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REVIEW

Nephrogenic Diabetes Insipidus

Jeff M. Sands, MD, and Daniel G. Bichet, MD

Clinical Principles

Patients with diabetes insipidus produce large quantities of dilute urine.

Diabetes insipidus can result from failure of the posterior pituitary to make or secrete vasopressin (antidiuretic hormone) or end-organ (kidney) insensitivity.

Patients with congenital nephrogenic diabetes insipidus now live well into adulthood and need to be followed by internists to avoid bladder dysfunction, renal dysfunction, and complications related to inaccessibility to water.

Optimal therapy for nephrogenic diabetes insipidus involves drinking enough water to avoid dehydration, which can be difficult in patients at the extremes of age.

Additional therapy includes a very low-sodium diet, thiazide diuretics, and indomethacin.

Exogenous vasopressin is not useful because the kidney is insensitive to its actions.

Acquired nephrogenic diabetes insipidus can result from lithium therapy, protein malnutrition, hypercalcemia, or hypokalemia, or may occur after the release of urinary tract obstruction.

Normal aging can result in a partial form of nephrogenic diabetes insipidus.

Pathophysiologic Principles

Vasopressin (antidiuretic hormone) is secreted by the posterior pituitary.

Vasopressin acts on the collecting duct of the kidney to increase water reabsorption.

Transcellular water reabsorption is mediated by water channels (aquaporins).

Congenital nephrogenic diabetes insipidus can result from mutations in the type 2 vasopressin receptor or aquaporin-2.

A mild urine-concentrating defect results from mutations in the urea transporter-B.

Polyuria in hereditary hypokalemic salt-losing tubulopathies (the Bartter syndrome) can result from mutations in several transport proteins in the thick ascending limb.

Diabetes insipidus is a condition in which patients produce large quantities of dilute urine. Central or neurogenic diabetes insipidus results from the failure of the posterior pituitary to make or secrete vasopressin (also called antidiuretic hormone [ADH]). Nephrogenic diabetes insipidus (NDI), which can be congenital or acquired, results from failure of the kidney to respond to vasopressin. Most adults with NDI have an acquired abnormality, with the most common causes being lithium therapy, hypercalcemia, hypokalemia, protein malnutrition, and release of ureteral obstruction. However, internists will be seeing more adult patients with congenital NDI because genetic screening of newborns in families with a history of this disorder has resulted in improved therapy for these children, and most are now surviving into adulthood.

The standard method for diagnosing diabetes insipidus is a water deprivation test. **Figure 1** shows the typical changes in urine osmolality in response to water deprivation and to the administration of exogenous vasopressin in healthy individuals and in patients with diabetes insipidus. This test, which also distinguishes between persons with complete versus partial versions of each type of diabetes

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insipidus, is usually performed by restricting a patient's water intake, beginning after dinner. However, if the patient is producing more than 10 L of urine per day, then water restriction is only done during the day under close supervision and is not done after midnight. Spot urine samples for measuring osmolality are collected hourly, beginning at 7:00 a.m., until 3 successive measurements are within 50 to 100 mmol/kg of each other. Blood is then drawn to measure serum osmolality and plasma vasopressin levels. Next, vasopressin (or desmopressin) is administered and urine is obtained for osmolality every 30 minutes during the next 3 hours. This is done to account for a bladder with a large capacity and/or with the time-lag required to reconstruct the medullary gradient (1).

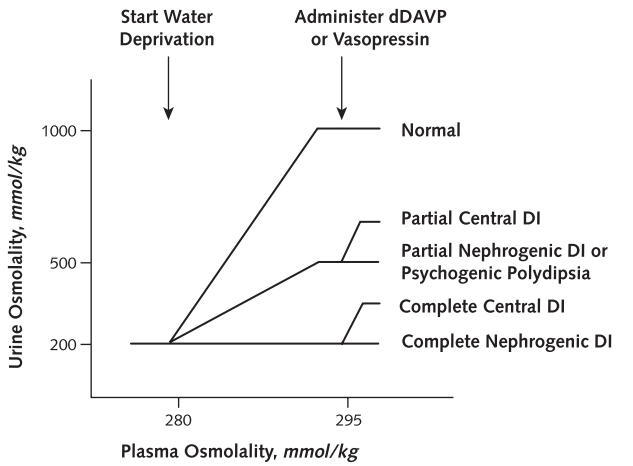
In healthy individuals, water deprivation increases plasma osmolality, which stimulates secretion of vasopressin by the posterior pituitary. This then acts on the kidney to increase urine osmolality to 1000 to 1200 mmol/kg and to restore plasma osmolality to normal levels. Administration of exogenous vasopressin does not increase urine osmolality further because it is already maximal in response to the individual's endogenous release of vasopressin. In patients with complete diabetes insipidus, water deprivation increases plasma osmolality but urine osmolality remains below 290 mmol/kg and does not increase. In those with complete central diabetes insipidus, urine osmolality will increase by approximately 200 mmol/kg in response to exogenous vasopressin. In contrast, vasopressin will not increase urine osmolality in patients with complete NDI. Patients with partial diabetes insipidus will have some increase in urine osmolality to 400 to 500 mmol/kg during water deprivation, levels that are well below those in healthy individuals. Administration of exogenous vasopressin will increase urine osmolality by approximately 200 mmol/kg in patients with partial central diabetes insipidus, but not in patients with partial NDI. A water deprivation study will not distinguish between patients with partial NDI and those with primary (psychogenic) polydipsia. Measuring urine volume during a water deprivation test is not useful.

It is useful to measure levels of plasma vasopressin in the differential diagnosis of polyuria. Patients with complete or partial central diabetes insipidus have levels of plasma vasopressin that are subnormal relative to plasma osmolality. In contrast, patients with complete or partial NDI or those with primary psychogenic polydipsia have elevated levels of plasma vasopressin (2).

Physiologic Principles Underlying NDI

During the past decade, our understanding of NDI has improved tremendously. The cloning of key genes led to advances in our knowledge of the cellular mechanisms involved in water reabsorption. Before the cloning of these key genes, it was known that water is reabsorbed across the collecting duct when it is stimulated by vasopressin (the collecting duct is impermeable to water in the absence of vasopressin) and when the kidney medulla is hypertonic. It was also known that the causes of NDI generally fall into 2 categories: defects in the ability of the collecting duct to respond to vasopressin and reabsorb water, and defects in the establishment of the medullary osmotic gradient needed to reabsorb water. However, the cellular mechanisms were not known, and it was not possible to screen individuals and families for disease-causing mutations, provide genetic counseling, and initiate appropriate therapy before the onset of clinical symptoms.

Figure 1. **Water deprivation test.**



The diagram shows the typical response after water deprivation in healthy individuals, in patients with complete or partial central diabetes insipidus (*DI*), in patients with complete or partial nephrogenic DI, and in patients with primary or psychogenic polydipsia. The 200 mmol/kg straight line is for schematic representation because patients with full phenotype (either central or nephrogenic DI) have a urine osmolality less than 100 mmol/kg. See text for additional details. dDAVP = desmopressin.

The ability to vary urine osmolality, and hence to vary water excretion, requires that the kidney be able to regulate water excretion independently of solute (primarily NaCl). The proximal tubule is responsible for reabsorbing large quantities of solute and water. This occurs isosmotically, so the proximal tubule cannot regulate water and solute reabsorption separately.

The portion of the kidney that is responsible for regulated water reabsorption is the collecting duct. Vasopressin is the key hormone regulating both the water permeability of the collecting duct and urine-concentrating ability. Vasopressin substantially increases permeability of the water in the collecting duct and, in the presence of a hypertonic medullary interstitium, increases water reabsorption (3). In the outer medulla, a hypertonic medulla is generated by active NaCl reabsorption from the thick ascending limb of the loop of Henle (**Figure 2**). This active NaCl reabsorption occurs through the Na-K-2Cl cotransporter (NKCC2/BSC1). Active NaCl reabsorption is crit-

Figure 2. **Urine-concentrating mechanism.**

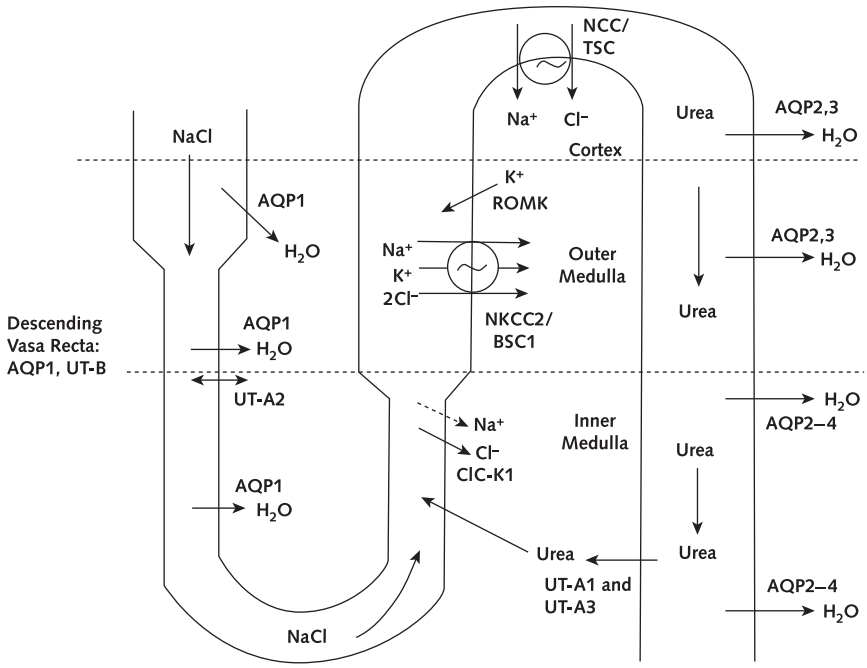


Diagram of the loop of Henle, distal tubule, and collecting duct showing the names and locations of the major transport proteins involved in the urine-concentrating mechanism. See text for additional details. AQP = aquaporin; ClC-K1 = chloride channel; NCC/TSC = Na-Cl cotransporter; NKCC2/BSC1 = Na-K-2Cl cotransporter; ROMK = renal outer medullary potassium channel; UT = urea transporter.

ical for establishing a hypertonic medullary interstitium and for delivering a dilute tubular fluid to the more distal nephron. Thus, inhibiting NKCC2/BSC1 with a loop diuretic interferes both with the ability to concentrate and to dilute the urine and results in isosmotic urine production.

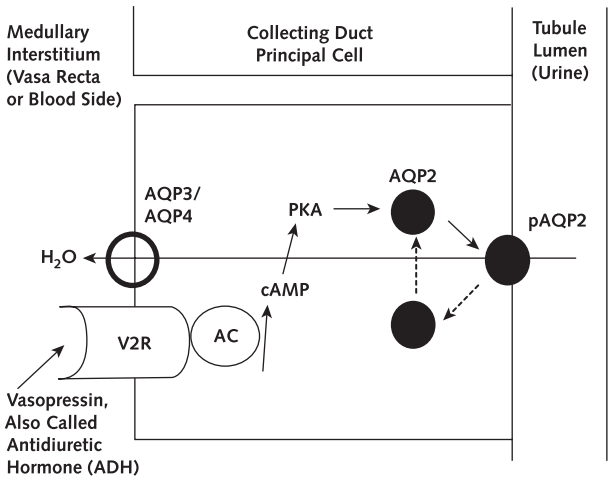
In the inner medulla, the most widely accepted mechanism for the production of concentrated urine is the passive reabsorption of NaCl in the thin ascending limb, driven by the chemical gradients for urea and NaCl between the thin ascending limb and the inner medullary interstitium (4, 5). The passive mechanism requires that the inner medullary interstitium have a high concentration of urea, and vasopressin stimulates urea reabsorption from the collecting duct into the inner medullary interstitium (6, 7). Thus, insufficient urea (as occurs in patients with protein malnutrition), genetic loss of urea transporters, or insensitivity of the collecting duct to vasopressin will reduce the interstitial concentration of urea, the concentrating ability of urine, and the ability to reabsorb water.

At the cellular level, water reabsorption occurs through principal cells in the collecting duct (8, 9). Vasopressin binds to type 2 vasopressin receptors (V2 receptors) in the basolateral membrane of principal cells (**Figure 3**). Activation of the V2 receptor results in the generation of cyclic adenosine monophosphatase (AMP) and activation of protein kinase A. Protein kinase A ultimately stimulates the insertion of aquaporin-2 (AQP2) water channels into the apical membrane of the collecting duct through pathways that are still being elucidated. Once AQP2 is inserted into the apical membrane, water molecules can enter the principal cell through AQP2. Water exits the principal cell through aquaporins 3 and 4 (AQP3 and AQP4) in the basolateral membrane, resulting in transcellular water reabsorption. When the stimulus for water reabsorption ends, AQP2 is removed from the apical membrane by endocytosis.

CONGENITAL NDI

Although acquired forms of NDI are more common in adults, we will first review the congenital causes of NDI because the mutations that cause it show the pathophysiologic principles involved in water reabsorption and establish the critical role of the V2 receptor, AQP2, and the urea transporter-B (UT-B). Most patients with congenital NDI (90%) have an X-linked pattern of inheritance; the remainder have either an autosomal recessive or dominant pattern of inheritance. With early detection (genetic diagnosis) and treatment of children born with NDI, most are now living to adulthood and will come under the care of internists. The clinical characteristics of NDI attributable to mutations in the V2 receptor or AQP2, regardless of the mode of inheritance or genetic mutation, include hypernatremia, hyperthermia, mental retardation, and repeated episodes of

Figure 3. **Water reabsorption in principal cells of the collecting duct.**



Vasopressin binds to the type 2 vasopressin receptor (*V2R*) on the basolateral membrane, activates adenylyl cyclase (*AC*), increases intracellular cyclic adenosine monophosphatase (*cAMP*), and stimulates protein kinase A (*PKA*) activity. Cytoplasmic vesicles carrying aquaporin (*AQP*) water channel proteins are inserted into the luminal membrane in response to vasopressin, thereby increasing the water permeability of this membrane. When vasopressin stimulation ends, water channels are retrieved by an endocytic process and water permeability returns to its low basal rate. The AQP3 and AQP4 water channels are expressed on the basolateral membrane and complete the transcellular pathway for water reabsorption. pAQP2 = phosphorylated aquaporin-2.

dehydration if patients cannot obtain enough water (10–12). Mutations in UT-B result in a very mild phenotype (1). In addition to congenital forms of NDI, there are congenital forms of central diabetes insipidus caused by mutations in the prepro-vasopressin-neurophysin II gene (13).

V2 Receptor Mutations

Mutations in the arginine vasopressin receptor 2 (*AVPR2*) gene that code for the V2 receptor are responsible for congenital NDI in approximately 90% of patients. This is an X-linked recessive mode of inheritance (the *AVPR2* gene is located in chromosome region Xq28), and the affected male patients do not concentrate their urine, even after the administration of exogenous vasopressin (14, 15). Heterozygous females have variable degrees of polyuria and polydipsia because of skewed X-chromosome inactivation (14). Mental retardation was prevalent in 70% to 90% of the patients reported in the original studies of NDI and was thought to be part of the disease (16–18). However, early recognition of NDI because of genetic screening in at-risk families and the subsequent treatment of congenital NDI with an abundant intake of water permit these children to have normal physical and mental development (14) and survive into adulthood. Thus, the mental retardation reported in the original studies probably resulted from repeated episodes of severe dehydration rather than from the genetic mutation. Currently, more than 180 putative disease-causing mutations in *AVPR2* in more than 280 families with a history of NDI have been identified (**Figure 4**).

In vitro studies show that most mutations in *AVPR2* result in V2 receptors that are trapped intracellularly and are unable to reach the plasma membrane (19, 20). A few mutated V2 receptors reach the cell surface, but they cannot bind vasopressin or properly trigger an increase in intracellular cyclic AMP (14). Of interest, nonpeptide V2 receptor antagonists were recently found to increase urine osmolality and to facilitate the folding of mutant V2 receptors in patients with several different mutations in the *AVPR2* gene (21). This finding is very important because it suggests that it may be possible to find pharmacologic agents that will enable mutant but partially functional V2 receptors to move to the membrane and restore partial vasopressin responsiveness and water reabsorption capability to the collecting duct.

Mutations in the *AQP2* Gene

Autosomal recessive or autosomal dominant modes of inheritance occur in approximately 10% of the families with congenital NDI who have been studied (14). These families generally have mutations in the *AQP2* gene (located in chromosome region 12q13), which codes for the vasopressin-sensitive AQP2 water channel. Currently, more than 30 putative disease-causing *AQP2* mutations in more than 40 families with a history of NDI have been identified (**Figure 5**). In vitro studies show that misrouting of mutant AQP2 proteins is the major mechanism underlying autosomal recessive NDI and that these mutant AQP2 proteins are retained within the endoplasmic retic-

Figure 4. **Type 2 vasopressin receptor.**

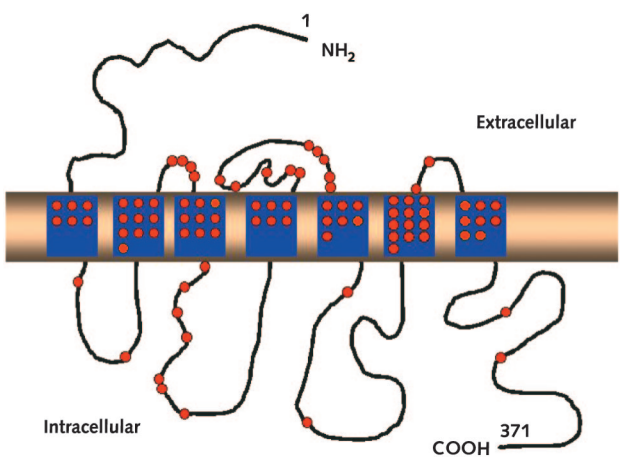


Diagram showing the type 2 vasopressin receptor (V2 receptor) protein and identifying putative disease-causing mutations in the arginine vasopressin receptor 2 gene (*circles*). Mutations are present in the extracellular, transmembrane, and cytoplasmic domains of the V2 receptor. The numbers 1 and 371 refer to amino acids 1 and 371, respectively. COOH = carboxy-terminus of the protein; NH_2 = amino-terminus of the protein.

Figure 5. **The aquaporin-2 protein.**

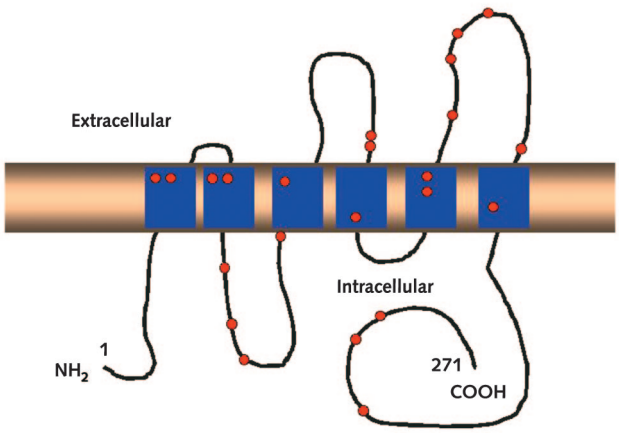


Diagram showing the aquaporin-2 (AQP2) protein and identifying putative disease-causing mutations in AQP2 (*circles*). Mutations are present in the extracellular, transmembrane, and cytoplasmic domains of AQP2. The numbers 1 and 271 refer to amino acids 1 and 271, respectively. COOH = carboxy-terminus of the protein; NH_2 = amino-terminus of the protein.

ulum (22–25). Autosomal dominant mutations in *AQP2* primarily result from mutations in the carboxy-terminus (19, 26–28).

Congenital Disorders Affecting the Generation of a Hypertonic Medulla

Polyuria can also occur in hereditary hypokalemic salt-losing tubulopathies, such as the Bartter syndrome, because mutations in thick ascending limb transport will result in an inability to generate the medullary osmotic gradient needed to reabsorb water. Patients with hypercalciuria and hyposthenuria or isosthenuria have been found to have mutations in *KCNJ1* (renal outer medullary potassium channel [ROMK]) and *SLC12A1* (NKCC2/BSC1). Patients with profound polyuria, hyponatremia, hypochloremia, metabolic alkalosis, and sensorineural deafness were found to have *BSND* mutations or to have a digenic defect in the *CLCNKA* and *CLCNKB* chloride channel genes (29, 30). For many of these patients with the Bartter syndrome, their mothers' pregnancies were complicated by polyhydramnios (31). The patient's polyuria can be quite severe (up to 7 mL/kg per hour) with maximal urine osmolality of less than 350 mmol/kg (32, 33). These observations show the critical importance of the proteins ROMK, NKCC2/BSC1, and Barttin to transport NaCl into the medullary interstitium and thereby generate, together with urea, a hypertonic milieu (**Figure 6**).

Polyuria, polydipsia, electrolyte imbalances, and dehydration also occur in cystinosis. The polyuria may be as mild as persistent enuresis but may also be severe enough to contribute to death from dehydration and electrolyte abnormalities in infants with cystinosis who have acute gastroenteritis.

Urea Transporters

Although most medical textbooks continue to state that urea is freely permeable across all cell membranes, its permeability across lipid bilayers is very low, as would be expected for a polar molecule (34). The permeability of urea is not 0, and it will diffuse across cell membranes and achieve equilibrium in the steady state given sufficient time. However, fluid traverses the collecting duct and erythrocytes traverse the vasa recta much too rapidly to permit urea concentrations to achieve equilibrium by diffusion alone (7, 35). The cloning of 2 urea transporter genes and several cDNA isoforms confirmed that these proteins exist (36–39).

Urea transporter-B is the erythrocyte-facilitated urea transporter, and the *SLC14A1* gene is located on chromosome 18q12 (40–42). The UT-B protein is also the Kidd (or Jk) antigen, a minor blood group antigen, and several mutations of this gene have been reported (40–44). People

Figure 6. **Thick ascending limb.**

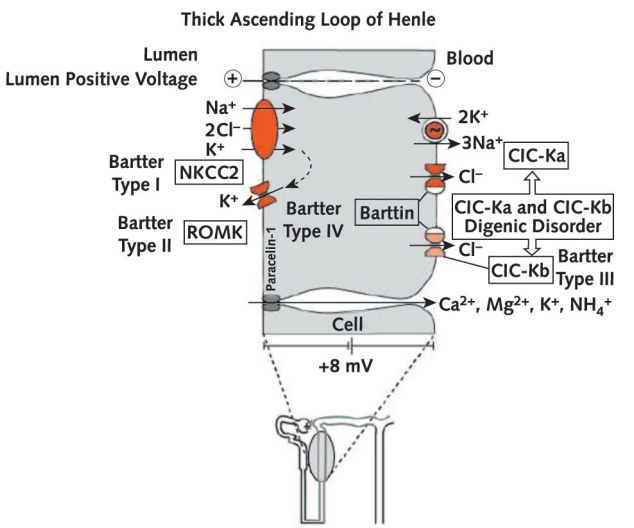


Diagram showing the transport pathways involved in transepithelial NaCl reabsorption in a thick ascending limb cell from the loop of Henle. The Bartter syndrome results from recessive mutations in the genes that encode the Na-K-2Cl cotransporter (*NKCC2/BSC1*), the renal outer medullary potassium channel (*ROMK*), the chloride channel (*ClC-Kb*), and Barttin; these are named types I to IV, respectively. A fifth type of the Bartter syndrome has recently been shown to be a digenic disorder that results from loss-of-function mutations in the genes that encode the ClC-Ka and ClC-Kb chloride channels. Normally, potassium is recycled back into the tubule lumen by ROMK, thereby maintaining a lumen-positive gradient that drives the paracellular reabsorption of calcium, magnesium, potassium, and ammonium. In addition, paracellin-1 is needed for the paracellular transport of calcium and magnesium. In the Bartter syndrome, regardless of subtype, a lumen-positive voltage cannot be generated, thereby preventing paracellular reabsorption of positively charged ions.

lacking the Kidd antigen have a mild form of partial congenital NDI; they cannot concentrate their urine above 800 mmol/kg, even after overnight water deprivation and administration of exogenous vasopressin (1). It is thought that UT-B is necessary for efficient countercurrent exchange between the ascending and descending vasa recta and that any decrease in countercurrent exchange reduces the concentrating ability of the urine (45–47).

The human urea transporter A (UT-A) gene (*SLC14A2*) is located on chromosome 18, adjacent to the UT-B gene (36–38). Currently, no mutations have been reported in any of the 6 UT-A protein isoforms. However, UT-A2 contains single nucleotide polymorphisms that are associated with variations in blood pressure in men but not in women (48). For a more detailed discussion of the physiologic regulation and molecular biology of urea transporters, the reader is referred to some recent reviews (36–39).

Role of the Practitioner in the Care of Adults with Congenital NDI

Now that most patients with congenital NDI are living to adulthood, internists will play an increasingly important role in their care. Unfortunately, the mainstay of therapy is for the patient to drink enough water to prevent dehydration. As these patients age, this becomes a more serious concern if they cannot sense thirst because of neurologic impairment or are physically unable to obtain water (for example, because of a broken hip). Because the kidney is unresponsive to vasopressin, there is no benefit to providing exogenous vasopressin. Patients with NDI may excrete up to 20 L of urine per day. Drinking and excreting this much fluid per day is challenging. These patients rarely sleep more than 1 to 2 hours at a time because of the need to urinate and drink. An extremely low-sodium diet ($<$ 500 mg/d) and a thiazide diuretic can be beneficial in decreasing urine volume. Indomethacin can also be beneficial but has serious gastrointestinal side effects. These patients can develop bladder dysfunction, which can lead to renal failure if unrecognized and untreated. Patients should have bladder and renal ultrasonography annually to ensure that bladder dysfunction is detected and renal dysfunction is prevented. The diagnosis of diabetes insipidus should be considered in any patient producing large quantities of dilute urine. If the family history is positive for polyuria, then the practitioner should consider the possibility of a congenital form of diabetes insipidus. The patient should be evaluated by using the water deprivation test and by measuring levels of plasma vasopressin (discussed previously) to determine whether the diabetes insipidus is central or nephrogenic. It is very important that any patient or family with suspected congenital NDI is referred for genetic testing, both to allow genetic counseling and to facilitate screening of any newborns shortly after birth. When NDI is detected early in infants and dehydration is avoided, these children do much better and do not develop mental retardation. Unfortunately, genetic testing for NDI is not routine. Information on genetic testing can be obtained from Dr. Bichet.

Causes of Acquired NDI

Lithium Therapy

Lithium is used to treat bipolar (manic-depressive) disorders and has become the most frequent cause of acquired NDI (49, 50). Nephrogenic diabetes insipidus occurs in approximately 55% of patients receiving long-term lithium therapy, and approximately 20% of patients produce more than 3 L of urine per day (51). Lithium causes NDI, at least in part, by inhibiting adenylyl cyclase in principal cells in the collecting duct (52, 53). However, the mechanism by which lithium inhibits adenylyl cyclase is not known. The lithium concentration in the urine of well-controlled patients receiving lithium therapy (10 to 40 mmol) is sufficient to inhibit adenylyl cyclase and reduce formation of cyclic AMP (52–54). Of interest, amiloride can reduce lithium uptake into principal cells in the collecting duct in patients receiving long-term lithium therapy, which could lessen the inhibitory effect of intracellular lithium on production of cyclic AMP and water reabsorption (55).

Lithium also causes NDI by reducing the protein abundances of AQP2, UT-A1, and UT-B, thereby reducing medullary interstitial osmolality (52, 56, 57). In the inner medullary membranes of rat kidneys, lithium causes marked downregulation of AQP2 protein abundance that is only partially reversed by discontinuation of lithium therapy, water restriction, or desmopressin treatment, consistent with the clinical observation of a slow recovery from lithium-induced NDI (56–58). Reducing AQP2 will decrease water reabsorption across the apical membrane in the collecting duct in response to vasopressin, thereby reducing transepithelial water reabsorption. Lithium also reduces UT-A1 protein abundance and interferes with the ability of vasopressin to phosphorylate UT-A1 (57). Reducing UT-A1 and phosphorylated UT-A1 will decrease vasopressin-stimulated urea reabsorption across the inner medullary collecting duct, thereby reducing the accumulation of inner medullary interstitial urea and urine-concentrating ability. Lithium also reduces UT-B protein in the inner medulla (57). Reducing UT-B will decrease urea recycling and the efficiency of countercurrent exchange, which will reduce the ability to concentrate urine. The effect of lithium on NKCC2/BSC1 is controversial because it increased it in 1 study (58) but not in another (59). Thus, lithium interferes with several components of the urine-concentrating mechanism and results in NDI. Lithium-induced NDI often becomes irreversible if it is not diagnosed quickly and if lithium therapy is not discontinued (49, 50). However, the mechanism by which lithium-induced NDI becomes irreversible is not known.

Other Causes

Hypercalcemia, hypokalemia, low-protein diets, and the release of ureteral obstruction are causes of acquired NDI. These acquired types are rarely as severe as congenital NDI but can result in urine outputs of 3 to 4 L/d. Hypercalcemia, hypokalemia, low-protein diets, and the release of bilateral or unilateral ureteral obstruction have been shown to downregulate the expression of AQP2 protein in the medulla of rat kidneys (60–66). Hypokalemia and release of a ureteral obstruction also reduce the abundances of UT-A1, UT-A3, and UT-B protein in the kidney medulla in rats (67, 68). Thus, these different causes of acquired NDI all result in downregulation of aquaporins and urea transporters, thereby interfering with the patient's ability to concentrate urine.

Aging

Normal aging results in a reduced maximal urine-concentrating ability in both people and rats (69–71). Kidneys from aged rats have reduced levels of aquaporins (AQP2, phosphorylated AQP2, and AQP3) and urea transporters (UT-A1, UT-A3, and UT-B) (72–74). Although aged rats have a normal ability to secrete vasopressin, they do not have an increase in AQP2 protein after water restriction (74–76), which suggests that normal aging results in partial NDI. However, a supraphysiologic dose of desmopressin increases urine osmolality and the abundances of AQP2, AQP3, UT-A1, and UT-B protein in aged rats (77), which is more consistent with partial central diabetes insipidus. Thus, the urine-concentrating defect in aging may be attributable to both partial nephrogenic and partial central diabetes insipidus.

SUMMARY

Nephrogenic diabetes insipidus is a relatively rare disorder in which the kidney is unresponsive to the water-retaining action of vasopressin. This can result from a genetic abnormality in any of the key components of cellular water reabsorption in the collecting duct or in the transporters involved in generating a hypertonic medulla. The most common abnormalities are mutations in the V2 receptor or the AQP2 water channel. Fortunately, early diagnosis and therapy to prevent dehydration permits children with NDI to develop without mental retardation and survive into adulthood. Practitioners who treat adults will need to follow bladder and renal function in these patients and provide genetic testing and counseling.

Adult patients can develop acquired NDI. The most common cause is lithium therapy for bipolar disorders. Other causes of acquired NDI are prolonged hypokalemia, hypercalcemia, protein malnourishment, and the release of bilateral or unilateral ureteral obstruction. In addition, normal aging can result in partial NDI.

The current therapeutic options are limited and are only partially beneficial. Exogenous vasopressin is ineffective because the kidney is insensitive to its actions. The most important therapy is ensuring adequate water intake. This is difficult at the extremes of age if the patient cannot sense thirst and obtain water. A very low-sodium diet, a thiazide diuretic, and indomethacin may partially decrease urine volume. In acquired NDI, treating or removing the underlying cause, if possible, is often beneficial. However, prolonged lithium therapy can lead to irreversible NDI, even after lithium therapy is withdrawn.

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