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Lysergic Acid Diethyl Amide (LSD-25): XXXVII. Antiserotonin Action of Lysergic Acid Derivatives in Allergy and Neuropsychiatry

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Although derivatives of d-lysergic acid have been employed in medicine for many years, the knowledge of their unique action on the central nervous system is dependent upon comparatively recent studies. The antiserotonin action of these compounds makes them of special value in the study of allergic mechanisms. Antiserotonin drugs may possibly lead to a more general method of therapy. It is the purpose of this communication to briefly review, and coordinate where possible, the reports of some pertinent investigators looking toward future research.

General Remarks

For many years the dominant notion in the therapy of the allergic state was based on neutralizing the effects of histamine. There were many contradictions and paradoxes to this view, especially the failure of the antihistamines in the treatment of asthma. More recently serotonin (5-hydroxytryptamine) has been brought into the picture not only as an agent possibly connected with emotional disturbances, but also as a mediator in the symptoms of allergic phenomena.[1] Thus Waalkes[2] and his coworkers have shown that serotonin is released in vitro from rabbit platelets following antigen-antibody reactions and in vivo during anaphylaxis because clumped platelets and white cells collect in pulmonary vessels during the anaphylactic response. In the rabbit the quantity of both serotonin and histamine in the lung is increased.

O'Brien, Hughes and Newberne[3] point out that serotonin is known to be involved in the anaphylactoid reaction elicited by dextran and egg white. The same authors showed that d-lysergic acid diethylamide (LSD-25) blocked the course of experimental allergic encephalitis. Fifty mcg triweekly reduced the incidence of paralysis, the mortality rate and the severity of the histopathologic lesions in guinea pigs with allergic encephalitis.

The experiences just briefly cited are amongst a host of others which have been reported correlating the antiserotonin action of d-lysergic acid derivatives like LSD and Sansert with their antiserotonin actions.

If the antiserotonin era is about to supplement the antihistamine and steroid eras, physicians should become aware of the nature of the action of drugs like LSD-25, and Sansert. These two drugs together with 1-methyl

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derivatives of LSD-25, namely, 1-methyl d-lysergic acid diethylamide (MLD), are amongst the most powerful antiserotonin drugs studied in the group of compounds related to d-lysergic acid.[4] All three of these produce important psychic effects in nonpsychotic subjects although the dosage varies considerably. Thus the threshold dose of 1-methyl d-lysergic acid diethylamide in nonpsychotic subjects is about three times that of LSD-25 while that of Sansert is about 150 times that of LSD-25 at its threshold of activity.[5]

It is important to note that important antiserotonin effects are present in other d-lysergic acid derivatives. Thus it is surprising that systematic investigation of 1-methyl d-lysergic diethylamide (MLD) which has an antiserotonin action approximately equal to that of Sansert, has not been studied more intensively.[4] It has been safely taken in high dosages without psychic effects by ambulatory subjects in my studies of tolerance to LSD. Certainly the side effects of the 1-methyl derivative of LSD should be no greater, and indeed much less, than those of the butanolamide (Sansert).

Table 1 illustrates some of the compounds which have been studied in nonpsychotic subjects and their antiserotonin values. The first column indicates the relative strength in regard to LSD as determined by the Cold Spring Harbor questionnaire, and the second column indicates the antiserotonin effects as reported by Cerletti and his coworkers.

The argument has been advanced that the quantity of a compound like MLD required to give the theoretical antiserotonin action of methysergide (UML) would lead to undesirable side-effects. The writer[6] has found that MLD develops tolerance to itself rather rapidly certainly as rapidly as methysergide develops tolerance to itself. Therefore the antiserotonin or other effect responsible for the action of methysergide in migraine could be readily tested by studying the effect of slowly increasing the dosage of MLD.[7]

The investigation of the compounds under discussion in disturbances of mental and allergic states is bound to open new avenues for research and treatment.

TABLE I

A Comparison of Psychotomimetic and Antiserotonin Activity of Derivatives of d-Lysergic Acid

	Psychological Activity	Anti-Serotonin Activity (Cerletti)
d-lysergic acid diethylamide (LSD)	100	100
acetyl d-lysergic acid diethylamide (ALD)	91	210
oxymethyl d-lysergic acid diethylamide (OML)	66	59
l-methyl d-lysergic acid diethylamide (MLD)	36	370
d-lysergic acid morpholide (SLM)	11	2
2 brom d-lysergic acid diethylamide (BOL)	7.2	103
d-lysergic acid pyrrolidide (LPD)	5.3	5
d-lysergic acid ethylamide (LAE)	3.4	12
l-methyl d-lysergic acid butanolamide (UML)	.66	400

Safety and Side Effects of LSD (Lysergic Acid Diethylamide); Delysid

There is a considerable body of evidence showing that compounds like LSD-25 and Sansert are safe to use when administered by physicians. Thus in a careful statistical survey Cohen[8a] points out that *no instance of serious prolonged physical side effects* was found either in the literature or in the answers covering more than 25,000 administrations of LSD or mescaline. He points out that the literature records directly only one suicide in a schizophrenic patient and a small number of short self-limited psychotic reactions. He concluded that the administration of LSD is safe when given to a healthy selected group. With the application of certain safeguards, many side effects can be avoided. Ditman, Hayman and Whittlesey[8] studied the effect of administration of 100 mcg of LSD-25 orally in a permissive but non-treatment setting. Using a questionnaire they studied the effect of the LSD experience without psychotherapy. Claims of therapeutic value of the LSD experience were made by 74 of their 87 subjects. The early claims of the subjects were comparable to the most optimistic claims of other investigators who used it with prolonged and intensive psychotherapy. For one and a half years after exposure to LSD a very high percent of alcoholic patients claimed to have decreased their drinking and about one third claimed complete abstinence. *There is no evidence of brain damage in this group, only improvement occurring in a very large fraction.* The writer has worked with these compounds continuously since 1951 and has administered them hundreds of times without noting the deleterious effects either in "normals", neurotics or hospitalized psychotics. It seems important to stress at this time that many derivatives of d-lysergic acid play a most important role in medical treatment.[9] To label any one of these derivatives as the cause of "chronic brain damage" without direct evidence, validated statistically, constitutes a disservice to science and to the practice of medicine. It is the purpose of this communication to balance anxiety with some of the more positive and statistically valid aspects of the actions of these drugs.

UML (Methysergide; Sansert; 1-Methyl D/Lysergic Acid Butanolamide; Deseril

Of particular interest to the readers of this communication is the remarkable effect reported for Sansert in the treatment of migraine.[7] Certain cases of migraine are well known to be caused by allergic reactions to foods. The published side effects of Sansert are very similar indeed to the effects of LSD-25 although at times the autonomic and psychic side effects may be overshadowed by the vasomotor phenomena of the high dosage of the ergot derivative compared with the threshold activity of LSD-25 or MLD. It is unfortunate that the similarity of the side effects of Sansert to those of LSD is denied by some of the workers in the field. In spite of the alleged danger of LSD and similar compounds, there are no valid data showing any correlations between

the use of any of these drugs and permanent psychic injury. For example, Sandison[10] has pointed out that in 500 cases of LSD therapy, only one conceivable case could probably be considered to be deleteriously effected. Contrary to rumor these drugs are not addictive. As a matter of fact I have given LSD-25, its derivatives and congeners over a period of seven years to subjects for twenty-seven weeks every winter without any indication of the development of addiction. I have seen no valid report of addiction.

At this time I am using the psychic effects of methysergide (Sansert) as an adjunct to psychotherapy in the way that I have reported using LSD for more than a decade.[11] As a matter of fact, the work of Bender[12] and her colleagues pioneering in the study of the use of compounds in autistic children, led me directly to use methysergide as an adjunct in psychotherapy.

Recent studies with d-lysergic acid diethylamide (LSD-25) and 1-methyl d-lysergic acid butanolamide (Sansert) by Bender and her coworkers indicate that both of these compounds are of great value in the treatment of hospitalized disturbed children. Thus Bender, Faretra and Cobrinik report the results of treatment of autistic children, showing all degrees of severity of symptoms of anxiety. When treated with both LSD and Sansert (UML-491) they showed changes in facial expressions and in appropriate reactions to situations for the first time. In another group, verbal children 6 to 12 years of age, there was a change in superficial interpersonal relationships with improvement. Thus childish flights into fantasy and distortions gave way to more controlled reality in both reactions. Many of the children became aware of the realistic situation of their hospitalization, of family problems and achieved new insights into their psychological deviations. The results of psychological testing confirmed the improvement in the level of functioning from an overall point of veiw. *There was no evidence of increased brain damage in these children.* Indeed they were helped adapting to life. *It is important to emphasize that the dosages of LSD given daily were well above the adult threshold levels.*

A preliminary report given by Shelley and Resnik at a meeting of the American Medical Association describes a new technique to gradually degranulate circulating basophiles thus heading off histamine reaction in allergic patents.[12] The drug that they employed was Sansert (methylsergide). Studies were performed on groups of five adult males. Fifty subjects were tested. The familiar side effects were encountered in patients including vertigo, parathesis, nausea, flushing and leg cramps. These were reduced or eliminated in most instances by employing a minimal dosage schedule of 2 mg. a day, slowly increasing to 6 mg. daily. The report stressed the necessity of administering the medication with meals so that side reactions were lessened. 50 mg. per kilogram of methysergide prevented fatal antiphylactic shock in 75% of guinea pigs sensitized to egg albumen. On the basis of these findings the authors suggested that histamine liberators like methysergide be considered a means of "safe yet rapid pharmacologic hyposensitization of highly allergic individuals". In view of the side effects that the authors report for methyl-

sergide,[8] confirming similar side effects observed by other investigators in the treatment of migraine, I should like to emphasize again that a compound like MLD (1-methyl d-lysergic acid diethylamide) would be a natural compound to investigate as a histamine liberator of the type described by Shelley and Resnik

Discussion

It seems clear from the cogent data presented at a recent symposium sponsored by the New York Academy of Science and the National Multiple Sclerosis Society, January 20–22, 1964, that experimental allergic encephalitis in animals has the immunologic qualities of a truly allergic process. The evidence presented includes (1) A specific low molecular weight protein in the allergen. (2) Passive transfer of sensitized adult lymphoid cells induces susceptibility to this allergen. (3) A delayed type of hypersensitivity is present. (4) The disease may be suppressed by passive transfer of encephalomyelitis serum. (5) Serum containing circulating antibody to whole brain induces demyelinization of neurons in tissue culture.

A recent paper by Levine and Wenk[13] shows that experimental allergic encephalomyelitis is an inflammatory auto-immune disease of the nervous system. *Aqueous pertussis vaccine* mixed with nervous tissue homogenally produced this disease in rats when injected intraperitonally. This laboratory model of disease provides a new basis for testing the effects of the antiserotonin action of derivatives of d-lysergic acid.

It is regretted that I must add to a scientific paper a comment on the difficulties of research on man. The extraordinary effects of derivatives of d-lysergic acid mentioned in this paper cannot be studied in man without the most complicated attention to unnecessary shackles imposed by many unrealistic rules in the United States. I am afraid that the achievements of scientists in the laboratories in the United States will not be matched by the clinical investigators dealing with man unless a more realistic approach is made to clinical research by suitable Congressional action.

Summary

The antiserotonin action of derivatives of d-lysergic acid like d-lysergic acid diethylamide (LSD), 1-methyl d-lysergic acid diethylamide (MLD) and 1-methyl d-lysergic acid butanolamide (UML), is described in connection with anaphylactic reactions, experimental allergic encephalitis, the treatment of autistic behavior in children, rapid pharmacologic hyposensitization, and the treatment of auto-immune diseases. There is a need for re-evaluation of the ponderous rules governing clinical research in the United States. The compounds under discussion offer much promise which will inevitably be unduly delayed under present regulations.

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