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Classical Renin-Angiotensin System in Kidney Physiology

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Abstract

The renin-angiotensin system has powerful effects in control of the blood pressure and sodium homeostasis. These actions are coordinated through integrated actions in the kidney, cardio-vascular system and the central nervous system. Along with its impact on blood pressure, the renin-angiotensin system also influences a range of processes from inflammation and immune responses to longevity. Here, we review the actions of the "classical" renin-angiotensin system, whereby the substrate protein angiotensinogen is processed in a two-step reaction by renin and angiotensin converting enzyme, resulting in the sequential generation of angiotensin I and angiotensin II, the major biologically active renin-angiotensin system peptide, which exerts its actions via type 1 and type 2 angiotensin receptors. In recent years, several new enzymes, peptides, and receptors related to the renin-angiotensin system have been identified, manifesting a complexity that was previously unappreciated. While the functions of these alternative pathways will be reviewed elsewhere in this journal, our focus here is on the physiological role of components of the "classical" renin-angiotensin system, with an emphasis on new developments and modern concepts.

Introduction

The renin-angiotensin system (RAS) is one of the major control systems for blood pressure and fluid balance. The major biologically active hormone generated by this system, angiotensin (Ang) II, is produced by sequential cleavage of peptides derived from the substrate molecule angiotensinogen (Agt). Ang II binds to specific receptors, triggering a broad range of biological actions impacting virtually every system on the body including the brain, heart, kidney, vasculature, and immune system. But a primary function of the RAS is in circulatory homeostasis, protecting body fluid volumes, and abnormal activation of the

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RAS can contribute to the development of hypertension, cardiac hypertrophy, and heart failure. In this regard, pharmacological inhibitors of the synthesis or activity of Ang II have proven immensely useful in cardio-vascular therapeutics. For example, angiotensin converting enzyme (ACE) inhibitors are effective and widely used for the treatment of hypertension, congestive heart failure, and kidney diseases (26,65,145,154,155,207,208,391).

Here, we will review the physiology of the classical RAS, depicted in Figure 1, focusing on its role in the kidney. For simplicity, we have organized the manuscript around the individual components of the system from protein substrate to enzymes to receptors, to highlight the integrated functions of this complex system.

Angiotensinogen

Angiotensinogen (Agt) is the only known substrate of renin which cleaves a 10 amino acid peptide from its N-terminus, Ang I, which is subsequently cleaved by ACE to form Ang II, the major biologically active peptide generated by the RAS (382). Agt was first cloned in 1983 from rat liver by Ohkubo et al. (268). The human angiotensinogen (*AGT*) gene is located on chromosome 1, whereas the mouse *Agt* gene is on chromosome 8. Agt homologues are present throughout vertebrates and there is an ortholog in fish and the shark *Callorhinchus milii* (88,348). While the C-terminal sequences encoding Ang I are conserved across vertebrates, there is variable homology in other domains of Agt (56), resulting in species specificity to the Agt-renin reaction. For example, human Agt cannot be cleaved by mouse renin and vice-versa (43).

Agt belongs to the superfamily of noninhibitory Serpin A8 proteins, which are a large and diverse superfamily of protease inhibitors and related proteins. The signature structural elements of serpins consist of three β sheets and 8 to 9 α helices (199). Zhou and colleagues recently resolved the structure of the Agt protein by x-ray crystallography (397). This report showed that the renin cleavage site which ultimately results in the liberation of the decapeptide, Ang I, buried within the N-terminal tail of this large protein (397). When Agt is oxidized, there is a conformational change permitting access and cleavage by renin releasing Ang I as shown in Figure 2. As such, renin has a fourfold higher catalytic activity for Ang I formation when Agt is oxidized compared to the reduced form of Agt.

Studies from mice with genetic ablation of the *Agt* gene have provided valuable insights into the physiological functions of Agt. Mice completely deficient in Agt have a characteristic phenotype characterized by increased perinatal mortality, profound hypotension, and abnormalities of the kidney including hydronephrosis, hypertrophic lesions of renal arteries and arterioles, and an impaired ability to concentrate urine (173, 255). This phenotype is virtually identical to that of mice with deficiencies of ACE, renin, or combined deletion of type 1a angiotensin (AT_{1A}) and type 1b (AT_{1B}) receptors (186, 274, 362, 387) indicating that the major physiological role of Agt is its contribution to the generation of Ang II.

Agt is synthesized by hepatocytes and is secreted into the circulation after removal of the 33-amino acid signal peptide. The half-life of Agt in the plasma has been estimated to be ~5 h from iodinated-tracer studies (133, 206). However, it has yet to be defined exactly how

much intact Agt versus Agt degradation product [the so-called des-(Ang I)-Agt] remain in the circulation. As such, the relative proportions of intact Agt versus des-(Ang I)-Agt in the circulation is unknown. Furthermore, it has been suggested that des-(Ang I)-Agt may have physiologic functions, including a role in angiogenesis (43). However, evidence of a physiological role for des-(Ang I)-Agt has not been apparent from studies of Agt knockout mice.

While the liver seems to be the major source of Agt in the circulation, other tissues have been reported to synthesize Agt including adipose tissue, brain, spinal cord, heart, kidney, lung, adrenal gland, large intestine, stomach, spleen, ovaries, and blood vessels (32, 37, 38). Furthermore, it has been suggested that independent regulation of levels of Agt in individual tissue compartments may form the basis of local or tissue RAS operating independently of the circulatory RAS (31, 151, 258, 269). Aspects of the nonclassical RAS is discussed in more detail in Chappell et al. (44).

Synthesis of Agt in proximal tubule of the kidney may be augmented by the chronic administration of Ang II (179), whereas high levels of Ang II inhibit the circulating RAS by suppressing release of renin at the juxtaglomerular (JG) apparatus. This has been taken as evidence of an intrarenal RAS that is regulated independently of the systemic RAS with a “feed-forward” effect impacting the function of epithelial cells along the nephron to enhance sodium reabsorption and hypertension (180). Furthermore, it has been suggested that Agt in urine primarily reflects secretion of Agt protein synthesized by proximal tubule epithelia and thus urinary Agt could be a useful biomarker for monitoring activation of the intrarenal RAS. In this regard, several studies have correlated increases in urinary excretion of Agt with hypertension and some forms of chronic kidney disease including diabetic nephropathy (168,179,182,241).

On the other hand, studies by Matsusaka and colleagues using, cell-specific gene targeting, have suggested that the liver is the primary source of Agt protein accumulating in the mouse kidney, at least in the absence of any induced disease (233). These investigators showed that specific deletion of Agt from the hepatocytes markedly reduced Agt and Ang II levels in the kidney, but did not affect urinary excretion of Agt. On the other hand, while deletion of Agt from the proximal tubule was associated with reduced urinary Agt excretion, it had no effect on renal Agt or Ang II levels. Moreover, disruption of the glomerular filtration barrier increased both tubular and urinary Agt (233). These findings suggest that under normal circumstances, most Agt and Ang II in the kidney are derived from liver whereas Agt in urine comes primarily from proximal tubule epithelia. Indeed, Nakano et al. demonstrated by multiphoton imaging that the vast majority of urinary Agt originates from the tubules rather than glomerular filtration (257). If these characteristics are modified by hypertension or kidney disease and whether there are functional differences in the utilization of Agt in the urinary compartment compared to the rest of the kidney is not clear.

A variant of the human *AGT* gene resulting in a methionine substitution for threonine at position 235 (M235T) has been associated with increased plasma Agt levels and with the development of hypertension (161). Interestingly, the threonine 235 is portion of the *AGT* sequence which is not conserved across phylogeny, and is distinct from the Ang sequences.

As such, it was not clear how variation of this amino acid would affect Agt levels. A potential explanation was established when the M235T variant was found to be in tight linkage disequilibrium with another variant in the 5 untranslated region of the *AGT* gene (152). This second variant, a single nucleotide substitution in the promoter of the *AGT* gene, was associated with increased transcriptional activity of the gene (152). In humans, plasma concentrations of Agt are typically near the Michaelis constant (K_m) for renin (110) so that changes in plasma concentration could have significant influence on the rate of Ang I generation at any given level of renin. Furthermore, gene titration studies in transgenic mice engineered to carry from 0 to 4 copies of the *Agt* gene showed an almost linear relationship between the number of *Agt* gene copies, plasma levels of Agt, and blood pressure, consistent with the proposed mechanism of action of the human mutation (173).

Estrogens induce *AGT* gene transcription in the liver (221). Plasma Agt levels increase during pregnancy and during administration of synthetic estrogens such as oral contraceptive pills (74). Furthermore, the M235T variant of the *AGT* gene has been associated with preeclampsia (375) and Zhou and colleagues demonstrated that patients with preeclampsia had higher circulating levels of the oxidized form of Agt in their plasma (397). In normal individuals, the ratio of reduced:oxidized Agt is 40:60. In preeclampsia this ratio falls to 30:70. As discussed above, since oxidized Agt may be a more efficient substrate for renin, both of these studies suggest that altered levels or activity of Agt might contribute to blood pressure elevation in preeclampsia.

Renin

Renin is an aspartyl protease that catalyzes the first step in the activation of the RAS. Active renin specifically cleaves the 10 amino acids from the N-terminus of Agt to form Ang I. In humans, there is an excess of Agt in serum. Likewise, ACE is ubiquitous in the endothelium and plasma (288). Accordingly, the amount of renin in the bloodstream is a key rate-limiting step determining the level of Ang II and thus the activity of the RAS. The primary source of renin in the circulation is the kidney, where its expression and secretion are tightly regulated at the JG apparatus by two distinct mechanisms: a renal baroreceptor (24, 33) and sodium chloride (NaCl) delivery to the macula densa (13, 216, 217). Through these sensing mechanisms, levels of renin in plasma can be incrementally titrated in response to changes in blood pressure and salt balance. These regulatory principles provide a basis for many of the physiological characteristics of the RAS as discussed by Kanwar et al. in the *Handbook of Physiology* (169).

Here, we will provide an overview of renin gene structure and expression, as well as summarize the biochemical and physiological mechanisms regulating renin expression and release in the developing and adult kidney.

Renin gene

The renin gene is highly conserved, and homologs have been identified in multiple species such as human, mice, rats, dogs, and zebra fish. Its structure is similar to that of pepsinogen, a related aspartyl protease, suggesting a common evolutionary origin (135). The human renin gene spans 12 kb of DNA on chromosome 1 and contains 10 exons separated by 9

introns (124). The transcript encodes a protein with 406 amino acids, including a pre- and a pro-segment carrying 20-23 and 43-47 amino acids, respectively (8, 149, 243). Removal of the 23 amino acid residues from the C-terminus of pre-pro-renin generates pro-renin. Active renin is generated by removal of the N-terminal peptide pro-renin fragment, presumably by proteases in the JG cells of the kidney (142). Whether intact pro-renin has a distinct physiological role remains to be determined; however, there is evidence suggesting specific contributions of the pro-renin molecule in some normal and disease states (266, 379), including evidence that pro-renin binds to and activates a specific pro-renin receptor (266).

Humans have a single renin gene located on chromosome 1. Mice, on the other hand, may have one or two renin genes depending on the strain. Mouse strains with a single renin gene have a conserved allele, *Ren1*^{c}, whereas mouse strains with two renin genes have a slightly modified variant of the *Ren1* allele, *Ren1*^{d}, with ~99% homology to *Ren1*^{c}, along with the second renin gene, *Ren2*, with ~97% homology to the *Ren1* allele. In contrast to *Ren1*, which is mainly expressed in the kidney, *Ren2* is also highly expressed in the submandibular gland (87). Initial reports have indicated that mice with two renin genes have differences in their plasma renin levels and blood pressure compared to mice with one renin gene (220). However, follow-up studies demonstrated that there were no differences in renin expression between strains with one or two genes (122). In an effort to determine the physiological significance of the *Ren1* and *Ren2* genes, Mullins and colleagues have ablated the *Ren1*^{d} and *Ren2* genes in mice (55, 332). Their data show that while ablation of *Ren2* leads to viable and healthy mice (332), ablation of *Ren1*^{d} results in altered morphology of the macula densa of the kidney distal tubule and complete absence of JG cell granulation (55).

In the rat, the renin gene is located in chromosome 13, with ~80% homology to the mouse and ~68% homology to human (96). Similar to the mouse gene, it contains 9 exons separated by 8 intervening sequences. Inbred Dahl salt hypertension sensitive (S) and inbred Dahl salt hypertension resistant (R) rats exhibit significant polymorphism in their renin genes, which have been suggested to contribute to their differences in blood pressure (372). Similar to the mouse, ablation of the renin gene in rats results in abnormal kidney morphology such as a rudimentary inner medulla, cortical interstitial fibrosis, thickening of arterial walls, and abnormally shaped glomeruli (244).

Regulation of renin

Because renin level is a key rate-limiting step in determining Ang II levels, factors regulating expression and secretion of renin have the potential to significantly impact overall activity of the RAS. Accordingly, the following sections summarize the factors controlling renin expression and release.

Renin expression during kidney development

During mouse development, renin is first detected at embryonic day 14.5 in a few scattered cells in the developing kidney (162). By embryonic day 15.5, renin is detected in the developing renal artery, interlobar arteries, and arcuate arteries of the metanephric kidney (262). Yet, lineage tracing studies using the *Ren1*^{d} promoter have suggested that renin producing cells originating from mesenchymal precursors can be identified around

embryonic day 11.5 days before vessel development (331). As development progresses, renin expression is found in newly developed afferent arterioles while it disappears from interlobular arteries around the time of birth (315). At all stages, renin is expressed in cells that are insulated from the inner media layer of the renal vessels (315). After birth, renin expression gradually becomes progressively restricted to the terminal portion of the afferent arterioles in the JG area. This highly plastic pattern of renin expression seems to be common during development in all mammals; however, the mechanisms regulating this switching on and off of renin expression remains poorly understood. A detailed discussion of kidney development during embryogenesis is discussed by Spitzer et al. in the *Handbook of Physiology* (343). Some studies have shown correlation between embryonic expression of renin and sympathetic innervation of the kidney (302), along with expression of transforming growth factor β type II receptor suggesting a possible role in regulating renin expression during development (213). In addition, genetic disruption of adrenergic receptors reduces renin expression along the developing glomerulus implicating signaling though β-adrenergic receptors (264). Similarly, deletion of the Gsα protein, a key receptor mediating the intracellular signaling of cAMP, abolishes renin expression in the developing kidney; a phenotype accompanied by aberrant formation of the preglomerular arterial tree (262).

Renin expression in the adult kidney

In the adult kidney, renin is predominantly expressed in specialized cells in the JG area termed JG cells. These cells have an epithelial-like shape and are located in the media layer of afferent arterioles at the last branching point leading to the glomerular capillary network. Cells in the medial layer of efferent arterioles or extraglomerular mesangial cells rarely express renin. Low levels of renin have been detected in the renal proximal tubule, connecting tubule, and collecting duct (300,306,307).

Renin in the juxtaglomerular cell

Despite the importance of JG cells in regulating blood pressure and electrolyte homeostasis, characterization of their molecular and cellular properties are incomplete. Based on the presence of myofilaments in their cytoplasm, it was postulated that JG cells derive from smooth muscle lineages in the kidney (169, 350). However, later studies suggested that JG cells originate from metanephric mesenchyme, migrating and incorporating into the developing afferent arterioles of the embryonic kidney, but only later acquiring smooth muscle markers (330).

JG cells are mainly defined by their unique localization in the JG region of the renal afferent arteriole and their ability to synthesize and secrete renin (325, 350). They have a large nucleus, hypertrophic rough endoplasmic reticulum and distinct Golgi apparatus. JG cells carry two types of secretory granules: large electron-dense, mature granules containing active renin, Ang peptides, and cathepsins, along with smaller, electron-lucent proto-granules containing active renin and pro-renin (94). JG cells have a distinct transcriptional signature compared to other renal cell types, consisting of arterial, interstitial cell, and pericyte markers, as well genes associated with endocrine and contractile functions (27).

In the adult kidney, environmental stimuli, such as chronic ischemia, prolonged adrenergic activation, and sodium depletion, produce an increase of the number of cells expressing renin along the afferent arteriole, in the interstitium and inside the glomerulus, in a pattern partially recapitulating embryonic distribution of renin expression (105, 107, 328) (Figure 3). This process is known as JG recruitment (328). Although the exact cellular and genetic mechanisms of this phenomenon remain poorly understood, it potentially involves dedifferentiation of arteriolar smooth muscle cells (SMCs), mesangial cells and interstitial cells from the renin cell lineage, which then reacquire the renin phenotype. Recent studies using genetically labeled renin expressing cells have indicated that the reacquisition of renin expression by arteriolar SMCs is controlled by epigenetic/transcriptional mechanisms (106,290) as well as microRNAs (miRNAs) (237); small 22-nucleotide noncoding RNAs that regulate gene expression at the posttranscriptional level. Furthermore, recent data suggest that adult stromal progenitor cells derived from bone marrow and kidney can express renin and acquire JG-like characteristics upon stimulation with LXRα and/or cAMP (235, 371). Moreover, *in vivo*, sodium depletion results in activation of cells that express mesenchymal stem cell markers in the kidney suggesting that renal progenitor cells might contribute to JG recruitment (371).

Renin in the distal nephron

Although the JG area is the main localization of renin expression in the adult kidney, more recent studies suggest that under certain conditions, renin expression can also be detected in distal nephron segments (300, 307). For example, chronic Ang II infusion increases renin mRNA and protein levels in principal cells from connecting tubules and collecting ducts (300,307) and this up regulation is prevented by AT_1 receptor blockade (301). By contrast, Ang II induced hypertension is accompanied by reduced levels of renin expression in the JG area. Additionally, renin expression in the distal nephron is also increased in experimental models of diabetes and chronic kidney disease (294). These effects are mediated via the PR91 receptor (also called SUCNR1) which binds succinate, a tricarboxylic acid cycle intermediate, that can rapidly accumulate in local tissues when energy supply and demand are out of balance. The PR91 receptor is expressed in the luminal membrane of macula densa cells of the JG apparatus in close proximity to renin-producing granular cells, the cortical thick ascending limb, as well as in the cortical and inner medullary collecting duct cells (306). These findings open the possibility of a new mechanism for local control of renin synthesis and release by endogenous metabolic intermediates (293).

Renin in mast cells

Mast cells can also express and secrete active renin (200,222, 336). Because of the ubiquity of mast cells, they provide a unique paradigm for understanding local renin-angiotensin systems in all tissues (336). Release of renin by cardiac mast cells can be induced by ischemia resulting in release of norepinephrine and generation of cardiac arrhythmias (222). Furthermore, kidney mast cells can also make chymase which can augment Ang II production and microvascular function in diabetes (286). Still the physiological importance of these mechanisms remains to be determined.

Processing and secretion of renin in JG cells

Renin is initially synthesized as a pre-pro-renin protein. After cleavage of the pre-fragment, pro-renin is transferred to the Golgi. From there, pro-renin can be immediately secreted by the constitutive pathway or sorted to the dense-core secretory granules for regulated exocytosis (94). It appears that release of pro-renin through the constitutive pathway depends directly on the levels of renin synthesis *per se*, including levels of transcription per cell and the total number of renin-producing cells (299). Acute stimulation of renin release involves exocytosis of mature renin secretory granules that contain active renin only; whereas chronic stimulation results in release of both pro-renin and renin into the circulation (359).

The sorting of proteins to dense core secretory granules for regulated exocytosis involves a number of different mechanisms allowing interaction of the granules with the cell membrane, enzymatic cleavage of pro-renin, modulation of the local pH or other factors favoring aggregation of granule material (324). The correct sorting of pro-renin to the regulated secretory pathway depends on the presence of a paired basic amino acid site in the pro-renin molecule, which serves as a protease-processing site. As cathepsins are co-localized with pro-renin in the secretory granules, it was suggested that these proteases might be responsible for the conversion of pro-renin to renin (113). However, renin processing was not impaired in cathepsin B deficient mice suggesting that cathepsin B is not essential for renin processing (239).

Studies in renin knockout mice suggest that glycosylation is crucial for pro-renin sorting into the dense core secretory granules. Ren1 and Ren2 proteins differ in their glycosylation patterns and studies using knock out mice for *Ren1* or *Ren2* gene show differences in their renin processing. Indeed, deletion of the Ren2 gene alone did not cause an apparent phenotype (332). In contrast, the kidneys in Ren1 deficient mice showed a very low number or complete absence of dense-core renin vesicles (55). It has been postulated that glycosylation differences may be responsible for these phenotypic differences (55).

Renin release also depends on polarization state of the membrane potential of the JG cell. Depolarization results in suppression of renin release whereas hyperpolarization increases the levels of renin exocytosis (40). In that context, inhibition of renin release by Ang II or release of renin stimulated by cAMP depends on changes in membrane potential mediated by K+ channels expressed by JG cells. JG cell membranes also contain NKCC1 and calcium (Ca^{2+})-activated chloride channels, which might also mediate inhibition of renin by Ang II and perhaps other vasoconstrictors. Increased intracellular free calcium, which typically triggers secretion in other secretory cells, inhibits renin secretion. This unique feature of renin secretion is commonly referred to as the “calcium paradox” (9,114).

Intracellular signals controlling renin release

As shown in Figure 4, renin expression and release at the cellular level is controlled by three main intracellular mediators: cAMP, cGMP, and Ca^{2+}, which we will discuss individually below.

The cyclic AMP pathway in renin release

cAMP is an important second messenger mediating intra-cellular signal transduction in several biological processes. Stimulation of seven transmembrane receptors coupled to Gs proteins triggers the activation of adenylyl cyclases, which in turn generate cAMP from adenosine triphosphate. cAMP then activates protein kinase A, which phosphorylates a number of other proteins such as transcription factors of the cAMP response element-binding protein/activating transcription factor-1 (CREB/ATF1) family, regulating gene expression and hormonal release (196). cAMP is degraded by phosphodiesterases, which therefore limit cAMP action. The cellular concentration of cAMP is determined by a balance between the rates of cAMP synthesis by adenylyl cyclases and cAMP degradation by phosphodiesterases (Fig. 4).

Abundant evidence indicates that cAMP is the main regulator of renin release. For example, direct activation of adenyl cyclase with forskolin triggers release of renin by JG cells (114). Similar effects are observed following exposure to cAMP analogs (92). Extracellular ligands, such prostaglandin E_2 (PGE_2), prostacyclin I_2 (PGI_2), and adrenergic hormones, acting via their respective Gs-coupled receptors in renin producing cells, stimulate adenyl cyclase activity, cAMP production and renin release. Accordingly, mice with specific genetic deletion of the *Gs*α gene in JG cells display lower plasma renin levels and reduced JG cell renin stores (Fig. 5) (47). Moreover, renin secretion in response to isoproterenol or PGE_2 is similarly diminished in JG cells isolated from Gsα deficient mice (2, 47). Conversely, administration of selective inhibitors of the phosphodiesterases (PDE)-3 and PDE-4 increases renin secretion (50,51,191). Yet, the molecular pathways downstream of cyclic AMP stimulating renin secretion are not well defined and further research is required.

Calcium in renin release

While cAMP is the dominant second messenger for renin secretion, Ca^{2+} appears to modulate the integrated activities of the enzymes that balance cAMP synthesis and degradation (Fig. 4) (9). In contrast to cAMP, increased levels of intracellular Ca^{2+} inhibit renin release (114). For example, exposure of JG cells to agents such as 1,2-bis(o-aminophenoxy)ethane-N,N,N,N-tetraacetic acid, which deplete intracellular Ca^{2+} stores, stimulates renin release (276), whereas exposure to thapsigargan, which increases intracellular Ca^{2+} levels, blocks renin release (327). Moreover, several mediators with putative actions to inhibit renin release, such as vasopressin (193), Ang II (248), and endothelins (305), increase intracellular Ca^{2+} concentrations in JG cells. The inhibitory effect of Ca^{2+} on renin release appears to be mediated by protein kinase C (193). Schweda and colleagues have shown that Ca^{2+} can also block cAMP generation through Ca^{2+} inhibitable adenylyl-cyclase V (114).

Nitric oxide and the cyclic GMP pathway in regulation of renin

Increases in intracellular levels of cGMP in JG cells can be triggered by various stimuli such as nitric oxide (NO) and atrial natriuretic peptide (Fig. 4) (190). Depending on the circumstances, they can either inhibit (131) or stimulate renin release (322). NO stimulation *in vivo* consistently results in increased renin release (194), and the endothelial form of nitric

oxide synthase (eNOS) is required for renin cell recruitment (263). It has been suggested that NO stimulates renin release through the formation of cGMP, which can inhibit PDEs, thereby attenuating cAMP hydrolysis (93,191). In parallel, cGMP can potentially suppress renin secretion through activation of cGMP regulated protein kinase type II (cGKII) and inhibition of renin by cGMP agonists is lost in mice with targeted disruption of cGKII (368). Levels of cGKII are subject to regulation in the JG cell (98), but the impact of this regulation on control of renin release has not been established.

Regulation of renin by microRNAs

Endogenous miRNAs, noncoding RNA species 18 to 22 nucleotides in length, play an important role in cell differentiation and homeostasis by modulating target gene expression (238). miRNAs are encoded within the genome and initially are transcribed as primary miRNA precursors (about 100-1000 nucleotides in length). These precursor transcripts are then released in the cytoplasm and processed by the sequential activity of the RNase III-type endonucleases *Drosha* and *Dicer* to produce mature miRNAs of 21 to 22 nucleotides in length (175). Sequeira-Lopez and associates showed that deletion of *Dicer* specifically in the renin cell lineage resulted in disappearance of renin-producing cells from the kidney, reduced renin expression, and hypotension (329), indicating a role for miRNAs in renin regulation (329). Subsequent work identified miR-330 and miR-125 as important determinants of JG cell identity (237). In humans, miR-663 and miR-181a are differentially expressed in kidneys of hypertensive males, and these miRNAs bind to the 5 untranslated region of the renin (*REN*) mRNA and regulate its expression (227). In addition, a number of miRNAs have been shown to regulate the expression of genes involved in β-cell exocytosis (218), but whether any of these miRNAs affect renin release is not clear (329).

Local control of renin release

As discussed above, renin-producing cells are localized to the distal part of the afferent arteriole, adjacent or in close proximity to macula densa. Physiological control for renin synthesis and release by these cells is regulated by three main pathways.

Renal perfusion pressure (renal baroreceptor)

Numerous studies have shown that renin secretion is inversely related to renal perfusion pressure or pulse amplitude (24,120,176,267,339). As such, the baroreceptor is an independent mechanism for controlling renin, residing within the kidney and clearly separate from regulation by the sympathetic nervous system (120). Yet, identification of its precise nature has been elusive. Various models have been proposed to explain the mechanism for pressure sensing and consequent signal transduction including direct stretch of the JG cells due to transmural pressure across the afferent arteriole (33,91) or indirect pathways involving secondary release of autocoids (277). Some of these candidate soluble factors include NO (178,191,292), and prostanoids (67,103), which are stimulatory, or endothelins, which are inhibitory (251). Gene targeting in the mouse has been utilized to examine the role of some of these mediators in the baroreceptor response. In one study, genetic deletion of eNOS had no effect on renin release in response to changes in renal perfusion pressure (10). On the other hand, the absence of the prostacyclin (IP) receptor, the

single known receptor for PGI_2 conferred substantial resistance to hypertension and hyperreninemia after unilateral renal artery stenosis (95). This suggests an absolute requirement for PGI_2 in triggering renin release after baroreceptor activation, but a number of questions remain concerning the mechanism and cell lineages controlling synthesis of key mediators such as PGI_2, and the cellular targets for these mediators affecting renin release (89).

The baroreceptor mechanism also appears to depend on extracellular Ca^{2+} concentration. For example, Kurtz and colleagues demonstrated that when the extracellular level of Ca^{2+} is lowered, the inhibitory effect of renal perfusion pressure on renin release is abolished (320). A potential mediator in this process may involve connexin proteins, which form gap junctions between JG cells and the adjacent endothelial cells. Disruption of connexin40 (Cx40) in the mouse, either through gene deletion or point mutation, results in hyperreninemia, hypertension, and loss of pressure control of renin release (185,219,367), similar to the effect observed when extracellular Ca^{2+} concentration is lowered (320). Yet, mice with renin cell-specific deletion of Cx40 maintain the ability to recruit additional renin producing cells in response to salt depletion and ACE inhibition, whereas this response is eliminated in mice with global deletion of C×40. These observations suggest that gap junction coupling is not required for recruitment of additional renin cells during homeostatic challenges, but it appears to be necessary for proper localization of these cells both under basal conditions and during prolonged renin stimulation (83).

NaCl reabsorption at the macula densa

The second major pathway for physiological regulation of renin is the macula densa mechanism whereby cells at the macula densa sense a reduction in chloride ions in the filtrate of the distal tubule, triggering renin release (216). In this circumstance, release of renin and the consequent generation of Ang II are believed to serve as a mechanism for enhancing renal sodium reabsorption in states of fluid volume depletion. The anatomical association of the macula densa with the JG apparatus stimulated the first speculation by Goormaghtigh of its physiological function (109). The macula densa is made up of specialized epithelial cells at the terminal portion of the thick ascending limb. Their basolateral membrane is in contact with glomerular mesangial cells, which, in turn, are contiguous with granular cells in the JG apparatus (13). The role of the macula densa in renin regulation was initially hypothesized by Vander in 1967 (340, 353, 363) and there is now general consensus that this mechanism provides a control of renin secretion that is directly determined by NaCl delivery to the distal nephron (340, 353). Moreover, several studies indicate that chloride flux through the NKCC2 regulates the signaling pathways linked to renin secretion (229). Increased chloride delivery to the macula densa inhibits, whereas reduced chloride delivery stimulates renin release (184,217,320).

In addition to the well-studied NKCC2 transporter, the sodium/hydrogen exchanger isoform 2 (NHE2) expressed on the apical surface of the macula densa also plays a role in renin release, perhaps through its effect on macula densa cell volume. A study by Peti-Peterdi and colleagues demonstrated that NHE2-deficient mice have significantly increased renal tissue renin activity and plasma renin concentration (121). These changes were associated with

increased renal expression of cortical cyclo-oxygenase 2 (COX-2) and membrane-associated PGE synthase (mPGES), suggesting that the mechanisms responsible for increased renin levels are maculadensa specific, since these mice have been characterized to have normal blood pressure (201).

Several candidate signaling pathways linking distal tubule solute concentration to control of renin have been proposed. These include adenosine, NO, and prostanoids. The most compelling evidence suggests that macula densa stimulation of renin involves the activation of COX-2 (125). Constitutive expression of COX-2 at high levels in the macula densa, generate abundant PGE_2 (318, 325). PGE_2 then activates a prostaglandin E_2 (EP) receptor on granular cells in the JG apparatus to stimulate renin release (325). The EP4 receptor is likely the major EP receptor that mediates the actions of PGE_2 in this process. Facemire et al. demonstrated that EP4 receptor deficient mice display a ~70% reduction in renal renin expression and plasma renin concentration compared to wild-type mice after treatment with furosemide (84). By contrast, deletion of EP2 receptors in mice had no effect on renin stimulation by furosemide. Interestingly, this study suggested that the source of PGE_2 in this pathway is not dependent on mPGES1 or mPGES2. The capacity for PGE_2 to directly stimulate renin secretion has been long recognized (11,376). Moreover, studies using specific inhibitors and COX-2 deficient mice have clearly demonstrated the importance of COX-2 in the macula densa pathway (48, 123). In addition, the activity of various components of this system has been demonstrated in the isolated perfused macula densa segments (295) and JG cell lines (388). However, at least one study (95) has failed to confirm a nonredundant role for individual EP receptors for PGE_2 in furosemide-stimulated renin release *in vivo*.

Initial evidence suggesting a role for adenosine in macula densa signaling came from studies using the selective A1 adenosine receptor antagonist 8-cyclopentyl-1, 3-dipropylxanthine. These studies demonstrated that renin release decreases as luminal NaCl concentration drops and this response is abrogated by blocking the A1 adenosine receptor (377). Later studies using A1 adenosine receptor deficient mice confirmed the role of adenosine is primarily restricted to the arm mediating the inhibition of renin release. In A1 adenosine receptor deficient mice, renin-inhibitory actions of enhanced sodium chloride delivery to the macula densa are blocked, whereas stimulation of renin secretion caused by reduced sodium chloride transport at the macula densa are unaffected (174).

Macula densa cells express high levels of neuronal nitric oxide synthase (nNOS) (249,378). The role of NO in regulation of renin was first tested using nonselective inhibitors of NO synthesis, which attenuated renin release stimulated by reduced luminal NaCl concentrations (128, 352). The specific role of the individual NOS isoforms has been examined using mice with targeted deletion of nNOS or eNOS. In these studies, activation of the macula densa pathway was achieved by administration of NKCC2 blocking loop diuretics *in vivo* and in isolated perfused mouse kidneys. Deficiency of either nNOS or eNOS alone did not significantly affect macula densa-dependent renin secretion (41), while nonspecific NOS blockade attenuated renin stimulation by loop diuretics. This suggests that NO plays a permissive rather than a primary role in the macula densa control of renin release (41). However, as discussed above, eNOS appears to be required for new recruitment of renin-

producing cells to the afferent arteriole (263), highlighting the complicated role of NO in renin regulation.

β_1-adrenergic stimulation in renin release

The capacity for sympathetic nerve activation to stimulate renin has been long recognized. For example, β-adrenergic receptors are abundant in the JG apparatus of kidneys from various species (205). Furthermore, numerous studies have demonstrated that *β*-adrenergic agonists stimulate renin release (171). Chronic renal nerve activation also stimulates renin (138,139) along with its affects to modulate renal blood flow and tubular function. In experiments controlling for these factors, a clear relationship between increasing renal sympathetic nerve activity and renin secretion is maintained (75, 177). However, as discussed above, renal denervation does not abolish the capacity of the baroreceptor (21, 22) or macula densa mechanisms to stimulate renin (90, 137, 360). Accordingly, it appears likely that β-sympathetic tone has a modulatory, rather than primary role in the regulation of renin.

Short loop feedback: Regulation of renin by Ang II

AT_1 receptors are also highly expressed in the JG apparatus and Ang II may exert an inhibition of renin release by the short-loop feedback mechanism. Treatment with RAS antagonists or genetic ablation of the AT_{1A} receptor in mice increases renin mRNA expression and causes JG apparatus expansion with recruitment renin-containing cells (354). In addition, infusion of Ang II into isolated perfused kidneys inhibits renin release (192). AT_1 receptors couple to Gq proteins and activation of these receptors by ligand increases intracellular Ca^{2+} concentrations in JG cells (53, 326). As discussed above, the inhibitory effect of Ca^{2+} on renin release appears to be mediated by protein kinase C since stimulation of protein kinase C inhibits renin secretion, whereas blockade of protein kinase C attenuates the inhibitory effect on renin secretion (52,54,193). There is also evidence that the effects of Ca^{2+} on renin release are mediated in part by a calmodulin-dependent process, since inhibition of calmodulin activity stimulates renin secretion (70, 285). On the other hand, in kidney cross transplantation experiments with AT_{1A} receptor deficient mice indicated that stimulation of renin expression was more directly associated with reduced blood pressure rather than direct modulation by AT_1 receptors (60).

Genomic regulation of renin expression

The multiple levels of control for release of renin protein at the JG apparatus are accompanied by a parallel, complex regulation of renin gene expression. The regulatory region of the renin gene has been studied extensively *in vitro* utilizing a renin expressing cell line isolated from a mouse renal tumor (termed As4.1 cells) (335) coupled with *in vivo* studies utilizing transgenic mouse lines. These systems have identified two regions acting in conjunction to control renin expression, including a proximal promoter element (284,297) and a 242-base pair enhancer region.

The proximal renin promoter refers to the 5′-regulatory sequence located between base pairs −197 and −50. This region is necessary for maximal renin expression (25, 297) with

sequences that are highly homologous in human, mouse, and rat renin including a conserved TATA box. It also contains a number of important cis-regulatory elements including an E26 transformation-specific (Ets)-binding site, homeobox (HOX)/pre-B cell leukemia transcription factor (PBX)-binding site, a CRE that binds transcription factors such as CREB/ATF1, and a putative binding site for an actin-related protein 1 homolog A (ARP-1) termed chicken ovalbumin upstream promoter transcription factor II (COUP-TFII) (25,183). Additional important sites include a cAMP negative regulatory element (CNRE) involved in cAMP effects modulated by the nuclear receptor liver X receptor-α (LXRα). Although mice lacking LXRα show reduced basal renin levels and attenuated response to adrenergic stimulation (242), *in vivo* deletion of the LXRα binding motif within the mouse promoter had no effect on either basal expression or the regulation of the renin gene (349). More recently, a retinol binding protein (RBP)-J/Su(H)/Lag1 site involved in the Notch-signaling pathway has also been identified in the proximal renin promoter region. Notably, deletion of the RBP-J, the common downstream effector of all Notch receptors, reduced renin expression under normal and sodium-depleted conditions, and lowered blood pressure (39).

The 242-bp enhancer element is located at −2866 to −2625 in the mouse *Ren1*^{c} gene. Within the enhancer there are three distinct DNA binding sites that are conserved between mouse and human. These elements are essential for renin expression (282) comprising: (i) a CRE recognized by CREB, the cAMP responsive element modulator, and nuclear factor kappa B (Nf-κB) (358); (ii) an E-box that binds upstream stimulatory factors 1 and 2 (USF-1/2) (282); and (iii) two TGACCT motifs, constituting hormone response elements (HRE) (334). These sites can be bound by the retinoic acid receptors/retinoic X receptors promoting renin expression (334), as well as a nuclear orphan receptor (EAR2) and vitamin D receptor with inhibitory effects on the enhancer (212,214). Interestingly, the human renin HRE differs from the mouse sequences both in the spacer between the HREs and the proximal HRE. This difference seems to account for the lower trans-activating capacity of the human kidney renin enhancer and may contribute to the dramatic differences in renin levels between mice and humans (~1000 vs. ~3 ng Ang I/mL/h, respectively) (156).

The transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) can also bind the enhancer region through a canonical PPAR response element (356), and play an important role in renin regulation. Indeed, selective reduction of PPAR-γ expression reduces renin expression (73). Still, there are might be differences between species as the effects of PPAR-γ in human renin transcription seem to be also dependent on a proximal promoter palindromic repeat with 3-bp spacer (Pal3) site (357). Finally, there are several important binding sites for transcriptional regulators such as nuclear transcription factor Y (NF-Y), Wilms' tumor suppressor, nuclear factor I (NFI) and specificity protein (Sp)1/Sp3 located both in enhancer and proximal renin promoter (104). Mutations of the NFI/Sp1/Sp3 binding sequences almost completely eliminates activity of the renin promoter, indicating a crucial role for these transcription factors in the control of renin gene expression (283). It remains to be clarified whether these multiple renin promoter-binding sites are redundant or have different functions. Nonetheless, the importance of the enhancer in renin expression *in vivo* is controversial. In transgenic mice that express human renin from a 160-kb P1 artificial chromosome, Zhou et al. showed that the enhancer of the human renin gene is not critical

for the stimulation of renin gene expression by ACE inhibition (398). Moreover, the enhCRE and CNRE sites were shown to be dispensable for the cell-specific expression of the human renin gene in the afferent arteriole (72). This contrasts with other studies using mice lacking an endogenous renin locus (226) or transgenic mice where expression of green fluorescent protein is driven by renin regulatory elements lacking the enhancer region (104). In both cases, the enhancer region appeared to be necessary for full activation of renin transcription by ACE inhibition alone or in combination with low salt diet. These discrepancies might reflect species differences in regulation of renin between humans and mice or experimental differences in the specific regions of the enhancer that were deleted. On the other hand, rather than regulating absolute levels of promoter activity, it has been also postulated that the enhancer acts like an on/off switch allowing renin transcription (245). We suggest that further experiments are necessary to dissect these mechanisms and to determine their physiological importance.

Angiotensin converting enzyme

ACE is a dicarboxypeptidase that generates the vasoactive peptide Ang II by cleaving 2 amino acids from the c-terminus of the inactive precursor Ang I (58). There are two distinct forms of ACE, somatic and testicular, both generated by alternative splicing of a single gene (81,144,197). A testis-specific form of ACE is generated from the ACE gene through alternative transcription, beginning at the 13th exon of the ACE gene, 7.2 kb downstream of the translation start site of somatic ACE in mice (141). Somatic tissues splice from exon 12 to exon 14 and thus remove exon 13 as if it were intronic. In the male germ cell, transcription is initiated at exon 13, providing testis ACE with its unique 66 amino-acid N-terminal sequence (140). The remainder of the protein corresponds exactly to the carboxyl half of somatic ACE. Mice lacking testis ACE have a phenotype of impaired fertility do to defective migration of sperm into the oviduct and reduced binding to the zona pellucida (252). These studies clearly demonstrated the key role for testis ACEs in male fertility in mice. While reduced fertility has not been described in male patients on ACE-inhibitors, the molecular mechanism by which testis ACE promotes fertility is not clear, including whether it depends on carboxypeptidase activity. In contrast, somatic ACE is expressed as an ectoenzyme on the surface of endothelial cells throughout the body and is particularly abundant in lung, intestine, choroid plexus, placenta, and on brush border membranes in the kidney. A soluble form of ACE that circulates in plasma is formed by enzymatic cleavage of tissue-bound ACE at its transmembrane domain (12). Since its original description, additional physiological roles for ACE have been reported and were recently reviewed by Bernstein (15); these will be described briefly below.

As with other components of the RAS, molecular variants of the human *ACE* gene have been proposed as candidate genes in hypertension, cardiovascular, and kidney diseases (316). Insertion (*I*) and deletion (*D*) polymorphisms of the human *ACE* gene are common and have been associated with significantly altered levels of ACE in plasma (303, 366). In some cohorts but not others, these *ACE* gene variants have been linked to differing susceptibilities to hypertension, cardiovascular, and renal diseases (316,347). The strongest association between *ACE* polymorphisms and disease exists for diabetic nephropathy (265, 374). In a meta-analysis of published studies, homozygosity for *I* allele was associated with

significant risk reduction for diabetic nephropathy (265) and in a separate study, protection from the *I* allele was also observed in expanded renal outcomes (374). Conversely, the *D* allele has been associated with increased risk of diabetic renal disease in both type1 and type 2 diabetes (160). Finally, studies in mice have also demonstrated this effect (143). Diabetic mice with three copies of the *Ace* gene had a 25% increase in ACE levels and more proteinuria than mice with fewer copies of the *Ace* gene. However, the human *ACE* locus has not been emerged as a susceptibility locus in a series of genome-wide association studies of large cohorts of patients with hypertension, diabetic nephropathy and other cardiovascular diseases (311).

The actions of ACE to generate Ang II from Ang I are central to its biological functions as Ang II is the major effector molecule of the RAS. In addition to Ang I, there are other biologically active peptide substrates for ACE. Perhaps the most important of these is bradykinin (225). ACE degrades bradykinin into an inactive peptide, representing a significant biological pathway for bradykinin metabolism *in vivo* (30); in older literature, ACE was referred to as kininase II. Since bradykinin has vasodilator and natriuretic properties (225), it has been suggested that one mechanism of blood pressure reduction with ACE inhibition is blockade of this kininase activity. This was clearly demonstrated by Brown and associates, who showed that the antihypertensive efficacy of ACE inhibitors is attenuated by simultaneous administration of a bradykinin receptor antagonist (Fig. 6) (97), (15, 16). Beyond a role in blood pressure lowering, bradykinin acting via its receptors may also play a role in modifying kidney injury in diabetes. For example, studies in mice lacking bradykinin receptors show that they have dramatic acceleration of albuminuria and glomerular pathology, indicating a protective effect of bradykinin in diabetic nephropathy (164-167, 361). These studies suggest that ACE activity has the potential to modulate renal disease in diabetes via degradation of bradykinin, and that one potential mechanism underlying the benefits of ACE inhibition in diabetic nephropathy (207, 209) might be potentiation of bradykinin effects.

Gene targeting in mice has proven a very useful tool in deciphering gene function and many of the functions of RAS components were clarified in this way (351). The effort to dissect functions of ACE is a prime example with a large body of work to support its diverse physiological roles (15). Work largely by the Bernstein group has expanded the function of ACE to include diverse roles such as hematopoiesis, major histocompatibility class I peptide processing, resistance to tumors and infection, in addition to normal kidney development and male fertility and is nicely described in their detailed review (15,351).

Using genome-based strategies, homologues of ACE have been identified (76, 355, 393, 394). One of these, ACE2, exhibits more than 40% identity at the protein level with the catalytic domain of ACE (76, 355). Similar to ACE, ACE2 is expressed on the surface of certain endothelial cell populations. However, compared to the ubiquitous distribution of ACE, the expression pattern of ACE2 is more limited with most abundant expression in kidney followed by heart and testis (76, 355), although the physiological importance of ACE2 in other tissues such as the brain, adipose, and pancreas is emerging (19, 20, 77, 344, 384, 385). Their substrate specificities also differ; ACE2 hydrolyzes Ang II with high efficiency, but has much lower activity against Ang I (76,365). Hydrolysis of Ang II by

ACE2 (or prolyl endopeptidases) generates Ang (1-7), a biologically active 7-amino acid peptide (Asp-Arg-Val-Tyr-Ile-His-Pro). Ang (1-7) subsequently acts upon the Mas receptor (312) and has several opposing actions to Ang II, such as the release of vasodilatory products such as NO, PGE_2, and bradykinin (256). Accumulating evidence indicates that this peptide causes vasodilation, natriuresis, and may promote reduced blood pressures (85). It has been further suggested that ACE2 may be the major pathway for synthesis of Ang 1-7 (86). Thus, the functions of ACE2 may be determined by its distinct actions to metabolize Ang II and to generate Ang 1-7. Chappell has a detailed discussion of the nonclassical RAS in the *Handbook of Physiology* (44).

ACE2 was originally identified and cloned from a cDNA library prepared from ventricular tissue of a patient with heart failure (76). Initial studies in separate lines of ACE2-deficient mice suggested a role for ACE2 in cardiac function (59, 386) and in blood pressure regulation (115). Taken together, these studies using mouse lines with targeted deletion of the *Ace2* gene have provided a number of contributions to understanding the role of ACE2 in cardiovascular functions (116). Despite a lack of uniformity in certain phenotypes, some common themes have emerged from these studies. ACE2 appears to have only modest effects on baseline cardiovascular functions and blood pressure control, but these effects can be substantially modulated by genetic and, perhaps, environmental factors. On the other hand, the activity of ACE2 may have more profound effects on susceptibility to pathological states such as hypertension and cardiac hypertrophy. Recent work by many groups has demonstrated roles for ACE2 in renal diseases such as diabetic and nondiabetic kidney disease (279,341,380,383) and hypertension (278,396) in both experimental models and human cohorts. Furthermore, ACE2 was also identified as a receptor for the severe acute respiratory syndrome coronavirus and in acute lung diseases (187-189) and shown to have a role in the gastrointestinal tract to regulate amino acid transport (29,126,291).

A third member of the ACE gene family, collectrin, was identified as a gene that is upregulated in the sub-total nephrectomy model of chronic kidney disease (393). Collectrin is highly homologous to the transmembrane portion of ACE2, but lacks the carboxypeptidase domain (393). Its physiological functions are emerging (66, 223, 224); and appear to regulate amino acid transport by the kidney and intestines (29,108). A recent report by Cechova et al. suggests collectrin directly regulates l-arginine uptake in endothelial cells leading to endothelial NOS coupling. Lack of collectrin led to vascular dysfunction, exaggerated salt sensitivity and impaired pressure natriuresis and hypertension (42).

Angiotensin receptors

The biological actions of Ang II are mediated by cell surface receptors that belong to the large family of 7 trans-membrane receptors (145,354). The angiotensin receptors can be divided into two pharmacological classes: AT_1 and AT_2, based on their differential affinities for various nonpeptide antagonists (Fig. 1). Studies using these antagonists suggested that most of the classically recognized functions of the RAS are mediated by AT_1 receptors including regulation of TG feedback (319), stimulation of renal tubular sodium reabsorption, release of aldosterone from the adrenal glomerulosa, SMC contraction, and stimulation of

hypothalamic thirst sensors (354). Gene targeting studies have confirmed these conclusions (62).

AT_1 receptors from a number of species have been cloned (150,253,313) and two subtypes, designated AT_{1A} and AT_{1B}, have been identified in rat (158, 159, 163, 310) and mouse (314). In the classical view, AT_1 receptors signal through $G_{\alpha q}$-linked signaling pathways involving phospholipase C, inositol triphosphate (IP_3), and increases in intracellular Ca^{2+} (69). However, the AT_1 receptor has also been linked to Janus kinase and signal transducer and activator of transcription activation (228), as well as β-arrestin-dependent pathways linked to extracellular signal-regulated kinases (ERK) activation (1, 333). In addition, other studies have shown that the AT_1 receptor has the capacity to transactivate the epidermal growth factor receptor (80). This pathway may contribute to chronic kidney injury and renal epithelial cell hypertrophy (46,198).

The murine AT_1 receptors are products of separate genes and share substantial sequence homology (28,159,163). AT_{1A} receptors predominate in most organs except the adrenal gland and regions of the CNS, where AT_{1B} expression may be more prominent (28, 99, 215). Commercially available antibodies to the AT_1 receptor are unreliable, so precise characterization of receptor distribution requires gene expression analysis coupled with radioligand binding studies (132). The murine AT_{1B} isoform was also recently detected within the glomerular podocyte, and pharmacologic blockade of this isoform afforded protection from proteinuria and renal injury in a mouse model of autoimmune nephritis, thereby directly illustrating the detrimental actions of glomerular AT_1 receptors in mediating progressive kidney disease (63). An early report that the AT_{1B} receptor was detected in humans has not been confirmed (181), and only a single AT_1 receptor gene was identified in the sequence of the human genome. Thus, the murine AT_{1A} receptor is considered to be the closest homologue to this single human AT_1 receptor.

The binding signatures of the AT_{1A} and AT_{1B} receptors are virtually identical (49), making it difficult to discriminate their *in vivo* functions pharmacologically. Experiments using gene targeting have provided insights into the discrete functions of the two AT_1 receptor genes (270,271,274). Although the AT_{1B} receptor has a unique role to mediate thirst responses (68), AT_{1A} receptors have the predominant role in determining the level of blood pressure (157, 234, 346) and in mediating vasoconstrictor responses (157, 270). The phenotype of markedly reduced blood pressures and profound sodium sensitivity in mice lacking the AT_{1A} receptor (157,272) under-scores its importance in blood pressure control. Moreover, similarities in blood pressure reduction with genetic deletion versus blockade of the AT_1 receptor confirm that hypotension seen in global AT_{1A} “knockout” mice is not due to a developmental abnormality (157). Conversely, overexpression of the AT_{1A} receptor in gene titration experiments yields step-wise increases in blood pressure corresponding to gene copy number (173), whereas constitutive activation of the AT_{1A} receptor leads to hypertension and both cardiac and renal fibrosis (18). AT receptors may also have a role to promote aging since mice with genetic deficiency of AT_{1A} receptors have increased longevity (14).

AT_{1A} receptors are expressed in all of the key organ systems involved in coordinately determining the level of blood pressure, including the kidney, vasculature, adrenal gland, heart, and both central and peripheral nervous systems. A renal cross-transplantation approach using wild-type and *Agtr1a*$^{-/-}$ kidneys (Fig. 7) illustrated equal and non-redundant contributions of AT_1 receptors in kidney and non-renal, systemic AT_1 receptors to the maintenance of normal blood pressure (61), suggesting that AT_1 receptors inside and outside of the kidney work together in maintaining blood pressure and preventing circulatory collapse in nonhypertensive mice. The importance of AT_1 receptors to regulating renal sodium handling even at baseline was evidenced in that only the transplanted animals lacking AT_1 receptors within in the kidney had significant increases in blood pressure during salt-loading. These studies also informed our understanding of renin mRNA regulation in the kidney, as renin expression was dramatically elevated in the hypotensive transplanted animals lacking AT_1 receptors in all tissues, but was not significantly increased in the "kidney knockout" mice lacking AT_1 receptors only within the kidney. According to these experiments, blood pressure rather than short-loop feedback through activation of renal AT_1 receptors is the more prominent regulator of renin generation at least at the RNA level (61).

The same kidney cross-transplantation technique coupled with the chronic Ang II infusion model of hypertension confirmed a dominant contribution of AT_1 receptors in the kidney to promoting sodium retention and blood pressure elevation in hypertension (60). As shown in Figure 8, after 2 weeks of Ang II infusion, the blood pressure elevation in the "systemic knockout" that retained AT_1 receptor expression only within the kidney recapitulated that seen in transplanted and non-transplanted wild-type controls. Conversely, the "kidney knockout" mice that lacked AT_1 receptors in the kidney showed only a diminutive and ephemeral increase in blood pressure during chronic Ang II infusion (Fig. 8). Thus, AT_1 receptors in the kidney were both necessary and sufficient to fully manifest Ang II-dependent hypertension (60). These studies further illustrated that activation of renal AT_1 receptors drives blood pressure elevation through sodium retention and intravascular volume expansion. Specifically, the hypertensive "wild-type" and "systemic knockout" cohorts that expressed AT_1 receptors in the kidney demonstrated blunted renal sodium excretion following the initiation of chronic Ang II infusion coupled with an increase in total body weight compared to the "kidney knockout" mice that lacked renal AT_1 receptors and remained normotensive during chronic Ang II infusion (Fig. 8). In subsequent studies, challenging the cross-transplanted animals with a low salt diet during chronic Ang II infusion illustrated that the major component of blood pressure elevation mediated through renal AT_1 receptor stimulation is indeed a consequence of sodium retention. However, a nontrivial component also accrues directly from the increase in renal vascular resistance due to AT_1 receptor activation, independent of renal sodium handling (64).

Subsequent generation of mice with conditional deletion of AT_{1A} receptors from epithelia of the proximal tubule of the kidney showed that AT_1 receptors in this cell lineage play a nonredundant role in maintaining blood pressure homeostasis and in the pathogenesis of Ang II-dependent hypertension (Fig. 9). These actions are mediated, at least in part, through modulation of solute and fluid reabsorption by the proximal tubule and by controlling abundance of sodium transporters including the NHE3 antiporter and the sodium phosphate

cotransporter (117,211,304). These *in vivo* findings were consistent with earlier *in vitro* studies showing that Ang II acting through AT_1 receptors on the basolateral surface of proximal tubules promotes sodium reabsorption by coordinately stimulating the sodium-proton antiporter on the luminal membrane along with the sodium-potassium ATPase on the basolateral surface (57, 100, 323). These actions also result in enhanced basolateral sodium bicarbonate flux (100). Thus, activation of AT_1 receptors in the renal proximal tubule stimulates sodium and fluid reabsorption, leading to intravascular volume expansion and blood pressure elevation.

In addition to the proximal tubule, AT_1 receptors are expressed on epithelial cells across the entire nephron. For example, they are expressed on the luminal and basolateral membranes of the epithelium in the medullary thick ascending limb (287, 298). However, their effects on activity of NKCC2 are inconsistent and appear to depend on local Ang II levels (4, 203). At lower concentrations of Ang II, inhibition of NKCC2 may occur (4, 203), whereas stimulation of NKCC2 may be seen at higher concentrations (4). Functions of AT_1 receptors in more distal segments of the nephron have also been examined. In cortical and outer medullary collecting ducts, activation of AT_1 receptors stimulates sodium-hydrogen exchange by increasing the density of the vacuolar sodium-hydrogen ATPase in the apical membrane of the type A intercalated cell, which in turn leads to an increase in bicarbonate reabsorption (7, 204, 289, 309). AT_1 receptors also modulate the activity of pendrin, a sodium-independent chloride transporter expressed by type B intercalated cells. Chronic activation of AT_1 receptors shifts pendrin distribution from the subapical space to the apical membrane leading to enhanced chloride reabsorption. These effects of AT_1 receptors to augment pendrin activity raise blood pressure *in vivo* (364). On the apical membrane of the principal cells in the cortical collecting duct, luminal Ang II stimulates amiloride-sensitive sodium transport by increasing activity of the epithelial sodium channel through an AT_1 receptor-dependent mechanism (296,370). However, preliminary studies suggest that cell-specific deletion of AT_1 receptors from principal cells does not have a significant impact on baseline blood pressure (345).

Along with their impact on sodium handing, AT_1 receptors also seem to play a critical role in controlling urinary concentrating mechanisms. The complete absence of AT_1 receptors in mice doubly deficient in AT_{1A} and AT_{1B} receptors is associated with atrophy of the renal papilla, polyuria, and a marked urinary concentrating defect (274, 275). A similar phenotype is seen in Agt and ACE-deficient mice indicating that Ang II acting through AT_1 receptors is essential for maintenance of the inner medulla and its functions to promote urinary concentration (82, 172). Similarly, AT_{1A} receptor deficient mice with preservation of inner medullary architecture also have a urinary concentrating defect due to a relative resistance to vasopressin, and this defect can be reproduced in wild-type mice by administration of an AT_1 receptor blocker (273). AT_1 receptor blockade also blunts the maximal urine concentrating capacity in 1-desamino-8-D-arginine vasopressin-challenged rats and this effect is associated with reduced expression of aquaporins-1 and -2 (195). In the medullary collecting duct, Ang II upregulates gene expression for the V_2 vasopressin receptor and the apical membrane targeting of the aquaporin-2 channel (210, 345, 373, 381). These effects are mediated through a protein kinase A-dependent pathway (381). Moreover, cell-specific

deletion of AT_1 receptors from the collecting duct is sufficient to cause a urinary concentrating defect (345). In this case, epithelial levels of aquaporin-2 protein were significantly diminished in the inner and outer medulla, whereas localization to the apical membrane was unaffected. Thus, direct effects of AT_1 receptors in epithelial cells of the collecting duct modulate aquaporin-2 levels and these actions are required to achieve maximal urinary concentration.

AT_1 receptors are widely expressed in vascular tissues and when activated by Ang II cause potent vasoconstriction. Stimulation of AT_1 receptors in vascular SMCs initiates a signaling cascade including increased intracellular Ca^{2+} concentration and alterations in the cytoskeleton, inducing contraction with consequent increases in vascular resistance (112). This response is virtually absent in mice deficient in both the AT_{1A} and AT_{1B} receptor isoforms, confirming the importance of AT_1 receptors in this response (157,274). The vasoconstrictor actions of Ang II play a central role in maintaining circulatory homeostasis in a number of tissues, including the kidney. In the kidney, the hemodynamic actions of Ang II impact renal blood flow, glomerular filtration rate, excretion of salt and water, and progression of renal damage in disease states. Infusion of Ang II increases filtration fraction. Accordingly, it has been suggested that AT_1 receptor activation in the glomerular microvasculature causes greater constriction of the efferent compared to the afferent arteriole (254,321). However, experimental studies are not in complete agreement on this point. Work by Navar and colleagues indicates that the rise in filtration fraction occur in parallel with concomitant increases in resistance of both the afferent and efferent arterioles (35,36). On the other hand, Denton et al. showed that despite preferential constriction of the afferent over the efferent arterioles in response to Ang II, resistance was higher on the efferent side due to smaller resting luminal dimensions of efferent arterioles (71). This is discussed in great detail by Navar et al. in the renal microcirculation section of the *Handbook of Physiology* (260). In hypertensive states, such as chronic Ang II infusion, the increased glomerular pressure from AT_1 receptor stimulation can promote renal injury (23, 79, 261). The apparent actions of Ang II to promote increased glomerular hydrostatic pressure in diabetes were a major rationale for using ACE inhibitors in diabetic nephropathy (392).

Outside of the kidney, the role of vascular AT_1 receptors in promoting direct vascular damage is complex. Along with their effects on vascular tone, AT_1 receptors may also stimulate growth and hypertrophy of SMCs (101), thereby directly contributing to vascular remodeling in hypertension. It has been suggested that nonhemodynamic actions of AT_1 receptors, including enhanced generation of reactive oxygen species (ROS) may promote changes in vascular structure that perpetuate the development of hypertension (153). Further-more, angiotensin receptor blockers (ARBs) reverse vascular remodeling in patients with hypertension suggesting a direct role for vascular AT_1 receptors in this process (317). On the other hand, deletion of AT_1 receptors from SMC lineages reduced oxidative stress in vascular tissue but did not affect the degree of vascular remodeling induced by hypertension (342), indicating a key role for pressure in hypertensive vascular injury (60,342).

Cardiovascular control centers in the central nervous system (CNS) also have a powerful capacity to influence blood pressure and fluid homeostasis through activation of the

sympathetic nervous system. Within the CNS, AT_{1A} receptors mediate the systemic pressor effects of Ang II whereas activation of AT_{1B} receptors stimulates the drinking response and thereby regulates water balance through a central neurogenic mechanism (68). The pressor response is mediated through stimulation of AT_{1A} receptors along the subfornical organ (SFO)-rostral ventrolateral medulla pathway leading to local Ras-related C3 botulinum toxin substrate 1 (Rac1)-dependent generation of ROS (399, 400). Accordingly, targeted expression and/or stimulation of AT_{1A} receptors directly within the rostral ventrolateral medulla can raise blood pressure independently of other systemic or renal AT_1 receptors (3,45). Inhibition of endoplasmic reticulum stress within the SFO by infusing tauroursodeoxycholic acid or by enhancing local activity of an endoplasmic reticulum chaperone glucose-related protein (GRP78) abrogates the chronic hypertensive response to Ang II (390). Thus, some of the effects of Ang II in the SFO to drive blood pressure elevation occur through potentiation of endoplasmic reticulum stress.

Ang II mediates damage to the heart and kidney in part by stimulating inflammatory responses (246,247). Furthermore, activation of T lymphocyte populations during chronic Ang II infusion has the capacity to modulate the chronic hypertensive response (6,118). Although Ang II can directly enhance lymphocyte proliferation *in vitro* (136, 259), recent studies have uncovered potentially immunosuppressive effects of AT_1 receptors on mononuclear cells in the setting of hypertension (64,395). For example, deletion of AT_1 receptors solely from T lymphocytes promotes T cell differentiation toward a proinflammatory “Th1” phenotype, leading to exaggerated levels of albuminuria and glomerular podocyte damage in Ang II-induced hypertension (395). Thus, whether Ang II activates the immune system through direct stimulation of AT_1 receptors on inflammatory cells remains controversial. Alternative mechanisms through which Ang II mediates immune activation may involve AT_1 receptor activation in the CNS and/or the endothelium (130,230).

Pharmacological and genetic studies have thus confirmed that virtually all of the classically recognized functions of the RAS are mediated by AT_1 receptors (Fig. 10). However, exploring the physiological role of AT_2 receptors has received considerable attention in recent studies particularly as new specific AT_2 receptor agonists have been identified and are being considered for clinical use (369). AT_2 receptors are found in abundance during fetal development (111, 240) but their expression generally falls after birth. Nevertheless, persistent AT_2 receptor expression can be detected in several adult tissues including the kidney, adrenal gland and the brain, and absolute levels of AT_2 receptor expression may be modulated by Ang II and certain growth factors (147). Likewise, it has been suggested that AT_2 receptor expression may be increased in pathological states.

AT_2 receptors appear to signal by coupling to $G_{\alpha i2}$ and $G_{\alpha i3}$ proteins (17). Using site-directed mutagenesis, the intermediate portion of the third intracellular loop of the AT_2 receptor was found to be necessary for normal receptor signaling (127, 202). Moreover, it has been suggested that activation of AT_2 receptors stimulates bradykinin, NO, and cGMP (34, 337), and these pathways may mediate actions of the receptor to promote natriuresis and blood pressure lowering. *In vitro* data further indicate that AT_2 receptor activation similarly directs angiogenesis in the hypoxic heart via downstream stimulation of the

bradykinin B_2 receptor and NO generation (250). Phosphorylation of eNOS underlies the increase in NO bioavailability in the vasculature following AT_2 receptor activation (134, 389). AT_2 receptor stimulation counteracts AT_1 receptor-induced constriction in the vasculature by inhibiting activation of the phospholipase D signaling pathway (5). Finally, there is evidence that AT_2 receptors signal via nonclassical eicosanoid signaling pathways. For example, hydroxy-eicosatetraenoic acids (HETEs) act as second messengers for AT_2 receptors in the kidney, leading to ERK 1/2 phosphorylation (78). Moreover, AT_2 receptors are upregulated during inflammation, and AT_2 stimulation in this setting reduces organ damage both by inhibiting epoxyeicosatrienoic acid synthesis and by limiting activation of NF-κB (308).

Targeted disruption of the mouse *Agtr2* gene did not cause a dramatically abnormal phenotype at baseline. However, these animals clearly manifest increased sensitivity to the pressor actions of Ang II (129, 148) and to Ang II-induced vascular damage that promotes aortic aneurysm progression (119). One of the AT_2 deficient lines manifested increased baseline blood pressure and heart rate (129). Inter-estingly, behavioral changes were also observed in AT_2-deficient mice; they had decreased spontaneous movements and rearing activity and impaired drinking response to water deprivation (129, 148). Transgenic mice that overexpress the AT_2 receptor gene under control of a cardiac-specific promoter have decreased sensitivity to AT_1-mediated pressor and chronotropic actions (231). Moreover, the pressor actions of Ang II are significantly attenuated in these transgenic mice. This attenuation was completely reversed following pretreatment with a specific AT_2 receptor antagonist. Some target effects of AT_2 receptor activation may relate to renin regulation. Stimulation of AT_2 receptors inhibits the processing of pro-renin in JG cells, which in turn diminishes active renin content (146,338).

More recent studies with compound 21 (C21), a putative specific AT_2 receptor agonist, suggest that AT_2 receptor activation may limit progressive cardiovascular and renal damage in a mirror image of the actions of AT_1 receptors to promote such injury. For example, treatment with C21 provides neuro-protection to stroke-prone rats, limits the extent of the infarct zone in a model of myocardial ischemia, and mitigates renal inflammation and proteinuria in hypertension (102,170,236). The renoprotective effects of C21 may relate to increases in NO bioavailability accruing from AT_2 receptor stimulation (232). In contrast to the effects of AT_1 receptors in the kidney to drive sodium retention, activation of renal AT_2 receptors by Ang II augments natriuresis (280). Indeed, natriuresis mediated by activation of the renal dopamine D_1 receptor may require recruitment of AT_2 receptors to the apical membranes of epithelial cells in the proximal tubule (281). Taken together, these data are consistent with a primary function of the AT_2 receptor to negatively modulate the actions of the AT_1 receptor.

Conclusion

Because of their efficacy in a wide range of disorders from hypertension to heart failure to kidney disease, pharmacological inhibitors of the RAS are widely used in clinical medicine and understanding of their optimal use in patients is still evolving. While it has been more than 100 years since the discovery of renin, basic research on the RAS continues to unlock

novel features of its functions in normal physiology and in disease. During the past two decades, the use of transgenic animals has been particularly fruitful in providing a rich molecular overlay of the physiological actions of the RAS. In this chapter, we have attempted to provide an in-depth overview of the physiological functions of the RAS, with a focus on more recent studies where molecular mechanisms of RAS functions have been defined. In the context of the robust nature of current research into the "classical RAS," we also anticipate significant advances in a number of areas in the future. These include emerging data on the structural biology of RAS components, new understanding of the complexity of angiotensin receptor signaling, and the development of novel agonists and biased ligands for manipulating RAS activity *in vivo*. Along with advancing the scientific field, such understanding should facilitate translational approaches for improving the safety and efficacy of RAS inhibition in the clinic.

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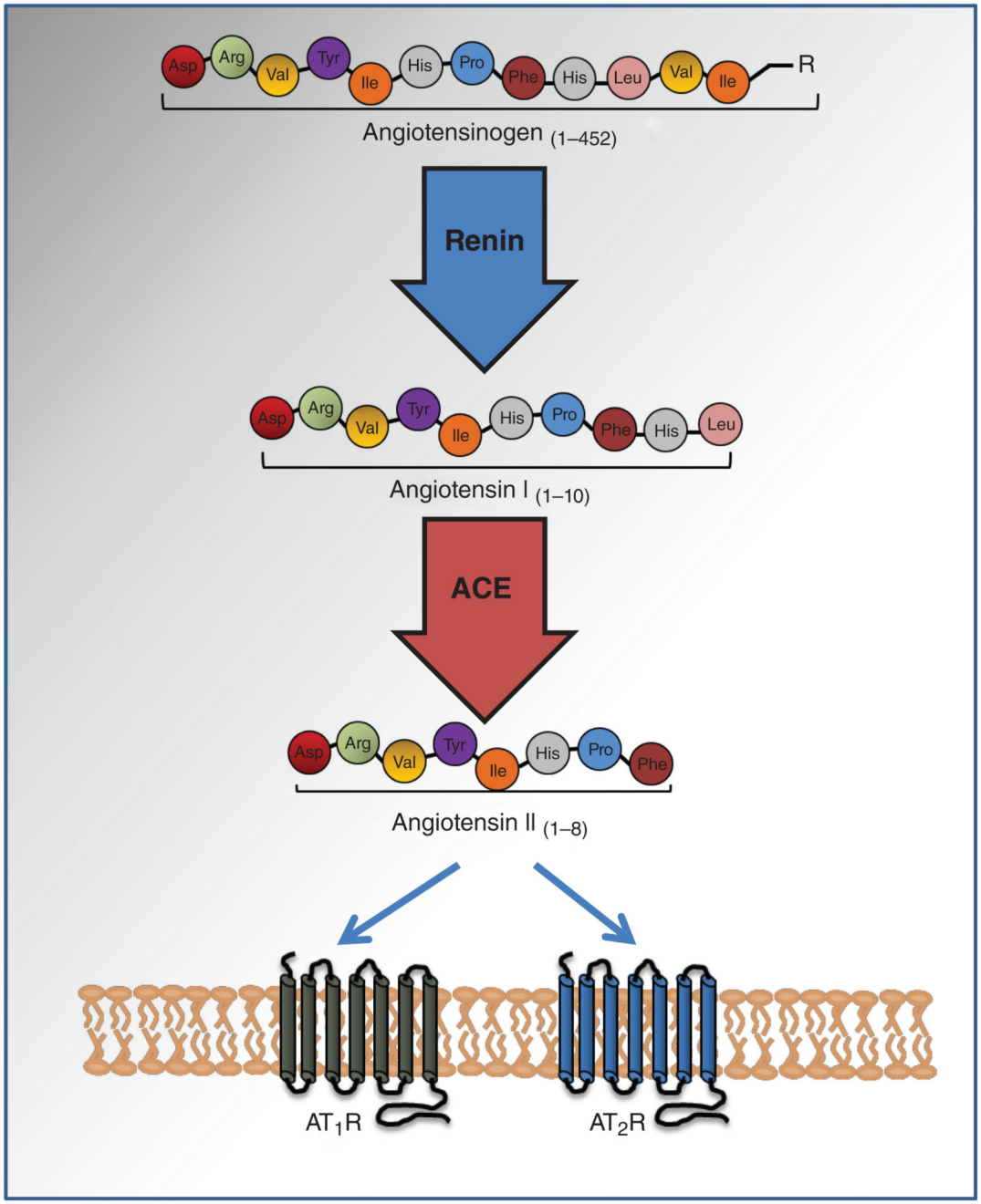

Figure 1.

Classical renin-angiotensin system (RAS). Through sequential cleavage of protein substrates by specific proteases, the multi-functional peptide hormone *angiotensin II* is generated by the "classical" RAS. The primary substrate for the RAS is *angiotensinogen*. While the liver is the primary source of *angiotensinogen*, it is also produced in other tissues including the kidney. *Renin* is an aspartyl-protease that catalyzes cleavage of the 10-amino acid peptide *angiotensin I* from the N-terminus of the *angiotensinogen* molecule. In a sequential reaction, the dicarboxyl-peptidase *angiotensin converting enzyme* (ACE) removes 2 amino acids from the C-terminus of *angiotensin I* to form *angiotensin II*. The biological actions of the

"classical" RAS are executed through high affinity binding of *angiotensin II* to specific *angiotensin receptors*. These receptors belong to the large family of G-protein coupled receptors (GPCRs) and can be separated into two pharmacological classes, AT_1 and AT_2, each with distinct functions linked to specific intra-cellular signaling pathways.

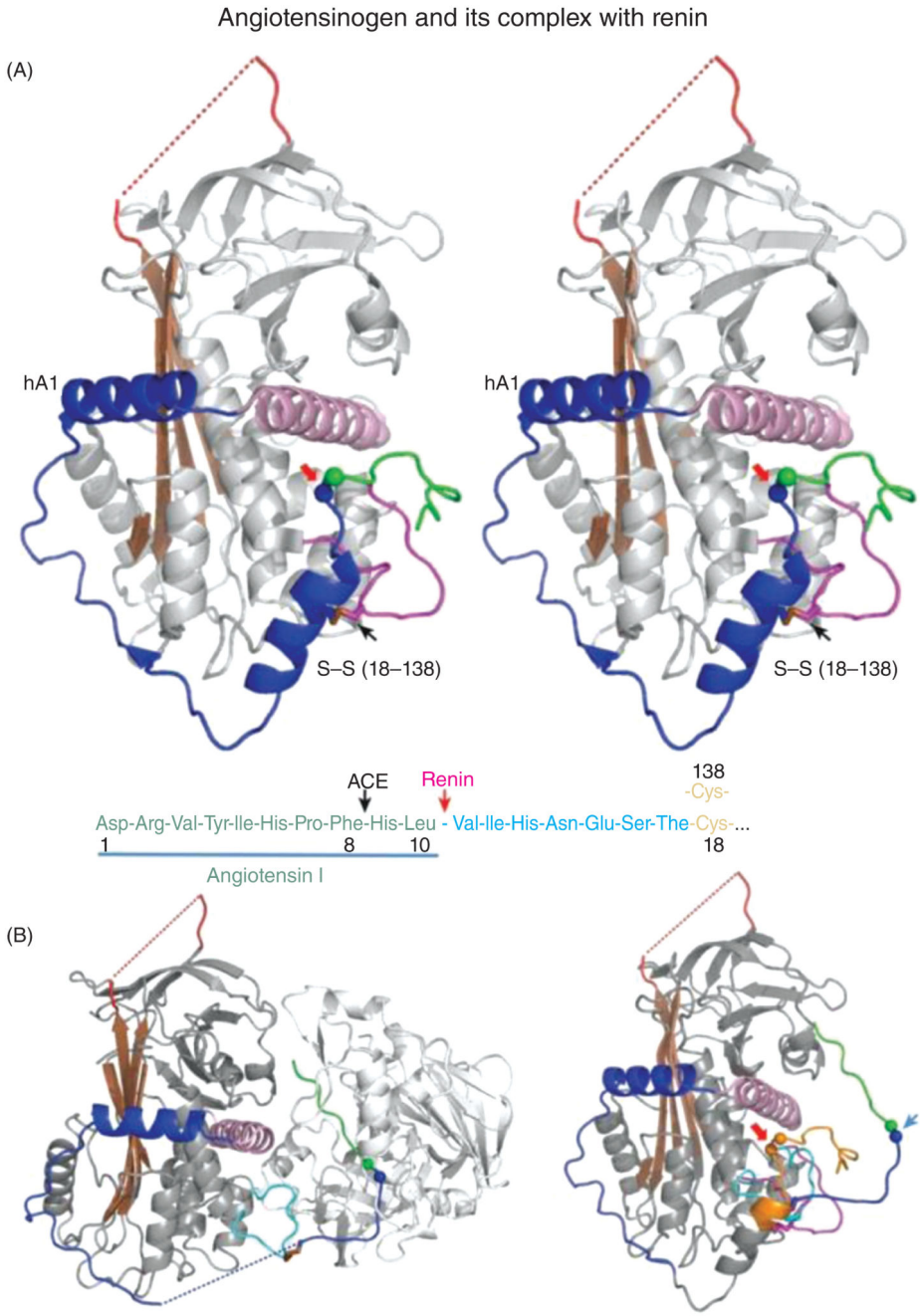

Figure 2.

Angiotensinogen and its complex with renin (used with permission from Zhou et al. *Nature* 468: 108-111, 2010). (A) Stereo image of human angiotensinogen. Serpin template in grey and helix A in purple with the A-sheet in brown, the unresolved reactive loop in red, and in dark purple the CD loop containing Cys 138. The amino-tail is in blue with the new helix A1 and a second helix A2 containing Cys18 (linked in brown to Cys 138); the terminal angiotensin I segment is in green with the renin-cleavage site shown as green and blue balls. The sequence below (same color coding) also indicates the subsequent cleavage by

angiotensin converting enzyme (ACE) releasing the octapeptide angiotensin II. (B) the initiating complex formed by angiotensinogen with inactivated (Asp292Ala) renin (left), and on right superimposed on the unreacted form (brown) showing the displacement of the CD loop and the movement of the aminoterminal peptide (visible to Cys 18), into the active cleft of renin.

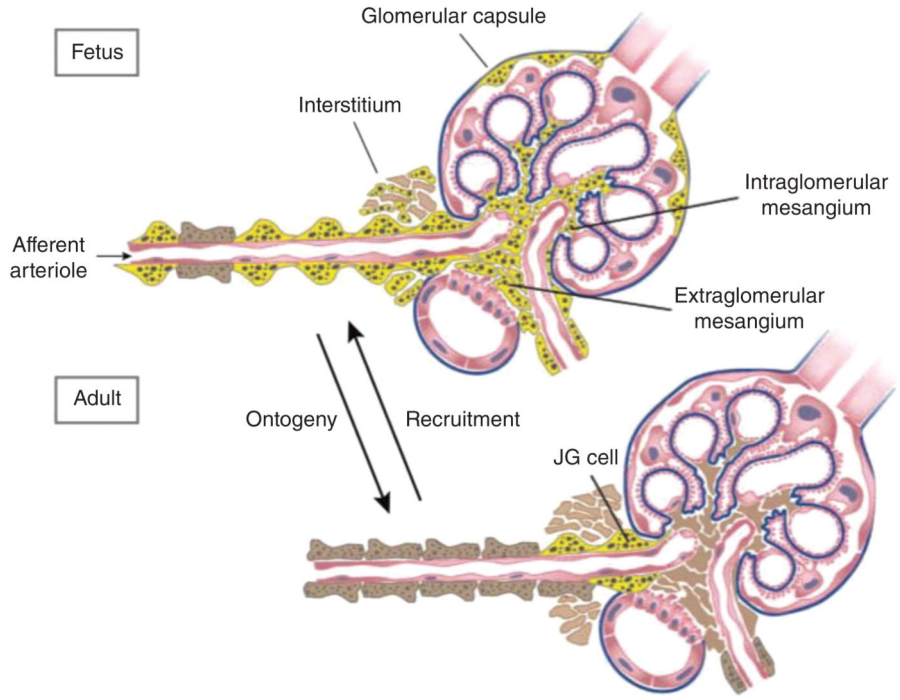

Figure 3.

Renin expression (used with permission from Gomez et al. *Kidney Int*., 2009, 460-462). During embryonic development, renin-expressing cells (depicted above as yellow with black dots) can be found along the intrarenal arteries, the glomeruli and the interstitium. This pattern is progressively restricted and in the adult kidney renin can be only found in a few cells in the juxtaglomerular (JG) area. However, in response to various physiological stimuli such as severe sodium depletion, renal cells can reacquire renin expression (recruitment). In these cases, renin expression can be observed mainly in cells along the afferent arteriole as well as in the interstitium, the mesangium, glomerular capsule, and efferent arteriole.

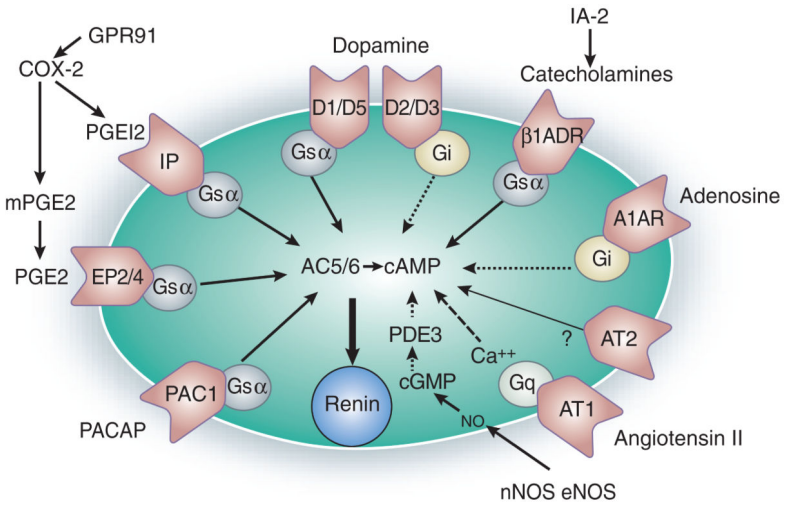

Figure 4.

Overview of the major signaling pathways involved in regulation of renin. Figure is reproduced, with permission, from Schnermann and Briggs, 2012; *Kidney Int* 81, 529-538. Details about the effects of each pathway (stimulatory or inhibitory) are described in the text. A1AR, A1 adenosine receptor subtype; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase; NO, nitric acid; PACAP, pituitary adenylate cyclase-activating polypeptide; PDE3, phosphodiesterase 3; PGE_2, prostaglandin E_2.

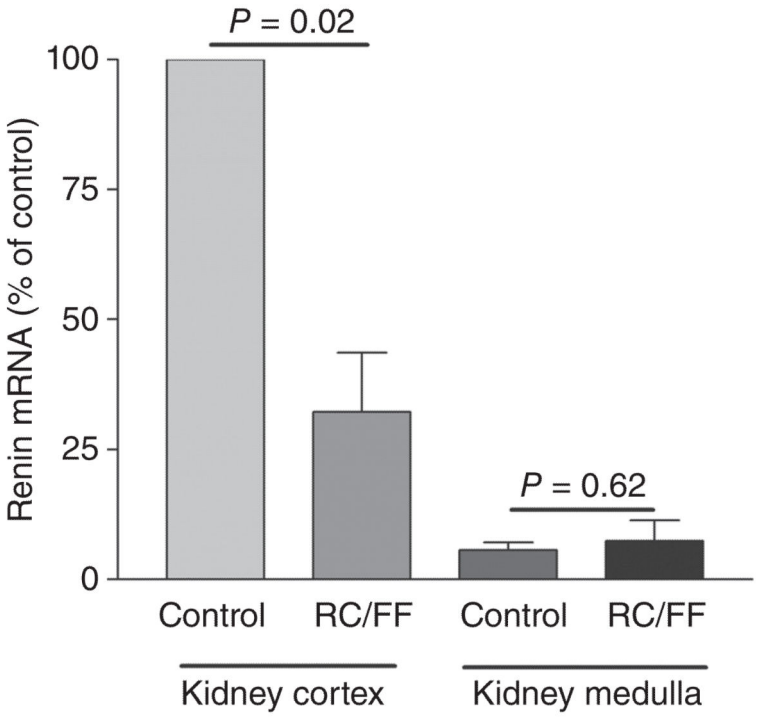

Figure 5.

Renin mRNA in kidney cortex and kidney medulla from Gsα-deficient mice. (Used with permission from Chen et al. *Am J Physiol Renal Physiol* 2007, F27-F37) RC/FF mice (*n* 6) relative to control animals (*n* 12; 9 RR/GG and 6 RR/FF) as determined by quantitative are given for comparisons between genotypes. PCR. Significances are given for comparisons between genotypes.

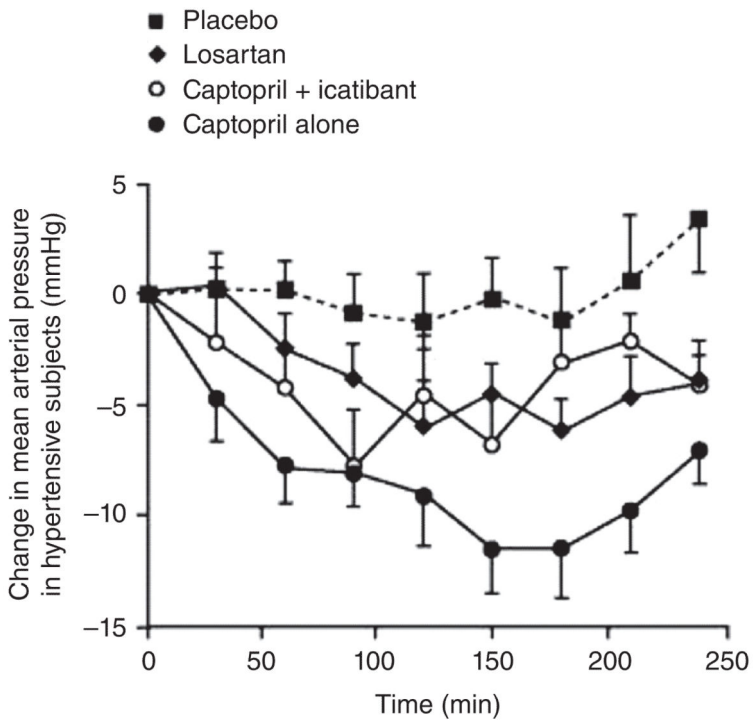

Figure 6.

Attenuation of the antihypertensive efficacy of ACE inhibitors with the B2 bradykinin receptor antagonist icatibant. (Used with permission from Gainer et al. *N Engl J Med* 339: 1285-1292, 1998.) Mean arterial pressures (MAP) were measured over 250 min in hypertensive patients treated with placebo, ACE inhibitor alone, ACE inhibitor + icatibant, and angiotensin receptor blocker (ARB). The largest blood pressure reduction was seen with ACE inhibitor alone, and this was attenuated when icatibant was given along with the ACE inhibitor. The extent of blood pressure lowering was intermediate and equivalent in the groups receiving the ARB or ACE inhibitor + icatibant.

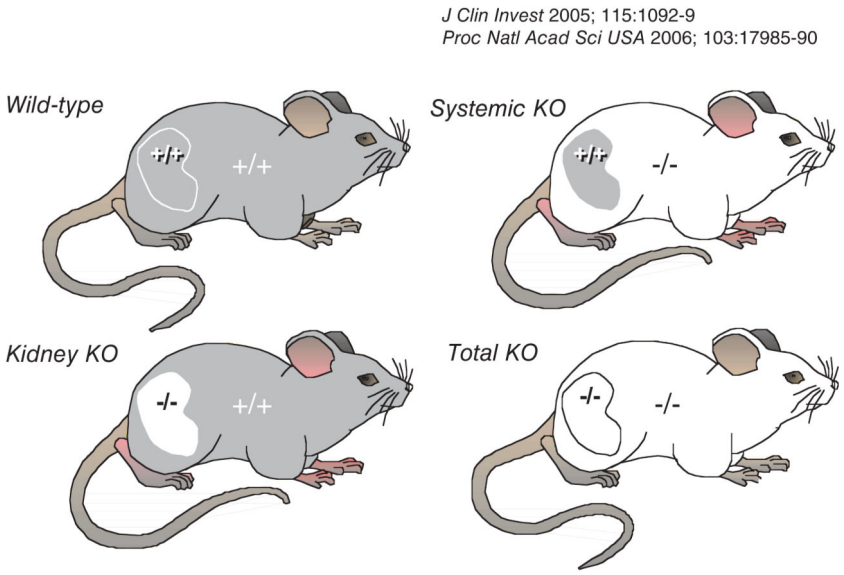

Figure 7.

Kidney cross-transplantation groups. Wild-type ($^{+/+}$) or AT_{1A} ($^{-/-}$) receptor-deficient mice were transplanted with kidneys from wild-type or $AT_{1A}{}^{-/-}$ mice. Group I animals (Wild-type) had a full complement of AT1A receptors. Group II animals (Kidney KOs) expressed AT_{1A} receptors only outside the kidney. Group III animals (Systemic KOs) expressed AT_{1A} receptors only within the kidney. Group IV animals (Total KOs) completely lacked AT_{1A} receptors.

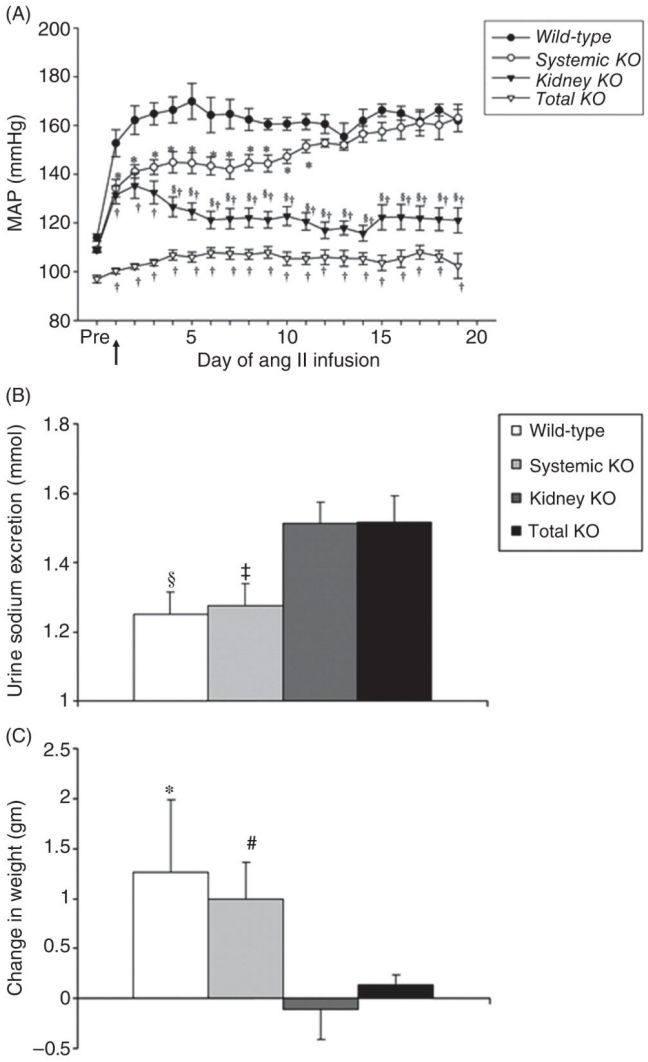

Figure 8.

Blood pressures and urinary sodium excretion during chronic Ang II infusion in mice after kidney cross-transplantation. (A) Daily, 24-h blood pressures in the experimental groups before ("pre") and during 21 days of Ang II infusion (*, $P \leq 0.03$ vs. *Wild-type*; §, $P < 0.008$ vs. *Systemic KO*; †, $P < 0.006$–0.0001 vs. *Wild-type*). (B) Cumulative sodium excretion during the first 5 days of Ang II infusion. (§, $P < 0.02$ vs. *Kidney KO* and $P = 0.03$ vs. *Total KO*; ‡, $P = 0.03$ vs. *Kidney KO* and *Total KO*). (C) Change in body weights after 5 days of Ang II infusion. (*, $P = 0.03$ vs. "pre"; #, $P = 0.05$ vs. "pre").

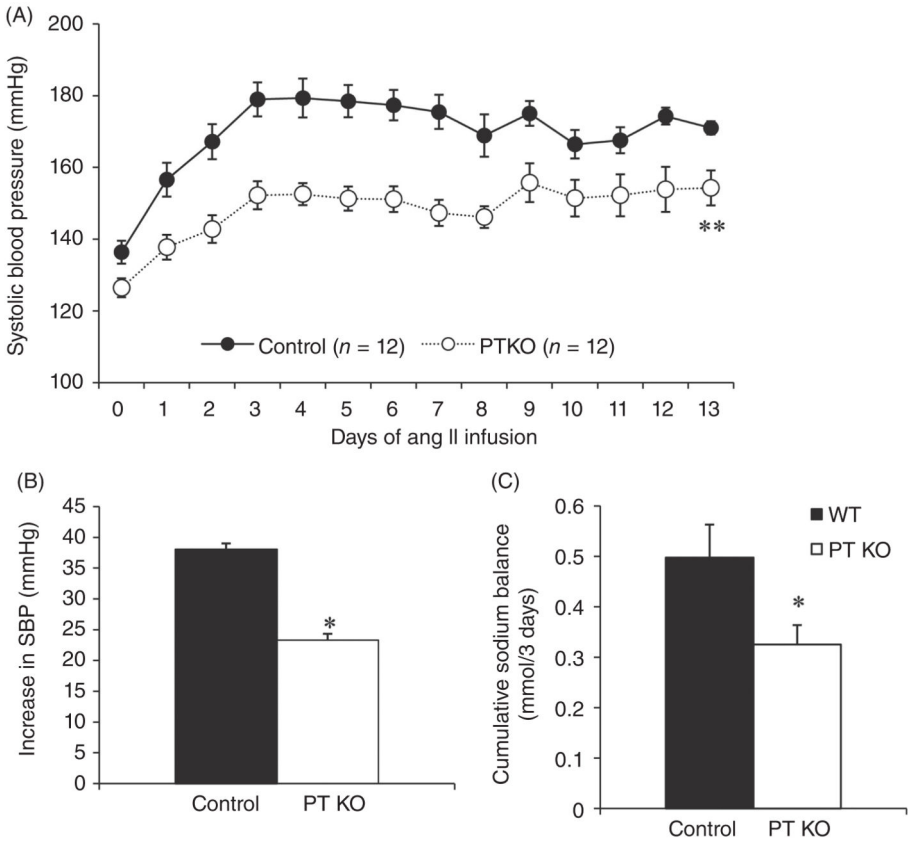

Figure 9.

AT_{1A} receptors in the proximal tubule promote hypertension (A) With infusion of ang II (1000 ng/kg/min), BPs increased significantly in both control and PTKO mice but the hypertensive response to angiotensin II was significantly attenuated in the PTKOs (**; $P <$ 0.001). (B) The mean increase in BP during the angiotensin II infusion was significantly less in the PTKOs (23 ± 3 mmHg) compared to controls (black bars; 38 ± 5 mmHg, *; P 0.0005). (C) Cumulative sodium balance was significantly lower in the PTKOs (n = 8) than controls (n = 7, *; P = 0.046) during the first 3 days of Ang II infusion. Error bars represent SEM.

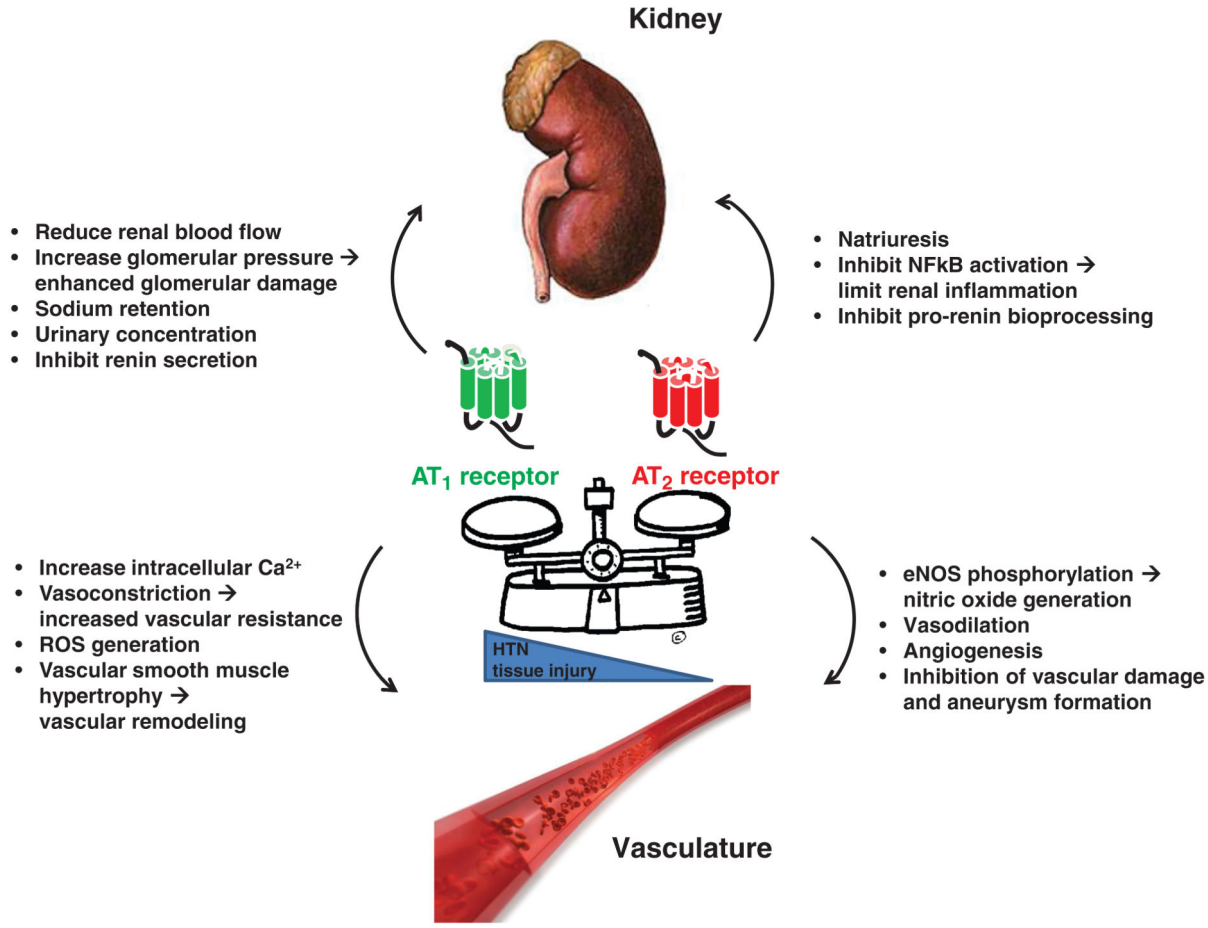

Figure 10.

The myriad actions of angiotensin receptors in the kidney and vasculature. In cardiovascular control centers, the effects of AT_2 receptor stimulation oppose and ameliorate the prohypertensive and proinflammatory effects of AT_1 receptor stimulation.