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ORIGINAL INVESTIGATION

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Comparison of interactions of D_1-like agonists, SKF 81297, SKF 82958 and A-77636, with cocaine: locomotor activity and drug discrimination studies in rodents

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Abstract *Rationale:* Recent data suggest that dopamine (DA) D_1-like receptor full agonists may be potential pharmacotherapeutic agents for treating cocaine abuse. The structurally novel isochroman D_1-like agonist, A-77636, has not been well characterized and may prove to be useful as such an agent. *Objectives:* The interactions of cocaine and A-77636 were compared to those obtained with the better investigated benzazepine D_1-like dopamine agonists, SKF 82958 and SKF 81297. The alterations in the locomotor stimulant and discriminative-stimulus effects of cocaine by the full D_1-like dopamine receptor agonists were investigated across a full range of doses in order to characterize their interactions. *Methods:* Drug-naive Swiss-Webster mice were pretreated with SKF 81297, SKF 82958 or A-77636 (1–10 mg/kg) and cocaine (5–56 mg/kg) prior to a 30-min period in which locomotor activity was assessed. Rats were trained on a fixed ratio 20 (FR20) schedule to discriminate IP saline from cocaine (10 mg/kg) injections. Cocaine alone (1–10 mg/kg) and with either A-77636 (0.56–1.7 mg/kg), SKF 82958 (0.01–0.1 mg/kg) or SKF 81297 (0.1–0.56) were injected IP 5 min prior to a 15-min test session. *Results:* Cocaine maximally stimulated activity at 20–40 mg/kg with higher and lower doses stimulating activity less. Each D_1-like agonist produced a dose-related decrease in cocaine-induced locomotor activity and lowered its maximal rate. Each of the D_1-like agonists partially substituted for cocaine, with maximal substitution approximating 49, 35, and 24% for SKF 81297, SKF 82958, and A-77636, respectively. SKF 82958 significantly shifted the cocaine dose-effect curve approximately 3-fold to the left. With SKF 81297, there was a trend towards a leftward shift of cocaine dose effects, however the change was not statistically significant. In contrast to the other two D_1-like agonists, A-77636 either did not affect the cocaine dose-effect curve or shifted it to the right. *Conclusions:* All three agonists produced similar effects on cocaine-induced locomotor activity, however the discriminative-stimulus effects of cocaine were affected differently by the D_1 agonists. These results suggest fundamental differences in the actions of these D_1 agonists. Because A-77636 consistently attenuated the present effects of cocaine, it may prove more useful than the others as a pharmacotherapy to treat cocaine abuse.

Keywords Dopamine · D_1 dopamine receptors · Cocaine · Drug discrimination · Locomotor activity · A-77636 · SKF 81297 · SKF 82958 · Drug interactions

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Introduction

The number of cocaine-related emergency room visits and drug mentions has risen steadily from 1991 to 1998 (Office of Applied Science 2000), affirming the need for effective treatment for cocaine abuse. Several studies have suggested that D_1-like agonists have the potential to be effective, novel pharmacotherapies for treating cocaine abuse. In an early study, the partial D_1-like agonist SKF 38393 administered to squirrel monkeys self-administering cocaine selectively decreased responding for cocaine, while responding for food was relatively unaffected (Katz and Witkin 1992).

These findings were extended in later studies using full D_1-like agonists. Stimulation of D_1-like receptors with the full D_1-like agonists ABT-431 (a prodrug for the full D_1-like agonist A-86929), SKF 82958 or SKF 77434 attenuated cocaine self-administration in rats (Caine et al. 1999; Self et al. 2000). In rhesus monkeys self-administering cocaine, pretreatment with the D_1-like agonists SKF 82958 or R-6-Br-APB produced a downward shift in the cocaine dose-effect curve (Caine SB et al. 2000), although food maintained responding was also decreased. In a reinstatement model of relapse, cocaine

reliably increased responding of squirrel monkeys whose cocaine self-administration behavior had previously been extinguished. However, when cocaine was given with D_1-like agonists such as SKF 81297 and SKF 82958, those effects were attenuated (Khroyan et al. 2000). In human drug abusers, administration of ABT-431 dose-dependently decreased the subjective effects of smoked cocaine such that ratings such as "high" and "drug liking" were significantly decreased (Haney et al. 1999). Taken together, these studies suggest that D_1-like agonists may be effective treatments for cocaine abuse, although in the study by Haney et al., the D_1-like agonist ABT-431 did not alter the choice of cocaine over money reinforcement.

Both SKF 81297 (K_i=2.2 nM; D_1/D_2 ratio>454.5) and SKF 82958 (K_i=0.5 nM; D_1/D_2 ratio=176) are selective full D_1-like agonists (Andersen and Jansen 1990). Due to their affinity and efficacy profiles, SKF 81297 and SKF 82958 are commonly used as standards against which putative full D_1-like agonists are measured (Izenwasser and Katz 1993; Bergman et al. 1996; Lewis et al. 1998) It should be noted, however, that although SKF 82958 is commonly used as such a standard, in-vitro data indicate that some of its effects, and possibly those of other D_1-like agonists, may be mediated by a somewhat selective depression of slowly inactivating potassium currents (Nisenbaum et al. 1998).

Unlike the most fully studied D_1-like agonists (such as SKF 81297 and SKF 82958), A-77636 is not a benzazepine derivative. The isochroman, A-77636, has a relatively high affinity (K_i=39.8 nM) for D_1-like receptors and lower affinity for D_2 receptors, with a D_1/D_2 selectivity ratio of 59.2 (Andersen and Jansen 1990; Kebabian et al. 1992; Domino and Sheng 1993). Thus, A-77636 appears to have a somewhat weaker affinity and selectivity for D_1-like receptors as compared to SKF 81297 and SKF 82958. Using stimulation of adenylate cyclase as a measure of efficacy, the intrinsic activity of A-77636 is similar to or greater than dopamine (range=92–134% of dopamine) (Kebabian et al. 1992; Mottola et al. 1996), which is comparable to the intrinsic activity of SKF 82958 (range=94–109% of dopamine).

In vivo experiments with A-77636, although relatively uncommon, also indicate parallels with SKF 81297 and SKF 82958. Like SKF 81297 and SKF 82958, A-77636 elicits contralateral turning behavior in rats with unilateral lesions (Asin and Wirtshafter 1993; Boldry et al. 1995; Ruskin et al. 1999). In addition, A-77636 and SKF 82958 show similar efficacy in eliciting turning behavior in monkeys with unilateral MPTP lesions (Domino and Sheng 1993). Although they have significantly different durations of action (A-77636=>20 h; SKF 82958=~1 h), both SKF 82958 and A-77636 stimulated motor activity in MPTP-lesioned monkeys. As in repeated in-vitro administration experiments, there was desensitization to the behavioral effects of A-77636 (Blanchet et al. 1996).

Cocaine (5–20 mg/kg) produces reliable dose-dependent increases in locomotor activity (Dews 1953) which is attenuated when animals are pretreated with D_1-like antagonists such as SCH 23390 (Ushijima et al. 1995). Like cocaine, (Ushijima et al. 1995; Kita et al. 1999) D_1-like agonists such as SKF 81297 and SKF 82958 also produce increased locomotor activity (Halberda et al. 1997; Mori et al. 1997). Using another measure of motor activity (rotational or circling behavior), dopamine-depleted animals treated with cocaine, A-77636 or SKF 82958 increase circling behavior (Domino and Sheng 1993; Garrett and Holtzman 1996; Kimmel et al. 1997). Repeated administration of A-77636 prior to cocaine challenge attenuated cocaine-induced locomotor activity: a result that was attributed to D_1-like receptor desensitization (Asin et al. 1994). Taken together, these findings indicate that the stimulation of locomotor activity produced by cocaine may be mediated, at least in part, by D_1-like DA receptors and that D_1-like DA receptors may serve as a target for a pretreatment that could alter the effects of cocaine.

D_1-like receptors also may be involved in the underlying mechanism of the discriminative-stimulus effects of cocaine. Pretreatment with D_1-like antagonists, such as SCH 23390 (0.35 mg/kg) or SCH 39166 (0.1 mg/kg), reduce cocaine-appropriate responding when co-administered with cocaine, and shift the cocaine dose-effect curve to the right (Barrett and Appel 1989; Callahan et al. 1991; Spealman et al. 1997). Data from partial D_1-like agonists, such as SKF 38393, and cocaine drug discrimination are inconsistent. SKF 38393 (5–15 mg/kg) has been shown to partially substitute for cocaine in rats trained to discriminate 10 mg/kg cocaine from saline in some cases (Callahan et al. 1991; Witkin et al. 1991), but not in primates (Kleven et al. 1990; Spealman et al. 1991). In monkeys trained to discriminate 3 mg/kg cocaine from saline, putative full D_1-like agonists SKF 81297 (0.3 and 1.0 mg/kg) and SKF 82958 (0.1 and 0.3 mg/kg) generalized to the discriminative-stimulus effects of cocaine with approximately 40% responding on the cocaine-paired lever. When co-administered with cocaine, the D_1 agonists shifted the cocaine dose-effect curve to the left, a potentiation of cocaine's discriminative-stimulus effects (Spealman et al. 1997). These data suggest an involvement of D_1-like receptors in the discriminative-stimulus effects of cocaine.

The purpose of the current study is 2-fold. First, A-77636 was further characterized with regard to its behavioral effects in comparison to SKF 81297 and SKF 82958. Second, given the historical indication of D_1-like receptor involvement in the behavioral effects of cocaine and the recent data suggesting that D_1-like agonists are potential pharmacotherapies for cocaine abuse, three putative full D_1-like agonists, SKF 81297, SKF 82958 and A-77636 were used to investigate the potential of D_1-like agonists to modify the behavioral effects of cocaine.

Materials and methods

Subjects

Locomotor activity

Drug naive male Swiss Webster mice (Taconic Farms) weighing 18–25 g were group housed (five or six per cage) with free access

to water and food under a 12-h light/dark cycle (lights on at 7:00 a.m.). All testing was performed between 8:00 a.m. and 12:00 p.m.

Drug discrimination

Sprague-Dawley rats (Charles River Laboratories) were individually housed with water freely available, under a 12-h light/dark cycle (lights on at 7:00 a.m.). Rats were maintained at 85% of their free-feeding weight (typically 275–325 g at the start of the study). Every 30 days, the weights were increased by 5% to account for normal growth. This typically occurred five times (resulting in weights ranging from 351–415 g at the end of the study). All testing was performed between 1 p.m. and 4 p.m. Rats were fed daily rations at least 1 h after behavioral testing.

Drugs

Drugs used were (–)-cocaine hydrochloride, A-77636 [(–)-(1R,3S)-3-adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1H-2-benzapyran hydrochloride], SKF 82958 [6-chloro-7,8, dihydroxy-3-allyl-1-phenyl-2,3,4,5,-tetrahydro-1H-3-benzazepine hydrobromide] and SKF 81297 [R(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide]. All drugs were purchased from Sigma/RBI Chemical Co. and were dissolved in 0.9% NaCl. Doses were calculated as the salt forms, and all drugs were administered IP in volumes of 1 ml/kg (rats) or 10 ml/kg (mice). Two injections were administered whenever a single drug or drug combination was studied. When we refer to a drug alone, the drug was administered with a second vehicle injection as a control for the drug combinations.

Procedure

Locomotor activity

Ambulatory activity was studied using 40-cm^3 clear acrylic chambers placed inside monitors (Omnitech Electronics, Columbus, Ohio, USA) that were equipped with light-sensitive detectors spaced 2.5 cm apart along the two perpendicular walls. Mounted on opposing walls were infrared light sources that were directed at the detectors. One count of horizontal activity was registered each time the subject interrupted a single beam. Mice were pretreated with vehicle, SKF 81297 (1–10 mg/kg), SKF 82958 (1–10 mg/kg), or A-77636 (1–10 mg/kg), and vehicle or cocaine injection (5–56 mg/kg) just prior to being placed in the apparatus for 30 min, with horizontal activity counts collected every 10 min. Each dose was studied in eight mice and mice were used only once.

Drug discrimination

Rats were trained to press either of two levers under a fixed-ratio (FR) schedule of food presentation: the 20th consecutive response on one of the levers produced a food pellet (one 50 mg Precision Food Pellet; BioServe, Frenchtown, N.J., USA). Training sessions were conducted daily, Monday through Friday, within a sound-attenuating, lightproof experimental chamber. On the front wall of the chamber were two response keys (levers), stimulus lights above each of the keys, a houselight near the ceiling, and an opening through which food pellets could be delivered. Which of the two levers on which responses produced food pellets depended on whether the subject received an injection of cocaine or saline before the experimental session. Cocaine injections (10 mg/kg) were delivered on a double alternation sequence across daily sessions (e.g. vehicle-drug-drug-vehicle).

Subjects were injected and immediately placed within the chamber. During the first 5 min, no stimulus lights were illuminated and responding had no scheduled consequences. This period served to allow uptake and distribution of the drug treatments. After this pretreatment time, a 15-min session began. The houselight and the lights above the levers were on and responses on the appropriate lever counted towards completion of the FR requirement. Once a food pellet was delivered, the houselight and keylights were turned off for a 20-s time-out period during which responding had no scheduled consequences. The session ended either at the end of 15 min or after 20 food pellets were earned, whichever occurred first.

Testing began after the following criteria were met for four consecutive daily training trials: at least 80% correct overall responding during the entire session, 80% correct responding during the first FR20 only, and a response rate of at least 0.02 responses/s. After these criteria were met, animals received test doses of cocaine (0, 1, 3 and 10 mg/kg) and were randomly assigned to the A-77636 (n=6; 0.56–1.7 mg/kg), SKF 81297 (n=5; 0.1–0.56 mg/kg) or SKF 82958 (n=6; 0.01–0.1 mg/kg) test groups. Test sessions were not conducted without 2 immediately before training sessions in which the criteria were met. If the criteria were not met on both of these sessions, testing resumed after the criteria were met for four consecutive training sessions. All drug injections were given just before the start of the session, i.e. 5 min before testing, with the various doses administered in a mixed sequence.

Statistical analysis

Locomotor activity

Two-way analyses of variance (ANOVAs; α=0.05) were performed on each test drug such that the effects of cocaine, the test drug and the interaction were assessed. Tukey HSD post-hoc tests provided pair-wise comparison information for significance of individual doses compared to controls. Dunnett's pairwise comparisons (q') were used to determine differences in maximal locomotor activity.

Drug discrimination

Two-way ANOVAs (α=0.05) with Tukey HSD post-hoc tests were performed on the distribution of responses on the two keys, and on response rate data. The effects of cocaine, the test drugs, and their interactions were assessed on the distribution of responses on the two levers (from rats with response rates greater than 0.02 responses per second) and the overall rate of responding. The ED_{50} values for each drug were calculated by linear regression (Snedecor and Cochran 1967) on the full cocaine dose-effect curve or that portion that did not significantly deviate from linearity. Linear regression was used to determine any deviations of linearity.

Results

Locomotor activity

Given alone, cocaine produced effects that were similar to those reported previously. For example, cocaine at intermediate to high doses (10, 20, 40 and 56 mg/kg) produced dose-related and significant increases in locomotor activity [$F(5,90)=19.56$, $P<0.001$; Fig. 1: black circles]. The value of approximately 100 counts/min for locomotor activity obtained after two vehicle injections was increased to approximately 175 counts/min at 20–40 mg/kg cocaine. At the highest dose (56 mg/kg), locomotor activity was increased as compared to vehicle, but less so than at lower doses.

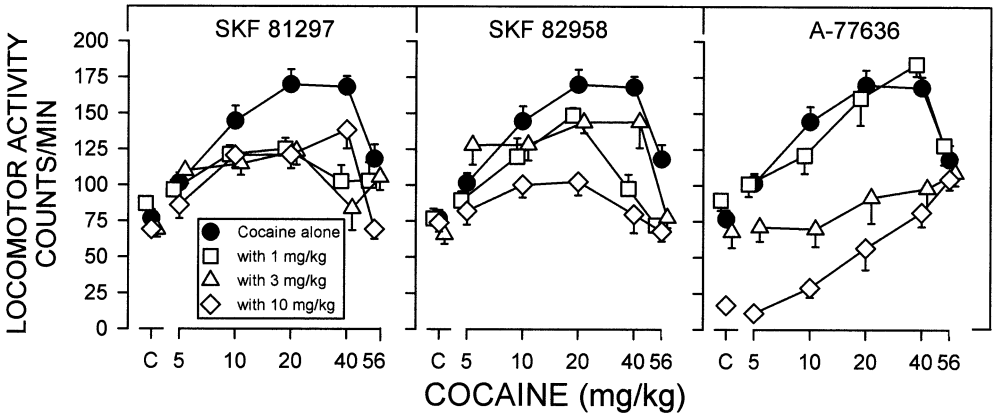

Fig. 1 The interaction between D_1-like agonists and cocaine expressed as mean locomotor counts made during a 30-min locomotor activity session. *C* indicates cocaine vehicle. The same cocaine curve is represented in all panels. *Top panel* illustrates the interaction between SKF 81297 and cocaine. SKF 82958 attenuated cocaine-induced locomotor activity and the low and moderate doses (1 and 3 mg/kg) decreased peak cocaine-induced locomotor activity. *Middle panel* illustrates the interaction between SKF 82958 and cocaine. SKF 82958 produced dose-dependent attenuation of cocaine-induced locomotor activity and the high dose (10 mg/kg) decreased peak cocaine-induced locomotor activity. *Bottom panel* illustrates the interaction between A-77636 and cocaine. The low dose of A-77636 (1 mg/kg) did not alter cocaine-induced locomotor activity, while higher doses (3 and 10 mg/kg) produced dose-related attenuation and decreased peak responding to cocaine

Significant effects were obtained with SKF 81297 [$F(3,217)=15.35$, $P>0.001$], cocaine [$F(5,217)=21.66$, $P>0.001$] and their interaction [$F(15,217)=4.40$; $P<0.001$]; however, post-hoc tests indicated no significant effects of the various doses of SKF 81297 alone compared to control (Fig. 1, left panel: compare open symbols to black dot symbols above C). All doses of SKF 81297 significantly attenuated cocaine-induced locomotor activity (Fig. 1, top panel, connected points: compare black circles to open squares, triangles, and diamonds), and the maximal cocaine-induced activity was significantly decreased at low and moderate doses (1 and 3 mg/kg) of SKF 81297 (q'=2.591 and 2.677, respectively).

As with SKF 81297, significant effects of SKF 82958 [$F(3,217)=27.08$, $P>0.001$], cocaine [$F(5,217)=28.62$, $P>0.001$] and their interaction [$F(15,217)=3.06$; $P<0.001$] were obtained. Again, over the dose range studied there were no significant effects (revealed by post-hoc tests) of the D_1-like agonist alone compared to control (Fig. 1, middle panel: compare open symbols to black circles above C). Increasing doses of SKF 82958 (1, 3 and 10 mg/kg) produced successively greater attenuation of cocaine-induced locomotor activity (Fig. 1, middle panel connected points: compare black circles to open squares, triangles, and diamonds), and the highest dose (10 mg/kg) of SKF 82958 also decreased maximal activity (q'=3.039).

Significant effects of A-77636 [$F(3,214)=77.11$, $P>0.001$], cocaine [$F(5,214)=27.24$, $P>0.001$] and their interaction [$F(15,214)=4.10$; $P<0.001$] were also obtained. In contrast to the effects observed with the benzazepines, over the dose range studied there were significant decreases in locomotor activity (revealed by post-hoc tests) produced by A-77636 alone compared to control (Fig. 1, right panel: compare open symbols to black circles above C). When administered alone, 1 and 3 mg/kg A-77636 produced little change in locomotor activity, whereas 10 mg/kg produced a significant and substantial decrease in locomotor activity.

As with the benzazepines, A-77636 attenuated cocaine-induced locomotor activity in a dose-dependent manner; the lowest dose (1 mg/kg) produced no appreciable effects while the two higher doses (3 and 10 mg/kg) significantly attenuated cocaine-induced locomotor activity (Fig. 1, right panel: compare open squares, triangles, and diamonds to black circles). At moderate and high doses (3 and 10 mg/kg), A-77636 reduced the maximal activity produced by cocaine (q'=4.989 and 5.384, respectively).

Drug discrimination

Given alone, cocaine produced dose-dependent increases in responding on the drug-paired lever (Fig. 2, top panels: black circles), with vehicle and 1 mg/kg cocaine producing little responding on the cocaine-paired lever. The dose of 3 mg/kg cocaine produced an intermediate level of cocaine-appropriate responding that was significantly greater than vehicle (based on post-hoc comparisons) only for the group studied with A-77636. The 10 mg/kg produced almost exclusive responding on the cocaine-appropriate lever, which was significantly different from vehicle in all groups. Response rates were not affected by cocaine administration (Fig. 2, bottom panels: black circles).

Significant effects were obtained with SKF 81297 [$F(3,57)=4.12$, $P>0.01$], cocaine [$F(3,57)=31.67$, $P>0.001$], but not their interaction [$F(9,57)=1.30$; $P=0.26$]. SKF 81297 alone partially generalized to the discriminative-stimulus effect of cocaine; low to moderate doses (0.1 and 0.3 mg/kg) of SKF 81297 produced little responding on the cocaine-appropriate lever, whereas the high dose (0.56 mg/kg) significantly (based on post-hoc tests) increased responding on the cocaine-appropriate lever to

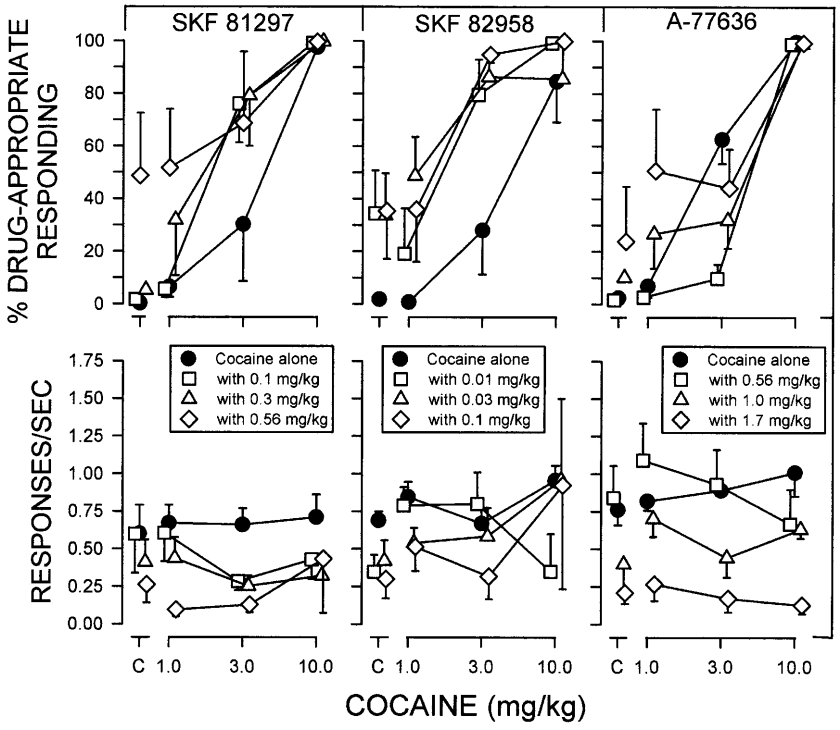

Fig. 2 Effects of D_1-like agonists on rats discriminating 10 mg/kg cocaine from vehicle under an FR20 response schedule of food presentation. *Bars* indicate standard error of the mean. *C* indicates cocaine vehicle. *Top row* illustrates the effects of the D_1-like agonists on the distribution of responses on two levers as expressed as a percentage of responding on the cocaine appropriate lever. SKF 81297 partially generalized to the discriminative-stimulus effects of cocaine and potentiated cocaine appropriate responding when co-administered with 3 mg/kg cocaine. SKF 82958 partially generalized to the discriminative-stimulus effects of cocaine and potentiated cocaine appropriate responding when co-administered with 3 mg/kg cocaine. Moderate and high doses of A-77636 (1.0 and 1.7 mg/kg) significantly reduced cocaine appropriate responding when co-administered with 3 mg/kg cocaine. *Bottom row* illustrates the effects of the D_1-like agonists on the rate of responding. Response rates were suppressed by cocaine plus SKF 81297. Response rates were not significantly affected by SKF 82958. A-77636 dose-dependently decreased response rates

approximately 50% (Fig. 2, top left panel: compare diamonds to black circles over C). SKF 81297 significantly decreased response rate, with increasing doses producing progressively lower response rates [$F(3,63)$= 8.766; Fig. 2, bottom left panel: compare open symbols to black circles].

SKF 81297 altered the discriminative stimulus effects of cocaine when the two compounds were administered in combination (Fig. 2 left panels, compare open symbols to black circles). Although the administration of 0.56 mg/kg SKF 81297 and 1.0 mg/kg cocaine increased cocaine-appropriate responding to approximately 50%, as compared to approximately 8% with cocaine alone, this difference was not significant. When SKF 81297 was co-administered with 3 mg/kg cocaine, however, post-hoc tests indicated that animals given the high dose (0.56 mg/kg) of SKF 81297 responded on the cocaine-appropriate lever significantly more than cocaine alone (approximately 75% as compared to approximately 35%). There was no effect of SKF 81297 on 10 mg/kg cocaine, as all animals responded almost exclusively on the cocaine-appropriate lever. Despite the effect at 3.0 mg/kg, there was no significant shift of the cocaine dose-effect curve, as indicated by the overlapping confidence limits of the cocaine alone and SKF 81297 plus cocaine ED_{50} values (Table 1).

Significant effects were obtained with SKF 82958 [$F(3,73)=7.96$, $P>0.001$], cocaine [$F(3,73)=25.79$, $P>0.001$], but not their interaction [$F(9,73)=0.93$; $P=0.51$]. All doses of SKF 82958 (0.01–0.1 mg/kg) partially and equally substituted (approximately 34%) for the discriminative-stimulus effects of cocaine (Fig. 2, top middle panel: open symbols above C). While SKF 82958 produced a trend towards decreasing response rate, the progressively lower response-rates were not significantly lower than those of cocaine alone (Fig. 2, bottom middle panel: compare open symbols to black circles).

SKF 82958 also altered the effects of cocaine when the two compounds were administered in combination (Fig. 2, top middle panel: compare open symbols to black circles). Enhanced cocaine-appropriate responding was obtained when any dose of SKF 82958 (0.01, 0.03 or 0.1 mg/kg) was co-administered with 1.0 mg/kg cocaine (approximately 40% as compared to 5% with cocaine alone). The distribution of responses was also altered when any dose of SKF 82958 was co-administered with 3 mg/kg cocaine, with approximately 80–95% cocaine-appropriate responding, as compared with approximately 30% after cocaine alone. In the presence of 10 mg/kg cocaine, however, lever choice was unaltered as all animals (with or without SKF 82958 dose) pressed

Table 1 ED_{50} values for the cocaine discrimination dose-effect curves (with lower and upper 95% confidence limits)[a] for each D_1-like agonist and cocaine

Compound	D_1-like agonist dose (mg/kg)	ED_{50} value (95% CL)
Cocaine alone		3.54 (2.44–5.37)
Cocaine with SKF81297	0.1	1.55 (0.18–3.06)
Cocaine with SKF 81297	0.3	2.35[b] (1.67–3.08)
Cocaine with SKF 81297	0.56	NS[c]
Cocaine alone		4.34 (2.9–7.56)
Cocaine with SKF 82958	0.01	1.92 (0.93–3.15)
Cocaine with SKF 82958	0.03	0.78 (0.002–1.74)
Cocaine with SKF 82958	1.0	1.18 (0.3–2.03)
Cocaine alone		2.65 (2.22–3.1)
Cocaine with A-77636	0.56	5.16 (4.88–5.57)
Cocaine with A-77636	1.0	4.15 (3.19–5.06)
Cocaine with A-77636	1.7	3.41 (1.29–5.02)

[a] Overlapping confidence limits indicate no significant difference in ED_{50} values of cocaine alone and those of the test drug plus cocaine. Boldface indicates no such overlap, and therefore a significant difference

[b] The value is an estimate due to a significant deviation from linearity

[c] The value was not calculated due to a lack of a significant effect of dose

almost exclusively on the cocaine-appropriate lever. With SKF 82958 there was a significant leftward shift of the cocaine dose-effect curve, as indicated by the non-overlapping confidence limits of the cocaine alone ED_{50} values and those of 0.03 and 1.0 mg/kg SKF 82958 plus cocaine confidence limits (Table 1).

Significant effects were obtained with A-77636 [$F(3,75)=6.12$, $P>0.001$], cocaine [$F(3,75)=85.32$, $P>0.001$], as well as their interaction [$F(9,75)=2.87$; $P=0.01$]. A-77636 significantly altered lever selection and produced dose-dependent partial generalization to cocaine (Fig. 2, top right panel: compare open symbols with black circles). The lowest dose (0.56 mg/kg) produced very little responding on the cocaine-appropriate lever (2%) and the highest dose (1.7 mg/kg) produced approximately 25% cocaine-appropriate responding. Unlike cocaine, A-77636 dose-dependently decreased response rates [$F(3,80)=20.182$; Fig. 2: bottom right panel: compare open symbols and black circles] from 0.84 responses per second (0.56 mg/kg) to 0.21 responses per second (1.7 mg/kg).

In contrast to the effects of the benzazepines, A-77636 did not shift the cocaine dose effect curve to the left (Fig. 2C: top panel: compare black circles to open symbols). At the lowest dose of cocaine A-77636 produced a dose-related increase in responding on the cocaine-appropriate key. In contrast at the intermediate dose of cocaine, A-77636 (1.0 and 1.7 mg/kg) significantly reduced cocaine-appropriate responding as compared to cocaine alone. At the highest dose of cocaine (10 mg/kg), lever selection was not altered as all animals (with or without A-77636) pressed almost exclusively on the cocaine-appropriate lever. The portion of the cocaine dose-effect curve that was linear in the presence of A-77636 (3.0–10.0 mg/kg) was significantly shifted to the right by 0.56 and 1.0 mg/kg A-77636, as indicated by the lack of overlap of the confidence limits for the ED_{50} values (Table 1).

Discussion

Cocaine produced reliable dose-dependent increases in horizontal locomotor activity, as has been previously shown (Dews 1953; Sahakian et al. 1975; Kelly and Iversen 1976; D'Mello and Stolerman 1977; Ushijima et al. 1995; Kita et al. 1999), with peak activity occurring at either 20 or 40 mg/kg. Although neither benzazepine increased horizontal motor activity, others have found increases at doses similar to, or lower than, the lowest dose used in the current experiment (Arnt et al. 1992; O'Neill and Shaw 1999). It is possible that the doses used in the current experiment were beyond those that would increase locomotion.

Across the doses studied, the D_1-like agonist A-77636, but not SKF 81297 or SKF 82958, produced significant decreases in locomotor activity when administered alone, though the benzazepines would have likely decreased activity at sufficiently high doses. The locomotor depression produced by A-77636 is consistent with a previous report showing a decrease in the locomotor activity of rats after a single dose of A-77636 (Asin et al. 1994). These same authors reported an increase in contralateral rotation in nigrostriatal lesioned rats after injection of A-77636 (Asin and Wirtshafter 1993). Much of the current literature on the motor effects of A-77636 focused on effects in animals with DA depletions and/or brain lesions (Kebabian et al. 1992; Asin and Wirtshafter 1993; Pearce et al. 1995), leaving a gap in information on the effects of this drug in intact subjects.

As has been reported many times, rats trained to discriminate cocaine from saline showed a dose-dependent generalization to test doses of cocaine (e.g. Jarbe 1978; Colpaert et al. 1979). When administered alone, all of the D_1-like agonists studied partially substituted for cocaine. These findings are generally corroborated by previous findings; however, there are currently no published studies in which rodents are trained in a cocaine-discrimination procedure and challenged with these full D_1-like agonists. Squirrel monkeys trained to discriminate cocaine from saline pressed the cocaine-appropriate lever approximately 40–70% when given SKF 81297 or SKF 82958 challenge (Spealman et al. 1991, 1997). Cocaine partially substituted in monkeys trained to discriminate SKF 81297 from saline (Rosenzweig-Lipson and Bergman 1993), and in rats trained to discriminate SKF 82958 from saline (Haile et al. 2000). It is interesting to note that experimental history may also affect degree of substitution, as Caine SM et al. (2000) have found that several D_1 agonists (including SKF 82958) substitute for cocaine only in rats with less discrimination experience (9 months as opposed to 24 months). In the current study,

both SKF 82958 and SKF 81297 partially substituted for cocaine. Perhaps a truncated training procedure would result in a greater degree of substitution.

Because of suggestions in the literature that D_1-like dopaminergic agonists might serve as potential treatments for cocaine abuse (e.g. Spealman et al. 1992; Bergman 1994), the present study examined the effects of the present full D_1-like agonists in combination with cocaine. Previous studies have shown that D_1-like antagonists and partial agonists attenuated the reinforcing and discriminative-stimulus effects of cocaine (e.g. Katz and Witkin 1992; Spealman et al. 1997; Katz et al. 1999; Caine SB et al. 2000). These studies have focused primarily on antagonists and partial agonists; however, recent reports by Caine SB et al. (1999, 2000) have suggested that full agonists can also substantially alter the effects of cocaine. In those studies, the full agonists, SKF 82958 in rats or rhesus monkeys and R-6-Br-APB in rats decreased the maximal rate of responding maintained by cocaine. In the present study, the full agonists SKF 81297, SKF 82958, and A-77636, each produced a decrease in the maximal amount of cocaine-induced stimulation of locomotor activity. The alterations in these dose-effect curves were reminiscent of those presented by Caine and his colleagues for cocaine self-administration.

The decreased response to cocaine generally occurred across the range of cocaine doses, and occurred at doses of the benzazepine D_1-like agonists that were inactive when administered alone. However, only doses of A-77636 that were active when administered alone were active in altering the locomotor stimulant effects of cocaine. With regard to this comparison of the potencies to alter cocaine effects and those for "intrinsic" actions, the effects of the present benzazepine agonists are similar to those obtained with D_1-like antagonists (Katz et al. 1999). In contrast with D_2-like dopamine antagonists, alterations in the effects of cocaine are obtained only at doses that by themselves have activity (Chausmer and Katz 2001). It is not currently clear whether a comparison of the potencies to alter cocaine effects and those for "intrinsic" actions has any predictive validity for a therapeutic index, if these compounds are eventually utilized in a therapeutic setting.

The interactions between the benzazepine agonists and cocaine in rats trained to discriminate cocaine from saline are similar to reports in the literature. For example, Spealman et al. (1997) reported that SKF 81297 and SKF 82958 each shifted the dose-effect curve for cocaine to the left approximately 2-fold. Similar results were reported for the full agonists 6-Br-APB (Platt et al. 2000) and SKF 83189 (Spealman et al. 1997). This type of finding, a potentiation of the interoceptive effects of cocaine, may be best considered as a type of potential "agonist therapy" like methadone for heroin-dependent patients.

In contrast to the effects of the benzazepines, A-77636 produced a small but significant shift to the right in the cocaine dose-effect curve. This unexpected interaction is obviously more similar to what would be expected for an antagonist, though the mechanism for it is currently not clear. It should be noted that at the lowest dose of cocaine, A-77636 enhanced the effects of cocaine, an effect similar to that obtained with the benzazepines. In contrast, A-77636 decreased effects at the intermediate, but not the highest, dose of cocaine. However, with these particular subjects, the effects of cocaine alone were greater than those obtained with the others (compare black circles across the three panels of Fig. 2). Had these subjects responded to cocaine as did the others, it is unlikely that A-77636 would have significantly attenuated the effects of the intermediate dose of cocaine. Nonetheless, it is apparent from the present study that behaviorally active doses of A-77636 have effects in combination with cocaine that differ from those of the benzazepines.

Both SKF 81297 and SFK 82958 are self-administered (Grech et al. 1996; Weed et al. 1997; but see Caine et al. 1999). Although A-77636 has yet to be investigated in a self-administration experiment, ABT-431, a drug that is metabolized to the D_1-like agonist A-86929, is not self-administered by monkeys (Giardina et al. 2000). A-86929 shares some structural characteristics with A-77636 (Shiosaki et al. 1996), suggesting that A-77636 might also fail to support self-administration. These data, coupled with its long duration of action, suggest that A-77636 may be a possible pharmacotherapeutic agent to treat cocaine abuse.

It is now clear that there are some interesting differences among drugs classified as D_1-like agonists. Studies with genetically altered D_1 knockout mice indicate that despite the absence of this receptor "prototypical" D_1 agonist effects are obtained (Clifford et al. 1999). Further, studies of the atypical benzazepine, SKF 83959, show that "prototypical" D_1 agonist effects can be obtained with a compound that does not stimulate adenylyl cyclase (Deveney and Waddington 1995). Finally, there appears to be a class of D_1-like receptors that express their actions through phospholipase C signal transduction pathways (Undie et al. 1994). These studies together indicate a rich diversity in the pharmacology and mechanisms for D_1 dopamine systems that needs to be more fully explored and may illuminate new avenues for understanding the effects of psychomotor stimulants and their abuse.

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