Does Angiotensin-(1–7) Contribute to Cardiac Adaptation and Preservation of Endothelial Function in Heart Failure?

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In the late 1890s, the Finnish physiologist Robert Tigerstedt made the fundamental observation that aqueous extracts of kidneys caused a prolonged rise in the blood pressure of anesthetized animals. The clinical significance of this finding remained unappreciated for more than 30 years until Hessel, a disciple of Volhart, provided evidence for the participation of renin in the production of what they termed “white hypertension.” Even in our current setting, roughly a century later, application of the observations made by the Scandinavian investigators continues to provide an illuminating example of the complexity of the scientific endeavors that make medical science an art of unrelenting inquiry and often of late recognition. In fact, continuing efforts to understand the biological actions of the renin-angiotensin system have led to impressive clinical applications that are reflected in current therapeutic approaches to the treatment of high blood pressure and the prevention of stroke, congestive heart failure, and end-stage renal disease. The introduction of angiotensin converting enzyme (ACE) inhibitors expanded knowledge of the mechanisms through which the renin-angiotensin aldosterone system acts as a mediator of cardiovascular pathology and became the basis for the later development of orally active angiotensin II antagonists. Although the majority of clinical endeavors and research efforts continues to concentrate on pharmacological strategies aimed at interrupting the actions of angiotensin II (Ang II), emerging concepts suggest that the important homeostatic functions regulated by the renin-angiotensin system may be influenced, in part, by the actions of other angiotensin peptides derived from either angiotensin I (Ang I) or Ang II.

Among the various molecular forms of endogenously produced angiotensin peptides, the mechanisms of synthesis, action, and downstream intracellular signaling effects mediated by the amino-terminal heptapeptide fragment, angiotensin-(1–7) (Ang-[1–7]), have began to carve an important and promissory niche in the understanding of the biological actions of the renin-angiotensin system, as well as implicating a role of Ang-(1–7) in the metabolism of vasodilator peptides such as bradykinin and atrial natriuretic factor. In animal studies, Ang-(1–7) has been proven to exert physiological and pharmacological actions that include vasodilation, inhibition of protein synthesis, and natriuresis. The vasodilator actions of Ang-(1–7) depend on an as yet not fully characterized intracellular signaling mechanism that may depend on secretion of prostacyclin, release of nitric oxide, or amplification of the vasodilator effects of bradykinin, alone or in combination.

In the present issue of Circulation, Loot and colleagues report that Ang-(1–7) may preserve cardiac function and improve coronary perfusion and aortic endothelial function in an experimental rat model of heart failure produced by ligation of the left coronary artery. Two weeks after coronary artery ligation, an 8-week continuous intravenous infusion of Ang-(1–7) prevented further deterioration of myocardial function characterized as changes in left ventricular end-diastolic pressure and the maximal rate of rise in left ventricular pressure. Preservation of left ventricular function was accompanied by maintenance of baseline coronary flow and restoration of bradykinin-induced maximal coronary flow vasodilation. In their study, rats exposed to chronic infusions of Ang-(1–7) had myocardial capillary densities similar to those determined in sham-operated animals and significantly greater than those observed in vehicle-treated infarcted rats. Furthermore, they showed that vascular endothelial dysfunction present in the aorta of rats with myocardial infarction was fully reversed in those rats receiving a chronic infusion of Ang-(1–7). These studies provide provocative evidence of a cardioprotective role of Ang-(1–7) under conditions in which there is an activation of the renin-angiotensin system, as well as implicating a role of Ang-(1–7) in contributing to the beneficial therapeutic effects of angiotensin converting enzyme inhibition and Ang II type 1 (AT₁) receptor blockers in heart failure.

The interpretation provided by the authors is consistent with our previous demonstration that ACE is responsible for the degradation of Ang-(1–7) into the inactive fragment Ang-(1–5), as well as the observation that the heptapeptide may act as an endogenous inhibitor of the N-domain of the somatic form of ACE. In keeping with this interpretation, long-term administration of ACE inhibitors results in significant elevations in plasma and urinary concentration of Ang-(1–7) in animals and humans, whereas blockade of Ang-(1–7) receptors or inhibition of Ang-
Ang-(1–7) activity partially reverses the antihypertensive effect of long-term administration of lisinopril alone or in combination with losartan.14

As discussed by Loot et al., an antitrophic effect of Ang-(1–7) was first reported in another model of vascular injury, in which a 12-day infusion of Ang-(1–7) prevented neointima proliferation after endothelial denudation of a carotid artery.15 Whereas the doses of Ang-(1–7) infused into carotid-artery injured rats15 were similar to those used by Loot et al8 in their current experiments, plasma concentrations of Ang-(1–7) in the studies performed by Strawn et al15 were in line with those found in rats with long-term exposure to ACE inhibition and were much lower than those reported by these investigators. Whether the difference is the product of the much longer time of Ang-(1–7) exposure remains to be investigated, as it is the question of whether the cardioprotective effects recorded by Loot and colleagues8 could be achieved with a shorter period of infusion. The authors also suggest that the effects of Ang-(1–7) on cardiac failure reflect the increases in circulating Ang-(1–7) rather than a direct tissue effect through a paracrine or autocrine mechanism. There is evidence for a cardiac renin-angiotensin system,16 and in dogs the infusion of Ang I through microdialysis probes inserted into the left ventricle was associated with an 800-fold rise in interstitial fluid Ang-(1–7).17 In addition, coronary artery ligation in the dog is associated with a significant rise in the concentration of Ang-(1–7) in the blood emanating from the coronary sinus.18 Therefore, it is equally conceivable that the beneficial effects observed by Loot and colleagues8 could be a result of myocardial trapping or cellular uptake of Ang-(1–7). In this connection, we have found that Ang-(1–7) is distributed throughout cardiac myocytes in healthy cardiac tissue of the Lewis rat strain. Moreover, the remodeling of cardiac tissue 4 weeks after coronary artery ligation is associated with loss of Ang-(1–7) immunoreactivity within the area of the infarct and an apparent increased expression of the peptide in the zones bordering the infarcted region of the left ventricle (Figure). These new data suggest that Ang-(1–7) is present in significant quantities in the myocardium, a finding that suggests local synthesis of the heptapeptide.

Notwithstanding the interpretative caveats discussed above, the findings reported by Loot and associates8 pave the way for a more intensive investigation of the role of Ang-(1–7) in the regulation of cardiac function and the signaling mechanisms that impact on cardiac dynamics.

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References


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