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ORIGINAL INVESTIGATION

Xavier Lamas · S. Stevens Negus · Michael A. Nader
Nancy K. Mello

Effects of the putative dopamine D_3 receptor agonist 7-OH-DPAT in rhesus monkeys trained to discriminate cocaine from saline

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Abstract These studies were designed to evaluate the effects of the putative dopamine D_3 receptor agonist 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetraline (7-OH-DPAT), alone and in combination with cocaine, in four rhesus monkeys trained to discriminate cocaine (0.4 mg/kg, IM) from saline under a fixed-ratio 30 schedule of food presentation. Under these conditions, cumulative doses of cocaine (0.013–1.3 mg/kg) produced a dose-dependent and complete generalization to the training dose of cocaine in all monkeys, while producing only minimal effects on response rates. The discriminative stimulus effects of cocaine were antagonized by the non-selective dopamine receptor antagonist flupenthixol (0.018 mg/kg, IM) in all four monkeys. The effects of 7-OH-DPAT (0.01–1.8 mg/kg) were inconsistent across monkeys. In two of the four monkeys (monkeys L990 and L958), 7-OH-DPAT consistently and completely generalized to cocaine and decreased response rates in a dose-dependent manner. Both the cocaine-like discriminative stimulus effects and rate-decreasing effects of 7-OH-DPAT were antagonized by flupenthixol in these two monkeys. Pretreatment with low doses of 7-OH-DPAT (0.01–0.032 mg/kg) had no effect on the cocaine dose-effect curve in monkeys L990 and L958; however, higher doses of 7-OH-DPAT (0.032–0.32 mg/kg) shifted the cocaine dose-effect curve to the left. In the other two monkeys (monkeys 150F and 89B036), 7-OH-DPAT produced a dose-dependent decrease in response rates but did not consistently generalize to cocaine. Flupenthixol did not antagonize the rate-decreasing effects of 7-OH-DPAT in these two monkeys, and pretreatment with 7-OH-DPAT (0.1–0.32 mg/kg) produced a decrease in response rates but had no effect on the cocaine dose-effect curve. Time-course experiments revealed that 7-OH-DPAT (0.32 mg/kg) displayed a slower onset and a longer duration of effect than the training dose of cocaine. Finally, the D_3/D_2 dopamine agonist quinpirole completely generalized to cocaine in three monkeys, and partially in the fourth monkey. Quinpirole showed the highest potency in those monkeys in which 7-OH-DPAT consistently generalized to cocaine. The results of the present study suggest that, in rhesus monkeys, 7-OH-DPAT produces cocaine-like effects and may modulate the discriminative stimulus effects of cocaine in some monkeys.

Key words Cocaine · Discrimination · Dopamine receptors · Quinpirole · Rhesus monkeys · 7-OH-DPAT

Introduction

The high prevalence of cocaine abuse and dependence has stimulated efforts to develop pharmacotherapies that could be used in the treatment of cocaine abuse. Cocaine inhibits the reuptake of dopamine into presynaptical terminals (Ritz et al. 1987; Johanson and Fischman 1989), which suggests that drugs acting on dopaminergic systems might be useful in modulating cocaine's effects. Two major families of dopamine receptors have been described, the D_1 and D_2 dopamine receptors (De Keyser 1992; Gingrich and Caron 1993). D_1 and D_2 dopamine receptor antagonists have been found to antagonize, at least partially, both cocaine's

This paper is dedicated to the memory of Xavier Lamas, who died on 26 August 1995 on Mount Everest

X. Lamas · S.S. Negus (✉) · N.K. Mello
Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill St., Belmont, MA 02178, USA

M.A. Nader
Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157, USA

M.A. Nader
Department of Comparative Medicine, Bowman Gray School of Medicine, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157, USA

discriminative stimulus (Barrett and Appel 1989; Kleven et al. 1990; Spealman et al. 1991; see also Nielsen 1993) and reinforcing effects (Woods et al. 1987; Bergman et al. 1990; Kleven and Woolverton 1990a; Caine and Koob 1994; Winger 1994). However, these compounds produce negative subjective effects and prominent extrapyramidal side effects that limit their therapeutic usefulness (Kumor et al. 1986). The reinforcing and discriminative stimulus effects of dopamine receptor agonists have also been examined. It has been postulated that dopamine agonists might serve as maintenance drugs for cocaine abuse treatment, analogous to the use of the mu-opioid agonist methadone in the treatment of opioid dependence (e.g. Skjoldager et al. 1993). Like cocaine, both D_1 and D_2 receptor agonists are self-administered by rhesus monkeys (Woolverton et al. 1984; Weed et al. 1993), and pretreatment with the D_2 selective agonist bromocriptine was reported to decrease cocaine self-administration in rhesus monkeys (Kleven and Woolverton 1990b). However, bromocriptine-induced decreases in cocaine self-administration were usually accompanied by side effects such as locomotor activation and decreases in food-reinforced responding. Furthermore, in drug discrimination procedures, D_1 and D_2 agonists administered alone or in combination do not completely generalize to cocaine (Barrett and Appel 1989; Kleven et al. 1990; Spealman et al. 1991; Witkin et al. 1991).

Taken together, these data suggest that the effects of cocaine are not mediated entirely by the classically defined D_1 and D_2 dopamine receptor types. Other dopamine or non-dopamine receptors may also be involved, and drugs acting at these other receptors may be more effective than traditional D_1 and D_2 agonists and antagonists in modulating the effects of cocaine. The recently cloned dopamine D_3 receptor has been shown to be structurally and functionally related to the D_2 receptor, and in vitro studies indicate that, like the D_2 receptor, the D_3 receptor may function as both a presynaptic autoreceptor and as a postsynaptic receptor mediating the trans-synpatic or non-synaptic actions of dopamine (Sokoloff et al. 1990; Diaz et al. 1995). However, the D_3 receptor presents a distinct neuroanatomical distribution, with the highest densities in the olfactory tubercle-island of Calleja complex and in nucleus accumbens (Sokoloff et al. 1990; Diaz et al. 1995). Since dopamine release in the nucleus accumbens has been implicated in both the reinforcing (Koob 1992) and discriminative stimulus (Wood and Emmett-Oglesby 1989) effects of cocaine, D_3 receptors may mediate some of cocaine's effects related to its high abuse potential, and drugs acting at D_3 receptors may be effective in modulating cocaine's effects. Different compounds have been shown to present different affinities for D_3 versus D_2 receptors (Sokoloff et al. 1990). Among dopaminergic agonists, quinpirole and 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) show relatively high affinities for D_3 receptors, with K_i values of 5 nM and 1 nM, respectively (Lévesque et al. 1992; MacKenzie et al. 1994). In in vitro studies, both 7-OH-DPAT and quinpirole bound to D_3 receptors with about 10^2-fold higher affinity compared to D_2 receptors (Lévesque et al. 1992). However, 7-OH-DPAT is a more selective D_3 agonist, since quinpirole displays higher affinity for D_4 receptors (Schwartz et al. 1992).

Recent studies have evaluated the behavioral effects of 7-OH-DPAT in animals trained to discriminate or self-administer cocaine. In drug discrimination studies, 7-OH-DPAT was reported to produce a dose-dependent and complete generalization to cocaine in rats (Geter-Douglass et al. 1994) and a partial generalization to cocaine in squirrel monkeys (Spealman 1994). In addition, 7-OH-DPAT was self-administered in cocaine-trained rats, and pretreatment with 7-OH-DPAT shifted the cocaine dose-effect curve to the left (Caine and Koob 1995). 7-OH-DPAT also maintained self-administration when substituted for cocaine in cocaine-trained rhesus monkeys; however, naive monkeys could not be trained to self-administer 7-OH-DPAT under conditions in which cocaine self-administration was acquired (Nader and Mach, 1996, in press). It is not clear if these behavioral effects of 7-OH-DPAT reflect a selective stimulation of D_3 receptors, but these data suggest that 7-OH-DPAT has effects that are similar to cocaine and may modulate cocaine's reinforcing effects (Caine and Koob 1993, 1995; Geter-Douglass et al. 1994; Spealman 1994). The finding that 7-OH-DPAT is not self-administered by cocaine-naive monkeys further suggests that it may have relatively low abuse liability, even though it maintains drug self-administration in cocaine-experienced monkeys (Nader and Mach, 1996, in press).

Drug discrimination assays have been extensively validated as a tool for evaluating cocaine's mechanisms of action in both rodents (Barrett and Appel 1989; Witkin et al. 1991) and primates (de la Garza and Johanson 1983; Woods et al. 1987; Kleven et al. 1990; Woolverton 1991). Thus, drug discrimination assays could be a good model to evaluate the mechanism of action of 7-OH-DPAT in comparison with cocaine, and to examine further the interactions between 7-OH-DPAT and cocaine. The purpose of the present study was to extend the characterization of the behavioral effects of 7-OH-DPAT alone and in combination with cocaine and the non-selective dopamine antagonist flupenthixol in rhesus monkeys trained to discriminate cocaine from saline.

Materials and methods

Subjects

Four adult male rhesus monkeys (*Macaca mulatta*) served as experimental subjects. All monkeys had a previous history of cocaine

discrimination. Monkeys weighed 4.8–7.0 kg; their weights were maintained with a daily diet of multiple vitamins, fresh fruit, and four to six Lab Diet Jumbo Monkey biscuits (PMI Feeds, St Louis, Mo.) in addition to banana pellets which they could earn during daily operant sessions. Water was continuously available. Monkeys were individually housed in well-ventilated, stainless-steel cages (66 × 76 × 91 cm). A 12-h light/dark cycle was in effect (lights on 7:00 a.m.–7:00 p.m.).

Apparatus

Experimental sessions were conducted in the home cages, which were modified to include an operant panel (28 × 28 cm) mounted on the front wall. The panel contained three Plexiglas response keys (6.4 × 6.4 cm), 2.54 cm apart in a horizontal row 3.2 cm from the top of the panel. Keys could be transilluminated by white, green or red stimulus lights. The central key was not functional during these experiments. The operant panel supported an externally-mounted pellet dispenser (Gerbrands, model G5210) that delivered 1 g banana-flavored pellets (P.J. Noyes, Lancaster, N.H.) to a receptacle mounted on the cage beneath the response panel. During sessions, the experimental room was provided with white noise to mask extraneous sounds. Programming and recording were accomplished with Apple IIGS computers located in an adjacent room.

Discrimination training

Experiments were conducted 5 days per week (Monday–Friday) between 9:30 a.m. and 4:30 p.m. in sessions composed of one to five cycles. Each cycle consisted of a 15-min time-out period followed by a 5-min response period. During time-out periods, stimulus lights were off and responding had no scheduled consequence. During response periods, the left and right response keys were transilluminated either red (for one key) or green (for the other key) and monkeys could earn up to ten food pellets by responding under a FR 30 schedule of food presentation. If 10 reinforcers were obtained before 5 min had elapsed, stimulus lights were extinguished and responding had no scheduled consequences for the remainder of the response period. The side of the red and green key was across monkeys.

Each monkey was trained to respond differentially on the two response keys, depending on whether saline or cocaine (0.4 mg/kg) was injected IM. Injections were given during each time-out period, 10 min before the start of each response period. Following the administration of saline, only responding on the green key (the saline-appropriate key) produced food, whereas following the administration of cocaine, only responding on the red key (the drug-appropriate key) produced food. Responses on the inappropriate key reset the FR requirement. If cocaine was administered, it was only administered during the last cycle. Monkeys were considered to have acquired discrimination when the following three criteria were met in all cycles for seven of eight consecutive sessions: 1) the percent of injection-appropriate responding prior to the delivery of the first reinforcer was greater than or equal to 80%; 2) the percent of injection-appropriate responding for the entire cycle was greater than or equal to 90%; and 3) response rates during saline cycles were greater than 1.0 responses/s.

Discrimination testing

Once the criteria for cocaine discrimination were met, test sessions were conducted on Tuesdays and Fridays, with training sessions continuing on Mondays, Wednesdays and Thursdays. Test sessions were run only if the three criteria for discrimination were met during the immediately preceding training session. During test sessions, responding on either key produced food, although responding on one key still reset the ratio requirement on the other key.

Dose-effect curves

Dose-effect curves for cocaine (0.013–1.3 mg/kg, IM), 7-OH-DPAT (0.01–3.2 mg/kg, IM) and quinpirole (0.01–1.0 mg/kg, IM) were determined using a cumulative dosing procedure. In this procedure, increasing doses of cocaine, 7-OH-DPAT or quinpirole were administered during each time-out (10 min before the start of each response period) of a multiple cycle session. Each injection increased the total, cumulative dose by 1/4 or 1/2 log units. Cumulative dose-effect curves for cocaine alone were determined on four occasions for each monkey during the course of the study. Cumulative dose-effect curves for 7-OH-DPAT alone were determined twice in monkeys L990 and L958 and three times in monkeys 150F and 89B036. Cumulative dose-effect curves for quinpirole were determined once in each monkey.

Pretreatment studies

Subsequently, a single dose of the dopamine antagonist flupenthixol (0.018 mg/kg, IM) was administered 25 min (monkeys 150F, L990 and L958) or 55 min (monkey 89B036) before the start of the first cycle, and cumulative dose-effect curves for cocaine or 7-OH-DPAT were redetermined. The dose and pretreatment times for flupenthixol were based on preliminary results in these monkeys (X. Lamas, unpublished data). In addition, cocaine dose-effect curves were redetermined in all four monkeys following pretreatment with 7-OH-DPAT (0.01–0.32 mg/kg). In these experiments, 7-OH-DPAT was administered at the beginning of the first cycle (i.e. 5 min before the first dose of cocaine). In all pretreatment studies, dose-effect curves were determined once.

Time-course studies

Three monkeys (150F, L990 and L958) were included in this experiment. Sessions consisted of the administration of a single dose of cocaine (0.4 mg/kg, i.e., the training dose) or 7-OH-DPAT (0.32 mg/kg) followed by a 5-min response period starting at 10, 20, 30, 60, 100, 180, 300 or 420 min after drug administration. Each time point was tested on a different test day.

Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Rockville, Md.), *cis*-flupenthixol dihydrochloride (Research Biochemicals, Natick, Mass.) and racemic 7-OH-DPAT (7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin hydrobromide; Research Biochemicals, Natick, Mass.) were dissolved in 0.9% bacteriostatic saline solution. Quinpirole hydrochloride (LY-171555; Research Biochemicals, Natick, Mass.) was dissolved in sterile water. All drugs were administered IM in a volume of 0.1–1 ml.

Data analysis

The percent of cocaine-appropriate responding for the entire response period was computed for individual subjects in each cycle as [(total number responses on cocaine key/total number responses on both keys) × 100]. Response rates for each response period were calculated as (total number of responses on both keys/total time stimulus lights were illuminated). If a monkey failed to receive a

reinforcer in a test cycle, the results of that cycle were not included in the percent of drug-appropriate responding, although they were included in the analysis of response rate. A test drug was considered to have generalized to the training dose of cocaine if at least one dose of the test drug produced greater than 90% cocaine-appropriate responding.

Mean and individual subjects data of the percent cocaine-appropriate responding for the entire response period and the response rate were plotted as a function of the dose of cocaine or 7-OH-DPAT in log scale. Under any condition in which a drug produced at least 50% cocaine-appropriate responding, linear regression interpolation of the log dose-effect curve was used to calculate the dose producing 50% cocaine-appropriate responding (ED_{50} value). If dose-effect curves for a drug were determined more than once in a monkey, mean ED_{50} values in that monkey were calculated by averaging the logs of the ED_{50} values of each determination of the dose-effect curve.

Results

During training sessions immediately preceding test days, individual monkeys made an average of more than 99% injection-appropriate responses after the administration of saline or the training dose of cocaine (0.4 mg/kg). Average response rates in individual monkeys ranged from 1.97 to 3.33 responses/s during saline training cycles and from 2.13 to 3.38 responses/s during cocaine training cycles.

Cumulative doses of cocaine (0.013–1.3 mg/kg) produced a dose-dependent and complete generalization to the training dose of cocaine in all four monkeys while producing only minimal effects on responses rates (Fig. 1). ED_{50} values for individual monkeys, corresponding to four determinations of the cocaine dose-effect curve, are shown in Table 1. Pretreatment with flupenthixol (0.018 mg/kg) produced a surmountable antagonism of the discriminative stimulus effects of cocaine, as shown by rightward shifts in the cocaine dose-effect curve in all monkeys (Fig. 1). In individual monkeys, ED_{50} values for cocaine increased 2.9- to 7-fold after flupenthixol pretreatment (Table 1). In addition, flupenthixol decreased cocaine-appropriate responding elicited by the training dose of cocaine in each monkey. At the dose and pretreatment time tested, flupenthixol did not have a marked effect on the rates of responding.

The discriminative stimulus effects of 7-OH-DPAT in cocaine-trained monkeys are shown in Fig. 2. 7-OH-DPAT produced a dose-dependent and complete generalization to cocaine during two determinations of the dose-effect curve in monkeys L990 and L958. Doses of 7-OH-DPAT that generalized to cocaine in monkeys L990 and L958 (0.1–0.32 mg/kg) produced only small decreases in response rates. A higher dose of 7-OH-DPAT (1.0 mg/kg) decreased response rates further or eliminated responding. The overt behavioral effects of 7-OH-DPAT in these two monkeys resembled those of cocaine (data not shown). In monkeys 89B036 and 150F, complete generalization to cocaine was observed

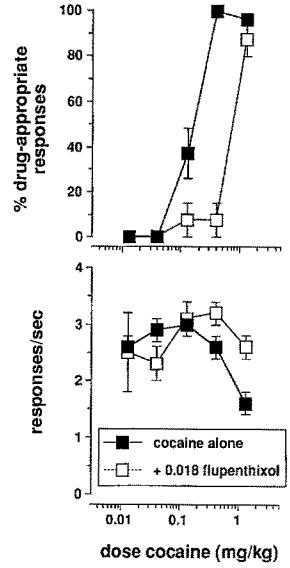

Fig. 1 Effects of cocaine alone (*filled squares*) and after pretreatment with flupenthixol (0.018 mg/kg; *open squares*) in four rhesus monkeys trained to discriminate cocaine (0.4 mg/kg) from saline. *Abscissae*: dose of cocaine (mg/kg), log scale. *Ordinates*: percent cocaine-appropriate responding for entire response period (*top panel*), and response rate (responses/s; *bottom panel*). For cocaine alone, each data point corresponds to four determinations of the dose-effect curve in each monkey. Data for flupenthixol plus cocaine correspond to one determination of the dose-effect curve. Bars represent sem, and are not shown when they are smaller than the symbol

during one determination of the 7-OH-DPAT dose-effect curve; however, in monkey 89B036, complete generalization was observed only at a high dose of 7-OH-DPAT (1.8 mg/kg) that produced a substantial decrease in response rates. This dose could not be tested in other determinations of the dose-effect curve due to elimination of responding. During other determinations of the 7-OH-DPAT dose-effect curve in these monkeys, 7-OH-DPAT elicited only saline-appropriate responding up to doses that eliminated responding. After the administration of cumulative doses of 7-OH-DPAT, these two monkeys appeared catatonic and sedated, resembling the effects of flupenthixol. ED_{50} values for the cocaine-like discriminative stimulus effects of 7-OH-DPAT in individual monkeys are shown in Table 1.

The effects of pretreatment with flupenthixol (0.018 mg/kg) on the 7-OH-DPAT dose-effect curves in individual monkeys are shown in Fig. 2. In monkeys L990 and L958, flupenthixol antagonized the cocaine-like discriminative stimulus effects of 7-OH-DPAT, shifting the 7-OH-DPAT dose-effect curves to the right and increasing the ED_{50} values 9.5- to 27-fold (Table 1). Flupenthixol pretreatment also shifted the 7-OH-DPAT dose-effect curves for response rates to the right in monkeys L990 and L958. After pretreatment with flupenthixol in monkeys 150F and 89B036, 7-OH-DPAT elicited only saline-appropriate responding up to doses that markedly decreased or eliminated

Table 1 ED_{50} values (mg/kg) for cocaine-appropriate responding induced by cocaine, 7-OH-DPAT or quinpirole alone or combinations in individual monkeys. The range of ED_{50} values for cocaine and 7-OH-DPAT alone is shown in parentheses

Treatment		Monkey			
		L990	L958	150F	89B036
Cocaine	Alone	0.131 (0.072–0.238)	0.167 (0.13–0.228)	0.13 (0.072–0.227)	0.167 (0.072–0.226)
	+0.18 Flu[a]	0.92	0.72	0.72	0.50
	+0.01 DPAT[b]	0.23	–	–	–
	+0.032 DPAT	0.049	0.072	–	–
	+0.1 DPAT	0.016	0.20	0.072	ND[c]
	+0.32 DPAT	–	ND[c]	0.23	0.18
DPAT	Alone	0.069 (0.053–0.093)	0.10 (0.056–0.18)	0.18[d]	1.3[d]
	+0.018 Flu	1.8	0.95	ND[e]	ND[e]
Quinpirole	Alone	0.058	0.12	0.39	ND[e]

[a] Flupenthixol; [b] 7-OH-DPAT; [c] not determined because all values for cocaine-appropriate responding were greater than or equal to 50%; [d] 7-OH-DPAT generalized to cocaine during only one determination of the 7-OH-DPAT dose-effect curve; [e] not determined because cocaine-appropriate responding never exceeded 50%; (–) not performed

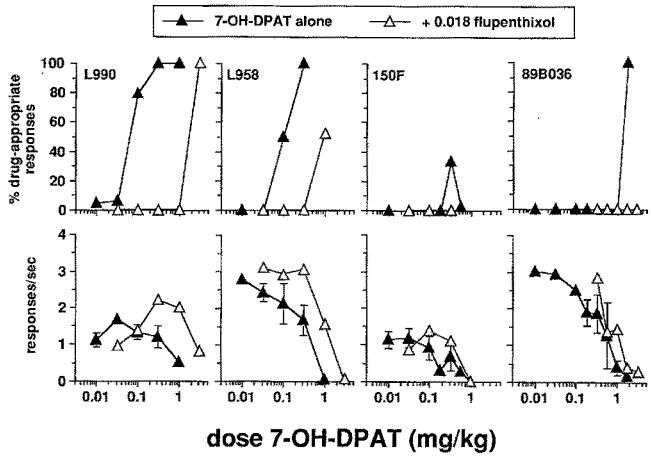

Fig. 2 Effects of 7-OH-DPAT, alone (*filled triangles*) and after pretreatment with flupenthixol (0.018 mg/kg; *open triangles*) in rhesus monkeys trained to discriminate cocaine (0.4 mg/kg) from saline. *Abscissae*: dose of 7-OH-DPAT (mg/kg), log scale. *Ordinates*: percent cocaine-appropriate responding for entire response period (*top panels*), and response rate (responses/s; *bottom panels*). For 7-OH-DPAT alone, each data point corresponds to two (monkeys L990 and L958) or three (monkeys 150F and 89B036) determinations of the dose-effect curve. In monkey 89B036, the highest dose (1.8 mg/kg) was tested only once. Data for flupenthixol plus 7-OH-DPAT correspond to one determination of the dose-effect curve. Error bars in the top panels have been omitted for clarity. Other details are as in Fig. 1

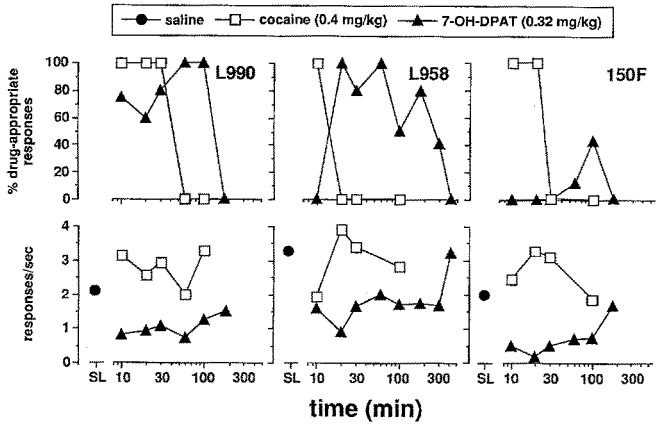

Fig. 3 Time-course of the discriminative stimulus effects of cocaine (0.4 mg/kg; *squares*) and 7-OH-DPAT (0.32 mg/kg; *triangles*) in rhesus monkeys trained to discriminate cocaine (0.4 mg/kg) from saline. *Abcissae*: time after drug administration (min), log scale. *Ordinates*: percent cocaine-appropriate responding for entire response period (*top panels*), and response rate (responses/s; *bottom panels*). Data above "SL" (*circles*) correspond to average response rates after saline administration on training days immediately preceding time-course test days. See Methods for other details

responding. In addition, flupenthixol pretreatment did not antagonize the rate-decreasing effects of 7-OH-DPAT in monkeys 150F and 89B036 (Fig. 2).

7-OH-DPAT (0.32 mg/kg) displayed a slower onset and a longer duration of action than the training dose of cocaine (Fig. 3). Cocaine (0.4 mg/kg) elicited 100% cocaine-appropriate responding within 10 min in all three monkeys tested, but after 60 min, none of the monkeys responded on the cocaine-appropriate key. Cocaine produced only small changes in response rates over time. 7-OH-DPAT (0.32 mg/kg) decreased response rates within 10 min after its administration, but peak effects on cocaine-appropriate responding were observed from 20 to 100 min after its administration. The effects of 7-OH-DPAT were no longer evident after 180 min in monkeys 150F and L990 and after 420 min in monkey L958. During these time-course experiments, 7-OH-DPAT produced complete generalization to cocaine only in monkeys L990 and L958; in monkey 150F, 7-OH-DPAT produced a maximum of 43% cocaine-appropriate responding.

The effects of 7-OH-DPAT pretreatment (0.01–0.32 mg/kg) on the discriminative stimulus effects of cocaine are shown in Fig. 4. In monkeys L990 and L958, after pretreatment with low doses of 7-OH-DPAT (0.01 mg/kg in L990; 0.032 and 0.1 mg/kg in L958), the effects of cocaine were within the variability of the dose-effect curves for cocaine alone (Fig. 4, dashed area). In

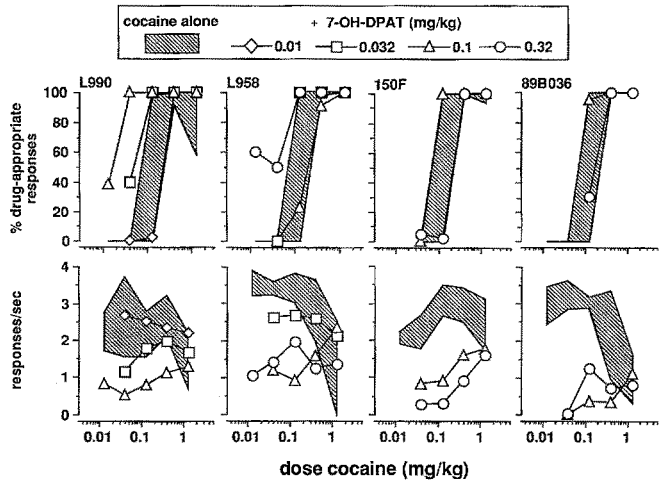

Fig. 4 Effects of cocaine alone (*dashed area*) and after pretreatment with 7-OH-DPAT in rhesus monkeys trained to discriminate cocaine (0.4 mg/kg) from saline. *Abscissae*: dose of cocaine (mg/kg), log scale. *Ordinates*: percent cocaine-appropriate responding for entire response period (*top panels*), and response rate (responses/s; *bottom panels*). *Dashed areas* correspond to the range of effects of cocaine alone in four determinations of the dose-effect curve in each monkey. Data for each dose of 7-OH-DPAT plus cocaine correspond to one determination of the dose-effect curve. Other details are as in Fig. 1

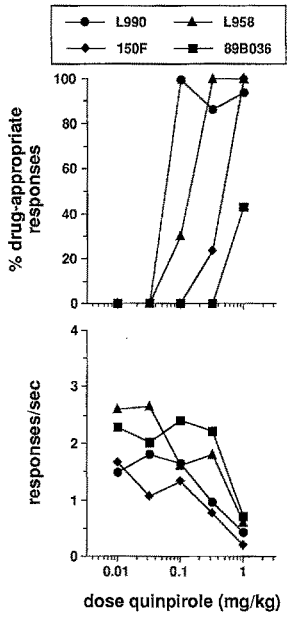

Fig. 5 Effects of quinpirole in rhesus monkeys trained to discriminate cocaine (0.4 mg/kg) from saline. *Abscissae*: dose of quinpirole (mg/kg), log scale. *Ordinates*: percent cocaine-appropriate responding for entire response period (*top panel*), and response rate (responses/s; *bottom panel*). Data points correspond to one determination of the quinpirole dose-effect curve

contrast, doses of 7-OH-DPAT that generalized to cocaine by themselves (0.032–0.1 mg/kg in L990; 0.32 mg/kg in L958) produced leftward shifts in the cocaine curve. After pretreatment with 7-OH-DPAT, response rates were dose-dependently decreased in these two monkeys. In monkeys 150F and 89B036, pretreatment with 7-OH-DPAT decreased response rates but did not alter cocaine's discriminative stimulus effects compared to cocaine alone. ED_{50} values for cocaine discrimination following 7-OH-DPAT pretreatments in individual monkeys are shown in Table 1.

The discriminative stimulus effects of quinpirole in cocaine-trained monkeys are shown in Fig. 5. Quinpirole elicited complete generalization to cocaine in monkeys L990 , L958 and 150F, whereas partial generalization (43% cocaine-appropriate responding) was observed in monkey 89B036 at a dose (1.0 mg/kg) that markedly suppressed responding. Response rates were decreased in a dose-dependent manner in all four monkeys. ED_{50} values for quinpirole's discriminative stimulus effects in individual monkeys are shown in Table 1.

Discussion

The purpose of these studies was to evaluate the effects of the putative dopamine D_3 agonist 7-OH-DPAT administered alone and in combination with cocaine in rhesus monkeys trained to discriminate cocaine from saline. As has been shown in previous studies in rodents (Colpaert et al. 1979), pigeons (Johanson and Barrett 1993), non-human primates (Kleven et al. 1990; Spealman et al. 1991; Lamas et al. 1995; Negus et al. 1995) and humans (Oliveto et al. 1995), cocaine produced robust discriminative stimulus effects in this study, and the training dose (0.4 mg/kg) was reliably discriminated from saline. The cumulative administration of cocaine produced a dose-dependent and complete generalization to the training dose of cocaine while producing only minimal effects on response rates (Fig. 1). In addition, the potency of cocaine in producing its discriminative stimulus effects was similar across monkeys. The non-selective dopamine antagonist flupenthixol (Möller-Nielson et al. 1973; Hess and Creese 1987) antagonized the discriminative stimulus effects of cocaine in all four monkeys, as evidenced by rightward shifts in individual cocaine dose effect curves. These findings agree with previous studies indicating that flupenthixol (Spealman et al. 1991; Mello et al. 1995) as well as more selective D_1 and D_2 dopamine receptor antagonists (Barrett and Appel 1989; Kleven et al. 1990; Witkin et al. 1991; Johanson and Barrett 1993) usually block the discriminative stimulus effects of cocaine. In addition, the present findings concur with these previous studies in suggesting that the discriminative stimulus effects of cocaine are mediated at least in part by dopaminergic systems and involve the stimulation of dopamine receptors.

The behavioral effects of 7-OH-DPAT differed dramatically across monkeys in the present study. In two of four monkeys (L990 and L958), 7-OH-DPAT completely and consistently generalized to cocaine and produced overt behavioral effects resembling the effects of cocaine (e.g. visual checking, increase in locomotor activity). These cocaine-like stimulus effects of 7-OH-DPAT extend previous studies reporting that 7-OH-DPAT generalized partially to cocaine in squirrel monkeys (Spealman 1994) and completely to cocaine

in rats (Geter-Douglass et al. 1994). Moreover, flupenthixol antagonized both the cocaine-like discriminative stimulus effects and the rate decreasing effects of 7-OH-DPAT in monkeys L990 and L958, suggesting that 7-OH-DPAT acted as an agonist at dopamine receptors in these monkeys. Finally, pretreatment with 7-OH-DPAT shifted the dose-effect curve for cocaine discrimination to the left in monkeys L990 and L958, in agreement with the findings in rats that 7-OH-DPAT shifted the dose-effect curve for cocaine self-administration to the left (Caine and Koob 1993, 1995), and that quinpirole increased cocaine-appropriate responding induced by a low dose of cocaine (Callahan and Cunningham 1993). In dramatic contrast to the effects of 7-OH-DPAT in monkeys L990 and L958, the cumulative administration of 7-OH-DPAT in monkeys 150F and 89B036 elicited primarily saline-appropriate responding and produced overt behavioral effects (i.e. decreased responsiveness to external stimuli, ataxia) that were different from the effects of cocaine. Moreover, in monkeys 150F and 89B036, flupenthixol pretreatment did not alter the rate-decreasing effects of 7-OH-DPAT. Finally, pretreatment with 7-OH-DPAT did not alter the discriminative stimulus effects of cocaine in monkeys 150F and 89B036. These results suggest that 7-OH-DPAT did not act primarily as a dopamine agonist in monkeys 150F and 89B036.

The role of specific dopamine receptor subtypes, and in particular of D_3 versus D_2 receptor subtypes, in mediating the effects of 7-OH-DPAT in monkeys L990 and L958 cannot be determined with certainty from the present results. First, 7-OH-DPAT binds with relatively high affinity to dopamine D_2 receptors (Sokoloff et al. 1990), and under some conditions, 7-OH-DPAT appears to display little selectivity for D_3 versus D_2 receptors (Liu et al. 1993; Potenza et al. 1994). Second, flupenthixol has been shown to bind to D_1, D_2 and D_3 dopamine receptors with high affinity (Hess and Creese 1987; Boundy et al. 1993; Kula et al. 1994), so antagonism by flupenthixol does not by itself imply a selective role of D_3 receptors in the behavioral effects of 7-OH-DPAT. However, the results of this study and of previous research with quinpirole suggest that stimulation of D_3 receptors may contribute to the cocaine-like discriminative stimulus effects of 7-OH-DPAT. In the present study, quinpirole produced complete generalization to cocaine in three monkeys, and partial generalization to cocaine in the remaining monkey. Quinpirole was most potent in those monkeys (L990 and L958) in which 7-OH-DPAT consistently generalized to cocaine (Table 1, Figs. 2 and 5). This finding suggests that 7-OH-DPAT and quinpirole may act through similar neural mechanisms and, like 7-OH-DPAT, quinpirole is at least moderately selective for D_3 over D_2 receptors (Lévesque et al. 1992). In addition, quinpirole has also been reported to generalize completely to cocaine in at least some subjects in rats, pigeons and squirrel monkeys, whereas other D_2 agonists showing relatively low affinity for D_3 receptors usually induce lower levels of cocaine-appropriate responding (Spealman et al. 1991; Callahan and Cunningham 1993; Johanson and Barrett 1993; Terry et al. 1994). Since compounds with higher selectivity for D_3 versus D_2 receptors appear to engender higher levels of cocaine-appropriate responding, D_3 receptors may play an important role in mediating the cocaine-like stimulus effects of these compounds. It should be noted that the present results contrast with a report that quinpirole (0.05–0.2 mg/kg, IV) did not generalize to cocaine in rhesus monkeys trained to discriminate IV cocaine from saline (Kleven et al. 1990). The discrepancy may be related to route of administration (IM versus IV) or the drug history of the animals used.

This is, to our knowledge, the first study to evaluate the time-course of the effects of 7-OH-DPAT in an assay of operant behavior. The present study compared the time courses of 0.4 mg/kg cocaine (the training dose) and 0.32 mg/kg 7-OH-DPAT, which were the lowest doses of each drug that consistently produced levels of cocaine-appropriate responding above 90% in monkeys L990 and L958. As previously shown (Lamas et al. 1995), the discriminative stimulus effects of the training dose of cocaine were characterized by a rapid onset and short duration of action. By comparison, 0.32 mg/kg 7-OH-DPAT produced a slower onset of effects than cocaine, as shown by lack of complete generalization to cocaine at 10 min after drug administration, and a longer duration of action than cocaine. In general, the time course of the rate-decreasing effects of 7-OH-DPAT paralleled the time course of its discriminative stimulus effects. Furthermore, the effects of 7-OH-DPAT in the time course experiments were consistent with those obtained in cumulative dosing experiments, since 7-OH-DPAT completely generalized to cocaine in monkeys L990 and L958 but elicited primarily saline-appropriate responding in monkey 150F.

The mechanism of action underlying the rate-decreasing effects of 7-OH-DPAT in monkeys 150F and 89B036 is not known, and the reason for the individual differences in the behavioral effects of 7-OH-DPAT is not clear. One possibility is that the different behavioral effects of 7-OH-DPAT resulted from different behavioral or drug histories of the monkeys; however, all monkeys had equivalent training and drug exposure histories. Another possibility is that 7-OH-DPAT acted as a partial agonist at dopamine receptors with sufficient efficacy to produce consistent generalization in some, but not all, monkeys. According to this hypothesis, 7-OH-DPAT should have acted as a dopamine antagonist in those monkeys (i.e. 150F and 89B036) in which it did not produce dopamine agonist effects (Kenakin 1993). The overt behavioral effects of 7-OH-DPAT were similar to those of the dopamine antagonist flupenthixol in monkeys 150F and 89B036, providing some support for this possibility. However,

unlike flupenthixol, 7-OH-DPAT did not antagonize the discriminative stimulus effects of cocaine in monkeys 150F and 89B036. Moreover, if the rate-decreasing effects of 7-OH-DPAT in monkeys 150F and 89B036 resulted from a flupenthixol-like antagonism of dopamine receptors, it might be expected that flupenthixol pretreatment would shift the 7-OH-DPAT dose-effect curve for rate suppression to the left; however, flupenthixol did not alter the rate-decreasing effects of 7-OH-DPAT in these monkeys. As a result, it does not appear that the individual differences in the behavioral effects of 7-OH-DPAT can be attributed to partial agonist effects of 7-OH-DPAT at dopamine receptors. A final possibility is that 7-OH-DPAT produces multiple effects, and the integration of these effects may vary across individuals such that different effects predominate in different monkeys. Dopamine agonist effects apparently predominated in monkeys L990 and L958, whereas in monkeys 150F and 89B036, 7-OH-DPAT may have produced dopamine agonist effects that were obscured by other effects that eliminated responding. Consistent with this possibility, 7-OH-DPAT did generalize completely to cocaine during one of three determinations in both 150F and 89B036, suggesting that when high enough doses could be probed, dopamine agonist effects could be revealed. In any case, further research with other antagonists would be required to determine the specific receptor types involved in the behavioral effects of 7-OH-DPAT.

The overall profile of effects of 7-OH-DPAT suggests that this compound, and possibly other agonists acting selectively at dopamine D_3 receptors, may have some usefulness as substitutes for cocaine in the pharmacotherapeutic treatment of cocaine abuse and dependence. First, 7-OH-DPAT decreased self-administration of high unit doses of cocaine in rats (Caine and Koob 1995), suggesting that 7-OH-DPAT may decrease cocaine taking behavior under some conditions. Second, 7-OH-DPAT functioned as a reinforcer in monkeys (Nader and Mach, 1996, in press) and rats (Caine and Koob 1993) trained to self-administer cocaine, and substituted at least partially for cocaine in rhesus monkeys (present study), squirrel monkeys (Spealman 1994) and rats (Geter-Douglass et al. 1994) trained to discriminate cocaine from saline. These data suggest that 7-OH-DPAT might produce cocaine-like effects that could facilitate compliance in a drug treatment program. Finally, drug naive monkeys did not acquire 7-OH-DPAT self-administration under conditions in which cocaine self-administration was acquired (Nader and Mach, 1996, in press), suggesting that 7-OH-DPAT may have relatively low abuse liability in drug naive subjects. However, 7-OH-DPAT produced leftward shifts in the dose-effect curves for cocaine self-administration in rats (Caine and Koob 1995) and cocaine discrimination in some monkeys (present study), and the ability of 7-OH-DPAT to enhance the effects of low cocaine doses would compromise its clinical utility. Further parametric studies should clarify the extent to which dopamine D_3 receptor agonists can modulate the reinforcing and discriminative stimulus effects of cocaine in primates, and whether or not the behavioral effects of 7-OH-DPAT reflect an activation of D_3 receptors or different dopamine receptors in combination.

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