AQP2 trafficking in health and diseases: an updated overview

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Abstract

Renal collecting duct principal cells play a key role in controlling body water balance. Principal cells express the water channels AQP2, AQP3, and AQP4 that mediate renal water reabsorption. AQP3 and AQP4 are expressed at the basolateral membrane constitutively. Conversely, AQP2 is localized in intracellular vesicles and translocates to the plasma membrane under vasopressin action. Stimulation with vasopressin activates the cAMP/PKA signal transduction pathway that induces the redistribution of AQP2 from an intracellular pool to the apical plasma membrane. AQP2 trafficking and function depend on multiple post-translational modifications. Moreover, several proteins control different steps activated by the vasopressin stimulation that triggers the redistribution of the AQP2 vesicles. A-kinase anchoring proteins (AKAPs) together with phosphodiesterases and adenylate cyclases play crucial roles in modulating local changes of cAMP. Soluble N-ethylmaleimide sensitive fusion factor attachment protein receptors (SNARE), cytoskeletal proteins, and the small GTPases of the Rho family regulate the fusion and the endocytotic retrieval of AQP2 vesicles. Abnormal vasopressin signaling and altered AQP2 expression or trafficking can lead to disorders characterized by water unbalanced. This review provides updated data on the molecular signals regulating vasopressin induced AQP2 trafficking in health and disease.

Introduction

Water balance is strictly regulated by the antidiuretic hormone vasopressin (AVP) and a complex osmoreceptors network tightly modulates the external osmotic environment within a narrow range of 280-295 mOsm/Kg. Osmoreceptors play key roles in controlling the thirst and releasing AVP from the posterior pituitary. Specifically, when the plasma osmolality overcomes the threshold limit, the AVP is secreted linearly to plasma osmolality. Beyond controlling body water homeostasis, AVP is involved in modulating several human functions including blood pressure, cell proliferation, survival, and gluconeogenesis (Aoyagi et al., 2009; Bankir et al., 2017; Ghosh et al., 2001). However, it exerts its main actions in the kidneys by binding two distinct vasopressin receptor subtypes: V1R and V2R. Along the nephron, V2 receptors are localized in the thick ascending limb and mainly in the collecting ducts. In the thick ascending limb, AVP promotes sodium reabsorption by the Na-K-2Cl (NKCC2) transporters (Bankir, 2001). In the cortical and outer medulla, AVP stimulates sodium reabsorption through the epithelial channel ENaC. In the deep part of the collecting duct, vasopressin facilitates the urea uptake via UT-A1 and UT-A3 transporters. Together, sodium and urea contribute to increasing the interstitial osmolality that constitutes the driving force for water reabsorption and urine concentration. A rapid transcellular water flow is ensured by specific proteins known as aquaporins. Peter Agree has been awarded in 2003 the Noble Prize for the discovery and the functional characterization of the first water channel, AQP1(Agre et al., 2002; Agre et al., 1987; Preston et al., 1992). Human kidneys generate about 180 L of primary urine per day and 90% of water is reabsorbed in the proximal tubules that express the water channel AQP1. The remaining 10% is reabsorbed in the renal collecting ducts under the control of AVP. In a long term, an elevated circulating level of AVP increases the expression of AQP2 and AQP3 in renal tissue (Terris et al., 1996). In a short term, AVP binds the specific vasopressin 2 receptors (V2R) located at the basolateral membrane of principal cells and coupled to the heterotrimeric GTP-binding protein Gs. This binding activates the cAMP/PKA signal transduction pathway that promotes the translocation of the AQP2 bearing

vesicles from an intracellular pool to the apical plasma membrane where water reabsorption occurs. Several regulatory proteins participate in this process. The heterotrimeric GTP-binding proteins of the Gi family, expressed in the AQP2 vesicles, are involved in the fusion process (Valenti et al., 1998). More recently, it has been found that Gi protein modulates the potassium channel TASK-2 gating, promoting the osmotic AQP2 vesicle swelling that precedes the fusion to the plasma apical membrane (Centrone et al., 2018). The water permeability of the basolateral side is ensured by the water channels AQP3 and AQP4 that are constitutively expressed at the plasma membrane.

Defective vasopressin signaling and alteration in AQP2 expression and trafficking can cause water balance disorders such as congenital Nephrogenic Diabetes Insipidus, Syndrome of Inappropriate Antidiuretic Hormone Secretion, Nephrogenic Syndrome of Inappropriate Antidiuresis, and Autosomal Dominant Polycystic Kidney Disease. Therefore, targeting the vasopressin-AQP2 axis can represent a useful therapeutic approach. In the present review, we will be focused on the molecular and cellular signaling controlling AQP2 trafficking. Some disorders associated with abnormal AQP2 expression and trafficking are also described.

Role of post-translational modifications (PTMs) in controlling AQP2 trafficking

In the last few years, numerous studies revealed that AQP2 undergoes different PTMs that have a potential key role in AQP2 function. It is known that multiple connections between phosphorylation and ubiquitylation may profoundly impact intracellular signaling (Hunter, 2007, 2012). A dynamic and temporary combination of PTMs can generate a PTM code playing a role in cell signaling regulation. Proteomic studies from Mark Knepper's laboratory can be considered a breakstone in the understanding PTMs affecting AQP2 (Barile et al., 2005; Hoffert et al., 2006). Massive data were generated, although a complete understanding of PTMs roles on AQP2 function is still missing and this may constitute a challenge for future studies.

Phosphorylation of AQP2

The intracellular signaling, stimulated by the hormone vasopressin that leads to the translocation of the AQP2 vesicles from an intracellular pool to the apical plasma membrane of the renal collecting duct principal cells, includes the phosphorylation of AQP2 at multiple sites within the C-terminal domain (Hoffert et al., 2006). Specifically, the vasopressin-dependent activation of the cAMP-dependent kinase A (PKA) is responsible for the phosphorylation of AQP2 at serine 256 (S256) which can be considered as a priming event for downstream phosphorylations at S269 and S264 (Hoffert et al., 2008). Moreover, stimulation with the hormone vasopressin results in significant dephosphorylation of AQP2 at S261 (Hoffert et al., 2006).

Phosphorylation at serine 256

The role of AQP2 phosphorylation at S256 has been widely investigated by several groups over the world (Kuwahara et al., 1995; Nejsum et al., 2005; Procino et al., 2003). Under the basal condition, AQP2-pS256 is localized at the plasma membrane and in intracellular vesicles, likely suggesting that a minimal portion of AQP2 is constitutively phosphorylated even when the circulating level of AVP is low (Christensen et al., 2000). Stimulation with AVP activates and increases the abundance of AQP2-pS256 at the plasma membrane, where at least three monomers in the tetramer should be phosphorylated (Kamsteeg et al., 2000). Replacement of serine with alanine by site-directed mutagenesis revealed that phosphorylation at S256 is required for the cAMP-induced AQP2 exocytosis and function (Fushimi et al., 1997; Katsura et al., 1997). Indeed, inhibition of the constitutive endocytosis by using the cholesterol-depleting agent methyl-beta-cyclodextrin accumulated both the wild type AQP2 and AQP2-S256A at the plasma membrane indicating that the constitutive trafficking is independent of phosphorylation at S256, which is instead a prerequisite for the vasopressin dependent AQP2 trafficking (Lu et al., 2004). By contrast, the constitutively phosphorylated AQP2-S256D mutant is localized at the apical plasma membrane independently of the intracellular level of cAMP (van Balkom et al., 2002). Interestingly, AQP2 trafficking may occur independently of the activation of the cAMP/PKA signaling. In LLC-PK1 cells, the nitric oxide (NO)

donors' sodium nitroprusside (SNP), which increases intracellular cGMP, stimulates the AQP2 translocation at the plasma membrane possibly through the involvement of PKG. No effect on AQP2 trafficking was found in cells expressing the AQP2-S256A mutant indicating that phosphorylation at S256 is necessary for this signaling (Bouley et al., 2000). Accordingly, treatment with the cGMP phosphodiesterase type 5 (PDE5) inhibitors sildenafil citrate, which increases the intracellular level of cGMP, promotes AQP2 trafficking, therefore, mimicking the action of the hormone vasopressin (Bouley et al., 2005).

Phosphorylation at serine 261

Stimulation with vasopressin causes rapid phosphorylation at S256 (t1/2 = 41 s) followed by dephosphorylation at S261 (t1/2 = 10.6 min) (Hoffert et al., 2008). PP2C has been proposed as a possible protein phosphatase responsible for the dephosphorylation of AQP2 at S261 because sanguinarine, a selective PP2C inhibitor, impaired the vasopressin induced AQP2 dephosphorylation at S261 (Cheung et al., 2017). In LLC-PK1 cells stimulation with vasopressin promotes the membrane expression of both AQP2-S261A and AQP2-S261D likely suggesting that S261 does not play a role in controlling the intracellular localization of AQP2 (Lu et al., 2004). By contrast, it has been also shown that phosphorylation at S261 follows AQP2 ubiquitylation and internalization, and possibly it retains AQP2 in an intracellular pool (Tamma et al., 2011). Inline, ATP and dopamine that prevent the AVP-dependent water reabsorption cause AQP2 ubiquitylation, internalization, and increased phosphorylation at S261 (Boone et al., 2011).

Phosphorylation at serine 264

Serine 264 resides within the phosphorylation consensus site for PKC and casein kinase type 1 (Brown et al., 2008). In Brattleboro rats, stimulation with dDAVP increases S264 phosphorylation about 4-fold compared with control animals. Acute stimulation with dDAVP promotes the translocation of AQP2-pS264 at the apical and basolateral membranes. By contrast, after prolonged stimulation with dDAVP, the targeting of AQP2-pS264 at the basolateral membrane disappears (Fenton et al., 2008). Interestingly, basolateral targeting of AQP2 has been described by several

groups (de Seigneux et al., 2007; Jeon et al., 2003; van Balkom et al., 2003). In addition, a transcytosis pathway for AQP2 has been also found even if the mechanism regulating this process is not completely clear. It cannot be excluded that phosphorylation at S264 might be considered an important regulatory step in controlling the cellular distribution of AQP2. Further studies would be needed to better clarify the exact role of S264 phosphorylation in controlling AQP2 trafficking.

Phosphorylation at serine 269

Mass spectrometry and immunoblotting analysis using phospho-specific antibodies demonstrated that vasopressin stimulation causes phosphorylation of AQP2 at S269. AQP2-pS269 localizes exclusively at the apical plasma membrane (Hoffert et al., 2008; Moeller et al., 2009) where it is excluded from endocytosis possibly for a reduced interaction with the endocytotic machinery that includes Hsp70, Hsc70, dynamin, and clathrin heavy chain (Rice et al., 2012). Importantly, S269 is within the class I PDZ-ligand motif. Vasopressin-dependent S269 phosphorylation, by adding a negative charge on this PDZ domain, modifies the interaction of AQP2 with PDZ domain-containing protein Sipa1l1 (signal-induced proliferation-associated 1 like 1), that controls the internalization of AQP2 (Wang et al., 2017).

Interestingly, S269 phosphorylation is prevented in AQP2-S256A mutant indicating that phosphorylation at S269 requires, as priming event, phosphorylation at S256 (Hoffert et al., 2008). Phosphorylation at S269 occurs in the pS256-positive AQP2 population (Yui et al., 2017). Nevertheless, it has been also found that S269 can be phosphorylated without pS256 and through the inhibition of Src with dasatinib (Cheung et al., 2019). This study proposes a novel mechanism and independent pathways promoting the accumulation of AQP2 at the apical plasma membrane, thereby offering alternative approaches to target membrane expression of AQP2 when the vasopressin signal transduction is not functioning properly.

Ubiquitylation of AQP2

Ubiquitylation, which originally has been described as a molecular kiss of death, has multiple functions beyond its initial role as a tag for degradation. Site-directed mutagenesis showed that AQP2 can be ubiquitylated with one K63-linked chain at K270 (Kamsteeg et al., 2006). AVP removal or hormones activating PKC significantly increases AQP2 ubiquitylation that mainly occurs at the plasma membrane where precedes and promotes AQP2 internalization (Kamsteeg et al., 2006). Phosphorylation at S261 follows ubiquitylation and may stabilize AQP2 intracellularly (Tamma et al., 2011). Inline, the AQP2-S256D-S269D mutant that is mainly expressed at the plasma membrane showed a higher extend of ubiquitylation than AQP2-wt (Moeller et al., 2014). The AQP2-S256D-K270R-Ub mutant is always expressed in intracellular vesicles, likely suggesting that the constitutively apical sorting of AQP2-S256D can be overruled by constitutive ubiquitylation (Tamma et al., 2011). These observations suggest that short-chain ubiquitylation plays a role in controlling the cellular distribution of AQP2. Electron microscopy analysis indicates that a translational fusion of AQP2 with ubiquitin (AQP2-Ub) is mainly expressed in the internal vesicles of multivesicular bodies (MVBs), whereas AQP2-K270R mutant, that cannot undergo ubiquitylation, is mainly located at the apical membrane (Kamsteeg et al., 2006). Consistently, it has been also demonstrated that AQP2-Ub is highly degraded in the lysosomes compared with AQP2-K270R and AQP2-wt (Kamsteeg et al., 2006). Together, these data suggest that short chain ubiquitylation may represent a process activated upon AVP removal to desensitize the signaling activated by AVP thereby reducing water reabsorption. By contrast, stimulation with forskolin reduces AQP2 polyubiquitylation and protects AQP2 from degradation through the inhibition of p38-MAPK that is one of the kinases committed to phosphorylate AQP2 at S261 (Nedvetsky et al., 2010a).

By integrating multiple large-scale proteomic and transcriptomic datasets, 377 E3-ligases have been classified for their probability to bind AQP2 (Medvar et al., 2016). NEDD4 and NEDD4L, AMFR, STUB1, ITCH, ZFPL1 are the ones showing the highest probability to interact with AQP2 (Medvar et al., 2016). In mpkCCDc14 cells, the expression of siRNA of NEDD4 or CUL5 slows down the

extend of AQP2 degradation (Lee et al., 2011). Moreover, in HEK293 cells NEDD4/NEDD4L plays a key role in AQP2 degradation via NEDD4 family interacting protein 2 (NDFIP2) (Trimpert et al., 2017). Indeed, in MDCK and COS1 cells stably expressing AQP2, co-expression of VACM-1/Cul5 reduces AQP2 abundance (Le et al., 2012). Additional studies identified the E3-ligase CHIP involved in AQP2 binding and degradation (Centrone et al., 2017; Wu et al., 2018). Interestingly, Wu and coworkers found that CHIP knockout mice display an increase in AQP2 abundance and abnormal renal handling compared to control animals. In CCD cells, indeed, shRNA knockdown of CHIP increases AQP2 stability and decreases AQP2 ubiquitylation (Wu et al., 2018). Centrone and colleagues demonstrated that the expression of CHIP-wt increases the proteasomal degradation of AQP2. However, the expression of the CHIP-delUbox mutant, having a loss of E3 ligase activity, still causes AQP2 degradation likely indicating that the E3-ligase CHIP cannot directly ubiquitylate and degrade AQP2. By contrast, the expression of CHIP-delTPR, a mutant lacking the domain that is responsible for binding Hsc70/HSP70 and HSP90, increases the AQP2 half-life. HSP70 can bind other E3 ligases including MDM2. Co-expression of CHIP and MDM2 is associated with an increase in AQP2 degradation. Conversely, co-expression of CHIP with MDM2-delRING, displaying a loss of E3-ligase activity, is associated with a relevant impairment of AQP2 degradation. Together, these observations revealed that CHIP is a pivotal regulator of AQP2 through the interaction with HSP70 that anchors MDM2 E3 ligase which appears to be directly involved in AQP2 degradation (Centrone et al., 2017). These observations raised the possibility that in CHIP knockout mice, the increased AQP2 stability might result from the loss of the tethering of MDM2 through the CHIP-Hsc70/HSP70 and HSP90 machinery.

Glutathionylation of AQP2

Emerging data reveal that Reactive Oxygen Species (ROS) are important players in modulating signal transduction pathways. Some of the beneficial effects of ROS have been uncovered (Russell and Cotter, 2015). ROS can act as signaling mediators in different pathways controlling the function and the activity of receptors, channels, and kinases including AKT, Src, PKA, MAPK (Russell and Cotter,

2015). The exact mechanism of ROS signaling is far to be understood. Nevertheless, it is well accepted that Cys residues, in the target proteins, can be reversible or irreversible modified. S-glutathionylation is a reversible post-translational modification sensitive to changes in intracellular redox conditions. It has been hypothesized that this modification may prevent irreversible protein degradation. We have found that AQP2 is subjected to S-glutathionylation in renal tissue and HEK-293 cells stably expressing the water channel AQP2 possibly at Cys75 and Cys79on cytosolic B-loop (Tamma et al., 2014b). Specifically, in cells expressing the wild-type human calcium-sensing receptor (hCaSR-wt) and the gain of function variants (hCaSR-R990G; hCaSR-N124K), S-glutathionylation of AQP2 significantly decreased secondary to a low level of ROS and a decreased basal intracellular calcium (Tamma et al., 2014b). In mpkCCDc14 cells, stimulation with AVP increased S-glutathionylation of several proteins likely suggesting that hormonal stimulation includes the participation of the ROS signaling (Sandoval et al., 2013). Further studies would be needed to better clarify the physiological relevance of AQP2 S-glutathionylation.

Cytoskeleton Remodeling during AQP2 trafficking

Several studies provide evidence that the dynamic reorganization of the cytoskeleton plays a role in the AQP2 shuttle.

Microtubules

The role of microtubules on AQP2 trafficking has been extensively investigated. Numerous evidence in different experimental models describes the involvement of specific motor proteins in inducing the movement of intracellular vesicles along the microtubules that act as dynamic and efficient cellular tracks (Spiliotis and Kesisova, 2021). In collecting ducts, the motor proteins dynactin and dynein have been found in immunoisolated AQP2-vesicles (Barile et al., 2005; Marples et al., 1998). In the inner medulla collecting ducts, the AQP2 shuttle is accompanied by microtubules reorganization and redistribution of the small GTPase Rab11 that controls intracellular AQP2 positioning (Vossenkamper et al., 2007). Rab11 depletion impairs the intracellular trafficking of AQP2 vesicles

from the EEA1- positive early endosomes to the subapical storage compartment (Tajika et al., 2005). Under the basal condition, indeed, depolymerization of microtubules impairs the perinuclear localization of AQP2 and Rab11 (Vossenkamper et al., 2007). Interestingly, myosin Vb has been shown to regulate Rab11-FIP2-dependent recycling of AQP2 (Nedvetsky et al., 2007). In perfused rabbit collecting ducts and renal-like epithelia, treatment with nocodazole impairs vasopressin-dependent water reabsorption (Phillips and Taylor, 1989; Valenti et al., 1988).

Other authors observed that colchicine redistributed AQP2 from an apical and subapical location on vesicles scattered within the cytosol (Sabolic et al., 1995). The network of microtubules can also be disrupted by a cold treatment that redirected AQP2 at the basolateral membrane likely suggesting the existence of a trancytotic pathway of AQP2 that shuttles between the apical and the basolateral membrane respectively (Breton and Brown, 1998; Yui et al., 2013). A clear picture of the actors and signals regulating the transcytosis process is still not completely clarified. Interestingly, chlorpromazine, an inhibitor of clathrin-mediated endocytosis, causes an increase in AQP2 abundance at the basolateral membrane paralleled by a reduced basolateral F-actin that do not appear to function as a physical barrier but rather bridge AQP2 vesicles to the microtubules that target the vesicles to the apical side (Bouley et al., 2020). These interesting findings underline the critical role of a functional link between actin and microtubules and point to the existence of two differential regulated F-actin pools at the apical and the basolateral membrane respectively.

Actin

The involvement of actin filaments in controlling the AVP-induced renal water permeability has been postulated considering that the F-actin depolymerizing agent, cytochalasin D, impairs the AVP response in toad bladders (Pearl and Taylor, 1983). Later, in toad bladder granular cells, it has been demonstrated that stimulation with AVP is associated with a 30% depolymerization of actin filaments (Holmgren et al., 1992). Inline, in rabbit collecting duct CD8 cells, treatment with okadaic acid, an inhibitor of PP1A and PP2A, resulted in F-actin depolymerization and an increase in the AQP2 dependent water reabsorption (Valenti et al., 2000b). AVP-dependent F-actin depolymerization is

deeply correlated with the level of AQP2 expression independently of the polarity of AQP2 targeting (Yui et al., 2012). 2D gels studies demonstrated that AQP2 can bind β- and γ-isoforms of actin directly (Noda et al., 2004). Noda and coworkers found that phosphorylation of AQP2 at S256 causes a significant decrease in the interaction between AQP2 and G-actin and an increase in the binding of AQP2 with tropomyosin-5b (Noda et al., 2008; Noda and Sasaki, 2008). Klussmann and colleagues demonstrated that inhibition of the small GTPases of the Rho family causes partial depolymerization of F-actin and redistribution of AQP2 at the plasma membrane that increases the water permeability (Klussmann et al., 2001; Tamma et al., 2001; Tamma et al., 2003a). Conversely, RhoA-dependent actin polymerization, secondary to stimulation with bradykinin or sulprostone, a prostaglandin-E2 analog, reduces the membrane insertion of AQP2 indicating that RhoA activity is crucial in defining the cellular localization of AQP2 by interfering with actin filament reorganization (Tamma et al., 2005a; Tamma et al., 2003b). Super-resolution microscopy depicts a 3D network of AQP2 vesicles revealing that one pool of AQP2 vesicles is located with the subcortical layer of F-actin and a second one is distributed between the F-actin layer and the plasma membrane (Holst et al., 2021). Moreover, constitutively phosphorylation of AQP2 at S256 increases the association between the AQP2-bearing vesicles and the layer of F-actin (Holst et al., 2021).

The ezrin-moesin-radixin (ERM) proteins are scaffolding elements cross-linking actin filaments with the plasma membrane. They also modulate the Rho signaling to control actin dynamics (Kawaguchi et al., 2017). In renal collecting duct CD8 cells, Y27632, a selective inhibitor of Rho-kinase, reduced the phosphorylation of moesin at T558, its interaction with F-actin, and increased the abundance of AQP2 at the plasma membrane (Tamma et al., 2005b), likely indicating that AQP2 trafficking includes the functional involvement of ERM proteins through Rho signaling. Moreover, coimmunoprecipitation experiments reveal that ezrin, through its FERM domain, can bind the C-terminus of AQP2. Silencing ezrin expression with shRNA caused a significant increase of the AQP2 abundance at the plasma membrane suggesting that ezrin-AQP2 interaction targets AQP2 to endocytosis (Li et al., 2017). Consistently, more recently it has been demonstrated that mice deficient

of the Programmed Cell Death 10 (PDCD10), displaying polyuria, showed a higher expression level of ezrin at the plasma membrane, a reduced expression of AQP2 at the plasma membrane and, the downregulation of its phosphorylation (Wang et al., 2021).

Involvement of PKA Anchoring Proteins (AKAPs) in AQP2 Shuttle

A Kinase Anchoring Proteins (AKAPs) are scaffolding proteins binding to the regulatory subunit of PKA through a conserved helical domain. This interaction provides a specific subcellular distribution and compartmentalization of PKA that can be targeted to pools of second messengers and downstream effectors thereby generating compartmentalized signalosome for PKA. Renal collecting duct principal cells express two PKA catalytic subunits, PKA-Cα and PKA-Cβ (Raghuram et al., 2020). Interestingly, these subunits exert different cellular functions which may be due to binding with distinct A-kinase anchoring proteins (Raghuram et al., 2020). Several studies revealed that PKA-AKAP interaction is needed for the proper trafficking of AQP2 vesicles. In IMCD cells, incubation with the synthetic peptide S-HT31 which disrupts the interaction between the regulatory subunit of PKA and AKAPs counteracted the cAMP-dependent AQP2 translocation to the plasma membrane (Klussmann et al., 1999). Later, it has been found that AKAP18δ, which is expressed in AQP2 vesicles, can bind to PKA and PDE4D. Importantly, vasopressin stimulation promotes the translocation of AQP2 and PDE4D to the plasma membrane where it is activated through PKA phosphorylation. Local PDE4D activation quenches the vasopressin-dependent cAMP signaling causing a reduction in water reabsorption (Henn et al., 2004; Stefan et al., 2007). Moreover, yeast two-hybrid screening shows that AKAP220 binds AQP2. The two proteins are colocalized in the cytosol of the inner medulla collecting ducts (Okutsu et al., 2008). Knocking down AKAP220 in organoid culture and mice results in a significant disgregation of the apical actin network altering RhoA and AQP2 localization (Whiting et al., 2016). Besides anchoring activity, several AKAPs display several other functions. AKAP-Lbc holds a GEF activity for RhoA. By disrupting RhoA to AKAP-Lbc interaction with Scaff10-8, RhoA activation is impaired. This, in turn, results in an

increase in AQP2 abundance at the plasma membrane (Schrade et al., 2018). Indeed, the E3-ligase STUB1, which controls AQP2 polyubiquitylation, can also function as an A-kinase anchoring protein bridging PKA to cyclin-dependent kinase-18 (CDK18) that modulate AQP2 phosphorylation at S261 (Dema et al., 2020). Based on these findings, disruption of the AKAP-PKA interaction may represent an alternative therapeutic approach to face disorders associated with deregulated AQP2 trafficking.

SNARE proteins in the vesicular translocation of AQP2

The final step in the vasopressin-dependent translocation of the AQP2 bearing vesicles is the docking and fusion of AQP2-bearing vesicles to the apical plasma membrane of renal collecting duct principal cells. Annexin-2 is a protein involved in the exocytotic and endocytic pathways and it is expressed in the kidney (Markoff and Gerke, 2005). In renal collecting duct CD8 cells, stimulation with the cAMP-elevating agent forskolin recruits annexin-2 in the lipid rafts microdomains. Moreover, in vitro studies reveal that a peptide of annexin-2 containing the binding site for calcium inhibits the fusion process and impairs the forskolin-induced water transport in intact cells. These findings strongly suggest that annexin-2 is functionally involved in controlling the fusion of AQP2 bearing vesicles to the plasma membrane (Tamma et al., 2008).

The specificity of the fusion process is mediated by SNARE proteins (soluble N-ethylmaleimide sensitive factor attachment protein receptors), including vesicle (v) SNAREs and target membrane (t) SNAREs, that are expressed in the collecting duct principal cells and colocalized with AQP2-bearing vesicles (Franki et al., 1995; Nielsen et al., 1995). The v-SNARE, VAMP-2, and VAMP-3 are associated with AQP2-vesicles (Barile et al., 2005; Gouraud et al., 2002; Nielsen et al., 1995); whereas t-SNARE, Syntaxin-3 and Syntaxin-4 are found respectively in the apical membrane and in the basolateral membrane of collecting duct cells (Li et al., 2002; Procino et al., 2008). Other studies demonstrated that VAMP-8 colocalized with AQP2 vesicles (Wang et al., 2010). Deficient mice for VAMP8 showed hydronephrosis as a result of an impairment of the vasopressin-induced AQP2 exocytosis (Wang et al., 2010). Furthermore, the functional involvement of VAMP2 in the targeting

of AQP2 vesicles to the plasma membrane was demonstrated in MCD4 cells (Gouraud et al., 2002). Gouraud and coworkers demonstrated that tetanus toxin, which proteolytically cleaves VAMP-2 at a single site (Link et al., 1992), completely abolished the forskolin-induced translocation of AQP2 to the apical membrane (Gouraud et al., 2002). Furthermore, i*n vitro* studies, provide evidence for the functional involvement of VAMP2, VAMP3, Stx-3, and SNAP23 in FK-dependent AQP2 trafficking to the apical plasma membrane. Interestingly, this complex fusion machinery is negatively controlled by Munc18b (Procino et al., 2008).

Calcium and CaSR signaling downregulates AQP2 trafficking and function

In the renal collecting duct, AVP stimulation includes a calcium response (Yip and Sham, 2011). The kidney plays an important role in controlling the body's calcium homeostasis. The ability to sense extracellular calcium levels in the urine and the interstitial fluid is due to the expression of an extracellular calcium-sensing receptor (CaSR). The renal localization and function of the CaSR have been extensively reviewed elsewhere (Brown and MacLeod, 2001; Hebert et al., 1997; Hofer and Brown, 2003; Pearce and Thakker, 1997; Riccardi and Brown, 2010; Riccardi and Valenti, 2016; Ward and Riccardi, 2002).

Several studies have suggested that CaSR signaling regulates the vasopressin-induced trafficking and expression of AQP2 (Bustamante et al., 2008; Earm et al., 1998; Procino et al., 2004; Procino et al., 2012; Ranieri et al., 2015; Ranieri et al., 2018; Renkema et al., 2009; Sands et al., 1997; Valenti et al., 2002; Valenti et al., 2000a). In this respect, it has been suggested that during antidiuresis, the vasopressin promoting water reabsorption from the lumen causes an increase in Ca^{2+} concentration secondary to urine concentration. A high luminal calcium level activates the CaSR located on the apical membrane of the principal cells. The activation of the CaSR reduces the vasopressin-stimulated insertion of AQP2 into the plasma membrane, decreasing the rate of water reabsorption thereby reducing the risk of Ca^{2+} supersaturation (Procino et al., 2004; Procino et al., 2012) that may lead to kidney stones formation and other renal disorders (Riccardi and Valenti, 2016). In cultured renal cells

and microdissected collecting ducts, the inhibitory effect of CaSR signaling on AQP2 trafficking to the plasma membrane is associated with a significant reduction in cAMP-induced AQP2 phosphorylation at serine 256 and AQP2 trafficking (Ranieri et al., 2015). Therefore, the CaSR-AQP2 interplay may be useful to mitigate the effect of hypercalciuria on the risk of calcium precipitation during antidiuresis. Furthermore, stimulation of the CaSR, due to a high level of luminal calcium, resulted in a significant increase of AQP2 phosphorylation at serine 261 possibly through p38-MAPK (Nedvetsky et al., 2010b; Ranieri et al., 2018; Trepiccione et al., 2014).

In enuretic children, urinary AQP2 and calciuria correlate with the severity of enuresis (Valenti et al., 2000a). Interestingly, a low calcium diet administered to hypercalciuric enuretic children decreases overnight urine output, reduces nocturnal enuresis, and increases nighttime AQP2 excretion and urine osmolality (Valenti et al., 2002). In agreement with these observations, bedrest studies demonstrated that immobilization causes a rise of urinary calcium excretion secondary to bone demineralization paralleled by a significant reduction in urinary AQP2 (Tamma et al., 2014a).

Altered AQP2 expression and trafficking in human diseases

Altered AQP2 expression and trafficking are associated with several water-balance disorders such as Nephrogenic Diabetes Insipidus (NDI), Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD), and other disorders characterized by impaired urine concentration including the Autosomal Dominant Polycystic Kidney Disease (ADPKD) (Figure 1). Water balanced disorders have been recently discussed (Kortenoeven and Fenton, 2014; Ranieri et al., 2019; Valenti and Tamma, 2021).

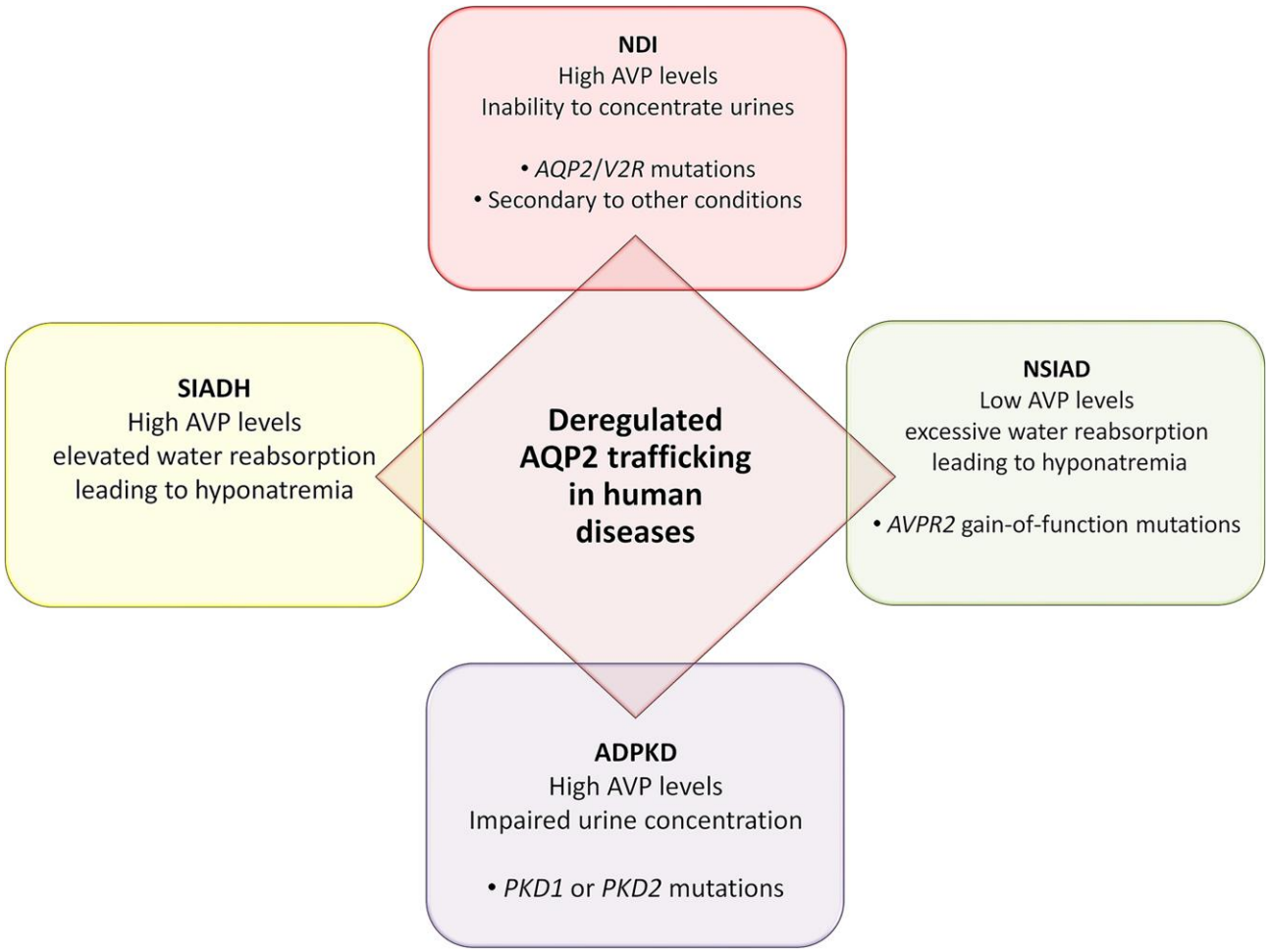

Figure 1. AQP2 trafficking alterations in human diseases.

Alterations of the AQP2 trafficking, principal features, and causes of selected water balance disorders.

Nephrogenic diabetes insipidus (NDI)

Nephrogenic diabetes insipidus (NDI) is a rare genetic water balance disorder, characterized by the physiological inability of the kidney to concentrate urine, despite normal or elevated levels of AVP, resulting in polyuria and polydipsia that can end up in dehydration and hypernatremia (Bockenhauer and Bichet, 2017).

Congenital NDI

Congenital NDI is characterized by a non-functional vasopressin-2 receptor (X-linked NDI) or by mutations of the gene coding for the water channel aquaporin-2 (AQP2).

X-linked NDI represents the most cases of congenital NDI (90%) and is caused by loss-of-function mutations of the V2R gene with an X-linked recessive inheritance pattern (van den Ouweland et al.,

1992). NDI-associated V2R mutations are missense/nonsense mutations, deletions, and insertions, which result in truncated and misfolded V2 receptors. Alternatively, mutant receptors display a decreased binding capacity to vasopressin (Fujiwara and Bichet, 2005; Robben et al., 2006).

Congenital NDI is also caused by loss-of-function mutations in the AQP2 gene (10%). 40 mutations in the AQP2 gene are associated with the autosomal recessive form of NDI. Most of them are missense mutations. Two nonsense mutations have been found as well (Wesche et al., 2012). Mutations are located within transmembrane helices, water-conducting pore, and loop regions (Frick et al., 2014). Functional studies in Xenopus laevis oocytes show that missense mutants partially retain water transport ability likely suggesting that the clinical phenotypes might result from an abnormal cellular distribution of AQP2 (Bichet, 2006; Wesche et al., 2012). These observations might offer novel therapeutic approaches to target AQP2 to a proper cellular compartment.

In contrast, dominant autosomal NDI is characterized by mutations located within the C-terminus of AQP2, which affect the intracellular trafficking of functional AQP2 (Kuwahara et al., 2001). In dominant autosomal NDI, mutations are deletions, insertions, or missense/nonsense mutations that result in AQP2 mutants forming heterotetramers with WT-AQP2, which are misrouted to other subcellular compartments rather than the plasma membrane (Kamsteeg et al., 1999; Marr et al., 2002).

A more detailed description of NDI has been extensively reviewed elsewhere (Bichet, 2020; Bichet and Bockenhauer, 2016; Bockenhauer and Bichet, 2015; Robben et al., 2006). Several therapeutic approaches to increase cell surface expression of V2R and AQP2 have been tested, however, specific therapy for NDI is still missing. Interestingly, treatment with statins reduced urine output by increasing urinary concentration through inhibition of the small GTPases RhoA (Li et al., 2011; Procino et al., 2011). The approved pharmacologic therapy used to reduce polyuria consists of thiazide diuretics, Amiloride, a potassium-sparing agent or indomethacin, a prostaglandin inhibitor (Milano et al., 2017; Priya et al., 2021).

Acquired NDI

Acquired NDI is much more common than hereditary NDI, it is due to the resistance of the kidney to the action of antidiuretic hormone (AVP), and is most commonly caused by pharmacological treatments, electrolyte abnormalities, and urinary tract obstruction (Khanna, 2006).

A meta-analysis study demonstrated that several drugs including antibiotics, antifungals, antineoplastic agents, and lithium may cause acquired NDI (Garofeanu et al., 2005).

Lithium (Li) is commonly used as a mood stabilizer; it enters the principal cells through epithelial sodium channels (ENaC). *In vivo* study demonstrated that Li treatment results in a down-regulation of the water channel AQP2 with consequent polyuria (Kwon et al., 2000). Importantly, lithium exposure may alter several intracellular signaling processes, such as gene expression, cytoskeletal organization, apoptosis, and cell proliferation (Nielsen et al., 2008). In the short term, after 4 hours of exposure, lithium increases urine output, upregulates ERK and p38 signaling, and phosphorylation level of AQP2 at S261 which is reduced by selective inhibitors of ERK and p38α-MAPK. (Trepiccione et al., 2014). Conversely, in microdissected collecting ducts, RNA-seq and mass spectrometry analyses reveal that exposure to lithium for 72 hours promotes several signaling pathways including Wnt, p53, and NFkB pathways. The latest might be involved in AQP2 downregulation possibly through ERK (Sung et al., 2019). Treatment of rats with dexamethasone, at anti-inflammatory doses, counteracts the effect of lithium on AQP2 expression (Sung et al., 2019).

The molecular mechanisms leading to a reduction of AQP2 expression and subsequent polyuria remain unclear. It has been proposed that lithium might decrease AQP2 expression by promoting lysosomal degradation possibly through GSK3-beta (Kaiser and Edemir, 2020). On another hand, lithium-induced SNX27 decrease might play a role in autophagy-lysosomal degradation of AQP2 (Choi et al., 2020). Interestingly, treatment with chloroquine, an autophagy inhibitor, mitigates the lithium-dependent downregulation of AQP2 and polyuria (Du et al., 2020). So far, several approaches have been proposed to counteract the effect of lithium on AQP2 expression to control urine output (Cheung et al., 2016; Lin et al., 2017; Luo et al., 2019; Tingskov et al., 2018). Indeed, a partial

recovery of AQP2 expression and urinary concentration occurs after the ending of the lithium therapy (Marples et al., 1995).

Electrolyte imbalance like hypokalemia and hypercalcemia can cause mild NDI. Recent studies have demonstrated that AQP2 down-regulation observed during hypokalemia and hypercalcemia may be mediated by autophagic degradation (Khositseth et al., 2017; Khositseth et al., 2015).

Acquired NDI may rise in obstructive uropathy (Frøkiaer et al., 1997; Frøkiaer et al., 1996). In vivo studies demonstrated that AQP2 expression was significantly reduced in bilateral obstructed kidneys, compared to unilateral obstruction, where AQP2 reduction is observed only in the obstructed kidney (Frøkiaer et al., 1997; Frøkiaer et al., 1996). This reduction may be caused by increased AQP2 lysosomal degradation (Stødkilde et al., 2011).

Furthermore, acquired NDI may rise as a complication in Cystinosis (Bockenhauer and Bichet, 2013; Bockenhauer et al., 2010; Holliday et al., 1967; Katzir et al., 1988; Knoepfelmacher et al., 1994; Lemire and Kaplan, 1984). Cystinosis is an autosomal recessive lysosomal storage disease, representing the most common hereditary cause of Renal Fanconi syndrome in children, often causing chronic kidney disease (Bockenhauer and Bichet, 2013; Elmonem et al., 2016; Luciani et al., 2018). Despite the great progress in understanding the molecular basis of cystinosis, the investigation of secondary NDI as a complication of this severe disorder remains still unraveled. Recently, Amlal and colleagues developed a new mouse model of cystinosis by using CRISPR technology on C57/BL6 mice (Amlal et al., 2020). Interestingly, the homozygous mutant (Cyst−/−) mice showed AVP resistance and urinary concentrating defect in association with a significant reduction in AQP2 water channel protein abundance with respect to the wild-type and the heterozygous (Cyst+/−) mice (Amlal et al., 2020), providing important hints to the study of the molecular basis of the secondary NDI in Cystinosis.

Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)

Syndrome of inappropriate antidiuretic hormone release (SIADH) may be considered an opposite disease compared to NDI. SIADH was first described in 1957 in two patients with bronchogenic carcinoma, by William Schwarz and Frederic Bartter, who developed the criteria for SIADH diagnosis, which is still valid up to date (Schwartz et al., 1957). SIADH is a disease characterized by high levels of vasopressin and hyponatremia (serum sodium concentration <136 mmol) (Hannon and Thompson, 2010). The increase in AVP production leads to the transcription and production of AQP2 water channels that play an important role in inappropriate water retention (Fujita et al., 1995). Water intake is associated with an increase in eGFR, suppression of aldosterone secretion, decrease in sodium reabsorption in the proximal tubules with the consequent increase in urinary sodium excretion (Cooke et al., 1979).

The therapeutic strategies, depending on the severity of the symptoms, aim to correct and maintain plasma sodium levels within the physiological range by limiting oral water intake and administrating salt tablets or intravenous saline (Adrogué and Madias, 2000). Furthermore, for the most severe form of SIADH, vasopressin receptor antagonists such as tolvaptan are also available and approved (Greenberg and Verbalis, 2006).

Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD)

It is also known as a hereditary form of SIADH, Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD), an X-linked recessive disease, associated with a gain-of-function mutation in the AVPR2 gene, which encodes the vasopressin V2 receptor (V2R). In 2005, Feldman and co-workers identified two unrelated male infants affected by hypertension, excessive water reabsorption, and hyponatremia associated with low or undetectable plasma vasopressin levels (Feldman et al., 2005). DNA sequencing of the V2R gene resulted in the substitution of arginine to leucine in codon 137 in one patient (R137L) and cysteine in the other (R137C). The residue R137 is located in the highly conserved DRY/H domain of the second intracellular loop which plays an important role in the stabilization of V2R in its active and inactive forms (Audet and Bouvier, 2012). In contrast, the

substitution of the same arginine residue to histidine is associated with loss of function of V2R signaling and causes NDI (Barak et al., 2001; Bernier et al., 2004). Since this first description, several activating mutations of V2R have been described, including F229V, I130N, and L312S (Carpentier et al., 2012; Erdélyi et al., 2015; Tiulpakov et al., 2016). The characterization of the intracellular signaling pathway activated in V2R-R137L, V2R-R137C, and V2R-F229V shows some important differences. It has been demonstrated that constitutively AQP2 translocation to the plasma membrane in the R137L/C mutants occurs via alternative PKA-independent signaling through ROCK-induced phosphorylation at S/T269-AQP2 and independently of S256 of AQP2. In contrast, in the V2R-F229V mutant, the constitutive AQP2 insertion to the plasma membrane relies on the exacerbated activation of the physiological cAMP/PKA axis associated with the activation of V2R-WT, determining the increase of the PKA-dependent pS256-AQP2 (Ranieri et al., 2020).

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Autosomal Dominant Polycystic Kidney Disease is a dominantly inherited disease characterized by the formation of fluid-filled cysts with slow, gradual, and massive bilateral kidney enlargement, leading to kidney failure in most individuals between 50 and 70 years of age (Bergmann et al., 2018). It is caused by mutations in *PKD1* or *PKD2* genes, encoding polycystin 1 (*PKD1*) or polycystin 2 (*PKD2*), respectively, which are associated with decreased cytosolic calcium content and increased intracellular cAMP levels, with consequent disruption of molecular pathways involved in cellular proliferation, tubulogenesis, and fluid secretion, eventually causing the development of fluid-filled cysts (Chebib and Torres, 2016; Sussman et al., 2020).

ADPKD patients show increased levels of AVP and its surrogate copeptin, which has been associated with disease severity and progression, measured as kidney function decline and kidney volume increase (Boertien et al., 2013; Boertien et al., 2012; Meijer et al., 2011). In line with these findings, previous studies showed that V2R, AQP2, and AQP3 mRNA are dramatically overexpressed in kidneys from cpk cystic mice at 7 days of age (Gattone et al., 1999) and that AQP2 expression level significantly increased along with cyst size in end-stage human ADPKD kidneys.

In PCK rats, an orthologous model of human PKD, it has been shown that vasopressin directly regulates cyst growth (Wang et al., 2008). PCK rats and vasopressin-deficient Brattleboro rats were crossed to generate rats with PKD and not expressing AVP (Wang et al., 2008). Interestingly, this model presented lower levels of cAMP and almost completely inhibited cystogenesis, while the administration of dDAVP recovered the full cystic phenotype, suggesting AVP as a powerful modulator of cystogenesis.

Recently, it has been demonstrated that steviol, a major metabolite of the sweetening compound stevioside, first isolated from the plant Stevia rebaudiana, could inhibit cyst growth by reducing AQP2 expression in both $Pkd1^{-/-}$ and MDCK cells (Noitem et al., 2018). Steviol inhibited AQP2 expression at the transcriptional level and also enhanced both proteasome and lysosome mediated AQP2 degradation, resulting in decreased water transport into the cyst lumen and retarded cyst growth (Noitem et al., 2018).

So far, no drug is effective to cure ADPKD, the current treatments are only capable to reduce the cyst's growth rate. Currently, the only treatment for patients with rapidly progressive disease approved in Europe, Japan, Canada, and United States is tolvaptan, a V2R antagonist.

A novel V2R antagonist, lixivaptan, initially developed for the treatment of hyponatremia (Bowman and Rosner, 2013), was shown to prevent the increase in intracellular cAMP, AQP2 trafficking, and water reabsorption in response to vasopressin in cortical collecting duct cells (Di Mise et al., 2019).

Conclusions

Over recent years numerous evidence reveals that the targeting of AQP2 to the plasma membrane is very complex (Figure 2). Several proteins including G proteins, cytoskeletal elements, AKAPs, fusion proteins contribute and are required to regulate the abundance of AQP2 at the apical plasma membrane. Post-translational modifications also play a crucial role to modulate the localization and the function of AQP2. In this review, some of the players and pathways controlling the AQP2 trafficking were described. Abnormal expression level or altered cellular distribution of AQP2, due to deregulated signal molecules, can cause several water unbalanced disorders. Deeper investigations

would improve the molecular signaling knowledge providing new insight to face water balance diseases including NDI and water retention conditions.

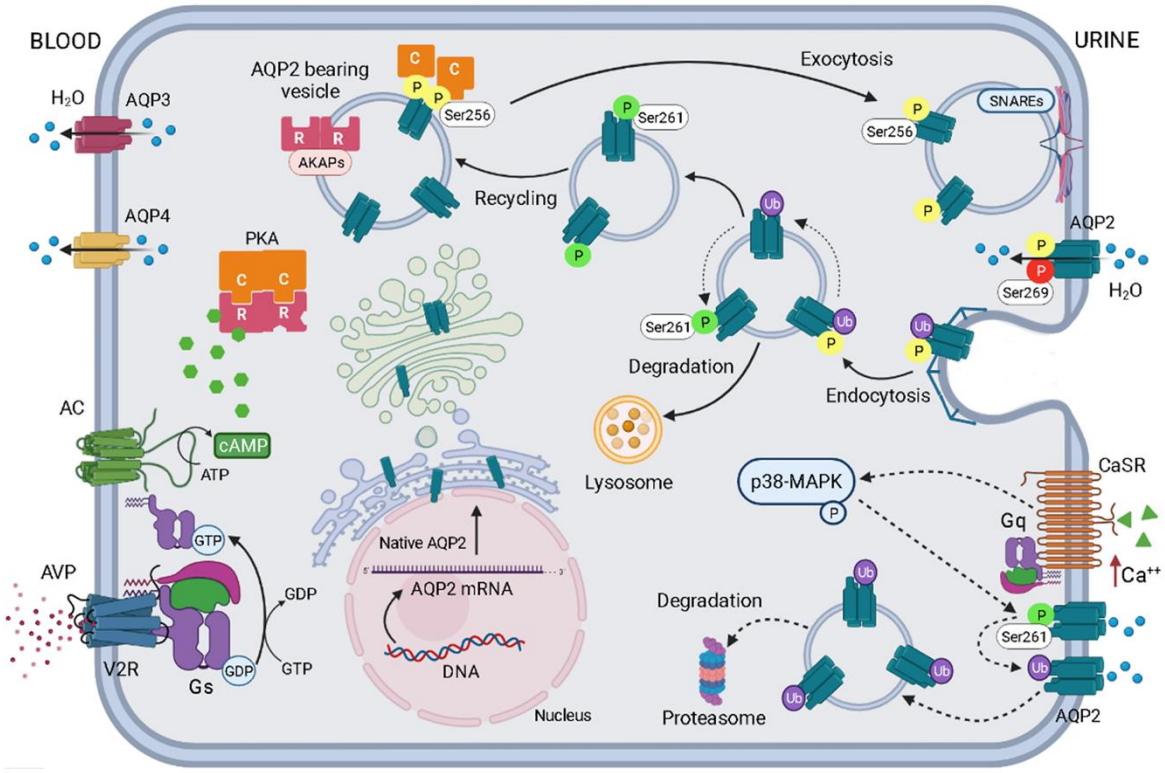

Figure 2: Representative model of AQP2 trafficking.

Vasopressin binds to V2R and induces AQP2 translocation to the apical plasma membrane via cAMP/PKA signaling that promotes AQP2 phosphorylation. AVP removal is associated with AQP2 phosphorylation at S261, ubiquitylation, and internalization. Stimulation of the CaSR signaling impairs the AQP2 trafficking.

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