

CORRESPONDENCE



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

© The Author(s), under exclusive licence to Springer Nature Limited 2022

Molecular Psychiatry (2022) 27:3562; <https://doi.org/10.1038/s41380-022-01545-3>Elnaz Khani ¹ and Taher Entezari-Maleki ^{1,2}✉¹Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. ²Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. ✉email: tentezari@gmail.com

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 1 α (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.

REFERENCES

1. Hashimoto Y, Suzuki T, Hashimoto K. Mechanisms of action of fluvoxamine for COVID-19: a historical review. *Mol Psychiatry*. 2022;1–10. Online ahead of the print.
2. Rosen DA, Seki SM, Fernández-Castañeda A, Beiter RM, Eccles JD, Woodfolk JA, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci Transl Med*. 2019;11:eaa5266.
3. Hsiao JR, Chang KC, Chen CW, Wu SY, Su JJ, Hsu MC, et al. Endoplasmic reticulum stress triggers XBP-1-mediated up-regulation of an EBV oncoprotein in nasopharyngeal carcinoma. *Cancer Res*. 2009;69:4461–67.
4. Gonzalez-Farre B, Rovira J, Martinez D, Valera A, Garcia-Herrera A, Marcos MA, et al. In vivo intratumoral Epstein-Barr virus replication is associated with XBP1 activation and early-onset post-transplant lymphoproliferative disorders with prognostic implications. *Mod Pathol*. 2014;27:1599–611.
5. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens*. 2021;10:763.
6. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med*. 2021;18:e1003773.
7. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* 2022;375:296–301.

AUTHOR CONTRIBUTIONS

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

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Taher Entezari-Maleki.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 24 January 2022 Revised: 10 March 2022 Accepted: 22 March 2022
Published online: 6 April 2022