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Force-Proportional Reinforcement: Pimozide Does Not Reduce Rats' Emission of Higher Forces for Sweeter Rewards

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KIRKPATRICK, M. A. AND S. C. FOWLER. *Force-proportional reinforcement: Pimozide does not reduce rats' emission of higher forces for sweeter rewards.* PHARMACOL BIOCHEM BEHAV 32(2) 499–504, 1989.—A two-step force-proportional reinforcement procedure was used to assess the efficacy of a sucrose reward under neuroleptic challenge. The force-proportional reinforcement method entails an increase in the quality of reward contingent upon higher force-emission. This paradigm was conceived as a rate-free means of addressing the putative anhedonic effects of dopaminergic receptor-blocking agents. Results failed to support the anhedonia interpretation of neuroleptic-induced response decrements: Pimozide did not diminish the ability of a high-concentration sucrose solution to maintain elevated response forces. Alternatives to the anhedonia interpretation were discussed with emphasis on the drug's motor effects in the temporal domain.

Neuroleptics Pimozide Response force Force-proportional reinforcement Sucrose Rats

WHILE it is well documented that relatively high doses of dopamine-blocking neuroleptic drugs produce motor impairment in both humans [e.g., (2,3)] and laboratory animals [e.g., (10, 21, 24)], it is not clear whether such effects are responsible for the suppression of appetitively motivated behaviors at lower doses. Low-dose response decrements may be due to motoric processes similar to, or additional to those which produce catalepsy in experimental test animals and extrapyramidal side effects in human patients [e.g., (6, 7, 9, 17)]. Alternatively, drug-induced reductions in operant behavior have been attributed to an attenuation of the hedonic value of incentive-motivational stimuli [e.g., (26)]. One difficulty that has beset efforts to distinguish between these two alternatives has been reliance on response rate as the single dependent measure. Since rate may be expected to decline with either a diminution of a reward's hedonic value or the appearance of a motor deficit, a means of assessing reinforcement efficacy independent of response rate is needed.

One promising method for determining the efficacy of rewards in a free operant lever press situation independent of the frequency of responding is the force-proportional reinforcement paradigm (11, 12, 14, 22). This operant procedure varies quantity or quality of reward in relation to response force. Fowler (14) evaluated the effects of three different force-proportional contingencies on peak force and rate of response. The force-elevating effects of increasing concentrations of sucrose were compared with different quantities in varying numbers of incrementing steps. While response rate was shown not to differ among groups, the highest forces were engendered by a two-step contingency in which responses between 8–23 g produced an 8% sucrose solution, while forces 24 g or above yielded 24%.

The present study employed a two-step force-proportional reinforcement procedure in the fashion of Fowler (14). With this procedure, the ability of higher sucrose concentrations to maintain higher forces was assessed during neuroleptic challenge. If anhedonia is a major factor by which low-dose response decrements are produced, a high concentration of sucrose should lose its ability to maintain higher forces as its hedonic value is diminished. The failure of force to decrease with increasing dose of pimozide may be taken as evidence that the efficacy of the reward is retained under neuroleptic challenge.

METHOD

Subjects

Sixteen male Sprague-Dawley rats, approximately 50

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days old upon receipt form the Holtzman Company, were used. Animals were housed individually in home cages located in a vivarium maintaining a 12-hr light-dark cycle of illumination (lights off 10:00 p.m. to 10:00 a.m.). The rats were maintained on a food deprivation regimen (with water continuously available in the home cage) that provided 1-hr access to Lab Chow approximately 30 min after experimental sessions.

Apparatus

Two simultaneously operative, sound-attenuating operant conditioning boxes were used. Each wooden enclosure contained a 24×20×20 cm operant chamber constructed of two Plexiglas sides and a Plexiglas top. Flooring consisted of equally spaced 6.5-mm dia. stainless steel rods running parallel to the front of the chamber. The front wall of the chamber constituted the intelligence panel and was of aluminum construction. Centered on the front panel approximately 4 cm from the top was a 24-volt house light (GE1819), which provided low-level illumination during all experimental sessions. Below the light and approximately 3.5 cm to the left of the center of the front panel was a 3.0 cm wide and 2.0 cm high rectangular opening, the bottom of which was 6.0 cm above the floor of the chamber. The opening in each chamber permitted access to a silent, virtually isometric force-sensing manipulandum produced by Sanborn Company (Model FTA-100) and serviced by electronic circuitry that had a low pass frequency of 10 Hz. The top surface of each force transducer was an 18 mm circular disk, the center of which was located on the outside of the chamber 2.5 cm from the aperture in the front panel. The horizontal surface of the disk was centered 0.5 cm above the lower edge of the opening, thereby making it available for downward vertical press responding only by an extended forelimb. In the lower right quadrant of each front panel was a rectangular recess through which the animal gained access to either of two solenoid-operated dippers. The recess measured 7.3 cm wide, 4.8 cm high, and 4.4 cm deep. Its bottom was 0.7 cm above the floor of the chamber, and the center of the opening was 7.9 cm from the center of the transducer access aperture. The dipper access holes were located side by side, equidistant from the center of the opening. Each dipper carried a different concentration of sucrose solution during the force-proportional reinforcement phase of the experiment. In this manner, the two different concentrations were simultaneously available and discriminable by virtue of position as well as taste.

Programming of contingencies and recording of data were accomplished via an Apple IIe microcomputer and a Franklin Ace 1000 microcomputer, each with associated peripherals. System details are provided by Fowler (15). Each computer controlled an A/D converter that sampled the analog voltage from the transducer every 0.01 sec. From the digitized measurements were recorded the maximum force amplitude (peak-force) and duration of each response meeting or surpassing a 4 g threshold. Response rate was based on all responses above the 4 g threshold.

Procedure

Following acclimation to the deprivation regimen, the animals were randomly divided into two groups of eight. Throughout magazine training, shaping, and an initial continuous reinforcement (CRF) session, dippers alternated and carried the same 16% sucrose. Dippers, having a volume of 0.1 ml, were made available for a duration of 4 sec for each reinforcement. Magazine training began with dipper presentation on a variable time schedule. Upon completion of magazine training, rats were manually trained, via the method of successive approximations, to reach through the aperture in the intelligence panel. For shaping purposes, the manipulandum was initially positioned tangent to the opening in the chamber and was gradually moved back to its standard 2.5 cm distance from the outside chamber wall. Shaping was considered complete when each rat emitted 10 unassisted reinforced responses (i.e., 4 g or more). Following magazine training/shaping, all animals received one 15-min session of CRF training under a 16 g force criterion (minimum force required for reinforcement delivery).

After the one session of 16 g–16% CRF training, differential group treatment began with 15 min daily exposure to their respective force-proportional reinforcement contingencies. The force-proportional group (PRO) gained access to an 8% (by weight, sucrose mixed with tap water) sucrose solution for response forces ranging from 8 g to 23 g. A 24% sucrose solution was available for all responses meeting or exceeding a 24 g force criterion. Responses falling between 4 g and 8 g had no programmed consequences. An inverse proportional group (INV) was treated similarly, except that the lower range of forces (8 g to 23 g) was rewarded with a 24% sucrose solution, while responses of 24 g or more received an 8% solution. The inverse proportional group was required in order to assess potential force elevating effects associated with the higher concentration independent of the contingency, and to demonstrate that rats in either group could learn to emit forces appropriate for obtaining the higher concentration regardless of whether the force requirements were high or low. Sucrose concentration presented via either dipper was counterbalanced between animals, so the concentration farthest to the right was lower for half the subjects, and higher for the other half. Following 15 days of PRO or INV training, assessments of drug effects were carried out.

Three doses of pimozide (PIM; 0.125, 0.25, and 0.50 mg/kg) were evaluated in all subjects. Injections were counterbalanced between animals in an approximated Latin square design, with PIM injections occurring on every third day. Two training sessions separated drug days, with the second of the two training days including injections of the vehicle (an 0.1 N solution of tartaric acid in bacteriostatic saline) without PIM. All injections on drug and vehicle days preceded each session by four hours, and each was administered intraperitoneally (IP) at a volume of 1.0 ml/kg.

Due to disk drive failure, data for the second drug day were lost for half of the subjects in each group. As a result, the second vehicle and drug determination were repeated as a fourth administration following the last scheduled drug day. These determinations were spaced in the same fashion described above, with one injection-free day interceding between the third drug day and the fourth vehicle exposure. For all subsequent analyses, the fourth drug and vehicle exposures replaced the second drug day where data were absent, and were averaged with the subjects' performance on the second drug day where information had not been lost, thus providing data for all animals at three different doses. Prior to analysis of variance procedures, all data for peak force and duration were log transformed in order to correct for heteroscedastic distributions. No such transformations were carried out for the rate data, where variances were more homogenous.

RESULTS

Separate analyses were conducted for acquisition and drug effects. The effects of the force-proportional contingency on response acquisition (see Fig. 1) were assessed for each dependent measure via a 2×15 (group by session) split plot factorial analysis of variance (SPF-ANOVA) with repeated measures on the second factor. Analysis of response rate data indicated that the total number of responses differed across sessions, $F(14,196)=4.769$, $p<0.0001$. A significant group-by-session interaction, $F(14,196)=6.70$, $p<0.0001$, revealed differences in the across session trends dependent upon group membership, as is visually apparent in Fig. 1A.

Acquisition effects on peak force provided evidence that the proportional contingencies were learned. The PRO group increased their peak forces while response force in the INV group declined, $F(1,14)=37.991$, $p<0.0005$. The initial similarity and subsequent divergence of forces was further substantiated by a significant group-by-session interaction, $F(14,196)=16.607$, $p<0.0001$. These are pictured in Fig. 1B. Duration (see Fig. 1C) also differed significantly across training sessions, $F(14,196)=5.228$, $p<0.0001$, and a group-by-session interaction was confirmed, $F(14,196)=7.211$, $p<0.0001$. Between group differences for duration approached significance, $F(1,14)=4.247$, $p<0.10$.

Dose effect analyses of PIM were performed for each of the three dependent variables (see Fig. 2). Response rate data for the proportional reinforcement group (PRO) and the inverse proportional group (INV) were entered into a 2× 4 SPF-ANOVA. A significant dose effect was obtained, $F(3,42)=9.334$, $p<0.0005$, indicating that the overall amount of responding declined as a function of dose (Fig. 2A). A significant group-by-dose interaction was also observed, $F(3,42)=3.916$, $p<0.05$, indicating that the effects of dose differed between the two groups. Visual inspection of Fig. 2A reveals a sharper rate decline for the INV group and a flattening of the dose effect curve for the PRO group.

An SPF-ANOVA for peak force yielded a significant group effect, $F(1,14)=51.870$, $p<0.0001$, demonstrating that the PRO and INV groups differed in their force emission (Fig. 2B). Visual inspection and comparison of group means across doses (PRO=28.57 g; INV=15.14 g) reveals higher forces in the PRO group. Unlike results from other studies [e.g., (16,17)], pimozide did not significantly increase peak force, nor was a significant dose-by-group interaction observed.

Analysis of the duration data indicated that the mean time required for completion of a response differed between groups, $F(1,14)=6.371$, $p<0.05$. Examination of means for the two groups showed longer durations for the PRO group (PRO=0.14 sec; INV=0.08 sec). The dose effect was marginally significant, $F(3,42)=2.746$, $p=0.054$.

Although it seems reasonable to assume that mean peak force (i.e., the mean of the distribution of peak forces emitted by a single rat in one session) adequately reflects the force emission performance during vehicle and drug treatment, it is possible that the drug acted in such a manner as to raise the number of responses near 24 g (but still below 24 g) and to reduce the number of responses well above 24 g (but still above 24 g) resulting in no change in the mean. One way to rule out this possibility is to inspect the shape of the peak force distributions for each individual subject on vehicle and drug days in the PRO group. Our visual inspection of these distributions provide no evidence for the occurrence of such a drug-induced "clumping" of peak forces near the 24 g

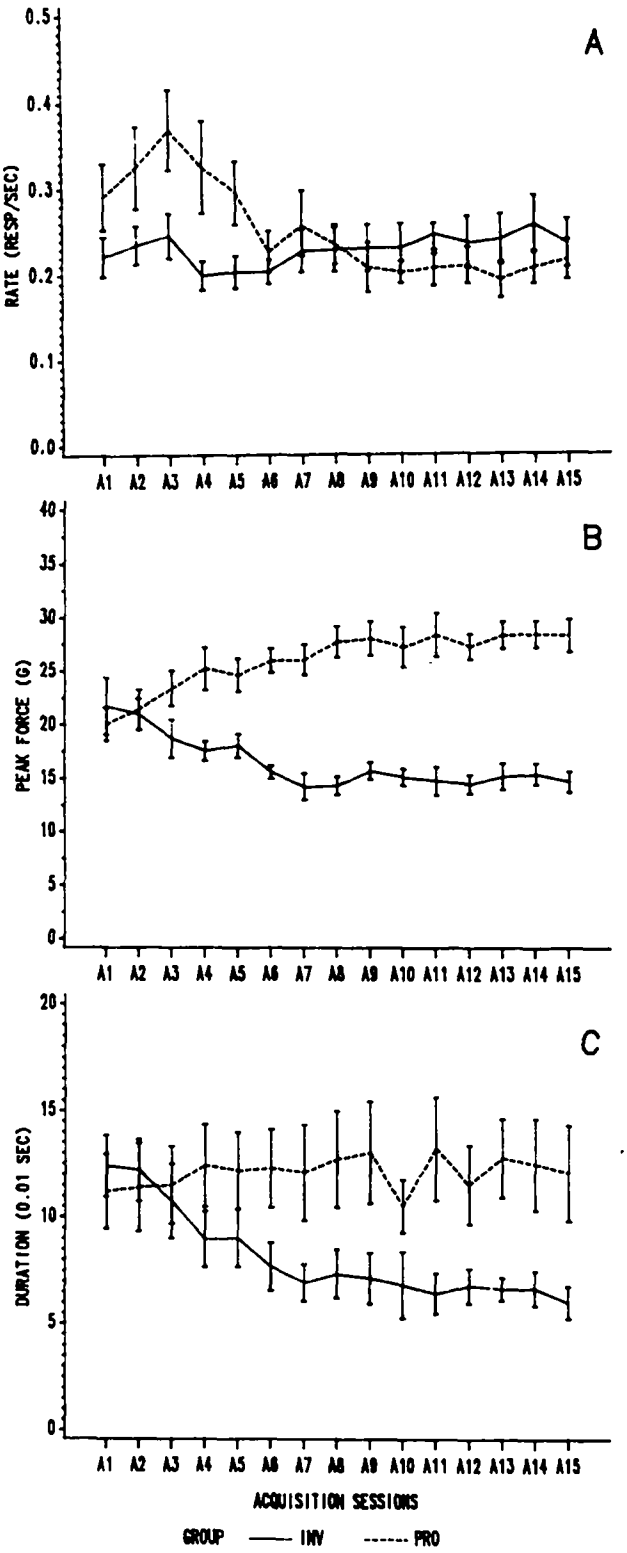

FIG. 1. Response rate (Panel A), mean peak force (Panel B), and average duration (Panel C) as a function of daily sessions of exposure either to a two-step force-proportional reinforcement contingency (PRO) or to an inverse force-proportional contingency (INV). Brackets on the vertical lines indicate two standard errors of the mean.

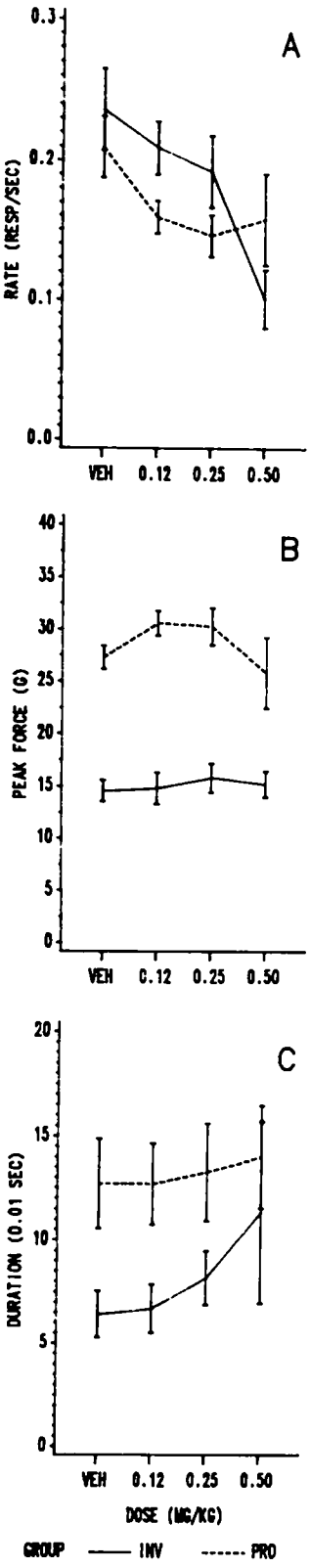

FIG. 2. Effects of the indicated doses of pimozide on response rate (Panel A), mean peak force (Panel B), and average duration (Panel C) for PRO and INV groups. Brackets enclose two standard errors of the mean.

criterion for the higher concentration of sucrose. More quantitatively, we calculated the percent of responses in the PRO group below 24 g and above 24 g for the first vehicle and drug days; for the eight PRO animals the mean percent of peak forces below 24 g on vehicle day 1 was 32.96%, and the mean percent of peak forces above 24 g was 67.03%. On drug day 1, the mean percent below 24 g had dropped to 27.15%, while 72.85% of the responses were above 24 g. These percentages indicate that pimozide did not somehow increase the amount of low-force responding (i.e., below 24 g) without changing the mean peak force.

DISCUSSION

Acquisition

The significant force differences observed between PRO and INV groups during acquisition demonstrated that rats learned the force-proportional contingency (see Fig. 1B). Both groups clearly adjusted their force emission in order to procure 24% rather than 8% sucrose. Initially, force emission was nearly equal for the two groups, but by the 15th session response forces for the two groups were substantially different. These results are consistent with previous findings that a two-step force-proportional contingency will effectively shape peak force in the direction that produces the more preferred reward (14).

Early differences in response rate across sessions, as well as a significant group by session interaction, appear to be consequences of the degree of success with which 24% sucrose was obtained. Casual observations revealed that rats tended to not consume the 8% when it appeared, but responded until the 24% sucrose was available. The initially low forces in the PRO group therefore suggest that early in training these subjects spent less time away from the operandum consuming rewards compared to the INV group. Under force-proportional conditions, the number of responses not producing the higher reward tends to diminish across training sessions (11). As forces conformed more closely to the criterion for 24% in the PRO group, more time was spent consuming rewards. Rate changes across sessions thus reflect the stabilization of response force across acquisition.

Pimozide Treatment

Contrary to previous work (16,17) reporting statistically significant, but small, peak force elevations produced by neuroleptics, such a result was not seen here. A possible reason for this outcome is the fact that in the current study both groups had the benefit of relatively rich feedback following their force emissions, and both groups probably explicitly learned to have greater control over their forces than in situations where simpler contingencies prevailed, as in the aforementioned reports. Thus, force may have been less susceptible to disruption by PIM than in the previous studies because the force emission was under greater control of interoceptive and exteroceptive stimuli. This interpretation is supported by the peak force data from acquisition which clearly suggest that the rats learned to control their forces as a function of training sessions. Furthermore, it should be noted [consistent with (16,17)] that PIM did not reduce peak force in either group.

The effects of PIM on peak force under proportional reinforcement conditions failed to support the anhedonia interpretation of neuroleptic action (26). Had PIM attenuated

the efficacy of the 24% sucrose, a significant dose-dependent force decline or a dose by group interaction should have been evident. However, increasing doses of PIM failed to attenuate force emission in either group, suggesting that the 24% sucrose retained its reinforcing efficacy and maintained elevated, as well as lowered, levels of force. Given the absence of force-reducing drug effects, the dose-dependent rate decline and concomitant trend toward increased duration appear more consistent with theoretical formulations emphasizing the motor effects of neuroleptics. That is, rate may be viewed in part as an index of response initiation, which is impaired by neuroleptics (1,23). Duration increases may be seen as a neuroleptic-induced motor effect restricted to the temporal domain of behavior (16). Similar dose-dependent duration increases have been observed with various neuroleptics in both lever-pressing (8, 9, 13, 16, 17, 25) and licking paradigms (19,20). Furthermore, the Fowler, LaCerra and Ettenberg (17) study revealed that haloperidol-induced increases in response duration could be attributed in part to increases in the fall time from the peak amplitude of response. That is, the time required to terminate a response increased, consistent with the view that neuroleptics exaggerate static postural support mechanisms (5,27). If this view is correct, and if pimozide exhibits a profile similar to that of haloperidol along these temporal dimensions, then the rate decline and parallel trend toward increased durations observed in the present experiment may be at least partially due to motor mechanisms independent of the incentive/motivational value of hedonic stimuli.

Interestingly, the PRO group displayed a less precipitous rate decline across doses than was found for the INV group. The group by dose interaction for response rate may provide a modicum of evidence in favor of the stimulus efficacy hypothesis (4). According to this view, neuroleptics blunt the associational efficacy of behavior-controlling stimuli; the more intense the stimuli the less the behavioral disruption produced by neuroleptics. It is possible that the kinesthetic and proprioceptive feedback associated with higher forces remains more salient and therefore more efficacious under PIM challenge. Consistent with this perspective, responding at the highest dose in the INV group was more attenuated under conditions of comparable gustatory stimulation because interoceptive response feedback stimuli were of a lesser magnitude than in their higher force counterparts (PRO). As a consequence, INV response rates were lower than PRO response rates at the highest dose.

Regardless of one's theoretical stance, the demonstration that pimozide does not attenuate forces shaped upward by the force proportional contingency shows that pimozide does not compromise motor capacity in the force domain of behavior and that the pimozide-treated rat is capable of emitting forces appropriate to the incentive/motivational conditions even if its overall behavior is slowed.

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