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Physiology and pathophysiology of the vasopressin-mediated renal water reabsorption

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The connecting tubule and collecting duct are essential renal tubular segments for the regulation of body water homeostasis. Water reabsorption in these tubular segments is controlled by arginine vasopressin (AVP), which is a peptide hormone inducing osmotic water transport across the epithelia. In particular, AVP induces both intracellular trafficking of aquaporin 2 (AQP2)-containing vesicles to the apical plasma membrane and transcription of *Aqp2* gene to increase AQP2 protein abundance. The signaling pathways, including AQP2 phosphorylation, RhoA phosphorylation, intracellular calcium mobilization, and actin depolymerization, play a key role in the intracellular translocation of AQP2. Importantly, AVP actions are associated with the changes in phosphorylation of the AQP2 protein at four serine sites (S256, S261, S264, and S269) in the C-terminus. Phosphorylation of AQP2 could influence the interaction between AQP2-containing vesicles and cytoskeleton, microtubules, or accessory cross-linking proteins. Long-term regulation of AQP2 is presented by changing AQP2 protein abundance and dysregulation of AQP2 protein expression plays a critical role in the pathophysiology of both water-losing and water retention disorders. These long-term actions are thought to be associated with regulatory processes at the transcriptional or post-transcriptional level. Transcriptional regulation of AQP2 is mainly dependent on the vasopressin-induced increase in intracellular cAMP levels with concomitant activation of protein kinase A. Vasopressin increases the half-life of the AQP2 protein. AQP2 is degraded in the proteasome and lysosome. The process of endocytosis and subsequent targeting to the proteasome and lysosome is likely to be regulated by ubiquitylation of the C-terminal tail of the AQP2 protein at lysine 270. Identification of E3 ubiquitin-protein ligases specific to AQP2 degradation (e.g., NEDD4 and CHIP) is currently under the investigation. In addition to the transcriptional regulation of AQP2, microRNA (miRNA) appears to play a role in the post-transcriptional regulation. A recent in silico analysis predicted miRNAs regulating AQP2 expression (miR-32 and miR-137). Mutations in the AQP2 gene also lead to autosomal recessive nephrogenic diabetes insipidus in human patients. This talk will summarize recent data demonstrating the regulation of AQP2, as the underlying molecular mechanisms for body water homeostasis.