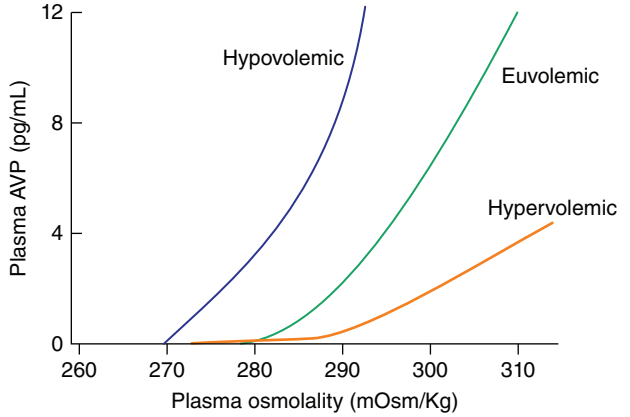


**FIGURE 63-1 Circulating levels of vasopressin (AVP) in response to changes in osmolality.** Plasma AVP becomes detectable in euvolemic, healthy individuals at a threshold of ~285 mOsm/kg, above which there is a linear relationship between osmolality and circulating AVP. The vasopressin response to osmolality is modulated strongly by volume status. The osmotic threshold is thus slightly lower in hypovolemia, with a steeper response curve; hypervolemia reduces the sensitivity of circulating AVP levels to osmolality.

the thick ascending limb of Henle and principal cells of the collecting duct (CD), increasing intracellular levels of cyclic AMP and activating protein kinase A (PKA)–dependent phosphorylation of multiple transport proteins. The AVP- and PKA-dependent activation of $Na^+$-$Cl^-$ and $K^+$ transport by the thick ascending limb of the loop of Henle (TALH) is a key participant in the countercurrent mechanism (Fig. 63-2). The countercurrent mechanism ultimately increases the interstitial osmolality in the inner medulla of the kidney, driving water absorption across the renal CD. However, water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (Fig. 63-2). Water transport across apical and basolateral aquaporin-1 water channels in the descending thin limb of the loop of Henle is thus involved, as is passive absorption of $Na^+$-$Cl^-$ by the thin ascending limb, via apical and basolateral CLC-K1 chloride channels and paracellular $Na^+$ transport. Renal urea transport in turn plays important roles in the generation of the medullary osmotic gradient and the ability to excrete solute-free water under conditions of both high and low protein intake (Fig. 63-2).

AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the CD, resulting in transepithelial water absorption down the medullary osmotic gradient (Fig. 63-3). Under "antidiuretic" conditions, with increased circulating AVP, the kidney reabsorbs water filtered by the glomerulus, equilibrating the osmolality across the CD epithelium to excrete a hypertonic, "concentrated" urine (osmolality of up to 1200 mOsm/kg). In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the CD is essentially abolished, resulting in secretion of a hypotonic, dilute urine (osmolality as low as 30–50 mOsm/kg). Abnormalities in this "final common pathway" are involved in most disorders of water homeostasis, e.g., a reduced or absent insertion of active aquaporin-2 water channels into the membrane of principal cells in diabetes insipidus.

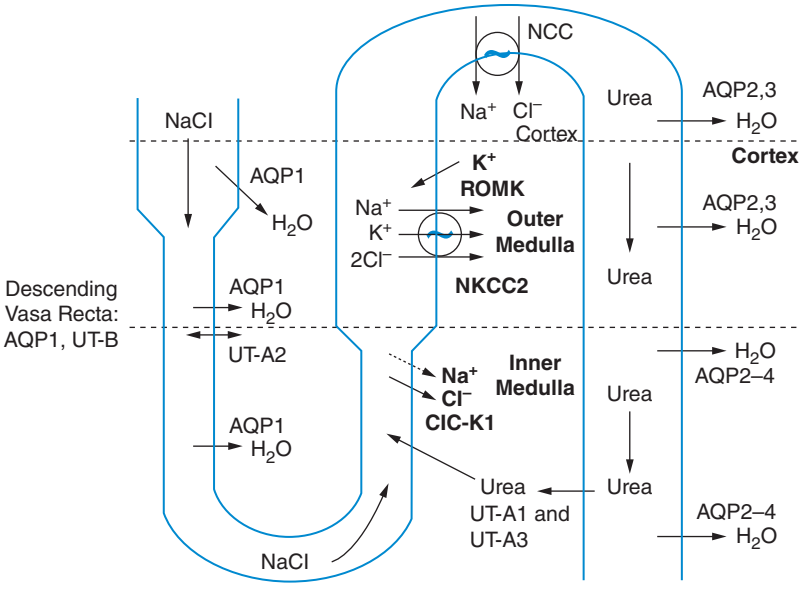


**FIGURE 63-2 The renal concentrating mechanism.** Water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (see text for details). Diagram showing the location of the major transport proteins involved; a loop of Henle is depicted on the *left*, collecting duct on the *right*. AQP, aquaporin; CLC-K1, chloride channel; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary $K^+$ channel; UT, urea transporter. *(Used with permission from JM Sands: Molecular approaches to urea transporters. J Am Soc Nephrol 13:2795, 2002.)*

**Maintenance of Arterial Circulatory Integrity** Sodium is actively pumped out of cells by the $Na^+/K^+$-ATPase membrane pump. In consequence, 85–90% of body $Na^+$ is extracellular, and the ECF volume (ECFV) is a function of total-body $Na^+$ content. Arterial perfusion and circulatory integrity are, in turn, determined by renal $Na^+$ retention or excretion, in addition to the modulation of systemic arterial resistance. Within the kidney, $Na^+$ is filtered by the glomeruli and then sequentially reabsorbed by the renal tubules. The $Na^+$ cation is typically reabsorbed with the chloride anion ($Cl^-$), and, thus, chloride homeostasis also affects the ECFV. On a quantitative level, at a glomerular filtration rate (GFR) of 180 L/d and serum $Na^+$ of ~140 m*M*, the kidney filters some 25,200 mmol/d of $Na^+$. This is equivalent to ~1.5 kg of salt, which would occupy roughly 10 times the extracellular space; 99.6% of filtered $Na^+$-$Cl^-$ must be reabsorbed to excrete 100 m*M* per day. Minute changes in renal $Na^+$-$Cl^-$ excretion will thus have significant effects on the ECFV, leading to edema syndromes or hypovolemia.

Approximately two-thirds of filtered $Na^+$-$Cl^-$ is reabsorbed by the renal proximal tubule, via both paracellular and transcellular mechanisms. The TALH subsequently reabsorbs another 25–30% of filtered $Na^+$-$Cl^-$ via the apical, furosemide-sensitive $Na^+$-$K^+$-$2Cl^-$ cotransporter. The adjacent aldosterone-sensitive distal nephron, comprising the distal convoluted tubule (DCT), connecting tubule (CNT), and CD, accomplishes the "fine-tuning" of renal $Na^+$-$Cl^-$ excretion. The thiazide-sensitive apical $Na^+$-$Cl^-$ cotransporter (NCC) reabsorbs 5–10% of filtered $Na^+$-$Cl^-$ in the DCT. Principal cells in the CNT and CD reabsorb $Na^+$ via electrogenic, amiloride-sensitive epithelial $Na^+$ channels (ENaC); $Cl^-$ ions are primarily reabsorbed by adjacent intercalated cells, via apical $Cl^-$ exchange ($Cl^-$-$OH^-$ and $Cl^-$-$HCO_3^-$ exchange, mediated by the SLC26A4 anion exchanger) (Fig. 63-4).

Renal tubular reabsorption of filtered $Na^+$-$Cl^-$ is regulated by multiple circulating and paracrine hormones, in addition to the activity of renal nerves. Angiotensin II activates proximal $Na^+$-$Cl^-$ reabsorption, as do adrenergic receptors under the influence of renal sympathetic innervation; locally generated dopamine, in contrast, has a *natriuretic* effect. Aldosterone primarily activates $Na^+$-$Cl^-$ reabsorption within the aldosterone-sensitive distal nephron. In particular, aldosterone activates the ENaC channel in principal cells, inducing $Na^+$ absorption and promoting $K^+$ excretion (Fig. 63-4).

Circulatory integrity is critical for the perfusion and function of vital organs. "Underfilling" of the arterial circulation is sensed by ventricular and vascular pressure receptors, resulting in a neurohumoral activation (increased sympathetic tone, activation of the