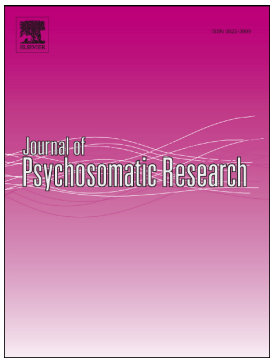
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Famotidine: A Potential Mitigator of Mast Cell Activation in Post-COVID-19 Cognitive Impairment

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We have read the article titled "Efficacy and Safety of Famotidine in Improving Cognitive Impairment, Depression, and Anxiety Symptoms in Post-COVID-19 Patients" authored by Momtazmanesh et al. [1] with great interest. We would like to commend the authors for their insightful study, which investigates the potential benefits of famotidine, a selective histamine H2 receptor antagonist, in addressing the cognitive impairment, depression, and anxiety symptoms that develop following COVID-19.

The authors reported significant improvements in cognitive functioning after six and twelve weeks of treatment with famotidine. Furthermore, participants in the famotidine group experienced a statistically significant larger reduction in depression and anxiety levels compared to the placebo group. However, the authors did not explain these findings concerning the mechanism of action of famotidine, which we wish to complement in their discussion.

Emerging evidence suggests a potential association between mast cell activation and the pathogenesis of long COVID, a condition characterized by persistent symptoms following acute SARS-CoV-2 infection [2]. Mast cells, critical players in the immune system, have been implicated in chronic inflammatory disorders. In the context of long COVID, ongoing immune dysregulation and inflammation may trigger mast cell activation, releasing various inflammatory mediators [3].

Studies have shown that activated mast cells can interact with various immune cells, potentially amplifying the inflammatory response and contributing to the sustained immune dysregulation observed in long COVID [4,5]. The release of histamine, cytokines, chemokines, and other inflammatory substances by activated mast cells may perpetuate immune responses and contribute to the wide range of persistent symptoms observed in long COVID, including cognitive impairments.

Histamine, a key molecule released by activated mast cells, is known to contribute to neuroinflammation and has been implicated in the pathogenesis of various neurological and psychiatric conditions, including cognitive impairment, depression, and anxiety [6,7]. Furthermore, mast cells can release inflammatory mediators and secrete neurotransmitters such as serotonin, dopamine, and norepinephrine, which play crucial roles in regulating mood and emotional well-being [8,9]. Dysregulated mast cell activation and resultant alterations in neurotransmitter levels may perturb normal neuronal functioning, contributing to the development of mood and anxiety disorders. Moreover, mast cell activation can disrupt the blood-brain barrier (BBB), resulting in increased permeability and the subsequent entry of inflammatory molecules and immune cells into the brain [10]. This BBB dysfunction may trigger neuroinflammation and neuronal damage, further contributing to depression and anxiety.

Famotidine, the focus of the study being discussed, is a selective histamine H2 receptor antagonist that has the potential to modulate mast cell activation and the subsequent release of inflammatory mediators. Famotidine acts by selectively blocking histamine H2 receptors, which are found on the surface of mast cells. By inhibiting the binding of histamine to these receptors, famotidine can reduce the activation of mast cells and the subsequent release of inflammatory mediators. Furthermore, famotidine has been shown to exhibit anti-inflammatory properties, and it has been suggested that it can inhibit the production and release of pro-inflammatory cytokines [11,12]. By suppressing cytokine release, famotidine may help to dampen the inflammatory response associated with mast cell activation.

In conclusion, we highly commend the authors for their valuable contribution to exploring the efficacy and safety of famotidine in improving cognitive impairment, depression, and anxiety symptoms in post-COVID-19 patients. The potential role of mast cell activation in both long COVID and psychiatric conditions presents exciting opportunities for further research and therapeutic interventions, particularly through the use of selective histamine H2 receptor antagonists like famotidine. However, it is imperative to conduct additional investigations to fully understand the complex relationship between mast cell activation, neuroinflammation, and psychiatric symptoms.

Therefore, we urge researchers to delve deeper into the mechanisms underlying mast cell activation and its impact on neuroinflammation, neurotransmitter dysregulation, and the development of mood and anxiety disorders in post-COVID-19 patients. By understanding these processes comprehensively, we can pave the way for developing targeted and effective interventions. Continued research in this field will undoubtedly contribute to the improved management and well-being of individuals experiencing long COVID and associated psychiatric symptoms.

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