Angiotensin converting enzyme 2 activation: a novel potential Covid-19 therapeutic strategy

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Abstract

Not applicable

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In late December 2019, the Covid-19 epidemic, caused by a novel coronavirus SARS-CoV-2, emerged in Wuhan, Hubei province, China. This epidemic has a doubling period of 1.8 days, and there are concerns about its progression to pandemic scales due to its exponential rate of spread. No specific drugs or vaccines are currently available for the treatment and/or prevention of SARS-CoV-2 infection. Hence, there is an imperative need to search for a safe and effective therapeutic strategy for Covid-19 infected patients, especially the critically ill individuals.

Angiotensin-converting enzyme 2 (ACE2) is a crucial component of the renin-angiotensin-system (RAS) axis because it converts Angiotensin II into angiotensin (1–7), which exerts an antifibrotic, antihypertrophic and vasodilatory effect. ACE2 is a membrane-bound aminopeptidase which has been reported to be a functional receptor for coronaviruses, including SARS-CoV and SARS-CoV-2. The first step of SARS-CoV-2 infection is binding of the spike protein of the virus to ACE2 which is widely distributed on the alveolar type II cells and capillary endothelium (Lu et al., 2020). It has been demonstrated that SARS-CoV downregulates ACE2 protein in mice, contributing to severe lung injury (Kuba et al., 2005). This suggests that augmented ACE2 activation may result in enhanced binding with SARS-CoV-2. Thus, increasing ACE2 activation may have a dual function to both neutralize the virus and rescue cellular ACE2 activity protecting the lung from damage.

Diminazene (DIZE) is an antitripanosomal drug which has been shown to serve as an ACE2 activator and reduce bleomycin-induced pulmonary fibrosis (Shenoy, Qi, Gupta, Katovich & Raizada, 2012). In addition, it has been reported that activation of ACE2 by DIZE prevented asthma progression in rats by altering AKT, p38, NF-ϰB and other inflammatory markers. DIZE also halted the development and progression of experimentally induced pulmonary hypertension in rats, improved right ventricular function, and diminished proinflammatory cytokines effects that were accompanied with increased lung ACE2 activity. Given the reported safety of DIZE administration in humans (Hutchinson & Watson, 1962; Pepin & Milord, 1994) and the pressing need for Covid-19 therapeutic, in addition to the well-documented pharmacological effects of DIZE, clinical studies are warranted to elucidate the potential safety and efficacy of DIZE in Covid-19 infected patients.

In conclusion, SARS-CoV-2 represents a global health challenge. Unfortunately, no specific therapeutic options are currently available. Thus, there is an imperative need for a safe and effective drug in order to put this pandemic to an end. DIZE has a reported acceptable safety profile. Moreover, DIZE increased lung ACE2 activity in different experimental models, an effect which conferred lung protection against various

insults. Taking into consideration the reported effect of SARS-CoV-2 on pulmonary ACE2 activity, it could be suggested that DIZE administration could offer some therapeutic merit for SARS-CoV-2 infected patients. However, clinical studies are required to unravel the potential safety and efficacy of DIZE administration in Covid-19 infected patients.

Competing interests The author declares no competing interests.

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References

Hutchinson M, & Watson H (1962). Berenil in the treatment of Trypanosoma gambiense infection in man. Transactions of the Royal Society of Tropical Medicine and Hygiene 56**:** 227-230.

Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B*, et al.* (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature medicine 11**:** 875-879.

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H*, et al.* (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet 395**:** 565-574.

Pepin J, & Milord F (1994). The treatment of human African trypanosomiasis. Advances in parasitology 33**:** 1-47.

Shenoy V, Qi Y, Gupta D, Katovich M, & Raizada M (2012). Small moleculae ACE2 activator, diminazene aceturate attenuates bleomycin-induced pulmonary fibrosisEur Respiratory Soc.