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Effects of Clozapine, Chlorpromazine and Haloperidol on Schedule-Controlled Behavior[1,2]

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WENGER, G. R. *Effects of clozapine, chlorpromazine and haloperidol on schedule-controlled behavior.* PHARMAC. BIOCHEM. BEHAV. 11(6)661–667, 1979.—The effects of clozapine, chlorpromazine, and haloperidol were determined in mice and pigeons responding under a multiple fixed-ratio 30, fixed-interval 600 sec schedule of food presentation. In both species, low doses were without effect and moderate to high doses of all three antipsychotics decreased responding. In contrast to other behavioral tests used to predict antipsychotic activity, clozapine was equipotent or more potent than chlorpromazine in decreasing responding under the multiple fixed-ratio 30, fixed-interval 600 sec schedule. The order of potency observed in the mouse was: haloperidol > chlorpromazine ≥ clozapine. The order of potency in the pigeon was: haloperidol > clozapine > chlorpromazine. In mice and pigeons, the rate of responding under the fixed-ratio component was decreased at lower than, or the same doses of clozapine as that required to decrease fixed-interval responding. However, in both species, chlorpromazine and haloperidol decreased fixed-interval responding at lower doses or the same dose as that required to decrease fixed-ratio responding.

Clozapine Chlorpromazine Haloperidol Fixed-interval Fixed-ratio Pigeon Mouse

THE antipsychotic drug clozapine is of considerable interest because of the reported lack of extrapyramidal side effects typically associated with antipsychotic drugs of the phenothiazine and butyrophenone groups [1, 2, 3, 6, 11, 12]. Clozapine has also been reported to be much less potent than haloperidol or chlorpromazine in behavioral tests (induction of catalepsy, inhibition of conditioned avoidance responding, and antagonism of apomorphine-induced stereotypies) considered to be useful for predicting the antipsychotic activity of new drugs [18,19].

To date, clozapine has not been extensively compared with other antipsychotics under various schedules of reinforcement. Although these procedures are not as widely used for predicting antipsychotic activity, compared to conditioned avoidance responding, induction of catalepsy, or antagonism of apomorphine-induced stereotypies, the sensitivity of behavior maintained by schedules of intermittent reinforcement to a wide range of drugs has been well documented. In one study [4], the effects of clozapine were compared with the effects of chlorpromazine and diazepam on the rate of lever pressing and adjunctive licking of rats. Under a fixed-ratio 20 (FR 20) schedule of reinforcement, clozapine and chlorpromazine decreased the rate of responding and were approximately equipotent. Over the same dose range, chlorpromazine also decreased the rate of responding under a fixed-interval 120 sec (FI 120 sec) schedule of reinforcement, and clozapine was without effect. Thus, it would appear that, at least in rats, under some schedules of reinforcement clozapine is equipotent with chlorpromazine while under other schedules olozapine is less potent.

To extend these findings, in the present study the effects of clozapine were compared with chlorpromazine and haloperidol in pigeons and mice responding under a multiple fixed-ratio 30, fixed-interval 600 sec schedule of reinforcement. In both species the qualitative effects on the rate of responding were compared, as well as the comparative potencies across schedules and across species.

METHOD

Subjects

The subjects were 14 male C57BL type mice derived from a C57BL/6J strain and 4 male white Carneaux pigeons. Four mice were used to study the effects of chlorpromazine, five mice were used to study the effects of haloperidol, and the remaining five mice were used to study the effects of clozapine. All three drugs were studied in the one group of four pigeons.

The pigeons ranged in weight from 450–500 g when given free access to food and water. Under the same conditions, the mice ranged in weight from 25–30 g. At the start of the experiment, both the pigeons and the mice were food deprived until their body weights were reduced to 80% of their free feeding weights. They were maintained at that weight

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[2]A preliminary abstract of this study appears in the *Fedn Proc.* 37: 3368 (abstract), 1978.

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throughout the experiment by supplemental feedings in their home cages at the end of the day. Pigeons were housed individually, and mice were housed 2–4 mice per cage. Tap water was always available in their home cages, but not in the experimental chambers. Testing was conducted during the normal working day (08:00–17:00), Monday through Friday.

Apparatus

The experimental chamber used for the experiments with pigeons was a similar chamber to that described previously [9]. A translucent plastic response key, 2 cm in dia., was mounted on a false wall inside the chamber about 20 cm above the floor. A minimum force of about 15 g was required to operate the key. Opening of the key contacts defined a response. The key could be transilluminated by two 7.5 W colored bulbs. Directly below the key was a rectangular opening through which the pigeon could be given access to grain. The chamber was illuminated at all times with a 25 W bulb (houselight), except during magazine presentations. During magazine presentations the key lights and the houselight were extinguished, and a light illuminating the grain hopper was turned on.

The experimental chamber used for the experiments with mice has been previously described [21,22]. In this apparatus, a beam of light crossed the width of a blind corridor striking a photocell mounted on the opposite wall of the corridor. Interruption of the light beam defined the response. Relay programming and recording apparatus were used in both the mouse and pigeon experiments.

Procedure

Both mice and pigeons were trained to respond under a multiple fixed-ratio 30, fixed-interval 600 sec (mult FR 30, FI 600 sec) schedule. Responding of pigeons was maintained under this schedule by 3-sec access to grain, and the responding of mice was maintained by a 10-sec presentation of a dipper of evaporated milk. This schedule of reinforcement has been described in detail elsewhere [9]. Briefly, in the presence of a blue key light in the pigeon experiments, and a stimulus light in the mouse experiments, 30 responses resulted in the presentation of grain to the pigeons or milk to the mice (FR 30). In the presence of a different stimulus, a red key light in the pigeon experiments, and a clicking relay in the mouse experiments, the first response to occur following the completion of the 600 sec interval produced access to the grain or milk (FI 600 sec). In both the pigeon and the mouse experiments, if 30 responses were not completed within 60 sec after the stimulus associated with the fixed-ratio (FR) component was turned on, the schedule changed; the stimulus associated with the FR component was turned off, and the FI 600 sec schedule began. If no response was made within 60 sec following the completion of the 600 sec fixed-interval (FI), the schedule changed back to the FR component. The pigeon experiments terminated after 16 component presentations; about 80 min, and the mouse experiments terminated after 10 component presentations; about 50 min.

Drugs

The drugs used were: chlorpromazine·HCl (Smith Kline and French Laboratories, Philadelphia, PA), haloperidol (McNeil Laboratories, Inc., Fort Washington, PA), and clozapine (Sandoz Pharmaceuticals, East Hanover, NJ). All doses are expressed un μmoles/kg of body weight. Chlorpromazine was dissolved in physiological saline. Stock solutions of chlozapine and haloperidol were made by dissolving the drug in 1 ml of 1 N acetic acid and adding physiological saline to obtain a total volume of 10 ml. The stock solutions were then further diluted with physiological saline to obtain the desired concentrations. All drug concentrations were made so that the desired dose could be administered in a volume of 1 ml/kg of body weight to pigeons or in a volume of 1 ml/100 g of body weight to mice. Drugs were administered IM to pigeons and IP to mice. All injections were made 5 min before the start of the session. Drugs were administered no more frequently than twice per week, typically on Tuesday and Friday. A control day was defined as a day preceded by a non-drug day, typically Thursday.

Measurement of Drug Effects

Average rates of responding were computed as responses per second from digital counters and elapsed time meters separately for the FR and FI components. The effect of drug administration is expressed as a ratio of the rate of responding after drug administration (drug rate) divided by the average rate of responding on all non-drug control days (control rate) for each component of the schedule.

The effect of a drug on the rate of responding was considered to be different from that of the mean control value if the mean drug effect was observed to be more than 2 standard errors away from the control mean. The standard error was defined as the total standard deviation of all control data divided by the square root of n; where n equals the smallest pool size in the study. In this experiment, the smallest pool size was the smallest number of observations at any given dose level of the drug in question.

For analysis of the dependency of the drug effect on the control rate of responding, the FI was divided into 10 equal segments of 60 sec each. The responses in corresponding segments of each interval were accumulated for each session, and a mean rate was determined for each segment of the FI. A ratio of the drug rate to the control rate was determined for each segment of the FI. The mean ratio for all subjects in a given study was plotted on a log-log plot as a function of the control rate in each segment. A regression line was fitted by the method of least squares to the points obtained from the 10 segments of the FI [8]. The data from the FR were also plotted, but were not used for determining the regression line.

RESULTS

Control Performance

The control performance of the pigeons responding under the mult FR 30 FI 600 sec was similar to that previously described for pigeons [9] under similar conditions. The mean rates of responding on non-drug control days for the entire study were 2.25 responses/sec for the FR 30 component and 0.71 responses/sec for the FI 600 sec component. The non-drug control FI quarter-life value, the percentage of the FI required to emit 25% of all the responses made during the entire FI 600 sec component [13], for the entire study was 54.8%, computed according to a previously published method [10].

The control performance of the mice responding under the mult FR 30 FI 600 sec schedule was similar to previous

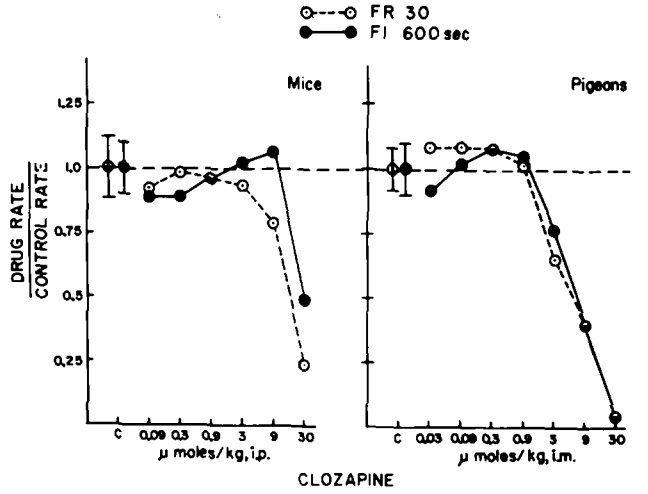

FIG. 1. Effect of clozapine on the average rate of responding of mice and pigeons in each component of the mult FR 30 FI 600 sec schedule. Abscissa: dose in μmoles/kg of body weight on a log scale; ordinate: ratio of the rate after drug administration to the average rate on non-drug control days. Vertical lines at C represent the control mean plus or minus 2 standard errors of the mean. The broken horizontal line represents the mean control value. Each point represents the mean of duplicate determinations in each of 5 mice (left panel) or each of 4 pigeons (right panel). Mean control rates for mice were: FR=1.81 responses/sec, FI=0.61 responses/sec; and for pigeons: FR=2.45 responses/sec, FI=0.69 responses/sec. 3 μmoles/kg clozapine=1 mg/kg clozapine.

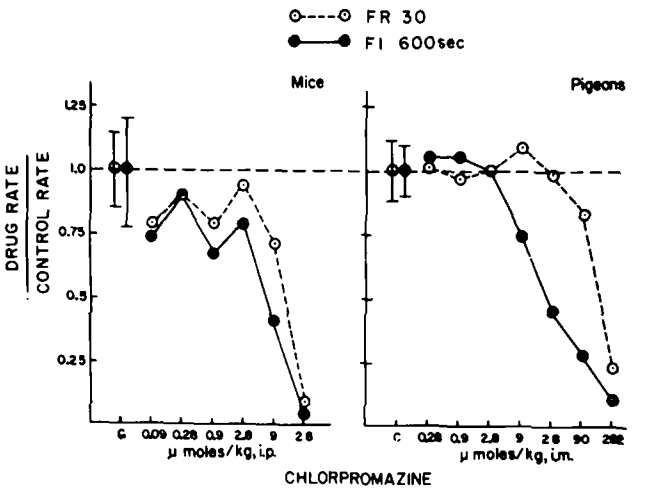

FIG. 2. Effect of chlorpromazine on the average rate of responding of mice and pigeons in each component of the mult FR 30 FI 600 sec schedule. Data presented as in Fig. 1. Each point represents the mean of duplicate determinations in each of 4 mice (left panel) or each of 4 pigeons (right panel). Mean control rates for mice were: FR=2.21 responses/sec, FI=0.63 responses/sec; and for pigeons: FR=2.28 responses/sec, FI=0.76 responses/sec. 2.8 μmoles/kg chlorpromazine=1 mg/kg chlorpromazine·HCl.

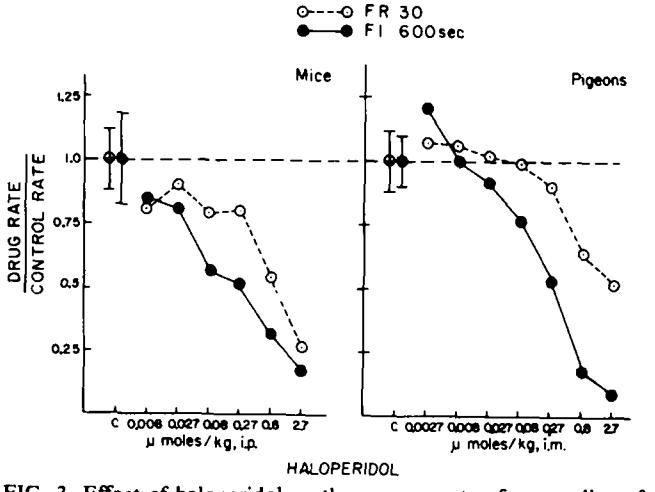

FIG. 3. Effect of haloperidol on the average rate of responding of mice and pigeons in each component of the mult FR 30 FI 600 sec schedule. Data presented as in Fig. 1. Each point represents the mean of duplicate determinations in each of 5 mice (left panel) or each of 4 pigeons (right panel). Mean control rates for mice were: FR=1.94 responses/sec, FI=0.63 responses/sec; and for pigeons: FR=2.03 responses/sec, FI=0.69 responses/sec. 2.7 μmoles/kg haloperidol=1 mg/kg haloperidol.

reports of mice responding under this and similar schedules [20, 21, 22]. The mean rates of responding under non-drug control days for the entire study were 1.99 responses/sec for the FR 30 component and 0.62 responses/sec for the FI 600 sec component. The non-drug control FI quarter-life value, computed according to a previously published method [10], for the entire study was 51.2%.

Effects of Antipsychotic Drugs on Mean Rates of Responding

The effect of clozapine on the rate of responding of mice and pigeons under the mult FR 30 FI 600 sec schedule is seen in Fig. 1. In mice, FR responding was decreased at doses of 9 μmoles/kg and higher. At doses of 0.9–30 μmoles/kg, the effect of clozapine on FI responding in mice was inconsistent. Although the mean effect observed in Fig. 1 shows no rate increases in FI responding, FI responding was increased in every mouse following the administration of at least one of the doses in this range. In each mouse, only a small increase in dose, above that which produced an increase in rate, resulted in a dramatic decrease in rate.

In pigeons, doses of 3 μmoles/kg and higher decreased the FR and the FI rate of responding. Although the overall effect was consistent, responding in individual FI's within a session showed large increases while responding in other FI's in the same session was decreased. This variability was not related to the time since drug administration. The mean effect of clozapine in both species was a dose-dependent decrease in responding with increasing doses. The decreases observed in the pigeon were slightly larger at a given dose than those observed in the mouse. In pigeons, the decrease in the rate of responding following a given dose of clozapine was about equal for both components of the schedule. In mice, there was a small indication that the rate of FR responding was more sensitive to the rate decreasing effects than was FI responding. This difference, however, was small and was not significant.

The effect of chlorpromazine on the rate of responding of both species under the mult FR 30 FI 600 sec schedule is seen in Fig. 2. In pigeons, no effect was observed on FR responding below a dose of 90 μmoles/kg. At this dose and

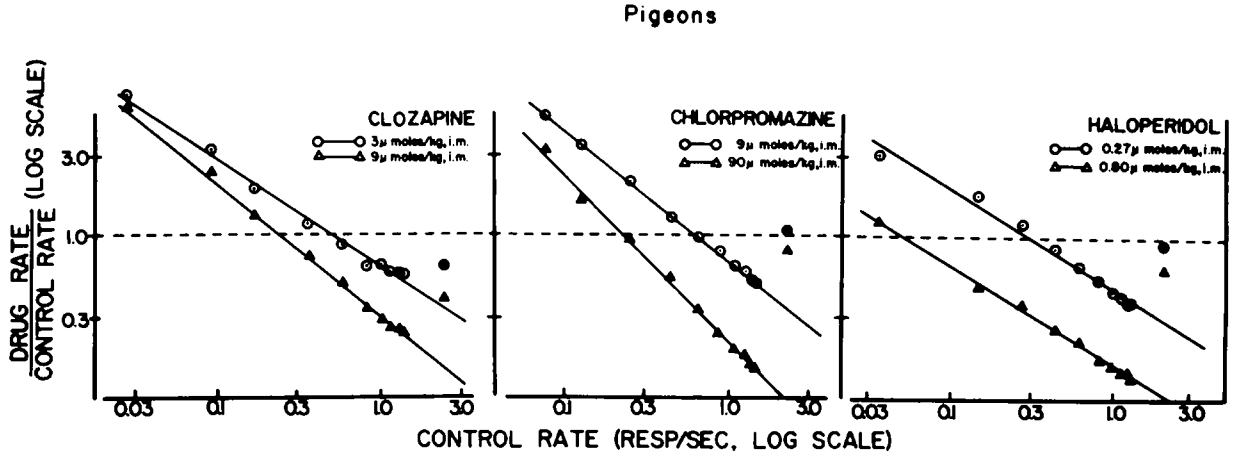

FIG. 4. Dependence of the effect of clozapine, chlorpromazine, and haloperidol on the control rate of responding in pigeons. Abscissa: average rate of responding on a log scale in each 60 sec segment of the FI 600 sec schedule (open circles and triangles), and under the FR 30 response schedule (filled circles and triangles); ordinate: ratio of the average rate after drug administration to the average rate on non-drug control days. Each point represents the mean of duplicate determinations in each of 4 pigeons. See Table 1 for the corresponding slopes and Y-intercepts.

higher, FR responding was decreased. FI responding was decreased in a monotonic dose-dependent fashion at doses of 9 μmoles/kg and higher. Thus, in the pigeon, responding under the FI component was decreased 50% by a dose of approximately 28 μmoles/kg. This is approximately a 10 fold lower dose than that which was required to produce a similar decrease in FR responding.

In mice, chlorpromazine decreased responding in both components of the schedule to a similar extent. There was a greater decrease in FI responding than FR responding following a dose of 9 μmoles/kg, but otherwise there was no indication of a schedule difference in sensitivity to the rate decreasing effects.

In comparing clozapine (Fig. 1) and chlorpromazine (Fig. 2), chlorpromazine may be slightly more potent than clozapine in mice, but the difference is small and the two drugs should probably be considered to be equipotent. However, in the pigeon clozapine is at least 10 times more potent than chlorpromazine. These potency relationships were observed in every subject.

Figure 3 shows the effects of haloperidol on responding of mice and pigeons under the mult FR 30 FI 600 sec schedule. At doses of 0.8 and 2.7 μmoles/kg, the responding of pigeons under the FR component was decreased; lower doses were without effect. Responding under the FI component was decreased at doses of 0.08 μmoles/kg and higher. The lowest dose tested, 0.0027 μmoles/kg, produced a small increase in FI responding.

The effect of haloperidol on the responding of mice was similar to that observed in pigeons. FI responding was decreased at doses of 0.08 μmoles/kg and higher. Only small decreases were observed in FR responding at doses below 0.08 μmoles/kg. Thus, in both species, FI responding appeared to be more sensitive to the rate decreasing effects of haloperidol than was FR responding. Haloperidol appeared to be equipotent in the mouse and pigeon, and was more potent than either clozapine or chlorpromazine in both species.

Effects of Antipsychotic Drugs on the FI Quarter-life

In both species, all three antipsychotic drugs produced no effect on the FI quarter-life at low doses. As the dose of each antipsychotic was increased, the only effect seen was a decrease in the quarter-life value in both species. Clozapine decreased the quarter-life at doses equal to or greater than 3 μmoles/kg in the mouse and 0.9 μmoles/kg in the pigeon. Chlorpromazine decreased the quarter-life at doses equal to or greater than 9 μmoles/kg in the mouse and 0.3 μmoles/kg in the pigeon. Haloperidol decreased the quarter-life at doses equal to or greater than 0.08 μmoles/kg in the mouse and 0.27 μmoles/kg in the pigeon.

The Dependence of the Drug Effect on the Control Rate of Responding

The effects of clozapine, chlorpromazine, and haloperidol were dependent upon the control rate of responding. Figure 4 shows that in the pigeon all three drugs increased low rates of responding and decreased high rates. The high rates of responding observed under the FR component, however, were not decreased as much as would have been predicted by an extrapolation of the regression line of the FI data. The failure of the FR points to fall on the regression line generated from the FI schedule does not negate the influence of the control rate on the drug effect. It merely shows that other factors, such as schedule differences, can modify the expected effect of rate. Although not shown, similar results were obtained in the mouse.

In Figure 4, the large differences in transition rates, that rate above which rates of responding are decreased and below which rates are increased [15], is seen. Clozapine and chlorpromazine decreased the transition rate to about the same extent following doses which decreased the average rate to about the same extent. Both the 3 μmoles/kg dose of clozapine and the 9 μmoles/kg dose of chlorpromazine decreased the average rate of responding under the FI to about

TABLE 1

PIGEON				MOUSE			
Dose (μmoles/kg)	Slope	Y-intercept*	Transition Rate†	Dose (μmoles/kg)	Slope	Y-intercept*	Transition Rate†
			Clozapine				
0.3	−0.21	0.98	0.91	0.3	−0.07	0.87	0.14
0.9	−0.50	0.95	0.90	0.9	−0.08	0.93	0.40
3.0	−0.67	0.65	0.53	3.0	−0.05	0.98	0.67
9.0	−0.83	0.31	0.24	9.0	−0.24	1.00	1.00
			Chlorpromazine				
2.8	−0.61	0.93	0.89	0.28	−0.09	0.89	0.27
9.0	−0.78	0.69	0.63	0.90	−0.24	0.60	0.12
28.0	−0.89	0.39	0.35	2.80	−0.06	0.78	0.02
90.0	−1.00	0.23	0.23	9.00	−0.41	0.35	0.08
			Haloperidol				
0.027	−0.06	0.91	0.21	0.027	−0.13	0.81	0.20
0.08	−0.15	0.78	0.19	0.08	−0.16	0.59	0.04
0.27	−0.62	0.49	0.32	0.27	−0.11	0.51	0.002
0.80	−0.62	0.16	0.05	0.80	−0.25	0.32	0.01

*Y-intercept is defined as the $\frac{\text{drug rate}}{\text{control rate}}$ when X=1 response/sec.

†Transition rate is defined as that rate, responses/sec, above which rates of responding are decreased and below which rates are increased [15].

75% of control, and the transition rates for these doses were 0.53 and 0.63 responses/sec for clozapine and chlorpromazine, respectively. The highest doses plotted in Fig. 4 for both clozapine and chlorpromazine decreased the average FI rate to about 30–40% of control and for both drugs at those doses, the transition rates were about 0.24 responses/sec. In comparison to the effects of clozapine and chlorpromazine on transition rates, haloperidol produced a lower transition rate at doses which produced similar decreases in the average rate under the FI. Following 0.27 and 0.8 μ moles/kg haloperidol, the average rate of responding was decreased to approximately 60% and 20% of control, respectively. The transition rates following these same doses were 0.32, and 0.05 responses/sec.

Table 1 shows the slopes, Y-intercepts, and the transition rates of the rate-dependency regression lines following several doses of the three drugs in pigeons and mice. For both mice and pigeons, the lowest dose of each drug in Table 1 is a dose which produced no effect on the mean rate of FI responding (Figs. 1, 2 and 3). In the pigeon, over a dose range of 0.3–9 μmoles/kg clozapine, an increase in dose resulted in an increase in the negativity of the slope and a decrease in the Y-intercept. Over a similar 30-fold increase in the dose of chlorpromazine, 2.8–90 μmoles/kg, an increase in dose resulted in an increase in the negativity of the slope and a similar decrease in the Y-intercept. The change in slope, after chlorpromazine, was not as great as the change in slope seen with clozapine; although, the absolute negativity of the slope was larger after chlorpromazine. Finally, haloperidol produced only a small change in slope and Y-intercept at the 0.027 and 0.08 μmoles/kg doses, but the increase from 0.08–0.27 μmoles/kg produced a large increase in slope. An additional increase in dose, however, produced a parallel line with a slope of −0.62. Thus, it would appear that below a dose of 0.27 μmoles/kg, haloperidol produces only minimal rate-dependent effects, and at doses of 0.27 μmoles/kg and higher, haloperidol produces large rate-dependent effects.

In the mouse, it can be seen that increasing the dose of clozapine increases the negativity of the slope only at the 9 μmoles/kg dose, but at this dose, there is no real change in the Y-intercept. Over this dose-range it should be noted that the transition rates are increasing as the dose is increased. This is in contrast with the results obtained in the pigeon with clozapine and with the results obtained in both species with chlorpromazine and haloperidol. The doses of clozapine in the mouse, however, are on the ascending limb of the dose-response curve. No regression line was calculated for the next higher dose, 30 μmoles/kg, since in mice this dose produced total suppression of responding for a portion of the session.

Although not as orderly as the pigeon data, the effect of chlorpromazine in the mouse reflects the results seen in the pigeon. With the exception of the 2.8 μmoles/kg dose, increasing the dose of chlorpromazine from 0.28–9 μmoles/kg results in an increase in the negativity of the slope and a decrease in the Y-intercept.

Haloperidol, in the mouse, at doses of 0.027–0.27 μmoles/kg, does not produce large changes in the slopes of the regression lines. An increase in dose to 0.8 μmoles/kg produced a slightly more negative slope. However, unlike clozapine, haloperidol in the mouse produced a decrease in the Y-intercept over the entire 30-fold range of doses. For all three drugs, the regression lines relating the dependence of the drug effect on the control rate of responding are less

negative in the mouse than in the pigeon, and the transition rates after chlorpromazine and haloperidol are lower in the mouse than in the pigeon.

DISCUSSION

The present study compared the effects of clozapine, chlorpromazine, and haloperidol on the responding of pigeons and mice under a multiple fixed-ratio, fixed-interval schedule of reinforcement. In the present study and in previous reports, chlorpromazine [14, 15, 17] and haloperidol [14] have been shown in pigeons, to decrease FI responding at doses lower than those required to decrease FR responding. The present study shows that a similar greater sensitivity of FI responding compared to FR responding exists for the rate decreasing effects of haloperidol in mice.

Clozapine, however, does not show a differential potency to FR or FI responding in pigeons or mice. As seen in Fig. 1, the rate of responding in both components is decreased to a similar extent by clozapine in both species. In the mouse there is a suggestion that responding under the FR is more sensitive to the rate decreasing effects of clozapine than is responding under the FI component, but this difference is not statistically significant. A similar observation was reported following clozapine administration to rats responding under either a FR 20 or a FI 120 sec schedule [4]. Rats responding under the FR 20 schedule received significantly fewer food presentations compared to control at doses of 5 and 10 mg/kg (15 and 30 μmoles/kg), but rats responding under the FI 120 sec schedule responded at a slightly higher rate than control (although not significant at the 0.05 level) after receiving 5 mg/kg clozapine, and the rate of responding was not significantly decreased at 10 mg/kg.

Clozapine, like chlorpromazine and haloperidol, produced rate-dependent effects on responding in this study. In both species, low rates were increased, but the effect was larger in the pigeon. At a control FI rate of 1 response/sec, clozapine produced a larger decrease of responding in the pigeon than in the mouse. In a previous report [4], clozapine was reported to produce rate-dependent effects in rats responding under a FI 120 sec schedule. Following a dose of 5 mg/kg (15 μmoles/kg), clozapine increased responding during the early and middle portions of the FI, but the high rates during the final portion of the FI were not effected. Following a dose of 10 mg/kg (30 μmoles/kg) clozapine, responding during the early portions of the FI were unaffected or slightly increased while the high rates during the final segments of the FI were decreased.

Chlorpromazine, in the present study, was shown to produce large rate-dependent effects in the pigeon and somewhat smaller rate-dependent effects in the mouse. Similar rate-dependent effects have been reported previously with chlorpromazine in pigeons [7, 14, 15, 16] and in rats [4,5]. The two species used in this study differed, however, in that in the pigeon low rates were increased and high rates were decreased, but in the mouse the transition rate was much lower, thus, the majority of the measured rates during the FI were decreased.

It had been previously reported [14] that in pigeons haloperidol did not produce rate-dependent effects on responding during the FI component. In the present study, low doses of haloperidol (doses below 0.27 μmoles/kg) did not produce rate-dependent effects in pigeons responding under the FI component. However, at 0.27 and 0.8 μmoles/kg, a rate-dependent effect was observed with the two doses producing parallel regression lines. The reason for the present observation of rate-dependent effects and the failure to observe such effects in the previous study [14] with pigeons, is unclear. The previous study [14] used a 300 sec FI while in the present study, a 600-sec FI was employed, but this difference probably would not produce such a qualitative difference.

In the mouse the rate-dependent effects of haloperidol were small and of the same order of magnitude (negativity of the slope of the regression line) as observed with clozapine. Haloperidol, however, decreased all measured rates during the FI. The same magnitude of rate-dependent effects after clozapine in the mouse resulted in a small rate increase of the low rates during the early portions of the FI.

Unlike the reported effects of clozapine in other behavioral tests (induction of catalepsy, inhibition of conditioned avoidance responding, and antagonism of apomorphine induced stereotypies), in mice and pigeons responding under a mult FR 30 FI 600 sec schedule of food presentation, clozapine was not observed to be much less potent than chlorpromazine. In the mouse, clozapine was approximately equipotent with chlorpromazine, and in the pigeon clozapine was 10 times more potent than chlorpromazine. In both species, however, clozapine and chlorpromazine were less potent than haloperidol. The differences observed between clozapine and the standard antipsychotics (chlorpromazine and haloperidol) in this study related to the relative differences in sensitivity of FR 30 and FI 600 sec responding to rate-decreasing effects of the drugs. In the pigeon, chlorpromazine and haloperidol decreased FI responding at lower doses than those required to decrease FR responding. This differential sensitivity was not observed with clozapine in the pigeon. In the mouse, a similar differential sensitivity was observed after haloperidol and possibly after chlorpromazine. However, after clozapine this was not observed, and in fact there was a suggestion that FR responding of mice may be more sensitive to the rate-decreasing effects of clozapine than FI responding, but the difference was not significant.

It is not possible to determine a mechanism of action of the behavioral effects of a drug in most behavioral tests. It is also difficult to extrapolate from the behavior of laboratory animals to a given human behavioral abnormality such as psychosis. Thus, the effects reported here may or may not reflect the antipsychotic properties of these drugs. The same cautions, however, must also apply to behavioral tests such as induction of catalepsy, inhibition of conditioned avoidance responding, and the antagonism of apomorphine induced stereotypies. These tests have been accepted as being useful in the evaluation of the antipsychotic activity of drugs because the potency relationships observed for most drugs agree well with the observed clinical effects. Clozapine is the notable exception in the traditional screen for antipsychotic activity. As shown in these studies, the potency of clozapine, compared to haloperidol and chlorpromazine, on behavior maintained under a mult FR 30 FI 600 sec schedule of reinforcement agrees quite well with the observed clinical potencies. However, further studies on the effects of clozapine on schedule-controlled behavior are required before these effects can be evaluated in terms of antipsychotic activity.

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