Potential role of memantine in the prevention and treatment of COVID-19: its antagonism of nicotinic acetylcholine receptors and beyond

To the Editor:

Recently, Leung *et al.* [1] proposed that α7-subtype nicotinic acetylcholine receptor (α7-nAChR) antagonists might decrease angiotensin-converting enzyme (ACE)2 receptor expression in respiratory epithelium and, hence, prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invasion of pulmonary epithelial cells. Let us further theoretically evaluate this assertion and contribute to the quest for potential medications that might reduce virulence and pathogenicity of coronavirus disease 2019 (COVID-19). Smoking may be associated with progression and negative outcome of COVID-19 [1]. The receptor-binding domain of the S protein (spike) on the surface of SARS-CoV-2 interacts with the ACE2 receptor, which is an entry point of the virus into host respiratory cells [2]. On the respiratory epithelium cells of smokers and patients with COPD there is higher expression of this "viral receptor" (ACE2 receptor) [1]. Nicotine binds and stimulates nAChR, specifically the α7 subtype, which are localised in lungs and various other tissues, especially in the central nervous system. Increased expression of ACE2 receptors is mediated by stimulation of α7-nAChR. Nicotine, by its agonism on α7-nAChR, might promote entry of SARS-CoV-2 into the respiratory epithelium through ACE2 receptors [1]. Additionally, some evidence suggests that SARS-CoV-2, along with other human coronaviruses, is neurotropic and neurovirulent [3]. Altogether, it is of utmost importance to search for medications that might exert protective effects both at the periphery, at the entry point of SARS-CoV-2 infection, but also in the central nervous system where the virus might propagate.

Memantine reduces excitotoxity in the central nervous system by its noncompetitive antagonism of the *N*-methyl-D-aspartate (NMDA) glutamate receptors [4]. Memantine has greater affinity for extrasynaptic than synaptic NMDA receptors, enabling glutamate to exert its physiological role in the processes of learning, memory formation and neuronal plasticity by stimulating synaptic NMDA receptors [4]. However, in conditions of excessive extracellular accumulation of glutamate, initiated by various inflammatory and oxidative processes, memantine significantly blocks extrasynaptic NMDA receptors, protecting cells from the glutamate excitotoxity [4]. The effectiveness of memantine in the treatment of different neuropsychiatric disorders, from various forms of dementia, autism, schizophrenia and depression to neuropathic pain and Parkinson's disease, has been tested in more than 100 trials [4]. It is approved as a safe and effective medication by both the US Food and Drug Administration and the European Medicines Agency for the treatment of "moderate to severe Alzheimer's disease" [4]. Memantine, in addition to its noncompetitive NMDA receptor antagonism, is very potent α7-nAChR antagonist [5]. By its α7-nAChR antagonism, it blocks meningitic *Escherichia coli* K1 bacteria neuroinvasion in mice [5]. It may also exert its protective, anti-inflammatory effects by suppression of cytokine expression, as demonstrated in an experimental model of lung injury [6]. As an adamantane derivate, in cell cultures memantine inhibits human coronavirus strain OC43 (HCoV-OC43) replication after virus attachment to the cell receptor, acting as an antiviral drug [7]. Infection with HCoV-OC43, in particular mutated surface protein S, increases levels of inflammation by release of pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-1 and interleukin-6, and by inducing

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Memantine, as an antagonist of α7-nAChR and NMDA receptors, may decrease ACE2 receptor expression and reduce oxidative stress and inflammation. Hence, memantine may potentially reduce SARS-CoV-2 virulence. https://bit.ly/2AZHiVg

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microphage/microglial hyperactivation in the central nervous system [7, 8]. Memantine may counteract these deleterious effects by inhibiting activity of microglia [8, 9]. Moreover, neuroinvasion with mutated surface protein S variants of HCoV-OC43 resulted in paralysis of experimental animals due to glutamate excitotoxicity. Memantine ameliorated these motor disturbances, reduced mortality rates and inhibited coronavirus replication rate in the central nervous system, dose-dependently [7, 9]. Additionally, memantine might exert anti-inflammatory effects by reducing angiogenesis and brain lymphocyte infiltration, as shown in mice infected with Japanese encephalitis virus [10]. In conclusion, we hypothesise that memantine may reduce virulence and pathogenicity of SARS-CoV-2 and potentially exert its effects both in lungs and brain. However, such claims require further thorough experimental, epidemiological and clinical confirmation.

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