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The Effects of Cimetidine on Schedule-Controlled Responding and Locomotor Activity in Rats[1]

S. K. RASTOGI[2] AND D. E. McMILLAN[3]

Department of Pharmacology and Interdisciplinary Toxicology
University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205

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RASTOGI, S. K. AND D. E. McMILLAN. *The effects of cimetidine on schedule-controlled responding and locomotor activity in rats.* PHARMACOL BIOCHEM BEHAV **20**(1) 63–67, 1984.—The effect of intraperitoneal injections of cimetidine, a selective histaminergic H_2-receptor blocking agent, on operant behavior and locomotor activity were examined in rats. Cimetidine (1–100 mg/kg) failed to show any significant effect on responding maintained under a fixed-ratio (FR) 30 fixed-interval (FI) 5-min schedule of food presentation. A higher dose of cimetidine (300 mg/kg) produced decreases in both FR and FI rates of responding. In contrast, 100 mg/kg of cimetidine increased the response rate and decreased reinforcement rate in rats performing under a schedule requiring the temporal spacing of responses (DRL-10 sec). Cimetidine (10–300 mg/kg) did not induce significant changes in locomotor activity in the rat. These data suggest that cimetidine is more potent in altering the steady low rate of responding under a DRL schedule of food presentation, than responding maintained under a multiple FR FI schedule, and that cimitidine is even less potent in altering locomotor activity.

Cimetidine Rats Schedule-controlled behavior Motor activity

CIMETIDINE, a selective blocker of histaminergic H_2 receptors has been used extensively during the last few years in the treatment of peptic ulcers. Recently, a possible role of cimetidine in the treatment of hyperthyrodism during uremia has also been suggested [5,11]. Despite extensive use of cimetidine, few CNS side effects have been reported in clinical patients [4,12]. There is increasing evidence that in the mammalian CNS, physiological effects of histamine are due to its action on two types of receptors designated as H_1 and H_2 [2,3]. Various bicohemical studies have shown that H_2 receptors are coupled with activation of adenylate cyclase and are selectively blocked by cimetidine [10,13]. Further, several tricyclic and second generation antidepressants also are potent inhibitors of cerebral H_2 receptors [13,14]. Although the behavioral effects of antidepressants have been studied in detail, considerably less is known about the behavioral effects of cimetidine. The only report on the effects of cimetidine on operant behavior was by Goldberg [6], who showed that cimetidine did not reverse the effects of histamine on punished responding in squirrel monkeys.

The present work was undertaken to examine the effects of cimetidine on schedule-controlled responding in rats. Spontaneous locomotor activity was also monitored in cimetidine treated rats to provide an additional measurement of the behavioral effects of cimetidine.

METHOD

Subjects

For the study of schedule-controlled responding, 20 male Sprague Dawley rats were maintained at 80% (250–300 g) of their free-feeding weights by food presentation during experimental sessions and by post-session supplemental feedings. The rats used to measure locomotor activity were maintained at body weights between 250–275 g.

Apparatus

Rates of lever pressing for food were determined in two sound-attenuating Gerbrands test chambers. Each chamber was illuminated by 28 V DC houselights. The chamber used to study behavior under the multiple fixed-ratio fixed-interval schedule contained two response levers, but only presses on the right lever could produce food. A force of 15 g was required to register a response. The reinforcer was a 97 mg food pellet (P. J. Noyes Co.) delivered by a pellet feeder (Gerbrands Co.). Two pairs of 28 V DC cue lights were located above each lever. Responses were recorded on digital counters, timers and on a cumulative response recorder in an adjacent room. A similar test chamber was used for the experiment on temporally spaced responding, but this chamber

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[2]Research Associate.
[3]Requests for reprints should be addressed to: D. E. McMillan at the above address.

contained only one lever and one set of stimulus lights. Electromechanical relay programming and recording equipment in an adjacent room were used to control the environmental stimuli and feeder and to record lever presses.

Locomotor activity was monitored by an animal monitor (Automex Activity Monitor, Columbus Instruments, Columbus, OH) with a sensitivity setting of 9.5, and an activity setting of slow. The rats were tested between 8:00 and 12:00 a.m. in plastic cages (8 inches high × 9 1/2 inches wide and 18 inches long) covered by a flat metal top. Lights were on between 7:00 a.m. and 7:00 p.m.

Procedure

A multiple fixed-ratio 30-responses, fixed-interval 5-min schedule of food presentation (mult FR 30, FI 5 min) was used to maintain lever pressing in 4 rats. During the FR component, the chamber was illuminated by cue lights located above the left lever; 30 responses were required to produce the food pellet. Under the FI component of the schedule, the chamber was illuminated both the by houselight and cue lights above the right lever; the first response after 5 min elapsed produced a food pellet. A limited hold of 60 sec applied to both components of the schedule; this meant that the rat had 60 sec to make the 30 FR responses or to make a single response after 5 min had elapsed in the FI component to obtain the food pellet. Schedule components alternated with food delivery or expiration of the limited hold. After the delivery of the food, or at the end of the 60-sec limited hold, there was a 15-sec time-out period during which the chamber was dark and lever pressing had no programmed consequences. Each session lasted until 20 components had occurred (10 of each component). Test sessions were conducted Monday through Friday.

Responding under the DRL schedule was studied in 6 rats. Under a DRL schedule, only responses separated from each other, or from the beginning of the test session, by a specified time interval are reinforced. After a few days of acquisition on a fixed ratio 1 (FR-1) schedule of food presentation, the DRL schedule was instituted. Only responses occurring 10–14 seconds apart were reinforced. Responses occurring earlier than the minimum time interval or later than the maxixum time interval reset a timer reinitiating the interval. The experimental session lasted one hour.

Locomotor activity was measured in ten animals. After the stabilization of baseline responding, rats were tested individually and activity counts were cumulated for an hour. The animals were tested five days a week with drug injections twice a week (on Tuesday and Friday) and vehicle injections once a week (on Thursday). The weight of the rats was kept approximately constant during the study. Additionally, two more animals were studied as noninjection controls. They did not receive any treatment on any day of locomotor activity recording.

Measurement of the Effects of Cimetidine

Average rates of responding during the FR and FI components on injection days and noninjection control days were computed in response per second from digital counters and elapsed time meters. The number of responses within successive tenths of the FI-5 min schedule was recorded. From the total number of responses recorded in each tenth of the FI duration over the entire session, the percentage of the interval taken for the first quarter of the responses to occur was determined. This estimated quarter life value provided an indication of the temporal patterning of FI responding which is relatively independent of FI rates of responding [7]. When fewer than 100 responses occurred under the FI component during a session, quarter life values were not determined.

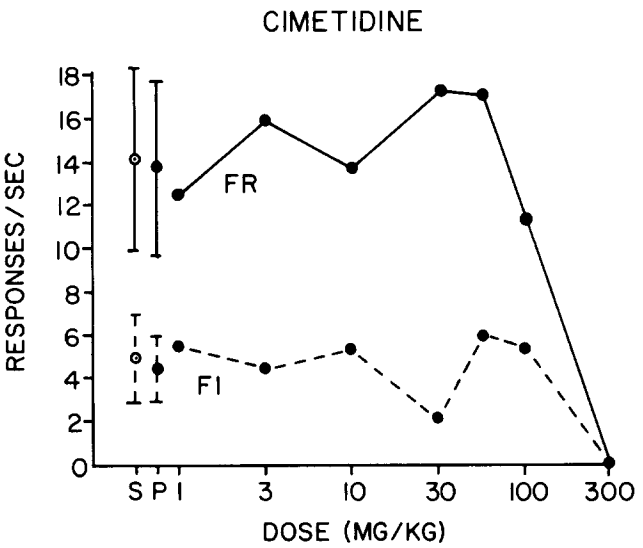

FIG. 1. Effects of different doses of cimetidine on the average rate of responding under the FR and FI schedules of food presentation. Abscissa: dose, log scale. Ordinate: rate of responding during a complete session. ●–●, FR component; ●--● FI component. The filled circles with brackets at S or solid circle with brackets at point P are the means of the control injections (saline or diluted phenol injection). The brackets show two standard deviations above and below the mean rate. Each drug point represents the mean of two observations (except drug point at 1 mg/kg which was a single observation) in each of four rats.

The rate of responding under the DRL-10 schedule for an entire session was computed in responses per second. Interresponse time distributions (IRT's) were recorded. All IRT's less than 18 seconds were recorded in 9 class intervals with an interval width of 2 seconds and all IRT's longer than 18 seconds registered in the 10th class interval. IRT's were used to calculate conditional probabilities (interresponse times divided by opportunities to respond in a class interval, or IRT/OPS) of responding within each class interval [1].

The motor activity was computed for each individual animal and then averaged across the animals for each drug dose and control. Differences between drug and control data were considered to be significant when the rate after drug was more than 2 S.D. from the mean control rate.

When observation of the daily performance of the rats suggested that the performance was no longer changing systematically, drug treatments were initiated.

Drugs

Cimetidine (Tagamet; Smith, Kline and French Laboratories, Philadelphia, PA), suitably diluted in distilled water, was injected by the intraperitoneal route in a volume of 1 ml/kg of body weight, 5 min before the start of the test session. Dosages (1–300 mg/kg) are expressed as the free base. Drugs were administered in an ascending and descending

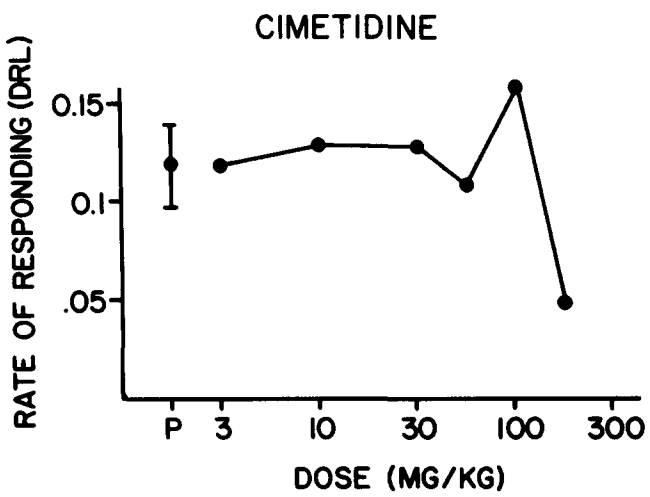

FIG. 2. Effects of cimetidine on the rate of responding under the DRL schedule where responses 10–14 sec apart were reinforced. Abscissa: milligrams per kilogram of cimetidine, log scale. Ordinate: rate of responding during a complete session. The point and brackets above P indicate the mean±2 standard deviations for control rates of responding. Each drug point is the mean of one observation in each of four rats.

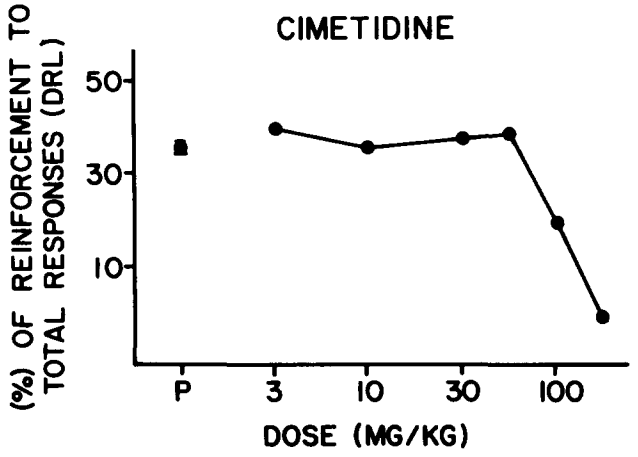

FIG. 3. Effect of cimetidine on percentage of reinforced responses under the DRL schedule where responses 10 to 14 sec apart were reinforced. Abscissa: milligram per kilogram of cimetidine, log scale. Ordinate: percentage of reinforced responses. The point and bracket above P indicate the mean±2 standard deviations of the mean for the control (non-injection) days. Each drug point is the mean of one observation in each of four rats. Reinforcement rate was decreased below control levels after both 100 and 175 mg/kg of cimetidine.

dosage series with half the animals receiving the highest dose first and half the animals receiving the lowest dose first. Diluted phenol solutions, similar to the Tagamet vehicle, were used for vehicle injections. Saline solutions (0.9%) also were used during additional control sessions.

RESULTS

Effects of Cimetidine on Responding Under the Multiple Schedule

The effect of cimetidine, 1–300 mg/kg, on rate of responding under both components of the multiple schedule are shown in Fig. 1. No effect on rate of responding was observed of cimetidine at doses of 1 to 100 mg/kg under either schedule component. A dose of 300 mg/kg cimetidine produced a complete suppression of responding during both components on the multiple schedule. In two rats out of the four tested, 56 mg/kg cimetidine increased the high rate of responding under the FR component, but there was no rate increase for the group. The low rate of responding under the FI component was slightly increased only in one animal (data not shown). At doses of 1–100 mg/kg, cimetidine had little effect on quarter life. Too few responses occurred after 300 mg/kg cimetidine to calculate quarter life.

Effect of Cimetidine on DRL-10

Performance under DRL schedules is characterized by a low stable rate of responding [15]. Cimetidine at doses of 3–56 mg/kg did not change the rate of responding or the percentage of reinforced responses (Figs. 2 and 3). However, doses of 100 mg/kg of cimetidine produced a significant increase in rate of responding and decrease in the percentage of reinforced responses. The rate of responding as well as the percentage of reinforced responses decreased below control levels after 175 mg/kg of cimetidine.

Details of the effect of cimetidine on the pattern of DRL responding can be seen in the relative frequency of IRT's (Fig. 4). Relative frequency (IRT/OPS, or conditional probability) is defined as the number of IRT's in a class interval divided by the number of opportunities to respond in

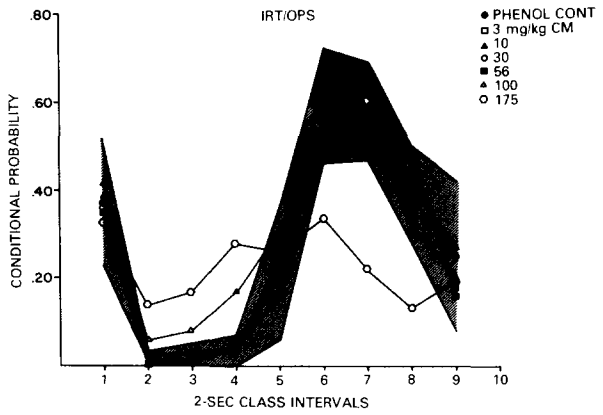

FIG. 4. Effects of varying doses of cimetidine on the conditional probability (see text) of responding within each class interval under the DRL schedule. Abscissa: successive 2-second class intervals. Class interval 1 includes 0 to 2 seconds, class interval 2 includes 2 to 4 seconds, and so on. Class intervals 5 and 6 include 10 to 14 seconds where IRT's were reinforced. Ordinate: conditional probability of a response occurring within a class interval given that a previous response has not prevented the opportunity to respond in that class interval. The shaded areas show the ranges of conditional probabilities for each class interval, determined during four noninjection control days. The points connected by solid lines show the conditional probabilities at various doses of cimetidine. Conditional probabilities were not plotted unless the animal had at least 10 opportunities to respond within a class interval.

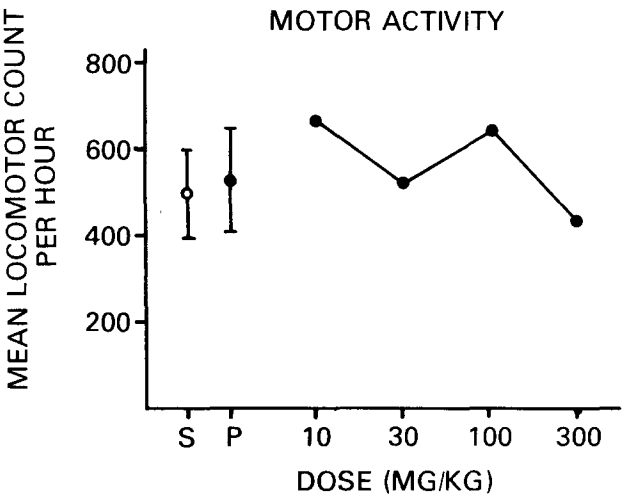

FIG. 5. Effects of varying doses of cimetidine on spontaneous locomotor activity in rats over a period of one hour. Abscissa: milligrams per kilogram of cimetidine, log scale. Ordinate: mean locomotor activity counts per hour. The unfilled circle with brackets at point S and filled circles with brackets at point P indicate the mean±2 standard deviations of the mean for the control activity after saline or dilute phenol injection. Each drug point is the mean of one observation in each of eight rats.

that class interval, given that a response has not prevented the opportunity to respond in that class interval. The increased reinforcement and decreased response rate caused by 100 mg/kg of cimetidine was associated with an increased conditional probability of short IRT's in the 2nd, 3rd and 4th class intervals (Fig. 3). The 175 mg/kg dose increased the conditional probability of these short IRT's and decreased the conditional probability of longer IRT's in the 6th, 7th and 8th class intervals. The IRT distribution was not affected at lower doses of cimetidine, 10–56 mg/kg.

Effect of Cimetidine on Locomotor Activity

Figure 5 shows the dose-effect curve for cimetidine on locomotor activity in rats. Cimetidine produced a marginal increase in locomotor activity when administered at a dose of 10 mg/kg. However, doses of 30, 100 and 300 mg/kg of cimetidine did not change the average locomotor activity counts over the recorded period of one hour.

DISCUSSION

The results of the present study demonstrate that higher doses of cimetidine are required to produce effects on locomotor behavior than on schedule-controlled behavior in the rats. However, fairly large doses of cimetidine were required to affect any of the behaviors studied. Griffiths *et al.* [8] have reported poor penetrability of cimetidine in to the brain after parenteral injection. This may explain why high doses of cimetidine were required to produce behavioral effects. Similar high doses of cimetidine (3–30 mg/kg) have failed to restore responding suppressed by histamine in squirrel monkeys [6].

Responding under the DRL schedule was affected at lower doses of cimetidine than those that affected rates under either component of the multiple schedule. In contrast to schedule-controlled behavior, cimetidine did not decrease motor activity. Thus, the order of sensitivity of behavioral measures to the effects of cimetidine was DRL>mult FR FI>locomotor activity.

Cimetidine effects on behavior may be of central origin, despite its poor penetration to the CNS. Neural dysfunction in the form of confusion, delirium and hallucination have been observed with higher doses of cimetidine in humans [4,12]. Further, lower doses of cimetidine antagonize the electrophysiological and behavioral responses produced by intracerebral injection of histamine [14]. Moreover, cimetidine and several antidepressant drugs of diverse chemical groups caused competitive inhibition of H_2 receptors coupled to adenylate cyclase activation in brain homogenates as well as slices from human and guinea pig hippocampus and neocortex [9, 13, 16]. However, the blocking of cerebral H_2 receptors coupled to adenylate cyclase may not represent the molecular mechanism of therapeutic action of the drug or be responsible for behavioral side effects observed during therapy [14]. Similarly, cimetidine's block of cerebral H_2 receptors may or may not be related to the effects of the drug on schedule-controlled responding in our experiments.

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