

Behavioral Effects of 5-Methoxy-N,N-Dimethyltryptamine and Dose-Dependent Antagonism by BC-105

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Abstract. The discriminative effects of 5-methoxy-N,N-dimethyltryptamine (5-OMeDMT) were studied in rats trained to discriminate 1.5 mg/kg or 3.0 mg/kg 5-OMeDMT from saline. A series of antagonist and generalization tests revealed that (1) antagonism of the 5-OMeDMT stimulus response by the presumed serotonin antagonist BC-105 depended on the dose of 5-OMeDMT, (2) the 5-OMe DMT stimulus generalized to LSD, and (3) like 5-OMeDMT, antagonism of the LSD generalization response by BC-105 depended on the dose of LSD. In a second study, with rats responding under a variable-interval (VI) 15-s schedule of reinforcement, doses of 1.0–3.0 mg/kg 5-OMeDMT significantly decreased response rate. Furthermore, the decrease in responding produced by the administration of 1.5 mg/kg (but not by 3.0 mg/kg) 5-OMeDMT was blocked by BC-105. This dose-dependent antagonism was of particular interest since the 1.5 mg/kg and 3.0 mg/kg dose of 5-O-MeDMT had essentially the same effect on responding when given alone. The results of both studies emphasize the importance of 5-OMeDMT dose in antagonism experiments.

Key words: 5-OMeDMT – Discriminative stimulus – LSD – Hallucinogens – BC-105 – Operant responding – Serotonin

The ability of 5-methoxy-N,N-dimethyltryptamine (5-OMeDMT), a hallucinogenic tryptamine analog (Kantor et al. 1980), to serve as a discriminative stimulus was first reported by Glennon et al. (1979). In that investigation, the 5-OMeDMT cue generalized to DOM (a hallucinogenic phenylisopropylamine or amphetamine derivative) and the discriminative response produced by 5-OMeDMT and lysergic acid diethylamide (LSD) was attenuated by the serotonin (5-HT) antagonist BC-105 (pizotyline or pizotifen). A subsequent report (Glennon et al. 1980) presented evidence that the 5-OMeDMT cue generalized in a dose-related manner to 15 tryptamine-related analogs, including two other phenylisopropylamine analogs. In addition, the 5-HT receptor affinity (determined using an isolated rat fundus preparation) of the test compounds correlated highly with their behavioral 5-OMeDMT-like response. More recently, we have examined the possibility of a relationship between the 5-OMeDMT cue and the 5-HT receptor affinity values of a more extensive series of substituted phenylisopropylamines (or isomers). Of 36 compounds tested, generalization was found between the

5-OMeDMT cue and nine phenylisopropylamines. Those compounds to which the 5-OMeDMT cue generalized had relatively high 5-HT receptor affinities, although the correlation between these two variables was not statistically significant (Glennon et al. 1981).

From these data, we emphasized the probable involvement of a serotonergic mechanism that mediates the cue produced by 5-OMeDMT and of test compounds that produce 5-OMeDMT-like responding. This is not to imply an exclusive role for 5-HT in the neuropharmacology of these compounds, since other neurotransmitters might also be involved, to varying degrees, in the mechanism of action of these agents (e.g., Freedman and Halaris 1978). Nevertheless, the conclusion drawn from these behavioral investigations, that 5-HT is involved at least in part in the mechanism of action of 5-OMeDMT, is consistent with the effects of 5-OMeDMT upon the extensor hind limb reflex (Fuxe et al. 1972) and upon 5-HT neurones of the midbrain raphe nuclei when given systemically (Mosko and Jacobs 1977) or iontophoretically (DeMontigny and Aghajanian 1977).

Although 5-HT systems do seem to be primarily responsible for the discriminative stimulus effects of 5-OMeDMT, the exact neuropharmacological mechanism that underlies the 5-OMeDMT-induced cue has yet to be elucidated. In the present study, two different approaches were employed to confirm and extend the previous finding of antagonism of the effects of 5-OMeDMT by BC-105. With the first approach, two groups of rats were trained to discriminate 5-OMeDMT (1.5 or 3.0 mg/kg) from saline. After the discriminations were learned, antagonism of the 5-OMeDMT stimuli by BC-105 was examined. In a second study, the effects of various doses of 5-OMeDMT, administered alone or in combination with various doses of BC-105, were studied in rats responding under a variable-interval (15-s) schedule (VI 15-s) of reinforcement.

Materials and Methods

The animals used in the discrimination study were 22 male Sprague-Dawley (350–400 g) rats. The animals used in the schedule-controlled responding study were six male Sprague-Dawley (325–375 g) rats. All animals were housed individually and had unlimited access to drinking water. The animals were maintained at 80% of their expected free-feeding body weights by partial food deprivation.

Behavioral testing was conducted in standard operant chambers (Lehigh Valley Electronics model 1417). One wall of the chamber contained the intelligence panel, which consisted of two levers with a dipper for delivery of reinforce-

ment (0.01 ml sweetened milk) centered between the levers. A house light (28 V), located 24 cm above the dipper, provided illumination of the chamber. Each operant chamber was housed in a sound-insulated chamber (Lehigh Valley Electronics model 132-02). Standard electromechanical and solid-state programming and recording equipment were used.

Drug Discrimination Studies. The discrimination training procedure has been reported previously (Glennon et al. 1980, 1981). Briefly, the 22 animals were each trained to respond to a variable VI 15-s schedule of reinforcement on each lever. Lever response training on the VI 15-s schedule continued until rates of responding stabilized. At this point, the animals were divided into two groups and drug discrimination training was begun. The first group of 14 rats was injected IP with either 5-OMeDMT (3.0 mg/kg) or its vehicle (saline), and the second group of eight rats received 1.5 mg/kg 5-OMeDMT or saline. All rats received their injection 15 min before each session and were placed in the operant chambers with both levers present. Training sessions were of 15-min duration. To control for possible lever position preference, for half of the animals in each group the right lever was reinforced when 5-OMeDMT was given and the left lever was reinforced following saline injection, and these conditions were reversed for the remaining animals in each group. Saline or 5-OMeDMT was administered on a double-alternation schedule (i.e., 2 days saline, 2 days 5-OMeDMT).

On every fifth day the discrimination learning was assessed during an initial 2.5-min nonreinforced (extinction) period followed by a 12.5-min training session. Data collected during the 2.5-min extinction periods included total responses (responses/min) and percent correct responding on the 5-OMeDMT lever (number of responses on 5-OMeDMT-designated lever/total number of responses). After 40 training sessions, discrimination performance was stable for each group of animals (i.e., 5-OMeDMT, approximately 85%; saline, approximately 10%). The response rates were similar under all treatment conditions. The 5-OMeDMT versus saline discrimination was insured in each group by continuation of training sessions throughout substitution and antagonism testing. Test data were excluded from animals not discriminating 5-OMeDMT (i.e., less than 80% 5-OMeDMT-correct responding when given drug) from saline (i.e., more than 20% 5-OMeDMT lever responding when given vehicle) during training prior to substitution tests and antagonism tests.

Substitution Tests. During substitution investigations, test sessions were interposed between discrimination training sessions. During these test sessions the animals were allowed 2.5 min of nonreinforced lever responding and were then removed from the operant chambers. An odd number of training sessions, generally three, separated any two test sessions. The dose-response substitution tests assessed the 5-OMeDMT-appropriate responding of the rats following the administration of various doses of 5-OMeDMT and LSD. Doses of 5-OMeDMT or LSD were administered in a random sequence. LSD or 5-OMeDMT was administered 15 min prior to behavioral testing.

Antagonism Tests. In each 5-OMeDMT-trained group the purported 5-HT antagonist BC-105 (1.0 mg/kg) was injected 45 min prior to each training dose of 5-OMeDMT. In all antagonism tests the animals were tested for lever choice

responding 15 min after the 5-OMeDMT injection under extinction test conditions. Doses of BC-105 were increased or decreased in subsequent tests, depending upon the percent 5-OMeDMT responding produced by the initial BC-105 dose in combination with the 5-OMeDMT training doses. In addition, control studies were performed of the antagonists in combination with saline, rather than 5-OMeDMT. Each data point was determined from the responding of five to eight animals.

A second phase of antagonism testing used only the 3.0 mg/kg 5-OMeDMT-trained animals, which were injected with a constant dose of BC-105 (1.0 mg/kg) or saline (1.0 mg/kg) 45 min prior to the administration of various doses of 5-OMeDMT. As before, the test for lever choice responding occurred 15 min after the 5-OMeDMT injection under extinction test conditions.

The final antagonism tests examined the ability of BC-105 to attenuate the 5-OMeDMT generalization response produced by LSD doses. In the first phase of this antagonism test, both groups of 5-OMeDMT-trained animals were injected with either BC-105 or saline 45 min prior to the injection of 0.06 mg/kg LSD. A subsequent 15-min time interval elapsed before the animals were exposed to the 2.5-min nonreinforced test session. The initial dose of BC-105 was 1.0 mg/kg, and the degree of antagonism produced by this dose was used to determine subsequent BC-105 doses. The second part of this antagonism test used only the 3.0 mg/kg 5-OMeDMT-trained animals. With these animals, antagonism of the 5-OMeDMT generalization response produced by the administration of 0.18 mg/kg LSD by BC-105 was studied.

5-OMeDMT Effects on Scheduled-Controlled Responding. After stabilization at the reduced body weight, six animals were trained to respond on one of the two levers in the operant chamber. For three of the rats, responding on the right lever was reinforced, and responding on the left lever was reinforced for the other three rats. Incorrect responding had no programmed consequences. When responding was achieved under a fixed-ratio (FR-1) reinforcement schedule, the animals were then acclimated to a VI 15-s schedule of reinforcement. The behavioral response measure was expressed as the ratio of responses/min. Each animal was tested 5 days/week in a daily 15-min test session under the VI 15-s reinforcement schedule until stable response rates ($48.2 \text{ responses/min} \pm 8.3 \text{ SEM}$) were evident (10–15 sessions). In addition, the animals received saline injections during the last five sessions to accustom them to the subsequent drug injection procedure.

Dose-Response Tests. After stable responding was achieved for all animals, a 45-day period was used to establish an initial dose-response effect of responding with single doses of saline and 5-OMeDMT. The effect of BC-105 doses given alone on VI 15-s responding was also examined. Doses of 5-OMeDMT were administered IP 15 min prior to behavioral testing, while BC-105 doses were administered IP 60 min before behavioral testing. The effect of saline administration was studied with a 15-min presession time interval and a 60-min presession time interval. Doses of each drug were injected in a random order with at least 3 days intervening between each dose.

Antagonism Test. During the antagonism test, doses of BC-105 or saline were injected 45 min prior to the injection of 1.5 and 3.0 mg/kg 5-OMeDMT. A subsequent 15-min time interval elapsed before the animals were placed in the operant

Table 1. Percent 5-OMeDMT response during 2.5-min extinction sessions in rats trained to discriminate 1.5 or 3.0 mg/kg 5-OMeDMT from saline

Agent and dose (mg/kg)	N	5-OMeDMT (1.5 mg/kg) stimulus		N	5-OMeDMT (3.0 mg/kg) stimulus	
		Percent response (mean $\pm$ SEM)	Responses/min (mean $\pm$ SEM)		Percent response (mean $\pm$ SEM)	Responses/min (mean $\pm$ SEM)
<i>Saline</i>						
1.0 ml/kg	8	8 $\pm$ 2.1	13.5 $\pm$ 1.5	14	10 $\pm$ 3.4	14.2 $\pm$ 1.5
<i>5-OMeDMT</i>						
0.25	5	32 $\pm$ 8.5	13.2 $\pm$ 2.1	—		
0.30	—			14	30 $\pm$ 4.1	12.6 $\pm$ 1.9
0.75	5	54 $\pm$ 16.9	12.9 $\pm$ 1.9	14	52 $\pm$ 18.6	10.8 $\pm$ 2.3
1.00	5	74 $\pm$ 8.0	13.0 $\pm$ 1.3	14	55 $\pm$ 16.9	13.4 $\pm$ 2.1
1.50	5	93 $\pm$ 3.8	12.8 $\pm$ 2.2	14	70 $\pm$ 6.7	12.5 $\pm$ 1.7
3.00	5	—	0.0	14	95 $\pm$ 3.2	13.1 $\pm$ 1.4
<i>LSD</i>						
0.020	5	28 $\pm$ 6.0	12.6 $\pm$ 1.2	4	22 $\pm$ 7.5	11.9 $\pm$ 1.1
0.040	5	63 $\pm$ 19.4	11.8 $\pm$ 1.9	4	51 $\pm$ 17.2	13.1 $\pm$ 1.9
0.060	5	87 $\pm$ 7.5	11.5 $\pm$ 1.8	4	84 $\pm$ 8.0	12.3 $\pm$ 1.1
0.080	5	91 $\pm$ 3.8	8.4 $\pm$ 1.9	5	93 $\pm$ 2.0	13.4 $\pm$ 2.1
0.120	3	93 $\pm$ 4.1	7.1 $\pm$ 2.3	6	96 $\pm$ 1.5	12.9 $\pm$ 1.7
0.180	5	—	0.0	6	100 %	12.5 $\pm$ 1.3

chambers. Doses of BC-105 or saline in combination with 5-OMeDMT were administered in a counterbalanced sequence with at least 3 days intervening between each data point determination. Each data point was determined from the responding of six animals.

Drugs. Doses of the following drugs were based on the weight of the salt: 5-OMeDMT (Sigma Chemicals, St. Louis, MO, USA), which was converted to the hydrogen oxalate salt and BC-105 (pizotifen or pizytoline maleate, Sandoz, Pharmaceuticals, East Hanover, NJ, USA). Doses of *d*-lysergic acid diethylamide tartrate (NIDA, Rockville, MD, USA) refer to the equivalent free base concentration. All drugs were dissolved in sterile 0.9 % sodium chloride and were prepared immediately before use. All injections were given IP.

Results

Discrimination Studies. The 5-OMeDMT dose-response determinations revealed that the drug-induced cue, in both groups of animals, depended on the dose (Table 1). The challenge dose of 3.0 mg/kg 5-OMeDMT administered to the 1.5 mg/kg 5-OMeDMT-trained rats, however, disrupted behavior (i.e., no responding). Response rates under the remaining drug dose and non-drug conditions in each group were not significantly different from the response rates that occurred during discrimination training test sessions.

Table 1 also shows that the administration of LSD, in both groups of animals, produced dose-dependent choices of the 5-OMeDMT response. In the 1.5 mg/kg 5-OMeDMT-trained group, however, response rates began to decrease at 0.08 mg/kg LSD. Complete disruption of behavior (i.e., no responding) in these animals was noted at 0.18 mg/kg LSD. In comparison, the response rates of the 3.0 mg/kg 5-OMeDMT-trained group remained stable throughout the LSD dose response.

The results of testing for antagonism of the 5-OMeDMT training doses by BC-105 are summarized in Fig. 1. In the 1.5 mg/kg 5-OMeDMT-trained animals, pretreatment with BC-105 resulted in dose-related decreases in percent 5-OMeDMT-appropriate responding. At the pretreatment BC-105 dose levels of 1 and 3 mg/kg, percent responses on the 5-OMeDMT-correct lever, after the injection of the training dose, declined to saline response levels, indicating a complete antagonism of the 5-OMeDMT discriminative stimulus. Control doses of BC-105 in combination with saline (data not shown) resulted in saline-like responding (i.e., less than 20 % 5-OMeDMT lever responding). Response rates, at all drug combinations within this group of animals showed no significant change from the response rates that occurred during discrimination training test sessions.

In contrast, the administration of various doses of BC-105 (up to 10 mg/kg), in combination with the 3.0 mg/kg 5-OMeDMT training dose, resulted in no significant attenuation in percent 5-OMeDMT-appropriate responding. Control doses of BC-105 (up to 10 mg/kg), in combination with saline, resulted in saline-like responding. Response rates, however, began to show suppression with BC-105 (in combination with 5-OMeDMT or saline) at 5 mg/kg. At 12 mg/kg BC-105, disruption of behavior occurred under both drug (5-OMeDMT) and nondrug (saline) combinations.

Figure 2 shows the 5-OMeDMT dose-response functions in the 3.0 mg/kg 5-OMeDMT-trained animals in the presence and absence of BC-105 (1 mg/kg). The administration of saline in combination with the 5-OMeDMT doses resulted in percent 5-OMeDMT-appropriate responding (70 %–90 %) that is consistent with the dose-response data obtained previously (Table 1). In comparison, the administration of 1 mg/kg BC-105 prior to the injection of the 5-OMeDMT doses resulted in a 5-OMeDMT dose-dependent effect. BC-105 pretreatment prior to 1.5 and 2.0 mg/kg 5-OMeDMT produced saline-like responding (antagonism). However, when 2.5 mg/kg 5-OMeDMT was administered to these

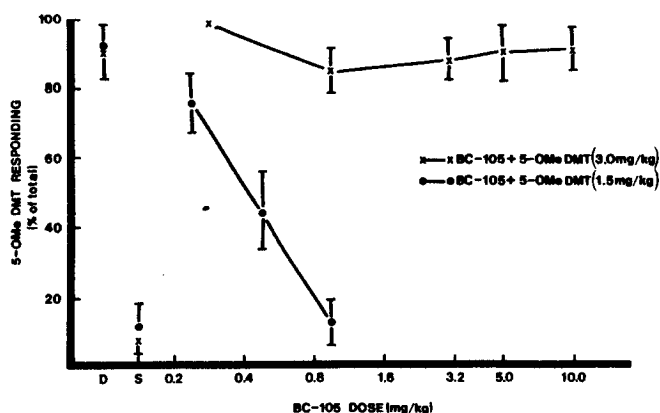


Fig. 1. The effects of various doses of BC-105 in combination with two training doses of 5-OMeDMT (1.5 and 3.0 mg/kg) in the respective group of animals. The discrimination response of 5-OMeDMT (D) and saline (S) during discrimination training test sessions prior to antagonism test are also presented

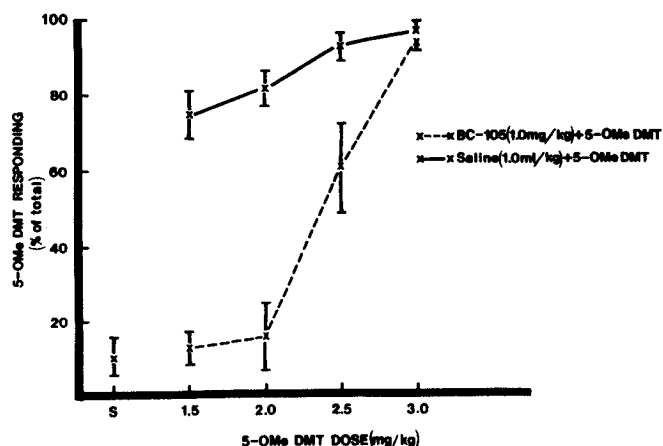


Fig. 2. The effects of the partial 5-OMeDMT dose response in the 3.0 mg/kg 5-OMeDMT-trained animals in the presence of BC-105 (1.0 mg/kg) or saline (1.0 ml/kg)

animals after the pretreatment with BC-105, only partial antagonism (60%) of 5-OMeDMT lever responding was observed. No attenuation of the 5-OMeDMT training dose response by BC-105 was seen, as was shown previously (Fig. 1). Response rates showed no significant change under either pretreatment condition (saline or BC-105 with 5-OMeDMT) from the response rates that were observed during drug discrimination test sessions.

The effects of saline and BC-105 pretreatment prior to LSD (0.06 mg/kg) administration are shown in Fig. 3. In both groups of animals the administration of saline prior to the injection of LSD resulted in 5-OMeDMT generalization responding that is consistent with that shown in the LSD substitution test (Table 1). However, when BC-105 doses (0.25–1.0 mg/kg) were administered prior to the injection of LSD, dose-related decreases in percent 5-OMeDMT-like responding were observed. At the BC-105 pretreatment dose level (1 mg/kg), percent responding on the 5-OMeDMT-correct lever declined to saline levels, indicating a complete antagonism of the 5-OMeDMT generalization response in each group. Response rates under both pretreatment conditions with 5-OMeDMT showed no change from the re-

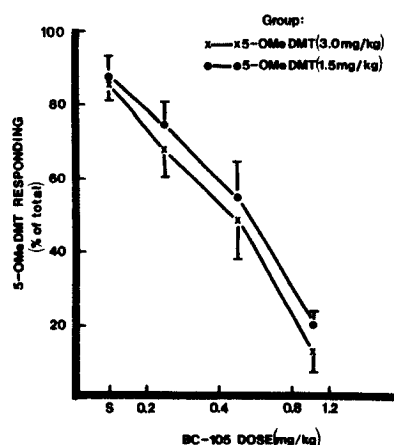


Fig. 3. The effects of BC-105 and saline (S) administration in 5-OMeDMT trained animals on the 5-OMeDMT generalization response produced by the administration of LSD (0.06 mg/kg)

sponse rates that occurred during discrimination training test sessions.

In contrast, the administration of various doses of BC-105 (up to 9.0 mg/kg), in combination with 0.18 mg/kg LSD, in the 3.0 mg/kg 5-OMeDMT-trained animals resulted in no significant attenuation of 5-OMeDMT-like percent responding (data not shown). Control doses of BC-105 (up to 9.0 mg/kg) in combination with saline resulted in saline-like responding. Response rates, however, began to show suppression with BC-105 (in combination with LSD and saline) at 6.0 mg/kg. At 11.0 mg/kg BC-105, complete disruption of behavior occurred under both drug (LSD) and nondrug (saline) combinations.

5-OMeDMT Effects on Schedule-Controlled Responding. The statistical analysis of the dose-response effects of 5-OMeDMT, and of the effect of BC-105 on operant behavior were accomplished by analysis of variance (ANOVA, repeated-measures design). Duncan's multiple-range tests were used for post hoc comparisons (significance level $P < 0.05$).

ANOVA revealed a significant dose effect ($F = 8.92$, $df = 6,30$, $P < 0.001$). Low doses of 5-OMeDMT (i.e., 0.05 and 0.10 mg/kg) had no statistically significant effects on response rate. In contrast, 1.0, 1.5, and 3.0 mg/kg 5-OMeDMT significantly decreased responding. Post hoc analysis also revealed no significant difference in the amount of behavioral disruption produced by the administration of 1.5 and 3.0 mg/kg 5-OMeDMT. ANOVA performed on the possible effects of BC-105 doses (given alone) on VI 15-s responding revealed no significant ($F = 1.71$, $df = 4,20$, $P > 0.10$) behavioral effects after the administration of various doses of BC-105 (0.50–6.0 mg/kg), including the two doses (1.0 and 6.0 mg/kg) of BC-105 that were used in the antagonism test.

The statistical analysis of the antagonism data revealed a significant treatment effect ($F = 3.01$, $df = 6,30$, $P < 0.05$). Post hoc comparisons revealed that the administration of saline in combination with either 1.5 or 3.0 mg/kg 5-OMeDMT produced significant decreases in the rats behavioral responding (Fig. 4). However, the administration of BC-105 (1.0 or 6.0 mg/kg) prior to the injection of 1.5 mg/kg 5-OMeDMT resulted in responding that was not significantly

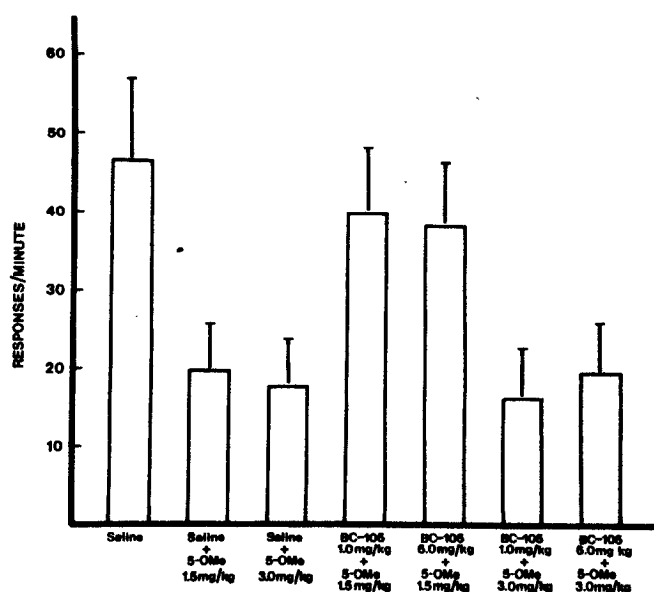


Fig. 4. The effects of saline or BC-105 (1.0, 6.0 mg/kg) in combination with 5-OMeDMT (1.5, 3.0 mg/kg) on operant responding

different from that of responding after saline administration. In contrast, the administration of BC-105 (1.0 mg/kg or 6.0 mg/kg) prior to the injection of 3.0 mg/kg 5-OMeDMT produced decreases in behavioral responding that were still significantly below that of responding after saline administration.

Discussion

The present data confirm and extend earlier reports (Glennon et al. 1979, 1981; Young et al. 1982) of the behavioral effects produced by 5-OMeDMT. In the discrimination studies, the generalization of the 5-OMeDMT training dose cues to LSD is consistent with earlier reports of the discriminative stimulus effects of 5-OMeDMT (Glennon et al. 1979; Young et al. 1982). In those investigations it was also noted that, when LSD is used as a training drug, the LSD cue generalized to 5-OMeDMT. From these data, it may be inferred that 5-OMeDMT and LSD share a similar behavioral effect, although not necessarily a similar mechanism of action.

The antagonism tests in the discrimination studies indicate that, in 5-OMeDMT-trained animals, the combination of BC-105 with 5-OMeDMT produced a dose-dependent discriminative stimulus effect. That is, BC-105 can significantly attenuate the 5-OMeDMT percent response produced by the administration of 1.5 mg/kg 5-OMeDMT (to the animals trained to either 1.5 or 3.0 mg/kg), but not the response to 3.0 mg/kg 5-OMeDMT (administered to animals trained to discriminate 3.0 mg/kg 5-OMeDMT from saline) even when ten times the dose of BC-105 is used. Similarly, the 5-OMeDMT generalization response produced by the administration of 0.06 mg/kg LSD can be blocked by BC-105, but not the response produced by the administration of 0.18 mg/kg LSD.

The administration of either 1.5 or 3.0 mg/kg 5-OMeDMT to rats responding on a VI 15-s schedule of reinforcement produced significant decreases in response

rate, but did not decrease rates of responding in the drug discrimination task. However, in the drug discrimination paradigm, a particular dose of a drug was given chronically. Behavioral tolerance developed to the disruptive effects of the drug, but not to the stimulus effects of the drug. In the present study, behavioral tolerance to the disruptive effects of either 1.5 or 3.0 mg/kg 5-OMeDMT is shown by the fact that response rates during extinction test sessions are similar after 5-OMeDMT and saline treatment conditions.

The antagonism tests in the study of schedule-controlled responding revealed that BC-105 (1.0 and 6.0 mg/kg) can significantly attenuate the behavioral disruptive effect produced by the administration of 1.5 mg/kg, but not 3.0 mg/kg 5-OMeDMT. As there was no statistically significant difference between the amount of behavioral disruption produced by these two doses of 5-OMeDMT when given alone, these data seem particularly difficult to interpret. However, the results of both studies are consistent and suggest that certain hallucinogenic agents apparently produce dose-dependent effects. Furthermore, the present studies indicate the importance of studying various concentrations of drug in the presence of a fixed concentration of antagonist and vice versa (Rosecrans and Glennon 1979).

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