N,N-DIMETHYLTRYPTAMINE: AN ENDOGENOUS HALLUCINOGEN

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I. Introduction

Hallucinatory phenomena, whether spontaneous or drug induced, have played a major role in the evolution of man's culture and experience and knowledge of himself, his world, and the "world beyond." Such phenomena were generally credited as having occult or religious significance, giving rise to the belief that the percipient of the hallucinations possessed magical powers, was a practitioner of evil, or was in contact with his respective god or gods. These explanations and uses for the hallucinatory experience, evolving through the entire history of man's cultures, have been replaced by scientific models which have sought to evaluate the significance of hallucinations, their etiology, and the biochemical mechanisms by which they are produced.

Thus, the scientific investigation of the plants, concoctions, and potions prescribed by various cultures for eliciting hallucinations led to the identification of several classes of substances which were responsible for the "visionary" states produced following their consumption.

Noting the structural similarity between the O-methylated hallucinogen

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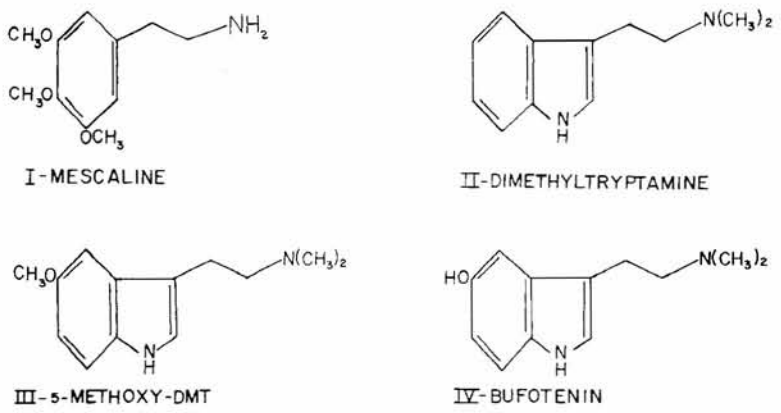

FIG. 1. Mescaline and the indole hallucinogens.

mescaline (I, Fig. 1) and the catecholamine neurotransmitters in man, Osmond and Smythies (1952) proposed that perhaps the hallucinatory phenomenon observed in the heterogeneous disease state known as schizophrenia may result from the endogenous synthesis of hallucinogens. In the 1950s and 1960s Axelrod (1961) described enzymes capable of O- and N-methylating not only catecholamines but also indoleamines, using *S*-adenosylmethionine (SAM) as the methyl donor. Thus, the "transmethylation hypothesis" of Osmond and Smythies was extended to include the possible *in vivo* formation of indole-containing hallucinogens (Benington *et al.*, 1965; Brune and Himwich, 1962) such as *N,N*-dimethyltryptamine (DMT, II, Fig. 1). This indole-containing hallucinogen has now been repeatedly identified as a naturally occurring product of tryptophan metabolism in man and other mammals (Rosengarten and Friedhoff, 1976).

DMT is found in a variety of plants that have been used for centuries by South American tribes to induce visionary states. Seitz (1967) and Diaz (1977) have presented the ethnopharmacological perspective of the use of DMT-containing snuffs and accounts of the effects of these preparations on the native practitioners. However, the following is an excerpt from the first personal account of the effect of pure DMT (75 mg, i.m.) on modern man (Szara, 1957):

> On the third or fourth minute after the injection vegetative symptoms appeared, such as tingling sensation, trembling, slight nausea, mydriasis, elevation of the blood pressure and increase of the pulse rate. At the same time eidetic phenomena, optical illusions, pseudo-hallucinations, and later real hallucinations appeared. The hallucinations consisted of moving, brilliantly colored oriental motifs, and later I saw wonderful scenes altering very rapidly.
>
> The faces of the people seemed to be masks. My emotional state was elevated sometimes up to euphoria. At the highest point I had compulsive athetoid movements in my left hand. My consciousness was completely filled by hallucinations, and my at-

> tention was firmly bound to them; therefore, I could not give an account of the events happening around me. After 3/4 to 1 hour the symptoms disappeared and I was able to describe what had happened.

In this article we will review the research to date concerning the biosynthesis, metabolism, pharmacology, and properties of DMT, leading to the conclusion that DMT may be a neurotransmitter in the mammalian brain. The identification of DMT and other hallucinogens in man may offer an explanation for the experience of hallucinatory phenomena in general.

II. Biosynthesis of DMT in Mammals

A. *In Vitro* Biosynthesis of DMT

Methyltransferases which catalyze the synthesis of hallucinogens (Fig. 2) such as *N,N*-dimethyltryptamine (DMT), 5-methoxy-DMT (III, Fig. 1), and bufotenin (IV, Fig. 1) have been described in human lung, brain, blood, and cerebrospinal fluid (Rosengarten and Friedhoff, 1976).

Porta *et al.* (1977), using gel filtration techniques, have estimated the molecular weight of a rabbit lung indole-*N*-methyltransferase (INMT) as approximately 30,000. The activity of this enzyme is neither stimulated nor inhibited by the presence of MG^{2+}, glutathione (Axelrod, 1962), or EDTA (Saavedra *et al.*, 1973). The enzyme is inhibited by *p*-chloro-mercuribenzoate, indicating the presence of essential sulfhydryls (Axelrod, 1962).

The mechanism of the transmethylation reaction has been described as an "ordered bi bi" reaction (Lin *et al.*, 1973; Porta *et al.*, 1977) according to Cleland's classification (Cleland, 1963). In this mechanism SAM first binds to the enzyme followed by the binding of the indolethylamine substrate; a methyl group is then transferred, followed by dissociation of the complex to give the indolealkylamine and *S*-adenosylhomocysteine (SAH) (Fig. 2). For example, Lin *et al.* (1973) have demonstrated that preincubation of the INMT from rabbit lung with SAM gives an increase in activity, in agreement with this proposed mechanism.

Axelrod (1962) has identified 5-hydroxytryptamine (5-HT) as the best substrate for the rabbit lung enzyme, with the indoles tryptamine (TA) and *N*-methyltryptamine (INMT) giving 81% and 39% of the activity of 5-HT, respectively. More recent studies of INMT activity from the same source have, however, identified NMT as the best substrate (Narasimhachari *et al.*, 1973; Thithapandha, 1972; Mandel *et al.*, 1971) with reported K_m of 5.0×10^{-5} *M* (Mandel *et al.*, 1971) and 8.33×10^{-5} *M* (Sangiah and Domino, 1977), followed by TA with K_m of 3.3×10^{-4} *M* (Mandel *et al.*, 1971) and 4.0×10^{-4} *M* (Porta *et al.*, 1977), and 5-HT with a K_m of 1.0×10^{-3} *M*

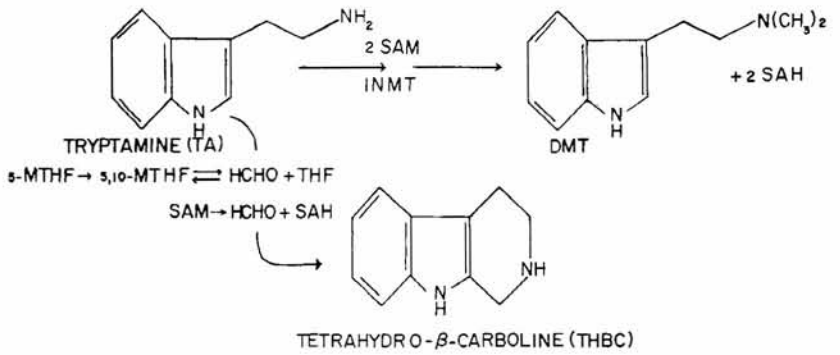

FIG. 2. The biosynthesis of DMT from TA and the mechanism for the formation of THBC.

(Mandel *et al.*, 1971). The K_m for SAM has been reported as 4.0×10^{-5} *M* (Porta *et al.*, 1977).

The INMT isolated from chick brain shows a different substrate affinity, with 5-HT being the best substrate (100%), followed by TA (60%) and NMT (47–50%) (Morgan and Mandell, 1969). Peak INMT activities from this source were identified in the supernatant and synaptosomal fractions (Morgan and Mandell, 1969). The INMT from sheep and human brain also demonstrates a variable substrate affinity with 5-HT (100%), TA (111%), and NMT (55%) (Mandell and Morgan, 1971). Highest INMT activities in human brain have been identified in the uncus, medulla, amygdala, and frontal cortex (Mandell and Morgan, 1971) and in the fronto-parietal and temporal lobes (Saavedra *et al.*, 1973). Studies in rodent brain also give a different substrate affinity with TA ($K_m = 2.78 \pm 1.5 \times 10^{-5}$ *M*) and NMT ($K_m = 3.68 \pm 1.36 \times 10^{-5}$ *M*) (Saavedra *et al.*, 1973). Cellular fractionation in rodent brain has been reported to give 70% of the INMT activity in the supernatant and 20% in the synaptosomal fractions. This may indicate that the enzyme is primarily localized in the soma of cells, which are disrupted by the homogenization process (Saavedra *et al.*, 1973). Based on subcellular distribution studies of rodent brain it has been suggested that INMT may be located postsynaptically (Saavedra *et al.*, 1973).

Indole-*N*-methyltransferase activity has also been described in human lung, CSF, blood plasma, serum, platelets and RBC, human liver, heart and lung, rabbit adrenal gland and kidney, toad, mouse, steer, guinea pig, and baboon brains, and various other tissues from these and other species. There is a distinct probability that INMT is composed of different isoenzymes in various organs from the same and other species.

Mack and Slaytor (1978) have identified two INMTs in the Australian pasture grass *Phalaris tuberosa,* using an affinity chromatography technique.

The two INMTs have distinctly different affinities for the primary indoleamine substrates, such as TA, and the secondary amine substrates, such as NMT, indicating the possible involvement of the two enzymes in the production of the tertiary amine. While the presence of two distinct INMTs has yet to be demonstrated in mammals, such a possibility would help to explain the varying substrate activities in different tissues from the same species. The presence of two enzymes would also allow for further regulation in the production of DMT *in vivo,* with one enzyme controlling the rate of conversion of TA to NMT and another regulating the conversion of NMT to DMT.

B. Regulation and Inhibition of INMT Activity

One of the more consistent findings in studies of INMT activity, regardless of the enzyme source, is the apparent presence of an endogenous dialyzable inhibitor. In a study of the developing rabbit neonate, Lin *et al.* (1974) observed that INMT activity in the lung increased rapidly after birth, reaching its maximum between the 15th and 19th postnatal days. The activity was then observed to decline to the mature level and remain constant thereafter. This decrease in activity was apparently due to a dialyzable inhibitor, the activities of dialyzed samples from mature animals returning to their previous high neonatal levels.

In a study of INMT activity in human blood, Wyatt *et al.* (1973a) also demonstrated the presence of an endogenous inhibitor, which was dilutable and dialyzable. In a comparison of normals with schizophrenics, these authors found no difference in the INMT activity measured in RBC or plasma between the two groups. However, the activity in platelets was greater for the schizophrenic group ($p < 0.001$) than for the normal group. The difference in the activities of the two groups approached zero when the platelets from normal patients were dialyzed. Wyatt *et al.* concluded that the difference in INMT activity observed between psychotic and normal subjects was not due to a quantitative difference in the enzyme, but rather the presence of a dialyzable inhibitor or of a substance capable of metabolizing DMT in normal subjects which was absent in the schizophrenics. Wyatt *et al.* (1973b) have also measured INMT activity in blood platelets from monozygotic twins discordant for schizophrenia. Using nondialyzed platelets, these authors observed elevated activity in the schizophrenic subjects but normal activity in their nonschizophrenic co-twins. Wyatt *et al.* (1973b) concluded from this study that elevated activity may be due to environmental and emotional stress in the psychotic patients rather than some aberration, such as a genetic factor. Christian *et al.* (1977), Beaton and Christian (1978), and Harrison and Chris-

tian (1979) have presented evidence that DMT production is increased under stress in rodent brain and adrenal gland, indicating a possible stress-induced mechanism for increasing INMT activity.

Dialysis of the tissue source in INMT studies not only leads to increased activity but also greatly reduces the amount of volatile and nonvolatile side-products which are produced *in vitro*. These products appear to arise from enzymatic and/or nonenzymatic formation of methanol, formaldehyde, and formic acid from oxidation of the methyl donor, SAM.

Following a report that extracts of bovine pineal gland were beneficial to some schizophrenics, Narasimhachari *et al.* (1974) characterized a potent INMT inhibitor from this tissue source. The inhibitor was water extractable, gave a positive ninhydrin and fluorescamine test, and was absorbed on a cation exchange resin from which it could be eluted with hydrochloric acid. These investigators proposed that the material was a low-molecular-weight peptide ($\sim$ 500–600) but it was not further characterized. Recently, Marzullo *et al.* (1977) have demonstrated the presence of a dialyzable INMT inhibitor in rabbit brain and confirmed the work of Lin *et al.* (1974) that such an inhibitor exists in rabbit lung. Separation of the inhibitor(s) by gel filtration gave three peaks with approximated molecular weights of 1500, 1300, and 1200. These materials were heat stable and digested by trypsin. Treatment of the 1300-amu component with carboxypeptidase A did not destroy its INMT inhibition activity, giving a smaller molecular-weight compound similar to the 1200-amu form.

Thus, INMT activity may be regulated by several endogenous peptides. The increased INMT activity observed in some schizophrenic subjects (for a review see Gillin *et al.*, 1978) could be due to a decreased production of this substance, which may be stress induced (Wyatt *et al.*, 1973c). In an interesting study of INMT activity in human plasma during various stages of sleep, Strahilevitz *et al.* (1977) presented data which suggest that plasma INMT activity may be increased in non-REM as well as the post-sleep-onset wake stages, indicative of some variable regulatory mechanism.

There is, of course, regulation of INMT activity by the substrates for and the products of the transmethylation reaction. The product arising from the transfer of a methyl group from SAM, SAH, is a potent inhibitor of INMT activity, as it is for other methyltransferase enzymes. Lin *et al.* (1973) observed SAH to have an IC_{50} of 5×10^{-5} *M* for INMT from rabbit lung and that the affinity of SAH for INMT was greater than that for SAM. This inhibition is competitive with respect to SAM, is noncompetitive with respect to the indolethylamine substrate, and is reversible (Lin *et al.*, 1973; Domino, 1976). Equimolar concentrations of SAH and SAM give > 90% inhibition of INMT activity. Thus the ratio of SAH to SAM would be very important in determining INMT activity *in vitro* and *in vivo*. Borchardt (1975) confirmed

the results of Lin *et al.* (1973) and demonstrated that INMT shows a high specificity for the structural features of the homocysteine portion of SAH. The inhibition of INMT by SAH has been demonstrated in two other studies (Lin *et al.*, 1974; Lin and Narasimhachari, 1975).

Thithapandha (1972) has shown that DMT at 10^{-4} *M* gives 90% inhibition of rabbit lung INMT and 100% inhibition of chick brain enzyme using NMT as substrate. Mandel *et al.* (1971) had shown similar results using rabbit lung enzyme with 10^{-4} *M* DMT giving 70% inhibition with NMT as substrate and 93% inhibition with TA as substrate. Domino (1976) has reported the IC_{50} of DMT on this enzyme as 1.8×10^{-4} *M* and to be of the noncompetitive type. Inhibition of INMT by DMT has been reported in other studies (Lin *et al.*, 1974; Lin and Narasimhachari, 1975). The INMT is also inhibited by other N,N-dimethylated indoles (Lin and Narasimhachari, 1975). Mandel *et al.* (1971) have demonstrated inhibition of INMT with high concentrations (3.3×10^{-3} *M*) of the substrate/product NMT. Similar findings have been described for high concentrations of TA (Wyatt *et al.*, 1973a).

Indole-*N*-methyltransferase has also been reported to be inhibited by several synthetic compounds and clinically active drugs. Chlorpromazine (Axelrod, 1962; Wyatt *et al.*, 1973a; Narasimhachari and Lin, 1974; Lin *et al.*, 1974; Sangiah and Domino, 1977) is a potent inhibitor of INMT activity with a reported IC_{50} of 2.5×10^{-5} *M* (Axelrod, 1962), as are several of its metabolites (Narasimhachari and Lin, 1974; Sangiah and Domino, 1977). Many other compounds have been tested for INMT-inhibiting activity including SAH analogs (Borchardt, 1975) and diamino-alkanes (Porta *et al.*, 1977).

Some of the most interesting and perhaps clinically useful compounds tested so far as INMT inhibitors are diazo-bicyclononene (DBN), *N,N'*-bis-(3-methyl-2-thiazolidinylidene) succinimide, and 2-imino-3-methylthiazolidine (Mandel, 1976; Mandel *et al.*, 1978). Mandel and co-workers observed these compounds to potently inhibit both *in vitro* and *in vivo* INMT activity. The compounds appear to be quite specific, showing little or no inhibition of other methyltransferases. The DBN has a K_i of 2.0×10^{-6} with NMT as a substrate using rabbit lung enzyme as the source and inhibition is noncompetitive.

C. 5-Methyltetrahydrofolate as the Methyl Donor

Laduron *et al.* (1974) reported that 5-methyltetrahydrofolate (5-MTHF) was also a methyl donor for the INMT reaction with indolethylamines. Banerjee and Snyder (1973) and Hsu and Mandell (1973) reported similar results. However, further research in this area resulted in the identification of

1,2,3,4-tetrahydro-β-carbolines (THBC) as the products of incubations using 5-MTHF and an indolethylamine (Lin and Narasimhachari, 1974; Rosengarten *et al.*, 1976; Barchas *et al.*, 1974; Hsu and Mandell, 1975; Mandel *et al.*, 1974; Stebbins *et al.*, 1976; Rommelspacher *et al.*, 1976; Wyatt *et al.*, 1975; Pearson and Turner, 1975; Hsu, 1976) (Fig. 2). The formation of the THBC compounds in incubations using SAM has also been reported (Rosengarten *et al.*, 1976; Boarder and Rodnight, 1979) or implicated (Boarder and Rodnight, 1976; Gomes *et al.*, 1976) (Fig. 2). Hahn and Ludewig (1934) were the first to show that tryptamines and aldehydes spontaneously condensed to form THBC compounds under physiological conditions. The formation of 2-methyl-THBC and THBC *in vitro* has been demonstrated in incubations of the methyl donors 5-MTHF and SAM (Rosengarten and Friedhoff, 1976) with the indoles *N*-methyltryptamine (NMT) and tryptamine (TA). Such activity has been observed in human platelets (Stebbins *et al.*, 1976; Barchas *et al.*, 1974), human brain (Wyatt et al., 1975), rodent brain (Shoemaker and Cummins, 1976; Rommelspacher *et al.*, 1976; Hsu, 1976: Hsu and Mandell, 1975; Mandel *et al.*, 1974), and chick heart (Mandel *et al.*, 1974). The formation of the THBC compounds in these tissues occurs via the enzymatic formation of HCHO from the methyl donors. This HCHO then condenses nonenzymatically with the indole substrates NMT and TA via a Pictet-Spengler reaction (Fig. 2). This mechanism is supported by the fact that trapping of HCHO produced from the methyl donors eliminates the formation of tetrahydro-β-carbolines *in vitro* (Rommelspacher *et al.*, 1976).

The enzymes responsible for HCHO production from the methyl donor 5-MTHF are 5,10-methylenetetrahydrofolate reductase (Stebbins *et al.*, 1976; Rommelspacher *et al.*, 1976; Pearson and Turner, 1975) and serine-hydroxymethyltransferase (Pearson and Turner, 1979) (Fig. 2). The mechanism of one-carbon transfer to tryptamines by the reductase involves oxidation of 5-MTHF to 5,10-methylenetetrahydrofolate and subsequent nonenzymatic production of HCHO from this folate derivative. In general, it has been suggested that this particular oxidation of 5-MTHF occurs slowly, if at all, under *in vivo* conditions (Kutzback and Stokstad, 1971; Buchanan *et al.*, 1964). Thus, investigators have concluded that the formation of the tetrahydro-β-carbolines *in vitro* is an artifact of 5-MTHF oxidation (Stebbins *et al.*, 1976; Rommelspacher *et al.*, 1976; Pearson and Turner, 1975; Taylor and Hanna, 1975; Burton and Sallach, 1975; Laduron and Leysen, 1975). However, the formation of tetrahydro-β-carbolines *in vivo* via the condensation of an aldehyde with an indolethylamine either enzymatically or nonenzymatically remains a point in question.

The production of HCHO from SAM, especially in human RBC, is most likely due to the action of a methanol-forming enzyme (Axelrod and Daly,

1965). The *in vitro* formation of HCHO from SAM and its subsequent condensation with indole-thylamines to form THBC compounds has been demonstrated in human blood *in vitro* (Meller *et al.*, 1974; Rosengarten *et al.*, 1976).

D. *In Vivo* Biosynthesis of DMT

Mandel (1976) and Mandel *et al.* (1977) have demonstrated the *in vivo* formation of DMT in the rabbit, with intravenous injection of [^{14}C]NMT leading to the production of [^{14}C]DMT in rabbit lung, the site of highest INMT activity in this species. When rabbits were given nonradioactive NMT intravenously, DMT appeared in carotid arterial blood, peaking within the first minute after injection of the precursor. Similar experiments by these investigators with rhesus monkeys and rats did not yield unequivocal evidence for the *in vivo* formation of DMT. Saavedra and Axelrod (1972) have, however, reported the *in vivo* formation of [^{14}C]DMT from [^{14}C]TA in rat brain.

Recently, Stramentinoli and Baldessarini (1978) demonstrated the *in vivo* conversion of intracisternally injected [^{14}C]TA to [^{14}C]DMT in rabbit lung. These investigators also studied the effect of precursor loading on the synthesis of DMT *in vivo* by administering acute and repeated doses of methionine and SAM. Such experiments are relevant to the transmethylation hypothesis of schizophrenia, several studies having demonstrated that acute injections of methionine to psychotic patients exacerbates their symptoms (Cohen *et al.*, 1974). This exacerbation of symptoms has been postulated to occur via increased production of the methylated hallucinogenic indoles. However, Stramentinoli and Baldessarini were unable to demonstrate any increase in DMT production *in vivo* following either acute or chronic methionine or SAM administration to rodents. Close examination of this data reveals, however, that repeated injection (i.v.) of saline, methionine or SAM prior to i.c. injection of [^{14}C]TA led to a 50% decrease in [^{14}C]NMT production and a 50% increase in the amount of [^{14}C]DMT recovered, versus acute saline injections. Furthermore, the methods of identification were equivocal, consisting of one TLC solvent system which does not separate DMT from tetrahydro-β-carbolines (Rosengarten and Friedhoff, 1976).

III. Metabolism of DMT

N,N-Dimethyltryptamine has been the most studied of the endogenous hallucinogens identified to date, due in part to its unique properties:

1. Intramuscular injection of DMT in man takes effect in 3–5 min and produces an intense hallucinogenic episode lasting 30–60 min (Szara, 1956; Sai-Halasz *et al.*, 1958; Rosenberg *et al.*, 1963; Gillin *et al.*, 1976).

2. Three studies have observed that tolerance to DMT does not develop (Cole and Pieper, 1973; Gillin *et al.*, 1973; Stoff *et al.*, 1977). A fourth study suggested only limited tolerance (Kovacic and Domino, 1974).

3. *N,N*-Dimethyltryptamine is rapidly cleared from the blood and is rapidly metabolized (Kaplan *et al.*, 1974; Gillin *et al.*, 1976). The fact that DMT is rapidly metabolized has been used as an explanation for the short-acting effects of this hallucinogen and for its failure to elicit tolerance (Gillin *et al.*, 1976). Several investigators have further concluded that differential levels of DMT have not yet been demonstrated in the psychotic population for the same reason (Gillin *et al.*, 1976).

A. Metabolism of DMT *in Vitro*

In the first *in vitro* study of DMT metabolism (Fish *et al.*, 1955), using a mouse liver homogenate, the major metabolite of DMT was identified as DMT-*N*-oxide (DMT-NO). Its formation was found to be NAD dependent. A mitochondrial fraction of the mouse liver converted DMT to DMT-NO and indole-3-acetic acid (IAA) but did not metabolize DMT-NO when it was used as a substrate. Fish *et al.* (1955) concluded that DMT-NO was the major metabolite in the absence of mitochondria and that the *N*-oxide was not an intermediate in the oxidative deamination of DMT by mitochondrial monoamine oxidase (MAO).

A second study of DMT metabolism, conducted by Szara and Axelrod (1959) using a liver microsomal fraction from rabbits pretreated with the MAO inhibitor (MAOI) iproniazid, identified five indolic compounds from their incubations; DMT, NMT, 6-hydroxy-DMT (6-OH-DMT), 6-OH-DMT-NO, and DMT-NO. The formation of NMT was accompanied by the liberation of formaldehyde (HCHO). These investigators did not discuss the relative abundance of the products but did observe their formation to be $NADP^+$ dependent. This study led to the hypothesis that 6-hydroxylation of the indole ring played an important role in the formation of an active metabolite which, in turn, was responsible for the hallucinogenic effects of DMT (Szara, 1956; Szara and Rockland, 1961).

Recently, Barker *et al.* (1978) studied the metabolism of DMT in brain and liver microsomes obtained from rodents pretreated with the MAOI iproniazid. The metabolites were identified as DMT-NO, NMT, and HCHO. The *N*-oxide was the major metabolite following a 30-min incubation period. No 6-hydroxy metabolites were identified, possibly due to the in-

hibition of 6-hydroxylation activity by iproniazid (Jaccarini and Jepson, 1968). Since rodent brain microsomes are reported to lack 6-hydroxylating activity toward indolalkylamines (Szara and Putney, 1961), the absence of 6-OH-DMT and 6-OH-DMT-NO in the brain microsome studies is not surprising. Studies of 6-OH-DMT formation in certain mammals (Jaccarini and Jepsen, 1968; Szara, 1968) indicate its presence following administration of DMT. However, 6-OH-DMT occurs as only a minor metabolite in man (Szara, 1968). It had been proposed that 6-OH-DMT is the active metabolite of DMT, responsible for the observed hallucinogenic effects of this compound (Szara, 1956; Szara and Rockland, 1961). However, Szara and Putney (1961) later found 6-OH-DMT formation to occur outside the CNS, primarily in the liver. Thus, the psychopharmacological activity of this compound would be dependent on its ability to cross the blood–brain barrier. In this regard, Rosenberg *et al.* (1964) have administered 6-OH-DMT, DMT, and placebo IM to human volunteers. Their results demonstrated that 6-OH-DMT does not produce any signs or symptoms that might be considered to be associated with the hallucinogen DMT. Administration of other DMT metabolites, DMT-NO (20.0 mg/kg) and NMT (30.0 mg/kg) i.p. to rodents trained in a Sidman avoidance schedule also fails to produce any measurable behavior disrupting effects in comparison with saline controls (Barker, 1978).

The formation of an *N*-oxide and a secondary amine from DMT coincides with the known metabolism of many tertiary amines (Bickel, 1969). For example, Bickel (1971) and Willi and Bickel (1973) have demonstrated that four simultaneous reactions occur in liver microsomes during the metabolism of tertiary amines, i.e., N-oxidation, *N*-oxide reduction, *N*-oxide demethylation, and tertiary amine demethylation.

With respect to the formation of IAA in assays of DMT metabolism, either *in vitro* or *in vivo,* it is probable that a large portion of the IAA arises via the oxidative deamination of NMT rather than by direct action of MAO on DMT. The relative rate of NMT oxidation by MAO has been measured as being 9 times greater than that for DMT and 280 times greater than that for DMT-NO, the *N*-oxide being essentially resistant to metabolism by this enzyme under aerobic conditions (Smith *et al.,* 1962; Fish *et al.,* 1955). *N,N*-Dimethyltryptamine per se is not only a poor substrate for MAO (Govier *et al.,* 1953; Ho *et al.,* 1970; Barlow, 1961) but is itself an MAOI (Barlow, 1961; Ho *et al.,* 1970; Ungar and Alivisatos, 1976). However, several studies have demonstrated that the behavioral effects and tissue levels of DMT in rats are potentiated by pretreatment with the MAOI iproniazid (Shah and Hedden, 1978; Lu and Domino, 1974; Moore *et al.,* 1975), leading to the conclusion by these investigators that DMT is mainly metabolized by MAO.

In a quantitative study of DMT metabolism in rat whole brain

homogenate using [5-^{3}H]DMT we (Barker *et al.,* 1980) have reported that IAA formation from DMT is inhibited by 83% in tissue obtained from rats pretreated with iproniazid. However, we also observed that the formation of NMT and DMT-NO was inhibited by 90% under these conditions (Table I). Accordingly, the reported extension of DMT half-life in brain (Shah and Hedden, 1978; Lu and Domino, 1974) and potentiation of its behavioral effects (Shah and Hedden, 1978; Lu and Domino, 1974; Moore *et al.,* 1975) following iproniazid pretreatment may be due to inhibition of the enzymes responsible for demethylation as well as N-oxidation of DMT, rather than strictly MAO inhibition.

Furthermore, we have observed that the incubation of 6.0×10^{-8} *M* [5-^{3}H]DMT for 30 min with rat whole brain homogenate yields IAA, NMT, DMT-NO, and 2-methyl-THBC (2-MTHBC) as metabolites. The major metabolite was IAA. Incubation of DMT at a higher concentration (2.0×10^{-5} *M*) also gave IAA, NMT, DMT-NO, and 2-MTHBC as metabolites. However, at this concentration, DMT-NO was the major metabolite at 30 min. Incubation of 2.7×10^{-8} *M* [5-^{3}H]DMT-NO yielded IAA, DMT, and 2-MTHBC as metabolites. Anaerobic incubation with [5-^{3}H]DMT-NO as substrate stimulated DMT and NMT production while IAA formation remained essentially unchanged. The formation of 2-MTHBC was also stimulated under these conditions (Table I).

The metabolism of [5-^{3}H]DMT at a concentration of 6.0×10^{-8} *M* as a function of time is presented in Fig. 3. Incubation of 2.0×10^{-5} *M* [5-^{3}H]-DMT with time showed (Fig. 4) that *N*-oxide formation was maximal at or before 30 min and was the major metabolite when measured at this time and concentration of DMT. Production of NMT peaked at 1 hr and then declined sharply. IAA was the major metabolite at the end of this 2-hr incubation period. However, 2-MTHBC formation was observed to be still increasing. We confirmed the results of these experiments using $\alpha,\alpha,\beta,\beta$-tetradeutero-DMT (DDMT) as a substrate by combined gas chromatographic/mass spectrometric (GC/MS) analyses with the identification of deuterated NMT and 2-MTHBC as metabolites of DDMT. Indole-3-acetic acid and DMT-NO could not be assayed by this method. However, using the GC/MS method, we also identified trace amounts of TA and THBC as metabolites of DDMT, having gone undetected in the [5-^{3}H]DMT assays (Figs. 5 and 6).

The formation of 2-MTHBC and THBC may have resulted from the condensation of the other DMT metabolites, NMT and trace amounts of TA, and HCHO. Free HCHO is produced during incubations of DMT with rodent brain (Barker *et al.,* 1978; Barker, 1978) and liver tissue (Szara and Axelrod, 1959; Barker *et al.,* 1978; Barker, 1978). To determine the contribution of this Pictet-Spengler reaction we included dimedone in an incubation mixture, serving as a HCHO trapping reagent. The GC/MS analysis of these in-

TABLE I

METABOLITES FORMED IN 30-MIN INCUBATIONS OF [5-^{3}H]DMT AND DMT-NO IN WHOLE RAT BRAIN HOMOGENATES

Substrate	Concentration (M)	Iproniazid pretreatment	Aerobic or anaerobic	Metabolites (μmol/min/mg protein $\times 10^8$)				
				2-MTHBC	NMT	DMT	DMT-NO	IAA
[5-^{3}H]DMT	6.0×10^{-8}	No	Aerobic	0.79	1.22	—	1.85	20.5
	6.0×10^{-8}	Yes	Aerobic	0.00	0.12	—	0.19	3.47
	2.0×10^{-5}	No	Aerobic	0.06	10.90	—	33.00	1.95
[5-^{3}H]DMT-NO	2.7×10^{-8}	No	Aerobic	0.09	0.92	0.42	—	2.74
	2.7×10^{-8}	No	Anaerobic	1.00	2.50	2.52	—	2.01

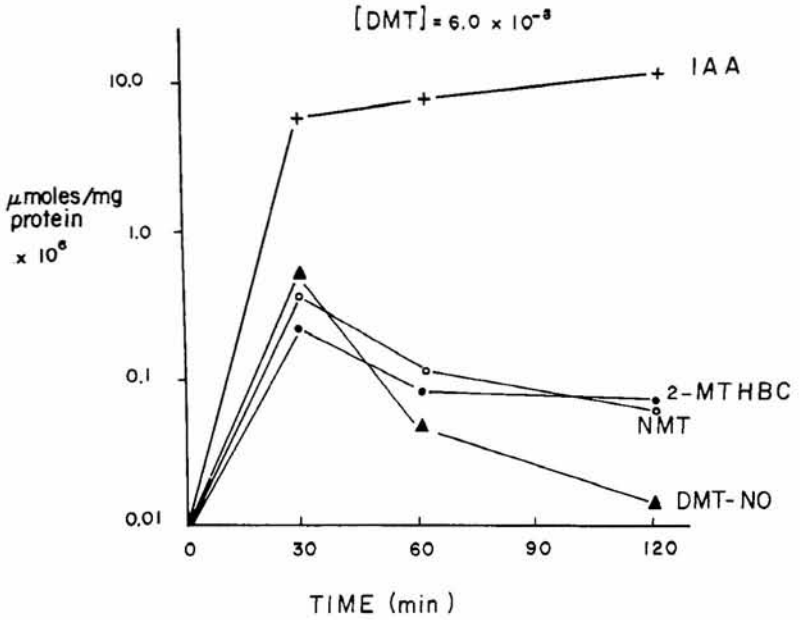

FIG. 3. The metabolism of 6.0×10^{-3} *M* DMT in rat whole brain homogenate as a function of time.

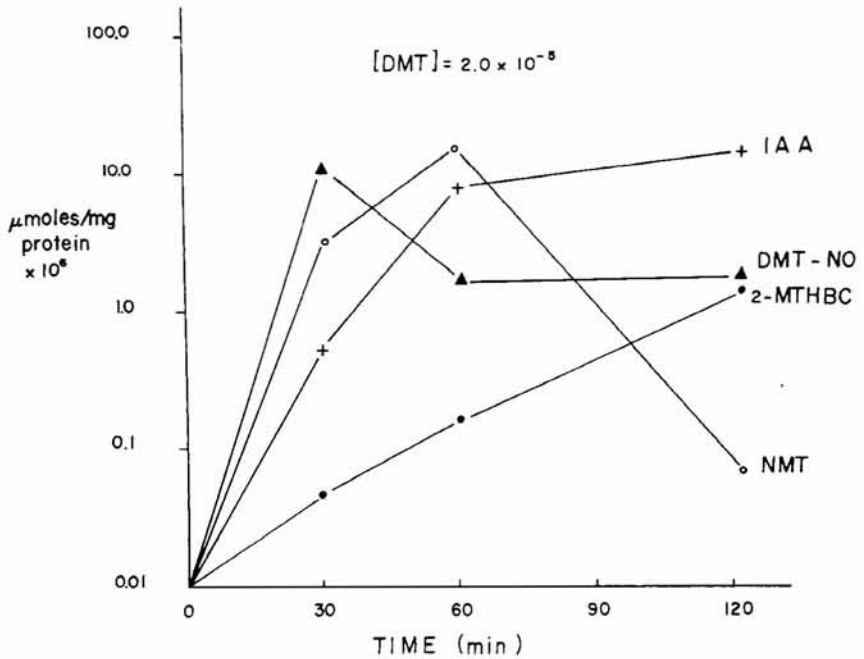

FIG. 4. The metabolism of 2.0×10^{-5} *M* DMT in rat whole brain homogenate as a function of time.

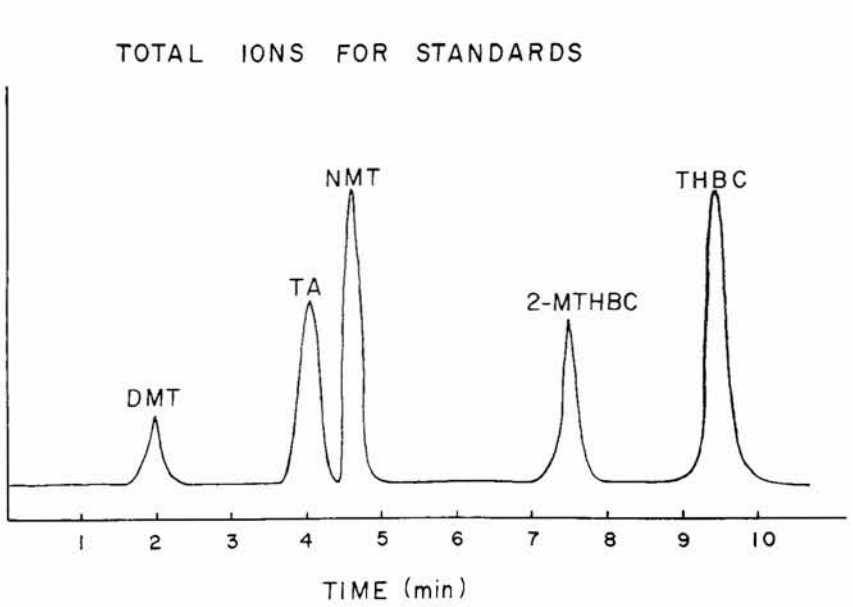

FIG. 5. A GC/MS chromatogram of standards used in the study of DDMT metabolism in rat whole brain homogenate.

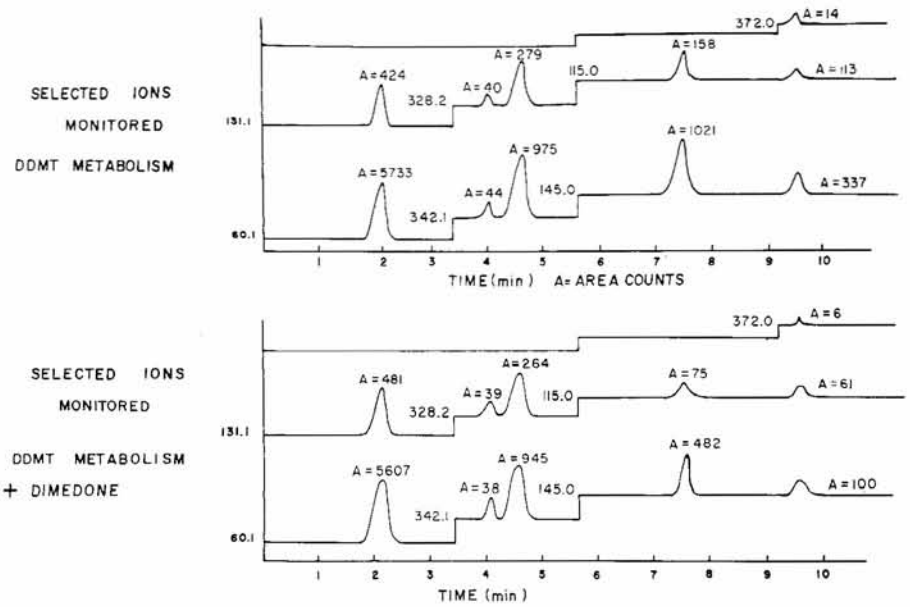

FIG. 6. The SIM results of DDMT and DDMT plus dimedone metabolism in rat whole brain homogenate.

cubations showed that approximately 50% of the β-carbolines formed could be accounted for by a reaction involving the condensation of NMT and TA with HCHO (Fig. 6). However, it is of interest to note that, mechanistically, intermediates in the formation of THBC from an amine and HCHO and those proposed in the demethylation of tertiary amines, by either direct C-hydroxylation or *N*-oxide rearrangement, are identical (Fig. 7). Thus, the formation of HCHO is not necessarily a prerequisite for the formation of THBC from DMT. Both mechanisms lead to the formation of an iminium ion which can cyclize to form THBC.

The metabolism of DMT-NO leads to the formation of 2-MTHBC, NMT, IAA, and DMT. Since the *N*-oxide appears to be the major intermediary metabolite in *in vitro* incubations (Fish *et al.*, 1955; Barker *et al.*, 1978; Barker, 1978; Barker *et al.*, 1980), it may play a pivotal role in the overall metabolism of DMT *in vivo*. As mentioned previously, four simultaneous reactions are known to occur during the metabolism of tertiary amines, i.e., N-oxidation, *N*-oxide reduction, tertiary amine demethylation, and *N*-oxide demethylation. At present, the relative contributions of these four reactions to the metabolism of DMT and DMT-NO are not known with any certainty and must await further research efforts to answer this question. However, in the case of indolethyl-tertiary amines, such as DMT, another reaction sequence may be added, i.e., THBC formation. Based on the results of our recent study we have proposed a pathway for the overall synthesis and metabolism of DMT in brain tissue (Barker *et al.*, 1980) (Fig. 8).

The question of the relative role of microsomal enzymes and MAO in the overall metabolism of DMT also remains unanswered.

In an attempt to determine the role of microsomal enzymes versus MAO

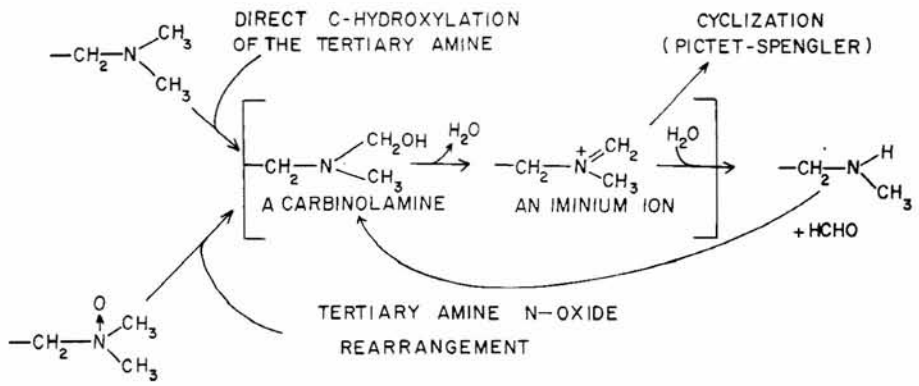

FIG. 7. Mechanisms for the demethylation of tertiary amines and tertiary amine *N*-oxides illustrating the intermediates which are identical with those proposed in the Pictet-Spengler reaction.

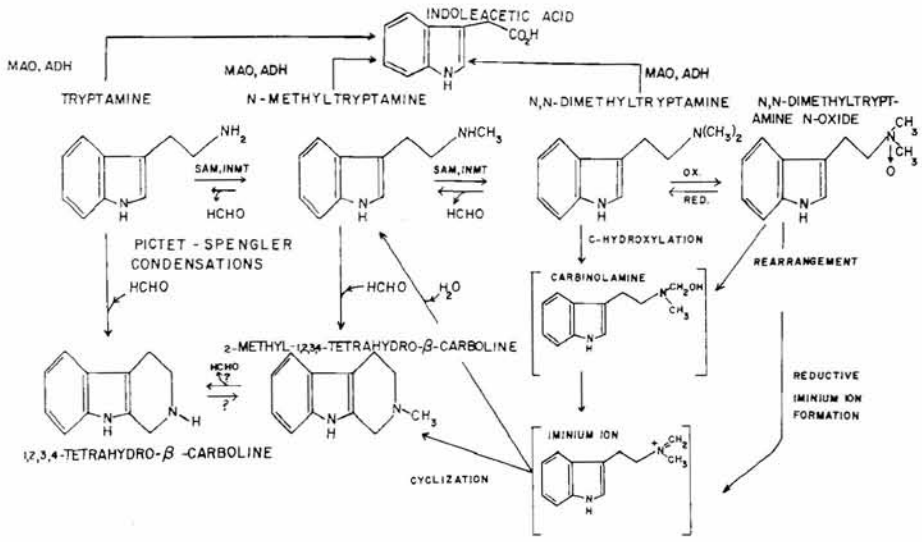

FIG. 8. Proposed pathway for DMT synthesis and metabolism in brain tissue. ADH, Aldehyde dehydrogenase.

in DMT metabolism, Shah and Hedden (1978) and Lu *et al.* (1978) administered SKF 525-A to rodents prior to the administration of DMT. These investigators did not observe any potentiation of DMT's behavioral effects or tissue half-life levels by SKF 525-A (50 mg/kg). Tertiary amine and tertiary amine-*N*-oxide demethylations are, however, inhibited by SKF 525-A (Bickel, 1969, 1971; Willi and Bickel, 1973). However, *N*-oxide formation is not inhibited by this agent. In fact, SKF 525-A stimulates excretion of *N*-oxides (Bickel, 1969). Lu *et al.* (1978) observed that SKF 525-A increases DMT levels in brain and liver and also significantly increases liver DMT half-life. However, the dose of SKF 525-A was twice that used by Shah and Hedden (1978), i.e., 50 mg/kg versus 100 mg/kg. Lu *et al.* (1978) also studied the effect of phenobarbital on brain and liver DMT concentrations. Chronic pretreatment with phenobarbital significantly decreased brain and liver DMT levels. Of the few studies concerning induction of tertiary amine *N*-oxidase, inducibility of *N*-oxide formation by phenobarbital is suggested (Bickel, 1969). Phenobarbital also stimulates *N*-oxide demethylation (Willi and Bickel, 1973).

Lu *et al.* (1978) have also found that certain neuroleptics affect brain DMT content. For example, these researchers found octoclothepin was > haloperidol > methiothepin in reducing brain DMT content whereas chlorpromazine and molindone increased it. The increased DMT levels seen with chlorpromazine may be due to a competition with demethylating and

N-oxidizing enzymes, for both have an *N,N*-dimethyl side-chain. Shah and Hedden (1978) obtained similar results, finding DMT levels significantly increased in brain tissues of chlorpromazine-pretreated animals.

B. Metabolism of DMT *in Vivo*

In the first *in vivo* study of DMT metabolism, Erspamer (1955) observed IAA as a metabolite in rodent urine. However, the amount of IAA that was recovered represented only 2.7% of the injected dose of DMT. Szara (1956) obtained similar results, recovering 8.3% of an original DMT dosage as free IAA in the urine of human volunteers. Neither study detected unchanged DMT in the urine samples. Kaplan *et al.* (1974) observed that less than 0.16% of an injected dose (i.m.) of DMT was recoverable as DMT in human urine following a 24-hr collection. These investigators further observed that DMT concentration peaked in 10–15 min in blood and essentially disappeared within 1 hr, only 1.8% of the injected dose ever being present in the blood at any one time. Gillin *et al.* (1976) reported similar results in man, blood levels of DMT reaching a peak within 10–15 min following i.m. injection. The concentration of DMT fell rapidly, reaching undetectable levels within 45–120 min.

Cohen and Vogel (1972) observed DMT to be rapidly absorbed from the peritoneal cavity of the rodent and to be distributed throughout the plasma, liver, and brain. The metabolism of DMT was also rapid, having essentially disappeared from brain, liver, and plasma within 30 min. By monitoring levels in blood, these investigators also found that DMT levels peaked within 5 min, remained at a plateau for 5 min, and decreased sharply thereafter to undetectable levels. Cohen and Vogel also observed that the brain:plasma ratio of DMT was 5:4 and interpreted these data as an indication of an active transport mechanism for DMT in rodent brain. Shah and Hedden (1978) recently expressed a similar conclusion having observed a brain:plasma ratio for DMT of 4:1 in rats.

Mandel *et al.* (1977) have shown that within 60 min after i.v. injection of [^{14}C]DMT in rabbits, less than 25% of the radioactivity remains unchanged in blood, lung, liver, and kidney. One-half of the radioactivity in brain was unchanged DMT. Trace amounts (0.2–1%) of [^{14}C]TA and [^{14}C]DMT were found in all tissues examined. The major polar metabolite was identified as [^{14}C]IAA, accounting for up to 23% of the radioactivity in the blood. However, the major portion (30–96%) of [^{14}C]DMT metabolites present in blood, lung, liver, kidney, and brain were not extractable by the method employed and were subsequently not identified.

Szara and Axelrod (1959) found DMT, NMT, 6-HDMT, TA, 6-HIAA,

and IAA to be *in vivo* metabolites of DMT as measured in urine from rodents pretreated with the MAOI iproniazid. These investigators had identified 6-HDMT-NO and DMT-NO *in vitro* (Szara and Axelrod, 1959) but did not observe these substances to be present in urine.

IV. Tolerance to DMT

An important aspect when considering DMT as an etiological factor in psychopathological conditions has been whether or not tolerance to this substance could be demonstrated (Gillin *et al.*, 1976). In this regard, Cole and Pieper (1973) have administered DMT to squirrel monkeys trained in fixed ratio schedules for food reinforcement. Injections of DMT (2.0 mg/kg i.m.) for 36–38 consecutive days failed to elicit tolerance to the behavior-disrupting effects of this compound.

Gillin *et al.* (1973), measuring EEG, coordination, posture, pupil dilation, and other physical symptoms, demonstrated that tolerance to DMT did not develop in the cat. Animals were treated with 3 mg/kg DMT i.p. for 7–15 days twice daily or every 2 hr for 24 hr. These researchers further noted that not only did tolerance not develop but rather an apparent increased sensitivity to repeated injections of DMT was observed. In the same study rapid tolerance to LSD was demonstrated.

Using higher doses (3.2–10 mg/kg) and more frequent injections (every 2 hr for 21 days, i.p.) Kovacic and Domino (1974) did elicit a partial tolerance to DMT in rats. These researchers also demonstrated a cross-tolerance to LSD (0.1 mg/kg) following tolerance to 3.2 mg/kg DMT but obtained only slight cross-tolerance to LSD after tolerance was obtained with 10.0 mg/kg DMT. Rosenberg *et al.* (1964) has found DMT to be only mildly cross-tolerant in humans made tolerant to LSD.

Stoff *et al.* (1977) administered 4 mg/kg DMT twice daily for 14 days (i.p.) to rodents and, again, tolerance was not observed to develop.

Thus, if tolerance to the effect of DMT occurs, it is at best aperiodic and short-lived.

V. DMT and 5-Hydroxytryptamine

In general, the mechanisms by which the hallucinogens produce their autonomic, somatic, and psychic effects on man is not known with any certainty. Although a common site of action has been proposed for hallucinogenic activity (Smythies *et al.*, 1970) it has become evident that this class of

compounds has complex and diversified mechanisms of action, thus eliciting behavioral and pharmacological effects through interaction with many identified and, perhaps, as yet unidentified biochemical systems. Now, with the identification of several indole-containing hallucinogens as normal products of mammalian metabolism, the possibility of explaining the mode of action of administered hallucinogens on the basis of effects on endogenous "hallucinogen receptors" and mechanisms is, however, enhanced.

Most theories have postulated this "hallucinogen receptor" to be the serotonin receptor and early attempts to explain the mode of action of the indole hallucinogens focused on this receptor. This was mainly due to the recognized structural similarities of the indole hallucinogens and 5-HT.

While many seemingly unrelated compounds produce perturbations in 5-HT systems, there is little doubt that some of the effects of the hallucinogens are mediated through 5-HT.

For example, Aghajanian *et al.* (1970) have observed that DMT administered i.v. produces a complete inhibition of the 5-HT containing raphe neurons in the rat and several investigators have reported that DMT has a depressant effect on the 5-HT containing visual systems of mammals (Evarts, 1958; Moore *et al.*, 1976; Khazan and McCash, 1965; Heiss *et al.*, 1973; Paulson and McClure, 1974). Furthermore, there are at least five reports that drugs known to inhibit some peripheral and central effects of serotonin also antagonize behavioral, autonomic, and electrophysiological changes induced by DMT; i.e., methysergide (Corne and Pickering, 1967; Winter, 1972), cinanserin (Winter, 1972), and methiothepin (DeFrance *et al.*, 1975; Moore *et al.*, 1975, 1976). However, Christian *et al.* (1977) have shown that 5-HT bound to rat-lysed synaptosomal membranes is not significantly displaced by even high concentrations of DMT (1×10^{-5} *M*) although DMT will completely displace LSD in the same system. Thus, the effects or lack of effects of DMT on certain 5-HT containing neurons may be more directly related to a secondary action of DMT binding at other tryptaminergic receptors. In many cases, 5-HT receptors may be only one of many sites of action for compounds such as the hallucinogen DMT and the effects may be the end result of complex synergism producing agonist, antagonist, or agonist–antagonist character.

In this regard, Szara (1956) has observed an increase in the excretion of IAA and 5-HIAA following administration of DMT to humans. An increase in 5-HT and decrease in 5-HIAA elicited by DMT has also been observed (Freedman *et al.*, 1970; Randic and Padjen, 1971). *N,N*-Dimethyltryptamine also decreases 5-HT depletion in rat brain following inhibition of 5-HT synthesis (Andén *et al.*, 1971; Fuxe *et al.*, 1972), although DMT itself does not appear to affect tryptophan hydroxylase (Andén *et al.*, 1971). Thus, DMT appears to mainly affect the rate of 5-HT turnover (Gillin and Wyatt, 1977) and

there may be a complex biochemical feedback mechanism involved in the interaction of these compounds *in vivo.*

VI. DMT and Dopamine

At present, two theories of schizophrenia are most prominent in the literature: the transmethylation hypothesis, related to the production of DMT *in vivo,* and the dopamine (DA) hypothesis, proposing an overactive dopaminergic component in the etiology of the disease. Recently, several researchers have joined the two concepts and have studied the effects of DMT on the DA system.

Using unilateral nigro-striatum lesioned rats, Pieri *et al.* (1974) have implied that DMT has no dopamine receptor agonist effect. In such a model, agents that induce dopamine release in the striatum from the nerve terminals of the intact side induce a rotation toward the side with the lesion (ipsilateral turning). Conversely, agents that stimulate dopamine receptors directly induce rotation toward the intact side (contralateral). Jenner *et al.* (1978) were also unable to demonstrate DMT (2.0 mg/kg) induced turning behavior using this model. However, Trulson *et al.* (1977) have presented data which indicate that DMT (10 mg/kg and 20 mg/kg) produces significant ipsilateral turning in this model, although the results were not indicative of a very potent DA releasing effect. Similar results have been reported by Stern and Dalsass (1976). Von Hungen *et al.* (1975) have observed that DMT is without effect on basal DA-sensitive adenylate cyclase activity in particulate fractions from the corpus striatum of rats, suggesting that DMT does not bind to DA receptors and may be an indication that this drug does not act directly at DA sites.

Smith (1977) reported that DMT, given acutely or chronically, enhances the rate of striatal DA synthesis *in vivo* in rodent brain. This finding was substantiated by the fact that 30 min after DMT injections, the level of DA extraneuronal metabolite, 3-methoxytyramine, significantly increased. Thus, it appeared that DA was released presynaptically at a faster rate than controls. The increase in DA turnover observed in this study was not attenuated even after one month's chronic treatment with DMT (5 mg/kg/day), consistent rises in striatal 3-methoxytyramine being observed. Thus, tolerance to this DMT effect on DA does not appear to be evident. However, two studies using whole rodent brain levels of DA as a measure of the effect of DMT on this system did not provide any evidence for increased DA synthesis (Leonard and Tongue, 1969; Anden *et al.,* 1971). Smith (1977) did find that neither acute nor chronic administration of DMT had any effect on norepinephrine levels or turnover rate in the diencephalon, in agreement with the work of Andén *et al.* (1971), Haubrich and Wang (1977), and Waldmeier and Maitre (1977).

In studies *in vivo* Haubrich and Wang (1977) observed up to a 42% decrease in the concentration of dopamine in the forebrain of rats following administration of DMT (20 mg/kg). The effect was maximal as early as 5 min and persisted for at least 1 hr. *N,N*-Dimethyltryptamine also produced a significant decrease in the concentration of acetylcholine (ACh) in the corpus striatum, but not in the cortex. These researchers concluded that the effects of DMT on DA concentration reflected changes which occurred largely within the nigro-striatal dopaminergic pathway and were produced by enhanced dopamine synthesis and release rather than any inhibition of DA synthesis. The reduction in striatal ACh was also postulated to occur by a similar mechanism.

Waldmeier and Maitre (1977) found DMT (50 mg/kg i.c.) to exhibit a potent short-lived MAO inhibitory effect on rat striatum and whole brain, decreasing the deamination of 5-HT and DA. These researchers also observed that DMT (30 mg/kg), administered 15 min prior to injection of [^{3}H]DOPA, produced a 600% ($p < 0.001$) increase (versus control) in [^{3}H]DA and [^{3}H]MT levels. This effect was similar to that seen on the administration of amphetamine. DMT also produced a short-lived depletion of endogenous homo-vanillic acid (HVA) and a pronounced depletion of 3,4-dihydroxyphenylacetic acid (DOPAC). These authors concluded that these effects were due to the MAOI properties of DMT and to a dopamine-releasing effect of this hallucinogen.

Thus, it is probable that DMT has an indirect effect on the dopaminergic system. This idea is further supported by the more recent data that neuroleptics, i.e., dopamine receptor blocking agents, can antagonize some of the physiological and behavioral effects of DMT (Moore *et al.*, 1975; Whitaker and Seeman, 1977; Jenner *et al.*, 1978; Gillin *et al.*, 1978; Shah and Hedden, 1978). However, it is also probable that many neuroleptics may have a direct "hallucinogen receptor" action, thus attenuating the action of the hallucinogens by receptor blockade.

VII. DMT at the Synapse

Many attempts have been made to correlate hallucinogenic activity with ability to bind at known neurotransmitter binding sites such as those for 5-HT and DA. The compound most often used in these studies is LSD, the most potent hallucinogen known. While LSD has been shown to bind in both receptor systems there has yet to be a complete understanding of the mode of action of this and other hallucinogens in man via these systems. Several studies have shown that DMT and other hallucinogens will inhibit the binding of LSD to synaptosomes or will displace LSD from its binding sites (Far-

row and Van Vunakis, 1972; Bennett and Snyder, 1975; Burt *et al.,* 1976; Lovell and Freedman, 1976; Christian *et al.,* 1977). DMT has also been observed to inhibit 5-HT binding on synaptic membranes ($IC_{50} = 2.2 \times 10^{-7}$ *M*; Whitaker and Seeman, 1978) or displace 5-HT from its high-affinity binding site ($DI_{50} = 5 \times 10^{-7}$ *M*; Fillon *et al.,* 1976). However, using rat-lysed synaptosomal membranes, Christian *et al.* (1977) did not obtain displacement of 5-HT from its high-affinity site with concentrations of DMT up to 1×10^{-5} *M* although this same concentration of DMT or 5-MeO-DMT completely displaced LSD in the same system. Several investigators have concluded that the binding sites for hallucinogens are not solely 5-HT sites (Fillion *et al.,* 1976; Christian *et al.,* 1977; Glennon *et al.,* 1978), although hallucinogens such as DMT do exhibit a certain affinity for these sites. However, binding affinity is not a singularly sufficient parameter to explain the mode of action or the potency of hallucinogens (Glennon *et al.,* 1978).

However, LSD has been shown to also bind at DA sites and to stimulate DA-sensitive adenylate cyclase (Von Hungen *et al.,* 1975; Bockaert *et al.,* 1976; Spano *et al.,* 1976). While LSD can exert such effects on DA systems, DMT apparently does not directly affect DA receptors (Von Hungen *et al.,* 1975; Burt *et al.,* 1976). However, several studies have shown that the effects of DMT are blocked by neuroleptics (Moore *et al.,* 1975; Whitaker and Seeman, 1978; Jenner *et al.,* 1978; Gillin *et al.,* 1978; Shah and Hedden, 1978). Whitaker and Seeman have shown that DMT significantly inhibits the binding of haloperidol in brain tissue, although it has a much weaker effect on apomorphine binding. The reverse effect was seen for LSD in the same system. Thus, it is odd that the hallucinogenic tryptamine DMT does not block the binding of the dopamine agonist (apomorphine) more effectively than the antagonist (haloperidol), especially with the knowledge that DMT is a poor competitor for the binding of dopamine. This may be an indication that neuroleptics possess a "hallucinogen receptor" binding component, which would add an interesting parameter to the possible mode of action of the neuroleptics in the treatment of schizophrenia and to the effects of DMT on dopaminergic function.

Recent research concerning the binding of DMT to synaptic membranes has yielded data suggesting that there are specific binding sites for DMT in brain tissues (Bearden *et al.,* 1978; Rosengarten and Friedhoff, 1978). Bearden *et al.* (1978) have described a high-affinity ($K_d = 3.0 \times 10^{-10}$ *M*) binding site for DMT on purified rat synaptosomal membranes. This site is apparently sensitive to low concentrations of LSD but not sensitive to 5-HT (McClain and Christian, 1975; Christian *et al.,* 1977). DMT has also been shown to lead to the production of cAMP in synaptosomal membrane preparations (Bearden *et al.,* 1978; Christian *et al.,* 1977). Addition of 5-HT to these systems has been shown to cause an increase in cAMP production,

which is additive (Bearden *et al.,* 1978; Christian *et al.,* 1977). Uzunov and Weiss (1972) have shown that DMT and other dimethyl tryptamines cause an increase in cAMP in rat brainstem slices as well as an increase in cAMP in rat cerebrum *in vivo.*

Christian *et al.* (1977) have presented data showing that DMT is localized in the synaptosomal fraction of rat brain and that a large portion of the DMT is further identifiable in the vesicular fraction. These investigators have further illustrated the Mg^{2+}- and ATP-dependent uptake of DMT by rat brain vesicles. This experiment would appear to demonstrate the active transport of DMT into brain vesicles. Sangiah *et al.* (1979) have recently shown that [^{14}C]DMT accumulates in rat brain cortical slices by a process that has many of the properties of an active uptake mechanism characteristic of that reported for other putative central nervous system neurotransmitters, and appears to possess both high- and low-affinity uptake sites. This uptake of DMT was inhibited by other indoleamines as well as the neuroleptics octoclothepin and methiothepin.

VIII. An Explanation for Hallucinatory Phenomena

In practice, any chemical substance that is a normal constituent of nervous tissue and has a defined excitatory or inhibitory action on nerve or muscle cells is potentially classifiable as a neurotransmitter. In this chapter we have presented the data to date that illustrate that DMT is a normal constituent of mammalian brain and other tissues. Enzymes capable of synthesizing DMT from TA and NMT have also been described. These enzymes are apparently controlled by small peptide-like compounds as well as by feedback inhibition from substrate and product. A cyclic metabolic pathway for DMT has been offered.

There is also evidence that DMT is taken up into synaptosomes and stored in vesicles by mechanisms identical to those described for known neurotransmitter substances. Specific binding sites for DMT have been suggested and DMT has been shown to lead to the production of cAMP, a secondary receptor messenger. As evidence of its electrophysiological activity Berridge (1972) and Berridge and Prince (1974) have shown that DMT stimulates fluid secretion from the salivary glands of blowflies, changes the transepithelial and intracellular potential of the gland, and increases the production of cAMP.

Thus, DMT may fulfill the criteria for consideration as a neurotransmitter or a neuromodulator per se. Much further research is needed to elaborate this possibility. However, it does provide a basis for further speculation as to the possible mode of action of hallucinogens and perhaps a general explanation for the hallucinatory experience. There may indeed exist a hallucinogen

receptor system distinct from 5-HT or DA sites. This receptor system may be the DMT system, consisting of its own presynaptic, postsynaptic, reuptake, and perhaps autoreceptor sites. As is the case with other putative transmitter systems, the DMT system may be affected by agonist or antagonist drugs or its mechanisms for synthesis, storage, uptake, and release may be altered. Thus, it is plausible that the mode of action of hallucinogens, such as LSD, may be their effect on these mechanisms, altering, perhaps, the levels of the endogenous hallucinogens, thus producing the observed effects on the psyche. Other drugs that are known to lead to the production of hallucinations may act by similar mechanisms and alterations in man's physiological state may lead to spontaneous hallucinations, mediated through the DMT system. Only further research will lend credence to, or nullify, these hypotheses.

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