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Evidence for Involvement of Both D1 and D2 Receptors in Maintaining Cocaine Self-Administration

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BRITTON, D. R., P. CURZON, R. G. MACKENZIE, J. W. KEBABIAN, J. E. G. WILLIAMS AND D. KERKMAN. *Evidence for involvement of both D1 and D2 receptors in maintaining cocaine self-administration.* PHARMACOL BIOCHEM BEHAV **39**(4) 911–915, 1991.—Rats trained to self-administer cocaine (0.75 mg/kg/infusion) on an FR-5 schedule were treated with selective D1 or D2 antagonists. A69045, a D1 antagonist with no appreciable affinity for 5-HT receptors increased cocaine self-adminstration to 147, 172 and 167% of baseline at doses of 2.5, 5.0 or 10.0 μmol/kg, SC respectively. SCH-23390 (0.007, 0.015 and 0.030 μmol/kg, SC) increased self-administration to 116, 147 and 165% of baseline, respectively. Both D1 antagonists decreased responding in some animals at the highest dose tested. The D2 antagonist YM-09151-2 showed a similar profile, increasing cocaine self-administration at 0.01 and 0.016 μmol/kg, SC and suppressing responding by most animals at the dose of 0.03 μmol/kg, SC. These data give further support to the hypothesis that both D1 and D2 receptors are involved in maintaining cocaine self-administration.

Cocaine Self-administration A69024 SCH-23390 YM-09151-2 Dopamine D1 receptors D2 receptors Rats

THERE is substantial evidence that the rewarding properties of cocaine are mediated by blockade of reuptake of endogenous dopamine and the subsequent enhanced activation of dopamine receptors (9, 20, 21, 33). A major part of the evidence that dopamine receptor activation mediates the rewarding properties of cocaine derives from data demonstrating that selective D2 or mixed D1/D2 receptor antagonists have effects similar to those obtained by reducing the concentration of cocaine in the injections. Pickens and Thompson (27) demonstrated that reduction of the magnitude of reinforcement by reducing the concentration of cocaine available resulted in an increase in the number of infusions the animal would administer. This has been interpreted as a compensatory response of the animal to maintain cocaine levels and therefore dopamine receptor occupancy at an optimal level for reward. Selective D2 or mixed D1/D2 receptor antagonists produce similar effects at low to moderate doses. They result in an apparently compensatory increase in the rate of cocaine self-administration (10, 27, 29).

Although the D1 and D2 dopamine receptors share many common functional features they differ in their second messenger systems, their localization and the effects of activation on other neurotransmitter systems (1, 11, 12, 18, 30, 32). There is a relative lack of information regarding the potential involvement of D1 receptors in mediating reward, no doubt due in part to the fact that specific D1 antagonists were not available until relatively recently. Koob et al. (22) reported that SCH-23390 increased the rate of responding for cocaine in a manner similar to that seen with D2 or mixed D1/D2 antagonists. Although having extremely high affinity for the D1 receptor [Ki = 0.3 nM (23)], SCH-23390 also has nM affinities for binding to 5HT receptors (7, 8, 14, 23, 25). This highlights the needs to provide additional data with other D1 antagonists in the attempt to define the potential role of the D1 receptor in mediating the rewarding properties of cocaine.

A69024 [1-(2-bromo-4,5-dimethoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrobromide] has high affinity for the D1 receptor and a high degree of selectivity relative to D2 receptors (19). We report here the further characterization of the binding affinities of A69024 for 5-HT and adrenergic receptors. We have used this selective D1 antagonist to characterize the pharmacology of cocaine self-administration. We have also extended the testing of D2 antagonists with the use of YM-09151-2, a compound with high affinity [4.1 nM (28)] and selectivity for the D2 receptor (13,28). These compounds along with SCH-23390 were tested for their effects on cocaine self-administration by rats.

METHOD

Animals

Male, Sprague-Dawley rats (Charles River, Portage, MI) weighing approximately 250 g at the time of surgery were anesthetized with pentobarbital sodium (50 mg/kg, IP) (Nembutal, Abbott Laboratories) and prepared with indwelling intravenous catheters. The catheters consist of a 7.5 cm length of Silastic tubing which was inserted into the right jugular vein to the level

of the right ventricle. The distal end of the Silastic tubing was joined to a coiled 6.5 cm segment of PE-10 tubing which is welded to a 16 cm length of PE-20 tubing which was externalized at the back of the neck. The PE-10 coil acts to absorb stresses put on the tubing by the animal's movement which might otherwise cause it to close. The external end of the catheter was plugged with a stainless steel stylet when not in use.

Training on Cocaine Self-Administration

Beginning approximately five to seven days following surgery animals were placed in the self-administration boxes to begin training. The boxes were standard rat operant boxes (Coulbourn Instruments) which contained a single lever capable of activating a syringe pump on a predetermined schedule. Each box was housed in a sound attenuating chamber containing a "house light" and a ventilation fan. When the animal was placed in the operant box the externalized catheter was attached to a length of PE-20 tubing connected to a 10 ml syringe in a syringe pump which was programmed to deliver 0.1 ml over approximately 3 s when activated. This volume provided an intravenous injection of 0.75 mg/kg of cocaine. The concentration of cocaine in the injectate was altered appropriately for studies demonstrating the effect of changes in the amount of cocaine per infusion.

Initially, rats were placed on an FR1 schedule. When the animals began responding regularly on the FR1 schedule the ratio was increased to FR3 then to FR5. They were maintained on the FR5 schedule for the duration of the studies. Animals were required to have 3 consecutive days of responding with less than 10% variability from the mean before the first day of testing with a dopamine antagonist. They were required to have at least 2 consecutive days of less than 10% variability between antagonist challenges. Approximately 60% of the animals which began training achieved baseline criteria. Animals which did not meet the criteria for establishing or maintaining stable baseline performance were not included in the study.

Antagonist Challenges

Once animals achieved stable responding they were injected with saline (1.0 ml/kg, SC) 30 min prior to being placed in the operant chambers to accustom them to the injection procedure. This process was followed routinely thereafter except on those days when animals were treated with antagonist instead of saline. A69024, SCH-23390 and YM-09151-2 were all dissolved in saline to a concentration to allow an injection volume of 1.0 mg/kg, SC. Animals were tested on up to four doses of a single antagonist with saline treatment on intervening days as noted above. The first dose of antagonist used was chosen to be intermediate and the subsequent doses were increased if the animal showed no response or decreased if the dose suppressed responding. Four of the five animals used for the studies with SCH-23390 were later used to test A69024. Three of these were then used to test YM-09151-2. Additional, previously untested, animals were added to the later two groups to the bring the total number to that indicated.

Behavioral Data Analysis

The mean of the number of responses for the two baseline days preceding the drug challenge was compared to the number of responses for the challenge day. Paired *t*-tests were performed using the actual number of responses over the 2 h of the session. (Note that for the sake of clarity, the data are graphically presented as the percent of control values rather than the actual number of responses.)

In Vitro Studies

The affinity and selectivity of A69024 for a variety of binding sites was determined using methods as described (DeNinno et al., in press). Binding to rat striatal D1 receptors was determined using [^{125}I]-SCH-23982 (Du Pont Co., NEN, Boston, MA) (150 pM final concentration) with nonspecific binding defined as that occurring in the presence of 1.0 μM SCH-23390. D2 receptor binding was determined using [^{3}H]-spiperone (Amersham, Arlington Heights, IL) (300 pM final concentration) in the presence or absence of 10 μM YM-09151-2. Alpha-1 and alpha-2 receptor binding was determined according to the general methodology described by Summers et al. (31) for alpha-2 binding. Alpha-1 adrenergic receptors from rat cortex were labeled with [^{3}H]-prazosin (final concentration 1.0 nM) (Du Pont Co., NEN, Boston, MA) in the presence or absence of 10 μM phentolamine to define nonspecific binding. Binding to alpha-2 adrenergic receptors was performed using rat cortex and [^{3}H]-rauwolscine (Du Pont Co., NEN, Boston, MA) (325 pM final concentration). Nonspecific binding was defined using 10 μM yohimbine. Beta-adrenergic receptor binding was defined with [^{125}I]-iodocyanopindolol (50 pM final concentration) with nonspecific binding determined by 10 μM propranolol as described by Zahniser et al. (35). Binding to 5-HT1a and 5-HT2 receptors was performed essentially described by Hoyer et al. (16) using the anterior third of the rat cerebral cortex. 5-HT1a binding was determined using [^{3}H]-8-OH-DPAT (Du Pont Co., NEN, Boston, MA) (800 pM final concentration) in the presence or absence of 10 μM spiroxatrine. 5-HT2 binding was identified using [^{3}H]-ketanserin (Du Pont Co., NEN, Boston, MA) (400 pM final concentration) in the presence or absence of 10 μM mianserin. Binding to 5-HT1c sites was determined using the procedure of Hower and Karpf (17). Tissue from homogenates of porcine choroid plexus were incubated with [^{125}I]-SCH-23982 (120 pM final concentration) in the presence or absence of 10 μM SCH-23390. In addition, The ability of A69024-HBr to block the reuptake of dopamine was assessed using fresh homogenates of rat striata incubated with [^{3}H]-dopamine as described by Peris et al. (26).

RESULTS

The selectivity of A69024 for the D1 receptor is evident in the data shown in Table 1. A69024 has very low affinity for 5-HT receptors (Ki>10,000 nM) (selectivity greater than 1000-fold) and for D2 receptors (Ki = 1267 nM). It is approximately 4-fold selective for the D1 relative to the alpha-2 receptor and approximately 12-fold selective relative to the alpha-1 adrenergic receptor. It shows no significant capacity to block the reuptake of dopamine and would not be expected to interact with cocaine by that mechanism.

Table 2 shows the baseline rates responding on an FR5 schedule for cocaine at a concentration of 0.75 mg/kg and also shows the effects of decreasing the concentration of cocaine to that which provided injections of 0.375 mg/kg. This 50% decrease in concentration resulted in a 76% increase in the number of infusions in the 2 h session and a 56% decrease in the mean interinfusion interval. The increased number of reinforcements compensated for the decreased dose per infusion resulting in a change of total cocaine intake per animal over the two hr session of less than 10% (not significant). Animals continued to show a very regular pattern of responding as indicated by small (the less than 10%) standard error of the mean for the interinfusion interval.

TABLE 1

BINDING AFFINITY OF A69024-HBr TO VARIOUS RECEPTOR SITES

Receptor	Radioligand	Tissue	Ki (nM) ± sem
D1	[^{125}I]-SCH-23982	Rat Striatum	14.0 ± 4.9
D2	[^{3}H]-Spiperone	Rat Striatum	1266.7 ± 33.3
Alpha-1	[^{3}H]-Prazosin	Rat Cortex	172.7 ± 70.5
Alpha-2	[^{3}H]-Rauwolscine	Rat Cortex	54.5 ± 24.5
Beta	[^{125}I]-I-Cynpndl*	Rat Striatum	>200,000
5-HT1a	[^{3}H]-8-OH-DPAT	Rat Ant. Cortex	>100,000
5-HT2	[^{3}H]-Ketanserin	Rat Ant. Cortex	>100,000
5-HT1c	[^{125}I]-SCH-23982	Porc. Chr. Plx.	>10,000
Dopamine Re-uptake	[^{3}H]-Dopamine	Rat Striatum	13,150 ± 2250

*[^{125}I]-I-Cynpndl = [^{125}I]-iodocyanopindolol.

Binding affinities for A69024 were determined as defined in the Method section. Shown are the means and standard errors of the independently calculated Ki values from 2 to 4 experiments.

The effects of SCH-23390 on cocaine self-administration are shown in Fig. 1. The grouped data (Fig. 1, upper graph) show a dose-related increase in responding at 0.007, 0.015 and 0.03 μmol/kg, SC. The lower portion of Fig. 1 shows data for individual animals and demonstrates that, as the dose was increased, the response rate also increased up to a point which responding began to decrease back to control values or below.

Figure 2 shows similar data for A69024. The group data are significantly higher for animals treated with 2.5 or 5.0 μmol/kg, SC and remains high (approximately 68% above baseline) at the dose of 10.0 μmol/kg, SC though this effect is no longer statistically significant. At this higher dose the response rate varied considerably. One animal continued responding at a rate of over 160% increase over baseline while another ceased responding completely. The remaining animals were distributed regularly between these two extremes.

The D2 antagonist YM-09151-2 produced a similar profile with increasing rates of responding at lower doses and decreased responding below baseline values at the higher doses (Fig. 3). The response rates were 106, 148, 163 and 58% of baseline respectively for doses of 0.003, 0.01, 0.016 and 0.03 μmol/kg, SC.

DISCUSSION

The functional relationship of D1 and D2 receptors as determined with selective agonists and antagonists is dependent upon both the nature of the response being monitored and the neurological status of the animal being tested (i.e., whether or not the animal has been subjected to lesions which would deplete brain dopamine). Locomotor activity by nonlesioned animals appears equally sensitive to blockade by either D1 or D2 antagonists (3).

TABLE 2

EFFECTS OF COCAINE CONCENTRATION ON RATE OF SELF-ADMINISTRATION

Dose of Cocaine mg/kg/Infusion	No. Infusions per 2 h	Interinfusion Interval	Total 2 h Intake mg/kg
0.75	20.9 ± 1.3	5.9 ± 0.3	15.3 ± 1.5
0.375	36.8 ± 2.9	3.3 ± 0.3	13.8 ± 1.4

Comparison of cocaine intake during 2-day baseline self-administration of 0.75 mg/kg/infusion of self-administration of cocaine at a dose of 0.375 mg/kg/infusion on the third day. N = 5 animals. Paired *t*-test comparison showed no significant difference in the total cocaine intake under these two schedules.

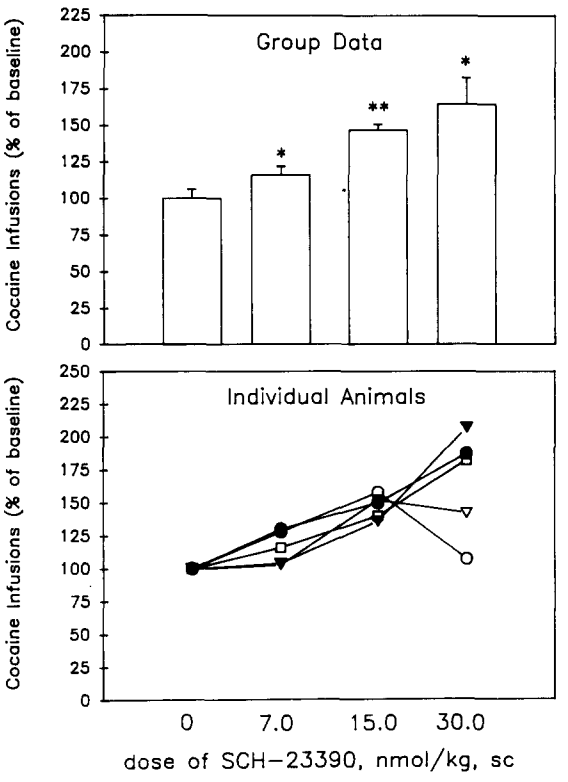

FIG. 1. Effects of SCH-23390 on self-administration of cocaine. The upper graph shows data for groups of animals (n = 5/group) expressed as percent of the mean baseline for each animal on the prior two days of testing. Significantly different from the mean (*$p<0.05$; **$p<0.01$). The lower graph shows individual animal's changes as a function of dose.

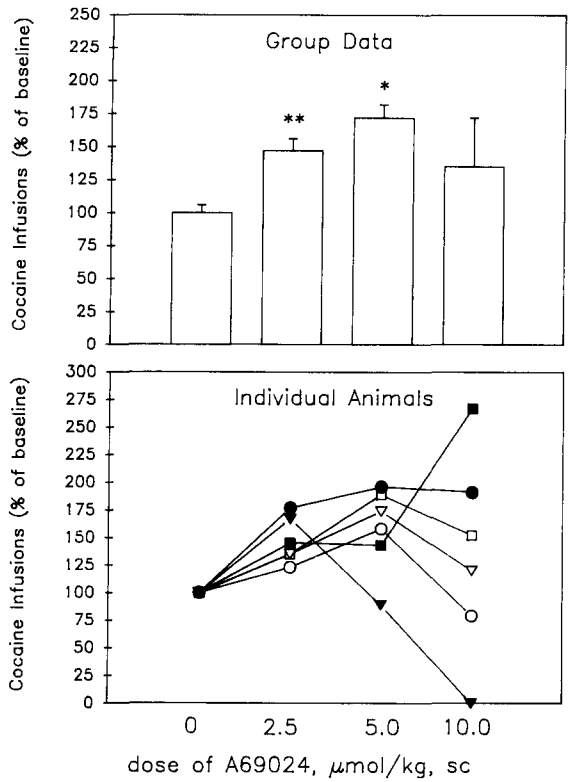

FIG. 2. Effects of A69024 on self-administration of cocaine. Upper graph shows data for groups of animals (n = 5/group) expressed as percent of the mean baseline for each animal on the prior two days of testing. Significantly different from the mean (*$p<0.05$; **$p<0.01$). Lower graph shows individual animal's changes as a function of dose.

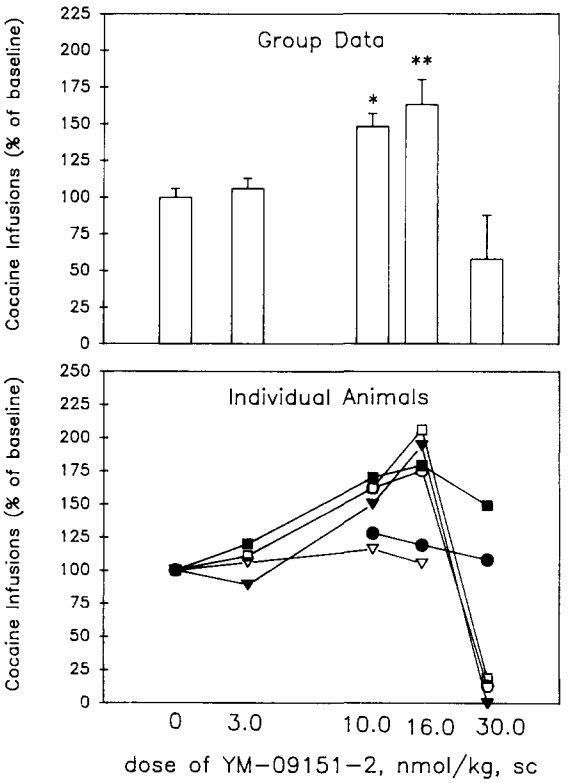

FIG. 3. Effects of YM-09151-2 on self-administration of cocaine. Upper graph shows data for groups of animals (n = 4–6/group) expressed as percent of the mean baseline for each animal on the prior two days of testing. Significantly different from the mean (*$p<0.05$; **$p<0.01$). Lower graph shows individual animals' changes as a function of dose.

Although they may do so by acting at different sites, both D1 and D2 agonists produce contralateral rotation in unilaterally 6-OHDA lesioned rats. Unlike the locomotor effect in nonlesioned animals, the rotation response is selectively blocked by the appropriate D1 or D2 antagonist [(2–4), Britton et al., submitted]. Thus, there appear to be conditions in which activation of both D1 and D2 receptors is required for a dopamine effect (locomotion in nonlesioned animals) and other conditions in which activation of either D1 or D2 alone is sufficient to produce the behavioral effect (contralateral rotation in rats with unilateral 6-OHDA lesions of the nigrostriatal pathway).

While the bulk of the information about the interaction of D1 and D2 receptors is from studies of stimulated motor activity such as locomotor hyperactivity or rotation, the role of these two receptor subtypes in mediating reward remains an important and less explored question. There is substantial evidence that the rewarding properties of cocaine are mediated through the actions of endogenous dopamine [see recent reviews (20,33)]. An important component of this evidence is that D2 dopamine receptor antagonists increase the rate of cocaine self-administration. We have demonstrated that another D2 antagonist, YM-09151-2, which was previously untested in this paradigm has similar actions. We have also replicated the earlier finding of Koob et al. (22) that SCH-23390 acts in a manner consistent with a reduction in reward value through competitive inhibition. At moderate doses, it has effects similar to those of reducing the concentration of cocaine; it increases the rate of self-administration thereby increasing the amount of synaptic dopamine which could compete for the receptor. These findings are contrary to those reported by Woolverton and Virus (34) who found that both D1 and D2 antagonists decrease operant responding by monkeys for both cocaine and food reward. Whether the differences are due to dose, procedures used or species remains to be determined. In fact, as shown for all compounds in the present study, higher doses tend to suppress responding, at least in some animals, just as dopamine antagonists suppress operant responding in other paradigms. The threshold at which the antagonists suppress rather than augment responding varies from animal to animal. This phenomenon is consistent with the hypothesis that, at some dose, the degree of dopamine receptor blockade is such that it cannot be overcome by the increased synaptic dopamine associated with cocaine self-administration.

The finding that A69024 pretreatment increases cocaine self-administration is the first report to our knowledge of a D1 antagonist other than SCH-23390 demonstrating interactions with reward mechanisms. SCH-23390 and A69024 are both relatively selective from the D1 receptor but neither is without at least moderate cross-reactivity with other receptors. Since they differ in their binding profiles for nondopaminergic receptors, the data gained with one antagonist can be supported by data from the other. The affinity for 5-HT sites shown by SCH-23390 is not shared by A69024. Likewise, the interaction of A69024 with alpha-adrenergic sites is not seen with SCH-23390. The difference in potency between the two D1 antagonists in altering cocaine self-administration roughly parallels their potencies in binding to the D1 receptor; SCH-23390 having considerably higher affinity for the D1 site than A69024.

While these findings taken in isolation could be interpreted

as indicating that D1 receptor blockade actually increases the reward value of cocaine and thereby increases self-administration, such an interpretation is not consistent with other reports of D1 antagonists having anhedonic effects in animal models (5, 6, 15, 24).

Taken together, these findings provide a strong basis for the conclusion that blockade of the D1 dopamine receptor reduces the rewarding efficacy of cocaine and thereby promotes a compensatory increase in the rate of cocaine self-administration.

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