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Crosstalk between (Pro)renin receptor and COX-2 in the renal medulla during angiotensin II-induced hypertension

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Abstract

Angiotensin II (AngII) is an octapeptide hormone that plays a central role in regulation of sodium balance, plasma volume, and blood pressure. Its role in the pathogenesis of hypertension is highlighted by the wide use of inhibitors of the renin-angiotensin system (RAS) as the first-line antihypertensive therapy. However, despite intensive investigation, the mechanism of AngII-induced hypertension is still incompletely understood. Although diverse pathways are likely involved, increasing evidence suggests that the activation of intrarenal RAS may represent a dominant mechanism of AngII-induced hypertension. (Pro)renin receptor (PRR), a potential regulator of intrarenal RAS, is expressed in the intercalated cells of the collecting duct (CD) and induced by AngII, in parallel with increased renin in the principal cells of the CD. Activation of PRR elevated PGE_2 release and COX-2 expression in renal inner medullary cells whereas COX-2-derived PGE_2 *via* the EP_4 receptor mediates the upregulation of PRR during AngII infusion, thus forming a vicious cycle. The mutually stimulatory relationship between PRR and COX-2 in the distal nephron may play an important role in mediating AngII-induced hypertension.

Introduction

The RAS has been known for more than a century as one of most important hormonal systems that regulate blood pressure, cardiovascular function, renal hemodynamics and tubular sodium reabsorption [1]. AngII is the major effector hormone in this system and produces vasoconstrictive, pro-inflammatory, anti-natriuretic, and anti-diuretic effects. Over the years, AngII has been shown to play important roles in the pathogenesis of hypertension, heart failure, cardiac remodeling, chronic kidney disease, diabetes, *etc*. [2]. Inhibition of AngII production with angiontensin converting enzyme inhibitor (ACEi) or AngII action with AT1 blockers is used as the first-line antihypertensive therapy. Despite the intensive investigation, the mechanism of AngII-induced hypertension is still incompletely understood.

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Conflict of interest

Nothing declared.

(Pro)renin receptor (PRR) is a new member of the RAS and it binds renin and its inactive precursor, prorenin, with almost equal affinity; this interaction elevates the catalytic activity [3]. Due to its ubiquous expression pattern, PRR is considered to play an important role in regulation of tissue renin activity thereby controlling the activity of local RAS [3]. In recent years, there is increasing recognition of local RAS as an important contributor of hypertension, cardiovascular disease, and kidney diseases [4,5]. Within the kidney, PRR expression is found in glomerular mesangial cells [3], the subendothelium of renal arteries [3], and the distal nephron [6]. Chronic infusion of AngII in rats increased renal PRR transcript levels and augmented the PRR activity in renal medullary tissues, which may contribute to increased renin activity in the CD during AngII hypertension [7]. Increased expression of CD PRR is also observed in 2K1C Goldblatt hypertensive model [8]. The activation of renal medullary PRR may serve as an important mechanism triggering the local renin response that may participate in regulation of blood pressure and fluid metabolism during AngII hypertension [7].

The renal medulla is a major site of production and action of prostaglandins (PGs).

Cyclooxygenase-2 (COX-2) is abundantly expression in the renal medulla where COX-2-derived products exert complex roles in regulation of fluid balance and blood pressure. Evidence is emerging to suggest that PRR and COX-2 stimulate the expression of each other in the renal medullary cells [9•,10••,11•]. This review will focus on recent findings regarding the mutually stimulatory relationship between the two mediators in the renal medulla and discuss its implication in the control of intrarenal RAS and blood pressure during AngII-induced hypertension.

The role of intrarenal RAS in AngII-induced hypertension

In recent years, a new paradigm has emerged that the activation of local RAS in the kidney (termed intrarenal RAS) serves as an important mechanism of AngII-induced hypertension [12•]. The existence of intrarenal RAS was first described over 20 years ago, where the level of renal interstitial and tubular fluid AngII was much higher than in plasma [13,14]. The existence of intrarenal RAS is further highlighted by the discovery of renin expression in the connecting tubules and cortical and medullary collecting ducts (CDs) [15,16] and angiotensinogen expression in the proximal tubule [17], the two key elements of paracrine tubular RAS. The regulation of intrarenal RAS by AngII is distinct from that of systemic RAS. AngII infusion elevates *de novo* AngII generation in the kidney due to augmentation of angiontensinogen [18,19] and renin in the collecting duct (CD) [20,21], indicating a positive feedback regulation of intrarenal RAS by AngII. This is completely opposite to the well-established view of the negative feedback regulation of juxtaglomerular renin by AngII. Subsequent functional studies using pharmacological and genetic approaches examine the role of intrarenal RAS during AngII-induced hypertension. Experiments in rats infused with Val^5-Ang II, an isoform of AngII that can be separated from endogenous AngII (Ile^5-Ang II) by high-performance liquid chromatography, demonstrated that the chronic Val^5-Ang II (exogenous AngII) infusion induces renal Ile^5-Ang II (endogenous Ang II) synthesis [22]. In another study, when endogenous AngII production was reduced by ACE inhibition, AngII-infused mice became normotensive [23,24]. The genetic absence of kidney

ACE substantially blunts the hypertension induced by AngII infusion [25]. In experiments involving kidney cross-transplantation between global AT1 KO mice and wild-type controls, AngII is shown to cause hypertension through stimulation of AT_1 receptors in the kidney [26]. Lastly, overexpression of renin in the CD causes spontaneous hypertension [27] and CD-specific deletion of renin attenuates AngII-induced hypertension [28••]. Together, these results represent compelling evidence for an essential role of intrarenal RAS in the pathogenesis of hypertension at least during AngII infusion. This mechanism may have a broad implication since activation of intrarenal RAS has been linked to salt-sensitive hypertension [29].

Role of PRR in regulation of COX-2 expression in the CD

To study the potential interaction between PRR and COX-2, Kaneshiro *et al.* assessed the expression and function of renal COX-2 in rats with transgenic expression of human PRR receptor [30]. In this study, the transgene expression was driven by a cytomegalovirus immediate early gene enhancer and rabbit β-actin gene terminator sequences. The transgenic rats with global overexpression of human PRR exhibited increased COX-2 expression in the macula densa and decreased renal cortical blood flow following COX-2 inhibition with NS-398 whereas this treatment was ineffective in wild-type rats [30]. In the transgenic rats, phospho-ERK was elevated in the cortex but tissue AngII levels were unaffected, suggesting that PRR may stimulate COX-2 expression *via* ERK-dependent and AngII-independent mechanism [30]. It is unclear why the global increase in PRR expression leads to the selective upregulation of COX-2 expression in the macula densa. This study focuses on macula densa as a site of COX-2 regulation by PRR. At this point, the effects of PRR activation on COX-2 expression in the renal medulla remain unclear.

Within the kidney, PRR is predominantly expressed in the intercalated cells of the CD. Renal medulla is a rich source of PG synthesis, where COX-2 is abundantly expressed at baseline and induced by various physiological stimuli including high salt loading [31] and water deprivation [32,33]. To exmaine the possible interaction between PRR and COX-2 in the renal medulla, Gonzalez *et al*. tested the effect of PRR activation on COX-2 expression in primary rat inner medullary (IM) cells [11•]. In this study, PRR and COX-2 were colocalized in intercalated and interstitial cells whereas principal cells did not express PRR or COX-2 [11]. Exposure of rat IM cells to rat recombinant prorenin (100 nmol/L) increased ERK 1/2 phosphorylation and COX-2 expression. Prorenin-induced COX-2 expression was blunted by siRNA-mediated knockdown of PRR, ERK1/2 inhibition but not AT1R blockade. These results suggest that PRR activation increases COX-2 expression in the renal medullary cells *via* ERK-dependent and AngII-independent pathway. Prorenin binding to PRR is known to induce two different signaling pathways, the activation of ERK and the non-proteolytic activation of prorenin. It is evident that the activation of ERK but not the enzymatic activity of prorenin mediates the increased COX-2 expression.

Renal medullary COX-2 expression has been detected in various cell types including interstitial cells [34,35], vasa recta and medullary capillaries [36], and epithelial cells [21]. Gonzalez *et al*. for the first time describe that COX-2 is colocalized with PRR to the intercalted cells of the CD in the rat [11•]. In recent years, increasing evidence suggests an

important role of intercalacted cells in the overal control of fluid metabsoslsim and blood pressure besides the regulation of urine adidification [37–41]. In response to increased urine flow, β-intercalated cells (β-ICs) produces ATP that triggers the erelease of PGE_2 that acts in a parachrine fashion to inhibit ENaC in the principalcells of the CD. The PGE_2-mediated communciation between ICs and pinciple cells of the CD contributes to the development of the hydroelectrolytic imbalance associated with distal renal tubular acidosis (dRTA) [42••]. The enzymatic sources of PGE_2 and its possible interaction with PRR in the ICs remain to be determined in future studies.

Role of COX-2/EP_4 pathway in regulation of renal medullary PRR expression during AngII-induced hypertension

In the renal cortex, COX-2 is expressed in the macula densa and mediates the expression and renin release in response to salt depletion or ACE inhibition [31,43–46]. Evidence is emerging that COX-2 exerts influence on intrarenal RAS by regulating PRR expression. This possibility is first suggested by the observation that transgenic overexpression of COX-2 in podocytes leads to albuminuria and glomerular injury accompanied with increased PRR expression [47]. Treatment with COX-2 inhibitor in the transgenic mice abrogates PRR upregulation and improves renal pathologies [47].

We recently examined the role of COX-2-derived metabolites in regulation of renal medullary PRR expression during AngII-induced hypertension [9•] and further determined the EP subtypes involved [10••]. In cultured primary rat IMCD cells, AngII treatment induced parallel increases in PRR expression, renin activity, and COX-2 expression [9•]. The induction of COX-2 expression at 4 h proceed that of the full-length PRR expression at 12 h, suggesting a causal role of COX-2-derived products in regulation of PRR [9•]. In this study, renin activity was assayed at a single time point of 12 h and was expected to be determined by the PRR level [9•]. Inhibition of COX-2 with NS-398 blocked AngII-induced PRR expression and renin activity. This phenomenon in cell culture has been recapitulated by animal experiments where COX-2 inhibition nearly completely abolished the upregulation of renal medullary PRR expression after 14-day AngII infusion and partially attenuated the hypertension in Sprague-Dawley rats [9•]. On the contrary to the suppressed plasma renin levels, urinary renin levels were elevated after AngII infusion and reduced by COX-2 inhibitor [9•]. These results suggest that COX-2 plays a key role in determining the activation of intrarenal RAS during AngII-induced hypertension. More recently, Gonzalez *et al*. report that renal medullary PRR and COX-2 expression in Sprague-Dawley rats is increased at day 3 but not day 14 of AngII infusion [48•]. It remains unclear why the time courses of PRR and COX-2 upregulation are different between Gonzalez's study and ours. Despite the discrepancy, both studies observe a similar antihypertensive effect of COX-2 inhibition at day 14 of AngII infusion.

COX-2 can exert a complex role in regulation of blood pressure depending on the type of hypertension. A series of previous studies support the view that renal medullary COX-2 functions a natriuretic and antihypertensive factor during high salt loading. In this regard, renal medullary COX-2 expression is increased in response to chronic salt loading [31] and intramedullary delivery of NS-398 induces salt-sensitive hypertension in rats [34,49].

However, increasing numbers of studies using COX-2 deficiency mice or COX-2 inhibitors demonstrate prohypertensive action of COX-2 in rodent models of AngII-induced hypertension [9•,48•,50–52] although COX-2-derived products may exhibit vasodilatory and antihypertensive actions during acute AngII infusion [53]. It remains uncertain how renal medullary COX-2 exerts distinct actions in blood pressure regulation during AngII infusion and chronic salt loading. It is possible that renal medullary COX-2 exerts prohypertensive action during AngII infusion through the activation of intrarenal RAS [9•,48•] but exhibit antihypertensive action during chronic salt loading *via* PGE_2-meidated natriuresis [54–56].

COX-2-derived prostanoids include PGE_2, $PGF_{2\alpha}$, PGD_2, PGI_2, and thromboxane A_2 with PGE_2 being the dominant one in the kidney [57,58]. Two lines of evidence point to PGE_2 as a major regulator of PRR expression in ICMD cells [9•]. First, exposure of the cells to exogenous PGE_2 increased PRR expression. Second, COX-2 inhibition attenuated AngII-induced PRR expression, which was completely reversed by addition of exogenous PGE_2 [9•]. The biologic action of PGE_2 is mediated by G-protein-coupled E-prostanoid receptors designated EP_1, EP_2, EP_3 and EP_4 [59]. These four subtypes of EP receptor couple to distinct signaling pathways. Among the four EP subtypes, the EP_4 receptor plays a dominant role in regulation of renin release from the juxtaglomerular apparatus [60,61]. Using pharmacological inhibitors and activators of the EP_4 receptor, we demonstrated an essential role of this EP subtype in mediating AngII-induced PRR expression both *in vitro* and *in vivo* [10••]. The *in vivo* EP_4 antagonism also attenuated AngII-induced hypertension and urinary renin level [10••]. The detailed signaling pathway downstream of the EP_4 receptor in the CD is not known. This EP subtype typically signals through the Gs protein, which elevates intracellular cAMP. It seems reasonable to speculate that cAMP pathway may be involved in EP_4-depenent stimulation of PRR expression during AngII hypertension. In addition, *in vitro* evidence suggests a potential role of the EP_1 receptor in mediating AngII- induced PRR expression in cultured IMCD cells [10••]. This finding needs to be validated by *in vivo* studies.

Summary

Transgenic overexpression of PRR increases COX-2 expression in the kidney. In cultured renal medullary cells, overexpression of PRR directly stimulates COX-2 expression *via* ERK1/2, independently of the activity of RAS. On the other hand, the COX-2/EP_4 pathway mediates the upregulation of PRR in the renal medulla during AngII-induced hypertension. The mutually stimulatory relationship between renal medullary PRR and PGs suggests existence of a vicious cycle that may play an important role in amplifying the local renin response to increased circulating AngII level (Figure 1). A thorough understanding of this vicious cycle will provide insight into the molecular mechanism of AngII-induced hypertension and contribute to the development of pharmacological approaches and discovery of new drugs for hypertension as well as kidney diseases.

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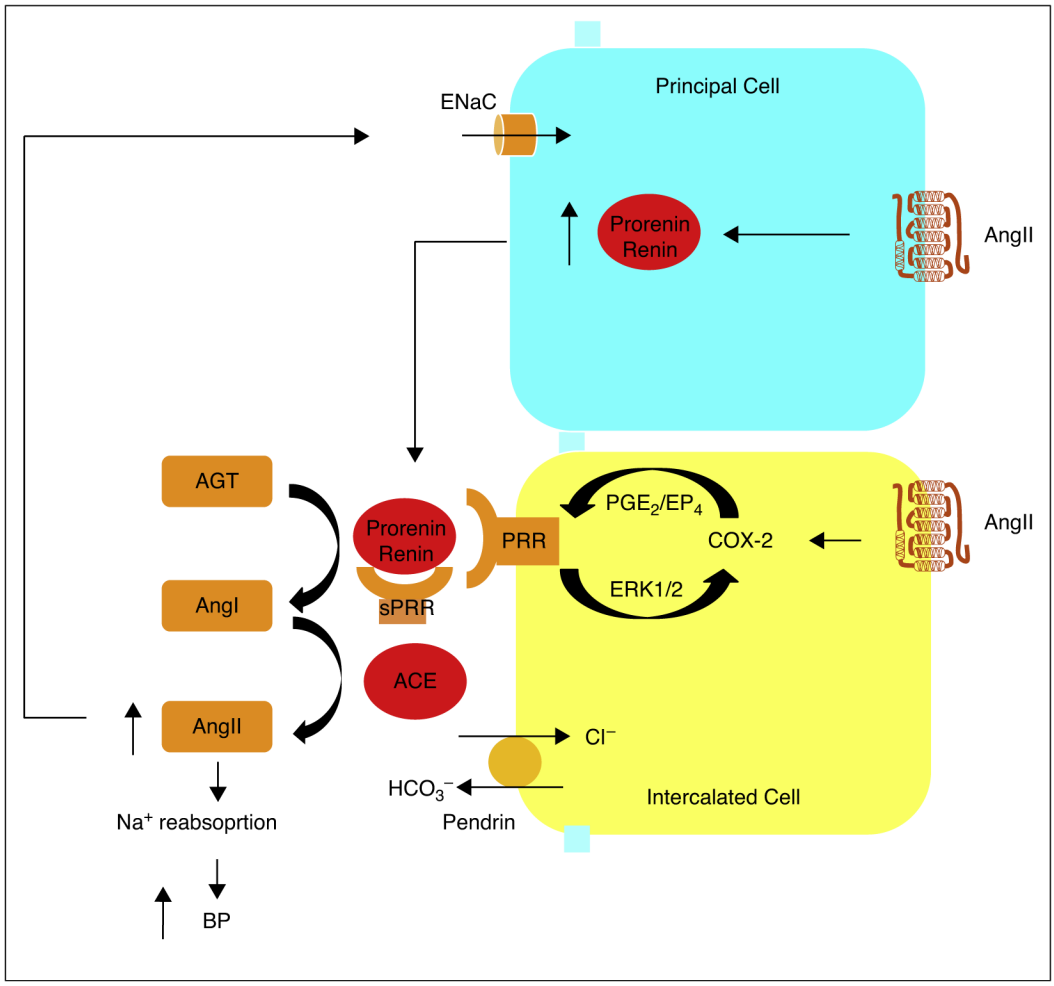

Figure 1.

Illustration of the interaction of PRR and PGs in the renal medulla during AngII-induced hypertension. Renin is expressed in the principal cells of the CD and its expression is induced by AngII. Prorenin and renin, released from the principalcells, bind PRR on the surface of intercalated cells or soluble PRR (sPRR) in the lumen to increase their catalytic activity. In the intercalated cells, AngII induces the expression of PRR that increases COX-2 expression *via* ERK1/2 and in turn COX-2-derived PGE_2 *via* the EP_4 receptor stimulates PRR expression, thus forming a vicious cycle in order to achieve the sustained activation of intrarenal RAS. This leads to heightened luminal AngII level that increases Na^+ reabsorption possibly *via* increased ENaC activity, eventually leading to elevated blood pressure.