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Selective D1 and D2 Dopamine Agonists Produce Opposing Effects in Place Conditioning but not in Conditioned Taste Aversion Learning

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HOFFMAN, D. C. AND R. J. BENINGER. *Selective D1 and D2 dopamine agonists produce opposing effects in place conditioning but not in conditioned taste aversion learning.* PHARMACOL BIOCHEM BEHAV 31(1) 1–8, 1988.— The neurotransmitter, dopamine (DA), has been implicated in place conditioning but the role of D1 and D2 receptors has not been investigated. In Experiment 1, the effects of SKF 38393 (0, 0.01, 0.1, 1.0, 10.0 mg/kg) and quinpirole (0, 0.01, 0.1, 1.0, 2.0, 4.0 mg/kg), preferential D1 and D2 receptor agonists, respectively, were evaluated and compared to (+)-amphetamine (0, 0.01, 0.1, 1.0, 2.0, 4.0 mg/kg). The experiment consisted of three phases. During the preexposure phase, rats explored two distinctive end compartments adjoined by a small tunnel. The time spent in each compartment was recorded. During the 8-day conditioning phase, rats were treated with drug and confined to one compartment for 30 min. On alternate days, rats received saline and were placed in the opposite compartment. Test days occurred over the remaining three days during which drug-free animals explored both compartments. Rats conditioned with (+)-amphetamine demonstrated a dose-dependent increase in time spent in the drug-paired environment from preexposure to test indicating the establishment of a conditioned place preference. Treatment with quinpirole also resulted in a conditioned place preference, however, only an intermediate dose was effective. In contrast, SKF 38393 produced a dose-dependent decrease in time spent on the drug-paired side suggesting the establishment of a place aversion. The idea that D1 receptors may be exclusively involved in mediating the aversive properties of psychomotor stimulants was tested in Experiment 2 employing a conditioned taste aversion paradigm. The results did not support this notion; it was found that both quinpirole and SKF 38393 produced a conditioned taste aversion. Overall, the evidence favors the D2 receptor in mediating the reinforcing effects of psychomotor stimulants. In contrast, both receptor subtypes appear to be involved in taste aversion learning.

Dopamine receptors (+)-Amphetamine Quinpirole SKF 38393 Conditioned place preference Conditioned taste aversion

THE place preference paradigm has become a popular approach for studying the reinforcing properties of drugs (3,4). After receiving several pairings of a drug injection with a distinctive environment, the now drug-free animal demonstrates a relative increase in the amount of time spent in this environment compared to an equally distinctive alternate environment. This shift in preference is attributed to the reinforcing properties of the drug.

The rewarding effects of dopaminergic agonists (e.g., amphetamine, methylphenidate, cocaine and apomorphine) have been demonstrated using this procedure (17, 18, 23, 27). Moreover, by studying the effects of selective dopaminergic lesions or pretreatment with dopamine (DA) receptor antagonists, the role of DA in mediating the reinforcing properties of these compounds has largely been substantiated. For example, amphetamine-induced place preference was attenuated in animals treated with haloperidol or alpha-flupenthixol (16, 17, 23) and place conditioning produced by ventricular injections of cocaine was blocked by systemic administration of pimozide (18). Central microinjections of amphetamine into the nucleus accumbens, but not other DA innervated areas, resulted in the establishment of a place preference (5). And finally, although Spyraki *et al.* (24) failed to attenuate cocaine-induced place conditioning in rats with 6-hydroxydopamine lesions of the nucleus accumbens, Issac *et al.* (11) discovered that if another DA innervated area, the medial prefrontal cortex, was removed by suction, place conditioning was disrupted.

The role of DA in reinforcement has become complicated by the discovery of subtypes of DA receptors: D1 receptors stimulate the enzyme, adenylate cyclase, whereas D2 receptors do not (13). Interest has focused on determining the possible behavioral functions of each receptor. This research has been greatly facilitated by the development of selective DA agonists and antagonists which preferentially activate or block one receptor subtype. Despite these pharmacological advances, however, there has been little success in differentiating the D1 and D2 receptor subtypes on a behavioral level.

The purpose of Experiment 1 was to investigate the role

of D1 and D2 receptors in the establishment of place conditioning. It has already been well-documented that concurrent stimulation of D1 and D2 receptors, by employing nonselective DA receptor agonists, results in the establishment of place preference. It is of interest, therefore, to determine if preferential stimulation of either receptor subtype alone contributes to this DA-mediated effect. Thus, in the present series of experiments, several doses of SKF 38393 and quinpirole (LY 171555), specific D1 and D2 receptor agonists, respectively (7, 22, 25), were examined in the place conditioning paradigm and compared to the effects of amphetamine.

The place conditioning procedure used in the present study has been referred to as a "balanced paradigm" (26). That is, animals show approximately equal preferences for the two compartments and within a group, the side used for drug conditioning is counterbalanced. In previous studies, animals often showed strong unconditioned preferences for one of the two environments and to maximize the place preference effect, investigators then paired the drug stimulus with the initially nonpreferred side. Although fairly large conditioned effects were documented, rarely did the animals spend more than 50 percent of the total test time in the drug-paired environment. Because the animals failed to show an "absolute" preference for the drug-associated side, the assertion that this paradigm measures the rewarding properties of drugs was questioned. As suggested by Schenk *et al.* (21), perhaps the drug simply decreased the aversive characteristics that were previously associated with the nonpreferred compartment. Consequently, it was suggested that an apparatus that minimizes strong unconditioned preferences is more advantageous for interpreting place conditioning effects [(26) but see also (4)].

EXPERIMENT 1

METHOD

Subjects

One hundred and seventy-four male Wistar rats (supplied by Charles River) weighed between 225 and 300 g at the start of the experiment. The animals were group-housed (n=8) in a temperature-controlled colony room on a 12-hour light/dark cycle and had free access to food and water throughout the study.

Apparatus

The experimental environment consisted of four similar rectangular boxes (84×27×36 cm) constructed of wooden sides and removable Plexiglas covers. Each box consisted of two compartments (38×27×36 cm) joined by a small tunnel (8×8×8 cm); entrance to the tunnel could be blocked by inserting wooden guillotine doors. The compartments differed in brightness, pattern and floor texture; in two of the experimental boxes, one compartment was painted brown and had a mesh (1 cm squares) floor and the other was painted in vertical black and white stripes (1 cm wide) with a grid (1 cm between grids) floor. In the remaining two boxes, the striped compartment had a mesh floor and the brown compartment had a grid floor. The four experimental chambers were located in a dimly lit room. The floors of the boxes were positioned on a fulcrum such that the weight of a rat in one end compartment caused a microswitch to close, initiating a timer in another room. Thus, the amount of time the animal spent in each compartment was recorded.

Procedure

The general procedure was adopted from Mithani *et al.* (17). The experimental design consisted of three phases which occurred over 14 consecutive days. The preexposure phase involved adapting the rats to the experimental boxes for 15 min on each of three days. With the guillotine doors removed, the rats were placed in a compartment (the start compartment) and allowed to explore the entire box. The choice of the start compartment was counterbalanced across rats and remained the same for each animal across days. On each of the three preexposure days, the amount of time the rat spent in each compartment was measured.

The conditioning phase consisted of eight 30-min sessions. The animals were confined to one compartment by blocking entrance to the tunnel. During four of the conditioning sessions, the rat was pretreated with drug and placed into the nonstart compartment. In the remaining four sessions, the animal received saline treatment and was confined to the start compartment. The drug and saline pairings occurred on alternate days with the drug pairings on days 1, 3, 5, and 7 and the saline pairings on days 2, 4, 6 and 8. Six groups of rats (n=7–8) were treated with saline or (+)-amphetamine sulphate (0.01, 0.1, 1.0, 2.0 and 4.0 mg/kg) and were placed into the nonstart compartment within 5 min following the injection. Similarly, six groups of rats (n=8–12) were administered saline or quinpirole hydrochloride (0.01, 0.1, 1.0, 2.0 and 4.0 mg/kg) 5 min prior to placement in the nonstart compartment on drug days. (+)-Amphetamine and quinpirole were dissolved in distilled water and injected IP in a volume of 1 ml/kg. Another five groups of rats (n=11–12) were injected with saline or SKF 38393 (0.01, 0.1, 1.0 and 10.0 mg/kg) 5 min prior to placement in the nonstart compartment. SKF 38393 was dissolved in distilled water, and was injected IP in a volume of 2 ml/kg. The saline injections on nondrug days were also injected at a volume of 2 ml/kg. A time delay of more than 5 min was not imposed between injection and placement because these drugs are known to be rapid-acting (20).

Treatment with the highest dose of SKF 38393, unexpectedly, produced a place aversion. This may have resulted from a peripheral effect of the drug. To test this hypothesis, an additional group of rats (n=8) was treated with 1.0 mg/kg SKF 82526. This compound is a D1 agonist that does not easily cross the blood-brain barrier (9). The dose of 1.0 mg/kg was chosen because this drug is approximately 100 times as potent as SKF 38393 (12). SKF 82526 was dissolved in distilled water and injected IP in a volume of 2 ml/kg.

The postconditioning test days occurred on the remaining three days. The guillotine doors were removed. Drug-free animals were placed in the start compartment and allowed to explore the entire box for 15 min. The time spent in each compartment was recorded.

RESULTS

Two animals which did not spend any time on one of the sides during a preexposure day were eliminated from the experiment. One rat was from the 1.0 mg/kg amphetamine group and the other from the saline condition of the SKF 38393 groups. In the majority of remaining rats, the apparatus did not result in strong unconditioned preferences for either side of the apparatus. Over 85 percent of the rats spent

TABLE 1

AVERAGE (±SEM) TIME (SEC) SPENT ON THE DRUG-PAIRED SIDE DURING PREEXPOSURE AND TEST

	Preexposure Average	Test 1	Test 2	Test 3
Amphetamine				
Saline	442 (27)	427 (43)	454 (40)	488 (37)
0.01	418 (25)	376 (50)	397 (67)	408 (57)
0.1	482 (34)	480 (54)	491 (49)	578 (47)
1.0	438 (34)	531 (46)	432 (19)	503 (46)
2.0	461 (25)	611 (40)†	469 (51)	564 (38)
4.0	427 (53)	606 (43)†	523 (90)	507 (53)
Quinpirole				
SAL	427 (26)	437 (44)	439 (39)	433 (40)
0.01	441 (24)	502 (31)	456 (32)	433 (35)
0.1	477 (25)	391 (30)	377 (41)	428 (67)
1.0	409 (16)	555 (44)*	548 (26)	529 (52)
2.0	430 (19)	486 (32)	472 (35)	437 (44)
4.0	453 (20)	491 (37)	475 (28)	459 (41)
SKF 38393				
SAL	477 (29)	549 (33)	549 (57)	538 (51)
0.01	437 (22)	458 (43)	438 (56)	402 (40)
0.1	442 (28)	462 (29)	447 (35)	389 (41)
1.0	418 (24)	382 (39)	419 (52)	416 (41)
10.0	467 (32)	299 (38)†	334 (56)	364 (66)
SKF 82526				
1.0	493 (15)	459 (51)	499 (56)	492 (69)

*$p<0.05$, †$p<0.01$.

between 35 and 65 percent of the preexposure session (900 sec) on the nonstart side (i.e., the drug-paired side) (also see Table 1).

During the preexposure sessions, the time spent in the drug-paired compartment did not differ significantly across days within any of the four drug conditions. Thus, for each animal, individual values for the three preexposure days were averaged to yield a baseline measure of the time spent on the drug-paired side prior to conditioning.

The average preexposure and test day scores for each dose of (+)-amphetamine, quinpirole, SKF 38393 and SKF 82526 are summarized in Table 1. Only the scores obtained on the first test day were included in the statistical analyses since previous studies have illustrated the strongest place conditioning effect on the first test day (17). For each drug, a two-way analysis of variance (ANOVA) with one repeated measure was conducted; the two variables analyzed were phase (preexposure versus test day one) and dose. Following a significant phase by dose interaction, tests of simple main effects on the phase variable were conducted at each dose. Separate error terms were calculated for each comparison because the phase variable was a repeated measure [see (14), p. 428]. A significant increase or decrease in time spent on the drug-paired side from preexposure to test suggests the establishment of a conditioned place preference or aversion, respectively.

Of the groups treated with amphetamine, the two-way ANOVA revealed a significant main effect of phase, $F(1,41)=12.96$, $p<0.01$, and a significant phase by dose interaction, $F(5,41)=5.26$, $p<0.001$. Tests of simple main effects on the phase variable at each dose revealed significant increases in time spent on the drug-paired side from preexposure to test in the 2.0 and 4.0 mg/kg groups, $F(1,7)=18.25$, $p<0.005$ and $F(1,7)=62.09$, $p<0.001$, respectively, suggesting the establishment of conditioned place preferences.

Quinpirole treatment was also effective in producing a place preference effect. A two-way ANOVA produced a significant phase effect, $F(1,54)=4.80$, $p<0.05$, and phase by dose interaction, $F(5,54)=2.76$, $p<0.05$. Subsequent analyses revealed a significant phase effect only in the 1.0 mg/kg group, $F(1,7)=7.76$, $p<0.05$.

A different picture resulted from SKF 38393 treatment. An overall two-way ANOVA of the five doses revealed a significant dose effect, $F(4,54)=4.52$, $p<0.005$, and a significant interaction, $F(4,54)=4.39$, $p<0.005$. Planned analyses of simple main effects demonstrated a significant phase effect in the 10.0 mg/kg group, $F(1,11)=15.61$, $p<0.005$, however it reflected a substantial decrease in time spent on the conditioned side from preexposure to test. Thus, treatment with 10.0 mg/kg SKF 38393 produced a conditioned place aversion.

To test the possibility that the aversive effects of SKF 38393 resulted from a peripheral action of the drug, a separate group of rats was tested with a comparable dose of SKF 82526, a DA D1 agonist which does not readily cross the blood-brain barrier. The average preexposure and first test day scores did not differ significantly ($p>0.05$).

To illustrate and compare dose effects within each drug condition, scores measuring the difference in the amount of time spent on the drug-paired side from preexposure to the first test day were calculated and are shown in Fig. 1. Treatment with amphetamine produced a dose-dependent effect on place preference conditioning with increasing doses yielding larger effects (Fig. 1). A linear trend analysis of the difference scores on the drug-treated groups was significant, $F(1,34)=25.64$, $p<0.001$. Comparisons between the saline group and amphetamine doses were made using Dunnett's multiple range test; treatment with 2.0 and 4.0 mg/kg produced a significantly greater change from baseline than saline treatment ($p<0.05$).

Neither a linear nor quadratic dose-response function was observed in rats treated with quinpirole (Fig. 1). A significant dose effect was obtained, $F(5,54)=2.76$, $p<0.05$, although post hoc comparisons (Dunnett's multiple range test) revealed that none of the doses differed reliably from saline.

Animals conditioned with SKF 38393 showed a dose-dependent decrease in time spent on the drug-paired side from pre- to postconditioning (as indicated by increasingly larger negative difference scores in Fig. 1). A linear trend analysis on the drug-treated groups was significant, $F(1,44)=11.07$, $p<0.005$. Furthermore, the substantial change observed in those rats treated with 10.0 mg/kg differed significantly from the saline group ($p<0.01$).

Finally, it appears that the saline group associated with the SKF 38393 groups showed an unusually large increase in time spent on the drug-paired side from preexposure to the first test day (Table 1). However, this difference was not significant, and furthermore, the difference scores (Fig. 1) obtained from the three saline groups were not significantly different ($p>0.05$). Thus, the large but nonsignificant increase from preexposure to test in this group is likely spurious.

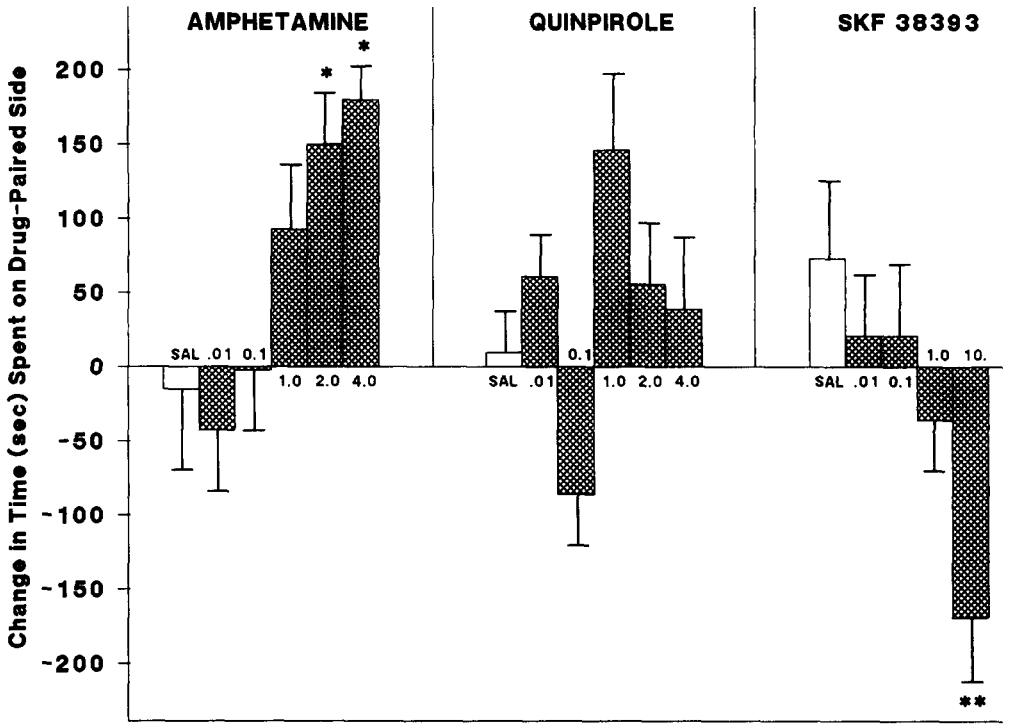

FIG. 1. Mean (±SEM) difference scores for each dose of (+)-amphetamine, quinpirole and SKF 38393. The scores were calculated by subtracting the time spent on the drug-paired side during the preexposure session (averaged over the three days) from the first test day. Thus, a positive score suggests a preference for the conditioned environment whereas a negative score suggests an aversion. *$p<0.05$, **$p<0.01$; differs significantly from saline.

DISCUSSION

The relative increase in time spent on the drug-paired side from preexposure to test in animals treated with certain doses of amphetamine and quinpirole suggests that the compounds produced conditioned place preferences. As the dose of amphetamine was increased, there was a corresponding increase in the place conditioning effect. A similar dose-dependent effect was not obtained with the D2 agonist, quinpirole. Rather, it appears that only an intermediate dose (1.0 mg/kg) was effective. The observation that the difference score obtained from this group did not differ significantly from saline is problematical, however, the significant increase in time spent in the drug-paired environment from pre- to postconditioning with quinpirole has now been replicated twice in this laboratory suggesting that quinpirole may produce a conditioned place preference. Conditioning with SKF 38393 produced a dose-dependent decrease in the amount of time spent on the conditioned side from preexposure to test with 10.0 mg/kg showing the largest effect. A peripheral action of the drug does not adequately explain this result because SKF 82526, a D1 agonist which does not readily penetrate the blood-brain barrier (9), failed to produce a place aversion. Thus, it appears that preferential stimulation of D1 and D2 receptors produced opposing effects in the place conditioning paradigm, aversion and preference, respectively.

EXPERIMENT 2

The behavioral differentiation of receptor subtypes seen in Experiment 1 may explain the ability of (+)-amphetamine to simultaneously establish a conditioned place preference and a conditioned taste aversion (CTA) in rats (19). That is, perhaps the D2 receptor underlies the rewarding qualities of psychomotor stimulants and the D1 receptor mediates the aversive properties. If this is true, one might expect SKF 38393, but not quinpirole, to produce a CTA. This hypothesis was tested in Experiment 2. To ensure comparability of results, a procedure was adopted which was similar in most details to the conditioned place preference method. Thus, unlike typical CTA protocols, the drug was administered immediately preceding presentation of the flavored solution. Because of the robust nature of the CTA paradigm, it was judged that only 4 conditioning days were necessary.

METHOD

Subjects

Forty-one male Wistar rats weighing 250 to 300 g were individually-housed in a temperature-controlled colony room on a 12-hr light-dark cycle. Animals were given limited access to water which consisted of two 30-min daily periods separated by 12 hr (0800 and 2000 hr). The water was always presented in two adjacent graduated Richter tubes (100 ml) attached to the front wall of the home cage. Food was continuously available.

Procedure

During one week of habituation to the colony room, all

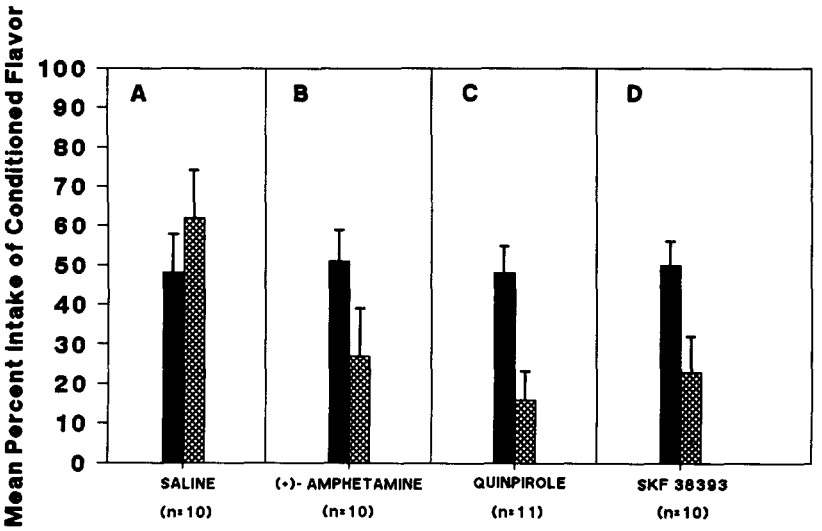

FIG. 2. Mean (±SEM) percent of conditioned flavor consumed during preexposure (solid) and test (cross-hatched) in rats treated with saline (A), 2.0 mg/kg amphetamine (B), 1.0 mg/kg quinpirole (C) and 10.0 mg/kg SKF 38393 (D).

rats were handled on several occasions. During the following week, animals were adapted to the drinking schedule (two daily 30-min sessions of tap water separated by 12 hr) for three consecutive days. On the following day, as usual, the animals received tap water for 30 min in the morning, however, 12 hr later (2000 hr) each rat was simultaneously presented with two novel flavored solutions: maple and almond (0.5% Blue Ribbon extract and 0.1% sodium saccharin). The positioning (i.e., right vs. left) of the flavors on the cage was counterbalanced across rats and days. As during the adapation period the flavors were presented for 30 min and the amount consumed (ml) was recorded. Preexposure to the two flavors was repeated on the following three evenings. The procedure of administering 30 min of tap water in the morning (0800) was continued during the preexposure period as well as throughout the remainder of the experiment to insure that the rats had sufficient fluid intake. Conditioning commenced on the evening following the last preexposure day. Rats were randomly assigned to four groups which differed on the basis of drug treatment. On evenings 1 and 3, immediately following an IP injection of either saline, 2.0 mg/kg amphetamine sulphate, 1.0 mg/kg quinpirole hydrochloride or 10.0 mg/kg SKF 38393, animals were given access to one flavor for 30 min (same flavored solution was presented in both tubes). These doses were chosen because they were effective in producing significant place conditioning effects in Experiment 1. Half of the animals in each group were presented with the almond flavor while the other half received maple. The drugs were prepared and injected in the same manner as in Experiment 1. On the second and fourth evenings, all rats were administered saline injections and presented immediately with the alternate flavored solution for 30 min.

Following the last conditioning day, rats received a 30-min presentation of the two flavors on each of four consecutive evenings. The procedure during the test phase was identical to that of the preexposure.

RESULTS AND DISCUSSION

Total fluid consumption among the four groups did not differ significantly during the preexpousre or test sessions, $F(3,37)=0.73$, $p>0.05$ and $F(3,37)=1.61$, $p>0.05$, respectively. However, on the first drug-pairing day, total fluid intake differed reliably among the four groups, $F(3,37)=21.23$, $p<0.01$. Dunnett's multiple range test revealed that amphetamine, quinpirole and SKF 38393 significantly reduced total intake relative to saline ($p<0.05$). Drinking levels in the drug groups were also significantly suppressed on the second drug-pairing day ($p<0.05$). This first day effect is not surprising given the adipsic properties of amphetamine; the similar results with quinpirole and SKF 38393 suggest that D1 and D2 receptors may be involved.

Consumption of the conditioned flavor was expressed as a percentage of total fluid intake. Values from the four preexposure days were averaged together as were the values from the four test days (Fig. 2). A significant increase or decrease in the percent intake of the conditioned flavor from preexposure to test signifies the establishment of a taste preference or aversion, respectively. In general, consumption of the conditioned flavor tended to approximate 50 percent of their total intake during preexposure. Following drug-pairings, percent intake of the conditioned flavor in the saline group showed a slight increase (Fig. 2A). In contrast, when the conditioned flavor was paired with 2.0 mg/kg amphetamine, 1.0 mg/kg quinpirole or 10.0 mg/kg SKF 38393, there was a large decrease in percent consumption (Fig. 2B, C, D).

A two-way ANOVA with one repeated measure (phase) was conducted on the four treatment groups. The group effect was not significant ($p>0.05$), but the phase effect and phase by group interaction were, $F(1,37)=19.09$, $p<0.001$ and $F(3,37)=7.14$, $p<0.001$, respectively. To examine the phase effect in each group, tests of simple main effects were conducted. Because the phase variable was a repeated

measure, separate error terms were calculated for each comparison [see (14), p. 428]. Rats treated with amphetamine, quinpirole or SKF 38393 demonstrated significant phase effects, $F(1,9)=6.38$, $p<0.05$, $F(1,10)=22.76$, $p<0.001$ and $F(1,9)=9.29$, $p<0.05$, respectively. The phase effect in the saline group was not significant, $F(1,9)=4.88$, $p>0.05$.

Thus, the hypothesis that the D1 receptor is exclusively involved in mediating the aversive qualities of psychomotor stimulants was not confirmed. Preferential stimulation of either D1 or D2 receptors resulted in significant CTAs similar to that produced by amphetamine.

GENERAL DISCUSSION

Given previous reports that DA receptor agonists produced conditioned place preferences (18,27) the purpose of Experiment 1 was to determine if preferential stimulation of either the D1 or D2 receptor subtype resulted in a similar effect. In agreement with previous studies (23), rats treated with the indirect-acting agonist, (+)-amphetamine, showed a dose-dependent conditioned place preference. Results with the selective D2 agonist, quinpirole suggested that conditioning with this compound also resulted in a significant place preference effect but only at one dose. However, the absence of a dose-dependent function and the failure to observe a significant difference between the groups treated with saline and 1.0 mg/kg does not allow unequivocal interpretation of the data. On the other hand, perhaps the effect produced by quinpirole was simply weaker than that observed with amphetamine. Selective stimulation of the D1 receptor produced an opposite effect; rats treated with SKF 38393 demonstrated a significant aversion to the drug-paired environment.

Together, these results are in agreement with those of Gilbert *et al.* (8) who reported that the D2 agonist, N-0437, produced a conditioned place preference whereas stimulation of D1 receptors with SKF 38393 produced a nonsignificant aversion. Also, in a separate series of experiments conducted in this laboratory, treatment with either quinpirole or another D2 agonist, bromocriptine, produced conditioned place preferences in rats (10). Although conditioning in quinpirole-treated animals was most evident in the intermediate dose range (0.025 and 1.0 mg/kg), only one dose (0.1 mg/kg) produced a significant increase in time on the drug-paired side from preexposure to test. This optimal dose is smaller than the effective dose of the present study. The reason for this discrepancy may be related to the fact that animals of the earlier study were housed individually while those of the present experiment were housed in groups. Perhaps isolated animals are more sensitive to the reinforcing effects of quinpirole thus shifting the dose-response curve to the left. There is some empirical support for this suggestion. Alexander, Coambs and Hadaway (1) demonstrated the importance of housing conditions in the oral consumption of morphine: When rats were given a choice between water and a morphine solution, animals housed in isolation consumed significantly more of the solution than the group-housed animals.

The rewarding properties of psychomotor stimulants have also been assessed in self-administration studies. Animals, including humans, learn to self-administer cocaine, amphetamine and apomorphine (2, 28, 30). Woolverton and colleagues have recently assessed the role of D1 and D2 receptors in this paradigm; their results were consistent with the place preference data. For example, Woolverton *et al.* (29) discovered that rhesus monkeys learned to press a lever to obtain intravenous injections of D2 agonists but failed to acquire this response for the D1 agonist, SKF 38393. Furthermore, Woolverton (28) examined the effects of the DA receptor antagonists pimozide and SCH 23390 on cocaine and piribedil (a D2 receptor agonist) self-administration. Typically, DA receptor antagonists produce an initial increase in self-administration rates followed by a gradual decline (30). Woolverton (28) observed a rate-increasing effect in cocaine and piribedil self-administration only in animals pretreated with intermediate doses of pimozide, a D1 and D2 blocker. SCH 23390, a D1 specific antagonist, produced no effect or decreased response rates in all but one monkey. Woolverton (28) concluded that the D2 receptor was involved in mediating the reinforcing effects of pscyhomotor stimulants.

Opposing effects of D1 and D2 stimulation were observed in place conditioning. If it was found that D1 but not D2 stimulation produced a CTA, this may have accounted for the discovery that amphetamine produces a conditioned place preference and a conditioned taste aversion (19). However, Experiment 2 showed that this prediction was not supported: SKF 38393 and quinpirole both produced significant taste aversions similar to that demonstrated by amphetamine. Thus, paradoxical rewarding and aversive effects like those of amphetamine were seen when D2 receptors were preferentially stimulated.

Recently, Carr and White (5) were able to anatomically disassociate amphetamine's rewarding and aversive actions. By injecting amphetamine directly into several discrete regions of the rat's brain, they discovered that place preference learning was mediated by DA terminals in the nucleus accumbens whereas taste aversion learning was mediated by an area below the area postrema (which includes the nucleus of the solitary tract and the dorsal motor nucleus of the vagus). Autoradiographic binding studies have demonstrated high levels of D1 and D2 receptors in the nucleus accumbens (6). In characterizing the functional nature of D1 and D2 receptors, it would be of considerable interest to determine if the SKF 38393-induced place aversion is also mediated within the nucleus accumbens. To our knowledge, autoradiographic binding studies have not investigated the possibility of D1 and D2 receptors in the dorsal motor nucleus of the vagus and the nucleus of the solitary tract. Whether SKF 38393 and quinpirole CTAs are mediated within this area will be the task of future research.

The present investigation supports the suggestion that preferential stimulation of the D2 receptor contributes to the reinforcing effects of psychomotor stimulants. Whether the D2 receptor is exclusively involved in reinforcement remains unknown; the observation that quinpirole produced a somewhat weak place preference effect may suggest otherwise. Moreover, a recent study has demonstrated that amphetamine-induced place conditioning is attenuated in rats pretreated with the D1 receptor antagonist, SCH 23390 (15). On the other hand, preferential stimulation of the D1 receptor is clearly not rewarding and in fact a strong place aversion was obtained. Studies assessing the effects of selective D1 and D2 receptor blockade on agonist-induced place conditioning are currently underway and may provide further understanding of the role of DA receptor subtypes in reward.

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NOTE ADDED IN PROOF

Following the preparation of this manuscript, a further anomaly of quinpirole-induced place conditioning was discovered. Separate groups of rats were conditioned with either 2.0 mg/kg amphetamine, 1.0 mg/kg quinpirole or 10.0 mg/kg SKF 38393 using the same procedure described above; however, during the test, the animals were again treated with the conditioning drug. Groups treated with amphetamine or SKF 38393 showed a significant change in time spent on the drug-paired side from the average preexposure to the first test day. The amphetamine group showed a place preference (average preexposure and first day scores were 429 and 672 sec, respectively) while the SKF 38393 group showed an aversion (437 sec vs. 192 sec). Rats conditioned with quinpirole failed to show any significant change from preexposure to test (439 sec vs. 387 sec). This suggests that the stimulus properties of quinpirole influenced the place preference effect. The reason for this drug-induced state-dependency remains unclear. Because animals always experienced the conditioned environment in the drugged state, others have suggested that during the test, the now drug-free animal may approach and spend more time on this side simply due to its perceived novelty (Mucha and Iversen, Psychopharmacology (Berlin) 82:241–247; 1984). This, however, may not adequately explain the quinpirole place preference; we tested an additional group of nondrugged rats which received minimal exposure to only one of the environments during conditioning and observed that they failed to show a preference (or aversion) for the relatively novel environment (453 sec vs. 421 sec). For further information, see Hoffman, D. C. The role of dopamine D1 and D2 receptors in operant and place conditioning in rats. Doctoral dissertation, Queen's University, Kingston, 1988.