



# Relationship Between ACE2 and Other Components of the Renin-Angiotensin System

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## Abstract

**Purpose of the Review** Angiotensin-converting enzyme 2 (ACE2) is a key counter-regulatory component of the renin-angiotensin system. Here, we briefly review the mechanistic and target organ effects related to ACE2 activity, and the importance of ACE2 in SARS-CoV-2 infection.

**Recent Findings** ACE2 converts angiotensin (Ang) II to Ang-(1–7), which directly opposes the vasoconstrictive, proinflammatory, and prothrombotic effects of Ang II. ACE2 also facilitates SARS-CoV-2 viral entry into host cells. Drugs that interact with the renin-angiotensin system may impact ACE2 expression and COVID-19 pathogenesis; however, the magnitude and direction of these effects are unknown at this time.

**Summary** High quality research is needed to improve our understanding of how agents that act on the renin-angiotensin system impact ACE2 and COVID-19-related disease outcomes.

**Keywords** COVID-19 · Angiotensin-converting enzyme · Renin-angiotensin system · Angiotensin receptor blockers · Angiotensin-converting enzyme inhibitors · Hypertension · Coronavirus infections · Chronic kidney disease · Cardiovascular disease

## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, is associated with a high risk of acute respiratory distress syndrome and mortality [1–4]. Angiotensin-converting enzyme 2 (ACE2) facilitates SARS-CoV-2 entry into host cells in the respiratory tract, and altered

ACE2 regulation is speculated to play a role in the pathogenesis of COVID-19 [5]. In the setting of the COVID-19 pandemic, there has been increasing interest in the physiologic and pathophysiologic function of ACE2 [6]. Here, we briefly review the role of ACE2 in the renin-angiotensin system, the therapeutic potential of ACE2, and potential interactions of ACE2 with SARS-CoV-2 and its role in COVID-19 pathophysiology.

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## Counter-Regulatory Effects of ACE2 in the Renin-Angiotensin System

ACE2 is a mono-carboxypeptidase with a single enzymatic binding site that acts as a key counter-regulatory component of the renin-angiotensin system [7]. ACE2 is the only known homolog of ACE; it shares 42% of sequence identity with somatic ACE and 61% similarity in the area surrounding the active site [8, 9]. ACE2 is expressed on the surface of endothelial and epithelial cells in membrane-bound form as well as soluble form in several tissues throughout the body, including the kidneys, heart, gastrointestinal tract, and lungs [10, 11].

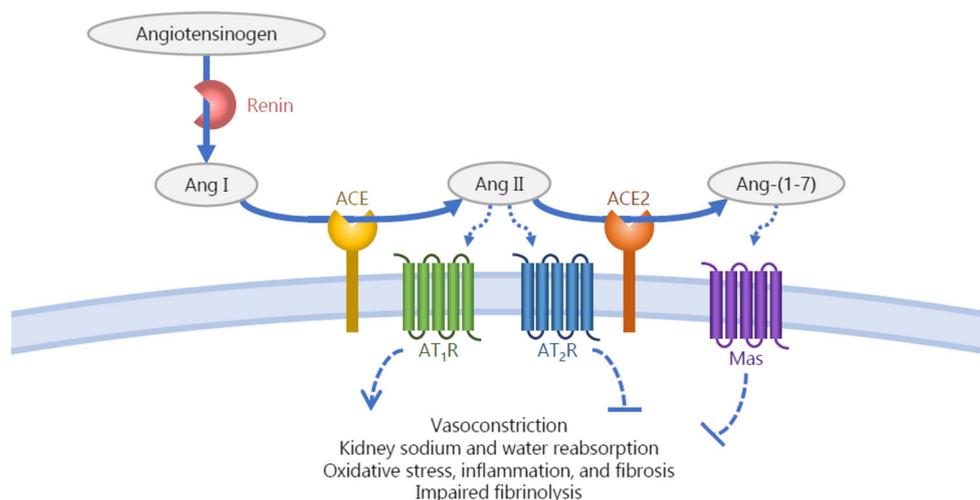
ACE converts angiotensin I (Ang I) to Ang II, which acts on the Ang II type 1 receptor (AT<sub>1</sub>R), resulting in vasoconstriction, sodium and fluid retention by the kidney, oxidative stress, inflammation, fibrosis, and impaired fibrinolysis [11, 12]. In direct opposition to the cascade of physiological effects of the ACE/Ang II pathway, the net effect of the ACE2/Ang-(1–7) pathway is vasodilation and anti-inflammation. ACE2 hydrolyzes Ang II, converting it to Ang-(1–7) (see Fig. 1). The conversion of Ang II to Ang-(1–7) diminishes the availability of Ang II to bind AT<sub>1</sub>R, forestalling the vasoconstrictive, proinflammatory, and prothrombotic effects of AT<sub>1</sub>R activation [7, 10–13]. Additionally, Ang-(1–7) acts on the Mas receptor, causing the release of nitric oxide, prostaglandin E<sub>2</sub>, and bradykinin [11] resulting in vasodilation, natriuresis, and a reduction in oxidative stress and inflammation [14, 15]. ACE2 also cleaves several other peptides, including converting Ang I to Ang-(1–9), which is a less-bioactive peptide [16].

## Systemic Effects of ACE2

ACE2 plays an important role in the development of several pathologic conditions, including hypertension, cardiac hypertrophy, and kidney disease. For example, in human kidney tissue, the ratio of ACE to ACE2 expression is higher in subjects with hypertension compared with those without hypertension [17]. These findings are consistent with more-pronounced vasoconstrictive and anti-natriuretic effects of ACE, compared with ACE2, activity in hypertensive individuals. Several experimental and human studies have also demonstrated a reduction in glomerular ACE2 expression in diabetic and non-diabetic kidney disease [8]. Correspondingly, experimental studies in mice show that pharmacologic inhibition of ACE2 promotes the development of microalbuminuria and diabetic nephropathy [18, 19]. Human data suggest that ACE2 may be upregulated in individuals with existing cardiovascular disease, which is speculated to be a compensatory response to counteract the deleterious effects of Ang II [20]. In SARS-CoV-2, while ACE2 facilitates viral entry in host cells, it may also have protective effects against severe acute lung injury [21].

## ACE2 as a Therapeutic Target

Given its vasodilatory, natriuretic, anti-inflammatory, and anti-fibrotic effects via increased Ang-(1–7) and decreased Ang II, soluble ACE2 has been proposed as a potential therapeutic target in hypertension, chronic kidney disease, cardiovascular disease, and viral respiratory disease. In experimental studies, chronic administration of soluble ACE2 has been



**Fig. 1** The counter-regulatory role of ACE2 in the renin-angiotensin system. This figure demonstrates the conversion of angiotensinogen to Ang I by renin, Ang I to Ang II by ACE, and Ang II to Ang-(1–7) by ACE2. Ang II acts on the AT<sub>1</sub>R receptor to increase vasoconstriction,

fluid and sodium retention by the kidney, and oxidative stress, resulting in increased blood pressure. Ang-(1–7) acts on the Mas receptor resulting in vasodilation, increased fluid and sodium excretion by the kidney, and a reduction in oxidative stress, resulting in reduced blood pressure

associated with degradation of Ang II and an increase in Ang-(1–7) [22–24]. Animal studies consistently demonstrate a reduction in blood pressure with recombinant ACE2 administration, and in mouse models, recombinant ACE2 attenuated diabetic kidney injury [22] and myocardial remodeling [24]. Recombinant ACE2 has also been proposed as a treatment for severe viral pneumonia and acute respiratory distress syndrome. Recombinant ACE2 reduces acute lung injury and acute respiratory distress syndrome in mice with viral pneumonia [25]. Children infected with respiratory syncytial virus have higher plasma Ang II concentration compared with healthy controls, suggesting upregulation of ACE/Ang II and downregulation of ACE2/Ang-(1–7), and supporting ACE2 as a potential therapy in respiratory syncytial viral lung disease in humans.

ACE inhibitors block the conversion of Ang I to Ang II, while Ang II receptor blockers directly inhibit AT<sub>1</sub>R. Both of these medications decrease blood pressure and inflammation and mitigate fibrosis in hypertension, cardiovascular disease, and chronic kidney disease. In several animal models, these antihypertensive agents have been shown to increase ACE2 expression in the heart and kidneys [26–29]. However, in humans, ACE inhibitors and Ang II receptor blockers have not been associated with increased kidney ACE2 expression or circulating ACE2 activity [30, 31•].

## The Relationship Between ACE2 and COVID-19

ACE2 is the binding site for the SARS-CoV-2 viral spike (S) protein and facilitates viral entry into the host cell. There has been recent speculation that ACE inhibitors and Ang II receptor blockers may increase the risk of development and severity of COVID-19 due to potential upregulation of ACE2 by these medications [32]. However, SARS-CoV-2 facilitates ACE2 endocytosis, downregulates ACE2 expression, and promotes ACE2 shedding from the cell surface, leading to an increase in Ang II concentration and a decrease in Ang-(1–7). This is likely important in COVID-19 pathophysiology due to the proinflammatory effects of Ang II with corresponding loss of Ang-(1–7)-mediated counter-regulation [33]. The prothrombotic effects of excess Ang II could underlie COVID-19 hypercoagulability [34, 35•]. Upregulation of ACE/Ang II with downregulation of ACE2/Ang-(1–7) in the vascular endothelium could promote COVID-19-associated vasculopathy [36, 37]. Extrapolating from SARS-CoV animal models, increased Ang II in patients with COVID-19 due to loss of ACE2 could mediate acute lung injury and acute respiratory distress syndrome [38]. In experimental models, Ang II administration induces AT<sub>1</sub>R-mediated ACE2 internalization and degradation [39]. ACE inhibitors and Ang II receptor blockers may have a therapeutic benefit in COVID-19

by reducing Ang II concentration and AT<sub>1</sub>R activation. Thus, it remains unclear if ACE inhibitors or Ang II receptor blockers have a beneficial or harmful effect in SARS-CoV-2 infection and COVID-19.

## Conclusions

ACE2 has important counter-regulatory effects on the renin-angiotensin system and has been implicated in COVID-19 pathogenesis. Medications that act on the renin-angiotensin system, including ACE inhibitors and Ang II receptor blockers, may impact COVID-19 infection and severity via potential interactions with ACE2; however, the direction and magnitude of these effects are unknown at this time. Several international societies have released statements discouraging discontinuation of ACE inhibitors and Ang II receptor blockers in patients who are treated with these medications for hypertension, heart failure, and chronic kidney disease amidst the COVID-19 pandemic [6•]. Given the clear benefits of these agents in hypertension, chronic kidney disease, coronary heart disease, and diabetes, there is an urgent need for further research to improve our understanding of the relationship between agents that act on the renin-angiotensin system and outcomes among individuals with COVID-19, with several studies currently underway [6•].

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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