# REVIEW ARTICLE

PHARMACOLOGY OF LYSERGIC ACID DIETHYLAMIDE AND SOME OF ITS RELATED COMPOUNDS

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THE mental disturbances and autonomic effects induced by lysergic acid diethylamide (LSD, I) in man have initiated increased interest among workers in neurophysiology, neuropharmacology, biochemistry and psychiatry in the old problem of the mode of action of psychotomimetic agents. Since the first paper appeared[1] in 1947 the literature has become so extensive that it seems advisable to review the present state of LSD studies and to assess the contribution of the drug to the recent advances made in the study of psychogenic agents. The scope of this review is limited to the main experimental results of the LSD problem.

(+)-Lysergic acid diethylamide (LSD) is one of the many partially synthetic derivatives of (+)-lysergic acid[2,3]. This acid is the link between natural, dihydrogenated and partially synthetic alkaloids of ergot. The natural and dihydrogenated alkaloids of ergot possess central actions which are non toxic. In 1923 the inhibition of the depressor reflexes was described[4]; in 1934 we showed that ergotamine potentiates the action of phenobarbitone without itself possessing a hypnotic effect[5]; and in 1945 we demonstrated the central actions of the hydrogenated alkaloids of the ergotoxine group[6].

(I)   (II)
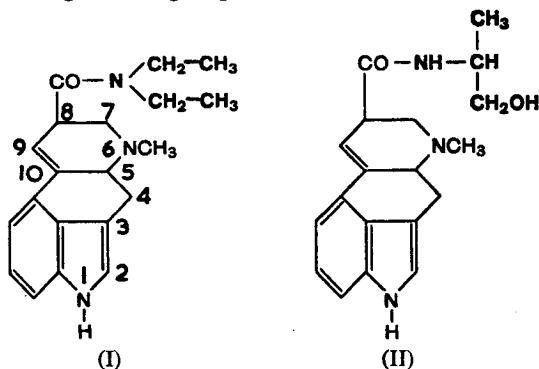
LSD is closely related to ergometrine (ergonovine, II) and was investigated pharmacologically in 1938. It proved to have a pronounced action upon the uterus of the rabbit both *in vitro* and *in vivo*, but its activity was 1·5 times weaker *in vivo* than ergometrine and its toxicity was higher. After intravenous injection of 0·1–0·2 mg./kg. in the anaesthetised rabbit we observed an unusual excitation combined with muscular cramps. Subcutaneous injection of 0·2 mg./kg. of LSD in the cat and dog induced motor effects like ataxia and spastic paresis and a change of the behaviour in a catatonic pattern. From these results it was not to be expected that

LSD would offer any clinical advantages, and therefore no further importance was attached to it.

As the drug was not considered for clinical trial, its psychogenic action in man went undetected until 1943, when Dr. Hoffman[7], the chemist engaged in its preparation, inadvertently ingested a minute quantity. The effect produced led him to repeat the experiment by taking orally 250 μg. which reproduced the same effects as before. This mental action of LSD was confirmed on myself and my staff and colleagues. We found the effective oral dose in normal subjects to be as small as 0·5 to 1·0 μg./kg. This unexpectedly potent activity in man is characteristic of LSD, since 3000–5000 times as much mescaline, a similarly acting substance, is required to produce similar psychic changes.

The first systematic psychiatric analysis of LSD was carried out[1] in our laboratory and in the Department of Psychiatry of the University Hospital in Zurich. This basic study of LSD on normal and schizophrenic subjects evoked great interest among neuropharmacologists, neurophysiologists and psychiatrists. Stoll's findings were subsequently confirmed and enlarged by numerous workers. I do not propose to discuss the specific psychiatric aspects of the LSD problem, but only the neurophysiology and pharmacology of this fascinating compound. However, the key of understanding of "psychosis" might lie, to quote Cholden[8], "in the reproduction of an experimental, predicable, controllable, reproducible state— an artificial psychosis". The interest of LSD lies primarily in the way it produces its psychic effects. We still do not know the drug's mechanism of action, but attempts at its elucidation have helped towards a fuller understanding of the normal and pathological functioning of the brain. Co-ordinated biochemical, neurophysiological and pharmacological investigations using psychological and psychiatric concepts are the only effective means of exploiting the potentialities of LSD and similarly active agents.

GENERAL PHARMACOLOGY

Toxicology

The intravenous acute LD50 of LSD varies according to species: 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[9,10] is: mouse 1, rat 2·8 and rabbit 150. None of the natural or hydrogenated ergot alkaloids exhibits so high an activity in acute toxicity experiments. Acute LSD poisoning is not specific; both autonomic and somatic symptoms are observed. These are mydriasis, piloerection, salivation, vomiting, increased reflex activity, ataxia and spastic paresis; death results from respiratory failure.

In chronic toxicity experiments, rats tolerated 2·5 mg./kg. intravenously daily for 30 days. The animals show increased reflex response, mydriasis, piloerection and slowing of growth. Since the maximum tolerated single intravenous dose in the rat is about 3·2 mg./kg., there seems to be no cumulative effect. Also animals pretreated chronically with LSD require the same LD100 as untreated animals; therefore no tolerance appears to develop.

Absorption, Distribution and Excretion

The tartrate of LSD is readily soluble in water and well absorbed when given orally. The fate of LSD in the body has been investigated in two ways. The first, a method in which the highly sensitive antagonistic action of LSD to 5-hydroxytryptamine (5-HT)[11] is used to determine LSD in the blood and tissue extracts[12], and the second, a method which measures the radioactivity in the same substrates after giving LSD-[14]C [13-15].

LSD is neither bound nor destroyed in the blood of the rat. In homogenates of liver and muscle its activity decreases by nearly 50 per cent in a few minutes with little further reduction during the next 17 hours[12]. In brain homogenates the activity of LSD was reduced to 42 per cent after 10 minutes and to 20 per cent after 17 hours. These investigations do not reveal whether the loss of activity is due to the binding of LSD by a tissue constituent or to biochemical transformation into an inactive metabolite. That the decrease of activity at both $3°$ and $38°$ is similar does not support the idea of a metabolic transformation in the homogenates.

The distribution of LSD in the blood and in different organs has been investigated by the first method in mice[12] after intravenous injection and by the second method in mice and rats[13-15] after intravenous or intraperitoneal injection. The results of the two methods are in good agreement. The 50 per cent disappearance time from blood was 7 to 10 minutes as measured by the radioactivity method, but 35 minutes when assayed by the 5-HT antagonism method. After two hours, only traces could be found in the blood and organs. The maximum level of LSD in most organs was reached after 10 to 15 minutes, but in the liver after 30 minutes. The amounts in the different organs in decreasing order 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 that in the blood. After 12 hours, 70 per cent of the radioactivity was found by Boyd and colleagues[13,14] to be in the intestinal contents. Only 7 to 8 per cent of the total radioactivity was excreted within 12 hours, half of this in the expired air and half in urine and faeces. In experiments with a bile fistula[15] 70 per cent of the total radioactivity was found in the bile. Thus we can say that LSD passes quickly from the blood, that it rapidly reaches a maximum in the organs and brain, that it is found in all organs, and is excreted quickly in the bile. Much of the LSD probably undergoes chemical change because the excreted compounds or metabolites are water-soluble in contrast to LSD. Paper chromatography[15] has revealed that the bile contains three different radioactive compounds, which have not yet been defined chemically or biologically because no reference substances are available.

Recently, Axelrod and colleagues[16] investigated the fate of LSD in the cat by spectrofluorophotometer, an instrument sensitive to as little as 0.001 μg./ml. of LSD. These authors found that 90 minutes after intravenous injection of 0.2 mg./kg., LSD was present, decreasing in amount in the following order of fluids and organs: bile, plasma, lung, liver, kidney, brain, intestine, spleen, cerebrospinal fluid, muscle and fat. The 50 per cent disappearance time in blood is 130 minutes for the cat

and 100 minutes for the monkey. These findings are in part agreement with our results. Axelrod and his colleagues confirm the overall distribution of LSD in the organism and also that its excretion is mainly through the bile. But they find that LSD is strongly bound (65 to 90 per cent) by a protein constituent of the blood of the cat, whereas Lanz and colleagues[12] could recover the total activity of LSD added to blood when assayed using 5-HT, showing that if LSD is bound in the rat's blood it still remains active. Stoll and colleagues[15] recovered from the bile of rats with a bile fistula 2 hours after the injection, 70 per cent of the total radioactivity, but found that the greater part of the LSD had undergone a biochemical transformation showing chromatographically three different metabolites, while the American authors report that the compound excreted into the bile is unaltered LSD. Axelrod and colleagues also show for the first time that LSD passes into the cerebrospinal fluid in measurable amounts. Unexpectedly, they find more LSD in the lungs than in the liver. They also report that guinea pig liver tissue is the only tissue that metabolises LSD *in vitro*. A careful study suggests that LSD is transformed *in vitro* into 2-oxyLSD by an "enzyme system, present in microsomes only, that requires oxygen and a reduced triphosphopyridine nucleotide generating system". The new compound does not possess the psychogenic action of LSD. So far two of the metabolites found in the bile by Stoll and colleagues do not correspond with 2-oxyLSD, but the question whether the third metabolite, which does not give the van Urk reaction, characteristic of lysergic acid and its derivatives, is identical with 2-oxyLSD, remains unanswered.
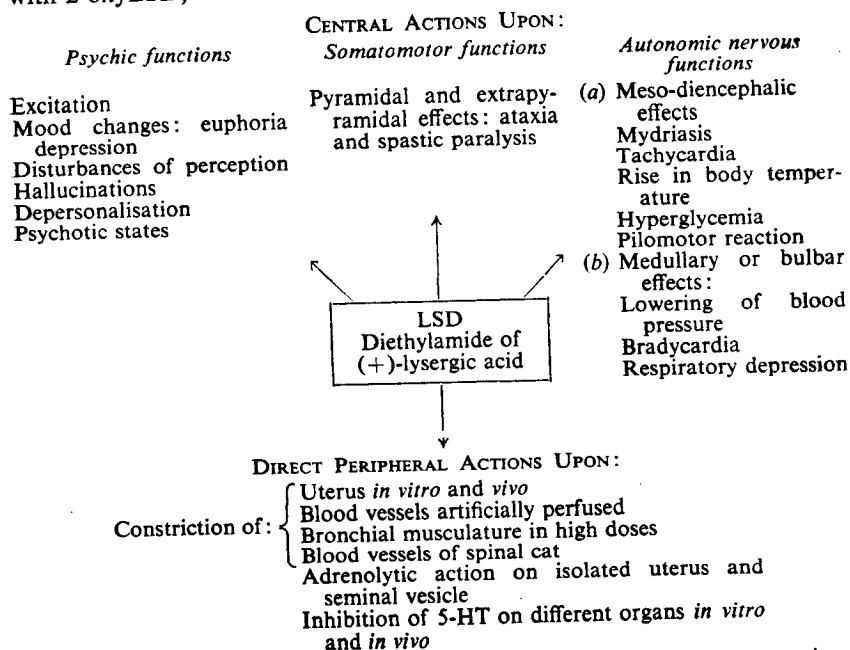
CENTRAL ACTIONS UPON:

Psychic functions	*Somatomotor functions*	*Autonomic nervous functions*
Excitation	Pyramidal and extrapyramidal effects: ataxia and spastic paralysis	(a) Meso-diencephalic effects
Mood changes: euphoria depression		Mydriasis
Disturbances of perception		Tachycardia
Hallucinations		Rise in body temperature
Depersonalisation		Hyperglycemia
Psychotic states		Pilomotor reaction
		(b) Medullary or bulbar effects:
		Lowering of blood pressure
		Bradycardia
		Respiratory depression

LSD
Diethylamide of
(+)-lysergic acid

DIRECT PERIPHERAL ACTIONS UPON:

Constriction of:
  Uterus *in vitro* and *vivo*
  Blood vessels artificially perfused
  Bronchial musculature in high doses
  Blood vessels of spinal cat
Adrenolytic action on isolated uterus and seminal vesicle
Inhibition of 5-HT on different organs *in vitro* and *in vivo*

FIG. 1. PHARMACOLOGICAL PROPERTIES OF LSD (DIETHYLAMIDE OF (+)-LYSERGIC ACID

Pharmacological Data

In Figure 1 the complexity of the actions of LSD is shown (after Rothlin and Cerletti[10]). We distinguish two basically different kinds of action: the direct peripheral actions and those upon the central nervous system.

Direct peripheral actions. LSD has a contracting effect *in vitro* and *in vivo* on the uterus of the rabbit which is 1·5 times weaker than that of ergometrine. The drug causes vasoconstriction in the perfused blood vessels of the rat's kidney[9,10] and rabbit's ear[17], and also in the spinal cat[9,10]. In the intact animal the depressant action on the vasomotor centre predominates, and results in a fall in blood pressure. The adreno-sympatholytic action characteristic of ergotamine, ergotoxine and other natural and hydrogenated ergot alkaloids with the tripeptide group is present but relatively weak.

LSD selectively antagonises 5-HT, named enteramine by Erspamer[18] and serotonin by Page[19]. This antagonism was discovered by Gaddum[20] in the isolated uterus of the rat, and can also be demonstrated on the smooth muscle of other organs, for example the gut of the guinea pig[20], blood vessels[21,22], and also blood vessels[23] and bronchial musculature *in vivo*[24,25].

LSD elicits an expansion of the chromatophores of the female guppy (*Poecilia reticulatus*). Long pretreatment with 5-HT can inhibit this effect[26]. LSD produces a maximum increase in the amplitude of the heart of *Venus mercenaria* without altering its sensitivity to acetylcholine[27]. The drug also mimics the action of 5-HT on the heart of this mollusc (5-HT seems to be a normal transmitter in this organ) with the difference that the action of 5-HT can be easily washed out whereas 30 minutes' washing of the heart treated with LSD produces if anything a further increase in amplitude.

Effects on the central nervous system. The central effects elicited by LSD are more numerous and interesting than the direct peripheral actions. They can be subdivided in three groups: autonomic, somatomotor and psychic effects.

Autonomic effects. Some of these are sympathetic and others parasympathetic in nature. Mydriasis is induced in various species, mouse, rat, rabbit, cat[28], and also in man[29-31]. LSD increases the blood sugar, and the heat-regulating centre exhibits a very high sensitivity to the drug[28] which provokes increase in body temperature in the cat, dog and rabbit[32], while in the rat only very high doses have the same effect, and smaller doses decrease the temperature. Piloerection is induced in various animals. All these autonomic responses to LSD are sympathetic and are of central origin since pretreatment with either ganglion-blocking agents as, for example, hexamethonium, or sympathicolytics like hydergine (the hydrogenated ergot alkaloids of the ergotoxine group) inhibits them[28].

LSD also evokes parasympathetic activity producing salivation and lacrimation, especially in the dog[9,10], with nausea and vomiting in higher doses.

Blood pressure is not affected significantly by small doses of LSD. However, 50 to 100 μg./kg. in anaesthetised cats causes bradycardia,

resulting from central vagus stimulation, and a fall in blood pressure, the latter action being due to a depressant action upon the vasomotor centre, since in the spinal cat LSD increases blood pressure and bradycardia is absent[9,10].

In man, the action of LSD on blood pressure[29,30], cerebral circulation and metabolism was thoroughly investigated in normal and schizophrenic subjects[31]. When the psychic effects reached a maximum 40 minutes after intravenous injection of 100 to 120 μg. of LSD, blood pressure was slightly increased, the internal jugular venous pressure was unchanged in normal subjects and slightly but significantly raised in schizophrenic patients. Cerebral blood flow, vascular resistance, oxygen consumption, glucose utilisation, arterio-venous glucose and oxygen differences and respiratory quotient showed no significant change despite the obvious occurrence of the characteristic psychological and mental effects of LSD. Mydriasis was also present.

Respiration[9,10] is affected by doses of 10 to 50 μg./kg., which produce stimulation or inhibition. Higher doses produce only inhibition, and death is due to respiratory paralysis. Similar respiratory changes were also observed by other authors[33,34].

From this multiplicity of autonomic centrally induced effects the most significant action is the response of the temperature regulation centre in the rabbit to LSD. Doses as small as 0·5 to 1·0 μg./kg. raise the temperature. This dose is comparable to the dose of LSD inducing psychic changes in man. These two responses show that LSD has not only an outstanding activity in the psychic sphere but also in the field of autonomic functions but this does not imply that the psychic and autonomic functions are related. The responses in man and in rabbit are accompanied by parallel effects in both in that tachyphylaxis develops and tolerance occurs, reproducible effects being obtained only after several days interval between experiments.

Somatomotor effects. These are both pyramidal and extrapyramidal in nature. The symptoms in cats and dogs are ataxia and show especially spastic paresis. High doses are necessary to produce these motor changes when compared with the minute amounts of LSD inducing mental disturbances in man and changes in temperature regulation in rabbits.

Psychic effects. The characteristic psychic changes induced in man by LSD administered by mouth are: alteration of the mood either towards euphoria or depression, alteration of the behaviour, hallucinations, mostly optical, distortion of the body image, a sense of depersonalisation, and "psychotic" states. Whether the psychic alterations correspond to a real psychotic state, with a pattern which can be regarded as a "model psychosis", as many psychiatrists define it, can only be discussed when agreement is reached on the definitions of psychosis. With Hoch and colleagues[35] we believe that the psychological disturbances produced by LSD and similarly active agents are chiefly linked to the category of functional psychoses not causing gross impairment of memory, orientation and awareness. This is especially so for the acute action of LSD in a single dose.

Characteristic of the psychological LSD response is the individual reaction, the actual psychic induction and the environment during the assay. A distinctive feature in the production of the psychic and autonomic changes by LSD in man is the long period of latency after oral administration. While the autonomic effects are seen in about 20 minutes after administration, the psychic effects do not appear until 40–60 minutes. The peak of the mental changes is reached after 2–3 hours, and the mean duration is 8–12 hours. A comparative study of the onset, peak and duration of the actions when the drug was given by different routes was made by Hoch[36] with the following results. The mean doses were: 120 μg. orally and intramuscularly, 100 μg. intravenously, and 20–60 μg. intraspinally. The onset of autonomic and psychic effects was slightly faster by the intramuscular route than orally, only several minutes after intravenous and practically instantaneous after intraspinal injection. The peak of the psychic symptoms is reached in 1 hour and lasts 9–10 hours after intravenous and intraspinal administration. No qualitative but only quantitative differences could be observed for the different routes. These were particularly in the onset of symptoms, less so in the duration of action. The overall pattern of psychic changes induced by LSD resembles that produced by mescaline in much higher doses.

The lengthy period before onset of the psychic changes after oral administration gave rise to the hypothesis[37] that LSD, active at 0·5 to 1·0 μg./kg., does not induce the mental changes in man by direct action on the brain but by a metabolite produced by a primary disturbance of the metabolism of another organ, probably the liver. The results of administering LSD by different routes, especially intravenously and intraspinally where onset of action is instantaneous, makes this unlikely.

NEUROPHARMACOLOGICAL AND NEUROPHYSIOLOGICAL DATA

The problem of the central actions of LSD has been approached by the newer neuropharmacological and neurophysiological techniques. When LSD was administered with the Feldberg-Sherwood[38] canula into the lateral ventricle of the brain, Gaddum and Vogt[39] found that doses up to 200 μg. induced only minor diffuse autonomic symptoms, but 800 μg. aroused the unanaesthetised cats to a display of "sham rage" beginning three minutes after the LSD and lasting 45 minutes. Subcutaneous injection of 3 mg. produced a similar pattern lasting for 2 hours. It is astonishing that such high doses are needed to produce apparent symptoms after intraventricular administration compared with the minute doses active orally in man or intravenously in the rabbit. Intraventricular administration is a promising pharmacological approach, but no better localisation of the point of attack of a drug is obtained in this way than by systemic administration.

The electrophysiological studies with LSD relate to spontaneous cortical activity and to effects on transmission in specific synaptic systems. Marrazzi and Hart[40,41] found that electrical submaximal stimulation

applied to an optical cortex in the cat slightly anaesthetised with thio-pentone sodium evokes a cortical potential transcallosal response at a symmetrical point in the contralateral cortex. After ipsilateral intra-carotid administration of 8 μg./kg. of LSD the amplitude of the post-synaptic response is apparently reduced. The same effect is obtained by mescaline, 5-HT, bufotenine, adrenaline, noradrenaline and adreno-chrome: thus this effect does not seem specific. Rovetta's[42] investigations on the cortical response to photic stimulation in anaesthetised cats by local administration of LSD in concentrations as high as 9 per cent as well as by intravenous injection of 40 μg./kg. have been without clear results. Purpura[43,44] found in unanaesthetised cats immobilised with suxamethonium, facilitation of the primary cortical responses in the auditory and visual system by small doses of LSD; higher doses, 40 to 60 μg./kg., intravenously, depressed the auditory response while facilitation for visual stimuli remained. These effects could not be reproduced by thiopentone anaesthetised cats. With 4 μg./kg. intravenously, Purpura observed activation of the recovery cycle consisting of a shortened initial recovery phase and a prolonged phase of supernormality. Evarts[45] who has recently made an excellent review on the electrophysiological studies, investigated the synaptic transmission in the visual system of the cat in pentobarbitone anaesthesia. Intracarotid injection of 30 μg./kg. of LSD caused a mean decreased of 80 per cent in the amplitude of the geniculate postsynaptic response to a single stimulus of the optic nerve, while trans-mission within the retina and between geniculate radiation fibres and cortical cells was resistant to LSD. Block of geniculate transmission by LSD was associated with absence of responsiveness to visual stimuli (behaviour blindness) while the cats respond briskly to auditive stimula-tion. The same effects were obtained with monkeys.

On the basis of recent investigations by Grundfest and Purpura[46] on the general problem of dendritic activity, Purpura suggests that LSD elicits differential actions on axodendritic and axosomatic synapses, that is, LSD inhibits the axodendritic and facilitates the axosomatic trans-mission. Dendrites are synaptically excitable only by the physiological transmitters and drugs, and not by electrical stimulation. In several studies it was found that the electrographic picture produced by stimula-tion of the reticular formation and the action of LSD are similar (arousal effect in the EEG). Purpura suggests in the light of the new experimental data that this common picture does not imply a direct action of LSD on the reticular formation but a diffuse effect on cortical as well as on subcortical synapses whose activation will facilitate or inhibit transmission. The quality of the effect depends on whether this activation causes depolarisa-tion or hyperpolarisation of the synaptic membrane. From this concept, the central actions of LSD and similarly active drugs seem to be diffuse rather than localised.

Cook and Weidley[48] investigated the behaviour effects of LSD using the "conditioned avoidance-escape response" (CR) in trained rats. LSD significantly blocked the conditioned response after subcutaneous in-jection of 1·5 mg./kg., but not the unconditioned response. The purpose

of this study was to antagonise the CR-blocking action of various agents with doses of 0·1 to 0·5 mg./kg. of LSD that had no measurable action themselves on the CR. These doses of LSD antagonised the CR-blocking action of chlorpromazine, morphine, reserpine and 5-HT. The latter depressed only the spontaneous locomotor activity in rats and mice, and there was no stimulant action. Mescaline failed to block the CR and did not antagonise the CR-blocking action of chlorpromazine, morphine, reserpine and 5-HT.

Apter and Pfeiffer[49] believe that cats are capable of having hallucinations when given nontoxic doses (0·10 mg./kg.) of LSD intraperitoneally and 150 mg./kg. of mescaline. Both compounds provoke spontaneous action potentials in both retina and optic nerve, appearing first in the retina and later in the optic nerve. Large spikes are recorded from the visual cortex in cats after LSD. These spikes are higher and larger than in the retinal potentials and they disappear after severing the optic nerve. From these findings the authors conclude that the spontaneous visual-system activity induced by LSD begins in the retina, travels through the visual pathways with facilitation at each synapse[43] with higher spikes from each nucleus and maximal activity in the cortex. The activity in the cortex depends on the intact connection with the retina. Thus the origin of optic hallucination by LSD is located in the retina.

Grenell[50] suggests that LSD acts directly on the cerebral cortex of the anaesthetised cat when administered intravenously or by local cortical perfusion (2·5 and 2 μg./ml. of LSD) by microcannulation into a pial vessel. The drug inhibits the cortical response to direct electrical stimulation. The most striking effect of LSD under these experimental conditions was in producing "dendritic spikes". This is in agreement with the assumption of Purpura[44]. But LSD can act more directly on the cortical response, because the inhibition of this response was also observed after interruption of the ascending reticular activating system.

Keller and Umbreit[51] observed that LSD induced a special locomotor behaviour in the guppy (*Lebistes reticulatus*). Previous or simultaneous exposure to 5-HT caused no observable effect on the typical LSD-response. No antagonistic action was seen with other indole derivatives and tryptophan, but the latter compounds prolonged the LSD induced behaviour for as long as a week after the drug, and in some cases for months. Fishes with this abnormal LSD-plus-indole-behaviour were completely restored to normal behaviour by reserpine. The action of 5-HT under the same conditions does not appear to have been studied. Changes of behaviour have been reported by Rothlin and Cerletti[9,10] who described an alertness pattern, and by Woolley[52] who compared the behaviour of LSD-treated mice with that of normal mice when placed on a tilting glass plate. He suggested that the behaviour of the LSD-treated mice was due to hallucinations. Any attempt to antagonise the LSD-induced behaviour by 5-HT failed.

The cells of oligodendroglia of the brain are characterised by a slow pulsating rhythmical movement in tissue culture. Benitez and colleagues[53] and Woolley[52] observed that LSD, 5 μg./ml., first causes relaxation and

vacuolisation of these cells of foetal human brain, and secondly causes contraction. When LSD is given with 5-HT the first effects of relaxation and vacuolisation are antagonised by 5-HT but the contraction is increased. Thus there are both antagonistic and additive effects between the two agents. The meaning of these cerebral actions of LSD and 5-HT is not evident, but there is an analogy with the actions of the two agents on isolated smooth muscle.

The results of several authors working on the spontaneous cortical activity (EEG) produced by LSD in animals under various experimental conditions and in man are in good agreement. Delay and colleagues[55] found in rabbits a decrease in the amplitude of spontaneous activity and no block of the LSD response to activation. Bradley and colleagues[56], in conscious unrestrained cats, recorded after oral LSD an EEG-pattern consisting of diffuse, fast activity with low amplitude. The same results have been described by Schwarz and others[57] using the intraventricular route. In pentobarbitone-induced narcosis Bradley and colleagues[56] and Evarts and colleagues[58,59] found the "barbiturate spindles" abolished. Himwich[60] and Rinaldi and Himwich[61] concluded that one of the central effects of LSD is the stimulation of the mesodiencephalic activating system (arousal response) but in contrast to these findings Killam and Killam[62] recorded an increase of the threshold for EEG-arousal to sciatic nerve and reticular formation stimulation.

In man, the LSD effect on the EEG of normal volunteers consisted in favouring or increasing the alpha-rhythm[63–65].

BIOCHEMICAL DATA

Hoagland[66] discusses the biochemical changes induced by LSD *in vivo* and suggests that these might be related to the phosphate metabolism. A marked reduction in urinary phosphate excretion was found in drug-free schizophrenic men as well as in LSD-treated normal men (dose 0·5 to 1·0 μg./kg. orally). ACTH in schizophrenic and LSD-treated subjects enhanced phosphate excretion[67]. The data is believed to be consistent with the view that some unknown metabolite in schizophrenic and LSD-treated normal subjects facilitates the conjugation of phosphates with some organic substances in the cells or the decrease of the phosphate turnover rate.

Bain[68] recently reviewed the *in vitro* biochemical work on LSD and similarly acting compounds like mescaline and adrenochrome. All these agents have been studied primarily in relation to the metabolism of carbohydrates. The most interesting finding by Mayer-Gross and colleagues[69] is that the homogenate of guinea pig brain in the presence of 4×10^{-9} M of LSD stimulates the glucose oxidation by some 30 per cent and inhibits the utilisation of hexose monophosphate by 40 per cent. This was not confirmed by Lewis and McIlwain[70] who did not find stimulation, but 40 per cent inhibition of glucose oxidation with brain slices, electrically stimulated, of the guinea pig and by applying concentrations up to 5×10^{-9}M of LSD. Unstimulated slices did not show any effect.

Under the same conditions, lactate production was inhibited by 40 per cent. Clark and others[71], and Bain[68], quoting Bain and Hurwitz and Bain and Morrison, confirmed the results of Lewis and McIlwain. Bain[68] found the mitochondria of liver and brain of the rat insensitive to LSD in uptake of oxygen and in associated phosphorylation in concentrations up to 10^{-4}M of LSD. Attempts to reverse the inhibition of glucose oxidation by LSD in electrically stimulated brain slices with 5-HT were without success.

Rudolph and Olson[72] investigating the metabolism of glucose-1-^{14}C and -6-^{14}C with prostate slices of dogs could not detect differences in the incorporation of ^{14}C into CO_2 and lactate in the tissue between normal and hypoglycemic animals. The total radioactivity in CO_2 from glucose-1-^{14}C was considerably higher than from glucose-6-[14]C. With 5×10^{-4} M of LSD in the system the labelled carbon in CO_2 was markedly increased with glucose-6-^{14}C but not with glucose-1-[14]C. The results were identical in both normal and hypoglycemic tissues.

Poloni and Maffezzoni[73] observed an increase of acetylcholine in the brain of guinea pigs after administration of LSD. Hence Thompson and others[74] investigated the action of LSD on cholinesterase and found a 50 per cent inhibition of the activity of the serum cholinesterase of human plasma and brain with 5×10^{-6} M of LSD. Only 10 per cent inhibition of true cholinesterase occurred with LSD-concentrations up to 5×10^{-5} M. Zehnder and colleagues[75] have confirmed these findings and found that 2-brom-lysergic acid diethylamide acts similarly. Of the natural ergot alkaloids only ergometrine was active, having one-fifth the activity of LSD. Inhibition of 50 per cent of the serum cholinesterase was also found by Fried and Antopol[76] in the same concentration (5×10^{-6} M) of LSD, and with 2×10^{-3} M of 5-HT the same effect was seen. When the non-enzymatic acetylcholine hydrolysis in the presence of the drug was subtracted from the total manometric values, a marked enhancement occurred with concentrations of 6×10^{-9} M of LSD (50 per cent) and 5×10^{-6} M of 5-HT (31 per cent). The antagonistic effect of the two drugs was not studied.

The inhibiting effect of LSD on serum cholinesterase may explain the accumulation of acetylcholine observed by Poloni and Maffezzoni in animals treated with LSD, but the primary question of whether this biochemical effect on the serum cholinesterase *in vitro* is correlated with the central activity of LSD on autonomic and mental functions has to be considered carefully (Thompson). Indeed the active concentration of LSD of 5×10^{-6} M in these *in vitro* experiments on the serum cholinesterase are in contrast with the doses of 0·5 to 1·0 μg./kg. which provoke the mental changes in man. Allowing a uniform distribution of the human dose, the concentration is at least 1000 times lower (10^{-9}). The sensitivity of true cholinesterase toward LSD is more than 10 times less and yet this enzyme is presumably more directly correlated with the nervous functions than is pseudoesterase. When discussing the sensitivity of these enzymes to LSD and other compounds it is wise to take into account the differences of the milieu *in vitro* and *in vivo*.

Compounds Related to LSD

The characteristic activity of LSD on mental functions in man prompted the synthesis of related compounds. Stoll and Hofmann[2] provided us with a series of substances for pharmacological testing obtained by partial synthesis with (+)-lysergic acid as a common link. These were screened by different tests. Table I gives the data on the antagonistic actions to 5-HT of the most interesting compounds on the isolated uterus of the rat[10]. This antagonism has the advantage of being specific, reproducible and a highly sensitive test for LSD. For a reliable analysis of the specificity of the 5-HT antagonism the following criteria must be considered: (1) the extent of the latency period for the maximum effect, (2) the reversibility of the antagonistic action and (3) the absence of the inhibiting action toward adrenaline and noradrenaline, acetylcholine and histamine at concentrations that cause significant 5-HT inhibition[20,77]. These criteria have not been considered for compounds of groups 4 and 5 in Table I (with the exception of LSD), because their activity was weak and transient.

TABLE I

INHIBITION OF 5-HT BY VARIOUS AMIDES OF LYSERGIC ACID (from ref. 10)

1. *LSD and its isomers*	Very active (standard)
(+)-Lysergic acid diethylamide (LSD)	
(−)-Lysergic acid diethylamide	Practically inactive, i.e., more than
(+)- and (−)-*iso*lysergic acid diethylamide	100 × weaker
2. *Derivatives of LSD obtained by saturation of the double bond*	
between C(9) C(10)	
Dihydro-(+)-lysergic acid diethylamide	1·6 × weaker
Lumi-(+)-lysergic acid diethylamide	Practically inactive
3. *Derivatives of LSD with substitution in the indole nucleus of*	
(+)-lysergic acid	
(+)-1-Methyl-LSD	3·5 × stronger
(+)-1-Acetyl-LSD	2·0 × stronger
(+)-2-Brom-LSD	1·5 × stronger
(+)-2-Iodo-LSD	2·0 × weaker
(+)-1-Oxy-methyl-LSD	1·5 × weaker
4. *Monosubstituted amides of (+)-lysergic acid*	
Monomethylamide of (+)-lysergic acid	15·5 × weaker
Monoethylamide of (+)-lysergic acid	8·5 × weaker
Monoisopropylamide of (+)-lysergic acid	5·0 × weaker
Monopropylamide of (+)-lysergic acid	2·5 × weaker
Monobutylamide of (+)-lysergic acid	1·5 × weaker
5. *Disubstituted amides of (+)-lysergic acid*	
Dimethylamide of (+)-lysergic acid	5·0 × weaker
Diethylamide of (+)-lysergic acid = LSD	= standard
Diisopropylamide of (+)-lysergic acid	4·0 × weaker
Dibutylamide of (−)-lysergic acid	3·0 × weaker

Group 1. It is surprising that of the diethylamides of the four known isomers of (+)-lysergic acid only the (+)-lysergic acid diethylamide (LSD) is a strong 5-HT antagonist. The other three isomers are more than 100 times weaker than LSD. None of these three isomers had a competitive effect toward LSD in the 5-HT antagonism and in other tests.

Group 2. These are compounds in which the double bond between C(9) and C(10), the most unstable of the five double bonds in the molecule of lysergic acid, is saturated either by two atoms of hydrogen giving the dihydro-(+)-lysergic acid diethylamide, or by the addition of H_2O at the same positions giving the so-called lumi (+)-lysergic acid diethylamide. While the first compound possesses an activity only 1·6 times weaker than LSD, the latter is inactive. This agrees with the fact that lumi-ergotamine also has no activity on the uterus *in vitro* and *in vivo* and no specific adrenolytic action.

Group 3. This group is the most interesting, and comprises derivatives with substitution in the nucleus of (+)-lysergic acid. (+)-1-Methyl-LSD, (+)-1-acetyl-LSD and (+)-2-brom-LSD are stronger antagonists of 5-HT than LSD, the methyl 3·4 times[81], the 1-acetyl- twice, and the 2-brom-compound 1·5 times as active. These compounds have not only this high sensitivity to 5-HT but also other effects which will be discussed later. The (+)-2-iodo-LSD and the (+)-1-oxymethyl-LSD are respectively twice and 1·5 times weaker 5-HT antagonists than LSD.

Group 4. Monosubstitution at the amide nitrogen of the (+)-lysergic acid amides gives rise to a series of homologues mono-methyl, mono-ethyl, mono-*iso*propyl, mono-propyl and mono-butyl compounds. The anti-5-HT activity of all compounds is stronger than that of (+)-lysergic acid amide but weaker than that of LSD. Following the sequence of the homologous series the anti-5-HT activity increases gradually from 15·5, 8·5, 5, 2·5 to 1·5 times lower than LSD. Hence the activity increases with the length of the side chain.

Group 5. Disubstitution at the amide nitrogen of the (+)-lysergic acid amide. In this final group, dimethyl, diethyl, di*iso*propyl and dibutyl amides of the (+)-lysergic acid were investigated and found to have a 5 to 3 times weaker anti-5-HT activity than LSD which belongs to this group.

The most important compounds 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 of intensity in different functions, and that agents with apparent anti-5-HT effect *in vitro* might be inactive *in vivo*[78,79]. 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[80]. *In vivo* the three compounds show about the same activity to 5-HT on the peripheral vessels in the anaesthetised cat, on the bronchial musculature of the guinea pig, and in the inhibition of the potentiation to barbiturates by 5-HT in mice. In contrast to some indole derivatives active only *in vitro*[78], these compounds also have a pronounced anti-5-HT activity *in vivo*[80]. There are difficulties in the quantitative evaluation of this antagonism in some functions. A disturbing factor is the above-mentioned tachyphylaxis.

While 1-acetyl-LSD induces similar psychic changes in man as does LSD, the 2-brom-LSD is inactive in this respect, as appear to be all other compounds in Table I with the exception of the monoethylamide of (+)-lysergic acid (LAE). The preliminary assays, in volunteers, of the other compounds in doses up to 10 times those of LSD which elicit autonomic effects, produced no apparent psychotogenic activity. 1-Methyl-LSD was not examined[81].

Of the derivatives of LSD and related compounds described, only the monoethyl amide of (+)-lysergic acid (LAE), the diethylamide of (+)-lysergic acid (LSD) and the 1-acetyl-diethylamide of (+)-lysergic acid induce apparent psychotic changes in man, and it is probable that 1-methyl (+)-lysergic acid diethylamide behaves similarly. The psychic effects induced by these three compounds are similar, but there are great quantitative differences. While LSD and acetyl-LSD are active in doses of 0·5 to 1·0 μg./kg., LAE required 8 to 10 times this amount[9,10].

From the chemical point of view it is noteworthy that only the monoethyl (LAE) and diethyl amide (LSD) compounds possess the psychogenic action, the mono and di-methyl, propyl and butyl derivatives do not produce psychic alterations. The latter compounds can elicit autonomic effects in animal and man in doses at which LAE is inactive. Thus 50 μg. of the dimethylamide of (+)-lysergic acid produces autonomic effects for which 500 μg. of LAE are necessary. But in this dose LAE elicits pronounced psychic changes. So the production of autonomic and psychic effects are probably not linked. It seems evident that the ethyl group or groups on the amide nitrogen of (+)-lysergic acid derivatives are of primary importance for the production of psychogenic action.

The presumed causal relationship between the psychic action of LSD and the inhibition of 5-HT by LSD is much more complicated than it appeared when the first arguments were presented by Gaddum[82] and Woolley[83]. The facts are that LSD was found to be a specific and highly active inhibitor of 5-HT on the isolated uterus of the rat and isolated blood vessels. Soon afterwards, 5-HT was detected in the brain by Page[84] and by Gaddum[85] and was admitted as a new neurohumoral transmitter playing an important role in cerebral functions. From this was derived the fascinating hypothesis that the inhibiting action of LSD towards 5-HT may be the key to the explanation of the cerebral action of LSD (Gaddum and Woolley).

That many substances antagonistic to 5-HT *in vitro* may have no such effect *in vivo* has already been mentioned. Of the numerous derivatives of LSD investigated by us, 2-brom-LSD was found to be as potent an inhibitor of 5-HT as LSD *in vitro* and *in vivo*[80]. The surprising fact is that 2-brom-LSD despite its pronounced anti-5-HT activity is without any effect on the psyche. Doses up to 650 μg. were administered to 19 volunteers in our laboratory, and only autonomic effects were observed. Hirsch and others[86] administered 5 to 7 μg./kg. in volunteers, Waldenström (personal communication) 1500 μg., Snow and others[87] up to 7500 μg. and Page (personal communication) 20,000 μg. of 2-brom-LSD in carcinoid patients without provoking significant changes in the psyche. The largest dose of 2-brom-LSD given to man is at least 200 times the usual active psychogenic dose of LSD.

The next step towards elucidating the relations of the psychic and 5-HT inhibiting action of LSD was a comparison of the pharmacological actions of LSD and 2-brom-LSD on different functions[9,10]. Table II summarises these results.

PHARMACOLOGY OF LYSERGIC ACID DIETHYLAMIDE

TABLE II

COMPARISON OF THE PHARMACOLOGICAL PROPERTIES OF LSD AND 2-BROM-LSD

Functions	LSD	2-brom-LSD
Uterus and vagina in anaesthetised rabbit	Contraction approximately 1·5× weaker than ergometrine	No contraction, in higher doses inhibition of spontaneous rhythm and relaxation
Adrenolytic action (seminal vesicle of guinea pig)	Approximately 50× weaker than ergotamine	Approximately 10× as strong as LSD
Blood vessels: perfused kidney of the rat and the rabbit ear	Constriction	No constriction
Blood pressure in anaesthetised cat	Decrease	No specific action
Heart rate in anaesthetised cat	Bradycardia	No effect
Eye, pupil	Mydriasis	No effect
Body temperature: rabbit, cat, dog 　″　　″　　rat	Increase in all doses Decrease, increase in toxic doses	Decrease in high doses Decrease in all doses
Blood sugar in normal rabbits	Increase	No effect
Behaviour in normal mice	Excitation	Sedation
Amphetamine-excitation in mice	Potentiation	Inhibition
Effect on walzing mice	Inhibition on walzing due to excitation	Inhibition due to sedation
Effect on EEG	Activation	No activation
Psychic action in man	Very pronounced	Absent
5-HT constriction on rat uterus 5-HT constriction on perfused blood vessels	Inhibition Inhibition	Inhibition ⎫ 1·5× as strong Inhibition ⎭ as LSD
5-HT constriction on bronchial musculature *in vivo*	Inhibition	Inhibition
5-HT-potentiating action to hypnotics in mice	Inhibition	Inhibition
Reserpine-potentiating action to hypnotics in mice	Inhibition	No inhibition
Effect on chromatophores of *Poecilia reticularis*	Spreading	Spreading 2·5× as strong as LSD
Effect on cholinesterase of brain slices *in vitro*	Inhibition	Inhibition

LSD produces mainly a sympathetic pattern of symptoms: mydriasis, increase of temperature and of the blood sugar, piloerection, behavioural alertness, activation in the EEG and the typical psychic changes in man. None of these effects is produced by 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. Both compounds have a strong anti-5-HT effect *in vitro* and *in vivo* and inhibit the potentiating action of 5-HT to barbiturates in mice. Yet 2-brom-LSD is without any psychotogenic effect. Sedation and the inhibition of the potentiation effect of 5-HT on barbiturates by 2-brom-LSD are of central origin. Therefore it cannot 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 the same anti-5-HT activity

on the rat uterus. We therefore concluded[80] that on the basis of these results with LSD and 2-brom-LSD it is difficult to admit a correlation of 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 it lacks the psychotogenic action.

The problem of interference of 5-HT and LSD in cerebral functions has been studied under various conditions. It became particularly attractive when the fundamental studies of Brodie and his associates[89] on the mode of action of reserpine provided evidence that the effects of this alkaloid are correlated with the metabolism of 5-HT. The actual concept of these authors[90] is as follows: reserpine primarily impairs the 5-HT binding sites in the brain but also those of the blood platelets and of the intestine. The consequence of this is the release of 5-HT in free form from the depots in the brain and elsewhere. Free 5-HT is rather an unstable substance and metabolised[91] easily by the action of monoamine-oxidase. But 5-HT is continuously synthesised and it persists free in low concentration in the brain. This free 5-HT has been considered to provoke the actions attributed to reserpine. 5-HT (serotonin) acts as the transmitter substance for the parasympathetic and noradrenaline for the sympathetic centres. LSD is supposed to block the "serotonergic" parasympathetic brain centres and by doing so unmasks the action of the opposing sympathetic system by causing an imbalance between the two antagonistic systems. This is a clever and attractive hypothesis, but, as the authors say, probably too simple to explain the differential functions of autonomic, somatic and psychic nature. Recently Carlsson and others[92] and Shore and Brodie[93] gave evidence that reserpine causes a long-lasting depletion of noradrenaline as well as of serotonin from brain and other organs. These results suggest a similar mechanism of action of reserpine on the catechol amines as on serotonin. Carlsson supposes that lack, rather than excess in free form, of serotonin and noradrenaline has to be considered as the cause of some pharmacodynamic effects of reserpine. These new results do not fit Brodie's theory based mainly upon the 5-HT releasing action of reserpine, since this agent provokes a long-lasting depletion of 5-HT and noradrenaline in the brain as well as in other organs.

In conclusion some experimental findings are presented that do not agree with the theory that the actions of LSD, and particularly its psychogenic effects, are caused by the relationship of LSD to 5-HT.

As well as the parallel and divergent effects of LSD and 2-brom-LSD previously noted, there exists the inhibition by LSD of the potentiating effect of reserpine to barbiturates, while 2-brom-LSD unexpectedly has no action. Therefore we suggest that reserpine does not potentiate by releasing 5-HT but by another mechanism. If reserpine acts by releasing 5-HT it is difficult to understand why 2-brom-LSD inhibits administered 5-HT as effectively as LSD and not the free 5-HT released by reserpine.

LSD causes a state of excitation with "sham rage" and antagonises the depressant action of 5-HT in unanaesthetised cats, when both drugs are given intraventricularly. LSD also antagonises the depressant action of

reserpine, but only temporarily, for the action of reserpine is of longer duration than that of LSD. When administered together there is no inhibiting influence by 5-HT on the alerting response of LSD. Therefore LSD antagonises the action of 5-HT but not vice versa.

Ergometrine is a strong anti-5-HT compound. It produces excitation and sham rage when given intraventricularly, and antagonises the depressant effect of 5-HT like LSD. Yet ergometrine has no psychogenic properties at all.

Mescaline induces similar psychic changes in man as LSD, but no relation with 5-HT is known.

Amphetamine produces similar autonomic and somatic functions as LSD, it induces the arousal pattern, reverses the depressant action of 5-HT and potentiates the effect of barbiturates, but does not provoke the psychic effects of LSD.

Morphine causes excitatory action and a sympathetic pattern similar to LSD and amphetamine but does not have the psychogenic property of LSD. Morphine and amphetamine have no anti-5-HT effects.

These experimental results are evidence that for the inhibition of the central effects of 5-HT and reserpine the anti-5-HT activity is not obligatory.

The effects of LSD and similar agents are not the result of circulatory changes (vasoconstriction or vasodilatation) nor metabolic factors as for example glucose and oxygen consumption. The neuropharmacological and electrophysiological findings, the alerting response due to the influence on the lower reticular formation activating system, the inhibition of the transcallosal synaptic response, and the postsynaptic geniculate synapse, the axodendritic inhibition and axosomatic facilitation are most valuable and stimulating. But present experimental results do not explain the profound mode of action of these agents in the brain, nor do they give coherent understanding of the production of psychic changes peculiar to psychotomimetic drugs. There is as yet no answer to the main question of whether these interesting experimental results have any relation with the psychic functions and their alterations by the psychotomimetic agents in man. While we have learned much about psychotomimetic drugs as a result of the advances in neurophysiology and neuropharmacology, the psychogenic activity of LSD and similarly acting agents still awaits a plausible explanation.

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