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Attenuation of the Effects of Cocaine on Milk Consumption in Rats by Dopamine Antagonists

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RAPOZA, D. AND W. L. WOOLVERTON. *Attenuation of the effects of cocaine on milk consumption in rats by dopamine antagonists.* PHARMACOL BIOCHEM BEHAV **40**(1) 133–137, 1991.—Recent research suggests the both D_1 and D_2 dopamine (DA) receptors play an important role in the behavioral effects of psychomotor stimulants. The present study utilized selective DA antagonists to examine the role of DA receptors in the effects of cocaine on milk intake in rats. Male Sprague-Dawley rats were given access to a milk solution (2:1 tap water:Bordens sweetened condensed milk) for 15 min each day. When milk intake was stable, dose-response functions were determined for cocaine (4.0–32 mg/kg, IP, 10 min presession) administered alone or in combination with the D_1 antagonist SCH 23390 (0.12–0.5 mg/kg, IP, 30 min presession) or the D_2 antagonist raclopride (0.25–1.0 mg/kg, IP, 30 min presession). As a control for the serotonin ($5\text{-}HT_2$) antagonist effects of SCH 23390, the $5\text{-}HT_2$ antagonist ketanserin (4.0–16 mg/kg) was evaluated as well. To control for nonspecific drug effects on fluid consumption, the effects of cocaine alone on water intake were determined in a separate group of rats. All drugs decreased milk intake when given alone. Both SCH 23390 and raclopride attenuated the effects of at least one dose of cocaine. Ketanserin did not alter the effects of cocaine. These results suggest that stimulation of both D_1 and D_2, but not $5\text{-}HT_2$, receptors is involved in the effects of cocaine on milk intake in rats.

Cocaine Dopamine D_1 receptors D_2 receptors SCH 23390 Raclopride Food intake Water intake Rat

A decrease in food intake following acute administration of cocaine has been demonstrated in a variety of feeding paradigms (2, 3, 6, 8, 10, 11, 17, 23, 28, 29). Although dopamine (DA) apparently plays a major role in several of the behavioral effects of cocaine, the role of DA (or other neurotransmitters) in cocaine-induced decreases in food intake has not been extensively examined. Heffner et al. (11) reported that pretreatment with the selective DA antagonist spiroperidol antagonized the cocaine-induced decrease in food intake. Similarly, DA antagonists have been found to antagonize or have no effect upon amphetamine-induced decreases in food intake (7, 9, 11). These findings suggest that DA receptors play a role in the effects of psychomotor stimulants on food intake.

As cocaine is an indirect DA agonist, its behavioral effects may involve D_1 or D_2 DA receptors or both. That spiroperidol, primarily a D_2 antagonist, can attenuate the effects of cocaine suggests a role for D_2 receptors. However, the role, if any, of D_1 receptors in the effects of cocaine on food intake has not been established. The D_1 antagonist SCH 23390 has been reported to antagonize the effect of either *d*- or *l*-amphetamine on food intake, and the D_1 agonist SKF 38393 was found to decrease food intake in a dose-dependent manner without inducing stereotypy (9). Thus, in addition to a role for D_2 receptors in this effect of cocaine, it seems likely that D_1 receptors play a role in cocaine's reduction of food intake. Indeed, D_1 receptors likely play an important role in other behavioral effects of cocaine (15, 27, 30).

The present study was designed to examine the roles of D_1 and D_2 receptors in the decrease in intake of a sweetened milk solution induced by cocaine. The necessity of D_1 and D_2 receptor stimulation for expression of this effect of cocaine was examined by administering the D_1 selective antagonist SCH 23390 (4, 13, 14) or the D_2 selective antagonist raclopride (1,16) in combination with cocaine. Since SCH 23390 is known to block $5\text{-}HT_{1C}$ and $5\text{-}HT_2$ receptors at concentrations near those that block D_1 receptors (5, 12, 21), ketanserin, a serotonin antagonist with a binding profile similar to that of SCH 23390 at $5\text{-}HT_{1C}$ and $5\text{-}HT_2$ receptors (26), was used as a control for nondopaminergic effects of SCH 23390. Raclopride was selected as a D_2 antagonist on the basis of its high selectivity for D_2 receptors and its rapid dissociation from the D_2 receptor in vivo (16). Since cocaine may nonspecifically interfere with consummatory behavior, a control experiment was conducted to examine the effects of cocaine on the motorically identical behavior of water drinking. Effects on milk intake that were not seen with water intake would suggest specificity for ingestion of food.

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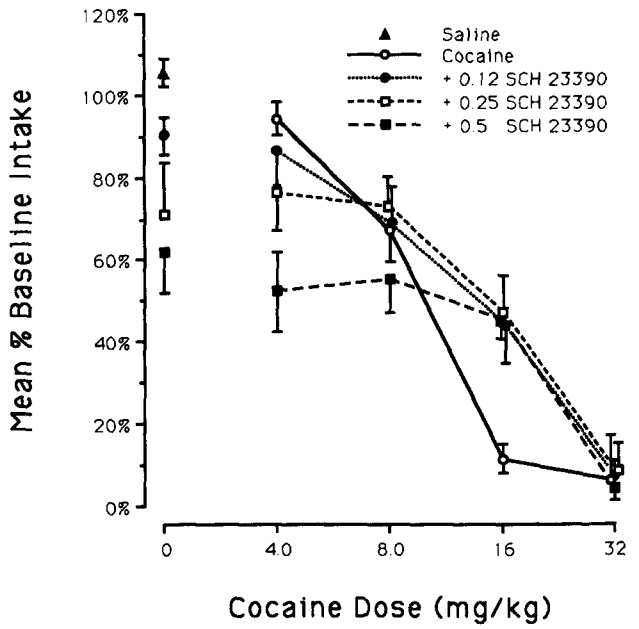

FIG. 1. Effects of cocaine and SCH 23390 on milk intake in rats. Food intake was restricted to access to a sweetened condensed milk solution for 15 minutes daily. Saline or 4.0–32 mg/kg IP cocaine was administered 10 minutes prior to sessions in combination with saline or 0.12–0.5 mg/kg IP SCH 23390 administered 30 minutes prior to the session. Each point represents the mean ± SEM of single observations in eight rats, with the exception of the cocaine-alone data points which represent the mean ± SEM of the average of two observations in eight rats. Mean baseline intake was 91 ml/kg (±0.8 SEM).

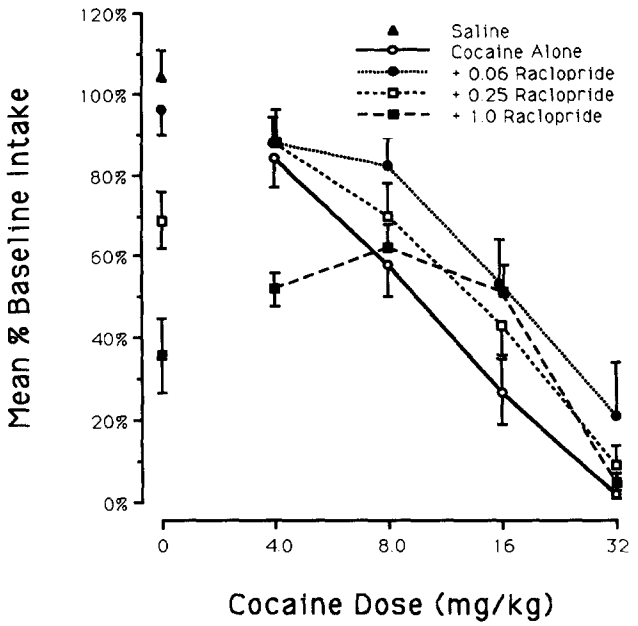

FIG. 2. Effects of cocaine and raclopride on milk intake in rats. Food intake was restricted to access to a sweetened condensed milk solution for 15 minutes daily. Saline or 4.0–32 mg/kg IP cocaine was administered 10 minutes prior to sessions in combination with saline or 0.06–1.0 mg/kg IP raclopride administered 30 minutes prior to the session. Each point represents the mean ± SEM of single observations in eight rats, with the exception of the cocaine-alone data points which represent the mean ± SEM of the average of two observations in eight rats. Mean baseline intake was 111.7 ml/kg (±0.7 SEM).

METHOD

Animals and Apparatus

Four groups of ten male Sprague-Dawley rats (250–300 g) were used in the study. They were individually housed in suspended stainless steel cages in a room maintained at approximately 24°C and 40% relative humidity and maintained on a 12-hour light-dark cycle (7 a.m.–7 p.m. light).

Procedure

Effects of SCH 23390 (group 1) and raclopride (group 2) on the decrease in milk intake caused by cocaine. For experimental sessions, sweetened condensed milk (Bordens Co., Columbus, OH, 1:2 milk:tap water, at room temperature) was prepared fresh each day and presented in 50 or 100 ml calibrated tubes attached to the front of the cage. Experimental sessions were 15 minutes in duration, were conducted seven days/week, and intake was recorded at the end of the session. Initially, body weights were prevented from falling below 80% of free-feeding weight by appropriate supplements of Teklad mouse and rat chow (Winfield, IA) immediately after the session. Dietary supplement was not necessary after the second week of the experiment and body weights increased gradually for the remainder of the study. Water was available ad lib except during the experimental sessions.

Once milk intake stabilized (less than 10% variation in an individual rat's intake for three consecutive sessions) experimental treatments began. First, a dose-response function was determined for cocaine (4.0–32 mg/kg, IP, 10 minutes prior to the session) in all rats. Then drug combinations were tested. Doses of SCH 23390 (0.12–0.5 mg/kg, IP, group 1), or raclopride (0.25–1.0 mg/kg IP, group 2) were administered 20 minutes prior to the administration of cocaine (4.0–32 mg/kg) or saline (i.e., 30 minutes presession). When combination tests were completed, cocaine dose-response functions were redetermined. Analysis of the initial data suggested that lower doses of raclopride should be tested, so tests of 0.06 and 0.12 mg/kg raclopride were subsequently conducted in group 2. All subjects received all of the treatment combinations for their group. Cocaine dose-response functions were collected according to a Latin-square design and cocaine plus antagonist dose-response functions were collected according to a separate double Latin-square design. Sessions with drug pretreatments were separated by at least three drug-free sessions.

Effects of ketanserin on the decrease in milk intake caused by cocaine (group 3). Combinations of cocaine (4.0–32 mg/kg, IP) and ketanserin (4.0–16 mg/kg, IP) were tested according to a protocol similar to that used for groups 1 and 2, except that the dose-response function for cocaine in combination with saline was not redetermined after the cocaine plus antagonist combination tests were completed and not all dose combinations were tested in all rats (minimum N = 7 for each dose combination).

Effects of cocaine on water intake (group 4). Water was presented in 50 ml calibrated tubes attached to the front of the cage for 15 minutes each day, and intake over the session was recorded. Teklad mouse and rat chow was available ad lib except during experimental sessions. Under these conditions body weights were stable for the duration of the experiment. Once water intake stabilized (less than 10% variation in mean intake for three consecutive session) test sessions began. Cocaine (4.0–32 mg/

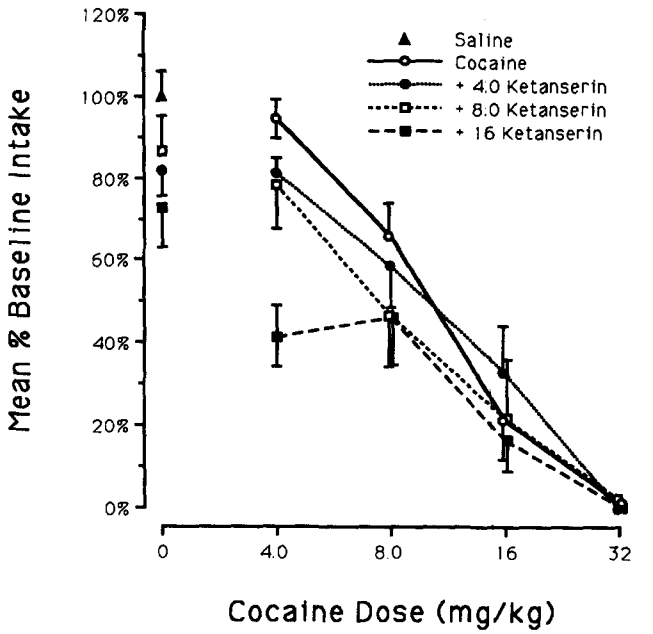

FIG. 3. Effects of cocaine and ketanserin on milk intake in rats. Food intake was restricted to access to a sweetened condensed milk solution for 15 minutes daily. Saline or 4.0–32 mg/kg IP cocaine was administered 10 minutes prior to sessions in combination with saline or 4.0–16 mg/kg IP ketanserin administered 30 minutes prior to the session. Each point represents the mean ± SEM of single observations in 7–10 rats. Mean baseline intake was 118 ml/kg (±5.6 SEM).

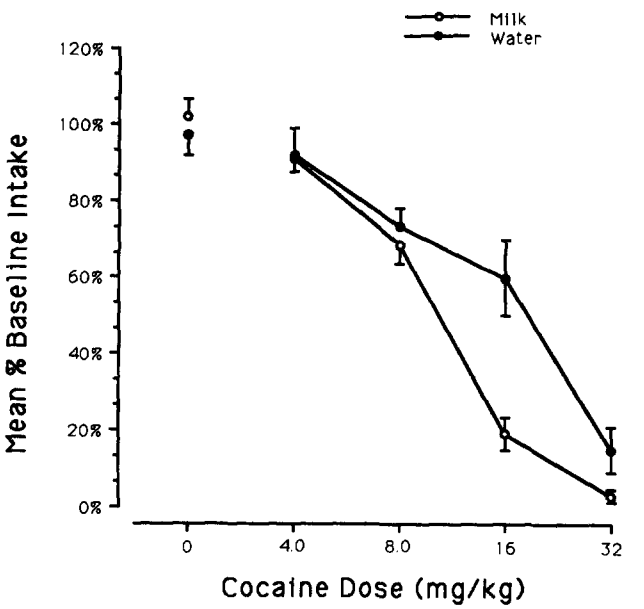

FIG. 4. Effect of cocaine on milk or water intake in rats. For milk intake determinations, food intake was restricted to access to a sweetened condensed milk solution for 15 minutes daily. The data are the mean intake of groups 1 and 2. For water intake determinations, access to water was restricted to 15 minutes in daily sessions. Saline or 4.0–32 mg/kg IP cocaine was administered 10 minutes prior to the sessions. Each point represents the mean ± SEM of single observations in eight rats, with the exception of the cocaine-alone data points which represent the mean ± SEM of the average of two observations in eight rats. Mean baseline water intake was 73.1 ml/kg (±1.4 SEM).

kg), or saline was administered IP 10 minutes prior to the 15-minute test sessions. Each animal received each dose of cocaine once. Test sessions were conducted according to a Latin-square design. Test sessions were separated by at least three drug-free sessions.

Data Analysis

Milk or water intake was normalized by conversion to ml/kg weight to correct for variation in intake that was a function of differences in body weight. Intake in the three sessions preceding a test session were averaged to yield baseline intake for individual rats. Intake in test sessions was expressed as a percentage of that baseline and the mean percentage calculated for the group. Two-way ANOVAs for repeated measures were used to assess the effects of cocaine alone and in combination with SCH 23390, raclopride, and ketanserin. For groups 1 and 2, data from the two determinations of the dose-response function for cocaine were not statistically different and, therefore, were averaged for use in the ANOVAs. Where a significant main effect or a significant interaction was found, selected individual points were compared using a paired *t*-test for repeated measures ($p \leq 0.05$) to determine dose combinations at which the effects of cocaine had been attenuated. A one-way ANOVA for repeated measures was used to assess the effects of cocaine on water intake. A two-way ANOVA was used to compare the effects of cocaine on water intake to the first determination of the effects of cocaine on milk intake (groups 1, 2, 3, combined). Where a significant main effect or interaction was found, selected individual points were compared using a *t*-test ($p \leq 0.05$). Eight rats, three each from groups 1 and 2 and one each from groups 3 and 4, died for undetermined reasons during the course of the study, and their data were discarded from the analysis.

Drugs

Cocaine HCl (National Institute on Drug Abuse, Rockville, MD), SCH 23390 (Schering-Plough Corporation, Bloomfield, NJ) and raclopride (Astra Alab, Sodertalje, Sweden) were dissolved in 0.9% saline. Ketanserin tartrate (Janssen Pharmaceuticals, Beerse, Belgium) was dissolved in sterile water. All injections were 1.0 ml/kg, and the concentrations varied appropriately. Doses were based on the salt.

RESULTS

Cocaine (4.0–32 mg/kg) caused a dose-dependent decrease in milk intake in all groups (Figs. 1, 2, 3). In combination with saline, SCH 23390 (Fig. 1) and raclopride (Fig. 2) caused dose-dependent decreases in milk intake. Ketanserin decreased intake but the effects were not systematically related to dose (Fig. 3). There was a statistically significant SCH 23390 dose × cocaine dose interaction [Fig. 1; $F(12,72) = 3.6$, $p < 0.003$]. All doses of SCH 23390 (0.12–1.0 mg/kg, IP) tested attenuated the decrease in milk intake induced by 16 mg/kg cocaine (paired *t*-test, $p < 0.025$, Fig. 1). Similarly, there was a significant raclopride dose × cocaine dose interaction [Fig. 2; $F(24,144) = 3.18$, $p < 0.0001$]. Raclopride (0.06 and 0.25 mg/kg) attenuated the effects of 8.0 mg/kg cocaine (paired *t*-test, $p \leq 0.02$), and 0.12 (data not shown for clarity) and 1.0 mg/kg raclopride attenuated the effects of 16.0 mg/kg cocaine (paired *t*-test, $p \leq 0.05$). In contrast, ketanserin (4.0–16 mg/kg) did not attenuate the effects

of cocaine (Fig. 3). Nonsystematic observation revealed marked akinesia and ptosis after the administration of 16 mg/kg ketanserin.

Cocaine caused a dose-dependent decrease in water intake that was different from the decrease seen with milk intake [fluid (milk or water) main effect: $F(1,139)=7.25$, $p<0.008$, Fig. 4]. At 16 mg/kg, cocaine had a significantly greater (paired t-test, $p<0.002$) effect on milk intake than water intake. At 32 mg/kg this difference approached but did not achieve statistical significance.

DISCUSSION

Cocaine caused a dose-dependent decrease in milk intake, in agreement with previous reports that it can decrease intake of a liquid diet in rats (8,29). Similarly, SCH 23390 and raclopride caused dose-dependent decreases in milk intake, in agreement with previous reports that both D_1 and D_2 antagonists can decrease intake of a liquid diet in rats (8,20). Pretreatment with SCH 23390 or raclopride attenuated the effects of at least one dose of cocaine on milk intake, suggesting that both D_1 and D_2 receptors are involved in this effect of cocaine. The failure of ketanserin to attenuate the milk intake reduction caused by cocaine argues that blockade of this effect of cocaine was specific to DA antagonists and suggests that 5-HT_{1C} and 5-HT_2 receptors do not play a major role in this behavioral effect of cocaine. Further, this finding supports the notion the SCH 23390 attenuates the effects of cocaine in this paradigm through its DA rather than 5-HT antagonist actions.

The water intake control was used to establish the specificity of the behavioral effects observed in the milk intake experiments. Cocaine decreased water intake, but 16 mg/kg cocaine deceased milk intake to a significantly greater extent than water intake. Similarly, in previous studies in rats a dose of 32 mg/kg cocaine almost completely suppressed milk drinking (8), while 36 mg/kg did not significantly reduce water intake (no greater than 34%) (25). A similar distinction was demonstrated with DA antagonists by Schneider et. al. (24), who found that doses of pimozide or haloperidol which decreased sham drinking of a sucrose solution by food-deprived rats failed to suppress sham drinking of water by water-deprived rats. Taken together, these results suggest that the effects examined in the present study were specific to food intake rather than mediated by the induction of behaviors incompatible with feeding, e.g., stereotypy. Therefore, they suggest that the effects of cocaine on food intake can be blocked by DA antagonists. In drawing comparisons between the water and milk intake studies, it should be considered that the deprivation states of the animals in these two experiments were not identical, therefore, results in the two experiments may not be comparable. Competing behaviors may cause nonspecific inhibition of fluid intake that is more readily overcome by the (perhaps greater) reinforcing efficacy of water for water-deprived rats as compared to the reinforcing efficacy of food for food-deprived rats. As such may be the case, inferences drawn from the results of the two studies can be interpreted only as suggestive evidence. Nevertheless, if the food intake reducing effects of cocaine are represented by the difference between the milk and water intake functions, similarity of the cocaine plus antagonist (SCH 23390 or raclopride) dose-response function for milk intake (Figs. 1 and 2) to the cocaine dose-response functions for water intake (Fig. 4) leads to the conclusion that blockade of D_1 or D_2 receptors can block the food intake reducing effects of cocaine.

Although milk intake could be decreased by any of several mechanisms, it should be noted that the present findings are also consistent with the proposal that the influence of dopaminergic tone on food intake follows an inverted U-shaped function (11). Treatments that either decreased (SCH 23390 and raclopride) or increased (cocaine) dopaminergic tone were associated with low milk intake, while intermediate dopaminergic tone (saline) was associated with higher intake levels. The findings are also consistent with the hypothesis that multiple dopaminergic systems may influence feeding, some in opposing manners. Thus injections of DA into the lateral prefornical area of the hypothalamus reduce food intake (19). Further, amphetamine-induced decreases in food intake appear to be mediated by DA receptors in the anterolateral hypothalamus, since direct administration of D_2 antagonists in that site can antagonize the anorexia produced by peripherally-administered amphetamine (18). On the other hand, injections of DA into the dorsocaudal far lateral hypothalamus enhance food intake as do injections of the catecholamine synthesis inhibitor Ro 4-1284 into the anterolateral hypothalamus (18). Antagonist treatments may, therefore, have decreased intake by decreasing activity in a system responsible for increasing food intake (hunger), while cocaine may have decreased intake by increasing activity in a system that normally restricts food intake (satiety). Only additional research can address these issues.

The present results suggest that both D_1 and D_2 receptor stimulation are necessary for full expression of the effects of cocaine on food intake. Indeed, a number of behavioral effects of cocaine, including locomotion, stereotyped-sniffing, and head-bobbing are attenuated by SCH 23390 or raclopride (22). In addition, the discriminative stimulus effects of cocaine [see (30) for review], have been found to be blocked by both D_1 and D_2 antagonists. Thus both types of DA receptors appear to play a role in several of the behavioral effects of cocaine. Although the precise nature of that role remains to be established, these experimental results are consistent with the hypothesis that D_1 and D_2 receptors play a necessary role in the expression of DA-mediated behaviors (15).

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REFERENCES

1. Anderson, P. H. Comparison of the pharmacological characteristics of [3H]raclopride and [3H]SCH 23390 binding to dopamine receptors in vivo in mouse brain. Eur. J. Pharmacol. 146:113–120; 1988.
2. Balopole, D. C.; Hansult, C. D.; Dorph, D. Effect of cocaine on food intake in rats. Psychopharmacology (Berlin) 64:121–122; 1979.
3. Bedford, J. A.; Lovell, D. K.; Turner, C. E.; Elsohly, M. A.; Wilson, M. C. The anorexic and actometric effects of cocaine and two coca extracts. Pharmacol. Biochem. Behav. 13:403–408; 1980.
4. Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L. C.; Barnett, A. Characterization of the binding of 3H-SCH 23390, a selective D_1 receptor antagonist ligand, in rat striatum. Life Sci. 35:1885–1893; 1984.
5. Bischoff, S.; Heinrich, M.; Sonntag, J. M.; Krauss, J. The dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT_2) receptors. Eur. J. Pharmacol. 129:367–370; 1986.
6. Blavet, N.; DeFeudis, F. V. Inhibition of food intake in the rat. Neurochem. Res. 7:339–348; 1982.
7. Foltin, R. W.; Woolverton, W. L.; Schuster, C. R. The effect of *d*-amphetamine and haloperidol alone and in combination on milk

drinking in rats. Psychopharmacology (Berlin) 80:342–344; 1983.
8. Foltin, R. W.; Woolverton, W. L.; Schuster, C. R. Effects of psychomotor stimulants, alone and in pairs, on milk drinking in the rat after intraperitoneal and intragastric administration. J. Pharmacol. Exp. Ther. 226:441–418; 1983.
9. Gilbert, D. B.; Cooper, S. J. Analysis of dopamine D_1 and D_2 receptor involvement in *d*- and *l*-amphetamine-induced anorexia in rats. Brain Res. Bull. 15:385–389; 1985.
10. Groppetii, A.; Zambotti, F.; Biazzi, A.; Mantagazza, P. Amphetamine and cocaine on amine behavior. In: Usdin, E.; Synder, S. H., eds. Frontiers in catecholamine research. New York: Pergamon Press; 1973:917–925.
11. Heffner, T. G.; Zigmond, M. J.; Stricker, E. M. Effects of dopaminergic agonists and antagonists on feeding in intact and 6-hydroxydopamine-treated rats. J. Pharmacol. Exp. Ther. 201:386–399; 1977.
12. Hicks, P. E.; Schoemaker, H.; Langer, S. Z. 5HT-receptor antagonist properties of SCH 23390 in vascular smooth muscle and brain. Eur. J. Pharmacol. 105:339–342; 1984.
13. Hyttel, J. SCH 23390-The first selective dopamine D-1 antagonist. Eur. J. Pharmacol. 91:153–154; 1983.
14. Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. J. Pharmacol. Exp. Ther. 226:462–468; 1983.
15. Kleven, M. S.; Anthony, E. W.; Woolverton, W. L. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. J. Pharmacol. Exp. Ther. 254:312–317; 1990.
16. Köhler, C.; Hall, H.; Ögren, S. O.; Gawell, L. Specific in vitro and in vivo binding of 3H raclopride. Biochem. Pharmacol. 34: 2251–2259; 1985.
17. Lazer, E. S.; Aggarwal, N. D.; Hite, G. J.; Nieforth, K. A.; Kelleher, R. T.; Spealman, R. D.; Schuster, C. R.; Woolverton, W. Synthesis and biological activity of cocaine analogs I: N-alkylated norcocaine derivatives. J. Pharmacol. Sci. 67:1656–1658; 1978.
18. Liebowitz, S. F. Brain catecholaminergic mechanisms for control of hunger. In: Novin, D.; Wyrwicka, W.; Bray, G., eds. Hunger, basic mechanisms and clinical implications. New York: Raven Press; 1976:1–18.
19. Leibowitz, S. F. Neurochemical systems of the hypothalamus: control of feeding and drinking behavior and water-electrolyte excretion. In: Morgane, P. J.; Panksepp, J., eds. Handbook of the hypothalamus. vol. 3. Behavioral studies of the hypothalamus. New York: Marcel Dekker; 1980:299–437.
20. Martin-Iverson, M. T.; Dourish, C. T. Role of dopamine D-1 and D-2 receptor subtypes in mediating dopamine agonist effects on food consumption. Psychopharmacology (Berlin) 96:370–374; 1988.
21. Nicklaus, K. J.; McGonigle, P.; Molinoff, P. B. [3H]SCH 23390 labels both dopamine-1 and 5-hydroxytryptamine 1c receptors in the choroid plexus. J. Pharmacol. Exp. Ther. 247:343–348; 1988.
22. Rapoza, D.; Woolverton, W. L. The interaction of cocaine with SCH 23390 or raclopride: Behavioral effects in rats. FASEB J. 4:A539; 1990.
23. Schmidt, G. Über die anorexiegene wirkung des cocains. Arch. Int. Pharmacodyn. 156:87–99; 1965.
24. Schneider, L. H.; Gibbs, J.; Smith, G. D-2 selective receptor antagonists suppress sucrose sham feeding in the rat. Brain Res. Bull. 17:605–611; 1986.
25. Stolerman, I. P.; D'Mello, G. D. Amphetamine-induced hypodipsia and its implications for conditioned taste aversion in rats. Pharmacol. Biochem. Behav. 8:333–338; 1978.
26. Titler, M.; Lyon, R. A.; Davis, K. H.; Glennon, R. A. Selectivity of serotonergic drugs for multiple brain serotonin receptors. Biochem. Pharmacol. 36:3265–3271; 1987.
27. Vanover, K. E.; Kleven, M. S.; Woolverton, W. L. Blockade of the discriminative stimulus effects of cocaine in rhesus monkeys with the D_1 dopamine antagonists SCH-39166 and A-66359. Behav. Pharmacol. 2:151–160; 1991.
28. van Rossum, J. M., Simmons, F. Locomotor activity and anorexogenic action. Psychopharmacology (Berlin) 14:248–254; 1969.
29. Woolverton, W. L.; Kandel, D.; Schuster, C. R. Tolerance and cross-tolerance to cocaine and *d*-amphetamine. J. Pharmacol. Exp. Ther. 205:525–35; 1978.
30. Woolverton, W. L.; Kleven, M. S. Multiple dopamine receptors and the behavioral effects of cocaine. In: Clouet, D.; Asghar, K.; Brown, R., eds. Mechanisms of cocaine abuse and toxicity. NIDA Research Monograph 88, U.S. Government Printing Office; 1988: 160–184.