Behavioral and Electroencephalographic Effects of LSD

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D-Lysergic acid diethylamide tartrate (LSD) was evaluated in cats with permanently implanted electrodes for effects on behavior-EEG correlations and on rates of responding for electrical stimulation to the lateral hypothalamus (self-stimulation) and responding for milk reward. Doses of 10 and 15 mcg./Kg. of LSD intraperitoneally increased responding for lateral hypothalamic self-stimulation, stimulated observable behavior, and caused a low-voltage fast cortical EEG to predominate. A dose of 25 mcg./Kg. of LSD produced slight decreases in self-stimulation responding. It also caused disorientation, howling, and periodic pacing and staring. This behavior was associated with a change in EEG pattern toward a slow-wave high-voltage response.

THE RESPONSE to the ingestion of lysergic acid diethylamide (LSD) in man is a syndrome characterized by hallucinations and abnormal behavior (1, 2). Because it was believed that this drug-induced effect might be similar to psychotic behavior, many pharmacological and clinical studies in the 1950's attempted to relate the effects of LSD to psychotic behavior (3, 4). This relationship was not realized; consequently, research in this area has become less frequent during the past few years.

One of the primary stumbling blocks to laboratory testing has been the lack of a reliable quantitative measure of the effects of LSD on animal behavior. This report describes quantitative tests for the stimulating activity of LSD and relates this action to its other central effects.

METHODS

Cats were prepared with chronic electrodes in the lateral hypothalamus and on various cortical areas in the manner described previously (5). They were subsequently trained to respond for a small electrical current delivered to the lateral hypothalamus (6). These same animals also were used in studies to include the concurrent recording of the spontaneous electrical activity of the cortex (EEG) and observable behavior. The rating scale of Horovitz and Chow (7) was used to characterize these parameters. These cats and others not prepared with electrodes were trained to respond to milk after 40 hours of food deprivation. They were tested on a variable interval reward schedule (VI-16 seconds) and a schedule involving differential reinforcement with a light discrimination. The latter required 12 seconds of nonresponding, after which a light stimulus was presented; the first-response to the stimulus was reinforced, and the response turned off the light, which reinstituted the schedule. A similar schedule was described by Carlton for rats (8).

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Rats also were implanted with electrodes in the lateral and preoptic hypothalamus and were trained to depress a lever for current in a fashion analogous to the cat self-stimulation procedure.

LSD was injected intraperitoneally as a 0.001% aqueous solution of the tartrate salt.

RESULTS

Figure 1 illustrates the effects of various doses of LSD on the response of a cat working for stimulation of the lateral hypothalamus. A small, but reliable increase in responding followed 10 mcg./Kg.; after 15 mcg./Kg., a marked increase occurred. Higher doses (25 and 40 mcg./Kg.) caused either no change or a decrease in total responding (Table I, col. I). Doses of 10 and 15 mcg./Kg. caused mydriasis and increased motor movement. After 25 mcg./Kg. the animal circled frequently and stopped to stare at the wall or mirror in the experimental chamber. Occasionally, he swatted at an imaginary object in the air or hissed and showed spontaneous fear responses. These periods of disorientation were intermingled with periods of high responding so that the resultant over-all rates were approximately normal. Higher doses decreased responding rates markedly.

Doses ranging from 5.0 to 40.0 mcg./Kg. were tested on rats working for stimulation of preoptic or lateral hypothalamus. There was no increase of

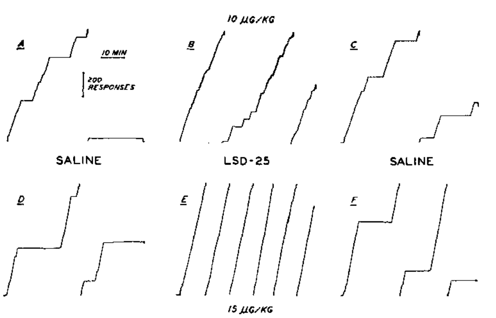

Fig. 1.—Cumulative records of the effects of intraperitoneal presession injections of LSD on a cat responding for stimulation of the lateral hypothalamus. Because responses are plotted cumulatively, the slope of each record is proportional to rate of responding. The recording pen was reset to the baseline when 1000 responses had been cumulated. Each session lasted 1 hour.

Table I.—Drug to Control Ratios[a]

Dose, mcg./Kg.	I Self-Stim.	II Variable Interval	III Discrimination
		1.19	
5.0	. . .	1.25	. . .
		0.99	
		0.82	
		$\bar{x}$ = 1.06	
	1.61	1.08	0.97
10.0	2.14	0.90	0.99
	1.73	0.91	0.98
		0.93	0.98
	$\bar{x}$ = 1.83	$\bar{x}$ = 0.96	$\bar{x}$ = 0.98
	3.25	0.98	1.81
15.0	1.97	0.88	1.07
	1.72	0.83	1.47
		1.03	1.33
	$\bar{x}$ = 2.31	$\bar{x}$ = 0.93	$\bar{x}$ = 1.42
	0.95	0.53	0.95
25.0	1.21	0.88	1.21
	1.08	0.69	1.08
		0.70	
	$\bar{x}$ = 1.08	$\bar{x}$ = 0.70	$\bar{x}$ = 1.08
	0.53		0.40
40.0	0.42	. . .	0.23
	0.54		0.30
	$\bar{x}$ = 0.49		$\bar{x}$ = 0.31

[a] Drug to control ratios of effects of LSD on self-stimulation in the cat lateral hypothalamus and on responding for milk on VI and discrimination schedules.

responding rates at any dose. Doses above 10 mcg./Kg. were definitely depressant.

The effects of 10 and 25 mcg./Kg. of LSD on the spontaneous electrical activity (EEG) of the cat are illustrated in Fig. 2. Most of the animals in this study normally exhibited high-voltage, slow-frequency EEG activity. LSD (10 and 15 mcg./Kg.) changed this to a fast, low-voltage activity. Other cats that normally did not become drowsy and had continuous periods of spontaneous fast, low-voltage EEG activity showed no difference in EEG after 10 and 15 mcg./Kg., of course, but always exhibited high-voltage, slow-EEG activity after 25 mcg./Kg. or higher doses.

The effects of 10, 15, and 25 mcg./Kg. of LSD on self-stimulation responding and EEG activity are illustrated in Fig. 3. The self-stimulation effects are plotted as a ratio of drug responding rate over pre- and postdrug day rates. A good correlation between the behavioral stimulation and EEG arousal was seen at the lower doses. After a dose of 25 mcg./Kg., observable behavior shows a trend toward stimulation (lower ratings) while the EEG is represented by a high-voltage, slow pattern (higher ratings). Self-stimulation responding is diminished by this dose of LSD.

Table I (cols. II and III) compares the effects of LSD on both the VI and discrimination schedules. LSD did not stimulate cats working on the VI schedule, but disorientation and decreased responding was produced by 25 mcg./Kg. Increases in discrimination rates were noted after 15 mcg./Kg. of LSD, but responding returned to control levels after 25 mcg./Kg.

DISCUSSION

It appears that any given response to LSD in animals is dependent on both dose and evaluation technique. The variation in response to dose is illustrated by a biphasic effect of LSD on self-stimulation on EEG activity and on discrimination. This same type of biphasic response has been described for the antidepressant, imipramine, and to a lesser degree for the phenothiazines on self-stimulation (9) and arousal thresholds (10, 11).

Imipramine and amphetamine previously were shown also to increase self-stimulation responding (9). Other stimulants such as pipradrol and methylphenidate increase this activity (Horovitz, unpublished data). Low doses of LSD will also increase self-stimulation responding from the lateral hypothalamus. A number of the behavioral and electrical signs associated with the stimulatory effect of LSD appeared to be similar to the sympathomi-

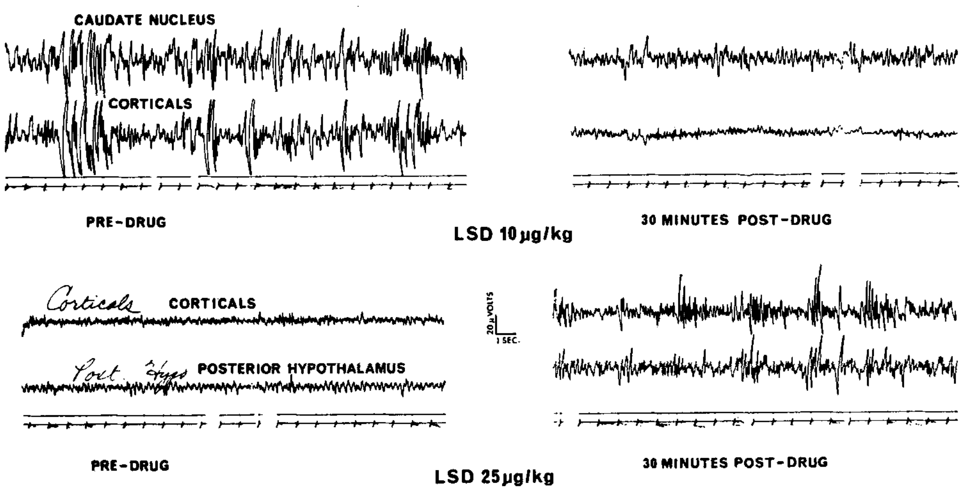

Fig. 2.—Effects of LSD on EEG of unrestrained cat.

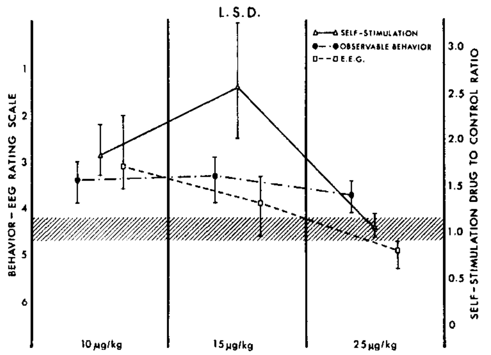

Fig. 3.—Effects of various doses of LSD on behavior-EEG ratings and self-stimulation responding of the cat.

metic effects of amphetamine, methylphenidate, and pipradrol—pupillary dilation, increased motor activity, and responding. This accords with Elder's view that "the evidence for sympathetic discharge in response to the administration of LSD is striking" (12).

Olds and Eiduson (13) have reported previously that LSD will depress self-stimulation responding in rats. The finding that lower doses will not cause increased responding in rats is in contrast to the cat data. However, it does parallel the effects of imipramine on self-stimulation responding—stimulation in the cat (9) but depression in rats (14).

The behavioral dissociation noted after 25 mcg./Kg. of LSD (high-voltage EEG associated with active, alert behavior) is quite similar to that described previously after atropine and other anticholinergics (15). The psychotomimetic compound Ditran, also a potent anticholinergic, produced the same type of behavioral-EEG dissociation (7). It is possible that a central anticholinergic component of LSD is related to its behavioral disorientation in cats.

The stimulant effect of LSD is not apparent above the dose of 15 mcg./Kg.; 25 mcg./Kg. did not increase self-stimulation responding rates. This lack of increase and the eventual decline in responding (40 mcg./Kg.) probably were due to the disorientation and erratic behavior described previously. The disorientation was observed in most test procedures, although the stimulatory phase was seen only in the self-stimulation and discrimination procedures. The disorientation was correlated with a shift in EEG pattern toward a slow-wave, high-frequency record. Because of the nature of the rating scale, observable behavior appears more stimulated because of the disorientation, even though operant responding was decreased. Bradley and Elkes (16) have reported on the fast low-amplitude EEG effects of LSD in animals. The high-voltage, slow-wave activity associated with disorientation has been reported in cats at 70–100 mcg./Kg. (17) and in rabbits at 20–60 mcg./Kg. (18).

The three different behavioral procedures used to study the effects of LSD illustrate the importance of the assessment technique in evaluating both the quantitative and qualitative effects of this compound. The VI schedule is similar to the discrimination procedure with respect to the reinforcement provided and is similar to the self-stimulation procedure in that both VI and self-stimulation did not involve a stimulus discrimination. The failure of the VI schedule to detect any stimulating action of LSD is likely therefore, due to the reinforcement contingencies imposed by this schedule. Since it is known that the human response to LSD depends a great deal on the environmental situation (19), it appears logical that these schedules would produce different responses because they provide the animal with different environmental situations.

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