

FIGURE 2-10

Mechanism of aldosterone action in the distal nephron [19]. Aldosterone, the predominant human mineralocorticoid hormone, enters distal nephron cells through the plasma membrane and interacts with its receptor (the mineralocorticoid receptor [MR], or Type I receptor). Interaction between aldosterone and this receptor initiates induction of new proteins that, by way of mechanisms that remain unclear, increase the number of sodium channels (ENaC) and sodium-potassium adenosine triphosphatase (Na-K ATPase) pumps at the cell surface. This increases transepithelial Na (and potassium) transport. Cortisol, the predominant human glucocorticoid hormone, also enters cells through the plasma membrane and interacts with its receptor (the glucocorticoid receptor [GR]). Cortisol, however, also interacts with mineralocorticoid receptors; the affinity of cortisol and aldosterone for mineralocorticoid receptors is approximately equal. In distal nephron cells, this interaction also stimulates electrogenic Na transport [20]. Cortisol normally circulates at concentrations 100 to 1000 times higher than the circulating concentration of aldosterone. In aldosterone-responsive tissues, such as the distal nephron, expression of the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) permits rapid metabolism of cortisol so that only aldosterone can stimulate Na transport in these cells. An inherited deficiency of the enzyme 11 β -HSD (the syndrome of apparent mineralocorticoid excess, AME), or inhibition of the enzyme by ingestion of licorice, leads to hypertension owing to chronic stimulation of distal Na transport by endogenous glucocorticoids [21].

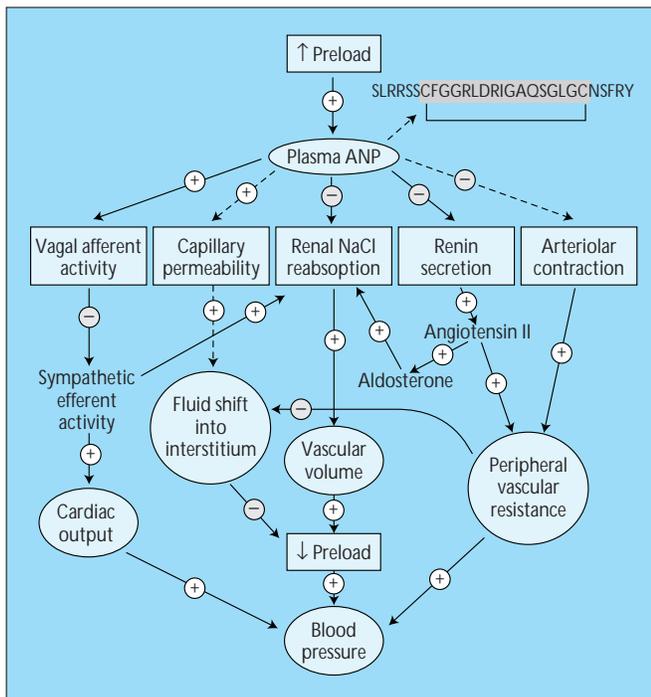


FIGURE 2-11

Control of systemic hemodynamics by the atrial natriuretic peptide (ANP) system. Increases in atrial stretch (PRELOAD) increase ANP secretion by cardiac atria. The primary amino acid sequence of ANP is shown in single letter code with its disulfide bond indicated by the lines. The amino acids highlighted in blue are conserved between ANP, brain natriuretic peptide, and C-type natriuretic peptide. ANP has diverse functions that include but are not limited to the following: stimulating vagal afferent activity, increasing capillary permeability, inhibiting renal sodium (Na) and water reabsorption, inhibiting renin release, and inhibiting arteriolar contraction. These effects reduce sympathetic nervous activity, reduce angiotensin II generation, reduce aldosterone secretion, reduce total peripheral resistance, and shift fluid out of the vasculature into the interstitium. The net effect of these actions is to decrease cardiac output, vascular volume, and peripheral resistance, thereby returning preload toward baseline. Many effects of ANP (indicated by solid arrows) are diminished in patients with edematous disorders (there is an apparent resistance to ANP). Effects indicated by dashed arrows may not be diminished in edematous disorders; these effects contribute to shifting fluid from vascular to extravascular tissue, leading to edema. This observation may help explain the association between elevated right-sided filling pressures and the tendency for Na retention [22]. (Modified from Brenner and coworkers [23].)

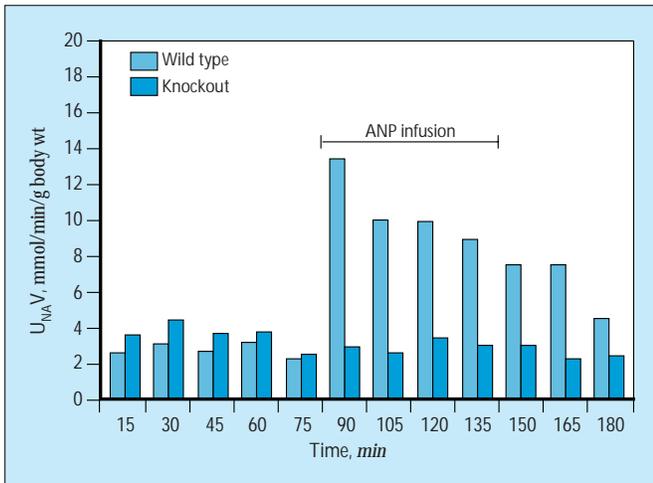


FIGURE 2-12

Mechanism of atrial natriuretic peptide (ANP) action on the kidney. Animals with disruption of the particulate form of guanylyl cyclase (GC) manifest increased mean arterial pressure that is independent of dietary intake of sodium chloride. To test whether ANP mediates its renal effects by way of the action of GC, ANP was infused into wild-type and GC-A-deficient mice. In wild-type animals, ANP led to prompt natriuresis. In GC-A-deficient mice, no effect was observed. $U_{Na}V$ —urinary sodium excretion volume. (Modified from Kishimoto [24].)

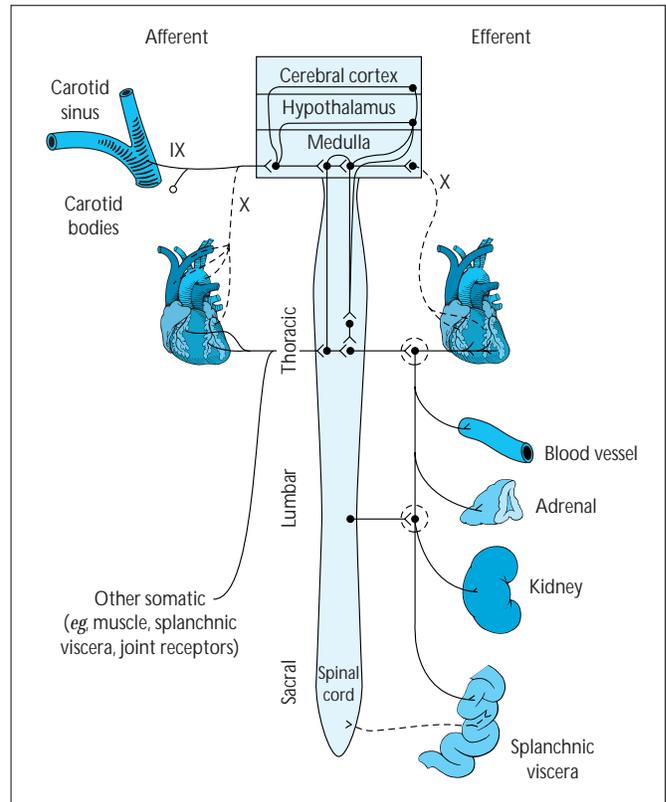


FIGURE 2-13

Schematic diagram of neural connections important in circulatory control. Although the system is bilaterally symmetric, afferent fibers are shown to the left and efferent fibers to the right. Sympathetic fibers are shown as solid lines and parasympathetic fibers as dashed lines. The heart receives both sympathetic and parasympathetic innervation. Sympathetic fibers lead to vasoconstriction and renal sodium chloride retention. X indicates the vagus nerve; IX indicates glossopharyngeal. (From Korner [25]; with permission.)

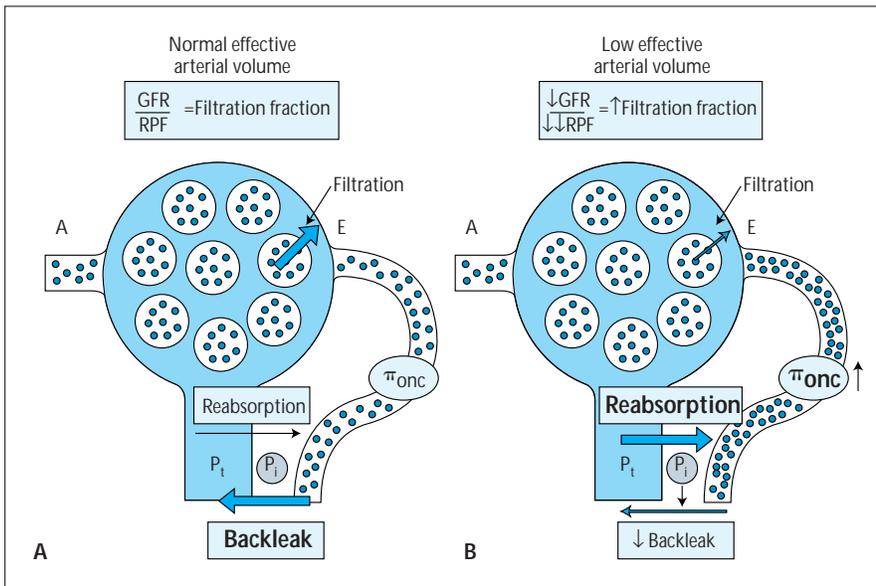


FIGURE 2-14

Cellular mechanisms of increased solute and water reabsorption by the proximal tubule in patients with “effective” arterial volume depletion. **A**, Normal effective arterial volume in normal persons. **B**, Low effective arterial volume in patients with both decreased glomerular filtration rates (GFR) and renal plasma flow (RPF). In contrast to normal persons, patients with low effective arterial volume have decreased GFR and RPF, yet the filtration fraction is increased because the RPF decreases more than does the GFR. The increased filtration fraction concentrates the plasma protein (indicated by the dots) in the peritubular capillaries leading to increased plasma oncotic pressure (π_{onc}). Increased plasma oncotic pressure reduces the amount of backleak from the peritubular capillaries. Simultaneously, the increase in filtration fraction reduces volume delivery to the

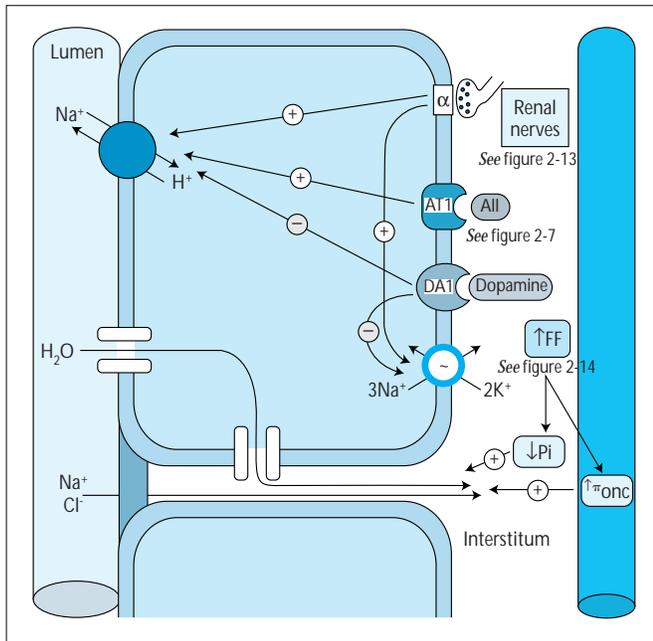
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FIGURE 2-14 (continued)

peritubular capillary, decreasing its hydrostatic pressure, and thereby reducing the renal interstitial hydrostatic pressure (P_i). Even though the proximal tubule hydrostatic pressure (P_t) may be

reduced, owing to diminished GFR, the hydrostatic gradient from tubule to interstitium is increased, favoring increased volume reabsorption. A—afferent arteriole; E—efferent arteriole.

Mechanisms of Sodium and Chloride Transport along the Nephron

**FIGURE 2-15**

Cellular mechanisms and regulation of sodium chloride (NaCl) and volume reabsorption along the proximal tubule. The sodium-potassium adenosine triphosphate (Na-K ATPase) pump (shown as white circle with light blue outline) at the basolateral cell membrane keeps the intracellular Na concentration low; the K concentration high; and the cell membrane voltage oriented with the cell interior negative, relative to the exterior. Many pathways participate in Na entry across the luminal membrane. Only the sodium-hydrogen (Na-H) exchanger is shown because its regulation in states of volume excess and depletion has been characterized extensively. Activity of the Na-H exchanger is increased by stimulation of renal nerves, acting by way of α receptors and by increased levels of circulating angiotensin II (AII), as shown in Figures 2-7 and 2-13 [25–28]. Increased levels of dopamine (DA1) act to inhibit activity of the Na-H exchanger [29,30]. Dopamine also acts to inhibit activity of the Na-K ATPase pump at the basolateral cell membrane [30]. As described in Figure 2-14, increases in the filtration fraction (FF) lead to increases in oncotic pressure (π_{onc}) in peritubular capillaries and decreases in peritubular and interstitial hydrostatic pressure (P_i). These changes increase solute and volume absorption and decrease solute backflux. Water flows through water channels (Aquaporin-1) Na and Cl also traverse the paracellular pathway.