HYPERTENSION AND HORMONE MECHANISMS
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Hypertension, a major risk factor for cardiovascular disease and stroke, is present in approximately one-quarter of the adult population of Western societies. Seven percent of deaths worldwide are attributed to hypertension, and the rate of end-stage renal disease due to hypertension has doubled since 1982. In the United States, 77% of persons with hypertension go untreated and 31% of these individuals are unaware of their high blood pressure. The substantial public health problem of hypertension, compounded by the recognition of health hazards of “high normal” blood pressure, has raised a call for better understanding of the pathophysiological mechanisms underlying primary hypertension.

Hormones and autacoids are substances of major critical importance to the pathophysiology of hypertension. Remarkable advances during the past 25 yr, and particularly in the last decade, have identified several hormonal mechanisms in the regulation of blood pressure. Among the hormonal systems playing a major role in blood pressure and hypertension are the renin–angiotensin system, the sympathetic nervous system, the renal dopaminergic system, insulin and other metabolic factors, endothelium-dependent factors, natriuretic peptides, sex steroids, and the lipoxygenase system. This book represents a systematic treatment of each of these hormonal systems in the pathogenesis of primary (essential) hypertension.

The renin–angiotensin system is undoubtedly the best-studied hormonal system in the regulation of blood pressure. However, in spite of the voluminous literature on this subject, an understanding of this complex system is far from complete. During the past decade, truly remarkable advances have been made in the identification of new components of the renin–angiotensin system. The renin–angiotensin system is increasingly being regarded as a tissue rather than a circulating hormonal system. The intrarenal renin–angiotensin system, discussed by Drs. Minolfa Prieto-Carrasquero, Hiroyuki Kobori and L. Gabriel Navar, is the best-developed of these cell-to-cell (paracrine/autocrine) systems. The cardiac and vascular renin–angiotensin systems, becoming widely appreciated as localized independent tissue systems, are covered by Drs. Rajesh Kumar, Kenneth M. Baker and Jing Pan. Angiotensin (1–7), a new peptide of the renin–angiotensin system and its newly discovered biosynthetic pathway, angiotensin converting enzyme-2 (ACE-2), are discussed by the pioneers of this area, Drs. Carlos M. Ferrario, David B. Averill, K. Bridget Brosnihan, Mark C. Chappell, Debra I. Diz, Patricia E. Gallagher, Liomar A. A. Neves, and E. Ann Tallant. Two relatively new angiotensin receptors, AT₂ and AT₄, are discussed by Drs. Robert M. Carey and Helmy M. Siragy (AT₂) and Drs. T. A. Jenkins, F. A. O. Mendelsohn, A. L. Albiston and S. Y. Chai (AT₄). The emerging role of the renin–angiotensin system in inflammation is covered by Drs. Rhian M. Touyz and Ernesto L. Schiffrin, and the role of aldosterone in vascular damage is discussed by Drs. Hylton V. Joffe, Gordon H. Williams, and Gail K. Adler.

The sympathetic nervous system has long been regarded as critical in blood pressure regulation. In this book, Drs. David Robertson, Andre Diedrich, and Italo Biaggione discuss the recent and compelling evidence for neurogenic human hypertension, and
Drs. Donald J. DiPette and Scott C. Supowit introduce the new role of calcitonin gene-related peptide in hypertension. Drs. Pedro A. Jose, Robert M. Carey, and Robin A. Felder cover important emerging area of renal proximal tubule dopamine and D_{1} receptors and their regulation induced by G-protein kinase-4 (GRK-4). Mutations of GRK-4 in humans are associated with salt-sensitivity and hypertension in several populations.

During the recent years, the importance of diabetes and obesity in hypertension has become evident. Dr. James R. Sowers discusses the insulin resistance (metabolic) syndrome, Dr. Brent M. Egan covers fatty acid metabolism, and Drs. Gregory M. Singer, John F. Setaro and Henry R. Black elaborate on goal-oriented hypertension management in diabetic and nondiabetic patients.

The 1998 Nobel Prize in medicine was awarded to Drs. Furchgott, Ignarro, and Murad for their discovery of nitric oxide and cyclic guanosine monophosphate as an endogenous vasodilator pathway. Their work highlighted the importance of the endothelium in hypertension. In a section devoted to endothelial factors, Drs. David L. Mattson and Alan W. Cowley discuss nitric oxide, Dr. Ernesto L. Schiffrin covers endothelin, and Drs. Julie and Lee Chao cover the kallikrein–kinin system in hypertension.

Recent advances in natriuretic peptides in hypertension are covered by Dr. Kailash N. Pandey. The role of sex steroids is discussed by Drs. Suzanne Oparil and Andrew P. Miller. The lipoygenase system is elaborated by Drs. Naftali Stern and Michael Tuck.

The focus of *Hypertension and Hormone Mechanisms* is on new developments in hormones/autocoids related to hypertension. Each of the chapters is written by the world’s experts in their fields. My hope is that the discussions in this book will open new doors to the understanding that will help propel us closer to knowing the etiology and pathogenesis of primary (essential) hypertension. I further hope that this book will stimulate active research in the fundamental mechanisms of hypertension so that new therapies and even prevention can be realized in the not-too-distant future.

Robert M. Carey, MD, MACP
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List of Color Plates

The images listed below appear in the color insert:

**Color Plate 1.** Chapter 3, Fig. 2. Expression of Ang-(1–7)-like cardiac immuno-reactivity in the rat. Ang-(1–7) staining was restricted to ventricular myocytes whereas it appeared as a granular reaction product throughout the cytoplasm (Panel A). The absence of Ang-(1–7) staining in endothelial and vascular smooth muscle cells of coronary vessels is best illustrated in the higher power magnification of Panel B. (See discussion on p. 46.)

**Color Plate 2.** Chapter 3, Fig. 3. Characteristics of Ang-(1–7)-like immunoreactivity in rat kidney. The most intense staining for Ang-(1–7) was in the thick-walled epithelial cells of the proximal-convoluted tubule (filled arrow in Panel A). A less intense staining for the peptide was observed in the thin-walled epithelial cells of collecting ducts (open arrow of Panel A). At both low (Panel A) and high (Panel B) power magnifications, there is essentially no staining for Ang-(1–7) in the glomerulus. Panel B also illustrates modest staining in the afferent arteriole (arrowhead in Panel B). (See discussion on p. 47.)

**Color Plate 3.** Chapter 3, Fig. 4. The major signal transduction pathways for Ang-(1–7). Ang-(1–7) activates the G protein-coupled mas receptor to increase the production of nitric oxide (NO) and prostacyclin (PGI2) to increase cGMP and cAMP, respectively. Ang-(1–7) also reduces the mitogen-activated protein kinases (MAPKs) by either increasing MAPK phosphatases or reducing the MAPK kinase MEK. The increase in cAMP and cGMP and the decrease in MAPK activity cause vasodilation and inhibit cell growth. (See discussion on p. 52.)

**Color Plate 4.** Chapter 11, Fig. 1. Prevalence of selected risk factors among subjects with metabolic syndrome. From ref. (15). (See discussion on p. 179.)

**Color Plate 5.** Chapter 11, Fig. 2. Algorithm for the treatment of hypertension. (See discussion on p. 180.)

**Color Plate 6.** Chapter 11, Fig. 3. Cumulative proportions of patients with the primary composite end point (doubling of baseline serum creatinine, development of end-stage renal disease, or death from any cause) in 1715 patients with nephropathy due to type 2 diabetes treated with irbesartan 300 mg, amlodipine 10 mg, or placebo in the Irbesartan Diabetic Nephropathy Trial. (See discussion on p. 183.)