The Kidney in Blood Pressure Regulation

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—atrial natriuretic protein; Cal—calmodulin; cGMP—cyclic GMP; DAG—1,2-diacylglycerol; $G_{o}$, $G_{i}$, $G_{s}$—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.

(Continued on next page)
1.8 Hypertension and the Kidney

**FIGURE 1-11 (Continued)**

B. Both afferent and efferent arterioles constrict in response to angiotensin II [22]. Ca²⁺ channel blockers, dilate only the afferent arterioles and prevent the afferent vasoconstriction responses to angiotensin II. In contrast, Ca²⁺ 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; PGF₂α—prostaglandin F₂α; PGF₂α—prostaglandin I₂; TXA₂—thromboxane A₂. (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-P-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].)
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**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 new 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 ionically (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.