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Review

Renal aquaporins and water balance disorders ☆

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ABSTRACT

Background: Aquaporins (AQPs) are a family of proteins that can act as water channels. Regulation of AQPs is critical to osmoregulation and the maintenance of body water homeostasis. Eight AQPs are expressed in the kidney of which five have been shown to play a role in body water balance; AQP1, AQP2, AQP3, AQP4 and AQP7. AQP2 in particular is regulated by vasopressin.
Scope of review: This review summarizes our current knowledge of the underlying mechanisms of various water balance disorders and their treatment strategies.
Major conclusions: Dysfunctions of AQPs are involved in disorders associated with disturbed water homeostasis. Hyponatremia with increased AQP levels can be caused by diseases with low effective circulating blood volume, such as congestive heart failure, or osmoregulation disorders such as the syndrome of inappropriate secretion of antidiuretic hormone. Treatment consists of fluid restriction, demeclocycline and vasopressin type-2 receptor antagonists. Decreased AQP levels can lead to diabetes insipidus (DI), characterized by polyuria and polydipsia. In central DI, vasopressin production is impaired, while in gestational DI, levels of the vasopressin-degrading enzyme vasopressinase are abnormally increased. Treatment consists of the vasopressin analogue dDAVP. Nephrogenic DI is caused by the inability of the kidney to respond to vasopressin and can be congenital, but is most commonly acquired, usually due to lithium therapy. Treatment consists of sufficient fluid supply, low-solute diet and diuretics.
General significance: In recent years, our understanding of the underlying mechanisms of water balance disorders has increased enormously, which has opened up several possible new treatment strategies. This article is part of a Special Issue entitled Aquaporins.

1. Introduction

Aquaporins (AQPs) are a family of small, approximately 30 kDa membrane proteins that act as semi-permeable channels. AQPs have been cloned from mammals, amphibians, plants, yeast, bacteria and various lower organisms. 13 mammalian aquaporins have been identified, named AQP0–12, which are expressed in various tissues such as the kidney, brain, liver, lungs and salivary glands [86]. Each AQP channel consists of six membrane spanning alpha-helices that have a central water-transporting pore [160,222]. Four AQP monomers assemble to form tetramers, which are the functional units in the membrane. Tetramers of one of the mammalian AQPs, AQP4, further assemble into supramolecular square arrays [252], which may further influence their activity and molecular regulation [57,215].

Although water can cross the lipid bilayer of biological membranes by simple diffusion, the water permeability of the membrane can be greatly enhanced by inserting AQPs. Besides water, a subset of the mammalian AQPs, the aquaglyceroporins AQP3, AQP7, AQP9 and AQP10 transport glycerol and urea [88–90,112], while both AQP7 and AQP9 are permeable for arsenite [137]. In addition, AQP9 has been shown to be permeable to a wide range of non-charged solutes, like mannitol, sorbitol, purines and pyrimidines [230]. AQP6 may function primarily as an anion transporter [85,253]. AQPs have also been proposed to transport other small molecules and gases, including carbon dioxide, ammonia, nitric oxide and hydrogen peroxide [149,162,242].

Maintaining water homeostasis by controlling both the blood osmolality and blood volume is essential for most physiological processes. Body water homeostasis is tightly controlled by regulating both water intake and urinary water excretion. In the kidney, 180 l of plasma is filtered by the human glomeruli each day [219]. Less than 1% of this volume is finally excreted in the urine. Approximately 67% of the filtered water is reabsorped in the proximal tubule and 15% in the descending thin limb of Henle, which both are constitutive processes. Depending on the body's needs, the remaining fluid can be reabsorbed in the connecting tubule and collecting duct, defining the final urine concentration. This process is tightly regulated, mainly by the hormone vasopressin (AVP), which allows the body to adapt to periods of water load or water restriction [219]. Eight of the AQPs are expressed in the

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kidney (Fig. 1) where several of them contribute to water absorption and maintenance of body water balance.

AQP1 is localized in the plasma membranes of proximal tubules, descending thin limbs of Henle and descending vasa recta [171,172,259]. AQP2, AQP3 and AQP4 are expressed in connecting tubule and collecting duct principal cells, where AQP2 is mainly expressed in the apical plasma membranes and membranes of intracellular vesicles, while AQP3 and AQP4 are localized to the basolateral plasma membranes [47,69,170,226]. AQP7 is localized in apical plasma membranes of the S3 segment of proximal tubules [87,166]. In contrast to these AQPs, AQP6, AQP8 and AQP11 are localized in intracellular membranes only and thus are unlikely to play a role in renal water reabsorption. AQP6 is localized in vesicles within intercalated cells of the connecting tubule and collecting duct [177,254]. AQP8 is localized intracellularly in proximal tubules and collecting ducts and AQP11 is localized to the endoplasmic reticulum of proximal tubules [50,157]. As AQP6, AQP8 and AQP11 have no known role in the urinary concentrating mechanism they will not be discussed further in this article, similar to the AQPs not expressed in the kidney, namely AQP0, AQP9, AQP10 and AQP12.

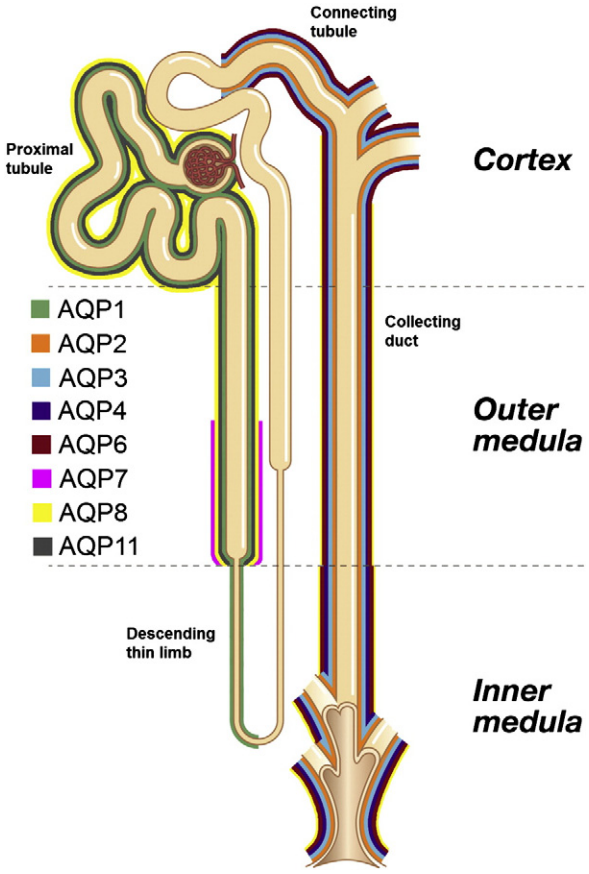

Fig. 1. Expression of renal aquaporins along the nephron. Blood is filtered at the glomerulus, and the filtrate is modified as it travels through the nephron to make the final urine. Most of the glomerular filtrate is reabsorbed through AQP1 in the proximal tubule and descending thin limbs of Henle, although AQP7 is also expressed in the S3 segment of the proximal tubule. AQP1 is also expressed in the descending vasa recta, facilitating the removal of water. In the connecting tubule and collecting duct, AQP2 is mainly expressed at the apical membrane and intracellular vesicles of principal cells, while AQP3 and AQP4 are present at the basolateral membrane of the principal cells, representing exit pathways for water reabsorbed via AQP2. In contrast to these AQPs, AQP6, AQP8 and AQP11 are localized in intracellular membranes only. AQP6 is localized to intercalated cells of the collecting duct and connecting tubule, AQP8 is expressed in proximal tubules and weakly in collecting ducts, while AQP11 is localized to proximal tubules.

1.1. Aquaporin 1 (AQP1)

AQP1 is localized to the apical and basolateral membrane of epithelial cells in the proximal tubule [172], where the majority of fluid filtered by the glomerulus is reabsorbed by an active near-isosmolar transport mechanism. AQP1 is also expressed in the descending thin limb of long looped nephrons, but not short-loop nephrons, and the descending vasa recta [171,259]. AQP1 expression is constitutively high, but it can be modulated by hypertonicity and angiotensin II [21]. The classical antidiuretic hormone AVP does not regulate the expression of AQP1 [227].

AQP1 plays an essential role in maintaining body water balance, which is highlighted by the severe renal phenotype of AQP1 gene knockout mice. AQP1 knockout mice have a reduced urinary osmolality compared with wild-type mice, which is not increased in response to water deprivation or injection of the synthetic vasopressin analogue dDAVP (1-desamino-8-D-arginine vasopressin, Desmopressin) [142]. AQP1 knockout mice become severely dehydrated after water deprivation, manifesting marked serum hyperosmolality and lethargy. The urinary concentrating defect observed in these mice is likely due to a combination of different mechanisms. The transepithelial osmotic water permeability of isolated microperfused S2 segments of the proximal tubule was fivefold less in AQP1 knockout mice, indicating that the major pathway for transepithelial water transport in the proximal tubule is AQP1 dependent [211]. In addition, the rate of proximal fluid reabsorption in AQP1 knockout mice was approximately 50% reduced relative to controls; although micropuncture flow measurements of distal nephron segments revealed that the single-nephron glomerular filtration rate of AQP1 knockout mice was also reduced thereby reducing distal fluid delivery to near-normal values [211]. Osmotic water permeabilities of microperfused thin descending limb of Henle and outer medullary descending vasa recta are reduced in AQP1 knockout mice as well [29,179]. The decreased water permeability in the thin limbs and vasa recta is predicted to reduce countercurrent multiplication and counter current exchange, respectively. This indicates that AQP1 deletion produces a urinary concentrating defect in mice primarily by preventing the formation of a hypertonic medullary interstitium. This conclusion is supported by the absence of an increase in urine osmolality in AQP1 knockout mice after dDAVP stimulation of collecting duct water permeability [142].

Consistent with the findings in AQP1 knockout mice, it was observed that humans with loss-of-function mutations in AQP1 have an impaired ability to concentrate their urine maximally when challenged by water deprivation [109].

1.2. Aquaporin 2 (AQP2)

AQP2 is abundantly expressed in the principal cells along the whole connecting tubule and collecting duct, where it is localized to the apical plasma membranes and intracellular membrane vesicles [69,170]. Although AQP2 is predominantly associated with the apical plasma membrane, AQP2 is to some extent found in the basolateral plasma membrane, especially in the connecting tubule and inner medulla collecting duct [33]. Abundance and cellular localization of AQP2 are regulated by a variety of hormones and signaling molecules, including AVP. In states of hypernatremia or hypovolemia, AVP is released from the posterior pituitary gland into the bloodstream [9,12,236]. AVP regulates the body's retention of water, increasing both the osmotic driving force for water reabsorption and the transcellular route for water transport, causing the kidneys to concentrate the urine. The transcellular route of regulation mainly occurs via modulating cell surface expression of AQP2. AVP binds to the vasopressin type-2 receptor (V2R), present in the basolateral membrane of renal collecting duct principal cells and connecting tubule cells [55,163], inducing a signaling cascade, involving Gs protein mediated activation of adenylate cyclase, a rise in intracellular cAMP, activation of protein kinases, and redistribution

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