Pharmacology Biochemistry & Behavior, Vol. 32, pp. 691–697. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

The Effects of a D_1 and a D_2 Dopamine Antagonist on Behavior Maintained by Cocaine or Food

WILLIAM L. WOOLVERTON*†‡ AND ROBERT M. VIRUS*

**Department of Pharmacological and Physiological Sciences*
†Department of Psychiatry and ‡Department of Behavioral Sciences
The University of Chicago, The Drug Abuse Research Center
5841 South Maryland Avenue, Chicago, IL 60637

Received 29 April 1988

WOOLVERTON, W. L. AND R. M. VIRUS. *The effects of a D_1 and a D_2 dopamine antagonist on behavior maintained by cocaine or food.* PHARMACOL BIOCHEM BEHAV **32**(3) 691–697, 1989.—The purpose of the present experiment was to determine whether a D_1 or a D_2 dopamine antagonist could alter responding maintained by cocaine at doses that did not affect responding maintained by food. Rhesus monkeys were trained to press a lever in daily experimental sessions under a 3 component multiple schedule of reinforcement. In the first and third components, food was available under a fixed-ratio 30/time-out 2 min (FR30/TO 2) schedule. In the second component, cocaine was available under identical schedule conditions. Each component lasted 15 minutes and there was a 15-minute TO between components. When behavior was stable, rates of responding for injections of saline or several doses of cocaine were determined by making each of these solutions available in the second component for at least 4 sessions. After dose-response determinations for cocaine had been determined, a dose of cocaine that maintained maximal rates of responding was available in daily sessions. When behavior was again stable in all 3 components, monkeys were injected daily before the session with each of several doses of the D_1 antagonist SCH 23390 or the D_2 antagonist pimozide for the same number of sessions that had been required for responding to decline to low levels when the monkeys were allowed to self-administer saline. Both antagonists caused a dose-related decrease in responding for both cocaine and food. Each antagonist decreased responding for food at the same doses that decreased responding for cocaine. Thus both a D_1 and a D_2 dopamine antagonist decreased behavior maintained by cocaine but only at doses that also decreased behavior maintained by another reinforcer, food.

Cocaine Self-administration Dopamine receptors D_1 D_2 SCH 23390 Pimozide Rhesus monkeys

CONSIDERABLE experimental evidence suggests that the catecholamines (CA) norepinephrine (NE) and dopamine (DA) are involved in the pharmacological actions of psychomotor stimulants such as amphetamine and cocaine. Psychomotor stimulants generally increase the availability of CA at central nervous system (CNS) synapses by increasing release, decreasing reuptake, and/or inhibiting metabolism of CA (12). DA, in particular, appears to be involved in the reinforcing properties of psychomotor stimulants. DA agonists have been shown to be self-administered by several species (3, 18, 21). In addition, numerous investigators have reported that pretreatment with intermediate doses of a DA antagonist can increase the rate of responding for injections of a psychomotor stimulant (2, 8, 13, 15, 16). Since reducing the unit dose of stimulant available for self-administration also results in an increase in response rate, this effect would be expected if a compound partially antagonized the reinforcing effect of the stimulant. High doses of DA antagonists can reduce the rate of self-administration as if the reinforcing effects were completely blocked.

DA receptors are of 2 types, D_1 and D_2. Studies with agonists suggest that D_2 but not D_1 receptors are of primary importance in the reinforcing effects of psychomotor stimulants (18,21) and studies with D_2 antagonists have been consistent with this conclusion (6, 13, 16). Recent studies with the D_1 antagonist SCH 23390, however, have been inconsistent. SCH 23390 has been reported to only decrease cocaine self-administration in rhesus monkeys (16), but to have rate-increasing effects at some doses in rats (8). Thus, although stimulation of D_1 receptors is not sufficient for the expression of a reinforcing effect, it is unclear whether D_1 receptors may play some other role in the reinforcing effects of psychomotor stimulants. Further studies with DA antagonists may help clarify this issue.

Interpretation of previous studies with DA antagonists is difficult for several reasons. The major problem derives from the fact that under the simple fixed-ratio schedules of reinforcement that have been utilized, rate of self-administration is an indirect function of dose. As dose is increased above a certain threshold, rate of responding for drug decreases. This occurs because an intravenously delivered drug can have at least 2 effects on ongoing behavior that may be opposite in direction. As a positive reinforcer, a drug injection will increase the probability that the behavior that led to the injection will be repeated. However, drug

injection may also decrease response rate by virtue of rate-decreasing effects that are independent of the reinforcing event (6,13). Therefore, response rate increases obtained when DA antagonists were administered to animals responding for psychomotor stimulants may be the result of antagonism of the rate-decreasing effects of the psychomotor stimulant independent of any alteration of reinforcing efficacy. Research under more complex schedule conditions suggests that this is, in fact, the case (6,17). Thus, it is unclear, at best, whether DA antagonists decrease the reinforcing properties of cocaine.

One way to obviate the problems encountered using simple fixed-ratio schedules of reinforcement is to design a procedure that minimizes the influence of rate-modifying effects of a self-administered drug. Several procedures that programmed a time-out period (TO) after an injection have been successfully utilized in the past (1,4). In these experiments, rate of responding for drug was a direct function of self-administered dose, probably because rate was largely unconfounded by rate-decreasing effects of the self-administered drug. Under these conditions a reduction in reinforcing efficacy (i.e., reduction in unit dose) resulted in a reduction in response rate and an antagonist of the reinforcing effects would be expected to reduce the rate of responding for the self-administered drug.

A second complication is whether the effects of a putative antagonist of the reinforcing effects of cocaine has actions that are specific for cocaine. Although high doses of DA antagonists can reduce responding for cocaine in a manner that suggests blockade of its reinforcing effects, the specificity of this effect for responding maintained by cocaine should be questioned. DA antagonists, like other drugs, have rate-decreasing effects that may be independent of the reinforcing event. Clearly, this group of compounds has prominent effects on motor performance and a substantial amount of research has questioned whether the motor or "hedonic" effects of these compounds are of primary importance in the modification of the effects of stimulants (14). The question of specificity of antagonist effects for the drug as reinforcer can be addressed by making additional reinforcers simultaneously (17) or sequentially (5) available to the animal. An important feature of a clinically useful compound is that its effects should be specific for cocaine. That is, behavior maintained by cocaine should be decreased while behavior maintained by other reinforcers should be unaffected.

In consideration of these problems, the present study was designed to examine the effects of DA antagonists on responding for cocaine under conditions in which the influence of the rate-decreasing effects of cocaine were reduced or eliminated by programming a TO after each injection. To assess the specificity of antagonist effects, responding for another reinforcer, food, was maintained in the same animals. To examine the possibility of different roles for DA receptor subtypes, both a D_1 and a D_2 antagonist were tested in these animals.

METHOD

Animals and Apparatus

The subjects were 3 rhesus monkeys, 2 females and 1 male. At the beginning of the experiment, the male (4007) weighed 7.8 kg and the females (3015 and 5016) weighed 4.3 and 4.6 kg, respectively. Monkeys 3015 and 4007 had previous experience with IV self-administration of cocaine and DA agonists and 5016 was experimentally naive. Water was continuously available and sufficient supplemental food (Purina Monkey Chow No. 5038, Ralston-Purina Co., St. Louis, MO) was provided daily to maintain stable body weight. A chewable multiple vitamin tablet was also provided daily to each monkey.

Each monkey was fitted with a stainless steel restraint harness and spring arm that attached to the rear wall of an experimental cubicle (68 cm wide × 84 cm deep × 91 cm high) in which the monkey was housed for the duration of the experiment. Each cubicle had a Plexiglas window in the door that allowed visual access to the laboratory at all times except during experimental sessions. 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 stainless steel food dish was mounted between them. Four jeweled stimulus lights, 2 white and 2 red, were mounted directly above each lever. Two houselights, 1 white and 1 red, were mounted in the ceiling of each cubicle and were covered by translucent Plexiglas. Intravenous injections (approximately 1.0 ml over 10 sec) were delivered by peristaltic infusion pumps (Cole-Parmer Co., Chicago, IL) and 1.0 g banana-flavored pellets (P. J. Noyes Co., Lancaster, NH) were delivered by electromechanical feeders (Ralph Gerbrands Co., Arlington, MA). All programming and recording of experimental events was accomplished by solid state equipment (BRS/LVE, Beltsville, MD) located in an adjacent room.

Procedure

After a brief period of preliminary training to lever press for food pellets, each monkey was removed from its cubicle and anesthetized with a combination of phencyclidine hydrochloride (1.0 mg/kg, IM) and atropine sulfate (0.04 mg/kg, IM), followed in 20–30 min by sodium pentobarbital (approximately 30 mg/kg, IV, to effect). When anesthesia was adequate, a silicone rubber catheter (0.031 cm inside diameter, North American Reiss Corp., Ronsil Rubber Division, Belle Meade, NJ) was surgically implanted in a major vein (internal or external jugular or femoral) under aseptic conditions. After surgery, each monkey was returned to its cubicle and the catheter was threaded through the spring arm, out the back of the cubicle, and connected to the infusion pump. As a prophylactic measure against postoperative infection, each monkey received IM injections of 25 mg/kg cephalothin sodium (Keflin, Eli Lilly & Co., Indianapolis, IN) twice daily for 7–10 consecutive days after surgery. If a catheter became nonfunctional during the course of the experiment it was removed and, after a 1- to 2-week period to allow any infection to clear, a new catheter was implanted.

After recovery from surgery, the monkeys were trained in daily experimental sessions to press the levers under a 3 component multiple schedule of reinforcement. In the first 15-min component, the white houselights and white right lever lights were illuminated to signal the availability of food pellets under a fixed-ratio 30 (FR30) schedule. The delivery of each pellet was followed by a 2-min time-out (TO 2) period during which all stimulus lights were extinguished and responses had no programmed consequences. After completion of the TO 2, the right lever lights were again illuminated and a food pellet was available under the FR30 schedule. After completion of this first food-reinforced component (FD1), there was a 15-min TO period during which all stimulus lights were extinguished and responses were counted but had no other consequence. At the end of this TO period, the illumination of the white houselight and white left lever lights signalled the availability of IV cocaine injections for responding on the left lever under a FR30 TO 2 schedule identical to that in effect in the FD1 component. During the 10 sec IV injection, the white houselight and white left lever lights were extinguished and the red houselight and red left lever lights were illuminated. The drug (D) component was immediately followed by a second 15-min TO period after which a FR30 TO 2 food-reinforced component (FD2), identical to the FD1 component, concluded the 75-min experimental session. Sessions were

conducted at the same time each day, 7 days/week.

For the first several sessions after surgery, 0.025 mg/kg/inj cocaine was available in the D component. Once responding was stable under these conditions (10% or less variation in response rates in all 3 schedule components for at least 3 consecutive sessions), saline was made available for self-administration in the D component. Subsequently, dose-response functions for IV self-administration of cocaine were determined. Each of 4 doses of cocaine (0.006–0.1 mg/kg/inj) was available for the same number of sessions that were required for responding to decline to low levels when saline was available. A baseline dose of cocaine was then selected for each monkey which was at or near the peak of the dose-response function and, as nearly as possible, maintained response rates similar to those maintained by food. The baseline dose was 0.025 mg/kg/inj for monkeys 4007 and 5016 and 0.05 mg/kg/inj for monkey 3015.

When responding was stable for the baseline dose of cocaine, testing of DA antagonists was begun. Each of several doses of pimozide (D_2 antagonist) or SCH 23390 (D_1 antagonist) was injected daily before the session for approximately the same number of sessions as had been required for responding in the drug component to decline to low levels when 0.9% saline was available. Occasionally, when there was an upward or downward trend in behavior at the end of this period, antagonist pretreatments were continued until responding was stable. In addition, if the behavioral effects (e.g., catalepsy) of antagonists were severe, the exposure was occasionally shortened out of concern for the monkey. Because of its slow onset and long duration of action, pimozide was administered IM 4 hr before the daily experimental session. On the other hand, SCH 23390 has a more rapid onset and brief duration of action and was administered SC, 15 min presession.

Drugs

A pimozide stock solution was prepared in a concentration of 10 mg/ml in a vehicle composed of equal volumes of 95% ethanol and Emulphor EL-620 (GAF Corporation, New York, NY). This solution was diluted to the appropriate concentration for injection with 0.9% saline. SCH 23390 [(R)-(+)-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H3-benzazepine-7-ol maleate; Schering-Plough Corporation, Bloomfield, NJ] and cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD) were dissolved in 0.9% saline. The concentrations of all drugs were adjusted for injection volumes of 0.1 ml/kg. Doses of cocaine and SCH 23390 are expressed as the salt. Pimozide doses are expressed as the base.

Data Analysis

The last 3 days of each treatment in all 3 schedule components were used in data analyses. Means and standard errors were calculated on an individual basis for the response rates.

RESULTS

Under control conditions, rates of responding for food ranged from slightly less than 1.0 to greater than 2.0 responses/sec (Fig. 1). When the dose of cocaine available in the D component was varied, response rate in that component was an increasing function of dose over a range of 0.006–0.025 (5016 and 4007) or 0.05 mg/kg. A higher dose of cocaine resulted in a lower rate of responding by 4007 and 3015. When saline was available responding declined to less that 0.25 responses/sec over 4–10 sessions and was characterized by a high rate of responding early in a D period followed by a complete cessation of responding (data not shown).

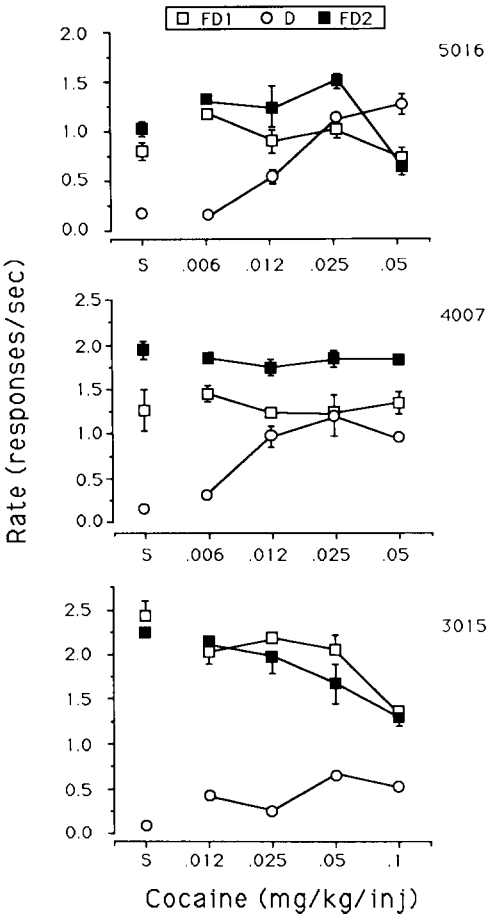

FIG. 1. Effects of varying self-administered dose of cocaine on responding in each component of the multiple schedule for monkeys 5016, 4007 and 3015. Ordinate: response rate in responses/second. Abscissa: dose of cocaine available in the drug component in mg/kg/injection. FD1: first component of the multiple schedule in which food was available under a FR30 TO 2 schedule of reinforcement; D: the second component of the multiple schedule in which cocaine was available under the same schedule of reinforcement; FD2: the third component of the multiple schedule in which food was again available under the same schedule of reinforcement. Each point represents the mean rate of responding in the last 3 sessions of availability of that dose of cocaine and vertical lines represent the SE. The points above S represent the rates of responding when saline was available in the D component.

Response rate in the FD components was not systematically altered by self-administered lower cocaine doses, although there was some variability in this measure. Response rate in the FD2 component was reduced in 2 of 3 monkeys when the highest dose of cocaine was available, probably due to a direct effect of cocaine on responding. Patterns of responding typical of fixed-ratio schedules, i.e., brief pauses before initiation of responding followed by responding at high rates, were seen in all components. The exception was 3015 who responded at unusually low rates for cocaine. Based on the results of these cocaine dose-response determinations, a dose of 0.025 mg/kg/inj (5016 and 4007) or 0.05 (3015) was chosen for examination in combination with DA antagonists.

When pimozide (0.006–0.1 mg/kg, IM) was given 4 hours before the session, rate of responding for cocaine was reduced in

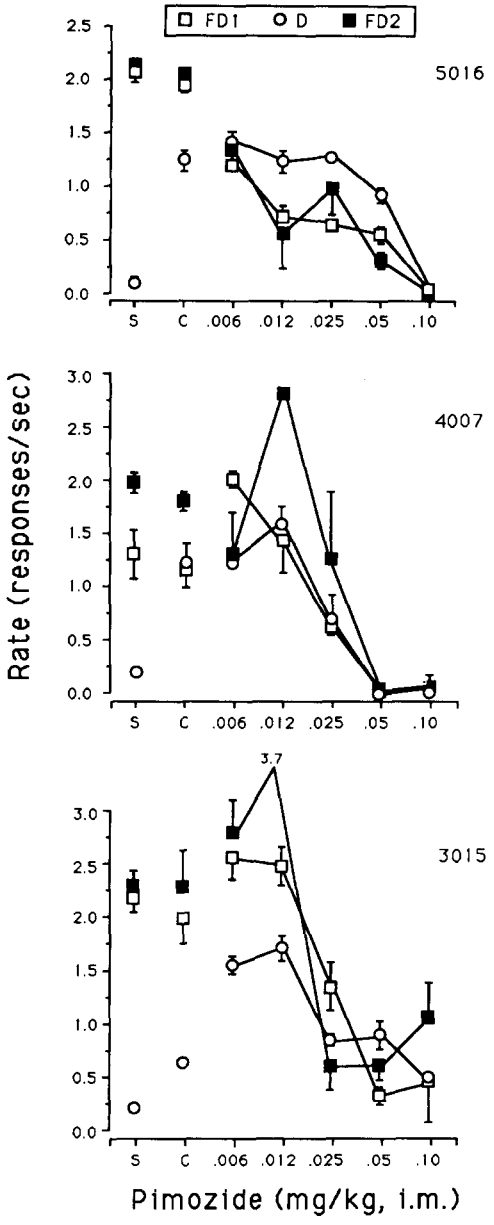

FIG. 2. Effects of varying the pretreatment dose of pimozide on responding in each component of the multiple schedule for monkeys 5016, 4007 and 3015. The baseline dose of cocaine was available for self-administration in the D component (5016 and 4007: 0.025 mg/kg/inj; 3015: 0.05 mg/kg/inj).The points above C represent the rates of responding when the baseline dose of cocaine was available and no pimozide was given. Other details are as in Fig. 1.

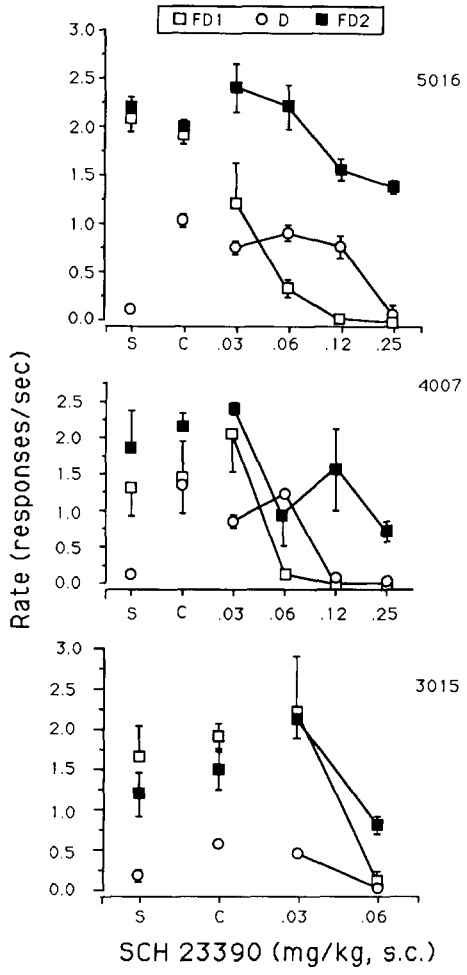

FIG. 3. Effects of varying the pretreatment dose of SCH 23390 on responding in each component of the multiple schedule for monkeys 5016, 4007 and 3015. Details are as in Fig. 2.

a dose-dependent manner in 5016 and 4007 (Fig. 2). In 3015, rate of responding for cocaine was increased by 0.006 and 0.012 mg/kg pimozide then decreased again at higher doses of pimozide. Responding for food in FD1 was decreased in a similar manner over this same dose range. Surprisingly, responding in FD2 was increased at 0.012 pimozide in both 4007 and 3015. In monkeys 5016 and 3015, responding maintained by food was slightly more sensitive to reduction than was responding maintained by cocaine. In monkey 4007 behavior maintained by the 2 reinforcers was comparably sensitive to reduction by pimozide.

When SCH 23390 (0.03–0.25 mg/kg, SC) was given 15 minutes before the session, rate of responding for cocaine was reduced in a dose-related manner in all 3 monkeys (Fig. 3). Rate increases were not seen at any dose in any monkey. Responding for food in FD1 was decreased over the same dose range by SCH 23390. Responding in FD2 was also reduced by SCH 23390 although it was less affected by SCH 23390 than was responding in FD1 or D.

If the reductions in responding for cocaine seen with pimozide or SCH 23390 were due to blockade of the reinforcing effects of cocaine, then the change in response rate in the D component over the sessions of repeated administration of the antagonist should be comparable to the change in responding when saline was available for self-administration in the D component. When saline was available, responding declined to low rates over 4–10 sessions (Figs. 4 and 5). As noted in Fig. 2, low doses of pimozide (0.006 and 0.012) either had no effect (5016 and 4007) or increased (3015) responding for cocaine over the period of daily administration (data not shown). Higher doses of pimozide (0.025 and 0.05 mg/kg) reduced rate of responding for cocaine over the first 1–5 days of repeated administration (Fig. 4). However, rates of

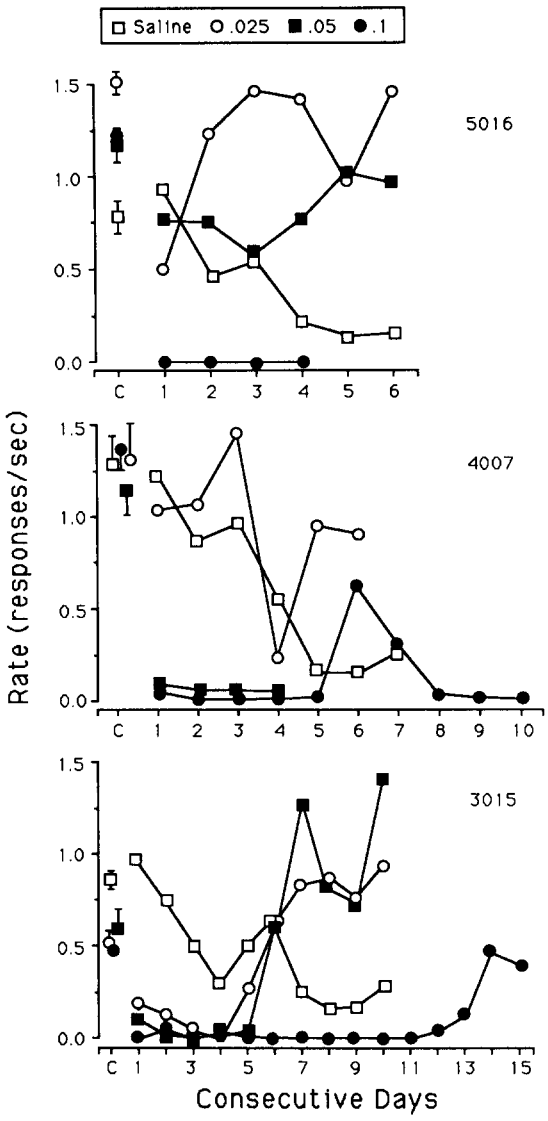

FIG. 4. Effects of repeated administration of several doses of pimozide on responding maintained by cocaine in the D component of the multiple schedule. Ordinate: response rate in responses/second. Abscissa: consecutive days of repeated administration. The points above C represent the mean rates of responding for cocaine over the 3 sessions that immediately preceded pimozide administration when the baseline dose of cocaine was available. The vertical lines represent the SE. Individual points represent the rate of responding in that session of pimozide administration at the doses indicated in the legend (mg/kg, IM, 4 hours presession).

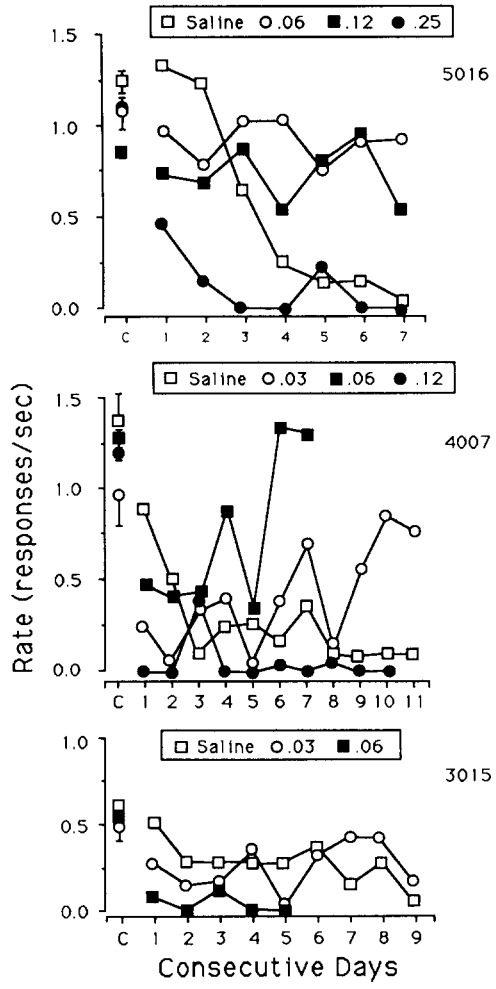

FIG. 5. Effects of repeated administration of several doses of SCH 23390 on responding maintained by cocaine in the D component of the multiple schedule. Details are as in Fig. 4 except that SCH 23390 was given SC 15 minutes presession.

responding often began to increase after this point and were at or near baseline levels at the end of the period of repeated administration. When the dose of pimozide was increased to 0.1 mg/kg responding was completely suppressed for several days but increased again over the last few days of repeated administration in 4007 and 3015.

Although there were individual differences in sensitivity to SCH 23390, overall the effects were comparable between monkeys (Fig. 5). Low doses (0.03 or 0.06 mg/kg) generally did not affect or decreased rate of responding for cocaine. With these doses, responding approximated baseline rates by the end of repeated injections. When higher doses (0.06–0.25 mg/kg) were tested, responding was more substantially reduced and at the end of the daily administration period rate was equal to or below the rate of responding for saline. This reduction probably was the result of suppression of responding since rates of responding in FD1 were comparably reduced at these doses.

DISCUSSION

When cocaine was available for self-administration in one component of a multiple schedule, rate of responding for cocaine was directly related to dose until a maximum rate was achieved. At higher doses, rate of responding for cocaine began to decrease in 2 of the 3 monkeys. This is consistent with what has been found in other experiments in which a TO was programmed after drug injections (1, 4, 5). Since an increase in cocaine dose is associated with an increase in reinforcing efficacy (7, 17, 19) it may be assumed that, under the present conditions, rate of responding for cocaine over the increasing portion of the dose-response curve was a direct measure of reinforcing efficacy.

If rate of responding was a direct measure of reinforcing

efficacy under these conditions, a drug that reduced the reinforcing efficacy of cocaine would be expected to reduce the rate of responding for cocaine. In fact, both a D_1 and a D_2 antagonist reduced the rate of responding for cocaine in a dose-related manner. That result, if taken alone, suggests that the reinforcing effect of cocaine can be reduced by blocking either type of receptor. However, several factors argue that the reduction in cocaine-maintained behavior was the result of a nonspecific suppression of responding rather than blockade of the reinforcing effects of cocaine. Behavior maintained by food was affected in the same way and was at least as sensitive to disruption by DA antagonists as was behavior maintained by cocaine. In contrast, Herling (5), using a similar procedure, found that codeine-maintained behavior was reduced by the administration of naltrexone at doses that did not affect behavior maintained by food. In addition, the pattern of responding for cocaine over several days of repeated administration of DA antagonists was not comparable to the pattern seen when saline, presumably without reinforcing effects, was made available for self-administration. Finally, when rate of responding for saline was low in the D period, it was usually the result of an initial burst followed by a complete cessation of responding, whereas the pattern of responding following DA antagonists was irregular or completely suppressed. Thus, it is likely that DA antagonists were reducing rate of responding in a nonspecific way rather than specifically reducing the reinforcing effects of cocaine.

Previous experiments have reported that DA antagonists increased responding maintained by cocaine over the same range of antagonist doses that decreased responding in the present experiment (13,16). It is likely that methodological variables account for this difference. In earlier experiments, injections of cocaine were not followed by a TO. Thus, rates of responding were at least partly determined by rate-decreasing effects of cocaine. Increases in rate of responding for cocaine following a DA antagonist may have been the result of antagonism of those effects rather than of reinforcing effects. In contrast, availability of cocaine was limited in the present experiment not only by providing a brief period of availability but also by programming a TO after each injection. The TO allowed the rate-decreasing effects of these doses of cocaine to dissipate between injections thereby minimizing the influence of this drug effect upon rate of responding for cocaine. Although still higher doses of cocaine would surely have reduced response rate even with the programmed TO, over the range of cocaine doses examined here the cocaine dose-response function was sigmoidal, a direct function of dose, rather than the usual inverted U-shape. At the doses that were examined with antagonists, the animals responded at or near maximal rates. In 2 of the monkeys these rates were comparable to rates of responding for food. It is interesting to note that the monkey in which rate-decreasing effects of cocaine were evident even with a TO (3015) did respond for cocaine at higher rates when pimozide was administered. Since this effect was different from that obtained by reducing the dose of cocaine, it is difficult to argue that the reinforcing efficacy of cocaine was reduced by pimozide. It should also be noted that, as has been found previously (16), a comparable rate-increasing effect was not seen in this monkey when SCH 23390 was administered.

It should be pointed out, however, that SCH 23390 had some of the properties of an effective cocaine antagonist. At some doses, responding in the D component was low while responding in the FD2 component occurred at or near normal rates. It is likely that the brief duration of action of SCH 23390 and consequent waning of its rate-decreasing effect during the experimental session contributed to this effect. Responding in FD1 was usually suppressed at these doses. It may be premature, however, to discard the possibility that a D_1 antagonist can block the reinforcing effects of cocaine. The observation that SCH 23390 can block the discriminative stimulus properties of cocaine (9) or *d*-amphetamine (10,20) suggests that further studies of this interaction are warranted. Continuous exposure to a D_1 antagonist while self-administering cocaine would help address this possibility.

At least at one dose in each monkey, with one or both types of antagonist, responding for cocaine was initially reduced for several sessions and returned to baseline after several sessions of repeated administration. Recovery in responding maintained by food was apparent as well (data not shown). This finding suggests that tolerance developed to the effects of the DA antagonists on responding maintained by cocaine and food when they were administered repeatedly. In contrast, Roberts and Vickers (11) have recently reported sensitization of the DA antagonist haloperidol when it was administered for 10 consecutive days to rats allowed to self-administer cocaine. Although the reasons for the difference between those results and the present results are unclear, it should be noted that Roberts and Vickers (11) examined the effects of repeated administration of haloperidol under conditions in which it increased the rate of cocaine self-administration. That, or other behavioral variables (e.g., schedule of reinforcement), may be important differences between experiments. Species differences may have played a role as well. Nevertheless, if tolerance develops to the rate-decreasing effects of doses of DA antagonists that do not completely eliminate responding, it suggests that these compounds may not be useful for long-term reduction in cocaine-maintained behavior.

The present results fail to support the hypothesis that either a D_1 or a D_2 DA antagonist selectively blocks the reinforcing effects of cocaine. It appears that self-administration of cocaine is effectively reduced only at doses of antagonist that comparably reduce behavior maintained by other reinforcers. It should be noted, however, that the data are consistent with the hypothesis that neuroleptics induce a state of "anhedonia" in which the efficacy of all reinforcing stimuli is reduced (14). If this is in fact the account of the present data, it may be the case with D_1 antagonists as well.

ACKNOWLEDGEMENTS

This research was supported by NIDA grant DA-00250. We gratefully acknowledge the technical assistance of E. W. Anthony and J. Gleason. We also thank Drs. M. S. Kleven and C. E. Johanson for their helpful comments on an earlier version and J. Clark for her help preparing the manuscript.

REFERENCES

1. Balster, R. L.; Schuster, C. R. Fixed-interval schedule of cocaine reinforcement: Effect of dose and infusion duration. J. Exp. Anal. Behav. 20:119–129; 1973.
2. de Wit, H.; Wise, R. A. Blockade of cocaine reinforcement in rats with the dopamine blocker pimozide but not with the noradrenergic blockers phentolamine or phenoxybenzamine. Can. J. Psychol. 31: 195–203; 1977.
3. Gill, C. A.; Holz, W. C.; Zirkle, C. L.; Hill, H. Pharmacological modification of cocaine and apomorphine self-administration in the squirrel monkey. In: Deniker, P.; Radouco-Thomas, C.; Villeneuve, A., eds. Proceedings tenth congress collegium international neuropsychopharmacologicum. New York: Pergamon Press; 1978:1477–1484.
4. Griffiths, R. R.; Bradford, L. D.; Brady, J. V. Progressive ratio and fixed ratio schedules of cocaine-maintained responding in baboons. Psychopharmacology (Berlin) 65:125–136; 1979.

5. Herling, S. Naltrexone effects on food- and codeine-maintained responding in rhesus monkeys. Eur. J. Pharmacol. 73:41–49; 1981.
6. Herling, S.; Woods, J. H. Chlorpromazine effects on cocaine-reinforced responding in rhesus monkeys: reciprocal modification of rate-altering effects of the drugs. J. Pharmacol. Exp. Ther. 214: 354–361; 1980.
7. Johanson, C. E.; Schuster, C. R. A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. J. Pharmacol. Exp. Ther. 193:676–688; 1975.
8. Koob, G. F.; Le, H. T.; Creese, I. The D_1 dopamine antagonist SCH 23390 increases cocaine self-administration in the rat. Neurosci. Lett. 79:315–320; 1987.
9. Kleven, M. S.; Anthony, E. W.; Goldberg, L. I.; Woolverton, W. L. Blockade of the discriminative stimulus effects of cocaine in rhesus monkeys with the D_1 dopamine antagonist SCH 23390. Psychopharmacology (Berlin) 95:427–429; 1988.
10. Nielson, E. B.; Jepsen, S. A. Antagonism of the amphetamine cue by both classical and atypical antipsychotic drugs. Eur. J. Pharmacol. 11:167–176; 1985.
11. Roberts, D. C. S.; Vickers, G. The effect of haloperidol on cocaine self-administration is augmented with repeated administrations. Psychopharmacology (Berlin) 93:526–528; 1987.
12. Weiner, N. Norepinephrine, epinephrine and the sympathomimetic amines. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. The pharmacological basis of therapeutics. 7th ed. New York: Macmillan Publishing Co.; 1985:145–180.
13. Wilson, M. C.; Schuster, C. R. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacologia 26:115–126; 1972.
14. Wise, R. A. Neuroleptics and operant behavior: The anhedonia hypothesis. Behav. Brain Sci. 5:39–87; 1982.
15. Woods, J. H.; Herling, S.; Winger, G. Chlorpromazine- and haloperidol-induced changes in some behavioral effects of cocaine and amphetamine. In: Deniker, P.; Radouco-Thomas, C.; Villeneuve, A., eds. Proceedings tenth congress collegium international neuro-psychopharmacologicum. New York: Pergamon Press; 1978:1485–1502.
16. Woolverton, W. L. Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol. Biochem. Behav. 24:531–535; 1986.
17. Woolverton, W. L.; Balster, R. L. Effects of antipsychotic drugs in rhesus monkeys given a choice between cocaine and food. Drug Alcohol Depend. 8:69–78; 1981.
18. Woolverton, W. L.; Goldberg, L. I.; Ginos, J. Z. Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. J. Pharmacol. Exp. Ther. 230:678–683; 1984.
19. Woolverton, W. L.; Johanson, C. E. Preference in rhesus monkeys given a choice between cocaine and *d,l*-cathinone. J. Exp. Anal. Behav. 41:35–43; 1984.
20. Woolverton, W. L.; Kamien, J. B.; Kleven, M. S. Blockade of the discriminative stimulus effects of cocaine and *d*-amphetamine in rhesus monkeys with the D1 dopamine antagonist SCH 23390. Pharmacologist 29:158; 1987.
21. Yokel, R. A.; Wise, R. A. Amphetamine-type reinforcement by dopamine agonists in the rat. Psychopharmacology (Berlin) 58: 289–296; 1978.