Novel mechanism of action of ACE and its inhibitors

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ANGIOTENSIN-CONVERTING ENZYME (ACE) is a dipeptidyl peptidase transmembrane-bound enzyme (for review see Ref. 2). A soluble form of ACE in plasma is derived from the plasma membrane-bound form by proteolytic cleavage of its COOH-terminal domain. There are two distinct isoforms of ACE: somatic and testicular. They are transcribed from a single gene at different initiation sites. The somatic form of ACE is a large protein (150–180 kDa) that has two identical catalytic domains and a cytoplasmic tail. It is synthesized by the vascular endothelium and by several epithelial and neural cell types. The testicular form of ACE is a 100- to 110-kDa protein that has a single catalytic domain corresponding to the COOH-terminal domain of somatic ACE and is only found in developing spermatids and mature sperm where it may play a role in fertilization.

ACE inhibitors have become important tools in the treatment of hypertension, heart failure, cardiac remodeling postmyocardial infarction, and renal diseases, especially diabetic nephropathy (Table 1). Until recently, most of the biological effects of ACE inhibitors have been attributed to inhibition of its well-characterized dipeptidyl peptidase activity, in particular, blockade of the conversion of angiotensin I to II and inactivation of kinins (1). We have shown that the tetrapeptide N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), which increases fivefold in blood after administration of an ACE inhibitor, also participates in its anti-fibrotic and anti-inflammatory effect (12–15). ACE hydrolyzes many other peptides, but their role in the therapeutic or side effects of ACE inhibitors is not known (Fig. 1).

ACE inhibitors have a number of effects that are not due to inhibition of the peptidase activity of ACE but rather to a direct effect on the bradykinin B2 receptor (4). Indeed, an ACE inhibitor amplified the effects of bradykinin in vessels that lacked measurable ACE activity (3). An ACE inhibitor also enhanced the effect of an ACE-resistant B2 kinin receptor agonist (3, 4). There is evidence that ACE inhibitors induced cross-talk between the transmembrane protein ACE and the B2 kinin receptor, probably by formation of a heterodimer (10, 11). ACE inhibitors also directly activate the bradykinin B1 receptor, acting at the Zn-binding pentameric consensus sequence HEXXH (195–199) of the B1 receptor, a motif that is present in the active center of ACE but absent from the B2 receptor (6). ACE inhibitors also induce phosphorylation of the ACE intracellular tail (Ser1270) via CK2, resulting in outside-in signaling that enhances expression of ACE and cyclooxygenase-2 (COX-2) (7, 8). The effect of the ACE inhibitor on COX-2 is due to the transcription factor activator protein-1 (AP-1). This results in increased release of prostacyclin and prostaglandin E2 by the endothelial cells that is independent of local accumulation of kinins (7).

In this issue of the AJP-Heart & Circulatory Physiology, Ignjacev et al. (5) report that soluble ACE, independent of its dipeptidyl peptidase activity, induces the transcription factor NF-κB and AP-1 and increases mRNA for the bradykinin B1 and B2 receptors in vascular smooth muscle cells. This is the second report showing that ACE has effects that are independent of its dipeptidyl peptidase activity. Recently, Kondoh et al. (9) described a novel glycosyl phosphatidylinositol (GPI)-anchored, protein-releasing activity of ACE by cleavage at the mannose-mannose linkage site. This GPIase activity was weakly inhibited by tightly binding ACE inhibitors and was not inactivated by substituting the core amino acid residues necessary for peptidase activity. Taken together with Ignjacev’s study, this suggests that neither of the two peptidase catalytic domains of ACE is responsible for ACE GPIase activity or induction of the transcription factor and mRNA for the B1 and B2 receptors. Thus in addition to its classical catalytic domain with peptidase activity, ACE may have other novel active catalytic domains, or it may act as an agonist for some receptor or via yet another undetermined mechanism (Fig. 2). The

Table 1. Therapeutic effects of ACE inhibitors

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<th>Effect</th>
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<tr>
<td>Antihypertensive</td>
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<tr>
<td>Reverse left ventricular hypertrophy and vascular disease</td>
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<tr>
<td>Prevent remodeling after myocardial infarction</td>
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<tr>
<td>Slow progression of heart failure</td>
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<td>Slow progression of renal disease (diabetes, microalbuminuria)</td>
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<tr>
<td>Prevent diabetes</td>
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<td>Prevent cancer and slow the aging process</td>
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Fig. 1. Effect of angiotensin-converting enzyme (ACE) due to its dipeptidyl peptidase activity, and possible mechanism of action of ACE inhibitors due to blockade of peptide activity. ACE inhibitors decrease formation of angiotensin II (ANG-II) and increase kinins, N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), ANG 1–7, and other peptides that may contribute to their antihypertensive and cardiovascular and renal protective effects. SNS, sympathetic nervous system; TXA2, thromboxane A2; PGH2, prostaglandin H2; NO, nitric oxide; PGs, prostaglandins and prostacyclins; EDHF, endothelium-derived hyperpolarizing factor; upt, uptake; IPA, tissue plasminogen activator; LHRH, luteinizing hormone-releasing hormone.

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challenge in the future is to determine whether these novel effects of ACE that are not mediated by its peptidase activity play a physiological or pathological role. In addition, it is important to determine whether some of the therapeutic effects of ACE inhibitors are mediated by its effects on phosphorylation of the intracellular tail of ACE and/or by cross-talk between the bradykinin receptors and the enzyme.

GRANTS

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REFERENCES


