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Letter to Editor

Fluvoxamine mediates specific, early, and delayed SARS-CoV-2 protection through antioxidant and cytoprotective pathways via sigma-1 receptor agonism

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Fluvoxamine is an affordable and widely available selective serotonin reuptake inhibitor (SSRI) antidepressant which is associated with reduced hospitalization, reduced severity, and mortality in outpatients with coronavirus disease 2019 (COVID-19).[1,2] Fluvoxamine's mechanisms of action in COVID-19 have been extensively discussed and is mainly mediated via its potent (Ki=36 nM) sigma-1 receptor (sigma-1R, σ1R, S1R) agonism.[3-5] Sigma-1R interferes with the early steps of virus-induced host cell reprogramming and protect against mitochondrial damage and endoplasmic reticulum (ER) stress in response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.[4] The reduction of cytokine production as indicated by sigma-1R's key role in systemic inflammation is supported by substantial evidence.[4] Finally, additional mechanisms may include acid sphingomyelinase (ASM) inhibition.[4] SARS-CoV-2 activates host ASM leading to ceramide accumulation-a product of ASM catalyzed sphingomyelin-which aids in SARS-CoV-2 cell entry. Unlike fluvoxamine, chlorpromazine-another ASM inhibitor-did not lead to reduced mortality in patients with COVID-19 implying that ASM inhibition may not be clinically relevant.[6]

We wish to highlight additional sigma-1R pathways that may be more pertinent in engendering fluvoxamine's specific, early, and delayed SARS-CoV-2 protection. Sigma-1R agonists fluvoxamine and dehydroepiandrosterone (DHEA) have been shown-in both *in-vivo* and *in-vitro* systems-to mediate robust cardioprotection through increases in **protein kinase B (Akt) phosphorylation, endothelial nitric oxide (NO) synthase (eNOS) levels and eNOS phosphorylation.**[7,8] In addition, fluvoxamine's cardioprotective effect is mediated via upregulation of cardiac sigma-1R expression.[7] Furthermore, stimulation of central nervous system sigma-1R may also inhibit sympathetic hyperactivation along with direct fluvoxamine stimulation of cardiac sigma-1R synergistically to improve hypertrophic cardiac dysfunction.[7] Newer studies also suggest that fluvoxamine stimulation of sigma-1R reduces susceptibility to right ventricular dysfunction, atrial fibrillation, and ventricular arrhythmias and enhances cardiac function by upregulating sigma-1R protein content, mitigating myocardial fibrosis, sympathetic and electrical remodeling.[9] Treatment with sigma-1R antagonists negated fluvoxamine-mediated eNOS upregulation and Akt-mediated eNOS phosphorylation. Moreover, all fluvoxamine-mediated cardioprotective effects are reduced, confirming that the sigma-1R modulates eNOS activity in the heart and blood vessels.[7,9] Pertinent to COVID-19-related lung afflictions, sigma-1R agonism alleviates airway inflammation and airway remodeling via increased expression of **AMP-activated protein kinase (AMPK)** and inhibition of C-X-C chemokine receptor type 4 (CXCR4) expression while sigma-1R, AMPK, and CXCR4 antagonisms reversed these protective effects.[10] Increased AMPK signaling appears beneficial in lung pathology as it reduces the inflammatory responses in lung emphysema, mitigates pulmonary hypertension, and protects against lipopolysaccharide-induced acute lung injury and acute respiratory distress syndrome (ARDS).[11] AMPK, a master cellular energy and redox-sensing protein, activated through several physiological and pathological conditions-such as hypoxia, caloric restriction, physiological exercise, aspirin and metformin-is also known to robustly induce eNOS in the endothelium.[12]

Sigma-1R's direct and AMPK-mediated-indirect effects on eNOS levels and phosphorylation, synergistically increase NO-production and bioavailability that underlie fluvoxamine's and DHEA's cardio- and vasculo-protective actions and mechanistically support specific and immediate anti-SARS-CoV-2 effects.[3,5] Increased NO-generation and bioavailability may counteract SARS-CoV-2-induced endotheliitis and even inhibit SARS-CoV-2 replication and infection at an early stage as shown by the inhibition of 1) the palmitoylation of the SARS-CoV-1/2 spike protein, essential for fusion to the angiotensin converting enzyme (ACE)2, its obligate receptor, and 2) early production of viral RNA by inhibiting SARS-CoV-2 main protease. Both these processes are critical for membrane fusion and virion infectivity.[13] In addition, inhibition of acetyl-CoA carboxylase by AMPK will directly inhibit palmitate synthesis further engendering anti-SARS-CoV-2 effects.[14] Later in the course of SARS-CoV-2 infection, sigma-1R/AMPK/eNOS-induced increase in NO-production and bioavailability may promote delayed cardiopulmonary, renal and vascular protection through lower oxidative stress, apoptosis,

and reduced systemic inflammatory responses.[15] In severe COVID-19 and related ARDS, lower soluble eNOS levels have been reported implying that pharmaceutical interventions that increase NO-generation and bioavailability, may protect patients from severe lung complications.[16]
Finally, sigma-1R agonism significantly increases **nuclear factor erythroid-derived 2-like 2 (Nrf2)**, a master regulator of inducible antioxidant responses, and heme oxygenase-1 (HO-1) expression in astrocytes. Thus, Nrf2 may have therapeutic potential in neuroinflammation and protection against oxidative stress with implications for long COVID-19 neurological complications.[17] Sigma-1R induction of AMPK will also phosphorylate Nrf2 resulting in subsequent expression of antioxidant genes.[12] Interestingly, expression of Nrf2-dependent genes is suppressed in biopsies from COVID-19 patients.[18] Recent data suggest that SARS-CoV-2 indeed represses the Nrf2/HO-1 antioxidant pathway while treatment of cells with Nrf2 agonists induced a strong antiviral program that limits SARS-CoV-2 replication.[18]
In conclusion, sigma-1R agonism promotes specific eNOS/NO-, AMPK-, and Nrf2/HO-1-mediateddefense mechanisms that actively suppress SARS-CoV-2 replication and transmission along with robust cardiovascular and neuroprotective effects. We thus strongly support the use of fluvoxamine as an affordable and widely available sigma-1R agonist for specific, early, and delayed protection against SARS-CoV-2 infection.

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