

# THE CURRENT COVID-19 PANDEMIC AND HYPERTENSION

## Pharmacology of renin-angiotensin-system blockers and COVID-19: confusion around ACE2

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The Renin-Angiotensin System (RAS) is one of the most important blood pressure regulating systems with several effectors, the angiotensin peptides. These are split off from the high-molecular protein angiotensinogen by the enzyme renin and are subsequently generated by other enzymes including the angiotensin-converting enzymes (ACE). The classical ACE, which is designated by the abbreviation "ACE", generates angiotensin II (Ang II) as the main effector peptide in the RAS by converting the decapeptide angiotensin I (Ang 1-10) into the octapeptide angiotensin II (Ang 1-8).

Twenty years ago, another enzyme, homologous to ACE was identified<sup>1</sup> and named ACE2<sup>2,3</sup>. Both ACE2 and ACE are very strongly membrane-bound enzymes<sup>2,3</sup>. On the other hand, smaller soluble molecules for ACE and ACE2 can be generated from the respective membrane-bound forms by cleavage and shedding from the membrane. These soluble forms circulate in blood plasma and other body fluids.

Initially, only basic but not clinical scientists were mainly concerned with ACE2, because its clinical relevance was considered low due to its potentially minor role within the RAS. The most important difference between ACE and ACE2, which was already described in the discovery, relates to the fact that ACE2 cannot be inhibited by ACE inhibitors (ACEI)<sup>1,4</sup>. This is due to important structural differences between ACE and ACE2, which affect the respective active center of the enzyme and also explain the differences in their functions. Thus, ACE is a dipeptidyl

carboxypeptidase and the most important enzyme for the conversion of Ang I to Ang II. ACE2, in contrast, is a mono-carboxypeptidase, which cleaves one amino acid at the end of peptides and forms another peptide from Ang II with only seven amino acids, i.e. Ang-(1-7). In addition, ACE2 can also cleave one amino acid from Ang I to form Ang 1-9 (Figure 1).

The main axis in the RAS cascade, which is crucial for blood pressure control and aldosterone secretion, concerns the signaling pathway from Ang II to the angiotensin type 1 receptor (AT<sub>1</sub>R)<sup>4</sup>. Importantly, by inducing prooxidative, proinflammatory and profibrotic changes, this Ang II/AT<sub>1</sub>R axis is also involved in organ injury not only in the cardiovascular system but also in the lung (Figure 1) and other organs<sup>4,5</sup>. In addition to this damaging axis, the RAS has at least two other counter-regulatory (protective) arms. One arm concerns the signaling pathway via the angiotensin type 2 receptor (AT<sub>2</sub>R), which is also mainly activated by Ang II but additionally also by Ang 1-9. The other, not so long known arm concerns the Mas receptor (MasR) signaling pathway, which is mainly activated by Ang 1-7<sup>3</sup>. Of interest, ACE2 has a pivotal role as the main enzyme responsible for Ang 1-7 formation. The ACE2/Ang 1-7/MasR axis mediates vasodilation, antioxidant, anti-inflammatory and antifibrotic protective functions<sup>5</sup>. ACE2 is formed in the epithelial cells of the upper and lower respiratory tract and in type II alveolar epithelia, among others<sup>5</sup>. In several lung injury models (e.g. sepsis) in animals, impressive protective effects of the ACE2/Ang 1-7/MasR axis have been demonstrated<sup>5,6</sup>.

In contrast, activation of the Ang II/AT<sub>1</sub>R axis promotes lung damage. Accordingly, treatment with ACEI or AT<sub>1</sub>R antagonists (angiotensin receptor blockers [ARB]) may protect the lung<sup>6</sup>.

### New perspective on ACE2 from SARS - coronary viruses

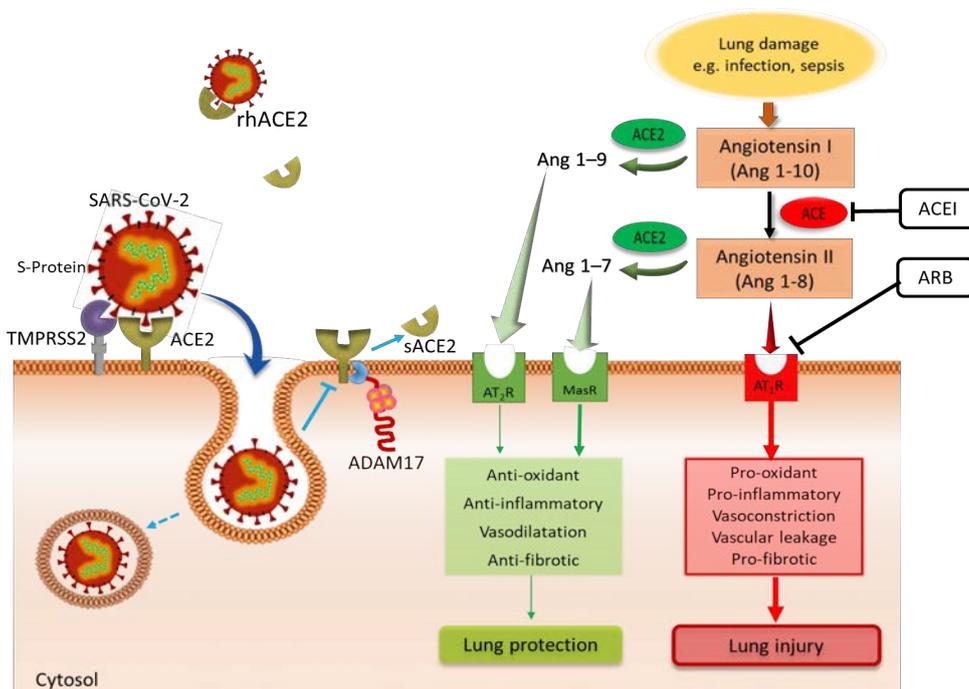
The view of ACE2 was impressively expanded in 2003 when ACE2 was discovered as a receptor for the binding of the coronary virus (SARS-CoV) responsible for the Severe Acute Respiratory Syndrome (SARS) disease<sup>7</sup>. This resulted in an unexpected new link between virology and cardiovascular medicine via ACE2 and the RAS. After this relationship had receded into the background after the end of the SARS epidemic in 2002 and 2003, the link between ACE2 and SARS-CoV-2 has currently regained a very strong prominence in the context of the COVID-19 pandemic (Figure). This resulted from the finding that ACE2 is also the binding receptor for SARS-CoV-2 responsible for COVID-19<sup>8</sup>. Accordingly, all cells expressing ACE2 and in addition co-express the cellular serine protease TMPRSS2 as another necessary cofactor on their cell surface, can potentially take up and replicate SARS-CoV-2 (Figure 1).

Since the beginning of the COVID-19 pandemic, this connection between ACE2 and COVID-19 has provoked numerous articles, comments and speculations in scientific journals, the press and social media. The concern was raised, that ACEI and ARB might increase the risk of infection and complicate the clinical course of COVID-19<sup>5,9</sup>. Although, as mentioned above, ACEI cannot bind and inhibit ACE2, there are several interactions and feedback loops between the individual components in the RAS<sup>4</sup>. The most well-known is the negative feedback between Ang II on renin secretion via AT<sub>1</sub>R, which explains the high renin levels under therapy with ACEI and ARB. The discussion on the link between ACE2 and the use of RAS blockers was fueled mainly by animal studies that showed a potential upregulation of ACE2 in cardiovascular organs and the kidney after treatment with RAS blockers (especially ARBs)<sup>5</sup>. It appears, however, that many authors speculating

on this link dismissed – among other issues such as concentration dependent basic pharmacological aspects<sup>9</sup> - to differentiate between the reported effects of RAS blockers on mRNA levels vs. membrane-bound ACE2 tissue protein or soluble ACE2 protein levels (e.g. in the urine), and the resulting potential to modulate COVID-19. If an upregulation of membrane-bound ACE2 protein in response to RAS blocker treatment would indeed occur in humans, one could assume that RAS blockers might increase infectivity for SARS-CoV-2 and thereby exhibit an unfavorable influence on COVID-19<sup>5</sup>. However, a comprehensive assessment of the complex interactions in the RAS and their modulation by RAS blockers as well as their relation to the pathogenesis of COVID-19 infection shows that fears of an increased risk from RAS blockers in COVID-19 are not justified according to current knowledge<sup>5,9</sup>. The decisive factor here is that a systematic evaluation of the findings published to date has not consistently demonstrated an upregulation of the ACE2 protein at the tissue level<sup>5</sup>. Most importantly, no significant effect of RAS blockers on ACE2 membrane-bound protein in the respiratory tract, as the key entry system for SARS-CoV-2, has been demonstrated<sup>5</sup>. In parallel with this critical appraisal, several statements were published by national and international societies including the European Society of Hypertension and the International Society of Hypertension.

In summary, it was recommended that the treatment with ACEI and ARB in stable patients with hypertension or other indications should not be discontinued or withheld due to concerns during a COVID 19 pandemic. Meanwhile, several well conducted important observational studies that included relatively large numbers of COVID-19 patients and that explored the impact of RAS blockers on COVID-19 were reported in May 2020 (summarized in [10]). Taken together, these studies did not find any evidence for a harmful effect of RAS-blocker use on COVID-19. More details and a clinical perspective on this topic will be discussed in an accompanying article of this issue by Murray Esler.

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**Figure 1 The Renin-Angiotensin-Systems (RAS) in the lung in the context of COVID-19.**

The special role of ACE2 as a key element in the counter regulatory axis (green) of the RAS is shown. ACE2 counteracts the negative effects of the Ang II/AT<sub>1</sub>R axis (red) on lung damage. ACE2 is produced in epithelial cells of the airways, including type II alveolar epithelial cells in the lung. SARS-CoV-2 binds to the membrane-bound ACE2 of the host cell via its viral spike protein. This enables the virus to enter the cell and subsequently replicate. SARS-CoV-2 additionally requires the cellular serine protease TMPRSS2 for cellular uptake. Down-regulation of ACE2 by SARS-CoV-2, as demonstrated for SARS-CoV infection, could further shift the balance between the arms of the RAS in favor of the damaging effect in the lung. ACE2, as a predominantly membrane-bound enzyme, can be cleaved in vivo by a disintegrin and metalloprotease 17 (ADAM17) into a soluble form (sACE2) that circulates in body fluids. Whether therapy with the soluble form as recombinant human ACE2 (rhACE2) can slow down the spread of infection by competitive binding to the virus is being investigated. Furthermore, an inhibitor of TMPRSS2 already approved for other diseases could be considered for the treatment of SARS-CoV-2 by inhibiting viral cell entry (further details are reviewed in [5]).

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