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Novelty-Induced Place Preference Behavior in Rats: Effects of Opiate and Dopaminergic Drugs

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BARDO, M. T., J. L. NEISEWANDER AND R. C. PIERCE. *Novelty-induced place preference behavior in rats: Effects of opiate and dopaminergic drugs*. PHARMACOL BIOCHEM BEHAV **32**(3) 683–689, 1989.—In Experiment 1, adult male rats were given eight 30-min exposures to one of two distinct environments. Control animals received either four exposures to each environment or were not exposed to either environment. When given free-choice access to both environments simultaneously, animals spent significantly more time in the novel environment relative to the familiar environment. In these same animals, horizontal and vertical activity rates were lower in the novel environment than in the familiar environment. In Experiments 2–5, animals were assessed for novelty preference behavior under the influence of either morphine (0, 0.1, 0.3, 1.0 or 3.0 mg/kg), naltrexone (0, 0.1, 0.3 or 1.0 mg/kg), amphetamine (0, 0.1, 0.3 or 1.0 mg/kg) or haloperidol (0, 0.03, 0.1, 0.3 or 1.0 mg/kg). Haloperidol produced a dose-dependent disruption in novelty preference behavior, while all other drugs tested were without effect. Haloperidol also disrupted the novelty-induced decrease in horizontal and vertical activity rates. These results suggest that haloperidol blocks the reinforcing and locomotor-depressant effects of a novel environment in a free-choice preference test.

Novelty Place preference behavior Locomotor activity Morphine Naltrexone Amphetamine Haloperidol

STUDIES conducted in the 1950's characterized various exploratory behaviors in rats exposed to a novel environment or exposed to novel objects (2, 3, 33). More recent work indicates that novelty-elicited behaviors involve, at least in part, a brain dopamine (DA) system. In particular, lesions of the mesolimbic DA system disrupt the increase in locomotion, rearing, and approach behaviors normally elicited by novel stimuli (7, 9, 24), while systemic administration of the DA antagonist haloperidol decreases novelty-induced grooming behavior (10). The DA agonist amphetamine also depresses exploratory behaviors in a novel environment (21,28). This latter effect may result from the hyperactive locomotor response which is incompatible with normal exploratory behaviors. Alternately, perhaps activation of DA systems by amphetamine reduces the relative arousing or reinforcing quality of novelty.

Endogenous opioid systems may also play a role in novelty-elicited behaviors. Evidence now indicates that opioid peptides modulate DA neurotransmission in the mesolimbic pathway (18) and that exposure to novelty induces a release of brain β-endorphin (17). Administration of opiate agonists such as morphine or Leu-enkephalin increases exploratory behaviors in a novel environment (19,20). Conversely, opiate antagonists such as naloxone or naltrexone decrease locomotor activity (1,29), grooming (10) and exploratory head-dipping (6) in a novel environment.

To date, the majority of studies cited have examined the role of DA and opioid systems in novelty-elicited behavior by testing animals in an inescapable novel environment. However, relatively little is known about the neuropharmacologic basis of novelty *preference* behavior. When given free-choice access to both a novel and familiar environment simultaneously, rats prefer the novel environment (5, 14, 16, 31). This preference is evident as an increased number of entries into and an increased duration spent in the novel environment. Some evidence suggests that this novelty preference behavior may also depend upon a DA system, as it is decreased by amphetamine (15,22) and apomorphine (23). However, little is known about the effect of opiate drugs on novelty preference behavior.

The purpose of the present study was to determine the effect of opiate and dopaminergic drugs on novelty-induced place preference behavior. In the first experiment, separate groups of rats were given free-choice access to either two familiar environments, two novel environments or both a novel and familiar environment. Measures of preference, horizontal locomotion and vertical rearing were taken in order to establish baselines for these behaviors in the present paradigm. Following this, four separate experiments were performed to determine the effects of morphine, naltrexone, amphetamine and haloperidol on animals given free-choice access to a novel and familiar environment.

METHOD

Animals

The animals were 211 male Sprague-Dawley rats obtained from Harlan Industries (Indianapolis, IN) at 225–250 g body weight. Animals were caged individually with food and water

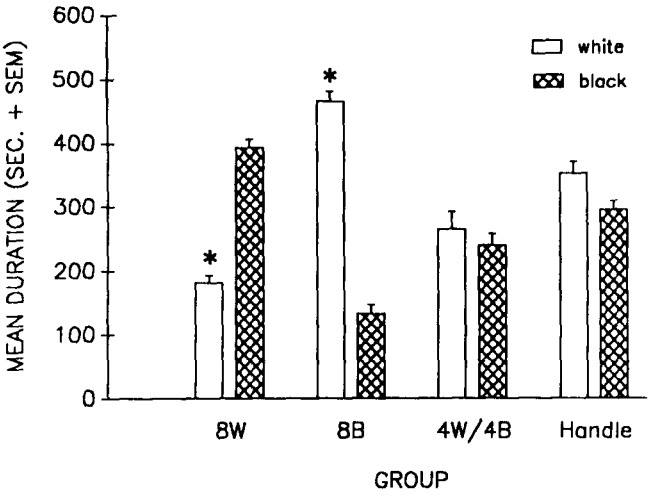

FIG. 1. Results from Experiment 1 showing that animals spent more time in the novel compartment than in the familiar compartment. Group 8W = 8 exposures to white; Group 8B = 8 exposures to black; Group 4W/4B = 4 exposures to white and 4 to black; and Group HANDLE = handled controls with no exposure to either white or black. *Represents significant difference from duration in black, $p<0.001$.

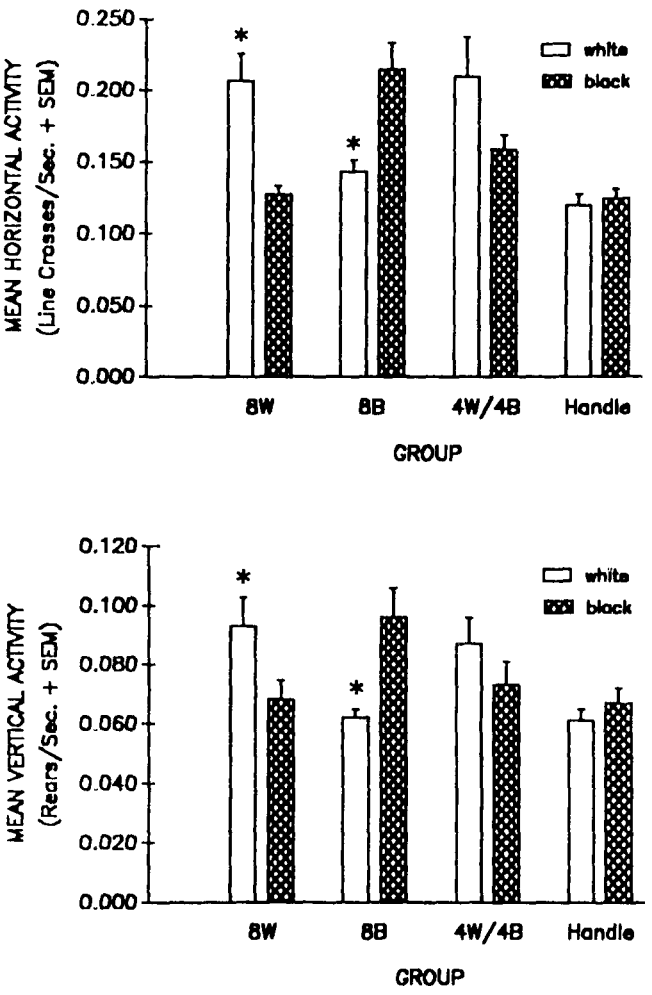

FIG. 2. Results from Experiment 1 showing that both horizontal and vertical activity rates were decreased in the novel compartment relative to the familiar compartment. Group designations were the same as in Fig. 1. *Represents significant difference from activity rate in black, $p<0.05$.

available continuously in the home cage. Prior to the start of each experiment, animals were acclimated to the colony room (22 ± 1°C, humidity 45 ± 5%) for at least one week and were handled for 2 days.

Apparatus

The apparatus consisted of a rectangular wooden chamber that had three different compartments separated by removable walls. The two end compartments measured 24 × 30 × 45 cm high, while the middle compartment was smaller and measured 24 × 10 × 45 cm high. One end compartment had white walls, a wire mesh floor, and pine bedding beneath the floor. The other end compartment had black walls, a metal grid floor, and cedar bedding beneath the floor. The middle compartment had gray walls and a solid wood floor. The walls partitioning the end compartments from the middle compartment could be replaced with similar walls containing a 10 × 10 cm opening, which allowed the animals access to all compartments. The apparatus was located in a laboratory room that was separate from the colony room and was equipped with a white noise generator (ambient background of 70 dB). Suspended from the ceiling above the apparatus was a video camera which was used to record the animals' behavior on test days.

Procedure

Experiment 1. Each animal was assigned randomly to one of four treatment groups (n = 10 per group): one group received eight placements into the white compartment (Group 8W); one group received eight placements into the black compartment (Group 8B); one group received four placements into white and four placements into black (Group 4W/4B); and one group received eight days of handling only (Group HANDLE). Placements occurred once daily for 30 min with the partitioning walls installed. For Group 4W/4B, placement into white or black was alternated daily in counterbalanced sequence. For Group HANDLE, animals were transported to the experimental room and were placed for 30 min in a holding cage similar to the home cage, except no food or water was present. On the day after the last placement, each animal was placed into the center gray chamber and allowed free access to all compartments for 15 min. Using a video monitor, an observer who was unaware of each animals' individual treatment recorded the following: duration spent in each compartment (defined as both front paws in compartment); number of entries into each compartment (defined as both front paws breaking the plane of partition between compartments); horizontal line-crossing activity in each compartment (defined as both front paws across a line drawn on video monitor screen that bisected each compartment parallel to partitioning wall); and vertical rearing activity in each compartment (defined as both front paws off floor).

Experiments 2–5. In each of these experiments, half of the animals received eight placements into white and half received eight placements into black as described previously. On the day after the last placement, each animal was assigned to one of the following drug treatment groups (n = 8–11 per group) which were counterbalanced for prior placements into either the white or black compartments: 0, 0.1, 0.3, 1.0 or 3.0 mg/kg morphine (Experiment 2); 0, 0.1, 0.3 or 1.0 mg/kg naltrexone (Experiment 3); 0,

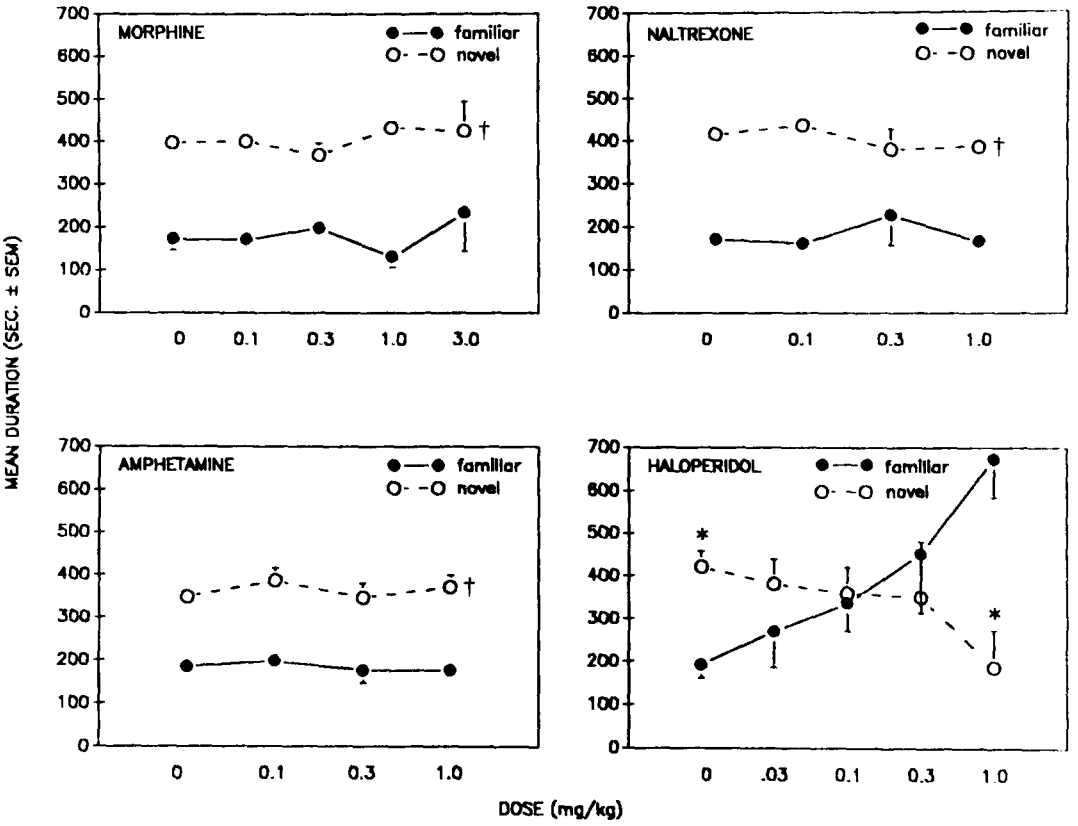

FIG. 3. Results from Experiments 2–5 showing that haloperidol, but not morphine, naltrexone or amphetamine, disrupted the animals' preference for the novel compartment. †Represents significant difference between novel and familiar collapsed across drug dose, $p<0.001$. *Represents significant difference from familiar within drug dose, $p<0.05$.

0.1, 0.3 or 1.0 mg/kg amphetamine (Experiment 4); or 0, 0.03, 0.1, 0.3 or 1.0 mg/kg haloperidol (Experiment 5). Each animal was injected and, 30 min later, was placed in the center gray compartment and allowed free access to all compartments for 15 min. Behavioral measures were recorded as described previously.

Drugs

Morphine sulfate (Elkins-Sinn, Cherry Hill, NJ), naltrexone hydrochloride (National Institute on Drug Abuse, Rockville, MD), and d-amphetamine sulfate (Sigma, St. Louis, MO) were mixed in 0.9% NaCl and injected SC. Haloperidol (McNeil, Spring House, PA) was mixed in 0.9% NaCl and injected IP. All dosages were based on the salt form of the drug.

Statistics

Each dependent variable was analyzed separately using a split-plot analysis of variance. For Experiment 1, the repeated measure was the behavior observed in the white and black compartments, whereas in Experiments 2–5, the repeated measure was the behavior observed in the novel and familiar compartments. In cases where significant interactions occurred, separate analyses of variance were performed comparing the repeated-measures differences within each treatment group. In all cases, statistical significance was declared at $p<0.05$.

RESULTS

Novelty Preference

As expected, animals from Experiment 1 showed a preference for the novel compartment relative to the familiar compartment (see Fig. 1). Analysis of the duration data revealed a significant interaction effect, $F(3,37)=56.76$, $p<0.001$. Subsequent tests showed that Group 8W spent significantly more time in black than white, $F(1,9)=94.06$, $p<0.001$, whereas Group 8B spent significantly more time in white than black, $F(1,9)=190.68$, $p<0.001$. There were no significant differences in the duration spent in white and black compartments for either Group 4W/4B or Group HANDLE.

The pattern of results for the entry data was similar to that seen with the duration data. That is, animals from Experiment 1 entered the novel compartment more than the familiar compartment (data not shown). Analysis of the entry data revealed a significant interaction effect, $F(3,37)=7.22$, $p<0.001$. Subsequent tests showed that Group 8W made more entries into black than white and Group 8B made more entries into white than black, although only the latter effect reached statistical significance, $F(1,9)=22.47$, $p<0.01$. There were no significant differences in entries into white and black for either Group 4W/4B or Group HANDLE. However, Group 4W/4B made significantly more entries than Group HANDLE into both white, $F(1,19)=24.17$, $p<0.001$, and black, $F(1,19)=11.62$, $p<0.01$.

Horizontal and Vertical Activity

The results from Experiment 1 also demonstrated that activity rates were decreased in the novel compartment relative to the familiar compartment (see Fig. 2). Analysis of these data revealed significant interaction effects for horizontal activity, $F(3,32)=$

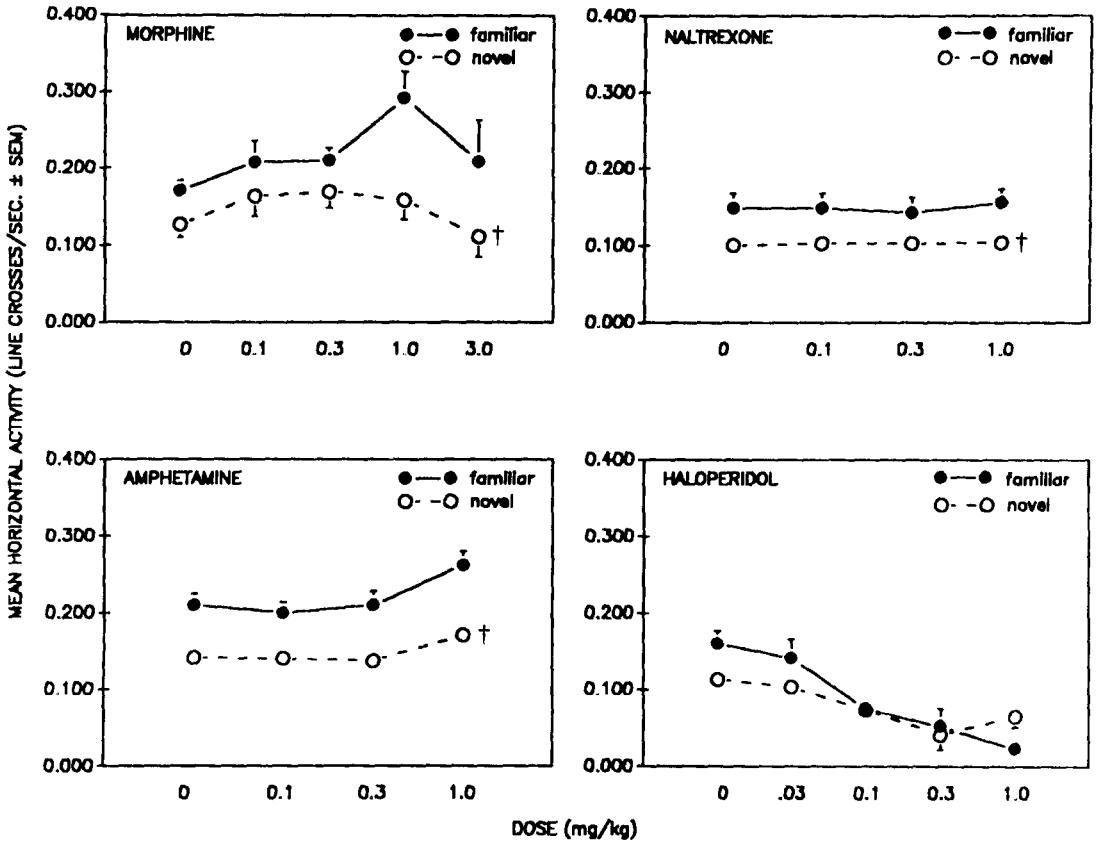

FIG. 4. Results from Experiments 2–5 showing that haloperidol, but not morphine, naltrexone or amphetamine, eliminated the novelty-induced decrease in horizontal activity rate. †Represents significant difference between novel and familiar collapsed across drug dose, $p<0.001$.

10.74, $p<0.001$, and vertical activity, $F(3,32)=9.17$, $p<0.001$. Subsequent tests indicated that Group 8W had significantly higher rates of both horizontal and vertical activity in white relative to black, $F(1,9)\geq 14.30$, $p<0.01$, whereas Group 8B had significantly higher activity rates in black relative to white, $F(1,7)\geq 10.23$, $p<0.05$. There were no significant differences in activity rate in white and black for either Group 4W/4B or Group HANDLE. However, Group 4W/4B had significantly more horizontal activity than Group HANDLE in both white, $F(1,16)=9.81$, $p<0.01$, and black, $F(1,16)=7.69$, $p<0.05$. Also, Group 4W/4B had significantly more vertical activity than Group HANDLE in white, $F(1,16)=5.17$, $p<0.05$.

Drug Effects on Novelty Preference

The results from Experiments 2–5 indicated that, while morphine, naltrexone and amphetamine were without effect on novelty preference, haloperidol produced a dose-dependent disruption of novelty preference (see Fig. 3). Animals spent significantly more time in the novel compartment than the familiar compartment regardless of treatment with morphine, $F(1,39)=40.44$, $p<0.001$, naltrexone, $F(1,36)=51.59$, $p<0.001$, or amphetamine, $F(1,40)=71.47$, $p<0.001$. In contrast, the results from the haloperidol experiment revealed a significant interaction effect, $F(4,37)=2.79$, $p<0.05$. Subsequent tests showed that animals given saline spent significantly more time in the novel compartment than the familiar compartment, $F(1,7)=12.46$, $p<0.01$, whereas animals given the highest haloperidol dose (1.0 mg/kg) spent significantly less time in the novel compartment than the familiar compartment, $F(1,7)=7.66$, $p<0.05$. For animals given intermediate haloperidol doses (0.03, 0.1 and 0.3 mg/kg) there was no significant difference in time spent in the novel and familiar compartments, indicating that novelty preference was disrupted.

The entry data from Experiments 2–5 indicated that animals made more entries into the novel compartment than the familiar compartment and that this entry preference was disrupted by haloperidol (data not shown). That is, there was a significant increase in the number of entries into the novel compartment across all doses of morphine, $F(1,39)=27.16$, $p<0.001$, naltrexone, $F(1,36)=9.66$, $p<0.01$, and amphetamine, $F(1,40)=8.53$, $p<0.01$, but not across doses of haloperidol. Regardless of whether the compartment was novel or familiar, there was a dose-dependent increase in total entries following morphine, $F(4,39)=6.10$, $p<0.001$, and amphetamine, $F(3,40)=5.86$, $p<0.01$. The dose-response function for morphine was an inverted-U, with 1.0 mg/kg producing the greatest increase, whereas the dose-response function for amphetamine was a linear increase. In contrast, haloperidol produced a significant linear decrease in total entries, $F(4,37)=27.51$, $p<0.001$. There was no significant effect of naltrexone on total entries.

Drug Effects on Horizontal Activity

In Experiments 2–5, animals given saline showed significantly less horizontal activity in the novel compartment relative to the familiar compartment. This novelty-induced decrease in horizontal

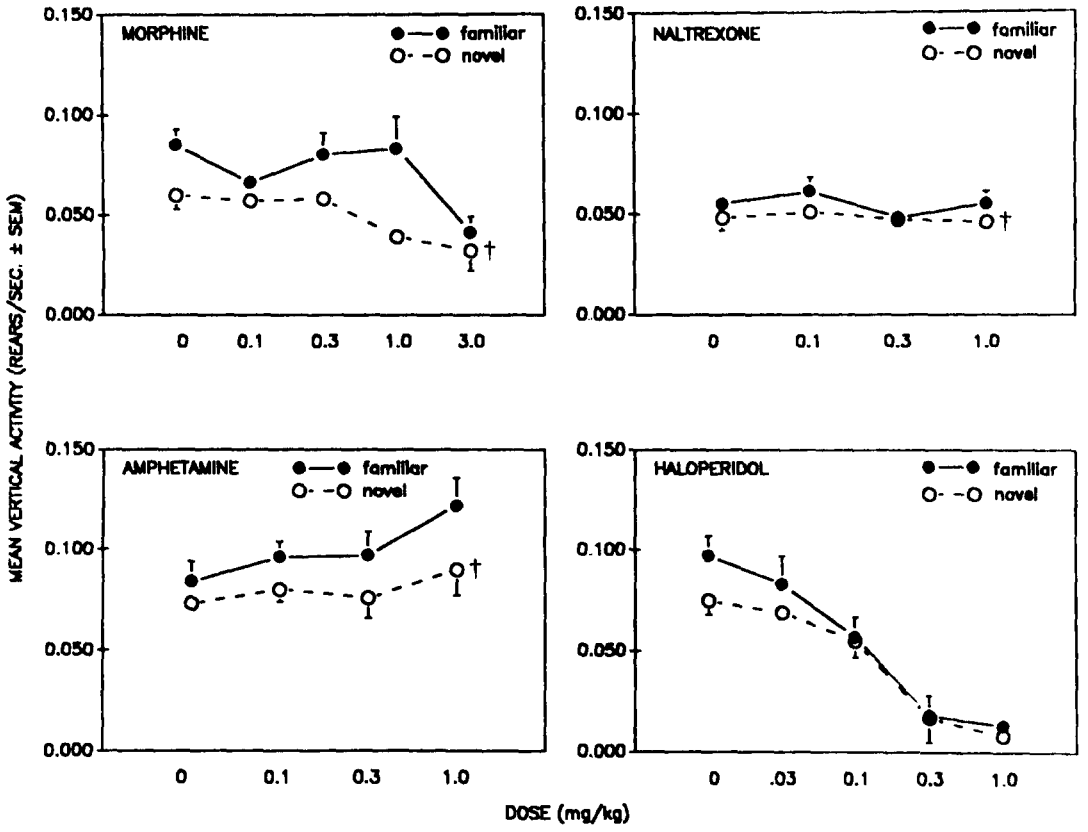

FIG. 5. Results from Experiments 2–5 showing that haloperidol, but not morphine, naltrexone or amphetamine, eliminated the novelty-induced decrease in vertical activity rate. †Represents significant difference between novel and familiar collapsed across drug dose, $p<0.01$.

activity was disrupted by haloperidol, but not by morphine, naltrexone or amphetamine (see Fig. 4). That is, horizontal activity was significantly lower in the novel compartment than in the familiar compartment across all doses of morphine, $F(1,37) = 14.99$, $p<0.001$, naltrexone, $F(1,35) = 39.03$, $p<0.001$, and amphetamine, $F(1,40) = 75.68$, $p<0.001$, but not across doses of haloperidol. In the haloperidol experiment, there was no significant main effect of compartment (novel vs. familiar) nor significant interaction effect between compartment and drug dose factors.

Regardless of whether the compartment was novel or familiar, horizontal activity was increased by amphetamine, $F(3,40) = 4.36$, $p<0.01$, and decreased by haloperidol, $F(4,31) = 13.26$, $p<0.001$. Neither morphine or naltrexone significantly altered horizontal activity rate across the doses tested.

Drug Effects on Vertical Activity

Similar to horizontal activity, animals given saline showed significantly less vertical activity in the novel compartment relative to the familiar compartment. This novelty-induced decrease in vertical activity was disrupted by haloperidol, but not by morphine, naltrexone or amphetamine (see Fig. 5). Vertical activity was significantly lower in the novel compartment than in the familiar compartment across all doses of morphine, $F(1,37) = 16.46$, $p<0.001$, naltrexone, $F(1,35) = 7.56$, $p<0.01$, and amphetamine, $F(1,40) = 16.55$, $p<0.001$, but not across doses of haloperidol. In the haloperidol experiment, there was no significant main effect of compartment (novel vs. familiar) nor significant interaction effect between compartment and drug dose factors.

Regardless of whether the compartment was novel or familiar, vertical activity was decreased by morphine, $F(4,37) = 4.86$, $p<0.01$, and haloperidol, $F(4,31) = 20.04$, $p<0.001$. Neither naltrexone or amphetamine significantly altered vertical activity rate across the doses tested.

DISCUSSION

The results from Experiment 1 demonstrate clearly novelty preference behavior in rats. In previous studies, novelty preference behavior was obtained following a single prolonged exposure (24 hr) to one of two distinct environments (14, 22, 23). In the present report, novelty preference behavior was obtained following eight brief exposures (30 min) to one of two distinct environments. Novelty preference behavior was evident regardless of which environment was novel (white vs. black). These results confirm that attraction to novelty is an important factor in an animals' place preference behavior (5, 16, 31).

Interestingly, animals also displayed a decreased rate of horizontal and vertical activity in the novel environment relative to the familiar environment. This finding is consistent with a previous study showing that rats given free-choice access to a novel and familiar environment displayed a reduced rate of exploratory activity in the novel environment (22). Perhaps approach responses to novelty are counteracted by an increase in freezing or grooming responses to novelty. However, the novelty-induced decrease in activity observed in the present report may be evident

only in free-choice situations, as rats display hyperactivity when exposed to an inescapable novel situation (3,24). In this latter situation, locomotor activation may reflect an increase in escape behaviors (33).

The present results also provide evidence that the novelty preference behavior observed here involves a DA mechanism. Within the dose ranges tested, haloperidol produced a dose-dependent disruption in novelty preference behavior. This finding is consistent with another report showing that the neuroleptic thioridazine blocks expression of novelty preference in mice (23). Moreover, the present report found that the highest dose of haloperidol (1 mg/kg) produced a novelty aversion. This latter effect must be interpreted cautiously however, as 1 mg/kg haloperidol induced severe motor impairment, with some animals spending the entire test period in one environment only.

In contrast to haloperidol, the present study found that amphetamine did not influence novelty preference behavior. This is somewhat puzzling, as two previous studies reported that amphetamine disrupts novelty preference behavior in mice and rats (15,22). Both previous studies, however, used methamphetamine (1–4 mg/kg), whereas the present study used lower doses of d-amphetamine (0.1–1.0 mg/kg). While these compounds are closely related, methamphetamine has more pronounced central effects than d-amphetamine (32). Perhaps higher doses of d-amphetamine than those used in the present investigation are required to produce a disruption in novelty preference behavior.

Morphine and naltrexone were also without effect of novelty preference behavior. Previous reports found that opiate antagonists, given in doses similar to those used in the present report, may alter various behaviors in a novel environment (1, 6, 10, 29). In these previous reports, however, behaviors were assessed in an inescapable novel situation, rather than in a free-choice situation. Thus, the present study indicates that novelty preference behavior, assessed in a free-choice test, may not involve an opioid mechanism.

In addition to disrupting novelty preference behavior, haloperidol produced a dose-dependent decrease in both horizontal and vertical locomotor activity. While this finding might suggest that the disruption in novelty preference simply reflects the locomotor depressant effect of haloperidol, several arguments can be made against this possibility. First, the locomotor depressant effect was evident regardless of whether the animal was in the novel or familiar environment. Thus, the tendency of haloperidol-treated animals to remain in the familiar environment should have been no greater than the tendency to remain in the novel environment. Second, morphine and amphetamine also produced dose-dependent alterations in both horizontal and vertical activity, but neither of these drugs altered novelty preference behavior. Third, a previous study reported that benzamide derivate drugs such as sulpiride and tiapride depress locomotor activity, but do not alter novelty preference behavior in mice (23). Taken together, these findings suggest that the haloperidol-induced disruption in novelty preference is not an artifact of its locomotor depressant action, but that novelty preference and locomotor activity are dissociable behaviors.

One interpretation of the present findings is that haloperidol disrupted novelty preference by inducing a state-dependent effect. State-dependency refers to the phenomenon in which learning that takes place under the influence of a drug does not generalize to another drug state or to an undrugged state (26,27). This phenomenon applied to the present study suggests that habituation to the familiar environment during preexposure sessions without drug may not have generalized to the test day when animals were tested under the influence of haloperidol. Stated differently, the haloperidol stimulus introduced on the test day was a novel event which may have rendered both environments novel. While the present experiments cannot rule out this possibility, this interpretation seems unlikely because neither morphine or amphetamine disrupted novelty preference behavior, even though these drugs are known to produce potent state-dependent stimulus effects (12,13).

An alternative interpretation of the present findings is that haloperidol blocked the reinforcing effect of novelty. Strong evidence now implicates the mesolimbic DA system in the reinforcing effect of various stimuli, including food, water, electrical brain stimulation, and drugs of abuse (4,34). In general, these reinforcing stimuli are thought to activate the mesolimbic DA system, while administration of DA antagonists such as haloperidol antagonize this action. Perhaps novelty-seeking behavior is reinforcing because it activates the mesolimbic DA system. Consistent with this, lesions of the mesolimbic DA system produce a deficit in novelty-elicited behaviors (7, 9, 24) and this lesion-induced deficit is reversed by administration of the DA precursor L-dihydroxyphenylalanine (8). In addition, novel stimulation which is stressful has been shown to increase turnover of DA (11, 25, 30). Unfortunately, little is known presently about the effect of novelty per se on DA turnover. Nonetheless, if novelty activates a DA reward system similar to that activated by other reinforcers, then this suggests the possibility that the rewarding value of different reinforcers may be altered in the presence of novel environmental stimuli.

ACKNOWLEDGEMENTS

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