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Mescaline and Lysergic Acid Diethylamide (LSD) as Discriminative Stimuli*

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Abstract. The observation that a particular drug state may acquire the properties of a discriminative stimulus is explicable on the basis of drug-induced interoceptive cues. The present investigation sought to determine (a) whether the hallucinogens mescaline and LSD could serve as discriminative stimuli when either drug is paired with saline and (b) whether discriminative responding would occur when the paired stimuli are produced by equivalent doses of LSD and mescaline. In a standard two-lever operant test chamber, rats received a reinforcer (sweetened milk) for correct responses according to a variable interval schedule. All sessions were preceded by one of two treatments; following treatment A, only responses on lever A were reinforced and, in a similar fashion, lever B was correct following treatment B. No responses were reinforced during the first five minutes of a daily thirty-minute session. It was found that mescaline and LSD can serve as discriminative stimuli when either drug is paired with saline and that the degree of discrimination varies with drug dose. When equivalent doses of the two drugs were given to the same animal, no discriminated responding was observed. The latter finding suggests that mescaline and LSD produce qualitatively similar interoceptive cues in the rat.

Key-Words: Mescaline — LSD — Discriminative Stimulus — Hallucinogen.

A discriminative stimulus is any feature of an animal's environment that is correlated with a schedule of reinforcement (Kelleher and Morse, 1968). Operant behavior which is reinforced only in the presence of a specified stimulus soon occurs with greater frequency in the presence of the stimulus than in its absence and the behavior is then said to be under the control of the stimulus. Discriminative stimuli may act on one or more of a variety of receptors, both external and internal. External stimuli, such as auditory or visual cues, act upon well defined sensory receptors. The observation that a particular drug state may acquire the properties of a discriminative stimulus may be explained on the basis of drug-induced interoceptive cues (Overton, 1968a).

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The present investigation was undertaken to determine (a) whether the hallucinogens mescaline and LSD could serve as discriminative stimuli when either drug is paired with the injection of saline and (b) whether discriminative responding would occur when the paired stimuli are produced by equivalent doses of LSD and mescaline. If discriminated responding occurred in the latter experiment, it would suggest that the interoceptive cues induced by mescaline and LSD are dissimilar. In contrast, the absence of discrimination would indicate that the difference between the interoceptive cues induced by the two drugs are insufficient to permit discriminated responding.

Methods

The subjects, female CFN strain rats (Carworth Farms) were maintained at 70—80% of their free-feeding weight, as determined from the growth chart provided by the supplier, by adjusted feedings after each experimental session. Sweetened condensed milk diluted 1:2 with water was the reinforcer. The equipment used was a standard two-lever operant test chamber (Lehigh Valley Electronics) equipped with a dipper for delivery of the reinforcer. After the rats learned to drink from the dipper they were trained to depress first one and then the other of the two levers with each bar press resulting in delivery of the reinforcer. After responding was established on both levers, discriminative training was begun. The procedure and schedule of reinforcement were similar to those described by Kubena and Barry (1969). In four preliminary sessions of twenty minutes duration, each correct bar-press was reinforced. Subsequent sessions were thirty minutes long with no responses being reinforced in the first five minutes and a variable interval 1 min schedule (VI 1) in effect for the final twenty-five minutes. All sessions were preceded by one of two treatments; following treatment A, only responses on lever A were reinforced and in a similar fashion, lever B was correct following treatment B. Lever A was the left lever for one-half of each group and for the other animals lever A was the right lever. In the four preliminary sessions, treatments A and B were alternated on successive days; thereafter, two sessions of one treatment were followed by two sessions with the other treatment.

Three groups of four rats each were used. For rats in group I, drug treatment A was mescaline (40 μmol/kg) and treatment B was isotonic saline. For group II, LSD (0.25 μmol/kg) and saline were the two treatments. After discrimination was established for groups I and II, dose-effect curves were obtained. The same animals continued to receive treatments A and B. However, two-fifths of the sessions were preceded by the injection of a variable dose of mescaline in group I and LSD in

group II. These sessions were of five minutes duration and were always preceded and followed by at least one training session. From the resultant curves, doses of mescaline and LSD which were equivalent in terms of their ability to produce discriminated responding when paired with saline were selected. These doses of mescaline and LSD (40 μmol/kg and 0.06 μmol/kg, respectively) were then used as treatments A and B for rats in group III. For groups I and II, the two-sample rank test (Goldstein, 1964) was used to determine the statistical significance of the difference between the percentage of drug-correct responses following the administration of drug and saline. The same test was applied to the difference between the percentage of LSD-correct responses following the injection of LSD and mescaline in group III. The level of significance selected was $P = 0.05$ (two-tailed test).

Mescaline HCl was purchased from Aldrich Chemical Company, Inc., Cedar Knolls, New Jersey. LSD tartrate was obtained from the National Institute of Mental Health. Both drugs were dissolved in 0.9% sodium chloride and injected i.p. in a volume of 1 ml per kilogram of body weight. Doses of LSD and mescaline are expressed as μmol/kg (0.25 μmol LSD tartrate = 120 μg; 40 μmol mescaline HCl = 9.9 mg).

Results

Fig. 1 A shows the results when the treatments were mescaline and saline (Group I). The percentage of mescaline-correct responses following mescaline is significantly different from the percentage of mescaline-correct responses after saline ($P < 0.01$). When the dose of mescaline was increased from 30 μmol/kg to 40 μmol/kg (session block 11), the degree of discrimination appeared to increase. Indeed, if discriminated responding is a consequence of the pharmacologic effects of mescaline, then the dose of mescaline and the degree of discrimination should vary concomitantly, i.e., one should observe a typical dose-effect relationship. Such a relationship is shown in Fig. 1 B. Doses of 5 and 10 μmol/kg resulted in responding appropriate for saline treatment, 20 μmol/kg produced essentially random responding, and doses of 40 or 80 μmol/kg were followed by a majority of responses on the mescaline-correct lever. The results for group II (LSD 0.25 and saline) are shown in Fig. 2. The mean of LSD-correct responses following LSD is significantly different from the mean after saline ($P < 0.01$). In retrospect, it is apparent that the dose of LSD selected for initial discrimination training (0.25 μmol/kg, Fig. 2 A) is relatively high, thus providing a possible explanation for the more rapid acquisition of the discrimination following LSD as compared with mescaline. Again, the expected dose-effect relationship was obtained (Fig. 2 B).

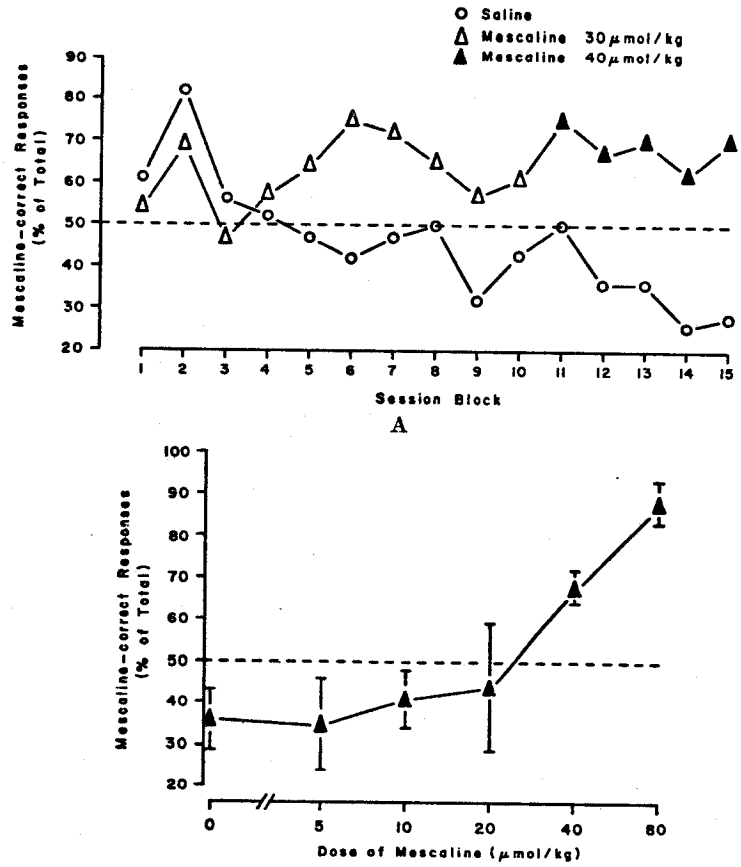
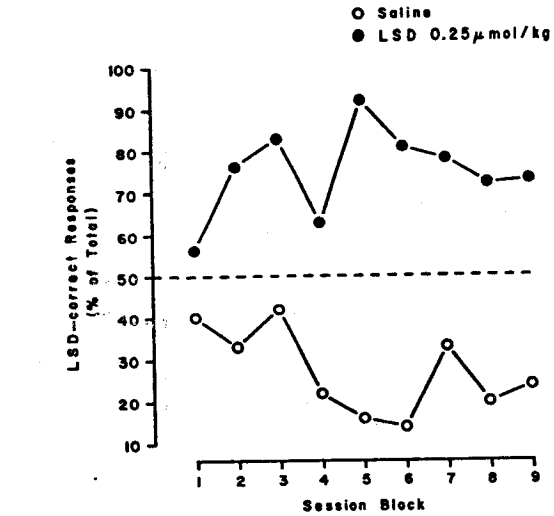


Fig. 1. A. Discriminated responding following the injection of mescaline or saline. Each point is the mean of two determinations in each of four animals. Circles represent experiments in which saline was injected five minutes before the session. Triangles represent identical experiments in which either 30 μmol/kg (△) or 40 μmol/kg (▲) of mescaline was given. Ordinate: number of responses on the mescaline-correct lever in the first five minutes of the session, expressed as a percentage of total responses. Abscissa: successive blocks of four sessions. Although the corresponding experiments with mescaline and saline are shown to be contemporaneous, on a given day two of the rats received mescaline and the other two were treated with saline. B. Dose-effect curve for discriminated responding after injection of mescaline. In sessions subsequent to those described in part A of this figure, the same animals continued to receive saline and mescaline (40 μmol/kg). However, two-fifths of the sessions were preceded by the injection of a variable dose of mescaline. Ordinate: number of responses on the mescaline-correct lever expressed as a percentage of total responses. Abscissa: dose of mescaline in μmol/kg plotted on a log scale. Each point represents the mean of four determinations in each of four animals. Vertcial lines indicate ± S.E. These values were estimated from the range of the mean values for the four subjects according to the method of Wilcoxin and Wilcox (1964)



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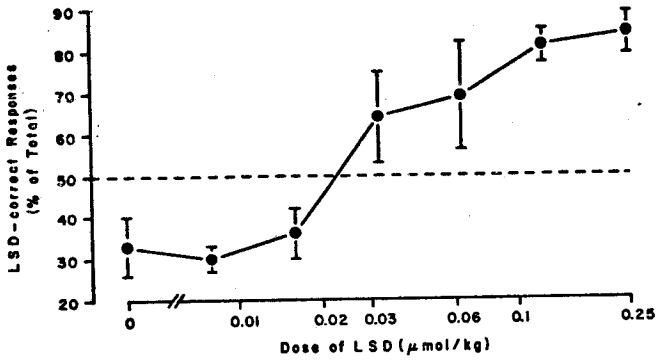

B

Fig. 2. A. Discriminated responding following the injection of LSD or saline. Closed circles: LSD (0.25 μmol/kg); open circles: saline. All other details are as in Fig. 1 A. B. Dose-effect curve for discriminated responding after injection of LSD. Each point represents the mean of three determinations in each of four animals. All other details are as in Fig. 1 B

The data of Figs. 1 B and 2 B show that 40 μmol/kg mescaline (Fig. 1 B, 68 % mescaline-correct responses) and 0.06 μmol/kg LSD (Fig. 2 B, 69 % LSD-correct responses) are equivalent in their ability to produce discriminated responding when paired with saline. The results obtained when these doses of mescaline and LSD were the two treatments (group III) are shown in Fig. 3. No consistent effect on discriminated responding

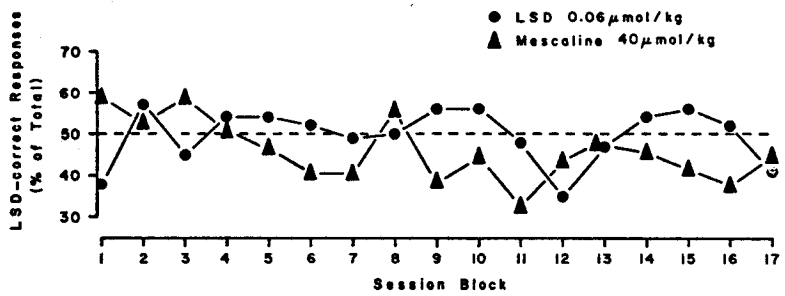

Fig. 3. Discriminated responding following the injection of equivalent doses of LSD and mescaline. Each point is the mean of two determinations in each of four animals. Circles: LSD (0.06 μmol/kg); triangles: mescaline, (40 μmol/kg)

Table 1. *Effect of drug treatment on overall rate of responding during the first five minutes of each session*

Group	Subjects/ group	Treatment (μmol/kg)	Re- plications	Rate (responses/min)
I	4	saline	10	5.14
		mescaline (40)	10	6.08
II	4	saline	22	7.94
		LSD (0.06)	12	6.28
		LSD (0.25)	18	5.46
III	4	mescaline (40)	34	7.36
		LSD (0.06)	34	7.20

was observed. For the 17 blocks of sessions tested, 50% of the total responses following LSD were on the LSD-correct lever while 46% of all responses following mescaline were on the LSD-correct lever. This difference is not statistically significant. The overall pattern in the 17 blocks appears cyclic and at times the data suggest that discriminated responding has occurred, e. g., blocks 5—7, 9—11 and 14—16. Despite these qualifications, there is no consistent evidence of discriminated responding following the repeated administration of these doses of LSD and mescaline.

The Table 1 summarizes the effect of LSD and mescaline on the overall rate of responding during the first five minutes (unreinforced) of each session. Correct as well as incorrect responses are included. The three groups are seen to be comparable in terms of response rate and only modest changes in rate followed the administration of LSD or mescaline.

Discussion

Results of the present experiments indicate that the hallucinogens, LSD and mescaline, can serve as discriminative stimuli in the rat when either drug state is paired with the injection of saline. These results and those of previous workers (Conger, 1951; Steward, 1962; Barry *et al.*, 1965; Overton, 1966, 1968b; Kubena and Barry, 1969) leave little doubt that animals can discriminate between drugged and non-drugged states. However, the question as to whether animals can distinguish the states produced by two different drugs is not so readily answered. If a subject shows differential responding under the influence of two drugs, we might conclude that a qualitative difference exists between the interoceptive cues produced by the drugs. However, Overton (1968b) has shown that rats can distinguish the effects of two different doses of the same drug (pentobarbital). Similarly, the data of Figs. 1B and 2B very strongly suggest that discriminated responding would occur following two different doses of either mescaline or LSD. Discriminated responding after two different drugs may thus reflect differences in degree rather than in kind. However, the dose-effect curves for mescaline and LSD permit us to select doses of the two drugs which are equivalent in terms of their ability to produce discriminated responding when paired with saline.

When equivalent doses of mescaline and LSD were paired, discriminated responding did not occur (Fig. 3). This observation is most simply explained by the assumption that the two drugs have similar effects in the rat. Although this assumption is congruent with the results of experiments in man (Holluster, 1968) and could be tested further by comparison of equivalent doses of drugs which in man produce different physical and subjective effects, other plausible explanations remain for the data of Fig. 3. For example, LSD and mescaline, when given on a daily basis, may produce an impairment of discrimination learning which is not apparent when either drug is paired with saline and administered only two or three times per week.

If discriminated responding following drug administration is dependent upin non-specific interoceptive cues produced by the drug, we might expect any effect of any drug to be able to serve as a discriminative stimulus. However, Overton (1968a) has stated that "many centrally acting drugs acquire control of differential responses very slowly, if at all" and that „barbiturates and anticholinergics acquire control via relatively unique drug actions". Whether or not Overton is correct in postulating a "unique drug action", the list of drugs able to produce discriminated responding must be extended to include LSD and mescaline.

A final point for discussion concerns our contention that dose-effect curves such as those shown in Figs. 1B and 2B permit the selection

of equivalent doses of two or more drugs. Overton (personal communication) has suggested that the training dose is an important variable in the dose-effect curve subsequently obtained. The present data do not warrant speculation on this point nor are we aware of published data which permit a definitive statement. However, two things are clear: (a) the hypothesis that a family of dose-effect curves will be obtained if a range of training doses is testable and (b) the use of the dose-effect curves for LSD and mescaline in the present study did, in fact, lead to the selection of doses of the drugs which proved to be equivalent as shown in Fig. 3.

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