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CHEMICAL BASIS FOR PSYCHOSIS

NEUROPHARMACOLOGICAL CONTRIBUTIONS TO OUR PRESENT CONCEPT

Edward V. Evarts

In the following chapter, Edward V. Evarts reports neuropharmacological experiments in monkeys and cats. They contribute to our knowledge of drugs which in humans cause mental alterations, often of a psychotic nature. The results of these experiments are evaluated by the author in relation to their relevance to a chemical concept of psychosis.

INTRODUCTION:

Within recent years three discoveries have led to increased prominence of psychotomimetic agents as research tools in experimental psychiatry. These three discoveries were: first, the demonstration of the remarkable psychological actions and potency of d-lysergic acid diethylamide (LSD); second, the isolation and chemical identification of 5-hydroxytryptamine (5-HT) (10, 30); and third, the demonstration that LSD is a potent antagonist of 5-HT *in vitro* (19, 41). In this chapter neuropharmacological studies in animals on the basis of these three fundamental discoveries are summarized, and as the result of these studies speculations about a chemical basis for psychosis in humans are offered.

SCOPE AND DELINEATION OF THE EXPERIMENTS:

The experiments were begun in an attempt to gain further knowledge about those behavioral and electrophysiological effects of LSD which might be relevant to an explanation of the effects of LSD on psychological processes in man. The hypothesis of Gaddum (20) and of Woolley and Shaw (41, 42) that the actions of LSD were related to its interaction with 5-HT served as a point of departure. One ap-

proach to obtaining further knowledge of the mechanism of action of LSD was to examine the effects of other substances whose actions might also be related to an interaction with 5-HT. One such obvious source is the class of structural congeners of 5-HT, and therefore a series of experiments was started with a small group of tryptamine and LSD derivatives. It was the purpose of these experiments to obtain information concerning the degree to which analogues of 5-HT might produce neuropharmacological effects which corresponded to those of the LSD. The first 5-HT congener which we studied was bufotenine, the N-dimethyl derivative of 5-HT. Figure 2 shows the structures of bufotenine, 5-HT (serotonin) and LSD. The investigations of the actions of bufotenine were undertaken on the basis of the theoretical considerations and as the result of Stromberg's (37) discovery that bufotenine is the principal alkaloid of cohoba (33), which the natives of Haiti used as a stimulating snuff. The possibility that bufotenine was the active agent in cohoba, and, therefore, a psychotomimetic agent, made the studies of its neuropharmacological actions of particular interest.

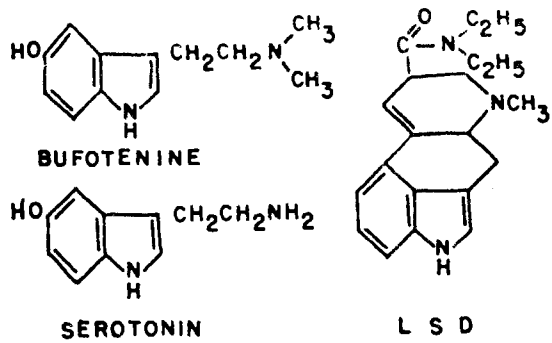

Fig. 2. *Structures of lysergic acid diethylamide (LSD), bufotenine, and serotonin.*

EXPERIMENTS ON MONKEYS:

Initial studies of the effects of bufotenine on the gross behavior of monkeys revealed that bufotenine induced a syndrome which was remarkably similar to the syndrome induced by LSD (11, 12). Following intravenous administration of bufotenine (5 milligrams per kilogram

body weight) and LSD (1 milligram per kilogram body weight) monkeys showed a gross but relatively selective alteration of behavior: diminished or absent responsiveness to visual stimuli, impairment of responses to several forms of somesthetic stimuli, but retention of responsiveness to auditory stimuli. Figures 1, 3, 4, 5, 6, 7

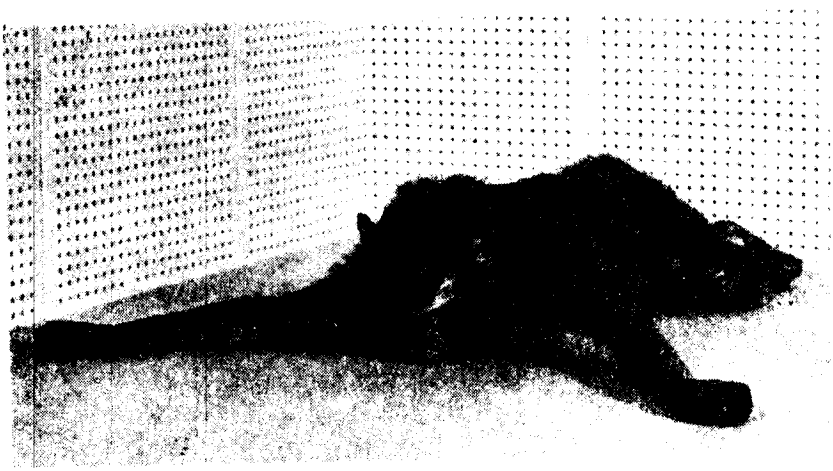

Fig. 3. *The effects of bufotenine on position.* This figure shows the position assumed immediately following intravenous injection of bufotenine 1 mg. kg

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illustrate some aspects of the gross disorder of behavior which followed intravenous administration of LSD and bufotenine. Within less than a minute of the administration of these drugs, monkeys assumed a prone position (Figs. 1, 3) which they rigidly maintained in spite of attempts by the experimenter to place them in some other position. In resisting attempts to move them about, the animals demonstrated good muscular power. When monkeys were elevated and made to grasp the experimenter's finger, they would suspend themselves (Figs. 4, 5) for considerable periods. Within about twenty minutes of the administration of the drugs, the monkeys began to move about in an ataxic manner. As the ataxia diminished, the animals would run about the floor with agility, but would bump into objects interposed in their path. Finally, within slightly more than an hour of the intravenous injection of LSD or bufotenine, the only grossly apparent residuum

Fig. 4. *Effects of LSD on motor power.* This figure demonstrates the ability of the subject to support its own weight immediately following administration of LSD.

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Fig. 5. *Effects of bufotenine on motor power.* This figure demonstrates the ability of the subject to support its own weight immediately following administration of bufotenine.

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of the drug-induced disorder of behavior was marked tameness and decreased general activity (Figs. 6, 7). After that, the monkeys continued to show a decrease of general activity for up to another one

Fig. 6. *Taming effects of LSD.* This figure shows tameness of the subject one hour following administration of LSD.

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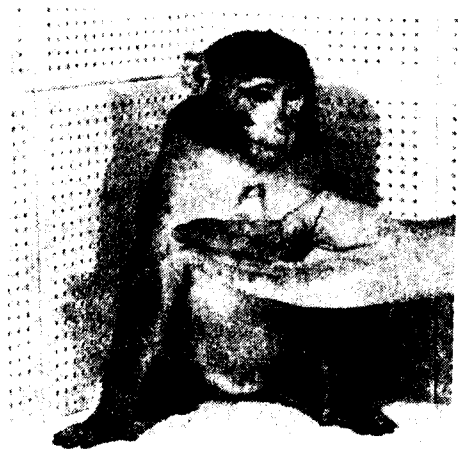

Fig. 7. *Taming effects of bufotenine.* This figure shows tameness of the subject one hour following administration of bufotenine.

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hour. Table 1 summarizes the character and duration of the symptoms which resulted from LSD and bufotenine.

As the figures and Table 1 show, LSD and bufotenine, in massive doses, produced strikingly similar gross behavioral disorders. Similarities between the actions of the two drugs were also apparent with smaller doses of the agents. In smaller doses, both drugs caused a decrease in the level of general activity of the experimental animals. Following LSD in intravenous doses of 0.03 milligrams per kilogram body weight, for example, monkeys showed a slowing of response in performance on tests of visual discrimination (though the accuracy of choices, when made, was not impaired). The effects of the very large doses of LSD and bufotenine have been presented in detail because of the uniqueness of the syndrome and the apparently selective disturbance of various perceptual processes which these doses induced. Several recent studies resulted in clear, objective measures of the behavioral effects of much smaller doses of LSD. These studies have demonstrated selective defects of some aspects of visual perception following administration of LSD. Blough (2) has shown that LSD in oral doses of 0.1 to 0.3 milligrams per kilogram body weight causes in pigeons an elevation of the threshold of brightness causing an increase in the accuracy of performance on a visual-discrimination problem in which discriminanda were illuminated at supraliminal intensities (3). Fuster (18) recently showed that in monkeys LSD in doses as low as 0.005 milligrams per kilogram body weight causes impairment of performance on a task involving tachistoscopic form discriminations. The clear defects in performance following very small doses of LSD, as demonstrated by Fuster, emphasize the importance of the nature of test conditions in studies which seek to elicit highly selective disorders of behavior.

The author's experiments in monkeys failed to demonstrate any impairment in the accuracy of visual discriminations following LSD administration in doses of 30 micrograms per kilogram body weight. The difference between the author's results and those of Fuster may be explained by the brief exposure of the discriminanda in Fuster's experiments. In the author's experiments, subjects were allowed up to thirty seconds to make a choice between the two continuously visible discriminanda, whereas in Fuster's experiments with LSD an exposure of the discriminanda was permitted for only twenty milliseconds.

Because of the apparent disturbed response to visual stimuli which

TABLE I

EFFECTS OF LYSERGIC ACID DIETHYLAMIDE AND BUFOTENINE ON THE MONKEY *

Observation	LSD 1.0 mg/kg		Bufotenine 5.0 mg/kg	
	Effect	Duration	Effect	Duration
Muscle power	Grossly normal		Grossly normal	
Deep tendon reflexes	Grossly normal		Hyperactive	15
Vestibular eye movements	Grossly normal		Grossly normal	
Reaction to auditory stimuli	Grossly normal		Grossly normal	
Pupillary light reflex	Present		Present	
Locomotion	Ataxic	55 (20-85)	Ataxic	50 (20-90)
Reaction to painful stimuli	Absent	65 (30-95)	Absent	67 (35-110)
Reaction to visual stimuli	Absent	77 (35-103)	Absent	69 (45-110)
Reaction to handling	Marked tameness	110 (85-130)	Marked tameness	105 (70-120)

*This table lists effects of LSD and bufotenine and gives their mean and range of duration in minutes.

occurred as one element in the syndrome that followed intravenous administration of bufotenine and LSD, it seemed possible to assume that the drugs alter some function in the primary ascending visual system. It is not necessary to point out that the disturbance of responsiveness to visual stimuli need not have indicated a specific alteration of function within the visual system, since it is well known that animals may show marked disturbances of visual reactions without any defect whatever in the primary visual pathways (24). One explanation for the pharmacologically induced disturbance of visually mediated behavior, however, was that administration of the drugs caused a disturbance of function at some point between the retina and the striate cortex. A series of studies in cats showed that LSD and bufotenine did, indeed, alter activity within this system (15). It was found that both of these drugs caused a reduction in the amplitude of the postsynaptic lateral geniculate response to electrical stimulation of the optic nerve. Whereas the amplitude of the lateral geniculate postsynaptic response was reduced by LSD, activity at the other points in the visual system was highly resistant to depression by LSD and bufotenine. As in the case of the monkey, LSD and bufotenine showed striking similarity in their effects on the activity of the primary visual system.

ELECTROPHYSIOLOGICAL EXPERIMENTS:

The electrophysiological experiments were first carried out in cats anesthetized with sodium pentobarbital. In these experiments, intracarotid administration of LSD in doses of thirty micrograms per kilogram body weight caused a mean decrease of eighty percent in the amplitude of the postsynaptic lateral geniculate response to a single near-maximal optic nerve volley. This sensitivity of the lateral geniculate postsynaptic response to LSD is of the same order of magnitude as the sensitivity of the transcallosal response to LSD in the experiments of Marrazzi and Hart (26). Bufotenine in intracarotid doses of 0.2 milligrams per kilogram body weight had effects which were similar to those of LSD. Figures 8 and 9 illustrate the effects of LSD and bufotenine on the lateral geniculate postsynaptic response in the anesthetized cat.

Whereas LSD administered intracarotidly in doses of 30 micrograms per kilogram body weight caused marked reduction of the post-

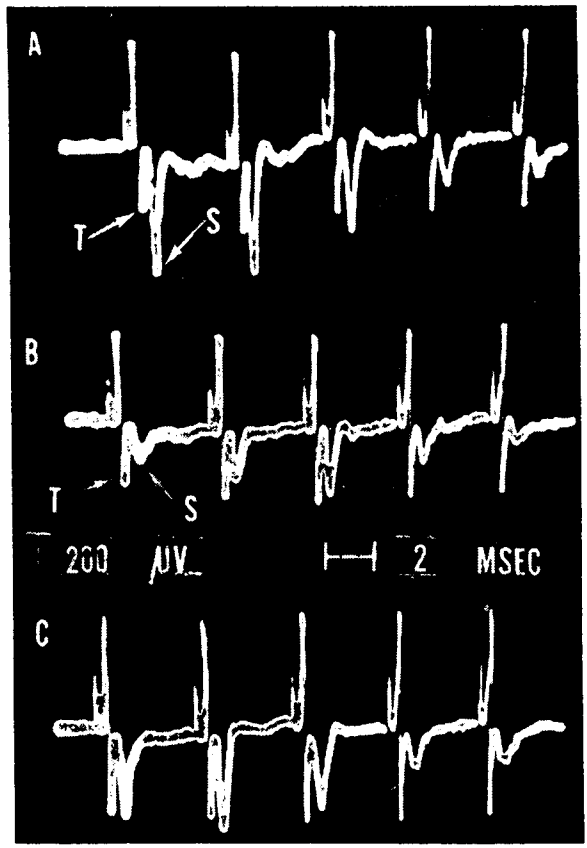

Fig. 8. *Effect of LSD on geniculate.* Response recorded in left lateral geniculate body to a train of five shocks at frequency 250/sec. applied to right optic nerve before (A) and after (B) 0.015 mg./kg. LSD via left carotid. Asphyxia, starting immediately after (B) and continued for 20 sec., caused an increase in amplitude of postsynaptic potentials (C). T = tract spike; S = postsynaptic spike. Positive is up.

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synaptic geniculate response in cats anesthetized with sodium pentobarbital, considerably larger doses of LSD, administered intravenously or intraperitoneally, to intact unanesthetized preparations with chronically implanted electrodes, were required to produce similar effects (13). It was found that sodium pentobarbital anesthesia caused an increase in the sensitivity of the lateral geniculate to depression by

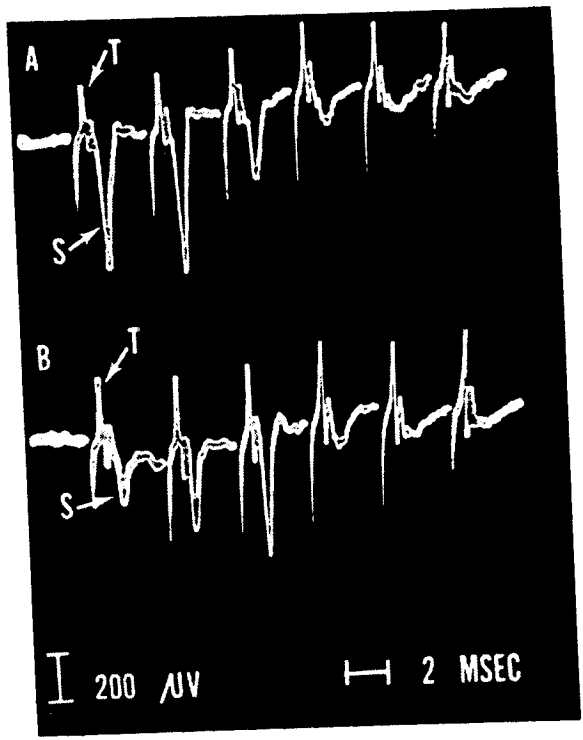

Fig. 9. *Effect of bufotenine on geniculate.* Response recorded in left lateral geniculate body to a train of 6 shocks at frequency of 295/sec. applied to right optic nerve before (A) and after (B) 0.2 mg. kg. bufotenine via left carotid. T = tract spike; S = postsynaptic spike. Positive is up.

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LSD. Figure 10 shows the effects of LSD on the geniculate response to optic tract stimulation in an intact preparation with chronically implanted electrodes. In this experiment in unanesthetized cats, one milligram per kilogram body weight (intraperitoneally) of LSD was required to produce geniculate depression of the degree that resulted from 0.03 milligrams per kilogram body weight administered intracarotidly in anesthetized cats. The dosage of LSD which depressed the postsynaptic response to optic tract stimulation in the intact cat preparation corresponds to the dose which causes the gross disorder of behavior in monkeys. In cats with implanted electrodes, the reduction of the geniculate postsynaptic response was associated with a failure of behavioral responsiveness to visual stimuli. While failing to respond to visual

stimuli, cats that had received large doses of LSD showed brisk and at times violent reactions to auditory stimuli, often jumping up, showing piloerection, hissing and orienting to the source of the auditory stimulus. This "rage" reaction in cats was in sharp contrast to the taming effect of LSD in monkeys. The preservation of responsiveness to auditory stimuli in association with a gross disturbance of responsiveness to visual stimuli was seen in both cats and monkeys.

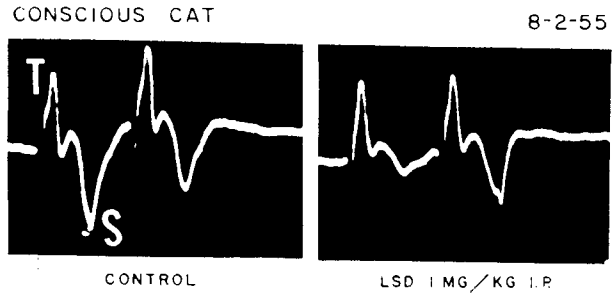

Fig. 10. *Effects of LSD on Lateral Geniculate Response to Optic Tract Stimulation.* The traces show the lateral geniculate responses to two shocks applied to the optic tract at an interval of 4 msec. LSD (1 mg./kg. intraperitoneally)[1] caused a reduction in the amplitude of the postsynaptic response (S) to the first shock. There was recruitment, and the postsynaptic response to the second shock was not depressed. The presynaptic tract response (T) was not altered. This preparation, which was an unanesthetized intact cat with chronically implanted electrodes, showed an absence of responsiveness to visual stimuli in association with this alteration of the lateral geniculate response. Positive is up.

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Compared with the postsynaptic lateral geniculate response to optic nerve stimulation, the postsynaptic cortical response to stimulation of the geniculate radiation fibers was highly resistant to depression by LSD and bufotenine. Purpura (28), employing somewhat different experimental procedures, observed a similar resistance of the cortical response to depression by LSD. Indeed, he actually observed facilitation of this response following small doses of LSD (28). In the author's experiments, doses of LSD and bufotenine, many times greater than those which caused reduction of the lateral geniculate postsynaptic response, failed to cause such depression of the cortical response to

geniculate radiation stimulation. Figures 11 and 12 illustrate the failure of large intracarotid doses of LSD and bufotenine to depress the cortical response to geniculate radiation stimulation in the anesthetized cat. In the experiment with LSD, illustrated in Figure 11, the cortical response was actually enhanced. This enhancement was apparent following LSD in a dosage many times greater than was found

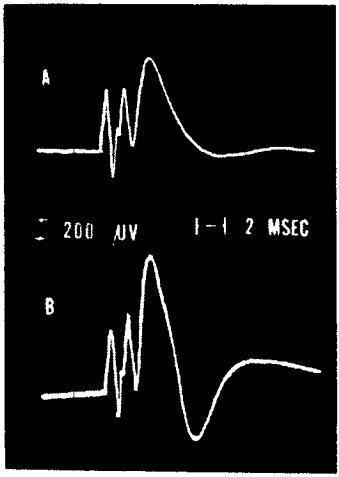

Fig. 11

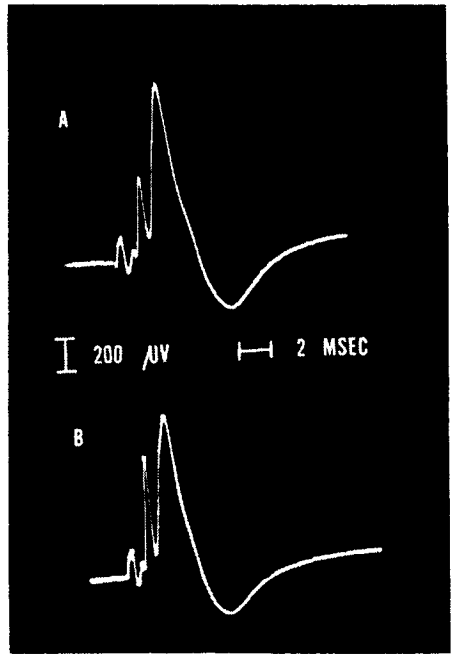

Fig. 12

Fig. 11. *Effect of LSD on cortex.* Left visual cortex response to single maximal shock applied to left optic radiations before (A) and after (B) 1.5 mg. kg. LSD via left carotid. Positive is up.

Fig. 12. *Effect of bufotenine on cortex.* Left visual cortex response to single maximal shock applied to left optic radiations before (A) and after (B) 10 mg. kg. bufotenine via left carotid. Positive is up.

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to be sufficient to depress the geniculate postsynaptic response in the anesthetized cat. This enhancement of the cortical response was not observed in unanesthetized intact preparations following a wide range of dosages of LSD (13).

Studies of the effects of LSD and bufotenine on the response of the optic tract to retinal photic stimulation showed that this response was highly resistant to the action of the two drugs. It appeared that under the conditions of the observations, the geniculate relay represented that point in the primary system which was most sensitive to depression by LSD. In terms of their actions on the three forms of evoked electrical activity in the visual system, LSD and bufotenine were similar. This physiological similarity suggested that the two substances might have similar mental effects in man.

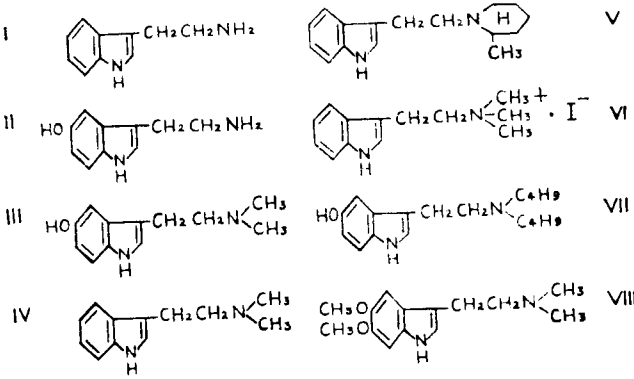

Fig. 13. *The structures of the tryptamine derivatives whose effects on geniculate transmission were studied.* I (tryptamine), III (bufotenine), and IV (dimethyltryptamine) caused depression of geniculate transmission. The remaining compounds, including II (5-hydroxytryptamine), were without effect on the lateral geniculate or the cortical responses to optic nerve shock.

DERIVATIVES OF LSD AND 5-HT:

To obtain further data concerning the degree to which the pattern of effect of LSD and bufotenine might be related to the psychotomimetic properties of these drugs, the effects of several additional LSD and 5-HT derivatives on the electrical activity of the visual system were studied (14). Figures 13 and 14 show the structures of the substances whose effects were investigated. Of these substances, only dimethyltryptamine (Fig. 13-IV) exerted effects similar to those which had been found to result from LSD and bufotenine. Tryptamine (Fig. 13-I) had effects which were qualitatively similar to those of

the other two compounds, but its duration of action was extremely brief. Table II summarizes the actions of these compounds on the postsynaptic geniculate response to optic nerve stimulation in anesthetized cats.

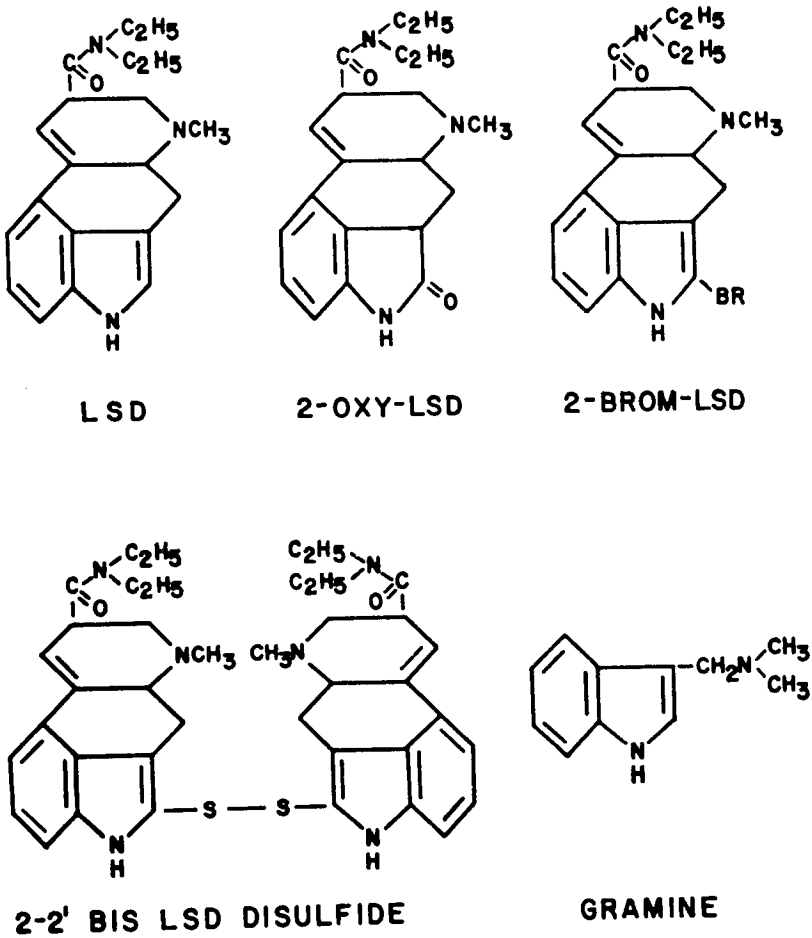

Fig. 14. *The structures of 4 LSD derivatives and gramine.* Of the 4 LSD derivatives, only LSD caused depression of geniculate transmission. The remaining 3 LSD derivatives were without effect on the geniculate or cortical responses to optic nerve shock. Gramine did not depress geniculate transmission; LSD administered following gramine did not block geniculate transmission.

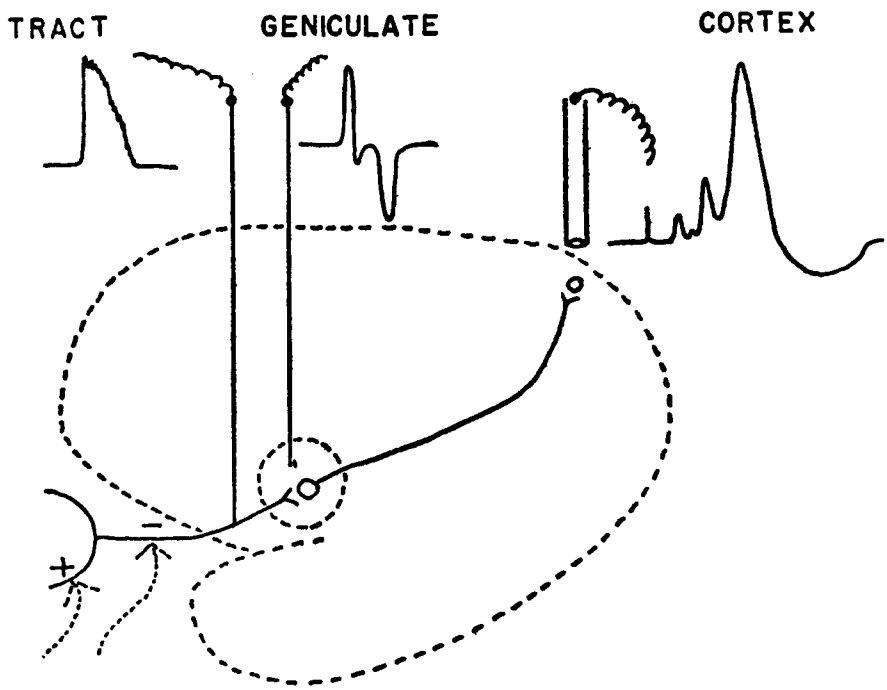

Fig. 15. *A schematic representation of the primary visual pathways.* In the acute experiments, the optic nerve was stimulated by square pulses delivered between the cut edge of the sclera (+) and the optic nerve (−). Such stimuli evoked responses which were recorded in the lateral geniculate nucleus and from the striate cortex. The form of these responses to a single optic nerve shock is illustrated under "geniculate" and "cortex" in the figure. In some experiments, stimuli were applied to lateral geniculate postsynaptic structures, evoking a cortical response similar in configuration to the one evoked by optic nerve shock, but lacking a synaptic delay. Tests of the retinal effects of LSD were made by recording the optic tract response to retinal photic stimulation. The form of the tract response to retinal photic stimulation is illustrated under "tract" in the figure above.

In the experiments on cats with chronically implanted electrodes, the electrodes were placed in the optic tract, the lateral geniculate nucleus, and the visual cortex.

TABLE II

THE EFFECTS OF A SERIES OF INDOLES ON GENICULATE TRANSMISSION

Drug	Dose (mg/kg)	% Decrease in postsynaptic response 1 minute following injection
I	0.2	70 (50-100)
II	0.2	
III	0.2	60 (50-90)
IV	0.4	90 (80-100)
V	4.0	
VI	0.2	
VII	1.0	
VIII	3.0	
LSD	0.03	80 (30-100)
2-oxy-LSD	0.3	
2-brom-LSD	0.3	
LSD-disulfide	1.5	
Gramine	15.0	

The structures of the drugs which correspond to I-VIII are shown in Figure 13. All drugs were given by the intracarotid route in nembutalized cats. The percent decrease is based on the change in the amplitude of the postsynaptic response to a single near-maximal optic nerve shock. The figures in parentheses indicate the range which was observed in the effects of the active compounds.

CONCLUSION:

The descriptions of some of the electrophysiological effects represent merely a very limited segment of the numerous investigations on the central electrophysiological actions of LSD and related indoles (1, 4, 5, 7, 8, 9, 21, 23, 25, 27, 28, 29, 31, 32). They do, however, indicate one approach to demonstrate a pattern of central electrophysiological effect which allows the selection of agents which have psychotomimetic effects.

The Psychotomimetic Agents. The similarity of the effects which were produced by bufotenine and LSD suggested that bufotenine might be an hallucinogenic agent. The fact that the effects of dimethyltryptamine closely resembled those of LSD and bufotenine led to the prediction that dimethyltryptamine, too, would exert psychotomimetic effects when administered to man (14). Studies by several in-

vestigators have confirmed this prediction. Fabing and Hawkins (16) demonstrated that bufotenine, in intravenous dosages of from 4 to 16 milligrams, causes hallucinations and alterations of mood in man. Isbell (22) confirmed these observations. Both Isbell (22), and Fabing and Hawkins (16) found that the duration of action of bufotenine was considerably shorter than that of LSD, and that the psychological effects of bufotenine were associated with a variety of cardiovascular changes. More recent studies by Szára have supported the speculation that dimethyltryptamine, too, is a psychotomimetic agent. Szára (39) studied the effects of parenteral administration of dimethyltryptamine in a series of normal subjects. In these experiments, dimethyltryptamine produced a variety of psychological effects similar to those which follow administration of LSD. Thus, experiments in man have now established the similarity of action of LSD, bufotenine and dimethyltryptamine which was inferred on the basis of neuropharmacological experiments.

What are the implications of the LSD-like properties of bufotenine and dimethyltryptamine for psychiatric research? The formulation of an answer to this question may be facilitated by a consideration of several additional data concerning the tryptamine derivatives under discussion. Bumpus and Page (6) have shown that bufotenine or some compound which bears a close structural resemblance to bufotenine may occur in the urine of man. Fish and Horning (17) have pursued this problem further, and have found that tryptamine is present in human urine and that at least one additional indole base, possibly bufotenine, is also present in human urine in extremely small quantities. The occurrence of bufotenine and tryptamine in man, and the possibility that dimethyltryptamine may also be naturally present in man, would seem to render the psychotomimetic properties which these drugs possess of considerable interest in any program of research which seeks to uncover hypothetical disorders of metabolism that may be related to psychotic behavior. To our knowledge, bufotenine is the only psychotomimetic agent which has been shown to occur in man. Of course, the trace amounts in which it appears may indicate that bufotenine has little if any importance in any physiological process. Nevertheless, the belief that bufotenine, dimethyltryptamine, tryptamine (Fig. 13-1), or some structurally related substance may be of significance in some mental disorders appears sufficiently plausible to warrant further investigation. Such investigation is also war-

ranted by the large body of data indicating that alterations in the status of 5-HT in the central nervous system are associated with changes in a variety of neurological and psychological processes. The experiments of Shore and others (34, 35), of Woolley and Shaw (40, 41, 42), and of many other workers have indicated that 5-HT (serotonin) may have some function in regulating central nervous system activity.

Much additional data might be presented in support of future research concerning the status of bufotenine and dimethyltryptamine in patients with mental disorders. It would appear that the above discussion has already supplied sufficient evidence to warrant additional investigation of the status of a number of indoles in a variety of psychotic populations.

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