Psychopharmacology (1985) 87:454–460

Psychopharmacology

The effects of pimozide on the establishment of conditioned reinforcement as a function of the amount of conditioning

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Abstract. In an attempt to understand some inconsistent findings, the present experiment investigated the effects of pimozide, a dopamine (DA) receptor blocker, on the establishment of conditioned reinforcement as a function of the amount of conditioning. In Experiment 1, rats received three phases of training in a two-lever box. The pre-exposure phase measured the operant rates of pressing the levers; one produced a 3-s tone and the other turned the lights off for 3 s. In the conditioning phase, with the levers absent, the light-off stimulus was paired with food for two or four sessions. The test phase again measured the rate of pressing the levers. Conditioned reinforcement was shown by a relative increase in responding on the light lever during the test. Of the groups receiving four conditioning sessions, pimozide (0.5, 1.0, 2.0 and 4.0 mg/kg) produced a dose-dependent attenuation of conditioned reinforcement, those rats treated with 4.0 mg/kg failing to demonstrate a significant effect. When 2 conditioning days were employed, pimozide treatment also produced a dose-dependent attenuation; however, in these less conditioned animals 2.0 mg/kg blocked the effect. The possibility that pimozide produced a conditioned taste aversion to the food was ruled out in Experiment 2. These data suggest that DA transmission may be necessary for the establishment of conditioned reinforcement and that the effects of receptor blockade may be related to the amount of conditioning.

Key words: Pimozide – Dopamine receptor antagonist – Conditioned reinforcement – Conditioned taste aversion – Dopamine

The neurotransmitter dopamine (DA) may play an important role in mediating the effects of reinforcement on behavior. For example, rats treated with DA receptor antagonists showed an intra- or inter-session decline in responding for reinforcing stimuli which resembled an extinction pattern (Beninger 1982; Faustman and Fowler 1982; Fouriezos and Wise 1976; Gray and Wise 1980; Gerber et al. 1981; Mason et al. 1980; Tombaugh et al. 1980; Wise et al. 1978). However, as decreased DA transmission results in hypokinesia and catalepsy (cf. Beninger 1983) it is difficult to determine whether neuroleptics reduce the efficacy of reinforcing stimuli or produce a general motor impairment.

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Conditioned reinforcement procedures can be used to partially overcome this difficulty (Beninger and Phillips 1980). The acquisition of conditioned reinforcement is a form of learning whereby a neutral stimulus acquires reinforcing properties by virtue of being paired with a primary reinforcing stimulus (e.g., food). This procedure reduces the possible motor confounds associated with neuroleptic treatment, as DA blockers are administered while the animal is being conditioned and later the animal is tested drug-free for acquisition of conditioned reinforcement learning.

Davis and Smith (1977) paired a buzzer with IV apomorphine, a DA agonist with reinforcing properties. They found that haloperidol prevented the establishment of conditioned reinforcement. Caution in interpretation is advised, however, because haloperidol may either have been blocking the sensory aspects or the primary reinforcing properties of apomorphine. Similar results were obtained by Beninger and Phillips (1980), who paired a tone with food pellets and found that rats treated with pimozide during pairings did not show a preference for the tone in a drug-free test. These results suggested that the establishment of conditioned reinforcement was dependent upon intact dopaminergic functioning.

On the other hand, rats pre-exposed to light-food pairings under pimozide were not impaired in tracking the light cue in a subsequent drug-free test. Similar results were obtained using a place preference paradigm; pimozide-treated animals, when tested drug-free, showed a preference for the chamber which contained food during conditioning (Tombaugh et al. 1982).

These results are difficult to reconcile, especially in light of the large body of evidence supporting a role for DA in mediating the effects of reinforcement on behavior (cf. Beninger 1983). Perhaps the strength of conditioned reinforcement produced by different procedures interacts with the effects of pimozide. The present experiment addressed this possibility. A conditioned reinforcement procedure was employed similar in design to that of Beninger and Phillips (1980); to alter the strength of the effect, the amount of conditioning was varied (Bersh 1951) and the effects of pimozide evaluated. The hypothesis was that a larger dose of pimozide would be necessary to disrupt conditioned reinforcement when a greater amount of conditioning was employed. The second experiment examined an alternate interpretation for the results of Experiment I: the possibility that pimozide induces a conditioned taste aversion.

Experiment I

Materials and methods

Subjects. One hundred and seventy-three male Wistar rats with free-feeding weights of 275–300 g were individually housed in a temperature-controlled environment on a 12-h light-dark cycle. Animals were maintained at 80% of their free-feeding weights throughout the experiment.

Apparatus. The experimental environment consisted of four similar test chambers (23.0 × 29.0 × 17.5 cm) constructed of aluminum plate sides with clear Plexiglas tops and doors. Each chamber was located in a ventilated sound-attenuating box. Within each chamber, a 4.9 Khz tone generator (Sonalert) was mounted in the center of the 23 cm wall, at a height of 15.0 cm. Two illuminated 2-W light bulbs (8.5 cm apart) were situated one on either side of the Sonalert, 11.5 cm above the floor. Directly below the Sonalert, a feeder cup (2.0 × 4.0 cm) was positioned at a height of 2.5 cm. Inside each feeder cup was an infrared emitter and detector. Two removeable levers (4.7 × 7.5 cm) were located in the middle of each 29.0 cm wall at a height of 2.0 cm; the force requirement for the lever was approximately 9 g. Environmental contingencies and data collection were controlled by a Digital Equipment Corporation LSI11/2 computer variably interfaced with a screen or printer.

Procedure. Each of 20 different experimental groups was tested according to a design with three distinct phases. The paradigm group ($n=8$) was included to demonstrate that this procedure can be used to establish conditioned reinforcement. The following paragraphs present a detailed account of the procedure used to train the paradigm group. The second and third groups to be described served as controls for the paradigm group. The remaining groups were included to test the effects of pimozide on conditioned reinforcement when the amount of conditioning was varied.

The three phases of the experiment are referred to as the pre-exposure, conditioning, and test phases. The pre-exposure phase consisted of five 40-min sessions. There was one session per day for 5 consecutive days during which operant rates of pressing the two levers were measured. One lever produced a 3-s tone, and the other turned the lights off in the chamber for 3 s. In two experimental chambers, the tone lever was on the right and the light lever was on the left; this positioning was reversed for the other two chambers.

The conditioning phase consisted of 60-min sessions, one on each of the following 4 days. The levers were removed from the chambers. During each session the 3-s light-off stimulus was presented 80 times according to a random time 45-s schedule. That is, the average inter-light-off interval was 45 s. Each light-off presentation during the first conditioning session terminated with the delivery of one 45 mg food pellet (Bioserv). During the following three conditioning sessions a pellet delivery occurred only after a random 33% of the light-off presentations. This partial pairing procedure was employed because it produces a stronger conditioned reinforcement effect (Knott and Clayton 1966). The latency between food presentation and consumption was measured by determining the time lapse between pellet delivery and interruption of the infrared beam in the feeder cup by the rat's snout.

The test phase consisted of two 40-min sessions that occurred on the following 2 days. The levers were again present. Conditioned reinforcement was observed as a relative increase in the number of responses on the light-off lever during the test phase as compared to the pre-exposure phase.

The second and third groups were included as controls for the paradigm group. The negatively correlated group ($n=8$) received the same phases as the paradigm group, except that presentations of the light-off stimuli and food pellets were explicitly unpaired during the conditioning phase. That is, pellet presentations never occurred during or in the few seconds following the light-off stimulus. The food alone group ($n=8$) also received the same phases as the paradigm group; however, during the conditioning phase food pellets were presented in the absence of the light-off stimuli. If these groups fail to show a relative increase in the number of responses on the light-off lever during the test, then the preference observed in the paradigm group may be attributed to the contingency between food pellet presentation and the light-off stimulus, and can be interpreted as conditioned reinforcement.

For the remaining groups the amount of conditioning was varied and the effects of several doses of pimozide on the establishment of conditioned reinforcement were examined.

Five groups ($n=6$–8) received the three phases described for the paradigm group, except that each group was administered either an IP injection of pimozide (0.5, 1.0, 2.0 or 4.0 mg/kg) or its vehicle, tartaric acid, 4 h prior to each session of the conditioning phase. Pimozide (Janssen Pharmaceutica) was dissolved in a ratio of 3 parts tartaric acid to 1 part pimozide, by weight, in boiling distilled water and cooled prior to injection. The injection volume for the 0.5 and 1.0 mg/kg doses was 1.0 ml/kg and for the 2.0 and 4.0 mg/kg doses was 2.0 and 4.0 ml/kg, respectively. For vehicle control injections, tartaric acid was dissolved in distilled water at a concentration of 3 mg/ml and was injected in a volume of 1 ml/kg. With the high doses of the drug some rats failed to eat all of the pellets. These rats were eliminated from the experiment and additional rats added so that the groups numbered six or more.

The group receiving the highest dose of pimozide (4.0 mg/kg) showed an attenuated conditioned reinforcement effect. To explore the possibility that this occurred because of an accumulation of pimozide which might affect the animals' motor functioning in the test phase, a control group (homecage control, $n=12$) was added. This group received the same treatment as the paradigm group, except that during conditioning all rats were administered a dose of 4.0 mg/kg pimozide 1 h after each conditioning session in their home cage. If there is no accumulation of the drug over days then this group should evidence a conditioned reinforcement effect similar to the vehicle group.

Four groups of rats ($n=6$–10) received the three phases described for the paradigm group except that two conditioning sessions alternated over 4 days. Hence, 1 day of rest where the animals received no treatment was inserted between the 2 conditioning days, and another between the last conditioning day and the 1st test day. Groups were given IP injections of tartaric acid or pimozide (0.5, 1.0 and 2.0 mg/kg) 4 h prior to each conditioning session. A homecage control group ($n=6$) receiving a dose of 2.0 mg/kg pimozide injected 1 h after conditioning was included.

Results

The number used to represent responding in each of the pre-exposure and test sessions was calculated by subtracting the total number of responses on the tone lever from those made on the light-off lever. These numbers indicate how the responding on the light-off lever has changed from the pre-exposure to test phase, while at the same time accounting for unconditioned responding (i.e., pressing the tone lever). Because responding on the two levers in the pre-exposure phase was significantly greater in the first 10 min than in subsequent 10-min intervals, the final 30 min in each of the pre-exposure and test sessions was included in the data analysis. This decision ensured stable baseline rates. The 5 pre-exposure days were averaged together to represent responding in the pre-exposure phase and the 2 test days were averaged together to represent responding in the test phase. Thus, overall, the data were reduced to two numbers for each rat. Conditioned reinforcement is evidenced by an increase in the average difference score from pre-exposure to test phase.

The average difference scores ($\pm$SEMs) for the paradigm, negatively correlated, and food alone groups are illustrated in Fig. 1. A large conditioned reinforcement effect occurred in the paradigm but not the negatively correlated group. The food alone group showed a marginal effect. A two-way analysis of variance (ANOVA) with one repeated variable (phase) was conducted on the difference scores for the three groups. The analysis revealed a significant group effect [$F(2, 21)=4.00$, $P<0.05$], phase effect [$F(1, 21)=12.20$, $P<0.01$], and interaction [$F(2, 21)=6.05$, $P<0.01$]. Tests of simple main effects showed a significant effect of the phase variable in the paradigm [$F(1, 7)=9.78$, $P<0.02$] and food alone groups [$F(1, 7)=5.92$, $P<0.05$], but not the negatively-correlated group [$F(1, 7)<1$, $P>0.05$]. Thus, the light-off stimulus failed to become a conditioned reinforcer for the negatively-correlated group, but did gain reinforcing properties in the paradigm and food alone conditions. It is noteworthy, however, that the barpressing for the light-off stimulus in the food alone group was significantly less than that seen in the paradigm group during the test phase [$F(1, 21)=6.43$, $P<0.02$].

The average difference scores ($\pm$SEMs) for the drug groups receiving 4 days of conditioning are illustrated in Fig. 2. Two rats in each of the 1.0 and 2.0 mg/kg pimozide and homecage control groups, and 12 rats in the 4.0 mg/kg pimozide group did not eat all of the pellets during the first conditioning session and were eliminated. Inspection of the graphs indicates that 4.0 mg/kg attenuated the conditioned reinforcement effect, while the remaining pimozide doses had little or no effect; 4.0 mg/kg pimozide 1 h after each conditioning session also appears to have diminished

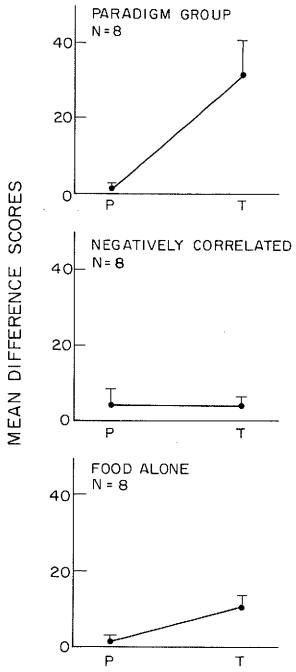

Fig. 1. The mean ($\pm$SEM) difference scores for the paradigm, negatively correlated, and food alone groups in Experiment I. Phase: P=pre-exposure; T=test

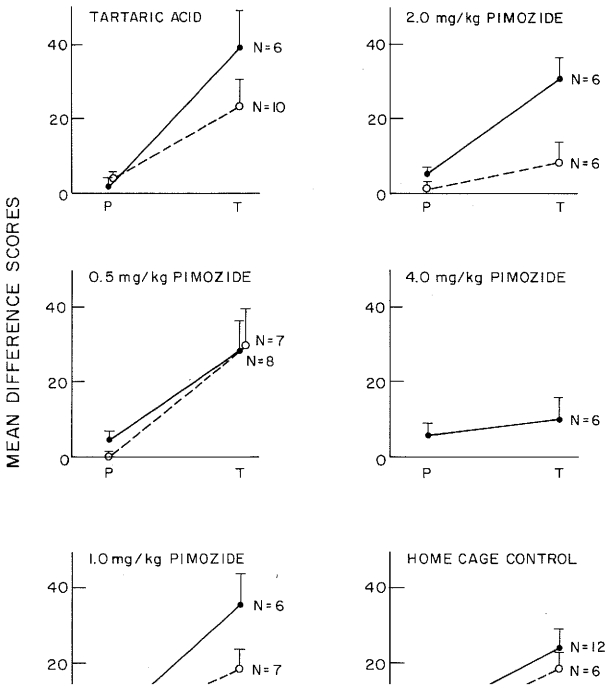

Table 1. *F*-ratios and corresponding levels of significance for the phase effect in each drug group receiving 4 days and 2 days of conditioning in Experiment I

Group	*df*	*F*	Significance[a]
	4-day		
Tartaric	1, 5	13.84	$P<0.05$
0.5 mg/kg	1, 7	13.82	$P<0.05$
1.0 mg/kg	1, 5	13.72	$P<0.05$
2.0 mg/kg	1, 5	29.28	$P<0.05$
4.0 mg/kg	1, 5	1.07	n.s.
Homecage	1, 11	18.33	$P<0.05$
	2-day		
Tartaric	1, 9	9.00	$P<0.05$
0.5 mg/kg	1, 6	8.33	$P<0.05$
1.0 mg/kg	1, 6	6.19	$P<0.05$
2.0 mg/kg	1, 5	1.04	n.s.
Homecage	1, 5	13.50	$P<0.05$

[a] A significant effect indicates that the light-off stimulus had been established as a conditioned reinforcer

doses of pimozide did have some effect; a linear trend analysis of the test phase scores (excluding the homecage group) was significant [$F(1, 27)=6.11$, $P<0.03$].

Because it has been demonstrated that pimozide influences motoric behavior and also that a delay of reinforcement affects the strength of conditioned reinforcement (Bersh 1951; Jenkins 1950), the latencies between food presentation and consumption were compared. Latencies during the first conditioning session were grouped into 2-s class intervals. In all groups, the majority of latencies occurred within 0–2 s. A one-way ANOVA conducted on the frequency of 0–2-s latencies revealed no significant group differences [$F(5, 38)<1$, $P>0.05$]. Thus, it appears that when all the pellets were eaten pimozide did not significantly affect the rat's latency to eat.

The mean difference scores ($\pm$SEMs) for the groups which received two days of conditioning are illustrated in Fig. 2. One rat in each of the 0.5 and 1.0 mg/kg and two rats in the 2.0 mg/kg pimozide groups did not eat all of the pellets during the first conditioning session and were eliminated. Results from the vehicle, 0.5 and 1.0 mg/kg groups suggest that 2 days of conditioning produced conditioned reinforcement. Furthermore, it appears that 2.0 mg/kg pimozide disrupted the establishment of conditioned reinforcement, whereas home cage injections of the same dose did not.

A two-way ANOVA on the five groups revealed no significant effect of group [$F(4, 31)=1.10$, $P>0.05$] or interaction [$F(4, 31)=1.35$, $P>0.05$]. However, the phase effect was significant [$F(1, 31)=28.3$, $P<0.0001$]. Planned tests of simple main effects (see Table 1) revealed a significant phase effect in the vehicle, 0.5 mg/kg, 1.0 mg/kg and homecage groups but not in the 2.0 mg/kg pimozide group. The lack of a significant effect in the latter group was due to a decrease in responding on the light-off lever during the test phase. The lower doses of pimozide had some effect on conditioned reinforcement as a linear trend analysis conducted on the test scores (excluding the homecage control group) approached significance [$F(1, 26)=3.45$, $P=0.0747$].

Unlike the 4-day procedure, pimozide appeared to have some effect on the feeding latencies. In comparing the number of latencies occurring within 0–2 s, the difference between the vehicle and 2.0 mg/kg pimozide groups approached significance ($P=0.0532$); this also held true for the vehicle and homecage groups ($P=0.0951$). The 2.0 mg/kg pimozide group and the homecage groups also had significantly more latencies greater than 6 s ($P<0.05$) relative to the vehicle group.

Discussion

The increase in difference scores from pre-exposure to test in the paradigm group but not the negatively correlated group is interpreted as evidence of conditioned reinforcement. The observation of a small conditioned reinforcement-like effect in the food alone group was not expected; however, this effect was significantly smaller than in the paradigm group.

In the 4-day conditioning procedure, pimozide treatment produced a dose-dependent attenuation of the conditioned reinforcement effect; only the group that received the highest dose (4.0 mg/kg) failed to demonstrate a significant effect.

Pimozide treatment within the 2-day procedure also yielded a dose-dependent attenuation of the conditioned reinforcement effect which approached significance. Unlike the 4-day procedure, the group which received 2.0 mg/kg pimozide failed to evidence a significant effect. Thus, it appears that a lower dose of pimozide was sufficient to disrupt conditioned reinforcement when a smaller amount of conditioning was employed.

Experiment II

There remains the possibility that pimozide may produce a conditioned taste aversion to the food pellets. Should this be the case, it follows that the light-off stimulus might gain few reinforcing properties, as it will be associated with a conditioned aversive stimulus, the food pellets. The purpose of Experiment II was to test the possibility that pimozide produces a conditioned taste aversion.

Materials and methods

Subjects. Forty male Wistar rats, housed as in Experiment I, had free access to rat chow throughout the experiment.

Procedure. All rats were adapted to a 30 min/day watering schedule for 6 consecutive days. At the same time every day, tap water was presented in 500 ml plastic bottles attached to the front of the home cage. The amount consumed was determined by weighing the bottles before and after each session.

By the sixth day the amount of water consumption each day had stabilized. The conditioning phase occurred on the following 4 consecutive days. For 30 min each day a 0.1% saccharin solution was presented to all rats and the amount consumed was recorded. Prior to this phase, the rats were randomly assigned to five treatment groups. Since lithium chloride (LiCl) is a potent agent for inducing a conditioned taste aversion (Nachman and Ashe 1973), one group (LiCl, $n=8$) was administered LiCl immediately after saccharin removal. A 0.15 M solution of LiCl (dissolved in physiological saline) was injected in a volume of 4 ml/kg to yield a dose of 25.5 mg/kg; on conditioning days 2–4, 8 ml/kg

were injected, yielding a dose of 51.0 mg/kg (Nachman and Ashe 1973). This group was included to ensure that the present procedure was a viable method for producing a conditioned taste aversion. To coincide with the drug dosages and injection times employed in Experiment I, two groups were given 2.0 mg/kg ($n=10$) or 4.0 mg/kg pimozide ($n=10$) 4 h prior to saccharin exposure and another was administered 4.0 mg/kg pimozide ($n=6$) 1 h after saccharin removal (pimozide was prepared and injected as described in Experiment I). A vehicle control group ($n=6$) was included which received tartaric acid 4 h prior to saccharin exposure. To counterbalance the design regarding the time of injection, a second injection was given so that all groups received two IP injections, one administered 4 h prior to the saccharin exposure and the other either immediately after or 1 h following removal of the solution.

Five rats in the 2.0 mg/kg pimozide group, six rats in the 4.0 mg/kg pimozide group (4 h prior to the saccharin exposure) and one rat in the 4.0 mg/kg pimozide (1 h after) and vehicle groups did not drink the saccharin solution on the 1st conditioning day and therefore were discarded from the experiment. During subsequent conditioning days if a rat did not drink more than 5 ml fluid then water was administered for 30 min immediately following saccharin solution removal. This actually occurred for only three rats across all 4 conditioning days.

Test days were conducted on the following 5 consecutive days. All rats received a 30-min two-bottle choice test. One bottle contained the 0.1% saccharin solution while the other bottle contained water. The position of the bottles (left, right) alternated between subjects, and was reversed each day for all rats. The amount consumed was recorded for each bottle.

Results and discussion

To determine if the groups differed in their water intake during pre-exposure, a two-way ANOVA was conducted on the amount consumed by each group for the 6 baseline days; there was no significant effect of group [$F(4, 24)<1$, $P>0.05$] or interaction [$F(20, 120)=1.45$, $P>0.05$]. The day effect was significant [$F(5, 120)=6.96$, $P<0.001$]. Thus, although the amount of fluid intake increased across days it did so at a similar rate for all groups.

A two-way ANOVA performed on the 4 conditioning days yielded a significant group effect [$F(4, 24)=5.71$, $P<0.01$], day effect [$F(3, 72)=17.07$, $P<0.001$], and interaction [$F(12, 72)=2.54$, $P<0.01$]. Significant group effects were observed on each of the 4 days ($P<0.05$). Using the Newman Keuls test, the majority of pairwise comparisons on the 1st conditioning day were significant; however, by the 2nd, 3rd and 4th days, with one exception only, the vehicle group was significantly different from the other groups. Hence, during the conditioning phase the vehicle group was drinking a greater amount of the saccharin solution than the other groups.

In the two-bottle choice test, preference was determined by calculating saccharin intake as a percentage of total fluid consumption. It should be noted that total fluid consumption among the five groups did not differ significantly [$F(4, 24)=0.97$, $P>0.05$]. The average percentages for each group for all 5 test days are illustrated in Fig. 3. A one-way ANOVA of the 1st day revealed a significant group effect [$F(4, 24)=5.8$, $P<0.005$]. Employing the Newman Keuls test, the LiCl group drank significantly less of the saccharin solution than the vehicle group [$Q(3, 24)=38.62$, $P<0.05$]. The groups which received pimozide either 4 h prior to or 1 h after saccharin exposure did not differ significantly from the vehicle group. Hence, administration of pimozide in doses of 2.0 and 4.0 mg/kg did not produce a conditioned taste aversion. Administering 4.0 mg/kg pimozide 1 h after saccharin exposure produced some avoidance of the saccharin solution. In fact, this group and the LiCl group did not differ significantly on the 1st conditioning day. However, by the 2nd test day this effect had disappeared.

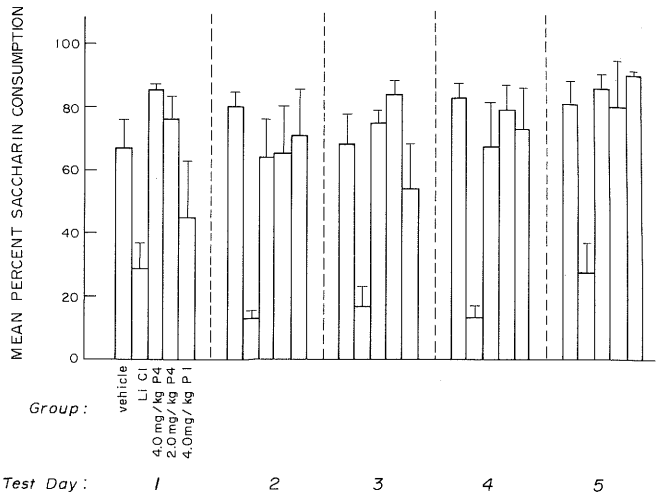

Fig. 3. Mean (±SEM) percent of saccharin solution consumed by each group during the five test sessions in Experiment II (*P4* = pimozide administered 4 h prior to conditioning; *P1* = pimozide administered 1 h after conditioning)

General discussion

The results appear to confirm the hypothesis that animals receiving a greater amount of conditioning would require a higher dose of pimozide to disrupt the establishment of conditioned reinforcement. When 4 days of conditioning were employed, animals treated with 4.0 mg/kg failed to demonstrate conditioned reinforcement. When a smaller amount of conditioning was utilized, the group given 2.0 mg/kg failed to produce a significant effect. It should be noted that these large doses of pimozide are not great enough to significantly affect noradrenergic (Anden et al. 1970; Pinder et al. 1976), cholinergic (Laduron and Leyson 1978) or serotonergic synapses (Niemegeers and Janssen 1979).

Several alternate interpretations of the pimozide-induced disruption of conditioned reinforcement were tested and ruled out. Conditioned taste aversion to the food appears unlikely, given the negative results of Experiment II. Furthermore, a cumulative drug effect over days affecting motor functioning in the test phase is also unlikely, in view of the conditioned reinforcement effects observed in the 4-day and 2-day homecage control groups.

Given pimozide's pronounced effect on motor functioning, the possibility that the disrupted learning was due to a delay between the conditioned stimulus and the unconditioned stimulus was also examined. Among the 4-day groups, there were no significant differences between the latencies measuring this time lapse. However, in the 2-day

procedure, rats treated with 2.0 mg/kg pimozide showed significantly more latencies greater than 6 s on conditioning day 1. It is noteworthy, however, that only 31% of the total number of latencies were above 6 s and the homecage control group which demonstrated conditioned reinforcement also had a high percentage (25%) of these longer latencies. The 2.0 mg/kg and homecage groups also had a similar number of latencies occurring within the 0–2 s interval (52% and 55%, respectively). Thus, it would seem that increased latencies to eat cannot account for the failure of the 2.0 mg/kg group to show conditioned reinforcement after 2 days of pairings.

If pimozide lessened the motivation to eat, the disruption of conditioned reinforcement might be attributed to a reduction in the reinforcing effects of food. Failures to eat, observed especially after the higher doses of pimozide, might support this interpretation. However, it was noted that once pimozide-treated animals found pellets in the food cup, they always ate them. Failures to eat appeared to result from failures to find the pellets which, in turn, may reflect reduced levels of exploration in hypokinetic pimozide-treated rats (note that the drugged rats had not previously been fed in the test chamber). Thus, it would appear that pimozide does not reduce the motivation to eat but rather decreases the likelihood of finding food. We recently tested this hypothesis by comparing the effects of pimozide on latencies to eat in rats previously fed in the test chamber versus rats never fed there; results supported the hypothesis that the effects of pimozide on feeding reflect hypokinesia and a resultant decrease in the likelihood of finding food by rats not previously fed in the test chamber (Hoffman and Beninger, submitted).

Another explanation which also can be dismissed is state-dependent learning. This hypothesis suggests that for pimozide-treated rats the stimulus which becomes associated with reinforcement during the conditioning phase is a combination of the light-off stimulus and drug-induced stimuli (Overton 1974). Accordingly, the expression of conditioned reinforcement is dependent upon the presence of the light-off stimulus as well as the drug in the test phase (Overton 1974). This explanation has difficulty in reconciling the observation that rats receiving 2.0 mg/kg pimozide in the 2-day conditioning procedure do not show conditioned reinforcement, yet animals in the 4-day procedure receiving the same dose do evidence a significant effect. One would expect state-dependency to occur in the 4-day procedure if it does in the 2-day procedure. In addition, Beninger and Phillips (1980) ruled out the possibility of state-dependent learning with the use of control groups.

In summary, the present results suggest that DA transmission may be necessary for the establishment of conditioned reinforcement; furthermore, the effects of DA receptor These observations may allow the conclusion that those conditioning procedures which produce strong conditioned reinforcement effects require a higher dose of pimozide to disrupt acquisition, whereas a lower dose is sufficient to disrupt learning in procedures which produce weak effects.

These results may suggest a possible explanation for some discrepancies regarding the role of DA in the establishment of conditioned reinforcement. Tombaugh et al. (1982) observed that pimozide (1.0 mg/kg) failed to disrupt the acquisition of conditioned reinforcement in sign-tracking or place preference tasks. Although it is difficult to compare the present conditioned reinforcement procedure with those of Tombaugh et al. (1982), it is noteworthy that in their procedures the rats received four and six conditioning sessions, respectively. One might expect this amount of conditioning to produce a strong conditioned reinforcement effect, and thus require a higher dose of pimozide to disrupt acquisition. The present observations may also explain the results of Beninger and Phillips (1980), who attenuated the establishment of conditioned reinforcement with 1.0 mg/kg pimozide. Although their procedure was similar in design to the present method, it produced a much smaller and less durable conditioned reinforcement effect. Presumably for this reason, a relatively smaller dose of pimozide was sufficient to disrupt the effect.

Spyraki et al. (1982), using a place preference task, demonstrated that rats treated with haloperidol failed to show a preference for the chamber which was paired with food in the conditioning phase, but the animals were no longer food-deprived during testing. Tombaugh et al. (1982) reported no disruption of the establishment of place preference in rats treated with pimozide; however, their rats were food-deprived during the test. Perhaps the deprivation level of the rats at the time of testing is another variable affecting the role of DA in the establishment of this learning.

Acknowledgements. Pimozide was the generous gift of Janssen Pharmaceutica. This research was supported by grants from the Natural Sciences and Engineering Research Council and the Ontario Ministry of Health to RJB.

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Received August 16, 1984; Final version February 15, 1985