CORRESPONDENCE

Fluvoxamine and long COVID-19; a new role for sigma-1 receptor (S1R) agonists

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TO THE EDITOR:

We read with interest Hashimoto et al. study about mechanisms of action of fluvoxamine in COVID-19 [1]. As they mentioned, fluvoxamine offers some key mechanisms against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It inhibits acid sphingomyelinase (ASM) activity, the formation of ceramide-enriched membrane domain, and attenuates SARS-CoV-2 cell entry. Interestingly, fluvoxamine acts as a potent sigma-1 receptor (S1R) agonist that may decrease SARS-CoV-2 replication and subsequent endoplasmic reticulum (ER) stress and inflammation.

Based on the evidence, S1R agonists prevent inositol requiring enzyme 1α (IRE1) from splicing of mRNA that encodes X-box binding protein-1 (XBP-1). Hence S1R-mediated reduction in XBP1 activation modulates the ER stress response pathway and reduces cytokine storm [2]. XBP1 plays a major role in the reactivation of the Epstein-Barr virus (EBV). It has been indicated that ER stress and unfolded-protein response induce the expression of lytic EBV gene in EBV-infected cells, suggesting a pathway in virus-associated complications [3, 4].

Gold et al. reported that ~70% of patients with long COVID-19 versus 10% of the control group were positive for EBV reactivation according to the early antigen-diffuse immunoglobulin G or EBV viral capsid antigen immunoglobulin M [5].

It has been suggested that more than 50% of patients who recovered from COVID-19 experienced long-term symptoms such as headache, fatigue, anxiety, depression, and cognitive features within 6 months [6].

These findings suggest that most of the long COVID-19 symptoms following the recovery from the acute disease might not be directly affected by SARS-CoV-2 but probably result from COVID-19-associated inflammation and EBV reactivation. Recently, infection with EBV was suggested as the possible leading cause for multiple sclerosis (MS), in which inflammation plays a key role [7].

Given the link between EBV replication and XBP1 activation and modulatory effects of S1R agonists in XBP1 and ER stress response, we proposed that fluvoxamine might have beneficial effects in reducing long-term symptoms of COVID-19. However, further clinical studies are required to confirm this hypothesis.

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AUTHOR CONTRIBUTIONS

EK: conceptualisation, writing—original draft. TEM: writing—review and editing, supervision.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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