The protective effect of DMT against neurodegeneration

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Abstract

This paper explores the therapeutic potential of DMT in neuroprotective strategies, particularly concerning ischemia-reperfusion injury (IRI) and neurodegenerative disorders. Besides its potent serotonin receptor actions, DMT is also an endogenous agonist of the sigma-1 receptor (Sig-1R). Sigma receptors are a unique family of proteins with high expression in the brain and spinal cord and have been involved in the etiology, symptom course and treatment of several central nervous system disorders. Our previous theoretical and experimental work strongly suggest that targeting sigma (and serotonin) receptors via DMT may be particularly useful for treatment in a number of neurological conditions like stroke, global brain ischemia, Alzheimer's disease, and amyotrophic lateral sclerosis. In this article, we briefly overview the function of Sig1-R in cellular bioenergetics with a focus on the processes

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involved in IRI and summarize the results of our previous preclinical (in vitro and in vivo) DMT studies aiming at mitigating IRI and related cellular neuropathologies. We conclude that the effect of DMT may involve a universal role in cellular protective mechanisms suggesting therapeutic potentials against different components and types of IRIs emerging in local and generalized brain ischemia after stroke or cardiac arrest. The multiple neuroprotective mechanisms facilitated by DMT may position it as a model molecule for developing pharmacological treatments for neurodegenerative disorders.

Abbreviations

5-HT	serotonin.
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine.
Aβ	β-amyloid.
AD	Alzheimer's disease.
ALS	amyotrophic lateral sclerosis.
ATP	adenosine triphosphate.
CHOP	C/EBP homologous protein.
DMT	N,N-dimethyltryptamine.
ER	endoplasmic reticulum.
INMT	indolethylamine N-methyltransferase.
IRI	ischemia-reperfusion injury.
MAM	mitochondria-associated membrane.
NF-κB	nuclear factor kappa B.
Nrf2	nuclear factor erythroid 2-related factor.
ROS	reactive oxygen species.
Sig-1R	sigma-1 receptor.
UPR	unfolded protein response.

1. Introduction

Research on dimethyltryptamine (DMT) has primarily centered on its psychotropic properties and serotonergic activity, largely overlooking its potential effects beyond the nervous system and on other receptor sites. Previous findings (Fontanilla et al., 2009) have identified DMT as an endogenous agonist ligand of the sigma-1 receptor (Sig-1R), which may illuminate previously unrecognized physiological mechanisms and therapeutic potentials linked to this compound. Specifically, current authors established in vitro and in vivo that DMT interacts with Sig-1R, suggesting that its effects may extend beyond traditional serotonergic pathways and into areas of cellular protection and stress response mechanisms (Szabo & Frecska, 2016). The Sig-1R is known to play a crucial role in alleviating various forms of intracellular stress, including mitochondrial, endoplasmic reticulum

(ER), and oxidative stress, while also safeguarding against apoptotic cell death and modulating immune responses (Pal et al., 2012; Weng, Tsai, & Su, 2017). This indicates that DMT administration could similarly influence these protective pathways and can be utilized in pathological conditions apart from the field of mental and behavioral disorders.

The present chapter reviews the existing literature on Sig-1R's role in cellular bioenergetics, particularly in the context of mitigation of cellular stress and addresses other receptor related – especially serotonin (5-hydroxytryptamine, 5-HT) mediated – mechanisms as well. For its therapeutic use we put into focus its potential effects against neurodegenerative processes and disorders with neurodegenerative-neuroinflammatory components, such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Furthermore, we also focus on potential therapeutic modalities in the prevention of ischemia-reperfusion injury (IRI) of the brain and related organs.

2. The Sig-1R chaperone

The Sig-1R has a complicated history. Initially classified as a member of the opioid receptor family, it was later considered an orphan receptor (Fukunaga, 2014), with no known endogenous ligand until DMT was identified as its endogenous agonist (Fontanilla et al., 2009). Today, Sig-1R is recognized as a non-G-protein coupled, non-ionotropic intracellular chaperone primarily located at the mitochondria-associated membrane that modulates Ca^{2+} signaling (Penke, Fulop, Szucs, & Frecska, 2018). The Sig-1R itself has enigmatic features. It is a protein with a unique amino acid sequence similar to fungal proteins (Moebius, Reiter, Hanner, & Glossmann, 1997), and displays a promiscuous pharmacological profile, binding to ligands with very diverse structures. These include small molecules like dextromethorphan, fluvoxamine, fluoxetine, haloperidol, methamphetamine, verapamil, chloroquine, donepezil, and others (Hayashi & Su, 2004). This broad binding capability emphasizes the potential for and endogenous ligand like DMT to interact with various signaling pathways, enhancing its therapeutic applicability.

While Sig-1R localizes mainly at the mitochondria-associated membranes (MAM), it also interacts with the binding immunoglobulin protein, another ER-chaperone (Hayashi & Su, 2007). Notably, Sig-1R is a transmembrane protein capable of dynamic translocation within cells. After stimulation of Sig-1R by agonists or in response to certain stimuli or stress

conditions, such as oxidative stress, ER stress, or neuroinflammation Sig-1R can dissociate from the MAMs or the binding immunoglobulin protein and move to other parts of the cell, including the plasma membrane (Su, Hayashi, Maurice, Buch, & Ruoho, 2010), nuclear envelope (Tsai et al., 2015), and can interact with cytosol proteins. This translocation capability enables Sig-1R to interact with various proteins and signaling pathways beyond their initial site at the MAMs, thereby amplifying their role in cellular signaling.

The central nervous system (CNS) and the mammalian cortex are considered the primary sites of Sig-1R activity and its physiological effects. Sig-1R is widely distributed throughout the CNS, with notable concentrations in regions such as the hippocampus, hypothalamus, midbrain, and olfactory bulb. Beyond the CNS, Sig-1R is also present in various peripheral tissues, including the liver, kidneys, lungs, and muscles, as well as in endocrine, immune, and reproductive tissue (Pabba, 2013). At the cellular level, Sig-1R is mostly expressed in cortical neurons, oligodendrocytes, brain vascular endothelial and ependymal cells. Within neurons Sig-1R is predominantly found in the pericarya and dendrites (Mavlyutov et al., 2012). This widespread distribution suggests that Sig-1R agonists can potentially influence a range of physiological and pathological processes within various organ systems (Su, Su, Nakamura, & Tsai, 2016).

3. The multiple functions of Sig-1R

The Sig-1R's function is essential for metabotropic receptor signaling, which, besides their cardinal role in regulating various neurotransmitter systems, second messengers and growth factor signaling pathways, also help cells to cope with stress. At the MAM its control of the Ca^{2+} efflux from the ER to the mitochondria is critical for maintaining mitochondrial respiration and high-energy phosphate synthesis (Hayashi & Su, 2007). By the promotion of mitochondrial Ca^{2+} uptake Sig-1R improves mitochondrial respiration, and ensures the production of energy through ATP synthesis in order to meet the demands of ER function. Furthermore, the activation of Sig-1R plays a protective role by attenuating free radical damage, via interactions with the Nrf2-antioxidant response element signaling pathway, which reduces oxidative stress in cells (Wang et al., 2015).

Under normal conditions, Sig-1R remains in a relatively inactive state. However, during extended or severe cellular stress, especially stress related to the ER, Sig-1R is upregulated. This process involves increased levels of mRNA transcripts and protein levels of Sig-1R, as well as its downstream signaling pathway elements (Hayashi, 2019; Pal et al., 2012). The activation of Sig-1R during this time fine-tunes oxidative phosphorylation, moderates apoptotic pathways, and participates in the unfolded protein response (UPR) by regulating stress signaling. Sig-1R ensures cell survival by mitigating ER stress and preventing the prolonged UPR, which could otherwise lead to cell death. Low Sig-1R activity hampers the detection of ER stress, reducing the efficacy of UPR and thus lowering cell survival (Chaudhari, Talwar, Parimisetty, Lefebvre d'Hellencourt, & Ravanan, 2014). Conversely, high activity of Sig-1R down-regulates apoptotic pathways by interacting with the signaling mechanisms across the mitochondria, ER, and nucleus.

Sig-1R's ability to translocate from the MAM to other cellular membranes adds versatility to its regulatory functions. This translocation allows Sig-1R to interact with various membrane-bound and cytosolic proteins, such as ion channels, receptors, and protein kinases, to further regulate cellular responses. Notably, Sig-1R can also translocate to the nuclear membrane, where it may influence gene transcription, adding another layer to its function as a pluripotent modulator in living systems. The dynamic ability of Sig-1R to move within the cell is believed to be key to its role in maintaining cellular homeostasis and promoting neuroprotection. This multifunctionality implicates Sig-1R in the etiopathology of numerous diseases, and its modulation is a target of therapeutic interest. Indeed, Sig-1R is increasingly recognized as a critical modulator in the UPR and a potential therapeutic target in diseases characterized by protein misfolding and cellular stress.

4. DMT and the Sig-1R

DMT is a naturally occurring classical psychedelic with significant affinity at 17 known receptor sites (Ray, 2010). The discovery of DMT as a natural ligand of the Sig-1R (Fontanilla et al., 2009) helped to clarify the decades-long perplexing history of both these molecules. DMT had been classified as an endogenous psychedelic (Christian, Harrison, Quayle, Pagel, & Monti, 1977; Hollister, 1977) with its exact physiological function unclear

(Barker, McIlhenny, & Strassman, 2012). More than 40 years of research was insufficient to provide a proper neurobiological explanation of the functions of this endogenous compound. This was in part due to a paradigm issue, wherein DMT has been primarily studied with a focus on its psychedelic effect mediated mostly by serotonin (5-HT1A, -2A, and -2C) receptors (Nichols, 2016). In our 2013 paper (Frecska, Szabo, Winkelman, Luna, & McKenna, 2013) we argued that the conventional conceptualization of DMT as predominantly a serotonergic psychedelic is too biased and narrow, attributing a pathological or potentially maladaptive function to it in humans and other species. We questioned why humans and animals would evolve an endogenous compound to produce hallucinations, as such perceptions of reality are not expected to be adaptive. Instead, we suggested that the Sig-1R action of DMT may turn out to be more revealing and relevant for its physiological and/or therapeutic functions.

DMT is a trace amine, which means it is present in the body in low concentrations under normal conditions, making it difficult to determine when it becomes mobilized. However, research has shown that there is a significant increase in DMT levels in the rat cortex following induced experimental cardiac arrest, suggesting that DMT may play a role during the physiological process of dying. This could imply that the activation of Sig-1R is beneficial under such conditions, as there is data supporting its increased expression in different causes of death, particularly under hypoxic conditions.

The affinity of DMT for the Sig-1R is modest, with a K_D of 14.8 μM (Fontanilla et al., 2009), meaning that higher concentrations of DMT are needed to fully saturate the receptor compared to its lower K_D at the 5-HT receptor subtypes. However, since its last-step synthesizing enzyme, the indolethylamine N-methyltransferase (INMT), is known to be co-localized with Sig-1R in neural tissue (Dean et al., 2019; Mavlyutov et al., 2012), it is possible that physiologically significant concentrations of DMT can be reached at or close to the Sig-1R site. To date, no higher potency endogenous ligand for the Sig-1R has been identified, but DMT and sphingosine have been proposed as potentially important compounds (Fontanilla et al., 2009; Ruoho et al., 2012; Su, London, & Jaffe, 1988).

In conclusion, while the dominant view has long been that DMT primarily functions as a serotonergic psychedelic, emerging evidence suggests that its role may be much more complex. The interaction between DMT and Sig-1R could provide important insights into its potential physiological and clinical effects, particularly under conditions such as hypoxia, where the activation of Sig-1R may be crucial.

4.1 Possible physiological and/or therapeutic roles of DMT

The Sig-1R has been implicated in the psychedelic effects induced by DMT, as suggested by Su, Hayashi, and Vaupel (2009) (Su et al., 2009). However, this assumption may not hold true, given that numerous drugs bind to Sig-1R without eliciting any psychedelic effects. Instead, our research has opened up an alternative perspective on the role of Sig-1R in mediating the effects of DMT. The receptor has been shown to ameliorate ER stress (Omi et al., 2014), promote neuronal survival against oxidative stress (Pal et al., 2012), and regulate immune processes (Jarrott & Williams, 2016). These findings suggest that DMT could similarly exert protective effects through Sig-1R activation (Frecska et al., 2013). Furthermore, the Sig-1R is known to regulate the morphogenesis of neuronal cells, including critical processes such as neurite outgrowth, myelination, and synaptogenesis (Ruscher & Wieloch, 2015). Therefore, it is reasonable to expect that DMT may also contribute to neuroregeneration.

In our paper (Frecska et al., 2013) we posited that the functional role of DMT may go beyond CNS activity, encompassing a more universal role in cellular protective mechanisms. This theoretical framework has been supported by experimental studies that verified the Sig-1R-mediated anti-inflammatory (Szabo, Kovacs, Frecska, & Rajnavolgyi, 2014) and anti-hypoxia (Szabo et al., 2016) effects of DMT in vitro. The evidence we provided, both indirect and direct, indicates that DMT's effects can orient research toward new directions and may support the development of a comprehensive framework regarding the fundamental roles of DMT in cellular adaptation.

Since the Sig-1R alleviates ER stress, improves neuronal survival against oxidative stress, regulates immune processes, ameliorates IRI, induces autophagy, and provides neuroprotection, it is reasonable to ascribe similar functions to DMT. Given that Sig-1R is recognized for its role in regulating the morphogenesis of neuronal cells, including processes like neurite outgrowth, myelination, and synaptogenesis, neuroregeneration can plausibly be expected from its activation by DMT. In a study conducted by Dakic et al. (2017) (Dakic et al., 2017) it was found that in brain organoids, 5-MeO-DMT (a compound closely related to DMT) positively influenced neuroplasticity and neuroprotection, maturation of dendritic spines, while inhibiting factors involved in neurodegeneration and apoptosis. In a rodent model, DMT reduced reactive oxygen species production, inflammatory gene expression caused by predator exposure and psychosocial stress, and modulated neuroplasticity-related genes.

Our 2013 paper (Frecska et al., 2013) concluded that the function of DMT may involve a universal role in different tissue protective mechanisms – not solely brain-related. This theoretical work was followed by experimental studies wherein the Sig-1R-mediated anti-inflammatory and anti-hypoxia effects of DMT were verified in vitro (Szabo et al., 2014; Szabo et al., 2016).

In summary, the evidence suggests that DMT may play a significant role in cellular protection and adaptation through its interaction with Sig-1R. The potential for DMT to influence neuroregenerative processes and provide neuroprotection opens new avenues for research into its therapeutic applications, particularly in the context of neurodegenerative diseases and other conditions characterized by cellular stress and inflammation. The convergence of theoretical and experimental findings supports the notion that DMT's effects include more than psychotropic activity, positioning it as a compound of interest in the exploration of cellular protective mechanisms across various tissue types.

4.2 Hypoxia, inflammation and other causes of ER stress

ER dysfunction can result from various causes, and its stress can be the outcome of hypoxia, defective mitochondria, disturbances in cellular Ca^{2+} levels, impaired redox regulation, or oxidative stress (Pal et al., 2012; Szabo et al., 2016). These stress factors may exhaust the ER's protein synthesizing mechanisms, leading to the accumulation of unfolded proteins, as protein folding represents the last energy-consuming step in the production line of the ER machinery (Weng et al., 2017). To restore ER homeostasis, unfolded proteins activate an adaptive process known as the UPR, which prevents the overloading of the ER cavity with newly synthesized proteins and activates the breakdown of unfolded proteins (Crouzier et al., 2021). If the ER stress is severe and/or prolonged, the UPR may fail to keep pace with the increased demand, resulting in unfolded proteins entering the mitochondria (Volgyi, Juhász, Kovacs, & Penke, 2015). This breach of cellular compartmentalization disrupts mitochondrial mechanisms and exacerbates the dysfunction in energy production initiated by the original stressor, such as hypoxia (Remondelli & Renna, 2017). As a last resort for the tissue, programmed apoptotic cell death pathways are triggered, primarily mediated by pro-inflammatory cytokines (Hiramatsu, Chiang, Kurt, Sigurdson, & Lin, 2015). Chronic ER stress may induce inflammatory processes (and vice versa) through UPR pathways, creating a molecular web of positive feedback loops that links ER stress, oxidative stress, mitochondrial dysfunction, protein misfolding and inflammation (Chaudhari et al., 2014).

This interconnectedness is associated with a wide range of diseases, including AD and Parkinson's disease, Huntington's chorea, ALS, traumatic brain injury, and frontotemporal lobe dementia (Penke et al., 2018).

The accumulation of non-normally folded proteins in the ER due to hypoxia has been shown to inhibit the synthesis of normal proteins, ultimately triggering ER stress (Safra, Ben-Hamo, Kenyon, & Henis-Korenblit, 2013). Furthermore, ER stress can affect mitochondrial biosynthesis and function, with the MAM playing a critical role in this interaction. Disruption of Ca^{2+} homeostasis due to ER stress can lead to cell death through the activation of mitochondrial apoptotic pathways. In addition, the UPR is activated in response to excessive stress perturbations, leading to the induction of CHOP, a transcription factor that promotes apoptosis when ER stress is prolonged (Hetz & Mollereau, 2014). The relationship between ER stress and various cellular insults, including oxidative stress and inflammation, highlights the importance of understanding these mechanisms in the context of disease pathology (Sovolyova, Healy, Samali, & Logue, 2014).

In summary, the interplay between hypoxia, ER stress, mitochondrial dysfunction, and inflammation forms a complex network that contributes to the pathogenesis of several neurodegenerative and inflammatory diseases. Continued research into these mechanisms is essential for developing therapeutic strategies aimed at mitigating the detrimental effects of ER stress and its associated pathways.

5. The pathomechanism of IRI

During ischemia, there is a lack of oxygen and nutrients, leading to a decrease in oxidative metabolism, accumulation of waste products, and depletion of high-energy phosphates, particularly ATP. The essence of ischemic injury lies in the inadequate blood perfusion, which diminishes the energy supply necessary for cellular homeostasis, resulting in deficient mitochondrial function and consequently impaired ER machinery. Ischemia initiates a cascade of complex processes that overlap in space and time, ultimately leading to cellular dysfunction (Eltzschig & Eckle, 2011). For limited periods, cells may compensate through anaerobic metabolism, which causes lactate accumulation and results in a decrease in intracellular pH. Eventually, the lack of efficient oxidative metabolism leads to the depletion of high-energy phosphate stores, halting biosynthesis and triggering ER stress

and the UPR. This breakdown of membrane functions and compartmentalization of cellular organelles culminates in necrotic cell death (Kalogeris, Baines, Krenz, & Korthuis, 2012; Zhang et al., 2024).

Paradoxically, after the restoration of blood flow, tissues may suffer additional injury from reperfusion (Zimmerman & Granger, 1994). Sudden reoxygenation increases intracellular levels of reactive oxygen species (ROS) and nitrogen radicals, which damage biomolecules and disturb redox potential, resulting in oxidative stress. These elements activate the inflammatory transcription factor NF-κB, leading to the release of pro-inflammatory cytokines that exacerbate damage caused by the reactive oxygen species (ROS) and other free radicals during reperfusion injury (Sies, Berndt, & Jones, 2017). The induction and early phase of reperfusion injury are largely characterized by the release and detection of self-derived "damage-associated molecular patterns". The immune mechanisms involved include dysregulation of glial cells in the brain, infiltration of circulating peripheral leukocytes in both the CNS and peripheral tissues, and perturbation of homeostatic regulatory processes of tissue-resident immune cells. Major mediators in this process include inflammatory cytokines, chemokines, adhesion factors, nitric oxide, inducible nitric oxide synthase, and ROS (Mizuma & Yenari, 2017; Wang et al., 2016). Tissue damage is primarily determined by the magnitude and duration of ischemia, with further damage developing during subsequent reperfusion.

Physiological adaptogenic capacity may manifest at various levels, including anti-inflammatory, anti-hypoxic, and anti-reperfusion injury effects in mammals. The simultaneous regulation of anti-hypoxic preconditioning, oxidative stress resistance, and anti-inflammatory responses is conceptually intertwined in human physiology. Autophagy, a powerful adaptive response induced by several stressors (including hypoxia, ischemic injury, inflammation, and toxin exposure), leads to lysosomal-mediated degradation of intracellular organelles (Jin, Liu, & Klionsky, 2013). This process allows the body to destroy and clear out damaged and potentially harmful cellular compartments, lipids, and proteins. Under conditions of hypoxia, ischemia-reperfusion, or inflammation, mitochondria in surrounding tissues become severely damaged, leading to a self-amplifying cascade of ROS production and self-induced pro-inflammatory processes. The induced autophagic degradation of these damaged mitochondria, termed "mitophagy," is considered an early physiological response that strongly promotes survival (Aggarwal, Mannam, & Zhang, 2016). DMT,

acting through the Sig-1R, may directly influence and fine-tune the mitophagic response, thereby preventing cell death and tissue injury.

IRIs result from these two consecutive pathological processes: one primarily involves necrosis-related irreversible losses caused by ischemia, while the other involves programmed apoptotic cell death processes. Based on results from previous in vitro studies, we offered indirect evidence that DMT may exhibit a protective role on both sides of ischemia-reperfusion injury through a Sig-1R-dependent mechanism that can mitigate hypoxic lesions (reduction of ischemic injury); furthermore, its anti-inflammatory effect is expected to decrease reperfusion injury as well. Direct evidence for the beneficial effects of Sig-1R agonists in ischemia-reperfusion injury has already been reported (Hosszu et al., 2017; Tagashira et al., 2013; Yabuki et al., 2015).

IRI is a multifaceted phenomenon affecting multiple medical domains such as organ transplantation, stroke, myocardial infarction, general brain hypoxia, cardiovascular surgery, neonatology, and cardiopulmonary resuscitation. We propose that DMT's effects may surpass the CNS, indicating a broader involvement in cellular protective mechanisms. Our in vitro and in vivo studies suggest that DMT may effectively mitigate IRI through both indirect and direct pathways.

6. In vitro DMT studies against inflammation and hypoxia

In our initial experiments (Szabo et al., 2014), we investigated the effects of DMT, its derivative 5-MeO-DMT, and the synthetic Sig-1R agonist PRE-084 on activated human primary monocyte-derived dendritic cells. Inflammation was induced using lipopolysaccharide, polyinosinic-polycytidylic acid, or other pathogen-derived stimuli. Our findings indicated that the administration of these Sig-1R agonists resulted in a suppression of pro-inflammatory cytokine production, specifically interleukin-1-beta, interleukin-6, interleukin-8, and tumor necrosis factor-alpha. Furthermore, the application of DMT was associated with an increase in the secretion of the anti-inflammatory cytokine interleukin-10. The model also demonstrated a reduction in T-cell activation, and the role of Sig-1R was confirmed through gene silencing techniques.

In our subsequent study (Szabo et al., 2016), we explored whether the activation of Sig-1R by DMT could enhance the survival of hypoxic

human cortical neurons derived from induced pluripotent stem cells, as well as monocyte-derived macrophages and dendritic cells. The results revealed that DMT provided a significant protective effect mediated by Sig-1R during severe hypoxic conditions (0.5 % O_2). The addition of DMT to the culture media resulted in an increase in cell survival rates by over two-fold compared to non-treated controls. This positive outcome was correlated with a decrease in the expression and activity of the alpha subunit of hypoxia-inducible factor 1. The critical role of Sig-1R in this phenomenon was also demonstrated using in vitro gene silencing.

Collectively, these findings suggest that DMT may exert a protective influence in the context of IRI through a Sig-1R-dependent mechanism. This mechanism appears to mitigate hypoxic damage while simultaneously exerting anti-inflammatory effects.

7. In vivo DMT studies against IRI of the brain

In a recent animal study conducted by our research team and published in 2020, we investigated the effects of DMT on reperfusion injury following an artificially induced stroke (Nardai et al., 2020). To induce transient occlusion, a filament was inserted into the right middle cerebral artery under general anesthesia for a duration of 60 min. Prior to the removal of the filament, one treatment group received an intraperitoneal bolus of DMT at a dosage of 1 mg/kg, followed by a continuous maintenance dose of 2 mg/kg/h delivered over a 24-hour period using osmotic minipumps. Concurrently, another group was administered BD-1063 (a Sig-1R antagonist (Sabino et al., 2009)), initially as a bolus dose of 1 mg/kg, followed by a maintenance dose of 2 mg/kg/h. Control animals were given a bolus of vehicle only. The volume of stroke lesions was assessed using magnetic resonance imaging 24 h after the procedure. Functional recovery was evaluated using the staircase method in two groups of pre-trained, post-stroke animals – one group received DMT, while the other received DMT in combination with BD-1063. The results indicated that animals treated with DMT exhibited a nearly 50 % reduction in lesion volume and significant improvements in functional recovery. Notably, the beneficial effects of DMT were diminished with the administration of BD-1063. Plasma samples from rats treated with DMT showed elevated levels of brain-derived neurotrophic factor and interleukin-10, while levels of interleukin-1-beta, interleukin-6, and tumor necrosis factor-alpha were decreased. We concluded that the reduction of post-stroke brain injury

following the administration of exogenous DMT is dependent on Sig-1R activation. This experimental setup appeared to align more closely with an anti-reperfusion injury model rather than an anti-ischemic one. In our most recent publication, we explored whether DMT could mitigate cerebral ischemic injury using a different experimental model (Szabo et al., 2021). Global forebrain ischemia was induced in anesthetized rats through the ligation of both common carotid arteries. To increase metabolic stress, we generated spreading depolarizations and imposed a brief (1-minute) period of hypoxia by reducing the oxygen concentration in the anesthetic gas. DMT, PRE-084 (a Sig-1R agonist), NE-100 (a Sig-1R antagonist), and asenapine (a broad-spectrum 5-HT receptor antagonist) were administered intravenously, either alone or in combination. The binding of the administered drugs to cerebral Sig-1Rs was assessed using a radioligand binding assay. The physiological effects of DMT were monitored by observing changes in cerebral blood flow, followed by histopathological analysis. Both DMT and PRE-084, as Sig-1R agonists, were found to reduce the extent of spreading depolarizations, although this effect was diminished in the presence of the Sig-1R antagonist NE-100. The involvement of 5-HT receptors was excluded, as DMT was still able to reduce spreading depolarizations amplitude even when these receptors were occupied by asenapine. Overall, DMT was shown to decrease neuronal loss and enhance astrocyte survival in a manner dependent on Sig-1R activation.

These findings align with other studies that have demonstrated the activation of Sig-1R by PRE-084 (Zhao et al., 2019) and dexmedetomidine (Zhao, Yu, Ling, Hao, & Liu, 2021) in the context of brain ischemia-reperfusion injury, suggesting that DMT has potential as an adjunctive treatment for acute cerebral ischemia. Further research is warranted to explore its potential applications in managing clinical death or neonatal asphyxia.

8. Receptor-based mechanisms for AD treatment

AD is a highly complex, multifactorial condition influenced by a diverse array of genetic and environmental factors, and it is primarily characterized by significant cognitive decline and memory impairment. The pharmacological properties of the Sig-1R and its involvement in AD have been extensively reviewed in the literature (Maurice & Goguadze, 2017; Nguyen et al., 2015; Tsai, Pokrass, Klauer, De Credico, & Su, 2014).

A functional deficiency of Sig-1R has been identified as a critical factor contributing to neuronal loss induced by β-amyloid (Aβ) peptides. Specific genetic combinations involving Sig-1R and apolipoprotein E genotypes have been shown to synergistically elevate the risk of developing AD, with the Sig-1R genotype serving as a significant risk factor in sporadic cases of the disorder (Feher et al., 2012).

While Sig-1R levels remain relatively stable during normal aging (Ramakrishnan et al., 2016), a marked decrease in Sig-1R expression has been observed in the brains of individuals diagnosed with AD (Mishina et al., 2008). Compounds that activate Sig-1R are regarded as having anti-amnestic and neuroprotective properties in neurodegenerative diseases such as AD (Marrazzo et al., 2005). Various Sig-1R agonists, including afobazole, have demonstrated protective effects on cultured neurons against Aβ 25–35 toxicity (Behensky et al., 2013). Additionally, these agonists have been shown to alleviate learning and memory deficits in mice following intracerebroventricular administration of Aβ 25–35 (Maurice, Su, & Privat, 1998).

Recently, a mixed muscarinic-1 and Sig-1R agonist known as AF710B has been utilized in mouse models of AD. AF710B exerts protective effects on synapses through the simultaneous activation of Sig-1R and a highly sensitive muscarinic-1 receptor, potentially via the formation of a hypothetical muscarinic-1-receptor-Sig-1R complex (Fisher et al., 2016). Anavex 2–73, which acts as an agonist for the intracellular Sig-1 chaperone protein, also functions as a mixed ligand for both sigma-1 and muscarinic receptors. It has been reported to bind to the Sig-1R in the high nanomolar range and to the muscarinic receptor in the low micromolar range. In the Aβ 25–35 mouse model of AD it blocked tau-hyperphosphorylation and Aβ 1–42 generation (Lahmy et al., 2013) with protective effect on mitochondria (Lahmy, Long, Morin, Villard, & Maurice, 2015).

Latest studies utilizing mouse AD model have revealed that the combination of Sig-1R agonists with donepezil produces a synergistic protective effect, indicating that Sig-1R-targeting drugs possess neuroprotective potential, especially when used in conjunction with other therapeutic agents (Maurice, 2016). Although the mechanisms underlying the neuroprotective and anti-amnestic effects mediated by Sig-1R are not yet fully elucidated, they may involve the regulation of intracellular calcium levels, modulation of Bcl-2 and caspase activity (Villard et al., 2009), and the attenuation of oxidative stress (Meunier, Ieni, & Maurice, 2006).

In a recent study, AD transgenic mice received chronic DMT treatment via intraperitoneal injection for three weeks before undergoing a water

maze test to assess cognitive function (Cheng et al., 2024). Researchers then measured Aβ accumulation in the brain and evaluated Sig-1 R levels following DMT treatment. Additionally, they investigated the effects of DMT on ER-mitochondrial contact sites and the expression of various MAM-associated proteins. The influence of DMT on calcium transport between the ER and mitochondria, as well as mitochondrial function, was also examined. Results showed a significant improvement in cognitive impairment within this model. Concurrently, Aβ accumulation was substantially reduced in both the hippocampus and prefrontal cortex. DMT treatment restored Sig-1 R levels, reinstated the expression of several MAM-associated proteins, and prevented abnormal calcium dynamics between the ER and mitochondria. In sum, DMT expresses anti-AD effects via Sig-1 R mediation by the protection of neuronal ER-mitochondria crosstalk.

8.1 Beyond the Sig-1R paradigm: DMT and neuroplasticity via serotonin receptors

The pro-cognitive and neuroplasticity-modulating roles of serotonin receptors are implicated in neurodegenerative diseases, such as Parkinson's, AD and other dementias (Winkelman, Szabo, & Frecska, 2023). This effect is mediated through multiple mechanisms (Svob Strac, Pivac, & Muck-Seler, 2016; Vann Jones & O'Kelly, 2020). One pathway involves the 5-HT2A receptor's regulation of neurotrophin gene expression, which enhances neuroplasticity in the hippocampus and neocortex (Vaidya, Marek, Aghajanian, & Duman, 1997). Another mechanism involves the 5-HT2A receptor's role in fine-tuning cortical signaling related to cognition, memory, and synaptic plasticity within cortical regions impacted by AD (Zhang & Stackman, 2015). Unlike the traditional view of neurotransmitter receptors being confined to the postsynaptic membrane within synapses, serotonin receptors are often located intraneurally at extrasynaptic sites, where they mediate prolonged metabotropic effects (Bockaert, Claeysen, Becamel, Dumuis, & Marin, 2006). Serotonin release from the raphe nuclei is crucial for restoring network function following CNS injury serving as a critical modulator in neural development, regeneration, and plasticity (Salvan et al., 2023).

Psychoplastogens are compounds capable of inducing structural and functional plasticity within brain circuits, making them promising treatments for neuropsychiatric diseases by regenerating pathological circuitry, restoring network-level function, and enhancing neuroplasticity. This

provides the brain with a critical protective constellation against long-term neurodegenerative processes (Winkelman et al., 2023). CNS plasticity arises from processes like axonal sprouting, long-term potentiation, and genomic responses, occurring across levels from gene expression to whole-brain networks.

Neuroplasticity encompasses changes in neural structure and connectivity in response to stimuli, involving mechanisms like synaptic and cortical plasticity, as well as cortical re-mapping (De Gregorio et al., 2021; Inserra, De Gregorio, & Gobbi, 2021). Neurogenesis, a component of neuroplasticity, promotes progenitor activity, precursor cell division, and dendritic and axonal growth for synapse formation. Neuroplasticity builds and reorganizes neural networks by adding or removing cellular components, including neurites and synaptic ends, and is central to learning and memory formation. It includes synaptic modification, synaptogenesis, dendritic remodeling, and axonal sprouting (Teter & Ashford, 2002), and also underlies behavioral adaptation to dynamic environments (Aleksandrova & Phillips, 2021). Besides its role in learning and adaptation, the molecular mechanisms involved may also slow down or prevent neurodegeneration at multiple levels.

Recent studies (reviewed in (Winkelman et al., 2023)) indicate that psychedelics may slow or reverse brain atrophy, large-scale neurodegeneration and associated neuroinflammation. Via their hypothetical plastogenic properties, serotonergic psychedelics are thought to catalyze neuroplasticity and reconfigure neuronal networks, activating neurotrophic pathways, neurogenesis, and cognitive flexibility to effect long-lasting neural changes (De Gregorio et al., 2021). Their rapid neuroplastic effects on cognition, learning, and memory are achieved through stimulation of synaptic plasticity, anti-inflammatory responses, and neurocircuitry reorganization, suggesting potential applications in neurodegenerative conditions characterized by cortical or subcortical atrophy (Bogenschutz et al., 2015).

Besides its Sig-1R modulatory capacity, and by targeting serotonin receptors, especially via 5-HT2A and partially 5-HT1A, DMT promotes structural plasticity and enhances connectivity in the brain (Inserra et al., 2021; Ly et al., 2018). The induced, long-term up-regulation of neurotrophic factors that support neuronal survival counteracts synaptic deficits and atrophy, a promising therapeutic domain for DMT in the potential treatment of AD and other neuropsychiatric disorders with significant neurodegenerative component (Sinha et al., 2024). While the acute perceptual and cognitive effects may stem from 5-HT2A receptor-mediated

synaptic activity, long-term neuroprotective changes appear linked to metabotropic serotonin receptor mechanisms (Bockaert et al., 2006). These findings suggest that DMT may modulate neurotransmitter systems to reverse neurodegenerative processes through inducing, maintaining and fine-tuning neuroplasticity.

9. Beyond the brain: ALS

ALS is a severe neurodegenerative disease marked by the progressive degeneration of motor neurons in the brainstem, motor cortex, and spinal cord, leading to paralysis and ultimately death. Key pathological features include calcium dysregulation, ER stress, mitochondrial dysfunction, accumulation of misfolded proteins, neuroinflammation, and motor neuron degradation (Fukunaga, Shinoda, & Tagashira, 2015; Mancuso et al., 2012). Research has shown that mutations in the Sig-1R gene and the loss of Sig-1R contribute to a juvenile form of ALS, with the collapse of MAM serving as a shared pathological mechanism in Sig-1R-linked ALS (Al-Saif, Al-Mohanna, & Bohlega, 2011; Watanabe et al., 2016). ALS patients have shown significantly reduced Sig-1R protein levels in the lumbar spinal cord. Furthermore, abnormal Sig-1R modifications, such as accumulation in ER structures and enlarged C-terminal regions, have been observed in alpha motor neurons during ALS progression (Prause et al., 2013). Given Sig-1R's role in regulating ER-associated degradation, its accumulation and co-localization with abnormal protein aggregates may indicate a compensatory effort to clear misfolded proteins in ALS.

Efforts to target Sig-1R in ALS treatment have shown promising results in both in vitro and in vivo models. The neuroprotective effect of Sig-1R in motor neurons has been confirmed in ALS mouse models (Mavlyutov, Guo, Epstein, & Ruoho, 2015), with the Sig-1R agonist SA4503 suppressing motor neuron damage in experimental settings (Ono et al., 2014). Additionally, treatment with PRE-084 extended lifespan and slowed ALS progression in an ALS mouse model (Mancuso et al., 2012), while chronic PRE-084 treatment improved motor neuron survival and locomotor function in the wobbler mouse, a model of spontaneous motor neuron degeneration (Peviani et al., 2014). These findings suggest that targeting Sig-1R with agonists may reduce protein aggregation and slow disease progression by enhancing Sig-1R's chaperone activity.

Sig-1R co-localizes in the C-terminals with INMT, the enzyme responsible for producing the Sig-1R agonist DMT (Mavlyutov et al., 2012). INMT methylation also neutralizes toxic sulfur and selenium derivatives, creating a synergistic effect with DMT that may reduce oxidative stress in motor neurons. Thus, small-molecule activation of Sig-1R and INMT presents a potential therapeutic approach for ALS treatment.

10. Conclusions

This paper offers both indirect support from existing literature and direct evidence from our published in vitro and in vivo studies suggesting that DMT may have beneficial therapeutic effects in brain IRI and neurodegenerative disorders. These findings could lay the groundwork for follow-up human trials and inform new therapeutic approaches for these conditions. Inspired by the outcomes of our DMT stroke study, Algernon Pharmaceuticals, a Canadian drug development and repurposing company, has completed a feasibility study and finalized its Phase 2 clinical trial design for a DMT stroke study. Algernon's goal is to determine whether DMT infused for several hours at sub-psychedelic concentrations can effectively treat ischemic stroke, potentially minimizing damage and enhancing recovery. Current medical interventions for IRI have limited effectiveness, with no robust preventive measures available for reperfusion injury following thrombolytic stroke therapy. While the ischemic phase of stroke is typically unpredictable, surgeries involving controlled artery clamping could leverage DMT's anti-hypoxia effects, addressing both aspects of IRI pathology.

Concerns may arise regarding DMT's clinical use due to its mind-altering effects, and some may argue that alternative Sig1-R agonists with different serotonin receptor profiles are available. However, as an endogenous ligand, DMT most likely engages a unique, multifaceted anti-hypoxia, anti-neuroinflammatory, neuroplastic, and neuroprotective mechanism that synthetic compounds may not fully replicate. It is important to note that the doses of DMT utilized in these animal studies were close to the psychedelic range, as indicated by head-twitching observed in previous rodent studies, which raises ethical and practical concerns regarding human clinical applications. DMT does possess psychedelic effects, which are often sought after by substance users. However, the potential for addiction and the risk of long-term psychological disturbances associated with DMT are considered to be

extremely low (Gable, 2007). The experiences induced by DMT typically do not create a strong desire for repeated use (Winstock, Kaar, & Borschmann, 2014). Furthermore, the medical emergencies that may benefit from DMT's clinical use often involve unconscious patients or those under general anesthesia. Notably, DMT has been shown to be safe in alert individuals under controlled medical supervision (Strassman & Qualls, 1994a, 1994b). Nevertheless, for stroke patients undergoing general anesthesia, DMT's psychedelic effects should be of minimal concern, and similar reasoning applies to unconscious patients undergoing cardiopulmonary resuscitation, who are at risk of permanent brain damage in a narrow treatment window. Our study on global brain hypoxia brings hope for these cases. In addition, DMT could be given along with a 5-HT 2 receptor antagonist which would block the psychedelic but not the Sig-1R-related effects.

Cardiac arrest remains a prevalent and often fatal condition, even when rapid and well-executed cardiopulmonary resuscitation is performed. While partially successful resuscitations may extend life, they do not necessarily improve long-term quality of life due to hypoxic brain damage. Each year, approximately 290,000 in-hospital cardiac arrests are reported in the United States. Despite its prevalence, options for pharmacological intervention are limited. If DMT could extend the critical period of clinical death, this might increase the success rate of resuscitation efforts and improve long-term functional outcomes. Additionally, testing DMT or its analogues in perinatal settings to prevent ischemic brain injury in newborns could lead to significant improvements in survival and quality of life. A more open stance on incorporating findings from new DMT research could enhance outcomes across various medical fields.

In conclusion, DMT possesses properties that extend beyond its psychedelic effects, exhibiting bioactivity with broader therapeutic potential. Its Sig-1R-mediated actions suggest a universal modulatory role in cellular stress responses at the endoplasmic reticulum-mitochondria interface. Our arguments advocate for a shift in research focus from DMT's traditional classification as a serotonin receptor-modulating psychedelic toward its potential in promoting adaptive somatic and neurophysiological processes.

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Conflict of interest

The authors declare that they have no conflict of interest.

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