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BRIEF COMMUNICATION

Serotonergic Drugs Do Not Substitute for Clozapine in Clozapine-Trained Rats in a Two-Lever Drug Discrimination Procedure

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WILEY, J. L. AND J. H. PORTER. *Serotonergic drugs do not substitute for clozapine in clozapine-trained rats in a two-lever drug discrimination procedure.* PHARMACOL BIOCHEM BEHAV 43(3) 961-965, 1992.—The atypical neuroleptic clozapine has been shown to have cue properties in two-lever drug discrimination procedures. Although it has been demonstrated that clozapine acts at several types of receptors in vitro and in vivo, including dopamine, serotonin [5-hydroxytryptamine (5-HT)], and acetylcholine receptors, the mechanism of action for its discriminative stimulus properties has not yet been determined. The present study examined the effects of haloperidol (D_2 dopamine antagonist), ritanserin (5-HT_2 antagonist), 1-αH,3-α,5-αH-tropan-3yl-3,5-dichlorobenzoate (MDL 72222) (5-HT_3 antagonist), and buspirone (5-HT_{1A} agonist) in stimulus substitution tests with rats trained to discriminate clozapine (5.0 mg/kg, IP) from vehicle in a two-lever drug discrimination procedure under a fixed ratio 30 schedule of food reinforcement. Analysis of the results revealed that, while clozapine produced dose-dependent responding on the clozapine lever, haloperidol and the three serotonin drugs failed to produce full substitution for clozapine at any of the doses tested. These results suggest that the discriminative stimulus properties are not mediated by D_2 dopamine receptor blockade, antagonism at 5-HT_2 or 5-HT_3 receptors, or agonistic activity at 5-HT_{1A} receptors. The neural basis of clozapine's discriminative stimulus properties has not yet been determined.

Clozapine Ritanserin MDL 72222 Buspirone Haloperidol Drug discrimination Neuroleptics Antipsychotics

IN the search for effective (atypical) antipsychotics that do not produce the extrapyramidal motor effects typically associated with administration of dopaminergic antagonists, recent clinical research has focused on 5-hydroxytryptamine$_2$ (5-HT_2) antagonists (4,5,25). Preclinical studies have suggested that drugs that act at 5-HT_3 (10,11,23) and 5-HT_{1A} (1) receptors also may have antipsychotic potential.

This current interest in serotonergic antipsychotics was sparked, in part, by the discovery that clozapine (CLZ), an atypical neuroleptic currently in limited clinical use in the United States, is a 5-HT receptor antagonist (12,18). In addition, CLZ interacts with a number of other neurotransmitter systems in vitro and in vivo, including dopaminergic, noradrenergic, and cholinergic pathways (24). Unlike many typical neuroleptics, CLZ has been shown to have cue properties in a two-lever drug discrimination procedure. This procedure represents an animal model of the subjective effects of drugs in humans (3); thus, it seems important to investigate whether or not drugs that act at receptors implicated in antipsychotic activity share CLZ's discriminative stimulus effects.

The present experiment tested the centrally acting serotonergic drugs buspirone (BSP), ritanserin (RIT), and 1-αH,3-α,5-αH-tropan-3yl-3,5-dichlorobenzoate (MDL 72222) for stimulus generalization in rats trained to discriminate CLZ from vehicle (VEH). BSP has high affinity at 5-HT_{1A} receptors (35) and is often classified as a 5-HT_{1A} agonist or partial agonist (15). In addition, its discriminative stimulus and other behavioral effects (14,16,29) may be mediated via this recep-

A preliminary report of these data was presented at the 21st Annual Meeting of the Society for Neuroscience, New Orleans, LA, November 1991. These data represent a portion of a dissertation submitted by J.L.W. as partial fulfillment of the requirements for a Ph.D. at Virginia Commonwealth University.

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tor. Like CLZ, BSP also has effects on dopaminergic and other neurotransmitter systems (20,38). RIT shows strong and selective affinity for central 5-HT_2 receptors in vitro and in vivo binding assays (28) and exhibits central antiserotonergic activity in behavioral tests with rats (9). Although RIT binds to D_2 dopamine receptors in vitro, it does not bind to D_2 receptors in vivo (28). RIT appears to be only partially competitive with [^{3}H]ketanserin (28), a 5-HT_2 antagonist that has been tested in CLZ-trained rats and failed to substitute for CLZ (31). Finally, MDL 72222 is a highly selective competitive 5-HT_3 receptor antagonist in the peripheral nervous system (34,36), as well as in the autonomic (19) and central nervous systems (27,33). In addition to the three serotonergic drugs, haloperidol (HAL), a D_2 dopamine antagonist, was tested.

METHOD

Subjects

Fifteen naive, adult, male Sprague-Dawley rats (375–475 g), obtained from Dominion Breeders (Dublin, VA), were individually housed in wire cages in a temperature-controlled (22°C) environment with 12 L : 12 D cycle (lights on at 6:00 a.m.). Rats were placed on a food-restricted diet and reduced to 85% of their free-feeding body weight. They were maintained at this weight for the duration of the experiment and received their daily food ration (10–20 g Agway Prolab MHR 3000 rodent chow) following experimental sessions. Animals had free access to water in their home cages.

Apparatus

Three standard operant chambers (BRS/LVE, Laurel, MD, model SEC-002), housed in sound-attenuated cubicles, were used. Each chamber contained two levers, mounted on either side of the intelligence panel 5 cm above the grid floor. A pellet dispenser (BRS/LVE, PDC/PPD series) delivered 45 mg BIO SERV (Frenchtown, NJ) food pellets to a food cup located between the two levers in the center of the intelligence panel 1.6 cm above the floor. Fan motors provided ventilation and masking noise for each chamber. A 7-W houselight was located on the intelligence panel 22.4 cm above the food cup. Solid-state programming equipment in an adjacent room was used to control the operant schedule and record data.

Drugs

HAL, CLZ, and RIT were prepared in a vehicle solution of 85% lactic acid (5–10 drops) and distilled water. MDL 72222 was prepared in a solution of 0.9% saline and lactic acid (5–10 drops). BSP HCl was dissolved in 0.9% saline. All doses of CLZ, HAL, and BSP were administered IP at a volume of 1 ml/kg body weight. RIT (15 and 20 mg/kg) and MDL 72222 (6 and 9 mg/kg) were administered IP at a volume of 2 ml/kg body weight. Doses of BSP refer to the salt; doses of all other drugs refer to the free base.

Procedure

Following reduction to 85% body weights and acclimation to the experimental apparatus, rats were trained to lever press for food reinforcement. Initially, rats were trained with a single lever present in each box according to a fixed ratio 1 (FR 1) food reinforcement schedule. While the ratio was being increased to the terminal FR 30 schedule, rats were injected daily with VEH or CLZ (5.0 mg/kg) 1 h presession in a double-alternation sequence (i.e., VVCCVVCC). Each type of injection was paired with one lever, and only the correct lever was present in the operant box. To control for olfactory cues (17), the position of the drug-associated lever (right vs. left) was counterbalanced among rats assigned to each chamber. When the FR 30 schedule was learned by all rats, both levers were inserted into the intelligence panel.

During subsequent training sessions, only one of the two levers present in the operant chamber delivered reinforcement. The position of the correct lever was determined by the type of injection the rat received. Responses on the incorrect lever reset the ratio requirement on the correct lever. The double-alternation schedule of injection was maintained throughout the experiment. Training and testing occurred during daily 15-min sessions Monday–Friday.

Rats were trained in this two-lever discrimination procedure for 40 sessions. The next 10 sessions served as an evaluation period. To begin acquisition testing, a rat must have met three criteria during each of the 10 sessions: a) the first completed FR 30 must have been made on the correct lever; b) percentage of correct lever responding during the 15-min session must have equaled or exceeded 85%; and c) response rate must have been greater than or equal to 30 responses/min.

The final phases of the experiment consisted of a) acquisition testing and b) stimulus generalization testing. During these phases, tests occurred on Tuesdays and Fridays; discrimination training continued on Mondays, Wednesdays, and Thursdays. On test days, responses on either lever delivered reinforcement, each according to an FR 30 schedule. To be tested on a given test day, a rat must have met the three evaluation criteria (described above) on the preceding day.

Acquisition testing was completed prior to testing for stimulus generalization. The acquisition test phase consisted of four sessions of injection with the training dose of CLZ or VEH in a single-alternation sequence. Successful completion of acquisition testing required that each rat meet the three evaluation criteria on four of five consecutive test sessions.

Following successful acquisition of the discrimination, stimulus generalization tests were conducted with the following drugs (presession injection times in parentheses): CLZ (1 h), HAL (45 min), RIT (30 min), MDL 72222 (30 min), and BSP (15 min). The five drugs were tested in the specified order. The order of administration of the doses of CLZ and HAL was determined with a randomized Latin square. Doses of RIT, MDL 72222, and BSP were given in ascending order. Between stimulus generalization tests with each drug, control tests were performed to assess continued retention of the discrimination. The procedure for control tests was identical to that of acquisition tests; however, rats were required to meet the evaluation criteria on one test session for VEH and one test session for CLZ. Rats that developed a preference for a specific lever position or whose responding or discriminative control deteriorated (as indicated by consistent failure to meet control criteria) were dropped from the study.

Data Analysis

For each test session, percentage of drug lever responding (i.e., number of responses on the CLZ lever divided by total number of responses and converted to a percentage) and response rate (i.e., responses/min) were calculated. A repeated-measures analysis of variance (ANOVA) comparing mean response rates across dose was performed separately for each drug. Duncan's posthoc tests ($\alpha = 0.05$) were used to specify differences revealed by significant ANOVAs (7). The ED_{50} for CLZ (with 95% confidence intervals) was calculated with the

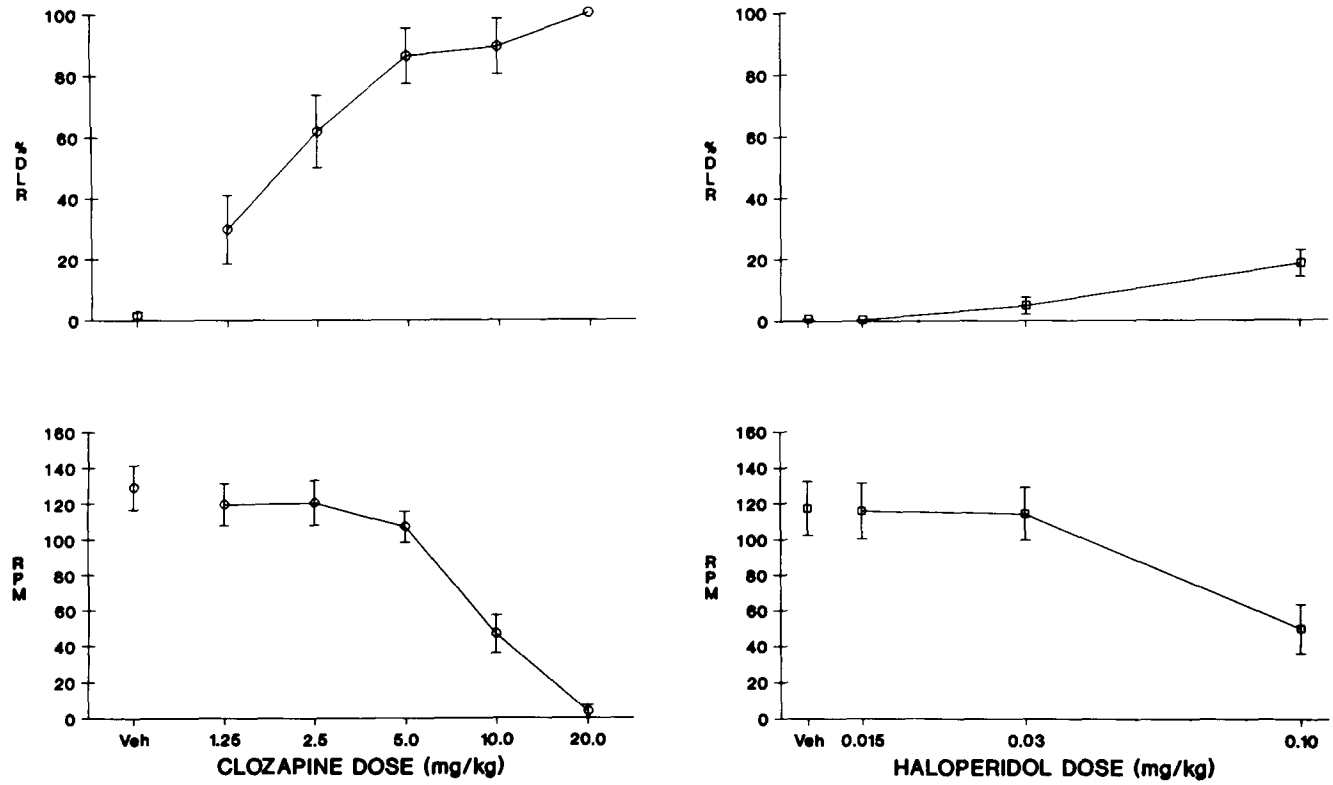

FIG. 1. Mean percentage of drug lever responding (±SEM) and mean response rate (±SEM) as a function of drug dose in rats trained to discriminate 5.0 mg/kg clozapine from vehicle. In both figures, calculation of mean responses/min includes all rats. Calculation of mean percentage of drug lever responding excludes rats that responded less than five responses/min at a dose. (For clozapine, upper left panel: n = 15 except at the 10-mg/kg dose, n = 11, and at the 20-mg/kg dose, n = 1. For haloperidol, upper left panel: n = 15 except at the 0.03-mg/kg dose, n = 14.)

least-squares method of linear regression on the linear part of the dose–effect curve (22) for percentage of drug lever responding (ordinate) plotted against $\log_{10}$ transformation of the dose (abscissa). (Data on percentage of drug lever responding for rats that had less than 5 responses/min during a test session were excluded from data analysis.)

RESULTS

Acquisition Training

All rats completed acquisition training in less than 100 sessions of two-lever discrimination training. Mean response rate (±SEM) for the two VEH acquisition tests was 125.54 (9.98) responses/min. Mean response rate (±SEM) for the two CLZ acquisition tests was 102.88 (5.70) responses/min.

Stimulus Generalization Tests With Clozapine and Haloperidol

CLZ (n = 15) generalized to the training dose (5 mg/kg) in a dose-dependent manner (ED_{50} = 2.0 mg/kg, 95% confidence interval = 1.2–3.3 mg/kg) (Fig. 1, upper left panel). The two highest doses of CLZ (10 and 20 mg/kg) significantly ($p < 0.05$) decreased response rate compared to VEH and to all other doses (Fig. 1, lower left panel).

In contrast with CLZ, HAL (n = 15) produced less than 50% drug lever responding at all doses tested (Fig. 1, upper right panel). The highest dose of HAL (0.10 mg/kg) significantly ($p < 0.05$) decreased response rate compared to VEH and to all other doses tested (Fig. 1, lower right panel).

Stimulus Generalization Tests With Serotonergic Drugs

Fourteen rats were tested for stimulus generalization with RIT (0–15.0 mg/kg). (For the purpose of data analysis, the group mean response rate for the 20-mg/kg dose was substituted for missing data for one rat that died during the dose-response determination.) Similar to HAL, RIT failed to substitute for CLZ at any dose tested (Fig. 2, upper left panel). The 10.0-, 15.0-, and 20.0-mg/kg doses of RIT significantly ($p < 0.05$) decreased response rate compared to VEH and to lower doses (Fig. 2, lower left panel).

MDL 72222 (n = 10) produced a maximum of 71.4% CLZ lever responding at the 9.0-mg/kg dose (Fig. 2, upper center panel). Mean response rate (±SEM) for the four rats whose data were included in this maximum value was 23.03 responses/min, approximately 20% of the VEH response rate (128.59 responses/min). The two highest doses of MDL 72222 (6.0 and 9.0 mg/kg) significantly ($p < 0.05$) decreased response rate compared to VEH and to lower doses (Fig. 2, lower center panel).

BSP (n = 10) produced less than chance (50%) levels of drug lever responding (Fig. 2, upper center panel). The 2.0-mg/kg dose of BSP significantly ($p < 0.05$) decreased re-

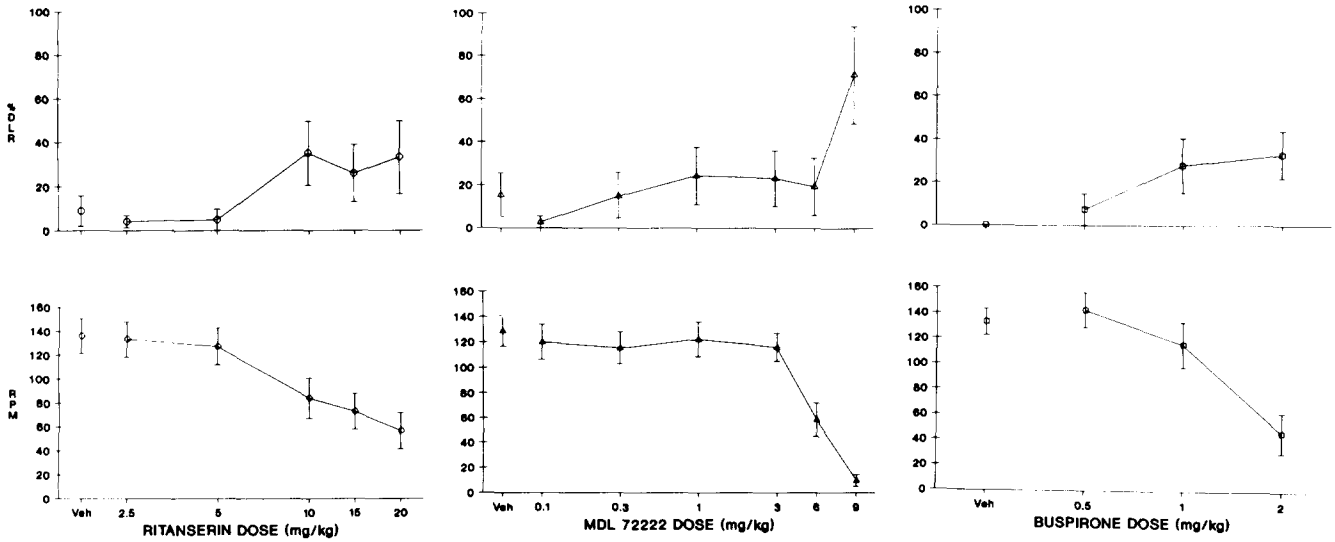

FIG. 2. Mean percentage of drug lever responding (±SEM) and mean response rate (±SEM) as a function of drug dose in rats trained to discriminate 5.0 mg/kg clozapine from vehicle. (For ritanserin, upper left panel: n = 14 except at the 10-mg/kg dose, n = 11, at the 15-mg/kg dose, n = 10, and at the 20-mg/kg dose, n = 9. For MDL 72222, upper center panel: n = 10 except at the 6-mg/kg dose, n = 8, and at the 9-mg/kg dose, n = 4. For buspirone, upper right panel: n = 10 except at the 2-mg/kg dose, n = 9.)

sponse rate compared to VEH and to lower doses (Fig. 2, lower center panel).

DISCUSSION

All rats met the acquisition criteria within 100 sessions. This result supports previous reports that CLZ can serve as a discriminative stimulus (6,21,37). In stimulus generalization tests with CLZ, mean percentage of CLZ lever responding exhibited a gradual dose-dependent increase to a maximum value at a test dose of 10 mg/kg CLZ (ED_{50} = 2.0 mg/kg). This pattern of responding resembles the pattern observed following substitution tests with CLZ in other CLZ discrimination studies (37).

Consistent with the results of previous studies (6,21,37), HAL produced less than chance levels (50%) of CLZ lever responding at all doses tested. In other studies, the typical neuroleptic, chlorpromazine (21), and atypical neuroleptics, thioridazine (6) and sulpiride (32), also did not substitute for CLZ in CLZ-trained rats. The facts that all these drugs act as antagonists at D_2 dopamine receptors and none substitutes for CLZ suggest that the discriminative stimulus properties of CLZ are not mediated by antagonism at D_2 dopamine receptors.

Similarly, the CLZ cue is probably not mediated by D_1 dopamine receptors. Nielsen (31) and Villanueva et al. (37) reported that SCH 23390, a D_1 dopamine receptor antagonist, failed to substitute for CLZ in rats trained to discriminate CLZ from VEH. In addition, Kamien and Woolverton (26) unsuccessfully attempted to train rats to discriminate SCH 23390 from vehicle. This result suggests that D_1 dopamine antagonists may be similar to D_2 receptor blockers in being weakly discriminable, unlike CLZ, which shows moderate to high discriminability. Based upon the results of these studies, antagonism at D_1 dopamine receptors does not appear to be responsible for producing the CLZ cue.

None of the other drugs tested in the present study fully substituted for CLZ. Although MDL 72222 (9.0 mg/kg) produced a mean of 71.4% CLZ lever responding in rats that met rate criteria (n = 4), response rate in these animals was severely decreased, suggesting that unconditioned effects of MDL 72222 on rate may have influenced lever choice at this dose. RIT and BSP produced less than 50% CLZ lever responding at every test dose. The BSP results are consistent with a report that CLZ does not substitute for BSP in pigeons trained to discriminate BSP from saline (29). These results suggest that the CLZ cue is not mediated by antagonism at 5-HT_2 or 5-HT_3 receptors nor by agonistic action at 5-HT_{1A} receptors.

Based upon clinical data, dopamine or serotonin receptor antagonism is the most probable mechanism of action for CLZ's antipsychotic effect (30). The fact that CLZ does not share discriminative stimulus effects with other dopamine antagonists or with drugs that act at receptors implicated in the potential antipsychotic action of some serotonergic drugs raises the possibility that the discriminative stimulus effects of CLZ may not be correlated with its antipsychotic effects. On the other hand, the discriminative stimulus effects of CLZ may be correlated with its reduced liability for production of extrapyramidal motor effects (EPS) in humans. Several researchers (2,8,13) hypothesized that the anticholinergic properties of CLZ and other atypical neuroleptics may be responsible for their decreased EPS liability. If the discriminative stimulus properties of CLZ are mediated by anticholinergic action (6,31), drugs that share discriminative stimulus properties with CLZ may be those that produce few extrapyramidal motor effects. These drugs may not share CLZ's antipsychotic action.

In summary, the discriminative stimulus properties of CLZ do not appear to be mediated by antagonism at dopamine D_1 or D_2 receptors, by blockade of 5-HT_2 or 5-HT_3 receptors, or by agonistic action at 5-HT_{1A} receptors. Based upon the results of the present study and previous research, determination of the receptor(s) mediating the CLZ cue is inconclusive. It is probable that one of the other receptors to which CLZ binds

(e.g., muscarinic, noradrenergic, or histaminergic) mediates its discriminative stimulus properties. The behavioral correlates of CLZ's discriminative stimulus properties is speculative until localization of its mechanism of action is achieved.

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