FIGURE 2-4

Schema for the kidney blood volume pressure feedback mechanism adapted from the work of Guyton and colleagues [6]. Positive relations are indicated by a plus sign; inverse relations are indicated by a minus sign. The block diagram shows that increases in extracellular fluid (ECF) volume result from increases in sodium chloride (NaCl) and fluid intake or decreases in kidney volume output. An increase in ECF volume increases the blood volume, thereby increasing the venous return to the heart and cardiac output. Increases in cardiac output increase arterial pressure both directly and by increasing peripheral vascular resistance (autoregulation). Increased arterial pressure is sensed by the kidney, leading to increased kidney volume output (pressure diuresis and pressure natriuresis), and thus returning the ECF volume to normal. The inset shows this relation between mean arterial pressure (MAP), renal volume, and sodium excretion [4]. The effects of acute increases in arterial pressure on urinary excretion are shown by the solid curve. The chronic effects are shown by the dotted curve; note that the dotted line is identical to the curve in Figure 2-3. Thus, when the MAP increases, urinary output increases, leading to decreased ECF volume and return to the original pressure set point. $U_{Na}V$—urinary sodium excretion volume.
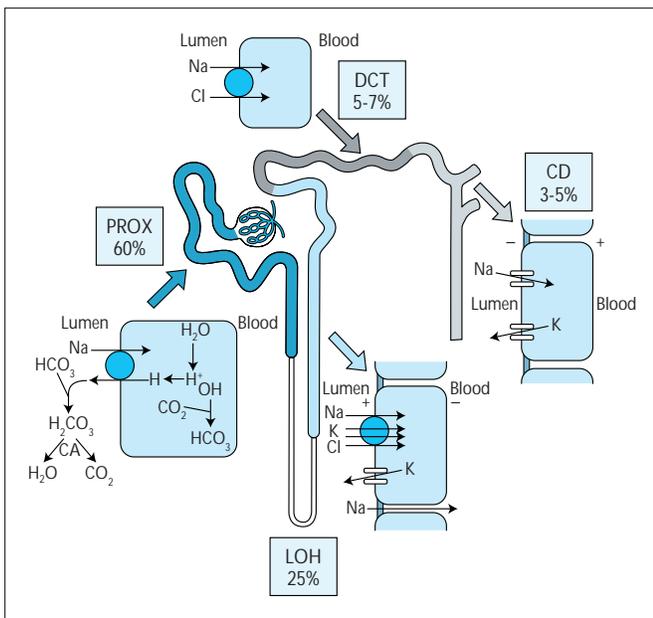

FIGURE 2-5

Sodium (Na) reabsorption along the mammalian nephron. About 25 moles of Na in 180 L of fluid daily is delivered into the glomerular filtrate of a normal person. About 60% of this load is reabsorbed along the proximal tubule (PROX), indicated in dark blue; about 25% along the loop of Henle (LOH), including the thick ascending limb indicated in light blue; about 5% to 7% along the distal convoluted tubule (DCT), indicated in dark gray; and 3% to 5% along the collecting duct (CD) system, indicated in light gray. All Na transporting cells along the nephron express the ouabain-inhibitable sodium-potassium adenosine triphosphatase (Na-K ATPase) pump at their basolateral (blood) cell surface. (The pump is not shown here for clarity.) Unique pathways are expressed at the luminal membrane that permit Na to enter cells. The most quantitatively important of these luminal Na entry pathways are shown here. These pathways are discussed in more detail in Figures 2-15 to 2-19. CA—carbonic anhydrase; Cl—chloride; CO_2—carbon dioxide; H—hydrogen; H_2CO_3—carbonic acid; HCO_3—bicarbonate; K—potassium; OH—hydroxyl ion.

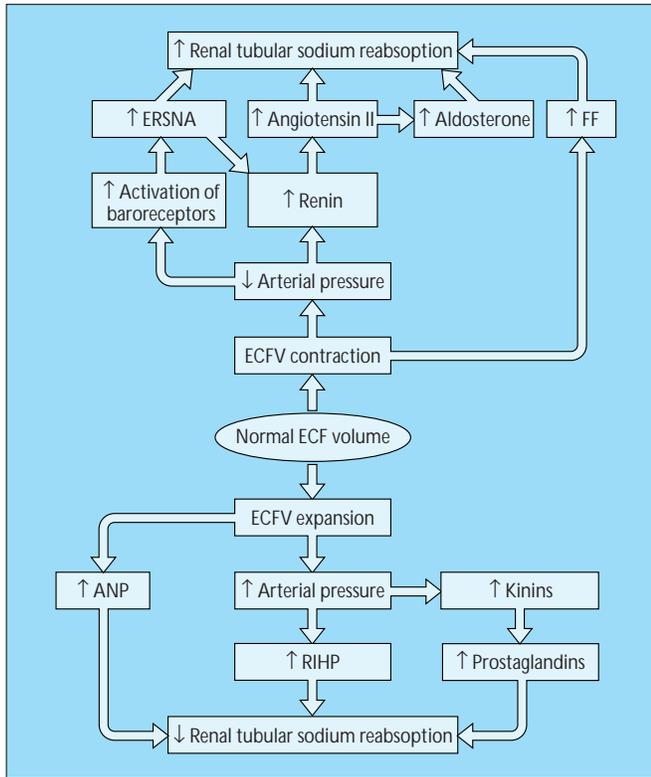# Mechanisms of Extracellular Fluid Volume Control

FIGURE 2-6

Integrated response of the kidneys to changes in extracellular fluid (ECF) volume. This composite figure illustrates natriuretic and antinatriuretic mechanisms. For simplicity, the systems are shown operating only in one direction and not all pathways are shown. The major antinatriuretic systems are the renin-angiotensin-aldosterone axis and increased efferent renal sympathetic nerve activity (ERSNA). The most important natriuretic mechanism is pressure natriuresis, because the level of renal perfusion pressure (RPP) determines the magnitude of the response to all other natriuretic systems. Renal interstitial hydrostatic pressure (RIHP) is a link between the circulation and renal tubular sodium reabsorption. Atrial natriuretic peptide (ANP) is the major systemic natriuretic hormone. Within the kidney, kinins and renomedullary prostaglandins are important modulators of the natriuretic response of the kidney. AVP—arginine vasopressin; FF—filtration fraction. (*Modified from* Gonzalez-Campoy and Knox [7].)
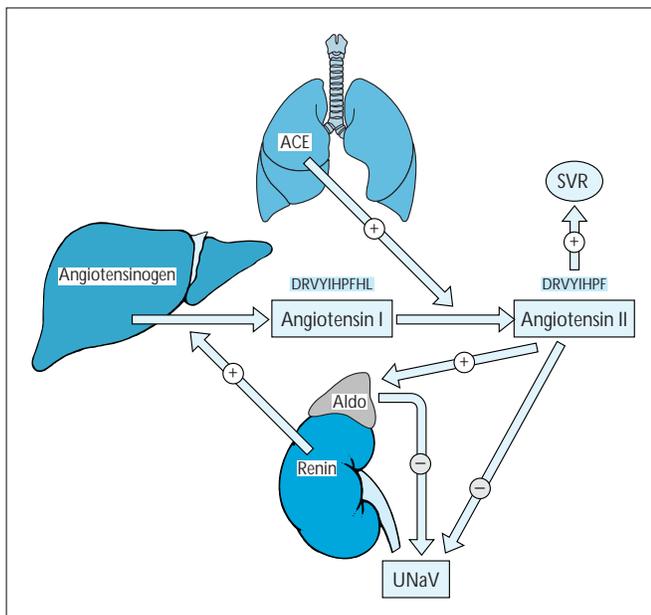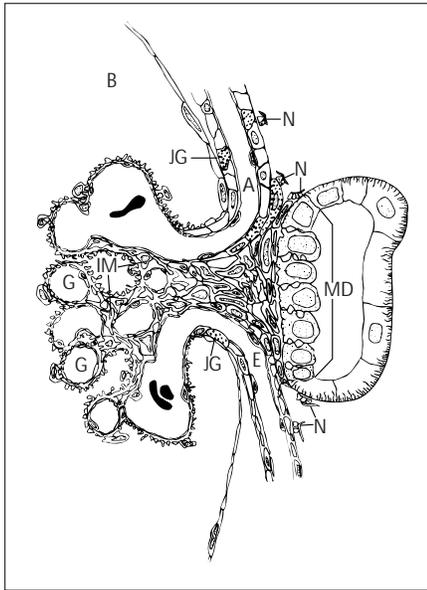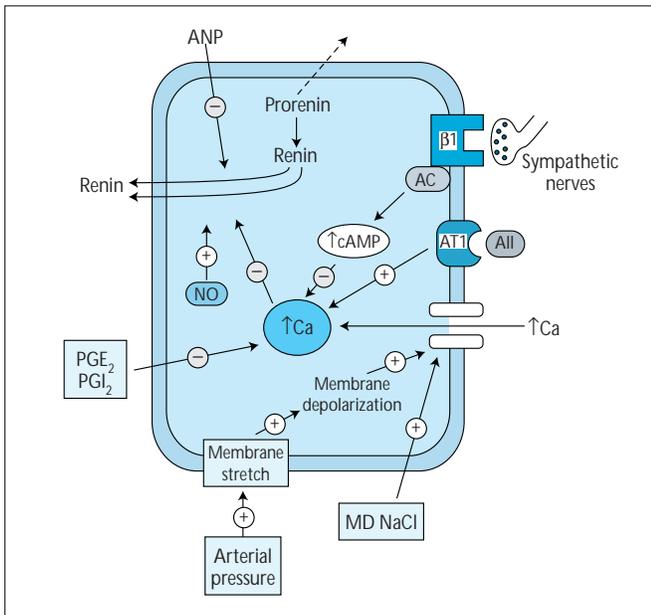

FIGURE 2-7

Overview of the renin-angiotensin-aldosterone system [8,9]. Angiotensinogen (or renin substrate) is a 56-kD glycoprotein produced and secreted by the liver. Renin is produced by the juxtaglomerular apparatus of the kidney, as shown in Figures 2-8 and 2-9. Renin cleaves the 10 N-terminal amino acids from angiotensinogen. This decapeptide (angiotensin I) is cleaved by angiotensin converting enzyme (ACE). The resulting angiotensin II comprises the 8 N-terminal amino acids of angiotensin I. The primary amino acid structures of angiotensins I and II are shown in single letter codes. Angiotensin II increases systemic vascular resistance (SVR), stimulates aldosterone secretion from the adrenal gland (indicated in gray), and increases sodium (Na) absorption by renal tubules, as shown in Figures 2-15 and 2-17. These effects decrease urinary Na (and chloride excretion; $U_{Na}V$).

The juxtaglomerular (JG) apparatus. This apparatus brings into close apposition the afferent (A) and efferent (E) arterioles with the macula densa (MD), a specialized region of the thick ascending limb (TAL). The extraglomerular mesangium (EM), or lacis "Goormaghtigh apparatus (cells)," forms at the interface of these components. MD cells express the Na-K-2Cl (sodium-potassium-chloride) cotransporter (NKCC2) at the apical membrane [10,11]. By way of the action of this transporter, MD cells sense the sodium chloride concentration of luminal fluid. By way of mechanisms that are unclear, this message is communicated to JG cells located in and near the arterioles (especially the afferent arteriole). These JG cells increase renin secretion when the NaCl concentration in the lumen is low [12]. Cells in the afferent arteriole also sense vascular pressure directly, by way of the mechanisms discussed in Figure 2-9. Both the vascular and tubular components are innervated by sympathetic nerves (N). B—Bowman's space, G—glomerular capillary; IM—intraglomerular mesangium. (*From* Barajas [13]; with permission.)

Schematic view of a (granular) juxtaglomerular cell showing secretion mechanisms of renin [8]. Renin is generated from prorenin. Renin secretion is inhibited by increases in and stimulated by decreases in intracellular calcium (Ca) concentrations. Voltage-sensitive Ca channels in the plasma membrane are activated by membrane stretch, which correlates with arterial pressure and is assumed to mediate baroreceptor-sensitive renin secretion. Renin secretion is also stimulated when the concentration of sodium (Na) and chloride (Cl) at the macula densa (MD) decreases [12,14]. The mediators of this effect are less well characterized; however, some studies suggest that the effect of Na and Cl in the lumen is more potent than is the baroreceptor mechanism [15]. Many other factors affect rates of renin release and contribute to the physiologic regulation of renin. Renal nerves, by way of β receptors coupled to adenylyl cyclase (AC), stimulate renin release by increasing the production of cyclic adenosine monophosphate (cAMP), which reduces Ca release. Angiotensin II (AII) receptors (AT1 receptors) inhibit renin release, as least in vitro. Prostaglandins E_2 and I_2 (PGE_2 and PGI_2, respectively) strongly stimulate renin release through mechanisms that remain unclear. Atrial natriuretic peptide (ANP) strongly inhibits renin secretion. Constitutive nitric oxide (NO) synthase is expressed by macula densa (MD) cells [16]. NO appears to stimulate renin secretion, an effect that may counteract inhibition of the renin gene by AII [17,18].