CHAPTER

71 Nephrogenic and Central Diabetes Insipidus

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Diabetes insipidus is a disorder characterized by the excretion of abnormally large volumes (greater than 30 mL per kilogram of body weight per day for an adult patient) of dilute urine (less than 250 mmol per kilogram). 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 per hour. Four basic defects can be involved. The most common, a 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 can also result from renal insensitivity to the antidiuretic effect of AVP, which is referred to as nephrogenic diabetes insipidus. Excessive water intake can result in polyuria, which is referred to as primary polydipsia; it can be due to an abnormality in the thirst mechanism, referred to as dipsogenic diabetes insipidus, or it can be associated with a severe emotional cognitive dysfunction, referred to as psychogenic polydipsia. Finally, the increased metabolism of vasopressin during pregnancy is referred to as gestational diabetes insipidus.

ARGININE VASOPRESSIN

Synthesis

The 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 transient receptor potential channel 1 (TRPV1) (Fig. 71.1)[1] and peripheral osmoreceptor neurons expressing TRPV4.[2] AVP and its corresponding carrier, neurophysin II, are synthesized as a composite precursor by the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus.[3] 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. Preprovasopressin has 164 amino acids and is encoded by the 2.5 kb AVP gene located in chromosome region 20p13.[4,5] 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 a head-to-head orientation. Data from transgenic mouse 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.[3] It is phylogenetically interesting to note that cis and trans components of this specific cellular expression have been conserved between the Fugu isotocin (the homolog of mammalian oxytocin) and rat oxytocin genes.[6] 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. Provasopressin is generated by the removal of the signal peptide from preprovasopressin and from the addition of a carbohydrate chain to the glycopeptide (Fig. 71.2). Additional posttranslation processing occurs within neurosecretory vesicles during the transport of the precursor protein to axon terminals in the posterior pituitary, yielding AVP, neurophysin II, and the glycopeptide. The AVP-neurophysin II complex (Fig. 71.3) forms tetramers that can self-associate to form higher oligomers.[7] Neurophysins should be seen as chaperonelike 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 (hypernatremia, osmotic regulation) and by more pronounced decreases in extracellular fluid (hypovolemia, nonosmotic regulation). Oxytocin and neurophysin I are released from the posterior pituitary by the suckling response in lactating females.

Immunocytochemical and radioimmunologic studies have demonstrated that oxytocin and vasopressin are synthesized in separate populations of the supraoptic nuclei and the paraventricular nuclei neurons,[8,9] the central and vascular projections of which have been described in great detail.[10]

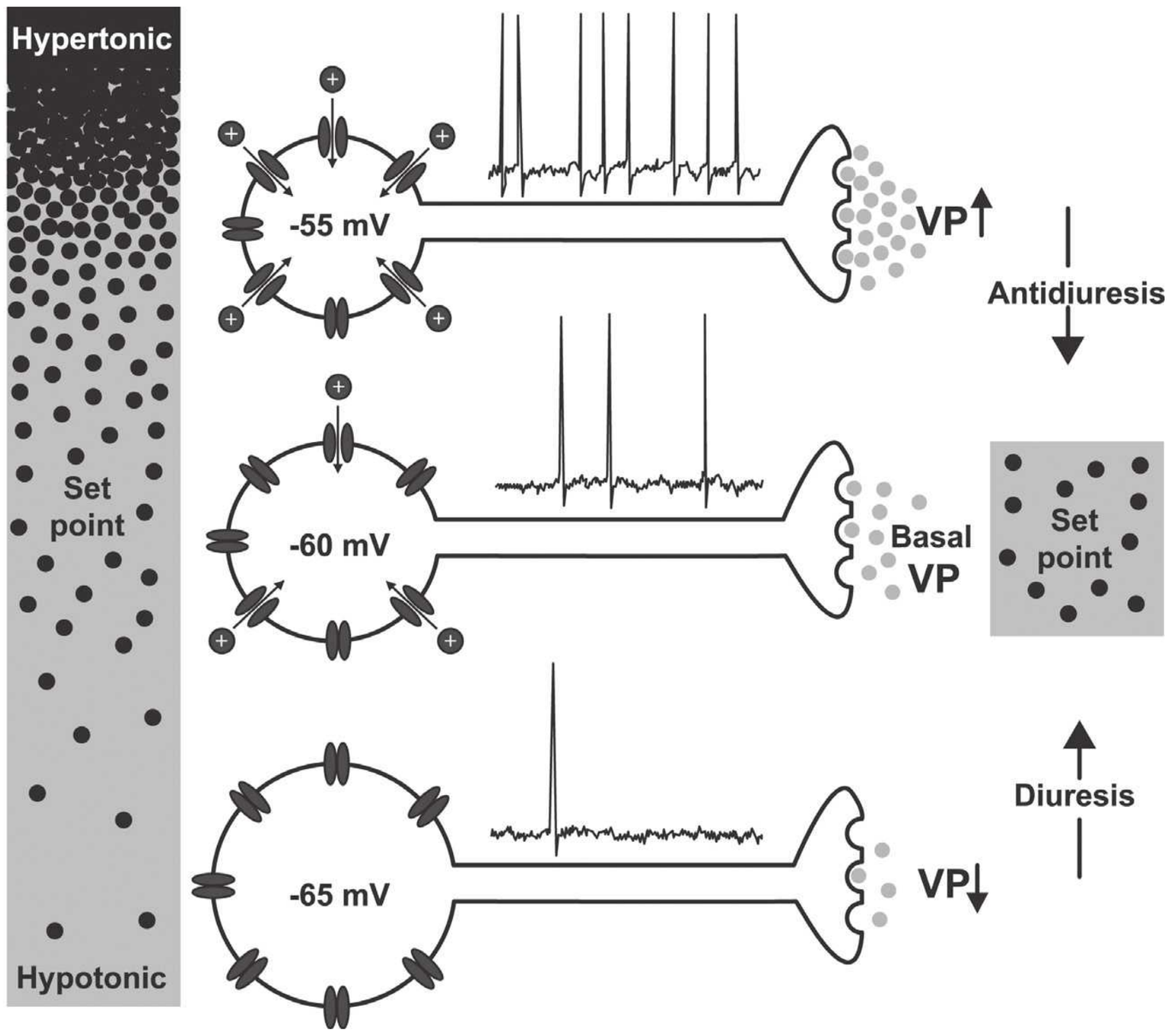

FIGURE 71.1 Osmoreception in vasopressin neurons. Changes in osmolality cause inversely proportional changes in soma volume. Shrinkage activates nonselective cation channels (NSCCs) and the ensuing depolarization increases the action potential firing rate and vasopressin (VP) release from axon terminals 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 the inhibition of firing reduces VP release and promotes diuresis. (Modified from Prager-Khoutorsky and Bourque.[15])

Some cells express the AVP gene and other cells 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 adrenocorticotropic hormone (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 neuroanatomic studies have shown the existence of short

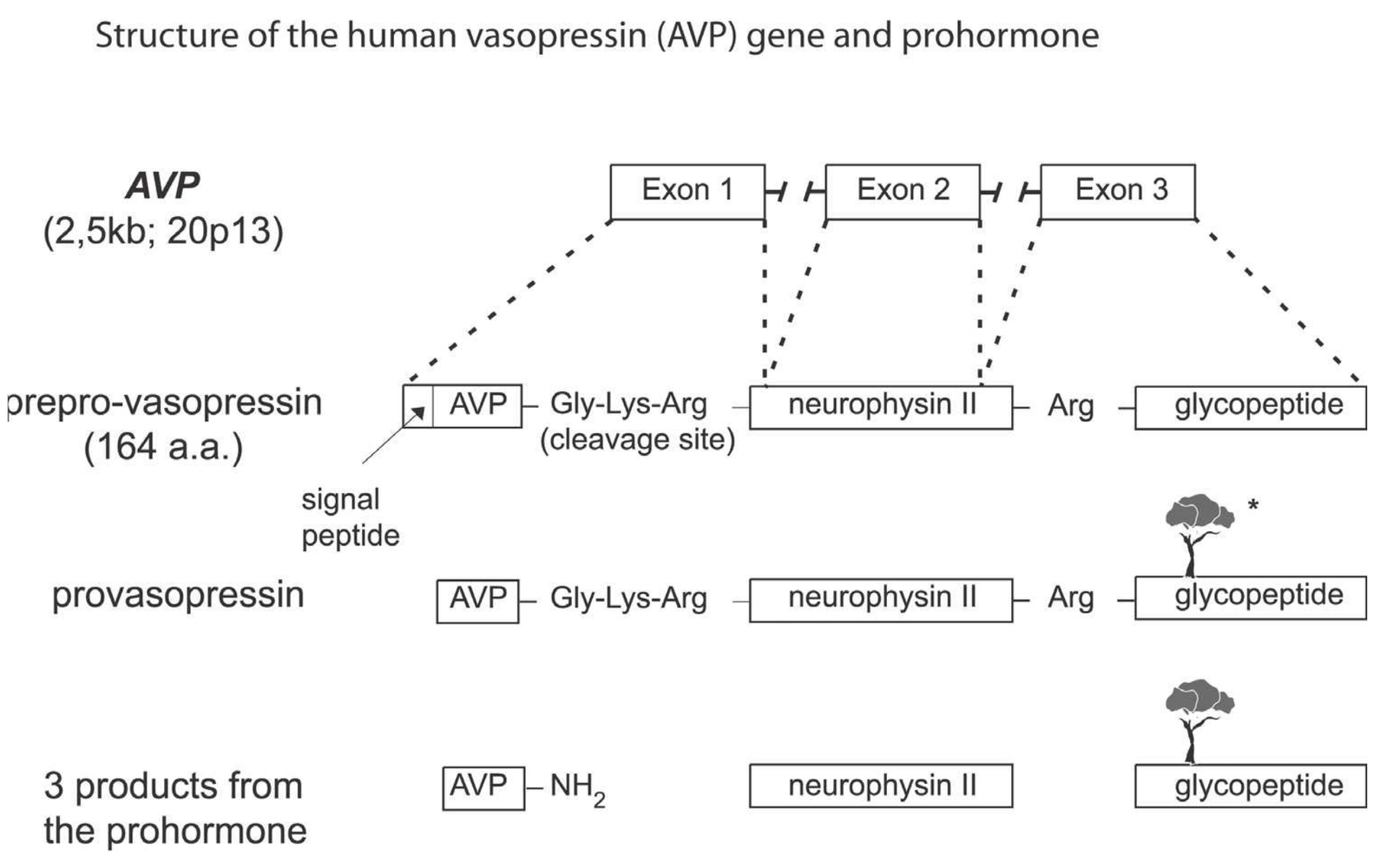

FIGURE 71.2 The structure of the human vasopressin (AVP) gene and prohormone. The cascade of vasopressin biosynthesis and signal peptide; AVP and arginine-vasopressin; neurophysin; and glycoprotein.

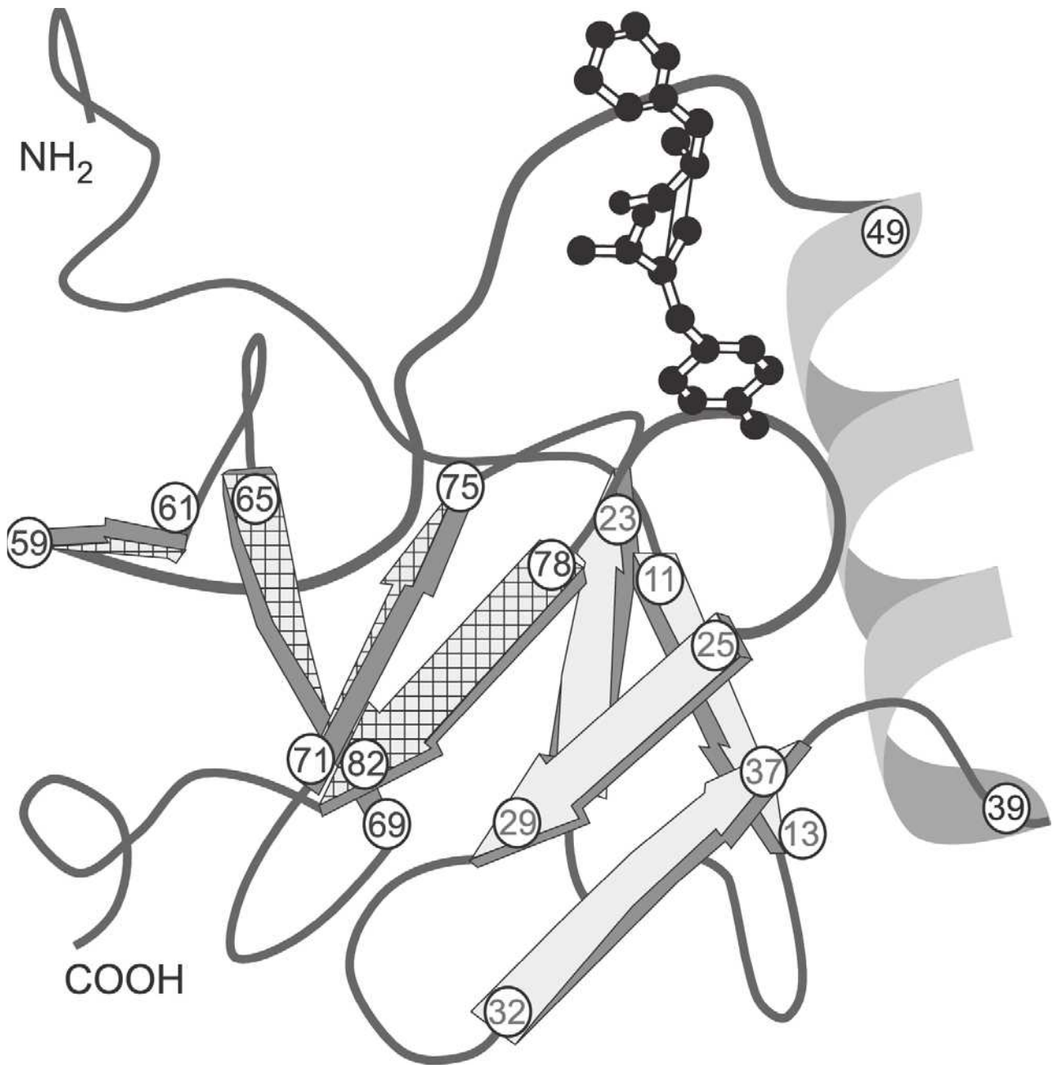

FIGURE 71.3 A three-dimensional structure of a bovine peptide-neurophysin monomer complex. The structure of each chain is 12% helix and 40% β-sheet. The chain is folded into two domains as predicted by disulfide-pairing studies. The amino-terminal domain begins in a long loop (residues 1–10), then enters a four-stranded (residues 11–13, 19–23, 25–29, and 32–37) antiparallel β-sheet (sheet I; *four solid arrows*), followed by a three-turn 3_{10}-helix (residues 39–49) and another loop (residues 50–58). The carboxyl-terminal domain is shorter, consisting of only a four-stranded (residues 59–61, 65–69, 71–75, and 78–82) antiparallel β-sheet (sheet II; *four cross-hatched arrows*).[7] The arginine vasopressin molecule (balls and sticks model) is shown in the peptide-binding pocket of the neurophysin monomer. The strongest interactions in this binding pocket are salt-bridge interactions between the $\alpha NH3^+$ group of the peptide, the γ-COO^- group of Glu^{NP47} (residue number 47 of the neurophysin molecule), and the side chain of Arg^{NP8}. The γ-COO^- group of Glu^{NP47} plays a bifunctional role in the peptide-binding pocket: (1) it directly interacts with the hormone, and (2) it interacts with other neurophysin residues to establish the correct, local structure of the peptide-neurophysin complex. Arg^{NP8} and Glu^{NP47} are conserved in all neurophysin sequences from mammals to invertebrates.

portal vessels that allow communication between the posterior and anterior pituitary. Therefore, in addition to parvocellular vasopressin, magnocellular vasopressin is able to influence ACTH secretion.[11,12]

OSMOTIC AND NONOSMOTIC STIMULATION

The regulation of ADH release from the posterior pituitary is dependent primarily on two mechanisms involving the osmotic and nonosmotic pathways (Fig. 71.4).[13] Although magnocellular neurons are themselves osmosensitive, they require input from the lamina terminalis to respond fully to osmotic challenges (Fig. 71.5). 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 of circulating hormones, such as angiotensin II (AT-II), relaxin, and atrial natriuretic peptide (ANP). Although circulating AT-II and relaxin excite both oxytocin and vasopressin magnocellular neurons, ANP inhibits vasopressin neurons.[14]

The nonosmotic pathways are more physiologically described now as "osmoregulatory gain."[15] A stable and approximately linear relation is normally observed between vasopressin concentration and plasma osmolality under resting conditions (Fig. 71.4A).[16] The slope of this relation reflects the overall sensitivity of this homeostatic mechanism and the term "osmoregulatory gain" refers to this parameter. Osmoregulatory gain is increased during hypovolemia to help maintain arterial pressure and restore blood volume.[17] Conversely, osmoregulatory gain is attenuated during hypervolemia to promote homeostasis by favoring diuresis (Fig. 71.6). The enhancement of osmosensory gain is mediated by circulating AT-II: neurons in the SFO (Fig. 71.5) contain AT-II and the release of this peptide during hypovolemia or hypotension can lead to an increase in the osmotic activation of magnocellular cells producing vasopressin. Good et al.[18] and Zhang and Bourque[19] found that AT-II enhances osmosensory gain by amplifying mechanosensory transduction, an F actin–dependent phenomenon probably part of a scaffolding complex.

In addition to an angiotensinergic path from the SFO, the OVLT and the median preoptic nucleus provide direct glutaminergic and GABAergic projections to the hypothalamoneurohypophyseal system. Nitric oxide may also modulate neurohormone release.[3] The neuropeptide apelin is colocalized with AVP in supraoptic nucleus (SON) magnocellular neurons, and physiologic experiments indicate that AVP and apelin are conversely regulated to facilitate systemic AVP release and to suppress antidiuresis.[20]

The cellular basis for osmoreceptor potentials has been characterized 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 TRPV1 is an osmotically activated channel expressed in the magnocellular cells producing vasopressin[21] and in the circumventricular organs, the OVLT, and the SFO.[22] Because osmoregulation still operates in $Trpv1^{-/-}$ mice, other osmosensitive neurons or pathways must compensate for the loss of central osmoreceptor function.[21–23] Afferent neurons expressing the osmotically activated ion channel TRPV4 in the thoracic dorsal root ganglia that innervate hepatic blood

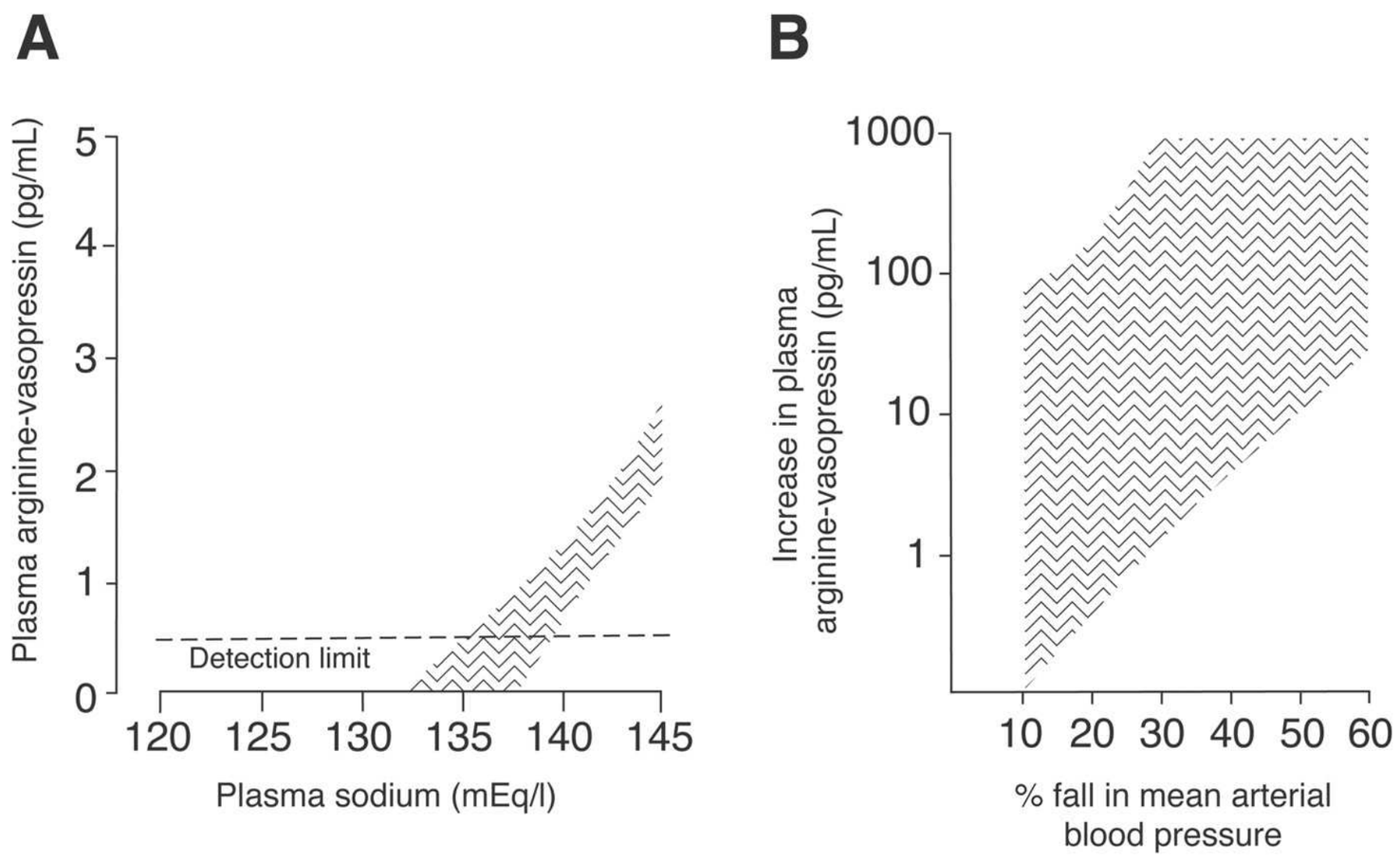

FIGURE 71.4 **A:** The osmotic and nonosmotic stimulation of arginine vasopressin (AVP). The relationship between plasma AVP (P_{AVP}) and plasma sodium (P_{Na}) in 19 normal subjects is described by the area with *vertical lines*, which includes the 99% confidence limits of the regression line P_{Na}/P_{AVP}. The osmotic threshold for AVP release is approximately 280 to 285 mmol per kilogram or 136 mEq of Na per liter. AVP secretion should be abolished when plasma sodium is less than 135 mEq per liter.[214] **B:** The increase in plasma AVP during hypotension (*vertical lines*). Note that a large diminution in blood pressure in normal humans induces large increments in AVP. (From Zerbe RL, Henry DP, Robertson GL. Vasopressin response to orthostatic hypotension: etiological and clinical implications. *Am J Med.* 1983;74:265, with permission.)

vessels and detect physiologic hypo-osmotic shifts in blood osmolality have recently been identified.[2]

In mice lacking the osmotically activated ion channel TRPV4, hepatic sensory neurons no longer exhibit osmosensitive inward currents and the 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 hyponatremia perceived in the portal vein from hepatic afferents.[2] TRPV1 (expressed in central neurons) and TRPV4 (expressed in peripheral neurons) thus appear to play entirely complementary roles in osmoreception. McHugh et al.[24] have therefore identified the primary afferent neurons that constitute the afferent arc of a well-characterized reflex in man, which was recently identified in rodents. This reflex engages the sympathetic nervous system to raise blood pressure and stimulate metabolism.[25,26] 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]

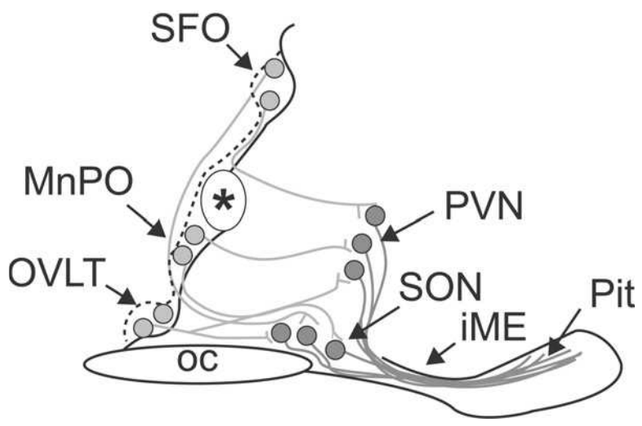

FIGURE 71.5 A schematic representation of the osmoregulatory pathway of the hypothalamus (sagittal section of midline of ventral brain around the third ventricle in mice). Neurons (*lightly filled circles*) in the lamina terminalis (OVLT), median preoptic nucleus (MnPO), and subfornical organ (SFO), which are responsive to plasma hypertonicity, 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 hypothalamoneurohypophyseal pathway that courses in the median eminence to reach the posterior pituitary, where neurosecretion of vasopressin and oxytocin occurs. (Modified from Wilson et al., 2002 with permission, Copyright (2002), National Academy of Sciences USA.)

The osmotic stimulation of AVP release by dehydration, hypertonic saline infusion, or both, is regularly used to determine the vasopressin secretory capacity of the posterior pituitary. This secretory capacity can be assessed directly by comparing the plasma AVP concentrations measured sequentially during the dehydration procedure with the normal values[33] and then correlating the plasma AVP values with the urine osmolality measurements obtained simultaneously (Fig. 71.7).

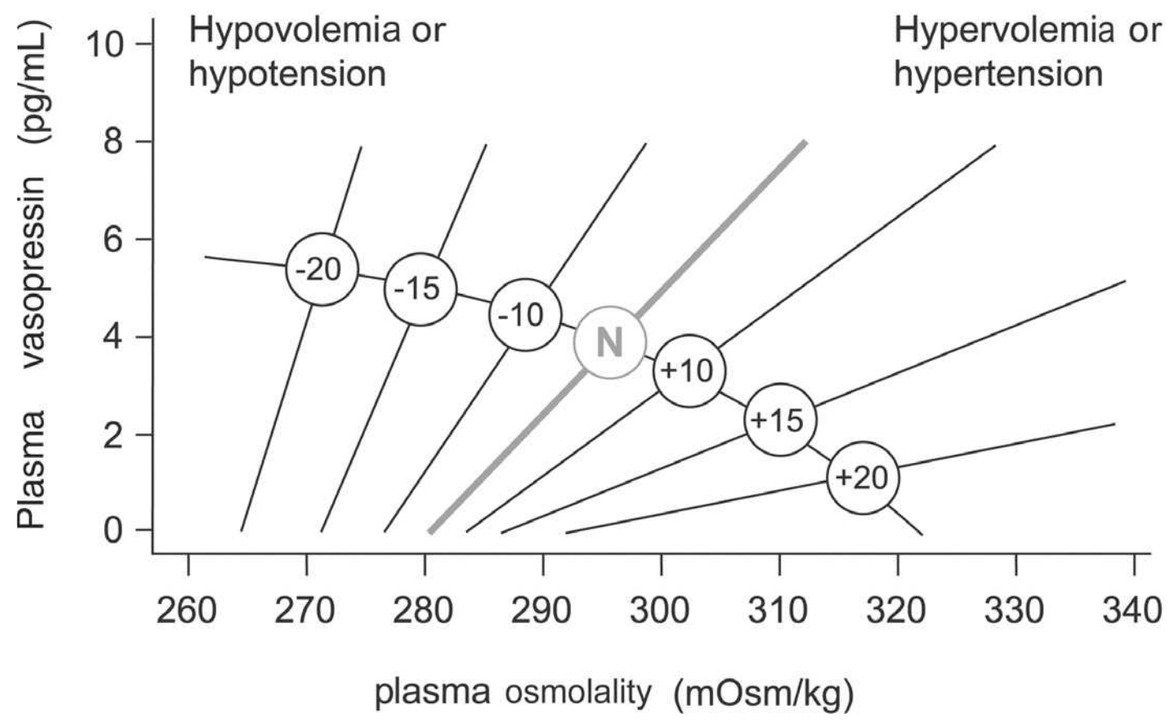

FIGURE 71.6 A schematic representation of the relationship between plasma vasopressin and plasma osmolality in the presence of differing states of blood volume and/or pressure. The line labeled *N* represents normovolemic normotensive conditions. Minus numbers to the left indicate a percent fall, and positive numbers to the right represent a percent rise in blood volume or pressure. Data from Vokes and Robertson.[230]

The AVP release can also be assessed indirectly by measuring plasma and urine osmolalities at regular intervals during the dehydration test.[34] The maximal urine osmolality obtained during dehydration is compared with the maximal urine osmolality obtained after the administration of vasopressin (Pitressin, 5 U subcutaneously in adults, 1 U subcutaneously in children) or 1-desamino-8-D-arginine vasopressin (desmopressin [dDAVP], 1 to 4 μg s.c. or intravenously [IV], over 5 to 10 minutes).

The nonosmotic stimulation of AVP release can be used to assess the vasopressin secretory capacity of the posterior pituitary in a rare group of patients with the essential hyponatremia and hypodipsia syndrome.[35] Although some of these patients may have partial central diabetes insipidus, they respond normally to nonosmolar AVP release signals such as hypotension, emesis, and hypoglycemia.[35] In all other cases of suspected central diabetes insipidus, these nonosmotic stimulation tests will not give additional clinical information.[36]

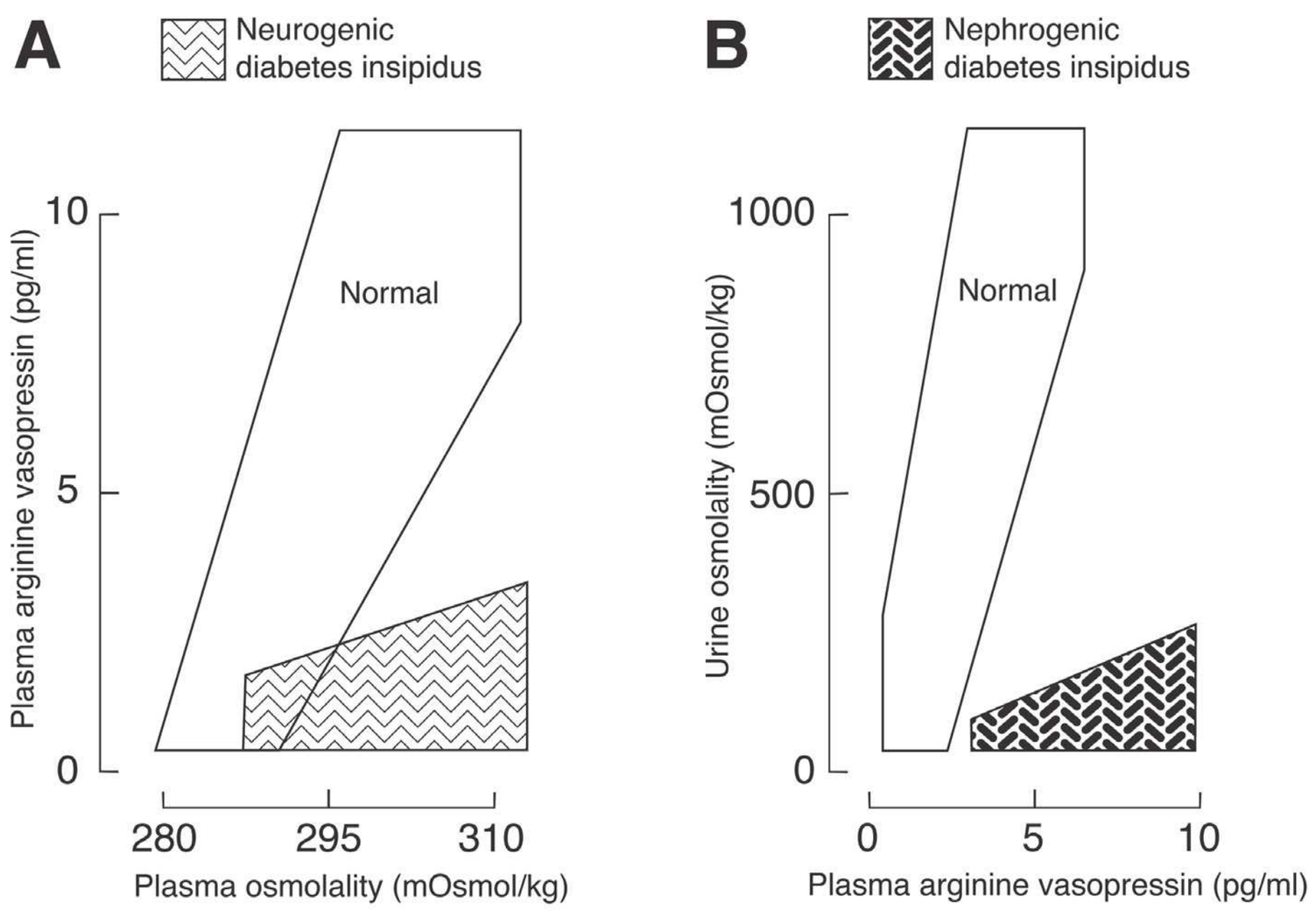

FIGURE 71.7 **A:** The relationship between plasma arginine vasopressin (AVP) and plasma osmolality during the infusion of a hypertonic saline solution. Patients with primary polydipsia and nephrogenic diabetes insipidus have values within the normal range (*open area*) in contrast to patients with neurogenic diabetes insipidus, who show subnormal plasma antidiuretic hormone (ADH) responses (*cross-hatched area*). **B:** The relationship between urine osmolality and plasma ADH during dehydration and water loading. Patients with neurogenic diabetes insipidus and primary polydipsia have values within the normal range (*open area*) in contrast to patients with nephrogenic diabetes insipidus, who have hypotonic urine despite high plasma ADH (*stippled area*). (Modified from Zerbe RL, Robertson GL. Disorders of ADH. *Med North Am*. 1984;13:1570.[231])

CLINICALLY IMPORTANT HORMONAL INFLUENCES ON THE SECRETION OF VASOPRESSIN

Angiotensin is a well-known dipsogen and has been shown to increase thirst in all the species tested.[37] However, knockout models for angiotensinogen[38] or for angiotensin-1A (AT-IA) receptor[39,40] did not alter thirst or water balance. Disruption of the AT-II receptor induced only mild abnormalities of thirst postdehydration.[41,42] However, as described earlier, AT-II enhances osmosensory gain. Earlier reports suggested that the intravenous administration of atrial peptides inhibits the release of vasopressin,[43] but this was not confirmed by Goetz et al.[44] Furthermore, Ogawa et al.[45] found no evidence that ANP, administered centrally or peripherally, was important in the physiologic regulation of plasma AVP release in conscious rats. A very rapid and robust release of AVP is seen in humans after a cholecystokinin (CCK) injection.[46] Nitric oxide is an inhibitory modulator of the hypothalamoneurohypophyseal system in response to osmotic stimuli.[47–50] Vasopressin secretion is under the influence of a glucocorticoid-negative feedback system,[51] and the vasopressin responses to a variety of stimuli (hemorrhage, hypoxia, hypertonic saline) in normal humans and animals appear to be attenuated or eliminated by pretreatment with glucocorticoids. Finally, nausea and emesis are potent stimuli of AVP release in humans and seem to involve dopaminergic neurotransmission.[52]

CELLULAR ACTIONS OF VASOPRESSIN

The neurohypophyseal hormone AVP has multiple actions, including the inhibition of diuresis, the contraction of smooth muscle, the aggregation of platelets, the stimulation of liver glycogenolysis, the modulation of adrenocorticotropic hormone release from the pituitary, and the central regulation of somatic functions (thermoregulation and blood pressure) and the modulation of social and reproductive behavior.[53] 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 brain) and V_{1b} (anterior pituitary) receptors act through phosphatidylinositol hydrolysis to mobilize calcium, and the V_2 (kidney) receptor is coupled to adenylate cyclase.[54–56]

The transfer of water across the principal cells of the collecting ducts is now known at such a detailed level that billions of molecules of water traversing the membrane can be represented; see useful teaching tools at http://www.mpibpc.gwdg.de/abteilungen/073/gallery.html and http://www.ks.uiuc.edu/research/aquaporins. The 2003 Nobel Prize in Chemistry was awarded to Peter Agre and Roderick MacKinnon, who solved two complementary problems presented by the cell membrane: How does a cell let one type of ion through the lipid membrane to the exclusion of other ions? And, how does it permeate water without ions? See Figure 71.8. This contributed to a momentum and renewed interest in basic discoveries related to the transport of water and indirectly to diabetes insipidus.[57,58] 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. 71.9). The human AVPR2 gene that codes for the V_2 receptor is located in chromosome region Xq28 and has three exons and two small introns.[59,60] The sequence of the cDNA predicts a polypeptide of 371 amino acids with seven transmembrane, four extracellular, and four cytoplasmic domains (Fig. 71.10). The activation of the V_2 receptor on renal collecting tubules stimulates adenylyl cyclase via the stimulatory G protein (Gs) and

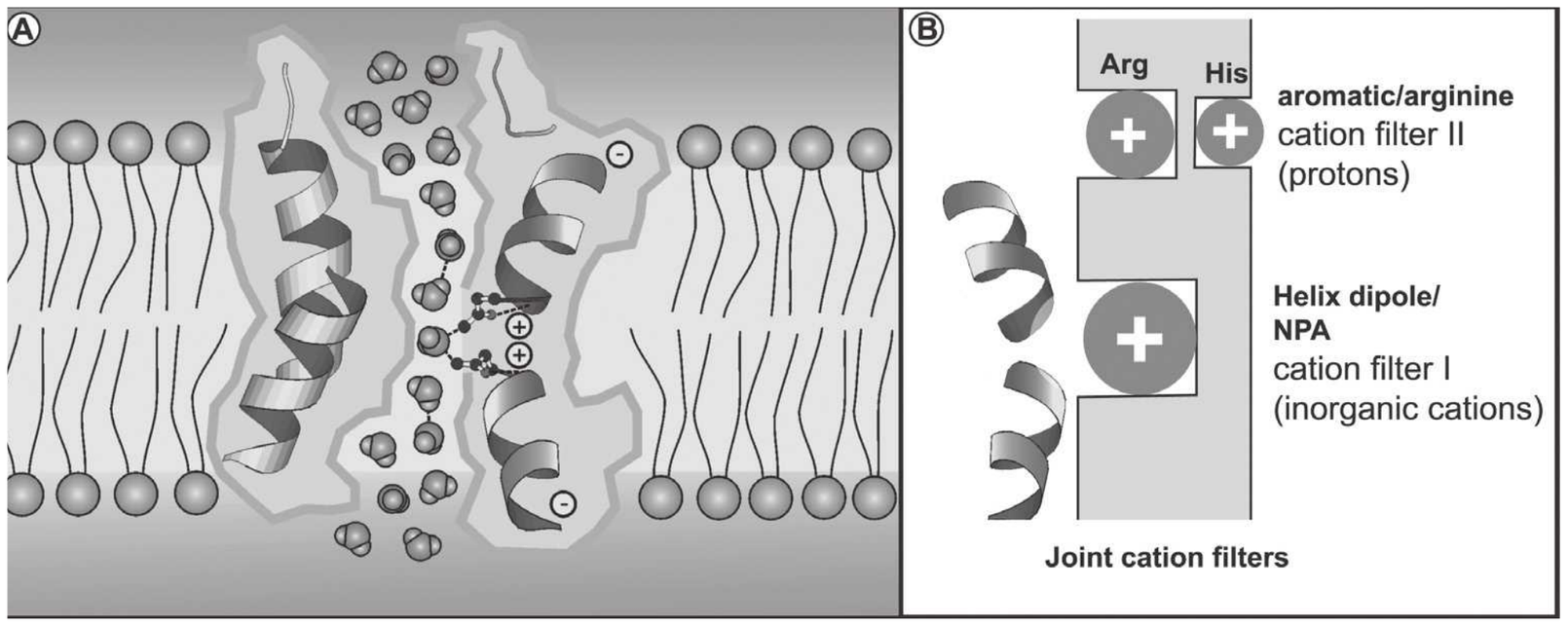

FIGURE 71.8 Schematic representations explaining the mechanism for blocking proton permeation of aquaporin 1 (AQP1). **A:** A diagram illustrating how partial charges from the helix dipoles restrict the orientation of the water molecules passing through the constriction of the pore. (From Murata K, Mitsuoka K, Hirai T, et al. Structural determinants of water permeation through aquaporin-1. *Nature*. 2000;407:599.) **B:** A diagram illustrating how primordial AQPs selected against inorganic cations, such as Na+ and K+, because of a positive electrostatic field from the helix dipoles and the lack of cation coordination sites in the NPA region (filter I); yet, protons leaked through. Later, a second cation filter evolved in the ar/R region, which fully excluded protons (filter II) and provided individual selectivity properties for water, glycerol, urea, and ammonia.[232]

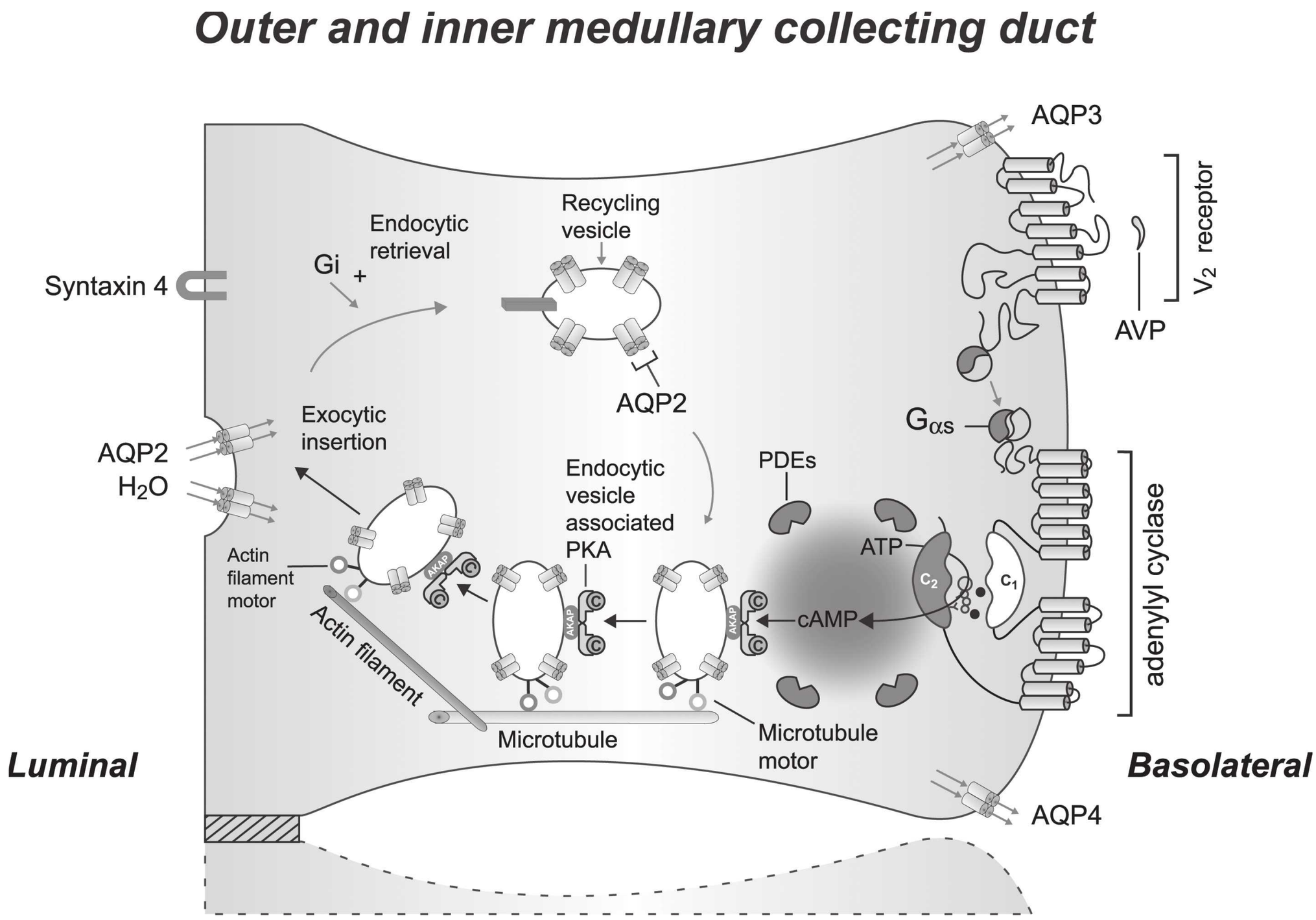

FIGURE 71.9 A schematic representation of the effect of vasopressin (AVP) to increase water permeability in the principal cells of the collecting duct. AVP is bound to the V_2 receptor (a G-protein–linked receptor) on the basolateral membrane. The basic process of G-protein–coupled receptor signaling consists of three steps: a heptahelical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein ($G_{\alpha s}$) that dissociates into subunits bound to GTP and bg 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 characterized 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 cofactors (Mg^{2+} or Mn^{2+} represented here as two *small black circles*), which enable the catalytic function of the enzyme.[233] 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.

promotes the cyclic adenosine monophosphate (cAMP)-mediated incorporation of water channels into the luminal surface of these cells. There are two ubiquitously expressed intracellular cAMP receptors: (1) the classical protein kinase A (PKA) that is a cAMP-dependent protein kinase, and (2) the recently discovered exchange protein directly activated by cAMP that is a cAMP-regulated guanine nucleotide exchange factor. Both of these receptors contain an evolutionally conserved cAMP-binding domain that acts as a molecular switch for sensing intracellular cAMP levels to control diverse biologic functions.[61] Several proteins participating in the control of cAMP-dependent aquaporin-2 AQP2 trafficking have been identifieD (e.g., A-kinase anchoring proteins tethering PKA to cellular compartments; phosphodiesterases regulating the local cAMP

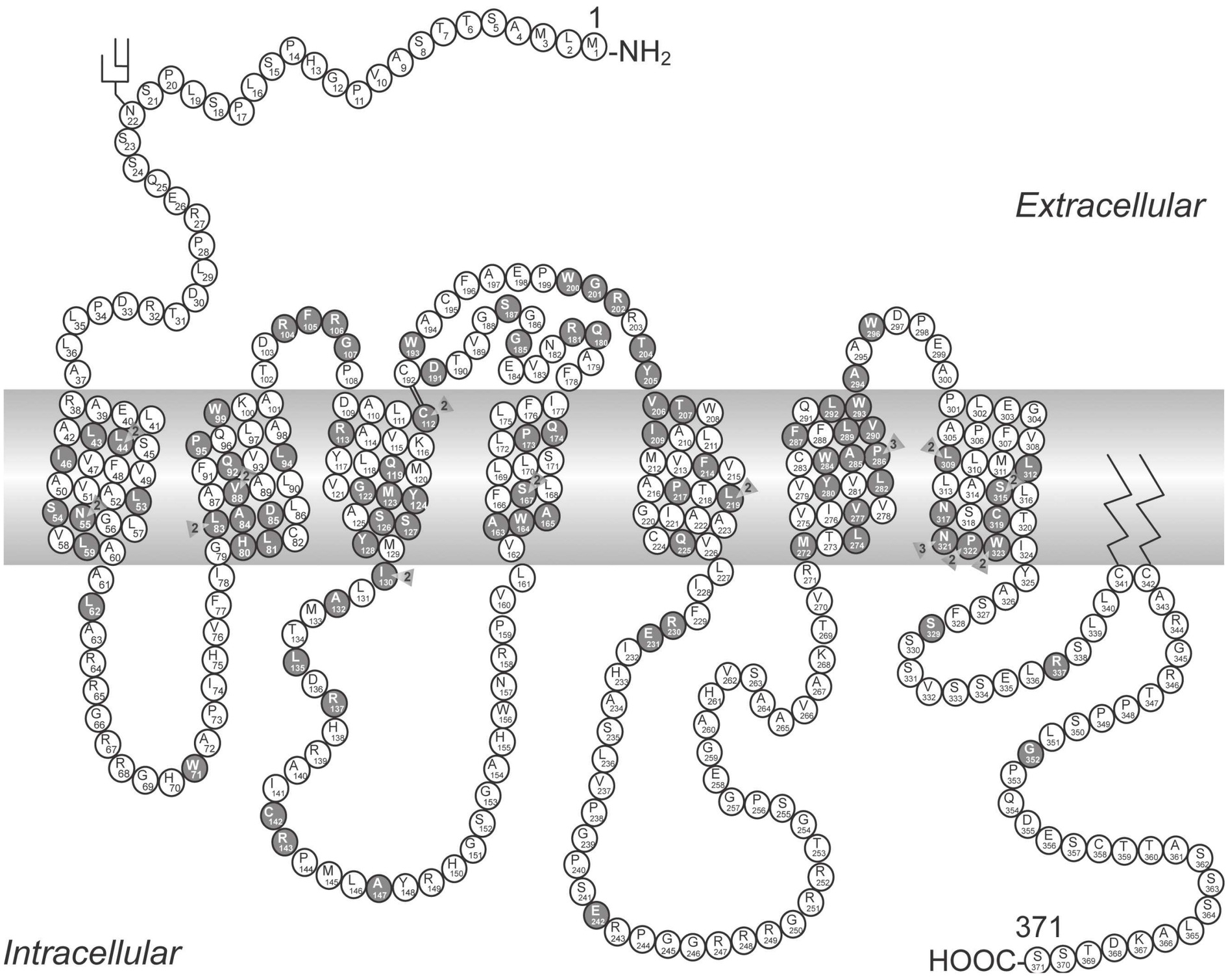

FIGURE 71.10 A schematic representation of the V_2 receptor and identification of 193 putative disease-causing AVPR2 mutations. Predicted amino acids are shown as the one-letter amino acid code. A *solid symbol* indicates a codon with a missense or nonsense mutation; a *number* indicates more than one mutation in the same codon; other types of mutations are not indicated on the figure. There are 95 missense, 18 nonsense, 46 frameshift deletion or insertion, 7 in-frame deletion or insertion, 4 splice site, 22 large deletion mutations, and 1 complex mutation.

level; cytoskeletal components such as F-actin and microtubules; small GTPases of the Rho family controlling cytoskeletal dynamics; motor proteins transporting AQP2-bearing vesicles to and from the plasma membrane for exocytic insertion and endocytic retrieval; soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors (SNAREs) inducing membrane fusions, hsc70, a chaperone important for endocytic retrieval). These processes are the molecular basis of the vasopressin-induced increase in the osmotic water permeability of the apical membrane of the collecting tubule.[62–64]

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.[65,66] AVP also increases the permeability of principal collecting duct cells to sodium.[67] Finally, the vasopressin V_2 receptor has been located in the primary cilium and Bardet-Biedl syndrome–derived unciliated renal epithelial cells were unable to respond to luminal AVP and to activate luminal AQP2.[68]

In summary, in the absence of AVP stimulation, collecting duct epithelia exhibit very low permeabilities to sodium urea and water. These specialized permeability properties permit the excretion of large volumes of hypotonic urine formed during intervals of water diuresis. By contrast, AVP stimulation of the principal cells of the collecting ducts 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 (PGE2), nitric oxide,[69] and by luminal calcium concentration. High levels of E-prostanoid-3 receptors are expressed in the kidney.[70] However, mice lacking E-prostanoid-3 receptors for PGE2 were found to have quasinormal regulation of urine volume and osmolality in response to various physiologic stimuli.[70] PGE2 is synthesized and released in the collecting duct, which expresses all E-prostanoid receptors.[71–73] An apical calcium/polycation receptor protein expressed in the terminal portion of the inner medullary collecting duct of the rat

has been shown to reduce AVP-elicited osmotic water permeability when luminal calcium concentration rises.[74] This possible link between calcium and water metabolism may play a role in the pathogenesis of renal stone formation.[74]

KNOCKOUT MICE WITH URINARY CONCENTRATION DEFECTS

A useful strategy to establish the physiologic function of a protein is to determine the phenotype produced by pharmacologic inhibition of protein function or by gene disruption. Transgenic knockout mice deficient in AQP1, AQP2, AQP3, AQP4, AQP3, and AQP4; CLCNK1; NKCC2; AVPR2; AGT; or adenylyl cyclase 6 (AC6) have been engineered.[75–84] Angiotensinogen (AGT)-deficient mice are characterized by both concentrating and diluting defects secondary to a defective renal papillary architecture.[76]

As reviewed by Rao and Verkman,[85] the extrapolation of data in mice to humans must be made with caution. For example, the maximum osmolality of mice (greater than 3,000 mOsmol per kilogram of H_2O) is much greater than that of human urine (1,000 mOsmol per kilogram of H_2O), and normal serum osmolality in mice is 330 to 345 mOsmol per kilogram of H_2O, substantially greater than that in humans (280 to 290 mOsmol per kilogram of H_2O). These differences are related to renal anatomy and metabolic rate: (1) the mouse kidney exhibits much larger loops of Henle in the inner medulla and papillae and (2) because of the large difference in body size (30 g to 70 kg) the mouse metabolic rate (and thus the food intake) per gram of body mass is 20 times greater than that of humans. The amount of osmoles that need to be excreted by the kidney is also disproportionately larger when expressed per gram of body mass or kidney mass. These two features account for the much higher urine concentrating ability of the mouse as compared to humans. Protein expression patterns, and thus the interpretation of phenotype studies, may also be species dependent. For example, AQP4 is expressed in both the proximal tubule and the collecting duct in mice but only in the collecting duct in rats and humans.[85]

The Aqp3, Aqp4, Clcnk-1, and Agt knockout mice have no identified human counterparts. Of interest, AQP1-null individuals have no obvious symptoms.[86] Yang et al.[87] have generated an AQP2-T126M conditional knockin model of nephrogenic diabetes insipidus (NDI), to recapitulate the clinical features of the naturally occurring human AQP2 mutation T126M.[88] The conditional knockin adult mice showed polyuria, urinary hypo-osmolality, and endoplasmic reticulum (ER) retention of AQP2-T126M in the collecting duct. The screening of candidate protein folding correctors in AQP2-T126M–transfected kidney cells showed increased AQP2-T126M plasma membrane expression with the Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG), a compound currently in clinical trials for tumor therapy. 17-AAG increased urine osmolality in the AQP2-T126M mice (without effect in AQP2 null mice) and partially rescued defective AQP2-T126M cellular processing. These proof-of-concept findings suggest the possibility of using existing drugs for therapy of some forms of NDI. Ethylnitrosourea-mutagenized mice heterozygous for the F204V mutation in the Aqp2 gene have been described.[89] The homozygous mice are viable because of a moderate phenotype with a possibility to concentrate urine from 161 to 470 mOsmol per kilogram of H_2O in response to dDAVP. Cell biology experiments performed on renal tissue from Aqp2F$^{204V/+}$ animals suggest that the mutant protein is being rescued by the wild-type protein.

Mice lacking the AVPR2 receptor failed to thrive and died within the first week after birth due to hypernatremic dehydration.[78] Li et al.[90] generated mice in which the Avpr2 gene could be conditionally deleted during adulthood by the administration of 4-OH-tamoxifen. Adult mice displayed all characteristic symptoms of X-linked NDI (XNDI), including polyuria, polydipsia, and resistance to the antidiuretic actions of vasopressin. Gene expression analysis suggested that the activation of renal EP4 PGE_2 receptors might compensate for the lack of renal V2R activity in X-linked NDI mice, and both acute and chronic treatment of the mutant mice with a selective EP4 receptor agonist greatly reduced all major manifestations of XNDI. This beneficial effect is likely secondary to the intracellular generation of cAMP at the principal cell level by EP4 PGE_2 receptors.

The absence of the gene coding for the NaK2Cl cotransport (NKCC2) in the luminal membrane of the thick ascending loop of Henle in the mouse also caused polyuria that was not compensated elsewhere in the nephron and recapitulated many features of the human classical Bartter syndrome.[79] The absence of transcellular NaCl transport via NKCC2 probably abolished the lumen-positive transepithelial voltage that enables paracellular reabsorption of Na and K across the wall of the thick ascending tubule. The combined absence of transcellular and paracellular transport of salt across the thick ascending limb cells prevents the establishment of the normal osmotic gradient necessary for urine concentration.

EXPRESSION OF THE VASOPRESSIN GENE IN DIABETES INSIPIDUS RATS (BRATTLEBORO RATS)

The animal model of diabetes insipidus that has been most extensively studied is the Brattleboro rat. Discovered in 1961, the rat lacks vasopressin and its neurophysin, whereas the synthesis of the structurally related hormone oxytocin is not affected by the mutation.[91] Its inability to synthesize vasopressin is inherited as an autosomal recessive trait. Schmale and Richter[92] isolated and sequenced the vasopressin gene from homozygous Brattleboro rats, and found that the defect is due to a single nucleotide deletion of a G residue within the second exon encoding the carrier protein neurophysin (Fig. 71.11). The shift in the reading frame caused by this deletion predicts a precursor with an

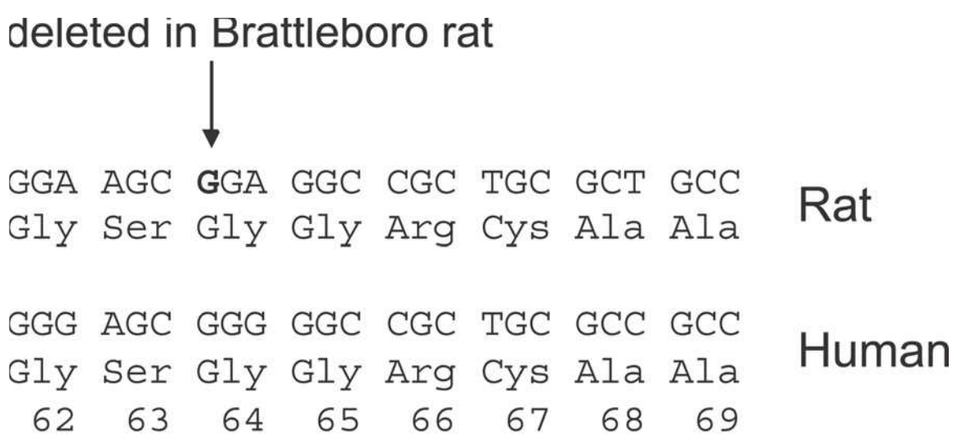

FIGURE 71.11 A neurophysin II genomic and amino acid sequence showing the 1 bp (G) deleted in the Brattleboro rat. The human sequence (GenBank entry M11166) is also shown. It is almost identical to the rat prepro sequence. In the Brattleboro rat, G1880 is deleted with a resultant frameshift after 63 amino acids (amino acid 1 is the first amino acid of neurophysin II).

entirely different C terminus. The messenger RNA (mRNA) produced by the mutated gene encodes a normal AVP but an abnormal NPII moiety,[92] which impairs transport and processing of the AVP-NPII precursor and its retention in the endoplasmic reticulum of the magnocellular neurons where it is produced.[93,94] Homozygous Brattleboro rats may still demonstrate some V2 (vide infra) antidiuretic effects since the administration of a selective nonpeptide V2 antagonist (SR 121463A, 10 mg per kilogram i.p.) induced a further increase in urine flow rate (200 to 354 ± 42 mL per 24 hours) and a decline in urinary osmolality (170 to 92 ± 8 mmol per kilogram).[95] This decline in urine osmolality following the administration of a nonpeptide V2r antagonist could also be secondary to the "inverse agonist" properties of SR121463A: the intrinsic activity, or tone, of the V2R would be deactivated by the SR121463A compound (for the inverse agonist properties of SR121463A (see reference 96). There is also an alternative explanation to this relatively high urine osmolality of 170 because, in Brattleboro rats, low levels of hormonally active AVP are produced from alternate forms of AVP preprohormone. Due to a process called molecular misreading, one transcript contains a 2-bp deletion downstream from the single nucleotide deletion that restores the reading frame and produces a variant AVP preprohormone that is smaller in length by one amino acid and differs from the normal product by only 13 amino acids in the neurophysin II moiety.[97] Oxytocin, which is present at enhanced plasma concentrations in Brattleboro rats, may be responsible for the antidiuretic activity observed.[98,99] Oxytocin is not stimulated by increased plasma osmolality in humans.

CLINICAL CHARACTERISTICS OF DIABETES INSIPIDUS DISORDERS

Central Diabetes Insipidus

Common Forms

Failure to synthesize or secrete vasopressin normally limits maximal urinary concentration and, depending on the severity of the disease, causes varying degrees of polyuria and polydipsia. Experimental destruction of the vasopressin-synthesizing areas of the hypothalamus (the supraoptic and paraventricular nuclei) causes a permanent form of the disease. Similar results are obtained by sectioning the hypophyseal-hypothalamic tract above the median eminence. Sections below the median eminence, however, produce only transient diabetes insipidus. Lesions to the hypothalamic-pituitary tract are often associated with a three-stage response both in experimental animals and in humans,[100] which consists of:

1. An initial diuretic phase lasting from a few hours to 5 to 6 days.
2. A period of antidiuresis unresponsive to fluid administration. This antidiuresis is probably due to vasopressin release from injured axons and may last from a few hours to several days. Because urinary dilution is impaired during this phase, continued water administration can cause severe hyponatremia.
3. A final period of diabetes insipidus. The extent of the injury determines the completeness of the diabetes insipidus and, as already discussed, the site of the lesion determines whether the disease will or will not be permanent.

A detailed assessment of water balance following transsphenoidal surgery has been reported.[101] There were 101 patients who underwent transsphenoidal pituitary surgery at the National Institutes of Health Clinical Center and were studied. Of the patients, 25% developed spontaneous isolated hyponatremia, 20% developed diabetes insipidus, and 46% remained normonatremic. Normonatremia, hyponatremia, and diabetes insipidus were associated with increasing degrees of surgical manipulation of the posterior lobe and pituitary stalk during surgery.

The etiologies of central diabetes insipidus in adults and in children are listed in Table 71.1.[102–104] Rare causes of central diabetes insipidus include leukemia, thrombotic thrombocytopenic purpura, pituitary apoplexy, sarcoidosis, and Wegener granulomatosis.[105] A distinctive syndrome characterized by early diabetes insipidus with subsequent progressive spastic cerebellar ataxia has also been described.[106] Five patients who all presented with central diabetes insipidus and hypogonadism as first manifestations of neurosarcoidosis have been reported.[107] Finally, circulating antibodies to vasopressin do not play a role in the development of diabetes insipidus.[108] Antibodies to vasopressin occasionally develop during treatment with ADH and, when they do, almost always result in secondary resistance to its antidiuretic effect.[108,109] Maghnie et al.[102] studied 79 patients with central diabetes insipidus who were seen at four pediatric endocrinology units between 1970 and 1996. There were 37 male and 42 female patients whose median age at diagnosis was 7 years (range, 0.1 to 24.8 years). In 11 patients, central diabetes insipidus developed during an infectious illness or less than 2 months afterward (varicella in 5 patients,

71.1 Etiology of Hypothalamic Diabetes Insipidus in Children and Adults[102–105]

	Children (%)	Children and Young Adults (%)	Adults (%)
Primary brain tumor[a]	49.5	22	30
Before surgery	33.5		13
After surgery	16		17
Idiopathic (isolated or familial)	29	58	25
Histiocytosis	16	12	—
Metastatic cancer[b]	—		8
Trauma[c]	2.2	2.0	17
Postinfectious disease	2.2	6.0	—

[a]Primary malignancy: Craniopharyngioma, dysgerminoma, meningioma, adenoma, glioma, astrocytoma.
[b]Secondary: Metastatic from lung or breast, lymphoma, leukemia, dysplastic pancytopenia.
[c]Trauma could be severe or mild.

mumps in 3 patients, and measles, toxoplasmosis, and hepatitis B in 1 patient each). Deficits in anterior pituitary hormones were documented in 48 patients (61%) a median of 0.6 year (range, 0.1 to 18.0 years) after the onset of diabetes insipidus. The most frequent abnormality was growth hormone deficiency (59%), followed by hypothyroidism (28%), hypogonadism (24%), and adrenal insufficiency (22%). Of the patients with histiocytosis of the Langerhans cells, 75% had an anterior pituitary hormone deficiency that was first detected at a median of 3.5 years after the onset of diabetes insipidus. The frequency and progression of histiocytosis of the Langerhans cells related to anterior pituitary and other nonendocrine hypothalamic dysfunction and their response to treatment in 12 adult patients has also been reviewed.[110] None of the patients with central diabetes insipidus secondary to AVP mutations developed anterior pituitary hormone deficiencies.

Rare Forms

Inherited neurohypophyseal diabetes insipidus (OMIM 125700)[111] is due to mutations in the AVP gene (OMIM 192340)[111] and Wolfram syndrome 1 (OMIM 222300)[111] is due to mutations in the WFS1 gene. Historically, Lacombe[112] and Weil[113] described a familial non–X-linked form of diabetes insipidus without any associated mental retardation. The descendants of the family described by Weil were later found to have autosomal dominant neurogenic diabetes insipidus.[114–116]

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,[117] 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 dDAVP. Growth retardation might be observed in untreated children with autosomal dominant FNDI.[118] Over 50 mutations in the prepro-arginine-vasopressin-neurophysin II AVP gene located on chromosome 20p13 have been reported in dominant FNDI (adFNDI). Knockin 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.[119,120] To date, recessive FNDI has only been described in two studies.[121,122] A study by Christensen et al.[123] 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 localized to the tips of neurites. The expression of regulated secretory proteins such as granins and prohormones, including provasopressin, generates granulelike structures in a variety of neuroendocrine cell lines due to aggregation in the trans-Golgi.[124] Costaining experiments unambiguously distinguished between these granulelike structures and the accumulations by pathogenic dominant mutants formed in the ER, because the latter, but not the trans-Golgi granules, colocalized with specific ER markers.[119] 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 disease and Parkinson disease.

WOLFRAM SYNDROME

Wolfram syndrome, also known as DIDMOAD, is an autosomal recessive neurodegenerative disorder accompanied by insulin-dependent diabetes mellitus and progressive optic atrophy. The acronym DIDMOAD describes the following clinical features of the syndrome: diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness. An unusual incidence of psychiatric symptoms has also been described in patients with this syndrome. These included paranoid delusions, auditory or visual hallucinations, psychotic behavior, violent behavior, organic brain syndrome typically in the late or preterminal stages of their illness, progressive dementia, and severe learning disabilities or mental retardation or both. Wolfram syndrome patients develop diabetes mellitus and bilateral optical atrophy mainly in the first decade of life, the diabetes insipidus is usually partial and of gradual onset, and the polyuria can be wrongly attributed to poor glycemic control. Furthermore, a severe hyperosmolar state can occur if untreated diabetes mellitus is associated with an unrecognized posterior pituitary deficiency. The dilatation of the urinary tract observed in DIDMOAD syndrome may be secondary to chronic high urine flow rates and, perhaps, to some degenerative aspects of the innervation of the urinary tract. The gene responsible for Wolfram syndrome, located in chromosome region 4p16.1, encodes a putative 890 amino acid transmembrane protein referred to as wolframin. Wolframin is an endoglycosidase H-sensitive glycoprotein, which localizes primarily in the endoplasmic reticulum of a variety of neurons, including neurons in the supraoptic nucleus and neurons in the lateral magnocellular division of the paraventricular nucleus.[125,126] Disruption of the Wfs1 gene in mice cause progressive beta cell loss and impaired stimulus-secretion coupling in insulin secretion but central diabetes insipidus is not observed in Wfs$^{-/-}$ mice.[127] Miner1, another endoplasmic reticulum protein, is causative in Wolfram syndrome 2,[128] and WFS1 negatively regulates a key transcription factor involved in ER stress signaling.[129]

THE SYNDROME OF HYPERNATREMIA AND HYPODIPSIA

Some patients with the hypernatremia and hypodipsia syndrome may have partial central diabetes insipidus. These patients also have persistent hypernatremia that is not due to any apparent extracellular volume loss, absence or attenuation of thirst, and a normal renal response to AVP. In almost all the patients studied to date, the hypodipsia has been associated with cerebral lesions in the vicinity of the hypothalamus. It has been proposed that in these patients there is a "resetting" of the osmoreceptor because their urine tends to become concentrated or diluted at inappropriately high levels of plasma osmolality. However, using the regression analysis of plasma AVP concentration versus plasma osmolality, it has been shown that in some of these patients the tendency to concentrate and dilute urine at inappropriately high levels of plasma osmolality is due solely to a marked reduction in sensitivity or a gain in the osmoregulatory mechanism.[130,131] This finding is compatible with the diagnosis of partial central diabetes insipidus. In other patients, however, plasma AVP concentrations fluctuate in a random manner, bearing no apparent relationship to changes in plasma osmolality. Such patients frequently display large swings in serum sodium concentration and frequently exhibit hypodipsia. It appears that most patients with essential hypernatremia fit one of these two patterns (Fig. 71.12). Both of these groups of patients consistently respond normally to nonosmolar AVP release signals, such as hypotension, emesis, or hypoglycemia, or all three. These observations suggest that (1) the osmoreceptor may be anatomically as well as functionally separate from the nonosmotic efferent pathways, and neurosecretory neurons for vasopressin and a hypothalamic lesion may impair the osmotic release of AVP while the nonosmotic release of AVP remains intact; and (2) the osmoreceptor neurons that regulate vasopressin secretion are not totally synonymous with those that regulate thirst, although they appear to be anatomically close if not overlapping.

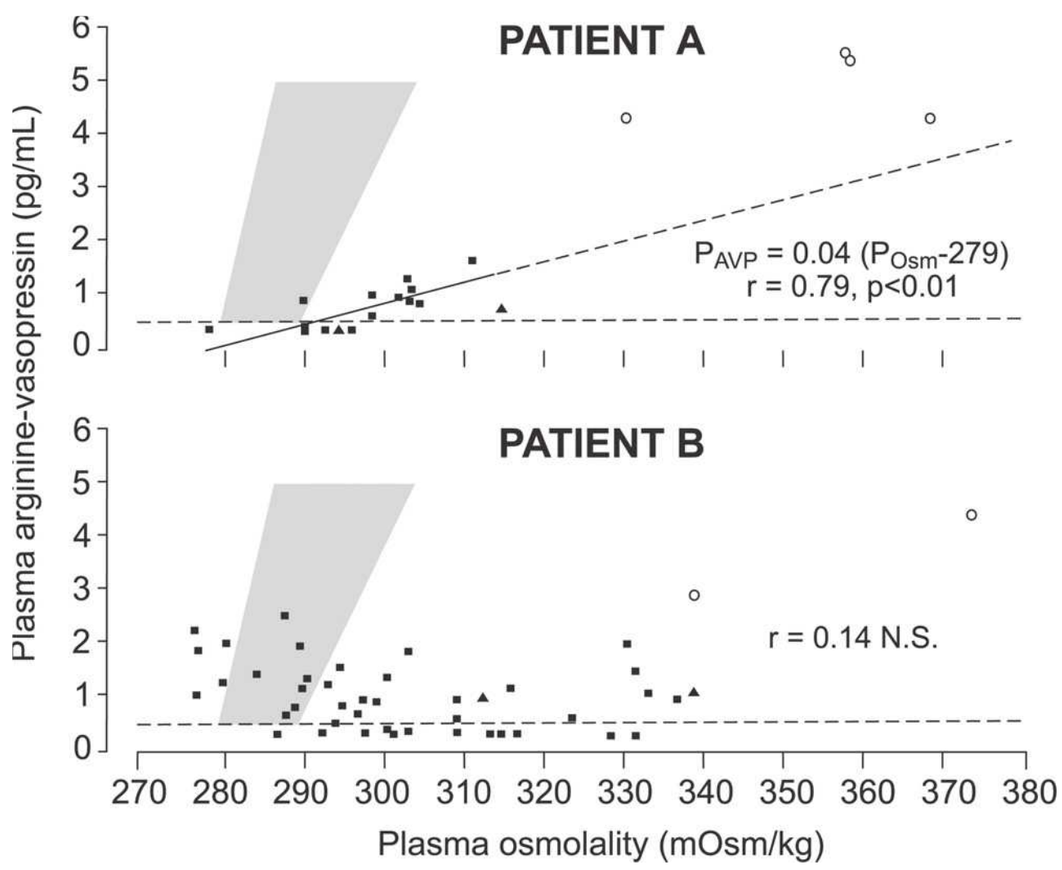

FIGURE 71.12 Plasma vasopressin (P_{AVP}) as a function of "effective" plasma osmolality (P_{OSM}) in two patients with adipsic hypernatremia. *Open circles* indicate values obtained on admission; *filled squares* indicate those obtained during forced hydration; *filled triangles* indicate those obtained after 1 to 2 weeks of ad libitum water intake; *shaded areas* indicate a range of normal values. (From: Robertson GL. The physiopathology of ADH secretion. In: Tolis G, Labrie F, Martin JB, et al., eds. *Clinical Neuroendocrinology: A Pathophysiological Approach*. New York, NY: Raven Press; 1979:247, with permission from Wolters Kluwer/Lippincott Williams & Wilkins.[234])

NEPHROGENIC DIABETES INSIPIDUS

In 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 recognized to avoid severe episodes of dehydration. Most (> 90%) of the 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 46 mutations have been identified in the AQP2 gene (AQP2) located in chromosome region 12q13; that is, the vasopressin-sensitive water channel (Fig. 71.13).[132] For the AVPR2 gene, 211 putative disease-causing mutations have now been published in 326 unrelated families with XNDI (Fig. 71.10). When studied in vitro, most AVPR2 mutations lead to receptors that are trapped intracellularly and are unable to reach the plasma membrane.[133] 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),[134] cystinosis, and autosomal dominant hypocalcemia,[135,136] nephronophthisis, and apparent mineralocorticoid excess.[137]

Clinical Presentation and History of X-Linked Nephrogenic Diabetes Insipidus

XNDI (OMIM 304800) is secondary to AVPR2 mutations, which result in a loss of function or dysregulation of the V_2 receptor.[138] Males who have an AVPR2 mutation have a phenotype characterized by early dehydration episodes, hypernatremia, and hyperthermia as early as the first week of life. Dehydration episodes can be so severe that they lower arterial blood pressure to a degree that is not sufficient to sustain adequate oxygenation to the brain, kidneys, and other organs. Mental and physical retardation and renal failure are the classical "historical" consequences of a late diagnosis and lack of treatment. Heterozygous females may exhibit variable degrees of polyuria and polydipsia because of skewed X chromosome inactivation.[139]

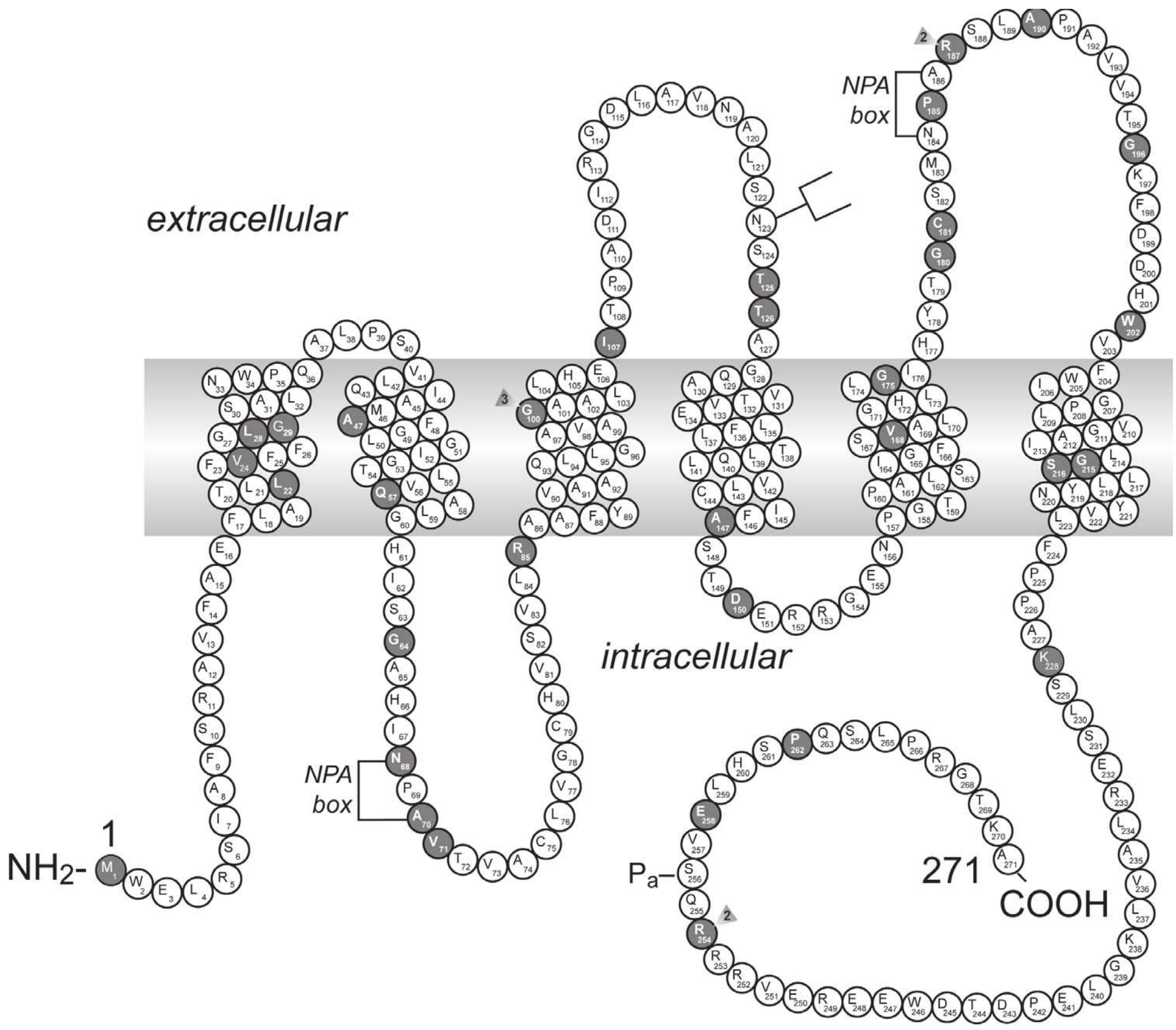

FIGURE 71.13 A schematic representation of the aquaporin-2 protein and indentification of 46 AQP2 mutations. A monomer is represented with six stetches of hydrophobic sequences that are suggestive of six transmembrane helices. The MIP proteins share an NPA (Asn-Pro-Ala) motiff in each of the two prominent loops. AQP1 (and, by analogy, AQP2) is homotetramer containing four independent aqueous channels. The location of the protein kinase A phosphorylation site is indicated. This site is possibly involved in the vasopressin-induced trafficking of AQP2 from intracellular vesicles to the plasma membrane and in the subsequent stimulation of endocytosis.

The "historical" clinical characteristics include hypernatremia, hyperthermia, mental retardation, and repeated episodes of dehydration in early infancy.[140] Mental retardation, a consequence of repeated episodes of dehydration, was prevalent in the Crawford and Bode study,[140] in which only 9 of 82 patients (11%) had normal intelligence. Early recognition and treatment of XNDI with an abundant intake of water allows a normal life span with normal physical and mental development.[141] Two characteristics suggestive of XNDI are the familial occurrence and the confinement of mental retardation to male patients. It is then tempting to assume that the family described in 1892 by McIlraith[142] and discussed by Reeves and Andreoli[143] was an XNDI family. Lacombe[112] and Weil[113] described a familial form of diabetes insipidus with autosomal transmission and without any associated mental retardation. The descendants of the family originally described by Weil were later found to have neurohypophyseal adFNDI (OMIM 192340).[144] Patients with adFNDI retain some limited capacity to secrete AVP during severe dehydration, and the polyuro-polydipsic symptoms usually appear after the first year of life when the infant's demand for water is more likely to be understood by adults.

The severity in infancy of NDI was clearly described by Crawford and Bode.[140] The first manifestations of the disease can be recognized during the first week of life. The infants are irritable, cry almost constantly, and although eager to suck, will vomit milk soon after ingestion unless prefed with water. The history given by the mothers often includes persistent constipation, erratic unexplained fever, and failure to gain weight. Even though the patients characteristically show no visible evidence of perspiration, increased water loss during fever or in warm weather exaggerates the symptoms. Unless the condition is recognized early, children will experience frequent bouts of hypertonic dehydration, sometimes complicated by convulsions or death; mental retardation is a frequent consequence of these episodes. The intake of large quantities of water, combined with the patient's voluntary restriction of dietary salt and protein intake, leads to hypocaloric dwarfism beginning in infancy. Affected children frequently develop lower urinary tract dilatation and obstruction, probably secondary to the large volume of urine produced. Dilatation of the lower urinary tract is also seen in primary polydipsic patients and in patients with neurogenic diabetes insipidus.[145,146] Chronic renal insufficiency may occur by the end of the first decade of life and could be the result of episodes of dehydration with thrombosis of the glomerular tufts.[140] More than 20 years ago our group observed that the administration of dDAVP, a V_2 receptor agonist, increased plasma cAMP concentrations in normal subjects but had no effect in 14 male patients with XNDI.[147] Intermediate responses were observed in obligate carriers of the disease, possibly corresponding to half of the normal receptor response. Based on these results, we predicted that the defective gene in these patients with XNDI was likely to code for a defective V_2 receptor (see Fig. 71.10).[147]

XNDI is a rare disease with an estimated prevalence of approximately 8.8 per million male live births in the Province of Quebec (Canada).[139] In defined regions of North America, however, the prevalence is much higher: we estimated the incidence in Nova Scotia and New Brunswick (Canada) to be 58 per million,[139] and is due to common ancestors. An early example is the Mormon pedigree, with its members residing in Utah (Utah families); this pedigree was originally described by Cannon.[148] The "Utah mutation" is a nonsense mutation (L312X) predictive of a receptor that lacks transmembrane domain 7 and the intracellular COOH-terminus.[149] The largest known kindred with XNDI is the Hopewell family, named after the Irish ship Hopewell, which arrived in Halifax, Nova Scotia, in 1761.[150] Aboard the ship were members of the Ulster Scot clan, descendants of Scottish Presbyterians who migrated to Ulster, Ireland in the 17th century and left Ireland for the New World in the 18th century. Whereas families arriving with the first emigration wave settled in northern Massachusetts in 1718, the members of a second emigration wave, passengers of the Hopewell, settled in Colchester County, Nova Scotia. According to the Hopewell hypothesis,[150] most patients with NDI in North America are progeny of female carriers of the second emigration wave. This assumption is mainly based on the high prevalence of NDI among descendants of the Ulster Scots residing in Nova Scotia. In two villages with a total of 2500 inhabitants, 30 patients have been diagnosed, and the carrier frequency has been estimated at 6%. Given the numerous mutations found in North American XNDI families, the Hopewell hypothesis cannot be upheld in its originally proposed form. However, among XNDI patients in North America, the W71X (the Hopewell mutation) mutation is more common than another AVPR2 mutation. It is a null mutation (W71X),[149,151] predictive of an extremely truncated receptor consisting of the extracellular NH_2-terminus, the first transmembrane domain, and the NH_2-terminal half of the first intracellular loop. Because the original carrier cannot be identified, it is not clear whether the Hopewell mutation was brought to North America by Hopewell passengers or by other Ulster Scot immigrants. The diversity of AVPR2 mutations found in many ethnic groups (Caucasians, Japanese, African Americans, Africans) and the rareness of the disease is consistent with an X-linked recessive disease that in the past was lethal for male patients and was balanced by recurrent mutations. In XNDI, loss of mutant alleles from the population occurs because of the higher mortality of affected males compared with healthy males, whereas a gain of mutant alleles occurs by mutation. If affected males with a rare X-linked recessive disease do not reproduce and if mutation rates are equal in mothers and fathers, then, at genetic equilibrium, one third of new cases of affected males will be due to new mutations. We and others have described ancestral mutations, de novo mutations, and potential mechanisms of mutagenesis.[139] These data are reminiscent of those obtained from patients with late-onset autosomal-dominant retinitis pigmentosa. In one fourth of patients, the disease is caused by mutations in the light receptor rhodopsin. Here too, many

different mutations (approximately 100) spread throughout the coding region of the rhodopsin gene have been found.[152]

The basis of loss of function or dysregulation of 28 different mutant V_2 receptors (including nonsense, frameshift, deletion, or missense mutations) has been studied using in vitro expression systems. Most of the mutant V_2 receptors tested were not transported to the cell membrane and were thus retained within the intracellular compartment. Our group and others also demonstrated that misfolded AVPR2 mutants could be rescued in vitro[153,154] and in vivo[155] by nonpeptide vasopressin antagonists acting as pharmacologic chaperones. This new therapeutic approach could be applied to the treatment of several hereditary diseases resulting from errors in proteins folding and kinesis.[156]

Only four AVPR2 mutations (D85N, V88M, G201D, P322S) have been associated with a mild phenotype.[157–159] In general, the male infants bearing these mutations are identified later in life and the classic episodes of dehydration are less severe. This mild phenotype is also found in expression studies: the mutant proteins are expressed on the plasma membrane of cells transfected with these mutants and demonstrate a stimulation of cAMP for higher concentrations of agonists.[157,159,160]

Gain of Function of the Vasopressin V_2 Receptor: Nephrogenic Syndrome of Inappropriate Antidiuresis

The clinical phenotype here is opposite to NDI. Rare cases of infants or adults with hyponatremia, concentrated urine, and suppressed AVP plasma concentrations have been described bearing the mutations R137C or R137L in their AVPR2 gene.[161–164] It is interesting to note that another mutation in the same codon (R137H) is a relatively frequent mutation causing classical NDI; however, the phenotype may be milder in some patients.[165] With cell-based assays, both R137C and R137L were found to have elevated basal signaling through the cAMP pathway and to interact with beta-arrestins in an agonist independent manner.[166] It is my opinion that AVPR2 mutations with gain of function are extremely rare. We have sequenced the AVPR2 gene in many patients with hyponatremia and never found a mutation. By contrast, we continue to identify new and recurrent loss-of-function AVPR2 mutations in patients with classical NDI.

Loss-of-Function Mutations of AQP2 (OMIM 107777)

The AQP2 gene is located on chromosome region 12q12-q13. Approximately 10% of NDI cases are due to autosomal mutations in AQP2, of which 40 mutations have been reported, which can be autosomal recessive (32 mutations reported) or autosomal dominant (8 mutations reported).[167] Males and females affected with congenital NDI have been described who are homozygous for a mutation in the AQP2 gene or carry two different mutations (Fig. 71.13).[158,168] Autosomal recessive mutations give rise to misfolded proteins that are retained in the ER and eventually degraded.[132] Autosomal dominant mutations are believed to be restricted to the C-terminal end of the AQP2 protein and operate through a dominant-negative effect where the mutant protein associates with functional AQP2 proteins within intracellular stores, thus preventing normal targeting and function.[167,169] To study the behavior of various AQP2 mutants on membrane water permeability, oocytes of the African clawed frog (Xenopus laevis) have provided a useful system. Functional expression studies showed that Xenopus oocytes injected with mutant cRNA had abnormal coefficient of water permeability, whereas Xenopus oocytes injected with both normal and mutant cRNA had coefficient of water permeability similar to that of normal constructs alone. These findings provide conclusive evidence that NDI can be caused by homozygosity for mutations in the AQP2 gene. A patient with a partial phenotype has also been described to be a compound heterozygote for the L22V and C181W mutations.[170] Immunolocalization of AQP2-transfected CHO cells showed that the C181W mutant had an endoplasmic reticulumlike intracellular distribution, whereas L22V and wild-type AQP2 showed endosome and plasma membrane staining. The authors suggested that the L22V mutation was key to the patient's unique response to desmopressin. The leucine 22 residue might be necessary for proper conformation or for the binding of another protein important for normal targeting and trafficking of the molecule. More recently, we obtained evidence to suggest that both autosomal dominant and autosomal recessive NDI phenotypes could be secondary to novel mutations in the AQP2 gene.[169,171–175] Reminiscent of expression studies done with AVPR2 proteins, studies also demonstrated that the major cause underlying autosomal recessive NDI is the misrouting of AQP2 mutant proteins.[88,171,173,176–179] To determine if the severe AQP2-trafficking defect observed with the naturally occurring mutations T126M, R187C, and A147T is correctable, cells were incubated with the chemical chaperone glycerol for 48 hours. Redistribution of AQP2 from the ER to the membrane-endosome fractions was observed by immunofluorescence. This redistribution was correlated to improved water permeability measurements.[177] We recently studied the ability of myo-inositol to stimulate water permeability in oocytes expressing six different mutant AQP2s. Only two mutants (D150E and S256L) were sensitive to the effect of myo-inositol, whereas no changes were seen with mutants A70D, V71M, and G196D.[180]

POLYURIA, POLYDIPSIA, ELECTROLYTE IMBALANCE, AND DEHYDRATION IN CYSTINOSIS, NEPHRONOPHTHISIS, AND APPARENT MINERALOCORTICOID EXCESS

Polyuria may be as mild as persistent enuresis and as severe to contribute to death from dehydration and electrolyte

abnormalities in infants with cystinosis who have acute gastroenteritis.[136] Nephronophthisis and apparent mineralocorticoid excess are also associated with low urine osmolality that is unresponsive to vasopressin.[137]

Polyuria in Hereditary Hypokalemic Salt-Losing Tubulopathies

Patients with polyhydramnios, hypercalciuria, and hypo- or isosthenuria have been found to bear KCNJ1 (ROMK) and SLC12A1 (NKCC2) mutations.[134,181] Patients with polyhydramnios, profound polyuria, hyponatremia, hypochloremia, metabolic alkalosis, and sensorineural deafness were found to bear BSND mutations.[182–185] These studies demonstrate the critical importance of the proteins ROMK, NKCC2, and Barttin to transfer NaCl in the medullary interstitium and, together with urea, to thereby generate a hypertonic milieu (Fig. 71.14).

Acquired Nephrogenic Diabetes Insipidus

Acquired NDI is much more common than congenital NDI, but it is rarely as severe. The ability to produce hypertonic urine is usually preserved even though there is inadequate

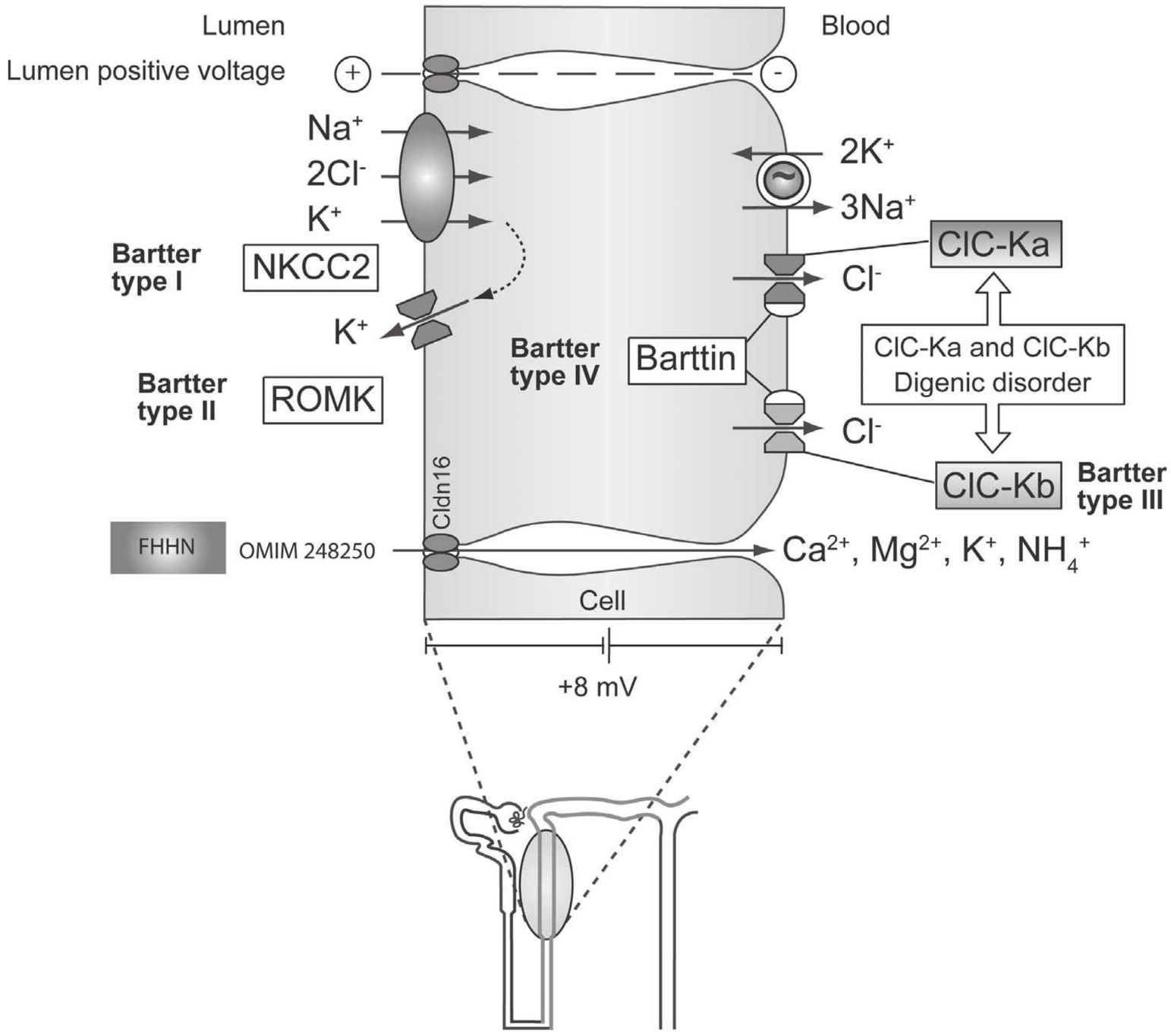

FIGURE 71.14 A schematic representation of transepithelial salt resorption in a cell of the thick ascending limb (TAL) of the loop of Henle. Of the filtered sodium chloride, 30% is reabsorbed in the TAL and most of the energy for concentration and dilution of the urine derives from active NaCl transport in the TAL. Filtered NaCl is reabsorbed through NKCC2, which uses the sodium gradient across the membrane to transport chloride and potassium into the cell. The potassium ions are recycled (100%) through the apical membrane by the potassium channel ROMK. Sodium leaves the cell actively through the basolateral Na-K-ATPase. Chloride diffuses passively through two basolateral channels, ClC-Ka and ClC-Kb. Both of these chloride channels must bind to the b subunit of barttin to be transported to the cell surface. Four types of Bartter syndrome (types I, II, III, and IV) are attributable to recessive mutations in the genes that encode the NKCC2 cotransporter, the potassium channel (ROMK), one of the chloride channels (CIC-Kb), and barttin, respectively. A fifth type of Bartter syndrome has also been shown to be a digenic disorder that is attributable to loss-of-function mutations in the genes that encode the chloride channels CIC-Ka and CIC-Kb.[223] As a result of these different molecular alterations, sodium chloride is lost into the urine, positive lumen voltage is abolished, and calcium (Ca^{2+}), magnesium (Mg^{2+}), potassium (K^{+}), and ammonium (NH_4^{+}) cannot be reabsorbed in the paracellular space. In the absence of mutations, the recycling of potassium maintains a lumen-positive gradient (+8 mV). Claudin 16 (CLDN16) is necessary for the paracellular transport of calcium and magnesium. (Modified from Bichet DG, Fujiwara TM: Reabsorption of sodium chloride—lessons from the chloride channels. *N Engl J Med.* 2004 350:1281–1283.[235])

concentrating ability of the nephron. Polyuria and polydipsia are therefore moderate (3 to 4 L per day).

Among the more common causes of acquired NDI, lithium administration has become the most frequent cause; 54% of 1105 unselected patients on chronic lithium therapy developed NDI.[186] Of the patients, 19% had polyuria, as defined by a 24-hour urine output exceeding 3 L. The dysregulation of aquaporin-2 expression is the result of cytotoxic accumulation of lithium, which enters via the epithelial sodium channel (ENaC) on the apical membrane and leads to the inhibition of signaling pathways that involve glycogen synthase kinase type 3 beta.[187] The concentration of lithium in urine of patients on well-controlled lithium therapy (i.e., 10 to 40 mOsmol per liter) is sufficient to exert this effect. For patients on long-term lithium therapy, amiloride has been proposed to prevent the uptake of lithium in the collecting ducts, thus preventing the inhibitory effect of intracellular lithium on water transport.[188]

Primary Polydipsia

Primary polydipsia is a state of hypotonic polyuria secondary to excessive fluid intake. Primary polydipsia was extensively studied by Barlow and de Wardener in 1959[189]; however, the understanding of the pathophysiology of this disease has made little progress. Barlow and de Wardener[189] described seven women and two men who were compulsive water drinkers; their ages ranged from 48 to 59 years except for one patient who was 24. Eight of these patients had histories of previous psychological disorders, which ranged from delusions, depression, and agitation, to frank hysterical behavior. The other patient appeared normal. The consumption of water fluctuated irregularly from hour to hour or from day to day; in some patients, there were remissions and relapses lasting several months or longer. In eight of the patients, the mean plasma osmolality was significantly lower than normal. Vasopressin tannate in oil made most of these patients feel ill; in one, it caused overhydration. In four patients, the fluid intake returned to normal after electroconvulsive therapy or a period of continuous narcosis; the improvement in three was transient, but in the fourth it lasted 2 years. Polyuric female subjects might be heterozygous for de novo or previously unrecognized AVPR2 mutations or autosomal dominant AQP2 mutations[169] and may be classified as compulsive water drinkers.[190] Therefore, the diagnosis of compulsive water drinking must be made with care and may represent our ignorance of yet undescribed pathophysiologic mechanisms. Robertson[190] has described under the term dipsogenic diabetes insipidus a selective defect in the osmoregulation of thirst. Three studied patients had, under basal conditions of ad libitum water intake, thirst, polydipsia, polyuria, and high-normal plasma osmolality. They had a normal secretion of AVP, but their osmotic threshold for thirst was abnormally low. Such cases of dipsogenic diabetes insipidus might represent up to 10% of all patients with diabetes insipidus.[190] Primary polydipsic rats had low serum sodium, suppressed AVP, low urine osmolality, and decreased AQP2 protein abundance in their inner medulla.[191]

DIABETES INSIPIDUS AND PREGNANCY

Pregnancy in a Patient Known to Have Diabetes Insipidus

An isolated deficiency of vasopressin without a concomitant loss of hormones in the anterior pituitary does not result in altered fertility and, with the exception of polyuria and polydipsia, gestation, delivery, and lactation are uncomplicated.[192] Patients may require increasing dosages of dDAVP. The increased thirst may be due to a resetting of the thirst osmostat.[193]

Increased polyuria also occurs during pregnancy in patients with partial NDI.[194] These patients may be obligatory carriers of the NDI gene[195] or may be homozygotes, compound heterozygotes, or may have dominant AQP2 mutations.

Syndromes of Diabetes Insipidus that Begin During Gestation and Remit After Delivery

Barron et al.[196] described three pregnant women in whom transient diabetes insipidus developed late in gestation and subsequently remitted postpartum. In one of these patients, dilute urine was present despite high plasma concentrations of AVP. Hyposthenuria in all three patients was resistant to administered aqueous vasopressin. Because excessive vasopressinase activity was not excluded as a cause of this disorder, Barron et al. labeled the disease vasopressin resistant rather than NDI.

A well-documented case of enhanced activity of vasopressinase has been described in a woman in the third trimester of a previously uncomplicated pregnancy.[197] She had massive polyuria and markedly elevated plasma vasopressinase activity. The polyuria did not respond to large intravenous doses of AVP but responded promptly to dDAVP, a vasopressinase-resistant analog of AVP. The polyuria disappeared with the disappearance of the vasopressinase. It is suggested that pregnancy may be associated with several different forms of diabetes insipidus, including central, nephrogenic, and vasopressinase mediated.[194,198–200]

DIFFERENTIAL DIAGNOSIS OF POLYURIC STATES

Plasma sodium and osmolality are maintained within normal limits (136 to 143 mmol per liter for plasma sodium, 275 to 290 mmol per kilogram for plasma osmolality) by a thirst-ADH-renal axis. Thirst and ADH, both stimulated by increased osmolality, have been termed a double-negative feedback system.[201] Therefore, even when the ADH limb of this double-negative regulatory feedback system is lost, the thirst mechanism still preserves the plasma sodium and osmolality within the normal range but at the expense of

pronounced polydipsia and polyuria. Consequently, the plasma sodium concentration or osmolality of an untreated patient with diabetes insipidus may be slightly higher than the mean normal value, but because the values usually remain within the normal range, these small increases have no diagnostic significance.

Theoretically, it should be relatively easy to differentiate between central diabetes insipidus, NDI, and primary polydipsia. A comparison of the osmolality of urine obtained during dehydration from patients with central diabetes insipidus or NDI with that of urine obtained after the administration of AVP should reveal a rapid increase in osmolality only in patients with central diabetes insipidus. Urine osmolality should increase normally in response to moderate dehydration in primary polydipsia patients.

However, these distinctions may not be as clear as one might expect because of several factors.[202] First, chronic polyuria of any etiology interferes with the maintenance of the medullary concentration gradient, and this washout effect diminishes the maximum concentrating ability of the kidney. The extent of the blunting varies in direct proportion to the severity of the polyuria and is independent of its cause. Hence, for any given level of basal urine output, the maximum urine osmolality achieved in the presence of saturating concentrations of AVP is depressed to the same extent in patients with primary polydipsia, central diabetes insipidus, and NDI (Fig. 71.15). Second, most patients with central diabetes insipidus maintain a small, but detectable, capacity to secrete AVP during severe dehydration, and urine osmolality may then rise above plasma osmolality. Third, many patients with acquired NDI have an incomplete deficit in AVP action, and concentrated urine could again be obtained during dehydration testing. Finally, all polyuric states (whether central, nephrogenic, or psychogenic) can

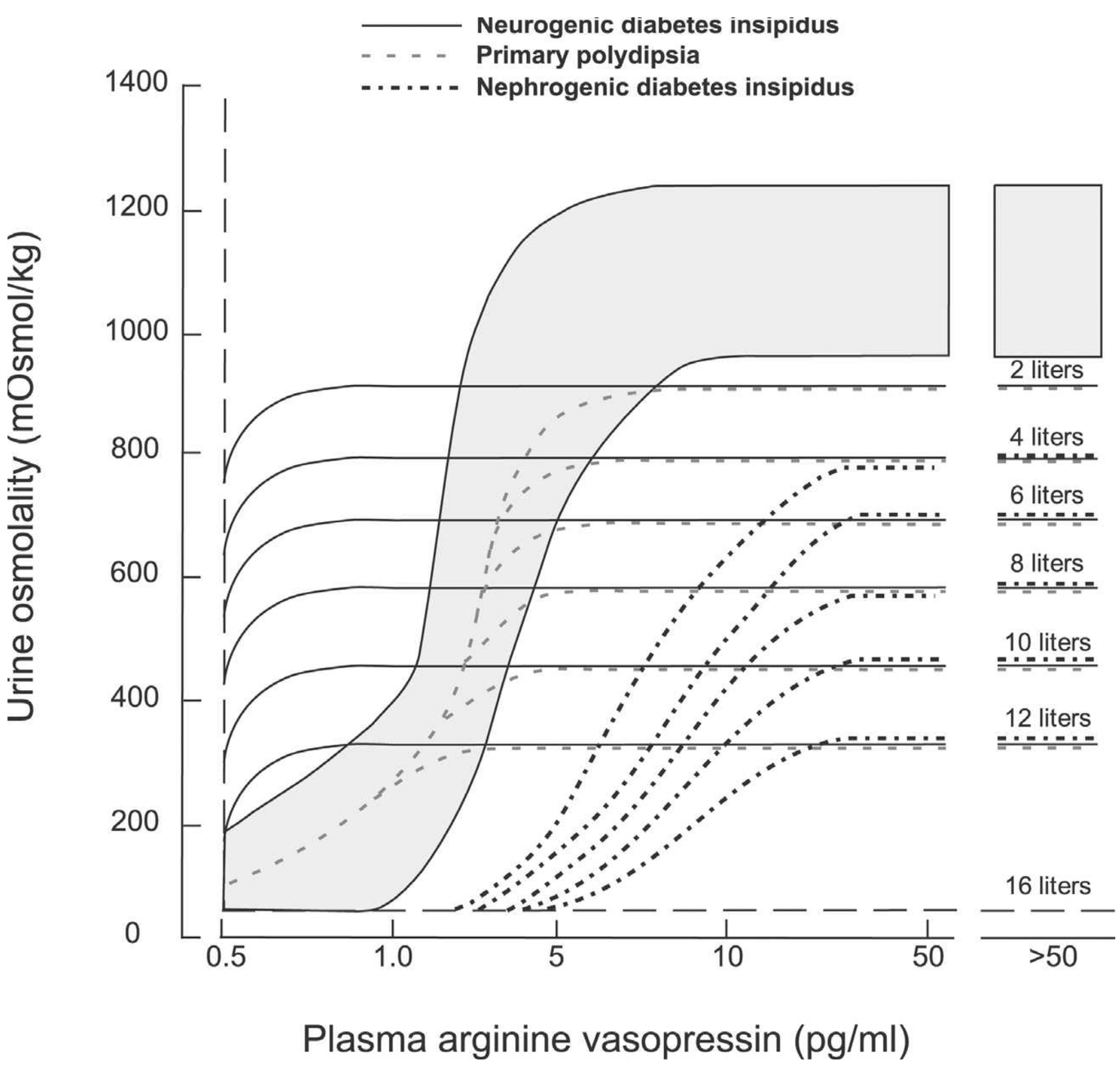

FIGURE 71.15 The relationship between urine osmolality and plasma vasopressin in patients with polyuria of diverse etiology and severity. Note that for each of the three categories of polyuria (neurogenic diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia), the relationship is described by a family of sigmoid curves that differ in height. These differences in height reflect differences in maximum concentrating capacity due to "washout" of the medullary concentration gradient. They are proportional to the severity of the underlying polyuria (indicated in liters per day at the right end of each plateau) and are largely independent of the etiology. Therefore, the three categories of diabetes insipidus differ principally in the submaximal or ascending portion of the dose-response curve. In patients with partial neurogenic diabetes insipidus, this part of the curve lies to the left of normal, reflecting increased sensitivity to the antidiuretic effects of very low concentrations of plasma AVP. In contrast, in patients with partial nephrogenic diabetes insipidus, this part of the curve lies to the right of normal, reflecting decreased sensitivity to the antidiuretic effects of normal concentrations of plasma arginine vasopressin. In primary polydipsia, this relationship is relatively normal. (From Robertson GL. Diagnosis of diabetes insipidus. In: Czernichow P, Robinson AG, eds. *Frontiers of Hormone Research,* Vol. 13. Basel, Germany: S. Karger; 1985:176, with permission.)

71.2 Urinary Responses to Fluid Deprivation and Exogenous Vasopressin in Recognition of Partial Defects in Antidiuretic Hormone Secretion[34]

	No. of Cases	Maximum U_{osm} with Dehydration (mmol/kg)	U_{osm} after Vasopressin (mmol/kg)	% Change (U_{osm})	U_{osm} Increase after Vasopressin (%)
Normal subjects	9	1068 ± 69	979 ± 79	9 ± 3	< 9
Complete central diabetes insipidus	18	168 ± 13	445 ± 52	183 ± 41	> 50
Partial central diabetes insipidus	11	438 ± 34	549 ± 28	28 ± 5	> 9 < 50
Nephrogenic diabetes insipidus	2	123.5	174.5	42	< 50
Compulsive water drinking	7	738 ± 53	780 ± 73	5.0 ± 2.2	< 9

induce large dilations of the urinary tract and bladder.[203–205] As a consequence, the urinary bladder of these patients may contain an increased residual capacity, and changes in urine osmolalities induced by diagnostic maneuvers might be difficult to demonstrate.

The Indirect Test

The measurements of urine osmolality after dehydration followed by vasopressin administration are usually referred to as indirect testing because vasopressin secretion is indirectly assessed through changes in urine osmolalities.

The patient is maintained on a complete fluid restriction regimen until urine osmolality reaches a plateau, as indicated by an hourly increase of less than 30 mmol per kilogram for at least 3 successive hours. After the plasma osmolality is measured, 5 U of aqueous vasopressin or 4 μg of dDAVP is administered subcutaneously. Urine osmolality is measured 30 and 60 minutes later. The last urine osmolality value obtained before the vasopressin injection and the highest value obtained after the injection are compared. The patients are then separated into five categories according to previously published criteria (Table 71.2).[34]

The Direct Test

The two approaches of Zerbe and Robertson[33] are used. First, during the dehydration test, plasma is collected and assayed for vasopressin. The results are plotted on a nomogram depicting the normal relationship between plasma sodium or osmolality and plasma AVP in normal subjects (Fig. 71.7). If the relationship between plasma vasopressin and osmolality falls below the normal range, the disorder is diagnosed as central diabetes insipidus.

Second, partial NDI and primary polydipsia can be differentiated by analyzing the relationship between plasma AVP and urine osmolality at the end of the dehydration period (Figs. 71.7 and 71.15). However, a definitive differentiation between these two disorders might be impossible because a normal or even supranormal AVP response to increased plasma osmolality occurs in polydipsic patients. None of the patients with psychogenic or other forms of severe polydipsia studied by Robertson[202] have ever shown any evidence of pituitary suppression. Zerbe and Robertson[33] found that in the differential diagnosis of polyuria, all seven of the cases of severe neurogenic diabetes insipidus diagnosed by the standard indirect test were confirmed when diagnosed by the plasma vasopressin assay. However, two of six patients diagnosed by the indirect test as having partial neurogenic diabetes insipidus had normal vasopressin secretion as measured by the direct assay; one was found to have primary polydipsia and the other, NDI. Moreover, 3 of 10 patients diagnosed as having primary polydipsia by the indirect test had clear evidence of partial vasopressin deficiency by the direct assay.[33] These patients were thus wrongly diagnosed as primary polydipsic! A combined direct and indirect testing of the AVP function is described in Table 71.3. Urinary vasopressin measurements and copeptin plasma levels might also be useful.[206,207]

The Therapeutic Trial

In selected patients with an uncertain diagnosis, a closely monitored therapeutic trial of desmopressin (10 μg intranasally twice a day) may be used to distinguish partial NDI from partial neurogenic diabetes insipidus and primary polydipsia. If desmopressin at this dosage causes a significant antidiuretic

71.3 Direct and Indirect Tests of Arginine Vasopressin Function in Patients with Polyuria[236]

Measurements of AVP cannot be used in isolation but must be interpreted in light of four other factors:
Clinical history
Concurrent measurements of plasma osmolality, urine osmolality, and maximal urinary response to exogenous vasopressin in reference to the basal urine flow

AVP, arginine vasopressin.

effect, NDI is effectively excluded. If polydipsia as well as polyuria is abolished and plasma sodium does not fall below the normal range, the patient probably has central diabetes insipidus. Conversely, if desmopressin causes a reduction in urine output without a reduction in water intake and hyponatremia appears, the patient probably has primary polydipsia. Because fatal water intoxication is a remote possibility, the desmopressin trial should be carried out with closed monitoring.

Recommendations

Table 71.4 lists recommendations for obtaining a differential diagnosis of diabetes insipidus.[208]

RADIOIMMUNOASSAY OF AVP AND OTHER LABORATORY DETERMINATIONS

Radioimmunoassay of Arginine Vasopressin

Three developments were basic to the elaboration of a clinically useful radioimmunoassay for plasma AVP[209,210]: (1) the extraction of AVP from plasma with petrol-ether and acetone and the subsequent elimination of nonspecific immunoreactivity, (2) the use of highly specific and sensitive rabbit antiserum, and (3) the use of a tracer (^{125}I-AVP) with high specific activity. More than 25 years later, the same extraction procedures are widely used,[211–214] and commercial tracers (^{125}I-AVP) and antibodies are available. AVP can also be extracted from plasma by using Sep-Pak C18 cartridges.[215–217]

Blood samples collected in chilled 7-mL lavender-stoppered tubes containing ethylenediaminetetraacetic acid (EDTA) are centrifuged at 4°C, 1000 g (3000 rpm in a usual lab centrifuge), for 20 minutes. This 20-minute centrifugation is mandatory for obtaining platelet-poor plasma samples because a large fraction of the circulating vasopressin is associated with the platelets in humans.[213,218] The tubes may be kept for 2 hours on slushed ice prior to centrifugation. Plasma is then separated, frozen at −20°C, and extracted within 6 weeks of sampling. Details for sample preparation (Table 71.5) and the assay procedure (Table 71.6) can be found in writings by Bichet et al.[213,214] An AVP radioimmunoassay should be validated by demonstrating (1) a good

71.4 Differential Diagnosis of Diabetes Insipidus[208]

1.	Measure plasma osmolality and/or sodium concentration under conditions of ad libitum fluid intake. If they are greater than 295 mmol per kilogram and 143 mmol per liter, the diagnosis of primary polydipsia is excluded, and the workup should proceed directly to step 5 and/or 6 to distinguish between neurogenic and nephrogenic diabetes insipidus. Otherwise,
2.	Perform a dehydration test. If urinary concentration does not occur before plasma osmolality and/or sodium reaches 295 mmol per kilogram or 143 mmol per liter, the diagnosis of primary polydipsia is again excluded, and the workup should proceed to step 5 and/or 6. Otherwise,
3.	Determine the ratio of urine to plasma osmolality at the end of the dehydration test. If it is < 1.5, the diagnosis of primary polydipsia is again excluded, and the workup should proceed to step 5 and/or 6. Otherwise,
4.	Perform a hypertonic saline infusion with measurements of plasma vasopressin and osmolality at intervals during the procedure. If the relationship between these two variables is subnormal, the diagnosis of diabetes insipidus is established. Otherwise,
5.	Perform a vasopressin infusion test. If urine osmolality rises by more than 150 mOsmol per kilogram greater than the value obtained at the end of the dehydration test, nephrogenic diabetes insipidus is excluded. Alternately,
6.	Measure urine osmolality and plasma vasopressin at the end of the dehydration test. If the relationship is normal, the diagnosis of nephrogenic diabetes insipidus is excluded.

71.5 Arginine Vasopressin Measurements: Sample Preparation

4°C—blood in EDTA tubes
Centrifugation 1000 g × 20 minutes
Plasma frozen −20°C
Extraction: 2 mL acetone + 1 mL plasma 1000 g × 30 minutes 4°C Supernatant + 5 mL of petrol-ether 1000 g × 20 minutes 4°C Freeze −80°C Throw nonfrozen upper phase Evaporate lower phase to dryness Store desiccated samples at −20°C

AVP, arginine vasopressin; EDTA, ethylenediaminetetraacetic acid.

correlation between plasma sodium or osmolality and plasma AVP during dehydration and infusion of hypertonic saline solution (Fig. 71.15) and (2) the inability to obtain detectable values of AVP in patients with severe central diabetes insipidus. Plasma AVP immunoreactivity may be elevated in patients with diabetes insipidus following hypothalamic surgery.[219]

In pregnant patients, the blood contains high concentrations of cystine aminopeptidase, which can (in vitro) inactivate enormous quantities (ng × mL^{-1} × min^{-1}) of AVP. However, phenanthroline effectively inhibits these cystine aminopeptidases (Table 71.7).

71.6 Arginine Vasopressin Measurements: Assay Procedure

Day 1: Assay Setup
400 µL/tube (200 µL sample or standard + 200 µL of antiserum or buffer) Incubation 80 hours, 4°C
Day 4: ^{125}I-AVP 100 µL/tube
1000 cpm/tube Incubation 72 hours, 4°C
Day 7: Separation dextran + Charcoal

AVP, arginine vasopressin.

71.7 Measurements of Arginine Vasopressin Levels in Pregnant Patients[212]

1,10-Phenanthrolene monohydrate (Sigma)
60 mg/mL—solubilized with several drops of glacial acetic acid
0.1 mL/10 mL of blood

AVP, arginine vasopressin.

Aquaporin-2 Measurements

Urinary AQP2 excretion could be measured by radioimmunoassay[220] or by quantitative Western analysis[221] and could provide an additional indication of the responsiveness of the collecting duct to AVP.[221,222]

Plasma Sodium and Plasma and Urine Osmolality Measurements

Measurements of plasma sodium and plasma and urine osmolality should be immediately available at various intervals during dehydration procedures. Plasma sodium is easily measured by flame photometry or with a sodium-specific electrode.[223] Plasma and urine osmolalities are also reliably measured by freezing point depression instruments with a coefficient of variation at 290 mmol per kilogram of less than 1%.

In our clinical research unit, plasma sodium and plasma and urine osmolalities are measured at the beginning of each dehydration procedure and at regular intervals (usually hourly) thereafter, depending on the severity of the polyuric syndrome explored.

In one case, an 8-year-old patient (31 kg body weight) with a clinical diagnosis of congenital NDI (later found to bear the de novo AVPR2 mutant 274insG)[224] continued to excrete large volumes of urine (300 mL per hour) during a short 4-hour dehydration test. During this time, the patient had severe thirst, his plasma sodium was 155 mEq per liter, his plasma osmolality was 310 mmol per kilogram, and his urine osmolality was 85 mmol per kilogram. The patient received 1 µg of desmopressin intravenously and was allowed to drink water. Repeated urine osmolality measurements demonstrated a complete urinary resistance to desmopressin.

It would have been dangerous and unnecessary to prolong the dehydration further in this young patient. Therefore, the usual prescription of overnight dehydration should not be used in patients, especially children, with severe polyuria and polydipsia (more than 4 L per day). Great care should be taken to avoid any severe hypertonic state arbitrarily defined as a plasma sodium greater than 155 mEq per liter.

At variance with published data,[33,213] we have found that plasma and serum osmolalities are equivalent (i.e., similar values are obtained). Blood taken in heparinized tubes is easier to handle because the plasma can be more readily removed after

centrifugation. The tube used (green-stoppered tube) contains a minuscule concentration of lithium and sodium, which does not interfere with plasma sodium or osmolality measurements. Frozen plasma or urine samples can be kept for a further analysis of their osmolalities because the results obtained are similar to those obtained immediately after blood sampling, except in patients with severe renal failure. In the latter patients, plasma osmolality measurements are increased after freezing and thawing, but the plasma sodium values remain unchanged.

Plasma osmolality measurements can be used to demonstrate the absence of unusual osmotically active substances (e.g., glucose and urea in high concentrations, mannitol, and ethanol).[225] With this information, plasma or serum sodium measurements are sufficient to assess the degree of dehydration and its relationship to plasma AVP. Nomograms describing the normal plasma sodium–plasma AVP relationship (Fig. 71.4) are equally as valuable as classical nomograms describing the relationship between plasma osmolality and effective osmolality (i.e., plasma osmolality minus the contribution of "ineffective" solutes: glucose and urea).

Magnetic Resonance Imaging in Patients with Diabetes Insipidus

Magnetic resonance imaging (MRI) permits the visualization of the anterior and posterior pituitary glands and the pituitary stalk. The pituitary stalk is permeated by numerous capillary loops of the hypophyseal-portal blood system. This vascular structure also provides the principal blood supply to the anterior pituitary lobe, because there is no direct arterial supply to this organ. In contrast, the posterior pituitary lobe has a direct vascular supply. Therefore, the posterior lobe can be more rapidly visualized in a dynamic mode after the administration of gadolinium (gadopentetate dimeglumine) as a contrast material during MRI. The posterior pituitary lobe is easily distinguished by a round, high-intensity signal (the posterior pituitary "bright spot") in the posterior part of the sella turcica on T1-weighted images. Loss of the pituitary hyperintense spot or bright spot on a T1-weighted MRI image reflects a loss of functional integrity of the neurohypophysis and is a nonspecific indicator of neurohypophyseal diabetes insipidus regardless of the underlying cause.[102,226] It is now reasoned that the bright spot represents normal AVP storage in the posterior lobe of the pituitary, that the intensity is correlated with the amount of AVP, and that, after 60 years of age, the signal is often less intense with irregularities in the normally smooth convex edge.[227,228] An MRI is reported to be the best technique with which to evaluate the pituitary stalk and infundibulum in patients with idiopathic polyuria. A thickening or enlargement of the pituitary stalk may suggest an infiltrative process destroying the neurohypophyseal tract.[229]

Treatment

In most patients with complete hypothalamic diabetes insipidus, the thirst mechanism remains intact. Thus, hypernatremia does not develop in these patients and they suffer only from the inconvenience associated with marked polyuria and polydipsia. If hypodipsia develops or access to water is limited, then severe hypernatremia can supervene. The treatment of choice for patients with severe hypothalamic diabetes insipidus is dDAVP, a synthetic, long-acting vasopressin analog with minimal vasopressor activity but a large antidiuretic potency. The usual intranasal daily dose is between 5 and 20 μg. To avoid the potential complication of dilutional hyponatremia, which is exceptional in these patients as a result of an intact thirst mechanism, dDAVP can be withdrawn at regular intervals to allow the patients to become polyuric. Aqueous vasopressin (Pitressin) or dDAVP (4.0 mg per 1-mL ampule) can be used intravenously in acute situations such as after hypophysectomy or for the treatment of diabetes insipidus in the brain-dead organ donor. Pitressin tannate in oil and nonhormonal antidiuretic drugs are somewhat obsolete and are now rarely used. For example, chlorpropamide (250 to 500 mg daily) appears to potentiate the antidiuretic action of circulating AVP, but the troublesome side effects of hypoglycemia and hyponatremia do occur.

In the treatment of congenital NDI, an abundant unrestricted water intake should always be provided, and affected patients should be carefully followed during their first years of life. Water should be offered every 2 hours day and night, and temperature, appetite, and growth should be monitored. The parents of these children easily accept setting their alarm clock every 2 hours during the night. Hospital admission may be necessary to allow for continuous gastric feeding. A low-osmolar and low-sodium diet, hydrochlorothiazide (1 to 2 mg per kilogram per day) alone or with amiloride, and indomethacin (0.75 to 1.5 mg per kilogram) substantially reduce water excretion and are helpful in the treatment of children. Many adult patients receive no treatment.

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