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*VI LSD No.94 (§102a)

antagonism to
serotonin (§90a)

M 453 potentiation of barbiturates (§109)

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Interaction of serotonin and lysergic acid diethylamide (LSD)
in the central nervous system.

Experientia 11, 272 (1955).

It has been postulated that 5-hydroxytryptamine (serotonin, enteramine) plays an important role in the central nervous system in the maintenance of normal mental processes, and that a deficiency of serotonin or interference with its action may contribute to the production of mental disorders¹. This postulate is based in part on the observations that serotonin occurs in the brain, and that lysergic acid diethylamide (LSD), which produces profound mental disturbances in man resembling those of schizophrenia², is antagonistic to the effects of serotonin on various smooth muscles *in vitro*³.

In this communication we have described an antagonism by LSD of a central action of serotonin in the intact animal.

Serotonin was found to markedly potentiate the hypnotic action of hexobarbital in mice. This was

¹ D.W. WOOLLEY and E. SHAW, Proc. Nat. Acad. Science **40**, 228 (1954).

² W. A. STOLL, Schweiz. Arch. Neurol. Psychiat. **63**, 279 (1947)

³ J. H. GADDUM, J. Physiol. **121**, 15P (1953).

shown by experiments in which the sleeping times of mice pretreated with serotonin were compared with those of mice injected with hexobarbital alone. Table 1 shows that mice given 20 mg per kilogram of serotonin 10 min prior to 100 mg per kilogram of hexobarbital slept for a considerably greater time than did animals given only the barbiturate.

Serotonin by itself in a dose of 20 mg per kilogram produced a mild depression, but doses as high as 100 mg per kilogram failed to produce hypnosis.

When serotonin was administered intravenously to mice which had just recovered from hypnosis induced by hexobarbital, the animals almost immediately fell asleep again. This shows that serotonin causes subhypnotic amounts of the barbiturate to become hypnotic. Thus, it acts like chlorpromazine and reserpine by increasing the sensitivity of the central nervous system to the barbiturate¹, rather than like β -diethylaminoethyl diphenylpropylacetate (SKF 525-A) which potentiates the activity of many drugs by interfering with their rate of detoxication².

Duration of hypnosis of hexobarbital in mice. Adult male mice were given the various drugs intraperitoneally. LSD (10 mg per kilogram) was given one hour before, and serotonin (20 mg per kilogram) given 10 min before hexobarbital (100 mg per kilogram). The duration of hypnosis is defined as the time from the loss to the return of the righting reflex. Values for duration of hypnosis are means $\pm$ standard deviations. Figures in brackets refer to numbers of animals in each series.

Hexobarbital alone min	Hexobarbital + Serotonin min	Hexobarbital + LSD + Serotonin min
19 $\pm$ 6 (12)	61 $\pm$ 7 (8)	30 $\pm$ 5 (9)

When mice were given 10 mgm per kilogram of LSD prior to the serotonin, the potentiating effects of serotonin were markedly diminished (Table). LSD in doses of 5 mg per kilogram had an almost equivalent effect and definite antagonism to serotonin was observed with doses as low as 1 mg per kilogram. LSD by itself had little or no effect on the hypnosis produced by the barbiturate.

The observations described here are in accord with the concept that serotonin has an important function in the brain and that LSD produces its mental disturbances by suppression of some central action of serotonin.

Zusammenfassung

Serotonin (5-Oxytryptamin) wirkt bei der Maus als mildes Sedativum und steigert den hypnotischen Effekt von Evipan deutlich. Diese Wirkungssteigerung kann durch Lysergsäure-diäthylamid (LSD) antagonisiert werden. Dieser Befund stimmt mit der Ansicht überein, dem Serotonin komme eine physiologische Rolle im Gehirn zu und dass LSD möglicherweise durch antagonistische Wirkung gegenüber Serotonin Psychose verursachen kann.

¹ B. B. BRODIE, P. A. SHORE, S. L. SILVER, and R. PULVER Nature (in press).

² J. AXELROD, J. REICHENTHAL, and B. B. BRODIE, J. Pharm. Exp. Therap. 112, 49 (1954).