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Effects of a D_1 and a D_2 Dopamine Antagonist on the Self-Administration of Cocaine and Piribedil by Rhesus Monkeys[1]

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WOOLVERTON, W L *Effects of a D_1 and a D_2 dopamine antagonist of the self-administration of cocaine and piribedil by rhesus monkeys* PHARMACOL BIOCHEM BEHAV **24**(3) 531–535, 1986 —Rhesus monkeys were surgically prepared with chronic intravenous catheters and allowed to self-administer the indirect dopamine (DA) agonist cocaine (0 03 or 0 1 mg/kg/inj) or the direct D_2 agonist piribedil (0 1 or 0 2 mg/kg/inj) on a fixed-ratio 10 schedule of drug delivery during daily 2 hour experimental sessions When responding was stable, they were injected IV with SCH 23390, a selective D_1 antagonist (0 003–0 3 mg/kg, 30 min pre-session) or pimozide, a selective D_2 antagonist (0 003–0 3 mg/kg, 2 hours pre-session) Intermediate doses of pimozide generally increased self-administration of cocaine or piribedil, though increases in piribedil self-administration were more reliable In contrast, intermediate doses of SCH 23390 either did not affect or decreased cocaine and piribedil self-administration High doses of each antagonist decreased the rate of self-administration of each compound and produced catalepsy The selective increase in responding maintained by cocaine or piribedil following pimozide pretreatment suggests a role for a D_2-like receptor in psychomotor stimulant self-administration

Dopamine receptors Cocaine Self-administration SCH 23390 Pimozide Rhesus monkey

PSYCHOMOTOR stimulants have a number of neurochemical effects, including the ability to increase the concentration of neurotransmitter in catecholaminergic synapses The mechanism for this effect may involve an increase in the release and/or a blockade of the reuptake of the neurotransmitter(s) It has been suggested that this effect in the central nervous system (CNS) is involved in the reinforcing effects of this class of compounds [19,20] The available data suggest that dopamine (DA), in particular, plays a prominent role in stimulant self-administration For example, direct DA receptor agonists functioned as positive reinforcers in several species [3, 19, 20] and destruction of central DA-containing neurons can reduce the rate of stimulant self-administration [12,13] In addition, pretreatment with DA receptor antagonists can increase the rate of stimulant self-administration in a manner that is similar to the effect of reducing the dose per injection of the stimulant and, therefore, is suggestive of antagonism of the reinforcing properties of the stimulant [2, 16, 18]

Research in recent years has emphasized complexity of CNS DA function For instance, it has become clear that multiple receptors for DA exist inside as well as outside the CNS [5, 10, 15] Characterization of the functional roles of these receptors in the CNS has been substantially advanced by the use of selective agonists and antagonists [6, 11, 14] Regarding the reinforcing properties of psychomotor stimulants, it has recently been shown that DA agonists of the D_2-type functioned as positive reinforcers while a D_1 agonist, SKF 38393, did not [19] This finding suggests that a D_2-like receptor may be involved in the self-administration of psychomotor stimulants

Another way to assess DA receptor mechanisms involved in stimulant self-administration is to determine the effects of antagonists selective for different DA receptors on the self-administration of these compounds The studies with DA receptor antagonists cited earlier used drugs with primarily D_2 actions or with mixed D_1-D_2 actions Recently, however, a DA antagonist selective for the D_1 receptor has been discovered (SCH 23390, [4, 8, 9]) The purpose of the present experiment was to provide further evidence concerning the DA receptors involved in psychomotor stimulant self-administration by comparing the effects of a D_1 and a D_2 antagonist on the self-administration of the indirect DA agonist cocaine and the direct D_2 agonist piribedil To the extent that the effects of DA antagonists on piribedil and cocaine self-administration are comparable, D_2 mechanisms are implicated in the self-administration of cocaine

METHOD

Animals and Apparatus

The subjects were 5 rhesus monkeys, 3 males and 2

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TABLE 1

NUMBER OF INJECTIONS TAKEN IN BASELINE SESSIONS DURING THE PERIOD OF TESTING OF EACH ANTAGONIST*

	Cocaine†				Piribedil†			
	SCH 23390		Pimozide		SCH 23390		Pimozide	
	hour 1	hour 2	hour 1	hour 2	hour 1	hour 2	hour 1	hour 2
Monkey								
1005	not tested		28(7 5)	14 5(2 3)	16 5(6 4)	14 8(10 9)	23 2(6 8)	15(6 3)
1033	13 5(2 4)	9 5(1 4)	14 6(1 6)	9 2(1 0)	not tested		11 8(5 0)	11 3(5 5)
1034	21 9(2 4)	14 8(2 5)	18 1(1 6)	15 1(2 8)	13 3(5 0)	9 4 (3 0)	21 5(5 0)	17(8)
2033	22 2(5 3)	16 8(4 4)	16 9(2 3)	12 4(2 1)	12 1(3 0)	12 6 (4 4)	12 2(4 1)	10 7(6 3)
3015	21 3(2 1)	13 9(3 1)	20 9(1 7)	13 1(1 2)	14 9(1 7)	10 8 (4 4)	12 1(5 6)	11 2(2 2)

*Numbers presented are the means (s d) of the number of injections taken in each hour of the 2 hour session, calculated for 6–10 baseline sessions Baseline sessions were the 2 sessions immediately preceding injection of a test dose of antagonist

†Baseline drug doses for cocaine were 0 03 mg/kg/inj (1005 and 1034) or 0 1 mg/kg/inj for the other monkeys and for piribedil were 0 2 mg/kg/inj (1005) or 0 1 mg/kg/inj for the other monkeys

females The males (1005, 1033, 1034) weighed between 8 0 and 10 7 kg and the females weighed 4 0 (2033) and 4 3 (3015) kg at the beginning of the experiment All animals had experience with the IV self-administration of DA receptor agonists before beginning this experiment Each was fitted with a stainless-steel restraint harness and spring arm which attached to the rear of an experimental cubicle (68 cm wide × 84 cm deep × 91 cm high) in which the monkey lived for the duration of the experiment Each cubicle had a Plexiglas window on the front wall that allowed the monkey visual access to the laboratory at all times except during experimental sessions Water was available continuously and each monkey received 100 to 150 g/day of Purina Monkey Chow after the session A multiple vitamin supplement in the form of a chewable tablet was provided 3 days/week

Two response levers (BRS/LVE, PRL-001, Beltsville, MD) were mounted on the inside front of each experimental cubicle 10 cm above the floor and a food dish was mounted between them Four jewelled stimulus lights, two red and two white, were mounted directly above each lever In addition, two 15 W houselights, one white and one red, were mounted on the ceiling of the cubicle and covered with translucent Plexiglas Drug injections were delivered by a peristaltic infusion pump (Cole-Parmer Co , Chicago, IL) All programming and recording of experimental events was accomplished by solid state equipment in an adjacent room

Procedure

Catheters had been previously implanted as follows Each animal was removed from the cubicle and injected with a combination of phencyclidine hydrochloride (1 0 mg/kg IM) and atropine sulfate (0 04 mg/kg IM) followed in 20 to 30 min by sodium pentobarbital (10–30 mg/kg IV) When anesthesia was adequate, a silicone catheter (0 08 cm inside diameter, Ronsil Rubber Products, Belle Mead, NJ) was surgically implanted in a major vein After surgery the monkey was returned to the experimental cubicle and the catheter was threaded through the spring arm, out the back of the cubicle and connected to the infusion pump If a catheter became nonfunctional during the experiment, a new catheter was implanted as before after a 1 to 2-week period to allow any infection to clear

Daily 2-hr experimental sessions were signaled by the illumination of the white lights Each animal had previously been trained to press the right lever under a FR 10 schedule for a 10-sec injection of 0 1 mg/kg of cocaine hydrochloride During an injection the white lights were extinguished and the red house light and lever lights were illuminated Responses occurring on the left lever were counted but had no other programmed consequences In the present experiment the animals were allowed to self-administer cocaine (0.03 or 0 1 mg/kg/inj) or piribedil (0 1 or 0 2 mg/kg/inj) during baseline sessions Baseline dose was adjusted to maintain roughly comparable rates of responding across animals

When responding was stable under baseline conditions (less than 10% variation in the number of injections/session for at least 3 consecutive sessions), test sessions were begun A test session consisted of a pretreatment with either SCH 23390 or pimozide given IV via the catheter The test drug was injected into the catheter followed by enough 0 9% saline to flush the drug into the animal (3–5 ml) The catheter was refilled with the baseline drug immediately before the session began SCH 23390 was given 30 minutes before the session and pimozide was given 2 hr before the session Pretreatments were administered no more frequently than every fourth day with the additional condition that responding was stable for at least 2 consecutive baseline sessions preceding the pretreatment Doses of antagonist ranged between one that had no effect on responding and one that reduced responding to less than 50% of usual levels Order of interaction testing was counterbalanced across monkeys and drug doses were tested in a random order in each monkey

Data Analysis

The number of injections in each half hour of the 2 hour session was counted as was the total number of injections per session Drug effects are presented as a percent of control using the mean injections/session of the 2 sessions immediately preceding each pretreatment as the control value The 95% confidence limits were calculated from values for pretreatment with drug vehicle Because of the brief duration of action of SCH 23390, recovery from this compound was evident in the second hour of the session Therefore, drug effects are presented for the first hour of the experimental session only To allow comparisons between the antagonists, pimozide data are presented for the first hour also

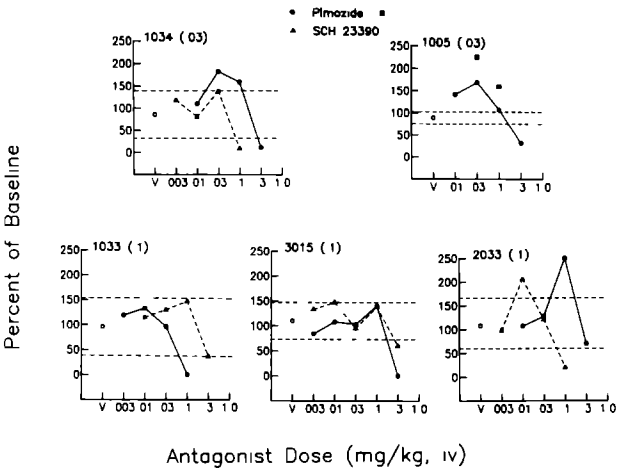

FIG 1 Effects of pimozide (●) and SCH 23390 (▲) on responding maintained by intravenous cocaine in five rhesus monkeys Ordinate Injections in the first hour as percent of control Abscissa Dose of antagonist in mg/kg The baseline dose of cocaine was 0 03 mg/kg/inj for monkeys 1034 and 1005 and 0 1 mg/kg/inj for the other monkeys Each point represents a single determination of the effect of that dose Horizontal dashed lines represent the 95% confidence limits (two-tailed) of the effects of presession injection of antagonist vehicle (V, combined for both antagonists) during the period of testing each antagonist Additional symbols for monkey 1005 (■) are the effects of pimozide over the entire 2 hour session

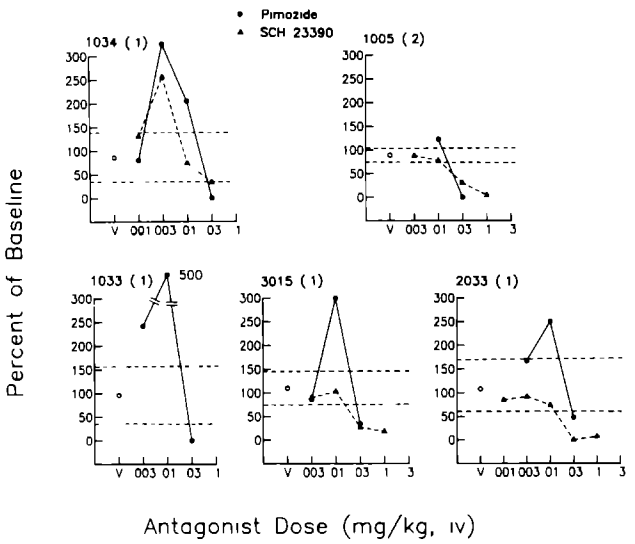

FIG 2 Effects of pimozide and SCH 23390 on responding maintained by intravenous piribedil in rhesus monkeys The baseline dose of piribedil was 0 2 mg/kg/inj for monkey 1005 and 0 1 mg/kg/inj for the other monkeys Other details are as in Fig 1

Drugs

SCH 23390 ((R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol) was dissolved in 0 9% saline for injection Pimozide was prepared in a 4 0 mg/ml stock solution using an emulphor 95% ethanol 1 1 vehicle This solution was then diluted to the appropriate concentration with 0 9% saline The concentration of each drug was appropriate for an injection volume of 1 0 ml/10 kg Cocaine HCl (National Institute on Drug Abuse) and piribedil monomethanesulfonate (Les Laboratoires Servier, Neuilly-sur-Seine, France) were dissolved in 0 9% saline

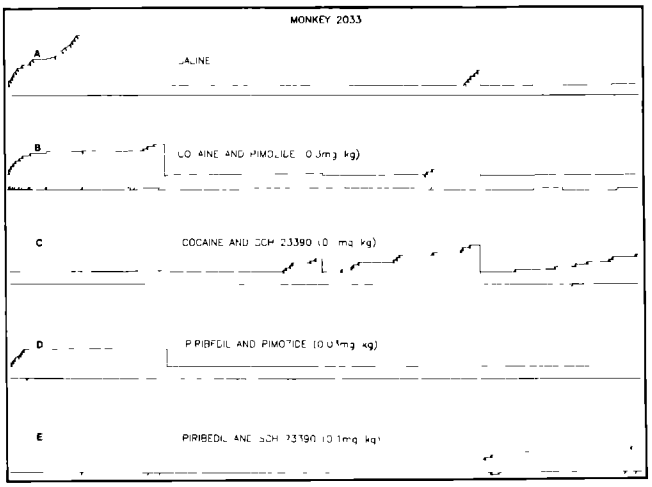

FIG 3 Cumulative response records for monkey 2033 Saline self-administration as well as the effects of high doses of each antagonist on self-administration of each agonist are shown The upper response pen stepped vertically with each correct response and diagonal marks designate injections The lower event pen deflected when the incorrect lever was pressed Each record is 2 hours in length and the correct response pen reset every 1/2 hour

RESULTS

The numbers of injections of cocaine and piribedil taken during baseline sessions are presented in Table 1 Since baseline rates of self-administration changed somewhat over the course of the experiment, separate values are presented for the period of the dose-response determinations of each antagonist As can be seen, under baseline conditions cocaine and piribedil maintained similar patterns of responding with slightly more than 50% of the injections taken in the first half of the session Average rates for each drug varied slightly between segments of the experiment but generally the variation in these rates overlapped In addition, as indicated by variability measures, responding for piribedil was less stable than responding for cocaine Individual animals occasionally stopped taking piribedil completely, an effect that was never seen with cocaine

The effects of pimozide and SCH 23390 on cocaine-maintained responding are shown in Fig 1 In 3 of the 5 monkeys tested, pimozide increased the rate of cocaine self-administration at least at one dose (0 03 or 0 1 mg/kg) At a higher dose of pimozide (0 3) responding was reduced and a relatively prolonged (greater than 2 hours) period of catalepsy was noted In contrast, SCH 23390 usually either did not affect or decreased responding for cocaine An increase in responding was seen following 0 01 mg/kg SCH 23390 in monkey 2033 As with pimozide, the highest doses of SCH 23390 (0 1 and 0 3 mg/kg) reduced responding for

cocaine and induced catalepsy of relatively brief duration (1 hour or less)

The effects of the two DA antagonists on piribedil-maintained responding are shown in Fig 2 Pimozide increased piribedil self-administration in all five of the monkeys, at least at one dose (0 003–0 01 mg/kg) Rate reductions and catalepsy were noted at 0 03 mg/kg SCH 23390 either did not affect or reduced responding at the higher doses Again, an increase in responding was seen at a single dose (0 003 mg/kg) in one animal (1034)

The effects of the highest dose of each antagonist on cocaine- and piribedil-maintained responding of one monkey are shown in the cumulative response records in Fig 3 Data from this monkey were selected because in this case the highest dose of antagonist reduced but did not eliminate responding under all conditions As can be seen, the effects of a high dose of pimozide on responding for cocaine (record B) or piribedil (record D) were similar to the effect of substituting saline for the baseline drug during an untreated self-administration session (record A) There was a burst of responding early in the session after which responding ceased In contrast, at doses of SCH 23390 that had comparable effects on overall rate of self-administration, responding was totally suppressed for the first portion of the session but returned with normal patterns of evenly spaced injections late in the session (record C and E)

DISCUSSION

As has been reported previously [2,3], intermediate doses of pimozide increased the rate of cocaine and piribedil self-administration This effect was similar to that reported previously for the DA antagonists haloperidol and chlorpromazine [3, 16, 18] Since pimozide is a selective D_2 antagonist, these results suggest that a D_2-like receptor is involved in the self-administration of cocaine and piribedil On the other hand, presession administration of the D_1 antagonist SCH 23390 resulted principally in dose-related decreases in the self-administration of both compounds This effect was similar to what has been reported previously when animals allowed to self-administer cocaine were pretreated with pentobarbital [7,17] and suggests that the effect is the result of non-specific effects on rate of responding Taken together, the specific D_2 antagonist effects, as well as the similarity between the effects of these antagonists on the self-administration of cocaine and a direct D_2 agonist, suggest the importance of a D_2-like receptor in the self-administration of cocaine In this regard, the present results are consistent with our earlier findings that D_2 agonists functioned as positive reinforcers in rhesus monkeys while a D_1 agonist did not [19]

In spite of the similarities in antagonist effects across agonists, some differences were also apparent Piribedil self-administration was increased more consistently and to a greater extent by pimozide pretreatment than was cocaine self-administration Although the somewhat lower rates of responding for piribedil under baseline conditions may have contributed to the magnitude of the effect in derived data (i e , % of baseline), this observation also suggests that there are differences between cocaine and piribedil in terms of central mechanisms involved in their self-administration It should also be noted in this context that piribedil self-administration was more variable than cocaine self-administration (Table 1) and was more difficult to maintain on a long term basis In addition, piribedil self-administration was sensitive to lower antagonist doses than was cocaine self-administration Considering that cocaine has known effects on CNS systems other than those involving DA, and that piribedil has effects other than those at central D_2 receptors (e g , alpha adrenergic effects) some differences in antagonist effects should not be surprising Although these results suggest that effects other than central D_2 effects play a role in cocaine self-administration under these conditions, precise clarification of the reasons for these differences between cocaine and piribedil requires further research Nevertheless, the consistencies in antagonist effects on the self-administration of these two agonists strongly suggest significant overlap in the central mechanisms involved in the self-administration of these agonists

Although SCH 23390 and pimozide act at different DA receptors, and the effects of low doses on agonist self-administration were different for each agonist, the observable behavioral effects of high doses of both antagonists were similar Both compounds induced a cataleptic state in which monkeys were observed to support themselves with their arms and to be quite insensitive to external stimuli Moreover, when placed in awkward positions (e g , one arm raised off the floor), they maintained these positions for extended periods of time The principal difference between the compounds in this regard was duration of action, with SCH 23390 being the shorter acting of the two Similar cataleptogenic effects of SCH 23390 have been reported previously in rats [1], and suggest that both D_1 and D_2-like receptors are involved in this effect Alternatively, it is possible that at high antagonist doses SCH 23390 loses its selectivity for CNS D_1 receptors or that D_1 and D_2 receptors are not independent in the CNS

Although the results presented here and elsewhere suggest the importance of a D_2-like receptor in psychomotor stimulant self-administration, one should be cautious in attributing these results to modifications in only the reinforcing properties of psychomotor stimulants The rate of responding for cocaine under the conditions studied here is determined not only by the reinforcing properties of the drug, but also by the direct rate-modifying effects of the drug Thus, an antagonist that increases the rate of responding for cocaine might do so by blocking its reinforcing effects, blocking its rate-reducing effects or by some combination of these The pattern of responding seen in Fig 3 suggests, however, that reinforcing properties were blocked by the highest dose of pimozide but not by SCH 23390 That is, the pattern of responding following pimozide was virtually identical to that seen in the first session of saline availability, suggesting an absence of reinforcing effect On the other hand, with SCH 23390 a complete suppression of responding for the first part of the session was followed by a return to normal patterns of self-administration when the drug effect had waned These results, though suggestive of blockade of reinforcing effects by pimozide, are indirect Additional research under more complex conditions is required to determine the specificity of these antagonist effects to the reinforcing properties of this class of compounds and to eliminate alternative accounts of the data

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