Dopamine D1- and D2-Like Receptor Mechanisms in Relapse to Cocaine-Seeking Behavior: Effects of Selective Antagonists and Agonists

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ABSTRACT

Dopaminergic mechanisms are thought to be critical in mediating relapse to cocaine-seeking behavior. This study examined the different roles of D1- and D2-like receptor mechanisms in the relapse process. Squirrel monkeys were given extended histories of i.v. cocaine self-administration under conditions in which responding was maintained jointly by response-contingent cocaine injections and a cocaine-paired visual stimulus (second-order schedule). Responding was then extinguished by substituting saline for cocaine injections and omitting presentations of the cocaine-paired stimulus. Subsequently, non-contingent priming injections of cocaine combined with reinstatement of the cocaine-paired stimulus induced dose-dependent reinstatement of drug-seeking behavior, with response rates approaching those maintained by active cocaine self-administration. The priming effects of cocaine were attenuated by several D1- and D2-like receptor antagonists and low efficacy agonists but not by the D3-prefering antagonists UH 232 and AJ-76. The priming effects of cocaine were mimicked by the D2-like receptor agonists R(-)-propylapomorphine hydrobromide (NPA) and quinpirole, less consistently by 7-OH-DPAT, and not by the D1-like receptor agonists SKF-81297 and SKF-82958, the D3-prefering agonist PD-128,907, or any low efficacy agonist. Cotreatment with NPA, PD-128,907, and 7-OH-DPAT did not alter reinstatement of drug-seeking behavior induced by a maximally effective priming dose of cocaine, whereas cotreatment with D1-like receptor agonists attenuated the priming effects of cocaine. The results suggest that D1- and D2-like receptors play fundamentally different roles in the relapse process. Although stimulation of D2-like, but probably not D3-like, receptors appears necessary for induction of relapse, either stimulation or blockade of D1-like receptors appears to be inhibitory with respect to relapse.

In abstinence cocaine users, the likelihood of relapse is high and limits the effectiveness of therapeutic interventions even after successful detoxification (Simpson et al., 1999). Thus, a major focus of drug addiction therapy is the development of treatment strategies that incorporate relapse prevention (Dejonc, 1994). Although factors responsible for the high rate of relapse are not fully understood, accumulating evidence suggests that drug priming (i.e., acute re-exposure to cocaine), drug-associated environmental stimuli, and stress can act as triggers of craving leading to relapse in humans (Jaffe et al., 1989; McKay et al., 1995, Robbins et al., 1997). As in people, cocaine priming injections, cocaine-associated stimuli, and stress can precipitate relapse to cocaine-seeking behavior in animals [see reviews by Carroll and Comer (1996), Self and Nestler (1998), and Spealman et al. (1999)].

Cocaine priming is a persistent effect in animals and can be associated with cocaine-associated stimuli, and stress can precipitate relapse to cocaine-seeking behavior in animals [see reviews by Carroll and Comer (1996), Self and Nestler (1998), and Spealman et al. (1999)].

Cocaine priming is a persistent effect in animals and can be observed for weeks after withdrawal from cocaine (Tran-
Experiments were conducted using a nonhuman primate model by cocaine priming and a cocaine-paired stimulus. The exponents and agonists of differing efficacy either mimicked or end, we assessed the degree to which selective DA antagonists of cocaine-seeking behavior. To this neutralize the effects of cocaine priming on responding engendered by cocaine and instead may serve as functional antagonists of the abuse-related effects of cocaine in animals (e.g., Katz and Witkin, 1992; Weed and Woolverton, 1995; Spealman et al., 1997; Pulvirenti et al., 1998). Because of their low intrinsic activity, these drugs may act predominantly as antagonists under conditions of high DA tone and as weak agonists under conditions of low DA tone (Ariens, 1983). Unlike DA high efficacy agonists, DA low efficacy agonists do not have behavioral effects comparable with cocaine and instead may serve as functional antagonists of the abuse-related effects of cocaine in animals (e.g., Katz and Witkin, 1992; Weed and Woolverton, 1995; Spealman et al., 1997; Pulvirenti et al., 1998). The effects of DA low efficacy agonists on reinstatement of cocaine-seeking behavior have not been systematically characterized. Weissenborn et al. (1996), however, reported that one D2-like low efficacy agonist, SDZ-208-911, enhanced rather than attenuated the priming effects of cocaine on responding maintained by a cocaine-associated stimulus in rats. This latter finding raises the possibility that DA low efficacy agonists may have different effects on cocaine-induced relapse compared with other abuse-related effects of cocaine.

DA antagonists can provide additional insight regarding the contributions of DA receptor mechanisms in reinstatement of cocaine-seeking behavior. Like DA low efficacy agonists, DA antagonists can attenuate many of the behavioral effects of cocaine in animals (see review by Mello and Negus, 1996). Some DA antagonists also have been found to attenuate the effects of cocaine priming on responding engendered by a cocaine-paired stimulus in rats (Weissenborn et al., 1996). Thus, the effects of DA antagonists on reinstatement of cocaine-seeking behavior warrant further investigation.

The purpose of this study was to investigate the contribution of D1- and D2-like receptor mechanisms in a nonhuman primate model of relapse to drug-seeking behavior. To this end, we assessed the degree to which selective DA antagonists and agonists of differing efficacy either mimicked or modulated reinstatement of drug-seeking behavior induced by cocaine priming and a cocaine-paired stimulus. The experiments were conducted using a nonhuman primate model of cocaine relapse, which simulated some presumably key features of cocaine use and relapse patterns in people (cf. Spealman et al., 1999). In this model, monkeys were given extended histories of i.v. cocaine self-administration under a second-order schedule (cf. Goldberg et al., 1975) in which persistent drug seeking was maintained jointly by cocaine injections and a cocaine-paired visual stimulus. Drug seeking subsequently was extinguished for periods of time up to several weeks with interposed test sessions to evaluate the effects of selected DA receptor ligands alone and in combination with cocaine priming.

Materials and Methods

Subjects. Adult male squirrel monkeys (Saimiri sciureus) weighing 0.7 to 1.0 kg were housed individually in a climate-controlled vivarium, where they had unlimited access to water and received a nutritionally balanced diet of monkey chow supplemented with fresh fruit. A total of seven monkeys were studied over a period of >2 years, with groups of three to five monkeys serving as subjects in each experiment (see below). All animals were trained under a second-order schedule of i.v. cocaine self-administration similar to the schedule described by Goldberg et al. (1975). Additionally, some of the monkeys had previous experience with self-administering direct and indirect DA agonists (Grech et al., 1996). Monkeys used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and of the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, 1996).

Surgery. Indwelling venous catheters were implanted in each monkey using aseptic surgical procedures as described by Carey and Spealman (1998). Briefly, monkeys were anesthetized with isoflurane, and one end of the catheter was passed by way of either a jugular or femoral vein to the level of the right atrium. The distal end of the catheter was passed s.c. and exited in the mid-scapular region. Catheters were flushed daily with 0.9% saline solution containing 200 U of heparin/ml and were sealed with stainless steel obturators when not in use. Monkeys wore nylon-mesh jackets (Lomir Biomedical, Canada) at all times to protect the catheter.

Apparatus. Experimental sessions were conducted in ventilated sound-attenuated chambers, which were provided with white noise to mask external noise. Within the chamber, monkeys were seated in a Plexiglas chair facing a panel that was equipped with a response lever and colored stimulus lights above the lever. Catheters were connected to motor-driven syringe pumps located outside the chamber. Each operation of the pump delivered a 200-ms infusion of 0.2 ml of vehicle or drug solution into the catheter.

Second-Order Schedule of Cocaine Injection. Monkeys were trained to self-administer cocaine under a second-order fixed interval (FI) (fixed ratio (FR):S) schedule of i.v. drug injection similar to the schedule described by Goldberg et al. (1975). Briefly, in the presence of a white light, completion of every 10th or 30th response (FR10 or FR30, depending on the particular experiment) during a 10-min FI resulted in a 2-s change in illumination from white to amber. Completion of the first FR after expiration of the FI resulted in an i.v. injection of cocaine simultaneous with the onset of the amber light (cocaine-paired stimulus: S). A 60-s time out (TO) period, during which all lights were off and responses had no scheduled consequences, followed each cocaine-stimulus pairing. If the FR requirement was not completed within 8 min following the expiration of the FI, the component ended automatically without an injection followed by a 60-s TO period. Daily sessions ended after completion of five cycles of the second-order schedule (maximum of 95 min). Initially, the dose of cocaine was varied over a 10-fold range (0.1–1.0 mg/kg/injection) to determine the dose that maintained maximum rates of responding for each monkey. For six monkeys, 0.3 mg/kg/
injection maintained maximum response rates, whereas for the remaining monkey, 0.56 mg/kg/injection maintained maximum response rates.

**Extinction and Effects of Cocaine Priming.** Following a 6- to 8-month period of stable cocaine self-administration, responding was extinguished by substituting saline for cocaine and omitting presentations of the cocaine-paired stimulus. Extinction sessions, including session and TO durations, were otherwise identical with those described above. Extinction sessions were conducted daily until responding declined and stabilized at ≤10% of the response rate maintained by cocaine self-administration (3–12 sessions depending on the subject).

Following extinction, a range of doses of noncontingent priming injections of cocaine as well as saline vehicle were assessed for their ability to reinstate drug-seeking behavior during test sessions in which only saline was available for self-administration. Response-contingent presentations of the cocaine-paired stimulus also were restored during these test sessions, because earlier studies showed that reinstatement of cocaine-seeking behavior was greatest when cocaine priming was accompanied by restoration of the cocaine-paired stimulus (Spealman et al., 1999). Priming injections of cocaine were administered i.v. immediately before the session followed by a saline flush to clear the catheter of residual drug solution. A range of priming doses of cocaine, as well as saline vehicle, were tested in three monkeys under the FI 10-min (FR 10:S) schedule and in five monkeys under the FI 10-min (FR 30:S) schedule. Three of the monkeys were tested using both parameters of the second-order schedule. Different doses of cocaine were tested on different days, with each test session separated by two or more extinction sessions as described above. The order in which each priming dose of cocaine was tested varied across monkeys. After completion of these experiments, cocaine self-administration was re-established using the procedures described previously until responding stabilized and there were no systematic trends in response rates over at least three daily sessions.

**Attenuation of Cocaine Priming by DA Antagonists.** Following test sessions with various priming doses of cocaine and re-establishment of stable cocaine self-administration, drug-seeking behavior was again extinguished over the course of three or more sessions by substituting saline for cocaine and eliminating the cocaine-paired stimulus as described above. Subsequently, the effects of several DA antagonists on cocaine-induced reinstatement of drug-seeking behavior were determined in groups of three to five monkeys per drug using testing procedures described above. DA antagonists used in this study included: the nonselective DA antagonist, flupenthixol; the D1-like receptor antagonist ecopipam (SCH-39166); the D2-like receptor antagonists eticlopride and nemonapride; the D3/D4 antagonist YM-43611; and the D3-prefering antagonists AJ-76 and UH 232. Monkeys received an i.m. pretreatment injection of the antagonist and were returned to their home cage. Following a predetermined interval (see below), monkeys were placed in the chair and received an i.v. cocaine prime followed by a saline flush to clear the catheter. The session was then started immediately. This testing procedure was used because of the relatively long pretreatment times required for many of the DA antagonists and the availability of data on appropriate i.m. doses of these drugs in squirrel monkeys (Bergman et al., 1991; Spealman et al., 1992; Spealman, 1996; our unpublished observations). Pretreatment times for the different antagonists were: 15 min for AJ-76; 30 min for ecopipam, YM-43611, UH 232, and nemonapride; 60 min for flupenthixol; and 120 min for eticlopride. A 10-fold or greater range of doses of each antagonist was tested, with each subject receiving all doses once in a different order. The priming dose of cocaine used in these experiments was based on effects in individual monkeys and was one that produced maximum reinstatement of drug-seeking behavior as determined in initial studies. Different doses of each antagonist were tested on different days, and each test session was separated by two or more extinction sessions as described previously. In addition, a test session with a maximally effective priming dose of cocaine alone was conducted during experiments with each antagonist to provide a comparative standard. As in reinstatement testing with cocaine alone, only saline was available for self-administration, and response-contingent presentations of the cocaine-paired stimulus were restored. Between testing with different antagonists, which required approximately 3 to 4 weeks per drug, i.v. self-administration of cocaine was re-established and maintained until responding was stable as described above. A series of extinction sessions then was conducted before subsequent testing with another antagonist.

**Priming Effects of DA Agonists.** After completing studies with the DA antagonists, selective D1- and D2-like receptor agonists were tested for their ability to mimic the priming effects of cocaine. The DA agonists used in these studies included: the D1-like high efficacy agonists SKF-81297 and SKF-82958; the D1-like low efficacy agonists SKF-89359 and SKF-38393; the D2-like high efficacy agonists NPA, quinpirole, 7-OH-DPAT, and PD-128,907; and the D2-like low efficacy agonists terguride and SDZ-208-911. The testing procedures were identical with those used to test the priming effects of cocaine. A 10-fold or greater range of doses of each DA agonist in addition to its corresponding vehicle was tested in groups of three to five monkeys, with each subject receiving all doses once in a different order. Reinstatement testing with each dose of an agonist was separated with two or more extinction sessions. An additional test session was conducted with a maximally effective dose of cocaine for comparative purposes. Between tests with different DA agonists, i.v. self-administration of cocaine was re-established and maintained until responding stabilized as described previously. Three or more extinction sessions, in which response rates fell to ≤10% of the rates maintained by cocaine self-administration, were then conducted before testing with another DA agonist.

**Modulation of Cocaine Priming by DA Agonists.** After completion of the experiments described above, additional studies were conducted to determine whether pretreatment with various DA agonists would alter the reinstatement of responding induced by a maximally effective dose of cocaine. The testing procedures were identical with those described previously, except that monkeys received both an i.v. injection of a maximally effective dose of cocaine and an i.v. injection of a DA agonist followed by a saline flush immediately before the start of the test session. The range of doses of the DA agonists used in these studies was similar to that used in agonist-induced reinstatement testing. Each drug was studied in a group of three to five monkeys, and each monkey was tested with each dose once in a different order. During testing with each DA agonist, priming with the maximally effective dose of cocaine alone was redetermined. Two or more extinction sessions separated testing with each dose of an agonist. Between experiments with different DA agonists, i.v. self-administration of cocaine was re-established and maintained until responding was stable. A series of extinction sessions was then carried out as described above before testing with another DA agonist.

**Data Analysis.** The rate of responding in individual monkeys was computed for each session by dividing the total number of responses by the total elapsed time (excluding responses and time during TO periods). For each experimental condition, the mean response rate ± S.E. was calculated for groups of three to five monkeys. In experiments examining the effects of DA antagonists or agonists in combination with cocaine, the percentage change of cocaine-induced reinstatement was calculated, based on rate of responding. (Percentage change = [cocaine prime alone − cocaine prime + DA drug]/cocaine prime alone). All data were analyzed by single-factor repeated measures ANOVA or paired t tests, as appropriate, to assess differences between control conditions and doses of test drugs. Multiple comparisons were conducted using Dunnett’s q statistic, which calculates differences among each treatment level relative to the control condition. The control conditions were either vehicle priming tests for experiments in which the drugs were tested alone, or cocaine
priming tests for experiments in which cocaine was combined with other drugs.

**Drugs.** Cocaine, YM-43611, eticlopride, flupenthixol, AJ-76, UH 232, quinpirole, 7-OH-DPAT, and PD-128,907 were dissolved in 0.9% saline solution. NPA, SKF-81297, SKF-82958, SKF-38393, and SDZ-208-911 were dissolved in a vehicle of 95% ethanol, 0.1% ascorbic acid, and sterile water (10:20:70 by volume). Terguride and SKF-83959 were dissolved in a small amount of 95% ethanol containing 0.1 N HCl and then diluted with 0.9% saline solution. Nemonapride and ecopipam were dissolved in 1% acetic acid and then diluted with saline. Nemonapride and YM-43611 were generously donated by Yamanouchi Pharmaceutical Co. (Tokyo, Japan), ecopipam was generously donated by Schering-Plough Research Institute, and SDZ-208-911 was generously donated by Sandoz Pharmaceuticals Ltd. (East Hanover, NJ). Other compounds were purchased from Toeris Cookson and Research Biochemicals, Inc. (Ballwin, MO).

**Results**

**Cocaine Self-administration and Priming.** Self-administered cocaine maintained consistently high rates of responding (averaging 1.1–1.5 responses/s) under both the FI 10-min (FR 10:S) and FI 10-min (FR 30:S) schedules of i.v. drug injection (Fig. 1, points above SA). Patterns of responding were similar to those described previously under this type of schedule (cf. Goldberg et al., 1975; Grech et al., 1996). Typically, a period of little or no responding at the beginning of each FI was followed by a rapid transition to high rates of responding that were maintained during the remainder of the interval, interrupted only by brief pauses at the completion of each FR. During extinction sessions, in which saline was substituted for cocaine and the cocaine-paired stimulus was omitted, responding declined and stabilized at low rates (averaging 0.01–0.03 responses/s; Fig. 1, points above EXT).

Priming injections of cocaine (0.1–1.0 mg/kg) before test sessions, in which the cocaine-paired stimulus was restored, produced a dose-dependent reinstatement of extinguished cocaine-seeking behavior (Fig. 1). ANOVA indicated a significant effect of cocaine-induced reinstatement under both the FI 10-min (FR 10:S) schedule \[F(3,6) = 24.14, P < .05\] and the FI 10-min (FR 30:S) schedule \[F(3,12) = 15.96, P < .05\]. Under both schedules, the 0.3 and 1.0 mg/kg doses of cocaine produced an increase in the rate of responding relative to vehicle priming injections (Dunnett’s test, \(P < .05\)). For individual animals, response rates engendered by priming with these doses of cocaine approached response rates maintained by active cocaine self-administration. In addition, temporal patterns of responding following cocaine priming were generally similar to those seen during cocaine self-administration (not shown). Priming with vehicle induced nonsignificant increases in response rate (averaging 0.02–0.09 responses/s; Fig. 1, points above VEH) compared with extinction (paired \(t\) test; \(P > .05\)).

**Attenuation of Cocaine Priming by DA Antagonist.** When administered as pretreatments before priming with a maximally effective dose of cocaine, the D1-like receptor antagonist ecopipam \([F(3,12) = 24.84, P < .05]\), the D2-like receptor antagonists eticlopride and nemonapride \([F(3,6) = 16.18\) and \(F(3,9) = 14.93\), respectively; \(P < .05\)], the D4/D3 antagonist YM-43611 \([F(3,9) = 6.30, P < .05]\), and the non-selective DA antagonist flupenthixol \([F(3,9) = 9.21, P < .05]\) dose-dependently attenuated cocaine-induced reinstatement of drug-seeking behavior (Fig. 2). The highest dose of each antagonist suppressed cocaine-induced drug seeking to levels similar to those observed in the absence of cocaine priming (Dunnett’s tests, \(P < .05\)). The D3-preferring antagonists AJ-76 and UH 232, on the other hand, had comparatively small effects on cocaine-induced reinstatement of drug-seeking behavior (ANOVA, \(P > .05\); Table 1). Because a higher dose of UH 232 (1.8 mg/kg) induced muscle rigidity and labored respiration in a preliminary experiment, doses of either UH 232 or AJ-76 greater than 1.0 mg/kg were not evaluated further.

**Priming Effects of DA Agonists.** Priming with the D1-like high efficacy agonists SKF-81297 and SKF-82958 and the low efficacy agonists SKF-83959 and SKF-38393 did not induce reinstatement of responding at any dose tested (ANOVA, \(P > .05\); Table 2). Maximum rates of responding engendered by these drugs were similar to those engendered by vehicle. Doses of SKF-81297, SKF-82958, SKF-83959, and

![Fig. 1. Dose-dependent reinstatement of extinguished drug-seeking behavior induced by cocaine priming combined with restoration of the cocaine-paired stimulus. Points above SA show responding maintained by cocaine self-administration; points above EXT show responding during extinction; and points above VEH show the effects of vehicle priming. Data are means (± S.E.) based on three [FI 10-min (FR 10:S) schedule] or five monkeys [FI 10-min (FR 30:S) schedule].](image1)

![Fig. 2. Dose-dependent attenuation of the priming effects of cocaine induced by pretreatment with various DA receptor antagonists. Points above COC show reinstatement of responding induced by a maximally effective dose of cocaine alone. Data are means (± S.E.) based on three to five monkeys per drug.](image2)
Lack of cocaine-like priming effects of selected DA agonists

TABLE 2

<table>
<thead>
<tr>
<th>Drug/Condition</th>
<th>Dose Range</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>responses/s</td>
</tr>
<tr>
<td>Cocaine self-administration</td>
<td>0.3–1.0</td>
<td>1.26 ± 0.19</td>
</tr>
<tr>
<td>Extinction</td>
<td>0.02 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Cocaine prime</td>
<td>1.0</td>
<td>0.06 ± 0.05</td>
</tr>
<tr>
<td>Vehicle prime</td>
<td>0.05 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>D1-like agonist prime</td>
<td>0.1–1.0</td>
<td>0.06 ± 0.05</td>
</tr>
<tr>
<td>SKF-81297</td>
<td>0.03–0.3</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>SKF-82958</td>
<td>0.3–3.0</td>
<td>0.10 ± 0.10</td>
</tr>
<tr>
<td>SKF-38393</td>
<td>0.03–3.0</td>
<td>0.04 ± 0.04</td>
</tr>
<tr>
<td>SKF-83959</td>
<td>0.003–0.1</td>
<td>0.20 ± 0.11</td>
</tr>
<tr>
<td>7-OH-DPAT</td>
<td>0.003–0.1</td>
<td>0.20 ± 0.15</td>
</tr>
</tbody>
</table>

Data are maximum response rates (means ± S.E.) based on at least four determinations on three or four monkeys per drug.

SKF-38393 higher than those tested in these studies were not evaluated because of the possibility of seizures, which have been observed following administration of high doses of D1-like agonists in previous studies (e.g., Britton et al., 1991; our unpublished observations).

In contrast to D1-like receptor agonists, the D2-like receptor agonists NPA and quinpirole induced dose-dependent reinstatement of cocaine-seeking behavior [F(4,12) = 5.52 and F(4,8) = 4.81, P < .05; Fig. 3]. Average response rates produced by priming with these high efficacy agonists were comparable to those induced by a maximally effective priming dose of cocaine (Fig. 3). In some cases, the highest doses of NPA and quinpirole induced vocalization and scratching. In contrast to NPA and quinpirole, reinstatement of cocaine-seeking behavior engendered by 7-OH-DPAT was not statistically significant (ANOVA, P > .05; Table 2) due to qualitatively different effects in individual monkeys. In this regard, priming with the highest dose of 7-OH-DPAT (0.1 mg/kg) induced reinstatement of responding comparable to that seen following priming with maximally effective doses of cocaine in two of the four monkeys (0.69 and 1.09 responses/s). In the remaining two monkeys, however, response rates engendered by this dose did not greatly exceed those engendered by vehicle (0.20 and 0.26 responses/s). Averaged for the group of four monkeys, the maximum rate of responding engendered by 7-OH-DPAT was approximately half the rate engendered by cocaine (Table 2).

PD-128,907 did not induce reinstatement of drug-seeking behavior at any dose tested (ANOVA, P > .05; Table 2). The maximum rate of responding engendered by PD-128,907 was approximately 11% of the rate engendered by a maximally effective priming dose of cocaine. Higher doses of PD-128,907 were not tested to prevent the induction of self-directed behaviors, which were observed in a previous study with squirrel monkeys (Spealman, 1996).

The D2-like low efficacy agonists terguride and SDZ-208-911 did not induce reinstatement of responding at any dose tested (ANOVA, P > .05; Table 2). Maximum rates of responding engendered by terguride and SDZ-208-911 were approximately 18% of the response rates induced by a maximally effective priming dose of cocaine. Higher doses of these latter two drugs were not evaluated, because 0.3 mg/kg terguride and 0.1 mg/kg SDZ-208-911 induced vocalization, scratching, and muscle rigidity in most monkeys.

**Modulation of Cocaine Priming by DA Agonists.** The D1-like high efficacy agonists SKF-81297 and SKF-82958 dose-dependently inhibited reinstatement of responding induced by a maximally effective priming dose of cocaine [F(3,9) = 6.68 and F(3,6) = 10.70, P < .05; Fig. 4]. Similarly, the D1-like low efficacy agonists SKF-83959 and SKF-38393 also dose-dependently inhibited reinstatement of responding induced by a maximally effective dose of cocaine [F(3,6) = 27.90 and F(3,6) = 20.26, P < .05; Fig. 4]. Priming with the highest dose of each D1-like agonist significantly reduced responding to levels similar to those observed in the absence of cocaine priming (Dunnnett’s tests, P < .05).

NPA, 7-OH-DPAT, and PD-128,907 over a 10-fold or greater range of doses did not consistently alter reinstatement of drug-seeking behavior induced by a maximally effective priming dose of cocaine (ANOVA, P > .05; Table 3). Moreover, the individual differences observed with 7-OH-DPAT alone (see above) were not reflected in interactions between 7-OH-DPAT and cocaine priming in individual monkeys. In contrast to these high efficacy agonists, the D2-like low efficacy agonists terguride and SDZ-208-911 dose-dependently inhibited reinstatement of drug-seeking behavior in-
induced by the cocaine prime alone (Dunnett's tests, agonists reduced responding to 7 to 10% of the response rates per drug.

Fig. 4. Dose-dependent attenuation of the priming effects of cocaine induced by cotreatment with D1-like agonists. Points above COC show reinstatement of responding induced by a maximally effective dose of cocaine alone. Data are means (± S.E.) based on three or four monkeys per drug.

TABLE 3
Lack of effect of D2-like receptor agonists on reinstatement of drug seeking induced by a maximally effective priming dose of cocaine (0.3–1.0 mg/kg, depending on monkey)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Maximum Change from Cocaine Prime</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPA</td>
<td>0.0005–0.01</td>
<td>−5.5 ± 19.6</td>
</tr>
<tr>
<td>7-OH-DPAT</td>
<td>0.01–0.1</td>
<td>7.0 ± 24.5</td>
</tr>
<tr>
<td>PD-128907</td>
<td>0.01–0.18</td>
<td>−26 ± 2.17</td>
</tr>
</tbody>
</table>

Data are means ± S.E. (n = 3–4).

Fig. 5. Dose-dependent attenuation of the priming effects of cocaine induced by cotreatment with D2-like partial agonists. Points above COC show reinstatement of responding induced by a maximally effective dose of cocaine alone. Data are means (± S.E.) based on three or four monkeys per drug.

Discussion
There is growing evidence that exposure to cocaine-associated cues and/or cocaine itself can play a fundamental role in eliciting craving and relapse in people (Jaffe et al., 1989; Robbins et al., 1997). In this study, priming injections of cocaine in conjunction with the restoration of the cocaine-paired stimulus induced a dose-dependent reinstatement of drug-seeking behavior in monkeys. At maximally effective doses, priming combined with the cocaine-paired stimulus engendered response rates comparable to those maintained by active cocaine self-administration. Moreover, high rates of responding could be induced repeatedly following successive cycles of self-administration and extinction over a >2-year period.

DA receptor mechanisms are thought to play a critical role in the effects of cocaine related to its abuse, including relapse (Wise et al., 1990; Self and Nestler, 1998; Spealman et al., 1999). Consistent with this view, the nonselective DA antagonist flupenthixol, the D1-like receptor antagonist ecopipam, and the D2-like receptor antagonists eticlopride and nemonapride attenuated the priming effects of cocaine in this study, suggesting that both D1- and D2-like receptor mechanisms are involved in relapse to cocaine-seeking behavior. Moreover, the potencies of these drugs as antagonists of cocaine priming in this study (nemonapride > eticlopride > flupenthixol > ecopipam) are similar to their potencies as antagonists of other behavioral effects of cocaine in squirrel monkeys (Spealman et al., 1992). On the other hand, AJ-76 and UH 232, which exhibit a modest (6–8-fold) selectivity for D3 receptors relative to D2 receptors (Audin et al., 1998), did not consistently attenuate the priming effects of cocaine. Previous studies have reported mixed results with these drugs as antagonists of other abuse-related effects of cocaine in rats and rhesus monkeys (Callahan et al., 1992; Vanover et al., 1993; Roberts and Ranaldi, 1995). Although it is conceivable that higher doses of AJ-76 or UH 232 would have been more effective in modulating cocaine-induced reinstatement of drug-seeking behavior in this study, these doses could not be evaluated systematically due to toxic side-effects. The limited ability of AJ-76 and UH 232 to block the priming effects of cocaine in our study, coupled with the complimentary findings that PD-128,907 neither mimicked nor enhanced the priming effects of cocaine (see below), suggests a minimal role for D3 receptor mechanisms in relapse to cocaine-seeking behavior. It is noteworthy, however, that the D4/D3 receptor antagonist YM-43611 attenuated the priming effects of cocaine to about the same degree as the other D2-like receptor antagonists, suggesting that D4 and/or D3 receptor mechanisms contribute in some way to cocaine-induced reinstatement of drug-seeking behavior. A more comprehensive understanding of the roles of different D2-like receptors in the relapse process undoubtedly will be facilitated by the development of antagonists exhibiting greater selectivity at the D2, D3, and D4 receptor subtypes.

In this study, none of the D1-like receptor agonists showed any tendency to mimic the priming effects of cocaine. Furthermore, each of these drugs attenuated the reinstatement of drug-seeking behavior induced by a maximally effective priming dose of cocaine with a rank order of potency (SKF-83959 > SKF-82958 > SKF-81297 > SKF-38393) similar to that observed in other behavioral studies with squirrel monkeys (Bergman et al., 1995; Spealman et al., 1997; Platt et al., 2000). These results extend recent findings that D1-like receptor agonists also attenuate the priming effects of cocaine in rats (Self et al., 1996; De Vries et al., 1999) and suggest that stimulation of D1-like receptors plays a largely inhibi-
tory role in relapse to cocaine-seeking behavior. As discussed previously, however, blockade of D1-like receptors also attenuates the priming effects of cocaine, indicating that D1-like receptor antagonists and agonists have similar rather than opposing effects on cocaine-induced reinstatement of drug seeking. The common effects of D1-like receptor agonists and antagonists could be due to a nonspecific suppression of operant behavior rather than a pharmacologically specific interaction with cocaine priming. However, doses of D1-like receptor ligands that attenuated the priming effects of cocaine in this study are typically lower than those that produce comparable reductions in other operant behaviors or that induce motoric side-effects that might impair responding (Bergman et al., 1995; Platt et al., 2000).

Accumulating data suggest that chronic exposure to cocaine and related drugs can profoundly alter the brain DA system. For example, long term cocaine self-administration in monkeys has been found to decrease D1-like receptor density (Moore et al., 1998), and persistent activation of D1-like receptors can desensitize receptor function (Lin et al., 1996). In subjects with extended histories of cocaine self-administration, it is possible that alterations in D1-like receptor transduction mechanisms diminish the impact of agonist-induced receptor stimulation, resulting in attenuation of cocaine priming. Another possibility is that the common effects of D1-like receptor agonists and antagonists in this study were mediated by D1-like receptors distinct from those linked to adenyl cyclase. Along these lines, several drugs classified traditionally as high efficacy agonists (based on their ability to stimulate adenyl cyclase) exhibit substantially reduced efficacy at D1-like receptors coupled to phosphoinositide metabolism (Undie et al., 1994). Resolution of these various possibilities might be accomplished by determining whether D1-like receptor agonists and antagonists have mutually opposing or additive effects with respect to inhibition of cocaine priming.

In contrast to D1-like receptor ligands, the D2-like high efficacy agonists NPA and quinpirole mimicked the priming effects of cocaine virtually completely, consistent with previous findings in rats (Wise et al., 1990; De Vries et al., 1999). On the other hand, 7-OH-DPAT had less consistent effects, and PD-128,907 did not induce substantial reinstatement of drug-seeking behavior in any subject. The different effects of 7-OH-DPAT and especially PD-128,907 relative to the other D2-like receptor agonists may reflect the different selectivities of these drugs for receptor subtypes within the D2-like receptor family. In this regard, PD-128,907 exhibits the greatest selectivity for the D3 compared with other D2-like receptors, whereas NPA exhibits the least (Freedman et al., 1994, Pugsley et al., 1995). Together with the limited ability of AJ-76 and UH 232 to block the priming effects of cocaine (see above), these results provide little evidence of a crucial role for D3 receptor mechanisms in relapse to cocaine-seeking behavior. This outcome was unexpected, given the potentially important role for D3 receptor mechanisms in both the discriminative stimulus and reinforcing effects of cocaine in other animal models (Caine and Koob, 1993; Spealman, 1996; Pilla et al., 1999).

In this study, neither NPA nor 7-OH-DPAT consistently altered the priming induced by a maximally effective dose of cocaine. 7-OH-DPAT, however, has been shown to enhance the priming effects of a low dose of cocaine (Self et al., 1996). Extrapolating from these two sets of findings, one might expect that combined priming with cocaine and a D2-like receptor agonist would have predominantly additive effects at low doses without producing a corresponding increase in the maximum effect at higher doses. This type of interaction would be consistent with the hypothesis that the relapse-inducing effects of cocaine and D2-like receptor agonists are mediated via common mechanisms and would provide further support for the hypothesis that D2-like receptor stimulation is crucial for cocaine-induced reinstatement of drug-seeking behavior. On the other hand, similar conclusions may not extend to combined priming with cocaine and selective D3 receptor agonists, because PD-128,907 did not alter cocaine-induced drug seeking in our study, and a D3 receptor partial agonist BP 897 inhibited cocaine-seeking behavior in a related experiment with rats (Pilla et al., 1999).

Unlike the high efficacy agonists, the D2-like low efficacy agonists terguride and SDZ-208-911 did not mimic the priming effects of cocaine and instead suppressed reinstatement of drug-seeking behavior induced by a maximally effective priming dose of cocaine. This finding is consistent with previous reports that D2-like low efficacy agonists can act as functional antagonists of cocaine self-administration in rats (Pulvirenti et al., 1998). Curiously, however, D2-like low efficacy agonists do not consistently block the discriminative stimulus effects of cocaine in monkeys (Spealman, 1995) and may actually enhance the priming effects of cocaine in rats (Weissenborn et al., 1996). These latter findings imply that the influence of D2-like low efficacy agonists on cocaine priming may vary across species and/or paradigm used.

In summary, the present results support the view that D1- and D2-like receptor mechanisms play fundamentally different roles in the reinstatement of cocaine-seeking behavior in monkeys. Stimulation of D2-like, but probably not D3-like, receptors appears to be sufficient to mimic the priming effects of cocaine, whereas stimulation of D1-like receptors appears to inhibit cocaine priming. Antagonists as well as low efficacy agonists at both D1- and D2-like receptors also inhibit reinstatement of cocaine-seeking behavior. Further exploration of neuropharmacological mechanisms underlying relapse to cocaine-seeking behavior may facilitate development of pharmacotherapies for cocaine addiction, because drugs that are effective in inhibiting reinstatement of drug-seeking in monkeys might also blunt craving and relapse in people.

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