Endocrine hypertension

ROBERT FRASER
MRC Blood Pressure Group, Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland

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SYSTEMIC ARTERIAL PRESSURE, blood pressure, is the result of cardiac output, total peripheral resistance, and intravascular volume. These can vary independently of each other, but each also interacts with and responds to changes in the others. Compliance of capacitance blood vessels is also important and decreases with age. Cardiac output comprises stroke volume and heart rate; total peripheral resistance depends on the muscle tone of the resistance vessels. Hormones affect all of these variables, both controlling and responding to changes in blood pressure. Moreover, the many endocrine systems contributing to blood pressure homeostasis interact with each other in a complex manner. For example, hormone-induced changes in sodium retention alter extracellular fluid volume but also affect vascular smooth muscle sensitivity to pressor agents. Some peptide hormones have apparently independent actions on electrolyte metabolism, vascular tone, and smooth muscle cell growth, while also acting on the brain as neurotransmitters. Interest has shifted from the systemic delivery of hormones to relatively distant target organs to studying their local secretion and action by paracrine and autocrine routes.

Blood pressure is a continuous variable in humans. The point at which it becomes high blood pressure or hypertension is therefore arbitrary, conventionally defined as 140/90 mm Hg in adults. More usefully, but less easily determined, it might be defined as that pressure at which the risk of vascular and organ damage becomes significant. Hypertension is a key risk factor for cardiovascular disease, renal disease, and stroke; an understanding of its etiology is of immense importance in both clinical and economic terms.

Many hormones can be shown experimentally to affect blood pressure; their relevance to human hypertension has been less easy to establish. While some rare forms of hypertension can be fully explained (for example, syndromes of primary endocrine excess), the vast majority of cases cannot, and must be consigned to the diagnostic category of essential (primary) hypertension. This is certainly heterogeneous, a complex interaction of genetic and environmental influences (61, 124, 173, 174, 306, 308) which is proving difficult to disentangle. Moreover, hypertension itself may alter hormonal action. For example, increased blood pressure causes vascular hypertrophy (20), which in turn should alter blood pressure sensitivity to pressor agents. Thus, in established hypertension, care must be taken to distinguish cause and effect. This chapter reviews the hormones that affect blood pressure and, where appropriate, the specific hypertensive syndromes in which they are involved. The possible endocrine component of essential hypertension is discussed where appropriate.

CORTICOSTEROIDS

The corticosteroids are synthesized from cholesterol in the adrenal cortex by a series of "hydroxylation" reactions and catalyzed by cytochrome P-450, containing mixed-function oxidases; oxidation-reduction reactions are catalyzed by hydroxysteroid dehydrogenases. These pathways are described in detail elsewhere (87, 88, 199). Corticosteroids exert two distinct types of effect.
The mineralocorticoids, principally aldosterone but also the less potent 11-deoxycorticosterone (DOC), promote Na⁺ retention in exchange for K⁺ and H⁺ loss in the distal nephron and other electrolyte-transporting epithelia, such as the salivary glands. Glucocorticoids are important control factors in intermediary metabolism, altering carbohydrate, protein, and lipid metabolism. It must, however, be emphasized that they also influence electrolyte metabolism, affecting Na⁺-H⁺ exchange in the proximal nephron and increasing the glomerular filtration rate. Cortisol is the principal glucocorticoid in humans. In common with other steroid hormones, corticosteroids bind to intracellular receptors, thereby altering the transcription rates of many genes (see Chapter 5).

There are two major pathways of control of adrenocortical function. These are described in detail elsewhere (87, 88, 199, 222). Zona glomerulosa function, that is, aldosterone secretion, increases during sodium depletion and decreases during sodium loading. It is also stimulated by hemorrhage and orthostasis (see Chapter 7). These effects are mediated by the pressor peptide angiotensin II (AII), which is released in the circulation by the renal enzyme renin. Aldosterone secretion is also highly sensitive to K⁺ levels. By contrast, the zona fasciculata, which produces cortisol and DOC among many other compounds, is controlled by corticotropin from the anterior pituitary gland. Secretion is therefore subject to a diurnal rhythm and responds to stress. Cortisol and synthetic glucocorticoids, such as dexamethasone, operate a negative-feedback inhibition of corticotropin secretion. Both mineralocorticoids and glucocorticoids affect blood pressure, but their mechanisms of action are different.

Corticosteroid production may not be restricted to the adrenal cortex but may occur in several extraadrenal tissues. Takeda et al. (274) reported aldosterone synthesis under the control of a local renin–AII system (see Renin–Angiotensin System, below) in rat mesenteric artery. Of considerable interest is the demonstration of aldosterone-synthesizing enzymes in the rat brain (315). It is now well established that only minute quantities of aldosterone administered intracerebrally are required to raise blood pressure (106). Moreover, a number of neurotransmitter substances alter aldosterone secretion (293). These extraadrenal systems may be of great significance in blood pressure homeostasis.

### Mineralocorticoid Hypertension

In disorders of mineralocorticoid excess, plasma exchangeable Na⁺ (Naₑ) levels and extracellular fluid volume are increased and renin secretion (and therefore AII concentration) suppressed. Blood pressure is high and proportional to Naₑ (15, 84, 147, 307). In studies of the development of human mineralocorticoid excess, there was an initial increase in cardiac output, which returned to normal as total peripheral resistance increased and remained high (299).

Plasma K⁺ and total body K⁺ are subnormal, often causing a neuromuscular dysfunction as the original presenting feature. These changes accompany excess of aldosterone, DOC, and a number of steroid drugs (208). In rare circumstances, cortisol may have similar effects (see Cortisol as a Mineralocorticoid, below).

#### Primary Hyperaldosteronism

Shortly after the discovery of aldosterone, Conn (43) described a syndrome in which hypermineralocorticoidism was due to a single benign adrenocortical adenoma. It is a rare disease (see, however, ref. 109). Subsequent reports described tumors varying in diameter from 0.5 to 2.5 mm and quantitatively variable effects on blood pressure, plasma aldosterone, etc. In addition, secretion of 18-hydroxyaldosterone and 18-hydroxycortisol is increased. Diagnosis is by measurement of plasma aldosterone and renin, and lateralization could be accomplished by adrenal vein blood sampling and analysis. These techniques are now aided by powerful scanning techniques (computed tomography, magnetic resonance imaging (170, 228, 290). Treatment is by surgical removal of the gland containing the adenoma or by long-term therapy using the specific aldosterone antagonist spironolactone or K⁺-sparing diuretics, such as amiloride, which blocks transepithelial Na⁺ channels. This subject has been extensively reviewed by Ferriss (84).

Typically, the aldosterone secretion rate in primary hyperaldosteronism (PHA) is more sensitive to corticotropin than normal and relatively unresponsive to AII, but there is considerable variation. The adenomas consist of lipid-laden cells, giving them a bright yellow appearance when cut. Despite their ability to synthesize aldosterone, most cells resemble zona fasciculata, but there is a variable component of less well-defined cell types (104, 189, 250, 310). The tumors themselves may therefore originate from different cell types (99). Tumor tissue expresses higher levels of aldosterone synthase and 11β-hydroxylase activity than surrounding tissue. Tumors also secrete cortisol, and the close proximity of cortisol and aldosterone synthase activity may explain the synthesis of 18-hydroxycortisol (283). Since the description of PHA, there have been sporadic reports of mild normokalemic cases who, although
harming adenomas, more closely resemble low-renin essential hypertension (LREHT). This may account for 10% or more of LREHT cases. Gordon et al. (107–109) remark on the variability of tumor biochemistry and include in their report a category of AI1-responsive tumors. They also suggest some familial component to this disorder.

**Idiopathic Hyperaldosteronism.** As more cases of PHA were tested and diagnosed, some patients with the same constellation of biochemical abnormalities and hypertension were shown not to have adrenocortical adenomas but a spectrum of pathological changes characterized as bilateral hyperplasia, with and without micronodules (8). This syndrome was designated idiopathic hyperaldosteronism (IHA). Surgery was much less efficacious in this group. Differential diagnosis was therefore essential. This field has been extensively reviewed (84).

Patients with IHA tend to be older than those with PHA and the biochemical abnormalities less severe. For example, Na+, may be raised only marginally (165). There is considerable overlap in all variables between the two conditions. However, there is at least one respect in which they differ qualitatively: in PHA, autonomous secretion of aldosterone suppresses renin and, consequently, AI1 levels. Thus, there is a negative correlation between plasma steroid and peptide levels (59). Moreover, aldosterone secretion is relatively insensitive to AI1 infusion. In contrast, these variables correlate positively in IHA and aldosterone secretion is more than normally sensitive to AI1 (89). There may also be a resemblance to I11-sensitive adenomas (107). The cause of hyperaldosteronism in these patients is not known. Similar adrenal pathology has been described in essential hypertension (174), where aldosterone levels are normal, and in symptom-free subjects as an incidental finding. It is possible that the adrenal AI1 receptor is in some way abnormally sensitive or that some other agonist, for example, a proopiomelanocortin (POMC)-derived peptide, might be responsible. This matter remains to be resolved.

**Glucocorticoid-Suppressible Hyperaldosteronism.** Glucocorticoid-suppressible hyperaldosteronism (GSH) was first described by Sutherland et al. (271). Patients have all the stigmata of PHA, though hypokalemia may be only mild or even absent, but differ from PHA in two important ways. Firstly, hyperaldosteronism can be corrected easily by long-term, low-dose dexamethasone, which suppresses corticotropin. Secondly, the condition is familial, with a clear autosomal dominant pattern of inheritance. During the intervening years, a large number of affected kindreds have been studied, and this has revealed a particular susceptibility to fatal stroke at a young age and possibly also of nephrosclerosis (169), though the level of aldosterone excess is usually only moderate.

The key to understanding the etiology of GSH lies in the corticotropin dependence of aldosterone secretion. It shows a cortisol-like nyctohemeral rhythm, responds with great sensitivity to corticotropin infusion (49), and is suppressed by dexamethasone, which inhibits corticotropin secretion. By contrast, aldosterone secretion in untreated GSH patients does not respond to AI1 infusion. However, after treatment with dexamethasone to correct electrolyte status, normal responsiveness to AI1 is restored (49). In these patients, two different pathways to aldosterone synthesis exist, which are controlled independently of each other.

The basic, genetically determined abnormality has been explained by Lifton et al. (172, see also refs. 216, 217). Briefly, the genes **CYP11B1** (11β-hydroxylase) and **CYP11B2** (aldosterone synthase) are highly homologous and lie close together on the same chromosome, 8q21-22 (197). Normally, their expression is confined to the zona fasciculata and the zona glomerulosa, respectively. Each gene can be conceived simply as an enzyme-coding region attached to a 5'-control region which responds to corticotropin (**CYP11B1** or **CYP11B2**). In GSH kindreds, as a result of a crossover event at meiosis, these control regions are exchanged, forming a third gene, coding for aldosterone synthase, controlled by corticotropin, and expressed ectopically in the zona fasciculata (172). This chimeric gene can be easily identified by conventional molecular biological techniques and forms the basis of the current diagnostic method of choice; neonates can be diagnosed from placental tissue (48, 138). Expression of the normal **CYP11B2** gene is permanently suppressed by the greater capacity and inappropriate control mechanism of the chimera; a normal expression pattern that is, response to AI1, is restored only when the chimera is suppressed.

Before this explanation became available, Ulick and Chu (41, 283) had identified high excretion rates of 18-hydroxy- and 18-oxocortisol in the urine of GSH patients, a valuable aid to diagnosis at that time. As mentioned earlier, these compounds are synthesized only when aldosterone synthase has access to cortisol, a situation which does not arise in the normal adrenal gland, where they occur in different zones. In GSH, chimeric aldosterone synthase must be responsible.
There now exists a comprehensive international register of GSH kindreds; surprisingly, the clinical phenotype is very variable. For example, blood pressure may vary from normal to severely disturbed (48). The reason for this is not known. It is not due to differences in the point of the crossover (140) since variability exists both within and between kindreds. Careful biochemical analysis suggests that patients may have an additional mild impairment of 11β-hydroxylase activity (139). Whether relatively small increases in plasma DOC levels consequent to this have significant effects remains to be determined.

Adrenal Carcinoma. Hypermineralocorticoidism due to adrenocortical carcinoma is rare, accounting for approximately one in 100 cases of apparent PHA. Such carcinomas are highly malignant, and early diagnosis and treatment are essential for an optimistic outcome. While cases of pure hyperaldosteronism due to carcinoma have been reported, in most of these a comprehensive corticosteroid analysis was not made. Where such an analysis was carried out, it showed that these tumors invariably secrete a complex, highly variable cocktail of steroids, including some in which aldosterone, DOC, or cortisol may predominate. This characteristic pattern is a useful diagnostic marker. The responsiveness of tumor steroid secretion to agonists such as ACTH or corticotropin also varies markedly, probably depending on the cell type from which the tumor originated (310). This subject has been reviewed briefly by Isles et al. (135). There is little information on the steroid molecular biology of these tumors.

Inherited Hydroxylase Deficiencies. The genes coding for each enzyme involved in corticosteroidogenesis are subject to mutation, and a well-defined syndrome has been described for each. These have been given the generic name congenital adrenal hyperplasia (CAH). They have been reviewed in detail and their effects on blood pressure discussed (88, 90, 137). Hypertension occurs in those forms of CAH in which DOC secretion is high; it is therefore another form of sodium-dependent, high-volume hypertension. Briefly, impairment of cortisol biosynthesis results in increased corticotropin drive (sometimes high enough to cause pigmentation), to maintain an adequate glucocorticoid supply. This causes hyperplasia. Where the capacity of an intermediate step in cortisol biosynthesis is limited by reduced expression of the relevant gene, massive amounts of precursors accumulate and are secreted. High DOC secretion occurs as a consequence of both 11β-hydroxylase and 17α-hydroxylase deficiency.

Subjects with 11β-hydroxylase deficiency have high concentrations of DOC and 11-deoxycortisol and low levels of their respective products, corticosterone and cortisol (79). High plasma corticotropin concentrations also stimulate adrenal androgen synthesis, causing virilization in females. Aldosterone, renin, and A1 production are suppressed. The changes are reversed or ameliorated by suppressing corticotropin dexamethasone.

Two types of mutation are responsible. Insertion or deletion mutations (301) cause a frameshift, altering crucial enzyme domains, for example, the heme-binding region, or insert a premature stop codon, resulting in the synthesis of a truncated, inactive protein. Point mutations, by causing amino acid substitutions, alter the physical properties of the protein in such a way as to reduce or obliterate its catalytic potency. Mutations of this kind occur most frequently in exons 6 to 8, which contain regions coding for the heme-binding domain. 11β-Hydroxylase deficiency is an autosomal recessive trait; the frequency and significance of heterozygotes are not known.

17α-Hydroxylase deficiency is also an autosomal recessive trait (17). A variety of mutations in the gene on chromosome 10q24-25 have been identified. These include nonsense mutations, deletions, duplications, and a number of point mutations (131). Two interesting cases turned out to be complex heterozygotes consisting of two different mutant alleles; it may be that only their combined effect elicited the syndrome (313).

Glucocorticoid Hypertension

The effects of glucocorticoids are myriad, and the ways in which they can affect blood pressure directly or indirectly are many, complex, and often obscure. Among the better established effects are the following. Cortisol increases the hepatic synthesis of angiotensinogen, which could alter the activity of the renin-angiotensin system if the substrate concentration is a limiting factor. Cortisol is also said to exert a direct effect on blood pressure without accompanying effects an electrolyte metabolism. This might be exerted through vascular receptors, possibly explaining the widespread influence of glucocorticoids on the rate of synthesis of vascular-derived hormones such as prostaglandins and nitric oxide (NO) (7, 223, 254, 257, 314). In this way, vascular reactivity to other agents, such as noradrenaline, also is altered. Indeed, steroid treatment potentiates the actions of noradrenaline and serotonin (240), at least in part by reducing extraneuronal catecholamine.
uptake and inhibiting catecholamine clearance or by inhibiting catechol O-methyltransferase activity (143, 162, 253, 302, 303). Glucocorticoids are reported to alter the balance between β and α receptors in a manner likely to increase blood pressure (116, 141). They may also act through brain glucocorticoid receptors (66). Finally, they may act as weak mineralocorticoids (160, 298).

Cortisol Excess. High doses of corticotropin or cortisol raise the blood pressure of normal human subjects significantly within 3 to 5 days (50). The effect is attenuated, but not abolished, by sodium restriction (51). During treatment, pressor sensitivity to phenylephrine, but not to AII, is increased (47, 304, 305) and is not reduced by inhibition of prostaglandin synthase (240). The effects of corticotropin in humans are entirely due to its stimulation of cortisol secretion and not to other corticotropin-dependent steroids since their effects are more or less identical. This may not be the case in sheep. Whitworth et al. (254, 303) have suggested that the presence of corticotropin-dependent, hydroxylated progesterone derivatives, inactive by themselves, is required to potentiate the effects of corticosteroids on blood pressure. This has been challenged (186).

However, high doses of glucocorticoid in humans also have caused profound mineralocorticoid-like changes quite different from those seen in clinical glucocorticoid excess. In Cushing’s syndrome, there is no evidence of Na+ retention or K+ loss and the activity of the renin angiotensin system is usually normal. The Na+ is normal and plasma DOC levels are not significantly raised (236). The cortisol secretion rate is usually only mildly or intermittently abnormal. [In cases of cortisol-secreting adrenal carcinoma or of ectopic corticotropin excess, clear signs of disturbed electrolyte metabolism frequently occur (128, 295).] Nevertheless, the prevalence of hypertension in Cushing’s syndrome is high, approximately 80% (112). Moreover, in the rat, significant increases in blood pressure can be elicited with very low-dose, continuous infusion of dexamethasone, insufficient to suppress endogenous glucocorticoid secretion completely (280). Interestingly, in this model, extracellular fluid volume and Na+ fell and plasma atrial natriuretic peptide (ANP) concentration rose; this is the opposite of mineralocorticoid hypertension (146). Thus, no single mechanism can explain the important effect of glucocorticoids on blood pressure. However, since specific glucocorticoid antagonists reverse these effects while mineralocorticoid antagonists do not (97, 114), it is probably activation of the glucocorticoid receptor, (GCR) which is important.

Glucocorticoid Receptor Abnormalities. The GCR gene is located on chromosome 10, consists of ten exons, and codes for a 777-amino acid protein (81). It is widespread in tissues. Its structure and function have been reviewed by Pratt (219, 220) and by Panarelli and Fraser (212). Briefly, the steroid-free receptor is associated with two molecules of heat shock protein (hsp) 90, which is required to ensure correct receptor folding. Also present are other hsp’s (hsp56, hsp70), other peptides (for example, p53), and other small molecules, such as polyunsaturated fatty acids and amino ether phosphoglycerides. Pratt (219, 220) suggests that these auxiliary components stabilize the receptor and facilitate its migration as a transportosome into the nucleus. Following agonist binding, the steroid–receptor complex dissociates from these other components and, as a dimer, interacts with the genome to alter the rate of synthesis of specific proteins. The process also depends on a number of transcription factors (212).

This process is complex, and altered responsiveness to glucocorticoids could theoretically arise from adverse changes in any individual component. So far, the majority of abnormalities described occur in the receptor protein itself. Mutations in the GCR gene result in the syndrome of glucocorticoid resistance (S, 40), which is frequently accompanied by hypertension. Reduced GCR affinity or concentration is compensated for by increased corticotropin drive to stimulate cortisol secretion to the very high levels necessary to operate the deficient receptor. The resultant hypertension is accompanied by the features of hypermineralocorticidism. This is probably again due to high DOC secretion (159, 289) but could also be due to cortisol binding to mineralocorticoid receptors.

Chrousos and Karl (40) and Werner et al. (300) have listed the biochemical changes and genetic defects in the GCR gene which have been described in glucocorticoid resistance. A variety of nucleotide sequence deletions and point mutations, particularly in the steroid-binding domain, correlate with reduced receptor affinity and concentration. In addition, Bronneggard et al. (24) found cases of increased receptor thermobility together with massively increased GCR gene expression rate, which suggest a defect in an hsp or in the hsp–receptor interaction. There is a similar abnormality in some rat models of hypertension (213).

Cortisol as a Mineralocorticoid. Children with the syndrome of apparent mineralocorticoid excess, New’s syndrome, show all the signs of hypermineralocorticidism, including severe hypertension, but secretion of aldosterone is suppressed and that of DOC normal (285). Abnormality of cortisol metabolism with normal
cortisol secretion rate was recognized early (284, 285). The urinary ratio of 11 β-hydroxy to 11-oxo metabolites of cortisol was abnormally high, evidence of impaired 11 β-hydroxysteroid dehydrogenase (11-HSD) activity. There were also other abnormalities of metabolism, possibly related to 5-reductase activity. In the sole reported adult case, Stewart et al. (263) confirmed that 11-HSD activity was indeed impaired and showed that low-dose dexamethasone, which suppresses cortisol secretion, controlled blood pressure and corrected biochemical abnormalities. Clearly, cortisol was acting as a potent mineralocorticoid. Roughly contemporary studies also showed that the isolated mineralocorticoid receptor could not distinguish between aldosterone and cortisol (95); since in vivo cortisol is approximately 1000-fold more concentrated than aldosterone and does not respond to variations in electrolyte status, in vivo discrimination must occur. This led to the “cortisol–cortisone shuttle” hypothesis (263, 265). This postulates that mineralocorticoid target organs, such as the kidney, also possess high 11-HSD activity, converting cortisol, which is capable of binding to the receptor, to cortisone, which is not. In New’s syndrome, this oxidation is deficient and cortisol escapes to access the mineralocorticoid receptor. Liquorice and its derivatives (for example, carbenoxolone) inhibit the enzyme, explaining the hypertensive effect of excessive consumption of these compounds (267, 276).

This hypothesis has received much experimental support. It is also possible that, in some forms of hypertension due to corticotropin excess and in normal subjects given high-dose corticotropin or cortisol (see Cortisol Excess, above), at least part of the mineralocorticoid-like effect was due to saturation of this enzyme system (268). Two isoforms, type 1 in the liver and type 2 in mineralocorticoid target organs such as the kidney, have been identified, but the enzymes are present in many tissues (1, 28, 241, 266, 275). It is the latter enzyme which is affected in New’s syndrome. The structure of its gene has been described, and the various mutations responsible for New’s syndrome, have been identified (201, 267, 309).

The case for a corticosteroid-related mechanism for essential hypertension has been discussed at length (91). Several mild abnormalities of steroid metabolism have been reported. For example, renin concentration is frequently low in relation to that of aldosterone and blood pressure levels are said to correlate positively with body Na⁺ levels and negatively with those of K⁺; no such correlations exist in matched normotensive subjects (14, 59). Evidence of mild 11 β-hydroxylation deficiency has been reported (68), and 11-HSD activity, evaluated by cortisol clearance rates (296) or urinary steroid metabolic ratios (153, 262), may be impaired. Also, GCR activity may be altered in some forms of animal hypertension (213). Thus far, no molecular biological explanation of these changes is available, and confirmation of their importance awaits further evidence.

**RENIN–ANGIOTENSIN SYSTEM**

The components and organization of the renin-angiotensin system have been the subject of many comprehensive reviews (33, 75, 76) and are dealt with elsewhere in this *Handbook* (Chapter 7). Briefly, the renal enzyme renin is secreted into the circulation, where it hydrolyzes a biologically inactive decapetide, Al from its specific substrate, angiotensinogen. The octapeptide AII is released from AII by angiotensin-converting enzyme (ACE), a zinc metalloproteinase situated on vascular cell surfaces and in the plasma, and rapidly destroyed by a variety of tissue and circulating peptidases or angiotensinas. The precise structures of these components are known, as are the loci and structure of the genes that code for renin, angiotensinogen, and ACE (96, 98, 120, 125, 129, 185, 193). Like many other secreted proteins, renin is synthesized as a larger precursor, prorenin, which is processed and glycosylated before being stored in intracellular granules, later to be secreted by exocytosis (115). During this process, an intermediate form, prorenin, is also released. Although long thought to be inactive, it has been suggested that prorenin may affect cardiovascular function.

Renin is stored in modified smooth muscle cells in the apparent glomerular arteriole, from which it is released in response to salt depletion or reduced intravascular volume. Again, these mechanisms are dealt with in detail elsewhere (Chapter 7). The renin-secreting cells are probably sensitive to “stretch” in the afferent arteriole (92). Among the response mechanisms, β-adrenergic receptors are important; the juxtaglomerular apparatus has a sympathetic supply (70). It is also likely that renal tubular sodium content influences renin release, but the precise mechanism is not known. Changes in renal perfusion pressure, which might influence both arteriolar “stretch” and tubular fluid composition, are powerful determinants of renin release (77, 259). Also, other agents which affect extracellular volume or vascular tone are expected to modify release, including prostaglandins (93), ANP (55), the endothelium-derived factors (158, 273, 292), and AII itself.

Angiotensin II is a potent pressor agent and an ad-
renocortical agonist. It acts through membrane receptors of two types, AT$_1$ (AT$_{1A}$, AT$_{1B}$ in the rat) and AT$_2$, which are distinguishable by their different susceptibilities to inhibitors (42, 78, 218, 279) and, to some extent, by their distribution. Binding of AII to AT$_1$ receptors operates the phosphatidylinositol turnover second-messenger system and inhibits adenylate cyclase activity (113). The mechanism of action is less clear for the AT$_2$ receptor, and its precise physiological role is not known.

Infusion of AII causes a rapid pressor response (see Chapter 7). The rise in blood pressure is transient, decaying with the rapid clearance of the peptide. The increase in vascular smooth muscle tone follows increases in intracellular free calcium levels, which depend on the inositol phosphate second-messenger response and possibly the opening of receptor-activated membrane calcium channels. Pressor sensitivity to AII is sodium-dependent; high sodium intake sensitizes and low sodium intake attenuates the response (26), probably by up- and downregulating receptor concentration, respectively (180). Also, AII has a “slow pressor” action (12, 25). Infusion of low rates of the peptide, insufficient to elicit an acute pressor response, will, if continued for a long time, eventually cause an increase in blood pressure. This appears to be due to vascular remodeling by smooth muscle cell hypertrophy. Of course, raising blood pressure will itself induce remodeling, but there is new good evidence that AII is an effective growth factor (see review in ref. 20), resulting in both hyperplasia and hypertrophy with polyploidy (103, 202, 211, 215, 251). This may indicate an effect on the vascular smooth muscle cell cycle (69).

In nephrectomized animals and anephric humans, activity of the renin–angiotensin system remains detectable in some tissues, suggesting extrarenal renin and AII synthesis (74, 249). Early evidence depended on biochemical assays of renin activity, hindering the interpretation that circulating renin of renal origin had merely been adsorbed or absorbed by a variety of organs. However, gene-expression measurements (that is, mRNA) and immunohistochemistry have clearly established the presence of renin and angiotensinogen synthesis in the adrenal cortex, brain, heart, blood vessels, salivary glands, and reproductive organs (74, 100, 175, 192, 200, 225, 249, 258, 311). In addition, rates of renin and/or angiotensinogen synthesis at these local sites appear to change in a physiologically meaningful way (200, 311). Finally, vascular cells in vitro have been shown to secrete renin (133, 225). The role of locally synthesized AII is enigmatic. There is much evidence, accumulated over many years, that blood pressure and the aldosterone secretion rate correlate closely with systemic renin or AII concentration (26). It is not known whether local AII, which may be generated intracellularly, acts in situ and, if so, by what mechanism or whether it merely contributes to total circulating AII. In the latter case, what is the secretion mechanism? Thus, its role in the development and maintenance of hypertension remains to be established.

Prorenin is secreted from the kidney at approximately tenfold the rate of renin (67, 256). It is secreted in very large quantities from several extrarenal tissues, notably the ovary, placenta, and uterus, which appear to secrete negligible quantities of renin (105, 136). Sealey (255) has briefly summarized the research of her group and others and has discussed possible roles for this peptide, previously considered to be inert. There is some evidence that plasma prorenin concentrations correlate with renal blood flow (117), that prorenin may act as a vasodilator, and that this is accomplished by a reversible activation-inactivation process which depends on changes of molecular shape (167). However, prorenin infusion had no demonstrable effect on blood pressure (168). Overexpression of the human prorenin gene in rats also failed to affect cardiovascular function (214), but these experiments were inconclusive since prorenin, though high for the rat, did not achieve human levels. It may therefore be necessary to overexpress the rodent gene to avoid this problem of species incompatibility.

The direct implication of the renin–angiotensin system in human hypertension is most obvious in two situations, renovascular disease and ectopic renin production. In the former condition, unilaterally reduced renal perfusion, for example, due to renal artery stenosis or atherosclerosis, leads to a “misconception” of reduced blood pressure by the kidney, a consequently inappropriate increase in renin, and therefore AII production (188). Untreated, this may lead to irreversible damage of the kidney contralateral to the stenosis. Hypertension is probably due to the pressor and vascular growth effects of AII. Pressure is correlated with plasma renin or AII concentrations. Therapeutic prevention of AII synthesis or its effects reduces blood pressure (21, 216). In the rat model of this condition, the two-kidney, one-clip model, plasma renin concentration is increased and blood pressure is high and remediable by AII receptor blockade in the acute phase but possibly not in the chronic phase (278). Autonomously secreted renin by a variety of neoplastic tissues has been described as a cause of severe hypertension (46). A comprehensive bibliography is provided by Robertson (237). The tumors are rare and most frequently derive from juxtaglomerular cells in the kidney, but renin-secreting renal oat cell carcinomas and nephroblastomas have also been described. A renin-secreting tumor of the adrenal gland, a site of extrar-
enal renin in normal animals, has also been described (132).

The importance of prorenin in hypertension is unclear. Preliminary studies (255) suggest that increased sensitivity of blood pressure to salt, tested in the Dahl salt-sensitive and salt-resistant strains of rat, might be related to a relative inability to secrete prorenin. The relevance of this to human disease is unknown.

There has been much research on many aspects of the renin–angiotensin system in essential hypertension; a verdict is awaited. However, pharmacological manipulation of its activity—for example, with ACE inhibitors, receptors, and antagonists (279)—has been a very successful form of treatment.

**CATECHOLAMINES**

The part played by the nervous system, central and peripheral, in the control of blood pressure is complex. A comprehensive examination of its components and the many neurotransmitters or “neurohormones” involved is beyond the scope of this chapter but attempts have been made (35, 36, 154). The nervous system influences intravascular volume and composition, for example, by controlling aspects of renal function. It also modulates both cardiac output and vascular smooth muscle tone directly (and indirectly by affecting the activity of systems such as renin release). Key transmitters of these effects are noradrenaline, adrenaline, and dopamine. Adrenaline is synthesized and stored in the adrenal medulla, where it is released into the circulation by “stress.” Noradrenaline, stored in sympathetic nerve endings and varicosities, is released into the synaptic cleft or at neuromuscular junctions in response to nerve stimulation. Both act by binding to cell-surface adrenergic receptors linked to several possible second-messenger systems.

Adrenergic receptors have been classified as α or β according to their relative responses to the agonists noradrenaline, adrenaline, and dopamine. Adrenaline is synthesized and stored in the adrenal medulla, where it is released into the circulation by “stress.” Noradrenaline, stored in sympathetic nerve endings and varicosities, is released into the synaptic cleft or at neuromuscular junctions in response to nerve stimulation. Both act by binding to cell-surface adrenergic receptors linked to several possible second-messenger systems.

Adrenergic receptors have been classified as α or β according to their relative responses to the agonists noradrenaline, adrenaline, and dopamine (4). They have been further subdivided on the basis of their interactions with a greater variety of pharmacological agents (149, 224, 269); currently, receptors β₁, -α₁a-c, α₂a-c have been identified. The adrenergic receptors have in common a protein structure comprising seven cell membrane-spanning domains, interacting with the agonist at the extracellular surface and with the second-messenger system at the intracellular surface. For example, β-receptor stimulation increases adenylyl cyclase activity (G, activation), while α₁-receptor stimulation (G, activation) has the opposite effect and may simultaneously alter Ca²⁺ and K⁺ flux. Finally, α₂-receptor stimulation, by activating phospholipase C, releases diacylglycerol, the activator of protein kinase C, and inositol triphosphate, resulting in the release of intracellular bound Ca²⁺ from cell membrane phosphoinositol.

Adrenergic receptors are widely distributed in tissues, exerting powerful effects on metabolism, respiration, and digestion in addition to cardiovascular function. Stimulation of cardiac β₁ receptors increases heart rate (chronotropic) and the force of contraction (inotropic), both tending to increase blood pressure. At the peripheral neuromuscular junction, for example, in the resistance vessels, noradrenaline release at nerve terminals binds to vascular smooth muscle α₁ receptors, causing contraction and, thus, vasoconstriction. At the same time, the released noradrenaline activates prejunctional α₂ receptors, inhibiting further noradrenaline release (homingotropic) and release of transmitter from cholinergic neurons (heterotropic). The major proportion (c.80%) of noradrenaline is rapidly reabsorbed for “recycling.” Activation of vascular smooth muscle cell β₁-receptors induces relaxation and, therefore, vasodilation. Conversely, activation of prejunctional β₂-receptors induces noradrenaline release and subsequent vasoconstriction. It is by this mechanism that adrenomedullary adrenaline release increases blood pressure (163).

Assessment of adrenergic activity at the neuromuscular junction is difficult for several reasons (82, 111, 118, 181, 291) but crucial to both diagnostic and research procedures. Since most intrajunctional noradrenaline is rapidly reabsorbed and much of the remainder rapidly metabolized, peripheral plasma concentrations may be a poor index of junctional events. However, measurement of the levels of noradrenaline, adrenaline, and their metabolites in plasma and urine is technically simple, and multiple sampling improves its value. Certainly, where secretion is pathologically high, as in pheochromocytoma, these are the methods of choice. Alternatively, following the dynamics of radiolabeled agonists allows assessment of the amount and time course of the component of released noradrenaline escaping from the neuromuscular junction into the circulation (“spillover”) during a given period (82). Finally, sympathetic nerve activity can be followed directly by inserting microelectrodes into skeletal muscle with the assumption that differences from normal also occur in vascular smooth muscle.

**Pheochromocytoma**

Pheochromocytoma is a disease of excess, often massive, secretion of catecholamines. The chief catecholamines are noradrenaline and adrenaline, but dopamine excess may also occur. It is rare but spectacular and
Alterations at one or more of several loci could be re-
tion or decreased kinetic parameters for those inducing
adrenergic receptors inducing smooth muscle contrac-
tion rates of adrenaline and noradrenaline. Again, it is
necessary to show that these changes predate the onset
of the disease, created by implanting tumor tissue into
a particularly susceptible strain, is also available for
research (149, 190).

Pheochromocytomas arise most frequently in the
chromaffin cells of the medulla and less commonly at
other abdominal sites. They may secrete catechola-
mines intermittently (hence, the paroxysmal hyperten-
sion) or continuously, and increased output may result
from a variety of factors, such as exercise, numerous
food constituents such as tyramine, psychological
stress, and anesthesia and pressure during surgical ma-
nipulation. Consequently, some interventional preop-
erative localization tests and surgery to remove the tu-

There is much support for the sympathetic nervous
system as a primary cause of essential hypertension.
Alterations at one or more of several loci could be re-
sponsible. Thus, increased numbers or affinity of those
adrenergic receptors inducing smooth muscle contrac-
tion or decreased kinetic parameters for those inducing
relaxation are obvious possibilities, as are raised secre-
tion rates of adrenaline and noradrenaline. Again, it is
necessary to show that these changes predate the onset
of established hypertension. Kaplan (144), Victor and
Mark (291), and Bolli et al. (22) have summarized the
evidence as follows. In young hypertensive subjects, the
various indices of raised activity of the sympathetic
nervous system (plasma catecholamine levels, spillover,
sympathetic nerve activity) are higher than in control
subjects and there is an enhanced vascular reactivity to
noradrenaline (3). That this is related to altered α-
adrenergic activity is indicated by the greater fall in
vascular resistance in hypertensive subjects when α-
blocking agents are administered. Blood pressure is
also reduced by β blockade (54). Similar differences
from normal in normotensive offspring of hypertensive
parents have also been reported. In rat models of es-
tential hypertension, there is similar evidence of in-
creased sympathetic nervous system activity, and symp-
patholytic drugs or dopamine β-hydroxylase inhibitors
prevent or alternate the rise in blood pressure (190).

These effects are likely to have a genetic component. Gavras et al. (102) have made a case for genetically
determined changes in the kinetics of the α receptor at
renal, vascular, and central nervous system sites in es-
tential hypertension, and a polymorphism of the β receptor gene associated with essential hypertension in
certain ethnic groups has been described (155).

An alternative hypothesis (27, 85) is that chronic
stress, through the agency of raised adrenaline secre-
tion and operation of the prejunctional β receptor,
eventually causes sustained hypertension. A possible
mechanism is progressive vascular smooth muscle hy-
pertrophy.

INSULIN AND GROWTH HORMONE

There is much interest at present in the frequent asso-
ciation of hypertension, obesity, and insulin resistance,
the so-called Reaven's syndrome [or syndrome X,
metabolic syndrome (130, 226)]. The possible role of
insulin in controlling blood pressure and its relevance
to human hypertension have been reviewed by
Berretta-Piccoli (13) and Morris et al. (198). It is clear
from them that the relationship is not simple. While
insulin levels tend to be higher, that is, lower insulin
sensitivity, in hypertensive than normotensive subjects,
not all subjects with hyperinsulinemia have raised
blood pressure nor do all hypertensive patients or an-
imals become insulin-resistant (29, 32, 242). More-
over, rare cases of insulin-secreting tumors have not
been found to be hypertensive (94). However, loss of
sensitivity to insulin is common in essential hyperten-
sion, and there is evidence that this insensitivity pre-
cedes the rise in blood pressure by some considerable
period in humans (248) and in genetically hypertensive
rats (227).

If a causal relationship between insulin resistance
and rise in blood pressure exists, what mechanisms
might be involved? Again, it is possible to speculate
only. Diabetics of both types have a greatly enhanced
risk of vascular (macro- and microangiopathic) disease
(9). Also, vascular muscle cell metabolism may be af-
fected (74, 198). Both may affect vascular reactivity;
pressor sensitivity has been shown to be raised in diab-
etics (53, 198). Insulin may have vasodilatory prop-
erties (see, however, ref. 53) so that impaired responsiveness may alter blood flow (30). Other studies have shown that exchangeable body sodium tends to be higher in diabetic subjects (13, 16, 65, 83, 209), one possible contributor to enhanced pressor sensitivity. Another is the action of insulin as a vascular smooth muscle growth factor, through insulin-like growth factor receptors (11). Action on skeletal muscle may also be altered in essential hypertension (204). Finally, there is evidence of altered cell electrolyte metabolism in these patients; for example, the activity of the sodium pump and the intracellular concentration of free calcium may be altered (210). However, the direct role of insulin in blood pressure control remains undetermined.

There is evidence of increased prevalence of hypertension in acromegaly (60, 90). Although many of the studies were not designed to measure this risk (see, however, ref. 187) and often were poorly controlled, a level of 35% of patients becoming hypertensive is certainly greater than would be expected in the nonaffected population. The mechanism of this susceptibility is not known. A striking finding is that Na\textsubscript{a} is increased in these patients to a greater extent than in primary hyperaldosteronism (58), raising the question of why hypertension is not more frequent and more severe. In this same study, although blood pressure and Na\textsubscript{a} were correlated in the whole group of untreated acromegals, the hypertensive group had not retained significantly more sodium than the normotensive group. Other studies have found no correlation (2, 261). There may be some relation between plasma volume and blood pressure (62). Davies et al. (58) found a stronger Na\textsubscript{a}:blood pressure correlation in older patients, a situation also described in essential hypertension (14). In interpreting clinical studies, severity and duration of acromegaly must be taken into account; such information is not always available. Growth hormone administration to experimental animals and humans may cause salt and water retention (18, 52). By contrast, Harrap et al. (121) could demonstrate no such action in intact rats despite pronounced effects on growth. Blood pressure, pressor sensitivity, and parameters of electrolyte metabolism were unchanged compared with controls. However, similar treatment in hypophysectomized rats did raise blood pressure (126), suggesting a role for growth hormone in maintaining normal blood pressure. Despite the high levels of body sodium, the activity of the renin–angiotensin system and the secretion rate of aldosterone generally have not been found to be markedly suppressed (60, 90, 196) nor is catecholamine metabolism apparently altered. This suggests that the pattern of sodium retention is different from that of mineralocorticoid excess, possibly with a greater proportion in bone and connective tissue. Nevertheless, there is evidence that intracellular sodium levels are altered. The activity of the sodium pump in leukocytes increases in response to growth hormone (205). The hormone also alters renal function, raising the glomerular filtration rate and renal plasma flow (39, 46).

Hypertension due to clinical growth hormone excess is therefore something of a paradox. Marked sodium retention is readily demonstrable in acromegaly, but there is no clear link between this and raised blood pressure since the changes usually associated with increased body sodium (suppressed renin–angiotensin system, increased pressor sensitivity, raised ANP levels, etc.) do not occur consistently.

**VASCULAR HORMONES: ENDOTHELIN AND NITRIC OXIDE**

In addition to the local renin–angiotensin system and vasoactive hormones originating from vascular nerve endings, the blood vessel secretes specific vasoconstrictor and vasodilator hormones, which act in a paracrine or autocrine manner. Principal among these are the endothelins, NO, and a number of prostaglandins. Disentangling their individual effects and assessing their importance in the maintenance of normal vascular tone or their relevance to hypertensive disease has been difficult because they behave, in relation to each other, in an active, reactive (counteractive), and interactive manner. A local pressor action elicits a vasorelaxant response and vice versa. Thus, “cause and effect” in hypertension have not been satisfactorily distinguished.

Three endothelins (ET-I, -II, and -III) have been identified. The first is principally the product of the vascular endothelium. Several comprehensive reviews of their biochemistry, physiology, and molecular biology are available (134, 177, 178). Briefly, endothelins are short (21-amino acid) peptides comprising a characteristic loop closed by disulfide bridges. Like many other such hormones, they are synthesized in a larger (pre-pro-) form, which is processed to the active hormone in the endothelial cytoplasm before secretion. There seems to be minimal intracellular storage. Proendothelin I is also secreted, and infusion studies suggest that extracellular activation may occur via an endothelin-converting enzyme.

The nature and loci of the three separate endothelin genes are known. They are expressed in different tissues in constitutive or inducible mode. Expression of the ET-I gene rises in response to such pressor agents...
as adrenaline, AII, and arginine vasopressin. Infusion of ET-I or administration to blood vessels in vitro results in a biphasic response, vasodilatory followed by prolonged vasoconstrictor response. In blood vessels stripped of endothelium, the initial vasodilation is abolished, evidence of compensatory responses in NO and prostacyclin secretion. Endothelins act through specific receptors, of which two, ETA on vascular smooth muscle cells and ETB on the endothelium, have been identified. A third, ETc, may also exist. Receptor ETA mediates the vasoconstrictor action. Cellular responses are thought to result from alterations in intracellular Ca2+ concentrations and through target cell membrane depolarization due perhaps to an effect on adenosine triphosphate-sensitive K+ channels (156, 191, 287, 297).

Subpressor infusion rates of ET-I potentiate the pressor actions of adrenaline and noradrenaline (122, 123). There is evidence also that ET-I has a mitogenic effect on vascular smooth muscle cells (73); it is possible that some of the in vivo hypertrophic action of AII is by this route. Finally, a rise in ET-I levels elicits a rise in local production of NO (250) and vasodilatory prostanoids (For examples, PGI2, PGE2) by the endothelium, probably mediated by the ETB receptor (123, 272). Conversely, increased NO production and administration of NO-releasing drugs or (cyclic guanosine monophosphate (cGMP), the second messenger for NO action, inhibit ET-I synthesis and secretion (23, 184).

The importance of the endothelins in hypertension remains to be established (123, 179, 184). Rare cases of hypersecretion from neoplastic tissue are unequivocally hypertensive (238). However, in mice lacking the ET-I gene, blood pressure was not lower than in normal controls, though they suffered from markedly abnormal embryological development (157). While infusions of specific endothelin antagonists into rat models of genetic [spontaneously hypertensive (SHR), spontaneously hypertensive stroke-prone rat. (SHRSP)] and secondary (DOC-salt) hypertension did reduce blood pressure, plasma ET-I levels were not different from their respective normal controls (72). (It should be emphasized that systemic circulatory levels may be a poor index of production rate for local tissue hormones.) The raised levels reported in rat renovascular hypertension (80) may be due to the very high plasma AII concentrations of this condition.

Local infusion of ET-I antagonists into normal human subjects caused a local increase in forearm blood flow, signaling vasodilation and a role for ET-I in maintaining vascular smooth muscle tone (72, 122). However, while the literature regarding plasma ET-I in human essential hypertension is contradictory (247), subjects with essential hypertension and normal renal function appear to have normal levels (56, 150).

It is difficult to avoid the opinion that such a powerful vasoactive substance is not in some way involved in abnormal blood pressure control; the answer may lie in the balance between the endothelin and vasodilator substances.

The complex biosynthesis of eicosanoids (in particular the prostanoids), control of their secretion, and their extremely diverse action have been comprehensively reviewed by Lands (161), Smith (260), Thierauch (277), and Quilley and McGiff (221), who also discuss the intricacies of their involvement in hypertensive disease. Again, the evidence is contradictory and inconclusive, though, as was mentioned above, the vasodilatory prostanoids PGI2 and PGE2 are produced in the vascular endothelium and are probably important in the vasorelaxant arm of control of vascular smooth muscle tone. Others (PGG2, PGH2) apparently have the opposite effect (145).

Nitric oxide has offered novel prospects. The exciting story of the identification of NO as the endothelium-derived relaxing factor, the revelation of its widespread importance in such fields as cardiovascular and brain physiology, and the immune response and working out of its biosynthesis, control of secretion, and mechanisms of action have been extensively reviewed (86, 194, 252, 281). Nitric oxide synthase (NOS) catalyzes the oxidative cleavage of NO from arginine. Being very reactive, its sphere of influence is small and its half-life short, the archetypal local tissue hormone. Of the three isoforms, NOS III is found in the endothelium in the particulate fraction, where it is expressed constitutively. Here, it is crucial to the maintenance of normal vascular smooth muscle tone. Nitric oxide may be the agent for vasodilators such as bradykinin, serotonin, and substance P, among others. Its response to pressor agents such as ET-I has already been mentioned. Similarly, increased stretch and shear forces enhance NO synthesis. Increases in NOS III activity are dependent on alterations in cell Ca2+ metabolism. Bing et al. (19) suggested that vascular NO responses might in some way be due to altered cell membrane viscosity, via a phosphatidylycholine–related mechanism.

Nitric oxide acts on vascular smooth muscle cells in at least two different ways. The better understood of these is stimulation of the soluble guanylate cyclase system, increase in cGMP synthesis, and activation of cGMP-dependent protein kinases. However, again like endothelin, it also manipulates intracellular Ca2+ levels and alters cell membrane K+ flux, thereby changing cell...
membrane potential. It may also act as an antimitogen (101). Again, although the capacity of NO (or NO-releasing drugs) to affect blood pressure is indisputable (286), its direct role in hypertensive disease has not been convincingly established. Administration of specific NOS inhibitors to rats caused hypertension of considerable severity (142), while dosage with arginine, the NO precursor, has been reported to ameliorate or prevent the development of hypertension in the SHR and other hypertensive rat models (38, 148, 178). Moreover, there has been some evidence indicating a reduced capacity to produce NO in hypertensive human subjects compared to normotensive controls and in genetically hypertensive rats (64, 166, 243 but see ref. 43). Current evidence has been evaluated in detail by Dominiczak and Bohr (71), van Zwieten et al. (288), and Cohen (44), who take a much more cautious view. They emphasize the need to control for age, presence of vascular disease, and other factors in human studies. In particular, van Zwieten et al. (288) suspect that much of the apparent NO response in both human and rat experiments may derive from capacitance and not from resistance vessels, which may be more important in blood pressure control. All three reviews present much data, which are unable to distinguish, in terms of NO metabolism, between normotensive and hypertensive rats or, indeed, human subjects. Human and animal data challenge the concept of generalized endothelial dysfunction in essential hypertension. This is not, of course, to say that it is not involved, nor that manipulation of NO (or ET-I) levels may not become an important therapeutic tool in treating hypertension. However, further research is required.

SODIUM-LOSING HORMONES

Excretion of sodium and reduction of extracellular fluid volume should predispose to lower blood pressures and a fall in vascular pressor sensitivity. Two groups of natriuretic substances have been identified. The role of the first of these, the digitalis-like factors, remains undermined. The isolation and identification of ouabain in tissues, for example, the adrenal cortex, is a fascinating story. However, at present, there is no general agreement on their presence or absence, provenance, or physiology, nor have the assay reagents become sufficiently standardized to allow a meaningful arbitration between protagonists and antagonists. Not surprisingly, therefore, although it is certain that infusion of ouabain raises blood pressure in animals (183), the role of these factors in human blood pressure homeostasis and hypertension is unknown. The subject has been reviewed by Hamlyn and Manunta (119) and Goto et al. (110). The second group comprises ANP brain natriuretic peptide (CNP). The structure, molecular biology, and physiology of these compounds are described in detail elsewhere in this Handbook (see Chapter 10), and there are many reviews which follow the progress of research into their properties since their discovery (610, 164, 203, 207, 229, 239, 246). Most of these studies deal with ANP. Davidson and Struthers (57) and Richards et al. (230) have reviewed the current knowledge of BNP. Briefly, ANP and BNP (despite the name) originate mainly from the atria of the heart, from which they are released in response to changes which influence the degree of atrial stretch. Plasma levels increase in response to high salt intake, changing from an upright to a supine position, and exercise. A positive correlation between plasma ANP concentration and exercise has been observed. There is considerable overlap in the control of ANP and BNP secretion and little information on CNP. In vitro, ET-I stimulates the release of BNP but possibly not ANP (127), whereas the natriuretic peptides inhibit ET-I release (152). It has been suggested that the second-messenger systems involved in ANP and BNP release are different (294). The natriuretic peptides interact with target tissues via cell membrane receptors ANPα, ANPβ, and ANPγ, differentiated by their different affinities for the different peptides. Receptors ANPα and ANPβ are linked to a guanylate cyclase moiety, and stimulation increases cGMP formation. Receptor ANPγ lacks this domain, and although it is perhaps the most widely distributed of the receptor types, its role is less certain. It has been called a “clearance receptor.” Infusion of ANP or BNP causes natriuresis and diuresis. These peptides may also have a direct vasorelaxant effect. They operate the same second-messenger system as NO. In vitro, they exert an antimitotic effect on vascular smooth muscle, which in vitro might predispose to lowering of blood pressure. Natriuretic peptide infusion reduces both renin and aldosterone in plasma, thus augmenting their renal influence as inhibitors of sodium retention. The effect on aldosterone secretion is not secondary to lower A11 levels since the same effect of ANP can be shown using zona glomerulosa tissue in vitro (34, 37). This effect provides one possible explanation for the blunted response of aldosterone secretion to agonists in salt-loaded subjects.

Reported effects of ANP on blood pressure vary. Infusion at rates which manipulate plasma concentration within the physiological range do not reduce blood pressure significantly in normal subjects; higher, pharmacological doses have inconsistent effects. Sagnella et al. (244, 245) have emphasized the importance of tak-
ing into account such variables as age, diet, and duration of ANP administration when comparing studies. At present, no casual link between blood pressure and ANP secretion in hypertension has been established. Predictably, plasma ANP is raised in such diseases as primary hyperaldosteronism in response to sodium retention and volume expansion (312). There is also a vast literature on the natriuretic peptides in heart disease (206, 207, 231, 282). However, in essential hypertension, the situation remains unconvincing. Again, comparison of studies is difficult; in addition to the criteria listed above, the degree of left ventricular hypertrophy resulting from hypertension may affect natriuretic peptide levels (63). However, in several, but not all, careful comparisons with normotensive control groups, levels of ANP and BNP have been shown to be mildly raised in essential hypertension (31, 230, 244, 245, 270, 312). In addition, Sagnella et al. (244, see also ref. 195) report a positive correlation between plasma ANP and blood pressure in hypertensive patients which is not present in normotensive controls. However, Beretta-Piccoli et al. (14) found a similar correlation of blood pressure and body sodium, again only in hypertensive patients; it seems at least possible that the ANP relationship may be secondary to this. Similarly, low-dose ANP infusion has a more consistent hypotensive effect in hypertensive subjects, but so, of course, do diuretic drugs. Finally, it has been suggested that among the general hypertensive population there exists a subset of patients with heightened pressor sensitivity to high salt intake; in these, the ANP response to salt loading is greater than normal (151, 244). The effects of BNP in hypertensive subjects have been reviewed separately by Richards et al. (230).

Whether or not the natriuretic peptides or their relative paucity have any direct causative role in human hypertension, it is still possible that optimizing their in vivo action may have some therapeutic value. One approach has been to inhibit the endogenous neutral endopeptidase responsible for their clearance, thus prolonging their half-lives in the circulation. Some preliminary studies have been published (233–235). The ultimate effect of such treatment will depend on achieving a suitable balance between increased “potency” of ANP and the concomitant inhibition of destruction of pressor peptides such as AI by the same agent.

SUMMARY

A key feature of blood pressure homeostasis is the multiplicity of systems, neural and endocrine, involved. New factors are continually being discovered. For example, the adrenal medulla secretes a hypotensive polypeptide, adrenomedullin, the role of which is now being actively research (232). New roles or new sites of origin are being discovered for other well-established hormones. It is probable that minor deficiencies or variations in one limb of blood pressure control will be at least partially compensated for by adjustments in the activities of some or all of the others.

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