Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Pharmaceutical Sciences 156 (2021) 105579

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Therapeutic Strategies for SARS-CoV-2 acting on ACE-2

ARTICLE INFO

Keywords:
RAS
SARS-CoV-2
ACE-2
Viral infection

Dear Editor,

Considering the mechanisms of intracellular penetration of SARS-CoV-2, the significant related risk factors, changes in ACE-2 concentration during infection, and the complex interaction of the RAS system with COVID-19, [1,2] modulation of RAS at certain stages of infection could be considered an important therapeutic strategy. In particular, observational clinical studies indicate that in most cases respiratory problems occur a few days after contracting SRAS-CoV-2 infection, suggesting that this may not be caused by direct viral damage, but suggesting that other mechanisms may be responsible, such as loss of ACE2 function and dysregulation of the RAS system pathways resulting in non-activation of the Ace-2/Ang [1–7]/Mas receptor axis [3,4] and hyperactivation of the axis Ace/Ang-2/ AT1r. Probably the binding of the peak coronavirus protein leads to exhaustion of ACE2 receptors, which in turn causes the loss of the protective pulmonary function of the ACE2/MAS axis. [5,6] In addition to the loss of protective function of the ACE2/MAS pathway, the resulting hyperactivation of the ACE/AngII/AT1r pathway leads to excessive tissue Ang II production and stimulation of AT1r with vasoconstriction, inflammatory and fibrotic effects contributing to the epithelial lesion of lung tissue. The presence and formation of pulmonary fibrotic tissue in particular can cause serious damage in the pulmonary architecture with consequent physiological dysfunction. [7] The ACE-2 activation pathway on the contrary leads to synthesis of Ang [1–7] and Ang [1–9] with stimulation of AT2r receptors with antifibrotic, antiflammatory and vasodilating effects. [8]

Based on this, we believe that in the early stages of viral infection, a decrease or blockage of ACE-2 could reduce the intracellular viral penetration, in the most severe stages of infection where lung dysfunction begins to occur, an increase of ACE-2 for example with soluble ACE-2 (rhACE2) or with RAS acting agents can protect against lung injury. While current evidence does not recommend discontinuation of treatments with RAS modifying agents, we believe that modifications of RAS and ACE-2 at the right time could be important to combat COVID-19 infection. Epidemiological studies are necessary to generate the necessary evidence. [9,10]

References

Baig, A.M., Khaleeq, A., Ali, U., Syeda, H., 2020 Mar 13. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS ChemNeuroscienc. https://doi.org/10.1021/acschemneuro.0c00122.

Liu, Z., Xiao, X., Wei, X., Li, J., Yang, Tan H., Zhu, J., Zhang, Q., Wu, J., Liu, L.J., 2020 Feb 26. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV. MedVirol. https://doi.org/10.1002/jmv.25726.2.

Bader, M., 2010. Tissue renin-angiotensin-aldosterone systems: Targets for pharmacological therapy. Annu. Rev. Pharmacol. Toxicol. 50, 439–465.

Nehme, A., Zibara, K., 2017. Efficiency and specificity of RAAS inhibitors in cardiovascular diseases: How to achieve better end-organ protection? Hypertens. Res. 40, 903–909.

Juan Meng, Guohui Xiao, Juanjuan Zhang, Xing He, Min Ou, Jing Bi. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension, show all Pages 757-760 | Received 08 Mar 2020, Accepted 17 Mar 2020.

Vitiello, A., Ferrara, F., 2020. Correlation between renin-angiotensin system and Severe Acute Respiratory Syndrome Coronavirus 2 infection: What do we know? [published online ahead of print, 2020 Jul 14]. Eur J Pharmacol 883, 173373. https://doi.org/10.1016/j.ejphar.2020.173373.

Ferrara, F., Granata, G., Pelliccia, C., La Porta, R., Vitiello, A., 2020 Jun. The added value of pirfenidone to fight inflammation and fibrotic state induced by SARS-CoV-2: Anti-inflammatory and anti-fibrotic therapy could solve the lung complications of the infection? European Journal of Clinical Pharmacology. https://doi.org/10.1007/s00228-020-02947-4.

Zhang, Haibo, Penninger, Josef M., Li, Yimin, Zhong, Nanshan, Slutsky, Arthur S., 2020. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine.

Keidar, S., et al., 2005. Mineralocorticoid receptor blocker increases angiotensin- converting enzyme 2 activity in congestive heart failure patients. Circ. Res. 97, 946–953.

Ferrario, C.M., et al., 2005. Effect of angiotensin- converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin- converting enzyme 2. Circulation 111, 2605–2610.

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https://doi.org/10.1016/j.ejps.2020.105579
Received 2 September 2020; Accepted 25 September 2020
Available online 30 September 2020