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Effects of Pimozide on Emitted Force, Duration and Rate of Operant Response Maintained at Low and High Levels of Required Force

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FOWLER, S. C., S. E. GRAMLING AND R.-M. LIAO. *Effects of pimozide on emitted force, duration and rate of operant response maintained at low and high levels of required force.* PHARMACOL BIOCHEM BEHAV **25**(3) 615–622, 1986.— The behavioral effects of pimozide (0.25, 0.5, and 1.0 mg/kg) were assessed in two separate experiments in which session mean peak force, maximum peak force, and response duration served as the dependent variables complementing operant response rate. In the first experiment, two groups of water-deprived rats were trained on a continuous reinforcement (CRF) schedule for reaching out and pressing downward on a force transducer with peak forces of at least 4 g (low-force group) or 40 g (high-force group). In the second experiment a pull-type response topography and fixed ratio 20 were used, and force requirements were 4 g for the low-force group and 100 g for the high-force condition. Under these conditions pimozide decreased response rate and increased response duration irrespective of response topography, required force, or schedule of reinforcement. Neither mean peak force nor maximum peak force were significantly decreased by the drug, and in the low-force CRF condition a small but significant dose-related rise in mean peak force was observed. It was hypothesized that neuroleptics exert their motor-impairing effects primarily in the temporal domain of behavior but do not appreciably affect the force dimension of performance capacity. And these temporal domain effects may be reflected in differences in the kinetic requirements for the overall behavior and not just the response itself. Additionally, the possibility that some of the observed effects could be accounted for by "anhedonia" was addressed.

Pimozide Neuroleptics Force of response Duration of response Response rate Rats

ALTHOUGH it has been widely observed that neuroleptics reduce the rate of appetitively motivated operant responding in rats, considerable disagreement exists regarding the relative contributions of the various behavioral processes proposed to account for this phenomenon. Three different, but not mutually exclusive, hypotheses have emerged from work in this area: the motor [7, 12, 13, 15], anhedonia [17, 25, 34, 36] and associative factors hypotheses [4, 5, 6, 27]. The motor hypothesis or more specifically the kinetic requirements hypothesis [11] was the primary heuristic for the work reported here.

When rats' operant behavior is maintained by electrical stimulation of the brain, Ettenberg *et al.* [11] found that alpha-flupenthixol decreased lever pressing rate much more than it lowered the rate of a nose-poking response. On the basis of these data it was hypothesized that the "kinetic requirements" of the operant response could be an important determinant of the behavioral effects of neuroleptics. Following up on this idea, at least two reports [2,3] have operationalized kinetic requirements in terms of force on a conventional operant lever required to register a response, and have observed whether the resulting response rate interacted with the neuroleptic's effect. Neither study found appreciable evidence for the kinetic-requirements hypothesis in this paradigm. However, the use of spring-loaded levers with different force requirements is problematic [28] because it confounds a change in the definition of the dependent variable (occurrence of responses over time, i.e., rate) with manipulation of the independent variable (required force). A related problem is that some motor characteristics of individual responses cannot be measured by switch closure; one cannot determine the degree to which forces may

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be in excess of the requirement, nor can one measure the presence of any unsuccessful attempts at switch closure. Under conditions conventionally defined as continuous reinforcement, rats come to adjust their forces so that about 60–70 percent of their responses exceed the force criterion for reinforcement [29], i.e., both sub- and supra-criterion responses are made. Furthermore, experimental conditions such as extinction [18, 20, 29], fixed ratio (FR) responding [22,29] or pull (instead of press) topographies [24] may lead to force emission dramatically higher than the required force, and force of response may be increased by manipulations that lower or do not affect rate [18]. Thus, a direct measurement approach (measurement of force and duration of individual responses) is required to observe adequately not only the effects of different kinetic requirements on operant responses but also the possible interaction of the force requirement with a neuroleptic.

Accordingly, the purpose of this work was to obtain descriptions of the effects of pimozide, a relatively specific dopamine receptor blocker [1], on peak force and duration of response under low or high force requirements. Two experiments are reported. In the first, water deprived rats made downward presses on a force transducer and received a water reinforcer on a continuous reinforcement basis for either 4 or 40 g of required force. The effects of three doses of pimozide were described in terms of mean emitted peak force, maximum peak force, response duration and conventional rate of response. The effects of pimozide on these variables were evaluated in a second experiment in which a relatively high-force generating pull-type topography [24] was used at two different levels of required force.

GENERAL METHOD

Subjects

Thirty-four male Sprague Dawley rats from the Holtzman Co. served as the subjects. In Experiment 1 the 14 rats averaged 310 g and the 20 rats in Experiment 2 weighed an average of 340 g. Food was continuously available in the individual home cages. Water was only available for about 4 min daily beginning 30 min after experimental sessions (the exact access time varied for each rat in an attempt to keep body weight constant at about 80% of pre-deprivation level). Subjects were run during the light portion (10:30 a.m.–10:30 p.m.) of the vivarium light-dark cycle.

Apparatus

Operant responses were measured in two chambers (23 cm long, 20 cm wide and 19 cm high) each contained in sound-attenuating plywood enclosures lined with sheetrock and overlaid on the inside with another layer of plywood painted flat white. Chamber front panels were fashioned of 0.16-cm aluminum, while the top and sides were 0.64-cm clear Plexiglas. Stainless steel rods 0.64-cm in diameter formed the floor. Illumination was provided during sessions by a 24-volt GE 1819 light bulb centered in the front panel 4 cm from the chamber top. Mounted on the lower right front panel was a cylindrical recession that permitted access to a solenoid operated dipper with a volume of 0.05 ml. A rectangular opening, 3.0 cm wide and 2.5 cm high, was centered in the front panel 5.5 cm above the grid floor. This aperture provided access to the manipulandum positioned outside the chamber. In Experiment 1, two Sanborn force transducers (model FTA-100) served as the silent, practically isometric force-sensing manipulanda. For each chamber the portion of the transducer available to the rat was an 18 mm diameter disk. Transducers were positioned (after the initial shaping) so that the center of the disk was 2.5 cm from the outside of the chamber wall and the surface of the disk was 0.5 cm above the lower edge of the access aperture. The disk itself protruded 3 mm above a stainless steel housing that provided 1 mm of clearance around the circumference of the disk.

For experiment 2, the chambers were equipped with "pull-type," wire bail manipulanda attached to Grass Instruments force transducers (model FT .03 with the 1 kg springs installed). The wire bail, which the animal grasped and pulled, was triangularly shaped with the plane of the triangle being parallel to the grid floor. The 18-mm base of the triangle was 2.5 cm from the outside of the chamber front wall, and the apex of the triangle was affixed to the transducer shaft. The wire used to make the bail was approximately 1 mm in diameter and underwent no deformations up to the maximum forces applied. In both experiments the electronic circuitry, which serviced the transducers, was set to filter out frequencies above 10 Hz, thereby completely rejecting natural frequency vibrations which occasionally resulted from a flick of the rats claws on the operanda.

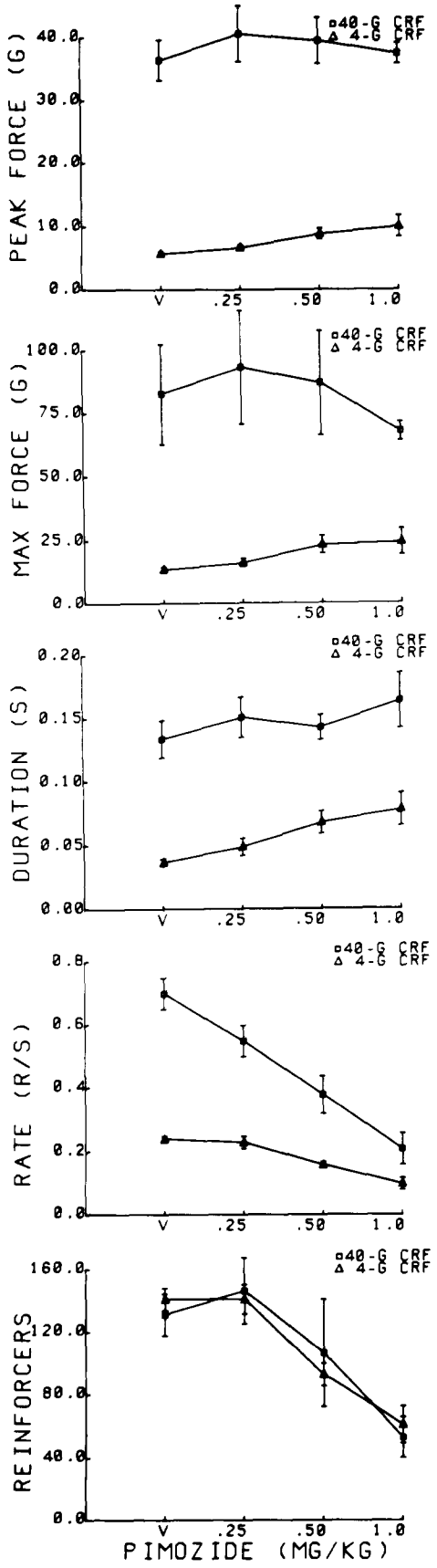
Contingencies were programmed and data were recorded with two microcomputers (an Apple IIe for one chamber and a Franklin 1000 for the other) and necessary peripherals. Details of these measurement techniques are described elsewhere [19,21]. Using an analog-to-digital converter the computer sampled the output of the transducers every 0.01 sec. These samples were used to define a response and its peak force and duration. Regardless of the force requirement a response was defined by the force amplitude rising above 4 g and then falling below 4 g. Peak force is the maximum value reached during this interval, and duration is the time between the upward and downward crossings of the 4-g threshold. In both experiments the peak force was used in two ways as a dependent variable. The mean of the peak forces for all responses in a session served as a measure for each subject, and this is called mean peak force. The maximum peak force for a session (a single value) was the second variable. Response forces were measured with a precision of 1 g and duration with a precision of 0.01 sec.

Drug

Pimozide (McNeil) was mixed with a quantity of 1 N tartaric acid sufficient to achieve solution which was then diluted with sterile saline to obtain a stock concentration of 0.5 mg/ml. An equivolume dilution of tartaric acid with saline served as the vehicle control injection. The doses, 0.25, 0.50, and 1.0 mg/kg, were injected (in 1.0 ml/kg volumes, achieved by further dilution of stock with saline) intraperitoneally 4 hr before the experimental sessions.

EXPERIMENT 1

Ford *et al.* [16] examined the effects of chlorpromazine and clozapine on peak force and duration of response under high and low force requirements and observed small but statistically significant drug-induced reductions in mean peak force at doses that greatly lowered rate of response. For rate and mean peak force of response, interactions be-



tween drug dose and required force were not seen, thereby suggesting that the kinetic requirements had little effect on degree of drug response. However, that study did not provide a strong implementation of the kinetic requirements concept because the use of an FR schedule resulted in a relatively small force difference between the two groups. Since chlorpromazine and chlozapine have appreciable anticholinergic activity [31] and chlorpromazine possesses additional antiadrenergic properties [1], neither drug is best suited for examining hypotheses specifically about dopamine blocking agents. For these reasons Experiment 1 examined the effects of pimozide on rats trained on a continuous reinforcement (CRF) schedule on either a low- (4 g) or high- (40 g) force requirement. In addition to recording the session mean peak force and the session mean duration for each rat, this experiment also recorded the maximum peak force value. It was thought that this variable would be one way to define experimentally (and independently of rate) the upper limits of performance capacity.

Procedure

Eight rats were assigned to a low-force condition in which presses of 4 g or more on the force-sensing disk produced a water reinforcer. Six additional rats were assigned to a high-force (40 g) condition. Even though 40 g of force was required for reinforcement in the high-force condition, all responses above the 4-g threshold were recorded just as in the low-force group. After one 30-min session of variable time 1-min magazine training with the manipulandum aperture covered, the rats' responses were shaped by a combination of automated and manual methods that involved gradually moving the manipulandum from its initial position flush with the outside of the chamber wall to its final position 2.5 cm away, as well as providing experimenter delivered reinforcers in order to keep the animals responding. Although shaping time varied somewhat for each rat, an average of three 15-min sessions was needed for the low-force group and ten 15-min sessions for the high-force group. After shaping, the rats received 14 daily, 10-min sessions of CRF training before drug evaluations commenced. Pimozide was given once at the 0.25 and 1.0 mg/kg doses and twice at the 0.5 mg/kg dose, with each drug treatment day preceded by a control injection day and with at least three sessions separating drug days. Injection control performances were averaged for each rat, as were the two sessions at 0.5 mg/kg, to yield data appropriate for a two way split-plot analysis of variance. Common logarithm transformations were performed on the force data to produce homogeneous variances suitable for analysis of variance hypothesis testing.

FIG. 1. Dose response functions for the indicated dependent variables for Experiment 1. Peak Force and Max Force on the ordinates refer to mean peak force and maximum peak force, respectively. V on the abscissa is for vehicle control injection. Rats reached through an opening in the operant chamber and pressed down on a force-sensing disk. The brackets show ±1 Standard Error of the Mean (SEM).

TABLE 1

EXPERIMENT 1 RESULTS OF ANALYSIS OF VARIANCE FOR THE INDICATED DEPENDENT VARIABLES

Type of effect	Dependent variable	Degrees of freedom	F-value	*p*-value
4g vs. 40 g	mean peak force	1, 12	184.568	<0.001
	maximum peak force	1, 12	21.982	<0.001
	duration	1, 12	35.386	<0.001
	average rate	1, 12	149.000	<0.001
	reinforcers	1, 12	—	—
Dose	mean peak force	3, 36	7.400	<0.001
	maximum peak force	3, 36	—	—
	duration	3, 36	9.401	<0.001
	average rate	3, 36	31.875	<0.001
	reinforcers	3, 36	20.582	<0.001
Interaction	mean peak force	3, 36	5.600	0.003
	maximum peak force	3, 36	—	—
	duration	3, 36	—	—
	average rate	3, 36	9.625	<0.001
	reinforcers	3, 36	—	—

These data are for the press topography and continuous reinforcement. Only significant F-tests are shown.

Results and Discussion

Data for Experiment 1 are shown in Fig. 1 and corresponding analysis of variance statistics are given in Table 1. Differences in force required for reinforcement resulted in large between-group differences for mean peak force, maximum peak force, duration, and average rate, but not for number of reinforcers obtained per session (see Table 1, top third). Except for maximum peak force, pimozide had significant effects on all the dependent variables (Table 1, middle third). As shown in Fig. 1 and confirmed by analysis of variance (Table 1, bottom third), drug treatment interacted with required force for two dependent variables: mean peak force and average rate. In the case of mean peak force, a simple main effects F-test showed that the interaction was due to a significant drug effect in the low-force group, $F(3,36)=14.000$, $p<0.001$, but an absence of a drug effect in the high force group. For response rate the interaction arose from a significant difference between groups in the dose-related downward linear trend, $F(1,12)=6.593$, $p<0.05$.

There was no difference between the two groups in terms of number of reinforcers received (see Fig. 1), even though large differences in rate were quite apparent. Such an outcome may seem impossible for a CRF schedule until one recalls that the rate data for the high-force group are based on all the responses above 4 g. Thus, the higher force requirement produced many responses that fell short of the force criterion for reinforcement, and these subcriterion responses more than doubled the rate measure for the high-force group.

Unlike previous work with chlorpromazine and clozapine [13] the present findings provide little evidence that pimozide decreases mean peak force or maximum peak force of response. In fact, in the low-force group a small but significant rise in peak force was observed. Under selected circumstances several experiments [10,29] have demonstrated an *inverse* relationship between amount of reinforcement and mean peak force; i.e., reductions in amount of reinforcement produce increases in mean peak force. Therefore, the mean peak force data for the low-force group appear to be consistent with the anhedonia hypothesis because the effect of pimozide here appears to be similar to reduction in amount of reward. However, the magnitude of the pimozide-induced force increase was well short of what one would expect to observe for extinction or other large reductions in amount of reinforcement under these measurement conditions [20,29]. In addition, the high-force group did not show a significant trend toward higher forces after pimozide treatment, despite the fact that the maximum peak force data suggest that a ceiling on mean peak force had not been reached.

Pimozide's lengthening effect on response duration is in accord with several investigations on neuroleptics which used a variety of different responses, including presses on an ordinary spring loaded lever [13, 14, 32], presses on an isometric force-sensing manipulandum [16,22], and licking from a fluid reservoir [26,27].

Overall, Experiment 1 provides a modicum of evidence for both the anhedonia hypothesis (drug related force rise in the low-force group) and for the motor-kinetic requirements hypothesis (duration effect and the drug-by-required-force interaction for the rate variable).

EXPERIMENT 2

One possible explanation for pimozide's failure to decrease mean peak force and maximum peak force in the high-force group is that the response requirements, in terms of both force and number of responses, were not demanding enough to permit a neuroleptic effect to emerge. Similarly, the force requirement in the low-force group may have been

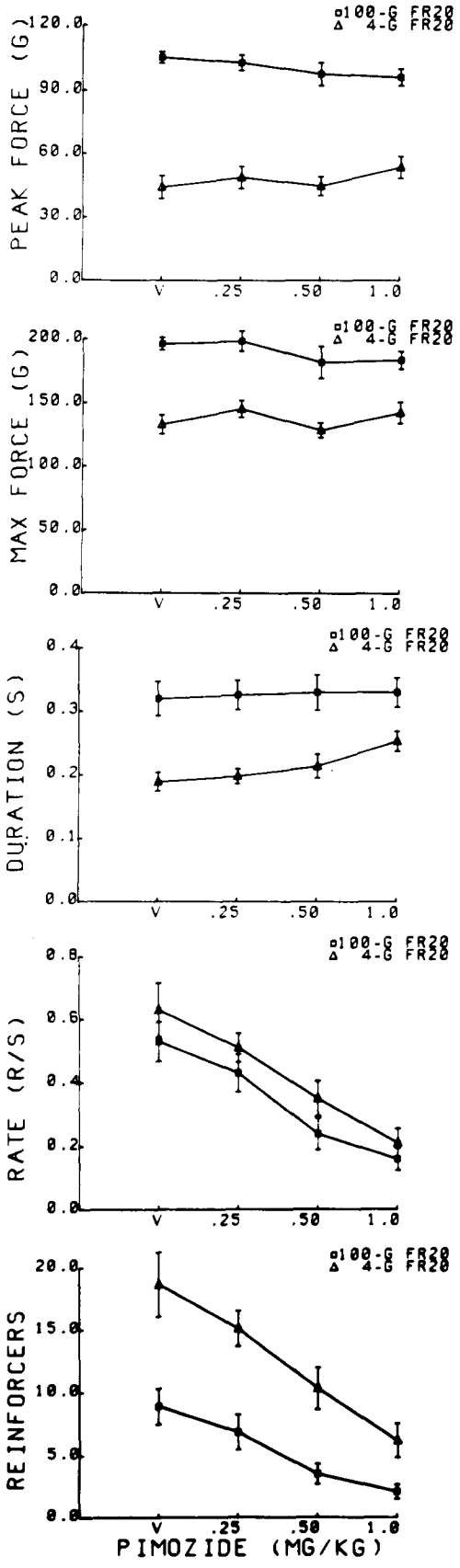


FIG. 2. Dose response functions for the dependent variables given on the ordinates of each set of axes (see caption for Fig. 1). These data are for Experiment 2 in which rats made operant responses by grasping and pulling on a wire bail attached to a force transducer. Brackets represent ±1 SEM.

so minimal that the force rise produced by pimozide was not caused by a direct force-incrementing effect of the drug but was secondary to some other process, such as postural changes and or response duration changes [8, 35, 18]. Accordingly, the purpose of Experiment 2 was to repeat the observations of Experiment 1, but to do so under conditions which required much greater response requirements per reinforcement than in Experiment 1. This was accomplished by (1) using a grasp-and-pull response topography which has previously been observed to elicit comparatively high levels of force emission [24], (2) using an FR 20 schedule of reinforcement, and (3) increasing the force requirement to 100 g for the high-force group, with the low-force group remaining at 4 g. Changing to the pull topography was also seen as a way of assessing the generality of the neuroleptic-induced tendency to lengthen response duration observed in Experiment 1 and elsewhere [13, 14, 16, 18]. Finally, the pull topography requires a grasping component not needed in the press task, thereby making the pull response more complex than the press response used in Experiment 1.

Procedure

Magazine training and shaping the operant were performed as in Experiment 1. All subsequent sessions were 10-min in length. After shaping, all 20 rats received 4 sessions of CRF training with a 4-g force requirement. The rats were then placed on an FR 10 schedule of reinforcement for 4 sessions, which was followed by 30 sessions of FR 20 before injections began. One rat in the low-force group died of unknown causes during this time, and one rat in the high-force condition was dropped from the experiment for failure to maintain responding on a consistent basis. Drug and vehicle injections were administered as described previously, except that at least 5 days separated drug dosings and the 0.5 mg/kg dose was administered only once.

Results

As shown in Fig. 2 and in Table 2 the difference in required force was successful in producing significant differences between groups on all of the dependent variables except for rate of response. The lack of a difference between groups on the rate variable is largely accounted for by the frequent occurrence of responses below 100 g in the high-force group; if these subcriterion responses had been omitted from the rate calculations (as would be the case when conventional levers are used to instrument different force requirements) then the rates of response would have been directly proportional to the number of reinforcements (shown in the bottom set of axes in Fig. 2) because of the FR schedule.

The pattern of results for dose of pimozide (Table 2, middle third) was the same as in Experiment 1 for maximum peak force, response duration, rate, and number of reinforcers. However, unlike Experiment 1, pimozide did not have a

TABLE 2

EXPERIMENT 2 RESULTS OF ANALYSIS OF VARIANCE FOR THE INDICATED DEPENDENT VARIABLES

Type of effect	Dependent variable	Degrees of freedom	F-value	*p*-value
4g vs. 100 g	mean peak force	1, 16	97.938	<0.001
	maximum peak force	1, 16	44.706	<0.001
	duration	1, 16	18.015	<0.001
	average rate	1, 16	—	—
	reinforcers	1, 16	21.698	<0.001
Dose	mean peak force	3, 48	—	—
	maximum peak force	3, 48	—	—
	duration	3, 48	4.020	0.012
	average rate	3, 48	26.238	<0.001
	reinforcers	3, 48	24.319	<0.001
Interaction	mean peak force	3, 48	2.983	0.039
	maximum peak force	3, 48	—	—
	duration	3, 48	—	—
	average rate	3, 48	—	—
	reinforcers	3, 48	—	—

These data are for the pull topography and fixed ratio 20 reinforcement. Non significant F-values are not presented.

significant effect on mean peak force in Experiment 2. Yet there was a significant interaction between required force and pimozide dose for mean peak force (Table 2, bottom third). Simple main effects analyses of variance showed that in neither group was the dose effect significant [low-force group, $F(3,48)=1.956$, $p>0.05$; high-force group, $F(3,48)=1.901$, $p>0.05$]. Further post hoc analysis indicated that the interaction was the result of the combined tendency for the highest dose to produce, in the low-force group, a force rise relative to vehicle control and, in the high-force group, a decrease in force relative to control (Tukey's HSD: $q=3.959 > q'=2.996$, $p<0.05$).

GENERAL DISCUSSION

Taken together the results from both experiments show that pimozide decreases response rate and increases response duration regardless of response topography, required force, or intermittency of reinforcement (CRF and FR 20 yielded similar results). Pimozide had small, but statistically significant, force-elevating effects when both required force and baseline force were relatively quite low (Experiment 1); a similar effect, but by itself not significant, was seen for the low-force condition in Experiment 2. A nonsignificant tendency for the highest dose to lower mean peak force in the high force condition was also seen in Experiment 2. Although the graphic trends in the dose-response functions for maximum peak force paralleled those obtained for mean peak force, maximum peak force was not significantly affected by pimozide.

Perhaps the most striking feature of these results is the resistance of the peak force variable to pimozide's effects, even in the face of substantial drug-related decrements in rate and small but consistent lengthening of response duration. That maximum peak force was not affected by pimozide indicates little or no reduction in performance capacity when defined in terms of peak force. This finding in turn suggests that performance capacity is separable into several sub-components of which peak force and duration are instances. Since response rate and response duration are basically speed measures, it is hypothesized that pimozide influences responding in the temporal domain, as opposed to the amplitude domain, of motor behavior. Of course, the present data do not offer any help in determining whether rate of response (defined primarily by the time between responses) and duration of response are manifesting the same or different pharmacological effects of pimozide. If, as argued elsewhere [23], neuroleptic-induced increases in response duration are the result of subtle effects on postural mechanisms, then rate and duration changes occasioned by pimozide may be reflective of the same basic process. Moreover, pimozide-induced intensification of postural reflexes [8,35] would be seen as longer times between responses because of retarded response initiation [30] and lengthened durations because of increased time required to terminate the response once it has been started.

The interaction between required force and dose for the rate variable in Experiment 1 and the lack of such an interaction in Experiment 2 suggest that the kinetic requirements concept applies to the temporal but not the force domain of behavior. The slopes of the dose response functions for rate are similar for the three conditions that produce relatively high rates, and yet for these same conditions emitted force ranges from 40 to 100 g. If the distinction between *response* requirements and overall *behavioral* requirements of the task is a valid one, then the kinetic requirements concept may apply to the behavioral requirements (in terms of sequencing and timing of responses) but not to the force requirements per se. During the course of an operant session a rat exhibits behaviors other than the operant itself, and these behaviors may be affected by drugs more than the

operant response (the component of the behavior that involves operandum contact). In the study by Ettenberg *et al.* [11], there were differences in locomotor/postural requirements for the nose poke and lever press responses, and it may have been these differences that accounted for the differential sensitivity of rate to the neuroleptic treatment and not the differences in difficulty of the specific operant chosen for reinforcement. In the present work the locomotor/postural aspects of the overall task were highly similar but the differences in difficulty of the specific responses were reasonably large. Thus, kinetic requirements was operationalized in very different ways in the two studies. An experiment by Gramling and Fowler [27] is also consistent with this interpretation (kinetic requirements are important in the temporal domain) in that neuroleptics were shown to have relatively greater effects on rate of operant licking (licks on a dry disk were reinforced with water in another part of the chamber) compared to reflexive licking (rats simply licked from a continuously available water reservoir). In light of this distinction between the overall behavioral requirements and the specific response requirements, the significant interaction between force requirement and dose for the rate variable in Experiment 1 may stem from the fact the high force group spent considerably more time making operant responses than the low-force group, which passed the predominant part of the session at the water dipper. Thus, compared to the low-force group, there was more behavior in the high-force group of the kind that neuroleptics affect (viz., behavior requiring changes in posture such as moving from a position suitable for reaching and pressing to a stance necessary for drinking from the dipper).

Although not inconsistent with the current results, other work [2,3] which examined the effects of neuroleptics on rate of response under different force requirements cannot be compared directly to the results reported here because those studies did not measure force of response and therefore did not include subcriterion responding in the response rate calculations. One cannot accurately assess the amount by which rate is affected by changes in required lever force because changing the required force sets a new limit on what qualifies as a response. Thus, the changes in reward summation functions (rate of response as a function of log concentration of sucrose reward) produced by two different force requirements [3] may have been the result of equal rates under the two conditions, but in the high force condition fewer of the paw contacts were forceful enough to be counted as responses. Moreover, under experimental conditions that hold response definition constant, available data suggest that force requirement cannot be varied without affecting the schedule of reinforcement [28,29], because response variability is always present to produce subcriterion responses.

Whereas selected portions of the current data (the small dose-related rise in mean peak force in the low-force group of Experiment 1) can be construed to support the anhedonia hypothesis, other aspects of the data (lack of drug-related increase in mean peak force for the remaining three groups) do not exclusively support this interpretation. On the other hand, in the absence of an evaluation of the effects of parametric variations in amount of reinforcement on mean peak force, maximum peak force, duration and rate, it is not meaningful to compare a dose response function for pimozide with a "single dose determination" of amount of reinforcement such as is provided here. Available evidence suggests, however, that extinction produces increases in mean peak force considerably larger than the increases induced by pimozide in Experiment 1 [20,29]. Yet the question remains a quantitative one, and inclusion of amount of reinforcement as an independent variable in further experimental work seems warranted, and such work may yield an estimate of the degree to which motor impairment and reward attenuation each contribute to the behavior decreasing effects of neuroleptics.

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