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Time-Response Effects of Pimozide on Operant Behavior and Schedule-Induced Polydipsia

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SNODGRASS, S. H. AND J. D. ALLEN. *Time-response effects of pimozide on operant behavior and schedule-induced polydipsia.* PHARMACOL BIOCHEM BEHAV **32**(4) 949–955, 1989.—Previous research has indicated that the administration of specific doses of pimozide results in the suppression of the acquisition of schedule-induced polydipsia in rats while not affecting operant behavior. The purpose of this study was to determine if these results were due to a specific action of pimozide on schedule-induced polydipsia or if they were due to an insufficient presession time of drug administration. Pimozide at 1.0 mg/kg was administered to three groups of rats at either 30, 60 or 120 minutes presession with control subjects receiving administration of the drug vehicle also at these times. The results of the study were that both operant behavior and the acquisition of schedule-induced polydipsia were affected in a nondifferential and time-dependent manner by pimozide. It was also found that pimozide caused an alteration in the temporal pattern of both schedule-induced polydipsia and operant responding. This latter result appears to have been caused by a disruption in sensorimotor integration due to the dopamine blocking properties of pimozide.

Pimozide Operant behavior Schedule-induced polydipsia Time-response effects Sensorimotor integration Dopamine Rats

WHEN a food-deprived rat is allowed free access to water while receiving small allotments of food on an intermittent basis, a stereotyped pattern of drinking known as schedule-induced polydipsia (SIP) gradually develops (5). Typically, rats will begin drinking immediately after consumption of the delivered food with the peak in lick rate occurring early in the period of time between pellet deliveries, i.e., the interpellet interval (IPI) (6). Rats will develop SIP even though they are not deprived of water nor experiencing any form of physiological fluid deficit (6,27).

While the neuroanatomical basis of SIP is unknown, it has been demonstrated that lesions of specific brain sites by electrolytic or chemical means influence the generation of SIP. These brain sites include the lateral hypothalamus (LH) in which electrolytic lesions have been reported to abolish SIP. However, lesions of the LH do not produce selective deficits in SIP in that they are also known to cause aphagia, adipsia, and a syndrome of sensory neglect (18). Selective deficits in the development of SIP have been reported with 6-hydroxydopamine lesions of the nucleus accumbens septi (22,30). The selectivity of effect of the lesions was shown by the fact that deprivation-induced drinking was not altered.

It has also been reported that 6-hydroxydopamine lesions of the lateral septal nucleus selectively affect the development of SIP by increasing the rate at which the behavior is acquired. Again, the selectivity or specificity of effect was demonstrated by the lack of change of deprivation-induced drinking by the lesioned subjects (28).

The administration of the dopamine blockers pimozide and spiperone has been reported by Porter *et al.* (21) to affect the acquisition of SIP without influencing operant bar pressing or deprivation-induced drinking. Thus, it is possible that the disruption of the dopamine system can cause specific behavioral effects, i.e., suppression of the acquisition of SIP, at levels of disruption which do not induce general behavioral deficits. However, it should be noted that the doses of pimozide and spiperone used by Porter *et al.* (21) have been reported elsewhere to cause suppression of operant bar pressing maintained by the presentation of intracranial stimulation or food pellets (8–10, 17, 19, 23, 29, 32). It has also been shown that pimozide (11) and spiperone (23) cause a reduction in water intake by water-deprived rats at doses equal to or lower than those used by Porter *et al.* (21).

The administration of the dopamine blocker chlorpromazine (2,16) or haloperidol (15) has been reported to suppress fully developed SIP as well as operant responding. Recent evidence has shown that the decrease in the amount of established SIP and the rate of operant responding due to the administration of haloperidol occurs in a dose-dependent and nonselective manner. It was also found that deprivation-induced drinking was suppressed at the same doses of haloperidol which affected SIP and operant behavior (25). Thus, there is no evidence that established SIP is affected by doses of dopamine blockers which do not cause general

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behavioral deficits.

While established SIP is not selectively affected by dopamine antagonists, the possibility remains that the acquisition of SIP may be affected at levels of dopaminergic disruption which do not result in the suppression of other behavior. If it is the case that developing SIP is more sensitive to the effects of dopamine blockers than is established SIP, then the results of the Porter *et al.* (21) study may be explained by the presession time at which pimozide and spiperone were administered. It is known that both of these drugs exert their maximal behavioral effects 120 to 240 minutes postadministration (12, 13, 19, 20, 23). Porter *et al.* (21) administered both pimozide and spiperone 60 minutes prior to session initiation. Thus, a less than maximal dose effect may have existed during the drug sessions which resulted in the selective suppression of the "weaker" behavior, i.e., developing SIP.

The purpose of the present study was to provide a detailed analysis of the effects of differing presession times of administration of pimozide on the acquisition of SIP and operant behavior in rats. The reasoning behind this study was that if the development of SIP is more sensitive to the effects of dopaminergic antagonism than is operant behavior, then this differential sensitivity should be revealed with relatively short presession times of administration of pimozide. At a longer presession time of administration, one which allows for the full effect of pimozide to occur, suppression of both operant behavior and SIP should result. However, if the acquisition of SIP is not differentially sensitive to dopamine blockade, then a selective effect of pimozide on SIP should not occur no matter the presession time of administration.

METHOD

Subjects

Twenty-seven adult male Long-Evans hooded rats obtained from the University of Georgia breeding colony served as subjects. They were individually housed in a large colony room with a 12-hour light-dark cycle (9:30 a.m. to 9:30 p.m. light period) in effect. The subjects had continuous access to water in the home cage and were randomly assigned to one of seven groups on their arrival at the colony room.

Apparatus

Sessions were conducted in three identical Lehigh Valley Electronics (Model 1714) operant conditioning chambers, $28 \times 28 \times 24$ cm, housed in sound-attenuating cubicles. A lever was mounted on the front wall of each of the chambers 3 cm from the left wall and 4 cm above the floor. Noyes Formula A 45 mg food pellets served as reinforcers and were delivered by a Ralph Gerbrands pellet dispenser to a food cup which was located in the center of the front wall, 1 cm above the floor. Water was available through a drinking tube which was recessed behind a 1.5 cm diameter opening in the front wall, 5.5. cm to the right of the food cup and 1.5 cm above the floor. The drinking tube was recessed behind the front wall in order to avoid incidental contact with the tube being recorded as licks. The drinking tube was connected to a 100 ml graduated cylinder through which the number of milliliters consumed was measured to the nearest milliliter. Licks at the tube were recorded by a Grason-Stadler drinkometer.

Recording of the subjects' bar pressing and licking behavior as well as control of the behavioral contingencies was accomplished through the use of two SYM-1 microcomputers which were networked with a PET/CBM 4032 microcomputer (1).

Procedure

Subjects were allowed one week to habituate to the colony room. They were then weighed once per day for five consecutive days in order to ascertain their free-feeding weights. Over the next seven days the subjects were gradually reduced to 80% of their free-feeding weights and were maintained at this weight for the duration of the study.

The subjects were trained to bar press for food pellets on a fixed ratio 1 schedule of reinforcement in which each bar press produces one food pellet. Water was available to the subjects during these sessions, and the amount consumed served as the baseline measure of water consumption. The baseline sessions were 30 minutes in length, and the subjects were able to earn 30 reinforcers per session, the maximum number of reinforcers that they were allowed to earn during the test sessions. The baseline sessions continued for five consecutive days after which the water bottles were removed from the operant chamber and training on a fixed-interval (FI) schedule of reinforcement was begun. According to this schedule of reinforcement, the first response after a fixed amount of time has elapsed since the delivery of the last reinforcer, produces the next reinforcer. The subjects were exposed to a 15- and then 30-second FI schedule for one session each. The FI value was then increased to 60 seconds and, following the procedure of Porter *et al.* (21), the subjects received two sessions of training on the FI 60-sec schedule before water was reintroduced into the chamber and acquisition sessions were initiated.

During the acquisition sessions, the subjects received one intraperitoneal (IP) injection of pimozide at a dose of 1.0 mg/kg or an equal volume of the drug vehicle before each session. Injections of pimozide were given 30 minutes (Pim-30 group), 60 minutes (Pim-60 group), or 120 minutes (Pim-120 group) prior to the beginning of the sessions. Each of the pimozide groups consisted of six subjects. Control injections of the drug vehicle were administered at 30, 60, and 120 minutes presession with three subjects serving as controls at each of these times.

The acquisition sessions continued for 15 consecutive days with each session being 30 minutes in length. The data collected during the session included the number of milliliters of water consumed, the number of bar presses and licks emitted, the number of pellets earned, the time it took the subjects to earn each pellet, and the number of bouts engaged in. A bout was defined as at least five licks occurring during an interpellet interval and provided a measure of the number of the delivered food pellets which generated drinking in that subject.

In order to determine the temporal pattern of bar pressing and licking, the 60-second interval was divided into seven consecutive time bins. Six of the bins were 10 seconds in length and the number of licks and bar presses which occurred during each of the bins was recorded. The seventh time bin served as an overflow bin in that any licks which occurred after the 60 second interval had elapsed, and before a pellet was earned, were recorded in this bin. Also, by definition, each reinforced response occurred after the 60-second interval had elapsed and was recorded in this bin.

Graphs depicting the time-response functions of pimozide were constructed by averaging the data of the subjects for each dependent measure on sessions 13, 14, and 15. These averages were then used to determine the standard error of the mean for each dependent measure. Statistical analyses of the data were conducted with a one-way analysis of variance, and the Tukey HSD test was used for post hoc analysis when the omnibus F-test revealed a significant effect. For the results of this study, significance was assessed at the $p = 0.05$ level.

Drugs

The appropriate dose (mg/ml) of pimozide was suspended in a solution containing three to four drops of Tween 80 (Sigma

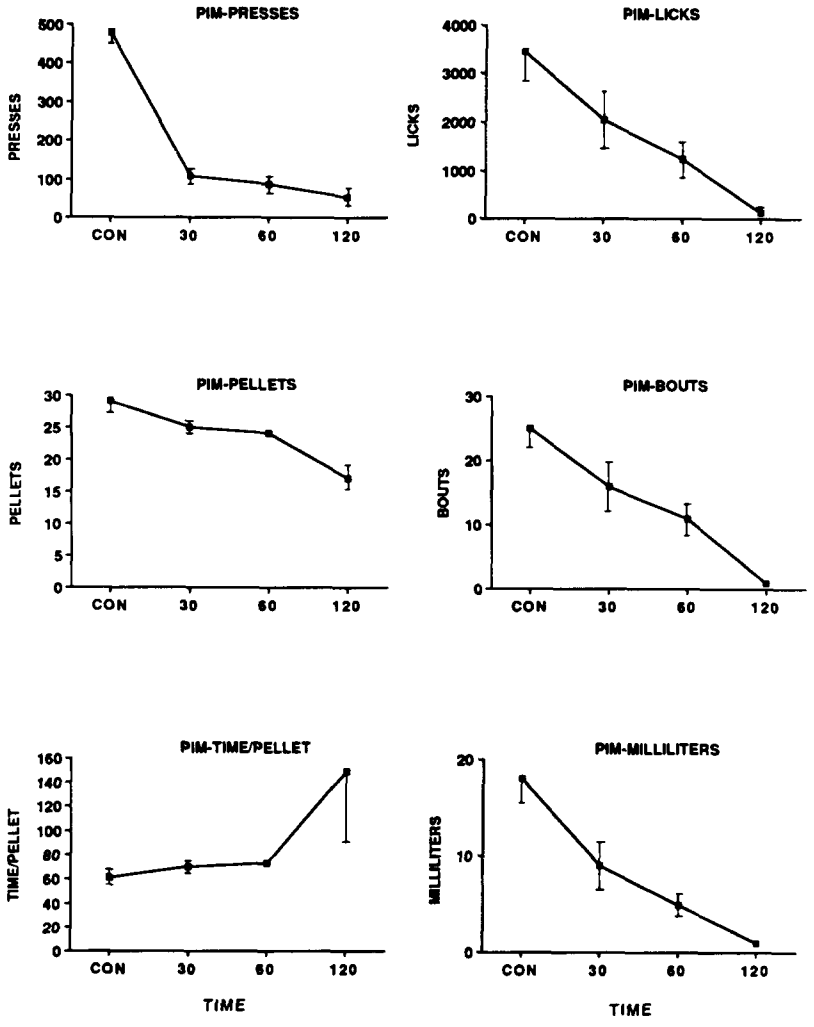

FIG. 1. The time-response effects of pimozide on operant behavior (left-hand panels) and schedule-induced polydipsia (right-hand panels) for the combined data of sessions 13, 14, and 15. The x-axis represents presession time of administration. The vertical lines indicate ±SEM. The term "CON" represents the combined data of the nine control subjects which received vehicle at 30, 60, and 120 minutes presession.

Chemical Company) per 10 milliliters of distilled water. The drug vehicle injections consisted of three to four drops of Tween 80 per 10 milliliters of distilled water. The drug and vehicle solutions were prepared daily and were administered at a constant volume of 1.0 ml/kg. All doses are expressed as the free base.

RESULTS

The effects of the differing presession times of administration of pimozide on operant behavior and the acquisition of SIP are illustrated in Fig. 1 for the combined data of sessions 13, 14, and 15. From this figure, it can be seen that the number of bar presses (top left panel) and pellets earned (middle left panel) were suppressed by the administration of pimozide. It can also be seen that there was an increasing trend in the time it took the subjects to earn the pellets (bottom left panel) due to the increasing presession time of drug administration.

The one-way analysis of variance of the number of bar presses revealed a significant drug effect, $F(3,23) = 50.945$, $p<0.001$. Post hoc analysis revealed that the control group emitted a greater number of presses than had the pimozide groups which did not differ in the number of bar presses emitted. The ability of the subjects to earn the food pellets was also affected by pimozide administration, $F(3,23) = 11.394$, $p<0.001$. Post hoc analysis with the Tukey test showed that the control, Pim-30 and Pim-60 subjects earned more reinforcers than did the subjects of the Pim-120 group. No other comparisons were significant. The analysis of the time/pellet data revealed that the administration of pimozide did not produce a reliable affect during the last three sessions, $F(3,23) = 2.684$, $p = 0.07$.

The right hand panels of Fig. 1 show that the number of licks (top panel), bouts (middle panel), and milliliters consumed (bottom panel) are each decreasing functions of the increase in the presession time of administration of pimozide. It can also be seen that the functions of these dependent measures are very similar.

The one-way analysis of variance of the number of licks emitted disclosed a significant drug effect, $F(3,23) = 8.150$, $p = 0.03$, as did the analysis of the number of bouts, $F(3,23) = 11.2$, $p<0.001$. Post hoc analyses of the lick and bout data showed that the control group emitted more licks and engaged in more bouts than did the Pim-60 and Pim-120 subjects. It was also found that the values of the Pim-30 subjects were greater than those of the

TABLE 1

MEAN MILLILITERS OF WATER CONSUMED DURING BASELINE AND SESSIONS 13, 14, and 15

		Session			
Group	N	BL	13	14	15
Control	(9)	0.6	17.2	18.2	17.9
Pim-30	(6)	1.2	8.8	9.3	8.3
Pim-60	(6)	1.1	3.8	5.3	5.5
Pim-120	(6)	1.1	0.2	1.0	1.0

The number of milliliters of water consumed during baseline (BL) and sessions 13, 14, and 15 for each group of subjects. The number of subjects in each group is indicated under the column headed N.

Pim-120 subjects. No other comparisons were found to be different.

The number of milliliters consumed by the subjects was also suppressed by pimozide administration, $F(3,23)=11.31$, $p<0.001$. Subsequent analysis with the Tukey HSD test revealed that the control subjects consumed more water than did the subjects of the pimozide groups, and that the Pim-30 subjects intake of water was greater than that of the Pim-120 subjects. There were no other differences between groups.

The number of milliliters consumed during baseline and the last three sessions of acquisition are presented in Table 1 for the control (top row), Pim-30 (second row), Pim-60 (third row), and the Pim-120 (bottom row) subjects. From inspection of Table 1, it can be seen that the control and Pim-30 subjects consumed much more water during the last three acquisition sessions than they did during the baseline sessions and had therefore developed SIP. The subjects of the Pim-120 group failed to increase their intake of water over the amount consumed during the baseline sessions and thus failed to develop SIP. In order to determine if the Pim-60 subjects had developed SIP by the last three sessions, a one-way repeated measures analysis of variance of their data with sessions as the repeated factor was conducted. The result of this analysis disclosed that a significant difference in the amount of water consumed during baseline and the last three acquisition sessions did exist, $F(3,15)=9.882$, $p<0.001$, and, thus, the subjects of the Pim-60 group had also developed SIP.

The effects of the drug vehicle and pimozide administration on the temporal pattern of bar pressing of the control group (top panel), the Pim-30 group (second panel), the Pim-60 group (third panel), and the Pim-120 group (bottom panel) for sessions 1, 5, 10, and 15 are illustrated in Fig. 2. Inspection of the top panel reveals that the control subjects' pattern of bar pressing was beginning to take on the characteristic scalloped pattern of responding engendered by fixed-interval schedules (7) by the fifth session. By the tenth session the control subjects' pattern of responding was scalloped, and the degree of scalloping increased slightly by the fifteenth session.

The pattern of bar pressing produced by the pimozide subjects became increasingly flattened as the presession time of administration increased. The pattern of the Pim-30 and Pim-60 subjects was scalloped, although to a lesser degree than for the control subjects, on session 15. The pattern of the Pim-120 subjects, however, was greatly disrupted by the administration of 1.0 mg/kg of pimozide.

A defining characteristic of SIP is the temporal pattern of postpellet drinking which develops concomitantly with increasing

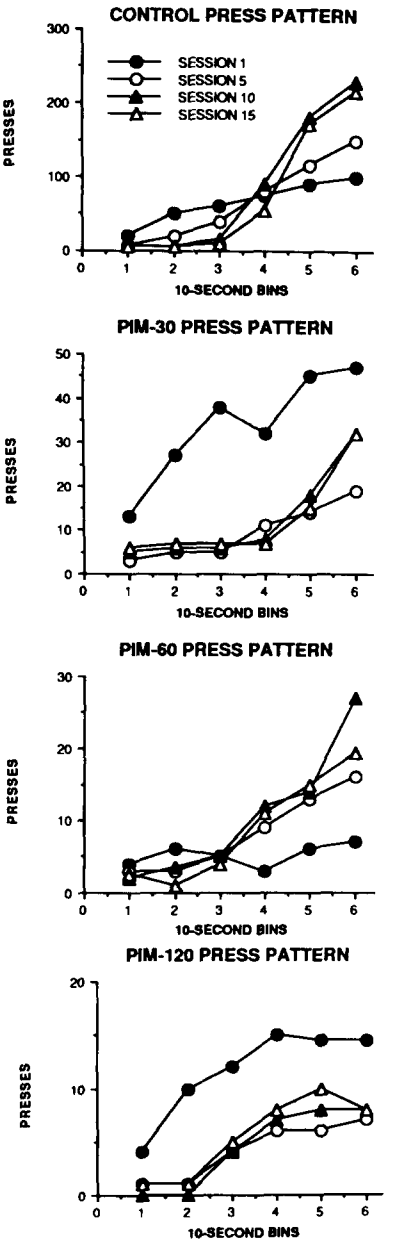

FIG. 2. The temporal pattern of bar pressing of the control (top panel), Pim-30 (second panel), Pim-60 (third panel), and the Pim-120 (bottom panel) groups for sessions 1, 5, 10, and 15. The x-axis represents the 60-second IPI of the fixed interval which has been divided into six 10-second time bins. The value of the y-axes differ among the graphs. The control data are the combined data of the nine control subjects which received vehicle at 30, 60, and 120 minutes presession.

water intake (5,6). Figure 3 illustrates the temporal pattern of licking of the control group (top panel), the Pim-30 group (second panel), the Pim-60 group (third panel), and the Pim-120 group (bottom panel) for sessions 1, 5, 10, and 15. While the Pim-120 group did not develop SIP, their lick pattern is included in this figure so that the effects of increasing presession injection times of pimozide can be assessed.

Inspection of the top panel of this figure shows that the control group developed the typical postpellet pattern of drinking over the

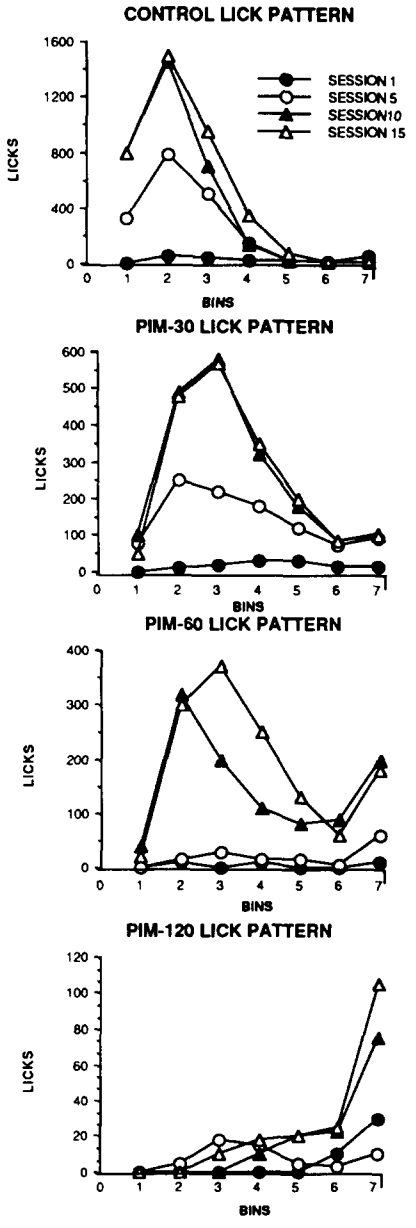

FIG. 3. The temporal pattern of licking of the control (top panel), Pim-30 (second panel), Pim-60 (third panel), and Pim-120 (bottom panel) groups for sessions 1, 5, 10, and 15. The X-axis is divided into seven bins with the first six bins being 10 seconds in length, which corresponds to the 60 seconds of the fixed interval. The seventh bin corresponds to the period of time in which a reinforcer was available, but had yet to be earned. The value of the Y-axes differ from graph to graph. The control data are the combined data of the nine control subjects which received vehicle at 30, 60, and 120 minutes presession.

15 sessions. The Pim-30 and Pim-60 subjects also developed a postpellet drinking pattern. However, the proportion of licks emitted in the first bin was lower, and the peak in licking was shifted further into the IPI, as compared to the pattern of the control group. These subjects also continued to drink during the seventh, or overflow, bin. In addition, it can be seen that the subjects of the Pim-120 group emitted the greatest proportion of their licks on sessions 10 and 15 during the overflow bin.

The control subjects licked very little, if at all, during the overflow bin during sessions 10 and 15. The reason for this lack of licking is that on the tenth and fifteenth sessions their average IPI was 60.9 and 60.8 seconds respectively. The mean IPI for the Pim-30 group during sessions 10 and 15 was 74.5 and 70.8 seconds while the Pim-60 group averaged 74.6 and 72.1 seconds for the same sessions. The average IPI of the Pim-120 subjects was 110.4 and 93.4 seconds for these sessions. Thus, in contrast to the behavior of the control subjects, the pimozide subjects allowed a period of time to elapse between when a reinforcer became available and when it was earned, and in some instances, continued to drink during this time.

DISCUSSION

The administration of 1.0 mg/kg of pimozide at 30, 60 and 120 minutes presession resulted in a decrease in the number of operant bar presses emitted and a time-dependent suppression of the acquisition of SIP. The number of reinforcers earned by the subjects of the Pim-120 group was also affected. While it appeared that the subjects of the Pim-120 group took longer to earn the reinforcers than did the other subjects, statistical analysis revealed that this difference was not reliable.

The results of the present study are not in agreement with those reported by Porter *et al.* (21). These authors stated that the administration of 1.0 mg/kg of pimozide 60 minutes presession resulted in the complete suppression of the acquisition of SIP while operant bar pressing was not affected. In the present study, the administration of 1.0 mg/kg of pimozide at 60 minutes prior to session initiation produced a large decrease in the number of times the subjects engaged in the operant response. SIP, however, was acquired by the subjects, albeit, to a lesser degree than for the control subjects.

The results of the present study are in agreement with those of a recent study in which the dose-effects of the dopamine agonist apomorphine on the acquisition of SIP and operant bar pressing were determined (26). In this latter study, it was found that the doses of 0.05, 0.50, and 1.0 mg/kg of the dopamine agonist apomorphine blocked the acquisition of SIP, and that the 0.50 and 1.0 mg/kg doses also suppressed the bar press rates of the subjects. While the 0.05 mg/kg dose did not influence the rate of bar pressing, the temporal pattern of this behavior was disrupted. Thus, it was found that if SIP was affected by pharmacological disruption of the dopamine system, that bar pressing was also affected.

Kaempf and Porter (14) have reported that the administration of pimozide at doses of 0.3 and 1.0 mg/kg four hours presession suppressed operant responding, but did not alter the pattern of bar pressing maintained by a FI 60-second schedule of reinforcement. These doses of pimozide also blocked the development of SIP by the subjects. In the present study, the bar press rates as well as the pattern of bar pressing were affected by pimozide administration. A possible explanation for the fact that the pattern of operant responding was affected in this study and not in the Kaempf and Porter (14) study is that bar pressing was well established in the subjects of the latter study at the time that chronic dosing was initiated. The subjects of the present study, however, had only two sessions experience with the FI 60-second schedule when drug dosing began. Thus, the difference in the effects of pimozide on the bar press patterns of the subjects of the two studies may have been due to the difference in the degree to which the behavior had become established as part of the subjects' behavioral repertoire.

The reasons for the discrepancy in the results of the present study and those of Porter *et al.* (21) are not clear. However, from the results presented above, it appears that the effects of dopa-

minergic disruption on behavior are general and not specific. This generality of effect is evidenced by the fact that the temporal patterning of both operant behavior and SIP was affected. The effects of pimozide on the scalloped pattern of responding engendered by FI schedules were found to be a flattening of the scallop, which indicates a decrease in the degree of acceleration of the terminal response rate, for the subjects of the Pim-30 and Pim-60 groups. Administration of pimozide at 120 minutes presession caused a flattened pattern of bar pressing to occur. For SIP, a shift in the peak of licking was produced by the administration of pimozide 30 and 60 minutes presession. This shift appears to have been due to the fact that, after pellet delivery, the subjects allowed a greater amount of time to pass prior to initiation of drinking as compared to the control subjects. Thus, the peak in lick rate for the Pim-30 and Pim-60 subjects was shifted further into the IPI as compared to that of the control group. Consequently, it appears that pimozide affected the underlying process which is necessary for the temporal integration of both operant behavior and schedule-induced polydipsia.

Because of the location of the food receptacle and the drinking tube, the subjects did have to move a slight distance in order to initiate licking after pellet ingestion. It has been proposed that the dopamine blockers depress behavior by interfering with the motor capabilities of the animals (8,23). It may be that pimozide caused a disruption in the ability of the rats to move the distance from the food receptacle to the drinking tube which resulted in the delayed initiation of licking. However, the pimozide subjects engaged in drinking during the overflow bin in which, typically, very little drinking occurs. This abnormal pattern of licking had previously been observed in this laboratory in nondrugged rats (25). The licking at the end of the IPI occurred for these subjects when they were exposed to fixed-interval values which were increased in length compared to the FI 90-second value which they had experienced for approximately 50 sessions. Because of the lengthened values of the fixed intervals, the temporal cues which previously controlled the behavior of the subjects were disrupted. During these sessions, the nondrugged subjects, while not consistently exhibiting the behavior, did occasionally drink in the extended overflow bin. It is also interesting to note that in the present study, the subjects of the Pim-120 group consumed the greatest amount of water during a period of time that a reinforcer was available, i.e., during the overflow bin.

It thus seems that the drinking by the pimozide subjects which occurred in the overflow bin was due to a loss of behavioral control by the stimulus cues which signal the increasing probability of reinforcer availability. That administration of a neuroleptic results in a functional decrease in the level of behavioral control by stimuli has been previously hypothesized (3, 4, 24, 25, 31). The results of this study are in agreement with this hypothesis and thus provide further evidence that the neuroleptics cause a deficit in the ability of the organism to integrate sensory input with motor output.

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