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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

☆ This article is part of a Special Issue entitled Aquaporins.

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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.

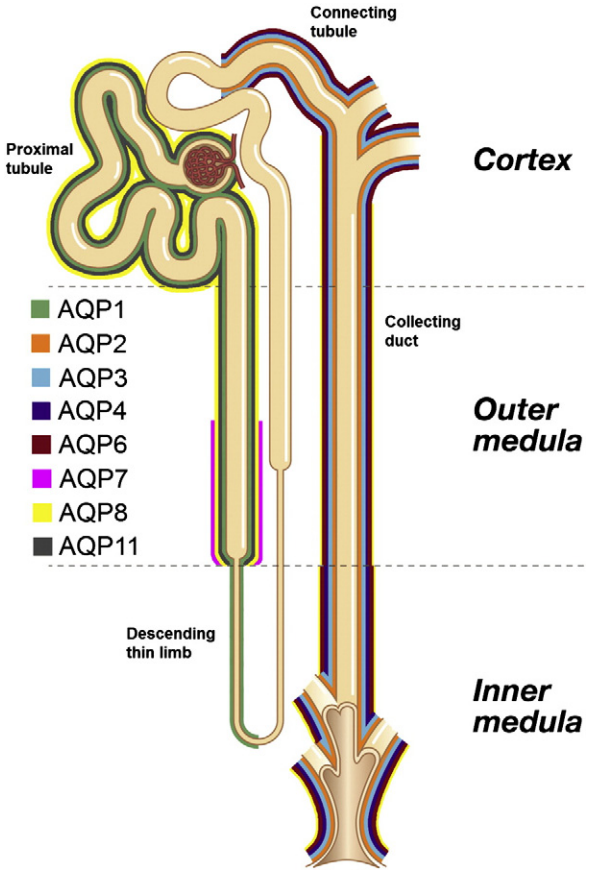

Fig. 1. Expression of renal aquaporins along the nephron. Blood is filtered at the glomerulus, and the filtrate is modified as it travels through the nephron to make the final urine. Most of the glomerular filtrate is reabsorbed through AQP1 in the proximal tubule and descending thin limbs of Henle, 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

of AQP2 water channels from intracellular vesicles to the apical membrane [104,122,169]. This greatly increases the rate limiting water permeability of the apical plasma membrane (see Fig. 2) [60,221]. Driven by the transcellular osmotic gradient of sodium and (in the medulla) urea, water enters the principal cells through AQP2 and leaves the cells through the basolateral membrane via AQP3 and AQP4 [47,226]. The overall process results in a concentration of the urine. Once the water balance is restored AVP levels drop and AQP2 is internalized, which returns the apical membrane water permeability to basal levels. AQP2 is retrieved to intracellular vesicles, resulting in either lysosomal degradation or intracellular storage and relocation to the plasma membrane upon re-stimulation with AVP [101,103].

A number of post-translational modifications of AQP2 are required for the shuttling of AQP2 to/from the apical plasma membrane (see for extensive review [153]). AQP2 can be phosphorylated at five residues, Thr 244, Ser256, Ser261, Ser264 and Ser269 (Thr269 in human AQP2, see Fig. 3) [82,83]. The role of Thr244 phosphorylation is unknown. Ser256, Ser264 and Ser269 phosphorylation are increased in abundance upon administration of dDAVP, phosphorylation of Ser261 is decreased [56,80,81]. AQP2 phosphorylated at either site shows distinct subcellular localizations. Phosphorylated Ser261-AQP2 is mainly found in intracellular vesicles and seems to be absent from the plasma membrane [81]. Phosphorylated Ser256-AQP2 and Ser264-AQP2 reside in intracellular vesicles and the plasma membrane, and upon treatment with dDAVP there is a change in distribution (or increase in abundance) to the plasma membrane [34,56]. Phosphorylated Ser269-AQP2 is solely found in the apical plasma membrane of principal cells [152]. The roles of each phosphorylation site in AQP2 function have been widely studied. Ser256 is phosphorylated by protein kinase A (PKA) upon AVP stimulation and this phosphorylation is essential for trafficking to the plasma membrane [68,104,233]. A study using oocytes as a model system for exogenous AQP2 expression showed that phosphorylation at Ser256 of at least three of four monomers of an AQP2 tetramer is needed to redistribute AQP2 tetramers from storage vesicles to the apical plasma membrane [100]. Other functions of AQP2 phosphorylation are thought to be apical plasma membrane retention of AQP2 [80] and interaction of AQP2 with proteins participating in the endocytic machinery [154] for Ser269 phosphorylation, while phosphorylation at Ser261 is thought to stabilize AQP2 ubiquitination [224]. In addition to phosphorylation, AQP2 is also modified by ubiquitination at Lys270 [101]. Ubiquitination of AQP2 is believed to mediate the endocytosis of AQP2 from the plasma membrane upon AVP removal.

In addition to playing an acute role in AQP2 localization, the AVP-mediated increase in cAMP also increases AQP2 expression via PKA-mediated phosphorylation of the cAMP responsive element binding protein (CREB) that subsequently stimulates transcription from the AQP2 promoter [84,148,255]. The increase in transcription requires hours to take effect [75,227]. The PKA–CREB pathway is involved in the initial rise in AQP2 levels after AVP stimulation, but not in the long-term effect of AVP [119]. Instead, long-term regulation of AQP2 abundance may involve the activation of the Exchange factor directly activated by cAMP (EPAC) [119]. EPAC might also play a role in the regulation of AQP2 localization, as perfusion of mouse inner medullary collecting ducts with an EPAC activator resulted in translocation of AQP2 to the apical membrane, which coincided with intracellular increases in Ca^{2+} [257].

Besides AVP, several other factors stimulate AQP2 abundance or translocation, for example extracellular tonicity, insulin or long-term aldosterone stimulation [23,76,77], while other factors decrease AVP-induced AQP2 expression or trafficking, like extracellular purines, prostaglandins and dopamine [18,167,245,258] (see for review [16]). Although prostaglandins antagonize AVP-induced water permeability, prostaglandins increase the translocation and abundance of AQP2 in the absence of high levels of AVP [133,178].

Studies on transgenic mice have demonstrated an essential role of AQP2 in water handling. Total AQP2 gene deletion in mice is lethal within the first few days of life [199]. In addition, mice with a Thr126Met mutation in the AQP2 gene, shown to result in a failure of delivery of mature AQP2 protein to the apical plasma membrane [223], also die within one week after birth [250]. Mice with collecting duct specific AQP2 knockout have polyuria and growth retardation, but are viable to adulthood, as are mice with an inducible AQP2 gene deletion resulting in >95% reduction of renal AQP2 [199,251]. Both mice models have

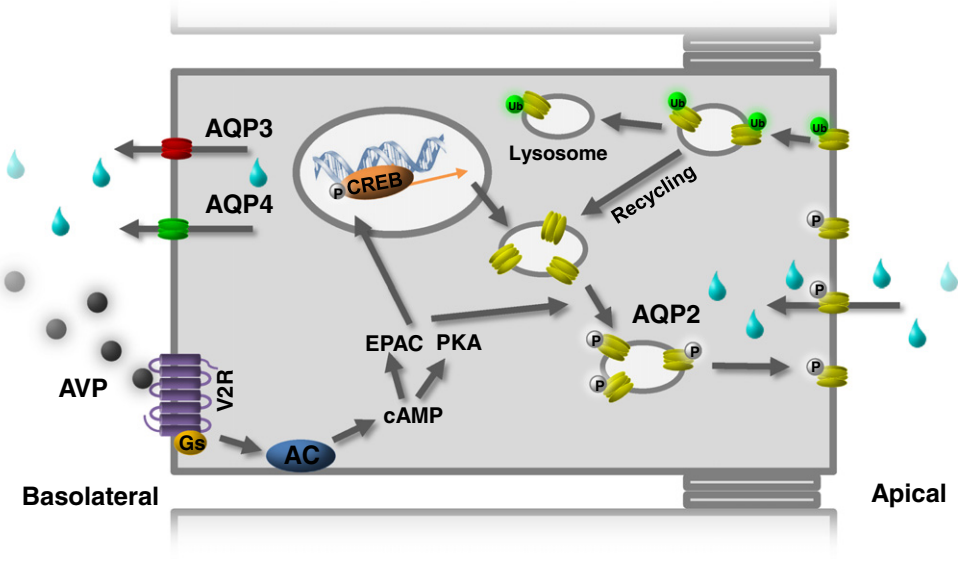

Fig. 2. Regulation of AQP2-mediated water reabsorption. AVP binds to the vasopressin type-2 receptor (V2R), present on the basolateral membrane of renal collecting duct principal cells and connecting tubule cells. This induces a signaling cascade, involving Gs protein mediated activation of adenylate cyclase, a rise in intracellular cAMP, activation of protein kinase A (PKA) and possibly the Exchange factor directly activated by cAMP (EPAC), and subsequent phosphorylation of AQP2 at Ser256. This results in the redistribution of AQP2 from intracellular vesicles to the apical membrane. Driven by the transcellular osmotic gradient, water then will enter principal cells through AQP2 and enters the blood via AQP3 and AQP4 water channels, which are expressed in the basolateral membrane, resulting in concentrated urine. On the long term, vasopressin also increases AQP2 expression via phosphorylation of the cAMP responsive element binding protein (CREB), which stimulates transcription from the AQP2 promoter. Once the water balance is restored, AVP levels drop and AQP2 is internalized via ubiquitination. Internalized AQP2 can either be targeted to recycling pathways or to degradation via lysosomes.

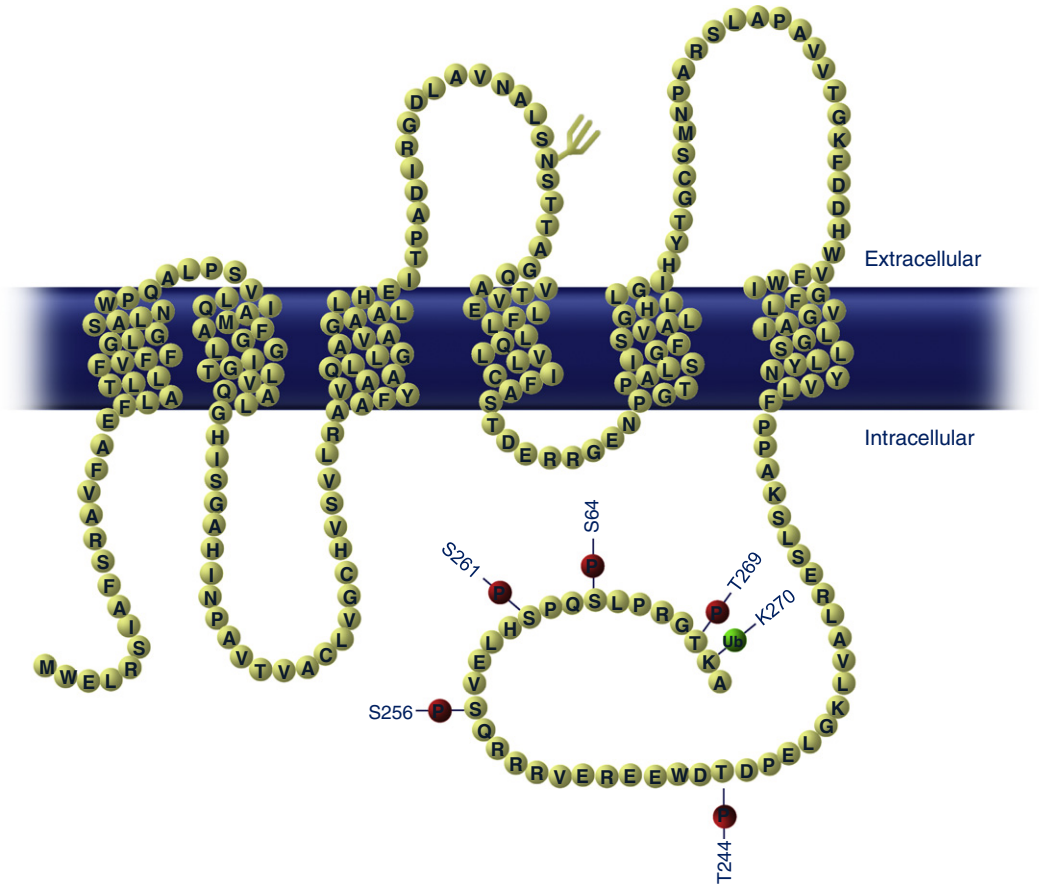

Fig. 3. Schematic representation of the human AQP2 protein. AQP2 is a 271 amino acid protein that is predicted to have six transmembrane domains with its N- and C-terminus intracellular. The ubiquitination site (Ub) and phosphorylation sites (P) in the C-terminus are indicated.

severe polyuria, accompanied by a very low urine osmolality. Water deprivation does not increase the urine osmolality in these mice. Specific deletion of AQP2 in the mouse connecting tubules results in a 1.5-fold increase in urine volume and a similar fold-decrease in urine osmolality [116], highlighting that AQP2 in the connecting tubules plays an important role in maintaining normal urine output. However, in contrast to the collecting duct specific knockout, these mice can concentrate their urine under conditions of increased circulating AVP, pointing towards the collecting duct having the major role in AVP-mediated antidiuresis, whereas the connecting tubule has a moderate, yet still significant contribution to water conservation. Alternatively, dysfunction of the connecting tubule can be compensated for by increased water reabsorption in the collecting duct. Although a loss-of-function mutation in the AQP2 gene is not lethal in humans, it does lead to a severe urinary concentrating defect known as NDI, confirming the importance of AQP2 in renal water handling [194].

1.3. Aquaporin 3 (AQP3)

AQP3 is localized to the basolateral membrane of the connecting tubule and collecting duct principal cells [37,47,91] and is thought to represent an exit pathway for water reabsorbed via AQP2. There is no evidence for short-term regulation of AQP3 by AVP-induced trafficking. However, prolonged increased AVP levels, as seen during water deprivation or AVP infusion, increase AQP3 protein and mRNA levels both in cortex and medulla [47,91,161,227].

AQP3 has been shown to be important for the urine concentrating mechanism, as AQP3 knockout mice have an increased urine volume, lower urine osmolality and a reduced osmotic water permeability of the basolateral membrane of the cortical collecting duct [140]. In addition, AQP2 expression in the cortical collecting duct of AQP3 knockout mice is decreased. AQP3 knockout mice are however able to modestly raise their urine osmolality after water deprivation or administration of dDAVP, which might be due to the expression of basolateral AQP4 or AQP2 in the same cells. In agreement with this, AQP3/AQP4 double-knockout mice have a greater impairment of urinary-concentrating ability than the AQP3 single-knockout mice [140].

Although AQP3 is permeable for both urea and glycerol, and the glycerol-transporting function of AQP3 has been shown to play an important role in skin hydration, the physiological role of renal AQP3-mediated glycerol or urea transport has not been delineated in detail. AQP3 knockout mice do however develop hypotriglyceridemia, which may be related to the glycerol-transporting function of AQP3 [140].

1.4. Aquaporin 4 (AQP4)

AQP4 is localized in the basolateral membrane of the principal cells in the connecting tubule and collecting duct, with highest levels in the inner medullary collecting duct, where it acts as an additional exit pathway for water reabsorbed via AQP2 [37,150,226]. In mice, AQP4 has been reported to be expressed in the basolateral plasma membrane of proximal tubule S3 segments as well, which may be species-dependent, as no AQP4 expression was detected in the human or rat S3 segment [235]. Rat AQP4 has six isoforms, formed by alternative splicing, of which three isoforms have been demonstrated to transport water: M1 consisting of 323 amino acids, the shorter M23 consisting of 301 amino acids, and the longer Mz consisting of 364 amino acids [151]. The M23 isoform gives rise to formation of supramolecular square arrays [67].

After prolonged increased AVP levels, no increase was found in AQP4 protein expression in the renal inner medulla, where AQP4 expression is constitutively high [226,227]. However, AQP4 mRNA was increased in the cortex, where unstimulated expression of AQP4 is low, and treatment with a V2R antagonist partly inhibited this increase in AQP4, suggesting a regulation of AQP4 by AVP [161]. In AVP-deficient Brattleboro rats, long-term administration with dDAVP increases AQP4 protein abundance in the connecting tubule, cortical collecting duct and outer part of the inner medullary collecting duct, while decreasing AQP4 abundance in the middle and inner segments of the inner medullary collecting duct [183]. In addition, chronic AVP infusion of Brattleboro rats increases the short AQP4 splice form M23, which has been associated with the formation of orthogonal arrays, and decreases the long splice form M1 [234].

Microperfused inner medullary collecting ducts of AQP4 knockout mice have a 4-fold reduced water permeability, indicating that AQP4 is responsible for the majority of basolateral water transport in the inner medullary collecting duct [30]. However, AQP4 knockout mice do not have a difference in urine osmolality compared to wild-type mice under basal conditions [141]. After water deprivation, urine osmolality was significantly reduced in AQP4 knockout mice compared to wild-type mice, and this could not be further increased by dDAVP administration, indicating that AQP4 knockout mice have a mild urinary concentrating defect. The large decrease in inner medullary water permeability and very mild impairment in maximal urinary concentrating ability in the AQP4 knockout mice suggests that the majority of collecting duct water reabsorption occurs in segments proximal of the inner medullary collecting duct, which is in agreement with micropuncture studies, showing that under antidiuretic conditions the amount of water reabsorbed in the late distal tubule (connecting tubule and initial collecting duct) is much larger than that absorbed in the medullary nephron [125].

1.5. Aquaporin 7 (AQP7)

AQP7 is expressed in the apical brush border of the S3 segment of the proximal tubule, a segment also expressing AQP1 [87,166]. Osmotic water permeabilities in apical membrane vesicles isolated from the proximal tubule of AQP7 knockout mice are slightly reduced [217]. However, AQP7 knockout mice do not exhibit an impaired urinary concentrating ability, which may be related to the abundant expression of AQP1 throughout the proximal tubule and descending thin limb. This idea is confirmed in AQP1–AQP7 double knockout mice, which have a significantly greater urine output accompanied by a proportional decrease in urine osmolality compared with AQP1 knockout mice, suggesting that the amount of water reabsorbed through AQP7 in the proximal straight tubules is physiologically substantial. AQP7 is an aquaglyceroporin, transporting both water and glycerol. AQP7 knockout mice show significantly increased renal glycerol excretion [217] and the main physiological role of AQP7 in the kidney might therefore be related to glycerol, rather than water, reabsorption.

2. Water homeostasis-associated pathologies

2.1. Water balance disorders associated with increased aquaporin levels

Disturbances of water balance occur frequently, and are characterized by hyponatremia, hypernatremia or polyuria. Several of these pathologies result from too high or too low levels of renal AQPs, mainly AQP2. Hyponatremia with high AQP2 abundance can be caused by osmoregulation disorders, but is most frequently caused by diseases with low effective circulating blood volume. Since in these conditions, maintaining volume balance overrules osmoregulation, development of hyponatremia is the mere consequence of the body's goal to maintain circulating volume.

2.1.1. Congestive heart failure

Congestive heart failure (CHF) is characterized by high levels of AVP that contribute to hyponatremia and increased extracellular volume [212]. Excretion of AQP2 is increased in the urine of CHF patients [181]. In CHF rat models, there are increased renal AQP2 levels and a marked redistribution of AQP2 to the apical plasma membrane [136,173,249], whereas AQP1 levels are unaltered and AQP3 levels are slightly decreased, indicating that the effect on AQP2 in CHF is selective [173]. Treatment of CHF rats with the V2R antagonist Mozavaptan inhibited the upregulation and trafficking of AQP2, and led to diuresis and a rise in plasma osmolality, indicating a major role for AQP2 in CHF-induced water retention [249]. In agreement with these animal data, V2R antagonists have been shown to increase diuresis and correct hyponatremia in CHF patients [6,70,213,248].

2.1.2. Hepatic cirrhosis

Hepatic cirrhosis is a chronic condition associated with water retention, hyponatremia and increased AVP levels [212]. The most important factor contributing to the development of hyponatremia in patients with cirrhosis is thought to be systemic vasodilation, which leads to increased AVP secretion and consequently water retention and hyponatremia. Unlike CHF, the changes in AQP2 protein levels vary considerably between different experimental models of hepatic cirrhosis. In several studies of rat models of liver cirrhosis induced by carbon tetrachloride, increased AQP2 protein and mRNA levels were found [8,66]. The mRNA expression of AQP2 in the kidney was furthermore found to correlate significantly with the volume of ascites in cirrhotic rats, suggesting that AQP2 plays an essential role in abnormal water retention followed by the development of ascites in liver cirrhosis [8]. In another study, total AQP2 levels were not changed, but an increase in plasma membrane expression of AQP2 was observed, as well as an increase in the expression of AQP1 and AQP3 [58]. In contrast, a rat model of liver cirrhosis induced by chronic common bile duct ligation displayed decreased levels of AQP2, AQP3 and AQP4, and unchanged levels of AQP1, suggesting that excessive water retention with hyponatremia can occur in the absence of increases in renal aquaporins [59].

Studies in cirrhosis patients have demonstrated a higher abundance of AQP2 in the urine compared to control subjects [36,94]. AQP2 levels were increased with the clinical severity of the cirrhosis and levels were found to be highest in patients with ascites, suggesting an essential role for AQP2 in cirrhosis-induced water retention. However, other studies have demonstrated no increase, or even a decrease, in urinary AQP2 in cirrhosis patients [51,181]. An explanation for the differences found between these studies is at present lacking.

2.1.3. Syndrome of inappropriate secretion of antidiuretic hormone

One disorder of disturbed osmoregulation is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The most common causes of SIADH are neoplasia (notably small-cell lung cancer), neurological diseases, lung diseases and a wide variety of drugs, particularly psychoactive drugs and chemotherapy [13]. In SIADH, AVP levels are abnormally increased, leading to excessive renal water reabsorption, which can result in life-threatening hyponatremia [180]. In a rat model of SIADH, AQP2 mRNA and protein levels are markedly increased. These increases can be blocked by a V2R antagonist, which correlates closely with a marked diuresis and a normalization of serum sodium levels; indicating that AQP2 plays an important role in water retention and development of hyponatremia in SIADH [66]. SIADH patients are normovolemic or slightly hypervolemic and most patients show excessive release of AVP that is totally unrelated to plasma osmolality, caused by for example ectopic AVP production by neoplasms. Other patients continue to regulate water excretion normally, but do so around a lower plasma osmolality set-point compared to normal. The underlying mechanism of this is unclear [13].

2.1.4. Nephrogenic Syndrome of Inappropriate Antidiuresis

Another origin of normovolemic hyponatremia is the Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD). The clinical presentation of NSIAD resembles those of SIADH and consists of hyponatremia and the lack of urinary dilution. However, in contrast to SIADH, the AVP levels in plasma are undetectable or very low [128]. NSIAD is a rare disorder in water balance caused by a mutation in the *AVPR2* gene, encoding the V2R. The mutation usually results in a change in amino acid 137 from an arginine into a cysteine or a leucine [53] (Fig. 4), although recently, an infant with NSIAD was shown to harbor a Phe229Val mutation [26]. These mutations cause the constitutive activation of the receptor, with the basal ability of the mutant V2R to induce cAMP increased compared to the wild-type V2R [26,53,225]. This gain of function due to constitutive activation of the V2R explains the inappropriate antidiuresis. In contrast, a change in amino acid 137 into a histidine, probably resulting in elevated V2R endocytosis, leads to the opposite disease phenotype with a loss of the kidney's ability to concentrate urine and nephrogenic diabetes insipidus [10]. NSIAD is an X-linked genetic disease (the *AVPR2* gene is located on the X chromosome), affecting mainly males. Although female carriers of the mutation are clinically asymptomatic, some of them demonstrate an impaired ability to dilute urine during a water-load test [42,189].

2.2. Water balance disorders associated with decreased aquaporin levels

Diabetes insipidus (DI) is characterized by an impaired renal water reabsorption, leading to polyuria and consequently, polydipsia. DI can present with hypernatremia, but patients most often have a normal plasma osmolality, provided the thirst mechanism is normal and there is adequate access to fluid.

2.2.1. Central DI

In central DI, also known as neurohypophysial DI, normal AVP production is impaired. AVP is produced by the magnocellular neurons of the supraoptic nucleus of the hypothalamus. Magnocellular neurons containing AVP project axons to the posterior pituitary gland, where they release AVP into the bloodstream upon activation [236]. Central DI can be congenital, but is usually acquired as a consequence of local inflammatory or autoimmune diseases, vascular diseases, Langerhans cell histiocytosis, sarcoidosis, intracranial tumors or trauma resulting from surgery or an accident [44]. In a model of central DI, the AVP-deficient Brattleboro rat, there is decreased expression of AQP2, which can be reversed by chronic AVP infusion; suggesting that patients lacking AVP are likely to have decreased AQP2 expression that can be treated by AVP administration [45]. In agreement with this, central DI patients excrete lower amounts of AQP2 in the urine and AQP2 excretion remains unchanged after hypertonic saline infusion, but increases after exogenous AVP administration [204,205]. As AVP regulates other proteins involved in urine concentration, such as AQP3 and AQP4 in connecting tubules and collecting ducts, urea transporters in inner medullary collecting ducts and the loop of Henle and the Na–K–Cl cotransporter 2 (NKCC2) in the thick ascending limb, these proteins are expected to also be affected in central DI patients. Administration of the synthetic AVP homolog dDAVP is usually able to drastically decrease urine output in central DI patients.

2.2.2. Familial neurohypophysial DI

The rarest form of central DI is familial neurohypophysial DI (FNDI), which is in almost all cases caused by an inherited mutation in the AVP gene. The AVP gene encodes a 164 long precursor peptide, consisting of a signal peptide, AVP, neurophysin II and copeptin. This precursor is enzymatically cleaved to form active AVP [124]. At least 70 different mutations resulting in a defective precursor peptide and a deficiency of active AVP have been identified in FNDI. All except a few, these mutations show an autosomal dominant pattern of inheritance (http://www.hgmd.org [5]). Most of the mutations are located in either the signal peptide or the neurophysin II moiety (Fig. 5). FNDI is characterized by severe polyuria and polydipsia. Although the carriers are normal at birth, symptoms of compulsive drinking and polyuria appear typically between the ages of 1 and 6 years of age, despite the existence of one normal allele. The mechanism by which the mutation causes FNDI is thought to involve the accumulation of mutant AVP precursor in the endoplasmic reticulum (ER), resulting in an aberrant endoplasmic morphology and possible cell dysfunction and death [5,92,202]. Mutant precursors also impair intracellular trafficking of the wild-type AVP precursor by forming heterodimers, thereby reducing the

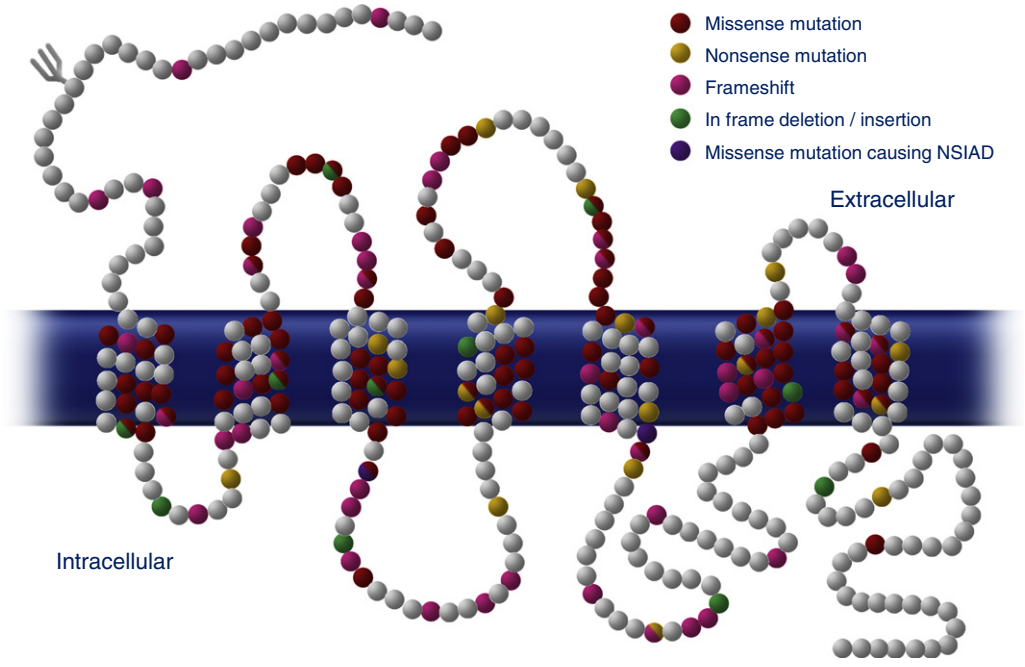

Fig. 4. Schematic representation of the V2R protein. Mutations causing NDI or NSIAD are indicated. Mutations affecting splicing, complex rearrangements and gross deletions and insertions are not shown.

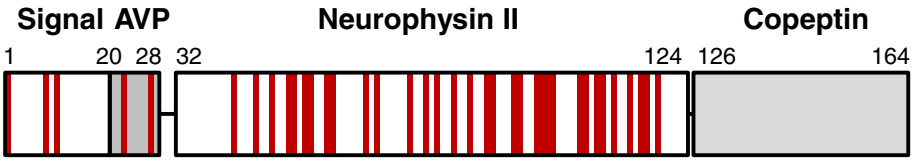

Fig. 5. Schematic of the peptide precursor of AVP. The precursor consists of a signal peptide, AVP, neurophysin II and copeptin. Numbers indicate amino acids of the human protein. The location of mutations causing FNDI is indicated in red.

bioavailability of active AVP by means of a dominant negative effect [5,93].

Patients with an autosomal recessive pattern of inheritance have a missense mutation in the region encoding the AVP domain and symptoms in these patients appear to be secondary to the reduced biological activity of the mutant AVP peptide [1,246]. In contrast to other forms of central DI, circulating AVP levels in these patients are high. In one family with autosomal dominant FNDI no mutations in the coding region, introns or the promoter of the AVP gene were found [256]. Linkage analysis indicated that the corresponding gene(s) responsible for FNDI in this family was/were located in a 7-cM interval on chromosome 20, implying a genetic diversity in the cause of FNDI.

2.2.3. Gestational DI

Another form of DI, gestational DI, is a transient form of DI that can occur during pregnancy. Gestational DI is due to an abnormal increase in vasopressinase, an AVP-degrading enzyme produced by the placenta, leading to AVP deficiency [4]. This form of DI may be associated with preeclampsia and HELLP syndrome (consisting of Hemolysis, Elevated Liver enzymes, and Low Platelets), possibly because the decreased hepatic function in these conditions leads to a decrease in vasopressinase degradation [74,105,165]. Since dDAVP is resistant to degradation by vasopressinase, it is an effective treatment for gestational DI [4].

2.2.4. Nephrogenic DI

Nephrogenic DI (NDI) is caused by the inability of the kidney to respond to AVP stimulation. NDI can be congenital or acquired. Congenital NDI can be divided into X-linked, autosomal recessive and autosomal dominant NDI. In congenital NDI patients, the urine concentrating defect is present from birth, and symptoms usually arise during the first weeks of life.

2.2.5. Congenital NDI

X-linked congenital NDI is caused by loss-of-function mutations in the *AVPR2* gene, encoding the V2R [138]. More than 90% of all congenital NDI patients suffer from X-linked NDI. Over 220 *AVPR2* gene mutations have been described to cause NDI (http://www.hgmd.org), see Fig. 4. Mutations in the *AVPR2* gene interfere with receptor signaling, thus making the principal cells of the collecting duct insensitive to AVP and resulting in a severe urinary concentration defect. The molecular mechanism underlying this insensitivity differs among mutants. The most common mechanism is misfolding of the protein caused by a missense mutation and consequently retention in the ER. Other mechanisms include mRNA instability, splicing errors, frameshifts or nonsense mutations resulting in truncation of the receptor, diminished binding of the Gs protein, reduced affinity for AVP, and misrouting of the V2R to different organelles in the cell [194]. X-linked NDI occurs mainly in males, however, due to skewed X-chromosome inactivation, some heterozygous females have variable degrees of clinical NDI symptoms [7,209].

Approximately 10% of the patients diagnosed with NDI have mutations in the *AQP2* gene. In more than 90% of patients there is evidence of autosomal recessive inheritance. In total, 52 AQP2 mutations have currently been described, of which 44 are involved in recessive NDI (http://www.hgmd.org), see Fig. 6. Of this group, 82% comprises

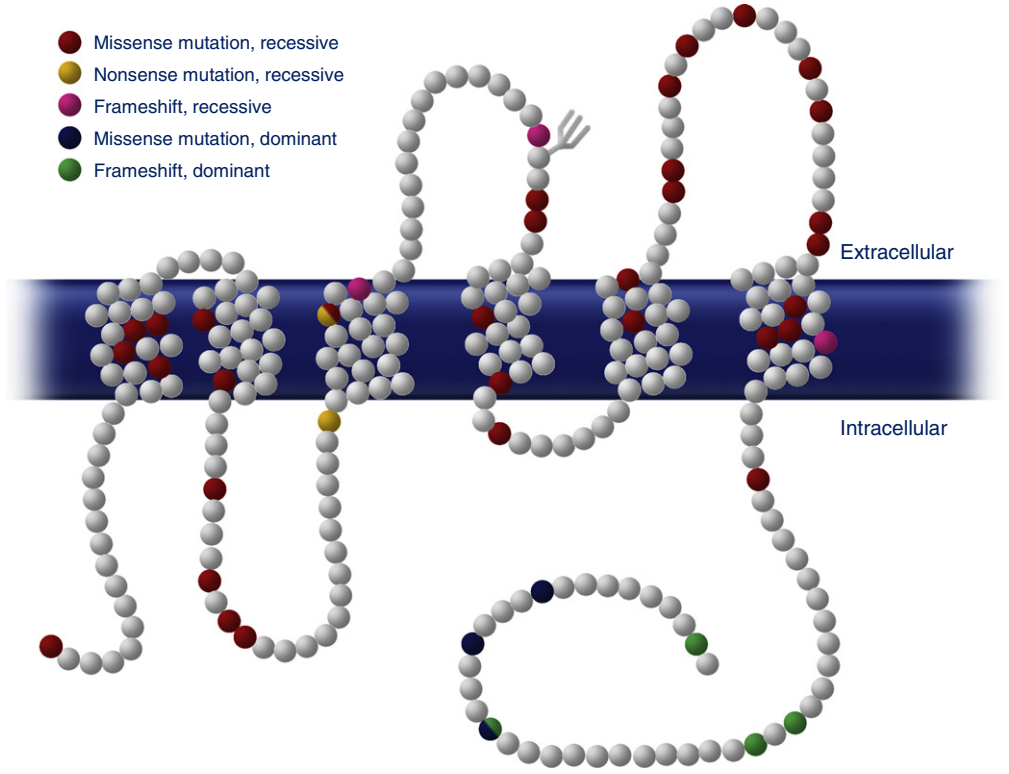

Fig. 6. Schematic representation of the AQP2 protein. Mutations causing NDI are indicated. Mutations affecting splicing are not shown.

missense mutations. The majority of mutations are found in between the first and the last transmembrane domain of AQP2 that forms the channel water pore. Nearly all mutations cause misfolding of the protein, which is consequently trapped in the ER, and rapidly degraded by the proteasome [194]. In agreement with extensive degradation, AQP2 could not be detected in the urine of recessive NDI patients [43]. Although AQP2 mutants are retained in the ER, overexpression in oocytes, where a fraction of the AQP2 mutants escape the cell's quality control system to the plasma membrane, revealed that several AQP2 mutations are able to function as water channels [25,146,147,159]. The healthy parents of patients with recessive NDI express both mutant and wild-type AQP2 proteins. However, since these AQP2 mutants are not able to form heterotetramers with wild-type AQP2, this leaves only the formation of the functional wild-type AQP2 homotetramers, likely explaining the healthy phenotype of the parents [102].

Currently, 8 different AQP2 mutations have been described to cause autosomal dominant NDI, the least occurring form of hereditary NDI. The mutations identified comprise missense mutations and small nucleotide deletion or insertions, see Fig. 6. All mutations are found in the carboxyl-terminal tail of AQP2, which is essential for correct intracellular routing of the protein. Dominant AQP2 mutants are able to form heterotetramers with wild-type AQP2 and are, due to the mutation, missorted to other cellular organelles than the apical plasma membrane e.g. late endosomes/lysosomes and the basolateral plasma membrane [102,194]. Since wild-type AQP2 is retained in mixed tetramers and also missorted, water reabsorption is severely affected, which explains the dominant mode of inheritance of NDI in these patients. Six of the mutations introduce a missorting signal, the remaining two, Arg254Leu and Arg254Gln, interfere with Ser256 phosphorylation of AQP2 and prevent the translocation of AQP2 to the plasma membrane and thus impair water reabsorption [41,210]. Heterozygous dominant NDI patients display generally milder symptoms than recessive NDI patients, suggesting that some wild-type AQP2 homotetramers are formed that are able to reach the apical plasma membrane [194].

Although mutations in the carboxyl tail of AQP2 are usually associated with dominant NDI, one mutation, Pro262Leu, causes recessive NDI. Like dominant NDI mutants, Pro262Leu-AQP2 is missorted to intracellular vesicles and is able to form heterotetramers with wild-type AQP2 [40]. However, when co-expressed with wild-type AQP2, wild-type/Pro262Leu-AQP2 complexes are targeted to the apical membrane of MDCK cells. This indicates that, in contrast to AQP2 mutants in dominant NDI, the apical sorting signal of wild-type AQP2 overrules the sorting signal in Pro262Leu-AQP2, thereby explaining the recessive NDI inheritance.

In contrast to subjects with AQP2 mutations, only a handful of subjects have been identified with loss-of-function mutations in other AQPs. Humans lacking functional AQP1 do not have polyuria and no obvious clinical phenotype under normal conditions. However, when challenged by water deprivation they have an impaired ability to concentrate their urine maximally [109]. Under non-stressed conditions, AQP3 null individuals do not suffer from any clear clinical abnormality [200]. Three unrelated children with a homozygous Gly264Val mutation in the AQP7 gene, which previously has been shown in oocytes to result in a lack of both water and glycerol permeability, were shown to have psychomotor retardation of unknown etiology, a mild platelet secretion defect and pronounced renal glycerol loss [73,113]. However, future studies are needed to investigate if individuals with defective AQP3 or AQP7 show a defective urinary concentrating ability. Human gene mutations abolishing AQP4 function have not been reported.

2.2.6. Electrolyte disorders

In contrast to the rare inherited forms of NDI, acquired forms of NDI are much more common. Hypokalemia and hypercalcemia, two common electrolyte disorders, cause NDI [71,201]. The precise underlying molecular mechanisms of hypokalemia- and hypercalcemia-induced NDI remain to be resolved. In rat models of hypokalemia the condition is associated with a decreased AQP2 mRNA and protein expression [98,145]. Besides AQP2, hypokalemia also decreases the expression of renal urea and sodium transporters in the distal nephron, which may contribute to the urinary concentrating defect by reducing interstitial tonicity [49,98,99].

Hypercalcemia decreases AQP2 abundance in rats also, but does not affect AQP2 mRNA levels; indicating that the effect is independent of AQP2 transcription but may result from increased AQP2 degradation or decreased AQP2 translation. Hypercalcemia also decreased the fraction of AQP2 at the apical membrane, suggesting an effect on AQP2 targeting [46]. Hypercalcemic rats have decreased AQP1 and AQP3 levels, while AQP4 levels were unchanged [239]. In addition, hypercalcemia has been shown to decrease the expression of renal sodium transporters such as NKCC2, decrease NaCl reabsorption in the thick ascending limb and reduce medullary tonicity; likely contributing to the decreased urine concentrating ability [127,182,238,240]. Prostaglandin E2 (PGE_2) excretion is also increased in hypercalcemic rats. However, although PGE_2 is known to reduce AVP-stimulated water reabsorption in the collecting duct, blocking prostaglandin production by indomethacin failed to improve the renal concentrating defect, suggesting that the mechanism of hypercalcemia-induced NDI in rats is prostaglandin independent [127].

In humans, little data exist for the effect of hypercalcemia on AQP2 levels. However, it was shown that in some children with enuresis, hypercalciuria is associated with a decrease in nocturnal AQP2 levels in the urine, and that a low calcium diet, decreasing urine calcium excretion, is associated with an increase in urine AQP2 and decreased nocturnal urine volume in these children [231,232]. In addition, in hypercalciuric subjects a higher baseline urine AQP2 excretion was found. In contrast to normocalciurics [187], dDAVP administration did not increase AQP2 excretion in these subjects, suggesting a disturbed AQP2 regulation.

The effects of hypercalcemia on AQP2 have been ascribed to activation of the apical calcium-sensing receptor (CaSR), which might be a defense mechanism to reduce the risk of calcium renal stone formation in states of high luminal calcium. Sands et al. showed that CaSR protein was expressed at the apical border of cells in the terminal IMCD and that purified subapical endosomes contained both CaSR and AQP2 [208]. Activation of the CaSR by high extracellular calcium antagonizes forskolin-induced AQP2 translocation to the apical plasma membrane and attenuates AVP-induced AQP2 expression in cultured cells [24,186,187]; suggesting that hypercalcemia-induced activation of the CaSR in vivo may have a similar effect resulting in subsequent urine concentration defects. Alternatively, high calcium may activate the protease calpain, expressed in the inner medullary collecting ducts, leading to degradation of AQP2 [188].

2.2.7. Obstruction of the urinary tract

A relatively common condition associated with long-term impairment of urinary concentrating ability is obstruction of the urinary tract. Urinary tract obstruction is a serious clinical condition and a common cause of end-stage renal disease. In children, obstruction is usually due to congenital abnormalities, whereas in adults it is mostly caused by stones, enlargement of the prostate, or urinary tract neoplasms [95]. During the recovery phase after release of the urinary tract obstruction, water reabsorption in the collecting duct and the response of the collecting duct to AVP is decreased, resulting in polyuria [111]. Experimental bilateral or unilateral obstruction of the ureters is associated with markedly reduced expression of AQP1, AQP2, AQP3 and AQP4 [64,130,131]. Both AQP2 protein and mRNA levels are decreased [63,220], with mRNA levels already decreased 2 h after the obstruction, while protein levels are significantly decreased after 12 h [220]. AQP2 redistributes to early endosomes and lysosomes after obstruction, suggesting degradation of AQP2 [220]. In addition, bilateral ureteral obstruction is associated with marked down-regulation of renal sodium transporters and urea transporters [129,132]. Following release of the obstruction, there is a marked polyuria during which period AQP1,

AQP2 and AQP3 levels remain down, providing an explanation at the molecular level for postobstructive polyuria [131].

Bilateral obstruction in rats is associated with increased renal cyclooxygenase-2 (COX-2) expression and increased prostaglandin PGE_2 excretion in the urine [28,175]. Several prostaglandins are increased in the inner medulla, and to a lesser extent in the cortex, of rats with ureteral obstruction. Treatment with specific inhibitors revealed that in these conditions COX-2 is the predominant isoform involved in the prostaglandin synthesis, with minor, but significant, contributions from COX-1 [176]. Treatment of rats with COX-2 inhibitors prevented the increase in PGE_2, the down-regulation of AQP2 and the development of polyuria [28,175]. Ureteral obstruction did not decrease AQP2 and AQP3 levels in cortex and outer medulla of COX-2 knockout mice, in contrast to wild-type mice, although a decrease in inner medullary AQP2 expression remained [174], indicating that COX-2-derived prostaglandins contribute to down-regulation of AQPs in the collecting duct in ureteral obstruction.

2.2.8. Lithium-induced NDI

The most common cause of NDI is lithium-induced NDI. Lithium is a frequently prescribed drug used by 1 in 1000 of the western population [143,228] to treat psychiatric diseases, such as bipolar disorders, schizoaffective disorders and depression. Unfortunately, more than 50% of patients undergoing lithium treatment develop an impairment of their concentrating ability and in 20% of patients this leads to the development of clinical NDI [19]. Lithium-NDI patients are at risk for dehydration-induced lithium toxicity, and prolonged lithium treatment may result in development of renal microcysts and end stage renal disease [52,228]. However, since the symptoms of the underlying psychiatric disorder have a high impact on the quality of life, cessation of lithium therapy is for many patients not an option.

Studies in rats showed that lithium-NDI develops in two stages. At the short term (10 days), lithium-NDI coincides with AQP2 and AQP3 down-regulation and natriuresis, without gross changes in renal morphology [126,144,158]. The lithium-induced natriuresis is suggested to be due to the reduced expression in some renal segments of the salt-transporting proteins NCC, the β- and γ-subunits of ENaC, and the Na–K-ATPase [123,126,168]. A study using connecting tubule specific AQP2 knockout mice suggested that lithium does not severely affect AQP2 in the connecting tubule, in contrast to the collecting duct [116]. Chronic lithium treatment (4 weeks) also leads to a severe decrease in the fraction of principal cells and an increase in the fraction of intercalated cells, which are involved in acid/base balance regulation [31,32], suggesting that part of the lithium-induced NDI might be explained by an epithelial remodeling. In agreement with these studies in rats, a study in humans showed that 4 weeks therapy with lithium carbonate leads to a reduced urinary AQP2 excretion [237].

In the mpkCCD mouse collecting duct cell line, which endogenously expresses AQP2, lithium does not affect AVP-induced cAMP generation, PKA-dependent AQP2 phosphorylation, or the phosphorylation of the AQP2 transcription factor CREB [135]. Furthermore, in AVP-deficient Brattleboro rats with clamped blood dDAVP levels, there are no differences in dDAVP induced cAMP generation after lithium treatment, indicating that lithium does not directly affect the pathway activated by AVP.

Several data indicate that lithium exert its effects by entering principal cells through the epithelial sodium channel ENaC. ENaC has a higher permeability for lithium than for sodium [106], the ENaC-blocker triamterene increases lithium excretion [244] and it has been shown in lithium-NDI patients that blocking ENaC with amiloride significantly reduces urine volume and increases urine osmolality [11,14,120]. In addition, in the mouse collecting duct cell lines $mCCD_{c11}$ and mpkCCD, co-incubation of lithium with the ENaC blockers amiloride or benzamil prevented the lithium-induced AQP2 downregulation and decreased the intracellular lithium concentration [115], showing that ENaC is the major cellular entry pathway for lithium. These cell studies were confirmed by in vivo experiments, where simultaneous treatment of rats with amiloride and lithium decreased urine volume and increased urine osmolality relative to lithium alone treatment [115]. Dual treatment also attenuated AQP2 down-regulation, and completely prevented the reduction of principal/intercalated cell ratios. Confirming the ENaC mediated lithium entry pathway, Christensen et al. determined that collecting duct specific αENaC knockout mice do not demonstrate polyuria or a reduction in urine osmolality when treated with lithium, and AQP2 protein levels are only decreased in the inner medulla of these mice [35].

After entry into the cell, lithium leads to inactivation of intracellular glycogen synthase kinase (Gsk) 3β, which is temporally related to increased COX-2 expression in the kidney and in cultured principal and interstitial cells [115,117,190,192]. Consistent with the role of COX-2 in prostaglandin production, lithium increased excretion of PGE_2 in the urine of rats and mice [121,192]. As PGE_2 reduces AVP-stimulated water reabsorption in the perfused collecting ducts [78,164], this suggests a possible role for PGE_2 in the development of lithium-induced NDI. This theory is supported by studies showing that blocking prostaglandin production by indomethacin reduces the urine volume of lithium-treated rats [107] as well as of patients with lithium-induced NDI [2,243]. In mpkCCD cells, prostaglandins do not affect AQP2 gene transcription, but increase lysosomal degradation of AQP2 [117], suggesting that prostaglandins might have a role in lithium-induced NDI by decreasing AQP2 protein stability.

In mpkCCD cells, lithium decreases AQP2 protein abundance as well as AQP2 transcription independently of endogenous prostaglandin production. The pathway leading to a decreased AQP2 transcription is not known. However, not only lithium, but also other Gsk3 inhibitors lead to a down-regulation of AQP2 expression in mpkCCD cells [115], suggesting an important role of Gsk3β. In agreement with a Gsk3β regulation of AQP2, collecting duct specific Gsk3β knockout mice are polyuric and have reduced AQP2 mRNA and protein levels after water deprivation compared to wild-type mice [191]. The decrease in AQP2 transcription in lithium-induced NDI might therefore be a consequence of inhibition of one of the pathways driven by Gsk3β.

3. Treatment of AQP2-related pathologies

3.1. Treatment of pathologies resulting from increased aquaporin levels

In cases of euvolemic or hypervolemic chronic hyponatremia, caused either by CHF, liver cirrhosis, SIADH or NSIAD, fluid restriction is generally tried first [48]. However, this is not always successful, and not all patients comply. Fluid restriction can be combined with oral intake of urea or with loop diuretics. The most effective treatments however seem to be demeclocycline and, in recent years, use of V2R antagonists.

3.1.1. Demeclocycline

Demeclocycline is a bacteriostatic antibiotic of the tetracycline group that causes water diuresis and NDI [61,216]. Due to the effect on water diuresis, demeclocycline is currently used to treat sustained hyponatremia in patients with SIADH [214]. Demeclocycline restores the sodium plasma concentration in SIADH patients to normal levels, permitting unrestricted water intake in these patients [62]. Wilson et al. showed that the aquaretic effect of demeclocycline is exerted by selective inhibition of water reabsorption in the distal part of the nephron [247]. Others have shown that demeclocycline inhibits the AVP-induced osmotic water flow in the toad urinary bladder [54,79,216], a model system of the mammalian collecting duct. Recently it was shown that in mpkCCD cells, demeclocycline decreases AQP2 protein abundance as well as AQP2 gene transcription. In addition, demeclocycline decreases dDAVP-induced cAMP generation and adenylate cyclase 3 and 5/6 abundances [118]. In a rat model of SIADH, demeclocycline increases urine volume, decreases urine osmolality

and reverts hyponatremia. In agreement with the findings in mpkCCD cells, demeclocycline was found to decrease AQP2 and adenylate cyclase 5/6 abundances in the renal inner medulla of these rats, suggesting that demeclocycline attenuates hyponatremia by reducing adenylate cyclase expression, and consequently cAMP generation and AQP2 gene transcription in the inner medullary collecting duct [118].

3.1.2. V2R antagonists

Recently, several vasopressin-receptor antagonists, or vaptans, have been developed. In rat models of SIADH, CHF and liver cirrhosis, administration of the V2R antagonist OPC-31260 (Mozavaptan) increased the urinary flow rate, lowered the urinary osmolality and attenuated the hyponatremia [65,229,249]. OPC-31260 has also been shown to produce water diuresis and improve hyponatremia in SIADH patients [203]. Four other vaptans, the V2R antagonists Tolvaptan, Lixivaptan and Satavaptan and the V2R/V1a antagonist Conivaptan, have been tested in patients with euvolemic or hypervolemic hyponatremia due to a variety of causes including CHF, liver cirrhosis and SIADH. These vaptans were found to increase diuresis and correct hyponatremia [6,70,72,213,218,248]. Altogether, this suggests that V2R antagonists are promising drugs for the treatment of AQP2-mediated hyponatremia.

3.2. Treatment of pathologies resulting from decreased aquaporin levels

Central DI can be effectively treated by administration of dDAVP, either as an intranasal spray, tablet or sublingual melting formulation [198]. Since dDAVP is resistant to degradation by vasopressinase, it is also an effective treatment for gestational DI [4]. In contrast, treatment of the majority of NDI patients with dDAVP is not effective. The main strategy for treating NDI is the replacement of urinary water losses by a sufficient supply of fluid. This is usually combined with a low-solute diet to reduce the renal osmolar load, thereby decreasing obligatory water excretion. Additionally, treatment with thiazide diuretics, alone or in combination with indomethacin or amiloride, can efficiently decrease the degree of polyuria in NDI patients, although usually not to normal levels and not in all patients.

3.2.1. Diuretics

Currently, thiazide diuretics are used to reduce excessive urine output in NDI patients. The first published study that showed that hydrochlorothiazide could decrease urine volume and increase urine osmolality in patients with central DI and congenital NDI was in 1960 [38]. Also later studies showed that in patients with congenital NDI, as well as lithium-induced NDI, thiazide diuretics successfully decrease urine volume and increase urine osmolality [3,61,96]. The precise mechanisms by which thiazide diuretics elicit their paradoxical anti-diuretic effect are largely elusive. The distal convoluted tubule, where the thiazide-sensitive NaCl-cotransporter NCC is located, is water impermeable; therefore, the water-preserving effect of thiazides is unlikely related to a direct effect on this tubule. Thiazide antidiuretic action might be secondary to an increased renal sodium excretion, causing a decreased extracellular volume leading to an activation of the renin–angiotensin–aldosterone system, a decrease in glomerular filtration rate and an increased proximal sodium and water reabsorption. As a result, less water is delivered to the distal tubules, and less is excreted in the urine. Recently it has been shown that thiazide blocks not only NCC, but also the Na^+-dependent Cl^-/HCO_3^- exchanger NDCBE in the intercalated cells of the collecting duct, which might further contribute to this mechanism [119]. However, it has also been shown that thiazide directly enhances water permeability of isolated collecting ducts [27], and that thiazide treatment increases the expression of AQP2 in lithium-induced NDI [108], suggesting a direct effect of thiazide on the collecting duct.

The combined administration of hydrochlorothiazide with a prostaglandin synthesis inhibitor e.g. indomethacin, is more effective in reducing urine volume than the thiazide-diuretic alone [96,155,193]. Similarly, combining administration of hydrochlorothiazide with the ENaC-blocker amiloride is more effective than the thiazide-diuretic alone [3,110,114]. Besides this, amiloride also prevents hypokalemia and metabolic alkalosis, common side-effects of thiazide therapy [3,114].

3.3. Future therapies

In recent years many promising therapies for NDI have been identified. One of these is treatment with cell-permeable non-peptide V2R antagonists. Most V2R mutations associated with congenital NDI result in misfolding of the receptor and ER retention, but the retained receptor may still be functional. It was shown that plasma membrane expression of one of these mutant receptors could be rescued by a group of compounds known as 'chemical chaperones', including glycerol and DMSO, probably by stabilization of the receptor conformation [196]. To increase specificity and reduce toxicity, V2R antagonists have been tested for their efficacy as chaperones, thereby leading to correct folding of the protein and consequently membrane expression of the V2R. Once the antagonist-bound receptor reaches the plasma membrane, it will require displacement by AVP or its synthetic analogue dDAVP to allow activation of the receptor (Fig. 7). The cell-permeable V2R antagonists Satavaptan, Lixivaptan, Mozavaptan and Tolvaptan indeed stabilize ER-retained V2R mutants, allowing the receptor to escape from the ER and reach the plasma membrane in cultured cells [156,197]. Subsequent AVP treatment leads to cAMP generation in these cells, showing a functional rescue of the receptors [197]. The V1a receptor antagonist SR49059 (Relcovaptan, with moderate affinity for V2R) can also rescue cell surface expression of V2R mutants. Furthermore, SR49059 significantly reduced the urine volume in X-linked NDI patients, proving in principle that pharmacological chaperones can rescue V2R mutant activity in vivo [15]. A limitation of non-peptide antagonists is that their efficiency may depend on the type and location of the V2R mutation. Thus, different mutations may require different compounds to achieve V2R rescue and some mutants may be insensitive to all antagonists [139].

Another treatment strategy for X-linked NDI is the use of cell permeable non-peptide V2R agonists (Fig. 7). The non-peptide V2R agonists OPC51803, VA999088 and VA999089 are able to functionally rescue ER-retained V2R mutants in polarized renal cells [195]. The agonists are able to induce a cAMP response, eventually leading to an increase in translocation of AQP2 to the apical cell membrane in six out of seven tested dDAVP insensitive V2R mutants. Moreover, incubation with the non-peptide agonists did not affect ER localization of the mutants and failed to induce receptor maturation, indicating that the observed signal was derived from ER-retained receptors. Recently, three structurally related non-peptide agonists MCF14, MCF18 and MCF57 were demonstrated to increase cAMP levels of intracellularly retained V2R mutants. However, this coincided with an increased membrane expression and improved maturation of the V2R mutants [97], indicating a different mechanism of rescue.

In other forms of NDI where these strategies cannot be used, like V2R mutants which are not functional or insensitive to rescue, acquired NDI or congenital NDI caused by AQP2 mutations, alternative therapies might be applied which bypass the V2R signaling cascade and promote AQP2 translocation or expression via activation of another pathway. One possibility is to stimulate prostaglandin receptors. Although prostaglandin PGE_2 antagonizes AVP-induced water permeability, PGE_2 increases collecting duct water permeability in the absence of AVP stimulation, probably via activation of its receptors EP2 and/or EP4 [78,164,206]. As mentioned above, blocking general prostaglandin synthesis with indomethacin has been shown to have significant effects in NDI patients. However, specific EP2 or EP4 agonists might be more effective, since no activation is expected of prostaglandin receptors involved in decreasing collecting duct water permeability. Agonists specific for EP2 (butaprost) and EP4 (CAY10580) were shown to increase

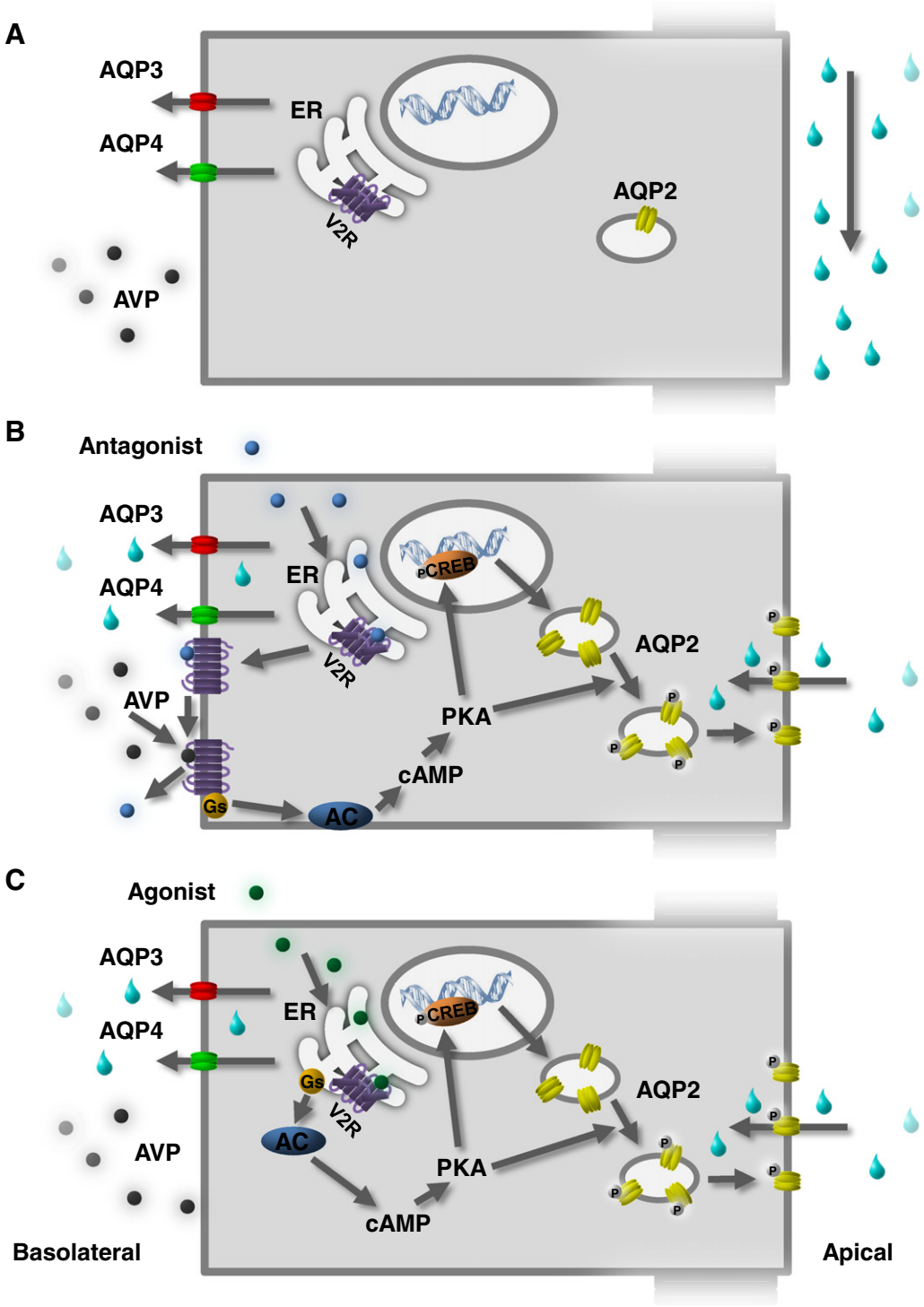

Fig. 7. Potential treatment strategy for X-linked NDI. A. X-linked NDI is caused by mutations in the *AVPR2* gene, encoding the V2R. Most mutations cause misfolding of the protein and retention in the endoplasmic reticulum (ER). B. Rescue of plasma membrane expression of the V2R by cell-permeable antagonists. Antagonists bind to misfolded mutant V2R mutants, present in the ER. This aids the correct folding of the V2R and allows the V2R to escape the ER and reach the plasma membrane. In the plasma membrane, the antagonist is displaced by AVP to allow activation of the receptor, leading to increased AQP2 at the plasma membrane. C. Activation of misfolded V2R mutants by cell-permeable agonists. The agonists reach the misfolded V2R in the ER. This allows signaling to occur from ER-retained receptors, leading to increased AQP2 trafficking. Other cell-permeable agonists also aid proper folding, leading to increased expression at the plasma membrane.

AQP2 trafficking in MDCK cells [178]. The EP4 agonist ONO-AE-329 has been shown to increase urine osmolality, decrease urine volume and increase AQP2 expression in a mouse model for X-NDI, while the EP2 agonist butaprost has been shown to reduce urine volume and increase urine osmolality in rats treated with a V2R antagonist, suggesting that specific EP2 or EP4 agonist could be promising treatment strategies for NDI [133,178].

An alternative method to bypass the V2R-cascade is via stimulation of intracellular cGMP levels. An increase in cGMP, mediated by atrial natriuretic peptide or nitric oxide, has been shown to increase the expression of AQP2 at the apical plasma membrane [17,20,241]. cGMP did however not increase the total expression of AQP2 in mpkCCD cells [17]. Preventing cGMP degradation by the PDE5 inhibitor sildenafil results in an increased expression of AQP2 at the plasma membrane

both in transfected cells and in AVP-deficient Brattleboro rats [22]. Recently it was shown that sildenafil reduces polyuria and increases membrane AQP2 levels in rats with lithium-induced NDI [207], indicating that sildenafil could be a potential treatment for NDI.

Another option to increase AQP2 trafficking is by the use of statins. Statins (or HMG-CoA reductase inhibitors) are a class of drugs that competitively inhibit the rate-limiting enzyme HMG-CoA in cholesterol biosynthesis, and are therefore used in the treatment of hypercholesterolemia. It has been shown that fluvastatin, lovastatin and simvastatin can increase the apical plasma membrane expression of AQP2 in cultured cells by inhibiting AQP2 endocytosis [134,184,185]. The mechanism behind the decreased AQP2 endocytosis is not completely understood, but has been suggested to be due to a decrease in active Rho involved in regulation of the cytoskeleton and AQP2 trafficking [134]. In vivo studies showed that simvastatin can decrease urine output, increase urine osmolality and increase AQP2 plasma membrane expression in AVP-deficient Brattleboro rats [134]. In mice, fluvastatin was able to increase renal AQP2 expression, reduce the urine volume and increase the urine osmolality [185]. In addition, atorvastatin was shown to prevent the downregulation of AQP2 abundance and increase urine osmolality after bilateral ureteral obstruction in rats [39]. Future studies have to determine if statins can indeed be used as a therapy for NDI.

4. Conclusion

Regulation of aquaporins is critical to osmoregulation and the maintenance of body water homeostasis. Considering the important role of aquaporins in cell water transport, it is not surprising that a variety of aquaporins, especially AQP2, are involved in disorders associated with disturbed water homeostasis. In the last 10 years, our understanding of the molecular and cell biological mechanisms of these disorders has increased enormously. These advances in our knowledge have opened up several possible treatment strategies. However, the exact molecular mechanisms which regulate the different aquaporins in different conditions are largely unknown. Future basic and translational studies are needed to fully understand and treat various water balance disorders.

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