MIND FOUNDATION

Not in your third eye

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Is there DMT in the brain? What could it be doing there? These questions have been on the minds of psychedelic researchers for decades, and answering them was never going to be simple. New research goes beyond attempts to prove romantic ideas about DMT release from the pineal gland during near-death experiences. Through looking at individual neurons, this research indicates that DMT might have a role as a non-canonical neurotransmitter involved in protecting the brain from physical and psychological stress. A theme emerging from the research updates the original question: what if DMT is naturally neuroprotective?

From the Amazon to the West and back to Ancient Egypt

Neurotransmitters are small molecules secreted in the nervous system to relay information between different neurons. Many of them – serotonin, dopamine, and adrenaline, to name a few – belong to the chemical class of monoamines. The most potent naturally occurring psychedelic, N,N-dimethyltryptamine (DMT), belongs to this same class of molecules. DMT can be found in trace amounts in animal nervous systems (including mammals), but it hasn't been directly proven to act as an endogenous neurotransmitter.1 It is more common and better understood in plants, where it helps defend some species from herbivorous animals.2

Humans have been extracting DMT from plants for centuries. It isn't orally active due to the presence of monoamine oxidase (MAO), an enzyme that degrades DMT, in the human digestive tract. Amazonian shamans have known how to circumvent this for centuries, combining a DMT-containing vine with plants containing MAOIs, or monoamine oxidase inhibitors, that stop the degradation of DMT. The psychedelic brew resulting from this mixture is known as *ayahuasca*, from aya (*spirit*) and waska (*vine*).3

Ayahuasca is inseparably intertwined with the mythogenesis and spirituality of South American indigenous tribes. Analogously, as DMT entered Western awareness, it easily found its place in literature and philosophy. Its biological properties have also intrigued scientists since its first synthesis in 1931. Because of DMT's

similarity with serotonin, it was tempting to hypothesise that it might naturally occur as a neurotransmitter in the human body. Where could such a peculiar neurotransmitter be found? Popular conjecture, borrowing concepts from both science and mythology, placed it in the pineal gland.

The primary role of the pineal gland is regulating sleep patterns by producing melatonin. But the history of this pea-sized structure in the forebrain is much more romantic. In ancient Egypt, it represented the eye of the sky god Horus, while in India it has been associated with the “third eye”, a mythical gate to higher consciousness. A modern incarnation of these stories originated from *DMT: The Spirit Molecule,* a book in which author and psychiatrist Rick Strassman, MD, postulates that large quantities of DMT may be secreted in the dying brain, enabling the transition of consciousness from one life to the next.4

Life and death

Since the inception of Strassman’s theory, the presence and purpose of DMT in the pineal gland have been subjects of heated debate. While it hasn’t thus far been isolated directly from human brains, experiments in both humans and rats demonstrate that their brains – including the pineal gland – contain enzymes necessary for the synthesis of DMT.1

DMT’s potential involvement in near-death experiences is hard to either prove or disprove in humans, but attempts have been made in rats. Research has shown that rat brains contain DMT and that its concentration increases following induced cardiac arrest.1,5 Could this mean that these lab rats have gone through a near-death experience? Is this experience mediated by DMT, or is DMT just a metabolic waste product of a stressed organism?

Experimental results offer limited insight. If anything, DMT might be just one part of the veritable brainstorm of neurotransmitters (including serotonin, dopamine and, noradrenaline) that gets released in response to the severe stress of cardiac arrest.1 Moreover, even though the concentration of DMT increased, it was not possible to determine whether the increase corresponded to an exogenous psychedelic dose. While some researchers believe this to be the case, others point out it is unknown how low physiological quantities of endogenous DMT could be stored to be released *en masse,6* as well as the biological reaction that such a release would trigger. Current scientific knowledge lacks the smoking gun needed to directly implicate DMT in near-death experiences: a well-characterised biochemical mechanism.

The smoking gun?

One-size-fits-all solutions are rare in biology. Neurotransmitters and psychedelic compounds alike act upon multiple brain regions, interact with different receptors with varying specificity, and trigger a wide spectrum of biochemical and genetic signalling cascades. DMT is no different, and while it was originally considered to exert its effects mainly via the serotonin 2A receptors, new targets for it have been found. One of these new targets, the sigma-1 receptor (Sig1R), is not *the* answer to the puzzle of DMT. It does, however, present us with several intriguing puzzle pieces.

Sig1R is unusual. Its origins are a mystery: In evolutionary terms, it is more closely related to a fungal enzyme called sterol isomerase than to any mammalian neurotransmitter receptor.7 Scientists are uncertain about how to interpret this finding, especially considering the fact that this particular fungal enzyme was first isolated from a fungus that produces alkaloids similar to LSD.

While many receptors specialise in relaying neurotransmitter signals either on the cell membrane, inside the cell, or in the nucleus, Sig1R is unusual because it can do all three. On the membrane, it can interact with other neurotransmitter receptors and change their function by forming complexes with them. When it’s inside

the cell, it binds anti-stress proteins and aids them in performing their functions.8 In the nucleus, it recruits other proteins that bind to DNA and activate or deactivate different genes via epigenetic mechanisms.9

This multifunctional receptor is known as an ‘‘orphan”, which means scientists haven’t yet identified its main activating neurotransmitter. It was first suggested that Sig1R could be a subtype of opioid receptors, but scientists later found that other compounds bind to it as well, including cocaine and the sex hormone progesterone.10 More recently, evidence has mounted for speculations that DMT might activate this receptor.

The first indication that this might be the case came from cell culture research, where it was demonstrated that DMT can bind to Sig1R. Mouse research expanded on this finding and showed that mouse behaviour under the influence of DMT doesn’t change when serotonin and dopamine receptors were blocked. But after their Sig1R receptor had been deactivated, the mice stopped reacting to DMT. These results have led the researchers to conclude that Sig1R is one of DMT’s main targets.11 Another clue comes from the fact that in the synapses connecting different neurons, Sig1R is located close to an enzyme involved in DMT synthesis.12 This led some researchers to wonder whether Sig1R, rather than 5HT-2A, is the main mediator of DMT’s psychedelic effects.

The powers of the sigma 1 receptor

What happens in the cell when DMT activates Sig1R? Some answers come from cell culture research. Recent studies have found a role for DMT in both the immune response and the anti-stress response of individual human cells. In immune cells, DMT was shown to activate the production of anti-inflammatory molecules.13

In a similar study, human neurons in cell culture were deprived of oxygen. Neurons quickly die when they don’t have enough oxygen, but treatment with DMT and the subsequent activation of Sig1R enabled more of them to survive.14 This finding offers a link back to Rick Strassman: If DMT helps stressed *cells*, could it also be helping whole organisms in states of stress – when close to death and severely oxygen-deprived? While it is tempting to speculate, it is important to keep in mind that neurons in the brain function in a complex, context-dependent way. Observing individual neurons in culture shows scientists what is happening inside them, but says little about how they interact with each other in a living, 3D brain.

Presently, this gap has not yet been bridged. Researchers have not tested Sig1R activity in intact brains undergoing hypoxia or other types of physiological stress. In a dying brain, DMT might be helping neurons to survive—but survival alone doesn’t tell us what those neurons are doing or how their activity might create the visions characteristic of near-death experiences. Lacking direct evidence, we may take some hints from brain imaging studies and attempt to connect them with known Sig1R mechanisms.

Looking at people’s brains on DMT and ayahuasca, researchers observe altered activity in the visual and auditory centres of the brain, as well as memory-related regions. These include centres for perception and processing of negative emotions and sad memories, memory retrieval centres, and the amygdala (a brain region commonly associated with social and emotional processing, including fear, anxiety and aggression).15,16

Dr. Antonio Inserra, a researcher from Flinders University in Adelaide, attempted to reconcile the molecular and whole-brain perspectives and formulated an intriguing hypothesis about the roles Sig1R could play in these brain activities.7 His analysis focuses specifically on the role of DMT in trauma processing, a phenomenon which garnered his interest due to anecdotal reports from PTSD patients whose symptoms were reduced after ayahuasca sessions. He speculates that Sig1R might form complexes with other receptors and boost signal transmission and synaptic plasticity in memory centres, which could help retrieve and reprocess traumatic memories. He further points out that Sig1R in the nucleus serves as an epigenetic regulator,9

meaning that it recruits enzymes that add different tags to DNA and histones (the proteins around which DNA is coiled in the cell) in order to turn genes on and off. It has long been understood that epigenetic mechanisms have an important role in all aspects of memory forming and remodelling. Because of this, Inserra suggests that some of the mechanisms through which ayahuasca treats trauma may be mediated by Sig1R epigenetics in the brain's memory centres.

Back to the Amazon: will new research bridge the gap?

A new study from Dr. Simon Ruffell, a research associate at the King's College London, also links DMT, Sig1R, and epigenetic regulation. His team, supervised by Prof. Celia Morgan (University of Exeter), followed participants in ayahuasca ceremonies in the Amazon to investigate how these experiences impacted their traumatic memories. The participants reported significant, long-lasting decreases in depression, anxiety, and general distress. In order to find out why, Ruffell's team collected saliva samples from them and analysed changes in the epigenetic tags on their DNA. They discovered that the Sig1R gene is epigenetically changed in some participants (unpublished results presented at the ICPR2020 conference). Since we know the receptor itself is involved in epigenetic modulation, this might be just the beginning. Which other genes do we see epigenetically modified after ayahuasca sessions? Ruffell's epigenetic research may offer more clues not only about how DMT works with Sig1R on an epigenetic level but also about the epigenetics of memory as such. No matter what other results come out of this study, it already serves as an important bridge between the lab and the ceremony; between the cell, the brain, and the experience.

The current state of DMT research resembles disjointed puzzle pieces. While there are several indicators that there might be naturally occurring DMT in the human brain, its locations and functions remain elusive. More data is available about how ayahuasca and exogenous DMT work, both in the cell and in the brain, but we can't yet justify extrapolating the roles of endogenous DMT from these findings.

Nevertheless, a variety of speculative theories have recently surfaced. While some researchers are focusing on DMT's potential anti-inflammatory and neuroprotective roles, others look at the brain imaging and trauma studies and point towards its possible effects on memory-remodelling. Both might prove to be true, and both can be placed in the context of Rick Strassman's theory that DMT is present in human brains to alleviate the effects of massive physiological stress, such as in oxygen-deprived neurons during near-death experiences. Could the dying brain be releasing endogenous DMT to keep itself alive for as long as possible? If so, the commonly reported characteristics of near-death experiences—including visions and one's "life flashing before one's eyes" —might simply be side effects. In the cases of neuron survival and memory processing, research so far points towards the multifunctional, mysterious Sig1R receptor as a key actor in these processes.

While the intricacies of its molecular mechanisms have yet to be fully described, the multifunctional Sig1 receptor is now firmly established as a target of DMT, and this opens new lines of inquiry. Perhaps the most exciting new research will include investigations into how DMT and Sig1R affect epigenetic regulation. Information about which genes they activate or deactivate could put the findings from cell culture research into the context of whole organisms. Epigenetic mechanisms lie at the very foundation of our dynamic interactions with the world, and with our own minds. Understanding how these mechanisms help store and remodel memories may help us formulate a coherent biological model of the therapeutic effects of the psychedelic experience.

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