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Effects of haloperidol on the multitrial partial reinforcement extinction effect (PREE): evidence for neuroleptic drug action on nonreinforcement but not on reinforcement

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Abstract. Two experiments investigated the effects of haloperidol (0.1 mg/kg) on the partial reinforcement extinction effect (PREE). In experiment 1 two groups of rats were trained to run in a straight alley using six trials/day with an intertrial interval (ITI) of 5–8 min. The continuously reinforced (CRF) group received food reward on every trial. The partially reinforced (PRF) group was rewarded on a quasi-random 50% schedule. All animals were then tested in extinction. Haloperidol was administered in a 2 × 2 design, i.e., drug-no drug in acquisition and drug-no drug in extinction. In experiment 2 two groups of rats were trained to press a lever in an operant chamber using a discrete trial procedure of ten trials/day with an ITI of 60 s. The CRF group was rewarded on each trial and the PRF group was rewarded on a quasi-random 50% schedule. Haloperidol was administered for 22 days prior to the start of the PREE procedure as well as throughout acquisition and extinction. The PREE, i.e., increased resistance to extinction of PRF as compared to CRF animals, was obtained in both experiments in all drug conditions. In both experiments haloperidol increased the rate of extinction. Experiment 1 revealed that this effect was entirely dur to the administration of the drug in extinction, independently of the drug condition in acquisition. In contrast to previous results in a one trial/day procedure, the administration of haloperidol to CRF animals did not increase resistance to extinction, failing to support the notion that neuroleptics attenuate the rewarding properties of reinforcement.

Key words: Haloperidol – Partial reinforcement extinction effect – Continuous reinforcement – Instrumental learning – Extinction – Rat

The mechanism of the behavioral action of neuroleptic drugs has been a matter of prolonged debate. The two central explanations are motor impairment (blockade of response initiation and/or maintenance) and a reduction of the rewarding value of primary reinforcers (e.g., Wise 1982; Salamone 1987; Ettenberg 1989). Ettenberg and Camp (1986a, b) have obtained impressive evidence supporting the "anhedonia" hypothesis. These authors showed that continuously reinforced animals that were periodically (10 out of 30 trials) treated with haloperidol (HAL) exhibited subsequently increased resistance to extinction (in a non-drugged state) comparable to that obtained in no-drug animals which received partial reinforcement training, i.e., showed a partial reinforcement effect. However, if HAL reduces the rewarding properties of reinforcement, then continuous administration of the drug to continuously reinforced animals should also lead to increased resistance to extinction, because reducing the magnitude of reward in continuously reinforced training leads subsequently to increased resistance to extinction (Mackintosh 1974). In addition, the administration of HAL to partially reinforced (PRF) animals should lead to decreased resistance to extinction in these animals, as is typically found when small rewards are given during PRF training (Mackintosh 1974). Feldon et al. (1988) tested these predictions using the partial reinforcement extinction effect (PREE) paradigm, which compares extinction rate following continuous and partial reinforcement training. The PREE is based on the fact that PRF animals show increased resistance to extinction as compared to CRF animals (Mackintosh 1974). Two groups of rats were trained to run in an alley for food reward. The continuous reinforcement (CRF) group received a reward on every trial. The partial reinforcement (PRF) group received a reward only on 50% of the trials. In the second stage of the experiment both groups were tested in extinction, i.e., no rewards were delivered on any trial. Similarly to Ettenberg and Camp (1986a, b) we used a one trial/day procedure. In addition, we used a drug-no drug design, in which HAL was administered in acquisition only, in extinction only, in both stages or in neither in order to evaluate separately the action of the drug in acquisition (CRF and PRF) and

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in extinction, as well as its combined action in both stages.

Our results showed that, as predicted, continuous administration of HAL during CRF training led to increased resistance to extinction in much the same way as the periodic administration of the drug. This finding provided support for the notion that neuroleptics attenuate the rewarding property of reinforcement (Wise et al. 1978a; Wise 1982) and suggested that the mechanism underlying this attenuating effect is akin to a reduction in the magnitude, or size, of the reward. Contrary to expectations, PRF animals trained under HAL did not show increased extinction rate. Thus, whereas the effect of HAL administered in acquisition to CRF animals was consistent with the notion that this drug acts to decrease the functional magnitude of reward, the results obtained in PRF animals failed to support it.

The purpose of the present experiments was to investigate further the effects of HAL on the PREE, using a multitrial training procedure, i.e., short intertrial intervals (ITI) rather than a 24 h ITI. In addition, we sought to determine the generality of HAL effects across experimental situations, namely, runway and operant chamber, as well as the influence of chronic HAL administration. In expt 1, rats were trained to run and extinguished in a straight alley, using six trials/day with a 5–8 min ITI. HAL (0.1 mg/kg) was administered in acquisition only, in extinction only, in both stages or in neither. In expt 2, rats were trained to press a lever in an operant chamber. In order to avoid the interpretative difficulties that stem from the use of response rate measures (Ettenberg 1989), we used a discrete trial procedure (Feldon and Weiner 1989). HAL was administered for 22 days prior to the start of the PREE procedure, as well as throughout the acquisition and extinction.

Experiment 1

Materials and methods

Subjects. The subjects were 56 male Wistar rats (Tel-Aviv University Medical School, Israel) approximately 4 months old. Throughout the experiment, they were fed for 1 h a day, commencing at least 1 h after the last animal had been run that day. Water was freely available.

Apparatus. The apparatus consisted of a straight alley made out of transparent perspex with black rubber curtains covering the sides. The runway was 140 cm long, 15 cm wide and 35 cm high, with a startbox (20 cm long) and a goalbox (20 cm long) separated by a run section (100 cm long). The floor consisted of a metal grid composed of equally spaced rods. The startbox door was made of transparent Plexiglass and opened vertically downwards. The door was operated by a solenoid controlled by a pushbutton. The goalbox door was of metal and could be raised and lowered manually. The food pellets were placed in a recessed compartment 4 cm wide and 2.5 cm deep at the far side of the goalbox. There were three light photobeams and photocells, the first one 2 cm beyond the startbox, the second 2 cm before the goal section and the third inside the goalbox. The latter was interrupted when the rat contacted the food compartment. The photobeams operated three electronic timers, accurate to 0.01 s. The first timer timed the start section (from the opening of the start door to the first photobeam); the second timed the run section (from the first to the second photobeam) and the third, the goal section (from the second to the third photobeam). Prior to each trial, the goalbox door was raised and, on rewarded trials, food was manually placed in the food compartment. Each reward consisted of ten 45 mg Campden Instruments food pellets. Once the animal interrupted the goalbox photobeam, the goalbox door was lowered. A Single Board Computer (SBC 09) and Micro-Vax I computer were used for equipment programming and data recording.

Procedure. Following 1 week of food restriction, all animals were handled daily for 2 weeks and given 6 days of pretraining. On the first 3 days all alley doors were open and food pellets were available in the goal compartment. On day 1 of pretraining, animals were introduced into the alley in groups of four for 20 min. On day 2, animals were placed in the alley in pairs for 10 min. On day 3, each animal was placed individually in the alley for 5 min. The experimenter ensured that all animals reached the goalbox and ate from the food compartment. Days 4–6 of pretraining consisted of continuous reinforcement training, and were used for gradually increasing the number of daily trials and for introducing the drug (see Drug injections). On each trial, the animal was placed in the start section, and following the opening of the start door, traversed the alley and consumed the reward in the goal box. On day 4, each animal was given one trial, on day 5, two trials with a 5–8 min intertrial interval (ITI), and on day 6, three such trials. On the following day, the acquisition stage, consisting of 9 days, began. On each day, each subject was run for six trials, with a 5–8 min ITI. On each trial, the animal was placed in the start section and the three time measurements for the start, run and goal sections were recorded. The CRF subjects received a reward on every trial throughout the 9 acquisition days. The PRF animals were rewarded on days 1–7 on a quasi-random 50% schedule, i.e., three reinforced and three nonreinforced trials, according to the following schedule; day 1 – NRNRNR; day 2 – NRNNRR; day 3 – NNRRNR; day 4 – RNRNNR; day 5 – RNNRNR; day 6 – NNRNRR; day 7 – NRRNNR, where R is a rewarded trial and N is a nonrewarded trial. On nonrewarded trials the goalbox confinement time was 30 s. The experimenter ensured, on rewarded trials, that the animal consumed all food pellets. There were no observable differences in consumption times between the drug-injected and vehicle animals. On days 8–9 of acquisition, the PRF groups received reward on every trial (see Drug injections). Following acquisition, 5 days of extinction were given. In extinction, animals were run exactly as in acquisition but no rewards were given. As on nonrewarded trials during acquisition, goalbox confinement time was 30 s. Any subject failing to move from one section of the alley to the other within 100 s was removed from the apparatus and returned to its homecage. After two consecutive 100 s trials in one session, the animal was dropped from the experiment and given a score of 100 s for all sections of the runway on all subsequent extinction trials.

The rats were randomly assigned to one of eight conditions in a $2 \times 2 \times 2$ factorial design consisting of drug in acquisition (HAL or vehicle), drug in extinction (HAL or vehicle), and reinforcement schedule in acquisition (CRF or PRF).

Drug injections. The appropriate drug, either 0.1 mg/kg haloperidol dissolved in 1 ml saline [prepared from an ampule containing 5 mg haloperidol in 1 ml solvent containing 6 mg lactic acid (Abic Ltd, Israel) diluted with 49 ml saline], or an equivalent volume of vehicle was given IP 60 min prior to the daily session. Days 4–6 of pretraining were used for gradually introducing the drug in the HAL-vehicle and HAL-HAL groups. The last 2 days of acquisition (8–9) were used for gradually tailing-off the drug in the HAL-vehicle groups and gradually introducing the drug in the vehicle-HAL groups. The HAL-HAL groups received vehicle on day 4 of pretraining, 0.05 mg/kg haloperidol on day 5 of pretraining, and 0.1 mg/kg from day 6 of pretraining onwards. The HAL-vehicle groups received vehicle on day 4 of pretraining. 0.05 m/kg haloperidol on day 5 of pretraining, 0.1 mg/kg haloperidol on day 6 of pretraining and on days 1–7 of acquisition, 0.05 mg/kg haloperidol on day 8 of ac-

quisition and vehicle from day 9 of acquisition onwards. The vehicle-HAL groups received vehicle during pretraining and on days 1–7 of acquisition, 0.05 mg/kg haloperidol on day 8 of acquisition and 0.1 mg/kg haloperidol from day 9 of acquisition onwards. The vehicle-vehicle groups received vehicle from day 4 of pretraining onwards.

Data analysis. The data were subjected to a logarithmic transformation to allow the use of analysis of variance. ANOVAs were performed for the acquisition and extinction phases. For each phase, start, run and goal data were analysed separately. The analysis of acquisition included two main factors of reinforcement schedule (CRF, PRF) and drug in acquisition (HAL, vehicle), and a repeated measurements factor of days. The analysis of extinction included three main factors: reinforcement schedule (CRF, PRF), drug in acquisition (HAL, vehicle), drug in extinction (HAL, vehicle), and a repeated measurements factor of days. The analysis of the extinction data included the last day of acquisition. Three subjects (one from each of the following groups: HAL-vehicle-CRF, HAL-vehicle-PRF, HAL-HAL-CRF) were dropped from the experiment because they failed to acquire the running response during the first 3 days of acquisition. Thus, the final analysis was performed on 53 subjects.

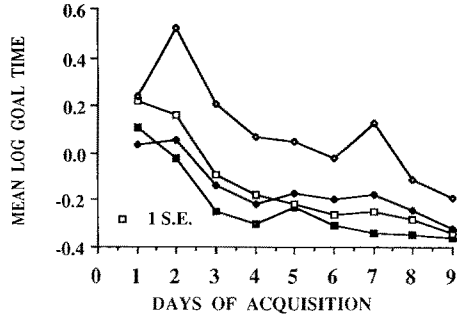

Fig. 1. The course of acquisition in the Goal section of the runway expressed as mean log times of six daily trials for continuously reinforced (CRF) and partially reinforced (PRF) animals in the vehicle (VEH) and haloperidol (HAL) conditions. The bar on the *left hand side* of the figure represents 1 standard error derived from the error term of the ANOVA. —■— VEH-CRF; —□— VEH-PRF; —◆— HAL-CRF; —◇— HAL-PRF

Results

Acquisition. Figure 1 presents the mean log times of the four groups in the Goal section of the alley. These results are representative of the Run and Start sections. Table 1 presents the results of the ANOVA for the Start, Run and Goal sections.

As can be seen in Fig. 1, PRF groups were slower than CRF groups. This was supported in the Start and in the Goal by the significant main effect of Reinforcement and in the Run and the Goal by the significant Reinforcement × Days interaction. In addition, the administration of HAL led to slower times as compared to vehicle. This was supported in all sections by the significant main effect of Drug and the significant Drug × Days interaction. In addition, in the Goal section, there was a significant Reinforcement × Drug interaction, reflecting the fact that the effect of HAL was more pronounced in the PRF than in the CRF animals.

Extinction. Figures 2 and 3 present the mean log Goal times of the four groups which received vehicle in extinction and the four groups which received HAL in extinction, respectively. Table 2 presents the results of the ANOVA for the Start, Run and Goal sections.

As can be seen in Figures 2 and 3, a PREE, i.e., faster times of the PRF as compared to CRF groups, was obtained in all drug conditions. The presence of the PREE was supported in all sections by the significant main effect of Reinforcement and the significant Reinforcement × Days interaction. The comparison of the extinction course of the four groups which received vehicle in extinction (Fig. 2) and the four groups which received HAL in extinction (Fig. 3), reveals that the administration of HAL increased the rate of extinction. This was supported in all sections by the significant main effect of Drug in extinction and by the significant Drug in extinction × Days interaction in the Run and in the Goal. In addition, the analysis yielded a significant Drug in extinction × Reinforcement × Days interaction in the Run and Goal sections. As can be seen in Fig. 4, which depicts this interaction for the Goal (collapsed over drug condition in acquisition), this outcome reflects the fact that HAL in extinction slowed down CRF animals more at the beginning of extinction (days 2 and 3) and PRF animals at the end of extinction (days 4 and 5).

The factor of Drug in acquisition was not significant in any of the alley sections, nor were any interactions with this factor.

Table 1. A summary of the outcomes of the ANOVAs for the Start, Run and Goal data in acquisition

	Start			Run			Goal		
	F	*df*	*P*	*F*	*df*	*P*	*F*	*df*	*P*
Reinf		n.s.			n.s.		17.50	1/49	<0.001
Drug	22.47	1/49	<0.001	12.18	1/49	<0.001	14.58	1/49	<0.001
Reinf × Drug		n.s.			n.s.		4.09	1/49	<0.05
Days	82.77	8/392	<0.001	53.69	8/392	<0.001	45.27	8/392	<0.001
Reinf × Days	2.54	8/392	<0.02	6.80	8/392	<0.001	2.58	8/392	<0.01
Drug × Days	4.16	8/392	<0.001	3.71	8/392	<0.001	2.80	8/392	<0.006
Reinf × Drug × Days		n.s.			n.s.			n.s.	

Table 2. A summary of the outcomes of the ANOVAs for the Start, Run and Goal data in extinction

	Start			Run			Goal		
	F	*df*	*P*	*F*	*df*	*P*	*F*	*df*	*P*
Dr acq		n.s.			n.s.			n.s.	
Dr ext	6.73	1/45	<0.02	7.04	1/45	<0.02	9.27	1/45	<0.004
Reinf	27.78	1/45	<0.001	49.77	1/45	<0.001	9.66	1/45	<0.001
Dr acq × Dr ext		n.s.			n.s.			n.s.	
Dr acq × Reinf		n.s.			n.s.			n.s.	
Dr ext × Reinf		n.s.			n.s.			n.s.	
Dr acq × Dr ext × Reinf		n.s.			n.s.			n.s.	
Days	161.27	5/225	<0.001	155.53	5/225	<0.001	159.97	5/225	<0.001
Dr acq × Days		n.s.			n.s.			n.s.	
Dr ext × Days		n.s.		4.49	5/225	<0.001	5.15	5/225	<0.001
Reinf × Days	18.42	5/225	<0.001	23.97	5/225	<0.001	28.01	5/225	<0.001
Dr acq × Dr ext × Days		n.s.			n.s.			n.s.	
Dr acq × Reinf × Days		n.s.			n.s.			n.s.	
Dr ext × Reinf × Days		n.s.		2.24	5/225	0.05	2.36	5/225	<0.04
Dr acq × Dr ext × Reinf × Days		n.s.			n.s.			n.s.	

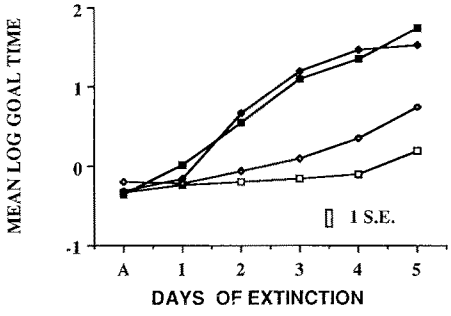

Fig. 2. The course of extinction in the Goal section of the runway expressed as mean log times of six daily trials for continuously reinforced (CRF) and partially reinforced (PRF) animals in the vehicle (VEH) and haloperidol (HAL) conditions. All groups represented in this figure were injected with vehicle throughout extinction. The point marked *A* on the abscissa represents the mean of the last day of acquisition. The bar on the *right hand side* of the figure represents 1 standard error derived from the error term of the ANOVA. For symbol see legend of Fig. 1

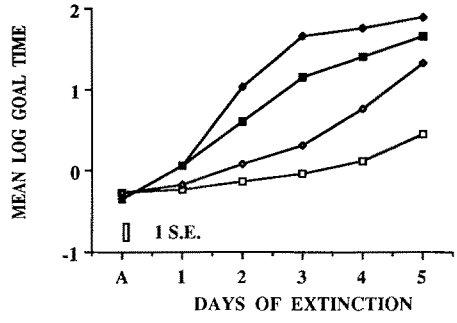

Fig. 4. The course of extinction in the Goal section of the runway expressed as mean log times of six daily trials for continuously reinforced (CRF) and partially reinforced (PRF) animals in the vehicle (VEH) and haloperidol (HAL) conditions collapsed over drug condition in acquisition. The point marked *A* on the abscissa represents the mean of the last day of acquisition. The bar on the *left hand side* of the figure represents 1 standard error derived from the error term of the ANOVA. For symbols see legend of Fig. 1

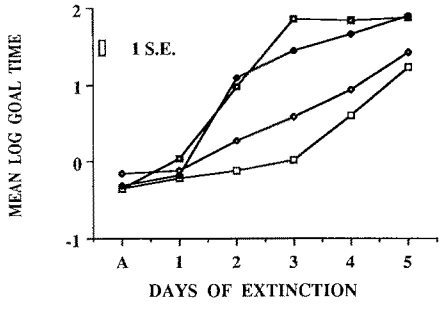

Fig. 3. The course of extinction in the Goal section of the runway expressed as mean log times of six daily trials for continuously reinforced (CRF) and partially reinforced (PRF) animals in the vehicle (VEH) and haloperidol (HAL) conditions. All groups represented in this figure were injected with 0.1 mg/kg haloperidol throughout extinction. The point marked *A* on the abscissa represents the mean of the last day of acquisition. The bar on the *left hand side* of the figure represents 1 standard error derived from the error term of the ANOVA. For symbols see legend of Fig. 1

Experiment 2

Materials and methods

Subjects. Thirty-six male Wistar rats, approximately 4 months old, were housed four to a cage under reversed cycle lighting. They received water for 1 h each day, with food freely available.

Apparatus. Four Campden Instruments operant chambers with two retractable levers were used. The right-hand lever was in the retracted position throughout the experiment. The 2.8-W house light was mounted in the roof of the chamber and was lit throughout the experimental session. The boxes were equipped with dippers in the food trays, which delivered 0.1 ml saccharin-sweetened water (144 mg sodium saccharin/1 l water) as reinforcement. The tray was illuminated following animals' response. Entrance to the food tray was by pushing a perspex panel, hinged at the top. Movements of the panel were monitored with the aid of a microswitch. Equipment programming and data recording were controlled by a micro Vax microcomputer.

Procedure. All animals received several days of pretraining. For the first 2 days rats were given 15-min sessions during which the lever was retracted and saccharin solution was delivered on a variable-time (VT) 30-s schedule. From the third day, rats were given 30-min sessions in which free fluid was discontinued, and the animals were placed on a fixed ratio (FR)–1 schedule. The lever was available in the box throughout the session. Following 20 reinforcements on FR–1 pretraining was completed. An animal which reached this criterion, was left on subsequent days in its home cage. When the last animal completed pretraining, all animals were given an additional 30-min session consisting of ten discrete trials with an ITI of 60 s. At the start of each trial, the retractable lever was inserted into the box. Following a lever press, the tray-light came on. As the rat made a tray exit, the tray light came off. Two animals failed to acquire the response and were dropped from the experiment. The remaining 34 animals were divided randomly into two equal groups, chronic HAL and vehicle. All animals were returned to their home cages for 21 days, during which they received daily drug treatment (see Drug treatment). On day 21, animals in the chronic HAL and the vehicle conditions were randomly divided into CRF and PRF groups as follows: vehicle-CRF, $n=8$, vehicle-PRF, $n=9$; HAL-CRF, $n=8$; HAL-PRF, $n=9$.

On day 22, all animals received a retraining session with five discrete FR–1 trials as on the last day of pretraining. On the next day, the acquisition stage was initiated and lasted 8 days. Each daily session consisted of ten discrete FR–1 trials with an ITI of 60 s. The continuous reinforcement (CRF) animals received a reward on each of the trials. The partial reinforcement (PRF) animals received a reward on a quasi-random 50% schedule, i.e., five reinforced and five nonreinforced trials. Following acquisition, 4 days of extinction commenced. The procedure during extinction was identical to that of acquisition except that no rewards were delivered on any of the trials.

Two time measurements were recorded for each trial: Start time – the time between the insertion of the lever into the box and the lever press, and Goal time – the time between the press and tray entry. The prodecure was programmed such that a maximal duration of 60 s was allowed for the Start and Goal times. If any of these times reached 60 s, the lever was retracted and the trial terminated. A score of 60 s was given for each uncompleted segment.

Drug treatment. For 21 days, the chronic HAL group received a daily IP injection of 0.1 mg/kg HAL (prepared as in expt 1), and the vehicle group received an equivalent volume of vehicle. The injections were given in the home cages between 9 and 10A.M. Water was given each day between 3 and 4 P.M. From day 22 onwards the appropriate drug, either 0.1 mg/kg HAL, or an equivalent volume of vehicle was injected IP 60 min prior to the daily session throughout acquisition and extinction.

Data analysis. A logarithmic transformation was carried out on the Start and Goal times to allow the use of analysis of variance. Separate analyses were performed for the acquisition and extinction data. Both analyses included main factors of drug (chronic HAL, vehicle), reinforcement (CRF, PRF) and a repeated measurements factor of days (eight for acquisition and five for extinction). The analysis of the extinction data included the last day of acquisition. During acquisition, four animals which had at least five uncompleted (60 s) trials (see above) on 2 consecutive days, were dropped from the experiment (one vehicle-CRF, two HAL-CRF, one vehicle-PRF). Thus, the final analysis was performed on 30 animals.

Results

Acquisition. Figure 5 presents the mean log Goal times of the CRF and PRF groups in the vehicle and chronic HAL conditions. These results are representative of the Start results.

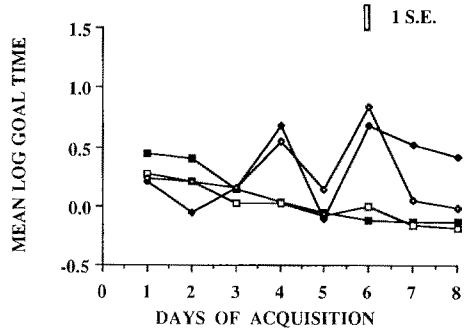

Fig. 5. The course of acquisition of a discrete trial lever-press response in an operant chamber expressed as mean log goal times of ten daily trials for continuously reinforced (CRF) and partially reinforced (PRF) animals in the vehicle (VEH) and haloperidol (HAL) conditions. Haloperidol (0.1 mg/kg) or vehicle were injected for 21 days and throughout acquisition. The bar on the *right hand side* of the figure represents 1 standard error derived from the error term of the ANOVA. For symbols see legend of Fig. 1

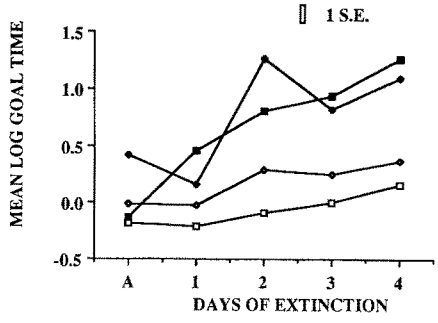

Fig. 6. The course of extinction of a discrete trial lever-press response in an operant chamber expressed as mean log goal times of ten daily trials for continuously reinforced (CRF) and partially reinforced (PRF) animals in the vehicle (VEH) and haloperidol (HAL) conditions. Haloperidol (0.1 mg/kg) or vehicle were injected for 21 days and throughout acquisition and extinction. The point marked *A* on the abscissa represents the mean of the last day of acquisition. The bar on the *right hand side* of the figure represents one standard error derived from the error term of the ANOVA. For symbols see legend of Fig. 1

As can be seen, HAL-treated animals exhibited slower Goal times and a much more variable pattern of acquisition as compared to vehicle animals. This was supported by the significant main effect of Drug [$F(1,26)=5.40$, $P<0.03$] and by the significant Drug × Days interaction [$F(7,182)=6.48$, $P<0.001$]. Likewise, in the analysis of mean log Start times, there was a significant main effect of Drug [$F(1,26)=8.16$, $P<0.01$] and a significant Drug × Days interaction [$F(7,182)=9.07$, $P<0.001$].

Extinction. The course of extinction, expressed in mean log Goal times, is presented in Fig. 6. As can be seen, a PREE, i.e., shorter times of PRF as compared to CRF groups, was evident in both the vehicle and the chronic HAL conditions. This was supported in the Goal and in

the Start by the significant main effect of Reinforcement [$F(1,26)=53.33$, $P<0.001$], and [$F(1,26)=30.91$, $P<0.001$], respectively, and by the significant Reinforcement × Days interaction [$F(4,104)=14.12$, $P<0.001$], and [$F(4,104)=10.23$, $P<0.001$], respectively. In addition, HAL speeded up extinction. This was supported in the Goal by the significant Drug × Days interaction [$F(4,104)=11.54$, $P<0.001$] and in the Start, by the significant main effect of Drug [$F(1,26)=6.31$, $P<0.02$] and by the significant Drug × Days interaction [$F(4,104)=16.87$, $P<0.001$]. An inspection of Fig. 6 reveals that in comparison to vehicle animals, HAL-PRF animals exhibited decreased resistance to extinction throughout extinction, whereas HAL-CRF group showed a highly variable pattern of responding. These outcomes were supported by the significant Drug × Reinforcement × Days interaction in the Goal [$F(4,104)=8.49$, $P<0.001$] and in the Start [$F(4,104)=5.47$, $P<0.001$]. The overall mean log Goal times of the four groups were as follows: vehicle-CRF = 0.80; Vehicle-PRF = 0.04; haloperidol-CRF = 0.75, haloperidol-PRF = 0.17.

Discussion

In both the runway and the operant chamber, HAL-treated animals (CRF and PRF) exhibited slower responding in the acquisition stage. This result could be due to the fact that neuroleptics increase the duration of individual operant responses (Faustman and Fowler 1981; Ettenberg 1989; Liao and Fowler 1990). However, contrary to other reports (Wise et al. 1978a, b), there was no progressively greater decrease of responding on successive training days. In the runway a clear *increase* in responding was evident over successive days (see Fig. 1). In the operant chamber, day to day responding was characterized by marked fluctuations but there was no greater decrease in responding *each* day (Fig. 5).

In contrast to our previous results (Feldon et al. 1988), and those of Ettenberg and Camp (1986a, b), HAL administration in acquisition in Expt 1 did not affect the rate of extinction. It will be recalled that in a one trial/day procedure used in these experiments, either periodic or continuous administration of HAL to CRF animals produced subsequently a marked increase in resistance to extinction, supporting the notion that neuroleptics attenuate the rewarding properties of reinforcement. The present results show that this effect of HAL disappears when a multitrial procedure is used. Mason et al. (1980) failed to observe increased resistance to extinction following periodic administration of pimozide during CRF training in rats shifted from a 24 h ITI in acquisition to a short ITI in extinction. However, these results are impossible to interpret since such a shift in the ITI by itself reduces or completely abolishes the PREE (Amsel et al. 1971; Capaldi et al. 1971). The present results demonstrate that when animals are trained and extinguished with short ITIs, the administration of HAL in acquisition does not lead to increased resistance to extinction in CRF animals.

In both the runway and the operant chamber, HAL-treated animals exhibited an increased rate of extinction. In the runway experiment, which tested the effects of HAL administration confined to acquisition or confined to extinction, increased rate of extinction was entirely due to the administration of the drug in extinction, independently of the drug condition in acquisition. This result is in line with numerous reports that neuroleptics produce more rapid extinction (Phillips and Fibiger 1979; Gray and Wise 1980; Mason et al. 1980; Tombaugh et al. 1980; Feldon et al. 1988).

Finally, in both experiments, a normal PREE, i.e. slower extinction of PRF as compared to CRF animals, was obtained under HAL treatment. The development of the PREE was not affected by slower responding exhibited by HAL-treated animals in acquisition, demonstrating a dissociation between the drug effects on motor performance or on the qualitative aspects of operant responding, and on learning processes underlying the establishment of the PREE. It has been argued that in order to obtain such a dissociation, the response requirement in the presence of the neuroleptic drug should be minimal and the test stage should be conducted without the drug (Beninger 1983; Ettenberg 1989). The present results show that both requirements may not be necessary. Similar outcomes were obtained by others. Tombaugh et al. (1983) showed that pimozide-treated rats were able to learn a light-dark discrimination in a T-maze, although the rate of running was significantly reduced. Likewise, Evenden and Robbins (1983) showed that alpha-flupenthixol reduced response rate but did not impair the response choice measure. These findings demonstrate, in contrast to the prevailing emphasis on the disruptive effects of neuroleptics on behavior, that numerous learning tasks are not disrupted by treatment with these drugs, even when animals are trained and/or tested under the drug. This more "positive" view of neuroleptic action is more congenial to their clinical definition, which emphasizes the beneficial effects of these drugs (Worms et al. 1983).

The sparing of the PREE is particularly notable in expt 2, in which animals received chronic pretreatment with HAL for 21 days before entering the experimental procedure, itself conducted under the drug. Recently, Ferre et al. (1990) showed that chronic HAL treatment (0.5 mg/kg for 21 days) given 2 weeks prior to training, did not affect the percentage of correct responses in a position discrimination and its reversal in a T-maze, although it produced longer response latencies. Interestingly, similarly to the results of expt 2, chronic HAL treatment increased the rate of extinction. The results of both studies suggest that at least with multitrial procedures (Ferre et al. used ten daily trials), chronic treatment with HAL affects extinction while exerting no effects on acquisition (except for producing longer response duration/latency).

The effects of HAL in a multitrial PREE have some interesting implications for its mechanism of action. The

fact that in this procedure, unlike the one trial/day, HAL did not retard extinction when given in acquisition shows that the reward-attenuating effect of HAL is determined by the experimental parameters of the training situation. In the case of one trial/day versus a multitrial procedure, the critical parameter is the ITI. It is well documented that resistance to extinction at short and long ITIs is governed by different learning processs (Mackintosh 1974; Gray 1975). At short ITIs, the association between the outcome of one trial and the outcome of the next forms a critical part of the set of events controlling animals' responding. In other words, at short ITIs, a direct association is formed between the outcome of the preceding reinforced trials and reinforcement, so that stimuli produced on reinforced trials are established as signals for further reinforcement. Since with a 24 h ITI, animals may forget the specific outcome of preceding trials, a direct association between successive trials cannot be formed. Under these conditions, the association between the outcomes of successive trials in mediated via the apparatus cues. According to this analysis, the fact that HAL-treated CRF animals exhibit increased resistance to extinction when trained with a 24 h ITI but not with short ITIs, suggests that the reward attenuating action of this drug is effective when reinforcement sustained responding is controlled by contextual cues but not when it is controlled directly by the outcomes of preceding trials. This possibility is speculative, but it is worth noting that a similar mechanism underlies the differential effects of amphetamine on a one trial/day versus a multitrial PREE (Feldon and Weiner 1991). Whatever the mechanism underlying the differential effect of HAL in a one trial/day and a multitrial procedure, this outcome limits the generality of the "anhedonia" hypothesis and demonstrates that neuroleptic treatment and a reduction in the magnitude of reward do not always produce comparable behavioral outcomes, because in purely behavioral experiments, a reduction in the magnitude of reward during CRF training decreases subsequent rate of extinction at both short and long ITIs (Mackintosh 1974).

In contrast to its action in acquisition, the action of HAL in extinction is not affected by the ITI: when administered in extinction, this drug exerts an identical effect, i.e. speeds up extinction, at both short and 24 h ITI (Feldon et al. 1988). Thus, the ITI modulates the influence of HAL on extinction rate only when the drug is given during the acquisition of an instrumental response, but not when it is given during extinction. This suggests that HAL exerts a more pervasive effect on the extinction of rewarded responses than on their acquisition, and that these two effects are subsreved by different mechanisms. We argued (Feldon et al. 1988) that the effects of HAL on extinction can be best understood by postulating that this drug enhances the behavioral impact of nonreinforcement. The present results imply that in multitrial PREE procedures, HAL increases the behavioral impact of nonreinforcement without decreasing the behavioral impact of reinforcement. Moreover, the results of expt 2 as well as those of Ferre et al. (1990) show that the latter pattern is obtained with chronic HAL treatment. These results are of particular importance in view of the fact that in clinical use, neuroleptics begin to exert their therapeutic effects only after 2–3 weeks of administration, and that often these effects are described as "anhedonic". Consequently, the effects of chronic HAL treatment on the behavioural impact of reinforcement as well as of the removal of reinforcement contingency in animals are highly relevant to their clinical action.

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