REVIEW

Administration of N,N-dimethyltryptamine (DMT) in psychedelic therapeutics and research and the study of endogenous DMT

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Abstract

As with all drugs, the route, form, and/or dose of a substance administered or applied can play a defining role in its overall pharmacology and use as a therapeutic. This review will focus on these factors as they relate to the psychedelic N,N-dimethyltryptamine (DMT). It will examine the positive and negative aspects of different formulations and routes of administration of DMT and the observed effects from such administrations in the form of ayahuasca teas; oral "pharmahuasca"; injections by intravenous (IV) and intramuscular (IM) routes; inhalation, insufflation; and other routes; and high-dose, low-dose, and "micro-dose" effects. The review will consider possible oral route of administration alternatives that would not require concomitant use of a monoamine oxidase inhibitor. The review will then address the current research findings for DMT from in vivo and in vitro studies as well as the possibility that these findings may be revealing the role of endogenous DMT in normal brain function.

Keywords Dimethyltryptamine · Psychedelic therapeutics · Ayahuasca · Sigma-1 receptor · Monoamine oxidase inhibitor · Pharmahuasca · Deuterhuasca

Introduction

The administration of psychedelics as therapeutics has begun to show great promise for the treatment of depression, post-traumatic stress disorders, substance abuse and addiction, as well as many other often intractable maladies (Tupper et al., 2015; Carhart-Harris and Goodwin, 2017; Andersen et al., 2021). Both in vitro and in vivo studies are also showing that the psychedelics possess significant neuroplastogenic, effects, such as reducing infarct size and enhancing functional recovery following brain ischemia (Nardai et al., 2020). It is thought that their effects on neural plasticity may explain what appears to be the observed long-lasting behavioral effects related to mood and anxiety in humans.

This article belongs to a Special Issue on Psychopharmacology on Psychedelic Drugs

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As with all drugs, the route, form, and/or dose of a substance administered or applied can play a defining role in its overall pharmacology and use as a therapeutic. This review will focus on these factors as they relate to the psychedelic N,N-dimethyltryptamine (DMT, **1**). It will examine the positive and negative aspects of different formulations and routes of administration of DMT and the observed effects from such administrations in the form of teas (ayahuasca, a combination of DMT and harmala alkaloids), oral "pharmahuasca" (DMT and a monoamine oxidase inhibitor or MAOI), and administration of DMT alone by intravenous (IV) and intramuscular (IM) injection routes, inhalation, insufflation, and other routes, as well as high-dose, low-dose, and "micro-dose" effects. The review will consider possible oral-route-of-administration alternatives that would not require concomitant use of a monoamine oxidase inhibitor. The review will then address the current research findings for the pharmacology of DMT from in vivo and in vitro studies as well as the possibility that these findings may be revealing the role of endogenous DMT in normal brain function (Fig. 1).

Fig. 1 Structures of compounds discussed. DMT, N,N-dimethyltryptamine; d, deuterium; 5 h, 5-hydroxy; 5 MeO, 5-methoxy
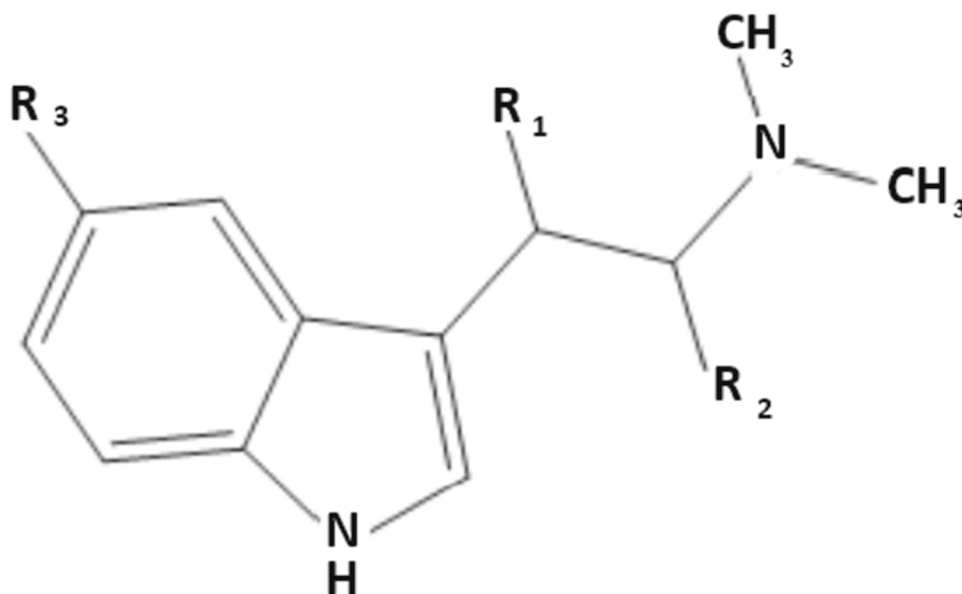
DMT: R1 = R2 = H2; R3 = H, **1**

5HDMT: R1 = R2 = H2; R3 = OH, **2**

5MeODMT: R1 = R2 = H2; R3 = OCH3, **3**

d4DMT: R1 = R2 = d2; R3 = H, **4**

d45MeODMT: R1 = R2 = d2; R3 = OCH3, **5**

Administration of DMT

Ayahuasca as a source of DMT in psychedelic therapeutics

There has already been a significant and historical record for the medicinal use of DMT occurring long before the advent of psychedelic therapy. Like many foundational therapeutics, N,N-dimethyltryptamine (DMT) literally has botanical roots and an archaic cultural history of use for medicine and religious ritual, much as does psilocybin. As a psychoactive ethnobotanical medicine utilized by many of the indigenous tribes of the Basin of South America, the DMT-containing tisanes or teas known collectively as yage, caapi, hoasca, or ayahuasca have been in use for hundreds of years in these cultures (Samorini 2019). Ayahuasca, a Quechua tribal term meaning ''vine of the souls,'' is used in the context of shamanistic ritual, as historically practiced among aboriginal peoples for curing, divination, diagnosis of the imbalances of the body and soul, and as a ready pharmacological path to the mythological supernatural.

The major active component, DMT, comes from the leaves of the Psychotria species, mainly *P. viridis*. Since the major metabolic route for DMT in humans involves

conversion to indol-3-acetic acid by MAO (Barker et al., 1981), teas made from Psychotria species alone are not orally active, but when combined with the harmala MAOIs (harmine, harmaline) of *Banisteriopsis caapi*, it becomes a potent hallucinogenic beverage (Schultes, 1957; McKenna et al. 1984, 1998; Andritzky, 1989).

The effects of consuming ayahuasca have been variously summarized as "… inducing changes in the perceptual, affective, cognitive, and somatic spheres, with a combination of stimulatory and visual psychoactive effects of longer duration and milder intensity than those previously reported for intravenously administered DMT." (Riba et al. 2001; Riba 2003). Pharmacological studies of acute ayahuasca administration to healthy volunteers and mental health assessments of long-term ayahuasca consumers suggest that this ethnobotanical medicine is relatively safe and effective (Callaway et al. 1999; dos Santos, et al. 2011, 2016a, 2016b, 2017). However, questions remain about the ability to provide a consistent "batch" of ayahuasca for further study and therapeutic use on a larger scale.

One of several difficulties that has arisen for the use of ayahuasca as a clinical therapeutic involves its uniformity and stability. A recent study of the main ayahuasca alkaloids (DMT, harmine, tetrahydroharmine, and harmaline)

in brewed ayahuasca stored under three different conditions (1 year stored in a refrigerator either in plastic or glass containers, 7 days at 37 °C and after three freeze–thaw cycles) found that there was no significant degradation of DMT concentration over time in all tested environments. However, the harmala alkaloids all showed significant degradation under long-term storage and at elevated temperature as well as possible alkaloid inter-conversion. It was concluded by the authors that ayahuasca tea component quantification before administration under controlled conditions would be mandatory (Silveira et al. 2020). Similarly, batch-to-batch ayahuasca preparation variation as well as alterations in ayahuasca alkaloid content as a function of season, location, soil, and climate conditions, and other variables related to plant growth, have been consistently observed, leading to wide-ranging dosing levels, and making adjustment of ayahuasca by dilution or addition of components necessary to obtain a relatively consistent material for use. The use of large batch, freeze-dried material administered in a gelatin capsule can overcome some of these issues (Riba and Barbanoj 2005), but not all. Therapeutic use of ayahuasca suggests that it can have prolonged antidepressant, anxiolytic, and anti-addictive effects (dos Santos et al. 2016a, 2016b), and is also quite safe (dos Santos et al. 2016a, 2016b; Osório et al. 2015; Frecska et al., 2016).

To understand the potential of ayahuasca to contribute to modern medicine and its use in psychedelic therapeutics, it must be more thoroughly examined in the laboratory and in controlled clinical trials and medicinal studies (Kuypers et al., 2016; Palhano-Fontes et al., 2019). Nonetheless, an approach to its therapeutic use has been outlined and described (McKenna 2004). While ayahuasca obviously holds promise in many social, cultural, and therapeutic paradigms, including treatment of addiction, anxiety, and depression in psychiatry and many other possible applications, it is, nonetheless, a complex mixture of perhaps thousands of compounds. A further complication in its use in therapeutics and research is that the potent MAOI activity of the harmala alkaloids not only protects DMT from metabolic degradation but also suppresses the metabolism of other neurotransmitters and MAO-sensitive compounds in the brain and periphery. These compounds also have their own unique pharmacology. Thus, it is difficult to know exactly which of the compounds or combination of compounds plays a role in what observed effect (Ona et al., 2020), making it difficult to compare to studies conducted using DMT alone.

2. Administration of DMT with and without a MAOI: doses, routes, and effects

Oral administration of DMT alone is rendered neurochemically inactive by MAO during first-pass metabolism. Thus, other routes for the administration of DMT have been designed to avoid or mitigate this fate. These have predominantly required intravenous (IV) or intramuscular (IM) administration, inhalation (smoking or sublimation) or insufflation (nasal sprays, snuffs), and use of transdermal, sublingual, or buccal absorption. Other routes have been attempted with little reported success. It is of interest to note that intranasal free-base DMT is inactive (0.07–0.28 mg/kg; Turner and Merlis 1959) as is DMT administered rectally (De Smet 1983).

Szára (1956, 1961) reported that the effects of intramuscular DMT (0.7 mg/kg) were like mescaline and LSD (visual illusions and hallucinations, distortion of body image, speech disturbances, mood changes, and euphoria or anxiety). Other studies using either IV or IM administrations (Turner and Merlis 1959; Rosenberg et al. 1964; Gillin et al. 1976; Strassman et al. 1994a, 1994b) have observed similar results. The intramuscular effects of DMT (0.2–1 mg/kg; Szára 2007) generally had a rapid onset (2–5 min) and lasted 30–60 min. The IM effects were considered less intense than the IV route. As a comparison, the subjective effects of DMT from ayahuasca administration (0.6–0.85 mg/kg DMT; Riba et al. 2003) usually appear within 60 min, peak at 90 min, and can last for approximately 4 h (Cakic et al. 2010), due, in part, to the MAOI effects of the constituent harmala alkaloids. Riba et al. (2015) have reported the comparative effects of oral and vaporized DMT. Oral ingestion of pure DMT produced no psychotropic effects, as expected. Vaporized DMT was found to be a highly psychoactive route of administration, however. Doses for vaporized or inhaled free-base DMT are typically 40–50 mg, although larger doses have been reported (100 mg; Shulgin and Shulgin 1997). Pallavicini et al. (2021) have reported that vaporization of approximately 40 mg of DMT, administered in a natural setting, produced potential electroencephalographic markers of mystical-type experiences in 35 volunteers. The onset of effects for inhaled DMT is rapid, similar to that of IV administration, but lasts less than 30 min (Riba et al. 2015; Davis et al. 2020). However, smoked, vaporized, or insufflated DMT can often be harsh and is not always well-tolerated. Thus, these routes may not be the most consistent and suitable choices for therapy.

Strassman et al. (1994a, 1994b) have reported dose–response data for intravenously administered DMT fumarate in a group of experienced hallucinogen users (n=11). DMT was administered IV at doses of 0.05, 0.1, 0.2, and 0.4 mg/kg and showed peak DMT blood levels and subjective effects within 2 min after drug administration, becoming negligible at 30 min. IV DMT was also shown to elevate blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to elevating blood concentrations of β-endorphin, corticotropin, and cortisol in a dose-dependent manner, with prolactin and growth hormone levels rising equally, regardless of dose. The lowest dose that produced statistically significant

effects relative to placebo and that was also hallucinogenic was 0.2 mg/kg (Strassman 1991, 1996, 2001; Strassman et al. 1996). For exogenously administered DMT, we know plasma concentrations between 12 and 90 ng/ml (Callaway et al. 1999; Yritia et al. 2002; Riba et al. 2003) must be attained to produce hallucinogenic effects. However, the concentrations attained in whole brain or in specific brain cells or areas that are required to produce hallucinogenic effects from such administrations in humans remains unknown.

The use of a simple mixture of DMT and harmaline and/ or harmine or other MAOIs, a so-called "pharmahuasca" (Ott 1999; Brierley and Davidson 2012), has been proposed as a "cleaner," orally administered substitute for ayahuasca itself or of greater use in conducting ayahuasca research as a pharmaceutical version of the entheogenic brew. For administration of pharmahuasca, 50 mg DMT:100 mg harmaline is usually the recommended dosage. However, combinations of 50 mg harmaline:50 mg harmine and 50 mg DMT have been tested with success. The harmalas and DMT are typically put into separate gelatin capsules, with the harmaline/ harmine being taken first and the DMT being taken 15 to 20 min later. The use of moclobemide, a reversible inhibitor of MAO-A, has also been reported in DMT "pharmahuasca" studies (Kaasik et al. 2020; Ruffell et al. 2020).

The further study of "pharmahuasca," as well as more research on low-dose ayahuasca, may prove to be rewarding for their use as psychedelic therapeutics. However, as with ayahuasca, the concomitant use of an MAOI remains a drawback.

3. Micro-dosing or low-dosing of non-hallucinogenic amounts of DMT

More recently, data and anecdotal reports concerning the physiological effects of administration of psychedelics in very low doses, or micro-dosing, have gained significant public attention. Micro-dosing of psychedelics refers to the ingestion of low to very low doses (5 and 10% of a standard hallucinogenic dose) on an established schedule (every other day) with the intention of avoiding hallucinogenic or short-term debilitating effects (Fadiman and Korb, 2019; Kuypers et al. 2019; Kuypers, 2020; Liechti 2019, Bershad et al. 2019 Cameron et al. 2020). However, regardless of the identity of the psychedelic, there are no scientifically established dose ranges that have been accepted for micro-doses of these substances (Kuypers et al. 2019; Passie 2019; Lea et al. 2020). In its popular practice, micro-dosing is said to enhance productivity, focus, and creative problem solving (Dean 2017; Glatter 2015; Cameron et al. 2020) and as a self-regulated treatment for depression, anxiety, and other perceived mental disorders (Waldman 2017; Hutten et al. 2019). Recent randomized controlled trials, mainly with LSD or psilocybin, have reported changes in time perception (LSD; Yanakieva

et al. 2019), dose-related increases in ratings of "vigor" (psilocybin; Bershad et al. 2019), and improved performance on problem-solving tasks (psilocybin mushrooms; Prochazkova et al. 2018). However, the number of such studies is currently too small to draw any scientifically significant conclusions.

Similarly, there are but a handful of such DMT micro- or low-dosing studies, conducted in species other than humans (predominantly the rat), published in the scientific literature. However, the translational aspect of a low dose in rats and a micro-dose in a human is not yet established and no scientifically sound conclusions can yet be drawn. Nonetheless, Ly et al. (2018) observed that a low dose of DMT caused changes in the frequency and amplitude of spontaneous excitatory postsynaptic currents (EPSCs) in the prefrontal cortex (PFC) of rats that lasted long after the drug had been cleared from the body. Cameron et al. (2019) examined these observations further by subjecting male and female Sprague–Dawley (SD) rats to behavioral testing following the chronic, intermittent administration of low doses of DMT (approximately for 2 months, every third day, 1 mg/ kg, IP). The behavioral and cellular effects observed were distinct from those induced following a single high dose of DMT (10 mg/kg IP), producing an antidepressant-like phenotype and enhanced fear-extinction-learning without impacting working memory or social interaction. At this low dose, DMT showed a distinct lack of anxiogenic effects, a striking difference between low dose and a single high dose of DMT, which is known to produce intense initial anxiogenic effects in several animal behavioral tests and in humans. A similar phenomenon was observed by Strassman et al. (1994b) wherein a single 0.1 mg/kg dose of DMT administered IV to humans, which was sub-hallucinogenic, produced an apparent anxiolytic effect.

Tested in rats in other behavioral paradigms (foot shock; cued fear learning) low-dose DMT showed no difference from placebo, whereas a single high dose of DMT significantly increased freezing levels immediately following foot shocks (Cameron et al. 2019). When the cued memory test was repeated, the low-dose DMT-treated animals froze significantly less than the vehicle controls ($p = 0.03$), suggesting that chronic, intermittent, low doses of DMT facilitate fear-extinction learning. In the forced swim behavioral test, however, both low-dose intermittent DMT and single high-dose DMT elicited an antidepressant-like effect, consistent with anecdotal reports from human use. Chronic, intermittent, low doses of DMT had no effect on working/short-term memory or social interaction, seemingly in contradiction to the beneficial effects of psychedelic micro-dosing reported by humans (Cameron et al. 2019).

A previous study had shown that a single intraperitoneal (IP) high dose of DMT (10 mg/kg IP) in rats increases dendritic spine density in the prefrontal cortex (Cameron et al. 2018). However, Cameron et al. (2019) showed no such

effect from low-dose intermittent IP administration of DMT in male SD rats. Rather, they reported a significant decrease in dendritic spine density in females under these conditions when compared to placebo controls ($p = 0.03$). The expression of several key prefrontal cortex genes (egr1, egr2, arc, and fos) associated with neuronal plasticity was also examined following low-dose intermittent administration, as acute doses of psychedelics are known to increase their expression (Martin and Nichols 2017). However, low doses of DMT did not alter the expression of any of these genes nor did it increase the expression of BDNF, which is increased in rat cortex following both acute (Vaidya et al., 1997; administration of DOI: 4-iodo-2,5-dimethoxyphenylisopropylamine) and chronic administration (Martin et al. 2014: administration of LSD) of high doses of psychedelics. An interesting finding was that 5HT2A receptor gene expression was unchanged despite chronic exposure of the 5HT2A receptor to DMT for nearly 2 months. These data suggest that psychedelic micro- or low dosing with DMT may be effective in treating symptoms of mood and anxiety disorders, though much further investigation is clearly required. However, they also suggest the possibility that two pharmacologies are at work: one for high dose and one for low dose. The work of Cameron et al. (2018, 2019) is thus informative in this regard and, perhaps, a warning for those who choose microdose or low-dose experimentation without first knowing the data or before scientifically controlled research and safety studies have been conducted.

How do we best administer therapeutic or research doses of DMT?

While the use of a pharmahuasca formulation could serve to standardize ayahuasca administrations, lower the dose needed to obtain desired outcomes, avoid many side effects observed from the use of ayahuasca itself, and provide a convenient oral route for its use as a therapeutic; it suffers from one of the same problems as ayahuasca—the necessary, general, system-wide inhibition of MAO, producing a mixed pharmacology that will be difficult to scientifically untangle even while simplifying some therapeutic applications.

Indeed, there seems to be no ideal or "conveniently unobtrusive" route for routine administration of DMT for general or common therapeutic use, although this may depend on whether an acute or prolonged dosing regimen is required. Any administration route using IV or IM routes, or inhalation or insufflation will be useful for conducting acute exposures where prescribed and rendered tolerable. One may assume that formulations for possible dosing by sublingual or buccal administrations could be developed that overcome their individual issues and difficulties (taste,

salivary clearance, adsorption rates) while avoiding first-pass metabolism. New developments in "patch" dermal delivery systems as well as drug delivery "pumps" may also be applicable for time-release DMT administration. Metered dosing of an aerosolized solution of DMT using an inhaler-type device has also been suggested (Arnold et al. 2021) and "vaping" is already a popular, though anecdotal, route of use. However, a simple orally administered pill is often the most desirable for pharmaceutical use for most therapeutics, especially if repeated dosing and longer term therapy is found to be successful. The pill need not be simple, however. Newer technology in delayed release, sustained release, and complex excipient combinations may also prove to have their place for DMT as well as other psychedelic therapies for routine low- or high-level dosing.

The need to provide an orally administered DMT that resists metabolism, without necessitating an add-on MAOI, that still retains potency and efficacy for a desired treatment, for which it may eventually be deemed appropriate, can be accomplished by slight modifications of the structure of the DMT molecule. These modifications mainly involve altering the ability of MAO to bind and cleave the DMT molecule at the side chain carbon-alpha to the nitrogen, which is the mechanism of action of MAO (Vianello et al. 2012) in the process of converting ethylamine indolic side chains to the corresponding indole acetic acid.

Another approach commonly used in medicinal chemistry is to change the dimethyl groups on the side chain nitrogen to larger and/or branched alkyl substituents to again limit the ability of MAO to bind and metabolize the molecule. A combination of both may prove successful as well. Literally locking the side chain into a ring, as is seen in lysergic acid dimethylamide (LSD), also has its advantages. The complicating factors in these modifications may be that, while they inhibit DMT's metabolism and clearance, such alterations may cause them to fail to properly bind, altering the binding characteristics at, for example, the 5HT2a receptor, or may produce an overall differing pharmacology or toxicology. They could also prove to be more effective.

However, two studies have shown that alteration of the alpha and beta hydrogens on the side chain of DMT and its structural relative, 5MeODMT (**3**) may protect the molecule from MAO metabolism, elevate the brain and circulating levels of an administered dose, and prolong the effects of these molecules without altering the measured parameters for DMT pharmacology. In administrations of DMT and α,α,β,β-d4-DMT (**4**) at doses of 2.5, 5.0, and 10.0 mg/kg to rats by a subcutaneous route (SC; Barker et al. 1982), resulting analyses (GC/MS) of brain levels of the parent compounds showed that d4DMT (**4**) attained concentrations 2–3 times greater than DMT itself at the same dose and remained at higher levels as a function of time, remaining detectable in brain at least two times longer. A follow-on study

(Beaton et al. 1982) showed that d4DMT (2.5 and 5.0 mg/kg SC) had a shorter time to onset, a greater level of disruption in a food reward behavioral paradigm and a greater duration of action than an equal dose of proteo-DMT. In a similar study, Halberstadt (Halberstadt et al. 2012) examined 5-methoxy-α,α,β,β-d4-DMT (d45MeODMT, **5**) versus proteo-5MeODMT and 5MeODMT in combination with the MAO inhibitor pargyline in a behavioral paradigm measuring locomotor activity and patterning. Halberstadt et al. (2008) had previously observed that 1.0 mg/kg 5MeODMT (SC) had biphasic effects on locomotor activity in rats pretreated with a behaviorally inactive dose of the MAOI pargyline (10 mg/kg). Regardless of dose (1.0 mg/kg SC or greater), administration of 5MeODMT alone produced only reductions in locomotor activity, a possible sedative or anxiolytic effect. Although low doses of d45MeODMT (5; 0.3 and 1.0 mg/kg, SC) produced only hypoactivity as well, a dose of 3.0 mg/kg caused a biphasic locomotor profile like that produced by the combination of 5MeODMT and pargyline, a potent MAO-A inhibitor. However, a further contribution of the study was that receptor binding experiments showed that deuterium substitution had little measurable effect on the binding affinity of d45MeODMT for a wide variety of neurotransmitter binding sites.

Taken together, these two studies take advantage of the deuterium kinetic isotope effect (Barker et al. 1982; Halberstadt et al. 2008) to render DMT and 5-MeODMT partially resistant to metabolism by MAO, increase their potency and duration of action while maintaining binding affinity and behavioral effects, creating, essentially, the same pharmacology as seen with the co-administration of these compounds with a MAOI, but without the unwanted additional effects of such a drug on other MAO-sensitive bio-compounds. Thus, the use of deuterium essentially creates a single compound ayahuasca or "pharmahuasca" and could be expected to perform in the same manner, as this "deuterhuasca." One might also expect that the deuterated analogs of these drugs may also be orally active. However, the oral bioavailability of these compounds has, unfortunately, not yet been examined/published, although there should be every expectation that this will be the case. Nonetheless, "deuterhuasca" could still be administered by any of the other routes as well. Thus, a dxDMT therapeutic could possibly be derived that can be administered orally, or by IM, IV or other routes, require a lower dose for effect, provide a longer duration of action, and avoid the unwanted effects on other systems by not requiring the co-administration of an MAOI. It is also anticipated that d4DMT is resistant to not only MAO-A but also MAO-B. Other deuterated analogs of d4DMT would also be expected to exhibit some of these same characteristics. Research has shown that the beta position deuteration has little to no effect in slowing metabolism by MAO (Boulton

and Yu, 1981), suggesting that an alpha, alpha-dideutero analog could be just as effective. Several deuterated species of DMT have been synthesized and have been suggested for use as biochemical probes for understanding the role different positions play in transport, metabolism, binding, and clearance (Morris and Chiao 1993). In this regard, one would also expect that alpha deuteration of other psychedelic DMT-related therapeutics, such as psilocybin, would also make the drug more orally bioavailable, potent, and longer lasting without otherwise altering its pharmacology. In fact, Rands et al. (2020) have submitted a patent application that follows this scenario. The invention relates to compositions comprising DMT, deuterated DMT, and/or partially deuterated DMT or a combination of DMT and 2% or more by weight of one or more deuterated N,N- dimethyltryptamine compounds selected from α,α-dideutero-DMT and α,α,β,β-tetradeutero-DMT. Additional and alternative compositions include a combination of DMT and 2% or more by weight of one or more partially deuterated DMT compound selected from α,β,β-trideutero-DMT, α,β-dideutero-DMT, and α-deutero-DMT. Methods of synthesizing compositions and methods of use of described compositions in treating psychiatric or psychocognitive disorders, such as major depressive disorder, are also provided (Rands et al. 2020).

Another approach to resisting the metabolism of DMT by MAO is to alter the alpha hydrogen(s) by adding a methyl or other small functional group(s), such as fluorine. As noted, selected alterations of the alkyl groups added to the side chain terminal nitrogen, such as diethyl and diisopropyl, lead to compounds with 5HT2a and related pharmacological activity, as does the addition of select functional groups to the aromatic ring of the indole molecule. The number of compounds in this class are legion (Shulgin and Shulgin 1997) and medicinal chemistry labs and pharmaceutical houses have been making them for years, examining structure–activity relationships (SARs) mainly related to their hallucinogenic potency. The selection of the most appropriate structures for use as a therapeutic can be readily made from the available literature with each requiring, as does DMT, much further research into safety, efficacy, and appropriateness of use for particular therapeutic outcomes.

It has been suggested that a given compound's ability to produce hallucinations may prove unnecessary (Olson, 2021) to produce enduring therapeutic effects. There is, however, conflicting evidence and opinion in this regard (Yaden and Griffiths, 2021). In many cases, the choice of compound structure, route of administration, and dose will come down to these needed results and the desired application, of which most have yet to be defined. For example, Dunlap et al. (2020) have demonstrated that DMT can be engineered to lack hallucinogenic potential while retaining

the ability to promote neural plasticity, identifying key features of the "psychoplastogenic pharmacophore" to develop psychoplastogens that are easier to make, have improved physicochemical properties (stability, metabolic profiles), and show a reduced or absent hallucinogenic potential compared to DMT. This would most likely also be the case for other psychedelics as well. Given the new discoveries regarding psychoplastogenic properties of the psychedelics and the possibility to attain therapeutic effect without hallucinogenesis, several side-lined chemical analogues of the psychedelics, which showed no hallucinogenic activity, may have newfound success in the medicinal laboratory as psycho- or neuro-plastogens. Would this not be one of the many possible futures and successes of psychedelic therapeutics?

The in vivo and in vitro effects of exogenous DMT

Regardless of route of administration, binding of DMT and related psychedelics to the 5-HT2A receptor is thought to be involved in production of its more dramatic and well-studied subjective hallucinogenic effects. However, there are other non-hallucinogenic substances that exhibit the same binding characteristics. Indeed, 5-HT2C and 5-HT1A receptors may also play a role (see reviews by Nichols 2004, 2016; Halberstadt 2015; Carbonaro and Gatch 2016) as well as other known and, perhaps, unknown receptors or compounds yet to be identified in what may be a far more complex system than we know. How psychedelic compounds modulate the 5-HT receptor family is not well understood.

We also know from in vitro and in vivo studies that DMT interacts with not just serotonin receptors but other receptors as well (Cumming et al. 2021), such as ionotropic and metabotropic glutamate receptors, dopamine, acetylcholine, trace amine-associated receptors (TAAR) (Carbonaro and Gatch, 2016), opioid receptors (Ruffing et al. 1979; Ruffing and Domino 1981, 1983; Nichols, 2004, 2016; Carbonaro and Gatch 2016), and neuroendocrine system functions (Schindler et al., 2018), and is the only known endogenous ligand agonist of sigma-1 receptors (Fontanilla et al., 2009; Su et al. 2009; Carbonaro and Gatch 2016). Indeed, Mavlyutov et al. (2012) have reported the presence of the sigma-1 receptor in c-terminals of motoneurons and its colocalization with the N,N-dimethyltryptamine forming enzyme, indole-N-methyl transferase (INMT). Setting aside for the moment our reasonable historical fascination with the psychedelic state, research into the overall non-hallucinogenic pharmacology of DMT, especially regarding sigma-1 receptors, has yielded fascinating results and what appear to

be real potential contributions to the field of therapeutics in general.

Sigma-1 receptors are inter-organelle signaling molecules which have been implicated in synaptic plasticity primarily by enhancing the function of N-methyl-D-aspartate receptors (NMDAR) (Pabba and Sibille 2015) as well as many other cellular functions. Sigma-1 receptor agonists are potentially neuroprotective (Frecska et al. 2013; Nguyen et al. 2017; Ryskamp et al., 2019; Zhao et al. 2019; Szabo et al. 2021) and DMT has been shown to reduce brain inflammation via the sigma-1 receptor (Szabo et al. 2014, 2016; Szabo 2015; Szabo and Frecska 2016). DMT can also induce neuronal plasticity, a longer duration brain recuperative and repair process (Tsai et al. 2009; Ruscher et al. 2011; Kourrich et al. 2012; Ly et al. 2018; Olson 2018, 2021). DMT has been shown to reduce infarct size and improve functional recovery following transient focal brain ischemia in rats (Nardai et al. 2020), suggesting possible efficacy in post-ischemia and in stroke treatment or prevention and to prevent renal ischemia–reperfusion injury in a rat model as well (Peto et al., 2018; Nemes et al. 2019). Sigma-1 receptors can also regulate cell survival and proliferation (Collina et al. 2013; Frecska et al. 2013). Regulation of intracellular calcium overload, a pro-apoptotic gene expression occurring via sigma-1 receptors and NMDAR, can result in neuroprotection during and after ischemia and acidosis (Pabba and Sibille 2015). Further benefit could occur through sigma-1 receptor–dependent plasticity changes (Tsai et al. 2009; Ruscher et al. 2011; Kourrich et al. 2012; Frecska et al. 2013). It has also been shown that administered DMT's ability to effect early gene stimulation through second messenger systems affects the rate of transcription, such that DMT activates the transcription factors c-fos (Frankel and Cunningham 2002), egr-1, and egr-2, all associated with synaptic plasticity (O'Donovan et al. 1999; González-Maeso et al., 2007).

DMT may also be involved in fetal brain and/or other organ ontogeny. INMT activity in rabbit lung is relatively high in the fetus, increasing rapidly after birth and peaking at 15 days of age. It then declines to mature levels and remains constant through life (Lin et al. 1974). These data are quite similar to those observed by Beaton and Morris (1984) for DMT in rat pups where peak levels were attained in whole brain at 17 days and declined over time in developing rat pups. The possible linkage of these findings suggests that DMT-mediated sigma-1 receptor activity may induce neuronal plasticity changes that are seen in newborns. Selective sigma-1 receptor agonists, such as DMT, have also been shown to be protective against excitotoxic perinatal brain injury (Griesmaier et al. 2012) and ischemic neurodegeneration in neonatal striatum (Yang et al. 2010). Expression of INMT also seems to be important for pregnancy success (Nuno-Ayala et al. 2012). Thus, the use of DMT and other

psychedelics, with or without modifications, may also prove of use in neonatal and pediatric medicine for the treatment of brain developmental issues.

Brain-derived neurotrophic factor (BDNF) is associated with synaptic plasticity and increases in its expression have been observed following DMT administration. BDNF (O'Donovan et al. 1999; Olson, 2018; Almeida et al. 2019) is also involved in cognitive processes such as memory (Jones et al. 2001; Bekinschtein et al. 2008, 2014; Notaras and Buuse, 2020), attention (DeSteno and Schmauss 2008; Shim et al. 2008), and modulation of efficacy and plasticity of synapses (Soulé et al. 2006; Lu et al. 2014; Leal et al. 2015). Frecska et al. (2013) have further suggested that DMT may be protective during cardiac arrest, beneficial during perinatal development, immunoregulation, and may aid in reducing cancer progression. It has also been proposed (Frecska et al. 2013) that DMT is part of a biological recuperative-defense mechanism serving a universal regulatory role in oxidative stress-induced changes at the endoplasmic reticulum–mitochondrial interface, all suggesting that understanding DMT pharmacology may have vast ramifications and applications in medicine and therapeutics. Indeed, such physiological functions could provide needed physiological adaptations in cases of general hypoxia and in local anoxia (myocardial infarct or stroke). Morales-Garcia et al. (2020) have reported that the N,N-dimethyltryptamine in ayahuasca regulates adult neurogenesis in vitro and in vivo, implicating a possible pharmaceutical target for treatment of stroke, dementia, Alzheimer's, and other forms of brain cell disease, damage, and injury. There will, no doubt, be further findings of significance in this field.

Endogenous DMT and its possible relationship to recent research findings from in vitro and in vivo studies

Since the proposal that the symptomology for the syndrome known as schizophrenia could be ascribed to the formation of endogenous hallucinogens related to mescaline, and then extended to the possible formation of psychedelic N,N-dimethyltryptamines (DMTs; Benington et al. 1965), the transmethylation hypothesis (Osmond and Smythies 1952) has been thoroughly debated and researched. Though its basic premise remains unproven, research on this hypothesis did, in part, lead to the discovery of an enzyme that methylates tryptamines, an indole-N-methyltransferase (INMT). This enzyme biosynthesizes known hallucinogenic DMTs from tryptamine (TA) or serotonin (5-HT) and S-adenosylmethionine (SAM), acting as the methyl donor, forming N,N-dimethyltryptamine (DMT, **1**), 5-hydroxy-DMT (bufotenine; 5HDMT, **2**), and/or 5-methoxy-DMT (5MeODMT, **3**). INMT has been detected and characterized in numerous tissues in the mammalian periphery

(Rosengarten and Friedhoff 1976; Barker et al. 1981; Thompson and Weinshilboum 1998; Thompson et al. 1999; Carbonaro and Gatch 2016; Barker 2018a; Rodrigues et al., 2019) and, as of late, in the brain and central nervous system tissues of rat (Dean et al. 2019), primate (Cozzi et al. 2011), and human species (Dean 2018; Dean et al. 2019).

As part of the early research of the transmethylation hypothesis, and following the discovery of DMT in human cerebrospinal fluid, Christian et al. (1976) published evidence that DMT possessed all the necessary properties to be considered a neurotransmitter in mammalian brain. Additional research on DMT since that time has added proof to this hypothesis (Christian et al. 1977; Barker et al. 1981; Berge et al. 1983; Whipple et al. 1983; Barker et al. 1984; Nagai et al. 2007; Cozzi et al. 2009; Frecska et al. 2013; Barker et al., 2013; Blough et al. 2014; Carbonaro and Gatch 2016; Barker 2018a; Dean, 2018, Dean et al., 2019; Rodrigues et al., 2019). There have also been some 70 published studies conducted that reported the detection and/or quantitation of DMT in human blood and urine (Barker et al. 2012). However, only a handful of studies have attempted to detect endogenous DMT in human brain, and that in an indirect manner through evaluation of cerebrospinal fluid (Christian et al. 1975; Corbett et al. 1978; Smythies et al. 1979). There have been a few attempts at detecting and/or quantitating DMT using whole brain from rodents (Beaton and Morris 1984; Karkkainen et al. 2005) with widely differing results (Beaton and Morris 1984; pooled whole brain (2 g) of 17-day-old rats at an average of 17.5 ± 4.18 ng/g and in older rats in the range of undetected to 1–2 ng/g or as high as 11.0 ng/g; Karkkainen et al. 2005; 10 and 15 pg/g). However, it has long been thought that sequestered DMT is lost in the processing of the tissues from whole-brain homogenates (Barker, unpublished observations; Karkkainen et al. 2005; Burchett and Hicks, 2006) and may explain the differences and difficulties so far observed. Nonetheless, these results have led to speculation that DMT is only a "trace" amine in the brain (Nichols, 2018a, 2018b). But is that true?

In 2013, Barker et al. (2013; Barker 2018a, 2018b) reported the presence of DMT in pineal gland/cerebral/visual cortex micro-dialysis perfusates of live, freely moving rats but did not provide quantitative results. In a follow-on study, however, Dean et al. (2019) reported that normal rat brain extracellular micro-dialysis perfusates from the cerebral cortex contain DMT at concentrations ranging from 0.05–1.8 nM, with an average of 0.56 nM. It was also determined that removal of the pineal gland (pinealectomy) gave concentrations of DMT ranging from 0.25–2.2 nM with an average of 1.02 nM. Although appearing higher, due to variability and small sample size, there was no statistical significance between these levels with or without the presence of the pineal gland, suggesting DMT was either not formed in

the pineal or that there was compensatory total biosynthesis producing a higher average level of DMT arising from other perfused brain areas (Dean et al., 2019).

DMT was also monitored in rat brain micro-dialysis perfusates from the cerebral cortex several hours prior to and then during induction of cardiac arrest. It was observed that DMT concentrations following cardiac arrest increased significantly over baseline in both brains of the pineal-intact group ($p = 0.00027$) and the pinealectomized group ($p = 0.034$). Under similar conditions, following induction of cardiac arrest, a dramatic elevation of other neurotransmitters has also been observed (Borjigin et al. 2013; Li et al., 2015) in pineal-intact animals. Since several neurotransmitter systems are also elevated at the time of death, the precise role of DMT in this event is still unclear and the theories behind it, speculative (Strassman 2001; Nichols and Nichols 2020).

To probe the relative abundance of extracellular DMT to 5-HT in cortical dialysates from the same rats, Dean et al. (2019) quantified brain 5-HT and DMT in the animals without the pineal gland. Mean extracellular concentration of 5-HT was 2.10 ± 1.67 nM and basal DMT levels were 1.02 ± 0.63 nM from the same cortical dialysate samples (Dean et al. 2019). These findings for DMT are well within the concentration range accepted for 5-HT (mean of 0.87 nM, range 0.12–3.4 nM), norepinephrine (mean 1.77 nM, range 0.19–4.4 nM), and dopamine (mean 1.5 nM, range 0.07–4.9 nM) (Fitzgerald 2009). This places the "normal" concentration of DMT in the rat brain at the same range as the other canonical neurotransmitters.

A further finding by Dean et al. (2019) was that the enzymes necessary for the biosynthesis of DMT from tryptamine, formed by aromatic amino acid decarboxylase (AADC) metabolism of tryptophan to tryptamine, and indole-N-methyltransferase (INMT) were co-localized in the brain, in specific brain areas, in both rat and human brain tissue slices. INMT mRNA expression was defined in human cerebral cortex, choroid plexus, and pineal tissues, suggesting that such DMT biosynthesis may similarly occur in the human brain. The punctate and robust co-localized levels of INMT and AADC in pineal suggest that DMT is indeed capable of being synthesized in this gland and that its removal may induce compensatory homeostatic biosynthesis from other brain areas in response, such as from the cerebral cortex or choroid plexus.

These data and the previously cited studies regarding DMT's characterization as a neurotransmitter show that the biosynthesis and measured levels of DMT in rat brain are significant and, as with any transmitter substance, will be further concentrated into vesicles and released at the synaptic cleft, along with possible mechanisms for its reuptake, which would permit elevated concentrations of DMT to exist in specific cells/brain areas. These concentrations may be sufficient, under altered physiological conditions, to elicit its known pharmacological actions as a psychedelic but could

certainly be present at concentrations necessary to carry out what may be its homeostatic effects as a putative neurotransmitter, part of its apparent non-hallucinogenic pharmacology. As shown by Dean et al. (2019), it may also be the case that brain DMT biosynthesis is inducible in response to specific physiological effects, causing an increase in concentration in specific cell types and areas in response. Finding rat brain concentrations of DMT comparable to those of the canonical neurotransmitters and the significant increase of DMT concentrations in rat brain following induced cardiac arrest (Dean et al. 2019), all provide additional evidence for DMT's possible role and function as a neuroregulatory/neurotransmitter substance, as do many recent studies that have examined DMT's non-hallucinogenic, non-5-HT (5-hydroxytryptamine) receptor pharmacology.

The formation of an endogenous compound with psychedelic potential such as DMT in brain tissues and its subsequent characterization as a neurotransmitter have always been of great interest, if not controversy, especially given the fact that the mechanisms of action for administered psychedelics, which are best known for their production of profound hallucinatory experiences, are not fully understood (Swanson 2018). In this regard, there is even less known about the possible roles and functions of endogenous DMT in brain tissues. Certainly, its primary homeostatic role and function does not involve routine creation of the profound psychedelic phenomena that occur from its exogenous administration. Concern over this lack of knowledge has been made even more relevant and acute by our not knowing what role(s) or regulatory functions DMT may possibly be playing, not only in normal brain function, but also in the results being observed in the burgeoning field of psychedelic therapeutics and psychedelic research. There has yet to be any study examining the possibility that the positive findings thus far obtained from psychedelic administration therapy are, in part, acting on, by enhancing or otherwise altering, the same pathways involved for the endogenous hallucinogen's normal functions. Indeed, it was proposed some 40 years ago (Barker et al., 1981) that there exists an endogenous hallucinogen neuronal system that, itself, may be acted upon by certain common therapeutic pharmaceuticals but also by the various classes of the known hallucinogens, acting as agonists, antagonists, or otherwise modulating this system and its normal function. Given the effects seen from DMT administrations and from in vitro DMT research, consideration of such a possibility is reasonable.

Conclusions

Psychedelic therapy offers new ways for treating depression, substance abuse, post-traumatic stress disorders (PTSD) and addiction, and other maladies currently being

or not yet examined. It is obvious that a new understanding of the biochemistry, of the causes and results from any successful therapy, is needed. Several placebo-controlled trials for psychedelic-assisted therapies have already been published and support the efficacy of psychedelic therapy across at least five mental health conditions: post-traumatic stress disorder (PTSD), anxiety/depression associated with a life-threatening illness, unipolar depression, addiction and social anxiety among autistic adults (dos Santos et al. 2018; Muttoni et al. 2019; Luoma et al. 2020; Inserra et al., 2020; Aday et al. 2021), and we can expect this list to continue to expand. There is no doubt that the scientific study of psychedelics as therapeutics has entered a new age. This explosion in interest is also reflected in potential positive changes in the laws regarding psychedelics' access and the public perception of psychedelics, as well as the number of prestigious Universities opening well-funded psychedelic research units throughout the world. And there are, without doubt, many more yet to come as "Big Pharma" eventually lurches into the field.

In the pursuit of the use of DMT in psychedelic research and therapy, several various forms and routes of administration are being used. While all may eventually have their place and usefulness, it will be difficult to separate and compare the results from ayahuasca studies or from pharmahuasca studies and results from routes such as inhalation sufflation from IV or IM administrations. Clearly, the complications created from concomitant use of a MAOI that also effects many other neurotransmitters and those observed from other routes of administration are somewhat insurmountable. Similarly, the methods of inhalation, sufflation, or snuffing will have to be made more tolerable before they could be accepted as routine therapeutic techniques. While IV, infusion, or IM administrations can readily be performed, it involves another layer of medical intervention that is also not always ideal. As suggested, a modified DMT, such as a deuterhuasca, that may be orally active and can be taken as a pill, obviates many of these issues and could also be used for other routes of administration as well. For one, it may allow a more useful comparison of study results between researchers and a better ability to apply in vitro results to therapeutic measures.

While psychedelic research and therapeutics are showing highly desirable results, we still lack the molecular and foundational knowledge to understand how this is being accomplished. During this developmental stage of the science, I am of the opinion that gaining an understanding of the brain distribution and role(s) of DMT at "normal," endogenous concentrations needs to be better understood so as to prescribe and apply the use of psychedelic therapeutics more appropriately and, perhaps, effectively. Given that DMT is an endogenous compound, a potential neurotransmitter with significant sigma-1, 5-HT,

and other receptor interactions, we must be curious enough to consider if the overall pharmacology thus far observed for DMT, and perhaps other psychedelics, is indicative of what constitutes the normal homeostatic functions for DMT. The effects observed and the biochemical and physiological parameters measured in any of these studies, whether high or low or micro-dose, should be viewed as an opportunity to add needed insight into the role and function of endogenous DMT and even of its possible involvement in the mode of action of the hallucinogens in general. Of all of the known psychedelics currently being tested for therapeutic effect DMT and 5MeODMT are the only ones known to naturally occur in humans.

Indeed, if we consider the totality of DMT's pharmacology, we see, perhaps, the brain's use of DMT as its physiological and biochemical response for neuroprotection (Frecska et al., 2013). More recent in vitro and in vivo data are suggesting that endogenous DMT may also play an even more substantive role in the development, growth, maintenance, and repair of the brain, and similar data are being seen for many of the other known psychedelics.

Psychedelics could become "common" therapeutic medications, administered several times daily at home (Noorani 2020; dos Santos et al. 2021). While there are many possible routes of administration and compounds to be examined, there remains much further research to be conducted into low-dose treatments and more studies to examine the safety and efficacy of their use (Strassman 1984; Tittarelli et al. 2015; Gardner et al., 2019). Regardless of the dose regimen selected, until we better understand the overall mechanisms involved in what is being discovered, we may well miss several therapeutic opportunities. Evidence suggests that treatments at lower doses, not producing hallucinations, and higher doses that do, may well be one of the many possible futures of psychedelic therapeutic research (Yaden and Griffiths 2021; Olson 2021). The same is true of chemically modified structures and the intelligent design modifications of known hallucinogens (Dunlap et al. 2020) that enhance certain aspects of psychedelic pharmacology, or even eliminate parts of it.

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