The Intrarenal Renin-Angiotensin System in Hypertension

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The renin-angiotensin system (RAS) is a well-studied hormonal cascade controlling fluid and electrolyte balance and blood pressure through systemic actions. The classical RAS includes renin, an enzyme catalyzing the conversion of angiotensinogen to angiotensin (Ang) I, followed by angiotensin-converting enzyme (ACE) cleavage of Ang I to II, and activation of AT_1 receptors, which are responsible for all RAS biologic actions. Recent discoveries have transformed the RAS into a far more complex system with several new pathways: the (des-aspartyl[1])-Ang II (Ang III)/AT2 receptor pathway, the ACE-2/Ang (1-7)/Mas receptor pathway, and the prorenin-renin/prorenin receptor/mitogen-activated protein kinase pathway, among others. Although the classical RAS pathway induces Na^+ reabsorption and increases blood pressure, several new pathways constitute a natriuretic/vasodilator arm of the system, opposing detrimental actions of Ang II through Ang II type 1 receptors. Instead of a simple circulating RAS, several independently functioning tissue RASs exist, the most important of which is the intrarenal RAS. Several physiological characteristics of the intrarenal RAS differ from those of the circulating RAS, autoamplifying the activity of the intrarenal RAS and leading to hypertension. This review will update current knowledge on the RAS with particular attention to the intrarenal RAS and its role in the pathophysiology of hypertension.

Key Word: Kidney, Renin, Angiotensin, Hypertension, Sodium

INTRODUCTION

Hypertension (HT) is the world's most prevalent cardiovascular disorder (approximately one third of adults have HT in most communities worldwide) and one of the leading risk factors for disability and death.[1-3] The relationship between blood pressure (BP) and cardiovascular risk is continuous, consistent, and independent of other risk factors and the higher the BP, the greater the chance of cardiovascular events, stroke, and kidney disease.[2] Approximately 90% of patients with HT have primary (essential) HT, the causes of which remain unknown.[1-3] However, genetic and environmental factors that affect BP are currently being studied. Genetic factors include inappropriately high activity of the renin-angiotensin system (RAS) and the sympathetic nervous system and susceptibility to the effects of salt on BP (salt sensitivity of BP). Environmental factors include excess dietary salt intake, obesity, and possibly sedentary lifestyle. Of the secondary causes of HT, the most prevalent condition by far is primary aldosteronism (5%-10%), followed by CKD, renal vascular disease, sleep apnea, and a variety of uncommon endocrine conditions, including pheochromocytoma.[4]

The RAS is a well-studied hormonal cascade important in the control of BP.[5] Angiotensin (Ang) II, the principal Ang effector peptide, binds to 1 of 2 distinct receptors, the Ang II type 1 receptor (AT_1R) and Ang II type 2 receptor (AT_2R). The vast majority of the actions of Ang II are transduced by AT_1Rs, including cellular dedifferentiation and proliferation; vasoconstriction; reduced vascular compliance; cardiac contractility; increased renal tubular sodium (Na^+) reabsorption; aldosterone, vasopressin, and endothelin secretion; salt appetite; thirst; and activation of the sympathetic nervous system, all of which can raise BP and contribute to the pathogenesis of HT.[5] Ang II also inhibits renin secretion through AT_1Rs on renal juxtaglomerular cells, serving as a short-loop negative feedback mechanism that limits the activity of the system.[5] In contrast, AT_2Rs generally oppose the actions of Ang II through AT_1Rs under most circumstances, inducing vasodilation and natriuresis but acting in concert with AT_1Rs to suppress renin secretion.[6-8]

Despite many years of study, the RAS continues to reveal new pathways, including additional enzymes, peptides, receptors, and actions that can contribute to HT (Fig 1).[5,9] In addition to the classical renin/ACE/Ang II-AT_1R pathway, at least 3 new axes have been described, including the [des-aspartyl[1]]-Ang II (Ang III)/AT_2R pathway, the ACE2/Ang(1-7)/*Mas* receptor pathway, and the (pro)renin receptor (PRR)/mitogen-activated protein (MAP) kinase pathway. The concept that Ang II is the only active peptide of the RAS is now outmoded because angiotensinogen (Agt) can be hydrolyzed by various enzymes to generate Ang (1-7), Ang III, and alamandine, each of which has newly described biologic actions.[5,9]

One of the most important characteristics of the RAS is its function not only as a circulating (endocrine) system but also as an independent local tissue (paracrine) and/or cellular (autacrine or intracrine) system.[5] The intrarenal RAS is such a local tissue system that has the capacity to regulate its activity independently of the circulating system. The goal of this brief review is to discuss the role of the intrarenal RAS (independently of aldosterone) in the pathophysiology of HT.

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EVIDENCE FOR AN INDEPENDENT FUNCTIONAL INTRARENAL RAS

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 and characterized.[10-12] The initial evidence came from in vivo studies demonstrating that inhibition of the RAS with intrarenal infusion of angiotensin-converting enzyme (ACE) inhibitors or Ang II receptor blockers, at infusion rates that did not alter systemic BP during the experimental period, markedly increased renal plasma flow, glomerular filtration rate, and sodium (Na^+) and water excretion.[10] These results were later confirmed using more rigorous approaches showing that small intrarenal doses of Ang II receptor blocker, while not altering pressor responses to systemically administered Ang II, induced marked increases in renal hemodynamic and tubular function.[11,12] These results were interpreted as indicating that Ang II acting at AT_1Rs exerts baseline tonic inhibition on Na^+ excretion. Later, the mRNAs and proteins for all the known RAS components (Agt, renin, ACE, and AT_1Rs) were found expressed in a site-specific manner within the kidney and it was shown that intrarenal formation of Ang II occurs independently of the renal uptake of the peptide from the circulation.[5] Additional evidence for an independent tissue RAS included observations that Ang II concentrations are elevated 1000-fold higher in renal interstitial fluid compared with circulating plasma, intrarenal Ang II content is markedly increased compared with circulating levels in response to Na^+ restriction, and this response could be abolished by selective intrarenal renin inhibition.[13,14]

CLINICAL SUMMARY

- The intrarenal RAS, the most important independently functioning tissue RAS, is activated in hypertension.
- Unlike the systemic RAS, the intrarenal RAS can autoamplify Ang II production, providing a continuing source of the peptide to maintain vasoconstriction, antinatriuresis and hypertension.
- The intrarenal actions of Ang II via AT1Rs are opposed by several counter-regulatory RAS components, including the Ang III/AT2R pathway, the ACE-2/Ang (1-7)/Mas receptor pathway and possibly the newly described alamandine/MrgD pathway. These pathways represent potential new therapeutic targets for hypertension.

ROLE OF THE INTRARENAL RAS IN BP CONTROL

Definitive molecular studies now indicate the importance of the intrarenal RAS in the control of BP and the pathogenesis of HT. Transgenic overexpression of Agt selectively within the mouse kidney induced chronic HT independently of the systemic RAS.[15] Transgenic mice expressing the Agt gene selectively in the proximal tubule (through the kidney androgen-related promoter), when bred to mice expressing human renin systemically, had a major increase in BP in spite of having normal circulating Ang II. The HT was Ang II dependent as it was abolished by AT_1R blockade. This constituted the first available evidence that systemic HT could be induced by isolated renal tissue RAS activation.[15] In addition, selective proximal tubule overexpression of human renin and Agt increased BP, in strong support of the concept that intratubular RAS activation can induce HT.[16]

Elegant cross-transplantation studies in mice later demonstrated the importance of, and indeed requirement for, renal AT_1Rs in the pathophysiology of Ang II-induced HT.[17-19] Kidneys from wild-type (WT) mice were transplanted into mice with whole-body AT_1R knockout, creating a model of exclusive renal AT_1R expression, and kidneys from animals with AT_1R knockout were transplanted into WT animals, creating a model of exclusive renal AT_1R knockout.[17,18] When the animals were infused with Ang II systemically, only the animals with intact renal AT_1Rs developed sustained HT and cardiac hypertrophy.[18] Thus, kidney AT_1Rs are necessary and sufficient for the development of Ang II-dependent HT.[18] Additional studies employing Cre/Lox technology have demonstrated that selective deletion of proximal tubule AT_1Rs alone is sufficient to reduce basal BP despite intact systemic and renal AT_1Rs outside the proximal tubule.[19] Conversely, studies have demonstrated that transfer of Ang II/cyan fluorescent protein and/or AT_1 receptors selectively into the proximal tubule is sufficient to increase BP.[20,21] Thus, the activity of the intrarenal RAS is critically important in the control of BP in experimental animals, and this concept is also likely to apply to humans. However, demonstrating a role for the intrarenal RAS in humans is replete with difficulty and will require the availability of specific urinary markers such as Ang II, Agt, or other RAS components.

ROLE OF THE INTRARENAL RAS IN HT

Currently, the intrarenal RAS is considered to be the most important of the tissue RASs (vasculature, heart, brain, adrenal, etc.) in the control of BP and HT in experimental animals.[5] Indeed, there is growing recognition that inappropriate activation of the intrarenal RAS prevents the kidney from maintaining normal Na^+ balance at normal renal perfusion pressures and is an important cause of HT.[22-24] Several experimental models support the concept of an overactive intrarenal RAS in the development and maintenance of HT; these include 2-kidney, 1-clip Goldblatt HT; Ang II-infused HT; transgenic rat mRen2-27 HT with an extra renin gene; remnant kidney HT; several mouse models overexpressing the renin or Agt gene; and, perhaps most importantly, spontaneously hypertensive rats (SHR).

SHR are inbred rats that develop HT with increasing age and are widely employed as a model of human primary HT.[25] Young prehypertensive SHR exhibit increased renal proximal tubule Na^+ reabsorption, where normal Na^+ excretion is achieved only at the expense of elevated renal perfusion pressure.[26,27] Over time, the kidneys reset to require elevated BP to excrete a normal Na^+ load.[28] Evidence for this pathophysiologic principle includes