

Possible Neurological and Mental Outcomes of COVID-19 Infection: A Hypothetical Role of ACE-2/Mas/BDNF Signaling Pathway

Hypothesis

The outbreak of coronavirus (COVID-19) infections is a public health emergency during the years 2109–2020 and cause international concern. Coronaviruses are a group of viruses that cause diseases in mammals and birds.^[1,2] In humans, coronaviruses cause respiratory tract infections that are typically mild, such as the common cold, though rarer forms such as SARS (severe acute respiratory syndrome), Middle East respiratory syndrome coronavirus (MERS) and COVID-19 (coronavirus disease-19) can be lethal.^[1,2] Symptoms vary in humans: but according to current data, they cause upper respiratory tract diseases and between 2 and 3% of infected persons will die in high-risk. Also, there is no enough information about long-term sequels of infection by the family of the mentioned virus in the infected person. But some indirect evidence suggested that which infection caused by coronavirus family can lead to neurological and mental sequels, but it is not proven yet.^[2-4] Based on the recent data released, angiotensin-converting enzyme 2 (ACE2) can act as functional and host receptor for coronaviruses, especially COVID-19,^[5,6] and it seems that some parts of sequels of this virus in respiratory and probably cardiovascular system was mediated via inhibition of ACE-2, but this was not exactly clarified.^[6] On the other way, it was suggested that ACE-2 is one of the

main enzymes, which by the mediation of some important protein such as Mas protein, regulates normal brain function and release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF)^[7,8] BDNF has a critical role in neurodevelopment, neurogenesis, inhibition of occurrences of neurodegeneration, and normal mood behavior such as mood stability and cognitive function.^[9] According to this concept, it was approved that decrease activity of ACE-2 or reduction of its expression by some natural and acquired accident can disturb normal neurological and mental activity and can remain long term sequels.^[8,10,11] Taken together according to recent studies, it was suggested that ACE-2 can be a target for COVID-19 in a strategic organ such as the brain and based on these data, it can be assumed that infection by COVID-19 may cause inhibition of ACE-2 and its downstream, BDNF, thus, it can instigate neurodegeneration (increase of oxidative stress, neuroinflammation, and apoptosis) and can probably cause mentally related disorders such as anxiety, depression, and cognition impairment. Although this claim is a hypothesis and effect of COVID-19 infection should be evaluated in an infected person [Figure 1].

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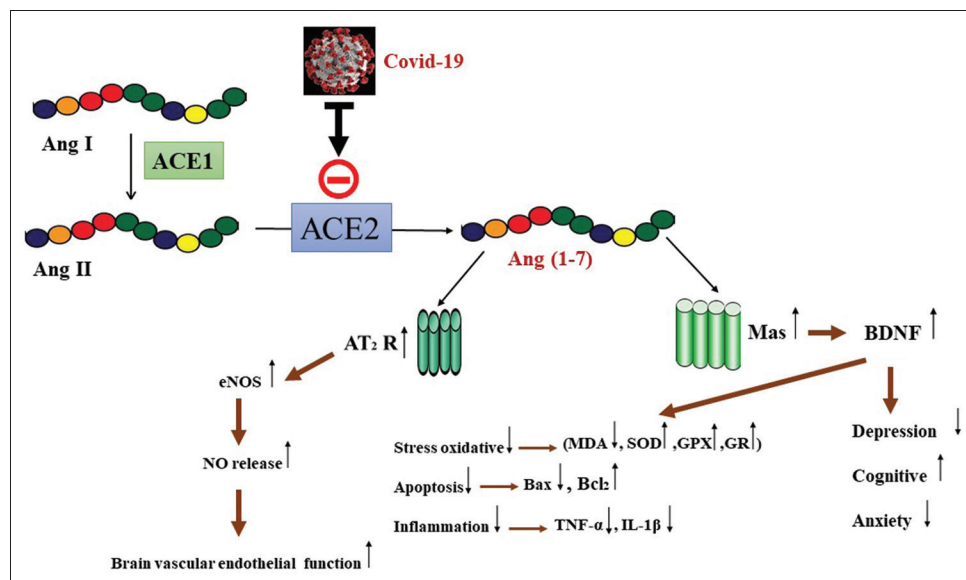


Figure 1: Angiotensin-converting enzyme 2 (ACE2) causes the production of angiotensin (1-7) Ang-(1-7) from angiotensin-2 (AngII). Ang (1-7) causes the production of Mas protein, which leads to the formation of brain-derived neurotrophic factor (BDNF), as the main protein in neurogenesis, and inhibits occurrences of oxidative stress, inflammation and apoptosis and also cause modulation of the mood-related disorder. Ang (1-7) causes activation of AT_2R , which is angiotensin receptor type-2. Activation of AT_2R plays a critical role in the management of the normal function of brain vascular endothelial. According to some indirect evidence, it seems the infection by the COVID-19 virus can cause distributing ACE-2/Mas/BDNF signaling pathway and can have unknown neurological and mental sequels. eNOS: Endothelial-derived nitric oxide synthases; NO: Nitric oxide; MDA: Malondialdehyde; SOD: Superoxide dismutase; GPX: Glutathione peroxidase; GR: Glutathione reductase; TNF- α : Tumor necrosis factor-alpha; IL-1 β : Interleukin 1- β

Conflicts of interest

There are no conflicts of interest.

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