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Clozapine Effects on Responding Maintained Under Shock Presentation and Shock Termination Schedules[1]

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BACOTTI, A. V. *Clozapine effects on responding maintained under shock presentation and shock termination schedules.* PHARMAC. BIOCHEM. BEHAV. 15(3) 415–418, 1981.—Clozapine, a novel antipsychotic, was studied in different squirrel monkeys responding under a 3-min fixed-interval schedule of stimulus-shock termination and a multiple 5-min fixed-interval schedule of shock presentation, 5-min fixed-interval schedule of stimulus-shock termination. Some doses (0.1–1.0 mg/kg IM) of clozapine increased responding under each fixed-interval schedule, whereas higher doses (3.0 and 5.6 mg/kg IM) usually decreased responding under each schedule. Lower response rates maintained under the stimulus-shock termination schedule were increased relatively more by clozapine than were higher rates of responding maintained under the fixed-interval schedule of shock-presentation. The present results illustrate that the effects of clozapine on schedule-controlled behaviors of squirrel monkeys differ from those of other antipsychotics.

Clozapine Fixed-interval schedules Shock Stimulus-shock termination Squirrel monkeys

CLOZAPINE, a dibenzodiazepine, has been used effectively as an antipsychotic agent in humans [7,8]. Clozapine differs from other antipsychotics, such as those from the phenothiazine class, in certain of its actions. For example, clozapine does not produce catelepsy or extrapyramidal effects, does not antagonize apomorphine-produced stereotyped activity, and has effects different from those of phenothiazines and related drugs on brain dopamine [4, 8, 11, 12, 22].

Much less is known about the effects of clozapine on schedule-controlled behaviors, but several studies indicate that the effects of clozapine differ from those of chlorpromazine in laboratory animals. In one study [13], rats discriminated between clozapine and chlorpromazine by responding differently in the presence of each drug. In other studies [5, 9, 17, 21] chlorpromazine decreased responding of mice, rats and squirrel monkeys maintained under fixed-ratio and fixed-interval schedules, whereas some doses of clozapine increased responding under fixed-interval schedules. It has also been reported that clozapine increased and chlorpromazine decreased responding of squirrel monkeys maintained under a differential-reinforcement-of-low-rate schedule [6]. Further analysis of the effects of clozapine on schedule-controlled responding is necessary in order to fully characterize the action of this novel antipsychotic.

In the present study, the effects of clozapine were studied in squirrel monkeys when responding was maintained under fixed-interval schedules of shock presentation and stimulus-shock termination.

METHOD

Subjects

Four adult male squirrel monkeys (*Saimiri sciureus*) with extensive prior laboratory experiences under stimulus-shock termination and shock presentation schedules, including exposure to a variety of drugs, were maintained in individual cages at unrestricted body weights (S-528, S-532, S-534, S-535).

Apparatus

Experiments were conducted with monkeys seated in a restraining chair enclosed in a sound-attenuating chamber. Electric shocks (650-volt AC, 200 msec) were delivered through variable series resistance to metal electrodes that rested on a shaved portion of the tail. A response lever (BRS/LVE No. 121-05), requiring a minimal downward force of approximately 20 g for activation, was mounted on a clear Plexiglas panel facing the monkey. Colored 7-W lights were mounted behind this panel.

Procedure

Lever pressing of all monkeys had been established prior to the present study. Each monkey was studied 5 days per week at approximately the same time each day.

Fixed-interval schedule of stimulus-shock termination. Monkeys S-528 and S-535 responded under a 3-min fixed-

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interval (FI 3-min) schedule of stimulus-shock termination for 21 sessions prior to clozapine administration. under this schedule, the first response after 3-min terminated the schedule and shock delivery and turned off the correlated stimulus lights (white). After the 3-min FI elapsed, 5 mA shocks occurred every 3-sec (t=3 sec) if a response did not occur. A maximum of 10 shocks could be delivered if responding did not occur (limited hold, LH, 30 sec). A 30 sec period during which responses had no scheduled consequences and the chamber was dark (timeout, TO, 30 sec) separated each FI. Sessions ended after 30 FI cycles.

Multiple shock-termination, shock-presentation schedule. Monkeys S-532 and S-534 responded under a 5-min FI stimulus-shock termination schedule (t=5 sec, 10 mA) in the presence of red lights and a 5-min FI shock-presentation schedule in the presence of white lights for 55 sessions prior to clozapine administration. Under the shock-presentation schedule the first response after 5-min produced a 10 mA shock [16]. A LH 30 sec and TO 30 sec were in effect for each schedule. Schedules and correlated stimuli alternated sequentially throughout each session, starting with the shock-termination schedule. Sessions terminated after exposure to 10 cycles of each FI schedule.

Drug procedure. Clozapine (base) was dissolved in 1N acetic acid and diluted further with 0.9% sodium chloride. Drug was administered in a calf muscle in a volume of 0.5 ml/kg body weight on Tuesdays and Fridays immediately before sessions. Performances on Thursdays served as control with which to compare the effects of drug. Each dose was administered twice in an irregular order.

RESULTS

Fixed-Interval Stimulus-Shock Termination

The effects of clozapine on responding maintained under a 3-min FI stimulus-shock termination (t=3 sec) schedule are shown in Fig. 1. Performances on control days were characteristic of those obtained under FI schedules, with zero or low rates of responding maintained early in the interval, followed by a transition to higher rates of responding that were maintained until the end of each interval. Few shocks were delivered on control days and rarely was more than one shock delivered at the end of the FI during any session. Response rates of both S-528 and S-535 were higher with intermediate doses of clozapine (0.3, 1.0, and 3.0 mg/kg) than on control days or with injection of vehicle concentrations (V_1,V_2) of 20% and 60% (1N acetic acid in saline). The highest doses (5.6 mg/kg for S-528; 3.0 mg/kg for S-535) decreased responding below control levels, although the decrease for S-528 was only slightly below 1 SD of control performance and within the range of vehicle administration. The lowest doses (0.03 mg/kg) did not change responding from control rates or rates with vehicle. As shown in Fig. 1, a wider range of doses (0.1–3.0 mg/kg) increased responding of S-528 above control rates than for S-535 (0.3 and 1.0 mg/kg). Note that control rates of S-535 were somewhat higher than for S-528.

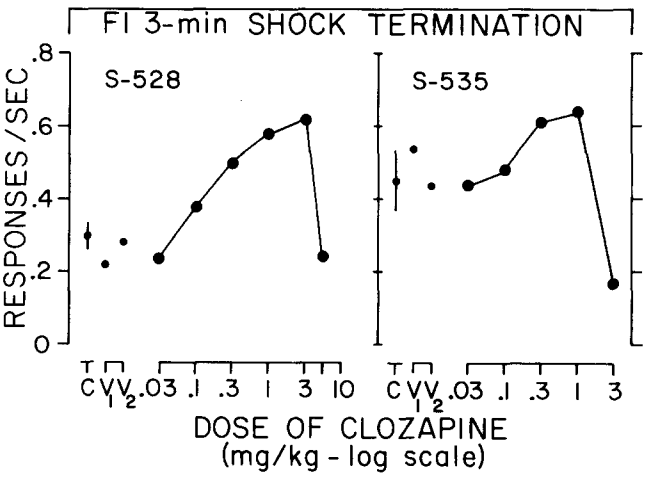

FIG. 1. Effects of clozapine on response rates maintained under a 3-min fixed-interval schedule of stimulus-shock termination (t=3 sec). Control rates (C) with variability (±1 S.D.) and vehicle concentrations of 20% (V_1) and 60% (V_2) of 1 normal acetic acid in saline are shown to the left of each dose-effect curve. Control rates are the means of at least 6 sessions; all other points are the means from two administrations.

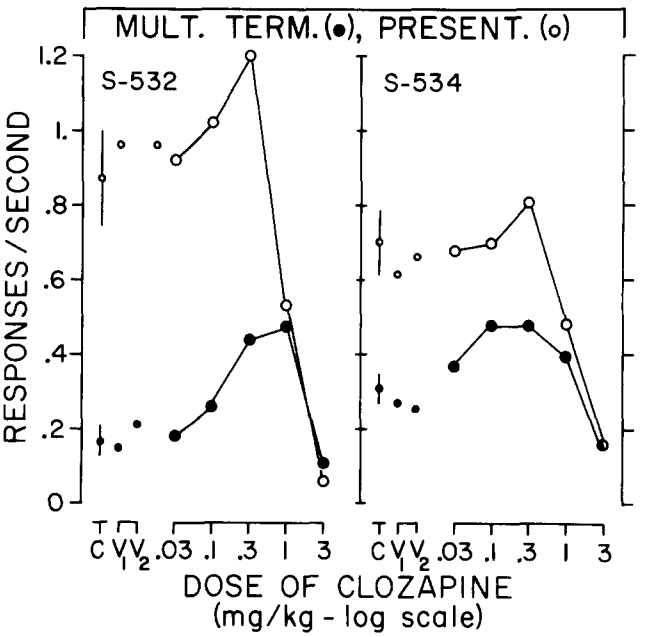

FIG. 2. Effects of clozapine on response rates maintained under a multiple 5-min FI stimulus-shock termination (t=5 sec; filled circles), 5-min FI shock-presentation (open circles) schedule. Control rates (C) with variability (±1 S.D.) and vehicle concentrations of 20% (V_1) and 60% (V_2) of 1 normal acetic acid in saline are shown to the left of each dose-effect curve. Control rates are the means of at least 6 sessions; all other points are the means from two administrations of drug or vehicle.

Multiple Shock-Termination Shock-Presentation

Control performances and the effects of clozapine on responding maintained under a multiple 5-min FI stimulus-shock termination (t=5 sec), 5-min FI shock-presentation schedule are shown in Fig. 2. Although characteristic FI patterns of responding were maintained under each FI

schedule, response rates maintained under the shock-presentation schedule were consistently higher than response rates maintained under the shock-termination schedule. Few, if any, shocks were delivered under the shock-termination schedule during control sessions and little or no responding occurred during timeout periods. For S-532 intermediate doses (0.1 and 0.3 mg/kg) of clozapine increased responding under each schedule. For S-534 one dose (0.3 mg/kg) of clozapine increased responding slightly under the shock-presentation schedule. Intermediate doses (0.1–1.0 mg/kg) increased responding of S-534 under the shock-termination schedule. A dose of 1.0 mg/kg increased the lower rate of responding maintained under the shock-termination schedule and decreased the higher rate of responding maintained under the shock-presentation schedule for both S-532 and S-534. For each monkey a wider range of doses (0.1–1.0 mg/kg) increased responding under the shock-termination schedule than under the shock-presentation schedule. Vehicle administrations of 20% and 60% of 1N acetic acid in saline (V_1,V_2) and the lowest dose of drug (0.03 mg/kg) generally did not increase response rates above control levels. The highest dose (3.0 mg/kg) decreased responding below control levels, although for S-532 rates under the shock-termination schedule were only slightly below 1 SD of control rates.

DISCUSSION

Clozapine increased responding under each fixed-interval schedule regardless of whether responding was maintained by shock-presentation or shock-termination. These effects are consistent with other reports of the effects of clozapine on schedule-controlled performances. For example, doses of clozapine that decreased responding of mice and rats under a fixed-ratio food-presentation schedule increased or did not change responding under a fixed-interval food-presentation schedule [5,21].

The effects of clozapine on schedule-controlled responding can be differentiated from the effects of other drugs. For example, psychomotor stimulants, such as amphetamines, have been reported to increase low rates of responding maintained under fixed-interval schedules [10, 15, 19]. Clozapine had similar effects in the present study. However, amphetamine generally does not increase punished responding but clozapine has been shown to do so [20].

The effects of clozapine in the present study differ from those of anxiolytic drugs. Both chlordiazepoxide and pentobarbital increased responding of squirrel monkeys maintained under fixed-interval schedules of food presentation, but decreased responding maintained under fixed-interval schedules of shock presentation and stimulus-shock termination [1,2]. In contrast, clozapine increased responding under comparable fixed-interval schedules of shock presentation and stimulus-shock termination in the present study. This rate increasing effect not only distinguishes clozapine from pentobarbital and chlordiazepoxide, but also from chlorpromazine, a phenothiazine antipsychotic. Previous studies generally have shown that in a variety of species chlorpromazine only decreased responding under fixed-interval schedules [6, 17, 21].

The present data indicate that the effects of clozapine may be related to the control rate of responding or to the type of event maintaining responding (e.g., shock-presentation or shock-termination). Under the multiple schedule response rates were higher in one component (fixed-interval shock presentation) than in the other component (fixed-interval stimulus-shock termination). Response rates under the schedule which maintained the higher response rates were either decreased or increased less by clozapine than response rates under the schedule which maintained the lower response rates. For example, one dose of clozapine (1.0 mg/kg) increased responding under the shock-termination schedule and decreased responding under the shock-presentation schedule. The relation between control rates and drug effects has been discussed previously for a number of drugs (e.g., [10, 15, 19]).

In the present study, different control rates were correlated with the different events that maintained responding so that it is not possible to specify which variable best predicts the differences in drug effects. Previous studies have shown that under certain conditions the event maintaining responding can be an important determinant of the effects of a drug. Typically, this has been shown when responding was maintained under fixed-interval schedules [1,16]. Other studies have shown that quantitative characteristics of responding can override the influence of different events [14,18]. For example, a recent study showed that clozapine had comparable effects on responding maintained under fixed-ratio schedules of food presentation and stimulus-shock termination [18]. Thus, a variety of factors, including behavioral history, current conditions, schedule of reinforcement, response rate and event, operating alone or in combination may influence the effects of a drug on behavior.

The present data offer further behavioral evidence that clozapine differs in certain of its actions from other antipsychotics. These behavioral differences may be related to the evidence showing differences in the effects of clozapine and chlorpromazine on dopaminergic neurons and to the general lack of extrapyramidal side effects found with clozapine [3, 4, 7, 8]. In addition to characterizing the behavioral effects of clozapine, the present data demonstrate the utility of schedule-controlled responding in differentiating the effects of neuroleptic drugs.

REFERENCES

1. Barrett, J. E. Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. *J. Pharmac. exp. Ther.* **196:** 605–615, 1976.
2. Barrett, J. E., S. I. Dworkin and R. R. Zuccarelli. Effects of *d*-amphetamine, chlordiazepoxide and promazine on responding of squirrel monkeys maintained under fixed-interval schedules of food presentation and stimulus-shock termination. *Pharmac. Biochem. Behav.* **7:** 529–535, 1977.
3. Bunney, B. S. and G. K. Aghajanian. The effect of antipsychotic drugs on the firing of dopaminergic neurons: a reappraisal. In: *Antipsychotic Drugs: Pharmacodynamics and Pharmacokinetics*, edited by G. Sedvall, B. Uvnas and Y. Zotterman. New York: Pergamon Press, 1975, pp. 305–318.
4. Bürke, H. R., E. Eichenberger, A. C. Sayers and T. G. White. Clozapine and the dopamine hypotheses of schizophrenia, a critical appraisal. *Pharmakopsychiatrie* **8:** 115–121, 1975.

5. 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.
6. Canon, J. G. A comparison of clozapine, chlorpromazine and thioridazine upon DRL performance in squirrel monkeys. *Psychopharmacology* **64:** 55–60, 1979.
7. DeMaio, D. Preliminary clinical evaluation of a new neuroleptic agent: HF1854. In: *The Present Status of Psychotropic Drugs*, edited by A. Cerletti and F. J. Bové. Amsterdam: Excerpta Medica Foundation, 1969, pp. 485–488.
8. DeMaio, D. Clozapine, a novel major tranquilizer. *Arzneimittel-Forsch.* **22:** 919–921, 1972.
9. Dews, P. B. and J. DeWeese. Schedules of reinforcement. In: *Handbook of Psychopharmacology*. edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. New York: Plenum Press, 1977, pp. 107–150.
10. Dews, P. B. and G. R. Wenger. Rate-dependency of the behavioral effects of amphetamine. *Adv. Behav. Pharmac.* **1:** 167–227, 1977.
11. Gelenberg, A. J. and J. C. Doller. Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double blind study. *J. clin. Pharmac.* **40:** 238–240, 1979.
12. Gerlach, J., K. Thoren and R. Fog. Extrapyramidal reactions and amine metabolites in cerebrospinal fluid during haloperidol and clozapine treatment in schizophrenic patients. *Psychopharmacologia* **40:** 341–350, 1975.
13. Goas, J. A. and J. E. Boston. Discriminative stimulus properties of clozapine and chlorpromazine. *Pharmac. Biochem. Behav.* **8:** 235–241, 1978.
14. Katz, J. L. and J. E. Barrett. Ethanol, pentobarbital, and chlordiazepoxide effects in squirrel monkeys responding under fixed-ratio food presentation and stimulus-shock termination schedules. *Psychopharmacology* **56:** 153–155, 1978.
15. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of behavioral effects of drugs. *Ergebn. Physiol.* **60:** 1–56, 1968.
16. McKearney, J. W. Maintenance of responding under a fixed-interval schedule of electric shock-presentation. *Science* **160:** 1249–1251, 1968.
17. McKearney, J. W. Effects of *d*-amphetamine, morphine, and chlorpromazine on responding under fixed-interval schedules of food presentation and electric shock presentation. *J. Pharmac. exp. Ther.* **190:** 141–153, 1974.
18. McKearney, J. W. Fixed-ratio schedules of food presentation and stimulus shock termination: Effects of *d*-amphetamine, morphine, and clozapine. *Psychopharmacology* **70:** 35–39, 1980.
19. Sanger, D. J. and D. E. Blackman. Rate-dependent effects of drugs: a review of the literature. *Pharmac. Biochem. Behav.* **4:** 73–83, 1976.
20. Spealman, R. D. and J. L. Katz. Some effects of clozapine and punished responding by mice and squirrel monkeys. *J. Pharmac. exp. Ther.* **212:** 435–440, 1980.
21. Wenger, G. R. Effects of clozapine, chlorpromazine and haloperidol on schedule-controlled behavior. *Pharmac. Biochem. Behav.* **11:** 661–668, 1979.
22. Zivkovic, B., A. Guidotti, A. Revuelta and E. Costa. Effects of thiozidazine, clozapine, and other anti-psychotics on kinetic state of tyrosine hydroxylase and on the turnover rate of dopamine in striatum and nucleus accumbens. *J. Pharmac. exp. Ther.* **194:** 37–46, 1975.