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Effects of Haloperidol on the Biophysical Characteristics of Operant Responding: Implications for Motor and Reinforcement Processes

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FOWLER, S. C., M. M. LACERRA AND A. ETTENBERG. *Effects of haloperidol on the biophysical characteristics of operant responding: Implications for motor and reinforcement processes.* PHARMACOL BIOCHEM BEHAV **25**(4) 791–796, 1986.—Food-deprived rats were reinforced with sweetened condensed milk for pressing a force-sensing operandum on a continuous reinforcement basis. Force was continuously recorded (every 0.00195 sec) during each response, and measures derived from the resulting force-time waveforms served as the basis for evaluating neuroleptic challenge in the form of haloperidol (0.04, 0.08, 0.16 mg/kg). Significant dose-related drug effects included a decrease in response rate, an increase in mean emitted peak force, and an increase in overall response duration. Additional quantitative analyses revealed that the drug-induced increase in response duration resulted primarily from a slowing in the animal's paw removal from the force-sensing operandum. The findings are analogous to deficits in Parkinson's disease and suggest a behavioral mechanism that might account for much of the rate attenuating effects of neuroleptics. Implications for motor and reward interpretations of the actions of dopamine antagonists are also discussed.

Haloperidol Neuroleptics Force of response Duration of response Motor effects Anhedonia Rats

IT is well known that dopamine (DA) antagonist neuroleptic drugs can produce motor impairments in both humans and animals (e.g., [3, 8, 9, 38]). However, controversy exists concerning whether or not such behavioral incapacities can account for the robust effects that are routinely observed with low to moderate doses of these drugs (e.g., [5, 19, 37]). For example, operant response rate of food-reinforced rats is decreased at doses that apparently have little or no cataleptogenic effect [30]. One explanation offered for these rate decreases is that the reinforcer efficacy is reduced by neuroleptics and rate declines secondary to a loss in the potency of the reinforcing stimulus (i.e., the "anhedonia theory" [36,37]). Other researchers have argued that much of the rate-reducing effect of these drugs might be a result of some form of performance deficit [7, 12–14, 16]. In fact, studies that have directly measured the emitted force and duration of individual operant responses have produced evidence for the presence of subtle motor impairments even at low subcataleptic doses of these drugs [15,24].

Two widely accepted pharmacological principles appear to be relevant to these issues : (1) drugs have multiple actions; (2) and the extent of each individual action depends upon the dose administered. The first principle is consistent with the idea that motor [7, 12–14, 16], anhedonic [18, 25, 37, 39], and associative [1, 2, 6, 26, 32, 33] effects might all result from neuroleptic treatment. The second principle suggests that if catalepsy is pronounced at high doses one might expect it to be present at progressively lower doses until some threshold dose is reached below which motor effects become nonexistent or immeasurable. The present study was devised to assess whether or not low to moderate doses of neuroleptic drug produce some subtle motor impairment which, once identified, might account for some portion of the slowing of operant response rates during drug treatment.

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The behavior of a rat reinforced with food after every lever press consists of the initiation of a lever press, the termination of that lever press, the initiation of the consummatory response, and so on. Obviously, a slowing in any one of these components would result in a net reduction in response rate. In addition, changes in motivational or reinforcement parameters may also affect response rate, thereby making it difficult to estimate the relative roles played by different behavioral processes in the observed rate changes. Indeed, the adequacy of response rate as a reliable measure of reward strength has been questioned repeatedly (e.g., [4, 11, 19, 28, 31, 34]). In an attempt to overcome the interpretive difficulties inherent in employing response rate as the sole dependent variable, the present work also examined the biophysical characteristics of the response itself [31].

Hungry rats were required to reach through a hole in the operant chamber wall and exert pressure on a force-sensing disk located outside the chamber. In addition to recording the number of responses per unit time (i.e., response rate), two dynamic and three temporal properties of each individual operant response were also recorded. The dynamic measures were: (1) the amount of force the animal continuously applied for the duration of the response (i.e., emitted force was sampled 512 times per second starting from the point that the animal's paw contacted the disk until paw removal) and (2) the maximum force (i.e., peak force) that the animal applied during the response. The three temporal measures of response were: (1) total response duration (i.e., the amount of time elapsed between initial contact with the disk and paw removal), (2) the "rise time" or amount of time required to go from initial contact with the operandum to the peak force, and (3) the "fall time" or the amount of time from the point of peak force to the cessation of the response (i.e., paw removal). Previous studies employing similar methods have identified characteristic changes in these measures resulting from manipulations of reinforcement schedules and reward magnitude ([10,31]; for a brief review see [19]). Therefore, it was of interest to assess (1) whether neuroleptic challenge produced dynamic and temporal effects on responding comparable to those already observed for reward attenuation, and (2) to identify precisely the response components most susceptible to low-dose neuroleptic treatment with the aim of isolating the behavioral mechanism by which rate of operant behavior is reduced by these drugs.

METHOD

Subjects

Nine male Sprague-Dawley (Charles Rivers) rats, averaging 290 g in body weight, served as subjects. The rats were maintained on a food-deprivation regimen that supplied enough food in the home cage to keep body weight nearly constant (90% of ad lib) throughout the experiment. Feeding in the home cage occurred about 30 min after experimental sessions, and training and/or drug treatments were administered in the early afternoon during the light portion of the 7:00 p.m. to 7:00 a.m. light-dark cycle.

Apparatus

Operant responses were measured in one operant chamber (23 cm long, 20 cm wide and 19 cm high) which was enclosed within a sound-attenuating plywood enclosure painted flat white inside and out. The chamber front panel was fashioned of 1.6-mm aluminum, while the top and sides were 6.3-mm clear Plexiglas. Stainless steel rods 6.3-mm 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 0.1 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 maniplandum positioned outside the chamber. A Sanborn force transducer (model FTA-100) served as the silent, isometric force-sensor. Attached to the transducer shaft was an 18 mm diameter disk. It was 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. The mass of the disk was sufficiently small to allow recording of force fluctuations up to 100 Hz without contamination by natural frequency vibrations that can occasionally occur (e.g., following a flick of the rat's claws) when the mass of the transducer manipulandum system is somewhat higher. Frequencies above 100 Hz were removed by electronic filtering.

Contingencies were programmed and data were recorded with a Corona PC equipped with a customized John Bell Engineering PC Universal I/O board. Descriptions of these measurement techniques are given elsewhere [20,22]; however, the methods used here were somewhat more advanced than those previously published because of the high natural frequency of the manipulandum-transducer system, the relatively high A/D sampling rate, and the digital waveform recording. The software (written in Turbo Pascal and available through Life Science Associates) directed the A/D converter to sample the output of the transducer at 512 Hz (one sample every 0.00195 sec). These samples were used to define a response and its peak force and duration. A response was defined as any emitted force rising above a threshold value of 4 g and attaining a peak force value of at least 10 g. Every waveform that qualified as a response was recorded on floppy disk for later analysis of rise and fall times. Response forces were measured with a precision of 1 g and duration with a precision of 0.00195 sec. Although the peak force and duration variables were recorded online and in real time, the calculations of the average time to peak attainment and the average time from peak to release of the operandum were performed after the data were collected. These same waveform data were time-averaged by a peak alignment method and printed for visual inspection (an example is provided in Fig. 3).

Drug

Haloperidol (free base, McNeil) was prepared in a vehicle solution of warm lactic acid (0.002 M) and injected intraperitoneally 45 min prior to testing. Each dose (0.04, 0.08, 0.16 mg/kg was administered in a volume of 1.0 ml/kg.

Procedure

The experiment was performed in four successive phases: magazine training (1 session), establishing the operant through shaping (2 sessions), continuous reinforcement (CFR) responding (9 sessions), and evaluation of drug effects during CRF (8 sessions—3 vehicle, 3 drug, and 2 intervening no drug CRF sessions). Each session was conducted on a

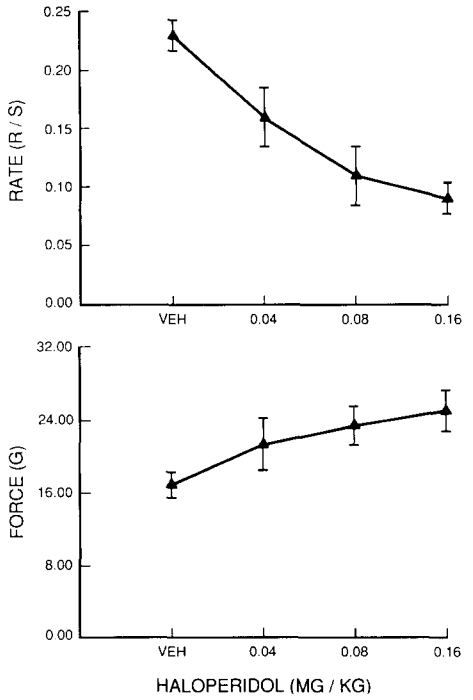

FIG. 1. Rate (top) and mean peak force (bottom) as a function of dose of haloperidol for a group of nine rats maintained on a continuous reinforcement schedule of sweetened condensed milk. VEH designates treatment with the lactic acid vehicle. The vertical brackets indicate ±1 Standard Error of the Mean (SEM).

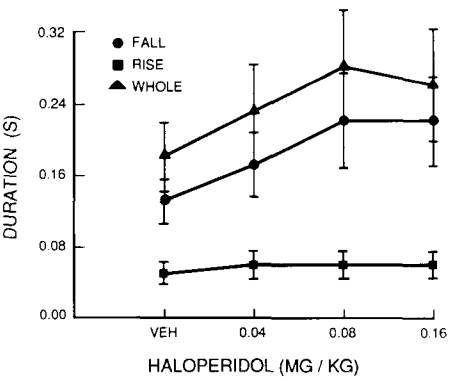

FIG. 2. Differential effects of dose of haloperidol on different components of response duration. Triangles represent mean response duration for the response taken as a whole, whereas the squares signify the mean time for the emitted force to reach its peak value, and the filled circles indicate the mean time for force to drop from its peak value to response termination. Brackets show ±1 SEM.

different day. Except for magazine training and shaping all sessions lasted 15 min. Magazine training consisted of 30-min exposure to a variable time 1-min schedule of 4-sec dipper presentations. From shaping through the remainder of the experiment dipper presentation time was 2.5 sec. The reinforcer was Borden's sweetened condensed milk diluted with an equal volume of distilled water [29].

During the drug-plus-CRF phase each rat received all three different doses of haloperidol (0.04, 0.08, 0.16 mg/kg, at 72 hr intervals) in a completely counter-balanced order. The counter-balancing protocol was particularly important since order effects of repeated haloperidol dosing appear to occur independently of dose [15, 36, 37]. Forty-five minutes before each of the three sessions preceding the drug sessions, rats were treated with 1.0 ml/kg of vehicle solution.

Dependent Variables

For each drug (or vehicle) treatment session six dependent variables were calculated from each rat's data. Thus, for example, if during a session a rat made 200 responses, the mean peak force of response for that particular subject was obtained by finding the average of the 200 separate peak values recorded for each response. Likewise, mean duration (or simply duration) was based on an average of 200 duration values. Similarly, since each response had both a rise component and a fall component, means were computed from each of these portions of the response. Response rate was the number of responses per session divided by the 900 sec of session time. A sixth dependent variable was the rat's latency to make the first response after placement in the operant chamber. Care was taken to place the rats in the operant chamber in a consistent manner, and the experimenter pressed a session-start switch as soon as the placement was completed. Closure of this switch directed the computer to begin timing the latency to the first operant response.

Dose response data for each dependent variable were analyzed with randomized blocks analyses of variance (ANOVA). Data from the three vehicle sessions were averaged for each subject and served as the zero dose condition in these ANOVAs.

RESULTS

The dose effects of haloperidol on rate and peak force of response are shown in Fig. 1. Haloperidol produced a reliable dose-dependent reduction in operant response rate as many others have previously reported, $F(3,24)=12.000$, $p<0.001$. When the rate data were analyzed for the effect of dosing order independently of dose (i.e., order of drug administration was used as the treatment variable in the ANOVA), the $F(2,16)=15.000$ was significant ($p<0.001$). Although response rate was quite sensitive to haloperidol, the drug effect for the latency variable (time from placement in the chamber to the first response) only neared statistical significance, $F(3,24)=2.440$, $p=0.080$ (based on natural log transformed data), but latency did tend to increase at the two lower doses. ANOVA also comfirmed the graphic impression (see Fig. 1) that peak force was elevated by haloperidol treatment $F(3,24)=8.966$, $p<0.001$; however, unlike the case for response rate, the peak force variable did not display an order-of-administration effect, $F(2,16)<1$, $p>0.05$.

Figure 2 illustrates the dose-response data for the temporal response variables. Mean total response duration (time from initial paw contact with the operandum to paw removal) was increased by haloperidol, $F(3,24)=4.000$, $p<0.02$; the effect of order of administration was not significant for response duration, $F(2,16)<1, p>0.05$. A two-way randomized blocks ANOVA applied to the separate rise and fall components of response duration revealed a significant dose-by-component interaction, $F(3,24)=3.480$, $p<0.03$. When assayed with a test for simple main effects, the fall component

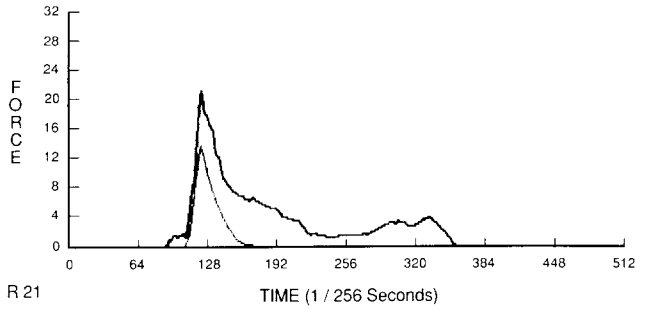

FIG. 3. Averaged force-time waveforms for vehicle (light line) and haloperidol 0.08 mg/kg (heavy line) for subject 21. The waveforms were averaged digitally by the peak alignment method. The ordinate is in gram-equivalent weights.

(time from point of peak force to paw removal) was found to be significantly affected by drug treatment, $F(3,24)=4.707$, $p<0.05$, but the rise component (time to reach peak) was not, $F(3,24)<1$, $p>0.05$.

Figure 3 provides an example of one representative subject that showed a relatively large drug effect (at the 0.08 mg/kg dose) on the fall component relative to the rise component of the response. The long "tail" to the right of the peak for the heavy-lined curve shows that, on the average, haloperidol lengthened the time to terminate the response but not the time to reach the peak force value. Other rats showed this same effect to varying degrees as confirmed by the ANOVA.

Inasmuch as haloperidol produced a pattern of lowered rate and increased peak force, it is possible that these two dependent variables would negatively covary regardless of the treatment conditions. Such redundancy of information would then call into question the value of the peak force variable in describing the behavioral effects of neuroleptics or other drugs. Furthermore, if the variable provides no information beyond rate, its presence in experimental analyses may only serve to obscure relationships between the independent and dependent variables. An examination of cumulative records (not shown here) from the CRF vehicle sessions suggested a way to address this issue. In the undrugged condition all subjects displayed a noticeable decrease in response rate toward the end of the session, probably resulting from satiation effects. Modification of our data reduction software allowed us to examine the last three minutes of responding and to compare this "satiated" responding with the data for the whole session. Response rate was significantly lower in the last three minutes: 0.140 responses/sec compared to 0.230 responses/sec for the whole session, $t(8)=5.001$, $p<0.001$. This same comparison for peak force approached significance, with peak force tending to be lower (not higher as in the drug condition) during the relatively satiated portion of the session compared to that for the whole session (i.e., for the last three minutes the mean peak force was 15.44 versus 16.78 for the session, $t(8)=1.960$, $p=0.080$). Thus, although satiation lowered response rate by an amount approximately equivalent to a haloperidol dose of between 0.04 and 0.08 mg/kg (see the top panel of Fig. 1), satiation did not increase peak force as haloperidol did in this experiment. Consequently, rate and peak force are probably not providing redundant information about the rat's behavior. Finally, response duration was significantly longer during the last three minutes of the session compared to that observed for the session as a whole: 0.210 sec vs. 0.180 sec, $t(8)=2.970$, $p=0.020$.

DISCUSSION

The monotonic rate decreases induced by increasing doses of haloperidol were accompanied by significant monotonic increases in peak force. This pattern is congruent with a recently completed study of pimozide's effects on peak force [24], although not observed for chlorpromazine or clozapine in a different experimental setting [17, 21, 23]. Since previous work has shown that force elevations are associated with decreases in amount of reinforcement [10,31], the force-incrementing effects of haloperidol seen here are consistent with the anhedonia hypothesis of neuroleptic action [36,37]. This hypothesis is also supported by the observation that successive experiences with haloperidol during food-reinforced responding led to progressively larger response rate decrements independently of dose. Such a pattern of results is similar to what one observes with successive experiences of nonreward and is, therefore, compatible with the notion that neuroleptics can attenuate food reinforcement [36,37]. Casual observations of the rat's behavior during the drug condition indicated that the rats always approached and licked from the reinforcement dipper when it was presented. Thus, the drug-related force rise observed here was probably not simply the result of reward omission [31].

Although both the rate and peak force data appear to support rather directly the anhedonia hypothesis, certain features of the results leave room for an alternative interpretation of the peak force increase produced by haloperidol. If anhedonia is "responsible" for both the observed order effect on response rate and the peak force rise, then why doesn't peak force (or duration) exhibit an order effect? It is possible that the peak force changes occasioned by haloperidol were the result of the drug's effects on postural [9,38] and/or motor [24] mechanisms which may not be susceptible to "sensitization" (increasing effects as a function of repeated treatments with a constant dose). Indeed, the fact that response fall time (i.e., time from peak force to response cessation) was selectively elevated suggests that subtle motor effects were produced by haloperidol treatment. Furthermore, since haloperidol did not reduce the rats' ability to emit relatively high forces, the motor effects occasioned by this drug appear to manifest themselves primarily in the temporal domain [24]. It would seem that a major factor contributing to neuroleptic-induced reductions in operant behaviors stems from a drug-induced slowing of response termination. This reduced capacity to release the operandum may be a manifestation of the drug's tendency to exaggerate static postural support mechanisms [9,38]. The current results also agree with the data from human Parkinson's disease patients, who show deficits in limb movement time [35] and impairment in making rapidly alternating limb movements [27]. To our knowledge, similar data have not been collected from psychiatric patients receiving neuroleptics. Failure of the drug to affect rise time does not contradict the analogy with Parkinson's disease because the initiation component of the response has already occurred once the rat's paw contacts the operandum.

If it is true that neuroleptics affect motor function in a manner that is distinguishable from a reinforcement/motivation mechanism, then a portion of the dose-related rate de-

cline seen for these drugs may be accounted for by pharmacological effects on motor mechanisms. In other words, one of the factors that reduces response rate may be primarily motoric in nature (probably extrapyramidal and posturally related [9,38]) while another factor may involve reinforcement and/or associative mechanisms. The order effects seen here and elsewhere cannot easily be accounted for by a motor hypothesis, and appropriate control procedures have effectively ruled out drug accumulation as an explanation for these order effects (e.g., [15, 36, 37]). The pairing of the drug state with operant exposure leads to an across-session decline in response rate similar to that produced by repeated exposure to nonreinforcement. This effect has been interpreted as anhedonia [36,37] or as some type of sensorimotor conditioning resulting from response-produced aversive stimuli generated in the drugged animal [33]. The results presented here do not favor either hypothesis, but it is apparent that experiments that rely exclusively on response rate are unlikely to rule out one of these two explanations.

When viewed in the context of the drug data, the satiation results raise an interesting possibility for further elucidating the processes through which neuroleptics affect behavior. In the present experiment moderate satiation produced a decline in both response rate and peak force, while the conditions presumed to represent lowered reinforcement (drug plus CRF) resulted in lower response rates but higher peak force. Since satiation is generally regarded as a condition of low motivation, comparison of response characteristics during mildly satiated conditions with those under reduced reward conditions (or drug-plus-reward conditions) may permit us to distinguish between motivational and reinforcement consequences of neuroleptic challenge. This possibility is now under investigation in our laboratories.

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REFERENCES

1. Beninger, R. J. and A. G. Phillips. The effects of pimozide during pairing on the transfer of classical conditioning to an operant discrimination. *Pharmacol Biochem Behav* **14:** 101–105, 1981.
2. Beninger, R. J. and B. L. Hahn. Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. *Science* **220:** 1304–1306, 1983.
3. Berger, P. A., G. R. Elliot and J. D. Barchas. Neuroregulators and schizophrenia. In: *Psychopharmacology: A Generation of Progress*, edited by M. A. Lipton, A. DiMascio and K. F. Killam. New York: Raven Press, 1978.
4. Beyra, M. The measurement of reinforcing brain stimulation. *Brain Res* **70:** 467–479, 1974.
5. Carlton, P. L. *A Primer of Behavioral Pharmacology*. New York: W. H. Freeman, 1983.
6. Clody, D. E. and P. L. Carlton. Stimulus efficacy, chlorpromazine and schizophrenia. *Psychopharmacology (Berlin)* **69:** 127–131, 1980.
7. Corradini, A., T. Tombaugh and H. Anisman. Effects of pimozide on escape and discrimination performance in a water-escape task. *Behav Neurosci* **98:** 96–106, 1984.
8. Costall, B. and R. J. Naylor. Detection of the neuroleptic properties of clozapine, sulpiride, and thioridazine. *Psychopharmacologia* **43:** 69–74, 1975.
9. DeRyck, M., T. Schallert and P. Teitelbaum. Morphine versus haloperidol catalepsy in the rat: A behavioral analysis of postural support mechanisms. *Brain Res* **201:** 143–172, 1980.
10. DiLolo, L. V., W. Ensminger and J. M. Notterman. Response force as a function of amount of reinforcement. *J Exp Psychol* **70:** 27–31, 1965.
11. Ettenberg, A. Conditioned taste preference and response rate as measures of brain stimulation reward: A comparison. *Physiol Behav* **24:** 755–758, 1980.
12. Ettenberg, A., G. F. Koob and F. E. Bloom. Response artifact in the measurement of neuroleptic-induced anhedonia. *Science* **213:** 357–359, 1981.
13. Ettenberg, A. and H. C. Carlisle. Neuroleptic-induced deficits in operant responding for temperature reinforcement. *Pharmacol Biochem Behav* **22:** 761–767, 1985.
14. Faustman, W. O. and S. C. Fowler. Use of operant response duration to distinguish the effects of haloperidol from nonreward. *Pharmacol Biochem Behav* **15:** 327–329, 1981.
15. Faustman, W. O. and S. C. Fowler. An examination of methodological refinements, clozapine and fluphenazine in the anhedonia paradigm. *Pharmacol Biochem Behav* **7:** 987–993, 1982.
16. Fibiger, H. C., A. P. Zis and A. G. Phillips. Haloperidol-induced disruption of conditioned avoidance responding: attenuation by prior training or by anticholinergic drugs. *Eur J Pharmacol* **30:** 309–314, 1975.
17. Ford, K. E., S. C. Fowler and G. L. Nail. Effects of clozapine and chlorpromazine upon operant response measures in rats. *Pharmacol Biochem Behav* **11:** 239–241, 1979.
18. Fouriezos, G. and R. A. Wise. Pimozide-induced extinction of intracranial self-stimulation: response patterns rule out motor performance deficits. *Brain Res* **103:** 377–380, 1976.
19. Fowler, S. C. Force and duration of operant response as dependent variables in behavioral pharmacology. In: *Advances in Behavioral Pharmacology, Vol 6*, edited by T. Thompson, P. B. Dews and J. E. Barrett. New York: Erlbaum, in press.
20. Fowler, S. C. Amplitude measures of operant response: Implementation with Apple Pascal. *Behav Res Methods Instrum Comput* **17:** 301–306, 1985.
21. Fowler, S. C. Some effects of chlordiazepoxide and chlorpromazine on response force in extinction. *Pharmacol Biochem Behav* **2:** 155–160, 1974.
22. Fowler, S. C. A minicomputer system for recording the dynamic properties of individual operant responses. *Behav Res Methods Instrum* **6:** 288–292, 1974.
23. Fowler, S. C., R. J. Filewich and M. R. Leberer. Drug effects on force and duration of response during fixed-ratio performance in rats. *Pharmacol Biochem Behav* **6:** 421–426, 1977.
24. Fowler, S. C., S. E. Gramling and R. M. Laio. 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:** 615–622, 1986.

25. Franklin, K. B. J. and S. N. McCoy. Pimozide-induced extinction in rats: Stimulus control rules out motor deficit. *Pharmacol Biochem Behav* **11:** 71–76, 1979.
26. Gramling, S. E. and S. C. Fowler. Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. *Pharmacol Biochem Behav* **22:** 541–545, 1985.
27. Hoehn, M. H. and M. D. Yahr. Parkinsonism: Onset, progression and mortality. *Neurology (Minneap)* **17:** 427–442, 1967.
28. Hodos, W. and E. S. Valenstein. An evaluation of response rate as a measure of rewarding intracranial stimulation. *J Comp Physiol Psychol* **55:** 80–84, 1964.
29. Hodos, W. and G. Kalman. Effects of increment size and reinforcer volume on progressive ratio performance. *J Exp Anal Behav* **6:** 387–392, 1963.
30. McMillan, D. E. and J. D. Leander. Effects of drugs on schedule-controlled behavior. In: *Behavioral Pharmacology*, edited by S. D. Glick and J. Goldfarb. St. Louis: C. V. Mosby, 1976.
31. Notterman, J. M. and D. E. Mintz. *Dynamics of Response*. New York: Wiley, 1965.
32. Posluns, D. An analysis of chlorpromazine-induced suppression of the avoidance response. *Psychopharmacologia* **3:** 361–373, 1962.
33. Tombaugh, T. N., C. Szostak, P. Voorneveld and J. W. Tombaugh. Failure to obtain functional equivalence between dopamine receptor blockade and extinction: Evidence supporting a sensory-motor conditioning hypothesis. *Pharmacol Biochem Behav* **16:** 67–72, 1982.
34. Valenstein, E. S. Problems of measurement and interpretation with reinforcing brain stimulation. *Psychol Rev* **71:** 415–437, 1964.
35. Ward, C. D., J. N. Sanes, J. M. Dambrosia and D. B. Calne. Methods for evaluating treatment in Parkinson's disease. In: *Advances in Neurology, Vol 137: Experimental Therapeutics of Movement Disorders*, edited by S. Fahn, D. B. Calne and I. Shoulson. New York: Raven Press, 1983.
36. Wise, R. A., J. Spindler, H. deWitt and G. J. Gerber. Neuroleptic-induced "anhedonia" in rats: Pimozide blocks the reward quality of food. *Science* **201:** 262–264, 1978.
37. Wise, R. A. Neuroleptics and operant behavior: the anhedonia hypothesis. *Behav Brain Sci* **5:** 39–87, 1982.
38. Wolgin, D. L. Forelimb placing and hopping reflexes in haloperidol- and morphine-treated cataleptic rats. *Behav Neurosci* **99:** 423–435, 1985.
39. Xenakis, S. and A. Sclafani. The dopaminergic mediation of a sweet reward in normal and VMH hyperphagic rats. *Pharmacol Biochem Behav* **16:** 293–302, 1982.