

## Role of Collecting Duct AT1a Receptors in Concentrating Urine

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Water-electrolyte homeostasis is pivotal for many, if not all, physiologic processes of the body. It is not surprising, therefore, that the control of water-electrolyte balance is extremely complex and multifactorial.<sup>1</sup> This involves regulation of thirst, salt appetite, sympathetic tone, and vascular contractility, as well as renal mechanisms modulating excretion of water and solutes. Systemic hormones, including angiotensin II (Ang II), affect a variety of targets in diverse tissues and organs to evolve a highly orchestrated response in pursuit of maintaining water-electrolyte homeostasis. A major challenge to physiologists is to identify the specific targets and mechanisms involved in this process and to understand the relative contributions of each in the integrated response. Recent advances in molecular genetics, which allow global and cell-specific manipulation of genes, as used by Stegbauer and colleagues<sup>2</sup> in an exciting study of the role of angiotensin receptors in the control of water homeostasis published in this issue of *JASN*, have been instrumental in elaborating details and identifying key components of regulation.

Since the discovery of the renin-angiotensin-aldosterone system, it is accepted that Ang II is central to controlling circulating volume and systemic BP.<sup>3</sup> In addition to its effect on sodium balance, Ang II also has a profound effect on water metabolism by promoting water thirst, stimulating AVP release, and enhancing urine-concentrating ability.<sup>4</sup> The majority of Ang II actions on water homeostasis are mediated by AT1 receptors, specifically the AT1a receptor subtype in mice. Taking advantage of animal models lacking AT1a receptors can elucidate the specific role of this receptor. Indeed, AT1a receptor-null mice have prominent polyuria with secondary polydipsia, modestly decreased systemic AVP levels, extreme serum hypertonicity during water restriction, and decreased capacity to concentrate urine.<sup>5,6</sup> However, it has not been possible to fully appreciate the contributions of specific tissues and mechanisms to the abnormal water metabolism apparent in

AT1a receptor-null mice because of the robustness and complexity of this homeostatic control system.

In this issue of *JASN*, Stegbauer and colleagues<sup>2</sup> make an important breakthrough advancing understanding of Ang II actions on water homeostasis by identifying key renal components and mechanisms involved in the control of water reabsorption in the collecting duct. Importantly, taking advantage of tissue-specific knockout, these investigators discriminate between the global actions of Ang II and the effects of this hormone as mediated by AT1a receptors on the water-permeable portion of the nephron as controlled by the expression of aquaporin 2 (AQP2) water channels in the apical membrane of collecting duct principal cells. This precision enabled important new conclusions to be made about the direct actions of Ang II on control of water permeability in the distal nephron isolating direct effects on this portion of the nephron from secondary actions manifesting from systemic influences. The striking conclusion made by Stegbauer and colleagues<sup>2</sup> that the actions of Ang II on the collecting duct as mediated by the AT1a receptor accounts for the bulk of the role played by this hormone in water metabolism highlight the power of this targeted gene-deletion approach to understanding complex physiology.

Through an elegant and complementary approach involving a Cre-LoxP strategy to delete AT1a receptors specifically in the collecting duct (Hoxb7-Cre<sup>+</sup>Agtr1a<sup>fllox/fllox</sup>) and AQP2-expressing cells (AQP2-Cre<sup>+</sup>Agtr1a<sup>fllox/fllox</sup>; collecting duct principal cells), this study provides the first direct evidence of a role for AT1a receptors in modulating vasopressin (AVP)-induced water transport in principal cells. Deletion of AT1a surprisingly interferes with AVP-dependent increases in AQP2 abundance rather than affecting the osmotic draw for water. This demonstrates that Ang II signaling converges with that of AVP to modulate the gateway for water reabsorption in the distal nephron, which is limiting for renal water excretion during states of water deprivation. Extrapolation of these findings argues that Ang II also may play a role in the control of water excretion during normal conditions. This notion emphasizes an important aspect that is not often fully appreciated about the treatment currently favored to address elevated BP combining a diuretic with an Ang II receptor blocker: disruption of both the osmotic draw as well as the pathway for water reabsorption in the distal nephron yields the best results.

It is important to note that the phenotype with respect to water homeostasis of mice with AT1a receptor deletion in the distal nephron and specifically in principal cells resembles that of mice having global AT1a receptor knockout.<sup>2,5</sup> This underlines a major role for renal mechanisms in Ang II regulation of water homeostasis. Indeed, both models demonstrate mild disturbances of water balance during basal conditions but marked resistance to vasopressin under physiologic (water deprivation) and pharmacologic (dAVP administration) stimuli. Interestingly, AT1a receptor elimination does not interfere with AVP-induced AQP2 translocation to the apical plasma mem-

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brane but rather compromises AVP-dependent, but not basal, expression of water channels. This finding suggests that the point of convergence between the Ang II and AVP cascades is neither signal transduction nor AQP2 trafficking but rather the capacity to express the protein. More specifically, it suggests that Ang II enhances the ability of AVP to promote AQP2 expression at the genomic level, inferring that Ang II signaling either leads to *trans*-activation of the AQP2 gene in the presence of AVP signaling or facilitates *trans*-activation in some manner by AVP signaling. The mechanism of this transcriptional control remains elusive. Other studies also have documented reduced levels of adenylate cyclases III and V/VI in the innermedullary collecting duct of AT1a receptor-null mice<sup>5</sup> that were not apparent in the study by Stegbauer and colleagues.<sup>2</sup> This discrepancy remains unresolved.

One of the more striking observations made investigating collecting-duct-specific AT1a receptor knockout mice is that the effect of AT1a receptor deletion on water transport in the distal nephron does not arise from changes in the osmotic draw for water reabsorption but rather is restricted to the route of reabsorption. Unlike the case in the proximal tubule, where AT1a receptor deletion disturbs renal sodium handling and pressure natriuresis,<sup>7</sup> deletion of the AT1a receptor in principal cells of the distal nephron does not produce measurable changes in sodium excretion and does not appear to affect the abundance of the epithelial Na<sup>+</sup> channel. The activity of this channel is limiting for sodium reabsorption in this portion of the nephron. However, additional research is called for here in this model because it was only touched upon in brief in this study. It is also interesting that collecting duct and principal cell-specific AT1a receptor-null mice do not exhibit the morphologic abnormalities apparent in global AT1a receptor-null mice that have modest atrophy of innermedullary collecting duct and papilla. This finding suggests that other Ang II receptors play an important role in development. The shortening of the nephron in global AT1a receptor-null mice likely accounts for these animals having concentrating problems under all conditions and differences in serum AVP levels. That collecting-duct-specific AT1a receptor-null mice have normal kidney anatomy and yet show resistance to AVP-dependent water reabsorption is consistent with this model providing a more precise understanding of the role of AT1a receptors in renal water metabolism.

This study by Stegbauer and colleagues<sup>2</sup> also offers additional appreciation from a broader physiologic perspective. It exemplifies that complex biologic functions often are modulated by coordinated but discrete input from converging signals, in this case Ang II and vasopressin, to achieve appropriate outcomes, namely water excretion and urinary concentrating ability. Although complex, the final result is a product of how individual contributions integrate. Thus, detailed understanding of discrete control systems, as provided by Stegbauer and colleagues for AT1a in the collecting duct, is fundamental to understanding physiology and treating disease.

## DISCLOSURES

None.

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See related article, "AT<sub>1</sub> Receptors in the Collecting Duct Directly Modulate the Concentration of Urine," on pages 2237–2246.

## The Renal Papilla: An Enigma in Damage and Repair

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It is now well established that organ-specific adult stem cells exist in a variety of tissues throughout the body where their survival, proliferation, and multipotency are regulated by the niche in which they reside. The controversy over whether such populations also exists in a relatively nonproliferative, nonregenerative organ such as the kidney has been the topic of debate for almost a decade.<sup>1</sup> A variety of interstitial and epithelial populations have been identified

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