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JOURNAL OF HEALTH SCIENCES
A. J. Health Sci.

Volume 2 Supplement 1/ 2020, 45-49

Review

The Relationship Mechanism Between Covid-19 and Renin-Angiotensin System

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Abstract: Coronaviruses (CoVs) are a group of ribonucleic acid (RNA) viruses that can cause respiratory, intestinal and central nervous system infections in humans and animals. Especially two strains caused severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). In addition to these strains, SARS-coronavirus 2 (SARS-CoV-2), appeared in Wuhan, China in December 2019. It soon affected the whole world and was declared a pandemic by the World Health Organization. The disease caused by the SARS-CoV-2 virus is called coronavirus disease (Covid-19). There are studies in the literature, infection mechanism of Covid-19, is binding of the virus to the receptor of angiotensin converting enzyme-2 (ACE2) and subsequently internalization of the complex by the host cell. The recognition of ACE2 as a co-receptor for SARS-CoV-2 suggest that there is cellular entry in ACE2 expressing tissues, including lung, heart, kidney, brain and intestine. The studies, have extensively studied the RBD-ACE2 complex, spike protein, and free RBD systems of SARS-CoV-2 and SARS-CoV using protein-protein docking and molecular dynamics simulations. The free binding energy of SARS-CoV-2 to RBD-ACE2 has been shown to be lower than the free binding energies of other coronavirus types. It was emphasized that this situation could be related to the more contagious SARS-CoV-2. While it seems such as clear that SARS-CoV-2 infects with binding mechanism the human ACE2 receptor of the RBD domain, the molecular mechanisms still remain mysterious. The present findings are expected to be useful for the disease prevention and control as well as drug and vaccine development of Covid-19.

Keywords: *Covid -19; ACE1; ACE2; renin; angiotensin*

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1.Introduction

Coronaviruses (CoVs) are a group of RNA viruses. Coronaviruses can cause respiratory, intestinal, liver, and central nervous system infections in humans and animals (Chen & Guo, 2016; Fang, 2020). Six coronavirus strains have been identified that can infect humans. Especially two strains caused severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), two large-scale pandemics (He, 2020). In addition to these strains, a new SARS-CoV-2 appeared in Wuhan, China in December 2019. It soon affected the whole world and was declared a pandemic by the World Health Organization (WHO). The disease caused by the SARS-CoV-2 virus is called coronavirus disease (Covid-19). The epidemic has become a global public health crisis with its continuous development and rapid spread (He, 2020; Sun et al., 2020). Covid-19, is also called SARS-CoV-2 due to its close relationship to SARS-CoV (Sun et al., 2020). The most common clinical manifestations of the patients are fever, cough, shortness of breath and fatigue, and some patients have radiographic ground-glass lung changes and finally died from acute respiratory distress syndrome (ARDS) (Sun et al., 2020; Zhou et al., 2020). Covid-19 was found to be caused by SARS-CoV-2 virus-induced pneumonia by clinicians based on clinical symptoms and other criteria, including a rise in body temperature, decreased lymphocyte count, and decreased white blood cells (Zhou et al., 2020). SARS-CoV-2 cell penetration occurs through the receptors. This receptor binding sites (RBD) of SARS-CoV-2 on the protein coat are functional for infection and virus viability in the host cell. Although the binding mechanism of SARS-CoV-2 human cell infection by RBD and angiotensin converting enzyme 2 (ACE2) receptor seems clear, its molecular mechanisms are still unknown. According to some studies showing that the mechanism of infection of Covid-19 is binding of the virus to the receptor of ACE2 and infects by the host cell (He, 2020). This review will examine physiological aspects of the Covid-19 and renin-angiotensin system (RAS) in different organs/systems. It is shown in the literature that the studies on this subject are contradictory.

2. Covid-19 in ACE2 and Renin Angiotensin System

When the molecular structure of SARS-CoV-2 is investigated it consists of spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins (Du L., 2009; Sun et al., 2020). The S protein has two regions. The role of the S1 protein is to bind to the receptor on the host cell membrane. The S1 protein also has an N-terminal domain (NTD) and three C-terminal domains (CTD1, CTD2, CTD3). S2 protein is responsible for fusion to the host membrane (Gui et al., 2017; Li, 2016; Wu et al., 2020). SARS-CoV the RBD is located in the CTD1 of the S1 region. SARS-CoV attaches to RBD protein by binding of human host cells to ACE2. Therefore, the prerequisite for the infection of SARS-CoV to human is the interaction between RBD and ACE2. Due to the high similarity between SARS-CoV and Covid-19, Covid-19 was expected to use the ACE2 molecule as a receptor to infect humans (Song, Gui, Wang, & Xiang, 2018; Xu et al., 2020). Studies show that Covid-19 has a higher affinity for binding ACE2 than SARS-CoV (Wrapp et al., 2020). The total free energy of S protein of SARS-CoV-2 appears to be low compared to that of SARS-CoV. This may also provide insight into the evolution of SARS-CoV-2 because SARS-like CoVs are thought to be caused by bats known to have a higher body temperature than humans (Cui, Li, & Shi, 2019; He, 2020). SARS-CoV-2's RBD has better solubility than SARS-CoV may explain that Covid-19 has higher infectivity than SARS-CoV (He, 2020). ACE2 is the aminopeptidase responsible for the separation of angiotensin-I (AngI) and angiotensin-II

(AngII) into angiotensin-(1-9) and angiotensin-(1-7) peptides (Mali et al., 2020). It is expressed in a variety of tissues in the human body, including the lung, heart, kidney, small intestine, vascular endothelium, renal proximal tubular epithelium, intestinal epithelium, macrophages and the brain. Testis ACE, which has a smaller ACE isoform, is expressed only in the adult testicle (Masuyer et al., 2014). ACE2 expression in the lungs is concentrated in type II alveolar cells, macrophages and moderate bronchial and tracheal epithelial cells (Hamming et al., 2004; Kai, 2020).

3. Treatments Targeting ACE2 and AngII

Covid 19 disease has been observed to be higher in individuals with chronic disease. There are concerns about whether to increase the severity of Covid-19 in hypertension and cardiovascular disease (CVD) patients who take their angiotensin receptor blocker (ARB) and ACE inhibitor (ACEI) (Kang et al., 2020). In contrast, it has attracted attention in publications that argue that ARBs are useful in the prevention and treatment of lung damage caused by Covid-19 (Vaduganathan M, 2020). There are no data on the effects of ARBs and ACEIs on lung ACE2 expression in animal models or humans (Kai, 2020). A small case study reported that plasma AngII levels were markedly elevated and linearly associated with viral load and lung injury severity in Covid-19 pneumonia patients. (Liu et al., 2020). The beneficial net effects of ARB have been proposed in acute lung damaged rodents infected with SARS-CoV (Kai, 2020; Kuba K, 2005). Another treatment is transmembrane protease serine 2 (TMPRSS2), a membrane protease for ACE2 preparation, a very important step for Covid-19 and fusion of target cell membranes and consequently entry into viral cells (Hoffmann M, 2020). Clinical studies on TMPRSS2 inhibitors for the treatment of Covid-19 are ongoing (Kai, 2020).

Conclusion

This review is written considering the data from the most recent studies on Covid-19 and the renin-angiotensin system mechanism. The contradictions in the literature clearly attract attention. We think that the ongoing clinical studies on RAS will eliminate the existing uncertainty.

Conflict of Interest

Authors declare no conflict of interest.

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