ELSEVIER

European Journal of Pharmacology 388 (2000) 125–131

ejp

www.elsevier.nl/locate/ejphar

The dopamine D_1 receptor agonist SKF-82958 serves as a discriminative stimulus in the rat

Colin N. Haile [1], Galen Carey [*], Geoffrey B. Varty, Vicki L. Coffin

CNS / CV Biological Research, K15-2-2600, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-1300, USA

Received 26 August 1999; received in revised form 26 November 1999; accepted 30 November 1999

Abstract

We examined the discriminative stimulus effects of the high-efficacy dopamine D_1 receptor agonist (±)6-chloro-7,8-dihydroxy-3-ally1-phenyl-2,3,4,5-tetrahydro-1*H*-3benzazepine hydrobromide (SKF-82958) in rats trained to discriminate SKF-82958 (0.03 mg/kg) from vehicle in a two-lever food-reinforced drug discrimination task. SKF-82958 produced dose-related increases in responding to the SKF-82958 appropriate lever with full substitution occurring at the training dose. Pretreatment with the dopamine D_1/D_5 receptor antagonist (−)-*trans*-6,7,7a,8,9,13*b*-hexahydro-3-chloro-2hydroxy-*N*-methyl-5*H*-benzo-[*d*]naphtho-{2,1-*b*}azepine (SCH-39166) (0.01 mg/kg) attenuated the discriminative stimulus effects of SKF-82958. Pretreatment with the dopamine D_2 receptor antagonist raclopride (0.03 mg/kg) had no effect. The high-efficacy dopamine D_1 receptor agonist *R*(+)6chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF-81297) fully substituted for SKF-82958, whereas the low-efficacy dopamine D_1 receptor agonist (±)1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride (SKF-38393) produced only partial substitution. The dopamine D_2 receptor agonist *trans*-(±)-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-propyl-1*H*-pyrazolo[3,4-g]quinoline dihydrochloride (quinpirole) and the indirect dopamine agonist cocaine did not substitute fully for the SKF-82958 discriminative stimulus cue. These results demonstrate that the high-efficacy dopamine D_1 receptor agonist SKF-82958 can serve as an effective discriminative stimulus in the rat, and that these effects are mediated by a dopamine D_1-like receptor mechanism.

Keywords: Dopamine; Dopamine D_1 receptor agonist; Drug discrimination; SKF-82958; SCH-39166; Cocaine; (Rat)

1. Introduction

Cocaine abuse continues to be a major health concern in most of the areas of the world and the lack of suitable pharmacotherapies underscores the need for research into the neurobiological mechanisms that mediate its effects (Mendelson and Mello, 1996). The ability of cocaine to act as an indirect agonist at the central dopamine receptor is thought to underlie its subjective and reinforcing effects (Wise and Rompre, 1989; Spealman et al., 1992; Koob and Nestler, 1997). This notion is supported by the well-established role of the mesolimbic dopamine system and dopamine receptors in psychostimulant reinforcement (Roberts and Koob, 1982; Roberts et al., 1977; Caine and Koob, 1994).

The drug discrimination paradigm has proven useful in determining the receptor subtypes involved in producing the stimulus properties of drugs in vivo. Cocaine drug discrimination studies have shown that in general, both dopamine D_1-like (D_1 and D_5) and dopamine D_2-like receptors (D_2, D_3, and D_4) are involved in producing its interoceptive effects (Witkin, 1994; Callahan et al., 1997). For instance, both dopamine D_1 and D_2 receptor agonists were shown to substitute for cocaine in rats (Witkin et al., 1991; Callahan and Cunningham, 1993; Kantak et al., 1995) and monkeys (Kleven et al., 1990; Spealman et al., 1991), though other studies have failed to replicate these findings (Barrett and Appel, 1989; Kleven et al., 1990; Broadbent et al., 1991; Filip and Przegalinski, 1997). Furthermore, dopamine D_1 receptor antagonists such as SCH-23390 and (−)-*trans*-6,7,7a,8,9,13*b*-hexahydro-3-

* Corresponding author. Tel.: +1-908-740-3648; fax: +1-908-740-3294.

E-mail address: galen.carey@spcorp.com (G. Carey).

[1] Present address: Department of Neurosurgery, Thomas Jefferson Medical College, CNS Gene Therapy Center, 1025 Walnut Street, Philadelphia, PA 19107.

0014-2999/00/$ - see front matter
PII: S0014-2999(99)00864-X

chloro-2hydroxy-*N*-methyl-5*H*-benzo-[*d*]naphtho-{2,1-*b*} azepine (SCH-39166) appear to block the discriminative stimulus properties of cocaine more effectively than dopamine D_2 receptor antagonists in rats (Barrett and Appel, 1989; Callahan et al., 1991, 1994; Witkin et al., 1991; Baker et al., 1993), rhesus monkeys (Kleven et al., 1990), and squirrel monkeys (Spealman et al., 1991; 1997). Thus emphasizing a significant contribution of a dopamine D_1-like receptor mechanism in producing the interoceptive stimulus properties of cocaine (Callahan et al., 1994, 1997; Witkin, 1994).

A number of studies had evaluated whether dopamine D_1 receptor agonists can serve as discriminative stimuli in drug discrimination experiments. For example, the low-efficacy dopamine D_1 receptor agonist (±)1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride (SKF-38393) was shown to serve as a reliable discriminative stimulus in the rat where its effects are blocked by the dopamine D_1 receptor antagonist SCH-23390, but not dopamine D_2 receptor antagonists (Cunningham et al., 1985; Kamien and Woolverton, 1985; Kamien et al., 1987; Arnt, 1988). Furthermore, the high-efficacy dopamine D_1 receptor agonist *R*(+)6chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF-81297) produced discriminative stimulus effects in rats (Reavill et al., 1993) and in squirrel monkeys (Rosenzweig-Lipson and Bergman, 1993) that were blocked by the dopamine D_1 receptor antagonists SCH-23390 and SCH-39166, but not by dopamine D_2 receptor antagonists, demonstrating specificity of the interoceptive stimulus properties of SKF-81297 at dopamine D_1 receptors. Moreover, several studies have demonstrated that the discriminative stimulus effects of certain dopamine D_1 receptor agonists are not reproduced by the indirect dopamine receptor agonists cocaine or D-amphetamine. For instance in rats, neither cocaine nor D-amphetamine fully substituted for the dopamine D_1 receptor agonists SKF-81297 (Reavill et al., 1993) and dihydrexidine (Schechter, 1995). Similarly in squirrel monkeys, Rosenzweig-Lipson and Bergman (1993) demonstrated that cocaine or D-amphetamine did not reproduce the discriminative stimulus effects of SKF-81297. Together, these results suggest that the discriminative-stimulus effects of high- and low-efficacy dopamine D_1 receptor agonists are mediated by a D_1-like mechanism, and that psychostimulants do not fully reproduce these effects.

To our knowledge, the high-efficacy dopamine D_1 receptor agonist (±)6-chloro-7,8-dihydroxy-3-ally 1-phenyl-2,3,4,5-tetrahydro-1*H*-3 benzazepine hydrobromide (SKF-82958) has not been used as a discriminative stimulus in rat. Therefore, the purpose of the present study was to extend the above findings by determining (a) whether SKF-82958 could indeed serve as a discriminative stimulus in rats, (b) if the effects of SKF-82958 are mediated by a dopamine D_1-like receptor mechanism in vivo, and (c) whether cocaine would substitute for SKF-82958 cue.

2. Materials and methods

2.1. Animals and housing

Eight experimentally naive male Sprague Dawley rats (Charles River Breeding, Wilmington, MA) weighing 250–350 g at the beginning of the study were used. Rats were housed individually in hanging wire-mesh cages in a temperature-controlled environment under a 12:12 light/dark cycle (lights on at 0700 h). Water was available ad libitum. Food (rat chow) was available on a limited basis, in order to maintain rats at 85% of their free feeding body weight. All studies were carried out in strict accordance with guidelines established by Schering-Plough and its Animal Care and Use Committee.

2.2. Apparatus

Drug discrimination training and testing were carried out in a separate experimental room in eight standard two-lever operant conditioning boxes. All equipment and software were supplied by MED Associates (East Fairfield, VT, USA). Two response levers were located on the front wall, 2 cm from the floor and approximately 7 cm apart. An amber stimulus light was located above each lever, with a ''houselight'' located on the opposite wall. A recessed food receptacle was located centrally (10 cm from the floor) between the two levers into which 45 mg food pellets (Bio-Serv, Frenchtown, NJ, USA) were dispensed. Testing boxes were housed in ventilated sound-attenuated chambers. Experimental parameters were scheduled using a WINDOWS-based software package linked to the testing chambers via an interface system. Real-time response records were recorded and observed using an additional software package (SmartCR, version 1.1) on a separate PC.

2.3. Drug discrimination training

Procedures that were used to train rats to discriminate injections of SKF-82958 (0.03 mg/kg) from saline were similar to those described by Kosten et al. (1999). Rats were first food restricted and maintained at approximately 85% of their free feeding body weight. During initial training, rats were placed into the operant chambers, where the stimulus light above one of the levers was illuminated to signal the beginning of the session. Lever pressing was shaped progressively until 30 responses [fixed ratio 30 (FR30)] were emitted to obtain one food pellet reinforcer. Once stable responding under the FR30 schedule was achieved on either lever, SKF-82958 discrimination training began. For half of the rats, the left lever was designated as the SKF-82958 appropriate lever and for the other half, the right lever as the SKF-82958 appropriate. On SKF-82958 training days, the drug was administered intra-

peritoneally (i.p.) and the rats were placed in the operant chamber. The session began 15 min later when the stimulus lights above the levers were illuminated. Every thirtieth response on the SKF-82958-appropriate lever produced a food pellet. On vehicle training days, vehicle was administered i.p. and 15 min later, every 30th response on the vehicle-appropriate lever produced a food pellet. Training sessions ended after 30 min of responding. During training, a double alternation sequence of drug or vehicle injection (SKF, SKF, saline, saline, SKF, etc.) was utilized, with training sessions occurring 5 days per week. Initially, 1.0 mg/kg SKF-82958 was used for the training dose, however, this dose profoundly disrupted lever pressing as shown by rate and response records. The training dose was then lowered to 0.3 mg/kg, where response disruption was also observed. Eventually, the training dose was adjusted to 0.03 mg/kg. At this dose, no overt rate disruption was observed. Discrimination training with this dose of SKF-82958 continued until rats met the following criteria: (1) the first completed FR30 was on the injection-appropriate lever and (2) $\geq 85\%$ of total responses made were on the injection-appropriate lever for six consecutive sessions.

2.4. Discrimination testing

Once the above criteria were met, substitution tests began. Tests were usually performed twice a week with the discrimination training occurring on the intervening days. If discrimination performance fell below 85% on these training days, testing was not performed, and rats were given further discrimination training. If rats maintained $\geq 85\%$ condition-appropriate responding on training days, tests were performed on the following day, otherwise at least two training sessions separated each testing session. Test sessions were identical to training sessions with the exception that rats could obtain food reinforcement by completing 30 responses on either lever.

Substitution tests were performed with different doses of SKF-82958 (0.003–0.1 mg/kg), SKF-81297 (0.1–1.0 mg/kg), SKF-38393 (0.3–5.6 mg/kg), *trans*-(±)-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-propyl-1*H*-pyrazolo-[3,4-*g*]quinoline dihydrochloride (quinpirole) (0.01–0.1 mg/kg) and cocaine (0.3–5.6 mg/kg). In antagonism studies, combinations of different doses of SKF-82958 and the dopamine D_1/D_5 receptor antagonist SCH-39166 (0.01 mg/kg) or the dopamine D_2 receptor antagonist raclopride (0.03 mg/kg) were studied. The order of substitution and combination agonist/antagonist tests was presented non-systematically across rats.

2.5. Drugs and injections

SKF-82958, SKF-81297, SKF-38393, quinpirole, cocaine hydrochloride, and *S*(−) raclopride L-tartrate, were all purchased from RBI (Natick, MA). SCH-39166 was synthesized at Schering-Plough (Bloomfield, NJ).

All compounds were freshly prepared on the day of the experiment in 0.9% NaCl and administered in a volume of 1 ml/kg. To ensure solubility, SKF-82958, SKF-81297, and SKF-38393 were sonicated in a heated water bath for 30 min (1 mg/ml) before dilution. Pretreatment time for each drug was 15 min and drugs were administered via i.p. injection with the exception of SCH-39166 and raclopride. Both SCH-39166 and raclopride were administered subcutaneously with a pretreatment time of 30 min. All doses are expressed as free base.

2.6. Data analysis

The percentage of SKF-82958 appropriate responding [i.e., (total SKF-82958 lever responses/total lever responses) × 100] and response rates (total lever responses/time for which stimulus lights were illuminated) were determined for each test session. Each data point is the mean (±1 S.E.M.) of six to seven rats. The criterion for full substitution was set at $\geq 85\%$, and partial substitution at 50–84% of the total responses on the SKF-82958 appropriate lever. Response rates were analyzed across doses with repeated measure analyses of variance (ANOVA) with treatment and/or pretreatment as within subject factors. Significance was set at $P < 0.05$.

3. Results

3.1. SKF-82958 dose response curve

At the training dose (0.03 mg/kg), seven rats acquired SKF-82958 discrimination in 33 training sessions. One rat failed to learn the discrimination within 78 training trials and was excluded from the study. Under training conditions, response rates were 1.73 ± 0.45 and 1.57 ± 0.42 responses/s following vehicle and SKF-82958 (0.03 mg/kg) administration, respectively. Administration of increasing doses of SKF-82958 (0.003–0.1 mg/kg) resulted in dose-dependent increases in responding on the SKF-82958 appropriate lever ($N = 7$; Fig. 1), with full substitution (> 85%) following administration of the SKF-82958 training dose (0.03 mg/kg). Increasing the dose of SKF-82958 also resulted in a significant reduction in response rate [$F(4,24) = 3.0$, $P < 0.05$; see Fig. 1].

3.2. Substitution tests

Administration of increasing doses of SKF-81297 engendered dose-related increases in responding on the SKF-82958 appropriate lever. An intermediate dose of SKF-

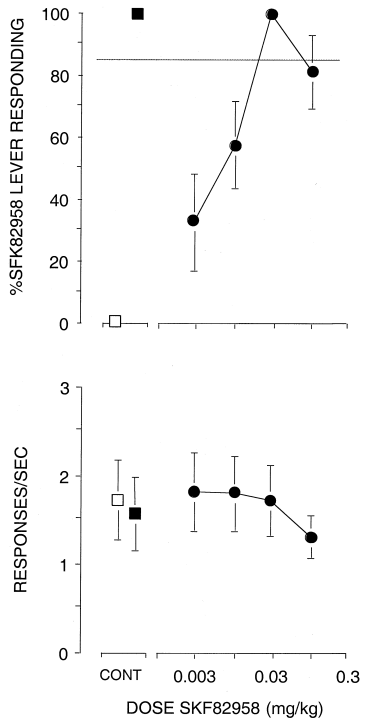

Fig. 1. Mean (±S.E.M.) percentage of responding to the SKF-82958 appropriate lever (upper panel) and mean (±S.E.M.) response rates (lever presses/s; lower panel) following administration of various doses of SKF-82958 in rats trained to discriminate SKF-82958 from vehicle. Data indicated over CONT represent mean (±S.E.M.) responding under SKF-82958 (■) and vehicle (□) training conditions.

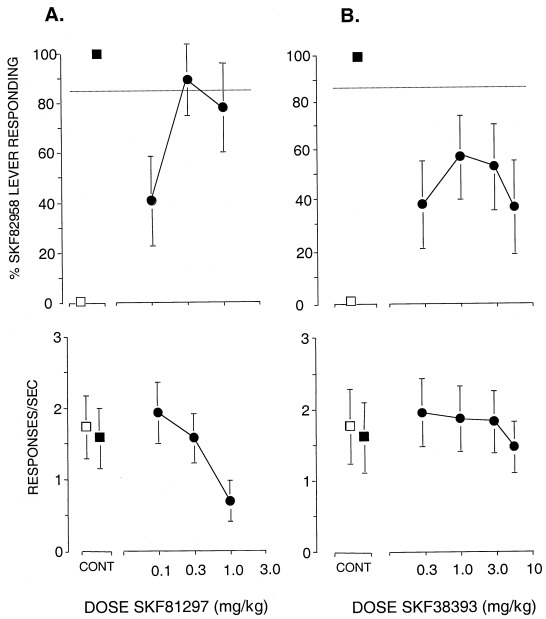

Fig. 2. Mean (±S.E.M.) percentage of responding to the SKF-82958 appropriate lever (upper panel) and mean (±S.E.M.) response rates (lever presses/s; lower panel) following administration of various doses of the D_1 agonists SKF-81297 (A) and SKF-38393 (B). Data indicated over CONT represent mean (±S.E.M.) responding under SKF-82958 (■) and vehicle (□) training conditions.

81297 (0.3 mg/kg) fully substituted for the SKF-82958 cue (89 ± 14%) (Fig. 2A). Administration of a higher dose of SKF-81297 (1.0 mg/kg) produced slightly less SKF-82958 lever responding (78 ± 17%). Increasing doses of SKF-81297 dose-dependently decreased rates of responding [$F(3,18) = 12.7$, $P < 0.001$, see Fig. 2A].

The effects of SKF-38393 are shown in Fig. 2B. SKF-38393 did not produce full substitution at any dose tested. Following administration of intermediate doses of SKF-38393 (1.0 and 3.0 mg/kg), partial substitution (55–59%) for the SKF-82958 cue was observed. Administration of a higher dose of SKF-38393 (5.6 mg/kg) did not produce further increases in SKF-82958 appropriate responding. At the doses tested, SKF-38393 produced dose-related decreases in response rate [$F(4,20) = 5.3$, $P < 0.01$].

The dopamine D_2 receptor agonist quinpirole (0.01–0.1 mg/kg) did not substitute for the SKF-82958 cue at any dose tested (26–38%, Fig. 3A) and significantly decreased response rate in a dose dependent manner [$F(3,15) = 16.9$, $P < 0.01$; see Fig. 3A]. The indirect dopamine receptor agonist cocaine (0.3–5.6 mg/kg) similarly did not engender full SKF-82958 appropriate lever responding (16–45%, Fig. 3B). Cocaine produced a maximum of approximately 45% SKF-82958 appropriate drug lever responding following a dose of 3.0 mg/kg. At the doses tested, cocaine had no effect on response rate [$F(4,24) = 1.04$, $P = 0.41$; see Fig. 3B].

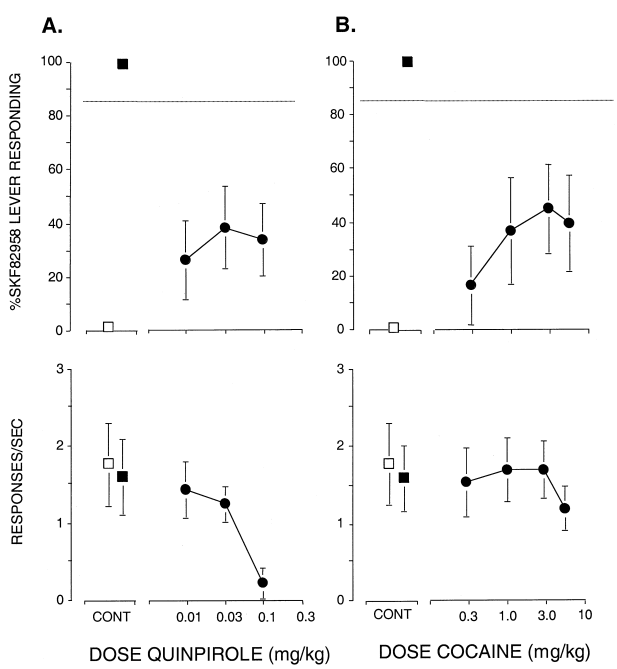

Fig. 3. Mean (±S.E.M.) percentage of responding to the SKF-82958 appropriate lever (upper panel) and mean (±S.E.M.) response rates (lever presses/s; lower panel) following administration of various doses of quinpirole (A) and various doses of cocaine (B). Data indicated over CONT represent mean (±S.E.M.) responding under SKF-82958 (■) and vehicle (□) training conditions.

3.3. Antagonism of the SKF-82958 cue

Pretreatment with the dopamine D_1/D_5 receptor antagonist SCH-39166 attenuated the discriminative stimulus effects of SKF-82958. Following administration of the training dose of SKF-82958 (0.03 mg/kg), SCH-39166 (0.01 mg/kg) reduced SKF-82958 appropriate lever responding from 100% to approximately 40% (see Fig. 4A). Furthermore, there was a significant effect of SCH-39166 to reduce response rate. Specifically, there was a significant main effect of SCH-39166 pretreatment [$F(1,15) = 9.9$, $P = 0.025$], no effect of SKF-82958 treatment [$F(3,15) = 0.76$, $P = 0.53$], and a significant pretreatment by treatment interaction [$F(3,15) = 5.9$, $P < 0.001$]. Analysis using paired samples *t*-tests indicated that lever pressing rate was decreased significantly at 0.003–0.03 mg/kg SKF-82958 ($P < 0.01$ at all doses) in combination with SCH-39166 (see Fig. 4A).

The results of the combination tests with various doses of SKF-82958 and raclopride (0.03 mg/kg, $N = 6$) are shown in Fig. 4B. A dose of raclopride that has been previously shown to block the discriminative stimulus effects of D-amphetamine (Varty and Higgins, 1997) did not systematically alter the discriminative stimulus effects of SKF-82958. However, raclopride decreased SKF-82958 appropriate lever responding (to 71 ± 16%) at the training dose (0.03 mg/kg). Response rate was appreciably decreased with every combination of raclopride and SKF-82958 tested (see Fig. 4B) but this effect did not reach significance (raclopride pretreatment [$F(1,15) = 1.8$, $P = 0.24$]; SKF-82958 treatment [$F(3,15) = 2.5$, $P = 0.12$]; raclopride–SKF-82958 interaction [$F(3,15) = 0.5$, $P = 0.7$]).

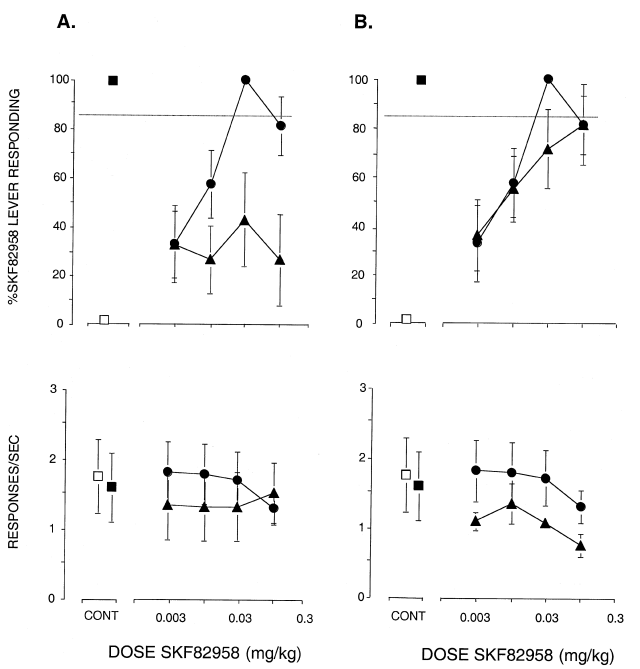

Fig. 4. (A) Mean (±S.E.M.) percentage of responding to the SKF-82958 appropriate lever (upper panel) and mean (±S.E.M.) response rates (lever presses/s; lower panel) following pretreatment with the D_1/D_5 antagonist SCH-39166 (0.01 mg/kg). Data points (●) indicate various doses of SKF-82958 alone and (♦) in presence of SCH-39166. (B) Data points (●) indicate doses of SKF-82958 alone and (♦) in presence of D_2 antagonist raclopride (0.01 mg/kg) in combination with various doses of SKF-82958. Data indicated over CONT represent mean (±S.E.M.) responding under SKF-82958 (■) and vehicle (□) training conditions.

4. Discussion

The present study demonstrates that the high-efficacy dopamine D_1 receptor agonist SKF-82958 can serve as an effective discriminative stimulus in the rat. Pretreatment with SCH-39166, a selective dopamine D_1/D_5 receptor antagonist, attenuated the discriminative stimulus effects of SKF-82958. In contrast, pretreatment with the dopamine D_2 receptor antagonist raclopride, did not result in appreciable antagonism. The antagonism of the SKF-82958 cue by a dopamine D_1 receptor antagonist is consistent with previous studies where the discriminative stimulus effects of the dopamine D_1 receptor agonists SKF-38393 and SKF-81297 were selectively attenuated by the dopamine D_1 receptor antagonist SCH-23390 (Cunningham et al., 1985; Kamien et al., 1987; Arnt, 1988; Reavill et al., 1993). Although not tested in this study, it would have been of interest to ascertain whether the antagonism of SKF-82958 by SCH-39166 was surmountable. Nonetheless, these results demonstrate clearly that the discriminative stimulus effects of SKF-82958 are primarily mediated by an interaction at dopamine D_1-like receptors.

Specificity of the SKF-82958 discriminative stimulus effects were further evident from substitution tests performed with the high- and low-efficacy dopamine D_1 receptor agonists SKF-81297 and SKF-38393, and the dopamine D_2 receptor agonist quinpirole, respectively. SKF-81297 fully substituted for the SKF-82958 cue at an intermediate dose, whereas the low-efficacy dopamine D_1 receptor agonist SKF-38393 only partially substituted even up to doses that markedly reduced responding. Furthermore, quinpirole did not reproduce the discriminative stimulus effects of SKF-82958 at the doses tested. Together, this pattern of substitution further confirms the D_1-like nature of the SKF-82958 discriminative stimulus.

High-efficacy dopamine D_1 receptor agonists are known to stimulate adenylate cyclase in in vitro rat brain preparations (Stoof and Kebabian, 1981; Izenwasser and Katz, 1993). SKF-82958 stimulates adenylate cyclase with efficacy similar to that of dopamine (O'Boyle et al., 1989, Anderson and Jansen, 1990; Izenwasser and Katz, 1993). In the same studies, SKF-81297 produced similar degrees of adenylate cyclase activation (81–100%) as dopamine and SKF-82958, whereas SKF-38393 stimulated adenylate cyclase to a lesser degree (45–60%). Together with the

present findings, these data suggest that when high-efficacy dopamine receptor agonists are used as discriminative stimuli, only agonists with similar degrees of intrinsic efficacy are able to reproduce these effects, as evidenced from the full and partial substitution patterns observed with SKF-81297 and SKF-38393, respectively. In contrast, these results are not consistent with Reavill et al. (1993) who showed that SKF-38393 fully substituted for the high-efficacy dopamine D_1 receptor agonist SKF-81297. More likely, this is due to differences in experimental testing procedures used between the studies and inherent differences in the stimulus properties of the two dopamine D_1 receptor agonists (Rosenzweig-Lipson and Bergman, 1993). In this regard, perhaps further research (i.e., using different training doses) will help characterize these compounds as discriminative stimuli.

The findings in the present study that the preferential dopamine D_2 receptor agonist quinpirole did not substitute for the SKF-82958 cue, even when used at doses that decreased response rate, is consistent with other studies showing that dopamine D_2-like receptor agonists do not substitute for dopamine D_1-like receptor agonists and vice versa (Cunningham et al., 1985; Kamien et al., 1987; Arnt, 1988; Reavill et al., 1993). Together, the findings that the discriminative stimulus effects of SKF-82958 are reproduced only by similar dopamine D_1 receptor agonists and not by a dopamine D_2 receptor agonist, and are attenuated by the selective dopamine D_1/D_5 receptor antagonist SCH-39166 but not by the dopamine D_2 receptor antagonist raclopride, suggest that the SKF-82958 interoceptive stimulus is mediated via an interaction at dopamine D_1 receptors.

Also in the present study, substitution tests with various doses of indirect dopamine receptor agonist cocaine did not fully substitute for the SKF-82958 discriminative stimulus cue. It is possible that administration of higher doses of cocaine (highest dose tested 5.6 mg/kg) would have fully reproduced the discriminative stimulus effects of SKF-82958, but they were not tested during the course of the present experiments. However, when the similarly efficacious dopamine D_1 receptor agonist SKF-81297 was used as the discriminative stimulus in squirrel monkeys, neither cocaine nor D-amphetamine fully substituted up to doses that disrupted responding (Rosenzweig-Lipson and Bergman, 1993). In addition, these data are consistent with others that show the converse to be true, where high- and low-efficacy dopamine D_1 receptor agonists do not reliably substitute for psychostimulants. For example, in rats, SKF-38393 did not substitute for cocaine (Barrett and Appel, 1989; Filip and Przegalinski, 1997) or D-amphetamine (Furmidge et al., 1991). Similarly, SKF-81297 did not fully reproduce the effects of D-amphetamine (Furmidge et al., 1991; Reavill et al., 1993), and dihydrexadine did not substitute for cocaine (Witkin et al., 1991). Also, in primates, the dopamine D_1 receptor agonists SKF-82958 and SKF-81297 only partially reproduced the effects of cocaine, even when used at doses that decreased response rates considerably (Spealman et al., 1991). Therefore, based on results from the present experiment and others, there does not appear to be full overlap between the mechanisms underlying the discriminative stimulus effects of dopamine D_1 receptor agonists such as SKF-82958 and psychostimulants such as cocaine and vice versa.

Recently, it has been suggested that dopamine D_1-like receptor agonists may serve as a possible 'replacement' pharmacotherapy for cocaine addiction in part because the high-efficacy dopamine D_1 receptor agonist SKF-82958, utilized in the present drug discrimination experiments, has been shown to block the reinstatement of cocaine self-administration in rats following a short extinction period (Self et al., 1996a). However, the doses of SKF-82958 utilized in the aforementioned studies produced marked rate disruption in our hands, suggesting that the blockade of cocaine reinstatement observed may have been due to behavioral disruption rather than a selective effect on cocaine reinforcement per se. Additionally, there is evidence that high-efficacy dopamine D_1 receptor agonists are self-administered in both rats and primates (Self and Stein, 1992; Self et al., 1996b; Weed and Woolverton, 1995; Weed et al. 1997; Grech et al. 1996) raising the possibility that they have inherent abuse liability. In contrast, dopamine D_1 receptor agonists with lower intrinsic efficacy are not readily self-administered (Woolverton et al., 1984; Katz and Witkin, 1992; Grech et al., 1996; Weed et al., 1997), and can serve as functional antagonists in vivo by blocking some of the behavioral effects of cocaine, suggesting a role for these drugs in the treatment of cocaine addiction (Katz and Witkin, 1992; Spealman et al., 1997). However, it remains to be determined whether other behavioral effects associated with dopamine D_1 receptor agonists preclude their use. Pre-clinical studies specifically designed to address the possibility of using partial dopamine D_1 receptor agonists as pharmacotherapies for cocaine abuse are warranted.

In conclusion, the present study demonstrates, for the first time, that the high-efficacy dopamine D_1 receptor agonist SKF-82958 can serve as a reliable discriminative stimulus in the rat and is mediated by a dopamine D_1-like receptor mechanism. Furthermore, although some overlap exists, the stimulus effects of the direct dopamine D_1 receptor agonist SKF-82958, are distinct from that elicited by the indirect dopamine receptor agonist, cocaine.

Acknowledgements

C.N. Haile would like to thank Dr. T.A. Kosten for helpful discussions during the process of writing this manuscript. The authors would also like to thank Mr. Michael Grzelak for his excellent technical assistance.

References

Anderson, P.H., Jansen, A.J., 1990. Dopamine receptor agonists: selectivity and dopamine D_1 receptor efficacy. Eur. J. Pharmacol. 188, 335–347.

Arnt, J., 1988. The discriminative stimulus properties of the D_1 agonist SKF-38393 and the D_2 agonist (−)-NPA are mediated by separate mechanisms. Life Sci. 42, 565–574.

Baker, L.E., Riddle, E.E., Saunders, R.B., Appel, J.B., 1993. The role of monoamine uptake in the discriminative stimulus effects of cocaine and related compounds. Behav. Pharmacol. 4, 69–79.

Barrett, R.L., Appel, J.B., 1989. Effects of stimulation and blockade of dopamine receptor subtypes on the discriminative stimulus properties of cocaine. Psychopharmacology 99, 13–16.

Broadbent, J., Michael, E.K., Riddle, E.E., Appel, J.B., 1991. Involvement of dopamine uptake in the discriminative stimulus properties of cocaine. Behav. Pharmacol. 2, 187–197.

Caine, S.B., Koob, G.F., 1994. Effects of D_1 and D_2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. J. Pharmacol. Exp. Ther. 270, 209–218.

Callahan, P.M., Appel, J.B., Cunningham, K.A., 1991. Dopamine D_1 and D_2 mediation of the discriminative stimulus properties of D-amphetamine and cocaine. Psychopharmacology 103, 50–55.

Callahan, P.M., Cunningham, K.A., 1993. Discriminative stimulus properties of cocaine in relation to dopamine D_2 receptor function in rats. J. Pharmacol. Exp. Ther. 266, 585–592.

Callahan, P.M., De La Garza, R. II, Cunningham, K.A., 1994. Discriminative stimulus properties of cocaine: modulation by dopamine D_1 receptors in the nucleus accumbens. Psychopharmacology 115, 110–114.

Callahan, P.M., De La Garza, R. II, Cunningham, K.A., 1997. Mediation of the discriminative stimulus properties of cocaine by mesocorticolimbic dopamine systems. Pharmacol. Biochem. Behav. 57, 601–607.

Cunningham, K.A., Callahan, P.M., Appel, J.B., 1985. Dopamine D_1 receptor mediation of the discriminative stimulus properties of SKF-38393. Eur. J. Pharmacol. 119, 121–125.

Filip, M., Przegalinski, E., 1997. The role of dopamine receptor subtypes in the discriminative stimulus effects of amphetamine and cocaine in rats. Polish J. Pharmacol. 49, 21–30.

Furmidge, L.J., Exner, M., Clark, D., 1991. Role of dopamine D_1 and D_2 receptors in mediating the D-amphetamine discriminative cue. Eur. J. Pharmacol. 202, 191–199.

Grech, D.M., Spealman, R.D., Bergman, J., 1996. Self-administration of D_1 receptor agonists by squirrel monkeys. Psychopharmacology 125, 97–104.

Izenwasser, S., Katz, J.L., 1993. Differential efficacies of dopamine D_1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat. Eur. J. Pharmacol. 246, 39–44.

Kamien, J.B., Goldberg, L.I., Woolverton, W.L., 1987. Discriminative stimulus properties of D_1 and D_2 dopamine agonists in rats. J. Pharmacol. Exp. Ther. 242, 804–811.

Kamien, J.B., Woolverton, W.L., 1985. The D_1 dopamine agonist SKF-38393 functions as a discriminative stimulus in rats. Psychopharmacology 87, 368–370.

Kantak, K.M., Edwards, M.A., Spealman, R.D., 1995. Effects of *N*-methyl-D-aspartate antagonists in rats discriminating different doses of cocaine: comparison with direct and indirect dopamine agonists. J. Pharmacol. Exp. Ther. 274, 657–665.

Katz, J.L., Witkin, J.M., 1992. Selective effects of the D_1 dopamine receptor agonists, SKF-38393, on behavior maintained by cocaine injection in squirrel monkeys. Psychopharmacology 109, 241–244.

Kleven, M.S., Anthony, E.W., Woolverton, W.L., 1990. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. J. Pharmacol. Exp. Ther. 254, 312–317.

Koob, G.F., Nestler, E.J., 1997. The neurobiology of drug addiction. J. Neuropsychiatry Clin. Neurosci. 9, 482–497.

Kosten, T.A., Haile, C.N., Jatlow, P., 1999. Naltrexone and morphine alter the discrimination and plasma levels of ethanol. Behav. Pharmacol. 10, 1–13.

Mendelson, J.H., Mello, N.K., 1996. Drug therapy: management of cocaine abuse and dependence. New Engl. J. Med. 334, 965–972.

O'Boyle, K.M., Gaitanopoulos, D.E., Brenner, M., Waddington, J.L., 1989. Agonist and antagonist properties of benzazepine and thienopyridine derivatives at the D_1 dopamine receptor. Neuropharmacology 28, 401–405.

Reavill, C., Bond, B., Overend, P., Hunter, A.J., 1993. Pharmacological characterization of the discriminative stimulus properties of the dopamine D_1 agonist, SKF-81297. Behav. Pharmacol. 4, 135–146.

Roberts, D.C., Corcoran, M.E., Fibiger, H.C., 1977. On the role of ascending catacholaminergic systems in intravenous self-administration of cocaine. Pharmacol. Biochem. Behav. 6, 615–620.

Roberts, D.C., Koob, G.F., 1982. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area. Pharmacol. Biochem. Behav. 17, 901–904.

Rosenzweig-Lipson, S., Bergman, J., 1993. Dopamine D_1 receptor involvement in the discriminative stimulus effects of SKF-81297 in squirrel monkeys. J. Pharmacol. Exp. Ther. 267, 765–775.

Schechter, M.D., 1995. The discriminative properties of the D_1 dopamine agonist dihydrexidine in the rat. Psychopharmacology 119, 79–84.

Self, D.W., Barnhart, W.J., Lehman, D.A., Nestler, E.S., 1996a. Opposite modulation of cocaine-seeking behavior by D_1- and D_2-like dopamine receptor agonists. Science 271, 1586–1589.

Self, D.W., Belluzzi, J.D., Kossuth, S., Stein, L., 1996b. Self-administration of the D_1 agonist SKF-82958 is mediated by D_1, not D_2, receptors. Psychopharmacology 123, 303–306.

Self, D.W., Stein, L., 1992. The D_1 agonists SKF-82958 and SKF-77434 are self-administered by rats. Brain Res. 582, 349–352.

Spealman, R.D., Bergman, J., Madras, B.K., Kamien, J.B., Melia, K.F., 1992. Role of D_1 and D_2 dopamine receptors in the behavioral effects of cocaine. Neurochem. Int. 20, 1475–1525.

Spealman, R.D., Bergman, J., Madras, B.K., Melia, K.F., 1991. Discriminative stimulus effects of cocaine in squirrel monkeys: involvement of dopamine receptor subtypes. J. Pharmacol. Exp. Ther. 258, 945–953.

Spealman, R.D., Bergman, J., Rosenzweig-Lipson, S., 1997. Differential modulation of behavioral effects of cocaine by low- and high-efficacy D_1 agonists. Psychopharmacology 133, 283–292.

Stoof, J.C., Kebabian, J.W., 1981. Opposing roles for D_1 and D_2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. Nature 294, 366–368.

Varty, G.B., Higgins, G.A., 1997. Investigation into the nature of a 7-OH-DPAT discriminative cue: comparison with D-amphetamine. Eur. J. Pharmacol. 339, 101–107.

Weed, M.R., Paul, I.A., Dwoskin, L.P., Moore, S.E., Woolverton, W.L., 1997. The relationship between reinforcing effects and in vitro effects of D_1 agonists in monkeys. J. Pharmacol. Exp. Ther. 283, 29–38.

Weed, M.R., Woolverton, W.L., 1995. The reinforcing effects of dopamine D_1 receptor agonists in rhesus monkeys. J. Pharmacol. Exp. Ther. 275, 1367–1374.

Wise, R.A., Rompre, P.P., 1989. Brain dopamine and reward. Annu. Rev. Psychol. 40, 191–225.

Witkin, J.M., 1994. Pharmacotherapy of cocaine abuse: preclinical development. Neurosci. Biobehav. Rev. 18, 121–142.

Witkin, J.M., Nichols, D.E., Terry, P., Katz, J.L., 1991. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. J. Pharmacol. Exp. Ther. 257, 706–713.

Woolverton, W.L., Goldberg, L.I., Ginos, J.Z., 1984. Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. J. Pharmacol. Exp. Ther. 230, 678–683.