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Modulation of cocaine's discriminative stimulus effects by dopamine D_1 agonists in rhesus monkeys

Rachna S. Sinnott[1], Michael A. Nader*

Center for the Neurobiological Investigation of Drug Abuse, Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1083, USA

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Abstract

Dopamine (DA) D_1 agonists are classified as high- or low-efficacy on the basis of in vitro functional measures as compared to DA. In monkeys self-administering cocaine, high-efficacy D_1 agonists have been shown to have reinforcing effects, while low-efficacy agonists do not. However, the relationship between D_1 agonist efficacy and cocaine-like discriminative stimulus effects, particularly in rhesus monkeys, is not clear. The present study investigated the discriminative stimulus effects of a high- (SKF 81297) and a low-efficacy (SKF 38393) D_1 agonist in rhesus monkeys ($n=4$) trained to discriminate cocaine from saline using a two-lever drug discrimination procedure. In a second experiment, the effects of agonist pretreatments, as well as pretreatment with a D_1 antagonist, on cocaine's discriminative stimulus effects were evaluated. SKF 81297 (0.01–1.7 mg/kg) fully substituted for cocaine in three of four animals (>80% cocaine-appropriate responding), while SKF 38393 (0.3–10 mg/kg) occasioned <50% cocaine-appropriate responding in all subjects. When given as a pretreatment, neither agonist altered cocaine's discriminative stimulus effects at the doses tested. In contrast, the D_1 antagonist SCH 23390 attenuated cocaine's discriminative stimulus effects. These results indicate that D_1 agonists have cocaine-like discriminative stimulus effects in rhesus monkeys that are consistent with their in vitro efficacies. However, when given in combination with cocaine, D_1 agonist efficacy does not appear to be a major factor in modifying cocaine's discriminative stimulus effects.

Keywords: Cocaine; Dopamine; Efficacy; Drug discrimination; SKF 81297; SKF 38393; SCH 23390; Rhesus monkeys

1. Introduction

The inhibition of dopamine (DA) uptake, and subsequent activation of DA receptors, has been shown to be primarily responsible for many of the effects of cocaine that contribute to its high abuse potential (e.g. Bergman et al., 1989; Kleven et al., 1990; Ritz et al., 1987). Thus, compounds targeting DA receptor subtypes can be useful tools for investigating cocaine's dopaminergic mechanisms and may provide an avenue for effective pharmacotherapy development. In this regard, numerous studies have shown that D_1- or D_2-like receptor agonists and antagonists can mimic or attenuate, respectively, the behavioral effects of cocaine in animals (for review see Mello and Negus, 1996; Witkin, 1994), suggesting that both receptor subtypes play important roles in cocaine's actions.

Within the D_1 family, agonists can be functionally defined as having high or low intrinsic efficacy, based on the level of adenylyl cyclase stimulation relative to DA in striatal tissue (Andersen and Jansen, 1990; Katz and Witkin, 1992; Witkin, 1994). Some recent studies have suggested that D_1 agonist efficacy may influence the behavioral effects of these compounds in nonhuman primates in that high-efficacy agonists have behavioral effects that overlap with those of cocaine, while low-efficacy agonists have behavioral effects that are more similar to those of D_1 antagonists (Katz et al., 1999; Rosenzweig-Lipson et al., 1994; Spealman et al., 1997). For example, in self-administration studies, high-efficacy agonists function as reinforcers while low-efficacy agonists do not (Grech et al., 1996; Weed and Woolverton, 1995; Weed et al., 1993). Interestingly, however, in prior investigations of cocaine's discriminative stimulus effects, neither high- nor low-efficacy agonists

* Corresponding author. Tel.: +1-336-716-8652; fax: +1-336-716-8501.

E-mail address: mnader@wfubmc.edu (M.A. Nader).

[1] Present address: Department of Veterans Affairs Medical Center (R&D 49), 3710 SW US Veterans Hospital Road, Portland, OR 97201, USA.

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have been shown to fully substitute for cocaine (Katz and Witkin, 1992; Katz et al., 1999; Kleven et al., 1990; Spealman et al., 1991, 1997).

In vitro studies of D_1 agonist efficacy have indicated that there may be a difference in the functional activity of D_1 agonists between rhesus and squirrel monkeys. For example, the D_1 agonist SKF 81297 has been reported to have high efficacy when tested in rhesus monkey tissue (Weed et al., 1997), but low efficacy in squirrel monkey tissue (Izenwasser and Katz, 1993). In contrast, the D_1 agonist SKF 38393 has similar low efficacy across species (Izenwasser and Katz, 1993; Weed et al., 1997). With regards to D_1 agonists in cocaine discrimination studies using monkeys, much of the work has been conducted in squirrel monkeys. Therefore, the present study sought to extend the investigation of the cocaine-like discriminative stimulus effects of SKF 81297 and SKF 38393 to rhesus monkeys. Furthermore, because of possible individual differences in the pharmacokinetics of these D_1 agonists, the influence of acute versus cumulative dosing procedures on substitution for cocaine was evaluated.

In addition to their potential differences in substituting for cocaine, high- and low-efficacy D_1 agonists may also exert opposite modulatory effects when combined with cocaine. In this regard, low-efficacy D_1 agonists have been shown to attenuate the rate-altering and reinforcing effects of cocaine in squirrel monkeys, in a manner similar to that of D_1 antagonists, while high-efficacy agonists have little influence on or enhance these effects of cocaine (Bergman and Rosenzweig-Lipson, 1992; Katz and Witkin, 1992; Spealman et al., 1997). However, the role of agonist efficacy in the modulation of cocaine's discriminative stimulus effects is less clear than for other behavioral effects of cocaine in squirrel monkeys (Katz et al., 1999; Spealman et al., 1997), and has not been thoroughly investigated in rhesus monkeys. Therefore, a second purpose of the present study was to investigate the interactions between cocaine and the D_1 agonists SKF 81297 and SKF 38393 in rhesus monkeys discriminating cocaine from saline, and to compare those results to the effects of the prototypical D_1 antagonist SCH 23390.

2. Methods

2.1. Subjects

Four individually housed, adult male rhesus monkeys (*Macaca mulatta*) served as subjects. One monkey was experimentally naïve (R-1273), and three monkeys had prior experimental histories involving indirect-acting DA agonists and D_2 agonists; three of the monkeys (R-987, R-9119, and R-5514) had prior drug self-administration histories (Nader and Bowen, 1995; Nader and Mach, 1996; Nader and Reboussin, 1994; Nader et al., 1997; Sinnott et al., 1999) and two (R-987, R-9119) had a history of cocaine drug discrimination (Nader et al., 1997; Sinnott et al., 1999). At least 3 months passed between the last test drug and the start of the current study. Animals' body weights (8.5–12.1 kg under free-feeding conditions) were maintained at approximately 90–95% of free-feeding weights by food earned during experimental sessions and by supplemental feeding of Lab Diet Monkey Chow no sooner than 30 min postsession. In addition, monkeys were given fresh fruit or peanuts two to three times per week. Monkeys were weighed approximately once a month (R-5514 was weighed once a week in a primate chair) and, if necessary, their diet was adjusted to maintain stable weights. Overall, body weights remained stable throughout the course of the study. Monkeys lived in temperature- and humidity-controlled colony rooms with lighting maintained on a 0600:2000 on/off schedule. Water was continuously available in the homecage.

2.2. Apparatus

Three of the monkeys were individually housed in sound-attenuating cubicles (91 cm wide × 91 cm deep × 91 91 cm high; Plas Labs, Lansing, MI), which also served as the experimental chamber. The front wall of each cubicle was Plexiglas to allow the monkey visual access to the laboratory; during experimental sessions, this wall was covered with a drape. Each cubicle was equipped with two response levers (BRS/LVE, PRL-001, Beltsville, MD) and a food-pellet dispenser (G5210, Model A, Gerbrands, Arlington, MA) located on the front wall. Above each lever were four stimulus lights, two covered with white lens caps and two covered with red lens caps; these lights were illuminated only during experimental sessions. Each monkey was fitted with a stainless-steel restraint harness and spring arm (Restorations Unlimited, Chicago, IL) that attached to the rear of the cubicle. Experimental events were controlled and counted by a Macintosh II computer and associated interfaces. Sessions began with illumination of the white stimulus lights above both levers. During food presentation, the white lights were extinguished for 2 s, and responding had no scheduled consequences.

Monkey 5514 was individually housed in one quadrant of a four-quadrant stainless steel primate cage. For experimental sessions, the subject was seated in a primate restraint chair (Model R001, Primate Products, Redwood City, CA) and wheeled across the hallway to the experimental chamber. Cocaine discrimination sessions were carried out in a ventilated and sound-attenuated chamber (1.5 m × 0.74 m × 0.76 m; Med Associates, St. Alban, VT). An intelligence panel (48 cm × 69 cm) was located on the right side of the chamber. The panel contained two retractable levers, positioned to be within easy reach of the monkey sitting in the primate chair, and three small stimulus lights centrally located above each lever. A food receptacle was located between the levers and a food-pellet dispenser was located on the top of the chamber. Operation of the chambers and

data acquisition were accomplished with a Power Macintosh computer system and National Instruments interface. Sessions began with illumination of the middle yellow light above both levers. During food presentation, the yellow lights were extinguished for 2 s, and responding had no scheduled consequences.

2.3. Training procedure

Monkeys were trained to discriminate cocaine from saline using a two-lever drug discrimination procedure in which responding was maintained by food presentation. Sessions were conducted at approximately the same time each day, 6–7 days/week. For three monkeys, the left lever was correct following cocaine administration and the right lever following saline administration, while the order was reversed for the other monkey. Cocaine training doses were individually determined and were the lowest doses that reliably maintained discrimination performance and stable response rates in each monkey (0.2 mg/kg for R-9119, R-1273, and R-5514; 0.3 mg/kg for R-987).

Discrimination sessions employed a multiple-component cumulative dosing procedure that was adapted from Negus et al. (1996). Monkeys were initially trained with one component per day until the discrimination was reliably achieved. Training sessions then consisted of one to five components each day, with either saline or the training dose of cocaine administered in each component. If cocaine was administered, it was only given during the last component of a session. The number of components per session varied randomly from day to day, and periodically only saline, or only cocaine, was administered during a session. Each component consisted of a 10-min time-out (TO) period followed by a 5-min response period. All stimulus lights were extinguished during the TO's, and responding during that time had no scheduled consequence. During the response period, the white/yellow lights above both levers were illuminated and food (1 g banana-flavored pellets, P.J. Noyes, Lancaster, NH) was available under a fixed-ratio (FR) 50 schedule.

During each component of the training session, an intramuscular injection of either saline or the training dose of cocaine was administered at the start of the TO. Fifty consecutive responses on the correct lever resulted in food delivery, while responses on the incorrect lever reset the FR value. The pre-component injection determined the correct response lever. A maximum of 10 pellets could be earned during each response period. If all available food pellets were earned before 5 min had passed, the stimulus lights above the levers were extinguished and responding had no scheduled consequences for the remainder of the component.

A few modifications to the general training procedure were made for some monkeys in order to maintain reliable discrimination performance throughout the study. To improve responding, it was necessary to increase the TO to 15 min in three of the four monkeys (R-9119, R-1273, and R-5514). For R-9119, this occurred following initial determinations of the SKF 81297 and SKF 38393 dose–response curves. The dose–response curves for cocaine, SKF 81297, and SKF 38393 were subsequently redetermined (3–8 months apart) and were not different from the original determinations. For R-987, the cocaine training dose was decreased from 0.3 to 0.2 mg/kg in order to improve discrimination performance following determination of the SKF 38393 + cocaine combination curves (see below); the cocaine dose–response curve was subsequently redetermined (5 months apart) and stable performance was reestablished before further testing was conducted. The data from these determinations are presented separately. For R-1273, responding was maintained under an FR 30 schedule and the maximum number of reinforcers delivered per component was five. Additionally, because this monkey's response rates greatly decreased during the later components of the session, a maximum of three components per session was conducted.

Training continued until the following criteria for stimulus control were met in every component of a session for seven of eight consecutive training sessions: (a) at least 80% of the responses before delivery of the first reinforcer were on the injection-appropriate lever; (b) at least 90% of the total session responses were on the injection-appropriate lever; and (c) the response rates during saline components were >1.0 response per second.

2.4. Testing procedure

Once the animals' performance met criteria for stimulus control, testing began. Test sessions were identical to training sessions except that 50 (or 30 for R-1273) consecutive responses on either lever resulted in food presentation. Test sessions were conducted no more than twice a week, and only if the training criteria had been met for the two preceding days and if both cocaine and saline training sessions had occurred in the interim. If a monkey's performance fell below criteria, the animal was returned to the training sequence until discrimination was at or above criteria for at least two consecutive days. Test sessions consisted of up to five components (three components for R-1273). The first component was usually preceded by a saline injection; in subsequent components, increasing doses of the test compound were administered, allowing for a determination of up to a 4-point dose–response curve in one session. Additional doses could be tested by administering overlapping dose ranges in test sessions on different days. Each point was determined at least twice in each monkey, and tests of one drug were typically finished before the next was begun.

2.4.1. Substitution studies

The first series of experiments evaluated the cocaine-like discriminative stimulus effects of saline, cocaine (0.01–0.56 mg/kg), the high-efficacy D_1 agonist SKF 81297 (0.03–1.7

mg/kg), and the low-efficacy D_1 agonist SKF 38393 (0.1–10 mg/kg) in four monkeys. For monkeys R-987, R-9119, and R-5514, the SKF 81297 and SKF 38393 dose–response curves were determined using cumulative and acute dosing procedures. The acute procedure consisted of a drug injection followed, 10 or 15 min later, by a single-component test session. To determine the duration of the cocaine-like discriminative stimulus effects of SKF 81297, the lowest dose that fully substituted for cocaine in each monkey was administered prior to the first component of the session, and saline injections were given in each subsequent component until the majority of responding no longer occurred on the cocaine-appropriate lever. Following the determination of the cocaine and SKF 81297 dose–response curves, monkey R-1273 failed to meet discrimination criteria and was removed from the study.

2.4.2. Pretreatment interaction studies

The second series of experiments evaluated the interactions between cocaine and the D_1 agonists SKF 81297 and SKF 38393. Doses chosen were the highest that did not occasion >50% cocaine-appropriate responding when given in combination with saline and which did not severely decrease response rates on their own. Agonist pretreatments were administered 5 min prior to the first (saline) injection of the session, and cumulative cocaine dose–response curves were subsequently determined. Because results from experiments evaluating the duration of action of SKF 81297 revealed that the cocaine-like discriminative stimulus effects of this agonist did not last for five components in any animal, combination experiments with this compound consisted of no more than three components per daily session. The effects of the D_1 antagonist SCH 23390 were evaluated in single-component test sessions, due to the short duration of action of this compound (Bergman et al., 1989). A dose of SCH 23390 was given in combination with a dose of cocaine that resulted in at least 80% cocaine-appropriate responding. SCH 23390 was administered 15 min (20 min for R-987) prior to the cocaine injection, 30 min before the start of the 5-min response period.

2.5. Data analysis

Three primary dependent variables were recorded for each 5-min response period during test sessions: (1) percentage of total responses on the cocaine-appropriate lever; (2) response rate (total responses/total time stimulus lights were illuminated); and (3) reinforcement frequency (food presentations/response period). Dose–response curves for all drugs were determined at least twice and are represented as the mean of all determinations, for each monkey. Doses of agonists were considered to have substituted for the discriminative stimulus effects of cocaine if at least 80% of the total session responses occurred on the cocaine-appropriate lever. Partial substitution was defined as 20–79% cocaine-appropriate responding. For doses that decreased response rates to the point that no reinforcers were obtained, rate of responding was calculated and included in the analysis, but percent cocaine-appropriate responding was not included.

2.6. Drugs

(−)Cocaine HCl (National Institute on Drug Abuse, Bethesda, MD) was dissolved in sterile 0.9% saline and diluted to concentrations of 0.1–5.0 mg/ml. SKF 81297, SKF 38393, and SCH 23390 (Research Biochemicals International, Natick, MA) were dissolved in sterile water and diluted to concentrations of 1.0–20 mg/ml. D_1 compounds were made fresh on the day of testing and, if necessary, heat and sonication were applied to assist with solubility. All drugs were administered intramuscularly in a volume of approximately 1 ml/10 kg. Saline was administered as a 0.5 ml injection.

3. Results

3.1. Control performance

Monkeys R-5514 and R-1273 were trained in the drug discrimination paradigm for this study. The number of sessions between the first injection of cocaine and achievement of reliable cocaine discrimination was 60 for R-5514 and 144 for R-1273. Previously, we reported that 90–120 sessions were necessary to train the cocaine discrimination in R-987 and R-9119 (Nader et al., 1997). All monkeys required approximately 60 additional sessions to meet criteria for stable performance in the cumulative dosing procedure. During training sessions, subjects typically received the maximal number of food presentations in each component.

Testing of cumulative doses of cocaine (0.01–0.56 mg/kg) resulted in dose-dependent increases in cocaine-appropriate responding in all monkeys, with full substitution observed at the higher cocaine doses (Fig. 1, open circles). Periodic redetermination of the cocaine dose-response curves throughout the course of the study showed that no changes in sensitivity to cocaine's discriminative stimulus effects had occurred (Figs. 1 and 2). Response rates during test sessions ranged from 1.2-3.8 responses/sec for saline and from 0.4-3.7 responses/sec for the training dose of cocaine (0.2 or 0.3 mg/kg); in two monkeys (R-987 and R-1273) response rates decreased as a function of cocaine dose (Table 1).

3.2. Substitution of SKF 81297 and SKF 38393

The high-efficacy D_1 agonist SKF 81297 (0.03–1.7 mg/kg) was studied using cumulative and acute dosing procedures. Overall, SKF 81297 produced complete substitution for cocaine in three of four monkeys. Under cumulative

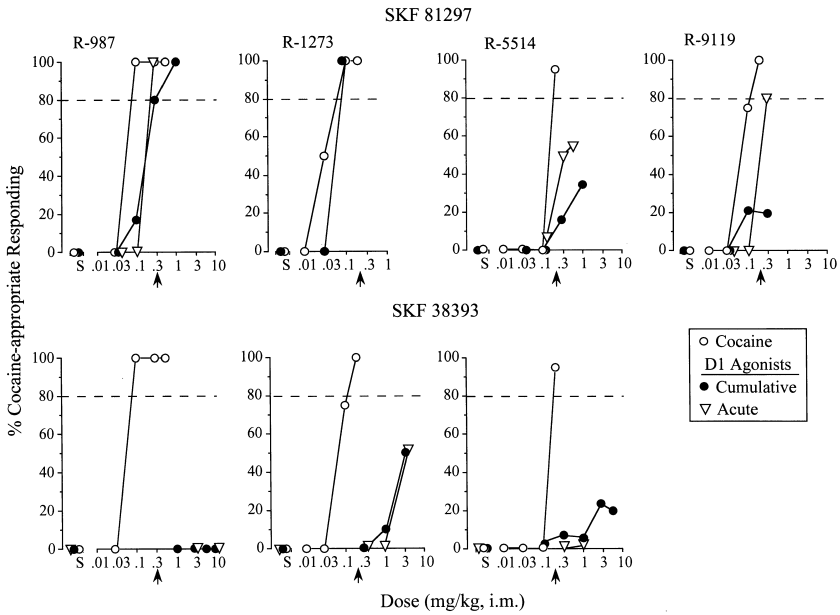

Fig. 1. Discriminative stimulus effects of cocaine, the high-efficacy D_1 agonist SKF 81297 (top panels) and the low-efficacy D_1 agonist SKF 38393 (bottom panels) in rhesus monkeys trained to discriminate cocaine (0.2 or 0.3 mg/kg) from saline (0.5 ml). Figures represent percent of total responses that occurred on the cocaine-appropriate lever. Different symbols represent: cumulative doses of cocaine (open circles), cumulative doses of the D_1 agonists (closed circles), and acute doses of the D_1 agonists (inverted triangles). Arrows on the abscissae indicate the training dose of cocaine. Dashed lines at 80% represent criteria for full substitution for cocaine. Symbols above "S" represent a test of saline vehicle. Each point is the mean of at least two determinations.

dosing conditions, SKF 81297 completely substituted for cocaine in two of four monkeys (Fig. 1, upper panels, closed circles), while under acute dosing conditions, SKF 81297 fully substituted in two of three monkeys (Fig. 1, upper panels, inverted triangles). In R-9119 and to a lesser extent R-5514, the level of substitution for cocaine's discriminative stimulus effects appeared to depend on the dosing procedure. In all monkeys, SKF 81297 was approximately 0.25–0.5 log units less potent than cocaine at producing cocaine-like discriminative stimulus effects. Doses of SKF 81297 that substituted for cocaine had durations of action of 60–90 min (data not shown).

SKF 81297 had comparable rate-decreasing effects in all monkeys, with the highest cumulative doses completely eliminating responding in monkeys R-9119 and R-5514 (Table 1). In R-987 and R-1273, the highest cumulative

Table 1
Mean (S.D.) rates of responding (responses per second) following cumulative doses (mg/kg) of cocaine, SKF 81297, and SKF 38393 for individual monkeys

Cocaine							
Monkey	saline (mg/kg)	0.01 (mg/kg)	0.03 (mg/kg)	0.1 (mg/kg)	0.2 (mg/kg)	0.3 (mg/kg)	0.56 (mg/kg)
R-987	3.33 (0.46)	–	3.81 (0.13)	2.56 (1.73)	2.50 (0.73)	2.34 (0.53)	2.25 (0.49)
R-1273	1.23 (0.28)	1.35 (0.01)	0.67 (0.24)	0.97 (0.10)	0.65 (0.39)	–	–
R-9119	3.65 (0.45)	3.63 (0.46)	3.53 (0.69)	3.93 (0.11)	3.63 (0.10)	–	–
R-5514	3.55 (0.52)	3.51 (0.66)	3.61 (0.35)	3.82 (0.39)	3.49 (0.59)	–	–
SKF 81297							
Monkey		0.03 (mg/kg)	0.1 (mg/kg)	0.3 (mg/kg)	0.56 (mg/kg)	1.0 (mg/kg)	1.7 (mg/kg)
R-987		3.55 (0.08)	3.59 (0.54)	3.53 (0.70)	–	1.37 (0.99)	–
R-1273		1.42 (0.27)	0.30 (0.00)	–	–	–	–
R-9119		3.37 (0.36)	3.01 (0.30)	1.91 (1.08)	0.00	–	–
R-5514		–	3.33	3.37 (0.18)	–	1.65 (1.75)	0.00
SKF 38393							
Monkey		0.3 (mg/kg)	1.0 (mg/kg)	3.0 (mg/kg)	5.6 (mg/kg)	10.0 (mg/kg)	
R-987		–	3.63 (0.09)	3.36 (0.23)	3.09 (0.06)	2.18	
R-9119		3.50 (0.11)	3.00 (0.49)	1.15 (1.71)	–	–	
R-5514		3.69 (0.25)	3.59 (0.17)	3.45 (0.28)	3.11	–	

Dashed line in spaces indicate that the dose was not tested in that animal.

SKF 81297 doses that fully substituted for cocaine reduced response rates by 70–75% compared to rates following saline administration. In general, the method of dosing did not differentially affect response rates. However, in R-5514, administration of an acute dose of 1.0 mg/kg SKF 81297 eliminated responding, while the same dose given cumulatively resulted in a mean response rate of 1.65 responses per second.

The low-efficacy D_1 agonist SKF 38393 was also studied using cumulative and acute dosing procedures. Doses were tested up to those that either substantially decreased responding or caused adverse effects (e.g. vomiting). In contrast to the effects of SKF 81297, acute or cumulative doses of SKF 38393 did not fully substitute for cocaine in any animal tested, although partial substitution was observed in two subjects (Fig. 1, lower panels). SKF 38393 (0.3–10 mg/kg) dose-dependently decreased response rates in two of three monkeys (Table 1).

3.3. Pretreatment with SKF 81297

Based on the time course data, cumulative dosing test sessions involving SKF 81297 pretreatment lasted no longer than 1 h; therefore, up to three cocaine doses were tested in combination with SKF 81297 during a single session. Low doses of SKF 81297 (0.03–0.1 mg/kg) did not have cocaine-like discriminative stimulus effects when given in combination with saline; however, a higher dose (0.3 mg/kg) partially or completely substituted for cocaine, and therefore was not tested in combination with cocaine (Fig. 2, upper panels). In general, pretreatment with SKF 81297 did not substantially alter the discriminative stimulus effects of cocaine, although in one case (monkey 5514) 0.1 mg/kg SKF 81297 given in combination with a cumulative cocaine dose of 0.1 mg/kg engendered 100% cocaine-appropriate responding compared to 0% cocaine-appropriate responding under baseline testing. SKF 81297 pretreatment did not affect response rates in any monkey (Fig. 2, lower panels).

3.4. Pretreatment with SKF 38393

In all monkeys, the low-efficacy agonist SKF 38393 (0.3–10 mg/kg) did not substitute for cocaine. In combination studies, up to four cocaine doses were administered during one test session; however, to confirm that the effects of SKF 38393 lasted throughout the session, separate test sessions were conducted in which SKF 38393 was given in combination with a single high dose of cocaine. No alteration of cocaine's discriminative stimulus effects was observed in this latter situation. In two monkeys (R-9119 and R-5514), pretreatment with a low dose of SKF 38393 (0.3 mg/kg) did not alter cocaine's discriminative stimulus effects in cumulative test sessions (Fig. 3, upper panels), while a dose of 1.0 mg/kg SKF 38393 shifted the cocaine dose–response curve slightly to the left. As with SKF 81297, response rates were not substantially altered by pretreatment with SKF 38393 (Fig. 3, lower panels). In R-987, pretreatment with higher doses of SKF 38393 (3.0–10 mg/kg) did not alter cocaine's discriminative stimulus

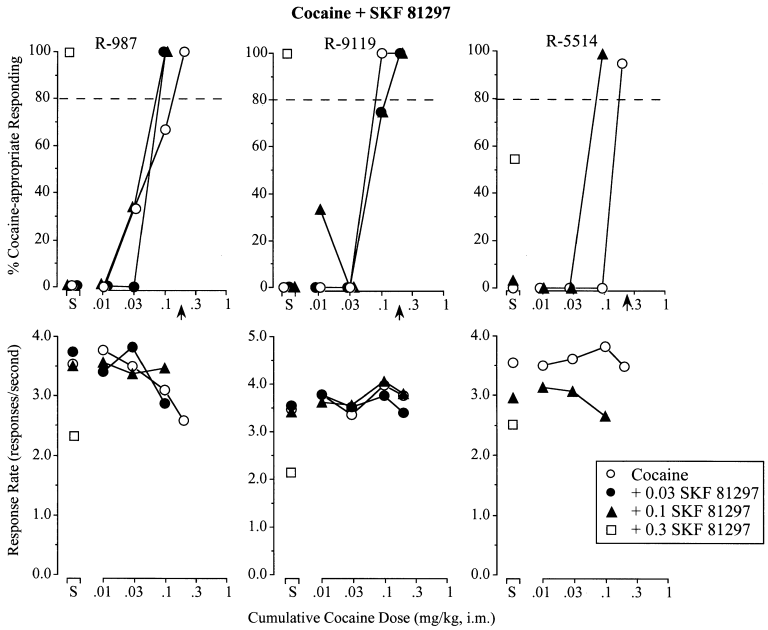

Fig. 2. Effects of pretreatment with the high-efficacy D_1 agonist SKF 81297 on the discriminative stimulus effects of cumulative doses of cocaine. Symbols above "S" represent effects of SKF 81297 given in combination with saline. Top panels: Percent of total responses that occurred on the cocaine-appropriate lever. Bottom panels: Response rate (responses per second) as a function of dose. Other details are as in Fig. 1.

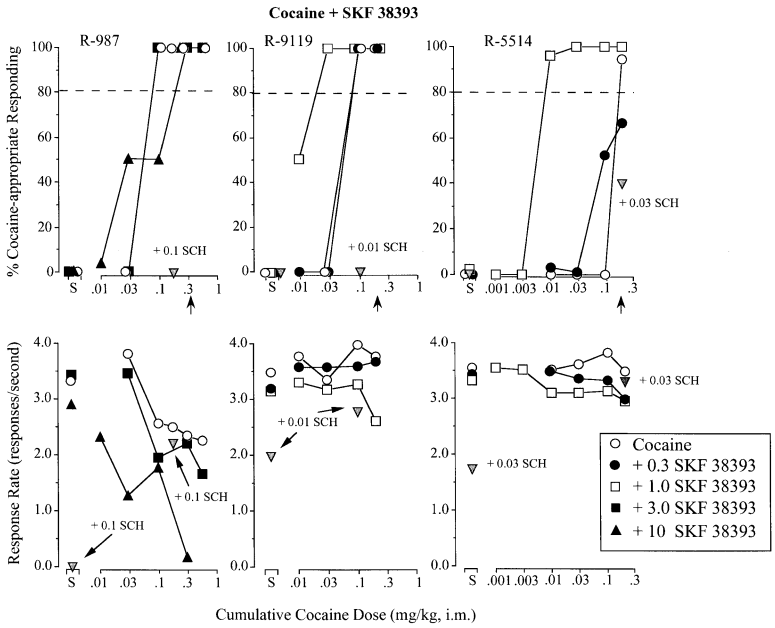

Fig. 3. Effects of pretreatment with the low-efficacy D_1 agonist SKF 38393 on the discriminative stimulus effects of cumulative doses of cocaine. Symbols above "S" represent effects of SKF 38393 or SCH 23390 given in combination with saline. Other details are as in Fig. 2.

effects, although response rates were dramatically decreased by 10 mg/kg SKF 38393 in combination with cocaine.

3.5. Pretreatment with SCH 23390

In contrast to the effects of SKF 38393 and SKF 81297, pretreatment with the D_1 antagonist SCH 23390 (0.01–0.1 mg/kg) attenuated the discriminative stimulus effects of cocaine (0.1 or 0.2 mg/kg) in all monkeys (Fig. 3, upper panels, inverted triangles). Different doses of SCH 23390 were effective in each monkey. In all subjects, SCH 23390 induced catalepsy; cocaine reversed this catalepsy and antagonized the rate-decreasing effects of SCH 23390 (Fig. 3, lower panels, inverted triangles).

4. Discussion

The present study evaluated the modulation of cocaine's discriminative stimulus effects by a high- and a low-efficacy DA D_1 agonist in rhesus monkeys. In substitution studies, the high-efficacy agonist SKF 81297 completely substituted for cocaine in three of four monkeys, while the low-efficacy agonist SKF 38393 did not substitute in any of three subjects tested. In interaction studies, cocaine's discriminative stimulus effects were not substantially altered by SKF 38393 or SKF 81297, but were blocked by the D_1 antagonist SCH 23390. Together, these data suggest that the substitution of D_1 agonists for cocaine in rhesus monkeys is influenced by intrinsic efficacy; however, efficacy may play a less prominent role in the modulation of cocaine's discriminative stimulus effects.

One goal of the present study was to extend D_1 agonist effects in cocaine discrimination studies to rhesus monkeys, since much of the earlier work involved squirrel monkeys. Using in vitro techniques, there is evidence that the intrinsic efficacy of SKF 81297 may differ among primate species. In experiments utilizing similar techniques (measurement of striatal adenylyl cyclase stimulation relative to DA), Izenwasser and Katz (1993) reported that SKF 81297 had an efficacy of 27% in squirrel monkey caudate tissue, while Weed et al. (1997) found an efficacy of 96% in rhesus monkey caudate. The present findings are consistent with the intrinsic efficacy of SKF 81297 as reported by Weed et al, in that SKF 81297 produced cocaine-like discriminative stimulus effects in rhesus monkeys. SKF 38393, which is a low-efficacy agonist in both primate species (Izenwasser and Katz, 1993; Pifl et al., 1991; Watts et al., 1993, Weed et al., 1997), did not fully substitute for cocaine in any monkey tested, which is in agreement with other substitution studies testing low-efficacy agonists in monkeys (Katz and Witkin, 1992; Kleven et al., 1990; Spealman et al., 1997). Although SKF 38393 poorly penetrates the blood–brain barrier (cf. Kamien et al., 1987), other studies have shown that the discriminative stimulus effects of SKF 38393 are centrally mediated (e.g. Kamien and Woolverton, 1985; Kamien et al., 1987).

In interaction studies, SKF 38393 did not antagonize the discriminative stimulus effects of cocaine, while the D_1 antagonist SCH 23390 blocked or attenuated the cocaine cue, indicating a difference in the interactions of cocaine with D_1 antagonists versus low-efficacy D_1 agonists. The present findings are consistent with a recent

study by Katz et al. (1999), who also found that SKF 38393 did not alter cocaine's discriminative stimulus effects in squirrel monkeys. However, these data contrast with another study in squirrel monkeys by Spealman et al. (1997) showing an antagonism of the discriminative stimulus effects of cocaine by SKF 38393. It is possible that antagonism would have been observed in the present study if higher doses of SKF 38393 were given. However, because doses above 1.0 mg/kg caused vomiting and eliminated responding in some monkeys during the course of the study, they were no longer given out of concern for the animals' health.

A second explanation for the differences between studies could be a consequence of different cocaine training doses. The monkeys in the Spealman et al. (1997) study were trained with a relatively high dose of cocaine (1.0 mg/kg), while Katz et al. (1999) used a training dose of 0.3 mg/kg, and the training doses in the present study were 0.2 or 0.3 mg/kg. Based on receptor theory, higher training doses should be more susceptible to antagonism by low-efficacy agonists compared to lower training doses, due to the different relative percentage of the receptor population that must be activated to produce a given effect (e.g. Picker et al., 1993). The present results, along with the earlier findings (Katz et al., 1999; Spealman et al., 1997), are in line with this hypothesis. Additionally, previous studies have noted that cocaine training dose can alter the discriminative stimulus effects of DA agonists (Schechter, 1997; Terry et al., 1994). For example, D_1 agonists fully substituted for cocaine in rats trained to discriminate 3.0 mg/kg cocaine, but not in rats trained to discriminate 10 mg/kg cocaine (Terry et al., 1994). Finally, it is important to point out that cocaine doses higher than 0.3 mg/kg would have been very difficult to train as a discriminative stimulus, due to the substantial rate-decreasing effects of higher doses. In contrast, squirrel monkeys can be trained to discriminate high (e.g. 1.0 mg/kg) cocaine doses (Katz et al., 1999; Spealman et al., 1997). These disparate results could be suggestive of an overall difference between rhesus and squirrel monkeys in sensitivity to the effects of cocaine and perhaps DA compounds.

The cocaine-like discriminative stimulus effects of SKF 81297 and SKF 38393 were consistent with their in vitro efficacies in substitution studies; however, efficacy appeared to have little influence on D_1 agonist interactions with cocaine. Because the indirect agonist actions of cocaine result in increased activity at multiple DA receptor subtypes, as well as at serotonin and norepinephrine receptors, it is possible that these other, non-D_1 actions of cocaine were a factor in the lack of interaction with the D_1 agonists. The present results, combined with findings of different levels of D_1 receptor involvement in the effects of cocaine on locomotor activity, response rate, and discriminative stimulus effects (Katz et al., 1999), indicate that D_1 agonist efficacy may play relatively distinct roles in the various behavioral effects of cocaine.

Individual differences in experimental history may have been a factor in the between-subject variability observed in the present study, although each animal's history was different enough that it is not likely to have contributed in an orderly fashion to the results. As pharmacological history has been shown to modify the discriminative stimulus effects of compounds with multiple receptor components (e.g. Barrett and Olmstead, 1989), differences in total cocaine intake and drug exposure may have affected each animal's sensitivity to the discriminative stimulus effects of cocaine and the D_1 compounds tested in the present study. Indeed, the observation that different doses of the D_1 antagonist SCH 23390 were effective in each monkey has been reported before in a similar study using monkeys with varied pharmacological histories (Kleven et al., 1990).

Recent attention has been focused on the use of low-efficacy D_1 agonists as potential pharmacotherapies for cocaine abuse. Because the effects of these agonists may depend on the prevailing dopaminergic tone of the system, low-efficacy agonists and partial agonists may be predicted to have low abuse liability in the presence of physiological levels of DA (see Pulverenti and Koob, 1994). In support of this, results from the present and previous studies (Katz and Witkin, 1992; Kleven et al., 1990; Weed and Woolverton, 1995) indicate that low-efficacy D_1 agonists do not have substantial reinforcing and cocaine-like discriminative stimulus effects. Additional support for the therapeutic utility of D_1 agonists comes from reports that they may prevent reinstatement of extinguished cocaine-seeking behavior in rodent and primate models of relapse (Barrett-Larrimore and Spealman, 1997; Khroyan et al., 2000; Self et al., 1996) and from clinical studies indicating that D_1 agonists may prevent craving in human cocaine abusers (Haney et al., 1999). Future studies investigating a range of high- and low-efficacy D_1 agonists, under multiple behavioral paradigms will be necessary before the role of this receptor subtype in cocaine abuse is fully understood.

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References

Andersen PH, Jansen JA. Dopamine receptor agonists: selectivity and dopamine D1 receptor efficacy. Eur J Pharmacol 1990;188:335–47.

Barrett JE, Olmstead SN. Spiroxatrine as a discriminative stimulus: effects depend on pharmacological history. Drug Dev Res 1989;16:365–74.

Barrett-Larrimore RL, Spealman RD. Reinstatement of cocaine-seeking behavior in a nonhuman primate model of relapse: effects of DA D1 and D3 agonists. NIDA Res Monogr 1997;178:283.

Bergman J, Rosenzweig-Lipson S. Cocaine-antagonist effects of limited-efficacy D1 agonists. NIDA Res Monogr 1992;119:185–9.

Bergman J, Madras BK, Johnson SE, Spealman RD. Effects of cocaine and related drugs in nonhuman primates: III. Self-administration by squirrel monkeys. J Pharmacol Exp Ther 1989;251:150–5.

Grech DM, Spealman RD, Bergman J. Self-administration of D1 receptor agonists by squirrel monkeys. Psychopharmacology 1996;125:97–104.

Haney M, Collins ED, Ward AS, Foltin RW, Fischman MW. Effect of a selective dopamine D1 agonist (ABT-431) on smoked cocaine self-administration in humans. Psychopharmacology 1999;143:102–10.

Izenwasser S, Katz JL. Differential efficacies of dopamine D1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat. Eur J Pharmacol 1993;246:39–44.

Kamien JB, Woolverton WL. The D1 dopamine agonist SKF 38393 functions as a discriminative stimulus in rats. Psychopharmacology 1985;87:368–70.

Kamien JB, Goldberg LI, Woolverton WL. Discriminative stimulus properties of D1 and D2 dopamine agonists in rats. J Pharmacol Exp Ther 1987;242:804–11.

Katz JL, Witkin JM. Effects of quinpirole and SKF 38393 alone and in combination in squirrel monkeys trained to discriminate cocaine. Psychopharmacology 1992;107:217–20.

Katz JL, Kopajtic TA, Myers KA, Mitkus RJ, Chider M. Behavioral effects of cocaine: interactions with D1 dopaminergic antagonists and agonists in mice and squirrel monkeys. J Pharmacol Exp Ther 1999;291:265–79.

Khroyan TV, Barrett-Larrimore RL, Rowlett JK, Spealman RD. Dopamine D1- and D2-like receptor mechanisms in relapse to cocaine-seeking behavior: effects of selective antagonists and agonists. J Pharmacol Exp Ther 2000;294:680–7

Kleven MS, Anthony EW, Woolverton WL. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. J Pharmacol Exp Ther 1990;254:312–7.

Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 1996;14:375–424.

Nader MA, Bowen CA. Effects of different food-reinforcement histories on cocaine self-administration by rhesus monkeys. Psychopharmacology 1995;118:287–94.

Nader MA, Mach RH. Self-administration of the dopamine D3 agonist 7-OH-DPAT in rhesus monkeys is modified by prior cocaine exposure. Psychopharmacology 1996;125:13–22.

Nader MA, Reboussin D. The effects of behavioral history on cocaine self-administration in rhesus monkeys. Psychopharmacology 1994;115:53–8.

Nader MA, Grant KA, Davies HML, Mach RH, Childers SR. The reinforcing and discriminative stimulus effects of the novel cocaine analog 2-beta-propanoyl-3-beta-(4-tolyl)-tropane in rhesus monkeys. J Pharmacol Exp Ther 1997;280:541–50.

Negus SS, Mello NK, Lamas X, Mendelson JH. Acute and chronic effects of flupenthixol on the discriminative stimulus and reinforcing effects of cocaine in rhesus monkeys. J Pharmacol Exp Ther 1996;278:879–90.

Picker MJ, Yarbrough J, Hughes CE, Smith MA, Morgan D, Dykstra L. Agonist and antagonist effects of mixed action opioids in the pigeon drug discrimination procedure: influence of training dose, intrinsic efficacy, and interanimal differences. J Pharmacol Exp Ther 1993;266:756–67.

Pifl C, Reither H, Hornykiewicz O. Lower efficacy of the D1 agonist, SKF 38393, to stimulate adenylyl cyclase in primate than in rodent striatum. Eur J Pharmacol 1991;202:273–6.

Pulverenti L, Koob GF. Dopamine receptor agonists, partial agonists, and psychostimulant addiction. Trends Pharmacol Sci 1994;15:374–9.

Ritz MC, Lamb JR, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 1987;237:1219–23.

Rosenzweig-Lipson S, Hesterberg P, Bergman J. Observational studies of dopamine D1 and D2 agonists in squirrel monkeys. Psychopharmacology 1994;116:9–18.

Schechter MD. Discriminative stimulus characteristics of high and low cocaine administration: effect of other psychostimulants. Pharmacol, Biochem Behav 1997;56:457–63.

Self DW, Barnhart WJ, Lehman DA, Nestler EJ. Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. Science 1996;271:1586–9.

Sinnott RS, Mach RH, Nader MA. Dopamine D2/D3 receptors modulate cocaine's reinforcing and discriminative stimulus effects in rhesus monkeys. Drug Alcohol Depend 1999;54:97–110.

Spealman RD, Bergman J, Madras BK, Melia KF. Discriminative stimulus effects of cocaine in squirrel monkeys: involvement of dopamine receptor subtypes. J Pharmacol Exp Ther 1991;258:945–53.

Spealman RD, Bergman J, Rosenzweig-Lipson S. Differential modulation of behavioral effects of cocaine by low- and high-efficacy D1 agonists. Psychopharmacology 1997;133:283–92.

Terry P, Witkin JM, Katz JL. Pharmacological characterization of the novel discriminative stimulus effects of a low dose of cocaine. J Pharmacol Exp Ther 1994;270:1041–8.

Watts VJ, Lawler CP, Gilmore JH, Southerland SB, Nichols DE, Mailman RB. Dopamine D1 receptors: efficacy of full (dihydrexidine) vs. partial (SKF 38393) agonists in primates vs. rodents. Eur J Pharmacol 1993;242:165–72.

Weed MR, Woolverton WL. The reinforcing effects of dopamine D1 receptor agonists in rhesus monkeys. J Pharmacol Exp Ther 1995;275:1367–74.

Weed MR, Vanover KE, Woolverton WL. Reinforcing effect of the dopamine D1 agonist SKF 81297 in rhesus monkeys. Psychopharmacology 1993;113:51–2.

Weed MR, Paul IA, Dwoskin LP, Moore SE, Woolverton WL. The relationship between reinforcing effects and in vitro effects of D1 agonists in monkeys. J Pharmacol Exp Ther 1997;283:29–38.

Witkin JM. Pharmacotherapy of cocaine abuse: preclinical development. Neurosci Biobehav Rev 1994;18:121–42.