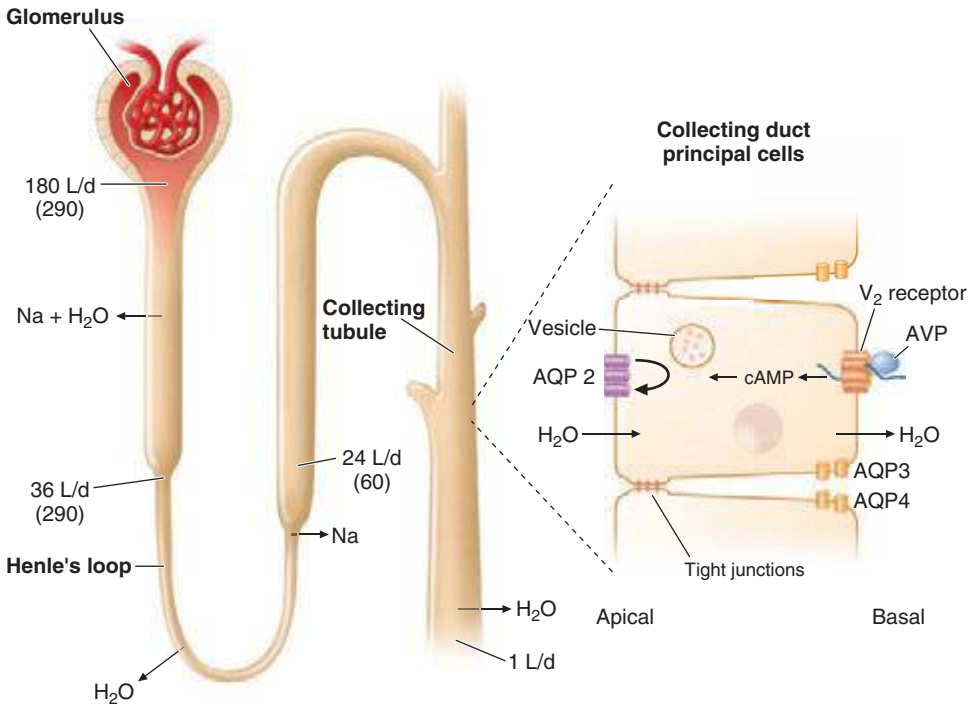

FIGURE 404-2 Antidiuretic effect of arginine vasopressin (AVP) in the regulation of urine volume. In a typical 70-kg adult, the kidney filters ~180 L/d of plasma. Of this, ~144 L (80%) is reabsorbed isosmotically in the proximal tubule and another 8 L (4–5%) is reabsorbed without solute in the descending limb of Henle's loop. The remainder is diluted to an osmolarity of ~60 mmol/kg by selective reabsorption of sodium and chloride in the ascending limb. In the absence of AVP, the urine issuing from the loop passes largely unmodified through the distal tubules and collecting ducts, resulting in a maximum water diuresis. In the presence of AVP, solute-free water is reabsorbed osmotically through the principal cells of the collecting ducts, resulting in the excretion of a much smaller volume of concentrated urine. This antidiuretic effect is mediated via a G protein–coupled V_2 receptor that increases intracellular cyclic AMP, thereby inducing translocation of aquaporin 2 (AQP 2) water channels into the apical membrane. The resultant increase in permeability permits an influx of water that diffuses out of the cell through AQP 3 and AQP 4 water channels on the basal-lateral surface. The net rate of flux across the cell is determined by the number of AQP 2 water channels in the apical membrane and the strength of the osmotic gradient between tubular fluid and the renal medulla. Tight junctions on the lateral surface of the cells serve to prevent unregulated water flow.

Five genetic forms of pituitary DI are now known. By far, the most common is transmitted in an autosomal dominant mode and is caused by diverse mutations in the coding region of one allele of the AVP–neurophysin II (or *AVP-NPII*) gene. All the mutations alter one or more amino acids known to be critical for correct processing and/or folding of the prohormone, thus interfering with its trafficking through the endoplasmic reticulum. The misfolded mutant precursor accumulates and interferes with production of AVP by the normal allele, eventually destroying the magnocellular neurons in which it is produced. The AVP deficiency and DI are usually not present at birth but develop gradually over a period of several months to years, progressing from partial to severe at different rates depending on the mutation. Once established, the deficiency of AVP is permanent, but for unknown reasons, the DI occasionally improves or remits spontaneously in late middle age. The parvocellular neurons that make AVP and the magnocellular neurons that make oxytocin appear to be unaffected. There are also rare autosomal recessive forms of pituitary DI. One is due to an inactivating mutation in the AVP portion of the gene; another is due to a large deletion involving the majority of the AVP gene and regulatory sequences in the intergenic region. A third form is caused by mutations of the *WFS 1* gene responsible for Wolfram's syndrome (DI, diabetes mellitus, optic atrophy, and neural deafness [DIDMOAD]). An X-linked recessive form linked to a region on Xq28 has also been described.

A primary deficiency of plasma AVP also can result from increased metabolism by an N-terminal aminopeptidase produced by the placenta. It is referred to as *gestational DI* because the signs and symptoms manifest during pregnancy and usually remit several weeks after delivery.

Secondary deficiencies of AVP secretion result from inhibition by excessive intake of fluids. They are referred to as *primary polydipsia* and can be divided into three subcategories. One of them, *dipsogenic DI*, is characterized by inappropriate thirst caused by a reduction in the set of the osmoregulatory mechanism. It sometimes occurs in association with multifocal diseases of the brain such as neurosarcoid, tuberculous meningitis, and multiple sclerosis but is often idiopathic. The second subtype, *psychogenic polydipsia*, is not associated with thirst, and the polydipsia seems to be a feature of psychosis or obsessive compulsive disorder. The third subtype, *iatrogenic polydipsia*, results from recommendations to increase fluid intake for its presumed health benefits.

Primary deficiencies in the antidiuretic action of AVP result in *nephrogenic DI*. The causes can be genetic, acquired, or drug induced (Table 404-1). The most common genetic form is transmitted in a semirecessive X-linked manner. It is caused by mutations in the coding region of the V_2 receptor gene that impair trafficking and/or ligand binding of the mutant receptor. There are also autosomal recessive or dominant forms of nephrogenic DI. They are caused by *AQP2* gene mutations that result in complete or partial defects in trafficking and function of the water channels that mediate antidiuresis in the distal and collecting tubules of the kidney.

Secondary deficiencies in the antidiuretic response to AVP result from polyuria per se. They are caused by washout of the medullary concentration gradient and/or suppression of aquaporin function. They usually resolve 24–48 h after the polyuria is corrected but can complicate interpretation of some acute tests used for differential diagnosis.

Pathophysiology In pituitary, gestational, or nephrogenic DI, the polyuria results in a small (1–2%) decrease in body water and a commensurate increase in plasma osmolarity and sodium that stimulates thirst and a compensatory increase in water intake. As a result, *hypernatremia and other overt physical or laboratory signs of dehydration do not develop unless the patient also has a defect in thirst or fails to increase fluid intake for some other reason.*