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Effects of Repeated Apomorphine and Haloperidol Treatments on Subsequent Behavioral Sensitivity to Apomorphine

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MATTINGLY, B. A. AND J. K. ROWLETT. *Effects of repeated apomorphine and haloperidol treatments on subsequent behavioral sensitivity to apomorphine*. PHARMACOL BIOCHEM BEHAV **34**(2) 345–347, 1989.—In a 2 × 2 factorial design, four groups of rats (n = 10 each) were injected daily with haloperidol (0.5 mg/kg IP) or its injection vehicle and apomorphine (1.0 mg/kg SC) or its vehicle for 21 consecutive days. Then, following a six-day drug-free rest interval, all rats were tested for locomotor activity in photocell arenas after an apomorphine injection on four additional days. Major findings were as follows: (a) rats pretreated with apomorphine were significantly more active following an apomorphine injection than rats pretreated with vehicle; (b) the development of sensitization to apomorphine was completely blocked by the concurrent administration of haloperidol during the pretreatment phase; and (c) pretreatment of rats with haloperidol alone did not affect subsequent sensitivity to apomorphine. These results suggest that the development of behavioral sensitization to apomorphine is related specifically to the stimulation of dopamine receptors.

Apomorphine Haloperidol Dopamine Locomotor activity Behavioral sensitization Rats

REPEATED treatment of rats with dopamine antagonists (e.g., haloperidol) produces a behavioral supersensitivity to dopamine agonists (e.g., apomorphine) (3). This increased sensitivity to dopamine agonists appears to be mediated, in part, by an increase in the number of dopamine receptors (3, 5, 12). Paradoxically, repeated treatments with dopamine agonists also result in a behavioral supersensitivity to dopamine agonists. This enhanced sensitivity to dopamine agonists with repeated exposure has been referred to as "reverse-tolerance," "up-regulation," and "sensitization," and has been demonstrated using several agonists (2, 4, 13, 15, 21).

Research in our laboratory has revealed a very strong sensitization effect in rats following repeated treatments with the dopamine agonist, apomorphine (8–11). Indeed, the second administration of this drug in doses greater than 1.0 mg/kg often produces twice the effect on locomotor activity as does the first injection with a three-day interval between injections (8). Moreover, this apomorphine increase in locomotor activity continues to grow larger for up to 10–12 administrations with intervals between injections as short as 24 hours and as long as seven days (9). Once established, this sensitization effect is maintained for at least 17 days following termination of drug treatment (9). Unlike chronic dopamine antagonist-induced behavioral supersensitivity, the neural mechanisms responsible for behavioral sensitization following repeated agonist treatments are unknown (8).

The main objective of the present experiment was to determine whether the development of behavioral sensitization to apomorphine is related specifically to the chronic stimulation of dopamine receptors. Consequently, groups of rats were chronically pretreated with apomorphine and/or the specific dopamine antagonist, haloperidol, for three weeks. Then, following a six-day drug-free rest interval, all rats were tested for locomotor activity following an injection of apomorphine alone. If the development of sensitization to apomorphine is related specifically to the chronic stimulation of dopamine receptors, then the concurrent administration of haloperidol with apomorphine should block the development of sensitization.

METHOD

Subjects

Forty male Wistar albino rats weighing between 250–300 g were experimentally naive at the beginning of testing. All rats were housed individually and maintained on ad lib food and water. All behavioral testing was conducted during the light phase of the 12-hour light-dark cycle.

Apparatus

Activity measures were taken in two BRS-Lehigh Valley cylindrical activity drums (Model 145-03). Each drum was 60 cm in diameter, 43 cm high, and was located in a separate experimental cubicle that was kept totally dark throughout testing. The interior of the drums was painted flat black and the floor was made

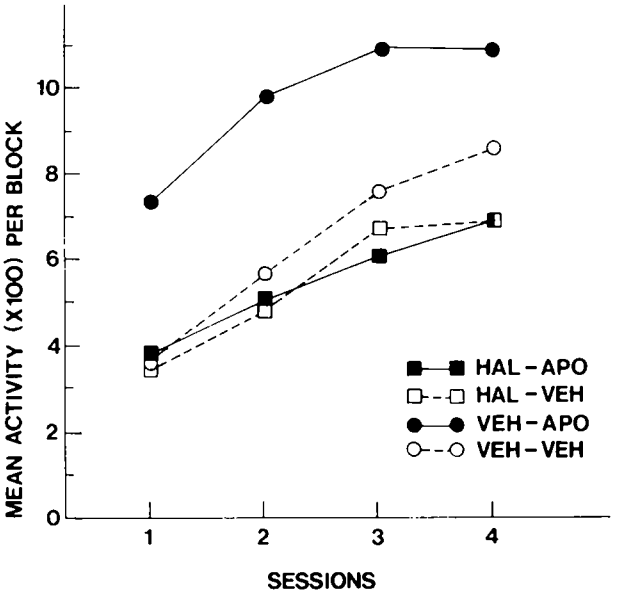

FIG. 1. Mean activity counts per 10-min block for rats pretreated for 21 days with either haloperidol (HAL) or its injection vehicle (VEH) and apomorphine (APO) or its vehicle (VEH). All groups were injected with 5.0 mg/kg apomorphine 15 minutes prior to each of the four activity test sessions.

of 4 cm diamond wire mesh. Each drum was equipped with two banks of three infrared photocells mounted on the outside of the drums. The photocells were approximately 12 cm apart and 2.5 cm above the drum floor. The photocell banks were connected to electromechanical counters in an adjacent control room by way of back-path eliminator diodes. Movement of the rat through a photocell beam sent a single pulse to the counters. Simultaneous pulses (i.e., pulses spaced less than 0.05 sec apart), such as might occur when two beams are broken near their intersection, were recorded as a single count by this method. Thus, activity was operationalized as the cumulative number of photobeam interruptions per unit time.

Design and Procedure

At the beginning of testing, the rats were randomly assigned, in equal numbers, to one of four groups in a 2×2 factorial design combining haloperidol or its injection vehicle and apomorphine or its vehicle. During each of the first 21 days of the study, the rats were first injected IP with either haloperidol (0.5 mg/kg) or its vehicle (1% lactic acid). Then, approximately 20 minutes later, each rat received a SC injection of apomorphine hydrochloride (1.0 mg/kg) or its vehicle (0.001 N HCl). Following the 21 daily injections, all rats were given a six-day drug-free rest interval. Following this rest interval all rats were then tested for locomotor activity for four additional days. On each of these test days each rat was given a SC injection of 5.0 mg/kg apomorphine hydrochloride fifteen minutes prior to activity testing. Activity counts were recorded at ten-minute intervals for a total of 20 minutes on each test day.

RESULTS

Figure 1 presents the mean activity counts per ten-minute block across the four test sessions for the four pretreatment groups. These data were analyzed with a four-factor mixed analysis of variance using agonist and antagonist pretreatment drug conditions as between factors and sessions and blocks of ten minutes within sessions as within factors. The groups decreased activity across the two ten-minute blocks within each session (block effect, $F = 119.42$, $p<0.0001$). Since this block effect did not significantly interact with either of the two pretreatment drug effects, the block data are not presented in Fig. 1.

As may be seen in Fig. 1, the rats pretreated with apomorphine only (VEH-APO group) displayed significantly greater locomotor activity on the first test session than the rats pretreated with either vehicle (VEH-VEH), haloperidol only (HAL-VEH), or haloperidol and apomorphine (HAL-APO). Moreover, although apomorphine produced a progressively greater increase in locomotor activity across the four test sessions for all groups, session effect, $F(3,108) = 86.14$, $p<0.0001$, the rats pretreated with apomorphine only remained more active than the other pretreatment groups across all four sessions, agonist effect, $F(1,36) = 4.81$, $p<0.05$, antagonist effect, $F(1,36) = 12.50$, $p<0.01$, and Agonist $\times$ Antagonist interaction, $F(1,36) = 4.83$, $p<0.05$. More important, sensitization to apomorphine was completely blocked by haloperidol. That is, although pretreatment with apomorphine resulted in a significantly enhanced locomotor activity response to apomorphine relative to vehicle pretreatments, the apomorphine-induced activity of rats pretreated with both apomorphine and haloperidol did not differ significantly from that of the vehicle pretreatment group on the first test session. Moreover, the two groups of rats pretreated with haloperidol actually displayed less activity in response to apomorphine than the vehicle-control rats on the last two test sessions (Newman-Keuls test, $p<0.05$).

DISCUSSION

It is evident from the present results that repeated intermittent treatment of rats with apomorphine leads to the development of behavioral sensitization. Indeed, rats pretreated with 21 daily injections of 1.0 mg/kg apomorphine were nearly twice as active following a 5.0 mg/kg injection of apomorphine as rats pretreated with vehicle. Although this sensitization effect is consistent with that observed in previous studies [e.g., (8,9)], it should be noted that the magnitude of this effect was considerably smaller than that observed previously. For instance, in one previous study, rats given 13 1.0 mg/kg apomorphine injections were found to be nearly four times as active as vehicle control rats (8). In this latter study, however, the rats were tested for locomotor activity following each of the 13 apomorphine injections, whereas in the present study the rats were not tested for activity until seven days following the last pretreatment injection. This procedural difference between the two studies probably accounts for the observed differences in the magnitude of the sensitization effect. Indeed, recent evidence indicates that the presence of drug-associated environmental stimuli facilitates and/or enhances the development of sensitization to apomorphine (10).

As discussed previously, chronic treatment with dopamine antagonists such as haloperidol have been reported to significantly increase subsequent behavioral sensitivity to apomorphine (3,12). Moreover, this behavioral supersensitivity to dopamine agonists appears to be related to an antagonist-induced up-regulation of dopamine receptors (12). Although the haloperidol dose and injection schedule used in the present experiment has been reported to result in a significant up-regulation of dopamine receptors (6), no evidence of agonist behavioral supersensitivity was observed in the present study. That is, the apomorphine-induced activity level of rats chronically pretreated with haloperidol did not differ significantly from rats pretreated with vehicle on the first activity test session and by the fourth and last test session the rats pretreated with haloperidol were actually less active

following an apomorphine injection than the vehicle-pretreated rats. This finding was not totally unexpected as most of the studies reporting behavioral supersensitivity to dopamine agonists following chronic antagonist treatment have used agonist-induced stereotypy, rather than locomotor activity, as the behavioral measure [e.g., (16)]. Consistent with the present results, other researchers have also found that chronic haloperidol treatments do not result in an enhanced activity response to the subsequent administration of apomorphine (18,19). Interestingly, there appears to be a double dissociation between the effects of chronic haloperidol and apomorphine treatments. That is, chronic haloperidol treatments appear to produce an increase in agonist-induced stereotypy, but not in agonist-induced locomotor activity. In contrast, chronic apomorphine treatments produce an increase in agonist-induced locomotor activity, but not in stereotypy (9). This dissociation suggests that chronic dopamine agonist and antagonist treatments may differentially affect different dopamine pathways [cf. (1, 7, 20)].

Although repeated treatments with haloperidol did not significantly enhance subsequent behavioral sensitivity to apomorphine, haloperidol combined with apomorphine treatments completely blocked the development of sensitization to apomorphine. This finding is consistent with a previous study using mice (17) and suggests that the development of sensitization to apomorphine with repeated exposure is related specifically to the stimulation of dopamine receptors. Thus, although no consistent changes in either the number or the sensitivity of dopamine receptors have been reported following chronic dopamine agonist treatments [e.g., (11, 14, 15)], the present results suggest that increased dopamine receptor activity is necessary for the development of behavioral sensitization.

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