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Detailed Investigations of 5-HT_3 Compounds in a Drug Discrimination Model

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DE LA GARZA, R., II, P. M. CALLAHAN AND K. A. CUNNINGHAM. *Detailed investigations of 5-HT_3 compounds in a drug discrimination model.* PHARMACOL BIOCHEM BEHAV **54**(3) 533–540, 1996.—Serotonin type-3 (5-HT_3) receptors modulate both dopamine (DA) release and locomotor stimulation induced by cocaine, yet appear to be ineffective at blocking its stimulus and reinforcing effects. To more thoroughly characterize a potential modulatory role of 5-HT_3 receptors in the stimulus effects of cocaine, rats (n = 8/group) were trained to discriminate cocaine (10 mg/kg, IP) or the 5-HT_3 agonist 1-(meta-chlorophenyl)-biguanide (mCPBG: 15 mg/kg, IP) from saline using a standard drug discrimination task. In rats trained to discriminate cocaine, mCPBG (2.5–20 mg/kg) produced, at best, a partial substitution while mCPBG (10 mg/kg) did not alter the cocaine dose-response relationship. The 5-HT_3 antagonists MDL 72222 (10 mg/kg) and ondansetron (1.25–16 mg/kg) did not attenuate the cocaine cue. In rats trained to discriminate mCPBG from saline, the 5-HT precursor *l*-5-hydroxytryptophan (12.5–50 mg/kg) dose-dependently substituted for mCPBG, whereas the 5-HT_3 antagonist zacopride (0.1–10 mg/kg) partially antagonized the mCPBG cue, demonstrating that mCPBG produces distinct discriminable effects that appear to be mediated by 5-HT, possibly 5-HT_3, receptors. However, cocaine (5–20 mg/kg) did not substitute in mCPBG-trained rats. Overall, these data support previous findings to suggest that 5-HT_3 receptors play little role in mediating the discriminative stimulus effects of cocaine and suggest that the neurochemical mechanisms and/or sites of action important for the generation of the discriminative stimulus vs. locomotor stimulatory effects of cocaine may be dissociable.

Cocaine Drug discrimination 5-HT_3 receptors mCPBG MDL 72222 Ondansetron Zacopride

THE NEURAL actions of cocaine are complex and, in addition to the blockade of dopamine (DA) reuptake, cocaine also inhibits the reuptake of serotonin (5-HT) and norepinephrine (18) and has affinity for one of the multiple 5-HT subtypes, the 5-HT_3 site (11). Cocaine also appears to function as an antagonist at 5-HT_3 receptors in the periphery (11), and a number of 5-HT_3 antagonists are structurally similar to cocaine (e.g., ICS 205-930 and MDL 72222). Recent reports suggest that 5-HT_3 antagonists attenuate cocaine-induced hyperactivity [(25,28,29); but see (9)], and the development of behavioral sensitization to repeated intermittent cocaine exposure (9). Such reductions in cocaine-induced behaviors may be a consequence of blockade of 5-HT_3-mediated increases in synaptic levels of DA in mesolimbic circuits (7,8,20).

Despite these observations, 5-HT_3 antagonists have not been efficacious as blockers of the behavioral effects of cocaine measured in operant assays. For example, both the discriminative stimulus (19,23) and reinforcing properties of cocaine (19,24) appear to be resistant to blockade by 5-HT_3 antagonists. In light of the apparent contradictions in the ability of 5-HT_3 antagonists to alter cocaine-mediated behaviors, we sought to more carefully analyze the potential modulatory actions of a 5-HT_3 agonist 1-*m*-chlorophenylbiguanide (mCPBG) and two 5-HT_3 antagonists (MDL 72222 and ondansetron) on the stimulus effects of cocaine (10 mg/kg). We further tested the hypothesis that the 5-HT_3 agonist mCPBG would support discriminative behavior and that cocaine might substitute in rats trained to discriminate mCPBG (15 mg/kg) from saline in a two-lever water reinforced task.

METHOD

Subjects

Experimentally-naive, male Sprague–Dawley rats (200–250 g: SASCO, Houston, TX) were housed in groups of two in Plexiglas shoebox cages with bedding. The colony was maintained at a constant temperature (21–23°C) and humidity (40–50%) on a 12 L : 12 D cycle (lights on 0700 h; lights off 1900 h). While food was accessible ad lib, the water each animal received was limited to the amount that was acquired during the

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training sessions in the operant chambers, after test sessions (10 min), and on weekends.

Apparatus

The apparatus and general procedure have been described in detail elsewhere (3). Briefly, eight two-lever operant chambers (Model 80001; Lafayette Instrument, Lafayette, IN) equipped with a water-filled dispenser mounted equidistant between two response levers on one wall and housed in a light- and sound-attenuating shell (Model 80015; Lafayette Instrument) were used. Illumination was provided by a 28-V house light while ventilation and masking noise were supplied by a blower. A computer was used to program and record all experimental events.

Behavioral Procedures

In separate experiments, rats (n = 8/group) were trained to discriminate cocaine (10 mg/kg) or mCPBG (15 mg/kg) from an equivalent volume (1 ml/kg) of saline (0.9% NaCl). The initial dose chosen for mCPBG studies was 5 mg/kg, which was subsequently increased in 2.5 mg/kg increments to a final dose of 15 mg/kg during discrimination training. Drug or saline was administered intraperitoneally (IP) 15 min prior to daily (Monday–Friday) sessions. Initially, training began under a schedule of continuous water reinforcement (FR 1) with only the stimulus-appropriate (drug or saline) lever present (errorless training); the schedule of reinforcement was then increased until all animals were responding reliably under a fixed ratio schedule for each experimental condition (FR 20). To control for the possible development of position cues based upon olfactory stimuli, a pseudorandom relationship was maintained between the lever programmed to deliver reinforcement for each consecutive subject run in the same experimental chamber (10). After responding stabilized on an FR 20 schedule, both levers were presented simultaneously and rats were required to respond on the stimulus-appropriate (correct) lever to obtain a reinforcer (water); there were no programmed consequences for responding on the incorrect lever (discrimination training). This phase of training continued until the performance of all animals reached criterion (individual mean accuracies of at least 80% correct prior to the first reinforcer for ten consecutive sessions).

Test Procedures

Test sessions were initiated once all animals achieved criterion (described above), and were conducted once or twice per week in irregular order. Regular training sessions with drug or saline intervened between test sessions to maintain discrimination accuracy. Only rats that met the 80% performance criterion during the preceding drug and saline sessions were tested. During test sessions, rats were placed in the chamber as during training sessions and upon completion of 20 responses on either lever or after the test session time (20 min) had elapsed, a single reinforcer was delivered, the house light was turned off and the animals were removed from the chamber. After return to the home cages, all rats were allowed 10 min of free access to water.

Two pharmacological test manipulations were performed during test sessions. In substitution (generalization) tests, rats were administered various doses of the training drug (dose-response tests), saline (control tests), or a test compound and tested for lever selection 15 (saline, cocaine, or mCPBG) or 30 min later (*l*-5-hydroxytryptophan: 5-HTP). In combination tests, an injection with mCPBG or a 5-HT_3 antagonist occurred 15 or 45 min before administration of the appropriate dose of the training drug; lever selection was assessed 15 min later.

Data Analysis

During training sessions, accuracy was defined as the percentage of correct responses to total responses before the delivery of the first reinforcer. In contrast, during test sessions, performance was expressed as the percentage of drug-appropriate responses to total responses prior to the delivery of the first reinforcer. Response rates (responses per min) were also evaluated during training and test sessions as a measure of behavioral disruption. For training sessions, the response rate was calculated as the total number of responses emitted on either lever before completion of the first FR 20. During test sessions, the response rate was calculated as the total number of responses prior to the completion of 20 responses on either lever divided by the number of minutes taken to complete that FR 20. Only data from animals that completed the FR 20 during test sessions were used.

Student's t-test for repeated measures was used to compare the percentage of drug-appropriate responding and response rates during test sessions with either the previous drug session (generalization tests) or the test dose of drug alone (combination tests). A two-way analysis of variance (ANOVA) for repeated measures was used to assess whether the percentage of cocaine-appropriate responding and response rate observed across several doses of cocaine differed in the presence vs. absence of a fixed dose of a test compound (combination tests); post hoc comparisons at each dose of cocaine with and without the test drug were made using the Student's t-test. All comparisons were made with an experiment-wise Type I error rate (alpha) set at 0.05. A compound was said to have substituted fully for the training drug if at least 80% of responses occurred on the drug-appropriate lever following at least one dose of that compound; similarly, a complete antagonism was said to occur when no more than 20% drug-appropriate responding occurred after pretreatment with at least one dose of an antagonist given in combination with the training drug.

Drugs

The order in which drugs were tested was the same in all animals. Doses of all drugs refer to the weight of the salt. Cocaine HCl (NIDA), *l*-5-hydroxytryptophan (Sigma, St. Louis, MO), *1-m*-chlorophenylbiguanide and MDL 72222 (Research Biochemicals Intl., Natick, MA), zacopride (Syntelabo Recherche, Bagneux, France), and ondansetron (Glaxo Group Research, Greenford, Middlessex, UK) were prepared in physiological saline (0.9% NaCl) and injected systemically in a volume of 1 ml/kg.

RESULTS

Cocaine-Saline Discrimination

Acquisition and dose-effect curve. The cocaine (10 mg/kg) vs. saline discrimination (n = 8) was acquired rapidly; the mean number of sessions to criterion (>80%) was 38 ± 7.1 (range 19–44). Throughout acquisition, response rates (±SEM; standard error of the mean) during cocaine sessions (35.9 ± 6.3 response/min) were not significantly different from those observed during saline sessions (33.1 ± 8.7 response/min).

Systemic administration of cocaine (0.625–20 mg/kg) pro-

duced a dose-dependent increase in drug-appropriate responding whereas saline administration engendered <10% drug-lever responses (Fig. 1). Response rates were stable across all test doses of cocaine and not significantly different from the previous cocaine session.

Substitution and combination tests. The 5-HT$_3$ agonist mCPBG (2.5–20 mg/kg) produced primarily saline-like responding; at best, a partial substitution was observed at the 10 mg/kg dose of mCPBG (Fig. 2). Response rates were significantly decreased (compared to saline) following 5, 10, and 20 mg/kg of mCPBG. Pretreatment with mCPBG (10 mg/kg) did not significantly alter the percentage of drug-lever responding, $F(1, 12) = 0.16, p = 0.697$, or response rates, $F(1, 12) = 4.22, p = 0.063$, observed following low doses of cocaine (0.625–2.5 mg/kg; Fig. 3).

Systemic administration of the 5-HT$_3$ antagonist ondansetron (1.6–12.8 mg/kg) did not alter the percent drug-lever responding observed at the training dose of cocaine (10 mg/kg; Fig. 4, right panel). A similar failure of MDL 72222 was previously reported by this lab (23), and these data are provided for comparison (Fig. 4, left panel). Response rates following the combination of these 5-HT$_3$ antagonists with cocaine were not different from those observed following cocaine (10 mg/kg) alone. In the present study, combination tests with 10 mg/kg of MDL 72222 (Fig. 5) indicated that this 5-HT$_3$ antagonist did not alter the percent drug-lever responding, $F(1, 12) = 1.39, p = 0.262$, or response rates, $F(1, 12) = 0.25, p = 0.628$, observed with cocaine (0.625–10 mg/kg). Ondansetron (1.6 mg/kg; Fig. 6) also did not alter the percent drug-lever responding, $F(1, 13) = 0.01, p = 0.925$, or response rates, $F(1, 12) = 0.33, p = 0.574$, engendered by cocaine (0.625–10 mg/kg).

mCPBG-Saline Discrimination

Acquisition and dose-effect curve. Discrimination training was attempted with consecutively increasing doses of mCPBG beginning with 5 mg/kg (24 sessions) and followed by 7.5 mg/kg (15 sessions), 10 mg/kg (40 sessions), and 12.5 mg (21 sessions) until a dose of 15 mg/kg. At 15 mg/kg, the discrimination between mCPBG and saline was acquired by a total of 10 rats; four animals were removed from the study due to an inability to learn the discriminative cue, and two others died from causes unrelated to the training regimen. The mean number of sessions to criterion at 15 mg/kg of mCPBG was 39 ± 6.3. Response rates after mCPBG (5.3 ± 1.2 response/min) were significantly lower than those observed after saline (40.2 ± 8.8 response/min). Overall, these animals underwent 139 training sessions (all training doses included) prior to successful acquisition of the mCPBG (15 mg/kg, IP) vs. saline discrimination. Systemic mCPBG (3.75–15 mg/kg) produced a dose-dependent increase in drug-appropriate responding while saline administration engendered <5% drug-lever responses (Fig. 7). Response rates following doses of 3.75, 7.5, and 11 mg/kg of mCPBG were significantly higher than those seen on the previous mCPBG training session ($p < 0.05$).

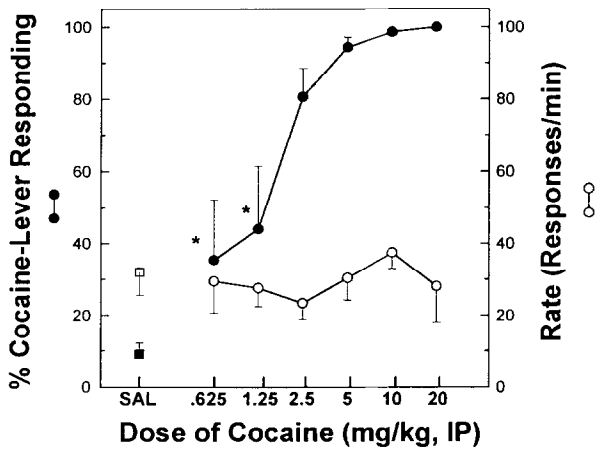

FIG. 1. Cocaine dose-response relationship in rats trained to discriminate cocaine (10 mg/kg) from saline. Data represent the mean percentage of cocaine-appropriate responses (±SEM) observed during test sessions with various doses of cocaine (filled circles; $n = 8/8$) or saline (filled square; $n = 8/8$). Response rates for cocaine (open circles) and saline (open square) are also illustrated. Asterisks denote values significantly different than previous cocaine training sessions ($p < 0.05$).

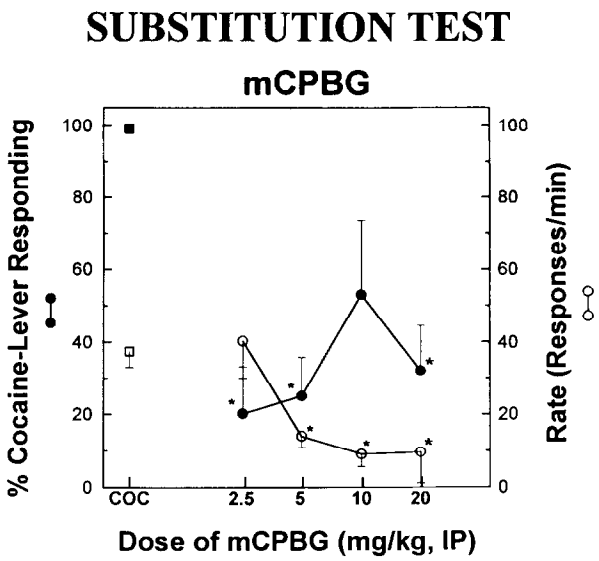

FIG. 2. Substitution tests with mCPBG in rats trained to discriminate cocaine (10 mg/kg) from saline. Data represent the mean percentage of cocaine-appropriate responses (±SEM) after various doses of mCPBG (filled circles; $n = 6–8/8$) and corresponding response rates (open circles). Percent cocaine-appropriate responses for the training dose of cocaine (10 mg/kg; $n = 8/8$, filled square) and corresponding response rate (open square) are illustrated for comparison. Asterisks denote values significantly different than previous cocaine training sessions ($p < 0.05$).

Substitution tests. The 5-HT precursor 5-HTP (12.5–50 mg/kg) engendered a dose-related and complete substitution for mCPBG (Fig. 8). Response rates at 12.5 and 25 mg/kg of 5-HTP were significantly higher than those observed on the previous mCPBG training session ($p < 0.05$). Cocaine (5–20 mg/kg) produced dose-related increases in drug-lever responding with a maximum of 49% observed at 20 mg/kg (Fig. 9). Response rates at both 5 and 10 mg/kg of cocaine were significantly different from response rates on the previous mCPBG session ($p < 0.05$).

Combination tests. Systemic administration of the 5-HT$_3$ antagonist zacopride resulted in a partial antagonism of the

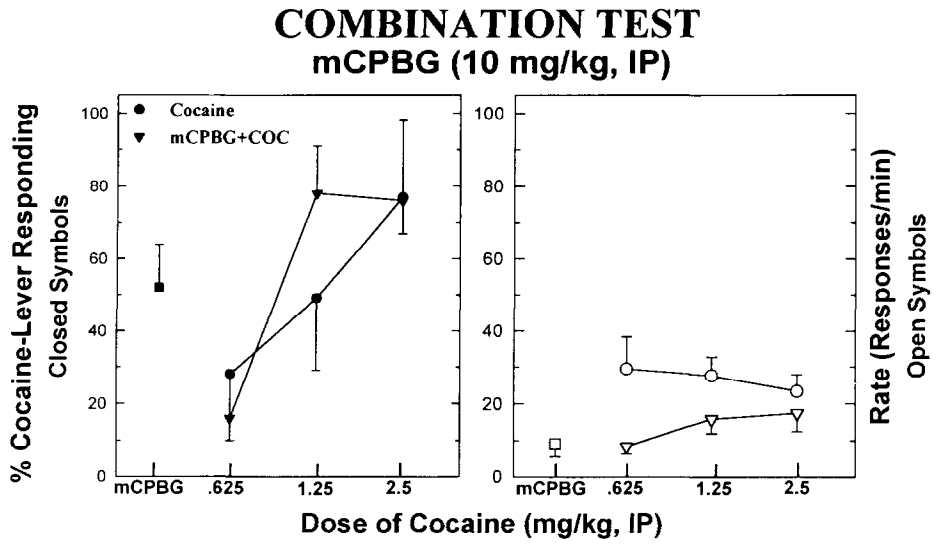

FIG. 3. Combination tests with mCPBG in rats trained to discriminate cocaine (10 mg/kg) from saline. Closed symbols (left graph) denote the mean percentage of cocaine-appropriate responses (±SEM) and open symbols (right graph) denote the mean response rate/min (±SEM) observed following different doses of cocaine alone (n = 8/8, circles) or various doses of cocaine (0.625–2.5 mg/kg) coadministered with a fixed dose of mCPBG (10 mg/kg; n = 6–8/8, triangles). Percent cocaine-appropriate responses and corresponding response rates for mCPBG (n = 6/8, 10 mg/kg) given alone (mCPBG; square) are illustrated for comparison.

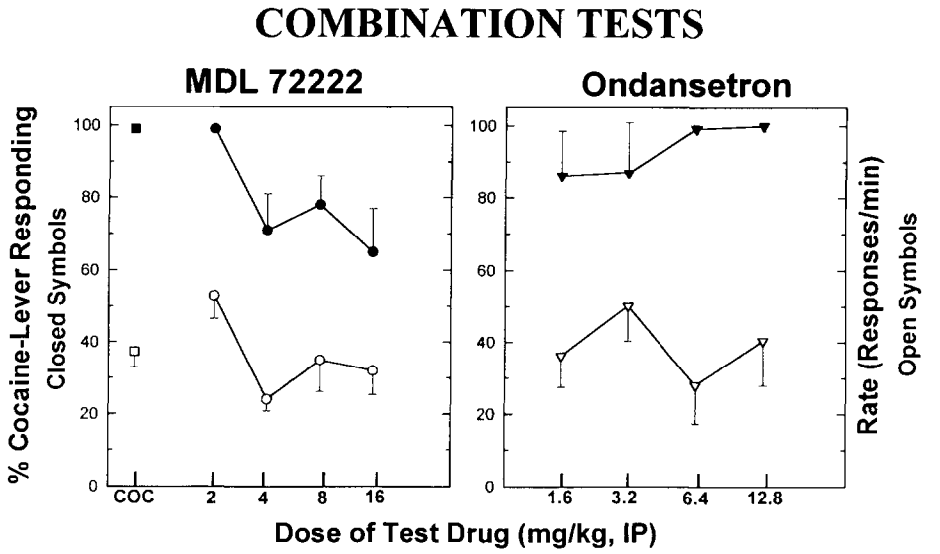

FIG. 4. Combination tests with 5-HT_3 antagonists in rats trained to discriminate cocaine (10 mg/kg) from saline. Data represent the mean percentage of cocaine-appropriate responses (±SEM) after various doses of MDL 72222 (filled circles; n = 6–8/8) or ondansetron (filled triangles; n = 6–8/8) and their corresponding response rates (open circles and triangles, respectively). Percent cocaine-appropriate responses for the training dose of cocaine (10 mg/kg: filled square) and corresponding response rate (open square) are illustrated for comparison. Asterisks denote values significantly different than previous cocaine training sessions ($p < 0.05$).

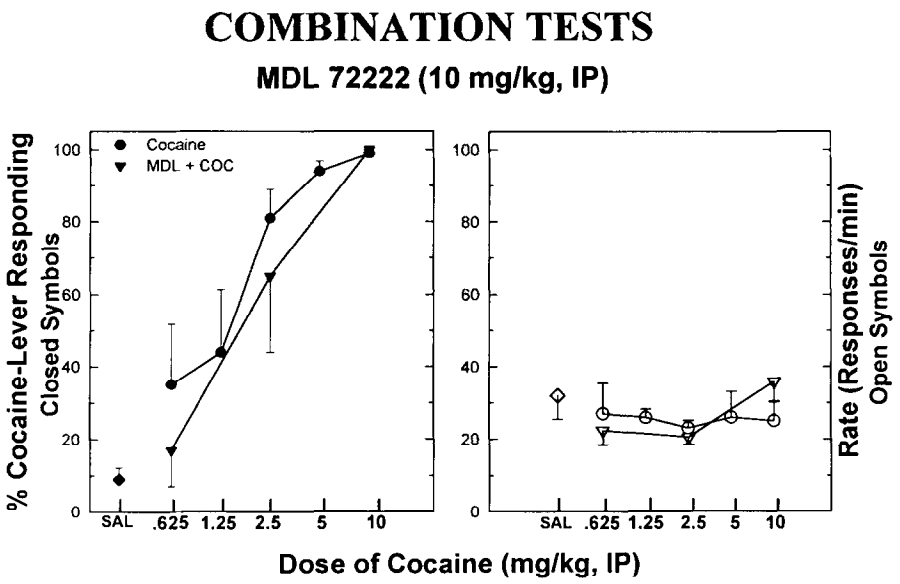

FIG. 5. Combination tests with MDL 72222 in rats trained to discriminate cocaine (10 mg/kg) from saline. Closed symbols (left graph) denote the mean percentage of cocaine-appropriate responses (±SEM) and open symbols (right graph) denote the mean response rate/min (±SEM) observed following different doses of cocaine alone (n = 8/8, circles) or various doses of cocaine (0.625–2.5 mg/kg) coadministered with a fixed dose of MDL 72222 (10 mg/kg; n = 7–8/8, triangles). Percent cocaine-appropriate responses and corresponding response rates for saline (n = 8/8, diamond) are illustrated for comparison.

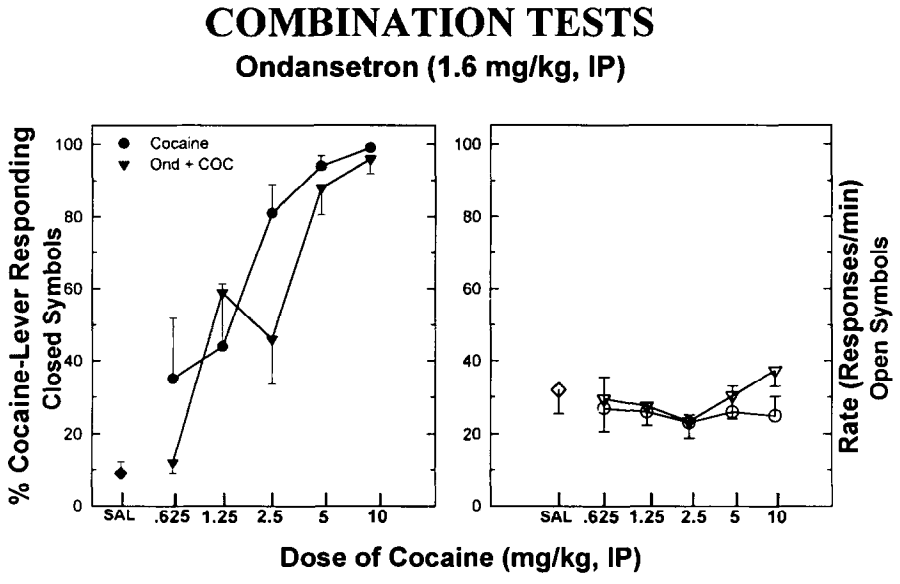

FIG. 6. Combination tests with ondansetron in rats trained to discriminate cocaine (10 mg/kg) from saline. Closed symbols (left graph) denote the mean percentage of cocaine-appropriate responses (±SEM) and open symbols (right graph) denote the mean response rate/min (±SEM) observed following different doses of cocaine alone (n = 8/8, circles) or various doses of cocaine (0.625–2.5 mg/kg) coadministered with a fixed dose of ondansetron (1.6 mg/kg; n = 6–8/8, triangles). Percent cocaine-appropriate responses and corresponding response rates for saline (n = 8/8, diamond) are illustrated for comparison.

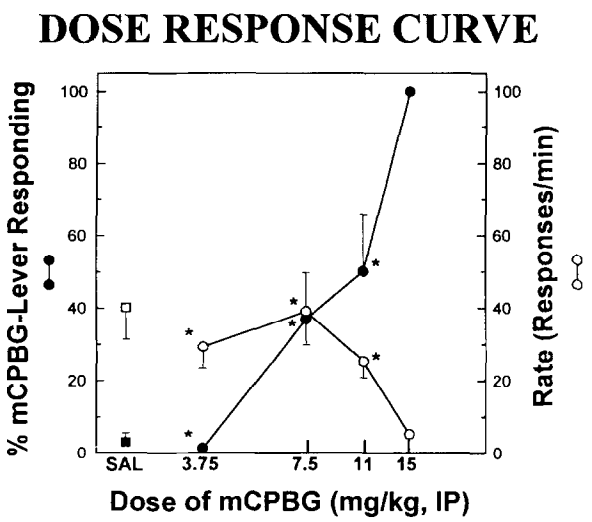

FIG. 7. mCPBG dose-response relationship in rats trained to discriminate mCPBG (15 mg/kg) from saline. Data represent the mean percentage of mCPBG-appropriate responses (±SEM) observed during test sessions with various doses of mCPBG (filled circles; n = 8-10/10) or saline (filled square; n = 8/8). Response rates for mCPBG (open circles) and saline (open square) are also illustrated. Asterisks denote values significantly different than previous mCPBG training sessions ($p < 0.05$).

mCPBG (10 mg/kg) cue (Fig. 10). The response rates observed at 1 and 10 mg/kg of zacopride administered prior to the

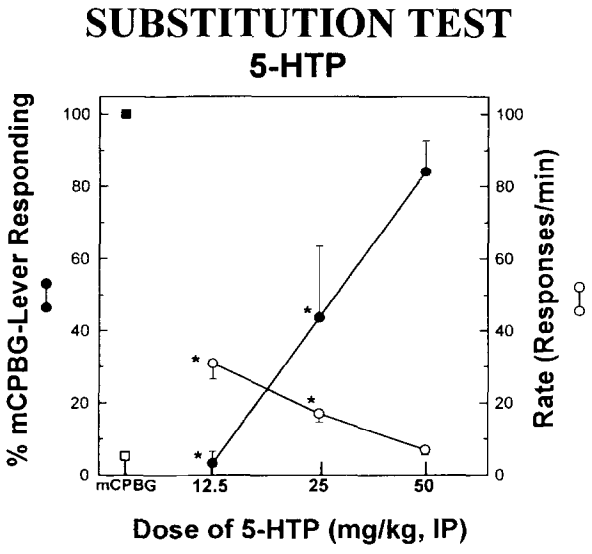

FIG. 8. Substitution tests with 5-HTP in rats trained to discriminate mCPBG (15 mg/kg) from saline. Data represent the mean percentage of mCPBG-appropriate responses (±SEM) after various doses of 5-HTP (filled circles; n = 6-8/8) and corresponding response rates (open circles). Percent mCPBG-appropriate responses for the training dose of mCPBG (15 mg/kg: filled square) and corresponding response rate (open square) are illustrated for comparison. Asterisks denote values significantly different than previous mCPBG training sessions ($p < 0.05$).

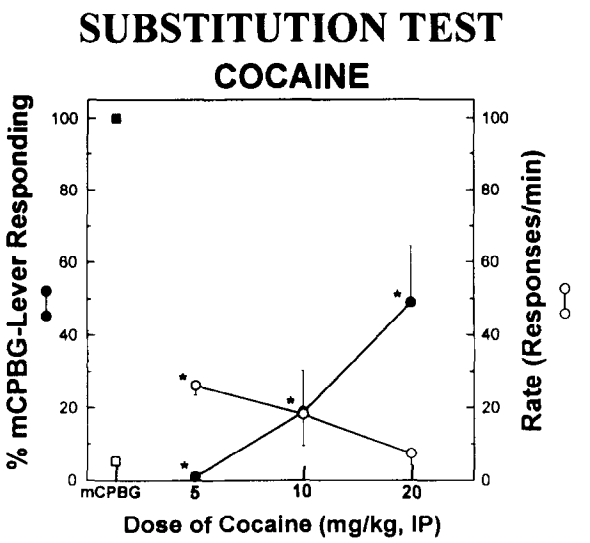

FIG. 9. Substitution tests with cocaine in rats trained to discriminate mCPBG (15 mg/kg) from saline. For explanation of figure legend, see Fig. 8.

training dose of mCPBG were significantly different from those observed on the previous mCPBG session ($p < 0.05$).

DISCUSSION

The neural activity of mesolimbic DA systems is thought to be modulated by activation of 5-HT_3 receptors, which are found in many forebrain regions (16,17). For example, the 5-HT_3 agonist 2-methyl-serotonin (2-Me-5-HT) enhanced striatal DA release in vitro (1), while intraventricular administration of 2-Me-5-HT (14,15) or another 5-HT_3 agonist 1-phenylbiguanide (5) dose-dependently increased extracellular DA levels in the nucleus accumbens. The above effects were blocked by 5-HT_3 antagonists. Cocaine also elevates extracellular levels of DA and 5-HT in vivo (2,21) and 5-HT_3 activated DA release appears to play a role in its behavioral effects. In fact, 5-HT_3 antagonists reportedly attenuate the increased extracellular DA levels (20) as well as the hyperactivity [(25,28,29); but see (9)] and behavioral sensitization (9) associated with cocaine administration.

Despite these observations, two previous studies had shown that the 5-HT_3 antagonists ICS 205-930, MDL 72222, and ondansetron did not block the stimulus effects of cocaine (19,23). To further analyze the possible involvement of 5-HT_3 receptors in this behavior, rats were trained to discriminate cocaine (10 mg/kg) from saline and substitution and combination tests were conducted with the 5-HT_3 agonist mCPBG and 5-HT_3 antagonists MDL 72222 and ondansetron in dose ranges that extended past those previously tested. In substitution tests, mCPBG elicited no more than 50% cocaine-appropriate responding up to doses which were behaviorally disruptive; combination tests indicated that mCPBG (10 mg/kg) did not alter the dose-effect relationship for cocaine. MDL 72222 decreased cocaine-appropriate responding only modestly (by approximately 40%) and a dose (16 mg/kg) higher than that previously analyzed (23) did not further enhance this antagonism; a dose of 10 mg/kg of MDL 72222 did not shift the dose-effect curve for cocaine. Ondansetron had

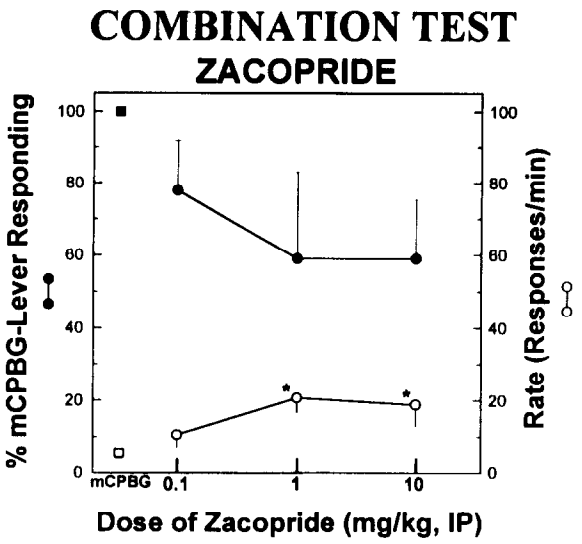

FIG. 10. Combination tests with zacopride in rats trained to discriminate mCPBG (15 mg/kg) from saline. Data represent the mean percentage of mCPBG-appropriate responses (±SEM) after various doses of zacopride (filled circles; n = 6-8/8) and corresponding response rates (open circles). Percent mCPBG-appropriate responses for the training dose of mCPBG (15 mg/kg; filled square) and corresponding response rates (open square) are illustrated for comparison. Asterisks denote values significantly different than previous mCPBG training sessions ($p < 0.05$).

previously been assessed only at very low doses (0.01-0.1 mg/kg). In the present study, ondansetron up to doses of 12.8 mg/kg did not alter the response to the training dose of cocaine; 1.6 mg/kg of ondansetron had no effect on the dose-effect curve for cocaine. Thus, the lack of effects of the 5-HT$_3$ agonist mCPBG and antagonists MDL 72222 and ondansetron in the present study agree with previous reports (19,23) and further demonstrate that, although it may be the case for locomotor hyperactivity induced by cocaine (25,28, 29), the stimulus effects of cocaine are not under the control of 5-HT$_3$ receptor systems.

Young and Glennon (30) reported that the 5-HT$_3$ agonist 2-Me-5-HT will support a drug discrimination apparently mediated by 5-HT$_3$ receptors. In the present study, we have found that another 5-HT$_3$ agonist (mCPBG) will also support discriminative behavior. The serotonin precursor 5-HTP engendered a dose-dependent and complete substitution for the mCPBG cue and the 5-HT$_3$ antagonist zacopride, which is known to have subnanomolar affinity for the 5-HT$_3$ receptor (17), partially antagonized the mCPBG discriminative stimulus as well as the rate-suppressant effects of mCPBG. These data suggest that the cue is serotonergic in nature and at least partially mediated by 5-HT$_3$ receptors. In substitution tests, cocaine failed to mimic the mCPBG cue, further supporting the contention that the role for the 5-HT$_3$ receptor in the stimulus effects of cocaine is minimal.

In contrast to their lack of effects on the discriminative stimulus and reinforcing effects of cocaine, 5-HT$_3$ antagonists have been shown to block the discriminative stimulus and reinforcing effects of other abused drugs, including ethanol (12,22), nicotine (4), and morphine (4,13). It is also interesting to note that 5-HT$_3$ antagonists reportedly reduce the behavioral consequences of withdrawal from drugs of abuse (6), and are suggested as medications that may be useful in the treatment of cocaine or amphetamine abuse in humans (26,27).

In conclusion, the role of 5-HT$_3$ receptors in the in vivo effects of cocaine appears to be complex such that 5-HT$_3$ antagonists inhibit some unconditioned behavioral effects of cocaine, but not its discriminative nor reinforcing effects. Thus, the neurochemical mechanisms and/or sites of action for elicitation of the unconditioned behaviors induced by cocaine (e.g., hyperactivity) may not be identical to those which mediate the discriminative stimulus and reinforcing properties of this abused psychostimulant.

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