Pharmacology Biochemistry & Behavior, Vol. 30, pp. 603–612. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Effects of Clozapine on Fixed-Consecutive-Number Responding in Rats: A Comparison to Other Neuroleptic Drugs

MITCHELL PICKER

Department of Psychology, University of North Carolina at Chapel Hill
Campus Box 3270, Chapel Hill, NC 27599

Received 10 August 1987

PICKER, M. *Effects of clozapine on fixed-consecutive-number responding in rats: A comparison to other neuroleptic drugs.* PHARMACOL BIOCHEM BEHAV 30(3) 603–612, 1988.—The effects of clozapine and several other neuroleptic drugs were examined in rats responding under fixed-consecutive-number (FCN) schedules with minimum response requirements of 4 and 8. Under these schedules, rats were trained to respond either 8 or more times or 4 or more times on one lever, and then respond once on a second lever. In one component of these schedules, an external discriminative stimulus was presented following the completion of the response requirement on the first lever, whereas no stimulus change was programmed under the other. Under the FCN 8 schedule without the external discriminative stimulus, clozapine produced large dose-dependent decreases in accuracy (percent of reinforced response runs), whereas molindone produced small decreases in accuracy. Neither clozapine or molindone, however, altered accuracy under the FCN 4 without the external discriminative stimulus. Under these same schedules, loxapine, chlorpromazine, haloperidol and thioridazine produced small increases in accuracy at intermediate doses without affecting accuracy at the low and high doses. None of the neuroleptics evaluated produced accuracy-altering effects under the FCN schedules with the external discriminative stimulus. In general, all of these drugs decreased response rates in a dose-dependent fashion. The order of potency for the rate-decreasing effects of these drugs was loxapine > haloperidol > molindone > clozapine = chlorpromazine > thioridazine. Thus, the effects of clozapine on accuracy under the FCN schedules without the external discriminative stimulus differed qualitatively from those of other neuroleptic agents.

Clozapine Conditional discriminations Fixed-consecutive-number Neuroleptics Stimulus control Rats

ALTHOUGH the dibenzodiazepine clozapine is clinically effective in reducing the symptoms of schizophrenia [15,36], some of its effects are different from those produced by other neuroleptics (antipsychotics). Of considerable importance is the finding that at clinically effective doses clozapine-induced motor side effects are less severe than those commonly associated with neuroleptics of the phenothiazine, butyrophenone and thioxanthene groups [3, 12, 35]. Clozapine also differs from the prototypical neuroleptics in its pharmacological and behavioral profile in nonhumans. Unlike the phenothiazines and butyrophenones, for example, clozapine does not produce catalepsy or muscle rigidity nor does it effectively antagonize apomorphine-induced stereotypies [1,11]. These pharmacological differences are also reflected in clozapine's discriminative stimulus properties. In rats trained to discriminate clozapine from saline, chlorpromazine and haloperidol fail to substitute for the clozapine stimulus. Conversely, in rats trained to discriminate chlorpromazine from saline, haloperidol, but not clozapine, substitutes for the chlorpromazine stimulus [16].

Recent investigations indicate that clozapine differs from other neuroleptic drugs in its effects on schedule-controlled behavior. For example, clozapine increases low rates of responding under fixed-interval [6, 37, 38] and interresponse-time [9] schedules. Although some notable interspecies differences have been reported [8,42], chlorpromazine and other neuroleptics typically decrease responding under these schedules [6, 9, 32, 37, 43]. In addition, clozapine increases responding suppressed by punishment operations [37] and responding maintained by the presentation of electric shock [4,38], while chlorpromazine and haloperidol only decrease response rates under these schedules [5, 37, 38].

Although the effects of clozapine on schedule-controlled behavior have been examined extensively, there are no reports of its effects in conditional discrimination tasks. In a typical conditional discrimination, reinforcement is dependent upon the presence of at least two stimulus properties of the environment. Thus, in contrast to schedule-controlled performance, conditional discriminations afford the simultaneous evaluation of the effects of drugs on response rate and accuracy of responding. Numerous investigations indicate that there are differences in the effects of various neuro-

leptics when evaluated under conditional discriminations such as the fixed-consecutive-number (FCN) and delayed matching-to-sample procedures (e.g., [21, 31, 40]). In pigeons, the phenothiazine chlorpromazine and the diphenylbutylamine pimozide have been reported to decrease accuracy under FCN [21,40] and delayed matching procedures [25,31] at doses that have no effect on response rates. The butyrophenone haloperidol, in contrast, has been shown to have no effect on accuracy under these tasks even at doses that markedly suppress response rates [21, 25, 31]. Considerably less is known, however, about potential differences in the behavioral effects of neuroleptic compounds in rats responding under conditional discrimination tasks (cf. [14, 17, 26]).

The purpose of the present investigation was to contrast the effects of clozapine with those of several other neuroleptics, including the phenothiazines chlorpromazine and thioridazine, the dihydroindoline molindone, the butyrophenone haloperidol and the tricyclic dibenzoxazepine loxapine on the performance of rats responding under a FCN schedule. Under this schedule, responding a fixed number of times on one lever and then responding once on a second lever is reinforced. Under one variant of this schedule, an external discriminative stimulus is presented following the completion of the response requirement on the first lever, while under the other no external stimulus change is programmed. Thus, the response requirements are the same under both variants of the FCN schedule; however, responding under one variant is controlled by an external discriminative stimulus while responding under the other is controlled by an internal discriminative stimulus. Although these variants of the FCN schedule engender comparable response rates, levels of stimulus control (as reflected in baseline accuracy levels) under the FCN schedule with the added external discriminative stimulus are typically higher than those obtained under the FCN schedule without the added stimulus. Thus, any differential effects observed between the schedules could result from the different baseline levels of stimulus control engendered by each of the schedules and not simply the presence of the added external discriminative stimulus. To examine further the relation between stimulus control and the behavioral actions of neuroleptic compounds, these drugs were evaluated in rats responding under FCN schedules with different minimum response requirements (four and eight). Finally, since repeated exposure to neuroleptics can result in the development of sensitivity or tolerance to their effects, probe tests were conducted during which a selected dose of each drug was redetermined following the completion of each dose-effect determination.

METHOD

Subjects

Eight experimentally-naive male Long-Evans hooded rats, about 4 months old at the start of the experiment, were used. Rats were food deprived to approximately 80% of free-feeding weights (range across rats 300–350 g) and were housed individually with unlimited access to water in a colony maintained on a 12 hr light-dark cycle.

Apparatus

Four plastic and aluminum operant conditioning chambers measuring 23 cm long, 19 cm high, and 20 cm wide were used. Each chamber was equipped with two 5 cm long response levers located 9 cm from the chamber floor and 1.3 cm from either wall. When operated, a pellet dispenser could deliver a 45 mg food pellet (P. J. Noyes Co., Lancaster, NH) into a pellet trough which was mounted 1 cm above the chamber floor and 6.8 cm from either side wall. Located approximately 15 cm from the floor and 2.5 cm above each lever were two stimulus lights. When illuminated, the lights located above the right lever were red and the lights located above the left lever were white. Two white houselights were mounted on the ceiling 2.5 cm from the rear wall and 8 cm from the either side wall. Each chamber was equipped with an exhaust fan for ventilation and white noise to mask extraneous sounds. Scheduling of experimental events and data collection were accomplished through the use of a TRS model IV microcomputer.

Behavioral Procedure

After preliminary lever press training, four rats were exposed to a fixed-consecutive-number schedule with an external discriminative stimulus (FCN SD). During the initial training sessions, two red stimulus lights located above the right lever (work lever) were illuminated, and a single response on the work lever turned off the red stimulus lights and turned on the white stimulus lights located above the left lever (reinforcement lever). A subsequent response on the reinforcement lever produced a food pellet, turned off the left lever lights, and illuminated the right lever lights. Although recorded, multiple responses on the reinforcement lever had no scheduled consequences. Over the next few sessions the minimum number of responses on the work lever before a response on the reinforcement lever was reinforced was gradually increased to eight. Under this schedule (FCN 8-SD) food was delivered if the rat responded eight or more times on the work lever and then responded on the reinforcement lever. Responding less than eight times on the work lever and then responding on the reinforcement lever reset the response requirement but had no effect on which stimulus lights were illuminated. The houselight remained darkened whenever the FCN 8-SD schedule was in effect. Under these conditions, sessions terminated after 50 reinforcers or 30 min, whichever came first.

When the percentage of reinforced response runs for individual rats showed no visually evident trend, rats were exposed to a multiple FCN schedule. Each session started with the FCN 8-SD, as described above, followed by the FCN 8. The contingencies under the FCN 8 were identical to those under the FCN 8-SD with the exception that when the FCN 8 was in effect the houselight was illuminated, the lever lights were darkened, and no stimulus change was associated with the completion of the minimum response requirement on the work lever. During the initial training sessions, the minimum response requirement on the work lever was gradually increased from 1 to 8. Each component of the multiple schedule was in effect for 5 min or until eight reinforcers were earned. If eight reinforcers were earned before the end of the 5 min component, all lights were darkened until the start of the next component. Each session started with the FCN 8-SD, followed by the FCN 8, and alternated thereafter until three components of each variant of the FCN schedule was completed. Experimental sessions were conducted 5 days per week, at about the same time each day.

For a second group of four rats the minimum response requirement on the work lever was four; that is, a multiple

FCN 4-SD/FCN 4 schedule was arranged. Otherwise, all experimental contingencies for this group of rats were identical to those previously described under the FCN 8-SD/FCN 8 schedule.

Pharmacological Procedure

After 45 sessions of exposure to the multiple FCN schedules described above, dose-effect curves were determined for molindone HCl (Dupont, Wilmington, DE) clozapine (Sandoz, E. Hanover, NJ), thioridazine HCl (Sandoz, E. Hanover, NJ) haloperidol (McNeil, Spring House, PA) loxapine HCl (Lederle, Carolina) (Puerto Rico) and chlorpromazine HCl (Smith Kline and French, Philadelphia, PA) in that order. At least six doses of each drug were given once, in an irregular order, that varied across rats. At the completion of each dose-effect determination, probes were conducted during which a selected dose of each drug, previously determined to decrease response rates by at least 50% under the FCN 8-SD/FCN 8 schedule, was redetermined. Sequences of probe tests were followed and preceded by a minimum of 7 drug free days. Probe testing with molindone HCl, clozapine, thioridazine HCl, haloperidol and loxapine HCl were conducted on 5, 4, 3, 2, and 1 occasions, respectively. During each dose-effect determination and redetermination of selected doses (probe tests), drugs were administered on Tuesday and Friday, whereas distilled water was injected on Thursday with the data obtained during these sessions serving as the nondrug control data.

All drugs and vehicle control were administered IP 30 min prior to the session at an injection volume of 1.0 ml/kg. Molindone HCl, thioridazine HCl and chlorpromazine HCl were dissolved in distilled water. Clozapine and haloperidol base were dissolved in a small amount of 1 N acetic acid and diluted further with distilled water. Solutions of loxapine HCl were obtained by diluting the commercial injectable preparation with a solution consisting of propylene glycol and distilled water. Doses of clozapine and haloperidol are expressed as a base and molindone HCl, thioridazine HCl, loxapine HCl and chlorpromazine HCl as salts.

Data Analyis

The percent of reinforced runs, overall rates of responding, and frequency distributions of run lengths were recorded during each of the FCN schedules. The percent of reinforced runs reflect the proportion of response runs during which a rat completed the minimum response requirement on the work lever (4 or 8) and then responded once on the reinforcement lever. Responding less than the minimum response requirement on the work lever and then responding once on the reinforcement lever was recorded as an error. Conditional probability functions were computed from run length distributions to determine possible drug-induced changes in response patterning. These functions reflect the conditional probability of switching to the reinforcement lever after completing individual response runs of any given length. Percent of reinforced runs and response rates were subjected to an analysis of variance (ANOVA) for each of the four FCN schedules. Comparison of the dose level for each drug was then compared with the control values using a Tukey pairwise comparison test. The p-values associated with these comparisons are stated throughout the results section.

TABLE 1

MEAN CONTROL VALUES FOR PERCENT OF REINFORCED RUNS AND RESPONSE RATES FOR INDIVIDUAL RATS UNDER THE MULTIPLE FCN 8-SD/FCN 8 AND FCN 4-SD/FCN 4 SCHEDULES

Rat (No.)	% Reinforced Runs	Responses/ Sec	% Reinforced Runs	Responses/ Sec
	FCN 8-SD		FCN 8	
1	87 (2.9)*	1.11 (0.04)	70 (5.0)	1.30 (0.05)
2	95 (0.4)	1.03 (0.04)	67 (2.9)	1.23 (0.05)
3	97 (1.2)	1.21 (0.04)	84 (3.7)	1.29 (0.07)
4	99 (0.7)	1.01 (0.04)	86 (1.8)	0.97 (0.03)
	FCN 4-SD		FCN 4	
5	98 (1.4)	0.75 (0.04)	63 (3.3)	0.84 (0.04)
6	98 (0.6)	0.79 (0.02)	78 (2.9)	0.77 (0.03)
7	100 (0.2)	0.83 (0.02)	88 (1.9)	0.94 (0.02)
8	99 (0.6)	0.84 (0.04)	73 (3.8)	1.00 (0.04)

*Data are based on the mean control values for individual rats during all dose-effect determinations. Values in parentheses indicate the standard error of the mean. All rats earned the maximum number of 24 reinforcers in each variant of the FCN schedules.

RESULTS

The percent of reinforced runs (accuracy) and the shape of the conditional probability functions under each variant of the FCN schedules were similar to those reported previously [28,33]. Data obtained during baseline and vehicle control sessions indicated that the FCN schedules with the added external discriminative stimulus engendered higher accuracy levels than the FCN schedules without the added stimulus, $F(3,92)=44.2$, $p<0.01$ (see Table 1). When a discriminative stimulus was presented following the completion of the response requirement on the work lever mean accuracy levels were 95% and 99% under the FCN 4-SD and FCN 8-SD, respectively; when no discriminative stimulus was presented mean accuracy levels were 76% and 77% under the FCN 4 and FCN 8, respectively. Although no differences in accuracy levels were obtained between the schedules with the different minimum response requirements, there were differences in the shape of the conditional probability functions (see control performance in Fig. 3). For example, the slope of the conditional probability functions under the FCN 4 was considerably steeper than that obtained under the FCN 8, while similar slopes were obtained under the FCN 4-SD and FCN 8-SD. In addition, the peak of the functions under the FCN 4-SD and FCN 4 occurred at runs lengths shorter than those under the FCN 8-SD and FCN 8. Differences between the schedules with the different minimum response requirements were also apparent in response rates, $F(3,92)=48.5$, $p<0.01$, with the FCN 4-SD and FCN 4 engendering response rates that were consistently lower than those obtained under the FCN 8-SD and FCN 8 $p<0.01$; mean response rates under the FCN 4 and FCN 4-SD were 0.80 and 0.89 responses/sec, respectively, and 1.09 and 1.20 responses/sec under the FCN 8 and FCN 8-SD, respectively. Across the course of the experiment, accuracy levels and response rates not change appreciably under either of the FCN schedules.

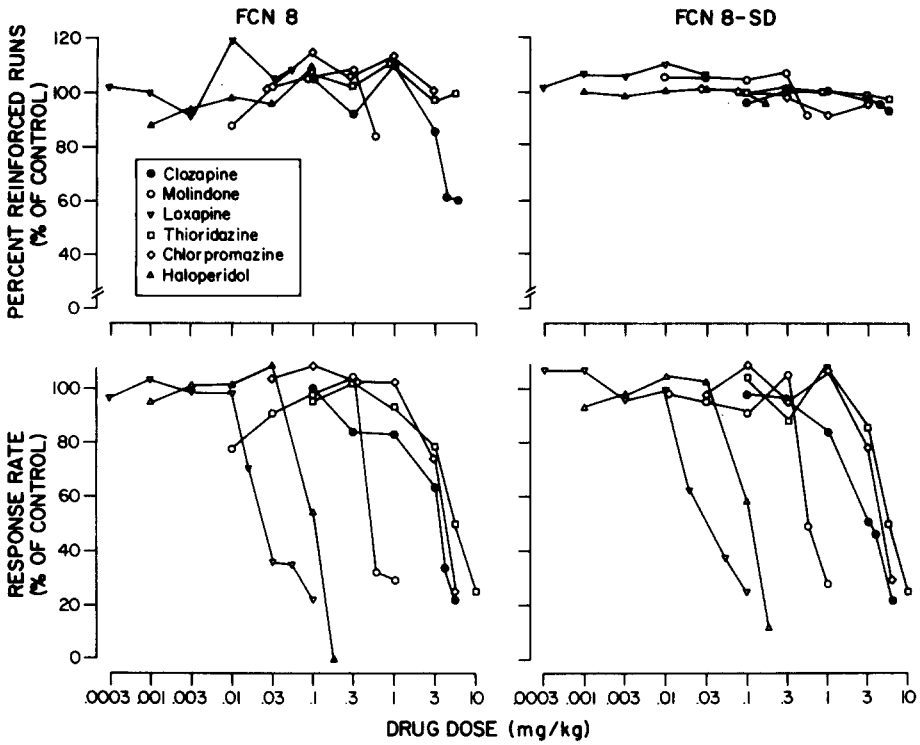

FIG. 1. Effects of clozapine, molindone, loxapine, thioridazine, chlorpromazine and haloperidol on the percent of reinforced runs and response rates in four rats responding under the multiple FCN 8-SD/FCN 8 schedule. For ease of comparison, drug data represent mean group performances expressed as the percent of individual control performances during all control sessions prior to drug administration. Under each variant of the FCN schedule, drug data for percent of reinforced runs were included only when an individual rat earned eight or more reinforcers during the session; data are not displayed for percent of reinforced runs when only one rat met this requirement.

Figure 1 shows the effects of clozapine, molindone, loxapine, thioridazine, chlorpromazine and haloperidol on the percent of reinforced runs and response rates under the FCN 8-SD and FCN 8. Under the FCN 8, clozapine produced large dose-dependent decreases in accuracy. Relative to control values, the 3.0, 4.2 and 5.6 mg/kg doses of clozapine reduced accuracy by 15%, 33% and 40%, respectively. Molindone decreased accuracy by 18% at the 0.56 mg/kg dose, but had no consistent effect at low and intermediate doses. Loxapine, thioridazine and chlorpromazine produced small increases in accuracy that were above the range of control values at intermediate doses under this schedule, but had no consistent effect at the low and high doses. Haloperidol failed to effect accuracy levels across the dose range evaluated. Table 2 shows the maximum increases and decreases in percent of reinforced runs for each of the drugs evaluated under the FCN 8 schedule; for ease of comparison, data are expressed as the mean percent of change from individual control performances. Under the FCN 8 schedule significant ($p<0.01$) increases in accuracy were obtained for loxapine (0.001 mg/kg) and chlorpromazine (0.1 mg/kg), whereas decreases in accuracy were obtained for molindone (0.56 mg/kg) and clozapine (3.0, 4.2 and 5.6 mg/kg). Even at doses that substantially suppressed mean overall response rates, haloperidol, loxapine and chlorpromazine failed to decrease accuracy. In most instances, doses that reduced response rates for individual rats under the FCN 8 had no effect on accuracy. Under the FCN 8-SD, none of the neuroleptics evaluated altered accuracy levels, $F(33,102)=1.48$, $p>0.01$. These drugs did, however, decrease mean response rates in a dose-dependent fashion under both variants of the FCN schedule. For individual rats, dose-response curves for molindone, thioridazine, haloperidol, loxapine and chlorpromazine were typically steep; that is, for individual rats the dose that eliminated responding was typically $^1/_4$–$^1/_2$ log-unit larger than a dose that had no effect on responding.

Figure 2 shows the effects of clozapine, molindone, loxapine, thioridazine, chlorpromazine and haloperidol on the percent of reinforced runs and response rates under the FCN 4-SD and FCN 4. Under the FCN 4, clozapine and molindone had no effect on accuracy across the dose range evaluated. Chlorpromazine, loxapine, thioridazine and haloperidol typically increased accuracy above the range of control values at intermediate doses under the FCN 4 without consistently affecting accuracy at low and high doses. These accuracy-increasing effects were significant ($p<0.01$) for haloperidol (0.03 mg/kg), loxapine (0.003, 0.01, 0.03 mg/kg) and chlorpromazine (1.0 mg/kg), but not for thioridazine. In addition, no accuracy-altering effects for any of these drugs were observed under the FCN 4-SD, $F(34,105)=0.71$, $p>0.01$. With the exception of thioridazine, which increased response rates at low doses under the FCN 4, these drugs produced dose-dependent decreases in response rates under

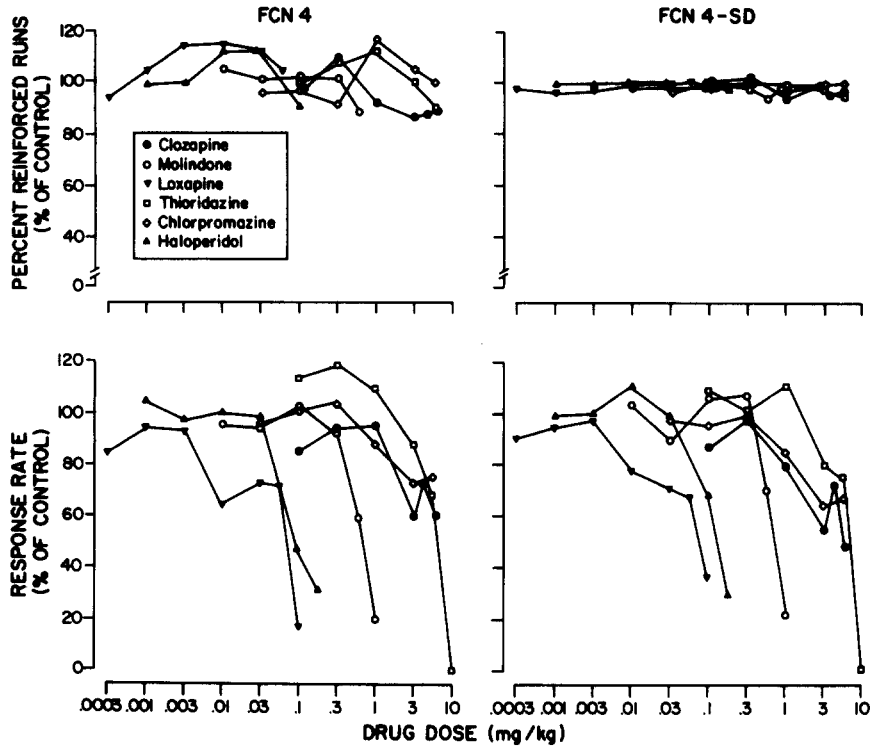

FIG. 2. Effects of clozapine, molindone, loxapine, thioridazine, chlorpromazine and haloperidol on the percent of reinforced runs and response rates in four rats responding under the multiple FCN 4-SD/FCN 4 schedule. Details are as described in Fig. 1.

TABLE 2

MAXIMUM PERCENT INCREASES AND DECREASES IN PERCENT OF REINFORCED RUNS IN RATS RESPONDING UNDER THE FCN SCHEDULES WITHOUT THE EXTERNAL DISCRIMINATIVE STIMULUS

Drug	Maximum Increases in % Reinforced Runs† (dose)		Maximum Decreases in % Reinforced Runs† (dose)	
	FCN 8	FCN 4	FCN 8	FCN 4
Molindone	8 (0.3)	6 (0.01)	18 (0.56)*	13 (0.56)
Clozapine	9 (1.0)	7 (0.3)	40 (5.6)*	13 (4.2)
Thioridazine	10 (1.0)	13 (1.0)	4 (3.0)	12 (5.6)
Haloperidol	7 (0.03)	14 (0.03)*	12 (0.001)	10 (0.1)
Loxapine	19 (0.001)*	15 (0.003, 0.01)*	7 (0.003)	6 (0.0003)
Chlorpromazine	15 (0.1)*	18 (1.0)*	1 (3.0)	8 (0.3)

*Tukey pairwise comparisons, significant at $p<0.01$.

†Data were included only when an individual rat earned 8 or more reinforcers under the FCN 8 or FCN 4 schedules. All data are expressed as the mean percent of change from individual control performances.

Note: Doses are expressed as mg/kg; for loxapine increases of 15% occurred at two doses.

both FCN schedules. In general, for individual rats responding under the FCN 4-SD and FCN 4 dose-response curves were more shallow than those obtained under the FCN 8-SD and FCN 8; that is, low doses had no effect on responding, intermediate doses produced a moderate reduction in responding and high doses produced a substantial reduction in responding.

Figures 3, 4 and 5 show the effects of clozapine and chlorpromazine, molindone and loxapine, and haloperidol and thioridazine, respectively, on the conditional probabil-

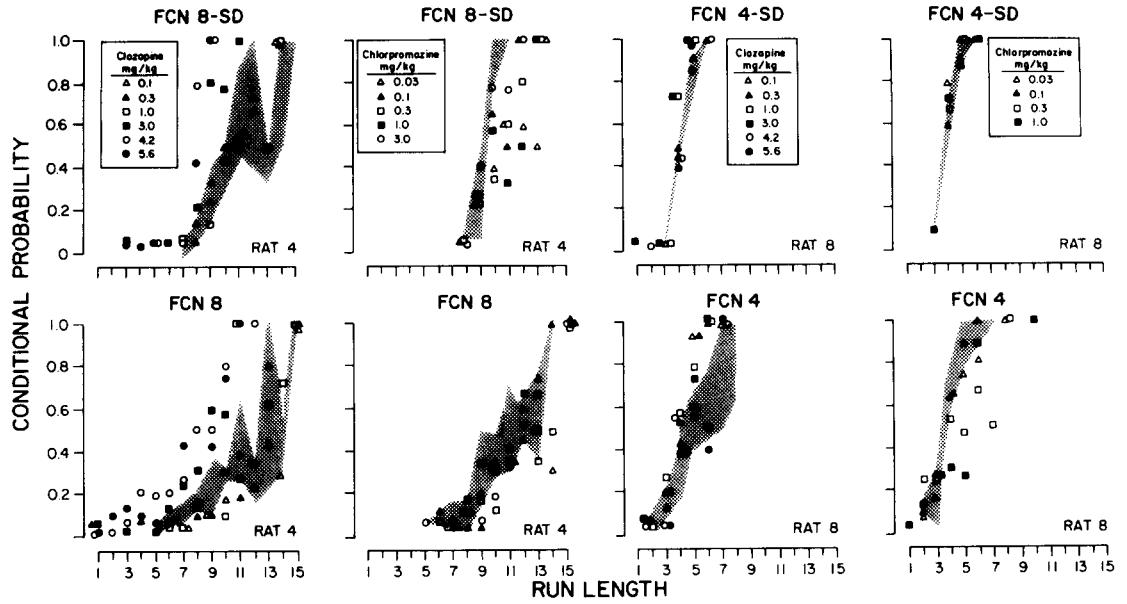

FIG. 3. Effects of clozapine and chlorpromazine on the conditional probability functions for one rat responding under the multiple FCN 8-SD/FCN 8 and one rat under the multiple FCN 4-SD/FCN 4. The ordinate gives the probability that the rat will stop responding after a number of consecutive responses on the work lever, indicated on the abscissa, and then respond on the reinforcement lever. The shaded areas represent the range over the control sessions which preceded drug administrations. Data at the run length value of 15 represent the conditional probability of making 15 or more consecutive responses on the work lever and then switching to the reinforcement lever. For simplicity, drug data were excluded from the figure when the conditional probability of switching to the reinforcement lever was zero.

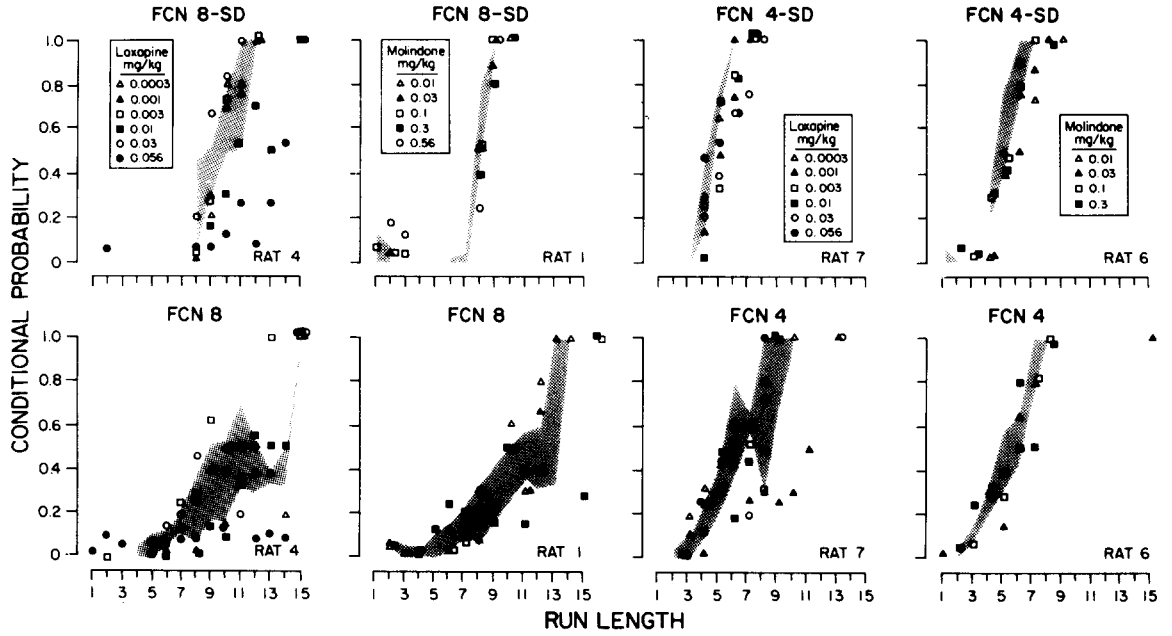

FIG. 4. Effects of loxapine and molindone on the conditional probability functions for one rat responding under the multiple FCN 8-SD/FCN 8 and one rat under the multiple FCN 4-SD/FCN 4. Details are as described in Fig. 3.

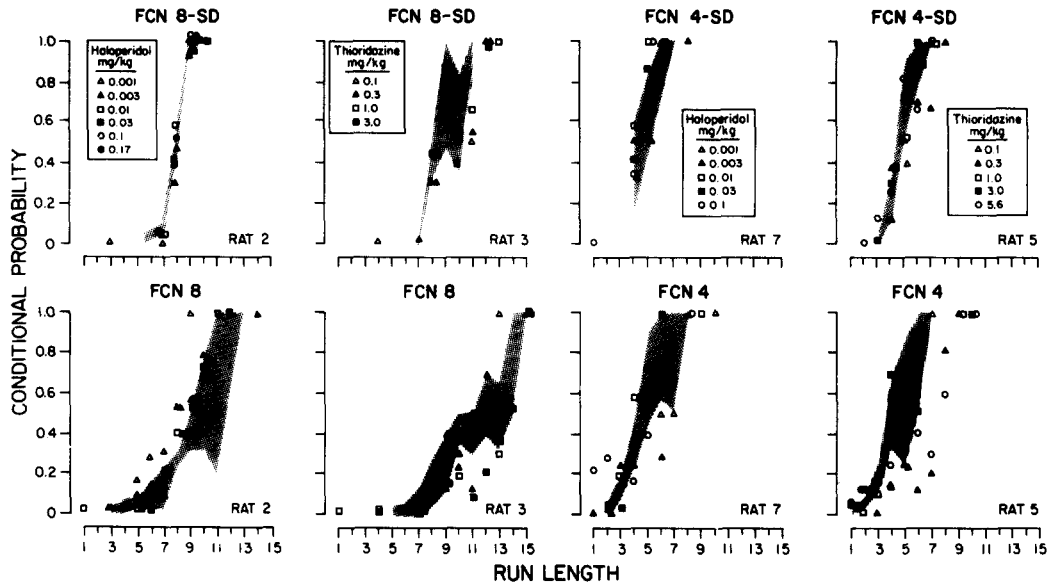

FIG. 5. Effects of haloperidol and thioridazine on the conditional probability functions for one rat responding under the multiple FCN 8-SD/FCN 8 and one rat under the multiple FCN 4-SD/FCN 4. Details are as described in Fig. 3.

ity functions for one rat responding under the FCN 8-SD/FCN 8 and one rat under the FCN 4-SD/FCN 4. Under the FCN 8, doses of clozapine that decreased accuracy increased the conditional probability of switching to the reinforcement lever before completing the minimum response requirement of eight on the work lever. No consistent disruption of stimulus control was apparent for this drug under the FCN 8-SD, FCN 4-SD or FCN 4. Haloperidol, thioridazine, chlorpromazine and loxapine failed to alter the conditional probability functions in any consistent manner under either of the FCN schedules. In addition, at doses of these drugs that increased accuracy levels above the range of control values, these drugs occasionally produced a small shift to the right in the conditional probability functions; that is, relative to control values these drugs decreased the relative frequency of response runs shorter than the minimum response requirement and increased the relative frequency of response runs longer than the minimum response requirement. In most instances, however, these values fell within the control range. Molindone had no consistent effect on the conditional probability probability functions under either of the FCN schedules.

Table 2 shows the effects of the initial determination and probe tests for selected doses of molindone, clozapine, thioridazine, haloperidol and loxapine. For ease of comparison, only the mean of the probe tests are shown. During probe tests, the effects of molindone, clozapine, thioridazine, haloperidol, and loxapine on percent of reinforced runs and response rates were not consistently different from those obtained during the initial determination of the selected doses of these neuroleptic compounds. Thus, no consistent trends that would indicate the presence of tolerance or sensitivity were observed.

DISCUSSION

The present investigation compared the effects of clozapine to several neuroleptic compounds in rats responding under FCN schedules with and without an external discriminative stimulus. Across the range of doses evaluated, there were substantial differences in the effects of these drugs on accuracy, but not on response rates. The most notable differences were obtained under the FCN schedules without the added external discriminative stimulus. Under the FCN 8, for example, clozapine produced large dose-dependent decreases in accuracy and molindone produced small decreases in accuracy. Neither clozapine or molindone, however, altered accuracy under the FCN 4. In contrast, loxapine, chlorpromazine, haloperidol and thioridazine produced small increases in accuracy at intermediate doses under both the FCN 8 and FCN 4 without affecting accuracy at the low and high doses. None of the neuroleptics evaluated altered accuracy levels under the FCN schedules with the added external discriminative stimulus. These data confirm and extend previous investigations which report differences between the effects of clozapine on schedule-controlled behavior and those produced by the neuroleptics of the phenothiazine and butyrophenone groups [5, 6, 10, 37, 38]. The effects of clozapine under the FCN schedules in the present investigation extends these findings to the accuracy of responding under conditional discriminations.

Previous investigations indicate that clozapine's unique behavioral effects may be due to its potent anticholinergic properties [22, 27, 38]. For example, in pigeons responding under a multiple fixed-ratio, fixed-interval schedule clozapine, but not the neuroleptic mezilamine, antagonized the rate-suppressing effects of the cholinergic agonist oxotremorine. Thioridazine, another neuroleptic possessing potent anticholinergic activity [22, 27, 38], similarly antagonized oxotremorine's rate-suppressing effects. Since clozapine and thioridazine produced qualitatively different effects on accuracy of responding in the present investigation, it is unlikely that these differential effects can be ac-

TABLE 3

MEAN VALUES FOR PERCENT OF REINFORCED RUNS AND RESPONSE RATES DURING THE INITIAL DETERMINATION AND PROBE TESTS FOR SELECTED DOSES OF EACH DRUG UNDER THE MULTIPLE FCN 8-SD/FCN 8 AND FCN 4-SD/FCN 4 SCHEDULES

	Response Rate		% Reinforced Runs*	
	Initial	Probe	Initial	Probe
	Molindone (1.0 mg/kg)			
FCN 8-SD	28 (25)†	39 (10)	92 (0)	89 (4)
FCN 8	29 (28)	37 (9)	95 (0)	97 (7)
FCN 4-SD	33 (20)	48 (12)	94 (4)	97 (2)
FCN 4	20 (17)	43 (11)	101 (1)	98 (7)
	Clozapine (5.6 mg/kg)			
FCN 8-SD	22 (14)	25 (8)	93 (1)	85 (9)
FCN 8	22 (12)	29 (9)	60 (14)	74 (9)
FCN 4-SD	49 (26)	28 (11)	98 (3)	95 (4)
FCN 4	61 (30)	28 (11)	89 (13)	92 (11)
	Thioridazine (5.6 mg/kg)			
FCN 8-SD	46 (23)	54 (12)	104 (1)	98 (3)
FCN 8	50 (24)	60 (13)	98 (2)	107 (8)
FCN 4-SD	76 (22)	22 (9)	95 (4)	100 (1)
FCN 4	69 (18)	23 (9)	88 (11)	93 (13)
	Haloperidol (0.1 mg/kg)			
FCN 8-SD	59 (27)	71 (18)	101 (4)	102 (2)
FCN 8	55 (31)	57 (22)	107 (11)	101 (9)
FCN 4-SD	69 (30)	59 (14)	101 (1)	96 (4)
FCN 4	48 (23)	60 (17)	90 (6)	84 (3)
	Loxapine (0.056 mg/kg)			
FCN 8-SD	37 (23)	77 (19)	105 (13)	99 (4)
FCN 8	35 (23)	72 (21)	107 (26)	106 (9)
FCN 4-SD	67 (23)	26 (21)	102 (1)	91 (15)
FCN 4	72 (24)	25 (23)	105 (11)	96 (0)

*Data for % of reinforced runs were included only when an individual rat earned 8 or more reinforcers during the session.

†Data are expressed as the percent of individual control values; values in parentheses represent the standard error.

counted for by clozapine's anticholinergic activity, at least when evaluated in rats.

The finding that clozapine decreased the accuracy of responding and disrupted the conditional probability functions under the FCN 8 at doses that had no effect under the FCN 8-SD and FCN 4-SD is consistent with a growing body of literature which indicates that the addition of an external discriminative stimulus can modulate the disruptive behavioral effects of drugs. Similar effects, for example, have been reported with the benzodiazepines [21, 29, 30], opioids [7,28], anticonvulsants [29,30] and psychomotor stimulants [21, 24, 33] under FCN schedules. Interestingly, clozapine also failed to alter the accuracy of responding under the FCN 4. These differential effects suggest that the minimum response requirement under the FCN schedules without the external discriminative stimulus plays an important role in modulating clozapine's accuracy-decreasing effects. Moreover, these findings suggest that the clozapine-induced decreases in accuracy under the FCN 8 cannot be attributed solely to the absence of the added external discriminative stimulus. Even though nondrug levels of accuracy under the FCN 4 and FCN 8 were similar, it is possible that the FCN 4 engender a higher level of stimulus control, and thus was less sensitive to disruption by drugs. Such as interactive relationship between the level of stimulus control and the magnitude of a drug's accuracy-decreasing effect have been reported under numerous experimental procedures (e.g., [13, 18, 20, 23]).

A second possible explanation for the failure to obtain accuracy-decreasing effects for haloperidol, thioridazine, loxapine and chlorpromazine in the present investigation may be related to the range of doses evaluated. For example, with the exception of clozapine, all of the neuroleptics evaluated produced relatively steep dose-response curves under the FCN 8 schedule; that is, the difference in the dose that had no effect on response rates and one that eliminated responding was typically less than $1/2$ log-unit, an effect most evident for individual rats but obscured when response rates are averaged across rats. Thus, it is possible that doses of haloperidol, thioridazine, loxapine and chlorpromazine that would decrease response rates to levels comparable to those produced by the higher doses of clozapine would similarly decrease accuracy. It should be noted, however, that for these neuroleptics there were instances in which these drugs substantially decreased response rates for individual rats but did not affect accuracy. Finally, since all rats were exposed to the same sequence of drug administration (molindone, clozapine, thioridazine, haloperidol, loxapine and then chlorpromazine), it is possible that tolerance to the accuracy-decreasing effects of these drugs occurred following exposure to molindone and clozapine, the only two drugs that decreased accuracy. Arguing against this interpretation, however, is the finding that clozapine continued to decrease accuracy during probe trials, whereas loxapine, haloperidol and thioridazine failed to do so.

Although little is known about the effects of neuroleptics in rats responding under conditional discriminations, some information is available. Under brightness, shock, and combination visual and tactile discrimination tasks, for example, chlorpromazine has been reported to both decrease and have no effect on accuracy [17, 19, 20, 23, 41]. Differential effects on accuracy have also been reported for alpha-flupenthixol in rats responding under visual discrimination tasks [14,34]. In many of these studies, like the present investigation, the type of discrimination task was an important determinant of the accuracy-altering effects of these drugs. In the present investigation, comparison of six neuroleptic agents representing five pharmacological classes indicated that some of these drugs could be differentiated on the basis of their accuracy-altering effects under the FCN schedules without the external discriminative stimulus. Whether these compounds can similarly be differentiated under other discrimination tasks remains to be determined.

The failure to find accuracy-decreasing effects for chlorpromazine and molindone under the FCN schedules in the present investigation is in contrast to those reported in pigeons responding under similar schedules. Previous studies have shown that chlorpromazine nonselectively decreases accuracy under both variants of the FCN schedule, whereas molindone decreases accuracy only under the FCN schedule without the external stimulus ([21], personal observation). Haloperidol, in contrast, has no accuracy-decreasing effects in pigeons responding under either variant of the FCN schedule [21], an effect similar to that observed in the present investigation. Although it is possible that pigeons are

more sensitive to the differential effects produced by neuroleptic drugs, the reasons for these interspecies discrepancies remain unclear. Nevertheless, these findings indicate that accuracy-decreasing effects are not a necessary consequence of neuroleptic administration in nonhumans.

The finding that clozapine, molindone, haloperidol, thioridazine and chlorpromazine decreased response rates under the FCN schedules is consistent with those reported in pigeons and squirrel monkeys responding under fixed-ratio schedules of food presentation [6, 10, 22, 43]. That loxapine produced similar rate-decreasing effects under the FCN schedules extents these findings to new group of neuroleptic compounds (i.e., tricyclic dibenzoxazepines). In the present investigation, the order of potency for the rate-decreasing effects of these drugs was loxapine > haloperidol > molindone > clozapine = chlorpromazine > thioridazine. With the exception of clozapine, which was less potent than chlorpromazine, the potency ranking for these drugs are similar to those observed in squirrel monkeys responding under schedules of food presentation [6,9]

ACKNOWLEDGEMENTS

This work was partially supported by a University of North Carolina Faculty Research Grant and U. S. Public Service Grant MH 42343 awarded to Mitchell Picker and Linda A. Dykstra. The author wishes to thank Linda A. Dykstra for comments on an earlier version of the manuscript and John Heise for the expert technical assistance he provided during the course of the experiment.

REFERENCES

1. Ackenheil, M.; Hippius, H. Clozapine. In: Usdin, E.; Forrest, I. S., eds. Psychotherapeutic drugs. New York: Marcel Dekker; 1977.
2. Altman, J. L.; Appel, J. B.; McGowan, W. T., III. Drugs and the discrimination of duration. Psychopharmacology (Berlin) 60:183–188; 1979.
3. Angst, J.; Bente, D.; Berner, P.; Heimann, H.; Helmchen, H.; Hippius, H. Das klinische Wirkungsbild von Clozapin. Pharmacopsychiatry 4:201–214; 1971.
4. Bacotti, A. V. Clozapine effects on responding maintained under shock presentation and shock termination schedules. Pharmacol. Biochem. Behav. 15:415–418; 1981.
5. Barrett, J. E. Antipsychotic drug effects on the behavior of squirrel monkeys differentially controlled by noxious stimuli. Psychopharmacology (Berlin) 77:1–6; 1982.
6. Barrett, J. E. Comparison of the effects of antipsychotic drugs on the schedule-controlled behavior of squirrel monkeys and pigeons. Neuropharmacology 22:519–524; 1983.
7. Bronson, M. E.; Moerschbaecher, J. M. Effects of mu, kappa and sigma opioids on fixed consecutive number responding in rats. Pharmacol. Biochem. Behav. 27:733–743; 1987.
8. Byrd, L. D. Modification of the effects of chlorpromazine on behavior in the chimpanzee. J. Pharmacol. Exp. Ther. 189:24–32; 1974.
9. Canon, J. G. A comparison of clozapine, chlorpromazine, and thioridazine upon DRL performance in the squirrel monkey. Psychopharmacology (Berlin) 64:55–60; 1979.
10. Canon, J. G.; Lippa, A. S. Effects of clozapine, chlorpromazine and diazepam upon adjunctive and schedule controlled behaviors. Pharmacol. Biochem. Behav. 6:581–587; 1977.
11. Costall, B.; Naylor, R. J. Detection of the neuroleptic properties of clozapine, sulpiride and thioridazine. Psychopharmacologia 43:69–74; 1975.
12. DeMaio, D. Clozapine, a novel major tranquilizer. Arzneimittelforschung 22:919–921; 1972.
13. Dykstra, L. A. Effects of morphine, diazepam and chlorpromazine on discrimination of electric shock. J. Pharmacol. Exp. Ther. 209:297–303; 1979.
14. Evenden, J. L.; Robbins, T. W. The effects of *d*-amphetamine, chlordiazepoxide and alpha-flupenthixol on food-reinforced tracking of a visual stimulus by rats. Psychopharmacology (Berlin) 85:361–366; 1985.
15. Gelenberg, A. J.; Doller, J. C. Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double blind study. J. Clin. Pharmacol. 40:238–240; 1979.
16. Goas, J. A.; Boston, J. E. Discriminative stimulus properties of clozapine and chlorpromazine. Pharmacol. Biochem. Behav. 8:235–241; 1978.
17. Hernandez, L. L.; Appel, J. B. An analysis of some perceptual effects of morphine, chlorpromazine, and LSD. Psychopharmacology (Berlin) 60:125–130; 1979.
18. Katz, J. L. Effects of drugs on stimulus control of behavior. II. Degree of stimulus control as a determinant of effect. J. Pharmacol. Exp. Ther. 226:756–763; 1983.
19. Koek, W.; Slangen, J. L. External stimulus control in a "drug-discrimination" procedure: Drug effects and inter-animal variation. Psychopharmacology (Berlin) 82:168–173; 1984.
20. Ksir, C.; Slifer, B. Drug effects on discrimination performance at two levels of stimulus control. Psychopharmacology (Berlin) 76:286–290; 1982.
21. Laties, V. G. The modification of drug effects on behavior by external discriminative stimuli. J. Pharmacol. Exp. Ther. 183:1–13; 1972.
22. Leander, J. D. Interactions of clozapine, thioridazine, and mezilamine with oxotremorine on schedule-controlled responding. Psychopharmacology (Berlin) 80:29–30; 1983.
23. Lloyd, M. A.; Appel, J. B.; McGowan, W. T., III. Effects of morphine and chlorpromazine on the detection of shock. Psychopharmacology (Berlin) 58:241–246; 1978.
24. Mechner, F.; Latranyi, M. Behavioral effects of caffeine, methamphetamine, and methylphenidate in the rat. J. Exp. Anal. Behav. 6:331–342; 1963.
25. Nielsen, E. B.; Appel, J. B. The effects of the discrimination of color following a variable delay period: A signal detection analysis. Psychopharmacology (Berlin) 80:24–28; 1983.
26. Paule, M. G.; McMillan, D. E. Incremental repeated acquisition in the rat: Acute effects of drugs. Pharmacol. Biochem. Behav. 21:431–439; 1984.
27. Pearl, J.; Spilker, B. A.; Woodward, W. A.; Bentley, R. C. Anti-cholinergic activity of anti-psychotic drugs in relation to their extrapyramidal effects. J. Pharm. Pharmacol. 28:302–304; 1976.
28. Picker, M.; Heise, J. W.; Dykstra, L. A. Evaluation of the effects of opioid agonists and antagonists under a fixed-consecutive-number schedule in rats. Pharmacol. Biochem. Behav. 27:73–80; 1987.
29. Picker, M.; Leibold, B.; Endsley, B.; Poling, A. Modulation of the behavioral effects of anticonvulsant drugs by an external discriminative stimulus in the pigeon. J. Pharmacol. Exp. Ther. 238:529–535; 1986.
30. Picker, M.; Leibold, L.; Endsley, B.; Poling, A. Effects of clonazepam and ethosuximide on the responding of pigeons under a fixed-consecutive-number schedule with and without an external discriminative stimulus. Psychopharmacology (Berlin) 88:325–330; 1986.
31. Poling, A.; Picker, M.; Thomas, J. Effects of chlorprothixene, haloperidol, and trifluoperazine on the delayed-matching-to-sample performance of pigeons. Pharmacol. Biochem. Behav. 21:721–726; 1984.
32. Pollard, G. T.; Howard, J. L. Similar effects of antidepressant and non-antidepressant drugs on behavior under an inter-response-time >72-s schedule. Psychopharmacology (Berlin) 89:253–258; 1986.

33. Rees, D. C.; Wood, R. W.; Laties, V. G. The roles of stimulus control and reinforcement frequency in modulating the behavioral effects of *d*-amphetamine in the rat. J. Exp. Anal. Behav. 43:243–255; 1985.
34. Robbins, T. W.; Evenden, J. L.; Ksir, C.; Reading, P.; Wood, S.; Carli, M. The effects of *d*-amphetamine, alpha-flupenthixol, and mesolimbic dopamine depletion on a test of attentional switching in the rat. Psychopharmacology (Berlin) 90:72–78; 1986.
35. Sayers, A. C.; Burki, H. R.; Ruch, W.; Asper, H. Anticholinergic properties of antipsychotic drugs and their relation to extrapyramidal side effects. Psychopharmacologia 51:15–22; 1975.
36. Shopsin, B.; Klein, H.; Aronson M.; Collora, M. Clozapine, chlorpromazine and placebo in newly hospitalized acutely schizophrenic patients. Arch. Gen. Psychiatry 36:657–664; 1979.
37. Spealman, R. D.; Katz, J. L. Some effects of clozapine on punished responding by mice and squirrel monkeys. J. Pharmacol. Exp. Ther. 212:435–440; 1980.
38. Spealman, R. D.; Kelleher, R. T.; Goldberg, S. R.; DeWeese, J.; Goldberg, D. M. Behavioral effects of clozapine: Comparison with thioridazine, chlorpromazine, haloperidol and chlordiazepoxide in squirrel monkeys. J. Pharmacol. Exp. Ther. 224:127–134; 1983.
39. Synder, S. H.; Greenberg, D.; Yamamura, H. I. Antischizophrenic drugs and brain cholinergic receptors. Affinity for muscarinic sites predict extrapyramidal effects. Arch. Gen. Psychiatry 31:58–61; 1974.
40. Szostak, C.; Tombaugh, T. N. Use of fixed consecutive number schedule of reinforcement to investigate the effects of pimozide on behavior controlled by internal and external stimuli. Pharmacol. Biochem. Behav. 15:609–617; 1981.
41. Tang, A. H.; Franklin, S. R. Acquisition of brightness discrimination in the rat is impaired by opiates with psychotomimetic properties. Pharmacol. Biochem. Behav. 18:873–877; 1983.
42. Waller, M. B. Effects of chronically administered chlorpromazine on multiple-schedule performance. J. Exp. Anal. Behav. 4:351–359; 1961.
43. Wenger, G. R. Effects of clozapine, chlorpromazine and haloperidol on schedule-controlled behavior. Pharmacol. Biochem. Behav. 11:661–667; 1979.