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he search for hidden truths behind established concepts and dogma is often a never-ending, uphill climb, and the history of science and medicine is full of examples of this. “To raise new questions, new possibilities, to regard old questions from a new angle, requires creative imagination and marks real advances in science” (Albert Einstein). The story of the renin-angiotensin system (RAS), hypertension, and kidney disease began nearly 2 centuries ago, with report of a clinicopathophysiologic study of albuminuria in patients followed by Goldblatt’s induction of hypertension in experimental dogs in the 1930s. It took 7 more decades of basic, translational, and clinical research to discover the pressor effect of renal extracts (ascribed to renin) in 1898 and another 10 decades of imaginative work by many to culminate in the discovery of angiotensin II (Ang-II), the primary effector peptide of the RAS, and its receptors (AT1R and AT2R) in 2000. Since then, expansion of the RAS to the renin-angiotensin-aldosterone (RAAS) system and discovery of several bioactive peptides produced through Ang-II degradation has contributed to the increasing complexity of the RAS (Figure), and the search continues.

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Since the 1990s, therapy based on inhibition of the effects of Ang-II with angiotensin-converting enzyme (ACE) inhibitors and AT1R blockers has dominated the experimental and clinical research arenas. Cumulative evidence has indicated that the RAS, through Ang-II generated primarily by the ACE, plays a critical role in the regulation of blood pressure, fluid and electrolyte balance, cardiovascular and renal homeostasis, and pathophysiology of hypertension and cardiovascular and renal disease. Ang-II was implicated in the concept of a regulatory arm of the RAS with an ACE/aldosterone blockade is used in selected patients. AT1R blockers may also result in enhanced vasodilation via unopposed AT2R activation and downstream AT2-mediated signaling. Other evidence indicates that angiotensin receptor blockers can also release kinins and increase bradykinin levels in hypertensive patients, which may augment benefits that are offset by the risk of cough and angioedema. Randomized clinical trials mounted to resolve well-known arguments for using AT1R blockers have shown benefits of both ACE inhibitors and AT1R blockers for controlling blood pressure in hypertension. A downside of chronic ACE-inhibitor therapy in heart failure patients is that Ang-II levels increase and symptoms worsen. Importantly, aging is associated with RAAS dysregulation and increased Ang-II and other RAS components, which in turn may contribute to increased cardiovascular remodeling and risk in elderly patients. In diabetic nephropathy, excessive RAAS activation results in progressive renal damage.

Up until a decade ago, the collective evidence favored the concept of a regulatory arm of the RAS with an ACE/Ang-II/AT1R axis that mediates vasoconstriction, whereas under AT1R blockade the AT2R mediates vasodilation (Figure, A). Evidence over the last decade unraveled existence of a counter-regulatory arm of the RAS via an Ang-(1–7)/ACE-2/mas receptor axis that opposes vasoconstrictor, proliferative, profibrotic, and prothrombotic actions of Ang-II (Figure). The Ang-(1–7)/Mas axis regulates several signaling pathways, such as phospho-inositide 3-kinase/AKT and extracellular signal–regulated kinase pathways and involves downstream effectors such as nitric oxide, forkhead box O1, and cyclooxygenase 2. In the counter-regulatory and vasodepressor arm, both ACE-inhibitors and AT1 receptor blockers can increase angiotensin-(1–7). This axis is a potential therapeutic target in cardio-renal disease.

In summary, RAAS blockade with ACE inhibitors or AT1R blockers is standard recommended therapy for hypertension, heart failure, and nondiabetic/diabetic chronic renal disease, and aldosterone blockade is used in selected patients. Clinicians recognize that optimal therapy is critical for survival
with a favorable outcome, and combination therapies are often needed. Over the last 2 decades, several laboratories have been searching for specific molecular targets that may lead to the development of therapies and strategies to optimize therapy of hypertension, heart failure, and chronic renal disease, prevent adverse remodeling, and improve outcome. Many studies have been conducted in experimental animal models and humans. However, therapy to limit adverse remodeling in patients with these diseases, especially the elderly, remains suboptimal, and hearts continue to enlarge after hypertension and heart failure.
In this issue of Circulation, Salem and colleagues\textsuperscript{14} tested the provocative and bold hypothesis that a novel peptide acts as an endogenous cofactor in Ang-II–mediated vasoconstrictive effects. The observation that plasma Ang-II concentrations were not increased in patients with heart failure and chronic kidney disease triggered the idea that unknown endogenous cofactors may be involved in the action of Ang-II.\textsuperscript{12,14} They present a large volume of compelling data suggesting that this peptide, a fragment of chromogranin-A that they named vasoconstriction inhibiting factor (VIF), modulates vasoconstrictive effects of Ang-II and exerts vasodilator effects mediated by AT\textsubscript{2}R, and may provide a potential counter-regulatory mechanism against hypertension.\textsuperscript{14} This interesting non-RAS peptide acting through AT\textsubscript{2}R further underscores the complexity of the RAS/RAAS (Figure, B) and need for more research to establish its importance as a potential target for the prevention and therapy of cardiovascular disease. Marie Curie, winner of separate Nobel Prizes for Physics and Chemistry, is credited with saying “be more curious about ideas.”

It is known that chromogranin-A is produced by chromaffin cells of the adrenal medulla and other tissues and is elevated in pheochromocytomas. It serves as precursor to several functional peptides, including vasostatin I, vasostatin II, pancreastatin, catestatin, and parastatin, which negatively modulate autocrine and paracrine functions.\textsuperscript{16-18} Some of these peptides, such as vasostatin I and vasostatin II, inhibit vasoconstriction while concentrations of catestatin are reduced and those of chromogranin-A are increased in hypertensive patients. Here Salem et al\textsuperscript{14} report at least 7 important findings. First, they nicely demonstrated that VIF released from the adrenal glands and derived from chromogranin-A modulates Ang-II–induced vasoconstriction by testing different VIF concentrations on Ang-II–induced vasoconstriction and calculating the EC\textsubscript{50}. Second, they probed mechanisms and showed that VIF impairs Ang-II–induced phosphorylation of p38MAPK but not extracellular signal–regulated kinase 1/2. Third, they present evidence suggesting that elevated plasma VIF may modulate the harmful effects of Ang-II in chronic renal disease and heart failure patients, especially since chromogranin-A is also elevated in these patients. Fourth, they showed that VIF reduced Ang-II–induced increase in blood pressure in vivo. Fifth, they confirmed absence of homology in amino acid sequences between VIF and the other main RAS receptors (AT\textsubscript{1}R, AT\textsubscript{2}R, and Mas) and produce significant physiological and pathophysiological effects. This possibility opens up a new area of research into other biologically active peptides. The authors have suggested testing for interactions of VIF with other angiotensin peptides (such as angiotensinogen, Ang-II, Ang-III, Ang-IV, and Ang-[1–7]), angiotensinogen, and alamandine.\textsuperscript{14} However, the possibility that peptide interactions may not always be beneficial but rather might be harmful and contribute to disease progression should also be considered.

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**Disclosures**

None.

**References**


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Expanding Saga of the Renin-Angiotensin System: The Angiotensin II Counter-Regulatory AT2 Receptor Pathway
Bodh I. Jugdutt

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