DMT: Exploring the Role and Function of Endogenous Hallucinogens in the Brain

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Abstract

Dimethyltryptamine (DMT) is a potent psychoactive substance that has been used for centuries by indigenous cultures for spiritual and medicinal purposes. Recently, DMT has gained popularity among individuals seeking a transformative experience or as a potential treatment for mental health conditions. This review article aims to provide a comprehensive analysis of the effects of DMT on the mind, including its mechanisms of action, potential therapeutic applications, and associated risks. The review also highlights the need for further research to fully understand the effects of DMT on the mind.

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***Keywords**: DMT, Neuroprotective, Tryptamine, Hallucinogen*

Introduction

DMT is a highly potent psychedelic compound that has been used for centuries in traditional shamanic practices, particularly in the Amazon region of South America. It is known for its ability to induce intense, vivid, and often mystical experiences in those who consume it. However, the discovery that DMT is also produced naturally within the human body has led researchers to question its possible role and function within the brain (Nichols, 2016).

DMT's Chemical Structure and Properties

DMT is a member of the tryptamine family of compounds, which also includes serotonin, melatonin, and other neurotransmitters. Its chemical structure consists of an indole ring, which is a common feature among tryptamines. DMT has a relatively simple structure, with two methyl groups attached to the nitrogen atom of the indole ring (N, N-dimethyltryptamine). This simple structure is thought to contribute to its potent psychedelic

effects, as it allows for a high degree of flexibility in binding to various receptor sites within the brain (Keiser et al., 2009).

Historical Background and Discovery

Canadian chemist Richard Manske synthesized DMT for the first time in 1931. However, it was not until 1956 that Hungarian chemist and psychiatrist Stephen Szara extracted DMT from the Mimosa hostilis plant and administered it to himself, discovering its hallucinogenic properties (Szara, 1956). This significant development established a connection between the contemporary scientific knowledge of DMT's chemical structure and its historical utilization as a sacramental substance in religious and cultural rituals, found in various DMT-containing plants (McKenna et al., 1998).

DMT Biosynthesis and Metabolism

One of the most intriguing aspects of DMT is its endogenous production within the human body. Studies have demonstrated that DMT can be produced through the synthesis of the amino acid tryptophan, which is abundantly present in dietary sourcesThis conversion occurs through two main enzymatic steps: the decarboxylation of tryptophan to form tryptamine, and the subsequent N, N-dimethylation of tryptamine to produce DMT (Barker et al., 2012).

Enzymes Involved in DMT Synthesis

The synthesis of DMT involves the participation of two crucial enzymes: aromatic L-amino acid decarboxylase (AADC) and indolethylamine-N-methyltransferase (INMT). AADC is responsible for converting tryptophan into tryptamine, whereas INMT facilitates the N, N-dimethylation of tryptamine, resulting in the formation of DMT. These enzymes are extensively present in the body, including the brain and various peripheral tissues (Saavedra et al., 1973; Cozzi et al., 2011).

DMT Metabolism

(In the body, DMT undergoes rapid metabolism, primarily facilitated by the enzyme monoamine oxidase A (MAO-A). This enzymatic process involves the breakdown of DMT into its primary metabolite, indoleacetic acid (IAA), which is subsequently eliminated from the body. Other minor metabolites of DMT include DMT-N-oxide (DMT-NO) and N-methyltryptamine (NMT), both of which are also substrates for MAO-A (Barker et al., 1980).

Detection in Biological Fluids and Tissues

DMT has been detected in various biological fluids and tissues, including blood, urine, cerebrospinal fluid (CSF), and brain tissue. However, the concentrations of DMT in these samples are often extremely low, making accurate detection and quantification challenging (Barker et al., 2012).

Blood and Urine Detection

Several studies have made efforts to establish a correlation between the presence or concentration of DMT in blood and urine samples and psychiatric diagnoses or other

physiological conditions. However, these studies have yielded inconsistent and often conflicting results, with no clear or repeatable correlations observed (Barker et al., 2012).

Crebrospinal Fluid (CSF) Detection

DMT has been identified in human cerebrospinal fluid (CSF) as well, although only a limited number of studies have endeavored to quantify its levels or establish a correlation between its presence and specific physiological or pathological conditions (Christian et al., 1975).

Brain Tissue Detection

Despite the difficulties involved in detecting and measuring DMT in biological fluids, a number of studies have effectively shown its existence in brain tissues, specifically within the pineal gland (Barker et al., 2013). This discovery provides support for the theory that DMT may play a role in diverse neurological processes and functions.

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Receptor Binding: 5-HT2A, TAARs, and Sigma-1 Receptors

The interaction of DMT with various receptors in the brain, such as serotonin (5-HT) receptors, trace amine associated receptors (TAAR), and sigma-1 receptors, has been demonstrated. These interactions are believed to be involved in the hallucinogenic effects of DMT, although the specific mechanisms through which DMT influences the brain are still not fully understood (Nichols, 2016).

5-HT2A Receptor Binding

The 5-HT2A receptor, belonging to the serotonin receptor family, plays a role in the mechanism of action of different hallucinogenic substances, including DMT. Research has shown that DMT binds tightly to the 5-HT2A receptor, and this interaction is believed to be accountable for a significant portion of its psychedelic effects (Keiser et al., 2009).

TAAR Receptor Binding

The trace amine-associated receptors (TAARs) represent another set of receptors that have been associated with the effects of DMT. These receptors play a role in modulating various neurotransmitter systems, such as dopamine, serotonin, and norepinephrine. Studies have indicated that DMT acts as an agonist for several subtypes of TAARs, although the exact contribution of these receptors to the effects of DMT is still not completely understood (Burchett and Hicks, 2006; Wallach, 2009).

Sigma-1 Receptor Binding

Sigma-1 receptors represent a unique class of proteins that have been associated with various neuroprotective and neuroregenerative processes. Research has demonstrated that DMT binds

moderately to sigma-1 receptors, and this interaction has been suggested to contribute to its potential neuroprotective effects (Fontanilla et al., 2009; Su et al., 2009).

DMT Administration

DMT is commonly administered through inhalation, intramuscular injection, or intravenous injection. The effects of DMT typically manifest rapidly and have a short duration, ranging from 15 minutes to an hour, depending on the administration method and dosage. Ingesting DMT orally is generally ineffective unless combined with a monoamine oxidase inhibitor (MAOI), such as in the case of the traditional Amazonian brew ayahuasca (Riba et al., 2015).

Intramuscular and Intravenous Administration

Intramuscular (IM) and intravenous (IV) administration of DMT have been shown to produce rapid and intense hallucinogenic effects, with peak blood levels and subjective experiences occurring within minutes of administration. These effects typically last for 30 to 60 minutes, depending on the dose used (Strassman et al., 1994a,b).

Oral Administration (Ayahuasca)

Oral administration of DMT, as occurs with the consumption of ayahuasca, results in a slower onset of effects and a longer duration of action. The effects of ayahuasca usually manifest around 60 minutes after ingestion, reach their peak at approximately 90 minutes, and can endure for up to 4 hours. The prolonged effects of ayahuasca are thought to be due to the presence of MAOIs in the brew, which inhibit the metabolism of DMT and allow for greater absorption into the bloodstream (Cakic et al., 2010).

Alternative Routes of Administration

In addition to the more traditional routes of administration, alternative methods such as intranasal and rectal administration of DMT have been explored. However, these methods have generally been found to be less effective in producing hallucinogenic effects (Turner and Merlis, 1959; De Smet, 1983).

Imaging Studies

Neuroimaging studies have provided valuable insight into the potential mechanisms by which DMT and other hallucinogenic compounds exert their effects on the brain. Despite the limited number of studies using DMT alone, research with other hallucinogens, such as LSD and psilocybin, has revealed changes in brain activity and connectivity that may be relevant to DMT's effects (dos Santos et al., 2016a,b).

fMRI (Functional Magnetic Resonance Imaging)

fMRI (Functional magnetic resonance imaging) research has indicated that hallucinogens, including DMT, have the ability to modify brain activity in different regions, such as the fronto-temporo-parieto-occipital cortex.

These changes in brain activity are thought to be responsible for the alterations in perception and consciousness experienced by users of these compounds (dos Santos et al., 2016b).

Structural Brain Changes

Long-term use of hallucinogenic compounds has also been associated with structural changes in the brain. For example, studies of long-term ayahuasca users have reported changes in the thickness of certain brain regions, as well as alterations in receptor binding patterns (dos Santos et al., 2016a).

Role of DMT in Signalling and Modulating Neuronal Activity

Given the endogenous production of DMT within the human body and its interactions with various receptor systems, researchers have postulated that DMT may serve as a neurotransmitter, neurohormone, or neuroregulatory substance. While the exact role and function of DMT in these capacities remain unclear, several lines of evidence suggest that it may be involved in various physiological and pathological processes within the brain.

DMT's Role in Neuroprotection and Neuroregeneration

Recent studies have highlighted the potential neuroprotective and neuroregenerative properties of DMT, particularly in relation to its interactions with sigma-1 receptors. These receptors have been associated with a range of neurobiological processes, such as cell survival, proliferation, and synaptic plasticity (Frecska et al., 2013).

DMT's Involvement in Mental Disorders

The potential involvement of endogenous DMT in the emergence and expression of different mental disorders has been investigated. For instance, the suggested association between elevated DMT levels in specific brain regions and the development of psychosis and other psychiatric disorders has been explored (Grammenos and Barker, 2015).

Therapeutic Potential of DMT

As our understanding of DMT's role and function in the brain grows, so does the potential for its therapeutic application. While the existing evidence supporting the use of DMT as a therapeutic agent is still limited, various areas of interest have emerged, including its potential for treating mental disorders, addressing substance abuse, and addressing neurodegenerative conditions.

DMT as Antipsychotic Substance

DMT has emerged as a potential therapeutic option for addressing different mental disorders, such as depression, anxiety, and post-traumatic stress disorder (PTSD). However, most research in this field has primarily concentrated on other hallucinogens like LSD and psilocybin, with limited available data on the specific effects of DMT alone (Bogenschutz and Pommy, 2012).

DMT – Use in De-addiction

Multiple studies have indicated the potential effectiveness of DMT and other hallucinogens in addressing substance abuse disorders, such as alcohol and tobacco addiction. However, similar to the treatment of mental disorders, the bulk of research in this domain has primarily

centered on other hallucinogenic substances, resulting in limited exploration of the potential therapeutic effects of DMT (Mangini, 1998; Krebs and Johansen, 2012).

DMT in the Treatment of Neurodegenerative Conditions

Due to its potential neuroprotective and neuroregenerative properties, DMT has been suggested as a potential treatment for neurodegenerative conditions like Alzheimer's disease and Parkinson's disease. Initial studies in this field have demonstrated promising results; however, further research is necessary to fully comprehend the therapeutic benefits of DMT in these specific conditions (Frecska et al., 2013).

Future Directions for DMT Research

As our understanding of DMT's role and function within the brain continues to grow, so too does the potential for new and innovative research in this area. Several key areas of future investigation have been identified, including:

- A more comprehensive investigation into the biosynthesis and metabolism of DMT in both the brain and peripheral tissues.
- The development of novel methods for detecting and quantifying DMT in biological fluids and tissues
- A comprehensive exploration of DMT's receptor binding profiles and mechanisms of action
- The use of neuroimaging techniques to investigate DMT's effects on brain activity and connectivity
- The exploration of DMT's potential therapeutic applications in the treatment of mental disorders, substance abuse, and neurodegenerative conditions

By pursuing these avenues of research, we may ultimately gain a more complete understanding of DMT's role and function within the brain, as well as its potential therapeutic applications.

Concluding Remarks. In conclusion, the study of endogenous DMT and its potential role and function within the brain represents an exciting and largely unexplored area of research. Although many questions remain unanswered, the available evidence suggests that DMT may serve as a neurotransmitter, neurohormone, or neuroregulatory substance, with potential implications for our understanding of consciousness, perception, and various mental disorders. As research in this area continues to advance, we may ultimately unlock the secrets of this enigmatic compound and harness its potential therapeutic benefits. The discovery of DMT's endogenous production within the human body has opened up new possibilities and raised intriguing questions about its role and function in the brain.

The chemical structure of DMT, with its simple yet flexible configuration, contributes to its potent psychedelic effects. Historical and cultural use of DMT-containing plants in religious and shamanic rituals further emphasizes its significance and potential relevance to human experiences.

The biosynthesis and metabolism of DMT involve specific enzymes, such as AADC and INMT, which are present in various tissues, including the brain. While detecting and quantifying DMT in biological fluids and tissues remains challenging, its presence has been confirmed, particularly within the pineal gland.

DMT's interactions with receptors, such as 5-HT2A, TAARs, and sigma-1 receptors, shed light on its mechanisms of action and its ability to induce hallucinogenic effects. Neuroimaging studies have provided valuable insights into the changes in brain activity and connectivity associated with DMT and other hallucinogenic compounds, offering potential explanations for altered perception and consciousness.

While the exact role and function of DMT in the brain are still not fully understood, research suggests its involvement in neuroprotection, neuroregeneration, and mental disorders. The neuroprotective properties of DMT, especially through its interaction with sigma-1 receptors, show promise in addressing various neurological conditions.

The therapeutic potential of DMT is an area of increasing interest. Although research has primarily focused on other hallucinogens like LSD and psilocybin, DMT has shown potential in the treatment of mental disorders, substance abuse, and neurodegenerative conditions. However, further investigation is needed to fully explore its therapeutic benefits and establish its safety and efficacy.

Looking ahead, future research directions include a comprehensive exploration of DMT's biosynthesis and metabolism, the development of improved detection methods, a deeper understanding of its receptor binding profiles, and further investigation of its therapeutic applications. Additionally, neuroimaging techniques can provide valuable insights into DMT's effects on brain activity and connectivity.

In conclusion, the study of endogenous DMT and its potential role and function within the brain represents a captivating and largely uncharted area of research. With continued exploration, we may uncover the mysteries surrounding this enigmatic compound and harness its full potential for understanding consciousness, perception, and the treatment of various mental and neurological conditions.

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Conflict of interest

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