



Control of Renin-Angiotensin-Aldosterone System by Oxidative Stress in Renal Diseases -Feedback and Feedforward Mechanism-

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Abstract

The Renin-Angiotensin-Aldosterone System (RAAS) plays pivotal role not only in controlling blood pressure or hydro-electrolyte balance but also in the pathogenesis of hypertension and renal diseases. Particularly, production of Reactive Oxygen Species (ROS) by increased angiotensinII (AngII) of the classical arm of RAAS is one of the important mechanisms in the pathogenesis of renal diseases. And increased ROS is reported to suppress renin gene expression, resulting in feedback mechanism in RAAS. Recently, (Pro) Renin Receptor (PRR) has been identified, and its importance in the initiation and progression of renal diseases has been frequently reported. Although PRR causes renal injury by increased oxidative stress by AngII-dependent and independent mechanism, genetic defect in PRR is reported to causes abnormal phenotypes. Recently, PRR has been reported to activate Vacuolar H⁺-ATPase (V-ATPase), that is essential for survive of cells as proton transporter across cell or organelle membrane resulting in extracellular and organelle acidification, and contributing to keeping cellular pH homeostasis. Moreover, loss of this V-ATPase activity has been reported to result in increased oxidative stress in addition to impaired cellular pH homeostasis. Thus activating PRR may suppress oxidating stress through V-ATPase activation. On the other hand, AngII dependent and independent increase of oxidative stress by PRR may cause suppression of renin gene expression by ROS mediated feedback mechanism. These mechanisms may be relevant to feedback suppression of renin activity such as primary aldosteronism in the clinical setting. But these effects of RAAS including PRR and renin expression on oxidative stress can cause feedforward activation of renin such as malignant hypertension.

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Received Date: 19 May 2016

Accepted Date: 14 Jun 2016

Published Date: 18 Jun 2016

Citation:

Murakami K. Control of Renin-Angiotensin-Aldosterone System by Oxidative Stress in Renal Diseases Feedback and Feedforward Mechanism. *Remed Open Access*. 2016; 1: 1006.

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Keywords: Renin-Angiotensin-Aldosterone system; Renin gene; Oxidative stress; Reactive Oxygen Species (ROS); (Pro) renin Receptor (PRR); V-ATPase, ATP6ap2

Introduction

Hypertension is a common but one of the most important health problems, because it is a major risk factor for cardiovascular diseases (CVDs) and renal diseases. The renin-angiotensin-aldosterone system (RAAS) plays an important role in the initiation and progression of hypertension and target organ damage [1], although RAAS plays a critical role in controlling blood pressure or hydro-electrolyte balance. And RAAS, not only in the systemic circulation but also in the local organs and tissues, plays a crucial role in the pathogenesis of hypertension, CVDs, and renal diseases [2-4]. In controlling RAAS, expression of renin gene and activation of prorenin play important roles in systemic and local RAAS.

Particularly, production of Reactive Oxygen Species (ROS) such as superoxide anion by increased angiotensinII (AngII) of the classical arm of RAAS is one of the important mechanisms in the pathogenesis of CVDs and renal diseases [5]. And increased oxidative stress caused by increased AngII suppresses renin gene expression, resulting in feed back mechanism of RAAS [6]. But in the past decade, (Pro) Renin Receptor (PRR) has been identified and its importance in the renal pathophysiology caused by hypertension or diabetes mellitus has been reported. Although PRR causes renal injury partially by increased oxidative stress by AngII-dependent and independent activations of local RAAS, genetic defect in PRR causes nerval or ocular abnormality and even results in fatal. Recently, PRR has been also reported to activate V-ATPase that is essential for survive of cells as proton transporter across cell or organelle membrane resulting in extracellular and organelle acidification, and constituting cellular pH homeostasis. Moreover, loss of this V-ATPase is reported to result in increased oxidative stress in addition to impaired cellular pH

homeostasis [7,8]. Thus PRR may suppress excessive oxidating stress through V-ATPase, which may lead to further activating renin gene expression by the loss of ROS mediated feedback mechanism in turn. On the contrary, the AngII dependent and independent increase of oxidative stress causes suppression of renin gene expression by ROS mediated feedback mechanism.

In the clinical settings, two contradictory pathophysiological conditions between RAAS activation and renin gene expression exist. One of them is feedback mechanism forming homeostasis of RAAS brought by suppression of renin gene expression by activated AT₁ or Mineralcorticoid Receptor (MR) following increased AngII or aldosterone such as primary aldosteronism. On the other hand, feedforward mechanism exists as further activation of RAAS by activated RAAS, generating vicious cycle as seen in AngII-dependent malignant hypertension.

We will discuss the mechanism and clinical relevance of these contradictory effects of these PRR on renin gene expression through oxidative stress from the viewpoint of recent findings such as PRR, V-ATPase, oxidative stress, acidification mechanism by H⁺ transporter.

Biology and regulation of renin gene expression and (Pro) renin receptor and oxidative stress

Renin is enzyme of glycoprotein with molecular weight of 40,000, produced and released from Juxta Glomerular (JG) cell in afferent arteriole of kidney into blood according to various stimulations. Renin mRNA is translated into preprorenin, and signal peptide in the N terminal is cleaved then into prorenin. Part of prorenin is secreted into blood by constitutional pathway. And another part of prorenin is cleaved of its propeptide and added by oligosaccharide chains and released into blood by regulated pathway as active rennin [9-11].

Production and excretion of renin is controlled mainly by AngII, although controversial, [6,12], macula densa [13], renal perfusion pressure [14], β_1 receptor [15], adrenomedullin [16], IL-1 β [17] and so on. Recently regulation of renin gene expression by oxidative stress [6], micro RNAs such as miR-181a [18] and has-miR-663 [19], proximal promoter, enhancer, and transcription factors [20] has been reported.

And, receptor protein for renin and prorenin, PRR, causing biological effect of renin other than classical arm of RAAS in AngII-dependent and independent ways, was identified from human kidney in 2002. PRR is a 350-amino acid single transmembrane receptor protein, expressed in brain, heart, lung, liver, kidney, skeletal muscle, pancreas, fat, placenta. Both prorenin and renin bind to the PRR [21]. After binding to PRR, nonproteolytic activation and conformational change of prorenin occur without cleavage of the prosegment, causing local AngII generation and AngII-dependent activation of tissue RAAS [22]. This may lead to increase oxidative stress through activation of AT₁ receptor. After the binding of prorenin and renin to PRR as ligands, AngII-independent signaling cascades are activated. Ang II -independent MAPK activation by human PRR and induction of glomerulosclerosis with increased TGF-beta1 expression was reported [23]. 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 [24]. These AngII-independent signaling pathways may also cause oxidative stress and further enhance end organ damage. Ichihara et al. [25]

reported that the binding of renin and prorenin to the PRR in 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. PRR may affect on vacuolar H⁺-ATPase (V-ATPase) which regulates the pH of cell and intracellular organelle [26], because hydrophobic membrane-binding fragment of PRR degraded by furin contains ATPase associated protein 2 (ATP6ap2). Bafilomycin, a specific inhibitor of V-ATPase, has been reported to inhibit phosphorylation of ERK by prorenin in the kidney [27]. Prorenin and its receptor-mediated Ang-II-independent pathways comprise of PRR-associated V-ATPase-linked Wnt/Frizzled signal transduction, including canonical- β -catenin and non-canonical Wnt-JNK-Ca⁺⁺ signals in the pathogenesis of cardiovascular and renal end-organ damage [28].

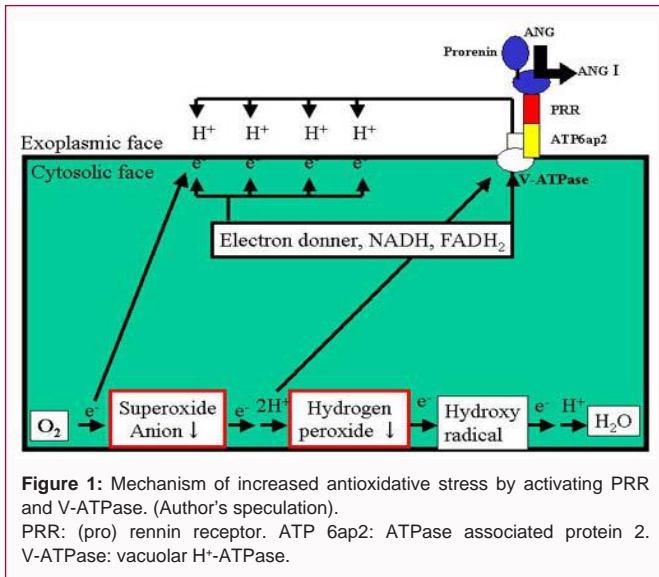
Although PRR plays a harmful role in the pathogenesis of renal diseases such as diabetic nephropathy, mutant of PRR is reported to have various abnormal phenotype. So it is suspected that PRR has some important function for cells to survive independent of RAAS. For example, abnormal pigmentation of skin or eye, neural cell death in zebrafish [29], malformation of head and tail, abnormal pigmentation of skin or eye in xenopus laevis [30], X linked recessive familial epilepsy in human [31,32], fulminant heart failure in mouse [33], have been reported. Since mutant of V-ATPase subunit in zebrafish shows similar phenotype as PRR mutant of zebrafish [29], V-ATPase seems have associated in phenotype of PRR mutant. Defect in acidification of organelle and others may be involved for that abnormal phenotype in PRR mutant. Mutations in the gene encoding subunit of V-ATPase are also reported to cause renal tubular acidosis with sensorineural deafness [34], infantile malignant osteopetrosis [35], and osteopetrosis [36]. Interestingly, already in 1995 it was reported that inhibitor of V-ATPase, bafilomycin, proteolytically processed mutant β -amyloid from familial Alzheimer's disease differently from wild-type one, both transfected to kidney cells [37]. And X-linked Parkinsonism caused by altered splicing of ATP6ap2 has been also reported [38].

But some reports show that PRR is regulating the production of intracellular ROS such as superoxide anion. In Yeast, mutants lacking V-ATPase subunits results in increased oxidative stress (may be extra-mitochondrial origin) [39,40]. Possible mechanism may be because positively charged cell membrane attracts intracellular electron (from NADH, FADH₂, electron donors) to the cytosolic face of plasma membrane electrically due increased H⁺ concentration of exoplasmic face of the plasma membrane as V-ATPase associated-protein from PRR activates V-ATPase and facilitate outward flow of H⁺. Thus decreased intracellular electron cause reduction in generation of intracellular ROS such as superoxide anion from triplet oxygen molecule, because intracellular triplet oxygen molecules interact less frequently with electron donors (Figure 1).

Increased oxidative stress through MR activation by aldosterone in renal tubular cell [41], endothelial cell [42], and endothelial progenitor cell [43] has been also reported.

Feed back mechanism in regulation of renin gene expression

Reactive Oxygen Species (ROS) production by AngII through AT₁ receptor of classical arm 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 AngII-stimulated ROS production is reported, first phase involves protein kinase C (PKC), and second phase involves Rac, Phosphatidylinositol-3'-kinase (PI₃K), c-Src kinase and epidermal growth factor (EGF) [44]. RhoA/Rho-kinase activation by increased NAD(P)H oxidase-dependent ROS is also reported, leading to vascular smooth muscle contraction [45]. Involvement of the glutathionylation-dependent uncoupling of endothelial nitric oxide synthase (eNOS) is also reported [46]. Pharmacological intervention to oxidative 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 [47]. Treatment of human vascular endothelial cells (HVEC) with ARB, Losrtan, or ACEI, Lisinopril, both reduced AngII-stimulated superoxide anion production [48]. 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 [49].

And increased oxidative stress caused by increased AngII suppresses renin gene expression. This regulation of renin gene expression by oxidative stress seems relevant, resulting in feedback and autoregulation of RAAS [6].

On the contrary, protective arms of RAAS such as ACE/ AngII/ AT₂ Axis and ACE2/Ang-(1-7)/Mas Axis have been reported to play a tissue-protective role against tissue injury of classical arm of RAAS by suppressig oxidative stress generated by this arm. Activation of AT₂ receptor has shown to cause protective effects by suppressing oxidative stress from AT₁ receptor stimulation by AngII. Inhibition of AT₂ receptor resulted in superoxide anion production in Human Umbilical Vein Endothelial Cells (HUVEC), and this effect involved src homology 2 domain containing inositol phosphatase (SHP-1) activation by AT₂ receptor [50]. Involvement of c-Src tyrosine kinase in SHP-1 phosphatase activation by AT₂ receptors in rat fetal tissues has been reported [51]. Increased NAD(P)H oxidase activity, p47^{phox}, and plaque area were reported in the aorta of double knock out mice of ApoE and AT₂ receptor [52]. Authors are speculating that AT₂ receptor stimulation antagonizes AT₁ 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 AT₂ receptor-mediated inhibitory effect on oxidative stress were caused through inhibition of Akt activation brought by AT₁ receptor activation, which is a prerequisite for the AT₂ receptor to exert its inhibitory effect on NAD(P)H oxidase activation.

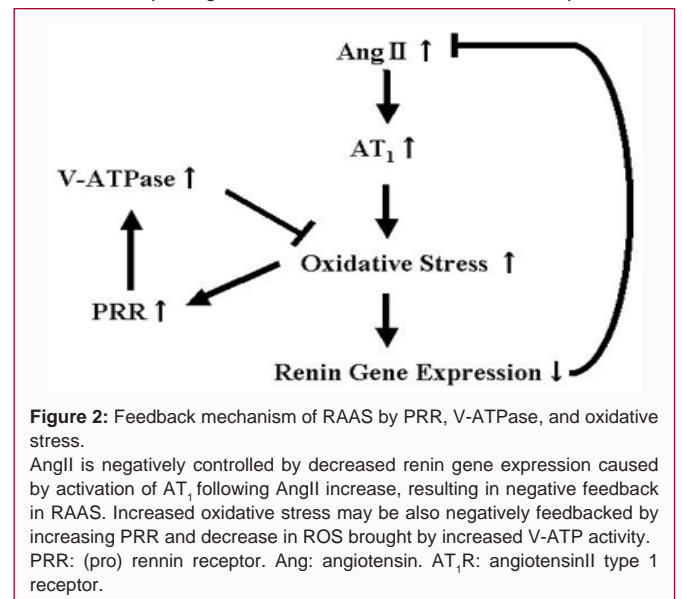
Mas receptor activation by angiotensin [1-7] (Ang-(1-7)) causes vasodilatory and protective cardiovascular effect. One possible mechanism is Mas-mediated phosphorylation of SHP-2 [53]. Authors of this report are speculating that Ang-(1-7) increases association between phosphorylated SHP-2 and c-Src of human endothelial cells treated by AngII, 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/ AngII/AT₂ Axis and ACE2/Ang-(1-7)/Mas Axis is reported as a mechanism of antiatherosclerotic of Ang-(1-7), using Mas-knockout and AT₂ receptor knockout mice [54]. Neointimal formation after cuff placement was 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 production, and increased ACE2 mRNA and AT₂ receptor mRNA but not AT₁ receptor mRNA, suggesting blockade of AT₁ receptor could enhance the activities of the ACE2/ AngII/AT₂ Axis and ACE2/Ang-(1-7)/Mas Axis.

The binding of renin or prorenin to the PRR is reported to ROS formation through both AngII-dependent and independent mechanisms. Authors of this report showed that PRR-mediated AngII-independent ROS formation is associated with activation of the MAPK/ERK1/2 and PI3/Akt signaling pathways using neuronal cells [55].

Following increased oxidative stress by AT₁ receptor, PRR, and MR, renin gene expression may be suppressed as mentioned, resulting in feedback mechanism (Figure 2).

Feed forward mechanism in regulation of renin gene expression

As mentioned above, ROSs are generated through AT₁ receptor stimulation by AngII from classical arm followed by NAD(P)



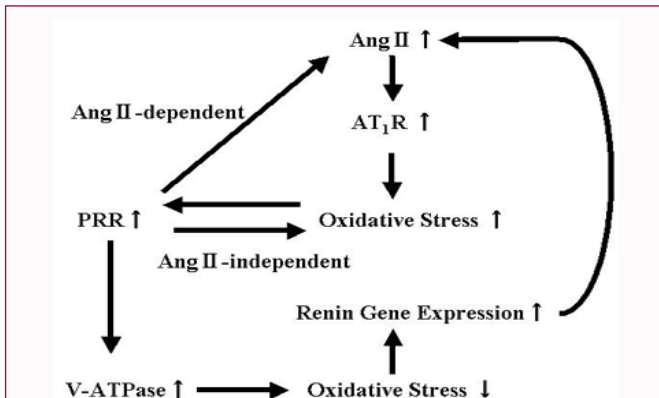


Figure 3: Feedforward mechanism of RAAS with PRR, V-ATPase, and oxidative stress.

AngII-dependantly and independently, increased PRR and oxidated stress result in feedforward loop formation. And increased AngII activates AT_1R , increases oxidative stress, PRR, V-ATPase, renin gene expression and increases AngII further, resulting another feedforward loop.

PRR: (pro) rennin receptor. Ang: angiotensin. AT_1R : angiotensinII type 1 receptor. V-ATPase: vacuolar H^+ -ATPase.

H oxidase activation [44-46]. AngII-dependent and independent ROS generation by PRR, stimulated by renin and prorenin, is also reported [55]. Increased oxidative stress through MR activation by aldosterone is also reported [41-43]. Following increased oxidative stress by AT_1 receptor, PRR, and MR, increased oxidative may increase PRR expression again. On the other hand, both mRNA and protein of PRR were reported to be upregulated by enhancement of AT_1 receptor-NADPH oxidase cascade activity in renal glomeruli and tubules in the streptozotocin-induced diabetic rat [56]. And both mRNA and protein of PRR were also increased through H_2O_2 -mediated epigenetic modification in mesangial cells from mouse [57]. As mentioned above, increased PRR expression may cause increased V-ATP activity resulting in suppression of oxidative stress. This may constitute another feedback loop (Figure 3).

Is effect of V-ATP independent with PRR?

It has been reported that full-length PRR is cleaved in the trans-Golgi by furin intracellularly into a soluble form of 28 kDa PRR (sPRR) and protein-binding hydrophobic domain [58]. Already before PRR was identified in 2002, 8.9 kDa protein was reported to bind to V-ATPase and the gene coding this protein was named as ATP6ap2 [59]. Truncated hydrophobic protein generated by cleavage of full-length PRR by furin turned out to contain ATP6ap2. So it is suggested full-length PRR is cleaved into sPRR that can activate prorenin non-enzymatically on the cell membrane and ATP6ap2 that binds to and activates V-ATPase. Recently Trepiccione et al. [60] reported that nephron specific deletion of ATP6ap2 caused decreased V-ATPase expression and activity, downregulation of the medullary NKCC2, autophagic defects, renal tubular acidosis using epithelial cells of medullary tubules of mouse. And interestingly, this nephron specific deletion of ATP6ap2 did not affect AngII production, AngII-dependent Blood Pressure regulation, or sodium handling in the kidney [60]. These findings indicate that suppression of V-ATPase causes various renal abnormalities even with unchanged RAAS activity, and malfunction of V-ATPase itself does not affect RAAS activity.

Clinical Implications

Despite above mentioned feedback mechanism (AT_1 receptor,

AT_2 receptor, Mas receptor), accerelated RAAS has known as ANG II-dependent malignant hypertension for decades. Interestingly enough, increased release of active renin from renal tissue by active renin, has been reported already in 1992 [61]. And Howard et al. [62] reported that following acute intrarenal administration of the direct renin inhibitor aliskiren in Cyp1a1-Ren2 transgenic rats with ANG II-dependent malignant hypertension, urine flow and sodium excretion increased and ANG II excretion decreased, demonstrating the importance of intrarenal renin activation and increase of ANG II in the pathophysiology of ANG II-dependent malignant hypertension. These findings may suggest the existence of intrarenal accerelating mechanism of RAAS. And Prieto et al. [63] demonstrated that upregulation of renin and the soluble form of PRR in the collecting duct of the kidneys from Cyp1a1Ren2 transgenic rats with malignant hypertension may constitute a leading mechanism to explain elevated formation of renal ANG II levels in ANG II-dependent malignant hypertension. These findings may suggest PRR play pivotal role in the accerelated activation of renin and generation ANG II in malignant hypertension.

On the other hand, feedback mechanism of RAAS exists, forming homeostasis of RAAS brought by suppression of renin gene expression by activated AT_1 or mineralcorticoid receptor (MR) following increased AngII or aldosterone, seen in primary aldosteronism.

Conclusions

Regulation of oxidative stress by RAAS such as PRR, V-ATPase, renin gene expression, and others may be involved in the pathogenesis of renal diseases via ether feedback and accerelating mechanism.

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