THE LSD PSYCHOSIS

I. PHARMACOLOGICAL ASPECTS
OF THE LSD PSYCHOSIS

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The exciting discovery by Hofmann in 1943 of the mental effects brought about in humans by mere traces of the ergot derivative LSD has made LSD one of the promising chemicals in the field of experimental psychiatry. The scope and complexity of the problem is related in the following articles.

The first is by Cerletti on the pharmacological aspects of LSD. Psychological effects are discussed by Rinkel, Chairman of the Symposium; Hofmann presents some of the essential chemistry of LSD and related compounds with emphasis on the spatial relation of molecular structure to mental effects.

A more general survey of the effects of drugs on mental activity is presented by Thuillier, who discusses LSD and other drugs in relation to psychosis. He emphasizes the study of metabolic deviation.

If the peculiar effect of lysergic acid diethylamide (LSD) on psychic functions in man is considered from a pharmacological point of view, the question arises whether it makes any sense to simply enumerate findings which were made in a large number of tests in vitro and in vivo. The pharmacologist undoubtedly has to establish an over-all picture of the properties of a compound he is testing, and as many data as possible have to be collected for this purpose. However, pure fact-finding alone does not answer the fundamental question, why and by what mechanism the astonishingly small amount of a very few micrograms of LSD cause, within the brain, such profound alterations. LSD is, for example, a well defined oxytocic drug, only slightly less active than ergonovine, when tested on a suitable uterus preparation. As interesting as this observation may be within the frame of comparative pharmacological studies of ergot compounds, it cannot be related in any way to its hallucinogenic property. There-
fore, the purpose of this paper is not to give a complete summary of the pharmacology of LSD, but to select and group specific findings in an attempt to show to what extent they can be integrated into hypotheses formulated to explain its psychotomimetic activity.

**GENERAL REMARKS:**

1. Studies on distribution and fate of LSD in the body have revealed that only a small fraction of the total dose administered reaches the brain (1, 3, 34, 49). But as in other organs the content of LSD in the brain decreases rather rapidly, and after one to two hours it is no longer detectable. Within this same period about 70 percent of the whole LSD dose is metabolized by the liver. Even after intracerebral injection, LSD disappears as rapidly as after intravenous administration from the brain and the cerebrospinal fluid and shows up in the bile (27). Since the metabolites excreted by the liver seem to be biologically inactive, it could be assumed that LSD is mainly responsible for triggering the psychotic reaction and that the further development is no longer connected with the presence of this amide or its derivatives in the brain tissue.

2. Since there is at present not enough evidence for the assumption that LSD acts on the brain indirectly, for example via the liver, only the different possibilities of an interference of LSD with brain functions will be considered. In spite of this restriction, a very large field covering experimental data as well as theoretical considerations remains open for discussion. Accepting a certain risk of simplification as a price for some didactic advantages, we will try to review our pharmacological knowledge on the direct central nervous system effects of LSD along four main lines, each corresponding to a possible mechanism of action underlying the mental effects of LSD.

**PHARMACODYNAMIC CONCEPTS OF THE**
**LSD PSYCHOSIS:**

1. **Influence of LSD on the central nervous system by its effects on brain metabolism and enzymes.** From results of studies *in vitro* it has been suggested that the psychic effects of LSD could be related to some alterations of oxygen utilization and/or carbohydrate metabolism in the brain. In brain homogenate of guinea pigs (under the
influence of small quantities of LSD), an increased oxygen consumption and accumulation of hexosemonophosphate was observed (38). A rise in blood hexosemonophosphate was reported by the same authors, also in human subjects after intake of a hallucinogenic dose of LSD. Other authors using higher concentrations of LSD found an inhibitory effect on the oxygen consumption of slices or homogenates of guinea pig brain (24). In electrically stimulated brain slices increased respiration and lactic acid formation were observed with $3 \times 10^{-6}$ moles of LSD. Higher concentrations had the opposite effect, and in resting brain tissue no change at all occurred (35). In spite of such promising observations in vitro, studies of cerebral metabolism (oxygen consumption, glucose utilization, respiratory quotient) and blood flow in normal and schizophrenic individuals did not show any changes under the influence of LSD (48).

The possibility of LSD interfering with the activity of different enzymes has been investigated several times, but without yielding any conclusive evidence. A slight inhibition of the succinic dehydrogenase system and stimulation of cytochrome C oxidase have been reported (13). From the brain cholinesterases only pseudocholinesterase is inhibited by LSD, whereas the true cholinesterase and tributyrinase remain unaffected (51). However, it has been claimed that higher concentrations of LSD increase the activity of cholinesterase in rat brain (52). Inhibition of serum cholinesterase by LSD can easily be demonstrated (26, 51, 55), but this property is also shared by the nonhalucinogenic brom-derivative of LSD (BOL-148). As far as mono- and diamino-oxidase are concerned, studies in our laboratory demonstrated that LSD is devoid of specific action on these enzymes (9). LSD also did not affect the activity of quite a number of other enzymes studied in our laboratory, such as 5-hydroxytryptophane decarboxylase, dopa decarboxylase, glutaminic acid decarboxylase, and amino acid oxidase.

2. Influence of LSD on the central nervous system by interaction with 5-hydroxytryptamine (serotonin, 5-HT). The structural analogy as well as the interactions between LSD and 5-HT led to the hypothesis that 5-HT plays a part in the maintenance of normal mental processes and that LSD, because of its antagonism, would interfere with these physiological functions of 5-HT (54). Actually a marked and specific antagonism of LSD against peripheral effects of 5-HT has been demonstrated many times in a considerable variety of tests e.g., on the isolated rat uterus (11, 21, 22, 34); the guinea pig ileum (22);
the vessels of the rabbit ear (21, 22, 45); the perfused hind leg of the cat, dog (25) and rabbit (39); the pulmonary vessels of the cat (25); the renal and mesenteric vessels of the cat (41); and the perfused rat kidney (9, 11). An antagonistic effect of LSD to serotonin-induced bronchoconstriction in the cat and guinea pig (2, 11, 28, 32), and the serotonin antidiuresis in the rat (17) have also been demonstrated.

It is, however, not very likely that this peripheral serotonin antagonism has anything to do with the hallucinogenic property of the drug. The brom-derivative BOL-148 has no hallucinogenic effect, in spite of its anti-5-HT potency being of the same magnitude as that of LSD (11, 12, 31). The acetyl and methyl derivatives of LSD (compounds ALD-52 and MLD-41) show a significantly higher antisero-
tonin activity than LSD (10) but are less hallucinogenic.

The possible interference of LSD with central effects of 5-HT are of course of major interest from the point of view of the psychic actions of these drugs. In this respect, unfortunately, the evidence is not at all as comprehensive as that of the peripheral interactions. In this context it is to be mentioned, first of all, that LSD does not cause serotonin depletion in the brain. Furthermore, the releasing effect of reserpine on the brain serotonin is not affected by LSD (5). Serotonin has the ability to potentiate the barbiturate narcosis in various laboratory animals. It has been shown many times that this potentiating effect can be inhibited by LSD in mice (11, 35, 46, 47, 50), as well as in rats (7) and rabbits (8), but this antagonism does not appear to be related to the hallucinogenic property of the drug, since the same antagonism can be demonstrated with the nonhallucinogenic substance BOL-148 (50). If introduced into a cerebral ventricle, 5-HT produces a lethargic state in the cat, a cataleptic condition in the dog. The lethargic cat can be aroused by an intraventricular injection of LSD, but very large amounts of LSD are needed for this purpose (23). In the dog, the cataleptic state induced by intraventricular injection of 5-HT can be lessened or blocked by much smaller doses of LSD (44). These effects are, however, not specific for LSD, since they can also be produced by a variety of other drugs that cause central sympathet-
ic stimulation.

Summarizing the results of the present state of research in this field, it can be said that the presence or absence of peripheral anti-
5-HT effects does not appear to determine the psychotic effects of the substances under consideration, and that our knowledge concerning
central interactions between 5-HT and LSD is not yet consistent enough to provide a satisfactory explanation for the particular effects of this latter drug on psychic functions.

3. Influence of LSD on the central nervous system by direct neuronal and synaptic effects. Several authors have made the point that LSD can interfere with the transmission of impulses across intracerebral synapses. Facilitation of the evoked auditory and visual primary response in the cortex of unanesthetized cats has been demonstrated after small doses of LSD. This synaptic facilitation also involves marked alteration in the recovery cycle of excitability. Larger doses of LSD depress the evoked auditory response whereas facilitation of the evoked visual primary response persists (15). In contrast to the specific afferent system, thalamic recruiting responses are inhibited by small doses of LSD. Excitatory LSD effects on specific afferent systems and inhibitory action on nonspecific corticocortical systems have been ascribed to a different action of LSD on axosomatic and axodendritic synapses (16). These findings are in accordance with and may also in part explain other findings demonstrating an inhibitory effect of LSD on transcallosal transmission in the optic cortex of cats (36, 37) and depression of synaptic transmission within the lateral geniculate body of the visual tract of the cat (19, 20).

In several electroencephalographic studies on cats and rabbits, a flattening of the cortical potentials and an alerting pattern have been observed after LSD administration. Electroencephalographic and behavior-arousal responses following sensory stimuli are facilitated by LSD (4, 6, 14, 29).

Without further discussion of all the facts available in the LSD literature it can be stated that the electrophysiological approach has brought a number of interesting findings. Some of them, however, have been obtained only by using large amounts of the drug. Others are not specific for LSD since other drugs were found to act in the same way. The demonstration of a dual and divergent action of LSD on different synapses with different functions in the central nervous system represents, certainly, an important finding. However, since changes of evoked cortical potentials or alterations in the electroencephalographic pattern cannot yet be related to distinct states of awareness, behavior or psychic functions, it must be admitted that we have still a long way to go toward the understanding of the effects of LSD on the basis of its action on neuronal and synaptic structures.
4. Influence of LSD on the central nervous system as measured by behavioral changes and by changes of vegetative functions. LSD effects on behavior of animals have been repeatedly examined in a large variety of species. In all these experiments, relatively high doses of LSD have been used as compared to those administered to humans. In most instances LSD produces predominantly symptoms of alertness, excitation, hostility or fear. Still higher doses of this drug induce muscular weakness and ataxia in cats, dogs and monkeys and inactivity in certain fishes, and they impair conditioned reflexes in rats (9, 18, 42, 53). To correlate such observations with the characteristic hallucinogenic effect produced in human beings, it will be necessary to increase our research in the field of animal psychology.

We have already commented several times on the fact that certain effects of LSD in animal experiments are obtained only with doses far beyond the human dose level of this drug. It is therefore interesting to note that several characteristic vegetative effects of LSD can be obtained in animals with similarly low amounts of the drug. A significant rise in body temperature of the rabbit, for example, can be observed after the injection of only 0.5 micrograms of LSD per kilogram body weight. Furthermore, small doses of LSD also produce mydriasis, hyperglycemia, piloerection, tachycardia and tachypnea in rabbits. All these effects point to a distinct sympathomimetic action of LSD in rabbits, the central origin of which is demonstrated by the inhibitory effect of hypnotics, ganglionic and adrenergic blocking agents as well as that of decerebration (30, 33, 40, 43). LSD also induces mydriasis and motor excitation in mice. In several tests the action of epinephrine, norepinephrine and amphetamine can be enhanced by LSD. LSD also induces a slight contraction of the nictitating membrane and potentiates in anesthetized cats, the rise of blood pressure following central sciatic nerve stimulation. All these findings suggest that LSD elicits a predominant syndrome of central sympathetic stimulation. However, LSD also exerts in some instances distinct depressive effects, which may be related partly to sympathetic inhibition, partly to parasympathetic stimulation. The barbiturate hypnosis in rats and mice can be potentiated by LSD. The body temperature as well as the oxygen consumption of rats is decreased by relatively small doses of LSD, and only very large doses are pyrogenic in this species. Blood pressure, heart rate, respiration, as well as the response to bilateral carotid occlusion in the anesthetized cat, are decreased by
LSD. In some in vitro and in vivo tests a slight adrenolytic effect can be demonstrated.

Considering all these vegetative effects, again a dualistic action of LSD can be observed: a predominant central sympathetic stimulation parallels a slight central and peripheral depression.

CONCLUSIONS:

The results of the biochemical investigations on metabolic and enzymatic effects of LSD do not yet permit the formulation of a hypothesis regarding its hallucinogenic effect. An increasing number of observations suggest that the peripheral antiserotonin effect of LSD is not related to its specific central action. These findings, however, still leave open the possibility that LSD may interfere with the metabolism of sympathetic amines or 5-HT within the central nervous system.

Despite the findings that LSD disappears very rapidly from the brain, characteristic effects of LSD on synaptic transmission within the central nervous system and on a variety of vegetative functions have been demonstrated in animals with doses of LSD which are equal or up to twenty times higher than those producing hallucination in man. In both instances a dual action of LSD could be demonstrated: facilitation and stimulation in some systems, with a slight depression or inhibition in others. In this respect an analogy between LSD and the pharmacological and clinical action of morphine is to be emphasized. Based on these findings, the hypothesis could be formulated that the bivalent and partially opposing effects of LSD on the central nervous system, and especially on the vegetative centers of the brain stem, produce a disequilibrium which may cause a change in psychic functions from normal to psychotic states.

SUMMARY:

An attempt was made to group and integrate the numerous results of experimental investigation of LSD. A hypothesis could be formulated that suggests the possible mechanism of its action. However, many more data on this interesting drug are needed in order to understand the exact mechanism of its hallucinogenic property. Undoubtedly such findings would enlarge our understanding of normal and pathological psychic functions.
REFERENCES


CHEMICAL CONCEPTS OF PSYCHOSIS


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