

## Lysergic Acid Diethylamide (LSD) as a Discriminative Cue: Drugs with Similar Stimulus Properties\*

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**Abstract.** Rats were trained to choose between the arms of a T-maze apparatus according to whether they were injected i.p. with 0.1  $\mu\text{mol/kg}$  LSD or 0.9% saline. The LSD drug-state acquired the properties of a discriminative stimulus, possibly by producing interoceptive cues. Doses of 9.0  $\mu\text{mol/kg}$  psilocybin and 90 and 120  $\mu\text{mol/kg}$  mescaline produced cueing effects which were not significantly different from the cueing effect of LSD. However, d-amphetamine (14.8 and 29.6  $\mu\text{mol/kg}$ ) did not appear to produce an LSD-like cue. These results suggest that LSD, mescaline and psilocybin, when administered in functionally equivalent doses, produce qualitatively similar interoceptive cues in the rat.

**Key words:** LSD — Mescaline — Psilocybin — State-Dependent Learning.

### Introduction

LSD and mescaline have been shown to act as discriminative stimuli in the rat when either drug is paired with saline (Hirschhorn and Winter, 1971). These investigators also reported that when equivalent doses of LSD and mescaline were administered to the same experimentally-naive rat, the animal was unable to learn to discriminate between them, and suggested that these two psychotomimetic agents produced qualitatively similar interoceptive cues. Clinical evidence has shown that three of the commonly abused psychotomimetic agents, viz., LSD, mescaline and psilocybin, produce basically similar clinical syndromes when administered to the same human subjects in doses found to be functionally equivalent (Hidalgo, 1960; Hollister and Hartman, 1962; Wolbach *et al.*, 1962; Hollister and Sjoberg, 1964). The present exploratory investigation sought to train rats to discriminate between the effects of intraperitoneally administered LSD (0.1  $\mu\text{mol/kg}$ ) and saline, and to test various doses of mescaline, psilocybin, and amphetamine to see if these agents could produce an LSD-like cueing effect.

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### Methods

Female CD rats, purchased from Charles River Breeding Laboratories (Wilmington, Mass.), were food deprived to 75% of their predicted free-feeding weights, and trained to choose between the arms of a T-maze according to whether they were injected with 0.1  $\mu\text{mol/kg}$  LSD or an equal volume of 0.9% saline. Training procedures were similar to those described previously (Schechter and Rosecrans, 1972). Those subjects that attained an 80% first choice response correct criterion for ten consecutive training days ( $N = 8$ ) were consequently tested with mescaline, psilocybin, and d-amphetamine to test the ability of these agents to produce an LSD-like cueing effect. The discrimination training sessions were continued on Mondays, Wednesdays and Fridays, with randomly assigned administration of either saline or LSD. Experimental drugs were given on Tuesdays and Thursdays and were administered 10 min prior to a single testing trial. Drugs were obtained from either Aldrich Chemical Co., Inc. Cedar Knoll, N.J., or the N.I.M.H., and were administered i.p. in a saline vehicle (1 ml/kg).

### Results

The results of discrimination trials on testing-training days with 0.1  $\mu\text{mol/kg}$  LSD and saline, as well as responses made with other drugs appear in Table 1. In the three experiments conducted, rats made the "LSD-correct" choice in 81.6–92.5% of the trials following LSD. In 3 trials, in each rat at each dose of mescaline, the two highest doses of mescaline (90 and 120  $\mu\text{mol/kg}$ ) elicited responses into the LSD-arm that were not significantly different than those after training doses of LSD. Analogous results were obtained with psilocybin as the "LSD-correct" arm was entered into 91.7% of the time following the administration of 9.0  $\mu\text{mol/kg}$  of this drug. In contrast to these results, the "LSD-correct" arm was entered in 35.7–42.9% of the time following 14.8 or 29.6  $\mu\text{mol/kg}$  of d-amphetamine. The results indicated that mescaline and psilocybin, but not amphetamine, were perceived by LSD trained rats as being like LSD.

### Discussion

The present study, employing a T-maze apparatus to successfully train rats to discriminate between 0.1  $\mu\text{mol/kg}$  LSD and saline, has shown that doses of psilocybin (9  $\mu\text{mol/kg}$ ) and mescaline (90 and 120  $\mu\text{mol/kg}$ ) produce cueing effects in the rat similar to the cueing effect produced by LSD. On a molar basis, this indicates that LSD is 90 times as potent as psilocybin and 900 times as potent as mescaline in eliciting the same behavioral response. The ability of a discriminative cueing effect produced by LSD to be transferred to mescaline and psilocybin indicates that these three hallucinogenic agents produce similar interoceptive cueing effects in rats. This is in agreement with observations of cross-tolerance

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Table 1. *Effect of mescaline, psilocybin, and amphetamine, on a discrimination between LSD and saline*

Drug	Dose <sup>a</sup>	No. of trials	% Responses into LSD-correct arm
<i>Experiment 1</i>			
Saline	—	80	15.0 <sup>d</sup>
LSD	0.1	80	92.5 <sup>e</sup>
Mescaline	30	24	45.8 <sup>d</sup>
	60	24	62.5 <sup>d</sup>
	90	24	83.3 <sup>d</sup>
	120	24	87.5
<i>Experiment 2</i>			
Saline	—	56	16.1 <sup>d</sup>
LSD	0.1	56	91.1 <sup>e</sup>
Psilocybin	3.0	24	58.3 <sup>d</sup>
	6.0	24	66.7 <sup>d</sup>
	9.0	24	91.7
<i>Experiment 3</i>			
Saline	—	49	12.4 <sup>d</sup>
LSD	0.1	49	81.6 <sup>e</sup>
Amphetamine	14.8	14	42.9 <sup>d</sup>
	29.6	14	35.7 <sup>d</sup>

<sup>a</sup> Doses of drugs were expressed as micromoles per kg (0.1  $\mu$ mol of LSD tartrate = 0.048  $\mu$ g; 30  $\mu$ mol of mescaline HCl = 7.43 mg; 3  $\mu$ mol psilocybin = 0.852 mg; 14.8  $\mu$ mol of amphetamine = 2 mg).

<sup>b</sup>  $n = 8$ .

<sup>c</sup>  $n = 7$ . One subject fell below criterion and was deleted from the analysis for that series.

<sup>d</sup> Probability of difference from LSD (0.1  $\mu$ mol/kg) score being due to chance;  $p < 0.001$ . Chi square test.

<sup>e</sup> Probability of difference from saline score being due to chance;  $p < 0.001$ . Chi square test.

between drugs in man (Balestrieri and Fontanari, 1959; Wolbach *et al.*, 1962) and rats (Freedman and Aghajanian, 1959; Appel and Freedman, 1968; Winter, 1971).

The hypothesis has been offered that, under certain conditions, LSD and amphetamine produce similar c.n.s. effects (Bradley and Key, 1958), and it has been suggested that both agents act as excitants on the reticular formation (Hamilton, 1960). The present study observed that 14.8 and 29.6  $\mu$ mol/kg (2–4 mg/kg) d-amphetamine sulfate, within the dose range used previously to condition state-dependent learning to amphetamine (Overton, 1971), did not produce an LSD-like cue in rats. In rats trained to discriminate between d-amphetamine and saline, LSD administration failed to produce an amphetamine-like cueing effect (Schechter and Rosecrans, submitted for publication). The observations

would suggest that LSD and amphetamine produce cueing effects that are different and distinguishable in the rat, recalling the observations that amphetamine does not exhibit cross tolerance with LSD in humans (Rosenberg *et al.*, 1963). However, this last observation should be viewed cautiously until a more comprehensive study comparing these two drugs can be made.

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*Abstract*  
The animal was placed in a goal box. In the presence of the drug, it readily and quickly learned which stimulus was associated with the administration of the drug.

During the experiment, the animal learned that the drug was associated with the goal box. It was often observed that the animal learned to associate the drug with the goal box before learning to associate the drug with the goal box. This suggests that the drug was associated with the goal box before learning to associate the drug with the goal box. Motivated behavior was observed.

The final result was that the animal learned to associate the drug with the goal box by water.