Physiology and Pathophysiology of the Intrarenal Renin-Angiotensin System: An Update

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ABSTRACT
The renin-angiotensin system (RAS) has a pivotal role in the maintenance of extracellular volume homeostasis and blood pressure through complex mechanisms. Apart from the well known systemic RAS, occurrence of a local RAS has been documented in multiple tissues, including the kidney. A large body of recent evidence from pharmacologic and genetic studies, particularly those using various transgenic approaches to manipulate intrarenal levels of RAS components, has established the important role of intrarenal RAS in hypertension. Recent studies have also begun to unravel the molecular mechanisms that govern intrarenal RAS activity. This local system is under the control of complex regulatory networks consisting of positive regulators of (pro)renin receptor, Wnt/β-catenin signaling, and PGE2/PGE2 receptor EP4 subtype, and negative regulators of Klotho, vitamin D receptor, and liver X receptors. This review highlights recent advances in defining the regulation and function of intrarenal RAS as a unique entity separate from systemic angiotensin II generation.

The renin-angiotensin system (RAS) has been known for over a century, since the first discovery of renin by Tigerstedt and Bergman in 1898.1 The systemic RAS requires interaction of multiple organs involving liver production of angiotensinogen (AGT) which is converted to angiotensin I (Ang I) by renin, a protease produced by juxtaglomerular apparatus (JGA), followed by a second cleavage to angiotensin II (Ang II) by angiotensin converting enzyme (ACE) located on the surface of lung endothelium. Apart from the well known systemic RAS, production of multiple RAS components has been found in a variety of tissues including the kidney.2,3 Inappropriate activation of intrarenal RAS has been recognized as an important mechanism for hypertension and renal disease. To date, the anti-RAS regimen represents the cornerstone therapy for both diseases. No matter hypertension or renal disease, there is no clear evidence for increased plasma renin activity (PRA), renin, or Ang II. Furthermore, the RAS interventions are capable of lowering blood pressure (BP) in the presence of suppressed or elevated PRA4 despite a wide range of data variability.5,6 These findings have led to the hypothesis that these inhibitors may exert a large part of their effect at a local level.

The general knowledge of intrarenal RAS has already been covered by a number of comprehensive reviews.7–9 The major objective of this article is to review recent advances in defining the intrarenal RAS, including its function, and positive and negative regulators in the settings of hypertension and renal injury.

EXISTENCE OF INTRARENAL RAS
As opposed to the systemic RAS, the circulation-borne endocrine system, the intrarenal RAS refers to a local autocrine/paracrine system in the kidney which involves both angiotensin-dependent and independent actions. A hallmark of intrarenal RAS is the high level of intratubular Ang II that exceeds the plasma concentration.10,11 Strong evidence suggests that intrarenal RAS contains all elements necessary to generate Ang II. AGT is synthesized in the proximal tubule (PT) and can be secreted to the tubular lumen12,13 or act within the PT.7 During systemic Ang II infusion, AGT expression in the renal cortex and urinary AGT excretion are elevated in an Ang II type 1 receptor–dependent (AT1R-dependent) manner.14,15 Consistent with this finding, overexpression of an intracellular cyan fluorescent Ang II in the PT via AT1R induces renal cortical mRNA and protein expression of AGT, without affecting circulating levels of AGT or renin activity.16 Immunoreactive renin is found in principal cells of the connecting segment and collecting duct (CD) of both murine and human kidneys.
secreted to tubular lumen in response to salt depletion.\textsuperscript{17} Subsequently, CD renin is shown to be upregulated under pathologic conditions such as Ang II–induced hypertension\textsuperscript{18} and diabetes.\textsuperscript{19} Both ACE and AT1R are found abundantly throughout the apical nephron surface. Direct evidence for local synthesis of Ang II is demonstrated by using radiolabeled Ang II.\textsuperscript{20} Although circulating 125\textsuperscript{I}-Ang II is accumulated in the renal tissue sites, the endogenous renal Ang II levels are up to 100 times higher than the plasma levels of endogenous Ang II.\textsuperscript{20} This result was further validated by the substitution of isoleucine (Ile[5] Ang II) at position five with valine (Val[5]-Ang II).\textsuperscript{21}

The complexity of intrarenal RAS stems from the evidence supporting the circulating source of intrarenal RAS components. Nearly all major components of the RAS including AGT, prorenin, renin, Ang I, and Ang II will be filtered by the glomerulus and taken up by the PT. The uptake of circulating Ang II by the PT is mediated by AT1R\textsuperscript{22–27} as well as the multiligand endocytic receptor megalin.\textsuperscript{28,29} Besides Ang II, other RAS components including AGT, prorenin, Ang I, and Ang II are also taken up by the PT through the same megalin-dependent mechanism.\textsuperscript{26,29} The seminal work by Matsusaka et al. demonstrates hepatic origin of intrarenal AGT\textsuperscript{30}: renal AGT protein and Ang II levels are unaffected by renal-specific AGT deletion using the KAP-Cre but are significantly reduced by liver-specific AGT deletion. A caveat is that urinary AGT is reduced (by approximately 50\%) in renal-specific AGT knockout (KO) mice not in liver-specific AGT KO mice. Furthermore, the valuable models are only analyzed under basal condition and after podocyte injury.\textsuperscript{5,30} These results can’t rule out the possible role of intrarenal AGT under other physiologic or pathologic conditions. Recently, another strain of renal-specific AGT KO mice generated by using an inducible Pax8-\textsuperscript{rtTA} system shows a remarkable reduction of urinary AGT associated with hypotension.\textsuperscript{31} However, this study is limited in that the Pax8-\textsuperscript{rtTA} system also causes partial deletion of AGT in the liver as reflected by reduced circulating AGT level. Therefore, more vigorous studies are needed to determine the contribution of intrarenal AGT versus liver AGT to the overall control of BP as well as kidney injury.

**ROLE OF INTRARENAL RAS IN HYPERTENSION**

Several lines of pharmacologic and genetic evidence demonstrate an essential role of intrarenal RAS in the pathogenesis of experimental hypertension. When ACE inhibitor lisinopril was administered systemically, Ang II–infused mice became normotensive with attenuation of the up-regulation of components of intrarenal RAS, particularly CD renin, ACE, and AT1R.\textsuperscript{32,33} Despite the limitations of the systemic approach, this study provides the first functional evidence that the pressor response of the end product Ang II relies on the upstream enzyme ACE which drives *in situ* Ang II synthesis. Subsequent studies using genetic approaches to manipulate a key component of the RAS at the level of the whole nephron or a specific nephron segment greatly facilitate understanding of the role of intrarenal RAS in hypertension. Bernstein’s group generated mice lacking renal ACE but having sufficient ACE in other tissues (termed ACE 3/3 and ACE 10/10) that were able to maintain normal serum levels of Ang II and normal kidney structure and BP under basal condition.\textsuperscript{34} The genetic ablation of renal ACE remarkably attenuated the pressor response to Ang II infusion at 400 ng/kg per minute, accompanied with reduced renal Ang II content and suppressed expression of renal Na\textsuperscript{+} transporters.\textsuperscript{35} Additionally, ACE 10/10 mice were also protected against L-NAME–induced hypertension.\textsuperscript{36} Together, these results suggest that ACE-dependent activation of intrarenal RAS may represent a common pathway leading to pressor responses to different hypertensive stimuli. Of note, these models were generated by using a promoter-swamping strategy so that the control of ACE expression is switched from the endogenous ACE promoter to liver-specific albumin promoter (3/3) or macrophage-specific *c-fms* promoter (10/10). Therefore, it remains uncertain whether the BP phenotype is directly related to the lack of ACE expression in the kidney versus the blood vessels or other tissues. To address this issue, the use of a nephron-specific deletion approach will be needed.

Studies using renal crosstransplantation demonstrated a significant role of renal AT1R in BP regulation independent of aldosterone.\textsuperscript{37} Furthermore, conditional deletion of AT1R in the PT reduced baseline BP and attenuated Ang II–induced hypertension.\textsuperscript{38} In the PT, AT1R activation appears to primarily target Na\textsuperscript{+}/H\textsuperscript{+} exchanger 3 to induce Na\textsuperscript{+} retention and hypertension.\textsuperscript{7}

The functional role of CD renin has been examined by Ramkumar et al., who generated mice with CD-specific overexpression or deletion of renin.\textsuperscript{39,40} Overexpression of renin in the CD causes spontaneous hypertension.\textsuperscript{40,41} Although deletion of renin in the CD didn’t produce major disturbances in Na\textsuperscript{+} and water balance and BP, the null mice were protected against Ang II–induced hypertension.\textsuperscript{39} These results support an important role of CD renin in BP regulation.

As discussed above, the functional contribution of intrarenal RAS to hypertension is tested mostly by using the Ang II–infusion model which is of limited relevance due to the nonphysiologic doses of Ang II. In fact, alteration of intrarenal RAS has been documented in several other models of experimental hypertension, such as Dahl salt-sensitive rats;\textsuperscript{42} two-kidney, one clip Goldblatt hypertension;\textsuperscript{43} and spontaneously hypertensive rats.\textsuperscript{44} These models have a better relevance to human hypertension. Defining the functional role of intrarenal RAS in each of these models is expected to offer new perspectives on the pathophysiology of intrarenal RAS during hypertension.

**ROLE OF INTRARENAL RAS IN RENAL DISEASE**

An inappropriate activation of intrarenal RAS has been implicated in a variety of animal models of renal disease, such as...
5/6 nephropathy, adriamycin nephropathy, unilateral ureteral obstruction, and polycystic kidney disease, as an initial response to hypoperfusion and an important driver of the disease progression. Urinary AGT has been shown to be a strong predictor of intrarenal RAS activity and renal injury in both animal and clinical studies.

To date, the use of RAS inhibitors such as ACEi or AT1 blockers remains the cornerstone therapy for amelioration of albuminuria and renal disease progression. Yet, there is no clear evidence for enhancement of systemic RAS in patients with renal disease. Along this line, although ACEi treatment may acutely lower circulating Ang II, its long-term therapy in a subset of patients raises Ang II or aldosterone concentrations back to the baseline level. Overall, the concept of intrarenal RAS in renal disease has been well established. However, a number of issues still need to be resolved. For example, the precise intrarenal sites of RAS activation during renal injury and the detailed regulatory mechanisms still largely remain elusive. Furthermore, most studies in this area are limited in their descriptive or correlativeness. The precise contribution of intrarenal RAS to renal disease as compared with that of systemic RAS needs to be determined by functional studies, particularly those using mice with genetic manipulations of RAS components in a tissue-specific manner without perturbing systemic RAS.

**POTENTIAL REGULATORS OF INTRARENAL RAS**

(Pro)Renin Receptor as a Positive Regulator of Intrarenal RAS

In 2002, Nguyen et al. cloned a specific receptor for prorenin and renin, termed (pro) renin receptor (PRR). PRR is a unique 350-aa amino acid transmembrane protein consisting of a large N-terminal extracellular domain, a single transmembrane protein, and a short cytoplasmic domain. The extracellular domain is cleaved to generate a soluble form of PRR (sPRR) via furin or ADAM19. This cleavage results in three isoforms: the full length PRR, sPRR, and the intracellular domain M8.9. It is increasingly evident that PRR serves a multitude of functions in regulating embryogenesis, balancing sodium and water, modulating acid secretion, etc. Of note, complete PRR deletion in vertebrae leads to developmental alterations and early embryonic lethality probably as a result of PRR’s role in regulation of vacuolar H+-ATPase and Wnt/β-catenin signaling. Moreover, nephron-specific deletion of PRR causes severe autophagic defects in renal medullary tubules and acidosis.

The association between PRR and RAS has been extensively investigated but highly debated. Since its first identification from human mesangial cells, PRR was thought to be a component of the RAS on the basis of in vitro evidence. However, subsequent animal studies were unable to prove the renin-regulatory role of PRR. In particular, overexpression of human PRR failed to affect tissue Ang II concentrations. The definitive evidence for PRR as a component in Wnt/β-catenin signaling during embryogenesis and as an accessory protein of vacuolar ATPase further questioned its role in RAS regulation. Unraveling this issue has been difficult due to the controversial PRR inhibitor HRP67 and also the lack of viable PRR knockout mice.

Within the kidney, PRR is predominantly expressed in the intercalated cells of the CD. The expression of PRR in the CD is stimulated by chronic Ang II infusion or sodium depletion. In cultured CD cells, PRR expression was stimulated by low salt or Ang II and the stimulation was potentiated by the combined treatments. In light of the localization of PRR with renin in the CD, it is conceivable that PRR may regulate renin activity in the distal nephron, particularly during Ang II–induced hypertension.

Functional studies showed that a newly developed PRR decoy inhibitor PRO2071 administered via intramedullary infusion technique remarkably suppressed the increases in urinary and renal medullary renin activity during Ang II–induced hypertension. In vitro evidence further demonstrated that the action of PRO20 in inhibiting renin activity was direct. In agreement with these results, CD-specific deletion of PRR reduced the basal urinary renin activity by approximately 40% and almost completely abolished its response to Ang II at 300 ng/kg per minute, in parallel with the suppressed hypertensive response. This BP phenotype was similar to that of nephron PRR KO mice generated by Ramkumar et al. when Ang II was infused at 600 ng/kg per minute. However, another strain of nephron PRR KO model generated by Trepioccone et al. exhibited normal BP response to Ang II at 1 μg/kg per minute; renal Ang II level in these null mice was also unaltered. The exact reason for this discrepancy is unclear but could be related to differences in experimental protocols such as the doses of Ang II.

Despite the emphasis on the potential renin-regulatory role of PRR as discussed above, it is increasingly evident that PRR can also act in an RAS-independent manner. In cultured mpkCCD cells, activation of PRR by prorenin in the nanomolar range induced epithelial sodium channel activity, an effect that was unaffected by AT1 blockade. This result was recapitulated by using freshly isolated cortical CD with single-channel patch-clamp recording. In contrast, renin was largely ineffective in activating the Na+ channel. The in vitro data favors prorenin, but not renin, as a candidate physiologic ligand of PRR. However, it remains elusive whether the prorenin/PRR interaction truly occurs in vivo. PRR’s nanomolar affinity for prorenin/renin is many orders of magnitude above their levels in blood. Indeed, deletion of PRR in the CD or the neprhin produces a urine concentrating defect that is not seen in the CD renin KO model. Future studies are needed to determine whether prorenin or renin is the true physiologic ligand of PRR.
PGE₂/EP₄ Pathway as a Positive Regulator of Intrarenal RAS

E series prostaglandins (PGs) have long been recognized as important regulators of renin secretion from the JGA.⁷⁷–⁷⁹ In early studies in the isolated rabbit JGA, renin secretion in response to low NaCl was virtually abolished by nonspecific cyclooxygenase (COX) inhibition with flufenamic acid or flurbiprofen.⁸⁰ Subsequently, a large body of experimental evidence demonstrated that PGE₂ derived from COX-2 serves as a dominant mechanism in mediating renin secretion from the JGA via EP₂ and EP₄ receptors which signal through the cAMP pathway.⁸¹,⁸²

Besides the JGA, the CD is another major site of both production and action of PGE₂. Among the microdissected nephron segments, the highest amount of PGE₂ was detected in the CD.⁸³ At the distal nephron, PGE₂ exerts complex roles in regulation of Na⁺ and water transport depending on a specific EP subtype.⁸⁴ The PGE₂/EP₄ pathway is well recognized as an antidiuretic mechanism⁸⁵,⁸⁶ that complements vasopressin (AVP) action in the CD. Recent pharmacologic⁸⁷ and conditional EP₄ knockout studies⁸⁶ provide compelling evidence to support antidiuretic action of EP₄ receptors in the CD which is mediated by upregulation of AQP2 expression. Although most of the previous studies focused on the direct action of PGE₂ in regulation of tubular transport, recent studies suggested that the PGE₂/EP₄ pathway may modulate CD function via a previously undescribed mechanism involving concomitant activation of PRR and local renin response in the distal nephron.⁷²,⁷³ The capability of EP₄ to independently stimulate PRR and renin make it an effective regulator of intrarenal RAS leading to increased fluid reabsorption in the distal nephron. This mechanism contributes to physiologic maintenance of fluid balance during water deprivation.⁸⁷ The discovery of the PGE₂/EP₄/PRR pathway in the distal nephron is also of importance in BP regulation. Our studies suggest that inappropriate activation of this pathway contributes to Ang II–induced hypertension.⁷² EP₄ receptors signaling works through a number of pathways involving cAMP/PKA, phosphatidylinositol 3-kinase, and AKT.⁸⁸,⁸⁹ Among these candidate signaling mechanisms downstream of EP₄ receptors, cAMP/PKA, but not AKT or phosphatidylinositol 3-kinase, is shown to mediate the upregulation of PRR in the CD cells.⁸⁷

The fluid-retaining and prohypertensive action of EP₄ receptors in the distal nephron is opposite to the well recognized vasodilatory property of this EP subtype. In most vascular beds, PGE₂ functions as a vasodilator to buffer the action of vasoconstrictive stimuli such as Ang II. Central to the buffering actions of PGE₂ are the vasodilatory EP₄ receptors found in both vascular smooth muscle cells and endothelial cells. Endothelial EP₄ receptors contribute to the acute vasorelaxation of aortic rings induced by PGE₂ through cGMP-dependent dephosphorylation of eNOS at Thr⁴⁹⁵. It was recently shown that inducible vascular smooth muscle cell EP₄ deletion impairs PGE₂-induced mesentry artery relaxation but fails to affect Ang II–induced hypertension.⁹⁰ This result suggests that vascular EP₄ receptors may be less important for BP regulation despite their role in regulation of vascular tone.

**Wnt/β-Catenin Signaling as a Positive Regulator of Intrarenal RAS**

Wnt/β-catenin signaling is an evolutionarily conserved signaling cascade that plays a pivotal role in regulating embryogenesis and tissue hemostasis.⁹¹,⁹² Emerging evidence demonstrates that activation of Wnt/β-catenin signaling underlies pathogenesis of CKD, including diabetic nephropathy, polycystic kidney disease, chronic allograft nephropathy, etc.⁹³–⁹⁵ A link between Wnt/β-catenin signaling and intrarenal RAS is suggested by Zhou et al. who used a bioinformatics approach to demonstrate that β-catenin targeted putative T cell factor/lymphoid enhancer–binding factor binding sites found in promoter regions of multiple RAS genes including AGT, renin, ACE, AT₁R, and AT₂R.⁹⁶ It is interesting to note that despite their opposite roles in renal physiology and pathophysiology, AT₁R and AT₂R are both targeted by Wnt/β-catenin signaling. This raises a question as to whether Wnt/β-catenin signaling affects other components of the protective RAS axis such as the ACE2/Ang1-7/MasR axis. Additionally, the PRR gene also contains multiple T cell factor/lymphoid enhancer–binding factor binding sites in its promoter region, raising a possibility that PRR may also be a target gene of Wnt/β-catenin signaling. On the other hand, Ang II stimulates β-catenin signaling in cultured M-1 cortical CD cells leading to enhancement of fibronectin and collagen I as well as cyclin D1 and c-myc.⁹⁷ Therefore, there appears to be a mutually stimulatory relationship between Ang II and Wnt/β-catenin signaling during renal fibrosis.

The complex relationship between Wnt/β-catenin signaling and intrarenal RAS is also reflected by PRR as an upstream component of the Wnt/β-catenin pathway.⁶⁶,⁶⁷ We recently reported that sPRR is produced from intercalated cells of the CD and acts in a paracrine manner to interact with principal cell Fzrzed-8 (FZD8), leading to activation of β-catenin pathway and thus increasing AQP2 transcription and urine concentration.⁹⁸ On the basis of these observations, we propose the following hypothetic model: Wnt/β-catenin signaling pathway and intrarenal RAS may interact with each other to form a positive feedback loop where PRR upregulates the β-catenin pathway that in turn stimulates expression of multiple RAS genes. Activation of this positive feedback loop may underlie pathophysiologic of hypertension and renal injury.

**Klotho as a Negative Regulator of Intrarenal RAS**

Klotho is a well known antiaging gene as highlighted by the prominent aging phenotype of Klotho mutant mice, including shortened lifespan and cardiovascular disease.⁹⁹ Within the kidney, Klotho is selectively expressed in the distal convoluted tubule and the PT, serving as an obligate coreceptor for fibroblast growth factor 23 to control phosphate reabsorption. Apart from the involvement in phosphate metabolism, Klotho exerts a multitude of...
beneficial activities against hypertension and renal disease.45,99,101–103

Increasing evidence demonstrates that the renoprotective action of Klotho is conferred through inhibition of intrarenal RAS. In various rodent models of renal disease including 5/6 nephropathy, adriamycin nephropathy, and unilateral ureteral obstruction, renal Klotho expression is suppressed but RAS components are upregulated; administration of exogenous Klotho through hydrodynamic-based gel ameliorates renal pathologies associated with abolishment of the induction of RAS components.45 It has further been shown that Klotho may inhibit intrarenal RAS by targeting Wnt/β-catenin signaling as suggested by the observation that Klotho directly binds multiple Wnts, including Wnt1, Wnt4, and Wnt7a, to block Wnt-triggered nuclear translocation of β-catenin.104 These observations have been extended by the study of Zhou et al., who showed that Klotho exerted a direct inhibitory effect on aldosterone synthesis in adrenal glands.105 It is likely that Klotho may exert a multitude of actions to mitigate the activation of intrarenal RAS as well as systemic aldosterone production. Overall, strong evidence demonstrates the suppression of renal Klotho expression in renal disease and more vigorous functional studies are needed to define the renoprotective action of this antiaging protein as well as its relationship with intrarenal RAS.

**Nuclear Receptors as Regulators of Intrarenal RAS**

The nuclear receptor family of transcription factors acts primarily via interacting with consensus elements in the promoter regions of the target genes and plays diverse and important roles in development and the regulation of normal physiologic functions, particularly energy metabolism.106 A number of nuclear receptors such as peroxisome proliferator–activated receptors,107,108 liver X receptor (LXR),98 and vitamin D receptor (VDR)109 have been implicated in the regulation of plasma volume and electrolyte homeostasis, a primary function of the RAS. It is conceivable that a crosstalk between nuclear receptors and the RAS may exist.

VDR is a well established negative regulator of the RAS.110,111 Multiple clinical studies revealed an inverse relationship between plasma 1,25 (OH) 2D3 concentrations and the BP and/or plasma renin activity in hypertensive patients as well as in normal subjects.112–114 More definitive evidence linking VDR and the RAS came from the cardiovascular phenotype of VDR null mice that displayed hypertension and cardiac hypertrophy associated with increases in renin and Ang II levels in the plasma as well as in renin, AGT, and AT1R, and PRR in inflammatory cells.109 Although this model doesn’t allow differentiating the involvement of systemic versus local RAS, the renin response to low salt and volume stimuli, a measurement of systemic RAS, remains intact. At cellular level, VDR directly suppresses renin gene transcription by interfering with cAMP responsive elements in the renin gene promoter.115 In rats with 5/6 nephrectomy, VDR activation by paricalcitol decreases expression of multiple RAS genes including renin, AGT, AT1R, and PRR in the remnant kidney and improves hypertension and kidney injury.116 These results seem to suggest that VDR may primarily target the local RAS to confer cardiovascular and renal protection. Indeed, multiple small clinical studies showed an inverse association between serum vitamin D levels and hypertension.117–119 However, recent intervention trials reveal no significant effect of vitamin D supplementation on BP in hypertensive patients.120–123 As noted by Beveridge et al.,124 these trials have a number of limitations. For example, the largest trials to date enrolled only a few hundred patients. Other limitations of these trails include limited representation by black individuals and short duration of the studies. It is known that blacks in the United States have higher rates of hypertension and cardiovascular disease associated with lower circulating levels of 25-hydroxyvitamin D as compared with whites.125 Therefore, larger trials with improved representations by blacks for a longer duration of treatment will be needed. Another consideration is that the inconsistent results may be related to varied vitamin D dosages. Lastly, although BP is the primary outcome of these trials, the effect of vitamin D supplementation on cardiovascular events and renal disease remains unclear.

LXRs heterodimerize with the retinoid X receptor to regulate transcription of target genes involved in cholesterol, fatty acid, and glucose metabolism.126–128 LXRs have an established role in reverse cholesterol transport which leads
to cholesterol efflux from peripheral tissues to the liver.129 We recently discovered that administration of an LXR against TO901317 in mice induces polyuria, polydipsia, hypo-osmotic urine, and downregulation of renal AQP2 expression, all indicative of nephrogenic diabetes insipidus.98 This observation reveals a novel diuretic role of renal LXRs. This study further provides a mechanism by which LXRs control urine concentrating capability via suppressing renal PRR/sPRR and intrarenal RAS.72,130 This concept aligns well with the observation that chronic TO901317 treatment suppresses the induction of renin, AT1R, and ACE in the heart and kidney induced by a nonpressor dose of isoproterenol in wild-type but not LXR KO mice.131 The RAS-inhibitory and diuretic activities of TO901317 are likely ascribed to LXRs. However, during an acute setting, LXR activation stimulates renin expression at the JGA.132 The underlying mechanism and physiologic significance of the distinct effects of LXR activation on RAS under the two different experimental settings certainly warrant further investigation.

In conclusion, a large body of experimental evidence has firmly established the concept of intrarenal RAS as a unique entity despite the circulating source of some intrarenal RAS components such as AGT. In general, intrarenal RAS is featured as a local feedforward system for augmentation of intrarenal generation or actions of RAS components, which is counterintuitive to the normal feedback regulation. This local system plays an important role in pathogenesis of hypertension and renal disease as well as in physiologic regulation of fluid homeostasis. Recent studies have identified several important regulatory pathways that can affect intrarenal RAS (Figure 1), including PRR, Wnt/β-catenin signaling, and the PGE2/EP4 pathway in the positive arm, and Klotho, VDR, and LXR in the negative arm. The balance between the positive and negative regulatory pathways may be an important determinant of intrarenal RAS activity. A better understanding of the molecular basis for integrative control of intrarenal RAS may offer new perspectives on both pathophysiologic and therapy for hypertension and renal disease. Optimism has been generated from the therapeutic potential of new inhibitors of PRR (PRO20)72 and Wnt/β-catenin signaling (ICG-001),133 and activators of LXR (TO901317)134 and Klotho (soluble Klotho)135 in cardiovascular and/or renal diseases. In addition, the clinical implication is also suggested by circulating levels of sPRL101 and soluble Klotho136,137 as a predictor of a decline of renal function in patients with CKD.

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DISCLOSURES

None.

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