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PHARMACOLOGY OF LYSERGIC ACID DIETHYLAMIDE (LSD) AND SOME OF ITS RELATED COMPOUNDS

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The peculiar mental disturbances as well as the autonomic effects induced by lysergic acid diethylamide (LSD) in man incited an unusual impetus among research workers in neurophysiology, neuropharmacology, biochemistry, and psychiatry, to approach the old problem of the mode of action of psychotomimetic agents.

d-Lysergic acid diethylamide (LSD) is one of the numerous partially synthetized derivatives of *d*-lysergic acid[41]. The latter is the common link of all natural, dihydrated and partially synthetized alkaloids of ergot. It is known that the natural and the dihydrated alkaloids of ergot have non-toxic actions on the central nervous system; this is shown in the inhibition of the depressor reflexes by ergotamine[30], its potentiating effect with barbiturates without itself producing a hypnotic action[31], and the central action of the hydrogenated alkaloids of the ergotoxine-group[32].

LSD as a closely related compound of ergometrine or ergonovine proved to have a pronounced effect on the uterus of the rabbit *in vitro* and *in vivo* (1938) but its toxicity was very high compared with ergometrine. Accordingly no further importance was attached to LSD.

One day in 1943 Dr. HOFMANN, the chemist engaged in the preparation of LSD, felt so unwell that he had to leave the laboratory. He thought that the peculiar psychic symptoms he perceived might be caused by LSD, and he repeated the experiment in reproducible form by ingesting orally 250 μg. In doing so he discovered the specific mental action of LSD. By experiments on myself, on members of my staff, and associated co-workers, we confirmed Dr. HOFMANN's discovery. We learned that as little as 0.5–1.0 μg/kg body weight was an effective oral dose in normal subjects.

The first systematic psychiatric analysis of LSD was then carried out by W. A. STOLL[48], partly in our laboratory, partly in the Department of Psychiatry of the University Hospital in Zürich. This basic study of the acute LSD-effects on normal individuals and schizophrenic patients aroused unusual interest among neuropharmacologists, neurophysiologists, and psychiatrists. His findings were subsequently confirmed and enlarged by numerous investigators. It is not my intention to discuss specific psychiatric aspects of the LSD-problem, but to contribute to the knowledge of the pharmacology of this fascinating compound and its mode of action.

TOXICOLOGICAL DATA

The LD_{50} of LSD given intravenously varies greatly according to the species of animal: 46 mg/kg for the mouse; 16.5 mg/kg for the rat and 0.3 mg/kg for the rabbit. The corresponding relative toxicity is: 1 (mouse) 2.8 (rat) and 150 (rabbit)[31]. No

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compound of the natural and especially of the hydrogenated alkaloids of ergot exhibits such high activity in acute toxicity experiments. The syndrome of acute LSD-poisoning is not specific. One observes autonomic and somatic symptoms.

In chronic experiments rats tolerate 2.5 mg/kg of LSD administered daily intravenously for 30 days. The animals show increased reflex response, mydriasis, piloerection, and retardation of body weight increase. Since the maximal tolerated i.v. single dose in the rat is about 3.2 mg/kg there seems to be no obvious cumulative action in the rat. On the other hand, animals given chronic doses of LSD require the same $L.D._{100}$ as untreated animals; therefore no tolerance seems to develop.

Absorption, distribution and excretion

LSD in the form of the tartaric acid salt is easily soluble in water and very well absorbed when given orally. The biological fate of LSD in the body has been investigated (1) by a biological method using the highly sensitive antagonistic action of LSD toward 5-hydroxytryptamine to determine LSD in the blood and in tissue extract[21]; (2) using ^{14}C-radioactive LSD and determining the radioactivity in the same substrates[5, 42].

With regard to the distribution the results obtained with these two methods are in good agreement. The half-time value of the blood was 7–10 min in the experiment with labelled LSD, but 35 min when assayed biologically. Two hours after the i.v. administration only traces could be found in the blood and in the various organs. The maximum level of LSD in most organs was reached after 10–15 min, but in the liver after 30 min. The order of decreasing amounts of LSD in the various organs was: gut (inclusive of contents), liver, kidney, adrenals, lung, spleen, pancreas, large intestine, heart, muscle, skin, brain. The concentration in the brain was always lower than in the blood. Twelve hours after the injection 70 % of the total radioactivity was found in the intestinal contents[5] and 7–8 % of the total radioactivity were excreted within 12 h, 50 % of it in the expired air and 50 % in the urine and faeces. In experiments with bile fistula[42] 70 % of the total injected radioactivity in form of ^{14}C-labelled LSD was found in the bile 2 h after the i.v. injection.

About the fate of LSD in the body we can say that this agent disappears rapidly from the blood, that the maximum LSD-level is quickly reached in the organs and also in the brain, that it is found in all organs, and that the excretion goes chiefly and rather rapidly through the liver into the bile. The greater part of LSD probably undergoes chemical transformation, because the excreted compounds or metabolites are water-soluble, in contrast to LSD. Paper chromatography[42] revealed that the bile contains three different radioactive compounds that have not yet been defined chemically or biologically for lack of material.

Recent investigations into the fate of LSD[2] revealed that 90 min after the i.v. injection of 0.2 mg/kg in the cat, LSD was present in the various organs and fluids decreasing in amount in the following order: bile, plasma, lung, liver, kidney, brain, intestine, spleen, cerebrospinal fluid, muscle, fat. The half-time value of the blood was 130 min in the cat and 100 in the monkey. These findings partly agree with and partly differ from the previously mentioned results. The authors[2] find that LSD is strongly bound by a protein constituent of the cat's blood, while we could find the total activity of LSD added to the blood and biologically tested. Whereas the re-collected compounds in rats with bile fistula gave chromatographically three different metabolites of

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LSD[42], AXELROD *et al.*[2] report that the excreted compound is unaltered LSD.

On the other hand, the latter authors show that the liver tissue (guinea pig) is the only tissue that metabolizes LSD *in vitro*. This study gives evidence that LSD undergoes chemical transformation *in vitro* by an "enzyme system, present in microsomes only, that requires oxygen and a reduced triphosphopyridine nucleotide generating system" and formation of 2-oxy-LSD is the result. This new compound does not possess the psychogenic action of LSD.

PHARMACOLOGICAL DATA

In Fig. 1 the complexity of LSD action is tabulated. We distinguish two basically different kinds of action: direct peripheral actions and actions upon the central nervous system.

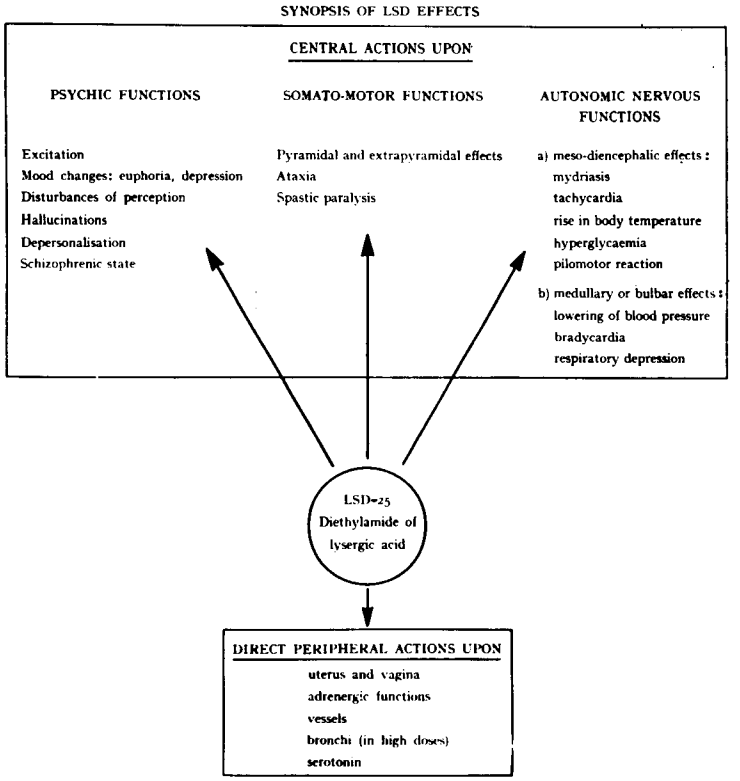

Fig. 1.

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Direct peripheral actions

LSD has a contracting effect on the uterus *in vitro* and *in vivo* that is 1.5 times weaker than that of ergometrine or ergonovine. A vasoconstrictive effect is regularily manifested on perfused blood vessels of the rat[34], the rabbit's ear[36] and also in the spinal cat[31]. In the whole animal the depressive action on the vasomotor centre predominates and usually leads to a drop in blood pressure.

LSD possesses a selective antagonistic activity toward 5-hydroxytryptamine (5-HT), named enteramine by ERSPAMER[9], serotonin by PAGE[26]. This antagonistic effect of LSD toward 5-HT discovered by GADDUM[10], can also be demonstrated in the isolated intestine of the guinea pig[12] and on blood vessels[13, 15, 33], and bronchial musculature *in vivo*[17, 22].

Actions on the central nervous system

The central effects elicited by LSD are more numerous and remarkable than its direct peripheral effects. They can be subdivided in three groups:

(a) *Autonomic effects.* Some of them are sympathetic and others parasympathetic in nature. Mydriasis is induced in various animal species[35] and in man[29, 40]. LSD increases the blood sugar and provokes increases in body temperature[20, 35] in the cat, dog and rabbit. Piloerection is characteristic for various animals. All these autonomic effects are sympathetic in nature and are induced by stimulation of bulbar or mesodiencephalic centres, since pretreatment either with ganglionic blocking agents like hexamethonium or with adreno-sympathicolytic agents like hydergine (the hydrogenated alkaloids of the ergotoxine group) inhibits all these sympathetic central responses to LSD[35].

On the other hand, LSD elicits autonomic symptoms of parasympathetic character: salivation and lacrimation especially in the dog[35] and nausea and vomiting.

Blood pressure is not affected significantly by small doses of LSD. However, 50–100 μg/kg of LSD in anesthetized cats provoke bradycardia by central vagus stimulation and a drop in blood pressure. The latter is due to a depressant action on the vasomotor centre since in the spinal cat LSD increases blood pressure and bradycardia is absent[31]. In man the action of LSD on blood pressure[29], cerebral circulation, and metabolism, was thoroughly investigated in normal and schizophrenic individuals[19]. At the maximum of the psychic symptoms, 40 min after the i.v. injection of 100–120 μg of LSD, blood pressure was slightly increased, and the internal jugular venous pressure unchanged in normal subjects and slightly but significantly raised in schizophrenics. With regard to cerebral blood flow, vascular resistance, oxygen consumption, glucose utilization, arterio-venous glucose and oxygen differences and R.Q. there was no significant change, despite the obvious occurrence of the characteristic psychological and mental effects of LSD.

Respiration[16, 21, 31] is distinctly affected by doses of 10–50 μg/kg in terms of stimulation or inhibition. Higher doses produce only inhibition, and death of the animals is due to respiratory standstill.

Of all the various autonomic functions influenced by LSD the most sensitive is the temperature regulation in the rabbit. Doses as minute as 0.5–1.0 μg/kg increase the temperature; the same dose of LSD induces psychic changes in man. This outstanding sensitivity of these two responses to LSD does not imply identity or interference of mechanism of action.

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(b) *Somatomotor effects.* These effects are both pyramidal and extrapyramidal in nature. They lead to ataxia and especially to spastic paresis in cats and dogs. Rather high doses are needed for the production of these symptoms when compared with the minute amounts that can induce mental changes in man.

(c) *Psychic effects.* The pattern of psychic changes in man resembles that provoked by mescaline, although about 5000 times as much of the latter substance is needed. A characteristic feature of the psychic disturbances in man is the long period of latency after oral administration. While the autonomic effects set in approximately 20 min after the administration of LSD, the psychic changes appear only after a period of 40–60 min. The peak of the mental symptoms is reached after 2–3 h and the mean duration is 8–12 h. A comparative study of the onset, peak, and duration of the action of LSD when applied by different routes gave the following results[18]. The onset of autonomic and psychic symptoms was quicker after i.m. administration; when given intravenously symptoms occurred after several minutes and after intraspinal injection practically instantaneously. After intravenous and intraspinal administration the peak of the symptoms is reached in 1 h and the duration is 9–10 h. The long period of latency when the drug is applied orally suggested that LSD, in such small amounts as 0.5–1.0 μg/kg, does not induce mental changes by direct action on the brain but by a metabolite produced as a result of disturbance of the metabolism of another organ, most probably the liver. The results obtained by administering LSD by different routes make such an assumption unlikely.

BIOCHEMICAL DATA

Such data for LSD are scarce. All the psychotomimetic agents have been studied primarily with respect to the metabolism of carbohydrates. The most interesting finding, that homogenates of guinea pig brain in the presence of $4.10^{-9} M$ of LSD stimulate the glucose oxidation and inhibit the utilisation of hexose monophosphate[25], was not confirmed, since different authors[23] did not find stimulation but inhibition of glucose oxidation when brain slices of the guinea pig were electrically stimulated and concentrations of LSD up to $5 \cdot 10^{-5} M$ applied to them. Unstimulated slices did not show any effect. Confirmation of these results were given by different investigators[3, 4, 8].

After administration of LSD to guinea pigs an increase of acetylcholine in the brain was observed[28]. Hence the action of LSD on cholinesterase was investigated and it was found that $5 \cdot 10^{-6} M$ LSD inhibits the activity of pseudocholinesterase of human plasma and brain[15]. True cholinesterase of erythrocytes and brain was inhibited only slightly by LSD concentrations up to $5 \cdot 10^{-5} M$; this was confirmed[10].

The inhibiting effect of LSD on pseudocholinesterase may explain the accumulation of acetylcholine in animals treated with LSD, but the primary question whether the biochemical effect of LSD on the pseudoesterase *in vitro* is correlated with the central action of LSD on the autonomic and mental functions must be treated with some restraint[15]. Indeed the active concentration ($5 \cdot 10^{-6} M$) of LSD in these *in vitro* experiments is in great contrast with the doses of 0.5–1.0 μg/kg that can provoke mental changes in man.

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COMPOUNDS RELATED TO LSD

The peculiar effect of LSD on mental functions in man was a great incitement to the chemist to synthesize related compounds. We were provided[41] with a whole series of substances obtained by partial synthesis, with *d*-lysergic acid as a common link, for pharmacological testing. They were screened by different tests. In Table I data are given of the most interesting compounds with regard to their antagonistic action toward 5-HT in the isolated uterus of the rat. This antagonism has the advantage of being specific, regularly reproducible and a highly sensitive test for LSD.

TABLE I

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 *d*- and *l*-Isolysergic acid diethylamide	practically inactive, *i.e.*, 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-Methyl-LSD	3.5 times *stronger*
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*	
Mono-methylamide of *d*-lysergic acid	15.5 times weaker
Mono-ethylamide of *d*-lysergic acid	8.5 times weaker
Mono-propylamide of *d*-lysergic acid	2.5 times weaker
Mono-isopropylamide of *d*-lysergic acid	5.0 times weaker
Mono-butylamide of *d*-lysergic acid	1.5 times weaker
5. *Distributed amides of d-lysergic acid*	
Dimethylamide of *d*-lysergic acid	5 times weaker
Diethylamide of *d*-lysergic acid (= LSD-25)	= *standard*
Diisopropylamide of *d*-lysergic acid	4 times weaker
Dibutylamide of *d*-lysergic acid	3 times weaker

Group 1. It is surprising that of the diethylamides of the four known isomers of *d*-lysergic acid only the *d*-lysergic acid diethylamide, *i.e.* LSD, is a strong 5-HT antagonist. The three other isomers are more than 100 times weaker than LSD. It is worth mentioning that none of these three isomers has a competitive effect toward the active isomer LSD either in the 5-HT antagonism or in other tests.

Group 2. Here are included those compounds in which the double bond between the position C_9 and C_{10}, which is the most unstable of the five double bonds of the molecule of lysergic acid, is saturated either by two atoms of hydrogen, giving the

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dihydro-*d*-lysergic acid diethylamide, or by the addition of H_2O at the same position giving the so-called lumi-*d*-lysergic acid diethylamide. While the first compound is only 1.6 times weaker than LSD, the latter is practically inactive.

Group 3. These are the derivatives with the substitution in the nucleus of lysergic acid. Three of them are of most interest: 1-methyl-LSD, 1-acetyl-LSD and 2-brom-LSD are stronger antagonists to 5-HT than LSD. Not only for this great sensitivity toward 5-HT but also for their other properties these compounds will be discussed further in this paper. The 2-iodo-LSD and 1-oxymethyl-LSD are respectively 2 and 1.5 times weaker 5-HT antagonists than LSD.

Group 4. Related compounds with monosubstitution of the amide nitrogen of the *d*-lysergic acid amide. We find here a series of homologues such as: mono-methyl, -ethyl, -isopropyl, -propyl and -butyl substituents. Following the sequence of the homologous series the anti-5-HT activity increases gradually. Hence it is obvious that the activity increases with the length of the side chain.

Group 5. Derivatives with disubstitution of the amide nitrogen of the *d*-lysergic acid amide, *viz.* dimethyl-, diethyl-, diisopropyl- and dibutylamide of *d*-lysergic acid, demonstrate an anti-5-HT activity 3–5 times weaker than that of the standard compound LSD which belongs to this group.

The most interesting of all these related substances are without doubt the three derivatives of LSD with substitution in the indole nucleus of the lysergic acid: 1-methyl-, 1-acetyl- and 2-brom-LSD, which possess a stronger anti-5-HT activity than LSD on the isolated uterus of the rat. It is known that differences do exist in the anti-5-HT effect with respect to intensity in different functions and that agents with obvious anti-5-HT action *in vitro* might be inactive *in vivo*[37]. A comparison of the 5-HT-inhibiting action of LSD, 1-acetyl-LSD and 2-brom-LSD on various functions *in vitro* and *in vivo* shows that 2-brom-LSD is significantly stronger on the isolated uterus of the rat and in the artificially perfused renal vessels of the rat and the cat, and that 1-acetyl-LSD is twice as active as LSD. In the *in vivo* experiments these three compounds show about the same activity towards 5-HT in the peripheral vessels of the anesthetized cat, on the bronchial musculature of the guinea pig and in the inhibition of the potentiating effect on barbiturates by 5-HT in mice[41].

While 1-acetyl-LSD induces psychic effects in man similar to those induced by LSD, the 2-brom-LSD is absolutely inactive in this respect. This seems to be true for all other compounds given in Table I, with the exception of the monoethylamide of *d*-lysergic acid (LAE).

We shall now discuss the following two questions:

1. Which compounds induce psychic changes?

2. What are the arguments in support of the hypothesis that psychic changes caused by LSD are correlated with the antagonism of 5-HT and LSD?

The psychic effects induced in man by the minute doses of 0.5–1.0 μg kg of LSD administered by mouth are: alterations of the mood either in the direction of euphoria or of depression, alterations of the behaviour, hallucinations (mostly optical), distortion of the body image, sense of depersonalization, and "psychotic" states. Most characteristic for the psychological LSD-response is the individual reaction, the actual psychic situation and the environment.

Of the above-mentioned derivatives of LSD and related compounds only mono-

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ethylamide-, the diethylamide, and the 1-acetylamide of the *d*-lysergic acid induce apparent psychic changes in man. Whether the 1-methyl-*d*-lysergic acid amide is active is not known[6]. The quality of the psychic effects of these three compounds is similar, but there are great quantitative differences. While LSD and 1-acetyl-LSD are active in doses of 0.5–1.0 μg kg, monoethyl lysergic acid amide (LAE) needs doses 8–10 times as large. From the point of view of chemical constitution and psychic action it is evident that for the production of the typical psychic pattern the ethyl group or groups in the three active compounds of *d*-lysergic acid derivatives are of primary importance.

2. The answer to the second question concerning the presumed relationship between the psychic action of LSD and the inhibition of 5-HT by LSD is very much more complicated than it appeared when the first arguments were put forward by GADDUM[11] and WOOLLEY[18]. The facts are that LSD was found to be a specific and highly active inhibitor of 5-HT in the isolated uterus of the rat and in isolated vessels. Soon afterwards followed the discovery of 5-HT in the brain by PAGE[26] and by GADDUM[1]; this substance was revealed to be a new neurohumoral transmitter playing an important role in cerebral functions. From these results was deduced the rather fascinating hypothesis that the inhibiting action of LSD to 5-HT may be the key to the explanation of the peculiar psychic action of LSD (GADDUM AND WOOLLEY).

We have mentioned that many substances with anti-5-HT activity *in vitro* may have no such effect *in vivo*. Among the numerous derivatives of LSD many of them are active *in vitro* but not *in vivo*, whereas it was found that the compound 2-brom-LSD is as potent an inhibitor of 5-HT as LSD in experiments *in vitro* and *in vivo*. The surprising fact is that 2-brom-LSD despite its pronounced anti-5-HT activity is without any effect on the psyche in man. Doses up to 650 μg were administered in 19 normal volunteers in our laboratory, and only slight sedative effects were observed. HIRSCH[19] *et al.* administered 5–7 μg/kg to volunteers, WALDENSTRÖM[17] 1,500 μg, SNOW *et al.*[30] up to 7,500 μg, and PAGE[27] 20,000 μg of 2-brom-LSD to carcinoid patients, without provoking significant changes in the psyche. The highest dose of 2-brom-LSD administered in man is at least 200 times the usual active psychogenic dose of LSD.

The thorough pharmacological comparison of the action of LSD and the 2-brom-LSD compound on different functions *in vitro* and *in vivo* are summarized in Tables II and III. In some aspects their action is identical, in others differential. LSD produces mainly a sympathetic pattern of symptoms: mydriasis, increase of temperature and of blood sugar, piloerection, behavioural alertness, activation in the EEG and the typical psychic changes in man. None of these effects are present after administration of 2-brom-LSD. Instead of sympathetic stimulation and behavioural alertness, 2-brom-LSD induces general sedation, inhibition of the stimulatory effects of amphetamine, and no activation of the EEG-pattern. Identical for both compounds is the strong anti-5-HT effect *in vitro* and *in vivo* and the inhibition of the potentiating action of 5-HT on barbiturates[7, 28]. Yet 2-brom-LSD is without any psychogenic effect at all. Sedation and the inhibiting action of the potentiation of 5-HT by 2-brom-LSD are of central origin. Therefore it can not be argued that 2-brom-LSD is unable to produce mental changes because it does not penetrate into the brain. Moreover, 2-brom-LSD could be detected in the brain in the same way as LSD. Brain extracts of mice treated with LSD and 2-brom-LSD exerted an equal anti-5-HT activity on the rat's uterus. We therefore concluded[7] that on the basis of these differential results

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TABLE II

COMPARISON BETWEEN THE PHARMACOLOGICAL ACTIONS OF LSD AND BOL (BROM-LSD): I

	LSD	*BOL*
Rabbit uterus and vagina *in vivo*	Contraction Approx. 1.5 times weaker than ergonovine (ergometrine)	No contraction In higher doses, inhibition of the spontaneous rhythm
Adrenolytic effect (seminal vesicle of guinea pig)	Approx. 50 times weaker than ergotamine	Approx. 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 Rat	 Rise (in all doses) Decrease; toxic doses: rise	 Decrease in high doses Decrease (in all doses)
Heat production (calorimeter)	Primarily no increase; secondary rise	Not investigated
Blood sugar	Increased	No change

TABLE III

COMPARISON BETWEEN THE PHARMACOLOGICAL ACTIONS OF LSD AND BOL (BROM-LSD): II

	LSD	*BOL*
Behaviour 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. rat i.v. rabbit i.v.	$L.D._{50}$ 46 mg/kg 16.5 mg/kg 0.3 mg/kg	20 mg/kg 6 mg/kg

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with LSD and 2-brom-LSD it is difficult to admit a correlation between the psychic effects induced by LSD and its anti-5-HT property, since 2-brom-LSD possesses the same anti-5-HT activity *in vitro* and *in vivo* but lacks completely the psychogenic action of LSD.

The problem of interference of 5-HT and LSD in cerebral functions has been studied under various conditions by a number of investigators. It became particularly attractive when the fundamental studies of BRODIE and associates[38] on the mode of action of reserpine provided evidence that the effects of this alkaloid are correlated with the metabolism of 5-HT. A discussion of these new findings, though connected with the LSD-problem, is not in the scope of this report. Instead, I shall briefly present some experimental arguments that are difficult to bring in line with the hypothesis that the action of LSD and particularly its psychic effects are caused by the relationship of LSD to 5-HT.

1. LSD and 2-bromo-LSD are both strong antagonists to 5-HT. LSD induces psychogenic changes in man in doses as small as 0.5–1.0 μg/kg, whereas 2-brom-LSD in doses up to 200 times higher is completely without this characteristic action. LSD inhibits the potentiating action of 5-HT on barbiturates, and 2-brom-LSD does the same in equal doses. LSD also inhibits the potentiating effect of reserpine on barbiturates, but 2-brom-LSD does not. We suggest therefore that reserpine does not potentiate the effect of barbiturates by releasing 5-HT but by an other mechanism. If reserpine acted by releasing 5-HT it would be very difficult to explain why 2-brom-LSD inhibits exogenously administered 5-HT just as well as LSD but not the 5-HT released by reserpine. LSD causes a state of excitation and "sham rage" and antagonizes the depressant action of 5-HT in unanesthetized cats when both drugs are administered intraventricularly[14]. Temporarily, it has the same effect on the depressant action of reserpine. When 5-HT and LSD are administered together there is no inhibiting influence on the alerting response of LSD by 5-HT. Therefore LSD antagonizes the action of 5-HT but not vice versa.

2. Ergometrine or ergonovine is a strong anti-5-HT compound. It produces excitation and "sham rage" when applied intraventricularly and like LSD reverses the depressant behaviour of 5-HT. However ergometrine has no psychogenic properties[14].

3. Mescaline induces psychic changes in man similar to those caused by LSD, whereas no correlation with 5-HT is known.

4. Amphetamine has similar pharmacological and neurophysiological effects on autonomic and somatic functions: it induces a sympathetic arousal pattern, reverses the depressant action of 5-HT and its potentiating effect on barbiturates like LSD, but does not elicit the characteristic psychic pattern of LSD.

5. Morphine, like LSD and amphetamine provokes similar excitatory effects of a sympathetic pattern but unlike LSD it does not induce psychic changes. Morphine and amphetamine have no inhibiting action on 5-HT.

These experimental results provide evidence that for the inhibition of the central action of 5-HT and reserpine anti-5-HT activity is not obligatory. If the psychic action of LSD depended on this anti-5-HT effect, one would expect that 2-brom-LSD, which is as potent an antagonist to 5-HT as LSD, would have the same action.

There remains the primary question whether all these experimental findings of interaction on cerebral functions by various agents, including the potentiating effect

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of 5-HT on hypnotics and its inhibition by LSD and 2-brom-LSD, have any correlation with the psychic functions and their alteration by LSD in man? I consider there is no proof for such a correlation. Despite the fact that we have learned a great deal about psychotomimetic drugs from the recent advances in neurophysiology and neuropharmacology, one must admit that the mechanism of action of the psychic activity of LSD and agents with similar effects has yet to be plausibly explained.

SUMMARY

LSD is one of the partially synthetized derivatives of lysergic acid; LSD provokes basically two different types of action:

1. *Direct peripheral effects*: action on the uterus, blood vessels and muscles. It has a weak adrenolytic effect. The most important action is the pronounced antagonism toward 5-hydroxytryptamine (enteramine, serotonin) = 5-HT.

2. *Central actions*, which may be subdivided into three groups:

(*a*) *Autonomic effects*, brought about by stimulation of the centres in the mesencephalon and in the medulla: mydriasis, change in body temperature, hyperglycaemia, piloerection, inhibition of depressor reflexes in circulation. The autonomic effects of central origin produced by LSD are mainly sympathomimetic in nature. They can be inhibited or abolished by ganglion blockers or sympathicolytics. Some of these effects, such as the increase in body temperature, can be produced in the rabbit with the same doses which cause psychic changes in man, *i.e.* 0.5–1.0 μg/kg.

(*b*) *Motor effects*. These are pyramidal and extrapyramidal in nature, leading to ataxia and especially to spastic paresis.

(*c*) *Psychic effects*. These are very characteristic for LSD: change of mood either in the direction of euphoria or depression, hallucinations (mainly optical), sense of depersonalization and schizophrenic-like states. The mental changes resemble those produced by mescaline, though some 3–5000 times as much of the latter substance are needed.

The LSD-problem was given a considerable impetus by the detection of 5-HT in the brain and by the important role which 5-HT seems to play in cerebral functions. In this connection the pronounced antagonism of LSD towards 5-HT became of special interest. The hypothesis was put forward that the psychic effects induced by LSD are due to this antagonism.

Substances related to LSD

1. *Activity of the antagonistic effect* toward 5-HT in the isolated uterus of the rat. Of all the investigated compounds: isomers of LSD, dihydro-LSD, H_2O-LSD (Lumi-LSD), mono- and disubstituted compounds in the amide-nitrogen of the lysergic acid amide, only the derivatives with substitution in the indol-nucleus of the lysergic acid produce an equal or even stronger 5-HT-antagonistic effect than LSD itself.

2. *Psychic effects*. Of all the substances related to LSD, only some of the mono- or diethylamides of the *d*-lysergic acid induce psychogenic changes. The ethyl group or groups in the amide-nitrogen are particularly important in this respect.

3. The most interesting of all these derivatives of LSD is the compound *2-brom-LSD*. Although LSD and 2-brom-LSD agree in certain of their properties, there are fundamental differences between them. 2-brom-LSD has absolutely no action on the psyche, its central action being mainly sedative in character; central effects upon autonomic functions are also absent. However, 2-brom-LSD is at least as powerful an antagonist of 5-HT as LSD in experiments *in vitro* and *in vivo*. These facts make it difficult to correlate the psychic effects of LSD with its anti-5-HT property and are a strong argument against the hypothesis that proposes such a correlation.

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