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Pharmacology of LSD-25

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IN RECENT TIMES, an unusually wide and growing interest has developed for the substance known as LSD-25* (lysergic acid diethylamide). The peculiar and frequently described effects of LSD on psychic functions, in conjunction with the modern concept that mental illness also may be a biochemical phenomenon, are responsible for this interest. It has been known for a long time that certain pharmacologic agents may elicit characteristic disturbances of the intellect and psyche. For this reason alone, LSD would not warrant any greater interest than cocaine, hashish, mescaline, opium, etc. The peculiarity of LSD however, does not rest so much in *what* it produces, but *how* it produces its effect. We are still quite remote from an understanding of the latter question, but elucidation of this mechanism may be of eminent importance for the understanding of the pathogenesis of mental illness, as well as its prophylaxis and therapy. With these considerations in mind, we feel justified, as pharmacologists, in taking part in a psychiatric discussion.

LSD was first synthetized in the Sandoz research laboratories seventeen years ago. Starting with lysergic acid, a specific component of all ergot alkaloids, Stoll and Hofmann[1] in 1938, succeeded in synthetically producing the natural alkaloid ergonovine, as well as a larger number of new lysergic acid amides, among which LSD-25 was included. In accordance with its close relationship to ergonovine, we were able to show that LSD exhibited oxytocic activity only slightly weaker than that of ergonovine. Particular attention, however, was directed towards LSD in 1943 when A. Hofmann, stimulated by an apparent laboratory intoxication, discovered the specific psycho-activity of this substance in a series of reproducible experiments on himself. As a result of further experiments on members of the staff and associated co-workers in the laboratory, the observations of Hofmann were fully confirmed. It was soon learned that an effective oral dose in normal subjects was

*Known as Delysid, a registered trade-mark of Sandoz Pharmaceuticals.

between 0.5 to 1.0γ/Kg. body weight. This tremendous activity was characteristic for LSD, since other similarly active substances, such as mescaline, require doses 5,000 times greater, and more, to produce psychic effects. A more extensive psychiatric analysis of the LSD activity seemed indicated, and the young psychiatrist, W. A. Stoll undertook the project. His investigations, partly carried out in our laboratories and partly in the Department of Psychiatry of the University Hospital in Zurich, were published in 1947, in the framework of a basic study of the problem.[2] The detailed description of the clinical picture of the acute LSD effect on normals and schizophrenics given by W. A. Stoll, was subsequently confirmed by numerous other investigators. We must abstain from discussing the many clinical papers on LSD which have since appeared, as it is not within our scope to discuss specific psychiatric aspects of the LSD problem, but rather to contribute to the knowledge of this substance in the realm of pharmacology. Moreover, it must be said that it is hardly possible today to understand the enormous activity which LSD exercises on the human psyche in terms of its pharmacodynamic action. Nevertheless, the systematic analysis of the pharmacologic properties of LSD is an important pathway in the understanding of the pathogenesis of emotional and mental disturbances, from a biologic and biochemical point of view.

CHEMISTRY

LSD is the diethylamide of lysergic acid which constitutes an essential component of all natural ergot alkaloids. Since, aside from lysergic acid, an isomeric isolysergic acid exists and both are optically active, there are correspondingly four stereo-isomers of lysergic acid, as well as four different LSD isomers. From a pharmacological point of view as well as in regard to effectiveness in man, only d-lysergic acid diethylamide is interesting, inasmuch as the l-form and the d and l derivatives of isolysergic acid are pharmacologically inactive.

ABSORPTION, DISTRIBUTION and EXCRETION

LSD-25 is easily soluble as a salt of tartaric acid and as such is highly active by mouth. Contrary to the complicated molecular structures of the peptide-containing ergot alkaloids, the simple derivatives of lysergic acid, ergonovine or LSD, are quickly and completely absorbed.

Investigations on the distribution of LSD in the body have given a

surprisingly clear picture. At first we studied the problem with a biological method, using the inhibition of serotonin (5-oxytryptamine) by LSD for determination of small quantities of LSD in tissue extracts.[3] As a result of the availability of tagged LSD,[4] a second means of studying the fate of this substance in the body was found. On the basis of the studies carried out in two different laboratories,[5,6] the following may be said:

LSD administered intravenously disappears relatively rapidly from the blood and can be found within a very short time in different organs, the highest tissue concentration being reached ten minutes after administration. LSD is clearly demonstrable also in the brain though in much lesser concentration than in many other organs, particularly liver, spleen, kidney, adrenals. Tissue concentration of LSD declines rapidly, since, within a short time, all the LSD is excreted through the liver and bile into the intestinal tract from which it is eliminated. In the course of the elimination process through the liver, LSD is altered in its properties in that it is present in bile in the form of metabolites which still appear to be closely related to LSD chemically. The fact that in warm-blooded animals LSD is not truly broken down, and/or enters the general metabolism, is suggested by the observation that of the total C_{14}-LSD radioactivity, hardly any appears in the urine or is exhaled through the lungs (CO_2). However, the greater portion of radioactivity is found within a few hours in the content of the intestinal tract. Further studies on the LSD metabolites excreted through the liver are in progress, but there is reason to assume that these differ only slightly from LSD inactivated by some detoxification process.

TOXICOLOGIC DATA

The acute toxicity of LSD differs considerably according to animal species. Relatively speaking, mice tolerate the highest doses so that in determining the LD_{50}, 50-60 mg./Kg. must be injected intravenously. In the rat the intravenous LD_{50} of LSD drops to 16.5 mg./Kg. and is thus approximately four and one-half times smaller than that of ergonovine. An even higher toxicity of LSD in relation to ergonovine is present in the rabbit where 0.3 mg./Kg. LSD i.v. constitutes the LD_{50}. Among all the natural ergot alkaloids no representative is known which exhibits such high activity in the acute toxicity experiment. The picture of LSD poisoning is devoid of any specific features. Ataxia, paralysis and sometimes increased reflex response may be seen in addition to various vege-

tative symptoms. Death occurs as a result of respiratory failure. Disturbances of respiration which sometimes develop into respiratory arrest may occasionally be seen in animals after the relatively small LSD doses of 50-100γ/Kg., and seem to be the expression of the LSD effect on the respiratory center.

In chronic experiments in rats we have been able to give 2.5 mg./Kg. LSD daily i.v. for a period of 30 days without losing any animals. Since the maximum tolerated single dose in the rat is approximately 3.2 mg./Kg., no cumulative factors seem to be present in the light of what we know about the excretion of LSD. Vice versa, no toleration appears to develop in that the animals pretreated with LSD require the same LD_{100} as the untreated animals. Rats submitted to chronic LSD effects exhibit tremor, increased reflex response and pilo-erection. These symptoms, however, are relatively unspecific and decline in intensity within a few days. Nevertheless, the animals are retarded in weight increase compared with the controls. Histologic tissue examinations of these animals are not available at the present time. Following chronic administration in dogs degenerative changes of ganglionic cells in the brain have been described.[7]

PHARMACOLOGY

The most important pharmacodynamic properties of LSD may be grouped as follows:

Peripheral Effects

1. LSD increases the contractility of the uterine muscle and in this respect practically has the activity of ergonovine.

2. The smooth muscle of the vasculature contracts after large doses of LSD, but this effect is manifested only in isolated vessels and spinal animals. In the presence of intact nervous innervation, the effect of LSD on the central nervous system predominates and decreases the vasomotor tone.

3. The specific adrenolytic action so characteristic of the peptide alkaloids of ergot is not demonstrable for LSD. However, LSD exhibits a marked antagonism toward 5-oxytryptamine (serotonin, Enteramine), as detailed below.

CNS Effects

LSD precipitates a multiplicity of vegetative reactions, some of which are sympathetic and others parasympathetic in nature:

1. Characteristic of LSD is the mydriatic action present in various animal species and which can be inhibited by adrenosympathicolytic agents.

2. In the rabbit, LSD produces a hyperglycemia which can be inhibited by the hydrogenated ergot alkaloids.

3. High sensitivity toward LSD is exhibited by the centers of heat regulation. In the cat, dog, and rabbit LSD provokes an increase in body temperature. The rabbit particularly is so sensitive that doses of 0.5-1γ/Kg. i.v. regularly produce a pyrogenic response. Under anesthesia and by pretreatment with hydrogenated ergot alkaloids of the ergotoxine group, this pyrogenic effect (similar to the glycemia) can be inhibited.

4. Animals treated with LSD have an increased pilo-erection indicating increased sympathetic activity.

5. In contrast to the LSD effects already mentioned, other symptoms seem to be essentially of vagal origin. Thus, increased salivation and lacrimation are particularly evident in the dog.

6. 50-100γ/Kg. LSD in the anesthetized cat produced bradycardia by a central vagal mechanism. At the same time, a blood pressure decrease may be observed which also is of central origin since it is absent in the spinal cat.

7. Respiration is effected by LSD doses of 10-50γ Kg. which are distinctly active both in terms of inhibition or stimulation. Large doses of LSD produce respiratory standstill and death.

8. Other CNS effects appear only with doses exceeding 100γ/Kg., and include increased intestinal peristalsis, vomiting, ataxia, paralysis of the extremities, etc.

In summarizing, we can say that LSD produces a multiplicity of pharmacologically well-defined effects, the majority of which appear to be of CNS origin. Of greatest interest are effects which are reproducible with very small doses and in this relation the action of LSD on body temperature regulation in the rabbit is outstanding. The minimum effective doses are readily comparable to those effective in man. This does not imply any identity of the two effects—the pyrogenic action in the rabbit and the psychic effect in man. At most, however, there is an analogy which may be confirmed further, in that both in man and the rabbit, tachyphylaxis and tolerance develop quickly. Moreover, it must be emphasized that a considerable number of simple lysergic acid derivatives as well as the natural ergot alkaloids equally

raise body temperature, however, large doses are usually required. Also others of the aforementioned pharmacologic actions of LSD are not specific in the sense that they are produced by other substances chemically related to LSD. Marked vegetative stimulation similar to that of LSD was observed by us in animals and man following administration of substances which, though structurally closely related to LSD, would be devoid, in the doses used, of any psychic effect (lysergic acid dimethylamide, lysergic acid pyrrolidine, etc.). So far only the monoethylamide of lysergic acid (LAE 32) proved to be qualitatively similar to LSD, even though the dose required was ten times larger. It may be possible that the ethyl groups may be of decisive importance for the psychic effect of LSD, the vegetative effects being common to a greater number of lysergic acid amides.

The marked antagonism between LSD and serotonin first found by Gaddum[8] as well as the presence of serotonin in the brain[9,10] have given rise to new ideas concerning the possible mechanism of action of LSD. More recent observations render any formulation of such hypotheses[11,12,13] very difficult at the present time.

THE ANTAGONISM TO 5-OXYTRYPTAMINE

A number of peripheral effects of 5-oxytryptamine can be selectively inhibited by LSD. Our own observations cover not only LSD, but a large number of LSD derivatives and LSD homologues. Without discussing details, it can be said that more or less marked inhibition of serotonin is characteristic of a large number of lysergic acid derivatives. It is of interest that the psychic action of LSD and serotonin antagonism do not run parallel as was most clearly established for an LSD derivative in which bromine is substituted in position 2.[14] Investigation of this substance shows that serotonin effects on smooth muscle (uterus, vessels, bronchial musculature), is at least as strongly inhibited as by LSD. On the other hand, both in pharmacologic tests and in human experiments, all other effects of LSD were not inherent in the bromine derivative. No psychic effect of bromine LSD could be elicited with doses of 1-2 mg. We are thus faced with the fact that an LSD derivative has lost all properties typical of LSD and yet exhibits definite serotonin antagonism. It is therefore not possible to relate the unique psychic effect of LSD to its serotonin inhibitory properties. One might well assume that bromine LSD does not enter the central nervous system and its serotonin-inhibitory effect may, therefore, be limited to the periphery only. However, the presence of

bromine LSD in the brain could be demonstrated in the same manner as for LSD itself. If, in addition to the purely peripheral smooth muscle action of serotonin, the potentiation of barbiturates is used for testing, the serotonin effect may be equally inhibited with bromine LSD as with LSD. Without wishing to exclude the possibility that serotonin may be somehow involved in the production of the "LSD psychosis," the relationship seems to be considerably more complicated than the assumption of a simple competitive serotonin-LSD antagonism on smooth muscle.

In reviewing all the facts that pharmacologic analysis has so far yielded, we must admit that we are far from a satisfactory explanation of the mechanism of action which is responsible for the unusual psychic effects of the minute parts of this substance. The assumption of involvement of enzymatic processes is obvious, but despite considerable research in this direction (LSD and cholinesterase, LSD and amino-oxydase, and enzymes of carbohydrate metabolism) no results have yet been obtained which contribute to the understanding of the problem. It is to be hoped, however, that the great efforts made in psychoneuropharmacologic research today may allow new insight into the relationship between psychic function and biochemical processes, and that in the course of these developments LSD may yield more and more of its secrets.

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