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Effects of Pimozide on Accuracy of Performance and Distribution of Correct Responding on a Simultaneous Discrimination Task in the Rat[1]

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TOMBAUGH, T. N., M. A. RITCH AND D. T. SHEPHERD. *Effects of pimozide on accuracy of performance and distribution of correct responding on a simultaneous discrimination task in the rat.* PHARMAC. BIOCHEM. BEHAV. 13(6)859–862, 1980.—After training rats in a simultaneous discrimination problem, pimozide, a dopamine receptor blocker, was administered to determine whether accuracy of performance would be disrupted. Each animal received five doses of pimozide (vehicle, 0.05, 0.10, 0.30, and 0.60 mg/kg) delivered in a Latin Square sequence with five non-drug days between injections. Pimozide did not disrupt well established discrimination behavior at any of the doses even though a decrease in rate of responding was observed at the two higher doses. These results provide additional evidence that DA neurons are not essential in the mediation of previously learned associations.

Pimozide Simultaneous discrimination Learning Dopamine Rats

ONE strategy commonly used to determine whether dopaminergic (DA) neurons are involved in learning processes is to assess various changes that occur during pharmacological blockade of DA receptors. The neuroleptic drug pimozide frequently has been employed in this context because of its relatively specific action on dopamine receptors [2,6]. However, it is unclear whether its well documented ability to suppress responding in simple runway or bar-press tasks [11, 12, 13] actually represents an interference with associative processes or more appropriately reflects the effects of such nonassociative variables as the rewarding (motivational) attributes of stimuli and sensory-motor functioning. In an attempt to separate these factors Tombaugh [10] used pigeons in a successive discrimination task where it is generally assumed that response accuracy (percent correct) measures the degree to which associations between correlated stimuli are learned, while rates of responding measure the influence of nonassociative variables. Although pimozide produced the previously reported decrease in response rate, it did not decrease response accuracy. Similarly, Franklin and McCoy [4] found that pimozide did not alter the significance of a discriminative stimulus which originally had been acquired in a drug-free state where electrical self-stimulation served as the rewarding stimulus. Both results suggest that DA is not critically involved in the maintenance of an association learned prior to the introduction of the drug. The generality of this conclusion, however, may be somewhat restricted since both studies used similar conditioning procedures where the status (on-off) of a cue signalled the appropriateness of initiating or inhibiting the response. That is, while DA neurons may not be critical in situations where only the initiation or inhibition of a response is required, it is quite possible that they may be intimately involved when these two response tendencies are simultaneously present and animals are provided with the opportunity to select the appropriate stimulus on each trial. To test this possibility the present study used a two-bar simultaneous discrimination problem where a cue signals which alternative response is appropriate (e.g., left or right) rather than whether or not a single response should be performed (go, no-go). The current paradigm offers the additional advantage of assessing whether pimozide produces perseverative responding. Since previous research has shown that DA systems are involved in stereotyped responding [9], it might be expected that pimozide could produce position (bar) preferences.

METHOD

Subjects

Sixteen 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 120 days old and weighed between 400–450 g at the beginning of the experiment.

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TABLE 1
ACCURACY OF RESPONDING DURING BASELINE AND TREATMENT

Percent correct	Dose (mg/kg) of pimozide				
	Vehicle	0.05	0.10	0.30	0.60
Baseline	98.0 (±0.50)	97.9 (±0.49)	98.0 (±0.38)	98.1 (±0.52)	97.6 (±0.52)
Treatment	97.4 (±0.70)	97.8 (±0.62)	96.3 (±1.07)	93.4 (±1.79)	94.6 (±1.39)

Apparatus

Eight experimental chambers were used, each equipped with a 100 cfm Dayton blower for ventilation and white noise. Each chamber (61×71×74 cm) 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 and general illumination was provided by a 24 V DC incandescent lamp (no. 1819) positioned behind an opaque faceplate which was flush with the top of the cage. A retractable bar was mounted on the side of test cage one. The bar was calibrated for a 30 g force requirement and had a 1-sec cycle time. A standard Lehigh Valley pellet dispenser delivered a 45 mg Noyes pellet to an aperture located to the left side of the bar. Located immediately above this opening was a 24 V DC magazine cue lamp (no. 1819) covered with an opaque lens. The second test cage contained two fixed Gerbrands bars. Each bar was calibrated for 30 g force. The bars were mounted to the side wall of the test cage 4 cm above the floor separated by 15 cm center-to-center. A 24 V DC lamp (no. 1819) with an opaque jewel was located 5.5 cm above each bar. A Gerbrand pellet dispenser delivered 45 mg Noyes pellets into a 4.5 cm square aperture 2 cm above the grid floor and centered between the two bars.

Procedure

Preliminary training. Seven days prior to the beginning of the experiment all subjects were placed on a daily restricted feeding schedule of 15 g of Purina Laboratory Chow. Magazine training 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 two days. Bar-press training began on the following day. At intervals of 45 sec a retractable bar was presented for 45-sec periods on 30 successive occasions. Depression of the bar resulted in the delivery of the reinforcer and retraction of the bar. Failure to bar-press resulted in bar retraction at the end of the 45-sec period without a food pellet being delivered. Subjects which had fewer than 30 responses after two days of training were manually shaped to bar-press. On the two following days animals were trained under a variable ratio (VR) 5 and VR 10 schedule of reinforcement. Sixty reinforcements per day were delivered.

Discrimination training. On each trial the cue lamp positioned above each bar was illuminated (lamp-on) for 30 sec while the other cue lamp was not illuminated (lamp-off). The illumination of either the left or right lamp was varied randomly from trial to trial. For half the subjects lamp-on was associated with a 15 sec variable interval (VI 15 sec) schedule of reinforcement while no reinforcement was delivered during lamp-off. This relationship was reversed for the remaining half of the animals. Each session consisted of 100 trials and animals were run seven days a week. Rates of responding and accuracy of responding (percent correct) were judged to be stable after 20 days. Following this, subjects were tested five times with each test day preceded by five drug-free baseline sessions. On test days, each animal received one of five intraperitoneal (IP) injections of pimozide (vehicle, 0.05, 0.10, 0.30 and 0.60 mg/kg) determined by a Latin Square design. Pimozide was dissolved in acetic acid and dextrose (5.5%) added to make up a volume of 0.6 mg/ml. For the smaller doses the solution was diluted so that the final amount of solution injected was 1 ml/kg. The animals were placed in the experimental chambers four hours after injection.

RESULTS

Accuracy scores were computed by dividing the number of responses that occurred during reinforced (S+) periods by the total number of responses and multiplying this proportion by 100. A 100% score represents error free responding while 50% represents a total lack of stimulus control. Table 1 shows the mean level of accuracy (±SEM) during baseline (average accuracy on the two days prior to injection) and drug condition. Since subsequent analyses showed that the condition of the cue lamp associated with either S+ or S− failed to produce differential effects, $F(1,14)<1$, the data in Table 1 were collapsed across these conditions. Inspection of this table shows that the high degree of baseline accuracy was not altered by any of the pimozide doses. This observation was confirmed by an analysis of variance performed over scores representing percent change from baseline. Degrees of freedom appropriate to a Geisser-Greenhouse [7] conservative F-test were employed, $F(1,14)=3.53$, $p>0.05$.

The mean number of responses during S+ periods for both baseline and drug days are shown in Fig. 1 for each bar position (left and right). This figure shows (1) baseline responding was constant across drug treatments and (2) the two higher doses (0.30 and 0.60 mg/kg) produced a substantial response decrement. Furthermore, it is clear that the distribution of responses between the two bars was not altered by any of the drug doses. Subsequent analyses of variance performed over these data, transformed to percent of baseline scores (baseline responses/pimozide responses), showed only a significant dose effect, Cue on-off: $F(1,14)=3.02$, $p>0.05$; Dose: $F(1,14)=33.27$, $p<0.001$; Bar position: $F(1,14)<1.0$. A within session analysis was performed on the percent of S+ baseline responding that occurred over five consecutive six-minute test periods. The level of responding remained a constant 100% for the three lower doses. However, the two higher doses produced a different profile. A substantial decrease in accuracy observed during the first period (75% and 40% of baseline for

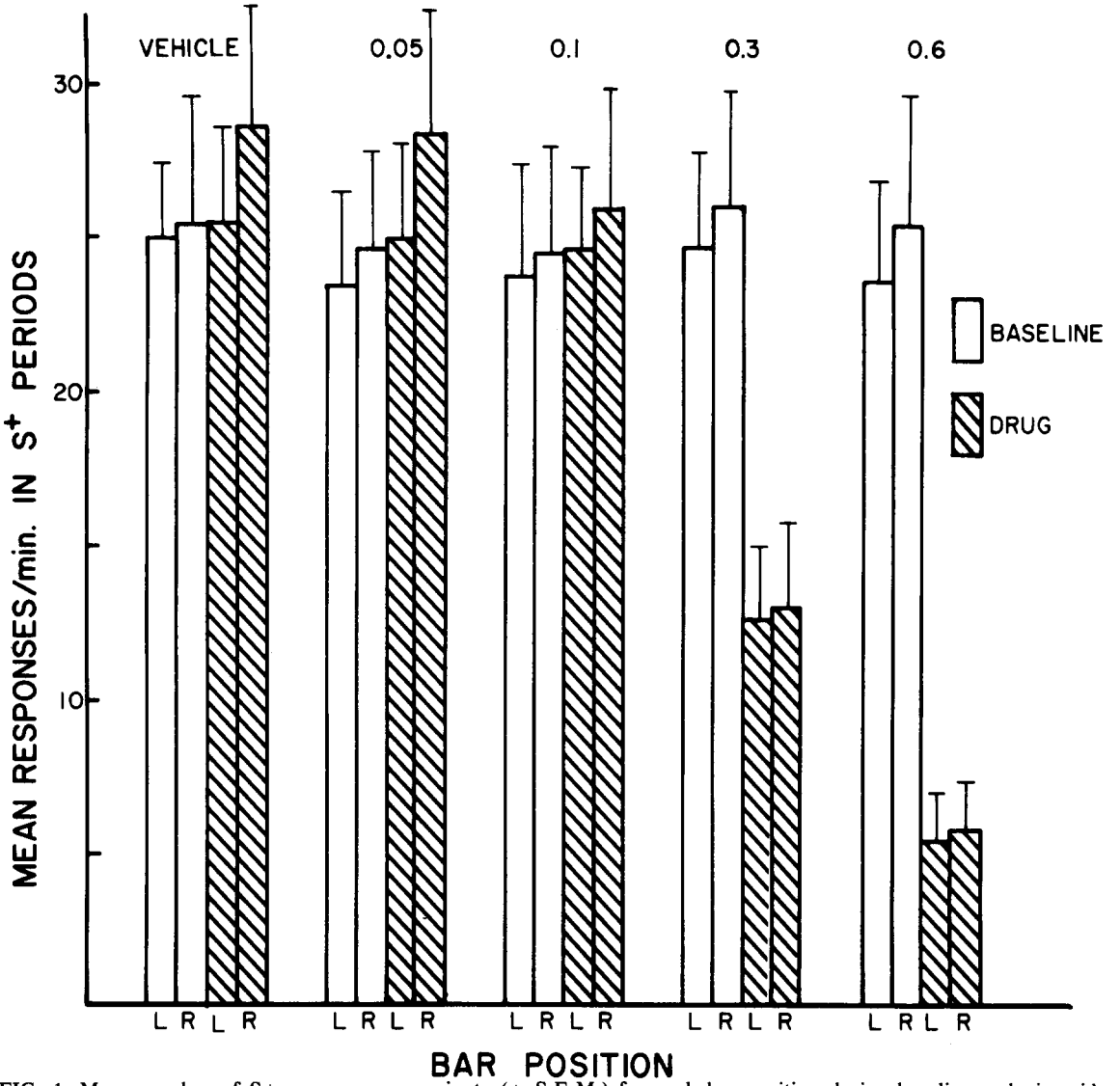

FIG. 1. Mean number of S+ responses per minute (± S.E.M.) for each bar position during baseline and pimozide treatment. Baseline was calculated as mean number of responses per min during the 2 days preceding a pimozide injection. Each animal received five pimozide injections (vehicle, 0.05, 0.10, 0.30, and 0.60 mg/kg) delivered in a Latin Square sequence.

0.3 and 0.6, respectively) was followed by a significant decrease in the second period, $Fs(1,14)=11.20$ and 6.93, $p<0.05$. No further response decrements were observed during the rest of the session.

DISCUSSION

The major finding of the present study is that pimozide did not disrupt well established discrimination behavior even though a substantial decrease in rate of responding occurred at higher doses. This relationship between maintained accuracy and decreased responding also has been reported using a successive discrimination problem with pigeons [10]. The within session decrements are also quite consistent with the previous study [10] suggesting that the pharmacological action of pimozide and the demand characteristics of the experimental situation interact to determine the final behavioral effect (cf [8, 10, 13] for a more complete discussion of this issue).

The congruence of the results between these two studies is important because it clearly demonstrates that the inability of pimozide to disrupt inhibitory and excitatory control over behavior is not limited to a single procedure or species. Moreover, the current data show that the response suppressing effect of pimozide did not interfere with the animal's ability to locate and accurately track significant cues within the test environment. This is well illustrated by the fact that decrements in responding were not accompanied by a change in the distribution of responses between the two manipulanda. Figure 1 and the accompanying analyses also showed that there was no tendency for pimozide to produce any type of perseverative responding. Inspection of data for individual subjects who had developed position preferences during baseline showed a similar effect. That is, pimozide did not modify the degree of position preference but rather proportionally reduced the number of responses to each bar. This is contrasted to previous experiments which have reported that response stereotypies can be induced by manipulating dopaminergic systems [9]. Thus, regardless of the types of nonassociative factors which may have been operating at higher doses to induce response suppression, they

exerted a symmetrical influence over choice behavior.

Finally, the current results are consistent with the data reported by Ahlenius and Engel [1] showing that pimozide did not affect choice performance in aversive conditioning. In addition, they are commensurate with other data [3,4] indicating that pimozide does not block the utilization of previously learned stimulus associations in appetitive or aversive situations. Overall, these results lead to the provisional conclusion that pimozide does not disrupt associations acquired in a drug-free state and suggest that DA-containing neurons are not essential in mediating previously learned stimulus associations. This conclusion has important implications for the dopamine theory of reward proposed by Wise [13,14]. The "anhedonic" theory assumes that reward processes are mediated by dopaminergic systems and predicts that blockade of dopamine receptors should block rewarding attributes of stimuli. Consequently, the administration of pimozide to animals who are responding for food should produce equivalent effects to those observed under extinction (nonreward) conditions. While this functional equivalence between pimozide and extinction has been repeatedly observed with continuous reinforcement (CRF) schedules [12, 13, 14], experiments employing intermittent schedules of reinforcement uniformly have shown that pimozide produces a more rapid cessation of responding than extinction [5,11]. Although this latter effect is difficult to explain solely on the basis that pimozide blocks the anhedonic or rewarding properties of food, it is possible that pimozide exerted its influences by reducing the effectiveness of *both* primary and secondary rewarding stimuli. Thus, it could be argued that the decrease in density of reinforcement which occurred when an intermittent schedule of reinforcement was employed, as contrasted with a CRF schedule, increased the importance of other maintaining, situational stimuli [5]. Within this framework the burden of explanatory power rests on the effects which extinction and pimozide have on secondary rather than primary reinforcement. Consequently, the finding that under conditions of intermittent reinforcement, pimozide produces a greater cessation of responding than does extinction can be readily explained by assuming that pimozide causes a greater decrease in the strength of secondary reinforcement. Presumably pimozide renders situational cues less effective by somehow weakening the previously conditioned association that exists between situational cues and reinforcement. One implication of this hypothesis is that pimozide should also diminish the amount of stimulus control observed in a discrimination situation by weakening the previously established association between the S+ and reinforcement. Consequently, animals should redistribute their responses so that proportionally fewer occur during S+ periods. Such a prediction is clearly at variance with the results of the present experiment where pimozide did not alter the distribution of responses. Even when the highest dose produced a 75–80% decrease in the absolute level of responding, 95% of the emitted responses were still assigned to the S+ bar. This unaltered amount of S+ control shows that pimozide did not change the degree to which animals used acquired cues to direct their responding.

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