# a review of recent studies of the biosynthesis and excretion of hallucinogens formed by methylation of neurotransmitters or related substances*

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There is a striking structural similarity between several classes of compounds found in plants that produce hallucinatory or psychedelic effects in man and several neurotransmitters found in the mammalian brain. These psychotomimetic substances are generally N- or O-methylated analogs of biogenic amine transmitters or of closely related endogenous compounds. Dimethyltryptamine (DMT), bufotenine, and 5-methoxydimethyltryptamine (5MeODMT) are present in *piptadenia peregrina*, used by South American Indians in their snuffs, and are psychotomimetic in man (Briggs 1972, Fabing and Hawkins 1956, Fuxe, Holmstedt, and Jonsson 1972, Gessner 1970, Gessner and Page 1962, Holmstedt 1965, Holmstedt and Lindgren 1967, Koslow 1974, and Szara 1956 and 1961). All of these substances are methylated analogs of tryptamine or serotonin, substances that can be derived from the brain (Green, Koslow, and Costa 1973, Martin et al. 1972, and Saavedra and Axelrod 1972a). Mescaline, a hallucinogenic derivative of the peyote cactus (*Iophophora williamsii*) (Kapadia and Fayez 1970), is structurally related to the methylated derivatives of the catecholamine neurotransmitters dopamine and norepinephrine (Ernst 1965).

The transmethylation hypothesis of schizophrenia (Osmond and Smythies 1952) was proposed after it was observed that the transfer of a methyl group to each of the hydroxyl groups of norepinephrine would transform this compound to one closely similar in structure to mescaline. This observation was made in the early 1950's before it was recognized that an important pathway for the inactivation of the catecholamines in mammals involves their O-methylation to structures more closely resembling mescaline-type hallucinogens than the parent catecholamines. The usual monomethylated metabolites of catecholamines are not hallucinogens and in fact are pharmacologically inert. However, these metabolites could serve as precursors for di- or tri-O-methylated derivatives, which do have the pharmacological effects of mescaline (Smythies and Sykes 1966, Smythies, Sykes, and Lord 1966, and Vacca et al. 1968). It was hypothesized, therefore, that a metabolic aberration in a methylating system could lead to the formation of hallucinogenic substances resembling mescaline in structure. Later the hypothesis evolved further to include the possibility that hallucinogens might also be formed from serotonin or tryptamine, compounds that could be transformed to bufotenine or DMT.

One of the assumptions implicit in this hypothesis is that drug-induced psychotic states resemble naturally occurring psychoses such as schizophrenia. Most observers agree, however, that there are major differences between symptoms produced by drugs such as mescaline or DMT and the so-called functional psychoses, although it is generally agreed that amphetamine psychosis is

*Most of the material referred to herein has been published since an earlier review in the *Bulletin* (Wyatt, Termini, and Davis 1971). For background and earlier work, see that publication.

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often indistinguishable from spontaneously occurring paranoid schizophrenia. The observed differences in the clinical picture associated with functional and induced psychoses provide some problems for the transmethylation hypothesis. On the other hand, it is not unlikely that a compound of exogenous origin and the same compound produced endogenously might have quite different effects.

Any chemical substance involved in naturally occurring psychotic disorders would presumably be produced chronically, whereas the effects of administered psychotomimetic agents are usually studied acutely. Also volunteers taking hallucinogenic drugs are usually aware that they have taken a drug, and thus have an available rationale for the impairment of their mental function, which would not be available to a person suffering from an illness like schizophrenia. W. A. Frosch (personal communication, 1975), who has been observing LSD abusers for more than 10 years (Frosch, Robbins, and Stern 1965), noted that individuals whose "friends" have given them hallucinogenic substances without their knowledge may react in a bizarre fashion and often feel that they are losing their minds. He has also found that some schizophrenics have the delusion that they have been given LSD, and resort to this idea for reassurance. Both of these observations support the idea that awareness of the causal agent, whether real or delusional, can minimize symptoms and secondary psychological elaborations. Recent reports in the lay press about the covert administration of hallucinogenic drugs are also consistent with the proposal that reactions under these circumstances may be more bizarre and severe.

A point raised by a number of investigators is that tolerance to most hallucinogenic substances develops very rapidly. If patients are synthesizing endogenous hallucinogens, why do they not rapidly become tolerant to these substances? Again, there are potential answers to these objections. We do not know whether tolerance to endogenously produced substances develops in the same way as that to administered substances. It has been found that one such substance, reported to be excreted by schizophrenic subjects, is found in the urine only intermittently (Braun et al. 1974 and Kalbhen and Braun 1973). Intermittent production of endogenous hallucinogens would tend to reduce the likelihood that tolerance would develop. Finally, Gillin et al. (1973) reported that DMT, unlike other hallucinogens, does not produce tolerance in cats. Thus, in evaluating the present status of the transmethylation proposal, it is necessary to weigh the apparent contradictions against the potential bases for their reconciliation with the hypothesis.

One of the strongest pieces of evidence in support of the hypothesis was the finding by Pollin, Cardon, and Kety (1961) that methionine administered with a monoamine oxidase inhibitor produced an exacerbation in the symptoms of schizophrenic subjects who were in partial remission. Other amino acids administered in the same way did not have this effect. The original observations of this group have since been confirmed by a number of other laboratories (see Cohen et al. 1974 for a review of 10 studies). An assumption implicit in these studies is that the administration of large doses of methionine increases the methylation of biogenic amines and possibly favors the formation of methylated hallucinogenic derivatives of amines. No direct demonstration that increased methylated metabolites were formed was provided, however, in the earlier work. Antun et al. (1971) were able to produce relapses in schizophrenic volunteers by the administration of methionine alone, without the concurrent administration of a monoamine oxidase inhibitor. They found no increase in the O-methylation of catecholamines in the subjects given methionine but did not investigate the excretion of N-methylated indoleamines. Israelstam et al. (1970) infused S-adenosylmethionine (SAM) and found no differences in the extent of methylation of biogenic amines in chronic schizophrenics in remission when they were compared with normal controls. These investigators did find, however, that there was delayed metabolism of the injected SAM in chronic schizophrenics.

Price (1972) attempted to study in-vivo methylation by measuring the rate of methylation of administered protocatechuic acid. He found no difference between schizophrenics and controls in either the rate of methylation of this substance or the extent of the methylation of the 3- or 4-hydroxyl group. This study is one of the few direct evaluations of the methylation of administered substances. One objection that can be made to this study is that the substance, protocatechuic acid, has not been established to be a biological substance associated with neural activity. Its metabolism, therefore, may reflect metabolic mechanisms reserved for drug inactivation rather than those involved with metabolism of endogenous substances.

Interest in the possibility that endogenous hallucinogens might have some normal or pathological role in

the central nervous system (CNS) has been increased by the discovery of enzymes in mammalian tissues that can catalyze the formation of several hallucinogens (Axelrod 1961 and 1962, Friedhoff et al. 1972, Friedhoff, Schweitzer, and Miller 1972a and 1972b, Mandel et al. 1972, Mandell and Morgan 1971, Morgan and Mandell 1969, Narasimhachari, Plaut, and Himwich 1972a, Saavedra and Axelrod 1972b, Saavedra, Coyle, and Axelrod 1973, and Schweitzer and Friedhoff 1972). These findings generated a number of studies attempting to determine whether endogenous psychotogens are synthesized in vivo and whether they play a role in psychosis or perhaps in some aspect of normal function.

In 1961 Axelrod described an enzyme in rabbit lung that was capable of N-methylating indolethylamine substrates to hallucinogenic substances using SAM as a methyl donor (figure 1). Later, Morgan and Mandell (1969) described a similar enzyme in the CNS that was found in the soluble fraction and also in synaptosomes and that displayed the highest concentration in brain stem and lowest in the cortical areas (Mandell and Morgan 1971).

The enzyme had a low specific activity and a relatively high $K_m$ (Michaelis constant, which is the substrate concentration that gives half maximal velocity). Saavedra and Axelrod (1972b) also described an enzyme in rat brain that catalyzed the N-methylation of tryptamine to monomethyl tryptamine and dimethyltryptamine. Saavedra, Coyle, and Axelrod (1973) found this enzyme confined to cerebral cortex and striatum and subcortical white matter, a different localization from that reported by Morgan and Mandell (1969). The enzyme had low specific activity and broad substrate specificity.

Various methyltransferases have been reported to be present in brain, blood cells, plasma, lung, and liver (Axelrod and Cohn 1971, Bhikharidas, Mann, and McLeod 1975, Friedhoff, Schweitzer, and Miller 1972a and 1972b, Heller 1971, Mandel et al. 1972, Mandel and Walker 1974, Narasimhachari, Plaut, and Himwich 1972b, Rosengarten, Meller, and Friedhoff 1972 and 1974, Walker et al. 1972, Wyatt et al. 1973b, and Wyatt, Saavedra, and Axelrod 1973). The level of the N-methylating activity in human blood constituents was very low (Meller, Rosengarten, and Friedhoff 1974, Rosengarten, Meller, and Friedhoff 1974 and in press, Wyatt et al. 1973b, and Wyatt, Saavedra, and Axelrod 1973), and less than 25 percent of extractable radioactive products were recovered on thin layer chromatography (TLC) in the area corresponding to N-methyltryptamine (NMT) and DMT. The reasons for this low recovery were not clear. Wyatt, Saavedra, and Axelrod (1973) also reported that they were unable to confirm the results reported by others (Narasimhachari, Plaut, and Himwich 1972b) of an elevation of this N-methyltransferase activity in the plasma of schizophrenic patients. They did find, however, an elevation of this activity in platelets of schizophrenics and psychotic depressives. In a study of monozygotic twins discordant for schizophrenia, they found elevated enzyme activity only in the platelets of the ill twins from which they inferred an environmental rather than a genetic cause.

As the reports of systems generating hallucinogens began to appear, so did discrepancies and inconsistencies in the results reported by different investigators (Banerjee and Snyder 1973, Hsu and Mandell 1973 and 1974, Saavedra and Axelrod 1972b, Saavedra, Coyle, and Axelrod 1973, Narasimhachari, Plaut, and Himwich 1972b, and Narasimhachari et al. 1971b). Product identification was not complete, however, in any of these studies (see table 1). In a series of studies carried out to determine some of the reasons for these conflicting findings (Meller, Rosengarten, and Friedhoff 1974 and Rosengarten, Meller, and Friedhoff 1974 and in press) it was found that red blood cell enzyme incubated with $C^{14}$SAM as methyl donor and N-methylserotonin (NMS) or NMT as substrate resulted in the formation of cyclized derivatives of indolethylamines—tetrahydro-β-carbolines (THBC)—which were difficult to resolve from authentic DMT or bufotenine on TLC, in the solvent systems that had been generally used (figure 1). When the extractable radioactivity was subjected to chromatography in strongly basic systems, only a negligible amount of radioactivity migrated on TLC with authentic DMT or bufotenine, whereas the major portion of radioactivity was isographic with the cyclized derivative. Similar results were obtained when rat brain was used as enzyme source, N-methyltryptamine as substrate, and $C^{14}$SAM as methyl donor (Rosengarten, Meller, and Friedhoff 1975a and in press).

Using techniques such as cocrystallization and derivatization, which permitted more confident proof of identity (Rosengarten, Meller, and Friedhoff 1974, 1975a, and in press), it was found that both N-methylation and β-carboline formation can occur when SAM is a methyl donor, depending on the tissue used as

## Table 1. Studies of enzymatic formation of hallucinogens and related compounds.

| Study | Methyl donor | Reaction, enzyme, and localization | Principal methods of product identification | Comments |
|---|---|---|---|---|
| S-adenosylmethionine (SAM) dependent reactions | | | | |
| Axelrod (1961) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in rabbit lung | Extraction properties and chromatographic characteristics | Formation of DMT and bufotenine from appropriate precursors demonstrated; subsequent studies using different techniques confirmed product identity |
| Morgan and Mandell (1969) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in chick, sheep, and rat brain | Extraction properties and chromatographic separation | Chromatography system used does not resolve DMT from THBC |
| Axelrod and Cohn (1971) | $C^{14}$SAM | SAM to methanol; methanol-forming enzyme in blood | Volatile substance formed from $C^{14}$ methyl group measured | Physiological significance of this enzyme, if any, has not been established |
| Mandell and Morgan (1971) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in human brain | Extraction properties and chromatographic separation | Chromatography system does not resolve DMT from THBC |
| Assicot and Bohuon (1971)<br>Poitou, Assicot, and Bohuon (1974) | $C^{14}$SAM | O-methylation of catecholamines; COMT in red cell ghosts and soluble fraction | Extracted radioactivity measured | Elevated COMT activity in ghosts, but not soluble fraction of red blood cells from schizophrenics; patients medicated |
| Mandel et al. (1972) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in human lung | Extraction properties | Consistent with earlier finding in rabbits |
| Matthysse and Baldessarini (1972) | $C^{14}$SAM | O-methylation of catecholamines; COMT in red cells | Extracted radioactivity measured | No significant difference between schizophrenics and controls |
| Narasimhachari, Plaut, and Himwich (1972a) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in human serum | Extraction properties and chromatographic separation | Chromatography systems do not resolve N-methylated indoleamines from THBC; schizophrenics and controls studied |
| Saavedra and Axelrod (1972b)<br>Saavedra, Coyle, and Axelrod (1973) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in rat brain; in-vivo formation of NMT and DMT | Extraction properties and chromatographic separation | Chromatography system does not resolve NMT and DMT from THBC |

**Table 1. Studies of enzymatic formation of hallucinogens and related compounds—*Continued.***

| Study | Methyl donor | Reaction, enzyme, and localization | Principal methods of product identification | Comments |
|---|---|---|---|---|
| Rosengarten, Meller, and Friedhoff (1972) | $C^{14}$SAM | O-methylation of indolethylamines; hydroxyindole-O-methyltransferase in red blood cell ghosts | Chromatography, cocrystallization of product to constant specific activity | Route for formation of melatonin in blood, but enzyme has low specific activity |
| Friedhoff et al. (1972) | $C^{14}$SAM | Di-O-methylation of catecholamines; guaiacol-O-methyltransferase in rat brain and liver and in human brain, liver, and blood | Extraction properties, chromatography, and cocrystallization of product to constant specific activity | Route for formation of DMPEA in vitro |
| Friedhoff, Schweitzer, and Miller (1972a) | $C^{14}$SAM | Methylation of desmethylmescaline to mescaline; mescaline-forming enzyme in rat brain and liver | Extraction properties, chromatography, and cocrystallization of product to constant specific activity | Route for formation of mescaline in vitro |
| Hsu and Mandell (1973) | $C^{14}$SAM | N-methylation of indolethylamines; brain N-methyltransferase | Extraction properties and chromatography | Chromatography system does not resolve DMT from THBC |
| Wyatt et al. (1973b) | $C^{14}$SAM | N-methylation of indolethylamines; N-methyltransferase in blood platelets | Extraction properties and chromatography | 75 percent of radioactive product not identifiable; schizophrenic monozygotic twins studied |
| Wyatt, Saavedra, and Axelrod (1973) | $C^{14}$SAM | N-methylation of indolethylamines; dimethyltryptamine-forming enzyme in human blood | Extraction properties and chromatography | Low recovery of radioactivity in DMT area; extraneous product probably THBC |
| Meller, Rosengarten, and Friedhoff (1974) | $C^{14}$SAM | Enzymatic formation of formaldehyde and condensation with N-methylserotonin; unspecified enzyme in blood | Extraction properties, chromatography, and cocrystallization | Formation of THBC's from indolethylamines demonstrated; subsequent studies showed similar reaction also with 5MTHF; chromatography system separates DMT from THBC |
| Rosengarten, Meller, and Friedhoff (1974) | $C^{14}$SAM | Enzymatic formation of formaldehyde and condensation with NMT; unspecified enzyme in blood | Extraction properties, chromatography, and cocrystallization | Chromatography system separates DMT from THBC |
| Rosengarten, Meller, and Friedhoff (1975 and in press a) | $C^{14}$SAM | Enzymatic formation of THBC from indolethylamine; unspecified enzyme in brain | Extraction properties, chromatography, derivatization, and cocrystallization | Chromatography system resolves indoleamines from carbolines |

**Table 1. Studies of enzymatic formation of hallucinogens and related compounds—*Continued.***

| Study | Methyl donor | Reaction, enzyme, and localization | Principal methods of product identification | Comments |
|---|---|---|---|---|
| Bhikharidas, Mann, and McLeod (1975) | $C^{14}$SAM | N-methylation of indolethylamine; N-methyltransferase in blood and liver | Extraction properties and chromatography | Chromatography system does not completely resolve DMT from THBC |
| 5-methyltetrahydrofolate (5MTHF) dependent reactions | | | | |
| Laduron (1972a) | 5MTHF | Dopamine to epinine; N-methyltransferase in adrenal | Extraction properties and chromatography | Chromatography system does not resolve epinine from TIQ |
| Laduron (1972b) | 5MTHF | Dopamine to epinine; N-methyltransferase in brain | Extraction properties and chromatography | Chromatography system does not resolve epinine from TIQ |
| Laduron (1973) | 5MTHF | Indolethylamines to N-methylated indolethylamines; N-methyltransferase in rat brain | Extraction properties and chromatography | Chromatography system used does not resolve N-methylated indoleamines from THBC |
| Banerjee and Snyder (1973) | 5MTHF | N- and O-methylation of indolethylamines; N-methyltransferase in rat brain and adrenal | Extraction properties and chromatography | Chromatography system does not resolve N- or O-methylated indoleamines from carbolines |
| Hsu and Mandell (1973) | 5MTHF | N-methylation of indolethylamines; n-methyltransferase in rat brain | Extraction properties and chromatography | Chromatography system does not resolve N- or O-methylated indoleamines from carbolines |
| Meller, Rosengarten, and Friedhoff (1975) | 5MTHF | Dopamine to TIQ; enzyme not specified | Extraction, chromatography, derivatization | Separation of TIQ from epinine by alkaline chromatography systems |
| Rosengarten, Meller, and Friedhoff (1975 and in press b) | 5MTHF | Indolethylamines to THBC; enzymes not specified | Extraction properties, chromatographic separation, and derivatization | Separation of THBC from N-methylated indoleamines by alkaline chromatography system |
| Barchas et al. (1975) | 5MTHF | Indolethylamines to THBC; enzymes not specified; in platelets and brain | Extraction properties, chromatographic separation, cocrystallization, and gas liquid chromatography/mass spectrometry | Separation of tryptolines (THBC) from N-methylated indoleamines by alkaline chromatography systems; additional identification of product by mass spectrometry |
| Hsu and Mandell (1975) | 5MTHF | Indoleamines to THBC; enzyme not specified; in brain | Extraction properties and chromatography | Separation of THBC from indolethylamines by alkaline chromatography system |

**Table 1. Studies of enzymatic formation of hallucinogens and related compounds—*Continued.***

| Study | Methyl donor | Reaction, enzyme, and localization | Principal methods of product identification | Comments |
|---|---|---|---|---|
| Mandel et al. (1974) | 5MTHF | Indolethylamines to THBC; enzyme not specified; in brain | Extraction properties, chromatography, and gas liquid chromatography/mass spectrometry | Separation of THBC from indolethylamines by alkaline chromatography system |
| Stebbins et al. (1975) | 5MTHF | Indolethylamines to THBC; $N^5,N^{10}$ methylene; $H_4$ folate reductase in platelets | Extraction properties and chromatography | Formaldehyde generating enzyme copurified with $N^5,N^{10}$-methylenetetrahydrofolate reductase |

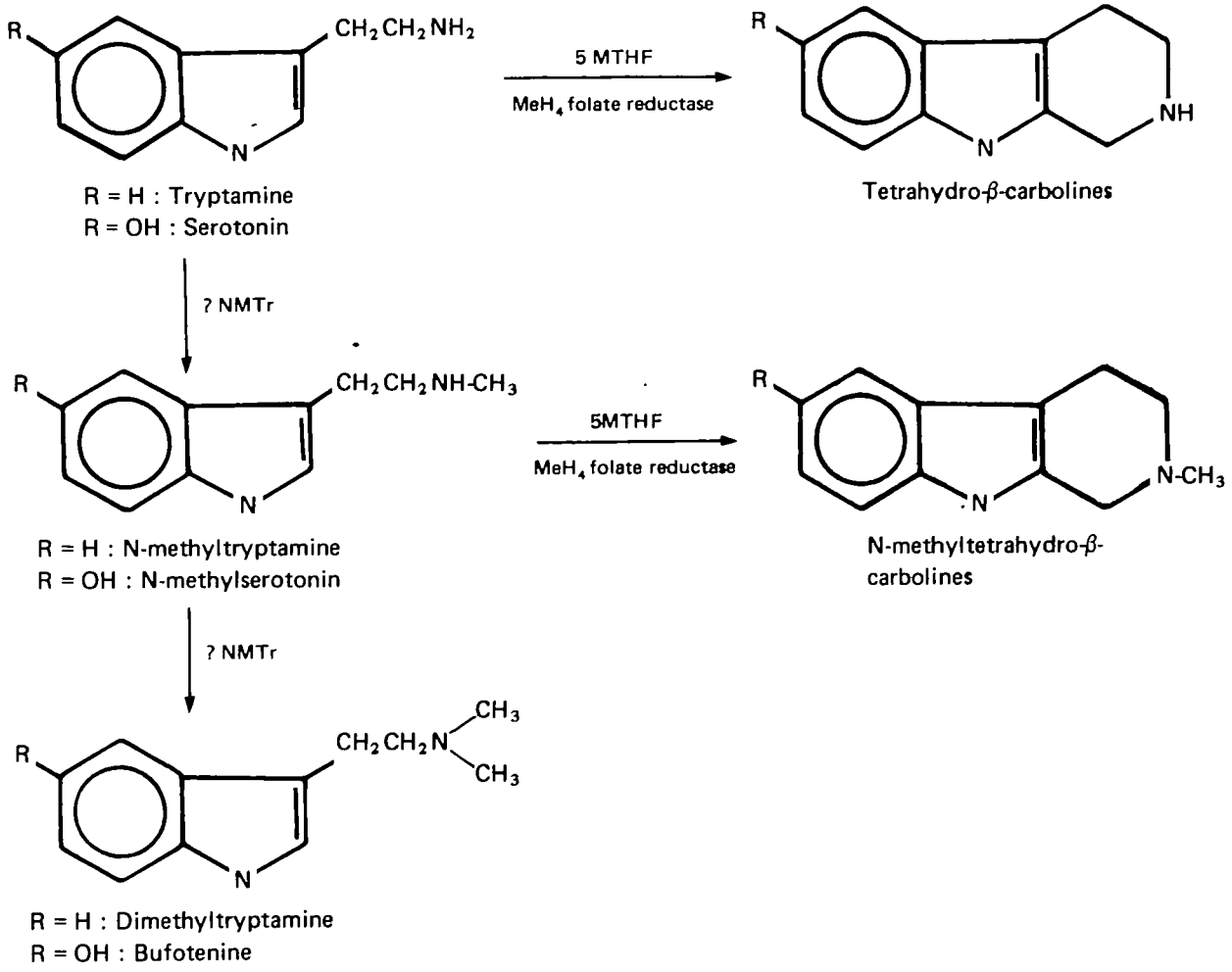
enzyme source. In mammals, the enzyme for the methylation reaction is present principally in lung and adrenals (Axelrod 1962), while in other tissues the formation of cyclized products predominates. Only trivial amounts of DMT are formed in rat brain tissue, while tetrahydro-β-carboline formation occurs readily (Rosengarten, Meller, and Friedhoff, in press). Red blood cells contain an enzyme capable of catalyzing the SAM-mediated methylation of water to methanol (Axelrod and Cohn 1971). Catalase present in the red cell is capable of converting methanol to formaldehyde (Tephly et al. 1965). It seems probable that this reaction may be involved, in red blood cells, in the conversion of SAM to formaldehyde via methanol. Formaldehyde can then condense, nonenzymatically, with indolethylamines, to form tetrahydro-β-carbolines. It is of interest that both methanol and formaldehyde are normal constituents of human blood (Western and Ozburn 1949).

Friedhoff and his associates (Friedhoff 1973, Friedhoff, Schweitzer, and Miller 1972b, Friedhoff et al. 1972, and Friedhoff, Schweitzer, and Miller 1973) have presented evidence for the in-vitro enzymatic formation of di-O-methyldopamine metabolites (figure 2). These authors reported that mono-O-methylated metabolites of catecholamines can be further O-methylated enzymatically by mammalian tissues. The responsible enzyme is present in the 100,000 × g supernatant fraction of the liver and brain of rats and in the liver, brain, and blood cells of man, and has been found to be capable of catalyzing the formation of dimethoxyphenethylamine (DMPEA) from its immediate precursor 3-hydroxy-4-methoxyphenethylamine (i-methoxytyramine), a minor dopamine metabolite. It is of interest that the major mono-O-methylated dopamine metabolite, 4-hydroxy-3-methoxyphenethylamine (n-methoxytyramine), is not a good substrate for the formation of DMPEA. It was also reported that another dopamine metabolite, N-acetyl-3-hydroxy-4-methoxyphenethylamine (Hartley and Smith 1973 and Van Winkle and Friedhoff 1968), could be enzymatically transformed to an active compound, N-acetyl-3,4-dimethoxyphenethylamine (NADMPEA) (Johnson et al. 1970). These findings are of interest because of the similarity of DMPEA to mescaline in structure and pharmacological effects and of the reports that DMPEA is present in the urine of schizophrenic patients (Friedhoff and Hollister 1966, Friedhoff and Van Winkle 1962a and 1962b, Hollister and Friedhoff 1966, Narasimhachari, Plaut, and Himwich 1972a). (See Wyatt, Termini, and Davis 1971 for a review of this matter, and the latter part of this article for more recent findings.)

Benington and Morin (1968) reported that an enzyme present in rat and rabbit liver is capable of hydroxylating 4-hydroxy-3-methoxyphenethylamine in the 5 position to 4,5-dihydroxy-3-methoxyphenethylamine, thus providing an intermediate in the pathway between dopamine and mescaline (figure 2). More recently these same authors reported that the enzymatic 5-hydroxylation of 3,4-dimethoxyphenethylamine can occur in mammalian tissue, which would provide another possible intermediate in the biosynthesis of mescaline from dopamine (Benington and Morin 1974). Friedhoff, Schweitzer, and Miller (1972a) found that mescaline can be synthesized in mammalian tissues from the precursor 4-hydroxy, 3-5-dimethoxyphenethylamine (4-desmethylmescaline), which itself can be formed through the action of the enzyme catechol-O-methyltransferase (COMT) on the dopamine metabolite described by Benington and Morin (1968) (figure 2).

From these studies it appears that both SAM and the enzyme COMT play a role in the in-vitro formation of

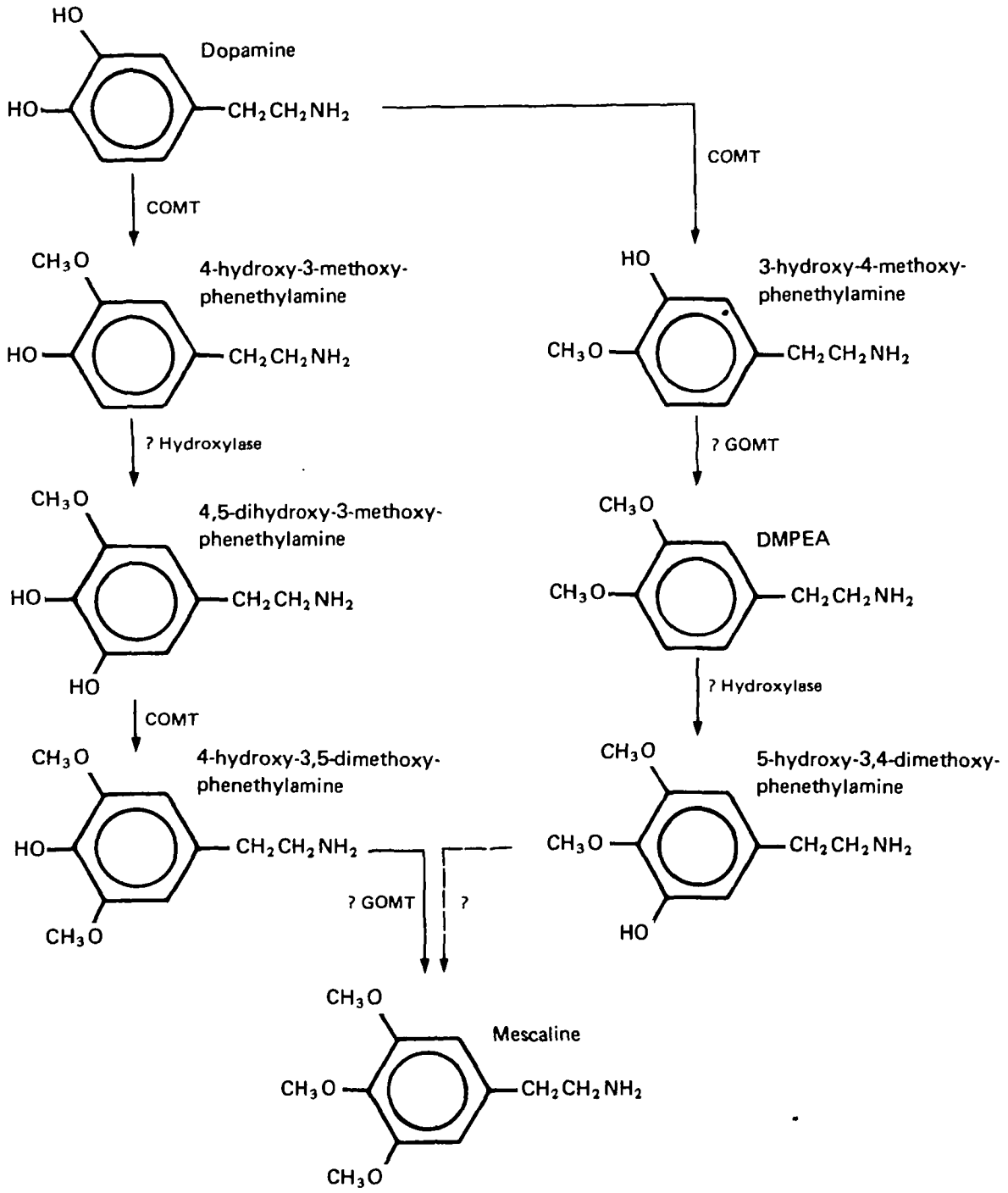
**Figure 1. Pathways in the in-vitro formation of N-methylated and β-carboline derivatives to tryptamine and serotonin.[1]**




[1] NMTr = N-methyltransferase not fully characterized; $MeH_4$ folate reductase = $N^5,N^{10}$-methylenetetrahydrofolate reductase; 5MTHF = 5-methyltetrahydrofolate.

endogenous hallucinogens. Matthysse and Baldessarini (1972) compared SAM concentration and COMT activity in the venous blood of schizophrenic and non-schizophrenic psychiatric patients. Most subjects were receiving medication. Their results did not show a significant difference between the two groups of subjects. Two distinct catechol-O-methyltransferases have been reported to be present, one in the soluble and one in the ghost fraction of red blood cells, which differ in their pH optimum, heat stability, kinetic properties, and immunochemical reactivity (Assicot and Bohuon 1971). The enzyme confined to the soluble fraction of red blood cells showed similar characteristics to liver COMT. This group subsequently studied the soluble and ghost COMT activity in medicated schizophrenic patients (Poitou, Assicot, and Bohuon 1974). They found elevated COMT activity in the ghost fraction of red blood cells of schizophrenics. No significant difference was observed in the COMT activity of the soluble fraction. Among the schizophrenics, no correlation was found between COMT activity and patient age, duration of illness, treatment, or clinical features. Although there appeared to be no effect of therapeutic psychotropic agents on COMT activity, the possible significance of

**Figure 2. Pathways in the in-vitro formation of DMPEA and mescaline.[1]**




[1] COMT = catechol-O-methyltransferase; GOMT = guaiacol-O-methyltransferase.

this study is lessened by the fact that most of the schizophrenics were on maintenance doses of various drugs.

## Folate-Dependent Reactions

Investigators in several laboratories have reported that 5-methyltetrahydrofolate (5MTHF) can serve as a methyl donor for the in-vitro enzymatic methylation of indoleamines and dopamine (Banerjee and Snyder 1973 and 1974, Hsu and Mandell 1973 and 1974, Laduron 1972a, 1972b, 1973, and 1974, Laduron, Gommeren, and Leysen 1974, Laduron and Leysen 1973, and Leysen and Laduron 1973 and 1974). The methylating enzyme, dependent on 5MTHF, was reported to be present in various tissues of several species. In some reports, both N- and O-methylation were described (Banerjee and Snyder 1973 and 1974 and Snyder and Banerjee 1973), whereas in others, only N-methylation was described (Leysen and Laduron 1974). Hsu and Mandell (1973) reported N-methylation of NMT to DMT in rat brain using 5MTHF as a methyl donor. Flavine-adenine dinucleotide and methylcyancobalamine in the presence of a reducing agent (mercaptoethanol) stimulated the reaction (Hsu and Mandell 1974).

The early reports that folate could serve as a methyl donor in the methylation of biogenic amines, in some cases to hallucinogenic structures, excited considerable interest, particularly since the rate of hallucinogenic product formation appeared to be quite high. However, some problems in replicating these studies began to emerge. Product identification was not unequivocal in any of the studies cited above. Also several investigators noted that the radioactive product formed from $C^{14}$ 5MTHF and indolethylamine substrate was not isographic with the expected N- or O-methylated products in alkaline chromatography systems.

It had previously been pointed out that $C^{14}$SAM could be transformed to $C^{14}$ formaldehyde enzymatically and that the formaldehyde could condense with indolethylamines to form cyclic structures including THBC (Meller, Rosengarten, and Friedhoff 1974 and Rosengarten, Meller, and Friedhoff 1974 and in press). These reports were followed by several studies that considered the possibility that β-carbolines could also be formed when 5MTHF replaced SAM in the reaction. It was found that THBC and not DMT was formed in rat brain when 5MTHF was used as a methyl donor (Hsu and Mandell 1975 and Rosengarten, Meller, and Friedhoff 1975a and 1975b). Mandel et al. (1974), Barchas et al. (1974), and Wyatt et al. (1975) also reported that pyridoindoles (another name for β-carbolines) were formed from NMT and 5MTHF. Finally, it does not appear that dopamine can be N-methylated to epinine via a 5MTHF-dependent reaction. Instead, a cyclic compound of the tetrahydroisoquinoline (TIQ) class is formed (Meller, Rosengarten, and Friedhoff 1975). It has been reported by Lin and Narasimhachari (1975) that folate is involved in the methylation of the indole nitrogen. This observation has not been confirmed by others, however, and it seems probable that these investigators were misidentifying the β-carboline as the 1-methyl derivative.

These reactions appear to proceed via the enzymatic formation of formaldehyde from 5MTHF (Meller, Rosengarten, and Friedhoff 1975) followed by the condensation of formaldehyde with the amine substrate; but the specific enzyme involved in the generation of formaldehyde has not been identified by any of the above investigators. Stebbins et al. (in press) found that $N_5$,$N_{10}$-methylenetetrahydrofolate reductase, when highly purified, retains the properties of the formaldehyde-generating enzyme and appears to be the enzyme involved in this reaction.

## Metabolites in Blood and Urine

There are many reports in the literature that DMT, bufotenine, and 5-MeOtryptamine are present in the urine and blood of schizophrenics (Fischer and Spatz 1970, Franzen and Gross 1965, Narasimhachari et al. 1971a and 1971b, Narasimhachari and Himwich 1972, 1973a, and 1973b, Narasimhachari, Plaut, and Leiner 1971, Narasimhachari, Spaide, and Heller 1971, Rosengarten et al. 1970a and 1970b, Sireix and Marini 1969, Tanimukai et al. 1967 and 1970, and Wyatt et al. 1973a). In many of these studies, adequate characterization of product was not carried out. This has led to a number of conflicting reports (Axelsson and Nordgren 1974, Greenberg 1973, and Wyatt et al. 1973a). Greenberg (1973) was able to identify eight endogenous N,N-dimethylated and N,N-diethylated indoleamines by gas liquid chromatography but did not confirm the identity of these compounds by alternative test proce-

dures such as mass spectrometry or TLC. Others have reported the positive identification, by mass spectrometry, of these compounds isolated from urine of schizophrenics (Narasimhachari and Himwich 1973b). Although mass spectrometry is considered to provide unequivocal proof of identity, there is a subjective element involved in interpreting spectra of compounds derived from biological material. Inasmuch as most of the isolation procedures available leave some measure of contaminants that may obscure certain characteristic peaks in the spectrum, it is often necessary to identify a biological compound on the basis of the coincidence of only a few peaks that coincide with the spectra of authentic reference. If peaks specific to the reference compound are not chosen, misidentification may result.

Wyatt et al. (1973a) used a gas chromatography-mass spectrometry isotope dilution determination, a more definitive technique, and found, within the limits of the sensitivity of their assay, no difference among normals, patients with psychotic depressions, and acute or chronic schizophrenics. These investigators found that DMT was not present in greater amounts or metabolized differently in schizophrenics as compared to normals. Their findings do not support the hypothesis that DMT excretion is related to schizophrenia.

Conflicting data regarding DMPEA excretion in the urine in part resulted from lack of quantitative methods.[1] In 1972, a procedure was developed that involved the preparation of an isotope derivative of the extracted amine and its ultimate separation by radioactive sequential cocrystallization with unlabeled carrier (Friedhoff 1972). This method was reported to make possible the quantitative reproducible and unequivocal identification of DMPEA in urine. Results of clinical studies using this method have not yet been published. More recently, Braun et al. (1974), using ion exchange and TLC of the dansylated amine, found intermittent excretion of DMPEA in the urine of schizophrenics with paranoid hallucinatory behavior. These authors propose that the intermittent production of this substance may prevent the development of tolerance that occurs with mescalinelike agents.

[1] Siegel and Tefft (1970) report the identification of DMPEA in equal concentration in urine of five normals and six schizophrenics (drug status not noted). DMPEA in this study was ultimately characterized by mass spectrometry.

## Summary and Conclusions

The original interest in the possibility that hallucinogens might be formed from neurotransmitters or other endogenous compounds stemmed from the proposal that these hallucinogens might play a role in the etiology and pathogenesis of psychosis. Much of the early work not reviewed here was concerned with the measurement of hallucinogens in body fluids and attempts to compare various psychiatric patient groups with relevant control populations. Probably because of the failure of those studies to resolve the issues under investigation, a great deal of the more recent work has been directed toward the improvement of technology and the development of basic information. As a corollary of this shift in emphasis, there has been a major change from the measurement of metabolites toward the investigation of enzymes involved in biosynthesis.

The main source of concern in this field, adequate compound identification, continues to be a problem. In some instances, traditional methods of radioisotope-labeled product identification have not been used. Authentic radio-labeled reference material for the various hallucinogens and derivatives, however, cannot always be obtained. Some identification problems have been resolved by the use of mass spectrometry, but the limited availability of adequate instruments has restricted the use of this approach. In other instances, the inherent limitations of the technique itself have not been fully recognized.

Despite these problems, a substantial advance has been made in our understanding of the mechanisms involved in the formation of endogenous hallucinogens, although we do not understand their role, if any, in the CNS. In the opinion of the reviewers, the following conclusions are warranted by the studies carried out to date by a large number of investigators.

- Tryptamine, or NMT, can be enzymatically converted to DMT by a SAM-dependent enzyme or enzymes shown to be highly active in lung or adrenal, particularly of the rabbit. This enzyme system can be demonstrated in brain, but its activity is very low. Similar findings have been made with regard to the formation of bufotenine from serotonin.
- In brain, red blood cells, and platelets, indolethylamines are transformed primarily to β-carbolines

(pyridoindoles, tryptolines) rather than methylated derivatives when SAM is used as a methyl donor.

- The formation of DMT from tryptamine or NMT has not been shown to occur in any tissue when 5MTHF is used as potential methyl donor instead of SAM.
- Dopamine can be transformed to N-methyldopamine (epinine) by a SAM-dependent enzyme found in adrenal tissue, but not by a 5MTHF-dependent enzyme in any tissue.
- In the presence of 5MTHF, indolethylamines are transformed to β-carbolines (pyridoindoles, tryptolines) and dopamine is transformed to TIQ rather than to methylated derivatives.
- Enzymes have been found in mammalian tissues that can catalyze, in vitro, each step in the transformation of dopamine to DMPEA and mescaline. The in-vivo biosynthesis of these compounds has not been demonstrated.
- A definitive assessment of the relationship of endogenous hallucinogens to the various psychotic states awaits the conduct of studies in which better product identification is carried out with drug-free subjects. Hallucinogenic substances, if they have a role, may be formed intermittently, or may be related to symptom pathogenesis rather than central etiology. Long-term longitudinal studies of carefully selected patients, in whom both symptoms and chemical parameters are studied, might result in important insights if they are adequately designed and use suitable methodology.

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