Cardiovascular Hormone Systems

Edited by
Michael Bader

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Part Two Peptide Hormones

Preface

Cardiovascular diseases have the highest morbidity and mortality world-wide. They comprise disorders like hypertension, myocardial infarction, cardiac and renal failure as well as stroke. Since the cardiovascular system is regulated by hormones and autacoids, which either are circulating or locally released in vascular tissues from endothelial cells and neurons, these hormones are of major pathophysiological importance for cardiovascular diseases.

The chemical nature of these hormones is quite diverse. There are steroids, such as the estrogens, androgens, mineralocorticoids and glucocorticoids; peptides, such as angiotensins, kinins, endothelins, vasopressin, apelin, natriuretic peptides, calcitonin gene-related peptide and adrenomedullin; biogenic amines synthesized from amino acids, such as serotonin, dopamine, norepinephrine, epinephrine and histamine; arachidonic acid products, such as prostaglandins, leukotrienes and cytochrome P450 metabolites; esters, such as acetylcholine; as well as nucleotides and even gases such as nitric oxide. The receptors with which they interact are markedly different. While the majority of the factors act on members of the huge family of G-protein-coupled receptors with seven-transmembrane domains, steroids bind to nuclear receptors, natriuretic peptides activate membrane-bound guanylate cyclases and nitric oxide acts on soluble guanylate cyclases. In addition, the direct activation of ion channels has been described for serotonin (5-HT_3 receptors), some steroids (nongenomic actions), acetylcholine (nicotinic receptor) and nucleotides (P_{2X} receptors).

The kinetics with which the hormone systems interfere with cardiovascular regulation also vary drastically. Steroid hormones induce their effects mainly on the transcriptional level. They start to be effective from hours up to days. Peptide hormones are released within minutes and are effective for hours. Autacoids such as the cytochrome P450 products, prostaglandins and nitric oxide are released in seconds, and their effects last for minutes. This allows a high flexibility of the organism to react to cardiovascular challenges at different time scales.

Furthermore, these hormone systems enable intensive networking between the cardiovascular tissues. The major player is the brain, which regulates all other organs in the cardiovascular system using the sympathetic and parasympathetic nerves with noradrenaline and acetylcholine as transmitters, respectively. Furthermore, it releases vasopressin targeting the kidney, and factors influencing steroid

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hormone generation in the adrenal gland and the gonads. The heart can signal to the rest of the cardiovascular system via the natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide). The kidney employs the renin–angiotensin system for the same purpose.

Due to the complexity of the cardiovascular system and its regulation, the study of cardiovascular hormones has been mainly limited to whole-organism models. As a consequence, transgenic technology employing the targeted alteration of the genome of a rat or mouse had a major impact on the study of these systems, and the description of such relevant animal models is a major focus of this book.

With the help of such models it was discovered that some of the hormones are already essential for the normal development of the cardiovascular system. For example, animals deficient for endothelins show drastic developmental defects in heart and vessels, and die shortly after birth. Also, most animals deficient for dopamine, norepinephrine and adrenal steroids are not viable for more than a few days. Mice lacking angiotensin exhibit abnormalities in kidney morphology; nevertheless, some of them reach adulthood.

The majority of common drugs for cardiovascular diseases interfere with the generation or signaling of the factors described in this book. For example, the renin–angiotensin system is the target of three classes of drugs: angiotensin-converting enzyme inhibitors, angiotensin AT_1 receptor antagonists and recently also newly developed renin inhibitors. Norepinephrine and its β-receptor are inhibited by β-blockers. However, these drugs not only affect a single hormone system but also interfere with other systems summarized in this book. For example, angiotensin-converting enzyme inhibitors stabilize bradykinin and β-blockers inhibit renin release. Thus, the sole view on one hormone system is not sufficient to understand the actions of these classical cardiovascular drugs. Therefore, this book was designed to give a comprehensive overview about cardiovascular hormones, their metabolism, physiological actions and therapeutic value. Each hormone system is described separately by one of the leaders in the field of research about this system.

I am very grateful to all of the coauthors of *Cardiovascular Hormone Systems* whose excellent contributions created a very valuable and comprehensive source of information for clinical and basic scientists interested in cardiovascular regulation, endocrinology and pharmacology.

Berlin, July 2008 *Michael Bader*

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Part One Steroid Hormones

1
Glucocorticoids and Mineralocorticoids

Eilidh Craigie, John J. Mullins, and Matthew A. Bailey

Glucocorticoids and mineralocorticoids are members of the corticosteroid hormone family, synthesized in the adrenal gland from the precursor sterol cholesterol via the intermediate pregnenolone (Figure 1.1). The principal glucocorticoid in humans is cortisol (in rodents corticosterone) and the principal mineralocorticoid is aldosterone. Sharing a common synthesis pathway, cortisol and aldosterone are structurally similar (Figure 1.1), and exhibit a degree of cross-receptor affinity and function. Nevertheless, small differences in structure permit important differences in physiological function. Aldosterone classically acts via the mineralocorticoid receptor (MR) to promote sodium transport in the kidney and gut, thereby regulating long-term electrolyte homeostasis and blood pressure control. Cortisol, by comparison, exhibits a wide range of metabolic and stress-related response effects.

1.1
Synthesis of the Corticosteroids

Steroid synthesis occurs principally in the adrenal gland but also occurs in the steroidogenic cells of the testes, ovary, placenta and brain. The intramitochondrial delivery of cholesterol is the rate-limiting step for steroid synthesis and is mediated by steroidogenic acute regulatory protein (StAR) [1]). Defects in cholesterol transport associated with mutations in StAR [2] cause the autosomal recessive disorder of lipoid congenital adrenal hyperplasia (CAH; Online Mendelian Inheritance in Man (OMIM) #201710). This rare condition presents with large adrenal glands containing high levels of cholesterol. Lipoid CAH is lethal within a few days without hormone replacement therapy. Over 30 mutations in StAR have been reported to cause lipoid CAH, all of which result in varying degrees of defective cholesterol transport (for review, see [3]). Mice null for StAR, generated by homologous recombination, emphasize the key role of this protein. Homozygous null pups fail to thrive and die within a week of birth: corticosterone and aldosterone levels are very low despite elevated ACTH (adrenal corticotropic hormone) and CRH (corticotropin-releasing hormone) [4]. Lipoid CAH can also arise from

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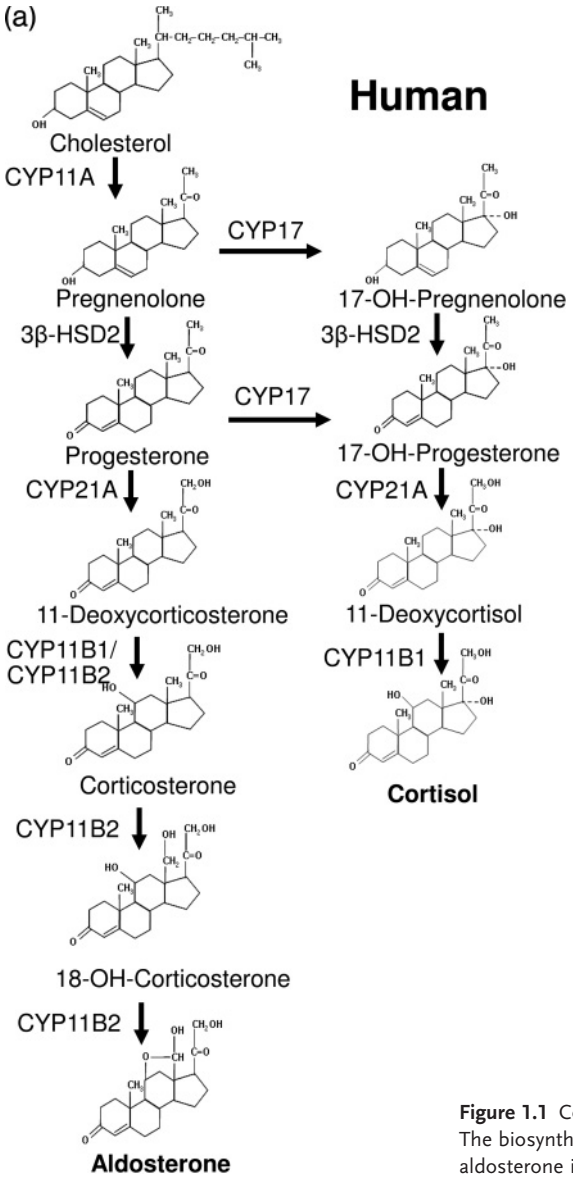

Figure 1.1 Corticosteroid biosynthesis. The biosynthesis pathways of cortisol and aldosterone in (a) humans and (b) rodents.

mutations in P450scc [5], an enzyme that cleaves cholesterol to produce pregnenolone – the common precursor for both cortisol and aldosterone synthesis (Figure 1.1). Indeed the biosysthetic pathways of both share a number of intermediates and enzymes (Figure 1.1), becoming fully exclusive only at 11-deoxycortisol (DOC; cortisol pathway) and 11-deoxycorticoisteroid (aldosterone pathway). In rodents, exclusivity occurs at 11-deoxycorticoisteroid (Figure 1.1b).

The final step in cortisol synthesis, the conversion of DOC to cortisol, is catalyzed by 11β-hydroxylase (CYP11B1 gene), while the final three stages of aldoste-