Review Article

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KIDNEY RESEARCH AND CLINICAL PRACTICE

New insights into the transcriptional regulation of aquaporin-2 and the treatment of X-linked hereditary nephrogenic diabetes insipidus

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The kidney collecting duct (CD) is a tubular segment of the kidney where the osmolality and final flow rate of urine are established, enabling urine concentration and body water homeostasis. Water reabsorption in the CD depends on the action of arginine vasopressin (AVP) and a transepithelial osmotic gradient between the luminal fluid and surrounding interstitium. AVP induces transcellular water reabsorption across CD principal cells through associated signaling pathways after binding to arginine vasopressin receptor 2 (AVPR2). This signaling cascade regulates the water channel protein aquaporin-2 (AQP2). AQP2 is exclusively localized in kidney connecting tubules and CDs. Specifically, AVP stimulates the intracellular translocation of AQP2-containing vesicles to the apical plasma membrane, increasing the osmotic water permeability of CD cells. Moreover, AVP induces transcription of the *Aqp2* gene, increasing AQP2 protein abundance. This review provides new insights into the transcriptional regulation of the *Aqp2* gene in the kidney CD with an overview of AVP and AQP2. It summarizes current therapeutic approaches for X-linked nephrogenic diabetes insipidus caused by *AVPR2* gene mutations.

Keywords: Arginine vasopressin, Aquaporin-2, Gene expression regulation, G-protein coupled receptors, Nephrogenic diabetes insipidus

Overview of arginine vasopressin and aquaporin-2

The kidney regulates the balance of water, electrolytes, and acids and bases (pH) in the body. Two critical components for urine concentration in the kidney are: 1) an interstitial osmolality, which provides a driving force for tubular water reabsorption; and 2) the osmotic water permeability of the tubular epithelia, which depends on expression of aquaporin (AQP) water-channel proteins in the cell membrane [1,2]. Consistent with these components, conditions that result in defective urine concentration, such as lithium treatment, are associated with decreased medullary organic osmolytes (e.g., betaine, myo-inositol, taurine, and glycerophosphocholine) [3]. Because of high osmotic permeability of water in the tubular epithelia, proximal tubules and descending thin limbs allow the reabsorption of a majority of the water filtered in the glomerulus, where aquaporin-1 (AQP1) mediates near-isosmotic fluid reabsorption [4–6]. AQP1 is also expressed in the descending thin limb and descending vasa recta and facilitates countercurrent exchange in

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the renal medulla, preventing the dissipation of the salt and urea gradient [7]. The connecting tubule and collecting duct (CD) reabsorb the remaining tubular fluid, which is tightly regulated by arginine vasopressin (AVP) [1,8–11].

Numerous studies have demonstrated that dysregulation of AQPs, solute (co)transporters, and acid-base transporters expressed in renal tubular epithelial cells leads to severe disturbances in water, electrolyte, and acid-base balance and blood pressure [1,10,12,13]. In particular, dysregulation of AVP-mediated water reabsorption in the CD is a primary pathophysiological mechanism underlying disease conditions involving body water disturbances, e.g., systemic water-retaining or water-losing states [1,10,14]. AVP is a peptide hormone produced in the hypothalamus. It is stored in and released from the neurohypophysis. Three exons in the *AVP* gene encode a signal peptide, AVP, neurophysin II, and copeptin [15]. The Verney receptor in the hypothalamus senses osmotic stimuli and releases AVP in response to a plasma osmolality higher than the physiological threshold (290–295 mOsm/kg H_2O) [16,17]. Copeptin, corresponding to the carboxyl terminal portion of provasopressin, is secreted in equimolar amounts to AVP and functions as a stable surrogate marker for AVP secretion [18]. The importance of copeptin measurement was demonstrated in a meta-analytic study of patients with heart failure, which revealed a positive correlation between plasma levels of copeptin and all-cause of mortality [19]. AVP is also secreted in response to non-osmotic stimuli through different pathways such as the parasympathetic afferent pathways [20]. Several factors activate the non-osmotic pathway to secrete AVP, including hypoxia, nicotine, altered hemodynamic states, adrenergic stimuli, adrenal insufficiency, and advanced hypothyroidism [20]. Once secreted into circulation and delivered to the kidney, AVP binds to arginine vasopressin receptor 2 (AVPR2) and induces free water reabsorption in the connecting tubule and CD [1].

In 1992, Lolait et al [21] cloned AVPR2 and subsequently, several studies identified that mutations in the *AVPR2* gene on the X-chromosome are associated with X-linked nephrogenic diabetes insipidus (NDI) in humans [21–24]. The exact incidence of X-linked NDI is unknown, however a study showed ~8.8 per million male live births in Quebec, Canada [25]. Autoradiographic localization of ^{3}H-AVP binding is restricted to the medulla of rat kidneys [26] and a study using *in situ* hybridization demonstrated the distribution of AVPR2 messenger RNA (mRNA) in the outer and inner medulla of rat kidneys [27]. A transcriptome study of microdissected renal tubular segments of rat kidneys confirmed AVPR2 mRNA in the connecting tubule and CD (from the cortical CD to the inner medullary CD); it was also expressed in the thick ascending limb and distal convoluted tubule [28]. Furthermore, V1a receptor (AVPR1a) mRNA is present in the distal convoluted tubule, connecting tubule and cortical CD of rat kidneys [28]. AVPR1a is primarily expressed in the medullary vasculature of the kidneys [29].

In CD principal cells, water reabsorption depends on AVP stimulation. AVP binds to the heterotrimeric G-protein α-subunit (Gαs)-coupled AVPR2 in the basolateral plasma membrane of principal cells and activates adenylyl cyclase 6. This activation increases intracellular cyclic adenosine monophosphate (cAMP) levels, activating kinases and enhancing transcellular water reabsorption in the CD [1,8,9,30–33]. AVPR2 activation by AVP also induces receptor internalization, which is associated with AVPR2 phosphorylation and recruitment of β-arrestin [34]. Aquaporin-2 (AQP2) is a water-channel protein localized in connecting tubule cells and CD principal cells that mediates AVP-induced osmotic water permeability [35,36]. The importance of AVP-regulated AQP2 for urine concentration and body water homeostasis is highlighted in *Aqp2* gene null mice and in other clinical conditions in which upregulation or downregulation of AQP2 expression in kidneys is closely associated with water-balance disorders [1,9,10,14,37].

Our studies showed [1,8,9] that AQP2 is regulated on a short-term or long-term basis for water reabsorption in the CD. AQP2 is immunolocalized at the apical plasma membrane and intracellular vesicles of CD principal cells [35]. Short-term regulation is rapidly mediated by AQP2 trafficking from intracellular vesicles to the apical plasma membrane [1,35,38,39]. The intracellular translocation of AQP2 to the apical plasma membrane is associated with phosphorylation of a serine residue in the carboxyl terminus of AQP2 via activation of the cAMP/protein kinase A (PKA) signaling pathway [39–41]. Long-term regulation or adaptation of CD water permeability following AVP stimulation is mediated by changing the half-life and abundance of AQP2 protein [42–45]. The

abundance of AQP2 protein is regulated by transcription of the *Aqp2* gene and translation, and post-translational modification of products, including ubiquitination and subsequent proteasomal and/or lysosomal degradation, which involve the actions of E3 ubiquitin-protein ligases (e.g., NEDD4 and CHIP) [43,46–52]. In addition, microRNAs (miRNA; e.g., miR-32 and miR-137) are important post-transcriptional modulators that regulate AQP2 protein abundance [53,54]. A recent study showed that miR-132 regulates hypothalamic AVP mRNA expression [55]. Methyl-CpG-binding protein-2 is a target of miR-132 that inhibits hypothalamic AVP synthesis by binding the methyl-CpG-binding protein-2 enhancer region [55].

NDI represents the inability of kidneys to concentrate urine despite AVP stimulation [1,10,11,56–58]. NDI is caused by genetic defects, with primary inherited forms caused by mutations in the *AVPR2* or *AQP2* genes, or acquired conditions. Secondary acquired forms are caused by drugs, electrolyte disturbances, renal failure, and other diseases [10,25,56,59–62]. In humans, AVP can concentrate urine and reduce the urine flow rate to ~0.7 L/day and increase urine osmolality to ~1,200 mOsm/kg H_2O [63]. In contrast, in the absence of AVP and AQP2 response, the urine flow rate can increase up to ~28 L/day and urine osmolality can decline to 50 mOsm/kg H_2O [62]. Thus, NDI is associated with AVP-resistant severe polyuria, dehydration, and electrolyte disturbance. This review presents new insights on the transcriptional regulation of the *Aqp2* gene and summarizes novel approaches for the treatment of hereditary NDI, particularly when caused by genetic defects in the *AVPR2* gene.

Regulation of *Aqp2* gene transcription

The regulatory mechanisms involved in the AVP-mediated increase of AQP2 protein, as a long-term response to AVP stimulation for hours or even days, have been widely studied. Two independent studies showed that AVP increases AQP2 mRNA and protein in inner medullary collecting duct (IMCD) cells isolated from rat kidneys [64,65]. In contrast, water loading decreases AQP2 mRNA and protein in rats continuously treated with dDAVP (an AVPR2-selective agonist), demonstrating "vasopressin escape" [42,66]. These studies on AVP-dependent or AVP-independent regulation of AQP2 abundance led to other studies on *Aqp2* transcription. AVP increases intracellular cAMP levels and activity of cAMP-responsive PKA by activating G protein-coupled receptor (GPCR) AVPR2, resulting in increased *Aqp2* expression and AQP2 insertion into the apical plasma membrane [8,33,38,39,67,68]. Hozawa et al [69] and Yasui et al [31] demonstrated that cAMP-responsive elements (CREs) within 350 bp upstream of the transcription start site of *Aqp2* in rat kidney IMCD cells are critical regulatory elements in AVP-mediated *Aqp2* transcription. Matsumura et al [30] confirmed impaired activity of the *Aqp2* promoter following deletion of the CREs. Consistent with those results was a study showing that knocking out both catalytic PKA subunits α and β (encoded from *Prkaca* and *Prkacb*) abolished expression of AQP2 mRNA and protein in mpkCCD cells treated with dDAVP [41]. These results demonstrate that cAMP/PKA signaling is a critical regulatory pathway for AVP-mediated AQP2 expression in the renal CD. However, other stimuli that regulate AQP2 expression have also been found under certain physiological and pathophysiological conditions (Table 1) [53,66,70–77]. For example, Kortenoeven et al [78] demonstrated that activation of cAMP-Epac, a guanine exchange factor directly activated by cAMP [79], is more important than the PKA-CRE pathway in the long-term regulation of AQP2. These findings suggest the need for more studies to further understand the transcription regulators of *Aqp2*.

The binding of transcription factors (TFs) and cofactors to enhancers can stimulate the transcription of an associated gene [80]. A recent study using high-throughput next-generation sequencing (NGS) techniques (ChIP-seq and ATAC-seq) revealed potential enhancer elements for *Aqp2* in the mouse cortical CD cell line mpkCCD [81–83]. Two enhancer elements were identified within a topologically associating domain containing *Faim2-Aqp2-Aqp5* genes, which is a CTCF-insulated loop regulated by a TF CTCF homodimer [84]. Although further functional studies are required to fully understand the roles of the identified enhancer elements in *Aqp2* transcription, this study provides insights into *Aqp2* transcription regulation mediated by genomic regulatory elements.

Promoters and enhancers are genomic regulatory elements with multiple TF-binding sites that facilitate transcription initiation mediated by transcriptional regulators [85]. Transcriptional regulation via a combination of TFs is complicated. These cell type-specific processes exist due to differential expression levels of TFs in vari-

Table 1. Regulatory mechanisms of AQP2 trafficking/expression in the renal collecting duct

Regulator	Regulation	Mechanism	Components
Hormones	Trafficking/ Expression	Signaling pathway activation	Vasopressin, oxytocin, angiotensin II, aldosterone, secretin, calcitonin, and their receptors
Kinases	Trafficking/ Expression	Signal transduction	cAMP/PKA, PI3K/Akt/AS160, MAPK (ERK, JNK, p38), GSK-3β, CaMKII, AMPK, Epac, and extracellular matrix-to-intracellular scaffold protein ILK
Transcription factors	Expression	Transcription	CREB family, c-Jun and c-Fos heterodimer (AP-1) and Rel family members, NF-κB, and NFAT subfamily
Cellular signaling	Trafficking/ Expression	Protein-protein interaction	(1) Between AQP tetramers. (2) Between AQP monomers. (3) Transient interactions with regulatory proteins: clathrin heavy chain; Hsc70; annexin II; LIP5; cytoskeletal or cytoskeleton-associated proteins such as actin, tropomyosin 5b, and ezrin; PDZ domain-containing protein, such as SPA-1 and Sipa1l1; and retromer complex (Vps35)
Protein-modification enzymes	Trafficking/ Expression	Post-translational modification	Phosphorylation, ubiquitination (E3 ligases), deubiquitination, glycosylation, and glutathionylation
Receptors/Agonists	Trafficking/ Expression	Signaling pathway activation	AVPR2, angiotensin II AT1a receptor, prostanoid receptor (EP2, EP4), frizzled receptor, β3-adrenergic receptor, serotonin receptor, calcitonin receptor, calcium-sensing receptor, epidermal growth factor receptor, bile acid receptor-coupled GPCR, and purinergic receptor
Extracellular microenvironment	Trafficking	Post-translational modification, cytoskeletal rearrangement	Tubular flow, medullary tonicity, and extracellular pH
MicroRNAs	Expression	RNA interference	AQP2-targeting microRNAs (miR-32, miR-137)

Akt, protein kinase B; AMPK, 5′ adenosine monophosphate-activated protein kinase; AP-1, activator protein 1; AS160, Akt substrate of 160 kDa; AVPR2, arginine vasopressin receptor 2; CaMKII, calcium/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; EP2, prostaglandin E2 receptor 2; EP4, prostaglandin E2 receptor 4; Epac, guanine exchange factor directly activated by cAMP; ERK, extracellular signal-regulated kinase; GPCR, G protein-coupled receptor; GSK-3β, glycogen synthase kinase-3β; Hsc70, heat shock cognate protein 70; ILK, integrin-linked kinase; JNK, c-Jun N-terminal kinase; LIP5, lysosomal trafficking regulator-interacting protein 5; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; Sipa1l1, signal-induced proliferation-associated 1 like 1; SPA-1, signal-induced proliferation-associated gene-1; Vps35, vacuolar protein sorting-associated protein 35.

ous cell types. Thus, investigation of TF-binding sites and regulatory proteins can provide direct information about mechanisms that regulate *Aqp2* transcription in the CD. *In-silico* analyses using bioinformatic tools indicate several potential conserved TF motifs found by scanning for TF consensus motif sequences along the genomic DNA of the *Aqp2* promoter [86–89]. However, sequence-specific DNA-binding TFs contain a conserved DNA-binding domain across the family with shared consensus DNA motifs in the genome, as shown in bioinformatic analysis by Hwang et al [89].

Many studies using *in vitro* and *in vivo* models identified TFs that regulate *Aqp2* transcription. Transcriptional activity of the *Aqp2* promoter mediated by specific TFs such as ELF3, ELF5, and GATA2 [86,90,91] has been evaluated using luciferase reporter assays. Some TF-knockout mice, such as mice deficient in GATA2 or farnesoid X receptor (FXR), show reduced *Aqp2* transcription with impaired urinary concentration [91,92]. Tonicity regulates *Aqp2* transcription mediated by TonEBP and Epac, but independent of AVP [93,94]. A study on tonicity-responsive AQP2 expression revealed that a calcium-dependent calcineurin-NFATc pathway also involves increased AQP2 mRNA expression [95]. An *in vitro* tubulointerstitial inflammation model of mpkCCD cells induced by lipopolysaccharides (LPS) showed that LPS-activated nuclear factor kappaB (NF-κB) reduces AQP2 mRNA expression [96,97].

High-throughput NGS techniques for genome-wide identification of TF binding sites, namely ChIP-seq (chromatin immunoprecipitation followed by NGS), provides direct evidence for the presence of TF-binding sites that could regulate *Aqp2* transcription. A recent ChIP-seq analysis of mpkCCD cells identified a binding site of TF C/EBPβ, which is known as a pioneer TF, 400 bp downstream of *Aqp2* [81]. Several high-throughput NGS techniques such as ChIP-seq, ChIP-exo, and cut-and-run, as well as conventional ChIP-PCR methods are important

tools for further studies to identify TFs that bind to genes of interest [98].

Genomic regions associated with gene expression are also regulated directly or indirectly by cofactors. Post-translational histone modifications by histone-modifying enzymes can alter chromatin structure [99]. Histone modifications at the N-terminal tails of histones, including methylation, phosphorylation, acetylation, ubiquitylation, and SUMOylation, lead to dynamic changes in chromatin structure and gene transcription [100,101]. Therefore, histone modifications in the vicinity of a gene mark its transcription status. For instance, a ChIP-seq analysis in mpkCCD cells showed that histone H3 acetylation at Lys27 (H3K27Ac) markedly increases at the *Aqp2* promoter following dDAVP treatment [41]. Moreover, an increase in H3K27 acetylation levels at the *Aqp2* promoter, which indicates activation, is consistent with enhanced binding of RNA polymerase II at the promoter and increased AQP2 mRNA expression [43]. However, precise cofactors such as acetyltransferases/deacetylases that directly modify histones and TFs at the *Aqp2* promoter region remain to be elucidated.

Lysine acetyltransferase CREB-binding protein (CBP, gene symbol: *Crebbp*) and P300 (gene symbol: *Ep300*) are transcription coactivating factors that acetylate histones and TFs [102,103]. A study showed that CBP and P300 cooperate with β-catenin [104]. CBP acetylates β-catenin at Lys49, leading to promoter-specific gene expression. Interestingly, β-catenin has been studied as a potential AVP-responsive transcription regulator. Protein mass spectrometry analysis of renal CDs showed that AVP increased phosphorylation of β-catenin at Ser552 and its translocation into the nucleus in CD cells [87,105–107]. Moreover, siRNA-mediated knockdown of β-catenin significantly impairs dDAVP-induced AQP2 expression in mpkCCD cells [107].

Beyond transcription regulatory proteins associated with genomic regulatory elements, chromatin modifications such as DNA methylation are potential epigenetic regulatory mechanisms of *Aqp2* expression. Several studies using bisulfite sequencing of targeted genomic regions or whole genomes identified methylated cytosines within CpG islands, which are called the DNA methylome. These studies reported that DNA methylation widely regulates gene expression in kidney cells [108,109] or tissues obtained from models of renal ischemia-reperfusion injury [110] and hypertension [111]. *Aqp2* has a CpG island in the fourth exon. However, the regulation of *Aqp2* expression associated with DNA methylation has not been explored yet.

Current approaches for treating *AVPR2* mutation-induced X-linked NDI

Hereditary NDI is a genetic disease caused by mutations in the *AVPR2* or *AQP2* genes [22,25,56,59–62]. Gene mutations in *AVPR2* result in X-linked NDI, which is the most common (~90%) form of inherited NDI [22,56,61,112,113]. To date, more than 250 different *AVPR2* mutations have been identified in more than 300 families (The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff; http://www.hgmd.cf.ac.uk) [56,114]. Deen and his associates [115] classified *AVPR2* gene mutations into five categories: 1) Class I indicates absence of AVPR2 protein due to defects in transcription, mRNA processing, or translation (e.g., promoter alterations, aberrant splicing, exon skipping, and most frameshift and nonsense mutations); 2) Class II indicates retention of fully translated AVPR2 proteins in the endoplasmic reticulum (ER) due to misfolding of AVPR2, preventing localization at the plasma membrane. The underlying mutations include missense, insertion, or deletions. Class II mutations are the most common form of *AVPR2* defect [11,56,57]. The treatment for many patients with X-linked NDI requires restoring plasma membrane expression of mutant AVPR2 [116,117]; 3) Class III indicates misfolding of AVPR2 leading to defective functions (e.g., impaired G protein binding and intracellular signaling), despite correct transport to the plasma membrane; 4) Class IV has no apparent defects in protein trafficking to the plasma membrane, but decreased binding affinity to AVP; 5) Class V indicates improper protein sorting to intracellular structures, e.g., β-arrestin-positive intracellular vesicles [118].

To treat NDI caused by *AVPR2* gene mutations (Table 2), the first strategy is restoration of AVPR2 plasma membrane expression using chemical chaperones (e.g., glycerol and dimethyl sulfoxide), since *AVPR2* mutations are fully functional, but misfolded AVPR2 protein is retained in the ER/Golgi (Class II) [119]. Previous studies demonstrated that several cell-permeable AVPR2 antagonists (pharmacological chaperones such as S121463, VPA-

Table 2. Potential therapeutic strategies for X-lined NDI associated with AVPR2 mutation

Evidence for therapeutic strategies
1. Chaperones that aid AVPR2 protein folding and induce export from the ER
2. Cell-permeable AVPR2 agonists that activate intracellularly retained AVPR2 protein
3. Activation of the cAMP pathway by stimulating other GPCRs
1) E-prostanoid receptors (EP2/EP4)
2) Calcitonin receptor
3) Secretin receptor
4) β3-adrenoreceptor
5) Bile acid receptor-coupled GPCR (TGR5)
4. Activation of the cGMP pathway, promoting AQP2 exocytosis by stimulating guanylyl cyclase or inhibiting PDE (PDE5)
5. Inhibition of EGFR induces AQP2 exocytosis
6. Activation of Wnt5-frizzled receptor promotes AVP-independent AQP2 phosphorylation
7. Statins that inhibit RhoA, promote actin depolymerization, and inhibit endocytosis of AQP2

AQP2, aquaporin-2; AVP, arginine vasopressin; AVPR2, arginine vasopressin receptor 2; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; EGFR, epidermal growth factor receptor; EP2, prostaglandin E2 receptor 2; EP4, prostaglandin E2 receptor 4; ER, endoplasmic reticulum; GPCR, G protein-coupled receptor; NDI, nephrogenic diabetes insipidus; PDE, phosphodiesterase; PDE5, PDE type 5; RhoA, Ras homolog gene family member A; TGR5, G-protein coupled bile acid receptor 1 (GPBAR1).

985, SR49059, conivaptan, OPC31260, and OPC41061) stabilize AVPR2 mutants in the ER and allow their escape for plasma membrane expression [116,120–122]. Cell-permeable, nonpeptide AVPR2 agonists (e.g., VA999088, VA999089, and OPC51803) bind intracellularly retained AVPR2 and activate a signaling pathway to induce cAMP accumulation without translocating receptors to the plasma membrane [123,124]. Other nonpeptide agonists (e.g., MCF14, MCF18, and MCF57) activate AVPR2 and translocate the receptors to the plasma membrane [125]. However, *AVPR2* mutations resulting in the absence of full-length AVPR2 protein (Class I promoter alterations, aberrant splicing, exon skipping, and most frameshift and nonsense mutations) cannot be treated by these approaches.

Another therapeutic approach relies on AVP-independent AQP2 trafficking to the plasma membrane. This can be achieved through bypassing AVPR2 signaling and inducing AQP2 accumulation in the membrane by translocating AQP2. These approaches have two categories: 1) intracellular cAMP elevation by activating other GPCRs or inhibiting phosphodiesterases (PDEs); and 2) cAMP-independent pathways. For elevating intracellular cAMP levels, studying endogenously expressed GPCRs in addition to AVPR2 in the renal CD is important. GPCRs naturally couple to GαS to increase cAMP levels and regulate AQP2 expression. The potential candidate GPCRs include the prostaglandin E receptors (EP2 and EP4), β3-adrenergic receptor (β3-AR), calcitonin receptor, secretin receptor, and TGR5 (a bile acid-activated membrane receptor) [10,77,126–132]. Li et al [129] demonstrated that an EP4 agonist increases cAMP levels in mouse kidney IMCD suspensions, increasing urine osmolality and decreasing urine volume in conditional *Avpr2*-knockout mice. Moreover, treatment with the EP2 agonist, butaprost, significantly decreases urine volume in rats pretreated with an AVPR2 antagonist OPC [130]. The β3-adrenergic receptor was immunolocalized at the basolateral plasma membrane of tubular epithelial cells in the thin and thick ascending limbs, distal convoluted tubule, and cortical and medullary CD, where AVPR2 is mainly expressed [126]. The same study demonstrated that the β3-AR agonist BRL37344 increases cAMP production in mouse kidney tubule suspensions and decreases urine output in mice that do not express functional AVPR2. Calcitonin induces increases in intracellular cAMP and AQP2 trafficking in AQP2-expressing LLC-PK1 cells. This increase is dependent on cAMP-PKA activity [132]. Calcitonin treatment in AVP-deficient Brattleboro rats is antidiuretic during the first 12 hours of treatment, although this effect is attenuated long-term [132]. Intravenous administration of secretin in rats decreases urine output [128]. Chu et al [127] demonstrated that secretin receptor-null mice have mild polydipsia and polyuria associated with reduced expression of AQP2 and AQP4 in the kidney. Another study further demonstrated that secretin increases intracellular cAMP levels in mouse IMCD tubule suspensions and that chronic infusion of secretin in *Avpr2* gene-deficient mice increases AQP2 mRNA and protein [133]. Furthermore, activation of bile acid receptor-coupled GPCR (TGR5) affects AQP2 trafficking and protein expression in inner medullary CD cells via a cAMP-PKA signaling pathway [77]. Importantly, TGR5 stimulation improves impaired urine concentration in mice with lithium-induced NDI by increasing AQP2 protein abundance [77]. These data indicate that in addition to AVPR2 in the renal CD, activation of endogenously

expressed GPCRs that naturally couples to GαS increases cAMP levels and regulates AQP2 expression and water reabsorption. In addition, AQP2 trafficking and abundance are affected by the cAMP-Epac pathway [78,134]. Since Epac is activated by a cAMP analog (8-pCPT-2′-O-Me-cAMP), Epac activators could be used to increase AQP2 expression in the membrane.

Inhibition of PDE is another strategy to induce intracellular cAMP levels. Sohara et al [60] showed that the PDE4 inhibitor rolipram increases urine osmolality in mutant AQP2 (763–772 del) knockin mice associated with increased cAMP levels in renal papillae. Another study demonstrated that cotreatment with PDE3 (milrinon) and PDE4 (rolipram) inhibitors reduces impaired urinary concentration ability in rats with hypercalcemia [135]. An additional study showed that increasing cGMP levels via PDE5 inhibitors or cGMP induces AVP-independent AQP2 trafficking to the plasma membrane. Consistent with these results, the PDE5 inhibitor sildenafil citrate induces AQP2 redistribution to the apical plasma membrane in rat kidney slices and reduced polyuria in rats with lithium-induced NDI [136,137].

An alternative approach is to find GPCRs in the kidney CD that do not couple to the GαS and cAMP pathway but regulate AQP2 expression. Ando et al [138] demonstrated that Wnt5a, a ligand for frizzled receptors, activates intracellular calcium release. The calcium-binding protein calmodulin and calmodulin-mimicking protein AA stimulate calcineurin, which decreases AQP2 phosphorylation at S261 and increases phosphorylation at S269, leading to AQP2 apical trafficking [138]. Wnt5 administration to mice pretreated with tolvaptan, an AVPR2 antagonist, increases urine osmolality and induces AQP2 trafficking to the apical plasma membrane [138]. Epidermal growth factor receptor (EGFR) inhibitors do not affect intracellular levels of cAMP and cGMP in LLC-AQP2 cells [139]. However, EGFR inhibitors increase AQP2 membrane accumulation in LLC-PK1 cells, reduce urine volume and increase urine osmolality in mice with lithium-induced NDI [139]. These results indicate that frizzled receptor and EGFR could be involved in AQP2 regulation independent of the AVP-cAMP/PKA pathway. An additional study demonstrated that tamoxifen, a selective estrogen receptor modulator, improves impaired urine concentration and reduces downregulation of AQP2 protein abundance in rats with lithium-induced NDI, although the underlying mechanisms are still unclear [140]. However, tamoxifen is unlikely to increase intracellular cAMP levels (unpublished data). Similarly, metformin, an AMPK activator, increases urine osmolality and AQP2 abundance in rats with AVPR2 blockade by tolvaptan treatment and *Avpr2* null mice [141], suggesting a complex mode of AQP2 regulation.

Another strategy is inhibition of AQP2 internalization. Treatment with statins can prevent AQP2 internalization and induce AQP2 accumulation at the plasma membrane [142]. Simvastatin is associated with increased apical membrane AQP2 expression in cultured cells and kidney

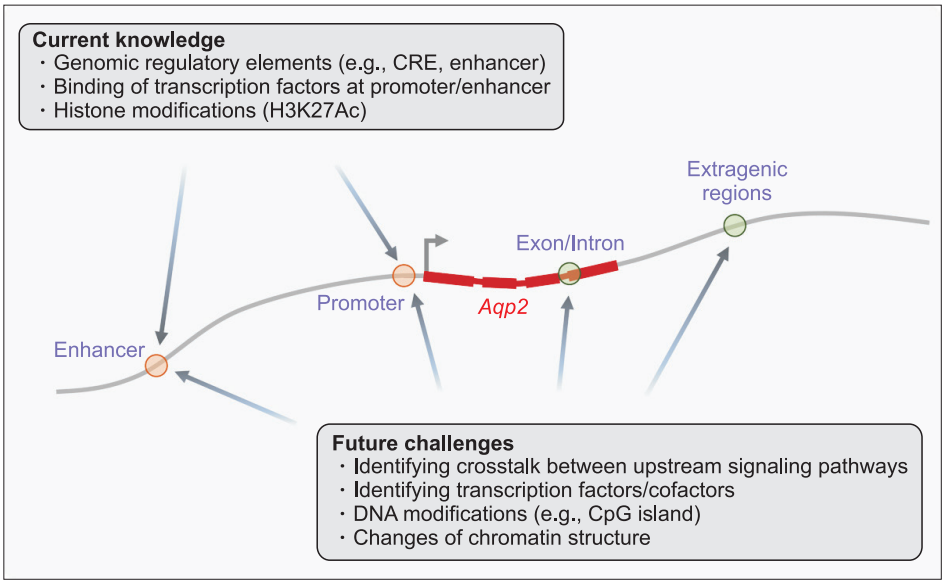

Figure 1. Future approaches to understanding the mechanisms of *Aqp2* gene transcription. A multiomics approach could provide comprehensive insights into transcriptional regulation cooperated by transcription regulator complexes, genomic regulatory elements, and signaling pathway crosstalk in X-linked hereditary nephrogenic diabetes insipidus. CRE, cyclic adenosine monophosphate-responsive elements.

slices from Brattleboro rats [142]. Fluvastatin increases AQP2 expression in the apical plasma membrane of the kidney CD in C57BL/6 mice [143] and a combination treatment of fluvastatin and secretin dramatically decreases urine output in *Avpr2* null mice [133]. These results suggest that statin treatment could be used to increase urine concentration in patients with X-linked NDI. Future clinical studies will confirm the efficacy of statin treatment in patients with hereditary NDI.

Summary and perspectives

Water reabsorption in the CD is regulated by the action of AVP. AVP stimulates the subcellular trafficking of AQP2-expressing vesicles to the apical plasma membrane, inducing osmotic water permeability in CD principal cells. Moreover, AVP activates *Aqp2* transcription, increasing AQP2 protein abundance. Hereditary NDI is a genetic disease caused by mutations in the *AVPR2* or *AQP2* genes. *AVPR2* gene mutations result in X-linked NDI, the most common form of inherited NDI. For treatment, restoration of AVPR2 expression in the plasma membrane using chemical chaperones or activation of intracellularly retained AVPR2 using cell-permeable AVPR2 agonists is suggested. Several approaches for bypassing AVPR2 signaling and inducing membrane AQP2 accumulation, i.e., AVP-independent AQP2 trafficking to the plasma membrane, have been demonstrated. Future approaches to treatment should aim to fully understand the mechanisms of *Aqp2* transcription under various physiological and pathophysiological conditions. A multiomics approach could provide comprehensive insights into: 1) transcriptional regulation via transcription regulatory complexes, 2) genomic regulatory elements, and 3) alterations in signaling pathways in the X-linked hereditary NDI (Fig. 1).

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

Hyun Jun Jung and Tae-Hwan Kwon participated in the conception and wrote the manuscript. All authors read and approved the final manuscript.

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