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COMPARATIVE DISCRIMINATIVE STIMULUS EFFECTS OF 5-METHOXY-N,N-DIMETHYLTRYPTAMINE AND LSD*

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Summary

Rats were trained to discriminate injections of either 5-OMe DMT (1.5 mg/kg) or LSD (0.096 mg/kg) from saline in a two-lever drug discrimination task. After stable discrimination performances were attained (> 85%) in each group, dose-response generalizations between the two groups of animals were examined. The results revealed that the 5-OMe DMT-stimulus response generalized to LSD and that the LSD-stimulus response generalized to 5-OMe DMT. Furthermore, both the 5-OMe DMT-stimulus and the LSD-stimulus could be significantly attenuated by the serotonin antagonist BC-105. However, the pattern of the dose-related antagonism by BC-105 was different between the drug stimuli. It was concluded that while the discriminative stimulus effects of 5-OMe DMT and LSD may be mediated via a common serotonergic system, the receptor interaction of these agents within that pharmacological system may be somewhat different.

The ability of hallucinogenic drugs to serve as discriminative stimuli in animals is well documented (1-3). Among these are lysergic acid diethylamide (LSD) and 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT). Although the exact neuropharmacological mechanisms by which these agents produce their stimulus effects are not known with certainty, several investigators have suggested that at least some of the effects of these drugs are mediated through putative 5-hydroxytryptamine (5-HT, serotonin) systems (4,5).

In a previous report (6) we noted that stimulus generalization was found to occur between 5-OMe DMT and LSD when either drug was used as the training stimulus. From these data we have emphasized the idea that LSD and 5-OMe DMT may share a common component to their CNS mechanism of action. The aim of the present study was to compare, in more detail, the stimulus effects produced by 5-OMe DMT and LSD. To accomplish this, two groups of rats were trained to discriminate LSD or 5-OMe DMT from saline in a drug discrimination procedure. After the discriminations were learned, antagonism of the stimulus responses by BC-105, a serotonin antagonist which is presumed to act postsynaptically (7)

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was examined. In addition, the ability of haloperidol, a specific dopamine antagonist, to attenuate each stimulus response was studied.

Methods

The animals used in this study were thirty-four 180-day old male Sprague-Dawley rats weighing between 350-420 g when allowed free access to food. The animals' weights were reduced to 80% of their ad lib weights by partial food deprivation.

Discrimination training: All animals were trained to lever-respond to a variable interval 15-second (VI 15s) schedule of reinforcement on both levers of a standard operant test chamber (Coulbourn Instruments). The reinforcer was sweetened condensed milk diluted 2:1 with tap water. After schedule-responding was established, the animals were divided into 2 groups and drug administration was begun; each daily 15-minute session was preceded by the injection of either drug or isotonic saline. The first group of 16 rats was injected intraperitoneally (i.p.) with either LSD (0.096 mg/kg) or saline five minutes before each session. The second group of 18 rats was injected i.p. with either 5-OMe DMT (1.5 mg/kg) or saline 15 minutes prior to each session. Depression of one of the two levers was reinforced after administration of drug (5-OMe DMT or LSD) while responses on the opposite lever were reinforced following saline administration. For one-half of the animals in each group, the right lever was reinforced when drug was given and the left lever was reinforced after saline administration; these conditions were reversed for the remaining animals in each group. Saline or drug was administered on a double alternation schedule (i.e., 2 days drug, 2 days saline). On every fifth day the rats discrimination learning was assessed during an initial 2.5-min non-reinforced (extinction) period followed by a 12.5-min training session. Data that were collected during the 2.5-min extinction periods included total responses (expressed as resp./min.) and percent-correct responding on the drug-lever (number of responses on drug-designated lever/total number of responses).

Generalization tests: After 40 discrimination training sessions, discrimination responding was relatively stable in each group of animals. During generalization investigations, test sessions were interposed between discrimination training sessions. During these test sessions the animals were allowed 2.5 min of non-reinforced lever-responding, and were then removed from the operant chambers. Generalization tests investigated the ability of the LSD-stimulus response to generalize to 5-OMe DMT and the 5-OMe DMT stimulus response to generalize to LSD. LSD-trained animals received 0.50, 1.00, and 1.50 mg/kg of 5-OMe DMT. Doses of 5-OMe DMT were administered in a random sequence with a 15-min injection time interval prior to the 2.5 min extinction test period. Each data point was determined from the responding of 16 animals. 5-OMe DMT-trained animals received 0.024, 0.048, and 0.096 mg/kg of LSD. Doses of LSD were administered in a random sequence with a 5-min injection-time interval prior to the extinction test period. Each data point was determined from the responding of 12 animals.

Antagonism tests: During antagonism tests, dose-response generalization curves of each training drug-cue were evaluated in the presence of several doses of the serotonin antagonist BC-105 (pizotyline or pizotifen), and several doses of the dopamine antagonist haloperidol. Specifically, in the 5-OMe DMT-trained animals, the percent 5-OMe DMT-appropriate responses produced by the administration of 0.5, 1.0 and 1.5 mg/kg of 5-OMe DMT were recorded after pretreatment of these animals with saline, 0.1, 0.3, and 1.0 mg/kg of BC-105, and 0.1, 0.3, and 0.5 mg/kg of haloperidol. Doses of BC-105 or haloperidol were injected 45 min prior to the injection of each 5-OMe DMT dose. A subsequent 15-min time interval elapsed before the animals were exposed to the 2.5-min non-reinforced test session. Each drug combination data point was determined from the responding 18 animals. Similarly, in the LSD-trained animals, the percent LSD-appropriate responses produced by the administration of 0.024, 0.048, 0.096, and 0.120 mg/

kg of LSD were evaluated after pretreatment of these animals with saline, 0.1, 0.3, and 1.0 mg/kg of BC-105, and 0.1, 0.3, and 0.5 mg/kg of haloperidol. Doses of BC 105 or haloperidol were injected 55 min prior to the injection of each LSD dose. A subsequent 5-min time interval elapsed before the animals were exposed to the 2.5-min extinction test session. Each data point was determined from the responding 16 animals.

Data analysis. Data from both substitution and antagonism tests were analyzed using an analysis of variance (ANOVA) repeated measures design. Individual means were then compared with Duncan's multiple-range test.

Drugs: Doses of the following drugs were based on the weight of the salt: 5-OMe DMT (hydrogen oxalate salt) and BC-105 (pizotifen or pizotyline maleate, Sandoz Pharmaceuticals). Doses of lysergic acid diethylamide d-tartrate (N.I.D.A.) refer to the equivalent free base concentration. These drugs were dissolved in 0.9% saline and were prepared immediately before use. Haloperidol was obtained from McNeil Laboratories. All injections were given intraperitoneally.

Results and Discussion

Analysis of discrimination-responding, over the course of the study, revealed that in both groups of animals responding was consistently maintained above 85% on the drug-designated lever when under the drug condition, while the percent responding on the same lever following saline administration never exceeded 20%. Response rates under drug and non-drug conditions, in both groups, were not significantly different.

TABLE 1

Discriminative Stimulus Generalizations between 5-OMe DMT and LSD

Dose LSD (mg/kg)	Percent 5-OMeDMT Appropriate Responding in 5-OMeDMT trained rats (Mean±SEM, n=12)	Responses/ Minute (Mean±SEM)	Dose 5-OMeDMT (mg/kg)	Percent LSD Appropriate Responding in LSD trained rats (Mean±SEM, n=16)	Responses/ Minute (Mean±SEM)
Saline	18%(5.2)	13.3(1.9)	Saline	18%(4.4)	14.7(2.8)
0.024	42%(4.9)	17.0(3.8)	0.5	29%(6.4)	18.6(1.9)
0.048	69%(7.5)	19.2(2.3)	1.0	68%(4.6)	20.3(2.7)
0.096	85%(3.5)	13.5(2.0)	1.5	77%(3.9)	18.5(1.8)
5-OMeDMT-(1.5mg/kg)	89%(1.4)	17.5(2.0)	LSD-(0.096 mg/kg)	91%(2.3)	17.0(2.3)

The results of generalization tests between the two training groups is shown in Table 1. As can be seen, administration of LSD to 5-OMe DMT-trained animals produce dose-dependent 5-OMe DMT-like percent responding. Table 1 also shows that administration of 5-OMe DMT to LSD-trained animals produces dose-dependent LSD-like percent responding. Statistical comparisons between the groups revealed no significant differences in percent drug-lever responding after the administration of 0.096 mg/kg of LSD and 1.5 mg/kg of 5-OMeDMT in each group of animals. Thus, these doses of each compound were considered equieffective in terms of the behavioral responses that they generated.

The fact that stimulus generalization occurs between 5-OMe DMT and LSD when either drug is used as the training stimulus provides support for the conclusion that these compounds may share a common component to their CNS mechanism of action (6). This is not to suggest that the mechanism of action of these agents is exactly the same, but only that 5-OMe DMT and LSD may be exerting stimulus control by affecting a neuronal system common to both agents.

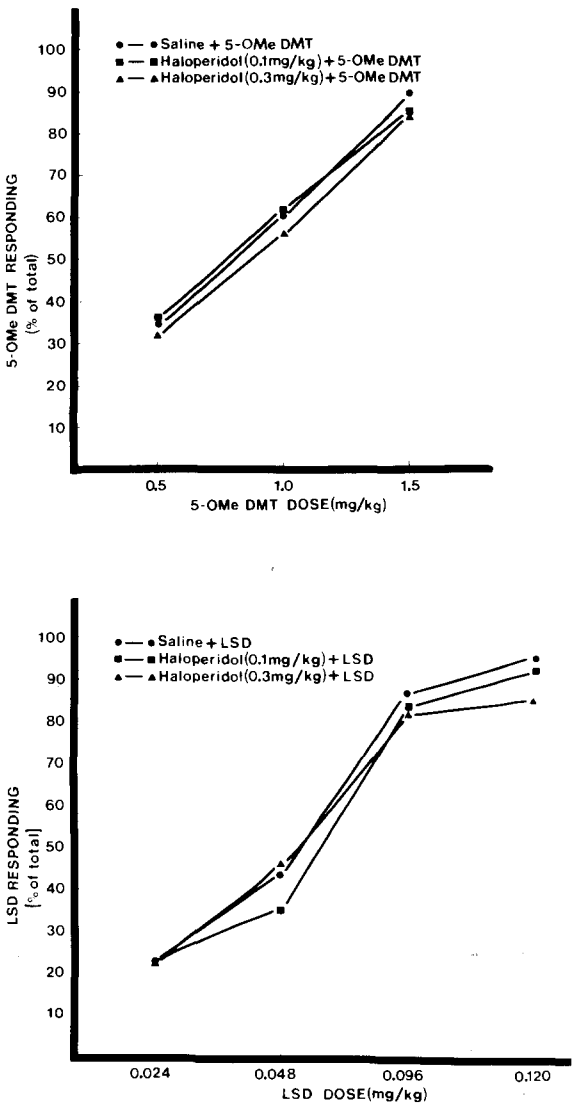

Fig. 1
The effects of various doses of haloperidol on 5-OMe DMT (left) and LSD (right) discriminative stimulus control.

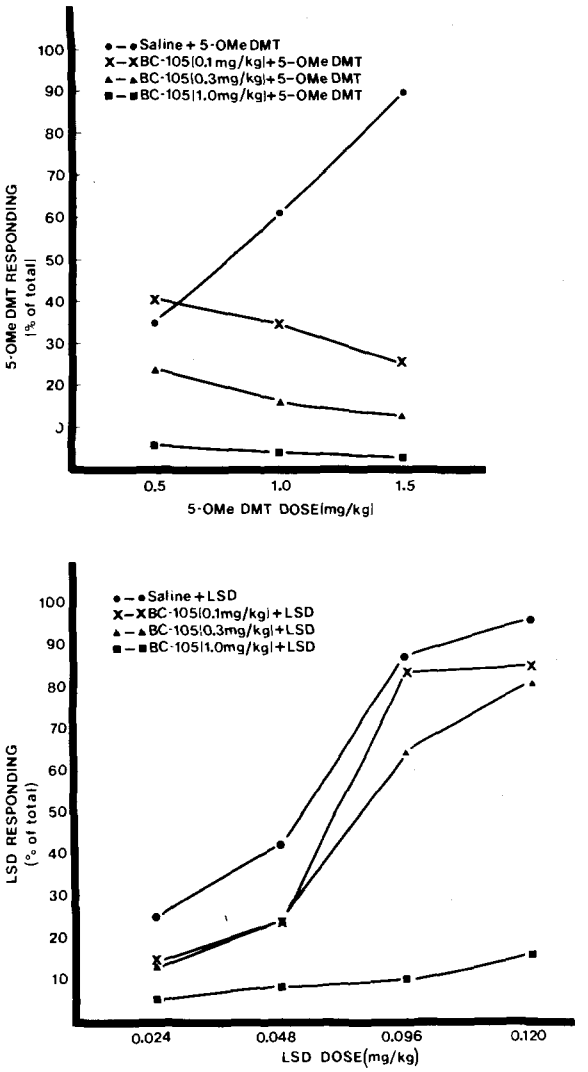

Fig. 2
The effects of various doses of BC-105 on 5-OMe DMT (left) and LSD (right) discriminative stimulus control.

The results of testing for antagonism of the drug stimuli by haloperidol and BC-105 are shown in Figures 1 and 2 respectively. In Figure 1 the results of tests with haloperidol in combination with various doses of 5-OMe DMT and LSD show that no significant shift occurred in either the 5-OMe DMT dose-response curve or the LSD dose-response curve. Pretreatment of the animals with 0.5 mg/kg of haloperidol in combination with 5-OMe DMT, and LSD resulted in complete disruption of behavior (i.e., no responding). These results are consistent with those of Kuhn, et al (8) who found that a variety of dopamine antagonists do not

attenuate the discriminative response of LSD (0.080 mg/kg). Taken together, these data suggest negligible involvement of dopamine systems in the stimulus effects produced by 5-OMe DMT and LSD.

In contrast, Figure 2 shows that pretreatment with BC-105 produces dose related decreases in percent 5-OMe DMT-lever responding and percent LSD-lever responding. At the pretreatment BC-105 dose level of 1.0 mg/kg the dose-response generalization curves of each training drug-stimulus declined to saline response levels, indicating a complete antagonism of each discriminative stimulus. However, it is of interest that the pattern of the BC-105 dose-response antagonism of these agents was different. In particular, this is shown by the fact that, even though both training stimuli effectively substituted for each other, the lower doses of BC-105 (0.1 and 0.3 mg/kg) produced significant attenuation of the 5-OMe DMT dose-response (1.0 and 1.5 mg/kg) while no significant attenuation of the LSD dose-response occurred. While difficult to explain, these data may reflect a subtle difference in the serotonergic aspects of their mechanism of action. Therefore, in conclusion, it might be stated that while the discriminative stimulus effects of 5-OMe DMT and LSD may be mediated, at least in part, via a common serotonergic system, the actions of these agents within that pharmacological system may be somewhat different.

Acknowledgements

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