Chapter 31
Pathophysiology of Hypertension

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Abstract Hypertension is a rather simple phenotype characterized by an increase in systemic blood pressure above an arbitrarily defined threshold. Yet, the mechanisms leading to the increase in blood pressure are extremely complex and involved a wide variety of neurohormonal, renal, metabolic, and vascular factors. The causes of hypertension differ substantially in young children, in middle-aged men and women, and in the elderly. In children, hypertension is often the appearance of a renal or endocrine disease, whereas in adults, the large majority of patients with hypertension have an *essential* hypertension, a denomination reflecting that the mechanisms are not fully understood although some well-defined pathogenic factors have been described in patients with hypertension associated with diabetes mellitus, obesity, hyperaldosteronism, renovascular hypertension, or renal diseases. In the elderly, hypertension is strongly associated with factors leading to vascular aging and loss of arterial elasticity. The purpose of this chapter is to review the pathophysiology of hypertension in these different clinical situations in light of the recent literature.

Keywords Renal • Sodium handling • Hormonal systems • Inflammation • Estrogens • Immunity

31.1 Introduction

Cardiovascular diseases remain the most common noncommunicable cause of death in the general population in particular after the age of 40 years [1]. Among the factors that contribute to the development of cardiovascular diseases such as stroke, myocardial infarction, congestive heart failure, or renal and vascular complications, hypertension is undoubtedly the major, modifiable, independent risk factor in terms of prevalence, clinical impact, and attributable risk. According to the most recent

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Table 31.1 Trends in prevalence of hypertension according to age in the National Health and Nutrition Surveys

Age category (years)	1988–1991 (%)	1999–2000 (%)
8–17	7.3[a]	9.7[b]
18–39	5.1	7.2
40–59	27	30.1
>60	57–9	65.4

From Refs. [2] and [3]
[a]These data were obtained from 1988 to 1994
[b]These data were obtained from 1999 to 2006

data of the National Health and Nutrition Health Surveys conducted between 1988 and the years 2000–2006, the prevalence of hypertension is increasing slowly in adults as well as in children [2, 3] (Table 31.1). However, looking at these data, it appears that hypertension is still rather uncommon below the age of 20 and affects more than 50 % of subjects older than 60 years. This age effect on hypertension prevalence suggests that the pathophysiology of hypertension may differ substantially depending on the age at which the elevated blood pressure occurs and depending on the clinical comorbidities in which it happens. Indeed, there is a good evidence that the pathophysiology of hypertension developing in infancy is not comparable to that of hypertension diagnosed in the very elderly or in patients with chronic kidney disease or obesity. Yet, it is interesting to note that events occurring very early in life may influence the occurrence of hypertension later on. Thus, for example, it has been shown that changes occurring during the fetal period and the early years of development determine the blood pressure (BP) and the cardiovascular risk later on in life [4, 5]. Therefore, it may be useful to approach the pathophysiology of hypertension not as a unique global phenomenon but rather as a panel of mechanisms acting at different periods of life (Chap. 30). In this chapter, we shall review the pathophysiology of hypertension distinguishing hypertension in children, in middle-aged men and women, and in elderly taking into account the mechanisms associated with concomitant factors such as obesity, diabetes mellitus, or chronic kidney disease.

31.2 Pathophysiology of Hypertension in Children and Adolescents

Hypertension in childhood is defined as a BP above the 95th percentile taking into account age, sex, and height [6]. The prevalence of hypertension in children and adolescents is generally well below 10 % in the population, but the exact figure depends very much on the conditions in which BP is measured and on the number of visits [7]. Thus, in a recent survey of a large group of schoolchildren, we found that the prevalence of hypertension decreased from 11 to 2.2 % between the first and the third visits. The prevalence of elevated BP in children and adolescents is associated with an excess of body weight, a high heart rate, and the family history of

hypertension. However, the precise role of obesity in the recent increase in the prevalence of hypertension in childhood is debated [8].

In small children (<6–7 years), the detection of hypertension is commonly associated with the presence of a disease such as congenital renal abnormalities, a renal parenchymal disease, a coarctation of the aorta, or eventually a renal artery stenosis, endocrine diseases, and more rarely genetic alterations leading to hypertension [9] (Table 31.2). Hence, the pathophysiology of hypertension is linked directly to the mechanisms associated with the type of secondary hypertension. In congenital renal malformations or parenchymal renal diseases, the reduced glomerular filtration leading to a diminished capacity to excrete water and sodium plays an important role in the development of hypertension together with an activation of the renin-angiotensin and sympathetic nervous systems. In renal artery stenosis, the stimulation of the renin-angiotensin system by the stenotic renal artery contributes to BP elevation in order to maintain sodium balance at the expense of a high systemic BP. In young patients, a coarctation of the aorta induces hypertension through a dysfunction of baroreceptors associated with an intimal and medial hypertrophy of large and small vessels and a stiffening of the aorta. These changes can induce a vascular endothelial dysfunction, a reduced vasodilatory response to acetylcholine, and an increased vasoconstrictive response of peripheral vessels to catecholamines. For these reasons, hypertension tends to persist after correction of the coarctation.

The pathophysiology of endocrine-mediated hypertension depends on the type of hormone overproduction or absence. Glucocorticoid- and mineralocorticoid-induced hypertensions are mediated primarily by the sodium- and water-retention

Table 31.2 Common causes of hypertension in children between 1 and 10 years

First year	Coarctation of the aorta
	Renovascular disease
	Renal parenchymal disease
	Iatrogenic (medication, volume)
	Tumor
Infancy to 6 years	Renal parenchymal disease
	Renovascular disease
	Coarctation of the aorta
	Tumor
	Endocrine causes
	Iatrogenic
	Essential hypertension
Age 6–10 years	Renal parenchymal disease
	Essential hypertension
	Renovascular disease
	Coarctation of the aorta
	Endocrine causes
	Tumor
	Iatrogenic

Adapted with permission from Ref. [9]

properties of these steroids. In addition, direct effects of these hormones on cardiac, vascular, and renal tissues participate in the elevation of systemic BP. For example, glucocorticoids increase the synthesis of angiotensinogen and reduce the synthesis of prostacyclin resulting in a greater vascular reactivity to angiotensin II and catecholamines. Aldosterone has well-described profibrotic effects in the heart, kidneys, and vessels [10]. Hypertension is also a clinical characteristic of acromegaly. In that situation, hypertension is the consequence of the excess of growth hormones which leads to vascular hypertrophy but also to a hyperdynamic state, due to an activation of the sympathetic nervous system, and renal sodium retention [11]. Excess growth hormone and insulin-like growth factor 1 that characterize patients with acromegaly have been shown to be associated with enhanced renal and extrarenal epithelial sodium channel activity [12].

Monogenic forms of hypertension are more frequent among children with hypertension. As shown in Table 31.3, these forms of hypertension are due primarily to specific mutations in the kidney affecting sodium or potassium transport systems and leading most of the time to increased sodium reabsorption as the main cause of the elevation of BP [13]. In accordance with this mechanism, patients with monogenic hypertension have a good BP response to diuretics.

In older children (>10 years), secondary forms of hypertension tend to become less frequent although their incidence remains higher than in adults. However, essential hypertension becomes more prominent in adolescents and its pathophysiology is probably closer, if not similar, to that of young and middle-aged adults as discussed below.

As discussed before, birth weight appears to be an important determinant of BP and hypertension in children and adolescents as suggested in the *Barker's hypothesis* [4]. According to this hypothesis, the link between birth weight and hypertension is a low number of glomeruli and an incomplete renal maturity [5]. However,

Table 31.3 Most common forms of monogenic hypertension

Syndrome	K	pH	Renin	Aldo	Transmission	Gene	Treatment
GRA	Low/N	High	Low	High	Autosomal dominant	Chimeric gene CYP11B1/11B2	Spironolactone, amiloride, glucocorticoids
Liddle's syndrome	Low/N	High	Low	Low	Autosomal dominant	β and γ subunit of ENaC	Amiloride, triamterene
AME	Low/N	High	Low	Low	Autosomal recessive	11β-HSD	Spironolactone
MR in pregnancy	Low	High	Low	Low	Unknown	Mutations of mineralocorticoid receptor	Delivery
Gordon's syndrome	High	Low	Low	Low	Autosomal dominant	WNK 1 and WKN4	Hydrochlorothiazide
HBS	N	N	N	N		Unknown	None

GRA glucocorticoid-remediable aldosteronism, *AME* apparent mineralocorticoid excess, *MR* mineralocorticoid receptor mutation, *HBS* hypertension brachydactyly syndrome, *ENaC* epithelial sodium channel, *WNK* with no kinase

other factors related to the low birth weight may contribute to BP elevation including an immaturity of the corticoid system, a glomerular hyperfiltration, and a renal tubular adaptation leading to an overexpression of some renal transporters.

Taken together, it is suggested that hypertension in childhood and adolescence has a specific pathophysiology. The mechanisms of hypertension in this age category are important to consider because increasing evidence suggests that hypertension in infants and adolescents is associated with early target organ damage [14] and persistence of hypertension in adulthood.

31.3 Pathophysiology of Essential Hypertension in Adults

BP is the main driving force that brings blood to all organs of the body; thus, the control of BP is critical for life. In this context, it is not surprising that the regulation of BP is a highly complex and sometimes redundant interplay between renal, neural, cardiac, vascular, and endocrine factors modulated by genetic and environmental factors.

31.3.1 Role of Kidneys in the Pathogenesis of Essential Hypertension

Regulating sodium and water excretion and hence extracellular volume homeostasis, the kidney plays a crucial role in BP control. Indeed, as proposed by Guyton (1990), BP and sodium homeostasis are closely related through the pressure-natriuresis mechanism which enables to stabilize BP around a set point [15]. If renal perfusion pressure increases, renal sodium output increases and extracellular fluid volume contracts so that BP returns to its baseline value. According to this hypothesis, hypertension results from a shift of the BP set point due to a defect of the pressure-natriuresis mechanism. The regulation of sodium excretion in the pressure-natriuresis phenomenon occurs essentially in the proximal segments of the nephron and changes in medullary blood flow are important for the pressure-natriuresis relationship. In addition, many endocrine factors such as the renin-angiotensin-aldosterone system, nitric oxide, and prostaglandins can shift the pressure-natriuresis to higher or lower set points. There is also a good evidence that sodium handling by the distal segments of the nephron is critical to the regulation of sodium balance in relation to changes in BP and that other factors such as the sympathetic nervous system, a local intrarenal inflammation, and the generation of reactive oxygen species (ROS) can modify the pressure-natriuresis relationship [16].

The contribution of the kidneys to the development of hypertension has been demonstrated nicely using cross-transplantation studies in animals. These studies have demonstrated that transplantation of a kidney of a hypertensive rat into a normotensive animal leads to the development of hypertension in this latter.

Conversely, transplantation of a normotensive kidney to a hypertensive rat normalizes BP showing BP follows the kidney [17]. More recent studies have used this technique in mice to investigate the role of the renin-angiotensin system in mediating the hypertension induced by cross-transplantation. These studies have demonstrated that AT_1 receptors in the kidney but also in the vasculature contribute equally to the development of hypertension [18]. Some results have also been gathered in human transplantation, but the evidence obtained in these studies is less convincing as more confounding factors could interfere with the interpretation of the results [19].

In support of the role of kidneys in the pathophysiology of hypertension, one should mention once again the description of monogenic forms of hypertension which are associated to mutations in renal transport systems influencing renal sodium reabsorption in various segments of the nephron [20]. In essential hypertension, polymorphisms of some of these transport systems such as the epithelial sodium channel, Nedd4, or alpha-adducin may actually contribute to generate hypertension [21] or eventually protect against hypertension [22], but the frequency at which this occurs remains unknown.

31.3.2 Sympathetic Nervous System and Renin-Angiotensin-Aldosterone System

There are also several neuroendocrine systems that increase BP and maintain the hypertension state in part through their effects on renal function. The two most important are undoubtedly the renin-angiotensin-aldosterone and the sympathetic nervous systems. As both systems are discussed in separate chapters (Chap. 35, Sympathetic and Renin-Angiotensin Activity in the Pathophysiology of Hypertension; Chap. 36, Drugs Targeting RAAS in the Treatment of Hypertension and Other Cardiovascular Disease) of the present book, we shall only briefly summarize some effects of these systems as potential causes of hypertension. The renin-angiotensin-aldosterone system (RAAS), which originates with the synthesis of renin from the juxtaglomerular cells of the kidney, participates in the pathophysiology of hypertension in multiple ways through its vascular, endocrine, central, and renal properties. In recent years, it became apparent that the RAAS exists not only as a circulatory system but also as a local tissue system. As reviewed by Kobori et al. [23], many components of the renin-angiotensin-aldosterone system have been localized within the kidney. Thus, in addition to being a potent vasoconstrictor and a growth-promoting peptide, renal angiotensin II controls BP through its effect on renal hemodynamic and glomerular filtration rate as angiotensin II modulates the tone of both afferent and efferent arterioles. Angiotensin II also modulates renal tubular sodium reabsorption at different sites along the tubule through direct and aldosterone-mediated effects on sodium transport. But angiotensin II also induces inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation, regulates the gene expression of bioactive substances, and activates multiple

intracellular signaling pathways, all of which may contribute to maintain a high BP and to promote the development of hypertension-induced complications. Interestingly, even a short-time exposure to angiotensin II may produce a long-term hypertension by provoking renal vascular lesions and a local inflammation [24, 25]. Of note, although an increased activity of renin-angiotensin-aldosterone system has been observed in many animal models of hypertension, not all hypertensive patients have an activated renin-angiotensin-aldosterone system; therefore, when measuring the activity of this system in hypertension, it should always be examined in the light of sodium intake as there is a strong interaction between sodium intake and the activity of the renin-angiotensin-aldosterone system.

Regarding the sympathetic nervous system, there is also abundant evidence that this system contributes to the regulation of BP and to the pathophysiology of hypertension [26]. Indeed, several animal models of hypertension are characterized by an increased sympathetic activity [27]. Moreover, in early stages of clinical hypertension, a combination of sympathetic hyperactivity and parasympathetic dysfunction has been observed in young subjects with an increased heart rate [28]. In the kidney, the sympathetic system has a major influence on renin secretion, renal hemodynamics, and tubular sodium handling [26]. The role of the sympathetic nervous system and of baroreflex control in the genesis of hypertension has led to the development of new interventional strategies to treat resistant hypertension (renal denervation, baroreflex sensitization) [29].

31.3.3 Prostaglandins

Another set of substances that regulate BP and may be involved in the genesis of hypertension are prostaglandins. Prostaglandins are the product of arachidonic acid metabolism [30]. Their production involves several steps: firstly, the release of arachidonic acid from membrane phospholipids under the action of phospholipase A_2; secondly, the catalysis of arachidonic acid by cyclooxygenases (COX 1, 2, or 3) to generate PGH_2; and thirdly, the generation of specific prostaglandins under the effect of prostaglandin synthases such as prostacyclin synthase leading to the formation of prostacyclin (PGI_2) or thromboxane synthase which generates thromboxane A_2 (Fig. 31.1). This cascade leads to the synthesis of several prostaglandins with multiple biological properties, including vascular, renal, and inflammatory effects. Phospholipase A_2 is activated by a variety of stimuli, including angiotensin II, norepinephrine, and bradykinin.

Prostaglandins act mainly near their sites of release because they are degraded rapidly by local metabolism into inactive products. At the vascular level, prostaglandins can produce either a vasoconstriction (thromboxane A_2, $PGF_2\alpha$) or a vasodilatation (PGE_2, prostacyclin). One important property of vasodilatory prostaglandins is their ability to modulate the vasoconstriction induced by potent vasoactive substances such as angiotensin II. In the normal adult kidney, both COX-1 and COX-2 are constitutively expressed. COX-1 is expressed in the glomerulus, the afferent

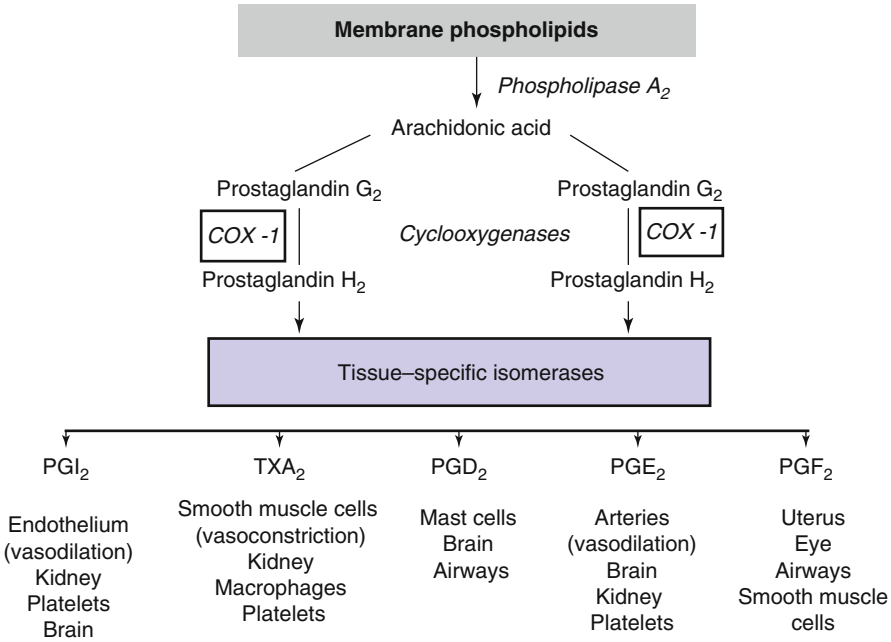

Fig. 31.1 Metabolism and systemic effects of prostaglandins. Schematic representation of the metabolism of prostaglandins and their effects on various tissues. Note that some prostaglandins can affect vascular tone and hence blood pressure through vasodilating prostaglandins (PGI_2 and PGE_2) as well as through the vasoconstrictor effect of thromboxane A_2 (TXA_2)

arteriole, and tubular cells, and COX-2 has been expressed in the afferent and efferent arterioles, the podocytes, the macula densa, and some tubular and interstitial cells. Intrarenal prostaglandins participate actively in the regulation of renal perfusion and glomerular filtration rate. They are also implicated in the maintenance of sodium, potassium, and chloride homeostasis and in the regulation of renin secretion [31, 32]. The impact of prostaglandins on vessels, renal electrolyte balance, and renin secretion may be of particular relevance to the genesis of hypertension [33]. Indeed, data have demonstrated that mice deficient in the PGI_2 receptor are resistant to the development of renovascular hypertension, a renin-dependent form of hypertension [34].

In hypertensive patients, a deficiency in vasodilatory prostaglandins has been reported [35], and an increase in thromboxane A_2 has been found in essential hypertension [36]. These observations lead to the hypothesis that there might be an imbalance between anti- and pro-hypertensive prostaglandins in hypertension. The potential role of prostaglandins in hypertension is further emphasized by the observation that selective and nonselective COX-1 and COX-2 inhibitors increase BP, favor sodium retention, and may cause hypertension in some patients [37]. However, it appears that the hypertensive effect of nonsteroidal anti-inflammatory drugs is more frequent among hypertensive than normotensive patients. This would indicate

that prostaglandins act as a counter-regulatory mechanism to limit the increase in BP in hypertension and may not be a primary hypertensive mechanism [35].

31.3.4 Role of Vasculature in the Pathogenesis of Essential Hypertension

As observed by Folkow in the 1970s [38], when BP increases persistently, blood vessels undergo an adaptation characterized by a structural remodeling leading to an increase in wall:lumen ratio. This adaptation actually maintains a chronic increase in vascular resistance in established hypertension. Clinically, it appears that this vascular remodeling occurs very early in the course of the pathogenesis of hypertension probably even before BP has reached the hypertensive range [39]. Today, several investigators have actually confirmed using gluteal biopsies that there is indeed a remodeling of small arteries in hypertensive patients, that small vessel remodeling may have a major impact on target organs, and that antihypertensive therapy can reverse it [40]. The mechanisms involved in this remodeling imply essentially an increased vascular tone and an increased activity of the sympathetic nervous system, angiotensin II which causes a proliferation of smooth muscle cells, endothelin-1, and perhaps inflammatory processes [41]. At the cellular level, the matrix rearrangement appears to involve integrins and tissue transglutaminase, one of a family of transglutaminase enzymes, which includes factor XIII [42].

31.3.4.1 Nitric Oxide

The endothelial layer of the vascular wall produces several substances, which are closely involved in the regulation of the circulation and vascular wall homeostasis. Some of these substances are direct vasodilators such as nitric oxide, prostacyclin, and endothelial-derived hyperpolarizing factor, and some are potent vasoconstrictors such as endothelin-1 and thromboxane. Nitric oxide is formed by the enzyme nitric oxide synthase (NOS) from the amino acid L-arginine. Once formed, NO diffuses to the underlying vascular smooth muscle cells, activates soluble guanylyl cyclase, and produces vasorelaxation [43]. Three forms of NOS have been described: a neuronal NOS present in neural cells, an inducible NOS (iNOS), and an endothelial NOS (eNOS) present essentially in the endothelium. In the vessels, NO is released from endothelial cells in response to physical stimuli (shear stress and hypoxia) and by the stimulation of endothelial receptors such as bradykinin and muscarinic receptors. NOS activity can be inhibited using endogenous analogues of L-arginine such as asymmetric dimethylarginine or N-monomethyl-L-arginine (L-NMMA). Some of these analogues are increased in disease states, for example, in patients with chronic renal failure.

The potential role of NO in the pathophysiology of cardiovascular diseases including hypertension has first been evoked with the demonstration that acetylcholine, in the absence of endothelium, is a vasoconstrictor rather than a vasodilator

[44]. Following this seminal observation, numerous studies have demonstrated the crucial role of the endothelium in the regulation of cardiovascular homeostasis and have led to the concept of endothelial dysfunction. Thus, endothelial dysfunction of large and small arteries has been described in animal models of hypertension as well as in patients with essential hypertension [45–47]. Several mechanisms are discussed whereby endothelial dysfunction results in hypertension. Studies have suggested an impaired NO synthesis and release, but endothelial dysfunction may also be consecutive to an increased breakdown of NO as the vasorelaxing properties of NO are counteracted by oxidative processes in tissues. Superoxide anions are potent scavengers of endothelial-derived NO. Whether endothelial dysfunction is a primary or secondary event in hypertension has been discussed because an elevation of blood pressure per se can cause endothelial dysfunction [48]. However, a blunted endothelium-dependent vasodilatation has been observed in offspring of hypertensive parents suggesting that endothelial dysfunction can precede the development of hypertension and may play a primary role in the genesis of the disease [49]. Of note, transgenic mice deficient for the eNOS develop a systemic hypertension associated with an increased peripheral vascular resistance [50, 51]

The role of nitric oxide in the pathogenesis of hypertension is controversial [52]. Nitric oxide can contribute to the etiology of hypertension by various other mechanisms, one of them being the development of atherosclerosis. Indeed, NO has been reported to decrease monocyte and leukocyte adhesion to endothelial cells, to inhibit platelet aggregation and platelet-vessel wall interaction, to decrease the transport of lipoproteins into the vessel wall, and to inhibit vascular smooth muscle cell proliferation as well as some components of the vascular inflammation. Another pathway by which NO can affect blood pressure is the interaction with the renin-angiotensin system. Nitric oxide has indeed been found to suppress renin release by juxtaglomerular cells and hence to reduce the activity of the renin-angiotensin system and to participate in the regulation of renal hemodynamics [53]. As discussed previously, NO also interacts closely at the vascular level with endothelin to limit the vasoconstrictor effect of endothelin. Some of these interactions may actually lead to an increased vascular tone. At last, the activity of nitric oxide is related to other vasoactive compounds such as prostanoids and bradykinins.

31.3.4.2 Endothelin

Endothelin (ET) is a very potent endogenous vasoconstrictor produced by the endothelium and identified by Yanagisawa et al. in 1988 [54]. There are three isoforms of endothelin (i.e., ET-1, ET-2, and ET-3), but endothelin-1 is the only relevant peptide in humans. Endothelin is derived from pro-endothelin, which is cleaved into a big endothelin and then converted to the active endothelin-1 by an endothelin-converting enzyme. Several stimuli induce endothelin release by endothelial cells including shear stress, thrombin, angiotensin II, vasopressin, catecholamines, and hypoxia [55]. The effects of endothelin are mediated by two receptors, i.e., the ET-A and ET-B receptors. The ET-A receptor is widely distributed and it is the principal receptor located on vascular smooth muscle cells and cardiomyocytes. In these cells, activation of ET-A

receptors leads to an activation of phospholipase C, to an increase in intracellular calcium, and, hence, to cell contraction. The ET-B receptor is located on both vascular smooth muscle and endothelial cells. In endothelium cells, activation of ET-B receptors releases vasodilating substances such as nitric oxide (NO), prostacyclin, and adrenomedullin. In muscle cells, activation of the ET-B receptor induces a vasoconstriction (Chaps. 34 and 45).

If vasoconstriction is the hallmark of endothelin's action, several other biological properties of endothelin have been described. Thus, renal function appears to be particularly responsive to the effects of endothelin [56]. Administration of low doses of endothelin-1 in animals and humans has been shown to decrease glomerular filtration rate and renal blood flow through the stimulation of vascular smooth muscle cells and contraction of mesangial cells and to reduce urinary sodium excretion. Similarly, overexpression of endothelin in the mouse kidney has been associated with the development of glomerulosclerosis, the development of interstitial fibrosis, and the development of renal cysts but not hypertension suggesting a role of endothelin in the development of some renal diseases independent of the hypertensive effect. These effects appear to be mediated by the activation of ET-A receptors. However, endothelin-1 can also lower BP and produce a natriuretic response through the activation of ET-B receptors which have been localized on renal tubular epithelial cells [57]. Recent data suggest that the renal medullary endothelin system is important for BP regulation. Indeed, transgenic rats deficient in endothelin-1 specifically in the collecting duct develop hypertension [58]. In the normal guinea pig heart and in isolated cardiomyocytes, endothelin-1 had positive inotropic and growth-promoting effects [59]. At the vascular level, as mentioned earlier, endothelin may contribute to the remodeling of small and large arteries [60].

Experimental data have demonstrated that endothelin-1 interacts very closely with nitric oxide via activation of ET-B receptors on endothelial cells. Indeed, endothelin-1 promotes the release of NO and thereby maintains a balance between the vasodilatory effect of NO and the vasoconstrictor effect of endothelin-1 itself. There is also a close interaction between endothelin and the renin-angiotensin-aldosterone system [61]. Angiotensin II enhances the vascular responsiveness to exogenous endothelin-1 and increases the release of endothelin-1 and the expression of preproendothelin in endothelial cells.

The role of endothelin as a potential pathogenic factor in hypertension has been suggested using several experimental and clinical approaches [60]. In rats, knockout of the ET-B receptor is associated with the development of severe salt-sensitive hypertension [62]. In humans with essential hypertension, plasma endothelin levels are usually not elevated except in Afro-Americans [63]. However, circulating concentrations of endothelin may not necessarily reflect the tissue concentrations because endothelin acts as a paracrine/autocrine system. Nonetheless, elevated circulating concentrations of endothelin have been reported in some human and experimental forms of hypertension such as the mineralocorticoid-induced and renovascular hypertension in the rat and hypertension in renal transplant patients and patients with diabetes or chronic renal failure. There are also data suggesting that endothelin plays a role in the development of hypertension in pregnancy-induced hypertension [64, 65].

The best demonstration of the role of endothelin in hypertension in humans has come from the use of selective endothelin antagonists. Indeed, in recent years, several selective and nonselective non-peptide antagonists of ET-A and ET-B receptors have been developed and investigated. In mild to moderate hypertensive patients, the dual ET-A and ET-B receptor antagonist bosentan (500–2,000 mg) lowered BP as effectively as the angiotensin-converting enzyme inhibitor enalapril (20 mg) [66]. Similarly, a significant decrease in blood pressure was found with darusentan, a selective ET-A endothelin receptor antagonist, in patients with a mild to moderate hypertension [67].

31.3.5 Metabolic Factors in the Pathogenesis of Essential Hypertension

31.3.5.1 Obesity

Essential hypertension is a common feature in patients with obesity, metabolic syndrome, and diabetes. Indeed, in obese subjects, hypertension is diagnosed in up to 50 % of patients, and similarly about 50 % of type 2 diabetic patients are hypertensive at the time of diagnosis [68, 69]. The pathogenesis of hypertension in these metabolic disorders has some specificity and implies, in addition to the sympathetic and renin-angiotensin systems, other mechanisms such as hyperglycemia, insulin resistance, adipokines (leptin and adiponectin) play.

In obese patients with hypertension, the elevated BP is associated with sodium retention and rightward shift of the pressure-natriuresis relationship. This shift is due in part to a sustained activation of the renin-angiotensin system and an increased sympathetic activity but also to the physical compression of the kidneys by surrounding visceral fat and increased renal sinus fat [70]. Considering the role of the renin-angiotensin system in obesity-induced hypertension, aldosterone appears to be particularly important to mediate an increase in BP observed in obesity as well as in patients with metabolic syndrome. Indeed, higher plasma aldosterone levels have been measured in obese patients and patients with the metabolic syndrome [71]. In the study by Goodfriend et al. (2004), oxidative stress and oxidized fatty acids derived from linoleic acid stimulated aldosteronogenesis and thereby promoted sodium retention [72]. These oxidized fatty acids are essentially produced by visceral fat, an observation that confirms that visceral fat contains all the components of the renin-angiotensin system.

31.3.5.2 Leptin

Regarding the sympathetic nervous system in obesity, many factors contribute to increase its activity including angiotensin II, baroreflex sensitivity, hyperinsulinemia, and sleep apnea but also hypoghrelinemia and hypoadiponectinemia and leptin resistance. An interesting observation made in animal models of obesity is that sympathetic tone is only moderately increased and that not all organs

demonstrate an elevated sympathetic activity [73]. Thus, some studies have shown that sympathetic drive is increased in the kidney and muscle but not necessarily in the heart [73]. Moreover, visceral fat rather than subcutaneous fat appears to participate in the increased sympathetic nerve activity. Leptin and adiponectin, the two molecules produced by adipocytes, may actually contribute to an increase in BP observed in obese patients through their effects on the sympathetic and renin-angiotensin systems. Plasma levels of leptin are proportional to the fat mass. Leptin acts on a specific leptin receptor localized in the brain where its stimulation reduces appetite and increase energy expenditure, thus lowering body weight [74]. Mice deficient in leptin develop hyperphagia, obesity, and insulin resistance. Leptin has also pro-inflammatory properties, which may contribute to the high cardiovascular risk associated with obesity. The ability of leptin to increase BP has been suggested by studies in which leptin was infused either in the brain or peripherally. These leptin administrations actually activated the sympathetic nervous system and progressively increased BP, an effect that could be blocked by administration of an alpha- and beta-adrenergic blocker [75]. In obese humans and rodents, elevated levels of leptin have been measured but surprisingly anorexia is generally absent. Therefore, it has been suggested that leptin resistance explains this discrepancy and that this resistance is frequent in obesity. Thereafter, the observation in animals of dissociation between the ability of leptin to stimulate sympathetic tone and to increase BP and the finding of an absence of simultaneous reduction of appetite and body weight has generated the concept of *selective leptin resistance* [76] as shown in Fig. 31.2. The concept of leptin resistance has been reviewed recently and the mechanisms of this dissociation are discussed in details by Mark et al. [77]. Of note, the actual role of leptin in mediating the obesity-induced hypertension in humans remains highly controversial as many conflicting results have been published [77].

31.3.5.3 Adiponectin

Adiponectin is another complex molecule secreted by adipocytes which has been associated with metabolic and cardiovascular diseases including hypertension [78] (Fig. 31.2). This molecule is present in the plasma in three molecular forms (high-molecular-weight, low-molecular-weight, and trimeric forms). Adiponectin acts on two distinct receptors localized in various tissues (muscle, liver, endothelium) where it can mediate the effects on peroxisome proliferator-activated receptors (PPAR), AMP kinase activation glucose uptake, and beta-oxidation [78]. In endothelial cells, adiponectin has also been shown to increase NO production by regulating endothelial NOS activity [79]. In obesity, low levels of adiponectin have been measured suggesting that hypoadiponectinemia is associated with an increase in BP. In animals, there is a close relationship between angiotensin II and the sympathetic nervous system and adiponectin. In rats, angiotensin II infusion decreases plasma adiponectin levels and inhibition of the renin-angiotensin system increases adiponectin through the PPARγ nuclear receptor [78]. As noted earlier, adiponectin is closely related to the sympathetic system. An increased sympathetic tone is associated with a reduction of plasma adiponectin and this may influence BP. The

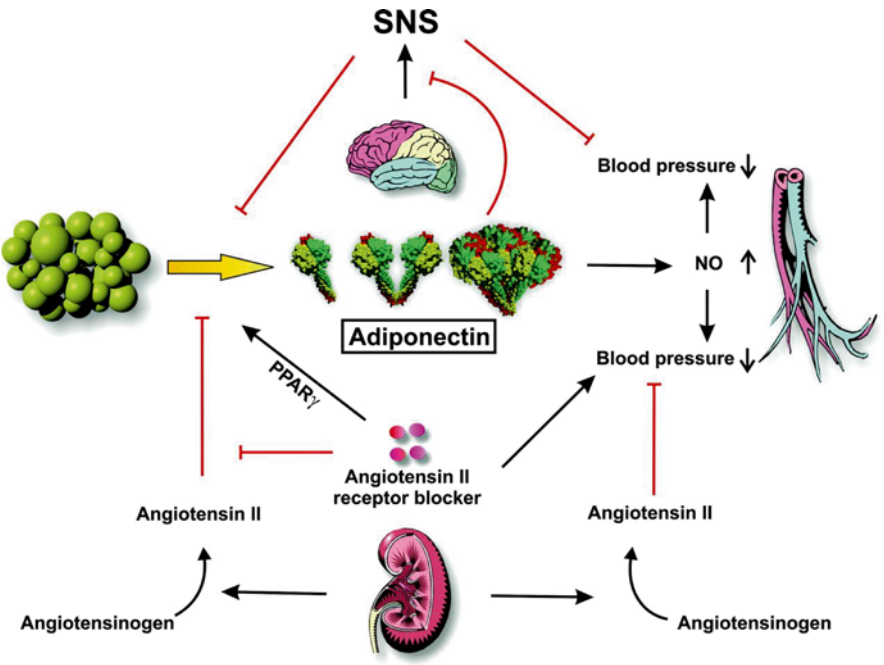

Fig. 31.2 Role of adiponectin in blood pressure control (Adapted with permission from Ref. [78]). Adipose tissue secretes three molecular forms of adiponectin into circulation. Adiponectin stimulates the production of NO, which is involved in the regulation of blood pressure. Renin secreted from the kidney cleaves angiotensinogen to produce angiotensin II. Angiotensin II plays an inhibitory role in adiponectin production. Angiotensin II AT_1 receptor blockers display pleiotropic effects on blood pressure control through receptor blocking and adiponectin stimulation. SNS overdrive increases blood pressure and inhibits the production of adiponectin. Also, adiponectin inhibits the activation of SNS through central actions. *Black arrows* indicate activation and *red lines* indicate inhibition

interaction between these two systems occurs in the periphery as well as in the brain and may be involved in the genesis of hypertension in obesity [80].

31.3.5.4 Insulin

Insulin is another hormone that is increasingly considered in the genesis of hypertension in obese patients and patients with the metabolic syndrome [81]. Hypertension, obesity, dyslipidemia, and glucose intolerance represent a cluster of risk factors which is called metabolic syndrome although this entity is often criticized. Insulin resistance in some peripheral tissues appears to be the main feature of metabolic syndrome. The peripheral insulin resistance is associated with an increased activity of the sympathetic nervous system and endothelin and a decrease in NO production [82]. Moreover, in the kidney, insulin has been shown to cause sodium retention, an effect which may further contribute to increased BP in this clinical context.

31.3.6 Other Hormonal Factors in the Pathophysiology of Essential Hypertension

In addition to the many system described above, several other hormonal factors may participate in the regulation of BP either through their vasodilating properties, which may be altered in hypertension, or through their vasoconstrictor effects. In this respect, one should consider natriuretic peptides, kinins, vasopressin, and dopamine.

31.3.6.1 Natriuretic Peptides

Natriuretic peptides were identified in the 1980s with the observation that rat atrial extracts had potent natriuretic and vasodilatory properties [83]. This original finding led to the identification of the atrial natriuretic peptide (ANP) and subsequently to the recognition of a family of four distinct natriuretic peptides: ANP (17 amino acids), BNP (32 amino acids), CNP (22 amino acids), and urodilatin (32 amino acids). ANP is synthesized and secreted predominantly by the atria. BNP was initially isolated from pig's and dog's brains but it is produced essentially by cardiomyocytes [84]. CNP has been localized in the brain and in the heart but also in several other peripheral tissues including the kidney, the adrenal glands, and the endothelium. ANP and BNP are released from the heart in response to changes in atrial or ventricular stretch. Plasma levels of natriuretic peptides are also influenced by the body position and the salt intake. Natriuretic peptides act by stimulating specific receptors (natriuretic peptide receptors A, B, and C). These receptors are widely distributed throughout the body including endothelium, smooth muscle cells, heart, adrenal gland, lung, brain, adipose tissue, and kidney [85]. Natriuretic peptides are degraded by the neutral endopeptidase [11, 24] and by a receptor-mediated clearance via the C receptor. Inhibition of neutral endopeptidase to increase plasma natriuretic peptides is today one approach to treat hypertension and heart failure in combination with a blocker of the renin-angiotensin system [86].

ANP and BNP possess diuretic, natriuretic, vasodilatory, and anti-hypertrophic, antifibrotic, antiproliferative, and anti-inflammatory properties. ANP also causes intravascular volume contraction as documented by increases in hematocrit and serum albumin when administered to binephrectomized rats [87]. ANP has an inhibitory action on aldosterone and renin secretion [88]. ANP and BNP antagonize vasoconstriction induced by norepinephrine or angiotensin II. There is also some evidence that the central effects of ANP contribute to fluid and electrolyte balance and to the regulation of systemic hemodynamics [89]. These central effects of ANP are mediated by an interaction between ANP and sympathetic tone in the brain stem.

Whether or not natriuretic peptides participate in the pathogenesis of hypertension is still debated. Experimentally, mice in which either the Pro-ANP or the ANP-A receptor genes were deleted developed hypertension [90, 91]. On the other

hand, mice overexpressing the ANP and BNP genes demonstrated a lower blood pressure than controls [92]. In rat models of hypertension, an altered ANP secretion in response to salt loading or to an increased atrial pressure has been observed suggesting a role of these peptides in hypertension [93]. In hypertensive patients, low to normal plasma ANP levels have been measured [94, 95]. However, some investigators have reported raised plasma ANP levels in patients with essential hypertension even though blood volume was generally not expanded in these patients. This observation may be explained by an increased central venous pressure owing to a greater venous return or to atrial distension in some hypertensive subjects. In offsprings of hypertensive parents, Ferrari et al. (1990) have reported a reduced ANP response to salt loading indicating ANP deficiency, which may be a predisposing factor to the development of hypertension [96]. A similar impaired ANP response to salt loading has been reported in Afro-Americans and in patients with salt-sensitive hypertension [97]. Today, several research groups are working on the role of genetic variants of the atrial natriuretic peptide gene to investigate the potential role of this peptide in the development of cardiovascular complications such as stroke or coronary heart disease [98, 99].

31.3.6.2 Kinins

The interest for kinins as effective mediators in cardiovascular control has grown with the development of angiotensin-converting enzyme inhibitors, which inhibit not only the generation of angiotensin II but also the degradation of bradykinin. The kallikrein-kinin system consists of proteases (kallikreins) that release kinins from kininogen, the precursor protein. Primarily, the liver synthesizes kininogen, but the mRNA for the high-molecular-weight (HMW) kininogen has been identified in endothelial cells. Kallikreins are present in plasma where they generate bradykinin from the HMW kininogen and in tissues, particularly in the kidney. Tissue kallikrein cleaves a low-molecular-weight kininogen to release *lys*-bradykinin (kallidin). Kallidin is then metabolized through an aminopeptidase into bradykinin. Kinins act by stimulating specific receptors (kinin B1, B2, and B3 receptors). The B1 receptor is involved in the chronic inflammatory and pain-producing response to kinins. The B2 receptor mediates most of the other actions of kinins. In the circulation and tissues, kinins are destroyed by aminopeptidases and carboxypeptidases. The dipeptidase kininase II (ACE) is the most important metabolizing enzyme within the cardiovascular and renal systems. The synthesis, activity, and release of renal kallikrein mRNA and protein levels are influenced by several hormonal systems including mineralocorticoids, glucocorticoids, testosterone, thyroxine, insulin, vasopressin, cathecholamines, and angiotensin II. Of note, renal kallikrein mRNA of females is twice that of males.

The very first clue that kinins could play a role in hypertension was published in the early 1930s when a reduction in urinary kallikrein excretion was found in hypertensive patients. Thereafter, little attention was given to this system. Later on, a similar observation was made in various groups of hypertensive patients

including African-Americans and patients with a low renin hypertension and in rats with hypertension [100, 101]. All genetic models of hypertension in the rat show abnormalities in the kallikrein-kinin system. With time, increased evidence for a role of kinins in blood pressure was reported. The B2 receptor knockout mouse receiving a high-sodium diet displayed a significantly increased blood pressure and renal vascular resistance, and reduced renal blood flow relative to the control mouse [102]. Similarly, selective B2 receptor blockade has been shown to cause a rise in blood pressure in various experimental models of hypertension in the rat [103, 104]. Conversely, overexpression of human tissue kallikrein lowered BP in mice [105]. More recent family studies have suggested that individuals with a greater urinary kallikrein excretion genotype were less likely to have one or two hypertensive parents and urinary kallikrein was recognized as a strong marker of a genetic component of essential hypertension [106, 107]. More recent data have suggested that the renal kallikrein-kinin system participates in the development of salt-sensitive hypertension and pharmacological interventions of this renal system may be a new pathway to lower BP in some individuals with hypertension [108].

31.3.6.3 Arginine-Vasopressin

Arginine-vasopressin (AVP) has been recognized as one of the most potent vasoconstrictor peptide in the body through the activation of V_1 vascular receptors. Moreover, vasopressin is a crucial determinant of fluid balance mediated by its activity on renal V_2 receptors. Vasopressin has long been known to play a role in blood pressure homeostasis in several physiological and pathological clinical conditions such as changes in posture, dehydration, hemorrhage, adrenal insufficiency, and heart failure [109]. More recently, the contribution of vasopressin to the progression of hypertension, diabetes, and chronic kidney diseases has been attributed to both V1 and V2 receptors, and there is some evidence that vasopressin could participate in the pathogenesis of some forms of hypertension [110].

When administered directly into the lateral or third ventricle of the brain, small doses of vasopressin V1 agonist induced a sudden rise in BP, which was not observed with a V2 agonist, and this effect may be due to an activation of sympathetic nervous system [89]. Elevated levels of vasopressin have been documented in several experimental rat models of hypertension including in the DOCA-salt-hypertensive rat, the SHR, and the Dahl salt-sensitive rat. However, the role of V2 receptors in these forms of hypertension remains debated [111–114]. In humans, the evidence for a role of vasopressin in the pathogenesis of essential hypertension is rather weak. In normotensive subjects and in hypertensive patients on a regular sodium diet, administration of an effective and selective V1 antagonist did not lower blood pressure [115, 116]. However, in patients with severe hypertension or malignant hypertension, the administration of a vasopressin receptor blocker was associated with a moderate decrease in blood pressure [117, 118].

31.3.6.4 Dopamine

Besides the abovementioned humoro-endocrine factors involved in the regulation of blood pressure, several other endocrine/autocrine systems can contribute to the development of hypertension. In recent years, evidence has shown that the intrarenal dopaminergic system contributes to BP regulation [119]. Data have been obtained in experimental and human studies indicating that abnormalities in dopamine production or dopamine receptor signaling can increase BP and augment the salt sensibility of BP. Particularly interesting observations have been made regarding the role of alterations in dopamine receptor function by GRK4, a G protein-coupled receptor kinase subfamily. Studies have demonstrated that the GRK4 gene locus is associated with the development of essential hypertension by promoting renal sodium reabsorption [120].

31.3.7 Is There a Role for Inflammation and Immunity in the Pathophysiology of Essential Hypertension?

Many of the pathogenic mechanisms discussed previously as causal in the early development and maintenance of an elevated BP in essential hypertension are actually associated with the induction of a micro-inflammation. This is the case, for example, of angiotensin II, salt, adipokines, and endothelial factors. These observations have revived the interest for inflammatory and immunological mechanisms in hypertension. In fact, historically, findings suggesting a role of immunity in the pathogenesis of hypertension have been published more than 30 years ago with the description of the role of the thymus in the development of hypertension in mice with a reduced renal mass and in the Lyon genetically hypertensive rat [121, 122].

As reviewed recently [123], many experiments were conducted in various models of hypertension such as the spontaneously hypertensive (SHR) or the deoxycorticosterone acetate-treated rat (DOCA) to investigate the impact on BP of transferring immune-competent cells or administering an immunosuppressive agent. In all these models, hypertension could be either induced or attenuated following an intervention on the immune system. These studies also focused the attention on the potential role of T cells in the pathogenesis of hypertension [124].

Today, the working hypothesis linking the immune system, inflammation, and the genesis of hypertension is based on the fact that hypertension-induced stimuli in target organs produce neoantigens, i.e., molecules that are normally not exposed to the immune system and generate an immune response (Fig. 31.3). Thus, factors like angiotensin II or salt, which cause a modest increase in BP initially, produce lesions in the vasculature or the kidney leading to the formation of neoantigens. These latter promote a T-cell activation and T cells penetrate the renal and vascular tissues. T-cell-derived signals such as IL-17 promote entry of other inflammatory cells such as macrophages. Consequently, inflammatory cells release cytokines that cause vasoconstriction and promote sodium and water absorption, ultimately increasing BP and causing sustained hypertension [124]. In this hypothetic model, some cytokines appear to play an important role as a

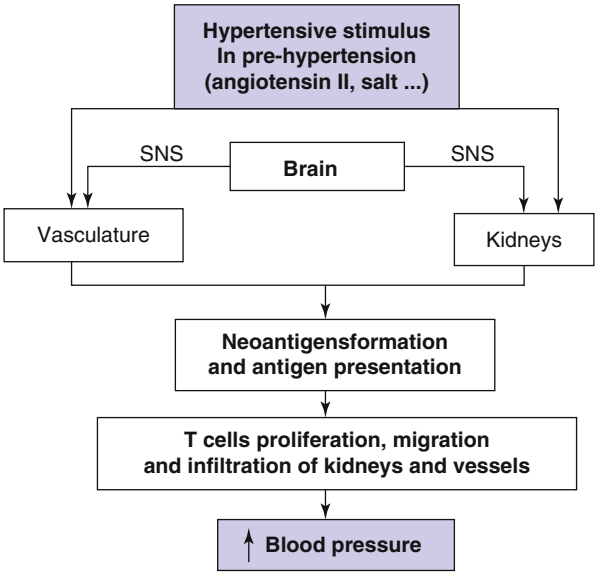

Fig. 31.3 Potential role of immunity in the pathogenesis of hypertension. Schematic representation of the potential role of immunity in the development of hypertension. Stimuli like angiotensin II or the sympathetic nervous system can induce small lesions in the vasculature and kidneys. This may lead to the formation of neoantigens from intracellular components. These latter will serve as antigens recognized by the immune system and will generate a cellular immune response which will develop against vessels and kidneys leading to an increase in blood pressure

promoter of hypertension, like interleukin-17, whereas other cytokines such as interleukin-10 may have a rather mitigating role to limit the increase in BP.

Taken together, the investigations of the role of immunity and inflammation in the genesis of hypertension are important as they might open new therapeutic approaches to treat hypertension.

31.4 Sex Differences in the Pathophysiology of Essential Hypertension

Epidemiologically, it is well recognized that men are at higher cardiovascular risk than women at least until women reach the time of menopause. Gender differences in BP may account for this finding as clear differences in BP with age have been demonstrated [125]. After the menopause, BP tends to increase in women and rejoin the levels of men [126]. This actually suggests that the pathogenic mechanisms causing hypertension may not be identical in males and females.

Similar sex differences in BP have been observed in animal models of hypertension as reviewed recently [127]. To investigate the role of sex hormones in the

development of hypertension in animals, several technical approaches have been used including castration of male, ovariectomy in females, or ovariectomy with estrogen replacement [127]. From these studies, it appears that testosterone plays a greater role than female sex hormones in the sexual dysmorphism. The main system mediating the effect of sex hormones on blood pressure is the renin-angiotensin system and to a lesser degree endothelin and nitric oxide [128]. There is also some evidence that the sex chromosomes per se are involved in sex difference in BP [129]. Thus, in male spontaneously hypertensive rats (SHR), the pressure-natriuresis relationship is shifted to the right and castration of male SHR has been found to restore it suggesting that androgens contribute to the higher blood pressure measured in males [130]. Androgen receptor blockade lowers blood pressure in male SHR to the level of female SHR [131], and the administration of testosterone to ovariectomized female SHR increases blood pressure [130]. This latter finding indicates that androgens play a role in the pathogenesis of hypertension that occurs after the menopause in some women. Thus, at the time of menopause, not only the loss of female hormones but also the relative change in estrogen/androgen ratio influences BP. Androgen receptors have also been localized in different parts of the renal tubule such as the proximal tubule in humans and the collecting tubule in rats [132, 133]. When injected in to rats, dihydrotestosterone, the main metabolite of testosterone, has been found to stimulate directly the proximal volume reabsorptive rate and hence to increase extracellular volume and blood pressure.

There is some evidence suggesting that female sex hormones (estrogens and progesterone) may protect against salt-induced changes in BP. When Dahl salt-sensitive (DS) rats receive a high-sodium diet, females become less hypertensive than male rats [134]. In this animal model, ovariectomy results in an accelerated development of salt-sensitive hypertension in females [134]. Interestingly, reversal of the diet to a low-salt intake reverses the hypertension in intact male and female DS rats, but this is not the case in ovariectomized female DS rats. The interpretation of this finding is that female sex hormones act to suppress sodium-dependent and sodium-independent increases in BP. A greater rise in blood pressure has also been reported in female SHR rats after ovariectomy [135]. More recent experimental data suggest that a loss of female hormones decreases the threshold of the hypertensive effect of salt [136].

Several studies have reported gender differences in various components of the renin-angiotensin cascade that could partially explain the gender differences in blood pressure [137]. In a normotensive population, a higher plasma renin activity (PRA) has been measured in men than in women regardless of age and ethnic heritage suggesting a higher risk of renal failure in males than in females [138]. Exogenous female sex hormones administered with oral contraception have also been shown to stimulate angiotensinogen production, which may lead to an increase in BP in some women [139]. Other studies have reported that PRA is higher in postmenopausal than in premenopausal women although PRA remains higher in men than in women for the same age [137]. In animals, the administration of testosterone to ovariectomized female rats increases PRA, which is lower in males after castration [140, 141]. Finally, in Sprague-Dawley rats, a positive linear correlation

between the levels of testosterone and plasma renin activity has been reported, suggesting that testosterone stimulates the renin-angiotensin system. In accordance with this observation, several studies have found that androgens, like estrogens, enhance renal angiotensinogen mRNA [140, 142]. Androgens also upregulate the expression and the affinity of AT_1 receptors for angiotensin II in male tissues [143].

Sexual hormones also affect the response to a stimulation of the renin-angiotensin system. Miller et al. (1999) have compared the renal hemodynamic response to the infusion of exogenous angiotensin II in young normotensive premenopausal women and in age-matched men and found striking differences [144]. Both groups exhibited an increase in blood pressure and a decrease in effective renal plasma flow with angiotensin II, but only men maintained their glomerular filtration rate (GFR) resulting in an increased filtration fraction. In women, the administration of angiotensin II decreased GFR leading to a reduction in filtration fraction.

Endogenous and exogenous female sex hormones have been found to influence systemic and renal response to salt in women [145]. In young normotensive women, whether or not under contraceptives, blood pressure is rather insensitive to salt, with a normal pattern of adaptation of renal proximal and distal reabsorption to changing salt intake [145]. In contrast, women become salt-sensitive after the menopause, which may explain the increase in blood pressure occurring at the menopause in some women. The renal hemodynamic response to salt and the regulation of sodium excretion is also modulated by female sex hormones.

Taken together, these data indicate that there are important differences in the pathogenesis of hypertension in male and females. These differences generate important clinical questions, which are still far from being resolved. For example, should therapeutic BP targets be the same in males and females? Does the BP-induced increase in cardiovascular risk similar in both sexes? These questions and the precise differences in the pathogenesis of hypertension deserve additional investigations to clarify the issues.

31.5 Pathophysiology of Hypertension in the Elderly (Chap. 30)

Hypertension is highly prevalent in subjects over 60 years of age. Indeed, in elderly and very elderly (>80 years), almost 60 % of subjects are hypertensive. However, hypertension in the elderly differs from that observed in younger subjects. Indeed, the main characteristic of hypertension in the elderly is an increase in systolic BP and a rather low diastolic (*isolated systolic hypertension*); hence, pulse pressure is increased. This hypertension phenotype develops as a result of reduced elasticity and compliance of central conduit arteries due to age-dependent arterial stiffening, development of atherosclerosis, and an accumulation of arterial calcium and collagen instead of elastin in arteries [146]. The remodeling of the arterial walls leads to an increased rigidity, which accelerates pulse wave velocity. Moreover, the remodeling is associated with an endothelial dysfunction, which further contributes to an increase in BP.

Among the pathogenic factors participating in the vascular remodeling, one has to cite the matrix metalloproteinase (MMP) family of enzymes [147]. Indeed, MMP9 and MMP2 plasma levels have been reported to positively correlate with BP and with the incidence of new cases of hypertension [148]. Conversely, animal studies have shown that inhibition of MMPs restore endothelial function and lower BP [149]. Another factor is the accumulation of calcium in the vascular wall. Usually, calcium load occurs in the tunica media and is linked to a change in the phenotype of smooth muscle cells, which behave like osteoclasts and retain calcium. A recent survey has shown an association between the presence of arterial calcifications and isolated systolic hypertension [150] (Chap. 4).

Another important factor to consider in the pathogenesis of hypertension in the elderly is salt intake (Chap. 30). Indeed, there is an association between BP and salt intake as assessed by urinary sodium excretion [151]. The association is stronger in hypertensive patients than in normotensive subjects, but it is also more pronounced in elderly subjects [151]. In the INTERSALT study, a high-salt intake was associated with a greater increase in BP with age [152]. The role of salt in mediating an elevation of BP in the elderly is not really a surprise. Indeed, elderly subjects are known to be more sensitive to a high-salt intake probably due to their age-related reduction in renal excretory capacity [153].

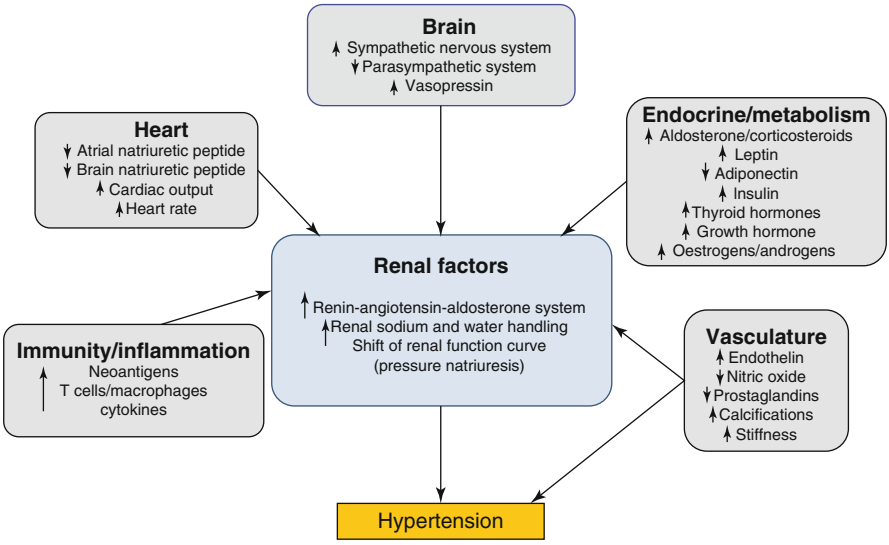

Fig. 31.4 Integrated scheme of the various factors potentially involved in the pathophysiology of hypertension. Stimulated or inhibited factors originating from the heart, the brain, the immune, and the endocrine systems act on the kidneys either to stimulate the renin-angiotensin-aldosterone system or to promote an increase in renal sodium reabsorption and hence a rightward shift of the pressure-natriuresis curve. This leads to an increase in blood pressure in order to maintain sodium balance. Note that the renal system plays a central role in the pathogenesis of hypertension

31.6 Concluding Remarks

The pathogenesis of hypertension is an extremely complex mosaic of neurohormonal factors as illustrated in Fig. 31.4. Their influence on blood pressure depends on many environmental factors as well as comorbidities and genetics. In this review, we addressed the major determinants of high BP in humans with respect to age and sex. We did not address the influence of genetic, nutritional, and environmental factors (such as calcium, potassium, magnesium, or air pollution) on blood pressure, which are discussed in separate chapters of this book. Due to space limitations, we also did not enter into all recent molecular mechanisms discovered in animal models of hypertension. Today, with the availability of transgenic mouse models, new molecules are regularly identified that appear to regulate BP. However, their exact role in the pathophysiology of human hypertension remains often unclear. Therefore, they deserve additional experimental and clinical studies.

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