The Angiotensin Converting Enzyme 2/Ang-(1-7) Axis in the Heart
A Role for Mas Communication?

James A. Stewart, Jr, Eric Lazartigues, Pamela A. Lucchesi

For decades, the literature has been inundated with evidence of the important role of the renin–angiotensin system (RAS) in cardiac remodeling and function with most in the field familiar with this classic, dogmatic story. The protease renin is synthesized and released from the kidney and acts on a circulating inactive peptide, angiotensinogen, produced by the liver, giving rise to angiotensin (Ang) I. Ang I is then transformed into the biologically active octapeptide, Ang II, through enzymatic cleavage by angiotensin-converting enzyme (ACE). Ang II is the main effector molecule of the RAS, acting in an endocrine, autocrine/paracrine, and intracrine hormone pathway on cardiac cells. Ang II binds and activates G protein–coupled receptors, the angiotensin type 1 (AT1R) and angiotensin type 2 (AT2R) receptors, to mediate its actions. Activation of AT1R mediates most of the cardiovascular responses attributed to Ang II (ie, vasoconstriction, mitogenic and hypertrophic effects, fibrosis, inflammation, and fluid retention). In contrast, AT2R activation may cause opposing physiological responses that are increased in several disease processes.  

Nearly 50 years after the discovery of ACE, a genomic based screening resulted in a characterization of ACE2, thus adding an unexpected twist into the well-known tale of the RAS. ACE2 is a carboxypeptidase that cleaves a single residue from Ang I to form Ang-(1-9), which is then converted to Ang-(1-7) by either ACE or neutral endopeptidases. This process is less efficient because of the requirement of 2 enzymatic processes. ACE2 also generates Ang-(1-7) from a single residue cleavage of Ang II with a higher affinity and thus may potentially be more physiologically relevant.  

Despite recent advances in our understanding of the ACE2/Ang II/Ang-(1-7) axis, the functional role of ACE2 in the heart is somewhat controversial. Crackower et al originally reported a progressive decrease in left ventricular contractile function in ACE2-null mice without significant changes in fibrosis, left ventricular and cardiac myocyte hypertrophy, or mean arterial pressure. Interestingly, whereas plasma and tissue levels of Ang II were increased, a decrease in blood pressure was only observed in 6-month-old male ACE2−/− homozygote mice but not in age-matched females or 3-month-old males. Conversely, Coffman and colleagues reported that ACE2 deletion enhanced the susceptibility to Ang II–induced hypertension but had no effect on cardiac structure or function. More recently, Raizada and colleagues used lentiviral-based ACE2 gene transfer to attenuate cardiac fibrosis and hypertrophy in SHR hypertensive rats and to improve left ventricular function and remodeling after myocardial infarction. Finally, Yamamoto et al reported that ACE2 deletion exacerbated pressure overload–induced cardiac dysfunction and remodeling that was associated with increased intracardiac Ang II levels and AT1R activation. The reasons for these discrepancies appear to reflect the genetic background of the mice used for ACE2 gene deletion, whether there was global versus tissue specific ACE2 manipulation, or whether cardiac responses were monitored under basal or pathophysiological conditions.

Although it is now generally accepted that ACE2 plays a role in cardiac remodeling, the exact means by which ACE2 activity affords cardioprotection are unclear. Potential mechanisms include increased Ang II degradation and increased formation of Ang-(1-7) (Figure). The relative contribution of decreased Ang II levels versus increased Ang-(1-7) is difficult to decipher when ACE2 levels are manipulated or when the RAS pharmacologically blocked. To circumvent this issue, many studies have used chronic Ang-(1-7) treatment or infusion. For example, Santos et al were the first to show that increases in circulating Ang-(1-7) levels in transgenic rats afforded cardioprotection against isoproterenol. Ang-(1-7) treatment improves myocardial performance and survival in SHR rats following ischemia/reperfusion injury. Grobe et al reported that coinfusion of Ang-(1-7) blunted cardiac remodeling in response to chronic Ang II infusion. These studies established a cardioprotective role for Ang-(1-7) but did not demonstrate the direct effects of this peptide on the heart.

In this issue of Circulation Research, Mercure et al present an innovative approach to address the cardiac specific role of increased Ang-(1-7) concentrations in vivo. Using a novel transgenic strategy to selectively overexpress Ang-(1-7) or Ang II in the heart, this study revealed no contractile defects under basal conditions at any of the ages examined.
Using chronic, systemic Ang II infusion to induce hypertensive hypertrophic and fibrotic effects of Ang II in the myocardium. ACE2 can directly cleave Ang II to form Ang-(1-7). Ang-(1-7) activates the Mas receptor on cardiac fibroblasts and cardiac myocytes to initiate signaling pathways that antagonize AT1R-mediated tyrosine kinase cascades. In this simplified scenario, Ang-(1-7) increases SHP-2 tyrosine phosphatase activity to inactivate src-dependent signaling. Mas receptor activation also acts other pathways such as NO-AKT,91 potentially eliciting AT1R-independent effects.

The question remains is how does Ang-(1-7) exert its actions? Most evidence points toward activation of the G protein–coupled Mas receptor, although interaction with, and inhibition of, the catalytic domain on ACE has been reported at higher doses (see Reudelhuber14 for a recent review). Mas receptor activation by Ang-(1-7) opposes many of the AT1R-mediated actions (vasoconstriction, hypertrophy, fibrosis), thereby improving cardiac function and remodeling and attenuating heart failure.15,16 Ang-(1-7) binds to specific Mas receptors on cardiac fibroblasts to inhibit the fibrotic and hypertrophic effects of Ang II.17 Mas receptors are also localized to cardiac myocytes and activate NO production.18 The exact mechanisms by which Mas receptor activation antagonizes cardiac AT1R signaling are unclear. The data presented by Mercure et al13 suggest that Ang-(1-7)–dependent activation of the protein tyrosine phosphatase SHP-2 may attenuate AT1R-mediated activation of src and p38 mitogen-activated protein kinase. The requirement for Mas receptors was not determined, and it is also possible that Ang-(1-7) activates signaling cascades that affect cell function independently from AT1R pathways. However, because minimal cardiac effects of ACE2 deletion are observed under baseline conditions, it is tempting to speculate that a primary function of Ang-(1-7) may be to antagonize the effects of Ang II during pathophysiological insults.

The observations of Mercure et al shed new light on the beneficial actions of the ACE2/Ang-(1-7) axis within the heart. The cardioprotective effects of ACE2 result from a one-two punch involving direct degradation of Ang II and inhibition of AT1R-mediated signaling via Ang-(1-7)/Mas receptor activation. Although further clarification of the role of Mas in the direct effects of Ang-(1-7) on the heart are warranted, the findings reported by Mercure et al indicate that Ang-(1-7) is a bona fide therapeutic target for cardiovascular disease. In this regard, an orally active Ang-(1-7) analog, AVE0991, mimics the cardioprotective effects of Ang-(1-7).17 This has important clinical implications because the use of ACE inhibitors and angiotensin receptor blockers, although effective in reducing cardiovascular morbidity mortality, has failed to stem the increasing prevalence of hypertensive and coronary artery–related heart disease.

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None.

References

Figure. Proposed ACE2-dependent mechanisms that antagonize the hypertrophic and fibrotic effects of Ang II in the myocardium. ACE2 can directly cleave Ang II to form Ang-(1-7). Ang-(1-7) activates the Mas receptor on cardiac fibroblasts and cardiac myocytes to initiate signaling pathways that antagonize AT1R-mediated tyrosine kinase cascades. In this simplified scenario, Ang-(1-7) increases SHP-2 tyrosine phosphatase activity to inactivate src-dependent signaling. Mas receptor activation also acts other pathways such as NO-AKT,91 potentially eliciting AT1R-independent effects.


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