Psychopharmacology 68, 147–153 (1980)

Psychopharmacology

The Effect of Pimozide on the Establishment of Conditioned Reinforcement

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Abstract. The effect of pimozide on conditioned reinforcement was determined by comparing rate of lever pressing for a tone in groups previously treated with or without the drug when the tone was paired with food. Eight groups of six to eight rats each received three phases of training in a two-lever box. The pre-exposure phase measured the operant rate of pressing the two levers, one of which produced a 3 s tone. In the conditioning phase, with the levers absent, the tone was paired with food over four sessions. The test phase again measured the rate of pressing the two levers. In an undrugged experimental group (i.e., Paradigm group), the number of presses on the tone lever significantly increased from the pre-exposure to the test phase, thereby confirming that the procedure could establish conditioned reinforcement. A control group receiving tones and pellets randomly during the conditioning phase also showed conditioned reinforcement but a group receiving negatively correlated tones and pellets did not. Groups receiving the dopamine-receptor blocker pimozide (1.0 mg/kg) prior to each conditioning session failed to show conditioned reinforcement in the test session. Control groups ruled out state dependent learning and drug-induced performance impairments as explanations of this pimozide-related effect. These data may indicate a possible role for dopamine neurons in mediating the control of behavior by certain positive reinforcing stimuli.

Key words: Pimozide – Conditioning – Food reinforcement – Dopamine blocker

The discovery that electrical stimulation of the brain could act as a reinforcing stimulus (Olds and Milner, 1954) has led to an extensive series of experiments aimed at identifying the neuroanatomical and neurochemical substrates of brain stimulation reinforcement (cf., Mogenson and Phillips, 1978; Wauquier and Rolls, 1976). Much of this research has focussed on the role of the catecholamine pathways (Crow, 1973; German and Bowden, 1974) and recent evidence has suggested an important, but not exclusive, role for dopamine (Fibiger, 1978; Phillips and Fibiger, 1978).

Dopaminergic pathways also have been implicated in the reinforcing effects of self-administered cocaine and amphetamine (Roberts et al., 1977; Yokel and Wise, 1975) thereby suggesting a more general role for these pathways in reinforcement. Wise and his coworkers have examined this possibility directly by comparing patterns of lever pressing under conditions of extinction or continuous food reinforcement after treatment with the dopamine receptor blocker pimozide (Wise et al., 1978). Both groups showed a similar reduction in response rate over several test sessions and this was interpreted as evidence for a reduction in the reinforcing properties of food following dopamine receptor blockade. Further support for this conclusion was provided in a related experiment where transfer occurred between three extinction sessions and a pimozide plus reinforcement session. Animals under this condition responded much less on the pimozide trial than animals receiving the drug for the first time again indicating the comparable effects of extinction and the blockade of dopamine receptors by pimozide. However, if these two treatments are indeed comparable, a similar transfer effect should be observed in an extinction test following 3 days of pimozide plus food reinforcement. Unfortunately, this prediction has not been confirmed (Mason et al., in press), and further experimentation is required to test the hypothesis that dopamine systems mediate the reinforcing effects of food.

A more appropriate procedure for a pharmacological analysis of the role of dopamine in reinforcement produced by food is one that separates the drug

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0033-3158/80/0068/0147/$01.40

treatment from the test of the drug's effect on reinforcement. The procedures used to study conditioned reinforcement offer such a possibility. A conditioned reinforcer is a previously neutral stimulus that has acquired reinforcing properties by repeated pairing with an unconditioned reinforcing stimulus such as food (Skinner, 1938). The conditioned reinforcing properties of the stimulus are confirmed in a test session that requires the subject to display a preference for the conditioned reinforcer or to acquire a new operant response using only the reinforcement provided by the conditioned reinforcer (MacIntosh, 1974). In the present context, a neutral stimulus can be paired with food in animals pretreated with the dopamine receptor blocker pimozide. (For a review of the pharmacological properties of pimozide see Pinder et al., 1976). If this treatment significantly attenuates the reinforcing effects of food, those subjects for whom a tone was paired with food after injections of pimozide should fail to show a preference for the tone when tested later in the drug-free state. The experiments reported here, similar in design to those of Stein (1958) and Knott and Clayton (1966), use the conditioned reinforcement procedure to overcome the problem of drug-related performance impairment in an investigation of the role of dopamine in reinforcement produced by food.

Materials and Methods

Subjects. Sixty-five male albino rats of the Wistar strain were individually housed in a climatically controlled colony room kept on a 12 h light/dark cycle. The rats weighed from 250–400 g and were maintained at 80% of these initial, satiated weights throughout the experiment.

Apparatus. The experimental environment consisted of two similar Plexiglas chambers (30.0 × 21.5 × 46.5 cm high) each housed in a ventilated sound-attenuating box. A removable lever (7.7 × 4.4 cm) was located in the middle of the opposite 21.5 cm ends of each chamber at a height of 4.0 cm. The force requirement for the levers was about 0.10 N. In the middle of one of the 30.0 cm sides of the chamber at a height of 1.5 cm was a feeder cup. A speaker that could be used as a tone source was mounted in the ceiling of each sound attenuating box. The tone in one box was a square wave 950 Hz signal and the tone in the other box was a square wave 1,400 Hz signal. Environmental contingencies and data collection were controlled by solid state switching and timing devices (BRS/LVE) for one chamber and by a Data General Nova 3 computer for the other.

Procedure. Each of eight different experimental groups was tested according to an experimental desgin with three distinct phases. The first of these groups (the paradigm group, $n = 6$) was included to demonstrate that this experimental procedure could be used to establish conditioned reinforcement. The following paragraphs present a detailed account of the procedure used to train the paradigm group followed by a description of the procedural variations used in training and testing the remaining groups.

The three phases of the experiment are referred to as the pre-exposure, conditioning, and test phases. The pre-exposure phase consisted of six 40 min sessions of exposure to the chamber with the two levers present. There was one session per day for 3 days, 2 days in the home cage, then the remaining three sessions on the next 3 days. During this phase, depressions of one of the levers (the tone lever) resulted in a 3 s presentation of the tone while depressions of the other lever (the no-tone lever) had no pre-arranged consequences. For the paradigm group the tone lever was on one side for three rats and on the other for the remaining three rats. The dependent variables were the number of responses on each of the two levers.

The conditioning phase consisted of four 75 min sessions. There was one session per day for the 2 days following the pre-exposure phase, then 2 days in the home cage followed by the remaining sessions on the next 2 days. During the conditioning phase the levers were absent from the chambers and Plexiglas plates covered the resulting apertures. During each session the 3 s tone was presented 100 times according to a random time 45 s schedule; i.e., the average intertone interval was 45 s. Each tone presentation during the first conditioning session terminated with the delivery of one 45 mg Noyes Precision Food Pellet and pellet delivery occurred only after a random 33% of the tone presentations in the next three sessions. This partial pairing procedure was employed because it produces more durable contitioned reinforcement (Knott and Clayton, 1966; Zimmerman, 1959; 1963).

The test phase consisted of one 40-min session, that occurred on the next day. The two levers were again present in the chamber and again one produced the 3 s tone. During the pre-exposure phase, half of the animals in the paradigm group produced the tone by depressing the lever on the left side and for the other half the tone was on the right; however, all animals showed a preference for the same lever reflecting a consistent side preference. For those animals that showed a preference for the tone lever (because it was on the preferred side), the tone lever was moved to the non-preferred side for the test session and therefore the magnitude of the conditioned reinforcement effect would not be biased by side preferences. Conditioned reinforcement was observed as a relative increase in the number of responses made on the tone lever during the test phase as compared to the pre-exposure phase.

The second and third groups were designated the random ($n = 6$) and explicitly unpaired ($n = 6$) groups and were included as controls for the paradigm group. The random group received the same phases as the paradigm group except that the presentation of tones and pellets during the conditioning phase was uncorrelated. The explicitly unpaired group also received the same phases as the paradigm group but during the conditioning phase pellet presentations never occurred during or in the few seconds following the tone; i.e., tone and pellet presentations were negatively correlated. If these groups fail to show a change in preference for the tone in the test phase as compared to the pre-exposure phase, then the observed change in the paradigm group can be attributed to the contingency between the tone and pellets and can be interpreted as evidence of conditioned reinforcement.

For the fourth group, the pimozide 0.5 group ($n = 6$), the three phases of the experiment were the same as those described for the paradigm group except than an IP injection of 0.5 mg/kg pimozide (dissolved in a ratio of 1 : 6 in boiling tartaric acid and then cooled to about 45° C before injection) was given 90 min prior to each session of the conditioning phase. The purpose of this group was to determine if this dose of pimozide given during the conditioning phase would eliminate the observation of conditioned reinforcement in the test phase.

The fifth group was the pimozide 1.0 group ($n = 6$). The treatment of this group was identical to the pimozide 0.5 group except that the dose of pimozide was doubled. The 0.5 and 1.0 mg/kg doses of pimozide were used because they have been shown to affect the acquisition of avoidance responding in a dose-related fashion (Beninger et al., in press). With the high dose of the drug some rats failed to eat all of the pellets presented during a session of the conditioning phase. Those rats that left any pellets uneaten in the conditioning phase were eliminated and additional rats added until

the group numbered six; a total of six rats were eliminated. Although all subjects in this final group ate all of the pellets delivered during the conditioning phase, they failed to show conditioned reinforcement in the test phase. The remaining groups were included to test various interpretations of this observation.

The state dep group ($n = 6$) received the same treatment as the pimozide 1.0 group during the pre-exposure and conditioning phases but also received an injection of pimozide (1.0 mg/kg) 90 min prior to the test session. This group was used to test the possibility that the pimozide 1.0 group failed to show conditioned reinforcement because of state dependent learning.

As a control for the possibility that an injection of pimozide prior to the test trial might produce a general disruption of lever pressing, the motor group ($n = 6$) was included in the overall design of the experiment. The procedure for this group was the same as for the state dep group insofar as a pimozide (1.0 mg/kg) injection preceded the test session; however, during the conditioning phase the pimozide injections followed, rather than preceded, the sessions by 60 – 70 min. This group was not drugged during conditioning but had the same drug history and treatment as the state dep group when tested. Observation of conditioned reinforcement in this group would rule out the possibility that the state dep group failed to show the effect because of some debilitation produced by the drug in the test phase.

A final group, the R-pimozide 1.0 group ($n = 8$), was tested as a replication of the pimozide 1.0 group. Once again, any rat that failed to eat all the food pellets in the conditioning phase was eliminated; nine rats were discarded in this group. For the remaining rats, a random sample of the latencies to eat the pellets presented in the conditioning phase was taken and compared to a similar sample taken from nondrugged rats. The purpose of these observations was to test the possibility that pimozide treated rats fail to show conditioned reinforcement because of a long delay between tone offset and pellet consumption.

Results

The purpose of the pre-exposure phase was to familiarize the rats with the experimental environment and to determine the rate of pressing on the tone and no-tone levers prior to conditioning. These initial lever-pressing rates (presses per session) were calculated by averaging the number of presses on each lever over the last three sessions of the pre-exposure phase. Lever-pressing rates for the test phase were simply the number of presses on each lever during the one test session. Thus, the data consisted of two pairs of numbers for each rat. The group means (± SEMs) of these numbers are shown in Fig. 1. Note that all groups consistently showed a preference for the no-tone lever in the pre-exposure phase. This reflected a *side* preference and was not related to the tone itself (see Procedure).

The results can be summarized as follows (see Fig. 1): Conditioned reinforcement, as evidenced by a relative increase in responding on the tone lever compared to the no-tone lever, occurred in the paradigm, random, and pimozide 0.5 groups. There was no evidence of conditioned reinforcement in the explicitly unpaired, pimozide 1.0, or R-pimozide 1.0 groups. Both the state dep and motor groups showed a decrease in responding from the pre-exposure to the test phase; however, the motor group showed a greater decrease in responding on the no-tone lever than on the tone lever, showing conditioned reinforcement, whereas the state dep group showed a similar decrease on both levers failing to show that the tone had become a conditioned reinforcer. Following is a description of the statistical analyses that confirm the significance of these observations.

The data were analyzed using a three-way analysis of variance with repeated measures on two variables. The variables analyzed were levers, phases, and groups, the first two being those with repeated measures. Only the first seven experimental groups were included in the

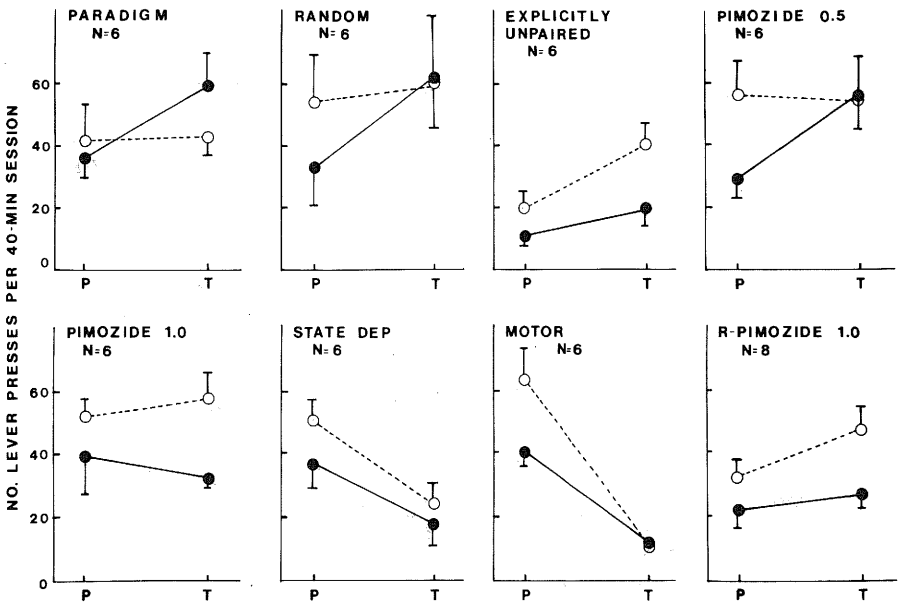

Fig. 1
Mean number (± SEM) of presses per session on the tone lever and the no-tone lever for each group during the last three sessions of the pre-exposure phase and during the test session. Phase: P = pre-exposure; T = test. ○ No-Tone Lever; ● Tone Lever

overall analysis; the results of the replication group were analyzed separately.

In the overall analysis of variance there was a significant lever effect, ($F = 26.38$, $d.f. = 1,35$, $P < 0.01$), but no significant group effect ($F = 1.79$, $d.f. = 6,35$, $P > 0.05$), or phase effect, ($F = 0.13$, $d.f. = 1,35$, $P > 0.05$). The lever effect is observed when all groups over both phases are combined and simply reflects the side preference discussed above. There was an interaction between phases and groups ($F = 10.35$, $d.f. = 6,35$, $P < 0.01$) and between phases and lever ($F = 9.02$, $d.f. = 1,35$, $P < 0.01$) but no significant interaction between levers and groups ($F = 2.01$, $d.f. = 6,35$, $P > 0.05$). Finally, there was a three way interaction among groups, levers and phases ($F = 2.93$, $d.f. = 6,35$, $P < 0.02$). The two significant interactions which include the group variable are the results that are of principle interest here.

The three-way interaction indicates that the two-way interactions between levers and phases differed from group to group. A significant lever by phase interaction confirms that the proportion of presses made on the tone lever was significantly larger in the test phase than in the pre-exposure phase. Where this occurred, the tone could be said to have become a conditioned reinforcer. Tests of simple interactive effects revealed that the tone had become a conditioned reinforcer in the paradigm, random, pimozide 0.5, and the motor groups. The tone failed to become a conditioned reinforcer for the explicitly unpaired, pimozide 1.0, and state dep groups (see Table 1 and Fig. 1).

From the overall analysis, the other significant interaction involving the group variable was the phase by group interaction. This occurs when, for each group, the combined total number of presses on both levers in the pre-exposure phase is compared to the total for both levers in the test phase. The significant interaction means that when this comparison is made from group to group, the groups differed. Of potential interest would be a significant increase in overall lever presses as this might indicate that general environmental stimuli had become associated with food. Tests of simple main effects revealed a significant increase in total lever presses from the pre-exposure to the test phase in the random group ($F = 5.52$, $d.f. = 1,35$, $P < 0.05$) and the explicitly unpaired group ($F = 4.86$, $d.f. = 1,35$, $P < 0.05$). There was a significant decrease in total presses from pre-exposure to test in the state dep group ($F = 10.22$, $d.f. = 1,35$, $P < 0.01$) and the motor group ($F = 35.46$, $d.f. = 1,35$, $P < 0.01$). The levers effect was insignificant for the paradigm group ($F = 2.78$, $d.f. = 1,35$, $P > 0.05$), the pimozide 0.5 group ($F = 2.38$, $d.f. = 1,35$, $P > 0.05$), and the pimozide 1.0 group, ($F = 0.06$, $d.f. = 1,35$, $P > 0.05$).

The two-way analysis of variance with repeated measures on both variables for the R-pimozide 1.0 group revealed no significant effect of phases ($F = 3.27$, $d.f. = 1,7$, $P > 0.05$), an overall difference in total number of presses on the two levers ($F = 11.91$, $d.f. = 1,7$, $P < 0.01$), and no significant interaction ($F = 4.09$, $d.f. = 1,7$, $P > 0.05$). Thus, the results for this group (see Fig. 1) replicated the results for the pimozide 1.0 group; i.e., they failed to show conditioned reinforcement.

For the R-pimozide 1.0 group a total of 244 observations of latencies to eat the pellets were recorded randomly during the four sessions of the conditioning phase. In 80 % of the cases the pellets were eaten within the first 3 s of delivery. A sample of 162 latencies from nondrugged control rats revealed that they ate the pellets, within the first 3 s of delivery, about 99 % of the time.

Table 1. *F*-ratios and corresponding levels of significance for the phase by lever interaction for each experimental group. A significant effect indicates that the tone had been established as a conditioned reinforcer

Group	*d.f.*	*F*	Significance
Paradigm	1,35	5.82	$P < 0.05$
Random	1,35	5.52	$P < 0.05$
Explicitly unpaired	1,35	1.35	n.s.
Pimozide 0.5	1,35	5.96	$P < 0.05$
Pimozide 1.0	1,35	1.28	n.s.
State dep	1,35	0.24	n.s.
Motor	1,35	6.49	$P < 0.05$

Discussion

The significant increase in pressing the tone-lever during the test phase by the paradigm group but not the explicitly unpaired group is interpreted as evidence of conditioned reinforcement. The observation of conditioned reinforcement in the random group was not expected although the effect is not unprecedented (e.g., Kremer, 1971; Kremer and Kamin, 1971; Quinsey, 1971). Possibly this effect occurred because of the high rate at which tones and pellets were presented (one of each every 45 s on the average during the first conditioning session) thus allowing enough fortuitous pairings for conditioning to occur. The group receiving the low dose of pimozide (0.5 mg/kg) during the conditioning phase also showed conditioned reinforcement. However, the groups pretreated with the high dose of pimozide (1.0 mg/kg) prior to conditioning showed no evidence of conditioned reinforcement.

Using a different test procedure from that employed here, others have reported that conditioned reinforcement is enhanced in animals pretreated with psycho-

motor stimulants (Hill, 1970; Robbins, 1975; 1976; 1978; Robbins and Koob, 1978). Using the procedure employed here we have observed the same effect (Beninger et al., in preparation). Psychomotor stimulants are known to affect the synaptic concentration of dopamine and noradrenalin (e.g., Scheel-Kruger, 1971) and it is possible that the enhancement of conditioned reinforcement by these drugs is related to this effect. This would be consistent with the present observation of a blockade of conditioned reinforcement by pimozide.

The disruption of conditioned reinforcement by pimozide cannot be attributed to state dependent learning (Overton, 1974). According to this theory, the stimulus that would become associated with reinforcement during the conditioning phase, in pimozide-treated rats, would be a combination of the tone and drug. If this was the case, animals with the drug-produced stimuli present again during the test phase would be expected to show conditioned reinforcement. However, the state dep group, which was included to test this possibility, showed no evidence of conditioned reinforcement.

The state dep group did show a decrease in overall responding from the pre-exposure to test phase. Pimozide is known to cause a decrease in activity (Schlecter and Butcher, 1972) and therefore the decreased responding in the state dep group was expected. The possibility remains that the conditioning effect may have been masked by a reduction in activity following the pimozide treatment. The motor group was included for precisely this reason. These animals had the same drug history as the state dep group when they reached the test phase and were injected with pimozide prior to this test, but they were never drugged during the four sessions of the conditioning phase. Although the overall response rate was reduced in the motor group, they did show conditioned reinforcement by reversing their lever bias from the no-tone to the tone lever. This observation would appear to rule out a drug-induced motor deficit as an explanation of the failure of the state dep group to show conditioned reinforcement. In reaching this conclusion, it is also important to rule out the possibility that it may represent a floor effect in which the significant interaction between phases and levers reflects the large difference in responding on the two levers in the pre-exposure phase and a minimal amount of responding in the test phase (see Fig. 1). This explanation appears unlikely because the state dep group was treated in a comparable manner to the motor group during the test phase, yet despite a reduction in response rate, they failed to show a significant phase by lever interaction. The state dep group maintained the same lever bias as it had in the pre-exposure phase, in dicating the absence of conditioned reinforcement.

It is possible that pimozide affected the perception of the tone in the pimozide 1.0 group thereby reducing the ability of the tone to become a conditioned stimulus. This possibility seems unlikely, however, since it has been shown that avoidance deficits observed in animals treated with 1.0 mg/kg of pimozide are not related to a failure to learn the association between the tone and shock (Beninger et al., in press).

The combined data from all eight groups thus support the conclusion that pimozide treatment can disrupt the establishment of conditioned reinforcement. There are several possible explanations for this effect, the most compelling of which include (i) a reduction in the level of motivation or (ii) the action of the drug on a dopaminergic substrate of reinforcement. The present findings cannot be attributed to a complete suppression of the motivation to eat, as all the pimozide-treated animals in this study ate pellets readily during the conditioning phase. Zis and Fibiger (1975) also have reported that food intake after 24 h of food deprivation is not affected by 0.5 mg/kg of pimozide but there are as yet no comprehensive reports on the effect of higher doses of pimozide. While it is clear that animals treated with 1.0 mg/kg of pimozide are still motivated to eat, quantitative changes in the level of motivation cannot be discounted. The fact that drugged animals took longer than 3 s to initiate eating in about 20 % of the cases sampled is consistent with a motivation hypothesis. Possibly, the strength of conditioned reinforcement can be influenced by the level of motivation. If so, the disruption of conditioned reinforcement in the present experiment may be due to the direct effect of pimozide on the level of motivation. Alternately, increased latencies to eat may have reflected simply an impairment in the ability to initiate the approach response to the feeder. Such deficits have been observed previously in neuroleptic-treated rats (Fibiger et al., 1975).

As indicated above, pimozide had a direct effect on latency to initiate the feeding response. This in turn raises the possibility that the present effect is due to delay of reinforcement which has been shown to affect the strength of conditioned reinforcement (Bersh, 1951; Jenkins, 1950). Fortunately pellets were eaten in the 3 s following 80 % of the tone presentations, thus assuring a high degree of contiguity between the tone and reinforcement. When these data are coupled with the fact that the random group showed conditioned reinforcement despite many fewer tone pellet pairings, it appears that delay of reinforcement cannot account for the present findings.

Another explanation that is harder to dismiss, because of the lack of relevant data, concerns the possible aversive effects of pimozide particularly as they may relate to difficulty of movement in the

drugged state. Such aversive effects could become associated with the food-related stimuli and thereby offset any conditioned reinforcement effects produced by the pellets. In this regard, it is gratifying to note that pimozide cannot be used to establish a conditioned taste aversion to food pellets (Wise et al., 1978).

Recent experiments by Wise and co-workers (1978) have employed an extinction procedure to compare the effects of pimozide on reinforcement with the removal of reward from undrugged animals. In certain situations comparable disruption of reinforced behavior was obtained with both manipulations. On the basis of these studies, it has been suggested that pimozide selectively attenuates the rewarding impact of food and other pleasurable stimuli (Wise et al., 1978). These experiments have been criticized on methodological grounds (Mason et al., 1979; Phillips and Fibiger, 1979). Furthermore, these subsequent studies have served to emphasize the difficulty in devising appropriate experimental designs which will provide unequivocal support for the disruption of reward processes by neuroleptic drugs. In this context, it is important to note that the present data are not inconsistent with the hypothesis that dopamine neurons form an important link in mediating the control of behavior by certain positive reinforcing stimuli. The difficulty arises in trying to specify whether the 'important link' is responsible for primary reinforcement or some related process such as incentive motivation. Further experimentation is required to answer this question and also to confirm that the effects of pimozide on conditioned reinforcement are related specifically to the blockade of dopamine receptors. Experiments employing other dopamine antagonists, local injections of 6-hydroxydopamine and pharmacological manipulations of other transmitter systems are now being carried out to test further the possible role of dopamine in conditioned reinforcement.

Acknowledgements. This research was supported by a grant from the National Research Council of Canada. R. J. Beninger is a MRC of Canada post-doctoral Fellow. A. G. Phillips is a Killam Senior Research Scholar.

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Received March 27, 1979; Final Version December 11, 1979