

# Introduction to the Hypothalamo-Pituitary-Adrenal (HPA) Axis

## (Lecture)

### OBJECTIVES:

- Identify appropriate hypothalamic factors that control the secretion of each of the anterior pituitary hormones, and describe their route of transport from the hypothalamus to the anterior pituitary.
- Contrast the anterior and posterior pituitary lobes with respect to cell types, vascular supply, development, and innervation (hypothalamic).
- Diagram the short-loop and long-loop negative feedback control of anterior pituitary hormone secretion. Predict the changes in secretory rates of hypothalamic, anterior pituitary, and target gland hormones caused by over-secretion or under-secretion of any of these hormones or receptor deficit for any of these hormones.
- Describe the biosynthesis, structure, and actions of ACTH.
- Explain the importance of pulsatile and diurnal secretion.
- Identify the functional zones in the adrenal gland (one medullary and three cortical zones) and the principal hormones secreted from each zone.
- Describe the biosynthesis of the adrenal steroid hormones (glucocorticoids, mineralocorticoids, and androgens) and the key structural features that distinguish each class.
- Predict the effects of inherited defects in  $17\alpha$ -,  $21\beta$ -, and  $11\beta$ -hydroxylase on glucocorticoid and mineralocorticoid production and activity.
- Understand the cellular mechanism of action of adrenal cortical hormones.
- Identify the major actions of glucocorticoids on metabolism and the target organs on which they are produced.
- Describe the actions of glucocorticoid hormones in injury and stress.
- Describe the components of the neuroendocrine axis that control glucocorticoid secretion and describe how factors in the internal and external environment influence the neuroendocrine axis.
- Identify the chemical nature of catecholamines, their biosynthesis, half-life in blood and how they are degraded and removed from the body. Identify how the structure of norepinephrine differs from epinephrine.
- Describe the biological consequences of activation of the adrenal medulla and identify the target organs or tissues for catecholamines along with the receptor subtype that mediates the response. Understand the mechanism by which epinephrine and norepinephrine can produce different effects in the same tissues.
- Name the key stimuli causing catecholamine secretion. List the factors that can modulate a) the secretory response and b) the responses of target tissues.
- Describe the interactions of adrenal medullary and cortical hormones in response to stress.

**KEY WORDS:**

adrenocorticotropin (ACTH)	hypothalamo-pituitary axis
adrenal gland	hypothalamo-pituitary-adrenal axis
adrenocortical hormone	luteinizing hormone (LH)
aldosterone	mineralocorticoid
anterior pituitary	pituitary gland
cortisol	posterior pituitary
corticotropin releasing hormone (CRH)	prolactin
follicle stimulating hormone (FH)	proopiomelanocortin (POMC)
glucocorticoid	thyrotropin releasing hormone (TRH)
gonadotropin releasing hormone (GnRH)	zona fasciculata
growth hormone (GH)	zona glomerulosa
growth hormone releasing hormone (GHRH)	zona reticularis

**OPTIONAL READING**

Boron and Boulpaep, Medical Physiology, 1st edition, Saunders 2003, pp 1049-1065.

**I. INTRODUCTION**

Together with the nervous and circulatory systems, the endocrine system is critical for the integration and coordination of various bodily functions. Not only is the endocrine system conceptually related to the other two systems but the function of the endocrine system in homeostatic maintenance of the body would be impossible without its functional integration with the central nervous system and circulatory system. The role of the circulatory system in endocrine function is contained in the definition of hormone as a signaling chemical that uses the blood circulation to reach the target tissues. The CNS, on the other hand, has a more active role in endocrine function as the CNS is directly involved in synthesis and release of some hormones (e.g. oxytocin) and it is directly involved in regulating the function of majority of endocrine glands. The primary interface between the CNS and the endocrine system is the hypothalamus, which is at the same time an integral part of the central nervous system and an endocrine gland. Via the pituitary gland the hypothalamus controls the function of the “peripheral” endocrine glands such as adrenal and thyroid glands. Here, we will discuss the organization and function of the hypothalamus (in the context of endocrine physiology), pituitary and the adrenal gland.

**II. HYPOTHALAMO-PITUITARY AXIS**

**A. Hypothalamus**

The hypothalamus contains neurosecretory neurons which synthesize peptides and catecholamines; these are released into the circulatory system and act as hormones. Some hypothalamic hormones are released into the systemic circulation to target distant tissues. Other hypothalamic hormones are released in the portal circulation for delivery to the anterior pituitary where they stimulate or inhibit release of the anterior pituitary hormones. All the hypothalamic hormones are peptides except dopamine, which is a catecholamine. The hypothalamic hormones are shown in Table 1.

**Table 1.** Hypothalamic hormones and their actions.

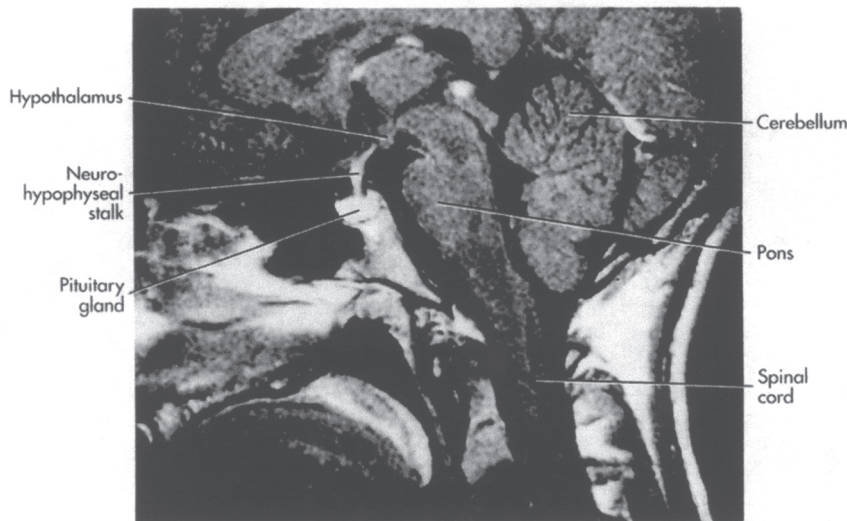
Hormones acting on the anterior pituitary	Action
GnRH (gonadotropin-releasing hormone)	stimulates release of leutinizing hormone (LH) and follicular stimulating hormone (FSH)
GHRH (growth hormone-releasing hormone)	stimulates release of growth hormone (GH)
Somatostatin	inhibits GH release
TRH (thyrotropin-releasing hormone)	stimulates release of thyroid stimulating hormone (TSH) and prolactin
Dopamine (a.k.a. PIH; prolactin-inhibiting hormone)	inhibits prolactin release
CRH (corticotropin-releasing hormone)	stimulates ACTH (adrenocorticopin) release
Hormones acting on distant tissues	Action
ADH (antidiuretic hormone; a.k.a. vasopressin)	discussed below and Organs block
Oxytocin	discussed below and Organs block

The hypothalamus serves as the integrating center for interoceptive (originating within the CNS) and exteroceptive (originating outside the CNS) stimuli. This diverse collection of nuclei at the base of the brain processes the stimuli and generates appropriate responses. These responses are mediated in large part by the neuroendocrine and endocrine signals originating along the **hypothalamo-pituitary axis**. For example, if a person finds him/her self dehydrated in the desert, the hypothalamus senses the increase in osmotic strength of the extracellular fluids. In parallel, the loss of extracellular volume is sensed by the peripheral nervous system and this information is also relayed to the hypothalamus. These stimuli result in a number of different responses, including the release of ADH in the posterior pituitary which will preserve the water in kidneys and stimulate thirst. An additional hypothalamic response in this situation might be release of CRH in response to stress. CRH will target the anterior pituitary to release ACTH and subsequently release glucocorticoids from the adrenal gland. In order to understand the mechanisms by which the hypothalamus and pituitary gland communicate to accomplish these effects, we need to understand the organization of the pituitary gland and the hypothalamo-pituitary connections.

## B. Pituitary Gland

### 1. Pituitary development

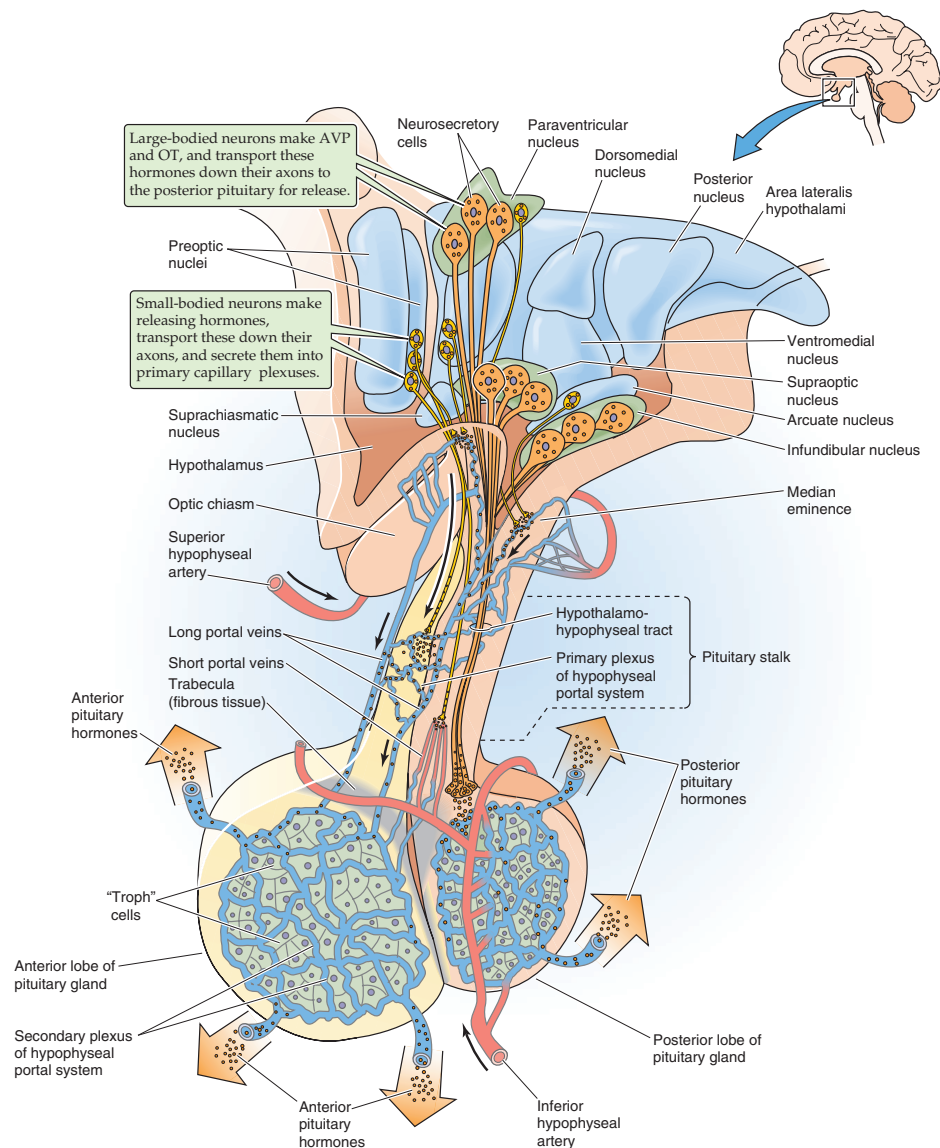
The pituitary gland is a complex gland consisting of hormone-producing adenoid (glandular) cells (anterior pituitary) and the axon terminals of neurosecretory cells originating in the hypothalamus (posterior pituitary). The **anterior pituitary** (or adenohypophysis) develops from an ectodermal pouch (Rathke's pouch) originating from the epithelial roof of the oral cavity, and the origin of the **posterior pituitary** (or neurohypophysis) is the neural ectoderm at the base of the third ventricle. While the anterior pituitary loses contact with the oral cavity during development, the posterior pituitary stays connected with the base of the hypothalamus. The two components of the gland are joined together and cradled in a recess in the sphenoid bone called the sella turcica (turkish saddle) at the base of the middle cranial fossa (see Figure 1). The gland is enclosed (and separated from the brain) by the reflection of the dura mater. An extension of the base of the hypothalamus called the neural stalk penetrates the dura and, through the median eminence, connects the gland with the base of the hypothalamus. So how does such a complex amalgam of cells communicate and seamlessly integrate its function with the hypothalamus? The key to the integration of the hypothalamo-pituitary axis is the organization of the pituitary blood supply.



**Figure 1.** Magnetic resonance image of the head. Hypothalamus, neurohypophyseal stalk and pituitary gland (nested in the sphenoid bone) are visible.

### 2. Organization of pituitary blood supply

The blood to the pituitary gland is supplied by the superior and inferior hypophyseal arteries (see Figure 2). The inferior hypophyseal artery provides blood to the posterior pituitary while the superior hypophyseal artery supplies the neural stalk as well as the anterior pituitary. The superior hypophyseal artery gives rise to the hypophyseal portal circulatory system. (As you recall, the portal circulatory system is the one that starts and ends in a capillary plexus.) The first capillary plexus in this portal system is investing the median eminence and neural stalk. This is the area where a subset of hypothalamic neurons releases hormones that will target appropriate adenohypophyseal cells



**Figure 2.** The hypothalamo-pituitary axis. (Boron and Boulpaep, Medical Physiology, 1st edition, Saunders 2003, Figure 46-3, page 1011.)

in the anterior pituitary. This capillary bed is drained by a set of long portal veins that give rise to the second capillary bed in the anterior pituitary. Thus, the inhibiting and releasing hormones that control adenohypophyseal secretions are delivered via long portal veins and to the anterior pituitary where they bind to appropriate receptors to regulate the adenohypophyseal cells. The veins originating in the neurohypophyseal capillary plexus give rise to the short portal veins that will also contribute to the adenohypophyseal capillary plexus and, thus, effectively connect the two circulatory systems. The venous blood from both the anterior and posterior pituitary is drained in the cavernous sinus and this is the path through which the anterior and posterior pituitary hormones are released into systemic circulation.



There are several other characteristics of this system worth mentioning. The short portal veins could enable reverse flow from the anterior pituitary to the posterior pituitary. This would result in a direct communication between the anterior pituitary and the hypothalamus via reverse axonal transport up the axons of the hypothalamic cells. This pathway would allow an easy communication between the endocrine and neural cells circumventing the blood-brain barrier and providing an easy short-loop feedback between the two sets of cells. In addition, it is possible that a two-way communication between the cerebrospinal fluid and the pituitary gland also exists. The capillary bed supplying the median eminence and neural stalk is invested by pituitary tanycytes, specialized ependymal cells originating at the base of the third ventricle (recall that the median eminence is the base of the third ventricle). These cells could facilitate communication between the pituitary and the cerebrospinal fluid. All of these possibilities are currently being investigated.

### 3. Posterior pituitary hormones

As described earlier, the posterior pituitary contains mostly axon terminals of the hypothalamic neurosecretory cells. These axon terminals are surrounded by the inferior hypophyseal artery capillary bed. ADH and oxytocin are the two hormones released by the posterior pituitary. You will recall that ADH is responsible for osmotic homeostasis (it decreases the free water clearance in kidneys and stimulates thirst) and, at higher plasma concentrations, is also a very potent vasoconstrictor. Oxytocin mostly acts at the uterine smooth muscle and the smooth muscle in the mammary glands. (You will learn much more about this hormone and its role in delivery and lactation in the Life Cycle block.)

### 4. Anterior pituitary hormones

There are six types of cells in the anterior pituitary, named after the primary peptide/protein hormones they produce: **ACTH** (adrenocorticotropin), **TSH** (thyroid stimulating hormone; thyrotropin), **FSH** and **LH** (follicle stimulating and luteinizing hormone or gonadotropins), **GH** (growth hormone or somatotropin) and **prolactin** (lactotropin). Upon stimulation of the anterior pituitary by hypothalamic hormones, these hormones are released and diffuse into the second portal capillary bed. These six hormones can be classified into three families: the glycoprotein family, the growth hormone/prolactin family, and the derivatives of the POMC molecule.

#### a. Glycoprotein family of anterior pituitary hormones

The four hormones that belong to this family are all peptides that are glycosylated to a different degree (glycosylation typically increases the half life of the hormone in circulation). All of them consist of a and b

subunits. They share a homologous a subunit, while the b subunits differ, conferring specificity.

1. LH stimulates ovulation and the gonadal production of sex hormones.
2. HCG (human chorionic gonadotropin) is the only hormone in the glycoprotein family not produced by the anterior pituitary but by the placental trophoblast. (Thus detection of the HCG is the basis of pregnancy tests). HCG is very similar to LH and has essentially the same function as LH.
3. FSH stimulates ovarian follicular development as well as development of spermatozooids. It also stimulates the production of estrogen.
4. TSH stimulates production and release of thyroid hormones ( $T_3$  and  $T_4$ )

(You will learn more about these hormones later in this block and the Life Cycle block.)

#### **b. POMC family of anterior pituitary hormones**

There are four members of this family of hormones, all of which are formed by proteolytic processing of the **proopiomelanocortin (POMC)** molecule: ACTH,  $\beta$ -lipotropin,  $\beta$ -Melanocyte Stimulating Hormone ( $\beta$ -MSH) and  $\beta$ -endorphin. (More on these hormones later.)

#### **c. Growth hormone/prolactin family of anterior pituitary hormones**

The two members of this family are so closely related that GH has as much prolactin-like activity as prolactin itself. GH (with the help of liver-produced IGF-1) stimulates growth of many tissues in the body. Overproduction of GH leads to gigantism. Prolactin also has effects on many tissues (for example, it affects reproductive and immune tissue), but its best characterized action is the stimulation of milk production during lactation.

### **5. Regulation of pituitary hormone secretion**

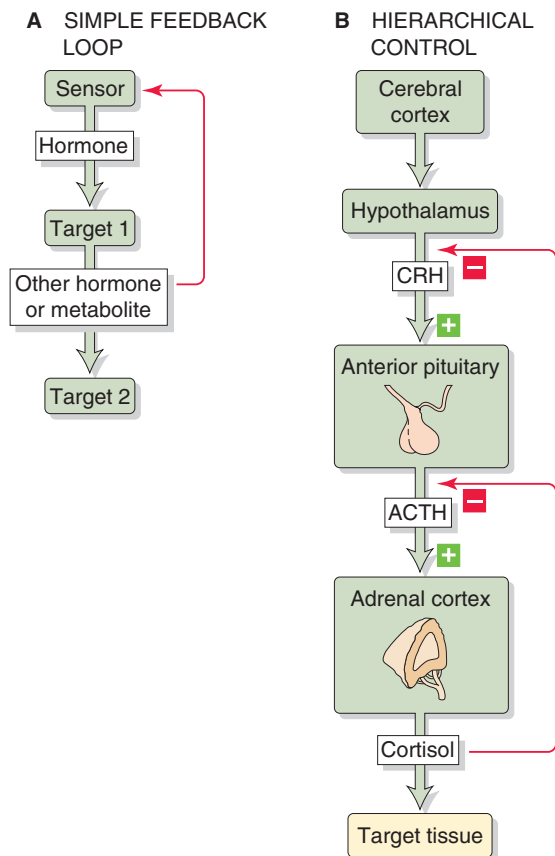
#### **a. Neural control**

As mentioned above, secretion of pituitary hormones is controlled by neural stimuli that originate at the periphery or in the central nervous system. An excellent example of the peripheral control of pituitary hormone is the release of oxytocin and prolactin during nursing. The suckling of a baby stimulates sensory nerves and activates the afferent pathway to the hypothalamus. The hypothalamus responds with the release of oxytocin in the posterior pituitary and the release of TRH (along with the decrease of dopamine release) to stimulate the release of prolactin in the anterior pituitary. Oxytocin acts on the smooth muscle cells in the ducts of the mammary gland to expel the milk and

the prolactin acts on the glandular tissue in the breast to stimulate milk production. As mentioned, the stimuli originating in the CNS can also stimulate pituitary hormone release. For example, many lactating mothers, when thinking about their baby, experience the ejection of a small amount of milk from the lactiferous ducts. This is brought about by the release of oxytocin in response to the mental images of the baby. Similarly, stimuli originating in the CNS during the REM phase of sleep induce the release of GHRH that results in the release of GH. Similarly, stimuli originating in the hypothalamic centers controlling circadian rhythms induce release of CRH approximately a couple of hours before waking to stimulate ACTH release. The opposite is true just before and/or at the beginning of sleep.

### b. Negative feedback

Often, target tissues for the anterior pituitary hormones are glands themselves (Figure 3). The hormones secreted by these glands can inhibit the release of their tropic hormone or its tropic hormone-releasing hormone. For example, FSH and LH stimulate production of sex hormones. Estradiol, progesterone and testosterone can inhibit both the release of gonadotropins as well as the release of GnRH.



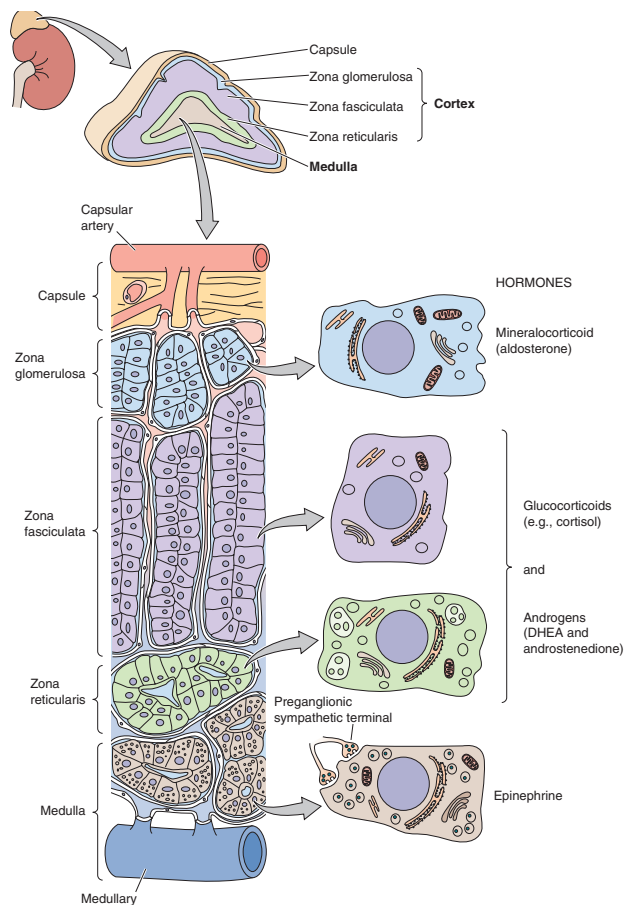
**Figure 3.** Feedback control of hormone secretion. (Boron and Boulpaep, Medical Physiology, 1st edition, Saunders 2003, Figure 46-2, page 1010.)



### III. ADRENAL GLAND

#### A. Structure

The **adrenal gland** consists of two distinct endocrine glands: the adrenal medulla, which secretes catecholamines; and the adrenal cortex, which secretes steroid hormones. The adrenal medulla is in effect an enlarged and specialized sympathetic ganglion whose neuronal cell bodies do not have axons, but release catecholamines directly into the blood. Adrenal medullary secretion is under sympathetic control by way of the greater splanchnic nerve. The adrenal cortex is divided into three zones: the **zona glomerulosa**, **zona fasciculata** and **zona reticularis** (Figure 4). The zona glomerulosa, which secretes aldosterone, is controlled primarily by the renin-angiotensin system, ACTH and other factors, while the zona fasciculata and zona reticularis, which secrete glucocorticoids, androgens and estrogens, is controlled primarily by ACTH.

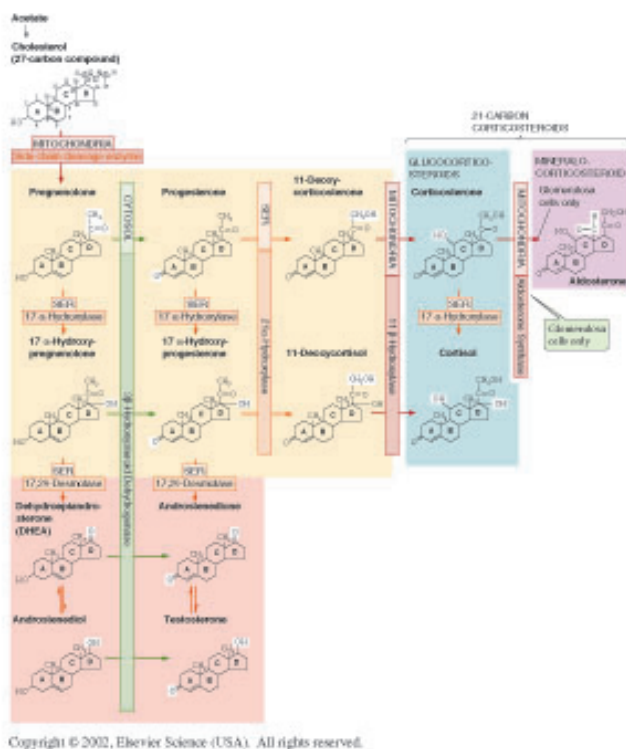


**Figure 4.** Anatomy of the adrenal gland. (Boron and Boulpaep, *Medical Physiology*, 1st edition, Saunders 2003, Fig. 49-1, p. 1050.)

#### B. Adrenocortical Hormones

##### 1. Steroid biosynthesis

Steroid hormones are derived from cholesterol. The pathways of steroid biosynthesis in the adrenal cortex are shown in Figure 5. Note that the early steps in this pathway are the same in the ovaries and testes. The



**Figure 5.** Biosynthesis of adrenal steroids. (Boron and Boulpaep, Medical Physiology, 1st edition, Saunders 2003, Figure 49-2, page 1051.)

principal steroids secreted by the zona fasciculata and zona reticularis are **cortisol**, corticosterone and dehydroepiandrosterone (DHEA).

The biosynthetic pathway in the zona glomerulosa differs from that in the zona fasciculata and zona reticularis in two important ways. First, the zona glomerulosa lacks the enzyme 17 alpha-hydroxylase and is therefore unable to synthesize cortisol, androgens or estrogens. Second, only the zona glomerulosa contains the enzymes that convert corticosterone to aldosterone. Therefore, the zona glomerulosa is the only zone capable of synthesizing this mineralocorticoid hormone.

Steroids are not stored in the adrenal gland, but diffuse into the blood as soon as they are synthesized.

## 2. Principal adrenocortical steroids

The principal **adrenocortical hormones** are listed in Table 2 together with their plasma concentrations and relative glucocorticoid and mineralocorticoid activities. The term “**glucocorticoid**” refers to actions

Steroid	Average Plasma Concentration (µg/dL, total)	Glucocorticoid Activity*	Mineralocorticoid Activity*
Cortisol	14	1.0	1.0
Corticosterone	0.4	0.3	15
Aldosterone	0.006	0.3	3000

of steroids on glucose metabolism while “**mineralocorticoid**” refers to actions on renal electrolyte excretion. Note the high concentration of the weak androgen DHEA, most of which is conjugated to sulfate and is inactive.

The remainder of this chapter is concerned with cortisol and other glucocorticoids. Aldosterone was covered in the Organs block last year.

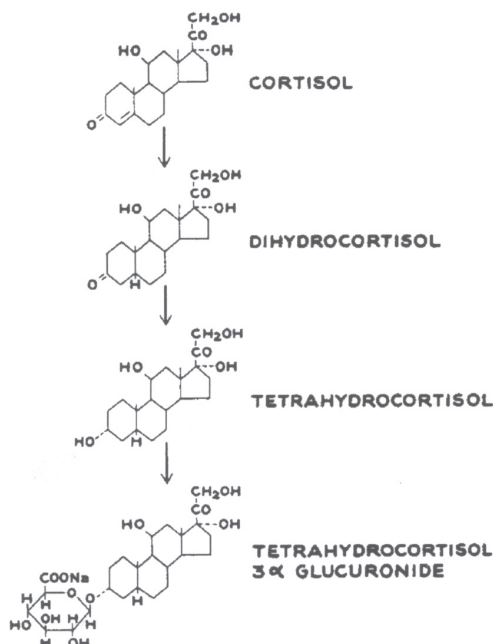
### 3. Cortisol and other glucocorticoids

#### a. Transport of cortisol in plasma

Approximately 75% of the cortisol in the circulation is bound to a plasma protein named transcortin or corticosteroid binding globulin (CBG). Another 15% is bound to albumin, and the remaining 10% is unbound or “free”. It is the free cortisol which is biologically active. It is also the free concentration that is regulated. **Transcortin** is produced by the liver. Its production is stimulated by estrogens and therefore plasma transcortin levels increase during pregnancy. As a result, more cortisol is bound, free cortisol concentration decreases and ACTH secretion increases. Cortisol production then increases until the free cortisol concentration returns to normal. For this reason, pregnant women have elevated blood cortisol levels but do not have symptoms of glucocorticoid excess. The same phenomenon occurs in women taking estrogen-containing oral contraceptives.

#### b. Metabolism of cortisol

Like most steroids, cortisol is metabolized in the liver. It has a half-life of 60-90 minutes in the circulation. Most of the cortisol is reduced to dihydrocortisol and then to tetrahydrocortisol which is conjugated to glucuronic acid (Figure 6). Some cortisol is converted to cortisone. Note that cortisone is an active glucocorticoid but that it is formed in



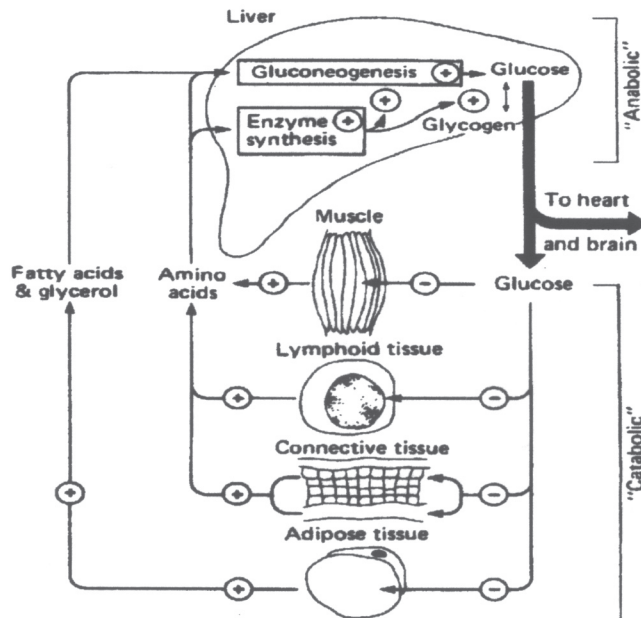
**Figure 6.** Metabolism of cortisol.

the liver, not in the adrenal. Cortisone is also reduced and conjugated to form tetrahydrocortisone glucuronide. The tetrahydroglucuronide derivatives of cortisol and cortisone are water soluble and are excreted in the urine.

### c. Effects of cortisol

Cortisol is one of the few hormones essential for life. Adrenalectomy in humans is always fatal unless glucocorticoids are administered. Exactly why adrenal insufficiency results in death is not well understood, but in view of the widespread actions of the glucocorticoids, it is not surprising that they are needed for life.

- i. Metabolism. Cortisol and other glucocorticoids exert anabolic effects (gluconeogenesis, glycogenesis) on the liver, and catabolic effects (proteolysis, lipolysis) at several sites including muscle, adipose tissue, connective tissue and lymphoid tissue (Figure 7).



**Figure 7.** Metabolic effects of cortisol.

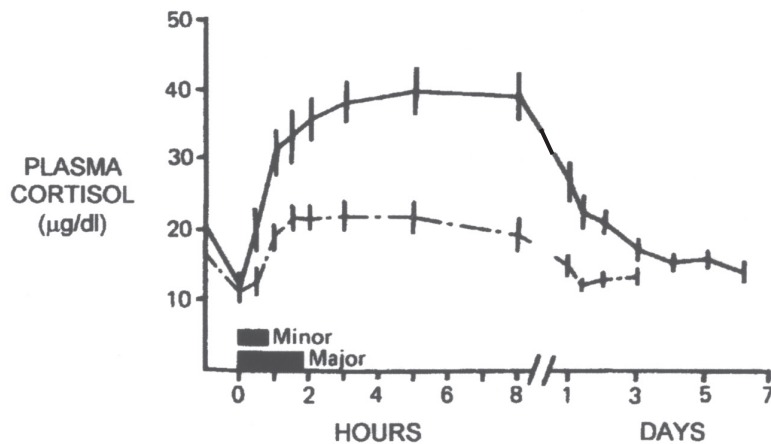
Glucose output by the liver increases and glucose uptake by muscle, adipose and other tissues decreases. As a result, blood glucose increases. These actions can be considered as a mechanism to mobilize energy sources (amino acids, fatty acids, glycerol) from some tissues to provide energy substrates, particularly glucose, for others, notably the brain and heart. The metabolic effects of glucocorticoids may be counterbalanced by those of other hormones, particularly insulin, the secretion of which is stimulated by the rise in blood glucose.

Cortisol also exerts permissive actions. This refers to the fact that the action of some hormones requires the presence of cortisol.

For example, cortisol must be present in order for glucagon and catecholamines to exert their calorogenic action, and for catecholamines to exert their lipolytic effect.

- ii. Inhibition of ACTH secretion. Cortisol inhibits ACTH secretion. This feedback inhibition is exerted both at the hypothalamus and at the pituitary. Note that it is free cortisol that is responsible for the inhibition. All glucocorticoids inhibit ACTH secretion, and the more potent the glucocorticoid, the greater the degree of inhibition.
- iii. Vascular reactivity. In addition to its effects on the organs and tissues directly involved in metabolic homeostasis, cortisol influences number of other organs and systems. Cortisol maintains the responsiveness of vascular smooth muscle to catecholamines and therefore participates in blood pressure regulation. This is another example of a permissive action of cortisol. In adrenal insufficiency, vascular smooth muscle becomes unresponsive to catecholamines. The decreased responsiveness, together with the associated hypovolemia caused by mineralocorticoid deficiency, can result in severe hypotension.
- iv. Effects on immune system and inflammatory responses. Glucocorticoids inhibit the inflammatory response to tissue injury. For example, cortisol (and all known glucocorticoids) suppresses synthesis and decreases the release of arachidonic acid, the key precursor for a number of mediators of inflammation (e.g. prostaglandins, leucotrienes). It also decreases differentiation and proliferation of local mast cells, stabilizes lysosomes and decreases production of platelet activating factor and nitric oxide. All of these effects are designed to suppress local inflammatory response. Glucocorticoids also suppress immune response by decreasing the number of circulating T<sub>4</sub> lymphocytes and by decreasing the production of interleukins and gamma interferon that are critical mediators of immune response. (Although cortisol also decreases recruitment and activation of B lymphocytes, its main effects are exhibited on cell-mediated immunity.)
- v. Effects on central nervous system. Cortisol can directly modulate electrical activity of the neurons via type I and type II glucocorticoid receptors that are expressed particularly in limbic system and hippocampus. Cortisol's ability to decrease hippocampal volume as well as memory has also been demonstrated. Cortisol decreases REM sleep but increases both slow-wave sleep and time spent awake. Excessive concentrations of cortisol in blood can cause insomnia and strikingly increase or decrease mood.

- vi. Effects on stress. ACTH and cortisol secretion are increased by stressful stimuli including surgery (Figure 8), trauma, pain, apprehension, infection, hypoglycemia and hemorrhage. The increase in cortisol production is necessary for survival, and stresses that are normally tolerated can become fatal in adrenal insufficiency. The reason that an increase in circulating glucocorticoid level is needed to resist stress is not well understood particularly in the context of the inhibitory effects of glucocorticoids on immune system. It has been suggested that basal (or slightly elevated) levels of cortisol have permissive action that is critical for initial metabolic response to stress (and even immune response – glucocorticoids mobilize neutrophils from the bone marrow). Conversely, the immunosuppressive effects of glucocorticoids are supposed to protect the organism from an overactive immune system.

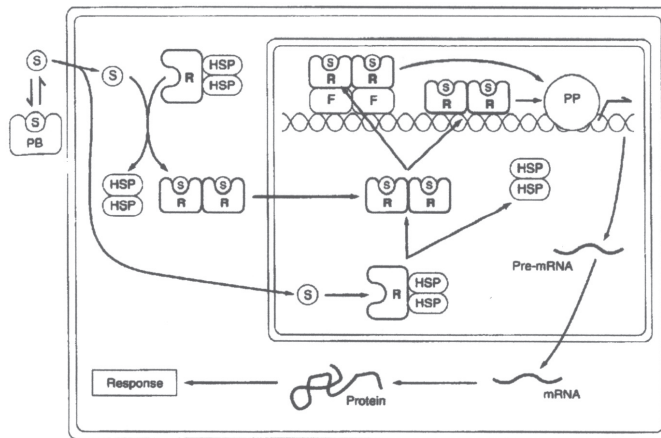


**Figure 8.** Cortisol response to a minor (dashed line) and major (solid line) surgery.

#### d. Mechanism of action

As with other steroid hormones, the multiple effects of glucocorticoids result from stimulation of DNA-dependent mRNA synthesis in the cells of the target tissues (Figure 9). Glucocorticoid receptors (R) are mostly located in the cytoplasm where they are associated with a heat shock protein (HSP) that prevents the receptors from binding to DNA. Some receptors are located in the nucleus. Steroid (S) binding to the receptor induces conformational changes that promote dissociation of the heat shock protein and expose a DNA binding site. The receptor then binds to a glucocorticoid receptor response element on the DNA,





**Figure 9.** Mechanism of action of steroid hormones. See text for abbreviations.

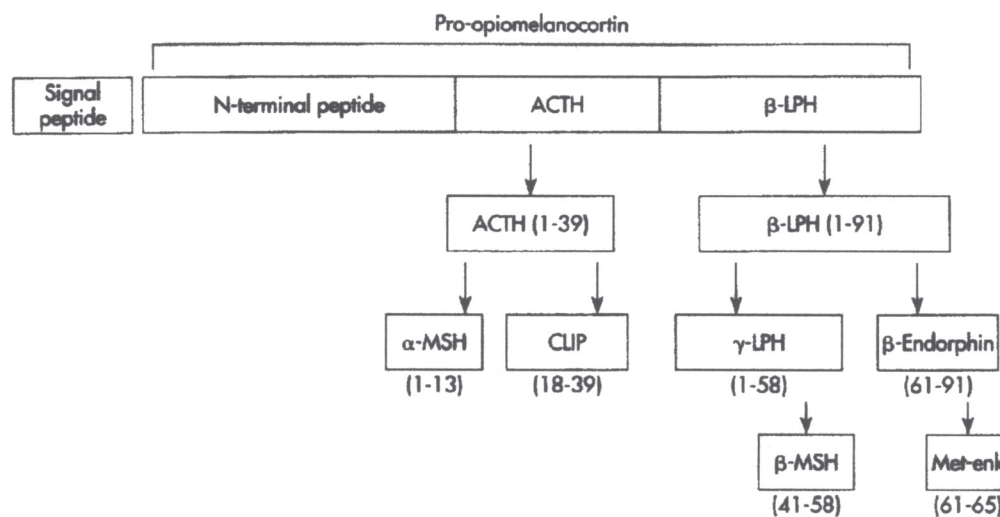
resulting in enhanced transcription, protein synthesis and, ultimately, the response to the steroid.

#### 4. Regulation of adrenocortical secretion

The synthesis of cortisol and other steroids by the zona fasciculata and reticularis is controlled by adrenocorticotrophic hormone (ACTH).

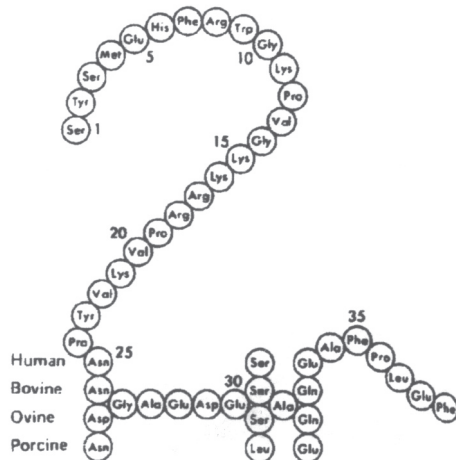
##### a. Structure and biosynthesis of ACTH

ACTH is synthesized as part of a larger precursor molecule known as pro-opiomelanocortin (POMC) (Figure 10). POMC is hydrolyzed to ACTH and  $\beta$ -lipotropin ( $\beta$ -LPH) which are released into the circulation. The function of  $\beta$ -LPH is not known. ACTH and  $\beta$ -LPH may in turn be cleaved to form a variety of peptides including  $\beta$ -endorphin (an endogenous opioid), and alpha- and  $\beta$ -melanocyte stimulating hormone (alpha- and  $\beta$ -MSH) which stimulate melanin synthesis causing darkening of the skin.



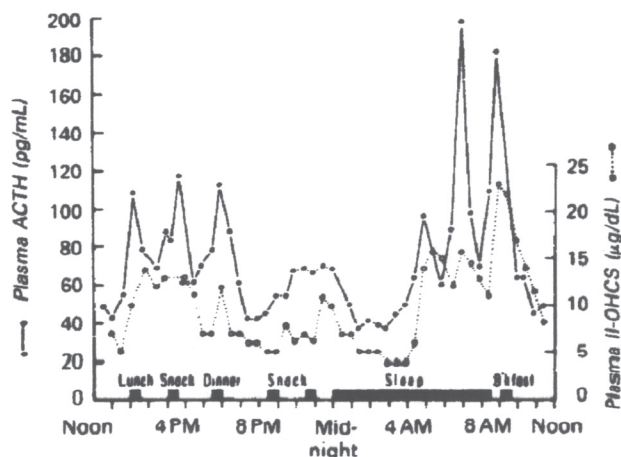
**Figure 10.** Synthesis of ACTH and related peptides in the anterior pituitary.

ACTH is a single chain 39-amino acid peptide (Figure 11). Biological activity resides in the first 23 amino acids of the peptide, and the synthetic 1-23 amino acid peptide (Cortrosyn) has full activity. Species differences in the structure of ACTH occur at positions 25, 31 and 33.

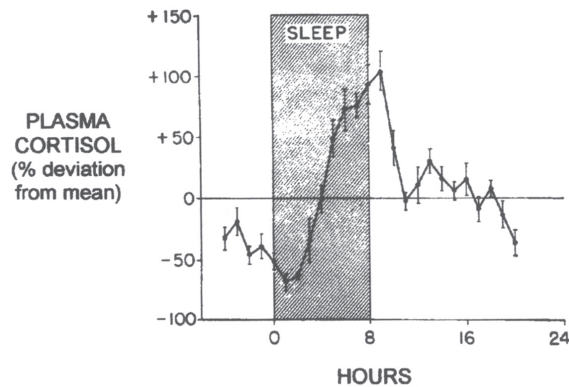


**Figure 11.** Structure of human ACTH showing species differences.

ACTH is secreted in irregular pulses throughout the day which cause parallel increases in plasma cortisol (Figure 12). Both the frequency and the amplitude of the pulses are the greatest in the early morning. This early morning increase in ACTH release is initiated by the release of CRH (**corticotropin releasing hormone**) and starts approximately a couple of hours before waking. The lowest levels of ACTH in blood occur just before or after falling asleep. This results in the characteristic diurnal rhythm in ACTH and cortisol secretion (Figure 13).



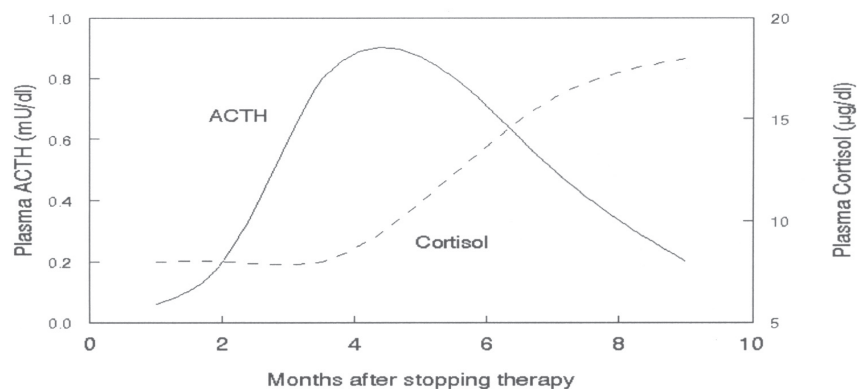
**Figure 12.** Pulsatile secretion of ACTH and cortisol.



**Figure 13.** Diurnal rhythm in plasma cortisol concentration.

### b. Actions of ACTH

- i. Steroidogenesis. Injection of ACTH stimulates cortisol production within minutes. The stimulation is mediated by activation of adenylyl cyclase. Cyclic AMP activates protein kinase A, which in turn activates cholesterol ester hydrolase. More free cholesterol is formed and converted to pregnenolone in the mitochondria.
- ii. Adrenal growth and responsiveness. Elevated levels of ACTH cause hypertrophy of the zona fasciculata and reticularis while lack of ACTH results in atrophy of these zones. ACTH deficiency also reduces the ability of the adrenal gland to secrete cortisol in response to ACTH. This decreased responsiveness occurs during treatment with glucocorticoids in doses that inhibit ACTH secretion and persists for some time after stopping treatment (Figure 14). Responsiveness can be restored by administration of ACTH. Changes in ACTH levels

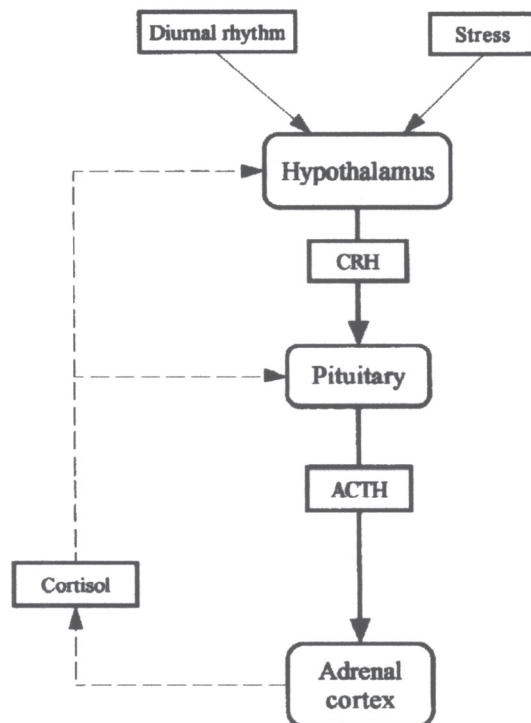


**Figure 14.** Plasma ACTH and cortisol concentrations after stopping long-term glucocorticoid treatment.

have little effect on the zona glomerulosa which is controlled primarily by the renin-angiotensin system.

**c. Control of ACTH secretion**

ACTH secretion is under stimulatory control by corticotropin releasing hormone (CRH) and negative feedback control by circulating cortisol (Figure 15).



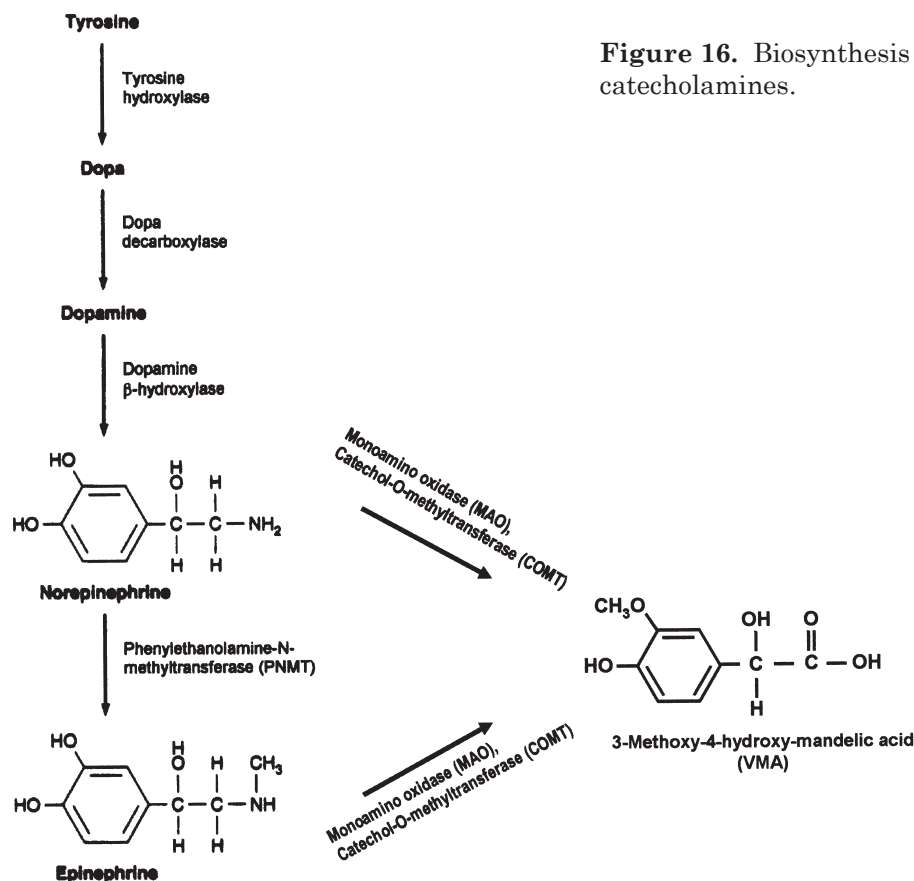
**Figure 15.** Regulation of secretion of CRH and ACTH. Cortisol inhibits secretion of CRH from the hypothalamus and ACTH from the pituitary, thereby downregulating its own secretion.

- i. Corticotropin Releasing Hormone. CRH is a 41-amino acid peptide that is synthesized by neurons in the hypothalamus. It is secreted by nerve endings in the median eminence into the hypophyseal portal system from and carried to the anterior pituitary where it stimulates the release of ACTH. CRH mediates the diurnal rhythm in ACTH secretion and the ACTH response to stress. Also, psychiatric disturbances, adrenergic agonists, interleukins and number of other factors can stimulate ACTH release.
- ii. Negative feedback. Circulating cortisol feeds back at the hypothalamus and pituitary to inhibit the secretion of CRH and ACTH.

## C. Adrenomedullary Hormones

### 1. Biosynthesis of catecholamines

The catecholamines are formed from tyrosine by a series of hydroxylation and decarboxylation reactions (Figure 16). The first step catalyzed by tyrosine hydroxylase is the rate limiting step.



**Figure 16.** Biosynthesis of catecholamines.

The enzyme PNMT is only present in the adrenal medulla and some parts of the brain so epinephrine synthesis occurs only at those sites. Adrenal PNMT is induced by the high concentration of cortisol in the blood draining from the cortex to the medulla.

Note that while all the epinephrine in the blood comes from the adrenal medulla most of the norepinephrine comes from sympathetic nerve endings throughout the body. Thus, plasma norepinephrine concentration does not decrease significantly after adrenalectomy.

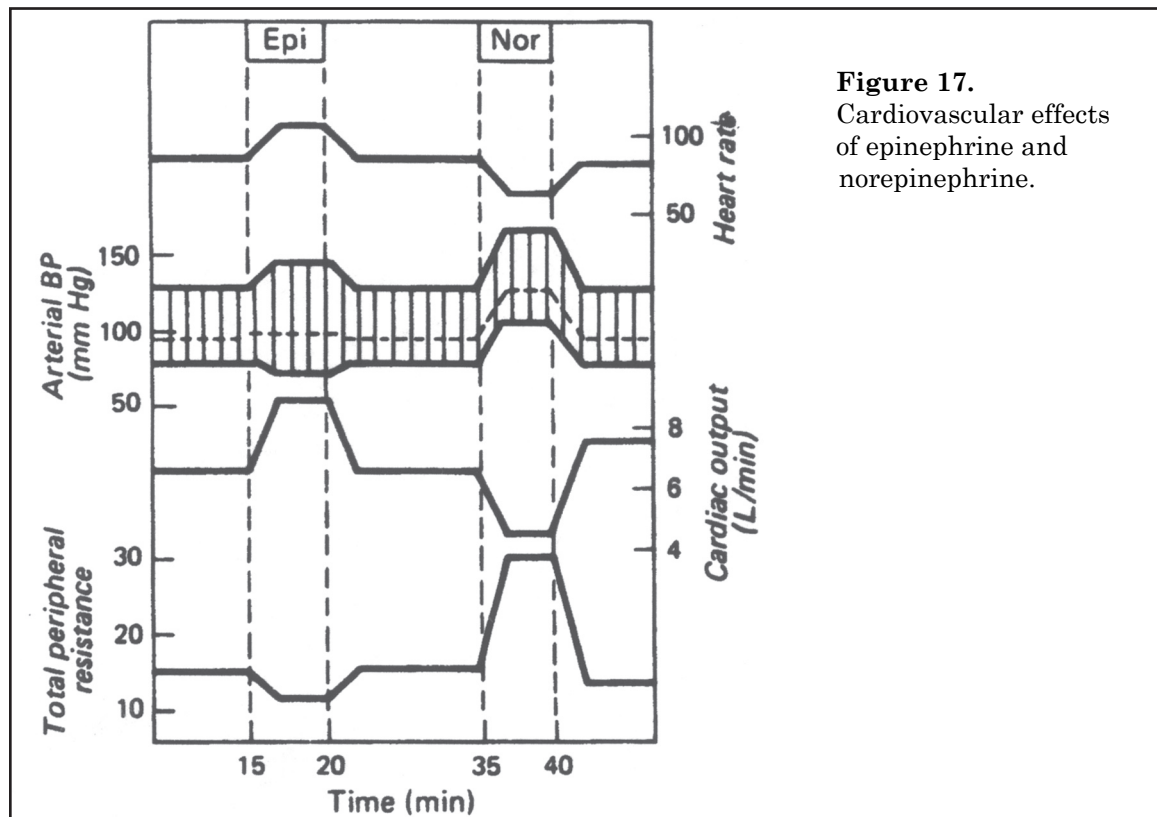
### 2. Metabolism of catecholamines

Catecholamines have a short half-life in the circulation (approximately 2 minutes). They are metabolized in many tissues by the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase.

### 3. Effects of catecholamines

The effects of catecholamines are mediated by  $\alpha$ - and  $\beta$ -adrenergic receptors located on the surface of cell membranes in target tissues.

The effects of  $\alpha$ - and  $\beta$ -adrenergic stimulation are shown in Table 3. Note that the actual response to a catecholamine depends on the relative proportion of  $\alpha$  and  $\beta$  receptors in the tissue, and whether the catecholamine is epinephrine or norepinephrine. Epinephrine and norepinephrine both increase blood glucose concentration and metabolic rate. The secretion of both insulin and glucagon is increased by  $\beta_2$ - and decreased by  $\alpha_2$ -adrenergic stimulation. However, the predominant effect of stimulation of the sympathetic nerves to the pancreas is stimulation of glucagon secretion and inhibition of insulin secretion. Epinephrine increases cardiac output (Figure 17). It causes vasodilation in skeletal muscle and liver ( $\beta_2$ ) but vasoconstriction in most other vascular beds ( $\alpha$ ), thus shunting blood to skeletal muscle and liver. The net effect is a decrease in total peripheral resistance that offsets the rise in cardiac output so that there is little change in mean arterial pressure. Norepinephrine causes vasoconstriction in most organs ( $\alpha$ ), resulting in increases in total peripheral resistance and blood pressure, and a reflex reduction in cardiac output (Figure 17).



**Figure 17.**  
Cardiovascular effects  
of epinephrine and  
norepinephrine.

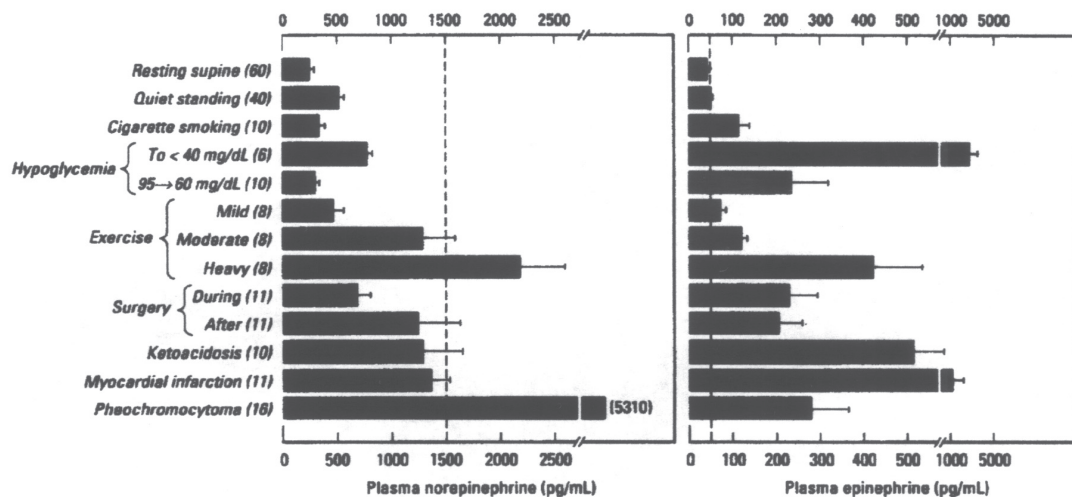


<b>Table 3: Adrenergic receptor/second messenger coupling</b>	
<b>Receptor</b>	<b>Signal Transduction</b>
$\alpha_1$	↑ Inositol triphosphate, diacylglycerol, $\text{Ca}^{++}$
$\alpha_2$	↓ cyclic AMP
$\beta_1$	↑ cyclic AMP
$\beta_2$	↑ cyclic AMP

#### 4. Regulation adrenal medullary secretion

**Adrenal medullary secretion increase in response to the same** stimuli that activate the sympathetic nervous system and is part of the diffuse sympathetic discharge that occurs in emergency “flight or fight” situations. Thus secretion increases in response to stress, pain, hypoglycemia, hypovolemia, hypotension, hypoxia, and strenuous exercise.

These stimuli are sensed by the central nervous system and the responses are initiated in the hypothalamus and brainstem. Release of acetylcholine by the greater splanchnic nerve depolarizes chromaffin cells, intracellular calcium concentration increases, and catecholamines are released by exocytosis. Interestingly, unlike other glandular tissue, the adrenal medulla is not controlled by negative feedback. Plasma catecholamine levels in various physiologic and pathologic states are shown in Figure 18.



**Figure 18.** Plasma catecholamine concentrations in blood in various physiologic and pathologic states. Dashed line indicates the threshold concentration at which physiologic effects are first observed.

<b>Table 4:</b> Effects of alpha- and beta-adrenergic stimulation		
	<b>Beta</b>	<b>Alpha</b>
Metabolic	Glycogenolysis	Gluconeogenesis
	Lipolysis	
	↑Metabolic rate	
Endocrine	Insulin secretion	↓Insulin secretion
	Glucagon secretion	↓Glucagon secretion
Cardiovascular	Cardiac output (rate and force of cardiac contraction)	↓Cardiac output (reflex)
	Vasodilation (skeletal muscle and liver)	vasoconstriction (renal, splanchnic, skin)
Other	Broncodilation	