Pharmacology Biochemistry & Behavior, Vol. 17, pp. 1049–1053, 1982. Printed in the U.S.A.

Effects of Clozapine, Haloperidol and Thiothixene on Schedule-Controlled Responding and Schedule-Induced Eating and Drinking of Rabbits

JAMES E. BARRETT[1]

Department of Psychiatry, School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814

Received 13 March 1982

BARRETT, J. E. *Effects of clozapine, haloperidol and thiothixene on schedule-controlled responding and schedule-induced eating and drinking of rabbits.* PHARMAC. BIOCHEM. BEHAV. **17**(5) 1049–1053, 1982.—Lever-lift responding by Dutch Belted rabbits was maintained either by the presentation of 0.25% saccharin solution or food pellets under a multiple fixed-interval 3-minute (FI), 30-response fixed-ratio (FR) schedule. Rabbits responding under the schedule of saccharin presentation were water deprived and had food available continuously. During experimental sessions these rabbits ate during the initial portion of many intervals. With rabbits responding under the food-presentation schedule, water was available continuously; these rabbits drank during the initial portion of the interval. Clozapine (0.1–1.0 mg/kg), haloperidol (0.003–0.03 mg/kg) and thiothixene (0.003–0.03 mg/kg) all increased responding under the FI schedules to a maximum of approximately 200 percent of control and generally did not affect or decreased responding under the FR schedules. These effects occurred under schedules where either food or saccharin maintained responding. Higher doses (1–3 mg/kg clozapine and 0.1 mg/kg haloperidol or thiothixene) decreased responding under all schedules. Doses of these drugs that increased responding also increased the amount of eating and drinking that occurred during the experimental session. Although clozapine, a novel antipsychotic compound, typically affects operant performances differently than other antipsychotic drugs, its effects on conditioned rabbit behavior appear similar to those of other antipsychotics. Further, although antipsychotic drugs generally decrease performances in several mammalian species, effects of these agents in the rabbit are similar to those found with humans and chimpanzees. The similarity of antipsychotic drug effects in the rabbit to those found in the human and chimpanzee, together with the comparable effects obtained even with "atypical" compounds, plus the development of schedule-induced eating and drinking suggest that the rabbit may be a very useful addition to research in behavioral pharmacology.

Schedule-controlled responding Schedule-induced behavior Antipsychotic drugs Rabbits
Haloperidol Clozapine Thiothixene Operant behavior Collateral behavior Eating Drinking

THE effects of antipsychotic drugs on schedule-controlled operant behavior have been studied in many species. In mammals such as the rat, mouse, squirrel monkey and rhesus monkey, compounds such as chlorpromazine and haloperidol characteristically only decrease responding maintained by food presentation [3, 8, 13]. However, increases in responding have been reported with chlorpromazine in the human [1] and chimpanzee [5]. Chlorpromazine has also been shown recently to increase responding of rabbits maintained under a multiple fixed-interval (FI), fixed-ratio (FR) schedule by food pellets or by a saccharin solution [4]. Thus, the rabbit appears unique in being a nonprimate mammal that shows increases in schedule-controlled behavior with an antipsychotic drug.

In this same study [4], chlorpromazine also increased eating that occurred under the saccharin schedule. Drinking, which occurred under the food-presentation schedule, however, was not increased by chlorpromazine. Eating occurred during the early portion of the FI when responding was maintained by saccharin solution and food was continuously available during the session and in the home cage for these water-deprived rabbits. Similar patterns of schedule-induced drinking occurred with rabbits under the food-presentation schedule that were deprived of food but not water. Eating and drinking did not occur during the FR component. Although schedule-induced drinking has been reported frequently [10], schedule-induced eating, i.e., eating under the temporal and regulatory control of the schedule, has not been reported previously.

In view of the somewhat atypical effects of chlorpromazine in the rabbit, and because of the occurrence of schedule-induced eating and drinking, the present experi-

[1]Supported in part by PHS Grants AA-02104, DA-01839 and DA-02873. Address correspondence to J. E. Barrett, Department of Psychiatry, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814.

ment was designed to examine further the effects of additional antipsychotic drugs—clozapine, haloperidol and thiothixene—on schedule-controlled performances and schedule-induced eating and drinking of rabbits. The effects of clozapine were of particular interest because this drug characteristically affects operant behavior differently than most antipsychotic compounds [2, 3, 6, 7, 13]. The effects of clozapine, haloperidol and thiothixene were studied on behavioral performances maintained by either saccharin solution or food presentation. As in the earlier study, rabbits responding under the food-presentation schedule drank during the early portion of the FI, whereas rabbits under the saccharin schedule ate during the early period of the FI. Thus, it was possible to examine drug effects on schedule-controlled and schedule-induced behaviors that have been previously shown to be sensitive to a variety of compounds.

METHOD

Subjects

The subjects were six female Dutch-Belted rabbits, approximately one year old, with prior experimental histories of schedule-maintained performances and drug administration. Rabbits R-1, R-5, R-16 and R-20 were maintained at 80 percent of their free-feeding body weights by limited daily access to water; food (Purina Rabbit Chow) was available at all times in the home cage. Rabbits R-18, R-19 and R-20 were maintained at 80 percent of their free-feeding body weights by limited daily access to food. Water was available continuously in the home cage. Body weights after deprivation ranged from approximately 1.5–2.0 kg. All rabbits were caged individually.

Apparatus

Behavioral performances were studied in an experimental chamber described previously in detail [4]. Briefly, the Plexiglas chamber (38×38×38 cm) was equipped with a Gerbrands (Model G-6312) rat lever that was inverted and extended by a 5×5 cm, 2 mm thick stainless steel plate; the plate protruded approximately 2.5 cm beyond the edge of the rat lever and was located 6 cm above the chamber floor and 5 cm from the right side of the front panel. A lifting force exceeding 35 g counted as a response and produced the click of a feedback relay mounted behind the front panel. Three pairs of differently-colored stimulus lamps were located behind the front panel and served as discriminative stimuli.

For rabbits responding under the schedule of saccharin presentation, the front panel of the chamber contained a centrally-located recessed opening into which a liquid dipper (Gerbrands model B-LH) provided access to 1.0 ml tap water containing 0.25% (w/v) saccharin. This chamber was also equipped with a 5×11 cm opening on the left side of the front wall. A dish containing Purina Rabbit Chow was positioned behind this opening; entries into the food well were detected by an infrared photocell and recorded automatically.

The chamber in which responding was maintained by food pellets contained a pellet dispenser Gerbrands (Model D-1) that delivered 97 mg rabbit pellets (Noyes, Formula D) into a small receptacle located in the center of the front wall. A water bottle was positioned on the left side of the front panel and provided continuous access to tap water. Contacts with the drinking spout were detected by a drinkometer circuit.

Procedure

Responding was maintained under a multiple fixed-interval (FI) 3-min, fixed-ratio (FR) 30-response schedule. In the presence of green lights (located on the extreme left of the front panel), the first response after 3 min (FI schedule) produced either 4-sec access to the saccharin solution (rabbits R-1, R-5, R-16 and R-20) or the delivery of one food pellet (rabbits R-18 and R-19). The completion of 30 responses in the presence of white lights (positioned on the right of the front panel) also produced reinforcement (FR schedule). If reinforcement was not obtained within 4 min after the onset of the FI component or within one minute under the FR schedule the component alternated automatically without reinforcement (limited hold). Experimental sessions consisted of 30 components of the multiple schedule and were conducted 5 days per week.

Drugs

Clozapine base (Sandoz) was dissolved in distilled water and 0.7 ml of 1 N acetic acid. Haloperidol (McNeil) was diluted with sterile distilled water from the commercial injectable preparation. Doses of clozapine and haloperidol are expressed as the base. Thiothixene HCl was dissolved in 0.9% sterile saline solution and doses are expressed in terms of the salt. All drugs were administered intramuscularly into the hind leg in a volume of 1.0 mg/kg body weight immediately before the sessions conducted on Tuesdays and Fridays. If responding on the preceding Monday and Thursday was not stable when compared with previous performances, drugs were not administered.

Data Analysis

Data collected on digital counters and elapsed time meters were used to calculate average overall response rates (responses per second) during the FI and FR components. Control data were obtained from stable performances during Thursday's sessions or from Tuesdays or Fridays when the appropriate vehicle was administered rather than a drug. Each dose was administered at least twice. Changes with drug administration are expressed as percentage changes from control performances. The water bottle and food dish were weighed prior to and after each session, with spillage, which occurred rarely, taken into account. The quantity of water ingested of food consumed is expressed in grams.

RESULTS

Control Performances

Representative control performances for rabbits responding under the saccharin schedule are shown in Fig. 1. These performances were similar to those found with other species under these schedules. Responding under the FI was characterized by an initial pause and a transition to an intermediate rate of responding that continued until reinforcement occurred. FR performances occurred at a high steady rate of responding that followed a very brief initial pause after reinforcement delivery under the FI schedule. Patterns of eating are also shown in these records for rabbits responding under the saccharin schedule. Eating occurred only during the pause preceding the initiation of responding during the FI component of the schedule; eating did not occur during every interval under control conditions. Rates and patterns of responding and drinking for rabbits under the food-presentation schedule were similar to those shown in Fig. 1.

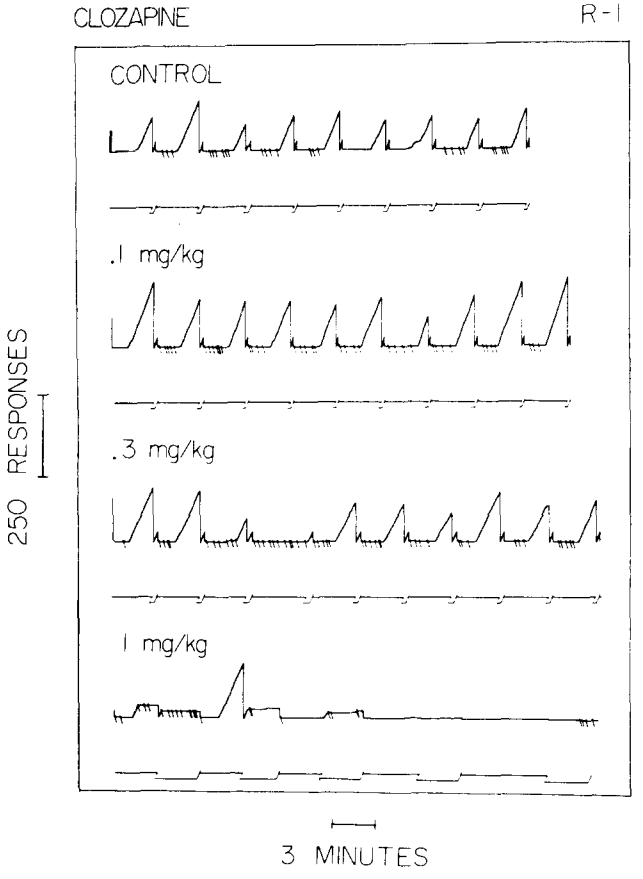

FIG. 1. Cumulative response records of control rates and patterns of responding and the effects of clozapine under the multiple FI 3-min FR 30-response saccharin solution schedule. Food was available behind an opening in the front wall of the chamber. Entries into the food well were detected by a photocell and are shown as diagonal slashes on the record. Eating occurred only during the FI schedule under control conditions and at intermediate doses of each drug. FR components are indicated by the displacement of the pen beneath each record. The pens reset after reinforcement. The effects of clozapine are shown in the three lower records. At the 0.1 and 0.3 mg/kg doses, clozapine increased both responding and eating. At the 1.0 mg/kg dose responding was markedly disrupted and eating occurred during both schedule components.

TABLE 1

CONTROL PERFORMANCES OF SCHEDULE-MAINTAINED RESPONDING AND SCHEDULE-INDUCED EATING*

Drug	Rabbit	FI	FR	Grams Consumed
Clozapine	R-1	0.51	2.63	13
		(0.03)	(0.10)	(0.79)
	R-5	0.13	0.69	2.70
		(0.03)	(0.02)	(1.00)
	R-18†	0.48	1.37	49
		(0.02)	(0.06)	(5.11)
	R-19†	0.33	1.45	3.00
		(0.02)	(0.05)	(0.85)
Haloperidol	R-1	0.57	2.62	9.40
		(0.02)	(0.07)	(0.71)
	R-5	0.21	1.17	13.90
		(0.03)	(0.11)	(1.12)
	R-18†	0.55	1.44	25.75
		(0.06)	(0.12)	(7.06)
	R-19†	0.27	1.49	3.00
		(0.01)	(0.09)	(1.00)
Thiothixene	R-16	0.51	1.84	5.40
		(0.07)	(0.07)	(1.72)
	R-20	0.28	2.03	7.20
		(0.04)	(0.29)	(1.10)
	R-18†	0.53	1.35	4.03
		(0.03)	(0.13)	(2.10)

*Data are average rates of responding (responses per second) for individual rabbits under the FI and FR schedules based on at least 7 non-injection control sessions or sessions in which either saline or, with clozapine, the vehicle was administered. Last column on the right shows amount of eating or drinking (measured in grams) that occurred during the session. Figures in parentheses represent 1 S.E. of the mean.

†Denotes rabbits studied under food-presentation schedules that engaged in schedule-induced drinking; other rabbits were maintained under saccharin schedules and engaged in schedule-induced eating.

The amounts of food or water consumed under control conditions during each drug series are shown in Table 1. This table also provides control data for average response rates under the FI and FR components. Rates of lever lifting were approximately three to five times higher under the FR schedules and were stable across drug conditions for individual animals.

Drug Effects

Clozapine (0.03–0.1 mg/kg) increased responding under the FI schedule for all rabbits but did not affect or decreased responding under the FR schedule (Fig. 2). These effects occurred under both saccharin- and food-maintained conditions. Higher doses of clozapine (1.0–3.0 mg/kg) decreased responding under both schedules.

Doses of clozapine that increased schedule-controlled responding also increased both eating and drinking. In addition, doses of 1.0 or 3.0 mg/kg that markedly decreased responding under the FI and FR schedules either increased or did not affect schedule-induced behavior for three of the four rabbits.

Haloperidol also increased responding under the FI schedule and, like clozapine, did not affect or decreased responding under the FR schedule (Fig. 3). Maximal increases in FI responding occurred at lower doses of haloperidol (approximately 0.001–0.01 mg/kg) than of clozapine but were generally of comparable magnitude. These doses of haloperidol also increased eating and drinking; however, higher doses of haloperidol (0.1 mg/kg) decreased these behaviors in all rabbits.

The effects of thiothixene on schedule-controlled responding and schedule-induced eating and drinking were generally similar to those found with both clozapine and haloperidol (Fig. 4). Doses of 0.003–0.03 mg/kg thiothixene increased responding under the FI schedule but did not affect or decreased responding under the FR schedule. Higher doses of thiothixene decreased performances under both

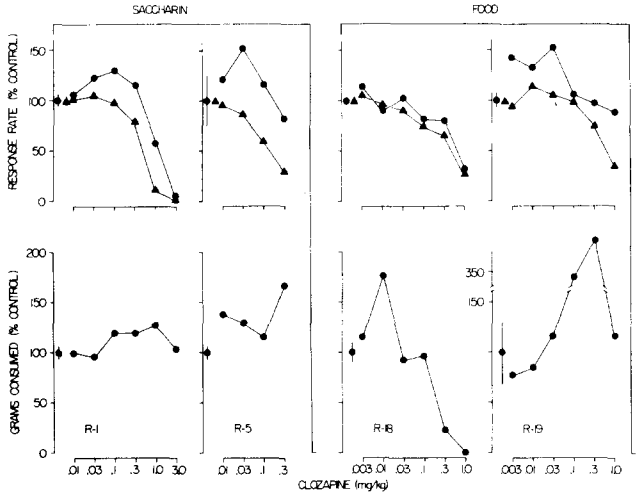

FIG. 2. Dose-effect curves of changes in schedule-controlled responding (top), eating (bottom left) and drinking (bottom right) with clozapine. Rabbits, in the panel labeled Saccharin, responded for 0.25% saccharin solution; food was available throughout the session and the amount eaten expressed as grams consumed. Panels on the right, labeled Food, represent rabbits responding for food pellets; water was freely available during the session. Water and food consumption were measured by weighing the bottle or food dish, respectively, before and after each session. All measures are expressed as percent changes from non-drug control rates and amounts. Points on left of each panel denote average control measures ±1 S.E. In the top half of the figure, FI performances are denoted by circles, FR by triangles.

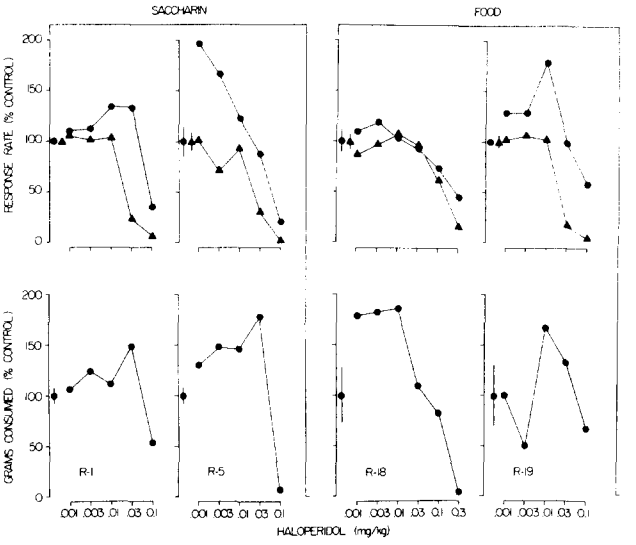

FIG. 3. Effects of haloperidol on schedule-controlled responding, eating and drinking in rabbits. Details are the same as those in Fig. 2.

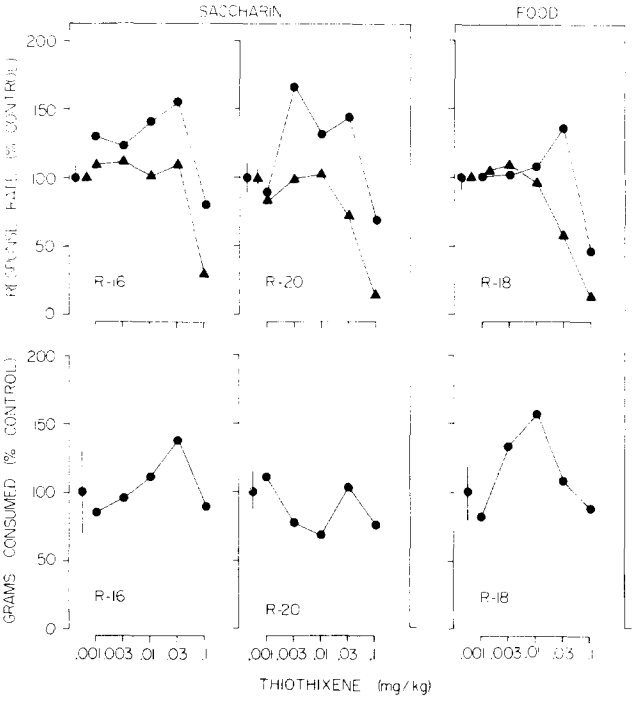

FIG. 4. Effects of thiothixene on schedule-controlled responding, eating and drinking in rabbits. Details are the same as those in Fig. 2.

schedules. Thiothixene increased eating for one of the two rabbits under the saccharin schedule and also increased drinking under the food delivery schedule. As with clozapine, doses of thiothixene that markedly decreased schedule-controlled responding did not affect eating or drinking.

DISCUSSION

Although rabbits have been used extensively in physiological and pharmacological research, as well as in respondent (classical) conditioning procedures, they have been studied infrequently in operant experiments and in behavioral pharmacology using schedule-controlled behavior. Previous research has shown that a number of compounds such as amphetamine and chlorpromazine produce effects on operant responding of rabbits that differ from those typically found with other species [4]. For example, in the rabbit responding under FI and FR schedules, intermediate-to-high doses of *d*-amphetamine (1.0–5.6 mg/kg) produced extremely high rates of stereotyped, perseverative lever lifting. Although amphetamine characteristically produces stereotyped behavior such as sniffing and grooming at high doses, the onset of stereotypical responses usually interferes with schedule-controlled responding and decreases this behavior. Chlorpromazine has also been shown to increase responding of rabbits [4]. With the exception of the human [1] and the chimpanzee [5], these effects are not characteristic of most mammals.

The effects of the various antipsychotic drugs on schedule-controlled responding studied in the present experiment resembled those reported previously for chlorpromazine in the rabbit: responding under the FI schedule was increased at doses that did not affect or decreased responding under the FR schedule. The rabbit, therefore, appears unique amongst nonprimate mammals in showing increases in behavioral performances with antipsychotic drugs.

Even clozapine, the relatively new and novel antipsychotic compound which, when compared with other antipsychotic drugs, characteristically produces atypical effects on schedule-controlled behavior [2, 3, 6, 15], also had effects on the behavior of the rabbit which were similar to other antipsychotic drugs. Thus, the rabbit also appears unique in being the one species studied in which the behavioral effects of a variety of antipsychotic drugs, including clozapine, are similar.

All three antipsychotic compounds studied in the present experiment also increased schedule-induced eating and drinking. In prior research under comparable conditions, chlorpromazine increased eating but not drinking [4]. The reason for this difference in chlorpromazine's effects on drinking remains unclear at the present time.

The patterns of eating and drinking observed in this study indicate that these behaviors were under schedule control. Except at high drug doses, eating or drinking never occurred during the FR component of the schedule. Instead, eating or drinking was confined to the early portion of the FI schedule where the occurrence of these behaviors did not affect reinforcement frequency. Previous work with schedule-induced drinking [10] has indicated that drinking also does not typically occur under FR schedules.

In preliminary work we have found that eating during the session where saccharin reinforcement was intermittent was excessive relative to that occurring in the home cage when a comparable quantity of saccharin solution was given all at once and eating was measured for a period for time comparable to the session length. Similar manipulations with rabbits maintained by food that drank during the session did not indicate that drinking under the intermittent schedule was excessive. At the present time it is not known whether schedule induced eating or drinking in the rabbit are related to the parameter value of the schedule, as has been shown with other schedule-induced or adjunctive behaviors [10]. The demonstration that eating was similar to other adjunctive behaviors would be of direct practical and theoretical import not only for studying drug effects but in elucidating variables related to food intake.

In summary, the rabbit appears to offer several advantages for behavioral pharmacological research not found with other species. The rabbit appears to engage in schedule-induced eating and drinking. These behaviors can provide additional information about drug effects on classes of behavior not frequently studied [14]. In addition, antipsychotic drugs produce similar rate-increasing effects on schedule-controlled behavior with the rabbit that differ from those found with most other species except the human and chimpanzee. Even clozapine, which typically produces effects on operant behavior different from those of other antipsychotic drugs, produced effects in the rabbit which were similar to other antipsychotic compounds. At present, it is not possible to determine whether the uniformity of effects with this class of drugs is due to species differences per se, or whether other factors, such as the topographical features of the operant response may also play a role. Topographical aspects of the response have been shown to affect drug action under other conditions (e.g., [9, 11, 12] and may also have contributed to the effects obtained in the present study. Further work with the rabbit may make this species a useful addition to comparative behavioral pharmacology.

ACKNOWLEDGEMENTS

I thank Jennifer A. Stanley for technical assistance in conducting the experiments, Myra J. Zimmerman for excellent help in the preparation of the manuscript, and Nancy A. Ator, Linda S. Brady and Jeffrey M. Witkin for helpful comments on the manuscript.

REFERENCES

1. Angle, H. V. Role of chlorpromazine in maintaining timing behavior in chronic schizophrenics. *Psychopharmacologia* **28:** 185–194, 1973.
2. Barrett, J. E. Antipsychotic drug effects on the behavior of squirrel monkeys differentially controlled by noxious stimuli. *Psychopharmacology* **77:** 1–6, 1982.
3. Barrett, J. E. Comparison of the effects of antipsychotic drugs on the schedule-controlled behavior of squirrel monkeys and pigeons. *Neuropharmacology*, in press.
4. Barrett, J. E. and J. A. Stanley. Effects of chlorpromazine and *d*-amphetamine on schedule-controlled behavior and schedule-related eating and drinking in the rabbit. *Psychopharmacology*, in press.
5. Byrd, L. D. Modification of the effects of chlorpromazine on behavior in the chimpanzee. *J. Pharmac. exp. Ther.* **189:** 24–32, 1974.
6. Canon, J. G. A comparison of clozapine, chlorpromazine, and thioridazine upon DRL performances in the squirrel monkey. *Psychopharmacology* **64:** 55–60, 1979.
7. Canon, J. G. and A. S. Lippa. Effects of clozapine, chlorpromazine and diazepam upon adjunctive and schedule controlled behaviors. *Pharmac. Biochem. Behav.* **6:** 581–587, 1977.
8. Dews, P. B. Interspecies differences in drug effects: Behavioral. In: *Psychotherapeutic Drugs*, edited by E. Usdin and I. S. Forrest. New York: Marcel Dekker, 1976, pp. 175–224.
9. Ettenberg, A., G. F. Koob and F. Bloom. Response artifact in the measurement of neuroleptic-induced anhedonia. *Science* **213:** 357–359, 1981.
10. Falk, J. L. The nature and determinants of adjunctive behavior. *Physiol. Behav.* **6:** 577–588, 1971.
11. Gerhardt, S. and J. M. Liebman. Differential effects of drug treatments on nose-poke and bar-press self-stimulation. *Pharmac. Biochem. Behav.* **15:** 767–771, 1981.
12. Graeff, F. G. and L. De Oliveira. Influence of response topography on the effect of apomorphine and amphetamine on operant behavior of pigeons. *Psychopharmacologia* **41:** 127–132, 1975.
13. McMillan, D. E. and J. D. Leander. Effects of drugs on schdule-controlled behavior. In: *Behavioral Pharmacology*, edited by S. D. Glick and G. Goldfarb. St. Louis: Mosby Press, 1976, pp. 85–139.
14. Sanger, D. J. and D. E. Blackman. Effects of drugs on adjunctive behavior. In: *Contemporary Research in Behavioral Pharmacology*, edited by D. E. Blackman and D. J. Sanger. New York: Plenum Press, 1978, pp. 239–287.
15. Spealman, R. D. and J. L. Katz. Some effects of clozapine on punished responding by mice and squirrel monkeys. *J. Pharmac. exp. Ther.* **212:** 435–440, 1980.