



Different Sides of Renin Angiotensin System

Renin Anjiyotensin Sisteminin Farklı Yönleri

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Abstract

The main physiological role of the renin angiotensin system (RAS) is to regulate blood pressure and water balance. It contains a group of related hormones that act together and called as angiotensins, receptors and enzymes. This system plays an important role in the pathology of many diseases. That is why the blockade or stimulation of the RAS components have important clinical applications. In this review we have tried to summarize the recent findings about RAS.

Key words: Renin angiotensin system (RAS), blood pressure, RAS blockade, RAS activation.

Özet

Renin anjiyotensin sisteminin (RAS) temel fizyolojik rolü kan basıncının ve su dengesinin düzenlenmesidir. Bu sistem bir grup ilgili ve beraber aktivasyon gösteren ve anjiyotensinler adını alan hormonlar, reseptörler ve enzimler içermektedir. Aynı zamanda RAS birçok hastalığın patolojisinde rol oynar. Bu nedenle de bu sistemin elemanlarının bloklanması veya stimülasyonu önemli klinik uygulamalara sahiptir. Bu derlemede RAS ile ilgili yeni buluşları özetlemeye çalıştık

Anahtar kelimeler: Renin anjiyotensin sistemi (RAS), kan basıncı, RAS bloklanması, RAS aktivasyonu.

History of Renin Angiotensin System

Renin had been investigated in 1898 by Finnish physiologists Tigerstedt and his student Bergman in Stockholm. They had observed that this substrate which was extracted from rabbit's kidney can elevate blood pressure. By this investigation the relationship between renin angiotensin system (RAS) and hypertension has been assembled a hundred years ago. Renin after its investigation had been remained unnoticed a period of over 40 years. This is because; partially related specialists about renin had failed to publish another study about this field. In 1934 Goldblatt had focused on an active substance secreted by kidney with his groundbreaking study about renal ischemia. The concept of milestones about kidney and

RAS had not been still clarified until 1950s when the molecular structure of AngII had been identified. The first clinical intervention about RAS has been made in 1970s and 1980s by developed inhibitors against to angiotensin converting enzyme (ACE). These drugs inhibit the conversion of angiotensin I (AngI) to Angiotensin II (AngII). After that in 1990s AngII receptor blockers (ARB), which are specific to AngII type 1 receptors (AT1R) had been investigated¹. Some principles have been taken under consideration for nomenclature components of this system to be able to standardize the RAS related studies. The sequence and number of amino acid has been accepted as a base for the naming of angiotensins².

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Article History / Makale Geçmişi:

Date Received / Geliş Tarihi: 15.01.2015
Date Accepted / Kabul Tarihi: 17.03.2015

Function of RAS

RAS has a fundamental role to regulate blood pressure and cardiovascular functions. Intervention to this system with the aim to regulate blood pressure and cardiovascular function constitute an important strategy. Renin digested angiotensinogen to AngI, which is a decapeptide. After that ACE converts AngI to AngII, which is an octapeptide. AngI can be occurred from AngII by other pathways except than ACE³.

The main classical physiological function of RAS is controlling of the extracellular fluid volume by its effect on sodium homeostasis. This system has several effects on brain, pituitary gland, heart, blood vessels, liver, kidney and adrenal gland to control blood pressure and water retention by cooperating with these organs^{4, 5}. The chronically activation of RAS leads to a wide spectrum of diseases such as hypertension, chronic renal disease, atherosclerosis, diabetes, heart failure, and also stroke⁶.

Tissue Specific RAS

According to traditional RAS definition, all components of the system are produced in specific tissues. For example angiotensinogen, renin and ACE are produced by liver, kidney and lung, respectively. On the other hand, recent studies have showed that local (tissue specific) RAS exists. The emergence of this new vision about RAS was held by the presence of its components in unusual places. For example it has been shown that renin, which is known as a kidney enzyme, is also present in the brain. Brain RAS has various effects such as regulation of blood pressure, water and also food intake, blood-brain barrier repair, regulation of reproduction, stimulation of transcription and translation. Tissue specific

RAS regulates tissue AngII concentration independent from circulating RAS. That is why it is believed that tissue specific RAS shows its effect independent—from circulating RAS activity. This system, which shows otocrine and paracrine properties, plays a critical role for hypertrophy and hypertension related organ pathologies. It has been suggested that description of this system by a new approach can help us for better understanding of electrolyte-fluid balance control, blood pressure and tissue homeostasis^{5, 7}.

Renin: A key enzyme for RAS

Renin is a glycoprotein structured enzyme which consists of 340 amino acids. It is a substance, which takes place in the first step of the RAS, catalyzes the rate limiting step. Renin activates system by converting angiotensinogen to AngI^{8,9}. Renin is generated as pre-renin protein and enters Golgi apparatus in the cell. Prorenin is secreted outside of the cell as an active form of renin which is converted in Golgi apparatus after various effects or inactive form of renin. The portion of active renin form is about one-fourth of the total renin. Conversion of prorenin to renin occurs mainly in the kidney. This event happens before the release of renin from the juxtaglomerular cells. Prorenin constitutes about 80-90% of circulating level of renin when extrarenal sources are taken into account. There is a 43 amino acids length prosegment which blocks active binding site of enzyme at N terminal of prorenin. This prosegment prevents angiotensinogen to reach active site of renin and form AngI. The interaction of circulating renin with renin receptors which exist in tissues can be a cause of its activation by proteolytic or non-proteolytic ways and hence the local formation of angiotensin. Basically releasing of active

renin is provided by the juxtaglomerular epithelioid cells. More active renin is secreted when stimulation of renin secretion is acute. If its secretion is induced chronically, both active renin and prorenin secretion occurs. On the other hand, chronic stimulation of RAS increases the conversion of prorenin to renin. Existing amount of the renin granules in the afferent arteriols or the volume of juxtaglomerular cells varies depending on salt or pharmacological effects. It has been observed that the number of juxtaglomerular cells and the number of renin granules for per afferent arteriolar is increased after low sodium diet or enalapril treatment. cAMP, cGMP and the amount of cytosolic free Ca^{++} are the most important intracellular signaling pathways that control the release of the renin. The most critical way is cAMP in terms of the renin secretion. The amount of cytosolic free Ca^{++} has inhibitory effect on secretion of renin contrary to expectations. This situation is called as "calcium paradox in renin release". The electrical properties of renin secreting juxtaglomerular cells and also the intercellular interaction mechanisms have importance for renin secretion¹⁰. We believe that clarification of many other intracellular mechanisms which control renin secretion will help for better understanding the role of renin in physiological and pathophysiological processes.

(Pro)renin Receptor

Although the presence of renin and prorenin binding proteins are known for a long time, specific renin/prorenin receptors were cloned in 2002 for the first time. These receptors that are called as (pro)renin receptors are found at high levels in heart, brain and placenta and at low level levels in kidney, pancreas and liver. (Pro)renin receptors play an important role in

local AngII production and cellular response to renin. By identification of the (pro)renin receptors, it has been clarified that renin shows direct cellular effect by binding to the (pro)renin receptor. Binding of renin to (pro)renin receptor may cause increased tissue fibrosis and cellular hypertrophy by activating cellular signaling pathways. The presence of these receptors is the evidence of that renin and prorenin may have direct physiological effects^{7,11}. The location of the prosegment changes when prorenin binds to its receptor. Thus, prorenin is active when it is bound to its receptor and is capable to form AngI. Prosegment is involved in the active zone of the enzyme and inhibits the binding of (pro)renin to angiotensinogen¹². Renin, which can bind to the (pro)renin receptor, provides four times more AngI production compared to the free renin in circulation. It is believed that if the importance of (pro)renin receptor in the development of renal disease in patients with cardiovascular disease and diabetes is taken into account, the drugs that inhibit both direct and indirect effects of the renin system can provide more effective treatment^{13,14}.

Function of Angiotensin Converting Enzyme 2 (ACE2)

In 2000, about 50 years later after the discovery of ACE, ACE2 which is a homologous of human ACE was found by the use of genomic techniques. The complete DNA of ACE2 codes 805 amino acids. ACE2 is a metallopeptidase, which has a molecular weight of 120 kDa. The specificity of ACE2 is not only against the peptides of RAS. ACE2 has also a high catalytic activity on the vasoactive peptides from other systems such as apelin-36 and apelin-13, quinine metabolites, neurotensin, opioid peptides as

well as its role in the formation of Ang 1-7⁵. Apelin-13 and apelin-36 are vasoactive substances and ligands of G protein related apelin receptor (APJ), which is a homologous of AT1R. Studies have shown that these hormones are physiological substrates of ACE2 enzyme. ACE2 can also hydrolyze these hormones by the same degree of its efficiency in hydrolysing AngII. This is regarded as an indicator of that ACE2 can be effective at other peptidergic systems. Apelin/APJ gene expressions change in a variety of clinical situations such as heart failure and atherosclerosis. The similar effect that ACE2 shows on AngII and apelin may suggest that these two pathways may have potential relationships. It is thought that important clinical benefits can be obtained by controlling and revealing the possible interactions between two systems¹⁵⁻¹⁸.

Function of Angiotensin II

AngII is the main effective peptide and provides the formation of the effects of RAS on tissues. AngII is a strong systemic vasoconstrictor agent. It forms an inflammatory response in vascular smooth muscle cells and has a relationship with atherosclerosis. AngII has a broad spectrum of target tissues such as adrenals, kidneys, brain, pituitary gland, vascular smooth muscles, and the sympathetic nervous system. Angiotensin is a hormone that is found not only in circulation but also it is produced in tissues such as brain, heart, kidney and blood vessels. Thus, AngII acts as a paracrine and also an autocrine hormone. It has undertaken important tasks which control proliferation and extracellular matrix formation in cell growth¹⁹. AngII is rapidly converted to AngIII, Ang 1-7, Ang IV and Ang 3-8 by peptidases that are generally called as

angiotensinase and are involved in the circulation or in tissues. From these angiotensins the effects of AngIII and Ang1-7 are better understood and the physiological roles of others are not fully explained⁵.

Receptors of Angiotensin II

Like the other peptide hormones AngII acts through receptors located in the plasma membranes of target cells. Two different receptor subtypes have been described for AngII as AT1 and AT2 by studies since 1980. Although subsequent studies have shown the presence of AT3 and AT4 receptors, the knowledge about the functions of these receptors is limited due to the insufficiencies in the cloning studies²⁰. The role of AngII in the regulation of cardiovascular hemodynamics has been proven strongly. AngII shows most of its effect on cardiovascular system (CVS) through AT1R but the contribution of the AT2R is not much known. AT1 and AT2 receptors have opposite effects on cell growth and regulation of blood pressure. While the dominant effects of RAS activation such as vascular hypertrophy, vasoconstriction, and hypertension development with the involvement of water and salt occur via the AT1R; other AngII dependent effects such as cell death, vasodilatation, and natriuresis occur via the AT2R²¹. It has been shown by the studies that increased AngII as a result of the blocking of the AT1R stimulates the AT2R and thus antagonistic effects can occur. It is known that AT2R increases the apoptosis, which is defined as the programmed cell death, in the remodeling of the CVS²². It has been shown that the signaling mechanism of AT2R is related with G protein. The activation of AT1R mediated mitogen-activated protein kinase (MAPK) is inactivated by the activation of the

AT2R. This effect describes the negative chronotropic effect of AT2R. AT2R induces apoptosis by performing the dephosphorylation and inactivation of Bcl-2, which is a MAPK and an intracellular protein, via activation of ERK phosphatase. The activation of AT2R leads to an increase in the amounts of bradykinin, NO and cGMP, which have vasodilator properties. The activation of AT2R activates the bradykinin (BK) B2 receptor. The activation of this receptor stimulates phosphorylation of nitric oxide synthase (NOS) from serine residues on a protein kinase A (PKA) dependent manner. This enzyme is activated as a result of the phosphorylation of NOS enzyme. This leads to activation of dissolved guanylate cyclase (sGC) thereby transformation of GTP to cGMP. cGMP plays a role in the vasodilatation. This explains the vasodilatory effects of the AT2R. Especially, its effect is observed on vascular structure and kidney tissue. In some cases, AT2R shows its effect through Gi proteins. This signaling mechanism provides delayed-type K⁺ channel activation in neurons and probably in other tissues. The activation of this receptor leads to the activation of phosphotyrosine phosphatase. This event shows adverse effect to the growth by rapidly inhibiting the uncontrolled proliferation of normal tissues. Additionally, it has been shown that T-type Ca⁺⁺ channels were closed by activation of AT2 receptors^{20, 21, 36}. The useful effects of AT1R antagonists are not completely mediated by the AT1R. Several studies suggest that useful effects of AT1R blockage are removed by AT2R antagonists. This has brought about the need for further studies and definitions about AT2 receptors in treatment strategies for hypertension and CVS patients. There are studies showing that the useful effects obtained by the inhibition of AT1R activity are

increased by increased AT2R activity. In order to support the idea that AT1R activity is associated with AT2R activity and to explain the physiological effects of RAS thoroughly needs further studies about AT2R²¹. Non-AT1 and non-AT2 receptors, elements of the brain angiotensin system, have been known, but have still not been explained in functional terms²³. One of study provides evidence for the existence of angiotensin-binding non-AT1 and non-AT2 receptors primarily on the outer surfaces of nerve cell membranes. In the same study it has been shown for the first time that new angiotensin binding sites are functional in neuronal death. The activities of these receptors are affected by extracellular redox status in the brain which means also angiotensin binding activities of these receptors increase in proportion to the increase in oxidative stress. However, the details of the possible mechanism to explain direct functionality and effect of these receptors on neuronal death have not been elucidated yet²⁴.

Other Mediators of RAS

Although the main mediator of RAS is AngII, AngIII (A 2-8), AngIV (A 3-8) and Ang1-7 which are originating from angiotensinogen (A0) also play a role. AngIII and AngIV are generated from AngII by the effect of aminopeptidases. Ang1-7 is produced by the effects of neutral endopeptidases, NEP 24.11, NEP 24.15 and NEP 24.26, which are also known as tissue endopeptidases on AngI²⁵. Several researchers have indicated that there is a regulatory pathway in RAS. In this pathway, Ang1-7 is produced from AngI or AngII as a result of the catalytic activity of ACE2. Ang1-7 has different effects from AT1R activation such as activation of vasodilation, natriuresis, anti-proliferation and bradykinin-NO system.

Functions of this pathway occur in opposite way to ACE/AngII/AT1 receptor pathway. However, ACE2/Ang1-7 pathway has not been explained clearly yet. G protein-coupled Mas receptor is the functional receptor of Ang1-7 and the molecular basis for the physiological effects of this biologically active heptapeptide. On the other hand, there is still no clear evidence for Mas-mediated intracellular signaling. It is supposed that many factors including protein kinase C and inhibition of MAPK occur in this pathway. Ang1-7 acts as the antagonist of AT1R. Further studies on this pathway may provide more explanatory information. It may nevertheless be said that this new pathway is expected to be an important factor in the treatment of cardiovascular and metabolic diseases. Studies have already shown that Ang1-7 has useful effects in cases such as cardiac contraction and coronary perfusion. Furthermore, it is reported that Ang1-7 injection reduced the development of heart failure after myocardial infarction (MI). This offers us a novel clinical use of this new angiotensin. It is accepted that the total effect of RAS is based on the balance between ACE and ACE2 activities. In this respect, ACE/AngII/AT1 receptor pathway assumes the role of “devil” and ACE2/Ang1-7/Mas pathway the role of 2 “angel”^{7, 26, 27}. What is probably most striking about Ang1-7 is its effect on long-term potentiation (LTP) related to learning and memory. Ang1-7 particularly enhances LTP by increasing the level of NO. A study has shown for the first time that Ang1-7’s effect of increasing NO level particularly in lateral amygdala is mediated by COX-2. This shows us the existence of a molecular relationship between COX-2 and NO, which regulates the neuronal plasticity^{28, 29}. The anti-proliferative

and anti-angiogenic effects of Ang1-7 inhibit the progress of cancer. It is supposed that Ang1-7’s anti-proliferative and anti-angiogenic effects are due to COX-2 inhibition, direct ERK-1 and ERK-2 inhibition, MAPK inhibition that phosphorylates ERK-1 and ERK-2 or MAPK kinase inhibition that activates MAPK. Alternatively, it is thought that Ang1-7 shows anti-proliferative and anti-angiogenic effects by activating MAPK phosphatase. Experimental studies provide in vitro and in vivo results related to the Ang1-7’s effect of preventing lung and breast cancer. That is why Ang1-7 has been used in clinical research as a potential chemotherapy drug^{28, 30}. Nagata et al. found another new angiotensin peptide. This peptide, a dodecapeptide, is named Ang1-12 (28, 31). Ang1-12 may be a precursor of bioactive angiotensin peptides in kidneys, in circulation or dependent on the localization of enzymes that transform it²⁸. In brain, the amount of Ang1-12 is more than the amount of AngI and AngII. Ang1-12 regulates the heart rate in nucleus tractus solitarius by means of AT1 receptors. However, it gains activity under hypertensive conditions in order to produce this effect³². Studies on cell culture reveal that ACE2 has the receptor for coronavirus (Sars-CoV), related to acute respiratory syndrome. There had been ongoing studies on the development of vaccination for inactivating ACE2/Sars-CoV interaction. Sars-CoV infection reduces ACE2 concentration. This causes the acute respiratory syndrome which is resulting from the infection remain worse. Studies conducted with ACE2 knock-out subjects provide evidence for the preventive effects of ACE2 for acute respiratory syndrome. The preventive effect results from the change in AngII concentration dependent on ACE/ACE2 ratio. The increase in the

amount of ACE shifts RAS towards generation of AngII, and this active peptide results in the development of acute respiratory syndrome caused by various pulmonary damages. Otherwise, Ang1-7 assumes the active peptide role of RAS and causes effects that are opposite to the effects of Ang II. Furthermore, the existence of ACE2 gene in the community polymorphically alters the rate of being affected by Sars-CoV among individuals^{7,33,34,37}.

Conclusion

RAS presents different mechanisms to sustain physiological homeostasis for vital survival. These mechanisms include several components and each of them has cross talks with other components in same system as well as other physiological processes elements. We suppose that if RAS components are recognized well it can provide easy intervention to RAS for especially diseases conditions. For this purpose, in this review, we tried to summarize literature about RAS components.

Conflict of interest

The authors report no conflict of interest.

References

- Jensen C, Herold P, Brunner HR. Aliskiren: the first renin inhibitor for clinical treatment. *Nat Rev Drug Discov.* 2008; 7(5):399-410.
- Members of the Nomenclature Committee of the International Society of Hypertension: Bangham DR, Boucher R, Bumpus FM, et al. Nomenclature of the renin-angiotensin system. Report of the nomenclature Committee of the International Society of Hypertension. *Hypertension.* 1979; 1(6): 654-6.
- Azizi M. Renin inhibition. *Curr Opin Nephrol Hypertens.* 2006;15(5):505-10.
- Goodfriend TL. Angiotensin receptors: history and mysteries. *Am J Hypertens.* 2000;13(4 Pt 1):442-9.
- Der Sarkissian S, Huentelman MJ, Stewart J, Katovich MJ, Raizada MK. ACE2: A novel therapeutic target for cardiovascular diseases. *Prog Biophys Mol Biol.* 2006;91(1-2):163-8.
- Weber MA, Giles TD. Inhibiting the renin-angiotensin system to prevent cardiovascular diseases: do we need a more comprehensive strategy? *Rev Cardiovasc Med* 2006;7(2):45-54.
- Paul M, Poyan Mehr A, Kreutz R. Physiology of Local Renin-Angiotensin Systems. *Physiol Rev.* 2006;86(3): 747-803.
- Maibaum J, Feldman DL. Renin inhibitors as novel treatments for cardiovascular disease. *Expert Opin Ther Patents.* 2003;13:589-603.
- Griendling KK, Murphy TJ, Alexander RW. Molecular biology of the renin-angiotensin system. *Circulation* 1993;87(6):1816-28.
- Schweda F, Friis U, Wagner C, Skott O, Kurtz A. Renin release. *Physiology (Bethesda).* 2007;22:310-9.
- Nguyen G, Delarue F, Burcklé C, Bouzahir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest.* 2002;109(11):1417-27.
- Nguyen G, Contrepas A. Physiology and pharmacology of the (pro)renin receptor. *Current Opinion in Pharmacology.* 2008;8(2):127-32.
- Danser AH, Deinum J. Renin, prorenin and the putative (pro)renin receptor. *Hypertension* 2005;46(5): 1069-76.
- Ichihara A, Suzuki F, Nakagawa T, et al. Prorenin receptor blockade inhibits development of glomerulosclerosis in diabetic angiotensin II type 1a receptor-deficient mice. *J Am Soc Nephrol.* 2006;17(7):1950-61.
- Vickers C, Hales P, Kaushik V, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. *J Biol Chem.* 2002;26;277(17):14838-43.
- Warner FJ, Smith AI, Hooper NM, Turner AJ. Angiotensin-converting enzyme-2: a molecular and cellular perspective. *Cell Mol Life Sci* 2004;61(21):2704-13.
- Hosoya M, Kawamata Y, Fukusumi S, et al. Molecular and functional characteristics of APJ. Tissue distribution of mRNA and interaction with the endogenous ligand apelin. *J Biol Chem.* 2000;275(28): 21061-7.
- Kalea AZ, Battle D. Apelin and ACE2 in cardiovascular disease. *Curr Opin Investig Drugs.* 2010;11(3):273-82.
- Wright JW, Krebs LT, Stobb JW, Harding JW. The Angiotensin IV system: Functional implications. *Front*

- Neuroendocrinol. 1995;16(1):23-52.
20. Gasparo MD, Catt KJ, Inagami T, Wright JW, Unger T. International union of pharmacology. XXIII. The Angiotensin II receptors. *Pharmacol Rev.* 2000;52(3):415-72.
 21. Berry C, Touyz R, Dominiczak AF, Webb RC, Johns DG. Angiotensin receptors: signaling, vascular pathophysiology, and interactions with ceramide. *Am J Physiol Heart Circ Physiol.* 2001;281(6):2337-65.
 22. Tan NY, Li JM, Stocker R, Khachigian LM. Angiotensin II-inducible smooth muscle cell apoptosis involves the angiotensin II type 2 receptor, GATA-6 activation, and FasL-Fas engagement. *Circ Res.* 2009;105(5):422-30.
 23. Karamyan VT, Stockmeier CA, Speth RC. Human brain contains a novel non-AT1, non-AT2 binding site for active angiotensin peptides. *Life Sci.* 2008;83(11-12):421-5.
 24. Rashid M, Arumugam TV, Karamyan VT. Association of the novel, non-AT1, non-AT2 angiotensin binding site with neuronal cell death. *J Pharmacol Exp Ther.* 2010;335(3):754-61.
 25. Touyz RM, Schiffrin EL. Signal Transduction Mechanisms Mediating the Physiological and Pathophysiological Actions of Angiotensin II in Vascular Smooth Muscle Cells. *Pharmacol Rev* 2000;52(4): 639-72.
 26. Iwai M, Horiuchi M. Devil and angel in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis vs. ACE2-angiotensin-(1-7)-Mas receptor axis. *Hypertens Res.* 2009;32(7):533-6.
 27. Santos RA, Simoes e Silva AC, Maric C, et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl Acad Sci U S A.* 2003;100(14): 8258-63.
 28. Varagic J, Trask AJ, Jessup JA, Chappell MC, Ferrario CM. New angiotensins. *J Mol Med.* 2008;86(6):663-71.
 29. Hellner K, Walther T, Schubert M, Albrecht D. Angiotensin-(1-7) enhances LTP in the hippocampus through the G-protein-coupled receptor Mas. *Mol Cell Neurosci.* 2005;29(3):427-35.
 30. Menon J, Soto-Pantoja DR, Callahan MF, et al. Angiotensin-(1-7) inhibits growth of human lung adenocarcinoma xenografts in nude mice through a reduction in cyclooxygenase-2. *Cancer Res.* 2007;67(6):2809-15.
 31. Nagata S, Kato J, Sasaki K, Minamino N, Eto T, Kitamura K. Isolation and identification of proangiotensin-12, a possible component of the renin-angiotensin system. *Biochem Biophys Res Commun.* 2006;350(4):1026-31.
 32. Arnold AC, Isa K, Shaltout HA, et al. Angiotensin-(1-12) requires angiotensin converting enzyme and AT1 receptors for cardiovascular actions within the solitary tract nucleus. *Am J Physiol Heart Circ Physiol.* 2010;299(3):763-71.
 33. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV — a target for vaccine and therapeutic development. *Nat Rev Microbiol.* 2009;7(3):226-36.
 34. Nicholls J, Peiris M. Good ACE, bad ACE do battle in lung injury, SARS. *Nat Med.* 2005;11(8):821-2.
 35. Carey RM, Park J. Role of angiotensin type 2 receptors in vasodilation of resistance and capacitance vessels. *Hypertension.* 2006;48(5):824-5.
 36. Albrecht D. Angiotensin-(1-7)-induced plasticity changes in the lateral amygdala are mediated by COX-2 and NO. *Learn Mem.* 2007;14(3):177-84
 37. Imai Y, Kuba K, Penninger JM. Angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Cell Mol Life Sci.* 2007;64(15):2006-12.