EXPERIMENTAL CELL RESEARCH 318 (2012) 1049–1056

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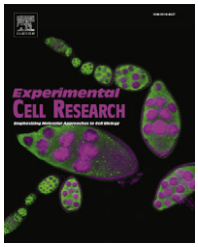

Review Article

Recent advances involving the renin–angiotensin system

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ARTICLE INFORMATION

Article Chronology:
Received 19 January 2012
Accepted 24 February 2012
Available online 3 March 2012

Keywords:
Renin
Angiotensin
Kidney

ABSTRACT

The renin–angiotensin system (RAS) exercises fundamental control over sodium and water handling in the kidney. Accordingly, dysregulation of the RAS leads to blood pressure elevation with ensuing renal and cardiovascular damage. Recent studies have revealed that the RAS hormonal cascade is more complex than initially posited with multiple enzymes, effector molecules, and receptors that coordinately regulate the effects of the RAS on the kidney and vasculature. Moreover, recently identified tissue-specific RAS components have pleomorphic effects independent of the circulating RAS that influence critical homeostatic mechanisms including the immune response and fetal development. Further characterization of the diverse interactions between the RAS and other signaling pathways within specific tissues should lead to novel treatments for renal and cardiovascular disease.

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Introduction

The renin–angiotensin system (RAS) is a master regulator of blood pressure and fluid homeostasis. As shown in Fig. 1, this system is a multi-enzymatic cascade in which angiotensinogen, the major substrate, is processed in a two-step reaction by renin and angiotensin-converting enzyme (ACE), resulting in the sequential generation of angiotensin I and angiotensin II. In recent years, several new enzymes, peptides, and receptors in this system have been identified, manifesting a complexity that was previously unappreciated. Although appropriate activation of the RAS is vital for preventing circulatory collapse and maintaining

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0014-4827/$ – see front matter
doi:10.1016/j.yexcr.2012.02.023

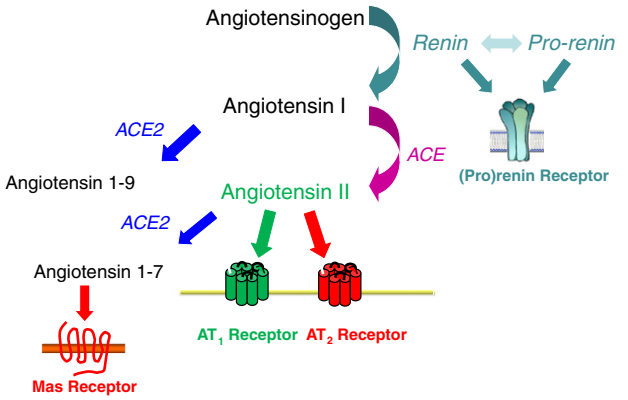

Fig. 1 – Schematic of the renin–angiotensin system.

intravascular fluid balance, dysregulation and/or persistent RAS activation can lead to inappropriate blood pressure elevation, target organ damage, and even reduced survival [1]. Accordingly, pharmacological agents that inhibit the synthesis or activity of angiotensin II are effective and widely used anti-hypertensive agents [2] that can ameliorate morbidity and mortality in cardiovascular diseases including congestive heart failure [3,4] and slow the progression of a wide range of progressive kidney diseases including diabetic nephropathy [5]. Angiotensin receptor blockers (ARBs), which block type 1 (AT_1) receptors, are similarly effective for treating these disorders [6–8]. Below, we will review selected recent advances in understanding the physiology of the RAS with an emphasis on actions impacting the kidney.

Renin and its putative receptor

The aspartyl protease renin is synthesized as a precursor protein, prorenin [9]. Active renin is then generated by removal of an N-terminal peptide fragment, presumably by proteases in the kidney. Active renin specifically cleaves the 10 amino acids from the N-terminus of angiotensinogen to form angiotensin I. As angiotensinogen and angiotensin converting enzyme (ACE) are present in excess, at least in the circulation, the level of renin is a key rate-limiting step determining the level of angiotensin II and thus the activity of the RAS. The primary source of renin in the circulation is the kidney, where its expression and secretion are tightly regulated at the juxta-glomerular (JG) apparatus by a renal baroreceptor [10] and sodium chloride delivery to the macula densa, which is sensed by chloride flux through the NKCC2 transporter expressed on the luminal side of macula densa cells [11,12]. Recent studies confirm that the pathway linked to triggering renin release by the macula densa involves generation of PGE_2 by cyclo-oxygenase (COX)-2 with subsequent activation of the EP4 receptor for PGE_2 [13]. Of note, activity of the pathway is unaffected by the absence of either of the two putative microsomal PGE synthase enzymes indicating a possible role for atypical or perhaps non-enzymatic pathways for PGE_2 synthesis. Microarray studies have affirmed the unique identity of the renin-producing JG cell [14] and have also elucidated a role for micro-RNAs to maintain the phenotype of JG cells and regulate their emergence from precursors among smooth muscle cells in the renal arteriole [15,16]. At a transcriptional level, Liver X receptors enhance renin generation within JG cells through interactions with the renin promoter [17] and can even induce differentiation of mesenchymal stem cells into renin-secreting "JG-like" cells [18]. However, other studies suggest that renin may also be generated in epithelial cells of the proximal, connecting, and/or collecting tubule of the nephron [19,20]. While there is some controversy regarding the physiological relevance of renin in the distal nephron, the impact of dietary salt, blood pressure and angiotensin II levels on its expression seems to be paradoxical compared to renin at the JGA. For example, angiotensin II suppresses renin at the JGA but stimulates renin mRNA and protein formation in the collecting duct [20], an effect that appears to be independent of blood pressure [21].

Along with the enzymatic actions of renin in the RAS, a receptor that binds prorenin and renin has been identified in the kidney glomerulus and the vasculature [22]. In cultured cells, activation of this receptor stimulates profibrotic and pro-inflammatory pathways independently of angiotensin II generation [23]. In addition, studies using a putative antagonist peptide synthesized from the handle-region of the pro-renin molecule suggest a role for the pro-renin receptor to promote kidney diseases such as diabetic nephropathy [24,25]. However, the effectiveness of this peptide appears to be inconsistent and its ability to block signaling at the pro-renin receptor has been questioned [26].

The pro-renin receptor appears to have other functions independent of the renin–angiotensin system. For example, it is found as part of a complex required for the normal function of V-ATPase in several cell lineages including cardiac myocytes [27]. The pro-renin receptor acts as an adaptor between the Wnt receptor and V-ATPase in a Wnt/β-catenin signaling complex required for normal CNS development [28]. Thus deletion of the pro-renin receptor gene causes a lethal phenotype at a very early embryonic stage, which contrasts significantly with the phenotype of renin knockouts [29], indicating important functions of the receptor that are independent of its actions in the RAS. Two groups have recently described studies of mouse lines in which the pro-renin receptor was deleted specifically from podocytes. In both cases, there was a similar, dramatic phenotype characterized by disruption of the glomerular filtration barrier, with marked proteinuria and abnormal podocyte structure, perhaps due to dysregulated autophagy [30,31]. Thus, while this molecule appears to play a critical role in the kidney, much remains to be learned about its functions in normal kidney physiology and disease, including the extent to which these functions are influenced by renin or pro-renin binding.

Regulatory actions of angiotensinogen

Angiotensinogen, the substrate for renin, is the source of all angiotensin peptides. While it has been suggested that there is an excess of angiotensinogen substrate in human plasma relative to renin, other studies suggest that alterations of plasma angiotensinogen levels can affect the relative activity of the RAS. For example, a variant of the human *AGT* gene that is associated with higher plasma levels of angiotensinogen is also associated with the development of hypertension [32]. In addition, gene titration studies in transgenic mice engineered to carry from 0 to 4 copies of the *Agt* gene demonstrated a positive correlation between the number of *Agt* gene copies, plasma levels of angiotensinogen, and blood pressure [33]. Furthermore, a recent study suggests