ENDOCRINE HYPERTENSION

Arterial hypertension is a prominent component of a number of endocrine disorders, most prominently those involving the adrenal glands (pheochromocytoma, primary aldosteronism) and the pituitary (ACTH producing tumors). Although the kidney is not an endocrine organ per se, its role as both the origin of, and target tissue for, the hormones that comprise the renin–angiotensin–aldosterone system makes hypertensive disorders of renal origin an appropriate subject on endocrine hypertension.

Hypertension of Adrenal Origin

Mineralocorticoid Hormone: Synthesis and Action

The biosynthetic pathway of the mineralocorticoid hormones are shown in Fig. 10-1. The major adrenal secretory products with mineralocorticoid activity are aldosterone and DOC (11-deoxycorticosterone). Cortisol also has high intrinsic mineralocorticoid activity, but its actions in the kidney are blunted by local degradation. Aldosterone is produced exclusively in the zona glomerulosa and is primarily controlled by the renin– angiotensin system. Other regulators include Na^+ and K^+ levels, ACTH and dopamine.

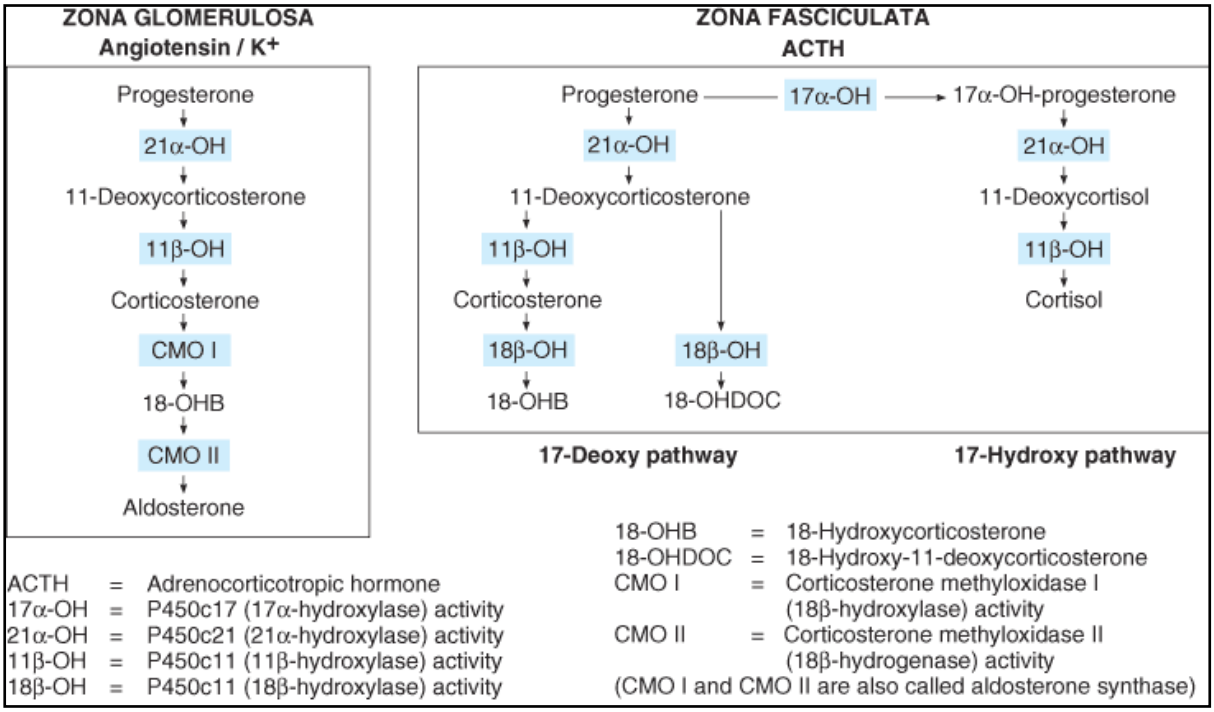

Figure 10-1. Biosynthetic pathways of the mineralocorticoids

Aldosterone binds weakly to corticosteroid–binding globulin (CBG) and circulates mostly bound to albumin. Free aldosterone comprises 30-50% of its total plasma concentration. DOC is secreted at the same rate as aldosterone, but only 5% or less is free. Aldosterone and DOC have equal and high affinities for the mineralocorticoid receptors and circulate at similar concentrations, but aldosterone is quantitatively the most important because much more of it is free. Aldosterone facilitates movement of Na^+ by regulating the luminal Na^+ channel. The

later effects include activation of Na^+-K^+ ATPase and alterations in cell morphology and energy metabolism.

Pathogenesis of Mineralocorticoid Hypertension

Mineralocorticoid hormones produce hypertension by several mechanisms. The initiating events are the physiologic consequences of mineralocorticoid–induced expansion of plasma and extracellular fluid volume. Initially, Na^+ and fluid retention occur, with an increase in body weight, ECF volume, and cardiac output. Renal K^+ wasting persists and arterial blood pressure continues to increase (Fig. 10-3)

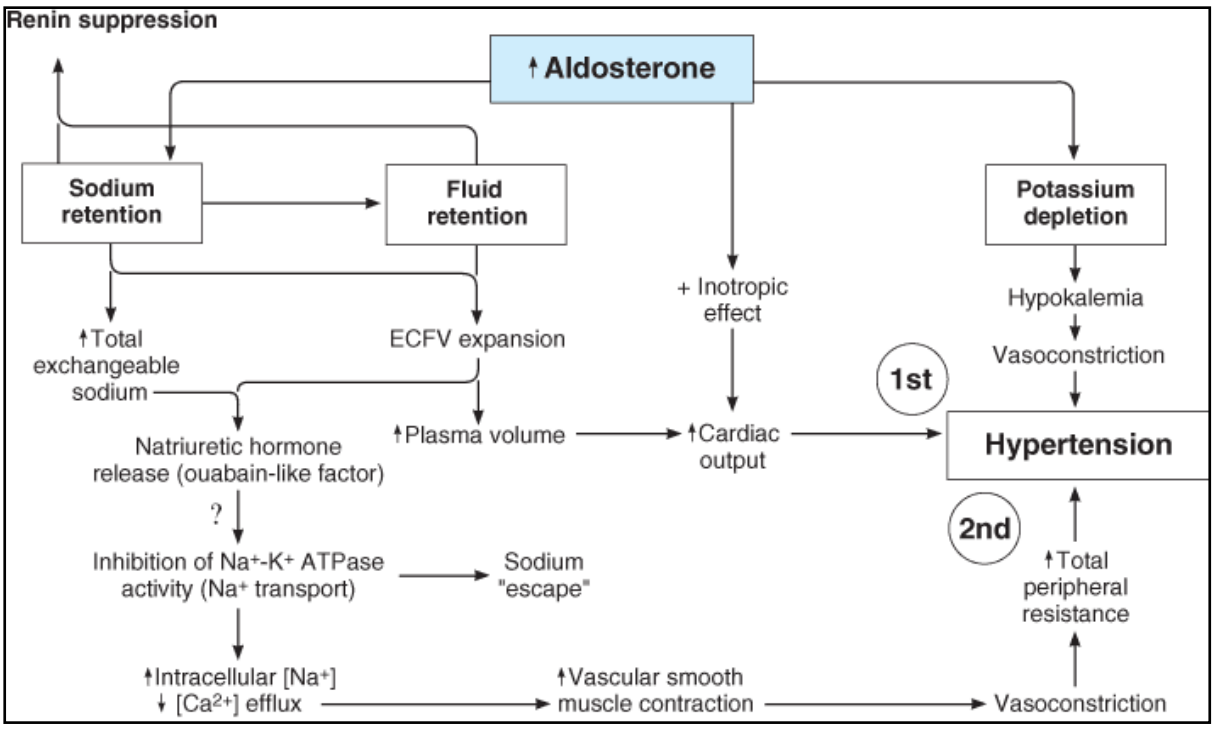

Figure 10-3. Mechanisms involved in mineralocorticoid hypertension. First, there is sodium retention, fluid retention, expansion of extracellular fluid volume and plasma volume, increased cardiac output, and hypertension. Second, there is vasoconstriction and increased total peripheral resistance and hypertension (ECFV, extracellular fluid volume).

Syndromes Due To Excess DOC Production

Deoxycorticosterone is the second most important naturally occurring mineralocorticoid hormone. Accordingly excess DOC production should be suspected in any hypertensive patients with hypokalemia and suppression of renin and aldosterone production.

17α-Hydroxylase Deficiency: It is recognized by the presence of hypertension, hypokalemia, and primary amenorrhea in the female and profound suppression of the renin-angiotensin system, as well as reduced aldosterone levels. The principal steroids present in excess are DOC, corticosterone, 18-OH corticosterone, and 18-OH Deoxycorticosterone.

11β-hydroxylase deficiency: Congenital adrenal hyperplasia due to 11β-hydroxylase deficiency is usually recognized in newborn and infants because of virilization and the presence of hypertension and hypokalemia. Plasma androgens, DOC, 11-deoxycortisol, 17α-hydroxyprogesterone are increased.

Cushing's Syndrome

Hypertension is a common finding of endogenous hypercortisolism. ACTH–dependent hypercortisolism (Cushing's disease and ectopic ACTH production) is frequently accompanied by increased levels of DOC and corticosterone. Glucocorticoids appear to cause hypertension by mineralocorticoid-independent mechanism (Figure 10-6). These include increased production of angiotensin II due to glucocorticoid-induced increase in the hepatic synthesis of angiotensinogen; inhibition of vasodilatory systems such as kinins and prostaglandins; shift in Na^+ from the intracellular to the extracellular compartment, resulting in increased plasma volume; and an increase in cardiac output from the increased production of epinephrine due to enhanced phenylethanolamine-N-methyltransferase activity in the adrenal medulla.

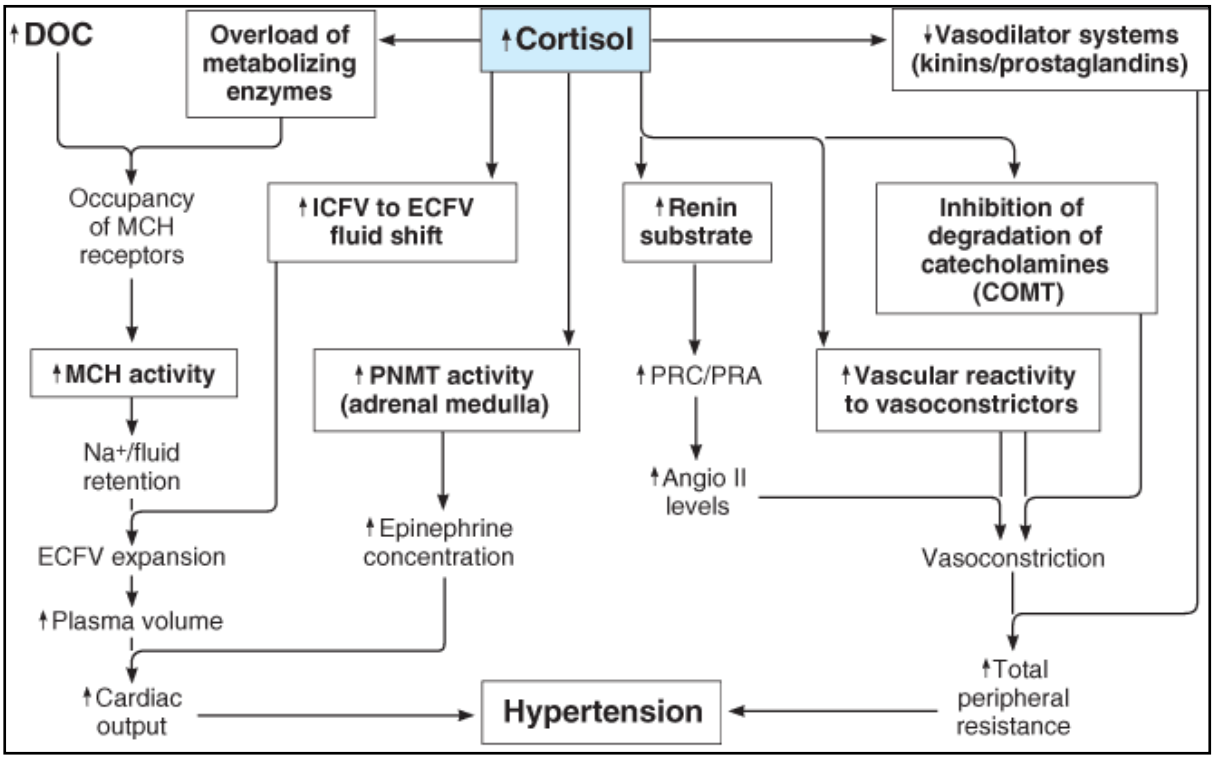

Figure 10-6. **Mechanisms involved in glucocorticoid hypertension** (DOC, deoxycorticosterone; MCH, mineralocorticoid hormone; ECFV, extracellular fluid volume; ICFV, intracellular fluid volume; PRC, plasma renin concentration; PRA, plasma renin activity; COMT, catechol-*O*-methyltransferase; PNMT, phenylethanolamine-*N*-methyltransferase).

Hypertension of Renal Origin

The Renin–Angiotensin System

Renin enzymatically cleaves an α_2–globulin substrate (angiotensinogen) to form a decapeptide (angiotensin I) that is subsequently cleaved by angiotensin–converting enzyme (ACE) to form an octapeptide (angiotensin II) with potent vasoconstrictor effect. Reducing blood flow to the kidney stimulates the renin-angiotensin system, resulting in an increase in blood pressure.

Renin

As the afferent arteriole enters the glomerulus (Fig. 10-9), the smooth muscle cells become modified to perform a secretory function. These juxtaglomerular cells produce and secrete renin, a proteolytic enzyme with a M.Wt. of 40,000. In close proximity are specialized tubular cells of the cortical ascending limb of the loop of Henle known as the macula densa. The juxtaglomerular cells of the afferent arteriole and the macula densa are referred to collectively as the juxtaglomerular apparatus that plays an important role in the regulation of renin secretion.

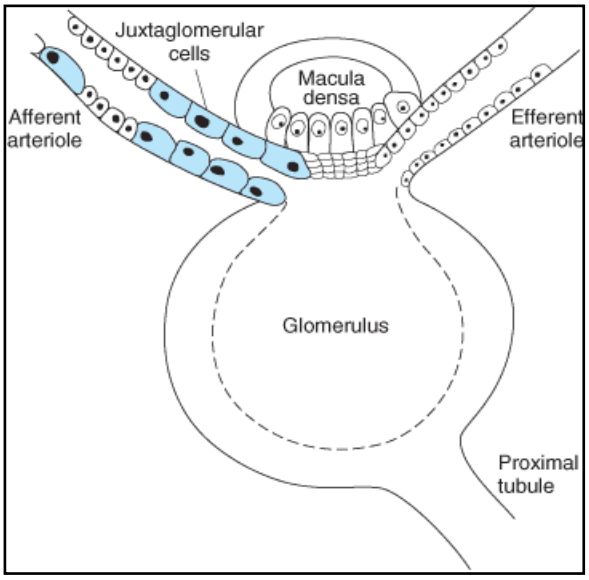

Figure 10-9. Diagram of a glomerulus, showing juxtaglomerular apparatus and macula densa.

The release of renin from secretory granules into the circulation is controlled by three major effectors:

1. Baroreceptors in the wall of the afferent arteriole that are stimulated by decrease in renal arteriolar perfusion pressure, perhaps mediated by local prostaglandins.

2. Cardiac and systemic arterial receptors that activate the sympathetic nervous system, resulting in increases circulating catecholamines and increased direct neural stimulation of juxtaglomerular cells via β1-adrenergic receptors.

3. Cells of the macula dense that appear to be stimulated by a reduction in Na^+ or Cl^- ion concentration in the tubular fluid delivered to this site. The Cl^- ion may be the primary mediator of this effect.

Once secreted, renin initiates a series of steps beginning with enzymatic cleavage of a decapeptide, angiotensin I from the amino terminal of angiotensinogen II (Fig. 10-10) by ACE. The concentration of ACE is greatest in the lungs. The half-life of angiotensin II in plasma is less than 1min.

Angiotensinogen: Angiotensinogen (renin substrate) is an α2-globuline secreted by the liver. It has a M.Wt. of 60,000. Hepatic production of angiotensinogen is increased by glucocorticoids and by estrogens. Stimulation of angiotensinogen production by estrogen–containing contraceptives may contribute to some of the hypertension encountered as a side effect of this treatment. In situation such as Na^+ depletion, where there is sustained high circulating level of renin, the rate of breakdown of angiotensinogen is greatly increased.

Angiotensin–Converting Enzyme (ACE): ACE is a carboxypeptidase, a glycoprotein with a M.Wt. of 130,000-160,000. Inhibitors of ACE are widely used to prevent the formation of angiotensin II in the circulation and thus block its biologic effects. In addition to ACE, a serine protease known as chymase has been shown in convert angiotensin I to angiotensin II identified in various tissues, most notably the cardiac ventricles.

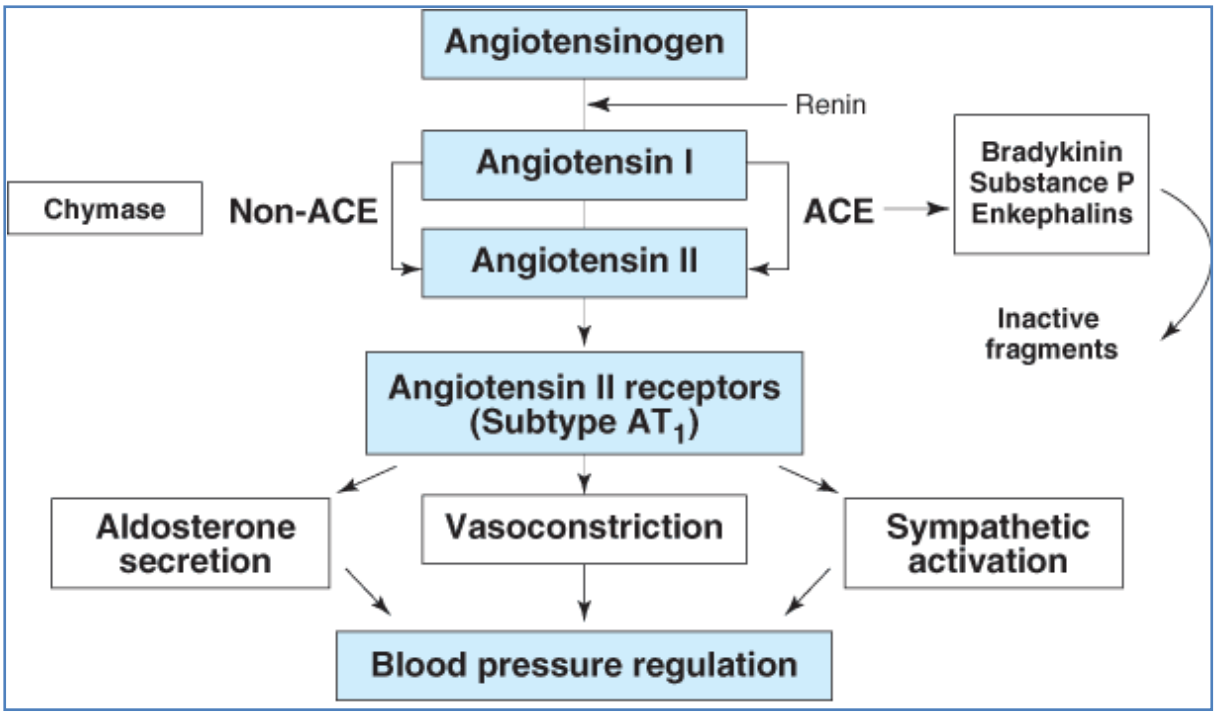

Figure 10-10. **The renin-angiotensin-aldosterone axis**. Angiotensin II is a critical hormone in the control of blood pressure.

Angiotensin II: similar to peptide hormones, angiotensin II binds to receptors on the plasma membrane of target cells. There are two classes of angiotensin II receptors (AT1 and AT2). AT1 appears to mediate virtually all the known cardiovascular, renal and adrenal-stimulatory effects of angiotensin II, AT2 may be involved in cell differentiation and growth. AT1 is linked to a G protein that activates phospholipase C, resulting in the hydrolysis of phosphoinositol to form inositol triphosphate and diacylglycerol.

Angiotensin II is a potent pressor agent, exerting its effects on peripheral arterioles to cause vasoconstriction and thus increasing total peripheral resistance. Angiotensin II may also increase the rate and strength of cardiac contraction. Angiotensin II also acts directly on the adrenal cortex to stimulate aldosterone secretion and in most situations is the most important regulator of aldosterone secretion. Angiotensin II thus plays a central role in regulating Na^+ balance. For example, during dietary Na^+ depletion, ECF volume is reduced. Subsequent stimulation of the renin-angiotensin system is important in two ways: its vasoconstrictor actions help to maintain blood pressure in the face of reduced ECF volume, whereas its actions to stimulate aldosterone secretion and thus Na^+ retention allow volume to be conserved.

Local Renin–Angiotensin System: In addition to the circulating renin-angiotensin system, it may be present in various tissues and function thereby to promote local production of angiotensin II. Such tissues include kidney, brain, heart, ovary, adrenal, testis, and peripheral blood vessels. In the kidney, local generation of angiotensin II directly stimulates Na^+ reabsorption in the early proximal tubule, in part by activation of the Na^+-H^+ antiporter in the luminal membrane. Angiotensin II of either local or systemic origin is also of critical importance in the maintenance of GFR during hypovolemia and reduced renal arterial flow.

The Renin–Angiotensin System and Hypertension

Essential Hypertension: Blood pressure is the product of cardiac output and peripheral vascular resistance. The hemodynamic abnormality that appears to underlie essential hypertension is an elevation in peripheral vascular resistance. The determinants of peripheral vascular resistance include a complex array of system and locally produced hormones and growth as well as neurogenic factors. However, the specific factor or factors that underlie the pathogenesis of essential hypertension remain to be determined.

Dietary Na^+ restriction enhances the adrenal but reduces the vascular responses to angiotensin II; Na^+ loading produces the opposite effect. Thus, for normal subjects ingesting a high–Na^+ diet, the Na^+ induced modulation of adrenal and vascular activities increases renal blood flow while attenuating renal reabsorption of Na^+; both events facilitate excretion of the load. It has been observed that about one-half of patients with essential hypertension with normal or high plasma renin levels may not modulate their adrenal and vascular responsiveness to a Na^+ load. These so-called "nonmodulators" do not increase their renal blood flow in response to a high-salt diet or increase aldosterone secretion in response to a low-salt diet. Thus, according to this model, these patients have an impaired ability to excrete a Na^+ load, leading to elevation in blood pressure. The proponents of this hypothesis suggest that there is an abnormality related either to local angiotensin II production or the angiotensin receptor such that target tissue responsiveness is not modified when Na^+ intake is altered. Adrenal and vascular responsiveness can be restored in these patients by reducing angiotensin II levels using ACE inhibitors.

Approximately 25% of patients with essential hypertension have low plasma renin levels. It has been suggested that the increase in blood pressure in this population are more likely to be salt-sensitive and that the greatest antihypertensive response may be achieved with a diuretic or calcium channel blocker. ACE inhibitors may be effective as well.

Recent studies have further implicated the renin-angiotensin system using molecular-genetic techniques. A genetic linkage has been described between an allele of the angiotensinogen gene and essential hypertension in affected siblings.

Renovascular Hypertension: the most common cause of renin–dependent hypertension is renovascualr hypertension. It is the most common correctable cause of secondary hypertension. It is usually due either to atherosclerosis or to fibromuscular hyperplasia of the renal arteries. Surgical correction of renal artery stenosis is effective. Medical treatment is used when the patient is considered unable to tolerate a surgical procedure or the diagnosis is uncertain. The ACE inhibitors and selective AT1 antagonists are particularly effective. Renovascualr hypertension may also respond to beta-adrenergic antagonists and calcium channel blockers.

Renin-secreting Tumors: They are extremely rare. Other renin-secreting neoplasms (e.g. Wilms' tumor) have been reported, including a pulmonary tumor that secreted excessive amounts of renin, producing hypertension and hypokalemia with secondary aldosteronism.

Accelerated Hypertension: it is characterized by marked elevations of diastolic blood pressure that can be abrupt in onset. This disorder is associated with progressive arteriosclerosis. The plasma levels of renin and aldosterone may be extremely high.

Estrogen therapy: Aldosterone levels may be increased during treatment with replacement estrogen therapy for oral contraception. This is due to an increase in angiotensinogen production and presumed increase in angiotensin II levels. Aldosterone levels increase secondarily.

Other Hormone System and Hypertension

Insulin: Hyperinsulinemia and insulin resistance have been implicated as potential factors in the generation of hypertension, particularly in obese patients (abdominal obesity). The association of hypertension, diabetes mellitus, abdominal obesity, and hyperlipidemia has been referred to as "syndrome X" or the syndrome of insulin resistance.

The hypertension observed in this clinical syndrome may be due to the hyperinsulinemia. Insulin accentuates the activity of the sympathetic nervous system, leading to greater vasoconstriction. In addition, insulin increase Na^+ reabsorption by the kidney, resulting in increased intravascular volume and blood pressure. It is noteworthy that weight loss lowers blood pressure, insulin levels, and insulin resistance in these patients. There is probably a critical interplay of genetic and hormonal factors in the pathogenesis of hypertension in patients with insulin resistance.

Natriuretic Peptides: Atrial natriuretic peptide (ANP) causes vasodilation, hyperfiltration, and natriuresis. The fall in blood pressure is thought to be largely to reduction of venous return and depression of cardiac output. In the kidney, ANP increases GFR. Natriuresis is due both to the increase in GFR and to the direct inhibition by ANP of Na^+ and water reabsorption by collecting duct cells. ANP inhibits secretion of renin, aldosterone, vasopressin, and ACTH as well as stimulation of heart rate mediated by the baroreceptors. When blood volume increases, the associated increase in atrial pressure and atrial stretch may trigger secretion of the peptide (ANP) and lead to natriuresis and blood pressure reduction.

Endothelium-Derived Relaxing Factor: EDRF has been identified as nitric oxide which diffuses within the cell or to adjacent cells such as smooth muscle cells, where it stimulates soluble guanylyl cyclase. The resulting increase in cGMP leads to a relaxation of vesicular smooth muscle cells and therefore vasodilation.

Sympathetic Nervous System: increased activity of the sympathetic nervous system has been implicated as a contributing factor in the pathogenesis of essential hypertension. This may be due to both genetic and environmental factors. It has been postulated that impaired baroreceptor function may prevent the normal inhibitory check on increases in sympathetic activity. The mechanisms by which increased sympathetic nervous system activity and catecholamines increase blood pressure is multifactorial, including augmented vasoconstriction, increased cardiac output, increased activity of the renin-angiotensin system, and enhanced Na^+ reabsorption by the kidney.