특별강연 I

Molecular Physiology of Vasopressin Action in Kidney

Mark A. Knepper, MD, PhD

National Heart, Lung and Blood Institute, Bethesda, Maryland

Vasopressin-mediated regulation of water excretion is a vital homeostatic process. The regulation goes awry in many patients when inappropriately high vasopressin levels result in dilutional hyponatremia (e.g. SIADH, congestive heart failure, cirrhosis of liver) or when failure to respond to vasopressin causes polyuria (nephrogenic diabetes insipidus). Effective management of water balance disorders depends on knowledge of the transport proteins that are regulated by vasopressin in the normal kidney. The regulation of water excretion depends largely on the function of two renal tubule segments, viz. thick ascending limbs and collecting ducts. Thick ascending limbs separate solutes and water, chiefly by actively reabsorbing NaCl and other salts in the absence of water movement. Thus, thick ascending limbs are key to both urine dilution and concentration. The collecting ducts receive a dilute tubule fluid and can either maintain the dilute state (in the absence of vasopressin) or change the tubule fluid from dilute to concentrated (in the presence of vasopressin). Vasopressin causes this transition by increasing the water permeability. It does so by binding to the V2 vasopressin receptor. V2 receptor binding regulates the water channel aquaporin-2 in two ways: 1) short-term regulation by causing the redistribution of AQP2 from intracellular vesicles to the apical plasma membrane (trafficking); and 2) long-term regulation by increasing the abundance of the AQP2 protein in collecting duct cells. The short-term regulation occurs through inhibition of endocytosis of the AQP2 water channel, as well as by stimulation of exocytosis of AQP2-containing recycling endosomes. The long-term regulation by vasopressin occurs by transcriptional regulation of the AQP2 gene and by increasing the half-life of the aquaporin-2 protein. Vasopressin signaling in the collecting duct cells involves both calcium mobilization in the cell and increases in intracellular cyclic AMP. Using protein mass spectrometry, we found that the carboxyl terminal tail of the aquaporin-2 protein contains a compact cluster of vasopressin-regulated phosphorylation sites (Ser256, Ser261, Ser264, and Ser269 in rat). Each of these is regulated differently by vasopressin and may play distinct roles in regulation of aquaporin-2 trafficking. Current studies are focusing on identification of the protein kinases responsible for these phosphorylation events.