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# THE POSSIBLE ROLE OF INHIBITION AT ADRENERGIC SYNAPSES IN THE MECHANISM OF HALLUCINOGENIC AND RELATED DRUG ACTIONS[1]

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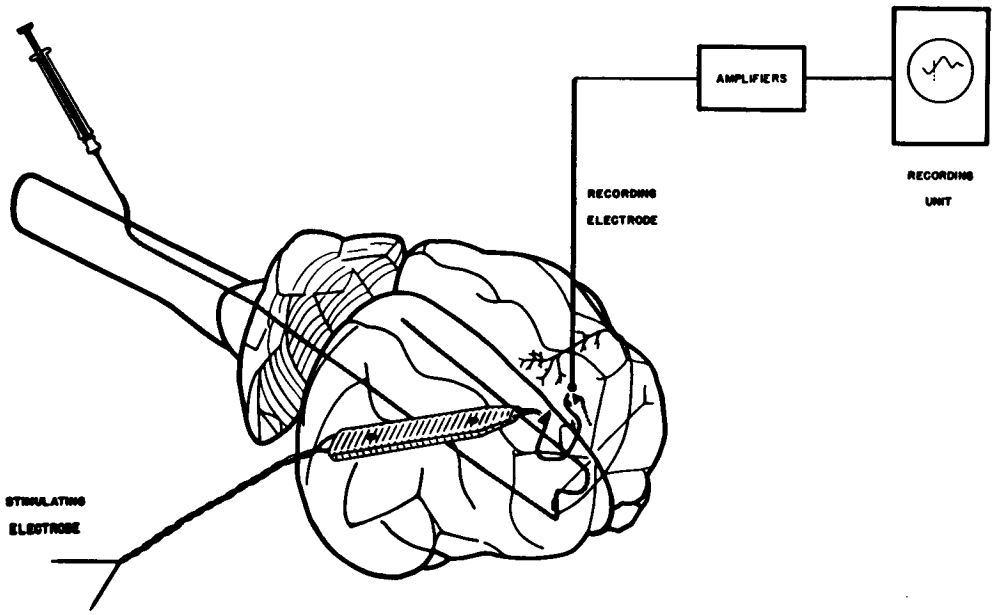
The value of approximation and analogy followed by analysis is well known. The appeal and instructiveness of a model are equally familiar. Starting with an inclination in favor of an organic basis, we have attempted to utilize the animal and its neural circuits as a model in which to study the mechanism of psychoses and in particular those influences of drugs and endogenous chemicals which may have a bearing on the genesis and course of behavioral disorders in animals or mental disturbance in man. This kind of knowledge of this type of drug is required for the treatment of mental disease.




TRANSPARENT MODEL OF BRAIN

TWO NEURON INTERCORTICAL (TRANSCALLOSAL) PATHWAY

SCHEMATIC BLOOD SUPPLY (ARTERIAL)

PATHWAY FOR INJECTED MATERIAL

FIG. 1.

Since hallucinations with a visual component characterize many psychoses, we thought it pertinent to examine the influence of hallucinogenic and related substances on transmission phenomena in the visual system of the cat. In view of the higher vulnerability of the synapses in neural pathways we designed our experiments to test the susceptibility of

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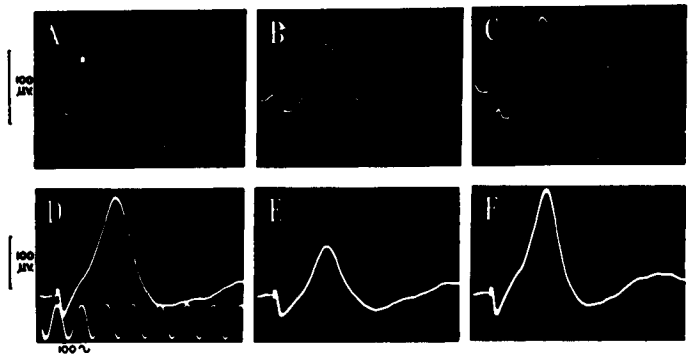


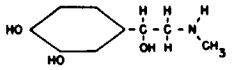
**CEREBRAL SYNAPTIC ACTION OF ADRENALINE AND OF NOR-ADRENALINE**

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

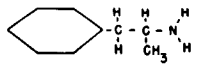
Potentials evoked in optic cortex by electrical stimulation of symmetrical point in contralateral cortex.
Adrenaline (10 μg./Kg.) injected ipsilateral carotid artery after A.
Nor-adrenaline (150 μg./Kg.) injected after D.

A, D - Controls B, E - Inhibition C, F - Recovery

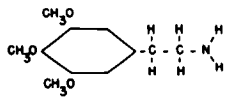
FIG. 2.



ADRENALINE (dihydroxy-phenyl-ethanol methyl amine)



AMPHETAMINE (phenyl-isopropyl amine)

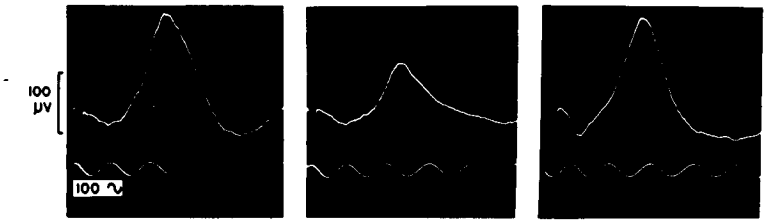


MESCALINE (trimethoxy-phenyl-ethyl amine)

**TYPES OF PHENYL-ETHYL AMINES PRODUCING MENTAL EFFECTS**

FIG. 3.

synapses to drugs. This was accomplished as illustrated in figure 1 by selecting a relatively simply pathway which connects symmetrical points in the optic cortices of the cat, initiating a test impulse by applying an electrical shock to one cortex and recording the electrical change produced by the nerve impulse arriving at the contralateral cortex immediately after having traversed one group of synapses. To achieve cerebral effects uncomplicated by actions upon the rest of the body, an initially higher concentration of drug in the cerebral hemisphere containing the synapses under study through action potential recording was achieved by injection into the common carotid artery of that side as illustrated in the transparent model (fig. 1). We had already had experience with the effects of adrenaline and noradrenaline in this preparation (1). The action potentials (as seen in fig. 2) show, following the stimulus artifact, a downward deflection or surface positive wave approximately corresponding to input to the synapse and an upward deflection or surface negative wave indicating arrival at the optic cortex, presumably following synaptic transmission. Following the control in the first column the intracarotid injection of 10 micrograms of adrenaline produces little or no effect on the portion of the curve corresponding to synaptic input but a considerable reduction of the surface negative wave. The third column indicates the recovery to the control level. This synaptic inhibition by adrenaline is reproduced in the next line by another neurohumor, noradrenaline, which takes, however, approximately 15 times the dose. Adrenaline, though




**CEREBRAL SYNAPTIC ACTION OF MESCALINE**
**IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM**

SPIKE POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT
BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS
MESCALINE HCl 15 MG./KG. INJECTION INTO FEMORAL VEIN

FIG. 4.

not a hallucinogen, does occasionally produce mental disturbance and supplies a lead because of its structural similarity (fig. 3) to amphetamine which produces mental disturbance somewhat more often, and mescaline which produces behavioral disorder in cats and mental disturbance with intense hallucinogenic effects regularly in man. We have therefore examined the effects of these substances also on the optic cortical preparation described, and they produce the same type of synaptic inhibition as that produced by adrenaline. The inhibition by mescaline is shown in figure 4.

Lysergic acid diethylamide (LSD-25) is an even more powerful disturber of mental processes than mescaline. In figure 5, its structure is compared to that of adrenaline and to its first oxidation product, adrenochrome, which is related to LSD-25 by the fact that like it, it contains the indole nucleus. Adrenochrome, in fact, has been claimed by Hoffer, Osmond and Smythies (2) to be capable of reproducing a schizophrenic-like syndrome in man when injected intravenously. LSD-25 through adrenochrome and adrenaline seems to be related to mescaline, and, therefore, it seemed of interest to determine the

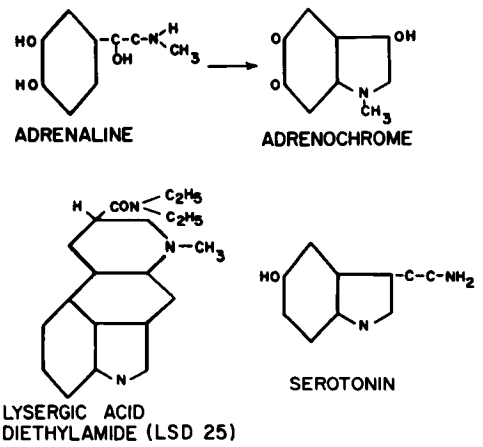
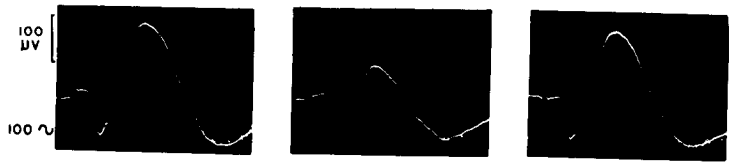



FIG. 5.

action of LSD-25 on the optic cortex. In keeping with the structural analogy drawn and the higher potency of LSD-25, it produces optic cortical inhibition (fig. 6) in a much smaller dose.

Serotonin or 5-hydroxy-tryptamine which (as seen in fig. 3) is another indole derivative having a close resemblance to adrenochrome has been suggested by Woolley and Shaw (3)




CEREBRAL SYNAPTIC ACTION OF L.S.D.25

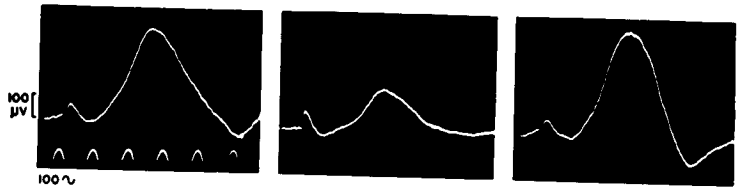
IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT

BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS

L.S.D.25 8 μG./KG. INJECTED INTO CAROTID ARTERY

FIG. 6.




CEREBRAL SYNAPTIC ACTION OF SEROTONIN

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT

BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS

SEROTONIN 2 μG./KG INJECTED INTO IPSILATERAL CAROTID ARTERY

FIG. 7.

as a possible competitive antagonist of LSD-25 because of the structural similarity with the latter as well. Trials on the same preparation reveal (fig. 7) that instead of antagonizing the synaptic inhibition, it produces the same type of inhibition and is considerably more potent in the cat than all of the other compounds mentioned. In fact, its effectiveness in gamma quantities qualifies this natural constituent of the brain for the role of a neurohumoral synaptic inhibitor. Instead of being an antidote for LSD-25, the findings suggest that serotonin or some related substance could well play the role of endogenous hallucinogen or cause of natural psychosis. Since we have previously demonstrated (1) in the synapses examined in this work and in a variety of other cerebral synapses that a balanced reciprocal relation exists between an adrenergic inhibitory mechanism and a cholinergic excitatory one, any factor tending to upset this balance could result in disturbance.

It seems plausible to postulate that cerebral synaptic inhibition plays a part in the action

of hallucinogens and other inducers of chemical psychoses of endogenous or exogenous origin, either by the direct disruption of normal patterns of synaptic activity responsible for behavior, or indirectly by inhibiting normal restraints and thereby releasing aberrant patterns of activity as a result of alteration in the normal balance between cholinergic excitation and adrenergic inhibition at susceptible cerebral synapses. A parallel hypothesis instead of placing emphasis on an excess of serotonin or a serotonin-like substance would place it on some other pathologic process creating an unusual sensitivity of certain synapses to such a normally-occurring substance. These considerations are basic to the development of effective and rational therapy of mental disease. It is evident that the search for therapeutic agents can at the same time quite effectively make use of drugs as tools in the analysis of the process which it is desirable to diagnose and to modify therapeutically.

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