J. Pharmacol. exp. Ther. 177, 461-467 (1971). LSD 2143

Vol. 177

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Vol. 177, No. 2
Printed in U.S.A.

EFFECT OF MESCALINE AND LYSERGIC ACID DIETHYLAMIDE ON FLICKER DISCRIMINATION IN THE RAT[1, 2]

MARTIN D. SCHECHTER[3] AND J. C. WINTER

Department of Pharmacology, School of Medicine, State University of New York at Buffalo, Buffalo, New York

Accepted for publication January 3, 1971

ABSTRACT

SCHECHTER, MARTIN D. AND J. C. WINTER: Effect of mescaline and lysergic acid diethylamide on flicker discrimination in the rat. J. Pharmacol. Exp. Ther. 177: 461–467, 1971. Rats were trained on a multiple schedule of positive reinforcement. A stationary light source flickering at 100 cps provided the discriminative stimulus (S^d). In the presence of S^d, reinforcement was contingent upon a fixed ratio 10 schedule. The same light source flickering at either 20 or 30 cps constituted the S^Δ period. Mescaline, at doses of 40 and 60 μmole/kg, produced a significant decrease in discriminative ability, whereas lysergic acid diethylamide (0.2, 0.3 and 0.4 μmole/kg) caused a significant increase. A dose of mescaline (20 μmol/kg) which by itself had no significant effect on discrimination, significantly reduced the increase caused by lysergic acid diethylamide. Likewise, a subeffective dose of lysergic acid diethylamide (0.1 μmol/kg) significantly antagonized the depression of discriminative ability caused by mescaline. These results indicate that flicker discrimination provides a sensitive measure of drug action in the rat. The pharmacologic data suggest that lysergic acid diethylamide and mescaline are mutually antagonistic in this system.

The clinical effects of mescaline and lysergic acid diethylamide (LSD) are quite similar although LSD is the more potent drug. In man, both substances produce alterations in visual perception including hallucinations (Hollister, 1968). In attempts to obtain an objective measure of the effects of drugs on visual perception, several investigators have studied drug-induced alterations in the critical flicker frequency (Adler *et al.*, 1950; Landis, 1954; Turner, 1968). Turner (1968) defines the critical flicker frequency (CFF) as the "fastest rate at which a flickering source of light appears to be flickering as opposed to being steady." In general, substances classified as depressants decrease the CFF whereas stimulants increase it. However, results of studies on the effect of LSD on CFF are contradictory. Holliday and Sharpley (1965) reported a significant decrease in CFF two hours after ingestion of LSD. In contrast, Landis and Clausen (1954) observed an increased CFF six hours after LSD administration. The same workers found that mescaline produced a decrease in CFF.

Measurements analogous to human CFF estimations may be employed with animal subjects (Symmes, 1962; Hendricks, 1966). With the use of operant conditioning techniques, an animal can be trained to respond differentially in the presence of steady and flickering light. By comparing the number of responses made during the steady light condition and those made during the flickering light phase a discrimination index (d.i.) can be calculated (Carlton, 1959). The effect of LSD on flicker discrimination was investigated by Becker and his associates (1967) in the pigeon. Subjects were trained to respond to either a key illuminated by a steady light or one illuminated by a flickering light. A significant increase in accuracy of discrimination resulted from the administration of 20 μg/kg of LSD.

Although Goldzband and Clark (1955) found the rat to be a suitable subject for the study of flicker discrimination, no investigations of drug-

Received for publication August 17, 1970.
[1] Supported in part by Graduate Training Grant 2-T01-GM 00107 from the Division of Medical Sciences, National Institutes of Health and in part by Grant MH-15406 from the National Institute of Mental Health.
[2] Some of the data were presented at the 54th Annual Meeting, Federation of American Societies for Experimental Biology, April 15, 1970 (Schechter and Winter, 1970).
[3] Present address: Department of Pharmacology, Medical College of Virginia. Richmond, Va.

Send reprint requests to: Martin D. Schechter, Ph.D., Department of Pharmacology, Medical College of Virginia, Richmond, Va. 23219.

induced changes in CFF in this species have been reported. Previous work in our laboratory, with a method similar to that of Becker and coworkers (1967), has confirmed the adequacy of the rat for this type of discrimination task (Schechter and Winter, 1969). In the present experiments, the effect of LSD and mescaline on the flicker discrimination of rats was determined. The coadministration of the two drugs was also tested to ascertain the degree of interaction between them.

METHODS. *Subjects.* The subjects were 10 female albino rats of CFN strain, purchased from the Carworth Farms, New City, N.Y. They were maintained at 70% of their predicted free-feeding weight by adjusted feedings after each experimental session. Water was freely available in the home cage. Prior to these experiments, the rats had received neither drugs nor behavioral training.

Apparatus. The experimental space was a 2-lever rat chamber (Lehigh Valley Electronics model 1417) measuring 25.4 cm × 30.5 cm × 30.5 cm. A lever (2.5 cm long, 1.3 cm in diameter) was mounted 3.8 cm above the grid floor on the front wall. A force of approximately 13 g was necessary to depress the lever 0.2 mm and close a microswitch. This activated a dipper which delivered 0.1 ml of a liquid reinforcer consisting of a mixture of 2:1 tap water and sweetened condensed milk. Two stimulus lights (General Electric-Ne 79) were mounted 6.4 cm above the lever. The lights were covered by a white plastic translucent filter and were the major source of illumination in the chamber. The experimental chamber was housed in a larger light-proof, sound-insulated box equipped with an exhaust fan. White noise was provided at the top of the chamber to further reduce outside sounds. Solid state programing equipment (Lehigh Valley Electronics, Fogelsville, Pa.) and a Gerbrands cumulative recorder were used to control the experiment and to record the results. Preliminary experiments were done to exclude the possibility that factors other than light stimuli were controlling the animal's behavior.

TABLE 1

Experimental protocol

Period	Time	S^d Frequency	S^Δ Frequency	Purpose
	min	*cps*	*cps*	
0	0–15	100	2	Warm-up
1	15–30	100	2	Control 1
2	30–60	100	20 or 30	Experimental
3	60–75	100	2	Control 2

Procedure. At approximately 8 weeks of age the rats learned to drink milk from a dipper which could be raised into the experimental space. They were then trained to press a lever, which caused the dipper to appear. Once lever-pressing was established the rats were placed on a fixed ratio (FR) schedule of reinforcement. During the FR schedule, the reinforcer was delivered after 10 bar presses had been made (FR 10). Rats were subsequently trained on a multiple schedule of positive reinforcement to discriminate between apparently steady and flickering light. The neon stimulus light source flickering at 100 cps, with an "on" phase of approximately 4 msec, provided the discriminative stimulus (S^d). In the presence of S^d, reinforcement was contingent upon fulfilling the requirements of the FR 10 schedule. The same light source flickering at 2 cps constituted the S^Δ phase and no responses were reinforced during this period. As the S^Δ flicker frequency is increased, the animal's ability to discriminate between S^d and S^Δ phases, as measured by the d.i. decreases (Schechter and Winter, 1969). Frequencies of 20 and 30 cps were chosen for use in the pharmacologic experiments because it was expected that drug-induced changes in discriminative ability, both positive and negative, could best be observed at some intermediate value of d.i. The duration of S^d and S^Δ phases was automatically and randomly determined by a Lehigh Valley Electronics modular probability gate (no. 335-10). The minimum duration of the S^d stimulus was 30 seconds with a mean of two minutes. Presentation of the S^Δ was programed to have the same parameters but, following the procedure originated by D. M. Page and described by Wilson and Keller (1953), each response in the S^Δ phase postponed the possibility of S^d presentation for a minimum of 20 seconds. This technique promotes the extinction of S^Δ responding by preventing adventitious reinforcement of a response in S^Δ by the onset of S^d.

The experimental protocol is given in table 1. In all cases, drug administration was preceded and followed by a saline control day at the same S^Δ flicker frequency. The purpose of the 0 period was to allow time for acclimation of the subjects to the experimental space. Period 1, of fifteen minutes duration at an S^Δ flicker frequency of 2 cps, allowed calculation of a base-line discrimination index. When the d.i. was below 0.90, the criterion for base-line performance, the daily session was terminated. The experimental period began 30 minutes after the subject was placed in the experimental chamber. The subject was removed from the chamber, injected with either saline or drug and returned to the chamber. The S^Δ flicker frequency was then adjusted to either 20 or 30

cps. After 30 minutes at this frequency, the S^{Δ} frequency was returned to 2 cps for a second 15-minute control period (3) to reestablish a base-line d.i. of 0.90 or higher.

In experiments designed to test drug antagonism, a fixed dose of mescaline was coadministered with one of a range of doses of LSD or a fixed dose of LSD was given with one of several doses of mescaline. Three treatments were used: 1) mescaline alone, 2) LSD alone and 3) mescaline plus LSD. The drug combination (3) was given in duplicate. The treatment on a given day was randomly determined and there was a minimum of one day between drug injections. LSD and mescaline were administered with separate syringes. The daily protocol of control and experimental periods was the same as for previous LSD and mescaline experiments.

Lysergic acid diethylamide tartrate[4] and mescaline hydrochloride[4] were dissolved in 0.9% saline and administered in a volume of 1 ml/kg b.wt. All injections were i.p. and drugs were given no more than 3 times per week. Drug doses are expressed as micromoles per kilogram body weight, with 0.1 μmol/kg of LSD tartrate equivalent to 0.047 mg/kg and 20 μmol/kg of mescaline HCl equal to 4.95 mg/kg. Drug effects were analyzed statistically with analysis of variance (Goldstein, 1964). $P < .05$ was chosen as the level of significance.

RESULTS. *Control patterns of responding under the multiple schedule.* The multiple schedule of food presentation generated patterns of responding in the rat which have been described previously (Ferster and Skinner, 1957). In the presence of the light source flickering at 100 cps (S^{d} component) responding occurred at a high and steady rate. In the presence of the light source flickering at 2 cps (S^{Δ} component) the response rate was very low. The ratio of responses in the S^{d} component to total responses, the discrimination index, ranged from 0.93 to 0.98. Figure 1 illustrates the contrasting response rates generated by the presentation of S^{d} and S^{Δ}. Experiments were conducted to determine whether any factor other than the light stimulus was controlling the animals' behavior. After establishment of the base-line d.i. of 0.90, rats were exposed to the same experimental conditions as described above except that the stimulus lights were blacked out by the insertion of dye-stained absorbent cotton. The mean d.i. with the S^{Δ} flicker frequency set at 2 cps was 0.93; the d.i. for the blacked-out test sessions, of equal duration, was 0.56. These results indicate the light stimulus was essential for discriminated responding and that extraneous stimuli, perhaps involved with the generation of the light stimulus, were not responsible for the pattern of responding which was observed.

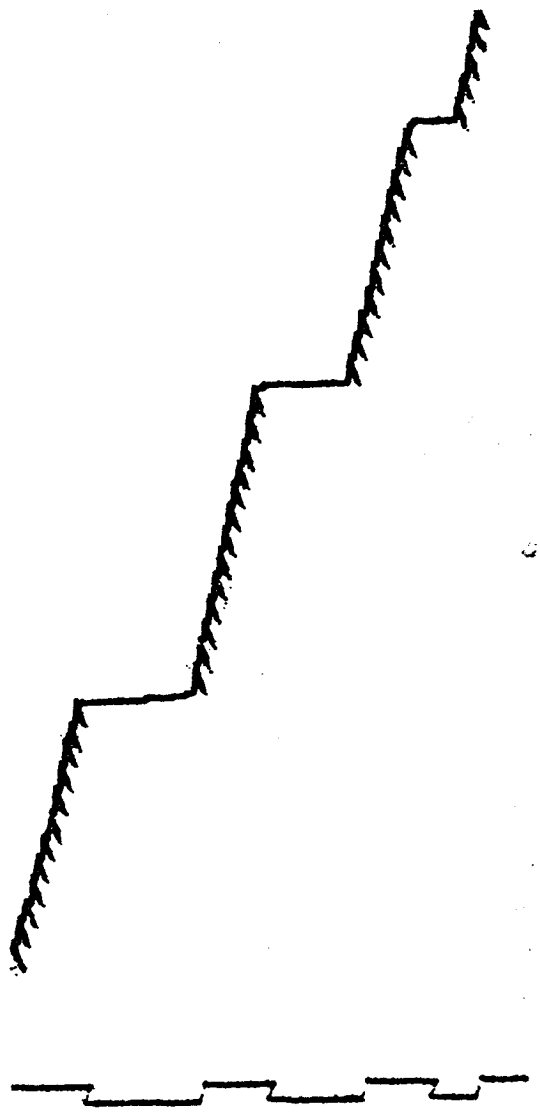

FIG. 1. Cumulative reecord of control performance of rat OG03 on a multiple FR20EXTINCTION schedule. Upper tracing, cumulated responses *vs.* time. Each downward movement of the pen indicates reinforcement. Lower tracing, record of stimulus presentation. Pen up, S^{d}; pen down, S^{Δ}.

[4] Mescaline hydrochloride was purchased from Aldrich Chemical Company, Inc., Cedar Knolls, N.J. (IND 4944). Lysergic acid diethylamide tartrate was provided by Dr. John A. Scigliano, Executive Secretary, FDA-NIMH Psychotomimetic Agents Advisory Committee (IND 5184).

Effect of mescaline on d.i. at S^{Δ} = 20 and 30 cps. The effects of various doses of mescaline on discrimination at S^{Δ} flicker frequencies of 20 and 30 cps are presented in figure 2 and are expressed as percentage of control. The d.i. during the experimental period after mescaline administration was compared with the corresponding period after injection of saline. Doses of 40 and 60 μmol/kg of mescaline significantly decreased the ability to discriminate between the S^{a} (100 cps) and the S^{Δ} (20 or 30 cps). It should be noted that the two sets of points are expressed as a percentage of two different control values. At 20 cps, control d.i. was 0.85 and at 30 cps, d.i. was 0.70. Thus, whereas mescaline had a greater effect relative to control at 20 cps, the absolute values of d.i. were lower at the higher frequency (table 2).

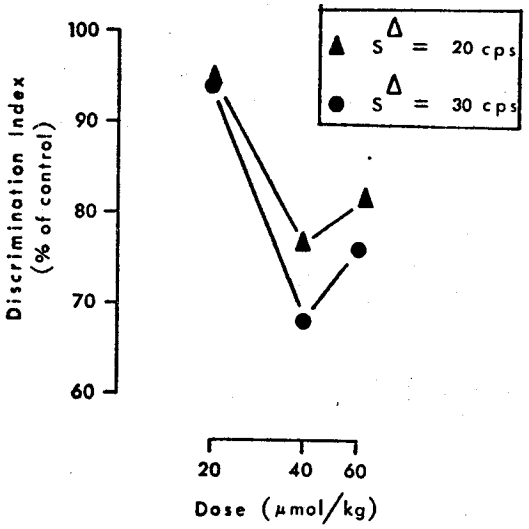

FIG. 2. Effects of mescaline on discrimination index. S^{a} = 100 cps; S^{Δ} = 20 cps (●) or 30 cps (▲). Ordinate, d.i. expressed as a percentage of control; abscissa, dose of mescaline in micromoles per kilogram. Each point represents the mean of at least four determinations in each of two subjects. Discrimination indices at S^{Δ} = 20 cps were significantly reduced at doses of 40 and 60 μmol/kg, $P < .05$.

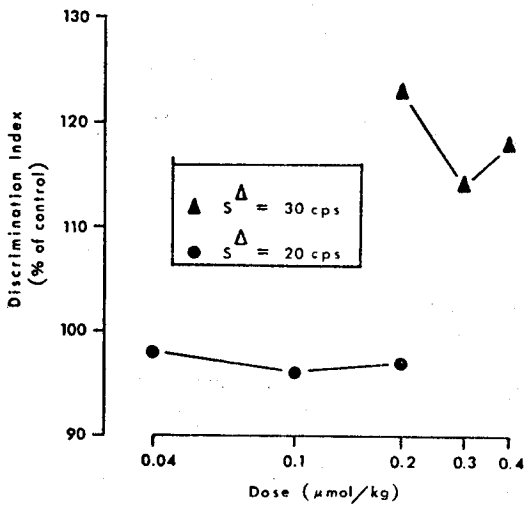

FIG. 3. Effects of LSD on discrimination index. S^{a} = 100 cps; S^{Δ} = 20 cps (●) or 30 cps (▲). Ordinate, d.i. expressed as a percentage of control; abscissa, dose of LSD in micromoles per kilogram. Each point represents the mean of at least four determinations in each of two subjects. Discrimination indices at S^{Δ} = 30 cps were significantly elevated at the three doses tested, $P < .05$.

TABLE 2

Mean values for discrimination indices after mescaline, LSD and saline at 20 and 30 cps

	Mescaline	N[a]	Mean d.i. × 100		LSD	N	Mean d.i. × 100	
			Mescaline	Saline			LSD	Saline
	μmol/kg				μmol/kg			
At 20 cps	20	21	74.2	79.1	0.04	8	82.7	84.8
	40	14	68.7[b]	88.1	0.1	8	88.9	90.2
	60	18	70.5[b]	87.0	0.2	8	93.0	94.5
At 30 cps	20	12	64.8	68.8	0.2	24	79.5[c]	64.7
	40	8	44.8[b]	65.7	0.3	14	83.9[c]	73.9
	60	24	57.3[b]	74.8	0.4	14	83.8[c]	71.4

[a] Number of pairs of trials. Drug and saline were administered on alternate days.
[b] Mean d.i. after mescaline significantly lower than mean d.i. after saline; $P < .001$.
[c] Mean d.i. after LSD significantly higher than mean d.i. after saline; $P < .001$.

Effect of LSD on d.i. at S^{Δ} = 20 and 30 cps. The effects of LSD on discrimination at S^{Δ} flicker frequencies of 20 and 30 cps are presented in figure 3. Doses of 0.04 to 0.2 μmol/kg of LSD had no significant effect on d.i. at S^{Δ} = 20 cps. At S^{Δ} = 30 cps, each dose tested caused a significant increase in d.i. when compared with saline control values (table 2). The apparent insensitivity at 20 cps may reflect the fact that control d.i. at this frequency was already near its maximal value.

Interaction between LSD and mescaline on d.i. Doses of 40 and 60 μmol/kg of mescaline produced a significant depression of d.i. at S^{Δ} = 30 cps. In contrast, doses of 0.2, 0.3 and 0.4 μmol/kg of LSD produced significant elevations of d.i. at this same flicker frequency. To ascertain the degree of interaction between the two drugs, a dose of mescaline (20 μmol/kg), previously observed to have no significant effect upon the mean d.i. at S^{Δ} = 30 cps, was coadministered with various doses of LSD. The results obtained with this procedure are presented in figure 4. Mescaline alone produced a relatively uniform pooled d.i.

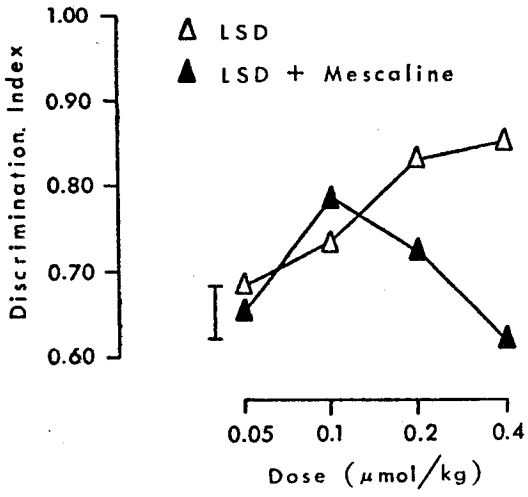

FIG. 4. Effect of LSD alone and in combination with mescaline on discrimination index. S^{Δ} = 30 cps. Ordinate, d.i.; abscissa, dose of LSD in micromoles per kilogram. △ represent experiments in which LSD was administered alone. ▲ represent identical experiments but with coadministration of 20 μmol/kg of mescaline. Each point represents the mean of four subjects. The vertical line indicates the range of values obtained after the administration of 20 μmol/kg of mescaline alone (four replications in each of four subjects). The effect of 0.2 and 0.4 μmol/kg of LSD is significantly altered by coadministration of mescaline, $P < .05$.

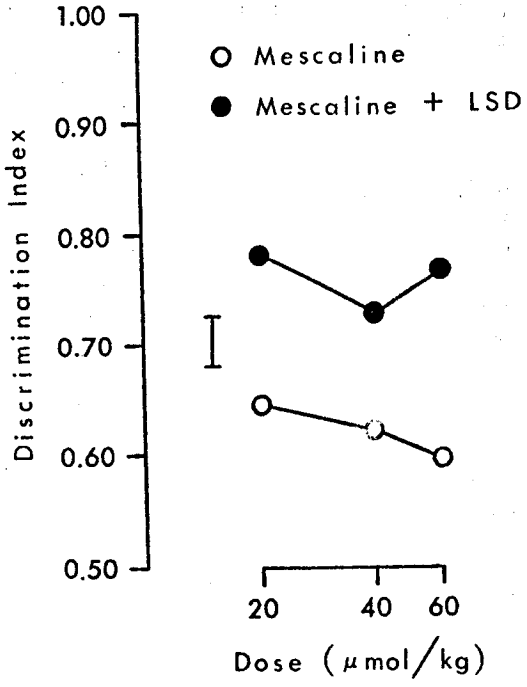

FIG. 5. Effect of mescaline alone and in combination with LSD on discrimination index. S^{Δ} = 30 cps. Ordinate, d.i.; abscissa, dose of mescaline in micromoles per kilogram. ○ represent experiments in which mescaline was administered alone. ● represent identical experiments but with coadministration of 0.1 μmol/kg of LSD. Each point represents the mean of four subjects. The vertical line indicates the range of values obtained after the administration of 0.1 μmol/kg of LSD alone (four replications in each of four subjects). The effect of 60 μmol/kg of mescaline is significantly altered by coadministration of LSD, $P < .05$.

(62.3–67.8%) throughout the experimental series. Increasing doses of LSD alone resulted, as in previous experiments, in an increasing mean d.i. The subeffective dose (20 μmol/kg) of mescaline, when coadministered with 0.2 and 0.4 μmol/kg of LSD significantly antagonized the LSD-induced elevation of d.i.

In a similar series of experiments, a fixed dose of LSD (0.1 μmol/kg), which by itself had no significant effect on d.i., was coadministered with various doses of mescaline (fig. 5). As in previous experiments, mescaline alone produced a dose related decrease in d.i. A relatively uniform d.i. (67.6–72.6%) was produced by the constant dose of LSD administered alone. The subeffective dose of LSD (0.1 μmol/kg) significantly antagonized the mescaline-induced decrease of d.i. In fact, at all mescaline doses tested, the LSD-mescaline

combination produced a higher d.i. than that obtained with either drug administered alone.

DISCUSSION. The present investigation has shown that LSD, at doses of 0.2 to 0.4 μmol/kg, increases the ability of the rat to discriminate between an S^q of 100 cps and an S^Δ of 30 cps. However, the same doses were without effect on d.i. when the S^Δ frequency was 20 cps. A similar observation was made by Becker and co-workers (1967) in the pigeon. They found that doses of LSD (0.04–0.17 μmol/kg) which were ineffective at $S^\Delta = 30$ cps produced a significant increase in discriminative ability when tested at an S^Δ of 70 cps. The authors suggested that the lower S^Δ frequency offered too easy a discriminative task in which LSD-induced enhancement would be difficult to observe. Because the "on" phase of the stimulus lights was fixed at 4 msec, there were differences in luminous flux as well as in flicker frequency during the S^q and S^Δ periods. Experiments were done (M. D. Schechter, unpublished observations) in which S^Δ of 40 msec duration was presented at 10 cps and the S^q was 4 msec at 100 cps. In this way both S^q and S^Δ had the same total "on" time. Under these conditions, d.i. was not significantly different from that observed when the "on" phase for both S^q and S^Δ was 4 msec. Nonetheless, the present data do not permit a definitive statement as to whether our behavioral task measures flicker discrimination or brightness discrimination.

Studies concerned with the effects of LSD on the activity of the retina, lateral geniculate nucleus and visual cortex of the cat do not lend themselves readily to an explanation of the behavioral effects observed in the present study. In brief, LSD causes an increase in spontaneous and evoked responses in the retina (Apter and Pfeiffer, 1957, 1960; Schwartz and Cheney, 1965), partially blocks transmission through the lateral geniculate nucleus (Evarts *et al.*, 1955; Evarts, 1958; Bishop *et al.*, 1958) and has little effect on activity in the visual cortex (Evarts, 1956). One might argue that an LSD-induced increase in retinal sensitivity is the basis for the enhancement of discriminative ability and that other effects, including that on the lateral geniculate nucleus, are of secondary importance. However, it is obvious that even tentative conclusions as to the anatomical site at which LSD acts to alter the discrimination of flicker in the rat are premature and have value only to the extent that they serve as a basis for further experimental observation.

The hypothesis that LSD and mescaline have a common site of action explains the observation that there is cross-tolerance between the two drugs in both the rat (Appel and Freedman, 1968) and man (Balestrieri and Fontanari, 1958; Wolbach *et al.*, 1962), and that the clinical effects are similar (Hollister, 1968). In addition, the similarity of the changes in blood and brain amines produced by the two substances in the rat (Giarman and Freedman, 1965), and the observation of a direct antagonism of mescaline by LSD in studies of unconditioned behavior in the mouse (Chen and Bohner, 1960; Borsy *et al.*, 1964) are compatible with this hypothesis. Similarly, the mutual antagonism of LSD and mescaline observed in the present investigation may most easily be explained on the basis of a common site of action. The observation that mescaline and LSD produce opposite effects on the discrimination index in the present work does not preclude the possibility of a common receptor site. Their individual effects may simply reflect differences in the pharmacologic properties of the two drugs rather than any difference in the receptor at which they act. It is of interest that Landis and Clausen (1954) observed a slight decrease in CFF measured two hours after injection of mescaline in psychiatric patients as compared with an increased CFF after LSD administration. These results, as to the direction of CFF alteration produced by the two drugs, are the same as in the present study in the rat.

CONCLUSIONS. This investigation has shown that rats can reliably discriminate between lights flickering at different frequencies. LSD and mescaline, administered at doses which produced no gross behavioral alterations, altered discriminative ability as measured by the discrimination index. The observation that LSD and mescaline produce opposite effects on the discriminative ability of the rat may be explained on the basis of different actions on the diffuse integrative mechanisms involved in responsiveness to external stimuli. Electrophysiologic investigations in the cat suggest an alternative explanation, namely, that enhancement or depression of input from the retina could result in an increase or decrease of discriminative ability.

LSD and mescaline are mutually antagonistic in this system. The simplest explanation is that the two drugs share a common receptor site.

Studies of cross-tolerance between mescaline and LSD, and the antagonism of mescaline by LSD in experiments with unconditioned behavior, have led to the same hypothesis. The present observation that mescaline and LSD produce opposite effects on the discrimination index does not preclude the possibility of a common receptor site. Their individual effects may simply reflect differences in the pharmacologic properties of the two drugs rather than any difference in the receptor at which they are presumed to act.

REFERENCES

ADLER, H. F., BUCKHART, W. L., IVY, A. C. AND ATKINSON, A. J.: Effects of various drugs on psychomotor performance at ground level and at simulated altitudes of 18,000 feet in a low pressure chamber. J. Aviat. Med. **21**: 221–236, 1950.

APPEL, J. B. AND FREEDMAN, D. X.: Tolerance and cross-tolerance among psychotomimetic drugs. Psychopharmacologia **13**: 267–274, 1968.

APTER, J. T. AND PFEIFFER, C. C.: Effect of psychotomimetic agents on the electroretinogram. Ann. N.Y. Acad. Sci. **66**: 508–514, 1957.

APTER, J. T. AND PFEIFFER, C. C.: Some effects of hallucinogenic drugs on the electrical activity of the visual pathways of cats. Amer. J. Opthalmol. **42**: 206–211, 1960.

BALESTRIERI, A. AND FONTANARI, D.: Acquired and crossed-tolerance to mescaline, LSD-25 and BOL-148. Arch. Gen. Psychiat. **1**: 279–282, 1958.

BECKER, D. I., APPEL, J. B. AND FREEDMAN, D. X.: Some effects of LSD on visual discrimination in the pigeon. Psychopharmacologia **11**: 354–364, 1967.

BISHOP, P. O., FIELD, G., HENNESSY, B. L. AND SMITH, J. R.: Action of *d*-LSD on lateral geniculate synapses. J. Neurophysiol. **21**: 529–537, 1958.

BORSY, J., HUSZTI, Z. AND FEKETE, M.: Antimescaline properties of some lysergic acid derivatives. Int. J. Neuropharmacol. **2**: 273–277, 1964.

CARLTON, P. L.: Discrimination learning. Science (Washington) **130**: 1341–1343, 1959.

CHEN, G. AND BOHNER, B.: A study of certain CNS depressants. Arch Int. Pharmacodyn. Thér. **125**: 1–20, 1960.

EVARTS, E. V.: Some effects of bufotenine and LSD on the monkey. Arch. Neurol. Psychiat. **75**: 49–53, 1956.

EVARTS, E. V.: Effects of a series of indoles on synaptic transmission in the lateral geniculate nucleus of the cat. Progr. Neurobiol. **3**: 173–194, 1958.

EVARTS, E. V., LANDAU, W., FREYGANG, E. AND MARSHALL, W. H.: Some effects of LSD and bufotenine on electrical activity in the cat's visual system. J. Physiol. (London) **132**: 594–608, 1955.

FERSTER, C. B. AND SKINNER, B. F.: Schedules of Reinforcement, Appleton-Century-Crofts, New York, 1957.

GIARMAN, H. J. AND FREEDMAN, D. X.: Biochemical aspects of the actions of psychotomimetic drugs. Pharmacol. Rev. **17**: 1–25, 1965.

GOLDSTEIN, A.: Biostatistics: An Introductory Text, The Macmillan Company, New York, 1964.

GOLDZBAND, M. G. AND CLARK, G.: Flicker fusion in the rat. J. Genet. Psychol. **87**: 257–264, 1955.

HENDRICKS, J.: Flicker thresholds as determined by a modified conditioned suppression procedure. J. Exp. Anal. Behav. **9**: 501–506, 1966.

HOLLIDAY, A. R. AND SHARPLEY, R. P.: The effects of LSD. I. Critical flicker fusion. Proc. West. Pharmacol. Soc. **8**: 48–50, 1965.

HOLLISTER, L. E.: Chemical Psychoses, LSD and Related Drugs, Charles C Thomas, Springfield, 1968.

LANDIS, C.: Determinants of critical flicker fusion threshold. Physiol. Rev. **34**: 259–286, 1954.

LANDIS, C. AND CLAUSEN, J.: Certain effects of mescaline and lysergic acid on psychological functions. J. Psychol. **38**: 211–221, 1954.

SCHECHTER, M. D. AND WINTER, J. C.: Behavioral determination of critical flicker frequency in the rat. Percept. Mot. Skills **29**: 655–660, 1969.

SCHECHTER, M. D. AND WINTER, J. C.: Effects of LSD and mescaline on discrimination of flicker in the rat. Fed. Proc. **29**: 619, 1970.

SCHWARTZ, B. E. AND CHENEY, C.: Effect of LSD on the tonic activity of the visual pathways of the cat. Life Sci. **4**: 771–776, 1965.

SYMMES, D.: Self-determination of critical flicker frequency in monkeys. Science (Washington) **136**: 714–715, 1962.

TURNER, P.: Critical flicker frequency and centrally-acting drugs. Brit. J. Opthalmol. **52**: 245–250, 1968.

WILSON, M. P. AND KELLER, F. S.: On the selective reinforcement of spaced responses. J. Comp. Physiol. Psychol. **46**: 190–193, 1953.

WOLBACH, A. B., ISBELL, H. AND MINER, E. J.: Cross-tolerance between mescaline and LSD-25 with a comparison of the mescaline and LSD reactions. Psychopharmacologia **3**: 1–14, 1962.