Very good paper. A

Can structure be tied to the function / active sites?

Hallucinogenic Drugs and Central Neural Systems: Biochemistry and Neurophysiology

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Introduction

This paper examines hallucinogenic drugs and the biochemistry and neurophysiology of central synapses and systems. An attempt is made to relate these in an effort to determine the mode of action of these drugs.

The treatment focuses on some of the findings relevant to the explanation of various phenomena observed under the influence of these substances; nothing is said about the religious, mystical, or theraputic uses of these drugs.

This type of analysis assumes that thought, perception, and behavior have underlying neurological correlates in the brain. It is quite possible that knowledge and work on hallucinogenic drug mechanisms will aid in the understanding of the brain.

The first section of this essay gives the structures and background of the different so-called "hallucinogenic" drugs. It is difficult to delimit this category of compounds. In a broad sense any drug which noticeably changes the state of conciousness might be considered hallucinogenic. This treatment, however, will include only those drugs which produce a marked perceptual disturbance and impairment of thought.

The question of classification of the different drugs in this category arises at this point. It might be reasonable to group them according to one or more of their pharmacological or physiological actions. Unfortunately not enough is really known about these substances to allow a definitive classification of this sort. The easiest and safest route appears to be grouping according to chemical structure.

Chemical Structures and Background

A) LSD D-lysergic acid diethylamide, LSD, was first synthesized at Sandoz Laboratories in Switzerland in 1938. It had been tested for useful pharmacological activity in animals and, none having been found, was shelved. It was not until 1943 when Albert Hofmann, a chemist at Sandoz, accidently ingested a minute amount that the amazing psychic effects of the drug were discovered. At this time World War II was in full force and the effects of the drug were kept classified because of the possible implications for chemical warfare. The first public account of the clinical and pharmacological effects was published in 1947 (Stoll, 1947).

LSD is as yet unsurpassed in potency among the psychedelic drugs. It is active at 1 ug/kg in humans producing perceptual alterations and impaired thought processes. A derivative of lysergic acid, LSD has only recently been identified naturally. It and many other related alkaloids are present in morning glory seeds, especially in Impomoea rubro and Rivea corymbosa. These alkaloids are designated the Ergot alkaloids because they are derivatives of lysergic acid, first isolated from Ergot, the rhizomorph of Claviceps Purpurea.

Efforts have been made to determine the essential structural components required for biological activity. Five main groups have been examined:

Group I - Optical isomers. Carbons five and eight are asymmetric generating four optically active isomers. LSD is most active.

Group II - The double bond between carbons nine and ten is saturated.

Both substances are inactive.

Group III - Substitutions on the indole nucleus.

Group IV - Monosubstitution derivatives of the amide nitrogen.

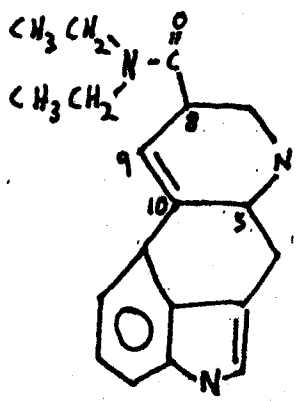
Group V - Disubstitution derivatives.

The results are best summarized in table 1 from Hoffer and Osmond, (1967). DL-Acetyl lysergic acid diethylamide is probably active due to the ease of hydrolyzation to LSD. Activity of these compounds is assessed by methods similar to Wolbach et. al., (1962) to be discussed later.

TABLE I

COMPARATIVE ACTIVITY OF SOME LYSERGIC ACID ALKALOIDS

Full name	Code	Toxicity in rabbits (intravenous)	Pyretogenic effect	Antiserotonin effect	Psychological effect in man	EEG activation
Group 1						
D-Lysergic acid diethylamide	D-LSD-25	100	100	100	100	Marked
L-Lysergic acid diethylamide	L-LSD	1.8	0	0	0	None
D-Isolysergic acid diethylamide	D-iso-LSD	3.7	0	0	0	
Group 3						
D,L-Methyllysergic acid diethylamide	MLD-41	5.6	5	370	40	Minimal
D,L-Acetyllysergic acid diethylamide	ALD-52	19	13	200	100	None
D-2-Bromlysergic acid diethylamide	BOL-148	5	5	103	0	None
4-L-Methyl-2-bromlysergic acid diethylamide	MBL-61	2	0	533	0	
Group 4						
D-Lysergic acid amide					10	
D-Lysergic acid ethylamide	LAE-32	34	17	12	5	
D-Lysergic acid dimethylamide	DAM-57	78	43	23	10	Moderate
D-Lysergic acid pyrrolidide	LPD-824	73	10	5	10	Moderate
D-Lysergic acid morpholide	LSM-775	43	10	2	20	Minimal
Group 5						
D,L-Methyllysergic acid monoethylamide	MLA-74	3.2	0	835	5	
D,L-Acetyllysergic acid monoethylamide	ALA-10	6	1	39	5	
D,L-Methyllysergic acid pyrrolidide	MPD-75	4	0	130	7	



D - Lysergic acid diethylamide

LSD

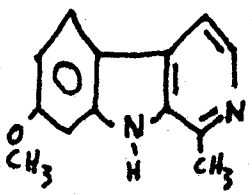
B) Indole Hallucinogens Derived from Tryptophan: Indolealkylamines

The indolealkylamines form another class of psychoactive compounds retaining the indole nucleus of LSD and tryptophan. Many occur naturally as plant alkaloids and have been used by man for their psychic effects for centuries.

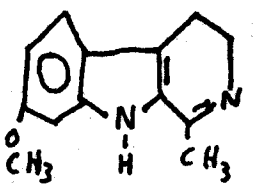
These compounds are structurally similar to tryptophan and serotonin as can be seen from figure 1 from Hoffer and Osmond, (1967), p. 447.

Dimethyltryptamine and related compounds have been found in plants of the Malpighiaceae family, especially Banisteriopsis caapi. It is one of the active ingredients of a snuff used by peoples in South America and Africa prepared from the plant.

Additional psychoactive alkaloids which can be isolated from Banisteriopsis caapi include harmine and harmaline:



Harmine



Harmaline

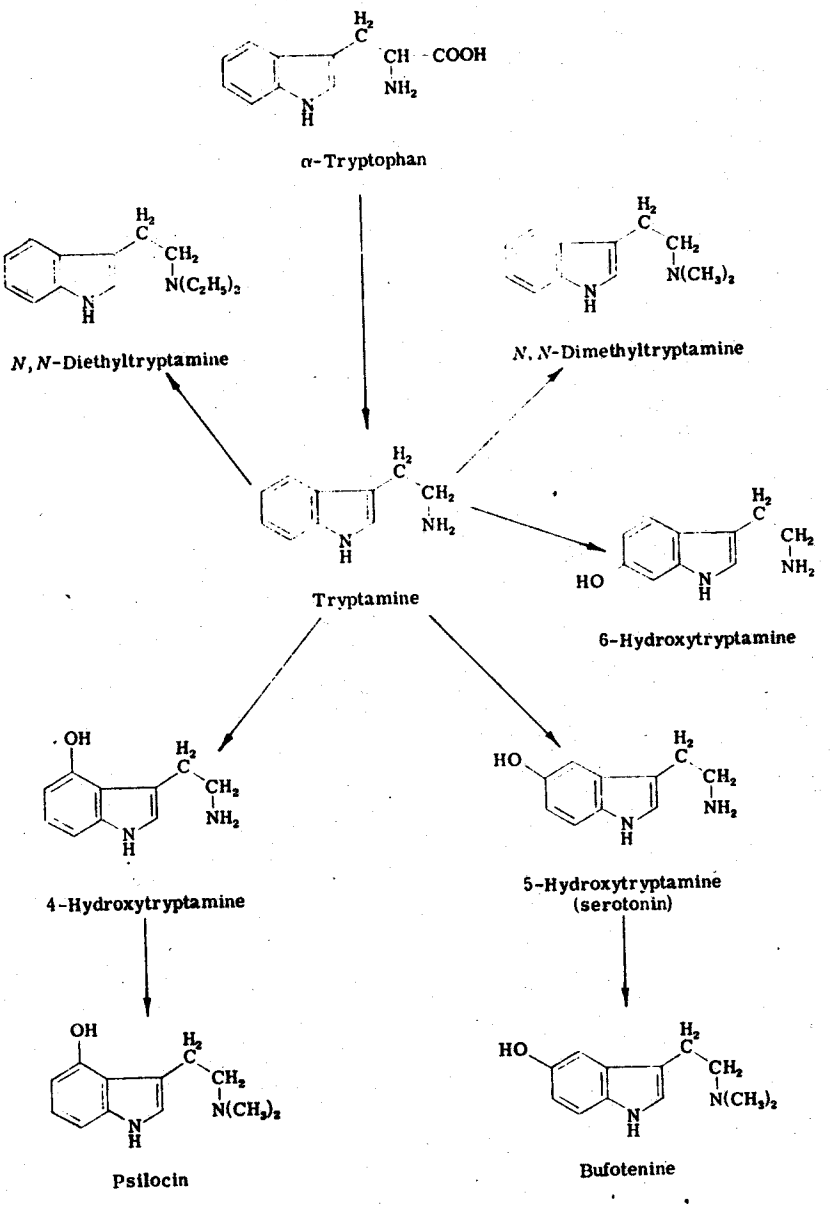
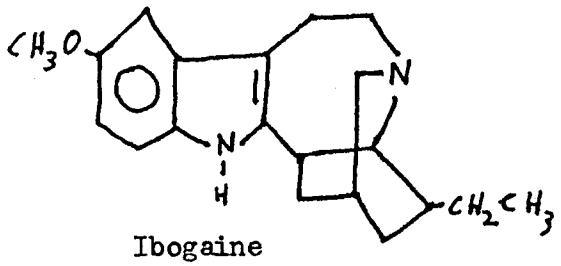
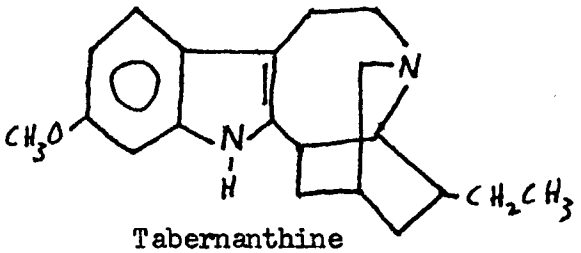


Figure 1

Compounds isolated from Tabernanthe Iboga form another group of active alkaloids:

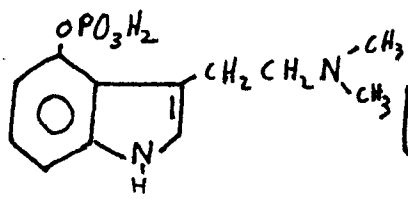


Ibogaine

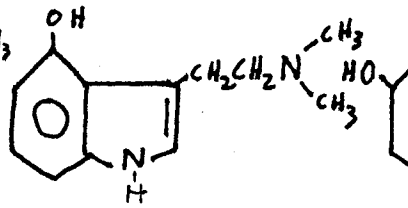


Tabernanthine

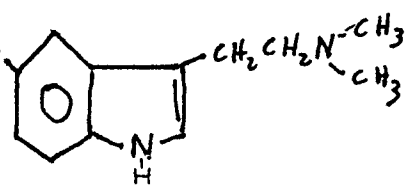
Bufotenine can be isolated from skin glands on the toad or from the plant Piptadenia peregrina. Psilocin and Psilocybin are present in mushrooms of the genus Psilocybe and Stropharia. Psilocybin is hydrolyzed in the body to Psilocin. Bufotenine and Psilocin differ only in the position of the hydroxyl group on the indole nucleus:



Psilocybin



Psilocin



Bufotenine

Again, variations in structure have been related to psychotropic dose. Some of the results of S. Szara are shown in table 2:

Effects were evaluated as described by Szara using questionaires assessing attention, loss of inhibition, feelings of unreality, anxiety, changes in body image and various somatic symtoms.

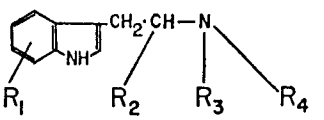
	Compound	 R_1	R_2	R_3	R_4	Psychotropic dose
1	Tryptamine (T)	-H	-H	-H	-H	500mg ?
2	DMT	-H	-H	$-CH_3$	$-CH_3$	60 mg i.m.
3	DET	-H	-H	$-C_2H_5$	$-C_2H_5$	60 mg i.m. or p.o.
4	Dipropyl-T	-H	-H	$-C_3H_7$	$-C_3H_7$	60 " " "
5	Diallyl-T	-H	-H	$-C_3H_5$	$-C_3H_5$	60 " " "
6	α-methyl-T	-H	$-CH_3$	-H	-H	20 mg p.o.
7	α-ethyl-T	-H	$-C_2H_5$	-H	-H	20 mg p.o.
8	Psilocybin	4-OPO_3H_2	-H	$-CH_3$	$-CH_3$	15 mg p.o.
9	Bufotenin	5-HO-	-H	$-CH_3$	$-CH_3$	16 mg i.v.

Table 2. From S. Szara in Psychotomimetic Drugs, ed. by D.H. Efron, Raven press, N.Y. 1970, p. 276.

C) Phenylisopropylamines and Phenylethylamines

These form the simplest compounds chemically. Mescaline is the representative compound; it is found naturally in the peyote cactus Anhalonium Lewinii (Lophophora Williamsii). It too has been used for thousands of years in the Southwestern United States for its psychic properties.

Lewis Lewin first did extensive work on mescaline and published a monograph in 1924 describing in detail the effects of the Anhalonium alkaloids, coining the term "phantasticum" for the bizarre psychological and perceptual changes (Lewin, 1964).

Mescaline is the only active phenylethylamine known, the rest are derivatives of phenylisopropylamines (amphetamines). Many occur naturally, others are not known to occur naturally. Figure 2 summarizes the compounds and their potency in "mescaline units (Shulgin, 1970). One MU=8 mg/kg in man.

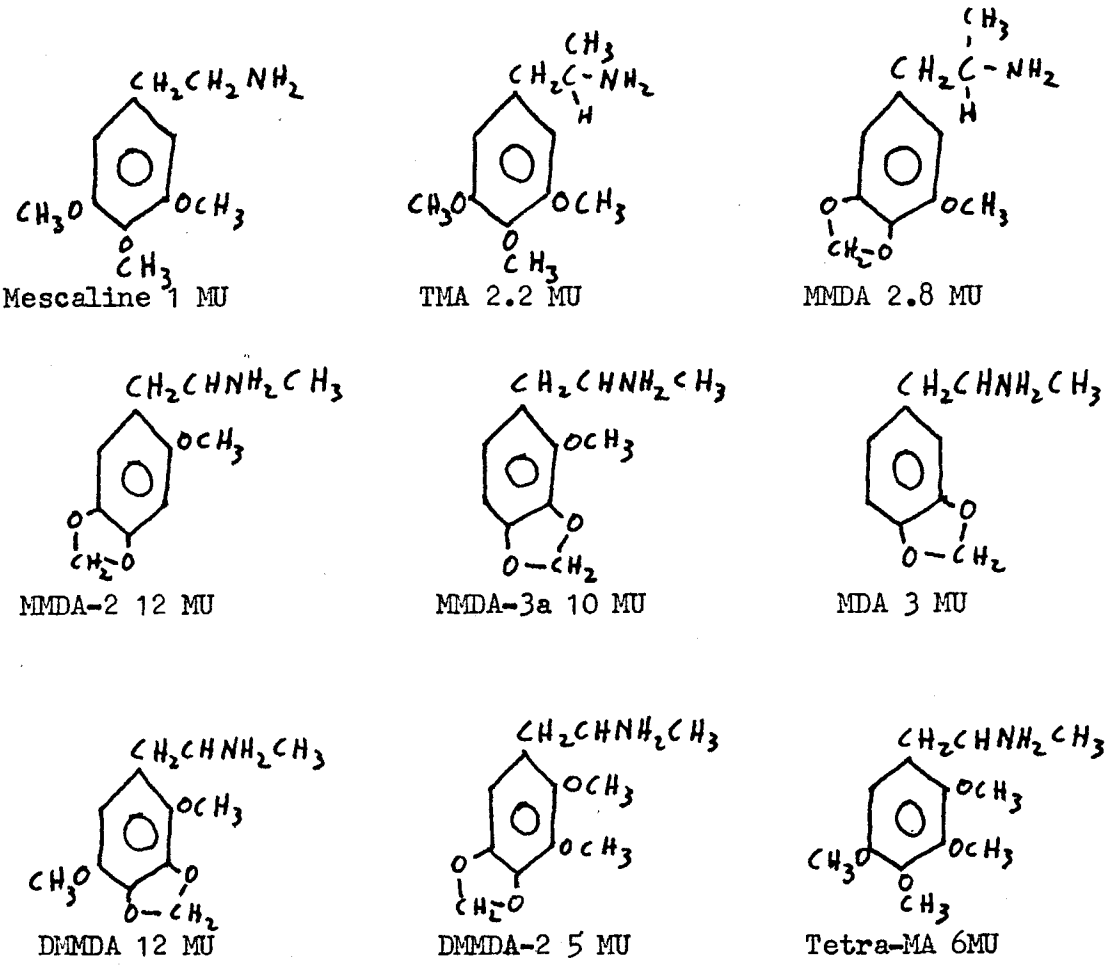
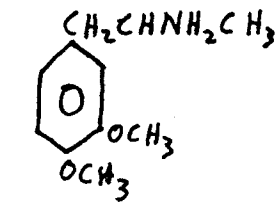
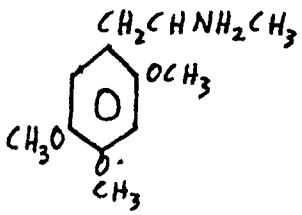


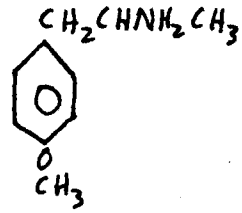
Figure 2. Substituted Amphetamines



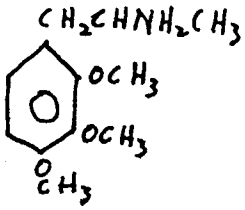
DMA 1MU



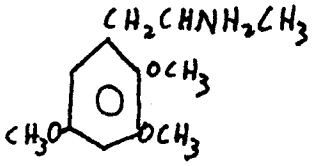
TMA-2 17 MU



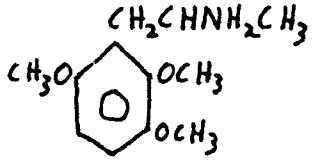
4-MA 5 MU



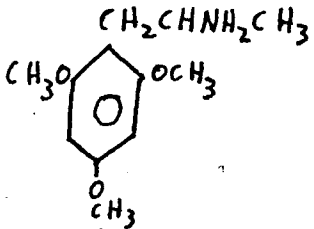
TMA-3 2 MU



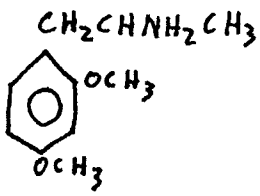
TMA-4 4 MU



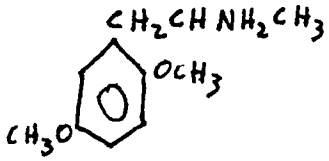
TMA-5 13 MU



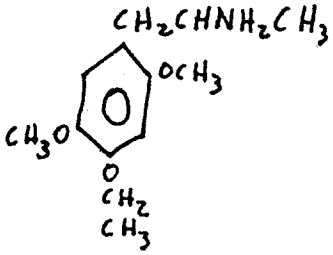
TMA-6 10 MU



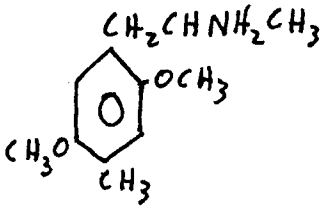
2,4-DMA 5 MU



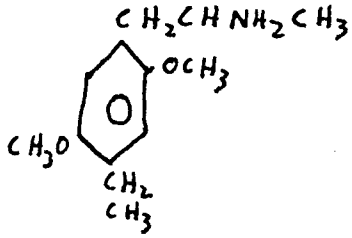
2,5-DMA 8 MU



MEM 15 MU



DOM 80 MU



DOET ?

Figure 2 Continued. Substituted Amphetamines.

Much work has been done attempting to correlate the highest occupied molecular orbital energy (electron donating capacity) with the potency of these drugs. Ambiguous results have been obtained (Snyder and Merril, 1965;

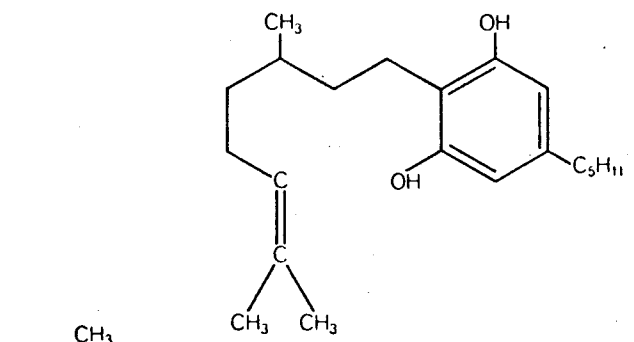
Kang and Green, 1970; Shulgin,1970). Studies on the ability of the substituted amphetamines to approximate the ring structure of LSD or the indolealkylamines have also been done with equivocal results (Snyder and Merril,1965; Shulgin, 1970; Smythies et al. 1970). Differences in the effects of the various compounds have generally been ignored in these studies.

D) Tetrahydrocannabinols and Related Compounds

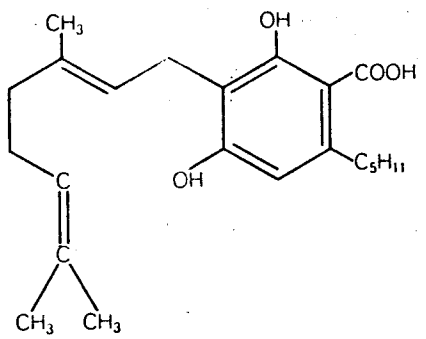
Tetrahydrocannabinol is a mild hallucinogen isolated from Cannabis Sativa. It is the active principle of the various Cannabis preparations including marihuana and hashish.

The use of Cannabis dates back to the 27th century B.C. in China. It has been used since by various cultures throughout the world for its ability to produce a euphoric state. More recently , in the 19th century, it appeared in the Western world as a drug used for treating ailments such as coughing, fatigue, rheumatism, asthma, delirium tremens and migraine headache. In the United States it appeared on the Pharmacopoeia as a mild hypnotic and analgesic until 1937. In the past ten years its use illegally in the U.S. as a euphoriant has increased tremendously; it has been estimated that 20 million Americans have smoked marihuana at one time or another.

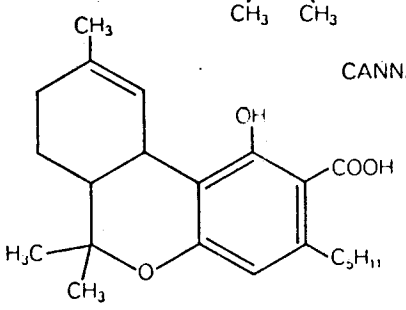
A crude extract of the plant using organic solvents yeilds a viscous red solution known as red oil. By distillation a substance called purified red oil can be obtained. Various related compounds can be identified in this mixture; see figure 3.



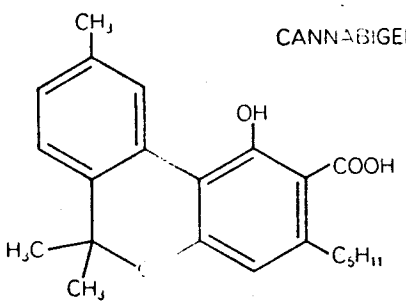
CANNABIGEROL



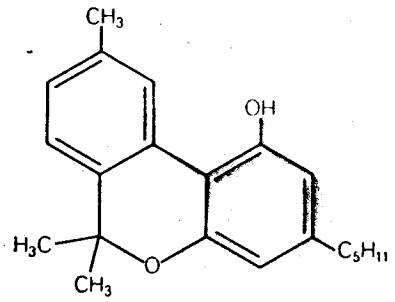
CANNABIGEROLIC ACID



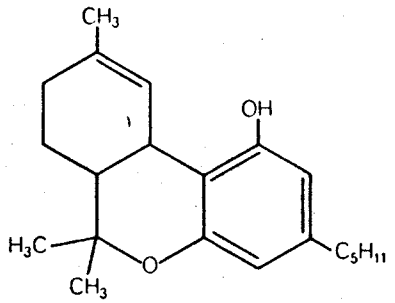
Δ¹-TRANS-TETRAHYDROCANNABINOLIC ACID



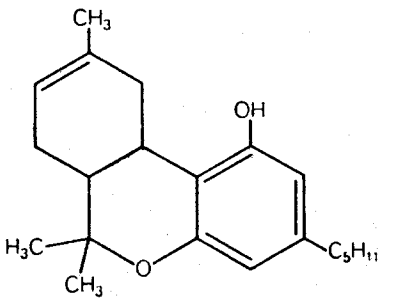
CA[illegible]INOLIC ACID



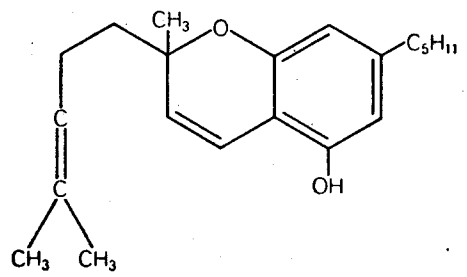
CANNABINOL



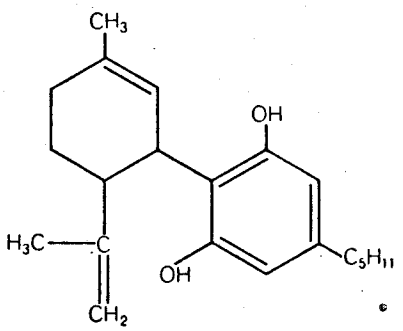
Δ^1-TRANS-TETRAHYDROCANNABINOL



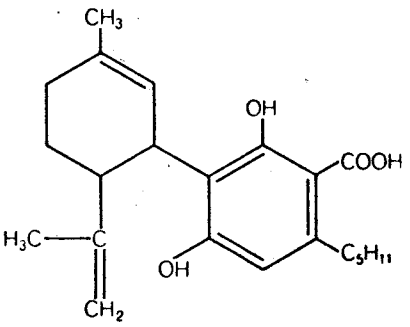
Δ^6-TRANS-TETRAHYDROCANNABINOL



CANNABICHROMENE



CANNABIDIOL

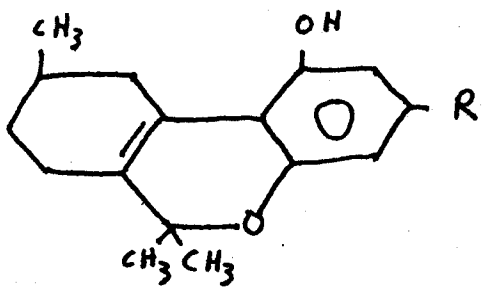


CANNABIDIOLIC ACID

Figure 3 continued. Constituents of Cannabis preparations. From Grinspoon, (1969) pp 20-21.

After much detailed chemical research the major activity of the plant extracts has been ascribed to Δ1-2 (Δ9) trans-tetrahydrocannabinol and Δ1-6 (Δ 8) trns-tetrahydrocannabinol (Hofmann, 1968). The positions of the double bonds in parentheses refers to a method of numbering the molecules consistently regardless of whether or not the ring containing oxygen is closed. A number of synthetic analogues of these compounds have been synthesized.

Synthetic compounds:



R = 1,2 Dimethylheptyl DMHP

R = n hexyl Synhexyl

DMHP was found more active than the natural compounds. Synhexyl was used clinically as a stimulant and antidepressant. The psychological effects of marihuana are subtle and it is not known whether the effects of these synthetic compounds are identical to those obtained from the natural subtances.

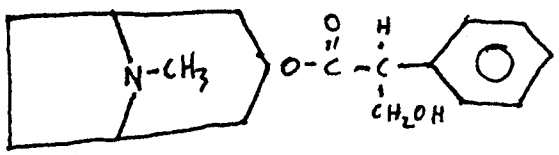
It is interesting that the tetrahydrocannabinols are the only known hallucinogens which do not contain any nitrogen.

The dosage generally used by people smoking marihuana is hard to determine, as resin content varies among preparations; heat destroys various amounts of the ingredients as well as isomerizing some, and smoking technique determines to a great extent the amount of condensation in the lungs. Dosages of about 200 ug/kg in man produce the subjective high. Tests in animals demonstrate doses of 2 mg/kg of $\Delta 9$ THC or $\Delta 8$ THC produce marked alterations in behavior involving memory or discrimination in cats, monkeys, and rabbits.

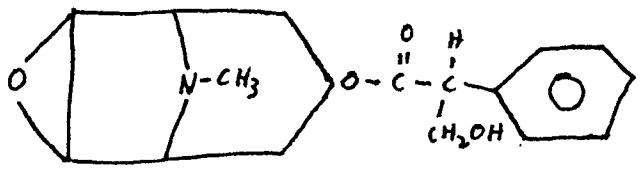
E) Miscellaneous Hallucinogens

These are a group of alkaloids widely classed as having anticholinergic or anesthetic actions. A number of them occur in plants. Extracts from Atropa belladonna, Hyoscamus niger, Datura stramonium, Scopolia japonica, and Duboisia myoporoides have been used for many years as poisons and mind-altering drugs.

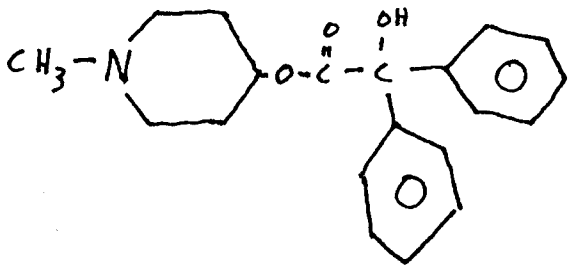
Included in this category are atropine, a muscarinic anticholinergic, hyoscamine, hyoscine, scopolamine, phenylglycolate esters (Ditran and related compounds), and phencyclidine. The structures of some typical compounds are as follows:



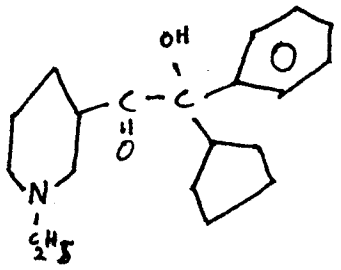
Atropine
Active at .5-2 mg/kg



Scopolamine

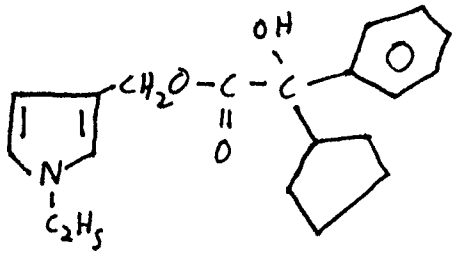


N-methyl-4-piperidyl benzilate



30%

Ditran



70%

Central Systems and Synapses

In order to evaluate the mechanism of hallucinogenic drugs it is necessary to consider what is meant by perceptual changes, behavior, thought, and conciousness. Any analysis of CNS function is based on the assumption that conciousness, thought, and behavior are manifestations of concurrent biochemical and neurophysiological events in the brain. Behavior, thought, perception, and any of the concious functions we so routinely perform eventually must be traced to action and interaction among functional systems in the brain.

It is reasonable to expect that neurons involved in similar functions are in some sense similar. Possibly they make similar anatomical connections, perhaps they fire in similar patterns, perhaps they utilize the same transmitter substances. In any case the ultimate goal of this type of explanation is the correlation of various biochemical and electrophysiological events with the thought and perceptual processes they represent.

The density of neurons in the brain is so great that a total "wiring diagram" is probably not possible. Indeed, every brain is unique, and it will probably never be possible to predict an individual's thoughts. Nonetheless, identification of brain mechanisms involved in thinking, motivated behavior, perception, attention, arousal, sleep and memory should be possible.

Studies of this type are extremely difficult to perform on the mammalian CNS. This high density of neuronal interconnection prevents isolation of individual neurons for study; likewise it is difficult to restrict application of exogenous substances to specific cells and synapses in vivo. As a result, the biochemistry of central synapses is poorly understood. It is virtually impossible to establish a substance as a transmitter. Recent techniques involving biochemical blockade and flourescence neuroanatomy have aided greatly in this respect. These procedures, in addition to radioactive labelling, lesioning, recording, and stimulation have allowed the identification and analysis of a few putative central transmitters and systems. The following is a review of work relavant to studies of the mechanism of hallucinogenic drugs.

Transmitters and Their Location

The transfer of information in the CNS is mediated by the synapse. It is through these junctions between neurons that the integration and modification of information is performed. Some electrical synapses have been identified, but chemical synapses are prominent. The transmitters at these synapses have been identified in only a few peripheral preparations.

In order for a substance to be considered a transmitter at a synapse, a few criteria should be met.

1) Identity. The substance should be located inside the presynaptic ending of the neuron. This can often be established by histochemical, autoradiographic or degeneration techniques.

2) Synthesis. The substance should be synthesized in the presynaptic neuron. Enzymes to perform the synthesis should be present. It is not necessary it be stored; it may be synthesized on demand.

3) Release. The substance should be released on depolarization of the presynaptic neuron. It should be possible to collect small amounts on presynaptic stimulation.

4) Termination. The action of the proposed transmitter must be terminated in some way following its release.

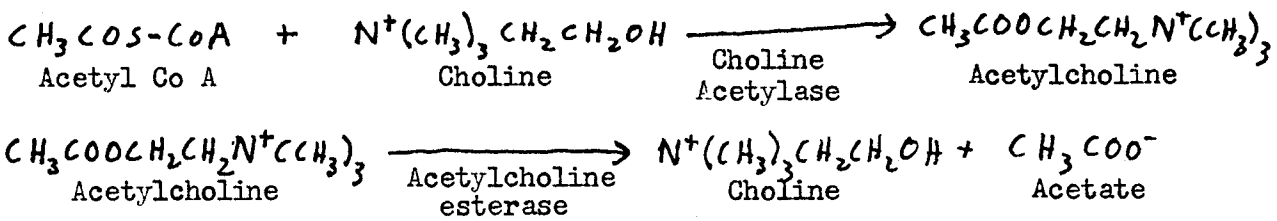
5) Action. Exogenous application of the substance should mimic the effect of physiological release.

6)Interaction with Drugs. The action of the proposed transmitter should be affected the same way by inhibitors and potentiators as is normally found at the synapse.

These are generally accepted as necessary for a substance to be established as a transmitter. Acetylcholine and Norepinephrine have been established at peripheral synapses as transmitters; Acetylcholine in the parasympathetic system and the neuromuscular junction, and Norepinephrine at sympathetic sites. Much of the work done on CNS putative transmitters is based on this information about the peripheral junction.

A) Acetylcholine (ACh). Acetylcholine has been identified at the neuromuscular junction. To identify small quantities of ACh muscle bioassays are often used. Additional techniques including biochemical and gas chromatography can be used to verify the bioassay. ACh has been found in the cerebral grey matter and the basal ganglia. Often the location of ACh is determined by the presence of its associated synthetic and degradative enzymes.

ACh is synthesized by choline acetylase and degraded by acetylcholine esterase:



It is believed that ACh is stored in vesicles easily seen under the electron microscope. Depolarization of the membrane is thought to cause the release of the vesicular ACh by a process of reverse pinocytosis, where the vesicles fuse with the membrane and release their contents into the cleft. Ca^{++} is required for this process; Mg^{++} and botulinum toxin inhibit it.

The action of ACh at the postsynaptic membrane is mediated by receptors; protein molecules located in the membrane specific for ACh. As yet two major types of receptors have been identified by the action of various pharmacological agents. Muscarine mimics the action of ACh at parasympathetic effector receptors, while atropine blocks the action of ACh at these sites. Nicotine mimics the action of ACh at the neuromuscular junction and at sympathetic ganglia, while here curare blocks the action.

ACh is degraded at the synapse by acetylcholine esterase. Choline is resorbed by the presynaptic terminal and recycled. The ACh synapse is summarized in figure 4.

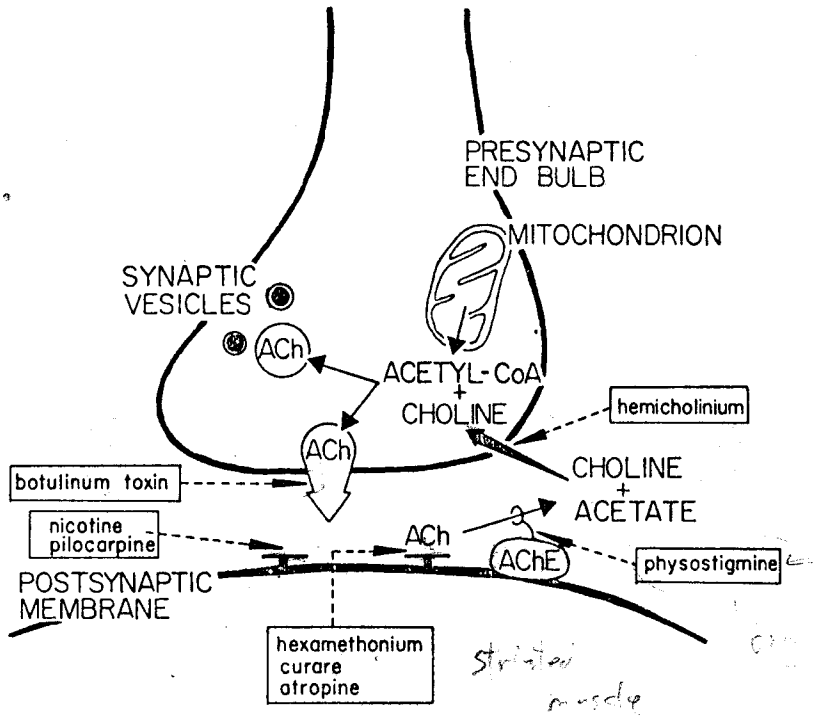
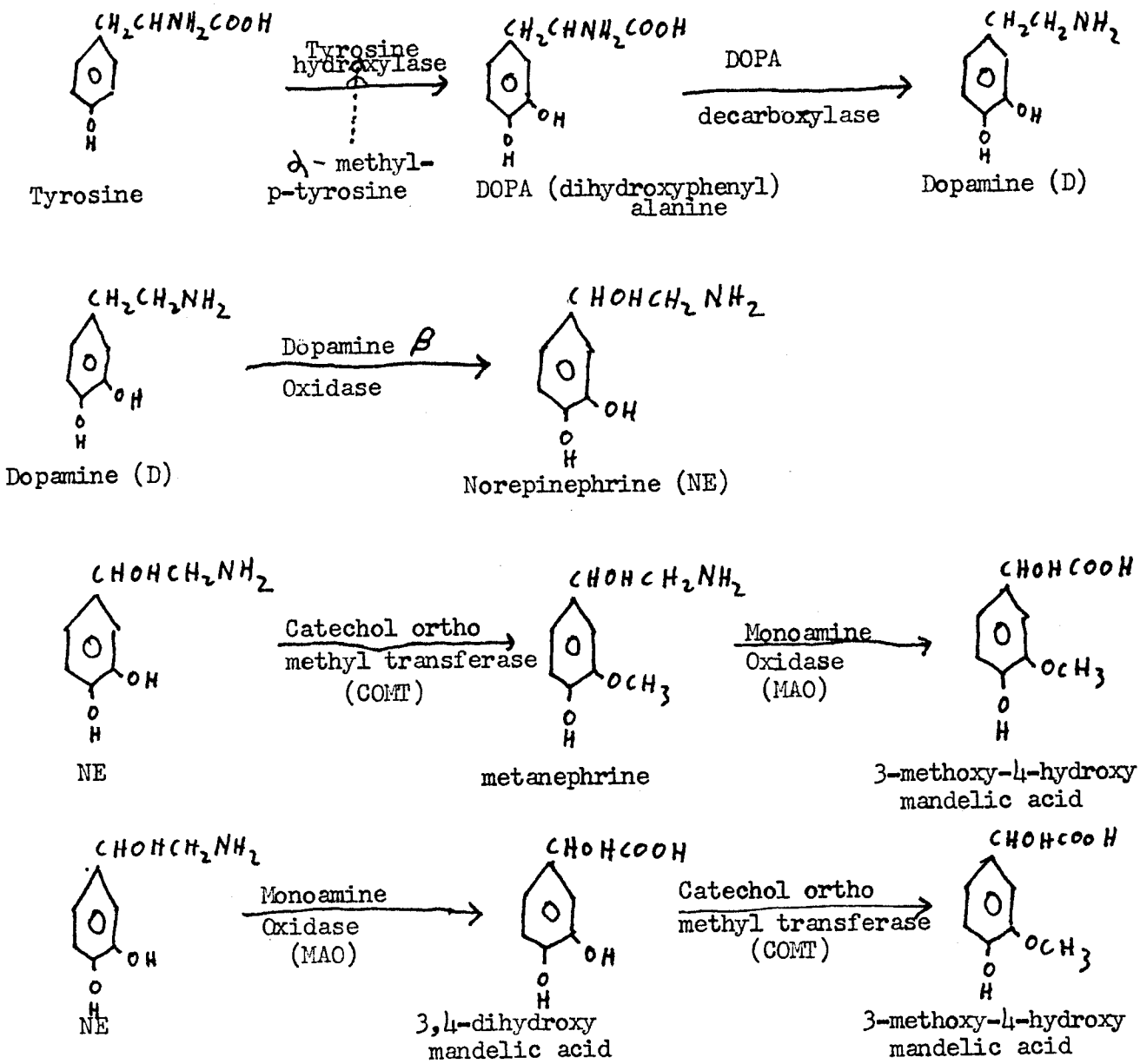
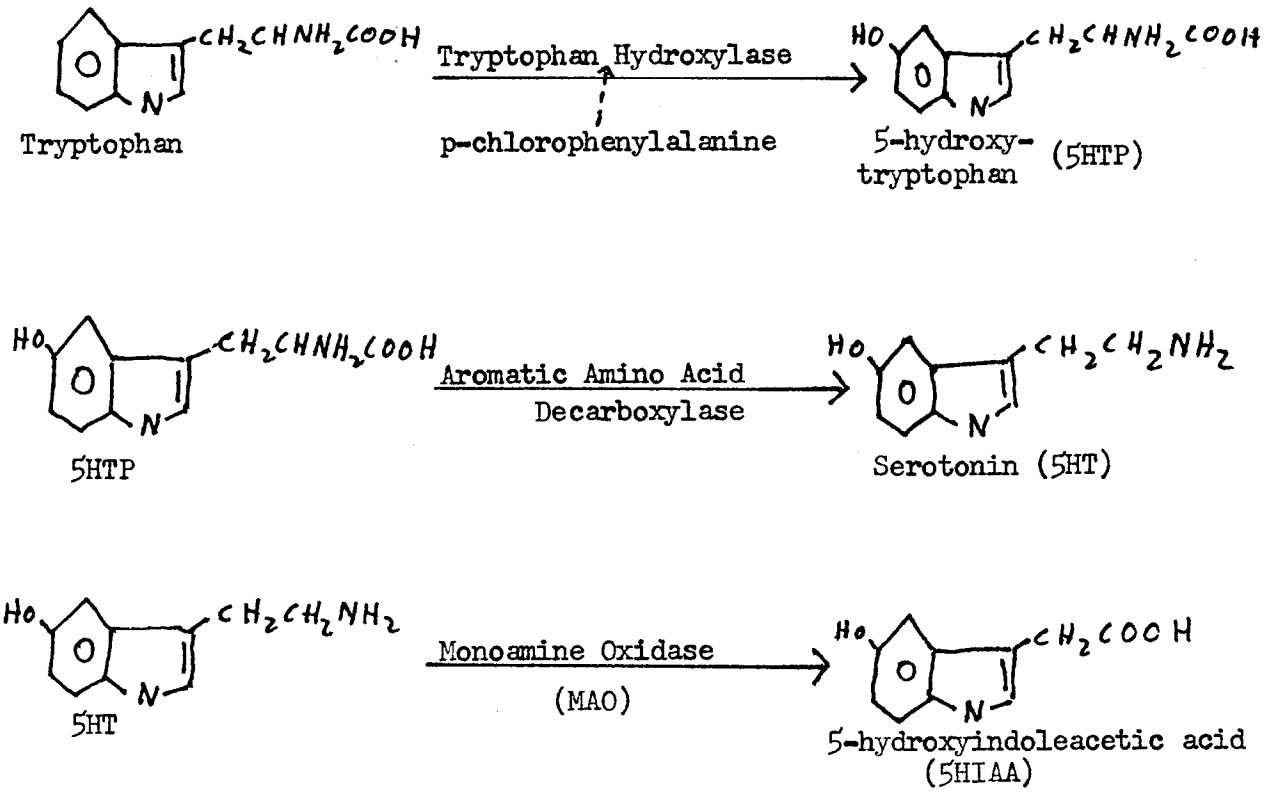


Figure 4. A Cholinergic Synapse. **From Rech and Moore, An Introduction to Psychopharmacology. Raven press, N.Y. 1971**

B) The Monoamines. Norepinephrine (NE), dopamine (D), and serotonin (5-hydroxytryptamine, 5HT) form a group of putative transmitters termed the monoamines. Recently the identification and precise localization of these amines was facilitated by the development of flourescence histochemical techniques. These involve the reaction of the monoamines with formaldehyde vapor and subsequent microscopic examination under ultraviolet light. The various derivatives flouresce with different wavelengths and permit differential identification (Falck et al. 1962; Falck, 1964; Dahlstrom and Fuxe, 1964; Fuxe, 1965).

The synthesis and degradation of the monoamines is summarized below:





Typical noradrenergic and serotenergic synapses are shown in figures 5 and 6.

The synthetic enzymes are found cytoplasmically, the rate limiting step being the aromatic ring hydroxylation by tyrosine hydroxylase in the case of NE and tryptophan hydroxylase in the case of 5HT. Tyrosine hydroxylase can be blocked by alpha-methyl-p-tyrosine, and tryptophan hydroxylase by p-chlorophenylalanine, allowing some interesting biochemical studies.

Degradation of the monoamines is performed intraneuronally by Monoamine Oxidase (MAO). This is localized in the mitochondria as determined by differential centrifugation. MAO is inhibited by various hydrazine derivatives such as nialamide or pargyline. The action of NE and D is terminated extraneuronally by Catechol-ortho-methyltransferase (COMT) and reuptake into the presynaptic terminal. Reuptake into the presynaptic bouton is the major mechanism of inactivation of all the monoamines.

Intraneuronal presynaptic vesicles are again present and store the amones. Recent work by Kopin et al.,(1968) indicates that newly synthesized NE is preferentially released in the splenic nerve. This has been interpreted as evidence of two storage pools of NE. Kopin has suggested that there are two types of vesicles with different turnover rates. It has also been suggested that NE

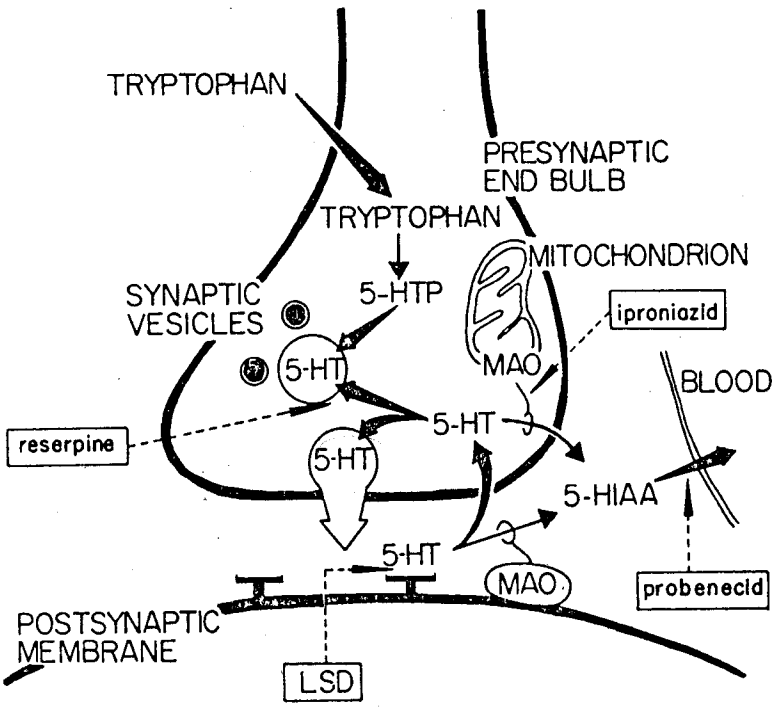


Figure 5. A serotonergic synapse. From Rech and Moore, An Introduction to Psychopharmacology, Raven press, N.Y. p. 110.

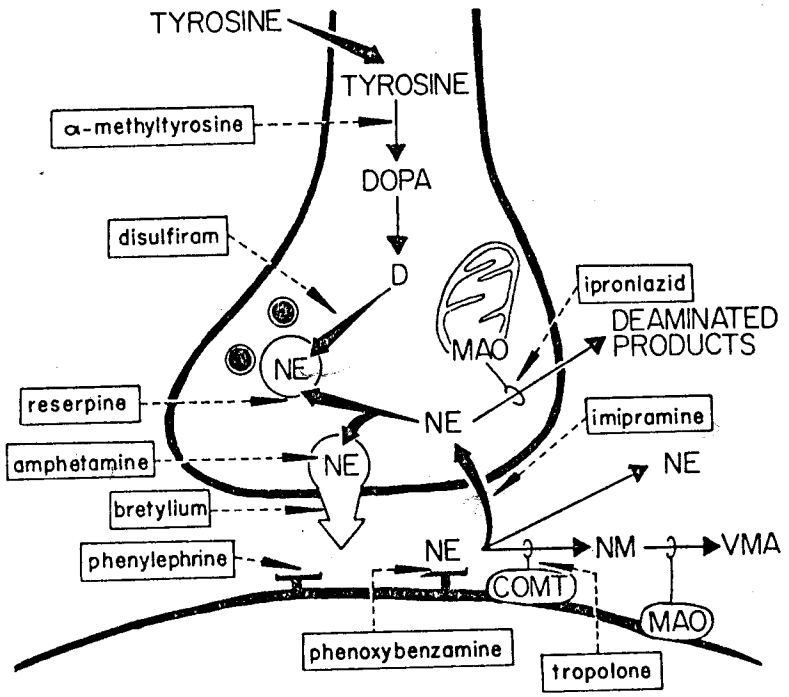


Figure 6. A noradrenergic synapse. From Rech and Moore, An Introduction to Psychopharmacology, Raven press, N.Y. p. 99.

is present in the presynaptic cytoplasm and membrane. This is quickly released and resorbed upon depolarization of the membrane. Some of the NE released is nonetheless from the vesicles, as chromogranin, a vesicular protein, is also released.

None of the monoamines have been conclusively shown to be transmitters in the CNS. The characteristic flourescence, however, has shown their existence in all parts of the brain.

The perikarya of serotonin containing neurons appear to be localized in the midline Raphé nuclei, while NE and D containing neurons originate in the locus coeruleus. Connections with the hypothalamus and limbic forebrain are prominent, but treatment with MAO inhibitors which intensify the flourescence and amine content demonstrates fine fibers descending the spinal cord and innervating the entire cerebral cortex. Table 3 summarizes work done on the localization of the monoamines.

Drugs Affecting Monoamines.

Receptors. Peripheral adrenergic receptors are distinguished by the action of a number of pharmacological agents. Alpha receptors, blocked by phentolamine and phenoxybenzamine, act in the peripheral blood vessels by causing constriction, in the spleen by causing contraction, and numerous other effects. Beta receptors act at the blood vessels by causing dilation, and by relaxing the bronchi of the lung among other effects. They are blocked by propanalol and dichloroisoproterenol. In the CNS it is thought that the phenthiazine tranquilizers may exert their effects through central blockade of NE receptors.

Release. Several drugs are known to block the release of NE from sympathetic neurons. These include bretylium and guanethidine. Central effects are unknown.

Storage. Stores of monoamines can be depleted by reserpine. It is unknown how reserpine causes the depletion, but it persists for up to two weeks following a single administration. It does not appear that the amines are released, for the metabolites consist mainly of deaminated products, suggesting intraneuronal degradation.

Inhibition of synthesis. Alpha methyl-p-tyrosine and p-chlorophenylalanine block the rate limiting steps in the syntesis of NE and 5HT respectively.

Inhibition of reuptake. Amphetamine and the tricyclic antidepressants appear to function by preventing the resorbtion of the amines into the presynaptic terminal. Recent work suggests that imipramine, chloroimipramine, and amytryptiline, which are tertiary amines, block the reuptake of 5HT se-

TABLE 3

Distribution of norepinephrine, dopamine and serotonin in the central nervous system as determined by chemical (in dog, cat, man) and histofluorescent (rat) techniques.

	NOREPINEPHRINE		DOPAMINE		SEROTONIN	
	μg/gm	histo-fluor. degree 0-5+	μg/gm	histo-fluor. degree 0-5+	μg/gm	histo-fluor. degree 0-5+
Cerebral cortex	.03–.24	1–2	.00–.10		.04–.24	
Caudate nucleus	.04–.22		*3.1–8.0*	4	*.27–1.6*	2
Corpus striatum	.02–.25		*1.6–5.3*	4	.08–.23	2
Olfactory bulb	.05	*1–3*	—		.11–.35	
Hippocampus	.14–.20	*1–4*	.13		.64	1
Amygdoloid nucleus		2–3		2		2–3
Septum	.03	*1–4*	.04		*.03–1.5*	1
Hypothalamus	*.76–2.05*	*1–5*	.26–.75		*1.70–2.0*	1–2
Diencephalon less hypothalamus	.17–.37		.09–.16			
Thalamus	.13–.24	*1–5*	.01–.07		.22–.24	1–2
Mesencephalon					*1.0–1.7*	
Inferior and superior colliculi	.11–.16	1–3	.10–.13			1–2
Substantia nigra	.04	1	.40		1–4	2
Red nucleus	.22		.19			
Brain stem reticular formation	.35	*1–4*				1–2
Cerebellum	.06–.17	1	.03–.02		.27	
Pons	*.04–.41*	*2–4*	0–.11		*.19–.70*	*1–3*
Medulla	*.37–.72*	*1–5*	.13		*.63–1.20*	*1–3*
Area postrema	*1.04*				.26	
Locus ceruleus		*3–4*				1–2
Cerebral white matter	0	–	.42	–	0–.13	—
Ant. horn—spinal cord	.18	*1–5*				*1–5*
Post. horn—spinal cord		*1–5*				1
(Sup. cervical ganglion)	*6.8*					

From The Neurosciences, ed. by Quarton and Schmitt, Rockefeller University press, N.Y. 1966. p. 445.

lectively over NE, while desmethylimipramine and protryptilinme, secondary amines, differentially block NE over 5HT. (Carlsson et al., 1969; Carlsson, 1970).

Formation of false transmitters. Dopamine β Hydroxylase converts a number of D analogs into substances which replace NE in the neuron but, when released, have little or no activity. This enzyme will convert alpha methyl dopamine into alpha methyl norepinephrine, meta tyramine into meta octopamine, para tyramine into para octopamine, and alpha methyl para tyramine into alpha methyl para octopamine.

C) Additional possible transmitters. The brain alone in the body contains a high concentration of Gamma Amino Butyric Acid (GABA). GABA is known to be

an inhibitory transmitter in invertebrates, and has been considered as a possible neurotransmitter in the mammalian brain. GABA is readily synthesized from glutamic acid via glutamic decarboxylase. This enzyme is located exclusively in grey matter. There is some evidence for GABA as a transmitter, but it does not seem to be contained in storage vesicles (Roberts and Kuriyama, 1968).

Other amino acids are present in the brain in high concentrations including glutamic acid and glycine. The evidence for these substances as transmitters is spotty, as is evidence for histamine, prostaglandins, and ergothioneine. Their roles, especially in the mechanism of hallucinogenesis, is far from obvious.

The Role of Monoamines

Serotonin containing neurons originating in the Raphé nuclei and NE and D containing neurons from the locus coeruleus send axons to innervate the entire brain via the medial forebrain bundle. The flourescence of these fibers is intensified by treatment with MAO inhibitors and decreased by reserpine and synthesis inhibitors. Much work has been done involving the monoamines in arousal and emotion, and since the hallucinogens seem to be involved in these systems it would be well to include this work.

Early studies on the monoamines simply measured the quantity of amine present after conditions of stress in rats (Maynert and Levi, 1964) or rage induced by stimulating the amygdala of cats (Reis and Gunne, 1965). Significant decreases in NE content of the brain were found, presumably due to increased release.

More recently work has been directed at the turnover of the amines in relationship to behavior. Blockade of synthesis allows one to follow the disappearance of the amine from the brain. Radioactive amines injected intraventricularly are rapidly absorbed by the proper terminals, and the rate of release can be easily measured as the radioactivity of the remaining pool.

These have allowed a better understanding of the dynamics of monoamines in the brain. Kety et al., (1967) found the turnover of NE to be substantially increased following one week of twice daily electroconvulsive shock in the rat. Electroconvulsive shock is one of the best treatments for depression, suggesting low NE levels may be involved in this disorder. It is known that reserpine produces depression in patients given large doses to control hypertension. The tricyclic antidepressants also enhance the activity of NE at synapses.

There is evidence that NE is involved in appetitive behavior through a

reward system in the CNS. Stein, (1964) has found that rats with implanted stimulating electrodes will increase self-stimulatory activity when given imipramine or amphetamine, but reserpine will suppress it. Self-stimulation via electrodes in the medial forebrain bundle can also be blocked by administration of disulfiram, a dopamine β hydroxylase inhibitor, and restored by intraventricular NE, suggesting NE and not D is involved in this behavior (Wise and Stein, 1969).

Slangen and Miller, (1969) have implicated NE in feeding behavior. By implanting cannulae in the hypothalamus in a region known to elicit feeding behavior when electrically stimulated, they found similar responses after administering small amounts of NE. Recently it has been found that the ventral noradrenergic bundle mediates satiety in rats. Electrolytic destruction of this bundle, or precise injection of 6 hydroxydopamine which is selectively absorbed and destroys NE containg neurons, produced hyperphagia and blocked amphetamine induced anorexia in rats (Ahlskog and Hoebel, 1973).

It is possible that the monoamines are involved in memory and learning. The release of biogenic amines has been suggested to initiate consolidation of the memory trace. An important event, detected through pain, reward, etc. produces the appropriate affective state and the release of monoamines. Recently activated synapses and neurons, those involved in the detection and recognition of the stimuli are caused to"remember" by the monoamines released from diffuse fibers, possibly by induced protein synthesis. Repetition of the event strengthens the memory by a process similar to signal averaging; the randomly activated neurons being only partially reinforced (Kety, 1970) Although plausible, this is highly speculative.

Serotonin is implicated in sleep, and since the hallucinogens are as well, studies on sleep will be reviewed in some detail. The states of sleep are characterized by EEG and EMG recordings. The awake,alert state produces a fast, low voltage EEG activity over most of the cortex. Relaxation corresponds to transition to an alpha rhythm, a slower (about 8-12 hz) higher voltage recording. Light sleep produces a slower, more synchronized tracing (8 hz), and deep sleep produces a very slow 4-6 hz activity. At certain times during sleep the EEG records a fast, low voltage activity similar to the awake, alert state. This coincides with a loss of tonus in skeletal muscles, especially the neck muscles, and rapid movements of the eye (REM's). Jouvet has termed this state of sleep, characterized by loss of tonus, REM's, and fast cortical ac-

tivity paradoxical sleep (PS), as opposed to the former state of slow synchronized activity, slow-wave sleep (SWS).

Work on sleep is usually done on the cat, because the cat alternates so frequently between wakefulness and sleep. About 70% of the day is spent in sleep of which about 16% is PS.

One of the first studies on sleep was done by Bremer,(1935). By preparing cats with transections at the collicular level (cerveau isolé) and the medullar level (encéphale isolé) he found the cats with cerveau isolé registered continuous cortical sleep while the encéphale isolé showed the normal sleep-waking pattern.

Much subsequent work involved the reticular activating system. The hypothesis was set forth that sleep is a passive result of decreased sensory input. This was eventually discarded because of increasing evidence that structures at the level of the mesencephalon somehow produced sleep. It was found that lesions of the dorsal Raphé nucleus in cats led to permanent wakefulness (Jouvet, 1967).

Earlier, in 1955, Dement had noticed the REM phenomenon in humans and had correlated it with dreaming. It was found in cats and Jouvet did electrophysiological studies characterizing, as he calls it, PS. PS was found to occur after initial SWS. It was found that it is more difficult to wake an animal in PS than in SWS, there is a loss of tonus in main postural muscles during PS, and there is a loss of tendon jerk (monosynaptic) reflexes. Also, a 4-6 Hz theta rhythm appears in the hippocampus and other limbic structures including the mesencephalic reticular system, and there is a peculiar spiking activity that can be recorded from the pons, geniculate nuclei, and occipital cortex denoted PGO spikes (Jouvet, 1967).

Studies have been done on PS deprivation. After prolonged deprivation PGO spikes begin to appear during SWS, and there is a marked rebound when the animal is allowed to sleep uninterrupted; much more time is spent in PS as if there was a deficit to be made up. Dement, (1960) has done experiments involving PS deprivation in humans. He awoke subjects whenever they entered PS. After a few days the subjects had marked personality changes, and when allowed to sleep freely, they too seemed to show a deficit. Dement suggested that there is an accumulation of some agent which is neutralized during PS.

Pharmacological studies of sleep have produced some intriguing results. Gamma-butyrolactone causes induction of SWS and subsequent PS at doses of

50-60 mg/kg i.p. in both normal and decorticate cats. Other short chain fatty acids do the same, and continuous infusion of higher doses can maintain PS alone for 70 hours. It is unknown whether this is a normal component of sleep or not.

Jasper et al.,(1965) have found that about three times as much GABA is released during sleep as during waking time. There also appears to be an increase in blood flow during PS of about twofold (Kety, 1967).

Some of the most interesting results involve the monoamines. As mentioned earlier, destruction of the dorsal Raphé nucleus produces permanent wakefulness in cats. Injection of 50 mg/kg of 5-hydroxytryptophan (5HTP) increases SWS and supresses PS even in PS deprived animals for 5-6 hours. Administration of DOPA at 50 mg/kg supresses all sleep for about 6 hours. Injection of MAO inhibitors increases SWS and supresses PS for a period of 3 to 4 days. In light of this, Jouvet has hypothesized that MAO is necessary for the transition from SWS to PS.

To examine further the roles of NE and 5HT in sleep, each was in turn enhanced following depletion of all the monoamines with reserpine. When reserpine alone is given, SWS is supressed for about 12 hours, PS is suppressed for about 24 hours, and the sleep patterns return to normal after a week. PGO activity occurs even during waking for 60 hours following administration. When 5HTP at 30 mg/kg is given following reserpine the PGO activity disappears and a SWS EEG appears. If DOPA at 30-50 mg/kg is administered following reserpine, the frequency of the PGO spikes is increased, and after about an hour brief periods of SWS and PS appear, including muscular atony.

Although far from being conclusive, it appears that 5HT is related to SWS, the metabolism of which involving MAO somehow triggers PS. NE seems to mediate the muscular atony of PS and is related to the polygraghic effects of this sleep state (Jouvet, 1967).

Another logical step in elucidating the role of 5HT in brain function is stimulation of serotonin containing neurons. Sheard and Aghajanian, (1968) took advantage of the fact that the cell bodies of the serotonergic neurons comprise the Raphé nuclei. Using single electrodes they stimulated this area and found an altered reactivity to sensory stimuli. The animals failed to habituate to repetitive stimuli, either auditory or somaesthetic. The effect was reversible and habituation returned following cessation of stimulation. No somnolence or hyperactivity was observed. Pretreatment with p-chlorophenyl-

alanine blocked the effects of Raphé stimulation, indicating that the failure to habituate was not due to current leaking into neighboring structures, but due to release of 5HT.

Mechanism of Hallucinogenic Drug Action

As will become evident, the mechanism of hallucinogenic drug action is far from established. There have, nonetheless, been a great number of reports published on this topic, many of which demonstrate interesting relations to sleep, monoamines, visual processes and schizophrenia.

The modern brain is viewed as a complex interconnecting network of neurons and neuronal systems. Under this view, there are a variety of places at which hallucinogens might act. They may influence the conduction of an action potential by changing its speed or amplitude. Possibly some sort of intraneuronal action is responsible. There are also a number of synaptic mechanisms avaliable. These include transmitter precursor transport, interference with synthetic enzymes, release, reuptake, storage, degradation, or interaction with receptors. Since no transmitters have been positively identified in the CNS, and since many transmitters probably remain undiscovered, this work is difficult. Hopefully, the following is a review of the salient research done on the mechanism of these drug's actions.

Electrophysiological and Biochemical Studies of LSD, DMT, Mescaline and Their Congeners

This class includes LSD, DMT, DET, DPT, Psilocybin, Psilocin, Mescaline, DOM, DOET, and certain related phenylisopropylamines. Although structurally quite diverse, it appears they have similar qualitative and physiological actions.

Physiological effects: Isbell (1959) compared the effects of LSD and psilocybin in man (see table 4 below). The effects were similar and dose de-

Table 4. *Comparison of total course of psilocybin and LSD reactions*

Measure	Placebo	Treatment				
		LSD-25		Psilocybin		
		1.0 mcg/kg	1.5 mcg/kg	57 mcg/kg	86 mcg/kg	114 mcg/kg
Temperature[1] . . .	+ 2,7 ± 0,32	+ 4.8* ± 0.44	+ 4.9* ± 0.48	+ 3.5* ± 0.26	+ 5.7* ± 1.35	+ 4.6* ± 0.26
Pulse rate[1]	+37.8 ± 14.5	+67.3* ± 17.8	+82.8* ± 10.9	+31.9 ± 8.9	+41.6 ± 10.4	+79.1* ± 12.6
Respiratory rate[1] :	+13.1 ± 3.1	+32.9* ± 3.9	+36.7* ± 7.1	+24.5 ± 8.1	+26.4 ± 8.2	+37.5* ± 7.1
Systolic blood pressure[1]	+15.6 ± 13.5	+64.8* ± 10.9	+94.6* ± 17.5	+31.4 ± 12.6	+61.7* ± 11,0	+47.8 ± 16.9
Diastolic blood pressure[1]	−17.5 ± 11.9	+ 9.1 ± 19.1	+35.2* ± 10.7	+ 8.2 ± 9.7	+15.7 ± 11,0	+ 6.6 ± 13.6
Pupillary diameter[1]	0.2 ± 1.4	+10.2* ± 1.18	+15.0* ± 2.1	+ 3.9* ± 0.9	+ 6.0* ± 1.4	+ 5.4* ± 1.9
Patellar reflex[1] . .	+20.7 ± 11.1	−50.9 ± 31.0*	−72.9* ± 21.7	+ 7.1 ± 19.2	−47.6* ± 10.4	−65.5* ± 23.8
No. positive answers[2]	0.1 ± 0.3	57.0** ± 23.2	98.0** ± 26.6	24.0** ± 5.9	38.0** ± 16.3	38.0** ± 11·0
Clinical grade[3] . . .	0 ± 0	2.2** ± 0.38	2.8** ± 0.17	1.2** ± 0.2	1.83** ± 0.4	2.0** ± 0.36

[1] Figures are means ± standard errors (9 subjects) of areas under time-action curves ("degree-hours", "beat-hours", etc.). The signs indicate increases (+) or decreases (−) in the measurement.

[2] Means ± standard errors of number of questions scored positively in the $7^1/_2$ hours after the drug which were not scored positively before the drug.

[3] Means ± standard errors of intensity of mental reaction based on a scale of 0—4.

* Significantly different from placebo ($P<0.05$).

** Significantly different from placebo ($P<0.05$, non-parametric test).

pendent. They include hyperthermia, increased pulse rate and blood pressure, and increased pupillary diameter (mydriasis). These are the general sympathomimetic effects of the hallucinogens. Mescaline has similar effects (Wolbach et al., 1962b) as do the indolealkylamine derivatives DMT, DPT, DET (Szara, 1956; Szara, 1967). Dosewise LSD was found 44 times as potent as psilocin or psilocybin, and psilocin about 66 times as potent as mescaline. Psilocybin is hydrolyzed to psilocin in the body and they are equivalent. DMT, DET, and DPT last only about 30 minutes, psilocin lasts about 4 hours, LSD about 8 hours, and the effects of mescaline are noticeable for 12 hours. These durations refer to doses of the hallucinogens required to produce the major perceptual and physiological changes. The time course of the LSD reaction follows its blood plasma level quite closely; it has a half life of about 3 hours in man and 20 minutes in the rat (Freedman, 1966).

This indicates the differences in duration of effect of the different hallucinogens might simply be due to differences in susceptability to metabolic degradation. Shulgin, (1970) has synthesized many of the phenylisopropylamine analogs of mescaline. The addition of a methoxy group in the para position always greatly increased the psychomimetic activity. He postulated that this position is important in deactivation and metabolism of these compounds and, working on this assumption, synthesized DOM and DOET. These compounds have methyl or ethyl groups in the para position. Presumably it is more difficult to metabolize these, and DOM and DOET indeed have a long effect reported as up to 24 hours. Szara, (1956) examined the excretion of metabolites of DMT and found they appear soon after injection as the corresponding indoleacetic acid and hydroxylated analogs.

conglomerate

Perceptual and Behavioral Effects: The hallucinogens produce a variety of effects on the different sensory modalities.

Vision. Changes in visual perception are perhaps the most vivid effect of the hallucinogens. Distances seem alternately greater and less, stationary objects appear to be moving. There is an extreme awareness of detail which is normally overlooked or uninteresting. Colorful kaleidoscopic imagery is often present, and if the eyes are opened these patterns can be projected onto or can be triggered by real objects; lacework and repetitive patterns are often seen on blank surfaces. There is a symmetry of visual patterns. Saturation and brightness of colors is increased. Movement is sometimes seen as a series of frames as if under a strobe lamp. There is often a prolongation of afterimages.

On occasion objects can take on characteristics the subject imagines, or events detected by other senses can be transformed into visual phenomena producing synaesthesia.

Auditory effects. Auditory acuity is usually increased. Often background noise can be heard which is normally dismissed or ignored. Sound seems to pulsate; a blind subject under LSD said the room seemed to be getting alternately larger and smaller. There are also a number of qualitative changes. Music sounds extraordinarily beautiful, and can often induce emotional reactions in the subject. Reverberations and tremelo are sometimes heard.

Taste.Alterations in taste and olafaction are subtle and usually involve texture.

Tactile phenomena. Awareness of temperature is altered. Subjects sometimes feel alternately hot and cold. There is an occasional increased awareness of tactile stimulation. Clothing is sometimes annoying. Two point discrimination is impaired.

Kinesthetic Changes. Changes in awareness of gravity and postural relationships occur. Subjects feel lightheaded, heavyheaded, or empty. There is a decreased awareness of limb position.

Body image. This is common to all the hallucinogens. It is often described as a feeling of having moved out of one's body.

Time. Perception of time is changed. It is often said to have stopped, speeded up, slowed down or run backwards. Estimation of time intervals shows increased variance over normal subjects.

Thought. Changes in both thought precesses and content occur. There are interposed thoughts, decreased concentration, memory changes, and impairment of the ability to perform simple arithmetic. There is an impairment of recognition of various visual and auditory stimuli. The content of thought is altered. Bizarre ideas, delusions, and ideas of reference are seen. There is often a euphoria, a free floating certainty, especially with the phenylisopropylamines. Judgement of reality is impaired (Hoffer and Osmond, 1967).

In animals there are comparatively few measurements of this sort possible. Only behavioral manifestations can be observed. A variety of methods have been used to try to quantify the effects of the hallucinogens. Florio et al. (1972) found that conditioned behavior in cats is disrupted and that this is about the most sensitive test. EEG results showed a mixed synchronization and activation. Generally bizarre behavior is the criterion used for action in these studies,

and this is far from acceptable as a consistent measure of drug effect.

The first biochemical studies on LSD were done by Gaddum, (1953) and Woolley and Shaw (1954). Using isolated rat uterus they found that LSD would block the effect of 5HT on this preparation. Serotonin was found in the brain, and the indole nucleus of LSD led to the so called serotonin hypothesis, that LSD exerted its action by blocking 5HT receptors at central synapses.

Subsequent studies have tempered this hypothesis. Cerletti and Rothlin, (1955) found that 2-brom LSD was as potent in blocking the peripheral effects of 5HT. 2-brom LSD is not hallucinogenic in man. It has also been shown that LSD at lower concentrations has a serotonin like action in smooth muscle preparations (Shaw and Woolley, 1956). Obviously the peripheral effects of LSD could not be generalized to its central action. In 1963 Sai-Halasz found that iproniazid, a MAO inhibitor, antagonized the effects of DMT (Sai-Halasz, 1963). Chase et al.,(1967) found that by letting rat brain slices accumulate H^3-5HT and then stimulating them electrically they could obtain release of 5HT which followed its endogeneous distribution. The addition of LSD at 2×10^{-4} M reduced the release by 63± 9 %. The relevance of studies such as these is hard to determine. The high concentrations used may be misleading, as were Gaddum's results.

Far more interesting results are obtained when investigating the turnover of monoamines in response to hallucinogens. LSD given to rats causes an increase in 5HT content in the brain and a decrease of its major metabolite, 5HIAA 20 minutes after administration of 200 ug/kg. A number of investigators have confirmed this finding and have shown the turnover of 5HT to be decreased after LSD, mescaline, phencyclidine, and Ditran (Tonge and Leonard, 1969; Diaz et al., 1968). Phencyclidine, mescalin, Ditran, and LSD also appear to deplete NE stores and to increase its turnover as seen by blocking tyrosine hydroxylase with α methyl para tyrosine (Leonard and Tonge, 1969). DOM has been found to increase the conversion of tyrosine to NE and decrease the conversion of tryptophan into 5HT. It also reduces the depletion of 5HT following para chlorophenylalanine (Leonard, 1972; Leonard, 1973). Psilocybin and DMT alter monoamine turnover in the same fashion (Andén et al., 1971). Andén had found earlier that the turnover of 5HT is decreased and that of NE was increased under LSD but not with 2-brom LSD or Methysergide (Andén et al., 1968).

These studies indicate that hallucinogens such as DMT, mescaline, DOM, LSD, phencyclidine, and Ditran may act by interfering with 5HT release. Aghajanian et al., (1968) indeed found that LSD at 10 ug/kg inhibited single unit firing in the Raphé nuclei. A more extensive investigation examined the effect of LSD,BOL(2-brom LSD),mescaline,DMT,scopolamine,atropine and phencyclidine. Single units in the Raphé were recorded and drugs were injected i.p.. In response to LSD, firing of all units tested in the dorsal Raphé decreased in rate in a dose dependent manner in accordance with the half life of LSD. (See figure 7). DMT also caused inhibition at 700 ug/kg and recovery within 2-3 minutes vs. 30 minutes for LSD. BOL had an effect only at higher concentrations.

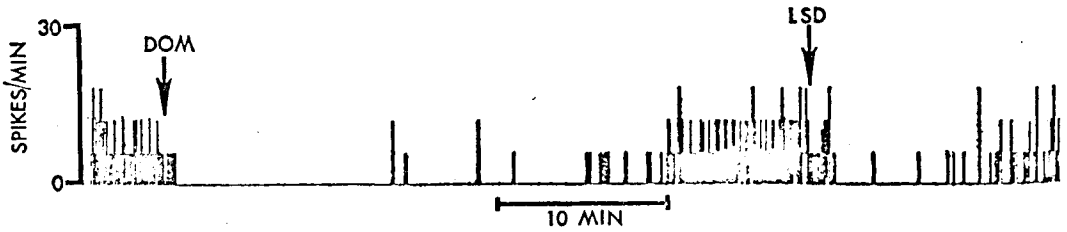


FIG. 9. Inhibition of a raphe unit by DOM. DOM, in a dose of 0.25 mg/kg, produced a prolonged inhibition of this unit. Once unit had recovered, LSD (10 μg/kg) was given and also produced inhibition. This unit was in the ventral portion of the dorsal raphe nucleus.

Figure 7. From Aghajanian et al., 1970.

Mescaline inhibited 21 of 47 dorsal and 6 median Raphé cells at 2-4 mg/kg. Those cells not inhibited by mescaline were by LSD. DOM was similar to mescaline (7of 15 cells). It is interesting that mescaline and DOM increased the rate of some units in light of previous work (Foote et al., 1969) which found amphetamine increases the firing rate of some Raphé cells. Phencyclidine, atropine and scopolamine had no effect and did not antagonize subsequent LSD inhibition, nor did chlorpromazine or p-chlorophenylalanine (Aghajanian et al., 1970).

Raphé cell firing has been shown to be influenced by a number of other conditions. Aghajanian has found that MAO inhibitors also depress Raphé firing (Aghajanian et al., 1970b) as do the more or less 5HT specific tricyclic antidepressants amitryptiline, imipramine and chlorimipramine (Sheard et al., 1972). It has been suggested that the rate of firing of Raphé cells is regulated by impulse controlled feedback (Meek and Fuxe, 1971) or chemical feedback (Aghajanian, 1972). In the latter report it is stated that administration of 5HTP does not depress Raphé firing whereas tryptophan loading does. Aromatic amino acid decarboxylase is not localized solely in the Raphé cells, but is present in endothelial cells throughout the brain, and 5HTP does not increase the flour-

escence of Raphé cells, while tryptophan does. Tryptophan hydroxylase is present solely in Raphé cells. This has been interpreted as evidence of serotonin feedback regulation of Raphé cell firing. Administration of p chlorophenylalanine however, which prevents the increase of flourescence of Raphé cells, did not prevent the decrease in firing rate. These results challenge the belief that 5HT is the exclusive or even predominent indoleamine within the Raphé neurons. It is possible that hydroxylated amine derivatives other than 5HT may be active in these fibers as has been suggested for serotonin containing neurons in the spinal cord (Aghajanian, 1972; Bjorkland et al. 1970).

At the present state of knowledge of central transmitters it is tempting to speculate that there is more than one serotonin-like transmitter and that there are many types of receptors responsive to them. The differential action of DOM and mescaline vs. LSD on Raphé units supports this if indeed they are interacting with serotonin receptors. It is likely that the varied effects of the hallucinogens are due to many actions at many loci.

The Raphé nuclei and the locus coeruleus have also been implicated in the relation of hallucinogenic drugs and sleep. McGinty and Harper (1972) using cats with chronically implanted electrodes have demonstrated a quite steady, about 60 impulse/minute, activity of Raphé neurons while awake. At the onset of SWS the firing of these Raphé neurons slows significantly to about 30 impulses/minute. At times during SWS this activity ceases and 1-4 seconds following this complete cessation the characteristic PGO spikes appear, and the cat enters PS. Simon et al., (1973) have shown that: 1) Lesions of the Raphé cause these PGO spikes in a manner dependent upon the number of these nuclei destroyed (See figure 8). 2) Unilateral parasaggital cuts 1.5 mm lateral to the nuclei cause similar phenomena. 3) The onset of p-chlorophenylalanine induced PGO spikes was accelerated in animals with lesions in the Raphé. 4) Stimulation of a pacemaker region of the pons on the side ipsilateral to an extensive parasaggital cut consistently evoked lateral geniculate responses during SWS and PS, but stimulation on the contralateral side evoked LG responses only during PS.

This is evidence to the effect that the Raphé inhibit the pacemaker region of the pons during normal waking and SWS via a serotonergic mechanism. The fact that the hallucinogens cause a cessation of firing of the Raphé cells as well leads to the question of whether LSD can cause these PGO spikes. Morgane and Stern, (1972) found that LSD at 40 ug/kg clearly increased the occurence

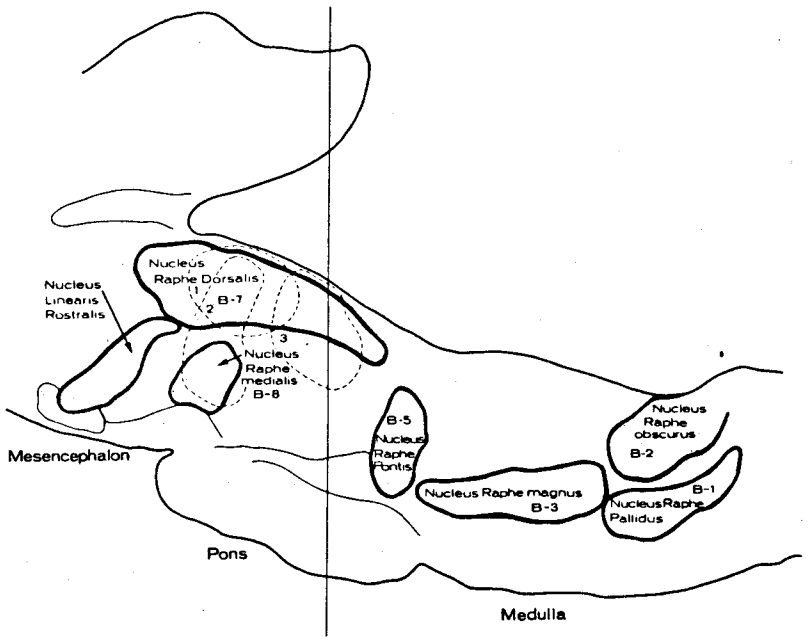


Figure 8. From Morgane and Stern, (1972). Anatomical relations of the Raphe nuclei.

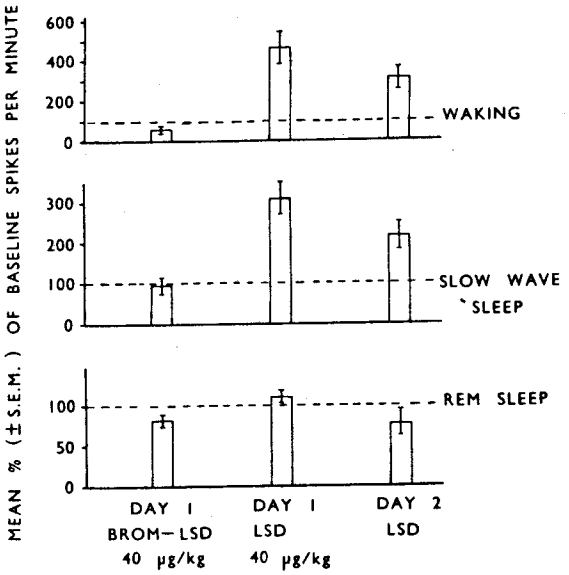


FIGURE 9. The effects of a single injection of brom-LSD or of LSD upon PGO spike rates in the lateral geniculate nucleus of cats (n = 4). The mean (± S.E.) PGO spike rates during baseline were: waking = 4.5 ± 0.2 spikes / min; slow-wave sleep = 4.9 ± 0.3; REM sleep = 41.9 ± 2.1. The sample time during which PGO spikes were counted averaged 45 min for waking, 155 min for slow-wave sleep, and 45 min for REM. The last column, day 2 LSD, refers to the day after LSD administration.

From Morgane and Stern, (1972).

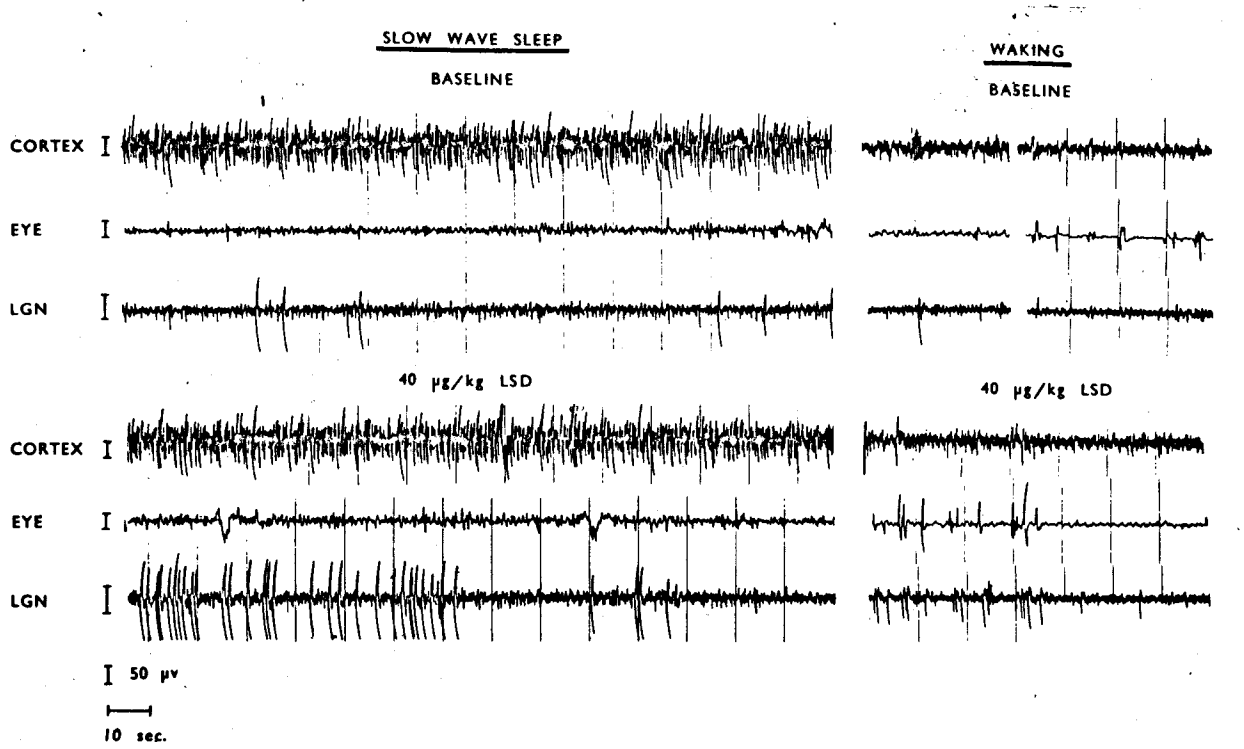


FIGURE . Baseline and post-LSD recordings of PGO spikes from the lateral geniculate nucleus of the cat during slow-wave sleep and waking. PGO spike rates during REM sleep were not affected by LSD. The "break" in the baseline waking record indicates two samples, one with eye movements and one without. Cortical EEG and eye movements shown are part of standard recordings in all animals.

From Morgane and Stern, (1972).

of PGO spikes during SWS and waking over control values (see figures 9 and 10) while the non-hallucinogenic 2-brom LSD (BOL) did not. They have suggested that these PGO spikes could be visual input at the level of the LG for the dreaming state.

As mentioned earlier, Dement has found that PS deprivation leads to marked personality changes and eventual delusions and hallucinations. It is plausible that prolonged sleep deprivation leads to the entry of these PGO spikes into wakefulness and induces concomitant visual and perceptual disturbances similar to dreaming or the action of hallucinogenic drugs. Muzio et al., (1966) found found that LSD at .08-.73 ug/kg given to human subjects before sleep or one hour after the onset of sleep leads to increased PS time and breif PS bursts during SWS. Safer, (1970) has shown similar phenomena in sleep deprived men. 1.5 ug/kg LSD given to normal and sleep deprived men caused a more rapid onset and increased intensity of behavioral and attention impairment in the sleep deprived subjects. Ancillary evidence on the involvement of serotonergic systems in sleep comes from Engelman et al., (1967). They demonstrated that cats given p-chlorophenylalanine have abnormally high levels of PS and do not com-

penate for PS deprivation. This is also true of humans given p-chlorophenylalanine, and indicates again that 5HT is involved in PS.

Jouvet (1967) has implicated NE in PS as well. He has suggested that NE triggers the effects of PS including the muscular atony. Since hallucinogens increase the turnover of NE (Leonard and Tonge, 1969), it would be interesting to examine the effect of hallucinogens on the firing rate of NE neurons in the locus coeruleus.

In any case, the data on sleep suggest that it is regulated by the same systems that control many of the homeostatic mechanisms of food intake, temperature, emotional and sexual behavior and primitive motor mechanisms, even though the physiological role of sleep is unknown. It appears that hallucinogenic drugs interfere with this system and cause the appearence of symptoms characteristic of PS during the waking state.

These same monoamine systems also appear to be involved in pain perception and habituation. As discussed earlier, Aghajanian found that stimulation of the Raphé produces dishabituation. Tenen, (1968) demonstrated that lesions in the Raphé reduce morphine analgesia. This was confirmed by Samarrin et al., (1970), and Harvey, (1971) has shown that these lesions increase sensitivity to pain. This and other evidence (Akil and Mayer, 1972; Mayer et al., 1971; and Herz et al., 1970) suggest that the Raphé is also somehow involved in the modulation of sensitivity to pain and of habituation.

The effects of LSD described by human subjects include extraordinary attention to detail, increased saturation and brightness of colors, a perception of auditory noise normally overlooked, and an increased awareness of clothing to which one is normally accustomed. The relation of serotonin neurons to habituation lends evidence that LSD might be mimicing the action of serotonin at certain synapses. Shaw and Woolley, (1956) as mentioned have shown that at the low concentrations of LSD which produce effects in man LSD has a serotonin mimicing effect on peripheral smooth muscle. Marchbanks et al. (1964) in binding studies found that LSD could inhibit binding of 5HT in nerve particle endings. This, and the chemical feedback regulation of Aghajanian for these 5HT containing cells indicate that LSD and the hallucinogens may indeed bind to some 5HT receptors.

There has also been some work focussing on the lateral geniculate nucleus, the retina, and the roles they may play in the alteration of perception induced by hallucinogenic drugs. Curtis and Davis, (1961) found that tryptamine,

bufotenine, LSD, psilocin, and psilocybin had this order of potency on the depression of post-synaptic spikes in the LG. Kawai and Yamamoto, (1968) recording from the superior colliculus of Guinea pig brain slices noted a decrease in the size of the response following LSD at $2x10^{-7}$ M or psilocybin at 10^{-5} M or mescaline at 10^{-4} M. McKay and Horn, (1971) found that spontaneous firing rates of single cells in the LG of cats was decreased in a dose dependent way following LSD. There were also a variety of effects on the center-surround units. These experiments demonstrate action at visual stations, but it is unknown whether they are due to other effects such as PGO activity or retinal processes.

Some work has been done on the retinal effects. Straschill, (1968) found that exogeneous 5HT applied to retinal ganglion cells depressed their spontaneous firing rate. Heiss et al., (1973) found a similar phenomenon with DMT. As the ganglion cells carry information in the negative sense, this depressing action on firing might be seen as light or visual hallucinations. These studies are really inconclusive, as 5HT depresses the rate of many cells when applied microiontophoretically, as do many substances (cells not necessarily receptive to 5HT).

Tolerance. There is an interesting correlation between tolerance among hallucinogens and their electrophysiological actions. Tolerance to these drugs develops quite rapidly. Wolbach et al., (1962) found a cross tolerance in humans among LSD and mescaline. Subsequently Appel and Freedman, (1968) found similar phenomena in rats. Using a fixed interval 30 milk reinforcement to quantify the disruptive effects of the drugs, he found that rats develop a tolerance to LSD, but they develop one to mescaline faster. He found that LSD produces a tolerance to LSD, psilocybin, and mescaline, but mescaline did not produce as effective a tolerance for LSD. This corresponds well to the effect of these drugs on Raphé cells. Mescaline inhibits only a few of these cells, a tolerance to hallucinogens at these cells alone would not protect the animal from LSD which inhibits all the Raphé neurons.

Schizophrenia. As of late there has appeared a good deal of evidence that schizophrenia is the result of a metabolic disturbance of such a nature to produce DMT in the body. The very word psychomimetic was based on the similarity in symptoms seen with the indole derivative hallucinogens and schizophrenia.

The following is evidence as it now stands:

1) DMT produces hallucinations and schizophrenic symptoms in man (Szara, 1956).

2) Enzymes necessary to produce DMT have been found in the lung and brain (Walker, 1972; Mandell and Morgan, 1971; Saavedra and Axelrod, 1972).

3) DMT is formed in brain tissue (Saavedra and Axelrod, 1972).

4) MAO is low in some schizophrenics and this is known to potentiate the effect of DMT (Murphy and Wyatt, 1972; Wyatt et al., 1973).

5) There is an elevated level of tryptamine in the urine of schizophrenics. Tryptamine is the precursor of DMT, and tryptamine is present in the brain along with the proper methyl-transferases (Saavedra and Axelrod, 1972).

6) Increasing brain 5HT with 5HTP ameliorates schizophrenic symptoms (Wyatt et al., 1972).

7) Administration of l-tryptophan, the precursor of tryptamine, and methionine, the precursor for the methyltransferase, intensifies the symptoms (Pollin et al., 1961; Tanimukai et al., 1967).

8) There is an unpublished report that cats fail to develop a tolerance to DMT by Gillin.

9) Sleep is implicated in schizophrenia. Wyatt et al.,(1971) have found that schizophrenics have abnormally high amounts of PS during SWS as judged by EEG and EMG studies. They also do not compensate for PS deprivation. This is similar to what is seen with treatment with PCPA and indicates a functional deficiency of 5HT (Dement et al., 1969).

It is possible that schizophrenics have a metabolic disorder where 5HT is deficient and DMT is produced instead, but the evidence is only that above.

Tetrahydrocannabinols. Marihuana is perhaps the most widely used drug yet the biochemical and physiological data on its mode of action is probably the scarcest of all the hallucinogens. It does not produce nearly the disturbance seen with the other drugs.

Byck and Ritchie, (1973) have reported that $\Delta 9$ THC causes a dose dependent decrease in the amplitude of the action potential in mammalian non-myelinated nerve fibers. The amplitude decrease appears to be chloride dependent.

Another effect was reported by Ng et al., (1973). They found that serum dopamine β hydroxylase, a measure of peripheral sympathetic activity, decreased in response to chronic administration of $\Delta 9$ THC in rats. This may relate

Δ^9 THC to effects on monoamines. It is known that $\Delta 9$ THC produces hypothermia (Grinspoon, 1969), and in this respect it appears to be a parasympathomimetic, although there is also a slight tachycardia. Leonard and Stonier, (1971) have found that LSD,mescaline, psilocybin, etc. are calorogenic as noted by Isbell, (1959) and that they can antagonize the hypothermia induced by reserpine. NE is implicated in temperature regulation.

NE is also involved in feeding behavior. Marihuana is the only hallucinogen which consistently produces hunger and thirt in human subjects, even after having eaten.

Although the evidence is slim, it seems that marihuana may be involved in NE systems in the brain. Further work is needed on this widely used drug.

Summary

It must be concluded that the action of hallucinogenic drugs is unknown. The role of hallucinogens awaits further analysis of the mechanism of mind and brain function; it is possible they will aid in this analysis through their ability to produce bizarre alterations in the biochemistry and neurophysiology of brain systems. Clearly there is a good deal of work to be done.

Educated speculation suggests a role of these mind altering drugs in neural circuitry and neurochemical systems involved in some of the more elementary processes such as emotional behavior, sleep, and habituation. There is good evidence that the hallucinogens interfere with mechanisms regulating sleep, possibly producing some of the components of dreaming during the awake state. The euphoriant action of these drugs may be linked to their effect on noradrenergic systems; almost all produce increased NE turnover and the phenylisopropylamines are structurally similar to amphetamine, which is implicated in reward and pleasure systems in the brain. Neurophysiological studies on the effect of these drugs on single cells in the locus coeruleus, a NE containing group of cells also involved in sleep,remain to be done.

There is little reason to believe that hallucinogens act only on known systems. It is likely that transmitters and various types of receptors exist in the brain which are as yet undiscovered. There is evidence of serotonin analogues in serotonin containg cells, and most probably hallucinogens act through a variety of brain systems.

The effect of Raphé stimulation on habituation and pain perception, and the possible serotonin mimicry of hallucinogens may account for some of the reported subjective effects of increased awareness of the environment in the hallucinogenic state.

Schizophrenia is also linked to hallucinogens both biochemically and through sleep phenomena. It is possible that schizophrenia is the result of a metabolic disorder producing hallucinogens in the central nervous system.

In any case, work on the hallucinogens has produced some though provoking hypothese and promises to aid in the understanding of brain mechanisms.

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