



FIGURE 332e-4 Determinants of sodium and water balance. **A.** Plasma Na⁺ concentration is a surrogate marker for plasma tonicity, the volume behavior of cells in a solution. Tonicity is determined by the number of effective osmoles in the body divided by the total body H₂O (TB H₂O), which translates simply into the total body Na (TB Na⁺) and anions outside the cell separated from the total body K (TB K⁺) inside the cell by the cell membrane. Net water balance is determined by the integrated functions of thirst, osmoreception, Na reabsorption, vasopressin release, and the strength of the medullary gradient in the kidney, keeping tonicity within a narrow range of osmolality around 280 mosmol/L. When water metabolism is disturbed and total body water increases, hyponatremia, hypotonicity, and water intoxication occur; when total body water decreases, hypernatremia, hypertonicity, and dehydration occur. **B.** Extracellular blood volume and pressure are an integrated function of total body Na⁺ (TB Na⁺), total body H₂O (TB H₂O), vascular tone, heart rate, and stroke volume that modulates volume and pressure in the vascular tree of the body. This extracellular blood volume is determined by net Na balance under the control of taste, baroreception, habit, Na⁺ reabsorption, macula densa/tubuloglomerular feedback, and natriuretic peptides. When Na⁺ metabolism is disturbed and total body Na⁺ increases, edema occurs; when total body Na⁺ is decreased, volume depletion occurs. ADH, antidiuretic hormone; AQP2, aquaporin-2.

connectivity and adjacency to a minimal blood-brain barrier, modulate the downstream release of vasopressin by the posterior lobe of the pituitary gland. Secretion is stimulated primarily by changing tonicity and secondarily by other nonosmotic signals such as variable blood volume, stress, pain, nausea, and some drugs. The release of vasopressin by the posterior pituitary increases linearly as plasma tonicity rises above normal, although this varies, depending on the perception of extracellular volume (one form of cross-talk between mechanisms that adjudicate blood volume and osmoregulation). Changing the intake or excretion of water provides a means for adjusting plasma tonicity; thus, osmoregulation governs water balance.

The kidneys play a vital role in maintaining water balance through the regulation of renal water excretion. The ability to concentrate urine to an osmolality exceeding that of plasma enables water conservation, whereas the ability to produce urine more dilute than plasma promotes excretion of excess water. For water to enter or exit a cell, the cell membrane must express aquaporins. In the kidney, aquaporin-1 is constitutively active in all water-permeable segments of the proximal and distal tubules, whereas vasopressin-regulated aquaporin-2, -3, and -4 in the inner medullary collecting duct promote rapid water permeability. Net water reabsorption is ultimately driven by the osmotic gradient between dilute tubular fluid and a hypertonic medullary interstitium.

SODIUM BALANCE

The perception of *extracellular blood volume* is determined, in part, by the integration of arterial tone, cardiac stroke volume, heart rate, and the water and solute content of extracellular fluid. Na⁺ and accompanying anions are the most abundant extracellular effective osmoles and together support a blood volume around which pressure is generated. Under normal conditions, this volume is regulated by sodium balance (Fig. 332e-4B), and the balance between daily Na⁺ intake and excretion is under the influence of *baroreceptors* in regional blood vessels and vascular hormone sensors modulated by atrial natriuretic peptides, the renin-angiotensin-aldosterone system, Ca²⁺ signaling, adenosine, vasopressin, and the neural adrenergic axis. If Na⁺ intake exceeds Na⁺ excretion (positive Na⁺ balance), then an increase in blood volume will trigger a proportional increase in urinary Na⁺ excretion. Conversely, when Na⁺ intake is less than urinary excretion (negative Na⁺ balance), blood volume will decrease and trigger enhanced renal Na⁺ reabsorption, leading to decreased urinary Na⁺ excretion.

The renin-angiotensin-aldosterone system is the best-understood hormonal system modulating renal Na⁺ excretion. Renin is synthesized and secreted by granular cells in the wall of the afferent arteriole. Its secretion is controlled by several factors, including β₁-adrenergic