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Mini Review

The ACE2 COVID-19 target in Alzheimer's disease

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Introduction

The COVID-19 pandemic is caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). SARS-CoV-2 spike proteins target the angiotensin-converting enzyme 2 (ACE2) receptors localized mainly in the lungs. Recent studies have shown that SARS-CoV-2 also targets the CNS neurons and glial cells, triggering a cytokine immune-inflammatory response, compromising the blood-brain barrier, and ultimately causing neuronal death [1,2]. Thus, neurological diseases like Alzheimer's disease (AD) are a particular comorbidity for COVID-19.

AD is the main form of dementia, mostly found in patients around 60 years. AD patients are especially vulnerable due to their social isolation, high dependency on caregivers or family members, and economic condition. Which, added to the COVID-19 isolation protocols, can worsen their mental health condition [3]. AD is a neurodegenerative disease characterized by synaptic and neuronal loss in brain regions related to memory and cognition. There is an extracellular accumulation of the amyloid-beta (A) peptide and the aberrant intracellular deposits of the Tau protein as neurofibrillary tangles (NFT) [4].

One of the relevant factors for the pathogenesis of AD is the renin-angiotensin system (RAS) through the Angiotensin II signaling cascade. Moreover, it has been described as protective for neurons [5]. Angiotensin II conversion into Angiotensin (1–7) by ACE2, and activation of the downstream Mas axis, enhanced learning and memory processing, as seen in mouse intracerebroventricularly injected with $(A\beta)_{1-40}$ [6]. Therefore, the RAS system has been addressed as protective for the CNS.

However, ACE2 expression in AD is quite controversial. Joo and colleagues' letter to the editors of the Journal of Infection showed that the brain cortex of 5xFAD mice model of AD and AD patients in different stages of the disease had high levels of the Ace2 gene using GWAS analysis [7]. Similar results were published in a preprint by Suzuki and colleagues, where western-blot of ACE2 showed higher protein levels in the brain of 13 AD patients compared to control subjects [8]. However, ACE2 protein expression remains upregulated independently of their A burden or NFT score ("ABC" score) [9], which means that ACE2 upregulation in AD is independent of the severity of the disease.

Interestingly, Miners and colleagues had probed before that ACE2 activity measured with SensoLyte® 390 assay kit is reduced in the mid-frontal cortex of 90 AD patients' post-mortem brain tissue compared with age-matched controls [10]. They also probed that ACE2 activity was reduced in the mid-frontal cortex at advanced Braak stages V-VI when neurofibrillary tangles have reached the neocortex (fully developed AD) [11]. Recently, a deeper analysis of ACE2 expression in AD was performed. Qiu and colleagues mapped the expression level of ACE2 in 12 brain regions of AD and non-AD age-matched donors through immunohistochemistry [12] classified using the "ABC" score [9]. They probed that ACE2 is differentially expressed among tissues in AD patient's brains. ACE2 was downregulated in the basal nucleus, hippocampus, entorhinal cortex, middle frontal gyrus, and visual cortex of AD patients. Interestingly, ACE2 expression was significantly different in neurons, not in microglia or astrocytes.

Altogether, these results highlight the importance of ACE2 as a target in the CNS when considering it for treatments and manage symptoms of COVID-19 in AD patients.

References

1. Baig AM, Khaleeq A, Ali U, Syeda H (2020) Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci 11(7): 995-998.
2. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, et al. (2019) Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? Viruses. 12(1): 14.
3. Kumar A, Salinas J (2021) The Long-Term Public Health Impact of Social Distancing on Brain Health: Topical Review. Int J Environ Res Public Health. 18(14): 7307.
4. Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. Science 256(5054): 184-185.
5. Kehoe PG, Miners S, Love S (2009) Angiotensins in Alzheimer's disease - friend or foe? Trends Neurosci. 32(12): 619-628.
6. Dong YF, Kataoka K, Tokutomi Y, Nako H, Nakamura T, Toyama K, et al. (2011) Perindopril, a centrally active angiotensin-converting enzyme inhibitor, prevents cognitive impairment in mouse models of Alzheimer's disease. FASEB J 25: 2911-2920.
7. Lim KH, Yang S, Kim SH, Joo JY (2020) Elevation of ACE2 as a SARS-CoV-2 entry receptor gene expression in Alzheimer's disease (Letter to the editor). J Infect 81(3): e33-e34.
8. Ding Q, Shults NV, Harris BT, Suzuki YJ (2020) Angiotensin-converting enzyme 2 (ACE2) is upregulated in Alzheimer's disease brain. bioRxiv 10.08.331157.
9. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, et al. (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 8: 1-13.
10. Kehoe PG, Wong S, Al Mulhim N, Palmer LE, Miners JS (2016) Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid-β and tau pathology. Alzheimers Res Ther 8(1): 50.
11. H Braak, E Braak (1995) Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 16(3):271-8; discussion 278-284.
12. Cui H, Su S, Cao Y, Ma C, Qiu W (2021) The Altered Anatomical Distribution of ACE2 in the Brain with Alzheimer's Disease Pathology Front. Cell Dev Biol Fcell 684874.