

Can Infection of COVID-19 Virus Exacerbate Alzheimer's Symptoms? Hypothetic Possible Role of Angiotensin-Converting Enzyme-2/Mas/ Brain-Derived Neurotrophic Factor Axis and Tau Hyper-phosphorylation

Hypothesis

During the years of the 2019–2020 outbreak of infection, one of the members of coronavirus, coronavirus disease-19 (COVID-19), becomes a global concern and is a public health emergency.^[1,2] Infection by coronaviruses causes mild respiratory tract disorder, such as the common cold, but rare forms of infections with this family of viruses such as severe acute respiratory syndrome, Middle East respiratory syndrome coronavirus, and COVID-19 can be lethal and can remain long-term sequels.^[2,3] Unfortunately, there is no enough information on long-term sequels of infection by COVID-19 in an infected person.^[3,4] However, based on some indirect evidence and documents, it can be hypostatized that infection with coronavirus family, especially COVID-19, can cause neurological disorder or exacerbate existing disease in an infected person, but it is not proven yet.^[4,5] According to recent studies, angiotensin-converting enzyme 2 (ACE2) can be acts as functional and host receptor of COVID-19.^[6,7] It seems that some parts of the sequels of COVID-19 in the respiratory and cardiovascular system were mediated via the inhibition

of ACE-2, but the mechanism of involvement of this ACE-2 was not exactly clarified.^[8,9] On the other way, it was suggested that ACE-2 is one of the main enzymes which by the mediation of some important proteins such as Mas protein regulates normal brain functions such as cognitive activity and release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF).^[10,11] Furthermore, there are novel studies that indicate that the reduced activity of the ACE-2/Ang (1–7)/Mas axis is strongly linked to Tau hyper-phosphorylation (inactivation) and aggregation of neural internal microtubules and amyloid- β ($A\beta$) peptides.^[12,13] According to these data, it was established that the reduction of ACE-2 activity or expression can disturb normal brain cognition activity or can exacerbate Alzheimer's disease.^[13,14] Thus, according to the mentioned studies, it was hypothesized that infection with COVID-19 can target and reduce ACE-2 activity, and/or expression, and probably its downstream Mas/BDNF axis, in the brain cells, and according to these data, it can be expected that infection by COVID-19 may cause disturbances in cognition activity and also exacerbate cognitive impairment in infected person with Alzheimer's disease [Figure 1].

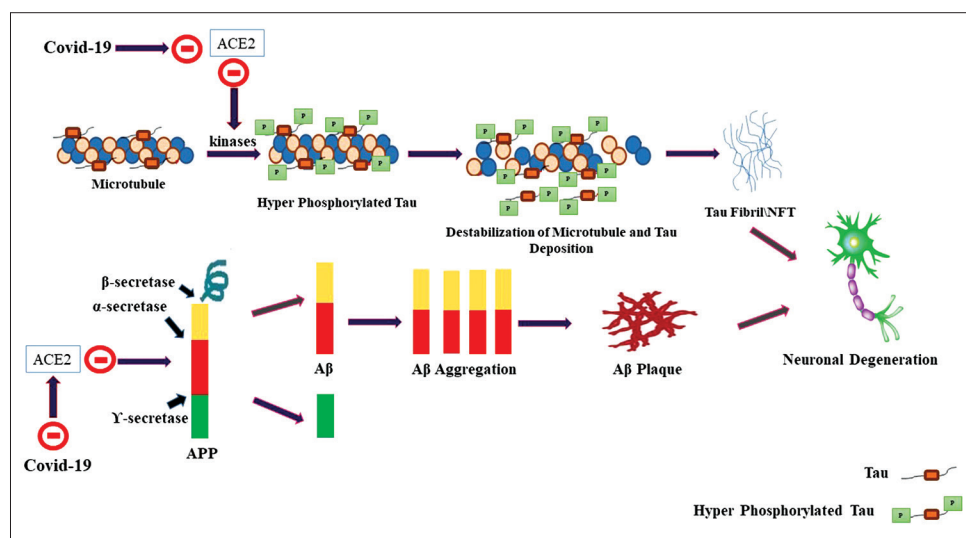


Figure 1: In the pathophysiology of Alzheimer's disease, some intrinsic and extrinsic triggers cause activation of some kinases which led to hyper-phosphorylation of Tau protein. This Tau hyper-phosphorylation causes disability of microtubules, which consequently causes aggregation of tau protein (Tau fibril) and neuro-filaments. On the other way, some intrinsic and extrinsic triggers cause activation of secretase family enzymes which initiate degradation of Amyloid precursor protein and led to production and formation of amyloid-beta. Amyloid-beta, Tau fibril/neuro-filament causes degeneration neural cells which cause Alzheimer's disease or dementia. As mentioned in the text, angiotensin-converting enzyme-2 causes inhibition of secretases family enzymes and kinases enzymes which can inhibit occurrences of Alzheimer's disease, dementia, or cognition impairment. According to some indirect evidence, it seems that infection with the COVID-19 virus can cause inhibition of the angiotensin-converting enzyme-2 signaling pathway, and it might be can have long-term neurological sequels such as activation of Alzheimer's or dementia triggers signaling pathway

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Sareh Kermanshahi, Mina Gholami¹, Majid Motaghinejad

From the Razi Drug Research Center, Iran University of Medical Sciences, ¹Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran


Address for correspondence:

Dr. Majid Motaghinejad,
Iran University of Medical Sciences, P. O. Box: 14496-14525,
Sheykhfazelolah Highway, Tehran, Iran.
E-mail: motaghinezhad.m@iums.ac.ir

References

1. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. *Lancet* 2020;395:809-15.
2. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420-2.
3. Paules CI, Marston HD, Fauci AS. Coronavirus infections – More than just the common cold. *JAMA* 2020;323:707-8.
4. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol* 2020;92:552-555.
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: A retrospective case series study. *JAMA Neurol* 2020;1127:E1-E8.
6. Kuhn JH, Radoshitzky SR, Wenhui Li, Wong SK, Choe H, Farzan M. The SARS coronavirus receptor ACE 2 a potential target for antiviral therapy. In: *New Concepts of Antiviral Therapy*. Springer; 2006. p. 397-418.
7. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, *et al.* Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* 2020;6:1-4.
8. Chen L, Hao G. The role of angiotensin converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease. *Cardiovasc Res* 2020. pii: cvaa093.
9. Diao B, Feng Z, Wang C, Wang H, Liu L, Wang C, *et al.* Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. *medRxiv*; 2020.
10. Jiang T, Gao L, Lu J, Zhang YD. ACE2-Ang-(1-7)-mas axis in brain: A potential target for prevention and treatment of ischemic stroke. *Curr Neuropharmacol* 2013;11:209-17.
11. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: Properties and future directions. *J Neurochem* 2008;107:1482-94.
12. Jiang T, Zhang YD, Zhou JS, Zhu XC, Tian YY, Zhao HD, *et al.* Angiotensin-(1-7) is Reduced and Inversely Correlates with Tau Hyperphosphorylation in Animal Models of Alzheimer's Disease. *Mol Neurobiol* 2016;53:2489-97.
13. Kehoe PG, Wong S, Al Mulhim N, Palmer LE, Miners JS. Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid- β and tau pathology. *Alzheimers Res Ther* 2016;8:50.
14. Bodiga VL, Bodiga S. Renin angiotensin system in cognitive function and dementia. *Asian J Neurosci* 2013;2013:1-18.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online	
Quick Response Code:	Website:
	www.advbiores.net
	DOI:
	10.4103/abr.abr_72_20

How to cite this article: Kermanshahi S, Gholami M, Motaghinejad M. Can infection of COVID-19 virus exacerbate Alzheimer's symptoms? Hypothetic possible role of angiotensin-converting enzyme-2/Mas/brain-derived neurotrophic factor axis and Tau hyper-phosphorylation. *Adv Biomed Res* 2020;9:36.

Received: 05 April 2020; **Revised:** 23 May 2020;
Accepted: 16 May 2020; **Published:** 28 August 2020

© 2020 Advanced Biomedical Research | Published by Wolters Kluwer - Medknow