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Letter to the Editor

The next bet for cerebral aneurysms treatment: Psychedelics

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INTRODUCTION

Years of stigma have impeded study into the medicinal benefits of psychedelic substances, despite their widespread use for millennia.[8] Following the adoption of the Controlled Substances Act in 1970, clinical research involving psychedelic substances ceased noticeably. Now, a handful of recent clinical investigations have been conducted after more than 2 decades. Consequently, new pieces of evidence emerged recently to back the usage of psychedelics in treating various diseases, including neurological conditions. Therefore, in this paper, we opt to present a discussion about the potential application of psychedelics as anti-inflammatory agents in treating intracranial aneurysms and possibly in growth prevention for unruptured ones.

The most extensively researched and culturally relevant psychedelics, including lysergic acid diethylamide (LSD), mescaline, psilocybin, and dimethyltryptamine, are considered "classical" psychedelics. Despite having a wide variety of molecular structures and targeted receptors, psychedelics share the ability to induce profound changes in consciousness, sensory perception, sense of time distortion, and reality perception. There is an evidence that stimulation of 5-HT2A receptors (a class of serotonin receptors) is the major mechanism underlying the psychological experience of these psychedelics and the anti-inflammatory action. However, these substances are known to operate at different receptors. In neuroscience and neurosurgery, psychedelics have been investigated to have a role in neuroplasticity, memory, brain injury, and neuroinflammation.[6]

The formation of intracranial aneurysms and their tendency to rupture is of clinical importance. Observation, along with expectant management, microsurgical clipping, and/or endovascular coiling are the current modes of management. Despite technological advancements, surgical procedures are invasive and linked to considerable risk of complications. However, recent investigations on humans and animals indicate that inflammation plays a crucial role in aneurysm development and progression to rupture. The modulation of this inflammatory process may have clinical relevance.[5] Psychedelics have been proposed to be the fourth anti-inflammatory group of drugs, along with nonsteroidal anti-inflammatory agents, steroids, and biologics.[8]

THE ANTI-INFLAMMATORY EFFECTS OF PSYCHEDELICS

Psychedelics promote their anti-inflammatory functions by activating the serotonin 5-HT2A receptor. 5-HT2A is the most abundant serotonin receptor in the body. It's on basically all tissues

and cell types, including immune-related types, and the brain has most 5-HT2A receptors.[6,8] Despite human trials investigating the psychedelics' inflammatory properties, which have not yet been established, animal models of human inflammatory-related disorders have revealed significant effects in the studies. Scientists have long recognized serotonin as a chemical related to inflammation, as inflamed tissues have raised serotonin levels and a greater number of serotonin receptors. Researchers have connected serotonin to neuroinflammation in the brain and demonstrated that SSRI antidepressants are anti-inflammatory.[3] It has not been determined if elevated serotonin levels and their receptors are causal or reactive. Depending on the tissue and region of inflammation, serotonin has both pro- and anti-inflammatory effects, according to studies.[2]

In contrast to steroids, which induce widespread systemic immunosuppression, psychedelics induce an anti-allergic pattern of cytokine production.[7] In other words, psychedelics may target several pathogenic immune responses without exposing the body to the risks of full immune suppression (e.g., severe infection) or the probable adverse effects of current biologics (e.g., malignancy and cardiovascular disease). Rather than an abrupt decrease of the response or "single-target" strategies, precise modulation of the inflammatory response is crucial for improved outcomes.

Preliminary research has shown that psychedelics, including LSD, inhibited inflammation induced by the master inflammatory cytokine tumor necrosis factor-alpha (TNF-α) in smooth muscle cells taken from rat aorta.[10] All psychedelics tested from various structural classes exhibit anti-inflammatory activity as potent as steroidal drugs for preventing TNF-mediated inflammatory processes in aortic smooth muscle cells. Therefore, a potential rationale may lead us to propose that the smooth muscle inflammation within the wall of the aneurysm in the brain may benefit from the treatment with psychedelics. In addition, the location of the aneurysm in the brain and the abundance of the 5-HT2A receptor intracranially may make a good place for the psychedelic agents to impose their pharmacological effects. Moreover, the precision of targeting the inflammation within the affected area in the brain instead of the systemic effects accompanying other agents such as steroids or biologics may render a good outcome in the patients. However, the psychedelics' effects on perception, and consciousness, may result in unfavorable medical options for the patients.

NEUROINFLAMMATION AND INTRACRANIAL ANEURYSMS

Hemodynamic stress and inflammation play an essential role in forming intracranial aneurysms. Inflammation is also associated with aneurysmal growth and subsequent rupture. Moreover, hemodynamic stress may also modify endothelial intrinsic signaling. Aoki *et al*. demonstrated that hemodynamic force activated the pro-inflammatory pathway PGE2-EP2, which then amplified chronic inflammation in an NF-B-dependent manner, resulting in elevated production of various cytokines, including IL-6, TNF-α, and IL-1.[1,5] These cytokines cause the recruitment of inflammatory cells (macrophages are the predominant) and the commencement of the inflammatory process in the aneurysm wall.[4,5] Several lines of management have been proposed for the medical treatment of this pathology, including biologics (tolylsam as a selective MMP-2 and MMP-9 inhibitor). However, the concept of using psychedelics to target the inflammatory pathways within the aneurysmal wall has not yet been established. Psychedelics may have a role in the early stages of treatment by counteracting the growth and preventing intracranial aneurysm rupture.

CONTROVERSIES

Psychedelics have anti-inflammatory properties, which may benefit patients with underlying intracranial aneurysms. This opinion may be backed up by the recent of these drugs in different medical illnesses. In addition, as the classical surgery that we know is in decline during the current (21st) century and novel noninvasive therapies are rising, there is a high probability of advancing treatments using medications with major potential, such as psychedelics.

The idea of using psychedelics in treating intracranial aneurysms has parallel examples in the literature. For instance, the application of ketamine in the management of cortical spreading depolarization waves that pathologically occur following specific conditions, including traumatic brain injury, subarachnoid hemorrhage, cluster migraines, and migraine headaches.[9] Although ketamine has anti-inflammatory, antidepressant, and analgesic effects, its primary action is inhibiting N-methyl-d-aspartate receptors, halting the continuous and excessive flow of afferent impulses generated in injured tissues. Therefore, it may counteract the pathological spreading of depolarization waves in the affected brain. The ideas of such drug applications are usually derived from redefining the basic science of the disease, then targeting certain critical factors that studies revealed with possible drugs.[9].

However, the clinical usage of such drugs in treating such patients may face resistance in the scientific communities and the public. Historical, cultural, scientific, and political perspectives are embedded within the story of using psychedelics as a medical therapy. Therefore, advocacy toward minimal invasiveness should be the guiding vector while addressing new potential treatments.

CONCLUSION

The psychedelics may represent a new addition to the armamentarium for medical doctors treating intracranial aneurysms. However, the pathway toward validation requires significant evidence to confirm their effectiveness and safety.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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