EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

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Senad Hasanagic, Fadila Serdarevic

Please cite this article as: Hasanagic S, Serdarevic F. Potential role of memantine in the prevention and treatment of COVID-19: its antagonism of nicotinic acetylcholine receptors (nAChR) and beyond. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.01610-2020).

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

Authors: Senad Hasanagic, MD, Fadila Serdarevic, MD, PhD

Affiliations:

1. Clinical Center University of Sarajevo, Department of Psychiatry, Sarajevo, Bosnia and Herzegovina

2. Erasmus MC, Department of Epidemiology, Rotterdam, Netherlands

Correspondence to: Senad Hasanagic, MD, Clinical Center University of Sarajevo, Department of Psychiatry, Sarajevo, Bosnia and Herzegovina

hasanagic.sen@gmail.com

Recently, Leung et al. proposed that α7-nAChR antagonists might decrease angiotensin-converting enzyme (ACE2) receptors expression in respiratory epithelium and, hence, prevent SARS-CoV-2 invasion of pulmonary epithelial cells (1). Let us further theoretically evaluate this assertion and contribute to the quest for potential medications that might reduce virulence and pathogenicity of COVID-19. Smoking may be associated with progression and negative outcome of coronavirus disease 2019 (COVID-19) (1). The receptor binding domain of S protein (spike) on the surface of SARS CoV-2 interacts with angiotensin-converting enzyme (ACE2) receptor- which is an entry point of 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" (angiotensin-converting enzyme-2 receptor) (1). Nicotine binds and stimulates nicotinic acetylcholine receptors (nAChR), specifically the α7subtype (α7-nAChR) that are localized in lungs and various other tissues, especially in 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). On the other hand, some evidence suggests that SARS-CoV-2, along with other human corona viruses is neurotropic and neurovirulent (3) Altogether, it is of utmost importance to search for medications that might exert its protective effects both at the periphery, at the entry point of SARS-CoV-2 infection but also in the central nervous system where 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 then 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 the 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). Effectivness of memantine in the treatment of different neuro-psychiatric disorders, from various forms of dementia, autism, schizophrenia, depression to neuropathic pain and Parkinson's disease have been tested in more then 100 trials (4). It is approved as safe and effective medication by both United States Food and Drug Administration and European Agency for the Evaluation of Medical Products (EMEA) for the treatment of "moderate to severe Alzheimer's disease"(4). Memantine, in addition to its noncompetitive NMDA receptors antagonism, is very potent α7-nAChR antagonist (5). By its α7-nAChR antagonism it blocks meningitic E. coli K1 bacteria neuroinvasion in mice (5). Also it may exerts its protective, anti-inflammatory effects by suppression of cytokine expression, as demonstrated in an experimental model of lung injury (6). As an adamantine derivate, in cell cultures memantine inhibits Human coronaviruse 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 level of inflammation by release of proinflammatory cytokines such as tumor necrosis factor alpha, interleukin 1, interleukin 6 and by inducing microphage/microglial hyper-activation in 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 corona virus replication rate in the central nervous system, dose-dependently (7,9). Also memantine might exert anti-inflammatory

effects by reducing angiogenesis and brain lymphocyte infiltration, as shown in mice infected with Japanese encephalitis virus (JEV) (10). In conclusion, we might hypothesize 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 confirmations.

Acknowledgement:

This study is not financially supported.

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