

Chapter 5

N,N-DIMETHYLTRYPTAMINE

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INTRODUCTION

A mystery that has been going on for centuries. The N,N-dimethyltryptamine (DMT) molecule, which is found in every living thing, especially in humans at the time of birth and death, and which some claim to open the door of the parallel universes, is a very harmful hallucinogen for some. This substance, which was used only by shamans who lived in different geographies in their time, and started to be in trance, spread to the whole world and started to attract the attention of artists and scientists. So what is this DMT?

Hallucinogens are described as psychoactive substances that cause changes in perception and mood without being addictive. Psychoactive substances have amazed and impressed people with their effects since their discovery. However, although they have existed in human pharmacology for thousands of years and played profound roles in the development of science, psychology and culture, the biochemical mechanisms of how hallucinogens change perception and consciousness remain unclear.^(1,2)

DMT (Figure 1) is an N-methylated indolamine derivative, which is a serotonergic hallucinogen tryptamine alkaloid found in various plants (especially *Prestonia amazonica* belonging to the *Apocynaceae* family), as well as in the mammalian brain,

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Although low levels of DMT can be used as an endogenous anxiolytic, high, “unnatural” levels of DMT (such as those associated with psychedelic/hallucinogenic activity) are reported to cause excessive changes in consciousness⁽¹¹⁾, but there is a need for a further investigation into its function and interaction with other neurotransmitter systems. Given the hypotheses put forward about DMT, we can state that it deserves a special situation for further research. Experimental studies with DMT are not sufficient, and it will take a long time and hard work to be able to state that DMT has clinically appropriate uses.

We think that increasing the frequency of sampling, focusing on sample collection storage conditions or using devices with high sensitivity and specificity such as Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) can be guiding in reaching clearer and more accurate data about DMT.

REFERENCES

1. De Rios MD, Grob CS, Baker JR. Hallucinogens and redemption. *Journal of psychoactive drugs*. 2002;34(3):239-48.
2. Estrella-Parra EA, Almanza-Pérez JC, Alarcón-Aguilar FJ. Ayahuasca: Uses, Phytochemical and Biological Activities. 2019;9(4):251-65.
3. Barker SA, McIlhenny EH, Strassman R. Critical review of reports of endogenous psychedelic N,N-dimethyltryptamines in humans: 1955–2010. *Drug Test. Anal.* 2012;4:617-35.
4. Barker SA. N,N-Dimethyltryptamine (DMT), an endogenous hallucinogen: past, present, and future research to determine its role and function. *Front Neurosci.* 2018; 6;12:536.
5. Dos Santos RG, Balthazar FM, Bouso JC, et al. The current state of research on ayahuasca: a systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging. *J. Psychopharmacol.* 2016; 30:1230-47.
6. Strassman, RJ. A doctor's revolutionary research into the biology of near-death and mystical experiences. Park Street Press; Rochester: 2001. DMT: the spirit molecule.
7. Carbonaro TM, Gatch MB. Neuropharmacology of N,N-dimethyltryptamine. *Brain Res. Bull.* 2016;126:74-88.

8. Strassman RJ, Qualls CR. Dose-response study of N,N-dimethyltryptamine in humans: I. Neuroendocrine, autonomic, and cardiovascular effects. *Arch Gen Psychiatry*. 1994; 51:85-97.
9. Servillo L, Giovane A, Balestrieri ML, et al. N-methylated tryptamine derivatives in Citrus genus plants: Identification of, N,N-trimethyltryptamine in bergamot. *J Agric Food Chem*. 2012; 60:9512-18.
10. Malcolm BJ, Lee KC. Ayahuasca: An ancient sacrament for treatment of contemporary psychiatric illness? *Ment Health Clin*. 2018;23;7(1):39-45.
11. Jacob MS, Presti DE. Endogenous psychoactive tryptamines reconsidered: an anxiolytic role for dimethyltryptamine. 2005;64(5):930-7.
12. Shen HW, Jiang XL, Yu AM. Nonlinear Pharmacokinetics of 5-Methoxy-N,N-dimethyltryptamine in Mice. *Drug Metab Dispos*. 2011 Jul;39(7):1227-34.
13. Araújo AM, Carvalho F, Bastos Mde L, et al. The hallucinogenic world of tryptamines: an updated review. *Arch Toxicol*. 2015;89:1151-73.
14. Gable RS. Risk assessment of ritual use of oral dimethyltryptamine (DMT) and harmala alkaloids. *Addiction*. 2007; 102:24-34.
15. McKenna D.J. Callaway J.C. Grob C.S. The scientific investigation of ayahuasca: a review of past and current research. *Heffter Rev. Psychedelic Res*. 1998;1:65-77.
16. Szára S. Dimethyltryptamine: its metabolism in man; the relation to its psychotic effect to the serotonin metabolism. *Experientia*. 1956;12(11):441-2.
17. Daumann J, Wagner D, Heekeren K, et al. Neuronal correlates of visual and auditory alertness in the DMT and ketamine model of psychosis. *J Psychopharmacol*. 2010;24(10):1515-24.
18. Grammenos D, Barker SA. On the transmethylation hypothesis: stress, N,N-dimethyltryptamine, and positive symptoms of psychosis. *J Neural Transm*. 2015;122:733-39.
19. Dos Santos RG, Valle M, Bouso JC, et al. Autonomic, neuroendocrine, and immunological effects of ayahuasca: a comparative study with d-amphetamine. *J Clin Psychopharmacol*. 2011; 31(6):717-26.
20. Pitó DL, Siéssere S, dos Santos RG, et al. Ayahuasca alters structural parameters of the rat aorta. *J Cardiovasc Pharmacol*. 2015; 66:58-62.
21. McKenna DJ. Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. *Pharmacol Ther* 2004; 102:111-29.
22. Loizaga-Velder A and Verres R. Therapeutic effects of ritual ayahuasca use in the treatment of substance dependence-qualitative results. *J Psychoactive Drugs*.2012;46: 63-72.
23. Callaway JC, Raymon LP, Hearn WL. Quantitation of N,N-dimethyltryptamine and harmala alkaloids in human plasma after oral dosing with ayahuasca. *J Anal Toxicol*. 1996;20(6):492-7.
24. Nichols, D. E. N,N-dimethyltryptamine and the pineal gland: separating fact from myth. *Journal of Psychopharmacology*. 2017;32(1):30-6.

25. Carbonaro TM, Gatch MB. Neuropharmacology of N,N-Dimethyltryptamine. *Brain Res Bull.* 2016;126(Pt 1):74-88.
26. Mavlyutov TA, Epstein ML, Liu P, et al. Development of the sigma-1 receptor in C-terminals of motoneurons and colocalization with the N, N'-dimethyltryptamine forming enzyme, indole-N-methyl transferase. *Neuroscience.* 2012; 206:60-8.
27. Karkkainen J, Forsstrom T, Tornaeus J, et al. Potentially hallucinogenic 5-hydroxytryptamine receptor ligands bufotenine and dimethyltryptamine in blood and tissues. *Scand J Clin Lab Invest.* 2005; 65:189-99.
28. Thompson MA, Moon E, Kim UJ, et al. Human indolethylamine N-methyltransferase: cDNA cloning and expression, gene cloning, and chromosomal localization. *Genomics.* 1999; 61:285-97.
29. McIlhenny EH, Riba J, Barbanoj MJ, et al. Methodology for determining major constituents of ayahuasca and their metabolites in blood. *Biomed. Chromatogr.* 2012;26:301-13.
30. Tourino, MC, de Oliveira, EM, Belle LP, et al. Tryptamine and dimethyltryptamine inhibit indoleamine 2,3 dioxygenase and increase the tumor-reactive effect of peripheral blood mononuclear cells. *Cell Biochem. Funct.* 2013;31:361-64.
31. Strassman RJ, Qualls CR, Berg LM. Differential tolerance to biological and subjective effects of four closely spaced doses of N,N-dimethyltryptamine in humans. *Biol Psychiatry.* 1996; 39(9):784-95.
32. Gardner D, Riet-Correa F, Lemos D, et al. Teratogenic effects of *Mimosa tenuiflora* in a rat model and possible role of N-methyl- and N,N-dimethyltryptamine. *J Agric Food Chem.* 2014;62(30):7398-401.
33. Oon MC, Murray RM, Rodnight R, et al. *Psychopharmacology.* 1977; 547:171.
34. Dean JG, Liu T, Huff S, et al. Biosynthesis and extracellular concentrations of N,N-dimethyltryptamine (DMT) in mammalian brain. *Sci Rep.* 2019;27;9(1):9333.
35. Keiser MJ, Setola V, Irwin JJ, et al. Predicting new molecular targets for known drugs. *Nature.* 2009;462:175-81.
36. Brown K, Tracy D. Lithium: the pharmacodynamic actions of the amazing ion. *Ther Adv Psychopharmacol.* 2013;3:163-76.
37. Nichols DE. Psychedelics. *Pharmacolog. Rev.* 2016;68:264-355.
38. West WB, Lou A, Pechersky K, et al. Antagonism of a PCP drug discrimination by hallucinogens and related drugs. *Neuropsychopharmacology.* 2000;22:618-25.
39. Cozzi NV, Gopalakrishnan A, Anderson LL, et al. Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. *J Neural Transm.* 2009;116:1591-99.

40. Griesmaier E, Posod A, Gross M, et al. Neuroprotective effects of the sigma-1 receptor ligand PRE-084 against excitotoxic perinatal brain injury in newborn mice. *Exp. Neurol.* 2012;237:388-95.
41. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER mitochondrion interface regulate Ca²⁺ Signaling and Cell Survival. 2007;131:596-610.
42. Tsai, SY, Hayashi T, Mori, et al. Sigma-1 receptor chaperones and diseases. *Cent. Nerv. Syst. Agents Med. Chem.* 2009;9:184-9.
43. Szabo A, Kovacs A, Riba J, et al. The endogenous hallucinogen and trace amine N, N-dimethyltryptamine (DMT) displays potent protective effects against hypoxia via sigma-1 receptor activation in human primary iPSC-derived cortical neurons and microglia-like immune cells. *Front Neurosci.* 2016;10:423.
44. Murray RM, Oon MC, Rodnight R, et al. Increased excretion of dimethyltryptamine and certain features of psychosis: a possible association. *Arch Gen Psychiatry.* 1979;36(6):644-9.
45. Ciprian-Ollivier J, Cetkovich-Bakmas MG. Altered consciousness states and endogenous psychoses: a common molecular pathway? *Schizophrenia Research.* 1997;28:257-65.
46. Gekker G, Hu S, Sheng WS, et al. Cocaine-induced HIV-1 expression in microglia involves sigma-1 receptors and transforming growth factor-beta1. *Int Immunopharmacol.* 2006; 6:1029-33.
47. Szabo A, Osman RM, Bacskai I, et al. Temporally designed treatment of melanoma cells by ATRA and polyI:C results in enhanced chemokine and IFN β secretion controlled differently by TLR3 and MDA5. *Melanoma Res.* 2012; 22:351-61.