Targeting of $5HT_{2A}$ receptors by Psychedelics as a Potential Treatment for Inflammatory Aspects of Multiple Sclerosis

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ABSTRACT

The number of multiple sclerosis patients is increasing each year with the total figure currently reaching around 3 million cases. Multiple sclerosis is a neurodegenerative autoimmune disease causing myelin degradation and axonal loss. Its etiology remains unknown and therefore it is necessary to at least treat the symptoms and find ways to slow down the progression of the disease. In the past years, it was shown that psychedelics present anti-inflammatory effects via interaction with $5HT_{2A}$ receptors. This finding poses an intriguing question of whether psychedelics could be used in multiple sclerosis patients as a novel treatment to fight the inflammation in the central nervous system. According to available information, psychedelics could indeed be the future of inflammation treatment.

BACKGROUND

Multiple Sclerosis

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS) troubling almost 3 million people around the world (Walton et al., 2020). Its prevalence is especially high in the countries of the northern hemisphere, namely the United States, Canada, Sweden, or Finland for instance. According to a survey by Walton et al. (2020), the number of MS patients has globally increased by 50% since the year 2013. The incidence has risen from 29.26 cases per 100,000 individuals to 43.95 cases per 100,000 individuals with Europe dominating the prevalence charts by having 142.81 cases per 100,000 individuals. The biggest difference in incidence between the years 2013 and 2020 was 87% observed in the Americas.

It has been almost 200 years since the first remarks concerning MS were observed and described. According to Compston (1988), the first references regarding MS date back to the year 1835 when Jean Cruveilhier illustrated lesions observed in MS patients in his pathological atlas. Besides Cruveilhier, Robert Carswell described similar phenomena in his own pathological atlas three years later in 1838. Yet, it was only in 1868 that Jean-Martin Charcot classified this condition as a unique disease and entitled it a distinct name (Compston, 1988).

Multiple sclerosis does not have a single mode of progression. There are four courses of disease - relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS). RRMS is characteristic of attacks, also known as relapses, causing typical MS symptoms. These relapses are interrupted by remission phases indicating healing or improvement of the condition. Although remission phases indeed present recovery, it is only to a certain extent. In other words, the neuronal tissue almost never fully returns to a healthy state and overall the condition keeps getting worse. RRMS usually progresses into SPMS, meaning the relapsing-remitting periods diminish and the symptoms just worsen progressively. The third type of MS is the PPMS. PPMS is characteristic of progressive intensifying of symptoms with no relapsing-remitting periods right from the onset of the disease. Lastly, the most severe case of MS is the PRMS. PRMS is a combination of progressive worsening of symptoms with relapsing attacks causing the condition to temporarily become even worse (Garg & Smith, 2015) (Figure 1).

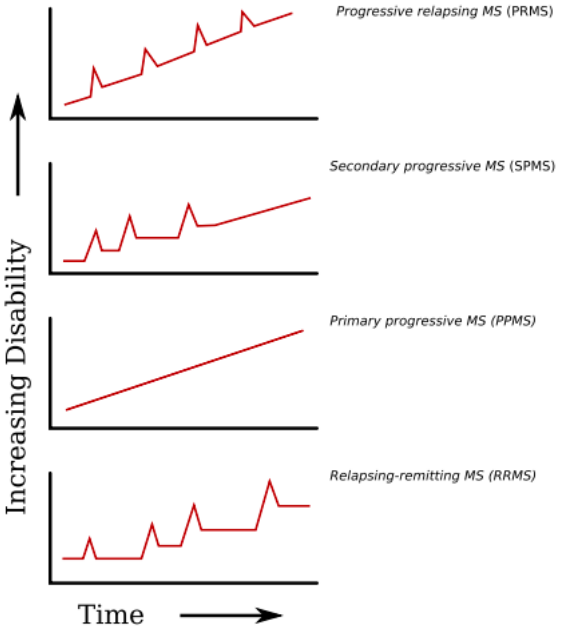

Figure 1: *Development of the 4 types of courses of MS.* (https://commons.wikimedia.org)

Although the exact etiology of MS remains unknown, a combination of genetic and environmental factors is thought to be part of the underlying cause (Stys et al.,

2012). Even though MS is not considered an inheritable disease, clusters of cases have been observed within families, indicating there is some genetic component. According to Garg & Smith (2015), there is a 10-50 times higher risk, compared to the general population, of development of the condition if a first-degree relative has been diagnosed with MS. Several studies (Barcellos et al., 2003; Sawcer et al., 2011) showed that there are certain genes posing risk for MS development. Namely the major histocompatibility complex (MHC) HLA DR15/DQ6 allele and several genes encoding interleukin receptors, such as interleukin-2 receptor alpha and interleukin-7 receptor alpha (Garg & Smith, 2015). Besides genetic predisposition, multiple environmental factors have been identified to increase the risk of MS onset. Considering the spread of the disease is monitored mostly in the northern hemisphere, vitamin D deficiency has been one of the susceptible environmental causes (Garg & Smith, 2015). Secondly, prior infection by the Epstein-Barr virus poses a 15- to 30-fold higher risk of developing MS later in life (Ascherio, 2013). Although the exact mechanism underlying this association is not completely understood, it was found to be related to B-cells mistakingly presenting the wrong antigens. After EBV infection, B-cells were found to present recombinant human oligodendrocyte glycoprotein instead of viral antigens, inducing an autoimmune reaction by cytotoxic $CD8^+$ T-cells (Guan et al., 2018).

MS is defined as an autoimmune inflammatory neurodegenerative disease characterized by demyelination of CNS and axonal loss (Garg & Smith, 2015). Inflammation is generally triggered by tissue injury or infection. The acute inflammatory response starts with phagocytic macrophages. Upon encounter with damaged tissue or pathogens, macrophages start to release different types of inflammatory mediators, such as cytokines, chemokines, vasoactive amines, or eicosanoids (Medzhitov, 2008). All of these lead to enhanced inflammation and recruitment of additional leukocytes to the damaged or infected area. One of the important consequences of the release of these signaling molecules is the increased permeability of endothelium and subsequent migration of the neutrophils into the affected tissue (Medzhitov, 2008). If the acute inflammatory response does not lead to the elimination of the stressful stimuli, the inflammatory state remains and the adaptive immune system (AIS) is activated. The AIS comprises B- and T-cells capable of targeting very specific antigens. In order for these cells to function properly it is crucial they are able to differentiate between self and non-self. In healthy individuals, these lymphocytes only respond to harmful non-self stimuli and develop self-tolerance towards self-antigens (Garg & Smith, 2015).

As previously mentioned, it is thought that the autoimmune aspect of MS stems from a violation of self-tolerance induced by the cross-presentation of self-antigens by B-cells (possibly caused by EBV). In the case of MS, false autoantigen presentation leads to activation of T-cells, causing them to become autoreactive towards myelin basic protein, illustrating the event of a so-called molecular mimicry (Garg & Smith, 2015). Molecular mimicry is a phenomenon in which immune cells mistake endogenous proteins for pathogenic exogenous proteins due to their structural resemblance (Rojas, 2018). After activation, myelin-reactive T-cells are able to cross the blood-brain barrier initiating CNS inflammation. Recognition of autoantigens, such as basic myelin protein, by myelin-reactive T-cells, triggers the inflammatory cascade by recruiting more leukocytes. Some of the key cytokines mediating the CNS inflammation of MS were found to be TNF-α, IL-2, or IFN-γ (Selter & Hemmer, 2013). Additional T-cells, B-cells, monocytes, macrophages, and microglia all trying to eliminate the apparent pathogen, lead to myelin damage and degradation (Frohman et al., 2006). Besides a specific subset of T-cells secreting pro-inflammatory cytokines, another subset releases anti-inflammatory cytokines, such as IL-4, -5, and -10, resulting in the opposite effect - alleviating the inflammation. Inflammatory centers causing myelin and axonal damage lead to the formation of the so-called MS plaques or lesions.

Psychedelics and 5-HT receptors

Because inflammation is one of the key characteristics of MS, the goal is to reduce it and therefore slow down the process of degradation. One of the possible treatments, thanks to its anti-inflammatory properties, could be psychedelics. The use of psychedelics dates back to more than 3700 years BCE (El-Seedi et al., 2005). Throughout history, it has been an essential part of rituals and ceremonies among various tribes, civilizations, and cultures all over the world. Current legislation, however, bans the use of these substances both for recreational and scientific purposes. In spite of this ban being in conflict with the majority of studies, research, and personal experience, it was imposed and hasn't been significantly changed since the 60s (Griffiths et al., 2008; Krebs & Johanssen, 2013; Nichols, 2016).

Psychedelics are a group of psychoactive substances interacting with our serotonergic system. Some of the psychedelic compounds include LSD, DMT, mescaline, and psilocybin (Insera et al., 2021). Besides their most famous effect causing an altered perception of reality, psychedelics interfere with many more processes and pathways within our organism. One of the most studied interactions is the one with serotonergic receptors, namely the $5HT_{2A}$ receptor (Flanagan & Nichols, 2018). The reason why these substances are able to interfere with our serotonergic system is because of their structural resemblance to the serotonin molecule.

Psychedelics can therefore be referred to as agonists or partial agonists of $5HT_{2A}$ receptors. The interaction of LSD with this particular receptor was first proved by a study by Glennon et al. (1983, 1984) and confirmed by multiple investigations that followed. After blocking the $5HT_{2A}$ receptors by ketanserin and pirenperone, Glennon et al. observed that psychedelics were not able to induce the psychedelic effects. Similarly, a study by Vollenweider et al. (1998) showed that psilocybin-induced effects are not present when $5HT_{2A}$ receptors are treated with ketanserin. In other words, selective $5HT_{2A}$ receptor antagonist ketanserin prevented psilocybin and LSD from causing the psychedelic effects. Besides psychedelic effects a growing number of studies point out the anti-inflammatory properties of these compounds. As inflammation represents an important component in MS pathology and psychedelics are emerging as compounds able to control inflammatory reaction in the CNS, is there a link in the literature suggesting that MS could be treated by psychedelics?

FINDINGS AND DISCUSSION

Psychedelics and Inflammation

$5HT_{2A}$ receptors in the brain were found to be expressed mostly in areas associated with cognition and sensory processing, namely the neocortex, thalamus, locus coeruleus, and ventral tegmental area (Nichols, 2016). The expression of these receptors in the cortex is high in all cortical layers with especially dense representation in the prefrontal cortex and temporal lobe (Beliveau et al., 2017) (Figure 2). Besides the brain, serotonin receptors have also been found on the surface of cells of both the innate and adaptive immune systems (Flanagan & Nichols, 2018).

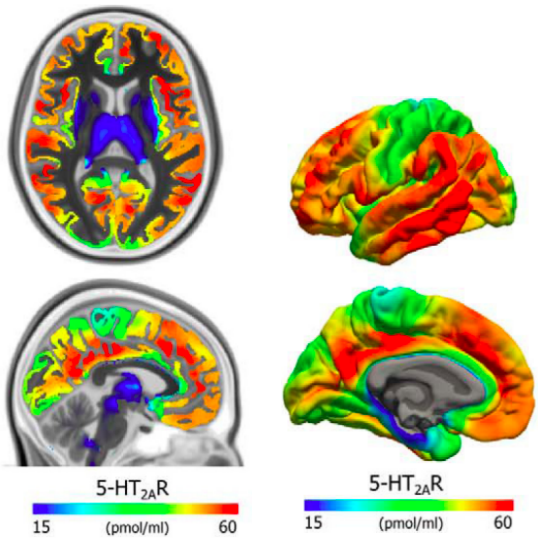

Figure 2: *The distribution of $5HT_{2A}$ receptors in the brain.* (Beliveau et al., 2017)

As previously mentioned, psychedelics were found to be potent anti-inflammatory agents, thanks to their interaction with serotonin receptors (Szabo, 2015). There is not, however, one mode of action for serotonin when it comes to inflammation. In the past years, multiple studies have come to contradictory conclusions. According to Ito et al. (2000), serotonin is associated with an elevated inflammatory response characterized by increased levels of proinflammatory cytokines such as IL-6 and TNF-α. Confirming this, exhaustion of serotonin leads to reduced expression of these mediators and alleviation of inflammation.

Contrary to Ito et al. (2000) and their hypothesis, Yu et al. (2008) observed a recession of inflammation after $5HT_{2A}$ receptor stimulation. An *in vitro* study performed by Yu et al. (2008) with (R)-DOI reacting to TNF-α induced inflammation showed the potential anti-inflammatory properties of psychedelics. (R)-DOI is a psychedelic compound and a selective $5HT_{2A}$ receptor agonist. In this study, inflammation was induced in rat aortic smooth muscle cells by TNF-α. Subsequently, multiple psychedelic compounds were added and the effect was observed. Although all of the psychedelics weakened the inflammation, (R)-DOI was the most potent one. It was able to repress the inflammation by inhibiting the transcription of genes encoding intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and pro-inflammatory IL-6. Furthermore, it interacted with NF-κB preventing it from activation and nuclear translocation. To confirm the effect was due to interaction with specifically $5HT_{2A}$ receptors, the experiment was performed with selective $5\text{-}HT_{2B}$ and $5\text{-}HT_{2C}$ receptor agonists as well. This combination, however, was not capable of inhibiting the TNF-α induced inflammation, demonstrating that the anti-inflammatory properties belong specially to the $5HT_{2A}$ receptor.

To test this phenomenon *in vivo* Nau et al. (2013) performed the same experiment on mice. First, the test subjects were injected with TNF-α to induce an inflammatory response, and subsequently, the same mice were treated with (R)-DOI. Similarly as with the *in vitro* version of the experiment, (R)-DOI exhibited anti-inflammatory effects via decreased expression of ICAM-1, VCAM-1, IL-6, and several other pro-inflammatory mediators. To justify the results, a selective $5HT_{2A}$ receptor antagonist was used to point out the lack of anti-inflammatory effects upon its administration, demonstrating the link between the $5HT_{2A}$ receptor and inflammation again.

Considering serotonin stimulation of $5HT_{2A}$ receptors was first described as pro-inflammatory, it is puzzling that stimulating the same $5HT_{2A}$ receptors by psychedelics seems to have the opposite effects. Flanagan & Nichols (2018) hypothesize that this could be explained by an event called functional selectivity. Functional selectivity is a phenomenon in which

stimulation of a receptor can lead both to activation and inhibition of the following cascades. The determining factor is the induced receptor conformation by that particular agonist. In this case, serotonin stimulates the receptor in such a way that the activated pathway has a pro-inflammatory effect. Conversely, psychedelics seem to stabilize the same receptor in a different conformation activating the anti-inflammatory pathway instead.

According to available information from the above-mentioned studies, psychedelics seem to be a potential medication for inflammation. By interacting with 5-HT_{2A} receptors, they suppress the synthesis of pro-inflammatory mediators leading to inhibition of inflammation (Nau et al., 2013). Since 5-HT_{2A} receptors are extensively expressed in the CNS (Beliveau et al., 2017), it can be hypothesized that they could represent a possible treatment for the inflammatory aspects of MS. By suppressing the synthesis of pro-inflammatory molecules, they are able to alleviate the inflammation symptoms and therefore could possibly decrease the progress of MS.

Some of the pro-inflammatory mediators are cell adhesion molecules, chemokines, and cytokines (Medzhitov, 2008). Cell adhesion molecules such as VCAM-1 and ICAM-1 enable the immune cells to cross the endothelial layer and subsequently enter the tissues and organs. By inhibiting their expression, leukocytes have decreased ability to invade tissues and therefore prevent the growth of inflammation (Medzhitov, 2008). This could be one of the processes helping with treating MS inflammation. Besides cell adhesion molecules, cytokines and chemokines also play an important role in the promotion of inflammation. One of the pro-inflammatory cytokines is IL-6. IL-6 is among other things able to cross the blood-brain barrier and therefore stimulate the spread and growth of inflammation in CNS (Banks et al., 1994). Psychedelics, however, were shown to be an effective way of inhibiting the expression of these molecules and thus could lead to further inhibition of inflammation in MS patients.

Some of the limitations of this review include a lack of information concerning the effects of psychedelics specifically on inflammation in MS patients. Since much of modern psychedelic research focuses on treating psychiatric diseases, there is a lack of experimental data concerning the actual effects on MS in particular. Further research should therefore aim attention at conducting experiments in order to obtain experimental data regarding the influence of psychedelics specifically on inflammation observed in MS. This will enable us to evaluate the potential of psychedelics more accurately and hence find out more about its potential use in the treatment of this disease.

CONCLUSION

Psychedelics have proved to be an effective tool against inflammation. Thanks to their resemblance to the serotonin molecule, they are able to stimulate the $5HT_{2A}$ receptors involved in inflammation. Activation of $5HT_{2A}$ receptors by psychedelics leads to decreased expression of cell adhesion molecules and reduction in synthesis of pro-inflammatory cytokines and chemokines and thus reducing the inflammation, potentially also in MS patients.

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