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Endogenous psychoactive tryptamines reconsidered: an anxiolytic role for dimethyltryptamine

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Summary The presence of the potent hallucinogenic psychoactive chemical *N,N*-dimethyltryptamine (DMT) in the human body has puzzled scientists for decades. Endogenous DMT was investigated in the 1960s and 1970s and it was proposed that DMT was involved in psychosis and schizophrenia. This hypothesis developed from comparisons of the blood and urine of schizophrenic and control subjects. However, much of this research proved inconclusive and conventional thinking has since held that trace levels of DMT, and other endogenous psychoactive tryptamines, are insignificant metabolic byproducts. The recent discovery of a G-protein-coupled, human trace amine receptor has triggered a reappraisal of the role of compounds present in limited concentrations in biological systems. Interestingly enough, DMT and other psychoactive tryptamine hallucinogens elicit a robust response at the trace amine receptor. While it is currently accepted that serotonin 5-HT_{2A} receptors play a pivotal role in the activity of hallucinogenic/psychedelic compounds, we propose that the effects induced by exogenous DMT administration, especially at low doses, are due in part to activity at the trace amine receptor. Furthermore, we suggest that endogenous DMT interacts with the TA receptor to produce a calm and relaxed mental state, which may suppress, rather than promote, symptoms of psychosis. This hypothesis may help explain the inconsistency in the early analysis of endogenous DMT in humans. Finally, we propose that amphetamine action at the TA receptor may contribute to the calming effects of amphetamine and related drugs, especially at low doses.
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Introduction

Scientific knowledge pertaining to the chemical *N,N*-dimethyltryptamine (DMT) began inconspicuously with its synthesis by Manske [1] in 1931. More than two decades later, in the 1950s, DMT was identified as one of the active compounds in a potent psychoactive snuff prepared from the seeds of the Amazonian plant *Anadenanthera peregrina* [2–4]. This snuff, variously called *cohoba* and *yopo*, is used by Amazonian tribes in shamanic rituals. *Epena*, another intoxicating Amazonian snuff prepared from the bark resin of plants of the genus *Virola* and also used ritualistically, was shown in the 1960s to contain DMT [2–4]. DMT has since been described in hundreds of organisms: fungi, marine sponges, tunicates, frogs, legumes, and grasses [5]. DMT is perhaps most well known for its presence in the plant *Psychotria viridis*, which

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is used in combination with the vine *Banisteriopsis caapi*, to prepare the hallucinogenic brew *ayahuasca* or *yagé*, used by indigenous peoples in the Amazon basin in shamanic ceremonies [6]. The potent hallucinogenic effects of pure DMT in humans were first reported by Szara [7] in 1956. Then, in 1965, DMT, tryptamine and 5-hydroxy-*N*,*N*-dimethyltryptamine (bufotenine) were reported as normal constituents of human urine and blood [8].

Despite DMTs ubiquitous presence throughout the plant and animal kingdoms, and even in the human body, it was classified as a Schedule One controlled substance with the implementation of the US Controlled Substances Act in 1970. A Schedule One controlled substance is defined by the US government as a substance that demonstrates a high potential for abuse, has no accepted medical use, and lacks accepted safety for use, even under medical supervision. The placement of DMT and other hallucinogenic/psychedelic compounds in Schedule One has significantly impeded scientific research pertaining to these exceedingly interesting, neurochemically-active molecules [9,10]. DMT is essentially non-toxic to body organs and does not cause physiological dependence or addictive behaviors. Thus, its classification as a dangerous drug is based primarily on socio-political reasons rather than clinical-scientific evidence. DMT is also internationally classified as a Schedule One substance by the 1971 United Nations Convention on Psychotropic Substances.

Soon after the discovery of endogenous DMT in humans, psychiatric researchers began to report correlations between increased levels of DMT in human fluids and schizophrenia [11–15]. It was suggested that excess DMT biosynthesis may promote psychotic symptoms. This proposal (which is sometimes known as the ''transmethylation hypothesis,'' because it involves methylated amines) attracted interest in the 1960s and 1970s. In more recent years, the transmethylation hypothesis has been eclipsed by the dopamine hypothesis of schizophrenia, wherein psychotic symptoms are related to excessive activity in certain dopaminergic circuits in the brain. Recent biochemical and genetic characterization of a new family of receptors, the trace amine (TA) receptors, found in mammalian central and peripheral nervous tissues, has renewed interest in a potential role for trace amines in psychosis [16]. It is believed that tryptamine, a necessary metabolic precursor to DMT, can act as a neurotransmitter at the TA receptor [16]. As DMT also shows activity at the TA receptor [17], endogenous DMT may function as a neurotransmitter in the TA system. Ten years ago, a series of double-blind, placebo-controlled studies of DMT in humans included analysis of biological responses (neuroendocrine, autonomic and cardiovascular) as well as the subjective effects [18,19]. In these studies, administration of a non-hallucinogenic dose of DMT (0.05 mg/kg) produced a relaxed and comfortable mental state in many subjects. We propose that the main effect of endogenous DMT may resemble low-dose, non-hallucinogenic DMT administration, providing a homeostatic response to *alleviate*, rather than promote, psychotic symptoms.

Endogenous human DMT and schizophrenia: the early research

It was originally suggested by Osmond and Smythies [20] in 1952 that a disorder in metabolism might produce a psychotomimetic substance and prompt schizophrenic symptoms. Although Osmond and Smythies proposed that the methylation of nor-adreneline might produce such a psychotomimetic substance, Axelrod [21] demonstrated that mammalian tissue could produce DMT and Osmond and Smythies' theory was later extended by Brune and Himwich [22] to include the possibility of methylated tryptamines acting as an endogenous trigger for psychoses. In a short half-page report in *Nature*, Franzen and Gross [8] reported the presence of *N*,*N*-dimethyltryptamine in human blood ($\sim 8 \times 10^{-9}$ g/mL) and urine ($\sim 4 \times 10^{-5}$ g/24 h). Subsequent research found these levels to be too high and that the average concentrations in normal subjects tended to be around 5×10^{-10} g/mL in blood [12] and 4×10^{-7} g/24 h in urine [23]. (It should be noted that the threshold dose to produce subjective effects in humans is about 5×10^{-5} g/kg, which leads to peak blood concentrations of $\sim 1 \times 10^{-8}$ g/mL [18,24]). After Franzen and Gross' discovery, psychiatric researchers reported increases in the urinary excretion of DMT in schizophrenic patients [12–15]. Murray et al. [11] found a statistically significant increase in the levels of DMT in the urine of schizophrenics ($\sim 1 \times 10^{-6}$ g/24 h), but found that not all schizophrenic patients excreted increased amounts of DMT. The authors concluded that DMT did not play a causal role in schizophrenia, but could be an intermediary factor, exacerbating certain features of psychosis. Other research proved inconclusive and results between studies were often contradictory with either no correlation between schizophrenia and excreted DMT, or no statistically significant difference [25–27].

DMT is no longer considered to be a likely cause of schizophrenia, but it is still recognized as playing a potential role in psychotic symptomatology. A review by Ciprian-Ollivier and Cetkovisch-Bakmas [28] summarizes this updated hypothesis. In their review, Ciprian-Ollivier and Cetkovisch-Bakmas report results from several studies they completed in the 1980s wherein they found a significant correlation between increased urinary excretion of DMT and the severity of psychotic symptoms. The authors readily recognize the complexity involved in schizophrenia, suggesting a complicated interaction among biogenic amines, including serotonin, dopamine, and the *N*-methylated tryptamines. It is interesting to note that researchers in Finland recently found higher levels of bufotenine (a psychoactive *N*-methyl derivative of serotonin) in the urine of psychiatric patients (up to 3×10^{-5} g/mL [29]).

Several challenges have prevented a more precise examination of the role of endogenous DMT in general: (1) the key enzymes that produce methylated tryptamines have not been adequately characterized in vivo; (2) no neurochemical system has been linked with endogenous, psychoactive tryptamines at low, non-hallucinogenic concentrations; (3) modern analytical techniques have not been used to examine the blood and urine concentrations of DMT and its metabolites. The remainder of this paper will address these issues, specifically the first two, in light of recent discoveries.

DMT biogenesis: new research

The biochemistry of DMT production in vitro was studied significantly in the 1970s [30]. Fig. 1 summarizes the three short steps necessary for the complete biosynthesis of DMT from the readily abundant amino acid, tryptophan. The decarboxylation of tryptophan by aromatic amino acid decarboxylase (AADC), produces the trace amine, tryptamine (TYP). 5-hydroxytryptohphan and L-DOPA are the most well known substrates for AADC, en route to the synthesis of serotonin (5-HT, 5-hydroxytryptamine) and dopamine, respectively. Nonetheless, tryptophan (as well as other trace amine precursors such as tyrosine and phenylalanine) can act as a substrate for AADC, consistent with the observation that AADC is the rate-limiting enzyme in TYP formation [31]. The discovery of the trace amine (TA) family of receptors has triggered a reconsideration of the role of AADC. In fact, the human AADC gene can undergo alternative splicing, fashioning two different isoforms [32]. One isoform, $AADC_{480}$, catalyzes the decarboxylation of 5-hydroxytryptohphan and L-DOPA; the other, $AADC_{442}$, was unable to decarboxylate either. It was noted that the substrate for $AADC_{442}$ is unclear, but that phenylalanine, tryptophan, and tyrosine may act as substrates [32]. No further research has investigated the possibility of a unique AADC isoform specific to the trace amine pathway.

The pathway shown in Fig. 1 concludes with two successive methylation reactions. First, TYP can act as a substrate for indolethylamine-*N*-methyltransferase (INMT) and is methylated to give *N*-methyltryptamine (NMT). Second, NMT can act as a substrate for INMT as well, thus forming DMT. Biosynthesis of DMT is dependent upon the enzymatic efficiency and specificity of INMT. In preparations of rabbit lung enzyme (the most widely studied INMT), NMT shows the lowest K_m (commonly interpreted as high binding affinity) for INMT, followed by TYP [33,34]. 5-hydroxytryptamine (serotonin, 5-HT) shows a higher K_m in rabbit lung, suggesting a lower affinity of serotonin for the enzyme [33]. The physiological significance of these values has been recently brought under criticism.

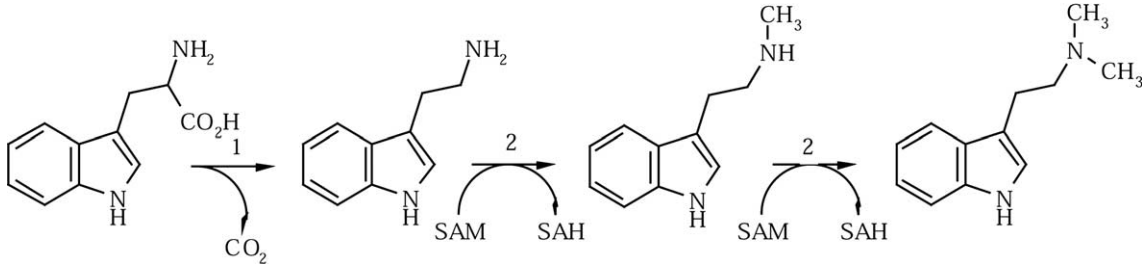

Figure 1 Biosynthesis of DMT from the amino acid tryptophan: (1) aromatic amino acid decarboxylase (AADC) catalyzes the formation of tryptamine from tryptophan; (2) indolethylamine-*N*-methyltransferase (INMT) transfers a methyl group from SAM (S-adenosylmethionine) to tryptamine, yielding *N*-methyltryptamine (NMT). A repeat of this reaction (2) with NMT as the substrate transfers another methyl group and yields DMT and two equivalents of SAH (S-adenosylhomocysteine).

A contemporary investigation, utilizing modern genetic and structural techniques, has provided a more detailed analysis of INMT, but does not provide a complete story. In two studies, Thompson et al. [35,36], cloned, expressed, localized, and characterized the activities of rabbit and human INMT. Using Northern blot analysis, they found rabbit INMT transcripts expressed heavily in the lung, moderately in the liver, and weakly in the brain. Human INMT was expressed in the lung, thyroid, adrenal gland, heart, muscle, and spinal cord, but not in the brain. The authors observe high K_m values (an order of magnitude higher than in previous studies [33,34]) of TYP for recombinant human INMT and an absence of INMT mRNA transcripts in the brain. Thus, Thompson et al. conclude that the production of DMT in humans is not physiologically significant. Their conclusion places much weight on the significance of observed K_m values for recombinant human INMT and does not take into account several additional genetic and enzymatic concerns.

Despite years of research, there is no universally accepted understanding of the biophysics of enzyme function [37]; thus, the meaning of K_m values, especially for in vivo biochemical pathways, is still open to interpretation. Although Thompson et al. argue that high K_m values signify an enzyme–substrate combination that is not biologically meaningful, a meta-analysis of recent research has shown that high K_m values are significant in biological systems [38]. Although enzyme–substrate complexes with high K_m values show less binding affinity, catalysis often proceeds at a faster reaction rate. In fact, Ferhst [38] identifies many enzymes in glycolysis that operate at ''very high'' K_m values – showing catalytic efficiency despite having mM affinity. Ferhst argues that affinity becomes less important in intracellular systems where high concentrations of necessary metabolites are present and suggests that the specificity constant k_{cat}/K_m is the best indicator of enzyme–substrate efficiency. Thus, we advise against the placement of undue emphasis on numerical values of K_m when interpreting in vitro activity. The structure of human INMT needs to be determined and its in vivo kinetic parameters more thoroughly assessed before *N*-methylation of tryptamines can be written off as physiologically irrelevant. The results of Thompson et al. should also be taken with caution because their measurements reflect the activity of a recombinant enzyme, removed from its natural environment where cellular compartmentalization could significantly alter its activity.

Genetically speaking, the absence of constitutively produced INMT transcripts in the brain does not mean that they are *never* produced; many events could potentially trigger INMT transcription in the brain. A brief report published in 1977 claimed that INMT activity increases under stress (electric shock and forced swim) in the rodent brain [39]. Thus, a stress response which produces large amounts of TYP in tissues could lead to significant production of DMT. In addition, given the presence of INMT transcripts in peripheral tissues, DMT production could occur outside the brain and still have activity in the brain because DMT can readily cross the blood brain barrier. This would be different from most neurotransmitters, which do not have significant blood–brain-barrier permeability and thus must be produced within the brain.

DMT: physiology and psychological effects

A double-blind, placebo-controlled study of DMT in humans was conducted by Strassman et al. [18,19,40] in 1994. Upon intravenous administration of DMT to healthy, normal subjects, increases in blood pressure, heart rate, pupil diameter, and rectal temperature, as well as increased blood concentrations of β-endorphin, corticotrophin, cortisol, prolactin, and growth hormone were measured. In addition, using a Hallucinogen Rating Scale (HRS) developed for the study, Strassman and colleagues reported the subjective effects of DMT on mental state. At intravenous doses of 0.2 and 0.4 mg/kg, there was a ''nearly instantaneous onset of visual hallucinatory phenomena, bodily dissociation, and extreme shifts in mood, which totally replaced subject's previously ongoing mental experiences.'' The HRS includes the following six categories: Somaesthesia, Affect, Perception, Cognition, Volition, and Intensity. Subjects reported statistically significant, dose-dependent increases in each category during DMT administration.

Strassman's studies provide an excellent methodology for future research with psychoactive tryptamines. However, most of the psychedelic doses may be too high to be of relevance in understanding endogenous DMT activity. Nonetheless, it is interesting that Strassman et al. [19] found that their HRS was able to distinguish between placebo and a low dose (0.05 mg/kg) of DMT better than physiological measurements of neuroendocrine, cardiovascular, and autonomic variables. In other words, subjects were aware of subjective mental state changes even when statistically significant physiological changes were not measurable. This low dose may be more indicative of the effects of endogenously produced DMT, because it leads to

blood concentrations closer to some levels observed in human subjects in the 1970s, although still higher by an order of magnitude. Aspects of Strassman's work thus provides a vital first step in characterizing the role DMT might play in vivo.

An essential characteristic of DMT pharmacology also investigated by Strassman that differentiates it from many other psychedelic substances is that DMT does not appear to lead to tolerance in mammals. Absence of tolerance has been shown in rats [41], cats [42] and in humans [43]. This provides additional evidence that endogenous DMT may play a physiological role, especially if its mechanism requires consistent and repeated activity.

DMT: a neurotransmitter in the trace amine pathway?

If DMT plays a physiological role, via what neurochemical pathway does it operate? Although serotonin 5-HT_{2A} receptors are thought to play a major role in the activity of hallucinogenic drugs, the complex effects of these chemicals on mental state is largely not understood [44–46]. The discovery of receptors for trace amines (tyramine, phenethylamine, tryptamine) in the vertebrate brain and periphery [47], with greater activation by hallucinogens such as DMT and LSD (lysergic acid diethylamide) than by serotonin [17], adds to the complexity of the situation. Might endogenous DMT play a neurochemical role here?

In addition to demonstrating significant activity at the TA receptor, DMT has shown very high affinity for synaptosomal membranes [48] and involvement in active transport processes indicative of a reuptake mechanism [49]. Activation of the G-protein-coupled TA receptor leads to the production of cAMP and the activity of various ''exogenous'' compounds at the TA receptor has been measured by comparing levels of cAMP production relative to tyramine [17]. Tyramine, which exhibits nanomolar affinity for the TA_1 receptor, is the proposed endogenous ligand for this receptor. In a study conducted in vitro with 1 micromolar concentrations of ligand, DMT activity at the rat TA_1 receptor was almost equal to that of tyramine [17]. The hallucinogen LSD triggered a slightly lower production of cAMP and MDMA (methylenedioxymethamphetamine, street name ''ecstasy'') slightly lower still. 5-HT elicited less than 50% maximal cAMP production when compared to tyramine [17]. Thus, the TA receptor demonstrates a robust response to many hallucinogens, and a substantially lesser response to serotonin. In the late 1970s, several researchers speculated on the existence of a DMT receptor [30]. It was reported at that time that a receptor was present on rat synaptosomal membranes which showed sub-nanomolar affinity (3.0×10^{-10}) for DMT and LSD, led to the production of cAMP [48], and showed much less affinity for 5-HT [50]. Perhaps these researchers had in fact discovered the trace amine receptor over twenty years ago. Additional evidence in support of a neurotransmitter role for DMT comes from research suggesting that DMT is actively transported into rat nerve cells, perhaps evidence for a reuptake mechanism [49].

DMT likely exerts much of its potent hallucinogenic response via the 5-HT system, but it seems most probable that endogenous DMT would interact at TA receptors, especially given it presence at very low (nanomolar) concentrations. Because there is about an order of magnitude difference in the resulting blood concentrations between the low, non-hallucinogenic dose of DMT (0.05 mg/kg IV) and the peak hallucinogenic dose (0.4 mg/kg IV), we propose that low dose administration is more likely to provide a window into DMT's role during endogenous production. Strassman et al. [19] suggested that the different effects of low dose (0.05 mg/kg IV) and higher dose (0.2 mg/kg and greater IV) DMT administered to his human subjects was due to agonism at both 5-HT_{1A} and 5-HT_{2A} receptors. It is reported that the 5-HT_{1A} and 5-HT_{2A} receptors produce opposing cellular responses and are often expressed on the same cell [51]. In a subsequent study, Strassman [24] used pindolol, a 5-HT_{1A} antagonist, in combination with a sub-hallucinogenic dose of DMT (0.1 mg/kg IV) and found a two- to three-fold enhancement of DMT's effects (according to the HRS). Thus, it appears that the 5-HT_{1A} is suppressing DMTs hallucinogenic activity. In his review, Nichols [45] notes that other receptor systems may modify the psychopharmacological response of hallucinogens and that 5-HT_{2A} mediated phosphoinositide hydrolysis (PI) cannot fully account for the effects of hallucinogens. For example, DMT shows only about 20% maximum PI hydrolysis at the 5-HT_{2A} receptor when compared to 5-HT [52].

We propose that the subjective subtleties of low doses of DMT may be due to agonism at trace amine receptors, rather than, or in addition to, effects on the 5-HT system. This stems from the observation that DMT elicits a strong response at the TA receptor as well as possibly showing sub-nanomolar affinity. Subjects in the Strassman et al. study reported that low doses (0.05 mg/kg IV) of DMT had mildly mood-elevating properties. The subjective activity

recognized at the low dose demonstrates a conceivable physiological role for DMT that manifests psychologically as a calm and relaxed mental state.

The TA system is well suited for interacting with the emotional systems in the human body. Human TA_1 mRNA was found to be present in moderate amounts in the stomach (100 copies/ng cDNA) and lower levels in the amygdala (15—100 copies/ng cDNA, [47]). In the rat, TA_1 mRNA was found to be widely distributed in the brain and in peripheral tissue, including the gastrointestinal tract [47]. Much research has shown that the amygdala plays a critical role in the regulation of emotion [53]. It is less well known that research into the nervous system of the gut (the enteric nervous system) is leading to a reconsideration of the dominance of the brain in establishing mood [54]. It is possible that DMT may play a role in both the brain and the gut as a neurotransmitter, exerting subtle effects on mental state and mood, such as those seen during non-hallucinogenic, low-dose administration of DMT.

Recent studies have uncovered several potential links between the TA system and schizophrenia. TA receptor mRNA is expressed in the stomach, kidney, lung, and brain with receptor sequences mapped to human chromosome 6q23.2, a genetic locus that has been implicated in playing a role in schizophrenia [47,55,56]. Researchers have already suggested that irregularities in TYP or phenethylamine metabolism may be involved in schizophrenia and depression [16,57]. Increased AADC activity has been observed in schizophrenic patients [58], as well as decreased MAO activity [59]; both of these enzymes would be expected to strongly affect the levels of trace amines in the bloodstream. As mentioned earlier, evidence may also exist for an AADC isoform with unique affinity for substrates other than 5-hydroxytryptophan [32]. If $AADC_{442}$ is found to have specificity for tryptophan, such a discovery would be quite significant because it would demonstrate that tryptamine synthesis is enzymatically specific, making DMT biosynthesis all the more likely.

DMT: an endogenous anxiolytic?

DMT appears to have affinity for the TA system, which is a receptor system that is linked to the emotional centers of the body and shows possible connections to many psychiatric conditions. Thus, the DMT-TA hypothesis prompts a new interpretation of the presence of DMT in the fluid of schizophrenics. Perhaps, increased DMT production reflects a homeostatic response to calm or suppress psychotic activity, rather than exacerbate it. At low levels, DMT may be an endogenous anxiolytic, whereas higher, ''unnatural'' levels (such as those associated with psychedelic/hallucinogenic activity) produce extreme shifts in consciousness. This might explain the inconsistent reports of DMT's presence in schizophrenic patients. The proposed DMT-TA hypothesis is also consistent with the observation of increased AADC activity and decreased MAO activity in schizophrenic patients, conceivably to produce more symptom-alleviating tryptamine or DMT. It is also known that the smoking of tobacco leads to decreased levels of MAO activity in schizophrenics [60], possibly producing increased levels of endogenous DMT and thereby contributing to the high prevalence of tobacco/nicotine use amongst this population. This DMT-TA hypothesis, offers a sensible explanation for the observation that INMT activity and thus DMT production increase during stress, although this needs to be more thoroughly examined in humans.

Amphetamine, methamphetamine, and MDMA have significant efficacy at the trace amine receptor [17]. In addition to the well-known stimulant effects of these amphetamine-class chemicals, these compounds also produce calming effects in humans, especially at low doses [61]. Consistent with our hypothesis that the action of endogenous DMT at the TA receptor is to produce a calming, anxiolytic effect, we propose that the calming effect of amphetamine and related drugs may also be mediated by the TA receptor.

The dopamine hypothesis of schizophrenia still remains dominant today, although it is increasingly believed that abnormalities in other neurotransmitter systems — serotonin, glutamate, GABA, opioid, and more may also contribute to this condition [62]. Given a possible role for the trace amine receptor, the complexity of the relationship between psychosis and neurochemistry only increases. It may be valuable to re-examine human urine and blood with modern analytical techniques to examine the concentrations of DMT and its metabolites in new light. In studies of schizophrenia, blood levels of dopamine are not as informative as levels of the dopamine metabolite homovanillic acid as a peripheral indicator of dopaminergic activity. Since earlier studies of endogenously produced DMT studied blood levels of DMT exclusively, it would be worth investigating the indoleacetic acid metabolite as well as dimethylkynuramine, a metabolite produced via the oxidative opening of the pyrrole ring by an enzyme present in human blood [63].

Conclusions

Tryptamine biochemistry is far subtler than previously believed. This includes a physiological role for trace amines and their *N*-methylated derivatives. We have reviewed the current research on INMT and AADC activity, illustrating that their participation in DMT biosynthesis is biochemically very reasonable. We have also proposed a major role for DMT in the trace amine system. This proposal offers a neurochemical explanation for heretofore ill-understood aspects of DMT pharmacology, especially at low doses. Our proposed scenario also includes the hypothesis that increased DMT or tryptamine production could suppress psychotic activity, rather than aggravate it.

Brain circuitry and synaptic chemistry are extraordinarily complex. Moreover, the more we learn about the brain, the more complex and interconnected it is shown to be. Indeed, it appears that every possibility discovered which allows for additional regulation at the molecular level is in fact exploited in the nervous system. Anything not forbidden is mandatory, some might say. Relating these cellular and molecular processes to mental states such as those experienced in psychosis or those resulting from consciousness-changing drugs remains as interesting and as challenging an endeavor as ever.

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