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Differences in the Stimulus Properties of Barbital and Hallucinogens[1]

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HIRSCHHORN, I. D. AND J. C. WINTER. *Differences in the stimulus properties of barbital and hallucinogens.* PHARMAC. BIOCHEM. BEHAV. 3(3) 343–347, 1975. – The present investigation sought to determine whether drugs which produce markedly different perceptual effects in man, barbital and mescaline or LSD produce different stimuli in rats. In a standard 2 lever operant test chamber, rats received sweetened milk for correct responses according to a variable interval schedule. All sessions were preceded by 1 of 2 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 5 min of a daily 30 min session. It was found that barbital can serve as a discriminative stimulus when this drug is paired with saline. Previously, we had demonstrated that mescaline or LSD can serve as discriminative stimuli. When barbital was administered to animals trained to discriminate mescaline or LSD and saline, they made either random responses or responses appropriate to saline treatment. This observation suggests that the stimulus properties of barbital are difference from those of the hallucinogens. A subsequent demonstration of discriminated responding when barbital and mescaline or LSD were paired as discriminative stimuli supports this conclusion. The present results extend previous findings which suggest that the degree of similarity or difference of drug stimuli in rats is congruent with the degree of similarity or difference of perceptual drug effects in man.

Discriminative stimulus Hallucinogens Mescaline Lysergic acid diethylamide (LSD) Barbital Sedative-hypnotics

MANY drugs have among their most prominent actions, effects which are perceptual or sensory in nature. The hallucinogens are a prime example of this kind of drug. Hallucinogens have been defined [2] as drugs "which will consistently produce changes in thought, perception, and mood, occurring alone, or in concert, without causing major disturbances of the autonomic nervous system or other serious disability." Alterations in thought, perception, and mood are readily studied in man but selection of relevant variables in nonverbal species is a matter of controversy. For this reason, a wide variety of variables have been utilized, ranging from unconditioned behavior such as web building in spiders [12] to conditioned behavior [10], but none of these has received widespread acceptance. However, the observation that drugs can serve as controlling or discriminative stimuli in animals [1,8] indicates that these agents produce effects which animals can distinguish from the nondrug condition. The discriminative stimulus effect of drugs seems a more appropriate behavioral variable for studying perceptual drug effects than others heretofore employed. There is evidence which suggests that drugs which produce similar perceptual effects in man produce similar effects in animals. For example, we have previously reported [6] that either mescaline or lysergic acid diethylamide (LSD), which produce similar clinical syndromes, can function as a discriminative stimulus in the rat when either drug state is paired with the injection of saline. However, when mescaline and LSD were paired as discriminative stimuli in the same animals, no discriminated responding occurred. The present investigation was undertaken to further explore the validity of the drug discrimination model as an animal analogue of perceptual drug effects in man. Specifically, we sought to determine whether drugs which produce markedly different perceptual effects in man, barbital and mescaline or LSD, produce different stimuli in rats. This was tested in stimulus generalization experiments and in experiments which paired as discriminative stimuli, barbital with mescaline and barbital with LSD.

METHOD

Animals and Apparatus

The animals were CFN strain female rats obtained from Carworth Farms, New City, N.Y. They were maintained at

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80 percent of their expected free feeding weight, as determined from the supplier's growth chart, by adjusted feedings after each experimental session. Water was freely available in individual home cages. The equipment used was a standard operant test chamber (Lehigh Valley Electronics) with 2 levers on the same wall and a dipper for delivery of reinforcement centered between them. Sweetened condensed milk diluted 1:2 with water was the reinforcer. The discrimination training procedure has been previously described [6]. Prior to discrimination training, rats were trained to press each of the 2 levers. In 4 preliminary sessions of 20 min duration, each correct bar press was reinforced. Subsequent sessions were 30 min long with no responses being reinforced in the first 5 min and a variable interval 1 min schedule (VI-1) in effect for the final 25 min. All sessions were preceded by 1 of 2 treatments; following Treatment A, only responses on Lever A were reinforced and, in a similar fashion, Lever B was correct following Treatment B. In the 4 preliminary sessions, Treatments A and B were alternated on successive days; thereafter, 2 sessions of one treatment were followed by 2 sessions with the other treatment.

Procedure

Five groups of 4 rats each were used. The drug treatments for these various groups are presented in Table 1. The rats of Groups 3, 4 and 5 had no prior drug or behavioral experience. Groups 1 and 2 had been used in a previous study [6] in which they had been trained to discriminate mescaline and saline or LSD and saline, respectively. Because rats can distinguish the effects of two different doses of the same drug [8], it is essential when two different drugs are paired as discriminative stimuli, that their doses are equated. The doses of barbital and mescaline used in Group 4, and barbital and LSD in Group 5 are equivalent in terms of their ability to produce discriminated responding when paired with saline. These doses were obtained from dose-effect curves (see below).

Dose-effect curves for Groups 1, 2 and 3 were obtained after discrimination was established. The same animals continued to receive Treatments A and B. However, approximately two-fifths of the sessions were preceded by the injection of a variable dose of mescaline in Group 1, LSD in Group 2 and barbital in Group 3. Variable doses were administered in a mixed sequence. These sessions were of 5 min duration and were always preceded and followed by at least one training session. The procedure used to obtain stimulus generalization curves is essentially the same as that described for dose-effect functions. Instead of the injection of a variable dose of the training drug, various doses of a novel drug were given. Wilcoxon's signed-ranks test [4] was used to test the statistical significance of the differential responding after Treatments A and B. The level of significance selected was $p = 0.05$ (two-tailed test). Standard errors for dose-effect curves were estimated from the range of the mean values for each subject according to the method of Wilcoxon and Wilcox [11].

D-lysergic acid diethylamide tartrate (LSD) was obtained from the National Institute of Mental Health. Mescaline HCl was purchased from Aldrich Chemical Company, Inc., Cedar Knolls, New Jersey. All drugs were dissolved in 0.9% sodium chloride and injected, IP, in a volume of 1 ml/kg 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). Drugs were injected 5 min prior to the start of experimental sessions.

RESULTS

Figure 1a shows the results of stimulus generalization tests with barbital in rats trained to discriminate mescaline and saline (Group 1). In the regular training session (see Methods) during these stimulus generalization tests, 65 percent of the total responses (in the unreinforced initial 5 min) following mescaline were on the mescaline-correct lever, while 37 percent of all responses following saline were on the mescaline-correct lever. Each of the four doses of barbital tested resulted in approximately 50 percent mescaline-correct responses. It was not possible to test a higher dose of barbital because 160 mg/kg produced acute effects, most notably salivation and ataxia; animals stopped responding within 10 min of injection. The results of stimulus generalization tests with barbital in rats trained to dis-

TABLE 1

ASSIGNMENT OF DRUG TREATMENTS

Group	Number of Rats	Treatment* A	Treatment* B
1	4	Mescaline (40 μmol)	Saline
2	4	LSD (0.06 μmol)	Saline
3	4	Barbital (80 mg)	Saline
4	4	Barbital (80 mg)	Mescaline (40 μmol)
5	4	Barbital (80 mg)	LSD (0.06 μmol)

*All doses per kg body weight

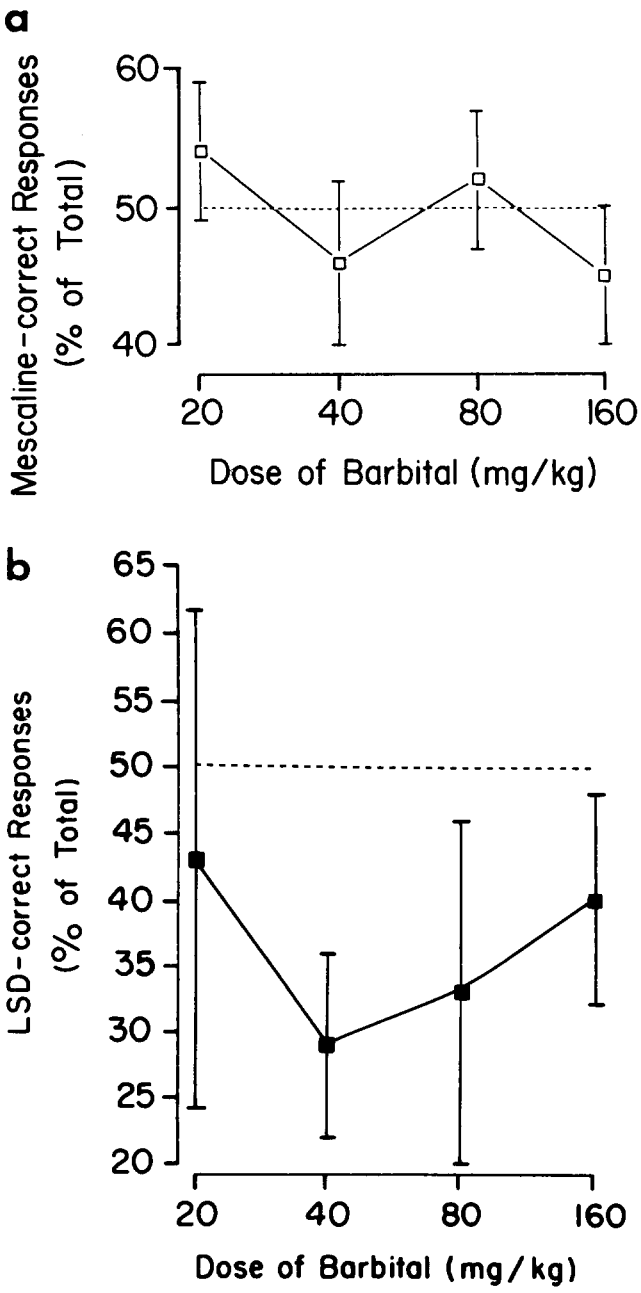

FIG. 1. Generalization of discriminated responding after the injection of mescaline and saline (a) or LSD and saline (b) to barbital. After animals learned to discriminate mescaline from saline or LSD from saline, 5 min test sessions in which no responses were reinforced, were interposed among discrimination training sessions. Various doses of barbital were administered in test sessions. Each point is the mean of 3 determinations in each of 4 animals. Ordinate: number of responses on mescaline-or LSD-correct lever expressed as a percentage of total responses. Abscissa: dose of barbital in mg/kg plotted on a log scale. Vertical lines indicate ± S. E. M.

criminate LSD and saline (Group 2) are shown in Fig. 1b. A high degree of discrimination was maintained during the regular training session; 78 percent of the total responses following LSD were on the LSD-correct lever and 25 percent of the responses after saline were on the LSD-correct lever. All doses of barbital tested produced responding appropriate for saline treatment. The data of Figs. 1a and 1b suggest that the stimulus effects of barbital differ from the stimulus effects of mescaline and LSD. A demonstration of discriminated responding when barbital and mescaline or LSD are paired as discriminative stimuli would provide further support for this conclusion.

Figure 2a shows that barbital can serve as a discriminative stimulus when this drug is paired with saline (Group 3). In Session Block 6, the dose of barbital was increased in order to increase the degree of discrimination. The mean percentage of barbital-correct responses is 54 percent after barbital and 30 percent after saline ($p<0.01$). One rat of the four in this group had a severe response bias toward the saline-correct lever (25 percent barbital-correct responses during barbital sessions, 12 percent barbital-correct responses during saline sessions) which lowered the mean percentage of barbital correct responses for both barbital and saline sessions in Fig. 2a. The difference between responding following barbital and responding after saline was statistically significant ($p<0.01$) for this animal. However, since this pattern of discriminated responding was atypical, data from this animal were excluded from the dose-effect function (Fig. 2b). Barbital has an extremely long duration of action in man [5]. Therefore, one might ask whether effects from the first day of barbital administration are still present when barbital is given again on the following day. This would result in a cumulative effect of barbital on the second day of administration and, possibly, a greater percentage of barbital-correct responses as compared to the first day of barbital administration. However, these rats responded almost equally on both days; they averaged 54 percent barbital-correct responses on the first day they received barbital and 56 percent barbital-correct responses on the second day.

From the dose effect relationship (Fig. 2b), it is apparent that 80 mg/kg of barbital produced 71 percent barbital-correct responses. This degree of discrimination is approximately equivalent to the 68 percent mescaline-correct responses produced by 40 μmol/kg of mescaline and the 69 percent LSD-correct responses produced by 0.06 μmol/kg of LSD [6]. The results obtained when these doses of barbital and mescaline were the two treatments are shown in Fig. 3a. Rapid development of discriminated responding is apparent ($p<0.01$). Similarly, when barbital and LSD were paired as discriminative stimuli (Fig. 3b) discriminated responding occurred ($p<0.01$).

DISCUSSION

The results of the present investigation indicate that the stimulus properties of barbital are markedly different from the stimulus properties of both mescaline and LSD. Evidence for this conclusion comes from two kinds of experiments. In the first, mescaline and LSD each were paired with saline as discriminative stimuli. After discriminated responding was established these rats were given various doses of barbital in stimulus generalization tests. Neither the mescaline nor the LSD stimulus generalized to barbital. In the second kind of experiment, barbital was paired with mescaline and with LSD as discriminative stimuli. Discriminated responding occurred in both cases. The observation that barbital produces a stimulus in rats which is different from that of mescaline or LSD is consistent with clinical data. Barbital, a sedative hypnotic [5], produces perceptual effects in man which are very different from those of the

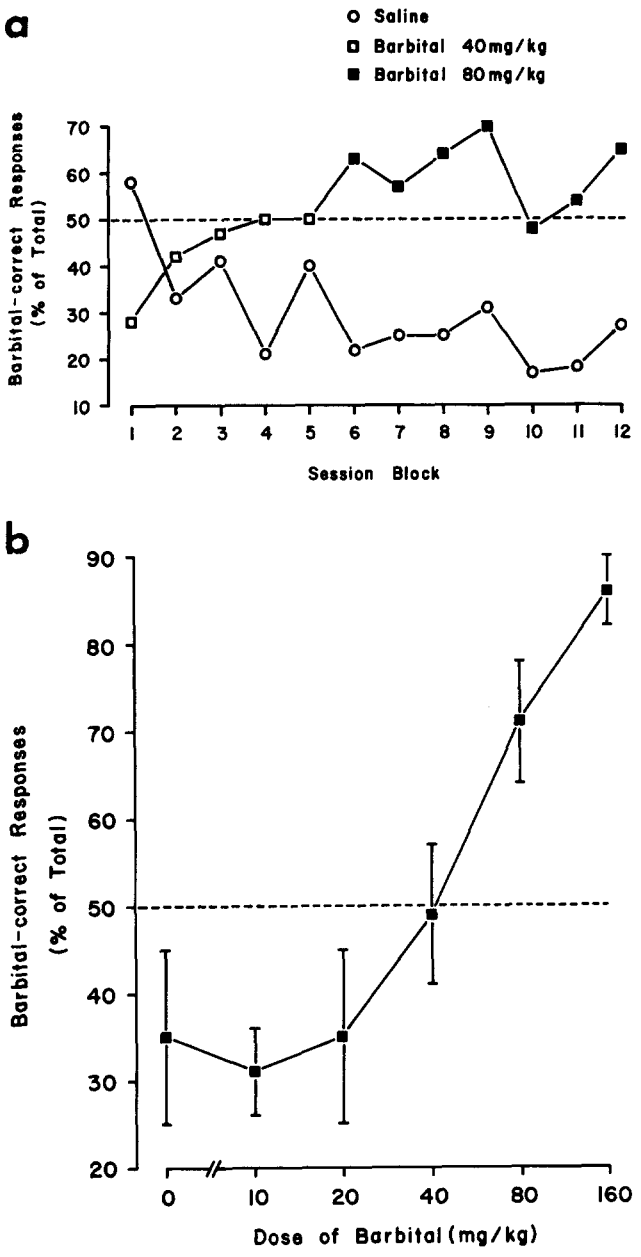

FIG. 2. (a) Discriminated responding following the injection of barbital or saline. Each point is the mean of 2 determinations in each of 4 animals. On any given day, one-half of the animals were given barbital and the remainder given saline. Ordinate: number of responses on the barbital-correct lever expressed as a percentage of total responses. Abscissa: successive blocks of 4 sessions each. (b) Dose-effect curve for discriminated responding after injection of barbital. Five min test sessions during which no responses were reinforced, were interposed among discrimination training sessions subsequent to those shown in Fig. 1a. Various doses of barbital were administered in test session. Ordinate: number of responses on the barbital-correct lever expressed as a percentage of total responses. Abscissa: dose of barbital in mg/kg plotted on a log scale. Each point represents the mean of 3 determinations in each of 3 animals. Vertical lines indicate ± S. E. M.

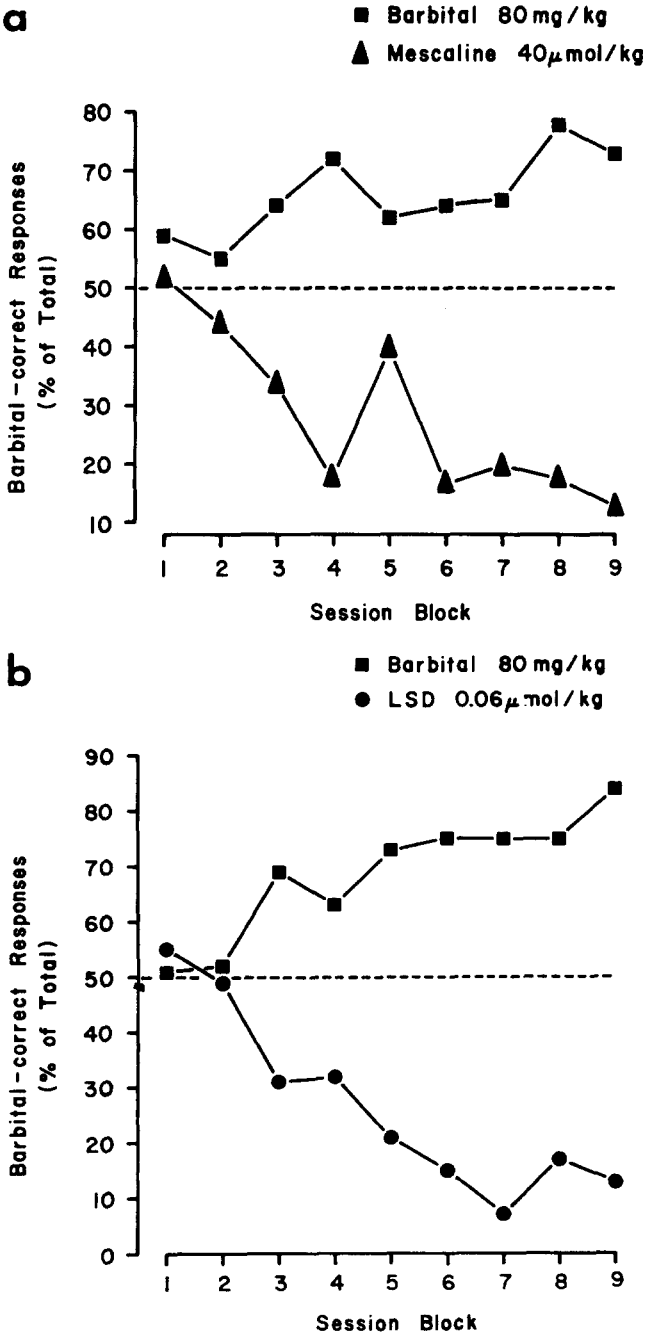

FIG. 3. Discriminated responding following the injection of barbital and mescaline (a) or barbital and LSD (b) Each point represents the mean of 2 determinations in each of 4 animals. Ordinate: number of responses on the barbital-correct lever expressed as a percentage of total responses. Abscissa: successive blocks of 4 sessions each.

hallucinogens, mescaline and LSD. These results extend previous findings [3, 7, 9] which suggest that the degree of similarity or difference of drug stimuli in rats is congruent with the degree of similarity or difference of perceptual drug effects in man. Further investigation of the stimulus properties of drugs as a measure of perceptual drug effects seem warranted.

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