Pharmacology Biochemistry & Behavior, Vol. 12, pp. 931–935. Printed in the U.S.A.

Effects of Pimozide on Lever Pressing Behavior Maintained on an Intermittent Reinforcement Schedule[1,2]

T. GRAY AND R. A. WISE

Psychology Department, Concordia University, 1455 de Maisonneuve Blvd. West, Montreal, Quebec, Canada H3G 1M8

Received 29 September 1979

GRAY, T. AND R. A. WISE. *Effects of pimozide on lever pressing behavior maintained on an intermittent reinforcement schedule*. PHARMAC. BIOCHEM. BEHAV. 12(6)931–935, 1980.—Lever pressing for food on a variable interval (2.5 min) schedule was challenged by pretreatment with a 1.0 mg/kg dose of the dopamine receptor blocker pimozide. Large decreases in response rate were recorded even during the first few minutes of the test session before the rats had received any reinforcement. Pimozide also caused extinction-like effects, but it was clear, from comparisons between pimozide-treated rats that were rewarded and pimozide-treated rats that were not rewarded, that the rewarding effects of food were not totally blocked. It is suggested that an important aspect of the pimozide-produced response decrement is its effect on the incentive motivational properties of food-associated apparatus cues known to be important in sustaining responding under extinction and partial reinforcement conditions.

Neuroleptic Pimozide Reward Anhedonia

A NUMBER of drugs with antischizophrenic effects apparently act by blocking central dopaminergic synapses [10,13]. This finding has encouraged both pharmacological and behavioral research into the basic actions of dopamine blockers on the behavior of normal animals, and such studies support the notion that among the effects of the neuroleptic pimozide is the ability to produce a state in which the reward value of usually reinforcing events is blocked or attenuated [4, 6, 7, 15, 18].

These studies have shown that in food-rewarded tests the animals were clearly capable of responding at normal rates during the first drug test, but experience with the drug over 4 test days produced progressively lower rates of responding. Appropriate controls, involving home cage administration of the drug, ruled out the possibility that these effects were produced by a pure pharmacological effect of drug accumulation. It seems clear that the attenuation of bar-press rate seen during these drug tests cannot be attributed solely to general debilitation produced by sedation or motor side effects of the drug.

Wise *et al.* [15] have suggested that some motivational aspect or consequence of the sensory properties of food was not normally effective in the pimozide treated animals. It was suggested that pimozide acted to take the "goodness" out of the taste of food for the rats in these experiments, as it has been reported elsewhere to take the euphoria out of the response to intravenous amphetamine in man [9].

Fibiger, Carter and Phillips [5,11] have argued on the other hand that some of the behavioral deficits observed in animal studies are due at least in major part to less specific debilitation in the form of a performance incapacity. Although it is clear, as previously mentioned, that the possibility of the operant response deficits being entirely due to general debilitation can be ruled out, it is acknowledged that some degree of general debilitation may be present along with reward-attenuating doses of pimozide [16]. Further research is needed to tease out the specific from the more general deficits.

The experiments of Wise *et al.* [15,16] have thus far been restricted to animals that were trained on continuous reinforcement schedules. An advantage of using animals that have been trained, instead, on an intermittent reward schedule is that such animals will lever press for long periods of time without actually receiving a food pellet. The effect of the neuroleptic can thus be tested on hunger-motivated behavior for a significant time without food being present. It would be possible, using this feature of partial reinforcement schedules, to test the effect of pimozide on the animal's hunger-motivated behavior for several minutes before it received it first food pellet in a given test session. Any decrements found in this period could not be attributed to a direct effect of pimozide on the taste or immediate motivational consequences of food itself. In a more general sense tests on animals trained on intermittent schedules are necessary to extend the generality of the findings based on continuous reinforcement experiments. The research reported here,

[1]The authors would like to thank Joan Spindler and Michael Kleiza for their help in conducting the experiments.
[2]The research was partly supported by Natural Science and Engineering Research Council (Canada) grants to T. Gray and R. A. Wise.

therefore, deals primarily with the effects of pimozide on lever pressing behavior maintained on a variable interval reinforcement schedule.

EXPERIMENT 1

METHOD

Subjects and Apparatus

Subjects were experimentally naive, male, hooded rats that weighed between 250 and 300 g when they were received from Canadian Breeding Farms (Quebec, Canada). The apparatus consisted of eight commercially available conditioning units individually housed in sound attenuating boxes. The appropriate Grason Stadler and Gerbrands timers, relays, and counters necessary for automatic control of the units were located in an adjacent room.

Procedure

Initial training was identical for all animals. Over a period of 10 days, all animals were food deprived to 80% of ad lib weights and they were maintained on a once-a-day feeding schedule (Purina rat chow). During a "magazine training" session animals were familiarized with the reinforcement mechanism by the presentation of 30 reward pellets that appeared according to a 1.0 min VI programme. Bar presses during this phase also produced an immediate reinforcement. All animals learned to press readily within an hour and no specific shaping was necessary. This initial session was followed by 5, daily, 2-hr bar-press sessions for food on a 2.5 min VI schedule (20 sec-5 min).

After the fifth bar-press training day the 32 animals of Experiment 1 were assigned to the four testing conditions. Since eight conditioning units were available, eight animals could be tested at a time. Four "squads" of eight animals were tested each day in 2 hour sessions starting at 9:30 a.m., 11:30 a.m., 1:30 p.m. and 3:30 p.m., respectively. Animals were assigned to a "squad" so that time of day and conditioning unit was systematically counterbalanced for each experimental group. The groups tested were designated as follows: Group PF: On the drug test days this group was injected intraperitoneally with 1.0 mg/kg of pimozide in a tartaric acid vehicle and was tested during a normal VI reinforced bar press session; i.e., these animals received food pellets on the usual schedule except during the first 20 min (see below). Group PNF: Also received 1.0 mg/kg of pimozide, but was tested during an extinction session; i.e., no reinforcements were delivered during test days. Group TAF: Was treated identically to Group PF except that it was injected with the tartaric acid vehicle. Group TANF: Was treated identically to Group PNF except that it also received only the tartaric acid vehicle. In summary then the four conditions on test days were: (a) pimozide and food reward (PF); (b) pimozide and no food reward (PNF); (c) tartaric acid and food reward (TAF); (d) tartaric acid and no food reward (TANF).

An essential feature of Experiment 1 was that no reinforcements were given for any group during the first 20 min of the 120 min test session. It was thus possible to examine the effects of the pimozide on the bar-pressing behavior during a time period before any animal had received a food pellet. It should be noted that a number of minutes without reinforcements was not unusual for these animals that had been trained on the variable interval schedule.

The number of bar-presses was recorded every 2 min during the first 20 min of the session and every 4 min thereafter. There was a total of 4 drug-test days. After each of the first three drug-test days the animals received 2 recovery sessions which were simply a return to the conditions of the variable interval schedule bar-press training days.

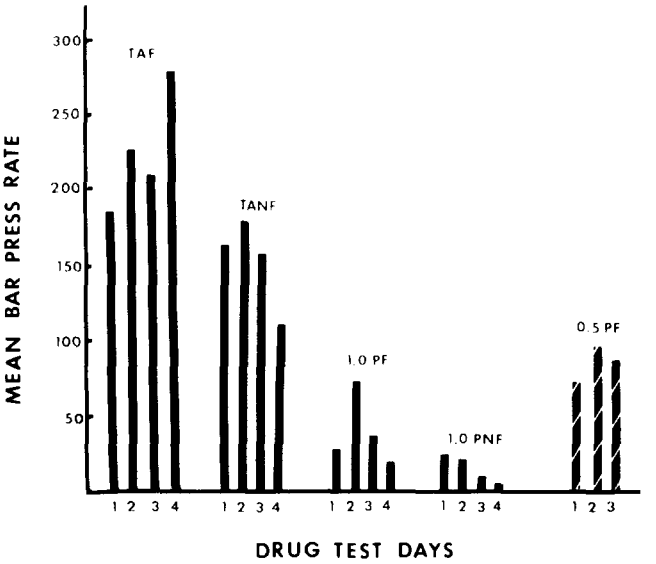

FIG. 1. Mean bar press rates for the first 10 min of each session on the drug-test days for the pimozide and vehicle treated animals of Experiment 1.

On the day after the fourth (final) drug-test day all animals were given an extinction test; that is, bar-press rates were recorded during a session in which no reinforcements were delivered for any group at any time during the session.

Animals were injected (IP) with the pimozide or vehicle 4 hours before the start of the bar-press session. The dose was always 1.0 mg/kg.

RESULTS AND DISCUSSION

Figure 1 presents the mean number of bar-presses that was made during the first 10 min of the 4 drug test sessions. The striped bars on the right of Fig. 1 are from 3 test days for a group of animals treated identically to group PF except that the pimozide dose was only 0.5 mg/kg. This latter group, run separately from Experiment 1, is presented for comparison purposes only.

The differences between the pimozide treated animals and the non-drugged control animals were clear cut. There was no overlap in the bar-press rates of the drug versus control groups on the first test day, and very little on subsequent days. For example, the mean rates on the first test day for the TAF (food reward); TANF (extinction group); (PF (pimozide and food), and PNF (pimozide no food) groups were 187, 164, 27, and 23 respectively.

The rate for the TAF group which experienced neither drug treatment nor non-reward (extinction) experience continued to increase over days, while the rate for the TANF group in general decreased as the animals experienced the four extinction test sessions.

Differences between the test sessions within the drug groups were evident. Although the overall rates were low and the magnitude of the differences was small, the fourth test session rate was significantly lower than the first session

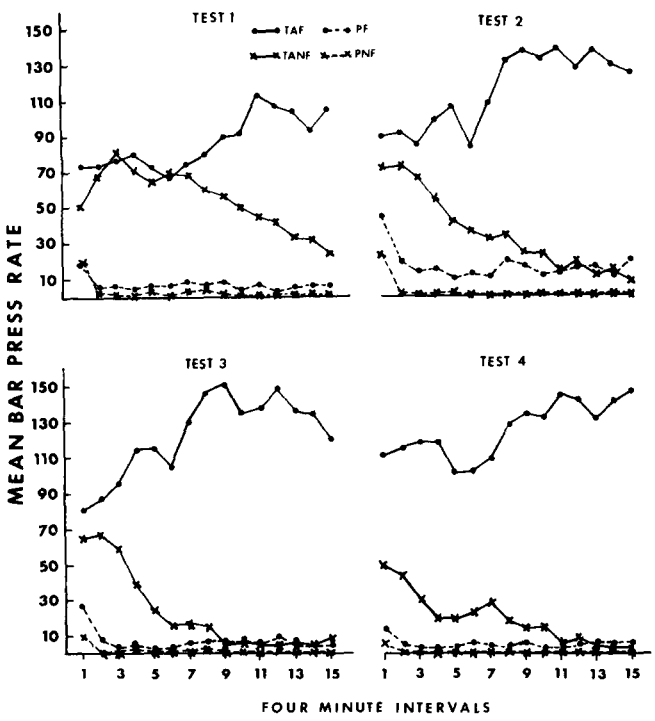

FIG. 2. Detailed changes in mean rate of bar pressing during the first hour of the testing sessions for the animals of Experiment 1.

rate in the PNF group (Wilcoxon, two-tail, $p<0.02$). The decrease between the second and fourth test sessions in the 1.0 PF group was also reliable (Wilcoxon, two-tail, $p<0.02$) as was the increase between sessions one and two.

Only 3 test days were given to the 0.5 mg/kg pimozide group and this group was run separately from the other groups in Experiment 1. The results, therefore, are not directly comparable. It is, however, clear that the overall rates are, as would be expected, intermediate between the 1.0 PF and the TAF groups.

In summary, then, the main finding of Experiment 1 was that very large decreases in response rates were produced by the pimozide treatment. The decrease was evident on the first test day and appeared even during the early part of the test session when no food reward was available to any animal. Although response rates were low, a decrease over test sessions was evident in the PNF group and a similar decrease was evident over the second, third and fourth test sessions for the PF and the TANF groups.

As previously indicated the bar-press rates were recorded every 2 min for the first 20 min of each session and every 4 min thereafter. Data were presented for the first 10 min of the session because the large changes were evident during this period. After the first 20 min during which no animal received food pellets the appropriate reinforcement schedule either extinction (no food) or variable interval reinforcement (2.5 min VI) was reinstated. Figure 2 shows the response rates over the first hour of the session in 4 min intervals. It is clear that the TANF (extinction control) group is learning to discriminate extinction test sessions from the reinforced recovery days because extinction occurs more rapidly over the 4 sessions. The gradually increasing rate for the TAF group that never receives extinction sessions is also evident. Of more importance is the indication that, although the PF group's rate is severely depressed, the animals never stop pressing completely. This is in marked contrast to the PNF animals who stop pressing completely after the first few minutes of the session.

To emphasize this important difference that cannot be clearly seen in the presentation of mean rates in Fig. 2, Table 1 is presented showing the median rates for the PF and PNF groups for each of the last 15 four-min periods.

The low but consistent rate in the PF group was not an artifact produced by 1 or 2 persistent bar-pressers. It appears that the reinforcements obtained by the PF group were effective in maintaining a low rate of responding. That this experience was important is evident in the recovery day data that are presented in Fig. 3. It will be recalled that all groups received 2 days of reinforced (VI 2.5) bar-pressing after drug test sessions 1, 2, and 3, and a final non-reinforced (extinction) test after drug test Day 4. Figure 3 shows the response rates for the first hour of the first recovery day after drug Days 1 and 3 and for the extinction test session. The main feature of interest is that the PF group is different from all other groups in its pattern of responding. It is as though the pimozide tests, which severely suppressed the bar-pressing, allowed the animals to learn that a lowered but steady rate of

TABLE 1

MEDIAN BAR-PRESS RATES FOR THE PF AND PNF GROUPS DURING THE LAST 60 MINUTES OF EACH OF THE 4 TEST DAYS

Test Day	Group	Last 60 minutes of Test Sessions 4 minute Periods 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	PF	3.0	1.0	2.5	3.5	7.5	5.0	1.0	1.5	4.0	2.0	2.0	0.5	2.0	0.5	5.5
	PNF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	PF	9.5	15.0	12.0	11.0	16.0	11.0	10.0	9.5	11.5	8.5	8.5	12.0	11.0	15.5	15.0
	PNF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	PF	3.0	2.0	3.0	2.0	5.5	3.5	3.0	7.0	5.0	6.5	3.5	2.5	1.0	1.5	2.0
	PNF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	PF	2.5	4.5	1.0	1.0	7.5	5.5	6.0	5.5	2.5	6.0	1.0	7.0	6.5	8.5	9.0
	PNF	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

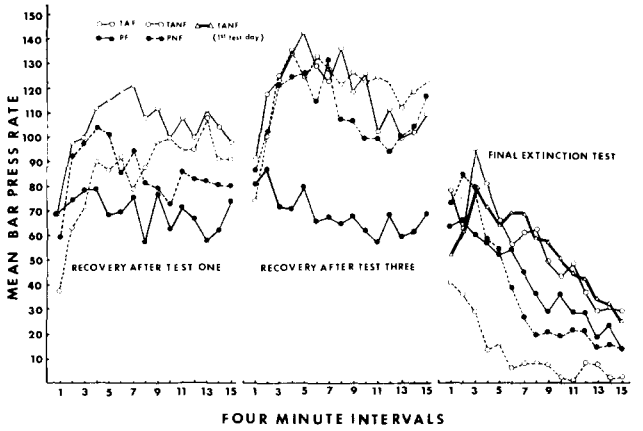

FIG. 3. Detailed changes in mean rate of bar pressing during the first hour of the recovery days after the first and third tests and during the final extinction session for animals in Experiment 1.

pressing could still produce about as many reinforcements as gained by the other animals with this reinforcement schedule. The pattern of responding on the final no-drug extinction test day is also of interest. The TANF group which had 4 sessions of extinction experience showed the expected rapid decline in response rate. The TAF group for which this was the first extinction session produced data virtually identical to those produced by the TANF on its first extinction session (heavy line and triangles). The 2 pimozide groups produced intermediate rates. The PNF group, although it had received 4 prior extinction sessions with pimozide, did not now extinguish as rapidly as the TANF group which had received 4 prior extinction sessions without pimozide. In effect the pimozide plus no food sessions for this group had previously produced virtually zero response rates after the first few minutes. The bar-press response was, therefore, not being extinguished in the four test sessions because the animals were not bar-pressing; that it, nonperformance of the response protected it from extinction. It is clear from the recovery day data and the final extinction day data that the drug test sessions for the pimozide plus food (PF) did not provide experience identical to a complete extinction (TANF) procedure.

EXPERIMENT 2

The animals in Experiment 1 were all trained on a VI 2.5 min reinforcement schedule. Previous experiments [15,16] looked at the effect of pimozide on the behavior of animals trained on a continuous reinforcement schedule (1 food pellet for each response: CRF). Experiment 2 was performed to check that the same basic response patterns could be reproduced in CRF trained animals with the same general procedures employed in Experiment 1, which differed from previous experiments in both degree of deprivation and amount of pre-training.

Three groups of naive male hooded rats, 8 per group, were treated identically to the rats in Experiment 1 up to the beginning of their bar-press training day. After the usual magazine training day they were given 5, daily, 2-hr sessions for food reward on a CRF schedule. They were then tested in a sequence of sessions similar to Experiment 1 but using the CRF schedule. During the drug test days one group (TANF)

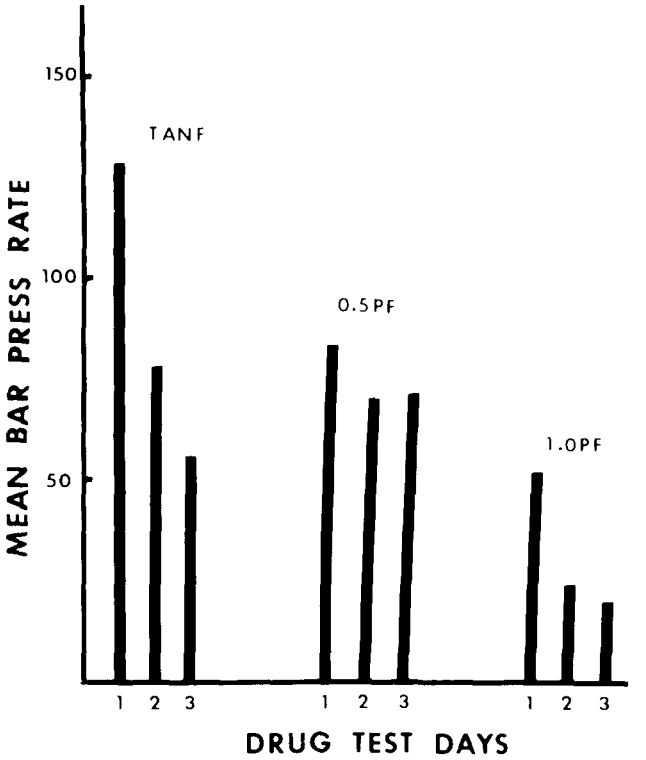

FIG. 4. The mean bar press rates for the first 10 min of the three drug test sessions of Experiment 2.

was injected with the tartaric acid vehicle and tested in an extinction (no food reward) session. Two other groups were injected with pimozide at doses of 0.5 mg/kg and 1.0 mg/kg respectively. These two groups, tested during food reward sessions, were designated PF 0.5 and PF 1.0. Three drug test sessions were conducted, and each session was followed by 2 recovery training days in which all animals pressed for food reward on the CRF schedule.

RESULTS AND DISCUSSION

Figure 4 presents the mean bar-press rates for the first 10 min of each of the 3 drug test sessions. The normal session-to-session decrease in the responding of the extinction-tested, non-drugged control animals (TANF) is quite clear cut. The decrease over test sessions in the PF 1.0 group was reliable. Session 1 differed significantly from session 2 and from session 3 (Wilcoxon $p<0.02$). The first session rate for the 1.0 PF group was different from the first session of the TANF control group (Mann-Whitney $U=4$, $p=0.001$). No differences were evident between the 3 sessions of the 0.5 PF group.

Perhaps the most important finding here is that although the strain of animal, deprivation schedule, and length of initial training in this experiment were different from those employed in the studies by Wise *et al.* [15,16], the same pattern of responding between test sessions was clearly demonstrated in the 1.0 PF group. It must be noted, however, that in contrast with previous findings, suppression of the CRF trained bar-pressing was evident in the first test session.

GENERAL DISCUSSION

Experiment 1 demonstrated a profound and immediate

depression of food-motivated bar-pressing. This result stands in marked contrast to previous (CRF) findings where the suppressive effect of pimozide did not appear until the animals had experienced the drug in successive test sessions [15]. It was, however, demonstrated that a session by session effect was still evident in that the bar-press rates for the pimozide treated animals decreased further over test sessions in essentially the same pattern as found for the non-drugged extinction control animals (TANF).

A suppressive effect of pimozide on CRF trained behavior was evident on the first test session of Experiment 2. This finding contrasts with previous reports [15] that found no differences between the pimozide group and no-drug controls on the first session. However there was, as previously reported, a significant decrease over sessions, and there were, as previously noted, many differences between the present and previous studies using CRF training. The animals in the present Experiment 2 received, for example, far fewer training sessions before the first drug test.

It is clear that the large suppressive effect of pimozide in the first experiment cannot be due to a drug-induced alteration of the rewarding impact of food itself, since the decrement appeared before the animals received their first food pellet in the session. The large immediate decrease that occurred in animals having no prior experience with pimozide cannot be explained by the simple anhedonia hypothesis of Wise *et al.* [15].

It is clear also from the comparison of the PF and PNF groups in Experiment 1 (Fig. 3 and Table 1) that pimozide does not cause a total reward deficit. It is clear that the pellets received are still having some rewarding effect, a finding that confirms some similar recent data of Phillips and Fibiger [11]. Pimozide may markedly attenuate the rewarding effect of food, but it does not make food rewarded sessions identical to a no-food extinction session.

Other explanatory hypotheses that invoke sedative or motor deficit side-effects [1, 5, 12] cannot easily account for the many reports that show that rats were capable of performing at control levels under their first pimozide test [6, 7, 14, 15] and in the present experiments; although the first test suppressive effect was larger than previously reported for CRF trained animals, there was still a progressive effect of the successive drug experiences.

The pimozide-produced performance deficits cannot, then, be clearly attributed to a total blocking of the primary reward value of food nor can they be clearly explained as resulting from a general debilitation.

The performance deficit produced by the pimozide, is, we suggest, at least partly due to its blocking of the reward value of food, but we suggest further that pimozide also reduces the effectiveness of the incentive motivational stimuli [2] present in the situation. General apparatus cues, or specific stimuli, can acquire incentive motivational properties by virtue of being associated with primary reinforcements such as food. These conditioned motivational stimuli, also referred to as secondary reinforcers, are assumed to play a major role in the elicitation and maintenance of behavior particularly important in eliciting and sustaining behavior that has been only intermittently rewarded with a primary reinforcer. It might be that "general debilitation" occurs because pimozide weakens the effectiveness of the apparatus cues as behavior instigators. In fact, as Franklin and McCoy [8] have recently demonstrated, a stimulus (light) that has been specifically associated with reward, will, at least temporarily, reinstate behavior that has been suppressed by pimozide. According to the present suggestion the light in the Franklin and McCoy experiment was capable of reinstating performance because it, specifically, had acquired higher incentive motivational properties than the general apparatus cues.

It is suggested, then, that in addition to attenuating the motivational impact of food itself, pimozide also attenuates the motivational impact of food-associated incentive stimuli. This suggestion needs more direct support, and specific experiments to test the notion are underway.

REFERENCES

1. Ahlenius, S. An analysis of behavioral effects produced by drug-induced changes of dopaminergic neurotransmission in the brain. *Scand. J. Psychol.* **20:** 59–64, 1979.
2. Bindra, D. A motivational view of learning, performance, and behavior modification. *Psychol. Rev.* **81:** 199–213, 1974.
3. Bolles, R. C. Reinforcement, expectancy, and learning. *Psychol. Rev.* **79:** 394–409, 1972.
4. deWitt, H. and R. A. Wise. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide but not with the noradrenergic blockers phentolamine or phenoxybenzamine. *Can. J. Psychol.* **31:** 195–203, 1978.
5. Fibiger, H. C., D. A. Carter and A. G. Phillips. Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: Evidence for mediation by motor deficits rather than by reduced reward. *Psychopharmacology* **47:** 21–27, 1976.
6. Fouriezos, G., P. Hansson and R. A. Wise. Neuroleptic-induced attenuation of brain stimulation reward. *J. comp. physiol. Psychol.* **92:** 659–669, 1978.
7. Fouriezos, G. and R. A. Wise. Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. *Brain Res.* **103:** 377–380, 1976.
8. Franklin, K. B. J. and S. N. McCoy. Pimozide-induced extinction in rats: Stimulus control of responding rules out motor deficit. *Pharmac. Biochem. Behav.* **11:** 71–75, 1979.
9. Gunne, L. M., E. Anggard and L. E. Jonsson. Clinical trials with amphetamine-blocking drugs. *Psychiat. Neurol. Neurochir.* **75:** 225–226, 1972.
10. Iversen, L. L. Dopamine receptors in the brain. *Science* **188:** 1084–1089, 1975.
11. Phillips, A. G. and H. C. Fibiger. Decreased resistance to extinction after haloperidol: Implications for the role of dopamine in reinforcement. *Pharmac. Biochem. Behav.* **10:** 751–760, 1979.
12. Rolls, E. T., B. J. Rolls, P. H. Kelly, S. G. Shaw, R. J. Wood and R. Dale. The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. *Psychopharmacologia* **38:** 219–230, 1974.
13. Seeman, P. and T. Lee. Antipsychotic drugs: Direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* **188:** 1217–1219, 1975.
14. Wise, R. A. Neuroleptic attenuation of intracranial self-stimulation: Reward or performance deficits? *Life Sci.* **22:** 535–542, 1978.
15. Wise, R. A., J. Spindler, H. deWitt and G. J. Gerber. Neuroleptic-induced "anhedonia" in rats: Pimozide blocks the reward quality of food. *Science* **201:** 262–264, 1978.
16. Wise, R. A., J. Spindler and L. Legault. Major attenuation of food reward with performance-sparing doses of pimozide in the rat. *Can. J. Psychol.* **32:** 77–85, 1978.
17. Yokel, R. A. and R. A. Wise. Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. *Science* **187:** 547–549, 1975.
18. Yokel, R. A. and R. A. Wise. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology* **48:** 311–318, 1976.