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Haloperidol Induces a Partial Reinforcement Extinction Effect in Rats: Implications for a Dopamine Involvement in Food Reward

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ETTENBERG, A. AND C. H. CAMP. *Haloperidol induces a partial reinforcement extinction effect in rats: Implications for a dopamine involvement in food reward.* PHARMACOL BIOCHEM BEHAV 25(4) 813–821, 1986.—The hypothesis that dopamine antagonist drugs attenuate the reinforcing properties of food was investigated in hungry rats trained to traverse a straight runway for food reward. Testing consisted of a single trial per day during which latencies to leave the start box and to traverse the alley were recorded. In each experiment, a reinforcement phase lasting 30 consecutive days was immediately followed by a 21 day extinction phase. The runway responses of animals that experienced intermittent food reward during the reinforcement phase of the experiments, was later found to be more resistant to extinction than those of continuously reinforced animals. This "partial reinforcement extinction effect" (PREE) was also observed in animals that experienced periodic reductions in the quantity, but not quality, of food reward. Intermittent pretreatment with 0.15 mg/kg of haloperidol during the reinforcement phase produced a PREE that was indistinguishable from that produced by reward omission on those same trials. Control groups for motor debilitation and for non-associative drug effects did not demonstrate a PREE. These results are consistent with the view that central dopamine substrates play a role in the neural basis of food reward.

Dopamine Food reward Neuroleptics Haloperidol Partial reinforcement extinction effect Positive reinforcement Anhedonia

WHILE neuroleptic drugs have long been known to produce reductions in positively reinforced operant behaviors [12,37], the precise mechanism through which these drugs exert their effects remains unclear. For some investigators, the reductions in operant responding are best accounted for by neuroleptic-induced attenuations in the rewarding properties of reinforcing stimuli [20–24, 45–49, 51]. In this "anhedonia" view, animals cease responding during neuroleptic challenge because the reinforcer has lost much or all of its rewarding value through the pharmacological actions of these drugs. Since the neuroleptics employed in the operant literature (e.g., pimozide, haloperidol, alpha-flupenthixol, etc.) are known to have potent dopamine (DA) receptor antagonist properties [3, 30, 36], proponents of the anhedonia hypothesis postulate a role for central DA substrates in the neurochemical basis of reinforcement. However, DA antagonist drugs are also known to induce Parkinsonian-like motor deficits [4, 24, 41], impair spontaneous nonreinforced behaviors [15, 26, 34] and, at high doses, have strong sedative and cataleptic effects [5, 19, 26]. Therefore, one might account for the reductions in operant behavior during neuroleptic challenge by some form of motor impairment independent of any changes in the rewarding properties of the reinforcer.

The task of dissociating reward from performance deficits in drugged animals is made difficult by the fact that such animals exhibit reductions in a wide variety of behaviors of which operant responding is only one. This problem is particularly relevant since, with very few exceptions (e.g., [17,32]), the conclusions drawn in the literature have been based upon observations of animals that were drugged at the time of testing. Clearly, a more optimal test procedure would be one in which investigation of the putative reward deficits was conducted some time after the direct pharmacological effects of the drug had subsided. In this way the behavioral measures would not be confounded by drug-induced motoric or general sedative properties. The present study describes a series of experiments which employed a behavioral test procedure that permitted identification of reward-attenuating actions of neuroleptic drugs in nondrugged animals.

Animals trained on schedules of intermittent or partial reinforcement (PRF) subsequently make many more responses during extinction than animals trained on a continuous schedule of reinforcement (CRF). This phenomenon has been called the "partial reinforcement extinction effect" (PREE) and it is well established in the animal learning literature (see review [27, 28, 40]). Its relevance for the present study is that the procedures employed to demonstrate a PREE involve a reward manipulation during training (i.e., periodic reward omission) which alters behavior of animals

some time later, during extinction trials. If neuroleptic drugs greatly attenuate reward, then one might predict that periodic drug treatment in continuously reinforced animals, might later be reflected by an increased resistance to extinction in much the same way that periodic reward omission produces an enhanced resistance to extinction. The present set of experiments was devised to test this hypothesis.

METHOD

Subjects

The subjects were naive male Wistar rats (325–350 g) obtained from Simonsen Laboratories Incorporated. The animals were individually housed in metal wire hanging cages which were located within a temperature controlled, 12 hour light/dark (lights on 7:00 a.m.) environment. Initially, all animals had ad lib access to standard laboratory food (Purina Brand) and water.

Apparatus

The apparatus consisted of a wooden straight runway 155 cm long × 15 cm wide × 20 cm high located in a small sound-attenuated room. A white start box (24×25×20 cm) was attached to one end of the runway and a black goal box of the same dimensions was attached to the opposite end. The floor of the apparatus was made of wire mesh. A guillotine door provided access from the start box to the runway. Opening the start box door triggered a digital precision timer (Synesthesia Reaction Timer; Model S-2) that was wired to stop timing upon interruption of an infrared photocell beam located 15 cm inside the runway at a height of 5 cm above the wire floor. This provided an automated measure (accurate to $^1/_{100}$ of a second) of the animal's latency to leave the start box once the guillotine door was lifted (i.e., "Start Latency"). The location of the photocells inside the runway (an emitter on one side wall and a corresponding detector on the opposite wall) was to ensure that the animal could not interrupt the infrared beam without actually leaving the start box. The electrical signal generated upon interruption of the photocell beam also served to activate a second identical timer whose timing stopped when another pair of infrared photocells detected the animal's presence in the goal box (i.e., the second photocell pair was located 8 cm from the end of the runway inside the goal box). This second timer provided a measure of the animal's latency to traverse the runway once it had left the start box (i.e., defined here as "Goal Latency"). To enter the goal box, the rats were required to push through a clear Plexiglas door that was hinged at the top and had a "stop" (i.e., the door only swung inwards) to prevent retracing.

General Procedure

Pretraining. Seven days were allowed for the animals to acclimate to the lab and home cage environments. During this period, every animal was carried into the lab, weighed and handled for several minutes each day. In each experiment, the subjects were then placed on a restricted food diet designed to reduce their body weights to 85% of free feeding values. All subjects continued to have ad lib access to water in their home cages.

Once the rats had reached their "target" weights, a program of shaping was initiated to familiarize the animals with the test apparatus and to train them to traverse the runway for food reward (in the form of part of their daily food ration). The remainder of their food ration was provided 15 minutes after the completion of each animal's daily shaping/training session. This phase of the study lasted 10 days in the initial experiment ("Manipulation of reward quality and quantity"; see below), but was increased to 21 days in the two drug experiments in order to reduce day to day variability in running latencies during "reinforcement" trials.

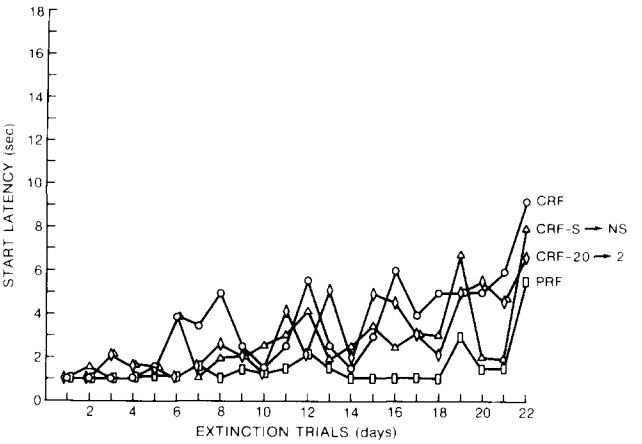

FIG. 1. Mean start latencies (i.e., latencies to leave the start box) for each group of rats on each trial/day during the extinction session. See the text for descriptions of group treatments. Although the partial reinforcement group continues to respond on each trial with shorter latencies than the other groups, there were no statistically reliable effects on start latencies.

Reinforcement trials. Thirty consecutive days of "reinforcement" immediately followed the completion of the shaping/training regimen. During this phase of the experiment, subjects received only one trial in the runway per day. On each trial, a hungry animal was placed into the start box for 10 sec after which the start box door was opened and the latency to leave the start box, as well as the latency to traverse the runway, were recorded. Once in the goal box, the animal was allowed 90 sec to consume a reward of 45 mg Noyes food pellets (the precise number and type of pellets varied for different experimental conditions as described below). The food reward was located inside a small metal dish whose shape prevented the animals from seeing its contents from outside the goal box area. Upon completion of the trial the animal was immediately returned to its home cage where, 15 min later, it received the remainder of its daily food ration.

Extinction trials. On the day following the final (30th) reinforcement trial, the first of 21–22 consecutive daily extinction trials was initiated. These trials were run in the identical manner as that described for the reinforcement trials with the sole exception that no food reward was provided in the goal box on any trial. On any given trial, if an animal did not leave the start box after 90 sec had elapsed, a "start latency" of 90 sec was recorded for that animal after which the experimenter manually directed the animal out the door. Once out of the start box, if an animal did not enter the goal box within 120 sec it was again manually aided by the experimenter and a "goal latency" of 120 sec was recorded for that animal on that trial.

Experimental Conditions

Manipulation of reward quality and quantity. Although it

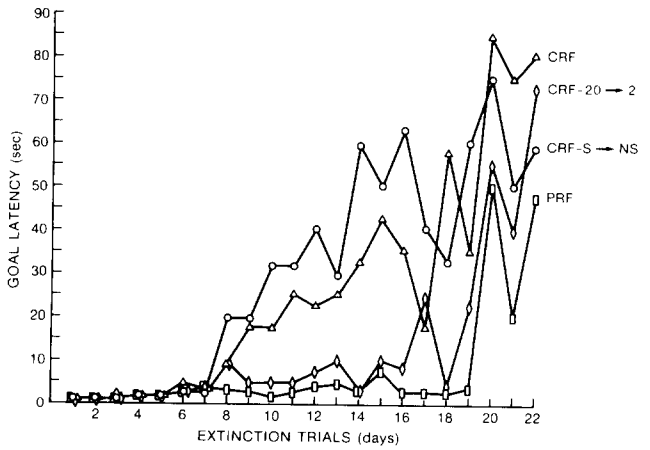

FIG. 2. Mean goal latencies (i.e., latency to enter goal box after leaving the start box) for each group on each extinction trial. Animals that experienced partial reinforcement during the reinforcement phase of the experiment (PRF), responded with shorter latencies during extinction than animals that had earned food on every reinforcement trial (CRF). This Partial Reinforcement Extinction Effect (PREE) was also observed in animals who experienced periodic reductions in the quantity of reinforcement during acquisition (i.e., the CRF 2→20 group) but not in animals who experienced periodic reductions in the quality of the reinforcer (CRF S→NS).

was originally proposed that neuroleptic drugs might completely block the rewarding properties of positive reinforcers (e.g., [20,48]), most now describe their putative behavioral action as a consequence of reward attenuation and not reward blockade. Therefore, it was important to establish whether or not a PREE could be produced by periodic reductions in the quantity or quality of the reinforcer during training, and not just periodic reward omission.

Thirty-two rats were randomly distributed across four groups (n=8/group). On two-thirds of the Reinforcement trials, all animals earned a high incentive food reward of 20 Standard Noyes Formula "A" pellets containing 1% saccharin. However, the remaining 10 trials were "targeted" as reinforcement manipulation trials (randomly distributed throughout the 30-day Reinforcement period) during which the four experimental groups experienced different conditions. A continuous reinforcement group (CRF) was treated on these trials in the same way as on any other trial (i.e., they earned a food reward of 20 saccharin pellets). A partial reinforcement group (PRF) earned no food reward on the 10 "target" trials. A third group earned 20 nonsaccharin pellets on the "target" trials (CRF S→NS). This group provided a means of assessing the effects of periodic shifts in the quality or incentive value of food reward (i.e., from saccharin to nonsaccharin pellets) on subsequent responding during extinction. It should be noted that pilot data confirmed that the saccharin pellets were highly preferred over the regular nonsweetened Formula "A" pellets in hungry rats. A fourth and final group received only two saccharin pellets (instead of the "normal" 20) on "target" trials (CRF 20→2) as a means of determining whether a reduction in reward quantity might be adequate to subsequently produce a partial reinforcement extinction effect.

Comparison of the effects of periodic haloperidol and reward omission on extinction responding. Thirty naive rats were randomly assigned to one of three groups (n=10/group). During the 30 day reinforcement phase of the experiment, food reward consisted of ten unsweetened 45 mg Noyes food pellets. Ten days were randomly selected during which drug/reward manipulations occurred. On the ten "target" days, one of the three groups of rats received an intraperitoneal (IP) injection of 0.15 mg/kg haloperidol. This dose was identified in pilot studies as one that produced patterns of responding resembling those of nonreward conditions (i.e., in an operant lever-press task for continous food reinforcement, this dose produced a 75% reduction in total responding and produced "extinction-like" response curves during 20 min test sessions). The haloperidol was prepared in a heated vehicle solution of 0.002 M lactic acid and injected 45 min prior to testing in a volume of 1.0 ml per kilogram of body weight. The haloperidol group (CRF/HAL) still earned their "normal" ten pellets of food reward on injection days. A vehicle control group (CRF/VEH) was treated identically to the drug group except that their injections consisted of the vehicle solution without the drug. A final group (PRF/VEH) was also pretreated with vehicle injections, however, these animals earned no food pellets on the ten injection days (i.e., a partial reinforcement group comparable to the PRF group in the previous experiment).

Control conditions. Thirty-six naive rats were randomly assigned to one of four treatment groups (n=9/group). Animals were reinforced with ten 45 mg Noyes pellets on each reinforcement trial, as previously described. Two of the treatment groups were identical to those in the haloperidol experiment above: the continuous reinforcement (CRF/VEH) group and the partial reinforcement (PRF/VEH) group. Two additional conditions were tested:

(a) Haloperidol control group—A PREE results from the animals' experience of reward omission (or reduction) on some trials during the reinforcement phase of an experiment. If the CRF/HAL group in the previous experiment was to demonstrate a prolonged resistance to extinction, it would be important to ensure that this effect was attributable to the animals' experiences in the runway and not some generalized nonassociative action of the drug. To control for this possibility, an additional group (CRF/HAL-C) was tested in which the animals received the identical haloperidol treatment as the CRF/HAL group in the previous experiment, but never traversed the runway while in the drugged state. On the ten haloperidol days, the animals were given the food reinforcer in a plastic holding cage instead of in the goal box of the runway.

(b) Motor debilitation control group—One might argue that motor debilitation itself could be responsible for any reduction in reward produced by neuroleptic drugs. Put simply, the food reward might be effectively reduced if the effort required to earn it is sufficiently increased by the administration of a motor-debilitating drug. To control for this possibility, a sodium pentobarbital (Nembutal) group was included in the experiment (CRF/NEM). While these animals earned food on every reinforcement trial, on the ten treatment trials they were administered a 9 mg/kg dose of Nembutal (injection volume was 1.0 ml/kg) seven minutes prior to testing. Preliminary experiments indicated that this dose produced an impairment in goal latencies that was comparable to that observed with the haloperidol treatments.

RESULTS

Manipulation of Reward Quality and Quantity

Animals that experienced intermittent nonreinforced

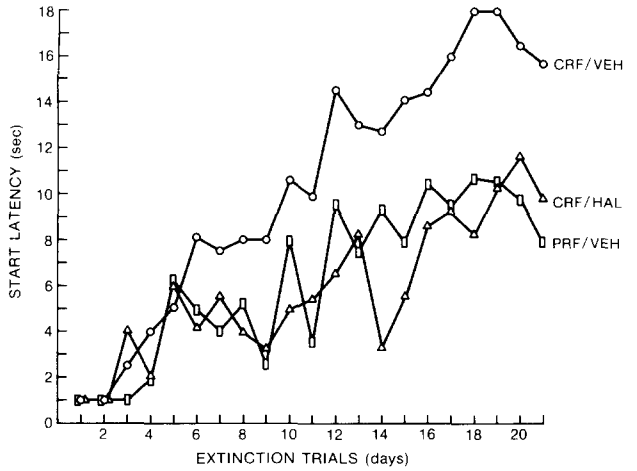

FIG. 3. Mean start latencies for three groups of rats during 21 trials/days of extinction. Animals that were continuously reinforced during the reinforcement phase of the experiment (CRF/VEH) extinguished more rapidly than animals that had previously experienced either no-reinforcement (PRF/VEH) or reinforcement-plus-haloperidol (CRF/HAL) on one-third of their acquisition trials.

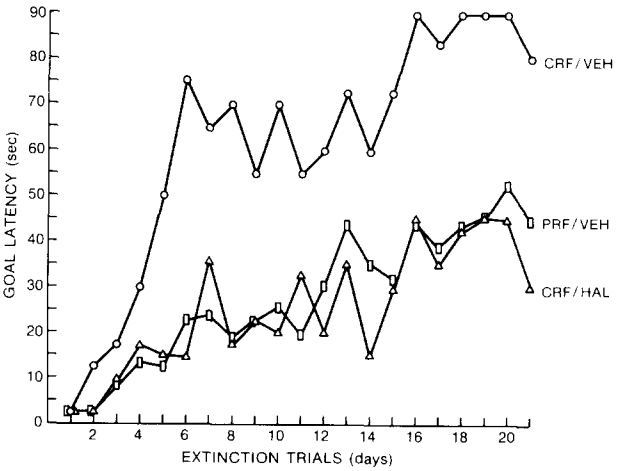

FIG. 4. Mean goal latencies for three groups of rats during 21 trials/days of extinction. Prior experience during the reinforcement phase of the experiment produced reliable differences in performance during extinction. Intermittent no-reinforcement (PRF/VEH) and intermittent reinforcement-plus-haloperidol (CRF/HAL) both subsequently produced an increased resistance to extinction.

trials during the reinforcement phase of the experiment (i.e., the PRF group), or an intermittent reduction in the number of food pellets (i.e., the CRF 20→2 group), demonstrated a statistically reliable prolongation of extinction responding compared to animals that received the full number of food pellets on every trial (i.e., CRF S→NS and CRF groups). The mean start and goal latencies for each group on each trial are depicted in Figs. 1 and 2. Two-Factor Analyses of Variance (with repeated measures on one factor) were computed on both start and goal latencies. Start latencies were affected over Trials, $F(21,588)=4.60$, $p<0.001$, however, no reliable Group differences emerged, $F(3,28)=1.74$, $p>0.05$, nor was there a Group × Trial interaction, $F(63,588)=0.68$, $p>0.05$. These results suggest that all groups left the start box in essentially the same manner throughout the 22 day extinction period.

There were, however, highly reliable differences in group goal latencies. The ANOVA revealed a strong effect of Trials, $F(21,588)=21.28$, $p<0.001$, i.e., goal latencies, like the start latencies, lengthened as extinction progressed. There was also a reliable difference between Groups, $F(3,28)=5.37$, $p<0.005$. The rate at which the groups extinguished, as indicated by the Group × Trial interaction, was also reliably different for goal latencies, $F(63,588)=2.01$, $p<0.001$. These effects are clearly illustrated in Fig. 2. While the CRF and CRF S→NS groups demonstrated elevated Goal latencies as early as the 8th to 9th day of extinction, the remaining two groups (PRF and CRF 20→2) continued to respond with very short latencies until the 17th to 20th day of extinction.

Comparison of the Effects of Periodic Haloperidol and Reward Omission on Extinction Responding

The pattern of extinction responding produced by intermittent reward during reinforcement trials, was indistinguishable from that produced by CRF animals who experienced intermittent haloperidol administration. Both the PRF/VEH group and the neuroleptic CRF/HAL group demonstrated a robust partial reinforcement extinction effect (PREE). These two groups continued to respond throughout the extinction phase of the experiment with short latencies compared to the continuously reinforced nondrugged CRF/VEH group. The mean start and goal latencies during the 21 days of extinction are depicted in Figs. 3 and 4. Note that the resistance to extinction in this experiment was far weaker in all three groups (animals began to slow down earlier in extinction) compared to what was observed in the previous experiment. This result was presumably a consequence of the increase in the number of training trials prior to the reinforcement phase of the experiment (21 days in this experiment and only 10 days in the previous experiment). The net effect was a more robust PREE and a more sensitive indicator of group differences.

Analyses of both start and goal latencies revealed statistically reliable differences in group performance. The ANOVAs confirmed that animals tended to increase their response latencies as extinction progressed (Effect of Trials; start latencies, $F(20,540)=16.55$, $p<0.001$; goal latencies, $F(20,540)=11.68$, $p<0.001$). Response latencies also varied across groups (Main Effect of Groups; start latencies, $F(2,27)=5.01$, $p<0.02$; goal latencies, $F(2,27)=11.92$, $p<0.001$). Finally, the rate at which the groups extinguished responding, as indicated by the Group × Trials interaction, was also reliably different for start, but not goal latencies (start latencies, $F(40,540)=1.46$, $p<0.04$; goal latencies, $F(40,540)=1.33$, $p>0.05$).

To assess potential motor debilitating effects of the neuroleptic, the CRF/HAL group's performance on drug trials (i.e., during reinforcement phase) was compared to that of the vehicle treated CRF/VEH group. Due to large inter-subject variability, each animal's mean response latency during the ten injection days was expressed as a percent of that animal's mean latency on noninjection days. It should be noted that performance over the course of the 10 injection days remained extremely stable for each subject. There were no signs of behavioral tolerance or sensitization; a fact that was probably due, at least in part, to the one-

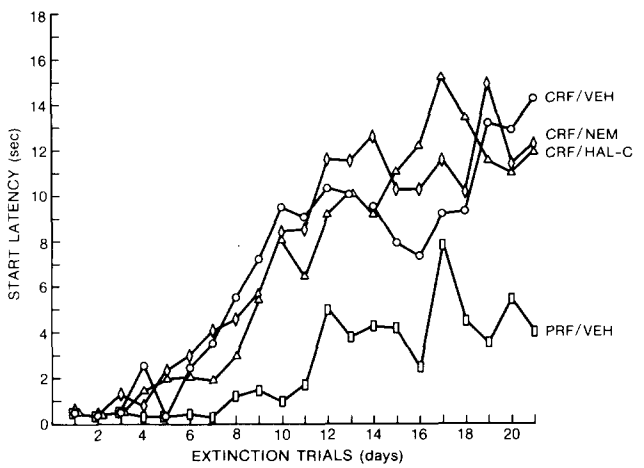

FIG. 5. Mean start latencies for four groups of rats during 21 trials/days of extinction. Control groups for drug treatment (CRF/HAL-C) and for drug-induced motor impairment (CRF/NEM) produced extinction curves comparable to continuously reinforced nondrugged animals (CRF/VEH). Neither of these two control conditions resulted in response patterns comparable to that produced by either periodic no-reinforcement (PRF/VEH) or by periodic haloperidol treatment in continuously reinforced rats (see Fig. 3).

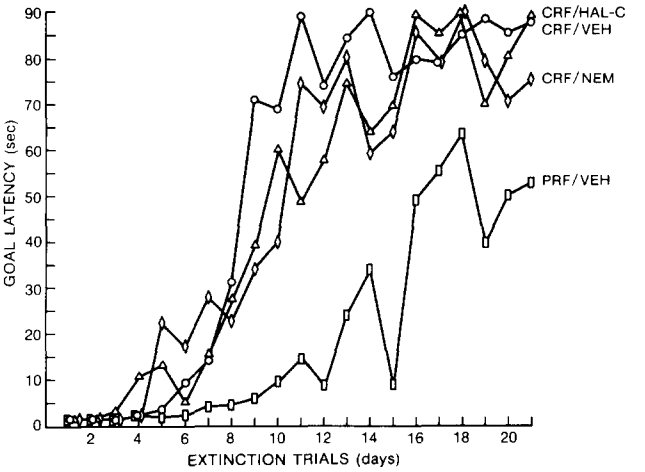

FIG. 6. Mean goal latencies for four groups of rats during 21 trials/days of extinction. As also indicated in Fig. 5, control groups for drug treatment (CRF/HAL-C) and for drug-induced motor impairment (CRF/NEM) produced extinction curves comparable to continuously reinforced nondrugged animals (CRF/VEH). Neither of these two control conditions resulted in response patterns comparable to that produced by either periodic no-reinforcement (PRF/VEH) or by periodic haloperidol treatment in continuously reinforced rats (see Fig. 4).

trial-per-day test protocol. Lactic acid vehicle injections produced start latencies (±S.E.M.) that averaged 113.7% (±17.59) of baseline/nonvehicle values. The neuroleptic treatments resulted in start latencies that were 132.0% (±22.2) of noninjection values. A post-hoc noncorrelated t-test (two-tailed) computed on these percent shifts from baseline revealed no statistically reliable difference in start latencies, $t(18)=0.62, p>0.05$. With respect to goal latencies, performance on vehicle treatment days was 76.3% (±9.22) of that on noninjection days while haloperidol injections produced a mean shift from baseline of 174.1% (±20.79). The difference between the effects of haloperidol and vehicle treatments on goal latencies was statistically reliable, $t(18)=4.30, p<0.001$. These results suggest that while haloperidol did not impair the animals' ability to leave the start box it did elevate their latency to reach the goal box (see the left portion of Fig. 7). Despite this fact, no animal required assistance in leaving the start box or entering the goal box on any trial in any group (i.e., while the drug slowed performance the animals still responded within the respective 90 and 120 sec cut-off points for start and goal latencies). Finally, it is worth noting that every haloperidol animal consumed all ten of its food pellets on each of the ten drug trials.

Control Conditions

Once again, animals that experienced periodic reward ommission during the initial reinforcement phase of the experiment (i.e., the PRF/VEH group) demonstrated a reliable increase in their resistance to extinction compared to continuously reinforced animals (i.e., the CRF/VEH group). However, neither the haloperidol control group (CRF/HAL-C) nor the motor debilitation control group (CRF/NEM) demonstrated response latencies different from those of the nontreated CRF/VEH group. These results are clearly illustrated in Figs. 5 and 6 which depict the mean start and goal latencies for each group during extinction. A two-factor ANOVA (with repeated measures on one factor) was computed for both the start and goal latency data. Highly reliable results were obtained over Trials (start latencies, $F(20,640)=25.71, p<0.001$; goal latencies, $F(20,640)=47.21, p<0.001$), between Groups (start latencies, $F(3,32)=9.54, p<0.001$; goal latencies, $F(3,32)=14.61, p<0.001$), and for Group × Trial interactions (start latencies, $F(60,640)=1.36, p<0.05$; goal latencies, $F(60,640)=1.97, p<0.01$).

An examination of Figs. 5 and 6 suggests that these statistically reliable results are probably attributable to the performance of the PRF/VEH group since all three CRF groups responded in an equivalent manner. To confirm this, a simple "main effects" test, in the form of a one-factor ANOVA, was computed on the mean response latencies averaged across all extinction trials. The mean (±S.E.M.) start and goal latencies (in seconds) for the four groups were as follows: start latencies, CRF/VEH=6.9 (±0.4); CRF/HAL-C=7.0 (±0.9); CRF/NEM=7.4 (±0.9); and PRF/VEH=2.6 (±0.7); goal latencies, CRF/VEH=50.9 (±3.5); CRF/HAL-C=47.9 (±4.7); CRF/NEM=46.5 (±4.4); and PRF/VEH=21.4 (±1.9). The one-way ANOVAs on these data produced highly reliable differences between treatment groups (start latencies, $F(3,32)=9.42, p<0.001$; goal latencies, $F(3,32)=13.43, p<0.001$). Post hoc Newman-Keuls tests confirmed that for both start and goal latency data the only reliable differences were between the PRF/VEH group and each of the other three conditions ($p<0.01$). To further substantiate that the statistically reliable results were predominantly a consequence of the actions of the PRF/VEH group, we found that no Group nor Group × Trials effects were identifiable for either start or goal latencies when the PRF/VEH group was not included in the original two-factor analyses of variance.

To ensure that the nembutal group was an effective "motor debilitation" control, it was important to establish

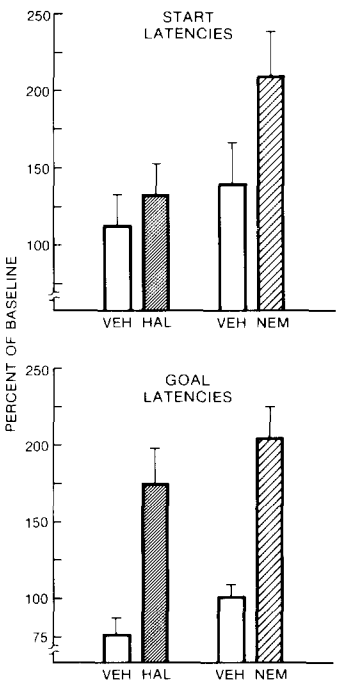

FIG. 7. A comparison of the mean (±S.E.M.) start and goal latencies of CRF animals pretreated with haloperidol (HAL) or its lactic acid vehicle (left-most VEH bars), nembutal (NEM) or its saline vehicle (VEH bars on right side) during acquisition trials. Each hashed bar represents the mean performance of a drug group over 10 drug trials. The clear (VEH) bars represent the mean performance of the corresponding vehicle-treated CRF groups during the same 10 injection trials. The data are expressed as a percent shift from "baseline" responding, which was defined as the mean performance of each group on the 10 non-drugged trials that immediately preceded injection trials. Note that haloperidol selectively elevated goal latencies but not start latencies while the sedative properties of nembutal produced an elevation in both response measures.

that the drug did, in fact, retard response latencies on treatment days. As in the previous experiment, each animal's mean performance on the ten injection trials (during the reinforcement phase) was expressed as a percent change from that animal's mean performance on noninjection/baseline trials. Although the CRF/VEH group demonstrated a mean increase from baseline start latencies of 140.6%±25.67, this was smaller than that observed in the CRF/NEM group which increased its start latencies by 210.3%±27.13 over baseline performance, $t(16)=1.97$, $p<0.06$. Goal latencies were unchanged by vehicle injections (mean shift from baseline 101.4%±3.56), however, nembutal elevated response latencies by a mean of 204.4%±20.61, $t(16)=6.02$, $p<0.001$. As was the case with the haloperidol data presented earlier, rats under the influence of Nembutal performed with remarkably stable, albeit elevated, response latencies across each of the 10 injection trials.

Figure 7 compares the relative effects of haloperidol and nembutal on start and goal latencies during the reinforcement phase of the experiment. While the neuroleptic produced increases in only goal latencies, the motor-debilitating effects of nembutal administration resulted in elevations of both start and goal latencies. These differences in performance impairment suggest that the mechanism by which haloperidol interferes with responding is different from that produced by the sedative properties of nembutal.

DISCUSSION

Animals that experienced intermittent food reward during the reinforcement phase of the experiments, subsequently demonstrated an increased resistance to extinction relative to continuously reinforced animals. These results are comparable to the "partial reinforcement extinction effect" (PREE) that others have described in the animal learning literature [2, 27, 28, 40]. A PREE was also observed in animals that experienced periodic reduction in the amount of food reward, again confirming results reported by others (e.g., [31,50]). Of particular significance for the present discussion, was the demonstration of a PREE in continuously reinforced animals that were periodically pretreated with the neuroleptic drug haloperidol. The response patterns generated during extinction by rats who had experienced reward plus haloperidol on some reinforcement trials, was virtually indistinguishable from those of other rats who had experienced reward omission on those same trials. These data cannot easily be explained by some form of general drug-induced performance effect since they were collected during extinction when the drug was no longer present. In view of the fact that haloperidol is known to be a potent antagonist of central dopamine post-synaptic receptors [3,43], the present data support the notion that dopamine substrates are involved in the mediation of the reinforcing properties of food.

A similar experiment to that described here was reported by Mason *et al.* [35] who were unable to demonstrate a PREE following periodic treatment with another neuroleptic drug, pimozide. However, these investigators did not follow the conventional procedures for demonstrating robust effects of partial reinforcement on extinction responding. A critical feature in such experiments is that the extinction trials be conducted in the identical manner as the reinforcement trials (see [33] for a discussion of this issue). The only varying factor should be the schedule of reinforcement presentation. In this way, the animal is not provided with any procedural cues that might indicate that the conditions of the experiment have changed (i.e., that reinforcement has been replaced with extinction trials). Mason *et al.* [35] trained their rats on a one trial per day schedule (similar to the one employed in the present study). However, during extinction they switched to a massed trials procedure where each animal was tested five times per day. Changing the intertrial interval during extinction from what was used during acquisition has already been identified as a procedure that can abolish the PREE [1,10]. Therefore it seems reasonable to presume that Mason *et al.*'s shift in daily test procedures during extinction in large part contributed to their failure to observe a neuroleptic-induced PREE. The test protocol employed in the present study has been replicated several times in our laboratory (e.g., [9,13]) indicating that the PREE paradigm may be a useful assay for identifying treatments that attenuate the rewarding properties of positive reinforcers.

Of course, one might still suggest alternative explanations for the results which we have reported. For example, since the present experimental protocol involved administering a drug during one phase (reinforcement) and testing later when the drug was no longer present (extinction), one might be concerned about the possible occurrence of state-dependent

learning (SDL; e.g., [38]). However, it has already been widely reported that learned behaviors acquired in the presence of neuroleptic drugs can be quite readily demonstrated when the animals are later tested in an undrugged state [1, 6–8, 25]. In addition, more recent demonstrations of SDL reveal that the phenomenon is far less dramatic than was originally believed (e.g., [11,39]). In any event, if SDL had indeed occurred, then (a) the CRF/HAL and CRF/HAL-C conditions should both have behaved identically during extinction since both would have been unaware of their drugged experiences (in fact only the CRF/HAL group demonstrated a PREE); and (b) since there were ten drugged reinforcement trials, the animals should have responded as though they had ten fewer reinforcement trials—an effect which has been shown to result in a decreased resistance to extinction (see [25] for numerous examples). It is, therefore, difficult to reconcile a state dependent learning hypothesis with the observed increased resistance to extinction observed in the neuroleptic-treated CRF/HAL rats.

An alternative explanation for the behavior of the CRF/HAL group in this study, might be that requiring the animals to overcome the motoric or sedative properties of haloperidol served to reduce the net rewarding impact of the food reinforcer. In this way one could conceivably account for the increased resistance to extinction observed in the CRF/HAL group by a reward attenuation that occurred only secondary to a drug-induced motor deficit. The fact that neuroleptics are known to have motor debilitating actions [4, 5, 19, 26, 41] would seem to lend credence to such a hypothesis. However, in the present study, the motor-debilitation control group did not demonstrate a PREE. Animals treated with a small dose of nembutal (i.e., the CRF/NEM group), were reliably slower in traversing the runway (as were the haloperidol animals) on drug trials, but produced no observeable increases in their resistance to extinction. It would seem that requiring the animals to overcome the motor incapacitating effects of the drug treatment cannot in and of itself account for the behavior of the CRF/HAL animals.

One result that was not expected, was that intermittent reductions in the quality of the reinforcer (i.e., the CRF S→NS group) were insufficient to produce a change in subsequent resistance to extinction. Others have demonstrated that treatments with another neuroleptic agent, pimozide, produced effects on food consumption that were comparable to reducing the palatability of the food [22,49]. For example, Geary and Smith [22] have recently demonstrated that the "sham" intake of a rewarding sucrose solution was reduced by pimozide in a similar fashion to that produced by decreasing the sucrose concentration of the solution. These authors concluded that pimozide decreased the food reward either by reducing the sensory intensity of the tasted fluid (i.e., it no longer tasted as sweet), or by affecting the reward potency of the sensory stimulus (i.e., it tasted normal but had reduced reward value). However, the present data indicate that reductions in the presumed hedonic sensory properties of food reinforcement (i.e., periodically giving subjects nonsweetened instead of sweetened pellets) may not be comparable to the effects of neuroleptic challenge. We realize, of course, that our animals were maintained at 85% of their free-feeding weight and were, therefore, highly motivated to respond for food. Indeed, every animal on every trial (including drug trials) consumed all of the food reinforcement within the allotted time. Therefore, it seems reasonable to assume that the reductions in reinforcer quality produced in the CRF S→NS group were not of a sufficient magnitude to produce a positive result in our test paradigm. Additional work is currently underway using nondeprived animals to more accurately assess the effects of alterations in the hedonic sensory properties of food reinforcement in this task.

A final point worthy of mention concerns the differences observed between haloperidol's effects on start and goal latencies. While nembutal treatments elevated both start and goal latencies, haloperidol only increased goal latencies (see Fig. 7). This is particularly relevant in view of the recent controversy regarding whether neuroleptics differentially or preferentially affect measures of response initiation versus response maintenance [42, 44, 46]. Some studies of the effects of neuroleptics on operant behaviors attributed their response-attenuating properties to deficits in the animal's ability to initiate movements (e.g., [18,44]). More recently, Tombaugh *et al.* [42] have similarly reported that pimozide selectively increased rats' latencies to initiate eating, while having little or no effect on the amount of time that rats spent eating (i.e., response maintenance) once the eating actually commenced. These results have been challenged by Wise and Colle [46] who reported that while pimozide did induce some increase in feeding initiation latencies, its maximal effect was on eating duration. The data from the present study appear to support this latter view. Although haloperidol did slightly increase the latency to leave the start box (i.e., a measure of response initiation) these effects were not statistically reliable. Note that this differed dramatically from the profile observed following nembutal administration which produced a marked elevation in both start and goal latencies. Whatever the nature of the behavioral deficit observed following haloperidol treatment, it would seem to be qualitatively different from the general sedative incapacitation induced by sodium pentobarbital. It is certainly clear that in a discrete trial procedure such as that employed here, the neuroleptic-treated animal is capable of initiating the runway response with normal, or near normal latencies. This result is, of course, consistent with numerous demonstrations that neuroleptic-treated animals tend to commence operant test sessions with response rates at or near nondrugged control levels. Only after reinforced responding has begun are reductions in response rates typically observed [15, 20, 21, 23].

Taken together, these data strongly support the contention that dopamine receptor antagonism can result in an attenutation in the rewarding properties of food [22, 46–49]. Furthermore, the present results were free of possible motor-confounds since the data were collected in nondrugged animals. Although dopamine substrates have also been implicated in brain stimulation (e.g., see [29]), water [23], and stimulant rewards [16,51], it is important to note that opiate reward [16,32] and heat reinforcement [14] appear to survive neuroleptic challenge. It would seem, therefore, that DA neurons may only represent one of several central substrates of positive reinforcement.

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