The Kidney in Blood Pressure Regulation

L. Gabriel Navar
L. Lee Hamm

Despite extensive animal and clinical experimentation, the mechanisms responsible for the normal regulation of arterial pressure and development of essential or primary hypertension remain unclear. One basic concept was championed by Guyton and other authors [1–4]: the long-term regulation of arterial pressure is intimately linked to the ability of the kidneys to excrete sufficient sodium chloride to maintain normal sodium balance, extracellular fluid volume, and blood volume at normotensive arterial pressures. Therefore, it is not surprising that renal disease is the most common cause of secondary hypertension. Furthermore, derangements in renal function from subtle to overt are probably involved in the pathogenesis of most if not all cases of essential hypertension [5]. Evidence of generalized microvascular disease may be causative of both hypertension and progressive renal insufficiency [5,6]. The interactions are complex because the kidneys are a major target for the detrimental consequences of uncontrolled hypertension. When hypertension is left untreated, positive feedback interactions may occur that lead progressively to greater hypertension and additional renal injury. These interactions culminate in malignant hypertension, stroke, other sequelae, and death [7].

In normal persons, an increased intake of sodium chloride leads to appropriate adjustments in the activity of various humoral, neural, and paracrine mechanisms. These mechanisms alter systemic and renal hemodynamics and increase sodium excretion without increasing arterial pressure [3,8]. Regardless of the initiating factor, decreases in sodium excretory capability in the face of normal or increased sodium intake lead to chronic increases in extracellular fluid volume and blood volume. These increases can result in hypertension. When the derangements also include increased levels of humoral or neural factors that directly cause vascular smooth muscle constriction, these effects increase peripheral vascular resistance or decrease vascular capacitance. Under these conditions the effects of subtle increases in blood volume are compounded because of increases in the blood volume relative to

CHAPTER 1

the capacitance, often referred to as the *effective* blood volume. Through the mechanism of pressure natriuresis, however, the increases in arterial pressure increase renal sodium excretion, allowing restoration of sodium balance but at the expense of persistent elevations in arterial pressure [9]. In support of this overall concept, various studies have demonstrated strong relationships between kidney disease and the incidence of hypertension. In addition, transplantation studies have shown that normotensive recipients from genetically hypertensive donors have a higher likelihood of developing hypertension after transplantation [10].

This unifying concept has helped delineate the cardinal role of the kidneys in the normal regulation of arterial pressure as well as in the pathophysiology of hypertension. Many different extrinsic influences and intrarenal derangements can lead to reduced sodium excretory capability. Many factors also exist that alter cardiac output, total peripheral resistance, and cardiovascular capacitance. Accordingly, hypertension is a multifactorial dysfunctional process that can be caused by a myriad of different conditions. These conditions range from stimulatory influences that inappropriately enhance tubular sodium reabsorption to overt renal pathology, involving severe reductions in filtering capacity by the renal glomeruli and associated marked reductions in sodium excretory capability. An understanding of the normal mechanisms regulating sodium balance and how derangements lead to altered sodium homeostasis and hypertension provides the basis for a rational approach to the treatment of hypertension.

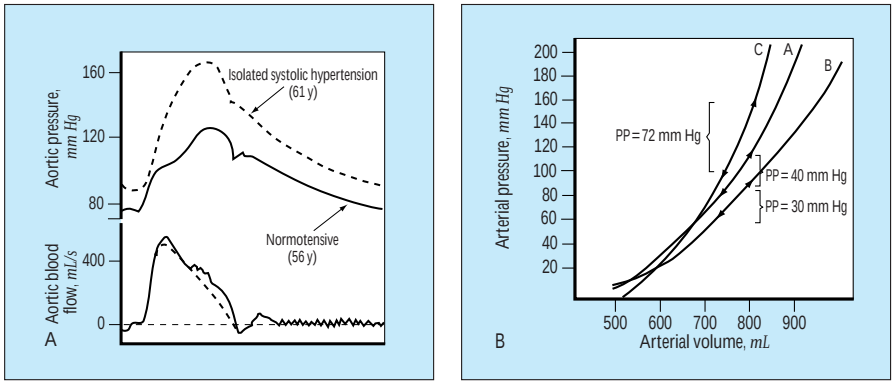


FIGURE 1-1

Aortic distensibility. The cyclical pumping nature of the heart places a heavy demand on the distensible characteristics of the aortic tree. **A**, During systole, the aortic tree is rapidly filled in a fraction of a second, distending it and increasing the hydraulic pressure. **B**, The distensibility characteristics of the arterial tree determine the pulse pressure (PP) in response to a specific stroke volume. The normal relationship is shown in *curve A*, and arrows designate the PP. A highly distensible arterial tree, as depicted in *curve B*, can accommodate the stroke volume with a smaller PP. Pathophysiologic processes and aging lead to decreases in aortic distensibility. These decreases lead to marked increases in PP and overall mean arterial pressure for any given arterial volume, as shown in *curve C*. Decreased distensibility is partly responsible for the isolated systolic hypertension often found in elderly persons. Recordings of actual aortic pressure and flow profiles in persons with normotension and systolic hypertension are shown in *panel A* [11,12]. (Panel B *Adapted from* Vari and Navar [4] and Panel A from Nichols *et al*. [12].)

HEMODYNAMIC DETERMINANTS

For any vascular bed:

$$\text{Blood flow} = \frac{\text{Arterial pressure gradient}}{\text{Vascular resistance}}$$

For total circulation averaged over time:

Blood flow = cardiac output

Therefore,

$$\text{Cardiac output} = \frac{\text{Arterial pressure - right atrial pressure}}{\text{Total peripheral resistance}}$$

and:

Mean arterial pressure = Cardiac output × total peripheral resistance

FIGURE 1-2

Hemodynamic determinants of arterial pressure. During the diastolic phase of the cardiac cycle, the elastic recoil characteristics of the arterial tree provide the kinetic energy that allows a continuous delivery of blood flow to the tissues. Blood flow is dependent on the arterial pressure gradient and total peripheral resistance. Under normal conditions the right atrial pressure is near zero, and thus the arterial pressure is the pressure gradient. These relationships apply for any instant in time and to time-integrated averages when the mean pressure is used. The time-integrated average blood flow is the cardiac output that is normally 5 to 6 L/min for an adult of average weight (70 to 75 kg).

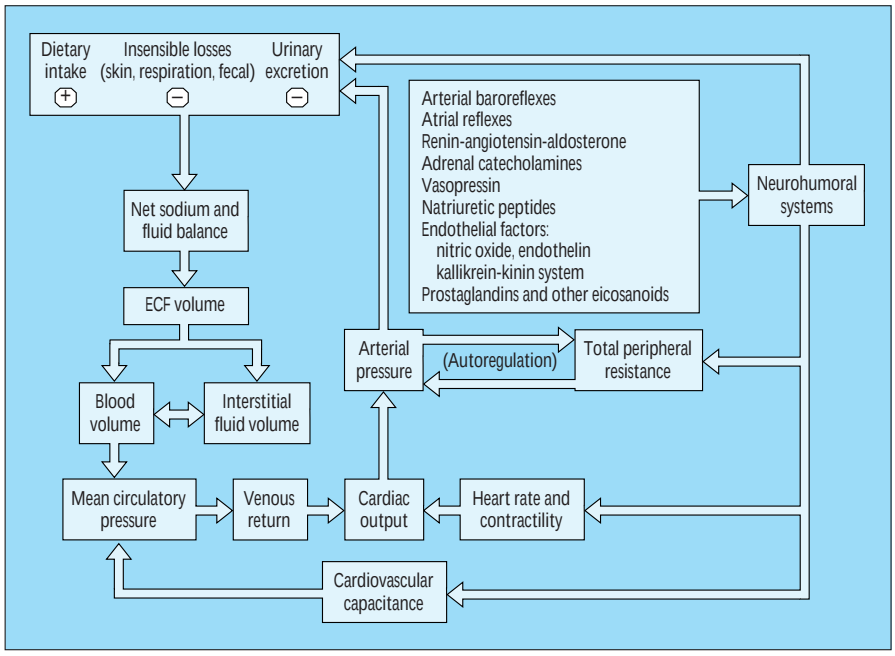
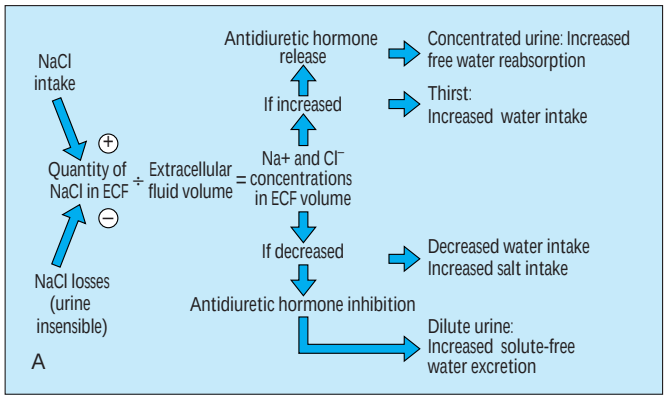


FIGURE 1-3

Volume determinants of arterial pressure. The two major determinants of arterial pressure, cardiac output and total peripheral resistance, are regulated by a combination of short- and long-term mechanisms. Rapidly adjusting mechanisms regulate peripheral vascular resistance, cardiovascular capacitance, and cardiac performance. These mechanisms include the neural and humoral mechanisms listed. On a long-term basis, cardiac output is determined by venous return, which is regulated primarily by the mean circulatory pressure. The mean circulatory pressure depends on blood volume and overall cardiovascular capacitance. Blood volume is closely linked to extracellular fluid (ECF) volume and sodium balance, which are dependent on the integration of net intake and net losses [13]. (*Adapted from* Navar [3].)



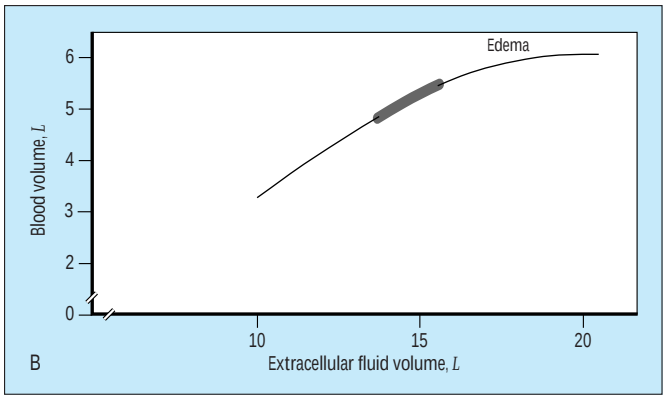


FIGURE 1-4

A, Relationship between net sodium balance and extracellular fluid (ECF) volume. Sodium balance is intimately linked to volume balance because of powerful mechanisms that tightly regulate plasma and ECF osmolality. Sodium and its accompanying anions constitute the major contributors to ECF osmolality. The integration of sodium intake and losses establishes the net amount of sodium in the body, which is compartmentalized primarily in the ECF volume. The quotient of these two parameters (sodium and volume) determines the sodium concentration and, thus, the osmolality. Osmolality is subject to very tight regulation by vasopressin and other mechanisms. In particular, vasopressin is a very powerful regulator of plasma osmolality; however, it achieves this regulation primarily by regulating the relative solute-free water retention or excretion by the kidney [13–15]. The important point is that the osmolality is rapidly regulated by adjusting the ECF volume to the total solute present. Corrections of excesses in extracellular fluid volume involve more complex interactions that regulate the sodium excretion rate.

B, Relationship between the ECF volume and blood volume. Under normal conditions a consistent relationship exists between the total ECF volume and blood volume. This relationship is consistent as long as the plasma protein concentration and, thus, the colloid osmotic pressure are regulated appropriately and the microvasculature maintains its integrity in limiting protein leak into the interstitial compartment. The *shaded area* represents the normal operating range [13]. A chronic increase in the total quantity of sodium chloride in the body leads to a chronic increase in ECF volume, part of which is proportionately distributed to the blood volume compartment. When accumulation is excessive, disproportionate distribution to the interstitium may lead to edema. Chronic increases in blood volume increase mean circulatory pressure (*see* Fig. 1-3) and lead to an increase in arterial pressure. Therefore, the mechanisms regulating sodium balance are primarily responsible for the chronic regulation of arterial pressure. (Panel B *adapted from* Guyton and Hall [13].)

Intrarenal Mechanisms Regulating Sodium Balance

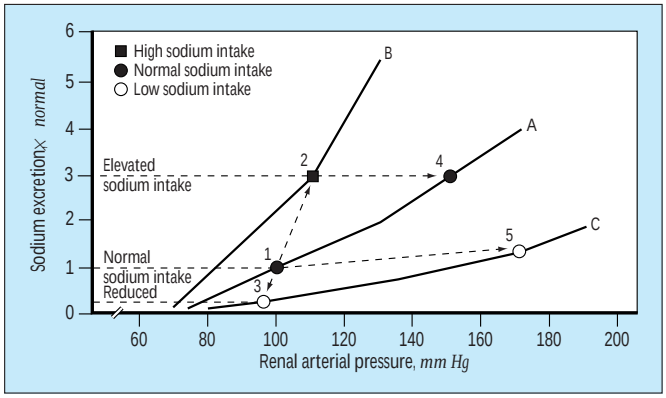


FIGURE 1-5

Arterial pressure and sodium excretion. In principle, sodium balance can be regulated by altering sodium intake or excretion by the kidney. However, intake is dependent on dietary preferences and usually is excessive because of the abundant salt content of most foods. Therefore, regulation of sodium balance is achieved primarily by altering urinary sodium excretion. It is therefore of major significance that, for any given set of conditions and neurohumoral environment, acute elevations in arterial pressure produce natriuresis, whereas reductions in arterial pressure cause antinatriuresis [9]. This phenomenon of pressure natriuresis serves a critical role linking arterial pressure to sodium balance. Representative relationships between arterial pressure and sodium excretion under conditions of normal, high, and low sodium intake are shown. When renal function is normal and responsive to sodium regulatory mechanisms, steady state sodium excretion rates are adjusted to match the intakes. These adjustments occur with minimal alterations in arterial pressure, as exemplified by going from point 1 on *curve A* to point 2 on *curve B*. Similarly, reductions in sodium intake stimulate sodium-retaining mechanisms that prevent serious losses, as exemplified by point 3 on *curve C*. When the regulatory mechanisms are operating appropriately, the kidneys have a large capability to rapidly adjust the slope of the pressure natriuresis relationship. In doing so, the kidneys readily handle sodium challenges with minimal long-term changes in extracellular fluid (ECF) volume or arterial pressure. In contrast, when the kidney cannot readjust its pressure natriuresis curve or when it inadequately resets the relationship, the results are sodium retention, expansion of ECF volume, and increased arterial pressure. Failure to appropriately reset the pressure natriuresis is illustrated by point 4 on *curve A* and point 5 on *curve C*. When this occurs the increased arterial pressure directly influences sodium excretion, allowing balance between intake and excretion to be reestablished but at higher arterial pressures. (*Adapted from* Navar [3].)

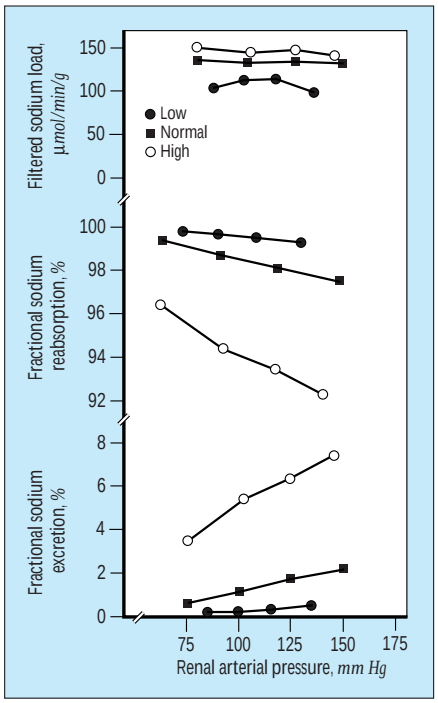


FIGURE 1-6

Intrarenal responses to changes in arterial pressure at different levels of sodium intake. The renal autoregulation mechanism maintains the glomerular filtration rate (GFR) during changes in arterial pressure, GFR, and filtered sodium load. These values do not change significantly during changes in arterial pressure or sodium intake [3,16]. Therefore, the changes in sodium excretion in response to arterial pressure alterations are due primarily to changes in tubular fractional reabsorption. Normal fractional sodium reabsorption is very high, ranging from 98% to 99%; however, it is reduced by increased sodium chloride intake to effect the large increases in the sodium excretion rate. These responses demonstrate the importance of tubular reabsorptive mechanisms in modulating the slope of the pressure natriuresis relationship. (*Adapted from* Navar and Majid [9].)

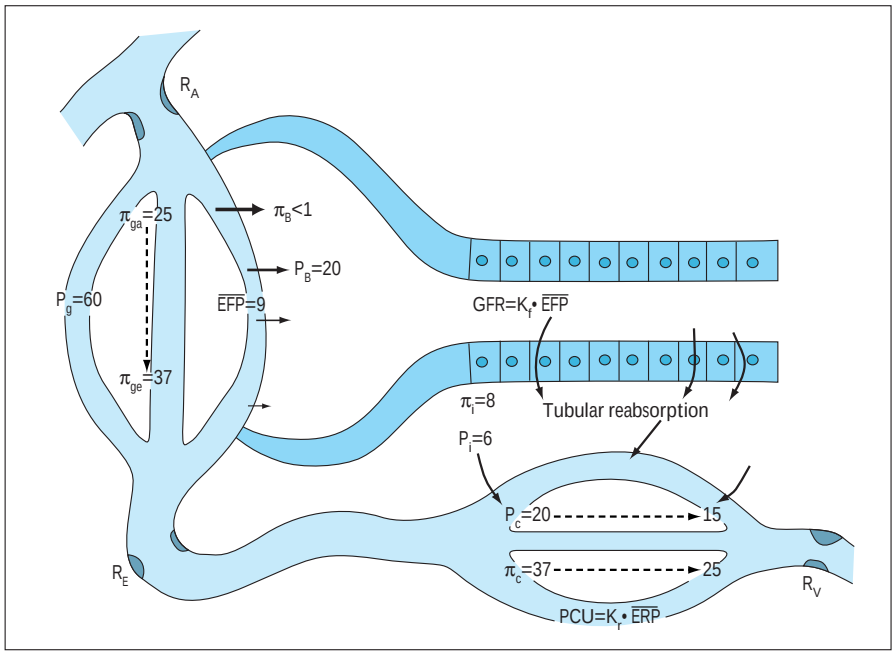


FIGURE 1-7

Hemodynamic mechanisms regulating sodium excretion. Many different neurohumoral mechanisms, paracrine factors, and drugs exist that can influence sodium excretion and the pressure natriuresis relationship. These modulators may influence sodium excretion by altering changes in filtered load or changes in tubular reabsorption. Filtered load depends primarily on hemodynamic mechanisms that regulate the forces operating at the glomerulus. As shown, the glomerular filtration rate (GFR) is determined by the filtration coefficient (K_f) and the effective filtration pressure (EFP). The EFP is a distributed force determined by the glomerular pressure (P_g), the pressure in Bowman's space (P_B), and the plasma colloid osmotic pressure within the glomerular capillaries (π_g). The π_g increases progressively along the length of the glomerular capillaries as protein-free fluid is filtered such that filtration is greatest in the early segments of the glomerular capillaries, as designated by the *large arrow*. The glomerular forces, EFP, and blood flow are regulated by mechanisms that control the vascular smooth muscle tone of the afferent and efferent arterioles and of the intraglomerular mesangial cells. The filtration coefficient also is subject to regulation by neural, humoral, and paracrine influences [17]. Changes in tubular reabsorption can result from alterations of various processes governing both active and passive transport along the nephron segments. Peritubular capillary uptake (PCU) of the tubular reabsorbate is mediated by the net colloid osmotic pressure gradient (π_c - π_i). As a result of the filtration of protein-free filtrate, the plasma colloid osmotic pressure entering the peritubular capillaries is markedly increased. Thus, the colloid osmotic gradient exceeds the outwardly directed hydrostatic pressure gradient (P_c - P_i). Appropriate responses of one or more of these modulating mechanisms allow the kidneys to respond rapidly and efficiently to changes in sodium chloride intake [3,17]. π_B—colloid osmotic pressure in Bowman's space; π_{ga}—colloid osmotic pressure in initial parts of glomerular cappillaries; π_{ge}—colloid osmotic pressure in terminal segments of glomerular capillaries; R_A—resistance of preglomerular arterioles; R_E—efferent resistance; R_V—venous resistance. (*Adapted from* Navar [3].)

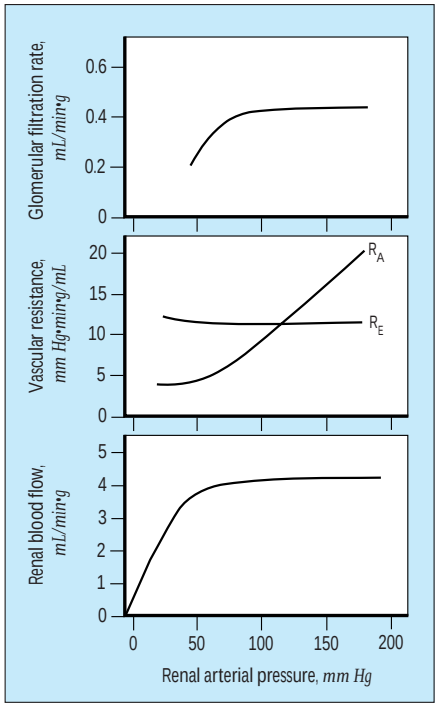
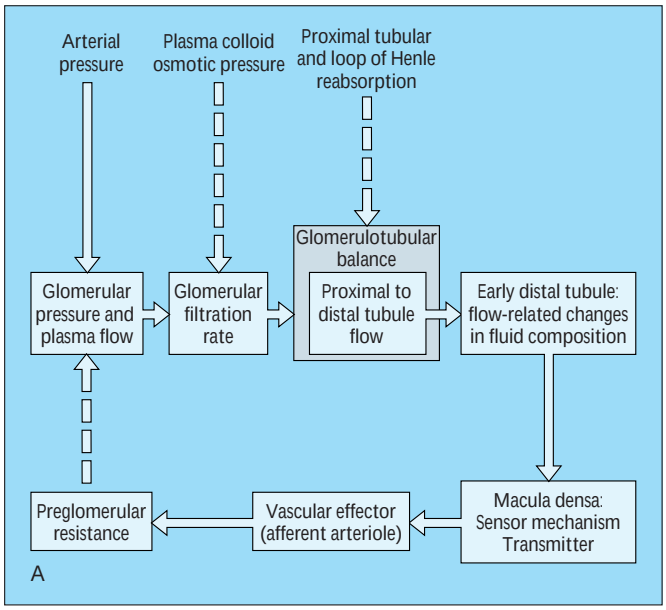
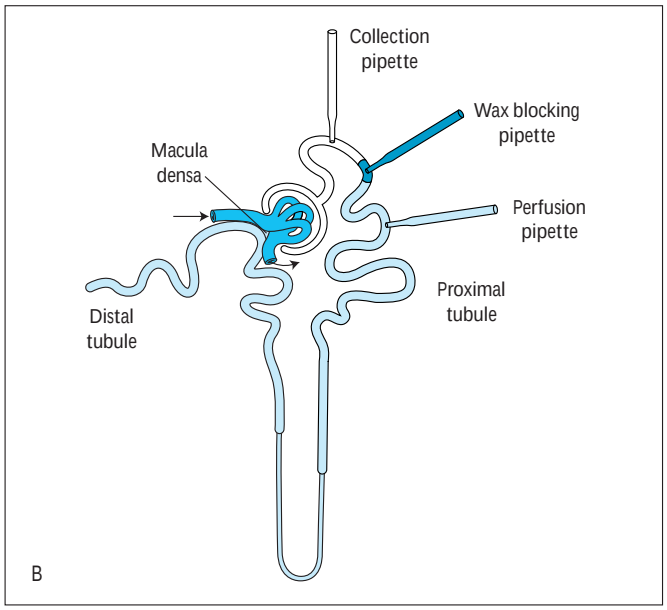


FIGURE 1-8

Renal autoregulatory mechanism. Because the glomerular filtration rate (GFR) is so responsive to changes in the glomerular forces, highly efficient mechanisms have been developed to maintain a stable intrarenal hemodynamic environment [16]. These powerful mechanisms adjust vascular smooth muscle tone in response to various extrinsic disturbances. During changes in arterial pressure, renal blood flow and the GFR are autoregulated with high efficiency as a consequence of adjustments in the vascular resistance of the preglomerular arterioles. Although efferent resistance also can be regulated by other mechanisms, it does not participate significantly over most of the autoregulatory range. The GFR, filtered sodium load, and the intrarenal pressures are maintained stable in the face of various extrarenal disturbances by the autoregulatory mechanism. (*Adapted from* Navar [3].)





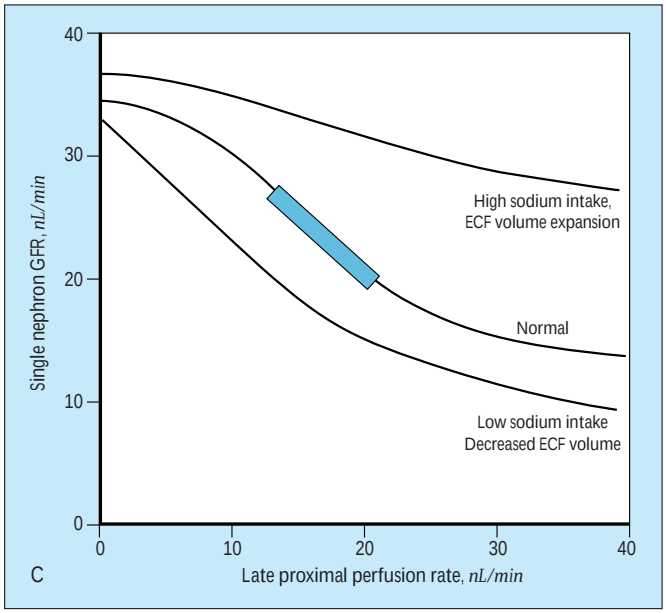


FIGURE 1-9

Tubuloglomerular feedback (TGF) and myogenic mechanisms. Two mechanisms are responsible for efficient renal autoregulation: the TGF and myogenic mechanisms. The TGF mechanism is explained here. **A,** Increases in distal tubular flow past the macula densa generate signals from the macula densa cells to the afferent arterioles to elicit vasoconstriction, whereas decreases in flow cause afferent vasodilation [16,18,19]. Blocking flow to the distal tubule or interrupting the feedback loop attenuates the autoregulatory efficiency of the glomerular filtration rate (GFR), glomerular pressure, and renal blood flow. **B,** Individual tubules can be blocked and perfused downstream, while collections are made or pressure measured in an early tubular segment. **C,** When the tubule is perfused at increased flows, the glomerular pressure and GFR of that nephron decrease. The *shaded area* in the normal relationship represents the normal operating level of the TGF mechanism. This mechanism helps stabilize the filtered load and the solute and sodium load to the distal nephron segment. The responsiveness of the TGF mechanism is modulated by changes in sodium intake and in extracellular fluid (ECF) volume status. At high sodium intake and ECF volume expansion the sensitivity of the TGF mechanism is low, thus allowing greater spillover of salt to the distal nephron. During low sodium intake and other conditions associated with ECF volume contraction, the sensitivity of the TGF mechanism is markedly increased to minimize spillover into the distal nephron and maximize sodium retention. The hormonal and paracrine mechanisms responsible for regulating TGF sensitivity are discussed subsequently.

The myogenic mechanism is intrinsic to the vessel wall and responds to changes in wall tension to regulate vascular smooth muscle tone. Preglomerular arteries and afferent arterioles but not efferent arterioles exhibit myogenic responses to changes in wall tension [16,20]. The residual autoregulatory capacity that exists during blockade of the tubuloglomerular feedback mechanism indicates that the myogenic mechanism contributes about half to the autoregulatory efficiency of the renal vasculature. (*Figure adapted from* Navar [3].)

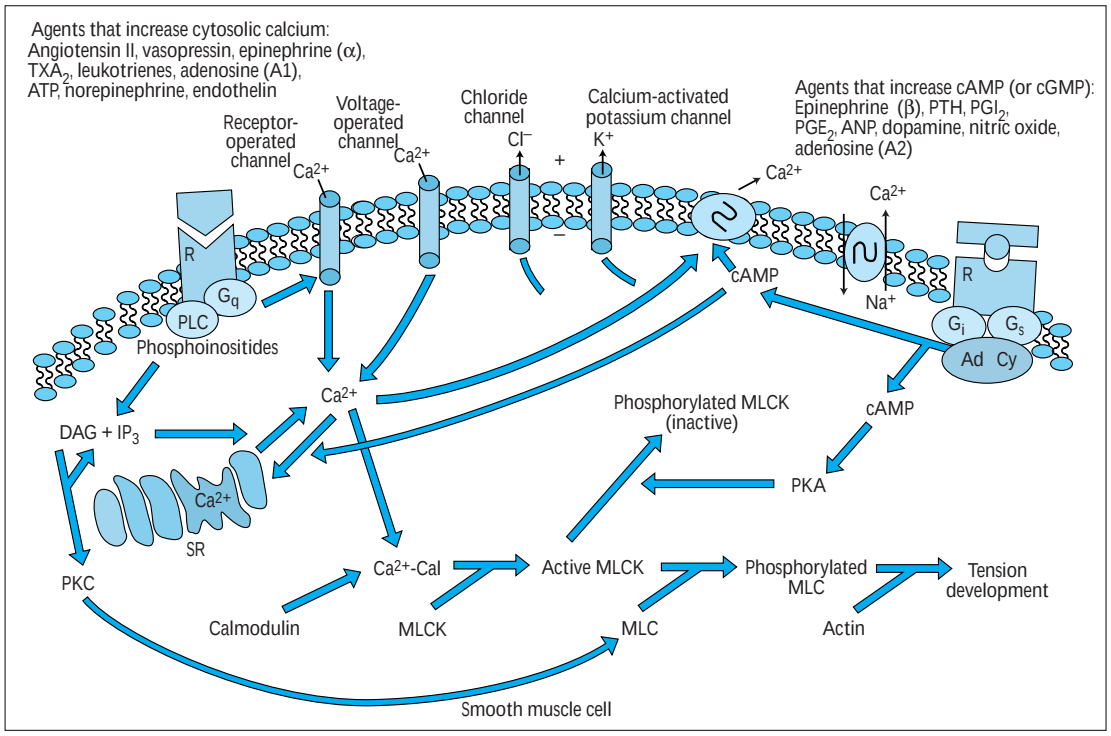


FIGURE 1-10

Cellular mechanisms of vascular smooth muscle contraction. The vascular resistances of different arteriolar segments are ultimately regulated by the contractile tone of the corresponding vascular smooth muscle cells. Shown are the various membrane activation mechanisms and signal transduction events leading to a change in cytosolic calcium ions (Ca^{2+}), cyclic AMP (cAMP), and phosphorylation of myosin light chain kinase. Many of the circulating hormones and paracrine factors that increase or decrease vascular smooth muscle tone are identified. Ad Cy—adenylate cyclase; ANP—atrial natriuretic protein; Cal—calmodulin; cGMP—cyclic GMP; DAG—1,2-diacylglycerol; G_q, G_i, G_s—G proteins; IP_3—inositol 1,4,5-triphosphate; MLC—myosin light chain; MLCK—myosin light chain kinase; PGE_2—prostaglandin E_2; PGI_2—prostaglandin I_2; PKA—protein kinase A; PKC—protein kinase C; PLC—phospholipase C; PTH—parathyroid hormone; R—receptor; SR—sarcoplasmic reticulum; TXA_2 —thromboxane A_2. (*Adapted from* Navar *et al.* [16].)

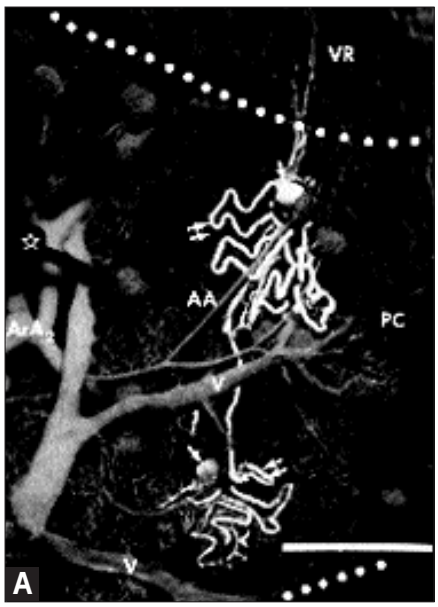


FIGURE 1-11

Differential activating mechanisms in afferent and efferent arterioles. The relative contributions of the activation pathways are different in afferent and efferent arterioles. Increases in cytosolic Ca^{2+} in afferent arterioles appear to be primarily by calcium ion (Ca^{2+}) entry by way of receptor- and voltage-dependent Ca^{2+} channels. The efferent arterioles are less dependent on voltage-dependent Ca^{2+} channels. These differential mechanisms in the renal vasculature are exemplified by comparing the afferent and efferent arteriolar responses to angiotensin II before and after treatment with Ca^{2+} channel blockers. **A**, These experiments were done using the juxtamedullary nephron preparation that allows direct visualization of the renal microcirculation [21]. AA—afferent arteriole; ArA—arcuate artery; PC—peritubular capillaries; V—vein; VR—vasa recta.

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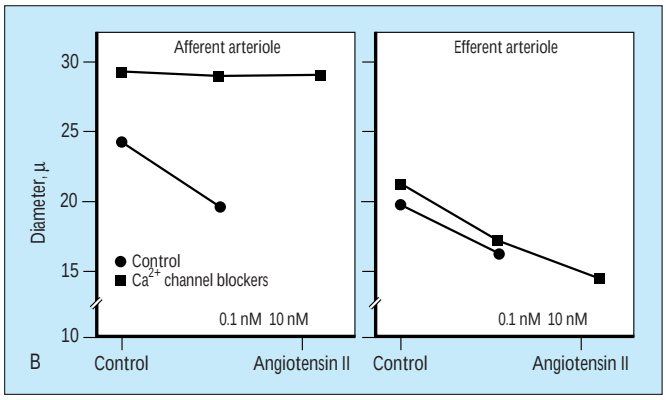


FIGURE 1-11 (*Continued*)

B, Both afferent and efferent arterioles constrict in response to angiotensin II [22]. Ca^{2+} channel blockers, dilate only the afferent arterioles and prevents the afferent vasoconstriction responses to angiotensin II. In contrast, Ca^{2+} channel blockers do not significantly vasodilate efferent arterioles and do not block the vasoconstrictor effects of angiotensin II. Thus, afferent and efferent arterioles can be differentially regulated by various hormones and paracrine agents. (*Panel A from* Casellas and Navar [21]; *panel B from* Navar *et al.* [23].)

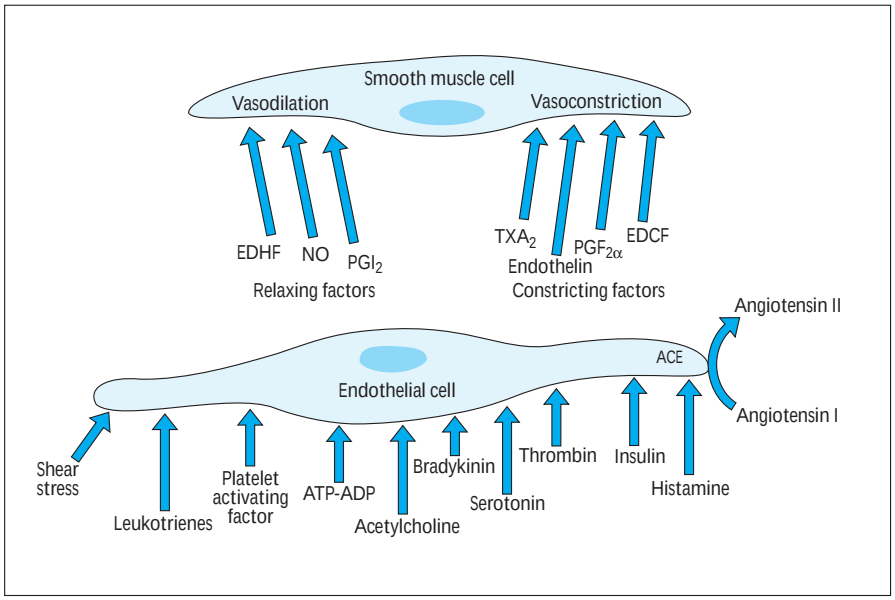


FIGURE 1-12

Endothelial-derived factors. In addition to serving as a diffusion barrier, the endothelial cells lining the vasculature participate actively in the regulation of vascular function. They do so by responding to various circulating hormones and physical stimuli and releasing paracrine agents that alter vascular smooth muscle tone and influence tubular transport function. (Examples are shown.) Angiotensin-converting enzyme (ACE) is present on endothelial cells and converts angiotensin I to angiotensin II. Nitric oxide is formed by nitric oxide synthase, which cleaves nitric oxide from L-arginine. Nitric oxide diffuses from the endothelial cells to activate soluble guanylate cyclase and increases cyclic GMP (cGMP) levels in vascular smooth muscle cells, thus causing vasodilation. Agents that can stimulate nitric oxide are shown. The relative amounts of the various factors released by endothelial cells depend on the physiologic circumstances and pathophysiologic status. Thus, endothelial cells can exert vasodilator or vasoconstrictor effects. At least one major influence participating in the normal regulation of vascular tone is nitric oxide. EDCF—endothelial derived constrictor factor; EDHF—endothelial derived hyperpolarizing factor; $PGF_{2\alpha}$—prostaglandin $F_{2\alpha}$; PGI_2—prostaglandin I_2; TXA_2—thromboxane A_2. (*Adapted from* Navar *et al.* [16].)

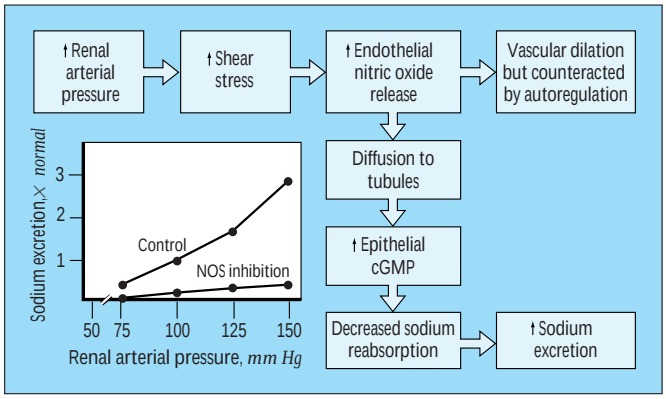


FIGURE 1-13

Nitric oxide in mediation of pressure natriuresis. Several recent studies have demonstrated that nitric oxide also directly affects tubular sodium transport and may be an important mediator of the changes induced by arterial pressure in sodium excretion, as described in Figure 1-5 [9,24]. Increases in arteriolar shear stress caused by increases in arterial pressure stimulate production of nitric oxide. Nitric oxide may exert direct effects to inhibit tubule sodium reabsorptive mechanisms and may elicit vasodilatory actions. Nitric oxide increases intracellular cyclic GMP (cGMP) in tubular cells, which leads to a reduced reabsorption rate through cGMP-sensitive sodium entry pathways [24,25]. When formation of nitric oxide is blocked by agents that prevent nitric oxide synthase activity, sodium excretion is reduced and the pressure natriuresis relationship is markedly suppressed. Thus, nitric oxide may exert a critical role in the regulation of arterial pressure by influencing vascular tone throughout the cardiovascular system and by serving as a mediator of the changes induced by the arterial pressure in tubular sodium reabsorption. (*Adapted from* Navar [3].)

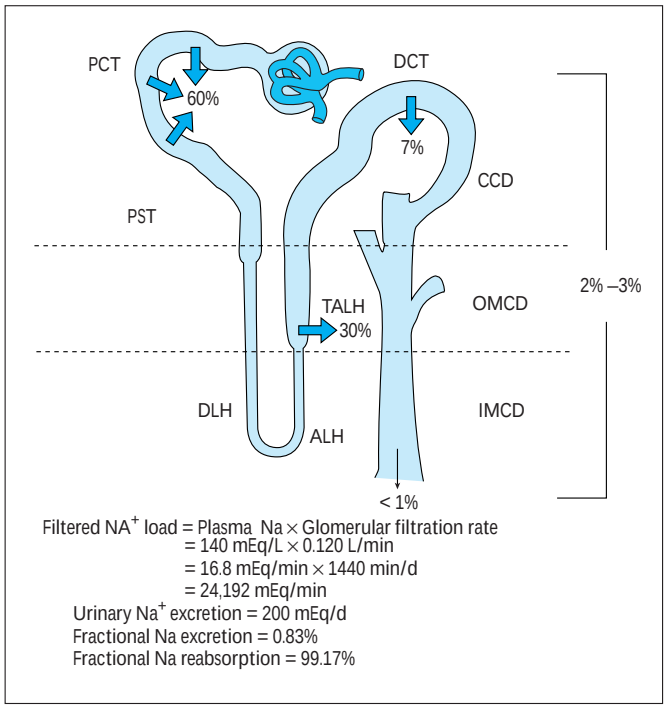


FIGURE 1-14

Tubular transport processes. Sodium excretion is the difference between the very high filtered load and net tubular reabsorption rate such that, under normal conditions less than 1% of the filtered sodium load is excreted. The percentage of reabsorption of the filtered load occurring in each nephron segment is shown. The end result is that normally less than 1% of the filtered load is excreted; however, the exact excretion rate can be changed by many mechanisms. Despite the lesser absolute sodium reabsorption in the distal nephron segments, the latter segments are critical for final regulation of sodium excretion. Therefore, any factor that changes the delicate balance existing between the hemodynamically determined filtered load and the tubular reabsorption rate can lead to marked alterations in sodium excretion. ALH—thin ascending limb of the loop of Henle; CCD—cortical collecting duct; DCT—distal convoluted tubule; DLH—thin descending limb of the loop of Henle; IMCD—inner medullary collecting duct; OMCD—outer medullary collecting duct; PCT—proximal convoluted tubule; PST—proximal straight tubule; TALH—thick ascending limb of the loop of Henle.

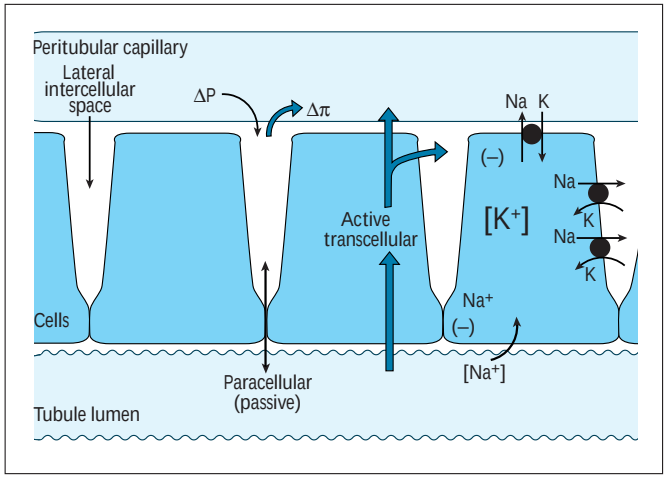


FIGURE 1-15

Proximal tubule reabsorptive mechanisms. The proximal tubule is responsible for reabsorption of 60% to 70% of the filtered load of sodium. Reabsorption is accomplished by a combination of both active and passive transport mechanisms that reabsorb sodium and other solutes from the lumen into the lateral spaces and interstitial compartment. The major driving force for this reabsorption is the basolateral sodium-potassium ATPase (Na^+-K^+ ATPase) that transports Na^+ out of the proximal tubule cells in exchange for K^+. As in most cells, this maintains a low intracellular Na^+ concentration and a high intracellular K^+ concentration. The low intracellular Na^+ concentration, along with the negative intracellular electrical potential, creates the electrochemical gradient that drives most of the apical transport mechanisms. In the late proximal tubule, a lumen to interstitial chloride concentration gradient drives additional net solute transport. The net solute transport establishes a small osmotic imbalance that drives transtubular water flow through both transcellular and paracellular pathways. In the tubule, water and solutes are reabsorbed isotonically (water and solute in equivalent proportions). The reabsorbed solutes and water are then further reabsorbed from the lateral and interstitial spaces into the peritubular capillaries by the colloid osmotic pressure, which establishes a predominant reabsorptive force as discussed in Figure 1-7. ΔP—transcapillary hydrostatic pressure gradient; Δπ—transcapillary colloid osmotic pressure gradient.

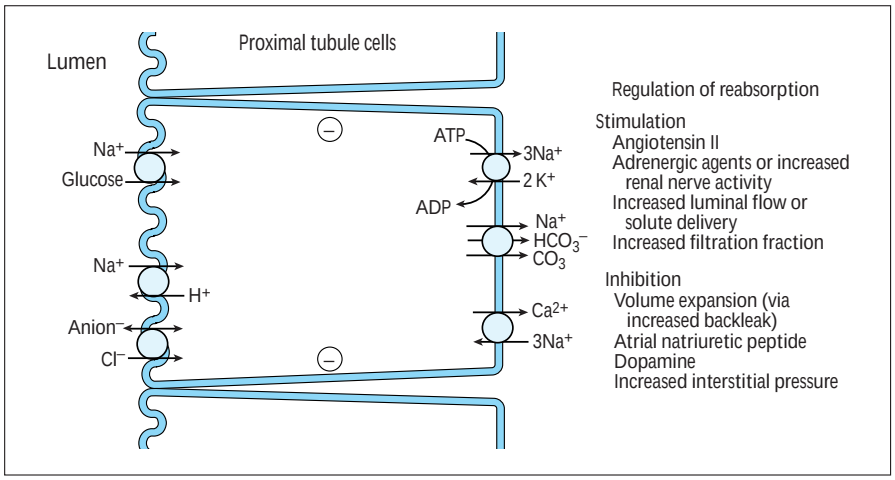


FIGURE 1-16

Major transport pathways across proximal tubule cells. At the apical membrane, sodium is transported in conjunction with organic solutes (such as glucose, amino acids, and citrate) and inorganic anions (such as phosphate and sulfate). The major mechanism for sodium entry into the cells is sodium-hydrogen exchange (the isoform NHE3). Chloride transport pathways across the apical membrane may include a coupled sodium chloride entry step or chloride anion exchange that is coupled with sodium-hydrogen exchange. Major transport pathways at the basolateral membrane include the ubiquitous and preeminent sodium-potassium ATPase (Na^+-K^+ ATPase) that creates the major driving force. The other major pathway is a sodium-bicarbonate transport system that transports the equivalent of one sodium ion coupled with the equivalent of three bicarbonate ions (HCO^-_3). Because this transporter transports two net charges out the electrically negative cell, membrane voltage partially drives this transport pathway. A basolateral sodium-calcium exchanger is important in regulating cell calcium. Not shown are several other pathways that predominantly transport protons or other ions and organic substrates. Several major regulatory factors are listed.

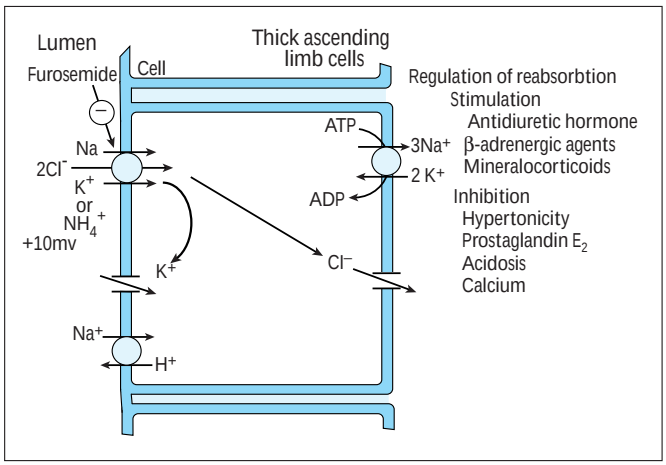


FIGURE 1-17

Sodium transport mechanisms in the thick ascending limb of the loop of Henle. The major sodium chloride reabsorptive mechanism in the thick ascending limb at the apical membrane is the sodium-potassium-chloride cotransporter. This electroneutral transporter is inhibited by furosemide and other loop diuretics and is stimulated by a variety of factors. Potassium is recycled across the apical membrane into the lumen, creating a positive voltage in the lumen. An apical sodium-hydrogen exchanger also exists that may function to reabsorb some sodium bicarbonate. The sodium-potassium ATPase (Na^+-K^+ ATPase) at the basolateral membrane again is the driving force. The basolateral chloride channel and possibly other chloride cotransporters are important in mediating chloride efflux across the basolateral membrane. Sodium and chloride are reabsorbed without water in this segment because water is impermeable across the apical membrane of the thick ascending limb. Thus, the tubular fluid osmolality in this nephron segment is hypotonic.

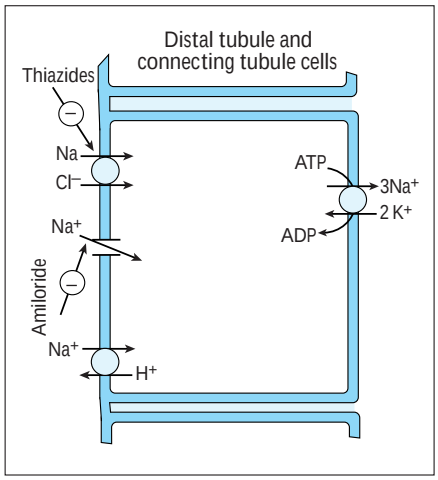


FIGURE 1-18

Mechanisms of sodium chloride reabsorption in the distal tubule. The distal convoluted tubule and subsequent connecting tubule have a variety of sodium transport mechanisms. The distal tubule has predominantly a sodium chloride cotransporter, which is inhibited by thiazide diuretics. In the connecting tubule, sodium channels and a sodium-hydrogen exchange mechanism also are present. Amiloride inhibits sodium channel activity. Again the sodium-potassium ATPase (Na^+-K^+ ATPase) on the basolateral membrane provides most of the driving force for sodium reabsorption.

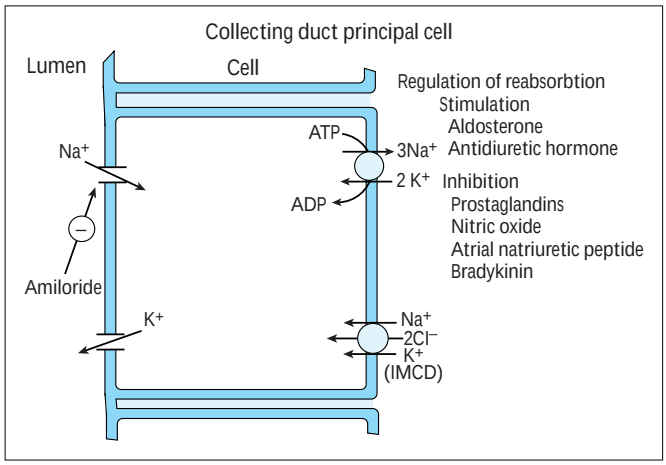


FIGURE 1-19

Mechanism of sodium chloride reabsorption in collecting duct cells. Sodium transport in the collecting duct is mainly via amiloride-sensitive sodium channels in the apical membrane. Some evidence for other mechanisms such as an electroneutral sodium-chloride cotransport mechanism and a different sodium channel also has been reported. Again, the basolateral sodium-potassium ATPase (Na^+-K^+ ATPase) creates the driving force for overall sodium transport. There are some differences between the cortical collecting duct and the deeper inner medullary collecting duct (IMCD). In the cortical collecting duct, sodium transport occurs in the predominant principal cell type interspersed between acid-base transporting intercalated cells. The principal cell also is an important site of potassium secretion by way of apical potassium channels and water transport via antidiuretic sensitive water channels. Regulation of sodium channels may involve either insertion (from subapical compartments) or activation of preexisting sodium channels.

Systemic Factors Regulating Arterial Pressure and Sodium Excretion

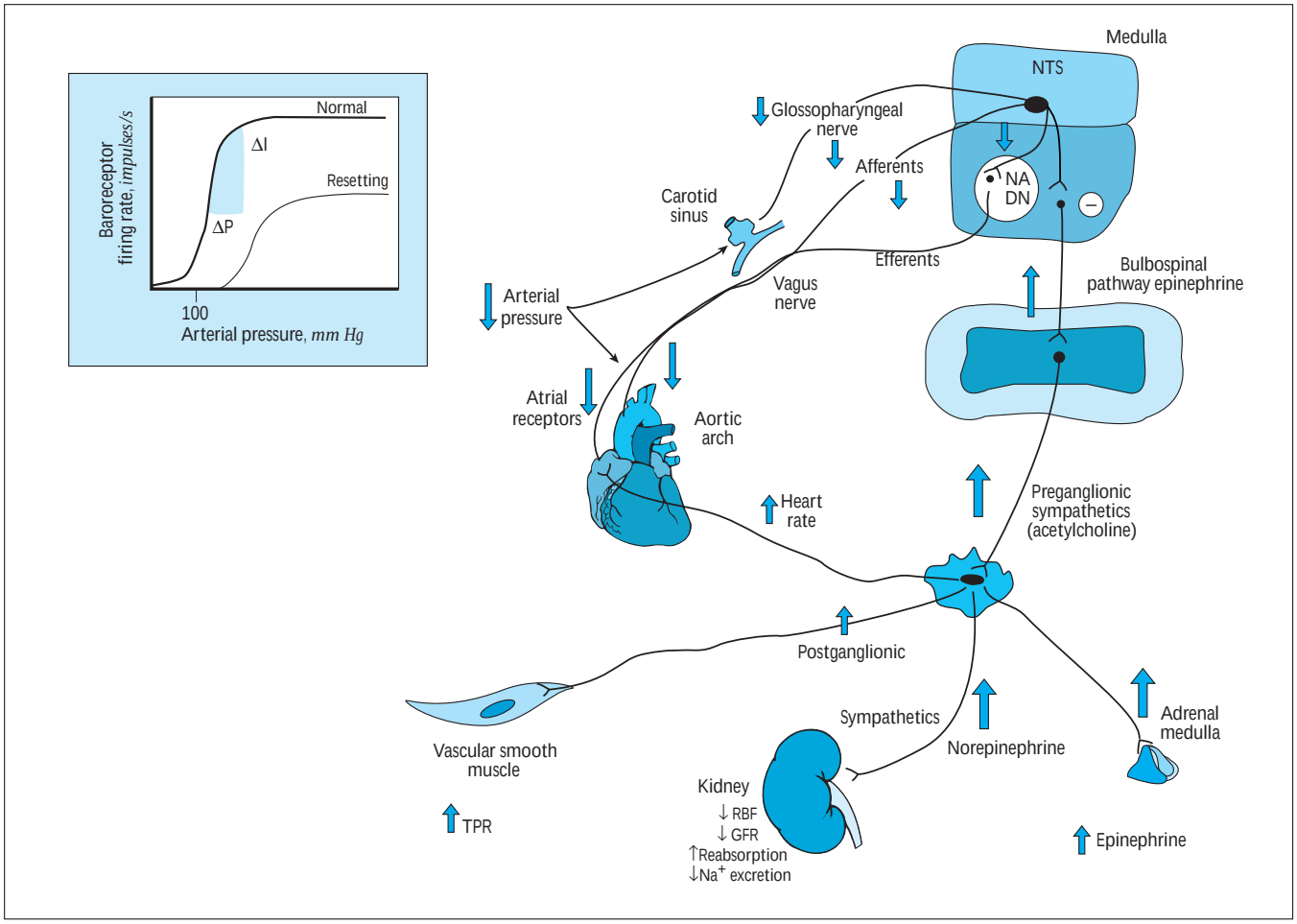


FIGURE 1-20

Neural and sympathetic influences. The neural reflexes serve as the principal mechanisms for the rapid regulation of arterial pressure. The neural reflexes also exert a long-term role by influencing sodium excretion. The pathways and effectors of the arterial baroreflex and atrial pressure-volume reflex are depicted. The *arrows* indicate increased or decreased activity in response to an acute reduction in arterial pressure which is sensed by the baroreceptors in the aortic arch and carotid sinus.

The *insert* depicts the relationship between the arterial blood pressure and baroreflex primary afferent firing rate. At the normal level of mean arterial pressure of approximately 100 mm Hg, the sensitivity ($\Delta I/\Delta P$) is set at the maximum level. After chronic resetting of the baroreceptors, the peak sensitivity and threshold of activation are shifted to a higher level of arterial pressure.

The cardiovascular reflexes involve *high-pressure* arterial receptors in the aortic arch and carotid sinus and *low-pressure* atrial receptors. In response to decreases in arterial pressure or vascular volume, increased sympathetic stimulation participates in short-term control of arterial pressure. This increased stimulation does so by enhancing cardiac performance and stimulating vascular smooth muscle tone, leading to increased total peripheral resistance and decreased capacitance. The direct effects of the sympathetic nervous system on kidney function lead to decreased sodium excretion caused by decreases in filtered load and increases in tubular reabsorption [26].

The decreases in the glomerular filtration rate (GFR) and filtered sodium load are due to increases in both afferent and efferent arteriolar resistances and to decreases in the filtration coefficient (*see* Fig. 1-7). Sympathetic activation also enhances proximal sodium reabsorption by stimulating the sodium-hydrogen (Na^+-H^+) exchanger mechanism (*see* Fig. 1-16) and by increasing the net chloride reabsorption by the thick ascending limb of the loop of Henle. The indirect effects include stimulation of renin secretion and angiotensin II formation, which, as discussed next, also stimulates tubular reabsorption. ΔI—change in impulse firing; ΔP—change in pressure; DN—dorsal motor nucleus; NA—nucleus ambiguous; NTS—nucleus tractus solitarii; RBF—renal blood flow; TPR—total peripheral resistance. (*Adapted from* Vari and Navar [4].)

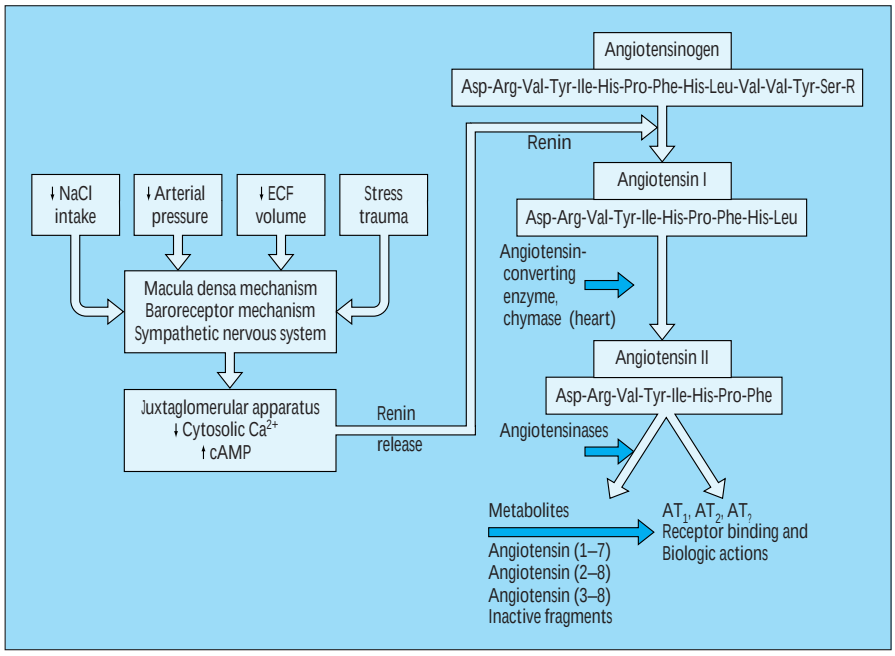


FIGURE 1-21

Renin-angiotensin system. The renin-angiotensin system serves as one of the most powerful regulators of arterial pressure and sodium balance. In response to various stimuli that compromise blood volume, extracellular fluid (ECF) volume, or arterial pressure—or those associated with stress and trauma—three major mechanisms are activated. These mechanisms stimulate renin release by the cells of the juxtaglomerular apparatus that act on angiotensinogen to form angiotensin I. Angiotensinogen is an α_2 globulin formed primarily in the liver and to a lesser extent by the kidney. Angiotensin I is a decapeptide that is rapidly converted by angiotensin-converting enzyme (ACE) and to a lesser extent by chymase (in the heart) to angiotensin II, an octapeptide. Recent studies have indicated that other angiotensin metabolites such as angiotensin (2–8), angiotensin (1–7), and angiotensin (3–8) have biologic actions.

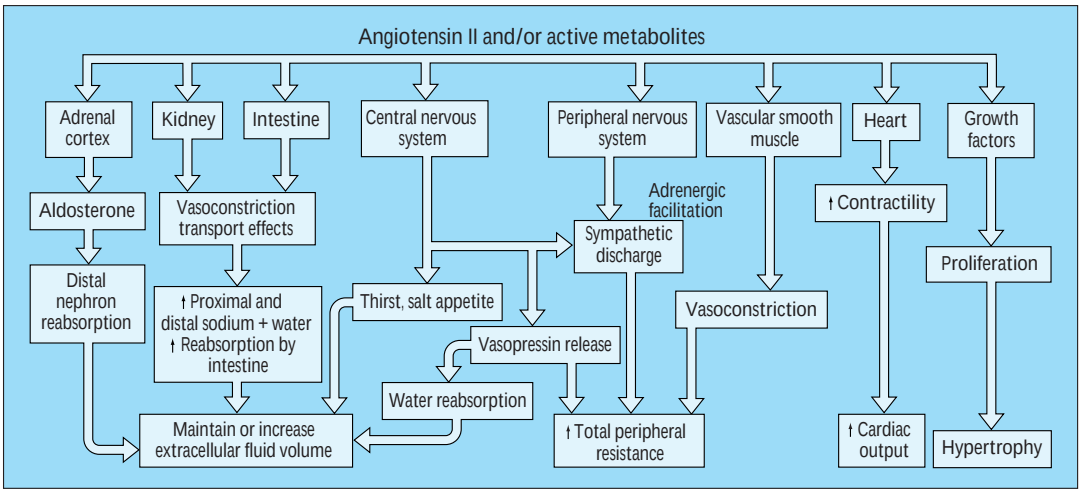


FIGURE 1-22

Multiple actions of angiotensin. Angiotensin II and some of the other angiotensin II metabolites have a myriad of actions on many different vascular beds and organ systems. Angiotensin II exerts short- and long-term actions, including vasoconstriction and stimulation of aldosterone release. Angiotensin II also interacts with the sympathetic nervous system by facilitating adrenergic transmission and has long-term actions on vascular smooth muscle proliferation by interacting with growth factors. Angiotensin II exerts several important effects on the kidney that contribute to sodium conservation. (*Adapted from* Navar [3].)

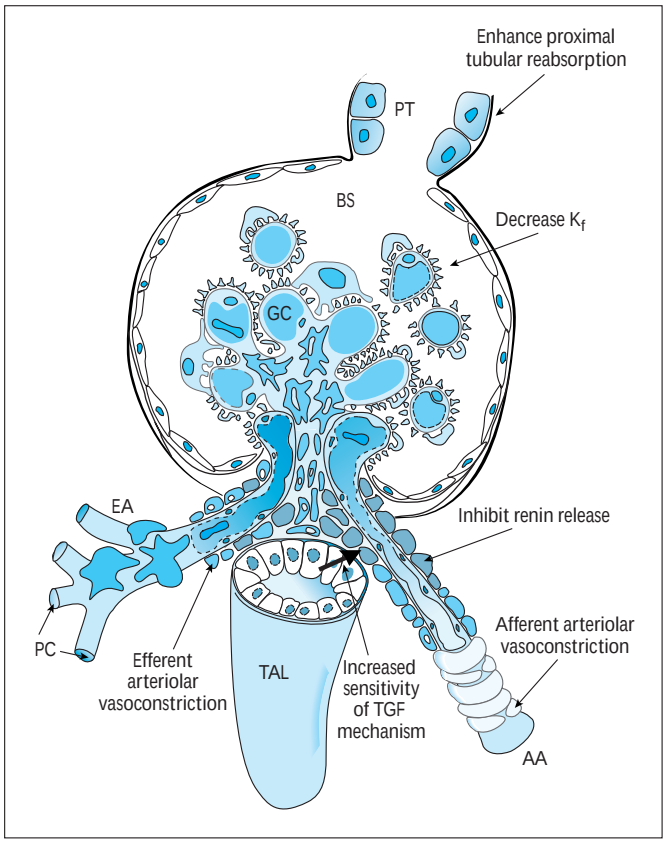


FIGURE 1-23

Angiotensin II actions on renal hemodynamics. Systemic and intrarenal angiotensin II exert powerful vasoconstrictive actions on the kidney to decrease renal blood flow and sodium excretion. At the level of the glomerulus, angiotensin II is a vasoconstrictor of both afferent (AA) and efferent arterioles (EA) and decreases the filtration coefficient K_f. Angiotensin II also directly inhibits renin release by the juxtaglomerular apparatus. Increased intrarenal angiotensin II also is responsible for the increased sensitivity of the tubuloglomerular feedback mechanism that occurs with decreased sodium chloride intake (*see* Fig. 1-9) [17,27,28]. BS—Bowman's space; GC—glomerular capillaries; PC—peritubular capillaries; PT—proximal tubule; TAL—thick ascending limb; TGF—tubuloglomerular feedback mechanism. (*Adapted from* Arendshorst and Navar [17].)

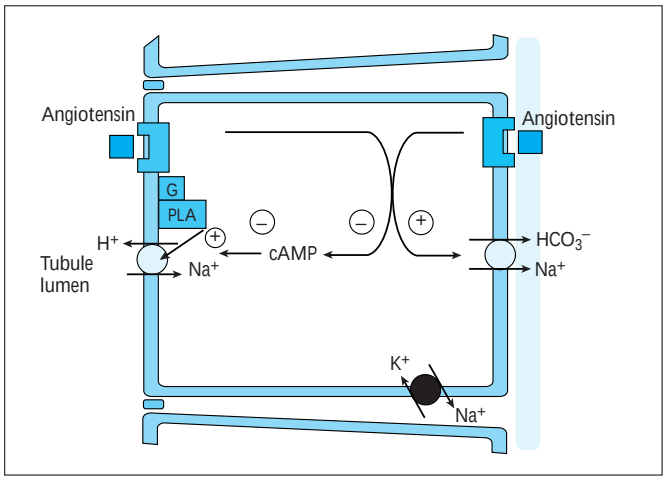
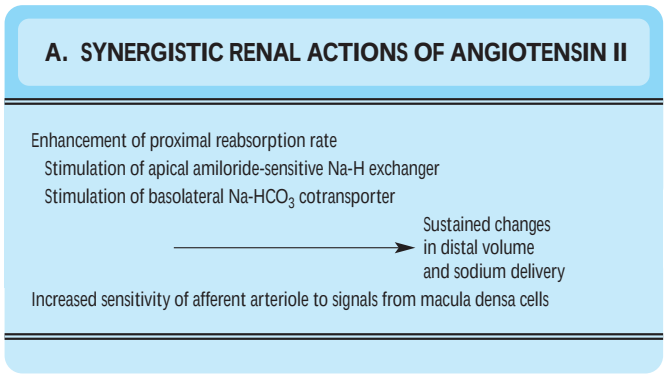
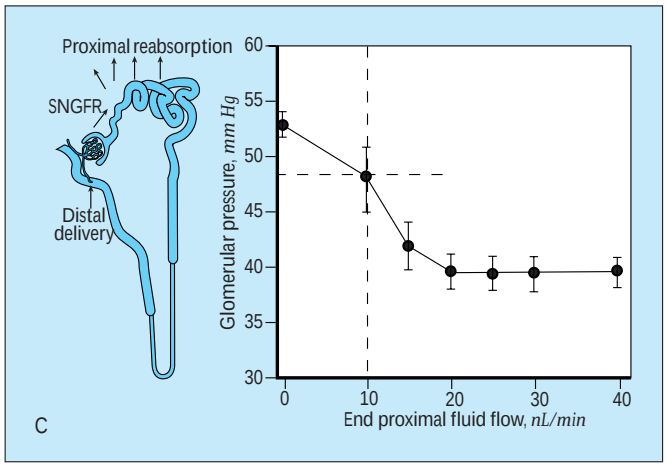


FIGURE 1-24

Angiotensin II actions on tubular transport. Angiotensin II receptors are located on both the luminal and basolateral membranes of the proximal and distal nephron segments. The proximal effect has been studied most extensively. Activation of angiotensin II-AT_1 receptors leads to increased activities of the sodium-hydrogen (Na^+-H^+) exchanger and the sodium-bicarbonate (Na^+-HCO^-_3) cotransporter. These increased activities lead to augmented volume reabsorption. Higher angiotensin II concentrations can inhibit the tubular sodium reabsorption rate; however, the main physiologic role of angiotensin II is to enhance the reabsorption rate [28]. cAMP—cyclic AMP; G—G protein; PLA—phospholipase A. (*Adapted from* Mitchell and Navar [28].)





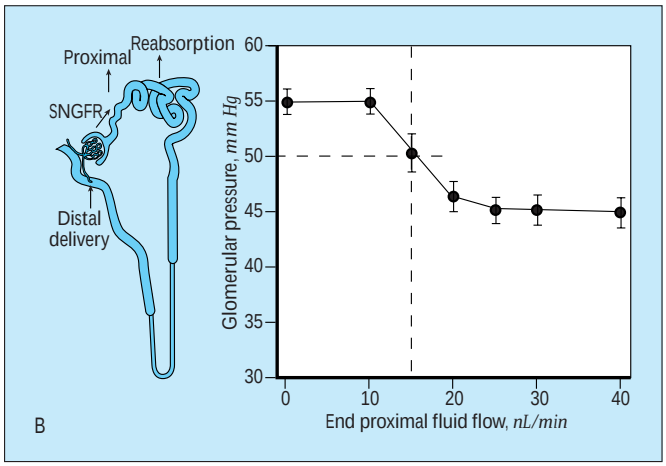


FIGURE 1-25

A–C, Synergistic effects of angiotensin II on proximal reabsorption and tubuloglomerular feedback mechanisms. The actions of angiotensin II on proximal nephron reabsorption and the ability of angiotensin II to enhance the sensitivity of the tubuloglomerular feedback (TGF) mechanism prevent a compensatory increase in glomerular filtration rate caused by the reduced distal tubular flow. These actions allow elevated angiotensin II levels to exert a sustained reduction in sodium delivery to the distal nephron segment. This effect is shown here by the shift of operating levels to a lower proximal fluid flow under the influence of elevated angiotensin II [27]. The effects of angiotensin II to enhance TGF sensitivity allow the glomerular pressure (GP) and nephron filtration rate to be maintained at a reduced distal volume delivery rate that would occur as a consequence of the angiotensin II effects on reabsorption. SNGFR—single nephron glomerular filtration rate. (Panels B and C *adapted from* Mitchell *et al.* [27].)

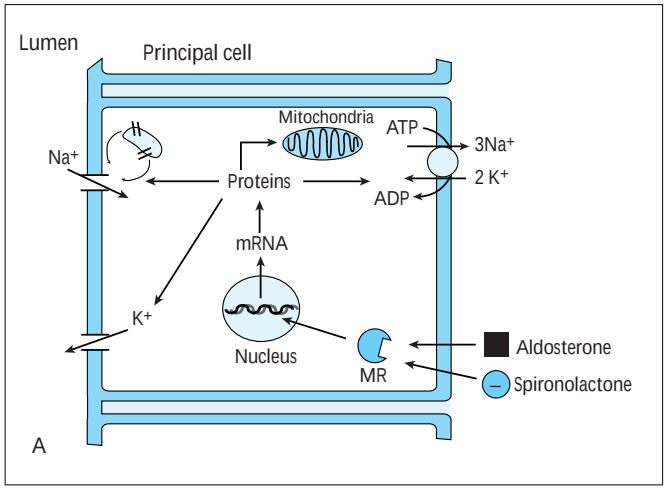


FIGURE 1-26

Effects of aldosterone on distal nephron sodium reabsorption. **A,** Mechanism of action of aldosterone. Angiotensin II also is a very powerful regulator of aldosterone release by the adrenal gland. The increased aldosterone levels synergize with the direct effects of angiotensin II to enhance distal tubule sodium reabsorption. Aldosterone increases sodium reabsorption and potassium secretion in the distal segments of the nephron by binding to the cytoplasmic mineralocorticoid receptor (MR). On binding, the receptor complex migrates to the nucleus where it induces transcription of a variety of messenger RNAs (mRNAs). The mRNAs encode for proteins that stimulate sodium reabsorption by increasing sodium-potassium ATPase (Na^+-K^+ ATPase) protein and activity at basolateral membranes, increasing mitochondrial ATP formation, and increasing the sodium and potassium channels at the luminal membrane [29]. Growing evidence also exists for nongenomic actions of aldosterone to activate sodium entry pathways such as the amiloride-sensitive sodium channel [30].

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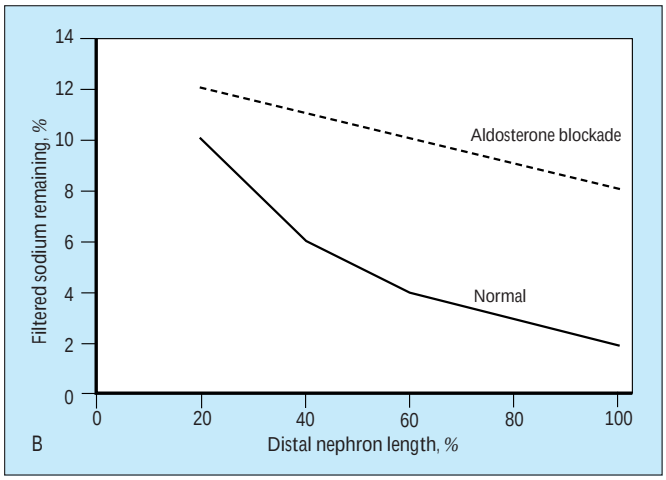

FIGURE 1-26 (*Continued*)

B, The net effect of aldosterone is to stimulate sodium reabsorption along the distal nephron segment, decreasing the remaining sodium to only 2% or 3% of the filtered load. The direct action of aldosterone can be blocked by drugs such as spironolactone that bind directly to the mineralocorticoid receptor.

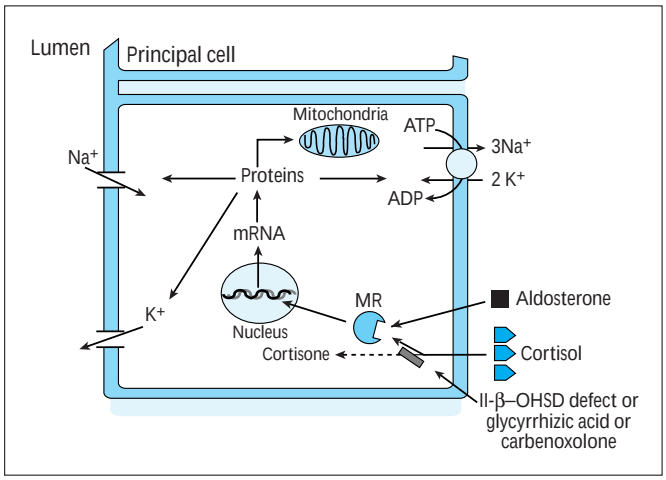

FIGURE 1-27

Syndrome of apparent mineralocorticoid excess and hypertension. Aldosterone increases sodium reabsorption and potassium secretion in the distal segments of the nephron by binding to the cytoplasmic mineralocorticoid receptor (MR). Cortisol, the glucocorticoid that circulates in plasma at much higher concentrations than does aldosterone, also binds to MR. However, cortisol normally is prevented from this by the action of 11-β-hydroxysteroid dehydrogenase (11-β-OHSD), which metabolizes cortisol to cortisone in mineralocorticoid-sensitive cells. A deficiency or defect in this enzyme has been found to be responsible for a rare form of hypertension in persons with the hereditary *syndrome of apparent mineralocorticoid excess*. In these persons, cortisol binds to the MR receptor, causing sodium retention and hypertension [31]. This enzyme also is blocked by glycyrrhizic acid (in some forms of licorice) and carbenoxolone. The diuretic spironolactone acting by way of inhibition of MR is able to block this excessive action of cortisol on the MR receptor.

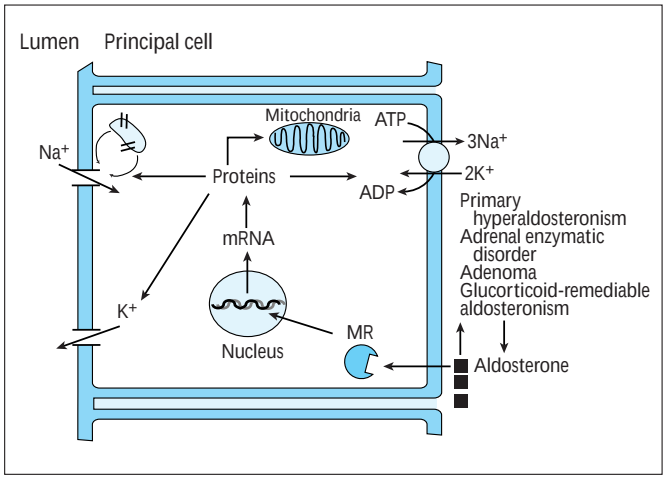

FIGURE 1-28

Hyperaldosteronism and glucocorticoid-remediable aldosteronism. Hypertension can result from increased aldosterone or from increases in other closely related steroids derived from abnormal adrenal metabolism (11-β-hydroxylase deficiency and 17-β-hydroxylase deficiency). The most common cause is an aldosterone-producing adenoma; bilateral hyperplasia of the adrenal zona glomerulosa is the next most common cause. In glucocorticoid-remediable aldosteronism, a DNA crossover mutation results in a chimeric gene in which aldosterone production is regulated by adrenocorticotropic hormone (ACTH). Increases in aldosterone also can result secondarily from any state of increased renin such as renal artery stenosis, which leads to increased circulating concentrations of angiotensin II and stimulation of aldosterone release [31]. MR—mineralocorticoid receptor; mRNA—messenger RNA.

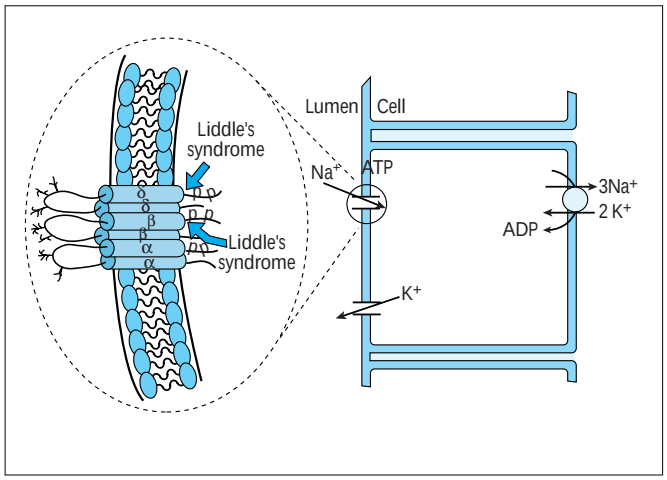

FIGURE 1-29

Excess epithelial sodium channel activity in Liddle's syndrome. The epithelial sodium channel responsible for sodium reabsorption in much of the distal portions of the nephron is a complex of three homologous subunits, α, β, and γ each with two membrane-spanning domains. Liddle's syndrome, an autosomal dominant disorder causing low renin-aldosterone hypertension often with hypokalemia, results from mutated β or γ subunits. These mutations increase the sodium reabsorptive rate by way of these channels by keeping them open longer, increasing sodium channel density on the membranes, or both. The specific problem appears to reside with proline (P)-rich domains in the carboxyl terminal region of β or γ that are involved in regulation of the channel membrane localization or activity. The net result is excess sodium reabsorption and a reduced capability to increase sodium excretion in response to volume expansion [31,32].

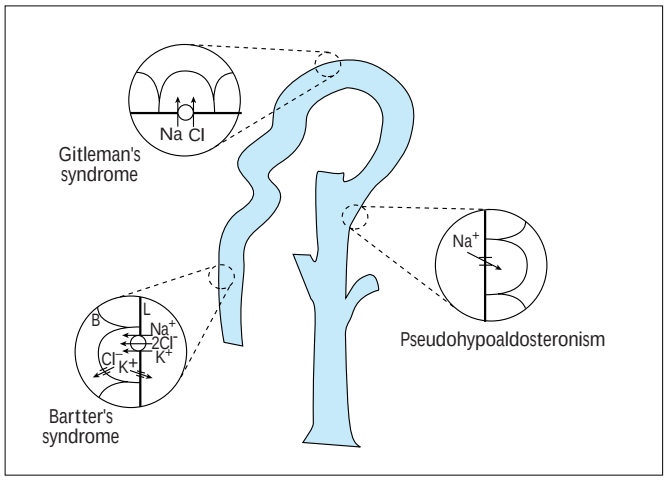

FIGURE 1-30

Syndromes of diminished sodium reabsorption and hypotension. Recently, a variety of syndromes associated with salt wasting, and usually hypotension, have been attributed to specific molecular defects in the distal nephron. Bartter's syndrome, which usually is accompanied by metabolic alkalosis and hypokalemia, has been found to be associated with at least three separate defects (the three transporters shown) in the thick ascending limb. These defects are at the level of the sodium-potassium-2chloride (Na^+-K^+-$2Cl^-$) cotransporter, apical potassium channel, and basolateral chloride channel (*see* Fig. 1-17). Malfunction in any of these three proteins results in diminished sodium chloride reabsorption similar to that occurring with administration of loop diuretics. Gitelman's syndrome, which was originally described as a variant of Bartter's syndrome, represents a defect in the sodium chloride cotransport mechanism in the distal tubule. Pseudohypoaldosteronism results from a defect in the apical sodium channels in the collecting ducts. In contrast to Bartter's and Gitelman's syndromes, hyperkalemia may be present. These rare disorders illustrate that defects in sodium chloride reabsorptive mechanisms can result in abnormally low blood pressure as a consequence of excessive sodium excretion in the urine. Although these conditions are rare, similar but more subtle defects of the heterozygous state may contribute to protection from hypertension in some persons [31]. B—basolateral side; L—lumen of tubule.

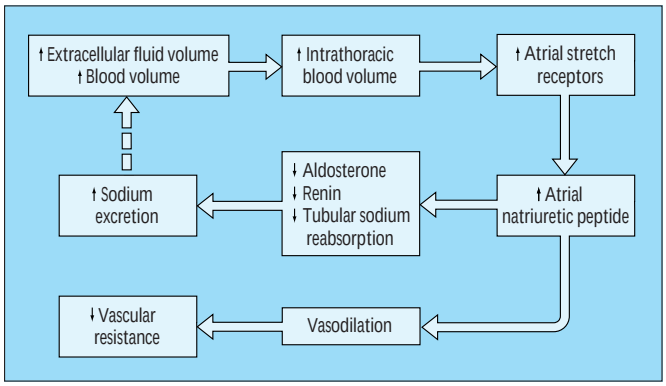

FIGURE 1-31

Atrial natriuretic peptide (ANP). In response to increased intravascular volume, atrial distention stimulates the release of ANP from the atrial granules where the precursor is stored. Extracellular fluid volume expansion is associated with increased ANP levels, whereas reductions in vascular volume and dehydration elicit decreases in plasma ANP levels. ANP participates in arterial pressure regulation by sensing the degree of vascular volume expansion and exerting direct vasodilator actions and natriuretic effects. ANP has been shown to markedly increase the slope of the pressure natriuresis relationship (*see* Figs. 1-5 and 1-6). The vasorelaxant and transport actions are mediated by stimulation of membrane-bound guanylate cyclase, leading to increased cyclic GMP levels. ANP also inhibits renin release, which reduces circulating angiotensin II levels [33–35]. Related peptides, such as brain natriuretic peptides, have similar effects on sodium excretion and renin release [36].

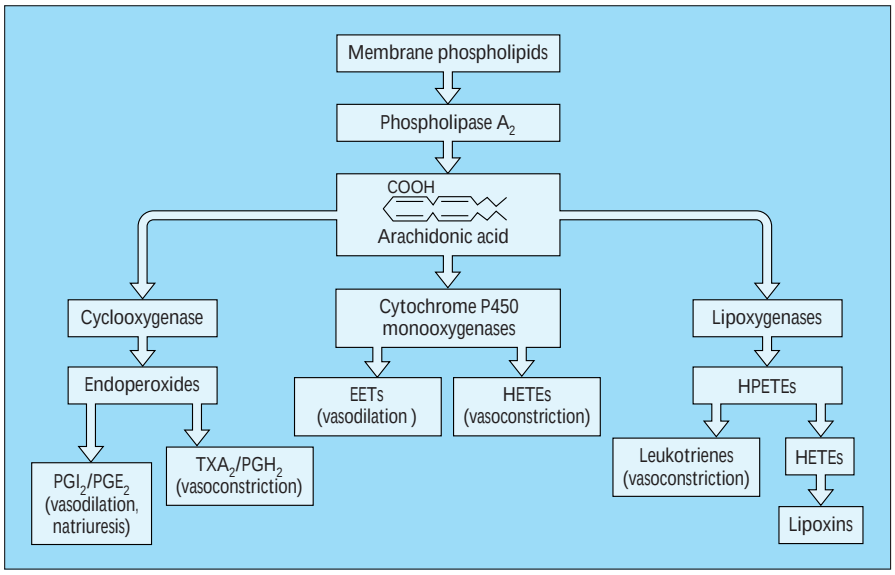

FIGURE 1-32

Arachidonic acid metabolites. Several eicosanoids (arachidonic acid metabolites) are released locally and exert both vasoconstrictor and vasodilator effects as well as effects on tubular transport [16,37]. Phospholipase A_2 catalyzes formation of arachidonic acid (an unsaturated 20-carbon fatty acid) from membrane phospholipids. The cyclooxygenase pathway and various prostaglandin synthetases are responsible for the formation of endoperoxides (PGH_2), prostaglandins E_2 (PGE_2) and I_2 (PGI_2), and thromboxane (TXA_2) [38,39]. States of volume depletion and hypoperfusion stimulate prostaglandin synthesis [16,17,38].

The vasodilator prostaglandins attenuate the influence of vasoconstrictor substances during activation of the renin-angiotensin system, sympathetic nervous system, or both [33]. These prostaglandins also have transport effects on renal tubules through activation of distinct prostaglandin receptors [40]. In some pathophysiologic conditions, enhanced production of TXA_2 and other vasoconstrictor prostanoids may occur. The vasoconstriction induced by TXA_2 appears to be mediated primarily by calcium influx [17,40].

Leukotrienes are hydroperoxy fatty acid products of 5-hydroperoxyeicosatetraenoic acid (HPETE) that are synthesized by way of the lipoxygenase pathway. Leukotrienes are released in inflammatory and immunologic reactions and have been shown to stimulate renin release. The cytochrome P450 monooxygenases produce several vasoactive agents [16,37,41,42] usually referred to as EETs and hydroxy-eicosatetraenoic acids (HETEs). These substances exert actions on vascular smooth muscle and epithelial tissues [16,41,42]. (*Adapted from* Navar [3].)

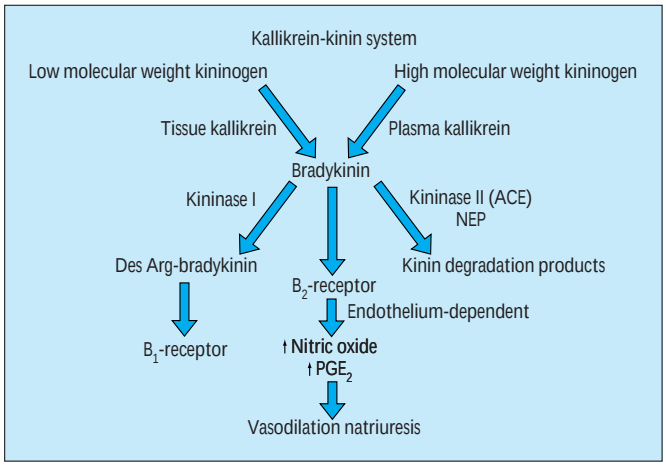

FIGURE 1-33

Kallikrein-kinin system. Plasma and tissue kallikreins are functionally different serine protease enzymes that act on kininogens (inactive α_2 glycoproteins) to form the biologically active kinins (bradykinin and lysyl-bradykinin [kallidin]). Kidney kallikrein and kininogen are localized in the distal convoluted and cortical collecting tubules. Release of kallikrein into the tubular fluid and interstitium can be stimulated by prostaglandins, mineralocorticoids, angiotensin II, and diuretics. B_1 and B_2 are the two major bradykinin receptors that exert most of the vascular actions. Although glomerulus and distal nephron segments contain both B_1 and B_2 receptors, most of the renal vascular and tubular effects appear to be mediated by B_2-receptor activation [16,17,43,44]. Bradykinin and kallidin elicit vasodilation and stimulate nitric oxide, prostaglandin E_2 (PGE_2) and I_2 (PGI_2), and renin release [45,46]. Kinins are inactivated by the same enzyme that converts angiotensin I to angiotensin II, angiotensin-converting enzyme (ACE). The kallikrein-kinin system is stimulated by sodium depletion, indicating it serves as a mechanism to dampen or offset the effects of enhanced angiotensin II levels [47,48]. Des Arg—bradykinin; NEP—neutral endopeptidase.

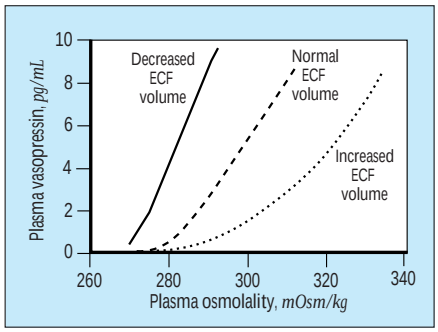

FIGURE 1-34

Vasopressin. Vasopressin is synthesized by the paraventricular and supraoptic nuclei of the hypothalamus. Vasopressin is stored in the posterior pituitary gland and released in response to osmotic or volume-dependent baroreceptor stimuli, or both. Atrial filling inhibits vasopressin release. Increases in plasma osmolality increase vasopressin release; however, the relationship is shifted by the status of extracellular fluid (ECF) volume, with decreases in the ECF volume increasing the sensitivity of the relationship. Stress and trauma also increase vasopressin release [15]. Therefore, when ECF volume and blood volume are diminished, vasopressin is released to help guard against additional losses of body fluids. (*Adapted from* Navar [8].)

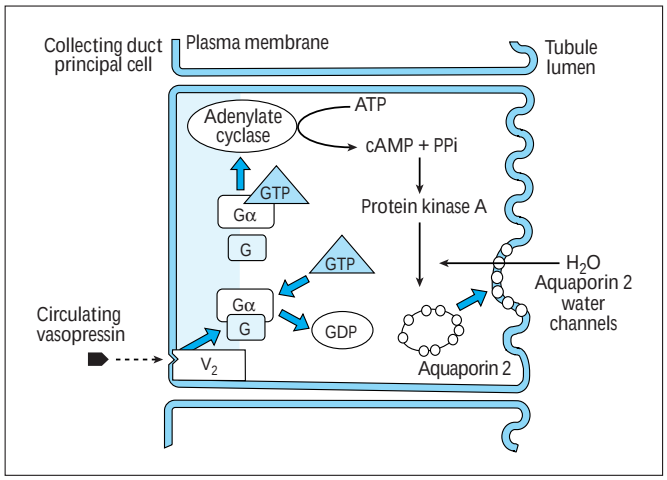

FIGURE 1-35

Vasopressin receptors. Vasopressin exerts its cellular actions through two major receptors. Activation of V_1 receptors leads to vascular smooth muscle constriction and increases peripheral resistance. Vasopressin stimulates inositol 1,4,5-triphosphate and calcium ion (Ca^{2+}) mobilization from cytosolic stores and also increases Ca^{2+} entry from extracellular stores as shown in Figure 1-10. The vasoconstrictive action of vasopressin helps increase total peripheral resistance and reduces medullary blood flow, which enhances the concentrating ability of the kidney. V_2 receptors are located primarily on the basolateral side of the principal cells in the collecting duct segment. Vasopressin activates heterotrimeric G proteins that activate adenylate cyclase, thus increasing cyclic AMP levels. Cyclic AMP (cAMP) activates protein kinase A, which increases the density of water channels in the luminal membrane. Water channels (aquaporin proteins) reside in subapical vesicles and on activation fuse with the apical membrane. Thus, vasopressin markedly increases the water permeability of the collecting duct and allows conservation of fluid and excretion of a concentrated urine. An intact vasopressin system is essential for the normal regulation of urine concentration by the kidney that, in turn, is the major mechanism for coupling the solute to solvent ratio (osmolality) of the extracellular fluid. As discussed in Figure 1-4, this tight coupling allows the confluence of homeostatic mechanisms regulating sodium balance with those regulating extracellular fluid volume. Gα and G—proteins; PPi— inorganic pyrophosphate. (*Adapted from* Vari and Navar [4].)

Hypertensinogenic Process

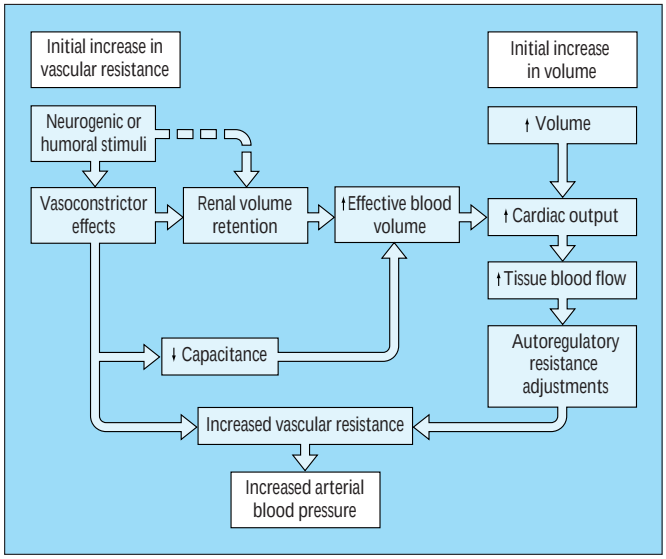

FIGURE 1-36

Overview of mechanisms mediating hypertension. From a pathophysiologic perspective, the development of hypertension requires either a sustained absolute or relative overexpansion of the blood volume, reduction of the capacitance of the cardiovascular system, or both [4,49,50]. One type of hypertension is due primarily to overexpansion of either the actual or the *effective* blood volume compartment. In such a condition of *volume-dependent hypertension*, either one or more of the physiologic mechanisms described in this chapter fails to respond appropriately to intravascular expansion or some pathophysiologic process causes excess production of one or more sodium-retaining factors such as mineralocorticoids or angiotensin II [51,52]. Through mechanisms delineated earlier, overexpansion leads to increased cardiac output that results in overperfusion of tissues; the resultant autoregulatory-induced increases in peripheral resistance contribute further to an increase in total peripheral resistance and elevated arterial pressure [2,53,54].

Hypertension also can be initiated by excess vasoconstrictor influences that directly increase peripheral resistance, decrease cardiovascular capacitance, or both. Examples of this type of hypertension are enhanced activation of the sympathetic nervous system and overproduction of catecholamines such as that occurring with a pheochromocytoma [45,54,55]. When hypertension caused by a vasoconstrictor influence persists, however, it must also exert significant renal vasoconstrictor and sodium-retaining actions. Without a renal effect the elevated arterial pressure would cause pressure natriuresis, leading to a compensatory reduction in extracellular fluid volume and intravascular volume. Thus, the elevated systemic arterial pressure would not be sustained [2,8,54]. Derangements that activate both a vasoconstrictor system and produce sodium-retaining effects, such as inappropriate elevations in the activity of the renin-angiotensin-aldosterone system, lead to an even more powerful hypertensinogenic mechanism that is not easily counteracted [27]. These dual mechanisms are why the renin-angiotensin system has such a critical role in the cause of many forms of hypertension, leaving only the option to increase arterial pressure and elicit a pressure natriuresis. (*Adapted from* Navar [3].)

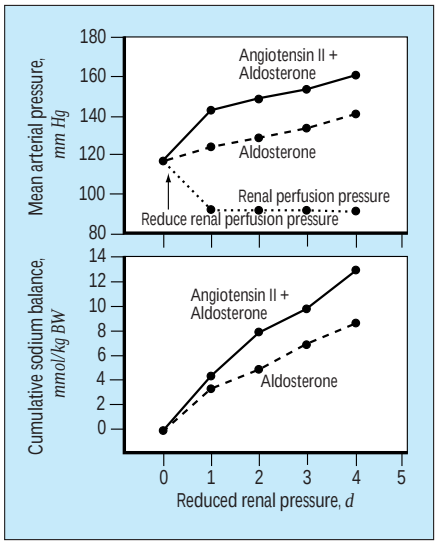

FIGURE 1-37

Predominance of the renin-angiotensin-aldosterone mechanisms. Collectively, the various mechanisms discussed provide overlapping influences responsible for the highly efficient regulation of sodium balance, extracellular fluid (ECF) volume, blood volume, and arterial pressure. Nevertheless, the synergistic actions of the renin-angiotensin-aldosterone system on both vasoconstrictor as well as sodium-retaining mechanisms exert a particularly powerful influence that is not easily counteracted. In a recent study by Seeliger and coworkers [56], renal perfusion pressure was lowered to 90 to 95 mm Hg. The angiotensin II and aldosterone levels were not allowed to decrease and were fixed at normal levels by continuous infusions. The results demonstrated that all compensatory mechanisms (such as increased release of atrial natriuretic peptide and reduced activity of the sympathetic system) could not overcome the hypertensinogenic influence of maintained aldosterone or aldosterone plus angiotensin II as long as renal perfusion pressure was not allowed to increase. Thus, under conditions of increased activity of the renin-angiotensin system, an increased renal arterial pressure seems essential to reestablish sodium balance.

In conclusion, regardless of the specific intrarenal mechanism involved, the net effect of a long-term hypertensinogenic derangement is a reduced capability for sodium excretion at normotensive arterial pressures that cannot be completely compensated by other neural, humoral, or paracrine mechanisms, leaving only the option to increase arterial pressure and elicit a pressure natriuresis. (*Adapted from* Seeliger *et al.* [56].)

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