward. Psychopharmacology (Berl.) 97:175–178; 1989.
7. 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.
8. Carroll, M. E.; Lac, S. T.; Asencio, M.; Kragh, R. Intravenous cocaine self-administration in rats is reduced by dietary L-tryptophan. Psychopharmacology (Berl.) 100:293–300; 1990.
9. Chen, J.; van Praag, H. M.; Gardner, E. L. Activation of 5-HT$_3$ receptor by 1-phenylbiguanide increases dopamine release in the rat nucleus accumbens. Brain Res. 543:354–357; 1991.
10. Cunningham, K. A.; Appel, J. B. Neuropharmacological reassessment of the discriminative stimulus properties of *d*-lysergic acid diethylamide (LSD). Psychopharmacology (Berl.) 91:67–73; 1987.
11. Frazer, A.; Maayani, S.; Wolfe, B. B. Subtypes of receptors for serotonin. Annu. Rev. Pharmacol. Toxicol. 30:307–348; 1990.
12. Gold, L. H.; Koob, G. F. Methysergide potentiates the hyperactivity produced by MDMA in rats. Pharmacol. Biochem. Behav. 29:645–648; 1988.
13. Higgins, G. A.; Joharchi, N.; Nguyen, P.; Sellers, E. M. Effect of the 5-HT$_3$ receptor antagonists, MDL 72222 and ondansetron, on morphine place conditioning. Psychopharmacology (Berl.) 106:315–320; 1992.
14. 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.
15. 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 (Berl.) 101:262–266; 1990.
16. 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.
17. McGregor, A.; Lacosta, S.; Roberts, D. C. S. L-Tryptophan decreases the breaking point under a progressive ratio schedule of intravenous cocaine self-administration in the rat. Pharmacol. Biochem. Behav. (in press).
18. 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.
19. Peltier, R.; Schenk, S. The effects of serotonergic manipulations on cocaine self-administration in rats. Neurosci. Abstr. 17: 889; 1991.
20. 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 serotonin systems on cocaine and amphetamine self-administration in rats. Life Sci. 45:1529–1535; 1988.
21. 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.
22. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to the self-administration of cocaine. Science 237:1219–1223; 1987.
23. 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.
24. 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.
25. Roberts, D. C. S.; Bennett, S. A. L.; Vickers, G. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology (Berl.) 98:408–411; 1989.
26. Roberts, D. C. S.; Goeders, N. Drug self-administration: Experimental methods and determinants. In: Boulton, A. A.; Baker, G. B.; Greenshaw, A. J., eds. Neuromethods. vol. 13. Clifton, NJ: Humana Press; 1989:349–398.
27. Roberts, D. C. S.; Loh, E. A.; Vickers, G. Self-administration of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. Psychopharmacology (Berl.) 97:535–538; 1989.
28. Shearman, G. T.; Tolcsvai, L. Effect of the selective 5-HT$_3$ receptor antagonists ICS 205-930 and MDL 72222 on 5-HTP-induced head shaking and behavioral symptoms induced by 5-methoxy-*N*,*N*,dimethyltryptamine in rats: Comparison with some other 5-HT receptor antagonists. Psychopharmacology (Berl.) 92:520–523; 1987.
29. Silveira Filho, N. G.; Graeff, F. G. Effect of tryptamine antagonists on self-stimulation. Psychopharmacology (Berl.) 52:87–92; 1977.
30. Simon, H.; Stinus, L.; Le Moal, M. Effects de la lesion des noyaux du raphe sur l'autoadministration de *D*-amphetamine chez le rat: Augmentation considerable de l'appetence au toxique. CR Acad. Sci. Paris 290:225–258; 1980.
31. 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.
32. Wilson, M. C.; Schuster, C. R. Cholinergic influence on intravenous cocaine self-administration in the rhesus monkey. Pharmacol. Biochem. Behav. 1:643–649; 1973.
33. 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; 1986.
34. Yokel, R. A.; Wise, R. A. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. Psychopharmacology (Berl.) 48:311–318; 1976.