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BRIEF COMMUNICATION

Effects of 5-HT_3 Antagonists on Fixed-Interval Behavior in Rats

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WETTSTEIN, J. G. AND J. L. JUNIEN. *Effects of 5-HT_3 antagonists on fixed-interval behavior in rats.* PHARMACOL BIOCHEM BEHAV 41(3) 659–662, 1992.—The effects of 5-hydroxytryptamine$_3$ (5-HT_3) antagonists were studied in rats responding under a fixed-interval (FI) schedule of food presentation. BRL 43694, GR 38032F, ICS-205,930 and zacopride had no effect on FI responding up to 10.0 mg/kg IP. Response rate decreases were observed only at high doses (30.0 or 56.0 mg/kg); rate increases were not observed. In comparison, caffeine (1.0–10.0 mg/kg) and cocaine (3.0–18.0 mg/kg) increased and lorazepam (0.3 mg/kg) decreased FI responding. The effects of caffeine, cocaine, and lorazepam were unchanged when coadministered with the 5-HT_3 antagonists. The results show that 5-HT_3 antagonists, when given alone or with other CNS-active drugs, have little effect on FI responding of rats.

5-HT_3 antagonists Caffeine Cocaine Lorazepam FI behavior Drug interaction

DRUGS that are antagonists at 5-hydroxytryptamine$_3$ (5-HT_3) recognition sites eventually may be useful as psychotherapeutic agents. For example, based on selected animal studies 5-HT_3 antagonists have been considered to have value in the treatment of drug addiction and withdrawal in addition to having possible antipsychotic or anxiolytic effects (3,4,12). As 5-HT_3 antagonists are a relatively new class of compounds, there have been few detailed studies regarding their behavioral effects. It has been shown in mice, for example, that zacopride attenuated the locomotor effects of cocaine but not those of caffeine (11). Goudie and Leathley (8) suggested that GR 38032F may alter benzodiazepine-related effects as selected doses of GR 38032F attenuated certain signs of withdrawal in chlordiazepoxide-treated rats. Moreover, it has been suggested that GR 38032F and zacopride have anxiolytic-like effects at doses as low as 0.0005 mg/kg PO, a plateau effect can be reached quickly, and the same effect can be maintained for over a 1000-fold dose range (2,9). The anxiolytic-like effects of 5-HT_3 antagonists, however, may not be readily reproducible (6,7).

The purpose of the present study was to determine the effects of 5-HT_3 antagonists under schedule-controlled conditions whereby behavior could be measured over a substantial period of time. A fixed-interval (FI) schedule of food presentation was chosen as steady baseline behavior in individual subjects can be easily maintained for single experimental sessions lasting up to 60 min over a duration of many months (10). Furthermore, FI schedules have proven useful in obtaining information regarding overall behavior profiles of drugs, especially when studied in combination with other like or unlike compounds. In addition to four 5-HT_3 antagonists (BRL 43694, GR 38032F, ICS-205,930, and zacopride), a benzodiazepine anxiolytic, lorazepam, and two CNS stimulants, caffeine and cocaine, were studied under a 2-min FI schedule in rats. In addition, BRL 43694, ICS-205,930, and zacopride were administered together with selected doses of lorazepam, caffeine, and cocaine to determine if 5-HT_3 antagonists could alter the behavioral effects of known CNS-active drugs under operant conditions.

METHOD

Subjects

Eleven adult, male rats (Wistar, Iffa-Credo, France) were studied in daily experimental sessions (Monday–Friday). Approximate animal weights at the beginning and end of the study were 200 and 370 g, respectively. Rats lived in individual home cages (42 × 26 × 15 cm) between sessions and had regulated access to food (U.A.R. A113 pellets); water was freely available. All subjects were naive and untrained at the beginning of the study.

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Apparatus and Behavioral Schedule

For experimental sessions, rats were placed in Plexiglas-aluminum modular cages (Coulbourn Instruments) within ventilated, sound-attenuating chambers. A response lever was mounted on an aluminum wall in front of the rat; each press of the lever with a minimal force of 25 g produced an audible click within the chamber and was recorded as a response. A panel of three colored lights above the response lever could be illuminated to serve as visual stimuli. Sweetened condensed milk (Nestlé) could be delivered to an opening in the front wall of the cage via a dipper. Experiments were controlled and monitored with a SKED-11 software-Digital PDP-11/53 computer system.

Rats were trained to respond under a 2-min FI schedule of food presentation. Initially, each subject was trained to press a lever for food under an automatic continuous reinforcement procedure; this was followed by a progressive FI schedule. Under final conditions, in the presence of the multicolored light, the first response after 2 min produced 0.1 cc sweetened milk followed by a short (5-s) timeout period. During a time-out, the chamber was dark and responses had no scheduled consequence. If a response was not made within 20 s after the 2-min FI elapsed, the 5-min timeout started automatically without presentation of milk. Each experimental session began with a long (5-min) timeout and was followed by 10 consecutive FI components. Daily control sessions lasted approximately 27 min.

Drugs and Injection Procedures

BRL 43694, GR 38032F, ICS-205,930, and zacopride were synthetized in the Department of Therapeutic Chemistry at the Institut de Recherche Jouveinal. Lorazepam was generously donated by Wyeth Laboratorie, cocaine was obtained from the Hospital Pitié-Salpêtrière; and caffeine was purchased from Sigma Chemical Co.

BRL 43694, GR 38032F, ICS-205,930, zacopride, caffeine, and cocaine were dissolved in sterile water. Lorazepam was suspended in sterile water with Tween-80 (Sigma Chemical Co.). Solutions were prepared daily. Each dose was injected IP in a volume of 2.0 ml/kg body weight or less. Vehicle-control injections (sterile 0.9% saline) were similar in volume and given IP almost daily.

Drugs were studied using a single-dose procedure and were administered either 15 min (caffeine and cocaine) or 30 min (all others) before the start of experimental sessions. Each test session was preceded by a control session during which rates and patterns of responding were stable. Drugs were studied no more frequently than twice a week. In experiments with drug combinations, selected doses of each drug were injected according to the time parameters set previously.

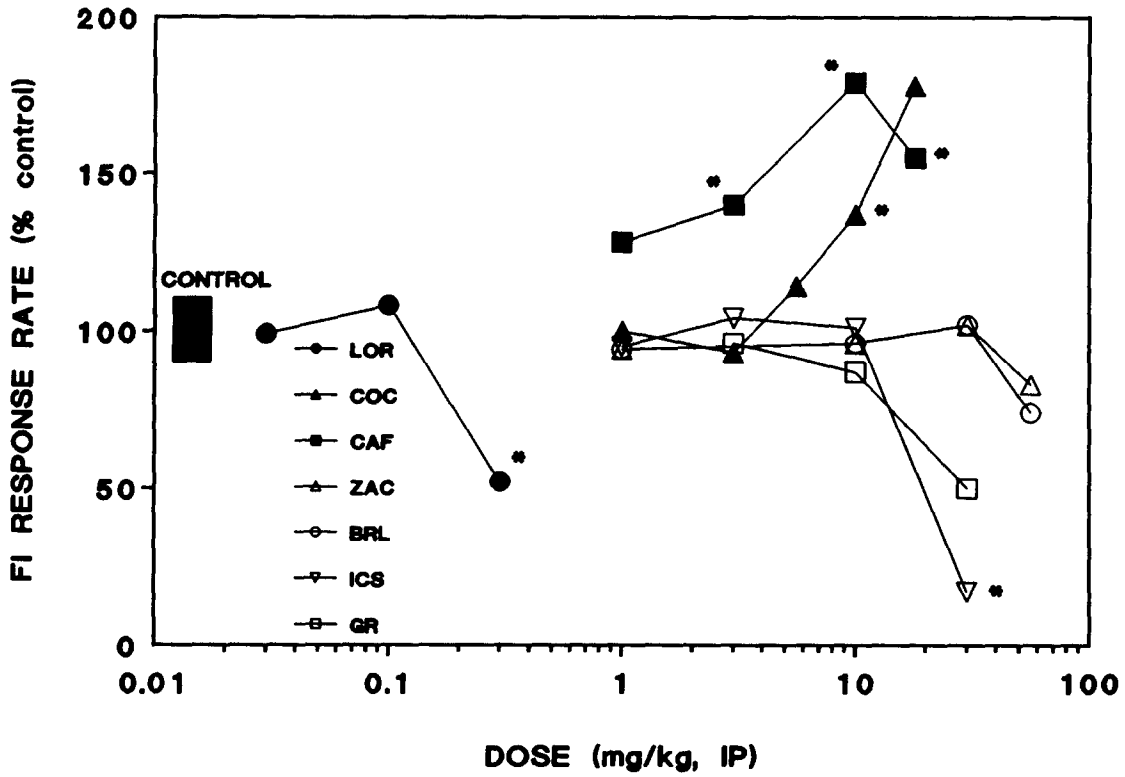

FIG. 1. Effects of BRL 43694, GR 38032F, ICS-205,930, zacopride, lorazepam, caffeine, and cocaine under the FI schedule of food presentation. Abscissa: cumulative dose, log scale. Ordinate: response rate as percent control. Symbols are means based on single or duplicate determinations in at least six rats (four rats with 56.0 mg/kg zacopride and BRL 43694). Filled bar at "control" represents the mean ± SEM control response rate in the group of eleven rats. *Effect of a dose of drug was significantly different from control.

TABLE 1

EFFECTS OF 5-HT$_3$ ANTAGONISTS IN COMBINATION WITH OTHER DRUGS ON FI RESPONDING OF RATS

Treatments	Saline	Zacopride (1 mg/kg)	BRL 43694 (1 mg/kg)	ICS-205,930 (1 mg/kg)
Saline	100 ± 10*	94 ± 11	94 ± 6	95 ± 5
Cocaine (10 mg/kg)	137 ± 14	142 ± 7	131 ± 28	143 ± 19
Caffeine (10 mg/kg)	179 ± 19	190 ± 27	195 ± 13	179 ± 16
Lorazepam (0.1 mg/kg)	108 ± 7	106 ± 7	101 ± 9	101 ± 13
Lorazepam (0.3 mg/kg)	52 ± 12	51 ± 19	72 ± 26	70 ± 21

Values are response rates ± SEM expressed as a percent of control response rates; n = 8–11 for the effects of individual drugs and n = 6 for the effects of drug combinations.

*Control value for the group of 11 subjects.

Measurement of Drug Effects

Rates of responding were calculated by dividing the total number of responses in a component by the total time the component was in effect. For each subject, rates of responding were relatively stable for the duration of the experiment. The day before each drug test session served as the respective control day: Drug effects were expressed as a percent of control determined on the previous day. Results were first calculated for individual subjects and then presented as the mean ± SEM for the group. Multiple comparisons between the effects of drugs, drug combinations, and control were made using an analysis of variance (ANOVA) followed by a studentized range test.

RESULTS

Control response rates averaged 0.58 ± 0.06 responses/s for the group of 11 rats during FI components (range for individual subjects: 0.21 ± 0.01 to 0.94 ± 0.02 responses/s). Patterns of responding were characteristic of those observed previously under FI schedules: A pause at the beginning of each FI was followed by acceleration in responding as the interval progressed.

BRL 43694, GR 38032F, ICS-205,930, and zacopride had little or no effect on FI responding over the dose range of 1.0–10.0 mg/kg (Fig. 1, unfilled symbols). At 30 mg/kg, GR 38032F and ICS-205,930 decreased responding to 50% and 17% of control, respectively. At 56.0 mg/kg, zacopride and BRL 43694 slightly decreased FI rates to 83% and 74% of control, respectively.

Lorazepam had little effect on FI rate at 0.03 and 0.1 mg/kg and decreased rate to 52% of control at 0.3 mg/kg (Fig. 1, filled circles). Caffeine (1.0–10.0 mg/kg) and cocaine (5.6–18.0 mg/kg) produced dose-dependent increases in FI responding; both drugs increased rate to a maximum of approximately 180% control (Fig. 1, filled squares and triangles).

BRL 43694, ICS-205,930, and zacopride (all at 1.0 mg/kg) were studied in combination with doses of caffeine (10.0 mg/kg) and cocaine (10.0 mg/kg) that increased responding and with doses of lorazepam (0.1 and 0.3 mg/kg) that either had no effect or decreased responding. Neither BRL 43694, ICS-205,930, nor zacopride altered the rate-increasing or rate-decreasing effects of caffeine, cocaine, or lorazepam (Table 1).

DISCUSSION

The 5-HT$_3$ antagonists decreased FI responding only at relatively high doses; rate increases were not observed. These findings are surprising in view of other reports citing behavioral effects with these compounds at low doses (2,3,9). Drugs having potential anxiolytic, antipsychotic, or other therapeutic effects could be expected to have some effects on FI rate at doses that can be reasonably correlated with their respective receptor binding affinities. The 5-HT$_3$ antagonists tested in the present study bind to 5-HT$_3$ receptors in the CNS with low nanomolar affinity (1).

Neither BRL 43694, ICS-205,930, nor zacopride augmented or attenuated the rate-increasing effects of caffeine and cocaine or the rate-decreasing effects of lorazepam under the FI schedule. Selected 5-HT$_3$ antagonists have been shown to interact directly or indirectly with certain CNS-active drugs similar to those used in the present study. For example, the increase in locomotor activity produced by cocaine in mice was attenuated by zacopride (11) and the behavioral suppression observed in rat social interaction or mouse black/white box tests after withdrawal from diazepam was attenuated by GR 38032F (4). The latter tests differ from schedule-controlled behavioral procedures in that they are based on an animal's inherent exploratory activity rather than a conditioned behavior, a distinction that may explain the different results found in the various procedures. Nevertheless, the results concerning the lack of interaction with caffeine, cocaine, or lorazepam in the present study suggest that 5-HT$_3$ antagonists do not have obvious effects on the neuronal systems related to the effects of the former drugs that are revealed under FI schedules of food presentation in rats.

These results also infer that 5-HT$_3$ antagonists exhibit obvious behavioral effects only when given under very specific behavioral or environmental conditions. This may be a favorable profile of action regarding the antiemetic effects of these drugs in man (5) as it may be possible to treat nausea and emesis with doses of 5-HT$_3$ antagonists that have relatively few secondary effects on the CNS.

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