Prorenin Receptor, a Necessary Component in Urine Concentration Mechanism

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In this issue of the Journal of the American Society of Nephrology (JASN), Wang et al.1 unravel an intriguing new signaling cascade that involves the prorenin receptor (PRR) in the kidney collecting ducts (CDs) as a necessary component of the physiologic ability of the kidneys to concentrate urine. The pathway includes serial coupling between the vasopressin (AVP) V2 receptor, the prostaglandin E2 (PGE2) EP4 receptor, and PRR, all associated with CDs. Many factors are known to modulate urine concentration—both hormones, like angiotensin II, aldosterone, cortisol, and endothelin and paracrine factors, like ATP—whereas few are true mediators. It is fascinating to uncover what seems to be a new and nonredundant mediator pathway downstream from the AVP V2 receptor. Here, at the intrarenal level, the findings indicate hierarchical interpositions of local PGE2 EP4 receptor-driven renin/prorenin-PRR interaction as necessary sequential mediators for the AVP V2 effect on CD transepithelial water transport.

The PRR was cloned in 2002 by Nguyen et al.2 In its native form, it is a 35-kD protein that undergoes intracellular proteolysis. This gives rise to a full-length membrane integral form and a soluble PRR. The soluble form is cleaved by intracellular proprotein convertase-serine endoprotease furin and released into plasma and urine with the ability to bind renin and activate prorenin.3 Finally, a truncated form is associated with the vacuolar H\(^+\)-ATPase,4 with activity that is enhanced by prorenin.5 PRR ligands comprise prorenin and active renin, with proteolytic activities that are enhanced by binding.2 In the kidney, PRR is predominantly associated with the CDs and the distal nephron.6 The PRR is most abundant in microvilli at the apical surface of A-type intercalated cells.6

Several groups have, in parallel studies, contributed converging observations on renal PRR and thus, bits to the puzzle. A prequel paper was published in October of 2015 showing the effect of nephron-specific deletion of PRR.7 The phenotype was nephrogenic diabetes insipidus with lower levels of the apical water transport protein AQP2 in kidney tissue and impaired AVP V2 receptor–induced cAMP formation in medulla tissue.7 Impaired vasopressin signaling with attenuated cAMP formation had already been shown in vitro after siRNA depletion of PRR in MDCK cells.8 On the basis of this, PRR seemed to be necessary for AVP signaling in principal cells of CDs and thus, baseline urine concentration. Previous data supported the observation indirectly, because C\(\text{p}2\l_1^{\text{tra/tra}}\) (Grainyhead transcription factor) mice, which lacked type A–intercalated cells (that express PRR) in CDs, displayed mild polyuria.8 What were the mechanisms by which PRR promoted cAMP signaling and the link to normal physiology? A physiologic role for PGs in the regulation of PRR was indicated by the observation that stimulation of medullary PRR and renin by angiotensin II depended on a PGE2 EP4 receptor.9 An unequivocal function for the PGE2 EP4 receptor in renal water handling was shown in 2015.10 The EP4 receptor couples to a G\(\alpha\) protein, leading to adenylyl cyclase stimulation and formation of cAMP. In the kidney, the EP4 receptor is associated with CDs, glomeruli, and renal resistance vessels.11–13 Although first observations in mice with global EP4 receptor deletion showed a mild diuresis only after low salt intake, no electrolyte disturbances, and impaired renin release from juxtaglomerular cells,14,15 the 2015 data indicated that EP4 receptors were physiologically stimulated by water deprivation in renal medulla.10 Moreover, renal tubule– and CD–specific EP4 receptor deletion resulted in increased baseline diuresis, normal electrolyte excretion, impaired urine concentrating ability with attenuated AQP2 protein abundance, and impaired cAMP formation but intact circulating levels of AVP.15 Thus, similar to CD–specific PRR deletion, the CD EP4–deleted phenotype exhibited nephrogenic insipidus. This observation provided a mechanistic clue to the previous observations that, in experimental nephrogenic diabetes insipidus models in rats and mice, EP4 receptor agonists alleviated increased diuresis.16,17 Similar to the PRR, EP4 receptor seems necessary for baseline renal water conservation and urine concentration ability through an intrarenal mechanism. This article by Wang et al.1 takes off at this site with putative roles for CD EP4 receptor and PRR in urine concentration and shows their interaction by a series of complementary pharmacologic and genetic in vivo and in vitro intervention approaches.

Water deprivation stimulated intercalated cell production of PRR, release of soluble PRR, and prorenin protein and mRNA abundance in medulla tissue and renin in urine but not plasma. Both PRR and renin stimulation depended on the EP4 receptor.1 Intrarenal infusion of PRR antagonist attenuated
physiologic urine concentrating ability and medullary AQP2 protein level,\(^1\) showing the dynamic nature of the response and ruling out nonspecific effects in published murine models with targeted deletion of PRR. Moreover, the putative in vivo stimulatory response of prorenin on AQP2 was robust; it could be reproduced in vitro by addition of nanomolar prorenin concentrations to primary cultured rat CD cells, and three independent ways of inhibiting/deleting the PRR receptor abolished the response.\(^1\) More importantly, the response of AQP2 to AVP and EP\(_4\) receptor agonist stimulation in vitro was inhibited similarly by the inhibitory PRR protocols. Together, these data established PRR as a relevant common regulator of AQP2 protein abundance downstream of AVP V\(_2\) and EP\(_4\) signaling.

The paper by Wang et al.\(^1\) in this issue of the JASN corroborated a necessary role for EP\(_4\) in AVP signaling and AQP2 stimulation. In addition, it showed that EP\(_4\) antagonism abrogated the intrarenal renin response to water deprivation/AVP stimulation, which suggests that PGE\(_2\) through EP\(_4\) receptor drives intrarenal CD prorenin/renin expression and release, much like the role for EP\(_4\) receptor in the juxtaglomerular cells.\(^15\) The paper by Wang et al.\(^1\) also presents mice with a CD-specific deletion of PRR that displayed a nephrogenic diabetes insipidus phenotype as in the work by Ramkumar et al.,\(^7\) but important additional information was reported. Increased urine renin activity after water deprivation was abrogated, suggesting that PRR is, indeed, contributing to water deprivation–induced tubular renin activation. An attempt to merge these findings into a physiologic cascade could include the following steps. In conditions of water deprivation, the AVP V\(_2\) signal contributes to local medullary PGE\(_2\) synthesis—both directly as shown in this paper\(^4\) and likely indirectly through elevated interstitial osmolality, which enhances cyclooxygenase-2 (COX-2) activity in medullary interstitial cells.\(^18,19\) COX-2 activity leads to PGE\(_2\) release and stimulates local EP\(_4\) receptor and medullary synthesis of prorenin and PRR.\(^20\) Prorenin is next released and stimulates PRR to enhance AQP2 abundance. The intracellular mechanisms by which PRR transduces ligand to control AQP2 are not elucidated in the study by Wang et al.\(^1\) Also, the role for interstitial hypertonicity in the reported responses is not clear. Finally, the question appears of why the renin inhibitor aliskiren in clinical use and the common over the counter painkiller NSAIDs do not impair urine concentration, because the findings by Wang et al.\(^1\) imply nonredundant mechanisms? First, studies have shown that renin and prorenin with active sites blocked by aliskiren do not display impaired binding and activation of PRR.\(^21\) Second, because both COX-1 and -2 are highly expressed in the medulla and because NSAIDs display variable selectivity, there is likely sufficient PGE\(_2\) to support the mechanism, despite NSAID intake. In support of this, experiments in rats given both COX-1 and -2 blockers in separate series showed no measurable change in urine PGE\(_2\) excretion while dehydration–induced AQP2 up-regulation was inhibited, completely in line with the findings by Wang et al.\(^1\) in this issue of the JASN.\(^22\) Moreover, mice with phospholipase A2 deletion that is upstream of COX enzymes and therefore, broadly lowers prostanois synthesis, in fact, display impaired urine concentration,\(^23\) which was also observed in COX-2\(^{-/-}\) mice.\(^24\) In contrast, mPGE synthase deletion did not abrogate but enhanced urine concentration.\(^25\) Some opposing findings clearly await additional experimentation. Along this line, PRR is associated with intercalated cells,\(^6\) but AQP2 is found in principal cells. How is the renin/prorenin–PRR response then transmitted? Because renin/prorenin of CD origin is released to urine and not measurably released to plasma, is the response via the apical membrane where PRR is found in microvilli? And if so, in proteinuria, how can local renin/prorenin signals not be overridden by luminal pro(renin)? What are the perspectives of these findings? Nephrogenic diabetes insipidus can be acquired, which is the case with chronic lithium ingestion, and can be inherited, which is caused typically by X–linked loss–of–function mutations in the V\(_2\) receptor gene, and the disease can be seriously debilitating because of the large urine volume and constant need to drink large volumes. Little can currently be done to help these patients, and both EP\(_4\) agonists and PRR agonism are attractive ways to stimulate CDs and bypass defect V\(_2\) receptor function. It shall be interesting to follow the development in coming years, and the work by Wang et al.\(^1\) sets the stage for many new hypotheses.

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