LSD 78

Science 121, 365 (1955).

Relationship of Hallucinogens to Adrenergic Cerebral Neurohumors

Amedeo S. Marrazzi and E. Ross Hart

Clinical Research Division and Neurology Branch, Chemical Corps Medical Laboratories, Army Chemical Center, Maryland

The study of cerebral synaptic transmission, by recording the postsynaptic electric response evoked by presynaptic stimulation, has demonstrated that an adrenergic synaptic transmission mechanism is present and capable of operating in the cat's brain. Marrazzi (*1*) has reviewed the evidence for this in a recent article in which he describes the use of the relatively simple transcallosal pathway connecting symmetrical points in the right and left optic cortex of the cat, thus making it possible to study one cortex when test stimuli are applied to the other. The electrocortical record so obtained indicates the activity at the terminal synapses by a surface positive wave corresponding to the inflow of impulses into the synapses and a surface negative wave indicating the outflow. In such a preparation, adrenaline, noradrenaline, and the so-called "adrenaline preservatives" cause a decrease in the surface negative wave generated by synaptic outflow without causing a change in the surface positive wave generated by the inflow—that is, a differential reduction in output or a synaptic inhibition.

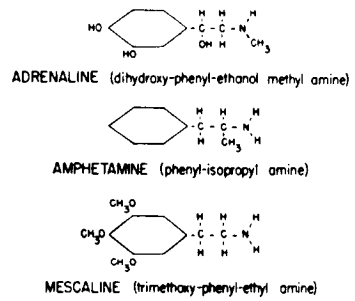

Fig. 1. Types of phenylethyl amines producing mental effects.

Because of the structural similarity (Fig. 1) between adrenaline, which occasionally causes mental disturbances in man, amphetamine, which does so more often, and mescaline, which is a powerful hallucinogen, it was decided to compare the effects of the three on cerebral synaptic transmission. We had al-

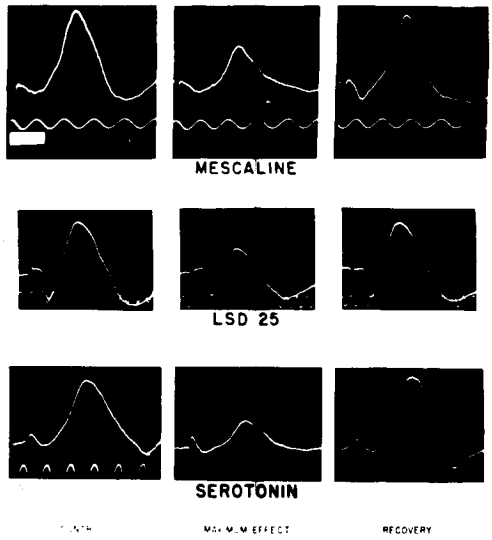

Fig. 2. Inhibition at cortical terminal synapses of transcallosal pathway in cat's brain. Potentials evoked in optic cortex of cat by electric stimulation of contralateral cortex. The drugs injected into carotid artery on recording side were mescaline, 15 mg/kg; lysergic acid diethylamide (LSD-25), 8 μg/kg; and serotonin, 1 μg/kg. Negativity is up. Sodium pentobarbital was used as the anesthesia.

ready shown that adrenaline and amphetamine, and other adrenalinelike compounds (*2*) produce cerebral synaptic inhibition in the cat. Figure 2 illustrates that the effects of mescaline on the synapses of the optic cortex of the cat are qualitatively identical with those of the other two members of the series. Thus, mescaline also produces a synaptic inhibition. It seems warranted to propose an empirical correlation between the synaptic inhibition and the disturbances in conduct observed on administration of mescaline to the unanesthetized cat and the marked hallucinations induced in man.

Additional similarities can be noted by comparing (Fig. 3) the chemical structures of adrenaline, adrenochrome—a possible breakdown product of adrenaline claimed to be capable of simulating schizophrenia (*3*)—and the very potent hallucinogen, lysergic acid diethylamide (LSD-25), as well as the chemical structure of serotonin, suggested by Woolley and Shaw (*4*) as the cerebral metabolite whose deficiency may be responsible for schizophrenia. The similarity between LSD-25 and serotonin is on the basis of the indole ring that they possess in common with adrenochrome, the possible metabolic product of adrenaline, through which the two series of hallucinogens examined are thereby linked.

The theoretical considerations advanced, as well as the suggestion that LSD-25 and serotonin might oppose each other's actions on the nervous system, made it logical to determine their effects on cerebral synaptic transmission in the brain of the cat, utilizing the preparation discussed earlier. Figure 2 demonstrates that LSD-25 has qualitatively the same synaptic inhibitory action as mescaline and adrenaline. The same is true of serotonin (Fig. 2), except that it is about 6 to 8 times as potent as LSD-25 and about 25 to 30 times as potent as adrenaline. Thus, the suggestion, arising from structural similarities, that all members of these series would produce cerebral synaptic inhibition is borne out, while a cerebral antagonism between LSD-25 and serotonin is not found. Competition among the members of these series can be expected, but, since serotonin is far more potent than the others in producing the same kind of synaptic action (inhibition), it would hardly be expected to offset the others, and its deficiency could not reasonably be expected to lead to the same type of effects as those exercised by LSD-25.

The high potency of serotonin, which is in the same range as that for acetylcholine (*1*) on these synapses, and its reported natural presence in the brain (*5*) make one speculate concerning the possible role it might play in the natural function of the nervous system, possibly as a humoral inhibitor. The synaptic inhibitory action of serotonin in the gamma doses used is unaccompanied by any significant change in circulation, as indicated by blood pressure. There is, therefore, little or no basis for assuming changes in cerebral blood flow sufficient to interfere with synaptic transmission. Furthermore, the synaptic effects of anoxia are quite delayed, while that of serotonin is achieved within 30 to 40 sec, reaching a maximum in about 1 min and receding by 3 min. It is clear from the cerebral action of serotonin, introduced into the circulation, that serotonin must pass the blood-brain barrier, although the comparative rate is not established.

The actions described here for one group of synapses are probably typical of more generalized effects, since they have also been recorded at a variety of synapses for adrenaline and adrenalinelike compounds (*1–2*) and in the ciliary ganglion for serotonin (*6*). With generalized synaptic inhibition, the resulting pattern of over-all activity would be a func-

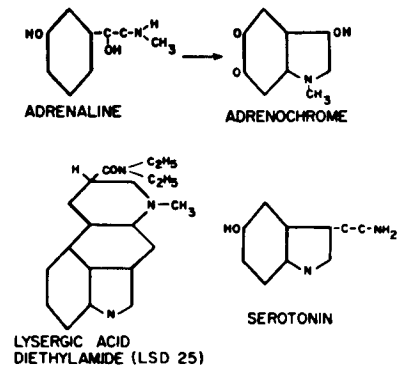

Fig. 3. Chemical structure of adrenaline, adrenochrome, lysergic acid diethylamide (LSD-25), and serotonin.

tion of the variations in synaptic thresholds. In this preliminary stage of correlation, an interpretation of hallucinations as stimulatory phenomena, rather than as derangements owing to partial inhibition, offers no real difficulty, since synaptic inhibition could readily result in release from normal restraining influences with consequent stimulation.

A disturbance of adrenergic or related cerebral neurohumoral mechanisms appears to be implicated in the actions of the hallucinogens studied. The resulting imbalance in the reciprocal relationship (*1*) between adrenergic inhibition and cholinergic excitation in the most susceptible cerebral synapses might be an underlying mechanism in mental disturbance.

References

1. A. S. Marrazzi, *Science* **118**, 367 (1953).
2. E. R. Hart and A. S. Marrazzi, *J. Pharmacol. Exptl. Therap.* **106**, 394 (1952); ———, *Electroencephalog. Clin. Neurophysiol.* **5**, 317 (1953).
3. A. Hoffer, H. Osmond, and J. Smythies, *J. Mental Sci.* **100**, 29 (1954).
4. D. W. Woolley and E. Shaw, *Science* **119**, 587 (1954).
5. I. H. Page, *Physiol. Revs.* **34**, 563 (1954).
6. I. H. Page and J. W. McCubbin, *Circulation Research* **1**, 354 (1953).

18 November 1954.