PRINCIPLES AND PRACTICE OF ENDOCRINOLOGY AND METABOLISM

THIRD EDITION

Kenneth L. Becker, Editor

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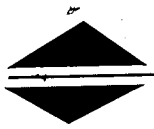

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With 330 Contributors

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There is a close relationship between neural cells of the sympathetic ganglia and chromaffin cells. Small numbers of ganglion cells can be found in the adrenal medulla, and chromaffin cells occur in the sympathetic ganglia. Hence, neoplastic disorders affecting either cell type can arise throughout this system.

The diagnosis of adrenal medullary hyperplasia depends on an increased volume of adrenal medulla in relation to the cortex. There is a diffuse nodular proliferation of normal medullary elements. This condition is seen mainly in families with multiple endocrine neoplasia type 2A and is considered a preneoplastic condition (see Chap. 188).

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas arise from neuroblasts. These tumors form a continuum from least to most differentiated and from malignant to benign. Neuroblastoma usually is a tumor of infancy and childhood, with a median incidence at the age of 2 years. It originates in the paraganglia of the sympathetic nervous system or the adrenal medulla, and 60% arise in the abdomen. Grossly, it is a multinodular tumor with areas of hemorrhage, necrosis, and cystic degeneration.[24] The cells are arranged in nests and contain small, dark-staining nuclei with little cytoplasm. Although the light-microscopic features are not necessarily distinct from those of other childhood tumors, electron microscopic examination shows characteristic cytoplasmic neurosecretory granules. Neuroblastomas usually secrete catecholamines, their metabolites, or both. Characteristically, these tumors grow rapidly and metastasize early to local lymph nodes, the liver and other abdominal organs, and bone. Although spontaneous regression or differentiation into a more benign tumor may occur, mortality is high and treatment often includes combinations of palliative surgery, radiation, and chemotherapy.[25] Ganglioneuroblastomas contain some mature ganglion cells and have a better prognosis. Ganglioneuromas are benign tumors arising from mature neuronal elements.[26,27]

Pheochromocytomas arise from chromaffin cells. As expected from their cellular origin, 95% or more are in the abdomen, with most being in the adrenal glands.[28] Similar to chromaffin cells, however, they occasionally can be found anywhere along the sympathetic chain of ganglia from the base of the skull to the neck of the urinary bladder. Ten percent of patients with sporadic pheochromocytomas and 50% of those with familial pheochromocytomas have bilateral tumors. The pheochromocytoma that may occur in von Hippel-Lindau disease commonly is bilateral.[29,30] Although only 5% to 10% are malignant, it is often impossible to distinguish benign from malignant neoplasms histologically. Pheochromocytomas are highly vascular tumors with local hemorrhage and cystic degeneration. Microscopically, they often have a chaotic pattern of pleomorphic elongated cells with prominent cytoplasmic granules (see Chap. 86). Although the light-microscopic features may not be diagnostic, electron microscopic examination demonstrates characteristic dense catecholamine secretory granules.

ADRENAL MEDULLARY HYPOFUNCTION

The adrenal medulla is affected by the same systemic diseases (tubercular and fungal infections, sarcoidosis, amyloidosis) as is the cortex and also is often the initial site of hemorrhage. Isolated adrenal medullary hypofunction is uncommon and usually occurs in the setting of diffuse autonomic insufficiency. Sparse amounts of medullary tissue may be found in some elderly persons, but no specific abnormality has been described.

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CHAPTER 72

SYNTHESIS AND METABOLISM OF CORTICOSTEROIDS

PERRIN C. WHITE

The adrenal glands are endocrinologically complex organs that are composed of two distinct endocrine tissues derived from

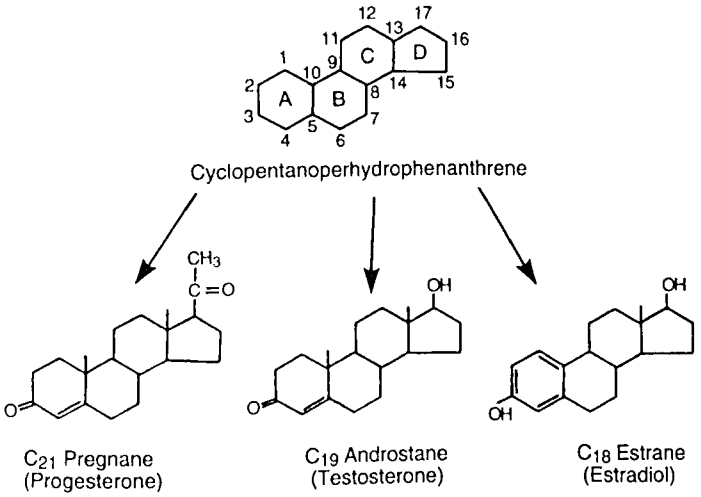

FIGURE 72-1. The steroid nucleus. The four rings are labeled *A*, *B*, *C*, *D*, and the carbons are numbered as shown. Examples are shown of steroids from each of the three structural categories of steroid hormones: the 21-carbon pregnane derivatives, the 19-carbon androstane derivatives, and the 18-carbon estrane derivatives. The names of the individual steroids shown are indicated in parentheses.

source of the steroid hormones, whereas the adrenal medulla is the source of catecholamines. Although the adrenal cortex and medulla are in close proximity, they function independently. This chapter describes the biosynthesis, metabolism, mechanisms of action, and regulation of the steroid products of the adrenal cortex.

Three major groups of hormones are produced by the adrenal cortex: *mineralocorticoids*, *glucocorticoids*, and *sex steroids*. Mineralocorticoids are produced primarily by the zona glomerulosa; glucocorticoids are produced by the zona fasciculata; and sex steroids originate primarily from the zona reticularis. The hormonal products of the adrenal cortex share cholesterol as a common precursor. Cholesterol is also the precursor for the gonadal steroids, vitamin D and derivatives, and the bile acids.

STRUCTURE AND NOMENCLATURE

Steroids have a common structure with 17-carbon atoms arranged in three six-membered rings and a fourth five-membered ring labeled A, B, C, and D, respectively (Fig. 72-1). Each of the 17 carbons is numbered in a standard way. Two additional carbons, numbered 18 and 19, may be attached at carbons 13 and 10, respectively. Carbon atoms 20 and 21 may be attached at the 17 position. These various additions yield three steroid families: the C_{18} *estranes* with an aromatic ring (estrogens); the C_{19} *androstanes* (androgens); and the C_{21} *pregnanes* (corticoids and progestins) (see Fig. 72-1). The steroid nucleus lies in a plane that can be modified by the addition of substituents either above or below (Fig. 72-2). The *α-substituents occur below the plane* (indicated by dotted lines in Fig. 72-2) and the *β-substituents lie above the plane* (indicated by solid lines). The A and B rings may be attached so that the substituents at positions 5 and 10 are in either the *cis* or *trans* orientations (see Fig. 72-2).

A multiplicity of *trivial* and *systematic* or *biochemical* names exist for each steroid (Table 72-1). Between 1930 and 1950, two groups under the direction of Reichstein and of Kendall isolated most of the naturally occurring steroids. Each group labeled steroids alphabetically in the order in which they were discovered, with the result that the same compound was sometimes given two different alphabetical designations. Thus, Kendall's compound A is not the same as Reichstein's

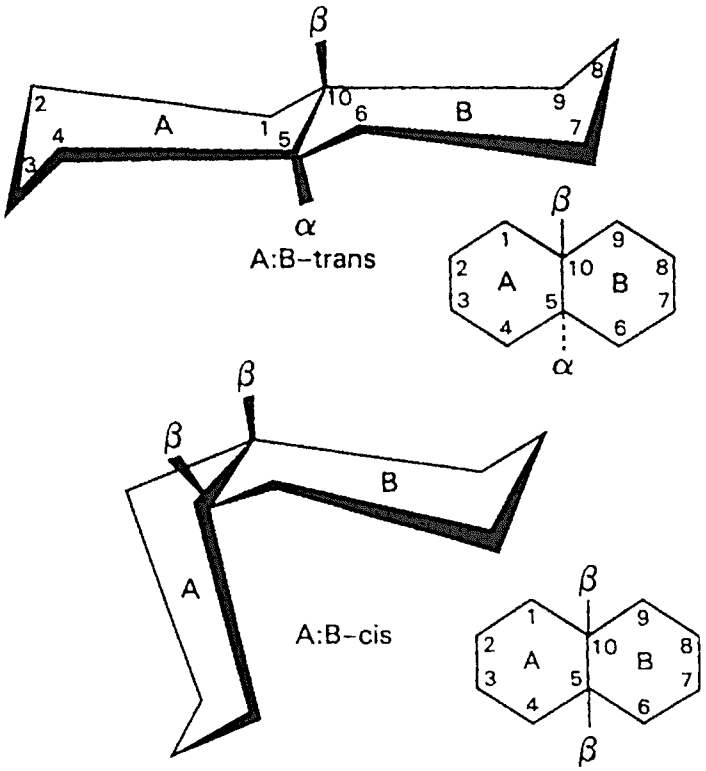

FIGURE 72-2. *Cis-trans* orientation of the steroid nucleus and location of the α- and β-substituents.

BIOSYNTHESIS

IMPORTATION INTO MITOCHONDRIA

The rate-limiting step in steroid biosynthesis is importation of cholesterol from cellular stores to the matrix side of the mitochondria inner membrane where the cholesterol side-chain cleavage system (CYP11A, adrenodoxin, adrenodoxin reductase) is located. This is controlled by the *steroidogenic acute regulatory protein (StAR)*,[2,2a] the synthesis of which is increased within minutes by trophic stimuli such as adrenocorticotropic hormone (ACTH) or, in the zona glomerulosa, by increased intracellular calcium. StAR is synthesized as a 37-kDa phosphoprotein that contains a mitochondrial importation signal peptide. However, importation into mitochondria is not necessary for StAR to stimulate steroidogenesis; to the contrary, the likeli-

TABLE 72-1.
Adrenal Steroidogenesis: Nomenclature

Nomenclature of the Major Naturally Occurring Steroid Hormones		
Common Name	*Biochemical Name*	*Letter*
Aldosterone	Pregn-4-en-11β,21-diol-18-al-3,20-dione	
Corticosterone	Pregn-4-en-11β,21-diol-3,20-dione	B
Cortisol (hydrocortisone)	Pregn-4-en-11β,17α,21-triol-3,20-dione	F
Cortisone	Pregn-4-en-17α,21-diol-3,11,20-trione	E
Dehydroepiandrosterone (DHA, DHEA)	Androst-5-en-3β-ol-17-one	
Deoxycorticosterone (DOC)	Pregn-4-en-21-ol-3,20-dione	
Deoxycortisol	Pregn-4-en-17α,21-diol-3,20-dione	S
Estradiol	Estra-1,3,4(10)-trien-3,17β-diol	
Progesterone	Pregn-4-en-3,20-dione	
Testosterone	Androst-4-en-17β-ol-3-one	

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