ACS Chemical Neuroscience
Cite This: ACS Chem. Neurosci. 2018, 9, 2344−2357
Review
pubs.acs.org/chemneuro

Dark Classics in Chemical Neuroscience: *N,N*-Dimethyltryptamine (DMT)

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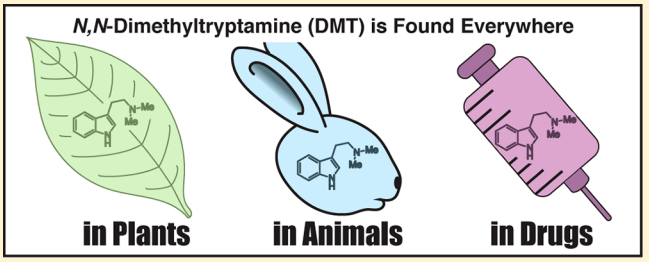
ABSTRACT: Though relatively obscure, *N,N*-dimethyltryptamine (DMT) is an important molecule in psychopharmacology as it is the archetype for all indole-containing serotonergic psychedelics. Its structure can be found embedded within those of better-known molecules such as lysergic acid diethylamide (LSD) and psilocybin. Unlike the latter two compounds, DMT is ubiquitous, being produced by a wide variety of plant and animal species. It is one of the principal psychoactive components of ayahuasca, a tisane made from various plant sources that has been used for centuries. Furthermore, DMT is one of the few psychedelic compounds produced endogenously by mammals, and its biological function in human physiology remains a mystery. In this review, we cover the synthesis of DMT as well as its pharmacology, metabolism, adverse effects, and potential use in medicine. Finally, we discuss the history of DMT in chemical neuroscience and why this underappreciated molecule is so important to the field of psychedelic science.



KEYWORDS: *N,N-Dimethyltryptamine, DMT, ayahuasca, psychedelic, hallucinogen*

INTRODUCTION

For centuries, humans have consumed *N,N*-dimethyltryptamine (DMT) as a key ingredient in various tisanes and snuffs used during religious ceremonies in Central and South America.[1] Cited as early as the 15th century, these concoctions were made from vines, roots, and shrubs native to these regions and were purportedly used by indigenous peoples to facilitate their communication with the gods. Accounts of such rituals indicate that users of these botanical concoctions were left feeling peaceful and enlightened, most likely due to the profound psychoactive effects of their chemical constituents. Of the natural products in these mixtures, DMT has garnered significant interest as it causes intense hallucinogenic effects in humans at doses above 0.2 mg/kg.[2,3] Initial scientific studies on DMT conducted in the late-20th century suggested that at lower doses, it had mood-elevating and calming properties.[2] Today, it is thought that DMT and related alkaloids might be used to treat depression and other neuropsychiatric disorders. These compounds are produced by a wide variety of botanical sources.[1,4] Ayahuasca, also known as hoasca, natema, iowaska, daime, or yagé, is an Amazonian tisane that is made by boiling the bark of the *Banisteriopsis caapi* vine and the leaves of the *Psychotria viridis* plant. The former contains a variety of monoamine oxidase (MAO) inhibiting β-carbolines, such as harmine, harmaline and tetrahydroharmine, while the latter contains large amounts of DMT, the principle hallucinogenic component of this mixture (vide infra). Together, they constitute ayahuasca (Figure 1), a Quechua word meaning

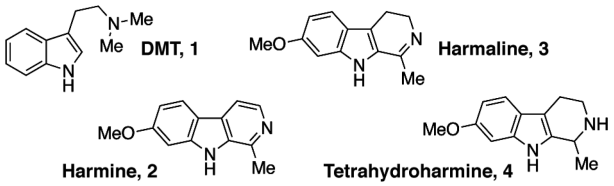


Figure 1. Chemical structures of the key psychoactive alkaloids found in ayahuasca.

"vine of the soul"—*aya* meaning soul, ancestors or dead persons, and *wasca* (*huasca*) meaning vine or rope.[5] Some have even dubbed DMT the "spirit molecule" due to its profound effects on the human psyche.[6]

In addition to its potent effects on perception, ayahuasca is beginning to be appreciated as a robust antidepressant and anxiolytic in both humans and animals.[7−10] However, DMT is a controlled substance in the United States and many other

Special Issue: DARK Classics in Chemical Neuroscience

Received: March 1, 2018
Accepted: July 6, 2018
Published: July 23, 2018

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

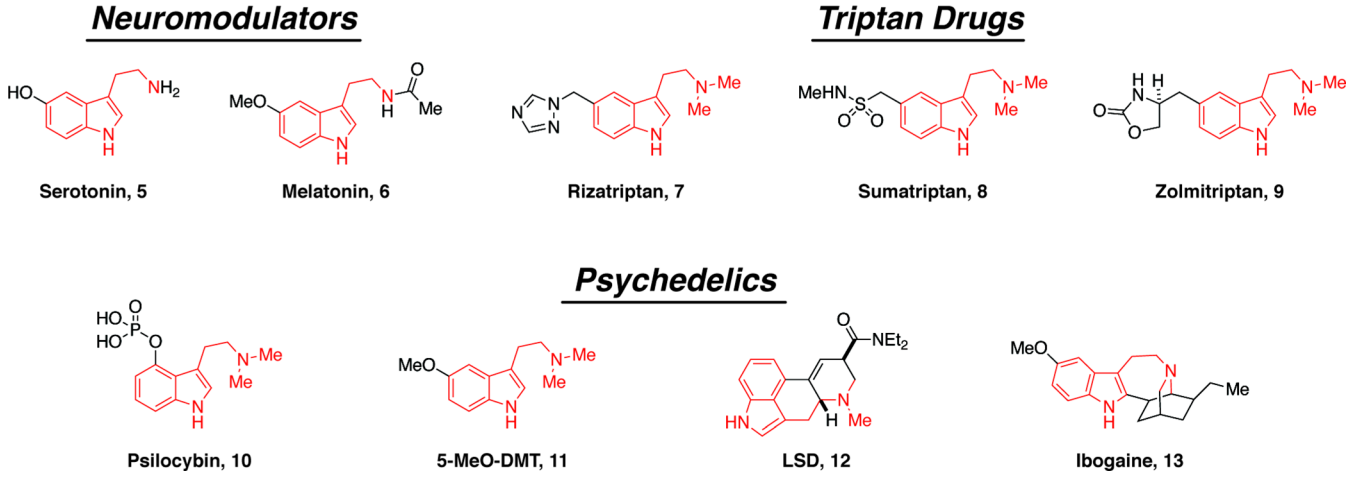


Figure 2. Structural relationship between DMT and other compounds that influence brain function. Overlapping features of DMT and these compounds are highlighted in red.

countries, making research on the effects of DMT and ayahuasca challenging to conduct. In 2006, the use of ayahuasca for religious purposes was protected under the Religious Freedom Restoration Act,[11] though DMT itself remains classified as a Schedule I compound. Schedule I compounds, including drugs such as tetrahydrocannabinol (THC), heroin, and gamma hydroxybutyric acid (GHB) are among the most highly regulated chemicals in the United States as the government deems them to have high potential for abuse with no medicinal value. It is not surprising that Brazil, where ayahuasca is legal, has become the epicenter of research into the effects of this botanical mixture. Furthermore, União do Vegetal (UDV) and Santo Daime—two of the most prominent ayahuasca-using churches[12]—have their roots in Brazil. Thus, the cultural and political climate in Brazil has been very conducive to the study of DMT and DMT-containing concoctions.

Structurally, the most striking aspect of DMT is its simplicity. It is small (molecular weight of the free base = 188.27 g/mol) and hydrophobic (log P = 2.573),[13] characteristics that enable it to readily cross the blood−brain barrier (BBB).[14] Chemically, it is related to the natural compounds serotonin and melatonin, as all three molecules possess a tryptamine core (Figure 2). The DMT core structure is also a prominent feature of a class of medications known as the triptans (Figure 2); however, the effects of DMT on the central nervous system are quite distinct from these compounds. Serotonin is a key neurotransmitter and neuromodulator that regulates a variety of behaviors, while melatonin is a hormone that plays a critical role in sleep homeostasis and circadian rhythms. The triptan drugs are vasoconstrictors used to treat migraines and cluster headaches.[15] Importantly, the triptans demonstrate that it is possible to make slight modifications to the structure of DMT to produce nonhallucinogenic analogues of great medicinal value. Other DMT analogues have shown promise for treating Alzheimer's disease and depression in preclinical models.[16]

Functionally, DMT is most similar to the serotonergic psychedelics—compounds that have "mind-manifesting" properties and are infamous for their effects on perception.[17] In fact, the structure of DMT constitutes the core of several important psychedelic compounds, including lysergic acid diethylamide (LSD), ibogaine, psilocybin, and 5-MeO-DMT (Figure 2). There is a plethora of drug discrimination data in rats suggesting that DMT produces interoceptive effects similar to both tryptamine and phenethylamine psychedelics. For example, DMT fully substituted (i.e., >75% correct responding) for 5-MeO-DMT,[18] (−)-2,5-dimethoxy-4-methylamphetamine (DOM),[19] and (+)-lysergic acid diethylamide (LSD)[20,21] when rats were trained to discriminate these drugs from saline. Moreover, DMT fully substituted for (−)-2,5-dimethoxy-4-iodoamphetamine (DOI) when rats were trained to discriminate DOI from the 5-HT2A antagonist ketanserin.[22] Finally, LSD and DOM fully substituted for DMT in rats trained to discriminate DMT from saline.[23]

Despite its simple structure, DMT binds with high affinity to a variety of neuroreceptors and elicits robust behavioral responses (vide infra). An excellent review covering various aspects of DMT neuropharmacology was published recently,[24] which we expand upon here. Specifically, we address the synthesis (both biosynthetic and chemical), pharmacology, metabolism, and adverse effects of DMT as well as the evidence supporting and refuting a possible role for endogenously produced DMT in mammalian physiology. Additionally, we discuss the psychoplastogenic (plasticity-promoting) effects of DMT and its potential use for treating depression, addiction, and anxiety disorders. Finally, we highlight the historical importance of this structurally simple, but highly significant, psychedelic compound.

SYNTHESIS

Like serotonin and melatonin, DMT is a product of tryptophan metabolism.[25] Following tryptophan decarboxylation, tryptamine is methylated by an *N*-methyltransferase (i.e., INMT) with *S*-adenosylmethionine serving as the methyl donor. A second enzymatic methylation produces DMT (Figure 3A).[26] This biosynthetic pathway seems to be operational in both plants and animals.[27−30] Like Nature, chemists have found simple ways to synthesize DMT with the two most popular approaches from the peer-reviewed literature highlighted in Figure 3B. In addition to these, Shulgin has reported that DMT can be produced from the demethylation of various *N*,*N*,*N*-trimethyltryptammonium salts.[31]

Perhaps the most straightforward method to prepare DMT is via reductive amination under acidic conditions employing tryptamine, formaldehyde, and sodium cyanoborohydride.

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

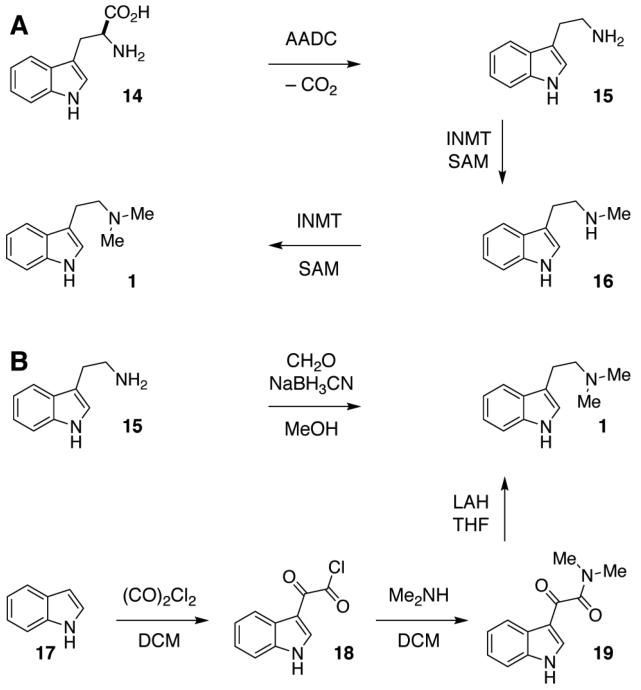


Figure 3. Synthesis of DMT. (A) Biosynthesis of DMT. (B) Chemical syntheses of DMT.

This method is fast, simple, and produces DMT in reasonably high yields (ca. 70%) in a single step. However, if the stoichiometry of the acid, formaldehyde, and reducing agent are not carefully controlled, byproducts such as *N*-methyl-*N*-cyanomethyltryptamine, 2-methyltetrahydro-β-carboline, and tetrahydro-β-carboline can become an issue.[32] These latter two compounds are often found as significant byproducts under reaction conditions where the initially formed iminium ion is not rapidly reduced, as this allows Pictet–Spengler cyclization to effectively compete with the reduction.

The simplicity of the reductive amination protocol for producing DMT has made it incredibly popular; however, it requires the use of tryptamine and is not amenable to making diverse analogues. Another common route for synthesizing DMT takes advantage of chemistry developed by Speeter and Anthony for acylating indole at the 3-position with oxalyl chloride.[33] The resulting acyl chloride is then reacted with dimethylamine to produce an amide that is subsequently reduced with lithium aluminum hydride (Figure 3B). This 3-step procedure, though cumbersome, is quite reliable and was the method of choice for producing the DMT used in the human clinical studies conducted by Strassman and coworkers (vide infra).[34] Furthermore, it enabled the synthesis of a wide variety of DMT analogues, including those with varying amino groups[35] and indole substitution patterns.[36]

The isolation and purification of DMT also warrant some discussion. The reactions used to synthesize DMT are often followed by a basic aqueous workup involving the extraction of DMT free base into an organic solvent. Chloroform is usually the solvent of choice, as DMT has been reported to react with dichloromethane (DCM) to produce *N*-chloromethyl-*N*,*N*-dimethyltryptamine chloride. However, this reaction is quite slow, and the byproduct is easily removed via aqueous workup.[37] Typically, DMT is purified via sublimation of the free base under reduced pressure, crystallization/recrystallization of a DMT salt form, or a combination of the two. The fumarate salt of DMT is perhaps one of the easiest forms to work with and store as other salts (e.g., acetate, citrate, hydrochloride, etc.) tend to be hygroscopic. As with most indole-containing compounds, DMT should be stored in a dark freezer to avoid decomposition.

PHARMACODYNAMICS

Serotonergic System. Unmetabolized DMT reaching the brain interacts with various receptors, including a large number of serotonin receptors (Table 1). It binds with nanomolar affinities to the 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT6, and 5-HT7 receptors.[38] A variety of pharmacological and genetic experiments has shown that many of DMT's biological effects are mediated, at least in part, by the 5-HT2A, 5-HT1A, and 5-HT2C receptors,[39,40] where it acts as an agonist or partial agonist depending on the specific assay (Table 2). The interoceptive and hallucinogenic effects of DMT are believed to result primarily from agonism of the 5-HT2A receptor[18] and are modulated by mGlu2/3 receptors.[41]

Table 1. Receptor Affinity Profile for DMT at Human Serotonin Receptors[a]

receptor	radiolabeled ligand	radioligand classification	K_i (nM)
5-HT1A	^{3}H-8-OH-DPAT	agonist	183
5-HT1B	^{3}H-5-CT	agonist	129
5-HT1D	^{3}H-5-CT	agonist	39
5-HT1E	^{3}H-5-HT	agonist	517
5-HT2A	^{3}H-LSD	agonist	127
5-HT2B	^{3}H-LSD	agonist	184
5-HT2C	^{3}H-LSD	agonist	360
5-HT5A	^{3}H-LSD	partial agonist	2135
5-HT6	^{3}H-LSD	partial agonist	464
5-HT7	^{3}H-LSD	partial agonist	206

[a]Radioligand binding assays were performed using stably or transiently expressing cell lines (HEK, HEKT, or CHO).[38]

The effects of DMT on 5-HT2A receptor signaling are the best characterized. This G_q-coupled protein is found in many mammalian brain regions including the cortex, striatum, hippocampus, and amygdala, with particularly high expression on layer V pyramidal neurons of the cortex.[45] DMT acts as an agonist of 5-HT2A receptors, causing an increase in phosphoinositide hydrolysis.[22] Furthermore, DMT increases both the frequency and amplitude of spontaneous excitatory postsynaptic currents (EPSCs) in layer V cortical pyramidal neurons,[46] a phenomenon previously observed by Aghajanian and Marek upon stimulation of 5-HT2A receptors with serotonin.[47,48] Structure–activity relationship (SAR) studies have demonstrated that the relatively small methyl groups of DMT are critical for achieving high affinity for the 5-HT2A receptor, as *N*-substituents larger than isopropyl drastically reduced 5-HT2A receptor affinity.[49] Furthermore, hydroxylation at either the 4- or 5-position was shown to increase the affinity about 10-fold.[49] Interestingly, the 5-HT2A receptor does not desensitize to DMT over time,[22] which perhaps explains why tolerance to DMT does not develop in humans.[50]

Stimulation of 5-HT2A receptors appears to underlie the psychoplastogenic effects of DMT. Ly and coworkers demonstrated that DMT increases the complexity of cortical neuron dendritic arbors and promotes increased dendritic spine density. This DMT-mediated enhancement of structural

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344–2357

Table 2. Functional Assay Profile for DMT[a]

receptor	ligand classification	experiment performed	cell type	% max efficacy	DMT EC_{50} (nM)	5-HT EC_{50} (nM)	reference
5-HT1A	agonist	inhibition of forskolin-stimulated cAMP production	rat hippocampus	115 (8-OH-DPAT)	4000	ND	42
5-HT1A	agonist	^{35}S-GTPγS binding	HEK-293	100 (5-HT)	1490	15.7	43
5-HT2A	agonist	^{3}H-IP formation	NIH 3T3	90 (5-HT)	983	ND	22
5-HT2A	partial agonist	^{3}H-IP formation	HEK-293	39 (5-HT)	269	43	43
5-HT2A	agonist	^{3}H-AA release	HEK-293	105 (5-HT)	260	7.8	43
5-HT2A	partial agonist	Ca^{2+} release	HEK-293	23 (5-HT)	118	6.6	38
5-HT2A	agonist	Ca^{2+} release	HEK-293	83 (5-HT)	38.3	ND	44
5-HT2C	agonist	^{3}H-IP formation	NIH 3T3	85 (5-HT)	49	ND	22

[a]The maximal efficacy of DMT is expressed as a percent relative to the agonist indicated in parentheses. IP = inositol monophosphate; AA = arachidonic acid; ND = not determined.

plasticity occurs through an mTOR-dependent mechanism that involves activation of 5-HT2A receptors.[46] Specifically, Ly and coworkers utilized the 5-HT2A antagonist ketanserin to effectively block the ability of DMT to promote cortical neuron neurite growth and spinogenesis.[46] Neural plasticity in the prefrontal cortex is critical to the behavioral effects of fast-acting antidepressants like ketamine, so it is possible that 5-HT2A receptor agonism underlies the known antidepressant effects of serotonergic psychedelics.[51] An important goal of future research will be to determine the exact role of 5-HT2A receptors in the rodent behavioral effects of DMT[52] and in the antidepressant properties of ayahuasca.[7−9,53]

Like the 5-HT2A receptor, the 5-HT2C receptor is coupled to G_q and increases phosphoinositide hydrolysis upon activation. DMT acts as a partial agonist of the 5-HT2C receptor[22] with a binding affinity approximately half that of the 5-HT2A receptor (Table 1). However, unlike the 5-HT2A receptor, the 5-HT2C receptor desensitizes to DMT over time.[22] Additionally, it does not seem to play a role in the interoceptive effects of DMT.[41]

In contrast to 5-HT2A and 5-HT2C receptors, 5-HT1A receptors are inhibitory G-protein coupled receptors (GPCRs) expressed on target cells localized mainly in cortical and subcortical regions.[54] These receptors can also serve as autoreceptors found on the somas and dendrites of serotonergic neurons in the dorsal raphe.[55] Compared to its affinity for other neuroreceptors, DMT is a good ligand for 5-HT1A receptors (183 nM),[38] where it acts as an agonist (Table 2). It has been shown that 5-HT1A agonists acutely inhibit dorsal raphe firing, likely through stimulation of these autoreceptors.[56,57] Blier and colleagues elegantly demonstrated that increased activation of these autoreceptors decreases serotonin release in other brain regions.[58] However, chronic treatment with antidepressants restores normal 5-HT neuron activity through desensitization of somatodendritic and terminal autoreceptors.[59] It is because of this that many agonists of the 5-HT1A receptor are thought to exert anxiolytic and antidepressant properties. In the case of DMT, a 5-HT1A agonist, this mechanism may also contribute to its therapeutic effects.

Finally, there are reports that DMT also binds with high affinity to 5-HT1D, 5-HT6, and 5-HT7 receptors,[38,60,61] but little work has been done to fully characterize the interaction of DMT with these receptors beyond initial binding studies. Given DMT's affinity for the 5-HT1D, 5-HT6, and 5-HT7 receptors (39, 464, and 206 nM, respectively),[38] it is not surprising that a wide variety of 5-HT1D, 5-HT6, and 5-HT7 ligands possess DMT-containing backbones. As 5-HT6 and 5-HT7 receptors have been implicated in various aspects of learning, memory, plasticity, and cognition,[62−66] it will be critical for future research to evaluate their roles in the behavioral and therapeutic effects of DMT and ayahuasca.

Sigma-1 Receptor. The sigma-1 receptor has been well studied due to its potential role in the treatment of depression and anxiety.[67] However, relatively few endogenous ligands of the sigma-1 receptor are known. Unlike steroids that tend to antagonize sigma-1 receptors (e.g., progesterone, testosterone, etc.), DMT is one of the only known endogenous sigma-1 agonists (K_d = 15 μM), but the affinity of DMT for sigma-1 receptors is 100-fold lower than that for 5-HT2A receptors.[68] The relatively weak affinity of DMT for sigma-1 receptors coupled with the low circulating levels of endogenous DMT (vide infra) make it unlikely that sigma-1 receptors play a significant role in the function of endogenous DMT. However, exogenously administered sigma-1 agonists, such as (+)-SKF 10,047 and igmesine, produce behavioral responses similar to exogenously administered DMT (vide infra) such as a reduction in the number of entries into the open arms of an elevated plus maze and reduced immobility in the forced swim test.[69,70] Moreover, sigma-1 receptor knockout mice exhibit a depressive phenotype,[71] and sigma-1 receptors regulate the secretion of brain-derived neurotrophic factor (BDNF)[72,73] and various forms of structural and functional neural plasticity.[72,74−77] As DMT produces both antidepressant behavioral responses and promotes neural plasticity, it is reasonable to conclude that the sigma-1 receptor may play some role in the effects of exogenously administered DMT, though these hypotheses require additional experimental validation. Finally, it has been recently shown that DMT can protect human cortical neurons from oxidative stress via a sigma-1 receptor-dependent mechanism.[78] While the authors attribute this protective effect to the sigma-1 receptor's known influence on the ER stress response,[79] it could also be due to the pro-survival properties of BDNF secretion following sigma-1 stimulation.

Trace Amine-Associated Receptor 1 (TAAR1). TAAR1 has also been suggested as a target of DMT. A study by Bunzow and coworkers elegantly demonstrated that DMT activates TAAR1 to increase cAMP production in a TAAR1-expressing HEK293 cell line.[80] Like DMT, several other trace amines, psychedelics, and psychostimulants have been shown to bind to and activate TAAR1 to a greater extent than traditional neurotransmitters like serotonin, dopamine, or norepinephrine. While DMT was shown to activate TAAR1

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

at 1 μM, lower concentrations were not employed in these studies, and therefore, the exact EC_{50} value for DMT remains unknown.

Serotonin Transporter (SERT) and Vesicular Monoamine Transporter (VMAT). By analyzing binding-to-uptake ratios, Cozzi and coworkers determined that DMT acted as a substrate, rather than an inhibitor, for SERT and VMAT2.[81] This result is supported by an additional study demonstrating that DMT accumulates in brain slices via an active-transport mechanism.[82]

Dopaminergic System. The binding affinity of DMT for dopamine receptors is quite low ($K_i \approx 5$ μM) compared to ergolines such as LSD ($K_i \approx 20$ nM).[83] Furthermore, DMT does not stimulate dopamine sensitive adenylyl cyclase systems.[84] At high doses of DMT (10 and 20 mg/kg) rats with unilateral 6-hydroxydopamine lesions engage in a weak ipsilateral turning behavior reminiscent of dopamine agonism,[85] and at least one report has suggested that DMT increases dopamine synthesis,[86] but this is controversial.[87] Finally, pretreatment with a dopamine antagonist blocked DMT-induced hyperactivity in rats, leading the authors to conclude that the dopaminergic system was involved.[88] However, these studies were completed prior to fully understanding the pharmacology of these compounds, including their effects on the serotonergic system. It is now appreciated that haloperidol, pimozide, and methiothepin, the three antipsychotics used in this study, also have affinity for a variety of serotonin receptors (including the 5-HT2A receptor). It is possible that serotonergic antagonism is responsible for their ability to block DMT-induced effects.

Cholinergic System. The effects of DMT on the cholinergic system have been poorly studied. Administration of DMT to rats had no effect on the level of acetylcholine in the cortex, but did decrease its concentration in the corpus striatum.[87] Decreases in acetylcholine concentrations are often observed when its rate of release is enhanced.[87] As administration of 5-hydroxytryptophan (the precursor of serotonin) and a serotonergic neurotoxin leads to reduced and increased acetylcholine levels, respectively, it is likely that DMT stimulation of the serotonergic system mediates its effects on acetylcholine levels.

Behavioral Studies. With the exception of a few reports of unconditioned responses[41,88−90] and a seminal study demonstrating that DMT increases the activity of pargyline pretreated rodents,[88] very little is known about the effects of DMT on rodent behavior. In C57BL/6 mice, DMT produces a 5-HT2A-dependent head-twitch response (HTR)[41]—a characteristic behavioral phenotype of serotonergic psychedelics.[91] However, this behavioral response is highly dependent on the mouse strain employed. In C57BL/6 mice, DMT was shown to produce far fewer head twitches per unit time than the structurally related tryptamine psychedelic *N*,*N*-diisopropyltryptamine or the structurally dissimilar phenethylamine psychedelic DOI.[41] However, in 129S6/SvEv mice, DMT produced a HTR comparable to DOI,[92] while in NIH Swiss mice, DMT did not produce a HTR.[93]

Unlike mice, administration of DMT to rats causes rapid induction of flat-body posture, hind limb abduction, tremor, walking backward, and abdominal contractions,[88] all of which are characteristic symptoms of serotonin syndrome. These effects can be observed within 5 min following injection of a hallucinogenic dose of DMT and peak around 15 min.[88] In total, they last for approximately 30−90 min depending on whether or not a MAO inhibitor is coadministered, with animals resuming normal home cage behavior around this time.[52] It is important to consider these acute effects of DMT on motor function when studying the impact of hallucinogenic doses on other behaviors. For example, DMT was hypothesized by Walters and coworkers to have anxiolytic effects in rats, as it decreased shock-induced fighting.[94] However, the authors of this study failed to take into account the acute locomotor effects of DMT, and thus, any reduction in fighting could be easily attributed to the motor impairments induced by DMT during the first 30 min postadministration. In order to avoid the confounding influence of a hallucinogenic dose (>2 mg/kg) of DMT on motor function, our group has adopted the practice of administering DMT at least 1 h prior to behavioral testing in rats.[52] Pic-Taylor and coworkers have used a similar protocol when studying the behavioral effects of ayahuasca.[95]

Besides DMT's rapid and transient influence on posture, its best-characterized behavioral effects are related to locomotion and exploratory activity. Seminal studies by Geyer and coworkers have demonstrated that DMT and other tryptamine-based psychedelics reduce horizontal activity, decrease exploratory behaviors such as rearings and holepokes, and promote avoidance of the center of the arena when measured in the Behavioral Pattern Monitor (BPM).[96−99] As these effects are not typically observed when animals are tested in a familiar environment, Geyer and coworkers have suggested that many psychedelics potentiate neophobia. Cameron and coworkers have also observed acute anxiogenic effects of DMT in Sprague Dawley rats dosed at 10 mg/kg. These include reduced novelty-induced locomotion and rearing, increased percentage of time spent in the closed arms of an elevated plus maze, and increased freezing immediately following a series of foot shocks.[52]

Despite the initial anxiogenic effects induced by DMT, an acute hallucinogenic dose (10 mg/kg) facilitates cued fear extinction in rats.[52] This finding is consistent with reports of entactogens and serotonergic hallucinogens, such as MDMA and psilocybin, enhancing fear extinction in mice.[100,101] Additionally, this dose of DMT produces an antidepressant response in the forced swim test comparable to the prototypical fast-acting antidepressant ketamine.[52] Like DMT, ketamine promotes fear extinction in rats[102] and has potent psychoplastogenic effects due to its impact on BDNF signaling. The similar behavioral phenotypes produced by DMT and ketamine are likely due to their shared ability to increase spino- and synaptogenesis in the prefrontal cortex[46,103]—a critical brain region involved in both the extinction of fear memory and in eliciting effortful responses to behavioral challenges.[104,105] Changes in neural plasticity induced by DMT could explain why this compound can produce behavioral changes long after it has been cleared from the body (vide infra).

METABOLISM AND PHARMACOKINETICS

The metabolism and pharmacokinetics of DMT play a prominent role in how it is typically administered as well as why it produces a qualitatively different experience than other psychedelics. First, the subjective effects of DMT administered to humans via IV injection are rapid and transient, peaking at 5 min and ceasing after 30 min.[50] Similar effects are observed when DMT is smoked. Furthermore, only 1.8 and 0.16% of an injected dose of DMT can be measured in the blood and urine

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

of humans, respectively, at any given time.[106] A high brain:plasma ratio (ca. 2−6) is rapidly established following administration of DMT.[107−109] In rats, the accumulation of DMT appears to be the greatest in the cortex and amygdala, brain structures that play key roles in the behavioral effects of the compound (vide supra).[110] In brain slices, DMT has been shown to accumulate via an active transport mechanism that is saturable, sensitive to metabolic inhibitors, and temperature-, glucose-, and sodium-dependent.[82]

In addition to quickly accessing brain tissue following systemic administration, DMT is rapidly metabolized by MAO-A as well as liver enzymes.[27] The half-life of DMT in vivo is approximately 5−15 min and can be extended by treating with a MAO inhibitor.[111] In fact, DMT is not orally active due to rapid degradation by MAO-A in the gut and liver.[112,113] In the case of ayahuasca, the tisane can be ingested because it also contains MAO-A inhibitors like harmine, enabling sufficient amounts of orally administered DMT to reach the brain. Some of the major metabolites of DMT have been identified as indoleacetic acid (**20**), DMT-*N*-oxide (**21**), *N*-methyltryptamine (NMT, **16**), 2-methyl-1,2,3,4-tetrahydro-*β*-carboline (2-MTHBC, **23**), tryptamine (TA, **15**) and 1,2,3,4-tetrahydro-*β*-carboline (THBC, **22**) (Figure 4).[114]

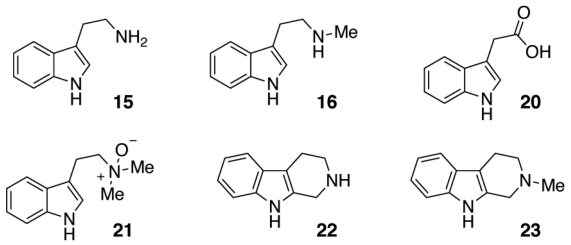


Figure 4. Metabolites of DMT produced from rat brain homogenates.

■ ADVERSE EFFECTS

Smoking is the preferred route of administering DMT among recreational users (i.e., nonreligious use) rather than imbibing ayahuasca.[115] Those who have consumed DMT recreationally also tend to administer a wide variety of other illicit substances including narcotics, psychostimulants, depressants, cannabis, and alcohol, confounding any conclusions that can be drawn regarding potential negative health effects of using DMT.[115] Owing to its rapid onset (a few minutes) and short duration of action (less than an hour) when smoked, the use of DMT in the 1960s became known as a "businessman's lunch." Like with most tryptamine psychedelics, DMT can cause some adverse physical effects including diarrhea, nausea, and vomiting. Additionally, elevated heart rate, blood pressure, and rectal temperature have been observed following DMT administration.[3] Based on rodent studies, the human LD_{50} values for intravenous and oral administration of DMT have been estimated to be approximately 1.6 and 8 mg/kg, respectively.[116] Death by ayahuasca—one of the more common ways to administer DMT—is quite rare.[116]

Psychologically, DMT can cause short-term emotional distress, and in some cases precipitate long-lasting psychosis. However, the latter is exceptionally rare and tends to be an issue only for people who abuse other drugs, have been previously diagnosed with a mental illness, or have a family history of schizophrenia, schizophreniform disorder, or mania.[117] However, when administered in controlled clinical settings where participants are carefully screened for factors that could predispose them to long-term adverse psychological effects, both DMT and ayahuasca appear to be exceptionally safe.[117] Furthermore, the prevalence of schizophrenia is not higher in religious groups that regularly consume ayahuasca as compared to the general population.[116] In fact, studies conducted on populations that regularly use ayahuasca for religious purposes have demonstrated that it is relatively safe and could possibly promote mental well-being.[118−120]

Owing to their Schedule I status, a common misconception is that serotonergic psychedelics such as DMT are addictive and associated with significant health risks. However, DMT and ayahuasca do not promote compulsive drug-seeking in humans.[116] In general, psychedelics are not considered to be addictive and are substantially safer than drugs like alcohol or nicotine.[121] In fact, several populations use these mind-altering substances chronically as part of religious ceremonies, and these people do not suffer from decreased cognitive function[122] or increased mental health issues.[123] On the contrary, lifetime use of psychedelics is associated with significantly decreased psychological distress, suicidal thinking/planning, and suicide attempts, while other drugs of abuse tend to increase these measures.[124] In contrast to alcohol, people report that psychedelic use has largely positive effects on their mental and physical health.[125] Ayahuasca users in particular report improved psychological well-being as compared to people who do not use psychedelics,[126] and ayahuasca has been shown to reduce impulsivity, boost mood, and improve cognitive performance.[127]

Due to its known ability to produce hallucinations and delusions,[39,40] DMT was originally thought to be an endogenous schizotoxin.[128−130] However, this hypothesis is no longer generally accepted for several reasons. First and foremost, DMT levels have not conclusively been proven to be greater in schizophrenia patients than controls.[129] In fact, DMT can be measured in a larger percentage of controls than patients.[131] Furthermore, DMT produces visual hallucinations, while patients with schizophrenia primarily suffer from auditory hallucinations. Despite these facts, several researchers still believe that stress-induced increases in DMT levels might exacerbate positive symptoms (i.e., delusions and hallucinations) in a subset of people with schizophrenia,[132] even though the evidence that stress is capable of increasing endogenous production of DMT is only preliminary.[133] Furthermore, exogenous DMT is still used to model psychosis.[134,135]

■ ENDOGENOUS PRODUCTION IN ANIMALS

The biosynthesis of DMT is not limited to plants. In fact, it has been found to be endogenously produced in a number of animals, including rabbits,[136] rats,[137,138] and humans.[139] A recent review analyzed 69 published studies from 1955−2010 that attempted to measure putative endogenous psychedelics such as DMT, 5-OH-DMT (i.e., bufotenin), and 5-MeO−DMT in human body fluids (e.g., urine, blood, and cerebral spinal fluid).[131] The authors conclude that there is overwhelming evidence that humans produce DMT and 5-OH-DMT, but that data regarding 5-MeO−DMT is less conclusive. Many early studies measuring DMT levels in animals have been criticized for their lack of specificity; however, these early results have been confirmed recently using highly sensitive and specific modern analytical methods such as liquid chromatography tandem mass spectrometry (LC−MS/MS).[138] Furthermore, specific diets, antibiotics, and other medications do not

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

seem to influence DMT levels in humans,[131] making it likely that DMT is produced endogenously rather than originating from the ingestion of plant material, the production by gut microbiota, or the metabolism of pharmaceutical agents. Now that the presence of DMT in humans has been firmly established, further research needs to be done to determine if endogenously produced DMT can influence brain function or is simply an insignificant metabolic product of tryptophan metabolism.

The enzyme indolethylamine *N*-methyltransferase (INMT) catalyzes the methylation of a variety of biogenic amines, and is responsible for converting tryptamine into DMT in mammals.[140] Homologous proteins to human INMT have been found in several animals[141,142] with the human and rabbit forms being 88% identical.[140] Human INMT is expressed in most tissues including the brain with the lungs exhibiting the highest levels of expression.[140,143] Interestingly, the ex vivo activity of INMT varies as a function of age with INMT preparations from the perinatal period exhibiting the greatest activity.[26] This difference in activity does not seem to be a result of changes in enzyme expression as a function of age, but rather from changes in the levels of an unidentified endogenous, dialyzable, peptidic inhibitor of INMT that represses native activity of the enzyme.[144,145] In principle, rapid degradation of this inhibitor could allow for precise temporal control of DMT biosynthesis.

Our current understanding of the function (or lack thereof) of endogenous DMT is severely limited by our lack of knowledge regarding exactly when and where this molecule is produced in the body.[131] To date, most studies have attempted to measure DMT levels in body fluids (e.g., blood and urine); however, measuring local changes in metabolism within specific regions of the body is likely to yield more useful information due to the rapid metabolism of DMT as well as the fact that INMT activity varies as a function of tissue type (e.g, it is highest in the lungs). Microdialysis experiments are useful in this regard, and one such study recently detected DMT in the pineal gland of rats.[138] Several authors have hypothesized that DMT secreted from the pineal gland might give rise to dreams, mystical states, and various sensations associated with near-death experiences.[6,146] However, others have argued that the small size of the pineal gland make it unlikely to be able to produce the quantity of DMT estimated to be necessary to produce a mystical experience (ca. 25 mg of DMT within a few minutes for a 75 kg individual).[147] As DMT rapidly crosses the blood−brain barrier after entering the bloodstream (vide supra), a large, highly vascularized peripheral organ expressing high levels of INMT, such as the lungs, seems a more likely source of DMT than either the brain or pineal gland. Though challenging, lung microdialysis studies[148] would shed light on this issue.

While very little is known about the synthesis and biodistribution of endogenous DMT, it is clear that under normal physiological conditions, DMT is produced in exceedingly small quantities, causing it to be labeled a trace amine. The single most important question for the field to answer is whether or not endogenous DMT is produced in sufficient quantities to have meaningful biological effects. As DMT is an inhibitor of INMT,[143,149] it is likely that such product inhibition of the enzyme limits the amount of DMT that can be synthesized rapidly, making it unlikely that the concentration of endogenous DMT could exceed the threshold for inducing hallucinogenic effects or mystical experiences, except for maybe under extreme conditions. However, endogenous DMT does not need to reach high concentrations to exert significant effects on mammalian physiology. Ly and coworkers demonstrated that a subhallucinogenic dose of DMT in rodents (based on allometric scaling of a hallucinogenic human dose)[150] can produce long-lasting changes in neural plasticity.[46]

Currently, we do not know how DMT concentrations change as a function of age, sex, or behavioral state. There is preliminary evidence from the 1970s suggesting that endogenous DMT production in rats increases following stress, specifically after experiencing electric shocks.[133] Both our lab and others have demonstrated that high acute doses of DMT result in anxiogenic effects such as increased immediate freezing following foot shocks, decreased exploratory activity in the open field, and less time spent in the open arms of an elevated plus maze.[52,98,151,152] However, we have also shown that DMT promotes structural and functional plasticity in the prefrontal cortex[46] and facilitates fear extinction learning.[52] It is possible that in rodents, endogenous DMT produced during stress serves an adaptive or protective role by (1) potentiating initial fear responses (e.g., increased freezing and reduced time spent in open spaces) and/or (2) promoting structural plasticity in the prefrontal cortex, thus facilitating fear extinction learning and preventing the formation of pathological fear memories. If true, this would have important implications for understanding the pathophysiology of post-traumatic stress disorder. However, it is also possible that stress does not increase endogenous DMT concentrations to levels sufficient for causing changes in behavior or plasticity.

As a final thought, endogenous DMT might play a greater role in neurodevelopment than in adult physiology. First, INMT activity is highest during development.[26] Second, Ly and coworkers have demonstrated that DMT is a potent psychoplastogen capable of inducing the growth of dendrites and dendritic spines while also promoting synaptogenesis.[46] Moreover, DMT likely mediates its effects on neural plasticity via an evolutionarily conserved mechanism, as psychedelics are capable of promoting neurite outgrowth in both *Drosophila* and rodent neurons.[46] At this point, any potential role for endogenous DMT in normal mammalian physiology should be considered highly speculative at best, and new research in this area is necessary to close this knowledge gap.

■ POTENTIAL USE IN MEDICINE

The effects of psychedelic compounds have been known for centuries with a variety of cultures consuming psychedelic-rich plants and fungi during religious or healing ceremonies.[153] Ayahuasca is perhaps one of the better-known psychedelic-rich traditional medicines.[154] This Amazonian tisane can be prepared by boiling the *Banisteriopsis caapi* vine and the leaves of the shrub *Psychotria viridis*.[155] The former is rich in *β*-carboline alkaloids, while the latter contains substantial amounts of DMT (Figure 1).[156] Ayahuasca is of significant interest to the medical community as this concoction has demonstrated powerful antiaddictive, antidepressant, and anxiolytic effects in both humans[10,53,157−160] and rodent models.[95,161,162] Religious users of ayahuasca tend to have a lower prevalence of substance abuse, and their illicit drug use tends to decrease after joining the church. Whether this is due to a true antiaddictive effect from the concoction or social factors resulting from being part of a supportive community is unclear.[157,163]

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

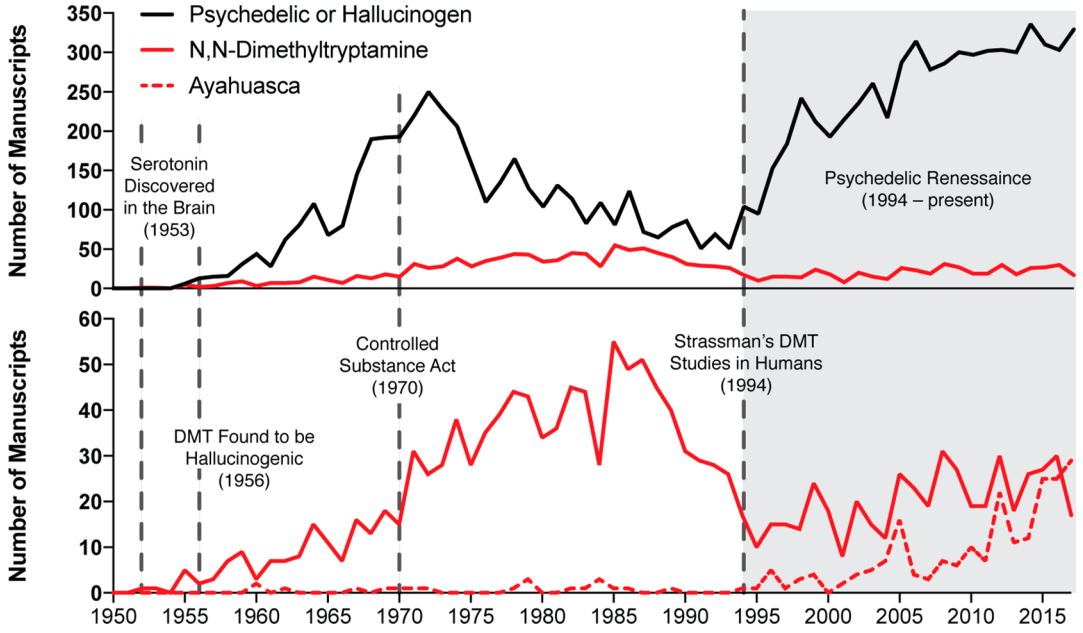


Figure 5. Timeline of important events related to research on DMT and other psychedelics. Note the different *y*-axis scales for the two graphs. Data related to DMT are presented on both graphs. The data presented here were obtained from *Scifinder* (Chemical Abstracts Service: Columbus, OH, 2017; accessed Nov 20, 2017) using the search terms "psychedelic or hallucinogen," "*N*,*N*-dimethyltryptamine," and "ayahuasca".

The alkaloid composition of ayahuasca can vary significantly depending on the preparation of the tisane and the analytical method used to determine its constituents.[156] While a large number of diverse compounds comprise ayahuasca, researchers have focused on the effects of DMT and harmine, though it is still unclear what specific roles they play in the antidepressant and anxiolytic properties of the tisane. While it is tempting to assume that harmine simply increases the oral bioavailability of DMT through inhibition of MAO, that does not seem to be the case, as harmine and other harmala alkaloids themselves can have profound effects on mood and anxiety.[164] Furthermore, harmine and other MAO inhibitors have a long history of being used as antidepressants in humans. Unlike the MAO inhibitors, there has not been a human clinical trial assessing the anxiolytic and/or antidepressant effects of DMT administered alone, though there have been a number performed using psilocybin, a close structural analogue (Figure 2).[165] Studies utilizing psilocybin to treat depression, anxiety, and addiction have been overwhelmingly positive.

A single dose of ayahuasca has shown efficacy for treating patients with recurrent depression,[10,53,160] and it appears to be relatively safe as long-term ayahuasca users do not display cognitive impairments or have increased mental health issues.[119] In light of the fact that current antidepressants often lack efficacy and fast therapeutic onset, this provides an exciting new avenue for treating these diseases. Much of what we know about DMT comes from studies using ayahuasca; however, there have been a few reports detailing DMT's influence on animal behavior. Recently, Cameron and coworkers demonstrated that DMT (administered alone) produced a characteristic antidepressant response in the forced swim test and displayed therapeutic efficacy in a rodent behavioral model of post-traumatic stress disorder.[52] These results are consistent with previous studies using other dissociatives, serotonergic hallucinogens, and entactogens that have also proven effective in these tasks, such as ketamine, psilocybin and MDMA.[100−102] The antidepressant and anxiolytic effects of DMT are correlated with increased dendritic spine density as well as increased frequency and amplitude of spontaneous EPSCs in the medial prefrontal cortex.[46] Importantly, structural and functional neural plasticity following BDNF signaling and mTOR activation is believed to underlie ketamine's antidepressant effects.[103] Understanding how DMT and ketamine produce similar cellular and behavioral responses despite binding to disparate receptors is an important area for future research.

In addition to its effects on neural plasticity and behaviors relevant to neuropsychiatric diseases, DMT has demonstrated potent anti-inflammatory properties. Through activation of the sigma-1 receptor, both DMT and 5-MeO-DMT inhibit the production of pro-inflammatory cytokines while enhancing the secretion of IL-10, an anti-inflammatory cytokine.[166] Sigma-1 agonists like DMT might also prove useful for treating neurodegenerative disorders by reducing inflammation.[167]

■ HISTORY AND IMPORTANCE IN NEUROSCIENCE

Originally synthesized in 1931 by Canadian chemist Richard Manske,[168] DMT was not believed to be of particular interest. Years later, the Hungarian chemist and psychopharmacologist Stephen Szára became interested in DMT after reading an article published in the *Journal of the American Chemical Society* describing the identification of bufotenin and DMT in the South American snuff known as "cohoba."[169] At the time, it was not known which natural product(s) was responsible for endowing cohoba with its psychoactive properties. It was not until 1956, 3 years after Twarog's and Page's seminal discovery of serotonin in the brain,[170] that Szára and coworkers found DMT to be hallucinogenic in humans.[171] The acute hallucinogenic effects were rapid (within 5 min) but lasted only for 30−60 min.[172,173] The original reports of DMT use were described as "similar to LSD or mescaline, but with a shorter duration of effect."[174]

Following the discovery of the hallucinogenic and euphoric properties of DMT and other emerging psychedelics, low

DOI: 10.1021/acschemneuro.8b00101
ACS Chem. Neurosci. 2018, 9, 2344−2357

doses of psychedelics quickly became suggested as an adjunct to psychotherapy, a trend that continued for several decades.[165,175,176] In the early 1960s, Julius Axelrod described an enzyme capable of *O*- and *N*-transmethylating indolamines, using SAM as the methyl donor, demonstrating that endogenous DMT production was indeed possible.[177,178] Several years later, Franzen and Gross published a highly influential paper, claiming that they had isolated DMT from human blood and urine.[179] This was followed by several other reports detailing the presence of DMT in various human body fluids including cerebrospinal fluid.[131] The fact that a hallucinogen was produced endogenously generated massive interest in the scientific community. As described above, DMT was originally thought to be a schizotoxin.[128−130] While that hypothesis has fallen out of favor (vide supra), the value of using DMT to model the positive symptoms of schizophrenia has been appreciated. In one of the few clinical studies on DMT, Gouzoulis-Mayfrank and coworkers found that DMT and (*S*)-ketamine were better at modeling the positive and negative symptoms of schizophrenia, respectively.[135]

The Drug Abuse Control Amendments of 1965 and the Controlled Substances Act of 1970 classified many hallucinogenic molecules, including DMT, as Schedule I substances. This designation severely limited access to these compounds by the scientific community and caused a massive decline in psychedelic research (Figure 5). Curiously, research on DMT did not mirror the general downward trend observed with other psychedelics such as LSD and psilocybin and instead peaked during the mid 1980s (Figure 5). Despite increased research activity related to DMT following passage of the Controlled Substance Act, the drastic general reduction in the number of scientific manuscripts about psychedelics during this time (Figure 5) made it abundantly clear that Schedule I designations imposed substantial political, social, and economic barriers to studying these compounds. In Rick Strassman's words, "The most powerful members of their profession discovered that science, data, and reason were incapable of defending their research against the enactment of repressive laws fueled by opinion, emotion, and the media."[6]

After decades of relative quiescence, clinical psychedelic research began to revive in the 1990s with DMT studies being among the first reported. In 1994, Strassman published a series of studies detailing the autonomic and subjective effects of DMT in humans. He chose DMT for his studies in large part due to its relative obscurity as a psychedelic:

> *"I noted that one of the best reasons for choosing DMT was that very few people had heard of it. When the media discovered my research, it would draw much less attention than would an LSD project."*

Strassman's studies demonstrated that it was possible to navigate the regulatory hurdles and convoluted process associated with doing modern day research on Schedule I compounds. Additionally, key personnel changes at the Food and Drug Administration (FDA) and the excitement associated with new clinical studies on psychedelic agents led to a surge in psychedelic research. Following Strassman's 1994 studies, many seminal papers on psychedelics were published, including dose−response, pharmacokinetic, mechanistic, and behavioral studies. In fact, psychedelic research has continually gained momentum since 1994, and today, approximately 300 papers each year are published on the topic (Figure 5). Though DMT was among the first compounds investigated at the beginning of the "psychedelic renaissance," it continues to remain underappreciated and understudied. In fact, research on ayahuasca constitutes the majority of the work on DMT being conducted today (Figure 5).

The DMT structure constitutes the core of many indole-containing serotonergic psychedelics, and thus, it is fitting that this basic compound played such a significant role in the recent resurgence of psychedelic research. These facts certainly justify its inclusion on a list of classic molecules in chemical neuroscience, with numerous questions about DMT still remaining. As we do not yet know what role this endogenous psychedelic plays in mammalian physiology, or how it might be used to treat neuropsychiatric disorders, we hope that this review will spark a renewed interest in this incredibly simple but extraordinarily important small molecule.

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Author Contributions

D.E.O. conceived the structure of the review. D.E.O. and L.P.C. performed relevant literature searches and wrote the manuscript together.

Funding

This work was funded in part by the UC Davis Department of Chemistry and Department of Biochemistry & Molecular Medicine.

Notes

The authors declare no competing financial interest.

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