



Letter to Editor

ACE 2 in the Context of COVID 19 – An Opportunity for us or the Virus

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In 2000, a homologue of ACE was cloned by two independent groups and termed angiotensin-converting enzyme 2 which was found to be an important part of the RAS system. This trans membrane metallopeptidase, removes a single residue from Ang I to yield Ang (1–9) and cleaves a single residue from Ang II to generate Ang (1–7).^[1, 2] Expression of ACE 2 has also been reported in type 2 pneumocytes,^[3] and limited human pathological studies demonstrate that the respiratory tract is a major site of SARS-CoV infection and morbidity.^[4, 5]

The extracellular domain of ACE 2 has been demonstrated as a receptor for the spike (S) protein of SARS-CoV,^[6] human corona virus NL63^[7] and recently, for the SARS-CoV-2.^[8] The SARS-CoV-2 binds ACE2 with higher affinity than SARS-CoV.^[9] Although ACE 2 provides cellular entry to the Corona Virus, from animal studies we know that ACE2 plays a protective role in acute lung injury. Mechanistically, the negative regulation of Ang II levels by ACE2 account, in part, for the protective function of ACE2 in ARDS.^[10] This seemingly paradoxical process underlies the pathogenesis of SARS from Corona Virus which involves binding of the coronavirus spike protein to ACE2, leading to ACE2 down regulation, which in turn results in excessive production of angiotensin by the related enzyme ACE, while less ACE2 is available for converting it to the vasodilator heptapeptide angiotensin 1–7. This in turn contributes to lung injury, as angiotensin-stimulated AT1R results in increased pulmonary vascular permeability, thereby mediating increased lung pathology.^[11, 12]

There is also a soluble form of ACE2 which lacks the membrane anchor and circulates in small amounts in the blood.^[13] It has been found that the soluble form of ACE2, blocks association of the S1 domain and viral replication in SARS coronavirus (SARSCoV)- permissive Vero E6 cells.^[14, 15]

The S protein of HCoV-NL63 virus circulating in the human population which is only modestly pathogenic in most cases, and the S proteins of SARS-CoV bind overlapping regions of ACE2 that include a critical loop between its fourth and fifth β -strands.^[16] Potent neutralizing activity directed against NL63-S protein has been detected in virtually all sera from patients 8 years of age or older, suggesting that HCoV-NL63 infection of humans is common and usually acquired during childhood.^[7]

From animal experiments we have been able to synthesise inhibitors of ACE 2 like GL1001, which is a selective and potent ACE2 inhibitor,^[17] and it has been seen to exhibit anti-inflammatory effects in the upper gastrointestinal tract of the mouse^[18, 19] and protects against NSAID-induced gastric damage in rats.^[20]

In the light of the above information we propose the following therapeutic options for further research and testing in COVID 19.

1. Soluble ACE 2 can be a potential therapeutic option in SARS CoV 2 cases as it competes for the Viral Spike S protein making it less available for binding with the transmembrane ACE 2. It can be given in an inhaler or

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nebulised form because the main site of SARS CoV 2 attack is the respiratory track.

2. Although attempts to make a vaccine based on viral proteins is underway, it may take more than a year to become available and may not be so useful given the ability of the virus to undergo frequent mutations. Therefore we should attempt to make an antibody against the ACE 2 receptor which can compete with the virus for binding. This can be delivered to the lungs again via inhaler or nebulizer and simultaneously ACE 2 analogues or Ag 1-7 infusion can be systemically administered to benefit from its anti-inflammatory effects.
3. A selective potent inhibitor of ACE 2 again delivered via inhalation or nebulization can prove useful.
4. Co-infection with human corona Virus NL 63 can make the disease less severe owing to same receptor binding and being less pathogenic and as most individual are already immune to NL 63.

Disclosures

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