Review

ISSN 1738-5997 (Print) • ISSN 2092-9935 (Online)
Electrolyte Blood Press 11:41-45, 2013
http://dx.doi.org/10.5049/EBP.2013.11.2.41

Recent Update of Renin-angiotensin-aldosterone System in the Pathogenesis of Hypertension

Ju-Young Moon, M.D.

Division of Nephrology, Department of Internal Medicine, KyungHee University, College of Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Korea

The activation of renin-angiotensin-aldosterine system (RAAS) is one of the main pathogenesis of hypertension. All the components of RAAS are present in the kidneys at higher concentrations compared to plasma levels, and intrarenal formation of angiotensin II (Ang II) is independent of the systemic RAAS. There are some unique features in intrarenal RAAS compared to systemic RAAS. Unlike JG cells where Ang II inhibits renin release via the AngII type 1 (AT1) receptor by negative feedback, in the collecting duct Ang II stimulates renin expression via the AT1 receptor. Upregulated renin produced in the distal nephron may be able to support continued intrarenal Ang II formation leading to amplification or maintenance of the hypertensive state.The recently discovered angiotensin-converting enzyme-related carboxypeptidase 2 (ACE2)-Angiotensin-(1-7) Ang-(1-7)] -Mas receptor axis has an opposing function to that of the ACE-Ang II-AT1 receptor axis.The ACE2 deficiency was associated with an increase in blood pressure, and ACE2 knockout mice have highlighted hypertensive response to Ang II infusion associated with exaggerated accumulation of Ang II in the kidney. Recently, several numbers of patients have been evaluated as the activators of ACE2-Ang-(1-7)-Mas receptor axis, which can be divided into two main classes: aimed to increase the activity of ACE2, and directed to stimulate the Ang-(1-7) receptor Mas. In order to investigate new targets for hypertension and kidney disease, further research on the function of the ACE-Ang-(1-7)-Mas receptor axis is required.

Key Words: Renin angiotensin aldosterone system, Hypertension, ACE2, Angiotnesin-(1-7)

Received: November 18, 2013
Accepted: December 19, 2013
Corresponding Author: Ju-Young Moon, M.D., Division of Nephrology, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong Sangil-dong 149, Gangdong-gu, Seoul, 134-727, Korea
Tel: +82-2-440-6262, Fax: +82-2440-8150
E-mail: jymoon@khu.ac.kr

Introduction

Hypertension is the most frequently treated disease, and can lead to cardiovascularand renal complications in patients who could not achieve their blood pressure goals. The activation of renin-angiotensin-aldosterine system (RAAS) is one of the established pathogenesis of hypertension, and blocking agents of renin, angiotensin converting enzyme (ACE), angiotensin II (Ang II) type 1 (AT1) receptor, and aldosterone of RAAS are useful medications in the clinical settings. However, there are some discrepancies between the expected results and the real clinical results and treatment responses in RAAS. Despite the diabetic nephropathy is a prototype disease of RAAS activation, that showed low serum renin levels compared to that of normal controls[1]. And, it has been hypothesized that complete inhibition of RAAS with direct renin inhibition and ACEI or ARB leads to the prevention of cardiovascular events. However, in the recently published aliskirentrial in type 2 diabetes mellitus using cardiorenal end points (ALTITUDE), aliskiren was associated with a trend toward higher composite cardiovascular events compared to placebo[2]. The recent discovery of ACE-related carboxypeptidase (ACE2), angiotensin 1-7 Ang-(1-7) and its receptor of Mas has changed the way in which

RAAS is viewed. Since they have been known to play an opposite function of ACE-Ang II-AT1 receptor axis, they are reevaluated to be an important pathogenesis and a treatment tool for hypertension. Here we review the difference between intrarenal RAAS and systemic RAAS, and the recent update of hypertension related ACE2-Ang-(1-7)-Mas receptor axis.

Intrarenal RAAS

The main source of systemic RAAS is liver angiotensinogen and is converted to Ang I by juxtaglomerular (JG) cell secreting renin. The Ang I is cleaved by ACE from lung and kidney to eight peptide of Ang II. It is known that the concentration of serum Ang II is 50-100 pmol/L. Ang II elevates blood pressure by activating symphathetic nerve activity and arteriolar vasoconstriction. Ang II increases sodium and water retention by tubular reabsorption, and is accelerated when aldosterone is secreted by the adrenal gland. Ang II stimulates anti-diuretic hormone secretion in the pituitary gland leading to increased water reabsorption in the collecting duct. Those systemic effects of Ang II increase water and sodium retention and the effective circulating volume result in increased perfusion to JG apparatus leading to decreased renin secretion by negative feedback.

The kidney contains all the elements of RAAS, and intrarenal formation of Ang II is independent of the circulating RAAS. The concentration of intrarenal Ang II is 3-5 nM and it has 50-100 times higher concentration compared to systemic Ang II[3]. Intrarenal angiotensinogen is produced mainly in the proximal tubule. In addition, renin is secreted from JG cells, connecting duct, and collecting duct, and ACE is generated from the proximal tubule to the collecting duct, it is also expressed well in the endothelial cell. The AT1 receptor is widely distributed among vascular, glomerular, and tubular elements of the kidney, consistent with this receptor's role in regulating renal hemodynamics, glomerular filtration, sodium reabsorption, and renin release. Urinary angiotensinogen is used as the marker of intrarenal RAAS activation because the molecular weight of angiotensinogen is 44KDa and cannot be filtrated by normal glomeruli[4]. However, recent reports demonstrated that liver angiotensinogen is highly expressed in the kidney when there is an abnormal increase in the permeability of the glomerular capillary wall to angiotensinogen, which characterizes proteinuric kidney diseases. Liver angiotensinogen is also an important source of the synthesis of renal AngII in the kidney angiotensinogen knock out animal model[5].

There are some unique features in intrarenal RAAS compared to systemic RAAS. First, renin is released from JG cells. It is highly regulated and is easily stimulated by slight changes such as, a decrease in renal perfusion pressure, a decrease in the delivery of Cl to the macula densa, or by sympathetic nerve stimulation. In addition to JG cells, renin mRNA and protein have been found in the connecting tubule and collecting duct. Unlike JG cells where Ang II inhibits renin released via the AT1 receptor, in the collecting duct Ang II stimulates renin expression via the AT1 receptor. It is a well-demonstrated phenomenon in the two kidney one clip animal model as a classic Ang II increase hypertension model. The JG cellular renin is increased clipped kidney in an early phase of the two kidney one clip model. After the acute stage, however, renin secretion is also increased in the collecting duct in non-clipped kidney. During periods of JG renin suppression, upregulated renin is produced in the distal nephron and it may be able to support continued intrarenal Ang II formation leading to amplification or maintenance of the hypertensive state[6]. Therefore, unlike ACEI or ARB treatment increases the renin expression in JG cell, decreases renin mRNA and protein levels in distal nephron. Second, proximal tubular production of angiotensinogen is activated by Ang II via AT1 receptor. Increased renal angiotensinogen is converted to Ang II by intrarenal renin and ACE, and intrarenal Ang II increases renal vasculature tone and tubular sodium reabsorption. Elevated reactive oxygen species (ROS) in hypertension or diabetes mellitus is known to produce oxidized form of angioten- sonogen. It was demonstrated recently that the oxidized angiotensinogen has a more potent capa-

bility to bind renin leading to readily undergo a transition to angiotensin release and increase blood pressure in pre-eclampsia, which is a serious hypertensive complication of pregnancy[7]. The third, increase of Ang II activates intrarenal ACE expression. The infusion of Ang II increases the proximal tubular secretion of ACE and ACE binding activity. The absence of kidney ACE reduces renal Ang II accumulation, sodium and water retention in response to Ang II infusion.

Recent update of RAAS in Hypertension (HTN)

ACE2 is a functional component of the RAS. ACE2 metabolizes Ang II and produces Ang-(1-7), thereby contributing to the regulation of blood pressure and progression of renal disease.

ACE2 is a type 1 integral membrane glycoprotein that is found in most tissues, with its highest expression observed in the kidneys, endothelium, and heart[8,9]. ACE2 is an exopeptidase that catalyzes the conversion of Ang I to the nonapeptideAng-(1-9) and the conversion of Ang II to the heptapeptideAng-(1-7). The primary role of ACE2 is to convert 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)[10]. ACE2 is associated with a reduction in Ang II and an increase in Ang-(1-7) levels. ACE2 protein levels are significantly decreased in the kidneys of hypertensive patients, and patients with late diabetic nephropathy[11,12]. The heptapeptide Ang-(1-7), generated from either Ang I or Ang II, acts by opposing the vasoconstrictor, proliferative, and profibrotic actions of Ang II in the circulation and in cardiac, vascular, and renal tissues[13,14]. Ang-(1-7) also binds to the Mas receptor, a seven transmembrane protein with domains containing sequences characteristic of G-protein coupled receptors. The Mas receptor is expressed in renal proximal tubular cells, afferent arterioles, cardiac myocytes, and neuronal cells. Therefore, this is a review of the recent update of ACE2-Ang-(1-7)-Mas receptor axis related hypertension.

1) Genetic study

The ACE polymorphism is one of the most frequently studied subjects to identify the association between pathogenesis of disease and genetic polymorphism. The DD allele of the ACE gene is highly associated with diabetic nephropathy, however, the effect of the D allele on hypertension was not noticeable because hypertension itself has multi-factorial pathogenesis[15]. However, ACE among RAAS component has the strongest association with hypertension after an adjustment for age, sex, and weight in genome wide association study (GWAS) of Korea and other countries[16]. A recent GWAS study of ACE2 polymorphism among Chinese and Caucacians reported significant associations in women with HTN or diastolic blood pressure[17]. In Korea, GWAS in Seongnam and Anseong cohort did not show significant associations between ACE2 single nucleotide polymorphism and hypertension.

2) Animal study

To evaluate the role of ACE2 in hypertension, various genetically manipulated animal models were developed for the ACE2 deletion or overexpression. In ACE2 knockout mice, circadian dipping is still preserved, suggesting that at least in the healthy state, dipping is not regulated by ACE2 but showed a mild increase in blood pressure. The increase of blood pressure is dependent on the background of the mice model. In the C57BL/6 background, ACE2 deficiency was associated with a modest increase in blood pressure, whereas the absence of ACE2 had no effect on baseline blood pressures in 129/SvEv mice[17]. Interestingly, ACE2 knockout mice have highlighted hypertensive responses to Ang II infusion associated with exaggerated accumulation of Ang II in the kidney. After acute Ang II infusion, an increase of plasma and kidney concentrations of Ang II was confirmed by MALDI-TOF mass spectrometry in ACE2-deficient mice than in controls. Although the absence of functional ACE2 causes enhanced susceptibility to Ang II-induced hypertension, there are few evidences that ACE2 plays a role in the regulation of cardiac structure or function. The transgenic ACE2 overexpression in spontaneous hypertensive rat (SHR) sho-

wed a reduction of mean arterial pressure irrespective of heart rate. This ACE2 overexpression model showed an increase of Ang-(1-7) in plasma and kidney, attenuated blood pressure elevation response to Ang II infusion. Ang-(1-7) has hypotensive action by vasodilatory effects through the release of bradykinin, prostaglandin, endothelium-dependent nitric oxide via Mas receptor[18]. The opposing actions of Ang-(1-7) on Ang II are not limited to the prevention of vasoconstriction. There are various actions in Ang-(1-7) such as anti-growth actions, natriuresis via inhibition of the renal tubular Na^+-K^+ ATPase pump, attenuate oxidative stress via inhibition of the NADPH oxidase.

3) Clinical approach of ACE2-Ang-(1-7)-Mas receptor axis

ACEI and ARB can partially affect the ACE2-Ang-(1-7) system. ACEI increases the production of Ang I, which is converted to Ang-(1-7) by ACE2, and endopeptidase. The antihypertensive actions of ACEI are obtained by increased excretion of Ang-(1-7), which was observed in urine samples of patients with essential hypertension whose blood pressure was controlled by 6 months of treatment with captopril[19]. It is well known that ACEI can reduce the urinary protein excretion in diabetes mellitus, however, in ACE2 knock-out mice disappear the antiproteinuric effect of ACEI. ARB may be particularly important because the increase in the concentration of Ang II will stimulate greater production of Ang-(1-7). In addition, the low affinity binding of Ang-(1-7) to the AT1 receptor may allow the peptide to act as an antagonist in the presence of Ang II.

The blockades of ACE-Ang II- AT1 receptor axis are well known pathways as the anti-hypertensive and antiproteinuric medication in clinic. Recently, some patients have been evaluated as the activators of ACE2-Ang-(1-7)-Mas receptor axis, which can be divided into two main classes: (1) aimed to increase the activity of ACE2, which will impact the system by increasing the inactivation of Ang II and (2) increasing the production of Ang-(1-7) and directed to stimulate the Ang-(1-7) receptor

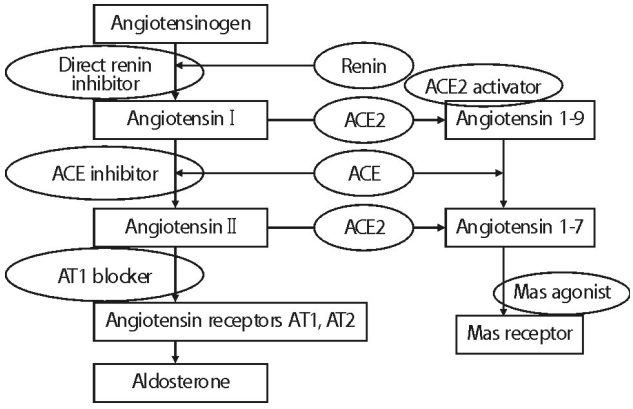

Fig. 1. Scheme of the renin-angiotensin-aldosterone system and the sites of the therapeutic interventions.

Mas (Fig. 1). In case of ACE2, small molecules have been developed which activate ACE2[20]. A leading compound ACE2 activator, XNT, reduces the blood pressure and improves cardiac function in SHR. Recombinant human ACE2 was also developed as an alternative approach to the therapeutic potential of ACE2. Treatment with rhACE2 attenuates diabetic nephropathy though a mechanism involving a reduction in Ang II and an increase in Ang-(1-7) signaling[21]. AVE 0991 was the first nonpeptide synthetic compound developed with the objective to stimulate the Ang-(1-7) receptor. This compound was orally active Mas agonist and mimics the effects of Ang-(1-7) in vessels, kidney, and heart. AVE0991 prevents end organ damage in SHR, induced by L-NAME treatment by preserving left ventricular contractility, preventing blood pressure elevation, and decreasing urinary protein excretion[22]. CGEN-856 and CGEN-857 are two novel peptides for the other activator of G protein coupled receptor, and were designed for having high specificity for Mas receptor[23].

Conclusion

Since the discovery of renin from renal extracts in 1898, the RAAS is still an interesting research field in hypertension, cardiovascular and kidney disease. The new findings of intrarenal RAAS activation without negative feedback via AT1 receptor may be able to support continued intrarenal Ang II formation leading to amplification or maintenance of the hypertensive state. The recent

discovery of ACE2 and Ang-(1-7) has modified the way in which the RAAS is viewed from a purely deleterious system in cardiovascular disease to an useful system to protect target organs. Targeting the ACE2-Ang-(1-7)-Mas receptor axis may be a novel therapeutic strategy for hypertension and kidney disease.

References

1. Price DA, Porter LE, Gordon M, et al.: The paradox of the low-renin state in diabetic nephropathy. J Am Soc Nephrol 10:2382-2391, 1999
2. Parving HH, Brenner BM, McMurray JJ, et al.: Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 367:2204-2213, 2012
3. Kobori H, Nangaku M, Navar LG, Nishiyama A: The intrarenalrenin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 59:251-287, 2007
4. Navar LG, Prieto MC, Satou R, Kobori H: Intrarenalangietensin II and its contribution to the genesis of chronic hypertension. Curr Opin Pharmacol 11:180-186, 2011
5. Matsusaka T, Niimura F, Shimizu A, et al.: Liver angiotensinogen is the primary source of renal angiotension II. J Am Soc Nephrol 23:1181-1189, 2012
6. Prieto-Carrasquero MC, Kobori H, Ozawa Y, et al.: AT1 receptor-mediated enhancement of collecting duct rennin in angiotensin II-dependent hypertensive rats. Am J Physiol Renal Physiol 289:F632-637, 2005
7. Zhou A, Carrell RW, Murphy MP, et al.: A redox switch in angiotensinogen modulates angiotensin release. Nature 468:108-111, 2010
8. Donoghue M, Hsieh F, Baronas E, et al.: A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 87: E1-9, 2000.
9. Tipnis SR, Hooper NM, Hyde R, et al.: A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 275:33238-33243, 2000
10. Vickers C, Hales P, Kaushik V, et al.: Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem 277:14838-14843, 2002
11. Crackower MA, Sarao R, Oudit GY, et al.: Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 417:822-828, 2002
12. Tikellis C, Johnston CI, Forbes JM, et al.: Characteriza tion of renal angiotensin-converting enzyme 2 in diabetic nephropathy. Hypertension 41:392-397, 2003
13. Gallagher PE, Chappell MC, Ferrario CM, Tallant EA: Distinct roles for ANG II and ANG-(1-7) in the regulation of angiotensin-converting enzyme 2 in rat astrocytes. Am J Physiol Cell Physiol 290:C420-426, 2006
14. Esteban V, Heringer-Walther S, Sterner-Kock A, et al.: Angiotensin-(1-7) and the g protein-coupled receptor MAS are key players in renal inflammation. PLoS One 4:e5406, 2009
15. Sayed-Tabatabaei FA, Oostra BA, Isaacs A, van Duijn CM, Witteman JC: ACE polymorphisms. Circ Res 98:1123-1133, 2006
16. Song SB, Jin HS, Hong KW, et al.: Association between renin-angiotensin-aldosterone system-related genes and blood pressure in a Korean population. Blood Press 20: 204-210, 2011
17. Burrell LM, Harrap SB, Velkoska E, Patel SK: The ACE2 gene: Its potential as a functional candidate for cardiovascular disease. Clin Sci 124:65-76, 2013
18. Rentzsch B, Todiras M, Iliescu R, et al.: Transgenic angiotensin-converting enzyme 2 overexpression in vessels of SHRSP rats reduces blood pressure and improves endothelial function. Hypertension 52:967-973, 2008
19. Luque M, Martin P, Martell N, et al.: Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. J Hypertens 14:799-805, 1996
20. Hernández Prada JA, Ferreira AJ, Katovich MJ, et al.: Structure-basedidentification of small-moleculeangiotensin-converting enzyme 2 activators as novel antihypertensiveagents. Hypertension 51:1312-1317, 2008
21. Oudit GY, Liu GC, Zhong J, et al. Human recombinant ACE2 reduces the progression of diabetic nephropathy. Diabetes 59:529-538, 2010
22. Wiemer G, Dobrucki LW, Louka FR, Malinski T, Heitsch H: AVE 0991, a nonpeptide mimic of the effect of angiotensin-(1-7) on the endothelium. Hypertension 40: 847-852, 2002
23. Shemesh R, Toporik A, Levine Z, et al.: Discovery and validation of novel peptideagonists for G-protein-coupled receptors. J Biol Chem 283:34643-34649, 2008