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A Partial Reinforcement Extinction Effect in Water-Reinforced Rats Intermittently Treated With Haloperidol

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ETTENBERG, A. AND C. H. CAMP. *A partial reinforcement extinction effect in water-reinforced rats intermittently treated with haloperidol.* PHARMACOL BIOCHEM BEHAV **25**(6) 1231–1235, 1986.—Thirsty rats were trained to traverse a straight runway for 30 sec access to water reinforcement. The experiment consisted of daily single trials during a 30-day reinforcement phase followed by 21 days of extinction. Animals that experienced no water reward on 33% of the reinforcement trials subsequently demonstrated an increased resistance to extinction of the runway response compared to continuously reinforced (CRF) animals. This "partial reinforcement extinction effect" (PREE) was also observed in CRF animals pretreated with the neuroleptic drug haloperidol (0.075 or 0.15 mg/kg) on 33% of the reinforcement trials. Thus, periodic dopamine receptor antagonism produced behavioral results comparable to those produced by periodic reward omission. These data cannot easily be accounted for by some form of general drug-induced performance deficit since the extinction trials were conducted in undrugged animals. It was concluded that dopaminergic substrates may play a role in mediating the behavioral effects of water reinforcement.

Dopamine Neuroleptics Water reinforcement Haloperidol Partial reinforcement extinction effect Anhedonia

SEVERAL investigators have reported that antipsychotic neuroleptic drugs produce dose-dependent reductions in liquid and/or water-reinforced operant behaviors [10–12, 22, 23]. Such findings are consistent with the view that neuroleptics can attenuate the rewarding properties of water reinforcement. However, interpretations about the significance of the behavioral consequences of neuroleptic challenge have been complicated by the fact that researchers have drawn their conclusions almost exclusively from observations of drugged animals. This is particularly problematic since animals treated with neuroleptics exhibit deficits in a wide variety of behaviors of which operant responding is only one (e.g., [6, 14, 15]). As we have indicated previously [5], a more appropriate behavioral assay for neuroleptic-induced reward-attenuation would be one in which the testing is conducted at some time after the direct pharmacological effects of the drugs have subsided.

We have recently described a test paradigm in which a neuroleptic-induced deficit in food reward was identified in animals who were undrugged during testing [5]. Our procedures were drawn from those employed in the animal learning literature to produce a well established phenomenon called the "partial reinforcement extinction effect" (PREE) [16, 17, 21]. Put simply, behaviors that are intermittently reinforced are more resistant to extinction than behaviors that are continuously reinforced. The relevance of this finding to the present research is based upon the fact that a PREE results from a reward manipulation at one time (i.e., intermittent reinforcement during training) which produces an effect on behavior at some later time (i.e., during extinction). We hypothesized that if neuroleptic administration greatly attenuated the rewarding properties of positive reinforcers, as has been suggested (e.g., [18,29]), then periodic administration of the drug on some reinforced trials might have an effect on the animals' extinction behavior comparable to that produced by periodic reward omission.

In our previous work [5], hungry animals were trained to traverse a straight runway once each day for food reward. After 30 days, the reinforcement was withdrawn and the animals were tested, once a day, during 21 consecutive extinction trials. Intermittent treatment with the neuroleptic drug haloperidol during reinforced trials subsequently produced an increased resistance to extinction that was comparable to that produced by intermittent reinforcement. Since the extinction trials commenced several days after the final drug trial, these data could not easily be accounted for by some form of general performance incapacitation. Such results provided strong support for the view that dopamine antagonist neuroleptic agents can reduce the rewarding properties of food [9, 30, 31]. In the present experiment we employed the same PREE methodology to test the hypothesis that haloperidol can also attenuate the rewarding properties of water reinforcement.

METHOD

Subjects

The subjects were 30 naive male Sprague Dawley rats

(325–350 g) obtained from Charles River Laboratories. The animals were individually housed in metal wire hanging cages located within a temperature controlled (22°C), 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 was the same as that previously described [5] and consisted of a wood-constructed 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 $^1/_{100}$th 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 this first 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). The 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

Training. 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 where it was weighed and handled for several minutes each day. On the eighth day, the water bottles were removed from the front of each home cage. Forty-eight hours later, a program of shaping was initiated to familiarize the animals with the test apparatus and to train them to traverse the runway for water reinforcement (i.e., 30 sec access in the goal box to a graduated drinking tube containing regular tap water). Each animal was given a single trial in the runway each day. After the 30 sec of drinking in the goal box, subjects were removed and returned to their home cages where, 30 min later, they were given access to a water bottle for an additional 15 min. Preliminary data confirmed that this procedure instilled in the animals a strong motivation to work for water while at the same time providing a sufficient amount of fluid to maintain good health. Animals were individually tested in this way each day for 21 consecutive days.

Reinforcement trials. Thirty consecutive days of "reinforcement" were initiated immediately following the training/shaping regimen. During this phase of the experiment, subjects continued to receive only one trial in the runway per day. On each trial, a thirsty 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 30 sec to drink from the water tube located there (timing of the 30 sec commenced with the animal's actual contact with the spout of the water bottle). The amount of water consumed by each rat on each trial was also recorded. Upon completion of the trial, the animal was immediately returned to its home cage and later given additional limited access to water as described above during training.

Each rat was assigned to one of four different treatment groups. Ten of the 30 reinforcement trials were then randomly selected to serve as "reward manipulation" trials during which each group of subjects was treated as follows: Group 1 (HAL-H; n=8) was continuously reinforced (i.e., the goal box contained water on each of the 30 reinforcement trials) but was pretreated 45 min prior to testing with a 0.15 mg/kg dose of the neuroleptic drug, haloperidol. Group 2 (HAL-L; n=8) was treated comparably except that they were administered a smaller 0.075 mg/kg dose of haloperidol prior to the 10 selected trials. For each of these two groups the haloperidol was prepared in a warm vehicle solution of 0.002 M lactic acid and injected in a volume of 1.0 ml per kilogram of body weight. Group 3 (CRF; n=7) was also continuously reinforced but received injections of only the vehicle solution prior to testing. Finally, Group 4 (PRF; n=7) was similarly pretreated with the lactic acid vehicle solution but these animals found an empty water bottle in the goal box on the 10 selected trials.

Extinction trials. On the day following the final (30th) reinforcement trial, the first of 21 consecutive daily extinction trials was initiated. These trials were run in the same manner as that described for the reinforcement trials with the only differences being that no water reinforcement and no injections were administered on any trial. During extinction, 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.

RESULTS

Animals that experienced intermittent reinforcement (Group 4; PRF) in the runway subsequently demonstrated a prolongation of extinction responding. This was observed as shorter Start and Goal Latencies compared to those of the continuously reinforced nondrug group (Group 3; CRF). Although not as pronounced as that produced by partial reinforcement, CRF animals that experienced intermittent administration of haloperidol (Groups 1 and 2) also demonstrated a statistically reliable dose-dependent increase in their running responses' resistance to extinction. These data are illustrated in Fig. 1 (Mean Start Latencies) and Fig. 2 (Mean Goal Latency).

A Two-Factor (Groups/Trials) Analysis of Variance (with Repeated Measures on One Factor) was computed for both the Start and Goal Latency data. These analyses confirmed that there were statistically reliable differences in Group performance for both Start Latencies, $F(3,36)=3.64$, $p<0.025$;

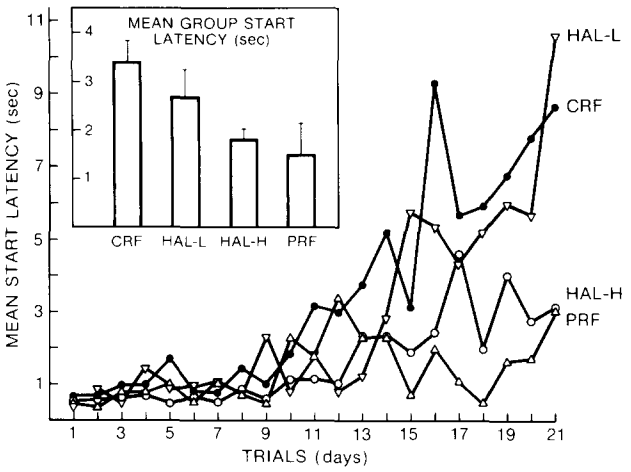

FIG. 1. Mean start latencies (in seconds) for each group of rats during each daily extinction trial. The inset shows the mean start latency (±S.E.M.) for the four groups averaged over all 21 trials. Animals that experienced intermittent reinforcement (i.e., the PRF group), or CRF with periodic pretreatments of haloperidol (i.e., the HAL-H group), demonstrated an increased resistance to extinction compared to continuously reinforced rats (i.e., the CRF group).

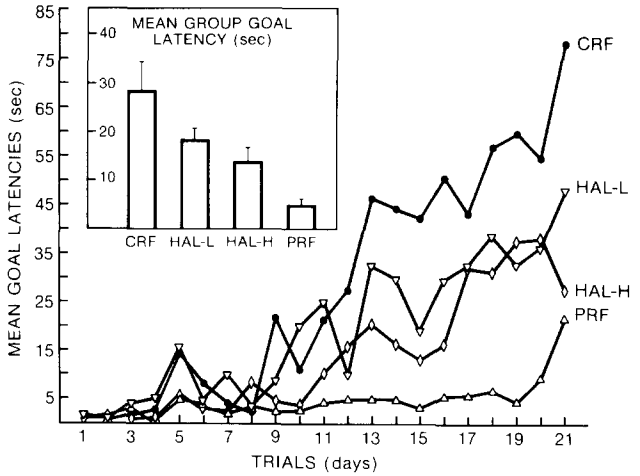

FIG. 2. Mean goal latencies (in seconds) for each group of rats during each daily extinction trial. The inset shows the mean goal latency (±S.E.M.) for the four groups averaged over all 21 trials. A partial reinforcement extinction effect (PREE) was produced in CRF animals periodically pretreated with either 0.075 or 0.15 mg/kg of the neuroleptic drug, haloperidol. The strength of the PREE was, however, weaker than that produced by periodic reward omission (i.e., the PRF group).

and Goal Latencies, $F(3,36)=7.83$, $p<0.001$. In addition there were reliable effects over Trials [Start Latencies, $F(20,520)=9.71$, $p<0.001$; Goal Latencies, $F(20,520)=11.87$, $p<0.001$] as would be expected in an extinction session where responding weakens over consecutive trials/days. The four groups also differed in the response patterns generated over the course of the 21-day extinction session as revealed by statistically reliable Group × Trials interactions [Start Latencies, $F(60,520)=1.78$, $p<0.001$; Goal Latencies, $F(60,520)=1.72$, $p<0.001$]. As can be clearly seen in the figures, the interaction effects are undoubtedly due to the fact that the PRF animals continued to respond with very short latencies while the remaining groups demonstrated varying degrees of response slowing as extinction progressed.

The mean overall response latencies for each group are illustrated in the insets of the two figures. To determine which groups differed from each other, a One-Way Analysis of Variance was computed on both the Start and Goal Latencies followed by Fisher post-hoc Least Significant Difference Tests [27]. As expected on the basis of the larger two-factor ANOVAs, the one-way analyses confirmed the presence of a statistically reliable difference in Group performance for both Start Latencies, $F(3,36)=3.78$, $p<0.025$; and Goal Latencies, $F(3,36)=7.78$, $p<0.001$. The Post Hoc comparisons revealed that the PRF and the HAL-H groups were reliably different from the CRF group ($LSD=1.337$, $D=1.94$, $p<0.05$ and $LSD=1.295$, $D=1.65$, $p<0.05$ respectively). The mean overall performance of the low haloperidol group was not reliably different from that of the continuously reinforced no-drug group. Similar results were obtained from post hoc analyses of mean Goal Latencies. Once again the partial reinforcement group (PRF) and the CRF-haloperidol (high dose) group (HAL-H) were reliably different from the no-drug CRF group ($LSD=10.007$, $D=23.06$, $p<0.05$ and $LSD=9.75$, $D=14.38$, $p<0.05$ respectively). The low dose of haloperidol again did not produce mean Goal Latencies that were different from the CRF control group. However, the partial reinforcement group did respond with reliably shorter Goal Latencies than even the high-dose haloperidol group (PRF versus HAL-H; $LSD=9.75$, $D=14.38$, $p<0.05$) indicating that the 0.15 mg/kg dose of haloperidol may not have completely antagonized the rewarding efficacy of the water reinforcement.

To assess potential motor debilitating effects of haloperidol, the mean performance of each drug group during the ten injection trials was compared to that of the vehicle-treated CRF group. As reported previously [5], haloperidol did not impair the animals' ability to leave the start box [Mean (±S.E.M.) Start Latencies: CRF vehicle-treated group, 0.96±0.2 sec; HAL-L group, 0.87±0.4 sec; HAL-H group, 1.13±0.7 sec]. There was, however, a tendency for a dose-dependent increase in Goal Latencies induced by haloperidol treatments [Goal Latencies: CRF group, 2.5±0.3 sec; HAL-L group, 3.1±0.6 sec; HAL-H group, 4.4±1.0 sec]. A one-way ANOVA on these data just failed to reach significance, $F(2,20)=2.89$, $p=0.07$. A final point worth mentioning is that on every drug trial every animal did make it to the Goal Box without experimenter assistance and in each case the animals drank from the water tube. Although there were very slight reductions in water consumption between drugged and undrugged groups these differences were not statistically reliable. The mean (±S.E.M.) Goal Box consumption of water for each group over the 10 treatment days was as follows: CRF group, 1.1±0.2 ml; HAL-L group, 0.9±0.2 ml; HAL-H group, 0.8±0.4 ml, $F(2,20)=1.87$, n.s.

DISCUSSION

A Partial Reinforcement Extinction Effect (PREE) was

observed in animals that experienced intermittent reinforcement during the initial 30 day portion of the experiment. These animals continued to respond with very short latencies during extinction compared to continuously reinforced rats. Such results confirm the PREE phenomenon that has been described numerous times in the animal learning literature [16, 17, 21]. Although not as strong as that observed in the partial reinforcement group, of particular significance for the present discussion was the demonstration of a PREE in continuously reinforced animals that were intermittently pretreated with the neuroleptic drug, haloperidol. These animals found and ingested water reinforcement on each of their first 30 trials, however, pretreatment with haloperidol on 33% of those trials was sufficient to produce a dose-dependent increase in the resistance to extinction of the running response. While many investigators have demonstrated that neuroleptic challenge and reward omission do not produce equivalent states for the animal (e.g., [25,28]), the present data suggest that these two experimental manipulations can have highly comparable behavioral effects.

It seems reasonable to presume that the dose-dependent results observed in the present study occurred as a consequence of some underlying dose-dependent neuropharmacological action of haloperidol. Thus the "high" dose was presumably more effective at producing a PREE because it had a more potent effect at its critical site(s) of action. Since haloperidol (at the doses employed here) has been characterized as a highly potent and relatively specific competitive dopamine receptor antagonist [1,26], our results support the view that central dopaminergic substrates are involved in mediating the rewarding properties of water reinforcement [10, 23, 29].

Several previous studies have demonstrated that neuroleptic treatments attenuate liquid and/or water-reinforced operant behaviors (e.g., [10–12, 22, 23]). However, the conclusions drawn in these studies have varied; for some the decrease in reinforced behavior was best accounted for by a drug-induced reward deficit (e.g., [10,23]), others emphasized the motor-impairing actions of the drugs (e.g., [12,22]), while others reported both reward and performance consequences of neuroleptic challenge (e.g., [11]). There can be little doubt that neuroleptic drugs do in fact interfere with normal motoric capacity. Such drugs have been shown to induce Parkinsonian-like deficits [2, 19, 24], impair spontaneous nonreinforced behaviors [6, 14, 15] and, at high doses, have strong sedative and cataleptic effects [3, 7, 15]. Furthermore, by closely examining the actual biophysical characteristics of operant responding, we have recently shown that motoric consequences of neuroleptic challenge can be directly observed even at the relatively low doses typically employed in the operant literature [8]. Indeed, in the present study, as in our previous work with food reinforcement [5], we observed a slight elevation in Goal Latencies on drugged trials which is undoubtedly the consequence of haloperidol's performance-impairing properties.

In each of the previous water-reinforcement studies, the data were collected from drugged animals. Since both motor and reward explanations of neuroleptic action typically make similar predictions about the behavior of drugged animals, a more appropriate assay for a neuroleptic-induced reward deficit would be one in which the animals were undrugged at the time of testing. In the present study the behavioral consequences of neuroleptic challenge were observed during the extinction portion of the experiment which began days after the last drug trial. Since no drug was presented during extinction it is difficult to reconcile the present results with those of some general sedative or motor explanation of haloperidol action. A motoric interpretation would also not account for the fact that the drug groups showed enhanced rather than attenuated operant responding. It is also unlikely that the PREE observed in the haloperidol-treated animals is due to a reduced reinforcement resulting from having to work harder to earn the reinforcer on drugged trials. In our previous work with food reinforcement [5], CRF animals intermittently treated with a motor-debilitating injection of sodium pentobarbital (Nembutal) did not subsequently produce a PREE. It would seem then, that working harder to overcome the debilitating actions of a drug, is in and of itself insufficient to account for the haloperidol results. The present data are also unlikely to be the consequence of some form of drug-accumulation over days/trials. Again in our earlier work, we demonstrate that neither state-dependent learning nor repeated injections of haloperidol can alone account for the PREE observed in the CRF-HAL groups [5].

Others have implicated central dopamine substrates in homeostatic thirst regulation [4, 13, 20, 33]. Consequently, another explanation for our results might be that the haloperidol produced a reduction in water motivation as opposed to water reinforcement. While we cannot rule out this possibility, one might expect such a hypothesis to predict that "less thirsty" animals would be slower to leave the start box and would drink less upon entering the goal box. However, we observed no reliable drug-induced elevations in Start Latencies nor reductions in the amounts of water consumed during the 30 sec access periods. In another study, Xenakis and Sclafani [32] have shown that the neuroleptic drug pimozide reduced the consumption of a glucose-saccharin solution more so than it did the consumption of water, and that these effects were independent of the level of water deprivation. Such results are, of course, consistent with a reward-attenuation rather than a purely motivational explanation of neuroleptic actions. A more direct assessment of the effects of motivational factors is currently underway in our laboratory using high-incentive liquid reinforcers in non-deprived animals. However, at present, the strongest explanation for our results is that haloperidol can act to attenuate the positive reinforcing actions of water.

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