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The Effects of Selective Dopamine D1 or D2 Receptor Antagonists on the Establishment of Agonist-Induced Place Conditioning in Rats

DIANE C. HOFFMAN[1] AND RICHARD J. BENINGER

Department of Psychology, Queen's University, Kingston, Ontario K7L 3N6

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HOFFMAN, D. C. AND R. J. BENINGER. *The effects of selective dopamine D1 or D2 receptor antagonists on the establishment of agonist-induced place conditioning in rats.* PHARMACOL BIOCHEM BEHAV **33**(2) 273–279, 1989.—The ability of the dopamine D1 antagonist, SCH 23390 (0.01, 0.1, 1.0, 2.0 mg/kg) or the D2 antagonist, metoclopramide (1.0, 10.0, 20.0 mg/kg), to block the establishment of place conditioning with either the nonselective dopamine agonist, amphetamine (2.0 mg/kg), the D1 agonist, SKF 38393 (10.0 mg/kg), or the D2 agonist, quinpirole (1.0 mg/kg), was evaluated in rats. The experimental protocol consisted of three phases. During the preexposure phase, rats explored two distinctive compartments joined by a small tunnel. During the 8-day conditioning phase, rats were pretreated with either saline, SCH 23390 or metoclopramide; 1 hr later the animals were treated with an agonist 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 3 days during which drug-free animals were allowed access to both compartments. A significant increase or decrease in the amount of time spent in the drug-paired environment was indicative of a place preference or aversion, respectively. SCH 23390 and metoclopramide were effective in blocking amphetamine-induced place preference and SKF 38393-induced place aversion. At lower doses, the D1 and D2 antagonist blocked the place preference induced by quinpirole, however, higher doses were not effective. In general, these data suggest that both receptor subtypes participate in the establishment of place conditioning with amphetamine, SKF 38393 or quinpirole.

Amphetamine Dopamine D1 and D2 receptors Quinpirole Metoclopramide Place conditioning
SCH 23390 SKF 38393 Rats

PSYCHOMOTOR stimulants (e.g., cocaine, amphetamine) are self-administered by both human and nonhuman animals. The rewarding properties of these substances have also been demonstrated using the place conditioning paradigm. After receiving several pairings of a drug injection with placement in one side of a box and not the other, the undrugged animal subsequently shows a preference for the drug-paired side. Although some controversy exists [e.g., (31)], this shift in preference from pre- to postconditioning is assumed to reflect the rewarding properties of the drug.

Several lines of evidence suggest that the central neurotransmitter, dopamine (DA), is involved in the acquisition of place conditioning. First, many drugs which produce place preferences exert their primary central effects on dopaminergic neurons (16,26). Secondly, DA receptor antagonists such as haloperidol or pimozide inhibit the establishment of amphetamine- or cocaine-induced place conditioning (27,33), and finally, selective neurotoxic lesions of ascending dopaminergic neurons attenuate the establishment of amphetamine-induced place preferences (33).

Two DA receptor subtypes exist and they are classified according to their association with the enzyme, adenylate cyclase (12,13). Whereas D1 receptors stimulate the synthesis of cyclic adenosine monophosphate (cAMP) through activation of adenylate cyclase, D2 receptors are unrelated or in some areas of the brain (pituitary, striatum but not the nucleus accumbens) inhibit the enzyme (4,35).

A limited number of studies have investigated the relative involvement of each receptor subtype in mediating the rewarding effects of psychomotor stimulants. Using the place conditioning procedure, it was shown that preferential stimulation of the D2 receptor with quinpirole or bromocriptine (6, 22, 36) resulted in the establishment of a place preference (8,9); in contrast, the D1 receptor agonist, SKF 38393 (32), produced a dose-dependent aversion to the drug-paired environment (8). These finding are consistent with self-administration studies in which animals were shown to self-administer the D2 agonists, bromocriptine or piribe-

[1]Requests for reprints should be addressed to Diane C. Hoffman, Ph.D., Center for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, 1455 de Maisonneuve Blvd., West, Montreal, Quebec H3G 1M8.

dil but not the D1 agonist, SKF 38393 (39).

Although the results from these studies suggest a more important role for the D2 receptor, there is reason to question this conclusion. First, the D2 agonists were effective in establishing place conditioning only within a limited dose range [see (8)], and second, unlike amphetamine or SKF 38393, the place conditioning observed with quinpirole was state-dependent. That is, rats conditioned with quinpirole only showed a place preference when tested drug-free; if the animals were given quinpirole during the test, they no longer showed a preference for the drug-paired side (8). The reason for this state-dependency is presently unclear. In self-administration studies, furthermore, it has been found that the D1 receptor blocker, SCH 23390, produced a significant and dose-dependent increase in the rate of cocaine self-administration in rats suggesting that the reinforcing efficacy of cocaine was reduced (15). Thus, D1 receptors may also be involved in mediating the rewarding effects of DA agonists.

To assess further the possible contribution of D1 and D2 receptors in mediating the reinforcing properties of psychomotor stimulants, the ability of selective DA receptor antagonists in altering agonist-induced place conditioning was examined. Several doses of the selective D1 and D2 antagonist, SCH 23390 (11) and metoclopramide (18, 23, 28), respectively, were tested concurrently with an effective dose of either amphetamine, quinpirole or SKF 38393. If D2 receptor stimulation exclusively mediates reward, then amphetamine-induced place conditioning should be blocked by the D2 antagonist, metoclopramide, but not the D1 antagonist, SCH 23390. Similarly, metoclopramide but not SCH 23390 may block the place preference produced by quinpirole.

METHOD

Subjects

Two hundred and thirty-two male Wistar rats (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-hr light (0600–1800)/dark cycle and had free access to food and water. During 1 week of habituation to the colony room, all rats were handled on several occasions.

Apparatus

Four similar rectangular chambers (84 × 27 × 36 cm) were constructed of wooden sides and removable Plexiglas covers. Each chamber 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 on the walls and floor texture; in two chambers, 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 rod (1 cm between rods) floor. In the remaining two chambers, the striped compartment had a mesh floor and the brown compartment had a rod floor. The floors of the chamber were positioned on a fulcrum such that the weight of a rat in one compartment caused a microswitch to close initiating a timer in another room. Thus, the amount of time spent in each compartment was recorded. Each chamber was enclosed in a sound-attenuating wooden box which was ventilated by a small fan and indirectly illuminated by a dim light (7.5-watt) located between the two end compartments.

Drugs

(+)-Amphetamine sulphate (Smith, Kline & French), quinpirole hydrochloride (Lilly) and SKF 38393 hydrochloride (Smith, Kline & French) were dissolved in distilled water and injected intraperitoneally (IP) 5 min prior to confinement in one compartment. Amphetamine and quinpirole were injected in a volume of 1 ml/kg; SKF 38393 was injected in a volume of 2 ml/kg due to solubility limitations. SCH 23390 (Schering) was suspended in a small quantity of the polymer, polyoxyethylene sorbitan monooleate (Tween 80) and added to distilled water to an appropriate concentration to yield an injection volume of 1.0 ml/kg. Metoclopramide hydrochloride (Nordic) was dissolved in distilled water to yield an injection volume of 1.0 ml/kg. SCH 23390 and metoclopramide were injected IP 1 hr prior to testing.

Procedure

The general procedure (and apparatus) was adapted from Mithani *et al.* (24). The experimental design consisted of three phases which occurred over 14 consecutive days. The preexposure phase involved adapting the rats to the experimental chambers and obtaining a baseline measure of the amount of time spent in each compartment for 15 min on each of 3 days. With the guillotine doors removed, the rats were placed in a compartment (designated the Start compartment) with access to the entire chamber. The choice of the Start compartment was counterbalanced across rats and remained the same for each animal across days. On each of the 3 preexposure days, the amount of time the rat spent in each compartment was measured.

This was followed by the conditioning phase that 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. On the remaining four sessions, the animal received saline 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. Separate groups of rats (n = 8) were pretreated with either saline, the D1 receptor antagonist, SCH 23390 (0.01, 0.1, 1.0 or 2.0 mg/kg), or the D2 receptor antagonist, metoclopramide (1.0, 10.0 or 20.0 mg/kg). One hr later, rats were injected with either 2.0 mg/kg amphetamine, 1.0 mg/kg quinpirole or 10.0 mg/kg SKF 38393 and placed in the Nonstart compartment. These doses of agonists were chosen because they were previously shown to produce place conditioning (8). On the alternate nondrug days, rats were injected twice with saline: one hr before and immediately prior to placement in the Start compartment.

Six additional groups (n = 8) were included to determine the effects of SCH 23390 or metoclopramide alone on place conditioning. Thus, on drug-pairing days, saline, SCH 23390 (1.0 or 2.0 mg/kg) or metoclopramide (1.0, 10.0 or 20.0 mg/kg) was injected 1 hr prior to a saline injection and placement in the Nonstart compartment.

The postconditioning test occurred on the remaining 3 days. The guillotine doors were removed. Drug-free animals were placed in the Start compartment with access to the entire chamber for 15 min. The time spent in each compartment was recorded.

Statistical Analyses

The amount of time spent on the drug-paired side of the apparatus during the preexposure and test phases was analysed using analysis of variance (ANOVA). Whenever repeated measures were included in the analysis, the Geisser-Greenhouse adjusted degrees of freedom were used to reduce the positive bias in the F values resulting from violation of homogeneity assump-

tions [see (14)]. The p values based on these degrees of freedom were provided by the BMDP4V Statistical Software package.

RESULTS

Six animals which did not spend any time on one of the sides during a preexposure day were eliminated from the experiment. An additional two rats were excluded from the study due to methodological errors. In the majority of remaining rats, strong unconditioned preferences for either side of the apparatus were not seen. Over 85 percent of the rats spent on average between 35 and 65 percent of the preexposure sessions on the drug-paired side and there were no marked deviations between groups.

Prior to analysing for the presence of place conditioning, steps were taken to simplify the data. The amount of time spent on the drug-paired side during the preexposure did not vary significantly over the 3 days in any of the agonist conditions (including the saline control groups). Thus, for each animal, individual values for the 3 preexposure days were averaged to yield one baseline measure.

The 3 test days were not averaged together because in the amphetamine and quinpirole groups, the amount of time spent on the drug-paired side differed significantly across the 3 test days, $F(1.94, 104.61) = 5.49$, $p<0.01$, and, $F(1.99, 105.38) = 3.11$, $p<0.05$, respectively. These main effects represent a decline in time over days; the values collapsed across groups for the amphetamine condition were 525, 470 and 465 sec, and for the quinpirole condition were 507, 488 and 464 sec.

To analyse for place conditioning, the average preexposure was compared to the first test day. This test day was chosen because previous studies, as well as the present study, have illustrated the strongest place conditioning effect on this day (24). 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.

The average preexposure score and the three test day scores for the groups treated with amphetamine and pretreated with saline or SCH 23390 are illustrated in Fig. 1A. A two-way ANOVA with one repeated measure was conducted; the two variables analysed were PHASE (preexposure versus Test Day 1) and GROUP. Of the groups treated with amphetamine and SCH 23390 (including the saline group), the phase effect was highly significant, $F(1,34) = 24.75$, $p<0.001$, while the group effect and phase by group interaction were nonsignificant. These results suggest that pretreatment with SCH 23390 failed to influence the conditioned place preference produced by amphetamine; however, it appears from Fig. 1A that 2.0 mg/kg was effective in blocking place conditioning and furthermore, the phase by group interaction approached significance, $F(4,34) = 2.34$, $p = 0.08$. To analyse these data further, planned tests of simple main effects were conducted on the phase variable at each group, using separate error terms (14). The phase effect was significant in the groups pretreated with saline, 0.01 or 0.1 mg/kg SCH 23390, $F(1,6) = 11.14$, $p<0.025$, $F(1,7) = 16.17$, $p<0.01$, or $F(1,7) = 15.32$, $p<0.01$, respectively, although the effect at 1.0 mg/kg approached significance, $F(1,7) = 4.37$, $p = 0.07$. These results suggest that the two highest doses of the D1 receptor antagonist attenuated or blocked the establishment of place conditioning with amphetamine.

The average preexposure and test day scores for amphetamine place conditioning in rats pretreated with saline or metoclopramide are shown in Fig. 1B. A two-way ANOVA with one repeated measure (PHASE) revealed a significant phase effect, $F(1,26) = 9.83$, $p<0.005$. The group effect and phase by group interaction failed to reach significance. Despite the nonsignificant interaction,

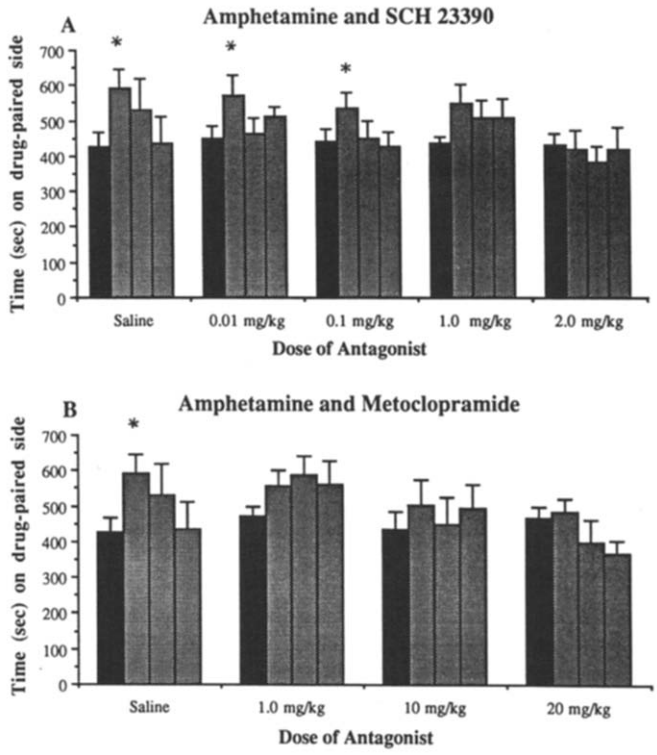

FIG. 1. Mean (±SEM) time spent on the drug-paired side during the average preexposure (black bar) and each test day (3 shaded bars). (A) Rats treated with amphetamine and SCH 23390 (saline, 0.01, 0.1, 1.0 or 2.0 mg/kg). (B) Rats treated with amphetamine and metoclopramide (saline, 1.0, 10.0 or 20.0 mg/kg). The same saline-amphetamine group is shown in the top and bottom panels. *$p<0.05$, differs significantly from preexposure.

planned tests of simple main effects were conducted on the phase variable at each group. These tests were justified because the comparison had a theoretical basis and was built into the design of the experiment (38). None of the groups treated with metoclopramide showed a reliable phase effect suggesting that the D2 receptor antagonist inhibited amphetamine-induced place conditioning at all doses. However, the phase effect associated with the lowest dose of metoclopramide approached significance, $F(1,7) = 4.68$, $p = 0.07$.

Results from the quinpirole place conditioning groups pretreated with SCH 23390 are illustrated in Fig. 2A. It appears that only the lower doses of SCH 23390 attenuated place conditioning. Following a significant phase by group interaction, $F(3,26) = 3.15$, $p<0.05$, tests of simple main effects revealed a significant phase effect in the saline and high dose conditions, $F(1,7) = 9.14$, $p<0.025$, and, $F(1,7) = 7.09$, $p<0.05$, respectively. Thus, it appears that the two lower doses of SCH 23390 were effective in antagonizing place conditioning but the highest dose of 1.0 mg/kg was not.

A strikingly similar picture resulted when the quinpirole animals were pretreated with metoclopramide (Fig. 2B). Here, only the intermediate dose of the drug was effective in blocking place conditioning. A two-way ANOVA indicated significant main effects of phase, $F(1,28) = 34.33$, $p<0.001$, and group, $F(3,28) = 4.03$, $p<0.025$, and the phase by group interaction approached significance, $F(3,28) = 2.47$, $p = 0.08$. Tests of simple main effects revealed significant phase effects ($p<0.025$) in all

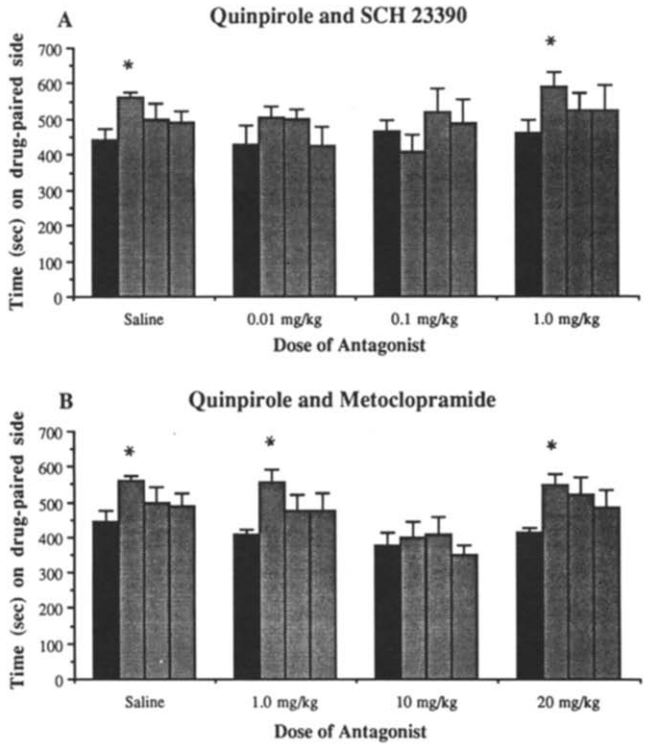

FIG. 2. Mean (±SEM) time spent on the drug-paired side during the average preexposure (black bar) and each test day (3 shaded bars). (A) Rats treated with quinpirole and SCH 23390 (saline; 0.01, 0.1 or 1.0 mg/kg). (B) Rats treated with quinpirole and metoclopramide (saline, 1.0, 10.0 or 20.0 mg/kg). The same saline-quinpirole group is shown in the top and bottom panels. *$p<0.05$, differs significantly from preexposure.

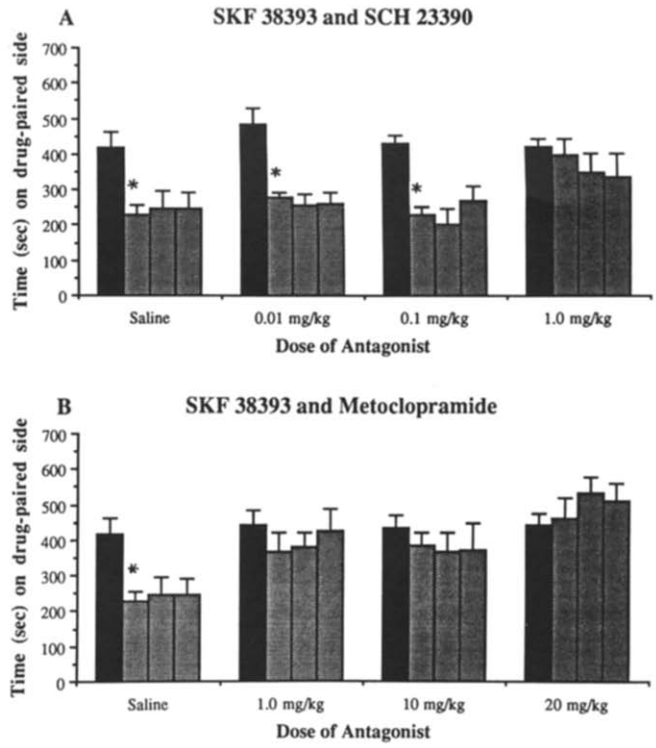

FIG. 3. Mean (±SEM) time spent on the drug-paired side during the average preexposure (black bar) and each test day (3 shaded bars). (A) Rats treated with SKF 38393 and SCH 23390 (saline, 0.01, 0.1 or 1.0 mg/kg). (B) Rats treated with SKF 38393 and metoclopramide (saline, 1.0, 10.0 or 20.0 mg/kg). The same saline-SKF 38393 group is shown in the top and bottom panels. *$p<0.05$, differs significantly from preexposure.

groups except the 10.0 mg/kg metoclopramide group. Again the results suggest that a high dose of the antagonist was no longer effective in blocking place conditioning. To ensure that this latter place conditioning effect was reliable, a new group of rats (n = 7) was tested with the same treatment. A similar pattern of results emerged; there was a significant increase in time spent on the drug-paired side from preexposure to test, $F(1,6) = 10.45$, $p<0.025$.

The average preexposure and test day scores for SKF 38393 place conditioning in rats pretreated with SCH 23390 are shown in Fig. 3A. The D1 agonist produced a place aversion and only the highest dose of SCH 23390 appears to have inhibited the aversive properties of this drug. This was confirmed statistically; a two-way ANOVA revealed a significant interaction, $F(3,27) = 4.38$, $p<0.025$, and tests of simple main effects demonstrated a reliable phase effect ($p<0.005$) in each group except the one pretreated with the highest dose of SCH 23390. Metoclopramide was also effective in antagonizing place conditioning with SKF 38393 but in this case all doses of metoclopramide were effective (Fig. 3B). A two-way ANOVA resulted in a significant phase by group interaction, $F(3,27) = 3.09$, $p<0.05$, but only in the saline group was the simple main effect of phase significant, $F(1,7) = 18.56$, $p<0.005$.

The average preexposure and test day scores from the control groups treated with saline and SCH 23390 are depicted in Fig. 4A. A two-way ANOVA (PHASE, GROUP) resulted in no significant effects. Furthermore, planned tests of simple main effects on the phase variable of each group also revealed no reliable effects. The data from the saline and metoclopramide control groups are shown in Fig. 4B. A two-way ANOVA conducted on the four groups revealed a significant main effect of phase, $F(1,28) = 5.66$, $p<0.025$, and tests of simple main effects demonstrated reliable phase effects in the 10.0 and 20.0 mg/kg groups, $F(1,7) = 7.91$, $p<0.05$, and, $F(1,7) = 12.70$, $p<0.01$, respectively.

DISCUSSION

The main results can be summarized as follows.

1) Both the D1 and D2 receptor blockers antagonized the establishment of amphetamine-induced place preference with the highest dose of each blocker being the most effective.

2) Whereas the the two lowest doses of SCH 23390 inhibited the establishment of place conditioning with the D2 agonist, quinpirole, the place preference reappeared when animals were pretreated with the highest doses of SCH 23390. A strikingly similar picture resulted when rats were pretreated with the D2 receptor antagonist, metoclopramide. An intermediate dose of the drug blocked conditioning, whereas a high dose did not.

3) Both SCH 23390 and metoclopramide blocked the establishment of the place aversion produced by SKF 38393. In each case, the highest dose of the antagonist was the most effective.

4) High doses of SCH 23390 administered alone failed to produce place conditioning. Metoclopramide at doses of 10.0 or 20.0 mg/kg produced a significant increase in the amount of time

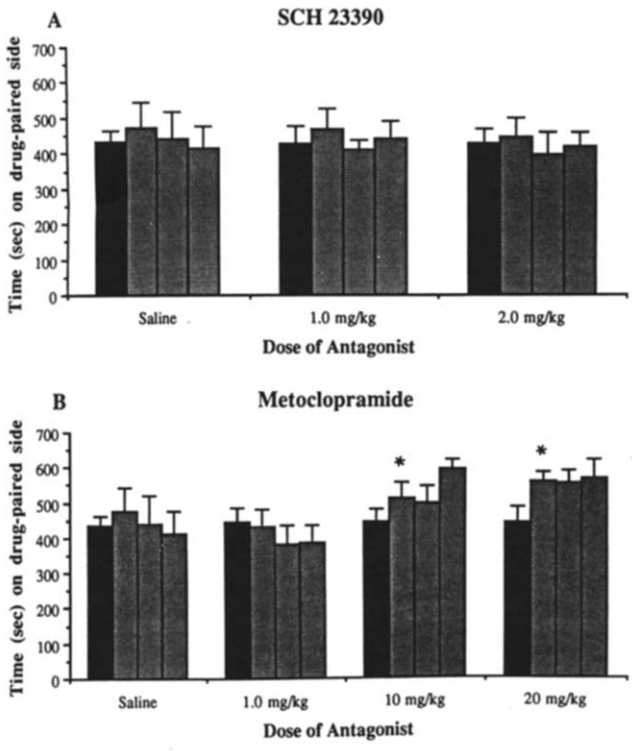

FIG. 4. Mean (±SEM) time spent on the drug-paired side during the average preexposure (black bar) and each test day (3 shaded bars). (A) Rats treated with saline and SCH 23390 (saline, 1.0 or 2.0 mg/kg). (B) Rats treated with saline and metoclopramide (saline, 1.0, 10.0 or 20.0 mg/kg). The same saline-saline group is shown in the top and bottom panels. *$p<0.05$, differs significantly from preexposure.

spent on the conditioned side from preexposure to test suggesting the establishment of a place preference.

The Effects of DA Receptor Antagonists on Amphetamine-Induced Place Conditioning

It has been shown previously that DA receptor antagonists which bind predominantly to D2 receptors or to both D1 and D2 receptors attenuate the rewarding properties of amphetamine and cocaine (27,33). The finding in the present study that metoclopramide antagonized the amphetamine-induced place preference is consistent with these earlier reports. More recently, it was demonstrated that blockade of D1 receptors with SCH 23390 blocked the establishment of amphetamine-induced place conditioning in rats (17). This also is in good agreement with the present results; however, a much higher dose of SCH 23390 was required in the present study. The reason for this discrepancy is unknown but may be related to the time or route of SCH 23390 administration (e.g., IP vs. subcutaneous, 60 min vs. 10 min prior to conditioning) or to the dose of amphetamine (2.0 mg/kg vs. 1.0 mg/kg). Furthermore, the relatively large dose employed in this experiment raises the possibility that some loss of dopaminergic selectivity may have occurred [see (2)].

The Effects of DA Receptor Antagonists on Quinpirole-Induced Place Conditioning

The observation that low to intermediate doses of SCH 23390 or metoclopramide attenuated the effect suggests that the functional operation of both receptors may be necessary for the establishment of quinpirole-induced place conditioning. Ironically, high doses of either antagonist failed to affect conditioning with quinpirole. As the high dose of metoclopramide itself produced a significant effect, this may account for the place preference observed with this antagonist. On the other hand, an intermediate dose of metoclopramide when given alone also induced a significant place preference yet this dose was *effective* in blocking quinpirole conditioning.

There is some difficulty in interpreting the establishment of conditioning when high doses of the antagonists were employed. Nevertheless, the inhibition produced by low doses (which themselves either had no effect or produced a place preference) suggests that the functional integrity of both receptors may be necessary for the acquisition of the quinpirole-induced place preference.

The Effects of DA Receptor Antagonists on SKF 38393-Induced Place Conditioning

The place aversion observed in rats treated with SKF 38393 is consistent with previous studies (8,39), but the generalization of these results is limited given that only one D1 receptor agonist, namely, SKF 38393, has ever been tested. This may be relevant because SKF 38393, although one of the most selective D1 agonists available that crosses the blood-brain barrier (5), acts only as a partial agonist in stimulating adenylate cyclase (32).

As expected, the SKF 38393-induced place aversion was attenuated by the D1 antagonist, SCH 23390. The D2 antagonist was also effective; however, as animals conditioned with metoclopramide alone demonstrated a place preference, this may have independently influenced the attenuation of the place aversion. This interpretation, however, has some difficulty accounting for the finding that the lowest dose of metoclopramide (1.0 mg/kg) attenuated the aversion yet alone produced no significant place conditioning effect. Thus, it would seem that the D2 receptor may indeed play a role in acquisition of the SKF 38393-induced place aversion.

The Effects of DA Receptor Antagonists Alone in the Place Conditioning Paradigm

Rats treated with the D1 antagonist, SCH 23390, showed little evidence of place conditioning. In contrast, treatment with intermediate to high doses of the D2 antagonist produced significant place preferences.

Recently, it was found that metoclopramide enhanced the locomotor stimulant effects of amphetamine (10). Although this appears consistent with the similar effects of amphetamine and metoclopramide in the present study, there is some reason to suspect that the place conditioning induced by these two drugs reflects different underlying mechanisms. That is, when these drugs were administered together, place conditioning was no longer observed. If the effects found with either amphetamine or metoclopramide were similar, in that they each reflect rewarding properties of the drug, then one might expect enhanced conditioning in rats treated concurrently with the two compounds; this was not the case, all doses of metoclopramide blocked amphetamine-induced conditioning.

The difference between these two drugs may lie in their potential to act as rewarding stimuli. It is well-documented that amphetamine's effects are reinforcing; both animals and humans readily self-administer the stimulant. This does not appear to be

the case for metoclopramide; this drug is widely used in humans for its powerful antiemetic action yet cases of abuse have not been reported (7,29). In addition, rats pretreated with metoclopramide, like other neuroleptics, showed a compensatory increase in the self-administration of cocaine suggesting that the rewarding properties of the stimulant were reduced (30). Thus, there does not appear to be any evidence (with the exception of the present study) suggesting that metoclopramide possesses rewarding properties. Although this difference between metoclopramide and amphetamine does not unequivocally implicate distinct mechanisms for inducing place conditioning, it is in agreement with such a proposal and does support the notion that rewarding processes may be involved only in amphetamine-induced place conditioning.

An alternative mechanism for the metoclopramide-induced place preference may be related to novelty effects. As suggested by the results of Carr *et al.* (3), an animal may spend more time in an environment simply because of its perceived novelty. It is conceivable that drugs which decrease locomotor activity prevent the animal from fully exploring the drug-paired environment, and consequently, during the drug-free test, this compartment is perceived as more novel. This may explain the place preference produced by metoclopramide as this drug has been shown to decrease locomotor activity (1).

Evidence for DA Receptor Subtype Interaction

One of the most striking observations from these results is the similar effect SCH 23390 and metoclopramide had within each agonist condition (amphetamine, quinpirole and SKF 38393). This may not be surprising in the case of amphetamine as this drug is an indirect-acting agonist which enhances the release of DA from terminals; the increased concentration of synaptic DA presumably binds to both D1 and D2 receptors. Furthermore, these results are consistent with previous findings showing that D1 and D2 receptor antagonists blocked amphetamine- and apomorphine-induced unconditioned behaviors (11,21). This suggests that each receptor type contributes to the behavioral effects of amphetamine and apomorphine (a direct-acting D1/D2 agonist).

Quinpirole and SKF 38393 are direct-acting and bind predominantly to one receptor subtype, yet again it was observed that the alternative receptor antagonist inhibited the behavioral effects of these drugs. There is an increasing amount of evidence demonstrating that SCH 23390 blocks behavioral effects associated with quinpirole (19, 20, 34, 37) and metoclopramide antagonizes the behavioral effects of SKF 38393 (25). Together, these findings have important implications for understanding the functional organization of the two receptor subtypes: they suggest that the two receptors do not exist independently with clearcut behavioral functions. The observation that a D1 antagonist disrupted the behavioral and physiological effects of a D2 agonist (or vice versa) suggests that tonic endogenous DA which normally interacts with the D1 receptor is important for observing the D2-mediated effect. This also seems to hold true for D1-mediated effects.

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