*Pharmacology Biochemistry & Behavior*, Vol. 10, pp. 751–760. Printed in the U.S.A.

# Decreased Resistance to Extinction After Haloperidol: Implications for the Role of Dopamine in Reinforcement

ANTHONY G. PHILLIPS AND HANS C. FIBIGER

*Department of Psychology and Division of Neurological Sciences, Department of Psychiatry University of British Columbia, Vancouver V6T 1W5, Canada*

(Received 6 November 1978)

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**(5) 751–760, 1979.—Previous experiments have noted that the reduction in operant behavior following treatment with neuroleptic drugs resembles an extinction curve. From this it has been argued that neuroleptic drugs disrupt operant responding by blocking the hedonic properties of primary reinforcers. The present series of experiments challenge this interpretation on several grounds. Rats were trained to bar-press either for food or for brain-stimulation reward on a variable interval (VI-60 sec) schedule. They were subsequently put into a condition of non-reward (i.e. extinction) and the effects of haloperidol (0.1 mg/kg) on the rate of responding during extinction were examined. According to the anhedonia hypothesis haloperidol should not further reduce responding during extinction. Contrary to the prediction it was found that the rate of responding during haloperidol and extinction was greatly reduced compared to that measured during extinction alone. Furthermore, the anhedonia hypothesis has maintained that following neuroleptic treatment, response patterns change only after the animal has been reinforced on several occasions. However, in the third experiment of the present study which employed a VI-4 min schedule of food reinforcement, the response rate often was attenuated prior to the first reinforcement. These data indicate that the effects of neuroleptics on operant behavior cannot be accounted for in terms of unitary actions such as specific motor impairments or blockade of primary reinforcement. Rather these drugs appear to have multiple behavioral effects.

Extinction Reinforcement VI-schedules Brain-stimulation reward Dopamine Haloperidol Rats

CURRENTLY there is debate as to the mechanism underlying the attenuation of reinforced behavior by neuroleptic drugs. At appropriate doses the neuroleptics block dopamine (DA) receptors [1] and also produce akinesia [22]. Therefore the disruption of operant behavior could simply reflect motor impairment [9, 21, 25]. However, other factors appear to be involved as rats injected with pimozide maintain normal responding during the initial phases of test sessions that require bar-pressing [11,27] or running [12] for food or brain-stimulation reward (BSR). Wise and co-workers have emphasized the similarity between patterns of response decrement under pimozide as compared with extinction following non-reward in tests with different reinforcers [24, 26, 27, 28]. On the basis of these data, it was concluded that neuroleptics cause a reduction in operant responding by blunting the rewarding qualities of a variety of reinforcers including food, BSR and intravenous injections of psychomotor stimulants [26]. Specifically it was suggested that neuroleptics induce a state of anhedonia [27].

In a recent series of experiments, Fouriezos *et al.* [11,12] compared response patterns during reinforcement-drug conditions to those seen during normal extinction. Similar decrements in responding under both conditions were interpreted as a reduction in reinforcement following pimozide treatment. However, an important condition was omitted in these experiments, namely one in which the drug was present during extinction. The anhedonia hypothesis posits that the blockade of DA receptors reduces certain sensory qualities of the primary reinforcer which provide reward and that this reduction in reward value is directly responsible for the decline in responding. Two predictions follow from this interpretation. If the main effect of pimozide is to disrupt primary reinforcement, then neuroleptic drugs should have no effect on performance during extinction because of the absence of primary reinforcement. On the other hand, if neuroleptic drugs block the hedonic state produced by primary and conditioned reinforcers, response patterns during the reinforcement-drug condition should resemble those seen when pimozide is given during an extinction trial. The present experiments were designed to test these and other predictions of the anhedonia hypothesis.

## EXPERIMENT 1

The previous study comparing the effect of neuroleptics and extinction on barpressing with BSR [9] employed a continuous reinforcement schedule (CRF). It is well established that extinction of self-stimulation following CRF can be extremely rapid [13]. Therefore a procedure that would prolong extinction might allow a more detailed comparison between patterns of response decrement following (a) extinction with or without neuroleptic treatment and (b) reinforcement with or without drug injections.

Pilot tests confirmed that extinction was slower after experience with reinforcement delivered on a variable interval (VI) schedule [5]. Consequently a VI-60 sec schedule was used in the first experiment. The animals were treated with the neuroleptic drug haloperidol at a dose (0.1 mg/kg) that has been shown to block DA receptors selectively [1].

## METHOD

### *Animals*

The animals were four male Wistar rats weighing 300–320 g at the time of surgery. They were housed in individual cages with free access to food and water prior to experimental testing.

### *Surgery and Histology*

Each animal was anaesthetized with sodium pentobarbital (50 mg/kg IP), placed in a Kopf stereotaxic instrument and small diameter (0.005 in.) bipolar nichrome electrodes were implanted chronically in the lateral hypothalamus. The coordinates for the electrode placements according to de-Groot [7] were anterior −5.0 mm, lateral 1.8 mm and ventral 8.6 mm below the skull. At the conclusion of the experiment the animals were asphyxiated with $CO_2$ and their brains were rapidly removed and stored in 10% Formalin. Brains were frozen and sectioned at 40 $\mu$; sections containing electrode tracts were mounted and stained with thionin.

### *Procedure*

Following recovery from surgery, the animals were placed on a 22 hr food deprivation schedule to facilitate future comparison with food reinforced behavior. Water was available ad lib. Testing for self-stimulation was conducted in Plexiglas chambers (46×30×24 cm). Depression of a lever protruding through one wall activated a constant current stimulator which delivered a 0.2 sec train of 60 Hz sine wave current to the animal's electrode assembly. Stable responding was established with a current intensity of 25 $\mu$A delivered on a CRF schedule for a 1 hr test session.

In the second phase of the experiment, BSR (25 $\mu$A, 1.2 sec duration) was programmed to be available on a VI-60 schedule. The animals maintained barpressing throughout this transition and stable behavior (i.e., less than 10% variation) was obtained after three 1 hr sessions. Following the establishment of stable responding on the VI-60 schedule, each animal was tested under the following conditions: (a) BSR (VI-60)—no drug; (b) BSR (VI-60)—haloperidol (0.1 mg/kg); (c) extinction—no drug; (d) extinction—haloperidol (0.1 mg/kg). The order of testing was varied amongst animals, with at least 6 days between each of the drug or extinction conditions. Animals were tested 5 days per week. All animals received a final extinction—no drug test at the end of the experiment. Cumulative records were taken for each animal on every daily test session. Haloperidol was injected IP, 45 min prior to testing.

TABLE 1

EFFECT OF HALOPERIDOL (0.1 mg/kg) ON BAR-PRESSING RATES/60 MIN FOR BRAIN-STIMULATION REWARD DELIVERED ON A VI-60 SEC SCHEDULE OR DURING EXTINCTION

| | Conditions | | | |
|---|---|---|---|---|
| Animal | VI-60 no-drug | VI-60 + haloperidol | Extinction no-drug | Extinction + haloperidol |
| 1 | 1403 | 231 | 257 | 31 |
| 2 | 990 | 252 | 219 | 21 |
| 3 | 1097 | 503 | 149 | 31 |
| 4 | 848 | 148 | 236 | 55 |
| Mean ( ± SEM) | 1085 ± 77 | 284 ± 76 | 215 ± 23 | 35 ± 7 |

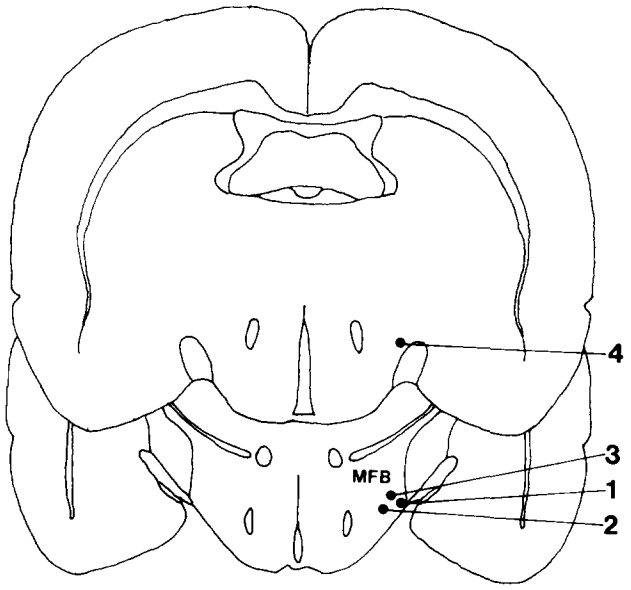



FIG. 1. Location of electrode tips in far-lateral hypothalamus. Numerals refer to specific electrode placements of the four animals.

## RESULTS

The electrode placements of the four animals were confirmed histologically to be in the lateral hypothalamus (see Fig. 1).

Individual and group scores from each of the four experimental conditions are contained in Table 1. Treatment with haloperidol reduced barpressing for BSR to 26% of the BSR (VI-60)—no drug scores, $t(3)=6.28$, $p<0.01$. Similarly, barpressing was significantly reduced to 20% during the extinction—no drug condition, $t(3)=8.94$, $p<0.01$. Barpressing rates underwent an even greater reduction in the extinction—haloperidol condition with scores that averaged 3% of the BSR (VI-60)—no drug value. The barpressing rate in the extinction—drug condition differed significantly from the mean rate in the extinction—no drug session, $t(3)=7.90$, $p<0.01$.

Samples of the cumulative records of one animal under each of the four conditions are shown in Fig. 2. As may be seen in the upper trace, very stable responding can be elicited by delivering BSR on a VI-60 schedule. It also is evident that the pattern of responding changes drastically following treatment with haloperidol. As noted above, the rate is reduced significantly, with the decline being greater in the later stages of the session. In this respect, the curve appears

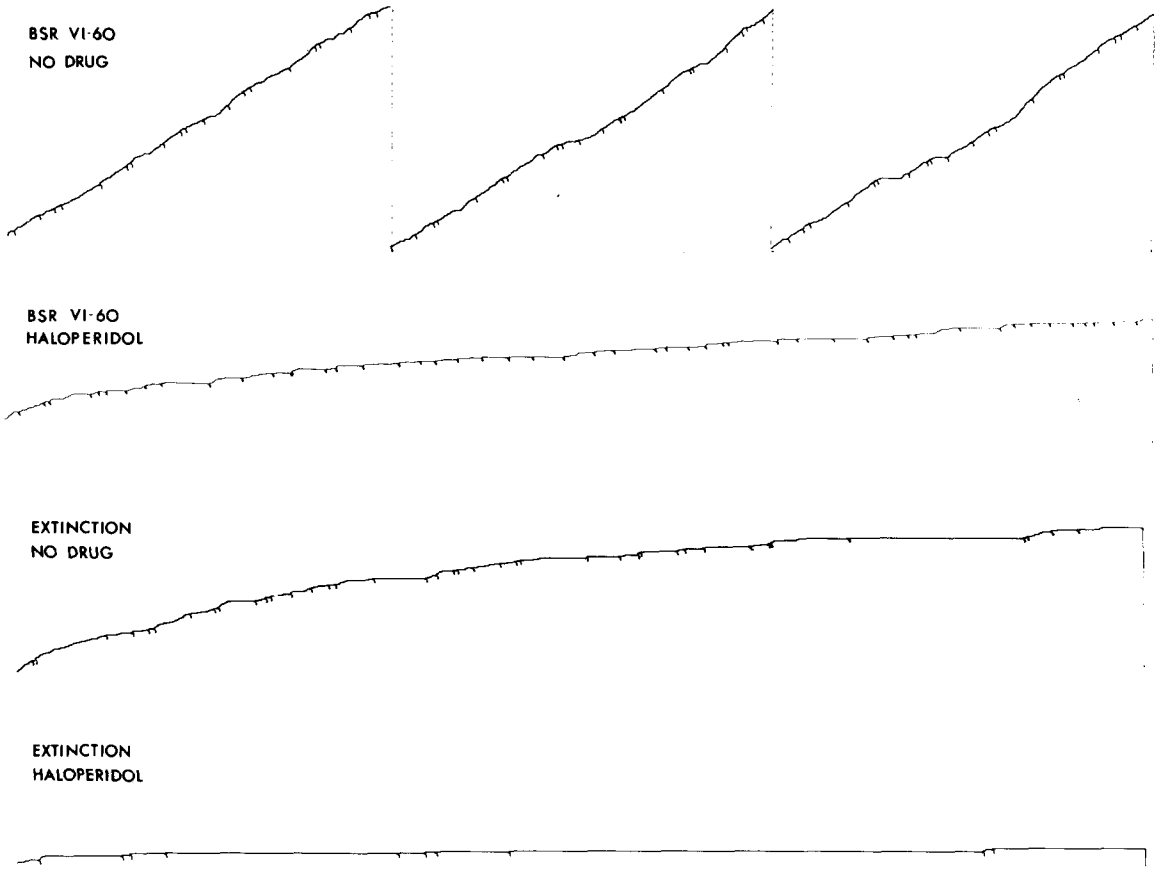



FIG. 2. Effects of haloperidol (0.1 mg/kg) on (a) lever pressing for lateral hypothalamic brain-stimulation delivered on a variable interval-60 sec schedule (compare 2 upper traces) and (b) extinction of these responses (compare 2 lower traces) during a 60 min test session. Deflections on record indicate activation of the stimulator. The response rate under each condition is given for S no. 1 in Table 1.

to resemble the extinction curve depicted below it. However, there are some subtle differences between these graphs that are noteworthy. During the BSR (VI-60)—haloperidol tests there were no pauses in responding greater than 2 min in duration. The animals pressed at a slow but steady rate, and obtained every available train of BRS. However, under the extinction condition, the animals would cease responding for periods between 2 to 10 min, with these pauses increasing in duration in the later phases of the 1 hr test session. The most important observation in this experiment is the enhanced attenuation of responding in the extinction—haloperidol compared to the extinction—no drug condition. This is seen clearly by comparing the two lower tracings in Fig. 2.

## DISCUSSION

The observation of stable barpressing for hypothalamic stimulation delivered on a VI-60 schedule confirms previous reports of stable performance for BSR on intermittent reinforcement schedules [2,3]. Although the animals in the present study were food deprived it is noteworthy that nondeprived animals also will work at comparable rates for BSR delivered on similar random ratio schedules [3]. The present results with a VI schedule also extend previous observations of neuroleptic disruption of self-stimulation with CRF schedules [14, 15, 18, 25].

At first glance, the pattern of response decrement under both BSR (VI-60)—haloperidol and extinction—no drug conditions would appear to confirm reports of extinction-like behavior after treatment with neuroleptics [11,12]. However, the longer periods of no responding seen in the extinction—no drug condition suggest that the drug effects are not identical to the effect of non-reinforcement. Furthermore, the finding that animals responded significantly less in the extinction—haloperidol condition than during extinction alone fails to support the hypothesis that neuroleptics decrease operant responding only by blocking primary reward.

## EXPERIMENT 2

The results of Experiment 1 challenge the conclusion that the response decrement for BSR after treatment with neuroleptics is due simply to the blunting of reward [26, 27, 28]. However, the argument for the anhedonia hypothesis does not rest solely on data from self-stimulation experi-

ments. Rats trained to bar-press for food or saccharin reward show comparable within session and between session response patterns when pretreated with neuroleptics or tested in a non-reward condition [27,28]. Accordingly, it is suggested that neuroleptics also selectively block the rewarding quality of food for hungry rats.

In order to determine whether the results of Experiment 1 can be generalized to behavior reinforced by conventional rewards, the present experiment examined the effect of haloperidol on bar-pressing for food on a VI-60 schedule. The experimental design was identical to that employed in Experiment 1.

## METHOD

### *Animals*

Four male Wistar rats were housed individually. Purina lab chow was available in the home cage for 2 hr per day and water was available ad lib.

### *Procedure*

The animals were adjusted to the 22 hr food deprivation schedule for 2 weeks prior to being trained to bar-press for food pellets (45 mg. Noyes Co.) on a CRF schedule for 30 min per day. Following the establishment of stable responding on the CRF schedule, each animal was placed on a VI-60 schedule and the test sessions were extended to 1 hr per day. The test boxes and levers were the same dimensions as those used in the self-stimulation experiment with a food cup located 8 cm from the bar. The boxes were housed in sound-attenuating chambers and the delivery of the pellets and recording of responses was controlled by programming equipment (LHV/BRS-Digibits). An empty pellet dispenser was activated during extinction trials.

The experimental conditions consisted of (a) food (VI-60)—no drug, (b) food (VI-60)—haloperidol (0.1 mg/kg), (c) extinction—no drug, (d) extinction—haloperidol (0.1 mg/kg). Again, cumulative records were collected for all daily test sessions.

## RESULTS

Individual and group scores for each experimental condition are shown in Table 2. Injection of haloperidol reduced responding for food pellets to 36% of the no-drug control level, $t(3)=6.55$, $p<0.02$. Comparable reductions (i.e., to 47% of control) were observed in the extinction—no drug condition, $t(3)=11.67$, $p<0.01$. A facilitation of extinction was observed again after treatment with haloperidol. A comparison of scores during extinction—no drug and extinction—haloperidol revealed a significant difference, $t(3)=6.10$, $p<0.02$.

To facilitate the comparison of the present results with those from Experiment 1, samples of the cumulative records of one animal under each of the four conditions are shown in Fig. 3. These records differ from those obtained in Experiment 1 as the pattern of responding was very similar in both the food (VI-60)—drug and extinction—no drug conditions. However, as was seen in Experiment 1, responding during the extinction—haloperidol condition was markedly different from that seen during extinction—no drug. In the former instance, the animals responded at near normal rates for the first several minutes of the session, but response rates declined rapidly and only occasional responses were made in the last half of the trial.

TABLE 2

EFFECT OF HALOPERIDOL (0.1 mg/kg) ON BAR-PRESSING RATES/60 MIN FOR FOOD DELIVERED ON A VI-60 SEC SCHEDULE OR DURING EXTINCTION

| | Conditions | | | |
|---|---|---|---|---|
| Animal | VI-60 no-drug | VI-60 + haloperidol | Extinction no-drug | Extinction + haloperidol |
| 5 | 1156 | 457 | 595 | 227 |
| 6 | 853 | 401 | 357 | 115 |
| 7 | 1576 | 628 | 590 | 43 |
| 8 | 1151 | 232 | 531 | 48 |
| Mean ( ± SEM) | 1184 ± 148 | 430 ± 81 | 557 ± 55 | 108 ± 43 |

## DISCUSSION

Although no attempt was made to equate food reward to BSR, operant responding for these two classes of reinforcement was very similar in both pattern and magnitude. This observation emphasizes further the similarity between BSR and more conventional reinforcers [2, 3, 16, 23].

The results obtained with haloperidol in Experiment 1 appear to generalize to behavior reinforced by food pellets. Bar-pressing for food on a VI-60 schedule was disrupted by the drug treatment confirming an earlier observation [9]. Furthermore, the rate of bar-pressing during extinction was significantly reduced by haloperidol. The implication of these findings will be discussed in the General Discussion.

## EXPERIMENT 3

Part of the argument that neuroleptics block reinforcement without attendant motor impairment, rests on the observation of normal performance prior to experiencing reward in the drug test sessions [11, 12, 26]. This is illustrated best in a runway experiment in which animals injected with pimozide displayed normal start latencies and running speed on the first few trials [11]. Performance declined only after several trials, thus resembling the pattern of extinction seen with non-rewarded control animals.

Variable-interval schedules offer an alternative procedure for determining whether the pattern of response disruption caused by neuroleptics is comparable to that seen during non-reward. By definition, animals tested on VI schedules do not know exactly when reinforcement will occur and therefore respond at stable rates during periods of non-reward. For such animals with experience on VI-schedules with long inter-reinforcement intervals, the first phase of an extinction session is indistinguishable from a regular reinforced test session. Consequently, during extinction stable responding is displayed for an extended period of time before performance declines. These circumstances afford an excellent opportunity to analyse the effect of neuroleptics on operant responding. According to the anhedonia hypothesis [26, 27, 28], responding during the first phase of a reinforcement-drug session should be indistinguishable from a reinforcement—no drug test. However, should haloperidol

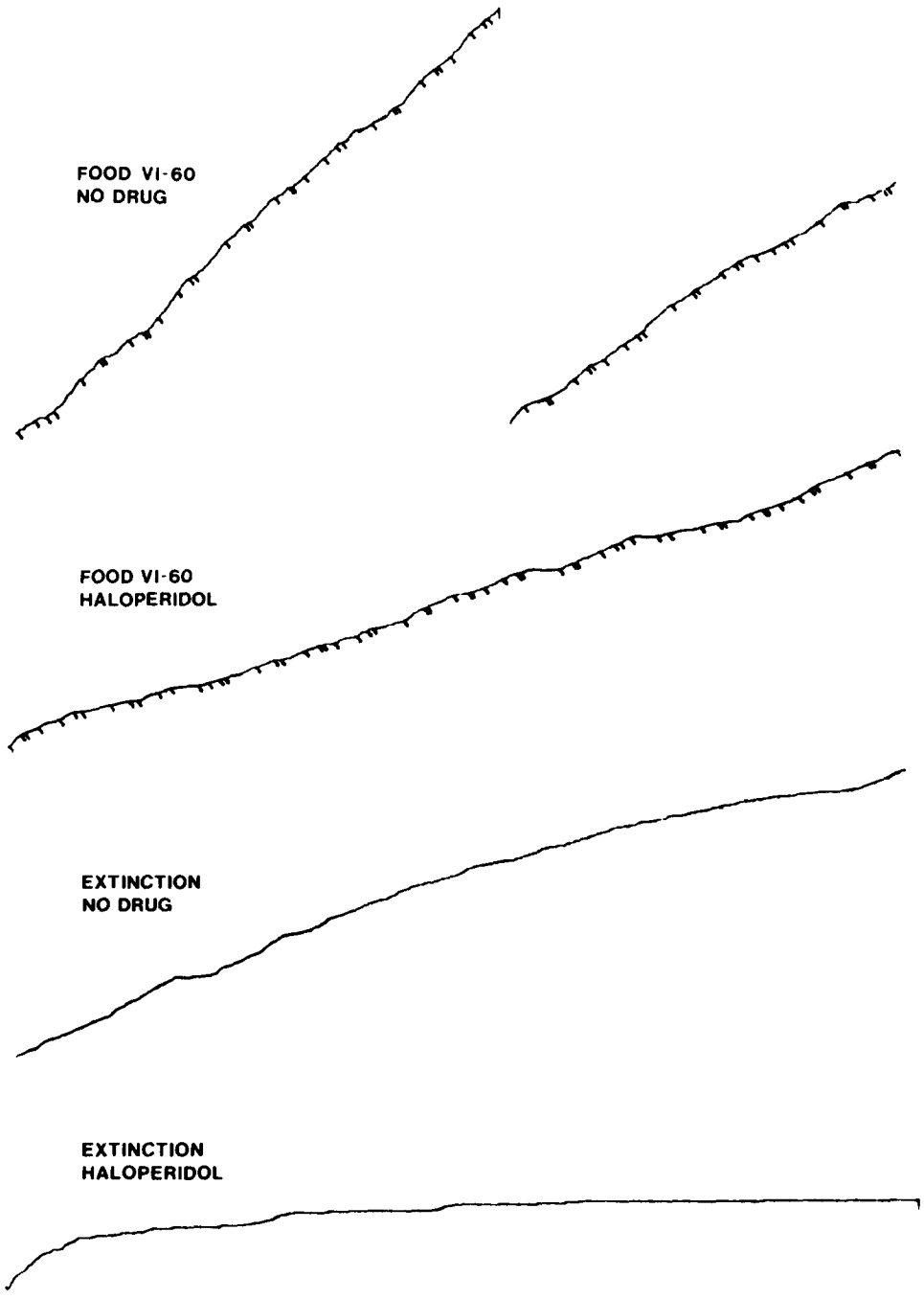



FIG. 3. Effects of haloperidol (0.1 mg/kg) on (a) lever pressing for food pellets delivered on a variable interval-60 sec schedule (compare two upper traces) and (b) extinction of this food reinforced response (compare 2 lower traces) during a 60 min test session. Deflections on the 2 upper traces indicate activation of pellet dispensor. This mechanism was also activated during extinction tests, but this was not recorded on the graphs. The response rate under each condition is given for S no. 6 in Table 2.

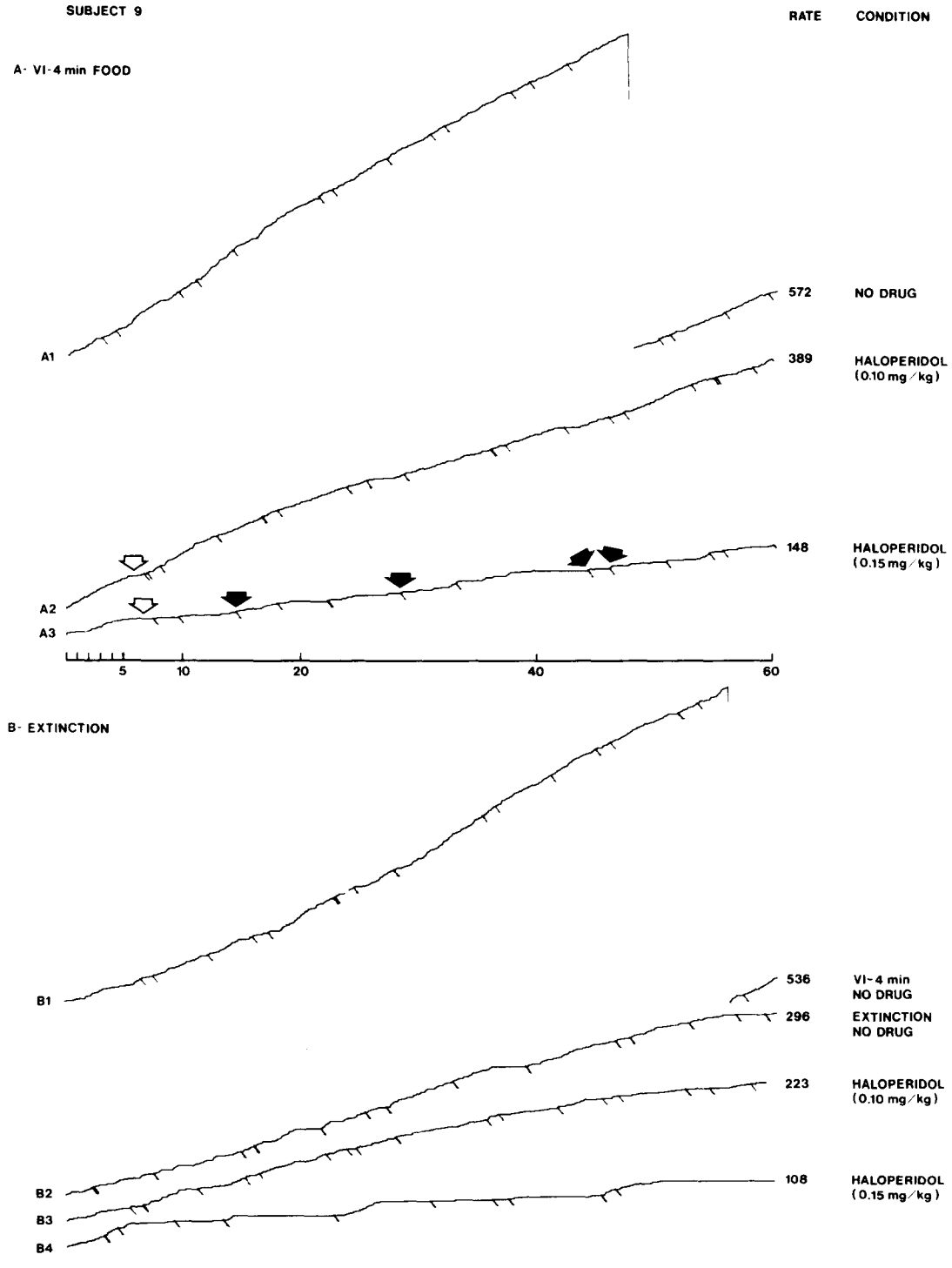
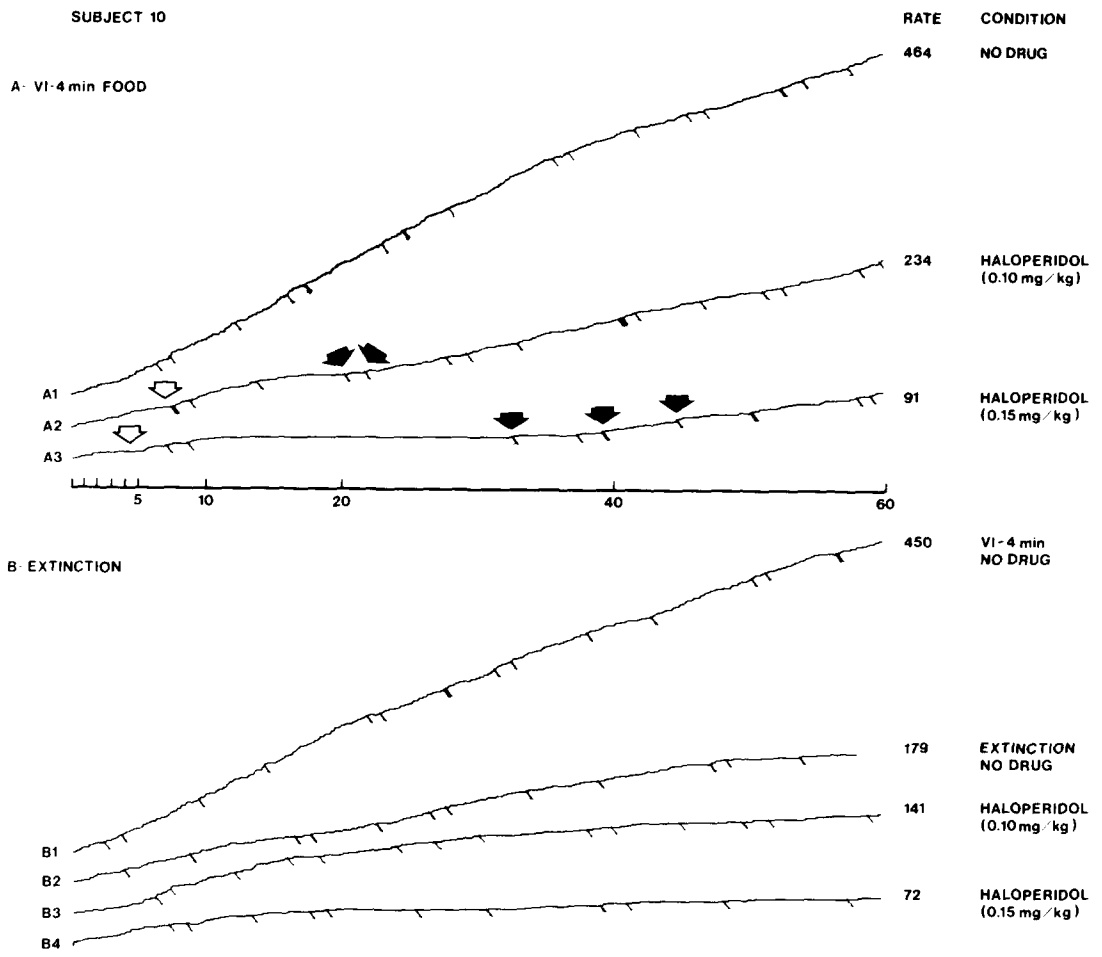

SUBJECT 9
RATE
CONDITION
A- VI-4 min FOOD
A1
572
NO DRUG
389
HALOPERIDOL
(0.10 mg/kg)
A2
148
HALOPERIDOL
(0.15 mg/kg)
A3
5
10
20
40
60
B- EXTINCTION
B1
536
VI-4 min
NO DRUG
296
EXTINCTION
NO DRUG
223
HALOPERIDOL
(0.10 mg/kg)
B2
108
HALOPERIDOL
(0.15 mg/kg)
B3
B4

FIG. 4.




FIGS. 4 and 5. Effects of haloperidol (0.1; 0.15 mg/kg) on (a) lever pressing for food pellets delivered on a variable interval 4 min schedule (traces $A_1$–$A_3$) and (b) extinction of this response (traces $B_1$–$B_4$). Open arrows illustrate pauses in responding prior to delivery of the first food pellet. Closed arrows indicate a burst of responding after delivery of a food pellet.

alter performance prior to delivery of the first reward, it would indicate that factors other than the blockade of primary reward are involved.

In the following experiment, animals were trained to barpress for food on a VI-4 min schedule and their performance was compared on drug (haloperidol) and no-drug test sessions. As in Experiments 1 and 2, the animals also were tested for extinction under drug or no-drug conditions.

## METHOD

### *Animals*

Two male Wistar rats were housed individually with food available for 2 hr per day. Water was available ad lib.

### *Procedure*

The deprivation schedule, equipment, and testing procedures were similar to those employed in Experiment 2. One major difference was increasing the VI from 60 sec to 4 min. This schedule was introduced to provide longer periods prior to the first reward, in which to examine the effects of haloperidol. Another difference was the use of 2 doses of haloperidol (0.10 mg/kg and 0.15 mg/kg). Again the drug was injected 45 min prior to the start of the 1 hr test session. Each of the following experimental conditions was presented in a random order: (a) food (VI-4 min)—no drug; (b) food (VI-4 min)—haloperidol (0.10 mg/kg); (c) food (VI-4 min)—haloperidol (0.15 mg/kg); (d) extinction—no drug (2 sessions); (e) extinction—haloperidol (0.10 mg/kg); (f) extinction-haloperidol (0.15 mg/kg). An empty pellet dispenser was activated by lever presses on extinction trials. The number of responses per hr and a cumulative record of responses was obtained for each test session.

## RESULTS

Cumulative records for each animal from each of the experimental conditions are shown in Figs. 4 and 5. Comparable results were obtained with both animals, although Animal 10 responded at a slightly lower baseline rate. The lower dose of haloperidol (0.1 mg/kg) suppressed responding for food in both animals by 32% and 50%. However, the animals obtained and ate every food pellet during the test. Responding was disrupted to a much greater extent (i.e., by 75–80%) after treatment with the higher dose of haloperidol (0.15 mg/kg). In both instances, the animals continued to respond throughout the 1 hr test, but there were longer periods of non-responding with the higher dose of haloperidol. As expected, the response rate also declined during the extinction sessions. The combination of non-reward and haloperidol produced a further dose-related suppression of responding.

In addition to these main effects observed in the different experimental conditions, subtle but important differences could be observed in response patterns during the initial phases of the various tests. One important comparison is between the records from the VI-4 min—no drug and the VI-4 min—haloperidol tests. Upon close inspection of the VI-4 min—haloperidol record, it is evident that there is often an acceleration in responding immediately after the delivery of each food pellet. As may be seen in Fig. 4, Animal 9 responded at a consistent rate for the first 5 min of the respective sessions, but under the influence of 0.1 mg/kg of haloperidol responding declined prior to delivery of the first food pellet. This effect is even more pronounced with the higher dose of haloperidol. Similar patterns may be seen for Animal 10 by comparing the 3 upper traces in Fig. 5. Secondly, it is important to compare the cumulative records from extinction—no drug ($B_2$) and extinction—haloperidol ($B_3$,$B_4$) tests. Extinction is more rapid in the drug conditions.

## DISCUSSION

The effects observed in the present experiment with a VI-4 min schedule of food reward were very similar to those seen with a VI-60 sec regimen in Experiment 2. Barpressing for food was attenuated by haloperidol and responding during extinction was also suppressed. Both effects were greater with the higher dose of haloperidol (i.e., 0.15 mg/kg).

The VI-4 min reinforcement schedule was particularly useful as it permitted a detailed analysis of responding prior to the initial presentation of food reward. When compared to the VI-4 min no-drug control, the response profile for both animals declined prior to the first reward, after treatment with the neuroleptic drug. This pattern was not observed in the extinction—no drug condition as both animals responded at normal rates well beyond the previous maximal interreinforcement interval. Under this latter condition, responding declined only after the temporal parameter indicated that the contingency had changed to non-reward. It is also worth noting that both animals consumed all food pellets in the reinforcement-drug tests, and also in many instances, showed increased bursts of responding for a short time after the delivery of the food pellets.

# GENERAL DISCUSSION

The suggestion that neuroleptic drugs disrupt operant responding solely by reducing the effectiveness of reinforcement [11, 12, 26, 27, 28] is not supported by the present results. One observation that is at variance with a simple anhedonia interpretation is the interaction between extinction and drug treatment. If these two manipulations are merely different ways of terminating primary reinforcement, then treatment with neuroleptics during extinction should have no additional effect on the animal's behavior. However, this was not the case and the accelerated rate of extinction produced by haloperidol indicates that the attenuation of responding during reinforcement and extinction sessions cannot be explained solely in terms of a blockade of primary reinforcement. It could be argued that the accelerated extinction produced by haloperidol is due to a drug-mediated blockade of reward provided by secondary reinforcing cues in the test environment such as the click of the unloaded pellet dispenser. However, if neuroleptics block reinforcement provided by both primary and conditioned reinforcers then several results would be predicted. First, the rate and pattern of responding in the reinforcement-drug condition, in which both primary and secondary reinforcement is blocked, would differ substantially from the extinction—no drug condition in which only the primary reinforcement is absent. Second, the rate and pattern of responding in the reinforcement-drug and the extinction-drug conditions would be predicted to be similar inasmuch as primary and secondary reinforcers would be blocked in both of these situations. Inasmuch as neither of these predictions were supported by the data, it appears very unlikely that the accelerated rate of extinction produced by haloperidol can be attributed to blockade of secondary reinforcement. The present observations, therefore, raise serious questions concerning the adequacy of the extinction paradigm utilized by Wise and co-workers as a test of the anhedonia hypothesis.

It may be argued that the drug treatment leads to faster extinction rates because the animals are in a different state during the extinction tests. Such an explanation would be consistent with the claim that extinction is faster, the greater the difference in test conditions between acquisition and extinction. However, unless state dependency is unique to neuroleptic treatment, recent findings with the serotonin synthesis inhibitor parachlorophenylalanine (PCPA) would argue against this interpretation. Treatment with PCPA increased resistance to extinction for bar-pressing when food was previously available on a CRF schedule and had no effect following experinece with a random-interval 64 sec schedule [4].

Implicit in the anhedonia hypothesis is the assumption that performance in the reinforcement-drug tests should not change before the animals learn that the reward contingencies have been altered. Close examination of the cumulative records from animals responding for food on a VI-4 min schedule reveals that the response rate is attenuated on drug tests prior to reinforcement. In contrast, the patterns of responding on the initial part of the no-drug reinforcement and no-drug extinction sessions are almost identical. Secondly, it should be noted that reinforcement typically produced a transient period of accelerated responding even after the high dose of haloperidol (see black arrows, Figs. 4 and 5). This observation would not be predicted if the sole effect of the drug was to block the primary reward value of the food pellets.

The present results are in general agreement with the view that neuroleptics reduce operant behavior at least in part by producing motor deficits which interfere with the animal's capacity to maintain high rates of responding. Specifically, the low, but relatively steady rates of responding for food or for BSR which were observed throughout the session after haloperidol pretreatment are compatible with previous proposals that neuroleptics decrease the ability of the animal to initiate operant or voluntary motor responses [9,10]. A number of recent studies suggest, however, that some of the effects of neuroleptics on operant behavior cannot be explained solely in terms of a response initiation deficits. For example, under some but not all circumstances, neuroleptics appear to have minimal effects on the rate of responding during the early part of an experimental session, whereas pronounced decreases in responding subsequently appear ([11,12] but see Figs. 4 and 5). Although this might, as suggested by Fouriezos and Wise [11,12], be due to blockade of primary reinforcement, the possibility that neuroleptic-induced increases in sedation or fatigue might contribute significantly to this phenomenon has not been adequately ruled out [8]. A more convincing demonstration that neuroleptics have effects on operant behavior in addition to those due to response initiation deficits has recently been provided by Wise *et al.* [27,28]. These investigators demonstrated that repeated daily injections of pimozide had progressively greater disruptive effects on food-reinforced responding and that this could not be attributed to cumulative drug effects.

In view of these considerations, it would appear that neuroleptics have complex and multiple effects on operant behavior. On the one hand, few investigators would argue that neuroleptics do not have significant, dose-related effects on motor performance and we have previously proposed that these drugs act selectively to block a dopaminergically-mediated response initiation mechanism [9,10]. On the other hand, insofar as BSR is critically mediated by dopaminergic neurons at certain electrode placements [8,19] and intravenous cocaine and amphetamine-induced reinforcement appears to be mediated by central dopaminergic mechanisms [20,26], it is conceivable that neuroleptics, which block central DA receptors, might also block or reduce the rewarding value of primary reinforcers such as food [26, 27, 28]. That neuroleptics have effects on both motor and reinforcement mechanisms might have been predicted on the basis of the widespread projections of the DA-containing systems in the brain [6,17]. It is possible, for example, that the motor deficits result primarily from the blockade of DA receptors in one part of the brain (e.g. striatum), while the anhedonic [27,28] properties of these compounds are a consequence of receptor blockade in other regions such as the nucleus accumbens, frontal cortex, septum or amygdala.

In summary, these considerations indicate that all the effects of neuroleptics on operant behavior cannot be accounted for in terms of single actions such as specific motor impairments or blockade of primary reinforcement. Rather, these drugs appear to have multiple and at present only partly specified actions, each of which contribute to the behavioral effects of these compounds. Furthermore, it should be recognized that a specific behavioral task may be sensitive to only one of the different behavioral effects of neuroleptics. Therefore it will be important to study the effects of these drugs with a variety of different behavioral paradigms. An interesting challenge for future research will be to identify the various regions of the brain which are affected directly by neuroleptics and which contribute to each of the various psychopharmacological and neurological properties of these drugs.

ACKNOWLEDGEMENTS

Supported by the Medical Research Council. A.G.P. is Killam Senior Research Scholar.

## REFERENCES

1. Anden, N. E., S. G. Butcher, H. Corrodi, K. Fuxe and U. Ungerstedt. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.* **11**: 303–314, 1970.
2. Beninger, R. J., F. Bellisle and P. M. Milner. Schedule control of behavior reinforced by electrical stimulation of the brain. *Science* **196**: 547–549, 1977.
3. Beninger, R. J., A. Laferriere and P. M. Milner. An investigation of responding on schedules of brain-stimulation reinforcement. *Can. J. Psychol.* **32**: 106–115, 1978.
4. Beninger, R. J. and A. G. Phillips. PCPA enhances resistance to extinction of lever-pressing operant established with food reinforcement. Paper presented to *Can. Psychol. Ass.*, Ottawa, June, 1978.

5. Brown, S., and J. A. Trowill. Lever-pressing performance for brain stimulation on F-I and V-I schedules in a single-lever situation. *Psychol. Rep.* **26:** 699–706, 1970.
6. Carter, G. A. and H. C. Fibiger. Ascending projections of presumed dopamine containing neurons in the ventral tegmentum of the rat as demonstrated by horseradish peroxidase. *Neuroscience* **2:** 569–576, 1978.
7. deGroot, J. The rat hypothalamus in stereotaxic coordinates. *J. comp. Neurol.* **113:** 389–400, 1959.
8. Fibiger, H. C. Drugs and reinforcement mechanisms: A critical review of the catecholamine theory. *Ann. Rev. Pharmac. Toxic.* **18:** 37–51, 1978.
9. 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. *Psychopharmacologia* **47:** 21–27, 1976.
10. Fibiger, H. C., A. P. Zis and A. G. Phillips. Haloperidol-induced disruption of conditioned avoidance responding: Attenuation by prior training or by anticholinergic drugs. *Eur. J. Pharmac.* **30:** 309–314, 1975.
11. Fouriezos, G., D. Hansson and R. A. Wise. Decreased intracranial self-stimulation after neuroleptics: mediation by reduced reward, not performance debilitation. *J. comp. physiol. Psychol.* **92:** 661–671, 1978.
12. 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.
13. Gallistel, C. R. Electrical self-stimulation and its theoretical implications. *Psychol. Bull.* **61:** 23–34, 1964.
14. Liebman, J. M. and L. L. Butcher. Effects on self-stimulation behavior of drugs influencing dopaminergic neurotransmission mechanisms. *Naunyn-Schmiedeberg's Arch. Pharmac.* **277:** 305–318, 1973.
15. Liebman, J. M. and L. L. Butcher. Comparative involvement of dopamine and noradrenaline in rate-free self-stimulation in substantia nigra, lateral hypothalamus and mesencephalic central grey. *Naunyn-Schmiedeberg's Arch. Pharmac.* **284:** 167–194, 1974.
16. Mogenson, G. J. and J. Cioe. Central reinforcement: A bridge between brain function and behavior. In: *Operant Conditioning*, edited by W. K. Honig and J. Staddon. New York: Appleton, 570–595, 1976.
17. Moore, R. Y. and F. E. Bloom. Central catecholamine neuron systems: Anatomy and physiology of the dopamine systems. *Ann. Rev. Neurosci.* **1:** 129–169, 1978.
18. Phillips, A. G., S. M. Brooke and H. C. Fibiger. Effects of amphetamine isomers and neuroleptics on self-stimulation from the nucleus accumbens and dorsal noradrenergic bundle. *Brain Res.* **85:** 13–22, 1975.
19. Phillips, A. G. and H. C. Fibiger. The role of dopamine in maintaining intracranial self-stimulation in the ventral tegmentum, nucleus accumbens, and medial prefrontal cortex. *Can. J. Psychol.* **32:** 58–66, 1978.
20. Roberts, D. C. S., M. E. Corcoran and H. C. Fibiger. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmac. Biochem. Behav.* **6:** 615–620, 1977.
21. 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:** 19–230, 1974.
22. Schlechter, J. M. and L. L. Butcher. Blockade by pimozide of (+)-amphetamine induced hyperkinesia in mice. *J. Pharm. Pharmac.* **24:** 408–409, 1972.
23. Trowill, J. A., J. Panksepp and R. Gandelman. An incentive model of rewarding brain stimulation. *Psychol. Rev.* **76:** 264–281, 1969.
24. 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.
25. Wauquier, A. and C. J. E. Niemegeers. Intracranial self-stimulation in rats as a function of various stimulus parameters. II. Influence of haloperidol, pimozide and pipamperone on medial forebrain bundle stimulation with monopolar electrodes. *Psychopharmacologia* **27:** 191–202, 1972.
26. Wise, R. A. Neuroleptic attenuation of intracranial self-stimulation: reward or performance deficits? *Life Sci.* **22:** 535–542, 1978.
27. Wise, R. A., J. Spindler, H. deWit and G. J. Gerber. Neuroleptic-induced anhedonia in rats: pimozide blocks the reward quality of food. *Science* **201:** 262–264, 1978.
28. Wise, R. A., J. Spindler and L. Legault. Blockade of food reward but not performance capacity in rats with the dopamine receptor blocker pimozide. *Can. J. Psychol.* **32:** 77–85, 1978.