DOI: 10.1002/jmv.25826

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19

To the Editor,

I have read with great interest the paper by Li et al[1] entitled "The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients." I would like here to provide arguments indicating that an alteration of the dopamine synthetic pathways is possibly involved in the pathophysiology of COVID-19. A simple bioinformatics approach to predict new roles for any given gene consists in identifying the coexpression network it integrates with. To unravel putative neural impacts of SARS-CoV2 infections, such a "culprit-by-association" strategy may be applied to Angiotensin I Converting Enzyme 2 (*ACE2*), the gene encoding the main receptor to SARS-CoV2, SARS-CoV, and MERS-CoV. To this aim, multiexperiment matrix (MEM)[2] is a robust web tool allowing to combine and integrate correlation links between messenger RNA (mRNA) levels across a large number of human microarray datasets (precisely 2811). Surprisingly, according to MEM, the gene exhibiting the most statistically significant coexpression link with *ACE2* is Dopa Decarboxylase (DDC) (*P*: 2.39E-61; Pearson correlation test). Based on the hypothesis put forward by Li et al[1], this observation is possibly interesting for several reasons. DDC is indeed a major enzyme of both the dopamine and the serotonin synthetic pathways as it converts L-3,4-dihydroxyphenylalanine (L-DOPA) into dopamine and L-5-hydroxytryptophan into serotonin. In addition, DDC also supports the conversion of histidine into histamine. That *ACE2* coregulates with *DDC* indicates a possible functional link between the ACE2-mediated synthesis of angiotensin 1-7 and the DDC-mediated synthesis of dopamine and serotonin. Arguing for the existence of such a link, brain dopamine contents were shown to be increased following infusion of angiotensin 1-7 in the hypothalamus of rats.[3] Along this line, angiotensin 1-7 was shown to stimulate the renal synthesis of dopamine.[4] Conversely, that *ACE2* coregulates with *DDC* also implies that any SARS-CoV2-induced downregulation of ACE2 expression, a process previously demonstrated for SARS-CoV,[5] might be paralleled by alterations of both the dopamine and serotonin synthetic pathways. Supporting this view, *ACE2* knockout (KO) mice were reported to exhibit dramatically low serotonin levels in both the blood and brain.[6] Dopamine levels were not assessed in this study but should be explored in future studies. While patients with COVID-19 might suffer from of a central autonomic failure of respiratory functions, it is important to keep in mind that *ACE2* and *DDC* may coexpress and coregulate in nonneuronal cell types. Indeed, among the microarray datasets compiled in MEM, the most significant correlations between *ACE2* and *DDC* mRNA levels are found in studies exploring colorectal adenocarcinoma samples. Confirming this observation, a survey of the database "Human Protein Atlas," the currently largest protein expression atlas of normal human tissues, shows that ACE2 and DDC are both highly expressed in intestinal epithelial cells. Since intestinal epithelial cells were shown to convert L-DOPA into dopamine[6] and to provide an important source of blood-circulating dopamine,[7] one may hypothesize that a defective expression of *ACE2* and *DDC* in intestinal cells may translate into altered levels and/or regulation of dopamine in the blood of patients with COVID-19. This is all the more interesting as experiments performed in mice demonstrate that dopamine may shape lung immunity via dopamine receptors expressed by alveolar epithelial cells,[8] lung macrophages,[8] and lung terminal nerves.[9] In particular, in a murine model of endotoxin-induced acute lung injury, the dopamine D1 receptor agonist fenoldopam was shown to dampen inflammation as well as lung permeability and pulmonary edema.[8] The potential protective role of dopamine in the context of viral infections has been poorly investigated until now. In this regard, it is worth noting that in a recent work, DDC was found to negatively regulate the replication of the Flaviviridae viruses dengue and hepatitis C.[10] Experimental research works are needed to clarify the links between ACE2 and DDC during SARS-CoV2 infection. Moreover, in patients suffering from severe forms of COVID-19, the hypothesis of a systemic failure of the dopamine synthetic pathway should be taken into account and further explored.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

Serge Nataf[1,2,3]

[1]*Bank of Tissues and Cells, Hôpital Edouard Herriot, Lyon University Hospital, Lyon, France*
[2]*CarMeN Laboratory, INSERM 1060, INRA 1397, INSA, Oullins, France*
[3]*Department of Cytology/Histology, Lyon-Est School of Medicine, University Claude Bernard Lyon-1, Lyon, France*

Correspondence
Serge Nataf, Bank of Tissues and Cells, Hôpital Edouard Herriot, Lyon University Hospital, F-69000 Lyon, France.
Email: serge.nataf@inserm.fr

ORCID

Serge Nataf http://orcid.org/0000-0003-3462-579X

REFERENCES

1. Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure

of COVID-19 patients [published online ahead of print April 4, 2020]. *J Med Virol*. https://doi.org/10.1002/jmv.25826

2. Adler P, Kolde R, Kull M, et al. Mining for coexpression across hundreds of datasets using novel rank aggregation and visualization methods. *Genome Biol*. 2009;10(12):R139. https://doi.org/10.1186/gb-2009-10-12-r139
3. Pawlak R, Napiorkowska-Pawlak D, Takada Y, et al. The differential effect of angiotensin II and angiotensin 1-7 on norepinephrine, epinephrine, and dopamine concentrations in rat hypothalamus: the involvement of angiotensin receptors. *Brain Res Bull*. 2001;54(6):689-694. https://doi.org/10.1016/S0361-9230(01)00489-0
4. Banday AA, Diaz AD, Lokhandwala M. Kidney dopamine D1-like receptors and angiotensin 1-7 interaction inhibits renal Na+ transporters. *Am J Physiol Renal Physiol*. 2019;317(4):F949-F956. https://doi.org/10.1152/ajprenal.00135.2019
5. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-879. https://doi.org/10.1038/nm1267
6. Klempin F, Mosienko V, Matthes S, et al. Depletion of angiotensin-converting enzyme 2 reduces brain serotonin and impairs the running-induced neurogenic response. *Cell Mol Life Sci*. 2018;75(19):3625-3634. https://doi.org/10.1007/s00018-018-2815-y
7. Xue R, Zhang H, Pan J, et al. Peripheral dopamine controlled by gut microbes inhibits invariant natural killer T cell-mediated hepatitis. *Front Immunol*. 2018;9:2398. https://doi.org/10.3389/fimmu.2018.02398
8. Bone NB, Liu Z, Pittet J-F, Zmijewski JW. Frontline science: D1 dopaminergic receptor signaling activates the AMPK-bioenergetic pathway in macrophages and alveolar epithelial cells and reduces endotoxin-induced ALI. *J Leukoc Biol*. 2017;101(2):357-365. https://doi.org/10.1189/jlb.3HI0216-068RR
9. Wang W, Cohen JA, Wallrapp A, et al. Age-related dopaminergic innervation augments T helper 2-type allergic inflammation in the postnatal lung. *Immunity*. 2019;51(6):1102-1118. e7. https://doi.org/10.1016/j.immuni.2019.10.002
10. Frakolaki E, Kalliampakou KI, Kaimou P, et al. Emerging role of l-dopa decarboxylase in flaviviridae virus infections. *Cells*. 2019;8(8):E837. https://doi.org/10.3390/cells8080837