Institut Pasteur
Microbes and Infection 15 (2013) 866–873
www.elsevier.com/locate/micinf

Review

# ACE2 – From the renin–angiotensin system to gut microbiota and malnutrition

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Received 29 July 2013; accepted 6 August 2013
Available online 17 August 2013

**Abstract**

The renin–angiotensin system (RAS) is a complex network that regulates blood pressure, electrolyte and fluid homeostasis, as well as the function of several organs. Angiotensin-converting enzyme 2 (ACE2) was identified as an enzyme that negatively regulates the RAS by converting Ang II, the main bioactive molecule of the RAS, to Ang 1–7. Thus, ACE2 counteracts the role of angiotensin-converting enzyme (ACE) which generates Ang II from Ang I. ACE and ACE2 have been implicated in several pathologies such as cardiovascular and renal disease or acute lung injury. In addition, ACE2 has functions independent of the RAS: ACE2 is the receptor for the SARS coronavirus and ACE2 is essential for expression of neutral amino acid transporters in the gut. In this context, ACE2 modulates innate immunity and influences the composition of the gut microbiota, which can explain diarrhea and intestinal inflammation observed in Hartnup disorder, Pellagra, or under conditions of severe malnutrition. Here we review and discuss the diverse functions of ACE2 and its relevance to human pathologies.


*Keywords:* Renin–angiotensin system; Virus receptor; Amino acid transport; Microbiota; Malnutrition

## 1. An overview of the renin–angiotensin system

The renin–angiotensin system (RAS) regulates several body functions on a systemic level or locally in various organs [1]. The systemic or circulatory RAS is involved in regulating blood pressure as well as electrolyte and liquid homeostasis, whereas local or tissue RAS regulates functions of numerous organs such as heart, kidney, or the lung. Within the RAS, regulation is achieved through a cascade of proteases that generate several bioactive peptides. The glycoprotein angiotensinogen is mainly produced and secreted by the liver and cleaved by renin, which is generated by the juxtaglomerular apparatus in the kidney, to result in the decapeptide angiotensin I (Ang I) [2]. Ang I can subsequently be cleaved to the octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). ACE is expressed in endothelial cells of the vasculature and also locally in a variety of tissues such as kidney, heart, lung, or the brain [3].

Ang II represents the main bioactive component within the RAS and signals through the G-protein-coupled receptors angiotensin II receptor type 1 ($AT_1$) and angiotensin II receptor type 2 ($AT_2$) [4]. Signaling through $AT_1$ is a well established route to mediate vasoconstrictive effects, whereas $AT_2$ receptor activation has opposing effects through activation of a vasodilatory cascade including effectors such as bradykinin, NO, or cGMP [5]. Ang II can further be processed by angiotensin-converting enzyme 2 (ACE2) to form the heptapeptide Ang 1–7, thereby removing the main activating peptide of the RAS from the system. Ang 1–7, in turn, binds to the Mas receptor [6] to counteract the activity of Ang II binding to $AT_1$. Therefore, the ACE2/Ang 1–7/Mas axis is considered to be a negative regulator of the RAS, opposing the activity of the ACE/Ang II/$AT_1$ axis [7] (Fig. 1).

Apart from signaling through the Mas receptor, Ang 1–7 can also act as an $AT_1$ receptor antagonist, therefore further counteracting the ACE/Ang II/$AT_1$ axis [8,9]. In alternative

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http://dx.doi.org/10.1016/j.micinf.2013.08.003

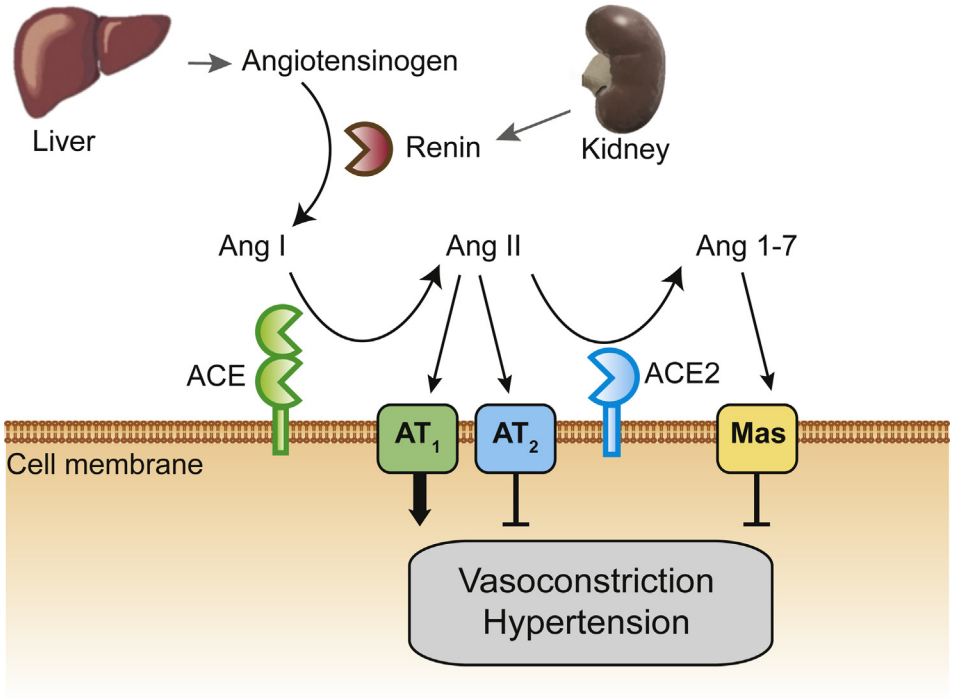


Fig. 1. Simplified diagram of the renin–angiotensin system. Angiotensinogen is secreted by the liver and gets converted to Ang I by renin, which is mainly produced in the kidneys. Ang I gets cleaved by ACE to result in Ang II. Ang II is a ligand for the $AT_1$ receptor and promotes vasoconstriction and hypertension. Alternatively, Ang II can bind to the $AT_2$ receptor to inhibit vasoconstriction. ACE2 processes Ang II to Ang 1–7 which binds to the Mas receptor to induce vasodilation.

pathways, Ang I can be cleaved by chymase to form Ang II or by other peptidases such as prolyl-endopeptidase (PEP), neutral endopeptidase (NEP), and thymet oligopeptidase (TOP), to directly generate Ang 1–7 [10]. However, in this review we will solely focus on the ACE/ACE2 peptidase system. ACE2 can potentially also act on other peptide systems, in particular on the apelin/APJ system [11]. Apelin is produced as a 77 amino acid pre-pro-hormone which is further processed to apelin-36 and apelin-13. Apelin signals through its receptor APJ and was shown to have vasodilatory effects [12]. ACE2 can cleave the carboxyterminal phenylalanine of apelin-36 and apelin-13 [11], thereby removing the vasodilator apelin, and might therefore counteract its own vasodilatory role within the RAS. Due to the fundamental role of Ang II in blood pressure control, several $AT_1$ receptor antagonists and ACE inhibitors are used successfully in the clinic as a treatment for hypertension as well as for renal and cardiac diseases. Importantly, none of these inhibitors in clinical use have been reported to also block the enzymatic activity of ACE2 [13].

## 2. Angiotensin-converting enzyme 2 – ACE2

ACE2 was discovered as a homolog of ACE and mapped to the X chromosome in humans, rats, and mice [14–16]. ACE2 is expressed at high levels in kidney, heart, and testis [14], but is also found in many other tissues such as lung, small intestine, and liver [17–19]. The *ace2* gene spans 18 exons and codes for an 805 amino acid type I transmembrane glycoprotein. ACE2 contains a short intracellular cytoplasmic tail and a longer extracellular domain that exhibits carboxy-monopeptidase activity [1]. The active site of ACE2 contains the HEMGH motif, characteristic for zinc-metallopeptidases and shares approximately 42% sequence homology with the amino-terminal domain of ACE [15]. The carboxy-terminal domain of ACE2 is about 48% homologous with Collectrin (also known as Tmem27) [20]. Therefore, evolutionary, ACE2 is a chimeric protein consisting of the amino-terminal carboxypeptidase domain of ACE, whereas the carboxy-terminal part of ACE2 lacking enzymatic activity shares homology with Collectrin. Another homolog of ACE was discovered in 2007 and termed ACE3 [21]. However, due to the presence of several deletions and insertions in the genomic sequence, ACE3 seems to lack catalytic activity as a metalloprotease. So far no physiologic functions could be identified and it has been suggested that *ace3* is a pseudogene [21,22].

## 3. Physiologic functions of ACE2 within the RAS

The carboxy-peptidase domain of ACE2 efficiently cleaves the C-terminal phenylalanine of Ang II to produce the vasodilator Ang 1–7 [14,15]. ACE2 also shows activity towards Ang I by cleaving the C-terminal leucine, which results in the supposedly biological inactive peptide Ang 1–9, which can further be processed by ACE to Ang 1–7. However, ACE2 shows a clear substrate preference for Ang II over Ang I [11]. Solving the crystal structure of ACE2 revealed a hinge-bending motion upon ligand binding, characteristic for several metallopeptidases. Moreover, compared to ACE a