Chapter

Renin Angiotensin Aldosterone System Functions in Renovascular Hypertension

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Abstract

The renin angiotensin aldosterone system (RAAS) plays a key function in renovascular hypertension induced by renal artery stenosis (RAS). RAS causes a decrease in renal perfusion in the stenosed kidney which in turn stimulates renin the rate limiting enzyme in RAAS. This stimulation triggers a series of events starting with renin release leading to Ang II production, decrease in sodium excretion, increase sympathetic tone; all contributing to the development of renovascular hypertension. In RAS increase of superoxide reduce nitric oxide in the afferent arteriole increasing vasoconstriction and a marked decrease in glomerular filtration rate. In renovascular hypertension prostaglandins mediate renin release in the stenosed kidney. Targeting different RAAS components is part of the therapy for renovascular hypertension, with other options including renal nerves denervation and revascularization. Different clinical studies had explored revascularization, RAAS blocking and renal nerves denervation as a therapy. We will discuss organ, cellular and molecular components of this disease.

Keywords: Renin angiotensin aldosterone system, renovascular hypertension, renin, renal nerves, oxidative stress

1. Introduction

Renal artery stenosis (RAS) is a common condition in patients suffering from atherosclerosis and fibromuscular dysplasia [1–6], with an overall prevalence disease rate of 15.4% [4]. Progression to severe stenosis is well documented and leads to hypertension and kidney damage [7–9]. Clinically, renovascular hypertension is one the most important causes of secondary hypertension and kidney damage. In patients with RAS, 65% are hypertensive and 26.5% suffer kidney failure [4, 6]. Advancement to end stage renal disease is known to increase cardiovascular events [10]. The clinical trials Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) [11], and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) [12] targeted renal vascularization to improve disease outcomes but failed to show any improvement in renal function, cardiovascular events or mortality [11, 12]. Furthermore, prospective studies in ASTRAL and CORAL concluded that 15-22% of patients suffering from renovascular disease will progress to renal "end point" within 3 to 4 years [13]. The NHLBI Cardiovascular Health Study used a non-invasive screen and found that 6.8% elderly patients (both African American

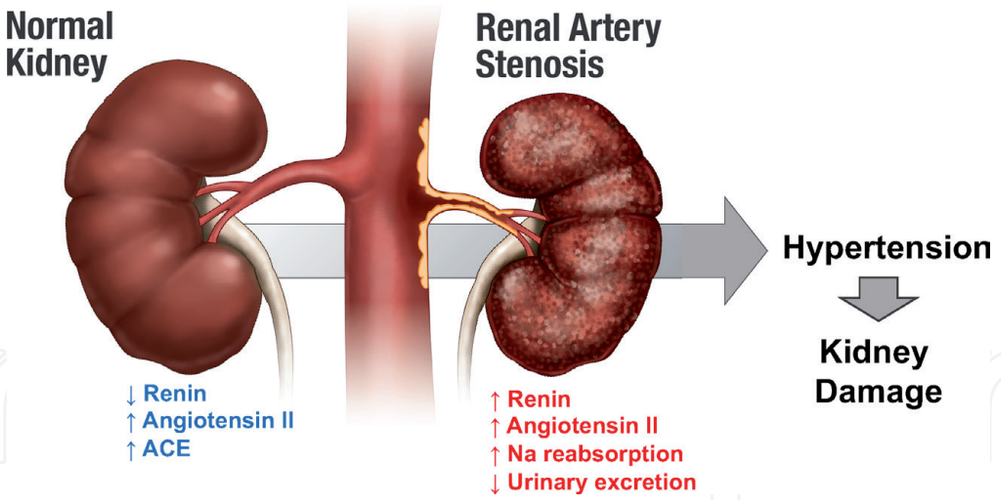

Figure 1.
Renin Angiotensin Aldosterone System (RAAS) key role in renal artery stenosis (RAS) induction of renovascular hypertension and kidney damage. Deterioration of renal perfusion in the stenosed kidney cause a decrease in renal pressure which in turn stimulates RAAS. This stimulation triggers a series of events starting with renin release leading to angiotensin II production; decrease in sodium excretion, increase sympathetic tone; ending in hypertension.

and white) had more than 60% RASten or renal artery occlusion [14, 15]. The renin angiotensin aldosterone system (RAAS) plays a key role in hypertension, with renin recognized as the driver of renovascular hypertension (**Figure 1**). In humans, plasma renin activity (PRA) is used as biomarker for the activation of RAAS in hypertension and in patients with atherosclerotic RAS, high PRA is associated with increased risk for cardiovascular events and high mortality [16]. These suggest an important function for RAAS in renovascular hypertension onset and the need to target different components of RAAS for therapy.

2. Renin angiotensin aldosterone system function in renal artery stenosis

Renal artery stenosis causes a decrease in renal perfusion in the stenosed kidney which in turn stimulates RAAS. This stimulation triggers a series of events starting with renin release leading to angiotensin II (Ang II) production, decrease in sodium excretion, increase sympathetic tone; all contributing to the development of hypertension (**Figure 1**) [17, 18]. When there is a need for renin expression and release, the number of renin expressing cells increase a process known as Juxtaglomerular (JG) cell recruitment [19–24] involving the trans differentiation of vascular smooth muscle cells into renin expressing cells along the afferent arteriole [20, 21, 23]. JG cell recruitment is well documented in this model [25–27]. Activation of the renal baroreceptor in RAS causes renovascular hypertension through RAAS activation [28]. In uni- and bi-lateral RAS aldosterone levels are upregulated [29–32]. Moreover, in renovascular hypertension prostaglandins mediate renin release in the stenosed kidney [33–36], and catecholamines mediated by an increase in cAMP and activation of protein kinase A (PKA) [37–39]. Decrease renal perfusion cause a decline in renal function and increase kidney injury [40, 41]. This decrease in renal function starts with endothelial damage, decrease in nitric oxide and increase in vasoconstrictors and oxidative species [42]. Reactive oxidative stress (ROS) increase renal vascular tone, tubuloglomerular feedback, and endothelial disfunction decreasing glomerular filtration rate [43].

Successful treatments for hypertension such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) alleviate hypertension,

but need close examining for kidney failure and hyperkalemia [4]. Aliskiren, a direct renin inhibitor, may still be a potential option for the treatment of high blood pressure in some forms of hypertension such as chronic kidney disease (CKD) and renovascular hypertension [44]. In a clinical study, aliskiren combined with olmesartan reduced proteinuria by about 40% from baseline in patients with CKD with persistent proteinuria [45]. In non-diabetic CKD patients, aliskiren combined with ARBs, safely reduced proteinuria and attenuated the decline in glomerular filtration rate (GFR) [46]. These results indicate that a complete treatment of renal artery stenosis induced renovascular hypertension and kidney damage may need targeting both the angiotensin II-dependent and the Ang II-independent arms of RAAS.

Renal artery stenosis is common in diabetic patients placing them at higher risk of end organ damage causing end stage renal disease [9, 47–49]. In older patients, RAS is the most common problem of end stage renal failure [50]. In RAS renin is recognized as the disease driver [6, 16, 51–54]. RAS is common in atherosclerotic patients and caused hypertension, oxidative stress, and kidney damage [7, 9]. Increased oxidative stress has been reported in humans as well as in two kidney one clip (2K1C) animal model and other hypertensive animal models [24, 55–60]. Changes in renal perfusion activate RAAS and increase the sympathetic activity of the afferent renal nerves contributing to renovascular hypertension and end-stage renal disease during RAS [61]. In the 2K1C model renal denervation decreases hypertension [62, 63]. Clinical trials (Renal Denervation in Patients With Refractory Hypertension (HTN-1) (Symplicity HTN-1), Renal Denervation in Patients With Uncontrolled Hypertension (Symplicity HTN-2), The Renal Denervation for Hypertension (DENERHTN), and Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL)) report that using renal denervation as therapy for hypertension has good outcomes [64–67]. The therapeutic effects of renal denervation have been attributed to removal of sympathetic efferent and/or afferent fibers [68]. Renin secretion is stimulated by renal efferent nerves, which also stimulate tubular sodium reabsorption [62] without perturbations to glomerular filtration rate or albumin urinary secretion [69]. These indicates that initially, renal artery stenosis induces RAAS and in later stages other organs involved in blood pressure homeostasis are involved in the induction of renovascular hypertension such as renal nerves and adrenal gland.

3. Central nervous system input in renal artery stenosis

Different experimental models of hypertension showed the crucial role play by the central nervous system (CNS) in this disease. Specifically, sympathetic efferent outflow augments during hypertension. It has been shown that both Ang II and aldosterone actions are mediated by the CNS [70, 71]. In experimental models of hypertension, ablation of the forebrain surrounding the anteroventral third cerebral ventricle (AV3V) inhibited hypertension [72, 73]. In the CNS the AV3V contains the median preoptic eminence, the organum vasculosum of the lateral terminalis, and the preoptic periventricular nucleus [74]. This forebrain region is responsible for cardiovascular regulation, and includes the subfornical organ, the organum vasculosum of the lamina terminalis, which are circumventricular organs lacking a blood-brain barrier [75]. Production of ROS in these brain regions strongly influences blood pressure [76]. Several reports showed that actions on these brain regions are responsible for Ang II hypertension and increase oxidative stress with NADPH oxidase playing a key role [77–80]. Renal vasculature and tubular segments are controlled by the efferent sympathetic renal nerves and promote arteriolar

vasoconstriction and renin release and increases sodium reabsorption [81]. In the afferent arterioles Ang II activates the alpha1 adrenergic receptor, which increases oxidative stress and constriction of the afferent arterioles, reducing renal blood flow [82]. Contrary, activation of the b1-adrenergic receptor activation inhibits ROS generation promoting vasodilation [83]. In different hypertension animal models renal denervation inhibit the induction of hypertension, showing that ablation of renal efferent induction of ROS is important in hypertension development [84, 85]. These data indicate that oxidative stress control efferent and afferent renal nerve actions in the development of hypertension.

Renal artery stenosis activates RAAS and increases the activity of the afferent renal nerves resulting in hypertension and end-stage renal disease [61]. It is known that in the 2K1C model renal denervation decreases hypertension [62, 63]. Removal of sympathetic efferent and/or afferent fibers controls hypertension [68], and the renal efferent nerves stimulate renin secretion and tubular sodium reabsorption [62]. During renal artery stenosis, there is an increase in Neutrophil Oxidase Factor p47 (p47phox) and p67phox [86–88]. Furthermore, in renal artery stenosis generation of ROS induced renal damage [88, 89], with the main source of ROS being NADPH oxidase [90, 91].

In the induction of renovascular hypertension, the renal nerves as well as the renin angiotensin aldosterone system activation cause the increase in blood pressure and dysregulation of sodium secretion, with renal denervation alleviating the central nerve system input decreasing blood pressure.

4. Oxidative stress in renal artery stenosis

Oxidative stress in the kidney and vasculature contribute to hypertension development. NADPH oxidase is a major source of oxidative stress in mammalian cells [75]. Most of the renal cells express NADPH oxidase and there are several stimuli that cause its activation leading to organ injury and hypertension development [75, 92, 93]. Reactive oxygen species (ROS) produced by NADPH oxidase in the kidney cause vasoconstriction and organ injury. Specifically, increase of superoxide reduces nitric oxide (NO) in the afferent arteriole increasing vasoconstriction and a marked decrease in GFR. In rabbits, Ang II-induced hypertension increase the p22phox subunit of NADPH oxidase causing endothelial dysfunction in the afferent arteriole [94]. Moreover, in spontaneous hypertensive rats, superoxide is generated in the afferent arteriole in response to endothelin-1 (ET-1) [95, 96]. Podocytes are important components of the renal filtration system. Dahl salt-sensitive rats had increase glomerular expression of p22phos and NOX2 that increases oxidative stress causing podocyte injury, glomerular sclerosis and proteinuria, with the antioxidant tempol (4-Hydroxy-TEMPO) correcting this glomerular injury [97, 98]. Plasminogen causes podocyte injury through stimulation of NOX2 and NOX4 expression [99], Ang II stimulates ROS generation in the mitochondria stimulating autophagy [100], Ang II-induced ROS production caused glomerulosclerosis [101], and oxidative stress disrupts nephrin – caveolin-1 crosstalk in podocytes disrupting of glomerular filtration barrier [102]. In the vasculature, increased oxidative stress causes hypertension in different animal models [103–108]. During renal artery stenosis, generation of ROS is recognized as the main mechanism of renal damage [88, 89, 109, 110] with the activation of NADPH oxidase as the source of ROS [90, 91], and associated with an increase in p47phox and p67phox [19, 86–88].

It is important to recognize that renal artery stenosis increase the production of reactive oxygen species leading to renal damage. ROS production influences not only organ damage but also contributes to the increase in blood pressure.

In the therapy of this disease multiple molecules are involved leading to increases in oxidative stress, blood pressure and renal injury and all start with the activation of the renin angiotensin aldosterone system.

5. Angiotensin II dependent and independent action in renal artery stenosis

In renal artery stenosis induction of renovascular hypertension, renin is recognized a key molecule, and as such in the therapy of renovascular hypertension Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor blockers (ARBs) are used [4]. Moreover, sympathetic nervous systems action in the kidney promotes renin secretion through renal efferent nerves, which also stimulate tubular sodium reabsorption [62], and in the 2K1C model denervation inhibit the onset of hypertension [62, 63]. Renal artery stenosis causes renovascular hypertension, which is associated with deterioration of kidney function [20]. Reduction in renal flow is recognize as a source of hypoxia during renovascular hypertension [21]. Arterial stenosis causes thrombosis, and ischemia in renovascular hypertension [22]. During renal artery stenosis generation of ROS is recognized as the main mechanism of renal damage [88, 89], causing increased in vasoconstrictors, cell death and decrease in the activity of nitric oxide [109, 110]. A swine model of renal artery stenosis presented an increase in ROS, renal and cardiac damage [23, 86–89, 111–113]. In renal artery stenosis activation of RAAS increase ROS generating by the activation of NADPH oxidase [90, 91], associated with is an increase in p47phox and p67phox [86–88]. Phosphorylation of p47phox by PKC is a key step in NADPH oxidase activation [114–118]. Hypertension is associated with PKC activation and increase oxidative stress [119], which caused endothelial nitric oxide synthase (eNOS) disfunction and uncoupling producing ROS instead of NO. This uncoupling is a key mechanism for endothelial dysfunction in angiotensin II-induced hypertension [120–122]. Increase in NOX2 activity requires increase NOX2 expression and p47phox association and activation of NOX2 [19]. Furthermore, increase in oxidative stress is well documented in 2K1C model [55–59, 123, 124]. All the actions mentioned above are Ang II mediated.

New evidence places (pro)renin receptor (PRR) as an effector molecule in the Ang II-independent RAAS [125]. PRR binds both renin and prorenin [125–129]. There is an association of PRR with different pathophysiology of diseases [130–135]. PRR binds renin causing an increase in Ang I [125] and it can activate prorenin by promoting a conformational change [125–129]. PRR mRNA is expressed in different organs such as kidney, heart, brain, eye, adipose tissue and vascular SMCs [125, 134], It has been proposed that PRR activates the Ang II-independent RAAS with tissue specificity [136]. My laboratory and others are uncovering new functions of the Ang II independent pathway in blood pressure, oxidative stress and organ damage. New studies will define the relevance of this arm of RAAS and possible define new molecular targets for therapy.

6. Concluding remarks and future perspectives

In the definition of the molecular pathways involved in the development of renovascular hypertension, the Goldblatt two kidney one clip animal model has been critical. This animal mode has been extensively used with different animals all showing that renal artery stenosis strongly stimulates renin overexpression and release promoting renovascular hypertensions and kidney injury. In renovascular

hypertension renin is key and promotes the increase in Ang II leading to hypertension. Renin being the rate limiting step in the production of Ang II in RAAS, has been investigated as a possible target for the therapy. However, the main therapies used are angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Direct renin inhibition by aliskiren, is potential therapy for hypertension in chronic kidney disease (CKD) and renovascular hypertension. Combination of aliskiren with olmesartan in the clinic, reduced proteinuria in patients with CKD with persistent proteinuria. In non-diabetic CKD patients, aliskiren combined with ARBs, reduced proteinuria and protected from the decline in glomerular filtration rate. We have shown here clinical and research data that indicates the during renal artery stenosis induced renovascular hypertension RAAS is activated and play a critical role in this pathology. It is important that a complete treatment of renovascular hypertension may need targeting both the angiotensin II-dependent and the Ang II-independent arms of RAAS.

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