Letter to the Editor Regarding the Viewpoint "Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanism"

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Dear Editor,

I have read with interest the viewpoint entitled *Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanisms* by Baig et al.[1] This letter is supposed to supplement the aforementioned article with expanded scope on pathophysiological mechanisms which could prove salient in elucidating pathogenesis, seeking treatment, or considering clinical implications.

1. RECEPTORS FOR VIRAL ENTRY AND THEIR DISTRIBUTION

Besides the heart, kidneys, and testes having been found as initial sites of angiotensin-converting enzyme 2 (ACE2) expression, endothelial and neuronal presence was confirmed, with ultimate consensus stating the receptor is almost ubiquitous.[2,3] Although mRNA expression showed a clear presence of ACE2 receptor in various human neuronal regions, immunohistochemistry for ACE2 receptor of central nervous system (CNS) tissue, though with limited description, failed to show neuronal or glial positivity but did confirm it in the brain vasculature.[4] Translating the known about the severe acute respiratory syndrome coronavirus (SARS-CoV), it has been shown that full interaction of the virus with the ACE2 receptor is enabled once the viral spike protein is cleaved by surface proteases, namely, transmembrane serine protease 2 (TMPRSS2),[5] although some findings argue against the strict necessity of the step.[6] Moreover, lysosomal related components, namely, cathepsin L, 1-phosphatidylinositol 3-phosphate 5-kinase, and two pore channel-2 also have a role in initial viral interaction with the host cell.[6,7] An additional receptor binding the spike protein has been possibly recognized in CD147 by an in vitro experiment.[8] Both cathepsin L and CD147 are widely present in the CNS.[9,10] TMPRSS2 is only scantly present in the brain (brainstem, globus pallidus, insula, temporal lobe, occipital lobe, and postcentral gyrus).[11] A detailed study of nasal epithelium did not show TMPRSS2 presence in the neuronal component but did on the respiratory epithelium.[12]

Notably, SARS-CoV was confirmed in postmortem neurons and glial cells of human patients with fatal systemic manifestations.[13] A non-peer-reviewed report claims there was a case of symptomatic encephalitis with detected SARS-CoV-2 in cerebrospinal fluid.[14]

2. HOST–VIRUS INTERACTION ROUTES

The spread of the virus and the neuroinvasive potential have been proposed according to the known routes of SARS-CoV[15] and a growing body of findings specific for SARS-CoV-2.[16] Although hematologic spread is a known route for systemic viral dissemination, it has been postulated that the virus could also advance from the periphery to the CNS via retrograde neuronal transport and synaptic connections, notably vagal nerve afferents from the lung.[16] The concept of the pentapartite synapse as a nexus of endothelial, glial, neuronal, and immune cells opens a possibility for this mechanism.[17] However, with the growing findings of SARS CoV-2 infecting cells in the gastrointestinal tract,[18] the neuroinvasive potential could encompass the enteric nervous system and subsequent vagal and sympathetic afferents to the CNS. Previous experimental work on coronaviruses has shown retrograde neuronal transport as a viable route for viral invasion,[19] but it remains to be established for SARS-CoV-2 in particular. Exosomal cellular transport has also been shown as a mode of systemic viral dissemination, and it could include SARS-CoV-2.[20] Following SARS-CoV-2 infection and immune activation, CD4^{+} T-cells produce granulocyte-macrophage colony-stimulating factor which further induces macrophage lines to secrete interleukin-6 (IL-6), occasionally causing a vicious cycle of cytokine storm, a most concerning clinical presentation. However, lymphatic spread of the virus via immune cells has not been postulated as no experimental data confirmed viral presence in these cells or the presence of ACE2 receptor[4,21]

3. CLINICAL PATHOPHYSIOLOGICAL IMPLICATIONS

Secondary neuroinflammation related to systemic immune activation could be mediated by lymphatic routes[22] which could contribute to encephalopathy, a common neurological manifestation of SARS-CoV-2 infection.[23,24] Per experimental experience with SARS-CoV, aside from this secondary neuroinflammation, primary neuronal infection results in

increased secretion of IL-6,[15] an already recognized salient molecule implicated in cytokine storm. The aforementioned case of encephalitis may corroborate such a notion.[14] Additionally, systemic inflammation related metabolic and homeostatic derangements contributes to encephalopathy, but it may also predispose one to stroke, which has been noted to occur more commonly in severe clinical presentations.[25] Besides the acute neurological manifestations of SARS CoV-2 infection, further monitoring for long-term sequelae may reveal viral contribution in pathophysiology or increased risk for neuroinflammatory and neurodegenerative diseases. It has been shown in animal and human studies that coronaviruses could possibly be implicated in the pathogenesis of Parkinson's disease,[26] acute disseminated encephalomyelitis,[27] or multiple sclerosis.[23,28] In already established neurologic patients and even more so, those under active immunomodulating therapies, noticing trends in acute and chronic disease presentation or course may provide valuable insights in guiding acute management and determining the neuropathologic aspects of SARS-CoV-2. Exemplary neurologic features of SARS CoV-2 include anosmia and dysgeusia.[29] For the former, it could be argued it is more, or even exclusively, related to the respiratory epithelium infection and subsequent inflammation, but for the latter it still remains an open question. High expression of ACE2 was found on tongue epithelium,[30] but animal studies show ACE2 expression in the nucleus of the solitary tract,[31] which could point to central cause of dysgeusia and a possible neuroinvasive route by continuous local or retrograde vagal axonal transport. Further research is warranted, and this letter should supplement the original publication to expand the scope and understanding of pathogenesis, and posit some reasonable hypotheses that could be scientifically scrutinized.

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Notes

■ REFERENCES

(1) Baig, A. M., Khaleeq, A., Ali, U., and 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*, 995.

(2) Xia, H., and Lazartigues, E. (2008) Angiotensin-converting enzyme 2 in the brain: properties and future directions. *J. Neurochem. 107* (6), 1482−1494.

(3) Harmer, D., Gilbert, M., Borman, R., and Clark, K. L. (2002) Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett. 532* (1−2), 107−110.

(4) Hamming, I., Timens, W., Bulthuis, M., Lely, A., Navis, G., and van Goor, H. (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol. 203* (2), 631−637.

(5) Hoffmann, M., Kleine-Weber, H., Schroeder, S., et al. (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell,* DOI: 10.1016/j.cell.2020.02.052.

(6) Ou, X., Liu, Y., Lei, X., et al. (2020) Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun. 11* (1), 1620.

(7) Iwata-Yoshikawa, N., Okamura, T., Shimizu, Y., Hasegawa, H., Takeda, M., Nagata, N., and Gallagher, T. (2019) TMPRSS2 Contributes to Virus Spread and Immunopathology in the Airways of Murine Models after Coronavirus Infection. *J. Virol. 93* (6), e01815-18.

(8) Wang, K., Chen, W., and Zhou, Y.-S. (March 14, 2020) SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *bioRxiv,* DOI: 10.1101/2020.03.14.988345.

(9) Podvin, S., Wojnicz, A., and Hook, V. (2018) Human brain gene expression profiles of the cathepsin V and cathepsin L cysteine proteases, with the PC1/3 and PC2 serine proteases, involved in neuropeptide production. *Heliyon. 4* (7), e00673.

(10) Catepsin L. *The Human Protein Atlas*, https://www.proteinatlas.org/ENSG00000172270-BSG/brain (accessed 2020-03-31).

(11) TMPRSS2. *The Human Protein Atlas*, https://www.proteinatlas.org/ENSG00000184012-TMPRSS2/brain (accessed 2020-03-31).

(12) Brann, D., Tsukahara, T., Weinreb, C., Logan, D. W., and Datta, S. R. (March 28, 2020) Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients *bioRxiv,* DOI: 10.1101/2020.03.25.009084.

(13) Xu, J., Zhong, S., Liu, J., et al. (2005) Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin. Infect. Dis. 41* (8), 1089−1096.

(14) Beijing hospital confirms nervous system infections by novel coronavirus. *XinhuaNet*, 2020, http://www.xinhuanet.com/english/2020-03/05/c_138846529.htm (accessed 2020-03-31).

(15) Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., and Perlman, S. (2008) Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2. *J. Virol. 82* (15), 7264−7275.

(16) Li, Y., Bai, W., and Hashikawa, T. (2020) The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J. Med. Virol.,* DOI: 10.1002/jmv.25728.

(17) De Luca, C., Colangelo, A. M., Virtuoso, A., Alberghina, L., and Papa, M. (2020) Neurons, Glia, Extracellular Matrix and Neurovascular Unit: A Systems Biology Approach to the Complexity of Synaptic Plasticity in Health and Disease. *Int. J. Mol. Sci. 21* (4), 1539.

(18) Wong, S. H., Lui, R. N., and Sung, J. J. (2020) Covid-19 and the Digestive System. *J. Gastroenterol. Hepatol.,* DOI: 10.1111/jgh.15047.

(19) Dubé, M., Le Coupanec, A., Wong, A. H. M., Rini, J. M., Desforges, M., Talbot, P. J., and Diamond, M. S. (2018) Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. *J. Virol. 92* (17), e00404-18 DOI: 10.1128/JVI.00404-18.

(20) Alenquer, M., and Amorim, M. (2015) Exosome Biogenesis, Regulation, and Function in Viral Infection. *Viruses 7* (9), 5066−5083.

(21) ACE2. *The Human Protein Atlas*, https://www.proteinatlas.org/ENSG00000130234-ACE2/blood (accessed 2020-03-31).

(22) Louveau, A., Herz, J., Alme, M. N., et al. (2018) CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat. Neurosci. 21* (10), 1380−1391.

(23) Savarin, C., and Bergmann, C. C. (2017) Viral-induced suppression of self-reactive T cells: Lessons from neurotropic coronavirus-induced demyelination. *J. Neuroimmunol. 308*, 12−16.

(24) Filatov, A., Sharma, P., Hindi, F., and Espinosa, P. S (2020) Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy. *Cureus,* DOI: 10.7759/cureus.7352.

(25) Li, Y., Wang, M., and Zahou, Y. (2020) Acute Cerebrovascular Disease Following COVID-19: A Single Center, Retrospective, Observational Study. *Lancet,* DOI: 10.2139/ssrn.3550025.

(26) Fazzini, E., Fleming, J., and Fahn, S. (1992) Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov. Disord. 7* (2), 153−158.

(27) Ann Yeh, E., Collins, A., Cohen, M. E., Duffner, P. K., and Faden, H. (2004) Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. *Pediatrics 113* (1), e73−6.

(28) Dessau, R. B., Lisby, G., and Frederiksen, J. L. (2001) Coronaviruses in brain tissue from patients with multiple sclerosis. *Acta Neuropathol. 101* (6), 601−604.

(29) AAO-HNS: Anosmia, Hyposmia, and Dysgeusia Symptoms of Coronavirus Disease. *ENTConnect,* https://www.entnet.org/content/aao-hns-anosmia-hyposmia-and-dysgeusia-symptoms-coronavirus-disease (accessed 2020-03-31).

(30) Xu, H., Zhong, L., Deng, J., et al. (2020) High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int. J. Oral Sci. 12* (1), 8.

(31) Yamazato, M., Ferreira, A. J., Yamazato, Y., et al. (2011) Gene transfer of angiotensin-converting enzyme 2 in the nucleus tractus solitarius improves baroreceptor heart rate reflex in spontaneously hypertensive rats. *JRAAS 12* (4), 456−461.