Update understanding of Renin-angiotensin system

Ihm Soo Kwak, M.D.

Department of Internal Medicine, School of Medicine, Busan National University

Abstract

The renin-angiotensin system plays a crucial role in maintaining cardiovascular homeostasis. Renin, an enzyme produced by the juxtaglomerular apparatus (JGA) in the kidney, converts angiotensinogen to angiotensin I, which is then converted to the potent vasoconstrictor angiotensin II by angiotensin-converting enzyme (ACE). The renin-angiotensin system (RAS) is involved in the regulation of blood pressure, electrolyte balance, and volume homeostasis. Changes in the RAS can lead to hypertension, heart failure, and kidney disease.

The RAS is activated in response to decreases in blood pressure or sodium intake, stimulating renin secretion from the JGA. Renin cleaves angiotensinogen to form angiotensin I, which is ultimately converted to angiotensin II by ACE. Angiotensin II, in turn, stimulates the secretion of aldosterone, which enhances sodium retention.

The RAS is tightly regulated by various factors, including temperature, potassium, angiotensin II itself, and the sympathetic nervous system. Angiotensin II also has significant effects on endothelial function, vascular tone, and smooth muscle cell proliferation. The renin-angiotensin system can be activated by ACE inhibitors, which are commonly used to treat hypertension.

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농도(치밀반 기전)이다. 레닌, 프로레닌 수용체는 레닌과 프로레닌에 결합하여 효소 활성을 증가시키고 세포내 신호 전달 체계를 활성화 하고 섬유화 단백을 발현시킨다. 안지오텐신 전환 효소 2 (ACE2)는 안지오텐신 II에서 안지오텐신 1-7을 생성하는 mono 카르복시펩티다게이다. ACE2는 세뇨관 상피세포와 사구체 상피세포에 분포하고 안지오텐신 II를 대사하여 비활성형으로 전환시킨다. 안지오텐신 II의 작용은 노르에피네프린 보다 40배나 강한 혈압 상승 효과를 나타낸다. 신장에서 신혈관 수축을 일으키고 근위세뇨관에서 나트륨 재흡수를 증가시키고 알도스테론을 본비 시켜 피질 집합관의 나트륨 흡수를 증가시킨다. 안지오텐신 II는 수입 및 수출소동맥 모두를 수축시키지만 수출 소동맥이 상대적으로 혈관 직경이 작아 수출 저항이 수입 세동맥에 비해 세배까지 높아져 신혈류량은 감소하나 사구체여과율은 유지할 수 있다. 안지오텐신 II는 이러한 생리적 작용 외에 염증반응, 세포 발육, 분열, 세포자멸사, 이동, 분화, 섬유화, 그리고 조직 손상에 관여하는 세포내 신호전달 체계 조절에 다양한 작용을 하고 있다. 국소 안지오텐신 II는 순환 안지오텐신 II와 별도로 지속적인 신혈관 수축과 나트륨 축적에 중요하다. 레닌 안지오텐신계를 조절하는 많은 약제들이 개발되어 사용되고 있으며 레닌 안지오텐신계는 아직 완전히 규명되지 않고 있으며 향후 지속적인 기전과 약제에 대한 연구로 많은 질환의 치료에 기여할 수 있을 것으로 기대된다.

Key words: renin, prorenin, angiotensin II, renin-angiotensin system

The discovery of renin more than 100 years has turned out to be of importance in a number of fields. There is no doubt that it makes a major contribution to numerous aspects of homeostasis under physiological circumstances and to the patterns of disordered functioning in a number of disease states. In recent years, The attention that had been paid upon the Renin-angiotensin system(RAS) as regulation of blood pressure and body fluid homeostasis has shifted to the role in the progression of diseases. It is appropriate to review the knowledge regarding the RAS and to consider future prospects (Fig.1).
Historical profile of the renin–angiotensin system

The physiologist Robert Tigerstedt injected extract of rabbit kidneys into other rabbit and found a rise in blood pressure and their paper, in which proposed the term ’renin’ in 1898. In 1909, Janeway performed a unilateral nephrectomy following ligation of one of the renal artery branches on contralateral side in three dogs. Blood pressure rose by 13–33 mmHg. Goldblatt and his colleagues showed that clamping the renal artery and excising the contralateral kidney (one–kidney one–clip Goldblatt hypertension) or leaving the contralateral kidney (two–kidney one–clip Goldblatt hypertension) caused a marked rise in blood pressure in 1934. Pickering and Prinzmetal show, in 1938, that renin could be extracted from normal kidneys and partly purify this kidney extract. Kohlstedt et al. proposed that renin was an enzyme in 1938. The first reports of blood–pressure raising substance in plasma was described simultaneously by two research groups in 1949, Braun–Menendez et al. called the term hypertensin, whereas Page and Helmer called angiotonin. In 1958, however, Braun–Menendez and
Page\textsuperscript{8}) proposed an alteration of the nomenclature to 'angiotensin'.

In 1952 Leonard Skeggs and his co-workers\textsuperscript{9}) were the first to isolate angiotensin from blood and followed by the identification of angiotensin I and II\textsuperscript{10}) in 1954, and described the angiotensin-converting enzyme (ACE). Skeggs et al, and Elliot and Peart almost simultaneously published the amino-acid sequence of the octapeptide angiotensin II\textsuperscript{11,12}). Skeggs' group\textsuperscript{13,14}) described the active part of angiotensinogen as a 14-amino-acid sequence in 1956 and 1957. Simpson and Trait\textsuperscript{15}) had presented a physiochemical method for the detection of a previously unidentified adrenal hormone, aldosterone, with this discovery the identification of the important components of the RAS was complete, exception of the discovery of prorenin by Lumbers\textsuperscript{16}) in 1971.

\textbf{Renin and the control of renin secretion}

Renin is late limiting in generation of the bioactive octapeptide angiotensin II. Angiotensinogen is primarily formed and constitutively secreted by hepatic cells into circulation. Circulating angiotensinogen is abundant, 1000 times as much as Ang I and Ang II.

Thus, renin activity determines the rate of Ang I formation. Control of renin is secured by a complex system of feedforward and feedback relationships\textsuperscript{17}). Prorenin is also secreted into the systemic circulation, accounting for 50–90\% of circulating renin. Prorenin is converted to active renin by a trypsin-like activating enzyme. Essential input for the setting of basal renin generation rates is provided by β-adrenergic receptors acting through cyclic adenosine monophosphate, the primary intracellular activation mechanism for renin mRNA generation. Other major control mechanism include COX-2 and nNOS affecting renin through PGE2, PGI2, and nitric oxide. Angiotensin II provides strong negative feedback inhibition of renin synthesis, largely an indirect effect mediated by baroreceptor and macular densa input. Adenosine appears to be a dominant factor in the inhibitory arms of the baroreceptor and macular densa mechanism.

The most important macroscopic control mechanism of renin release are BP (the renal baroreceptor mechanism), renal sympatetic tone through β-adrenergic receptors, and tubular NaCl concentration in the macular densa segment of the nephron (the macular densa mechanism).
Angiotensin II: It has been a widely accepted notion that the effect of angiotensin II on renin expression is the reflection of a direct interaction of the peptide with Junxtaglomerular (JG) cells. But increase in renin expression and JG cell hyperplasia were seen independent of whether JGA did or did not express AT1 receptors. At least part of the feedback effect of angiotensin II is baroreceptor mediated. Increased arterial blood pressure rather than any direct effect of angiotensin II may also be responsible for the inhibition of renin expression.

Renin secretion caused acutely by the furosemide, hydralazine, or isoproterenol.

Furosemide stimulates renin secretion through the macular densa and hydralazine through the baroreceptor.

Arachidonic acid increase and indomethacin reduced plasma renin. The effect of PGE2 are elicited by the activation of four types of G protein-coupled receptors (EP1–EP4). Basal plasma renin concentration was significantly lower in EP4-deficient than EP1–, EP2–, or EP3-deficient mice. Single PGE2 receptors have identified the Gsα-coupled EP4 as the most important receptor for stimulation of renin. Renin release in response to a high PGE2 concentration was increased in isolated perfused kidney of EP4−/− and EP2−/− mice, suggest that PGE2 acts through EP4 and EP2 to increase renin release. Prostacyclin is another prostaglandin with renin stimulatory properties. Chronic inhibition of COX-2 enzyme activity by inhibitors such as rofecoxib does not always produce the same inhibition of renin expression that is seen with genetic COX-2 deletion. A possible explanation for this dissociation may lie in the observation that pharmacological COX-2 inhibition is associated with a marked upregulation of renal COX-2 expression and partly compensate for enzyme blockade. One experimental observation is that inhibition or genetic deletion of COX-2 attenuates the stimulatory effect of Ang II blockade on renin expression. Thus, a reduction in Ang II signaling, probably at the level of the macular densa and/or TAL cells, appear to lessen tonic feedback inhibition of COX-2 and thereby enhance renin expression.

Nitric Oxide (NO): In nNOS-deficient mice, renin secretion markedly reduced. Upregulation of nNOS in AT1a/AT1b knockout mice was noted. The implication of these observation is that AGII inhibit nNOS expression in macular densa and vascular smooth muscle cells.
just as it inhibits COX-2 expression in the macular densa.

Cathecholamines: Adult β 1/β 2 adrenergic receptor-deficient mice have greatly reduced level of renin in plasma and renal tissue. Changes of renin release by furosemide, ACEI/ARB, or dietary salt intake occurred in the absence of β 1/β 2 adrenergic receptors, but the magnitude of the secretory response was markedly smaller. The response of renin release to an injection of isoproterenol was significantly reduced in mice deficient in either AC5 or AC6, suggesting that these Ca-inhibited adenyl cyclases are causal in the generation of cAMP that mediate the increase in renin secretion with β-adrenergic stimulation \(^{21}\).

Adenosine: Adenosine causes dose-dependent inhibition of renin secretion in isolated JG cells and kidney slices, indicating a direct inhibitory interaction of adenosine with JG cells. Studies with selective receptor agonists have established that the inhibitory effect is mediated by the A1 adenosine receptor subtype (A1AR). Examination of the stimulatory arm by furosemide showed maintenance of increased renin release in A1AR-deficient mice. Thus, activation of A1AR by adenosine contributes to the inhibition of renin secretion by increased perfusion pressure or increased NaCl at the macular densa, although the stimulatory arms of these regulatory pathways are largely A1AR independent.

**Renin and Prorenin Receptor**

The specific receptor for renin and for its inactive proenzyme form, prorenin, was cloned in 2002 and called for (pro)renin receptor (PRR) \(^{23}\). The (pro)renin receptor (PRR)-bound renin and prorenin display increased enzymatic activity, and activates intracellular signaling, upregulating the expression of profibrotic proteins. Native PRR undergoes intracellular processing to generate three molecular forms of PRR, a full-length integral transmembrane PRR, a soluble PRR, and a truncated form composed of the transmembrane and cytoplasmic domains associated with the V-ATPase. PRR is a multifunctional protein also involved in the control of intracellular and extracellular pH via its interaction with the V-ATPase, canonical Wnt/β-catenin and noncanonical Wnt/planar cell polarity pathway which are essential for adult and embryonic stem
cell biology, for embryonic development, and for disease such as cancer.

PRR activation may activate different intracellular signaling pathways, triggers the mitogen activated protein (MAP) kinases ERK1/2 phosphorylation, which in turn upregulates the expression of profibrotic genes such as TGF-β, plasminogen activator inhibitor type 1, collagen, and fibronectin\textsuperscript{24}.

**Angiotensin Converting Enzyme 2**

ACE2 is monocarboxypeptidase that degrades Ang II with high efficiency leading to the formation of angiotensin-(1-7). ACE2 has a more widespread distribution in mammalian tissue include the kidneys, testes, intestines, and heart. ACE2 within the kidney is largely localized in tubular and glomerular epithelial cells.

Degradation of Ang II is a complex process that involves pathways other than those driven by ACE and ACE2. ACE2 degrades Ang II leading to Ang-(1-7), this peptide degraded to Ang-(1-5) by the action of ACE. The primary role of ACE2 is converting Ang II into Ang-(1-7) with an efficacy >400-fold greater than that of the hydrolytic action of ACE2 in forming Ang-(1-9). Other pathways include aminopeptidase A, which cleaves Ang II to form Ang(2-8), known as Ang III. Aminopeptidase N can subsequently convert Ang-(2-8) to Ang IV. Ang II can also be degraded to Ang IV by the action of dipeptidylaminopeptidase I-II. Another pathways involves nephrilysin, endopeptidases, and carboxypeptidases. ACE2 changes in the same direction as ACE dose under physiological conditions. Under pathophysiological conditions, a disassociation between the activities of the enzymes may occur, leading to changes in opposite directions. Ang-(1-7) appears that under conditions of normal RAS activity, its role is limited however Ang-(1-7) may assume an important role in increased intrarenal RAS activity. Ang-(1-7) binds to Mas receptor and shows actions differnet from those of AT1-receptor stimulation, such as antiproliferation and increase in the bradykinin - nitric oxide systems\textsuperscript{25}). Much of the expected therapeutic benefit of ACE2 amplification stems from its ability to lower the levels of Ang II while concomitantly increasing the formation of ang-(1-7)\textsuperscript{26}).
Angiotensin II Receptor

AngII receptor belongs to the class of seven-transmembrane G-protein-coupled receptor. The effects of Ang II are mediated by binding to specific Ang II receptors; AT1 and AT2. Most of the Ang II actions are attributed to AT1 receptors. AT2 receptor is highly expressed in organ mesenchyme during fetal life and decreases dramatically after birth. It has been suggested that AT2-receptor activation counteracts AT1 receptor effects.

Action of Ang II

The main peptide of the RAS has several adverse effects including cell growth and apoptosis, fibroblastic proliferation, expression of proinflammatory endothelin-1 and extracellular matrix deposition, endothelial dysfunction, plaque rupture, vascular remodeling, and coagulation. These effects are mediated by AngII receptor type 1(AT1), as are Ang II–induced vasoconstriction and hypertrophy. By contrast, AT2–receptor exert a count–regulatory effect of AT1 and mediate antifibrotic, antihypertrophic, antiproliferative and anti–inflammatory effects27. Three enzymes capable of forming Ang II are ACE, chymase and cathepsin.

Two major systemic effects of AngII were vasoconstriction and sodium and water retention. Renal sodium and water reabsorption; This occurs by direct stimulation of Na+ reabsorption in the early proximal tubule and enhanced Na+ transport in the cortical collecting tubule by increased secretion of aldosterone. Proximal effects appear to result in part from activation of the Na+-H+ antiport in the luminal membrane. Ang II may be responsible for as much as 40–50% of Na+ and water reabsorption in the initial S1 segment of the proximal tubule. Vascular effects; In addition to direct action of AngII on vascular smooth muscle to be mediated by protein kinase C generation, enhanced sensitivity and facilitated release of norepinephrine, Ang II induces many vascular effects, including vasoconstriction, inflammation, vascular remodeling, thrombosis, and plaque rupture. Stimulation of oxidative stress mediates several effects of Ang II. Regulation of GFR; Ang II can effect renal blood flow and the GFR in part by the local generation of the thromboxane A2. Although both afferent and efferent arteriols are constricted, the efferent arteriolar has a
smaller basal diameter, as result, the increase in efferent resistance may be as much as three times greater as that at the afferent arteriole. The net effect is a reduction in RBF and an elevation in the hydraulic pressure in the glomerular capillary, which tends to maintain the GFR. Excessive renal vasoconstriction is minimized because Ang II also stimulates the release of vasodilator prostaglandins from the glomeruli. Ang II constricts the glomerular mesangium at higher concentrations, thereby lowering the surface area and sensitizes the afferent arteriole to the constricting signal of tubuloglomerular feedback.

In addition to physiological roles, Ang II induce inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation, regulate gene expression of bioactive substance, and activate multiple intracellular signaling pathways, all of which contribute to tissue injury.

AT1 receptor regulates the expression of profibrotic factors, such as TGF-β, CTGF. The Smad signaling pathway and the Rho/Rho kinase system are two novel mechanism involved in AngII–induced matrix regulation. Ang II via AT1 activates the Smad signaling system, independently of TGF-β, caused a rapid and direct activation of Smad2.

Ang II causes the adhesion of circulating cells to endothelial and mesangial cells, and the migration of inflammatory cells, mediated by upregulation of adhesion molecules, cytokines and chemokines. Ang II via AT1 receptors upregulates many proinflammatory genes, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), IL-6, and MCP-1, through the activation of several intracellular signaling systems, including the NF-κB, mitogen-activated protein kinase (MAPK) cascade, Rho proteins and redox pathways.

Local renin–angiotensin systems

Local Ang II production is important for the regulation of local processes. Activation of local RAS may be mediated by local factor such prostaglandins, nitric oxides, and endothelin. The proximal tubule contain ACE and Ang II receptors, suggesting that local Ang II formation can occur and stimulate Na+ reabsorption. Concentration of Ang II in peritubular capillary and proximal tubule is approximately 1000 times
higher than that in the systemic circulation\textsuperscript{29}. Ang II appears to be responsible for persistent renal vasoconstriction and sodium retention, even though the plasma levels of renin and Ang II are similar to those in hypertensives with normal renal perfusion. Local generation of Ang II also occur in vascular endothelium, where it may play an important role in the regulation of vascular tone and hypertension. Thus, the elevation in blood pressure in this low (plasma) renin form of hypertension was mediated by local renin release.

**Conclusion**

The pharmaceutical industry has produced an array of increasingly specific anti-RAS drug classes which curtail RAS activity at different points and therefore can add to each other in effectiveness. RSA is not completely elucidated, further studies are likely to uncover additional novel mechanism and therapeutic effectiveness.

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