Vasopressin regulation of renal sodium excretion

James D. Stockand[1]

[1]Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Vasopressin promotes renal water reabsorption decreasing excretion of free water to dilute plasma and lower serum osmolality. We have good understanding of the causes, mechanisms and consequences of this vasopressin-dependent renal water movement. In comparison, vasopressin actions on renal electrolytes including sodium excretion and its consequences have been less well understood. This is so for investigation and discussions of the renal actions of vasopressin are framed primarily around water metabolism rather than any direct effect on salt handling. The fact that water moves in biological systems, to include the mammalian kidney, only by osmosis passively down its concentration gradient is implicit in such discussion but often not overtly addressed. This can cause confusion. Moreover, although vasopressin action on renal sodium excretion via the V2 receptor is critical to water transport, it is masked easily being situational—for instance, dependent on hydration state. It is now clear that an increase in sodium reabsorption along the distal nephron (CNT + CD) mediated by activation of the epithelial Na^+ channel (ENaC) by vasopressin makes an important contribution to maintenance of the axial corticomedullary osmotic gradient necessary for maximal water reabsorption. Thus, we need to modify slightly our understanding of vasopressin and its renal actions to include the idea that while vasopressin decreases free water excretion to dilute plasma, it does this, in part, by promoting sodium reabsorption and consequently decreasing sodium excretion via ENaC activated along the distal nephron.

Kidney International (2010) **78,** 849–856; doi:10.1038/ki.2010.276; published online 25 August 2010

KEYWORDS: renal epithelial cell; renal tubular epithelial cells; tubular epithelium; vasopressin; water–electrolyte balance

Correspondence: *James D. Stockand, Department of Physiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, Texas 78229-3900, USA. E-mail: stockand@uthscsa.edu*

Received 29 March 2010; revised 11 May 2010; accepted 15 June 2010; published online 25 August 2010

Vasopressin is thought to possess antinatriuretic actions along with its better described antidiuretic actions.[1–8] This is supported by a preponderance of findings from cultured renal cell lines, and renal tissue studied in isolation, including perfused tubules and split-open collecting ducts, demonstrating that vasopressin increases luminal to serosal sodium reabsorption by activating the epithelial Na^+ channel (ENaC).[2,3,7,9–23] This effect should reduce sodium excretion *in vivo*. However, investigation of water and electrolyte handling in animals and humans show vasopressin to have variable effects on net sodium excretion.[4–6,8,24–33] New understanding of the cellular mechanism and systemic consequences of vasopressin action, in combination with reconsideration of earlier findings, reveals why this is so.

VASOPRESSIN SIGNAL TRANSDUCTION

Vasopressin targets two receptor types, V1 and V2.[34–37] Both are seven transmembrane G-protein coupled receptors. The former couples to phospholipase C via $G_{q/11}$ and the latter to $G_{s,}$ ultimately increasing cyclic adenosine monophosphate (cAMP) by stimulating adenylyl cyclase. V1 receptors are most abundant in vascular smooth muscle cells and their stimulation favors contraction. V2 receptors are in epithelial cells, such as principal cells of the distal nephron, and their stimulation increases renal water reabsorption.[34–37] Stimulation of V1 receptors, although not directly involved in control of tubular water and electrolyte transport, increases sodium excretion because of the influences on blood pressure, effective circulating volume, glomerular filtration rate and circulation in the vasa recta system.[24,34,38,39] As illustrated in Figure 1, activation of V2 receptors in the distal nephron by vasopressin stimulates free water reabsorption by promoting cAMP-dependent trafficking of aquaporin 2 water channels to the luminal membrane of principal cells allowing back diffusion of water down its concentration gradient. In addition, as a focus of the current review, vasopressin via V2 receptors also modulates discretionary sodium reabsorption across principal cells mediated by ENaC. This facilitates free water reabsorption by supporting the axial corticomedullary hyperosmotic gradient. Vasopressin via V2 receptors also activates urea transporters, such as UTA1, in the distal nephron to facilitate urea reabsorption and urea recycling, which allows maximization of sodium reabsorption in the thick ascending limb via NKCC2 supporting the axial hyperosmotic gradient drawing water from the distal nephron (reviewed by Sands and Layton[40] and Fenton[41]).

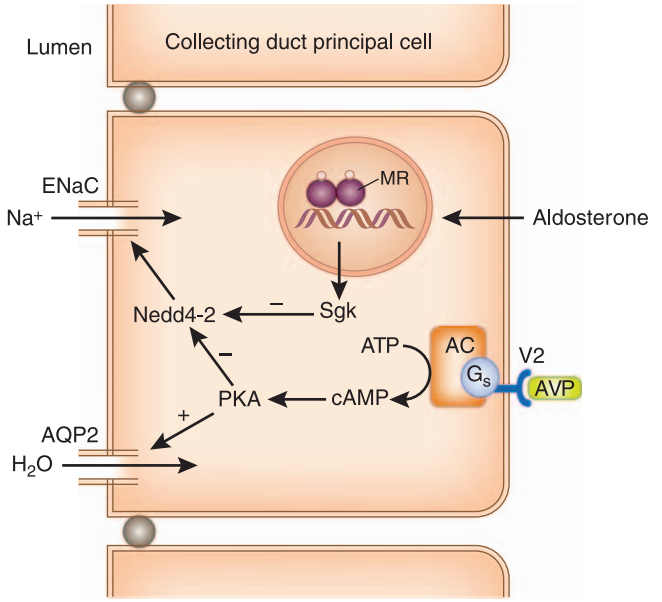

Figure 1 | Vasopressin signal transduction. AC, adenylyl cyclase; AQP2, aquaporin 2; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; ENaC, epithelial Na^+ channel; MR, mineralocorticoid receptor; Nedd4-2, neural precursor cell expressed developmentally downregulated 4-2; Sgk, serum and glucocorticoid-inducible kinase.

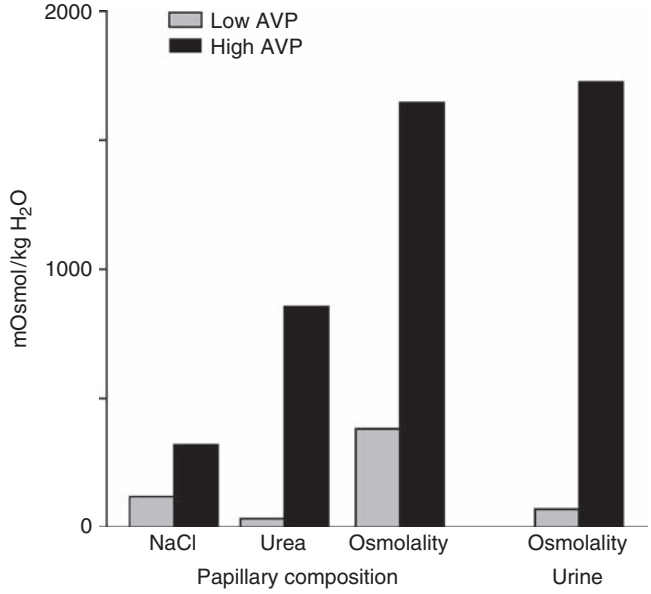

Figure 2 | Vasopressin increases papillary sodium and urea concentrations while concentrating urine. Figure regenerated from data presented originally in Levitin *et al.*[42] AVP, arginine vasopressin.

HISTORICAL PERSPECTIVE

The first clues that vasopressin might decrease renal sodium excretion came from early micropuncture studies and renal tissue fluid sampling circa 1950–60.[42,43] As reproduced in Figure 2, these studies demonstrated that '… antidiuretic hormone enhances the sequestration of sodium in the interstitial fluids of the medulla and papilla'.[42] Importantly, vasopressin increased the absolute amount of sodium per unit of dry solids showing that increases in medullary sodium concentration were independent of effects on water. The converse was also established where decreases in vasopressin lowered the absolute amount of sodium in medullary interstitial fluid. Such findings combined with our understanding of osmotic water movement demonstrate that the effects of vasopressin on sodium transport are primary and contribute to water movement. Also established by pioneering work in renal physiology is that the ability to concentrate urine is dependent on systemic sodium levels with sodium depletion, hyponatremia and removal of plasma sodium with dialysis compromising this ability.[44–48]

SYSTEMIC CONSEQUENCES OF VASOPRESSIN ACTION

Elevated and lower than normal urinary sodium concentrations and excretion have been reported for humans with hyponatremia resulting from upregulated and uncontrolled vasopressin secretion.[24,25,49–51] This is so, as discussed below, because the effects of vasopressin on renal sodium excretion are situational and easily obscured. The renal consequences of vasopressin on sodium excretion include both primary causative actions as well as secondary responses. Moreover, vasopressin controls excretion of free water by manipulating both water permeability and the movement of solute, notably urea and sodium.[34–37] The latter makes control of systemic water and sodium linked to some degree with one in some instances capable of masking or impairing proper regulation of the other. When considering vasopressin action on sodium excretion, it is important to understand that it is only one component of a larger multifactorial homeostatic control system governing systemic sodium balance with most input into this system responding to changes in plasma sodium levels rather than water levels. Thus, vasopressin effects on sodium excretion in the whole animal cannot be considered in isolation and must be viewed in the context of other signals also affecting systemic sodium balance. Similarly, a change in renal sodium excretion in response to vasopressin is just one component of a larger homeostatic control system governing systemic water balance and must be considered in the context of other input, such as the activity of the renin–angiotensin II–aldosterone system (RAAS).

A recent study by Perucca *et al.*[26] that precisely teased apart contribution from specific V1 and V2 receptor agonism and antagonism to renal water and sodium handling in rats demonstrated that vasopressin via V2 receptors decreases renal sodium excretion in addition to decreasing water excretion. As recapitulated in Figure 3, specific V2 agonism acutely decreased sodium excretion in a dose-dependent manner, while promoting free water reabsorption and lowering urea excretion. Antagonism of this receptor results in the opposite response: increased sodium and water excretion and urine dilution. Addition of exogenous vasopressin capable of stimulating both V1 and V2 receptors decreases sodium excretion and promotes free water