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BIOCHEMICAL ASPECTS OF THE ACTIONS OF PSYCHOTOMIMETIC DRUGS[1]

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I. INTRODUCTORY REMARKS: SCOPE AND DEFINITIONS

To the fundamental question of how biochemical change can become behaviorally manifest we have few clues and no clear answers. The most satisfactory causal links between neurochemistry and behavior are purely and solely hypothetical. Few biologists, of course, would be attracted to the notion that no relationship exists, and, in fact, there are numerous examples of established interrelationships, *e.g.*, drug-induced alteration of behavioral patterns. Yet we are not only ignorant of basic mechanisms of control in neurons (36), but also faced with the fact that the link of a biochemical mechanism to any physiologic effect (and certainly to a behavioral effect) entails causal sequences at a wide range of levels, from the enzymatic to the psychosocial. The distances between biochemical mechanisms and the particular substrata for perception and behavior—in a rigorous sense—are appallingly vast. Such considerations are consequential for current studies, largely in the realm of interpretation and formulation of research strategies. In this respect there are two basic sources of uncertainty: 1) implicit notions about what does or does not comprise a satisfactory causal linkage in biology; 2) differing evaluations of our ignorance about brain and behavior which lead to disagreements about whether a set of findings does or does not contain usable information.

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With reference to causal linkages, multiple rather than single factors, correlations rather than simple cause–effect relationships generally apply in contemporary biology. With precise control not only of biochemical and physiological variables, but also of behavioral patterns (39, 162), time-locked sequences of each order of events can be achieved and meaningful relationships established. But what aspect of biochemistry is to be correlated with a specific dimension of behavior? The fact is that neither neurochemistry nor clinical psychiatry can offer any compelling *a priori* reasons to select one or several systems from the universe of biochemical reactions for special study. An approach which focuses on the biochemical sequelae of drug administration provides an initial grip upon the problem and a tangible path to possible basic control mechanisms. The importance of this does not lie in an identity between such drug-induced changes and the operative biochemical pathways in clinical disorders; rather, the clear identification of any relevant neurochemical sequence would complement conjecture with at least one detailed demonstration of how a peculiar and interesting mental state can be achieved.

The generic grouping of drugs as psychotomimetic, while useful for classification, is useless for discrete psychopharmacologic studies. In view of the fact that there are various psychoses, any attempt to correlate one or several biochemical changes globally with "psychosis" (or for that matter with "surgical condition") is patently without reference; this also applies to correlations with the total group of psychotomimetic drugs. There is, in fact, no typical array of pharmacological and behavioral effects in animals which defines a general class of such drugs. This does not mean that different patterns of behavioral effects of different drugs have not been documented in man. It does indicate that when we speak of psychotomimetic effects or actions in animals we actually mean the effects of a particular drug which is psychotomimetic in man and which in animals shows dose-dependent effects on an array of autonomic, neurophysiologic, and behavioral responses.

Psychotomimetic drugs such as D-lysergic acid diethylamide (referred to throughout this paper as LSD and synonymous with LSD-25) reliably and consistently produce periods of altered perception and experience without clouded consciousness or marked physiological changes (131); mental processes that are usually dormant and transient during wakefulness become "locked" into a persistent state (43). The usual boundaries which structure thought and perception become fluid; awareness becomes vivid while control over input is markedly diminished; customary inputs and modes of thought and perception become novel, illusory and portentous; and with the loss of customary controlling anchors, dependence on the surroundings, on prior expectations, or on a mystique for structure and support is enhanced. Psychiatrists recognize these primary changes as a background state out of which a number of secondary psychological states can ensue, depending on motive, capacity and circumstance. This is reflected in the terminology that has grown around these drugs: if symptoms ensue, the term psychotomimetic or psychosomimetic (66a, 162) or psychodysleptic (38a) is used; and if mystical experience, religious conversion, or a

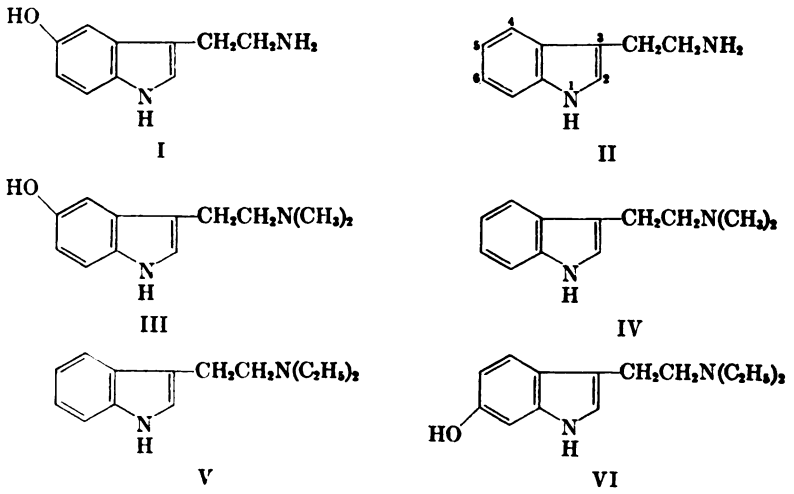
therapeutic change in behavior is stressed, the term psychedelic or mind "manifesting" (120) has been applied. Interestingly, "telepathine" was the suggestive term employed for alkaloids containing harmine and harmaline used for ritual hallucinations by South American tribes (123). There has been wide interest, partly as a basis for speculation about possible mechanisms, in the variety of chemical structures related to LSD, indolealkylamines, and substituted phenethylamines which are isolated as alkaloids from various plants consumed for ritual trance and altered subjective experiences. In this review, we have generally selected as psychotomimetic those drugs for which there are clinical data in man which appear to be at least minimally reliable, and about which there are some data relevant to biochemical mechanisms. The piperidyl glycollates and some anticholinesterase compounds differ from the psychotomimetic indolealkylamines and phenethylamines in time of onset, duration, and patterns of somatic and psychological changes (20). For other compounds, such as bufotenine, and especially adrenochrome, a consensus about the occurrence of psychotomimetic effects is not available (45, 140, 158). The general pharmacology of LSD and congeners (32, 91, 130), mescaline (101) and other substituted phenethylamines (5), and piperidyl glycollates (2) has been reviewed as well as the chemistry, structure, and synthesis of these various compounds (40).

II. ASPECTS OF METABOLISM OF PSYCHOTOMIMETIC SUBSTANCES RELEVANT TO MECHANISMS OF ACTION

Several facts have stimulated investigations of amine metabolism: many amines have potent and striking actions on a number of tissues; they are ubiquitous in nature and present in the human diet; some naturally occurring amines are psychotomimetic; finally, changes in the metabolism of endogenous amines have been associated with patterns of excitement and sedation (26), or with altered mental function (113, 165). Today a whole strategy of research revolves around this central theme. The search may be for endogenous psychotoxins, for the presence in the animal of enzymatic mechanisms for producing psychotoxic metabolites; or a search may be instituted for changes in the balance of endogenous amines or in their normal metabolic pathways or in some related receptor substance. In some cases, it has been possible to link certain metabolites to psychotoxicity.

A. N-Methylation

Axelrod (9) found an enzyme, highly localized in rabbit lung, that catalyzes the N-methylation of serotonin (5-HT, I) and tryptamine (II) to form the psychotomimetic metabolites, bufotenine (III) and N,N-dimethyltryptamine (IV). In addition, this enzyme catalyzes the N-methylation of phenethylamine derivatives, such as mescaline and dopamine. Axelrod speculated that the exacerbation of symptoms observed in schizophrenic patients following L-methionine or L-tryptophan (127) might occur because these amino acids can serve as methyl donor and precursor, respectively, for the psychotomimetic compounds, bufotenine and N,N-dimethyltryptamine.



B. 6-Hydroxylation of indolealkylamines

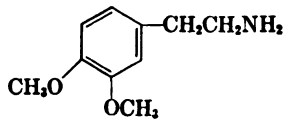
One of the most detailed series of investigations on the relation of metabolites to psychotoxicity embodies the work of Szara (143, 147, 148), which is concerned with the psychotomimetic tryptamine derivatives, particularly N,N-dimethyltryptamine (DMT) and N,N-diethyltryptamine (V, DET). Szara currently holds the view that 6-hydroxylation of N-alkylated tryptamines is an important step in the conversion of the parent molecule to a psychoactive metabolite or a precursor thereof. He was led to this position by the following pieces of evidence:

1) He and Axelrod (148) first described an enzyme in rabbit liver microsomes that could hydroxylate and N-demethylate DMT. From the urine of rats given DMT they isolated a product which they first believed was 7-hydroxyindoleacetic acid, but later showed was 6-hydroxyindoleacetic acid.
2) It was found that the liver microsomal system could 6-hydroxylate the lower homologues of the series DMT, DET and N,N-dipropyltryptamine, all of which were psychotomimetic, while dibutyl- and dihexyltryptamines were not 6-hydroxylated and were behaviorally inactive (147).
3) In rats, mice, and monkeys 6-hydroxy-DET (VI) was more effective in disorganizing behavior than the nonhydroxylated parent compound (150); a two-phase effect with the parent compound and the different time courses of the effects of the parent compound and the active metabolite, monitored by objective measures of behavior, supported this view.
4) The synthetic 6-fluoro-DET was not hydroxylated (indicated by the absence of urinary 6-hydroxyindoleacetic acid), and, while producing autonomic effects, had no apparent psychotomimetic effect in man (96).
5) The intensity of the psychotomimetic effect produced in man by DET paralleled the amount of the 6-hydroxy metabolite excreted in the urine (143).

As convincing as this correlation seems to be, however, it is weakened by the finding that while 6-hydroxylation of DET is a major pathway in the rat, it is a

minor pathway in man, accounting for only 4 to 7% of the administered drug (see 42). Rosenberg *et al.* (128a) have compared DMT, 6-hydroxy DMT and placebo in former opiate addicts. The results of their study suggested that 6-hydroxy DMT is not the metabolite responsible for the psychotomimetic and autonomic effects produced in man by DMT, but factors such as comparative rates of degradation and relative penetration rates into brain were not studied. Szara has continued to search for active metabolites of the 6-hydroxy derivatives (personal communication).

Finally, as mentioned below, Szara believes that the 6-hydroxy metabolite of tryptamine derives its psychotomimetic activity, directly or indirectly, from an action restricted to the hypothalamus, or portions thereof, and related to 5-HT. In support of this hypothesis Szara found that psychotomimetic tryptamine derivatives increase 5-HT levels in the hypothalamus (*vide infra*, 147). Szara has sought to extend this idea to the psychotomimetic action of LSD with the finding that an enzyme in rat (but not guinea pig) liver microsomes could hydroxylate the LSD molecule, probably in the 13-position, which corresponds to the 6-position of the indole nucleus (146). This hydroxylation is inhibited by DET, presumably by competitive antagonism; whether such interactions are evident in cross-tolerance with these compounds is not known.



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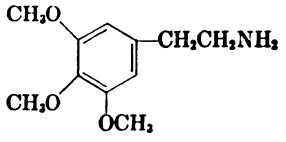

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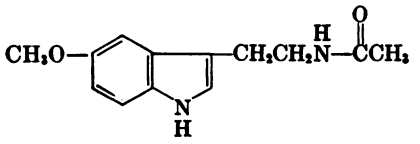
C. O-Methylation

Another interesting series of studies implicating an endogenous psychotomimetic metabolite of an amine has been that carried out by Friedhoff and Van Winkle (62, 63, 64). Engaged in an investigation of the metabolism of catecholamines, these workers discovered the presence in urine of schizophrenic patients of a metabolite identified as 3,4-dimethoxyphenylethylamine (VII), which is closely related to mescaline, 3,4,5-trimethoxyphenylethylamine (VIII, 62). It was later shown that dopamine was probably the source of this metabolite, since tritiated dopamine given to schizophrenic patients appeared as labeled 3,4-dimethoxyphenylacetic acid in the urine (63). Furthermore, Friedhoff and Van Winkle (64) reported that liver obtained from schizophrenic patients by autopsy and biopsy was capable of O-methylating both catechol–hydroxyl groups of dopamine, while liver from normal subjects did not carry out this reaction. The possible significance of these findings was suggested by an observation that 3,4-dimethoxyphenylethylamine had marked effects in animals, similar to those produced by mescaline. The psychotoxicity and relative potency of the dimethoxyarylalkylamines require further investigation (14). Since methionine is probably the methyl donor in the methylations described by Friedhoff and Van Winkle, the observations that methionine causes deterioration in the mental status of schizophrenic patients (31, 127) may be related to these biochemical

phenomena. It should, however, be noted that such symptomatic changes evoked by amino acids appear after pretreatment with an inhibitor of monoamine oxidase, an as yet largely unexplained fact that seriously complicates precise interpretation of the underlying biochemical modes of action.

Even though other investigators have confirmed, by different methods, the presence of 3,4-dimethoxyphenylethylamine in the urine of some schizophrenic patients, but not normal subjects (104, 133), one must view these observations with caution since Takesada *et al.* (152) found 3,4-dimethoxyphenylethylamine in the urine of 50% of their "normal" subjects, as well as in 92% of the schizophrenic patients studied. These investigators suggested that the presence of amine may be contingent on the diet or bacterial flora of the gastrointestinal tract. There is a conflict over methodology in this field, and at least one group of investigators failed to find 3,4-dimethoxyphenylethylamine in the urine of schizophrenic patients (124); they also suggested a dietary source for this amine.

O-Methylation of indolealkylamines produced compounds capable of disrupting trained animal behavior. In a comparative study with a series of compounds related to 5-HT, Gessner *et al.* (69) demonstrated that the O-methyl derivatives were the most active in disorganizing behavior, the most potent compound being the O-methyl derivative of bufotenine (III), which was more potent than bufotenine.



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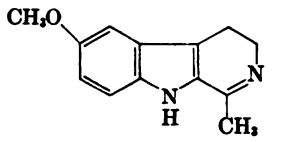

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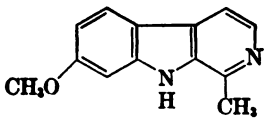

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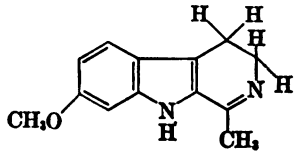

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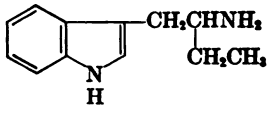

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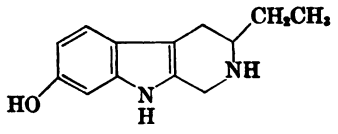

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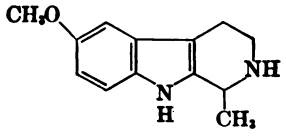


XV

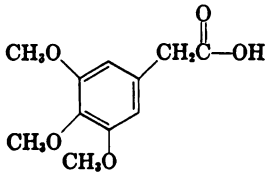
D. Conversion of tryptamines to β-carbolines

Interest in O-methylation was enhanced when melatonin (IX), the skin-lightening hormone, was shown to be the O-methyl derivative of N-acetylserotonin (107); this compound is formed in the pineal body from 5-HT. Melatonin is without psychotomimetic activity in man (Freedman and Lerner, unpublished data); but McIsaac (111) demonstrated that one of the proposed metabolites of melatonin, 10-methoxyharmalan (X), produced autonomic and behavioral changes in animals. This compound is structurally related to the psychotomimetic alkaloids, harmine (XI) and harmaline (XII), and like LSD, is a potent antagonist of serotonin in peripheral systems (111, 112).

Harmine and harmaline may be regarded as tryptamine derivatives in which the side chain has been cyclized into a third ring. Studies of the metabolism of α-methyl- and α-ethyltryptamine (XIII), both of which are inhibitors of monoamine oxidase, have led to the speculation that one of the urinary metabolites in man of the latter drug, which was used for a short period as an antidepressant (etryptamine), had a tetrahydro-β-carboline structure (XIV, mentioned in 85). This compound, the aldosterone-releasing hormone of the pineal body (46), adrenoglomerulotropin (XV), and the suggested metabolite of melatonin (X) are the only β-carbolines thus far isolated from animal tissues. The role they may play in psychotoxic episodes remains to be clarified.

E. Metabolism of mescaline

Within the last several years doubt has been expressed about whether mescaline is directly psychotomimetic or whether this action is effected *via* intermediates in its metabolism (61, 84). This question was raised because of two considerations: 1) the psychotomimetic dose of mescaline is considerably higher than that

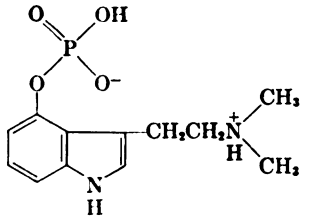


XVI

of other such agents; and 2) the behavioral effects of mescaline do not coincide with the time of its maximum concentration in brain of animals (61). As a matter of fact, in human volunteers the period of maximal behavioral changes elicited by mescaline followed the period of maximal blood level and excretion of the drug by 1 to 2 hours (116). The oxidation of mescaline (VIII) to trimethoxyphenylacetic acid (XVI) by rabbit liver preparation *in vitro* has been recognized since 1938 (16); but even earlier, this acid had been shown to be pharmacologically inert (141). Friedhoff and Goldstein (61), therefore, decided to compare the behavioral effects of the amine itself with its alcoholic and aldehydic intermediates in the formation of the acid. Using appropriate enzyme-blocking agents, these investigators found that either 3,4,5-trimethoxyphenylethanol or 3,4,5-

trimethoxyphenylacetaldehyde formed from mescaline produced effects in rats in much lower doses than are required for mescaline itself. These findings were further validated by the direct administration of synthetic 3,4,5-trimethoxyphenylethanol. Recently, however, Neff *et al.* (117) have reported their failure to find any metabolites of mescaline in cat brain except labeled trimethoxyphenylacetic acid after the administration of C^{14}-mescaline. Maximum concentration of mescaline in the brain was attained between ½ and 2 hours, and this corresponds roughly to the period of maximal intoxication determined by gross observation. Thus the matter of whether mescaline owes its central pharmacology to a metabolite is still unsettled.

Another line of thought started with the suggestion that mescaline might be cyclized *in vivo* to an indolic compound (77). In point of fact, Fischer (48) stated that mescaline is converted *in vivo* to an LSD-like compound which is responsible for the psychotomimetic response. He proposed that the hypothetical LSD-like molecule may be derived from partially demethylated mescaline and a tyramine-like compound, 5-HT, or norepinephrine. Evidence for this biosynthesis in mammalian tissue is not available; but the biosynthesis of LSD in a fungus has been described with the postulation that oxidized 5-hydroxytryptophan is a precursor (83). In addition, Block (18) has claimed that tyramine is an activator of the enzymatic incorporation of mescaline in the mouse liver without affecting the "mescaline oxidase." The implication is that small amounts of a compound structurally similar to LSD might be formed *in vivo* from mescaline and tyramine. Such far-reaching ideas require rigorous experimental proof.



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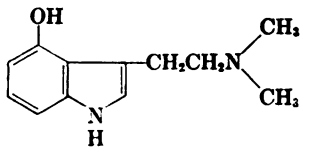


XVIII

F. Metabolism of psilocybin

Similar suggestions concerning intermediation by a metabolite have been made for psilocybin (XVII), the O-phosphorylated ester of psilocin (XVIII). The pharmacological actions of these two psychotomimetic substances are quantitatively and qualitatively so similar (33, 161) that it was assumed that the phosphoric ester group of psilocybin is rapidly hydrolyzed in the body and the active form is psilocin (95). Horita (92) has presented evidence that, in fact, this dephosphorylation takes place at a rapid rate, both *in vitro* and *in vivo*, in the rat. While a considerable amount of psilocin is excreted unchanged, some of this compound is further metabolized, presumably to inactive products (92). Gessner *et al.* (68) studied the relationship of the metabolic fate of psilocybin and its pharmacologic actions in comparison with bufotenine and 5-HT.

G. Metabolism of LSD

Because of the astonishingly high potency and great rapidity of action of LSD (XIX), investigators have readily assumed that its psychotomimetic action is elicited by the unchanged drug. Studies of the fate of this drug, therefore, have not been concerned primarily with the elucidation of psychotoxic metabolites. Thus, Axelrod *et al.* (11) demonstrated an enzyme system in the liver microsomes of the guinea pig which is capable of transforming LSD to 2-oxy-LSD, a product that did not exert LSD-like effects in either cats or human subjects. This metabolite was synthesized by two different techniques by Freter *et al.* (59) and by Troxler and Hofmann (157), but its high lability precluded a satisfactory identification with the metabolite. Boyd (21) reported the presence of two Ehrlich-positive metabolites in rat bile after administration of C^{14}-LSD; it was suggested that these were the β-glucuronides of hydroxy-LSD and hydroxy-iso-LSD (139). Szara (146), studying intermediate metabolites of psychotomimetic drugs (*vide supra*), observed the production from administered LSD of a product, probably 13-hydroxy-LSD, which is formed in the liver of the rat and guinea pig. Since this position on the lysergic acid ring system is equivalent to the 6-position of the indole nucleus, Szara was prompted to suggest the possibility that the already highly active LSD may be transformed into an even more active metabolite. The significance of this metabolic conversion obviously must await the demonstration of 13-hydroxy-LSD or a conjugate in human urine after administration of LSD, and the demonstration of a psychotomimetic action of the metabolite in the human subject.

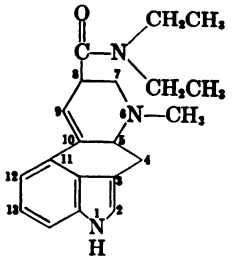
In the rat, unchanged LSD reached a peak in brain within 1.5 minutes and was just detectable 45 minutes after intravenous administration; in this species, the onset of grossly observable autonomic effects and of an array of behavioral effects closely followed the time of peak levels of LSD in brain (*i.e.*, they occurred at 2 to 4 minutes), and recovery from the acute phase of these effects generally occurred at 45 minutes (54, 56). There are effects such as bradycardia and salivation (55) and certain behavioral changes (73, 82) which outlast this acute phase and obviously are not correlated with changing brain level of LSD. Similarly, effects in man are known to last 10 hours or more. Whether these effects are due to the presence of minimal amounts of unchanged drug in brain or plasma, to the elaboration of an active metabolite, or to other processes is not known. In general, far smaller amounts of LSD than are usually found in brain after parenteral administration are necessary to initiate and maintain a response (81), but plasma levels are measurable during and after peak effects in animals (Freedman and Coquet, unpublished data) and in man (4).

III. INTERRELATIONSHIPS WITH BRAIN NEUROHUMORS AND SUGGESTED MECHANISMS OF ACTION

Rigorous assignment of a mechanism of drug action to a particular biochemical system, at best a formidable task, is now impossible in the case of the psychotomimetic agents. The major difficulty lies not in finding enzymes affected by the drug nor even in the more difficult problem of observing neurochemical changes

induced by the drug, but rather in relating such alterations to the drug-induced change in function, *i.e.*, in behavior, perception, and autonomic response. Brodie and his colleagues (29) have argued effectively against the implication of ubiquitous enzyme systems, important in general metabolism, as possible molecular sites of action of psychotropic drugs. In this context, Kety (98) failed to find differences in cerebral oxygen consumption (as a measure of overall energy utilization) between normal conditions and those associated with schizophrenia and LSD-induced psychosis. Nevertheless, numerous studies have been directed toward the effect of psychotomimetic substances on a variety of enzymatic reactions important in the animal economy. These have included, among others, effects on phosphate metabolism (136); oxidative phosphorylation of brain mitochondrial systems (1); turnover of rat brain proteins (126); glucose transport into brain (80); and respiration of stimulated cerebral cortex, *in vitro* (119). These and other similar data cannot at this time be incorporated into any satisfactory hypothesis of psychotomimetic drug action.

It would appear, therefore, that the appropriate biochemical systems to explore are those that are unique to the specialized functions of the brain and nervous system. There is little argument today that the chemical events which take place in the process of synaptic transmission of nerve impulses represent biochemical sequences closely linked to nerve function. Partly as a result of this a great deal of experimental effort has been directed toward synaptically active neurohumors and their associated enzymes in investigations of mechanism of action of neuro- and psychopharmacologic agents.



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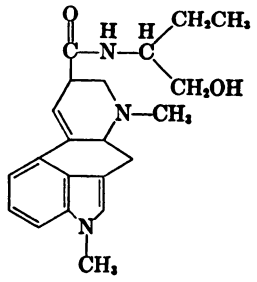

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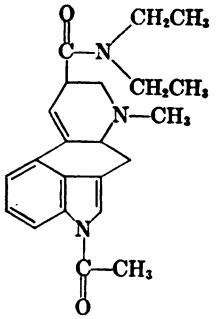

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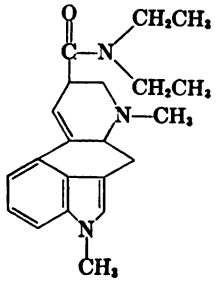


XXII

A. LSD and structurally related compounds

1. LSD–serotonin (5-HT) interrelationship. The well-documented antagonism between LSD and 5-HT in peripheral structures, first observed by Gaddum (65), is responsible for the concentration of experiments on interrelations between LSD and 5-HT in the nervous system. Hypotheses that deficiencies, and later, that excesses of brain 5-HT were related to the autonomic, mental, and behavioral effects of LSD and manifestations of schizophrenia were soon advanced (37, 66, 134, 164). Brodie *et al.* (28), seeking an explanation for an inhibition of the sedative effect of reserpine by LSD, found that LSD caused no depletion of 5-HT in rabbit brain, and did not prevent reserpine-induced reduction of brain 5-HT. These investigators suggested that LSD produced "sympathetic predominance" by blocking the interaction of 5-HT at central receptor sites for the amine. Brodie (25) later was struck by the properties and structure of LSD reminiscent of certain sympathomimetic amines; and Costa (38) stated that the psychotomimetic effect of LSD could not be correlated strictly with its anti-5-HT activity. This latter was borne out by investigations with more potent 5-HT antagonists in the lysergic acid series (34, 90). Indeed, it would appear that Brodie and Costa (26) are no longer sanguine about a role of the monoamines in the action of LSD, since this drug, among a large group of neuropsychopharmacologic agents, was omitted from consideration in their latest views on brain monoamines. In the absence of data on the relationship of LSD with other brain neurohumors, and in view of the complexity of peripheral autonomic changes evoked by LSD, early hypotheses that the drug acts by blocking "serotonergic" fibers (28) or by stimulation of central adrenergic receptors (25) seem hardly tenable. Nevertheless, numerous drug-interaction studies have supported some interaction between 5-HT and LSD in the CNS (22, 108, 153).

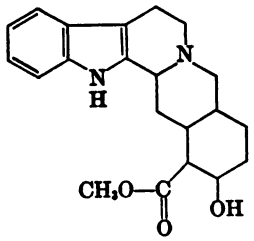
A measurable effect of LSD on brain 5-HT has been reported by Freedman and Giarman (57). These workers had found a small but statistically significant increase in cerebral 5-HT of rats treated with doses of LSD ranging from 130 μg/kg to 1500 μg/kg; the most interesting aspect of this finding was that all of the increase could be accounted for in particle-bound 5-HT. This effect differed from the change in subcellular distribution of 5-HT produced by other agents (such as iproniazid and 5-hydroxytryptophan) that raise brain levels of 5-HT (70). Freedman (49) first observed that if animals had been depleted of their brain 5-HT by pretreatment with reserpine, the LSD-induced rise in 5-HT was more apparent, more persistent, and less variable; he also showed that the increase in 5-HT was not an artifact of the bioassay (clam heart), because it also could be demonstrated by fluorescence spectrometry. Since Freedman and Giarman (57) could not find an influence of LSD on 5-hydroxytryptophan (5-HTP) decarboxylase, on monoamine oxidase (MAO), or on the brain transport system for 5-HTP, they concluded that LSD enhanced the binding of 5-HT by brain granules. This conclusion assumes greater significance when viewed in the light of the following observations:

1) Nonpsychotomimetic analogs of 5-HT (D-2-brom-LSD [BOL] and 1-methyl lysergic acid butanolamid [XX, UML, methysergide]) do not, in equivalent

doses, exert this effect on brain 5-HT; a slight effect of BOL is observed only with doses several times that of LSD (50).

2) Structurally related psychotomimetic analogs of LSD (D-1-acetyl-LSD [XXI, ALD] and D-1-methyl-LSD [XXII, MLD]) which, in equivalent doses, induce some degree of increased binding of 5-HT, show cross-tolerance with LSD in man (3, 93).
3) The onset of the effect of LSD on brain 5-HT corresponds with both the minimal dose and the minimal time required to elicit the onset of behavioral, EEG, and autonomic effects in the rat (56, 57).
4) In the dog brain the increase in 5-HT after 25 to 50 μg of LSD per kg was greatest in the midbrain, medial thalamus, and hypothalamus (57). Quantitatively greater increases were found in rabbit (52) and cat brain stem (Freedman and Coquet, unpublished data).

In addition, alteration of normal rates of binding and release of amines (by pretreatment with MAO inhibitors, reserpine, or tetrabenazine) changed the chemical, autonomic, and behavioral response to LSD (6, 128). Similarly, an altered amine state produced in man by pretreatment with a single dose of reserpine 24 to 48 hours after LSD resulted in prolongation of disturbed consciousness and mydriasis, and the occurrence of numerous extrapyramidal symptoms (51, 52). Pretreatment with reserpine diminished, rather than increased, the uptake of LSD in rat brain, but increased the amount of LSD bound in rat plasma (54). These findings, as well as those of others (7, 127), serve to emphasize that with alteration of mechanisms regulating metabolism of amines, the effects of LSD or amino acids are changed or enhanced.



XXIII

Furthermore, it is of some significance that other psychotomimetic indoleamines (145), yohimbine (XXIII, Freedman and Gaudio, unpublished data), and mescaline (57) produce similar increases in brain 5-HT at times when peak behavioral changes in rats are observed. The work of Szara is particularly interesting, because he found that simple alkylated derivatives of tryptamine which are psychotomimetic in man (such as diethyltryptamine, psilocin, α-methyltryptamine, 6-hydroxydiethyltryptamine) produce a characteristic regional shift in the distribution of 5-HT in rabbit brain, *i.e.*, an increase in the hypothalamus without significant change in the amygdala-hippocampal region; Brodey *et al.* (23) also reported an elevation of 5-HT in rabbit brain after psilocin. Szara did not observe a similar effect with LSD, but the dose he used (50 μg/kg) was below

the threshold dose (130 μg/kg) established by Freedman (52) for evoking changes in 5-HT level in the rabbit brain.

The earlier observation (35) that LSD reduced by more than 50% the urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) may now be interpreted as a result of the increased binding and storage of 5-HT. It is also possible to view the work of Siva Sankar *et al.* (137, 138), in the light of this mechanism. These investigators found that LSD, but not BOL, increased the content of labeled 5-HT in brain after 5-HTP-C^{14} was administered; the increase occurred in all areas of the brain studied except the cerebrum.

Further confirmation of the LSD-induced rise in brain 5-HT is found in the investigations of Glenn and Green (74). These workers, proceeding from the finding that certain steroids inhibit the biotransformation of LSD by liver (15), observed that the 5-HT increase produced by LSD could be prevented by steroids; they believed that this was due to the decreased conversion of LSD to its metabolites.

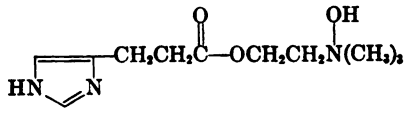
The altered binding of 5-HT produced by LSD might be regarded as the result of a change in the storage granule or in the conformation of the binding substance within the granule. In this regard it is extremely interesting that LSD (in a dose of 1 mg/kg) causes a sudden change in the electrophoretic pattern of liver protein (rat), which is reversible within 24 hours (115). In this context, Keup (105) asserted that the clinical symptomatology produced by LSD, like that of mescaline, was correlated better with protein-bound than with free drug, but these characteristics of the drug or of the clinical state were not well defined. The remarkable persistence of LSD in human plasma found by Aghajanian and Bing (4) might be indicative of a binding of the drug to blood protein, although this has not been measured; but in rat plasma, LSD rapidly dialyzes into buffered isotonic saline (54). By reason of structural analogy it seems likely that the proteins for which LSD would have the greatest affinity might be those architecturally suited to receive amines of the indolealkylamine class. If LSD, by attaching to a secondary site in close proximity to the active receptor site, produces a conformational change in the active receptor so that the rate of association with 5-HT was increased and the rate of dissociation decreased, one might expect a mimicking action of LSD followed by an antagonistic action toward the agonist. Such indeed are the actions seen in peripheral structures. Direct confirmation of this mechanism is not yet available, however. Pertinent in this regard is the finding of Szara (144) that psilocin and psilocybin, the former of which produces an increase in hypothalamic 5-HT (145), are 5-HT-like in some test systems and antagonistic to 5-HT in others. On the other hand, while Bloom *et al.* (19) found that LSD applied by microelectrophoresis to single neurons in the olfactory bulb occasionally mimicked the action of 5-HT by slowing the spontaneous rate of unit discharge, the psychotomimetic drug never blocked responses to 5-HT without interfering with response to norepinephrine. Obviously, interrelationships with the whole family of brain neurohumors must be defined before more meaningful hypotheses can be constructed. The evidence that LSD, in some way, enhances binding of 5-HT in brain is difficult to reconcile, however,

with the finding that this drug *inhibits* binding of 5-HT to so-called "nerve-ending particles" (109).

2. LSD and cholinesterases. The literature on the action of LSD on cholinesterases is voluminous and contradictory. The reason for variability in results is probably related to differences in techniques for measuring such activity, as well as to differences in sources and purity of the enzyme. While most investigators report some degree of inhibition, some have failed to find any effect, and a few have observed some increased activity of the enzyme by LSD.

There seems to be general agreement that LSD and 2-brom-LSD (BOL) are potent inhibitors of serum or nonspecific cholinesterase *in vitro*, whereas they are less potent on true or erythrocytic cholinesterase (60, 154, 166). A concentration of 8×10^{-6} M of BOL or LSD was found necessary to produce 50% inhibition of serum cholinesterase *in vitro* (76). The esterases in brain seemed to follow the same pattern: pseudocholinesterase activity in a number of areas of the human brain was inhibited 60% by 5×10^{-6} M LSD, a concentration which had no effect on true cholinesterase of human brain (154). These investigators found, in addition, that the pseudocholinesterase of human brain was more sensitive to inhibition by LSD than the corresponding enzyme in brains of other animal species studied (rat, guinea pig, chicken, rabbit, and monkey).

A complication was introduced with the finding that BOL, given to human volunteers in doses of from 16 to 256 μg/kg, produced no significant changes in either true or pseudocholinesterase of blood, although mental effects were noted at doses of 64 μg/kg and higher (17). These investigators expressed no surprise that the esterases were not inhibited, since they felt that the concentrations of BOL produced with their doses probably did not approximate the concentrations necessary for esterase inhibition *in vitro*. Another negative finding has been reported by Zsigmond *et al.* (168), who compared the anticholinesterase activity of psilocybin, bufotenine, and 5-HT in human plasma, erythrocytes, and homogenates of gray matter. These workers found no correlation between anticholinesterase activity *in vitro* and the psychotomimetic effects of these compounds. The matter is further complicated by the finding that very small amounts of LSD (6×10^{-9} M) led to 50% increase in the activity of human pseudocholinesterase, *in vitro* (60). Similarly, Tonini (156) found that LSD increased the activity of cholinesterase in rat brain.



XXIV

Tabachnick and Grelis (151) made the interesting observation that only human and mouse pseudocholinesterase (not that of cat, dog, or guinea pig) could hydrolyze dihydromurexine (imidazolepropionylcholine, XXIV), and that LSD inhibited the cholinesterase in only human and mouse sera. Similarly, these investigators found that in brain homogenates LSD was a potent inhibitor of cholinesterase only when the enzyme was capable of hydrolyzing dihydro-

murexine (as it was in mouse and rat brain homogenates). This curious display of specificity might indicate a basis for some of the inconsistency in results in the literature, namely that not enough attention has been paid to substrate–enzyme relationships with respect to inhibition by LSD. Evans (44) found further evidence for unexpected specificity in that, while LSD and BOL were potent inhibitors of serum cholinesterase, neither drug fitted into any of the three groups of inhibitors originally defined by their relative effectiveness as inhibitors of genetically determined typical and a typical human serum cholinesterase in the work of Kalow and Davies (97).

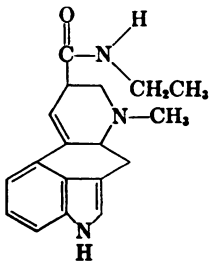
One of the obvious criticisms of all this work is that it has dealt largely with esterases in serum, and when brain was used, it was used in the form of homogenates of the whole organ, and any local or regional changes were not measurable. Goldberger (75) has made an attempt to circumvent this problem by working with sections of rat brain incubated with acetylcholine or with butyrylcholine with and without LSD in a concentration of 8×10^{-5} M. Under these conditions inhibition of pseudocholinesterase was not observed, while inhibition of specific cholinesterase occurred only in the cerebral cortex and was most marked in the lamina ganglionaris. Another approach to more discrete measurements in this field is the ingenious technique of Paulin (122), who has been able to estimate the acetylcholinesterase activity of single nerve cells of the nuclei reticularis gigantocellularis and reticularis pontis caudalis and oralis from the rat by the ampulla microdiver method. This investigator found that the activity of cells from the rostral part of the nucleus reticularis pontis caudalis was inhibited by LSD at concentrations higher than 2×10^{-5} M and activated at lower concentrations, in keeping with earlier findings.

In attempting to relate any or all of these findings to inhibition or activation of central cholinergic systems by BOL or LSD, it is important to bear in mind the great activity of the cholinesterases and the probability that such enzymes are widespread and in considerable excess relative to any concentrations of acetylcholine required to be destroyed. The crux of the problem, therefore, would seem to be the necessity of demonstrating that LSD and congeners can cause alterations in levels of acetylcholine at critical sites in the brain. Giarman and Pepeu (71) have shown already that while a series of cholinolytic psychotomimetic drugs can cause a fall in rat brain ACh (*vide infra*), neither LSD nor mescaline has such an effect. It remains to be seen whether local or regional changes in ACh are produced by LSD and its psychotomimetic analogs.

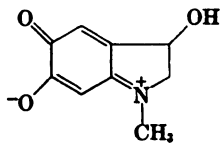
3. Interactions with miscellaneous neurochemical substances. A number of isolated and sporadic reports have appeared on the relationship of LSD to a variety of other biogenic substances found in the brain. Freedman (51, 52) has extended his initial observation that LSD caused an increase in brain 5-HT to an investigation of simultaneous changes in brain catecholamines, expressed as norepinephrine equivalents. This investigator found that the psychotomimetic substances, LSD, ALD (XXI) and psilocybin, all produce reductions in brain norepinephrine which are quantitatively similar to the respective increases seen in brain 5-HT. No such effects were observed after BOL or single doses of

methamphetamine, but McLean and McCartney (114) reported a similar pattern of effects on 5-HT and norepinephrine, that occur after repeated and increasing, and toxic doses of amphetamine. Himwich *et al.* (86) have correlated effects of bufotenine with release of catecholamines from peripheral binding sites. Brodie (24) has looked upon LSD as a phenylethylamine derivative and, as such, capable of stimulating central adrenergic sites.

One report in the literature linked LSD and the psychotomimetic D-lysergic acid ethylamide (LAE, XXV) to adrenochrome (XXVI) in man (89). LSD



XXV



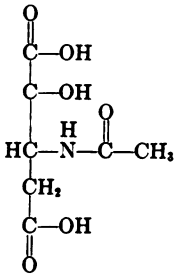
XXVI

reportedly increased blood levels of adrenochrome in alcoholic, normal, and schizophrenic patients. These investigators reported higher epinephrine oxidase activity, measured by the conversion of epinephrine to adrenolutin, in the blood of LSD-treated patients. It was possible to demonstrate also *in vitro* that LSD and LAE, but not BOL, could increase the activity of epinephrine oxidase. The presence of adrenochrome in the blood of hallucinating or normal subjects was not confirmed by several workers (41, 47, 149). However, adrenochrome has been found in mammalian salivary glands (10).

Beginning with the observation of Krivoy (102) that LSD (2.5×10^{-8} M) inhibited the disappearance of substance P when incubated with extract of guinea pig brain, some interest has been aroused in the possible interrelationship of these two substances *in vivo*. Substance P is a relatively poorly defined, naturally occurring polypeptide believed by some to be concerned with transmission in sensory nerve pathways. Krivoy (102) had found that LSD potentiated the response of the guinea pig ileum to substance P, and later showed in the decerebrate cat that LSD (10 μg/kg) potentiated actions of substance P (30 units/kg) on transmission of impulses from posterior spinal roots to secondary and internuncial neurons of the spinal cord, as evidenced by enhancement of the fourth potential of the dorsal root potential complex (103). In larger doses (70 μg/kg) LSD produced enhancement alone without the administration of exogenous substance P. These results have been interpreted to mean that LSD spares substance P from destruction. BOL was without such a preserving effect (102). The general significance of these findings with relation to the brain, however, has been called into doubt by the observation that LSD in large dose (17.7 mg/kg) did not alter the content of substance P in the mouse brain (106). Essentially the same lack of effect, except that the dose was smaller (10 mg/kg), had been observed previously (167).

Until very recently, brain histamine had not received the same amount of experimental attention as other brain amines. One report states that the administration of LSD and mescaline led to a decrease in the level of histamine in rat blood, while reserpine, chlorpromazine, iproniazid or amphetamine caused an increased concentration of the amine (160). There was obviously a need to investigate these phenomena in brain, and recently Siva Sankar *et al.* (135) found that LSD reduced total level of histamine in rabbit brain, but increased the bound form of the amine in the 12,000 × *g* fraction of brain homogenized in 0.25 M sucrose (mitochondrial sediment). These investigators suggested that the increased levels of bound histamine and bound 5-HT (57) might be responsible for the reported antianaphylactic action of LSD (121).

McIntosh and Cooper (110) have examined the effect of various psychoactive



XXVII

drugs on the brain level of N-acetylaspartic acid (XXVII), which, among amino acids, is second only to glutamic acid in amount present in the brain. These investigators found that LSD was one of the few drugs which altered the level of N-acetylaspartic acid, producing, like reserpine, a fall in the content of the amino acid in mouse brain. The role of this amino acid in brain function is unknown but it is believed to offset the "anion deficit" in the brain (113a).

B. Mescaline and related phenylethylamines

The similarity in structure between 5-HT and the psychotomimetic indolealkylamines was an important factor in the elaboration of theories of psychotomimetic action involving 5-HT. In the same fashion it was the structural similarity between mescaline and epinephrine that pointed to a possible significance of the catecholamines in psychotomimetic action (88). In addition, this relationship became more intriguing when it was suggested that both epinephrine and mescaline could serve as precursors of indolic compounds (87).

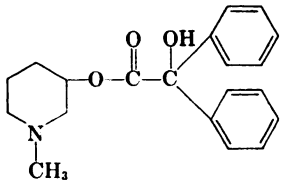
In terms of interaction with neurohumors, one striking fact seems to emerge from the few studies done to date with mescaline. With respect to 5-HT, norepinephrine, and histamine, mescaline has been shown to cause essentially the same shifts in brain and blood amines as those seen with LSD (*vide supra;* 160). Whether this indicates an interaction of the psychotomimetic substances and common receptor sites or not, it is enormously interesting in view of the many reports of cross-tolerance between mescaline and LSD both in animals and in man (12, 53, 163).

The likelihood that mescaline in some way engages brain amines in exerting its central effects is strengthened by the finding that an alteration in regulatory factors in the metabolism of monoamines in brain causes a change in some of the effects of mescaline. Steiner and Sulman (142) reported that after pretreatment with iproniazid, mescaline produced notched waves in the electroencephalogram and elicited an "anxiety reaction" in the conscious rabbit. Investigators from the same laboratory have reported also that while pretreatment with iproniazid changed the spontaneous electrical activity of the cortex induced by mescaline in the conscious rabbit, such pretreatment did not alter the fact that mescaline was without effect on blood sugar and urinary 5-HIAA (8). Evidence for an interaction of mescaline with epinephrine and acetylcholine in peripheral nerve transmission also has been presented. The curare-like blockade of neuromuscular transmission in the dog (peroneal-tibialis anticus nerve-muscle preparation) by mescaline (4 to 5 mg/kg) was shown to be antagonized by epinephrine and by the anticholinesterase drug, neostigmine (132).

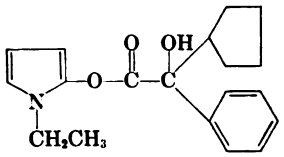
C. Cholinolytic compounds

The psychotomimetic effects of some anticholinesterase drugs are well documented (40); and this fact combined with the strong inference that acetylcholine plays a role in central transmission has attracted attention to possible cholinergic mechanisms in alterations of perception and behavior. In man, many of the symptoms produced by LSD are similar to those of atropine: *e.g.*, the facial flush, rise in blood pressure, mydriasis, and hyperthermia (125). Abood and Biel (2) have, therefore, synthesized and investigated a number of atropine-like derivatives (chiefly piperidyl glycollates), and found among them some striking psychotomimetic actions in man. While these investigators have sought to explain the action of these drugs on the basis of their potential effect on membrane depolarization and interference with cation movement, others have examined directly the action of these substances on brain ACh.

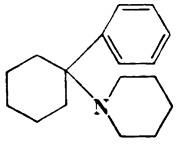
Giarman and Pepeu (72) established that large doses (25 to 100 mg/kg) of atropine and scopolamine in the rat produced significant reductions in level of



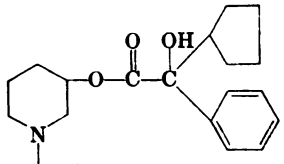
XXVIII



XXIX



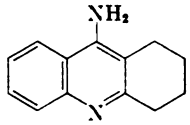
XXX



XXXI

total ACh in the whole brain, while causing either no gross change in behavior, or occasionally a pattern of alternating excitation and depression. In a subsequent, more detailed investigation of these interrelationships, these same workers examined the effect of four related compounds of the piperidyl benzilate class provided by Abood (71). Two of these were psychotomimetic agents in man (JB-336, XXVIII, and JB-8099, XXIX) and produced in the rat a reduction in brain ACh comparable to that found with scopolamine and atropine; while the other two were without psychotomimetic activity and caused no change in brain ACh. Since both LSD and mescaline were without effect on brain ACh, it was concluded that among certain cholinolytic psychotomimetic derivatives the psychotomimetic effects are linked with an alteration in the metabolism of ACh in brain. It was suggested that the most likely mechanism is that these drugs alter storage sites of ACh in a manner leading to reduced uptake of newly synthesized ACh or increased release of ACh from its bound form, or both. One interesting finding in this work that might provide a clue to the site of this action was that all of the reduction in brain ACh evoked by scopolamine (0.63 mg/kg), the most potent derivative studied, took place in the cerebral hemispheres of the rat, while no change was found in subcortical areas studied (71). Phenylcyclohexylpiperidine, XXX, the psychotomimetic drug "Sernyl," a piperidyl derivative without an ester grouping, appears to differ in that it did not produce a significant alteration in brain acetylcholine of the rat (72).

An antidote to the psychotomimetic as well as to the peripheral action of the piperidyl glycollate (JB-329, XXXI) has been found by Gershon (67) in the



XXXII

form of 1,2,3,4-tetrahydro-5-aminoacridine, XXXII. This acridine derivative is an inhibitor of cholinesterase and would be expected to raise brain levels of ACh. It is, therefore, intriguing to speculate that the increased ACh might serve to offset the decrease produced by the psychotomimetic drug and thereby relieve the cerebral disturbance.

IV. GENERAL SUMMARY

A wide variety of chemical structures is grouped generically under the classification of psychotomimetic drugs. Such a global grouping has little justification in terms of either somatic or behavioral effects, and there is little likelihood of discovering a unitary explanation of the mechanism of action of these drugs. Some subgroupings are based on common pharmacologic effects. In terms of cross-tolerance, effects on temperature and effects on amine levels, the indolealkylamines and substituted phenethylamines appear to be related (52); and the piperidyl glycollates and other cholinolytic compounds may similarly be grouped according to effects on brain acetylcholine (71). Yet if progress is to be made in

linking biochemical changes to psychotomimetic effects, a focus on neural sites of action and accessibility of drugs to those sites is required. Dose-dependent correlations with discrete and different autonomic, electroencephalographic and behavioral effects also are important to advances in this area. With LSD, for example, dose-dependent, centrally mediated effects (129), such as pyrexia, mydriasis, EEG alerting, hind limb ataxia, and certain behavioral effects (in rat) and mental effects (in man) show tolerance, while salivation and bradycardia do not (55, 56). Furthermore, effects can be elicited by low doses of LSD in rat (94), cat (99), and man (79), for which either biochemical or neurophysiological correlates are lacking. In addition, neurophysiological studies have served to identify different sites of action for 5-HT throughout the brain (100, 118), but these as yet have not been correlated with associated biochemical effects of LSD.

Studies of the metabolism of psychotomimetic drugs have shed little light on their modes of action. Intriguing avenues of research have been opened by Szara in his investigations of the 6-hydroxylation of psychotomimetic N-alkyl indolealkylamines (and their effects on brain 5-HT), and his study of the 13-hydroxylation of LSD, and by Friedhoff and Van Winkle in their reports of mescaline-like derivatives, arising possibly from dopamine, in the urine of schizophrenic patients. Other interesting leads have come from Gessner *et al.* in the possible harmaline-like metabolite of melatonin, and from Brune and Himwich (30) in their observation that acute exacerbations in chronic schizophrenic patients are associated with marked increases in urinary excretion of tryptamine, and smaller increases in the excretion of other tryptophan metabolites. It has been emphasized, however, that all of these studies are fraught with methodologic problems and rigorous proof of each hypothesis is lacking.

Few investigators in this area will argue against the proposition that biogenic amines, and related neurochemical substances, play an as yet undefined role in brain function and behavior. Some very compelling correlations between drug-induced behavioral change and the factors governing binding and release of 5-HT and norepinephrine have been made with the onset and recovery from stress-induced changes in psychophysiologic condition (13). Yet if binding and release of amines from central storage sites and interaction with critical central receptors are envisaged as mechanisms significant to the action of psychotomimetic drugs, more than regional brain analyses are required. Relevant physicochemical means of measurement of binding and release have not been satisfactorily devised (see review by Green, 78). New methodologies—as, for example, fluorescence microscopy, which may provide morphological correlates of neurochemical changes measured in broken-cell preparations, and pertinent neuropharmacological investigation at the level of single units (*e.g.*, by the micro-iontophoretic technique of drug application)—could contribute to specifying interactions with brain amines. In addition, pharmacological analysis (and eventually chemical characterization) of various types of receptors which engage monoamines, such as tryptamine receptors (153, 159) will provide important information.

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