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9

Renal aquaporins and water balance disorders

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Aquaporins (AQPs) are a 13 member family (AQP0-12) of proteins that act as channels, through which water and, for some family members, glycerol, urea and other small solutes can be transported. Aquaporins are highly abundant in kidney epithelial cells where they play a critical role with respect to water balance. In this review we summarize the current knowledge with respect to the localization and function of AQPs within the kidney tubule, and their role in mammalian water homeostasis and the water balance disorders. Overviews of practical aspects with regard to differential diagnosis for some of these disorders, alongside treatment strategies are also discussed.

Introduction

Aquaporins (AQPs), facilitate regulated water transport. In the kidney, which plays a critical role in regulation of body water balance, numerous AQPs are expressed in the renal tubules (AQP1-8 and AQP11). However, only AQP1-4 and AQP7 have been proposed to play any role in body water balance and are the focus of this review (see [1] for alternative roles of AQPs in the kidney). Aided by the osmotic gradient generated by active NaCl transport in the thick ascending limbs and countercurrent multiplication, AQPs transport water across the tubular epithelium into the interstitium, thereby maintaining blood osmolality under varying degrees of water intake [2]. Dysfunction of several of these

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AQPs results in clinical conditions where body water balance is altered. This review provides an overview of what is currently known about renal AQPs and water balance disorders.

Aquaporin 1 (AQP1)

In the kidney, AQP1 is expressed constitutively in apical and basolateral membranes of renal tubular cells in the proximal tubule and descending thin limb of Henle in long looped nephrons where it reabsorbs the vast majority of filtered water [3]. AQP1 is also expressed in the vasa recta [4]. Although AQP1 trafficking or expression is not altered by the antidiuretic hormone arginine vasopressin (AVP) [5], deletion of AQP1 in mice causes severe polyuria (reviewed in [6]). However, humans lacking Colton blood antigens have defective AQP1, and these individuals are asymptomatic and only present with a mild urinary concentrating defect following water restriction [7]. Although the role of AQP1 in human kidney epithelial cells appears to be relatively minor, AQP1 is also expressed in kidney endothelial cells [4]. Of particular importance is the expression of AQP1 in the endothelium lining peritoneal capillaries [8], where it facilitates osmotically driven water transport during peritoneal dialysis. Peritoneal dialysis is a technique of renal-replacement therapy that is frequently used to restore water balance in patients with end-stage renal disease (reviewed in [9]). Enhancement of AQP1 function increases water transport across the peritoneal membrane, suggesting that pharmacological targeting of AQP1 would be beneficial in treatment of end-stage renal disease.

Aquaporin 2 (AQP2)

AQP2 is expressed in the principal cells of the kidney connecting tubule and collecting duct [10], where its apical membrane expression is regulated by AVP. In the kidney, AVP binds to the basolateral G-protein coupled type II AVP receptor (V2R), resulting in increased intracellular cAMP levels and altered intracellular signaling. This altered signaling results in regulated trafficking of AQP2 to the plasma membrane, and in the long term, increased AQP2 abundance [11,12]. Combined, these processes greatly increase water reabsorption. As V2R-mediated regulation of AQP2 plays a pivotal role in regulated water transport by the kidney, a large proportion of this article focuses on their role in water balance disorders (*see later*).

Aquaporin 3 (AQP3)

AQP3 is localized at the basolateral membrane of collecting duct principal cells and is permeable to both glycerol and urea [13]. Chronic AVP exposure increases AQP3 abundance [14]. Mice lacking AQP3 are polyuric, but have a partial ability to increase urine concentration in response to desmopressin (DDAVP) (reviewed in [6]).

Aquaporin 4 (AQP4)

In the kidney, AQP4 is localized mainly at the basolateral membrane of inner medulla collecting duct cells (IMCD) [15]. Long-term AVP exposure can increase AQP4 levels, but there are differential effects along the collecting duct system [16]. AQP4 knockout mice have a mild urinary concentrating defect, despite AQP4 being the major exit route for water in the IMCD (reviewed in [6]). AQP4 has the ability to form orthogonal arrays, which are proposed to be regulated differently and have different water permeabilities [17].

Aquaporin 7 (AQP7)

AQP7 is localized in the late proximal tubule brush border, where it facilitates glycerol and water transport [14]. AQP7 knockout mice have no defect in urinary concentrating ability, but have increased urinary glycerol, suggesting that the primary function of AQP7 is to scavenge glycerol from the preurine [18]. However, mice with combined deletion of AQP1 and AQP7 have a reduced urinary concentrating