The Kidney in Blood Pressure Regulation

**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 N avar [8].)

**FIGURE 1-35**
Vasopressin receptors. Vasopressin exerts its cellular actions through two major receptors. Activation of V1 receptors leads to vascular smooth muscle constriction and increases peripheral resistance. Vasopressin stimulates inositol 1,4,5-triphosphate and calcium ion (Ca2+) mobilization from cytosolic stores and also increases Ca2+ 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. V2 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 N avar [4].)
Hypertension and the Kidney

Hypertensinogenic Process

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].)

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].)


