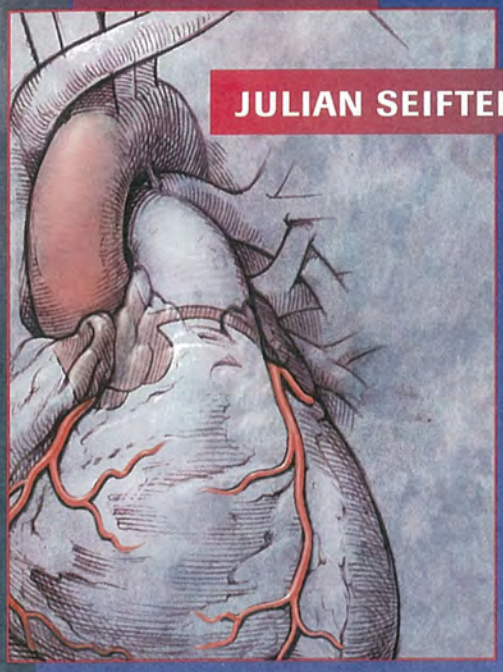
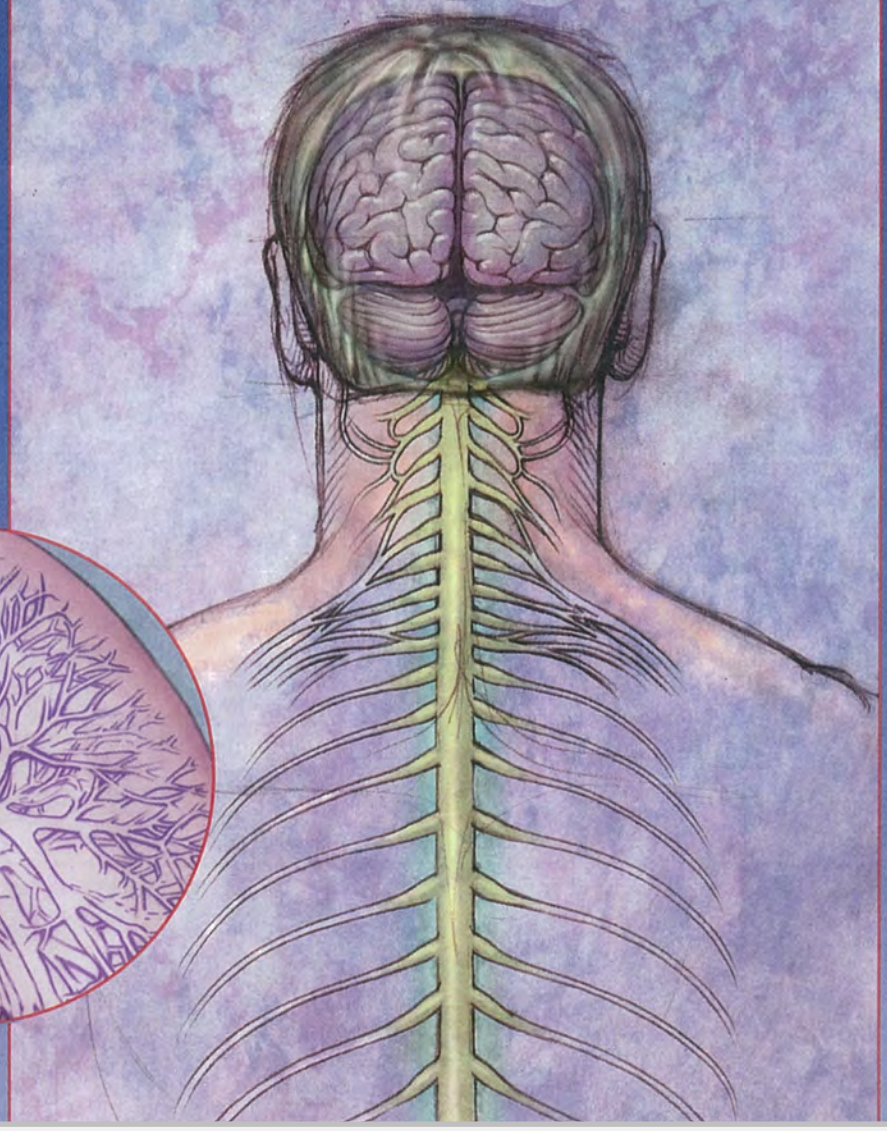
CONCEPTS IN MEDICAL PHYSIOLOGY

JULIAN SEIFTER • AUSTIN RATNER • DAVID SLOANE





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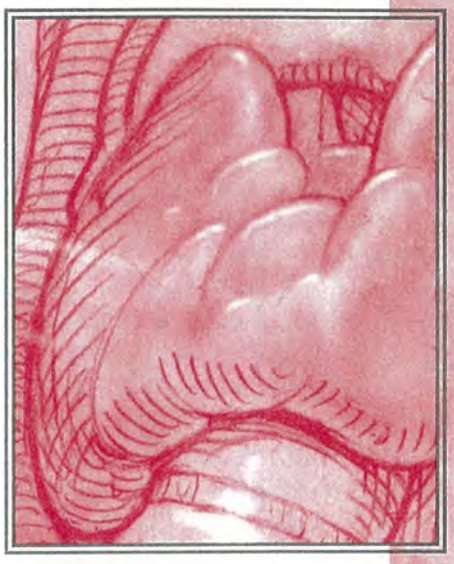


The Adrenal Gland

INTRODUCTION

The **adrenal gland** plays a pivotal role in human endocrine physiology. Although considered one gland anatomically, the adrenal gland functions as two distinct entities: the cortex and the medulla. These two portions of the adrenal originate from different embryonic tissues and have distinctly different physiologic roles.

The outermost shell of the adrenal gland, the **adrenal cortex**, produces three kinds of steroid hormones: aldosterone, cortisol, and androgens. **Aldosterone**, a mineralocorticoid, modulates electrolyte and fluid balance by stimulating sodium retention in the kidney's collecting ducts. **Cortisol**, a glucocorticoid, plays a crucial role in the body's stress response, in the regulation of protein, glucose, and fat metabolism, in the maintenance of vascular tone, and in the modulation of inflammation. The adrenal **androgens** are most important during fetal life as a substrate for placental estrogen production, but they play a minor role during adult life. The **adrenal medulla** is the inner core of the adrenal gland; it produces the catecholamines **epinephrine** and **norepinephrine**, which are also important components of the stress response.

Adrenal function is essential to human life. Adrenalectomy will lead to cardiovascular collapse and death within a few days from a lack of cortisol, which maintains blood vessel tone and blood pressure.

SYSTEM STRUCTURE: ADRENAL ANATOMY AND EMBRYOLOGY

The adrenals are triangular retroperitoneal organs located at the superior poles of the kidneys, lateral to the 11th thoracic and 1st lumbar vertebrae. These glands receive blood from the superior adrenal artery, a branch of the inferior phrenic; the middle adrenal artery, a branch of the aorta; and the inferior adrenal artery, a branch of the renal artery (FIGURE 34.1). This rich blood supply from three distinct locations explains why the adrenals are a frequent site of metastases from distant primary cancers. More importantly, the rich blood supply ensures the adrenals access to the bloodstream to facilitate hormonal secretion. The adrenal arteries anastomose (network) into a subcapsular plexus, which in turn branches into arteries that flow inward. Some of these arteries form capillary networks in the cortex and some form capillary networks in the medulla (FIGURE 34.2). The left adrenal vein drains into the left renal vein, while the right adrenal vein drains directly into the inferior

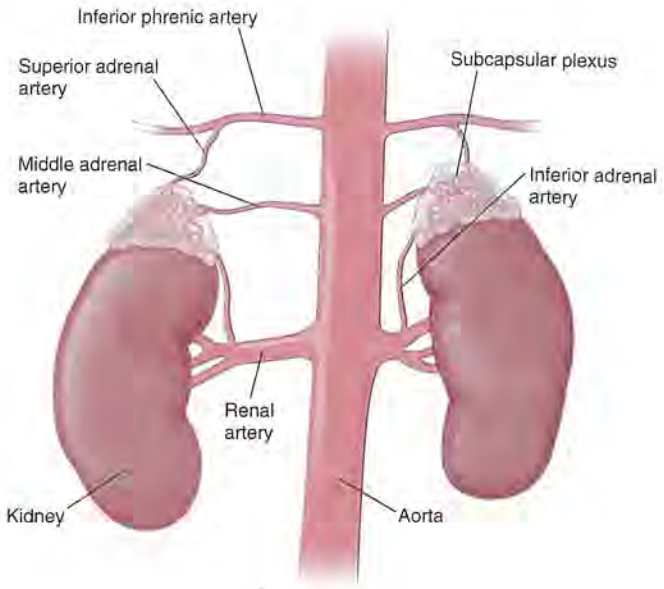


Figure 34.1 Arterial supply to the adrenal glands. The adrenal arteries are not drawn to scale, nor drawn in their exact anatomic locations.

testicular and ovarian veins. The left testicular/ovarian vein drains into the left renal vein, while the right testicular/ovarian drains right into the IVC.

The medulla and cortex of the adrenal glands are separate in structure, function, and embryologic origin. The cortex arises from the mesoderm, while the medulla derives from the ectoderm. The mesodermal gonadal ridge gives rise to the steroidogenic cells of the ovaries and testes as well as the adrenal cortex precursor cells, which migrate to the retroperitoneum. These mesodermal cortical cells are invaded by migrating ectodermal neural crest cells, which will become the medulla. Encapsulation of the adrenal gland around week 8 of fetal life creates a unified organ out of these two originally separate entities.

SYSTEM FUNCTION: THE ADRENAL CORTEX

The adrenal cortex makes up 80% to 90% of the adrenal gland by volume and comprises three histologically and functionally distinct zones, each of which makes a different steroid (FIGURE 34.3). Starting from the outermost, these layers are the **zona glomerulosa,** which produces aldosterone; the **zona fasciculata,** which produces cortisol; and the **zona reticularis,** which produces adrenal androgens, primarily DHEA (dehydroepiandrosterone) and androstenedione. (Some cortisol is produced in the

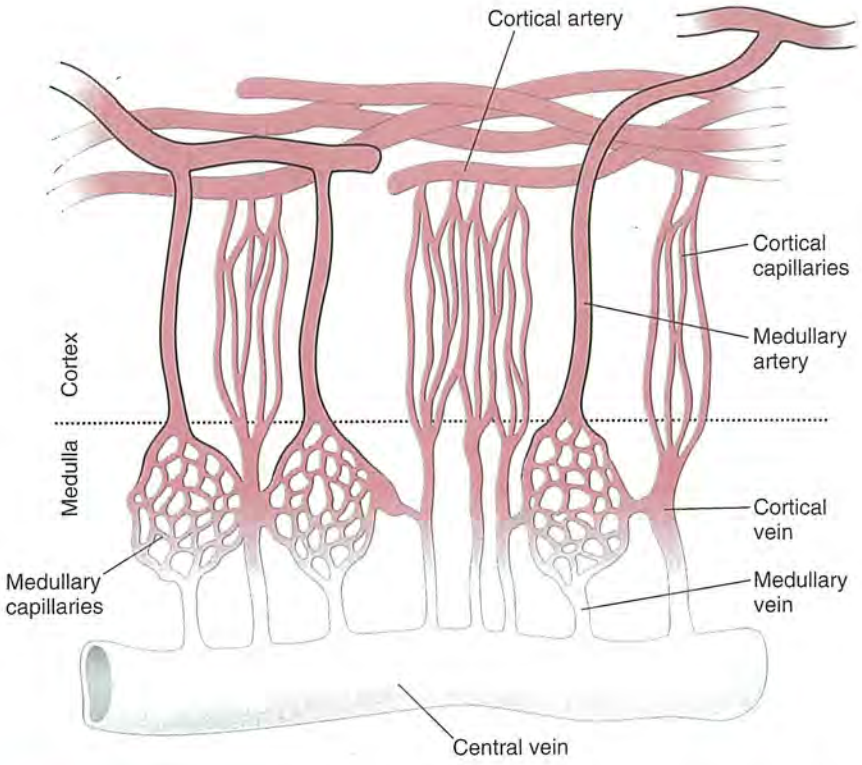
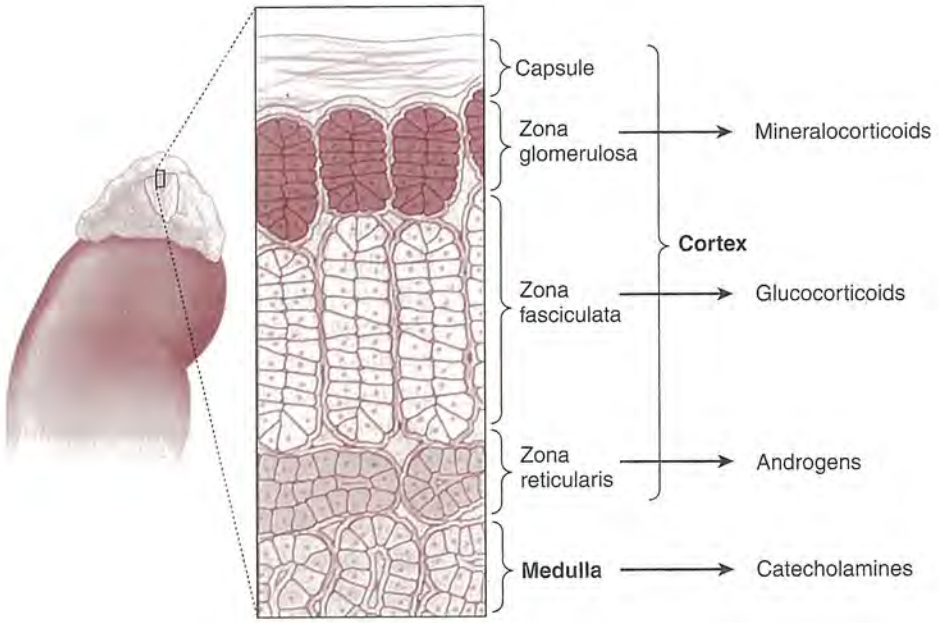


Figure 34.2 Vasculature inside the adrenal glands. The subcapsular plexus gives rise to arteries that form medullary capillary beds and to arteries that form cortical capillary beds.

CRH and ACTH

Production of the steroids in the adrenal cortex is regulated by the **hypothalamic-pituitary-adrenal (HPA) axis** (FIGURE 34.4). At the top of the HPA axis, the hypothalamus releases **corticotropin-releasing hormone (CRH)**, which stimulates the anterior pituitary to release *pro-opiomelanocortin*, a precursor molecule that is cleaved into four main products: *melanocyte-stimulating hormone*, *beta-lipotropins*, *beta-endorphins*, and **adrenocorticotropic hormone (ACTH)**. ACTH, also known as corticotropin, is released into the bloodstream and acts in the cortex, stimulating the synthesis and release of over 50



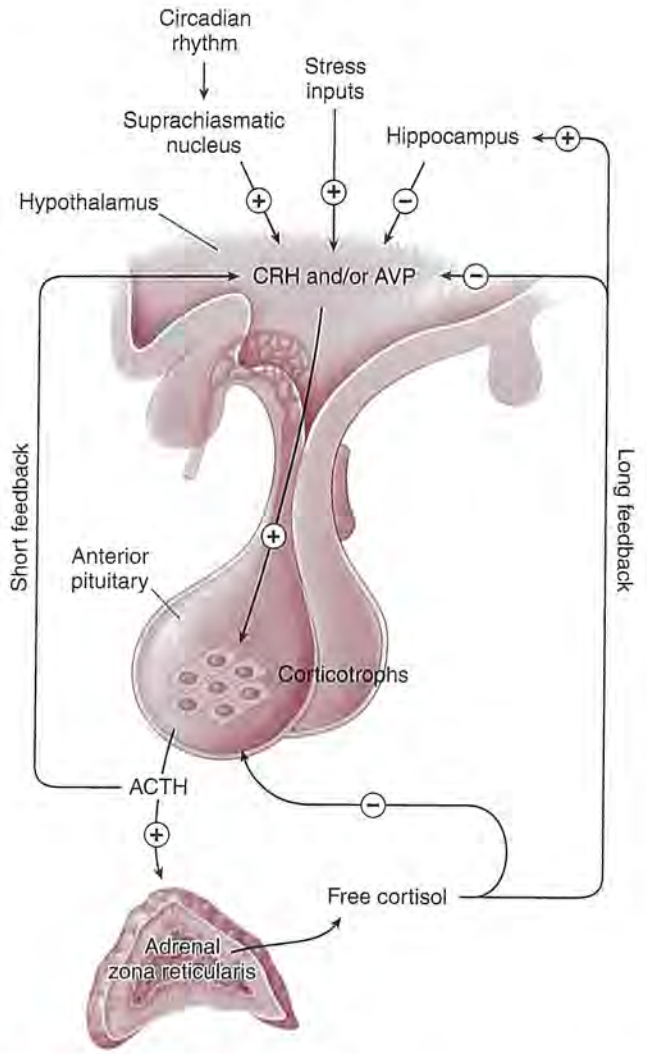


Figure 34.4 Hypothalamic-pituitary-adrenal axis. Stress, circadian rhythms, and negative feedback from cortisol all influence the paraventricular nucleus of the hypothalamus and modulate CRH output. Stressors may be organic in nature (such as hypoglycemia or infection) or psychological.

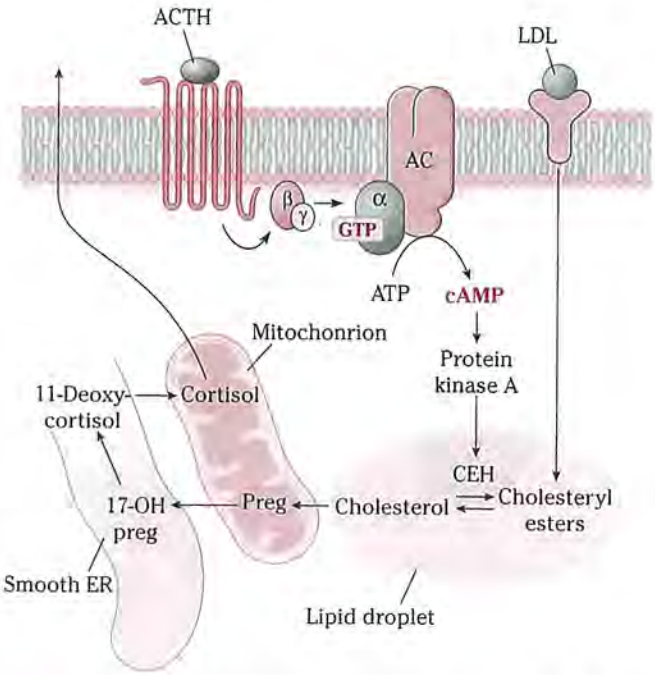


Figure 34.5 Action of ACTH on the adrenal cortex. AC, adenylyl cyclase; CEH, cholesteryl ester hydrolase; G, G protein (linking the receptor to the adenylyl cyclase); LDL, low-density lipoprotein; Preg, pregnenolone (cortisol precursor); R, ACTH receptor; Smooth ER, smooth endoplasmic reticulum.

steroid products, the most important of which are cortisol, the adrenal androgens, and aldosterone, although aldosterone is largely regulated in direct response to serum potassium levels and by *angiotensin II*, a hormone that helps to regulate blood pressure. In a classic endocrine feedback loop, cortisol directly inhibits both CRH production at the hypothalamic level and ACTH at the pituitary level, thereby acting as the main control mechanism for all adrenal cortical hormone production, with the exception of aldosterone.

The cortex responds dramatically to stimulation from ACTH, which elevates steroid production within minutes. It does so by activating a receptor on the cortical cell membranes that is linked to a G protein (FIGURE 34.5). The G protein, in turn, activates adenylyl cyclase and raises the cAMP level, activating a

activates the enzyme **cholesteryl ester hydrolase (CEH)**, which promotes the conversion of cholesteryl esters into free cholesterol. The free cholesterol then supplies the steroid synthesis pathways, as described below. Chronic stimulation with excessive ACTH causes bilateral adrenal hypertrophy, while removal or destruction of the pituitary, which is responsible for producing ACTH, conversely leads to adrenal atrophy.

Cortical Hormones: Their Actions and Regulation

As steroids, the cortical hormones all share certain functional features. They are all secreted into the adrenal blood vessels and circulate from the adrenal veins to target tissues all over the body. At the target tissues, they dissolve into the lipid membranes of the tissues and pass into the intracellular cytosol. There, the steroids bind cytosolic receptor proteins, which in turn bind to particular DNA sequences, thereby initiating the transcription of mRNA, resulting in the synthesis of new proteins.

As mentioned above and described in more detail below, the secretion of steroid hormones from the cortex is regulated by various kinds of negative-

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