All-natural 5-MeO-DMT sigma receptor 1 agonist and its therapeutic impact in mental and neurodegenerative diseases through mitochondrial activation

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Abstract: The sigma-1 receptor S1R is a chaperone that resides mainly at the mitochondrion-associated endoplasmic reticulum ER membrane MAM, it is considered a "pluripotent modulator" in living systems, plays a critical role in maintaining neuronal homeostasis and acts as a dynamic pluripotent modulator in living systems. Given its specific localization at the MAM, S1R plays a major role regulating mitochondrial function, it is a therapeutic target in mental and neurodegenerative diseases including Alzheimer's disease, Parkinson's disease. N,N Dimethyl Tryptamine DMT is the S1R endogen agonists and we review the role of all-natural 5-methoxi-N,N-dimethyltryptamine 5-MeO-DMT S1R agonist that produces high levels of ego dissolution or oceanic boundlessness higher ratings of satisfaction with life and lower ratings of depression and stress. In vitro the 5-Meo-DMT shows strong modulation of synaptic and cellular plasticity in neurons. 5-MeO-DMT neuropharmacological S1R agonist is implicated in cellular bioenergetics activation, antiapoptotic and mitochondrial regulation of epigenetic landscape in neurons. S1R has been considered as a controller of cell survival and differentiation in neurons. The pharmacological benefits of all-natural 5-MeO-DMT are currently under research. This review compendia results, highlighting the key molecular mechanisms of S1Rs on mitochondrial functions and epigenetic modifications involved in the health and sickness phenotype development, and describe the possible pharmacological use of all-natural 5-MeO-DMT to "rescue" patients from sickness phenotype through mitochondrial activation. We focus on all-natural 5-MeO-DMT its clinical therapeutic implications benefit long-term effects on mental health and well-being of the patient possibly reprogramming and remodeling the epigenome, particularly in mental and neurodegenerative diseases.

Keywords: Sigma1 receptor, mitochondria, energy, dysregulation, stress, ROS, epigenetic, disease, all-natural, 5MeO-DMT, therapy.

Introduction

Hundreds of millions of people worldwide are affected by the pandemic of mental[1] and neurodegenerative[2] diseases. Given the specific localization of the Sig-1R at the MAM, have been very explored as target regulations of the Sig-1R in mental and to neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), among others[3]. Sig-1R ligands are fundamental on mitochondrial dysfunction-induced neurodegeneration are addressed. DMT is the endogen agonist of sigma receptor and in this report, we particularly review, the role of all-natural 5-Meo-DMT as a pharmacological agonist for the Sigma 1 receptor[4]. All-natural 5-methoxy-N,N-dimethyltryptamine, hereinafter referred to as all-natural 5-MeO-DMT, is a entheogen substance found in the secretion from the parotoid glands of the Bufo alvarius toad is agonist of Sigma 1 receptor. The all-natural 5-MeO-DMT administrated in humans in naturalistic settings as a treatment of mental health problems and as a means for spiritual exploration is currently researched. Numerous patents and clinical studies that describe

the pharmacological benefits of 5-MeO-DMT are ongoing[5].

The mitochondria are the power station that provides the necessary energy for the processes that sustaining life[6]. The mitochondria perform diverse interconnected functions, producing ATP and many biosynthetic intermediates while also contributing to cellular stress responses such as autophagy, apoptosis and epigenetic regulation[7]. Mitochondria form a dynamic, interconnected network that is intimately integrated with other cellular compartments. In addition, mitochondrial functions extend beyond the boundaries of the cellular influence and organism's physiology by regulating communication between cells and tissues. These characteristics define mitochondria both as fundamental components of our cells specially in neurons[8]. Mitochondrial dysfunction has emerged as a key factor mental[9] and neurodegenerative disorders[10]. In this review we focus the regulation of cellular functions through the mitochondrial bioenergetic, signaling, antiapoptotic and epigenetics regulation pathways. Hence, we provide an innovative perspective in which we highlight the key molecular mechanisms advances in sigma-1 receptors on mitochondrial functions and epigenetic regulation on healthiness and sickness, with special focus on mental and neurodegenerative diseases and clinical implications of all-natural 5-MeO-DMT S1R agonist.

Mitochondria: In Healthiness and In Sickness

Mitochondria are critical to cell and organ function; Mitochondria play a key role in metabolic homeostasis, because of their central role in energy production, control of cytosolic Ca2+ (calcium ion) levels, lipid homeostasis, steroid synthesis, generation of Fe-S (iron–sulfur) centers, heme synthesis[11], innate immune response, and metabolic cell signaling[12–16]. For all the above mentioned, mitochondrial dysfunction and altered organellar regulation are also associated with some more common diseases, including cancers, mental, neurodegenerative diseases[12,13]. Mitochondria are the main regulator of cell survival/death as well as that for the ROS production.

Mitochondria produce ATP via oxidative phosphorylation (OXPHOS). In the matrix, tricarboxylic acid cycle (TCA) enzymes generate electron carriers (NADH and FADH2), which donate electrons to the IM-localized electron transport chain (ETC) and also generate reactive oxygen species (ROS) which can damage key components of cells, including lipids, nucleic acids, and proteins[15]. ROS has been suggested to contribute to diseases associated with mitochondrial dysfunction, including neurodegeneration.

Another central function of mitochondria is ROS signaling and sensing. Mitochondria operates as redox sensors that can alter energy states in response to the chemical environment of the cell and relative levels of endogenous metabolites such as iron (II), succinate, and ascorbate, as well as various forms of ROS. However, how ROS sensing is mediated by mitochondrial function and how different ROS sensing pathways overlap are not well understood. Changes in redox states influence DNA methylation because the oxidation of 5-methylcytosine to 5-hydroxymethylcytosine in CpGs can perturb recognition by methyl-binding proteins and subsequently alter methylation patterns and epigenetic regulation[7,15].

Metabolic epigenetics refers to nuclear alterations of chromatin and other factors that regulate gene expression resulting from changes in mitochondrial energetics and metabolism. The resulting metabolites, in turn, mediate gene expression changes that control cellular processes, including energy homeostasis[16]. Thus, energy status and metabolism are able to modulate epigenetic programming via chromatin structural changes and dynamics, DNA methylation, histone modifications, and non-coding RNA expression. Epigenetic modifiers include DNA methyltransferases, histone acetyl transferases, histone deacetylases, sirtuins (SIRTs), histone lysine demethylases, poly(ADP-ribose) polymerases, and others that work coordinately to regulate gene expression. For instance, reprogramming of energy metabolism has been identified as hallmark of cancer[17] and epigenetic control [18,19].

Mitochondrial distribution and dynamics are influenced by physical interaction between the mitochondrial outer membrane and diverse intracellular membranes, such as the plasma membrane, peroxisomes, ER, autophagosomes and lysosomes, termed mitochondria-associated membranes (MAMs). MAMs create unique environments or platforms for the localization and activity of components that function in shared inter-organellar functions, such as Ca2+ homeostasis and lipid biosynthesis[20-22]. MAM is critical in maintaining neuronal homeostasis. Thus, given the specific localization of the S1R at the MAM, we highlight and propose that the direct or indirect regulations of the S1R on mitochondrial dysfunctions intervenes to mental and

neurodegenerative diseases[3]. Neurons and muscle cells contain high levels of mitochondria due to a high demand of energy. The Central Nervous System (CNS) has a high rate of metabolism because neurons participate in facilitating the neurotransmission and extending axons and dendrites to neighboring cells for impulse transmission[23]. Neurons exert plasticity, exhibiting complex morphologies, and constitutively undergo synaptic modulations when stimulated. Therefore, mitochondrial dysfunction detrimental to neurons and has been extensively discussed in neurodegeneration[24].

Biological and physiological function of Sigma receptors in mitochondria

Biological and physiological function of Sigma receptors in mitochondria The S1R is a small (28 kDa), highly conserved, chaperone that resides mainly at the mitochondrion-associated endoplasmic reticulum (ER) membrane (called the MAMs) and acts as a dynamic pluripotent modulator in living systems[24]. Chaperones are proteins that assist the correct folding of other protein clients. The S1R is known to play a role in regulating the Ca2+ signaling between ER and mitochondria and in maintaining the structural integrity of the MAM[25]. The MAM serves as bridge between ER and mitochondria regulating multiple functions such as Ca2+ transfer, energy exchange, lipid synthesis and transports, and protein folding that are pivotal to cell survival and defense. Therefore, the S1R serves as a communicator that bridges these two organelles and plays pivotal roles in mitochondrial functions[26].

Interestingly, the percentage of newly synthesized proteins that are correctly folded and thus are able to exit the ER is usually less than 10%. Because the action of chaperones is fundamental to the cell, chaperones are implicated in many diseases including Huntington disease[28], Parkinsonism[29], stress disorders[30]. Under pathological conditions, the S1R is a receptor chaperone essential for the metabotropic receptor signaling and for the survival against cellular stress losing its global Ca2+ homeostasis the S1R translocates and counteracts the arising apoptosis[31].

The S1R receptor has a unique and versatile pharmacological profile[4,32] and its endogenous agonist is Dimethyl tryptamine (DMT). S1R ligands have therapeutic usages in regulating the stability of IP3 receptors as well as the associated interorganelle Ca2+ signaling from the ER to mitochondrion under normal or otherwise pathological conditions[33-36]. S1R bind with high affinity to several classes of chemically unrelated ligands such as neurosteroids[37], neuroleptics, dextrobenzomorphans [DEX] and several psychostimulants such as cocaine[37], methamphetamine [METH][37,38] methylenedioxymethamphetamine [MDMA][39] and methacathinone[37,40]. Consequently, it is thought that the SR may mediate the immunosuppressant, antipsychotic[41] and neuroprotective effects of many drugs[42] S1Rs regulate a number of neurotransmitter systems, including the glutamatergic [Glu], dopaminergic [DA], serotonergic [5HT], noradrenergic [NE] and cholinergic [Ch] systems. As these transmitters, which interact with the S1Rs, are involved in many neuropsychiatric disorders their role has been evaluated in a number of these disorders[43]. In fact, several lines of research have demonstrated that S1R play a role in the pathophysiology of neuropsychiatric disorders such as mood[44], anxiety disorders[45] and schizophrenia[26,46].

The acute S1R actions include the modulation of ion channels (e.g. K+ channel), N-methyl-D-aspartate receptors (NMDARs)[47], IP3R and s1R translocation. Chronic actions of S1Rs are considered to be the result of an up- or down regulation of the S1R itself. Recent in vitro and in vivo studies strongly point that S1Rs participate in membrane remodeling and cellular differentiation in the nervous system reconstitution in the brain implicated on drug abuse[48]. Metabolic studies support the view that S1R have functional significance in brain glucose metabolism as glucose utilization is affected by ligands in areas of brain that show high densities of sRs[48]. S1R might possess a constitutive biological activity, and that S1R ligands might merely work as modulators of the innate activity of this protein. The lack of postnatal development of receptors in the CNS, and the fact that S1R sites are much denser in peripheral organs, such as the liver[49], immune and endocrine tissues[50,51], suggest a universal role for sRs in cellular function. Because of their widespread modulatory role, S1R ligands have been proposed to be useful in several therapeutic fields such as amnesic and cognitive deficits, depression and anxiety, schizophrenia, analgesia and against some effects of drugs of abuse such as cocaine and METH and neurodegenerative diseases[40,52].

The mitochondrial role of the sigma1 receptor in neurodegenerative diseases

Given the specific localization of the S1R at the MAM, we highlight and propose that the direct or

indirect regulations of the S1R on mitochondrial functions intervenes to neurodegenerative diseases. These receptors represent compelling putative targets for pharmacologically treating neurodegenerative disorders. Neurodegenerative diseases with distinct genetic etiologies and pathological phenotypes appear to share common mechanisms of neuronal cellular dysfunction, including excitotoxicity, calcium dysregulation, oxidative damage, ER stress and mitochondrial dysfunction[53,54].

Sustained release of glutamate causes persistent activation of NMDARs leading to neuronal excitotoxicity, increasing intracellular calcium levels, followed by stochastic failure of calcium homeostasis and necrotic cell death[52]. This toxicity results from activation of the mitochondrial permeability transition pore opening triggered by membrane potential-dependent uptake of calcium into the mitochondrial matrix[53,54], contributing to neurodegeneration in acute and chronic CNS diseases, including ALS, AD, and PD disease[55-57]. Hence, one major mechanism by which S1R ligands may confer neuroprotection is through the regulation of intracellular calcium homeostasis[58].

The best evidence that ROS may be an underlying cause of neurodegeneration is the strong association between the detection of increased ROS production and the increased oxidative damage observed in CNS disorders such as PD, AD and ALS[59,60]. Activation of Sig-1Rs may also mitigate ROS accumulation, possibly through modulation of ROS-neutralizing proteins. Furthermore, Sig-1R knockout or knockdown can increase oxidative damage[61].

Protein aggregation occurs under calcium dysregulation, oxidative stress or aging, altering ER function and leading to the accumulation of unfolded or misfolded proteins within the ER lumen. This triggers a stress response by the ER known as the unfolded protein response (UPR) to restore protein folding homeostasis. The failure of protein homeostasis is a common mechanism for many neurodegenerative diseases AD, PD, and HD [62,63,64].

Mitochondrial fission and fusion are part of normal organellar maintenance, and are particularly significant in axons, in which mitochondria may have to travel long distances. Recent work has identified that the dynamin-related protein 1 (Drp1) is recruited to ER-mitochondria contact sites and mediates fission and it's been shown that homozygous knockout of Drp1 is lethal[65], while fragmented mitochondria and elevated or modified Drp1 (i.e., increased fission activity) are associated with AD, PD, and HD[66]. Mitochondria-MAM dysregulation has been proposed as the underlying cause of AD[67] and may contribute to neuronal loss in other disease contexts[68].

S1Rs may also influence the expression of anti- and pro-apoptotic signals that target the mitochondria. Sig-1R activity positively regulates Bcl-2 expression, possibly through nuclear factor kappa B (NF-kB) and/or extracellular signal-regulated kinase (ERK) pathways[68,69]. Since Bcl-2 has also been shown to interact with IP3Rs and enhance their activity[69], this positive regulation of Bcl-2 level may be another mechanism by which sigma 1 activity increases IP3R-mediated mitochondrial calcium uptake and ATP production, in addition to the S1R-IP3R interaction described above. Activation of S1Rs may also decrease expression of Bax and apoptosis associated caspases, further promoting cell survival[3,70,71].

Alzheimer Disease (AD) is a complex, multifactorial disease characterized by severe cognitive impairment and memory loss. Decreased S1R protein levels were observed in the human living and cortical postmortem brain tissue[72,73] and similar results were found in PET scan studies, in which Sig-1R expressions were lower in the brain of early AD patients[74].S1R expression may be involved in the therapeutic effect of HDAC6 inhibitor on AD pathology[75]. Preclinical evidences suggest that S1R agonists might be useful in treating AD, no selective S1R agonist is currently available for clinical use[3], specific sigma 1 receptor agonist as all-natural 5-MeO-DMT[4] has advantages to be consider in clinical use.

Parkinson's disease (PD) is a slowly progressing disorder, causing impaired motor functions such as bradykinesia or tremor, and other non-motor complications. The pathological characteristic of PD is a massive death of dopaminergic neurons in substantia nigra pars compacta (SNpc) and the deposit of Lewy bodies composed of α-synuclein, ubiquitin and neurofilaments. S1R expressions were lower in putamen of PD patients as demonstrated by PET studies[76]. S1R also attenuate Dopamine (DA) toxicity involved in the etiology of PD[61]. S1R agonists were found to reduce oxidative stress via several signaling pathways[77]. Endogenous S1Rs could tonically inhibit DA-induced NF-κB activation, which protects cell from death. Thus, S1R ligands may represent new therapeutic targets for PD[3]. These data suggest that S1Rs are one of the endogenous

substrates that counteract the dopamine cytotoxicity that would otherwise cause apoptosis[61].

Endogenous DMT and all-natural 5-MeO-DMT are sigma 1 receptor agonists - Mode of action

Endogenous DMT is Sigma 1 receptor agonist a molecule synthesized, stored, and released it is agonist of S1R[78] in cells periphery and central nervous system[79]. DMT is Central Nervous System neurotransmitter involved in sensory perception[80]. Enzyme indolethylamine-N-methyltransferase (INMT), is the responsible of DMT synthesis[81]. INMT is widely expressed in the body, primarily in peripheral tissue such as the lungs, thyroid and adrenal gland, skeletal muscle, heart, small intestine, stomach, retina, pancreas, lymph nodes and blood[82]. It is densely located in the anterior horn of the spinal cord[82–87]. Highest INMT activity has been found within the brain in the following areas: uncus, medulla, amygdala, frontal cortex[83], frontal-parietal and temporal lobes[87,88], pineal gland[87] and placenta[88]. DMT has been measured in several human body fluids, including blood[82], urine and cerebral spinal fluid. Endogenous DMT binds to sigma-1 receptors as an agonist at half maximal effective concentration EC50 = 14 μM. INMT co-localizes with sigma 1 receptor in C-terminals of motor neurons[89]. Only a small fraction of endogenous DMT is released into the bloodstream[90]. DMT has a transport process[91] accomplished via ATP-dependent uptake similar to the biological priority of glucose and amino acids, showing the universal role DMT in biological processes. The three-step process by which DMT is accumulated and stored in neurons are described[92]. Once uptake and storage of DMT has been completed, it has remained stored in vesicles for at least 1 week and to be released under appropriate stimuli[93]. Through these three steps, peripheral synthesis of DMT, consumption of DMT containing plant matter, or systemic administration of DMT can influence central nervous system functions[91]. In cardiovascular system the effect of DMT was determined, by administration of DMT to human volunteers, a progressive decrease in heart rate was observed over the four doses, but not in blood pressure [79].

Endogenous DMT plays a significant role in physiological mechanisms via S1R-MAM-mitochondrial pathway. S1R[94] agonists are neuroprotective via several mechanisms. DMT and also 5-MeO-DMT reduced inflammation via S1R and induced neuronal plasticity[95], which is a long-term regenerative process that goes beyond neuroprotection[96]. DMT and 5-MeO-DMT modulate innate and adaptive inflammatory responses through the S1R of human monocyte-derived Dendritic cells[97]. DMT mediated S1R activity induces neuronal plasticity changes in newborns[96]. Exogeneous DMT stimulates the *in vitro* differentiation of neural progenitors toward a neuronal phenotype through S1R. DMT *in vivo* action mediated by S1R improved performance in learning tasks that has been linked to hippocampal neurogenesis. Moreover, previous studies performed in humans[98], using the traditional medicine of native peoples of South America Ayahuasca which main component is DMT infusion[99] has antidepressant activity, a therapeutic effect usually linked to hippocampal neurogenesis[100].

All-natural 5-MeO-DMT is found as a natural extract from the secretions of the Sonoran Desert *Bufo alvarius* toad gland and is considered an Amerindian medicine Seris, an aboriginal group from the state of Sonora, in Mexico[5]. Some reports suggest that the secretion of the *Bufo alvarius* toad have been used historically by native peoples in the southwestern territory of the USA and northern Mexico[101]. This entheogenic sigma 1 receptor agonist has recently been associated with cognitive gains, antidepressant effects and changes in brain areas related to attention and neural regeneration[4]. 5-MeO-DMT is a neuroregulatory substance, sigma-1 receptor[4] is its neuropharmacological target. 5-MeO-DMT is the most potent entheogen with strong dissolution of the ego, a conscious state marked by a loss or diminution of one's sense of self and a lack of first-person experience[102], influence on perception[5], cellular bioenergetics activation, antiapoptotic[4] and mitochondrial regulation of epigenetics. 5-MeO-DMT mechanism of action is mediated S1R signaling pathway a "pluripotent modulator" in living systems, as a controller of cell survival and differentiation[25,58]. The S1R is the primary pharmacological molecular targets for 5-MeO-DMT and its mitochondrial activation play roles dissolving symptoms of some psychiatric and neurodegenerative disorders by the epigenetic regulate[91]. Possibly, 5-MeO-DMT shed light into the therapy on recovery patients health from mental diseases and neurodegenerative diseases.

In vivo pharmacology studies of 5-MeO-DMT[93] have been conducted in mice, rats, gerbils, hamsters, guinea pigs, rabbits, goldfish, cats, dogs, sheep, pigs and primates. The pharmacokinetics of 5-MeO-

DMT has been studied the maximum concentration (Cmax) in plasma is reached after 5–6 min following an intraperitoneal (IP) injection, the terminal half-life (t1/2) is 12–19 min in mice and Cmax = 5–10 min and t1/2 = 6–16 min in rats. 5-MeO-DMT presents a hydrophobic behavior (3.3 oil/water partition coefficient) and readily crosses the blood–brain barrier (BBB). 5-MeO-DMT is distributed to the liver, kidneys and brain. Brain concentrations of 5-MeO-DMT in the rat were 1.7-fold higher compared to plasma after IP injection, with highest concentrations in the cortex, thalamus, hippocampus, basal ganglia, medulla, pons and cerebellum. In the mouse brain, 5-MeO-DMT distributes to the cortex, hippocampus, hypothalamus and striatum after IP administration[4,92]. It has been demonstrated that the pharmacokinetics of 5-MeO-DMT follows a non-linear pattern for both IP and intravenous (IV) administration of high doses in mice. This non-linearity is also reflected in corresponding increases in brain concentration of 5-MeO-DMT. This enzyme mediates the production of the psychoactive metabolite bufotenine from 5-MeO-DMT[5].

Long-term potentiation (LTP) is a persistent strengthening of synapsis based on recent patterns of activity. These are patterns of synaptic activity that produce a long-lasting increase in signal transmission between two neurons[103]. The opposite of LTP is long-term depression, which produces a long-lasting decrease in synaptic strength. Specifically, 5-MeO-DMT modulates proteins associated with long-term potentiation. Proteins found upregulated by 5-Meo-DMT are NMDAR, CaMK2 (Ca2+/calmodulin-dependent protein kinase), and CREB (cyclic AMP-responsive element-binding protein)[20].

5-MeO-DMT is a weak 5-HT reuptake inhibitor but has no appreciable effects on monoamine release nor on noradrenaline or dopamine. S1R contributes to the brain plasticity effects of 5-MeO-DMT. S1R is an endogenous regulator of dendritic spine morphology and neurite outgrowth[104,105]. 5-MeO-DMT is a direct molecular mediator of plasticity, which has effects on cell surface and extracellular proteins involved in regulating synaptic architecture. An upregulation of integrins[98], netrins, plexins, and semaphorins were observed in 5-MeO-DMT-treated organoids, was also found in major depressive disorder patients who responded well to antidepressants, suggesting the importance of this class of proteins in brain plasticity. srGAP, an intracellular signaling molecule with a role in processes underlying synaptic plasticity, higher cognitive function, learning, and memory is significantly downregulated[106]. S1R agonists exert neuroprotective effects by regulating intracellular calcium levels[107], preventing expression of pro-apoptotic genes[108], and protecting mRNA against anti-apoptotic genes such as Bcl-23. Psychological effects such as changes in perception and thought, renewed sensation of novelty, ineffability, and awe[109] possible is derive directly from the strong modulation of synaptic and cellular plasticity promoted by 5-MeO-DMT.

Mitochondria-directed epigenetic changes and role of 5-MeO-DMT

Cells respond to environmental stressors through several key pathways, including
response to ROS, nutrient and ATP sensing, DNA damage response, and epigenetic alterations. Mitochondria play a central role in these pathways through energetics, ATP production, metabolites generated in TCA cycle, also through and mitochondria–nuclear signaling related to mitochondria morphology, biogenesis, fission/fusion, mitophagy, apoptosis, and epigenetic regulation[110].
Possibly the neuroprotective, neuroregeneration, anti-apoptosis and neuroplasticity[111] effects from 5-MeO-DMT agonist S1R is mediated through mitochondrial epigenetic regulation pathway. Each neuron contains up to 2 million mitochondria[112]. The energy-hungry brain is especially vulnerable to power station problems during mitochondrial damage[113]. Mitochondrial regulation of epigenetic landscape alterations are reversible, epigenetic processes early in life might play a role in defining inter-individual trajectories of human behavior and epigenetic mechanisms contribute to later-onset neurological dysfunction and disease[19]. Some epigenetics diseases targets with significant neuronal death and neurological dysfunction include Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), epilepsy, stroke and traumatic brain injury (TBI)[114]. Alterations of the S1R gene have been associated with severe neurodegenerative disorders[24].

mtDNA damage or mitochondrial damage has been associated with a mitochondrial damage checkpoint "mitocheckpoint"[115]. OXPHOS defect is checkpoint mechanism induced due to instability of the nuclear genome[116]. The mitocheckpoint coordinates and maintains the proper balance between apoptotic and anti-apoptotic signals. Upon damage

to mitochondria, mitocheckpoint is activated to help repair damage to mitochondria, restore normal mitochondrial function, avoid induction of mitochondria-defective cells and induce changes to the nuclear epigenome[117]. Cross talk between the nucleus and mitochondria of individual cells may lead to a mitochondrial damage response as a result of incurred damage. If mitochondria are severely damaged, such an event will trigger apoptosis. If damage to mitochondria is persistent and defective mitochondria accumulate in the cell, it would lead to instability of the nuclear genome[114].

DNA methylation is a major epigenetic modification of DNA gene expression possible mitochondria regulated[71]. Epigenetic modifications within the mammalian nuclear genome include DNA methylation (5-mC) or hydroxymethylation (5-hmC)[118,120]. Mammalian mitochondria have recently been identified to have mitochondrial DNA methyltransferase 1 (mtDNMT1) activity, 5-mC and 5-hmC. Shock et al. identified translocation of nuclear DNMT1 to the mitochondrial matrix is regulated by expression of a conserved mitochondria targeting sequence, upstream of the gene's transcription start site within the nuclear encoded gene[120]. Alterations in mtDNMT1 directly affected transcription from the light and heavy strands of mtDNA suggesting a correlation between 5-hmC and 5-mC mediated transcriptional regulation of mtDNA by a nuclear encoded gene. These findings provide new evidence implicating epigenetic regulation of the mitochondrial genome by nuclear encoded translocated mtDNMT1 relative to mitochondrial dysfunction[121–123]. Reduced levels of co-factors due to mitochondrial impairment/ dysfunction could have significant effects on regulation of the nuclear genome. Mitochondrial dysfunctions invoke mitochondria-to-nucleus retrograde responses in human cells[124].

Mitochondrially targeted DNMT1 transcript variant (mtDNMT1) comprises about 1–2% of total DNMT1 transcripts and is upregulated by the hypoxia-responsive transcription factors peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1a) and nuclear respiratory factor 1 (NRF1) and via the release of p53 from the DNMT1 promoter[125]. This finding suggests that mtDNMT1 plays a regulatory role during oxidative stress, confirming the link between oxidative stress and mitochondrial function. Similar capacities for mtDNMT1 and its nuclear counterpart were indicated by the finding that mtDNMT1 shows clear CpG-dependent mtDNA interactions proportional to the amount of CpGs in the target amplicons[126]. The reduced mtDNA methylation is the result or a consequence of this mitochondrial dysfunction. mtDNA methylation activation would be involved in mitochondrial biogenesis (LSP, HSP1) and maintenance of the electron transport chain (HSP2)[127].

Maternal mitochondrial imprinting and chromosomes imprinting from parents' patterns, would represent a biological memory of what the parents experienced[128]. Transmission caused by environmental factors, such as the parents' childrearing behavior[129]. That these transgenerational effects have been also epigenetically transmitted to their children. Integrating both hereditary and environmental factors through the lifetime, epigenetics adds a new and more comprehensive transgenerational transmission of trauma[130], nightmares[131], posttraumatic stress disorder PTSD[132], symptoms in mental diseases and the neurodegeneration. Moreover, the transmission may continue beyond the second generation and also include the grandchildren, great grandchildren and perhaps others as well. This process of transgenerational transmission of trauma (TTT) has been repeatedly described in the academic literature for more than half a century[131]. The epigenetic marks affect gene expression patterns in the nervous system and mitochondrial dysfunction and epigenetic imbalance show to influence the progression of many mental and neurological disorders[128]. S1R agonist[4] 5-MeO-DMT[5] are possible through epigenetic regulation by activation mitochondrial pathway reversible promote restoring to healthy cellular functions by restoring the epigenetic landscape.

Familial early-onset Alzheimer's disease (AD) is more probable in individuals coming from mothers diagnosed with AD than from fathers diagnosed with AD. Studies in animal models have shown maternal imprinting in the ovum lead to alterations genetic and/or epigenetic in the nuclear and/or the mitochondrial DNA. These modifications that are transmitted to the new living beings affect more mitochondrial proteins and, therefore, the mitochondrial function may be affected in adulthood by trends present in the ovum[133].

PD, AD[133], HD and other neurodegenerative diseases[123] and forms of acute brain injury[24]. In our perspective is possible activation of epigenetic

mechanism[7] through S1-R and mitochondrial function in mental and neurodegenerative diseases, whose restore by 5-MeO-DMT agonist promote activation mitochondrial pathways, mitochondria bioenergetics function[134–137], mitochondrial oxidative respiration[138] and mitochondrial epigenetic regulation, restored mtDNMT nuclear activity, increasing levels mitochondrial FAD and α-KG co-factors who have significant effects on regulation of the nuclear genome. 5-MeO-DMT modulates proteins involved in long-term potentiation (LTP), in addition to morphogenesis and maturation of dendritic spines, while inhibiting neurodegeneration and apoptosis. 5-MeO-DMT activate score for dendritic spine and cellular protrusion formation, microtubule and cytoskeletal organization. Biological functions such as neurodegeneration, apoptosis, and neuron lesion are inhibited by 5-MeO-DMT[4] through S1R-mitochondria pathway.

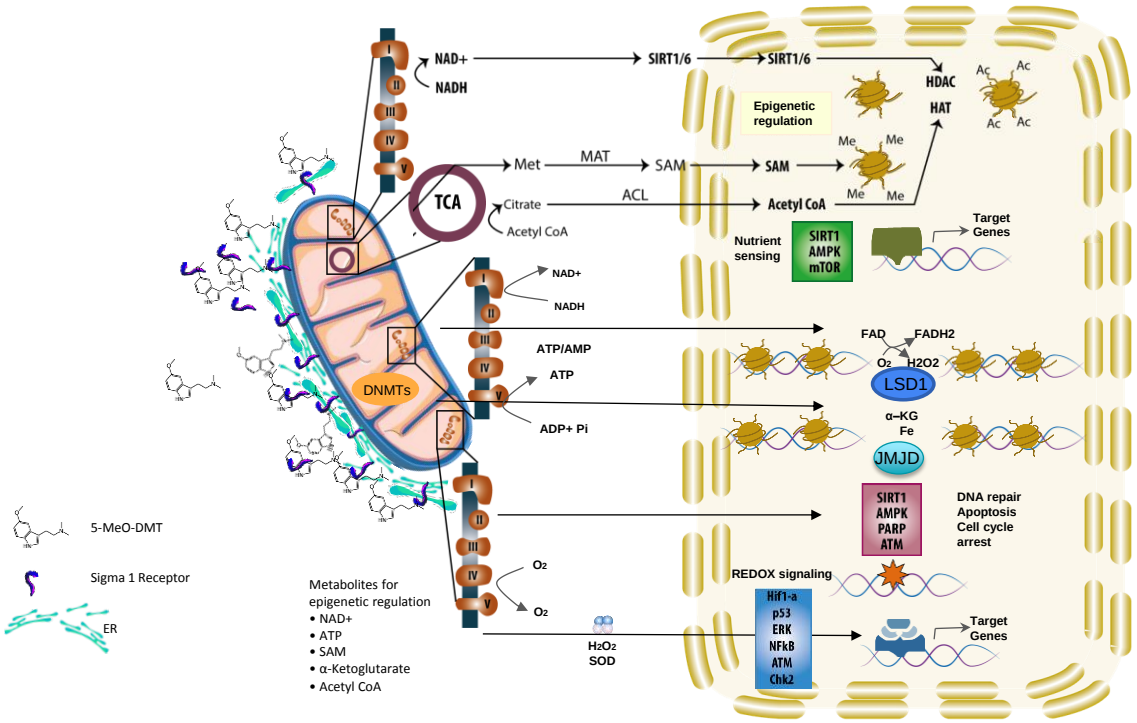

Figure 1: 5-MeO-DMT Sigma 1 receptor agonist nuclear epigenetic regulation/chromatin modification through mitochondria–via sirtuins (e.g., SIRT1 and SIRT6), HDACs, and HATs, which require acetyl CoA from the TCA cycle; nutrient sensing through the NAD+/NADH and ATP/AMP sensing; catalysis of H3K4me2 and H3K27me3, demethylation mediated by LSD1 and the JMJD protein family, catalyzed using mitochondria synthesized co-factors FAD and α-ketoglutarate. DNA repair and redox signaling pathways. Dialog mitochondria and nucleus: mtDNMTs are associated with healthy mitochondria. The reduced mtDNA methylation is the result of mitochondrial dysfunction. mtDNMT1 from nucleus are translocated in mitochondrial dysfunction.

Clinical implications of the therapeutic use of all-natural 5-MeO-DMT

All-natural 5-MeO-DMT[139] is high potency, ultra-rapid onset, and short duration of entheogen effects, primarily is sigma 1 receptor agonist. Native peoples of North, Central, South America, included Amazon region America possibly used the ancestral medicine in millenary sacred ritualist healing and consciousness evolution purposes according their cosmovision. All-natural 5-MeO-DMT produces profound altered state of consciousness and ego dissolution, including mystical experiences as inner experiences involving an intensely felt fading of the sense of self and/or feelings of increased connectedness, up to and including the sense of complete unity[163]. These kinds of feelings go well beyond our normal day to day sense of self-awareness. In ordinary consciousness, there is generally the impression that there is a me on the one hand and then, on the other hand, everything else. Under some circumstances, however, this sense of self –-during such moments, one's sense of self can fade into the background and become a part of, rather than apart

from, everything else[140], with beneficial long-term effects on mental health and well-being of the patient[139].

Naturalistic use of toad secretion containing 5-MeO-DMT was reported that the intensity of the experience is associated with improvements in measures of satisfaction with life and reduction of psychological distress in participants without an underlying mental health condition[141]. Effects following natural 5-MeO-DMT administration are alteration in auditory and time perception, emotional states amplifications, and strong ego dissolution short-lasting, and reliably induces a "peak" mystical spiritual experience[141], state consider to be a core predictor of the efficacy of entheogen all-natural 5-MeO-DMT[139]. 5-MeO-DMT cause rapid and sustained reductions in symptoms of depression, anxiety, and stress. 5-MeO-DMT also stimulates neuroendocrine function and immunoregulation[93].

Formulations of interest are smoked, vaped, IM, intranasal, intravenous for high bioavailability of 5-MeO-DMT because they avoid first-pass metabolism. Smoked and vaporized administration provides fast onset of subjective experiences with high intensity and short duration. At present, biopharmaceutical companies with an interest in synthetic 5-MeO-DMT are exploring and developing vaporized, intranasal, IM, and intravenous formulations for delivering 5-MeO-DMT[141,142]. In a dose-ranging Phase I clinical trial to assess safety and psychoactive effects of 5-MeO-DMT, demonstrated the safety of vaporized dosing up to 18 mg for administration via inhalation. Importantly, the rapid onset and short duration of the 5-MeO-DMT experience render it more suitable for individual dose-finding strategies compared with longer-acting psychedelics[143].

Clinical implication of the all-natural 5-MeO-DMT receptor sigma agonist and its role on mitochondrial activation it is possible applicated to the therapy of serious psychiatric disorders—Schizophrenia (SCZ), major depressive disorder (MDD), and borderline personality disorder (BPD) diseases with a different range of debilitating symptoms and prognosis, and show similar alterations in energy metabolism processes[144]. Proteomic data show that SCZ and BPD share 32 altered proteins, mostly related to mitochondrial electron transport, response to ROS and glycolysis. They share some pathophysiological traits and data analysis revealed seven proteins altered both in BPD and MDD, while five of those are different subunits of the NADH dehydrogenase complex in the electron transport chain[144]. This is consistent with previous reports of impaired functioning of OXPHOS complexes in MDD[144,145] and decreased nuclear expression of genes coding for mitochondrial respiratory mechanisms in BPD[146] both of which lead to reduced mitochondrial energy production. major depression has been described as the initial symptom of mitochondrial disease in a large sample size of adult patients[147]. Mitochondrial function and energy metabolism were shown to play an important role in regulating social behaviors[148]. Limited energy production impairs adaptive neuronal capacity and contribute to the development of psychopathologies such as SCZ, BPD, and MDD under stressful stimulus[149].

All-natural 5-MeO-DMT patented composition comprise its possible use in the therapy to mental and neurodegenerative diseases[139]. One of the most important benefit uses of all-natural 5-MeO-DMT reported are the patient's recovery from addiction prompted by cocaine[5]. S1R mediated cocaine has dose-dependent interaction between histone deacetylase (HDAC)1, HDAC3 and HDAC3 and to therefore affect chromatin compaction and gene expression[149]. All-natural 5-MeO-DMT via S1R activation trigger patients' recovery from symptom with persistent improvements in life satisfaction and psychopathological symptoms[139,141,150,151,152]. A single dose, 24-hour-treatment with 5-MeO-DMT, showed major downregulation of mGluR5 after treatment with 5-MeO-DMT. mGluR5 has a role in the rewarding effects for several drugs of abuse. It was shown that mice lacking the mGluR5 gene do not self-administer cocaine and show no cocaine-induced hyperactivity[153]. They also have attenuated somatic signs of nicotine withdrawal, and reduced ethanol consumption behavior[154], suggesting mGluR5 is involved in addiction[4,155].

All-natural 5-MeO-DMT-mediated S1R is involved in the reported retrieval and healing of traumatic memories[139,156]: "Epigenetic modifications, such as DNA methylation, occur in response to environmental influences to alter the functional expression of genes in an enduring and potentially, intergenerationally transmissible manner. As such, they may explain interindividual variation, as well as the long-lasting effects of trauma exposure"[132]. The

reconsolidation and fear extinction of traumatic memories require the involvement of epigenetic mechanisms. Several countries where 5-MeO-DMT is unregulated offer retreats and treatment programs[157]. A survey of 51 US Special Operations Forces Veterans from one such retreat, with combined 5-MeO-DMT and ibogaine treatments, indicated the experience was therapeutic for their traumatic experiences, suicidal ideation, depression and anxiety [155,157] In a survey of 20 individuals from the same retreat center, 75% reported a 'complete mystical experience', as measured by MEQ-30[155,158].

Notable features of natural 5-MeO-DMT are the reported high rates of the ego-dissolution and mystical experiences, with long-term positive therapeutic outcomes is calling for consistent pharmacognosy and clinical exploration[158]. Some of the benefits related to 5-MeO-DMT mediated by S1R and mitochondrial function to mitigate symptoms of some psychiatric and neurodegenerative disorders symptoms are linked possibly to these extensive epigenetic modifications produced by 5-MeO-DMT-S1R-mitochondrial epigenetic pathway. For this reason, all-natural 5-MeO-DMT S1R ligand is of great interest as possible therapeutic agent against CNS disorders[24,148].

Conclusion

Mental[159] and neurodegenerative[160] diseases are the possible epigenetics regulation complex products from under environmental or epigenetically inheritance stress manifested and controlled by S1R-MAM-mitochondrial dysfunction with large degree of variation depending on the neurons tissue affected. Endogenous and exogenous DMTs are sigma 1 receptor agonist and regulate adult neurogenesis in vitro and in vivo with mental health benefits and antidepressant effects in patients[98,99,100]. We have reviewed comprehensively a possible strongest neurobiological reprogrammed with the novel pharmacological sigma 1 receptor agonist the all-natural 5-MeO-DMT[139] ancestral healing via Sig-1R-MAM-mitochondrial activation. S1R is an ER resident chaperone that is highly enriched at the MAMs that controls mitochondria Ca2+ flux, bioenergetic, oxidative and stress responses and mitochondrial epigenetic regulation. Pharmacological S1R agonist 5-MeO-DMT therapeutic implications in mental and neurodegenerative diseases such as Alzheimer, Parkinson will drive the most important resources for expansion of all-natural 5-MeO-DMT successful legal therapy.

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The study did not involve humans or animals.

Conflict of Interest statement

The author is inventor on patent application describing therapeutic uses of all-natural 5-MeO-DMT.