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Haloperidol Blocks the Response-Reinstating Effects of Food Reward: A Methodology for Separating Neuroleptic Effects on Reinforcement and Motor Processes

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HORVITZ, J. C. AND A. ETTENBERG. *Haloperidol blocks the response-reinstating effects of food reward: A methodology for separating neuroleptic effects on reinforcement and motor processes.* PHARMACOL BIOCHEM BEHAV 31(4) 861–865, 1988.—To test the hypothesis that dopamine antagonist drugs attenuate the reinforcing properties of food, rats previously trained to traverse a straight runway for food reward subsequently underwent extinction sessions. After running speeds had substantially decreased, rats received a single food-rewarded trial either in the presence or absence of haloperidol (0, 0.15 or 0.30 mg/kg IP). Twenty-four hours later, animals were tested for reinstatement of the running response during a drug-free test trial. Animals that were nondrugged during the food-rewarded trial showed increases in running speed on the test trial relative to extinction baseline speeds. In contrast, animals under the influence of haloperidol during the food-rewarded trial failed to show test day increases in running speed. Additional control groups ruled out the possibility that the haloperidol results were due to either motor or state-dependent learning effects. The findings support the view that dopamine systems play a role in the neural substrates underlying food reinforcement. In addition, the study demonstrates a simple and effective methodology for separating neuroleptic effects on motor and reinforcement processes.

Dopamine Food reward Neuroleptics Haloperidol Anhedonia Positive reinforcement Incentive motivation

IT is well established that animals under the influence of neuroleptic drugs show decreased rates of operant responding for food (25,27), water (13), and brain stimulation reward (8, 9, 12). There has been considerable controversy, however, regarding the mechanisms underlying this neuroleptic-induced suppression of reinforced behavior.

The problem appears to stem largely from the fact that, with few exceptions [see for example (3)], past studies have assessed neuroleptic effects in animals that were drugged at the time of testing. Consequently, it has been difficult to dissociate putative reward-attenuating (9, 12, 27, 28) and motor-impairing (2, 7, 8, 10, 17) effects of neuroleptics, since explanations invoking either type of impairment make the similar prediction that drugged animals will show a suppression of operant responding. A survey of the recent literature in this area shows that the performance versus reward controversy is far from resolved [see for example (15,18)]. To be confident that neuroleptic-induced behavioral effects reflect a disruption of reinforcement over and above any effect on motor capacity, animals should ideally be tested in a nondrugged state. The present study was therefore designed to dissociate putative reward and motor effects of the neuroleptic drug haloperidol, by separating the drug treatment and the behavioral test phases of the experiment.

EXPERIMENT I

An operant response that has undergone extinction can be reinstated with a single presentation of the original reinforcer [e.g., see (23)]. Studies of this type have typically been conducted in order to investigate the "incentive motivational" properties of a reinforcing stimulus and involve "priming" an animal with a noncontingent presentation of the original reinforcer. The present study employed a modified version of this procedure. Animals were trained to traverse a straight runway for food reward during single daily trials. Once the operant was established, animals received daily nonreinforced trials, until running speeds had slowed substantially.

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In preliminary studies, we observed that a single reinforced trial in the midst of this extinction phase was sufficient to reinstate runway responding on the very next trial (i.e., 24 hr later). Since it has been suggested that neuroleptic drugs can attenuate the reinforcing properties of food (3, 6, 27), it was of interest to determine whether such a drug would prevent the response reinstatement resulting from a food-rewarded trial during extinction. This reinstatement paradigm assesses performance 24 hours after the food/drug trial, thus minimizing motoric influences of the drug on test day performance.

METHOD

Subjects

Thirty-five experimentally naive male Sprague-Dawley rats (250–350 g) obtained from Charles River Laboratories served as subjects. Each animal was individually housed in metal wire hanging cages located within a temperature-controlled (23°C) 12-hr light/dark vivarium environment (lights on at 0700 hr). Following two weeks of ad lib access to food (Purina Rat Chow) and water, the animals were placed on a restricted food diet designed to reduce their body weights to 85% of free-feeding values. They were maintained at this reduced weight for the duration of the experiment, receiving their ration of food one hour after completion of the daily runway sessions.

Apparatus

All trials were conducted in a straight-arm runway (155 cm long × 15 cm wide × 20 cm high), with a white start box and a black goal box (each 24×25×20 cm) attached to opposite ends. Walls of the apparatus were constructed of wood, while the floor and ceiling were constructed of wire-mesh. A guillotine door separated the start box from the runway. Lifting this door initiated the start of the trial, the timing of which terminated when an animal interrupted an infrared photocell beam detecting the animal's presence in the goal box. The data for each animal on each trial therefore consisted of the time required to leave the start box, traverse the runway, and enter the goal box.

Drug/Vehicle

Haloperidol (0.15 and 0.30 mg/kg) was dissolved in a vehicle solution of 0.002 M lactic acid. Intraperitoneal injections of haloperidol and vehicle solutions were delivered in a volume of 1 ml/kg of body weight 45 min prior to the treatment trial.

Procedure

The experiment was conducted in four successive phases: Acquisition, Extinction, Treatment trial, and Test day trials 1 and 2. During all phases of the experiment, running times were recorded for each animal on every trial.

Acquisition. Animals received one runway trial per day. On a given day, the animal was placed in the start box and, after 5 sec, the start door was raised, thereby initiating the trial. Once the animal reached the goal box, it found a small circular dish, containing ten 45 mg Noyes Food Pellets. After consumption of the food reward, the animal was returned to its home cage. Each animal received single daily acquisition trials until its running time was under 12 seconds on three out of four consecutive days (this required 8–12 trials).

Extinction. Extinction trials began on the day following the last acquisition trial. These trials were identical to those of the acquisition phase with the exception that animals found no food upon entering the goal box. Animals were left in the unbaited goal box for 50 seconds before being returned to their home cages. Each animal underwent one extinction trial per day until it performed at an arbitrary "extinction criterion," requiring that the animal run three times slower than its fastest acquisition speed, on three out of four consecutive days (this required an average of 24 trials).

Treatment day. Upon reaching the extinction criterion, animals were assigned to one of five groups (n=7/group). One group of animals received a vehicle injection 45 minutes prior to a single nonrewarded trial (VEH/NO FOOD); other animals received a vehicle injection 45 minutes prior to a food-rewarded trial (VEH/FOOD); two groups received a single IP injection of either 0.15 or 0.30 mg/kg haloperidol 45 minutes prior to a food-rewarded trial (HAL.15/FOOD and HAL.30/FOOD); a final, "motor control," group received the high dose (0.30 mg/kg) of haloperidol 45 minutes *after* a food-rewarded trial (F/HAL.30).

Test days 1 and 2. Twenty-four and forty-eight hours after the treatment trial, all animals traversed an unbaited runway, drug-free, for test trials 1 and 2, respectively.

RESULTS AND DISCUSSION

To control for heterogeneity of variance (common when employing response-latency measures) the raw data were converted from running times (X sec) to their reciprocals, speeds (1/X sec) (5). All analyses were conducted on the speed data.

The mean performance of each group across Baseline, Treatment and Test trials is depicted in Fig. 1. The primary concern of this experiment was to determine whether the treatment procedures produced changes in Test behavior relative to that observed during pretreatment Baselines. Consequently a Two-Factor Analysis of Variance (with repeated measures on one factor) was computed on the data from the Baseline and Test trials. This analysis revealed the following statistically reliable results: a) a main effect over Trials, $F(2,60)=22.77$, $p=0.0001$, reflecting the increased Test responding relative to Baseline that was observed across all groups; b) a main effect for Groups, $F(4,30)=3.76$, $p=0.013$, demonstrating differences in the running speeds of different treatment groups; and c) a Group × Trial interaction, $F(8,60)=2.62$, $p=0.016$, confirming that the increased running speeds observed during Test trials differed in magnitude for the different treatment groups.

The results are consistent with the hypothesis that haloperidol attenuates the reinforcing consequences of food presentation in hungry animals. It was observed that a single food-rewarded (Treatment day) trial during extinction was sufficient to dramatically reinstate operant runway responses in undrugged animals (the VEH/FOOD group). In contrast, those animals that received an additional extinction trial (no food on Treatment day; the VEH/NO FOOD group) did not demonstrate a reliable increase in running speed on Test day. Of particular significance here is the observation that haloperidol pretreatments (the HAL.3/FOOD and HAL.15/FOOD groups) prevented the response reinstatement otherwise produced by food presentation on Treatment day. Planned comparisons revealed that the only subjects to reliably increase running speeds from Baseline to Test, were those that experienced food in the absence of haloperidol on Treatment day, that is, the VEH/FOOD group, $t(6)=3.66$, $p=0.011$, and the FOOD/HAL.3 group, $t(6)=6.39$, $p=0.001$;

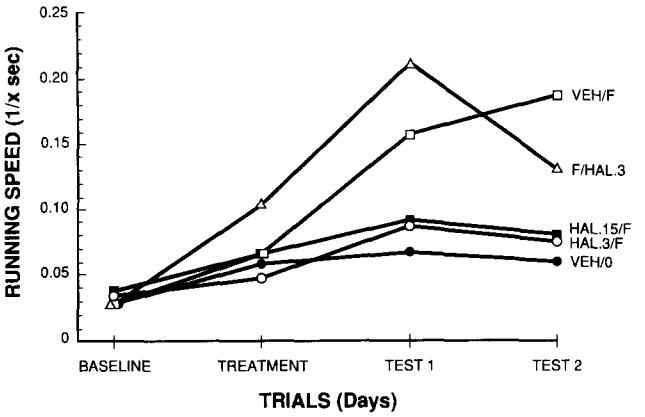

FIG. 1. Mean running speeds for all groups on Baseline, Treatment, and Test days 1 and 2; note that faster speeds are represented as higher points on the ordinate. Drug/vehicle injections were administered only on Treatment day. On the subsequent Test days, nondrugged, food-rewarded animals (i.e., the VEH/FOOD and FOOD/HAL groups) reinstated their operant runway response, while the haloperidol pretreated (HAL.15 and HAL.30/FOOD) and nonrewarded (VEH/NO FOOD) groups did not.

two-tailed tests. The latter of these two groups is particularly important. Since the FOOD/HAL.3 animals (injected 45 min *after* the Treatment day food trial) were able to demonstrate dramatic increases in running speed during subsequent Test trials, there is no evidence for residual drug-induced performance deficits 24 hr posthaloperidol treatment. It would seem then that the attenuation of running speeds observed in the two haloperidol *pre*treated (HAL/FOOD) groups, cannot easily be accounted for by some performance-impairing action of haloperidol. In fact, a one-way ANOVA performed solely on the Treatment day scores produced no reliable group differences in running speeds thereby providing no evidence for a performance deficit even while animals were under the influence of the drug, $F(4,30)=1.26$, n.s. This result is not surprising since it is well documented that neuroleptic-induced impairments in operant tasks are relatively weak at the onset of the test session and become progressively stronger as the session continues (7). A one-trial-per-day Test procedure, as employed in the present experiment, would therefore be expected to minimize the behavioral disruption produced by acute neuroleptic administration.

One final result that is of interest concerns the increase in running speed that was observed across all groups on Treatment day relative to Baseline, $F(1,30)=17.29$, $p=0.0003$. The injection procedure itself cannot account for this effect since the greatest speed elevations were seen in the FOOD/HAL.3 group which was not injected until after the trial. It seems reasonable to presume that the increased running speed of the food-rewarded groups may have been a consequence of a food odor emanating from the goal box; that is to say, the odor may have acted as an incentive stimulus (4). It seems likely that the food presented on the Treatment trials may have left a detectable odor that aroused even the hungry VEH/NO FOOD animals. Since no Group × Trial interaction was observed on the basis of Baseline and Treatment day scores, $F(4,30)=1.34$, n.s., there is no evidence to suggest that the haloperidol pretreatment blocked this motivational effect of food odor.

EXPERIMENT II

While the results of the first experiment suggest that haloperidol blocked the reinforcing effects of food reward, the results could alternatively be explained in terms of a State-Dependent Learning (SDL) hypothesis (16). This hypothesis postulates that in order for subjects to access previously learned information, they must be in a state similar to that under which the information was encoded. Accordingly, it could be aruged that the HAL.15/FOOD and HAL.30/FOOD groups failed to show response reinstatement on the Test trials because during these trials, while in a nondrugged state, they could not access information regarding the prior food-rewarded trial which was encoded under the influence of haloperidol. However, a further prediction derived from this hypothesis is that animals under the influence of the drug during both the food and Test trials should be capable of accessing the food-related information; consequently, these "same state" animals should run faster than animals not drugged during the food trial and drugged during the Test trial, that is, receiving food and test trials under alternate states. Experiment II was designed to test this prediction.

METHOD

Ten Sprague-Dawley rats underwent acquisition and extinction trials exactly as described in Experiment I. Following extinction, rats were randomly assigned to one of two groups (n=5/group). On Treatment day, one group was injected with haloperidol (0.30 mg/kg) 45 minutes prior to a food rewarded trial (HAL/FOOD). The second group was injected with the same dose of haloperidol, but received the injection one hour *after* the food trial (FOOD/HAL). On Test day 1, both groups were injected with the drug 45 minutes prior to the runway trial. The HAL/FOOD group was therefore under the influence of the drug during both the food and Test day 1 trials, whereas the FOOD/HAL group was nondrugged during the food trial and drugged during the Test day 1 trial. Note that both groups received haloperidol on each of the two days.

Twenty-four hours after the Test day 1 trial, a Test day 2 trial was conducted in which all animals traversed the unbaited runway *drug-free*.

RESULTS AND DISCUSSION

According to the SDL hypothesis, animals that were reinforced and tested under the influence of haloperidol ("same state"; the HAL/FOOD group) would be expected to show increases in running speed from Baseline to Test day 1, while those animals that were reinforced and tested under alternate pharmacological states (the FOOD/HAL group) should fail to show such increases in speed. As can be seen in Fig. 2, the results were not in agreement with this SDL prediction. Animals in the FOOD/HAL ("alternate state") group showed increases in speed from Baseline to Test day 1, while animals in the HAL/FOOD ("same state") group failed to show such elevations in speed. A Two-Factor Analysis of Variance (with repeated measures on one factor) computed on these Baseline and Test day 1 data revealed a statistically reliable Group × Trial interaction, $F(1,8)=15.34$, $p=0.005$, confirming that the changes in speeds from baseline to Test day 1 differed for the two treatment groups. The performance of the two groups on Test day 1 was inconsistent with that predicted by a SDL hypothesis.

The results, on the other hand, were consistent with the

view that haloperidol blocks the effects of food reinforcement on subsequent behavior. The FOOD/HAL group, reinforced drug-free on Treatment day, showed increased running speeds on both Test day 1 (drugged) and Test day 2 (nondrugged) trials, relative to Baseline. Haloperidol pretreatment (HAL/FOOD) blocked this response-reinstating effect of food reinforcement. A Two-Factor ANOVA (with repeated measures on one factor) conducted on Baseline and Test day 2 data revealed a significant Group × Trial interaction, $F(1,8)=5.50$, $p=0.047$, indicating that the shift in speed from baseline to the drug-free test trial differed for the two treatment groups.

These results cannot be accounted for by differences in baseline running speed, $F(1,8)=0.81$, n.s. Neither can the results be attributed to motoric effects of haloperidol treatment, since both groups received identical doses of the drug on both Treatment day and Test day 1. The two groups differed only in that the HAL/FOOD group received Treatment-day haloperidol administration *prior* to the food-reward trial, and the FOOD/HAL group received the drug *after* the food trial.

It should be noted that both groups showed slow Test-day running speeds relative to those observed in Experiment I. This may be due to the fact that animals in Experiment II received haloperidol on two consecutive days, compared to the single injection of haloperidol in Experiment I. It is thus possible that the Test-day 1 performance of animals in Experiment II was affected by factors related to drug accumulation. These cumulative drug effects, however, would be expected to affect both groups in Experiment II, and thus cannot account for the differences observed between the two groups.

Finally, it is quite interesting that, as in Experiment I, both the vehicle- and haloperidol-pretreated rats showed increases in speed from baseline to Treatment day, as confirmed by a reliable effect of Trials over these two days, $F(1,8)=13.50$, $p=0.006$. The significance of these results with respect to dopamine involvement in reinforcement versus incentive motivational processes is discussed at the end of the General Discussion section.

GENERAL DISCUSSION

Animals that experienced a single food-reinforced runway trial during extinction demonstrated a reinstatement of the operant running response when tested 24 hr later. This response-activating effect of food-reward was prevented by pretreatment with the DA receptor antagonist, haloperidol. It would seem that the response attenuating actions of haloperidol in Experiment I were not a consequence of some residual drug-induced motor impairment, since a) the Test trials were conducted 24 and 48 hr after drug/vehicle administration, and b) the animals receiving the high dose of haloperidol *after* completion of the food-reinforced trial (Experiment I; F/HAL.30) still demonstrated response-reinstatement when tested the next day (less than 24 hr postinjection). In addition, the results of Experiment II were directly opposite to those predicted by a State-Dependent learning hypothesis. Response reinstatement apparently does not require animals to be in a similar drug state during both the food and test trials, but rather requires that animals receive the food-trial in the absence of the neuroleptic.

One might argue that the relative reductions in Test-day running speeds seen in neuroleptic-pretreated rats are a consequence of some aversive action of the drug. However, we are aware of no evidence to suggest that neuroleptic treatments produce such aversive effects. On the contrary, repeated place- or taste-haloperidol pairings have failed to produce conditioned place or taste aversions, respectively (Ettenberg and Koob, unpublished data). Others have similarly failed to demonstrate conditioned place aversions with haloperidol, employing doses from 0.15 to 1.0 mg/kg (20–22). A haloperidol-induced aversive effect thus appears to be an unlikely explanation for the present results.

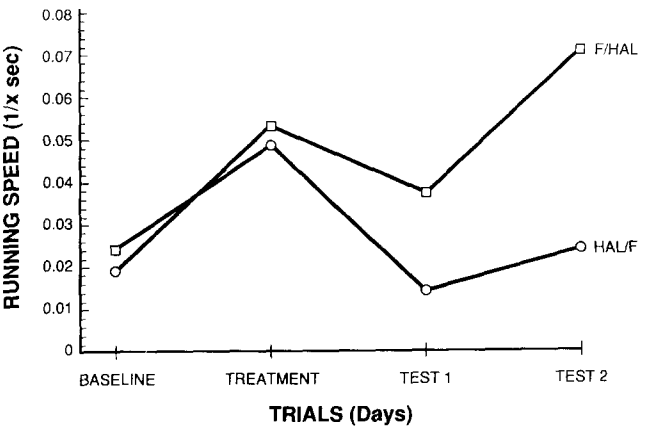

FIG. 2. State-dependent learning (SDL) controls. Mean running speeds for the HAL/FOOD (same state) and FOOD/HAL (alternate state) groups on Baseline, Treatment, and Test day 1 and 2 trials. These results were contrary to those predicted by an SDL hypothesis.

Yet another possibility is that the present findings reflect a haloperidol-induced change in the motivational state of the drugged subjects. For example, one might argue that neuroleptic-induced satiety on the Treatment trial could account for the apparent ineffectiveness of food to produce its response-reinstating effects on Test day. This argument would seem reasonable since it has been previously demonstrated that animals trained to traverse a runway under a low drive level (i.e., low levels of food deprivation) show slower running speeds than animals trained under a high drive, even when both groups are subsequently shifted to the same level of food deprivation (29). However, in the present experiment, all subjects, including the drugged animals, consumed the entire 10 Noyes pellet food reward on Treatment day. In addition, we have previously found that food-deprived rats administered haloperidol, at doses identical to those used here, show no increases in the time required to consume 10 Noyes pellets (unpublished observations). In accordance with these observations, past studies have failed to observe satiety-like effects of neuroleptic agents on home cage food consumption (8,25). Thus, while a satiety hypothesis cannot be unequivocally dismissed, we are aware of no evidence directly supporting such a view.

Past studies have suggested that neuroleptic drugs can attenuate the reinforcing effects of food [(3, 6, 20, 27, 28), but also see (14, 24, 25)]. The present findings are consistent with this view of neuroleptic action. Thus, while a single food-rewarded trial during extinction is normally sufficient to reinstate an operant running response, food experienced under the influence of haloperidol failed to exert such an effect. Haloperidol may have disrupted reinforcement substrates normally mediating this response-activating effect of food reward. Since haloperidol is known to have potent dopamine receptor antagonist properties (1), these results provide support for a dopaminergic involvement in the neural mediation of food reinforcement (19,27).

A second finding which emerged quite unexpectedly in both experiments, but which was seen most strikingly in Experiment II, was that animals under the influence of haloperidol *did* show elevated running speeds during the food-rewarded Treatment trial (relative to extinction baselines). It seems likely that these elevations in speed reflect an incentive motivational action of food odor (4) during the Treatment day trials. One might infer, then, that although haloperidol blocked the reinforcing effect of food on subsequent behavior, the incentive motivational or activating effect of food odor was *intact* under haloperidol treatment. Consistent with this notion, neuroleptics have been shown to attenuate the reinforcing effects of brain stimulation reward while leaving "priming" (i.e., motivational) properties of the same stimulation unaffected (11,26). A more direct test of neuroleptic effects on primary and secondary incentive motivational and reinforcement processes are currently in progress in our laboratory.

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