Physiological roles of angiotensin-converting enzyme 2

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Abstract. Angiotensin-converting enzyme 2 (ACE2) is a recently discovered homologue of the key enzyme of the renin-angiotensin system, the angiotensin-converting enzyme. The ACE2 enzyme is mainly expressed in cardiac blood vessels and tubular epithelia of the kidneys. Together with ACE2’s unique metalloprotease activity, the restricted tissue distribution suggests a distinctive physiological function in blood pressure, blood flow and fluid regulation. The ace2 gene was mapped to quantitative trait loci affecting susceptibility to hypertension in rats. Furthermore, ACE2 appears to be a negative regulator of ACE in the heart. ACE2 messenger RNA and protein levels are substantially regulated in the kidney of diabetic and pregnant rats. The mechanism of ACE2 function and its physiologic significance are not yet fully understood; however, as ACE2 differs in its specificity and physiological role from ACE, this opens a new potential venue for drug discovery aimed at cardiovascular disease, hypertension and diabetic complications.

Key words. Angiotensin-converting enzyme 2; knockout mice; renin-angiotensin system.

Introduction

For the last 50 years, angiotensin-converting enzyme (ACE) has assumed a central position in the renin-angiotensin system (RAS). The RAS is a major regulatory network that maintains blood pressure, fluid and electrolyte balance and electrolyte homeostasis. ACE functions primarily as a ‘peptidyl dipeptidase’, removing dipeptides from the C-terminus of peptide substrates [1]. Its primary substrate was identified as angiotensin I. ACE processes the decapeptide angiotensin I to the eight-amino-acid peptide angiotensin II, which functions as a strong vasoconstrictor. In parallel, ACE also inactivates the vasodilator peptides bradykinin and kallidin, and thus potentiates the vasopressor response mediated by angiotensin II [1]. Inhibition of ACE’s enzymatic activity has a powerful effect in reduction of blood pressure; thus small molecule inhibitors of human endothelial ACE are used for antihypertensive therapies [2]. In addition to their effectiveness in treating hypertension, ACE inhibitors have been found to lower the risk of coronary heart disease and stroke. Furthermore, they improve the prognosis of patients with cardiac failure and diabetic nephropathy (for review, see [3]).

With the discovery of ACE 2/ACEH by Donoghue [4] and Tipins [5], a new level of complexity was added to the RAS. The ACE2 gene is located in the region of the X chromosome (Xp22), which maps to quantitative trait loci (QTL) in hypertensive rats [6–8]. Consistent with a possible role in cardiorenal function, ACE2 was found to be predominantly expressed in endothelia of the heart and in tubular epithelia of the kidney [4, 5]. In humans, ACE2 was also found in the gastrointestinal tract [9]. Additionally, in mouse, ACE2 has been detected in lungs [10]. While ACE and ACE2 protein are similar in their metalloprotease catalytic domains, they differ in their substrate specificity [11]. Analysis of ACE2 expression and the
physiological role of its substrates suggest that ACE2 may act as a tissue-specific negative feedback regulator of the RAS [3]. Furthermore, the differences observed in phenotype between the genetically engineered *ace* and *ace2* mice [12] all suggest a role for ACE2 in heart pathophysiology. Moreover, since it has been shown that ACE2 acts not only on the angiotensin I and angiotensin II peptides, but also efficiently cleaves the C-terminal residues from several other peptides such as apelin-13 and dynorphin A 1–13, unrelated to angiotensin I [4], ACE2 function may not be limited only to RAS.

Substrate specificity of ACE2

In the classic pathway of RAS, angiotensin I is generated from the circulating precursor angiotensinogen by the action of renin, an enzyme secreted from juxtaglomerular cells at the renal afferent arterioles [13]. Angiotensin I has little effect on blood pressure and is converted by ACE to angiotensin II. Angiotensin II, a potent vasopressor, acts on the blood vessels and the kidneys by binding to the G-protein-coupled receptors AT1 and AT2. In contrast, ACE2 cleaves the C-terminal amino acid of angiotensin I to a nonapeptide angiotensin 1–9 [4]. In rat and human plasma angiotensin 1–9 levels are twice those of angiotensin II [14, 15], and angiotensin 1–9 accumulates in animals treated with ACE inhibitors [16]. The biological function of angiotensin 1–9 is still not well defined. However, angiotensin 1–9 is thought to potentiate angiotensin II-mediated vasoconstriction in isolated rat aortic rings and to have pressor effects in awake rats [17]. Angiotensin 1–9 was also shown to have weak pressor effects in anesthetized rats and dogs, and vasoconstricting activity in isolated rat aorta [17].

ACE2 directly converts angiotensin II to angiotensin 1–7 [4, 18]. In animals, angiotensin 1–7 has been proposed to be an important regulator of cardiovascular function, promoting vasodilatation, apoptosis and growth arrest [19, 20]. However, its functional significance in humans is still controversial. Aside from the degradation of the vasoconstrictor angiotensin II, the formation of the vasodilatory angiotensin 1–7 might reflect the negative regulatory function of ACE2 in the presence of an activated RAS. In addition to its activity as angiotensin-converting enzyme, ACE2 can remove in in vitro assays the C-terminal residue from other vasoactive peptides, including neurotensin, kinetensin (a neurotensin-related peptide) and des-Arg bradykinin (fig. 1). The kinin metabolites, des-Arg\textsuperscript{10}-kallidin (des-Arg\textsuperscript{10,15}-Lys\textsuperscript{1}-bradykinin) and des-Arg\textsuperscript{9}-bradykinin activate the G-protein-coupled \( B_1 \) receptor [21], which is upregulated in response to tissue injury and may be important in mediating inflammatory responses. Furthermore, ACE2 also acts on apelin-13 and apelin-36 peptides with high catalytic efficiency [18]. These two forms of apelin were recently identified as endogenous ligands for the human APJ receptor, which is a homolog of the angiotensin receptor AT1 [22]. The role of the apelins is not fully understood. Whereas systemic administration of apelin-13 promotes hypotension in rats [23], it has been shown that apelin-13 promotes vasoconstriction in endothelium-denuded coronary arteries [23]. Intraperitoneal injection of apelin-13 in rats increases water intake [23]. Two opioid peptides, dynorphin A 1–13 and

![Figure 1. Hypothetical model of ACE and ACE2 functions. Angiotensin I serves as a substrate for both ACE and ACE2. Angiotensin II is known to act as vasoconstrictor in vivo. The function of Angiotensin (1–9) is still not well understood. Both ACE and ACE2 are involved in the production of the vasodilator peptide angiotensin (1–7). From genetic experiments it appears that ACE and ACE2 have complementary functions by negatively regulating each other in the RAS.](image-url)