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Effects of selective drugs for dopaminergic D1 and D2 receptors on conditioned locomotion in rats

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Abstract. Classically conditioned locomotor activity has been demonstrated by pairing injections of dopamine agonists or antagonists with specific environmental stimuli. The present studies investigated conditioning using drugs with varying selectivity for the dopamine D1 or D2 receptor. Experiment 1 assessed conditioning in groups of rats using the indirect acting agonist (+)-amphetamine (2.0 mg/kg), and the D1 agonist SKF 38393 (10.0 mg/kg), the D2 agonist quinpirole (2.5 mg/kg), the D1 and D2 antagonists, SCH 23390 (0.05 mg/kg) and metoclopramide (25.0 mg/kg), respectively. Paired groups received nine 2-h drug-environment (automated activity monitoring chambers) pairings whereas Unpaired groups received the stimuli explicitly unpaired. Test revealed conditioned hyperactivity with each agonist and metoclopramide whereas conditioned hypoactivity was seen with SCH 23390. Experiment 2 assessed the interaction of these agonists and antagonists on the establishment of conditioned activity. Paired groups received an agonist and antagonist during conditioning sessions. SCH 23390 blocked conditioning based on (+)-amphetamine and SKF 38393 but not quinpirole. Metoclopramide (10.0 mg/kg) blocked conditioning based on quinpirole but not SKF 38393. Metoclopramide (25.0 mg/kg) also did not block (+)-amphetamine-induced conditioning. These studies suggested that drug-induced alterations at either D1 or D2 receptors may be involved in conditioned locomotion.

Key words: (+)-Amphetamine – SKF 38393 – Quinpirole – SCH 23390 – Metoclopramide – Conditioned locomotor activity

Several dopaminergic agents, including (+)-amphetamine, cocaine, and apomorphine, have been shown to produce classically conditioned locomotor activity. Thus, hyperactivity has been observed in rats with a history of CS (environmental cues) and UCS (drug) pairings when tested with presentation of the CS alone. The dopaminergic nature of this effect was suggested by the observation that the dopamine (DA) antagonist pimozide blocked the establishment of conditioning (Pickens and Crowder 1967; Tilson and Rech 1973; Schiff 1982; Barr et al. 1983; Beninger and Hahn 1983; Beninger and Herz 1986; Herz and Beninger 1987; Mazurski and Beninger 1987; Moller et al. 1987; Poncelet et al. 1987). Conditioning appeared quite robust as effects were seen following as few as two 60-min pairings (Mazurski and Beninger 1987).

Conditioned effects have also been demonstrated with DA antagonists. Thus, tolerance to the cataleptic effects of haloperidol showed conditioning (Poulos and Hinson 1982; deGraaf and Korf 1986). Similarly, conditioned increases in activity have been demonstrated with haloperidol or chlorpromazine, although the unconditioned response was a reduction in activity (see Post et al. 1984).

DA has two receptor subtypes: the D1 receptor is linked in a facilitatory manner to adenylate cyclase, whereas the D2 receptor appears to work either independently of, or in an inhibitory fashion on this enzyme (Kebabian and Calne 1979; Stoof and Verheijden 1986). The recent availability of drugs that are relatively selective for either receptor has permitted the investigation of their unique behavioural functions (see reviews by Clark and White 1987; Beninger et al. 1989; Miller et al. 1990).

In the present studies, experiment 1 examined the possibility that classically conditioned changes in locomotor activity could be produced using drugs differing in selectivity for the D1 and D2 receptor. Dopamine antagonists have been shown to attenuate the establishment of conditioning based on indirect acting dopamine agonists including amphetamine and cocaine (Beninger and Herz 1986; Herz and Beninger 1987). Thus, experiment 2 examined the possibility that D1 or D2 antagonists block conditioning based on amphetamine or the selective agonists.

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Materials and methods

Subjects. Two hundred and sixty-four male Wistar rats, initially weighing 225 (±25) g, had free access to food (Purina Rat Chow) and water for the duration of the study except during activity sessions. They were individually housed in wire mesh cages in a temperature controlled (20 ± 1° C) colony room kept on a 12 h light (0600–1800 hours)/dark cycle.

Apparatus. Activity was monitored in six Plexiglas chambers (41 × 50 × 37 cm), each enclosed in a styrofoam insulated outer box painted flat black. In each chamber light was provided by a 2.5 W bulb mounted on the ceiling and a fan behind the back wall provided ventilation and constant background noise. The floor was comprised of wire rods spaced 0.5 cm apart, approximately 5 cm above a removable metal tray. Each chamber was equipped with two sets of seven infrared emitters and detectors spaced 10 cm apart at 5 and 15 cm above the floor which detected horizontal and vertical activity, respectively. A more detailed description of the system can be found in Beninger et al. (1985).

Procedure. Twenty-four rats were assigned to each drug group. Each drug group was divided into Paired and Unpaired subgroups, and was treated the same except for the environment associated with the drug. The groups in experiment 1 included the indirect acting dopamine agonist (+)-amphetamine (2.0 mg/kg), the D1 agonist SKF 38393 (10.0 mg/kg), the D2 agonist quinpirole (2.5 mg/kg), the D1 antagonist SCH 23390 (0.05 mg/kg), and the D2 antagonist metoclopramide (25.0 mg/kg). In experiment 2 each group received an agonist and antagonist in conjunction. Doses were the same as in experiment 1 except that a 10 mg/kg dose of metoclopramide was tested with SKF 38393 and quinpirole.

Intraperitoneal injections were given for all drugs except SCH 23390, which was administered subcutaneously. Saline was used for non-drug injections, except for those associated with SCH 23390; in this case Tween 80 and distilled water (the vehicle for the drug) were used. Injection volumes were 1.0 ml/kg.

Initially all rats received five 60-min habituation sessions, conducted on consecutive days. No injections were administered during this phase. Table 1 provides a summary of the procedure. The training phase consisted of three blocks of three conditioning sessions. The first block consisted of conditioning sessions 1, 2 and 3 on days 7, 11 and 15 of the experiment, the second of conditioning sessions 4, 5 and 6 on days 23, 27 and 31 and the third of conditioning sessions 7, 8 and 9 on days 39, 43 and 47, respectively. Following each of the first two blocks, rats were given vehicle test sessions. The first test session was on day 19 and the second on day 35. After the third block two vehicle test sessions were given, each where only one-half of the subjects was tested. These took place on days 51 and 55.

Conditioning sessions were 2 h in duration and occurred 4 days apart. Rats were injected immediately prior to each session. A drug was given to the Paired groups and saline or Tween 80 to the Unpaired groups. Two days after each conditioning session the rats were injected in their home cages, where they remained until the next conditioning session. For these home cage injections Paired groups received the vehicle and Unpaired groups received the drug. This control procedure ensured that the Unpaired group was never drugged while in the chambers.

Each vehicle test session was 2 h in duration and occurred 4 days after the third and sixth conditioning sessions. The last test occurred either 4 or 8 days after the ninth conditioning session. Immediately prior to each test Paired and Unpaired groups received vehicle injections. No drugs were administered and no home-cage injections followed.

Statistical analyses. Results from each drug were analyzed separately. Only conditioning sessions 1, 5, and 9 were analyzed as they were typical of activity from the early, middle, and final part of training. Conditioning or test sessions were analyzed using three-way analyses of variance (ANOVA) with time (four 30-min intervals), session (three levels) and group (Paired and Unpaired) as the factors. Simple main effects analyses were used to further investigate significant interactions. The Greenhouse-Geisser corrected degrees of freedom were used for all repeated measures factors (see Keppel 1973).

Table 1. Summary of training procedures indicating the day in real time that animals received habituation, conditioning and test sessions

Day	Procedure
1–5	Habituation
7	Conditioning session 1 (C1)[a]
11	Conditioning session 2
15	Conditioning session 3
19	Test session 1 (T1)
23	Conditioning session 4
27	Conditioning session 5 (C5)
31	Conditioning session 6
35	Test session 2 (T2)
39	Conditioning session 7
43	Conditioning session 8
47	Conditioning session 9 (C9)
51 or 55	Test session 3 (T3)

[a] Codes in brackets indicate the three conditioning (C1, C5, C9) and the three test (T1,T2, T3) sessions that are shown in Figs. 1 and 2 and Table 2

Results

The habituation phase was included to familiarize the rats with the testing environment. Activity of the various groups tended to be similar during this time.

Experiment 1

Figure 1 shows activity during the conditioning and test sessions for each agonist. In one test session data from three Paired and Unpaired rats in the (+)-amphetamine group were not available due to equipment failure. The group averages were substituted for each missing value.

Conditioning with (+)-amphetamine, SKF 38393 or quinpirole. (+)-Amphetamine stimulated both horizontal and vertical activity. There were significant session by group [$F(1.74,38.36) = 4.68$, $P < 0.025$] and time by group interactions [$F(2.56,56.34) = 18.54$ $P < 0.001$] for horizontal activity. The first interaction occurred because the Paired group was significantly more active in the first and fifth but not ninth sessions and the second because the Paired group was more active in all but the first time interval. Vertical activity yielded a significant session by time by group effect [$F(3.09,67.88) = 7.45$, $P < 0.001$]. The time by group effect was significant in sessions 5 and 9. In session 5 the Paired group was more active at the fourth time interval. In session 9 they were less active than the Unpaired group at the first two times. Although there was no significant interaction for vertical activity in session 1, there was a highly significant group effect

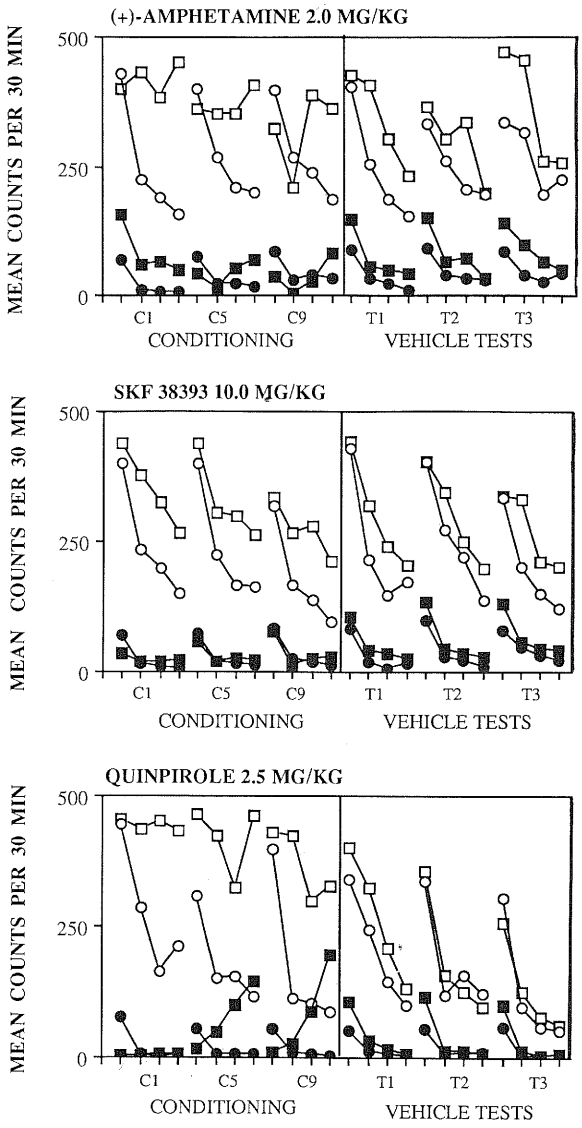

Fig. 1. Mean activity counts in each 30-min interval of conditioning sessions 1, 5, and 9 and three test sessions for Paired *(squares)* and Unpaired *(circles)* groups given (+)-amphetamine, SKF 38393 or quinpirole on horizontal *(open symbols)* and vertical *(closed symbols)* activity measures. All compounds stimulated horizontal and vertical activity. In test sessions, conditioned horizontal and vertical activity was seen following (+)-amphetamine, conditioned horizontal activity following SKF 38393 and conditioned vertical activity following quinpirole

[$F(1,22)=48.26$, $P<0.001$], (+)-amphetamine stimulating vertical activity.

SKF 38393 also stimulated both types of activity. There was a significant time by group effect on horizontal activity [$F(2.32,50.98)=3.18$, $P<0.05$]; the Paired group was more active at the last three time periods. With vertical activity the time by group effect was significant [$F(1.80,39.49)=6.25$, $P<0.01$], and comparisons determined that the Paired group was more active only at the fourth time interval.

Quinpirole clearly produced a stimulant effect on horizontal activity. The three-way interaction was significant [$F(4.76,104.69)=2.76$, $P<0.025$] and the time by group interaction was significant in each session. The Paired group was more active in the last three intervals in each session. Additionally, in session 5 they were more active in the first time interval. Examination of vertical activity yielded highly significant effects of all factors and interactions; for the three-way interaction $F(2.26,49.62)=8.33$, $P<0.0001$. The time by group interaction was significant in each session, and further analyses revealed that the Paired group was less active in the first time interval of each session. Furthermore, in sessions 5 and 9 the Paired group was significantly more active in the final three and two intervals, respectively.

Tests following (+)-amphetamine, SKF 38393 or quinpirole. Animals previously receiving (+)-amphetamine in the test environment showed conditioned activity. Horizontal and vertical activity of the Paired group was significantly greater [Fs(1,22)=9.34 and 6.73, Ps<0.01 and <0.025], respectively (see Fig. 1). Similarly, the Paired group treated with SKF 38393 was significantly more active on the horizontal measure [$F(1,22)=4.41$, $P<0.05$]. With vertical activity no effects interacted significantly with the group factor. With quinpirole no

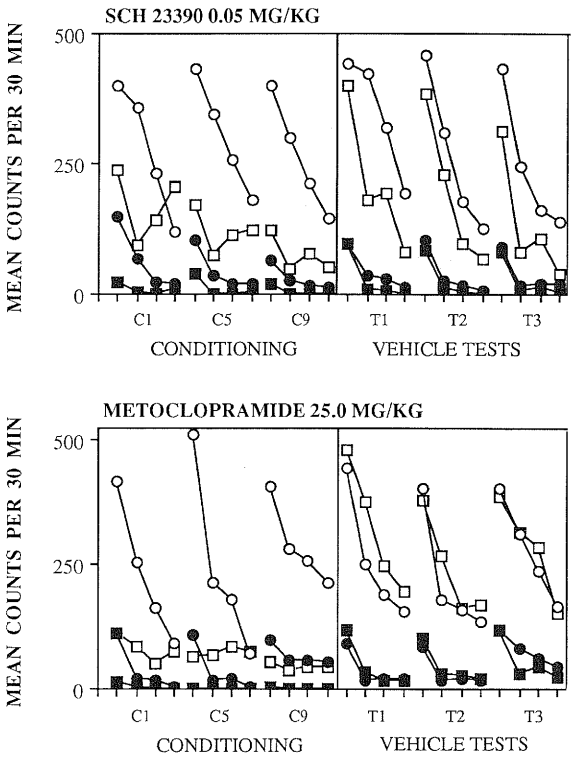

Fig. 2. Mean activity counts in each 30-min interval of conditioning sessions 1, 5, and 9 and three test sessions for Paired *(squares)* and Unpaired *(circles)* groups given an antagonist on horizontal *(open symbols)* and vertical *(closed symbols)* activity measures. Both SCH 23390 and metoclopramide decreased horizontal and vertical activity during conditioning sessions. In test sessions, conditioned decreases in horizontal and vertical activity followed SCH 23390. Following metoclopramide, the Paired group showed significantly more horizontal activity than the Unpaired group during the first test session

effects interacted with the group factor on horizontal activity, but with vertical activity there was a significant time by group effect, [$F(1.64,36.07)=20.66$, $P<0.001$], The Paired group was significantly more active at the first time interval.

Figure 2 shows the results from conditioning and tests with the two antagonists studied. Data from three Paired and Unpaired rats in the metoclopramide group were unavailable from one test session.

Conditioning with antagonists. SCH 23390 decreased activity. Analysis of horizontal activity yielded a significant time by group interaction [$F(2.66,58.57)=24.15$, $P<0.001$] (see Fig. 2). Comparisons at each time determined that the Paired group was less active at the first three time periods. Vertical activity yielded a significant time by session by group interaction [$F(2.21,48.61)=4.87$, $P<0.01$]. The time by group effect was significant in each session; thus the groups were compared at each time. In session 1 the Paired group was less active at the first three time periods. In sessions 5 and 9 the Paired group was less active at all time periods.

Metoclopramide also reduced horizontal activity. The three-way interaction was significant [$F(3.90,85.88)=4.03$, $P<0.01$], as was the time by group effect in each session. In session 1 the Paired group was less active at the first three time intervals. In session 5 the effect was present only in the first two time periods and in session 9 the Paired group was less active at all time periods. With vertical activity all effects were significant except the three-way interaction. The groups were compared at each session and at each time interval, and in all cases the Paired group was found to be less active.

Tests following antagonists. The SCH 23390 Paired group showed significantly less horizontal and vertical activity than its control [Fs $(1,22)=26.82$ and 5.83, Ps <0.001 and <0.025, respectively]. No group effects were seen with metoclopramide, although the session by group effect approached significance on horizontal [$F(1.77,38.96)=2.70$, $P=0.0858$] and vertical activity [$F(1.19,26.13)=4.31$, $P=0.0519$]. Further comparisons determined that the Paired group was significantly more active on the horizontal measure on the first test session.

Experiment 2

As the unconditioned and conditioned drug effects in experiment 1 were generally similar for horizontal and vertical activity, only horizontal activity will be reported. The activity profiles of the Unpaired groups in Experiment 1 were similar to one another and to those from experiment 2; therefore, for the sake of clarity and brevity, the data will be presented as difference scores, averaged over time, between the Paired and Unpaired groups for conditioning days 1, 5, and 9 and test days 1, 2, and 3. These data are shown in Table 2. (Table 2 also contains the comparable difference scores from experiment 1 to facilitate comparison between experiments.) Note that although data have been averaged over time, this variable was included in the analyses and significant time effects were reported.

SCH 23390 antagonized the unconditioned stimulant effects of (+)-amphetamine and no evidence of conditioned activity was seen. Analysis of conditioning sessions yielded significant session by group [$F(1.96,43.04)=3.36$, $P<0.05$] and time by group effects

Table 2. Difference scores (paired group–unpaired group) for horizontal activity for conditioning and test sessions for groups receiving an agonist or antagonist alone in experiment 1 or an agonist in conjunction with an antagonist in experiment 2

	Conditioning			Vehicle Tests		
	1	5	9	1	2	3
Experiment 1						
(+)-Amphetamine (2.0 mg/kg)	166.6[a]	98.8[a]	48.8[a]	91.8[a]	51.0[a]	93.8[a]
SKF 38393 (10.0 mg/kg)	104.5[a]	87.5[a]	94.3[a]	61.5[a]	40.0[a]	70.0[a]
Quinpirole (2.5 mg/kg)	167.5[a]	235.8[a]	194.5[a]	59.3[a]	−1.0	2.7
SCH 23390 (0.05 mg/kg)	−106.0[a]	−184.0[a]	−189.0[a]	−131.3[a]	−73.8[a]	−110.0[a]
Metoclopramide (25.0 mg/kg)	−150.5[a]	−171.8[a]	−244.8[a]	66.0[a]	25.8	6.5
Experiment 2						
(+)-Amphetamine (2.0 mg/kg) +SCH 23390 (0.05 mg/kg)	7.0	−37.3	−63.3[a]	−12.5	22.5	−22.3

[$F(2.61,57.47)=12.49$, $P<0.001$] on horizontal activity. The groups differed only during session 9, when the Paired group was less active. The Paired group was also less active at the first time period. During test sessions there were no significant effects incorporating the group factor.

Metoclopramide transiently blocked the stimulant effects of (+)-amphetamine but by the end of conditioning sessions stimulant effects were seen and conditioned activity was seen in the test. Analysis of conditioning sessions yielded significant effects of all factors and interactions except session on horizontal activity; [$F(4.94,108.75)=3.57$, $P<0.005$ for the 3-way interaction]. As the time by group effect was significant in each session, the groups were compared at each time (note that data for each time are not shown). In sessions 1 and 5 the Paired group was less active at the first two intervals. In session 1 they were also more active at the final period. In session 9 they were less active at the first time and more active at the final two times. In the test sessions, the Paired group was significantly more active [$F(1,22)=7.46$, $P<0.025$].

When administered with SKF 38393, SCH 23390 completely blocked the unconditioned stimulant effect of the D1 agonist and no evidence of conditioned activity was seen. In fact, the Paired group showed some evidence of a conditioned decrease in activity. Thus, in conditioning sessions the Paired group exhibited significantly less horizontal activity in comparison to its control group [$F(1,22)=54.44$, $P<0.001$]. There were also significant session by group [$F(1.94,42.60)=20.10$, $P<0.001$] and time by group effects [$F(2.53,55.74)=25.13$, $P<0.001$]. The Paired group was less active in each session and at the first two time intervals. In test sessions there was a significant session by group effect [$F(1.99,43.47)=3.41$, $P<0.05$]. Comparisons determined that the Paired group was significantly less active than the Unpaired group on the third test.

Metoclopramide antagonized the unconditioned stimulant effects of SKF 38393 but conditioned activity still was seen in test sessions. Thus, co-treatment with SKF 38393 and metoclopramide (10.0 mg/kg) resulted in significant effects of group [$F(1,22)=41.18$, $P<0.001$], session by group [$F(1.49,32.85)=13.17$, $P<0.001$], and time by group [$F(2.63,57.91)=46.41$, $P<0.001$] on horizontal activity. Comparisons at each session and each time determined that the Paired group was less active during sessions 5 and 9 and during the first two time periods. However, in the tests the Paired group was more active [$F(1,22)=5.08$, $P<0.05$].

Metoclopramide blocked the unconditioned and conditioned effects of quinpinole for both horizontal and vertical activity. During conditioning sessions there was only a significant time by group effect on horizontal activity [$F(2.60,57.22)=55.29$, $P<0.001$]. The Paired group was less active at the first time interval and more active at the final two periods. In the tests activity for quinpirole and metoclopramide revealed no significant effects incorporating the group factor.

Discussion

All drugs produced unconditioned changes in locomotor activity as evidenced by the differences between Paired and corresponding Unpaired groups during conditioning sessions. (+)-Amphetamine enhanced horizontal and vertical activity, although the effect was not observed throughout the study. SKF 38393 enhanced activity on both measures. Quinpirole also acted as a stimulant, although initially the drug reduced vertical activity. SCH 23390 and metoclopramide both reduced horizontal and vertical activity.

The D1 and D2 antagonists affected the unconditioned responses to the three agonists. SCH 23390 blocked the stimulant effect of all three agonists. Metoclopramide at 25.0 mg/kg attenuated (+)-amphetamine-induced hyperactivity; 10.0 mg/kg antagonized the stimulant effect of SKF 38393 and partially blocked that of quinpirole. These findings are in general agreement with many previous data (cf Miller et al. 1990).

Conditioned changes in activity as assessed by vehicle test sessions suggested that conditioning occurred on both measures with (+)-amphetamine. This finding is in good agreement with previous reports (Pickens and Crowder 1967; Tilson and Rech 1973; Beninger and Hahn 1983; Herz and Beninger 1987; Mazurski and Beninger 1987; Poncelet et al. 1987). Quinpirole, however, appeared to produce only conditioned vertical activity in agreement with previous findings (Mazurski and Beninger 1988). SKF 38393 similarly produced weaker conditioning, as only conditioned horizontal activity was seen. The Dl antagonist SCH 23390 produced conditioned reductions of both horizontal and vertical activity. With metoclopramide there was some evidence of conditioned hyperactivity on the horizontal measure in the first test session.

Numerous studies have shown sensitization to the stimulant effects of (+)-amphetamine (for a review see Robinson and Becker 1986). However, in the present

Previous studies have demonstrated that co-administration of a D2 antagonists (viz. pimozide) with indirect acting dopamine agonists during drug-environment pairings blocked the establishment of conditioned locomotor activity (Beninger and Hahn 1983; Beninger and Herz 1986). The present data suggest that D1 and D2 receptors may be differentially involved in this effect. To summarize these findings, it appeared that conditioning could be supported by either D1 or D2 stimulation, and blocked at the same receptor that was stimulated. With the indirect acting agonist, however, the results suggested that when both sites were stimulated, it was necessary for the Dl receptor to be active for the learning process to occur.

Rewarding stimuli increase the activity of an animal and increase the ability of reward-related stimuli to elicit approach responses (see Beninger 1983 for a review). If the drugs in the classical conditioning experiments presented here were rewarding one might expect that stimuli associated with the reward (i.e., the distinctive environment with which the drug was paired) may also elicit approach. [This can be understood as an example of incentive learning (see Beninger 1983)]. This response would likely be manifest as an increase in horizontal or vertical activity in the vehicle tests of animals previously receiving the drug in that environment in comparison to subjects with a similar drug history but the drug unassociated with the environment. Following this line of speculation, the data from the present studies suggest the possibility that both D1 and D2 receptors may be involved in mediating reward (cf Beninger et al. 1989; Miller et al. 1990).

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