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The Never-ending Story of Angiotensin Peptides Beyond Angiotensin I and II

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In this issue of *Circulation Research*, Lautner et al¹ report on the biochemical and physiological characterization of a novel peptide of the renin–angiotensin system, the heptapeptide Ala1-Arg2-Val3-Tyr4-Ile5-His6-Pro7 alamandine, in rats, mice, and humans. Just a decade ago, most students of the renin–angiotensin system considered this hormonal system a linear biochemical cascade whereby renin acting on angiotensinogen (Aogen) initiates angiotensin (Ang) II production through the intermediate step of Ang I degradation by angiotensin-converting enzyme. The discovery of the biological actions of Ang-(1–7),² the identification of the Mas receptor as the binding protein mediating the inhibitory actions of Ang-(1–7) on Ang II,³ and the demonstration that the cardioprotective actions of angiotensin-converting enzyme 2 are attributable to its actions on hydrolyzing Ang II into Ang-(1–7)⁴ have drastically changed this perception. Not mentioned in this report is the newly discovered Ang-(1–12), which is cleaved from Aogen by a yet-to-be-defined nonrenin enzyme.^{5,6} Ang-(1–12) is then converted to Ang II largely by chymase in the human heart, thus completing a non–renin-dependent Ang II-forming mechanism in human heart tissue.^{6–8} Ang-(1–7), Ang-(1–12), and other Ang peptides, Ang III and Ang IV, originate from 12 amino acids from the 485 amino acids of human Aogen. Although extensive research has confirmed a critical role of renin in the liberation of Ang I from Aogen, numerous other studies have suggested that there exist other proteases capable of cleaving the substrate^{6–11} (Figure).

Over the past 10 years, progress in mass spectrometric techniques has provided the opportunity to identify other angiotensin peptides such as Ang A and alamandine,

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attributable to substitution of aspartic acid with alanine in position 1. The new peptide alamandine differs from Ang-(1–7) only by the presence of an alanine residue, which results from a presumed carboxylase action on the aspartate residue in the amino terminus. A similar substitution of alanine for aspartate has been reported for the new angiotensin peptide Ang A, which has vasoconstrictive effects similar to those of Ang II. These new findings contrast with past research, which found that the amino acid composition in position 1 did not seem to play a dominant role in the biological, immunologic, or receptor binding activity of the Ang II molecule.^{12,13} It is of interest that mass spectrometry analysis demonstrates that the ratio of Ang A to Ang II, which cannot be distinguished by conventional immunoassay analysis, is higher in patients with end-stage renal disease compared with normal subjects.¹ In a similar fashion, the authors report that alamandine is increased in patients with chronic end-stage renal disease. In the present article, the authors demonstrate that the heart has the capacity for decarboxylation of exogenously given Ang-(1–7) administered to spontaneously hypertensive rat hearts, suggesting that this is not a mutation of Aogen but rather a decarboxylation that occurs after Ang-(1–7) formation. What controls this decarboxylation in the disease state for both Ang A and alamandine is unknown.

Another intriguing finding of the present investigation is the connection to the family of Mas-related G-protein-coupled receptor (MrgD), which have been known to be expressed in the sensory neurons of the dorsal root ganglia.¹⁴ It has been postulated that they are involved in the sensory perception of painful stimuli. The pathway to this connection is presented in a series of in vitro functional studies that suggest similarities of vasorelaxation to Ang-(1–7), but surprisingly, treatment with the Mas antagonist A-779 does not block the alamandine-induced vasorelaxation (Figure 2C), as previously described for Ang-(1–7). However, binding of alamandine to MrgD receptor is blocked by D-Pro7-Ang-(1–7), the MrgD ligand β -alanine, and PD-123319 but not by the Mas antagonist A-779. In addition, the vasorelaxation is preserved in aortic rings of Mas-deficient mice. On the basis of previous reports that Ang-(1–7) is a weak agonist of the MrgD receptor,¹⁵ the authors proceeded along this line of investigation. These findings now raise a series of intriguing questions on the regulatory role of the MrgD receptor and the modified Ang peptides: (1) What is the precise biological significance of what is likely a diversity of the carboxylase activity in disease states? (2) To what extent is the heterogeneity of MrgD receptor expression in the vessel wall in health or disease a mediator of acute or chronic changes in the functional activity of the system? (3) To what degree do species differences (ie, rodents versus humans) influence the expansion of knowledge of how the carboxylase activity regulates Ang peptide modification? (4) To what degree do these diverse pathways leading to the modification of Ang peptides provide evidence for independent regulation and actions in various tissues, plasma, and other body fluids? Whether the process of biotransformation of the aspartate residue in position 1 occurs downstream or upstream of Ang I remains an additional critical unanswered question, given our past¹⁶ and recent findings^{7,8,17,18} of additional steps in the generation of Ang II by the presence of alternative intermediate peptides and enzyme pathways upstream of Ang I (Figure). Much work remains in what now is clearly a never-ending story for angiotensin peptides in cardiovascular disease.

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Family of Tissue Enzyme Pathways

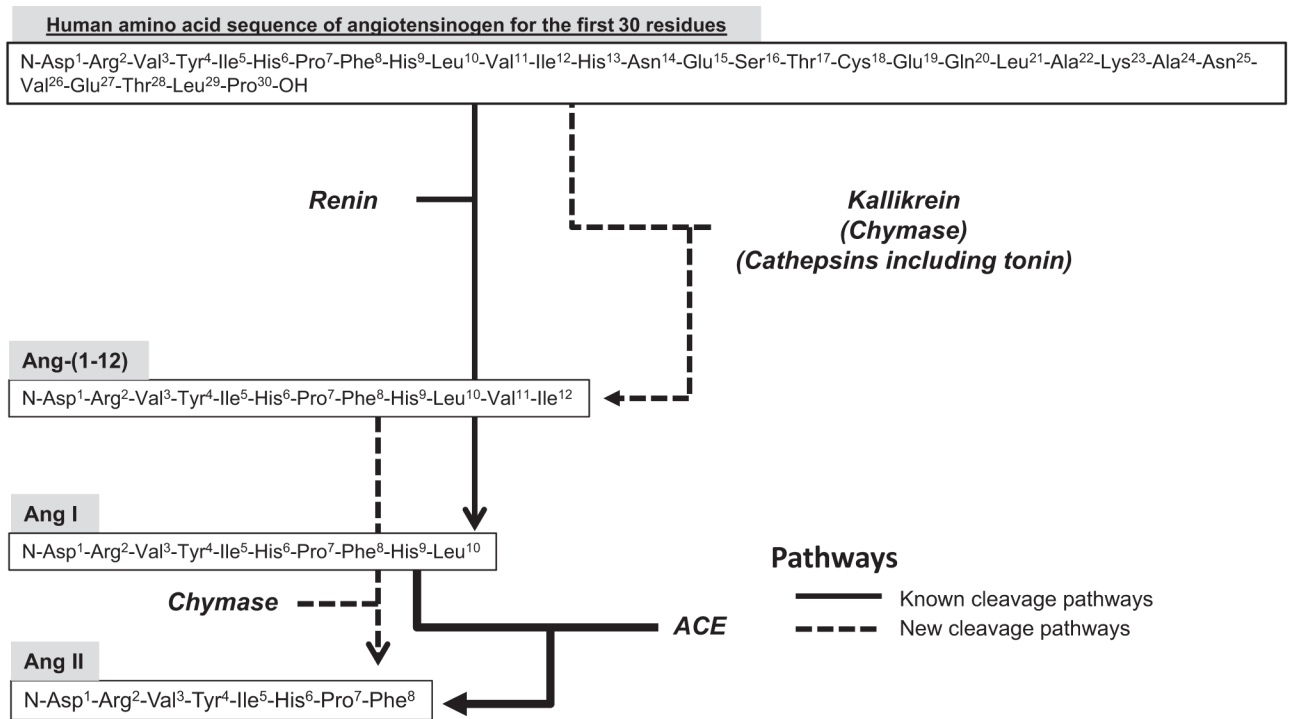


Figure. Summary of newly characterized pathways upstream from angiotensin (Ang I) in humans
 ACE indicates angiotensin-converting enzyme.