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Angiotensin converting enzyme

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Abbreviation: ACE, ACE2
Additional names: (1) angiotensin converting enzyme, dipeptidyl carboxypeptidase I, peptidase P, kininase II, angiotensin I-converting enzyme; (2) angiotensin converting enzyme 2, peptidyl-dipeptidase A, peptidyl-dipeptidase A.

ACE possesses dual actions to convert Ang I to Ang II, and degrade bradykinin. The development of an ACE inhibitor was the first effective drug for hypertension caused by high renin activity. ACE2 was identified as the receptor for the SARS (severe acute respiratory syndrome) coronavirus, which caused an epidemic in 2002–2003.

Discovery

ACE was discovered in the mid-1950s through the observation that the dialysis of plasma and kidney extract with water and saline before incubation produced two separate pressor substances, Ang I and Ang II, respectively.1 It was discovered for a second time in 1966 during the characterization of a bradykinin (BK)-degrading enzyme from the kidney. This was named kininase II, which later was found to be the same enzyme as ACE. ACE2 was discovered in 2000 when two independent research groups cloned homologous ACE that could convert Ang I to Ang1–9 and yet also be captopril-insensitive.2,3

Primary structure

Somatic and testis ACEs in humans contain 1306 and 665 aa residues, respectively (Fig. 42D.S1). The testis ACE only possesses one catalytic domain.

Properties

Mr. of ACE 195kDa; Mr. of testis ACE 90kDa; and Mr. of ACE2 92kDa. ACEs are membrane-bound enzymes.

Synthesis and release

Gene, mRNA, and mRNA

The ACE and ACE2 genes are located at chromosomes 17q23 and Xp22 in humans, respectively. The testis ACE is transcribed from the same gene with an alternative transcription starting site on the 13th intron of ACE, resulting in only a C-domain and a stalk segment with a unique additional 67 aa N-terminal sequence in humans. The two catalytic domains are the result of gene/domain duplication. The duplication occurred multiple times in evolution as the cnidarians, crustaceans, insects, and vertebrates possess ACE-like enzymes with one or two catalytic domains. No expression studies so far have been performed for nonmammalian ACE and ACE2.

Distribution of mRNA

Somatic ACE is expressed in various tissues, including the blood vessels, kidney, intestine, adrenal gland, liver, uterous, etc.; it is especially abundant in highly vascular...
organs such as the retina and lung. Testis *ACE* is expressed by postmeiotic male germ cells and high level expression is found in round and elongated spermatids. *ACE2* is expressed in the lung, liver, intestine, brain, testis, heart, and kidney.

### Tissue contents

The lung possesses the highest amount of *ACE*, and contributes to 0.1% of the total protein. Several enzymatic assays have been developed for the measurement of *ACE* activity in plasma and tissues. These assays utilized artificial substrates such as hipuryl-His-Leu or N-[3-(2-furyl) acryloyl]L-phenylalanyl-glycyl-glycine (FAPGG), in combination with *ACE* inhibition by captopril, to estimate the inhibitor-dependent consumption rate of the artificial substrates. These methods were developed in mammals but were also extended to other vertebrates, including birds, amphibians, and fish. However, these enzymatic methods may be erroneous because the enzyme specificity on the artificial substrates could be different. Lamprey *ACE* activities in different tissues were measured but captopril failed to decrease the *ACE* activities, indicating a possible nonspecific enzyme measurement. In amphibians, high captopril-sensitive *ACE* activities were found in the gonad, intestine, kidney, and lung; moderate activities were presented in the liver, heart, and skin; and low or negligible activities were observed in the plasma, muscle, and erythrocytes.

### Plasma concentrations

Serum *ACE* levels in humans ranged from 299.3 ± 49μg/L (DD) to 494.1 ± 88.3μg/L (II) with heterozygous individuals at 392.6 ± 66.8μg/L. (ID: see “Pathophysiological implications” for the genotype definition).

### Regulation of synthesis and release

The expression of *ACE* is affected by steroids and the thyroid hormone, but the details of the regulation are not clear. *ACE* is under promoter regulation by hypoxia-inducing factor 1α (HIF-1α), which upregulates the *ACE* expression under hypoxic conditions, resulting in an increase in Ang II concentration. Under hypoxia, *ACE2* will be downregulated; it was shown that it is indirectly controlled by Ang II, but not HIF-1α. Testis *ACE* expression control is highly specific and regulated by a tissue-specific promoter located immediately -59bp of the transcription start site, which is frequently used in testis-specific overexpression studies. Hypoxia induced by high temperature decreased the gill *ACE* activity.

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**FIG. 42D.1** Schematic showing the functional domains of *ACE* and *ACE2*. 

![Schematic showing the functional domains of *ACE* and *ACE2*.](image)
but had no effect on the kidney in the carp. Promoters of ACE2 from mammals, amphibians, and teleosts drive specific expression in the heart. Cis-Element search results discovered WGATAR motifs in all putative ACE2 promoters from different vertebrates, suggesting a possible role of GATA family transcriptional factors in ACE2 expression regulation.

**Receptors**

**Inhibitors**

The first ACE inhibitor was a peptide antagonist called SQ 20,881 (GWPRPEIPP); it was discovered from snake venom but was not orally active. The snake venom peptides were further studied to produce the first orally active form, captopril, which lowers the blood pressure of essential hypertensive patients. The most common side effects of captopril are a cough, skin rash, and loss of taste. Therefore, derivatives such as enalapril, lisinopril, and ramipril were developed with fewer side effects. After the discovery of the N- and C-domains of ACE, specific domain inhibitors were developed to increase specificity. Ang I is mainly hydrolyzed by the C-domain in vivo, but BK is hydrolyzed by both domains. Developing a C-domain selective inhibitor (RXPA380) would permit some degradation of BK by the N-domain; this degradation could be enough to prevent the accumulation of excess BK causing angioedema.

**Phenotype in gene-modified animals**

Ace-knockout mice display normal blood pressure under normal conditions, but are sensitive to changes in blood pressure such as through exercise. Ace-knockout also affected renal function, renal development, serum and urine electrolyte composition, hematocrit, and male reproductive capacity. Deficiency in testis Ace affects male fertility but its exact role is still not clear. Although the mice with testis Ace deficiency mate normally and their sperm quantity and motility are no different from wild-type mice, the survival of sperm in the oviduct and the fertilization rate are highly reduced.

The overexpression of Ace2 in hypertensive models, but not in normotensive animals, reduced the blood pressure. Ace2-knockout mice displayed progressive cardiac dysfunction resembling long-term hypoxia after coronary artery disease or bypass surgery in humans, which could be reversed by concurrent Ace-knockout. It was suggested that the cardioprotective function of ACE2 is to counterbalance the effects of ACE.

**Pathophysiological implications**

**Clinical implications**

The inclusion (II) or deletion (DD) of the 287bp Alu repeat in the 16th intron affects the human plasma ACE levels. The DD genotype is more frequently found in patients with myocardial infarction but no convincing evidence is available on the association of the DD genotype with hypertension. ACE2 was identified as the receptor for the SARS (severe acute respiratory syndrome) coronavirus. The SARS virus binding downregulates the cellular expression of ACE2, and the binding induces the clathrin-dependent internalization of the virus/receptor (SARS/ACE2) complex. Not only has ACE2 facilitated the invasion of the SARS virus for rapid replication, but also ACE2 is depleted from the cell membrane. Therefore, the damaging effects of Ang II are enhanced, resulting in the acute deterioration of lung tissues.

**Use for diagnosis and treatment**

ACE has been the target of hypertension control since the 1970s. ACE inhibitors are prescribed as the sole or combinational treatment for high blood pressure, for its dual effects of lowering Ang II and slowing down BK degradation. In human hypertensive patients, ACE2 levels are lower in both the kidney and heart compared to normotensive volunteers.
Supplemental information available on companion website

- Protein sequences and structural features of human ACE and ACE2/Fig. 42D.S1.
- Schematic diagram showing the functional domains of ACE and ACE2/Fig. 42D.S2.
- Protein sequences and structural features of ACE and ACE2 of humans/Fig. 42D.S3.
- Protein sequences and structural features of ACE and ACE2 of humans/Fig. 42D.S4.

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