Physiopathology of hereditary polyuric states: a molecular view of renal function

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Summary

Recent discoveries have shed new light on the understanding of water metabolism: (1.) in addition to hypothalamic osmoreceptor cells expressing a TRPV1 variant, there are peripheral TRPV4 receptors sensing tonicity in the portal vein and changing central vasopressin secretion and peripheral autonomic activity; (2.) the central osmoregulatory gain of angiotensin action participates in the non-osmotic release of vasopressin induced by hypovolaemia; (3.) prostaglandins EP2 receptors on principal cells of the collecting ducts positively regulate urine concentration mechanisms. These new developments are important clinically for the understanding of hereditary polyuric states. We recommend sequencing of the nephrogenic diabetes insipidus genes in all affected patients. This genomic information is key to the routine care of patients with congenital polyuria and, as in other genetic diseases, reduces health costs and confers psychological benefits on patients and families.

Key words: *hereditary diabetes insipidus; AVPR2; AQP2; TRPV1; TRPV4; thirst; osmoregulation; AVP; genetic testing*

Introduction

Over and above the multifactorial processes of excretion, brain circumventricular sensors (fig. 1) reacting to tonicity subserve the control of antidiuretic hormone secretion and thirst. Hypertonicity can mediate a proportional excitation of the brain's primary osmoreceptor neurons via mechanical modulation of nonselective cation channels encoded by *Trpv1* (transient receptor potential vanilloid-1 gene) [1]. Specifically, hypertonicity is sensed by organum vasculosum lamina terminalis (OVLT) neurons expressing *TRPV1*: OVLT serves as the brain's primary osmoreceptor area [2] and neurons in this nucleus transduce hyperosmotic conditions into proportional increases in action potential firing rate [3]. The information encoded by the electrical activity of these neurons is then relayed synaptically to diverse subsets of homeostatic effector neurons that induce appropriate osmoregulatory responses such as thirst, natriuresis and antidiuretic hormone release [4–8].

In this article I describe central (OVLT) and peripheral (hepatic neurons) osmoreceptors respectively expressing TRPV1 and TRPV4 cation channels, both critical in maintaining plasma osmolality within normal limits through control of antidiuretic hormone secretion and thirst.

I also explain the effect of vasopressin on principal cells of the renal collecting ducts in generating intracellular cyclic AMP and the insertion of the AQP2 water channels into the luminal membrane, a necessary step for distal water reabsorption.

I use these new physiopathological data to explain hereditary central and nephrogenic diabetes insipidus and to facilitate their early clinical recognition and molecular evaluation.

In a recent editorial Richard Lifton indicated that mutations causing more than 2000 Mendelian diseases have been identified, and this has led to rewriting of of pathophysiology textbooks on every organ system and the identification of rational targets for therapeutic intervention [9]. I use the new information provided by the *AVP*, *AVPR2* and *AQP2* genes to describe a molecular view of water conservation.

Plasma sodium and osmolality

Plasma sodium and osmolality are maintained within normal limits (136–143 mEq/l for plasma sodium; 275–290 mOsmol/kg for plasma osmolality) by a thirst-AVP-renal axis [7, 10]. Thirst and AVP release, both stimulated by increased osmolality, is a "double negative" feedback system [11]. Even when the AVP component of this "double negative" regulatory feedback system is lost, the thirst mechanism still preserves plasma sodium and osmolality within the normal range, but at the expense of pronounced polydipsia and polyuria. Thus, the plasma sodium concentration or osmolality of an untreated patient with diabetes insipidus and unlimited access to water may be slightly greater than the mean normal value, and a decrease in plasma sodium and osmolality might be observed in primary polydipsic patients, though these small increases have no diagnostic significance [12].

Mammals are osmoregulators: the cellular perception of tonicity

Mammals are osmoregulators: they have evolved mechanisms that maintain extracellular fluid (ECF) osmolality near a stable value. But, although mammals strive to maintain a constant ECF osmolality, values measured in an individual can fluctuate around the set-point owing to intermittent changes in the rates of water intake and water loss (through evaporation or diuresis) and to variations in the rates of Na intake and excretion (natriuresis). In humans, for example, 40 minutes of strenuous exercise in the heat [13, 14], or 24 hours of water deprivation, [15] causes plasma osmolality to rise by more than 10 mosmol/kg. In a dehydrated individual, drinking the equivalent of two large glasses of water (~850 ml) lowers osmolality by approximately 6 mosmol/kg within 30 minutes [16]. Similarly, ingestion of 13 g salt increases plasma osmolality by approximately 5 mosmol/kg within 30 minutes [17]. Although osmotic perturbations larger than these can be deleterious to health, changes in the 1–3% range play an integral part in the control of body-fluid homeostasis. Differences between the ECF osmolality and the desired set-point induce proportional homeostatic responses according to the principle of negative feedback [7]. ECF hyperosmolality stimulates the sensation of thirst, to promote water intake, and the release of vasopressin to enhance water reabsorption in the kidney. By contrast, ECF hypoosmolality suppresses basal VP secretion in rats and humans [18].

As summarised elegantly by Bourque [7], early studies provided clear evidence that "cellular dehydration" (that is, cell shrinking) was required to stimulate thirst and vasopressin release during ECF hyperosmolality: these responses could be induced by infusions of concentrated solutions containing membrane-impermeable solutes, which extract water from cells, but not by infusions of solutes that readily equilibrate across the cell membrane (such as urea). Verney coined the term osmoreceptor to designate the specialised sensory elements. He further showed that these were present in the brain and postulated that they might comprise "tiny osmometers" and "stretch receptors" that would allow osmotic stimuli to be "transmuted into electrical signals" [19]. Osmoreceptors are therefore defined functionally as neurons that are endowed with an intrinsic ability to detect changes in ECF osmolality and it is now known that both cerebral and peripheral osmoreceptors contribute to the body fluid balance (fig. 2). Although magnocellular neurons are themselves osmosensitive, they require input, by glutamatergic afferents, from the lamina terminalis in order to respond fully to osmotic challenges (fig. 1). Neurons in the lamina terminalis are also osmosensitive and because the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT) lie outside the blood-brain barrier, they can integrate this information with endocrine signals borne by circulating hormones, such as angiotensin II (Ang-II), relaxin, and atrial natriuretic peptide (ANP). While circulating Ang-II and relaxin excite both OT and vasopressin magnocellular neurons, ANP inhibits vasopressin neurons.

Figure 1

Schematic representation of the osmoregulatory pathway of the hypothalamus (sagittal section of midline of ventral brain around the 3rd ventricle in mice). Neurons (lightly filled circles) in the lamina terminalis (OVLT), median preoptic nucleus (MnPO) and subfornical organ (SFO) – that are responsive to plasma hyptertonicity send efferent axonal projections (grey lines) to magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON). The OVLT is one of the brain circumventricular organs and is a key osmosensing site in the mammalian brain (vide infra). The processes (dark lines) of these magnocellular neurons form the hypothalamo-neurohypophysial pathway that courses in the median eminence to reach the posterior pituitary, where neurosecretion of vasopressin and oxytocin occurs. (Modified from [80]).

Figure 2

Upper left: Cell autonomous osmoreception in vasopressin neurons. Changes in osmolality cause inversely proportional changes in soma volume. Shrinkage activates nonselective cation channels (NSCCs) and the ensuing depolarisation increases action potential firing rate and vasopressin (VP) release from axon terminals in the neurohypophysis. Increased VP levels in blood enhance water reabsorption by the kidney (antidiuresis) to restore extracellular fluid osmolality toward the set point. Hypotonic stimuli inhibit NSCCs. The resulting hyperpolarization and inhibition of firing reduces VP release and promotes diuresis.

Upper right: Whole cell current clamp recordings from isolated MNCs (left) and averaged data from multiple cells show that the depolarising and action potential firing responses induced by a hypertonic stimulus are significantly enhanced in the presence of 100 nM Ang II.

Lower right: Hypothetical events mediating central Ang II enhancement of osmosensory gain. Ang II released by afferent nerve terminals (e.g. during hypovolaemia) binds to AT1 receptor (AT1R) coupled to G proteins such as Gq or/and G12/13. Activated G proteins signal through phospholipase C (PLC) and protein kinase C (PKC) to activate a RhoA-specific guanine nucleotide exchange factor (RhoA–GEF), such as p115RhoGEF or LARG (leukaemia-associated Rho guanine–nucleotide exchange factor) Activation of RhoA–GEF converts inactive cytosolic RhoA (RhoA–GDP) into active, membrane-associated RhoA–GTP by promoting the exchange of GDP to GTP. Activated RhoA induces actin polymerisation and increases submembrane F-actin density to enhance the mechanical gating of non-specific cation channels.

(From [81]: Prager-Khoutorsky M, Bourque CW. Osmosensation in vasopressin neurons: changing actin density to optimize function. Trends Neurosci. 2010;33:76–83. © Elsevier, Oxford, UK, with kind permission.)

The non-osmotic pathways are more physiologically described now as "osmoregulatory gain" since angiotensin II amplifies osmosensory transduction by enhancing the proportional relationship between osmolality, receptor potential and action potential firing in rat supraoptic nucleus neurons [20]. Modifications in osmoregulatory gain induced by angiotensin explain why the changes in the slope and threshold of the relationship between plasma osmolality and vasopressin secretion are potentiated by hypovolaemia or hypotension and are attenuated by hypervolaemia or hypertension [21] (fig. 3).

Tonicity information is relayed by central osmoreceptor neurons expressing TRPV1 and peripheral osmoreceptor neurons expressing TRPV4

Osmotic regulation of the release of AVP from the posterior pituitary is primarily dependent, under normal circumstances, on tonicity information relayed by central osmoreceptor neurons expressing TRPV1 [7] and peripheral osmoreceptor neurons expressing TRPV4 [10].

The cellular basis for osmoreceptor potentials has been characterised using patch-clamp recordings and morphometric analysis in magnocellular cells isolated from the supraoptic nucleus of the adult rat. In these cells, stretch-inactivating cationic channels transduce osmotically evoked changes in cell volume into functionally relevant changes in membrane potential. In addition, magnocellular neurons also operate as intrinsic Na^+ detectors. The N-terminal variant of the transient receptor potential channel (TRPV1) is an osmotically activated channel expressed in the magnocellular cells producing vasopressin [22] and in the circumventricular organs, the OVLT and the SFO [3]. Since osmoregulation still operates in $Trpv1^{-/-}$ mice, other osmosensitive neurons or pathways must be able to compensate for loss of central osmoreceptor function [3, 22, 23]. Afferent neurons expressing the osmotically activated ion channel, TRPV4 in the thoracic dorsal root ganglia that innervate hepatic blood vessels and detect physiological

hypo-osmotic shifts in blood osmolality have recently been identified [10]. In mice lacking the osmotically activated ion channel, TRPV4, hepatic sensory neurons no longer exhibit osmosensitive inward currents and activation of peripheral osmoreceptors in vivo is abolished. In a large cohort of human liver transplantees, who presumably have denervated livers, plasma osmolality is significantly elevated compared to healthy controls, suggesting the presence of an inhibitory vasopressin effect of hyponatraemia, perceived in the portal vein from hepatic afferents [10]. TRPV1 (expressed in central neurons) and TRPV4 (expressed in peripheral neurons) thus appear to play entirely complementary roles in osmoreception. Lechner et al., have thus identified the primary afferent neurons that constitute the afferent arc of a well-characterised reflex in man and more recently also in rodents [24]. This reflex engages the sympathetic nervous system to raise blood pressure and stimulate metabolism [25, 26]. As a point of clinical interest, it has already been demonstrated that orthostatic hypotension and postprandial hypotension respond to water drinking [27–29]. Moreover, water drinking in man can prevent neutrally mediated syncope during blood donation or after prolonged standing [30]. Finally, water drinking is also associated with weight loss in overweight individuals [31]. Other peripheral sensory neurons expressing other mechanosensitive proteins may also be involved in osmosensitivity [32].

Arginine vasopressin synthesis

AVP and its corresponding carrier, neurophysin II, are synthesised as a composite precursor by the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus (for review see [33] fig. 4). The precursor is packaged into neurosecretory granules and transported axonally in the stalk of the posterior pituitary. En route to the neurohypophysis, the precursor is processed into the active hormone. Prepro-vasopressin has 164 amino acids and is encoded by the 2.5 kb AVP gene located in chromosome region 20p13 [34, 35]. The *AVP* gene (coding for AVP and neurophysin II) and the *OXT* gene (coding for oxytocin and neurophysin I) are located in the same chromosome region, at a very short distance from each other (12 kb in humans) in head to head orientation. Data from transgenic mouse
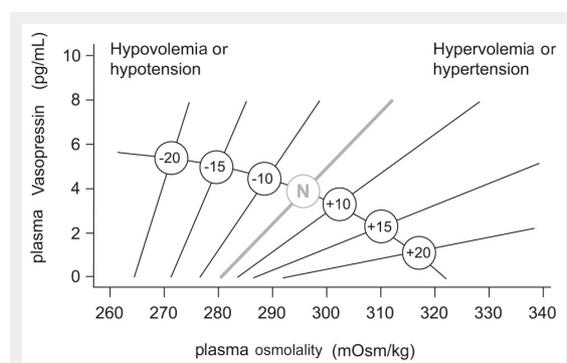
Figure 3

Schematic representation of the relationship between plasma vasopressin and plasma osmolality in the presence of differing states of blood volume and/or pressure.
The line labelled N represents normovolaemic normotensive conditions. Minus numbers to the left indicate percent fall, and positive numbers to the right, percent rise in blood volume or pressure.
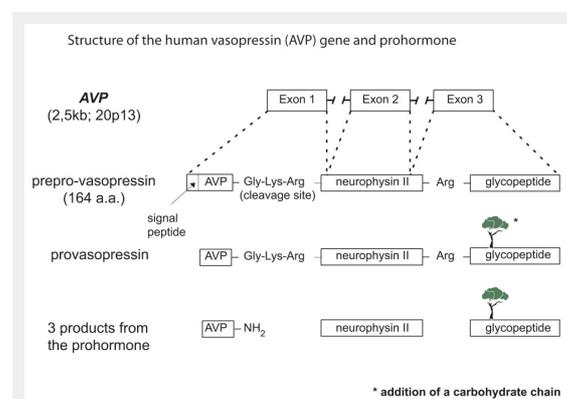
Figure 4

Structure of the human vasopressin (AVP) gene and cascade of vasopressin biosynthesis, signal peptide; AVP, arginine-vasopressin; neurophysin; glycoprotein.

studies indicate that the intergenic region between the *OXT* and the *AVP* genes contains the critical enhancer sites for cell-specific expression in the magnocellular neurons [33]. It is phylogenetically interesting to note that *cis* and *trans* components of this specific cellular expression have been conserved between the *Fugu* isotocin (the homologue of mammalian oxytocin) and rat oxytocin genes [36]. Exon 1 of the *AVP* gene encodes the signal peptide, AVP, and the NH_2-terminal region of neurophysin II. Exon 2 encodes the central region of neurophysin II, and exon 3 encodes the COOH-terminal region of neurophysin II and the glycopeptide. Pro-vasopressin is generated by removal of the signal peptide from prepro-vasopressin and from the addition of a carbohydrate chain to the glycopeptide (fig. 4). Additional post-translation processing occurs within neurosecretory vesicles during transport of the precursor protein to axon terminals in the posterior pituitary, yielding AVP, neurophysin II, and the glycopeptide. The AVP-neurophysin II complex forms tetramers that can self-associate to form higher oligomers [37]. Neurophysins should be seen as chaperone-like molecules facilitating intracellular transport in magnocellular cells. In the posterior pituitary, AVP is stored in vesicles. Exocytotic release is stimulated by minute increases in serum osmolality (hypernatraemia, osmotic regulation) and by more pronounced decreases in extracellular fluid (hypovolaemia, non-osmotic regulation). Oxytocin and neurophysin I are released from the posterior pituitary by the suckling response in lactating females.

Immunocytochemical and radioimmunological studies have demonstrated that oxytocin and vasopressin are synthesised in separate populations of the supraoptic nuclei and the paraventricular nuclei neurons [38, 39], whose central and vascular projections have been described in great detail [40]. Some cells express the *AVP* gene and others express the *OXT* gene. Immunohistochemical studies have revealed a second vasopressin neurosecretory pathway that transports high concentrations of the hormone to the anterior pituitary gland from parvocellular neurons to the hypophyseal portal system. In the portal system, the high concentration of AVP acts synergistically with corticotropin-releasing hormone (CRH) to stimulate adrenocorticotropin (ACTH) release from the anterior pituitary. More than half of parvocellular neurons coexpress both *CRH* and *AVP*. In addition, while passing through the median eminence and the hypophyseal stalk, magnocellular axons can also release AVP into the long portal system. Furthermore, a number of neuroanatomical studies have revealed the existence of short portal vessels that allow communication between the posterior and anterior pituitary. Thus, in addition to parvocellular vasopressin, magnocellular vasopressin is able to influence ACTH secretion [41, 42].

Cellular actions of vasopressin

The neurohypophyseal hormone AVP has multiple actions, including inhibition of diuresis, contraction of smooth muscle, platelet aggregation, stimulation of liver glycogenolysis, modulation of ACTH release from the pituitary, and central regulation of somatic functions (thermoregulation, blood pressure) [43]. These multiple actions of AVP can

be explained by the interaction of AVP with at least three types of G protein-coupled receptors; the V_{1a} (vascular hepatic) and V_{1b} (anterior pituitary) receptors act through phosphatidylinositol hydrolysis to mobilise calcium [44], and the V_2 (kidney) receptor is coupled to adenylate cyclase [45]. Oxytocin and vasopressin receptors are widely expressed in the brain and it is now well recognised that oxytocin and vasopressin are involved in adult-adult attachment [46] and in the modulation of autonomic fear responses [47].

The first step in the action of AVP on water excretion is its binding to arginine vasopressin type 2 receptors (hereafter referred to as V_2 receptors) on the basolateral membrane of the collecting duct cells (fig. 5). The human gene that codes for the V_2 receptor (*AVPR2*) is located in chromosome region Xq28 and has three exons and two small introns [48, 49]. The sequence of the cDNA predicts a polypeptide of 371 amino acids with seven transmembrane, four extracellular, and four cytoplasmic domains. The V_2 receptor is one of 701 members of the rhodopsin family within the superfamily of guanine-nucleotide (G) protein-coupled receptors [50]; see also perspective by [51]. The activation of the V_2 receptor on renal collecting tubules stimulates adenylyl cyclase via the stimulatory G protein (Gs) and promotes the cyclic adenosine monophosphate (cAMP)-mediated incorporation of water pores into the luminal surface of these cells. This process is the molecular basis of the vasopressin-induced increase in the osmotic water permeability of the apical membrane's collecting tubule [52–54].

AVP also increases the water reabsorptive capacity of the kidney by regulating the urea transporter UT-A1 that is present in the inner medullary collecting duct, predominantly in its terminal part [55, 56]. AVP also increases the permeability of principal collecting duct cells to sodium [57].

In summary, in the absence of AVP stimulation, collecting duct epithelia exhibit very low permeabilities to sodium urea and water. These specialised permeability properties permit the excretion of large volumes of hypotonic urine formed during intervals of water diuresis. By contrast, AVP stimulation of the collecting ducts' principal cells leads to selective increases in the permeability of the apical membrane to water, urea and sodium.

These actions of vasopressin in the distal nephron are possibly modulated by prostaglandin E2, nitric oxide [58], and by luminal calcium concentration. PGE2 is synthesised and released in the collecting duct, which expresses all four E-prostanoid receptors (EP1–4). Both EP2 and EP4 can signal via increased cAMP. Olesen et al. hypothesised that selective EP receptor stimulation could mimic the effects of vasopressin and demonstrated that, at physiological levels, PGE2 markedly increased apical membrane abundance and phosphorylation of AQP2 in vitro and ex vivo, leading to increased cell water permeability [59]. In their experiments, both EP2 and EP4 selective agonists were able to mimic these effects. Furthermore, an EP2 agonist was able to regulate positively urinary-concentrating mechanisms in an animal model of nephrogenic diabetes insipidus (NDI). These results reveal an alternative mechanism for regulating water transport in the collecting duct that has major im-

portance for understanding whole-body water homeostasis and provides a rationale for investigations into EP receptor agonist use in nephrogenic diabetes insipidus treatment. An apical calcium/polycation receptor protein expressed in the terminal portion of the rat inner medullary collecting duct has been shown to reduce AVP-elicited osmotic water permeability when luminal calcium concentration rises [60]. This possible link between calcium and water metabolism may play a role in the pathogenesis of renal stone formation [60].

Hereditary central and nephrogenic diabetes insipidus (table 1)

Diabetes insipidus is a disorder characterised by the excretion of abnormally large volumes (greater than 30 ml/kg body weight per day for an adult patient) of dilute urine (less than 250 mmol/kg). This definition excludes osmotic diuresis, which occurs when excess solute is being excreted, e.g. glucose in the polyuria of diabetes mellitus. Other agents that produce osmotic diuresis are mannitol, urea, glycerol, contrast media, and loop diuretics. Osmotic diuresis should be considered when solute excretion exceeds 60 mmol/hour. Four basic defects may be involved.

The most common, deficient secretion of the antidiuretic hormone (ADH) arginine vasopressin (AVP), is referred to as neurogenic (or central, neurohypophyseal, cranial, or hypothalamic) diabetes insipidus. Diabetes insipidus may also result from renal insensitivity to the antidiuretic effect of AVP, which is referred to as nephrogenic diabetes insipidus. Excessive water intake may result in polyuria, which is referred to as primary polydipsia; it may be due to an abnormality in the thirst mechanism, referred to as dipsogenic diabetes insipidus, or it may be associated with a severe emotional cognitive dysfunction, referred to as psychogenic polydipsia. Finally, increased metabolism of vasopressin during pregnancy is referred to as gestational diabetes insipidus.

Hereditary central diabetes insipidus

Most of the central diabetes insipidus cases seen in general practice are acquired, but the rare cases of hereditary autosomal dominant or recessive neurohypophyseal diabetes insipidus have provided further cellular understanding of the mechanisms responsible for pre-hormone folding, maturation and release. Autosomal dominant central diabetes insipidus is secondary to the toxic accumulation of vasopressin mutants as fibrillar aggregates in the endoplasmic

Figure 5

Schematic representation of the effect of vasopressin (AVP) to increase water permeability in the principal cells of the collecting duct. AVP is bound to the V_2 receptor (a G-protein-linked receptor) on the basolateral membrane. The basic process of G-protein-coupled receptor signalling consists of three steps: a hepta-helical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein ($G_{\alpha s}$) that dissociates into α subunits bound to GTP and βγ subunits after interaction with the ligand-bound receptor, and an effector (in this case, adenylyl cyclase) that interacts with dissociated G-protein subunits to generate small-molecule second messengers. AVP activates adenylyl cyclase, increasing the intracellular concentration of cAMP. The topology of adenylyl cyclase is characterised by two tandem repeats of six hydrophobic transmembrane domains separated by a large cytoplasmic loop and terminates in a large intracellular tail. The dimeric structure (C_1 and C_2) of the catalytic domains is represented. Conversion of ATP to cAMP takes place at the dimer interface. Two aspartate residues (in C_1) coordinate two metal co-factors (Mg^{2+} or Mn^{2+} represented here as two small black circles), which enable the catalytic function of the enzyme (305). Adenosine is shown as an open circle and the three phosphate groups (ATP) are shown as smaller open circles. Protein kinase A (PKA) is the target of the generated cAMP. The binding of cAMP to the regulatory subunits of PKA induces a conformational change, causing these subunits to dissociate from the catalytic subunits. These activated subunits (C) as shown here are anchored to an aquaporin-2 (AQP2)-containing endocytic vesicle via an A-kinase anchoring protein. The local concentration and distribution of the cAMP gradient is limited by phosphodiesterases (PDEs). Cytoplasmic vesicles carrying the water channels (represented as homotetrameric complexes) are fused to the luminal membrane in response to AVP, thereby increasing the water permeability of this membrane. The dissociation of the A-kinase anchoring protein from the endocytic vesicle is not represented. Microtubules and actin filaments are necessary for vesicle movement toward the membrane. When AVP is not available, AQP2 water channels are retrieved by an endocytic process, and water permeability returns to its original low rate. Aquaporin-3 (AQP3) and aquaporin-4 (AQP4) water channels are expressed constitutively at the basolateral membrane.
(From: Bonnardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Brenner BM (ed). The Kidney. 8th ed. New York: Harcourt Health Sciences; 2008. p. 1382-1419. © Elsevier, Oxford, UK, with kind permission.)
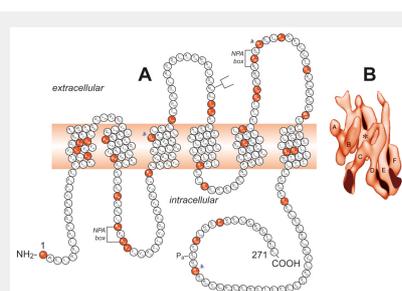

Figure 6

A Schematic representation of the aquaporin-2 protein and identification of 46 AQP2 mutations. A monomer is represented with six transmembrane helices. The location of the protein kinase A phosphorylation site (Pa) is indicated. The extracellular, transmembrane, and cytoplasmic domains are defined according to Deen et al. [82] Solid symbols indicate the mutations' location.
B A surface-shaded representation of the six-helix barrel of the AQP1 protein viewed parallel to the bilayer.
(From: Bonnardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Brenner BM (ed). The Kidney. 8th ed. New York: Harcourt Health Sciences; 2008. p. 1382–1419. © Elsevier, Oxford, UK, with kind permission.)

reticulum of hypothalamic magnocellular neurons producing vasopressin.

Inherited neurohypophyseal diabetes insipidus (OMIM 125700) [61] due to mutations in the *AVP* gene (OMIM 192340) [61]

Patients with autosomal dominant neurohypophyseal diabetes insipidus retain some limited capacity to secrete AVP during severe dehydration, and the polyuria-polydipsic symptoms usually appear after the first year of life [62], when the infant's demand for water is more likely to be understood by adults. In neurohypophyseal diabetes insipidus, termed familial neurohypophyseal diabetes insipidus (FNDI), levels of AVP are insufficient and patients show a positive response to treatment with dAVP. Growth retardation may be observed in untreated children with

Figure 7

Schematic representation of the V_2 receptor and identification of 193 putative disease-causing AVPR2 mutations. Predicted amino acids are shown as the one-letter amino acid code. A solid symbol indicates a codon with a missense or nonsense mutation; a number indicates more than one mutation in the same codon; other types of mutation are not indicated on the figure. There are 95 missense, 18 nonsense, 46 frameshift deletion or insertion, 7 inframe deletion or insertion, 4 splice-site, and 22 large deletion mutations, and one complex mutation.
(From: Bonnardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Brenner BM (ed). The Kidney. 8th ed. New York: Harcourt Health Sciences; 2008. p. 1382–1419. © Elsevier, Oxford, UK, with kind permission.)

Figure 8

A young patient thirsty since birth.

autosomal dominant FNDI [63]. Over 60 mutations in the prepro-arginine-vasopressin-neurophysin II *AVP* gene located on chromosome 20p13 have been reported in dominant FNDI (adFNDI). Knock-in mice heterozygous for a nonsense mutation in the AVP carrier protein neurophysin II showed progressive loss of AVP-producing neurons over several months correlated with increased water intake, increased urine output, and decreased urine osmolality. The data suggest that vasopressin mutants accumulate as fibrillar aggregates in the endoplasmic reticulum and cause cumulative toxicity to magnocellular neurons explaining the later age of onset [64, 65]. To date, recessive FNDI, with early polyuric manifestations has only been described in three studies [66–68]. Very early (first week of life) polyuric states are usually nephrogenic but we and others have observed autosomal recessive central diabetes insipidus patients with early polyuria, dehydration episodes responding to dDAVP with specific mutations of the AVP gene [66–69]. A study by Christensen et al. [70] examined the differences in cellular trafficking between dominant and recessive AVP mutants and found that dominant forms were concentrated in the cytoplasm, whereas recessive forms were localised to the tips of neurites. The expression of regulated secretory proteins such as granins and prohormones, including pro-vasopressin, generates granule-like structures in a variety of neuroendocrine cell lines due to aggregation in the trans-Golgi [71]. Co-staining experiments unambiguously distinguished between these granule-like structures and the accumulations by pathogenic dominant mutants formed in the ER, since the latter, but not the trans-Golgi granules, co-localised with specific ER markers [64]. As studies concerning both dominant and recessive FNDI accumulate, it is becoming evident that FNDI exhibits a variable age of onset and this may be related to the cellular handling of the mutant AVP. This progressive toxicity, sometimes called a toxic gain of function, shares mechanistic pathways with other neurodegenerative diseases such as Huntington's and Parkinson's.

It is of interest that no loss of function of the *TRPV1* or *TRPV4* genes has been linked to a defect in water excretion in humans, yet a rare polymorphism of *TRPV4* has been associated with human hyponatraemia [72].

Hereditary nephrogenic diabetes insipidus

In nephrogenic diabetes insipidus (NDI), AVP levels are normal or elevated but the kidney is unable to concentrate urine. The clinical manifestations of polyuria and polydipsia can be present at birth and must be immediately recognised to avoid severe episodes of dehydration. Most (>90%) of congenital patients with NDI have X-linked mutations in the *AVPR2* gene, the Xq28 gene coding for the vasopressin V_2 (antidiuretic) receptor. In less than 10% of the families studied, congenital NDI has an autosomal recessive inheritance and approximately 42 mutations have been identified in the AQP2 gene (*AQP2*) located in chromosome region 12q13; that is, the vasopressin-sensitive water channel (fig. 6) [73]. For the *AVPR2* gene, 211 putative disease-causing mutations have now been published in 326 unrelated families with X-linked NDI (fig. 7). When studied in vitro, most *AVPR2* mutations lead to receptors that are trapped intracellularly and are unable to reach the

plasma membrane [74]. A minority of the mutant receptors reach the cell surface but are unable to bind AVP or to trigger an intracellular cAMP signal. Similarly, *AQP2* mutant proteins are trapped intracellularly and cannot be expressed at the luminal membrane. This AQP2-trafficking defect is correctable, at least in vitro, by chemical chaperones. Other inherited disorders with mild, moderate, or severe inability to concentrate urine include Bartter syndrome (MIM601678) [75], cystinosis, and autosomal dominant hypocalcaemia [76, 77], nephronophthisis and apparent mineralocorticoid excess [78].

We are recommending the sequencing of the nephrogenic diabetes insipidus genes in all the affected patients. The genes involved are, with a few exceptions, relatively small and easy to sequence. This genomic information is key to the routine care of patients with congenital polyuria and, as in other genetic diseases, reduces health costs and provides psychological benefits to patients and families [79] (fig. 8).

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Table 1			
Hereditary central and nephrogenic diabetes insipidus			
	↓	↓	
	Hereditary central diabetes insipidus	**Hereditary nephrogenic diabetes insipidus**	
Clinical features	Polyuria, polydipsia, low urine osmolality during dehydration, increased urine osmolality after desamino-8D-arginine vasopressin (dDAVP)	Polyuria, polydipsia, low urine osmolality during dehydration, but little or no increase in urine osmolality after dDAVP	
Genetic analysis	Mutations in the ***AVP*** gene, most are autosomal dominant	↓ X-linked: *AVPR2* mutations, males affected but also expressing females	↓ Autosomal dominant or recessive: *AQP2* mutations

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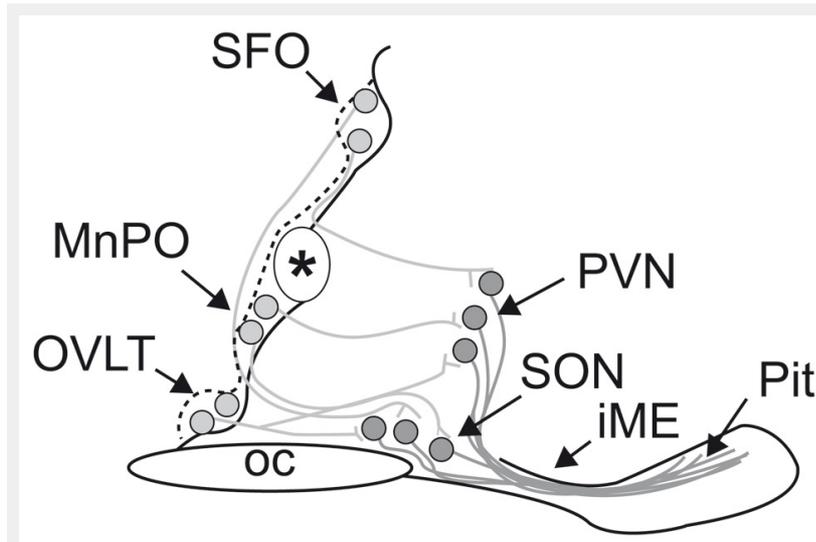
Figures (large format)

Figure 1

Schematic representation of the osmoregulatory pathway of the hypothalamus (sagittal section of midline of ventral brain around the 3rd ventricle in mice). Neurons (lightly filled circles) in the lamina terminalis (OVLT), median preoptic nucleus (MnPO) and subfornical organ (SFO) – that are responsive to plasma hyptertonicity send efferent axonal projections (grey lines) to magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON). The OVLT is one of the brain circumventricular organs and is a key osmosensing site in the mammalian brain (vide infra). The processes (dark lines) of these magnocellular neurons form the hypothalamo-neurohypophysial pathway that courses in the median eminence to reach the posterior pituitary, where neurosecretion of vasopressin and oxytocin occurs. (Modified from [80]).

Figure 2

Upper left: Cell autonomous osmoreception in vasopressin neurons. Changes in osmolality cause inversely proportional changes in soma volume. Shrinkage activates nonselective cation channels (NSCCs) and the ensuing depolarisation increases action potential firing rate and vasopressin (VP) release from axon terminals in the neurohypophysis. Increased VP levels in blood enhance water reabsorption by the kidney (antidiuresis) to restore extracellular fluid osmolality toward the set point. Hypotonic stimuli inhibit NSCCs. The resulting hyperpolarization and inhibition of firing reduces VP release and promotes diuresis.

Upper right: Whole cell current clamp recordings from isolated MNCs (left) and averaged data from multiple cells show that the depolarising and action potential firing responses induced by a hypertonic stimulus are significantly enhanced in the presence of 100 nM Ang II.

Lower right: Hypothetical events mediating central Ang II enhancement of osmosensory gain. Ang II released by afferent nerve terminals (e.g. during hypovolaemia) binds to AT1 receptor (AT1R) coupled to G proteins such as Gq or/and G12/13. Activated G proteins signal through phospholipase C (PLC) and protein kinase C (PKC) to activate a

RhoA-specific guanine nucleotide exchange factor (RhoA–GEF), such as p115RhoGEF or LARG (leukaemia-associated Rho guanine–nucleotide exchange factor) Activation of RhoA–GEF converts inactive cytosolic RhoA (RhoA–GDP) into active, membrane-associated RhoA–GTP by promoting the exchange of GDP to GTP. Activated RhoA induces actin polymerisation and increases submembrane F-actin density to enhance the mechanical gating of non-specific cation channels.

(From [81]: Prager-Khoutorsky M, Bourque CW. Osmosensation in vasopressin neurons: changing actin density to optimize function. Trends Neurosci. 2010;33:76–83. © Elsevier, Oxford, UK, with kind permission.)
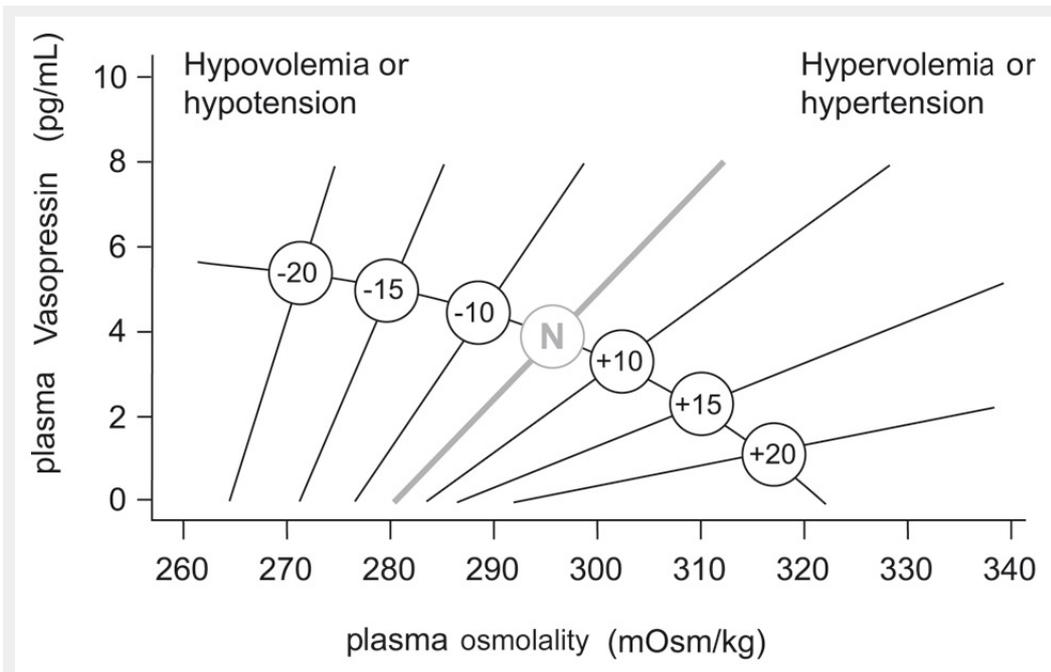
Figure 3

Schematic representation of the relationship between plasma vasopressin and plasma osmolality in the presence of differing states of blood volume and/or pressure.

The line labelled N represents normovolaemic normotensive conditions. Minus numbers to the left indicate percent fall, and positive numbers to the right, percent rise in blood volume or pressure.
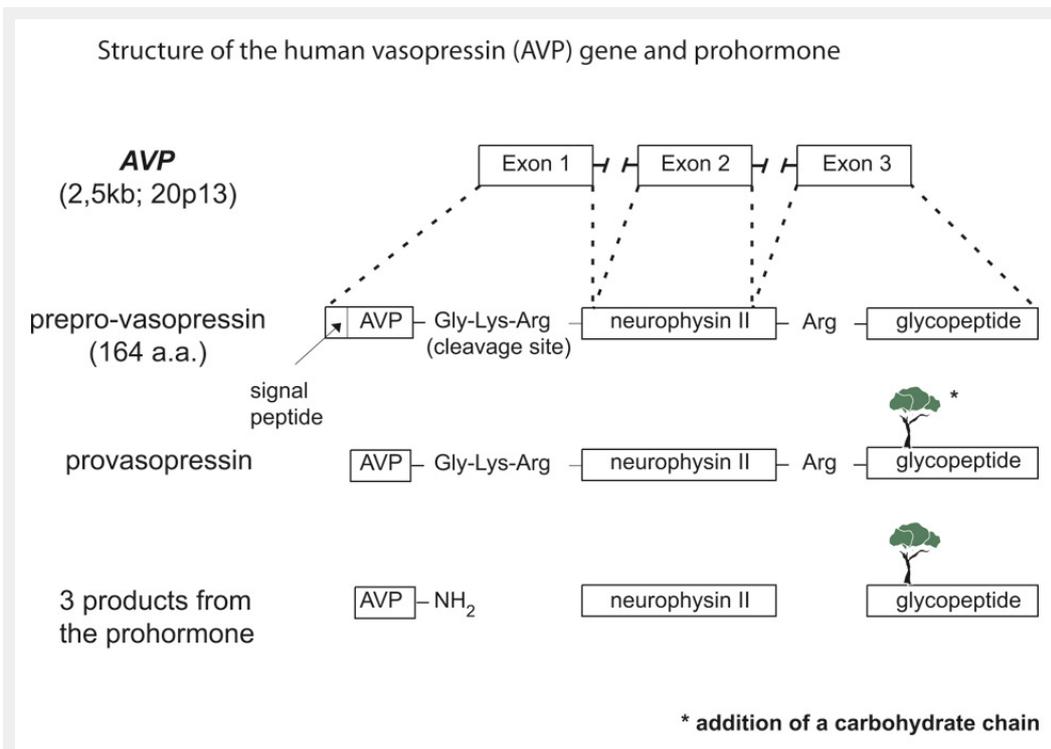

Figure 4

Structure of the human vasopressin (AVP) gene and cascade of vasopressin biosynthesis, signal peptide; AVP, arginine-vasopressin; neurophysin; glycoprotein.

Figure 5

Schematic representation of the effect of vasopressin (AVP) to increase water permeability in the principal cells of the collecting duct. AVP is bound to the V_2 receptor (a G-protein-linked receptor) on the basolateral membrane. The basic process of G-protein-coupled receptor signalling consists of three steps: a hepta-helical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein ($G_{\alpha s}$) that dissociates into▪▪ α▪▪ subunits bound to GTP and ▪▪$\beta\gamma$▪▪ subunits after interaction with the ligand-bound receptor, and an effector (in this case, adenylyl cyclase) that interacts with dissociated G-protein subunits to generate small-molecule second messengers. AVP activates adenylyl cyclase, increasing the intracellular concentration of cAMP. The topology of adenylyl cyclase is characterised by two tandem repeats of six hydrophobic transmembrane domains separated by a large cytoplasmic loop and terminates in a large intracellular tail. The dimeric structure (C_1 and C_2) of the catalytic domains is represented. Conversion of ATP to cAMP takes place at the dimer interface. Two aspartate residues (in C_1) coordinate two metal co-factors (Mg^{2+} or Mn^{2+} represented here as two small black circles), which enable the catalytic function of the enzyme (305). Adenosine is shown as an open circle and the three phosphate groups (ATP) are shown as smaller open circles. Protein kinase A (PKA) is the target of the generated cAMP. The binding of cAMP to the regulatory subunits of PKA induces a conformational change, causing these subunits to dissociate from the catalytic subunits. These activated subunits (C) as shown here are anchored to an aquaporin-2 (AQP2)-containing endocytic vesicle via an A-kinase anchoring protein. The local concentration and distribution of the cAMP gradient is limited by phosphodiesterases (PDEs). Cytoplasmic vesicles carrying the water channels (represented as homotetrameric complexes) are fused to the luminal membrane in response to AVP, thereby increasing the water permeability of this membrane. The dissociation of the A-kinase anchoring protein from the endocytic vesicle is not represented. Microtubules and actin filaments are necessary for vesicle movement toward the membrane. When AVP is not available, AQP2 water channels are retrieved by an endocytic process, and water permeability returns to its original low rate. Aquaporin-3 (AQP3) and aquaporin-4 (AQP4) water channels are expressed constitutively at the basolateral membrane. (From: Bonnardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Brenner BM (ed). The Kidney. 8th ed. New York: Harcourt Health Sciences; 2008. p. 1382-1419. © Elsevier, Oxford, UK, with kind permission.)
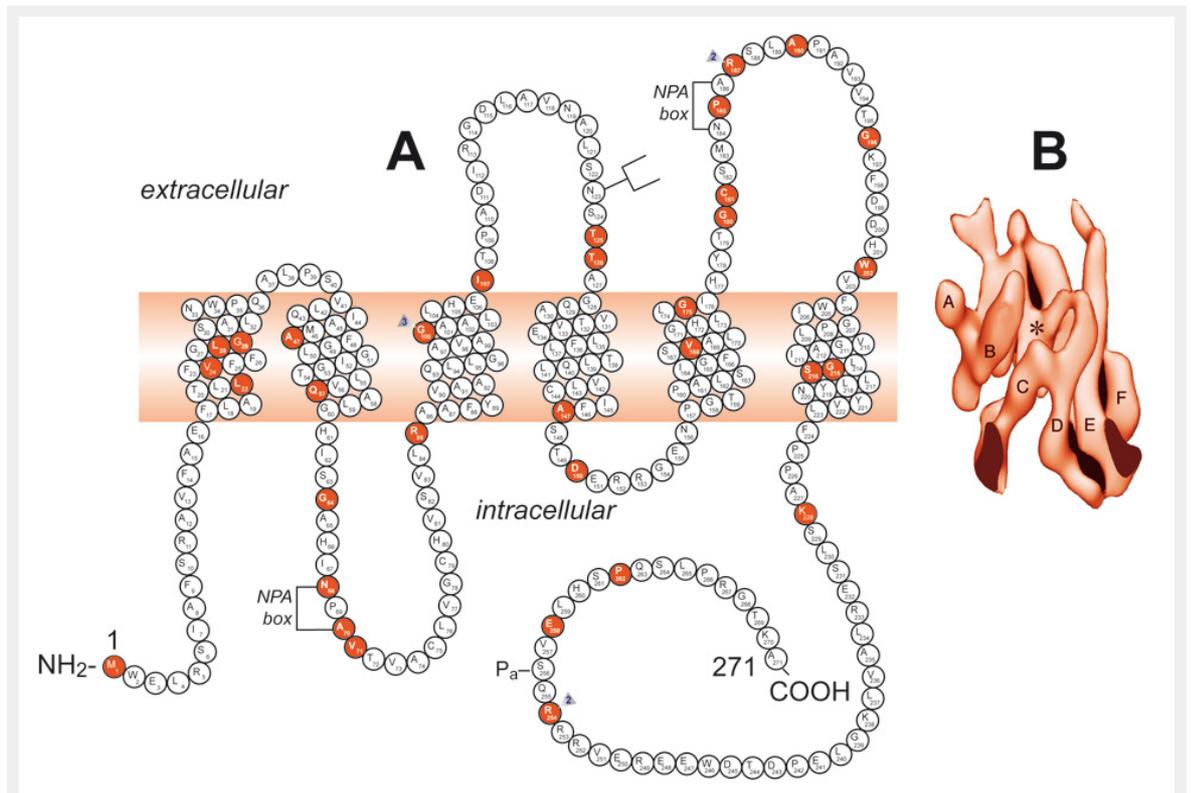
Figure 6

A Schematic representation of the aquaporin-2 protein and identification of 46 AQP2 mutations. A monomer is represented with six transmembrane helices. The location of the protein kinase A phosphorylation site (Pa) is indicated. The extracellular, transmembrane, and cytoplasmic domains are defined according to Deen et al. [82] Solid symbols indicate the mutations' location.

B A surface-shaded representation of the six-helix barrel of the AQP1 protein viewed parallel to the bilayer.

(From: Bonnardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Brenner BM (ed). The Kidney. 8th ed. New York: Harcourt Health Sciences; 2008. p. 1382–1419. © Elsevier, Oxford, UK, with kind permission.)
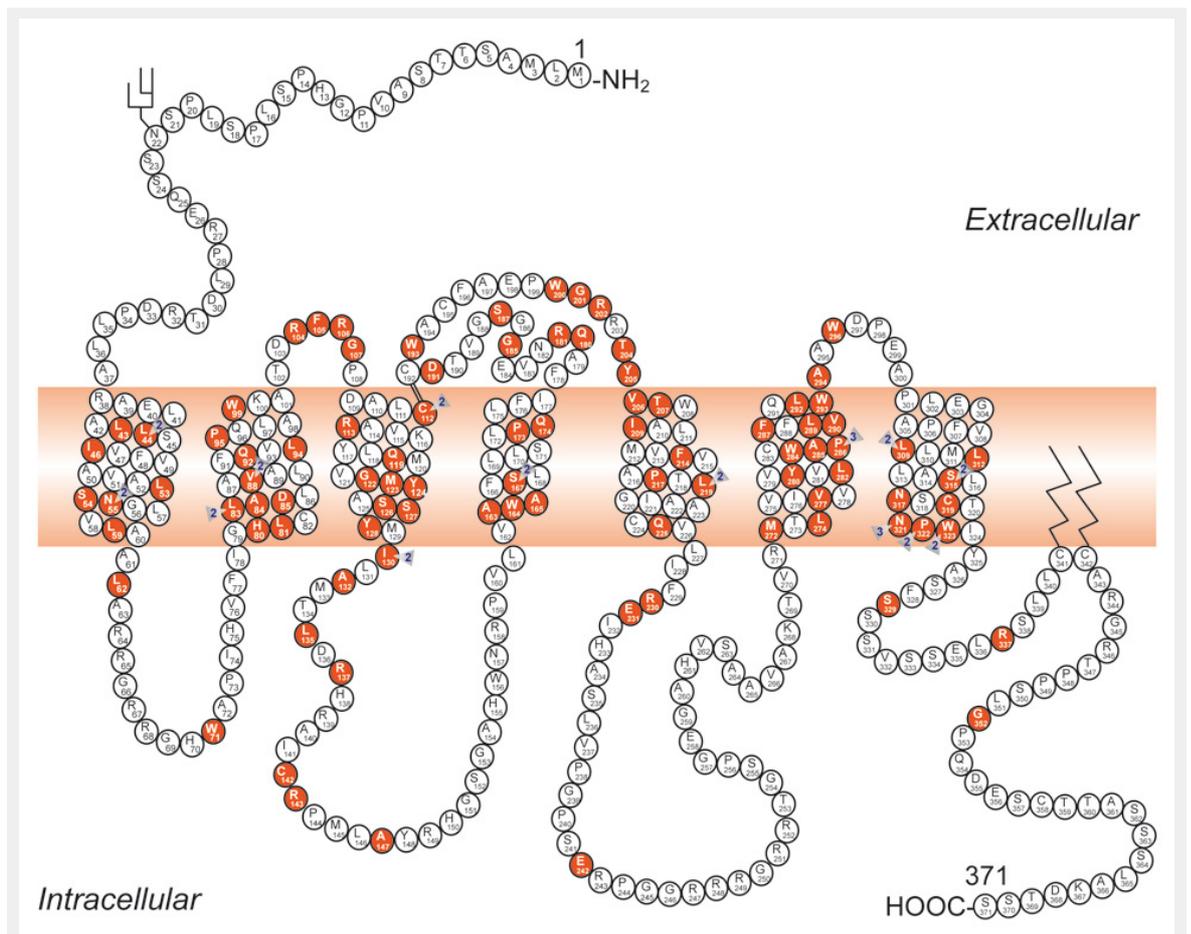
Figure 7

Schematic representation of the V$_2$ receptor and identification of 193 putative disease-causing AVPR2 mutations. Predicted amino acids are shown as the one-letter amino acid code. A solid symbol indicates a codon with a missense or nonsense mutation; a number indicates more than one mutation in the same codon; other types of mutation are not indicated on the figure. There are 95 missense, 18 nonsense, 46 frameshift deletion or insertion, 7 inframe deletion or insertion, 4 splice-site, and 22 large deletion mutations, and one complex mutation. (From: Bonnardeaux A, Bichet DG. Inherited disorders of the renal tubule. In: Brenner BM (ed). The Kidney. 8th ed. New York: Harcourt Health Sciences; 2008. p. 1382–1419. © Elsevier, Oxford, UK, with kind permission.)

Email received on Mar 21, 2010:

• My son was born in 2005. Ever since that date he has had near constant thirst. He would not take to breast feeding because the milk came out too slow. When he was of age to eat food he would scream for drink instead.

• By age 2 we were starting to get quite concerned with his size. He was only 21 lbs. He was also still constantly thirsty and urinating frequently. He would often wake up at night screaming frantically for a drink.

• My son's pediatrician currently thinks that his excessive thirst is behavioural. This is becoming very difficult since he is now finding more and more ways to sneak a drink secretly.

Response:

• Mrs., I do not think that the increased thirst and polyuria observed in your son are behavioural.

• We would appreciate receiving blood from your son and from you.

• Email sent, April 19th: *AVPR2* mutation V88M, mother is a carrier.

• Urine flow: 6mL/min; UOsm: 55 pre and 57 post dDAVP.

Figure 8

A young patient thirsty since birth.