The protective role of dimethyltryptamine and its analogues against ischemia-reperfusion injury: Commentary

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Introduction

The article entitled “N,N-Dimethyltryptamine [DMT] attenuates spreading depolarization and restrains neurodegeneration by sigma-1 receptor activation in the ischemic rat brain” by Szabo et al. published recently in Neuropharmacology [1] is the last one in the series of studies on the potential benefits of DMT administration in different clinical forms of ischemia-reperfusion injury (IRI). The larger scope of the project – initiated and organized by Ede Frecska – is to collect support for a hypothesized biological function of this and related endogenous hallucinogen compounds such as 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), 5-hydroxy-N,N-dimethyl-tryptamine (bufotenine) [2]. Establishing beneficial effects of these naturally occurring components of the mammalian body is a necessary but not satisfactory criterion for a physiological role. We wish to mention here early on, that regardless of the fulfilment of this second bold aim, if accumulating evidence with independent replications support our findings on the tissue (especially neuro-) protective effects of DMT and its analogues, than ways may open for therapeutic applications and their current classification as Schedule I agents may change for better. The latter carries a stigma and impedes scientific research of these neurochemically very potent and enigmatic molecules.

The hallucinogenic properties of DMT were discovered in 1956 by the Hungarian psychiatrist Stephen Szara [3], and since that time pharmacological studies have been concentrating on its nervous system effects under the umbrella of a psychopathological paradigm (notably experimental psychosis and transmethylation hypothesis of schizophrenia). DMT has significant affinity at 17 known receptor sites [4] and activation of the serotonin (5-HT) 2A receptor subtype is supposed to be responsible for hallucinations [5]. Since 5-HT_{2A} receptors play a key role in regulation of sensory processing and cognition, hypotheses on DMT’s biological function are mostly based on its involvement in sensory, emotional and cognitive integration [6]. The first break off from the ruling concept was in 2005, when the pathology of the endogenous psychoactive tryptamines was reconsidered with an assumed anxiolytic role for DMT at low doses [7]. Behind this reappraisal was the finding in 2001 that DMT and other tryptamine hallucinogens elicit a robust response at the trace amine receptor [8].

The next step was to move away from the dominating psychoactive focus into the direction of somatic effects by the discovery of sigma-1 receptor (Sig-1R) binding profile of DMT and [9] with the suggestion that DMT is an endogenous agonist at this site. Our series of DMT studies got started here with a theoretical framework elaborated in the paper on “A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity” [10].

The Sigma-1 Receptor (Sig-1R)

The Sig-1R is an intracellular chaperone molecule located between the endoplasmic reticulum...
and mitochondria in many cell types. Its function is essential for metabolic receptor signaling and for survival against cellular stress, particularly endoplasmic reticulum stress [11]. Prolonged endoplasmic reticulum stress results in unfolded protein response with an outcome of apoptotic cell death. The function of the Sig-1R can be conceptualized as a safety (some sort of buffer) mechanism against cellular stress by controlling Ca$^{2+}$ efflux from the endoplasmic reticulum to mitochondria and optimizing high-energy phosphate synthesis for the endoplasmic reticulum [12]. Sig-1R activation down-regulates the apoptotic cell death pathways by interacting with the mitochondron-endoplasmic reticulum-nucleus signaling mechanisms. By possessing both chaperone and receptor function the Sig-1R represents a pluripotent modulator in living systems and this fact suggests its involvement in the etiopathology and/or therapy of many diseases [11].

The endogenous hallucinogen DMT is one of the natural ligands of the Sig-1R. The affinity of DMT for Sig-1R is modest with a K$_D$ of 14.8 μM [9], which means – that depending on the number of sparse sites – higher concentrations of DMT might be necessary for saturation of the receptor as compared to its lower K$_D$ at the 5-HT receptor subtypes. However, the two DMT synthesizing enzymes (aromatic-L-amino acid decarboxylase and indolethylamine-N-methyltransferase) are co-localized in mammalian brain tissues [13], and the last one is in close vicinity to the Sig-1R in motor neurons [14]. These facts may indicate, that physiologically significant concentrations of DMT can be reached at the Sig-1R site.

**Possible Biological Role of DMT**

Originally, it was assumed that the Sig-1R might be involved in the DMT-induced psychedelic effects [15]; however, this does not seem to be correct, since many drugs bind to Sig-1R without any hallucinogenic effect. We have been depicting another view instead. Since Sig-1R stimulation mitigates intracellular stress, regulates immune processes and protects against apoptotic cell death, one may suppose similar outcome from DMT administration in several medical conditions like stroke, general brain hypoxia, traumatic brain injury, myocardial infarct and other pathologies including IRI's or neuroinflammation. Two recent reviews address the potential use of psychedelics (DMT included) in brain injury and inflammation [16,17]. The Sig-1R is also known to regulate morphogenesis of neuronal cells, such as neurite outgrowth, myelination, and synaptogenesis [18], therefore, neuroregeneration is reasonably expected from DMT action. Indeed, Dakic et al. [19] were the first to report that in brain organoids 5-MeO-DMT (a closely related congener of DMT) favorably influenced neuroplasticity and neuroprotection, apoptosis, morphogenesis/maturatation of dendritic spines, while inhibited factors involved in neurodegeneration and cell death. Alternative technique in monolayer neuronal cultures did not show the same effects, suggesting that a more complex network is required for these effects.

In the seminal 2013 paper [10] we went further, and concluded that the biological function of DMT may extend central nervous activity and encompass a more universal role in cellular protective mechanisms (i.e., not only neuroprotective but tissue protective in general). This theoretical work has set stage for experimental studies (described below) wherein we provided evidence of DMT effects that can orient its basic science research toward new directions (esp. role in cellular adaptation), and may support the development of a general framework regarding the clinical application of DMT – or its analogues – in different forms of IRI.

**The Ischemic/reperfusion Injury**

IRI (sometimes just one side of the dyad) remains one of the most challenging problems in emergency medicine, intensive care, cardiovascular surgery, stroke management, cardiorespiratory resuscitation, neonatology, sepsis therapy, and organ transplantation. Ischemic injury occurs when the blood supply to an area of tissue is cut off. During ischemia, the lack of oxygen and nutrients leads to depletion of high-energy phosphates, a decrease in oxidative metabolism, since the function of mitochondria and consequently the endoplasmic reticulum machinery becomes deficient. For a limited period, ischemic cells may compensate with switching to anaerobic metabolism. Eventually, due to lack of the efficient oxidative metabolism, the biosynthesis arrives at a standstill, resulting in severe endoplasmic reticulum stress and unfolded protein response. Finally, membrane functions break down, and the compartment-lesion of cellular organelles results in necrotic cell death [20].

After the return of blood flow, the tissues will suffer from an extra injury from reperfusion. Sudden reoxygenvation causes oxidative stress by the intracellular increase of reactive oxygen species and nitrogen radicals, compounds that change redox potential and cause destruction to biomolecules. In this early phase of reperfusion injury, “damage-associated molecular patterns” activate pro-inflammatory cytokines and chemokines which expand the pathological cascade and lead to apoptotic cell loss. In sum, tissue damage is determined primarily by the magnitude and duration of the ischemia but further injury develops during the subsequent reperfusion [21]. IRI is the outcome of these two consecutive processes.

**In vitro Studies Indicating Possible Benefits of DMT Administration in IRI**

Our theoretical paper [10] was followed by two in vitro studies [22,23]. In the first study [22] we evaluated the effects of DMT, its derivative 5-MeO-DMT and the synthetic Sig-1R agonist PRE-084 on human primary monocyte-derived dendritic cells after provoking inflammation by lipopolysaccharide, polyI:C or pathogen-derived stimuli. We found that treatment with Sig-1R agonists inhibited the production of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α, whilst also resulted in increased secretion of the anti-inflammatory cytokine IL-10. The T-cell activating capacity also diminished in this model. The involvement of Sig-1R was confirmed by gene silencing.

In another study [23] we tested if Sig-1R activation can improve survival of human cortical neurons (obtained from induced pluripotent stem cells), monocyte-derived macrophages and dendritic cells in hypoxia. Results showed that DMT was greatly effective through the Sig-1R in severe hypoxia (0.5% O$_2$). The outcome was associated with the decreased expression and function of the alpha subunit of the hypoxia-inducible factor 1.

Based on these findings we offered indirect evidence that the DMT may exhibit a protective role on both side of the IRI through a Sig-1R dependent mechanism by mitigating hypoxic lesions on
one hand and exerting anti-inflammatory effect on the other. There is already ample evidence indicating the beneficial effect of Sig1-R agonists in IRI [24-26].

Therefore, we planned in vivo animal experiments to test the hypothesis that DMT reduces either arm (or both) of the IRI process. A kidney IRI experiment [27] used DMT in the ischemic and reperfusion phase both, a stroke study has been completed [28] focusing on effects in reperfusion, and the last one [1] this comment is about targeted the ischemic side of the pathology.

In vivo Studies Indicating Benefits of DMT Administration in IRI

An experiment was carried out by Nemes et al. in 2019 [27] in order to investigate the metabolic, microcirculatory parameters and histologic changes after administration of DMT in a rat kidney model of IRI. Briefly, in anesthesia animals had their both kidneys exposed. In the experimental group, the right renal vessels were ligated, and after 60 minutes the right kidney was removed. The left renal vessels were also clamped for 60 minutes then released, which was followed by 120 minutes of reperfusion. Half of the experimental animals received intramuscular DMT in a dose of 7.2 mg/kg 15 minutes before the ischemia and 15 minutes before the reperfusion, while in the rest there was no additional treatment. In the control group, no surgical and/or pharmacological intervention happened besides the exposure. Blood samples were taken, laser Doppler measurement was performed for monitoring microcirculation, and both kidneys were evaluated histologically. The control and treated experimental groups had similar microcirculation after 120 minutes of reperfusion. Tubular necrosis was moderate under the effect of DMT, and severe without it. Histologic deformities were also less in the treated when compared to non-treated animals. In conclusion, the study showed that with the use of DMT microcirculation recovered at the end of 120 minutes reperfusion, and the histologic changes characteristic to IRI were reversible, hence DMT can be used for protection of the donor kidneys during transplantation.

In a more recent animal study published in 2020 by Nardai et al. [28] we examined the effects of DMT on reperfusion injury after experimentally induced stroke. Transient occlusion was induced under general anesthesia by placement of a nylon line into the right middle cerebral artery for 60 minutes. Before removal of the filament one treatment group received an intraperitoneal 1 mg/kg bolus of DMT followed by a maintenance dose of 2 mg/kg/h delivered over 24 hours via osmotic minipumps. In parallel with the DMT application, the Sig-1R antagonist BD-1063 was administered (1 mg/kg bolus +2 mg/kg/h maintenance dose) to another group. Control animals were given vehicle bolus only. 24 hours later the volume of the stroke lesions was measured by magnetic resonance imaging. Functional recovery was evaluated with the staircase method in two separate groups (DMT and DMT+BD-1063 treated) of pre-trained animals for 30 days. DMT treated animals indicated smaller lesion volume and better functional recovery, while BD-1063 mitigated the DMT effects. Plasma samples of DMT-treated rats showed higher brain-derived neurotrophic factor and IL-10 levels, while the concentration of IL-1β, IL-6 and TNF-α was decreased. The authors concluded that there was a Sig-1R dependent reduction of post-stroke brain injury following the administration of exogenous DMT administration.

The question if DMT can alleviate cerebral ischemic injury was addressed in our most recent publication [1]. In this complex study, global forebrain ischemia was induced in anesthetized rats by ligature of both common carotid arteries. In order to increase the metabolic stress investigators triggered spreading depolarizations (SDs) and superimposed a transient (1-minute) episode of hypoxia by controlled withdrawal of O2 from the anesthetic gas mixture. Drugs such as DMT, Sig-1R agonist PRE-084, Sig-1R antagonist NE-100 and the broad-spectrum 5-HT receptor antagonist asenapine were given intravenously alone or in combination. The affinity of drugs for cerebral Sig-1R was evaluated with a radioligand binding assay. The physiological effect of administered DMT was monitored by the assessment of cerebral blood flow changes followed by comprehensive histological examination. Both Sig-1R agonist (DMT and PRE-084) mitigated SDs, with less impact under NE-100 antagonism. The involvement of 5-HT1Rs were ruled out since when those were occupied by asenapine, DMT was still able to decrease SD amplitude. Altogether, DMT reduced neuronal loss and improved astrocyte survival in a Sig-1R dependent manner. Based on these findings, DMT may be considered as adjuvant in the treatment of acute cerebral ischemia, and further studies for the management of clinical death or perinatal asphyxia are warranted.

Future Directions

We have an ongoing retinal IRI animal study following a protocol similar to the outlined above. Soon we expect to repeat the two in vitro studies [22,23] on hypoxia and inflammation with the use of bufotenine and psilocyn (the latter not and endogenous hallucinogen, though). The usefulness of DMT in organ transplantation should have to be expanded by not only investigating its application under removal of the donor organ, but during its storage and implantation into the recipient (reperfusion phase). Global prevalence of ischemic stroke in 2019 was 77.2 million, and that of intracerebral hemorrhage was 20.7 million. The latter may also be a target in clinical studies. The Canadian company Algernon Pharmaceutical Inc. has recently announced their plan to conduct Phase 2 trials on the treatment of ischemic stroke by their DMT compound.

Nowadays, there are about 500,000 open-heart surgeries performed each year worldwide. In most of the cases, this invasive procedure is complicated by IRI and therapy can only address the consequences (e.g., arrhythmias, low cardiac output) and not the cause itself. Contrary to stroke, when the ischemic phase cannot be predicted, in surgery the clamping of the arteries is under full control, therefore the antihypoxia effect of DMT can be utilized influencing such way both arm of the IRI pathology. One may also come up with testing DMT or its analogues in perinatal indications against ischemia of the baby’s brain with a hope of life saved and made more meaningful.

Cardiac arrest is common and associated with a high mortality rate, frequently in spite of the timely and properly applied cardiopulmonary resuscitation (CPR). Partially successful CPRs may give years to life, but life to those years not. An estimated 290,000 in-hospital cardiac arrests occur each year in the United States. Despite this high prevalence, pharmacological management of this fatal condition is limited. If DMT can extend the critical period of clinical death, that may not only result in higher number of successful CPRs but better functioning on the long run. An increased awareness with regard to optimizing clinical care and new research with DMT analogues might improve outcomes.
Beyond practical applications, our main theoretical conclusion is that DMT (and possibly its analogues) is not only psychoactive but also bioactive in general. Its Sig-1R dependent actions point toward a universal regulatory role in cellular stress-induced changes at the endoplasmic reticulum-mitochondria interface. Our ongoing efforts are not based on the traditional model of the role of DMT as a serotonergic hallucinogen, but rather focused on its potential role in adaptive somato-physiological processes and possible use in medical emergencies.

References


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