Serotonin 5–HT₃ antagonists do not alter the discriminative stimulus properties of cocaine

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Received August 21, 1990 / Final version October 30, 1990

Abstract. The central nervous system (CNS) of the rat is known to contain serotonin (5-HT) type -3 receptors (5-HT₃). Behavioral evidence suggests that 5-HT₃ receptors interact with mesolimbic dopamine (DA) systems and that 5-HT₃ antagonists can interfere with the hyperlocomotive effects of amphetamine and cocaine and the rewarding and stimulus effects of morphine, nicotine and ethanol. Cocaine, which blocks the reuptake of DA, norepinephrine (NE), and 5-HT in the CNS, also may be an antagonist at 5-HT₃ receptors. The purpose of the present study was to determine whether systemic administration of the 5-HT₃ antagonists ICS 205930 or MDL 72222 could mimic or block the discriminative stimulus properties of cocaine. Once rats (N= 16) were trained to discriminate cocaine (10 mg/kg) from saline, substitution tests with various doses of cocaine (0.313-10 mg/kg), ICS 205930 (2-24 mg/kg), and MDL 72222 (2-16 mg/kg) were conducted. Cocaine produced a dose-related increase in cocaine-appropriate responding while the 5-HT₃ antagonists engendered primarily saline-lever responding. Neither ICS 205930 nor MDL 72222 were able to antagonize the stimulus effects of cocaine (5 mg/kg). Response rates were not significantly reduced when the 5-HT₃ antagonists were given in combination with cocaine. The results indicate that although 5-HT₃ antagonists can inhibit some of the unconditioned behavioral effects of psychomotor stimulants, the discriminative stimulus effects of cocaine remain intact.

Key words: Cocaine – Serotonin – 5–HT₃ – ICS 205930 – MDL 72222 – Drug discrimination - Behavior – Rat

The central nervous system (CNS) is known to contain several major classes of serotonin (5-hydroxytryptamine; 5-HT) receptors including the 5-HT₁, 5-HT₂, and 5-HT₃ subtypes (Peroutka 1988). There has been an interest to develop drugs that bind to 5-HT₃ receptors because antagonists at this site modulate a number of behavioral responses in animals. For example, 5-HT₃ antagonists can block the hyperlocomotion induced by dopamine (DA) infusions into mesolimbic brain areas or amphetamine administration (Costall et al. 1987a, b; Hagan et al. 1990). Because of their interactions with mesolimbic DA systems, it has been suggested that these drugs could be effective adjuncts in the pharmacotherapy of schizophrenia (Costall et al. 1987a). In other behavioral paradigms, 5-HT₃ antagonists have also been found to possess anxiolytic properties (Costall et al. 1988).

One interesting aspect of 5-HT₃ receptors is that their blockade can interfere with the behavioral effects of several drugs of abuse. The hyperlocomotive effects of an acute injection of cocaine or amphetamine can be blocked by prior administration of the 5-HT₃ antagonist ondansetron (Costall et al. 1987a; van der Hoek and Cooper 1990). Cocaine, which blocks the reuptake of the monoamines, DA, norepinephrine (NE) and 5-HT in the CNS (Koe 1976), is also a 5-HT₃ antagonist in the periphery (Fozard et al. 1979) and inhibits binding to brain 5-HT₃ receptors (Kilpatrick et al. 1987). A number of compounds that are structurally similar to cocaine (e.g., ICS 205930 and MDL 72222) are also 5-HT₃ antagonists (Fozard 1984; Richardson et al. 1985). The conditioned place preference elicited by morphine and nicotine, but not amphetamine, can be prevented by administration of 5-HT₃ antagonists (Carboni et al. 1988), while the discriminative stimulus properties of ethanol (Grant 1990) as well as ethanol consumption (Oakley et al. 1988) can be reduced by these drugs. The purpose of the present study was to determine whether systemic administration of the 5-HT₃ antagonists ICS 205930 or MDL 72222 could mimic or block the discriminative stimulus properties of cocaine.

Material and methods

Subjects

Experimentally-naive male Sprague-Dawley rats (N= 16; Harlan-Timco, Houston, TX) were housed in pairs in a standard controlled environment. Food was available continuously and water was restricted to daily training sessions, mid-week (15 min) and weekends (24-48 h).
Apparatus

Eight two-lever operant chambers (Model 80001; Lafayette Instrument, Lafayette, Ind), each equipped with a water dispenser mounted equidistant between two response levers on one wall and housed in a light- and sound-attenuating shell (Model 80015; Lafayette Instruments), were used. The chambers were illuminated with a houselight and a fan provided both ventilation and masking noise. A PC-compatible computer was used to program and record all experimental events.

Procedures

Discrimination training. Rats were trained to discriminate intraperitoneal (IP) injections of cocaine (10 mg/kg) from physiological saline (1 ml/kg, 0.9% NaCl). Drug or saline was administered 15 min prior to daily sessions. Training began under a schedule of continuous water reinforcement (FR 1) with both the right and left levers present. Only responses on the stimulus-appropriate (drug or saline) lever were reinforced. There were no programmed consequences for responding on the incorrect lever. To control for the development of olfactory cues, half of the animals were reinforced for left-lever responses following drug administration and for right-lever responses following saline; conditions were reversed for the remaining animals. During the training period, neither drug nor saline was administered for more than three consecutive (30 min) training sessions. As response rates (responses/min) stabilized, the schedule of reinforcement was increased until all animals were responding reliably under a fixed ratio (FR 20) schedule during each experimental condition. After responding stabilized, the training sessions were shortened to 15 min. This phase of training continued until performance of all animals attained criterion (individual mean accuracies of at least 85% correct for ten consecutive sessions).

Testing procedure. After animals reached criterion, dose-response, substitution and combination tests were initiated. Test sessions were conducted 1–2 times per week with training sessions intervening during the remaining days. In dose-response determinations, rats were tested after the administration of various doses of cocaine. In substitution tests, a range of doses of ICS 205930 and MDL 72222 were administered in place of the training drug. In combination tests, rats were injected with a dose of a 5-HT3 antagonist in addition to a dose (5 mg/kg) of cocaine that elicited 100% drug-lever responding when tested alone. During test sessions, rats were placed in the chamber as during training sessions and, upon completion of 20 responses on either lever, the animal received a single reinforcement. The lever upon which the animal completed the initial FR 20 was designated as the reinforced lever until the session time (20 min) had elapsed. At the end of the session (20 min), the houselight was turned off and the animal was removed from the chamber and returned to the colony.

Drugs

Dose-response and substitution tests were conducted 15 min (cocaine) or 60 min (ICS 205930, MDL 72222) after administration of the drug. For combination tests, an appropriate dose of the antagonist was administered 45 min prior to a fixed dose of cocaine (5 mg/kg). The rats were divided into two subgroups (N = 8/group), which were tested with either ICS 205930 or MDL 72222 in substitution and combination tests. The drugs and doses tested were administered in a pseudorandom schedule and are expressed as the salt in mg per kg of body weight. Cocaine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO). ICS 205930 and MDL 72222 were gifts from Sandoz Ltd (Basel, Switzerland) and Merrell-Dow Research Institute (Strasbourg Cedex, France), respectively, or were obtained from Research Biochemicals, Inc. (Natick, MA). Cocaine was dissolved in deionized water and the antagonists were first dissolved in a drop of 10% acetic acid and brought up to volume in 0.9% saline.

Data analysis

For training sessions, accuracy was defined as the percentage of drug-lever responses to total responses prior to completion of the first reinforcer. During test sessions, performance was expressed as the percentage of drug-lever responses to total responses upon completion of an FR 20 on either lever. The response rates (responses per min) were calculated as the total number of responses emitted before completion of the first FR 20 divided by the number of minutes taken to complete the first ratio. Analysis of variance (ANOVA) for repeated measures was used to compare the previous performance on cocaine and saline sessions with performance on all test compounds; comparisons were also made between performance following cocaine (5 mg/kg) alone and that following this dose of cocaine (5 mg/kg) plus a dose of an antagonist. Post-hoc comparisons of means (Tukey’s test) were made with an experimentwise Type I error rate (alpha) set at 0.05. Only data from animals that completed the FR 20 during substitution or combination tests and expressed greater than 80% accuracy on the previous cocaine and saline training days were analyzed.

Results

Cocaine dose-response tests

All animals (N = 16) acquired the cocaine-saline discrimination in an average of 36.5 sessions (range: 25–46). During maintenance sessions over the course of the study (N = 215), response rates during cocaine sessions (32.4 ± 0.98 responses/min) were higher than those during saline sessions (23.7 ± 0.91 responses/min; P < 0.05). In dose-response tests, cocaine (0.313–10 mg/kg) produced a dose-related increase in cocaine-appropriate responding (Fig. 1A); drug-lever responding observed at several doses of cocaine (0.313–2.5 mg/kg) differed from that observed in the immediately previous cocaine training session. Response rates during the cocaine-dose-response tests did not differ from those in the previous cocaine training session (Fig. 1B).

Substitution tests

Neither ICS 205930 (2, 4, 24 mg/kg) nor MDL 72222 (2–16 mg/kg) mimicked cocaine (Fig. 1A). Both drugs engendered primarily saline-lever responding (Fig. 1A) and decreased response rates at the highest doses tested (Fig. 1B).

Combination tests

Neither ICS 205930 nor MDL 72222 antagonized the stimulus effects of cocaine (5 mg/kg; Fig. 1C). The highest dose of MDL 72222 (10 mg/kg) did attenuate cocaine responding by approximately 39%, but this was not statistically significant. A higher dose of MDL 72222 was not tested in combination with cocaine as 16 mg/kg