SPECIAL TOPIC | Intracrine Renin-Angiotensin System: A New Paradigm

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Functional intracellular renin-angiotensin systems: potential for pathophysiology of disease

Robert M. Carey
Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia Health System, Charlottesville Virginia

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THE RENIN-ANGIOTENSIN SYSTEM (RAS) is a coordinated hormonal cascade playing a major role in cardiovascular, renal, and adrenal homeostasis (4). Derangements in the RAS have been implicated in the pathogenesis of many disease states, including hypertension and of target organ damage related to hypertension, diabetes mellitus, congestive heart failure, and postmyocardial infarction. Recognized for decades, the classical RAS is the circulating (endocrine) RAS, in which renin, secreted by the juxtaglomerular cells of the renal afferent arteriole, enters the systemic circulation and cleaves its substrate angiotensinogen (Agt) to form the biologically inactive decapeptide ANG I. Angiotensin-converting enzyme (ACE) in plasma then converts ANG I to the biologically active peptide ANG II, which binds to angiotensin type-1 receptors (AT1Rs) in tissues to induce its major biological actions. During the past 15 years, a revolution in our knowledge of the RAS has included the identification of new biologically active peptides [ANG (1–7), ANG (1–12)] and new functions for those already known [ANG III], new enzymes that generate these peptides [aminopeptidases A and N; ACE-2], novel receptors [the ANG type-2 receptor (AT2R), the ANG (1–7) mas receptor and the (pro)renin receptor], and new receptor-receptor interactions (4).

Among the major discoveries of recent years has been the recognition that the RAS serves not only as an endocrine system but also can function as a local independent tissue system (cell-to-cell, paracrine, or autocrine), not requiring hormone secretion into the systemic circulation (21). The stringent requirements for a local tissue RAS include 1) the presence of mRNAs for all of the system components necessary for the generation of a biologically active product (e.g., ANG II); 2) the synthesis of a biologically active product within the tissue; 3) the expression of receptors for the biologically active product within the tissue; 4) regulation of the biologically active product within the tissue, independently of the systemic circulation; and 5) a physiological response derived from reduction or elimination of the action of the product at the local tissue level. The existence of a local tissue RAS is often difficult to prove because of the requirement to exclude exposure of ANG II from the systemic circulation. In spite of this difficulty, the foregoing criteria have now been met for several local tissue RASs, including those within the kidney, heart, and brain, and most of the criteria have been fulfilled for tissue RASs in blood vessels, pancreas, adrenal gland, and adipose tissue (4). The most certain and generally accepted evidence for a functional tissue RAS separate from the systemic circulation has derived from studies in the kidney.

Although renin was identified in the brain and adrenal cortex in the late 1960s and early 1970s, the intrarenal RAS was the first independent functional tissue RAS to be described (15, 17, 18). The initial observations were from in vivo studies demonstrating that intrarenal inhibition of the RAS with ACE inhibitors or ANG receptor blockers, at infusion rates confined to the kidney during the experimental period, increased renal plasma flow, glomerular filtration rate, and sodium and water excretion (15, 17, 18). Later, it was demonstrated that the mRNAs and proteins for all of the system components (renin, Agt, ACE, and AT1Rs) are localized in a site-specific manner within the kidney and that intrarenal formation of ANG II occurs independently of renal uptake of the peptide (4). Definitive molecular evidence for the independent intrarenal RAS and its importance in the control of blood pressure was first obtained using a transgenic mouse model overexpressing Agt in the kidney or the systemic circulation (8). Expression of Agt selectively in the kidney induced chronic hypertension independently of the endocrine RAS (8). Within the kidney, there is now substantial evidence for a separate intratubular RAS, in which ANG II formation is autoamplified by ANG II-induced upregulation of Agt, creating a positive feedback loop that may play a role in renal tissue damage (20). Whether this kind of reinforcement occurs in other tissue RASs is currently unknown.

While evidence for a separate, independent brain RAS has existed since the late 1960s, this system has been debated for decades due to the relatively low renin expression level in the brain (11, 12, 24, 25). However, recent studies using a double-transgenic mouse model exhibiting brain-specific RAS activity have provided definitive evidence for a functional brain RAS that regulates body fluid and energy homeostasis (25). There is also substantial evidence for a separate RAS within the heart, although debate continues about the source of renin (uptake from the systemic circulation vs. intracardiac biosynthesis) (9). It is now apparent that the tissue RASs have a much larger role in fine physiological regulation and target-organ damage from disease processes than does the systemic endocrine system (4).
Another revolution is currently occurring in our understanding of the RAS: the capacity to synthesize ANG within cells wherein the peptides bind to receptors and initiate downstream signaling events, leading to cellular actions without exiting the cell of origin. This new paradigm is termed the “intracellular” or “intracrine” RAS. In 1981, Re et al. (23) first demonstrated nuclear binding of ANG II in hepatic and splenic tissue, and for the past 20 yr, Re has championed the concept of a complete independent intracellular RAS. Over this time, substantial evidence has accumulated for functional, entirely intracellular RASs in the heart and kidney, and their potential roles in physiology and disease.

The criteria for identification of an intracellular RAS are similar to those enumerated above for tissue RASs, but in this case, confined to cells (22). All of the components of the RAS are present within certain cell types, and the intracellular biosynthesis of ANG peptides has been demonstrated. Intracellular ligand-dependent activation of ANG receptors, initiation of signaling pathways, and biological actions have all been demonstrated within these cells. As has been recognized, extracellular ANG II can be internalized together with its AT1R after binding on plasma membranes, and it is difficult to prove that ANG II is synthesized intracellularly vs. introduced via uptake from outside the cell (22). However, recent molecular approaches are beginning to provide definitive evidence for intracellular RASs in several cell types. These new approaches and the definitive evidence accumulated thus far are discussed in detail in the accompanying four review articles on the intracellular RAS in this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology by leaders in the field (7, 10, 13, 16).

New cellular and molecular approaches have now been developed that will enable confirmation of the expression and physiological function of intracellular RASs and begin to identify their roles in the pathogenesis of disease. Among the most exciting and novel investigative paradigms is the introduction of a nonsecreted form of Agt into cells, in which the ANG II processed from Agt is retained completely within the cell of origin (7). Another compelling new approach is the creation of a transgenic mouse model expressing intracellular ANG II, independently of secreted Agt or ANG peptides (7). In this model, intracellular ANG II translocated AT1Rs to the nucleus. The mice were hypertensive and developed renal thrombotic microangiopathy, and microthrombosis in glomerular capillaries and small renal vessels. Another novel approach has been the development of renal proximal tubule (RPTC)-specific expression of an intracellular nonsecreted cyanfluorescent fusion form of ANG II (10). Animals harboring this form of ANG II displayed increased RPTC sodium reabsorption and hypertension. Studies in the heart are beginning to teach us that diabetes is a disease process associated predominantly with intracrine or intracellular RAS activation rather than endocrine, paracrine or autocrine activation and that cardiomyocytes synthesize ANG II intracellularly under high glucose conditions (16). ANG receptor subtypes have now been shown within the nucleus, where they are coupled to well-defined signaling processes (7, 13). Although many of the actions of intracellular ANG II are related to receptor binding on intracellular membranes, including the nuclear membrane, termed “canonical” actions, others may operate through mechanisms distinct from membrane receptor activation or “noncanonical” actions. Recently, a canonical functioning angiotensin system has been identified and characterized within mitochondria (1). In the mitochondrial angiotensin system, the predominant ANG receptor is the subtype-2 receptor (AT2R), which is coupled to nitric oxide release. It is also possible that intracellular ANG receptors may be activated on their own in the absence of their usual peptide ligand(s) and that constitutive receptor activation may contribute to certain disease processes at the cellular level (2, 19).

Through novel approaches, such as those indicated above, we are beginning to characterize the relative roles of the endocrine, paracrine/autocrine, and intracrine RASs in physiology and pathophysiology. From a disease standpoint, it is likely that the intracrine RAS may have an important role in certain disorders involving the heart and kidneys. Within the heart, for example, the intracrine RAS may be activated selectively in the advanced stages of heart failure (9). In addition, intracellular production of ANG II may be responsible for the process of cardiac remodeling after myocardial infarction (9). Recent evidence suggests that the intracellular RAS may have a preeminent role in target organ damage within the heart in diabetes mellitus (16). Also, there is emerging evidence that glucose may upregulate the prorenin receptor in renal mesangial cells by ligand-independent mechanisms generating downstream signaling via the tumor growth factor-β and Wnt signaling pathways and that this intracrine system may contribute to diabetic nephropathy (6, 14). Several of the molecular models of intracellular ANG production are hypertensive, manifest renal sodium retention, and/or exhibit microangiopathy, opening the door to define the role of the intracrine RAS in renal sodium transport, vascular disease, and hypertension. The findings that cells along the entire nephron seem to possess their own RASs and that ANG II augments intrarenal Agt biosynthesis sets up the possibility that renal function and renal tissue damage may be related, at least in part, to activation of a tubule intracrine RAS (20). In addition, the recent identification and characterization of a functional mitochondrial angiotensin system introduce the possibility that a reduction in mitochondrial AT1R may impair nitric oxide production during the aging process. If this is proven to be the case, it might be possible to ameliorate this process by chronic AT1R blockade and/or AT1R activation (3, 5). The recent evidence for a physiological role of the intracrine RAS discussed in the four accompanying reviews (7, 10, 13, 16) suggests several potentially exciting opportunities, such as these, for the identification of new therapeutic targets in cardiovascular and renal disease, as well as physiological processes, such as aging in humans.

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REFERENCES


