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The renin-angiotensin system (RAS) is a coordinated hormonal cascade, the major effector of which is angiotensin II (Ang II).1,2 The RAS regulates blood pressure and fluid and electrolyte balance through actions on the heart, blood vessels, kidneys, and adrenal glands. The classical RAS pathway begins with the biosynthesis, storage, and release of the glycoprotein enzyme renin by the juxtaglomerular cells of the renal afferent arteriole. Renin acts on the circulating precursor angiotensinogen (AGT) to form a dipeptide, angiotensin I (Ang I). Ang I has little or no biological activity but is converted across vascular beds, particularly in the lungs, to the octapeptide Ang II by the action of angiotensin-converting enzyme (ACE), an enzyme with soluble and membrane-bound forms. Most of the ACE is localized on the plasma membranes of vascular endothelial cells and the brush borders of epithelial (eg, renal tubular) cells. A potent vasopressor, Ang II acts at target cells by binding to 1 of 2 G protein-coupled receptors—angiotensin type-1 (AT1) and type-2 (AT2) receptors. The vast majority of the cardiovascular, renal, and adrenal actions of Ang II are mediated by the AT1 receptor, including vascular smooth muscle contraction, aldosterone secretion, diuresis, renin release, and pressor and chronotropic responses. Ang II also binds to AT2 receptors, inducing a counter-regulatory vasodilatation that is largely mediated by bradykinin (BK) and nitric oxide (NO). In addition to the conversion of Ang I to Ang II, ACE also inactivates two vasodilator peptides, BK and kallidin. Thus, ACE inhibition, which has constituted an important therapeutic approach to hypertension, derives its benefits by way of 2 mechanisms: inhibition of Ang II formation and facilitation of BK levels in plasma and tissues. Ang II is degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within seconds by peptidases, collectively termed angiotensinases, to biologically active (des-aspartyl1-Ang II degraded within 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inactive fragments, is via ACE itself. Therefore, ACE inhibition can increase Ang (1–7) levels while simultaneously reducing Ang II and augmenting BK. The unique patterns of angiotensin peptide metabolism by ACE and ACE 2 suggest biochemical and physiological counter-regulatory arms of the RAS in the regulation of cardiovascular function. ACE 2 seems to be a functional inhibitor of Ang II produced by ACE both by stimulating an alternative pathway for Ang I degradation and also by facilitating the production of Ang (1–7), a vasodilator peptide that opposes many of the potentially detrimental actions of Ang II via the AT1 receptor.12

Crackower et al13 in 2002 introduced a physiological role of ACE 2 by ablating the ACE 2 gene in mice. Loss of ACE 2 did not alter blood pressure but severely impaired cardiac function,
producing a major reduction in cardiac contractility and a thinning of the left ventricular wall without cardiac fibrosis or hypertrophy. ACE 2 knockout mice also had elevation of plasma Ang II levels, supporting the hypothesis that ACE 2 provides an alternative pathway for Ang I and II degradation. Interestingly, both the cardiac phenotype and the increased Ang II levels were reversed to normal when the mice were subject to a double knockout of both ACE and ACE 2. These observations suggest that ACE 2 may counter-balance the enzymatic actions of ACE and that the cardiac pathology of ACE 2 knockout mice may have been attributable to increased Ang II.

Another counter-regulatory component of the RAS is the AT2 receptor. Stimulation of the AT2 receptor leads to formation of a vasodilator cascade that includes BK, NO, and cyclic GMP. Recent studies have shown that when the AT1 receptor is blocked pharmacologically, Ang II becomes a sustained vasodilator and hypertensive agent. Also, stimulation of the AT2 receptor may account for at least some of the beneficial actions of AT1 receptor blockade, especially acutely. In the heart, overexpression of the AT2 receptor preserves left ventricular size and function during post-myocardial infarction remodeling. Thus, there are several potentially overlapping counter-regulatory components of the RAS.

In the current issue of Hypertension, Ishiyama et al provide an important study with possible therapeutic implications for cardiac remodeling post-myocardial infarction. Using normotensive Lewis rats, these investigators demonstrated the expected cardiac hypertrophy and left ventricular dysfunction 28 days after coronary artery ligation, accompanied by increased plasma concentrations of all Ang peptides I, II, and (1–7) and down-regulation of cardiac AT1 receptor expression. In response to coronary artery ligation, cardiac ACE and ACE 2 expression was unchanged. Two AT1 receptor antagonists, losartan and olmesartan, reversed cardiac hypertrophy; olmesartan improved ventricular contractility. Both AT1 receptor blockers further increased Ang peptide concentrations, returned AT1 receptor expression to normal, and increased ACE 2 expression in the heart by 3-fold. Because these effects were not reproduced by PD-123319, they cannot be attributed to an action of Ang II at AT1 receptors. The results suggest that AT1 receptor blockade may upregulate ACE 2 expression, which theoretically could contribute to the beneficial effects of AT1 receptor blockade by facilitating increased cardiac Ang (1–7) formation post-myocardial infarction. As cited by the authors, evidence exists that Ang (1–7) is formed within the heart and has beneficial actions on cardiac contractility, coronary perfusion, and endothelial function. From the data presented, it is not possible to determine the precise mechanism whereby AT1 receptor blockade increases cardiac ACE 2 expression, and this important question awaits further study.

Taken altogether, the results of this and other related studies support the hypothesis that the ACE 2/Ang (1–7) portion of the RAS may oppose the actions of the classical pathway in which ACE generates Ang II. The AT1 receptor probably constitutes a separate counter-regulatory pathway of the RAS. The results of Ishiyama et al provide hope that selective stimulation of the ACE 2/Ang (1–7) arm of the RAS may have beneficial effects in post-infarction ventricular remodeling and left ventricular function in congestive heart failure. Among other studies, it would be interesting to determine whether overexpression of ACE 2 in the heart would increase Ang (1–7) and attenuate the detrimental structural and functional consequences of cardiac injury.

References
Angiotensin Type-1 Receptor Blockade Increases ACE 2 Expression in the Heart
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