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Intrarenal Renin-Angiotensin System in Regulation of Glomerular Function

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Abstract

Purpose of Review—The purpose of this review is to provide an update on the current knowledge regarding the role of the intrarenal renin-angiotensin system (RAS) in the regulation of glomerular function including glomerular dynamics and filtration rate, glomerular permeability and structural alterations during chronic increases in intrarenal Ang II.

Recent Findings—Recent studies have continued to delineate the complex interactions among the various RAS components that participate in regulating glomerular function. While angiotensin (Ang) II acting on AT1 receptors remains as the predominant influence on glomerular dynamics some of these effects are indirectly mediated by Ang II modulating the sensitivity of the macula densa tubuloglomerular feedback mechanism as well as the more recently described feedback mechanism from the connecting tubule. Interestingly, the actions of Ang II on these systems cause opposite effects on glomerular function demonstrating the complexities associated with the influences of Ang II on glomerular function. When chronically elevated, Ang II also stimulates and/or interacts with other factors including reactive oxygen species, cytokines and growth factors and other hormones or paracrine agents to elicit structural alterations.

Summary—Recent studies have provided further evidence for the presence of many components of the RAS in glomerular structures supporting the importance of locally produced angiotensin peptides to regulate glomerular hemodynamics, filtration rate, macromolecular permeability and contribute to fibrosis and glomerular injury when inappropriately augmented.

Keywords

Renal blood flow; glomerular filtration rate; angiotensin converting enzyme; Ang II type 1 receptor; glomerular permeability; glomerular fibrosis

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Introduction

It has long been known that the renin-angiotensin system (RAS) exerts powerful influences to regulate many aspects of renal hemodynamic and transport function including the cortical and medullary circulations, glomerular hemodynamics and the glomerular filtration coefficient in normal physiological states as well as in pathological conditions (1). While these regulatory influences are often attributed to the intrarenal RAS, it is difficult to clearly separate the influences of the intrarenal RAS from those of circulating angiotensin (Ang) II. Nevertheless, there are circumstances where the intrarenal and circulating RAS are in concordance, such as during variations in salt intake (2;3), and other situations where the alterations in the intrarenal RAS are not mirrored by the changes in the systemic renin and Ang II levels as occurs in certain types of hypertension and diabetes mellitus. This review will cover both situations. For each section, there is a brief background citing older studies to provide a foundation for the discussion of recent reports. It is important to emphasize that the constraints imposed for these brief reviews prevent the citation of all but a few older studies which reported original seminal observations.

Regulation of Intrarenal RAS

While this review is intended to focus primarily on the most important articles published during the last 12–18 months, it is worthwhile to mention some older information that sets the stage for a discussion of recent findings (1;4–6). For any given level of salt intake, the changes in systemic and intrarenal RAS are in synchrony, but the Ang I and Ang II levels in the kidneys, expressed per unit wet weight are substantially greater than the circulating concentrations (5). The medullary levels are even greater than those in the cortex. Furthermore, the renal interstitial fluid and proximal tubular fluid Ang I and II concentrations are also much greater than the circulating concentrations thus indicating that there is substantial interstitial and intratubular formation of these peptides regulating the local concentrations. In normal animals, most of the angiotensinogen (AGT) that serves as the source for the angiotensin peptides is of liver origin (7), while in hypertensive models there is an augmentation of proximal and renal vascular AGT message and protein (8). There are abundant Ang II receptors throughout the various tissues in the kidneys including all the components of the cortical and medullary circulatory beds (5). In adults, most of the receptors are of the AT1 type with the AT1a being more abundant than the AT1b. Functional studies indicate that the afferent arterioles have both AT1a and AT1b receptors while the efferent arterioles have only AT1a receptors (9). There are physiologically significant abundances of AT2 receptors and the Ang 1-7 mas receptors which may counteract the actions of AT1 receptors. AT2 receptor activation with a specific agonist vasodilates the glomerular vessels and interacts with dopamine receptors (10;11). The increased renal blood flow (RBF) is not accompanied by increases in glomerular filtration rate (GFR) suggesting maintenance of glomerular pressure due to combined afferent and efferent arteriolar vasodilation (11). AT2 receptors are also upregulated in the remaining kidney after fetal uninephrectomy allowing a greater renal vasodilator effect when an AT1 receptor blocker is administered together with Ang II (12).

Because several studies in hypertensive models and patients have demonstrated increases in intrarenal Ang II levels and in urinary AGT excretion in response to a high salt diet (13–16), it has sometimes been suggested that the intrarenal RAS normally responds to a high salt diet in a paradoxical manner by having an increased intrarenal RAS activity (16). It is important to emphasize that the stimulation of the intrarenal RAS by a high salt diet is an inappropriate pathological response that occurs only in the presence of co-stimulatory factors such as increased oxidative stress and formation of cytokines which are often associated with high Ang II levels, hypertension or diabetes (14). Under normal physiological conditions, a high salt diet suppresses the intrarenal RAS (3) while a low salt diet markedly increases intrarenal renin and Ang II levels (2;17) with very minor or non-significant changes in urinary AGT excretion rate. However, there is a “paradoxical” increase in proximal tubular Ang II concentrations in anesthetized rats maintained on a high salt diet even though tissue Ang II levels are suppressed (18). The caveat is that micropuncture procedures requires extended periods of anesthesia and surgery which stimulate RAS during both normal salt and high salt conditions. The renin response can include recruitment of renin-producing cells mediated by endothelin derived nitric oxide (NO) (19). Thus, while there are either minor increases or no changes in uAGT or kidney AGT mRNA in normal animals fed a high salt diet (14;15), substantive increases in urinary AGT in response to a high salt diet are a pathological response that may contribute to the development and progression of renal injury (15;16). When this happens there are associated increases in glomerular Ang II levels which can contribute to podocyte injury and mesangial expansion (13;14).

The presence of an intraglomerular RAS is reflected by the metabolism of angiotensin peptides by mesangial cells, podocytes and endothelial cells. Ang I processing rates are comparable among glomerular cell types with abundant angiotensin converting enzyme (ACE) normally present. There is also conversion to Ang 1-7 reflecting the presence of ACE2 (20). Network modeling studies suggest a wider role for aminopeptidase A and neprilysin in the glomerular formation of bioactive angiotensin peptides (21). Angiotensin AT1 receptor-associated protein (Arap1) is present in mesangial cells and renal vasculature and interacts with the AT1 receptor to facilitate surface expression. Arap1 mRNA and protein are suppressed by Ang II in mesangial cells, but it remains unclear how Arap1 modulates AT1 receptor function (22).

Reductions in the glomerular levels of ACE2 are associated with increased glomerular lesions presumably because of reduced Ang 1-7 levels and decreased production of atrial natriuretic peptide (23) but could also be the consequence of reduced degradation and metabolism of local Ang II levels. Regardless, ACE2 deficiency is associated with increased oxidative stress, proinflammatory and profibrotic changes and reduced atrial natriuretic peptide levels which are partially restored by treating with Ang 1-7, ACE2 or the mas receptor agonist (23). Ang 1-7 acting via the mas receptor stimulates ERK1/2 phosphorylation via a cyclic AMP/PKA dependent pathway in mesangial cells (24). Such an effect is not entirely consistent with the concept that Ang 1-7 exerts renoprotective effects. In models of hypertension, there is upregulation of ACE and downregulation of ACE2 leading to increased Ang II levels along with reduced Ang 1-7 levels (6;25). However, there are decreased intrarenal levels of ACE in models of diabetes mellitus associated with

upregulation of ACE2 (26) and chymase (27). The reduced ACE activity may be partially renoprotective, but the increased chymase provides an alternative pathway for Ang II formation which may contribute to the progression of diabetic nephropathy (27).

While the presence of renin in afferent arterioles is firmly established, recent studies have examined the exocytotic process in greater detail (28) and the metabolic control of renin release by GPR91 (29). In addition to active renin, prorenin is also produced by the juxtaglomerular cells which is secreted into the interstitial space in and around the glomerular cells. Prorenin is not able to act directly on AGT to form Ang I, but it can be activated by the prorenin receptor (PRR) which has been shown to be localized at several sites in the kidney including glomeruli (25;30–32). Renal mesangial cells and podocytes have PRR and can activate prorenin either formed locally or delivered from the circulation leading to increased expression of transforming growth factor, plasminogen activation inhibitor I and fibronectin which can lead to Ang II independent mechanisms of cell injury especially under condition of elevated prorenin levels as occur in diabetes mellitus (31;33). Furthermore, high glucose directly upregulates the PRR in mesangial cells enhancing the likelihood of increased non-proteolytic activation of prorenin (32). In addition to glucose, a low salt intake enhances renal PRR expression in renal glomeruli as well as in proximal and distal tubules and collecting ducts (34). This occurs via the cGMP-PKG signaling pathway leading to increased binding of the cAMP response element binding protein I, NFκBp65 and c-Jun to PRR promoter (34). Treatments that increase cGMP increase PRR mRNA and protein while treatments that reduce cGMP levels decrease PRR expression (35).

These recent studies have established the presence of many components of RAS in glomerular structures thus suggesting important roles for locally produced angiotensin peptides which can influence glomerular hemodynamics and glomerular permeability. The increased permeability is due, in part, to loss of glomerular basement membrane anion charges caused by AT1 receptor activation and prevented by treatment with an AT1 receptor blocker (36). While there continues to be substantial controversy regarding the glomerular permeability to macromolecules including AGT, studies using multiphoton microscopy to visualize and quantify glomerular permeability have confirmed the extremely low glomerular permeability of albumin and AGT in healthy glomeruli (37). However, in various disease conditions, increased glomerular levels of Ang II combined with increased reactive oxygen species may activate various signaling pathways which together may increase glomerular permeability to macromolecules leading to increased filtration of AGT and albumin (38). During infusions of Ang II, the increases in glomerular permeability were abrogated by scavengers of reactive oxygen species and reduced by RhoA and Rac-1 inhibitors (38). Thus, under both physiological and pathological conditions, an augmented glomerular RAS activity decreases glomerular blood flow and filtration rate and may also decrease the filtration coefficient. However, if glomerular RAS is inappropriately upregulated and prolonged, increased permeability to proteins along with glomerular and podocyte injury leading to inflammation, oxidative stress and tissue fibrosis may occur (39). Overexpression of dopamine can partially mitigate the Ang II induced renal injury (40).

Actions of Angiotensin Peptides on Glomerular Function

The predominant vascular and glomerular effects of Ang II are to vasoconstrict preglomerular and efferent arteriolar vascular smooth muscle and mesangial cells, and to alter the glomerular filtration coefficient and the macromolecular permeability coefficient via its actions on mesangial cells and/or podocytes (1;4). Although still denied by some, there is now abundant evidence that Ang II has a very important role in the regulation of afferent arteriolar resistance (1;4;41) and even greater effects in chronic kidney disease and other pathological conditions (42;43). Ang II was shown to activate P47 (phox)/neutrophil oxidase 2 which increases NADPH oxidase activity leading to accentuation of afferent arteriolar constriction. Afferent arterioles from mice deficient in P47(phox) had lesser myogenic responses and reduced contractile response to Ang II and failed to show increased sensitivity to acute Ang II following chronic Ang II infusions (41). Thus, the level of oxidative stress contributes to the sensitivity of the afferent arterioles to Ang II. At the whole kidney level, increased intrarenal RAS reduces RBF with lesser decreases in GFR, but does not alter the overall capability of the kidney to autoregulate RBF and GFR unless the intrarenal RAS is chronically increased and coexisting with hypertension or other renal pathologies (1). Intrarenal arterial infusions of Ang I elicit effects very similar to those of Ang II indicating rapid and substantial intrarenal conversion of Ang I to Ang II. In addition to direct effects on the afferent and efferent arterioles, increased intrarenal Ang II levels modulate the sensitivity of the tubulo-glomerular feedback (TGF) mechanism thus augmenting the magnitude of the vasoconstrictor responses operating from the macula densa to the afferent arteriole (1;44). AT1 receptors are also present on the macula densa cells indicating that these actions are mediated not only by increasing the contractility of the vascular smooth muscle to TGF signals but also by increasing the intensity of the signals emanating from the macula densa cells (1). Aldosterone also acts directly on macula densa cells to release both NO and superoxide with the inhibitory effect of NO predominating (45). The increased superoxide levels partially buffer the effects of NO. An additional "TGF" mechanism operates from the connecting tubule to regulate afferent arteriolar tone (CTGF), but in a manner that counteracts the macula densa TGF (46;47). Increases in connecting tubule luminal sodium concentration cause dilation of the afferent arteriole which is thought to be mediated by release of prostaglandins and epoxyeicosatetraenoic acids. The specific role of this counteracting CTGF remains unclear but may mediate acute resetting of the macula densa TGF mechanism (47). By stimulating sodium channels (ENaC) in principal cells, Ang II enhances the CTGF responses (46). The Ang II effects are mediated via protein kinase C/NADPH oxidase 2/superoxide (PKC/NOX2/O₂⁻) pathway which does not participate in the feedback response in the absence of Ang II (48).

While the glomerular responses to agents that block the RAS have been somewhat variable due to the varying magnitude of the arterial pressure changes, the direct actions of ACE inhibitors and Ang II receptor blockers (ARBs) and renin inhibitors are to vasodilate both afferent and efferent arterioles, thus increasing RBF with smaller changes in GFR depending on the corresponding changes in glomerular pressure. GFR may also increase due to increases in the filtration coefficient. However, during the hyperfiltration phase of diabetes, AT1 receptor blockade reduces GFR back to normal levels (49). ARBs and ACE inhibitors

also decrease the sensitivity of the TGF mechanism and thus reduce the vasoconstrictor responses to increases in TGF signals. At the whole kidney level, RAS blockade increases RBF, but does not prevent RBF autoregulatory responses to variations in renal perfusion pressure (1). RAS blockade also markedly reduces the glomerular and interstitial injury that results in models of hypertension, diabetes, glomerulonephritis and chronic kidney disease (14;50;51).

The direct effects of angiotensin peptides on glomerular hemodynamics and filtration rate have been reasonably well characterized. Thus, most recent studies have probed the complex interactions between Ang II and other angiotensin peptides or other factors. The indirect effects of angiotensin peptides are complex and sometimes have opposite consequences. As discussed earlier, vasodilator actions due to AT₂ and mas receptor activation can counteract or mask AT₁ receptor actions (10;24). AT₁ receptor activation at the connecting tubule feedback segment can exert opposite effects on the afferent arterioles as demonstrated by studies showing that AT₁ receptor activation potentiates the vasodilation signals caused by increased sodium concentration (48).

The interactions between Ang II and members of the arachidonic acid cascade have also demonstrated complexity. The marked increases in Ang II levels that result from a very low sodium diet or in experimental hypertension activate cyclooxygenase 2 (COX2) which releases vasodilator prostaglandins and partially offsets the Ang II mediated vasoconstriction (52). In contrast, the COX2 mediated activation of thromboxane contributes to the hypertension elicited by chronic Ang II infusions (52). In mice, the absence of thromboxane receptors in vascular smooth muscle cells led to significant attenuation of Ang II induced hypertension and vascular remodeling (53).

In addition to the ability of NO to directly vasodilate the afferent and efferent arterioles, NO also serves to counteract the modulatory influence that Ang II and adenosine exert on the macula densa TGF mechanism (44). There is a synergistic interaction between adenosine and Ang II in that adenosine enhances the contractile response to Ang II and Ang II increases the contractile response to adenosine. Ang II also activates NADPH oxidase leading to increased generation of superoxide which exerts additional vasoconstrictor effects on the glomerular arterioles. However, in the presence of high NO levels, this contractile responses are abolished or attenuated (44). Likewise, when the intrarenal carbon monoxide levels are increased by stimulating heme oxygenase production, the plateau of the renal autoregulatory relationship is increased and the acute renal vascular contractile responses to Ang II administration are attenuated (54). In addition to the interactions of the intrarenal RAS with hormonal and paracrine agents, it has long been known that there are important interactions with the sympathetic nervous system. Increased renal sympathetic activity not only stimulates renin secretion, but also directly reduces RBF and GFR. The ability of AT₁ receptor blockade to attenuate the vasoconstrictor responses to renal nerve stimulation indicates that part of the hemodynamic responses are mediated by augmented intrarenal Ang II levels (55).

Intracellular Mechanisms

AT1 receptor mediated contractile mechanisms are complex and involve both intracellular calcium mobilization and calcium entry via calcium channels (1). Functional and molecular evidence indicates that afferent arterioles have both L-type and T-type calcium channels while the efferent arterioles do not utilize L-type channels under normal circumstances but efferent L-type channels are activated during NO synthase inhibition (56;57). Activation of chloride channels (58) and T-type calcium channels appear to initiate the depolarization process leading to intracellular calcium mobilization and calcium entry via L-type channels. Transient receptor potential canonical channels and the Na/Ca exchanger also contribute to Ang II mediated vasoconstriction (59), and P/Q-type calcium channels contribute to depolarization-induced vasoconstriction (60). The acute renal vascular constriction to Ang II was found to be attenuated in mice lacking Na⁺/Ca²⁺ exchanger in vascular smooth muscle (61). There is a myriad of intracellular signaling pathways that are activated by AT1 receptors including G-protein-derived second messengers, protein kinases, small G-proteins, growth factor receptors, NADPH oxidases and Rho and its effector Rho-kinase (62–64). Rho-kinase inhibition attenuates Ang II induced increases in renal vascular resistance and decreases in GFR (65). In mesangial cells, Ang II phosphorylates ETS-1 via AT1 receptors leading to fibronectin production (66).

Chronic Activation of Intrarenal RAS

Chronic Ang II infusions sufficient to cause hypertension impair renal autoregulatory capability and lead to glomerular injury (67;68). However, during the early stages of Ang II induced hypertension, GFR is only slightly reduced or maintained due to preservation or even enhancement of intrarenal NO system and antioxidant capacity (69). With continued Ang II mediated stimulation, there is a progressive increase in production of reactive oxygen species. Chronic Ang II infusions or L-NAME infusions activate lymphocytes which lead to an inflammatory response and also reduce renal function and impair autoregulation (68). These renal responses that occur with inappropriate activation of the intrarenal RAS are partially due to an augmentation mechanism by which there is a further stimulation of the AGT message and protein and further ACE dependent formation of Ang II (8;70;71). Superimposing a high sodium diet leads to further exacerbation involving marked increases in intrarenal Ang II as reflected by increased urinary excretion of AGT and are associated with glomerular and interstitial fibrosis (14). Interestingly, immunosuppressive therapy prevents lymphocyte infiltration, preserves renal autoregulatory function, and restores pressure natriuresis even though the magnitude of the hypertension is not significantly reduced (68;72).

Chronic Ang II infusions also stimulate increases in renal interstitial ATP concentrations due in part to the increased arterial pressure. The ATP activates P2 receptors which synergize with Ang II to increase afferent and efferent arteriolar resistance. Blocking the P2 receptors reduced the afferent and efferent arteriolar resistances and increased glomerular blood flow and single nephron GFR and the glomerular filtration coefficient (73). Thus, there is an enhanced P2 receptor mediated renal vasoconstriction in Ang II induced hypertension.

The Cyp11a1-Ren 2 transgenic rat provides a model of hypertension mediated by chronic activation of renin production and has been used to test the effects of the renin inhibitor, aliskiren (74;75). The increased intrarenal Ang II levels that occur over a period of several days up to 2 weeks reduce renal plasma flow and GFR as a consequence of afferent and efferent arteriolar vasoconstriction and reduced glomerular filtration coefficient indicating increased glomerular Ang II levels. In general, the pattern of glomerular and interstitial injury is similar to that occurring in the chronic Ang II infused model. However, this model is responsive to direct renin inhibition. Systemic treatment with aliskiren prevents the decrease in renal plasma flow and GFR and the increases in renal vascular resistance (76). However, infusion of aliskiren via the renal artery did not reduce arterial pressure or reverse the reduction in renal plasma flow or GFR indicating that, in this model, the very high circulating Ang II concentrations are sufficient to explain the renal vasoconstriction (77). Interestingly, the intrarenal infusions of aliskiren markedly increased urine flow and sodium excretion but decreased urinary Ang II excretion supporting an effect of the renin inhibitor to reduce intratubular Ang II formation.

Conclusion

In conclusion, recent studies have demonstrated further the intricate complexity of the intrarenal RAS and the various components that regulate glomerular function. Under physiological conditions, appropriate changes in Ang II levels contribute to regulate glomerular hemodynamics but are buffered by various counter-regulatory factors. When inappropriately activated and particularly in the presence of oxidative stress and inflammation associated with hypertension, diabetes or various kidney diseases elevated Ang II levels lead to mesangial expansion along with podocyte injury and glomerular fibrosis.

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Abbreviations

Ang	angiotensin
ACE	angiotensin converting enzyme
AGT	angiotensinogen
Arap1	angiotensin AT1 receptor-associated protein
ARBs	angiotensin II receptor blockers
AT1	angiotensin II type 1 receptor
COX2	cyclooxygenase 2
GFR	glomerular filtration rate
NO	nitric oxide

PRR	prorenin receptor
RAS	renin angiotensin system
RBF	renal blood flow
TGF	tubulo-glomerular feedback

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activity is required to have the augmentation of intrarenal Ang II that occurs in response to chronic Ang II infusions. [PubMed: 23619363]

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Key Points

- The presence of renin, PRR, ACE, ACE2, Ang II, Ang 1-7, AT1 and AT2 receptors and the mas receptor, support local formation of angiotensin peptides in glomeruli and glomerular arterioles.
- Ang II acting via AT1 receptors is the predominant angiotensin peptide regulating glomerular hemodynamics but AT2 receptors and Ang 1-7 as well as other paracrine agents buffer these actions.
- In addition to the macula densa TGF mechanism, there is an additional TGF mechanism that is stimulated by Ang II operating from the connecting tubule that vasodilates afferent arterioles.
- The complexity of the intracellular signaling mechanisms mediating Ang II actions continues to increase and involves interactions with nitric oxide, reactive oxygen species, arachidonic acid metabolites, and other humoral and paracrine agents.
- When inappropriately activated, increased glomerular Ang II levels stimulate cytokines and inflammatory factors leading to mesangial expansion, tissue injury, and glomerular fibrosis.