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The Effects of Pimozide and of Reward Omission on Fixed-Interval Behavior of Rats Maintained by Food and Electrical Brain Stimulation

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GREENSHAW, A. J., D. J. SANGER AND D. E. BLACKMAN. *The effects of pimozide and of reward omission on fixed-interval behavior of rats maintained by food and electrical brain stimulation.* PHARMAC. BIOCHEM. BEHAV. 15(2) 227–233, 1981.—Pimozide (0.125 to 2.0 mg/kg) was administered to rats whose behavior was maintained by a fixed-interval schedule in which the reward was either food (Experiment 1) or electrical stimulation of the brain (Experiment 2). The effects of the drug were compared with the effects of withholding reward (i.e., extinction) in both experiments. Reward omission and administration of pimozide both resulted in decreases in overall rates of responding and increases in the time taken by the subjects to complete a specified number of fixed-intervals. The typical patterning of responding during the sessions of reward omission was also characteristic of the effects of pimozide with food reward but not with brain stimulation reward. The duration of trains of brain stimulation which was under the control of the subjects in Experiment 2, was not altered by administration of pimozide. The differences between the effects of pimozide on behavior maintained by intermittent food reward or by intermittent brain stimulation reward limits a global interpretation of the effects of neuroleptics.

Pimozide Reward Food Brain stimulation Fixed-interval schedule

NEUROLEPTIC drugs decrease the rate of conditioned operant behavior at doses which do not affect unconditioned behavior [17, 29, 31]. It has been argued that these effects are mediated through actions on mechanisms controlling motor performance [1, 6, 9]. Wise, however, has proposed that the behavioral effects of neuroleptic drugs result from blockade of central reward or reinforcement mechanisms, thus producing "anhedonia" [32]. It has been suggested that "anhedonic" effects of neuroleptics should be similar to the effects of withholding reward, as in the procedure known as extinction [32,35]. In a series of experiments Wise and his associates have demonstrated effects of the neuroleptic drug pimozide which were similar to the effects of withholding rewards such as brain stimulation [10,11], injections of stimulant drugs [4,36], or food [34,35]. However, most of these studies used continuous reinforcement. Schedules of intermittent reinforcement lead to more prolonged and characteristic patterns of extinction that may allow for more sensitive comparisons between the effects of neuroleptics and extinction. The present experiments were designed to extend the analysis of the possible anhedonic effects of pimozide in this way. Recently other workers have also made use of intermittent schedules to investigate the actions of pimozide [13, 18, 27].

Operant behavior of rats was maintained by a fixed-interval schedule of intermittent reinforcement. In the first experiment the reinforcer was food, and dependent variables included schedule-induced drinking from a continuously available water bottle. When rats receiving intermittently delivered food have available a water bottle they show excessive levels of drinking [7] and this behavior has been found sensitive to the actions of a variety of drugs [23]. In the second experiment the reinforcer was a train of electrical stimulation delivered to the lateral hypothalamus, the duration of which was under the control of the subjects [21]. The duration of stimulation provided a further dependent variable in the assessment of the actions of pimozide. The effects of several doses of pimozide were compared with the effects of withholding the reinforcer in individual reward omission sessions. Although fixed-interval schedules have been widely used for investigating the behavioral effects of drugs, including neuroleptics [15, 27, 30], little work has been re-

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ported which has compared these drug effects with the changes in fixed-interval behavior which occur during extinction [27].

EXPERIMENT 1

In this experiment the effects of pimozide were compared with the effects of reward omission in rats whose lever pressing was maintained by food reinforcement delivered on a fixed-interval 60 sec schedule.

METHOD

Animals

Three female hooded rats were used. Throughout the study they were maintained at 85% of their pre-experimental body weights which were 216, 273 and 286 g. Water was available at all times both in the home cages and in the experimental chambers.

Apparatus

The experiment was carried out in three two-lever operant chambers (dimensions 24×24×20 cm) each equipped with a food hopper set into the wall between the levers. A water spout was available in each chamber [22]. The chambers were housed in light and sound attenuating outer cubicles, and the experiment was controlled by standard electro-mechanical programming equipment which was situated in an adjacent room.

Procedure

The rats were trained to press the lever situated to the left of the food tray. This behavior was reinforced by the delivery of 45 mg food pellets. Throughout the experiment each pellet was accompanied by a brief (100 msec) flash of a light situated in the food tray. After several sessions during which each response produced a pellet the schedule was changed to a fixed-interval 60 sec (FI 60 sec) so that the first response to be emitted at least 60 sec after the preceding pellet delivery operated the pellet dispenser. Sessions were terminated after 60 pellet deliveries or after 4,600 sec had elapsed, whichever occurred earlier. After at least 14 daily sessions, when baselines of schedule-controlled responding and schedule-induced drinking appeared stable, the effects of reward omission and of several doses of pimozide (0.25, 0.5, 1.0, 2.0 mg/kg) were investigated.

Reward omission was studied during three separate individual sessions, the first of which occurred prior to drug administration, the second after each animal had received each dose of pimozide on one occasion and the third after each dose of pimozide had been received on a second occasion by each animal. In these reward omission sessions the FI 60 sec schedule produced a flash of the tray-light and operation of the pellet dispenser, but no food pellets were delivered to the tray. The schedule of food reinforcement was reinstated on the day immediately following a reward omission session.

Pimozide was prepared as a suspension using a vehicle of 1% Tween 80 dissolved in physiological saline. The drug was injected intraperitoneally in a volume of 1 ml/kg three hours prior to an experimental session. Each dose was administered to each rat on two occasions. The doses were given in a mixed order, and no dose was repeated until each dose had been given once. At least three control sessions intervened between drug sessions or between a drug session and a reward omission session. Injections of the vehicle were given three hours prior to all non-drug sessions.

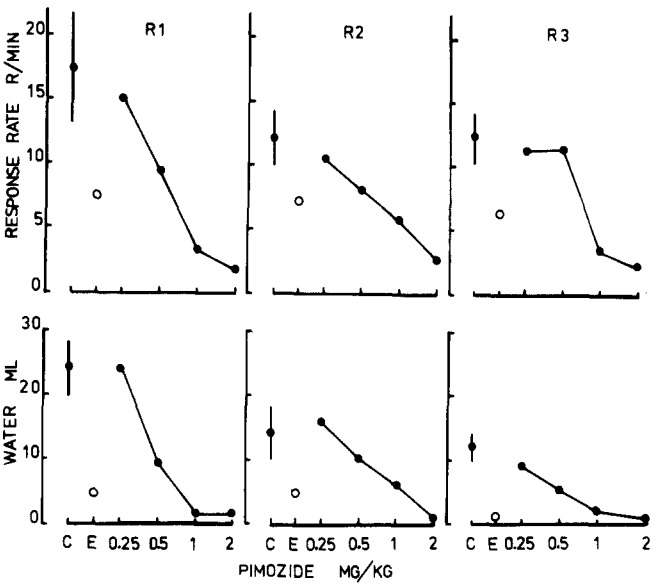

FIG. 1. The effects of several doses of pimozide and of reward omission on the overall response rates and volumes of water consumed for the three individual rats. Each dose of pimozide was given on two occasions. The points at E are the average values taken from three sessions when food was not available. C shows the means ± SD of values taken from the sessions immediately preceding drug sessions and reward withdrawal sessions.

RESULTS

The FI 60 sec schedule maintained patterns of responding which consisted of a pause after the delivery of each food pellet followed by either a constant or accelerating response rate until the next reinforcer was obtained. Schedule-induced drinking occurred after the delivery and consumption of the majority of food pellets. The effects of reward omission and the effects of pimozide on overall rates of lever pressing and also on volumes of water consumed by the three individual animals are presented in Fig. 1.

Reward omission resulted in a decrease in rates of lever pressing and volumes of water consumed during the session. Pimozide administration resulted in a dose-dependent decrease in these measures. The effects of pimozide upon these measures was generally greater than that of reward omission. The effects of reward omission and of pimozide upon the temporal patterning of responses are presented in Figs. 2 and 3. Figure 2 shows sample cumulative records from R2 to illustrate the patterns of lever pressing and licking at the water spout maintained by the FI schedule under control, drug and reward omission conditions respectively. It is apparent from the control record that regular patterns of lever pressing and licking were maintained by the schedule. There was a gradual decline in lever pressing over the session in the

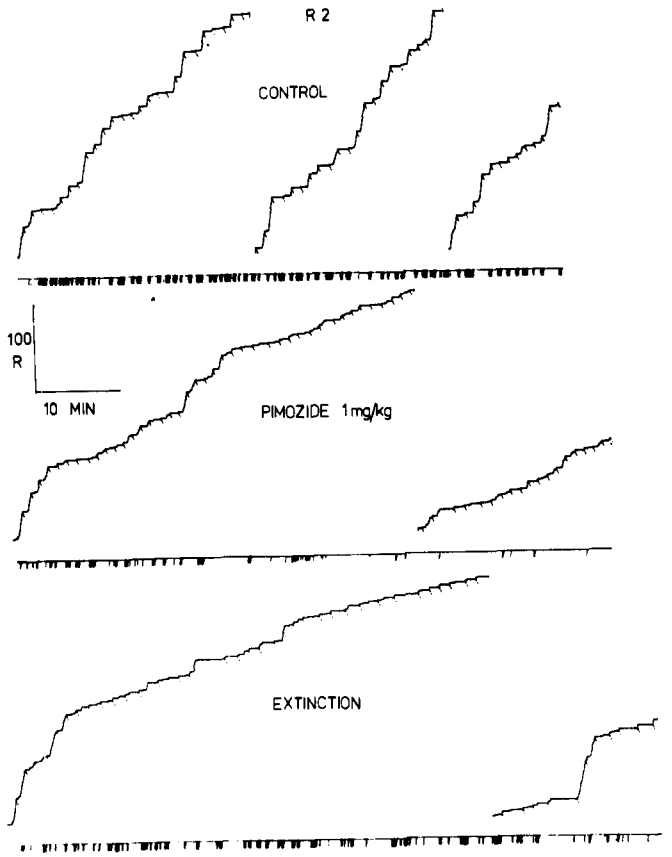

FIG. 2. Cumulative records illustrating the performance of one rat on the FI 60 sec schedule under control conditions, during a reward omission session (extinction) and after administration of a dose of pimozide. Both extinction and pimozide produced declines in responding as the session progressed. Deflections of the event pen show schedule-induced licking.

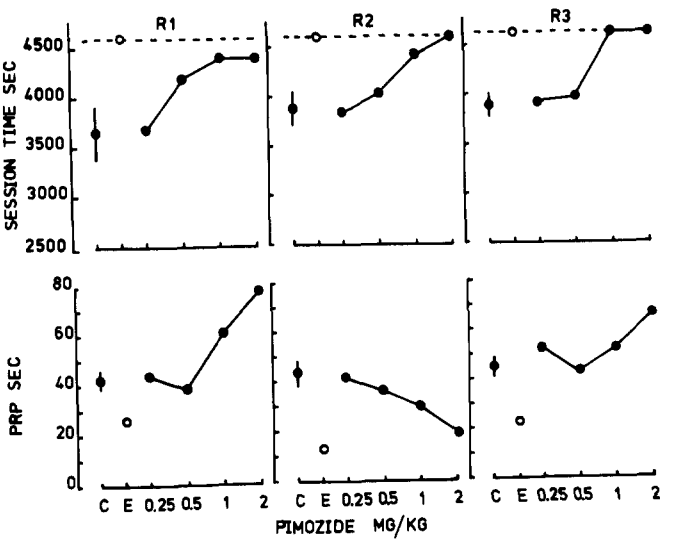

FIG. 3. The effects of several doses of pimozide and of reward omission on average session duration and average post-reinforcement pause duration in the three individual rats. The minimum session duration was 3,600 sec and sessions were terminated after 4,600 sec if 60 food pellets had not been obtained. See Fig. 1 for further explanation.

pimozide condition, reward omission had similar effects. Licking was decreased in both reward omission and pimozide conditions. However, in the pimozide condition licking occurred mainly in the early part of the session. No quantitative analysis of local licking rates was attempted. Figure 3 shows that in reward omission sessions the operant behavior of the subjects was reduced to the extent that the animals were removed from the chambers after 4,600 sec without having completed 60 fixed-intervals. The effects of pimozide on session duration are also presented. It is apparent from these data that although pimozide administration resulted in a dose-related increase in session duration, maximum session duration was only produced by the 1 mg/kg dose in R3, and the 2 mg/kg dose in R2 and R3. Post-reinforcement pause data are also presented in Fig. 3. Under control conditions the average duration of pauses was between 40 and 50 sec as typically occurs with an FI 60 sec schedule. During reward omission sessions the duration of pauses after the flash of the tray light and operation of the pellet dispenser was shorter than the average post-reinforcement pauses. Pimozide administration resulted in an increase in the average post-reinforcement pauses of two rats (R1 and R3) and a decrease in this measure for the third rat (R2). Observation of the animals during pimozide sessions showed that they always consumed the food pellets that were delivered.

Because it is known that under some circumstances repeated extinction sessions, even when widely separated, can produce cumulative effects the behavioral measures taken from the individual animals on each of the three reward omission sessions are presented in Table 1. The table shows that there were no systematic changes in any of the measures over the three sessions. Thus the average values presented in the figures provide an accurate representation of the effects of omitting food reinforcement. There were also no systematic differences between the behavioral changes which occurred on the two occasions when each dose of pimozide was administered. For the sake of clarity, therefore, data have not been presented for individual drug sessions.

DISCUSSION

In this experiment pimozide administration resulted in a decrease in responding maintained by an FI 60 sec schedule of food reinforcement. This result is consistent with other studies investigating the effects of neuroleptics on the operant behavior of rats [17]. The gradual decline in responding over the session when reward was omitted was also characteristic of the effects of pimozide. This result is similar to data reported by Wise and his co-workers [32,34]. Schedule-induced drinking was decreased by reward omission, and by administration of pimozide. However in the pimozide condition licking occurred mainly in the early part of the session. As no quantitative analyses of patterns of licking were carried out, however, this result is difficult to interpret. The

TABLE 1

BEHAVIORAL MEASURES DURING EACH OF THE THREE REWARD OMISSION SESSIONS IN THE THREE INDIVIDUAL RATS IN EXPERIMENT 1

	Extinction Session	Response Rate (R/min)	Session Duration (sec)	PRP (sec)	Water Consumed (ml)
	1	5.3	4600	34	5
R 1	2	12.0	4500	24	5
	3	5.3	4600	21	3
	1	11.2	4600	11	7
R 2	2	5.1	4600	8	3
	3	5.1	4600	20	3
	1	6.1	4600	27	2
R 3	2	7.1	4600	26	0
	3	5.5	4400	17	0

In each animal these sessions were separated by many sessions on which responding was reinforced by food.

effects of pimozide on measures of session durations and post-reinforcement pause durations appeared to differ in some respects from the effects of reward omission. The results of this experiment, therefore, are consistent with previous work showing differences between the effects of pimozide and extinction on fixed-interval responding [27].

EXPERIMENT 2

Wise and his colleagues have used various reinforcers in their attempts to support their "anhedonia" hypothesis of neuroleptic action [4, 32, 33, 35, 36], and have proposed that neuroleptic effects should mimic extinction whatever the reinforcer that normally maintains behavior. In attempts to avoid motor-decrement interpretations of neuroleptic action [1,9] measures of reinforcement that are independent of ongoing rates of responding have been used with intra-cranial electrical stimulation as a reinforcer [1, 12, 24, 25, 37]. This approach has not been combined with an analysis of neuroleptic action upon behavior maintained by an intermittent schedule of reinforcement such as FI 60 sec. In the present experiment an FI 60 sec schedule was used in which the reinforcer was electrical brain stimulation. The duration of the brain stimulation was under the control of the subjects, and provided a measure of reward which is independent of ongoing response rate. The purpose of this second experiment was to test the generality of the differences between reward omission and pimozide effects observed in the first experiment.

METHOD

Animals

Three female Wistar rats were used. The rats weighed between 200 and 250 g at the time of surgery. They were individually housed, food and water being constantly available in the home cages.

Surgery and Histology

The animals were implanted unilaterally with twisted bipolar electrodes (0.03 cm dia.) insulated except for a cross sectional area at the tip. The electrodes were implanted using a Kopf stereotaxic instrument. Stereotaxic coordinates were A.P. +0.53, LAT +0.16, VERT −0.38 based on König and Klippel [14]. Surgery was carried out under halothane anaesthesia in aseptic conditions.

Upon completion of the experiment the rats were sacrificed to verify electrode placement. Following perfusion of the heart with 0.9% saline followed by 10% Formalin the brains were removed. The frozen brains were sectioned at 50 μ and the sections were mounted and stained with haematoxylin.

Apparatus

The experiment was carried out in a two-lever operant test chamber (24×24×20 cm) equipped with a house light and a light above each lever. The chamber was housed in a light and sound attenuating chamber. A mercury-track commutator was used to connect the subjects to a constant current stimulator. Current level was continuously monitored on an oscilloscope connected through a 10 kΩ series resistor. Standard electromechanical programming equipment housed in an adjacent room was used to control the experiment.

Procedure

The rats were trained to press the left lever, this behavior was reinforced by the delivery of trains of sinusoidal electrical brain stimulation (50 Hz) at 36 μA for S1 and 70 μA for S2 and S3. Train-duration was equal to the duration of the lever-press that delivered reinforcement (to a maximum duration of four sec per train). Delivery of stimulation was paired with a light above the left lever which remained on for the duration of stimulation. When lever pressing was established the rats were transferred to an FI 10 sec schedule. The interval was then increased to 60 sec over two one-hour sessions. Subsequent sessions of FI 60 sec were terminated after the delivery of 45 reinforcers or after 3,600 sec had elapsed, whichever occurred earlier. After at least 14 days, when base-lines of schedule-controlled responding appeared stable, the effects of reward omission and of pimozide (0.125, 0.25, 0.5, 1.0, 2.0 mg/kg) were investigated. The procedures for drug administration and behavioral testing were as described for Experiment 1. In this experiment reward omission sessions were programmed identically to other sessions except that the stimulator was switched off.

RESULTS

The electrode placements of the three animals were confirmed histologically to be in the lateral hypothalamus (see Fig. 4). The effects of reward omission and pimozide administration upon session duration, rate of responding, and duration of brain stimulation are presented in Fig. 5. The data for S1 are from two reward omission sessions and single drug sessions for all but the 1 mg/kg dose which was given on two occasions. The implantation of the animal failed at this point and the animal was removed from the experiment.

Reward omission increased session duration to the maximum in each subject. Pimozide administration resulted in increased session durations but only in S2 at the highest dose was session duration increased to a maximum. In the reward omission condition response rate was decreased with each animal. Pimozide administration resulted in a dose-dependent decrease in response rate to levels similar to those

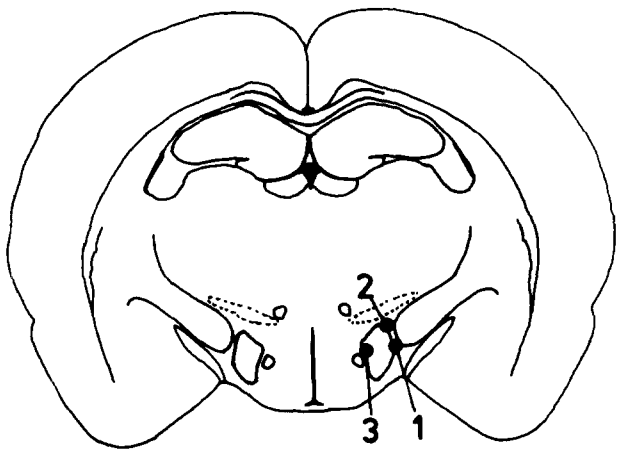

FIG. 4. Location of electrode tips in the lateral hypothalamus. Coronal section adapted from König and Klippel [14]. Numerals refer to specific placements of the three animals.

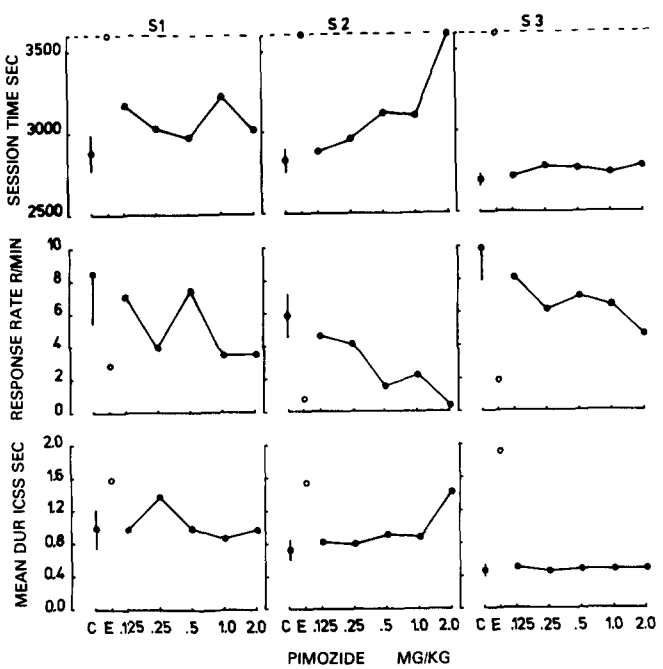

FIG. 5. The effects of several doses of pimozide and of reward omission on the average session durations, overall response rates and average duration of self stimulation for each of the three individual rats. Each dose of pimozide was given on two occasions. The points at E are the average values of three sessions when brain stimulation was not available. C shows the means ± SD of values taken from the sessions immediately preceding drug sessions and reward omission sessions. The data for S1 are from single administrations of each dose of pimozide except 1.0 mg/kg which was given on two occasions; and from two reward omission sessions (see text).

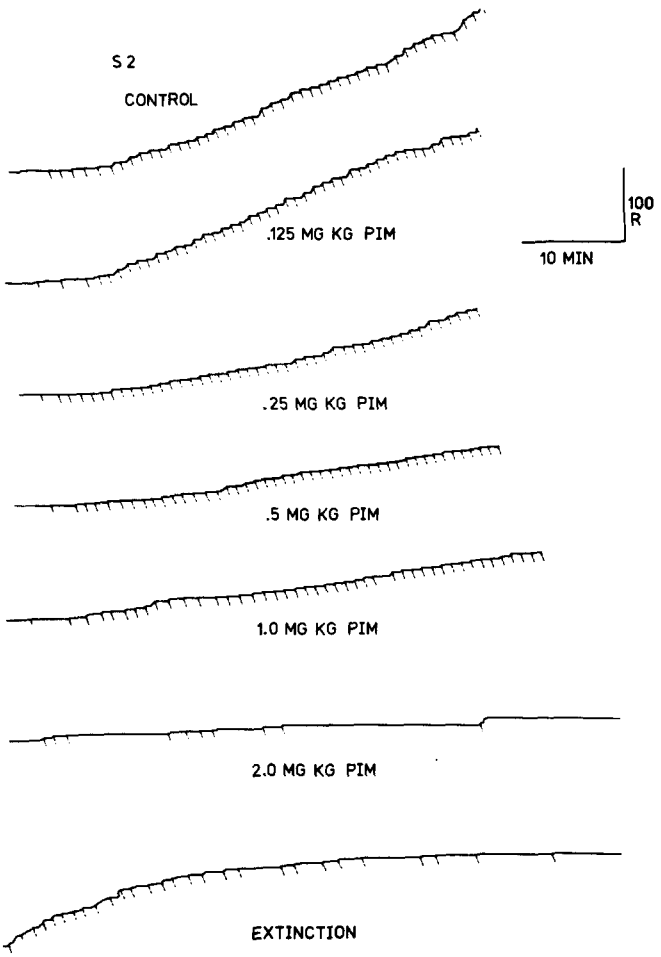

FIG. 6. Cumulative records illustrating the performance of one rat on the FI 60 sec schedule under control conditions, during a reward omission session (extinction) and after administration of each dose of pimozide. Extinction produced an increasing decline in responding over time whereas pimozide reduced responding evenly over the session up to the 2 mg/kg dose which markedly disrupted responding in this animal.

seen in the reward omission condition except for S3. With this animal pimozide failed to reduce response rate to the level seen with reward omission.

With all rats reward omission resulted in a marked increase in the duration of the lever press that normally delivered brain stimulation. The duration of brain stimulation was generally not changed by pimozide. In S2 at the 2 mg/kg dose there was an increase in this measure equal to the effect of reward omission. The 0.25 mg/kg dose resulted in an increase in this measure for S1. Post-reinforcement pause durations were recorded, but as reward omission had variable effects on this measure these data are not reported.

Sample cumulative records for control, drug, and reward omission conditions respectively (from S2) are presented in Fig. 6. From the control record it may be seen that electrical brain stimulation maintained typical behavior on an FI 60 sec schedule. The temporal patterning over the interval is similar

TABLE 2

BEHAVIORAL MEASURES DURING EACH OF THE REWARD OMISSION SESSIONS IN THE THREE INDIVIDUAL RATS IN EXPERIMENT 2

	Extinction Session	ICS Duration (sec)	Response Rate (R/min)	Session Duration (sec)
	1	1.86	3.8	3600
S 1	2	1.34	2.1	3600
	1	1.30	2.0	3600
S 2	2	1.52	0.3	3600
	3	1.86	0.3	3600
	1	2.26	2.2	3600
S 3	2	1.74	2.2	3600
	3	1.79	1.4	3600

In each animal these sessions were separated by many sessions in which responding was reinforced by electrical stimulation of the hypothalamus.

to that seen in Experiment 1, except that lower overall response rates were observed in the present experiment. Pimozide administration resulted in a dose-related reduction in responding throughout the session. Reward omission led to a characteristic gradual decline as the session progressed. This reward omission effect was never observed after pimozide administration.

Table 2 presents measures of behavior after individual reward omission sessions. In contrast to extinction of food reinforced behavior described in Experiment 1 there was a systematic decrease in response rates across the two or three sessions. There were, however, no systematic changes in the mean durations of the responses which would normally have produced brain stimulation. There were also no systematic differences between the effects of each pimozide dose with repeated administration.

DISCUSSION

In this experiment the rats' performance on an FI 60 sec schedule of electrical brain stimulation was observed to be similar to that maintained by food reward in the previous experiment. This supports the suggestion by Beninger *et al.* [2,3] that specialised training procedures [20] are not necessary to maintain extended schedule control with brain stimulation. The differences between the effects of reward omission and pimozide administration in the present experiment were greater than those observed in Experiment 1. There was little similarity in response patterning over the session between the two conditions. Reward omission consistently led to an increase in the duration of the lever-press that normally delivered brain stimulation, pimozide administration did not. In the two isolated cases where pimozide increased stimulation time this could not be interpreted as an extinction-like effect; one being at a low dose, and inconsistent with the effects of higher doses in the same animal, the other resulted from a dose at which the animal's behavior was markedly disrupted. Animals were removed from the chamber at maximum session duration in reward omission sessions. This effect was only observed with pimozide on one occasion at a dose that severely disrupted the behavior of one animal. The only similarity observed between the reward omission and pimozide conditions in this situation was a reduction in overall response rates.

Clearly no support for the proposal that pimozide blocks the rewarding properties of brain stimulation is provided by the results of this experiment.

GENERAL DISCUSSION

It has been demonstrated on a number of occasions that treatment with neuroleptics may result in behavior analogous to that associated with extinction [10, 11, 18, 33, 34, 35] or attenuation of reward [12, 24, 25]. However, the proposal that such effects are simply due to blockade of a reward system are not supported by the present results.

In Experiment 1 the temporal patterning of food-maintained behavior during drug sessions resembled the effects of reward omission but other measures appeared to be affected differently by the two variables. The differential effects of pimozide and of reward omission were seen even more clearly in Experiment 2. There were clear distinctions between pimozide and extinction particularly in the temporal patterning of lever pressing and the duration of brain stimulation. These data thus indicate that pimozide does not invariably produce extinction-like patterns of behavior.

The present findings are consistent with several other recent studies. Phillips and Fibiger [19] reported that a combination of haloperidol and extinction produced a greater disruption of responding maintained by either food or brain stimulation than either treatment alone. It was suggested that these additive effects demonstrated that neuroleptics have "multiple and complex effects upon operant behavior" not encompassed by the anhedonia hypothesis. Other recent studies have found similar results using pimozide and food-reinforced responding [13,18]. Also Tombaugh and his colleagues [27,28] reported that, in rats lever pressing for food, pimozide did not disrupt the performance of animals given injections of vehicle during training. Furthermore, rats shifted from pimozide to extinction displayed a pronounced increase in response rates, a phenomenon not observed in rats shifted from extinction to pimozide (see [33]).

Experiments in which responding has been maintained by electrical brain stimulation have previously provided the strongest support for an action of neuroleptics in blocking the central mediation of reward processes. This is because it is possible to differentiate between motor decrement and reinforcement modulation within self-stimulation paradigms [5, 12, 16, 24, 25, 26, 37]. Previous studies have suggested that drug effects on rate-independent measures reflect direct changes in the animal's perception of the level of reward [5, 12, 25, 26, 37]. The lack of congruence between these reports and the present results suggests that the schedule of reinforcement may be an important variable. It is possible, for example, that reinforcement density may be a significant determinant of the effects of neuroleptic drugs. In any event, the results presented here, together with recent data from other laboratories, demonstrate the utility of more complex behavioral analysis in investigating the mechanisms of action of such drugs.

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