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Hormone-dependent regulation of renin and effects on prorenin receptor signaling in the collecting duct

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Abstract

The production of renin by the principal cells of the collecting duct has widened our understanding of the regulation of intrarenal angiotensin II (Ang II) generation and blood pressure. In the collecting duct, Ang II increases synthesis and secretion of renin by mechanisms involving the activation of Ang II type 1 receptors (AT1R) via stimulation of the PKCα, Ca^{2+} and cAMP/PKA/CREB pathways. Additionally, paracrine mediators, including vasopressin (AVP), prostaglandins, bradykinin (BK) and atrial natriuretic peptide (ANP) regulate renin in principal cells. During Ang II-dependent hypertension, despite plasma renin activity suppression, the renin and prorenin receptor (PRR) are upregulated in the collecting duct and promote de novo formation of intratubular Ang II. Furthermore, activation of PRR by its natural agonists, prorenin and renin, may contribute to the stimulation of profibrotic factors, independent of Ang II. Thus, the interactions of RAS components with paracrine hormones within the collecting duct enables tubular compartmentalization of the RAS to orchestrate complex mechanisms that increase intrarenal Ang II, Na^+ reabsorption and blood pressure.

Keywords

Intrarenal Angiotensin II; Vasopressin; Bradykinin; Prostaglandins; Protein Kinase; Nitric Oxide

Introduction

The renin-angiotensin system (RAS) is critical for the regulation of electrolyte balance, extracellular volume, and blood pressure [1, 2]. In the RAS cascade, renin is the rate-step limiting enzyme for the generation of angiotensin II (Ang II). In the adult kidney, renin

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Conflict of interest

The authors declare no conflict of interest.

is synthetized by the juxtaglomerular (JG) cells, cuboid myofibroblast-like cells, that are localized in the media layer of the renal afferent arterioles [3]. Here glycosylated renin is contained in intracellular vesicles [4].

In humans, renin production begins with the transcription of the renin gene (*Ren 1c*), which then produces several mRNAs that are related with polymorphisms and the development of diseases [4,5]. The cAMP/protein kinase A (PKA) pathway stimulates CREB-mediated induction of *Ren 1c* and the transcription of pre-prorenin. To form prorenin, the pre-(pro)segment is removed and sorted upon glycosylation into two different paths: a constitutive pathway for the secretion of prorenin and a regulated pathway for the secretion of mature active renin [6]. Non-glycosylated prorenin which was initially believed to have no biological activity, is directed to well-known electron dense vesicles [7]; while only glycosylated prorenin is directed to the vesicular network in JG cells [7]. In the vesicular network of JG cells the (pro)segment of 43 amino acids is proteolytically removed to form active renin and then released [7, 8] (Table 1). When there is decreased extracellular volume, renin synthesis and secretion by JG cells increase in response to 3 stimuli: *(i)* Decreased kidney perfusion pressure, *(ii)* Decreased Na^+ load detected by the Na-K-2Cl (NKCC2) co-transporter in the macula densa, and *(iii)* Decreased arterial blood pressure sensed by baroreceptors that activates the sympathetic nervous system [9–12]. In JG cells, renin release involves exocytotic events mediated by the cAMP/PKA pathway in response to β1 adrenergic receptor activation [13,14]. Other pathways regulating renin release are mediated by nitric oxide (NO) and E-prostanoid 4 (EP4) receptor pathways, which increase intracellular cAMP [15]. The Ca^{2+}/protein kinase C (PKC) signaling, mediated by the Ang II type 1 receptor (AT1R), suppresses renin exocytosis in a phenomenon called the "Ca^{2+} paradox" [16]. The crosstalk between these Ca^{2+}-dependent mechanisms to lower intracellular cAMP levels, exerts a fine tune regulation on renin release. A secondary modulation of renin release in JG cells involves cGMP generation and protein kinase G type II (PKG-II) activation, which decreases renin secretion [4].

In the classical RAS cascade, renin secreted by JG cells cleaves angiotensinogen (AGT), an α-globulin primarily produced by the liver, and results in the formation of Ang I. Hereafter, Ang I is converted into the octapeptide Ang II by angiotensin converting enzyme (ACE or ACE1) [17]. Ang II via its specific membrane AT1 and AT2 receptors, elicits complex cellular effects and hormonal regulation of body homeostasis. Part of RAS complexity includes the paracrine/autocrine regulation of processes in different tissues and organs, which could explain the difference in Ang II amounts found in various organs/tissues ('organ uptake theory'). Nehme et al. [18] established an atlas for the RAS across 23 different human normal tissues that include genes encoding classical and novel components defined as extended RAS (extRAS). In the kidney, although increased Ang II levels are partially explained by AT1R-mediated uptake [19]; the highest intrarenal/intratubular Ang II formation is driven by enhanced expression and coordinated actions of extRAS components [20–24]. AGT is synthesized and secreted by the proximal tubule cells [25] and ACE activity is present along the nephron [26]. Furthermore, renin is produced and secreted by the principal cells of the collecting ducts [27], where it interacts with the prorenin receptor (PRR) to complement the regulation of water and sodium reabsorption and blood pressure [28]. In this scenario, ACE2, the homologue monocarboxypeptidase of ACE, functions

as the counter-regulatory endogenous enzymatic pathway as it degrades Ang I into the nonapeptide Ang 1–9 and Ang II into the heptapeptide Ang (1–7) [29]. The evidence that Ang II is produced via renin or prorenin synthesized in the collecting duct was initially reported in ANG II-dependent hypertensive rats [30]. Indeed, infusion of Ang II presented an attenuated hypertensive response in the collecting duct-specific renin knockout mice [31] and the overexpression of CD renin causes elevated blood pressure [32].

The "*Janus Effect"* of the kidney, has two facets: one related to hormones controlling the synthesis and release of renin by the JG cells (JG renin); and the other that is controlled by hormones regulating the production and secretion of renin by the collecting duct (CD renin) [33]. Differences in renin synthesis and release/secretion between juxtaglomerular (JG) cells and principal cells of the collecting duct are summarized in Table 1. In the present review, we discuss the paracrine/autocrine regulation of CD renin and its interactions with the PRR during hypertension.

Intrarenal RAS in the pathogenesis of kidney disease and hypertension

The cornerstone for intrarenal RAS activation is the local production of renin in the tubular segments of the kidney, including proximal tubule, connecting tubules, and collecting ducts [34–37]. In the kidney, the concentration of Ang I and Ang II in the lumen of proximal tubules is within the pM range, as are the levels found in the renal interstitium [20,21,38]. In contrast to Ang II's inhibitory effect on JG renin, in the distal nephron segments when Ang II is chronically infused inducing a hypertensive state in rat and mice it stimulates the synthesis and secretion of renin [31,32,34,35]. This stimulating effect was demonstrated in two-kidney, one-clip (2K1C) Goldblatt rat [23,26,27], and hypertensive mouse-Ren 2 transgenic rat (mRen2 TGR) [24] experimental animal models. While JG renin leads to systemic RAS activation in response to physiological stimuli; CD renin contributes to intrarenal RAS stimulation and pathogenesis and progression of hypertension. These findings support the hypothesis that in the kidney, renin exhibits a "*Janus effect*" (Figure 1).

Hormonal regulation of renin in the colleting duct

The distal nephron segment harbors paracrine mechanisms contributing to the regulation of blood pressure [33,37,38]. The expression of renin in the collecting duct is regulated in differential and dissociated fashions from JG renin as discussed below.

Angiotensin II.

During Ang II-dependent hypertension, increased intrarenal Ang II concentration is due to augmented AT1R binding with concomitant internalization of circulating Ang II [19, 39], and increased *de novo* Ang II formation [21,34,38]. Under these pathophysiological conditions, CD renin along with AGT-derived from proximal tubule segments, both seem to be major contributors to intrarenal content [25,27,30,33,39–40]. Although plasma renin activity (PRA) is suppressed in the Ang II-infused rat model, these rats elicit increases in urinary levels of renin and prorenin as consequence of augmented renin and prorenin secretion into the luminal fluid by the collecting duct cells. As result, there are increased renal cortical and medullary Ang II levels and augmented urinary Ang II excretion [30],

which further support the concept that the greater availability of renin, prorenin and AGT in the urine provides positive feedback towards intratubular Ang II formation.

Concomitant AT1R blockade with candesartan prevents the increase in RAS further emphasizes the hypothesis that systemic Ang II exerts a positive stimulation on the intrarenal RAS [30]. The molecular mechanism of AT1R activation involves a Ca^{2+}-dependent PKC pathway [40,41], which suggest that the Ca^{2+} paradox is exclusively present in JG cells but not in principal cells. This regulation is independent of mineralocorticoid receptor activation or epithelial sodium channel activity [42]. In mouse cortical collecting duct M-1 cells, Ang II further stimulates cAMP, renin transcription, and the production of renin and prorenin protein contents [42]. These responses are accompanied by increased renin activity in the extracellular culture media and are prevented by PKC inhibition with calphostin C, PKC-α dominant negative, and PKA inhibition in M-1 cells; thus, indicating that Ang II also stimulates CD renin secretion [43]. Furthermore, concomitant forskolin-induced accumulation of cAMP and renin in the cytosol are prevented by PKC inhibition and by Ca^{2+} depletion, which impairs Ang II-mediated CREB phosphorylation and the upregulation of renin. Remarkably, adenylate cyclase 6 siRNA attenuated the Ang II-dependent upregulation of renin [42]. Therefore, in the CD, renin secretion is regulated by both Ca^{+2}/PKC and cAMP/PKA pathways acting in synergism, while in the JG cells these pathways oppose each other (Figure 1).

Vasopressin (AVP)/V2 receptor.

Mice subjected to water deprivation during 48 h exhibit augmented immunostaining for prorenin and renin in renal inner medullary CDs while JG renin is suppressed [43]. In addition, the AVP/V2 receptor agonist, desmopressin (DDAVP), increases renin synthesis and secretion in M-1 CD cells via PKA/CREB, independently of Ang II/AT1 receptor [43]. Rozengurt et al. [44] further showed that PKC activation enhanced the accumulation of cAMP induced by forskolin and that this effect was prevented by the downregulation of PKC [45]. This modulatory effect of Ang II may be mediated by direct activation of adenyl cyclase (AC) [42]. We demonstrated that cAMP accumulation in M-1 cells also depends on intact PKC activity, since PKC inhibition partially suppressed cAMP accumulation in response to Ang II plus DDAVP treatment. The physiological significance of these studies is highlighted by the fact that volume depletion and augmented plasma osmolality can act synergistically through the stimulation of intrarenal RAS, contributing to sodium and water retention. From the studies from Ang II-dependent hypertension and water deprivation we delineate a molecular mechanism mediated by AT1R activation in the collecting duct: Ca^{2+}-dependent PKC activation that phosphorylates AC6 leading to the cAMP/PKA activation, and to CREB phosphorylation, which turns on the renin gene [43].

Prostaglandins.

During the early phase of Ang II-dependent hypertension, tubular PGE_2 is increased [42]. PGE_2 is the most prominent prostaglandin (PG) in rat and mouse kidney. PGE_2 exerts its effects through four types of E-prostanoid (EP) receptors: EP1, EP2, EP3, and EP4 [46]. The collecting duct segment expresses EP1, EP3, and EP4 receptors [46]. EP1 is a Gαq-coupled receptor that activates PKC and increases intracellular Ca^{2+}, whereas the EP3 receptor is

coupled to a Gαi protein that inhibits cAMP formation. The EP4 receptor is coupled to a Gαs protein, which enhances cAMP formation [47,48]. Using M-1 cells, we examined the role of different EP receptors and the most relevant intracellular pathways involved in the synthesis of renin. PGE_2-induced upregulated renin expression and strong perinuclear staining, suggested a possible pathway for secretion and intracellular activity. We also observed the augmentation of cAMP levels and CREB phosphorylation, which are prevented by inhibition and knockdown of the EP1 receptor. The induction of renin expression by PGE_2 was blunted by PKA inhibition and by the knockdown of CREB, supporting the involvement of the cAMP/PKA/CREB pathway in the upregulation of renin in M-1 cells [49]. Interestingly, CREB shRNA resulted in low levels of renin protein, reinforcing the hypothesis that CREB protein is essential for renin expression. We also demonstrated that PKCα is necessary for the cAMP production in CD cells [49] (Table 1, Figure 1).

Renin and natriuretic/vasodilator systems in the collecting duct.

The atrial natriuretic peptide (ANP) is an endogenous cardiac hormone primarily synthesized by atrial myocytes. It exerts multiple physiological effects on the cardiovascular system by stimulating diuresis and by reducing blood pressure [50–52]. Most of the actions of ANP on arterial blood pressure and sodium excretion are mediated via the ANP receptor (NPR type A, NPRA) [53–55]. The effects of the ANP/NPRA on renin synthesis and release seems to be dependent on age and the conditions of the experimental models used. The complete absence of NPRA causes hypertension in mice and leads to altered renin and Ang II levels. Studies with null Npr1 mice demonstrated that, at birth, the absence of NPRA allows higher renin and Ang II levels in comparison to wild-type mice [53]. In the adult null Npr1 mice, circulating renin and Ang II levels are dramatically decreased probably due to progressive elevation in arterial pressure [56]. However, it remains unclear how ANP-NPRA regulates CD renin. JG but not CD renin protein expression is significantly suppressed in Npr1 null mice [57]. To attenuate hypertension in Npr1 null mice, we used chronic administration of bendrofluomethiazide, a diuretic. After treatment for 7 days, JG renin-positive immunoexpression increased while CD renin was decreased, suggesting that JG and CD renin are differentially regulated by the ANP/NPRA/cGMP [57]. Further studies are required to elucidate the signaling pathway involved in ANP/NPRA/cGMP-mediated regulation of CD renin.

The role of the interaction between intrarenal RAS and kallikrein-kinin system (KKS) in the regulation of CD renin is evidenced using bradykinin type 2 receptor (B2R) transgenic mouse models. The conventional B2R knockout and the conditional B2R knockout in the collecting duct, elicit markedly decreased CD renin immunoreactivity, but regardless still maintain positive JG renin immunoexpression [58]. Physiological concentrations of bradykinin (BK) treatment of M-1 cells increase renin mRNA and prorenin and renin protein contents in a dose-dependent manner and increased renin content in the cell culture media via PKC. These effects are independent of PKA because B2R antagonism with Icatibant, prevents these effects [58]. BK-dependent stimulation of renin gene expression in collecting duct cells also involves the stimulation of the NO pathway as the augmentation of cGMP and the inhibition of NO synthase with L-NAME prevent these responses [58]. Since both,

KKS and natriuretic family peptides signaling pathways involve cGMP/PKG, it is important to clarify the influence of this pathway in CD renin regulation.

Interactions between renin and prorenin receptor (PRR) in the collecting duct and the impact on blood pressure and kidney disease.

The prorenin receptor (PRR) is encoded by a unique gene located on the X chromosome at locus p11.4 in humans, the *ATP6ap2* gene (ATPase 6 accessory protein 2) [59]. The gene was named as an ATPase accessory protein because PRR was initially found to be a truncated form co-purifying with V-ATPase (vacuolar H^+-ATPase) [60]. This interaction is not only physical, but also functional in the kidney and in the heart [60]. The mRNA is 2034 bp in length and has a long 3′ untranslated region and no alternative splicing product. The protein is 350 amino acids long and has a single transmembrane domain and a short cytoplasmic domain that has no intrinsic kinase activity [60]. Post-translational processing of the native PRR generates three different proteins. The full-length integral transmembrane protein PRR binds either renin or prorenin and mediates intracellular signaling [61]. The soluble form (sPRR) is intracellularly generated in the trans-Golgi apparatus by the action of various intracellular proteases, including furin, ADAM19 (A (Disintegrin and Metalloproteinase-19), and site-1 protease (SP1) [62–64]. Site-directed mutagenesis of the furin-cleavage site and the use of a furin-specific protease inhibitor abolished the generation of the 28 kDa PRR by cells in culture, whereas inhibitors of metalloproteases, ADAM17, and TNF-α protease had no effect [62]. Although earlier studies showed that the PRR cleavage was depended on furin or ADAM19 [62,63] only recent studies by Nakagawa et al. [64] and Fang et al. [65] demonstrated using different approaches that S1P is the predominant or only source of sPRR production. The soluble form can be found in plasma, where it is able to bind renin [64], and in urine [65], where it activates prorenin or enhances the activity of renin in the renal intratubular compartments [62, 66].

PRR specifically binds renin and prorenin and leads to Ang II formation. It has been shown that after 14 days of Ang II infusion, the since specific deletion of PRR in the collecting duct (CDPRR-KO mice) had lower renin and Ang II amounts in urine compared with wild-type mice. Two mechanisms have been described: (i) the non-proteolytic mechanism occurs when prorenin, the inactive proenzyme form of renin, becomes enzymatically active by a conformational change that does not require cleavage of the (pro)segment [61] and (ii) the proteolytic mechanism occurs when the (pro)segment is cleaved or renin itself binds PRR. In both mechanisms, AGT binds to the renin catalytic site and Ang I is generated, thus promoting a local RAS activation [62]. Moreover, PRR activation triggers intracellular signaling pathways. It is known that the affinity of PRR for prorenin is in the nM range [60, 66–68]. However, physiological prorenin concentrations are in the pM range, suggesting that PRR activation may occur under physio-pathological conditions where there is an augmented intrarenal renin concentration [59,69–71].

The main renin synthesis pathway in the principal cells is the constitutive pathway that secretes the precursor prorenin. In this way, it is tempting to say that a great part of intrarenal Ang II formation depends on the non-proteolytic mechanism. The presence of

PRR in the intercalated cells of the collecting duct, which neighbor the principal cells, further supports the concept of a paracrine interaction between prorenin/PRR within the collecting duct. The pathophysiological consequences of intrarenal Ang II accumulation include the development of tissue injury mediated by AT1 receptor activation [72]. AT1 receptor activation increases the β-catenin pathway which is associated with the stimulation of fibronectin and collagen I [73]. Stimulation of these factors is commonly observed in hypertensive kidney injury. The vicious cycle is established because Ang II/AT1 interaction activates CD renin.

The prorenin/PRR complex also triggers intracellular cascades through Ang II-independent mechanisms [74]. There are, at least, two intracellular pathways described until now, one related with kidney injury and the other related with the maintenance of hypertension in the late phase of chronic Ang II infusion [75]. We demonstrated in male Sprague-Dawley rats that during the early phase of chronic Ang II infusion (between days 0 and 5), when hypertension has not yet been developed, there was augmentation of full-length PRR expression on the plasma membrane and PRR-dependent stimulation of COX-2 expression in the renal inner medulla and excretion of PGE_2 in the urine. However, during the late phase (after day 7), sPRR effects predominate, leading to the production of intratubular Ang II. These changes were associated with increases in local renin and in ERK1/2 activity [49].

Growing evidence showing that prorenin binding to PRR increases renin activity and favors the activation of intracellular signaling pathways related to cell damage, have stimulated active investigations to evaluate the effects of interactions between renin and PRR on local RAS activation as well as investigations to evaluate the development of kidney injury in whole animal models. Currently, most of the studies have used transgenic animal models with tissue specific PRR deletion since the whole knockout animals are lethal. Additionally, peptides having a sequence identical to the handle region of the prorenin (pro)segment, such as handle region peptide (HRP) [76,77] and PRO20 [78] have been used to block the prorenin-PRR interaction. However, the use of the PRR blockers has shown conflicting results. The HRP is a peptide with a 10 amino acid sequence which inhibits the binding of prorenin to PRR decreasing intrarenal Ang I and Ang II formation in diabetic rats [79–81].

Kidney PRR seems to play an important role in the regulation of blood pressure and in the development of tubular fibrosis. Existing conflicting results using current PRR blockers, such as HRP and PRO20, could be due to technical approaches, including intrarenal medullary infusion of the peptides and delivery into plasma, which may impair its effective concentration and ability to reach the apical side of collecting duct cells to block the actions of prorenin and renin. Further studies are required to advance our knowledge of the mechanisms of actions and of the pharmacokinetic properties of this novel antagonist.

Blood pressure.

Blood pressure, sodium balance, and water homeostasis could be regulated by PRR in the collecting duct. Evidence from rat and transgenic mouse models demonstrates that renin/prorenin and PRR in the collecting ducts contribute to the production of intrarenal and intratubular Ang II levels [28, 82–84]. Mice with specific PRR deficiency in the collecting duct elicit increased systolic and diastolic blood pressures compared to wild-type mice

after 14 days of Ang II infusion (400 ng·kg-1·min-1). In this model, the attenuated blood pressure response is associated with decreased cleaved αENaC and γENaC expression and with diminished Ang II and renin contents in urine [28]. In these mice, decreased ENaC activity is due to fewer active ENaC channels and lower open probability [28,82,84,85]. PRR deficiency in the collecting duct also leads to inability to concentrate urine [46,82]. The presence of PRR and renin in the collecting ducts points out the high relevance of these RAS components in enhancing the *de novo* production of intrarenal Ang II and in the pathogenesis of hypertension. In various paradigms of Ang II-dependent hypertension such as chronic Ang II-infused rat and mouse, 2K1C Goldblatt rats and mice, and mRen2 transgenic rats; intrarenal Ang II concentration increases substantially more than systemic levels, despite decreased synthesis of JG renin [21–23,26,34,86]. These models also elicit upregulation of PRR and renin in the distal nephron segments [26,34,87]. Augmentation of intrarenal Ang II activity may also result from AT1R-mediated synthesis and secretion of AGT in proximal tubule cells [25,38,40]. Thus, urinary excretion of AGT is considered to some extent, an index of intrarenal RAS activation [20]. Further studies are required to elucidate how the interactions between PRR and renin modulate the actions of the RAS and to provide a better understanding of their role as a paracrine pathway to regulate cell physiology in the distal nephron segments [88], as well as to develop novel therapies to prevent, diagnose, and treat hypertension.

Kidney disease.

The pathophysiological role of the PRR in the development of renal injury has been suggested by the detection of glomerulosclerosis, proteinuria, and elevated blood pressure in rats with ubiquitous transgenic overexpression of the human PRR [85]. It is suggested that circulating prorenin is taken up by the kidney where it can contribute to the intrarenal Ang II synthesis accentuating tissue damage. Expression of the PRR (both mRNA and protein) is increased in the renal tubules in rats with congestive heart failure due to coronary ligation [86]. Continuous subcutaneous administration of the HR decoy peptide (PRO20) attenuated the development and progression of proteinuria and glomerulosclerosis [78]. This is a clear demonstration that the nonproteolytic activation of prorenin in glomeruli is involved in intrarenal RAS activation, leading to renal damage in hypertensive animals. A prospective study examining the role for the PRR in the pathogenesis of hypertension in humans showed a polymorphism in the PRR gene that was associated with a high blood pressure in men [86].

PRR intracellular signaling mechanism associated with kidney tubular damage.

The activation of PRR promotes the induction of fibrotic-related processes [89–91]. Induction of TGF-β, CTGF, PAI-I, and ROS occurs through PRR-dependent activation of MAPK and NOX-4 and COX-2-derived PGE_2 production and the activation of EP4 and Smad pathway in cultured collecting duct cells [89]. The processes involving renal fibrosis *in vivo* are more complex than anticipated and involve the activation of epithelial-mesenchymal transition and extracellular matrix deposition, production of myofibroblasts, and the secretion of a wide range of cytokines [91]. Reyes-Martinez et. al. [90], performed

chronic infusions of recombinant prorenin in mice with or without COX-2 inhibition. The results showed that the induction of collagen I, fibronectin, CTGF, TGF-β, and PAI-I in renal inner medullary collecting ducts was prevented by COX-2 inhibition. The same study further demonstrated that interleukin-1ß, a proinflammatory cytokine, was induced by prorenin infusion and prevented by COX-2 inhibition [90]. Using transgenic rats expressing prorenin that is not converted to renin (Cyp1a1 prorenin transgenic), Zhou et al [91], demonstrated that prorenin concentration increases and that blood pressure is augmented, whereas renal prorenin/renin protein expressions are unchanged. The results of this study suggest that prorenin, without being converted into renin, causes hypertension, renal and cardiac fibrosis via the induction of inflammation, oxidative stress, and upregulation of ERK 1/2, β-catenin, and Akt-mediated signals, thus substantiating the impression that PRR acts by inducing profibrotic factors independently of Ang II.

In the kidney, one of the main targets of prorenin/PRR is the collecting duct. It is likely that this complex activates intracellular signaling that mediates Na^+ reabsorption. In rat cultured collecting duct cells, sPRR stimulates Na^+ reabsorption by acute and chronic activations of ENaC and α-ENaC via distinct intracellular signaling pathways. The acute ENaC activation involves Nox4-derived ROS while the chronic α-ENaC stimulation involves a β-catenin-dependent transcriptional mechanism [92]. Since PRR is mainly expressed by the intercalated cells and ENaC is expressed in the principal cells, open questions remain. How does PRR activation augment ENaC activity and expression? A possible explanation could be obtained from studies showing the effects of soluble PRR (sPRR) on collecting duct cells. sPRR is increased by aldosterone and decreased by PRR decoy inhibitor treatments [92]. Decreased aldosterone-induced transepithelial Na^+ transport occurs in the presence of inhibition of PRR decoy and site-1 protease (S1P) [92]. Furthermore, the fact that these responses are restored by treatment with recombinant histidine-tagged sPRR suggest that sPRR may contribute to increased Na^+-retaining action of aldosterone in the distal nephron.

The PRR is involved on the development of diabetic nephropathy. In diabetic mice, renal PRR expression is upregulated and associated with the development of albuminuria, mesangial expansion, and glomerular hypertrophy [93]. Additionally, downregulation of PRR expression reduces albuminuria and glomerular hypertrophy in the same mouse diabetic model [94]. The proximal segments of the nephron are most affected by diabetes. This segment is responsible for tubular active reabsorption of glycose and contains a very high number of mitochondria. Streptozotocin-induced diabetic mice elicit reduction in the expression of PGC-1α, nuclear respiratory factor (NRF-1), mitochondrial transcriptional factor A (mtTFA), mitochondrial DNA copy number, and ATP production. Akhtar et al. [93] showed in diabetic mice that decreased mitochondrial biogenesis and renal function are reversed by renal PRR downregulation. PRR suppresses mitochondrial biogenesis and function via AMPK/SIRT-1/PGC-1α pathway in the kidney diabetic mice [93]. For an overview of the intracellular mechanism of PRR along the nephron segments and its multiple functions in the pathogenesis of kidney damage please see [95].

Conclusions and perspectives

The discovery of renin production and secretion by the principal cells of the collecting duct along with its interactions with the local PRR, have contributed to a better understanding of the regulation of the RAS and blood pressure by the distal nephron segments [33]. The hormonal mechanisms involved in the regulation of renin in the collecting duct are complex and result in intrarenal/intratubular Ang II *de novo* formation and interactions with local PRR. During Ang II-dependent hypertension and diabetes, there is increased intrarenal/intratubular Ang II content despite plasma renin activity suppression. During these pathological conditions, there is also upregulation of renin and PRR in the distal nephron segments along with all RAS components required to ensure intrarenal/intratubular Ang II formation. Equally important, the local activation of PRR by its agonists, prorenin and renin, contributes to the stimulation of signaling pathways leading to the expression of profibrotic factors, independent of Ang II generation. Pharmacological targeting of PRR might help to prevent tubulointerstitial fibrosis during hypertension and diabetic disease. As presented in this review, the interactions of renin, prorenin, and PRR with paracrine hormones targeting the collecting duct allow tubular compartmentalization of the RAS which is responsible for complex mechanisms that increase intrarenal/intratubular Ang II content, sodium reabsorption, and blood pressure. Novel therapeutic strategies of RAS blockade targeting renin and PRR in the distal nephron segments would be beneficial to maximize blood pressure control and to minimize the development and progression of renal fibrosis.

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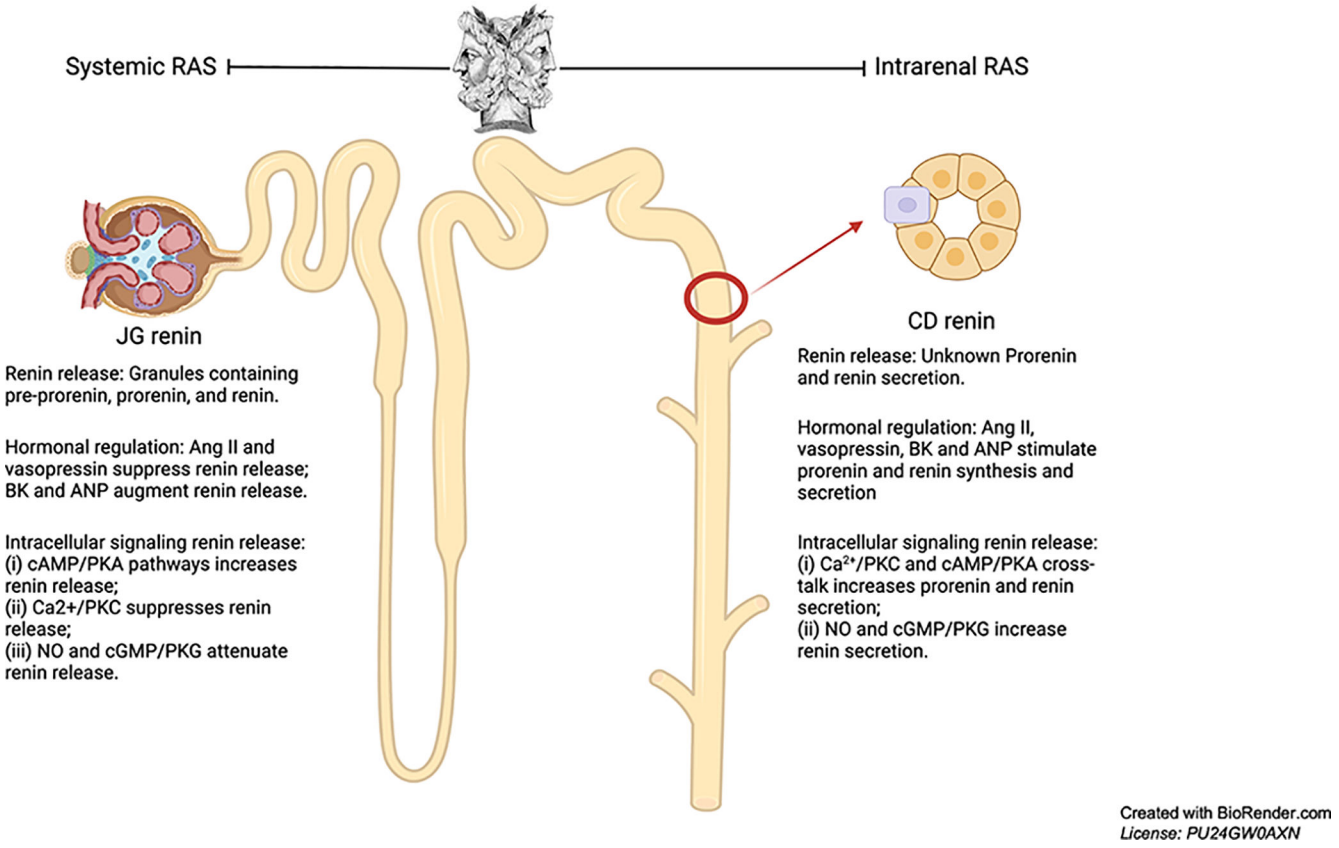

Figure 1.

The "Janus effect" mechanism. **(A)** Synthesis and release of JG renin: Transcription of *Ren 1c* gene gives rise to a pre-prorenin. Then, prorenin is formed by the removal of the (pro)segment and is sorted into two different pathways: a constitutive pathway for the secretion of the precursor prorenin and a regulated pathway for the secretion of mature renin. An example of Western blot detection for renin in collecting duct (CD) cells is provided. This sorting is determined by the glycosylation. Only glycosylated prorenin (46 kDa) can be directed to the vesicular network in the juxtaglomerular cells. The pro segment (a 43 aa segment) is proteolytically removed forming the active renin with approximately a 38 kDa molecular mass. Renin remains stored in vesicles awaiting controlled release. Non-glycosylated prorenin (41 kDa) is directed to a preeminent electron dense vesicular network that directly release prorenin that was initially believed to have no biological activity. Main regulatory regions in the *Ren 1c* gene that mediates activation or suppression of the transcription are mediated by CREB transcription factor, which is activated by cAMP/protein kinase A (PKA) pathway. Many receptors that induced PKA regulates positively renin gene expression such as β1 adrenergic and E-prostanoid 4 (EP4) receptors are mediated by CREB phosphorylation. The Ca^{2+}/protein kinase C (PKC) pathway mediated by the Ang II AT1R suppresses renin exocytosis in a phenomenon called the Ca^{2+} paradox. The crosstalk between these pathways exerts a fine tune regulation on renin release by a Ca^{2+}-dependent mechanism to lower intracellular cAMP levels. As a secondary modulation of renin in JG cells, cGMP generated by particulate guanylyl cyclase, activates protein kinase G type II (PKG-II) that inhibits renin secretion. **(B)** Synthesis and secretion of

CD renin: Molecular mechanisms involved in CD renin regulation. Ang II/AT1R increases intracellular Ca^{2+} mobilization and PKC activity (red pathway). The AVP/V2 receptor agonist, DDAVP, increases renin synthesis and secretion via PKA/CREB, independently of the Ang II/AT1R (green pathway), indicating that in the CD, both Ca^{2+}/PKC and PKA/CREB mediates the stimulation of CD renin. We proposed that these 2 pathways act synergistically to increase CD renin. BK- and ANP-dependent (yellow pathways) stimulation of renin gene expression in collecting duct cells involves the stimulation of nitric oxide (NO). BK/B2R also activates PKC-dependent renin release (yellow pathway). It remains unknown how NO and PKG act to increase CD renin (orange arrows). For more comprehensive diagrams of complete mechanisms of JG renin vs CD renin and their functional roles in the kidney, please consult to previous publications by our group [33, 96].

Table 1.

Differences in renin synthesis and release/secretion between juxtaglomerular cells and principal cells of the collecting duct.

	JG cells	Principal cells
INTRACELLULAR STORAGE; RENIN RELEASE/SECRETION	Granules containing pre-prorenin, prorenin, and renin. Renin release (7)	Unknown Prorenin and renin secretion (70)
HORMONES INVOLVED IN THE REGULATION / EFFECTS	Ang II and vasopressin suppress renin release (1) BK and ANP augment renin release (2,57)	Ang II, vasopressin, BK and ANP stimulate prorenin and renin synthesis and secretion (33,37,59,57,58)
SIGNALING PATHWAY	(i) cAMP/PKA pathways increases renin release (4,6) (ii) Ca2+/PKC suppresses renin release (4,6,16) (iii) NO and cGMP/PKG attenuate renin release (4,6)	(i) Ca2+/PKC and cAMP/PKA cross-talk increases prorenin and renin secretion (41,42,43) (ii) NO and cGMP/PKG increase renin secretion (58)

Abbreviations: JG, juxtaglomerular; Ang II, angiotensin II; BK, bradykinin; ANP, atrial natriuretic peptide; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PKC, protein kinase C, NO, nitric oxide; cGMP, cyclic guanosine monophosphate; PKG; protein kinase G.