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# Effects of Microgram Doses of Haloperidol on Open-Field Behavior in Mice

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CONCEIÇÃO, I. M. AND R. FRUSSA-FILHO. *Effects of microgram doses of haloperidol on open-field behavior in mice.* PHARMACOL BIOCHEM BEHAV **53**(4) 833–838, 1996.—This study was designed to evaluate the effects of low doses of haloperidol on the open-field behavior of mice. A three-phase effect of haloperidol on the motor activity of mice was observed (depression, no effect, depression). This three-phase action was clear-cut in three experimental approaches (amphetamine-induced hyperactivity, and apomorphine- and bromocriptine-induced hypoactivity). A differential action of haloperidol on dopamine receptors mediating motor stimulation and motor depression was proposed. The present data indicate that considerably more attention should be paid to the novel behavioral and biochemical actions of neuroleptic drugs in the microgram dose range.

Haloperidol Amphetamine Apomorphine Bromocriptine Open-field test

IT HAS REPEATEDLY been observed that mixed $D_1/D_2$ and selective $D_2$ dopamine (DA) receptor agonists (such as apomorphine and bromocriptine, respectively) dose-dependently affect locomotor activity biphasically in rodents. At high doses, these DA agonists cause hyperactivity and stereotyped behavior (20,24), whereas at low doses they inhibit locomotor activity (15,19,39). The effects of low doses of DA agonists are especially interesting, as low doses of both apomorphine and bromocriptine have been reported to improve psychotic symptoms in schizophrenics (10,14,28,34). In addition, low doses of DA agonists seem to be effective in Gille de la Tourette's disease (17) as well as neurologic hyperkinetic disorders such as Huntington's chorea and tardive dyskinesia (9,42,43).

A biphasic effect of predominant and selective $D_2$ DA receptor blockers (such as haloperidol and sulpiride, respectively) on motor activity in mice and rats has also been reported. Thus, high doses of these neuroleptics decrease spontaneous locomotion frequency and apomorphine-induced stereotyped behavior (4,18), whereas at low doses they attenuate the motor suppression caused by low doses of DA agonists and increase spontaneous locomotion frequency (12,15,29, 38). However, these effects of low doses of DA receptor blockers are rather controversial. Indeed, some studies have shown that haloperidol did not block apomorphine-induced hypomotility (40,44), and Ögren et al. (29) showed that this blocking action of haloperidol was age-dependent and only found in a narrow pharmacologic window. In addition, Strömbom (38) suggested that the stimulant effects of low doses of haloperidol depend on the baseline motor activity. Despite these discrepancies, low doses of DA receptor blockers, like low doses of DA receptor agonists, seem to have clinical implications, because depressive and negative symptoms in schizophrenic patients show a better response to low doses of neuroleptics (1,3).

The aim of the present study was to analyze further the effects of haloperidol at low doses on motor activity in mice. The actions of three low doses and one high dose of the neuroleptic were studied on open-field behavior of mice under four different approaches: a) spontaneous general activity; b) amphetamine-induced hyperactivity; c) apomorphine-induced hypoactivity; and d) bromocriptine-induced hypoactivity.

## METHODS

### *Animals*

Genetically similar male EPM-M1 mice weighing 25–32 g were used. The animals arrived at the experimental laboratory 7 days before the beginning of the experiments. They were

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immediately randomly housed in groups of 15 and placed under a 12 L : 12 D cycle (lights on at 0600 h). In each experiment, eight to 11 mice per group were used. The temperature was held constant at 22°C. Food and water were available ad lib. All experiments took place between 0900 and 1400 h.

*Drugs*

Apomorphine hydrochloride (APO; Sandoz, Basal, Switzerland), *d*-amphetamine sulfate (AMP; Sigma, St. Louis, MO), bromocriptine (BRC) (Sandoz), and haloperidol (HAL; Cristália, São Paulo, SP, Brazil) were used. The drugs were freshly diluted in distilled water, except bromocriptine, which was suspended in distilled water plus Tween-80 (three to four drops). Saline or saline plus Tween-80 (three to four drops) was used as a control solution. Haloperidol and bromocriptine were given intraperitoneally (IP), whereas apomorphine and amphetamine were administered subcutaneously (SC), in volumes not > than 10.0 ml/kg of body wt.

*Apparatus*

The open field was constructed as described by Capaz et al. (7). The open-field arena was a circular wooden box (40 cm in diam. and 30 cm high) with an open top; the floor was divided into 18 squares. A circle was marked in the center of the open field. We used hand-operated counters and stopwatches to score ambulation frequency (number of floor units entered), rearing frequency (number of times the animal stood on hind legs), and immobility duration (total seconds of complete lack of movement).

*Procedure*

We performed four experiments. In the first, the mice were randomly and equally divided into five groups: one control group and four experimental ones, acutely and IP-treated with 10 ml/kg saline (SAL) or haloperidol (0.01, 0.03, 0.05, or 1 mg/kg), respectively. Then, 30 min after these single treatments, all animals were placed individually in the open-field arena and behavioral parameters were observed for 6 min. There were 10 mice per group, except for the one treated with 1 mg/kg haloperidol ($n = 8$).

In the second experiment, mice were randomly divided into six groups: HAL 0.01 + AMP ($n = 11$); HAL 0.03 + AMP ($n = 11$); HAL 0.05 + AMP ($n = 11$); HAL 1 + AMP ($n = 10$); SAL + AMP ($n = 11$); and SAL + SAL ($n = 11$). Animals in the first four groups received 0.01, 0.03, 0.05, or 1 mg/kg haloperidol, IP, whereas mice in the last two groups received saline, IP. Then, 10 min after their specific treatments, animals in the first five groups were administered with 2 mg/kg amphetamine, SC, and mice in the SAL + SAL group received another injection of saline, SC. Twenty minutes later, we placed the animals individually in the open-field arena and observed behavioral parameters for 6 min. In the third and fourth experiments, the same procedure as in Experiment 2 was repeated, except that 0.06 mg/kg apomorphine, SC, or 2.50 mg/kg bromocriptine, IP, was substituted for amphetamine. In these two experiments, the number of mice per group was 10, except for group HAL 1 + APO in Experiment 3 ($n = 8$).

In the four experiments, the open-field apparatus was washed with water-alcohol (5%) before placement of the animals to obviate possible bias due to odor clues left by previous subjects. To minimize the possible effects of circadian changes on open-field behavior, experimental and control observations were alternated.

*Statistical Analysis*

We performed Bartlet's test (21) and concluded that the open-field data were parametric. An analysis of variance (ANOVA) followed by Duncan's test was used to study the open-field data. A probability of $p < 0.05$ was considered to show significant differences for all comparisons made.

## RESULTS

Figure 1 shows that none of the low doses of haloperidol significantly modified the spontaneous open-field behavior of the mice. However, 0.01 and 0.05 (but not 0.03 mg/kg) doses of haloperidol showed a strong tendency to decrease rearing frequency. As expected, the dose of 1 mg/kg not only decreased locomotion [$F(4, 43) = 19.86$; $p < 0.05$] and rearing frequencies [$F(4, 43) = 9.25$; $p < 0.05$] but also increased the duration of immobility [$F(4, 43) = 78.33$; $p < 0.05$].

Figure 2 shows the results of the second experiment. As expected, the SAL + AMP group presented a higher locomotion frequency [$F(5, 59) = 6.84$; $p < 0.05$) compared with the SAL + SAL group. This effect was antagonized by haloperidol doses of 0.01 and 1 mg/kg but not by 0.03 and 0.05 mg/kg. Concerning rearing frequencies and immobility durations, HAL 0.01 + AMP, HAL 0.05 + AMP, and HAL 1.00 + AMP presented smaller rearing and higher immobility values [$F(5, 59) = 15.20$, $p < 0.05$ for rearing; $F(5, 59) = 227.47$; $p < 0.05$ for immobility] than those of the SAL + SAL group, but only the HAL 0.01 + AMP and HAL 1 + AMP groups showed smaller rearing frequencies and higher immobility durations compared with the values of the SAL + AMP group.

Figure 3 presents the effects of different haloperidol doses on the open-field behavior of mice acutely treated with a small dose (0.06 mg/kg) of apomorphine (Experiment 3). Mice in the SAL + APO group showed less locomotion [$F(5, 52) = 22.91$; $p < 0.05$] and rearing frequency [$F(5, 52) = 23.95$; $p < 0.05$] but a longer immobility duration [$F(5, 52) = 34.09$; $p < 0.05$] than those in the SAL + SAL group. For the three parameters, these effects were significantly potentiated by the doses of 0.01 and 1 mg/kg haloperidol, but not by 0.03 and 0.05 mg/kg.

Figure 4 shows the effects of different doses of haloperidol on the open-field behavior of mice acutely treated with 2.5 mg/kg bromocriptine (Experiment 4). Mice in the SAL + BRC group exhibited less locomotion [$F(5, 54) = 22.51$; $p < 0.05$] and rearing frequency [$F(5, 54) = 31.41$; $p < 0.05$] compared with those in the SAL + SAL group. These effects were significantly potentiated by 1 mg/kg haloperidol for locomotion and by 0.01 and 1 mg/kg for rearing. Concerning immobility, the HAL 1 + BRC group showed significantly higher durations than those of SAL + SAL and SAL + BRC groups [$F(5, 54) = 130.68$; $p < 0.05$].

## DISCUSSION

The results of our study provide the first evidence of a three-phase effect of haloperidol on agonist-induced changes in motor activity in mice; for both the lowest (0.01 mg/kg) and highest (1 mg/kg) dose used, we observed depression, with no effect for doses between these extremes. This three-phase action was clear-cut in three experimental approaches (amphetamine-induced hyperactivity, and apomorphine- and bromocriptine-induced hypoactivity). In a fourth approach, although not statistically significant, a three-phase effect of haloperidol could also be observed in the spontaneous activity

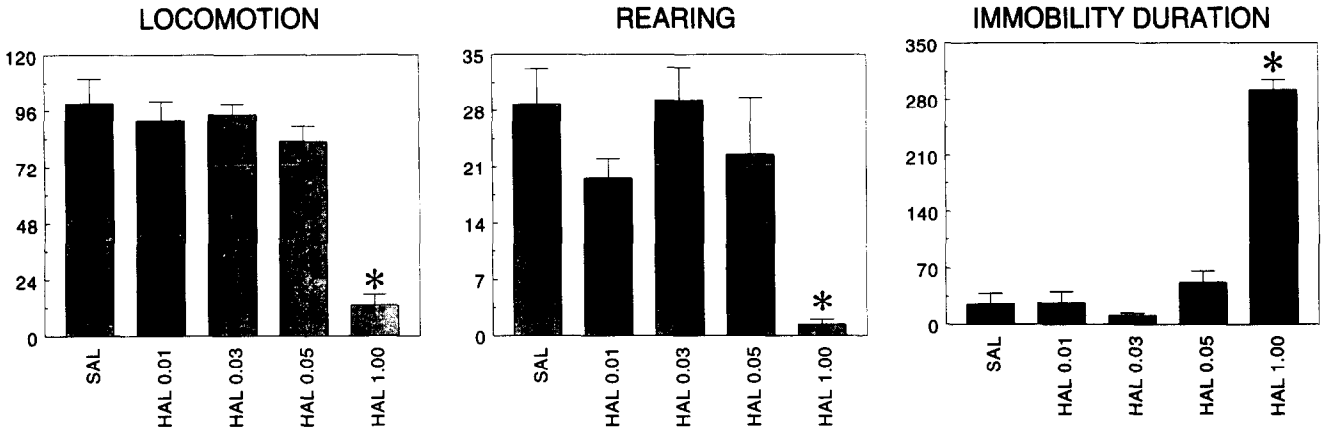


FIG. 1. Effects of single haloperidol (HAL) doses (mg/kg) or saline (SAL) treatments on spontaneous locomotion and rearing frequencies, as well as on immobility duration of mice observed in an open field. *Statistically significant difference from control animals at $p < 0.05$ (ANOVA, Duncan's test).

of mice (see data on rearing frequency and immobility duration).

As regards the mechanism of action underlying the three-phase action of haloperidol on the open-field behavior of mice described here, our data do not permit a firm conclusion; further experiments are required. However, this effect does not seem to be related to alterations in emotionality levels, because these doses of haloperidol did not modify defecation frequency in the open-field or plus-maze behavior of mice (data not shown).

The three-phase effect of haloperidol was observed in the three open-field behavioral parameters evaluated: locomotion and rearing frequencies, and immobility duration. Concerning the locomotion and rearing frequencies, these two responses have been previously shown to be differentially affected by DA-agonist treatment (5,6) and linked to different DA neurocircuitry. Indeed, locomotion and rearing were already related to the nucleus accumbens and nigrostriatal systems, respectively (11). In addition, locomotion and stereotypy (mainly rearing) produced by amphetamine can be differentially manipulated through selective 6-hydroxydopamine-induced lesions of dopaminergic systems; the nigrostriatal pathway is crucial for stereotypy and the mesolimbic dopaminergic neurons more involved in locomotion (13,23). As mentioned before, because the three-phase action of haloperidol was verified in both locomotion and rearing frequencies, it is tempting to suggest that the mechanisms underlying these effects of haloperidol would be present in both locomotion and rearing neuroanatomic substrates. However, it is worth pointing out that the three-phase effect of haloperidol seemed to be more prominent in rearing behavior (see, for example, spontaneous activity). From another standpoint, it seems unlikely that behavioral competition could account for the results described here: that is, one type of behavior (e.g., locomotor activity) decreases as the result of a large increase in other types of behavioral responses (e.g., rearing and/or stereotypy). In fact,

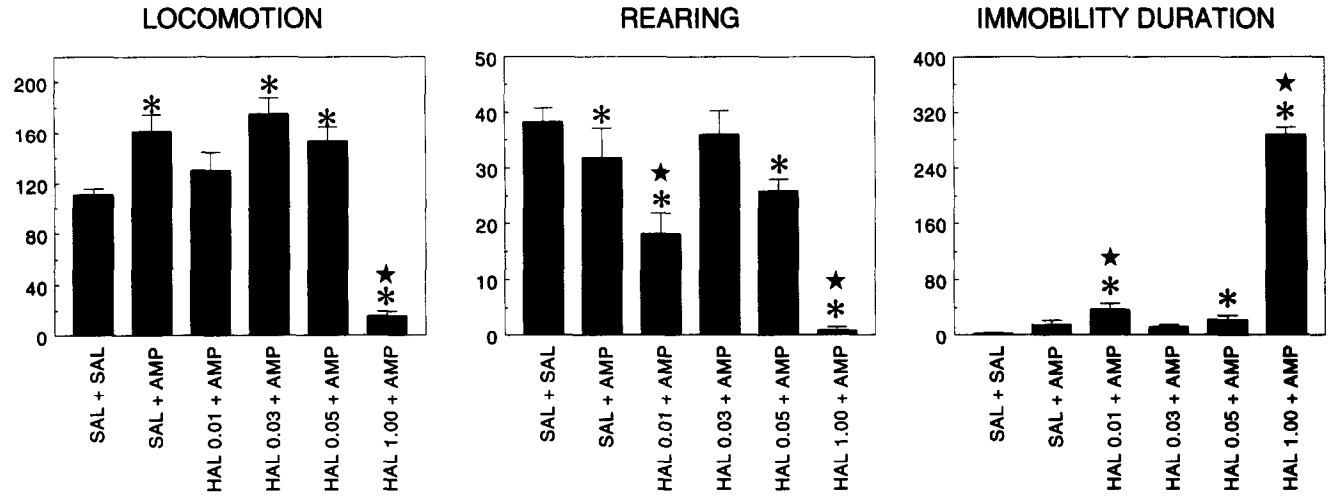


FIG. 2. Effects of single haloperidol (HAL) doses (mg/kg) or saline (SAL) administration on the open-field behavior of mice acutely treated with 2 mg/kg amphetamine (AMP). *Statistically significant difference from the SAL + SAL group at $p < 0.05$ (ANOVA, Duncan's test). ★Statistically significant difference from the SAL + AMP group at $p < 0.05$ (ANOVA, Duncan's test).

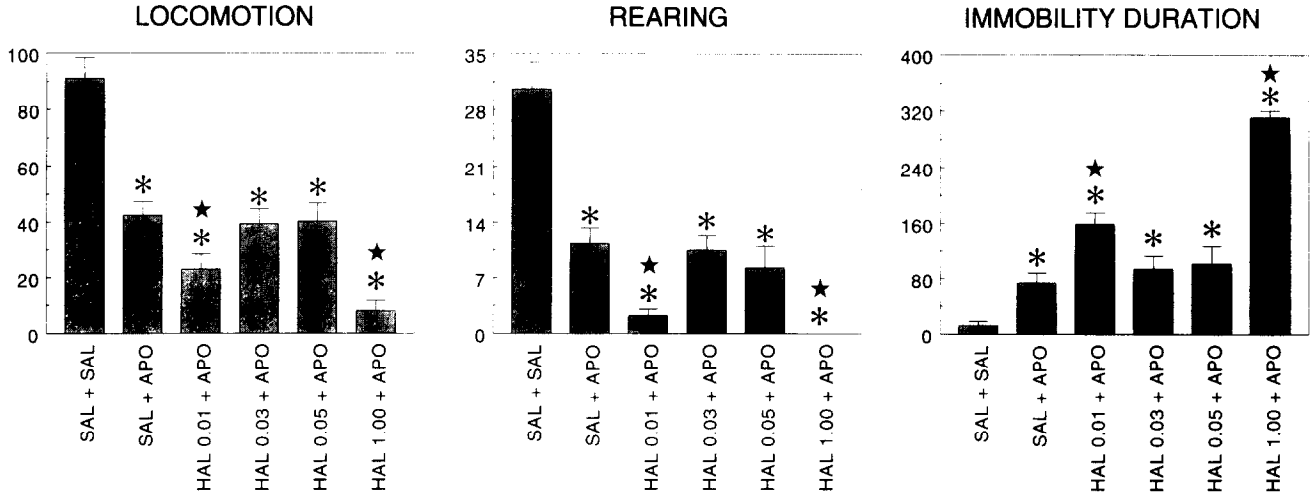


FIG. 3. Effects of single haloperidol (HAL) doses (mg/kg) or saline (SAL) administration on the open-field behavior of mice acutely treated with 0.06 mg/kg apomorphine (APO). *Statistically significant difference from the SAL + SAL group at $p < 0.05$ (ANOVA, Duncan's test). ★Statistically significant difference from the SAL + APO group at $p < 0.05$ (ANOVA, Duncan's test).

the observation of an inverted U function for both locomotion and rearing behaviors argues against behavioral competition, because they were both modified in the same direction.

It is also tempting, in light of these results, to question whether the three-phase effect of haloperidol on open-field behavior has to do with a differential action of the neuroleptic on pre- or postsynaptic DA receptors. In this respect, although the stimulant and depressant motor effects of high doses of DA-receptor agonists and antagonists, respectively, are considered to be due to their action on postsynaptic DA receptors (23,31), it was originally suggested that the effects of low doses of these agents (depression and stimulation, respectively) would be a consequence of modifications of synaptic levels of DA mediated by a preferential action on functionally defined presynaptic DA autoreceptors (8,29). However, the autoreceptor hypothesis has recently been questioned by several research groups [for a review, see (35)]. For example, Ståhle and Ungerstedt (36) concluded that DA-agonist-induced suppression of exploration was not related to reduced extracellular levels of DA, because it could be elicited by DA agonists in rats treated with amphetamine in doses that were shown to increase the extracellular level of DA. These authors suggested that DA-agonist-induced hypolocomotion would be mediated by stimulation of populations of particular postsynaptic DA receptors whose sensitivity to dopaminergic agents would be considerably higher than the sensitivity to the postsynaptic DA receptors mediating, for example, stereotyped behavior.

The present experimental design did not make it possible to distinguish between these hypotheses. However, the kind of dose-response curve observed here (inverted U) unexpectedly suggests that the DA receptors mediating motor stimulation (classical postsynaptic DA receptors) have higher sensitivity to haloperidol than the DA receptors mediating motor depres-

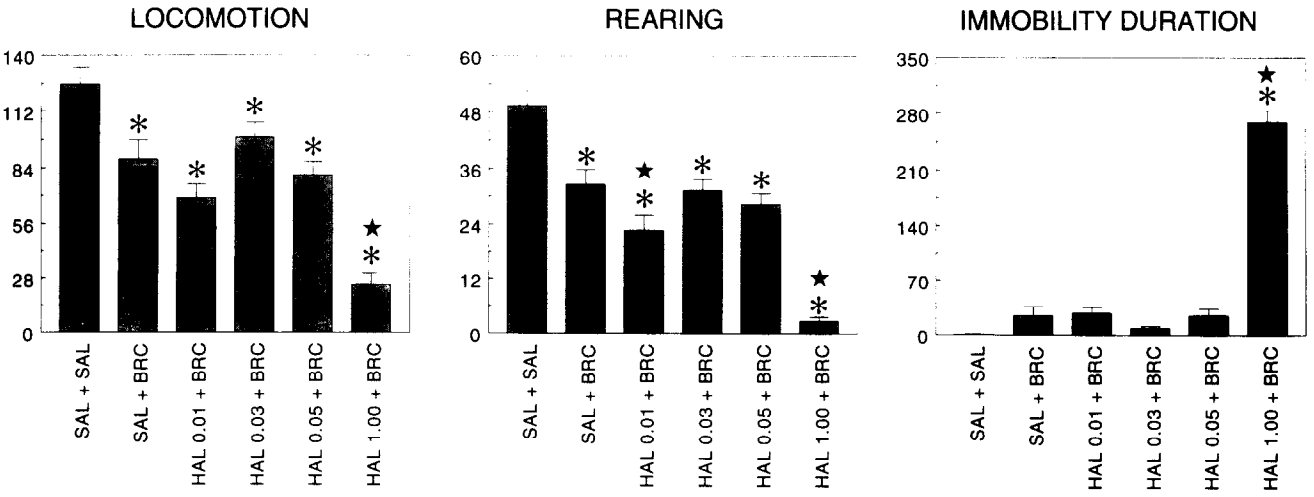


FIG. 4. Effects of single haloperidol (HAL) doses (mg/kg) or saline (SAL) administration on the open-field behavior of mice acutely treated with 2.50 mg/kg bromocriptine (BRC). *Statistically significant difference from the SAL + SAL group at $p < 0.05$ (ANOVA, Duncan's test). ★Statistically significant difference from the SAL + BRC group at $p < 0.05$ (ANOVA, Duncan's test).

sion (DA autoreceptors or hypothetical postsynaptic inhibitory receptors). Indeed, it might be hypothesized that at 0.01 mg/kg haloperidol, only DA receptors mediating motor stimulation would be effectively blocked, leading to significant decreases in locomotion and rearing frequencies, as well as significant increases in immobility duration. At slightly higher doses (0.03 mg/kg in some experiments and both 0.03 and 0.05 in others), although the magnitude of the blockade on DA receptors mediating motor stimulation would even be slightly higher, DA receptors mediating motor depression would also be effectively blocked, resulting overall in a normalization of motor activity. Finally, at the high haloperidol dose of 1 mg/kg, an additional blockade of DA receptors mediating motor stimulation would predominate, leading to hypoactivity once more. This hypothesis is consistent with the data of Andén and Grabowska-Andén (2), who showed that some neuroleptics (haloperidol, clozapine, and pimozide) were more effective in blocking rotational behavior (i.e., postsynaptic dopamine receptors) than inhibiting the presynaptic actions of apomorphine.

The existence of a considerable receptor reserve (spare receptors) in the receptor population controlling DA synthesis has recently been demonstrated (27). Similarly, a large receptor reserve has been suggested for the postulated populations of postsynaptic DA receptors mediating yawning and the suppression of exploration (36). In contrast, classical postsynaptic DA receptors mediating an increase of neostriatal acetylcholine content show no receptor reserve (26). A receptor reserve would implicate a higher sensitivity to agonists but a lower sensitivity to antagonists, further supporting the assumption that the DA-receptor population mediating motor stimulation has a higher sensitivity to haloperidol than the DA receptor population mediating motor depression.

As mentioned before, although the three-phase action of haloperidol was clear-cut under the conditions of apomorphine- or bromocriptine-induced hypoactivity and amphetamine-induced hyperactivity, it was much less evident when spontaneous activity was evaluated. One interpretation of this finding is that under physiologic conditions, endogenous dopaminergic tone at DA receptors mediating motor depression would not be high enough to cause strong behavior modifications after their blockade. In accord with this interpretation, and considering the autoreceptor hypothesis, DA autoreceptors are largely located outside the synaptic cleft, and so their dopaminergic tone seems to be much lower than at the DA postsynaptic receptors [see (16)].

It is well known that DA receptors can be divided into $D_1$ and $D_2$ subtypes (22), with $D_1$ receptors being positively linked to adenyl cyclase and $D_2$ receptors being negatively linked or not linked to adenyl cyclase. Whereas the autoreceptors belong to the $D_2$ type only, postsynaptic DA receptors show the characteristics of either the $D_1$ or $D_2$ type. Although haloperidol is not a pure $D_2$-selective blocker, it has a very weak $D_1$-blocking action [see (41)]. Thus, even though concurrent stimulation of both $D_1$ and $D_2$ receptors is required for the induction of classical dopaminergic behaviors such as stereotypy, rearing, and locomotion (25,30,37), it is unlikely that a differential action of haloperidol on $D_1/D_2$ receptor can account for the results described here. On the other hand, molecular biologic studies have recently cloned and identified five different DA receptors that fall into $D_1$-like or $D_2$-like receptor families; $D_1$-like receptors include $D_1$ and $D_5$ receptors, whereas $D_2$-like receptors include $D_2$, $D_3$, and $D_4$ [see (32,33)]. Hence, the possibility exists that the three-phase effect of haloperidol on the open-field behavior of mice may be a reflection of a differential blockade on $D_2$-like receptor subtypes.

The mechanisms proposed here to explain the three-phase effect of haloperidol on the open-field behavior of mice are speculative, and further work is needed to clarify and define them. This three-phase action is a provocative finding that should stimulate further study of this phenomenon.

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