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Viewpoints Sigma-1 receptor agonist fluvoxamine for multiple sclerosis

Kenji Hashimoto

Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba, 260-8670, Japan

A B S T R A C T

Accumulating evidence suggests that the Epstein-Barr virus (EBV) plays a key role in the development of multiple sclerosis (MS). Additionally, depressive symptoms often precede the onset of MS. Given the role of the XBP1-sigma-1 receptor complex in the endoplasmic reticulum during EBV reactivation, the author proposes that fluvoxamine, an antidepressant with sigma-1 receptor agonism, could be a suitable therapeutic drug for MS.

1. Text

Multiple sclerosis (MS) is an autoimmune and neurodegenerative disorder that affects approximately 3 million people worldwide. While a variety of genetic and environmental factors have long been thought to increase the risk of developing MS, the specific triggers for the disease's onset remain elusive. Since the 1980s, it has been suggested that infection with Epstein-Barr virus (EBV), one of the most prevalent viruses in humans, may contribute to the development of MS. A recent large-scale longitudinal study involving more than 10 million young adults found a 32-fold increased risk of developing MS following EBV infection, a risk not observed after infection with other viruses (Bjornevik et al., 2022). Another study underscored significant molecular mimicry between the EBV nuclear antigen 1 (EBNA1), a gene-regulating transcription factor protein of EBV, and the glial cell adhesion molecule (GlialGAM), a protein expressed in the central nervous system (Lanz et al., 2022). Taken together, accumulating evidence from various research disciplines supports the crucial role that EBV plays in the development of MS (Aloisi et al., 2023; Bjornevik et al., 2023). However, the mechanisms by which EBV contributes to neuroinflammation–whether through autoimmune or antiviral pathway–still need to be clarified to better understand the onset of MS. Although prophylactic or therapeutic EBV vaccines have been developed, as of now, no drugs specifically based on the EBV hypothesis exist to prevent the onset and progression of MS (Bjornevik et al., 2023).

Depression, the most common psychiatric symptom among individuals with MS, has been linked to a range of adverse outcomes including diminished quality of life, cognitive impairment, increased risk of suicide, exacerbated neurological symptoms, and a greater need for mental health services (Pérez et al., 2015; Wang et al., 2023). Epidemiological studies indicate that psychiatric symptoms, especially depression, often manifest as significant prodromal signs prior to a formal diagnosis of MS (Marrie et al., 2022). This underscores the importance of addressing depressive symptoms both before the onset of MS and in individuals who have already been diagnosed with the condition. Interestingly, the antidepressants including selective serotonin reuptake inhibitors (SSRIs) have been found to be effective not only in alleviating depressive symptoms but also in improving neurological symptoms in MS patients (Wang et al., 2023). Fluvoxamine treatment, an SSRI, initiated at 50 mg/day and gradually increased by 50 mg every 5 days to a maximum of 200 mg/day over 3 months, led to an improvement in depressive symptoms among MS patients receiving interferon β-1b. Notably, no patients experienced a severe exacerbation of MS symptoms during this period (Benedetti et al., 2004).

More than 90% of adults worldwide have been infected with EBV, yet most infected individuals remain asymptomatic. The specific factors that trigger MS in only a subset of those infected with EBV are not yet understood. One hypothesis suggests that depressive symptoms induced by stress-induced inflammation could contribute to the onset of MS in individuals with EBV infection. Research indicates that X-box-binding protein 1 (XBP-1) in the endoplasmic reticulum (ER) can activate EBV gene expression in combination with protein kinase D, pointing to a critical role of XBP-1 in EBV reactivation (Bhende et al., 2007) (Fig. 1). Additionally, the ER chaperone sigma-1 receptor has been shown to modulate the expression of ER stress-related proteins via XBP1 regulation (Hashimoto, 2023; Hashimoto et al., 2022) (Fig. 1). Given the pivotal role of the sigma-1 receptor in regulating XBP-1 within the ER, it is proposed that fluvoxamine, an SSRI with potent sigma-1 receptor agonism, could serve as a potential therapeutic drug for MS (Fig. 1). Among currently available antidepressants, fluvoxamine stands out as the most potent agonist at sigma-1 receptor (Hashimoto, 2023; Hashimoto et al., 2022).

In a rat model of experimental autoimmune encephalomyelitis (EAE), which serves as a model for MS, fluvoxamine has been

E-mail address: hashimoto@faculty.chiba-u.jp.

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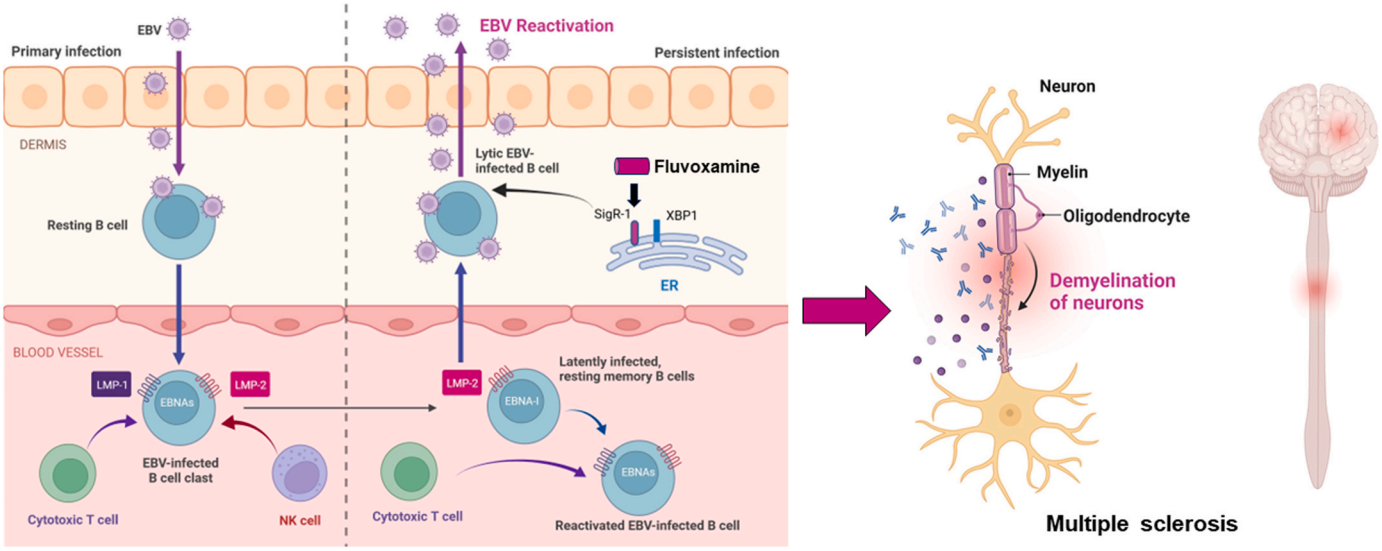

Fig. 1. Potential role of EBV reactivation in the development and progression of MS and therapeutic option of fluvoxamine
EBV directly infects resting B cells and epithelial cells, subsequently residing in the infected memory B cells in peripheral blood. These cells express latent membrane protein 2 (LMP-2) and EBV nuclear antigens (EBNAs). Under stress conditions, these B cells can trigger EBV reactivation, leading to severe systemic inflammation, neuronal demyelination, and the potential onset of MS. The interaction of the XBP-1 (X-box binding protein 1) with Sig1R (sigma-1 receptor) on the endoplasmic reticulum (ER) may be implicated in EBV reactivation. Consequently, this hypothesis suggests that sigma-1 receptor agonists like fluvoxamine could help in preventing EBV reactivation, thereby offering therapeutic advantages in the management and progression of MS. This figure incorporates elements from Figure 2 in Hashimoto (2023), with minor modifications, and was designed using resources from Biorender.com.

demonstrated to reduce the severity of EAE (Ghareghani et al., 2017). Rats treated with fluvoxamine in this model exhibited decreased serum levels of the pro-inflammatory cytokine interferon-γ and increased levels of the anti-inflammatory cytokine interleukin-4, compared to those receiving a vehicle control. Additionally, fluvoxamine significantly alleviated inflammatory infiltration and demyelination in the spinal cord of EAE rats (Ghareghani et al., 2017). The drug also enhanced the differentiation of neural stem cells (NSCs) into oligodendrocytes, astrocytes and neurons. However, this study did not investigate the role of sigma-1 receptor in fluvoxamine's beneficial effects. These preclinical results suggest that fluvoxamine may promote the proliferation and differentiation of NSCs into oligodendrocytes, which are crucial for myelin production (Ghareghani et al., 2017). It is important to acknowledge that, to our knowledge, this is the only one study demonstrating fluvoxamine's positive effects in animal models of MS. Further investigations, particularly involving rodents treated with EBV, are essential to clarify the roles of the EBV and sigma-1 receptor, and to determine the extent of fluvoxamine on the development and progression of MS-like phenotypes.

Fluvoxamine is known to inhibit the cytochrome P450 2D6 (CYP26D) enzyme which plays a crucial role in the metabolism of many medications. Consequently, inhibition of CYP2D6 by fluvoxamine may lead to altered concentrations of various drugs in the blood and tissues of MS patients. A positron emission study revealed that a single dose of fluvoxamine (ranging from 50 to 200 mg) binds to the sigma-1 receptor in the human brain (Ishikawa et al., 2007), suggesting receptor occupancy by fluvoxamine at therapeutic doses. Additionally, SSRIs, including fluvoxamine, have been associated with prolonged QTc interval on electrocardiogram (Pacher and Kecskemeti, 2004), indicating potential cardiovascular effects from long-term use. Therefore, the risk-benefit profile of fluvoxamine warrants careful consideration for long-term treatment.

In conclusion, given EBV's role in the pathogenesis of MS, sigma-1 receptor agonist fluvoxamine emerges as a potential therapeutic option for MS. Nonetheless, to substantiate fluvoxamine's efficacy in treating MS patients with EBV, further validation through randomized, placebo-controlled studies is necessary.

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Kenji Hashimoto: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

Dr. Hashimoto is the inventor of filed patent applications on "The use of *R*-Ketamine in the treatment of psychiatric diseases", "(*S*)-norketamine and salt thereof as pharmaceutical", "*R*-Ketamine and derivative thereof as prophylactic or therapeutic agent for neurodegeneration disease or recognition function disorder", "Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases or bone diseases", and "*R*-Ketamine and its derivatives as a preventive or therapeutic agent for a neurodevelopmental disorder" by the Chiba University. Dr. Hashimoto has also received speakers' honoraria, consultant fee, or research support from Abbott, Boehringer-Ingelheim, Daiichi-Sankyo, Meiji Seika Pharma, Japan, Seikagaku Corporation, Japan, Dainippon-Sumitomo, Japan, Taisho, Otsuka, Murakami Farm and Perception Neuroscience.

Data availability

No data was used for the research described in the article.

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