Chapter 5

N,N-DIMETHYLTRYPTAMINE

Kamile YUCEL[1]

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,

[1] Assistant Professor, KTO Karatay University, kamile_yucel@hotmail.com

blood and urine.[3,4] The secretion of the DMT molecule is out of our control. The discovery of endogenous hallucinogen DMT is considered to be useful in understanding perception and consciousness, as was the case for endogenous opioids. Recent research has resulted in this compound gaining more attention as a neuro-regulating agent.[3-5]

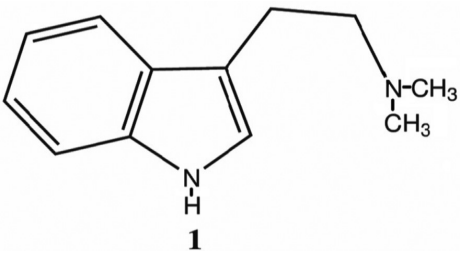

Figure 1: Structure of DMT[4]

In the late 1990s, Rich Strassman published his research on the effects of hallucinogens on people taking DMT in a book. Strassman deduced that DMT was a potent instrument for self-discovery and self-understanding, which could help attract interest in its recreational use, and accordingly, in recent years, there has been an increase in the recreational use of DMT (in general terms, recreation means 'revitalization and refreshment of human life').[6]

DMT is a hallucinogen belonging to the tryptamine family and the important feature that can make DMT special is that it is very compatible with some of our basic hormones such as serotonin and melatonin in terms of chemical structure. It is also referred to as 'the spirit molecule' because it provides an intense imaginative experience, and when taken orally, causes short episodic visual hallucinations.[6-8] In South America, DMT is also among the psychoactive substances in shamanistic compounds that have

been used for a long time here it is common to use DMT as part of shamanic rituals.[9-10] Due to the lack of information about its biological importance and the availability of a high amount of data on its hallucinogenic properties, DMT has been accepted as a neurotoxin. It has been claimed that DMT has no medical use, and thus it has been classified as a prohibited substance by the Controlled Substances Act of the United States. Although DMT does not cause addiction and is not toxic, it is classified as a dangerous drug based on sociological and political reasons.[11,12]

HISTORY OF DMT

Since prehistoric times, naturally occurring hallucinogens have attracted the attention of people due to their psychotropic properties.[4,13] DMT was first synthesized in 1931 by a Canadian chemist, Richard Manske, but at that time could not be evaluated for its pharmacological effects in humans.[4] Later, DMT was found in the content of ayahuasca, a traditional brew used in shamanic rituals by the indigenous peoples of South America.[14]

The hallucinogenic properties of DMT were demonstrated by Stephen Szara (1956), who administered the Mimosa hostilis extract intramuscularly, and as a result reported visual hallucinations, spatial distortions, speech disorders, and euphoria. This series of events have formed the link between modern science and the use of many plants containing DMT as part of cultural and religious rituals and provided information on the chemical structure of DMT and its effects on mental state.[15,16]

The demonstration of the hallogenogenic effects of DMT and its endogenous production even led to the idea that DMT might play a role in the etiology of schizophrenia. Different studies conducted for this purpose showed that DMT metabolites were increased in urine, and in particular revealed its association with clinical deterioration.[17,18]

PRESENCE OF DMT IN PLANTS

Besides being produced synthetically, it can be obtained from many plants. DMT is seen in many plants (*Phalaris arundinacea, Phalaris aquatic*, *Mimosa hostilis* and *Phalaris tuberosa*), containing *Psychotria viridis* (*P. viridis*), a plant used to make holy hallucinogenic teas (e.g., ayahuasca, hoasca). The term ayahuasca (aya = soul, ancestor and waska = vine), also known as the 'vine of the soul', originates from the Quechua culture in South America. The pharmacological activity of ayahuasca is unique in that it depends on the synergistic interaction between active alkaloids in plants.[19,20] Ayahuasca is tea prepared by mixing the leaves of the *P. viridis* plant containing DMT and the extract of *Banisteriopsis caapi* (*B. Caapi*), a large woody plant containing β-carboline, which is a powerful monoamine oxidase-A (MAO-A) inhibitor. This effect prevents the peripheral destruction of DMT, activates orally and ensures full form access to the area in the central nervous system. This interaction forms the basis of the psychotropic effect of ayahuasca.[19,21] Loizaga-Velder mentioned that ayahuasca was useful as a therapeutic tool because it acted as a catalyst that could make psychotherapeutic processes more effective in a shorter time, facilitating the interconnection between body-oriented, psychological and mental processes in humans.[2,22]

Ayahuasca has held a respectable position over a thousand years in the medical and religious pharmacology of some cultures and is the most common tea for use in cultural applications, containing a large amount of DMT.[23] Ayahuasca, which has some experimentally and clinically validated beneficial effects, has also been used by the natural healers of the Orinoco and Amazon basins as a healing agent specifically to treat psychological disorders. Locals in Amazon make DMT drinkable, either by coincidence or by making a mixture, without any written chemistry knowledge. In these regions, even touristic trips are organized for ceremonies with DMT.[2,22]

DMT SYNTHESIS

There are many studies showing the biosynthesis of DMT in mammals. It was reported that DMT was discovered in human blood in 1965 and DMT was found in brain tissue in 1972. This result clearly proved that DMT is an endogenous chemical and studies show that DMT is synthesized from tryptophan (Figure 2).[4,24]

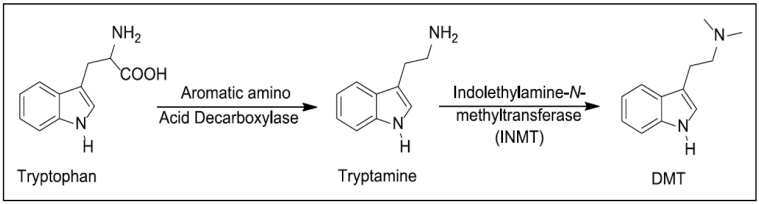

Figure 2. DMT biosynthesis from tryptophan[24]

In the biosynthesis of DMT, the tryptophan amino acid (2, Figure 3) is first converted to tryptamine (TA, 3, Figure 3) through aromatic amino acid decarboxylase (AADC). Using S-adenosyl-methionine (SAM) as a methyl source, TA is dimethylated to obtain first N-methyltryptamine (NMT; 4, Figure 3) and then DMT through indole-N-methyltransferase (INMT) (1, Figure 3). NMT can also act as a substrate for INMT-dependent DMT biosynthesis.[4,25]

DMT is synthesized in vivo in many tissues by the human INMT enzyme. The highest levels of INMT are found in the lungs, thyroid, and adrenal glands. The highest INMT activity in the human brain is seen in the uncus, medulla, amygdala, frontal cortex. It has been shown in some studies that the pineal gland also has INMT activity.[25,26] The demonstration that INMT in the rabbit lung has higher Km than in the rat brain suggests that INMT has several isoenzymes with different Km.[27,28]

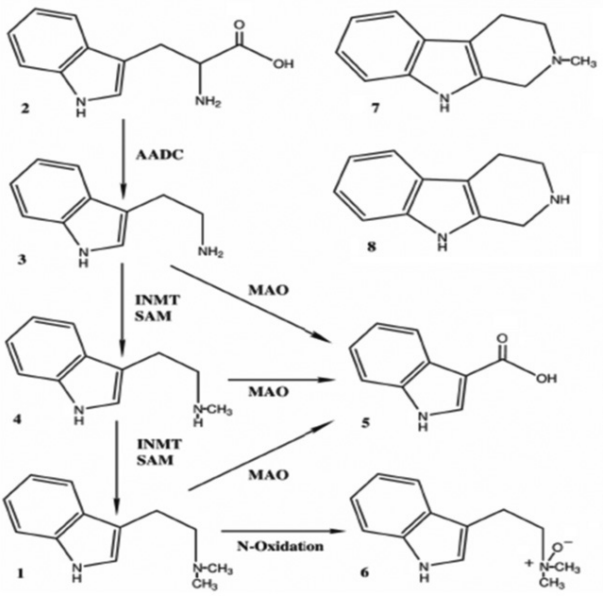

Figure 3: Biosynthesis and metabolism of DMT[4]

A study conducted in 2012, reported that INMT was located in the post-synaptic region of the C-terminal ends of rat motor neurons close to sigma 1 receptors (Sig-1R), which depend on the control of the activity of ion channels and G-protein bound receptors. Regarding the close association between INMT and Sig-1Rs it has been suggested that DMT is locally synthesized to strongly activate sigma-1 in motor neurons, and DMT is an endogenous Sig-1R regulator.[4,26]

DMT METABOLISM

Many studies have been conducted on the metabolism of DMT. Metabolism studies have shown that externally applied DMT (intravenous, intramuscular, etc.) is metabolized immediately and only a small part of it is excreted in the urine.[7,29]

The primary metabolism pathway for DMT (1, Figure 3) is the MAO-A pathway that yields indole-3-acetic acid (IAA) (5, Figure 3). Other metabolites formed include DMT-Nitric-oxide (DMT-NO) (6, Figure 3), the second most abundant metabolite, and smaller amounts of NMT (4, Figure 3), which, together with TA, constitute a substrate for MAO-A and both produce IAA. The inhibition of MAO causes an increase in DMT-NO and NMT amounts.[4,30]

Studies have reported that 0.2 mg/kg mg produces a statistically significant effect, at the same time, it is the lowest hallucinogenic dose, and that DMT must reach a plasma concentration of 12 to 90 ng/mL in order to have a hallucinogenic effect.[4,31]

The possibility of teratogenicity in the use of DMT is also among the risks. In pregnant rats, 50 times higher than the ritual dose were applied, and mortality was not observed in the study, but cleft palate and skeletal malformations was increased.[25,32]

Barker et al. (2012) examined 69 studies published between 1955 and 2010 that investigated the detection of endogenous N, N-dimethylated tryptamines (DMT, 5-hydroxy-DMT (bufotenine, HDMT), and 5-methoxy-DMT (MDMT)). Most of the studies reviewed have been made to investigate the presence and/or level of these compounds for psychiatric diagnosis. The adrenal gland and lungs are considered to have the highest amount of DMT production because the highest INMT levels are reported in these areas. However, it has also been concluded that successful measurements can be performed especially in cases where mass spectral evidence is provided, DMT and HDMT are endogenous, and generally in human body fluids.[3,4,29] Onn et al. (1977) reported that DMT and NMT concentrations in urine were stable when stored at -15 °C for up to 90 days.[33] Baker et al. reported that DMT concentrations could remain constant in the plasma for 60 days when stored at 6 °C.[3]

DMT RECEPTORS

There are still questions about the mechanism of action of hallucinogens. DMT interacts with serotonin receptors, dopamine, acetylcholine, TAAR and Sig-1R. DMT has binding affinity of 39 nM to 2.1 μM for 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6 and 5-HT7 receptors.[34,35] The 5-HT2 receptor family is mainly uses the phospholipase C second messenger system, as well as phospholipase A_2.[36,37] Phospholipase C hydrolyzes phosphatidylinositol membrane lipids that produce inositol-1,4,5-triphosphate (IP_3) and diacylglycerate. Diacetylglycerate leads to the activation of protein kinase C and increases the release of calcium from intracellular stores. Especially, protein kinase C plays a role in desensitizing 5-HT2A receptors during exposure to DMT. Phospholipase A_2 stimulation may lead to arachidonic acid formation. DMT, stimulates arachidonic acid secretion and less inositol phosphate formation through the 5-HT2A receptor. DMT, like other hallucinogens, increases the level of 5-HT, while increasing the excretion of IAA and 5-hydroxy IAA.[12,34]

An interesting approach in the past decade argues that it is important to prove the roles of serotonin and glutamate NMDA receptors in mediating the efficacy of DMT. Through its effect on NMDA receptors, DMT partially blocks the distinctive stimulating effects of phencyclidine, which causes hallucinations.[38] In addition, the activation of the Sig-1R by DMT may lead to increased activation of NMDA receptors.[39]

Amine-related receptors (TAARs) are a newly discovered class of receptors that may play a role in mediating the effects of DMT and other psychedelic drugs. However, there is insufficient information and studies on the effect of TAARs on the pharmacology of DMT.[25]

The ultimate target for the effect of DMT is the Sig-1R and this receptor has been reported to be associated with neurobiological diseases (eg addiction, depression, cancer, etc.).[40,41] Sig-1Rs are expressed in many tissues such as cerebellum, orbitofrontal cortex, nucleus accumbens. At the cellular level, Sig-1Rs are localized in the mitochondrial-associated endoplasmic reticulum membranes. They are also of great importance for neuronal morphogenesis through regulation of oxidative stress and mitochondria functions.[18,42]

Sig-1R agonists send a signal to the receptor to decompose itself, which results in the receptor acting like a chaperone to IP_3 receptors. This increases the calcium signal from endoplasmic reticulum to mitochondria, the tricarboxylic acid cycle, and increases ATP production. Sig-1R activation may also lead to the potentiation of NMDA receptors. Evidence suggests that sigma receptors regulate cell viability and proliferation.[25,40] Szabo et al. reported that DMT interacts with Sig-1Rs , greatly increasing the survival of some cell types in severe hypoxia. A reduced expression and function of the alpha subunit of hypoxia-inducible factor was also observed. DMT-related sigma 1 activation is thought to reduce hypoxia and cellular stress and increase the chances of cells survival.[43]

THERAPEUTIC USE OF DMT

The indication that DMT exists as an endogenous compound led researchers to investigate a schizophrenia model focusing on DMT in the 1960s and 1970s. Studies showed that endogenous DMT levels were increased in schizophrenic patients during psychosis and decreased with the improvement in their state, but no change was observed in DMT levels in manic depressive states. These findings have increased the interest in the transmethylation hypothesis suggesting that schizophrenia may occur due

to the production of stress-induced psychomimetic methylated derivatives of catecholamines or indole alkylamines in the brain.[44] The advocators of the transmethylation hypothesis have theoretically argued that extra methyl (CH_3) radicals are added to serotonin or tryptamine due to some congenital errors of metabolism, and thus derivatives with hallucinogenic properties may be formed.[18,45]

In their evaluation of the results obtained from various studies conducted in the 1980s, Ciprian-Ollivier and Cetkovisch-Bakmas reported an important relationship between increased urinary excretion of DMT and the severity of psychotic symptoms.[45]

Serotonin plays an important role in removing cancer cells and eliminating pathogens in the immune system. DMT may also play a role in immunoregulation through the activation of Sigma-1 and 5-HT2A receptors.[46] Through the formulation of ayahuasca, DMT was found to increase the levels of natural killer (NK) cells at concentrations as low as 1 mg/kg body weight.[19] In vitro DMT studies showed increased secretion of interferons in the NK cell and dendritic cell cultures. By increasing interferon secretion, DMT may contribute to the better elimination of malignant or infected cells.[7,47]

Result and suggestions

Although many years have passed since the synthesis of DMT has been proven, controversies and uncertainties still persist. In addition, the difficulties and obstacles in conducting research on hallucinogens also contribute to this. The substance has a high potential for abuse, its medical use is not accepted and there is a lack of safety parameters that have been accepted for its use. Although it does not have approved medical use, it can be used by researchers against certain rules in studies.

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 stuation 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 alertnee in the DMT and ketamine model of psyshosis. 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. Pitol 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 consantrations of 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 Ca^{2+} 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 IFNb secretion controlled differently by TLR3 and MDA5. Melanoma Res. 2012; 22:351-61.