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Some Effects of Pimozide on Nondeprived Rats Licking Sucrose Solutions in an Anhedonia Paradigm

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GRAMLING, S. E., S. C. FOWLER AND K. R. COLLINS. *Some effects of pimozide on nondeprived rats licking sucrose solutions in an anhedonia paradigm.* PHARMACOL BIOCHEM BEHAV 21(4) 617–624, 1984.—The present work examines the generalizability of the anhedonia phenomenon (extinction-like responding with repeated neuroleptic treatment) by examining rats' licking behavior, a response heretofore untested, in the anhedonia paradigm. Nondeprived rats learned to lick a sucrose solution (32%) and were then tested for eight consecutive days in either a no-reward condition (N=8) or two pimozide (PIM) with reward conditions (N=8 at each of these two doses: 0.5 and 1.0 mg/kg). PIM treated animals did not exhibit rates or patterns of responding equivalent to animals in the extinction condition. Instead of an across session decline in rate, PIM treated animals showed a trend towards recovery on the rate measure. Within session patterns of responding of PIM treated animals more closely resembled animals in a normally rewarded condition responding at a generally lower rate, than animals in an extinction condition. The experimental procedure included the use of home cage control animals, replication of the intermittent dosing procedure, and tests for transfer effects; all of these failed to produce patterns of responding typically obtained in the anhedonia paradigm when the response is lever pressing. Median lick duration and median interlick interval (ILI) were both lengthened with PIM treatment relative to injection control and extinction conditions, suggesting that pimozide treatment creates a motoric deficit. Taken together these results emphasize the importance of neuroleptics' motor vis a vis anhedonic effects.

Anhedonia Pimozide Licking Sucrose reward Nondeprived rats Lick duration Interlick interval

THE rate reducing effects of neuroleptics on operant behavior have been attributed in part to a drug induced state of "anhedonia," wherein neuroleptics are thought to blunt the hedonic value of positive reinforcers by diminishing the central effects of reward [24, 26, 27]. The anhedonia hypothesis seeks to account for the apparent similarities in patterns of responding occasioned by either neuroleptic treatment or by extinction procedures [26]. Extinction-like patterns of responding have been observed both across sessions (e.g., [24]) and within sessions (e.g., [10]) following neuroleptic administration. In both cases a motor impairment interpretation of these operant rate reductions have been questioned. However, other investigators (e.g., [1]) and other studies [3, 9, 15, 20], continue to implicate the motor effects of neuroleptics in producing operant rate reductions. Though it is generally acknowledged that neuroleptics act on both processes (e.g., [4, 26, 28], investigators continue to disagree on the importance of reward versus motor processes in accounting for neuroleptics' behavioral effects.

In this regard, the extinction-like patterns of responding produced by neuroleptics have been reported to be response dependent [3]. Rats nosepoking for intracranial stimulation (ICS) did not exhibit dose dependent decreases in rate, though dose dependent decreases were observed with these same animals and doses when the response was lever pressing [3]. Based on these observations the kinetic requirements of the response have been suggested as important determinants of the extinction-like patterns of responding produced by neuroleptically treated animals. However, it is important to note that the Ettenberg *et al.* [3] study did not include a comparison with nondrugged animals in an extinction condition. Further, the nosepoke response has not been examined in other procedures often employed to address the anhedonia hypothesis; i.e., the nosepoke response has not been tested in procedures involving home cage controls or tests for transfer. Heretofore, lever pressing has been the only response tested in the anhedonia paradigm in the free operant setting (though the running response has been tested in discrete trial procedures). Moreover, average rate is often the only dependent measure employed, and it has proved difficult to separate reward deficits from motor deficits on the basis of this one measure.

The purpose of the present experiment then, was to examine, in the anhedonia paradigm, a response with low kinetic requirements and to include behavioral measures presumed to reflect motor processes. The rat's licking behavior seemed

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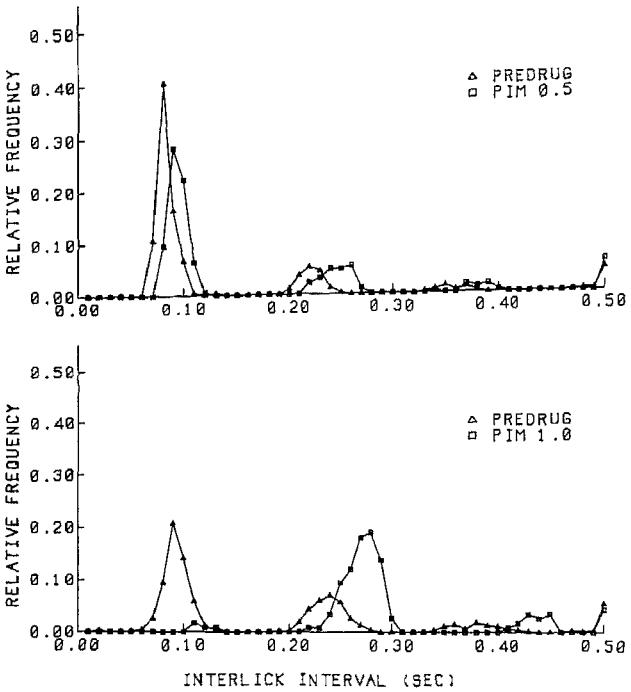

FIG. 1. Frequency distributions of interlick interval for two representative rats on the last day of predrug baseline (triangular symbols) with their respective performance on the first day of drug treatment (square symbols: 0.5 mg/kg top, 1.0 mg/kg bottom). Figure 2 gives data on the number of licks these kinds of distributions are based on. The 0.5 sec overage class at the far right of the distribution was chosen for graphic convenience and includes all the intervals within the session greater than or equal to 0.5 sec.

particularly appropriate in this context since it is at least as biologically primitive a response as nosepoking and it is a highly invariant, stereotypic response with well defined motor properties [2, 14, 23]. Specifically, the present experiment compared the within- and across-session patterns of sucrose licking exhibited by separate groups of rats exposed to either a neuroleptic with reward condition or a no-drug, no-reward condition. The treatment conditions used in the present experiment were closely similar to those used by Wise *et al.* [24] with a number of important exceptions. An eight consecutive day dosing regimen was employed rather than four intermittent dosings since failures to obtain anhedonic-like effects as a result of neuroleptic treatment have been explained by noting that the observation periods may have been too brief [26]. These same rats were also tested for transfer effects wherein conditions were reversed (either drug or extinction) following the eighth day of testing. Home cage control groups, which are typically included to rule out a drug accumulation deficit interpretation of across session declines in rate were included at each dose. Finally, the home cage control animals were also used in a replication of the intermittent dosing procedure used by Wise *et al.* [24], though previous work with the lever press response has shown that consecutive daily dosings produce results similar to those obtained with intermittent dosings [7].

The need to develop measures that will better separate neuroleptics reward reducing effects from their motor effects has been frequently noted (e.g., [20]). Thus an important feature of the present experiment is the inclusion of measures of individual response properties, namely interlick interval (ILI) and median lick duration. The frequency distribution of ILI's is a precisely timed multimodal phenomenon [2, 13, 14, 23], the first mode of which seems to reflect rats' licking as fast as motorically possible (5–6 licks/sec [23]; an ILI distribution is presented in Fig. 1). Changes in the distributional characteristics as well as duration of the lick response are presumed to be sensitive indices of the motoric aspects of licking [13]. In the lever press situation the response duration measure has provided behavioral information about drug effects non redundant with the rate of response measure [21], and has proved useful in detecting differences between no-reward and neuroleptic with reward conditions [5].

Additional methodological points on the present experiment concern the use of a sucrose solution reward, the absence of an explicit operant contingency, and the use of non deprived animals. A reinforcer that maintains responding by its stimulating properties seems most appropriate when testing for drug effects on the "hedonic" impact of reward. Reinforcers in this class previously tested in the anhedonia paradigm include ICS (e.g., [10]) and saccharine [25]. A much-agreed-on problem with the anhedonia hypothesis is that the range of reinforcers tested has been too narrow [26]; therefore, the use of a sucrose solution reward may extend the generality of the anhedonia phenomenon within this class of reinforcers. In addition, the use of non-deprived rats emphasizes the hedonic characteristics of the reward while minimizing the motivational factors of the behavioral procedures used in the anhedonia paradigm. By allowing the animals to lick the solution directly, secondary reinforcement and possible concomitant associative processes are diminished, thereby providing a relatively direct assessment of the reward reducing effects of neuroleptics when the response is licking.

METHOD

Animals

Forty male Sprague-Dawley rats (Holtzman Co.) were housed in individual home cages and given continuous access to food and water. The animals' weight averaged 400 grams at the onset of the experiment and increased to an average weight of 500 grams by the last day of testing. The food and water supply was carefully monitored to ensure that the animals remained nondeprived throughout the experiment.

Apparatus

Four simultaneously-operative experimental chambers measuring 23 cm long, 20 cm wide, and 19 cm high were constructed of an aluminum front panel with the remaining sides and tops being clear Plexiglas. Stainless steel rods (2 mm in diameter) running parallel to the front of the chamber served as a grid floor. A 15-watt light bulb was centered approximately 12 cm from the top of each chamber to provide illumination.

A 5 cm circular opening was centered in the front panel 5 mm above the floor and permitted head entry into a cylindrical recession that extended 4 cm from the front panel of the chamber wall. A 12 mm circular opening in the cylindrical recession was positioned parallel to the grid floor 1 cm from the front panel and permitted tongue access to a reservoir beneath. The reservoir was filled with a sucrose solution (32%) which was mixed daily with tap water and brought to

room temperature prior to the experimental session. The fluid level in the reservoir was raised to 10 mm beneath the cylindrical recession prior to each rat's session. During the course of a session the fluid level dropped less than 1 mm. The contact circuit used to record licking passed less than 1.0 microamp through the rat.

Each experimental chamber was serviced by a separate microcomputer (Apple II plus) which recorded the data. The data acquisition software utilized a real time clock which permitted measurement of individual lick durations (the amount of time the tongue was in contact with the fluid) as well as interlick intervals (ILI), the amount of time between licks, with a resolution of 0.01 sec.

Procedure

During the initial 10-minute session the cylindrical recession that provided access to the sucrose solution was baited with a few drops of 32% sucrose solution to speed the initiation of the lick response. Most of the animals began to lick from the reservoir during the first session. For the rats which did not lick initially, the fluid level was raised to the cylindrical opening and then gradually lowered until all animals were licking with the fluid level 10 mm beneath the recession.

During treatment all injections in all conditions preceded data collection by four hours. The drug, dose levels and time since injection were the same as those used by Wise *et al.* [24]. Pimozide (PIM, McNeil) was dissolved prior to the start of experimentation in a mixture of tartaric acid and water.

Following ten daily 10-minute sessions of licking, rats were randomly assigned to one of five different treatment conditions (N=8 per group). Baseline data for each group were collected for 8 additional days, in the same manner as the previous 10 days. All groups received normal reward during this baseline phase; however, one reward group (RWD) served as an injection control and received daily injections of 0.9% saline solution (1 ml/kg IP). Drug or extinction treatment began on the day following the eighth day of baseline. The RWD group then served in the no-reward (EXT) condition wherein these animals received daily injections of 0.9% saline solution (1 ml/kg IP) for 8 consecutive days with reservoirs of plain tap water substituted for reservoirs of sucrose solution (i.e., EXT Group = control injection and no-reward). Two additional groups, PIM 1.0 + RWD and PIM 0.5 + RWD, received daily injections of 1.0 and 0.5 mg/kg (IP) PIM, respectively, and had access to reservoirs of sucrose solution during the experimental session for these same eight consecutive days. "Home cage control" (HC) groups were also included at each dose (HC PIM 1.0 and HC PIM 0.5). These animals received injections of 0.5 and 1.0 mg/kg (IP) PIM, respectively, for four consecutive days concurrent with the first four days of drug administration in the PIM 1.0 + RWD and PIM 0.5 + RWD groups. However, during the first 3 days animals in the home cage control groups were not exposed to the testing situation, rather they remained in their home cages. On the fourth day these animals were returned to the testing situation for the standard experimental session, where they once again had access to reservoirs of sucrose solution. This home cage control procedure ensures that any across session decline in responding observed in the PIM 1.0 + RWD and PIM 0.5 + RWD is due to some effect other than a cumulative drug effect. Following the fourth day test session the home cage control animals served in a replication of the Wise *et al.* [24] intermittent-dosing, retraining procedure. In this procedure the animals received two days of control injections (1 ml/kg IP) and normal reward ("retraining"), alternated with one day of drug administration and normal reward, until four days of testing exposure with drug had been obtained. One rat's data in the HC PIM 0.5 group were not included due to procedural irregularities and hence the N for this group was 7.

After the eight days of no-reward or drug treatment for the EXT, PIM 1.0 + RWD, and PIM 0.5 + RWD groups, an experimental test of the transfer hypothesis was carried out. To test for transfer, animals with a history of nonrewarded responding (EXT) were subsequently tested for four days in the drug condition with reward (PIM 1.0 + RWD after EXT in Fig. 4). Additionally, animals with a history of reward in the drug condition were tested in the non drugged, no-reward (water only) condition for four days (Groups EXT after PIM 1.0 + RWD and EXT after PIM 0.5 + RWD in Fig. 4).

Drug effects were characterized by average lick rate (number of licks), median lick duration, and median ILI of the first mode of the ILI frequency distribution. Average lick rate was based on the total number of licks made during the session when examining across session changes in rate. Average rate within the session was based on the total number of licks emitted in successive one minute time bins. The average rate measure included all the licks and hence all the intervals (pauses) in a session, and is used here to characterize extinction-like patterns of responding. Average rate was calculated across sessions in all conditions and within session for the four eight consecutive day treatment groups.

Median lick duration was calculated by taking the median of the frequency distribution of all the lick durations throughout the session. Median ILI of the first mode was calculated by including only intervals less than 0.2 sec. The 0.2 sec cutoff value was an empirically derived criterion that fell between the first and second ILI modes for all rats on the last day of baseline (see Fig. 1). Essentially this procedure omits pausing which is reflected in number of responses per session (average rate) and hence only the shortest intervals (fastest licks) that the animal emits in a session are included in the ILI measure. That is, the first mode of the ILI distribution reflects the most rapid lick rates that the rat exhibits within the session. Rate of responding within the first mode is inferred from changes in the median ILI measure, since rate is the reciprocal of ILI plus duration. Both lick duration (of all licks) and median ILI of the first mode are used here to reflect motor processes of the rats licking behavior. The extremes of the ILI frequency distribution were examined as well, in order to characterize more fully PIM's motor and motivational effects.

RESULTS

Average Lick Rate

Across session. As depicted in Fig. 2, eight consecutive days of drug dosing did not produce an across session decline in rate at either dose level. The drug data and the no-reward data (in Fig. 2) were entered into a split-plot factorial analysis of variance (SPF-ANOVA). The across days repeated measure did not yield statistical significance; however, a significant interaction was obtained, $F(14,147) = 2.098$, $p<0.02$. The interaction was attributable to the trend towards increasing rates following initial rate reductions exhibited by the PIM treated animals. When the drug data only were analyzed, the visual impression in Fig. 2

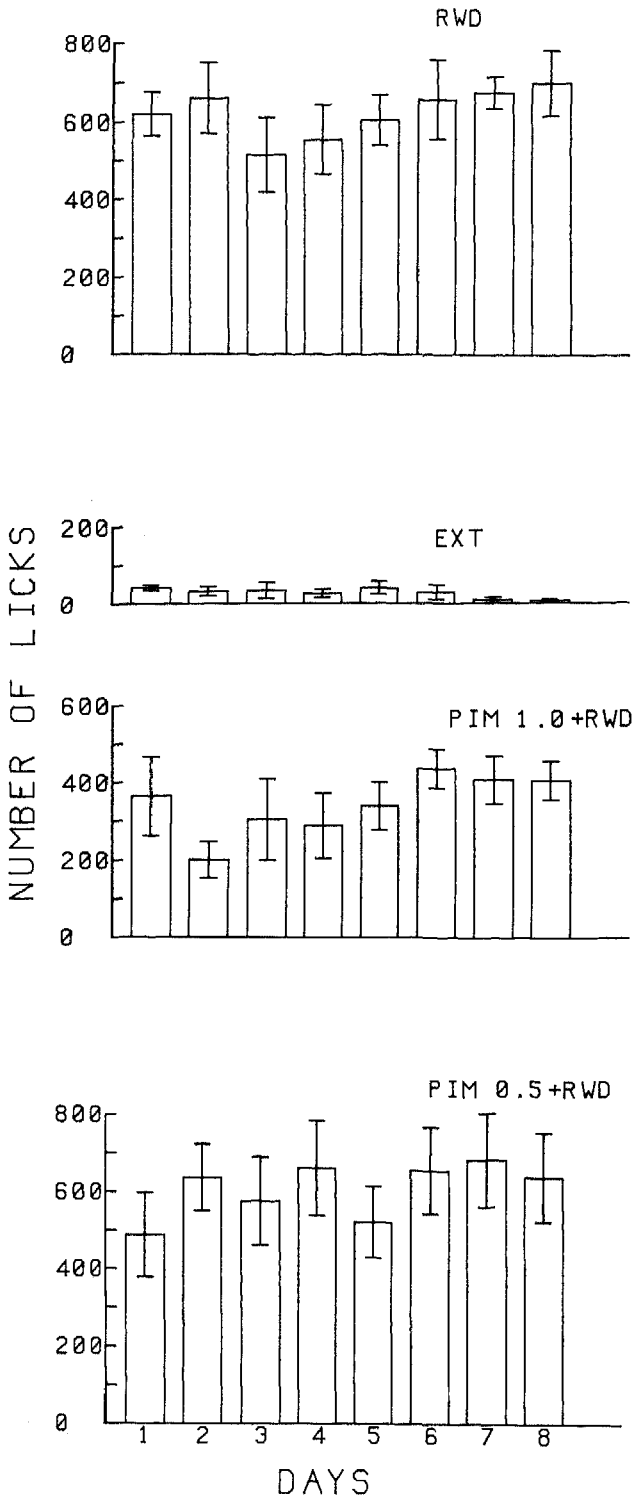

FIG. 2. Mean number of licks in daily 10-min session for 3 separate groups of rats. The vertical bars represent ±1 SEM. Group RWD (N=8) received control injections (1.0 ml/kg) during the last 8 days of baseline for all animals. For the next 8 consecutive days these animals received control injections and were exposed to no-reward (EXT). Two other groups of rats (PIM 1.0 + RWD and PIM 0.5 + RWD) received 8 consecutive days of pimozide (1.0 and .05 mg/kg respectively; N=8) with reward maintained on the same days that the group of rats (EXT) received extinction (tapwater).

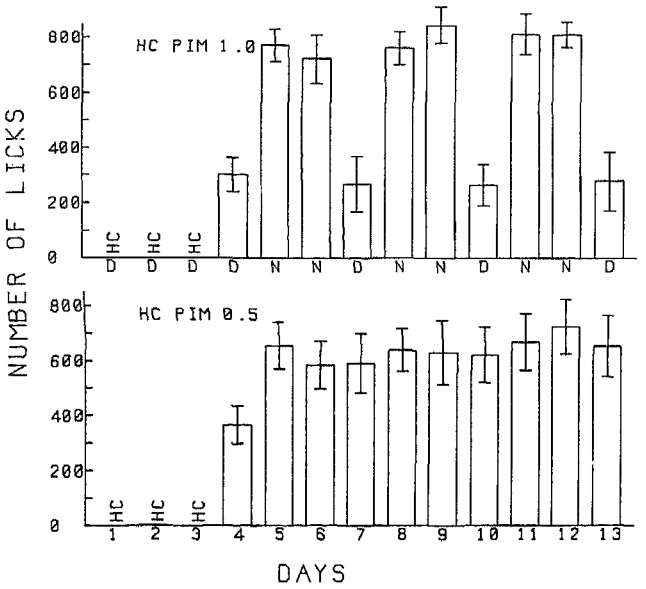

FIG. 3. Mean number of licks in 10-min sessions for 2 separate groups of rats. The vertical bars represent ±1 SEM. Group HC PIM 1.0 and HC PIM 0.5 served as home cage control rats and received 4 consecutive days of pimozide (1.0 mg/kg, N=8; 0.5 mg/kg, N=7, respectively) concurrently with the PIM treated animals in Fig. 2 but remained in the home cage for the first 3 days. On days 4–13 they received reward exposure in standard experimental sessions; however, 2 "retraining" days were interspersed between each of 4 drug assessments. On the abscissa of the upper set of axis, the Ds indicate drug treatment and the Ns no drug days for both groups.

was verified in that the across days repeated measure factor was significant, $F(7,98)=2.206$, $p<0.05$. The between-groups comparison for this same analysis (EXT, PIM 1.0 + RWD, and PIM 0.5 + RWD) yielded a significant difference between groups in overall amount of responding, $F(2,21)=19.938$, $p<0.0001$. A post-hoc Tukey HSD test revealed that the animals treated with 1.0 mg/kg PIM responded significantly less than animals treated with 0.5 mg/kg PIM, and that the animals in the EXT condition responded significantly less than animals in either of the PIM conditions. Thus, under these conditions, there is a clear difference in both the average rate of responding and the pattern of responding between PIM treated animals and animals in the EXT condition.

Moreover, home cage control animals (Fig. 3) failed to exhibit the typical anhedonic effect of comparatively high rates of responding on their fourth day of drug dosing and first day of testing. Compare day 4 for both groups in Fig. 3 with the corresponding day 4 performance of the drug groups in Fig. 2. Fourth day comparisons between drug-reward groups and their respective home cage controls revealed no significant differences (by independent groups t-tests on the rate measure). Moreover, as shown in Fig. 3, replication of the retraining day procedure with these home cage control animals did not produce an extinction-like pattern of responding across drug administrations, nor were there any significant differences between lick rates produced by four intermittent dosings of PIM and the first four days of drug

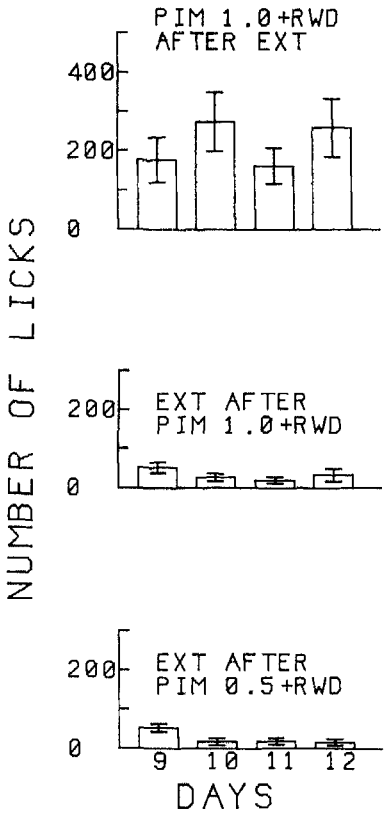

FIG. 4. Mean number of licks in 10-min sessions for 3 groups of rats tested for transfer effects. The vertical bars represent ±1 SEM. The data labeled PIM 1.0 + RWD AFTER EXT received 4 consecutive days of 1.0 mg/kg pimozide plus reward, while groups designated EXT AFTER PIM 1.0 + RWD and EXT AFTER PIM 0.5 + RWD received 4 consecutive days of control injections plus no-reward.

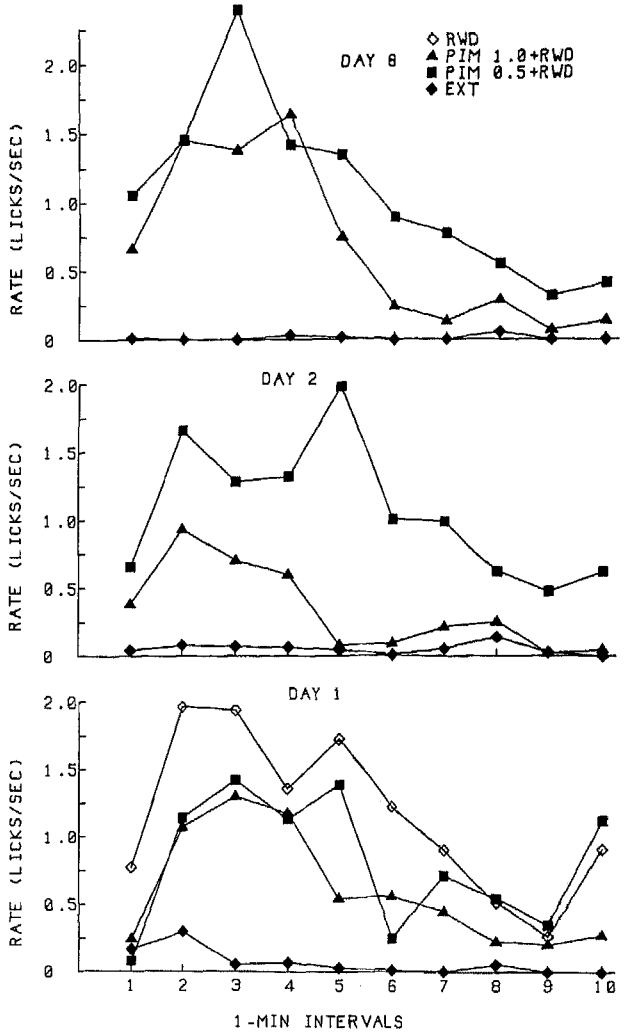

FIG. 5. Average rate of licking in licks/sec in 1 minute time bins for the four groups of rats in Fig. 2 on days 1, 2, and 8. Data for the RWD group were calculated by averaging each rat's performance over the last two days in the rewarded condition.

administration in the experimental groups. Use of retraining days, then, at least in this procedure, seems to have had little effect on the pattern of responding produced by PIM relative to a consecutive day dosing regimen.

Finally, the results of the transfer procedure were not comparable to those typically obtained in other anhedonia paradigms. When animals which had received eight consecutive days of drug dosing plus reinforcement exposure were switched to control injections and EXT for an additional 4 days of testing, they exhibited rates of responding comparable to animals during the first four days in the EXT condition (compare the lower two groups in Fig. 4 with EXT in Fig. 2). Conversely, animals which had received eight consecutive days of control injections in the EXT condition and were then switched to 1.0 mg/kg PIM injections and reinforcement exposure (top set of axes in Fig. 4) showed relatively high rates of responding indistinguishable from the first four days of the PIM 1.0 + RWD group (Fig. 2, days 1–4); a trend opposite of continued extinction. Since it is possible that transfer occurred on the first transfer day only, first day comparisons of these same groups were made via *t*-tests for independent groups. Each of these comparisons was nonsignificant.

Within-session analysis. The rate of responding produced by animals in the eight consecutive day treatment procedure (Fig. 2) were further analyzed to determine if the within session patterns of licking produced by the PIM treated animals were similar to animals in the EXT condition. The sessions were divided into ten, 1 minute time bins, and rates of licking were calculated for each bin on days 1, 2, and 8. These days were selected because days 1 and 2 show the greatest rate reductions for the PIM treated animals and day 8 represents the largest rate differences between the PIM treated animals and animals in the EXT condition.

As can be seen in Fig. 5 all four conditions (including no drug RWD), exhibited within session increases followed by declines in rate. Rate of responding was attenuated in a dose dependent fashion in the PIM treated animals; moreover, the patterns produced by the RWD group and the PIM treated groups were highly similar in that responding increased over

the first 3 minutes, then decreased through the middle of the session but increased in the last interval. The pattern produced by the EXT group was extinction-like as evidenced by the rate decreases observed early in the session. Moreover, Fig. 5 reveals that the rate of licking for the PIM treated animals increased across days 1, 2, and 8 for the PIM treated animals, whereas the pattern produced by the EXT animals was again much more extinction-like (across-session decreases in responses during the first minute of each session).

Since the animals in the EXT condition showed very rapid extinction during the first day of treatment, only the day one, within-session statistical analysis is reported. When the data from the two drug groups and one EXT group were analyzed with a SPF-ANOVA, a significant group effect, $F(2,21)=7.02$, $p<0.005$, a time bin effect, $F(9,189)=5.62$, $p<0.0001$, and an interaction effect, $F(18,189)=2.08$, $p<0.01$, were obtained. The group effect indicates that these three groups differ in the overall amount of responding in the session and is not surprising given the similar results obtained with the across-session analysis. The time-bin effect suggests that the within-session changes seen in Fig. 5 are genuine. However, the interaction seems to be largely attributable to the differential pattern of responding produced by the EXT animals relative to the PIM treated animals. This visual impression is verified by excluding the EXT animals from the analysis; this exclusion abolishes the significant interaction, $F(9,126)=1.13$, $p=0.349$. Thus, the significant interaction depended on the fact that the within-session pattern for the EXT group differed from the within-session patterns for the PIM treated groups.

ILI and Median Lick Duration

Across-session. On the measures of lick duration and median ILI of the first mode (intervals less than 0.2 sec), reliable drug effects were observed (see Fig. 6). Little or no licking by the EXT animals precluded an eight day comparison of this group with the PIM treated animals on the duration and the ILI measures (i.e., no responding results in an unacceptably high level of missing data on these measures, whereas with the average rate measure a zero value is a legitimate data point). A SPF-ANOVA on the ILI data revealed a significant dose response effect, $F(2,21)=8.558$, $p<0.01$, and the across-days repeated measures factor was not significant. The retraining day procedure used with the home cage controls also produced a lengthening of median ILI <0.2 sec on drug assessment days. When data from the four intermittent drug days (Fig. 3) and data from four randomly selected days of the injection control animals were entered into a SPF-ANOVA the dose response effect on ILI was also significant, $F(2,20)=25.400$, $p<0.0001$.

The duration of individual licks also tended to be lengthened by PIM treatment. Animals treated with 0.5 and 1.0 mg/kg PIM for eight consecutive days exhibited increased lick durations relative to injection control animals on each of these eight days (Fig. 6). By SPF-ANOVA the effect did not quite reach statistical significance, $F(2,21)=3.031$, $p=0.068$. Similarly, animals receiving the intermittent drug procedure exhibited a tendency to lengthen lick duration relative to baseline, though the effect fell short of statistical significance, $F(2,20)=2.980$, $p=0.074$.

First day comparisons. All the animals in the EXT condition licked to some extent on the first day of testing. Therefore, meaningful comparisons on this day could be made

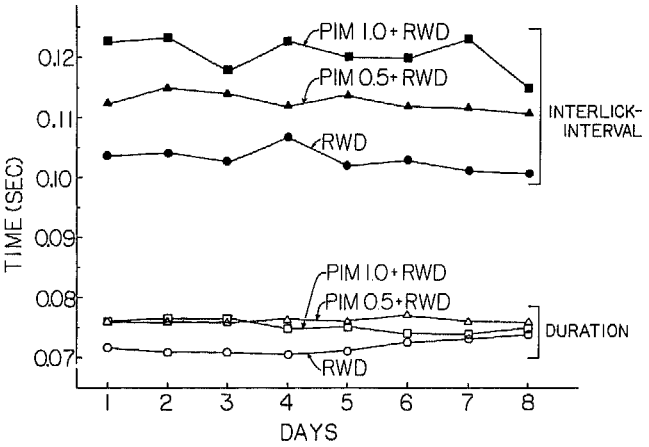

FIG. 6. Group means of interlick intervals for the first mode of the distribution and average median lick duration for rats receiving 8 consecutive days of either control injections plus reward (RWD) or pimozide plus reward (PIM 1.0 + RWD and PIM 0.5 + RWD). The corresponding rate data are depicted in Fig. 2.

between animals in the EXT condition and animals receiving PIM + RWD. A one way ANOVA for day 1 data revealed that the median ILI of intervals less than 0.2 sec was significantly lengthened in the PIM conditions relative to the EXT condition $F(2,21)=10.600$, $p<0.001$. The ILI group means (± 1 SEM) for extinction, 0.5 mg/kg and 1.0 mg/kg were, respectively, 0.097 ± 0.002, 0.113 ± 0.005, 0.122 ± 0.004 sec. Similarly, when the median duration data for these same animals were examined with a one way ANOVA a significant group effect was obtained, $F(2,21)=15.350$, $p<0.0001$, indicating that lick duration was lengthened by PIM treatment relative to EXT. The duration group means (± 1 SEM) for extinction, 0.5 mg/kg, and 1.0 mg/kg were, respectively, 0.064 ± 0.002, 0.076 ± 0.003, 0.076 ± 0.001 sec. Thus, these measures reveal that PIM affects the properties of individual licks in a manner significantly different from extinction.

An additional "motor" measure for the first day of testing was the 5th percentile of the ILI distribution, a statistic which gives the time below which 5% of the intervals fall, thereby providing a quantitative description of the fastest (shortest) intervals. The purpose of this analysis was to determine if the neuroleptically treated animals produced any licks at the extreme left of the ILI distribution that were as fast as those produced in the non-drugged, rewarded condition. Though the drugged animals may exhibit proportionately fewer of the fastest intervals, one might argue that motor capacity is demonstrated if any of the intervals are as short in the drug state as in the non drugged state. The 5% cutoff (5th percentile) was selected to ensure that the value obtained for each rat included a minimum of four 0.01-sec intervals and ensures that the measure is not overly influenced by spurious recordings (i.e., whisker contact with fluid) that may occasionally occur. A oneway ANOVA revealed that the 5th percentile of the intervals was significantly increased by PIM treatment relative to baseline (RWD) conditions. The group mean 5th percentile values (± 1 SEM) for the RWD, PIM 0.5 + RWD, and PIM 1.0 + RWD groups were, respectively, 0.076 ± 0.003, 0.088 ± 0.006 and 0.116 ± 0.016, sec. The tendency for PIM treatment to shift the ILI distribution to the right (i.e., towards longer intervals) is illustrated in Fig. 1.

Finally, the effects of PIM treatment on the animals' tendency to emit relatively long pauses was assessed by analyzing the proportion of intervals in the overage class of the ILI distribution. The overage class includes all pauses made during a session that were 0.5 sec or longer. PIM treatment did not significantly increase the proportion of long pauses relative to baseline, though the trend was in a lengthening direction. The data for the RWD, 0.5 + RWD, and 1.0 + RWD groups were subjected to a oneway ANOVA with the following results, $F(2,21)=2.64$, $p=0.091$. The means ± 1 SEM for these proportions for the three groups were, respectively, 0.064 ± 0.016, 0.076 ± 0.013, and 0.111 ± 0.016.

DISCUSSION

Eight consecutive days of PIM treatment produced clear behavioral effects but failed to produce patterns of responding similar to animals receiving no-reward. Rather than exhibiting across session declines in rate, PIM treated animals displayed some behavioral tolerance in that by the last day of testing the rate-decreasing effects of PIM were less pronounced. This trend towards recovery on the rate measure seems inexplicable within the anhedonia interpretation of neuroleptic action, particularly since the number of drug assessments typically obtained was extended from four to eight in the present study. Similarly, an analysis of the within-session pattern of responding revealed that the pattern produced by the PIM treated animals more closely resembled that of the normally rewarded group responding at a generally lower rate, rather than animals in a no-reward condition. Thus, though PIM treatment produced clear rate-reducing effects in this context, there was little evidence that the pattern of responding was extinction-like, either within or across sessions. Slight supersensitivity effects by days 6, 7, 8 may provide an explanation for the tolerance effect on the average rate measure [17] in Fig. 2.

In the transfer procedure the supposed similarity of neuroleptic treatment and extinction conditions was assessed by shifting animals with a history of PIM plus reward to an extinction condition and vice versa. Presumably, further decrease in rate should be observed in each case since both neuroleptic treatment and extinction procedures are hypothesized to exert their effects by the same neural mechanism, namely failure to activate the final common path of the reinforcement substrate of the brain [26]. However, transfer effects are typically obtained only when animals are shifted from an extinction condition to a PIM-plus-reward condition. Shifts from PIM-plus-reward conditions to extinction conditions often produce increases or no change in rate of responding [12, 18, 19, 24]. In the present experiment, animals switched from PIM treatment with reward, to a no-reward condition exhibited lower rates of responding in the no-reward condition. Though response rates were lower in the postshift, relative to preshift conditions, rates were indistinguishable from animals in the no-reward condition that had no prior history with PIM, and hence are not attributable to transfer effects. Conversely, the PIM 1.0 AFTER EXT animals showed increases in responding when switched from no-reward to the PIM plus reward condition. Moreover, these rates were indistinguishable from those of animals not having the previous no-reward history. In this transfer procedure then, the conditions (either drug or extinction) which produced increases or decreases in responding when reversed, were opposite those usually obtained with lever pressing, and did not seem to be due to exposure to the first condition. What is of note in these results is that prior exposure to either the no-reward or PIM + RWD conditions does not affect the post-shift rates of responding in either post-shift condition. Similar failures to observe transfer effects in either shift condition have also been reported [15].

PIM's dose dependent increase of median ILI and its lengthening of median lick duration suggest that PIM impairs the motor performance of the lick response. The assumption that these measures of individual responses are indicative of motoric processes seems warranted since licking is a biologically primitive, reflexive response, with a relatively invariant, stereotypic topography [2, 14, 23]. A rightward shift in the ILI frequency distribution indicates that the shortest times (fastest licks) that the animals produced in the drugged state are generally longer than in the nondrugged state. This shift to the right in the ILI distribution was observed even when only the very shortest times (the shortest 5%) at the extreme left of the distribution are considered. Moreover, in that PIM treatment significantly increased the duration of individual licks relative to non-drugged, no-reward conditions suggests that the lengthening of individual response properties cannot be easily attributed to reward or motivational deficits. Thus, the slowing of individual licks observed in the present study suggests that PIM impairs the ability of rats to lick as fast as normally motorically possible.

As has been observed elsewhere [13], the length of the intervals in the second mode of the ILI distribution are almost precisely the interval length that would be expected if the rat had skipped a lick during the lick burst. Our observations suggest that during these "skipped licks" the rat's tongue is rolled backward as if to bring the fluid further into the oral cavity, though others have suggested that the animal is simply licking at half speed [13]. The tendency for PIM treatment to shift the ILI distribution to the right was accompanied by an increase in the proportion of intervals in the second mode of the ILI frequency distribution. The increase in the proportion of intervals in the second mode was observed in nearly every PIM treated rat by visual inspection of computer generated plots similar to Fig. 1. This increase in "missed licks" was not quantified since shifts in the first mode seemed to characterize PIM's tendency to slow individual licks and the processes reflected by the "missed licks" are less clear. Since these longer intervals occur during bursts of licking they do not seem to reflect motivational deficits. Rather, if one were to look at the ILI distribution for motivational deficits, one should examine the intervals on the right hand side of the distribution, where the long pauses that occur between bursts of licking are reflected. Relative to baseline PIM treatment did not significantly increase the proportion of intervals greater than 0.05 sec. Any trend toward proportionately more long pauses would suggest that a part of PIM's rate reducing effects may be attributable to a motivational deficit. However, an impaired ability to initiate movement (e.g., [8]) may also account for increases in the proportion of longer pauses.

The data obtained by the present procedures seem to implicate motoric deficits rather than reward deficits in accounting for the effects of PIM on licking in non deprived rats. Specifically, these data seem congruent with previous research [3] which suggested that responses with low kinetic requirements do not show extinction like effects in response to neuroleptic challenge and hence the "anhedonia" phenomenon may be obtainable only by employing a response with high kinetic requirements (i.e., lever pressing). Upon

superficial examination, one published study on licking in rats appears to contradict this conclusion [22]; however, examination of the procedures showed that the rats in this study were required to rear up a considerable distance above the floor to contact the licking tube to receive brain stimulation. This rearing component of the operant increased the kinetic complexity of the response, and this may explain why neuroleptics' effects on bar pressing and licking were similar in the cited study.

Of course, neuroleptics exert their behavioral effects through multiple processes and neither reward deficits nor dissociative effects can be ruled out as partial explanations for the drug-induced rate reductions demonstrated in the present experiment. However, the methodology used here (response with low kinetic requirements, relatively extended testing, non deprived animals, reinforcer with high hedonic value, and detailed measurements of individual licks) high lights the important role motor phenomena play in neuroleptics' constellation of behavioral effects.

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