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Place conditioning with the dopamine D_1-like receptor agonist SKF 82958 but not SKF 81297 or SKF 77434

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Abstract

While self-administration and place conditioning studies have shown that dopamine D_2-like receptor agonists produce reward-related learning, the effects of dopamine D_1-like receptor agonists remain equivocal. The present study tested three dopamine D_1-like receptor agonists for their ability to induce a place preference. Like control rats treated with amphetamine (2.0 mg/kg i.p.), rats treated with SKF 82958 (±-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine hydrobromide; 0.05 but not 0.01, 0.025, 0.075, or 0.10 mg/kg s.c. and/or i.p.) during conditioning showed a significant increase in the amount of time spent on the drug-paired side during the drug free test. Neither SKF 81297 (±-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide; 0.25, 0.50, 1.0, 2.0, and 4.0 mg/kg i.p.) nor SKF 77434 (±-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; 0.20, 1.0, 5.0, and 10.0 mg/kg i.p.) produced place conditioning. Significant increases in locomotion were seen at some doses of all drugs. Results show for the first time that systemic administration of a dopamine D_1-like receptor agonist produces a place preference and are consistent with previous findings showing that dopamine D_1-like receptor activation produces reward-related learning.

Keywords: SKF 82958; SKF 81297; SKF 77434; Dopamine; Dopamine D_1-like receptor; Place conditioning; Learning, reward-related

1. Introduction

A great deal of work implicates mesolimbic dopamine transmission in reward-related learning (for review, see Willner and Scheel-Krüger, 1991), but less is known about how different dopamine receptor subtypes mediate this learning. Prior to identification of the five currently recognized dopamine receptor subtypes (D_{1-5}), dopamine receptors were divided into two groups based on their effect on the enzyme adenylate cyclase. Activation of dopamine D_1 receptors was shown to result in stimulation of adenylate cyclase, whereas dopamine D_2 receptor activation either inhibited or failed to affect this enzyme (Kebabian and Calne, 1979). Dopamine D_1 and D_5 receptors have been found to be D_1-like but at present pharmacological agents acting selectively at either subtype are not available. Dopamine D_2, D_3 and D_4 receptors are D_2-like (Seeman and Van Tol, 1994).

The place conditioning paradigm has been used extensively to ascertain the role of dopamine D_1- and D_2-like receptors in reward-related learning (see Beninger, 1993; Beninger and Miller, 1997 for reviews). Generally, results have supported a role for dopamine D_2-like receptors in reward, but corresponding data for dopamine D_1-like receptor involvement have been equivocal. Antagonism of either dopamine D_1- or D_2-like receptors abolished the rewarding properties of dopaminergic drugs in rats, suggesting that both families of dopamine receptors may be involved in reward-related learning (Spyraki et al., 1982; Mackey and van der Kooy, 1985; Mithani et al., 1986; Hoffman and Beninger, 1989; Hiroi and White, 1991). In agreement with these results, dopamine D_2-like receptor agonists produced a place preference (Morency and Beninger, 1986; Hoffman et al., 1988; Hoffman and Beninger, 1988, 1989; White et al., 1991). However, results with the dopamine D_1-like receptor agonist SKF 38393 were not straightforward. When injected into the nucleus accumbens, SKF 38393 produced a place preference (White et al., 1991), yet systemic administration

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produced an aversion (Hoffman and Beninger, 1988, 1989; White et al., 1991). Perhaps the aversion was the result of pharmacological properties specific to SKF 38393.

The possibility that pharmacological characteristics unique to SKF 38393 may be responsible for behavioral findings in place conditioning is supported by results from self-administration studies. In agreement with place conditioning results, pretreatment with either dopamine D_1- or D_2-like receptor antagonists disrupted self-administration of cocaine or amphetamine in rodents and primates, supporting the idea that both dopamine receptor families may be involved in reward (Yokel and Wise, 1975, 1976; Risner and Jones, 1976; De Wit and Wise, 1977; Roberts and Vickers, 1984, 1987; Koob et al., 1987; Bergman et al., 1990; Corrigall and Coen, 1991; Caine and Koob, 1994). Also similar to place preference studies, dopamine D_2-like receptor agonists were self-administered (Woolverton et al., 1984; Wise et al., 1990) and the dopamine D_1-like receptor agonist SKF 38393 was not (Woolverton et al., 1984; Weed and Woolverton, 1995). However, other dopamine D_1-like receptor agonists from the same chemical family (benzazepines) recently have been shown to support self-administration: SKF 82958 in rats and squirrel monkeys, SKF 81297 in rhesus and squirrel monkeys, and SKF 77434 in rats but not squirrel monkeys (Self and Stein, 1992; Self et al., 1993, 1996; Weed et al., 1993; Grech et al., 1996). When all four benzazepine-based compounds were compared in a single study of rhesus monkeys, only SKF 82958 and SKF 81297 were self-administered; responding for SKF 38393 and SKF 77434 was not different from responding for vehicle (Weed and Woolverton, 1995).

Differences in pharmacological properties of the dopamine D_1-like receptor agonists may help to make sense of these results. Thus, SKF 82958 has been shown to be a full dopamine receptor agonist in both the rat and squirrel monkey, with observations of adenylate cyclase activation ranging from 78–148% of dopamine (O'Boyle et al., 1989; Izenwasser and Katz, 1993). SKF 81297 has also been reported to be a high efficacy dopamine receptor agonist in the rat, with corresponding values of 68–88% (Anderson and Jansen, 1990; Arnt et al., 1992; Izenwasser and Katz, 1993). In contrast, SKF 77434 and SKF 38393 are generally considered to be low efficacy agents, with adenylate cyclase responses of about 48–55% and 44–59% of dopamine, respectively (Anderson et al., 1985; O'Boyle et al., 1989; Izenwasser and Katz, 1993). It has been suggested elsewhere that our understanding of the functional role of dopamine D_1-like receptors has been obscured by the use of SKF 38393 (Self and Stein, 1992).

Thus, despite negative results with SKF 38393, recent results from self-administration studies suggest that activation of the dopamine D_1-like receptor indeed may be important to reward. It is hypothesized here that administration of high efficacy dopamine D_1-like receptor agonists, previously shown to be self-administered, will result in a place preference. Three dopamine D_1-like receptor agonists (SKF 82958, SKF 81297, and SKF 77434) were administered systemically at a range of doses to test this hypothesis; amphetamine (2.0 mg/kg, i.p.) and distilled water (i.p.) were also tested as paradigm controls.

2. Materials and methods

2.1. Subjects

Two-hundred and nine male Wistar rats (Charles River, Canada), weighing between 200 and 250 g upon arrival at the colony had free access to both food and water in their home cages, and were group housed (four per cage) in a temperature controlled (21°C) facility with a 12 h light/dark cycle (lights on at 08.00 h). Care and treatment of the animals was in full compliance with guidelines set forth by the Canadian Council on Animal Care, the Animals for Research Act, and relevant Queen's University policy.

Rats were randomly assigned to treatment groups with approximately ten animals per group (see Fig. 1 or Section 2.4). Only five rats were treated with 4.0 mg/kg SKF 81297 because of insufficient amount of drug. The number of animals in the amphetamine group ($n = 20$) was larger than other treatment groups as a result of an attempt to ensure paradigm reliability. Not all animals treated with amphetamine were tested at once. Instead, four animals were run at a given time along with animals from another group (e.g. 0.01 mg/kg SKF 82958 s.c.). The large number of doses evaluated resulted in a relatively large number of animals in the amphetamine group.

2.2. Apparatus

The test environment consisted of two separate chambers ($38 \times 27 \times 34$ cm) connected by a tunnel ($8 \times 8 \times 8$ cm). Opaque guillotine doors could be used to block access to the tunnel. Six photocells (two in each section of the apparatus) were connected to a computer that monitored animal position and locomotor activity. The left and right chambers had different walls (either sealed wood or plexiglass with alternating black and white vertical stripes) and floors (either parallel stainless steel bars or galvanized hardware cloth). Four such units were employed; among the four units, each of the wall types appeared on both the left and right sides of the apparatus with each of the two floor types. Each unit was illuminated by its own 7.5 W bulb, and housed inside a styrofoam-insulated box to attenuate background noise. For more information see Brockwell et al. (1996).

2.3. Procedure

After arrival in the colony animals were handled daily for 6–8 days. The experimental protocol involved three

distinct phases: preconditioning, conditioning, and test, with each animal being tested once a day at approximately the same time each day during the light portion of the light/dark cycle for fourteen consecutive days.

2.3.1. Preconditioning

On days 1–3, animals were placed for 15 min in one of the two chambers with the tunnel open and then returned to their home cages. Start side was varied across animals, with half beginning on the right for all preconditioning days, and the other half on the left. The amount of time spent in each of the two chambers and tunnel was recorded to establish a baseline with which to compare test data.

2.3.2. Conditioning

On days 4–11 rats were injected systemically with a drug or its vehicle, held in a metal transporting cage (see below), and then confined to one chamber of the place conditioning apparatus for 30 min. Drug was given on conditioning days 1, 3, 5, and 7 (and always paired with one chamber) and the drug's vehicle on remaining conditioning days (and paired with the other chamber). Total number of photocell beam breaks was recorded to assess locomotor activity.

2.3.3. Testing

Days 12–14 were identical to preconditioning days. Animals were placed in the apparatus with the tunnel open for 15 min, then returned to their home cages. As before, half the rats began in the left compartment while the other half began in the right; each animal's start side during testing was the same as its start side during preconditioning. Note, however, that start side was varied across rats to control for any possible side bias. Again, the amount of time spent in each of the two chambers and tunnel was recorded.

2.4. Drugs

All drugs were prepared fresh daily. (+)-amphetamine sulfate (SmithKline Beecham Pharma of Canada) was dissolved in 0.9% NaCl, and injected i.p. in a volume of 1.0 ml/kg, in a dose of 2.0 mg/kg ($n = 20$), 5 min prior to placement in the apparatus. Non-drug control animals received injections of distilled water in a volume of 1.0 ml/kg ($n = 12$) 15 min prior to the beginning of a session.

SKF 82958 hydrobromide (±-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine hydrobromide) was purchased from Research Biochemicals International, Natick, MA (RBI), and dissolved in a volume of 1.0 ml/kg in distilled water. Groups were injected i.p. with doses of 0.01 ($n = 7$), 0.025 ($n = 9$), 0.05 ($n = 10$), 0.075 ($n = 12$), or 0.10 ($n = 10$) mg/kg 15 min prior to placement in the apparatus, while s.c. injected animals were given doses of 0.01 ($n = 10$), 0.05 ($n = 10$), or 0.10 ($n = 12$) mg/kg 15 min prior to the beginning of a session.

SKF 81297 hydrobromide (±-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide), also purchased from RBI, was dissolved in a volume of 1.0 ml/kg in distilled water and injected i.p. in doses of 0.25 ($n = 8$), 0.50 ($n = 13$), 1.0 ($n = 10$), 2.0 ($n = 12$), or 4.0 ($n = 5$) mg/kg 15 min prior to placement in the apparatus. Gentle heating was used in preparation of the 4.0 mg/kg dose.

Finally, SKF 77434 hydrobromide (±-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride), purchased from RBI, was dissolved in a volume of 2.0 ml/kg in distilled water, and injected i.p. in doses of 0.20 ($n = 8$), 1.0 ($n = 8$), 5.0 ($n = 12$), or 10.0 ($n = 7$) mg/kg 15 min prior to placement in the apparatus.

3. Results

Dependent variables included time spent on the drug-paired side and time spent in the tunnel on three pre-conditioning and one test days, and activity during eight conditioning sessions. Time and activity data will be treated separately.

3.1. Place conditioning

For all analyses, time spent on the drug-paired side for the three pre-conditioning sessions was averaged to provide the best measure of side preference prior to conditioning. It was decided prior to behavioral testing that only data from the first test session would be used, as conditioning was expected to be strongest on this day.

During pre-conditioning and test sessions, animals spent some time in the tunnel, mean (±S.E.M.) values ranging from 38.1 (±5.3) to 80.3 (±14.3) s per session (see Table 1). Because tunnel time was observed to differ from pre-conditioning (averaged for three sessions) to test for some groups, $F(1, 30) = 4.91$, $P < 0.05$, tunnel time was removed from all sessions to eliminate any possible bias due to this variable. Thus, place conditioning was evaluated by comparing the percentage of total session time (900 s – tunnel time) spent in the drug-paired side during pre-conditioning and in the test.

Percentage of time spent on the drug-paired side increased from pre-conditioning to test for the amphetamine but not the distilled water control group (Fig. 1). Groups treated with SKF 82958 s.c. during conditioning showed an increased proportion of time spent on the drug-paired side in the test with the strongest effect occurring at 0.05 mg/kg. Groups receiving this drug i.p. similarly showed an increase in percentage of time spent on the drug-paired side, except at the lowest dose, and again the strongest effect occurred at the 0.05 mg/kg dose. The effect of both SKF 81297 and SKF 77434 appeared to be systematic across doses, with the peak effect occurring in the middle

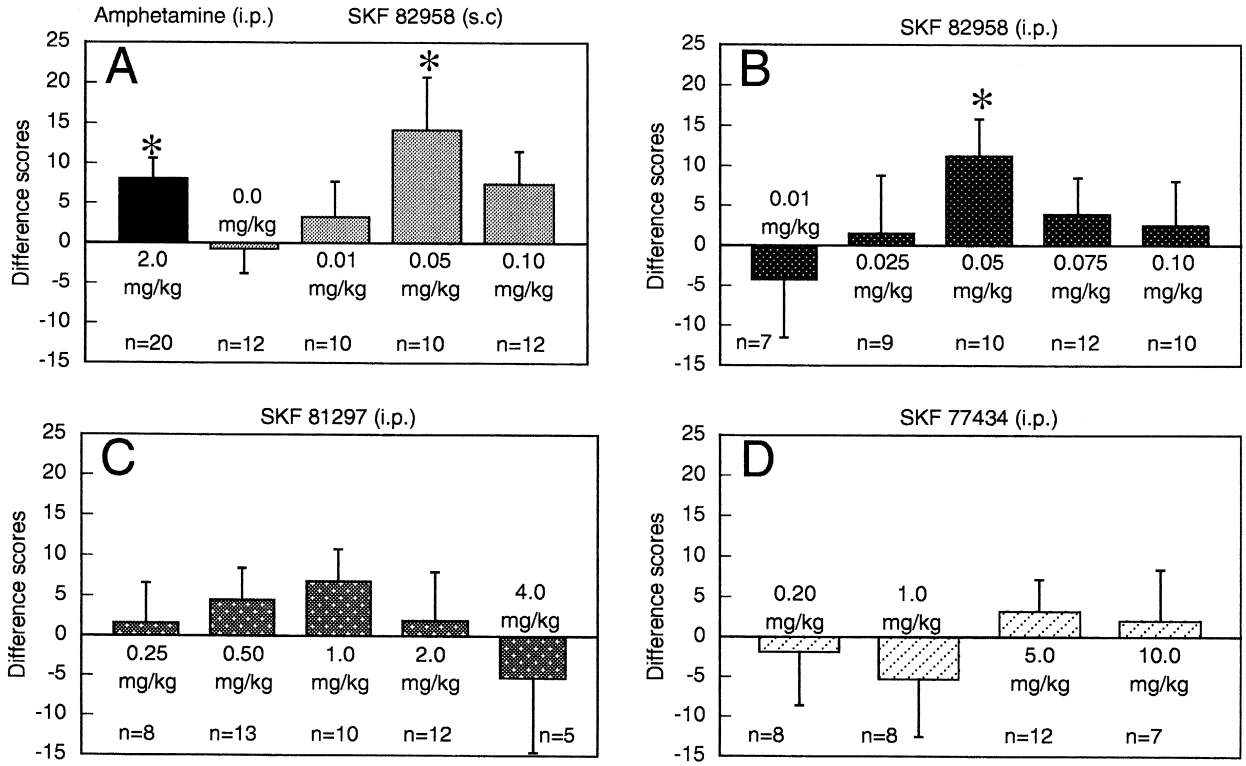

Fig. 1. Percentage of time spent on the drug-paired side as a function of total time spent on either side but not in the tunnel. Difference scores represent the percentage of time spent on the drug-paired side during the first test day minus the mean percentage of time spent on that side during pre-conditioning. Positive values indicate an increased amount of time on the drug-paired side during test. * Significant increase in proportion of time in the drug-paired side in test compared to pre-conditioning.

of the dose range tested for SKF 81297, but for neither drug did any of the doses produce an effect of the same magnitude as that seen with amphetamine or the 0.05 mg/kg doses of SKF 82958 (Fig. 1).

Statistical analyses generally confirmed this description of the results. A mixed design analysis of variance (ANOVA) with independent groups and repeated measures on phase (pre-conditioning versus test) was used to compare the percentage of time spent on the drug-paired side in pre-conditioning versus test for the amphetamine versus distilled water control groups. Results revealed a significant interaction, $F(1, 30) = 4.48$, $p < 0.05$, showing that the phase effect differed between the groups. Tests of simple effects confirmed that only the amphetamine group showed a significant increase in the proportion of time spent on the drug-paired side from pre-conditioning to test, $F(1, 30) = 10.04$, $p < 0.01$. Finally, planned comparisons of pre-conditioning and test for each group showed a significant effect only for the amphetamine group, $t(19) = 3.05$, $p < 0.01$.

The ANOVA for distilled water and SKF 82958 s.c. doses yielded a significant effect of phase, $F(1, 40) = 7.15$, $p < 0.05$, showing that when all groups were combined animals spent a greater proportion of time on the drug-paired side in the test than in the pre-conditioning sessions. In planned comparisons of pre-conditioning and test for each dose, only the 0.05 mg/kg s.c. dose produced a significant increase in proportion of time spent on the drug-paired side, $t(9) = 2.26$, $P < 0.05$.

A similar mixed design ANOVA for the distilled water and SKF 82958 i.p. doses yielded no significant effects. However, as was the case for groups given SKF 82958 s.c., planned comparisons showed that only the 0.05 mg/kg i.p dose produced a significant increase in the proportion of time spent on the drug-paired side from pre-conditioning to test, $t(9) = 2.41$, $P < 0.05$.

To directly compare the effects of those doses (0.01, 0.05, 0.10 mg/kg) of SKF 82958 that were given both by the s.c. and i.p. route, a three-variable ANOVA, with repeated measures on phase and independent dose and replication groups was conducted. Results revealed a significant main effects of phase, $F(1, 53) = 6.81$, $P < 0.05$, and a dose by phase interaction that approached significance, $F(2, 53) = 3.03$, $P = 0.0565$. None of the remaining main effects or interactions were significant. The lack of any significant effects involving the replication variable shows that administration of SKF 82958 by the two different routes did not affect significantly the action of the drug. As was the case for the analysis of groups receiving SKF 82958 s.c., the significant phase effect shows that when doses (from both routes of administration) were combined, animals spent a greater proportion of time on

the drug-paired side in the test than in the pre-conditioning sessions. The interaction suggests that the phase effect differed depending on the dose, with doses combined over replication. Tests of simple main effects of phase at each dose yielded a significant effect for the 0.05 mg/kg dose of SKF 82958, $F(1, 56) = 11.98$, $P < 0.001$, revealing the source of the interaction.

Neither the ANOVAs nor the planned comparisons of phase for each dose of SKF 81297 or SKF 77434 yielded any significant effects.

3.2. Locomotor activity

Mean number of beam breaks per min during the four drug conditioning sessions were averaged within and across sessions as were the corresponding values for vehicle sessions (Table 2). As expected, amphetamine stimulated activity and distilled water did not. Generally, low doses of the dopamine D_1-like receptor agonists had little effect or slightly decreased activity whereas higher doses increased activity. However, these effects were small, none of them being of the same magnitude as the amphetamine effect.

This description of the results was supported by statistical analyses. The amphetamine and distilled water groups were compared using a two variable mixed design ANOVA with independent groups and repeated measures on treatment. Results revealed significant group, $F(1, 30) = 31.08$, $P < 0.001$, and interaction effects, $F(1, 30) = 19.78$, $P < 0.001$. The interaction was significant because amphetamine produced a significant simple effect of treatment, $F(1, 30) = 54.85$, $P < 0.001$, whereas distilled water did not. Thus, amphetamine stimulated locomotor activity during conditioning sessions.

A similar ANOVA for the distilled water and SKF 82958 s.c. dose groups revealed significant effects of dose, $F(3, 40) = 5.37$, $P < 0.01$, treatment, $F(1, 40) = 8.63$, $P < 0.01$, and their interaction, $F(3, 40) = 2.85$, $P < 0.05$. Examination of simple main effects revealed significant treatment effects for the 0.05 and 0.10 mg/kg s.c. doses of SKF 82958, $F(1, 40) = 6.39$, $P < 0.05$ and $F(1, 40) = 11.21$, $P < 0.01$, respectively, but not for the 0.01 mg/kg dose or distilled water, revealing the source of the interaction.

Analysis of the distilled water and SKF 82958 i.p. dose groups revealed a significant dose by treatment interaction, $F(5, 54) = 2.52$, $P < 0.05$. The interaction was produced by the simple main effect of treatment for only the 0.05 and 0.075 mg/kg i.p. doses, $F(1, 54) = 4.16$, $P < 0.05$ and $F(1, 54) = 12.05$, $P < 0.001$, respectively.

Table 1
Mean (±S.E.M.) time (s) spent on the drug-paired side and in the tunnel during the mean of the pre-conditioning sessions and the first test session

Group	Drug paired side		Tunnel	
	pre-cond.	test	pre-cond.	test
Amphetamine				
2.0 mg/kg	434.8 (14.6)	498.9 (15.6)	46.1 (5.2)	52.8 (4.5)
0.0 mg/kg	426.3 (18.4)	413.7 (41.1)	48.0 (6.0)	57.4 (10.8)
SKF 82958 (s.c.)				
0.01 mg/kg	417.2 (19.9)	436.3 (46.0)	55.9 (6.5)	72.0 (11.7)
0.05 mg/kg	431.1 (32.1)	556.6 (54.7)	45.7 (4.7)	38.1 (5.3)
0.10 mg/kg	405.1 (28.8)	470.2 (46.1)	47.5 (5.4)	38.8 (7.9)
SKF 82958 (i.p)				
0.01 mg/kg	469.3 (38.0)	416.9 (39.4)	47.9 (6.8)	80.3 (14.3)
0.025 mg/kg	402.8 (50.6)	412.4 (44.2)	43.1 (6.7)	50.7 (5.6)
0.05 mg/kg	405.6 (25.7)	508.2 (46.7)	56.4 (6.7)	43.7 (4.9)
0.075 mg/kg	430.8 (30.6)	462.8 (32.3)	50.1 (7.3)	54.7 (7.8)
0.10 mg/kg	435.5 (35.5)	459.9 (49.6)	53.0 (7.1)	48.0 (2.6)
SKF 81297				
0.25 mg/kg	421.9 (24.5)	426.5 (38.6)	58.2 (7.2)	74.5 (9.2)
0.50 mg/kg	410.5 (21.6)	443.1 (34.4)	56.7 (7.0)	65.3 (7.3)
1.0 mg/kg	413.7 (31.6)	468.4 (41.3)	50.1 (5.9)	56.1 (5.5)
2.0 mg/kg	424.6 (31.0)	439.6 (42.9)	55.4 (7.2)	57.3 (11.5)
4.0 mg/kg	430.8 (34.0)	381.4 (56.5)	38.6 (6.6)	41.4 (12.4)
SKF 77434				
0.20 mg/kg	425.8 (15.8)	402.5 (59.3)	54.3 (7.3)	65.1 (10.0)
1.0 mg/kg	429.4 (29.1)	365.6 (35.4)	48.3 (7.7)	47.1 (9.8)
5.0 mg/kg	392.1 (20.5)	420.4 (34.6)	58.7 (7.4)	58.6 (6.5)
10.0 mg/kg	407.1 (34.7)	425.1 (63.5)	50.3 (8.9)	46.6 (9.1)

Table 2
Beam breaks per min during drug and vehicle conditioning sessions, expressed as an average across the four conditioning days of each type

Group	*n*	Drug (±S.E.M.)	Vehicle (±S.E.M.)
Amphetamine			
2.0 mg/kg	20	14.28 (1.09)[a]	8.23 (0.85)
Distilled water			
0.0 mg/kg	12	7.49 (0.45)	7.38 (0.41)
SKF 82958 (s.c.)			
0.01 mg/kg	10	6.88 (0.63)	6.95 (0.62)
0.05 mg/kg	10	10.50 (1.34)[a]	7.29 (0.47)
0.10 mg/kg	12	11.92 (1.25)[a]	8.04 (0.99)
SKF 82958 (i.p)			
0.01 mg/kg	7	7.75 (0.67)	8.07 (0.61)
0.025 mg/kg	9	7.05 (0.36)	7.51 (0.59)
0.05 mg/kg	10	7.14 (0.23)[a]	6.17 (0.27)
0.075 mg/kg	12	7.83 (0.56)[a]	6.36 (0.39)
0.10 mg/kg	10	6.70 (0.49)	6.25 (0.48)
SKF 81297			
0.25 mg/kg	8	6.58 (0.36)	6.90 (0.53)
0.50 mg/kg	13	6.65 (0.39)	6.17 (0.32)
1.0 mg/kg	10	7.78 (0.44)[a]	6.36 (0.49)
2.0 mg/kg	12	7.88 (0.43)[a]	6.50 (0.20)
4.0 mg/kg	5	9.78 (1.16)[a]	7.19 (0.51)
SKF 77434			
0.20 mg/kg	8	6.02 (0.47)	6.18 (0.63)
1.0 mg/kg	8	7.72 (0.40)	6.19 (0.29)
5.0 mg/kg	12	8.37 (0.75)	6.83 (0.46)
10.0 mg/kg	7	7.91 (1.09)	7.32 (0.26)

[a] Significantly different from vehicle in tests of simple effects following a significant interaction in ANOVA.

Comparison of the doses (0.01, 0.05, and 0.10 mg/kg) of SKF 82958 that were given by both routes of administration suggests that the profile of effects on activity was similar for each (Table 2). Thus, 0.01 mg/kg by either route produced a small decrease in activity whereas 0.05 and 0.10 mg/kg produced increases. However, the magnitude of increase produced by these higher doses was greater following s.c. administration. ANOVA followed by tests of simple main effects confirmed this description of the data. A three variable mixed design ANOVA revealed significant effects of replication, $F(1, 53) = 11.06$, $P < 0.01$, replication by dose, $F(2, 53) = 7.83$, $P < 0.01$, and replication by treatment, $F(1, 53) = 4.51$, $P < 0.05$; a significant treatment effect, $F(1, 53) = 8.38$, $P < 0.01$, was also observed, but as it occurs when replications are combined and shows an effect already described above, it will not be discussed further. The significant replication effect reflects the generally higher level of activity observed in the dose groups given SKF 82958 s.c. versus those injected i.p. The replication by dose interaction reflects the fact that activity averaged over treatment was higher in the groups receiving 0.05 and 0.10 but not 0.01 mg/kg SKF 82958 by the s.c. route versus the i.p. route. The replication by treatment interaction reflects the higher magnitude of the treatment effect in the s.c. dose groups combined versus the i.p. dose groups combined. All of this is consistent with the idea that activity levels were generally higher in groups receiving SKF 82958 s.c. versus i.p. However, the lack of a replication by treatment by dose interaction is consistent with the finding that although the magnitude of activity observed in the s.c. experiment was higher, the profile of activity effects produced by SKF 82958 given by the s.c. and i.p. routes was similar.

Analysis of the distilled water and SKF 81297 dose groups revealed significant dose, $F(5, 54) = 2.98$, $P < 0.05$, treatment, $F(1, 54) = 27.59$, $P < 0.001$, and interaction effects, $F(5, 54) = 5.76$, $P < 0.001$. Simple effects analyses revealed treatment effects for the 1.0, 2.0, and 4.0 mg/kg doses, $F(1, 9) = 11.52$, $P < 0.001$, $F(1, 11) = 13.15$, $P < 0.001$, and $F(1, 4) = 19.20$, $P < 0.001$, respectively, but not the lower doses, revealing the source of the interaction.

Analysis of the distilled water and SKF 77434 dose groups revealed a significant treatment effect, $F(1, 42) = 8.27$, $P < 0.01$, showing that when dose groups were combined, activity was higher on the drug conditioning than the vehicle days. Although the lack of a significant interaction precludes attributing this effect to specific doses, inspection of Table 2 reveals that doses of 1.0 and 5.0 mg/kg produced the largest effects.

4. Discussion

This study is the first to report that a place preference is produced by systemic administration of a dopamine D_1-like receptor agonist. The reliability of this result was confirmed in two separate experiments using two different routes of administrations (s.c. and i.p.). In contrast, the dopamine D_1-like receptor agonists SKF 81297 and SKF 77434 failed to produce place conditioning over a wide range of doses. Note also that all agents tested (excluding distilled water alone) stimulated locomotor activity at some doses, with greatest increases seen following amphetamine administration.

Different routes of administration were used in our evaluation of SKF 82958 because the behavioral effects of the dopamine receptor agonist apomorphine have been shown to differ depending on route of administration (Ungerstedt, 1979). Thus, once we found that only a single dose of SKF 82958 given by the s.c. route produced significant place conditioning, we decided to evaluate the reliability of this effect using the i.p. route. However, the original effect was replicated at the same dose and no difference was found.

The observation of a place preference following pairings of amphetamine with one side of the test apparatus is in agreement with many previous reports (reviews: Hoffman, 1989; Carr et al., 1989). The finding that animals treated with distilled water on both sides during conditioning showed little change in time spent on the designated side demonstrates that side preference assessed during pre-conditioning is stable over the course of conditioning sessions when no drug is given. Similarly small changes from pre-conditioning to test were seen with the lower doses of SKF 82958 and with all doses of SKF 81297 and SKF 77434.

Previous studies have evaluated the place conditioning potential of the prototypical dopamine D_1-like receptor agonist SKF 38393. Results revealed a place aversion following systemic administration (Hoffman and Beninger, 1988, 1989; White et al., 1991). Hoffman and Beninger (1989) showed that the dopamine D_1-like receptor agonist fenoldopam (SKF 82526), which fails to cross the blood brain barrier (Hahn et al., 1982), had no significant effect in a place-conditioning task, confirming that SKF 38393 produces its aversive effects by acting centrally. White et al. (1991), on the other hand, found a place preference following pairings of intra-accumbens injections of SKF 38393 with one side of a place conditioning apparatus, showing at least one site in the brain where stimulation of dopamine D_1-like receptors by SKF 38393 leads to a rewarding effect. Taken together these results suggest that SKF 38393 produces a place aversion by acting centrally at a site other than the nucleus accumbens.

Results from place conditioning studies evaluating dopamine D_1-like receptor agonists show a good fit with results of self-administration studies evaluating dopamine D_1-like receptor agonists. Thus, SKF 38393 failed to support self-administration in two reports (Woolverton et al., 1984; Weed and Woolverton, 1995) whereas SKF 82958 was found to be self-administered by both rats (Self and

Stein, 1992; Self et al., 1993, 1996) and monkeys (Grech et al., 1996). SKF 81297 also was self-administered (Weed et al., 1993; Grech et al., 1996) whereas SKF 77434 has been reported to produce both positive (Self and Stein, 1992) and negative results (Grech et al., 1996) in this paradigm. There appears to be a continuum of effectiveness of dopamine D_1-like receptor agonists in self-administration and place conditioning paradigms following systemic administration with the order from most to least effective being: SKF 82958 ≥ SKF 81297 > SKF 77434 > SKF 38393.

This rank order of effectiveness of the dopamine D_1-like receptor agonists in place conditioning and self-administration experiments parallels their ability to stimulate cyclic adenosine 3′,5′-monophosphate (cAMP). Thus, SKF 82958, SKF 81297, SKF 77434, and SKF 38393 have been reported to stimulate cAMP production relative to dopamine itself, in the following respective percentage ranges: 78–148%, 68–88%, 48–55%, and 44–59% (Anderson et al., 1985; O'Boyle et al., 1989; Anderson and Jansen, 1990; Arnt et al., 1992; Izenwasser and Katz, 1993). These results might suggest that the rewarding capacity of dopamine D_1-like receptor agonists is related to their efficacy at stimulating cAMP production. However, the observation by White et al. (1991) that intra-accumbens injections of SKF 38393 produce place preference conditioning is not consistent with this hypothesis and remains to be explained.

Our observation that SKF 82958, SKF 81297, and SKF 77434 produced a mild (relative to amphetamine) but significant stimulation of locomotor activity is consistent with previous findings (Murray and Waddington, 1989; Meyer and Shults, 1993). The fact that all agents (excluding distilled water alone) were able to increase locomotor activity at one or more doses, but place conditioning was seen only with 2.0 mg/kg amphetamine and 0.05 mg/kg SKF 82958 reveals a dissociation between the locomotor stimulating effect of the dopamine D_1-like receptor agonists SKF 81297 and SKF 77434 and their ability to produce place conditioning. A similar dissociation has been reported previously for adenosinergic agents (Brockwell and Beninger, 1996).

In conclusion, the present finding that dopamine D_1-like receptor stimulation is capable of supporting reward-related learning in the place conditioning paradigm is consistent with previous findings from self-administration studies (Woolverton et al., 1984; Self and Stein, 1992; Self et al., 1993, 1996; Weed et al., 1993; Grech et al., 1996). These data add to those from studies employing other reward paradigms (e.g., Beninger and Rolfe, 1995) and receptor subtype-specific dopamine antagonists (see reviews by Miller et al., 1990; Beninger, 1993; Beninger and Nakonechny, 1996; Beninger and Miller, 1997) in continuing to suggest an important role for D_1-like dopamine receptors in reward-related learning.

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