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Nephrogenic Diabetes Insipidus – The Novelly Potential Therapeutic Drugs

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1. Introduction

Water reabsorption in the kidney represents a critical physiological event in the maintenance of body water homeostasis. This highly regulated process relies largely on the antidiuretic hormone, vasopressin (VP), and on the VP-sensitive aquaporin-2 (AQP2) water channel that is expressed in the principal cells of kidney collecting duct. Under normal condition, AQP2 resides in the intracellular vesicles of the principal cells. Apical plasma membrane facing the primary urine of these cells therefore contains only low amounts of water channels and is relatively water impermeable. When there is increased plasma osmolality or hypovolemia, VP released from the neurohypophysis binds to its cognate VP type 2 receptor (V2R) that is expressed on the basolateral membrane of the collecting duct principal cells. This elevates intracellular cAMP concentration and promotes protein kinase A (PKA) activity that lead to phosphorylation of AQP2 at Ser^{256} (Christensen et al., 2000), as well as phosphorylation of Rho at Ser^{188} (Tamma et al., 2001; Tamma et al., 2003). AQP2 phosphorylation allows their redistribution from intracellular location to apical plasma membrane, whereas Rho phosphorylation results in a subsequent attenuation of Rho activity that favors the depolymerization of F-actin (Tamma et al., 2001; Tamma et al., 2003). This latter action allows removal of the cytoskeleton barrier that blocks the passage of AQP2 to the plasma membrane. Therefore, with the presence of AQP2 on the apical membrane of principal cells, a strong increase of water permeability of this membrane compartment is resulted. This allows acceleration of water reabsorption from primary urine, thus compensating for body water loss during hypovolemic or hypernatremic state.

Defects in the function of V2R and/or in AQP2 cell surface expression (known as nephrogenic diabetes insipidus or NDI) may perpetuate alteration of the biological boundaries that maintain plasma osmolality within a well defined, but very narrow physiological range. Patients having which are unable to concentrate their urine despite normal or elevated plasma concentrations of VP, thereby at the risk of hypernatremic dehydration and having manifestations including polyuria, polydipsia, hyposthenuria, recurrent episodes of dehydration, fever, and even growth failure. Despite the molecular defects underlying this disorder has now been revealed and has enabled a successful diagnosis, no cure is currently exists for NDI. Instead, this condition is managed by restriction in sodium intake combined with the administration of hydrochlorothiazide diuretics to reduce urine output, which might nonetheless lead to hypovolemia and

hypokalemia (Blanchard et al., 2008). The search for more effective therapeutic strategies for NDI therefore is needed. Consistent with this notion, identifying V2R-independent mechanisms that regulate AQP2 trafficking could definitely be beneficial for the exploration of novel therapeutic strategies in the treatment of NDI, as this disorder is most commonly resulted from mutations in V2R gene (~90%).

2. Factors involved in V2R-independent cAMP pathway

2.1 Secretin

Apart from VP, various other physiological factors that modulate AQP2 cell-surface localization via the cAMP pathway have been uncovered. One of such factors is secretin (SCT), a 27-amino acid peptide hormone that modulates transepithelial movement of water and electrolyte in varies tissues. Clinically, serum concentration of SCT was found to increase significantly in hemodialysis patients (Grekas et al., 1984) and in patients with chronic renal failure (Hansky, 1979) in comparison to controls, indicating that the peptide might be associated with clinical-pathological status of the kidney. Morphologically, the kidneys of SCT receptor (SCTR)-deficient ($SCTR^{-/-}$) mice were abnormal, characterized by increased mesangial area, enlarged urinary space, and frequent tubular dilation and hypertrophy in the collecting tubules of the medullary region (Chu et al., 2007), suggesting they might have altered water absorption and filtration processes. Consistent with this notion, in vitro treatment of SCT was found to induce a dose-dependent increase in AQP2 expression on the plasma membrane and a dose-dependent decrease in AQP2 expression in the intracellular vesicles (Cheng et al., 2009; Chu et al., 2007). This induced translocation of AQP2 was mediated via a cAMP/PKA-dependent pathway (Cheng et al., 2009), and was shown to be absent in the medullary tubules isolated from $SCTR^{-/-}$ (Chu et al., 2007), hence indicating that the peptide induces the movement of AQP2 upon binding with its receptor. Because SCT can be released from the hypothalamo-pituitary axis (Chu et al., 2009), and that $SCTR^{-/-}$ mice exhibit normal levels of plasma VP as well as V2R in their kidney when compared to their wild-type littermates (Chu et al., 2007), these data collectively indicated a role of SCT in VP-independent stimulation of the expression and movement of AQP2s in the kidney. This concept was further substantiated by the fact that Charlton *et al.* (Charlton et al., 1986) was able to show an antidiuretic effect of SCT as potent as VP in homozygous VP-deficient Brattleboro rats, whereas Chu *et al.* (Chu et al., 2007) detected an altered response in AQP2 movement to the plasma membrane during hyperosmolality in $SCTR^{-/-}$ mice. Therefore, all these data suggested that SCT could also be of great interest to the NDI community as it shows a direction of study for developing therapies to treat NDI that are independent of the VP pathway.

2.2 Calcitonin

The second factor that has been proven to by-pass the VP-dependent simulation of AQP2 translocation via the cAMP pathway is calcitonin, which is a 32-amino acid peptide hormone that was found to have its plasma concentration increase in acute and chronic renal failure (Ardaillou, 1975; Ardaillou et al., 1975). Early work by de Rouffignac and Elalouf (de Rouffignac and Elalouf, 1983) proposed that the peptide hormone could exert a VP-like effect on electrolyte transport by the thick ascending limb and/or on the water permeability of the cortical collecting ducts. This observation has recently been confirmed

by another group showing a stimulation of the membrane accumulation of AQP2 by calcitonin in the LLC-PK1 cells as well as in the cortical collecting ducts on rat kidney slices (Bouley et al., 2011). Using osmotic pumps implanted into VP-deficient Brattleboro rats, they also discovered that calcitonin-treated rats urinate less, and their urine was more concentrated than in the control group, indicating that the peptide could play a direct role in the urinary concentrating mechanism. Additional studies therefore are required to further examining the antidiuretic effect of calcitonin as well as to determine whether this peptide might be beneficial to patients suffering from X-linked NDI.

3. Factors involved in nitric oxide/cGMP pathway

Together with the canonical cAMP-induced pathway, the nitric oxide (NO)/cGMP signaling pathway has been shown to play a role in AQP2 trafficking/expression, prompting investigation of this signaling pathway as a means to develop alternative therapies for treatment of NDI. NO is a very active free radical that produced enzymatically by one of the three (i.e. endothelial, neuronal, and inducible) intracellularly located nitric oxide synthase (NOS) isoforms that convert L-arginine to citrulline. It plays an important role in overall excretory function of the kidney (Majid and Navar, 2001) and is involved in the development of kidney dysfunction in several diseases, including diabetes and hypertension (Palm et al., 2009). In the classical NO signaling pathway, NO acts on the soluble guanylyl cyclase (GC), leading to an increased production of the second messenger cyclic guanosine monophosphate (cGMP). This then influences various intracellular functions via activation of the protein kinase G. cGMP, however, can also affects cAMP signals (Stangherlin et al., 2011) as well as PKA activity (Yamada et al., 2006), which are both mediated via cGMP-regulated phosphodiesterases (PDEs) (Stangherlin et al., 2011). By binding to the regulatory GAF-B domain at the N-terminus of PDE2, cGMP potently activates its cAMP hydrolyzing activity (Martinez et al., 2002). Through such a regulatory mechanism, stimuli that elevate cGMP could attenuate cAMP-dependent signaling pathway (Michie et al., 1996). Conversely, cGMP could also act effectively as a competitive inhibitor of PDE3 cAMP-degrading activity (Shakur et al., 2001). As a consequence, PDE3 provides a means by which an increase in cGMP may lead to an increase in cAMP.

The components of the NO-cGMP signaling pathway were found to be expressed throughout the kidney (Bachmann et al., 1995; Tojo et al., 1994; Ujiie et al., 1994), supporting the notion that the NO-cGMP signaling pathway plays a key role in renal physiology, including fluid transport. In consistent with this notion, Bouley *et al.* (Bouley et al., 2000) found that AQP2 insertion could be accomplished by the activation of the cGMP-dependent pathway. They showed that NO donors, such as sodium nitroprusside and NONOate, as well as the NOS substrate L-arginine, appeared to induce AQP2 translocation from intracellular vesicles to the apical membrane by increasing cGMP levels in rat kidney slices and AQP2-transfected LLC-PK1 cells. Similarly, another study by Martin *et al.* (Martin et al., 2002) showed that water deprivation induced the expression of endothelial NOS and neuronal NOS in the outer medulla as well as both the outer medulla and the papilla, respectively, which could be subsequently decreased by water loading. Other evidence further supporting the idea that NO-cGMP plays a role in water homeostatic mechanisms came from the fact that 1) VP specifically increases neuronal NOS expression levels in the renal outer medulla and papilla (Martin et al., 2002), 2) an increased expression of AQP2

within the kidneys of cirrhotic rats was found to correlate with the increasing activities of NOS (Jun et al., 2010), and 3) simultaneous disruption of all three NOS isoforms led to reduce membranous AQP2 expression associated with tubuloglomerular lesion formation, as well as marked hypotonic polyuria, polydipsia, and renal unresponsiveness to VP (Morishita et al., 2005), all of which are characteristics consistent with NDI. Thus, AQP2 expression and trafficking, which is chiefly regulated by VP, may be additionally stimulated by NO-cGMP activity.

3.1 Atrial Natriuretic Peptide (ANP)

ANP is a 28-amino acid peptide that is well established to activate membrane-bound GC and modulates cellular functions via the intracellular second messenger cGMP. Consistent with this, studies have provided evidence for stimulation of cGMP production in various renal tubule segments in response to ANP (Nonoguchi et al., 1987; Takeda et al., 1986) and for the expression of the cGMP-coupled ANP receptor in these segments (Terada et al., 1991). However, the effect of ANP (through an increase in cGMP) on sodium and fluid transport in the collecting duct is still controversial. Some earlier studies showed that it decreases both sodium reabsorption and vasopressin-induced water transport in collecting ducts (Dillingham and Anderson, 1986; Nonoguchi et al., 1988; Nonoguchi et al., 1989), whereas later studies do not confirm these inhibitory effects (Bouley et al., 2000; Rouch et al., 1991). This might probably due to the fact that ANP has a biphasic effects on renal water reabsorption process. Wang *et al.* (Wang et al., 2006) in a more recent study demonstrated that ANP infusion (0.5 μg/kg/min) evoked a transient (peak at 10 min) but significant diuresis (~5 fold), with no changes in GFR as well as the subcellular localization of AQP2, followed by a decrease in water excretion, accompanied by a marked increase in apical targeting of AQP2, 90 min after infusion. This effect of ANP on AQP2 was further confirmed by both Bouley *et al.* (Bouley et al., 2000) and Wang *et al.* (Wang et al., 2006) in *in-vitro* studies using AQP2-expressing LLC-PK1 cells and AQP2-transfected HEK 293 cells, respectively. The former group also postulated that Ser^{256} of AQP2 is the target motif for stimulation by ANF. Because there are marked changes in water excretion seen in response to acute (10 min) and subacute (90 min) ANP treatment, a detail understanding of the underlying mechanisms that governs these processes is needed before considering whether ANP could be use as a therapeutic strategy for the treatment of NDI.

3.2 Sildenafil citrate (Viagra)

The use of Viagra, a selective PDE5 inhibitor, as potential therapeutic agents for NDI has been described. Bouley *et al.* (Bouley et al., 2005) found that 45-min exposure of AQP2-transfected LLC-PK1 cells to either Viagra or 4-{[3',4'-methylene-dioxybenzyl]amino}-6-methoxyquinazoline elevates intracellular cGMP levels and results in the plasma membrane accumulation of AQP2. They also demonstrated that exposure to PDE5 inhibitors for 60 min could induce an apical accumulation of AQP2 in renal medullary collecting duct principal cells both in tissue slices incubated *in-vitro* as well as *in-vivo* after intravenous injection of Viagra into rats. While Viagra has been successfully used in the clinical treatment of erectile dysfunction and that research data suggested that PDE inhibition by this drug may offer a promising approach for X-linked NDI therapy, further studies are needed in order to determine whether prolonged viagra or cGMP inhibition, or a combined therapeutic

approach, can improve water reabsorption in patients suffering from NDI who may express variable amounts of AQP2 in their principal cells.

4. Factors involved in AQP2 endocytosis and exocytosis

About 10% of NDI cases are associated with AQP2 mutations rather than with defects of V2R signalling. Interestingly, most mutations identified in the AQP2 gene in NDI are manifested as mis-routing errors rather than as structural defects that affect their ability in conducting water across the membrane. Some of these mutations, including L22V, L28P, A47V, V71M, T126M, A147T, V168M, P185A, R187C, E258K, and P262L have been characterized in Xenopus oocytes, yeast, and/or mammalian cells, and have been shown to have impaired folding, resulting in recognition by the endoplasmic reticulum (ER) quality control machinery, ubiquitination, and degradation by the 26S proteasome (Boccalandro et al., 2004; de Mattia et al., 2004; Deen et al., 1995; Kamsteeg et al., 2008; Kamsteeg et al., 2009; Levin et al., 2001; Marr et al., 2002; Mulders et al., 1997; Tamarappoo and Verkman, 1998). However, these AQP2 mutants are found to be intrinsically functional water channels when being characterized. In light of the fact that AQP2 rapidly and constitutively recycle between the plasma membrane and intracellular vesicles, even in the absence of any stimulation (Lu et al., 2004), and that channel gating of AQP2 is independent of the membrane insertion/trafficking process (Moeller et al., 2009), therapeutic strategies for NDI caused by AQP2 mutation could be bought either by agents that stimulate AQP2 excytosis, or agents that causes a reduction in the rate of AQP2 endocytosis. Consistent with this notion, an extensive accumulation of AQP2 at the cell surface was successfully accomplished within 30 min after inhibition of endocytosis by treatment with cholesterol-depleting drug, methyl-β-cyclodextrin (Lu et al., 2004; Russo et al., 2006), which prevents the formation and budding of clathrin-coated pits. This implies that while we are looking for V2R-independent signalling pathways to induce an increase translocation of AQP2 to the cell surface, any agent that inhibits the endocytosis of intrinsically functional AQP2 mutant may consequently represent an alternative strategy for therapeutic intervention in NDI.

4.1 Chemical chaperones

Chemical chaperones, which are protein-folding enhancers, have already been shown to act as the potential therapeutic agents for the control of many of the protein conformational diseases, including Alzheimer's disease (Evans et al., 2006), Prion's disease (Tatzelt et al., 1996), and cystic fibrosis (Brown et al., 1996). As most of the AQP2 mutants are associated with defect in folding, leading to their accumulation within intracellular compartment, an observation of the corrective effect of chemical chaperones on defective AQP2 trafficking in NDI is therefore not peculiar. In this regards, Tamarappoo and Verkman (Tamarappoo and Verkman, 1998) found that incubating chemical chaperones, including glycerol, trimethylamine oxide (TMAO), and dimethyl sulfoxide (DMSO), to AQP2 mutant-expressing cells could produced a nearly complete redistribution of the mutants from endoplasmic reticulum to membrane/endosome fractions, achieving functional correction of the processing defect. Similarly, another group also showed that Hsp90 inhibitor, 17-allylamino-17-demethoxygeldanamycin (17-AAG), produced partial correction of the

defective AQP2 cellular processing in transfected kidney cells (Yang et al., 2009). They also observed an increase urine osmolality in AQP2 mutant-expressing mice when intraperitoneally injected with 17-AAG, demonstrating a function of this chemical chaperones in improving urinary concentrating function. As 17-AAG is currently in phase 2 clinical trials for several cancer targets (Pacey et al., 2010), and that recent data showing promising therapeutic activity of the compound (Kurashina et al., 2009; Yao et al., 2010), 17-AAG or other chemical chaperones may be useful for therapy of some forms of NDI.

4.2 Simvastatin

Simvastatin, a family of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, was originally developed as therapeutic agents for reducing cholesterol and hence the prevention and treatment of cardiovascular diseases (O'Driscoll et al., 1997; Olsson et al., 2011). Recent studies, however, have revealed more of its pleiotropic effects including cognition enhancement (Douma et al., 2011), anti-inflammation (Nezic et al., 2009; Zhang et al., 2011), and anti-cancer activity (Miller et al., 2011). More interestingly, studies *in-vitro* also suggested that it could inhibit the endocytosis of proteins in proximal tubule cells via its inhibitory effects on prenylation and thereby the function of one or more GTP-binding proteins (Sidaway et al., 2004), suggesting a similar role of its in regulating AQP2 membrane presentation. Consistent with this notion, simvastatin was shown to induces AQP2 membrane accumulation via its inhibitory effect on AQP2 endocytosis, which was independent of cAMP/PKA activation and also Ser^{256} phosphorylation of AQP2 (Li et al., 2011). These authors also found that intraperitoneal injection of simvastatin to VP-deficient Brattleboro rats resulted in decreased urinary volume with simultaneously increased urinary osmolality, hence its effect on renal water reabsorption and urinary concentration. Therefore, even though the total reduction of urine output may seem to be modest with simvastatin-treated animals, simvastatin treatment might still be significant for NDI patients who may produce up to 10-15 liters of urine each day.

Factors involved in V2R-independent cAMP pathway
Secretin
Calcitonin
Factors involved in nitric oxide/cGMP pathway
Atrial natriuretic peptide
Sildenafil citrate (Viagra) and other PDE inhibitors
Factors involved in AQP2 endocytosis and exocytosis
Chemical chaperones
• Glycerol
• Trimethylamine oxide (TMAO)
• Dimethyl sulfoxide (DMSO)
• Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG)
Cholesterol-depleting drug
• Methyl-β-cyclodextrin
• Simvastatin

Table 1. List of the potential therapeutic drugs that increase membrane presentation of AQP2.

5. Conclusion

Recent advances in the understanding of AQP2 recycling and the signaling pathways that lead to the membrane accumulation of AQP2 in renal collecting tubular principal cells have opened up several possible strategies for inducing this process in the absence of conventional VP signaling via its receptor, which is defective in X-linked NDI (Table 1). Some of these strategies are potential to serve as basis for the development of novel therapies that may ultimately improve life quality of NDI patients. Therefore, identifying analogs of these potential agents with reduced cytoxicity and also improved pharmacological properties are necessary for preclinical development. Depending on the nature of the defect leading to this disorder, it is very likely that a combination of different approaches, directed by the basic research endeavors that are ongoing in many labs, will be needed to achieve a positive clinical outcome.

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Diabetes Insipidus

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The first chapter of the book reports on the management of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus and its associated endocrinological/neurological sequelae in the national survey. The next chapter addresses DI and head injuries. Next, the management of neuroendocrine instability during maintenance of potential organ donors is described. Organ transplants have gradually increased worldwide. To have maintenance of appropriate potential organs, AVP is needed. Furthermore, nephrogenic DI-the potential therapeutic drugs and analysis of membrane protein stability is the topic of the next two chapters, followed by new insights into the diagnosis and management of pregnancy-related DI. The seventh chapter reports on the problems with differential diagnosis in a case of central DI in a female patient with bipolar disorder. The lithium treatment usually resulted in nephrogenic DI. Finally, over the last years, the development of MRI imaging on the pituitary gland with the stalk and hypothalamus has advanced. The final chapter interprets imaging techniques in DI in detail.

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