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Michelle Boone, Marleen L. A. Kortenoeven, Joris H. Robben, Grazia Tamma and Peter M. T. Deen

Am J Physiol Renal Physiol, March , 2011; 300 (3): F761-F771.

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Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus

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Robben, Joris H., Nine V. A. M. Knoers, and Peter M. T. Deen. Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus. *Am J Physiol Renal Physiol* 291: F257–F270, 2006; doi:10.1152/ajprenal.00491.2005.—In the renal collecting duct, water reabsorption is regulated by the antidiuretic hormone vasopressin (AVP). Binding of this hormone to the vasopressin V2 receptor (V2R) leads to insertion of aquaporin-2 (AQP2) water channels in the apical membrane, thereby allowing water reabsorption from the pro-urine to the interstitium. The disorder nephrogenic diabetes insipidus (NDI) is characterized by the kidney's inability to concentrate pro-urine in response to AVP, which is mostly acquired due to electrolyte disturbances or lithium therapy. Alternatively, NDI is inherited in an X-linked or autosomal fashion due to mutations in the genes encoding V2R or AQP2, respectively. This review describes the current knowledge of the cell biological causes of NDI and how these defects may explain the patients' phenotypes. Also, the increased understanding of these cellular defects in NDI has opened exciting initiatives in the development of novel therapies for NDI, which are extensively discussed in this review.

osmoregulation; protein trafficking; genetic disorder; collecting duct; lithium; pharmacological chaperones

MAINTAINING BODY WATER HOMEOSTASIS is of vital importance for proper functioning of most physiological processes in the human body. Under normal conditions, the glomerular filtration rate (GFR) of the two kidneys amounts 180 l/day. Of this huge volume, also called the pro-urine, ~90% is reabsorbed in the proximal tubule and descending limb of Henle's loop, which is a constitutive process. According to need, the remaining fluid can be reabsorbed in the collecting duct. This process is tightly regulated by an elegant system, which allows the body to adapt to periods of water load or water restriction. The key hormone in this process is the antidiuretic hormone arginine-vasopressin (AVP), which is secreted by the posterior pituitary in response to states of hypovolemia or hypernatremia (94). In healthy individuals, secreted AVP will be transported by the blood to the kidney, where it can bind to vasopressin V2 receptors (V2R), which are mainly present on the basolateral (interstitial) side of the principal collecting duct cells (112). The activated V2R will induce an increase of intracellular cAMP levels via the stimulatory Gs protein and adenylate cyclase, which will eventually lead to activation of protein kinase A and to phosphorylation of aquaporin-2 (AQP2) water channels (45, 68). Phosphorylation of at least three of four monomers of an AQP2 tetramer is then sufficient to redistribute AQP2 homotetramers from storage vesicles to the apical membrane, rendering this membrane permeable to water (63, 157). Following an osmotic gradient of sodium and urea, water will then pass the apical membrane via AQP2 and will leave

the cells on the basolateral side via AQP3 and AQP4 (57, 69), thereby compensating for the hypovolemic or hypernatremic state of the body. This process is summarized in Fig. 1. When sufficient water is reabsorbed to restore homeostasis, serum vasopressin levels will decrease (94), and AQP2 will be internalized from the apical membrane, resulting in decreased water reabsorption. Katsura et al. (67) showed that this AVP-regulated recycling of AQP2 can occur at least six times with the same repertoire of AQP2 molecules. In addition to its direct regulation of water transport, AVP also increases sodium transport in the collecting duct via the epithelial sodium channel (ENaC) (8, 38) and urea transport via the UT-A1 transporter (141).

Malfunctioning of water reabsorption can lead to a variety of disorders, which can be of central or renal origin. Centrally, in the syndrome of inappropriate secretion of antidiuretic hormone, AVP levels are abnormally increased, leading to excessive renal water reabsorption, which might result in life-threatening hyponatremia (118). The most common causes of the syndrome of inappropriate secretion of antidiuretic hormone are neoplasia, like nonmalignant lung carcinoma, neurological disorders, congestive heart failure, liver cirrhosis, preeclampsia, and drugs like thiazide diuretics or selective serotonin reuptake inhibitor antidepressants. These effects have recently been reviewed in more detail and will not be discussed here (11, 110).

At the other extreme is diabetes insipidus (DI), in which patients are unable to concentrate their urine, resulting in polyuria and, consequently, polydipsia. With central DI, humans lack the ability to produce functional AVP and therefore to actively concentrate their urine. Sometimes, this is due to

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Fig. 1. Regulation of aquaporin-2 (AQP2)-mediated water transport by vasopressin (AVP). Shown is a nephron with a magnified principal cell. In this cell, the vasopressin V2 receptor (V2R), stimulatory GTP binding protein (G α s), adenylate cyclase (AC), ATP, cAMP, and phosphorylated proteins (O-P) are indicated. For details, see the text.

AVP gene mutations (3, 6, 44, 48, 128). Administration of the synthetic AVP homolog 1-desamino-8-D-arginine vasopressin (DDAVP), however, is usually able to drastically decrease urine output in these patients. A well-studied disturbance of water homeostasis, and the main topic of this review, is nephrogenic diabetes insipidus (NDI). In this disorder, patients are unable to concentrate their urine, despite increased serum AVP levels. This review focuses on the molecular causes underlying NDI and how this information may aid in identifying novel therapies for this disorder.

ACQUIRED NDI

Most commonly, NDI is acquired due to several conditions, which can be divided into three different groups.

Electrolyte Disturbances

Two clinically important electrolyte abnormalities, hypokalemia and hypercalcemia, lead to polyuria and urinary concentration effects. Hypokalemia is found in up to 21% of hospitalized patients, develops in ~50% of patients with secondary hyperaldosteronism or using furosemide/thiazide diuretics, and may lead to the development of polyuria, NDI, and reduced AQP2 expression (89, 171). Indeed, in potassium-deprived rats, a 70% reduction in expression and a redistribution from the plasma membrane to intracellular vesicles were observed for AQP2 compared with control rats (89). This effect has been attributed to a reduced pituitary AVP release, blunted renal response to AVP, intrarenal PGE₂ production, and impaired AVP-sensitive adenylate cyclase, but might also be due to a reduced interstitial tonicity, as hypokalemia-induced NDI coincides with a severe downregulation of major renal sodium and urea transporters (39, 60), and an elevated tonicity increases AQP2 expression in vitro (50, 66, 151).

Hypercalcemia, which is mostly due to primary hyperparathyroidism and malignancies such as lytic bone disease or humoral hypercalcemia, causes NDI, leading to severe dehy-

dration (123). Studies using excess vitamin D or parathyroid hormone rat models reveal that hypercalcemia-induced NDI is accompanied by a reduced GFR and interstitial tonicity and an increased urinary and fractional sodium excretion (166). The reduced expression of type 2 Na-P_i cotransporter, type-3 Na/H-exchanger, Na-K-ATPase, and Na-K-2Cl cotransporter in hypercalcemia-induced NDI likely contributes to the increased urinary sodium excretion and decreased urine concentration (166). Moreover, hypercalcemia-induced NDI coincides with diminished total and apical membrane expression of AQP2, at normal AQP2 mRNA levels, whereas AQP3 expression is also reduced (37, 165). The effects on AQP2 are ascribed to activation of the apical calcium-sensing receptor (CaSR) by hypercalciuria, which is thought to subsequently induce the internalization of AQP2 as a means of reducing antidiuresis and preventing renal stone formation (142, 154). Although the underlying molecular mechanism for the effect on AQP2 is still poorly understood, Sands et al. (142) identified in an elegant study a signaling pathway linking renal water and calcium metabolism, as in purified apical endosomes from inner medullary collecting duct (IMCD) cells; they found besides AQP2 and the CaSR, PKC δ , PKC ζ , and G α q/G α 11 GTP binding proteins, the latter two of which had been reported earlier to interact with the CaSR. In line with these findings, Procino et al. (125) found later that CaSR-mediated downregulation and internalization of AQP2 in transfected renal cells by extracellular calcium coincide with a strong activation of PKCs, reduced forskolin-induced cAMP levels, and increased F-actin content. The role of decreased cAMP levels in hypercalcemia-induced NDI is further corroborated by the finding of Wang et al. (165) that treatment of such rats with cAMP-phosphodiesterase inhibitors prevents polyuria and reduced AQP2 expression.

Urinary Tract Obstruction

Urinary tract obstruction is a serious clinical condition, which in children is usually due to congenital abnormalities of

the kidneys and urinary tract, whereas in adults is mostly caused by stones, enlargement of the prostate, and urinary tract neoplasms. After removal of the obstruction, a marked polyuria develops, which is restored to normal in time, although a somewhat decreased maximum concentrating ability persist for a long time (43). Although the mechanism remains poorly understood, several studies in rats, especially by the Frøkiær team (41, 81, 82, 122), have shown that obstruction-induced NDI is likely due to reduced expression of major renal sodium-transporting proteins [NHE3, Na-K-ATPase, NaPi-2, NKCC1, and the sodium-chloride cotransporter (NCC)] and AQP1–4, all along the nephron (for a recent review, see Ref. 42). A recent study shed some light on the underlying mechanism, as Norregaard et al. (113) found that the reduction in AQP2, NHE3, and NKCC1 expression in the inner medulla, but not in other parts of the kidney, coincided with increased cyclooxygenase-2 (COX-2) expression and prostaglandin release from interstitial cells in rats with bilateral ureteral obstructions. Also, treatment with the COX-2 inhibitor parecoxib prevented downregulation of these transporters. It remains to be determined whether COX-2 inhibitors can shorten the period of NDI after the obstruction is removed.

Lithium-Induced NDI

Lithium, which is the drug of choice for treating bipolar disorders, is successful in reducing both manic and depressive symptoms in 70–80% of patients and reduces the excessive mortality rate observed in this illness (27). Unfortunately, development of NDI is a common side effect. Because 0.1% of humans are on lithium therapy and severe forms of this side effect present in ~10–20% of patients, lithium-NDI is the most common acquired form of NDI (150). Chronic lithium treatment decreases the GFR (13) and, considering the narrow therapeutic index of lithium (0.6–1.2 meq/l), toxicity resulting from severe dehydration is a problem of significant clinical importance in lithium-NDI. Moreover, lithium-NDI is associated with hyperchloremic metabolic acidosis, renal tubular acidosis (35, 70, 107, 132), and increased natriuresis. Rat studies revealed that lithium-NDI coincides with decreased total AQP2 expression and a reduced expression of AQP2 in the apical membrane (88). Further rat studies revealed that the effect depends on the period of lithium treatment, as short-term (10–14 days) treatment downregulates AQP2 expression without affecting renal morphology, whereas long-term (i.e., 4 wk or longer) treatment also causes an increase in intercalated cells at the expense of principal cells (25, 70, 80). The lithium-induced natriuresis is suggested to be due to the reduced expression in some, but not all, renal segments, of several salt-transporting proteins, such as NCC, the α - and β -subunits of ENaC, and the Na-K-ATPase (80, 108, 109, 131). The mechanism underlying the metabolic and distal tubular acidosis in lithium-NDI is poorly understood. Surprisingly, with long term-lithium treatment, it coincides with strongly increased expression levels of apical H^+ -renal ATPase, which cannot be explained by the increased number of intercalating cells, and altered expression of several other acid-base transporters (70).

Recent studies shed some light on the mechanisms underlying the reduced AQP2 levels in lithium-NDI. As indicated for electrolyte and obstructive NDI, the reduced AQP2 expression

in lithium-NDI might be due to a reduced interstitial osmolality (131). Also, Rao et al. (126) arrived at the suggestion that increased PGE₂ expression, which counteracts AVP-induced AQP2 total and plasma membrane expression, might explain AQP2 reduction in lithium-NDI (126). In an elegant study, these authors found that polyuria in COX-1-deficient mice treated with lithium for 4 days resulted in increased COX-2 expression and PGE₂ release from interstitial cells and that polyuria and PGE₂ release were blunted on inhibition of COX-2 expression. Similar data were observed in Brattleboro rats, indicating that the observed effects were independent from AVP. In contrast, however, lithium-NDI due to a 4-wk lithium treatment in rats coincided with reduced COX-1 and COX-2 levels in the inner medulla, which were strongly increased with dehydration (75). At present, an explanation for these differences is lacking.

Analysis of direct effects of lithium on AQP2 expression have been hampered by the availability of a cell line endogenously expressing AQP2 in response to AVP. Recently, such a cell line was generated (49). We found that these murine cortical collecting duct (mpkCCD) cells are well suited for studying the effects of lithium on AQP2 in more detail, as treatment with clinically relevant concentrations of lithium resulted in a marked reduction in, and reduced plasma membrane expression of, AQP2 (83). Surprisingly, lithium did not affect AVP-induced cAMP generation, phosphorylation or stability of AQP2, or the phosphorylation of the AQP2 transcription factor, the cAMP responsive element binding protein (CREB). Instead, it caused a decrease in AQP2 mRNA levels, indicated that lithium reduces AQP2 gene transcription or mRNA stability. Although further data need to be obtained, an effect of lithium on AQP2 gene transcription is in line with our findings that lithium does not affect AQP2 protein levels in transfected Madin-Darby canine kidney (MDCK) cells in which AQP2 expression is directed from a non-AQP2-related promoter (Shaw S, Li Y, et al., unpublished observations). Our data seem to contradict earlier studies in which it was found that lithium treatment of rats interfered with adenylate cyclase activity, cAMP generation, and PKA activation in isolated renal tubules (26). However, whereas these rats were chronically treated with lithium and, therefore, the observed effects might be due to the changed cellular constitution of their renal collecting ducts (25) and/or reduced sensitivity of the renal collecting duct due to increased circulating AVP levels in lithium-NDI rats (83), our data are obtained with only a 2-day (cells) or short-term (rats) lithium treatment, periods at which a changed cellular constitution of cell layer and renal tubules was not observed (25).

CONGENITAL NDI

Congenital NDI can be divided into X-linked and autosomal recessive and dominant NDI. Here, we will discuss the genes and proteins involved in these forms of congenital NDI in humans and those only found in animals.

X-Linked NDI

The X-linked and most prominent form of congenital NDI is caused by loss-of-function mutations in the *AVPR2* gene, encoding the V2R (19, 85), which is a member of the family of G protein-coupled receptors (GPCR; Fig. 2). Over 180 *AVPR2*

Fig. 2. Proposed topology of the human V2R. The V2R has 7 transmembrane domains with its NH₂ terminus extracellular and its COOH terminus intracellular. The transmembrane domains are connected by 3 extracellular (ECL1–3) and intracellular (ICL1–3) loops. The N-glycosylation site (at N22) in its NH₂ terminus and the palmitoylated cysteines (C141–142) in its COOH terminus are indicated. Bright amino acids are conserved among V1R, V2R, and V3R.

gene mutations have been described (<http://www.medicine.mcgill.ca/nephros>), of which many result in severe interference with receptor signaling, thus making the principal cells of the collecting duct insensitive to AVP. The molecular mechanism underlying this insensitivity, however, differs among mutants. As upcoming pharmacological treatments for NDI likely depend on the underlying mechanism, we recently divided GPCR mutations into general and particular V2R mutations in five different classes according to their cellular fate (30, 129) (Fig. 3A and Table 1).

Class I comprises all mutations that lead to improperly processed or unstable mRNA, like promoter alterations, exon skipping, or aberrant splicing. This class also holds frame-shift and non-sense mutations, which result in truncated proteins like V2R-Q119X, -W293X, and -R337X.

Class II mutations are missense or insertion/deletion of one or more nucleotide triplets, resulting in fully translated proteins. Due to the mutation, however, mutant receptors are misfolded and retained in the endoplasmic reticulum (ER), as the ER is the organelle that has the cellular quality control over proper folding and maturation of synthesized proteins. Misfolded proteins are subsequently mostly targeted for proteasomal degradation (40). Intracellular entrapment of missense V2R mutants and their rapid degradation likely represent the most important cause for NDI, as >50% of the mutations in V2R are missense mutations and cellular expression revealed that most of these result in ER-retained proteins. The extent of ER retention, however, may differ among mutants and may represent differences in their folding state. Hermosilla et al. (51) recently reported that of eight V2R mutants that are

Fig. 3. Cellular fate of V2R mutants in nephrogenic diabetes insipidus (NDI) and their rescue. **A:** V2R mutation classes in NDI. Shown is a schematic view of a collecting duct cell. The different mutation classes are indicated by roman numerals. Mutation can lead to mRNA instability, splicing errors, and nonsense mutations (*I*); endoplasmic reticulum (ER) retention (*II*); impaired Gs coupling (*III*); impaired AVP binding (*IV*); and mislocation in the cell (*V*). See the text for details. **B:** pharmacological chaperones rescue class II V2R mutants. Class II V2R mutants are retained in the ER, but on binding of cell-permeable antagonists (CPA), stabilization of their structure allows them to exit the ER, mature in the Golgi, and subsequently translocate to the plasma membrane (*I*). At the membrane, displacement of the CPA by AVP will allow restoration of the cAMP cascade (*2*).

Table 1. V2R mutations involved in NDI

Nucleotide	Amino Acid	Referred/Analysis	Functionality	Conserved (Location)	Class	Diagnosis	Treatment
492T>C	L44P	(5;72;99;116;117;129)	F	Y (tmd1)	II	1 wk	dD:NR
488T>A	I46K	(120)	F	N (tmd1)	II	5 yr	ndD:NR
548T>C	L62P	(5;72)	?	Y (tmd1)	II?	21, 53 mo	dD:NR
545-553del	Δ62-64	(18;129)	G	N (tmd1)	II	?	?
574G>A	W71X	(17)		N (ICL 1)	I	?	dD:NR
612C>A	A84D	(3)	A	N (tmd2)	II	?	?
614G>A	D85N	(61;120;130)	F	Y (tmd2)	III	32 mo	ndD, dD-deh.:>400
623G>A	V88M	(72;160;163)	?	Y (tmd2)	II	16 mo	ndD:NR; deh.:>500, PS 158
692T>C	W99R	(3)	A	Y (ECL1)	II, IV	?	?
671C>T	R104C	(55;96)	F	Y (ECL1)	II	8 days	ndD:NR;dD:>300;thiaz., DDAVP
674T>G	F105V	(120)	A	Y (ECL1)	IV	?	?
698C>T	R113W	(72;136)	F	Y (tmd3)	II, IV	?	dD-deh.:NR
749A>T	I130F	(120;129)	F	N (tmd3)	II	1 mo	ndD:NR
771G>A	R137H	(9;17;92;61;133;134;138;139;144)	G	Y (ICL2)	II, III, V	?	dD-deh.:NR (292);dD:>400 PO(282)
860T>A	S167T	(115;117;129;172)	F	N (tmd4)	II	1 mo	dD:NR
861C>T	S167L	(72;115;117;129;170;172)	A	N (tmd4)	II	2 wk, 8 mo	ndD, dD:NR
902C>T	R181C	(18;72;129;144;146)	A	N (tmd4)	IV	6 mo	ndD:NR
914G>T	G185C	(145;158;160)	A	N (ECL3)	IV	7,9,108,128,204 mo	dD-deh.:>300
963G>A	G201D	(129;136)	F	Y (ECL3)	II, IV	?	dD-deh.:>400
965C>T	R202C	(3;6;145;155;169)	A	N (ECL3)	IV	18 mo	?
966-967 del	ΔR202	(2)	A	N (ECL3)	IV	?	dD:NR
972C>A	T204N	(72;124;129;161)	A	N (ECL3)	II	15 mo	dD:NR; dD:>200
975A>G	Y205C	(51;124;158;160;163)	A	Y (ECL3)	II	2 wk, 2.5 mo	dD:NR
978T>A	V206D	(72;124;128)	A	N (tmd5)	II	?	dD:NR
1431C>T	P322S	(2;163)	F	Y (tmd7)	III, IV	10 mo, 8 yr	dD-deh.:>400
1476C>T	R337X	(18;24;51;72;100;114;137;153;189)	A	N (C-tail)	I	4 mo	dD:NR, deh>300, PS 189

V2R, vasopressin V2 receptor; NDI, nephrogenic diabetes insipidus; F, functional; A, disturbed AVP binding; G, disturbed G_s protein binding; conserved (Y) or not (N) between vasopressin receptors; tmd, transmembrane domain; ECL, extracellular loop; ICL, intracellular loop; dD, infusion with DDAVP; ndD, nasal DDAVP; deh, dehydration; NR, nonresponsive; >400, urine >400 mosmol/kgH₂O; PO, plasma osmolality in mosmol/kgH₂O; PS, plasma sodium (mosmol/kgH₂O).

retained, only three were strictly kept in the ER, whereas the five other mutants were transported to the ER-Golgi intermediate compartment, followed by retrograde transport to the ER.

Class III comprises similar mutations to class II, but the resulting mutants are not considered misfolded by the ER and can continue their itinerary to the plasma membrane. However, these mutations disturb binding of the stimulatory G_s protein, leading to reduced activation of adenylate cyclase and thus formation of cAMP.

Class IV mutations also result in full-length receptors expressed at the cell surface, but here the mutation interferes with, or reduces, AVP binding. These mutations especially involve residues thought to be in or close to the AVP binding pocket, of which V2R-ΔR202 is a clear example (2).

Finally, class V mutations allow normal protein synthesis and maturation, but they cause misrouting to different organelles in the cell. The NDI R137H mutation, located in the well-conserved DRY/H motif of GPCRs, is a member of this class, as V2R-R137H is constitutively internalized from the plasma membrane and therefore only briefly available to bind AVP (10, 15).

Sometimes, mutants do not exert a full phenotype of a particular class and then often also show features of another class. For example, some V2R missense mutants are partially ER retained (class II) but are also partially expressed in the

plasma membrane, where they might show a reduced G protein coupling (class III) or AVP binding (class IV). Indeed, V2R-R113W, -G201D, and -T204N stably expressed in polarized MDCK cells are partially ER retained, whereas a considerable fraction is expressed in the basolateral membrane (129). As such, this provides an explanation for the observed small antidiuretic response to high doses of DDAVP in NDI patients harboring such mutations (124) (Table 1). For a full interpretation of these increased urine osmolalities with DDAVP, blood osmolalities and sodium levels are also important but have only been reported for a few patients (Table 1).

Autosomal Recessive NDI

Approximately 10% of the patients diagnosed for NDI have mutations in the AQP2 gene, which is mapped to chromosome 12q13 (34, 140). Of these, >90% suffer from recessive NDI. Most, but not all (28, 34), of these patients are of consanguineous lineage and have inherited two identical mutant AQP2 alleles. In total, 34 AQP2 mutations have been described, of which 27 are involved in recessive NDI (Table 2). Of this group, 78% comprise missense mutations. On expression of the encoded mutants in cell systems, nearly all mutants were misfolded and trapped in the ER (class II), followed by rapid proteasomal degradation (31, 33, 84, 90, 92, 104, 152). Con-

Table 2. *AQP2 mutations involved in NDI*

Nucleotide	Amino Acid	Homozygous/ Heterozygous	Recessive/ Dominant	Referred/Analysis	Functionality	Conserved (Location)	Class	Diagnosis	Treatment
64C>G	L22V	he3	r	(23)/(152)	P, (60%)	N (tmd 1)	II	(64)	dD
83T>C	L28P	ho	r	(90)/(90)		N (tmd 1)	II	1 mo	dD:NR
140C>T	A47V	ho	r	(90)/(90)	P (40%)	N (tmd 2)	II	?	dD-deh.:NR
170A>C	Q57P	he5	r	(84)/(84)	NF	N (tmd 2)	II	?	dD:NR
190G>A	G64R	ho	r	(162)/(31;92;162)	P (20%)	Y (b-loop)	II	1 mo	dD:NR
293A>G	N68S	ho	r	(104)/(92)	NF	Y (b-loop)	II	1.6 mo	e:dD-deh.:>300; dD:NR
211G>A	V71M	ho	r	(90)/(90)	NF	Y (b-loop)	II	?	ndD:NR
253C>T	R85*	ho	r	(163)/(163)			I	2 mo	dD:NR
299C>T	G100*	ho	r	(53)/(53)			I	?	dD:NR
299G>T	G100V	he5	r	(84)/(84)	NF	N (tmd 3)	II	?	dD:NR
369delC	Frameshift	ho	r	(162)/(162)			I	?	?
374C>T	T125M	ho, he8	r	(46;77)/(46;80)	P, (25%)	N (c-loop)	II	?	?
377C>T	T126M	ho	r	(92)/(46;82;104)	P (20%)	N (c-loop)	II	6 mo	dD-deh.:NR
439G>A	A147T	ho	r	(104)/(92;104)	F	Y (d-loop)	II	3 mo	dD-deh.:NR
450T>A	D150E	he7	r	(47)/(47)	NF	Y (d-loop)	II	?	?
502G>A	V168M	he4, ho	r	(20;163)/(20)	P (60%)	N (tmd 8)	II	?	he:ndD:NR; ho:dD<200
523G>A	G175R	ho, he8	r	(46;77)/(46;90)	NF	Y (tmd 5)	II	?	?
543C>G	C181W	he3	r	(23)/(102;152)	NF	N (e-loop)	II	(64)	?
553C>G	P185A	ho	r	(90)/(90)	NF	Y (e-loop)	II	1 wk	ndD:NR
669C>T	R187C	ho,he1	r	(33;162)/(92;162)	NF	Y (e-loop)	II	2 wk, 5 mo	dD-den.:NR
928G>A	A190T	he2	r	(28;77)/(28;77)	NF	N (e-loop)	II	?	dD:NR
587G>A	G196D	he7	r	(47)/(47)	NF	N (e-loop)	II	?	NR
606G>T	W202C/ splice	ho	r	(116)/(116)		Y (e-loop)	I	4–8 wk	dD:NR
c606+1G>A	splice	he6;all.2	r	(90)/(90)		(intr. 3)	I	2 wk	dD:NR
646T>C	S216P	he1, he4	r	(33)/(31;82)	NF	N (tmd 6)	II	3 mo	dD:NR
652delC	Frameshift	he6;all.1	r	(90)/(90)		N (tmd 6)	I	2 wk	dD:NR
721delG	Frameshift	he	d	(78)/(78)	F	N (C-tail)	IV	12 mo	ndD:NR; deh.:>300
727delG	Frameshift	he	d	(91)/(91)	F	N (C-tail)	IV	?	dD:NR
761G>T	R254L	he	d	(29)/(29)	F	N (C-tail)	IV	<12 mo	?
763-772del	Frameshift	he	d	(78)/(78)	F	N (C-tail)	IV	36 mo	ndD:NR
772G>A	E258K	he	d	(103)/(103)	F	N (C-tail)	IV	?	dD:>300
779- 780InsA	Frameshift	he	d	(62)/(62)	F	N (C-tail)	IV	6–1 mo	dD:NR:>300
785C>T	P262L	he2	r	(28;77)/(28;77)	F	N (C-tail)	IV	?	dD:NR
812-818del	Frameshift	he	d	(78)/(78)	F	N (C-tail)	IV	16 mo	dD:incr.:deh.:>300

AQP2, aquaporin-2; he, Heterozygous; ho, homozygous; all, allele; r, recessive; d, dominant; NF, nonfunctional; P, partial functional (level in % between brackets); conserved (Y) or not (N) between AQP proteins; >300, urine >300 mosmol/kgH₂O.

sistent with their extensive degradation, AQP2 proteins could not be detected in the urine of patients with recessive NDI due to AQP2 gene mutations, in contrast to those of healthy controls or of a female V2R NDI patient (32, 65). Although ER retained, overexpression in oocytes, where a fraction of the AQP2 mutants are found in the plasma membrane, revealed that AQP2-L22V, -A47V, -G64R, -T125M, -T126M, -A147T, and -V168M are functional as water channels on a molecular level (23, 90, 92, 104). Interestingly, AQP2-V168M yielded a less severe misfolding than other AQP2 mutants in NDI, which might explain the relatively mild form on NDI in a Mexican family encoding this mutant (20). In general, however, the urine concentrating ability of patients with recessive NDI due to AQP2 mutations are severely affected (urine osmolality <100 mosmol/kgH₂O), indicating that in vivo plasma membrane expression of functional AQP2 mutants is negligible. The inability of these AQP2 mutants to form heterotetramers with wild-type AQP2 (wt-AQP2), leaving only the formation of wt-AQP2 homotetramers, likely explains the healthy phenotype of the parents (64). For this, an increased wt-AQP2 expression from the normal allele does not seem to be necessary, because the AQP2 heterozygote knockout mouse, which has a healthy phenotype, expresses about half of AQP2 found in normal mice (173).

Most mutations in autosomal recessive NDI are found in between the first and the last transmembrane domain (Table 2). As this segment forms the AQP2 water pore (105), the misfolding resulting from mutations in this part of the protein illustrates the sensitivity of the pore to structural changes. Recently, one mutation in recessive NDI was found outside this region. Surprisingly, this mutation encodes the P262L exchange in the AQP2 COOH tail, a location that was until then destined to result in dominant instead of recessive NDI (28). This mutation was found in two independent patients, encoding, besides AQP2-P262L, AQP2-A190T and AQP-R187C mutants. Expression in oocytes revealed that the latter two mutants were ER retained (class II). The retention of AQP2-P262L in intracellular vesicles of polarized MDCK cells on stimulation with forskolin provided an explanation for its involvement in NDI, as in the patient neither AQP2-P262L nor AQP2-A190T/R187C would be expressed in the apical membrane of principal cells. However, the observed retention in a non-ER compartment was in still in line with a pattern encountered for AQP2 mutants in dominant NDI. Indeed, as found for mutants in dominant NDI, AQP2-P262L escaped the ER and formed heterotetramers with wt-AQP2, but not AQP2-A190T or AQP-R187C. On coexpression with wt-AQP2, however, wt-AQP2 appeared to target the wt-AQP2/AQP2-P262L com-

Fig. 4. Proposed topology of human AQP2. An AQP2 monomer consists of 6 transmembrane domains connected by 5 loops (A–E) and its NH₂ and COOH termini located intracellularly. Loops B and E meet each other with their characteristic NPA boxes in the membrane to form the water-selective pore. N-glycosylation (at N123) is indicated. Bright amino acids are conserved among different AQPs.

plexes to the apical membrane, indicating that, in contrast to AQP2 mutants in dominant NDI, the apical sorting signals of wt-AQP2 overrule the retention signals in AQP2-P262L, thereby explaining the involvement of AQP2-P262L in recessive instead of dominant NDI. The cellular phenotypes of patients in autosomal recessive and dominant NDI and their parents are summarized in Fig. 5.

Autosomal Dominant NDI

Being diagnosed in only seven families, autosomal dominant inheritance is the least prominent form of NDI. The mutations identified in these families comprise nucleotide deletion, insertion, as well as missense mutations (Table 2). By definition, these mutations are only found in one AQP2 allele. As water-selective AQPs are structurally similar and it was shown that, while expressed as homotetramers, an AQP1 monomer is the functional unit (59, 149, 159), we reasoned that AQP2 mutants in dominant NDI should be able to interfere with the functioning of wt-AQP2. Indeed, on expression in oocytes, these AQP2 mutants were not ER retained and were able to form heterotetramers with wt-AQP2 (64). Due to the mutation, however, these molecularly functional AQP2 mutants were missorted (class V) and, because of the formation of heterotetrameric complexes with wt-AQP2, also targeted wt-AQP2 to other subcellular destinations. Extrapolated to the principal cells of patients, this would lead to severely decreased amounts of AQP2 in the apical membrane, explaining the dominant mode of inheritance of NDI in their families (64).

Clinical analyses of patients with recessive and dominant NDI due to AQP2 mutations revealed three interesting differences (62, 78, 91, 103) (Table 2). First, the symptoms of NDI (polydipsia, polyuria) are already noticeable at birth in recessive NDI, whereas in dominant NDI they often become apparent in the second half of the first year or later. Second, urine osmolalities of patients with recessive NDI never exceed 200 mosmol/kgH₂O, whereas those of dominant NDI are sometimes higher. Third, patients with dominant NDI sometimes show a transient increase in urine concentration shortly after

DDAVP administration or dehydration. This transient increase seems not to be related to the identified AQP2 mutation, because some patients in the AQP2-insA family did not respond. The observation that a dominant disease is subclinically “milder” than the recessive form is not restricted to NDI, because it is also found for long-QT syndrome, myotonia congenita, osteochondrodysplasias, and Robinow syndrome/brachydactyly (1, 164, 168, 175).

Interestingly, all AQP2 mutations in dominant NDI are located in its COOH terminus (Figs. 4 and 5 and Table 2), which underscores the importance of this segment in trafficking of AQP2. Of the seven mutations described, six have shown or are likely to introduce a missorting signal. The first reported AQP2 mutant, AQP2-E258K, is missorted to the Golgi complex in oocytes, but to late endosomes/lysosomes in polarized cells (52, 103). This mutant is strongly retained in oocytes. Deletion of a small segment containing the E258K mutations greatly restored cell surface expression and water permeability, indicating that the introduced Lys instead of the loss of E258 caused the dominant feature (103). Although starting at different positions, all +1 frameshift mutations 721delG, 727delG, del763–772, and del812–818 resulted in a similarly extended COOH-terminal tail. In MDCK cells, AQP2–727delG localized to late endosomes/lysosomes, and to some extent the basolateral plasma membrane, whereas the other three mutants were present exclusively in the basolateral membrane (7, 78, 91). The molecular signature causing the missorting of these AQP2 mutants has remained elusive. In contrast, an adenosine insertion at position 779 (insA) found in another patient yields a +2 reading frame shift, resulting in a different and slightly extended COOH-terminal tail. Detailed analysis in MDCK cells revealed that this mutant was transported to the basolateral membrane, due to the introduction of two basolateral sorting signals in the changed COOH-terminal segment (62).

Finally, one family with dominant NDI was found in which R254 was exchanged for a leucine (29). In contrast to the others, this mutation did not introduce a missorting signal, but

Fig. 5. Cellular fate of AQP2 mutants in the different forms of autosomal recessive or dominant NDI. Shown is a schematic representation of a principal cell of the collecting duct of patients suffering from autosomal recessive NDI (28, 33) and their unaffected parents. For patients in autosomal dominant NDI, the carrier parent has a patient phenotype and is therefore not shown in this scheme. For details on the specific AQP2 mutants, see the text.

interfered with S256 phosphorylation of AQP2 by PKA. Consequently, the formed wt-mutant complexes were retained in intracellular vesicles that are likely similar to the storage vesicles in which unstimulated wt-AQP2 accumulates. This was supported by the similar subcellular distribution of AQP2-R254L, unstimulated wt-AQP2, and AQP2-S256A, which mimics nonphosphorylated AQP2, and their partial colocalization with the early endosome antigen-1 (EEA-1) marker protein.

Genes in Nonhuman NDI

To identify the physiological role of proteins, gene deletion by homologous recombination is often employed in mice. Using this knockout strategy, mice lacking AQP2 or the V2R appeared to suffer from severe NDI, resulting in perinatal death (173, 174). In contrast, mice lacking AQP3, SPA-1, Foxa1, CLC-K1, or all three nitric oxide synthase (NOS) isoforms, or expressing overactive PDE-III, showed milder forms of NDI (12, 76, 86, 93, 101, 106, 111, 156). While a role of AQP3 (exit of water from principal cells) and PDE-III (reduced intracellular cAMP levels) in AVP-induced AQP2-mediated water transport is obvious, this is not so clear for the others. The signal-induced proliferation-associated gene-1 (SPA-1) protein, which is a GTPase-activating protein (GAP) for Rap1 containing a PDZ binding domain, directly bind AQP2 and has a role in its routing. However, its precise function in AQP2 trafficking now needs to be uncovered. Foxa1 is a member of the winged helix family of transcription factors and is expressed in the collecting ducts of the kidney. However, as the expression of the V2R and AQP2 are not affected, its molecular role is still unclear. As an increased interstitial tonicity is essential for water reabsorption, it would be interesting to determine whether the lack of Foxa1 reduces expression of renal salt transporters. The kidney-specific CLC-K1 chloride

channel mediates transepithelial chloride transport in the thin ascending limb of Henle's loop (tAL) in the inner medulla and is involved in the generation and maintenance of the hypertonic medullary interstitium. While administration of DDAVP to these mice did not increase urine concentration, it is at present unclear whether this is only due to a reduced interstitial tonicity or also to reduced principal cell V2R or AQP2 expression. NDI in the triply nitric oxide synthase (NOS) knockout mice coincided with reduced membranous AQP2 expression associated with tubuloglomerular lesion formation and provide clear evidence of a critical role of the NOS system in maintaining renal homeostasis.

Although an occurrence of the loss of the three NOS proteins in humans is unlikely to be encountered, there is no report indicating that the lack of any of the above-mentioned genes causes NDI in humans. In fact, in nearly all our congenital NDI patients we have identified V2R or AQP2 gene mutations. Moreover, the discovery that humans lacking AQP3 are without any clinical phenotype (135) and that the lack of V2R or AQP2 is lethal in mice but not in humans seem to indicate that the urine concentrating mechanism is more sensitive in mice. Therefore, whereas the above-mentioned proteins might have a role in human renal osmoregulation, mutations in their genes are likely to lead to a subclinical phenotype in human water homeostasis or no phenotype at all.

THERAPIES IN CONGENITAL NDI

Conventional Therapies

The most important component of treatment for NDI is replacement of urinary water losses by adequate supply of fluid, in combination with a decreased solute diet to decrease obligatory water excretion. Diuretics such as hydrochlorothiazide and amiloride have been shown to effectively lower urine

volume in NDI, which is, at least for hydrochlorothiazide, more pronounced in combination with a low-salt diet (36, 71). The combined administration of hydrochlorothiazide with either a prostaglandin synthesis [or cyclooxygenase (COX)] inhibitor such as indomethacin ($2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) or the potassium-sparing diuretic amiloride was shown to be much more effective in reducing urine volume than the thiazide-diuretic alone (4, 58, 73, 74, 97, 127). Long-term use of prostaglandin-synthesis inhibitors, however, is often complicated by gastrointestinal and hematopoietic side effects. In addition, renal dysfunction has been described during indomethacin therapy, most often consisting of a reduction in GFR. Because of the known gastrointestinal safety of selective COX-2 inhibitors compared with nonselective COX inhibitors, a potential role for these drugs in the treatment of NDI has been put forward. In one male NDI infant, the effectiveness of a specific COX-2 inhibitor (rofecoxib) in decreasing urinary free water losses was indeed demonstrated (121). Nevertheless, in view of the recent discovery that prolonged use of that particular COX-2 inhibitor can cause severe cardiac side effects (148), we believe that COX-2 inhibitors should not be used in the treatment of NDI until it has been strictly determined which of these specific inhibitors are completely safe. However, while decreasing urine volume to a great extent, these treatments do not completely overcome the excess of water excretion, as adult patients with this conventional treatment still void 8–10 liters/day. Therefore, efforts into development of tailored therapies have been initiated.

Tailored Therapies

In general, renal gene therapy has been hampered by a low level of accessibility and the absence of selectivity of gene transfer techniques to and expression in particular renal cells (54, 79). In contrast, however, with the realization that success of pharmacotherapy depends on the cellular process disturbed by the disease-causing mutation, tailored pharmacotherapy has become highly promising:

Antibiotics to Bypass Stop Codons

A future therapy for patients harboring premature stop codon mutations (class I) is based on the ability of aminoglycoside antibiotics to cause translational read-through. Indeed, a gentamicin analog caused read-through of nonsense V2R mutants in vitro and in vivo (143, 147). However, the efficiency by which aminoglycosides confer read-through depends strongly on the nucleotides flanking the premature stop codon, and on the compound used, and some aminoglycosides exert toxic effects on the kidney, which severely limits their clinical use.

ANP and the cGMP Pathway

The paradigm for vasopressin signaling involves cAMP-mediated PKA activation, which results in the functionally critical phosphorylation of AQP2 on S256 in vitro and in vivo (29, 45, 63, 68, 157). As the AQP2 S256 phosphorylation site also fulfils the requirements for phosphorylation by cGMP kinase, Brown and co-workers (21, 22) came to the brilliant idea that the lack of cAMP generation in patients with X-linked NDI might be bypassed by pathways that activate cGMP kinase. Indeed, in an elegant study, they could show that acute elevation of cGMP levels by nitric oxide (NO), which thus

plays an important role in renal water homeostasis (101), L-arginine, and atrial natriuretic peptide (ANP), led to AQP2 membrane insertion in both transfected cells and regions of the kidney collecting duct (21). This occurred without increasing intracellular cAMP levels and is thus independent of the V2R signaling pathway. Consistently, inhibitors of type 5 cGMP phosphodiesterases, like sildenafil, also induced the phosphorylation and plasma membrane translocation of AQP2 in these specimen (22). In vivo, chronic ANP infusion also induced an increased S256 phosphorylation and apical targeting of AQP2, but as ANP also induces natriuresis, it is at present unclear whether these effects are due to hypovolemia-induced increases in AVP release (167). It will be exciting to uncover whether ANP or other cGMP kinase-activating compounds will be beneficial for patients with X-linked NDI.

“Pharmacological Chaperones” to Rescue V2R Mutants

Very promising are also the approaches recently developed for class II V2R mutants. While their in vivo expression is likely low, transient overexpression of class II mutant proteins in oocytes or HEK293/COS cells, with which a small fraction are often expressed in the plasma membrane, allows the determination of whether such mutants are molecularly functional. Indeed, using such techniques, several (partially) ER-retained V2R and AQP2 mutants in NDI appeared to be functional at the molecular level, as the AQP2 mutants conferred water permeability, whereas the V2R mutants were able to mediate a cAMP response on stimulation with DDAVP (23, 90, 92, 104, 124, 129, 170). In line with these findings, some patients harboring functional and partially ER-retained V2R mutants showed an increased urine concentration in response to high doses of AVP (95) (Table 1).

An important step forward in a putative treatment of these patients was the discovery that stabilization of mutant receptors by cell-permeable V2R antagonists, like SR121463B, aid in the mutant's folding, thereby facilitating their translocation to the plasma membrane (99, 153) (Fig. 3B). Because of their assistance in receptor folding, such cell-permeable ligands are termed pharmacological chaperones (14, 98). Although V2Rs with mutations at residues of major structural importance could not be rescued (e.g., H80R, W164R, S167L), the plasma membrane expression of most class II V2R mutants was restored (172). To be of therapeutic use, the rescuing antagonist has to be displaced by AVP after translocation of the V2R mutant to the basolateral membrane. As the competition between AVP and the rescuing ligand at the plasma membrane will determine functional rescue, low-affinity V2R ligands, like the V1R inverse agonist SR49059, are thought to be clinically more successful than high-affinity compounds such as SR121463B (15). Indeed, Bernier et al. (16) recently found that SR49059 showed a small, but significant, reduction in water intake and urine output in five NDI patients with missense V2R mutations, thus demonstrating the proof-of-principle that pharmacological chaperones can also rescue mutant V2R in vivo. Of great importance for this treatment, the relatively high blood levels of SR49059 came with a minimum of side effects, which is due to their high specificity for the V2R. As several other V1R and V2R antagonists have been developed and have been or are close to FDA approval, it will be exciting to find

out to what extent they are able to relieve X-linked NDI caused by functional class II V2R mutants.

In conclusion, research on congenital NDI during the last 15 years has evolved from the identification of the genes involved and analysis of the cellular fate of the V2R and AQP2 mutants to the development of different strategies to bypass or overcome the inability of V2R mutants in X-linked NDI to mediate an antidiuretic response. While it is at present unclear whether a remedy for autosomal NDI can be developed, further development of the above-mentioned highly promising approaches and, especially, clinical testing of these separate or combined strategies in patients with X-linked NDI is anticipated to bring us an exciting scientific and clinical future, as it will tell us whether we can relieve or cure the major form of congenital NDI, 50 years after its first discovery (87).

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