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# LYSERGIC ACID DIETHYLAMIDE AND RELATED SUBSTANCES

*By* E. Rothlin

*Pharmacological Laboratory, Sandoz, Ltd., Basle, Switzerland*

Ergot has a remarkable history. Man first made contact with it as a violent poison when the consumption of rye infected with ergot led to the severe symptoms of ergotism. How this poison came to be used as a remedy is not quite clear. Formal medicine was opposed to the therapeutic use of ergot, but midwives long ago availed themselves of it for promoting childbirth and for arresting postpartum hemorrhage. Starting with this knowledge, the American physician Stearns[1] published in 1808 the first scientific paper recommending ergot for these purposes. His publication aroused interest in the scientific study of ergot and its therapeutic applications, not only in America but also in Europe. Advances in chemistry and, especially, improvements in preparative techniques, have made it possible to isolate a series of substances, some of which occur elsewhere in nature, the biogenic amines for example, while others, the characteristic alkaloids, are specific to ergot. Until 1925, the use of these alkaloids in medicine was restricted to the fields of obstetrics and gynecology.

A second phase in the history of ergot began when we showed that the sympathicolytic properties of ergot, first described by Dale,[2] had a therapeutic application. Following the clinical trials that we instigated, first ergotamine alone and then the combination of ergotamine with belladonna alkaloids and phenobarbital were added to the therapeutic *armamentarium*.[3] Special interest was aroused by the use of ergotamine in migraine.[4]

The most recent and third phase in the history of ergot followed our discovery of the *central* actions of ergotamine. In 1923, the inhibition of the depressor reflexes was described;[5] in 1934, we were able to show that ergotamine potentiates the action of phenobarbital without itself possessing a hypnotic action; and in 1944, we demonstrated the central action of the hydrogenated alkaloids of the ergotoxine group.[6a, 6b]

The increased interest that followed this extension of the field of therapeutic indications also stimulated interest in the chemistry of ergot. Stoll and his associates[7] succeeded in carrying out a partial synthesis of ergonovine (ergometrine) and, as far back as 1938,[8] a rather closely related derivative, the diethylamide of lysergic acid (LSD), was synthesized by these workers. Like ergonovine, this compound proved to have a pronounced action on the uterus and the vagina when tested in the rabbit. The remarkable psychic effects of LSD were discovered by chance in 1943 when A. Hofmann, a chemist engaged in the preparation of this compound, inadvertently ingested a minute quantity of it.

In experiments on ourselves, my collaborators and I were able to confirm Hofmann's observation, and W. A. Stoll[9] undertook the first systematic psychiatric investigation of this "phantasticum," as he called it.

My object here is to furnish an account of the pharmacological characteristics of LSD and some of its related compounds.

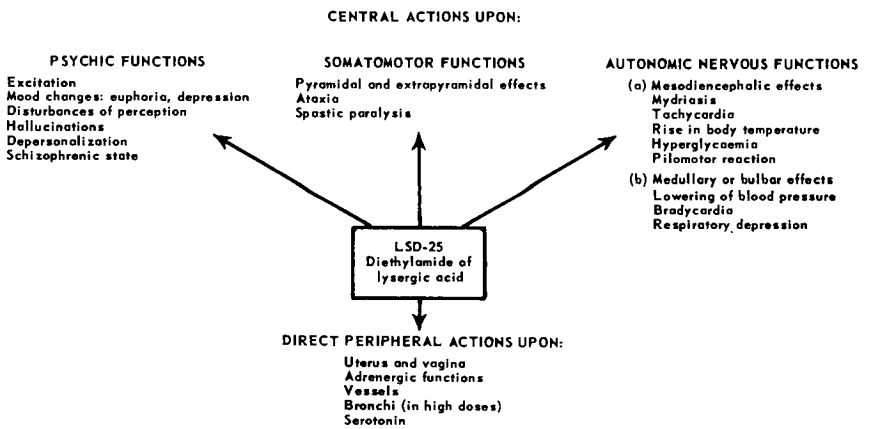


FIGURE 1

FIGURE 1 presents a summary of the complex actions of LSD. Basically, 2 different types of actions may be distinguished: direct peripheral actions and central actions.

### *Direct Peripheral Actions*

These include the actions on the uterus, vagina, blood vessels, and muscles. In addition, LSD exerts a weak adrenergic blocking action and, most important of all, a pronounced antagonism to serotonin, an effect first described by Gaddum.[10, 11]

### *Central Actions*

These actions may be subdivided to show the effects of LSD on 3 groups of functions:

(1) *Autonomic effects.* These effects are brought about by stimulation of the mesencephalon and the medullary centers, such as mydriasis, rise in body temperature, hyperglycemia, piloerection, and inhibition of depressor reflexes.

(2) *Motor effects.* These effects are both pyramidal and extrapyramidal in nature. They lead to ataxia and, especially, to spastic paresis.

(3) *Psychic effects.* The psychic changes are known to vary greatly from one individual to another, and a remarkable feature is the long period of latency. Whereas the autonomic effects set in approximately 20 minutes after administration of the drug, the typical psychic changes do not appear for a period of from 40 to 60 minutes, and they reach their maxima only after 1 to 2 hours. These effects take the form of changes of mood, either in the direction of euphoria or of depression. Particularly characteristic are optic hallucinations, sense of depersonalization, and schizoid states. The entire pattern of mental changes resembles that produced by mescaline, although about 5000 times as much of the latter substance is needed. It may be mentioned here that certain of the autonomic effects, for example an increase in body temperature,

TABLE 1

INHIBITION OF SEROTONIN BY VARIOUS AMIDES OF LYSERGIC ACID

| | |
|---|---|
| 1. LSD and its isomers | |
| *d*-Lysergic acid diethylamide (=LSD-25) | very active (standard) |
| *l*-Lysergic acid diethylamide<br>*d*+*l*-Isolysergic acid diethylamide | practically inactive, that is, more than 100 times weaker |
| 2. Derivatives of LSD obtained by saturation of the double bond ($C_9$ to $C_{10}$) | |
| Dihydro-*d*-lysergic acid diethylamide | 1.6 times weaker |
| Lumi-*d*-lysergic acid diethylamide | practically inactive |
| 3. Substituted derivatives of LSD | |
| *d*-1-Acetyl-LSD | 2 times stronger |
| *d*-2-Brom-LSD (= BOL 148) | 1.5 times stronger |
| *d*-2-Iodo-LSD | 2 times weaker |
| *d*-1-Oxy-methyl-LSD | 1.5 times weaker |
| 4. Monosubstituted amides of *d*-lysergic acid* | |
| Monomethylamide of *d*-lysergic acid | 15.5 times weaker |
| Monoethylamide of *d*-lysergic acid | 8.5 times weaker |
| Monoisopropylamide of *d*-lysergic acid | 5.0 times weaker |
| Monopropylamide of *d*-lysergic acid | 2.5 times weaker |
| Monobutylamide of *d*-lysergic acid | 1.5 times weaker |
| 5. Disubstituted amides of *d*-lysergic acid* | |
| Dimethylamide of *d*-lysergic acid | 5 times weaker |
| Diethylamide of *d*-lysergic acid (= LSD-25) | = standard |
| Di-isopropylamide of *d*-lysergic acid | 4 times weaker |
| Dibutylamide of *d*-lysergic acid | 3 times weaker |

* Preliminary results.

can be produced in the rabbit with doses not higher than those that cause psychic changes, that is, with approximately 0.5 to 1 μg./kg.

Of the various effects produced by LSD, the psychic effects in man have so far attracted the greatest attention. Not only has LSD been employed as a therapeutic agent in psychiatry, it has also been used to help in the elucidation of a number of theoretical questions that are of interest to the biochemist and the pharmacologist, as well as to the psychiatrist. This research work was given considerable impetus by the detection of 5-hydroxytryptamine (serotonin, enteramine) in the brain (Page,[12] Gaddum[13]) and by the demonstration of the important part played by this substance in cerebral metabolism. As already mentioned, Gaddum[11] demonstrated that LSD exerts a pronounced antagonism toward serotonin.

In the meantime, the chemists engaged in work on the synthesis of these compounds had not been idle. Stoll and his associates[14] provided us with a whole series of related compounds of *d*-lysergic acid for testing.

Thus we had the opportunity of comparing these compounds with LSD. In TABLE 1 are summarized the data concerning the antagonism of these substances to serotonin. We consider these results preliminary because we are not always certain in dealing with specific serotonin antagonism. A reliable analysis of serotonin antagonism requires consideration of the following criteria: (1) the extent of the latency period for maximum action; (2) the reversibility of this effect; and (3) the absence of inhibitory action toward acetyl-

choline, epinephrine, and histamine at levels of concentration that exhibit serotonin antagonism.

It is remarkable, if not altogether surprising, that of the diethylamides of the 4 known isomers of lysergic or isolysergic acid, only *d*-lysergic acid diethylamide is active (first group of TABLE 1). The other 3 isomers are more than 100 times less active as antagonists of serotonin than is the first, and they do not exert a competitive effect toward LSD.

In the second group of compounds we have those derivatives in which the double bond between $C_9$ and $C_{10}$ has been saturated either by the addition of hydrogen as in dihydro-*d*-lysergic acid diethylamide or by the addition of water to give the so-called lumi-LSD. The dihydro compound is 1.6 times less effective than LSD in inhibiting serotonin, and lumi-LSD is as much as 100 times less active.

In the third group we have the derivatives in which the lysergic-acid nucleus is substituted. These derivatives include *d*-1-acetyl LSD, *d*-2-brom-LSD, *d*-2-iodo-LSD, and *d*-1-hydroxymethyl LSD. The behavior of these derivatives is noteworthy because substitution of the lysergic acid nucleus yields compounds, such as acetyl-LSD and brom-LSD, which are 1.5 to 2 times as powerful as LSD in inhibiting serotonin, whereas all the derivatives in the other groups mentioned in this TABLE are weaker antagonists. Strangely enough, iodo-LSD is 1.8 to 2 times weaker than brom-LSD in inhibiting serotonin, and the hydroxymethyl derivative shows a similar behavior.

The fourth group comprises compounds having a single substituent at the amide nitrogen. These compounds form a homologous series in which the substituent is a methyl, ethyl, isopropyl, propyl, or butyl group. All these compounds are weaker antagonists of serotonin than is LSD, the comparative figures being in the same sequence: 15.5., 8.5, 5, 2.5, and 1.5 times weaker than LSD. We see here a significant increase of action with the length of the side chain.

Finally, we have the disubstituted amides of *d*-lysergic acid: the dimethyl, diethyl, di-isopropyl, and dibutyl amides. They are 3 to 5 times weaker than LSD in their antagonism toward serotonin.

The most important of these compounds is undoubtedly 2-brom-LSD. TABLE 2 shows a comparison between the effects of LSD and brom-LSD on a

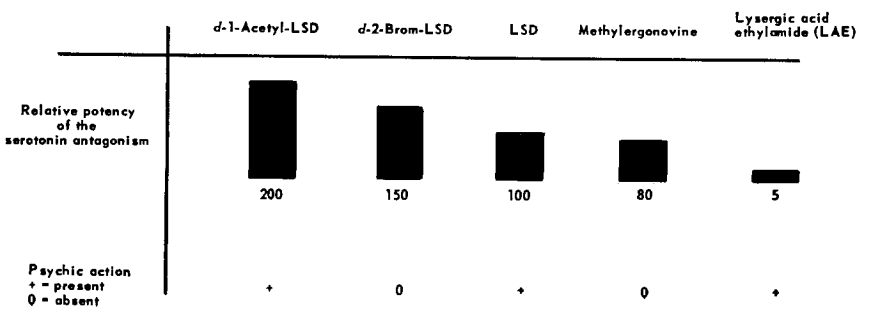


FIGURE 2

variety of functions. It will be seen that although the 2 substances agree in certain properties there are fundamental differences between them. Brom-LSD is completely devoid of action on the psyche. The action of this substance is mainly sedative in character, and central effects on autonomic functions are absent. If anything, however, brom-LSD is at least as powerful an antagonist of serotonin as is LSD.

As already mentioned, it is known that the serotonin antagonism of the various derivatives of *d*-lysergic acid is not of the same intensity in all functions. We have carried out a comparison among the serotonin-inhibiting effects of the 3 most interesting derivatives, LSD, acetyl-LSD, and brom-LSD, on various functions *in vitro* and *in vivo*. Whereas, in the case of LSD and brom-LSD, *in vitro* tests on the uterus and the renal vessels of the cat give identical results, acetyl-LSD is twice as effective in inhibiting the action of serotonin on the uterus as it is on the renal vessels. *In vivo* the effects of acetyl-LSD on the peripheral vessels and the bronchial musculature are of practically equal intensity, and this finding also applies to the potentiation of the action of barbiturates in the mouse.

Of no less interest than its serotonin antagonism is the ability of acetyl-LSD to produce psychic changes. It is certainly unexpected that brom-LSD produces no effects of this kind, whereas acetyl-LSD appears to have an activity of an order similar to that of LSD. So far we have had little experience with acetyl-LSD, but the results have been decidedly positive.

I now come to a discussion of the following questions: (1) Which compounds exert psychic effects? (2) Is there a parallel between serotonin antagonism and the effects on the psyche?

The answer to the first question is relatively simple (see FIGURE 2). Of all the derivatives of lysergic acid so far investigated, only the monoethylamide of *d*-lysergic acid (LAE), the diethylamide of *d*-lysergic acid (LSD-25), and the diethylamide of *d*-1-acetyl-lysergic acid produce changes in the psyche. Although the psychic effects of the 3 derivatives are qualitatively similar, there are considerable quantitative differences between them. In the case of the monoethylamide of *d*-lysergic acid, the average human dose required to produce psychic changes is 500 μg., whereas LSD and, probably, also acetyl-LSD are effective in 8 to 10 times smaller doses. It is noteworthy, from the *chemical point of view*, that only the monoethylamide and the diethylamide, whether of lysergic acid or of acetyl-lysergic acid, are able to produce significant psychic changes. Thus there can be no doubt that the ethyl group is particularly important in this respect. In this connection, it may be mentioned that the monomethylamide and dimethylamide and the monopropylamide and dipropylamide do not possess any psychic action. On the other hand, both in animals and in man the 4 latter compounds are capable of eliciting autonomic actions in doses in which the monoethylamide, for example, is completely inactive. Thus, a dose of 50 μg. of the dimethylamide of *d*-lysergic acid is sufficient to elicit marked autonomic responses, whereas as much as 500 μg. of the monoethylamide of *d*-lysergic acid are necessary to produce similar effects. With the latter compound, however, simultaneous psychic changes occur, whereas

TABLE 2

COMPARISON BETWEEN THE PHARMACOLOGICAL ACTIONS OF LSD AND BROM-LSD

| | LSD | Brom-LSD |
|---|---|---|
| Rabbit uterus and vagina *in vivo* | Contraction | No contraction |
| | Approximately 1.5 times weaker than ergonovine (ergometrine) | In higher doses, inhibition of the spontaneous rhythm |
| Adrenolytic effect (seminal vesicle of guinea pig) | Approximately 50 times weaker than ergotamine | Approximately 5 times weaker than ergotamine |
| Blood pressure in the cat | Decrease | Very weak action, non-specific |
| Heart rate | Bradycardia | No effect |
| Eye, pupil | Mydriasis | No effect |
| Body temperature: | | |
| Rabbit, dogs, cat | Rise (in all doses) | Decrease in high doses |
| Rat | Decrease; toxic doses: rise | Decrease (in all doses) |
| Heat production (calorimeter) | Primarily no increase; secondary rise | Not investigated |
| Blood sugar | Increased | No change |
| Behavior of normal mice | Excitation | Sedation |
| Amphetamine-excitation in the mouse | Potentiated | Inhibited |
| Effect on waltzing mice | Inhibition of waltzing due to excitation | Inhibition of waltzing due to sedation |
| Potentiation of pentothal effect in the mouse | Marked | Present but weaker than with LSD |
| EEG in the rabbit | Activation | No activation |
| Chromatophores (Poecilia) | Spreading | 2.5 times as strong as LSD |
| Psychic action in man | Very pronounced | Absent |
| Toxicity L.D.$_{50}$ Mouse *i.v.* | L.D.$_{50}$ 46 mg./kg. | 20 mg./kg. |
| Rat *i.v.* | 16.5 mg./kg. | — |
| Rabbit *i.v.* | 0.3 mg./kg. | 6 mg./kg. |

the monomethylamide and dimethylamide in doses sufficient to elicit autonomic responses cause no changes in the psyche.

The second question, whether there is either an interference or a causal relationship between the inhibition of serotonin and the psychic effect, is more complicated than would appear from the investigations that have been described. Perhaps this is because hypotheses have been formulated regarding this relationship that appear to be plausible but which, in our opinion, are far from being proved.[13, 15, 16] All the substances that have been investigated, including LSD and its derivatives, possess, to a certain extent, the property of inhibiting serotonin, particularly *in vitro*. From the studies of Woolley,[17] and others, we know that many serotonin antagonists are effective *in vitro*, but not *in vivo*. Consequently, the first condition that a serotonin antagonist should fulfill is that it should also inhibit serotonin *in vivo*. Both LSD and brom-LSD and, as far as we can tell at present, also acetyl-LSD exhibit this property to a significant degree. For example, as we have already indicated, they are able to inhibit the potentiating effect of serotonin on barbiturates. Of all the derivatives of *d*-lysergic acid so far investigated, however, only LSD, acetyl-LSD, and the monoethylamide of lysergic acid (LAE) exert a definite effect on the psyche. Although brom-LSD inhibits the potentiating effect

of serotonin on barbiturates in the same manner as LSD, it is without any effect upon the psyche. In experiments carried out on 19 normal subjects, all of whom worked in our laboratories, doses of up to 650 μg. were administered without causing any symptoms other than those referable to the autonomic nervous system. Hirsch, Jarvik, and Abramson[18] have also found that after the administration of doses of brom-LSD of the order of 5 to 7 μg./kg. no significant changes occurred whereas, with LSD, psychic effects were observed after the administration of only 1 μg./kg. Still more striking are the results of a therapeutic trial of brom-LSD in carcinoid patients. Waldenström[19] administered doses of up to 1.5 mg. (1500 μg.) without causing side effects of psychic changes, but also without producing any significant decrease in the symptoms of the disease. In one patient, Snow[20] administered up to 7.5 mg. of brom-LSD daily over a period of 3 weeks without observing any changes in the psyche. The therapeutic effect on the symptoms of the disease was insignificant. The dose of 7.5 mg. or 7500 μg. is, however, 100 times the dose of LSD needed to produce significant changes in the psyche. We therefore arrive at the following conclusions: that while brom-LSD has a highly specific anti-5-hydroxytryptamine effect in doses that fully antagonize the action of 5-hydroxytryptamine, brom-LSD shows no signs of antihistaminic, adrenergic, or cholinergic blocking effect.

As the hypothesis of the cerebral functions of 5-hydroxytryptamine is based to a great extent on the fact that lysergic acid diethylamide is a strong antagonist of 5-hydroxytryptamine, the present finding that brom-LSD is as active as lysergic acid diethylamide in antagonizing 5-hydroxytryptamine, but that it produces none of the mental disturbances, makes it necessary to reconsider this hypothesis. It cannot be argued that brom-LSD lacks cerebral actions because it does not penetrate into the brain tissue since the sedative action it produces is a central effect. In addition, after injection, brom-LSD could be detected in the same indirect way as lysergic acid diethylamide in extracts of the brain when tested for anti-5-hydroxytryptamine activity. Brain extracts of mice previously injected with either brom-LSD or lysergic acid diethylamide exerted an anti-5-hydroxytryptamine activity.

Our results with brom-LSD thus make it difficult to correlate the psychic effects of lysergic acid diethylamide with its anti-5-hydroxytryptamine property. At present, we are not justified in assuming a causal relationship between these 2 properties of lysergic acid diethylamide, although it may be found eventually that the 5-hydroxytryptamine in the brain is involved in the central actions of lysergic acid diethylamide. The mere existence of a pharmacological antagonism between lysergic acid diethylamide and 5-hydroxytryptamine, however, no longer provides evidence for the hypothesis that inhibition of the latter in the brain is the cause of the mental disturbances.

There is one final point I should like to mention. All of these compounds that produce changes in the psyche—LSD, LAE, and acetyl-LSD—also cause central autonomic effects. A thorough study of these effects in rabbits has shown that LSD elicits these responses in doses as small as those that cause psychic changes in man. The autonomic effects include rise in body temperature with a threshold dose of 0.5 μg./kg., hyperglycemia, mydriasis, piloerec-

tion, tachycardia, leucocytosis, and changes in the EEG that are characterized by disappearance of the spindle bursts and absence of slow wave activity. All of these effects are of a central nature, due to the stimulation of mesoencephalic and diencephalic structures, and they all have a pronounced *Sympathicotonic character*. They are suppressed both by ganglion-blocking agents (hexamethonium bromide) and by the hydrogenated alkaloids of the ergotoxine group (Hydergine). We emphasize this syndrome of sympathetic excitation produced by LSD for 2 reasons: first, brom-LSD does not cause this central stimulation of the sympathetic system and, second, this central sympathetic excitation produced by LSD may be considered the counterpart of the syndrome of central sympathetic depression produced by reserpine, which is characterized by the predominance of vagal functions and such symptoms as a fall in body temperature, bradycardia, miosis, and sedation. The actions of LSD and reserpine are of an opposite nature, not only with regard to autonomic functions, but also with regard to the psyche. Whereas the LSD psychosis is characterized by a hyperreactive condition and a schizophrenic-like behavior, reserpine exerts a sedative effect and not infrequently causes depression. Whether LSD and reserpine act on the same central mechanism, but in different ways, and whether their effects are perhaps correlated with one another, can be decided only by further study. In this connection, attention may be directed to the metabolism of 5-hydroxytryptamine (serotonin). According to Shore, Silver, and Brodie,[21] reserpine leads to a decrease in the content of serotonin in the brain. How LSD affects the cerebral metabolism of serotonin is not known but, as I have already mentioned, LSD is able to inhibit the potentiating effect of reserpine on barbiturates. It is not yet clear whether serotonin plays any part in this mechanism. In any case, it is important that brom-LSD, in contrast to LSD, is not able to inhibit the potentiating effect of reserpine on barbiturates. Although these findings may have taken us a stage further, the mechanism of the action of LSD on the psyche, and also the question of a possible connection between this action and serotonin metabolism, still need much more investigation.

In conclusion we should like to say that in the animal, a central sympathicomimetic syndrome predominates and that psychic changes are probably present, but difficult to interpret. In man, the psychic changes predominate, while the autonomic symptoms are apparently subordinated. We assume, however, that these 2 actions are not independent of each other, but are coupled in such a manner that their manifestation is effected by means of a common coordinative center. It would be desirable, therefore, that future clinical investigations should include an analysis of autonomic symptoms as thorough as that presently being devoted to the psychic changes.

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*Discussion of the Paper*

RICHARD TISLOW (*Wyeth Institute of Medical Research, Philadelphia, Pa.*): Have you tried brom-LSD (the 2-brom-diethylamide of lysergic acid) clinically as an antagonist of LSD-25 to determine whether it prevents the hallucinogenic effects of the latter compound?

ERNST ROTHLIN: No, as far as I know, this has not been tried clinically. We have tried, however, to prevent LSD effects in the animal by pretreatment with brom-LSD (BOL 148), and we were able to show partial inhibition of the highly specific pyretogenic LSD effect by brom-LSD.