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Pimozide Attenuates Acquisition of Lever-Pressing for Food in Rats[1]

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WISE, R. A. AND H. V. SCHWARTZ. *Pimozide attenuates acquisition of lever-pressing for food in rats.* PHARMAC. BIOCHEM. BEHAV. 15(4) 655–656, 1981.—Pimozide pretreatment produced a dose-dependent attenuation of acquisition of a lever-pressing habit motivated by food reward in hungry rats. No evidence of learning was seen in animals treated at 1.0 mg/kg, minimal learning was seen at 0.5 mg/kg, and retarded learning which ultimately did reach normal asymptote was seen at 0.25 mg/kg. Thus pimozide attenuates the response acquisition function as well as the previously studied response maintenance function of food reward.

Pimozide Reward

SELECTIVE dopaminergic receptor blockers attenuate lever-pressing for a variety of positive reinforcers, including food [1, 6, 8–12], intracranial electrical stimulation [3–5, 8] and intravenous psychomotor stimulants [2, 7, 13]. These demonstrations concern the effects of dopamine blockers on established habits, and it has been argued that since normally reinforcing events do not sustain responding under this drug treatment, the treatment attenuates one of the defining properties of a reward [2, 4, 5, 11–13]. While the ability to sustain a habit that is already learned is a critical property of a reward, the traditional defining property of reward is the ability to establish such a habit. If dopamine blockers attenuate the rewarding property of food, then they should attenuate response acquisition as well as response maintenance. While such a demonstration is not a sufficient condition for the argument that dopamine blockers attenuate reward function, it is a necessary condition; if response acquisition survives treatment with dopamine blockade, then it cannot be maintained that dopaminergic function is critical for the phenomenon of reward.

Tombaugh *et al.* [9] have reported survival of response acquisition under conditions of dopaminergic blockade. Their demonstration involved a retractable lever and a range of doses of pimozide which are known to block the response maintenance seen in a fixed lever task. It appears possible that this was an inappropriate range of doses for this task, however; conversely, it may be that this was an inappropriate task for this range of doses. Since this is the only response acquisition study in the literature in which positive reinforcement is challenged by dopamine blockade, the present study was undertaken to explore further the effects of dopamine receptor blockade on food-rewarded response acquisition.

METHOD

Subjects were 32 adult, male, Sprague-Dawley rats. They were housed individually and maintained in individual cages on a 22 hour food deprivation schedule. After one week of acclimation to this schedule, a series of once-weekly lever-press training trials was begun. Training was given 4 hours after treatment with pimozide or tartaric acid vehicle with 6 drug-free days between each of the four to eight training trials. Four groups were assigned doses of 0 (tartaric acid control), 0.25, 0.5, or 1.0 mg/kg of pimozide, respectively.

Each training session lasted 45 minutes and was performed in standard operant chambers with 45 mg Noyes pellet reinforcement. A reinforcement was earned by each lever press, and, in addition, "free" pellets were administered on a variable interval 1-min schedule during the initial sessions. A learning criterion of 150 responses was set and as soon as an animal reached this criterion, the "free" pellets were discontinued. Response counts were taken at 5-min intervals. Training continued for eight training trials or until responding reached the level of 200 responses for three consecutive days.

RESULTS

Response acquisition is shown in Fig. 1. Tartaric acid-treated control subjects reached asymptotic response levels by the second test session. Animals treated with the low (0.25 mg/kg) dose reached the same asymptote by the fifth test session. Animals trained under 0.5 mg/kg showed signs of learning but never reached the normal asymptote of responding; animals trained under the high dose (1.0 mg/kg) failed to show any signs of learning to lever-press.

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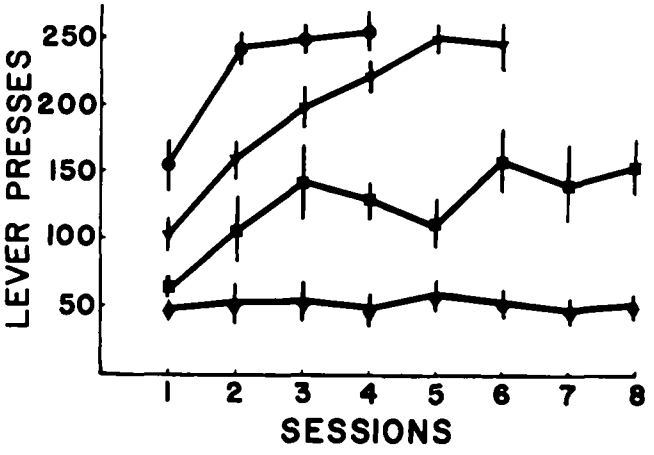

FIG. 1. Mean and standard error data for each session as a function of pimozide dose or tartaric acid injection. Circles—tartaric acid control condition; triangles—0.25 mg/kg pimozide; squares—0.5 mg/kg pimozide; diamonds—1.0 mg/kg pimozide.

Scores for the first four days were compared by analysis of variance and revealed significant effects of treatment, $F(3,28)=4.57, p<0.001$, and of days, $F(9,84)=2.64, p<0.001$. The treatment × days interaction was also significant, $F(9,84)=7.53, p<0.001$.

DISCUSSION

These data show clearly that pimozide causes a dose-related impairment of acquisition in a food-reinforced lever-pressing task. From this experiment alone it is not possible to say whether pimozide interfered with reinforcement, memory, or response processes; however other studies make it clear that memory and lever-pressing capability are adequate for this task at these pimozide doses. For example, lever-pressing performance is normal in animals trained under continuous reinforcement when they are tested for the first time under the present pimozide doses [12]; this shows that these pimozide doses do not impair memory or response capacity sufficiently to limit responding to the degree seen in the present study. At these same pimozide doses, however, and after ample time for drug clearance, responding does not remain normal in trained animals tested over four repeated drug tests [12]. This finding, taken with the present finding, indicates that the rewarding effects of food are not normal in pimozide-treated animals. Neither of the two defining properties of reinforcement are met in this task under these pimozide doses. Food neither serves to motivate the acquisition of the lever-press habit (either normally in the case of the 0.5 mg/kg dose, or at all in the case of the 1.0 mg/kg dose) in naive animals nor serves to sustain it in well trained animals [12]. Thus it seems clear that the reinforcing impact of food is compromised by these doses of pimozide.

It is equally clear from the literature that the reinforcing impact of food is not completely blocked at these same pimozide doses. The present data indicate that 1.0 mg/kg of pimozide retards acquisition of lever-pressing, but tests of savings would be required to determine that no learning at all occurred in this condition. Since animals will acquire a lever-pressing habit at the same dose of pimozide when a retractable lever is used (though they acquire it abnormally slowly), it seems clear that food still has some reinforcing impact even in animals tested at 1.0 mg/kg [9]. This is confirmed by the fact that while responding (for food or for brain stimulation reward) is not maintained at 1.0 or 0.5 mg/kg of pimozide, extinction is nevertheless prolonged by the presence of the usual food [6, 9, 12] or stimulation [4].

It is also possible that some degree of performance incapacitation is present at these pimozide doses. However, it is clear from the performance of well-trained animals on the first day of testing that such performance incapacitation as might accompany these doses is not sufficient to account for the degree of response abnormality seen in the present study. The fact that animals so treated are capable of 200 responses per session, considered against the fact that they fail to learn to make even 100, makes it clear that there is a motivational deficit in pimozide-treated rats.

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