T he renin-angiotensin system (RAS) plays a pivotal role in the regulation of blood pressure, volume homeostasis, vascular function, and cell growth. In what is considered the classic RAS, renin is released from juxtaglomerular cells of the kidney into the circulation where it converts angiotensinogen from the liver to angiotensin I. Angiotensin I is subsequently hydrolyzed by a peptidyl dipeptidase, angiotensin-converting enzyme (ACE), from the lung to form angiotensin II. Investigators have been cognizant of renin for more than a century after its initial discovery in 1898 by Tigerstedt and Bergman (see review1). However, it was not until the middle of the 20th century that the remaining components of RAS were purified and identified by Skeggs and colleagues. These included angiotensinogen, angiotensin I, angiotensin II, and ACE, which at the time was termed “hypertensin-converting enzyme” (see review1). Since that time, many components of the RAS, especially ACE, have received considerable attention as a focal point for researchers interested in better understanding the regulation of the cardiovascular system.

Considering the rapid progress in understanding the molecular physiology of RAS and its many complexities, it should not be surprising that details would continue to emerge. It is unexpected, however, that after 100 years of research major new concepts would surface requiring scientists and clinicians to rethink the system and its role in cardiovascular regulation. Even more astounding is that over the span of 3 years, two major conceptual changes would have to be considered regarding ACE. The first surprise occurred in 2000 with the discovery of ACE2, a “homologue” of ACE capable of producing angiotensin peptides such as Ang-(1-7), which may have vasodilator properties.2,3 Thus, ACE and ACE2 may ultimately have opposing physiological effects. The second new concept is described in this issue of Circulation Research.4

Introduction to ACE

The ACE gene yields two different protein products resulting from the use of different promoters most likely caused during evolution by genetic duplication.5 In humans, ACE resides on chromosome 17 (chromosome 11 and 10 in mouse and rats, respectively) and consists of 25 exons. Germinal ACE, expressed only in testes, arises from a promoter located within intron 12 (downstream of the gene duplication) and makes a protein with only a single domain and catalytic site.6 Its expression is critical for normal male fertility. Somatic ACE is a protein with two homologous domains and two catalytic sites (see review7). Gene-targeted deletions of somatic ACE in mice cause hypotension, improper kidney development, and reduced fertility in males.6,9

The somatic ACE isofrm has been the most extensively investigated because of its importance in cardiovascular homeostasis. The two homologous domains and the amino terminus of the ACE protein are located extracellularly. The protein is anchored in the membrane and contains a short intracellular domain at the carboxy terminal (see Figure). ACE is highly expressed in the vascular endothelium as well as in the brush border membranes of the kidney. The classic biological function of ACE is to hydrolyze a dipeptide from the carboxy terminus of a protein substrate. While ACE has the potential to hydrolyze many proteins, it is most appreciated for its enzymatic processing of angiotensin I to angiotensin II, the cardiovascular effects of which have been extensively reported. In addition, ACE mediates the hydrolysis of bradykinin, which is typically considered to have blood pressure–lowering and cardioprotective effects. Interestingly, ACE more readily hydrolyzes bradykinin than it does angiotensin I. Therefore, the net physiological effect of ACE is to increase the production of a vasoconstrictor and decrease the availability of a vasodilator.

This dual effect makes ACE a particularly appealing target for antihypertensive therapies; and indeed ACE has been an important therapeutic target for the treatment of hypertension since the development of captopril in the late 1970s. The initial benefit of ACE inhibition for patients with hypertension was thought to be due in large part to a decreased degradation of bradykinin. However, it has been recognized that long-term treatment with ACE inhibitors does not necessarily lower plasma or tissue levels of angiotensin II.10,11 Moreover, the effect of ACE inhibitors to prevent the degradation of bradykinin has been recognized as making an increasingly important contribution to the cardiovascular benefits for patients taking these drugs. Therefore, the physiological functions of ACE, its substrates, and its inhibitors are still evolving.

ACE as an Intracellular Signal Transducer

In this issue of Circulation Research, Kohlstedt et al4 skillfully elucidated a novel function for ACE as a key signal transduction molecule, thus reminding us that our understanding of the physiological role for ACE is still surfacing. These authors previously reported that a specific carboxy terminal serine residue of ACE (ser1270) was phosphorylated by protein

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**Editorials**


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ACE-mediated outside-in signaling pathway in endothelial cells. ACE inhibitors or substrate (bradykinin, BK) increases CK2-mediated phosphorylation of ser^{1270} on the carboxy terminal of ACE. Phosphorylation of ser^{1270} increases ACE-associated JNK activity, which phosphorylates c-Jun. c-Jun is translocated to the nucleus, and the expression of ACE and perhaps other genes is increased.

Using human umbilical vein endothelial cells or porcine aortic endothelial cells stably transfected with human somatic ACE as a model, the authors demonstrate that ramiprilat and perindoprilat increase CK2-mediated phosphorylation of ser^{1270}, which phosphorylates c-Jun. c-Jun is translocated to the nucleus, and the expression of ACE and perhaps other genes is increased.

By itself, the elucidation of this signaling pathway in cell culture is a novel and exciting finding that will likely alter perceptions on the physiological roles for ACE and lead to new areas of investigation regarding the beneficial effects of ACE inhibitors. What makes this study even more convincing is that the authors were able to demonstrate that the signaling pathway initiated by ACE inhibitors in cell culture can also be activated in the whole animal. This suggests that the intracellular signaling (termed “outside-in” signaling by the authors) mediated by ACE inhibitors and bradykinin may be an important physiological mechanism. Of course, understanding the full spectrum of physiological events initiated by ACE signaling will require additional studies.

With this, ACE joins other ectoenzymes, such as matrix metalloprotease-1 (MMP-1), which have been reported to link to intracellular signaling pathways. It is provocative to speculate that ACE may mediate intracellular signals in response to bradykinin while simultaneously destroying its ability to act as a vasodilator. Such a mechanism, although still unproven, would tightly regulate the local concentration of ACE “ligand.” Presumably, this level of control would not be exerted on ACE inhibitors since they would bind but not be catalytically processed. In closing, the study by Kohlstedt et al reminds us of the complexities of the RAS. It is likely that additional new details of this pathway as well as novel concepts will continue to emerge as these studies progress.

References


**KEY WORDS:** intracellular signaling | c-Jun N-terminal kinase | c-Jun | angiotensin-converting enzyme | angiotensin-converting enzyme inhibitors
ACE, ACE Inhibitors, and Other JNK
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