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ORIGINAL INVESTIGATION

Nicole H. Mutschler · Jack Bergman

Effects of chronic administration of the D_1 receptor partial agonist SKF 77434 on cocaine self-administration in rhesus monkeys

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Abstract *Rationale:* Dopamine D_1 receptor partial agonists have been proposed as candidate medications for the treatment of cocaine dependence. However, there currently is scant information regarding how chronic exposure to D_1 agonists may modify behavioral effects of cocaine and, especially, whether tolerance develops to their effects on cocaine self-administration. *Objective:* The present studies were conducted to evaluate the effects of chronic treatment with the D_1 receptor partial agonist SKF 77434 on IV cocaine self-administration in rhesus monkeys. *Methods:* A protocol was developed to rapidly evaluate the effects of chronic drug exposure on extinction behavior, threshold dose of self-administered cocaine, and the dose-effect function for cocaine self-administration behavior. Monkeys performed in daily sessions of IV cocaine self-administration under a fixed-ratio schedule of reinforcement and food presentation under either a fixed-ratio or fixed-interval schedule of reinforcement. When both types of performance were stable, chronic exposure to SKF 77434 followed with month-long regimens of IV treatment with each of two or three dosages. *Results:* The effects of SKF 77434 were dose-related. Exposure to 1.0 mg/kg per day of SKF 77434 yielded a moderate and persistent rightward shift in the descending portion of the dose-effect function for cocaine self-administration but did not alter the threshold dose and did not disrupt either extinction behavior or food-maintained performance. An increase in dosage to 3.2–5.6 mg/kg per day displaced the dose-effect function for cocaine self-administration downward from its prechronic position, altered threshold dose values, and disrupted food-maintained performance. *Conclusions:* Chronic treatment with D_1 receptor partial agonists produced dose-dependent effects on cocaine self-administration that may be relevant to their further evaluation as candidate medications for the treatment of cocaine dependence.

Keywords Dopamine · D_1 · Partial agonist · SKF 77434 · Cocaine · Self-administration · Chronic regimen · Rhesus monkey

N.H. Mutschler · J. Bergman (✉)
Harvard Medical School-McLean Hospital,
Alcohol and Drug Abuse Research Center, 115 Mill Street,
Belmont, MA 02478-9106, USA
e-mail: jbergman@hms.harvard.edu
Tel.: +1-617-8552464, Fax: +1-617-8552417

Introduction

Considerable pharmacological evidence has emerged to suggest the involvement of dopamine D_1 mechanisms in behavioral effects of cocaine. In rats or monkeys, for example, dopamine D_1 receptor agonists at least partially mimic the discriminative-stimulus effects of cocaine and exhibit reinforcing effects under both fixed-ratio and progressive-ratio schedules of IV self-administration behavior (e.g. Self and Stein 1992; Weed and Woolverton 1995; Spealman et al. 1997; Weed et al. 1997; Tidey and Bergman 1998; but see Grech et al. 1996; Caine et al. 1999, 2000a). Complementarily, D_1 receptor blockers may be used to antagonize the discriminative-stimulus effects of both D_1 agonists and cocaine and, as well, the reinforcing effects of cocaine (Bergman et al. 1990; Corrigall and Coen 1991). Studies employing ICSS or place conditioning to study reward mechanisms also indicate that D_1 agonists produce effects comparable to those of cocaine and that effective doses of D_1 receptor blockers attenuate those effects of both D_1 agonists and cocaine (Singh et al. 1997; Abrahams et al. 1998a, 1998b). Moreover, repeated administration of D_1 agonists, like cocaine, appears to induce sensitization processes, an effect that can be blocked by D_1 receptor blockade (Morelli et al. 1993; Henry et al. 1998). In conjunction, the above findings provide a strong pharmacological platform for current views regarding the role of dopamine D_1 mechanisms in the reinforcing and other abuse-related effects of cocaine.

The present research was conducted to extend previous studies of interactions of D_1 agonists and cocaine by determining how chronic treatment with the D_1 agonist

SKF 77434 might alter IV cocaine self-administration behavior. SKF 77434 recently has been characterized as a D_1 receptor partial agonist in behavioral studies in monkeys (Bergman et al. 1996; Tidey and Bergman 1998; Platt et al. 2000). Several lines of evidence suggest that partial agonist activity may provide a pharmacologically rational strategy for the development of dopaminergic compounds as medications for cocaine abuse and dependence (Bergman and Rosenzweig-Lipson 1992; Pulvirenti and Koob 1994; Tidey and Bergman 1998; Platt et al. 2000; Bergman et al. 2000). The present studies also were conducted to determine whether tolerance to changes in IV cocaine self-administration produced by SKF 77434 might appear during a regimen of chronic exposure. Tolerance previously has been shown to develop to behavioral effects of dopamine D_1 agonists in studies to evaluate their anti-parkinsonism effects in rats and monkeys (Asin and Wirthshafter 1993; Asin et al. 1995; Lin et al. 1995). The development of tolerance is an important consideration in the evaluation of candidate therapeutics for drug abuse because of the likely need to administer such agents on a repeated, or chronic, basis.

Results of the present studies indicate that chronic exposure to SKF 77434 (1.0, 3.2 or 5.6 mg/kg per day) dose-dependently altered IV cocaine self-administration behavior over the course of treatment, with no evidence of tolerance. The higher dosages of SKF 77434 (3.2 or 5.6 mg/kg) also produced varying disruptions in food-maintained performance in individual monkeys. However, indications of undesired side effects, such as weight loss or overt behavioral toxicity, were not observed.

Materials and methods

Subjects

Four adult ovariectomized and experimentally untrained female rhesus monkeys *(Macaca mulatta;* M1, M2, M3, M4), weighing 5.8–6.4 kg, were housed individually within a climate-controlled vivarium and had continuous access to water. Monkeys were prepared with double-lumen IV catheters for experiments within home chambers that had been customized for self-administration experiments (see Negus et al. 1996). Food intake during daily experimental sessions (1-g banana flavored pellets; P.J. Noyes Co., Lancaster, N.H., USA) was supplemented with a high-protein monkey chow (PMI Feeds, Inc., St Louis, Mo., USA), fresh fruit, and vegetables to maintain constant body weight over the course of the study.

Experimental protocol

All subjects were studied under an experimental protocol that involved two daily 2-h sessions of schedule-controlled behavior. The first daily session was comprised of three 20-min components, each followed by a 20-min timeout period. Key pressing during these components resulted in the delivery of banana-flavored food pellets according to schedule contingencies described below. In the second daily session, responding resulted in the IV infusion of cocaine or, during extinction, saline. The second session was comprised of three 35-min components, each followed by 5-min timeout periods.

Food-maintained behavior

The first of the two daily sessions (11 a.m. to 1 p.m.) comprised three 20-min components. During the three components of the session, stimulus lights illuminated the right response key. Subjects were trained using successive approximation to respond by pressing the illuminated key under the terminal schedules of food delivery: fixed-interval 3 min; timeout 60 s (FI3';TO 60": three monkeys) or fixed-ratio 30; timeout 60 s (FR30; TO 60": one monkey). Under these schedules, completion of the response requirement produced a 1-g food pellet followed by a 60-s period during which all lights were extinguished. Additionally, all stimulus lights were extinguished and responding had no consequences during the 20-min timeout periods of the test session.

Cocaine self-administration behavior

The second 2-h session of the day (3 p.m. to 5 p.m.) was comprised of three 35-min components of IV cocaine availability separated by 5-min timeout periods during which all stimulus lights were extinguished and responding had no scheduled consequences. During each component, stimulus lights illuminated the left response key, and monkeys could respond under an FR30; TO 60" schedule of IV cocaine self-administration. Under this schedule, completion of the 30th response produced a 1-s infusion of IV cocaine followed by a 60-s TO period during which all lights were off and responding had no scheduled consequences. During training, the unit dose of cocaine that was available for self-administration throughout the daily session was 0.032 mg/kg per infusion. After patterns of cocaine self-administration were consistent day-to-day, sessions of cocaine availability alternated with sessions during which saline replaced cocaine in the infusion pump and the center key was illuminated with stimulus lights. Initial training was complete when: 1) levels of cocaine self-administration behavior varied less than 15% from session to session and 2) levels of responding in the presence of saline fell to less than 20% of those maintained by cocaine within two consecutive sessions of saline availability. The effects of cocaine next were studied using a protocol for successive determinations of, in order, a) saline extinction, b) threshold dose for IV cocaine self-administration, and c) dose-effect functions for IV cocaine self-administration.

Saline extinction

During saline extinction, cocaine was replaced by saline in the syringe pump and the center response key was illuminated by stimulus lights. Infusions of IV saline (1 s) were available under the same FR30;TO 60" schedule as used for IV cocaine. The effects of saline were studied in successive sessions until responding throughout a single daily session was <20% of levels observed during cocaine availability (usually one or two sessions in trained subjects). In all cases, the threshold dose for IV cocaine self-administration was determined in the subsequent session.

Threshold determination

The threshold dose for IV cocaine self-administration was defined as the lowest unit dose of cocaine that maintained behavior reliably over the course of the self-administration session. Determinations were conducted by substituting a below-threshold unit dose of cocaine in the session following saline extinction. If response rates did not increase above those observed with saline in the preceding self-administration session, the unit dose of cocaine was increased in 0.5 log unit steps in successive daily self-administration sessions until persistent behavior was evident throughout the session. Dose-effect determinations for IV cocaine self-administration were conducted in subsequent sessions.

Rapid assessment of cocaine dose-effect functions

Dose-effect data for IV cocaine self-administration in single sessions were obtained by increasing the unit dose of cocaine that was available for self-administration in successive components of the session. Increases in unit dose occurred in 0.5 log unit steps and were accomplished by corresponding increases in the duration of infusion of a single concentration of cocaine (see Caine et al. 2000b for a discussion of methods). Thus, unit doses of x, 3.2x, and 10x mg/kg per infusion were delivered in successive components during which the durations of infusion were, respectively, 1, 3.2, and 10 s. Using this procedure, full dose-effect functions could be determined quickly by studying the effects of different ranges of doses in consecutive sessions (e.g. 0.003–0.03, 0.03–0.3, and, when necessary, 0.1–1.0 mg/kg per infusion in three successive sessions). Typically, dose-effect determinations began with a dose 0.5 log-unit higher than the threshold dose or, occasionally, with the threshold dose itself. Once the full dose-effect function for cocaine self-administration was established, the protocol was repeated, beginning again with saline-extinction in the next session.

Self-administration and change in response requirement

When self-administration behavior was stable under the FR30 schedule of IV infusions, the effects of changes in fixed-ratio value to FR3 and FR100 were studied in all monkeys (see Table 1). The response requirement of FR3 was studied first in monkeys M2 and M4 and second in monkeys M3 and M1. Each new condition was studied for at least 4 weeks to permit stable performance to emerge. When these manipulations were completed, the FR30 schedule of reinforcement was restored for all monkeys.

Chronic treatment with SKF 77434

Chronic administration of the D_1 receptor partial agonist SKF 77434 was begun when stability in all three indices of cocaine self-administration behavior was evident (see Data analysis). One monkey, M3, became ill following cocaine self-administration experiments described above and was removed from further studies. Thus, data from studies with chronically administered SKF 77434 are presented for a group of three monkeys.

SKF 77434 was administered chronically by intravenous infusion via the second lumen of the indwelling catheter. This lumen was attached by catheter tubing to a second syringe pump that, prior to chronic SKF 77434 infusions, delivered saline every 20 min to maintain catheter patency. During the chronic regimen, saline was replaced by SKF 77434 and monkeys received a 1-s infusion (0.1 ml) of SKF 77434 every 20 min throughout the day. This chronic dosing regimen previously has been used to insure continuous blood levels of treatment drugs like SKF 77434 for which pharmacokinetic data in monkeys are unavailable. The starting IV dosage of SKF 77434, 1.0 mg/kg per day, was selected on the basis of previous studies in which it produced limited effects in monkeys when administered acutely as an IM dose (Bergman et al. 1996; Spealman et al. 1997; Tidey and Bergman, 1998). Each dosage of SKF 77434 was studied for a period of 4 weeks in individual monkeys, with concentrations of SKF 77434 adjusted to intravenously deliver 1.0, 3.2, and, in monkey M4, 5.6 mg/kg of SKF 77434 daily. Concentrations of SKF 77434 were studied in an ascending order and changed without interruption of the chronic regimen. Changes in dosage always were made during the saline-extinction segment of the protocol. When studies with SKF 77434 were completed, chronic exposure was terminated by substituting IV saline for the D_1 receptor partial agonist. Daily sessions continued following the termination of chronic treatment to permit the re-determination of baseline values for cocaine- and food-maintained performance.

During each day of the chronic regimen, monkeys were examined in their chambers for overt signs of physical distress or behavioral abnormalities and to determine whether daily food supplements were consumed. When alterations in food-maintained performance during chronic treatment with SKF 77434 resulted in decreases in food delivery, the amount of food not obtained during the session was added, in grams, to the daily food supplement. Each monkey also was inspected daily to insure that the catheter remained patent. On several occasions during the chronic regimen, monkeys were mildly anesthetized with ketamine to repair the catheter and to determine body weight. No untoward interactions with ketamine were observed during these procedures.

Table 1 Overall response rates at fixed-ratio values of 3, 30, and 100 when saline or unit doses of cocaine were available under the FR schedule of IV self-administration (see Materials and methods). Values show response rates averaged for four monkeys (mean±SEM) studied prior to chronic exposure to SKF 77434 and correspond to data graphed as number of infusions per component in Fig. 2

Cocaine (mg/kg per injection)	Response rate (responses/s)		
	FR3	FR30	FR100
0.0 (saline)	0.02±0.001	0.06±0.03	0.10±0.05
0.003	0.60±0.001	0.14±0.07	0.42±0.06
0.01	0.32±0.003	0.92±0.05	0.69±0.29
0.032	0.39±0.003	0.80±0.04	0.80±0.09
0.1	0.14±0.004	0.40±0.07	0.53±0.06
0.32	0.02±0.001	0.15±0.05	0.33±0.10
1.0	0.004±0.001	0	0.10±0.01

Drugs

The National Institute on Drug Abuse, NIH (Bethesda, Md., USA), provided cocaine hydrochloride in crystalline form. SKF 77434 was prepared by Research Biochemicals International (Natick, Mass., USA) for use in the present studies. Both drugs were dissolved in sterile physiological saline and were passed through a 0.22-µl filter (Millipore) to insure sterility for IV delivery.

Data analysis

Data for sessions in which saline or a single unit dose of cocaine was studied were expressed as the average number of infusions per component. Dose-effect data were evaluated for individual monkeys by determining the number of infusions per component maintained by different unit doses of cocaine. During weeks 3 and 4 of exposure to 3.2 mg/kg per day of SKF 77434 in monkeys M1 and M2 and throughout exposure to 5.6 mg/kg per day of SKF 77434 in monkey M4, single unit doses of IV cocaine sometimes were studied in all three components of the session; data from those sessions are expressed as infusions per component to maintain consistency in data presentation (see Table 2). Values were averaged across dose-effect determinations for individual monkeys and are presented in Results for individual subjects (Fig. 1, Fig. 2 and Table 2) and as mean (±SEM) data for the group of monkeys (Fig. 2, Fig. 3 and Table 1). Generally, pre-chronic data for each monkey were averaged over the last two repetitions of the protocol (saline extinction, threshold, dose-effect function) to obtain values for baseline and for the effects of changes in FR requirement. For evaluation of chronic treatment, data for each treatment dose first were averaged across the entire period of chronic exposure. To assess time-dependent changes, data from the first and second 2 weeks of each treatment period with SKF 77434 were separately analyzed.

The effects of experimental manipulations, either change in fixed-ratio value or treatment with SKF 77434, on IV self-administration of saline or cocaine were considered significant for the group of monkeys when the number of infusions per component differed by more than 2 SEM from control values. Whenever possible, dose-effect data for the group of monkeys were further ana-

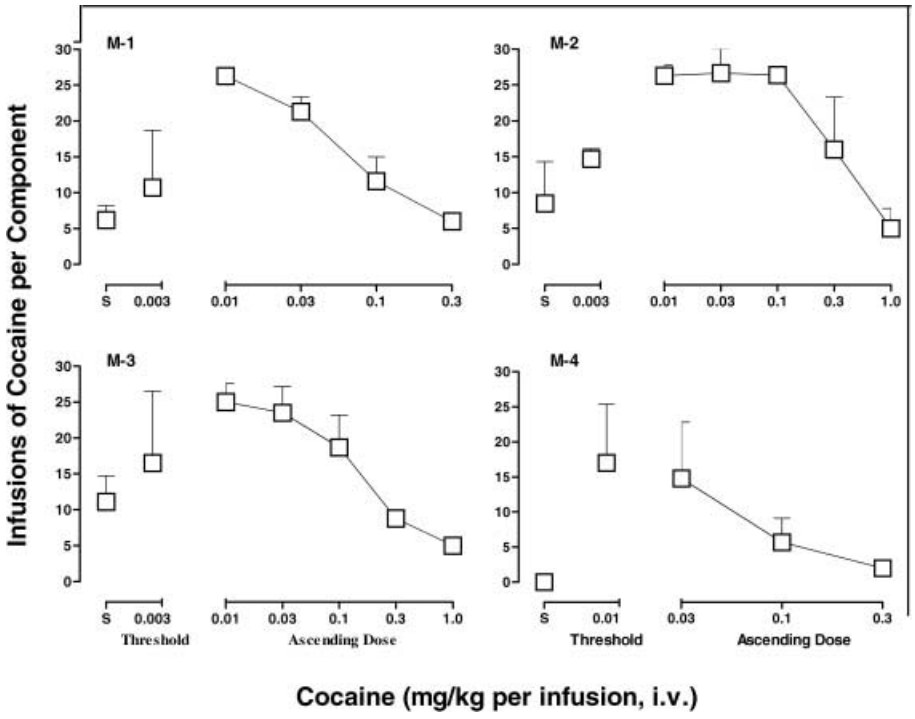

Fig. 1 Effects of cocaine in individual monkeys responding under an FR schedule of IV self-administration. *Abscissa*: unit dose of cocaine, log scale; ordinate: number of IV infusions per 35-min session component. Points are means (±SD) of data from last two determinations of the effects of saline and a range of self-administered doses of cocaine. Points above *S* show the number of infusions of saline per component averaged across the three components of the session. Points above *Threshold* show the number of infusions per component averaged across the three components of the session for the lowest unit dose that consistently maintained self-administration behavior over the course of threshold determinations. Points above *Ascending Dose* show the mean number of infusions per component of the session in which the unit dose was available during ascending dose-effect curve determinations. See Materials and methods for further details of procedure

Table 2 Number of IV infusions per component of cocaine (mean±SD) self-administered by individual monkeys under the rapid assessment procedure prior to chronic exposure to SKF 77434 (prechronic; data shown in Fig. 1) and during weeks 1–2 and weeks 3–4 of continuous exposure to 3.2 mg/kg per day of SKF 77434. Except when noted below, values show number of infusions per component of self-administration (see Materials and methods)

Monkey	Cocaine (mg/kg per infusion)						
	Sal[a]	0.003[a]	0.01	0.032	0.1	0.32	1.0
M1							
Prechronic	6±2	15±15	26±1	21±3	12±3	6±1	
SKF 77434							
Weeks 1–2	7±4	11±2	10	12±16	18±9	11±1	5±1
Weeks 3–4	5	4±1	11±4	0	2±2[b]	2[b]	2[b]
M2							
Prechronic	5	15	26	27±1	26±1	16±7	5±3
SKF 77434							
Weeks 1–2	5±5	24	19±6	16±9	17±11	10±7	8±8
Weeks 3–4[c]	2	1	1[b]	2±2[b]	0[b]	0[b]	
M4							
Prechronic	0	20	13±14	15±8	6±3	2	
SKF 77434							
Weeks 1–2	2±2	23	21±1	22±3	13±3	6±1	
Weeks 3–4	2±1	10	7±1	11±9	9±5	8±2	

[a] Average number of infusions per component in sessions used for saline-extinction and threshold values
[b] Average infusions per component from determinations in which the unit dose was studied for the entire session

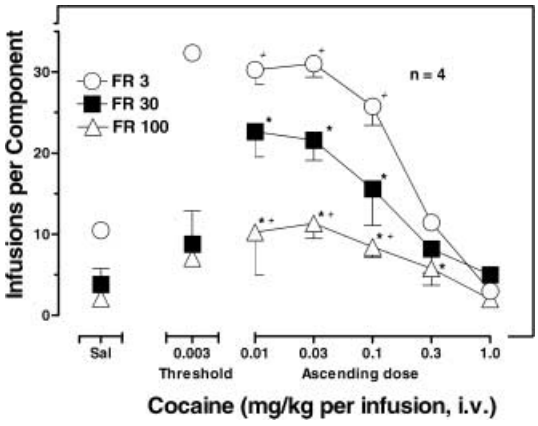

Fig. 2 Effects of cocaine in the group of four monkeys responding under different FR schedules of IV self-administration. Each point shows mean (±SEM) data in the group of four monkeys. *Asterisks* mark data obtained for unit doses of cocaine under the FR30 and FR100 schedules that differ significantly from values for the same unit dose under the FR3 schedule of IV self-administration. *Crosses* mark data obtained for unit doses of cocaine under the FR3 and FR100 schedules that differ significantly from values for the same unit dose under the FR30 schedule of IV self-administration. The criterion for significance was set a priori at $P<0.05$. Other details as in Fig. 1

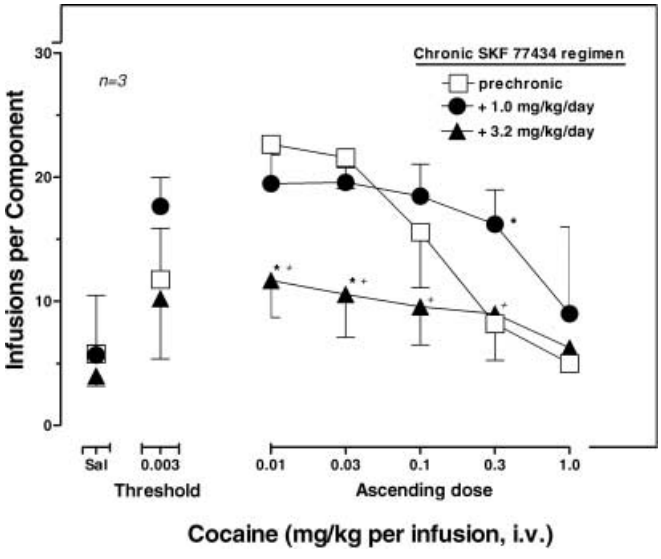

Fig. 3 Effects of chronic IV exposure to SKF 77434 on cocaine self-administration under the FR30 schedule. Each point shows mean (±SEM) data in the group of three monkeys. *Open squares* show mean data for cocaine self-administration prior to the chronic regimen. *Filled circles* show the averaged effects of 4 weeks of exposure to 1.0 mg/kg per day of SKF 77434, whereas *filled triangles* show the averaged effects of the same length of exposure to 3.2 mg/kg per day of SKF 77434. *Asterisks* mark values that differ significantly from prechronic data. *Crosses* mark values that differ significantly from data obtained during chronic treatment with 1.0 mg/kg per day of SKF 77434. Other details as in Fig. 1

lyzed by repeated-measures analysis of variance and, when indicated, weighted contrasts (Abacus Concepts, Inc., Berkeley, Calif., USA). The criterion for significance was set a priori at $P<0.05$.

Food-maintained behavior during the present studies was analyzed by calculating response rates under the FR and FI schedules of reinforcement. Response rates were calculated by dividing the total number of responses by the session duration, excluding the timeout periods that immediately followed delivery of reinforcement. Food-maintained performance in individual monkeys did not differ appreciably with regard to the experimental condition studied in the alternate daily session (i.e. saline extinction, threshold determination, or dose-effect determination). Therefore, each monkey's data were averaged across the three conditions of IV self-administration to obtain rates of food-maintained responding during all phases of the study.

Results

Cocaine dose-effect determinations

Cocaine maintained self-administration behavior in all monkeys under the present protocol. Performance under the FR30 schedule of IV cocaine infusion was characterized by a period of no responding followed by sustained key pressing until the fixed-ratio requirement was completed. Each reinforcing unit dose of cocaine maintained this pattern of behavior regardless of the session component in which it was available for IV self-administration. Saline or ineffective doses of cocaine were associated with responding that occurred primarily in the first portion of the first component of the self-administration session and declined through the remainder of the session. By way of contrast, the threshold unit dose of IV cocaine, 0.003 mg/kg, generally engendered responding that was sustained throughout the self-administration session.

When unit doses of cocaine were varied according to the rapid assessment protocol described in Materials and methods, overall self-administration behavior (including data with the threshold unit dose of cocaine) was characterized by a bitonic dose-effect function in all monkeys (Fig. 1).

Cocaine self-administration under the present procedures was sensitive to changes in response requirement (Table 1, Fig. 2). Under the lower fixed ratio requirement (FR3), the number of self-administered infusions of saline or cocaine generally increased in all monkeys. Saline intake during extinction testing was elevated from approximately four to approximately ten infusions per session and, although the threshold unit dose of cocaine was unaltered (0.003 mg/kg or, in monkey M2, 0.01 mg/kg), intake nearly tripled under the lower FR requirement (from approximately 11–12 to approximately 32 infusions per component). Similarly, unit doses of 0.01–0.1 mg/kg cocaine maintained higher levels of IV self-administration under the FR3 schedule than were observed under the FR30 schedule. Like the threshold unit dose of 0.003 mg/kg, unit doses of 0.01 and 0.032 mg/kg maintained persistent responding throughout components, resulting in maximal intake of approximately 30 infusions per component in all monkeys. The higher unit dose of 0.1 mg/kg was associated with slightly longer latencies to initiate FR responding, resulting in decreased intake (approximately 25 infusions per component.

In contrast to increased intake at FR3, an increase in response requirement to FR100 diminished cocaine intake. Values for saline extinction and threshold dose were not appreciably altered. However, self-administration of unit doses of cocaine at the peak of or on the descending portion of the dose-effect function under either the FR3 or FR30 schedules of reinforcement (>0.01 mg/kg) declined under the FR100 schedule of reinforcement. This resulted in an overall flattening of the dose-effect function (Fig. 2). The maximal number of infusions per component of any unit dose of cocaine averaged 10–11 (0.032 mg/kg) and was highly similar to values obtained during saline substitution under the FR3 schedule of reinforcement.

Chronic treatment with SKF 77434

SKF 77434 1.0 mg/kg per day

During chronic treatment with 1.0 mg/kg per day of SKF 77434, no change was observed in saline extinction, and the threshold unit dose for self-administration remained at 0.0032 mg/kg of cocaine. However, some alterations in IV self-administration of cocaine were observed (Fig. 3). Thus, throughout the 4 weeks of exposure the number of infusions per component of the threshold unit dose of cocaine, averaged for the group of three monkeys, increased from approximately 11 to approximately 18 infusions per component. Similarly, self-administration of the two highest unit doses of cocaine approximately doubled. These increases resulted in a rightward shift in the descending portion of the cocaine dose-effect function, consistent with surmountable antagonism. Although antagonist effects varied somewhat in magnitude among subjects, they were observed in all monkeys and resulted in a substantive increase in cocaine intake during the availability of higher unit doses for self-administration. For example, the total intake of the high unit dose of 1.0 mg/kg cocaine increased from approximately 5 mg/kg to 10 mg/kg per 35-min component.

SKF 77434 3.2 mg/kg per day

Chronic treatment with 3.2 mg/kg per day of SKF 77434 had pronounced effects on self-administration of cocaine, resulting in a flattening of the dose-effect function for the group of monkeys (Fig. 3). Inspection of data indicated that these effects emerged over the course of chronic exposure. Inconsistent disruptions in cocaine self-administration were observed during the first 2 weeks of exposure, whereas self-administration behavior markedly declined in all monkeys during the last 2 weeks of exposure (Table 1). In two of three monkeys, cocaine self-administration of one or more doses of cocaine that previously had maintained robust self-administration was nearly eliminated. In the third monkey (monkey M4), self-administration continued throughout chronic exposure to

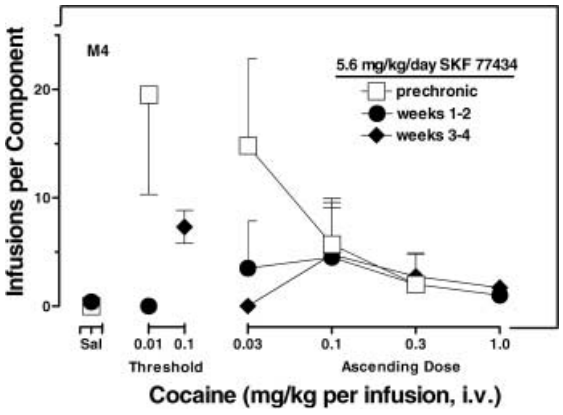

Fig. 4 Effects of chronic IV exposure to 5.6 mg/kg per day of SKF 77434 on cocaine self-administration under the FR30 schedule in monkey M4. *Open squares* show mean data for cocaine self-administration prior to the chronic regimen. *Filled circles* show the averaged effects during the first 2 weeks of exposure to 5.6 mg/kg per day of SKF 77434, whereas *filled diamonds* show the averaged effects of the same dosage during the second 2 weeks of exposure. Each data point during exposure to 5.6 mg/kg per day of SKF 77434 represents the mean of the average number of infusions per component (±SD) during sessions in which the unit dose was constant. Other details as in Fig. 1

daily 3.2 mg/kg SKF 77434; however, the dose-effect function was generally shifted downward and flat, i.e. unit doses of cocaine ranging from 0.003 to 0.32 mg/kg maintained comparable levels of self-administration behavior. In this monkey, self-administration of the higher unit doses of 0.1 and 0.32 mg/kg cocaine continued to be increased relative to prechronic values, indicating that the antagonist effects of SKF 77434 persisted throughout exposure to 3.2 mg/kg per day SKF 77434. Unit doses of cocaine >1.0 mg/kg were not studied in these experiments to avoid adverse effects of high doses of intravenous cocaine.

SKF 77434 5.6 mg/kg per day

Chronic treatment with 3.2 mg/kg per day SKF 77434 in monkey M4 was followed by an increase in daily dosage to 5.6 mg/kg SKF 77434. Following this increase in dosage, self-administration behavior immediately and markedly decreased throughout the month-long treatment period: the threshold unit dose for IV self-administration increased to 0.032 mg/kg and, over unit doses ranging from 0.1 mg/kg to 1.0 mg/kg, fewer than five infusions per component of any unit dose of cocaine were self-administered consistently (Fig. 4).

Food-maintained behavior

Preceding chronic studies, rates and patterns of food-maintained performance characteristic for FI and FR schedule-controlled performance were observed in, respectively, monkeys M1, M2 and monkey M4. Response

rates were 0.19±0.04 responses/s for monkey M1, 0.19±0.05 responses/s for monkey M2, and 4.83±0.08 responses/s for monkey M4. Chronic treatment with SKF 77434 had varying effects on food-maintained performance. Month-long exposure to the dosage of 1.0 or 3.2 mg/kg per day SKF 77434 altered rates of FI responding in qualitatively dissimilar ways. For example, during treatment with 3.2 mg/kg SKF 77434, response rates for monkey M2 decreased to and remained at 0.04±0.02 responses/s but, for monkey M1, remained elevated at 0.27 responses/s. In contrast, daily dosages of 1.0 or 3.2 mg/kg SKF 77434 did not significantly alter FR rates of food-maintained responding in monkey M4. Response rates averaged 4.71±0.20 responses/s, or 98% of prechronic baseline response rates, over the course of the month-long treatment with 3.2 mg/kg SKF 77434. However, a further escalation of daily dosage to 5.6 mg/kg SKF 77434 markedly disrupted food-maintained performance in monkey M4, and response rates during the last week of exposure to this dosage averaged 1.69±0.95 responses/s, or 35% of control values. Discontinuation of chronic dosing with SKF 77434 resulted in recovery toward previous baseline rates of responding in all monkeys.

Although baseline rates of food-maintained performance were markedly decreased in two monkeys during chronic exposure to SKF 77434, food chows delivered during supplemental feeding were regularly consumed and body weights of all monkeys remained within 10% of prechronic baseline body weights. Throughout chronic exposure to 1.0 and 3.2 mg/kg per day SKF 77434, monkeys were alert and active during daily observation and normative routines of grooming and home-cage behavior did not appear to be grossly disrupted. Exposure to 5.6 mg/kg per day SKF 77434 in monkey 4 produced some observable slowing in home-cage activity; however, this was not quantitatively evaluated.

Following discontinuation of chronic treatment with SKF 77434, uninterrupted dose-effect determinations for cocaine and sessions of food-maintained performance revealed that prechronic baseline values for cocaine self-administration (saline extinction, threshold, dose-effect function) were fully re-established within 1 week. Although not systematically evaluated, no evidence of untoward disruptions in home-cage behavior was noted in this time period.

Discussion

Rapid assessment of cocaine self-administration

Several aspects of the novel procedure used in the present studies deserve comment. First, dose-effect functions for cocaine self-administration in individual monkeys were highly similar in successive determinations as well as over the course of the studies. This is an important consideration for studies of how repeatedly or chronically administered treatments may alter self-administration behavior (e.g. Bergman et al. 1990; Negus et al. 1996). Second, the separate and frequent determination of extinction, threshold, and dose-effect function insured that treatment effects on various elements of self-administration behavior could be easily and rapidly identified. This allowed an assessment of whether such effects were transient and, if not, how they might contribute to subsequent changes in self-administration behavior. Third, self-administration behavior was sensitive to changes in reinforcement contingencies. This was evident by increases in IV infusions of the threshold or higher unit doses of cocaine as the FR requirement decreased from FR100 to FR3. These data agree with the results of previous parametric studies of self-administration under FR schedules (Winger 1993a, 1993b).

Effects of chronic treatment with SKF 77434

The present findings indicate that, like other D_1 receptor agonists, SKF 77434 reduces the effects of cocaine in self-administration studies in monkeys (Katz and Witkin 1992; Caine et al. 2000b). They also extend previous findings with D_1 receptor partial agonists to include conditions of chronic exposure to the treatment agent. In the present studies, the effects of chronic administration of the D_1 receptor partial agonist on IV cocaine self-administration behavior were related to dosage. The lower dosage, 1.0 mg/kg per day, increased intake of the threshold dose of IV cocaine and produced a moderate and persistent rightward shift in the descending portion of the dose-effect function for cocaine self-administration behavior, indicative of a surmountable antagonism. The absence of a corresponding change in the threshold unit dose of self-administered cocaine suggests that some aspects of the threshold dose remained sufficient to initiate cocaine-maintained responding, albeit at a higher rate than during pre-chronic threshold determinations. It is noteworthy that changes in cocaine self-administration behavior during chronic exposure to 1.0 mg/kg per day SKF 77434 were not accompanied by alterations in food-maintained performance or in extinction behavior. In this regard, previous studies have shown that acute treatment with the D_1 receptor partial agonist SKF 38393 attenuates cocaine self-administration in monkeys at doses lower than those that disrupt food-maintained performance (Katz and Witkin 1992; Caine et al. 2000a). In conjunction with those findings, the present results support the view that some doses of D_1 receptor partial agonists may alter cocaine self-administration in a behaviorally selective manner.

An increase in dosage of SKF 77434 to 3.2 mg/kg per day (and, for one monkey, then to 5.6 mg/kg per day) qualitatively altered the effects of chronic exposure to the D_1 receptor partial agonist in two ways. First, the position of the cocaine dose-effect function changed in a time-dependent fashion and, on average, was shifted downward rather than rightward from its original posi-

tion by the end of chronic exposure. Second, these latter changes in the position of the dose-effect function for self-administration were accompanied by changes in other behavioral measures, including threshold dose for self-administration and rates of food-maintained behavior. Although consistent and dramatic changes in overt behavior or physical condition were not apparent during the period of chronic exposure to 3.2 or 5.6 mg/kg per day SKF 77434, the emergence of disruptions in food-maintained behavior indicates that the D_1 receptor partial agonist's effects on cocaine self-administration were behaviorally selective over a limited range of daily dosage.

In previous studies, D_1 receptor partial agonists, like D_1 receptor blockers such as SCH 39166, produced rightward shifts in the acute behavioral effects of psychomotor stimulant drugs or D_1 full agonists (Bergman and Rosenzweig-Lipson 1992; Katz and Witkin 1992; Rosenzweig-Lipson and Bergman 1993; Spealman et al. 1997; Tidey and Bergman 1998). With regard to further comparisons, the effects of chronic exposure to dopamine receptor blockers on cocaine self-administration have been previously examined in two separate studies (Kleven and Woolverton 1990; Negus et al. 1996). In those experiments, chronic IV administration of the D_1-selective receptor blocker SCH 23390 or of the non-selective D_1/D_2 receptor blocker *cis*-flupentixol produced initial reductions in cocaine-maintained responding that, as the chronic regimens continued, were followed by recovery of cocaine self-administration behavior. Thus, tolerance developed to the effects of dopamine receptor blockade on cocaine self administration, contrasting qualitatively with the absence of tolerance to the effects of the chronically administered D_1 receptor partial agonist SKF 77434 in the present studies. Although higher dosage or longer exposure to SKF 77434 eventually may have yielded evidence of tolerance, the absence of tolerance in the present studies are consistent with the idea that activation of dopamine D_1 receptors, albeit by partial agonists, may lead to a different profile of behavioral effects than associated with D_1 receptor blockade (Tidey and Bergman 1998; Platt et al. 2000; Bergman et al. 2000).

Chronic exposure to the dopamine D_1 full agonist A 77636 has been reported to lead to D_1 receptor desensitization and consequent reductions in D_1 receptor density, actions that may play a role in the development of tolerance to the ameliorative motoric effects of D_1 agonists in preclinical models of parkinsonism (Lin et al. 1995). It currently is unknown whether chronic exposure to D_1 receptor partial agonists also can be associated with D_1 receptor desensitization. Based on studies with different dopamine D_1 agonists, cellular processes of receptor desensitization are highly dependent on the conditions of exposure and may vary from ligand to ligand (Gulwadi et al. 2001). From this perspective, the absence of tolerance in the present findings raises the possibility that long-term exposure to D_1 receptor partial and full agonists, e.g. SKF 77434 and A 77636, respectively, may have differing impact on D_1 receptor sensitivity. Alternatively, it may be that chronic exposure to SKF 77434 does lead to D_1 receptor desensitization and decreased D_1 receptor density, but that these changes are not associated with tolerance to reduction of the reinforcing effects of self-administered IV cocaine or of food delivery.

D_1 agonists as candidate medications for the treatment of cocaine abuse and dependence

Dopamine D_1 receptor partial agonists have been forwarded as candidate medications for the treatment of cocaine abuse and dependence on the basis of the behavioral selectivity with which they may produce cocaine-antagonist effects when administered acutely (Katz and Witkin 1992; Tidey and Bergman 1998; Bergman et al. 2000; Platt et al. 2000). The present findings that chronic exposure to a D_1 receptor partial agonist can produce persistent decreases in cocaine self-administration are noteworthy in view of the likelihood that anti-cocaine medications will need to be administered on a continuing basis for some segment of the treatment population. However, uncertainty regarding the attributes of a successful medication make it necessary to interpret the present findings cautiously. For example, it is unclear whether rightward, leftward, or downward shifts in the dose-effect function for cocaine self-administration best predict a successful treatment approach. Indeed, it seems reasonable to presume that differing types of effects on cocaine self-administration may be useful in guiding the development of medications for different segments of the treatment population (see Negus and Mello 1996 for discussion).

A second issue for the further development of D_1 receptor partial agonists as candidate medications is the relevance of behavioral selectivity in their anti-cocaine actions. In the present studies, for example, the daily dosage of 1.0 mg/kg SKF 77434 antagonized the effects of cocaine without appreciably altering food-maintained behavior. However, previous studies have shown that the strength of reinforcers such as cocaine or food depends critically on response requirements and the magnitude of reinforcement (e.g. Nader and Woolverton 1991; Winger 1993a, 1993b; Rowlett et al. 1996). Thus, a meaningful assessment of behavioral selectivity probably depends upon accurately gauging the strength of the reinforcing events with which cocaine is compared. Without such information, the presence or absence of disruptions in food-maintained responding is more difficult to interpret than information on other endpoints, e.g. overt behavioral toxicity. In this regard, the absence of consistent profound changes in home-cage behavior and general health during chronic exposure to SKF 77434 in the present studies supports the view that D_1 receptor partial agonists ought to be further evaluated as medications to combat cocaine abuse and dependence.

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