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BRIEF COMMUNICATION

The renin-angiotensin system and specifically angiotensin-converting enzyme 2 as a potential therapeutic target in SARS-CoV-2 infections

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Abstract
In March 2019, the global COVID-19 pandemic caused by the novel SARS-CoV-2 coronavirus began. The first cases of SARS-CoV-2 infection occurred in November 19 in Wuhan, China. Preventive measures taken have not prevented the rapid spread of the virus to countries around the world. To date, there are approximately 3 million deaths, and a massive worldwide vaccination campaign has recently begun. SARS-CoV-2 uses the ACE-2 protein as an intracellular carrier. ACE-2 is a key component of the renin-angiotensin system (RAS), a key regulator of cardiovascular function. Considering the key role of ACE-2 in COVID-19 infection, both as an entry receptor and as a protective role, especially for the respiratory tract, and considering the variations of ACE-2 during the phases of viral infection, it is clear the important role that pharmacological regulation of RAS and ACE-2 may take. In this article, we describe the importance of ACE-2 in COVID-19 infection, the pharmacological aspects of a modulation with RAS-modifying agents, new therapeutic strategies, trying to provide a deep understanding and explanation of the complex mechanisms underlying the relationship between the virus and ACE-2, providing opinions and personal hypotheses on the best strategies of therapeutic intervention.

Keywords RAS · ACE-2 · COVID-19 · SARS-CoV-2

Introduction

The global pandemic COVID-19

The 2019 global coronavirus pandemic (COVID-19) is caused by a new coronavirus, SARS-CoV-2. To date, COVID-19 has caused approximately 3 Mln deaths (World Health Organization 2021). The COVID-19 pandemic represents a health, social, and economic challenge for all countries. A massive vaccination campaign has recently begun worldwide (Vitiello et al. 2021e). To date, drug treatments are mostly experimental; some antivirals such as remdesivir have shown good efficacy in reducing mortality and healing time (Ferrara et al. 2020b; Vitiello and Ferrara 2020a; Vitiello et al. 2021a). COVID-19 infection in most cases is asymptomatic or slightly symptomatic; however in a small percentage of cases, especially in elderly people and those with pre-existing conditions, the infection can be severe and in some cases fatal (Ruan et al. 2020; Yang et al. 2020). Although respiratory symptoms are predominant (Ferrara et al. 2020a), in the most severe stages of infection, multi-organ dysfunction can occur (Vitiello et al. 2021c; Ferrara and Vitiello 2021a) due to an abnormal and generalized inflammatory response (Vitiello et al. 2021b; Vitiello and Ferrara 2021a, b), causing injury to vital organs such as the lungs, heart, liver, and CNS (Shi et al. 2020; Vitiello et al. 2020a). Most patients with COVID-19 have a good prognosis, and rapid healing times; however, patients with diseases, such as diabetes, hypertension, and heart disease, are at greater risk of serious complications; this suggests that during the COVID-19, infection treatment of the underlying diseases should not be interrupted (Ferrara 2020; Guo et al. 2020). SARS-CoV-2 has high structural homology with SARS-CoV, demonstrating that it also shares the same cell entry receptor, the angiotensin 2 conversion enzyme (ACE-2) (Walls et al. 2020). ACE-2 is a protein with a key role in the renin-angiotensin system (RAS). RAS is a key regulator of the cardiovascular system.

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RAS and COVID-19

The renin-angiotensin system (RAS) is a physiological mechanism with a key regulatory role in various functions of the cardiovascular system. RAS is an enzymatic cascade consisting of a "classical way" and a "non-classical way". In the main (classical) enzymatic pathway, renin converts angiotensinogen to angiotensin I (Ang I). Ang I is then converted to angiotensin II (Ang II) by the angiotensin conversion enzyme (ACE). In the non-classical enzyme pathway, ACE-2 converts Ang II to angiotensin 1–7 (Ang 1–7) and Ang I to angiotensin 1–9 (Ang 1–9). ACE-2 is expressed in renal, cardiovascular, pulmonary, and gastrointestinal tissues. The biological effects of Ang-II on AT-1r receptors are vasoconstriction and stimulant of aldosterone release, myocardial hypertrophy, interstitial fibrosis, endothelial dysfunction, increased inflammatory state, increased oxidative stress, and increased coagulation (Fig. 1).

Ang II can also cause increased inflammation through the production of IL-6, TNF (tumor necrosis factor), and other inflammatory cytokines (Yamamoto et al. 2011; Recinos et al. 2007). Ang 1–7 and Ang 1–9 have opposite biological effects to Ang II through stimulation of the Mas receptor (MASr) and angiotensin type II receptors (AT-2r). MASr are expressed on the surface of the bronchial muscle and alveolar epithelium of the lungs (Pai et al. 2017; Magalhães et al. 2015). Ang 1–7 and Ang1-9 have anti-inflammatory, anti-fibrous, vasodilation effects. Evidence shows that the RAS system varies in conditions of pathologies such as COPD or viral infections, suggesting a possible involvement in homeostasis and function of the respiratory system and other ongoing systems of certain diseases. Some data demonstrate the variation of RAS and ACE-2 during COVID-19 infection, in particular an increase of ACE-2 in the early stages of infection and a rapid decrease in the more severe stages. It may be possible that ACE-2 has a protective effect, and when it decreases, there is a worsening of the inflammatory pulmonary state (Vitiello et al. 2020b; Vitiello and Ferrara 2021c).

ACE-2

ACE-2 is expressed both on the cell surface (in bound form) and in plasma and urine (soluble form) (Warner et al. 2005) Evidence shows that membrane ACE-2, during SARS-CoV infection, is internalized into the cytoplasm at the time of virus binding. ACE-2 is expressed in almost all organs (Donoghue et al. 2000), including the oral and nasal mucosa, nasopharynx, lung, liver, kidney, and brain. Some data show that the greatest expression of ACE-2 is in the lungs, heart, and liver, suggesting a possible correlation between the tissue distribution of ACE-2, and the organs may be more vulnerable in the more severe stages of COVID-19 infection. Some proteases, in particular TMPRSS2, are also involved in viral infection. TMPRSS2 may promote membrane fusion between the virus and the host cell as a result of ACE2 involvement and activation of S-protein SARS-CoV-2 (Hoffmann et al. 2020). Evidence shows that ACE-2 decreases occur in severe COVID-19 patients. This variation could probably be one of the causes of the damage caused by COVID-19. As described above, the decrease in ACE-2 expression leads to a decrease in the ACE2-Ang (1–7)-MasR

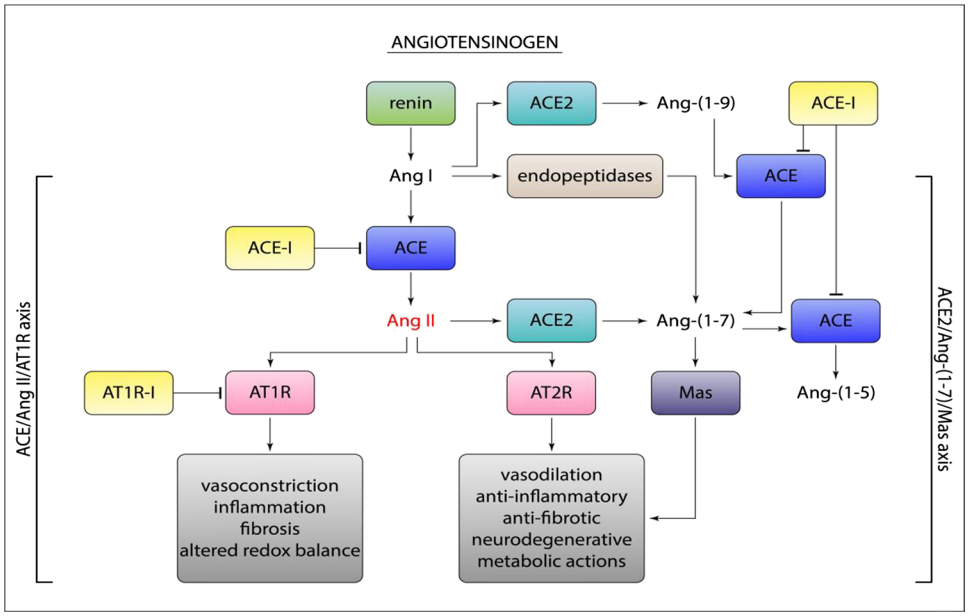

Fig. 1 The renin-angiotensin system (RAS) and the biological effects after activation of AT-1r, AT-2r, and MASr

axis and an increase in Ang-II. The imbalance between Ang 1–7 and Ang II leads to the prevalence of the biological effects of Ang II such as profibrotics, proinflammatory vasoconstriction, and indirect procoagulation (Vitiello and Ferrara 2020b). Biological effects may be responsible for pulmonary and cardiac lesions that may occur in severe COVID-19 patients (Vitiello et al. 2020c).

ACE inhibitor(ACE-i) and angiotensin-receptor blocker (ARB)

Recent studies have shown that the use of ACE-i or ARB can affect the expression of ACE-2 (Li et al. 2020a). Since the beginning of the COVID-19 pandemic, a scientific debate is ongoing on whether the use of ACE-i and ARB may represent a COVID-19 risk factor. To date, epidemiological evidence shows that they do not represent a risk factor, and it is not recommended to stop the therapeutic treatment (Reynolds et al. 2020). Moreover, according to the different mechanism of action, it is assumed that the use of ACE-i increases the expression of ACE-2, and the use of ARB causes a counter-regulation of the RAS system with an increase of ACE and ACE-2. Currently, it is not completely clear whether ACE-I and ARB increase ACE-2 expression in all tissues, whether under certain conditions and at what times and doses. For example, perindopril (ACE-i) has been able to increase ACE-2 expression in the liver under conditions of liver fibrosis (Huang et al. 2010). Ramipril (ACE-i) decreased the expression of the ACE-2 protein after myocardial infarction (Burchill et al. 2012). Losartan (ARB) may not only increase cardiac mRNA ACE2 expression but also significantly increase ACE-2 activity in the lung, suggesting that losartan may have protective effects on cardiac and lung lesions caused by COVID-19. In addition, in vivo experiments have shown that lozartan may protect against lung injury caused by SARS-CoV coronavirus by decreasing the production of pro-inflammatory cytokines (Ferrario et al. 2005; Kuba et al. 2005).

Pharmacological target of SARS-CoV-2

A causa della gravità della pandemia, sono urgentemente necessarie terapie efficaci contro la SARS-CoV-2. Come già descritto, l'ACE-2 è il recettore di ingresso cellulare della SARS-CoV-2, ed è anche un componente chiave del RAS. Pertanto, una piena comprensione della correlazione tra ACE-2 e SARS-CoV-2 sarebbe di fondamentale importanza per agire con strategie di intervento farmacologico mirate (Ferrara and Vitiello 2020; Vitiello and Ferrara 2021d; Ferrara and Vitiello 2021b; Muslim et al. 2020). Tuttavia, sebbene l'ACE-2 sia stato identificato come recettore della SARS-CoV-2, potrebbero esserci altri co-recettori della SARS-CoV-2 ancora da scoprire (Muslim et al. 2020). Ciò solleva ulteriori importanti implicazioni per i bersagli terapeutici della SARS-CoV-2 (Marovich et al. 2020; Vitiello et al. 2021d; Singh et al. 2021). One of the most important strategies to control viral infections is to block the initial binding of the virus to its functional receptors. Several candidate drugs have been developed to block binding of S protein and ACE-2, including drugs based on S protein and ACE-2. Monoclonal antibodies to COVID-19 act by neutralizing the spike protein of SARS-CoV-2, which blocks the binding of the spike protein to human ACE-2 receptors, thereby preventing subsequent viral entry into human cells and virus replication (Marovich et al. 2020; Tian et al. 2020). Treatment with a soluble recombinant human form of ACE2 (rhACE2) could prove useful as a trap effect for circulating SARS-CoV2 and decrease viral load and hinder infection (Monteil et al. 2020). Administration of recombinant soluble human ACE2 has shown good efficacy in subjects with acute respiratory distress syndrome (ARDS) (Muslim et al. 2020). From a molecular pharmacological point of view, administration of rhACE2 activates the Ang 1–7 and Ang 1–9 synthesis pathway of the RAS system (non-classical pathway) by decreasing Ang II levels with a tendency to lower the concentration of proinflammatory cytokines (Gaddam et al. 2014). Some clinical trials show excellent results when administered in combination rhACE2 and remdesivir (Monteil et al. 2021). Theoretically, administration of soluble ACE2 protein, in sufficient quantities, binding to the spike protein of SARS-CoV-2, could reduce the attachment to ACE-2 at the plasma membrane. This could be used therapeutically as a way to reduce infectivity in patients treated with COVID-19. Studies in healthy volunteers have demonstrated a reduction in Ang II after administration of soluble ACE-2 (Imai et al. 2005). In contrast, direct administration of Ang (1–7) failed to demonstrate significant effects in humans (Oudit and Penninger 2011). In addition, preclinical studies have shown that administration of soluble ACE-2 can decrease lung injury (Haschke et al. 2013). In patients with acute respiratory distress syndrome (ARDS), hrACE2 (GSK2586881) was well-tolerated (Khan et al. 2017). Human rACE2 caused a decrease in circulating Ang II levels (73), whereas angiotensin (1–5) and angiotensin (1–7) levels increased and remained elevated for 48 h (Khan et al. 2017). Some in vitro and in silico assays revealed two compounds (xanthenone and resorcinolnaphthalein) that increase ACE2 activity in a dose-dependent manner (Li et al. 2020b). They may be useful in increasing Ang II turnover in Ang (1–7). Finally, vitamin D is known for its anti-inflammatory effects. The hormonal form of vitamin D, calcitriol (1,25(OH)2D3), is a negative endocrine regulator of the RAS and inhibits renin biosynthesis, and it blocks the expression of ACE and Ang II and elevates ACE2

levels in LPS-induced acute lung injury (Xu et al. 2015). Thus, it could potentially play a role in combating SARS-CoV-2 infection and related complications.

Conclusions

The COVID-19 pandemic has caused about 1.34 million deaths and is currently ongoing. Due to this severity, effective therapies against SARS-CoV-2 are urgently needed. RAS and ACE-2 have an important correlation with SARS-CoV-2. A modulation of the system could represent a protective effect against SARS-CoV-2 infection. Interesting drug strategies are being developed. The blocking of SARS-CoV-2 cell entry is potentially the best pharmacological strategy to follow. Well-structured clinical trials are urgent in this direction to generate the necessary EBM.

Author contribution The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

Declarations

Conflict of interest The authors declare no completing interests.

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