PHARMACOLOGICAL REVIEWS
Vol. 24, No. 1

Printed in U.S.A.

The Pharmacology of Hallucinogens

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HALLUCINOGENS are amongst the oldest known psychoactive substances; their pharmacology has been under extensive investigation for over 20 years, yet the pharmacological and physiological bases of their hallucinogenic potency are not yet understood. Four explanations are available for this state of affairs. One, advanced by Appel (19), is that investigative methods have been too diverse to allow an integration of findings; yet even within the constraints of particular methods, results are often contradictory (139, 173). A second possibility is that the neural processes subserving perception are so complex and non-stationary as to evade elucidation with presently available methods. Without doubt, peripheral receptors are more convenient to study; yet the mechanisms of action of some centrally acting drugs (for example, strychnine and amphetamine) are yielding to experimental enquiry more easily than those of the hallucinogens. A third explanation is that hallucinogens have in fact diverse modes of action, admitting no general theory. Finally, they may have a commonality of actions

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which has not yet been discovered. There have been many attempts (38, 43, 44, 76, 96, 155, 170, 234, 237) to form a general theory of hallucinogenesis; unfortunately none can account for more than a small portion of the available data. The object of this report is to review the present state of factual knowledge about the mechanisms of action of hallucinogens, to evaluate the extent to which any general theory of their action is tenable, and to consider what investigative strategies now seem most appropriate.

The Class of Chemicals Known as Hallucinogens

The study of induced hallucinations and psychoses meets methodological difficulties at the outset just because the phenomena which constitute the explicandum are not directly accessible to an outside observer. Such may be said to comprise the core problem of psychophysiology. Thus we may find lively disagreements regarding what is and what is not a hallucination, and how to quantify such events. However, any and all kinds of what the Scheibels (189) have called non-object-bound sensory phenomena are reported by persons who suffer naturally occurring psychoses such as schizophrenia (17, 18, 33, 157, 232), organic syndromes (151, 205), affective disorders (149) or environmentally induced psychoses (43), and by persons who ingest various chemicals (75, 82, 84, 207, 209, 215, 216). These perceptual disturbances include misperceptions, illusions, misidentifications, eidetic imagery, paraesthesiae, and hypoaesthesiae, synaesthesiae, and simple and complex hallucinations in the classical sense. Since neither any known syndrome in man nor any known chemically induced state is invariably associated with any of these effects to the exclusion of others, a rigorously narrow definition of "hallucination" is not warranted. The evidence is that chemicals which can induce some of these effects can also induce the rest, although with varying frequency and intensity.

It is of more interest to examine the differences amongst chemicals which can induce hallucinations, not so much in terms of the kinds of hallucinations they cause, but rather in terms of their other central nervous system and behavioural effects. Now if a group of pharmacological materials displays n effects severally, there are 2^n ways of classifying those effects. An encyclopaedia of effects (for example, 231) will necessarily give rise to an unwieldy system of classification. Lewin (148) once grouped psychotropic chemicals according to their most pronounced effects, as hypnotica, euphorica, phantastica, excitantia, and inebriantia. If we follow this scheme, nearly all substances within the scope of this report will fall into his "phantastica" subdivision, which is not helpful. If we apply his method of focusing on most pronounced effects, however, we obtain a reasonably simple and heuristic grouping, as follows.

One class includes a substantial proportion of all known pharmacologically active substances which either in unusually high dosage or in the presence of idiosyncratic sensitivity induce toxic metabolic disturbances which may cause, amongst other things, organic brain syndromes accompanied by hallucinations. Toxic psychoses have been caused by sulphonamides; antibiotics such as penicillin and the tetracyclines; hormones such as adrenocorticotrophin (ACTH),

prednisolone, and thyroxine; cardiac glycosides; phenacetin; disulphiram; methyl and ethyl alcohol; sodium or potassium thiocyanate; industrial chemicals such as carbon disulphide, carbon tetrachloride, and the aromatic compounds found in glue and paint; most of the heavy metals; and antimetabolites such as actinomycin (109). For these chemicals, hallucinogenic potency depends more upon metabolic disruption of both neural and non-neural tissues than upon discrete neuropharmacological actions; it is therefore most appropriate to refer to them in this context as *poisons*. The pathogenesis of exogenous toxic psychoses lies outside the scope of this review.

A second well-defined class of hallucinogenic chemicals is marked by a capacity to induce delirious states, usually accompanied by hallucinations, without concomitant metabolic disturbances. Best known are the anticholinergic compounds (29), for example hyoscine, atropine, Ditran, phencyclidine, procyclidine, mecamylamine, benactyzine, diethazine, panthienate, benztropine, methane sulphonate, and trihexiphenidyl. Administration of these drugs leads to confusion, drowsiness, memory loss, unpleasant hallucinations, dysphoria, and agitation (1, 2, 82, 98). Characteristically, the state is that of confusion and hallucinosis without recall. It seems most appropriate to refer to these substances as *deliriants* (82).

In a third class, we have those substances which are best known for their hallucinogenic effects, and which characteristically induce neither general metabolic disturbances nor delirious states. Included here are several families of compounds: some ergot alkaloids, of which the best known is lysergic acid diethylamide (LSD); ibogaine; a group of chemicals found in *Banisteropis* and *Peganum*, for example, harmaline; the indolealkylamines; and substances which stem from peyotl, the phenylethylamines (199). The subjective and behavioral states induced by these compounds in man have been widely studied. Although there are certain differences, one can construct an imposing list of common effects (28, 75, 84, 112, 152, 204, 207, 209, 215, 216, 219, 221, 235):

(a) *physiological:* mydriasis, elevated heart rate and blood pressure, hyperreflexia, tachypnea, increased muscle tone; and occasionally, nausea, vomiting and ataxia;
(b) *sensory:* perceptual distortions which with sufficient dosage progress through simple to complex hallucinations, often in more than one modality;
(c) *psychic:* magical and paranoid thinking which evolves out of the perceptual disturbances, frequently accompanied by other elements of formal thought disorder; affective changes, highly subject-dependent and ranging from depression through emotional blunting to elation or extreme excitement.

There is no gainsaying the differences in subjective states, potency, and time course of action (19, 82, 100, 108, 112, 202, 207); nevertheless this combination of effects has about as much constancy as psychiatrists are accustomed to finding in naturally occurring psychopathological states. There is some justification, then, for speaking of a "psychomimetic syndrome." In some studies, especially with LSD, doses have been quite small (75, 215, 216) so that there has arisen the

belief that the effects of these compounds are confined to physiological and perceptual disturbances. This belief is mistaken, since with doses of LSD near or above 2 μg/kg in man, hallucinations are seen to lead to magical and paranoid thinking, clang associations, echolalia, and other manifestations of associative loosening (28, 84). The same progression from sensory to cognitive disturbance has been described frequently in schizophrenia (17, 18, 33, 43, 232). Another indication that these compounds form a pharmacological class in some meaningful sense is the frequent finding of cross tolerance amongst them in animals and man (3, 26, 88, 89, 108, 115, 117–120, 183, 184, 235, 236). Finally, the most reliable clinical antidotes of all these compounds are the phenothiazines and butyrophenones. We take all this as evidence of important similarities amongst group III hallucinogens, and we shall reserve for these drugs the term *psychotomimetic.*

Two classes of phantastica fall outside this classification. The group from the plant *Cannabis sativa*, though commonly described as psychotomimetic (132, 199), are better known for their euphoriant effects than for consistent hallucinogenesis (82, 113, 223). Careful descriptions of their effects under controlled conditions are scarce. The reports that are available suggest that these compounds have mixed deliriant, euphoriant, and hallucinogenic effects (116, 223), and that subject and situation dependence is even more marked than with psychotomimetics. Isbell *et al.* (116) were unable to demonstrate cross tolerance between LSD and tetrahydrocannabinol (THC). The pharmacology of this group of chemicals is so little understood at the present time that their inclusion in any classificatory scheme can have little meaning. For different reasons, the simple amphetamines (*d*-, *l*-, and *dl*-) resist classification. In single doses they are not hallucinogenic, but it is widely known that repeated use may result in a syndrome indistinguishable from paranoid schizophrenia (58, 107). As with THC, Isbell's group found no cross tolerance with LSD (119, 184).

There are clinical grounds, then, for regarding *psychotomimetics* as having many effects in common, and as sharing some differences from *poisons* and *deliriants* as defined here. In themselves, these similarities do not justify the presumption of a common mode of action. The notion of a "final common pathway" (43) for chemically induced psychoses is at best a hypothesis, perhaps improbable in the light of the diversity of chemicals which show this potency. Identical phenomenological states may be caused by disparate mechanisms. Cross tolerance may be due to enzyme induction rather than interaction at a common cellular receptor site. Antagonism of behavioural effects may or may not be due to an agonist-antagonist relation at the cellular level. The extent to which psychotomimetic chemicals share modes and sites of action, therefore, can be settled only by experiment, and not by theoretical considerations. The results of such experiments, however, will have theoretical significance both for pharmacology and psychiatry, especially with regard to our understanding of the pathophysiology of naturally occurring psychoses.

Structure-Activity Relations

If psychotomimetics form a class, it is pertinent to ask what they have in common structurally, and what relations hold between structure and activity. This

line of enquiry holds the promise both of providing some insight into mechanisms of action and for predicting the psychotomimetic activity of newly synthesized compounds (211). Several difficulties, however, limit the generality of results obtained on this method. (a) There is neither theoretical nor empirical justification for the assumption that all receptor sites affected by psychotomimetics are structurally identical. (b) There is no certainty, on the present evidence, that all psychotomimetics interact in the same way with any given receptor. (c) The identity of those receptors which are crucially involved in psychotomimetic action is unknown. Furthermore, if it is believed that the relevant receptors are enzymes, not membranes, the same difficulties arise. (d) In addition, potency will depend upon ease of passage through the "blood-brain barrier," and rates and mechanisms of neuronal uptake and degradation. Therefore, the finding of simple, monotonic relations between structural parameters and potency for all psychotomimetics appears to be an unrealizable objective for any structure-activity theory. At best, one may hope for limited, empirical relations which hold within certain classes of drugs, and that has been the usual result.

A first requirement for structure-activity studies is an objective and reliable method of quantifying potency. Effective doses (ED) vary enormously amongst species; for example with LSD, behavioural changes are discernible in the rat at 100 to 130 μg/kg (92) but in the cat at 25 μg/kg (36). In man, where we have the advantage of verbal reporting, the ED is less than 1 μg/kg (28). In the case of the methoxylated amphetamines, LD50 in animals (mice) correlates poorly with potency in man (201). For several psychotomimetics, effectiveness in disrupting maze performance in rats shows only fair rank order correlation with human effects (228). Since no single behavioural parameter in animals correlates reliably with hallucinogenic effect in man (19), the only recourse is to attempt an objectivization of the subjective effects in man. Shulgin *et al.* (200, 202) therefore introduced the mescaline unit, defined as the quotient of the effective dose of mescaline divided by the effective dose of the compound under study both calculated as the free base. For effective dose, he took the arithmetic mean of the threshold dose and the maximally effective dose. This measure seems no more arbitrary than any other, and has been widely applied, though as Shulgin *et al.* (203) have written, mescaline units values should not be considered accurate to closer than 25%.

Many derivatives of lysergic acid (LA) have been synthesized and assayed for psychotomimetic potency. It is of interest, but as yet unexplained, that only *d*-isomers are active. Examination of table 1 reveals that (a) if the amine side chains of LSD are lengthened, shortened or removed, potency is reduced or abolished; (b) if they are restrained, as in *d*-lysergic acid morpholide, potency is somewhat reduced; and (c) only some substitutions on the ring structure are permissible: 2-bromlysergic acid diethylamide (BOL) is inactive, but *d*-1-acetyl-LSD is as potent as LSD itself. Gessner (100) has reported that BOL acutely antagonizes the behavioural effects of LSD in the mouse, which raises the possibility of BOL-LSD antagonism at some central nervous system synapses.

From Snyder's laboratory has come the suggestion that psychotomimetic potency depends in part upon the degree to which a molecule tends to mimic the ring structure of LSD (210–212). In figure 1 this argument is illustrated for chano-

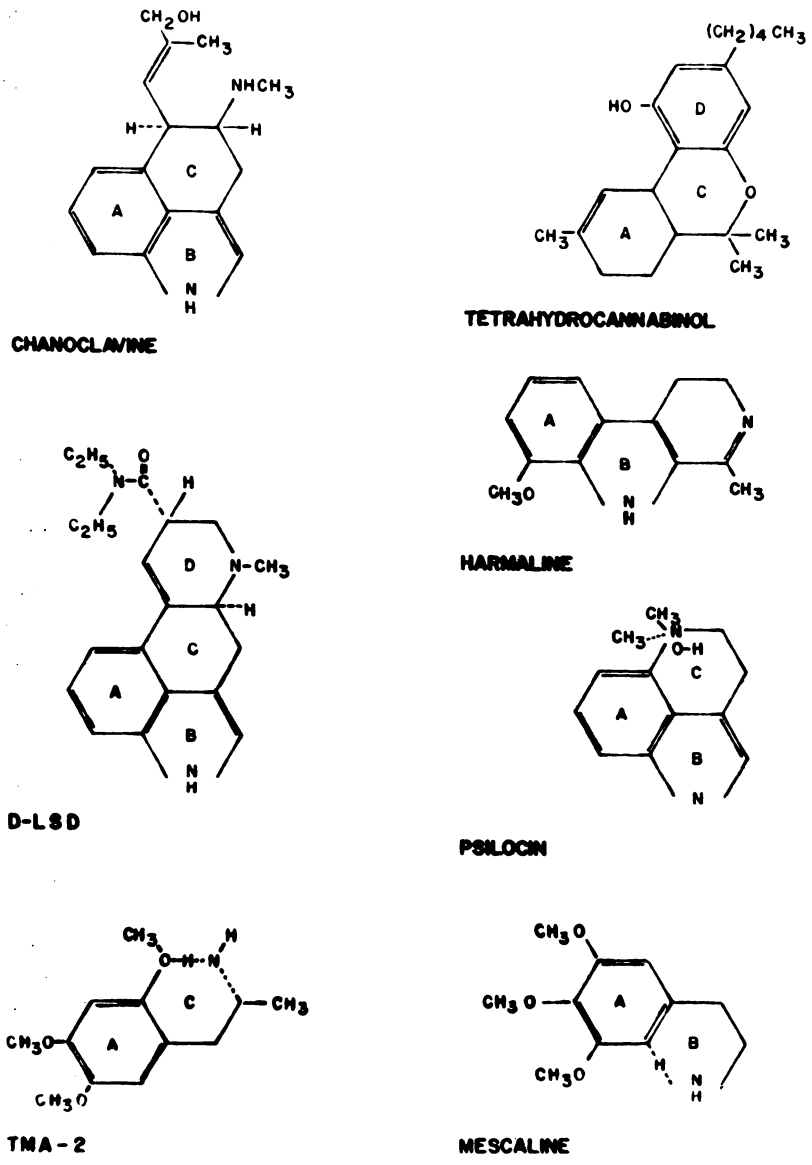


FIG. 1. Schematic diagrams of the structures of some hallucinogens, illustrating similarities to the ring structure of lysergic acid diethylamide (*d*-LSD). See text.

clavine, THC, harmaline, psilocin, a-trimethoxyamphetamine (TMA) and mescaline. Of all these, THC shows the least resemblance to LSD. In view of the scarcity of pharmacological data on THC (72, 158), and in view of the apparent absence of cross tolerance with LSD, the extension of the Snyder theory to cannabinols would be premature. In the case of indolealkylamines, methoxylated amphetamines and mescaline, the theory requires intramolecular hydrogen bind-

ing, which on the calculations of Snyder and Richelson (211) is physically possible. Although speculations regarding the morphology of receptors are presently beyond direct experimental test, it is worth noting that the Snyder theory postulates a rather large and complex receptor area with which an agonist molecule may interact at several sites. Smythies *et al.* (206) devised an ingenious indirect test of this concept: 1-methyl-1,2,5,6-tetrahydropyridine-N,N-diethylcarboxamide (THPC), the D ring of LSD, reduced the behavioural effects of LSD in rats but increased the effects of mescaline, which on the Snyder theory would occupy that receptor area corresponding to the A and B rings of LSD. By itself, THPC had no behavioural effects. This suggests that activity at A and B ring sites is related directly to psychotomimetic potency, while D ring site occupation either modulates reactivity or affects molecular approach to the A-B receptor site.

Some tryptamine hallucinogens may be shown to approximate the A, B and C rings of LSD. Snyder and Merrill (210) have calculated that psilocin (fig. 1), the most potent of this group, is most likely to assume a stable A-B-C configuration by intramolecular hydrogen binding. Bufotenine and 6-hydroxy-dimethyltryptamine, which are weak or inactive, are unlikely to form ring C; dimethyltryptamine (DMT) has some activity and yet is similarly unlikely to take the A-B-C configuration. An appropriate break in the pyridine nucleus of harmaline yields a tryptamine type of molecule, but again C ring formation appears unlikely. Ibogaine, which may be hallucinogenic (190, 226), resembles harmaline but has two cross-linked rings attached to the B ring, and does not fit easily into this scheme. Therefore, structural resemblance to LSD only partly accounts for the potencies of tryptamine-related psychotomimetics. Szara and Hearst (220) found that 6-hydroxylation of diethyltryptamine (DET) greatly increased potency (table 2), and that in man given DET, effects were more marked when subjects excreted large amounts of 6-hydroxy-DET in urine, which suggests that 6-hydroxylation may confer extra potency. Yet Snyder and Richelson (211) reported that 6-hydroxylation facilitated conjugation and excretion, and explained the impotency of 6-hydroxy-DMT on this basis. Gessner (99) has reported that bufotenine becomes active if it is O-acetylated, and suggests that the variable here is passage through the blood-brain barrier. Finally, methoxylation at position 4 or 5 confers added potency (101, see table 2); Gessner (100) has explained this also on the basis of increased lipid solubility.

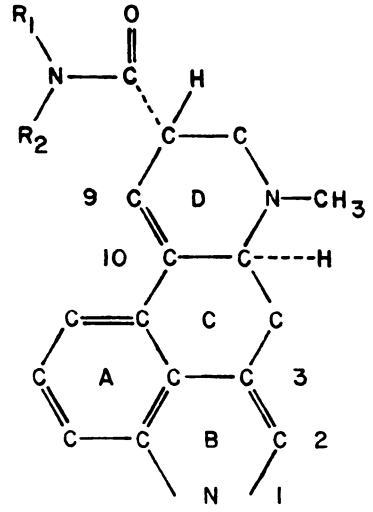
Shown in table 3 are a number of phenylethylamine-derivative psychotomimetics. Whether one characterizes them as derivatives of amphetamine or of mescaline is a matter of taste: 3,4,5-TMA is simply *alpha*-methyl mescaline. Addition of the *alpha*-methyl group doubles potency. The three carbon side chain length appears to be optimal, probably because of its resistance to monoamine oxidase (MAO); further lengthening, as in *alpha*-ethyl-mescaline, reduces potency (203).

Applying the Snyder theory to these compounds (212), we find that B ring formation requires hydrogen atoms at ring positions 2 and 6, or a hydrogen at position 2 with a methoxy radical at 6 sterically hindered by another methoxy group at 5. In the latter case, the 5-methoxy group hinders rotation of the 6-

methoxy radical into a plane favourable for a C ring formation. C ring formation requires a methoxy group at 2 or 6; a methylenedioxy group at 3–4 (as in 2-methoxy-3,4-methylenedioxyamphetamine (MMDA-3a)) offers less steric hindrance to a 2-methoxy radical than a methoxy group at 3 (as in 2,3,4-TMA).

TABLE 1

d-Lysergic acid diethylamide variants



Compound	R_1	R_2	1	2	Potency Taking $HP_{LSD} = 100$*
LSD†	C_2H_5	C_2H_5	H	H	100‡
DAM	CH_3	CH_3	H	H	10
LA	H	H	H	H	0
LSM	C_2H_4—O—C_2H_4		H	H	60
d-LA pyrrolidide	—$(CH_2)_4$—		H	H	10
LAE	C_2H_5	H	H	H	10
d-1-Acetyl LA diethylamide	C_2H_5	C_2H_5	CH_3CO	H	100
MLD	C_2H_5	C_2H_5	CH_3	H	70
d-1-Methoxy LA diethylamide	C_2H_5	C_2H_5	OCH_3	H	10
BOL	C_2H_5	C_2H_5		Br	0
UML	C_4H_8OH	H	CH_3	H	0

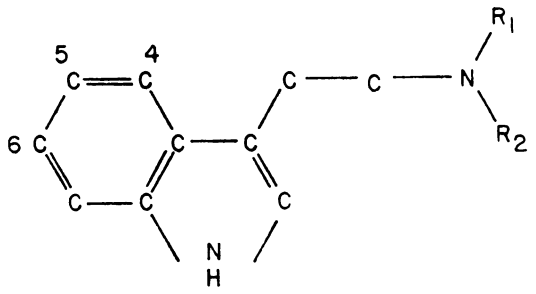
* Estimates from Snyder and Richelson (211).

† The abbreviations used in this table are: LA, *d*-lysergic acid amide; LSD, *d*-lysergic acid diethylamide; DAM, *d*-lysergic acid dimethylamide; LSM, *d*-lysergic acid morpholide; LAE, *d*-lysergic acid monoethylamide; MLD, *d*-1-methyl-lysergic acid diethylamide; BOL, *d*-2-bromlysergic acid diethylamide; UML, 1-methyl-lysergic acid butanolamide.

‡ 100 Snyder-Richelson units = 3700 mescaline units.

TABLE 2

Tryptamine derivatives



Compound	4	5	6	R_1 and R_2	Psychotomimetic Potency
					MU
5-HT*	H	OH	H	H	0
Bufotenine	H	OH	H	CH_3	?†
6-Hydroxy-DMT	H	H	OH	CH_3	0
Psilocin	OH	H	H	CH_3	31
4-Hydroxy-DET	OH	H	H	C_2H_5	+‡
6-Hydroxy-DET	H	H	OH	C_2H_5	25
DMT	H	H	H	CH_3	4
DET	H	H	H	C_2H_5	>4§
DPT	H	H	H	C_3H_7	+
5-Methoxytryptamine	H	OCH_3	H	H	+
5-Methoxy-DMT	H	OCH_3	H	CH_3	>31, <LSD¶

* The abbreviations used in this table are: 5-HT, 5-hydroxytryptamine; DMT, dimethyltryptamine; DET, diethyltryptamine; DPT, dipropyltryptamine.

† See text.

‡ + = Active, but potency not yet quantified.

§ See ref. 220.

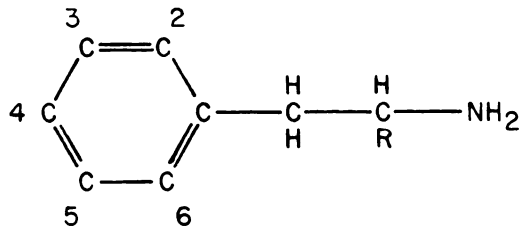
¶ See ref. 100.

Examination of table 3 reveals that compounds which can form ring C have higher potencies than those which are likely to form ring B.

Nonetheless, there remains, within the B ring and C ring forming groups of compounds, considerable variation in potency unexplained by these considerations. Following a suggestion of Szent-Gygorgi *et al.* (129), Snyder and Merrill (210) calculated *pi* charge, free valence, superdelocalizability, and energy of the highest occupied molecular orbital (HOMO energy) for several psychotomimetics and related compounds (table 4). They found that high potency correlated with high HOMO energy and not with the other parameters. Since HOMO energy is a relative measure of electron-donating capacity, they concluded that drug-receptor interaction for these compounds involves electron donation. In LSD reduction of the double bond at C_9–C_{10} (giving dihydro-LSD) or bromine substitution at C_2 (giving BOL) would markedly diminish HOMO energy. Kang and Green (128) have recently calculated HOMO energy (E_H) for a larger group of methoxylated amphetamines (table 3). We have plotted their data (fig. 2) as log

TABLE 3

Amphetamine and phenylethylamine derivatives



Compound	2	3	4	5	6	R	Psychotomimetic Potency	Possible LSD Ring	E_H
							MU		
Amphetamine	H	H	H	H	H	CH_3	0	B	0.5885
Mescaline	H	OCH_3	OCH_3	OCH_3	H	H	1	B	0.5226
TMA (3,4,5)*	H	OCH_3	OCH_3	OCH_3	H	CH_3	2	B	0.5218
α-ethylmescaline	H	OCH_3	OCH_3	OCH_3	H	C_2H_5	<2	B	
TMA-4 (2,3,5)	OCH_3	OCH_3	H	OCH_3	H	CH_3	4	B	0.5026
TMA-3 (2,3,4)	OCH_3	OCH_3	OCH_3	H	H	CH_3	<2	B	0.5274
MMDA-3a	OCH_3	O—CH_2—O		H	H	CH_3	10	C	
TMA-6 (2,4,6)	OCH_3	H	OCH_3	H	OCH_3	CH_3	10	C	0.5217
TMA-5 (2,3,6)	OCH_3	OCH_3	H	H	OCH_3	CH_3	13	C	0.5112
TMA-2 (2,4,5)	OCH_3	H	OCH_3	OCH_3	H	CH_3	17	C	0.5001
2,5-DMA	OCH_3	H	H	OCH_3	H	CH_3	8	C	0.5012
2,4-DMA	OCH_3	H	OCH_3	H	H	CH_3	5	C	0.5194
3,4-DMA	H	OCH_3	OCH_3	H	H	CH_3	<1	B	0.5238
4-MA (PMA)	H	H	OCH_3	H	H	CH_3	5	B	0.5262
3,4-MDA	H	O—CH_2—O		H	H	CH_3	3	B	
DOM	OCH_3	H	CH_3	OCH_3	H	CH_3	80	C	0.4929

* The abbreviations used in this table are: TMA, trimethoxyamphetamine; MMDA, 2-Methyl-3,4-methylenedioxyamphetamine; DMA, dimethoxyamphetamine; PMA, *para*-methoxyamphetamine; MDA, methylenedioxyamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine

potency (in mescaline units) against HOMO energy.* Of the six trimethoxyamphetamines, the three capable of C ring formation are more potent than the three capable of B ring formation; within each of these groups, log potency is linearly related to E_H. The three dimethoxyamphetamines for which data are available show a similar hallucinogenic potency (HP) to HOMO energy relation.

Thus potency is determined partly by electron-donating capacity, and partly by preferred ring formation. For example, 3,4,5-TMA, a B ring former, and 2,4,6-TMA, a C ring former, have identical E_H values; 2,4,6-TMA is five times more

* Expressed in negative energy units, such that high HOMO energy is indicated by a low E_H value.

TABLE 4

Energy calculations for diverse psychotomimetics (from Snyder and Merrill, ref. 210)

Compound	Psychotomimetic Potency (M.U.)	E_H*	Largest Negative *Pi* Charge†	Superdelocalizability‡
	MU			
LSD§	3700	0.2180	?	?
Psilocin	31	0.4603	−0.0770	−1.53
6-OH-DET	25	0.4700	−0.0800	−1.53
TMA-2	17	0.4810	−0.0854	+1.14
Bufotenine	?	0.5147	−0.0840	−1.43
DMT, DET	4	0.5164	−0.0810	−1.43
TMA	2.2	0.5357	−0.1040	+1.23
TMA-3	2	0.5696	−0.0716	+1.05
Mescaline	1	0.5357	−0.1040	+1.23

* E_H, energy of the highest occupied molecular orbital (HOMO), is a relative measure of the ability of an electron in the HOMO of a compound to be transferred to an acceptor molecule, expressed in negative energy (*beta*) units. Thus LSD is a better electron donor than TMA-3.

† *Pi* charge represents the net positive or negative charge measured at each atom of a molecule.

‡ Superdelocalizability is a measure, in reciprocal *beta* units, of the ability of each atom in a molecule to form a weak *pi* bond with an incoming attacking reagent when the *pi* system is unperturbed.

§ The abbreviations used in this table are: LSD, *d*-lysergic acid diethylamide; OH, hydroxy; DET, diethyltryptamine; TMA, trimethoxyamphetamine; DMT, dimethyltryptamine.

potent. Yet the theory does not account for all potency variations: 4-methoxyamphetamine, probably a B ring former, has less HOMO energy than 2,4-dimethoxyamphetamine, a C ring former, but the two compounds are equally potent. Another linear series can be formed with trimethoxyamphetamines having methoxy groups at positions 2 and 5. Methoxylation at position 3 (2,3,5-TMA) obstructs C ring formation (but not B) and increases HOMO energy; potency is diminished. On the other hand, methoxylation at position 4 (2,4,5-TMA) allows C ring formation but lowers HOMO energy; potency is increased. Replacement of the 4-methoxy radical by a methyl group (giving 2,5-dimethoxy-4-methylamphetamine, DOM) further lowers E_H; potency is increased by a full order of magnitude. Again an exception occurs, however, with 4-methoxylation of 2,3,5-TMA, forming 2,3,4,5-tetramethoxyamphetamine: potency is increased, although HOMO energy is lower.

Thus psychotomimetic potency is related to HOMO energy within some families of compounds characterized by (a) the type of ring which might be formed by intramolecular hydrogen binding, (b) the number and nature of substitutions on the A ring, and (c) side-chain composition. That is, potency depends upon at least four molecular parameters whose various contributions to drug-receptor interaction and rate of metabolic degradation are presently unclear. We appear to be far away from a general theory of structure-activity relations for the psychotomimetics.

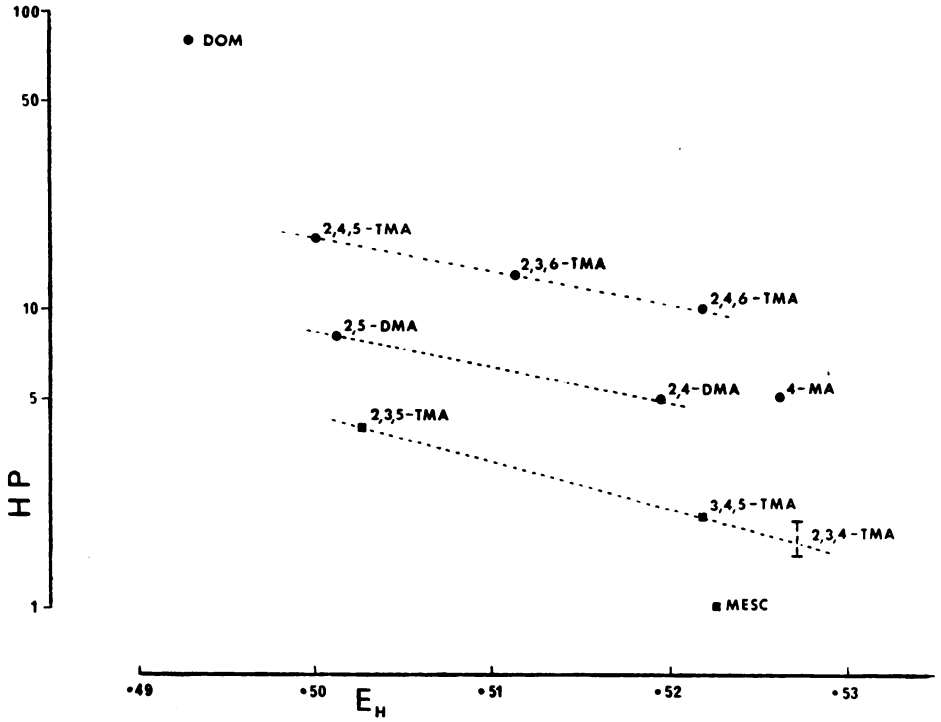


FIG. 2. A plot of some of the molecular orbital calculations of Kang and Green (128), relating HOMO energy (E_H) to hallucinogenic potency (HP) in man, in mescaline units. Log_{10} HP is linearly related to E_H for three C-ring forming trimethoxyamphetamines and for three B-ring forming dimethoxyamphetamines (see table 3).

No cholinergic compound has been shown to possess psychotomimetic properties. However, some—for example, muscimol (196), and arecholine (49)—have deliriant effects. Neither these compounds nor the anticholinergic deliriants can be shown to resemble LSD structurally. Abood and Biel (1, 2) examined the properties of several piperidyl glycolates, and found a correlation between anticholinergic and hallucinogenic potency. Gershon (98) found tetrahydroaminoacridine, an anticholinesterase, to be an antidote to Ditran, but not to LSD or phencyclidine; however, other anticholinesterases—for example, physostigime and di-isopropylfluorophosphate—were only slightly, if at all, antidotal. These are slender grounds for hypothesizing a mechanism of action.

In summary, structure-activity studies have succeeded in relating some molecular parameters to psychotomimetic potency, but the picture is far from complete. An implication of the Snyder theory is that the lysergic acid derivatives, indolealkylamines and phenylethylamines act upon the same central receptors. Although there is an early indication that this may be true for some cells in the raphe nuclei (see below), the hypothesis is largely untested. Indeed, it is untestable until there is identification of the receptors which are crucially related to psychotomimetic potency. Beyond this, until there is some direct knowledge

of receptor morphology, it will be difficult to identify with any certainty those aspects of a molecule's structure which confer activity. The interaction of a molecule with a receptor site is complex, involving not only structural moulding, but van der Waal's forces, electron donation, hydrogen bonding and perhaps chemical reaction (23, 24, 48, 166). The development of a technique for isolating certain kinds of receptors would allow a closer study of some of these factors, but this method also is subject to what is perhaps a crucial limitation: separation of the receptor from the cell removes the possibility of observing the effect. In addition, binding and reaction at the receptor site are likely to depend upon relations between a site and adjacent structures, and upon the configuration of the approach space to the receptor *in situ* (24, 166). There remains a need for pharmacological studies of intact cells in intact systems.

The Arousing Effect of Psychotomimetics

In Hofmann's original description of the effects of LSD ingestion (111, 216), the experience of anxiety was prominent. Early clinical studies of the drug's effects mentioned many components of what is now thought of as "arousal" (146, 186, 214): small increases in heart rate and blood pressure, salivation, and lacrimation, mydriasis, hyper-reflexia, increased reactivity to outside stimuli, and leucocytosis (28, 34, 75, 84, 215). Similarly, animal behavioural studies with LSD have described increased alertness (38, 136), excitement and aggressiveness (204, 221), and stimulus reactivity (35). Whether all of these peripheral autonomic effects are of central origin is unknown, but Forrer and Goldner (84) found that topical conjunctival LSD application caused less mydriasis than did systemic administration of moderate doses (0.5–6 μg/kg). Peripheral autonomic flooding of a very similar kind has been reported for psilocybin (152), diethyl- and dipropyltryptamine (219), DOM (209), adrenochrome (110), other methoxyamphetamines (207), mescaline and psilocin (112, 152, 204, 235) and several LSD-congeners (113).

The first attempt to study central neurophysiological aspects of this arousal was made by Forrer and Goldner (84), who found that in schizophrenic subjects no discernible electroencephalographic (EEG) changes were produced by up to 6 μg/kg of LSD. But within 2 years Delay *et al.* (66) in rabbits, Bradley *et al.* in man (75) and cats (35), and Rinkel *et al.* (178) and Gastaut *et al.* (97) in man reported that LSD caused *alpha* frequencies to accelerate, or abolished them altogether in which case the record was dominated by low voltage fast rhythms typical of "arousal" or alertness. This finding has been replicated for the human EEG (121) and for the electrocorticogram (ECoG) of the anesthetized (36, 78, 114, 160), and waking (76, 80, 193) cat, and the curarized (177) and waking (66, 168) rabbit. LSD also abolishes barbiturate spindles (78, 90). Similar ECoG-activating effects have been reported in some or all of these species with methamphetamine, amphetamine, *para*-methoxyamphetamine (PMA), TMA-2, DOM and dimethoxyamphetamine (DMA) (94); mescaline (54, 160); adrenochrome (160) *d*-l-methyl-LSD, and *d*-LA-monoethylamide, -dimethylamide, and -morpholide (195); bufotenine (160, 194); and psilocybin, psilocin, and dimethyl-

tryptamine (45). In contrast, anticholinergic deliriants induce slow and spindle activity in the EEG (122).

Killam and Killam (138), however, found that LSD (50–100 μg/kg) had no consistent effects upon the ECoG of the curarized cat. Chatelier and Borenstein in the macacque (53), and Lindsley *et al.* (150) and Adey *et al.* in the cat (4, 6) reported that relatively large amounts of LSD (150–200 μg/kg respectively) caused high-voltage slow ECoG rhythms. Brawley and Pos (unpublished experiments) have found that LSD (50 μg/kg) induces coherent 1–5 Hz rhythms in the thalamus and cortex of resting cats. A clue to the origin of these discrepancies lies in Evart's finding that the administration of 500 μg/kg of LSD to a cat in a quiet environment induced high-voltage slow ECoG rhythms associated with fixed postures and periods of several minutes of complete immobility, all of which upon mild (auditory) stimulation was replaced by low-voltage fast ECoG rhythms and excited, aggressive behaviour. Bradley and Key (38) also found, with much lower doses (5 μg/kg), that the ECoG-activating effect of LSD in the cat depended upon the level of environmental stimulation, and there have been clinical reports that the subjective effects of LSD ingestion were greatly attenuated under conditions of sensory restriction, and accentuated with environmental stimulation (56, 75). In this respect, the ECoG-activating effects of the hallucinogens differ from those of non-hallucinogens such as amphetamine (36), which activates the EEG or ECoG independently of the level of ambient stimulation. Non-psychotomimetic congeners of LSD such as *d*-iso-LSD, *l*-LSD and 1-methyl-LA-butanolamide have no activating effects (195) in the acute rabbit; BOL does in huge doses only.

Bradley and Elkes (36) were the first to notice that one very direct approach to the investigation of these differences lay in observing the ECoG effects of hallucinogens, their non-hallucinogenic congeners, and non-hallucinogenic stimulants in animals with brainstem transections at various levels. In cerveau isolé cats, neither 20 mg/kg of amphetamine nor 300 μg/kg of LSD evoked ECoG "alerting," but in encephale isolé preparations, the activating effect of amphetamine was unimpaired while the effects of LSD were still blocked. Results presented by Takagi *et al.* (222) were somewhat different: acute encephalé isolé cats developed low-voltage fast ECoG rhythms for about 1 hr after 50 μg/kg intravenously or 5 μg/kg intraventricularly. Cats sectioned at the T_3 level showed variable ECoG effects from 25 to 125 μg/kg LSD, but with pentothal, LSD (50 μg/kg) always reduced ECoG amplitude. In the rabbit (195) the activating effect of LSD was abolished by precollicular and postcollicular section, but was preserved in the encephale isolé; the activating effects of *d*-1-methyl-LSD, *d*-LA-dimethylamide and *d*-LA-morpholide were blocked by section at or above the level of the first cervical vertebra (C-1); *d*-LA-monoethylamide, which is not psychotomimetic, activated the ECoG after postcollicular section, but not after precollicular section. Similarly, *p*-methoxyamphetamine, TMA-2, and DOM activated the ECoG only if the section had been caudal to the medulla, whereas 3,4-dimethoxyamphetamine (HP <1) retained some alerting potency with pretrigeminal section (94). Again in the rabbit (194), sections at or above the C-1

level abolished the alerting effect of bufotenine while the similar effect of 5-hydroxytryptophane was preserved if the cut was caudal to the midbrain. Psilocybin, DMT, and psilocin did not activate the ECoG with sections rostral to the medulla, while MP-809, which is not hallucinogenic, did (45).

Psychotomimetics, therefore, have in common that their activating effect on the ECoG depends upon the integrity of connections between the spinal cord and the midbrain. Furthermore, their ECoG-activating potencies are relatively similar to their psychotomimetic potencies. These facts may be taken to support either or both of two hypotheses which have been advanced to explain the action of psychotomimetics: (a) behavioural and electrophysiological effects are due to actions on sensory systems, especially upon sensory collaterals to the reticular core of the spinal cord and brainstem (38, 133, 136), or (b) since the cell bodies of most of the 5-hydroxytryptamine (5-HT)-containing neurons in the central nervous system (outside of the pineal body) are limited to the raphe nuclei of the pons and medulla, and since many of the terminals of the cells are in the medulla, pons and spinal cord (95), the effects of LSD and its active derivatives, and perhaps other psychotomimetics, are due to actions upon a lower brainstem system of 5-HT-containing cells or 5-HT synapses, or both. Much of the work which has been done with LSD bears directly upon these two views.

The Serotonin Hypothesis

As an ergot alkaloid, LSD was regarded at the outset as having a high likelihood of affecting 5-HT synaptic function. Gaddum (96) found LSD to be the most potent of all ergot alkaloids in antagonizing 5-HT effects on the uterus of the rat and perfused ear of the rabbit; Woolley and Shaw (237) replicated Gaddum's result on rat uterus. In guinea pig ileum, Gaddum (96) found that LSD inhibited the D-receptors in smooth muscle but not the morphine-sensitive M-receptors in ganglia. LSD has been found to mimic the excitatory effects of 5-HT on rat uterus (59), on the clam heart (229), and on the formation of 3′,5′-adenosine phosphate in the liver fluke (153); in the latter two instances the potencies of lysergide and its congeners were similar to their psychotomimetic potencies (27, 238). These results prompted investigation of the effects of LSD upon both the metabolism and the pharmacology of 5-HT in the brain.

A. Metabolism

Freedman and Giarman (92) administered LSD to rats and estimated brain 5-HT with clam heart bioassay. LSD (130 μg/kg) alone induced small but reproducible increases in brain 5-HT of the order of 40 to 60 ng/g. This dosage also disrupted food-motivated maze performance (90); the peak effect on brain 5-HT coincided with the termination of measurable behavioural effects (90, 91), which was the time at which the plasma half-life was reached (9, 87, 91). In the rat, *d*-1-acetyl-LSD, psilocybin and mescaline also caused an increase in brain 5-HT, whereas BOL, *d*-1-methyl-LA-butandamide, and methamphetamine (5 mg/kg) did not (85). The coincidence of peak rise in brain 5-HT, plasma half-life of LSD and termination of behavioural effects has been replicated in the rabbit (11) and

the correlation between the termination of subjective effects and plasma half-life has been replicated in man (7, 85, 87). The effect of LSD on brain 5-HT has been confirmed with quantitative chemical assay, and in these studies it has been found that concomitant with the 5-HT rise there occurs a fall in 5-HIAA, indicating diminished 5-HT turnover (69, 70, 86, 182, 225). LSD has no effect on either aromatic acid decarboxylase or MAO (225). DOM, *d*-1-methyl-LSD, mescaline, diethyltryptamine, psilocybin and psilocin also diminish 5-HT turnover; the indolealkylamines have some MAO-inhibitory action, but simple MAO inhibition is not likely the sole basis of their 5-HT effects (93). BOL and 1-LSD have no 5-HT effects. MAO inhibitors, tricyclic anti-depressants, phenothiazines, and butyrophenones also cause increase in brain 5-HT at doses which are not toxic; the 5-HT depletor *para*-chlorophenylalanine (PCPA) evidently provokes hallucinations on daily administration (81); therefore there is no unique relation between brain 5-HT *level* and hallucinations. What psychotomimetic chemicals have in common is that, by some process, they slow 5-HT turnover.

B. Pharmacology

What is this process? One suggestion has been that LSD impedes presynaptic 5-HT release. Freedman and Giarman (92, 102) found that reserpine greatly increased the percentage increase in 5-HT caused by LSD, although inspection of their figure (92) reveals that the absolute rise in 5-HT was not different. Reserpine pretreatment potentiated the behavioural effects of LSD in rats (20) and in man (92). It is known (8, 154) that ^{3}H-5-HT is preferentially accumulated against a concentration gradient in tissue fractions rich in nerve endings, which argues for active transport or binding, or both, in synaptic vesicles and storage granules. That reserpine disrupts this transport or binding, or both, is indicated by the finding of Giarman *et al.* (103) that reserpine depletes more particulate (77%) than supernatant (60%) 5-HT. Likewise, the effect of LSD on brain 5-HT is mostly confined to the particulate fraction (92).

On this evidence presynaptic 5-HT release inhibition as a mode of action is plausible, but not confirmed. The direct data *in vitro* are inconclusive: Goodwin *et al.* (104) found LSD to inhibit 5-HT release from rat brain tissue slices, as did lithium, bromides and barbiturates but Marchbanks *et al.* (154) found that LSD *diminished* 5-HR binding to the cellular fraction rich in synaptosomes. On the other hand, there is now no doubt that LSD does have postsynaptic actions (see below); Anden *et al.* (15) offered a theory of the action of LSD which took this into account. They found that LSD mimicked the effects of 5-HT on spinal reflexes and tremor, and concluded that LSD was stimulating 5-HT receptors. Since LSD markedly reduced the rate of 5-HT depletion due to inhibition of 5-HT synthesis with *alpha*-propyldopacetamide, they proposed an inhibitory feedback mechanism to presynaptic 5-HT neurons to account for the diminished amine turnover. Tonge and Leonard (225) who found that LSD, Ditran, phencyclidine, and mescaline all diminished 5-HT turnover, also took this line of explanation. But there is presently no evidence to support the *ad hoc* supposition of an inhibitory feedback loop from 5-HT sensitive units to 5-HT-containing neurons.

Neither release inhibition nor partial agonism with inhibitory feedback, therefore, is directly supported by the present evidence. But diminished 5-HT turnover must imply some inhibition of 5-HT-containing neurons. Now many of the cell bodies of these units lie in the raphe nuclei of the medulla, pons and lower midbrain (95). Aghajanian *et al.* (9) recorded the firing rates of neurons in dorsal and median raphe nuclei of the rat while injecting LSD systemically (25–50 μg/kg). Of 17, 15 were inhibited, with recovery usually taking about 5 min. Later (10, 83) they showed that mescaline, DOM, and DMT had similar effects while atropine, phencyclidine, scopolamine and chlorpromazine (CPZ) did not. BOL and methysergide showed less than 5% of the inhibitory potency of LSD (13). More recently, this laboratory reported (12) that MAO inhibitors injected systemically also depressed raphe units, but with a much slower time course; also, a slight increase in firing rate was sometimes seen before inhibition began. PCPA pretreatment abolished these effects, but did not abolish the raphe-inhibitory action of psychotomimetics. Of course it is possible that MAO inhibitors have postsynaptic actions, but it seems unlikely that PCPA would block them. An alternative explanation is that because 5-HT synthesis is not subject to end-product inhibition (181), MAO inhibition will lead to an absolute 5-HT increase; since a prominent aspect of the central action of 5-HT is tachyphylaxis (124, 179), it is possible that MAO inhibition depresses raphe firing rates by increasing the amount of 5-HT released into the synaptic cleft, thus inducing tachyphylaxis. This would explain PCPA abolition of the effect. The effect of psychotomimetics on raphe neurons however, appears to be postsynaptic; Couch (61) has recently demonstrated that raphe units are themselves excited by iontophoretically applied 5-HT, and that iontophoretically applied LSD simultaneously blocks raphe excitations caused both by 5-HT and by stimulation of the midbrain reticular formation.

All this indicates that raphe neurons receive excitatory serotoninergic input, and that psychotomimetics slow 5-HT turnover by inhibiting these neurons *in the raphe via* a direct postsynaptic action. Iontophoretic dose-response studies might disclose whether this effect involves competitive antagonism for 5-HT receptors, although tachyphylaxis will render quantification difficult. There remains the question of the function of the raphe nuclei, and the physiological significance of their inhibition. The finding (20a) that both PCPA pretreatment and raphe lesions lower the dosage threshold for LSD-induced performance decrements on behavioural tasks such as bar-pressing for reward, indicates that raphe inhibition has some relation to the behaviour-disrupting capacities of psychotomimetics; we shall return later to a consideration of the nature of this relation.

The Sensory System Hypothesis

The brainstem transection experiments are compatible with a second theory of psychotomimetic drug action, framed in physiological rather than pharmacological terms and originally due to Bradley (37, 39, 40). On this view, it is held that LSD and other psychotomimetics increase the response of the brainstem reticular formation to input from sensory collaterals, but that they have little or no direct effect on reticulocortical transmission. The Bradley theory has gained wide cur-

rency because (a) it conforms with the contemporary preoccupation with the reticular formation amongst neurophysiologists and behavioural scientists; (b) there is a certain correspondence between the specifications of the theory and some subjective effects in persons who ingest hallucinogens, for example, increased stimulus sensitivity and awareness; and (c) it conforms to some objective data.

The Bradley theory may be regarded as a special case of a more general approach to the problem of the pharmacology of hallucinations, which we shall call the sensory system hypothesis. The simplest statement of this view is that psychotomimetic drugs exert their effects primarily through direct actions upon specific or non-specific, or both, sensory systems. On this assumption, a vast effort has gone into the investigation of the sensory system effects of these chemicals.

Actions on Specific Systems

A. The retina and optic tract

Do blind persons hallucinate with LSD? Forrer and Goldner (84) gave 1 μg/kg of LSD to one blind subject with methyl alcohol blindness and another with a gunshot wound to the optic chiasm; neither had visual hallucinations. (One admitted olfactory hallucinations and became paranoid, while the other became euphoric.) But a year later, Alema (14) reported a patient with bilateral enucleation whose visual hallucinations were worsened by LSD. Krill *et al.* (143) found that LSD (1 μg/kg) produced visual hallucinations in 13 of 16 blind subjects who ordinarily had spontaneous visual experiences (SVE), but none in four subjects who had denied SVE. LSD induced non-visual hallucinations more frequently in blind than in sighted subjects. Several of the subjects who visually hallucinated with LSD had been enucleated or showed marked phthisis bulbae, so Krill *et al.* concluded that a functioning retina is not necessary for LSD-induced visual hallucinations. Nevertheless, two of their three SVE-positive subjects who did *not* visually hallucinate with LSD showed electroretinographic (ERG) b-wave amplitude changes after LSD administration, as do sighted subjects (144, 180); thus LSD appears to have an independent effect on the retina.

These effects on the retina have been the object of several studies. LSD increases the absolute visual threshold (46, 50, 144). Apter and Pfeiffer (22) reported that LSD (100 μg/kg) caused "spontaneous" ERG potentials of a frequency of 0.5 to 1.5 Hz, and similar potentials in optic nerve and visual cortex of the cat. Severance of the optic nerves abolished the potentials central to the section. LSD also increased the "on" and "off" ERG responses to light. Yet Jacobsen and Gestring (123) found that optic nerve section abolished LSD-induced ERG potentials. We know of no published attempts to replicate these findings or to resolve the discrepancy.

Since the electroretinogram gives somewhat ambiguous information regarding retinal functioning (47), workers have preferred to record directly from optic nerve and tract. With coarse electrodes which recorded mass unit activity, Schwartz and Cheney (191) found that 100 to 250 μg/kg of LSD given intraperitoneally increased the levels of tonic discharge in the optic tract and lateral

geniculate nucleus in 18 of 20 cats, with a latency of about 5 min and a duration of about 50 min. They claimed that LSD caused no increase in eye movements, but did find that without LSD, head movements, flickering lights and patterned light also caused increases in the tonic discharge. Ten of these cats were anaesthetized with phenobarbital and eight were awake. Bishop *et al.* (32) found that close arterial injection of large amounts of LSD in the anaesthetized cat had no effect on latency, amplitude, or duration of the grossly recorded optic tract response to diffuse light stimuli. Recording from the lateral geniculate nucleus, Evarts *et al.* (76–79) and Bishop *et al.* (32) agreed that the presynaptic (optic tract) component of the light response was unaffected by LSD; nor did LSD in large doses (50 μg/kg) affect antidromic conduction. Mouriz-Garcia *et al.* (163) took the more refined approach of recording single unit activity in the optic tract of the paralyzed cat: 14 of 21 cells increased their firing rates by up to 300% after 50 to 100 μg/kg of LSD given intravenously, while 7 of 21 cells manifested a reduced tonic discharge, though never by more than 40%. Latency was 1 to 3 min and duration 50 min or more. Brawley and Bradshaw (unpublished experiments) found with a similar technique and smaller doses of LSD (5–15 μg/kg) in the dark-adapted cat, either paralyzed or anaesthetized lightly, that only 1 of 22 optic tract fibres manifested an increase in spontaneous firing rate, with a latency of 55 sec and a duration of 5 min. Amphetamine was used as a control. The one cell which increased its firing rate after LSD did so, and nearly identically, after amphetamine 0.1 mg (fig. 3). In all cases, there was a transient rise in blood pressure with amphetamine, and little or none with LSD. In no case did either LSD or amphetamine alter retinal on or off responses to unpatterned light.

On this evidence, it appears that LSD has effects on the retinal dark discharge, but (a) it is not clear that the effect is peculiar to LSD, or to psychotomimetics in general; (b) so far, there is little evidence that responses to light are affected; (c) the locus of the effect is unknown; and (d) the impact of the increased dark discharge on the reticular core needs investigation. Bilateral enucleation slows the firing rates of reticular formation (RF) cells in waking and sleeping cats (130),

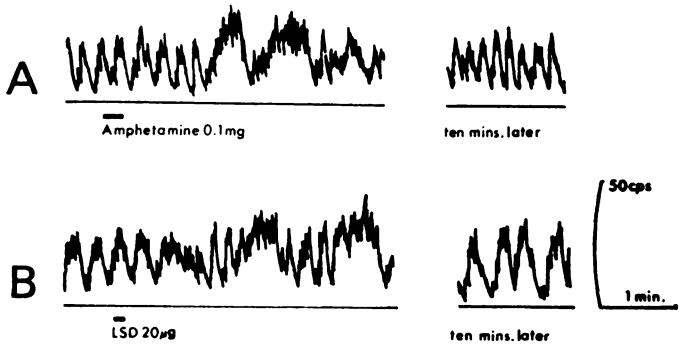


FIG. 3. Effects of *d*-amphetamine and LSD upon the dark discharge rate of retinal ganglion cell in a cat, recorded in the optic tract (see text). Note the similarity of LSD and amphetamine effects. Discharge rate was monitored on a ratemeter which received input from the oscilloscope *via* a pulse-height discriminator.

and acutely leads to a 10 to 15-sec period of EEG "silence" (55), from which it has been concluded that the retinal dark discharge plays a role in maintaining tonic activity in the RF. The influence of the dark discharge, however, upon RF stimulus *reactivity* is not known. A finding that psychotomimetic-induced augmentation of the retinal dark discharge increases RF responses to visual and other inputs would directly support the Bradley theory; the experiment has not been done. Finally, there remains the possibility that LSD-induced increases in ganglion cell tonic discharge rates are mediated by centrifugal, reticuloretinal pathways (105, 169, 174, 213).

B. Lateral geniculate nucleus

Evarts and his co-workers (77–79) were the first to study the effects of LSD on lateral geniculate function. As little as 10 μg/kg *via* intracarotid injection in the barbiturate-anaesthetized cat diminished the postsynaptic response to optic nerve shocks, and 30 μg/kg caused a response decrement of 80%. Bufotenine had a parallel but weaker effect. Intravenously, 160 μg/kg produced a 60% response decrement. In the decerebrate preparation, two or three times more LSD was required to give equivalent effects, which suggested to these workers that barbiturates increase neuronal susceptibility to LSD. In the chronic waking cat, 1 mg/kg was required to yield the effect given by 30 μg/kg in the barbiturate-anaesthetized cat. Evarts (76) noted that with 1 mg/kg, cats and monkeys appeared behaviourally blind. Also with this dosage, the cortical response to optic tract stimulation was reduced while the response to lateral geniculate nucleus stimulation was unaffected, and the presynaptic component of the lateral geniculate response to optic tract shocks was likewise unchanged. This localized the effect to lateral geniculate cells. Was LSD competitively antagonizing postsynaptic responses to retinal input? Evarts and Marshall (79) observed that a conditioning tetanus had the same effect on lateral geniculate response to paired stimuli as did 160 μg/kg of LSD if the stimulus pair fell within 170 msec of the tetanus. Repetitive stimuli (at 2 msec intervals) abolished the LSD effect (77). But competitive antagonism cannot be inferred on this evidence alone, since any inhibitory effect on lateral geniculate cells by LSD could yield the same results. Both Evarts (76) and the Killams (138) reported that LSD did not alter the recovery cycle in the thalamus. Bishop *et al.* (32) confirmed that LSD (5–100 μg intracarotidally) attenuated the postsynaptic lateral geniculate response to optic tract shocks, that the cerveau isolé was less sensitive to the drug, and that intravenous doses had to be about 15 times higher for equivalent effects. Ninety percent recovery from an 80 μg dose required a mean of 22 min. A dose of 200 to 250 μg had no effect on antidromic optic tract conduction. In their hands (30, 31), a 10-min optic tract tetanus overcame the LSD effect completely, from which they, like Evarts, concluded that LSD was competitively antagonizing optic tract-lateral geniculate synapses.

With the advent of microelectrophoresis, it became possible to test this suggestion more rigorously. Curtis and Davis (62, 63) observed in the barbiturate-anaesthetized cat that LSD diminished or blocked lateral geniculate cell responses to optic tract stimulation, but so did dopamine, noradrenaline, adrenaline, BOL,

tryptamine, and 5-HT, none of which are psychotomimetic. There was no effect on antidromic excitability, or on spike height. Phillis *et al.* (167) confirmed these results: iontophoretic dopamine, noradrenaline, 5-HT and LSD depressed lateral geniculate cell responses to optic tract stimulation and to iontophoretic acetylcholine and glutamate. With regard to the serotonin hypothesis, it is of interest that neither worker found LSD to antagonize 5-HT effects.

The nature of the action of psychotomimetics on the lateral geniculate nucleus is thus unclear; all that can be said is that LSD shares with a number of non-hallucinogenic substances the property of depressing spontaneous and evoked firing of lateral geniculate neurons. The theory advanced in the 1950's by Evarts (76) and by Bishop *et al.* (31, 32), that LSD antagonizes the action of the physiological transmitter at optic tract-lateral geniculate synapses, is not tenable until the transmitter has been identified. With respect to this question, the present position is as follows. Acetylcholine (ACh) excites most spontaneously active lateral geniculate cells, and this action is non-specifically opposed by 5-HT (64). Dihydro-*beta*-erythroidine antagonizes ACh excitations, but not excitations caused by optic tract stimulation. All geniculocortical cells are excited by ACh and inhibited by 5-HT (188). Most acidic amino acids excite thalamic units, and neutral amino acids depress them (62). In the medial geniculate nucleus, ACh also excites all geniculocortical units (224). Thus, though ACh might be the transmitter at retinogeniculate synapses, confirmation awaits the finding of an ACh antagonist which will simultaneously block physiological and iontophoretic excitations. The finding that 5-HT, LSD and several other biogenic amines inhibit ACh-driven and physiological lateral geniculate cell firing requires further investigation.

C. Other sensory systems

Oddly enough, no experiments on the effects of deliriants or psychotomimetics on levels of spontaneous discharge in other sensory systems have been published, even though non-visual hallucinations are not uncommonly produced by hallucinogen ingestion. Direct studies of the impact of LSD on sensory function have been confined to visual and auditory pathways, the latter studies having been done by Bradley's group in Birmingham. Bradley and Hance (37) found that the attenuation of evoked potentials recorded in the cochlear nucleus of the cat due to stimulation of the olivo-cochlear bundle was not affected by 1 to 30 μg/kg of LSD, nor by 5 to 10 μg/kg of CPZ, and thus ruled out the possibility that this centrifugal control mechanism was disturbed by the drug. Key (133) found that 5 to 10 μg/kg of LSD given intravenously did not alter the effects of midbrain stimulation on cochlear evoked potentials. He also found that in a quiet environment, 5 to 10 μg/kg of LSD caused an amplification of potentials in the dorsal cochlear nucleus evoked by tonal pips (2500 Hz, 45 db above the human threshold), but in an open laboratory, the only effect of LSD was an increase in the variability or response amplitude; this suggested that LSD's effect was non-specific (presumably reticular) rather than upon the auditory system.

Action on Non-specific Systems

A. Brainstem reticular formation

We have summarized the evidence that the ECoG-activating effects of many psychotomimetics depend upon the integrity of connections between the telencephalon and some structure or structures caudal to the midbrain. It is not clear, however, how activating and psychotomimetic effects are related. On the Bradley theory, psychotomimetics cause the brainstem reticular formation to become more reactive to collateral sensory input, so that the activating effect of psychotomimetics depends upon the level of environmental stimulation. This predicts that psychotomimetics will not independently and directly raise the level of activity in the reticular formation. The data are contradictory. Monnier and Krupp (160) claimed that LSD, mescaline, adrenochrome, cocaine and bufotenine all increased the ECoG-activation effect of reticular stimulation, and Apter (21) reported that in the cat, LSD—like picrotoxin and pentylenetetrazol—would restart respirations in a few seconds after a "lethal" dose (40 mg/kg) of pentobarbital. Rinaldi and Himwich (177) found that 1 to 5 μg/kg of LSD given intravenously decreased the threshold for ECoG activation due to midbrain stimulation in the curarized rabbit, yet Killam and Killam (138), Bradley and Key (39), and Key (134) found LSD to have no such effects in anaesthetized and curarized cats. Takagi *et al.* (222) had the same result in encephale isolé cats. In these latter four studies, doses of LSD were an order of magnitude greater than those used by Rinaldi and Himwich (177).

The data on activation due to peripheral stimulation are not much clearer. Elkes *et al.* (75) found that LSD increased the *alpha*-blocking potency of light flashes in man. Key (134) found that LSD lowered the threshold for ECoG activation by stimulation of the auditory pathway, but only if stimuli were delivered caudal to the infeior colliculus. This experiment encounters the difficulty that stimuli to a specific thalamic nucleus generally evoke only a local cortical response, the augmenting response (67, 68, 162), and less often a general activation, especially if care is taken to hold stimulus voltages below the level at which the voltage field directly invades neighbouring intrinsic thalamic nuclei, and in fact Key found that the threshold for ECoG activation was substantially higher in medial geniculate than it was in the brainstem, with and without LSD. Killam and Killam (138) were unable to show that LSD affected the threshold for ECoG activation by sciatic nerve stimulation. Morillo *et al.* (161) found that in curarized cats, 25 to 50 μg/kg of LSD had no effect on midbrain reticular responses to sciatic nerve stimulation; higher doses actually depressed responses slightly. It is not known whether midbrain reticular reactivity to visual input is directly increased by LSD, or if the increase in EEG effects of photic stimuli with LSD is due to thalamic or cortical effects, or both (see below).

Since the phenothiazines are clinical antagonists of the psychotomimetics, it might seem reasonable to expect that their pharmacology would be the inverse of that of the psychotomimetics. At the level of the single cell, this is not the case: the phenothiazines show *alpha*-adrenergic blocking, atropinic and local anaesthetic

effects, and some effects on 5-HT metabolism (49, 71). They also appear to inhibit noradrenaline uptake. LSD does slightly increase noradrenaline turnover (147), but shows no adrenergic potency in brainstem (42) or cortex (124, 179). It has some local anaesthetic potency in the spinal cord (62), and appears to have no specific cholinergic or anticholinergic potency, although some deliriants and psychotomimetics have been reported to suppress Renshaw cell discharge (65). At the physiological level, however, there are several ways in which the actions of the phenothiazines and psychotomimetics oppose each other. Killam and Killam (137, 139) found that CPZ increased brainstem reticular "filtering" of sensory stimuli; Bradley and Key (39) reported that 2 to 4 mg/kg of CPZ raised the threshold for ECoG activation by auditory stimulation; Key (134) replicated this finding, adding the condition that stimuli had to be delivered caudal to the colliculi. He also found (135) that LSD opposed, and CPZ facilitated habituation to repeated stimuli. Bradley and Wolstencroft (41) found that CPZ given intravenously depressed brainstem reticular polysensory units. With iontophoretic CPZ, 76 of 110 cells were inhibited and just two were excited. Only cells sensitive to noradrenaline were affected: 54 of 64 units inhibited by noradrenaline were also inhibited by CPZ, while CPZ antagonism of noradrenaline excitations could be demonstrated in 10 of 11 cells. Thus we have that CPZ depresses the reactivity of brainstem reticular polysensory cells, directly raises the threshold for ECoG activation, and enhances habituation, while LSD has no marked direct effects on brainstem polysensory units, lowers the threshold for ECoG activation in some circumstances, and opposes habituation.

LSD's effects at the brainstem level are largely confined to 5-HT-sensitive neurons. In an earlier study, Bradley and Wolstencroft (41) found that 31% of brainstem units were non-specifically depressed by iontophoretically applied LSD; there was no evidence of either noradrenaline or 5-HT antagonism. But more recently (34), Bradley's group has reported that without barbiturate anaesthesia (which masks 5-HT excitations) iontophoretically applied LSD antagonized 5-HT excitations in the bulbar reticular formation; in addition, LSD antagonized glutamate excitations of neurons which could be excited by 5-HT. In this study, units near the midline were avoided; therefore, the data indicate the presence of 5-HT-sensitive neurons outside the raphe. Now if the serotoninergic neurons of the lower brainstem constitute an inhibitory system with respect to the ascending reticular activating system of Magoun, LSD's anti-5-HT action in this region provides at least a partial explanation for its ECoG-activating properties. Indeed there is evidence that a lower brainstem, serotoninergic system does have inhibitory impact both rostrally and caudally, and that LSD opposes its action. Administration of 5-HT *via* the vertebral artery in cats causes ECoG synchrony, as does topical application of 5-HT to the area postrema, where some raphe units appear to terminate (95); topical application of LSD to the area postrema blocks both these effects (140). Fourth ventricle administration of either a barbiturate or a local anesthetic abolishes ECoG synchrony and induces activation. Raphe destruction (126, 127) and chronic PCPA administration (141) abolish sleep. Tetanic raphe stimulation abolishes habitua-

tion to repeated stimuli, although stimulation of neighbouring brainstem areas does not, and PCPA or reserpine pretreatment blocks this effect; since, as noted above, 5-HT-sensitive neurons show rapid and marked tachyphylaxis, it may be that the effect of tetanic raphe stimulation after a few seconds is inhibitory, the loss of habituation being due to exhaustion of an inhibitory system. Finally, LSD injected into the blood supply of the lumbar spinal cord blocks the inhibitory effect of raphe or brainstem stimulation upon monosynaptic spinal reflexes (55a).

This evidence suggests the following hypothesis. LSD causes ECoG activation and opposes habituation by its depressant effect upon that serotoninergic, inhibitory neuronal system, many of whose cell bodies lie in the raphe nuclei, and the depressant effect consists in antagonism of 5-HT-mediated excitations both on raphe neurons themselves, and on other 5-HT-sensitive neurons in the lower brainstem. Whether other psychotomimetics act similarly remains to be discovered with the application of topical pharmacological methods to these areas. Also, it would be appropriate to challenge this hypothesis by attempting a replication of the results of Koella and Czicman (140) on the area postrema, both in cats and in primates. It will be observed that confirmation of this hypothesis by further experiments would constitute a vindication of the early speculations of Gaddum (96) and Woolley and Shaw (237), but not *in toto*, since it has yet to be demonstrated that serotoninergic neurons of the lower brainstem have any functional impact upon more rostral sensory systems. In this regard it would be useful to examine the effects of raphe and medullary-reticular stimulation upon the spontaneous and stimulus-evoked firing of lateral geniculate neurons, and if there are effects, to study the influence of pharmacological agents on this system.

B. Actions on "intrinsic" thalamic nuclei

The data implicating effects of LSD upon non-specific thalamic nuclei are not impressive. Purpura (172) reported that 5 to 50 μg/kg of LSD depressed recruiting responses in cats which had been anaesthetized with pentobarbital and were being maintained with succinylcholine. Killam and Killam (138), however, working with curarized cats, found that 100 μg/kg of LSD had very little effect on recruiting responses; and Evarts (76) had the same result in chronic waking cats given 70 to 1000 μg/kg, although with a second 1-mg dose, responses became less regular and of a somewhat lower amplitude. Monnier *et al.* (159) found that the short-latency cortical response to stimulation of intralaminar nuclei was somewhat facilitated, and the longer-latency response was depressed by LSD. Ursin (227) found that 10 to 50 μg/kg of LSD had no effect on the threshold for arousal due to stimulation of intralaminar thalamic nuclei. The interpretation of these experiments is difficult, since changes in thalamic and cortical excitability cannot be discriminated on this technique. Some 5-HT neurons terminate in the intrinsic nuclei (95), but the function of these synapses is unknown.

Effects of Hallucinogens on Averaged Evoked Responses

Averaged evoked responses constitute probably the least satisfactory way of investigating sensory function, since (a) normative waveforms vary enormously

amongst species, individuals, and laboratories and (b) the physiological interpretation of averaged evoked response components is anything but straightforward. For example, it is arbitrary to assume that an increase in the "primary" or "specific" wave amplitude denotes improved transmission in afferent pathways, since the state of cortical-surface dendritic biassing (and therefore reactivity), which is unknown in this experimental procedure, will affect averaged evoked response amplitude. Therefore, averaged evoked response data must be interpreted with the greatest caution.

Purpura (171–173) was the first to study the effects of LSD on evoked responses. In pentobarbital-anaesthetized cats, 2 to 30 μg/kg suppressed the "secondary discharge" following sciatic nerve stimulation. In cats paralyzed with succinylcholine, the same dosage increased the amplitude of short-latency visual and auditory evoked response waves (171). On the grounds that this averaged evoked response component had a 40 msec latency and showed a phase reversal at a cortical depth of about 2 mm he identified it as the primary (specific) component. Higher doses (60 μg/kg) differentially suppressed the primary auditory evoked response. He concluded that LSD inhibited axo-dendritic synapses (non-specific afferents), and facilitated transmission at axo-somatic synapses (specific afferents). Since it has since been demonstrated that specific sensory cortical afferents terminate largely at axo-dendritic synapses (125) and that axo-somatic synapses are likely inhibitory and probably subserve intracortical transmission (57, 106, 125), this view is no longer tenable. Some of his findings, however, have been replicated. Koella and Wells (142) found that relatively low doses of LSD facilitated primary visual and auditory evoked responses in the unanesthetized rabbit, and Smythies *et al.* (208) found that 5 to 10 mg/kg of mescaline had the same effect on primary visual evoked responses in the same preparation. Roth (185) found that 1 μg/kg of LSD, 5 to 25 mg/kg of mescaline and small amounts of amphetamine reduced the amplitude of the secondary response to sciatic nerve stimulation. Shagass (197) reported that LSD diminished the somato-sensory averaged evoked response in man, and Chapman and Walter (51) had the same result for the human visual evoked response. In the macacque, Chatelier and Borenstein (52) found that large doses of LSD (100 μg/kg) reduced auditory and somesthetic evoked responses, primary and secondary, but increased the long-latency visual evoked response. Winters (233) found that many drugs, not all of them hallucinogenic, caused either increases in evoked response amplitude associated with diminished brain stem reticular massed unit activity or decreases in evoked response amplitude with heightened massed reticular unit activity.

The other evoked response parameter which has been studied is post-evoked response "ringing"—the near-sinusoidal wave train of *alpha* frequency which often follows the visual evoked response. Shagass (197) claimed that LSD increased ringing, but Rodin and Luby (180) and Chapman and Walter (51) reported the opposite. If ringing is subserved by the same physiological arrangements which give rise to the *alpha* rhythm (16), its presence or absence will depend critically on the level of cortical and thalamic excitability, which in turn is related to the level of "arousal". Furthermore, the relation is not monotonic,

since the propensity to *alpha* rhythmicity is small at both high and low arousal levels, and largest at some intermediate level of relaxed wakefulness (16). Thus drug dose is important in determining the degree of ringing, since the level of activation is dose-dependent. The experimental situation may also affect the level of arousal of subjects. Given all these indeterminacies, we conclude that averaged evoked response data offer little insight into the mode of action of psychotomimetics.

Actions on the Limbic System

Studies of the effects of psychotomimetics on limbic function have differed from sensory system and pharmacological investigations in the important respect that they have been related to no particular hypothesis of drug action. Rather, they have been undertaken on the plausible expectation that, since psychotomimetics induce affective, attentional and perceptual changes, and since the temporal lobe, hippocampal formation, amygdala, hypothalamus, cingulate gyrus and connecting pathways are implicated in such functions, then these drugs might exert some direct effect on these structures. Indeed there has been one report (25) that the behavioural effects of LSD are not seen after temporal lobectomy in monkeys.

Schwarz *et al.* (192) found that LSD and mescaline induced 2 to 7 Hz rhythms in temporal EEG leads. Passouant *et al.* (165) found that in chronic cats, 50 to 200 μg/kg of LSD induced long bursts of 3 to 4 Hz sinusoidal activity in the hypothalamus (including mammillary bodies) and septal area, roughly synchronous with similar activity in neocortex. Hippocampal activity was not markedly changed, nor were the threshold and duration of after-discharges. Fairchild *et al.* (80) found, also in chronic cats, that mescaline, TMA, methylenedioxyamphetamine (MDA), MMDA, and DMA induced 3 to 10 Hz rhythms in amygdala, supraoptic nucleus of hypothalamus, dorsomedial nucleus of thalamus, caudate, midbrain reticular formation and hippocampus, while the ECoG was low-voltage fast, but amphetamine caused low-voltage fast activity in cortical and subcortical areas alike. Eidelberg *et al.* (73, 74) found that the 40 Hz amygdaloid rhythm of the waking cat was abolished or suppressed by LSD, mescaline, and phencyclidine, but also by the non-hallucinogens *alpha*-methyl-*m*-tyrosine, pheniprazine, 5-HTP and reserpine; *alpha*-methyl-*m*-tyrosine, LSD, 5-HTP and pheniprazine also suppressed the 50 Hz olfactory bulb rhythm. Most worker's findings in the hippocampus have been at variance with those of Passouant *et al.* (165). Adey *et al.* (4) found that 25 μg/kg of LSD induced 4 to 5 Hz hippocampal "seizures" which became continuous at a dose of 100 μg/kg; above this latter dose, performance in a learned task ceased. At a dose of 25 μg/kg, the 4 to 5 Hz activity was seen also in neocortex (area 17), rostral midbrain and n. ventralis anterior of thalamus if the animal's surroundings were dark and quiet. This extends the findings of Evarts and Bradley's group in neocortex, and suggests that the dependence of the effects of hallucinogens on sensory input involves limbic structures as well as brainstem reticular and sensory pathways. Earlier, they had found (5) that phencyclidine likewise abolished

learned discrimination performance, while suppressing *theta* rhythms and inducing epileptiform rhythms in the hippocampus. In a later investigation (6), Adey's group found that hippocampal *theta* rhythm was amplified in cell layer Ca 1 for 4 to 7 days after one 80 μg/kg dose of LSD. Ursin (227) found that 10 to 50 μg/kg of LSD in the chronic cat had no effect on the threshold for arousal caused by stimulation of temporal cortex, amygdala, septal area, or caudate nucleus. Revzin and Armstrong (176) reported that 100 to 250 μg/kg of LSD increased the hippocampal response to septal and contralateral hippocampal stimulation; larger doses seemed to block all hippocampal responses. Stumpf *et al.* (218) found in the rabbit that while eserine (0.25 mg/kg) increased the amplitude of hippocampal *theta* rhythm, LSD caused the replacement of hippocampal *theta* by low-voltage fast rhythms, even though septal "B" units (which fire in synchrony with hippocampal *theta* rhythm and appear to drive it) showed no changes in firing pattern.

Because the hippocampus, amygdala, and septal area have been implicated in attentional, arousal, memorial, and affective functions, it may well be that these changes have close relation to the subjective and behavioural effects of hallucinogens. But before the relation can be investigated further, much more needs to be learned of the physiological and pharmacological aspects of normal function in these structures.

Actions on Neocortex

Changes in the EEG or ECoG, or in the cortical reactivity to subcortical or sensory stimulation, cannot be taken as evidence of direct effects on cortical function, since in such experiments changes in specific or non-specific afferent input to the cortex, originating peripheral to the cortex, cannot be ruled out. It seems to have been assumed that studies of inter- or intrahemispheric transmission might eliminate some of these imponderables; thus Marrazzi (154, 155, 156), Evarts (76) and Takagi *et al.* (222) reported that LSD blocked or suppressed the transcallosal response (TCR) and Marrazzi concluded from this that LSD directly inhibits cortical cells at axo-dendritic synapses. It is not clear, however, that suppression of the TCR necessarily implies direct cortical inhibition; LSD and other hallucinogens induce a low-voltage fast ECoG pattern, which is known to be associated with increased firing rates in most cortical cells and which must be accompanied by changes in dendritic "tuning," so an equally tenable explanation of TCR suppression is that, on the law of initial values, cortical cells under these conditions have a smaller response range upward. At the level of the single cell the position would be this: with a relatively synchronous ECoG, many cells fire in burst patterns with relatively long interburst intervals, during which one may record prolonged IPSP's; a strong afferent volley to a population of cells firing in this pattern will cause rather high amplitude EPSPs and field potentials (thus, evoked responses reach their highest amplitude in slow wave sleep); whereas a similar volley to more rapidly firing cells will evoke smaller field potentials (evoked potentials in rapid eye movement (REM) sleep, where the ECoG is low-voltage fast, are low-amplitude). Now if LSD had a direct

excitatory effect on some cortical cells, one would see smaller TCR potentials; therefore TCR suppression is consistent with cortical inhibition, excitation, or with wholly indirect effects.

It appears that we shall have to depend upon single unit studies with localized drug application for an understanding of the direct effects on cortical cells. The data are scarce. Krnjevic and Phillis (145) found that LSD and methysergide depressed glutamate-driven firing for up to 40 sec, but also had excitant properties with application of larger amounts; antidromic excitation was not affected. Psilocin, bufotenine, DMT and DET had quick depressant actions. Yohimbine and harmine were practically without effect. Roberts and Straughan (179) found that iontophoretically applied LSD, methysergide, and BOL tended to (non-specifically) depress firing rate and amplitude, but in addition antagonized 5-HT excitations (not 5-HT depressions), while glutamate and ACh excitations were not affected. LSD was a more potent and consistent 5-HT antagonist (7/11 cells) than either BOL or methysergide. Since Krnjevic's animals had been anaesthetized with barbiturates, which abolish 5-HT excitations in cortex (124, 179), he would not have had an opportunity to see these effects. The results of Roberts and Straughan may be interpreted as indicating specific antagonism by LSD of 5-HT at an excitatory cortical receptor, but the results need replication; and dose-response studies, although made difficult by 5-HT tachyphylaxis, need to be done. In any event, these results comprise the only available hard evidence relating to the presence and nature of a direct LSD effect upon cortical cells.

General Summary

From the foregoing there emerge a small number of reasonably well confirmed observations: (a) on the basis of similarity (though not identicality) of subjective and behavioural effects, cross-tolerance, and some structure-activity considerations, psychotomimetics form a pharmacological class of hallucinogenic materials whose common properties deserve further investigation; (b) there exist important differences in both chemical structure and in behavioral effects amongst these compounds, and there is little likelihood of finding a simple, unitary explanation of their mechanism of action; (c) a second and reasonably distinct class of hallucinogenic chemicals is formed by those anticholinergic substances which induce delirious states; (d) psychotomimetics appear to exert effects principally upon aminergic systems of the brain, whereas deliriants appear to act principally upon cholinergic systems; (e) the degree to which a molecule can assume the configuration of all or part of the structure of LSD partially predicts hallucinogenic potency in the case of psychotomimetics, but not in the case of deliriants; (f) investigation of some submolecular properties of psychotomimetics yields the conclusion that electron donation plays an important part in drug-receptor interaction for these substances; (g) no known psychotomimetic fails to diminish 5-HT turnover in brain; (h) psychotomimetics activate the ECoG and cause behavioural alerting if and only if connections between medulla and midbrain are intact; in this respect they differ from all known non-hallucinogenic activators; (i) several psychotomimetics depress the firing rates of some raphe

neurons; in the case of LSD, the mechanism appears to be 5-HT antagonism; (j) LSD antagonizes 5-HT excitations in some raphe, reticular, and cortical neurons; no antagonism of 5-HT depressions has been observed; data on other psychotomimetics in this respect is lacking; (k) LSD has non-specific depressant effects on neurons at many locations in the brain; (l) LSD increases the spontaneous firing rates of retinal ganglion cells; (m) LSD has an inhibitory effect upon transmission through the lateral geniculate nucleus, but so do several non-hallucinogenic substances.

In the context of the yawning abyss of ignorance and speculation which separates biochemical and behavioural data, the contribution of these few observations on psychotomimetics may be regarded as vanishingly small. Clearly, neither the serotonin nor the sensory system hypothesis gives a full account of the effects of these drugs. A few reasonably sure facts can, however, provide empirical bases for further investigation. For example, the odd and until recently unsuspected fact that neurons in the raphe nuclei both contain 5-HT and can be excited by 5-HT applied to their membranes allows an explanation of the slowed 5-HT turnover induced by psychotomimetics in terms of the postsynaptic, anti-5-HT effects of these drugs. Since there is very good evidence that the raphe nuclei form part of an inhibitory lower brainstem system, and since separation of the lower brainstem from the midbrain abolishes the ECoG-activating effects of psychotomimetics, it is very likely that both the ECoG-activating and the 5-HT turnover effects of psychotomimetics result from lower brainstem, anti-5-HT actions. The relation of these lower brainstem actions, however, to perceptual and cognitive functions—that is, the relation between the serotonin and sensory system theories—remains hypothetical until it is shown that the lower brainstem effects have an impact upon more rostral sensory systems. There appear to be no very strong reasons for assuming that these raphe and reticular effects are sufficient in themselves for the induction of psychotic functioning, and therefore it is to be hoped that the demonstrated effects of psychotomimetics on diencephalic and telencephalic structures—for example the retina, the lateral geniculate nucleus, the cortex, the hippocampus and amygdala—will attract further investigation. An explanation of psychotomimetic action must in the end relate drug effects to events at specified neural sites. In this regard, the application of recent improvements in histochemical technique for the study of more discrete brain areas ought to be rewarding. Microelectrophoresis, which allows under some circumstances reasonably quantitative dose-response studies of the impact of a drug on the physiological functioning of single neurons, can profitably be combined in experimental design with techniques of sensory physiology; in this regard the experiments of Satinsky (188) and Tebecis (224) are models, although dose-response studies were not attempted. Also, it would be useful to have dose-response data on more global effects of psychotomimetics, for example on temperature, activity, autonomic activity, and ECoG rhythms. Finally, it must be remembered that many of the general statements on psychotomimetic drug actions rest upon data regarding a single drug, lysergic acid diethylamide, and that the hypothesis implicit in these generalizations require confirmation

from experiments with the methoxylated amphetamines, indolealkylamines, and other lysergic acid derivatives before they can be admitted to the pharmacological archives.

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