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Angiotensin converting enzyme-2 as therapeutic target in COVID-19

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ABSTRACT

The pandemic of coronavirus disease 2019 (COVID-19) is a global health emergency that poses a significant threat to world people’s health. This outbreak causes major challenges to healthcare systems. Given the lack of effective treatments or vaccine for it, the identification of novel and safe drugs against COVID-19 infection is an urgent need. Angiotensin-converting enzyme 2 (ACE2) is not only an entry receptor of the SARS-CoV-2 virus, the virus that causes COVID-19, but also can protect from lung injury. In this view, we highlighted potential approaches to address ACE2-mediated SARS-CoV-2 virus, including 1) delivering an excessive soluble form of ACE2 (recombinant human ACE2: rhACE2) and 2) inhibition of the interaction between SARS-CoV-2 virus and ACE2 by some compounds with competitive effects (morphine and codeine). Further clinical trials in this regard can reveal a more definite conclusion against the COVID-19 disaster.

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1. SARS-CoV-2: prevalence, phylogenetics and angiotensin-converting enzyme 2 (ACE2) receptor

After the first emergence of novel Coronavirus (COVID-19) in China in December 2019, the pandemic is now spreading at an accelerating rate to other areas worldwide. As of April 28, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected a total of 3,002,303 confirmed cases, with 208,131 deaths in most countries across the world. Recent evidence showed that diabetic, hypertensive, obese, and elderly patients have the highest prevalence of COVID-19 infection [2].

The SARS-CoV-2 is a positive-sense single-stranded RNA (ssRNA) virus with an envelope constituted spike (S) protein as a critical mediator for entering to the host cells [3]. Based on recent evidence, SARS-CoV-2 has high phylogenetic similarities to the human SARS-CoV genome (responsible for the 2002 global outbreak) at the nucleotide sequences (~79%–82%). It has been supposed that the SARS-CoV-2 virus, similar to SARS CoV, exploits the same receptors, namely the angiotensin-converting enzyme 2 (ACE2) for entering host cells [4,5].

Heart, brain, oral and nasal mucosa, nasopharynx, kidney, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver and blood vessels are main organs expressing ACE2 and can be the target of SARS-CoV-2 virus [6,7]. Beyond that, lung alveolar epithelial cells have been known as the most dominate cell type for ACE2 expression [8]. It’s supposed that SARS-CoV-2 may interface with the renin-angiotensin system (RAS) via ACE2. RAS is a hormonal cascade that orchestrates key processes in human physiology, including blood pressure and volume homeostasis [9].

Angiotensinogen (AGT) as a key substrate of the RAS is mainly synthesized by the liver and is cleaved by renin to form Ang I (pro-angiotensin). In the pulmonary circulation, Ang I is easily activated to Ang II by angiotensin-converting enzyme (ACE). In this process, ACE acts as a “peptidyl dipeptidase” and processes the deca-peptide Ang I to the 8-amino acid peptide Ang II. Ang II is one of the most known vasoconstrictors [10]. ACE2 is another key enzyme in RAS cascade with a 17-amino acids N-terminal signal peptide and a C-terminal membrane anchor. This type I trans-membrane protein cleaves the C-terminal amino acid of angiotensin I (Ang I) to the nonapeptide Ang 1–9. ACE2 also directly converts Ang II to Ang 1–7, which activates C protein-coupled MAS receptor. ACE2/Ang 1–7/Mas axis is a vasodilator with antioxidant and anti-inflammatory properties. The catalytic domain of ACE2 is located at the extracellular side of the cell. This domain can be cleaved and released into blood by a disintegrin and metalloproteinase domain 17 (ADAM17) [11,12]. ACE2 as a key counterregulatory enzyme can attenuate vasoconstriction, sodium retention, pro-inflammatory
effects and pro-fibrotic effects of Ang II by its degradation to Ang 1–7, thereby attenuating its effects [13]. In other words, the ACE2/angiotensin 1–7 axis has opposite effect to the ACE/angiotensin II axis [14]. In general, it can be said that the ACE2 axis can negatively regulate the ACE axis.

The interaction between the SARS-CoV-2 virus and ACE2 has been supposed to be a potential feature in their infectivity [15]. There are some possible approaches to address ACE2-mediated SARS-CoV-2 virus, including:

1.1. Delivering excessive soluble form of ACE2

In animal models, it has been shown that SARS-CoV can down-regulate ACE2 protein (but not ACE) via binding its spike protein and intensify the lung damage [16]. Since, the ACE2/angiotensin 1–7 axis can be effective in protecting the lung from developing acute respiratory distress syndrome (ARDS) as a main complication of coronaviruses, recently, the recombinant human ACE2 (rhACE2; APN01, GSK2586881) has received a lot of attention [17,18]. With regards to previous studies, administration of rhACE2, which is purified from the supernatant of ACE2 transfected cells, can reduce plasma angiotensin II and increase plasma angiotensin 1–7 and shows the ability to prevent angiotensin II–induced myocardial hypertrophy, diastolic dysfunction, and myocardial fibrosis [19].

Generally, it supposed that excessive ACE2, especially soluble form of ACE2 may slow the virus entering and spreading. Also, it can prevent the lung from injury not only by neutralizing the virus but also release cellular ACE2 and enhance its activity. Extensive animal experimental research has shown that rhACE2 could attenuate severe acute lung injury in ACE2-deficient mice [20,21]. In human studies, it has been found that rhACE2 is safe, with no adverse effects in patients with ARDS and healthy volunteers [22–24]. Interestingly, the results of a pilot study showed that the infusion of rhACE2 tends to decrease the interleukin-6 (IL-6) concentration in patients with ARDS [23]. Recent investigations reported the increased level of IL-6 in patients with confirmed COVID-19 pneumonia and it has been shown that the level of IL-6 has a positive correlation with the severity of the disease [25,26]. Considering the importance of inflammatory cytokines modulation in patients with COVID-19, the rhACE2 may be regarded as a promising therapeutic option.

1.2. Inhibition of the interaction between SARS-CoV-2 virus and ACE2

The entry inhibitors of the ACE2 receptor has been considered for management of this outbreak, recently. Some compounds which directly bind to ACE2 receptor with high affinity can be suggested for competition with virus including morphine and codeine [27]. Morphine has been traditionally used for severe pain control and in anesthesia. Morphine as an analgesic drug and a natural opioid mediate their effects via three receptors termed μ, δ, and κ opioid receptors [28,29]. This opiate alkaloid (C17H19NO3) isolated firstly from the plant papaver somniferum (the opium poppy) and can produce synthetically nowadays. Based on AutoDock Vina data (molecular screening modeling for protein-ligand docking), it was assumed that morphine (~6.6 kcal/mol) and especially codeine or methyl-morphine (C18H21NO3; ~7 kcal/mol) be more effective compounds with high affinity for directly binding to ACE2 receptor (docking score < -10 kcal/mol) [27].

Based on primary care and community respiratory resource pack for using during COVID-19 provided under the strategic health authority of the National Health Service (NHS) in England, morphine sulfate administration can control breathlessness in severe patients of COVID-19 in their last days and hours of life [30]. Furthermore, Swedish researchers claimed that morphine could be a prime alternative treatment for managing the shortness of breath, coughing and pain in COVID-19 infected patients [31].

Beyond all these, overwhelming evidence indicates elevated level of some inflammatory cytokines (e.g., interferon-gamma (IFN-γ), IL-6, etc.) in COVID-19 infected patients [32]. This overproduction of pro-inflammatory cytokines or cytokine storm syndrome (CSS) may cause more damage to the host cells than the SARS-CoV-2 as a foreign invader [33]. Experimental investigations showed that morphine treatment significantly suppressed some inflammatory cytokines including IL-6, IFNs and tumor necrosis factor alpha (TNF-α) as well alleviated hyper-inflammatory status [34,35]. Since elevated levels of inflammatory cytokines and chemokines increased viral replication in bronchoalveolar; modulation of systemic immune responses by morphine may have a potential role in the treatment of patients with COVID-19 [36]. Also, it has been suggested that opioids such as morphine can regulate immune function through the central nervous system. This opinion perhaps provides new insight into the clinical treatment of severe patients infected by SARS-CoV-2 by inhibitory compounds of ACE2 receptor such as morphine and codeine. Generally, it should be noted that, using morphine and codeine in treating COVID-19 is only hypothetical and is based on the unpublished docking screening study [27,30]. Furthermore, morphine may cause sedation and respiratory depression [36].

2. Conclusion

Based on the available evidence, further clinical studies are needed to test the exogenous administration of rhACE2 in Covid-19. Furthermore, some compounds with competitive effects of the SARS-CoV-2 virus for binding to ACE2 receptors could be new fields of research to tackle with SARS-CoV-2.

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Authors’ contributions

Neda Roshanravan searched the literature, drafted the manuscript, and supervised the study. Samad Ghaffari and Mehdi Hedayati provided the overall principle and direction of the study. They critically revised the manuscript for relevant intellectual contents. All authors read and approved the final manuscript.

Declaration of competing interest

No potential conflict of interest disclosed.

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References

[1] Organization WH. Coronavirus disease 2019 (covid-19): situation report, vol. 74; 2020.
[2] Cure E, Cure MC. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be harmful in patients with diabetes during covid-19 pandemic. Diabetes Metabol Syndr: Clin Res Rev 2:14(4):349–50.
[3] Ghaffari S, Roshanravan N, Tutunchi H, Ostadahrimi A, Pourghaei M, Kafli B, Oleoylethanolamide, a bioactive lipid amide, as a promising treatment strategy for coronavirus/covid-19. Arch Med Res 2020. S0188-4409(20)30475-6.
[4] Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019
(covid-19) with a focus on congenital heart disease. Int J Cardiol 2020;15: 70–7.

[5] Zhang Y-Z, Holmes EC. A genomic perspective on the origin and emergence of sars-cov-2. Cell 2020.

[6] Li J-W, Han T-W, Woodward M, Anderson CS, Zhou H, Chen Y-D, et al. The impact of 2019 novel coronavirus on heart injury: a systemic review and meta-analysis. Prog Cardiovasc Dis 2020 [Epub ahead of print].

[7] Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ace2 protein, the functional receptor for sars coronavirus. A first step in understanding sars pathogenesis. J Pathol: A Journal of the Pathological Society of Great Britain and Ireland 2004;203(2):631–7.

[8] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. Sars-cov-2 cell entry depends on ace2 and trpmr2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–80.

[9] Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin-angiotensin-aldosterone system inhibitors and risk of covid-19. N Engl J Med 2020 [Epub ahead of print].

[10] Yim HE, Yoo KH. Renin-angiotensin system - considerations for hypertension therapy. Springer; 2017.

[11] Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. Vascular adam17 as a novel therapeutic target in mediating cardiovascular hypertrophy and perivascular fibrosis induced by angiotensin ii. Hypertension 2016;68(4):549–55. https://doi.org/10.1161/hypertensionaha.116.07620.

[12] Kawai T, Takayanagi T, Forrester SJ, Preston KJ, Obama T, Tsuji T, et al. Vascular adam17 (a disintegrin and metalloproteinase domain 17) is required for angiotensin ii/beta-aminohippurate-induced abdominal aortic aneurysm. Hypertension 2017;70(5):959–63. https://doi.org/10.1161/hypertensionaha.117.09822.

[13] Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ace2/angiotensin-(1-7)/mas axis of the renin-angiotensin system: focus on angiotensin-(1-7). Physiol Rev 2018;98(1):50–53. https://doi.org/10.1152/physrev.00023.2016.

[14] Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ace2/angiotensin-(1-7)/mas axis of the renin-angiotensin system: focus on angiotensin-(1-7). Physiol Rev 2018;98(1):505–53.

[15] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ace2) in sars coronavirus-induced lung injury. Nat Med 2005;11(8):875–9. https://doi.org/10.1038/nm1267.

[16] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ace2) in sars coronavirus—induced lung injury. Nat Med 2005;11(8):875–9.

[17] Zhang H, Baker A. Recombinant human ace2: acing out angiotensin ii in ards therapy. Crit Care 2017;21(1):305. https://doi.org/10.1186/s13054-017-1882-z.

[18] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, China. JAMA Intern Med 2020 [Epub ahead of print].

[19] Yan Y, Shen X, Gao Y, Zhang J, Wang Y, Cheng Y. Discovery of anti-2019-ncov agents from 38 Chinese patent drugs toward respiratory diseases via docking screening: 2020.

[20] Alimian M, Pournajaﬁan A, Khodabarın A, Ghodratty M, Rokhtabnak F, Yazdikhasti P. Analogic effects of paracetamol and morphine after elective laparotomy surgeries. Anesthesil & Pain Med 2014;4(2):e12912. https://doi.org/10.5812/aapm.12912.

[21] Borner C, Holtz V, Kraus J. Mechanisms of the inhibition of nuclear factor-kappab by morphine in neuronal cells. Mol Pharmacol 2012;81(4):387–97. https://doi.org/10.1124/mol.111.706620.

[22] England N. Improvement N. Primary care and community respiratory resource pack for use during covid-19.

[23] Ekstrom M, Dahlander B. Palliation in patients with severe covid-19. Lakartidningen 2020:117.

[24] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in wuhan, China. Lancet 2020;395(10223):497–506.

[25] Wang Y, Wang X, Ye L, Li J, Song L, Fulambarkar N, et al. Morphine suppresses ifn signaling pathway and enhances aids virus infection. PloS One 2012;7(2).

[26] Gomez-Flores R, Weber RJ. Differential effects of buprenorphine and morphine on immune and neuroendocrine functions following acute administration in the rat mesencephalon periaqueductal gray. Immuno-pharmacology 2000;48(2):145–56.

[27] Salimi V, Hennus MP, Mokhtari-Azad T, Shokri F, Janssen R, Hodemaekers HM, et al. Opioid receptors control viral replication in the airways. Harv Rev Psychiatry 2019:17;3(1):168–83.