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New Components of the Renin-Angiotensin-Aldosterone System and Oxidative Stress

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Abstract

Hypertension is a major risk factor of cardiovascular diseases (CVDs), and a most important health problem in developed countries. The rennin-angiotensin-aldosterone system (RAAS) plays a pivotal role in controlling blood pressure or hydro-electrolyte balance. Superoxide production by angiotensin Ⅱ (Ang Ⅱ) of the classical RAAS pathway is one of the important mechanisms in pathogenesis of CVDs. But in the past decade, many new components of RAAS, such as novel axis consisting of the angiotensin-converting enzyme 2 (ACE2), angiotensin (1-7) (Ang-(1-7)), and the G protein-coupled receptor Mas, has emerged and complicated classical concept of RAAS and pathophysiology of CVDs. In this review we will summarize the recent findings about these new components of RAAS mainly from the viewpoint of molecular mechanism and oxidative stress.

Keywords: Renin-Angiotensin-Aldosterone system; Oxidative stress; ACE2/ Ang-(1-7)/ Mas axis; Ang A/ Alamandine/MrgD axis; Ang-(1-12); AngⅢ/ AngⅣ/ AT_4/ IRAP Axis; (Pro)renin receptor (PRR); Clinical implication

Introduction

Hypertension is a common but one of the most important health problems, because it is a major risk factor for many CVDs. So it is very important to prevent, diagnose early and treat hypertension and its complications. Renin-angiotensin-aldosterone system (RAAS) has been reported to be associated with hypertension and target organ damage for a long time [1]. RAAS, not only in the systemic circulation but also in the local organs and tissues, has also been shown to play a crucial role in the pathogenesis of hypertension and CVDs [2-4]. And there are lots of evidences that inhibitors of ACE (ACEI) and antagonists of Ang Ⅱ (ARBs) are effective for the treatment of hypertension and related CVDs [5].

Interaction of Ang Ⅱ with its receptors, AT1 and AT2, plays the central role in the expressions of various biological functions of RAAS in kidney, heart, endothelium, brain and other tissues, However, multifunctional new components of RAAS have been identified such as various fragments of angiotensin peptides, enzymes forming these angiotensin peptides, and receptors of these peptides. These include Ang-(1-7), alamandin, Ang A, Ang-(1-12), AngⅢ, AngⅣ, and Ang-(1-9) as angiotensin peptides, and Mas (receptor for Ang-(1-7)), MrgD (receptor for alamandin), AT_4/IRAP (receptor for Ang Ⅳ) (pro)renin recptor (PRR, receptor for prorenin and renin) as receptors, and ACE2 and many other enzymes.

One of the important mechanisms of hypertension or CVDs caused by activated RAAS is increased oxidative stress by Ang Ⅱ through AT_1 receptor. Inhibition of RAAS by ACEI or ARB is reported to be associated with reduced free radical concentrations in the clinical setting [6]. But the reports on the alteration in oxidative stress level brought by these new components of RAAS are rare. In this review, outlines of the these new components of RAAS and recent findings on their effect on oxidative stress will be discussed.

Renin-angiotensin-aldosterone system with new components (Figure 1) and oxidative stress

ACE/ Ang Ⅱ / AT_1 axis: Ang Ⅱ is the major bioactive component of this classical axis in the RAAS. It is an octapeptide produced following the removal of C-terminal of Ang Ⅰ, a decapeptide produced by the cleavage of the N-terminal of angiotensinogen by renin. Carboxypeptidase ACE removes C-terminal dipeptide, His-Leu from Ang Ⅰ, but this process can be done by other enzymes other than ACE such as chymase, cathepsin G, tonin, and others [7], so these enzymes can produce Ang Ⅱ even under inhibition of ACE by ACEI. Ang Ⅱ exerts a potent biological effects such as blood pressure elevation by vasoconstriction, sodium retention, aldosterone release from adrenal gland, hypertrophy, proliferation, fibrosis, and increased oxidative stress by biding to AT_1 receptor [8]. On the other hand, Ang Ⅱ exerts a protective effects such as vasodilation, antihypertrophy, antiproliferation, antifibrosis, and NO release by biding to AT_2 receptor [9].

Oxidative stress has been shown to be involved in the pathogenesis of human essential hypertension, because hydrogen peroxide or superoxide anion are reported to be elevated in the plasma of those patients [10-14]. Griendling et al. reported that superoxide anion was produced NAD(P)H oxidase-dependently from the cultured smooth muscle cells from the animal model of hypertension by Ang Ⅱ administration [15].

Reactive oxygen species (ROS) production by Ang Ⅱ through AT_1 receptor is caused mainly by NAD(P)H oxidase, which is composed of $p22^{phox}$, $gp91^{phox}$ (Nox2), components of cell membrane, intracellular $p47^{phox}$, $p40^{phox}$, $p67^{phox}$, and small G protein Rac. And biphasic Ang Ⅱ -

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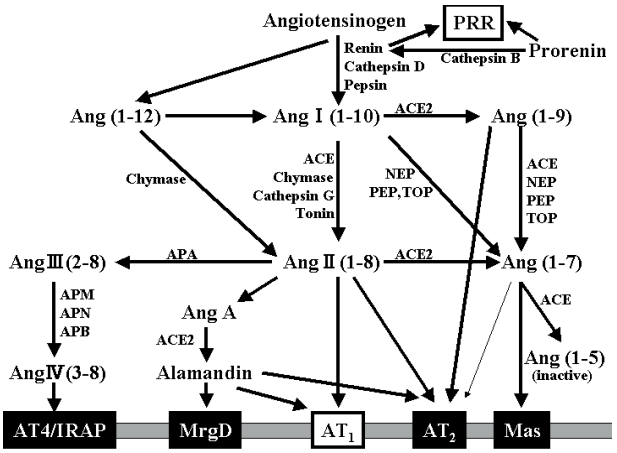

Figure 1: Outline of rennin-angiotensin-aldosterone system with new components. PRR: (pro) rennin receptor. Ang: angiotensin. ACE: angiotensin converting enzyme. NEP: neutral endopeptidase. PEP: prolyl endopeptidase. APA: aminopeptidase A. APM: aminopeptidase M. APN: aminopeptidase N. APB: aminopeptidase B. AT_1: angiotensin Ⅱ type 1 receptor. AT_2: angiotensin Ⅱ type 2 receptor. AT_4: angiotensin Ⅱ type 4 receptor. IRAP: insulin-regulated aminopeptidase. MrgD: Mas-related G-protein coupled receptor D. Mas: Ang-(1-7) receptor Mas. TOP: thimet oligopeptidase. Black rectangles are protective receptors

stimulated ROS production is reported, first phase involves protein kinase C (PKC), and second phase involves Rac, Phosphatidylinositol-3'-kinase (PI_3K), c-Src kinase and epidermal growth factor (EGF) [16]. RhoA/Rho-kinase activation by increased NAD(P)H oxidase-dependent ROS are also reported, leading to vascular smooth muscle contraction [17]. Involvement of the glutathionylation-dependent uncoupling of endothelial nitric oxide synthase (eNOS) is also reported [18]. Pharmacological intervention to oxidtive stress or RAAS are also reported. Glutathione (GSH) depletion by GSH synthase inhibitor buthionine sulfoximine (BSO) on Sprague-Dawley rats caused a marked elevation in blood pressure, and a significant reduction in the urinary excretion of the NO metabolite nitrate plus nitrite, which suggests depressed NO availability [19]. Treatment of human vascular endothelial cells (HVEC) with ARB, Losrtan, or ACEI, Lisinopril, both reduced Ang Ⅱ-stimulated superoxide anion production [20]. Telmisartan, another ARB, has been also reported to have reduced atherosclerotic lesion size, superoxide anion production, and NAD(P)H oxidase activity of aorta from ApoE KO mice [21].

On the contrary, activation of AT_2 receptor has shown to cause protective effects by antioxidant mechanism. Inhibition of AT_2 receptor resulted in superoxide anion production in human umbilical vein endothelial cells (HUVEC), and this effect involved src homology 2 domain containing inositol phosphatases (SHP-1) activation by AT_2 receptor [22]. Involvement of c-Src tyrosine kinase in SHP-1 phosphatase activation by AT_2 receptors in rat fetal tissues has been reported [23]. Increased NAD(P)H oxidase activity, $p47^{phox}$, and plaque area were reported in the aorta of double knock out mice of ApoE and AT_2 receptor [24]. Authors are speculating that AT_2 receptor stimulation antagonizes AT_1 receptor-mediated NAD(P)H oxidase activation, that is phosphorylation of $p47^{phox}$ and translocation of Rac1 to the plasma membrane, activation and translocation of NAD(P)H oxidase subunits. And authors are also suggesting AT_2 receptor-mediated inhibitory effect on oxidative stress were caused through inhibition of Akt activation brought by AT_1 receptor activation, which is a prerequisite for the AT_2 receptor to exert its inhibitory effect on NAD(P)H oxidase activation.

Another interesting mechanism of controlling oxidative stress is internalization of AT_1 receptor. Angiotensin Ⅱ type 1 receptor-associated protein (ATRAP) is reported to mediate this phenomenone. Overexprssion of ATRAP causes reduction in NAD(P)H oxidase activity [25].

ACE2/ Ang-(1-7)/ Mas axis: The most important peptide in this axis, Ang-(1-7), is produced after removing C-terminal phenylalanine from Ang Ⅱ by membrane-associated zinc metaloprotease ACE2, which is expressed in endothelial cells of coronary arteries, aorta, carotid artery, renal and mesenteric arteries and other tissues [26,27]. Less Ang-(1-7) is produced from Ang-(1-9) by ACE and other alternative enzymes such as prolyl endopeptidase, neutral endopeptidase, or thimet oligopeptidase [27,28]. Ang-(1-9) is produced from Ang Ⅰ by ACE2, carboxypeptidase A or cathepsin A [29,30]. Ang-(1-7) is endogenous ligand for G protein-coupled receptor (GPCR) Mas [31], eliciting antagonistic reaction against AT_1 receptor including vasodilation, antiproliferation in the vasculature, antihypertrophy, antifibrosis, antiarrythmia in the heart, and many other protective reactions in the kidney, and the brain etc [32]. Ang-(1-7) is also reported to bind to the AT_2 receptor in in vitro experiment [33], and in vivo study, causing the AT_2 receptor-mediated effects such as increased perfusion pressure of isolated mouse hearts [34], or vasodepressor effects in rats [35,36]. Interestingly, Ang-(1-9) has been demonstrated to bind to AT_2 receptor showing the antihypertrophic effects in adult rabbit cardiomyocytes [37].

Vasorelaxant effects caused by Ang-(1-7) was reported to be mediated by prostaglandins [38], or by the endothelium-dependent release of nitric oxide, involving a B2 bradykinin receptor [39]. NO release was reported to be inhibited by the selective Mas antagonist, A-779, and Akt-dependent pathway was involved in NO release change, using Chinese hamster ovary cells transfected with Mas cDNA [40]. And increased NO release by Ang-(1-7) was also inhibited by the the selective antagonist for Mas, D-Ala7- Ang-(1-7) [41], using cultured bovine aortic endothelial cells (BAECs). Authors report that moderate Ang-(1-7)-stimulated NO release was accompanied by a very slow concomitant superoxide anion, suggesting low formation of peroxynitrite. Thus, Ang-(1-7) might preserve the vascular system, among others, due to its low formation of cytotoxic peroxynitrite by the reaction between NO and superoxide anion.

Another important mechanism of ACE2/Ang-(1-7)/Mas Axis is generation of ROS by components of this axis. As mentioned above [41], low generation of superoxide anion was reported after Ang-(1-7) stimulation. This may be caused from eNOS uncoupling due to L-arginine shortage [42]. Still, Mas activation causes vasodilatory and protective cardiovascular effect. One possible mechanism is Mas-mediated phosphorylation of SHP-2 [43]. Authors of this report are speculating that Ang-(1-7) increases association between phosphorylated SHP-2 and c-Src of human endothelial cells treated by Ang Ⅱ, leadind to negative modulation of downstream targets of extracellular signal regulator kinase (ERK) 1/2 and NAD(P)H oxidase activity. Cross talk between ACE/ Ang Ⅱ/AT_2 Axis and ACE2/Ang-(1-7)/Mas Axis is reported as a mechanism of antiatherosclerotic of Ang-(1-7), using Mas-knockout and AT_2 receptor knockout mice [44]. Neointimal formation after cuff placement were more pronounced in Mas-knockout mice than wild-type mice. Treatment with azilsartan or Ang-(1-7) attenuated neointimal area, vascular smooth muscle cell proliferation, and superoxide anion, and increased ACE2 mRNA and AT_2 receptor mRNA but not AT_1 receptor mRNA, suggesting

blockade of AT_1 receptor coud enhance the activities of the ACE2/Ang Ⅱ/AT_2 Axis and ACE2/Ang-(1-7)/Mas Axis. The role of ACE2 in the vasculature is also reported, evaluating angiogenesis and atherosclerosis in endothelial cells of apoprotein E-knockout, ACE2-overexpressing and deficient mice [45]. ACE2-deficient mice exhibited impaired endothelium-dependent relaxation. ACE2 promoted capillary and neovessel maturation and reduced atherosclerosis, and attenuated Ang Ⅱ-induced reactive oxygen production in part through decreasing the expression of $p22^{phox}$ in an Ang-(1-7)-dependent fashion. And we would like to refer details to reviews that report the relationship ACE2/Ang-(1-7)/Mas Axis with oxidative stress [46,47]. Interactions between AT_1 receptor, Mas and NAD(P)H oxidase at signal transduction level from above mentioned reports [43] are summerized in Figure 2.

Ang A/ Alamandine/ MrgD axis: Angiotensin A (Ang A), an octapeptide, is produced by decarboxylatin of N-terminal aspartate of Ang Ⅱ into alanin**.** Ang A binds to both AT_1 and AT_2 receptors [48]. Its vasoconstrictive and pressor effect due to AT_1 receptor activation is reported [49,50].

By hydrolyzing the C-terminal amino acid of Ang A by ACE2, or decarboxylation of N-terminal aspartate of Ang-(1-7) into alanin, alamandine is produced [51]. Alamandine produced several biological effects including endothelial-dependent vasorelaxation in aortic rings of mice and rats or central cardiovascular effects. Microinjection of alamandine into rostal ventrolateral medulla (RVLM) increased blood pressure, and microinjection into caudal ventrolateral medulla (CVLM) decreased blood pressure, and modulated the baroreflex sensitivity after intra-cerebro ventricular (ICV) infusion [51]. Mas-related G-coupled receptor type D (MrgD) has been identified as the receptor for alamandine [51].

On the other hand, β-alanin has been established as a ligand for MrgD and responsible for their effects in the primary sensory neurons [52]. Surprisingly, MrgD agonist β-alanin did not relax abovementioned aortic rings, which was relaxed by alamandine. Thus signal transduction induced by alamandine in blood vessel seems to be different from that of β-alanin in primary sensory neurons. The former causes NO production and vasorelaxation. But the latter causes inhibition of KCNQ2/3 in primary sensory neurons [53]. Unfortunately, effect of Ang A/Alamandine/MrgD Axis on oxidative stress are not studied for detail.

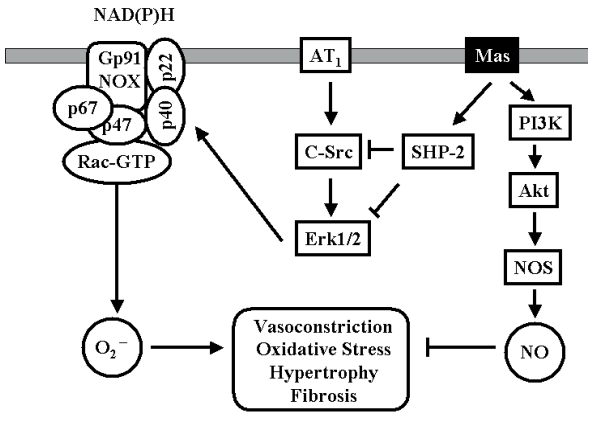

Figure 2: Interactions between AT_1 receptor, Mas and NAD(P)H oxidase at signal transduction level. ERK1/2: extracellular signal regulator kinase. C-Src: proto-oncogene tyrosine-protei kinase. NAD(P)H: nicotinamide adenin dinucleotide phosphate-oxidase. O_2-: superoxide anion. SHP-2: Src homology 2-containing inositol phosphatase 2. PI3K: phosphatidylinositol 3-kinase. Akt: protein kinase B. NOS: nitric oxide synthase. NO: nitric oxide.

Ang Ⅲ/ Ang Ⅳ/ AT_4/ IRAP axis: Angiotensin Ⅲ (Ang Ⅲ) is produced from Ang Ⅱ after removing N-terminal aspartate by aminopeptidase A. Ang Ⅲ normally binds to AT_1 receptor and to AT_2 receptor [54]. Ang Ⅲ causes blood pressure elevation in normal and hypertensive subjects [55], and aldosterone release [56].

Angiotensin Ⅳ(Ang Ⅳ) is produced from Ang Ⅲ after removing N-terminal arginine by aminopeptidase N, and directly from Ang Ⅱ by D-aminopeptidase. Centrally administered Ang Ⅳ causes improvement in learning or memory in animal model [57]. Ang Ⅳ also induces vasodilation in preconstricted endothelium-intact pulmonary artery [58], and increases endothelial NO synthase activity in pulmonary arterial endothelial cells [59]. Many effects of Ang Ⅳ are mediated by AT_4 receptor [55]. A fragment of the hemoglobin β-chain, Leu-Val-Hemorphin 7 (LVV-hemorphin 7), was isolated from sheep brain as endogenous ligand for AT_4 receptor that attenuates the deleterious effects of scopolamine on learning performance [60]. AT_4 receptor was identified as insulin-regulated membrane aminopeptidase (IRAP) and was proposed that AT_4 receptor ligands may inhibit the catalytic activity of IRAP, thereby extend the half-life of its neuropeptide substrates including arginine vasopressin, oxytocin and somstostatin which are reported to enhance memory [61]. And AT_4 receptor ligands may modulate glucose uptake by influencing intracellular vesicular trafficking of GLUT4, co-localized with IRAP, increasing glucose uptake by neurons [62]. Ang Ⅲ seems to activating NAD(P)H oxidase via activation of AT_1 receptor. And decreased ROS level by AT_4/IRAP receptor is speculated, but details are not investigated.

Angiotensin-(1-12): Ang-(1-12) is a peptide of 12 N-terminal amino acids of rat angiotensinogen, being substrate for Ang Ⅱ, expressed in the kidney and the heart [63]. Ang-(1-12) can be degraded into smaller peptides such as Ang-(1-7) by ACE, neprilysin or chymase [64]. Ang-(1-12) was also reported to bind AT_1 receptors, serving not only as a substrate for smaller active peptides, but also as a ligand [65]. This peptide does not exist in human tissues.

Prorenin/(pro)renin receptor (PRR)/ intracellular signaling axis

The (pro)renin Receptor (PRR) is a 350-amino acid single transmembrane receptor protein. Expressed in brain, heart, lung, liver, kidney, skeletal muscle, pancreas, fat, placenta, and others, but not in the systemic circulation. Both prorenin and renin bind to the PRR [66]. After binding to PRR, nonproteolytic activation and conformational change of prorenin occur without cleavage of the prosegment, causing local Ang Ⅱ generation and Ang Ⅱ-dependent activation of tissue RAAS [67]. This may lead to increase oxidative stress like above-mentioned mechanism through activation of AT_1 receptor. After the binding of prorenin and renin to PRR as ligands, Ang Ⅱ-independent signaling cascades are activated. AngII-independent MAPK activation by human (pro)renin receptor and induction of glomerulosclerosis with increased TGF-beta1 expression was reported [68]. And Renin-activated induction of ERK1/2 through a receptor-mediated, angiotensin II-independent mechanism in mesangial cells has been reported. This renin-activated pathway was reported to have triggered cell proliferation along with TGF-beta1 and plasminogen activator inhibitor-1 gene expression [69]. These Ang Ⅱ-independent signaling pathways may also cause oxidative stress and further enhance end organ damage as above-mentioned

activation of AT_1 receptor (Figure 2). PRR may affect on vacuolar H^+-ATPase (V-ATPase) which regulates the pH of cellular and intracellular vesicles [70], because hydrophobic membrane-binding fragment of PRR degraded by furin contains ATPase assciated protein 2 (ATP 6 ap 2). Bafilomycin, a specific inhibitor of V-ATPase, has been reported to inhibit phosphorylation of ERK by prorenin in the kidney [71]. Prorenin and its receptor-mediated Ang-II-independent pathways is reported to comprise of PRR-associated V-ATPase-linked Wnt/Frizzled signal transduction, including canonical-β-catenin and non-canonical Wnt-JNK-Ca(2+) signals in the pathogenesis of cardiovascular and renal end-organ damage [72]. On top of that, there is a possibility that PRR, by modulating intracellular H^+ concentration as V-ATPase associated-protein, is changing the production of intracelular ROS such as hydroperoxy radical or hydrogen peroxide (superoxide anion + $H^+ \Leftrightarrow$ hydroperoxy radical, peroxide + $2H^+ \Leftrightarrow$ hydrogen peroxide) (Figure 3: author's speculation).

Therapeutic Implications

Discovery of new components of the RAAS including ACE2/Ang-(1-7)/Mas Axis and others brought about changes of our concept on RAAS and understanding of pathophysiology on hypertension and CVDs. Development of novel therapeutic strategies for the better treatment of hypertension and related CVDs based on these new findings can be expected. We would like to review briefly the present status of them including experimental findings.

ACE2/Ang-(1-7)/Mas axis

Recombinant human ACE2 (rhACE2) is reported to be a potential candidate to treat diastolic and systolic heart failure [73]. Efficacy of lentiviral vector-mediated overexpression of ACE2 is reported to inhibit the myocardial and perivascular fibrosis of experimental Ang-II infusion rat and SHR [74,75]. Administration of rhACE2 was well tolerated by healthy human subjects. Despite marked changes in angiotensin system peptide concentrations , cardiovascular effects were absent, suggesting the presence of effective compensatory mechanisms in healthy volunteers [76]. A soluble form of rhACE2 is being assessed for acute lung injury and PAH.

Efficacy of synthetic enhancers of ACE2 activators, xanthenone (XNT), and resorcinolnaphthalein are reported to activate ACE2, decrease blood pressure, and reverse tissue remodeling [77], and diminazene aceturate (DIZE) to attenuate pulmonary hypertension in experimental models [78]. But some structural modifications are necessary for clinical use because of poor solubility in water and safety.

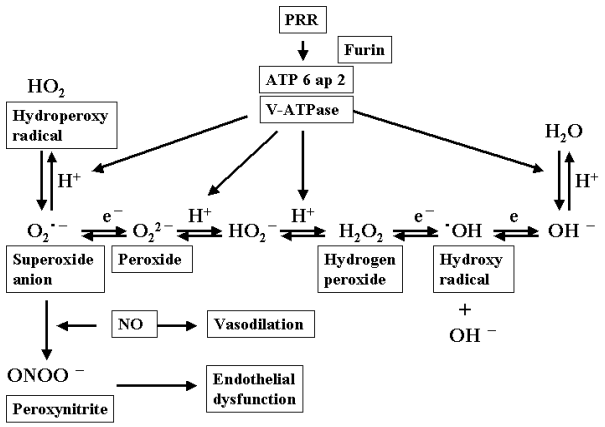

Figure 3: Interaction between PRR and ROS generation (Author's speculation). PRR: (pro) rennin receptor. ATP 6 ap 2: ATPase associated protein 2. V-ATPase: vacuolar H^+-ATPase.

Oral administation of Ang-(1-7) seems promising as a candidate for therapy. But its clinical use is limited because of short half-life in vivo. Cyclized Ang-(1-7) (thioether-bridged Ang-(1-7)) and angiotensin-(1-7) inclusion in cyclodextrin (Ang-(1-7)-CyD) exhibited better pharmacokinetic profile in vivo but in experimental models [79,80]. A synthetic analog of Ang-(1-7) TXA127 is in clinical trial for the treatment of PAH.

AVE-0991 is a first synthetic non-peptide agonist for the Mas receptor and produced beneficial effects in isolated perfused rat hearts and attenuated postischemic heart failure [81]. And two novel Mas agonists, CGEN-856S and CGEN-857 with high binding specificity for Mas, has been reported [82]. CGEN-856S induced antiarrythmogenic effect and decreased arterial pressure of conscious SHR.

Interestingly, it is reported that olmesartan, ARB, may activate ACE2 in hypertensive patients [83].

Ang A/Alamandine/MrgD axis

Oral administration of an inclusion compound of Ang-(1-7) or alamandine/β-hydroxypropyl cyclodextrin produced a long-lasting antihypertensive effect in SHR and antifibrotic effects in rats treated with isoproterenol [51,84].

PRR/intracellular signaling axis

Ichihara et al. reported that the binding of rennin and prorenin to the PRR and diabetic nephropathy were inhibited by a decoy peptide corresponding to the "handle" region for nonproteolytic activation of prorenin on PRR, and nonproteolytic activation of prorenin may be a significant mechanism of diabetic nephropathy and may serve as important therapeutic targets for the prevention of diabetic organ damage [85].

Conclusion

Targeting the emerging new components of RAAS is a promising strategy for developing novel therapy for hypertension and target organ damage. But improvement of safety and drug delivery, for example liposome modification, are necessary before future clinical application.

Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the author.

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