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Differential Effects of Haloperidol and Clozapine on the Reinforcing Efficacy of Food Reward in an Alleyway Reacquisition Paradigm

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WILEY, J. L. AND J. H. PORTER. *Differential effects of haloperidol and clozapine on the reinforcing efficacy of food reward in an alleyway reacquisition paradigm.* PHARMACOL BIOCHEM BEHAV **36**(3) 569–573, 1990.—Using the alleyway reacquisition procedure developed by Horvitz and Ettenberg (19), the present study compared the effects of a typical neuroleptic haloperidol (0.15 and 0.30 mg/kg) to those of an atypical neuroleptic clozapine (5.0 and 10 mg/kg) on running times 24 hours after a single food-rewarded trial administered during an extinction regimen. Rats that received food reward plus an injection of vehicle or 0.15 mg/kg haloperidol ran faster on the subsequent test day than did nonrewarded rats. The 0.30 mg/kg dose of haloperidol blocked this reacquisition effect, yielding results consistent with the anhedonia hypothesis (27). Clozapine (5.0 and 10 mg/kg), however, failed to block the reacquisition of alleyway running. Thus, unlike haloperidol, clozapine did not produce anhedonic effects in this reacquisition paradigm. These results suggest that neither motor nor anhedonic properties of neuroleptics appear to be crucial to the clinical efficacy of neuroleptics.

Dopamine Food reward Neuroleptics Haloperidol Clozapine Anhedonia Rats

NEUROLEPTICS have been shown to decrease the frequency of responding for food (24), water (15), and electrical stimulation of the brain (13). Traditional interpretations have attributed the observed neuroleptic-induced suppression of positively reinforced operant behavior in laboratory animals to motor deficits produced by neuroleptic blockade of dopaminergic pathways of the extrapyramidal motor system. Accumulating evidence, however, suggests that motor impairment is but one of the multiple effects of neuroleptic drugs. Wise (27), for example, has suggested that neuroleptics also have anhedonic effects; i.e., they decrease the hedonic value of rewards. Since both the anhedonia hypothesis and the motor deficit hypothesis predict that animals will exhibit a decrease in responding maintained by positive reinforcement following neuroleptic administration, separating the motor and anhedonic effects of neuroleptic drugs has been problematic.

Horvitz and Ettenberg (19) have described a reacquisition alleyway procedure in which drug injection and behavioral testing occur on different days. Thus, the effects of neuroleptics on reward value and on motor functioning are not confounded in this experimental situation. The reacquisition procedure involves training rats to run a straight-arm alleyway for food reward in single daily trials. Once the animals are trained, extinction conditions are initiated. When running has slowed to a criterion level, some rats are given a single priming trial with food reward. All rats are then given a single (nonrewarded) test trial 24 hours later. In the absence of drug, animals that receive food reward during the priming trial run faster during the nonrewarded test trial twenty-four hours later than do animals who do not receive the food priming trial. Using this procedure, Horvitz and Ettenberg found that rats injected with the typical neuroleptic haloperidol (0.15 and 0.30 mg/kg) prior to the food-rewarded priming trial failed to exhibit increased running speeds during the test day trial. Thus, haloperidol abolished the reacquisition effect. Wiley, Porter and Faw (26) also tested haloperidol (0.033, 0.10, and 0.30 mg/kg) in this paradigm and found similar results; i.e., all three doses blocked the reacquisition effect. Both studies suggest that the typical neuroleptic haloperidol has anhedonic effects at the doses tested.

A review of the literature on neuroleptics, however, fails to find reports of similar tests with atypical neuroleptics. Atypical

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neuroleptics are effective as antipsychotics in humans, but do not produce the motor side effects seen with typical neuroleptics (2). The purpose of the present study was to compare the effects of the typical neuroleptic haloperidol to the effects of the atypical neuroleptic clozapine in this alleyway reacquisition procedure.

METHOD

Subjects

Eighty adult male Sprague-Dawley rats (240–300 g) served as subjects. The rats were individually housed in wire cages in a temperature controlled (22°C) environment with 12-hour light-dark cycle (lights on at 6 a.m.). Throughout the experiment, the rats were maintained at 80% free-feeding body weight by restricting their daily ration of Agway Prolab MHR 3000 rodent chow. They had free access to water in their home cages.

Apparatus

The apparatus consisted of a straight-arm alleyway (150 × 15.5 × 18.5 cm) with attached start (21.5 × 21.5 cm) and goal (25.5 × 21 cm) boxes. The start and goal boxes had manually operated guillotine doors. Lifting the start box door triggered a switch which started the first sweep timer (Lafayette Instrument Co., model 54014). Interruption of an infrared photo cell beam in the alleyway (13 cm from the start box door) simultaneously stopped the first timer and started a second one. The second timer stopped when the rat interrupted a photo cell beam located in the goal box (7.5 cm from door). The first timer recorded latency to leave the start box (start latency); the second, latency to arrive in the goal box (goal latency). The sum of the start and goal latencies comprised the total running time.

Drugs

Haloperidol (Sigma Chemical Co.) was prepared in 0.15 and 0.30 mg/ml concentrations and clozapine (provided by Sandoz Research Institute) was prepared in 5.0 and 10.0 mg/ml concentration using a vehicle solution of 85% lactic acid (5–10 drops) and distilled water. Injections of haloperidol, clozapine, and vehicle were administered intraperitoneally at a volume of 1 ml/kg of body weight.

Procedure

Animals received one trial per day in the alleyway throughout the entire experiment. On the first day of adaptation each rat was placed in the center of the unbaited alleyway with both guillotine doors removed and was left for three minutes. On each of the next four days of adaptation, each rat was placed in the goal box (with door in place) with 10 BioServe rodent pellets (0.45 g) in the food cup. The rat remained in the goal box until all pellets were eaten or for five minutes. By day four, all rats had eaten all of the food pellets for at least two consecutive days. Following adaptation, the experimental protocol consisted of four consecutive phases: acquisition, extinction, injection day, and test day. A trial consisted of placing the rat in the start box, the start box door opening, the rat running the alleyway, entering the goal box, and consuming any available reward. Both start and goal box doors were closed subsequent to the animal's passing to prevent retracing. Start and goal latencies (sec) were recorded for each trial. Animals were allowed a maximum of 10 minutes running time (start and goal latency maximums of 5 minutes each) to complete each trial. Animals not exiting the start box or entering the goal box within the 5-minute maximum were manually placed in the alleyway or the goal box, respectively.

During the acquisition phase, rats traversed the alleyway and, upon reaching the goal box, were allowed to consume a reward of 10 food pellets. Criterion for acquisition was set at three out of four consecutive trials with a total running time of less than ten seconds. An animal's mean running time for the three acquisition criterion trials constituted its acquisition baseline. On the day following the final acquisition trial, the extinction phase began. Extinction trials were identical to acquisition trials, except that the food cup in the goal box was empty. The extinction criterion was three out of four consecutive trials, each with a running time exceeding three times the animal's acquisition baseline. Extinction baseline was calculated as the mean of the animal's running time during the three extinction trials that met the criterion.

On the day following each rat's final extinction trial, the drug injection trial was conducted. Rats were matched on acquisition baseline running times and assigned to one of the following six experimental conditions (n = 10) for the injection day trial:

(1) VEH + FOOD (V + F): animals received a vehicle injection 45 min before being placed in the baited alleyway;

(2) VEH + EXTINCTION (V + E): animals received a vehicle injection 45 min before being placed in the unbaited alleyway;

(3) HAL 0.30 + FOOD (H.3): animals received an injection of haloperidol (0.30 mg/kg) 45 min before being placed in the baited alleyway;

(4) HAL 0.15 + FOOD (H.15): animals received an injection of haloperidol (0.15 mg/kg) 45 min before being placed in the baited alleyway;

(5) CLZ 10 + FOOD (C10): animals received an injection of clozapine (10.0 mg/kg) one hour before being placed in the baited alleyway;

(6) CLZ 5 + FOOD (C5): animals received an injection of clozapine (5.0 mg/kg) one hour before being placed in the baited alleyway.

Two additional groups (n = 10) served as motor control groups. Animals in these two groups were drugged following the injection day trial:

(7) FOOD + HAL 0.30 (P-H.3): animals received an injection of haloperidol (0.30 mg/kg) on injection day one hour after a food-rewarded trial;

(8) FOOD + CLZ 10 (P-C10): animals received an injection of clozapine (10.0 mg/kg) on injection day one hour after a food-rewarded trial.

On test day (24 hours after the injection day trial), each animal was given a nonrewarded trial in the alleyway.

The eight animals were tested sequentially in two groups of forty, with five animals per condition in each group. The data for these two squads of rats were combined for analysis.

Data Analysis

Split-plot analyses of variance were performed on the means of the total running times (i.e., the sum of the start and goal latencies) comparing extinction baseline times vs. test day times separately for each drug (haloperidol and clozapine). In each of the ANOVA's, comparisons were made between subjects for experimental condition (V + E, V + F, H.3 and H.15 or C10 and C5, and P-H.3 or P-C10) and within subjects for trials (extinction baseline vs. test day). In addition, one-way ANOVA's were performed separately for each drug comparing injection day running times across experimental conditions. Duncan post hoc tests ($\alpha = 0.05$) were used to specify differences revealed by significant ANOVA's (6).

RESULTS

During the acquisition baseline, the mean running time for all

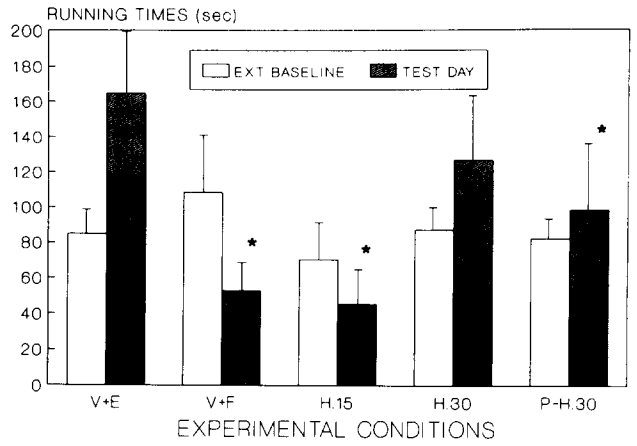

FIG. 1. Means (+SEM) of the total running times (sec) during extinction baseline and on test day for rats injected with haloperidol or with vehicle. An asterisk indicates that test day running time for the group was significantly different from that of the nonrewarded V+E group. *$p<0.05$.

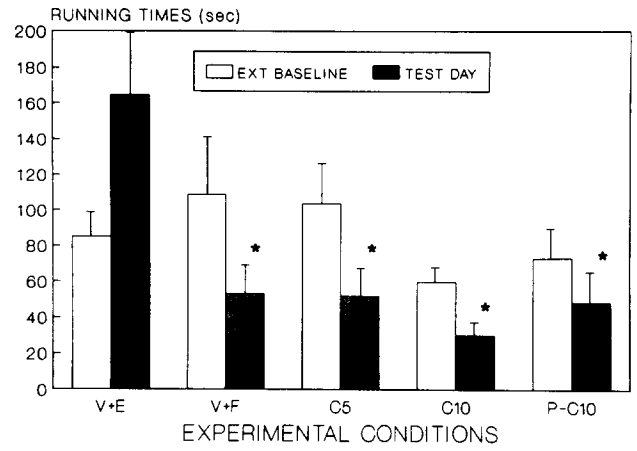

FIG. 2. Means (+SEM) of the total running times (sec) during extinction baseline and on test day for rats injected with clozapine or with vehicle. Note that the data for the V+E and V+F groups are the same as that in Fig. 1. Again, an asterisk indicates that test day running time for the group was significantly different from that of the nonrewarded V+E group. *$p<0.05$.

groups was 4.48 sec. The mean number of trials to acquisition was similar for each experimental group (range of group means = 4.6 to 6.4 trials), as was the mean number of trials to extinction (range of group means = 7.2 to 9.9 trials).

Figure 1 shows the mean of the total running times (+SEM) during extinction baseline and on test day for rats injected with haloperidol or with vehicle. An Experimental Conditions × Trials interaction ($p<0.01$) was obtained. While none of the groups had significantly different running times during the extinction baseline period, on test day the V+F, H.15, and P-H.3 groups ran significantly faster than did the V+E group. Test day running times for the H.3 group did not differ significantly from those of the V+E group. Further, the H.3 group ran significantly slower on test day than did the V+F and H.15 groups. Within subject comparisons across trials revealed that the V+E group ran significantly slower on test day than during the extinction baseline.

Figure 2 shows the mean total running times (+SEM) during extinction baseline and on test day for rats injected with clozapine or with vehicle. (Note that the data for the V+E and V+F groups are the same as in Fig. 1.) The ANOVA comparing test day vs. extinction baseline revealed a significant main effect for experimental conditions ($p<0.03$) and a significant Experimental Conditions × Trials interaction ($p<0.001$). Between group comparisons on test day revealed that all of the experimental groups (V+F, P-C10, C10, and C5) ran significantly faster than did the V+E group. The within subject comparisons across trials again revealed that the V+E group had significantly slower running times on test day than during extinction baseline. The V+F and C5 groups had significantly faster running times on test day than during extinction baseline.

In order to assess the effects of the drugs on motor behavior, the injection day running times were analyzed. Figure 3 shows the mean running times (+SEM) on injection day for all experimental conditions. ANOVA's for haloperidol and for clozapine were significant ($p<0.02$ and $p<0.008$, respectively). Rats that received 0.30 or 0.15 mg/kg of haloperidol on injection day ran significantly faster than the nonrewarded (V+E) rats; however, they did not run faster than the V+F group. Rats that received 5.0 mg/kg of clozapine also ran significantly faster than the V+E group, but did not run faster than the V+F group. Rats that received 10 mg/kg of clozapine, however, ran significantly slower than the V+F group and any of the other clozapine groups. Injection day running times for the C10 group did not differ significantly from those of the V+E group.

DISCUSSION

The results of the present study confirmed previous findings (19,26) which showed that the reacquisition effect can be reliably produced in undrugged rats that receive a single food-rewarded trial during extinction and that pretreatment with 0.30 mg/kg of haloperidol reliably disrupts this effect. While these previous studies have shown that lower doses of haloperidol also attenuated the reacquisition effect [0.15 mg/kg (19); 0.10 and 0.033 mg/kg (26)], the 0.15 mg/kg dose of haloperidol failed to block the reacquisition effect in the present study. Although the reason for this discrepancy is unclear, the results of the present study suggest that attenuation of the reacquisition effect may be dose-dependent.

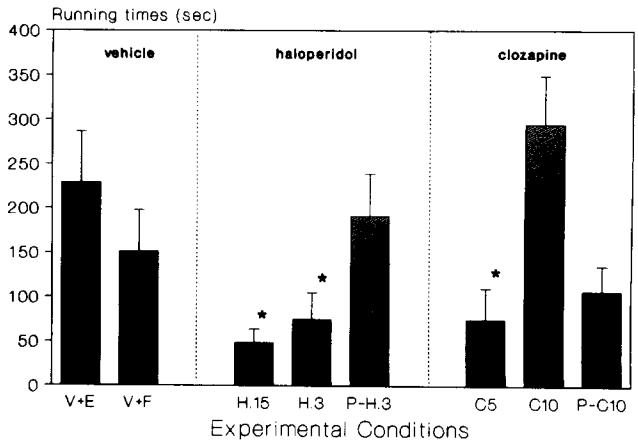

FIG. 3. Means (+SEM) of the total running times (sec) on injection day for all experimental conditions. An asterisk indicates that the running time for the group was significantly different from that of the nonrewarded V+E group. *$p<0.05$.

In any event, it is clear that the 0.30 mg/kg dose of haloperidol has produced reliable disruption of the reacquisition effect in each study.

Several hypotheses may be proposed to explain the observed attenuation of the reacquisition effect produced by the 0.30 mg/kg dose of haloperidol, including neuroleptic-induced motor deficits (1,12), state dependent learning (23), and neuroleptic effects on learning and memory. Since the injection day running times of rats that received either dose of haloperidol were similar to those of the V + F group, and significantly faster than those of the nonrewarded (V + E) group, motor impairment following neuroleptic administration in the present study seems unlikely. In addition, all three of the hypotheses mentioned above have been investigated and discounted in previous research [e.g., (3–5, 19)].

The disruption of running produced by the 0.30 mg/kg dose of haloperidol also may be cited as evidence supporting an anhedonia hypothesis of the neuroleptic suppression of operant behavior (27). Even though all of the haloperidol rats in the present study ran the alleyway and consumed all 10 food pellets on injection day, the test day running times of the rats injected with the 0.30 mg/kg dose of haloperidol did not differ significantly from those of rats that did not receive reward on injection day (i.e., the V + E group). This result is consistent with the anhedonia hypothesis and with the results of previous research; for example, haloperidol has been found to reduce the hedonic value of food (7, 19, 26), water (8), and electrical stimulation of the brain (9). Further, this anhedonic effect does not seem to be specific to haloperidol. Pimozide, another typical neuroleptic, has been shown to produce effects similar to decreased reward (14,28). Using water reinforcement instead of food, Horvitz and Ettenberg (20) found that pimozide (1.0 mg/kg) also blocked the reacquisition effect. Interestingly, however, similar to the effect of haloperidol (0.15 mg/kg) in the present study, a lower dose of pimozide (0.50 mg/kg) failed to block the reacquisition effect (20). In summary, then, higher doses of both haloperidol (0.30 mg/kg) and pimozide (1.0 mg/kg), the two typical neuroleptics that have been tested in this procedure, reliably attenuate the reacquisition effect.

Unlike typical neuroleptics, however, the atypical neuroleptic clozapine, tested in the present study, failed to disrupt the reacquisition effect. Regardless of whether the injection was given before or after the injection day trial, rats injected with either dose of clozapine (5.0 or 10 mg/kg) ran significantly faster on test day than did the V + E group. Thus, clozapine failed to produce anhedonic effects at either of the doses tested. This result is consistent with previous work by Faustman and Fowler (11) that showed that clozapine (10 mg/kg) did not produce an extinction-like pattern of responding over four days of repeated dosing in rats responding on a continuous reinforcement schedule. Faustman and Fowler (11) suggested that the behavioral difference seen in their study may be related to biochemical differences between clozapine and the typical neuroleptics, pimozide and fluphenazine.

A second possible explanation of the observed difference between the behavior of rats injected with haloperidol and those injected with clozapine is that these drugs may act on different neurochemical systems. Haloperidol is a relatively specific blocker of dopamine receptors; i.e., it has high affinity for dopamine receptors and only weak affinity for noradrenergic and serotonergic receptors in vitro (16). In vivo tests show that haloperidol has strong activity only as a dopamine antagonist (21). Clozapine, on the other hand, binds with high affinity to a variety of brain receptors including dopamine, acetylcholine, serotonin and norepinephrine receptors (2,16) and has strong pharmacological activity as an antagonist at all of these receptor sites (16,21). If the anhedonic effects of neuroleptics are related to their propensity for blockade of dopamine receptors, as proposed by Wise (27), the actions of clozapine on the other receptors may obscure the behavioral expression of antidopaminergic effects such as anhedonia. Wise (27) suggests that this explanation might account for the nonneuroleptic effects of some typical neuroleptics (e.g., chlorpromazine). In addition, haloperidol and clozapine may show selective binding to different types of dopamine receptors. Under chronic dosing conditions, differential binding appears to occur: haloperidol preferentially binds to D2 receptors; clozapine, to D1 receptors (22). Perhaps the anhedonic effects of haloperidol are mediated by D2 receptors.

In conclusion, although haloperidol and clozapine share clinical efficacy in treating schizophrenia, only haloperidol blunted the hedonic impact of food reward in the present study. Using a matching equation procedure (17) with a multiple reinforcement operant schedule, Porter, Freese and Jackson (25) reported similar differences between the effects of clozapine and pimozide. They found that pimozide reduced the reward value of food reinforcers; clozapine, on the other hand, did not decrease reinforcement efficacy. Similar to haloperidol, pimozide shows relatively specific binding to dopamine receptors (16). In addition, previous research [e.g., (10, 11, 18, 25)] suggests that the anhedonic effects of neuroleptics can be separated from their motor effects. Thus, different neuroleptics may show different profiles of motor and anhedonic properties. As evidenced by the behavioral effects produced by clozapine, however, neither motor nor anhedonic properties of neuroleptics appear to be crucial to their clinical effectiveness.

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