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# Failure to Obtain Functional Equivalence Between Dopamine Receptor Blockade and Extinction: Evidence Supporting a Sensory-Motor Conditioning Hypothesis

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TOMBAUGH, T. N., C. SZOSTAK, P. VOORNEVELD AND J. W. TOMBAUGH. *Failure to obtain functional equivalence between dopamine receptor blockade and extinction: Evidence supporting a sensory-motor conditioning hypothesis.* PHARMAC. BIOCHEM. BEHAV. **16**(1) 67–72, 1982.—The effects of pimozide were tested in a discrete trial paradigm. Following 8 days of continuous reinforcement training with a retractable bar, subjects were divided into 3 groups: Vehicle-Extinction; Pimozide-Extinction and Pimozide-Reinforcement. Pimozide rats received 1 mg/kg of drug 4 hours prior to test. On each of 3 test days reinforcement continued to be delivered on a continuous reinforcement schedule for the Pimozide-Reinforcement Group whereas it was no longer delievered for the other two groups. Each test day was separated by 4 drug-free days. The Pimozide-Reinforcement Group showed the least response suppression, followed by the Vehicle-Extinction and Pimozide-Extinction Groups. These results do not support the anhedonic hypothesis that dopamine containing neurons mediate reward processes and were interpreted within a sensory-motor conditioning framework.

Dopamine receptor blockade  Extinction  Sensory-motor conditioning hypothesis

THE anhedonic theory proposed by Wise *et al.* [15,16] postulates that dopamine (DA) is the critical neurotransmitter underlying neural mechanisms of reinforcement. If this is correct, the pharmacological blockade of DA receptors should blunt the rewarding properties of stimuli and produce behavioral profiles similar to those resulting from the removal of reward (i.e., extinction). In accordance with this hypothesis Wise *et al.* [15] found that following CRF training, extinction produced a reduction in responding which paralleled that seen among rats who continued to receive reward following the administration of pimozide, a specific DA receptor blocker. This finding has since been frequently replicated [10, 14, 16]. Similar results have also been reported using the same schedule parameters but with a variety of different reinforcers [1, 3, 4, 17, 18].

While these experiments provide considerable support for dopaminergic involvement in reward processes, other research suggests that this effect may occur only when high density reinforcement schedules (e.g., CRF) are employed. For example, using fixed-interval and fixed-ratio schedules of reinforcement Tombaugh, Anisman and Tombaugh [12] reported that pimozide produced a *greater* degree of response suppression than observed with extinction. Comparable results have been reported using variable interval schedules with both pimozide [6,13] and haloperidol [10]. Finally, Tombaugh *et al.* [14] demonstrated that pimozide did not produce any substantial response decrements in rats which had received limited CRF training using a retractable bar. Unfortunately, the results of this study are not directly comparable to other CRF findings because of the relatively few number of training and testing trials and the absence of an extinction condition. Nonetheless, these data suggest that not only is the previously reported equivalence between pimozide and extinction restricted to high density reinforcement conditions, but that under certain conditions it may not even be observed with a CRF schedule. The present experiment was specifically designed to test this possibility.

## METHOD

### *Subjects*

Twenty-four naive male Sprague-Dawley rats purchased from the Holtzman Company served as subjects. Upon receipt from the supplier the animals were individually housed and maintained on ad lib food and water for three weeks. All subjects were approximately 90 days old and weighed between 350/400 g at the beginning of the experiment.

### *Apparatus*

Eight experimental chambers were used, each equipped with a 100 cfm Dayton blower for ventilation and white

noise. Each chamber (61 cm long×71 cm wide×74 cm high) was constructed of 1.91 cm plywood and sound insulated with acoustic ceiling tile. Interchangeable test cages could be positioned in the center of each chamber. General illumination was provided by a 24 VDC incandescent lamp (no. 1819) positioned behind an opaque plate which was flush with the top of the case. A retractable bar was mounted on the side of the test cage. The bar was calibrated for a 30 g force requirement and had a 1-sec cycle time. A standard Gerbrands pellet dispenser delivered a 45 mg Noyes pellet into the food tray. The aperture for the tray (4 cm×4 cm) was centered 5 cm to the left side of the bar and 6.5 cm from the cage floor. Located 2 cm above this opening was a 24 VDC magazine cue lamp (no. 1819) covered with an opaque lens.

*Procedure*

Throughout the experiment all rats were maintained on a restricted food intake of 15 g/day Purina Lab Chow. The feeding schedule began 10 days prior to the beginning of magazine training. Water was continuously available in the home cage throughout the experiment. However, water was not available in the experimental chambers. On each of the initial two days of the study, a food cup containing five 45 mg Noyes pellets was placed in the home cage to familiarize rats with the type of food to be used as reinforcement. Magazine training began on the next day and consisted of delivering a 45 mg Noyes pellet every 45 sec. Magazine cycles were accompanied by the onset of a 1.5 sec cue light and offset of the house light. Animals received 30 such trials on each of the two days. Barpress training began the following day. Presentation of a retractable bar marked the start of a trial. Depression of the bar resulted in the delivery of reinforcement and retraction of the bar. Failure to press the bar within 30 sec resulted in the retraction of the bar without a food pellet being delivered. A 30-sec intertrial interval followed the bar retraction. Each session consisted of 60 trials. After eight days of training, subjects were divided into 3 groups matched on the basis of mean response latencies over the last two baseline days. The groups were designated as follows: Vehicle-Extinction; Pimozide-Extinction; Pimozide-Reinforcement. Four hours prior to each test session animals in the two pimozide groups received IP injections of pimozide (1.0 mg/kg) while the remaining subjects were injected with the vehicle solution (1 ml/kg). The 1.0 mg/kg dose was selected on the basis of previous CRF experiments where pimozide and extinction produced comparable effects. Pimozide was dissolved in 2 or 3 drops of glacial acetic acid and a heated dextrose solution (5.5%) was added to make up the final volume (1 mg/ml). Reinforcement continued to be delivered on a CRF schedule for the Pimozide-Reinforcement Group, whereas it was no longer delivered for the Vehicle-Extinction and Pimozide-Extinction Groups. The hopper and magazine light continued to operate during the extinction condition. Three test days were employed, each consisting of 120 trials. Each test day was preceded by four drug-free baseline sessions. Animals were run 5 days a week with test days on the fifth day. Number of responses and latency to respond were recorded.

## RESULTS

The number of barpresses in eight 15 trial blocks are shown in Fig. 1. An analysis of variance appropriate to a split plot design having one between effect (drugs) and two within effects (test day, and trials) was performed. The Geisser-Greenhouse conservative F test was used [7] resulting in adjusted degrees of freedom for the within effects. All main effects were statistically significant: Drug: $F(2,21)=27.90$, $p<0.01$; Days: $F(1,21)=47.06$, $p<0.01$; Trials: $F(1,21)=59.94$, $p<0.01$. (It should also be noted that the Pimozide-Reinforcement Group consumed the food pellet on each trial.)

The trial effect represented a tendency for the number of barpresses to decrease over trials and the days effect was due to the fewer number of barpresses occurring over successive test days. The drug effect showed that the Pimozide-Reinforcement Group emitted the most barpresses while the Pimozide-Extinction Group barpressed the least. Newman-Keuls paired comparison tests revealed that all differences between the three groups were statistically significant, $p< 0.05$. The interpretation of the main effects must be qualified because of significant drug × trial interaction, $F(2,21)=3.46$, $p=0.05$, which was due to a tendency for the differences among the drug groups to increase over trials. A significant days × trial × groups interaction also occurred, $F(2,21)=3.79$, $p<0.05$, indicating that somewhat different drug × trial effects occurred on each day. Clearly, some of the differences over days can be attributed to the Pimozide-Extinction Group which (1) decreased more rapidly than the other groups and (2) started at a lower level on each day. The remaining differences are attributable to the performance of the other two groups (Pimozide-Reinforcement and Vehicle-Extinction). Since one the main purposes of the experiment was to compare these two groups simple effects tests were performed over successive blocks of trials on each test day in order to examine the relationship between the two groups. On Days 1 and 2 there were significant drug effects, Day 1: $F(1,14)=4.63$, $p<0.05$; Day 2: $F(1,14)=6.10$, $p<0.05$, and trials effects, Day 1: $F(1,14)=11.76$, $p<0.001$; Day 2: $F(1,14)=15.60$, $p<0.001$; but no significant drug×trial interaction: Day 1: $F(1,14)=2.25$, $p>0.05$, Day 2: $F(1,14)=2.01$, $p>0.05$. On day 3 only the trial effect was significant, $F(1,14)=16.18$, $p<0.01$.

The mean barpress latency for all three groups on Day 1 are presented in Fig. 2. In order to assess response initiation latencies on trials when animals actually barpressed, non-response trials were eliminated from the analyses rather than assigning them a maximum score of 30 sec. Latency data are not presented for Days 2 and 3 owing to the high proportion of non-response trials. A repeated measures analysis of variance was performed over the latency data for the Pimozide-Reinforcement and Vehicle-Extinction Groups. (Group Pimozide-Extinction was excluded from the analysis because the large number of non-response trials prohibited obtaining reliable estimates of performance, and the data are presented in Fig. 2 only for descriptive purposes). Only the trial and drug × trial effects were reliable: Trial: $F(1,14)=19.67$, $p<0.01$; Drug×trial: $F(1,14)=5.64$, $p<0.05$. The trial effect is attributable to a general increase in latencies that occurred over trials. The significant interaction is due to the fact that the latencies for the Vehicle-Extinction Group were extremely low during the initial part of the session and then rapidly increased over the remaining portion of the session while the scores for the Pimozide-Reinforcement Group showed a less dramatic change. Newman-Keuls pairwise comparisons showed that the latency for Group Vehicle-Extinction was significantly shorter on the first block of trials than those for Group Pimozide-Reinforcement but were significantly longer on the last trial block, $p<0.05$.

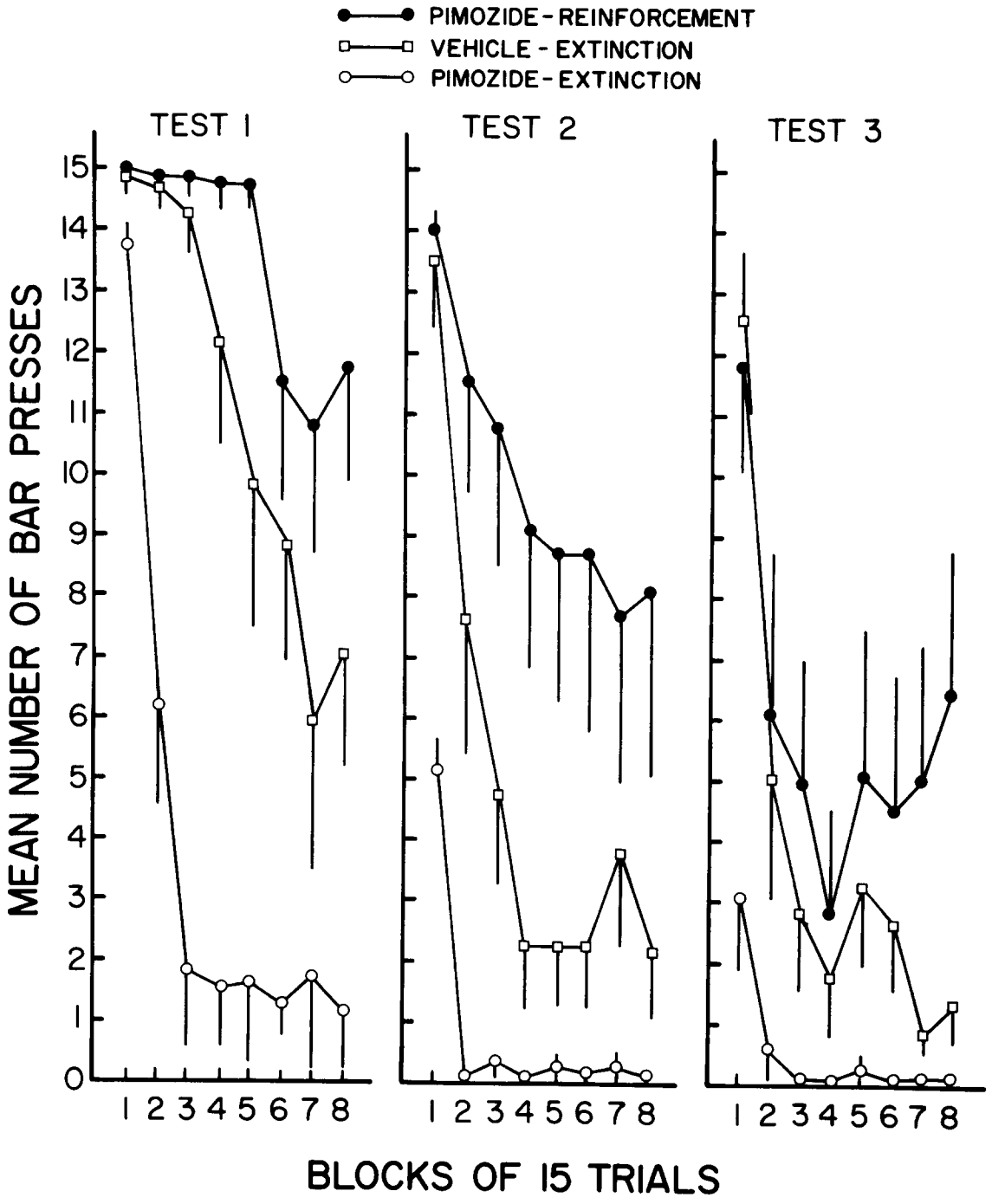


FIG. 1. Mean number of barpresses (±SEM) averaged in blocks of 15 trials for each of three test sessions. Following 12 days of CRF barpress training two groups of rats were injected with 1.0 mg/kg of pimozide and 4 hours later tested under either reinforced or nonreinforced (extinction) conditions. A third group was administered vehicle and tested under extinction. Four days of baseline responding separated test days.

## DISCUSSION

The current study is one of a series of experiments designed to determine the degree to which pimozide and extinction produce comparable behavioral effects. While a high degree of functional equivalence was initially reported, subsequent experimentation has indicated that this behavioral similarity may be specific to the continuous reinforcement schedule employed in all of the early investigations. The present results further restrict the generality of the original findings by demonstrating that even under a CRF schedule

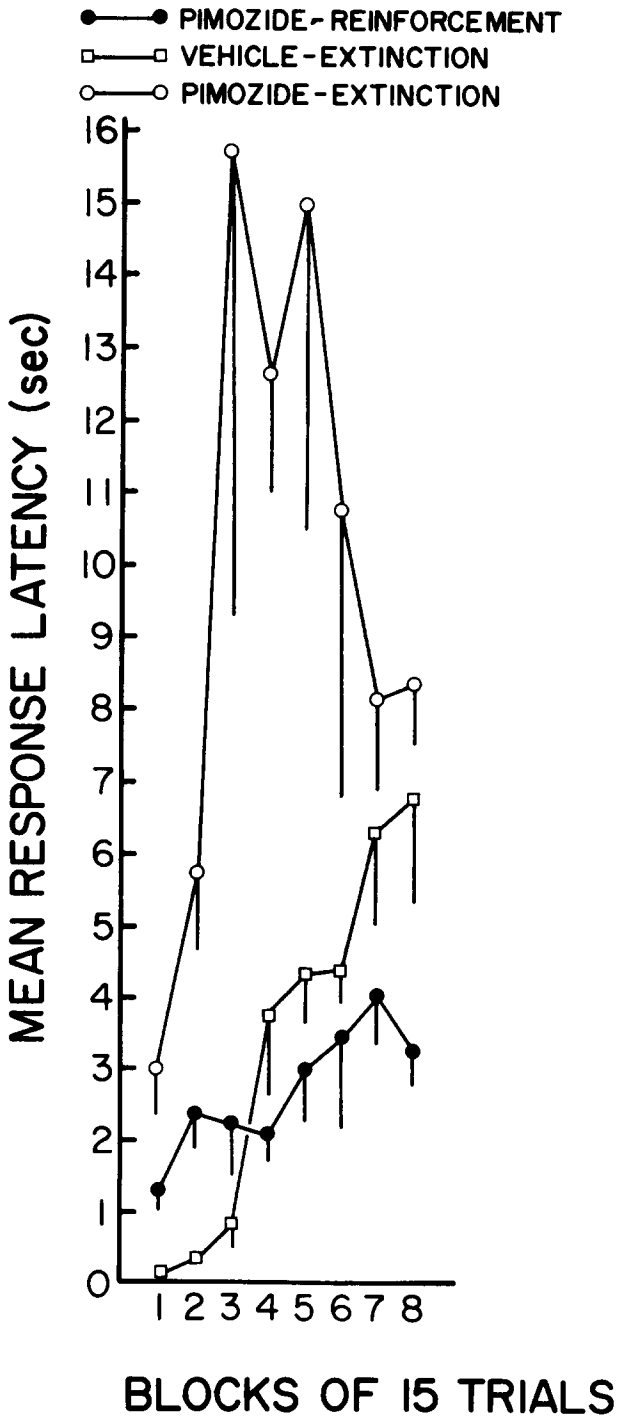


FIG. 2. Mean Latency (±SEM) to initiate barpresses in blocks of 15 trials for test session 1. Only latency data from response trials were included. Two groups of animals were injected with 1.0 mg/kg of pimozide and 4 hours later were tested under either reinforced or nonreinforcement (extinction) conditions. A third group was administered vehicle and tested under extinction.

pimozide effects are not always comparable to those produced by extinction.

The relationships exhibited among the three groups are also directly relevant to the anhedonic theory which postulates that the pharmacological blockade of DA receptors blunts the hedonic properties of rewarding stimuli, thus producing a state functionally akin to extinction. Consequently, pimozide-reinforcement and vehicle-extinction conditions should produce comparable patterns of behavior—a prediction supported by several studies using a fixed manipulandum and a CRF schedule. However, these findings are inconsistent with those presented here and it is difficult to understand how the anhedonic theory can explain the fact that the Pimozide-Reinforcement Group emitted a significantly greater number of responses than the Vehicle-Extinction Group. Moreover, if the two conditions are functionally equivalent then comparable response latencies would be expected, rather than the trial × groups interaction observed in Fig. 2.

One possible explanation of these results is that the 1.0 mg/kg dose of pimozide did not sufficiently reduce the rewarding properties of food. In this regard, it should be noted that most studies providing support for the anhedonic theory have used the same dose. Moreover, the effectiveness of this dose is illustrated in the present experiment by the bar press data for the Pimozide-Extinction Group as well as the increased response latencies observed during the early trials for the Pimozide-Reinforcement Group. It is also possible that secondary reinforcers may have maintained performance to a greater degree in Group Pimozide-Reinforcement than Group Vehicle-Extinction. However, according to Gray and Wise [6] pimozide not only blunts primary reinforcers but also reduces the secondary reinforcing (incentive motivational) properties conditioned to environmental stimuli, presumably through a process functionally equivalent to extinction. Consequently, the effects of pimozide on secondary reinforcers in the Pimozide-Reinforcement Group should be similar to those produced by extinction in Group Vehicle-Extinction. Thus, it dose not appear that the superior performance of Group Pimozide-Reinforcement can be attributed to secondary reinforcement processes. It is equally difficult to see why the performance of Group Vehicle-Extinction is higher than that of Group Pimozide-Extinction if pimozide "extinguished" the incentive motivational properties of stimuli. The performance of these two groups should be equivalent. Perhaps the integrity of the anhedonic theory can be maintained by assuming that pimozide reduces the strength of secondary reinforcers in Group Pimozide-Extinction by some process other than, or in addition to, extinction. This being the case, it remains to be explained how the presentation of food (Pimozide-Reinforcement Group) can overcome the powerful effects which pimozide exerts on the utilization of secondary reinforcement and still assume that pimozide blunts the primary rewarding properties of food.

In the present study the auditory and visual cues associated with the presentation and retraction of the bar are critical in explaining the lack of congruence that exists between the current data and those previously obtained using a fixed bar. These stimuli naturally elicit strong attentional and approach tendencies. This is evident in both the high operant level associated with the retractable bar as well as the fact that 80% to 90% of the animals in our laboratory learn to barpress without the aid of hand shaping. In addition to the natural eliciting properties of the retractable bar, the pairing

of the bar with food delivery makes it a discriminative stimulus for the subsequent presentation of reinforcement and as such may play a critical role in determining the behavioral effects of pimozide. The importance of stimulus control has been demonstrated in both simultaneous [13] and successive [11] discrimination experiments where pimozide did not disrupt accuracy of performance even though it reduced responding by as much as 80%. Moreover, Franklin and McCoy [5] demonstrated that presentation of previously established discriminative stimuli can temporarily reinstate pimozide-suppressed responding. In the present study it is likely that the attentional or discriminative aspects of the retractable bar was sufficient to ensure that pimozide-injected animals would continue to approach and press the amount of control exerted by the stimuli associated with the retractable bar was sufficient to insure that pimozide-injected animals would continue to approach and press the manipulandum during early test trials. However, responding was only maintained when food continued to be administered. Otherwise an abrupt cessation of responding occurred.

Comparison of these results with those previously obtained with a fixed bar suggests that without powerful eliciting stimuli animals do not overcome the decreased responsiveness produced by pimozide, even though responding may produce rewarding stimuli. It also indicates that pimozide may cause sensory deficits which make the animal inattentive to all but the most salient or biologically significant stimuli. This suggestion is consistent with the sensory-motor integration theory posited by Marshall *et al.* [8]. They reported that DA-depleted rats, who demonstrated a marked impairment in the integration of sensory information with motor performance, were able to overcome these deficits when provided with various forms of sensory stimulation.

Taking all of the above factors into consideration the present experimental findings provide little support for the view that blockade of dopamine receptors directly blunts the rewarding attributes of appetitive stimuli. Consequently, an alternative explanation for the effects of pimozide will be offered which assumes that the effects of pimozide and extinction do *not* reflect the same process, but rather reveal the existence of two different processes. This model focuses on the sensory-motor consequences of pimozide and is based on the well documented fact that pimozide causes a variety of different motor dysfunctions (e.g., akinesia, catalepsy). This interpretation assumes that pimozide-induced motor impairments influence performance in two ways. First, pimozide reduces the animal's capability for responding or makes it more difficult to respond. Second, when an animal actually performs a response the resulting motoric feedback produces an unpleasant or aversive condition reducing the animal's motivation to continue to respond. This lowered motivational level could be caused by any one of several mechanisms. Perhaps merely responding in the presence of pimozide is aversive [9], or alternatively pimozide may increase the amount of response-produced fatigue [2]. In any case, responding for food in the presence of pimozide has two consequences—(1) a positive or rewarding effect produced by food and (2) an aversive or punishing effect associated with performing the actual physical response. Essentially, the animal is placed in a conflict situation where performance is jointly determined by the relative strengths of these two factors. Accordingly, variables which increase appetitive motivation (e.g., reward magnitude, deprivation) should decrease the amount of pimozide-induced suppression, whereas conditions which increase the aversive consequences of responding (e.g., drug dose and physical effort) would tend to increase the amount of suppression.

Finally, the aversiveness associated with responding in the presence of pimozide becomes classically conditioned to the environmental test situation. The strength of this conditioning increases with successive trials causing the amount of inhibitory control exercised by the environment to increase over trials. This produces the progressive decline in responding observed to occur between test days, as well as within individual test sessions. This explanation is contrasted to that offered by the anhedonic theory which assumes that the similar response decline observed between the pimozide-reward and vehicle-extinction conditions occurred because pimozide decreased the rewarding attributes of response contingent stimuli. While this interpretation may be adequate in previous CRF experiments, it is difficult to apply to the present study, particularly in respect to the pimozide-extinction condition where the progressive effects were observed even though reward was absent. It is equally hard to understand how such an interpretation is relevant where intermittent schedules of reinforcement were employed during training and the pimozide-extinction condition also produced a progressive response decrement during testing [10,12].

In conclusion, it should be emphasized that although motivational variables play a central role in this model, pimozide does not produce its motivational effects by decreasing the rewarding value of food. To the contrary, response decrements are initially caused by a decreased ability to respond. Continued responding in the presence of pimozide produces a decreased motivational level that further inhibits performance. As previously indicated, the degree to which these inhibitory effects are demonstrated depends upon the (1) level of appetitive and aversive motivation, (2) amount of stimulus control exercised by the environment and (3) degree of conditioning.

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