J Mol Med (1998) 76:326–337

REVIEW

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The molecular basis of nephrogenic diabetes insipidus

Received: 23 April 1997 / Accepted: 3 September 1997

Abstract Nephrogenic diabetes insipidus (NDI) is characterized by resistance of the kidney to the action of arginine-vasopressin (AVP); it may be due to genetic or acquired causes. Recent advances in molecular genetics have allowed the identification of the genes involved in congenital NDI. While inactivating mutations of the vasopressin V_2 receptor are responsible for X-linked NDI, autosomal recessive NDI is caused by inactivating mutations of the vasopressin-regulated water channel aquaporin-2 (AQP-2). About 70 different mutations of the V_2 receptor have been reported, most of them missense mutations. The functionally characterized mutants show a loss of function due to defects in their synthesis, processing, intracellular transport, AVP binding, or interaction with the G protein/adenylyl cyclase system. Thirteen different mutations of the AQP-2 gene have been reported. Functional studies of three AQP-2 mutations reveal impaired cellular routing as the main defect. The great number of different mutations with various functional defects hinders the development of a specific therapy. Gene therapy may, however, eventually become applicable to the congenital forms of NDI. At present all gene-therapeutic approaches lack safety and efficiency, which is of particular relevance in a disease that is treatable by an adequate water intake. The progress with regard to the molecular basis of antidiuresis contributes to the understanding of acquired forms of NDI on a molecular level. Recent data show that lithium dramatically reduces the expression of AQP-2. Likewise, hypokalemia reduces the expression of this water channel. The exact mechanisms leading to this reduced expression of AQP-2 remain to be determined.

Key words Vasopressin V_2 receptor · Aquaporin-2 · Diabetes insipidus · Mutation · Signal transduction

Abbreviations *AQP-2* Aquaporin-2 · *AVP* Arginine-vasopressin · *ER* Endoplasmic reticulum · *GPCR* G protein-coupled receptor · *NDI* Nephrogenic diabetes insipidus · *PG* Prostaglandin · *PKA* cAMP-dependent protein kinase · *RT-PCR* Reverse transcription-polymerase chain reaction

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Communicated by: Hannsjörg W. Seyberth and Klaus Zerres

Introduction

Water homeostasis in humans is regulated through the action of the neurohypophyseal hormone arginine-vaso-

pressin (AVP), a cyclic nonapeptide, which is synthesized in the vasopressinergic neurons of the supraoptic and paraventricular nuclei as a precursor consisting of a cysteine-rich carrier protein (neurophysin), AVP, and a C-terminal glycoprotein of unknown function [1]. Following cleavage of the signal peptide the precursor is packed into vesicles containing the processing enzymes necessary for proteolytic release of the biologically active peptide. During axonal transport to the neurohypophysis AVP is released from the precursor by proteolysis. In response to stimuli such as an increase in plasma osmolarity (by ≥2%) or volume depletion (by ≥10%) AVP is secreted into the blood. In the kidney it activates the vasopressin V_2 receptors expressed in renal collecting ducts. The stimulation of V_2 receptors, which couple to adenylyl cyclase via the G protein G_s, leads to the insertion of vasopressin-sensitive water channels [aquaporin-2 (AQP-2)] into the luminal membrane, thereby increasing water permeability.

Diabetes insipidus includes those disorders involving both polyuria, i.e., the production of large amounts of hypotonic urine (>30 ml/kg of body weight in 24 h, <300 mosmol/kg) and polydipsia. In general three different forms are differentiated: (a) low or absent plasma levels of AVP due to impaired secretion of AVP from the neurohypophysis (central diabetes insipidus), (b) increased turnover of AVP by the placental vasopressinase (gestational diabetes insipidus), and (c) resistance of the kidney towards the action of AVP (nephrogenic diabetes insipidus, NDI). The following causes of NDI have been identified:

– Metabolic disorder
  Potassium depletion
  Hypercalcemia
– Chronic renal disease
  Tubulointerstitial renal disease
  Polycystic and medullary disease
– Anatomical disorder
  Postobstructive diuresis
– Systemic disease
  Sickle cell anemia
  Amyloidosis
  Sarcoidosis
– Side effect of drugs (frequently observed)
  Lithium
  Demeclocycline
– Side effect of drugs (rarely observed)
  Amphotericin B
  Aminoglycoside
  Methoxyflurane
– Congenital
  Inactivating mutations of the vasopressin V_2 receptor gene
  Inactivating mutations of the aquaporin-2 gene

Advances in molecular genetics have led to the identification of the genes involved in congenital diabetes insipidus and contributed to the understanding of vasopressin synthesis, processing, and its antidiuretic action. The present contribution describes the molecular mechanisms of the antidiuretic action of vasopressin and discusses the various causes of NDI.

Renal physiology of vasopressin action

The antidiuretic action of AVP is mediated via the vasopressin V_2 receptor, a member of the large family of G protein-coupled receptors [2]. Immunolocalization in the rat kidney reveals almost exclusive expression in principal cells of the epithelial layer of the renal collecting duct. Expression is low in cortical and strong in inner medullary collecting ducts. Immunostaining is found mainly at the basolateral surface of principal cells, but to a minor degree also at the apical surface. The physiological significance of these apically localized receptors is not well understood [3].

Stimulation of the V_2 receptor leads to the activation of adenylyl cyclase via the G protein G_s (Fig. 1). Increase in cAMP and activation of cAMP-dependent protein kinase (PKA) is followed by fusion of submembranously located vesicles, carrying AQP-2, with the luminal membrane ("shuttle hypothesis") [4, 5]. AQP-2 containing vesicles can also be found deeper within the cell, hence the existence of a rapidly releasable and a reserve pool is likely. The insertion of AQP-2 into the apical membrane is a rapid process and occurs in cortical collecting ducts less than 1 min after AVP treatment [6]. The presence of AQP-2 in the apical membrane causes a marked increase in water permeability, thereby providing the molecular basis for the movement of free water from the collecting duct into the principal cell. Water movement across the basolateral membrane is facilitated by the constitutively expressed AQP-3 [7] and AQP-4 [8]

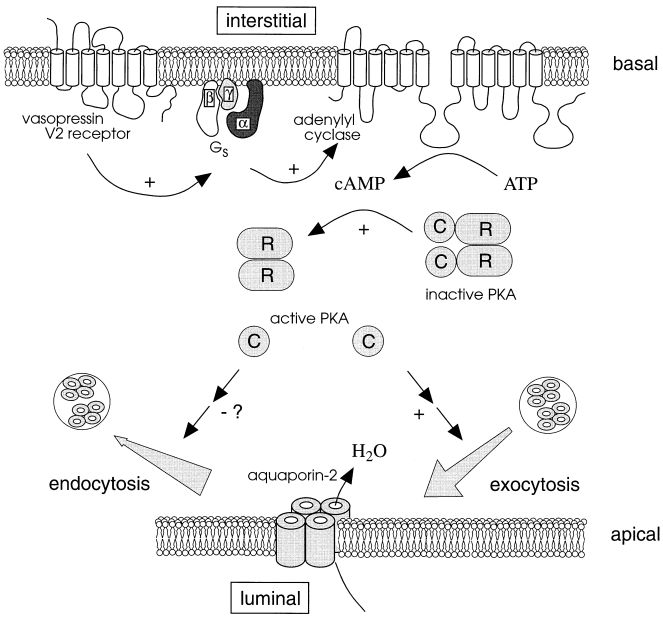

Fig. 1 Schematic presentation of a principal cell. For explanation, see text. Catalytic (*C*) and regulatory (*R*) subunits of the PKA are shown

Table 1 Structure and chromosomal localization of the vasopressin V_2 receptor (V_2R) and the aquaporin-2 (AQP-2) genes

Type	Size (kb)	Gene		Chromosome		Ref.
		Number and size (bp) of exons	Number and size (bp) of introns	Number	Region	
V_2R	~2.1	3 (98, 840, 664)	2 (361, 106)	X	Xq28	22
AQP-2	~5.3	4 (454, 165, 81, 761)	3 (~2900, 250, 700)	12	12q13	59

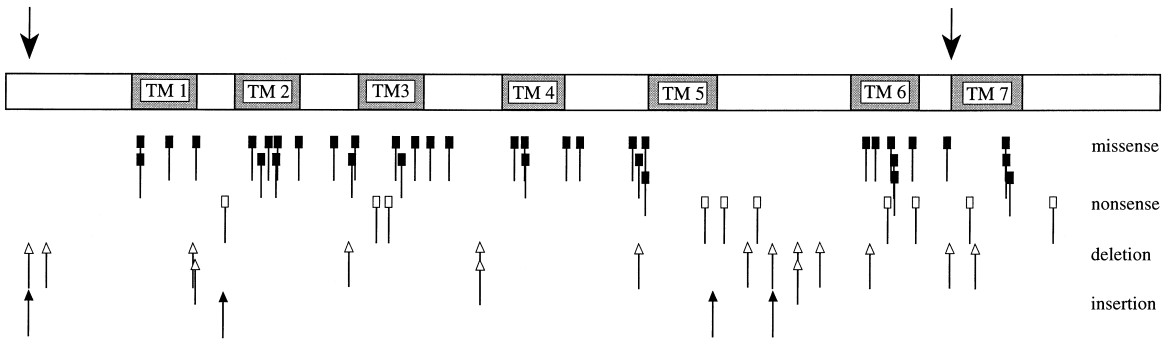

Fig. 2 Distribution of NDI causing mutations within the vasopressin V_2 receptor coding region. Shown are all reported mutations with the exception of four large deletions. Missense and nonsense mutations, insertions, and deletions of up to 35 bp are depicted at separate levels with different symbols. Since no intron mutation has been reported, only the positions of the introns within the V_2 receptor gene are indicated (*large arrows*). *Gray boxes*, hypothetical transmembrane regions (*TM*)

(not shown). The molecular basis for the translocation process of the AQP-2 containing vesicles remains elusive, but it is thought to be analogous with neuronal exocytosis [9]. This is supported by the identification in the vesicles of various proteins known to be involved in regulated exocytosis, for example, rab 3a and synaptobrevin II (VAMP2) or synaptobrevin II-like protein [10–12].

In contrast to neuronal exocytosis, which is triggered by Ca^{2+}, cAMP and PKA appear to be crucial for the translocation process [13, 14]. However, the target proteins of PKA have not been identified. The presence of a consensus site for PKA in the intracellularly located C-terminus of the AQP-2 has led to speculation that AQP-2 is regulated directly through phosphorylation by PKA. Expression of AQP-2 in *Xenopus laevis* oocytes leads to a strong increase in basal water permeability, suggesting a constitutive expression of water conducting AQP-2 at the cell surface in this system [15, 16]. Addition of forskolin or injection of cAMP leads to a further small increase in water permeability, indicating a modulation of the water conduction by PKA. This modulating effect of PKA is absent from AQP-2 mutants with amino acid exchanges in the PKA consensus site [17]. Experiments using vesicles derived from collecting ducts of rat kidney, however, have shown that the phosphorylation of AQP-2 by PKA does not alter its function [18]. The conflicting results concerning the influence of PKA on AQP-2 function may be due to the different systems used. Further investigations are needed to explain these contradictory data.

Congenital NDI

Congenital NDI is a rare disease with an estimated prevalence of 1 per 250,000 males and a calculated carrier frequency of 7.4×10^{-6} [19]. Two forms, differing in their mode of inheritance, are well described. In most cases (about 90%) an X-linked trait is found; a minority of patients (about 10%) show an autosomal recessive inheritance. The existence of an autosomal dominant form of the disease is supported by the report of a Japanese NDI family with three instances of male-to-male transmission and by other recent evidence [20, 21].

X-linked NDI

Shortly after localization of the gene causing X-linked NDI to Xq28 [22] and molecular cloning of the vasopressin V_2 receptor gene (Table 1) [2, 23, 24] the identification of a frameshift mutation in the V_2 receptor (ΔG804, [25]) gave final proof that V_2 receptor mutations are responsible for X-linked NDI. More than 70 different mutations have since been identified (for review see [26, 27]); the great majority are missense and nonsense mutations. Furthermore, 18 frameshift mutations due to nucleotide deletions or insertions (up to 35 bp) and four large deletions have been reported. The mutations are scattered throughout the coding region, without strong evidence for a hypermutable region (Fig. 2). Clusters of missense mutations, however, are found in the transmembrane regions (especially in transmembrane domains II and VI) and at the junctions of the transmembrane domains and the extra- or intracellular loops.

Missense mutations (Table 2) causing the exchange of a single amino acid reveal sites critical for receptor function. Many of the amino acids exchanged involve those identical among the human and rat vasopressin receptor

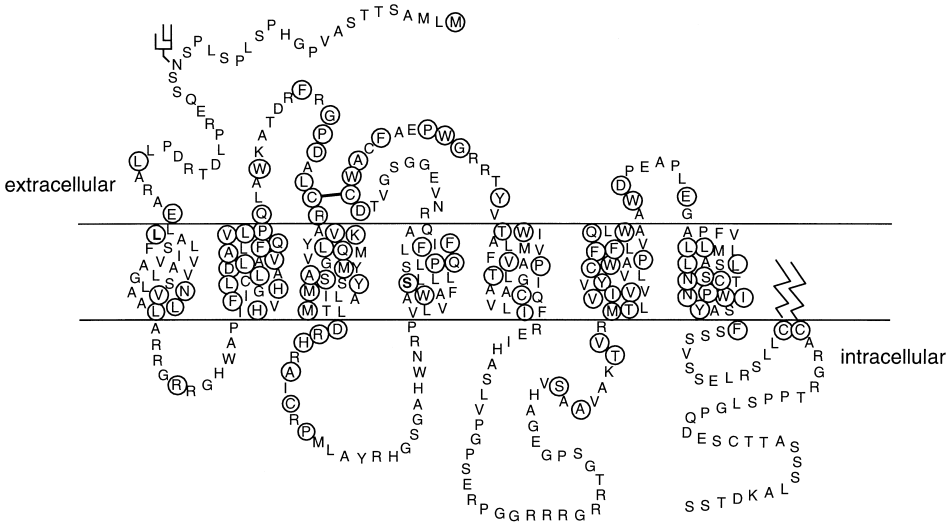

Fig. 3 Model of the human vasopressin V_2 receptor. The one-letter code for amino acids is used. Those common to human and rat vasopressin receptor subtypes (V_{1a}, V_{1b}, V_2) are circled. Potential glycosylation site (at asparagine 22), disulfide bond (between cysteines 112 and 192), and palmitoylation sites (at cysteines 341 and 342) are depicted

Table 2 X-linked NDI causing mutations leading to single amino acid exchanges or *in frame* deletions. Shown are the nucleotide(s) and the amino acid(s) replaced or deleted, the location of the exchange within the V_2 receptor protein, and the functional defect, if determined. (*TM* Transmembrane domain, *IL* intracellular loop, *EL* extracellular loop)

Nucleotide change	Amino acid replacement	Location in V_2 receptor	Major defect	Reference
T202C	L44P[a]	TM I	Defective processing	28, 29
C201T	L44F[a]	TM I	Defective binding	29, 30
T229G	L53R	TM I	n.d.	31
T256C	L62P[a]	TM I	n.d.	30
255del9	Δ62–64	TM I/IL I	n.d.	32
A310G	H80R[a]	IL I	n.d.	33
T319C	L83P[a]	TM II	n.d.	31
G324A	D85N[a,b]	TM II	n.d.	30
G333A	V88M[a]	TM II	n.d.	30, 32
C355T	P95L[a]	TM II	n.d.	31
C387T	R106C	EL I	n.d.	32
T405C	C112R[a,b]	EL I	n.d.	32
C408T	R113W[a]	EL I/TM III	About 20-fold increase in K_D	30, 31, 34–36
C448T	S126F[a]	TM III	n.d.	32
A454C	Y128S[a]	TM III	Defective binding	37–39
G481A	R137H[a,b]	TM III/IL II	Defective coupling	35, 40
G499C	R143P[a]	IL II	Defective transport	41
G562C	W164S[a,b]	TM IV	Defective processing	32
C571T	S167L[b]	TM IV	Defective processing	29–32
T570A	S167T[b]	TM IV	Defective processing	28, 29
C612T	R181C	TM IV/ELII	About 26-fold increase in K_D	37, 38
G624T	G185C	EL II	n.d.	42
C675T	R202C	EL II	Defective transport	31, 32, 42
C682A	T204N	EL II	n.d.	30
A685G	Y205C[a]	EL II	About 10-fold increase in K_D	31, 42, 43
T688A	V206D	EL II/TM V	n.d.	30
T901C	V277A[a]	TM VI	n.d.	44
del906-908	ΔV278/V279	TM VI	Defective transport	39, 41
A910G	Y280C[a]	TM VI	n.d.	44
G924C	A285P[a]	TM VI	n.d.	32
C928G	P286R[a,b]	TM VI	Defective binding	37, 38
C928T	P286L[a,b]	TM VI	n.d.	39
T946C	L292P	TM VI	n.d.	44
C1036A	P322H[a,b]	TM VII	n.d.	45
C1035T	P322S[a,b]	TM VII	n.d.	45
T1038A	W323R[a]	TM VII	n.d.	31

[a] Amino acids common to human and rat vasopressin receptors (V_{1a}, V_{1b}, V_2).
[b] Residues highly conserved among G protein-coupled receptors.

subtypes (V_{1a}, V_{1b}, V_2; Fig. 3) [2, 24, 46–50]. These amino acids may have a crucial role in ligand binding and/or G protein interaction, whereas other residues highly conserved among G protein-coupled receptors (GPCR) may be required for proper folding (e.g., the two cysteine residues in the first and second extracellular loop, which are assumed to form a disulfide bond) or may comprise motifs decisive for G protein coupling (E/D-R-Y/H motif at the junction of the third transmembrane domain and the second intracellular loop).

For three mutations which involve amino acids conserved among the vasopressin receptor family reduced or

abolished binding of AVP was demonstrated (R113W, Y128S, Y205C). While the Y128S mutant completely lacks binding ability [37] the Y205C mutant displays a roughly 10-fold decrease in ligand affinity [43]. Although not reported, a more complex functional defect of the Y205C mutant is likely, since a 10-fold decrease in receptor affinity for AVP may may not be sufficient to cause overt NDI. In addition, symptoms should be ameliorated by the administration of the selective V_2 receptor agonist desmopressin, generally used to establish the diagnosis of NDI. Several functional defects have been found in the R113W mutant [34], namely a decrease in ligand affinity (about 20-fold), a reduced ability to stimulate the G protein G_s (about 3-fold) and lowered expression at the cell surface (about 10-fold).

Defective processing and retention within the endoplasmic reticulum (ER) are found in some V_2 receptor mutants. These mutations involve amino acids highly conserved among GPCRs (S167T, S167L, W164S). The mutant with the *in frame* deletion ΔV278/279 and the R143P mutant also lack surface expression; however, these mutants show processing similar to that of the wild-type receptor [41]. Thus they appear to be retained within the Golgi or a post-Golgi compartment. For the R137H mutant, in which the arginine of the E/D-R-Y/H motif is replaced by histidine (within close proximity of R143), a lowered expression at the cell surface (about 10-fold) was also found [40]. This raises the question of whether this region of the second intracellular loop harbors structural information for correct intracellular transport. The structural importance of this amino acid for G protein-coupling and/or activation, however, is without doubt. This mutant does not have the ability to stimulate the G_s/adenylyl cyclase system. Similar data have been obtained for corresponding mutants of the β_2-adrenergic receptor [51] and of rhodopsin [52].

The strongest impact on receptor folding may arise from the substitution or the introduction of a proline or a charged amino acid within a transmembrane domain. It has been shown for rhodopsin, an ancient member of the GPCR family, that the introduction or replacement of a proline or a charged residue causes its accumulation within the ER [53]. For the M_3 muscarinic receptor replacement of three of the four highly conserved proline residues by alanine causes a 35- to 100-fold reduced expression [54]. For the V_2 receptor six mutations have been identified in which a proline residue is either replaced or introduced, giving rise to a defective receptor (see Table 2). In agreement with this hypothesis, the L44P mutant appears to be retained within a pre-Golgi compartment as it lacks complex glycosylation. In contrast, the L44F mutant is correctly processed and most likely expressed at the cell surface but is defective in AVP binding (leucine 44 is a conserved amino acid within the vasopressin receptor family, but not among GPCRs) [29]. Surprisingly, the P286R mutant, in which a highly conserved proline is replaced by a charged residue has been found to be defective in binding but is expressed at the cell surface similarly to the wild-type receptor [37].

Site-directed mutagenesis of the palmitoylation sites in the C-terminus of the V_2 receptor (Fig. 3) revealed that palmitoylation is important for proper trafficking and/or internalization, without influencing ligand affinity and G protein interaction [55]. Whether impairment of receptor palmitoylation (e.g., S-nitrosylation by NO; for review see [56]) may be causally involved in the imbalance of vasopressin-controlled water homeostasis awaits further investigation.

It is thought that most if not all mutations leading to premature termination of translation due to a frameshift or the introduction of a stop codon interefere with cell surface expression. For the glucagon receptor it has been demonstrated that only the receptor with seven transmembrane domains is detectable at the cell surface; truncated receptors having only one, three, or five transmembrane domains are retained intracellularly [57]. The same appears to be true for the V_2 receptor. The 804insG mutation is predictive for a protein with an altered amino acid sequence starting at residue 247 and a premature stop at residue 258, both within the third intracellular loop. Despite sufficient RNA levels no protein is detected [41]. Even a relatively minor truncation of the vasopressin receptor within the intracellular C-terminus (R337X) has been shown to be associated with NDI [30, 32, 44]. Intact COS cells expressing this mutant do not bind AVP, most likely due to intracellular retention of the truncated receptor (Oksche and Rosenthal, unpublished results).

Defects in protein folding, processing, intracellular transport, and surface expression have also been described for mutations in other GPCRs [53, 57], but the mechanisms responsible for intracellular retention at different levels (e.g., ER, Golgi) are not understood. Expression of a truncated V_2 receptor consisting only of the N-terminus and the first transmembrane domain reveals that this truncated receptor contains the necessary structural information for both correct insertion into the membrane of the ER and for complex glycosylation [58]. Further studies with naturally occurring and in vitro mutants may help to elucidate the steps from receptor synthesis to cell surface expression.

Autosomal-recessive NDI

Molecular cloning of the rat cDNA coding for AQP-2, the exclusive detection of AQP-2 transcripts in the kidney (more pronounced in the medulla than in the cortex), and the immunolocalization of AQP-2 at the apical membrane and in vesicles of principal cells provide strong evidence that AQP-2 is the ultimate effector protein in the signaling cascade initiated by vasopressin [15]. Subsequently the human cDNA [59] and the human gene [16, 60] coding for AQP-2 have been cloned (see Table 1). The identification of inactivating mutations of AQP-2 in a patient with NDI confirms that AQP-2 is the vasopressin-regulated water channel [15]. Meanwhile 13 different mutations causing NDI have been reported; 11 are missense mutations

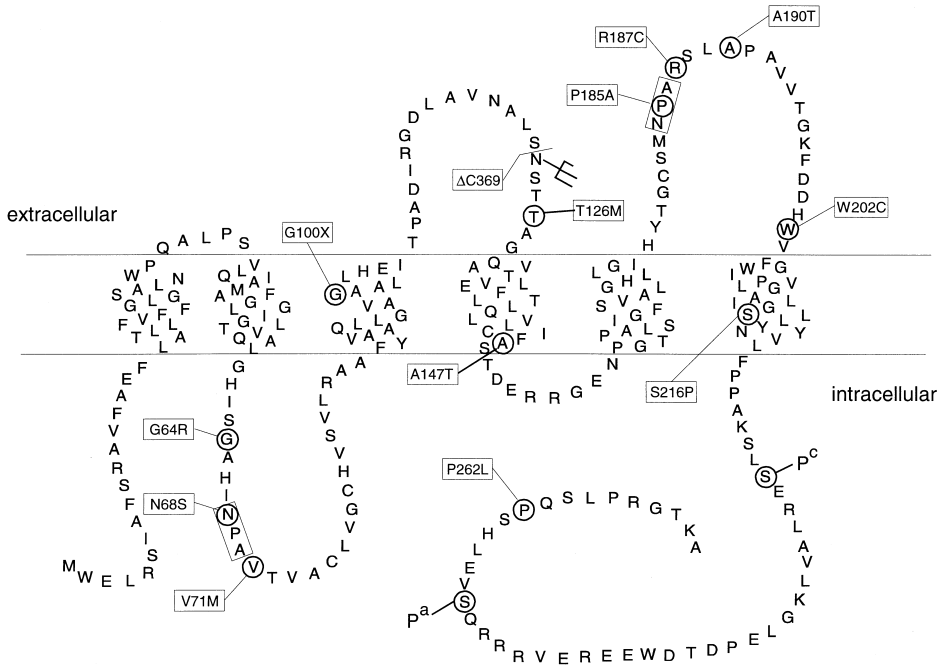

Fig. 4 Model of the human AQP-2. The one-letter code for amino acids is used. Potential glycosylation (at asparagine 123) and phosphorylation sites for PKC (P^c) and PKA (P^a) are indicated; *boxes*, the highly conserved NPA motifs of the first intracellular and the third extracellular loops; *circles*, mutations. The amino acid exchanges are indicated. In case of the only reported frameshift mutation the nucleotide deletion is shown

[16, 21, 61, 62, 63, 64], seven of which are located within either the first intracellular or the third extracellular loop (Fig. 4). This is of particular interest as both loops carry the highly conserved NPA motif, which is present in all water-channel proteins (bacteria, plant, vertebrate). It is speculated that the two NPA motifs fold to form the water pore, and that the mutations interfere with this process [65]. Expression of the mutant AQP-2 proteins, G64R, N68S, T126M, A147T, R187C, and S216P, in *X. laevis* oocytes reveals that the mutations affect mainly cellular routing, the AQP-2 being retained within the ER in each case [66]. It has been therefore suggested that NDI in these patients results from an impaired or abolished surface expression. Disturbed routing to the plasma membrane is of particular interest in the case of the mutant AQP-2 proteins, T126M and A147T. Both mutant proteins retain the ability to function as water channels – although to a lesser degree than the wild-type [63].

The process of AQP-2 translocation into the apical membrane of principal cells can be monitored by analyzing urine samples. In normal individuals there is measurable urinary excretion of AQP-2, which increases upon thirsting and AVP administration. In patients with congenital NDI, AQP-2 is reduced or not detectable in the urine, even under these testing conditions. Kanno et al. [67] found no AQP-2 excretion in patients with X-linked NDI. Deen and coworkers [68], however, found low levels of AQP-2 excretion in a patient with X-linked NDI, whereas in patients with autosomal recessive NDI AQP-2 was not detected. The lack of urinary AQP-2 excretion in the latter group may be due to complete absence of the mutant protein in the apical membrane of principal cells (intracellular retention), whereas in X-linked NDI low levels of AQP-2 may still be present in the apical membrane at resting cAMP levels.

Clinical findings in congenital NDI

The renal concentration defect is present shortly after birth. Thus infants with congenital NDI, irrespective of the underlying molecular defect (V_2 receptor, AQP-2) are threatened by recurrent periods of hypernatremia and dehydration. Recurrent fever and vomiting (due to hypernatremia) are the key symptoms. If the diagnosis is made early, and water is administered adequately, sequelae such as growth and mental retardation are avoided. A recent study of cognitive function in 17 NDI patients revealed a somewhat lower prevalence of mental retardation than former studies [69]. It is likely that improved diagnosis and managment of the disease in recent decades is responsible for this difference. In adult patients polyuria and polydipsia are the key symptoms. In severe cases polyuria may exceed 20 l a day. Sequelae of severe polyuria are hydronephrosis and hydrostatic nephropathy with renal insufficiency.

The onset and intensity of the renal concentration defect appear to be similar in patients with either X-linked or autosomal recessive NDI. Thus an interruption of the signal cascade at the receptor or the effector level has identical consequences.

Female carriers of X-linked NDI do not normally present with symptoms. In a few cases, however, symptoms have been observed [70–72]. This may be explained by an inactivation of the X chromosome carrying the wild-type V_2 receptor. In addition, symptoms may be unmasked during pregnancy in female carriers of X-linked NDI (Rosenthal and Oksche, unpublished). Congenital NDI is not associated with a polyhydramnion, in contrast to other congenital polyuric states such as hyperprostaglandin E syndrome [73].

Although X-linked and autosomal recessive NDI cannot be differentiated by their clinical symptoms, there are variations in laboratory findings. The intravenous infusion of desmopressin (0.3 μg/kg of body weight) normally causes vasodilation leading to facial flush, a slight decrease in the mean arterial pressure (hemodynamic response) and increase in factor VIII, von Willebrand factor, and tissue plasminogen activator in the blood (coagulation response) [74]. Hemodynamic and coagulation responses are not observed in patients with NDI due to a mutation in the V_2 receptor gene [74] but are retained in those with a mutation in the AQP-2 gene [70–72, 75]. The molecular basis for the hemodynamic and coagulation response are not understood. Stimulation of isolated or cultured endothelial cells (the assumed source of the released proteins) with desmopressin does not cause the release of factor VIII, von Willebrand factor, or tissue plasminogen activator [76, 77]. V_2 receptors of the kidney are probably not involved, as patients with chronic renal failure [78] still show coagulation response. However, there is evidence that the coagulation response is due to stimulation of monocytes that induce secretion by endothelial cells [79, 80].

The vasodilatory response in some blood vessels upon desmopressin treatment is thought to be involved in the release of nitric oxide from the vascular endothelium [81–83]. Evidence for extrarenal expression of V_2 receptors was first provided by reverse transcription polymerase chain reaction (RT-PCR) and in situ hybridization analysis of rat brain, where V_2R transcripts have been found in the epithelial and endothelial cells of the choriod plexus, the granular layer of the cerebellum, and the hippocampus. In the latter location expression is detected only in fetal rats and is lost within 2 weeks after birth [84]. In adult human lung V_2 receptor-mRNA has been identified by RT-PCR and northern blot analysis [84]. In contrast, in fetal lung tissue only very low levels of V_2 receptor-mRNA expression are found. In addition, V_2 receptor-mRNA expression has also been demonstrated by RT-PCR analysis of adult rat lung. It is speculated that vasopressin regulates fluid balance in the lung via the V_2R, as reported for fetal sheep, goats, and guinea pigs [85]. However, no data have yet been published so far on the identification of V_2 receptor-mRNA in the systemic vascular system, which might explain the above coagulation response.

Acquired NDI

Most cases of acquired NDI are due to metabolic disorders (hypokalemia, hypercalcemia), drugs (e.g., lithium, demeclocycline), chronic renal disease or postobstructive diuresis. Lithium is of particular interest as it is a widely used for drug therapy of bipolar psychosis. Analysis of several studies comprising more than 1000 patients on chronic lithium therapy has revealed a defective concentrating ability (54%) and polyuria (19%), whereas the glomerular filtration rate is well preserved [86]; after cessation of therapy the concentrating ability recovered only slowly. Irreversible lithium-induced polyuria has also been reported [87], which may be explained by tubular atrophy and focal interstitial sclerosis found in patients undergoing long-term lithium therapy [88]. Obviously, lithium has cytopathic effects when accumulated within epithelial cells of the collecting duct. Interestingly, the morphological changes are more pronounced when lithium is adminstered twice or three times daily rather than in a single dose schedule [89].

Lithium enters the renal tubular cells through amiloride-sensitive sodium channels. Its mechanisms of action within the cell are not clear. It may modulate the function of pertussis toxin sensitive G proteins and thereby lower the levels of cAMP [90].

Lithium treatment of rats over 25 days nearly abolishes the expression of AQP-2 [91]. Although experimental evidence has not been presented, it is likely that lithium affects the expression of AQP-2 at the transcriptional level. Among other regulatory elements found in the 5′ noncoding region of the AQP-2 gene there is a cAMP responsive element 314 bp upstream of the start codon [60]. Thus a lowered intracellular cAMP level may contribute to a decrease in the transcriptional rate and give rise to the polyuria observed during short-term lithium therapy.

Similarly to lithium, hypokalemia causes a decrease in the concentrating ability of the kidney, possibly at the level of the G_s/adenylyl cyclase system. While inner medullary tubules from hypokalemic rats show a normal intracellular cAMP formation in response to direct stimulation by NaF, they exhibit impaired cAMP levels upon AVP treatment [92]. The polyuria in patients with hypokalemia, however, is less severe and is reversed soon after normalization of plasma potassium levels. Similar to the data obtained with lithium, expression of AQP-2 has been shown to be lowered in hypokalemic rats [93]. As AQP-2 expression is not affected by the loop diuretic furosemide, which ablates medullary hypertonicity, an effect of interstitial osmolarity on AQP-2 expression can be excluded [93].

Demeclocycline is known to induce polyuria and is therefore used for the treatment of the syndrome of inappropriate secretion of vasopressin. Its mechanism of action is poorly understood. In cortical slices of rat cerebellum the chelating ability of tetracyclines for divalent cations (in particular in the case of demeclocyline) appears to be responsible for their interference with the adenylyl cyclase system [94]. Whether this is true for the kidney remains to be shown.

A reduction in the urinary concentration ability is an early manifestation of chronic renal failure. Several factors affect the concentration ability of the nephron. Alterations in the medullary architecture due to interstitial fibrosis and the increased load of solutes per nephron impairing the generation of medullary hypertonicity are involved. In addition, a decrease in the V_2 receptor transcripts has been demonstrated in the uremic rat, which may result from either a decreased transcription rate or a

decreased RNA stability [95]. Thus a decrease in the receptor number may contribute to the concentration defect in chronic renal failure with hyposthenuria. It is likely that the resulting lack of AVP-induced cAMP production also impairs the expression of AQP-2 (see above), which may explain the lack of hydrosmotic responsiveness of isolated collecting ducts from uremic rabbits to stimulation by Br-cAMP [96].

Therapy

The key management measure for congenital NDI consists of a water intake adjusted to the increased urinary output. Additional pharmacological therapy involves the use of thiazides, amiloride, and cyclo-oxygenase inhibitors.

The mechanisms of thiazide diuretics in reducing urinary output in NDI are not completely understood, but there is general agreement that volume contraction and loss of salt are a major factor in reducing the glomerular filtration rate and consequently urinary output. Combination of a thiazide with amiloride may be more effective than thiazide alone [97].

Prostaglandin (PG) E_2 blunts the antidiuretic action of vasopressin probably by suppressing basal and AVP-stimulated cAMP formation in the renal collecting duct [98]. It also inhibits solute resorption from the thick ascending limb of Henle and increases medullary blood flow [99, 100]; these factors contribute to a decrease in papillary osmolarity. As renal synthesis of PGE_2 itself can be stimulated by vasopressin via V_1 receptors [101], AVP may enhance polyuria in patients with X-linked NDI. Elevated levels of PGE_2 in congenital NDI have been reported [102, 103]. Indomethacin inhibits the production of PGE_2 and consequently reduces polyuria in congenital NDI as well as in drug-induced polyuria with elevated levels of PGE_2 [104]. It is the drug of choice for the treatment of patients with a hyperprostaglandinemia E syndrome (see above). In congenital NDI a combined therapy of amiloride and thiazides may be advantageous over a combination of indomethacin and thiazides, as the former has less potential adverse drug effects. PGE_2 inhibitors, in particular indomethacin, often cause headaches and dizziness, or increase the risk of gastrointestinal erosions or ulcers. In addition, indomethacin substantially reduces the glomerular filtration rate in the first year of life, thereby increasing the risk of nephropathy.

In acquired forms of NDI the restoration of metabolic homeostasis (normocalcemia, normokalemia) or the withdrawal of the NDI-inducing drug is usually sufficient. Thiazide diuretics should be used with care in lithium-induced NDI as they reduce lithium excretion and thus predispose for lithium toxicity. During lithium therapy amiloride is the drug of choice as it inhibits the accumulation of lithium within the principal cell [105]. Whether amiloride is also able to prevent histological changes of the renal parenchyma caused by long-term lithium therapy remains to be shown.

Future aspects

The majority of NDI-causing V_2 receptor mutations which have been functionally characterized result in processing or transport defective proteins which do not reach the cell surface. Intracellular retention is also likely for the truncation mutants. Lack of surface expression, irrespective of the fact that the mutant receptor may retain residual function (binding of AVP, stimulation of the G_s/adenylyl system), explains why even high doses of the synthetic selective V_2 receptor agonist desmopressin fail to restore the concentration ability of the kidney. Strategies to overcome the intracellular retention may be considered useful only in the case of mutants with residual function. To date only a few mutants with a transport defect but with measurable functional activity (R113 W, R143P) have been investigated. The mechanisms underlying the transport defects in such mutants are not known, but they are likely to be various (e.g., retention in ER, Golgi). For example, retention within the ER is likely in the mutants L44P, W164S, S167L, and S167T as they are not glycosylated. Other mutants such as R143P and ΔV278/279 are probably retained in or after the Golgi, as glycosylation similar to that of the wild-type protein is found.

Examination of kidney samples of two patients with congenital NDI reveal normal renal histology with the exception of proximal tubular atrophy, which may be secondary due to the dilatation of the urinary collecting system [106, 107]. However, as the genes of the patients coding for the V_2 receptor or the AQP-2 were not analyzed, it cannot be excluded that the intracellular retention of mutant V_2 receptors or AQP-2 proteins cause epithelial degeneration. This was shown to be the case for rhodopsin mutations causing autosomal dominant retinitis: mutant receptors are retained in the ER, accumulate, and eventually lead to retinal degradation [53, 108]. The histological changes in the retina are correlated with the extent of accumulation of the mutant protein [108].

The diversity of mutations and the different molecular phenotypes in X-linked NDI make strategies for the rescue of intracellularly retained mutant proteins difficult. In cystic fibrosis about 60% of the European patients share the ΔF508 mutant of the cystic fibrosis transmembrane conductance regulator, which is retained within the ER [109]. Thus it may be worthwhile searching for an approach to rescue this mutant, which has been shown to possess functional activity. Recent data show that the mutant is polyubiquinated and is degraded via the proteasome pathway. A mere inhibition of the degradative process, however, does not enable the mutant protein to exit from the ER [110].

For the V_2 receptor the possibility of a functional rescue of mutants with premature stops has been investigated, based on the assumption that proteins consist of individual folding domains which can be separately expressed and complemented to yield a functional protein. Successful complementation has been demonstrated for

the adrenergic receptor [111], for rhodopsin [112], and for the muscarinic M_3 receptor [113]; complementation of a truncated receptor with the missing domain(s) could also produce a functional receptor. As many V_2 receptor truncations occur within the third intracellular loop (see Fig. 2), only the peptide comprising the C-terminal sequence from transmembrane domain VI onwards must be expressed. In COS cells an approach to complement such truncated V_2 receptors has yielded receptors with the ability to stimulate adenylyl cyclase [114]. However, the absolute number of receptors expressed at the cell surface is low. Whether this approach will be applicable in patients with NDI is not clear.

The discovery of the genetic defects causing congenital NDI allows the easy identification of carriers in families with a history of the disease and the firm diagnosis of suspected patients immediately after birth. Thus the individual risk can be determined early and adequate measures can be taken. Despite the recent progress in the elucidation of the molecular basis of the disease, therapy of congenital NDI remains symptomatic. Gene therapy might be considered for treatment; however, many questions must be resolved beforehand in view of the fact that NDI can be treated adequately by a sufficient water administration.

Acknowledgements This review includes the work of our colleagues D.G. Bichet, J. Dickson, P. Kronich, U. Liebenhoff, K. Maric, A. Möller, H. Müller, C. Rutz, K. Schülein, and R. Schülein. Own work reported herein was supported by the Deutsche Forschungsgemeinschaft (SFB 249) and Thyssen Foundation.

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