Long-term regulation of urinary concentrating capacity

MARK A. KNEPPER
Laboratory of Kidney and Electrolyte Metabolism, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892-1603

Knepper, Mark A. Long-term regulation of urinary concentrating capacity. Am. J. Physiol. 275 (Renal Physiol. 44): F332–F333, 1998.—Urinary concentrating capacity is regulated in part by a long-term adaptational process involving changes in the absolute abundance of the aquaporin-2 water channel in collecting duct cells. Alterations in aquaporin-2 abundance play key roles in the pathophysiology of several water balance disorders. Escape from the antidiuretic action of vasopressin, e.g., in the syndrome of inappropriate antidiuretic hormone secretion, involves a selective downregulation of aquaporin-2 expression. Excessive water retention causing hyponatremia in volume-expanded states such as congestive heart failure appears to be due in part to a failure of this escape mechanism.

cortical collecting duct; vasopressin; water permeability

A READER of current textbooks on renal physiology would know that vasopressin regulates renal water excretion through its effect to increase water permeability of the renal collecting duct by triggering the shuttling of water channel vesicles to the plasma membrane. This fundamental mechanism of regulation, postulated on the basis of freeze-fracture analysis of the urinary bladder of the toad, has been directly confirmed by studies using antibodies to aquaporin-2 (the vasopressin-regulated water channel) as described in the accompanying article by D. Brown (1). However, studies carried out in the past 6 years have revealed that vasopressin regulates the water permeability of collecting ducts by a second mechanism that may be at least as important as the shuttling mechanism with regard to the pathophysiology of water excretion disorders. This process, "long-term" regulation of collecting duct water permeability by vasopressin (11), is a result of the action of vasopressin to increase the abundance of the aquaporin-2 water channel in collecting duct cells (2, 9). This action requires a sustained elevation of circulating vasopressin levels for 24 h or more and is thought to be a consequence of increased transcription of the aquaporin-2 gene (reviewed in Ref. 6). The increase in transcription may be the result of the ability of cAMP to activate protein kinase A, resulting in phosphorylation of transcription factors such as CREB (cAMP regulatory element binding protein) (5, 8, 12). However, other possible mechanisms of regulation (e.g., regulation of aquaporin-2 mRNA stability, regulation of aquaporin-2 mRNA translation, and regulation of aquaporin-2 protein degradation) have not been adequately investigated, in part because of the lack of adequate cultured cell models that naturally express aquaporin-2 and exhibit regulation of aquaporin-2 protein abundance in a manner similar to that seen in the intact kidney.

Overall regulation of collecting duct water permeability is presumably a manifestation of both the short-term shuttling mechanism and the long-term mechanism. In principle, defects in water balance could be the result of abnormalities of either the short-term regulatory mechanism, the long-term regulatory mechanism, or both. Rat models of acquired nephrogenic diabetes insipidus due to sustained lithium intake, sustained hypokalemia, or sustained ureteral obstruction have demonstrated a marked decrease in aquaporin-2 abundance, but apparently normal trafficking of aquaporin-2 to the plasma membrane (7). That is, the water transport defect appears to be largely a result of derangement of the long-term regulatory process. Recent studies of water retention associated with the development of hyponatremia in congestive heart failure have revealed both an increase in aquaporin-2 abundance in collecting duct principal cells and an increase in the trafficking of aquaporin-2 to the apical plasma membrane (reviewed by Knepper et al., Ref. 7). That is, both the short- and long-term regulatory processes are hyperactivated. Additional studies of the role of aquaporin-2 in the pathophysiology of water balance disorders have been reported, and further work is likely over the next few years.

Our understanding of the long-term regulation of aquaporin-2 abundance has been abetted by studies of
the mechanism of the “escape” from vasopressin-induced anti-diuresis (3). It has been known for many years that sustained elevations of vasopressin coupled with continued water intake result in sufficient water retention to cause hyponatremia but that the degree of hyponatremia is limited by the onset of the “vasopressin-escape” phenomenon, i.e., a progressive increase in water excretion associated with a decline in negative free water clearance despite a sustained high circulating level of vasopressin. Immunoblotting studies in rats using an anti-aquaporin-2 antibody revealed that the onset of vasopressin-escape was associated with a marked fall in aquaporin-2 abundance in the collecting duct (3). That is, the process by which vasopressin increases the abundance of aquaporin-2 had somehow been reversed. This effect appeared to be selective for aquaporin-2, since the abundance of the other three renal aquaporins was unchanged. The cellular and molecular mechanisms responsible for the fall in aquaporin-2 expression in the vasopressin-escape process are presently unknown but are sure to be the focus of intense research because of the potential clinical importance of the process. Not only is this process important in the limitation of hyponatremia seen in the syndrome of inappropriate antidiuretic hormone secretion (SIADH), but similar mechanisms could be important in the nephrogenic diabetes insipidus syndromes associated with lithium treatment, hypokalemia, ureteral obstruction, and hypercalcemia. Furthermore, in considering the important role of increased aquaporin-2 expression in the water retention associated with congestive heart failure (discussed above), one is led to wonder why the vasopressin-escape process is not activated and whether an understanding of this vasopressin-escape mechanism could lead to more effective treatments for the water retention associated with congestive heart failure and other volume-expanded states.

The regulation of aquaporin-2, emphasized in this short article, is only part of the story. Clearly, there is more to the control of water excretion than the regulation of collecting duct water permeability. Indeed, the countercurrent multiplication process responsible for water conservation involves the function of several solute transporters expressed in the loop of Henle (see accompanying article by S. C. Hebert, Ref. 4). Furthermore, the process which concentrates urea in the renal inner medulla is dependent on specialized urea transporters expressed in the inner medullary collecting duct and descending limb of Henle’s loop (see accompanying article by M. A. Hediger and colleagues, Ref. 10). Whether long-term regulation of these transporters may play a role in the long-term regulation of concentrating ability remains to be determined.

REFERENCES