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## **Intrarenal renin - angiotensin system**

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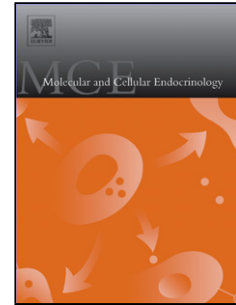
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**Intrarenal renin - angiotensin system**  
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## Abstract

Phylogenetically the renin–angiotensin system (RAS) is an ancient regulatory system which has attracted the attention of researchers for about a century. As a result of their efforts, different types of RAS inhibitors are now widely used as therapeutic medicines. The scientific enthusiasm toward RAS remains undiminished and new findings and discoveries are to be expected. Early investigators described the role of RAS in the local control of renal hemodynamic. This correlated well with the morphology of juxtaglomerular apparatus (JGA). Recently developed imaging techniques has allowed for in vivo visualization of cellular functions and the use of molecular biological tools have shed new light on the morphology and physiology of renal RAS, especially in connection with the tubular system. RAS has gained recognition to be more than just an endocrine regulatory system for regulating hemodynamics and water/salt metabolism. RAS is a local tissue and/or cellular regulator with a wide range of effects exerted via various receptors. Local RAS is crucially involved in basic physiological processes like ontogenesis and cell proliferation as well as pathophysiological conditions such as inflammation and tissue fibrosis. These findings may open new frontiers for novel therapeutic approaches. This review focuses only on some specific - less discussed and recently described or hypothesized - morphological and functional aspects of intrarenal RAS, including in vivo imaging of RAS, its effects on juxtaglomerular apparatus and possible cooperative mechanisms among various local renal RAS systems.

## Introduction

The history of RAS, a regulatory system present even in early phylogenesis, started a century ago when Tigerstedt described the renal vasoconstrictive effects of renal tissue extracts (Tigerstedt and Bergman, 1898). Ever since, interest in the RAS has continued to increase, in spite to the fact that RAS inhibitors were introduced more than two decades ago which are now widely used in clinical practice, especially in elderly hypertensive and renal and cardiac failure patients (Sarafidis et al 2008).

It was assumed, by early investigators, that swelling or shrinking of the granular cells of the juxtaglomerular apparatus control glomerular blood flow (Ruyter, 1925). Thus, local hemodynamic control was one initial function ascribed to the RAS by early investigators in this area (Leysac, 1976). RAS has been considered to be a local controller of renal blood flow based on the renin localization in granular cells of renal afferent arteriole (Navar and Rosivall, 1984).

Early morphologists described the unique, intimate, and consistent contact of granular cells with the extraglomerular mesangium and specialized cells of the early distal tubule (macula densa); they coined the term juxtaglomerular apparatus. The special juxtaposition of the macula densa to the afferent arteriole suggested the existence of mechanisms linking tubular function with control of arteriolar contraction (Golgi, 1889). Goormaghtigh, based on morphological studies (1937), proposed a complex endocrine function for the juxtaglomerular apparatus. He postulated the release of an agent by the granular cells that could activate or form a vasoactive substance which, in turn, could influence local vascular tone. This amazing theory, which was well ahead of his time, has subsequently proved to be correct. Although some investigators continue to support the notion that local control is the major function of the RAS, others have focused on non-renal functions of RAS including control of aldosterone release, regulation of systemic cardiovascular function, and pathophysiology of hypertension.

Since the 1970's, the availability of sophisticated biochemical, molecular biological and imaging techniques, have allowed investigators to reveal the complicated nature of the so-called circulating RAS (Dzau 1988, Ganten et al 1989). All the components of RAS have been demonstrated to be present in an ever-expanding list of tissues. These are referred to as local RAS. For instance, it is now known that local/tissue renin-angiotensin systems exist in nervous system, heart, vasculature, reproductive system, gastrointestinal tract and adipose tissues. In kidney, RAS is present not only in the juxtaglomerular apparatus and interstitium, but also in various segments of the nephron (Navar et al, 1994). Renal tubular RAS was recognized when the highest known angiotensin concentration in the body was measured in tubular fluid (Seikaly et al, 1990). Subsequently it was shown, that all components of RAS are present in vascular smooth muscle cells of afferent arterioles and glomerular podocytes, suggesting the involvement of intracellular renin-angiotensin system in local regulatory systems (Rightsel et al, 1982).

The presence of local RAS in tissues has led to the identification of new roles for angiotensins as paracrine and autocrine/intracrine systems (Paul, 2006, Kumar et al, 2008). Indeed, the RAS is now considered much more than an endocrine regulatory system involved in salt and water metabolism and hemodynamics. It is also involved as a local tissue and/or cellular regulator with a wide range of effects exerted via its various receptors. These receptors include angiotensin receptors (I, II, III, IV), receptors of angiotensin active metabolites and prorenin/renin receptors ((P)RR). RAS also plays a crucial role in other physiological processes including ontogenesis and cell proliferation as well as pathophysiological conditions like inflammation and tissue fibrosis. Due to the diverse effects of RAS, the RAS inhibitors (converting enzyme inhibitors, angiotensin receptor blockers, renin/prorenin receptor blockers, blockers of renin release) are beneficial in reducing blood pressure, increasing renal blood flow and GFR, decreasing the progression of renal tissue damage, albuminuria, cardiac hypertrophy, and cognitive disturbances (Paul et al, 2006, Kobori et al, 2007, Dandona et al, 2007, Bader and Ganten, 2008, Phillips and de Oliveira, 2008).

A number of extensive reviews focus on different aspects of RAS (Paul et al, 2006, Kobori et al, 2007, Dandona et al, 2007, Schweda et al, 2007, Bader and Ganten, 2008), while review - will mainly focus on some specific - less discussed and recently described or hypothesized - morphological and functional aspects. This will include in vivo imaging of RAS, its effects on juxtaglomerular apparatus and possible cooperative mechanisms among the different local renal RAS systems.

### **RAS and the kidney**

By its "simple" and "classical" definition, RAS is an endocrine system involving liver, kidney, lung and circulation. Renin is secreted into the lumen of afferent arteriole from the juxtaglomerular apparatus. The substrate of renin, angiotensinogen, is released from the liver and cleaved in the circulation, to form the decapeptide, angiotensin (ANG) I. Further cleavage occurs by angiotensin converting enzyme (ACE) to form to angiotensin II. ACE is predominantly expressed in and bound to the surface of endothelial cells in the pulmonary circulation. ANG II, considered the main effector peptide of RAS, acts on specific receptors, to induce vascular smooth muscle cell contraction or aldosterone release from adrenal glands (Paul et al, 2007). In contrast, what is presently known about the RAS is far more complicated and there continues to be a number of uncertainties (Lalouel et al, 2007, Hanner et al, 2008). New discoveries about different pathways of angiotensin formation, description of new active components, metabolites, receptors, different localizations, and regulatory mechanisms have added to our understanding and complexity of RAS.

## *Prorenin*

The vast majority of renin is synthesized as prorenin in granular cells of the renal afferent arteriole. Prorenin is converted to renin upon insertion into the endoplasmic reticulum. While small portion of prorenin is released via secretory granules, about two third of it is secreted constitutively into the circulation unlike renin whose secretion is regulated. There is a correlation between circulatory renin and prorenin concentrations. However, under some conditions, for example in diabetic nephropathy, prorenin concentration may increase in an isolated manner (Luetscher et al, 1985, Ichihara et al 2006/A, B, Toma et al., 2008). This increase of prorenin levels in kidney tissue and plasma, under diabetic conditions, may depend on the activation of GPR91, a kidney-specific G protein-coupled metabolic receptor (Toma et al., 2008).

Recently, an additional source of prorenin from collecting ducts has been described. A fluorogenic renin assay was used to calculate the difference in enzymatic activity of tissue homogenates before and after trypsin activation of prorenin. This assay demonstrated that prorenin is produced and secreted in collecting ducts. This secretion is not only important during basal conditions, but prorenin content and release from collecting ducts in diabetes may be more important than the release of prorenin from granular cells of afferent arteriole (Kang et al, 2008).

Prorenin was thought to be an inactive precursor of renin. Its concentration in plasma is several folds higher than that of renin (Luetscher et al, 1985, Krop et al, 2008). In experimental diabetic nephropathy the benefit of ACE inhibitors correlates better with prorenin than renin concentration. Thus, it is plausible to assume that either prorenin is converted to renin in the circulation or local tissue, or the prorenin has its own activity. While there is no evidence for the first assumption, more and more data support the special activity of prorenin.

Prorenin may have inherent enzymatic activity (Nguyen et al, 2002, Danser and Deinum, 2005). Activation of prorenin may occur by proteolytic or non-proteolytic ways. Binding of prorenin to its receptors may activate prorenin with no cleavage of pro segment, which would otherwise cover the binding site for angiotensinogen. It is assumed that binding of prorenin to its receptor induces a conformational change in the prorenin molecule just like low pH or cold temperature. The activated prorenin is able to generate angiotensin I from angiotensinogen. (P)RR - which binds renin and prorenin - was cloned by Nguyen et al (2002). It was shown that prorenin/renin binding may activate mitogen activated protein kinase. Over expression of prorenin receptor under experimental conditions in rats with normal renin level may cause an increase in blood pressure, plasma aldosterone level, and promote the development of glomerulosclerosis (Burcklé et al, 2006, Kaneshiro et al, 2006). These findings suggest that prorenin may have angiotensin-like, as well as angiotensin-independent effects through the non-internalized (P)RR. Based on these observations, RAS may be envisioned as a prorenin/renin - angiotensin system. Inhibition of RAS causes an increase in plasma renin and presumably prorenin concentration. However, the possible functional consequences of this increase during the inhibition of RAS by different agents, including converting enzyme inhibitors, angiotensin receptor blockers or direct renin inhibitor, is far from understood. More work needs to be focused on physiological conditions that alter or regulate (P)RR expression. It was demonstrated that an increase in prorenin concentration may decrease the (P)RR

expression which would serve as a negative feedback mechanism (Scheffe et al, 2006). It is worth mentioning that a familial elevation of prorenin concentration due to a mutant renin gene was not accompanied by elevated blood pressure (Villard et al, 1994). (P)RR has also been shown to be a necessary element for cell survival and proliferation and its mutation may be associated with mental retardation and epilepsy (Nguyen, G; Contrepass, A. 2008.).

## **Renin**

Cleavage of angiotensinogen by renin is the rate limiting step in the formation of ANG II. Renin secretion is highly regulated. There is a strong expression of renin in the distal wall of afferent arteriole, extending up-stream from the juxtaglomerular apparatus (Gomez, 1989). In addition, renin mRNA has been demonstrated in glomeruli, proximal, and distal tubules (Rohrwasser, 1999, Lantelme, 2002, Prieto-Carrasquero, 2004). Renin is also present in the connecting tubules in both mice and rats (Kang et al. 2008). Renin expression in JGA cells is tightly regulated by the beta adrenergic receptor, a macula densa mediated mechanism, renal baroreceptors, and an angiotensin II mediated mechanism. Renin is secreted as an active enzyme from the secretory granules (Schalekamp et al, 2008).

There are a number of studies describing the intracellular steps regulating renin expression, which are mainly based on *in vitro* renal studies. However, the detailed molecular mechanisms operating *in vivo* remain unclear. Recent advances in the development of sophisticated mouse models have provided a better understanding of the renin gene regulatory mechanisms. Using cell-specific cre-LoxP-mediated gene ablation, Chen et al. (2007) reported that the G-protein  $G_{\alpha_s}$  is an essential component of the signal transduction machinery which regulates renin expression and release. However, it still remains unclear as what DNA sequences control the tissue-specific, cell-specific, and regulated expression of the renin gene *in vivo*.

A potent transcriptional enhancer 2.6 kb upstream of the mouse renin gene has been identified (Petrovic, 1996). Analysis of the enhancer, using immortalized renin-expressing cell line *in vitro*, has led to the conclusion that several different transcription factors exhibiting either stimulatory or inhibitory effects on renin expression may bind to the enhancer. Renin levels in mice are much higher than in humans suggesting that the enhancer may be more active in mice. Although the enhancer is conserved among mammalian renin genes, there are some critical differences that markedly influence the level of enhancer activity (Zhou et al, 2006).

Several decades ago, the observation that renal renin secretion responds to osmotic change either in renal perfusate or in the microenvironment of juxtaglomerular cells, prompted many investigations. Animal studies have provided contradictory results. It was found that administration of osmotic diuretics such as mannitol and urea decrease baroreceptor-stimulated renin secretion and suppress plasma renin activity in dogs (Vander and Miller, 1964, Birbari, 1972). Other researchers, also using dogs, reported that intrarenal infusion of either urea or dextrose increased plasma renin activity (Young and Rostorfer, 1973). While changing intrarenal plasma osmolality by graded levels of hypertonic saline had no effect on renin secretion rate (Kopp and DiBona, 1983).

In an effort to avoid the complexity and ambiguity of whole animal studies, there has also been a larger number of *in vitro* studies using renin-releasing preparations such as kidney tissue (Frederiksen et al, 1975), isolated glomeruli (Holdsworth et al. 1976), isolated afferent arterioles (Twu et al 1989), cultured juxtaglomerular (JG) cells (Jensen and Skøtt, 1993). These studies have concluded that minor changes in the osmolarity of the fluid surrounding renin-containing cells inversely influence renin release.

Recently these data have been questioned by Kurtz and Schweda (2006) using an isolated, perfused kidney model. They found a direct relationship between increased osmolality of renal perfusate and rapid and pronounced renin secretion in both rat and mouse kidneys. This response was concentration dependent and further amplified cAMP-mediated renin secretion induced by isoproterenol and was blunted by angiotensin. These data suggest that renin response to an osmolar stimulus is not due to direct changes in second messengers such as intracellular calcium or cAMP, but acts synergistically with these signals. This study showed that renin secretion is independent of flow and also of an interaction with the macula densa pathway, suggesting that JGA cells serve as osmosensors.

Recently, using fluorescence confocal imaging technique, it was demonstrated in a JGA microperfusion model that increasing glucose concentration of the afferent arteriole perfusate triggers renin release and vasodilatation of the afferent arteriole (Toma et al 2008). This endothelium dependent effect of high glucose most likely involves NO and prostaglandins, since both NO synthase and cyclooxygenase inhibition abolished renin release.

Recent evidence suggests that succinate, long known as an intermediate in the citric acid cycle, may also have a signaling role by activation of GPR91 resulting in blood pressure increase via the renin-angiotensin system. GPR91 was detected mainly in proximal tubules and to a smaller extent, in the distal tubules and the juxtaglomerular apparatus (He et al., 2004). It was also demonstrated that disruptions in the Krebs-cycle leads to renin release specifically in the presence of succinate in afferent arteriole. This is associated with pronounced GPR91 immunostaining of the endothelium (Toma et al 2008). When *in vitro* microperfusion experiments were conducted in the JGA preparations from both GPR91<sup>+/+</sup> and GPR91<sup>-/-</sup> mouse kidneys, glucose-induced renin release was diminished in the GPR91<sup>-/-</sup> mouse. It was concluded that the endothelium dependent effect of high glucose on renin release is relatively insensitive to hyperosmotic stimulus, but significant responsive to a metabolic component involving the succinate receptor GPR91. Further studies are necessary to determine whether there is a similar role for succinate filtered into the tubular fluid.

The secretion of renin by granular cells of the afferent arteriole is also under the influence of stimuli transmitted through the JGA, initiated by changes in intratubular flow and sodium chloride concentration (Schweda et al, 2007). In this process macula densa (MD) cells serve as sensors and link tubular events to vascular RAS. Classically, MD cells are considered to sense low tubular sodium chloride concentration, causing renin secretion. The role of salt reabsorption through various NKCC2 isoforms in MD function and renin signaling is well established (Bell et al, 2003). In a recent study, another element of the MD salt sensing mechanism was described, i.e. the NHE2. According to this model, low tubular sodium chloride concentration leads to reduced MD NHE2 activity and the consequent cell acidification, leads to phosphorylation of MAP kinases, ERK1/2 activation and PGE2 synthesis through induction of COX-2 and mPGES (Hanner et al, 2008).

Connexins, which are integral membrane proteins that form large transmembrane channels, so called hemichannels, are important pathways for the molecular cross talk and signal transmission between cells. The JGA represents a local micro-regulatory center, which comprises several cell types coupled via gap junctions. The predominant connexin in this region is Cx40, which may serve as a communication channel between the endothelium, extraglomerular mesangium, and renin containing granular cells (Wagner, 2008). Within the vasculature, Cx40 is expressed almost exclusively in the endothelium. In a recent study Cx45 was also localized and functionally characterized in JGA (Hanner et al, 2008). Interestingly, juxtaglomerular renin-producing cells do not express Cx43 which is normally found in vascular smooth muscle cells (Hwang and Beyer, 2000). A role for connexin in regulation of renin secretion is supported by the recent experiments in which renal artery stenosis was

induced in Cx40-deficient mice. As opposed to what is found in normal mice, Cx40-deficient mice did not have increased blood pressure, elevated plasma renin concentration and renin secretion in the hypoperfused kidney. It was also shown that decrease in angiotensin did not lead to the expected increase in renin levels in Cx40-deficient mice (Wagner et al, 2007). Finally, deficiency of Cx40 interrupts the inhibitory macula densa signaling of renin-producing cells. Thus, loop diuretics normally stimulate the activity of the renin system in wild-type mice, whereas this stimulating effect is markedly attenuated in Cx40 knock-out mice (Kurtz et al, 2007). It is of interest to determine the relationship between renin secretion and connexins, under diabetic conditions and hyperglycemia. These recent studies of renin secretion regulating mechanisms demonstrate potentially new targets for therapeutic interventions. The complex regulation of renin release also underlines the importance of the control of RAS secretion.

Renin secretion under different pathological conditions is not the primary focus of this review. However, autosomal dominant polycystic kidney disease (ADPKD) deserves special attention. In a recent study, Mahmoud L-A et al. (2004) discussed the possible mechanisms of intrarenal RAS upregulation in ADPKD. They argued that polycystins could be involved in the regulation of renin production by modulating sodium or calcium fluxes across the cyst epithelium because the polycystin 1/polycystin-2 complex is a nonselective sodium/calcium channel (Gonzalez-Perrett, 2001, McPherson et al 2004) (Hanaoka et al, 2000). It has been shown that cilia which contain polycystins act as flow sensors in renal tubules, transducing mechanical fluid flow signals into calcium signals (Nauli et al. 2003). In cultured cells with a homozygous polycystin mutation, cilia fail to sense fluid flow, hence they speculated: “that increased renin expression by cyst-lining epithelia might be related to failure of mechanosensation resulting from polycystin mutations” i.e. alteration of cilia function. Whether it is true in ADPKD that cilia are involved in tubular renin secretion remains to be clarified.

While in the juxtaglomerular apparatus angiotensin inhibits renin secretion, the opposite has been observed in the collecting duct (Kang et al, 2008,). Similarly, in experiments performed in porcine proximal tubular cells it was found that angiotensin II stimulated the transcriptional activity of several renin promoter – luciferase constructs suggesting that this effect is mediated by tyrosine kinases and the JNK (c-JUN NH2-terminal Kinase) cascade (Terebessy et al., 2004). It was also shown that tubular expression of renin may be regulated by sodium chloride concentration. In general, the regulation of the renin release is widely studied – more in the JGA - yet it is not fully understood in its entire. This is true for the renin originating from afferent arteriole and even more so for that of tubular origin.

### ***Renin in different renal compartments***

The primary secretory pathway for renin into the interstitium or into the lumen of the arteriole has been debated for a long time. It has been demonstrated that the renin concentration in the afferent arteriolar blood is lower than that of the efferent arteriole (Leyssac 1979). Multiphoton fluorescence imaging has recently made it possible to visualize and study the dynamics of both the release and tissue activity of renin in isolated and perfused afferent arterioles with attached glomeruli dissected from rabbit kidneys. Supportive of renin release into the interstitium, was the observation that quinacrine-labeled renin-granules disappeared while there was a simultaneous increase in renin activity of fluid around granular cells of the

perfused afferent arteriole (Peti-Peterdi et al, 2004, Rosivall et al 2007). In addition, under most circumstances interstitial renin concentration is much higher than that of the circulating blood. These data argue that besides secretion of renin into the circulation, there must be a substantial amount of interstitial secretion.

Renin is a relatively large molecule (40-50 KD). Therefore, it was not clear how renin can get through the endothelium of the afferent arteriole (AA). It was demonstrated that the afferent arteriole, morphologically and functionally, consists of two different segments (Rosivall and Peti-Peterdi, 2007). The proximal part of AA is characterized by renin-negative smooth muscle cells lined with a non-permeable endothelium (Rosivall and Taugner, 1986). The distal part of AA is renin-positive lined with a fenestrated (permeable) endothelium in mammals including humans. The fenestrations in endothelial cells are present in capillaries, but not normally seen in high-pressure vessels like arterioles, except for arterioles of endocrine organs. In addition, it has been demonstrated *in vivo* that the length of fenestrated portion of AA strongly correlates with the length of renin-positive portion (Rosivall et al 2006). This fenestration was shown to be permeable not only to small ferritin (Rosivall et al. 1990) and lucifer yellow molecules, but also to larger molecules such as dextran (40 KD) in a lesser extent (unpublished data). The fenestrated endothelium i.e. the endothelial nano-channels may provide a communication link between the tubular and vascular elements, the two major local RAS system compartments.

It has been demonstrated that the granular cells in the distal portion of afferent arterioles are not the only source of intrarenal renin. There are a number of other sites in which renin has been localized. Kidneys from newborn animals or those treated with angiotensin-converting enzyme inhibitors also contain renin with positive immunostaining in the afferent arteriole extending well beyond the distal portion of the AA. Indeed, the interlobular artery as well as the larger arteries may contain renin granules (Gomez et al, 1989, Rosivall et al 2007). Using multiphoton laser microscopy, renin was visualized *in vivo* in cells of glomeruli (mesangial and podocytes) and proximal and distal nephron segments (Sipos et al, 2007). Renin was also detected in the urine suggesting its tubular formation (Bailie et al, 1983). Renin and other components of RAS, measured in urine, allow us to follow the changes in tubular RAS activity during RAS inhibition and/or under different pathophysiological conditions in humans.

### ***Renal angiotensinogen and conversion***

It is well known that angiotensinogen (AGT) is produced by the liver as part of the circulating RAS. Angiotensinogen escapes glomerular filtration because of its large molecular size. Yet it is present in urine (Kobori et al, 2003, 2008) as a consequence of its synthesis in proximal tubules (Kobori et al, 2006). AGT expression in the proximal tubule can be regulated by factors like circulating angiotensin II or dietary manipulation of sodium concentration in the plasma. It is difficult to determine whether these factors are acting through the basolateral membrane as circulating factors and/or as tubular regulatory factors through the apical membranes (Gociman et al, 2004). Based on unilateral nephrectomy experiments, it has been proposed that increased glomerular filtration per se may induce increased expression of AGT in proximal tubule with no concurrent changes of either renin or AGT extra-renal expression. The exact mechanism for the stimulatory effects of increased flow in proximal tubule is not yet known, but this is consistent with the observations that stretch in either cardiac myocytes or mesangial cells up-regulates AGT expression. It is also conceivable to assume that microvilli of epithelial cells of proximal tubules may serve as sensors (Essig et al, 2001, Essig and Friedlander, 2003). Experimental data support the idea that the urinary excretion of AGT

reflects a net tubular formation of AGT rather than activity of systemic RAS or GFR (Kobori et al, 2006). AGT is cleaved to ANG I in proximal tubule by tubular renin which originates from tubular cells and through the process of glomerular filtration. A role for tubular prorenin in formation of angiotensin I is not known.

The concentration of ANG I, ANG II, as well as angiotensinogen in proximal tubular fluid are many times greater than plasma ANG II levels in both normal and hypertensive rats (Mitchell et al 2007). It would be interesting to follow the exact intrarenal tissue angiotensin concentrations in various renal tissue compartments under different conditions affecting the kidney.

The so-called somatic form of angiotensin-converting enzyme (ACE) is an ectoenzyme, located on the endothelial cell surface in lung, intestine, and brush border membranes of tubular epithelial cells in the kidney. These enzyme molecules also get into the circulation and function as a circulating ACE. One of the homologs of ACE, the ACE2 (transmembrane metallopeptidase, carboxypeptidase) has been shown to be most abundant in kidney. It cleaves a single C-terminal residue and is mainly localized in the glomeruli, proximal and distal tubules, at the apical surface of epithelial cells. This is different from ACE which is found on both apical and basolateral surfaces (Tipnis et al 2000, Chappel and Ferrario, 2006, Lambert et al, 2008). Substrates for ACE2 are Ang I (forming: Ang 1-9, from which ACE may form: Ang 1-7), Ang II (forming: Ang 1-7,) and bradykinin (1-8, forming BK 1-7, part of the bradykinin degradation process). The major effect of ACE2 is in the hydrolysis of angiotensin giving rise to angiotensin 1-7, which binds to its own receptor (Ang 1-7 receptor, MAS-receptor), leading to natriuresis, increased NO, bradykinin and prostaglandin synthesis resulting in hypotension (Turner et al, 2002).

The physiological function of this enzyme is not fully understood. Its expression is increased in early and later stage of diabetes mellitus. It was demonstrated that ACE2-deficient mice exhibit accelerated glomerulosclerosis. Thus, ACE2 may be an important therapeutic target for disorders characterized by sodium and fluid retention like hypertension and congestive heart failure.

### ***Receptors and effects***

AT1 is responsible for most of the known classical effects of angiotensin II such as vasoconstriction and sodium reabsorption (Banday and, Lokhandwala 2008). AT2 receptor is abundant in the developing tissue and normally decreases after birth, while it is persistently expressed in kidney, adrenal gland and brain (Carey RM, Padia SH. 2008). The activation of AT2 receptors induces bradykinin and nitric oxide formation leading to natriuresis and vasodilation. It has been hypothesized that under some pathophysiological conditions, AT2 receptor expression is up-regulated in the kidney (Chen et al 2004, Widdop 2008).

The major role of angiotensin in the kidney is to regulate the renal hemodynamics and sodium excretion (Rosivall, 1995, Kovács et al, 2002). This regulation is through the direct alteration of proximal tubular sodium reabsorption and arteriolar vasoconstriction as well as through a number of different mechanisms like alteration of aldosterone excretion, tubuloglomerular feedback sensitivity, tubular flow velocity, sympathetic nerve activity, etc. In addition, angiotensin II exerts proinflammatory effects through the vascular smooth muscle cells, leukocytes, endothelial cells and platelets (Antus et al. 2001, Antus et al 2000.). It promotes atherosclerosis, thrombosis, plaque rupture, acute coronary syndrome, insulin resistance, obesity, metabolic syndrome, increased alcohol preference, etc (Moore et al, 2007, Sarzani et al 2008, Sedra et al 2008)

### **Summary**

Renal renin-angiotensin system has long been recognized to play important roles in many disease processes. Specifically developed medicines to block at various steps with the RAS are widely used as treatment modalities. Besides circulating RAS, the importance of local RAS in kidney as paracrine and autocrine regulatory systems is being intensively investigated. Despite the considerable progress that has been made, many details of RAS remain to be fully elucidated. Understanding prorenin/renin receptor physiology and pathophysiology together with the morphological changes in afferent arteriole which affect the function of JGA may be one of the most promising areas of research.

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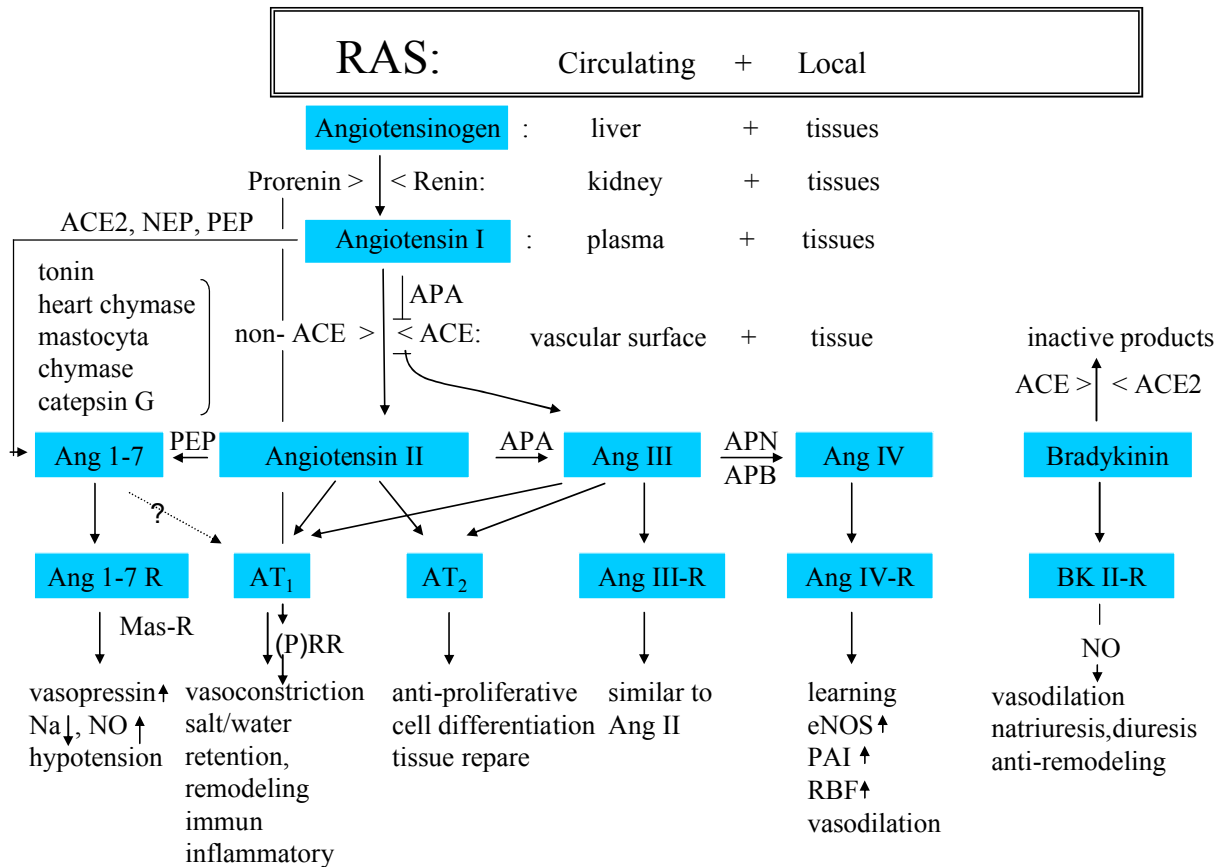
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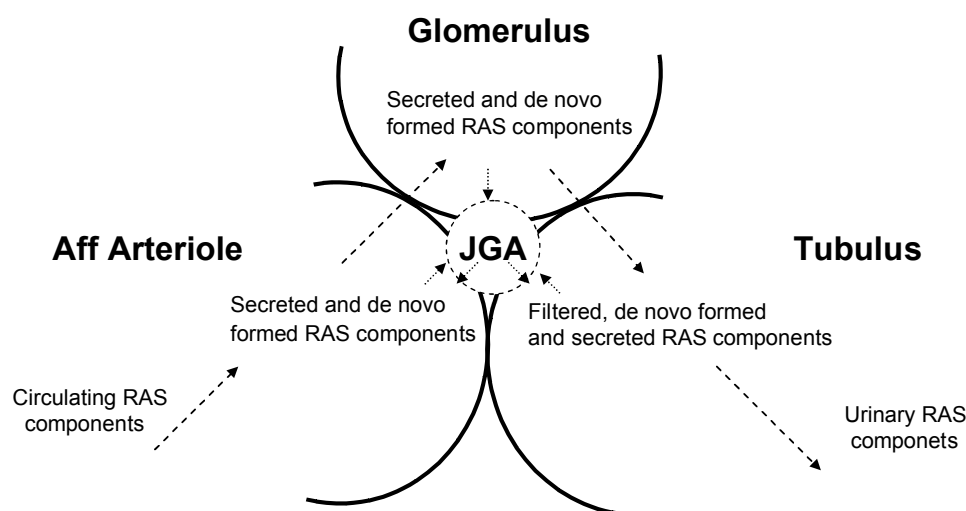
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**Figure 1. Scheme of RAS indicating the complexity of the system**

*APA: aminopeptidase A, APB: aminopeptidase B, APN: aminopeptidase N, NEP: neutral aminopeptidase, PEP: prolylendopeptidase, ACE: angiotensin converting enzyme, (P)RR: prorenin/renin receptor, Mas-R: Mas-receptor, Ang: angiotensin, NO: nitric oxide, RAS: renin-angiotensin system, PAI: plasminogen activator inhibitor, BK: bradykinin, R: receptor*



**Figure 2. Scheme of compartments of renal renin angiotensin system – functional and morphological interrelations.**

Juxtaglomerular apparatus (JGA) serves as a micro-regulatory center in each nephron. Signal transmission pathways between afferent arteriole and JGA, glomerulus and JGA, tubule and JGA (back and forth) include fluid movements, gap junctions, hemichannels, ion channels and electrical couplings. Concentration of RAS components in each compartment can be different and depends on circulating or filtered amount of that component as well as its local formation. The specific local effects of RAS depend on the local formation process of angiotensin II and other active metabolites. It also depends on the metabolism rate of the RAS components as well as the number and localization of receptors. Stimulation of RAS goes along with the activation of different counter acting systems. Therefore, evaluation of physiological or pathophysiological relevance and consequence of RAS activity requires a complex and critical approach. Nonetheless, there is still a degree of inherent uncertainty and therefore conclusions should be made cautiously.