Physiological Mini Reviews

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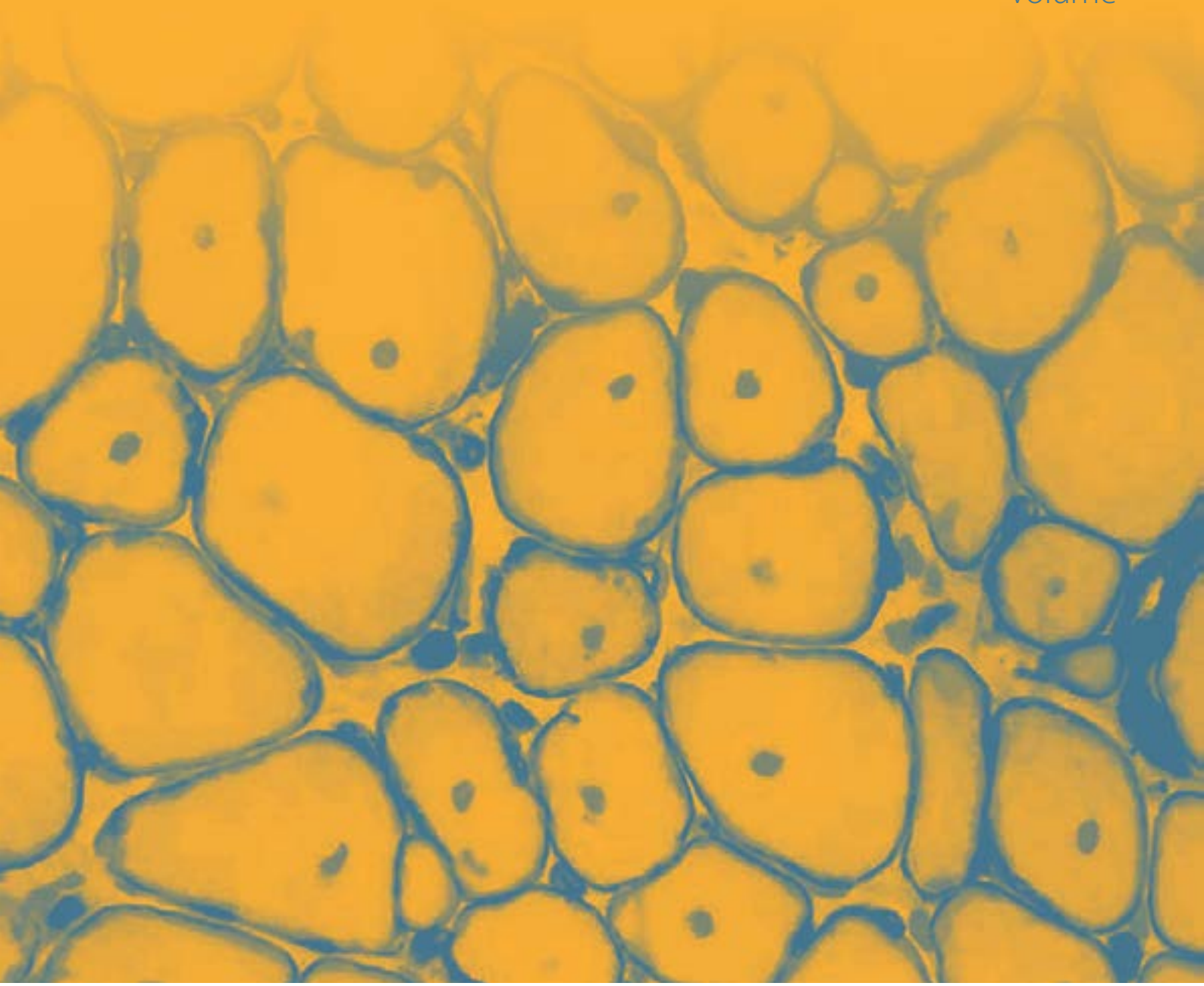

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Physiological Mini-Reviews is a scientific journal, publishing brief reviews on "hot" topics in Physiology. The scope is quite broad, going from "Molecular Physiology" to "Integrated Physiological Systems". As indicated by our title it is not our intention to publish exhaustive and complete reviews. We ask to the authors concise and updated descriptions of the "state of the art" in a specific topic. Innovative and thought-provoking ideas are welcome.

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ANGIOTENSIN-CONVERTING ENZYME 2: ANGEL OR EVIL?

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ABSTRACT

Angiotensin converting enzyme 2 (ACE2) is a key element of the protective arm of the renin-angiotensin system (RAS). ACE2 acts to oppose the actions of angiotensin (Ang) II by generating Ang-(1–7) to reduce inflammation and fibrosis and mitigate end organ damage. ACE2 also acts as the receptor for severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 to gain entry into human cells. SARS-CoV-2 is the etiological agent that causes coronavirus disease 2019 (COVID-19). The COVID-19 pandemic is associated with significant morbidity and mortality throughout the world, predominantly due to lung and cardiovascular injury. The present review is focused on ACE2, as a protective component of the RAS and as the receptor for SARS-CoV2.
Keywords: angiotensin-converting enzyme 2, angiotensin, COVID-19, renin-angiotensin system

RESUMEN

La enzima convertidora de angiotensina 2 (ECA2) es un elemento clave del brazo protector del sistema renina-angiotensina (SRA). La ECA2 actúa balanceando las acciones de la angiotensina (Ang) II al generar Ang-(1-7), lo cual resulta en una reducción de la inflamación y fibrosis y en el daño de órgano blanco. La ECA2 también actúa como receptor del coronavirus de tipo 2 que produce el síndrome respiratorio agudo severo (SARS-CoV2). El SARS-CoV-2 es el agente etiológico que causa la enfermedad por coronavirus 2019 (COVID-19). La pandemia de COVID-19 se asocia con una morbilidad y mortalidad significativas en todo el mundo, principalmente debido a lesiones pulmonares y cardiovasculares. La presente revisión se centra en la ECA2, como componente protector del RAS y como receptor del SARS-CoV2.
Palabras claves: enzima convertidora de angiotensina 2, angiotensina, COVID-19, sistema renina-angiotensina

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Angiotensin-Converting Enzyme 2 as "Angel"

Hypertension is one of the great health problems of today and despite the great advances in science, cardiovascular diseases continue to represent the main cause of morbidity and mortality in Western countries. Currently, one of the most therapeutic targets is the renin-angiotensin system (RAS), given its key role in the development of this pathology. Despite the fact that it was long thought that angiotensin (Ang) II was the main bioactive component of the RAS, today it is well known that other components of the RAS are biologically active and exert effects that may be similar, opposite or distinct from those displayed by Ang II (Figure 1). Like Ang II, Ang-[1-12], Ang A and Ang III bind primarily to angiotensin II type 1 (AT1) receptor and cause vasoconstriction, accumulation of inflammatory markers to sub-endothelial region of blood vessels and activate smooth muscle cell proliferation. On the other hand, Ang III can induce natriuresis responses through angiotensin II type 2 (AT2) receptor stimulation and contributes to blood pressure regulation. Other peptides like Ang-(1-9), Ang-(1-7), alamandine and Ang IV help in protecting from cardiovascular diseases by binding to their respective receptors [1-3]. Thus, currently the RAS is considered to be composed mainly by two axes. The pressor one represented by angiotensin converting enzyme (ACE), the main enzyme involved in Ang II generation, Ang II and the AT1 receptor, which mediates the pressor and trophic effects of Ang II. The other axis, the depressor and protective one, is represented by ACE2, the enzyme that catalyzes the conversion of Ang II into Ang-(1-7), Ang-(1-7) and the Mas receptor. This axis induces vasoprotective, antihypertensive, antiproliferative, antioxidant and anti-inflammatory effects, among other effects. In this way, this Ang- (1-7) / RMas / ACE2 axis opposes and regulates the pressor axis of the RAS [1-3]. Although the RAS exerts a pivotal role on electrolyte homeostasis and blood pressure regulation, their components are also implicated in higher brain functions, including cognition, memory, anxiety and depression and several neurological disorders. Overactivity of the pressor axis of the RAS has been implicated in stroke and several brain disorders, such as cognitive impairment, dementia and Alzheimer´ or Parkinson's disease [1-3].

ACE2 is a key element in the protective arm of the RAS. It was discovered 20 years ago when it was found to possess 42% similarity to ACE (4, 5). Whereas somatic ACE contains 2 active sites, ACE2 possesses only a single catalytic domain. Both ACE and ACE2 act as zinc metallopeptidases but they differ in their substrate specificities defining their distinct and counterbalancing roles in the RAS. Whereas ACE cleaves C-terminal dipeptide residues from susceptible substrates (a peptidyl dipeptidase), ACE2 acts as a simple carboxypeptidase able to convert Ang I into Ang-(1-9), and Ang II into Ang-(1-7) [4, 5] (Figure 1). ACE2 displays more affinity for Ang II yielding Ang-(1-7) with a catalytic efficiency 400-fold greater for Ang II than for Ang I [4, 5]. However, ACE2 has multiple substrates such as apelin, neurotensin, dynorphin, ghrelin, amyloid, among others [5]. The active sites of ACE and ACE2 differ and accordingly, ACE inhibitors do not inhibit activity of ACE2 [4, 5].

ACE2 is a glycoprotein metalloprotease that exists in two forms: membrane-bound and soluble. The membrane-bound form contains a transmembrane domain that anchors its extracellular domain to the plasma membrane [4, 5]. In its soluble form, it is cleaved and secreted as the N-terminal ectodomain and is found in very low concentrations in the circulation. The significance of circulating ACE2 is unclear, although the levels of this enzyme increase in various diseases such as type 1 or type 2 diabetes, hypertension, heart failure, and chronic kidney diseases. The reason for high levels of ACE2 in these patients may be that the increased ACE2 is a defensive response to counteract the adverse effect of Ang II.

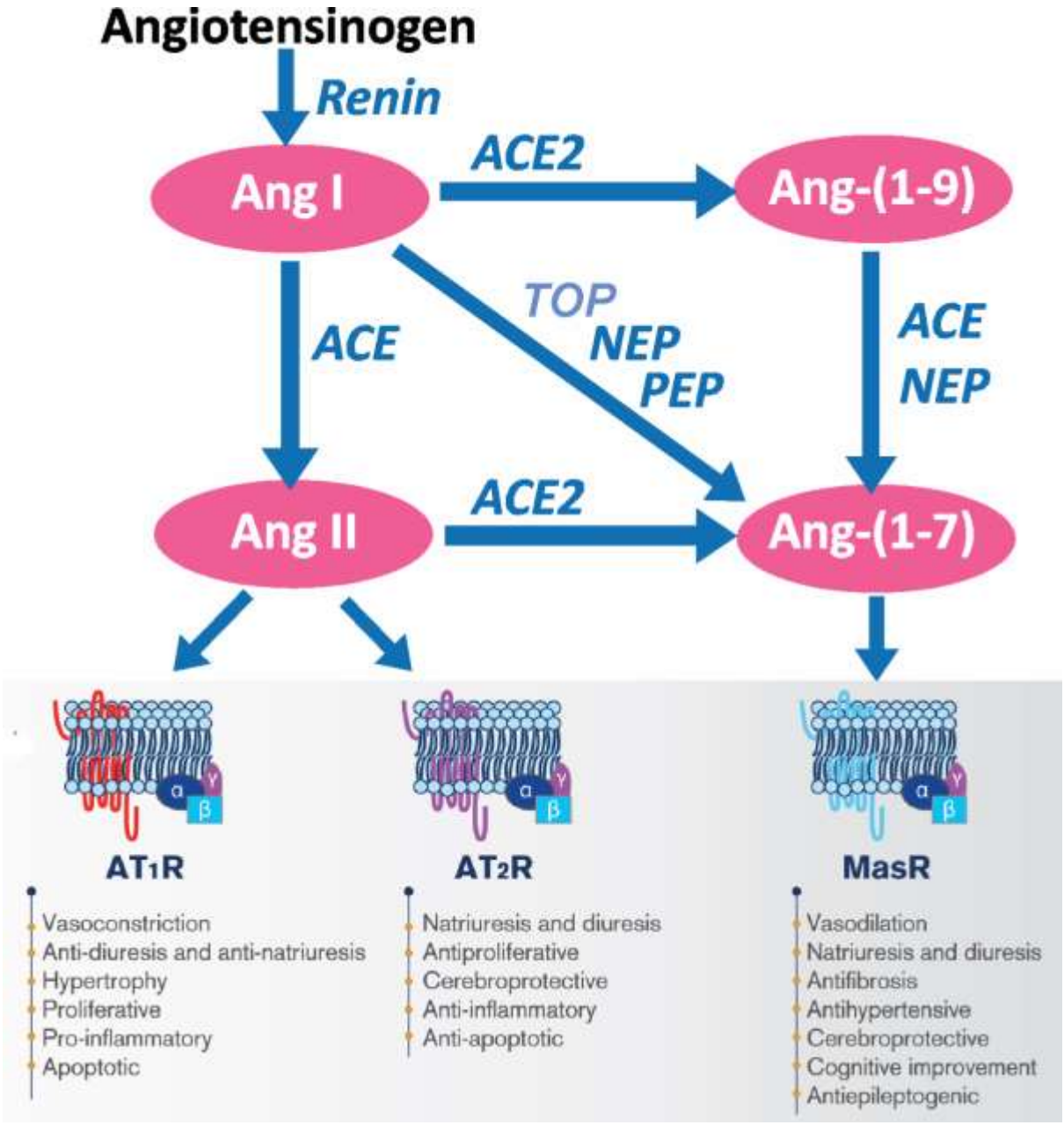

Figure 1. ACE2 in the renin-angiotensin system. ACE2 catalyzes the conversion of Ang I into Ang-(1-9) and Ang II into Ang-(1-7). Ang-(1-7) induces protective effects through MasR stimulation, opposing the pressor, trophic, fibrotic, inflammatory actions of Ang II. Brief scheme of the RAS depicting only the components directly linked to the focus of this review. For a complete scheme of the RAS please refer to reference 1 and 2. Abbreviations used: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; NEP, neutral endopeptidase (neprilysin); TOP, thimet oligopeptidase ; PEP, prolyl endopeptidase.

ACE2 can undergo cleavage or shedding to release the catalytically active ectodomain into the circulation by ADAM17 [6]. ADAM17, a member of the 'A Disintegrin And Metalloproteases' (ADAM) family, is a metalloprotease and disintegrin that lodges in the plasmatic membrane of several cell types and is able to cleave a wide variety of membrane-anchored proteins, cytokines, cell adhesion molecules, receptors, ligands and enzymes, including ACE [7]. ADAM17 is the main enzyme responsible for ACE2 shedding. ADAM17 is somatically expressed in mammalian organisms and its proteolytic action influences several physiological and pathological processes [7-9]. In fact, it has been previously shown that ADAM17 is responsible for the impairment of ACE2 compensatory function in neurogenic hypertension [10].

ACE2 is widely expressed in organs that contribute to blood pressure regulation (vessels, heart, kidneys) as well as in the ovaries, testes, small intestine and lungs [11]. Through single-cell ACE2 RNA sequencing, organs identified with high expression are lung, heart, esophagus, kidney, bladder, and ileum, and located specific cell types (i.e., type II alveolar cells, myocardial cells, proximal tubule cells of the kidney, ileum and esophagus epithelial cells, and bladder urothelial cells) [12]. ACE2 elicits protective effects in all of the tissues where it is expressed (Figure 2) and this protective role of ACE2 results from Ang II downregulation and Ang-(1-7) upregulation [11, 13].

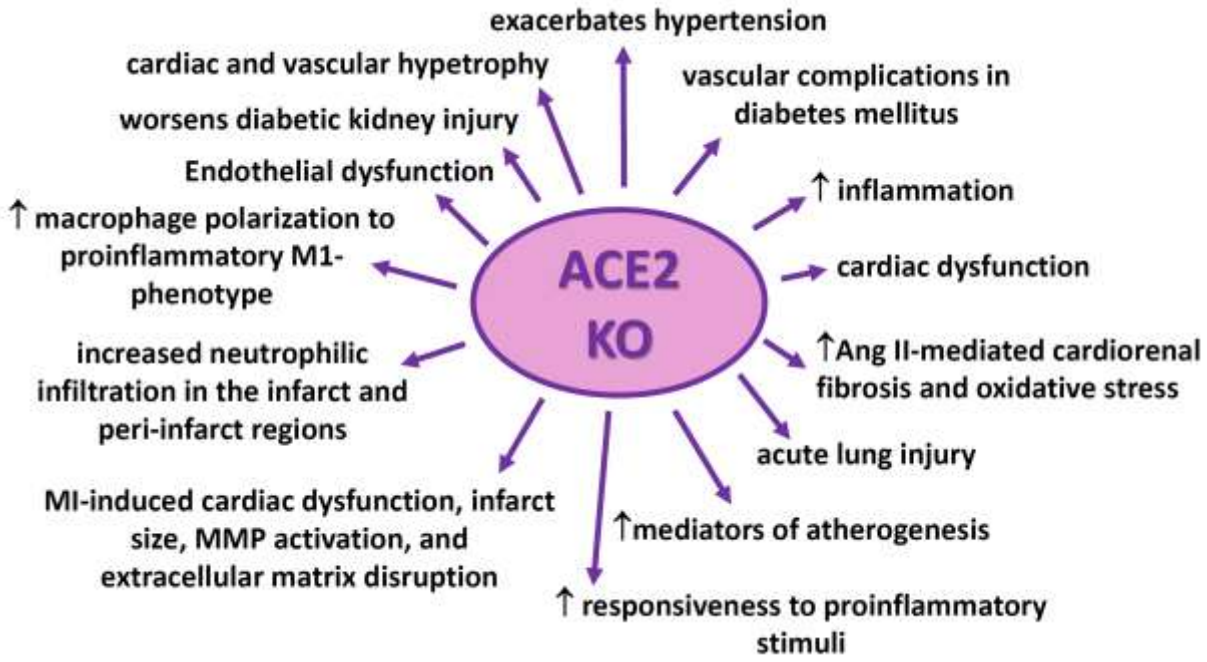

Figure 2. ACE2 deletion is associated with loss of organ protection. Abbreviations used: ACE2, angiotensin-converting enzyme 2; MI, myocardial infarction; MMP, matrix metalloproteinase

Angiotensin-Converting Enzyme 2 as "Evil"

Besides its enzymatic function, ACE2 also acts as the receptor for severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 (14). SARS-CoV-2 is the etiological agent that causes coronavirus disease 2019 (COVID-19) [15,16]. The spike (S) protein of coronaviruses facilitates viral entry into target cells. Entry depends on binding of the surface unit S1 of the S protein to the cellular receptor, which facilitates viral attachment to the surface of target cells. In addition, entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2' site and allows fusion of viral and cellular membranes, a process driven by the

S2 subunit. SARS-CoV-2 engages ACE2 as the entry receptor and employs the cellular type II transmembrane serine protease (TMPRSS2) for S protein priming (Figure 3) [14]. Furin may also activate the SARS-CoV-2 S protein, which may account for enhanced virulence [17]. Once inside the host cell, viremia and replication in the lung, and possibly the gastrointestinal tract, follow.

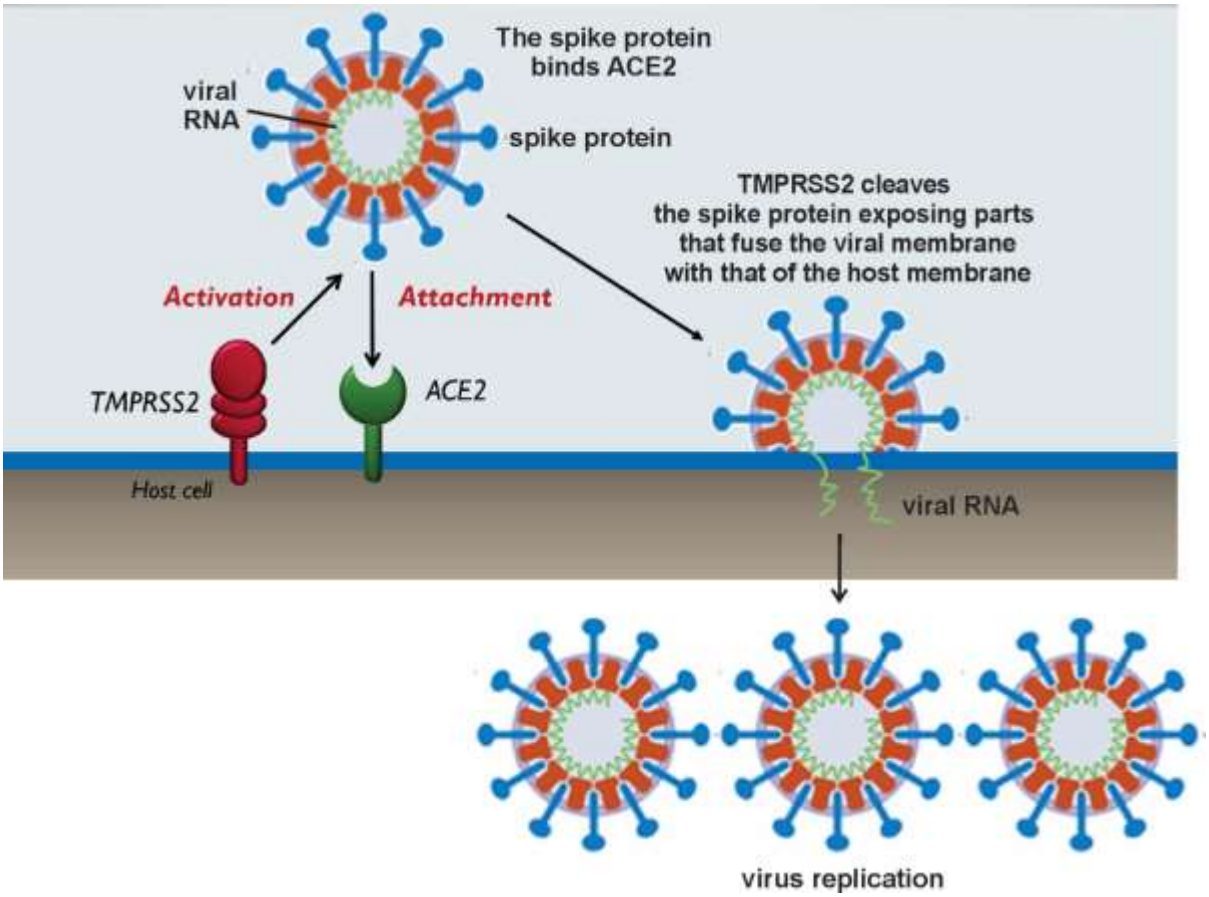

Figure 3. SARS-CoV-2 entry into the host cell. Abbreviations used: ACE2, angiotensin-converting enzyme 2; TMPRSS2, type II transmembrane serine protease

The binding affinity of SARS-CoV-2 with ACE2 is stronger than SARS-CoV, with alterations in several amino acid residues allowing for enhanced hydrophobic interactions and salt bridge formations, which may explain the considerably larger global influence of COVID-19 than the initial SARS. Due to SARS-CoV-2 interaction with ACE2, tissue ACE2 is downregulated from the membrane resulting in a systemic RAS imbalance, with an increase in the pressor arm and a decrease in the protective arm of the RAS, facilitating the development of multiorgan damage [18, 19].

Several evidences in animals have shown that chronic use of ACE inhibitors or Ang II receptor blockers (ARBs) upregulate ACE2 expression, and thereby theoretically increase the risk of SARS-CoV-2 infection [13, 20]. However retrospective clinical studies have shown no increase in hospitalization or death with the use of those antihypertensive therapies [21-23]. An observational multicenter cohort study with patients from USA and Spain showed no clinically significant increased risk of hospital admission with COVID-19 associated with ACE inhibitors or ARBs [23]. A transcriptomic analysis of over 700 lung samples of patients with comorbidities associated with severe COVID-19 revealed high expression of ACE2 compared to control

individuals, although hypertensive patients taking RAS inhibitors were not evaluated [24]. While this issue has not been resolved, prospective studies and clinical trials are ongoing. Recently, Wysocki et al [25] demonstrated that mice treated with the ACE inhibitor, captopril, or the ARB, telmisartan resulted in no alteration of lung ACE2 expression. In contrast, unpublished results from our lab showed that the amount of ACE2-expressing alveolar type II cells were enhanced in alveoli of smoker subjects under RAS blockade treatment.

Several factors have been associated with worse outcomes in COVID-19. It is possible that biological differences linked to the RAS could play some role. Among these factors we could mention male sex, racial and ethnic minority, obesity, older age, prior history of lung disease, smoking status, and lower socioeconomic status [18, 19]. The gene for ACE2 is contained on the X chromosome, thus differential ACE2 expression may occur with respect to sex. However, data reporting sex differences in ACE2 expression are conflicting. An integrated bioinformatics analysis of single-cell RNA sequencing data in humans indicated that men may have higher ACE2 expression in pulmonary alveolar type II cells compared with women [18, 19]. In agreement, soluble ACE2 is low in children and increases more in boys than girls, resulting in sex differences in adolescence/young adulthood [26]. Smoking and chronic obstructive pulmonary disease, which are more common in men, have been associated with higher ACE2 expression [27, 28]. Patients with obesity may have higher ACE2 expression in adipose tissue, as obesity is associated with increased ACE/Ang II relative to ACE2/Ang-(1-7) expression [29, 30]. However, it is unclear whether differential RAS expression according to these factors has any impact on SARS-CoV-2 infection or COVID-19 severity.

We have measured plasma levels of Ang-(1-7) and ACE2 in hospitalized patients with COVID-19 and we found that Ang-(1-7) levels decreased while ACE2 activity and protein levels increased compared to healthy subjects (unpublished results). We found no difference by sex. The fact that ACE2 activity was higher in COVID-19 patients suggests that these subjects would have higher levels of ACE2 in the membrane and therefore greater susceptibility to being infected by the virus. In agreement, recently it has been shown that soluble ACE2 is transiently elevated in COVID-19 and correlates with specific inflammatory and endothelial markers [31]. Reindl-Schwaighofer et al. [32] showed a sevenfold increase in ACE2 in patients with severe COVID-19 from early to late time periods during their disease course. ACE2 was associated with interleukin-6, supporting a link with inflammation. The observed increase in ACE2 in severe COVID-19 was accompanied by an increase in Ang-(1–7) [32]. We do not have an explanation between Reindl-Schwaighofer et al.'s results and ours regarding circulating Ang-(1–7) levels. Circulating Ang-(1–7) not only reflects ACE2 activity because other enzymes and other substrates of the RAS may be involved in Ang-(1–7) generation. I.e., Ang-(1–7) may be formed from Ang-(1–9) or from Ang I (Figure 1). On the other hand, ACE2 displays its catalytic activity on another substrates apart from Ang II [4, 5], thus the increase in ACE2 do not necessarily result in an increase in Ang-(1–7) levels.

Concluding remarks

Since the discovery of ACE2 in 2000, tremendous progress has been made in elucidating its biochemical actions and key as a protective component of the RAS, and more recently, as the SARS-CoV-2 receptor. ACE2 is a dominant mechanism for negative regulation of the RAS by converting Ang II into the beneficial peptide Ang-(1–7). The activation of the RAS axis due to binding of SARS-CoV-2 to ACE2, leading to direct loss of ACE2 and indirectly via proteolytic processing and shedding, partly drives the systemic manifestations of COVID-19. SARS-CoV-2 infection-caused ACE2 dysfunction worsens COVID-19 and could initiate multi-organ failure. Thus, ACE2 has long been a protective key component during 20 years, though the COVID-19 pandemic showed us that ACE2 may behave like an evil…

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My laboratory research has been focused on Mas receptor regulation in physiological and pathological conditions as in hypertension. Mas receptor mediates protective responses elicited by angiotensin-(1-7), a component of the protective arm of the renin-angiotensin system. We also investigated Mas receptor regulation due to heteromerization with others receptors and how this interaction influences its trafficking, affinity, signaling and biological activity. In the last year we have been involved in a project related to COVID-19. We investigated the content of angiotensin-converting enzyme 2, the receptor for the etiological agent of COVID-19, SARS-Co-V2, in subjects hospitalized with COVID-19.