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INVITED REVIEW

Physiology and pathophysiology of the vasopressin-regulated renal water reabsorption

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Abstract To prevent dehydration, terrestrial animals and humans have developed a sensitive and versatile system to maintain their water homeostasis. In states of hypernatremia or hypovolemia, the antidiuretic hormone vasopressin (AVP) is released from the pituitary and binds its type-2 receptor in renal principal cells. This triggers an intracellular cAMP signaling cascade, which phosphorylates aquaporin-2 (AQP2) and targets the channel to the apical plasma membrane. Driven by an osmotic gradient, pro-urinary water then passes the membrane through AQP2 and leaves the cell on the basolateral side via AQP3 and AQP4 water channels. When water homeostasis is restored, AVP levels decline, and AQP2 is internalized from the plasma membrane, leaving the plasma membrane watertight again. The action of AVP is counterbalanced by several hormones like prostaglandin E2, bradykinin, dopamine, endothelin-1, acetylcholine, epidermal growth factor, and purines. Moreover, AQP2 is strongly involved in the pathophysiology of disorders characterized by renal concentrating defects, as well as conditions associated with severe water retention. This review focuses on our recent increase in understanding of the molecular mechanisms underlying AVP-regulated renal water transport in both health and disease.

Keywords Water reabsorption · Aquaporin-2 · PKA phosphorylation · Protein trafficking · Nephrogenic diabetes insipidus · Polycystic kidney disease

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Introduction

Maintaining water homeostasis by controlling both the osmolality and intravascular blood volume is essential for terrestrial mammals to survive. Water is lost through breathing, sweating, defecation, and urination and is obtained through glucose metabolism, drinking, and urinary water conservation. While several of these processes occur autonomic in healthy individuals, body water homeostasis is tightly controlled by regulating both water intake (drinking) and urinary water excretion. Changes in intravascular blood volume are sensed by vascular volume- and baroreceptors, which regulate the release of the antidiuretic hormone arginine vasopressin (AVP) [151]. Changes in osmolality are sensed by osmoreceptors located within specific regions of the hypothalamus, the organum vasculosum lamina terminalis (OVLT) and the subfornical organ (SFO) [21, 229]. In states of hypernatremia, these receptors are activated, which results in the sensation of thirst and subsequent water intake. Furthermore, neurons from the OVLT and SFO project to the supraoptic and paraventricular nuclei, where AVP is synthesized. These neurons project to the posterior pituitary from where AVP is released into the blood and sets out for the kidney where water excretion is governed (reviewed in [21, 115]). Approximately 90% of all water filtered by the glomeruli is reabsorbed constitutively in the proximal tubule and descending loop of Henle. Depending on the body's needs, remaining water can be reabsorbed in renal collecting duct, defining the final urine concentration. The adjustment of water reabsorption mainly depends on the release of AVP. When reaching the kidney, AVP binds its vasopressin V2 receptor (V2R) in the basolateral membrane of principal collecting duct cells, initiating a signal transduction cascade that consists of activation of adenylate cyclase (AC) via the

stimulatory G (Gs) protein, an increase in intracellular cAMP levels, and activation of protein kinase A (PKA). Subsequently, aquaporin-2 (AQP2) water channels are phosphorylated and translocated from intracellular storage vesicles to the apical plasma membrane, rendering this membrane permeable to water [55, 162, 163, 228]. Due to the increase in water permeability, water is able to pass the apical membrane passively through AQP2 along the osmotic NaCl and urea gradient and leaves through AQP3 and AQP4, which are constitutively expressed on the basolateral side of these cells. When isotonicity is restored, reduced blood AVP levels results in AQP2 internalization, leaving the apical membrane watertight again.

Activation of AQP2 translocation

Adenylate cyclase in the renal collecting duct

It is widely accepted that short-term AQP2 regulation, meaning AQP2 shuttling between intracellular storage vesicles and the apical plasma membrane, requires a functional AVP-AC-cAMP-PKA signaling cascade (Fig. 1). Upon V2R stimulation by AVP, membrane-bound AC is activated to synthesize cAMP from ATP. So far, nine mammalian AC isoforms have been identified. In the outer medullary collecting duct (OMCD), Ca^{2+}-inhibitable isoforms AC5 and AC6 were detected by in situ hybridization [77]. AC6 was found in principal cells, whereas both AC5 and AC6 were detected in intercalated cells. In inner medullary collecting duct (IMCD), AC2-7 and AC9 mRNA were observed by RT-PCR [84]. So far, only AC3, a Ca^{2+}-stimulated isoform, and AC6 proteins have been detected in IMCD [84]. Their presence in principal cells suggests that one or both isoforms are responsible for the AVP-stimulated rise in cAMP. The contribution of each isoform to the cAMP increase, however, remains to be elucidated.

Epac signaling

Activation of AC increases intracellular cAMP levels. Traditionally, the role of intracellular cAMP in AQP2 translocation was thought to be restricted to the activation of PKA. Previously, a novel target of cAMP was discovered, namely "the exchange protein directly activated by cAMP" (Epac) 1 and 2 (also known as cAMP guanine-nucleotide-exchange factor) [37]. Epac1 and Epac2 activate specifically Rap1 and Rap2, monomeric G proteins of the Ras family, which are implicated in cellular functions like cell adhesion and cell-junction formation (reviewed in [17]). In addition, Epac has been associated with exocytosis, mitogen-activated protein kinase (MAPK) signaling,

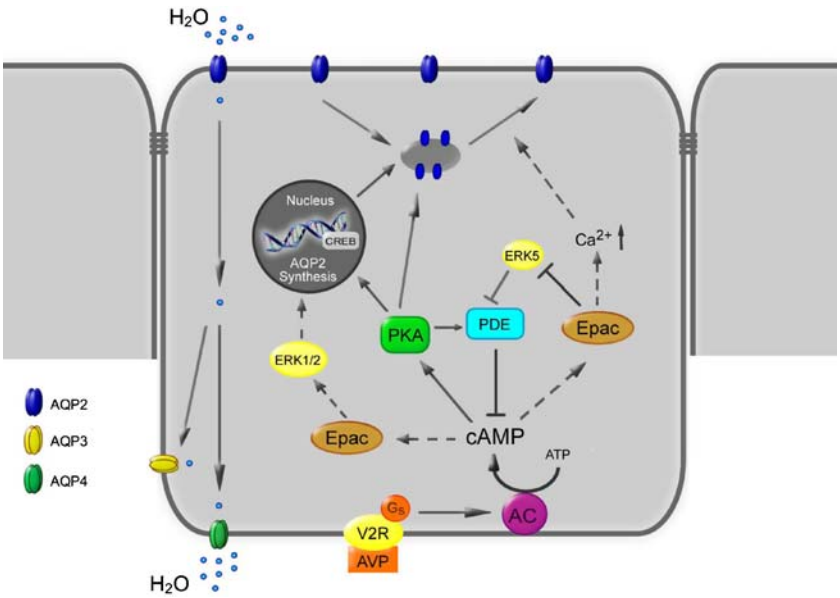

Fig. 1 Model of the regulation of water permeability in renal collecting duct cells. Binding of vasopressin (*AVP*) to the V2 receptor (*V2R*) in the basolateral membrane activates adenylate cyclase (*AC*) and increases intracellular cAMP levels. This activates protein kinase A (*PKA*), which induces translocation of AQP2-bearing vesicles to the apical membrane, rendering this membrane water permeable. In addition, cAMP can activate exchange protein directly activated by cAMP (*Epac*). Epac can increase cytosolic Ca^{2+}, which may facilitate AQP2 translocation. cAMP signaling is abrogated by phosphodiesterase (*PDE*)-mediated degradation of cAMP. Epac might control PDE activity by inhibiting ERK5, which inhibits PDE. PKA also increases AQP2 synthesis by phosphorylation of the cAMP-responsive element-binding (*CREB*) protein and its binding to the AQP2 promoter. Possibly, Epac enhances AQP2 synthesis by inhibiting extracellular signal-regulated kinases 1 and 2. Water, entering the principal cell via AQP2, can leave the cell via constitutively expressed AQP3 and AQP4

hormone gene expression, and phospholipase C-epsilon (PLC-ε) activation [17]. Recently, several studies demonstrated that Epac is also involved in the regulation of ion channel activity and, as such, Epac2 has been implicated in the release of Ca^{2+} from internal stores via ryanodine-sensitive Ca^{2+}-channels (see also further [5, 78, 105, 106]). Both Epac1 and Epac2 are highly expressed in kidney and might therefore be of interest in the regulation of AQP2. Yip provided the first evidence for a role of Epac in AQP2 regulation by demonstrating that activation of Epac with a specific agonist induces intracellular Ca^{2+} mobilization as well as AQP2 translocation [248]. Possibly, both PKA-mediated phosphorylation and Epac-activated Ca^{2+} mobilization play a role in AVP-activated AQP2 translocation towards the apical membrane. To which extent this novel pathway contributes to the AVP-induced water reabsorption remains to be established.

Ca^{2+} and AQP2-mediated water reabsorption

Ca^{2+} plays an important role in AQP2-regulated water reabsorption. While local increases in intracellular Ca^{2+} concentration are known to be of great importance for the fusion of vesicles with the plasma membrane (reviewed in [10, 71]), the importance of a transient Ca^{2+} increase for AQP2 translocation is still controversial. AVP induces a transient increase in the intracellular Ca^{2+} concentration and sustained Ca^{2+} oscillations in microdissected rat OMCD and IMCD tubules [29, 43, 136]. In perfused IMCDs, pre-incubation with BAPTA, which buffers intracellular Ca^{2+}, blocked the osmotic water permeability, indicating that intracellular Ca^{2+} is required for AQP2 membrane insertion [31, 247]. In addition, both ryanodine-sensitive Ca^{2+} stores and calmodulin are likely to be involved in the Ca^{2+}-dependent translocation of AQP2 since ryanodine and calmodulin blockers were shown to inhibit AVP-mediated AQP2 trafficking and water permeability in IMCD cells [31]. Lorenz et al., however, demonstrated that cAMP alone is sufficient to induce AQP2 shuttling, without the necessity of a cytosolic Ca^{2+} increase in IMCD cells [131]. Using Madin–Darby canine kidney (MDCK) cells stably transfected with AQP2 and stimulated with 1-desamino-8-D-arginine vasopressin (dDAVP), we found similar results (unpublished data). Combined, these data suggest that intracellular Ca^{2+} but not necessarily an AVP-induced increase in Ca^{2+} is needed for AQP2 translocation.

Phosphodiesterase in the renal collecting duct

Phosphodiesterases (PDEs) play an important role in the control of cAMP levels within specific cellular compartments. After its cAMP-induced activation and subsequent phosphorylation of PKA target proteins like AQP2, PKA signaling is abrogated by PDE-mediated cAMP degradation. The activity of PDE can have profound physiological effects because increased PDE activity was found to cause hereditary nephrogenic diabetes insipidus (NDI) in mice [88, 95, 209]. Activated PKA directly phosphorylates and activates the PDE4D3 isoform, thereby confining its own activity [28, 201]. Additionally, activated Epac1 is able to inhibit extracellular signal-regulated kinase 5 (ERK5), which inactivates PDE isotypes such as PDE3 and PDE4D3, thereby contributing to the control of cAMP signaling [40]. The PDE superfamily consists of 11 gene families, and several PDE transcripts are expressed along the nephron [41, 118, 243]. In the collecting duct, the Ca^{2+}- and calmodulin-dependent PDE1 and the cGMP-specific PDE5 were identified, as well as the highly expressed cAMP-specific PDE4 [243].

During the last decade, it has become clear that intracellular cAMP levels are locally regulated in which the so-called kinase-anchoring proteins (AKAPs) play a crucial role. AKAPs bind PKA, PKA substrates, phosphatases, and PDEs, and due to their unique targeting domains, they target these proteins, and thus cAMP-induced signaling cascades to various subcellular compartments (reviewed in [11, 203]). Indeed, in elegant studies, the Klussmann team identified AKAP18δ as the important anchoring protein in AQP2 regulation in IMCD cells; because PDE4D was recruited by AKAP18δ onto AQP2-bearing vesicles, AKAP18δ and AQP2 were co-translocated to the apical membrane upon AVP stimulation, and the interaction between AKAP18δ and PKA was abrogated by an increase in cAMP levels [79]. Moreover, using fluorescence resonance energy transfer on a PKA phosphorylation-sensitive probe, they showed in vivo IMCD cAMP dynamics to occur on AQP2-containing vesicles.

The cGMP pathway

Formerly, AQP2 translocation was thought to be the result of cAMP increase only. However, compounds increasing cGMP levels, like the hormone atrial natriuretic peptide (ANP), nitric oxide donors, nitric oxide synthase substrate, and cGMP phosphodiesterase inhibitors, also appear to stimulate AQP2 translocation to the plasma membrane [18, 19]. The exact pathway responsible for the cGMP-mediated AQP2 effect, however, is not clear yet as it is unknown whether the activated cGMP-mediated protein kinase G (PKG) directly phosphorylates AQP2 and induces its translocation or whether the effect could be due to PKG-mediated PKA activation. Moreover, the physiological relevance of these findings remains unclear since the effects of an increase in cGMP (through ANP) in vivo are controversial. Some studies show that ANP inhibits AVP-stimulated water permeability and sodium reabsorption,

whereas others do not [39, 171, 172, 192, 198]. In addition, a recent study demonstrated that ANP infusion induces a transient diuresis in rats [231].

Activation of AQP2 expression

Hypertonicity

In addition to short-term AQP2 regulation, AVP also increases long-term AQP2 expression in collecting duct cells, mediated through a cAMP-responsive element in the AQP2 promoter [149, 246]. However, recent studies reported that hypertonicity also increases AQP2 expression independent of AVP by activating two other pathways individually capable of increasing AQP2 transcription [70, 107, 126]. First of all, hypertonicity activates the transcription factor tonicity-responsive enhancer binding protein (TonEBP) by increasing its nuclear targeting, transactivation, and transcription. Subsequent binding of TonEBP to the AQP2 promoter increases the transcription of AQP2 [70]. Accordingly, TonEBP/NFAT5-deficient mice showed decreased AQP2 expression [130]. Secondly, activation of the nuclear factor of activated T cells c (NFATc) pathway can increase AQP2 expression in the collecting duct [126]. A hypertonicity-induced Ca^{2+} increase activates the protein phosphatase calcineurin that dephosphorylates NFATc. Subsequently, NFATc translocates to the nucleus to bind the AQP2 promoter and increases AQP2 transcription. Although both pathways independently increase AQP2 expression, cross-talk between these pathways increases AQP2 expression even further.

MAPK signaling

Several studies also indicate a role for MAPK signaling in AQP2 transcription. The V2R is capable of both inhibiting and activating ERK 1 and 2 (ERK1/2) MAPK activity. In this context, inhibition of ERK1/2 activation by V2R appears to be mediated by Gαs and activation of PKA, whereas activation of ERK1/2 by V2R was shown to be independent of G-protein coupling but involves the recruitment of β-arrestin [30]. Recently, the hormone insulin, which is known to play a role in renal water and sodium excretion, was shown to enhance AVP-induced AQP2 expression by increasing its mRNA levels [26, 167]. The effect of insulin on AVP-dependent AQP2 mRNA expression is mediated by both ERK1/2 and p38 MAP kinase activation [26]. Umenishi et al. demonstrated that inhibition of ERK blocked the AVP-induced AQP2 expression, whereas inhibitors of two other MAP kinases, p38 and JNK kinase, did not affect AQP2 expression, indicating a role for ERK in regulating AVP-mediated AQP2 expression [223]. Interestingly, this ERK activation was induced by the Epac-specific activator, 8CPT-2Me-cAMP. Together, these results suggest that AVP might initiate an alternative cAMP-Epac-ERK signaling pathway that contributes to AQP2 expression.

AVP-independent activation of AQP2-mediated water transport

While AVP plays a key role in the activation of AQP2-mediated water transport, there is emerging evidence for the existence of AVP-independent mechanisms, regulating both AQP2 trafficking and expression. Oxytocin has been demonstrated to induce AQP2 translocation, which could be prevented by blockage of the V2R, suggesting that oxytocin can activate AQP2-mediated water transport via V2R signaling [96]. It remains to be established, however, whether this also occurs at physiologically obtainable levels of oxytocin. Furthermore, in AVP-deficient Brattleboro rats, induction of hyperosmolality increased AQP2 expression and translocation, indicating the presence of an AVP-independent mechanism [124]. Possibly, the hormone secretin might be involved in this. Secretin is a hormone traditionally involved in regulating the pH of duodenum content by controlling gastric acid release and bicarbonate secretion. Recently, however, it was found that secretin receptor knockout mice demonstrate mild forms of polyuria and polydipsia, as well as reduced levels of AQP2 [33]. Also, in secretin receptor knockout mice, the effect of water deprivation on AQP2 translocation and expression was also clearly diminished. Moreover, in normal mice, secretin was able to induce AQP2 plasma membrane translocation, as well as AQP2 expression in inner medullary tubular cells. The exact way in which secretin changes AQP2 expression remains to be defined.

Inhibition of AQP2-mediated water transport

Upon withdrawal of AVP, AQP2 is internalized from the membrane into intracellular storage vesicles, decreasing water reabsorption in the collecting duct. In addition, several hormones have been reported to antagonize AVP-mediated water transport in kidney (Fig. 2).

Luminal AVP

In addition to the V2R, which is expressed at the basolateral membrane of principal cells, several studies suggest the presence of the V1a receptor (V1aR) in the apical membrane of the collecting duct, which, upon activation in the presence of basolateral AVP, reduce the

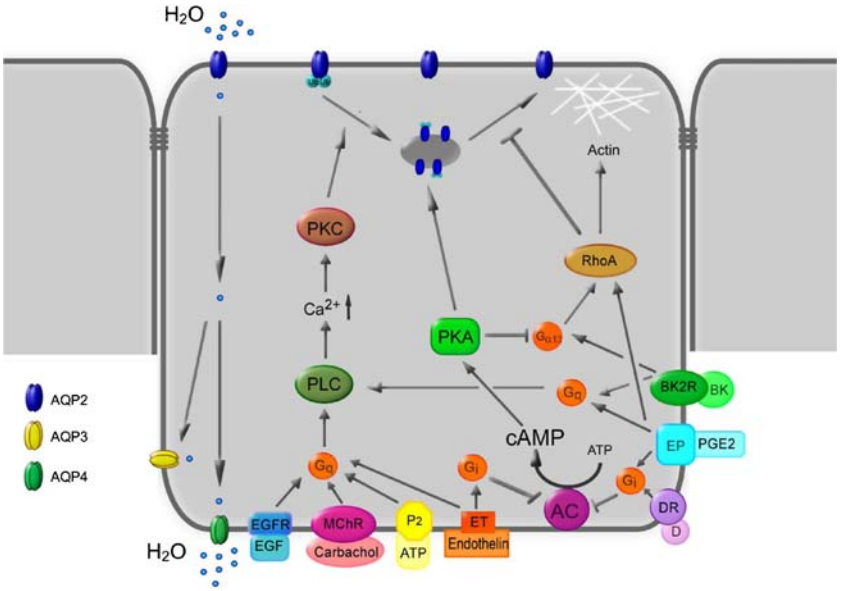

Fig. 2 Model of the inhibition of AQP2-mediated water reabsorption. Several hormones can antagonize AVP-induced water transport. Indicated are *AC* adenylate cyclase, *ATP* adenosine tri-phosphate, *BK(2R)* bradykinin (type-2 receptor), *cAMP* cyclic adenosine mono-phosphate, *D(R)* dopamine (receptor), *EGF(R)* epidermal growth factor (receptor), *EP* E-prostanoid receptor, *ET* endothelin receptor, $G_{\alpha 13}$ G protein involved in Rho family GTPase signaling, G_i inhibitory G protein, G_q PLC activating G protein, *MChR* muscarinic cholinergic receptor, *P2* purinergic receptor, *PGE2* prostaglandin-E2, *PKA* protein kinase A, *PKC* protein kinase C, *PLC* phospholipase C, *Ub* ubiquitin. For details, see text

V2R-mediated water reabsorption (reviewed in [170]). In the rabbit cortical collecting duct, luminal AVP was suggested to act via the V1R and to increase intracellular Ca^{2+} levels [3, 4, 93]. Others reported that V1aR activation stimulated the synthesis of prostaglandins, which reduce AVP-induced cAMP accumulation (see below; [8]). V1aR-mediated signaling might thus contribute to the inhibition of V2R-induced AQP2-mediated water reabsorption.

Prostaglandin E2

In the absence of AVP, prostaglandin E2 (PGE2) has been shown to stimulate water transport, but in its presence, PGE2 decreases water permeability [76]. The differences in PGE2-mediated actions on water permeability might be explained by the presence of four E-prostanoid receptor subtypes, denominated EP1, EP2, EP3, and EP4, and the different G proteins they couple to (reviewed in [22]). The stimulatory effect of PGE2 on basal water permeability was reported to be most likely mediated via the EP4 receptor, which couples to Gs, thereby activating AC and increasing cAMP levels [193]. The inhibitory effect of PGE2 on AVP-induced water reabsorption is most likely mediated by EP1 and/or EP3 receptors [73, 76], as EP1 receptors couple to G_q and their activation by PGE2 increases intracellular Ca^{2+} levels, while the EP3 receptor couples to G_i, thereby inhibiting cAMP generation. The molecular mechanism that underlies the PGE2-mediated inhibition of water transport, however, is far from complete understanding. PGE2 was demonstrated to impair AVP- but not forskolin-induced water permeability, suggesting that PGE2 affects water permeability at a step between the V2R and AC [155]. In other studies, PGE2 was shown to inhibit AVP-induced water permeability by activating protein kinase C (PKC) without affecting cAMP levels [74, 157]. A role for Ca^{2+} in mediating PGE2 action was also described [75]. In addition, PGE2 counteracts AVP action by retrieving AQP2 from the plasma membrane [161, 250].

Furthermore, modulation of the cytoskeleton by PGE2 is an important factor. Tamma et al. demonstrated that AVP inactivates the monomeric G protein Rho, which results in the depolymerization of the actin cytoskeleton and is a prerequisite for AQP2 translocation. Consistently, PGE2 binding to its EP3 receptor activates Rho, thereby inhibiting water permeability [114, 212, 215]. In line with an inhibitory function on AVP-induced water uptake, inhibition of PGE2 production by indomethacin increases urine osmolality in wild-type mice but not in EP3-deficient mice, suggesting that PGE2 indeed reduces AQP2 expression in the plasma membrane via the EP3 receptor [52]. Interestingly, however, in untreated EP3-deficient mice, urine volume and osmolality do not differ from wild-type mice, suggesting that PGE2 action through the EP3 receptor is not essential for the regulation of urinary concentrating mechanism under basal conditions [52]. Like EP3, EP1 is expressed along the collecting duct and could therefore also mediate the PGE2 effects on water transport. Indeed, in EP1-deficient mice, urine osmolality was diminished upon

water deprivation compared to wild-type mice [110]. However, the defect in urine concentration could not be contributed to EP1 expression in collecting duct because the EP1-deficient mice demonstrated normal collecting duct AQP2 expression and translocation. Instead, it was concluded that the lack of the EP1 receptor affected the AVP production in the hypothalamus [110].

Bradykinin

Bradykinin also antagonizes AVP-induced water permeability. Indeed, in bradykinin receptor knockout mice, both water deprivation and administration of a V2R agonist results in more concentrated urine [2]. The intracellular action of bradykinin is diverse. At first, bradykinin can act indirectly by stimulating prostaglandin production [176]. Directly, bradykinin has been shown to activate the bradykinin-2 receptor (BK2R), which couples to G_q and activates PKC [180]. Furthermore, bradykinin, like PGE2, inhibits AQP2 translocation by activating Rho [211]. This effect is independent of PGE2 since bradykinin also inhibits Rho-dependent AQP2 translocation in the presence of indomethacin, which blocks cyclo-oxygenase production and thereby prostaglandin synthesis.

Dopamine

Dopamine also decreases water permeability in the collecting duct by lowering cAMP production. In the cortical collecting duct, this effect is mediated by dopamine-induced activation of D4-like receptors [125, 206]. In the IMCD, the inhibitory effect of dopamine is mediated through α2-adrenoceptors, which can also be activated by catecholamines [46]. Like PGE2, dopamine also causes AQP2 internalization from the plasma membrane into intracellular storage vesicles independent of AQP2 dephosphorylation [161]. The mechanism, however, is unclear.

Endothelin-1

Collecting duct-derived endothelin-1 plays a key role in the regulation of systemic blood pressure and renal salt and water excretion (reviewed in [116]). Direct evidence for endothelin-1 functioning in renal water excretion originates from recent knockout studies. Collecting duct-specific endothelin-1 knockout mice showed reduced plasma AVP levels but normal plasma and urine osmolality, as well as urine volume [60]. An acute but not chronic water load was eliminated less efficient in the knockout mice compared to wild-type mice, and upon V2R agonist infusion, knockout mice demonstrated increased urine osmolality, AQP2 phosphorylation, and V2R expression [60]. Also, in these knockout mice, AVP-induced cAMP levels are increased, as well as AC5/6 protein levels [205]. Thus, collecting duct-derived endothelin-1 appears to inhibit AVP-induced actions. Endothelin-1 is reported to have opposite effects on sodium and water excretion in different parts of the kidney, which is most likely due to the fact that endothelin-1 can exert its effects via two distinct receptor subtypes, ET_A and ET_B [56, 57, 81]. Early studies suggested that endothelin-1 inhibits the AVP-induced water permeability in the renal collecting duct via activation of the ET_B receptor through coupling to a G_i protein and inhibition of cAMP generation and through G_q protein coupling and activation of PKC [47, 156, 173, 217]. This is thus in line with the data on the endothelin-1 knockout mice. However, collecting duct-specific ET_B knockout mice showed no differences in water intake and urine volume during normal or high sodium diet compared to their control littermates [47, 60, 61, 66, 87]. Surprisingly, collecting duct-specific ET_A knockout mice demonstrated higher AVP plasma levels, accompanied by a slightly increased ability to excrete acute water load [62]. Thus, signaling via the ET_A receptor reduces endothelin-1 inhibition of AVP actions. Clearly, the exact mechanism responsible for the effects on AVP-mediated water reabsorption by the collecting duct-derived endothelin-1 remains elusive.

Acetylcholine and epidermal growth factor

Acetylcholine exerts its effects by activating the muscarinic-type cholinergic receptors. Carbachol, an acetylcholine analogue, inhibits AVP-induced water flow but not cAMP production and mediates this effect by an increase in intracellular Ca^{2+} followed by PKC activation [67, 137]. Likewise, epidermal growth factor (EGF) inhibits AVP- and cAMP-stimulated water reabsorption through interaction with its EGF receptor, which also involves increased intracellular Ca^{2+} levels without affecting cAMP production [23, 67]. The exact molecular mechanism remains to be determined.

Extracellular purines

It has already been known for a long time that the extracellular purines, ATP and UTP, decrease AVP-induced water permeability by increasing intracellular Ca^{2+} levels, which is accompanied by activation of PKC [44, 112]. In addition, purines can also activate the Rho kinase pathway, which is involved in AQP2 trafficking, as described above [197, 212]. Extracellular purines can mediate their action via the ionotropic P2X receptors ($P2X_{1–7}$), as well as the metabotropic, G-protein-coupled P2Y receptors ($P2Y_{1, 2, 4, 6, 11–13}$) [186]. Various P2X receptors have been identified in the collecting duct, including $P2X_{3–6}$ receptors (reviewed in [199, 224]). Clearest evidence for the involvement in AQP2

regulation has been found for the $P2Y_2$ receptor. In principal cells, both $P2Y_1$- and $P2Y_2$-like receptors are expressed in the basolateral membrane, and mRNAs of $P2Y_4$ receptor, as well as $P2Y_6$ receptor, were found along the OMCD (reviewed in [7, 199]). Furthermore, $P2Y_2$ receptors were also localized to the apical membrane of collecting duct principal cells [7], although only basolateral ATP was shown to inhibit AVP-induced water permeability in perfused rat IMCD tubules [45]. Moreover, circulating AVP levels were shown to affect the expression of $P2Y_2$ receptors since in water-deprived rats, decreased expression of $P2Y_2$ receptors in IMCDs were found [113, 207]. Clearest evidence came from recent studies on $P2Y_2$ receptor knockout mice. Although net urinary reabsorption was not different compared to wild-type mice, these knockout mice showed increased renal medullary expression of AQP2, as well as elevated urinary cAMP excretion. In response to the V2R antagonist SR121463, P2Y2 receptor knockout mice showed greater diuresis and lower urine osmolality compared to wild-type animals, suggesting that in the absence of P2Y2 receptor, AVP enhances cAMP formation and AQP2-mediated water reabsorption. This study provides the first evidence that under normal conditions, a continuous activation of the P2Y2 receptor by ATP exists, resulting in reduced cAMP formation and AVP-induced water reabsorption [187]. Whether other P2 receptors contribute to the purinergic effect on AVP-mediated water reabsorption remains elusive.

There are also indications that ATP may affect AQP2-mediated water permeability indirectly. Hughes et al. showed that ATP also decreases the production of endothelin-1, thereby possibly affecting AVP-induced water transport through this hormone [90]. Moreover, extracellular purines stimulate $P2Y_2$ receptor-mediated release of PGE2, which reduces water reabsorption as well [235].

Extracellular Ca^{2+}

In addition to the hormones mentioned above, Ca^{2+} inhibits AVP-induced water transport by activation of the calcium receptor (CaR). Although the importance of a transient increase in intracellular Ca^{2+} levels for AQP2 trafficking is still controversial, extracellular Ca^{2+} exerts clear effects on AVP-mediated water transport. CaR agonists have been shown to inhibit AVP-induced water permeability in perfused IMCD tubules [196]. In addition, extracellular Ca^{2+}, acting through the CaR, was shown to antagonize forskolin-induced AQP2 trafficking in AQP2-transfected collecting duct cells [181]. In vivo studies support these effects because in hypercalcemic rats, AVP was unable to increase the osmotic water permeability in the IMCD, and AQP2 protein levels were decreased [195]. Similarly, Valenti et al. found that while in healthy children with normally increased nighttime AVP levels daytime urinary AQP2 levels were nearly half of the nighttime AQP2 levels, enuretic children with normal nocturnal AVP levels but with hypercalciuria displayed low nighttime urine AQP2 levels compared to daytime samples [226]. Moreover, a low-Ca^{2+} diet given to these enuretic hypercalciuric children restored AQP2 excretion and relieved enuresis in 80% of these children [225]. Although these findings suggest that high levels of Ca^{2+} in urine indeed contribute to the regulation of AVP-dependent water reabsorption, Raes et al. recently found that nocturnal polyuria in a group of hypercalciuric children coincided with nocturnal natriuresis, suggesting that the polyuria might be due to osmotic diuresis [185]. It would be interesting to know whether the children from the Valenti study showed the same differences in daytime–nighttime sodium excretion and whether the nocturnal enuresis in the patients from Raes et al. would be diminished when these children would receive a low-calcium diet.

Molecular regulation of AQP2 translocation

AQP2 phosphorylation

As mentioned, a prerequisite for AVP-mediated apical translocation is the phosphorylation of AQP2 at Ser-256 by PKA [55, 109, 228]. Although each AQP2 monomer forms a functional water channel, AQP2 is expressed as a homotetramer, and phosphorylation of at least three out of four monomers is required for apical membrane localization [102]. The role of other putative phosphorylation sites in AQP2, three putative casein kinase II sites (Ser-148, Ser-229, and Thr-244), and one PKC site (Ser-231) was also investigated but could not be associated with AQP2 trafficking [228]. Recently, three novel phosphorylation sites were identified in the C-terminus of AQP2, Ser-261, Ser-264, and Ser-269, which are of potential importance in AVP-induced AQP2 trafficking [86]. While AVP treatment increases the phosphorylation of Ser-256 of AQP2, Hoffert et al. demonstrated that phosphorylation of Ser-261 in the AQP2 C-terminus is reduced upon AVP treatment [85]. Also, the subcellular localization of these phosphorylated proteins is distinct: While AQP2 phosphorylated at Ser-256 is predominantly expressed in the apical membrane, AQP2 phosphorylated at Ser-261 localizes subapically and gives a punctuate staining [85]. These findings suggest a role for Ser-261 phosphorylation in the trafficking of AQP2. Further investigation is required to establish a role of Ser-261 phosphorylation in AQP2 trafficking and to find out to what extent phosphorylation of Ser-264 and Ser-269 might contribute to AQP2 trafficking, translocation, and water permeability.

Calcineurin, a Ser/Thr phosphatase, might also be involved in AQP2 trafficking. Calcineurin, also known as

protein phosphatase 2B, was found in a complex with AQP2 and could dephosphorylate AQP2 in vitro [97]. Paradoxically, mice lacking the α isoform of calcineurin A subunit were unable to concentrate their urine in response to dDAVP [64]. Accordingly, these mice showed a decrease in phosphorylated AQP2 levels in response to AVP and AQP2 appeared to be retained in an intracellular compartment. While these data indicate that phosphatase activity of calcineurin might be required for apical AQP2 translocation, its role in AQP2 regulation thus seems to be more complex than just a phosphatase that may dephosphorylate AQP2 at Ser-256.

AQP2-associated proteins

To date, only four proteins are known to directly interact with AQP2. Noda et al. identified two AQP2 interacting proteins, actin and signal-induced proliferation-associated protein 1 (SPA-1) [168, 169]. Translocation of AQP2 to the apical plasma membrane is associated with the depolymerization of the actin cytoskeleton (see below), and binding of AQP2 to actin might therefore be a key step for AQP2 translocation. SPA-1 is a specific GTPase-activating protein for Rap1 whose activity is required for AQP2 translocation to the apical membrane [168]. Interestingly, Epac 1 and 2 also activate Rap1 and have been shown to be involved in AQP2 translocation (see above). At present, however, it is unclear whether SPA-1 is involved in the Epac signaling cascade. Secondly, AQP2 interacts with heatshock protein 70 (Hsc70), which is part of the endocytotic machinery that regulates clathrin-mediated endocytosis [133]. In addition to Hsc70, AQP2 also interacts with other components of the clathrin-mediated endocytotic machinery, such as clathrin, dynamin, and the clathrin adaptor protein AP2. This is consistent with previous reports demonstrating that AQP2 is internalized via clathrin-mediated endocytosis [24, 132, 208]. Finally, a recent study by Kamsteeg et al. demonstrated that AQP2 interacts with myelin and lymphocyte-associated protein (MAL). MAL is constitutively expressed in the collecting duct apical membrane and was shown to increase AQP2 phosphorylation and decrease its internalization, thereby enhancing its apical membrane expression [101]. The interaction between AQP2 and MAL increases the apical membrane expression of AQP2 by decreasing AQP2 endocytosis. It will be interesting to determine whether AQP2 ubiquitination is involved and whether exocytosis from recycling endosomes is affected as well.

The microtubular network

Besides AQP2 phosphorylation, the microtubular network and cytoskeleton also play an important role in the trafficking of AQP2 bearing vesicles to the apical membrane. Intracellular trafficking requires a microtubular network and microtubule-associated motor proteins like dynein and dynactin of which several have been identified in AQP2-bearing vesicles [144, 178, 179]. The motor protein myosin Vb and its vesicular receptor Rab11 are involved in protein recycling and, recently, these proteins have been shown to play a role in AQP2 trafficking [122, 160]. Myosin Vb was shown to colocalize with AQP2 in principal cells of rat kidney slices. Upon expression of a dominant-negative myosin Vb mutant in AQP2-expressing CD8 cells, forskolin-induced AQP2 translocation to the apical membrane was abolished [160]. Similarly, it was demonstrated that Rab11 family interacting protein 2 (Rab11-FIP2), a protein that mediates interaction between myosin Vb and its vesicular receptor Rab11, plays a role in the trafficking of AQP2. A dominant-negative Rab11-FIP2 mutant, which disrupts Rab11-dependent recycling, impaired forskolin-induced AQP2 translocation to the apical membrane [160]. Thus, myosin Vb and Rab11-FIP2 play a role in the translocation of AQP2 to the membrane.

The cytoskeleton

Upon translocation to the apical plasma membrane, AQP2-bearing vesicles finally need to fuse with the membrane. This fusion is likely mediated by soluble *N*-ethylmaleimide sensitive fusion factor attachment protein receptors (SNARE) proteins. Several SNARE proteins like syntaxin-4 and synaptosome-associated 23-kDa protein have been found in collecting duct principal cells and are enriched in AQP2-bearing vesicles [94, 139, 140, 165]. Moreover, Gouraud et al. demonstrated that the vesicle-associated membrane protein 2 is required for AVP-induced AQP2 translocation [65].

Before being able to fuse, however, these vesicles have to pass the cytoskeleton. In mammalian collecting duct and toad bladder, vasopressin-induced AQP2 translocation to the plasma membrane is associated with depolymerization of the actin cytoskeleton [72, 202]. In this process, the small GTPase RhoA plays an important role in AQP2 translocation by modulating the actin cytoskeleton conformation. Inhibition of RhoA activity by PKA-mediated phosphorylation induces partial depolymerization of the actin cytoskeleton, thereby facilitating the translocation of AQP2-bearing vesicles to the apical membrane [114, 212, 214, 227]. AQP2 translocation also requires the Ezrin–Radixin–Moesin (ERM) protein moesin. ERM proteins play an important role in the regulation of F-actin cytoskeleton by cross-linking actin filaments with proteins in the plasma membrane. Tamma et al. demonstrated that functional moesin is required for AQP2 trafficking to the apical membrane [213]. ERM proteins function both upstream and downstream of the Rho GTPases and could

therefore be affected by RhoA signaling or affects RhoA activity itself. In addition, ERM proteins might affect AQP2 trafficking by mediating the interaction of actin with AQP2.

AQP2 internalization

Upon AVP withdrawal, AQP2 is internalized from the plasma membrane and accumulates in intracellular vesicles [108, 163]. In addition, activation of PKC by the phorbol ester 12-tetradecanoylphorbol-13-acetate causes internalization of AQP2 [228]. While phosphorylation of Ser-256 is essential for AVP-induced AQP2 translocation to the plasma membrane, dephosphorylation of AQP2 does not seem to be required for its internalization [228]. Retrieval of AQP2 from the plasma membrane was demonstrated to occur via clathrin-mediated endocytosis [24, 25]. Inhibition of clathrin-mediated endocytosis resulted in AQP2 accumulation at the plasma membrane [208].

The molecular mechanism underlying the internalization of AQP2 was not known. Recently, however, Kamsteeg et al. demonstrated that AVP removal or PKC activation by phorbol esters induces short-chain ubiquitination of AQP2, followed by endocytosis and subsequent sorting to multivesicular bodies [103]. While AQP2 has three putative attachment sites for ubiquitin (cytosolic lysines) at positions Lys-228, Lys-238, and Lys-270, analysis of cells expressing AQP2 mutants in which these lysines were replaced by arginines revealed that only Lys-270 is a substrate for ubiquitination. Consistently, AQP2-K270R was delayed in its internalization, demonstrating the importance of ubiquitination in AQP2 endocytosis [103]. However, although delayed, AQP2-K270R was still internalized, which indicated that there are other mechanisms involved in AQP2 endocytosis.

AQP2-associated pathologies

AQP2 has been demonstrated to play a role in the pathophysiology of several diseases associated with a disturbed water balance. Congestive heart failure (CHF), liver cirrhosis, and pre-ecclampsia are characterized by excessive water reabsorption. In these conditions, increased AVP levels, resulting from arterial underfilling and "suggestive" hypovolemia, induce excessive water uptake, often leading to hyponatremia. Consistently, in CHF rat models, increased AQP2 levels and clear apical plasma membrane expression were found [166, 239]. In liver cirrhosis, increased plasma AVP levels have been suggested to be responsible for impaired water excretion (reviewed in [164]). However, there are still some discrepancies between the various animal models. In several rat models of liver cirrhosis, increased AQP2 levels were found [6, 54]. In another study, however, total AQP2 levels were not changed, but an increase in plasma membrane expression of AQP2 was observed [49]. Moreover, other rat models of liver cirrhosis displayed decreased AQP2 levels and impaired water reabsorption [50, 98, 99]. An explanation for the differences found between these rat models is at present lacking.

In contrast to the conditions mentioned above, NDI is characterized by polyuria due to an AVP-induced impaired water reabsorption, and, consequently, polydipsia (reviewed in [189]).

Acquired NDI

NDI can either be acquired or present from birth (congenital). Acquired NDI was reviewed in detail recently and will only be discussed here briefly [164, 189]. Acquired forms of NDI result from various conditions. NDI is a common side effect in 10% to 20% of patients treated with lithium, the drug of choice to treat bipolar disorders. In rats, lithium was demonstrated to induce polyuria and a downregulation of AQP2 expression, which is, at an early stage, likely mediated by a lithium-induced inhibition of cAMP production [32, 127, 142]. At later stages of disease development, lithium also induces a loss of principal cells [32]. Other causes of NDI are hypokalemia and hypercalcemia. Like lithium therapy, hypokalemia and hypercalcemia decrease AQP2 expression in rats [42, 143]. Also, urinary tract obstruction, accompanied by decreased AQP2 expression, can cause urinary concentration problems because after removal of the obstruction, AQP2 levels are still downregulated [53, 123]. Finally, acquired NDI is also seen in acute and chronic renal failure. Several studies demonstrated decreased AQP2 expression and polyuria in rat models suffering from renal failure [48, 120, 121]. Patients with chronic renal failure have severe problems with water reabsorption, regardless of vasopressin plasma levels [216].

Congenital NDI

Congenital NDI can be due to mutations in the *AVPR2* gene, encoding the V2R (X-linked NDI) or mutations in the *AQP2* gene (autosomal recessive or autosomal dominant NDI). More than 90% of all congenital NDI patients suffer from X-linked NDI. Mutations in the *AVPR2* gene result in disturbed receptor signaling, rendering the renal principal cells insensitive to AVP, which results in a severe urine concentration defect. The molecular mechanisms underlying X-linked NDI can be divided in five different classes. The most common is misfolding of the protein and retention in the endoplasmic reticulum (ER; class II) [80, 188]. Others include (I) defective processing or unstable mRNA, (III) diminished binding of the Gs protein, (IV)

reduced affinity for AVP, and (V) misrouting of the V2R to different organelles in the cell [9, 14, 174, 175, 191, 236]. These defects have recently been reviewed extensively [189] and will not be discussed in more detail here.

Of all patients diagnosed with autosomal NDI, more than 90% suffers from recessive NDI. Most mutations found in recessive NDI are located in the core region of the AQP2 protein, which encompasses six transmembrane domains and five connecting loops. These mutations result in misfolded proteins that are retained in the ER and degraded rapidly [38, 128, 145, 147, 154]. The healthy parents of recessive NDI patients express both mutant and wild-type AQP2 proteins. Since the mutants do not tetramerize with the wild-type AQP2, as was shown for the AQP2-R187C mutation [104, 146], only homotetramers of wild-type AQP2 will be expressed on the apical membrane of the parents, allowing sufficient water reabsorption. The least occurring form of NDI, autosomal dominant NDI, is caused by mutations in the C-terminal tail of AQP2. These AQP2 mutants form heterotetramers with wild-type AQP2 and are, due to the mutation, missorted to other cellular organelles [104, 119, 146, 153]. Since wild-type AQP2 is retained in mixed tetramers and missorted, water reabsorption is severely affected, explaining the dominant inheritance of NDI in these patients.

Recent mouse models reveal that the mechanisms underlying congenital NDI in vitro also apply to the in vivo situation. Complete *AQP2* knockout mice, as well as recessive NDI *AQP2-T126M* knockin mice, die within a few weeks after birth due to severe urinary concentration problems and hydronephrosis [190, 244]. Although cortical collecting duct-specific *AQP2* knockout mice also demonstrated growth retardation and 10-fold increased urine production, these mice survived [190]. Several of the in vivo studies confirmed our current thoughts on congenital NDI. The *AQP2-T126M* knockin mice displayed a similar ER-glycosylation pattern as observed for the human mutant expressed in cells, demonstrating that ER retention also underlies recessive NDI in vivo [154, 210, 244]. Furthermore, in the first mouse model of dominant NDI, the *AQP2-763-772del* knockin mouse, mutant AQP2 formed heterotetramers with wild-type AQP2 and was missorted to the basolateral plasma membrane, as described for the in vitro situation [104, 146, 204].

However, different NDI mice models also provided new information on AQP2 regulation in NDI [129, 150, 190, 204, 245]. Several studies already suggested that the relative strength of the wild-type and mutant sorting signals determine the final destination of the tetramers and whether NDI is inherited as a recessive or dominant trait [35, 100]. In two families with recessive NDI, patients appeared to be heterozygotes for *AQP2* mutations of which one, AQP2-P262L, was located in the AQP2 C-tail. Mutations in the AQP2 C-tail usually cause dominant NDI [35]. In line with mutants in dominant NDI, in vitro studies demonstrated that AQP2-P262L was unable to interact with AQP2-R187C and did interact with wild-type AQP2. In contrast to mutants in dominant NDI, however, wild-type AQP2 rescued the misrouting of AQP2-P262L and directed the complex to the apical plasma membrane, thereby explaining the healthy phenotype of parents of the patients [35]. Interesting in this respect is that an S256L mutation in AQP2 causes recessive NDI in mice, whereas the R254L mutation causes dominant NDI in humans [36, 150]. As both mechanisms result in the lack of PKA to phosphorylate AQP2 at Ser-256, these data may be another indication that recessive or dominant NDI phenotype is determined by the strength of the apical sorting signal in wild-type AQP2 versus the strength of the missorting signal in the mutant.

Another surprising novelty from the mouse models was that mutations in the core region of AQP2 can lead to a variable level of misfolding and severity of NDI. While AQP2-T125M knockin mice die due to the lack of functional AQP2, mice with an F204V mutation in AQP2 have recessive NDI but do survive. This suggested that these mice had some residual water transport ability [129]. Indeed, while most AQP2-F204V was localized throughout the cytoplasm, some reached the membrane. Similarly, humans suffering from recessive NDI caused by a V168M mutation also demonstrate less ER retention and a less severe phenotype compared to other mutants in recessive NDI [16]. Surprisingly and in contrast to another mutant in recessive NDI, AQP2-R187C, AQP2-F204V also forms heterotetramers with wild-type AQP2 and is rescued to the plasma membrane in the heterozygote [100, 129]. As only AQP2-R187C is tested thoroughly in vitro, it may be that some AQP2 mutants causing human NDI are also less misfolded, interact with wild-type AQP2, and are transported to the apical membrane in parents of the patients with autosomal recessive NDI.

Polycystic kidney disease

Disturbances in AQP2-mediated water transport also play a role in hereditary cyst-associated disorders such as polycystic kidney disease (PKD), Bardet–Biedl syndrome, Meckel syndrome, von Hippel–Lindau disease, and nephronophthisis, and several acquired cystic diseases [15, 51]. Most common among these hereditary disorders is PKD, which affects one in 1,000 individuals. PKD displays an autosomal dominant (ADPKD) or autosomal recessive (ARPKD) pattern of inheritance. ADPKD is generally a late-onset disorder, characterized by the formation of multiple renal cysts, which may derive from all parts of the nephrons and collecting ducts and may cause kidney

enlargement and may eventually result in kidney failure. In ADPKD, extrarenal manifestations such as hepatic and pancreatic cysts, cranial aneurysms and hypertension also occur. ARPKD usually becomes apparent early in life and is characterized by collecting duct-derived renal cysts, as well as liver disease. ADPKD results from mutations in the *PKD1* or *PKD2* gene, and these genes give rise to the membrane glycoproteins, polycystin-1 and polycystin-2 [27, 91, 152, 194]. ARPKD has been associated with mutations in the *PKHD1* gene, which encodes the membrane glycoprotein fibrocystin [233, 238]. Polycystin-2 acts as a Ca^{2+}-permeable cation channel at the plasma membrane, the ER, and the primary cilia [63, 117]. Primary cilia are microtubular-based, hair-like organelles that project into the lumen of renal tubules and function as mechanosensors to detect fluid flow. Polycystin-1 is thought to be involved in the regulation and/or localization of polycystin-2 through direct interaction with this Ca^{2+}-channel [184, 220]. Furthermore, polycystin-1 is involved in G-protein-coupled signal transduction, able to induce cell cycle arrest via activation of the JAK-STAT signaling pathway, involved in activation of NFAT signaling pathway, and, most likely, plays a role in organization of the cytoskeleton, as demonstrated by its presence in a complex together with E-cadherin and catenins [13, 89, 177, 182]. Fibrocystin is also part of a complex with polycystin-2 and regulates intracellular Ca^{2+} levels [230, 237]. All three proteins affected in PKD are located in the primary cilia, the mechanosensors of the cell [234, 249]. Upon mechanical stimulation of the cilium, Ca^{2+} presumably enters the cell via the polycystin-1/polycystin-2 complex and triggers the release of Ca^{2+} from the ER, where the majority of polycystin-2 is expressed [159]. Increased Ca^{2+}, subsequently, initiates multiple intracellular signaling cascades.

Decreased Ca^{2+} levels, disruption of the Ca^{2+}-dependent signaling pathways, and subsequent accumulation of cAMP are thought to be the key factor in the formation of cysts, which is characterized by increased cell proliferation and apoptosis, a mitogenic response to increased cAMP and increased fluid secretion (Fig. 3; reviewed in [218]).

In normal renal epithelial cells, cAMP inhibits cell proliferation and growth and stimulates fluid reabsorption. In PKD-derived cells, however, the accumulation of cAMP promotes cell proliferation, growth, and fluid secretion [12, 69, 141, 241]. In cells derived from polycystic kidneys, cAMP activates B-Raf, which in turn stimulates the MAPK/ERK signaling pathway, leading to cell proliferation [241, 242]. In contrast, cAMP inhibits B-Raf and ERK activity in

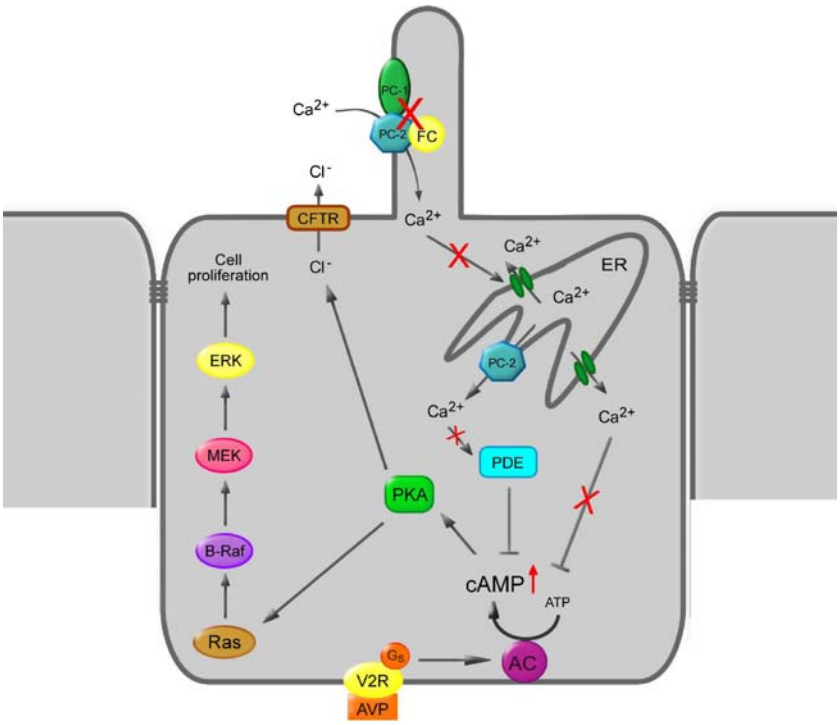

Fig. 3 Model of the pathways involved in polycystic kidney disease. Upon mechanical stimulation of the primary cilium, Ca^{2+} enters the cell via polycystin-2 (*PC-2*), which forms a complex with polycystin-1 (*PC-1*) and fibrocystin (*FC*). In addition, Ca^{2+} is released from the endoplasmatic reticulum (*ER*). Disruption of the polycystin/fibrocystin pathway results in decreased cytosolic Ca^{2+} levels. Reduced Ca^{2+} levels stimulate adenylate cyclase (*AC*) and inhibit phosphodiesterase (*PDE*), resulting in increased cAMP levels. Subsequent activation of protein kinase A (*PKA*) stimulates cell proliferation by sequential activation of *Ras*, *B-Raf*, *MEK*, and *ERK*. Furthermore, in polycystic kidney disease, cAMP-PKA signaling increases the permeability and expression of CFTR Cl^- channels, resulting in Cl^- extrusion. This increases the movement of Na and, subsequently, water into the lumen of the cyst

normal kidney cells, thereby repressing cell proliferation. In addition to cyst proliferation, cAMP accumulation also stimulates secretion of fluid into the lumen of the cyst. Cl^- enters the principal cells via the Na–K–$2Cl^-$ (NKCC1) co-transporter, expressed on the basolateral membrane, and is extruded into the lumen via the apically localized cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel whose cAMP-mediated permeability and expression is increased in PKD [34, 68, 92, 138]. The resulting negative lumen potential increases the movement of Na into the lumen, which then causes an osmotically driven water flux into the lumen of the cyst. ATP, which is secreted into the cyst lumen, was demonstrated to stimulate Cl^- secretion and thus may contribute to cyst expansion [200]. Several P2Y and P2X receptors are expressed in cells derived from PKD cysts [82, 200, 222]. Although P2X7-mediated signaling seemed to reduce the development of cysts [83], a recent study demonstrated that inhibition of endogenous P2Y receptors decreases the growth of MDCK-derived cysts, suggesting a role for P2Y-mediated ATP signaling in renal cystic diseases [221].

A decreased intracellular Ca^{2+} concentration appears to play a pivotal role in cyst development since increasing these calcium levels was shown to restore the normal phenotype in polycystic cells [240]. The effect of intracellular Ca^{2+} concentration on cAMP levels could be mediated by activation of AC6, which is present not only in principal cells but also in cilia and is repressed by Ca^{2+} [77, 148]. Recently, a molecule closely resembling forskolin, an activator of AC, was identified in collected cyst fluid, raising the possibility that this molecule also contributes to cAMP formation and, consequently, cyst expansion [183]. The origin of this molecule has not been reported yet. The decreased Ca^{2+} concentration may also increase cAMP levels by inhibiting Ca^{2+}-dependent PDE1, which is also localized in collecting duct [243]. Humans diagnosed with ADPKD or ARPKD, as well as animal models for PKD, suffer from a renal concentrating defect. A mouse model of ARPKD was found to lack a medullary-concentrating gradient, which could contribute to the urine concentration defect in these mice [58]. The lack of such a concentrating gradient may result from the distortion of the medullary structure in cystic kidneys. One could also speculate that the concentration defect results from decreased collecting duct expression of genes involved in urine concentration. Instead, increased levels of AVP and upregulation of V2R and AQP2 expression were found in the cystic kidneys of mice [58]. Inhibition of V2R signaling by using a V2R antagonist lowered cAMP levels and diminished the formation and expansion of renal cysts [58, 59, 219, 232]. In addition, decreasing the plasma AVP levels by increased water intake suppressed cAMP-dependent B-Raf/MEK/ERK activity and proliferation and slowed the progression of cystic disease in a rat model of PKD [158]. Although homozygous *PKD1* knockout mice models are embryonically lethal, heterozygous *PKD1* mice have a normal phenotype, with the exception of a limited amount of cysts at very old age [20, 111, 134, 135]. Therefore, this model was used to test whether the observed changes in water handling and V2R signaling occur prior to cyst development [1]. Although cAMP levels and both AQP2 and V2R mRNA levels were unaffected, these heterozygous *PKD1* mice showed inappropriate antidiuresis associated with lowered intracellular Ca^{2+} concentration, a decrease in phosporylated ERK, suppressed RhoA activity, and clear translocation of AQP2 to the apical membrane of collecting duct principal cells [1]. This study suggests a potential role for polycystin-1 in Ca^{2+}-signaling and AQP2 trafficking in renal collecting duct.

Concluding remarks

The role of the AQP2 water channel in vasopressin-regulated water reabsorption has been studied intensively since its original discovery in 1993. Tremendous efforts increased our knowledge of the importance of hormone-induced AQP2 shuttling to and from the apical plasma membrane and its underlying molecular mechanisms extensively. Besides its well-defined role in the pathophysiology of NDI, AQP2-mediated water transport has been increasingly associated with disorders characterized by excessive water reabsorption. Current research focuses on the quest for therapeutic compounds useful in the treatment of such disorders.

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