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CHAPTER 60

ADRENOCORTICOTROPIC HORMONE; ADRENOCORTICAL STEROIDS AND THEIR SYNTHETIC ANALOGS; INHIBITORS OF THE SYNTHESIS AND ACTIONS OF ADRENOCORTICAL HORMONES

Bernard P. Schimmer and Keith L. Parker

Adrenocorticotropic hormone (ACTH, also called corticotropin) and the steroid hormone products of the adrenal cortex are considered together in this chapter, because the major physiological and pharmacological effects of ACTH result from its action to increase the circulating levels of adrenocortical steroids. Synthetic derivatives of ACTH are used principally in the diagnostic assessment of adrenocortical function. As all of the known therapeutic effects of ACTH can be achieved with corticosteroids, synthetic steroid hormones generally are used instead of ACTH for therapeutic applications.

Corticosteroids and their biologically active synthetic derivatives differ in their metabolic (glucocorticoid) and electrolyte-regulating (mineralocorticoid) activities. These agents are employed at physiological doses for replacement therapy when endogenous production is impaired. In addition, glucocorticoids are potent suppressors of inflammation, and their use in a wide variety of inflammatory and autoimmune diseases makes them among the most frequently prescribed classes of drugs. Because they exert effects on almost every organ system, the clinical use of and withdrawal from corticosteroids are complicated by a number of serious side effects, some of which are life-threatening. Therefore, the decision to institute therapy with corticosteroids always requires careful consideration of the relative risks and benefits in each patient.

Agents that inhibit various reactions in the steroidogenic pathway and thus alter the patterns of secretion of adrenocortical steroids are discussed, as are synthetic steroids, such as mifepristone (see also Chapter 58), that inhibit glucocorticoid action. Agents that inhibit the action of aldosterone are presented in Chapter 29; agents used to inhibit growth of steroid-dependent tumors are discussed in Chapter 52.

History. The clinical importance of the adrenal glands was first appreciated by Addison, who described fatal outcomes in patients with adrenal destruction in a presentation to the South London Medical Society in 1849. These studies, published subsequently (Addison, 1855), were soon extended by Brown-Séquard, who demonstrated that bilateral adrenalectomy was fatal in laboratory animals. It later was shown that the adrenal cortex, rather than the medulla, was essential for survival in these experiments. Further studies demonstrated that the adrenal cortex regulated both carbohydrate metabolism and fluid and electrolyte balance. Efforts by a number of investigators ultimately led to the isolation and characterization of the various adrenocorticosteroids. Studies of the factors that regulated carbohydrate metabolism (termed *glucocorticoids*) culminated with the synthesis of cortisone, the first pharmacologically effective glucocorticoid to be available in large amounts. Subsequently, Tate and colleagues isolated and characterized a distinct corticosteroid, aldosterone, that had potent effects on fluid and electrolyte balance (and therefore was termed a *mineralocorticoid*). The isolation of distinct corticosteroids that regulated

carbohydrate metabolism or fluid and electrolyte balance ultimately led to the concept that the adrenal cortex comprises two largely independent units: an outer zone that produces mineralocorticoids and an inner region that synthesizes glucocorticoids and weak androgens.

Studies of the adrenocortical steroids also played a key part in delineating the role of the anterior pituitary in endocrine function. As early as 1912, Cushing described patients with hypercorticism, and later recognized that pituitary basophilism represented the cause of the adrenal overactivity (Cushing, 1932), thus establishing the link between the anterior pituitary and adrenal function. These studies ultimately led to the purification of ACTH (Astwood *et al.*, 1952) and the determination of its chemical structure. ACTH was further shown to be essential in maintaining the structural integrity and steroidogenic capacity of the inner cortical zones. The role of the hypothalamus in pituitary control was established by Harris (1948), who further postulated that a soluble factor produced by the hypothalamus activated ACTH release. These investigations culminated with the determination of the structure of corticotropin-releasing hormone (CRH), a hypothalamic peptide that regulates secretion of ACTH from the pituitary (Vale *et al.*, 1981).

Shortly after synthetic cortisone became available, Hench and colleagues demonstrated the dramatic effect of glucocorticoids and ACTH in the treatment of rheumatoid arthritis (Hench *et al.*, 1949). These studies set the stage for the clinical use of corticosteroids in a wide variety of diseases, as discussed below.

ADRENOCORTICOTROPIC HORMONE (ACTH; CORTICOTROPIN)

The sequence of human ACTH, a peptide of 39 amino acids, is shown in Figure 60–1. Whereas removal of a single amino acid at the amino terminus considerably impairs biological activity, a number of amino acids can be removed from the carboxy-terminal end without a marked effect. The structure–activity relationships of ACTH have been studied extensively, and it is believed that a stretch of four basic amino acids at positions 15 to 18 is an important determinant of high-affinity binding to the ACTH receptor, whereas amino acids 6 to 10 are important for receptor activation (Imura, 1994). As discussed in Chapter 23 and as schematized in Figure 60–1, ACTH is synthesized as part of a larger precursor protein, pro-opiomelanocortin (POMC), and is liberated from the precursor through proteolytic cleavage at dibasic residues by the enzyme prohormone convertase 1. Impaired processing of POMC due to a mutation in prohormone convertase 1 has been implicated in the pathogenesis of a human disorder presenting with adrenal insufficiency. Intriguingly, these patients also exhibit childhood obesity, hypogonadotropic hypogonadism, and diabetes (Jackson *et al.*, 1997), suggesting other proteolytic targets for prohormone convertase 1. A

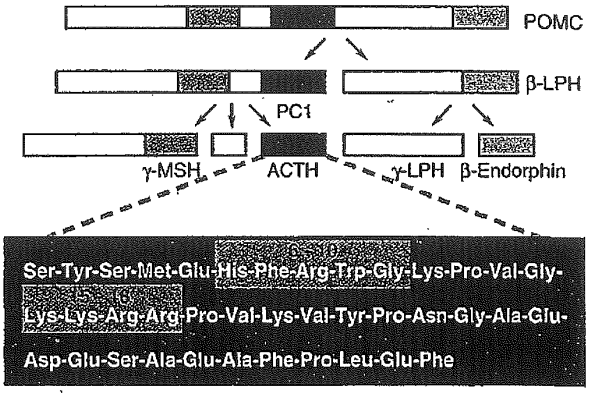

Figure 60–1. Processing of POMC to ACTH and the sequence of ACTH.

A schematic overview of the pathway by which pro-opiomelanocortin (POMC) is converted to ACTH and other peptides in the anterior pituitary is shown. The light blue boxes behind the ACTH structure indicate regions identified as important for steroidogenic activity (residues 6–10) and binding to the ACTH receptor (15–18). The amino acid sequence of human ACTH is shown. LPH, lipotropin; MSH, melanocyte-stimulating hormone; PC1, prohormone convertase 1.

number of other biologically important peptides, including endorphins, lipotropins, and the melanocyte-stimulating hormones (MSH), also are produced from the same precursor.

Actions on the Adrenal Cortex. ACTH stimulates the adrenal cortex to secrete glucocorticoids, mineralocorticoids, and weak androgens such as androstenedione and dehydroepiandrosterone, which can be converted peripherally into more potent androgens. Based on histological analyses, the adrenal cortex originally was separated into three zones: the zona glomerulosa, zona fasciculata, and zona reticularis. Functionally, it is more useful to view the adrenal cortex as two discrete compartments: the outer zona glomerulosa, which secretes the mineralocorticoid aldosterone, and the inner zonae fasciculata/reticularis, which secrete the glucocorticoid cortisol as well as the adrenal androgens (Figure 60–2). The biochemical basis for these differences in steroidogenic output has been defined in considerable detail. Cells of the outer zone have receptors for angiotensin II and express aldosterone synthase, an enzyme that catalyzes the terminal reactions in mineralocorticoid biosynthesis. In contrast, cells of the inner zones lack receptors for angiotensin II and express two enzymes, steroid 17α-hydroxylase ($P450_{17\alpha}$) and 11β-hydroxylase ($P450_{11\beta}$), that catalyze the production of glucocorticoids.

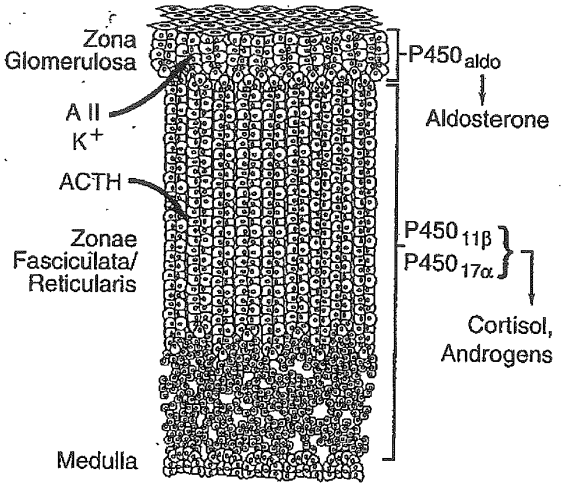

Figure 60–2. The adrenal cortex contains two anatomically and functionally distinct compartments.

The major functional compartments of the adrenal cortex are shown, along with the steroidogenic enzymes that determine the unique profiles of corticosteroid products. Also shown are the predominant physiologic regulators of steroid production: angiotensin II (A II) and K^+ for the zona glomerulosa and ACTH for the zonae fasciculata/reticularis.

In the absence of the adenohypophysis, the inner zones of the cortex atrophy, and the production of glucocorticoids and adrenal androgens is markedly impaired. Although ACTH acutely can stimulate mineralocorticoid production by the zona glomerulosa, this zone is regulated predominantly by angiotensin II and extracellular K^+ (*see* Chapter 31) and does not undergo atrophy in the absence of ongoing stimulation by the pituitary gland. In the setting of persistently elevated ACTH, mineralocorticoid levels initially increase and then return to normal (a phenomenon termed *ACTH escape*).

Persistently elevated levels of ACTH, due either to repeated administration of large doses of ACTH or to excessive endogenous ACTH production, induce hyperplasia and hypertrophy of the inner zones of the adrenal cortex, with overproduction of cortisol and adrenal androgens. Adrenal hyperplasia is most marked in congenital disorders of steroidogenesis, where ACTH levels are continuously elevated as a secondary response to impaired cortisol biosynthesis.

Mechanism of Action. ACTH stimulates the synthesis and release of adrenocortical hormones. As specific mechanisms for steroid hormone secretion have not been defined and since steroids do not accumulate appreciably in the gland, it is believed that the actions of ACTH to increase steroid hormone production are predominantly mediated at the level of *de novo* biosynthesis. ACTH, like most peptide hormones, interacts with a specific membrane receptor. As determined by gene cloning and sequencing, the human ACTH receptor is a member of the G protein–coupled receptor family, closely resembling in its structure the receptors for melanocyte-stimulating hormones (Cone and Mountjoy, 1993). ACTH acts through the G protein G_s to activate adenylyl cyclase and increase intracellular cyclic AMP content. Cyclic AMP is an obligatory second messenger for most, if not all, effects of ACTH on steroidogenesis. Mutations in the ACTH receptor have been associated with rare syndromes leading to familial resistance to ACTH (Clark and Weber, 1998).

Temporally, the response of adrenocortical cells to ACTH has two phases: an acute phase, which occurs within seconds to minutes, largely reflects an increased supply of cholesterol substrate to the steroidogenic enzymes; a chronic phase, which occurs over hours to days, results largely from increased transcription of the steroidogenic enzymes. A summary of the pathways of adrenal steroid biosynthesis and the structures of the major steroid intermediates and products of the human adrenal cortex are shown in Figure 60–3. The rate-limiting step in steroid hormone production is the conversion of cholesterol to pregnenolone, a reaction catalyzed by the cholesterol side-chain cleavage enzyme, designated $P450_{scc}$. Most of the enzymes required for steroid hormone biosynthesis, including $P450_{scc}$, are members of the cytochrome P450 superfamily, a related group of mixed-function oxidases that play important roles in the metabolism of xenobiotics such as drugs and environmental pollutants as well as in the biosynthesis of such endogenous compounds as steroid hormones, vitamin D, bile acids, fatty acids, prostaglandins, and biogenic amines (*see* Chapter 1). The rate-limiting components in this reaction regulate the mobilization of substrate cholesterol and its delivery to the $P450_{scc}$, located in the inner mitochondrial matrix.

The adrenal cortex uses multiple sources of cholesterol to ensure an adequate supply of substrate for steroidogenesis. These sources include (1) circulating cholesterol and cholesterol esters taken up *via* the low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-receptor pathways, (2) liberation of cholesterol from endogenous cholesterol ester stores *via* activation of cholesterol esterase, and (3) increased *de novo* biosynthesis.

The mechanism(s) by which ACTH stimulates the translocation of cholesterol to the inner mitochondrial matrix are not well defined. Several candidate mediators of the acute delivery of cholesterol to the mitochondria have been proposed, including a 30,000 dalton phosphoprotein induced by ACTH in all primary steroidogenic tissues, the peripheral benzodiazepine receptor, and sterol carrier protein-2. The cDNA encoding the 30,000 dalton phosphoprotein (designated the *S*teroidogenic *A*cute *R*egulatory Protein, or StAR) has been cloned and shown to activate steroidogenesis (Stocco and Clark, 1996). Significantly, mutations in the gene encoding StAR are found in patients with congenital lipoid adrenal hyperplasia, a rare

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