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# Effect of Pimozide on the Improvement in Learning Produced by Self-Stimulation and by Water Reinforcement[1]

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WHITE, N. AND R. MAJOR. *Effect of pimozide on the improvement in learning produced by self-stimulation and by water reinforcement.* PHARMAC. BIOCHEM. BEHAV. 8(5) 565–571, 1978. – When rats self-stimulate immediately after the training trial of an appetitive task their performance on a retention test is improved the next day. In the present study, this improvement was blocked by pretraining injections of pimozide, a dopaminergic blocker. In a second experiment, injections of pimozide retarded learning on the same task when the learning was reinforced by drinking water, but had no effect on learning which occurred in the absence of a reinforcer. The data made the hypotheses that the animal's behavior was a result of an action of pimozide on sensory or motor mechanisms, or that the drug produced state-dependent effects, highly unlikely. We concluded that neural systems involving dopamine mediate an effect of reinforcing events on behavior.

Self-stimulation Dopamine Pimozide Neuroleptic drugs Reinforcement Learning Memory

THERE has been considerable recent speculation about the role of dopamine (DA) and of the neural systems containing DA in behavior. Among the different functions that have been attributed to these systems by various investigators are: the control of the initiation of forward locomotion [4, 6, 20, 21, 28]; the mediation of the expression in behavior of certain generalized [2,10], or specific [3, 17, 30] motivational states; the integration of sensory-motor relations [15]; and the mediation of the ability to perform in situations which require some form of learning [8, 11, 23, 31]. Although it is sometimes difficult to distinguish among these hypotheses operationally, there has been a real question about whether the DA-containing neurons subserve some aspect of response elaboration or if a higher psychological function can be attributed to them (see [20, 21, 22, 25]). The data of the present study suggest that at least some of these neurons mediate certain effects of reinforcement on behavior.

In a recent paper [16] we described an experiment in which water-deprived rats bar pressed for reinforcing electrical self-stimulation of the lateral hypothalamus immediately following a single trial on a water-finding task. Twenty-four hr later the performance of these rats on the retention test was improved significantly over the performance of rats that did not self-stimulate after an identical training trial. When the self-stimulation session was delayed for 1 hr after the end of the training trial, the improvement in performance was significantly less than after immediate self-stimulation. We interpreted these findings as a retroactive improvement in memory produced by the self-stimulation. Additional experiments showed that self-stimulation with electrode placements in the nigro-neostriatal bundle or in area A9 of substantia nigra improved the rats' performance on retention tests, but that similar rates of self-stimulation, implying similar reward strength, with electrode placements in the medial part of LH or in the preoptic area had no effect on retention test performance. These findings led to the hypothesis that the nigro-neostriatal bundle may mediate the effects of brain stimulation reinforcement on memory, a suggestion that has also been made by Routtenberg [26].

The nigro-neostriatal bundle has been identified as a dopamine-containing system by all of the atlases of the catecholaminergic systems in the rat [12, 14, 19, 27], and it is highly likely that dopamine is the neurotransmitter at the synapses formed in the striatum by the fibers in this bundle [5]. If it is true that the effect of self-stimulation on memory is mediated by activation of these fibers, it should be possible to block this effect with pimozide, a drug which produces a reasonably specific blockade of post-synaptic dopamine receptors in the striatum [1], and a dose-dependent debilitation of bar pressing for reinforcing brain stimulation in the same dose range [13, 24, 25, 29]. In Experiment 1 we tested this hypothesis using a dose of

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pimozide (0.3 mg/kg) which produces a partial blockade of DA receptors. This dose was also known, from preliminary studies in our laboratory and from the studies cited above, to be just below the dose range in which large decreases in rates of bar pressing for lateral hypothalamic stimulation are observed.

## EXPERIMENT 1

### METHOD

*Animals*

The animals were 77 male, hooded rats weighing 300 to 350 g. Each was implanted with an electrode made from a single length of 0.15 mm rigid stainless steel wire, aimed at the dorso-lateral part of the lateral hypothalamus (deGroot [7] coordinates: 4.6, 2.0, −1.3). The indifferent electrode consisted of four skull screws. Surgery was done under 60 mg/kg sodium pentobarbital using standard stereotaxic techniques. One week after surgery each of these rats met a criterion of 180 responses in 5 min on a standard bar pressing self-stimulation test. The stimulation current was 60 Hz sine wave delivered in 0.5 sec trains, and ranged between 60 and 85 $\mu$A in the different animals.

*Procedure*

The animals were divided into three groups: the rats in one group (N = 30) received IP injections of 0.3 mg/kg of pimozide (Janssen Pharmaceuticals); the rats in a second group (N = 22) received IP injections of the tartaric acid vehicle (pH = 3.0); and the rats in the third group (N = 25) were untreated: they received no injections. Each of these main groups was divided into two subgroups, one of which self-stimulated after the training trial, the other of which did not self-stimulate. Each of these subgroups was further subdivided into two: in each case the rats in one of these subdivisions drank water on the training trial, the rats in the other subdivision did not receive any water.

One week after initial self-stimulation testing the four day experimental procedure began. Water was removed from the rats' cages on Day 1. All rats were handled and given a few minutes of open field experience on Days 1 and 2. On Day 3 the rats in the pimozide and vehicle groups were injected, starting at 10:00 a.m.. Starting at 2:30 p.m. each rat was given a training trial (in the same order as the injections) in a wooden box (37 × 64 × 46 cm) with an alcove (11 × 13 × 46 cm) in the middle of one wall and a floor of metal rods. A standard metal drinking tube protruded from the end wall of the alcove. A drinkometer circuit, constructed locally with an operational amplifier, connected the drinking tube and the floor of the test apparatus, and signalled licking. Each rat was placed into a corner of the box and the amount of time taken to contact the drinking tube was recorded. For the experimental condition when the rats received water, they were allowed to drink for a total of 30 sec after contacting the tube, and were then removed from the apparatus. For the experimental condition when the rats did not receive water, the tube was dry. These rats were allowed to remain in the apparatus after their first contact with the tube until they returned to the alcove, and were removed while they were in contact with the tube.

Within 30 sec of removal from the apparatus each rat was placed into a bar pressing cage and connected to the stimulator. For the experimental condition which required self-stimulation the rats were allowed to make 1000 responses and were then returned to their home cages. For the experimental condition which did not require self-stimulation the rats were left in the bar pressing cages for 25 min with the stimulator disconnected, and were then returned to their home cages. In their home cages all rats were given access to water for 30 min.

On Day 4 no injections were given. Each rat was given a retention trial in the same order as on the previous day, starting at 2:30 p.m. During this trial the drinking tube in the test apparatus contained water for the rats in all conditions of the experiment. Each rat was placed into the test apparatus and the time taken to contact the drinking tube was recorded. If a rat failed to contact the drinking tube within 300 sec the trial was terminated and the rat was assigned a score of 300.

Upon completion of experimental testing the rats in the self-stimulation groups were killed with an overdose of ether, and perfused with physiological saline and 10% buffered Formalin acetate. Their brains were removed, fixed, frozen and sectioned at 30 $\mu$ in the area of the track left by the stimulating electrode. The sections were stained with formol-thionin.

### RESULTS AND DISCUSSION

All rats in the self-stimulation groups bar pressed at a rate of at least 180 responses per 5 min period during the post-training trial sessions, and there were no significant differences in the distributions of the rates of the rats in the three treatment groups. The stimulation currents used ranged between 90 and 120 $\mu$A in the pimozide and vehicle groups, and between 60 and 100 $\mu$A in the untreated group. The results of examining the histological material from these animals are shown in Fig. 1.

The behavioral data of the experiment – the mean latencies to contact the drinking tube on the retention trial – are shown in Fig. 2. The performance changes interpreted as an improvement in memory [16] can be seen clearly in the untreated and vehicle groups. There is a decrease in the latency to contact the water tube in the water-self-stimulation (W–SS) groups relative to their respective water-no self-stimulation (W–NSS) control groups. At the same time, there is an increase in the latency of the no-water self-stimulation (NW–SS) groups relative to their respective no-water no-self-stimulation (NW–NSS) controls. This pattern of differences is absent in the pimozide groups.

To analyze the data statistically the latency scores were treated with a logarithmic transformation, and a 3 × 2 × 2 analysis of variance was computed. The factors in the analysis were the three drug conditions, the two self-stimulation conditions, and the two water conditions. The three-way interaction among these factors was significant, $F(2,65) = 5.53$, $p<0.01$. Simple effects tests were done within each drug group. In the untreated group, the mean latencies for the rats in the two self-stimulation groups were significantly different, $t(11) = 6.36$, $p<0.001$. The mean latency for the W–SS group was significantly lower than the latency for the W–NSS control group, $t(13) = 3.07$, $p<0.005$, and the mean latency for the NW–SS control group was significantly higher than the latency for the NW–NSS control group, $t(8) = 3.47$, $p<0.005$. The same pattern of differences was apparent in the vehicle group. The mean latencies for the rats in the two self-stimulation groups were significantly different, $t(8) = 4.08$, $p<0.005$.

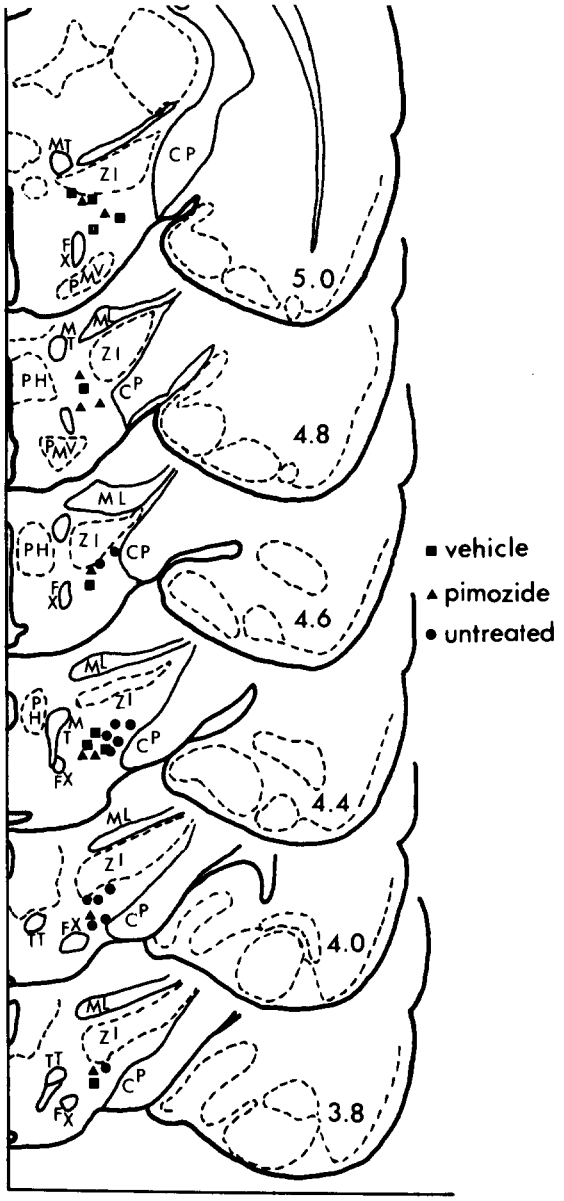


FIG. 1. Locations of the electrode tips for the rats in the three self-stimulation groups in Experiment 1. The numbers at the lower right of each section indicate its position in the anterior-posterior plane of the deGroot [7] atlas. Note that the placements for all three groups overlap within the dorso-lateral quadrant of the lateral hypothalamus, the area previously shown [16] to be the effective self-stimulation site for the memory enhancement phenomenon. Abbreviations: CP, cerebral peduncle; FX, fornix; ML, medial lemniscus; MT, mammillothalamic tract; PH, posterior hypothalamus; PMV, posterior ventral mammillary nucleus; TT, thalamo-tegmental tract; ZI, zona incerta.

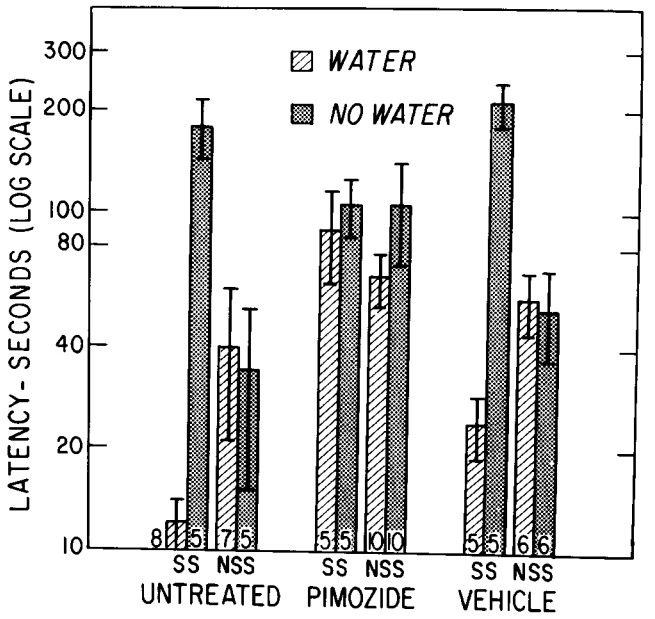


FIG. 2. Mean latencies to contact the drinking tube on the retention test of the rats in Experiment 1. The variability indicators are standard errors of the means. The numbers at the bottom of each bar show the N for each group. Abbreviations: SS, self-stimulation; NSS, no self-stimulationn.

The mean latency for the W–SS group was significantly lower than the latency for the W–NSS control group, $t(9) = 1.85$, $p<0.05$, and the mean latency for the NW–SS group was significantly higher than the latency for the NW–NSS control group, $t(8) = 3.47$, $p<0.005$. In the pimozide group none of these comparisons was significant.

An analysis of variance identical to the one described above was computed for the training trial latencies: no main effects or interactions were significant. Therefore, the various differences among the groups described above were not due to initial differences in the animals' latencies on the training trial. The test trial differences might also have been influenced by a residual effect of the pimozide, which could have produced motor impairment, or some related disability in the rats that received this drug. To check on this possibility additional simple effects tests were done comparing the test trial latency scores for the no self-stimulation groups with each other. The combined W– and NW–NSS latencies for the vehicle groups were not significantly different from the corresponding values for the untreated groups, $t(22) = 0.80$. However, the combined W– and NW–NSS latencies for the pimozide groups were significantly higher than the corresponding values for the untreated group, $t(30) = 3.93$, $p<0.005$. Therefore, pimozide did produce a residual increase in the test trial latencies. Although this residual effect could account for the absence of the expected decrease in the mean test trial latency of the rats in the pimozide W–SS group, it could not account for the absence of an increase in the NW–SS group, since both the pimozide residual and the expected effect of self-stimulation should have produced an increase in the latency of this group. Therefore, the lack of effect of self-stimulation in the pimozide groups was not a result of the residual increase in the latencies produced by the pimozide.

The interpretation of the effect of self-stimulation that was observed in the untreated and vehicle groups as an effect on memory is based on two main arguments. First, it is unlikely that the self-stimulation could have contingently rewarded the behavior of the animals in the test apparatus because the rats in all groups were removed from the test

apparatus while they were in contact with the drinking tube. The reduced latency of the rats in the water self-stimulation groups might have been produced by a contingent relationship between the response of approaching the tube and the rewarding consequences of the stimulation that began soon after the response was made. However, exactly the same contingency existed for the rats in the no water self-stimulation groups, and these animals had increased latencies on the retention test. Thus, the behavior of the no-water self-stimulation groups was incompatible with the contingent reward hypothesis. Second, in a previous paper [16], we reported an experiment similar to the one described here, in which the self-stimulation session was delayed for 1 hr after the training trial. Animals in this condition showed significantly less change in performance on the retention test than animals which self-stimulated immediately after the training trial. This suggests that the stimulation acts retroactively and not proactively; and that it acts on a consolidation gradient [18].

This explanation of the behavior changes produced by non-contingent self-stimulation is based on the assumption that the rats in the water and no water groups formed different sets of associations in the test apparatus during the training trial. For the rats trained in the water condition these associations represented the location of the familiar drinking tube in the test apparatus. For the rats trained in the no-water condition the associations formed included the information that the familiar drinking tube in the alcove was dry. In both cases, the behavior observed on the retention test can be understood on the hypothesis that the brain stimulation acted to strengthen these associations. Thus, the rats in the water groups quickly approached the drinking tube on the retention test, while the rats in the no-water groups explored the rest of the apparatus before entering the alcove, or simply failed to enter it at all

In the present experiment pimozide blocked the changes in performance that occurred following self-stimulation in untreated and vehicle treated animals. At least three hypotheses can account for this finding. It is possible that pimozide acted to impair the initial formation of the associations that constituted the memory. If the drug inhibited initial learning, there would have been no associations present to be strengthened during the self-stimulation session, and no change in performance on the retention test would have occurred. It is also possible that the associations that were formed under the influence of the drug on the training trial could not be retrieved in the no-drug state on the retention test. That is, the results may be a demonstration of state dependent learning. Finally, pimozide may have blocked the facilitatory effect of self-stimulation on the consolidation of the associations. Experiment 2 was done to distinguish among these three possible effects of pimozide.

## EXPERIMENT 2

### METHOD

*Animals*

Animals were 36 naive rats similar to those used in Experiment 1. None underwent any surgical procedures.

*Procedure*

The apparatus and the procedure, up to and including the first training trial, were identical to those described in Experiment 1. Immediately following the first trial all rats were returned to their home cages; 30 min later they were given access to water for 30 min. This procedure was repeated for six more days, giving a total seven identical trials.

There were three main groups. Each of the rats in one group (N = 12) received daily IP injections of 0.3 mg/kg pimozide 4.5 hr before testing on each of the first five days of the experiment, and injections of the tartaric acid vehicle on each of the last two days. Each of the rats in a second group (N = 12) received vehicle injections 4.5 hr before testing on each of the first five days, and injections of 0.3 mg/kg pimozide on each of the last two days. The rats in the third group (N = 12) were untreated for the entire seven days of the experiment. Each of these three groups were divided equally into a group that drank water on each of the daily trials, and a group that did not receive any water on the daily trials.

### RESULTS AND DISCUSSION

The mean latency scores for the rats in the six groups of the experiment are shown in Fig. 3. After the first two trials the difference between the water and the no water conditions is clear, showing that differential learning similar to that produced by self-stimulation after a single trial does in fact occur in this situation under natural conditions. Over the first five days pimozide had no effect whatsoever on behavior in the no water condition, but apparently retarded learning in the water condition. Switching the pimozide and vehicle groups on Days 6 and 7 had no apparent effect in the no-water condition, but may have had a small effect in the water groups.

Because of the extremely large differences between the data for the water and the no water groups, separate analyses of variance were computed for the two conditions. In addition, the data for Days 1–5 were analyzed separately from the data for Days 6 and 7. For the water groups, Days 1–5, the analysis of the log-transformed latencies showed a significant effect of days, $F(4,60) = 47.86$, $p<0.001$, and a significant effect of groups, $F(2,15) = 4.48$, $p<0.03$. Direct comparisons of the three groups showed that there were significant differences between the pimozide and untreated groups, $t(28) = 2.37$, $p<0.03$, and between the pimozide and vehicle groups, $t(28) = 2.78$, $p<0.005$. For the water groups on Days 6 and 7, there was significant effect of days, $F(1,15) = 7.77$, $p<0.05$, but the groups and interaction effects were not significant. For the no-water groups, Days 1–5, the analysis showed a significant effect of days, $F(4,60) = 14.64$, $p<0.001$. The main effect of groups was not significant. For Days 6 and 7, neither the days, nor the groups, nor the interaction effects was significant.

The only effect of pimozide in this experiment was to retard the decrease in the latency of the drug-treated group in comparison with the vehicle and untreated groups in the water condition. It it unlikely that this retardation was caused by motor impairment, or by an effect of the drug on the animals' motivational levels because if either of these factors had been operating it should have been observed in the vehicle group on Days 6 and 7 when the animals in this group received pimozide for the first time. For the same reason, we conclude that tolerance to the effects of pimozide did not influence these results.

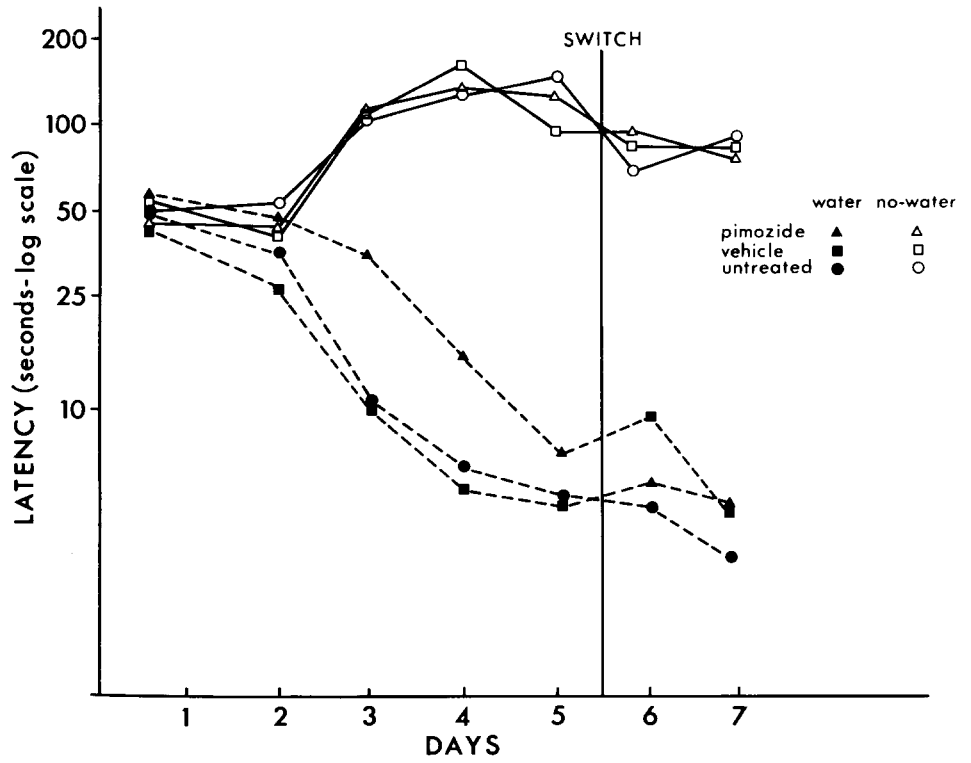


FIG. 3. Mean latencies to contact the drinking tube for the rats in the six groups in Experiment 2. Each group is represented by a continuous line. To the right of the line marked switch the symbols on some lines change to indicate that the injections given that group changed.

The role of state dependency in the results of this experiment can be assessed by a closer examination of the data for the groups that received pimozide on Days 1–5 and vehicle on Days 6 and 7. This switch had no apparent effect on the rats in the no-water group, but the means for the water group just before and after the switch suggest that state dependence may have had some influence on the data. To check on this possibility, post hoc $t$ tests were carried out. The mean latency for the rats in the pimozide group was not significantly different from the latencies for the vehicle or untreated groups on the last pimozide day; Day 6, pimozide vs vehicle: $t(10) = 0.89$; pimozide vs untreated: $t(10) = 1.23$. On Day 6, when the rats in the pimozide group were switched to vehicle, their mean latency was significantly higher than the mean for the untreated rats, $t(10) = 2.20$, $p<0.05$, one-tailed; (although significant, this test is inappropriate in the presence of the analysis of variance results reported above). The Day 6 mean for the pimozide group was not significantly different from the mean for the rats in the vehicle group, which received pimozide for the first time, $t(10) = 1.19$. As a further test for evidence of state dependence a comparison between the mean latency for the pimozide group on the last pimozide day, Day 5, and the first vehicle day, Day 6, was made. There was no significant difference between these means, $t(5) = 1.19$. In the absence of an overall behavioral pattern in both the water and no-water groups and given the extremely weak statistical support, we conclude that state dependence may have had a minor influence on the data of this experiment, but that it cannot have been a major factor governing the animals' behavior.

There remain two possible interpretations of the effects of pimozide in this experiment. It is possible that the drug impaired the formation of the associations necessary for the change in performance observed in the vehicle and untreated water groups to occur. However, it clearly had no effect on the formation of associations in the no-water condition, because if such an effect had been present the latencies of the rats in the no-water pimozide group would have increased at a slower rate than the latencies of the rats in the vehicle and untreated groups. Therefore, it seems unlikely that pimozide affects the formation of associations because this hypothesis implies that there is some qualitative difference in the way that the nervous system stores the associations formed in the water and the no-water conditions.

The second possibility is that pimozide blocked, or partially blocked the effects on behavior of the reinforcing features of the learning situation. To examine this hypothesis the nature of the learning situations in the water and the no-water conditions must be considered. In the water condition the 30 sec of drinking served as a reinforcer, and it can be argued that the pimozide blocked the retroactive, association-strengthening action of the water reinforcement on the associations formed during the first one or two trials. In the no-water condition, however, there was no reinforcing event present in the situation to strengthen the associations that were formed. The behavior change in this situation depended upon the rats learning that the familiar drinking tube in the alcove, from which they had obtained all of their water in the past, was dry in this situation. As there was no reinforcement in this condition no effect of

pimozide would be expected. Thus, the difference in the effect of pimozide in the water and no-water conditions is consistent with the hypothesis that this drug acted primarily to impair the ability of a reinforcer to strengthen associations.

## GENERAL DISCUSSION

The data of the two experiments described generally support the hypothesis that pimozide can block certain effects of reinforcers in learning situations. Experiment 2 showed that it is unlikely that the drug affects the formation of associations. Rather, the drug blocked the strengthening effect of a naturally reinforcing event on associations that were necessary to produce the observed change in behavior. In Experiment 1 pimozide blocked a similar strengthening effect of reinforcing brain stimulation. In this case, the brain-stimulation reinforcement was present in both the water and no-water conditions (as shown by the behavior of the vehicle and untreated groups on the retention test) so the effects of pimozide were observed in both conditions.

The most common assumption about the ability of reinforcing events to change behavior is that these events have positive or negative affective consequences which become associated with neutral stimuli or responses upon which they are contingent, resulting in changed behavior involving those stimuli and responses. As argued in Experiment 1, however, the hypothesis of a contingent relationship between the self-stimulation and the behavior of the rats on the water-finding task does not explain the animals' behavior. Therefore, the present data (and those of our earlier report [16]) raise the possibility that reinforcing events have another action as well: that they act retroactively to strengthen the associations formed by events that are contingently related.

In Experiment 1 it is likely that the self-stimulation was accompanied by positive affect which was contingent upon each response, and that this is why the rats pressed the bar at high rates. It is of interest that the dose of pimozide used had only a small effect on these rates of bar pressing, implying that it produced a minimal reduction in the rewarding effects of the stimulation. At the same time the pimozide completely eliminated the retroactive, association-strengthening action of the self-stimulation, as shown by the absence of behavior changes on the retention test in the rats which self-stimulated under its influence. Similarly, as argued in Experiment 2, the ability of rats to form associations was not affected by pimozide, but the normal strengthening action of a reinforcing event (drinking water) on these associations was impaired, as shown by the retarded acquisition of the water pimozide group.

The present data, together with our earlier findings [16], which implicate the nigro-neostriatal bundle in the strengthening action of reinforcers on associations, strongly support the hypothesis that this dopamine system, at least, plays an important role in learning. This conclusion is in general agreement with that reached by a number of other authors [8, 9, 11, 12, 22, 23, 31]. It seems possible, because of the close relationship between motivational states and behavioral reinforcement, that the motivational deficits described following lesions of the dopamine systems [2, 3, 10, 17, 30] could be results of the failure of reinforcers to act on associations involving instrumental behavior. However, it is unlikely that the sensory [15] and motor [4, 20, 21] deficits which follow the same lesions can be subsumed under the reinforcement function attributed to these systems here. Possibly different dopamine systems mediate the reinforcement and motor functions; or, the two functions may be mediated by the same system, which would imply that they are related.

## REFERENCES


1. Anden, E.-E., S. R. Butcher, H. Corvodi, K. Fuxe and U. Ungerstedt. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.* **11:** 303–304, 1970.
2. Antleman, S. M. and A. R. Caggiula. Norepinephrine-dopamine interactions and behavior. *Science* **195:** 646–653, 1977.
3. Baez, L. A., J. E. Ahlskog and P. K. Randall. Body-weight and regulatory deficits following unilateral nigrostriatal lesions. *Brain Res.* **132:** 467–576, 1977.
4. Clavier, R. M. and H. C. Fibiger. On the role of ascending catecholaminergic projections in intracranial self-stimulation of the substantia nigra. *Brain Res.* **131:** 271–286, 1977.
5. Connor, J. D. The nigro-neostriatal pathway: the effects produced by iontophoretic dopamine. *Pro. Soc. Res. nerv. Ment. Dis.* **50:** 193–206, 1972.
6. Cooper, B. R., G. R. Breese, L. D. Grant and J. L. Howard. Effects of 6-hydroxydopamine treatments on active avoidance responding: evidence for involvement of brain dopamine. *J. Pharmac. exp. Ther.* **185:** 358–370, 1973.
7. de Groot, J. *The Rat Forebrain in Stereotaxic Coordinates.* Amsterdam: N. V. Noord-Hollandische, 1959.
8. Fibiger, H. C., A. G. Phillips and P. Zis. Deficits in instrumental responding after 6-hydroxygopamine lesions of the nigro-neostriatal dopaminergic projection. *Pharmac. Biochem. Behav.* **2:** 87–96, 1974.
9. Fouriezos, G. and R. A. Wise. Pimozide-induced extinction of intracranial self-stimulation: response patterns rule out motor or performance deficits. *Brain Res.* **103:** 337–380, 1976.
10. Herberg, L. J., D. N. Stephens and B. J. Franklin. Catecholamines and self-stimulation: evidence suggesting a reinforcing role for nonadrenaline and a motivating role for dopamine. *Pharmac. Biochem. Behav.* **4:** 575–582, 1976.
11. Howard, J. L., L. D. Grant and G. R. Breese. Effects of intracisternal 6-hydroxydopamine treatment on acquisition and performance of rats in a double T-maze. *J. comp. physiol. Psychol.* **86:** 995–1007, 1974.
12. Jacobowitz, David M. and Miklos Palkovits. Topographic atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain. I. Forebrain (telencephalon, diencephalon). *J. comp. Neurol.* **157:** 13–28, 1970.
13. Liebman, J. M. and L. L. Butcher. Effects on self-stimulation behavior of drugs influencing dopaminergic neurotransmission mechanisms. *Naunyn-Schmied Archiv Pharmak. exp. Path. 277:* 305–318, 1973.
14. Lindvall, O. and A. Bjorklund. The glyoxylic acid fluorescence histochemical method: a detailed account of the methodology for the visualization of central catecholamine neurons. *Histochem.* **39:** 97–127, 1974.
15. Ljungberg, T. and U. Ungerstedt. Sensory inattention produced by 6-hydroxydopamine-induced degeneration of ascending dopamine neurons in the brain. *Expl Neurol.* **53:** 585–600, 1976.
16. Major, R. and N. White. Memory facilitation by self-stimulation reinforcement mediated by the nigro-neostriatal bundle. *Physiol. Behav.* **20:** 723–733, 1978.

17. Marshall, J. F., J. S. Richardson and P. Teitelbaum. Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *J. comp. physiol. Psychol.* **87**: 808–830, 1974.
18. McGaugh, James L. Time-dependent processes in memory storage. *Science* **153**: 1351–1358, 1966.
19. Morgane, P. J. and W. C. Stern. Chemical anatomy of brain circuits in relation to sleep and wakefulness. In: *Advances in Sleep Research,* edited by E. Weitzmann. New York: Spectrum, 1974.
20. Price, M. T. C. and H. C. Fibiger. Discriminated escape learning and response to electric shock after 6-hydroxydopamine lesions of the nigro-neostriatal dopaminergic projection. *Pharmac. Biochem. Behav.* **3**: 285–290, 1975.
21. Ranje, C. and U. Ungerstedt. High correlations between number of dopamine cells, dopamine levels and motor performance. *Brain Res.* **134**: 83–93, 1977.
22. Ranje, C. and U. Ungerstedt. Lack of acquisition in dopamine denervated animals tested in an underwater Y-maze. *Brain Res.* **134**: 95–111, 1977.
23. Ranje, C. and U. Ungerstedt. Discriminative and motor performance in rats after interference with dopamine neurotransmission with spiroperidol. *Eur. J. Pharmac.* **43**: 39–46, 1977.
24. Rolls, E. T., P. H. Kelley and S. G. Shaw. Noradrenaline, dopamine and brain-stimulation reward. *Pharmac. Biochem. Behav.* **2**: 735–740, 1974.
25. Rolls, E. T., B. J. Rolls, P. H. Kelly, S. G. Shaw, R. J. Wood and R. Dale. The relative attenuation of self-stimulation, eating and drinking produced by dopamine receptor blockade. *Psychopharmacologia* **38**: 219–230, 1974.
26. Routtenberg, A. Significance of intracranial self-stimulation pathways for memory consolidation. In: *Methods in Brain Research,* edited by P. B. Bradley. New York: Wiley, 1974.
27. Ungerstedt, Urban. Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta physiol. scand.* **367**: 1–48, 1971.
28. Smith, G. P., B. E. Levin and G. N. Ervin. Loss of active avoidance responding after lateral hypothalamic injections of 6-hydroxydopamine. *Brain Res.* **88**: 483–498, 1975.
29. Wauguier, A. and C. J. E. Niemegeers. Intracranial self-stimulation in rats as a function of various stimulus parameters. II. Influence of haloperidal, pimozide and pipamperone on medial forebrain bundle stimulation with monopolar electrodes. *Psychopharmacologia* **27**: 191–202, 1972.
30. Zigmond, M. J. and E. M. Stricker. Deficits in feeding behavior after intraventricular injection of 6-hydroxydopamine in rats. *Science* **177**: 1211–1213, 1972.
31. Zis, A. P., H. C. Fibiger and A. C. Phillips. Reversal by l-DOPA of impaired learning due to destruction of the dopaminergic nigro-neostriatal projection. *Science* **185**: 960–962, 1974.