Commentary on Tikellis et al
There Is More to Discover About Angiotensin-Converting Enzyme
Carlos M. Ferrario

Irvine H. Page used to say that the regular occurrence of constant amounts of a substance in the body is seldom without purpose and that organisms exhibit an inner economy and prudence by using one substance for several functions. Almost 50 years later, we are now challenged again to decipher just how complicated and how physiologically relevant are newly discovered biochemical pathways contributing to the formation of biologically active forms of angiotensin peptides. The need to revisit the role of angiotensin-forming enzymes was stimulated by the finding of a new gene encoding a protein having highest homology to the testes-specific isoform of angiotensin-converting enzyme (ACE).1,2

In 1991, we first suggested3 that angiotensin II (Ang II) should be viewed as one but not the sole principal product of the renin-angiotensin system. The proposal was based on the characterization of biological actions of the heptapeptide angiotensin-(1–7) [Ang-(1–7)] and its forming enzymes. There was reluctance to accept this concept in part because the potential role of Ang-(1–7) in cardiovascular regulation was still at an embryonic stage, there was little evidence that Ang II could act at more than one receptor, and a full characterization of other enzymic pathways for angiotensin peptide formation had not been achieved yet. The situation is quite different today; a growing body of literature now implicates Ang-(1–7)3–7 and angiotensin IV (Ang-3–8) 8 as components of the system, and additional work has identified chymase, prolyl endopeptidase 24.26, neutral endopeptidase 24.11, metalloendopeptidase 24.15,9 and now a homologue of ACE 10 as angiotensin prohormone convertases.

Fifty years after the discovery of ACE, a homologue of human ACE has been reported from genomics-based strategies. The protein identified by Tipnis et al1 and named ACEH was cloned from a human lymphoma cDNA library, and an identical human protein termed ACE2 was cloned from a cDNA library prepared from ventricular tissue from a patient with heart failure by Donoghue and associates.2 To prevent confusion and prudently wait for the International Enzyme Nomenclature Committee to define the proper nomenclature, we will refer to this discovery as ACEH/ACE2, recognizing that it is the name but not the nature of the enzyme that remains at question.

ACEH/ACE2 is a zinc metalloprotease consisting of 805 amino acids with considerable homology to ACE, but unlike somatic ACE, it functions as a carboxypeptidase rather than a dipeptidyl carboxypeptidase.1,2 The full-length cDNA encoding ACEH/ACE2 includes an N-terminal signal sequence and a hydrophobic region near the C-terminus with an overall 40% identity to the N- and C-domains of ACE. Contrasting with ACE, ACEH/ACE2 hydrolyses Ang I into Ang-(1–9), Ang II into Ang-(1–7), and bradykinin to [des-Arg9]-bradykinin (Figure). In other words, ACEH/ACE2 does not convert Ang I into Ang II; it does not cleave bradykinin itself, and, importantly, its enzymatic activity is inhibited by neither captopril or lisinopril. ACEH/ACE2 is a type I membrane protein that is primarily localized to the heart (myocytes), kidney (endothelium and tubular elements), and testes.2,10

A glimpse into the potential importance of ACEH/ACE2 in the regulation of cardiovascular function was demonstrated by Crackower et al,11 who localized the ACEH/ACE2 gene to the human X chromosome. This is an exciting finding, since the same locus on the X chromosome has been reported to show a significant logarithm-of-the-odds score in rat models of hypertension.12 Crackower and associates11 also found severe cardiac contractile dysfunction associated with mild ventricular dilation in ACEH/ACE2 knockout mice [(ACEH/ACE2(-/-)]. These changes in cardiac function were associated with upregulation of hypoxia-induced genes. Ablation of both the ACE and ACEH/ACE2 genes completely abolished the cardiac abnormalities, linking the cardiac abnormality to...
excess Ang II production and possibly loss of Ang-(1–7) formation.

Although these data suggest that ACE and ACEH/ACE2 have counterbalancing functions, the proper question is, which catalytic product is mediating this feedback regulation between the 2 enzymes? An important insight into this problem is gained by the demonstration that ACEH/ACE2 exhibits a high catalytic efficiency for the generation of Ang-(1–7) from Ang II–almost 500-fold greater than that for the conversion of Ang I to Ang-(1–9) and 10- to 600-fold higher than that of prolyl oligopeptidase and prolyl carboxypeptidase to form Ang-(1–7), respectively. From an array of more than 120 peptides, only dynorphin A and apelin 13 were hydrolyzed by ACEH/ACE2 with comparable kinetics to the conversion of Ang II to Ang-(1–7).10

These studies not only advance our understanding of the role that the renin-angiotensin system plays in the regulation of the hemodynamic control of tissue perfusion, but it also strengthens the suggestion that various negative feedback pathways intrinsic within the renin-angiotensin system have a role in fine-tuning the rate at which angiotensin peptides are formed and degraded. This interpretation is buttressed by the studies reported in this issue of Hypertension by Tikellis et al.,13 who explored the distribution of ACEH/ACE2 and ACE in the kidney of Sprague-Dawley rats with diabetes induced by administration of streptozocin. The highest expression of the ACEH/ACE2 mRNA found in renal proximal tubules was significantly reduced in the tubules from diabetic rats. These findings correlated with ACEH/ACE2 gene expression. The presence of ACEH/ACE2 in renal structures and the functional changes produced by chemically induced diabetes are a step in beginning to explore the potential role of ACEH/ACE2 in the regulation of renal function and glomerulosclerosis. The absence of an effect of ramipril on the expression and location of ACEH/ACE2 is in keeping with previous observations that show that the ACE homologue is insensitive to blockade with ACE inhibitors. Although the absence of functional correlates does not provide an insight into what product is ACEH/ACE2 modulating, we have shown that the expression of the ACEH/ACE2 protein in renal tubules of spontaneously hypertensive rats parallels that of Ang-(1–7).4,14 The colocalization of ACEH/ACE2 and Ang-(1–7) in renal tubules suggests functional interactions, an interpretation that is buttressed by the findings that combined inhibition of ACE and neutral endopeptidase 24.11 in patients with essential hypertension and the spontaneously hypertensive rat is associated with sustained increases in urinary excretion of Ang-(1–7).4,5 These data imply a possible role of ACEH/ACE2 in accounting for a shift in the conversion of Ang II into Ang-(1–7) as ACE inhibition increases plasma and tissue levels of Ang I while having no sustained effect on plasma Ang II levels. Previous studies demonstrating that Ang-(1–7) acts to counteract the pressor, trophic, and antinatriuretic actions of Ang II and that low renal expression of Ang-(1–7) is found in untreated essential hypertensive subjects suggest that this vasodilator peptide may be a critical link in mediating the negative regulatory feedback between ACE and ACEH/ACE2. The newly reported synthesis of a potent and selective chemical inhibitor of ACEH/ACE215 now paves the way to explore the function of ACEH/ACE2 and Ang-(1–7) in the regulation of cardiovascular function. These new studies should provide an underpinning to combine both genetic and pharmacological approaches to unravel the contribution of the intrinsic mechanisms that within the renin-angiotensin system regulate the synthesis and degradation of angiotensin peptides. It is thus obvious that there is more to be discovered about this system and that further analysis of the problem will be a fruitful endeavor.

References

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