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A Comparison of the Effects of Pimozide and Nonreinforcement on Discriminated Operant Responding in Rats

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BENINGER, R. J. *A comparison of the effects of pimozide and nonreinforcement on discriminated operant responding in rats.* PHARMAC. BIOCHEM. BEHAV. **16**(4) 667–669, 1982.—Some controversy surrounds the interpretation of the effects of dopamine receptor blocking drugs on conditioned operant responding. To assess the motoric versus the reinforcement-reducing consequences of these compounds, the effects of pimozide (1.0 mg/kg) and nonreinforcement on discriminated operant responding were compared. Rats were trained extensively on a successive discrimination implemented with the use of a multiple schedule. Rats subsequently injected with pimozide showed a significantly greater decrease in responding in the nonreinforced component than control rats showing that pimozide produces a decrease in general level of behavioral arousal. Additionally, pimozide injection resulted in an extinction-like decrease in reinforced responding over three test sessions indicating a reduction in the effects of reinforcement. However, animals treated with pimozide continued to discriminate. Transfer between pimozide and nonreinforcement was not observed probably because of the differential effects of the two procedures on behavioral arousal. Dopaminergic neurons may influence both general behavioral arousal and the effects of reinforcement but not stimulus-stimulus associative learnings.

Pimozide Extinction Reinforcement Successive discrimination Dopamine Multiple schedule Rats

ANIMALS treated with dopamine receptor blocking drugs are hypokenetic [8] and in addition show an extinction-like decrease in conditioned operant responding [4, 5, 9]. It has been suggested that this indicates a blockade of the normal effects of reinforcement [9] which are to enhance the incentive motivational properties of neutral stimuli [3]. By definition, incentive stimuli facilitate operant responding [3]. This incentive type of learning may be mediated by different neuronal mechanisms than stimulus-stimulus associative learning since dopamine receptor blockers fail to affect this latter form of learning [1, 2, 5, 7].

To further test this possibility the present experiment was undertaken to compare the effects of a high dose of pimozide (1.0 mg/kg) to those of nonreinforcement on a well-trained successive discrimination in rats. The discrimination was implemented with the use of a multiple schedule in which signalled periods of response-contingent reinforcement (S+) alternated with periods of nonreinforcement (S−). Animals treated with pimozide should respond less in both components because of the hypokenesia produced by the drug. Additionally, they should show a cumulative decrease in S+ responding because of the effects of pimozide on reinforcement. However, pimozide-treated rats should continue to discriminate the two components because the drug fails to interfere with learned stimulus-stimulus associations.

In comparing the behavioral effects of pimozide and nonreinforcement, Wise *et al.* [9] reasoned that there should be transfer between these two conditions. In support of this hypothesis, these authors reported that animals given pimozide following three sessions of nonreinforcement responded less than animals given pimozide following training with reinforcement. A further purpose of the present study was to examine the possibility of transfer from several discrimination sessions with pimozide to nonreinforcement in the S+ as well as transfer in the other direction.

METHOD

Subjects

Eighteen male albino rats of the Wistar strain were housed individually in a climatically controlled colony room kept on a 12 hr light/dark cycle. When free-feeding, the rats weighed from 235 to 275 g and were maintained at 80% of these weights throughout the experiment by daily feeding with measured rations.

Apparatus

Three similar test chambers (23.4×20.4×19.5 cm), constructed of Plexiglas sides and top, aluminum plate ends and a grid floor, were outfitted with a lever (Scientific Prototype) that was 5 cm wide and located in the middle of one of the end walls at a height of 5.5 cm; the force requirement for the lever was approximately 0.1 N. A feeder cup was located to the left of the lever at a height of 1.5 cm. Each test chamber was located in a ventilated, sound-attenuating box illumi-

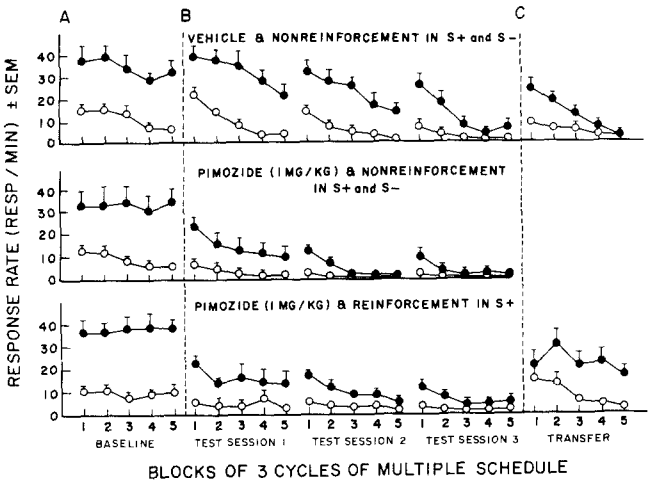

FIG. 1. A: Mean (±SEM) response rate (responses per min) for three groups of six rats on the successive discrimination during the twenty-fifth training session (Baseline). Sessions lasted for 30 min with 1-min S+ and S− components simply alternating; each point represents the average rate for 3 components for the group. Filled circles indicate S+ and open circles indicate S−. B: Mean response rate for each group in each component across 3 test sessions. The top group was injected with vehicle and tested with nonreinforcement in both S+ and S−; the middle group was injected with pimozide (1 mg/kg) and similarly tested; the bottom group was injected with pimozide (1 mg/kg) and continued to receive intermittent food pellets in the S+. C: Mean response rate for two groups in each component for one transfer session. The top group was switched to pimozide plus reinforcement in S+; the bottom group was switched to vehicle plus nonreinforcement in S+ and S−.

nated by an overhead light and fitted with a 2900 Hz tone generator (Sonalert). Environmental control and data collection were effected by solid state switching and timing devices (BRS/LVE).

Procedure

Thirty-min lever-press training sessions occurred at approximately the same time each day, five days a week. Each rat received 25 sessions of training on a successive discrimination with one-min components simply alternating, S+ being signalled by the tone (3 sec on, 3 sec off, etc.) and S− by the absence of the tone. During the S+, a response-contingent 45 mg Noyes Precision Food Pellet became available every 32 sec on the average. Thus, the schedule was a multiple random interval 32-sec extinction.

Following training, the rats were randomly assigned to three groups (N=6). The first group received an IP injection (1 ml/kg) of the pimozide vehicle, tartaric acid (40 μmol/ml) 4 hr prior to each session and was tested with nonreinforcement in both S+ and S−. The remaining two groups received an injection of 1.0 mg/kg of pimozide prior to each session; one group was tested with nonreinforcement in both components and the other received intermittent food pellets in S+.

On the following day, the possibility of transfer between pimozide and nonreinforcement was tested. The group that had received vehicle plus nonreinforcement in both S+ and S− was switched to pimozide and tested with food available in S+; the group that had received pimozide plus intermittent food pellets in S+ was switched to vehicle plus nonreinforcement in both components.

RESULTS

A cycle of the multiple schedule consisted of one S+ and one S− component. In order to observe intrasession changes, the data were analysed using 3-cycle blocks with 5 blocks per session. The mean response rate (resp/min) for each group in each component for each block for the 25th training session is shown in panel A of Fig. 1. The data indicate clearly that the three groups discriminated. Analysis of variance comparing the S+ rates for the three groups revealed no significant group differences, $F(2,15)<1$, $p>0.05$. Similarly, S− rates showed no significant differences among groups, $F(2,15)<1$, $p>0.05$.

The data from the 3 test sessions are shown in panel B of Fig. 1 and indicate that all groups continued to discriminate. S+ and S− rates were considered separately using three variable analyses of variance, the variables analysed being groups, sessions and blocks with the latter two as repeated measures. Rates in S− were higher for the vehicle group than for the 2 groups receiving pimozide, $F(2,15)=10.21$, $p<0.002$, with the latter two groups not differing significantly. Overall, S− rates declined both within, $F(4,60)=27.11$, $p<0.001$, and across sessions, $F(2,30)+18.61$, $p<0.001$; however, the groups differed marginally in the sessions effect, $F(4,30)=2.59$, $p<0.06$, the vehicle group showing the greatest decline, perhaps because its S− rates were higher in the first and second test sessions. In the S+ component, the rates of the vehicle group were higher than those of the two pimozide groups, $F(2,15)=11.00$, $p<0.001$, the latter two groups not differing significantly. Overall, S+ rates declined both within, $F(4,60)=28.16$, $p<0.001$ and across sessions, $F(2,30)= 25.30$, $p<0.001$.

The results of the transfer tests are shown in panel C of Fig. 1. When the vehicle plus nonreinforcement in both S+ and S− group was switched to pimozide and tested with food available in S+, there was no significant change in S+ or S− rates as compared to test session 3, $F(1,5)<1$, $p>0.05$ in both cases; nor were there any significant differences in S+ or S− rates when this transfer session was compared with test session 1 of the pimozide plus reinforcement in S+ group, $F(1,10)<1$, $p>0.05$ in both cases. When the pimozide plus reinforcement in S+ group was switched to vehicle plus nonreinforcement in S+ and S−, rates in both components increased as compared to test session 3, $F(1,5)=15.75$, $p<0.01$ for S+ and $F(1,5)=6.61$, $p<0.05$ for S−; however, when this transfer session was compared to test session 1 of the vehicle plus nonreinorcement in S+ and S− group, neither S+ nor S− rates differed significantly, $F(1,10)=2.06$, $p>0.10$ and $F(1,10)<1$, $p>0.10$, respectively.

DISCUSSION

The results showed that response rates in the S− component were reduced in groups treated with pimozide compared to the vehicle group and response rates in the S+ component for the pimozide plus nonreinforcement group were lower than the vehicle group. These data are in agreement with previous observations [4,6] and clearly show that dopamine plays an important role in general behavioral arousal. The cumulative decrease over sessions in S+ responding of the pimozide group that received reinforcement supports the hypothesis that pimozide blocks the ability of food to reinforce responding [9]. Previous studies have

shown that this decrease cannot be attributed to a buildup of pimozide with repeated dosing [4,9]. The observation that rats treated with pimozide continue to discriminate successive stimuli has not been reported previously; this finding is consistent with data from pigeons [6] and rats trained on a simultaneous discrimination [7] and is in agreement with data that show that dopamine receptor blockade does not affect stimulus-stimulus associative learning [1, 2, 5, 7].

The conclusion that dopamine is involved in general behavioral arousal has important implications for tests of transfer. Thus, the observation of transfer from vehicle plus nonreinforcement to pimozide plus reinforcement [6,9] and the lack of transfer in the other direction as shown here and by others [4,6] might be attributed to this variable. It may be possible to avoid this confound by comparing transfer rates to test session 1 rates of groups that began testing under the same conditions to which transfer occurred. However, the present results revealed no significant transfer in these comparisons. Perhaps there are contrast effects associated with the attenuation of behavioral arousal produced by pimozide; for example, responding during nonreinforcement may be elevated in rats undergoing several prior experimental sessions with pimozide. Whatever the variables involved, it appears that tests of transfer may not be appropriate tools for testing the hypothesis that treatment with pimozide mimics in part the effects of nonreinforcement.

In conclusion, dopamine neurons have at least two separate functions: one is a modulation of the level of general behavioral arousal; the other is to alter the incentive value of stimuli associated with reinforcement. It should be noted that once a neutral stimulus has become an incentive stimulus it for a time can act effectively in its capacity as a response facilitator even when dopamine function is blocked. Thus, trained animals treated with pimozide show extinction-like reductions in behaviour rather than immediately ceasing to respond.

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