Adrenal gland

Adrenocortical Hormones

The two *adrenal glands,* each of which weighs about 4 grams, lie at the superior poles of the two kidneys. As shown in Figure 77–1, each gland is composed of two distinct parts, the *adrenal medulla* and the *adrenal cortex.* The adrenal medulla, the central 20 per cent of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones *epinephrine* and *norepinephrine* in response to sympathetic stimulation. In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body.

The adrenal cortex secretes an entirely different group of hormones, called *corticosteroids.*These hormones are all synthesized from the steroid cholesterol, and they all have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.

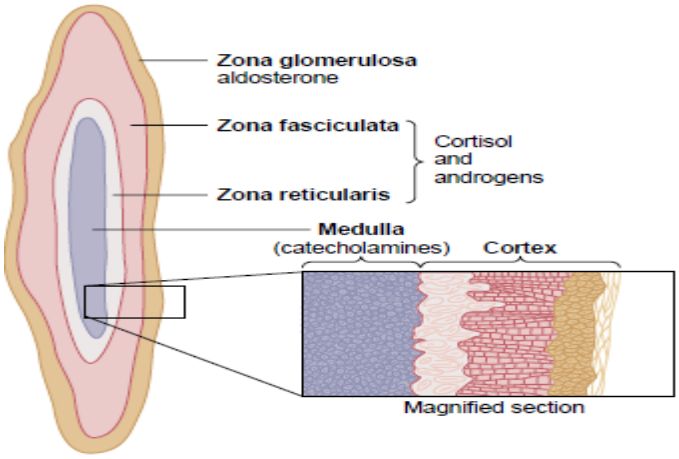

Figure 77–1

Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla.

Corticosteroids Mineralocorticoids, Glucocorticoids, and Androgens.

Two major types of adrenocortical hormones, the *mineralocorticoids* and the *glucocorticoids*, are secreted by the adrenal cortex. In addition to these, small amounts of sex hormones are secreted, especially *androgenic hormones*, which exhibit about the same effects in the body as the male sex hormone testosterone.

They are normally of only slight importance, although in certain abnormalities of the adrenal cortices, extreme quantities can be secreted (which is discussed later in the chapter) and can result in masculinizing effects.

The *mineralocorticoids* have gained this name because they especially affect the electrolytes (the "minerals") of the extracellular fluids-sodium and potassium, in particular.

The *glucocorticoids* have gained their name because they exhibit important effects that increase blood glucose concentration.

They have additional effects on both protein and fat metabolism that are equally as important to body function as their effects on carbohydrate metabolism.

More than 30 steroids have been isolated from the adrenal cortex, but two are of exceptional importance to the normal endocrine function of the human body: *aldosterone*, which is the principal mineralocorticoid, and *cortisol*, which is the principal glucocorticoid.

Synthesis and Secretion of Adrenocortical Hormones The Adrenal Cortex Has Three Distinct Layers.

the adrenal cortex is composed of three relatively distinct layers:

1. The *zona glomerulosa,* a thin layer of cells that lies just underneath the capsule, constitutes about 15 per cent of the adrenal cortex. These cells are the only ones in the adrenal gland capable of secreting significant amounts of *aldosterone* because they contain the enzyme *aldosterone synthase,* which is necessary for synthesis of aldosterone.

The secretion of these cells is controlled mainly by the extracellular fluid concentrations of *angiotensin II* and *potassium,* both of which stimulate aldosterone secretion.

2. The *zona fasciculata,* the middle and widest layer, constitutes about 75 per cent of the adrenal cortex and secretes the glucocorticoids *cortisol* and *corticosterone,* as well as small amounts of *adrenal androgens* and *estrogens.*

The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via *adrenocorticotropic hormone (ACTH).*

3. The *zona reticularis,* the deep layer of the cortex, secretes the adrenal androgens *dehydroepiandrosterone (DHEA)* and *androstenedione,* as well as small amounts of estrogens and some glucocorticoids .

ACTH also regulates secretion of these cells, although other factors such as *cortical androgen-stimulating hormone,* released from the pituitary, may also be involved. The mechanisms for controlling adrenal androgen production, however, are not nearly as well understood as those for glucocorticoids and mineralocorticoids.

Aldosterone and cortisol secretion are regulated by independent echanisms. Factors such as angiotensin II that specifically increase the output of aldosterone and cause hypertrophy of the zona glomerulosa have no effect on the other two zones. Similarly, factors such as ACTH that increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zona fasciculata and zona reticularis have little or no effect on the zona glomerulosa.

Adrenocortical Hormones Are Steroids Derived from Cholesterol.

All human steroid hormones, including those produced by the adrenal cortex, are synthesized from cholesterol. Although the cells of the adrenal cortex can synthesize de novo small amounts of cholesterol from acetate, approximately 80 per cent of the cholesterol used for steroid synthesis is provided by low-density lipoproteins (LDL) in the circulating plasma.The LDLs, which have high concentrations of cholesterol, diffuse from the plasma into the interstitial fluid and attach to specific receptors contained in structures called *coated pits* on the adrenocortical cell membranes. The coated pits are then internalized by *endocytosis,* forming vesicles that eventually fuse with cell lysosomes and release cholesterol that can be used to synthesize adrenal steroid hormones.

Transport of cholesterol into the adrenal cells is regulated by feedback mechanisms that can markedly alter the amount available for steroid synthesis. For example, ACTH, which stimulates adrenal steroid synthesis, increases the number of adrenocortical cell receptors for LDL, as well as the activity of enzymes that liberate cholesterol from LDL.

Once the cholesterol enters the cell, it is delivered to the mitochondria, where it is cleaved by the enzyme *cholesterol desmolase* to form *pregnenolone;* this is the rate-limiting step in the eventual formation of adrenal steroids. In all three zones of the adrenal cortex, this initial step in steroid synthesis is stimulated by the different factors that control secretion of the major hormone products aldosterone and cortisol. For example, both ACTH, which stimulates cortisol secretion, and angiotensin II, which stimulates aldosterone secretion, increase the conversion of cholesterol to pregnenolone.

Synthetic Pathways for Adrenal Steroids.

Figure 77-2 gives, the principal steps in the formation of the important steroid products of the adrenal cortex: aldosterone, cortisol, and the androgens. Essentially all these steps occur in two of the organelles of the cell, the *mitochondria* and the *endoplasmic reticulum*, some steps occurring in one of these organelles and some in the other.

Each step is catalyzed by a specific enzyme system.

A change in even a single enzyme in the schema can cause vastly different types and relative proportions of hormones to be formed.

For example, very large quantities of masculinizing sex hormones or other steroid compounds not normally present in the blood can occur with altered activity of only one of the enzymes in this pathway.

The chemical formulas of aldosterone and cortisol, which are the most important mineralocorticoid and glucocorticoid hormones, respectively,

Cortisol has a keto-oxygen on carbon number 3 and is hydroxylated at carbon numbers 11 and 21. The mineralocorticoid aldosterone has an oxygen atom bound at the number 18 carbon.

In addition to aldosterone and cortisol, other steroids having glucocorticoid or mineralocorticoid activities, or both, are normally secreted in small amounts by the adrenal cortex.

And several additional potent steroid hormones not normally formed in the adrenal glands have been synthesized and are used in various forms of therapy.

Some of the more important of the corticosteroid hormones, including the synthetic ones.

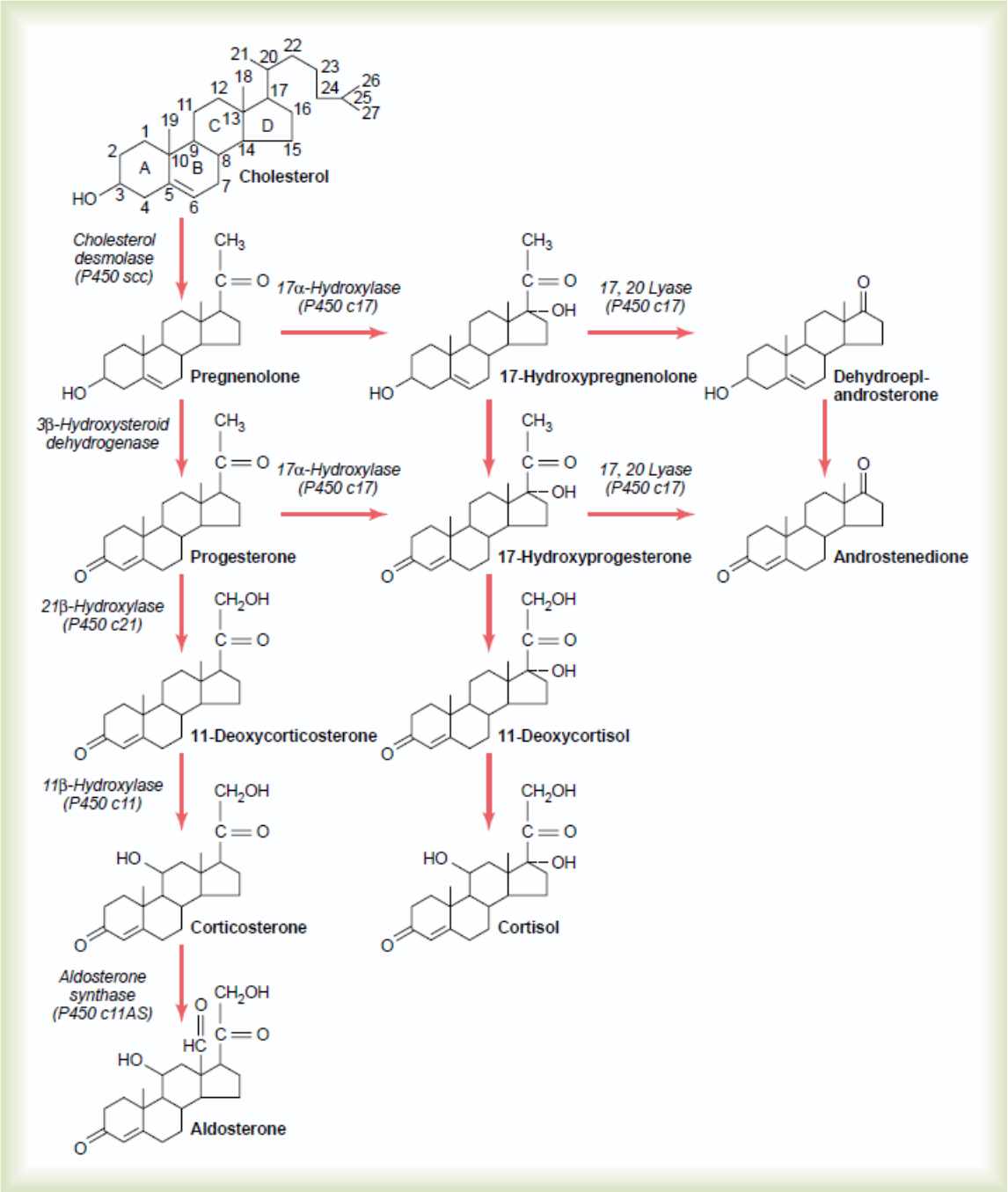

Figure 77–2

Pathways for synthesis of steroid hormones by the adrenal cortex. The enzymes are shown in italics.

Mineralocorticoids

• Aldosterone (very potent, accounts for about 90 per cent of all mineralocorticoid activity)

• Desoxycorticosterone (1/30 as potent as aldosterone, but very small quantities secreted)

• Corticosterone (slight mineralocorticoid activity)

• 9a-Fluorocortisol (synthetic, slightly more potent than aldosterone)

• Cortisol (very slight mineralocorticoid activity, but large quantity secreted)

• Cortisone (synthetic, slight mineralocorticoid activity)

Glucocorticoids

• Cortisol (very potent, accounts for about 95 per cent of all glucocorticoid activity)

• Corticosterone (provides about 4 per cent of total glucocorticoid activity, but much less potent than cortisol)

• Cortisone (synthetic, almost as potent as cortisol)

• Prednisone (synthetic, four times as potent as cortisol)

• Methylprednisone (synthetic, five times as potent as cortisol)

• Dexamethasone (synthetic, 30 times as potent as cortisol)

It is clear from this list that some of these hormones have both glucocorticoid and mineralocorticoid activities.

It is especially significant that cortisol has a small amount of mineralocorticoid activity, because some syndromes of excess cortisol secretion can cause significant mineralocorticoid effects, along with its much more potent glucocorticoid effects.

The intense glucocorticoid activity of the synthetic hormone dexamethasone, which has almost zero mineralocorticoid activity, makes this an especially important drug for stimulating specific glucocorticoid activity .

Adrenocortical Hormones Are Bound to Plasma Proteins.

Approximately 90 to 95 per cent of the cortisol in the plasma binds to plasma proteins, especially a globulin called *cortisol-binding globulin* or *transcortin* and, to a lesser extent, to albumin.This high degree of binding to plasma proteins slows the elimination of cortisol from the plasma; therefore, cortisol has a relatively long half life of 60 to 90 minutes. Only about 60 per cent of circulating aldosterone combines with the plasma proteins, so that about 40 per cent is in the free form; as a result, aldosterone has a relatively short half-life of about 20 minutes. In both the combined and free forms, the hormones are transported throughout the extracellular fluid compartment.

Binding of adrenal steroids to the plasma proteins may serve as a reservoir to lessen rapid fluctuations in free hormone concentrations, as would occur, for example, with cortisol during brief periods of stress and episodic secretion of ACTH. This reservoir function may also help to ensure a relatively uniform distribution of the adrenal hormones to the tissues.

Adrenocortical Hormones Are Metabolized in the Liver.

The adrenal steroids are degraded mainly in the liver and conjugated especially to *glucuronic acid* and, to a lesser extent, sulfates. These substances are inactive and do not have mineralocorticoid or glucocorticoid activity.

About 25 per cent of these conjugates are excreted in the bile and then in the feces.The remaining conjugates formed by the liver enter the circulation but are not bound to plasma proteins, are highly soluble in the plasma, and are therefore filtered readily by the kidneys and excreted in the urine. Diseases of the liver markedly depress the rate of inactivation of adrenocortical hormones, and kidney diseases reduce the excretion of the inactive conjugates.

The normal concentration of aldosterone in blood is about 6 nanograms (6 billionths of a gram) per 100 ml, and the average secretory rate is approximately 150 μg/day (0.15 mg/day).

The concentration of cortisol in the blood averages 12 μg/100 ml, and the secretory rate averages 15 to 20 mg/day.

Functions of the Mineralocorticoids- Aldosterone

*** Mineralocorticoid Deficiency Causes Severe Renal Sodium Chloride Wasting and Hyperkalemia.**

***Aldosterone Is the Major Mineralocorticoid Secreted by the Adrenals.** Aldosterone exerts nearly 90 per cent of the mineralocorticoid activity of the adrenocortical secretions, but cortisol, the major glucocorticoid secreted by the adrenal cortex, also provides a significant amount of mineralocorticoid activity. Aldosterone's mineralocorticoid activity is about 3000 times greater than that of cortisol, but the plasma concentration of cortisol is nearly 2000 times that of aldosterone.

Cortisol can also bind to mineralocorticoid with high affinity , However, the renal epithelial cells also contain the enzyme 11β-hydroxysteroid dyhydrogenase type 2 . which converts **cortisol** to **cortisone** . because cortisone dose not avidly bind mineralocorticoid receptors, cortisol dose not normally exert significant mineralocorticoid effects . However , in patients with genetic deficiency of11β-hydroxysteroid dyhydrogenase type 2 activity cortisol may have substantial mineralocorticoid effects .

This concision is called *apparent mineralocorticoid excess syndrome* (AME) because the patient has essentially the same pathophysiological change as patient with excess aldosterone secretion except that plasma aldosterone levels are very low. Ingestion of large amounts of Licorice , which contains glycyrrhetinic acid , may also cause AME due to its ability to block 11β-hydroxysteroid dyhydrogenase type 2 activity .

***Renal and Circulatory Effects of Aldosterone**

1. Aldosterone Increases Renal Tubular Reabsorption of Sodium and Secretion of Potassium.
2. Excess Aldosterone Increases Extracellular Fluid Volume and Arterial Pressure but Has Only a Small Effect on Plasma Sodium Concentration.
3. Excess Aldosterone Causes Hypokalemia and Muscle Weakness; Too Little Aldosterone Causes Hyperkalemia and Cardiac Toxicity.
4. Excess Aldosterone Increases Tubular Hydrogen Ion Secretion, and Causes Mild Alkalosis.

***Aldosterone Stimulates Sodium and Potassium Transport in Sweat Glands, Salivary Glands, and Intestinal Epithelial Cells.**

Cellular Mechanism of Aldosterone Action

Although for many years we have known the overall effects of mineralocorticoids on the body, the basic action of aldosterone on the tubular cells to increase transport of sodium is still not fully understood. However, the cellular sequence of events that leads to increased sodium reabsorption seems to be the following.

First, because of its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells.

Second, in the cytoplasm of the tubular cells, aldosterone combines with a highly specific cytoplasmic *receptor protein (MR)* a protein that has a stereomolecular configuration that allows only aldosterone or very similar compounds to combine with it.

Third, the aldosterone-receptor complex or a product of this complex diffuses into the nucleus, where it may undergo further alterations, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport.

Fourth, the messenger RNA diffuses back into the cytoplasm, where, operating in conjunction with the ribosomes, it causes protein formation. The proteins formed are a mixture of **(1)** one or more enzymes and **(2)** membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membrane.

One of the enzymes especially increased is *sodiumpotassium adenosine triphosphatase,* which serves as the principal part of the pump for sodium and potassium exchange at the *basolateral membranes* of the renal tubular cells.

Additional proteins, perhaps equally important, are epithelial sodium channel proteins inserted into the *luminal membrane* of the same tubular cells that allows rapid diffusion of sodium ions from the tubular lumen into the cell; then the sodium is pumped the rest of the way by the sodium-potassium pump located in the basolateral membranes of the cell.

Thus, aldosterone does not have an immediate effect on sodium transport; rather, this effect must await the sequence of events that leads to the formation of the specific intracellular substances required for sodium transport. About 30 minutes is required before new RNA appears in the cells, and about 45 minutes is required before the rate of sodium transport begins to increase; the effect reaches maximum only after several hours.

Regulation of Aldosterone Secretion

The regulation of aldosterone secretion is so deeply intertwined with the regulation of extracellular fluid electrolyte concentrations, extracellular fluid volume,blood volume, arterial pressure, and many special aspects of renal function .

The regulation of aldosterone secretion by the zona glomerulosa cells is almost entirely independent of the regulation of cortisol and androgens by the zona fasciculate and zona reticularis.

Four factors are known to play essential roles in the regulation of aldosterone. In the probable order of their importance, they are as follows:

1. Increased potassium ion concentration in the extracellular fluid greatly *increases* aldosterone secretion.

2. Increased activity of the renin-angiotensin system (increased levels of angiotensin II) also greatly *increases* aldosterone secretion.

3. Increased sodium ion concentration in the extracellular fluid *very slightly decreases* aldosterone secretion.

4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions .

Of these factors, *potassium ion concentration*and the *renin-angiotensin system* are by far the most potent in regulating aldosterone secretion. A small percentage increase in potassium concentration can cause a severalfold increase in aldosterone secretion.

Likewise, activation of the renin-angiotensin system, usually in response to diminished blood flow to the kidneys or to sodium loss, can cause a severalfold increase in aldosterone secretion. In turn, the aldosterone acts on the kidneys (1) to help them excrete the excess potassium ions and (2) to increase the blood volume and arterial pressure, thus returning the reninangiotensin system toward its normal level of activity. These feedback control mechanisms are essential for maintaining life.

With an angiotensin –converting enzume inhibitor after several weeks of a low-sodium diet that increases plasma aldosterone concentration .

Note that blocking angiotensin II formation markedly decreases plasma aldosterone concentration without significantly changing cortisol concentration; this indicates the important role of angiotensin II in stimulating aldosterone secretion when sodium intake and extracellular fluid volume are reduced.

By contrast, the effects of sodium ion concentration per se and of ACTH in controlling aldosterone secretion are usually minor. Nevertheless, a 10 to 20 per cent decrease in extracellular fluid sodium ion concentration, which occurs on rare occasions, can perhaps double aldosterone secretion. In the case of ACTH, if there is even a small amount of ACTH secreted by the anterior pituitary gland, it is usually enough to permit the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion.

Functions of the Glucocorticoids

1. Effects of Cortisol on Carbohydrate Metabolism

A. Stimulation of Gluconeogenesis.

1. Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells.

2. Cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle.

B . Decreased Glucose Utilization by Cells.

C. Elevated Blood Glucose Concentration and "Adrenal Diabetes."

2. Effects of Cortisol on Protein Metabolism

A. Reduction in Cellular Protein.
B. Cortisol Increases Liver and Plasma Proteins.
C. Increased Blood Amino Acids, Diminished Transport of Amino Acids into Extrahepatic Cells, and Enhanced Transport into Hepatic Cells.

3. Effects of Cortisol on Fat Metabolism

A. Mobilization of Fatty Acids.

B. Obesity Caused by Excess Cortisol.

4. Cortisol is Important in Resisting Stress and Inflammation

Some of the different types of stress that increase cortisol release are the following:

1. Trauma of almost any type

2. Infection

3. Intense heat or cold

4. Injection of norepinephrine and other sympathomimetic drugs

5. Surgery

6. Injection of necrotizing substances beneath the skin

7. Restraining an animal so that it cannot move

8. Almost any debilitating disease

5. **Anti-inflammatory Effects of High Levels of Cortisol**

When tissues are damaged by trauma, by infection with bacteria, or in other ways, they almost always become "inflamed." In some conditions, such as in rheumatoid arthritis, the inflammation is more damaging than the trauma or disease itself. The administration of large amounts of cortisol can usually block this inflammation or even reverse many of its effects once it has begun. Before attempting to explain the way in which cortisol functions to block inflammation .

There are five main stages of inflammation:

1. release from the damaged tissue cells of chemical substances that activate the inflammation processchemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes;
2. an increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called *erythema;*
3. leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary permeability, followed by clotting of the tissue fluid, thus causing a *nonpitting type of edema;*
4. infiltration of the area by leukocytes;
5. after days or weeks, ingrowth of fibrous tissue that often helps in the healing process.

When large amounts of cortisol are secreted or injected into a person, the cortisol has two basic *anti-inflammatory effects:*

1. it can block the early stages of the inflammation process before inflammation even begins, or
2. if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.

These effects are explained further as follows.

A. Cortisol Prevents the Development of Inflammation by Stabilizing Lysosomes and by Other Effects**.** Cortisol has the following effects in preventing inflammation:

1. *Cortisol stabilizes the lysosomal membranes*

2. *Cortisol decreases the permeability of the capillaries,*

3.Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells.

4. *Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly.*

5. *Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells,*

B. Cortisol Causes Resolution of Inflammation.

6. Other Effects of Cortisol

A. Cortisol Blocks the Inflammatory Response to Allergic Reactions.

B. Effect on Blood Cells and on Immunity in Infectious Diseases.

Regulation of Cortisol Secretion by Adrenocorticotropic Hormone from the Pituitary Gland ACTH Stimulates Cortisol Secretion.

Unlike aldosterone secretion by the zona glomerulosa, which is controlled mainly by potassium and angiotensin acting directly on the adrenocortical cells, almost no stimuli have direct control effects on the adrenal cells that secrete cortisol. Instead, secretion of cortisol is controlled almost entirely by ACTH secreted by the anterior pituitary gland.This hormone, also called *corticotrophin* or *adrenocorticotropin*, also enhances the production of adrenal androgens.

ACTH Secretion Is Controlled by Corticotropin-Releasing Factor from the Hypothalamus.

In the same way that other pituitary hormones are controlled by releasing factors from the hypothalamus, an important releasing factor also controls ACTH secretion. This is called *corticotropin- releasing factor* (CRF). It is secreted into the primary capillary plexus of the hypophysial portal system in the median eminence of the hypothalamus and then carried to the anterior pituitary gland, where it induces ACTH secretion. CRF is a peptide composed of 41 amino acids.The cell bodies of the neurons that secrete CRF are located mainly in the paraventricular nucleus of the hypothalamus. This nucleus in turn receives many nervous connections from the limbic system and lower brain stem.

The anterior pituitary gland can secrete only minute quantities of ACTH in the absence of CRF. Instead, most conditions that cause high ACTH secretory rates initiate this secretion by signals that begin in the basal regions of the brain, including the hypothalamus, and are then transmitted by CRF to the anterior pituitary gland.

ACTH Activates Adrenocortical Cells to Produce Steroids by Increasing Cyclic Adenosine Monophosphate (cAMP).

The principal effect of ACTH on the adrenocortical cells is to activate *adenylyl cyclase* in the cell membrane.This then induces the formation of *cAMP* in the cell cytoplasm, reaching its maximal effect in about 3 minutes. The cAMP in turn activates the intracellular enzymes that cause formation of the adrenocortical hormones. This is another example of cAMP as a *second messenger* signal system.

The most important of all the ACTH-stimulated steps for controlling adrenocortical secretion is activation of the enzyme *protein kinase A,* which *causes initial conversion of cholesterol to pregnenolone.* This initial conversion is the "rate-limiting" step for all the adrenocortical hormones, which explains why ACTH normally is necessary for any adrenocortical hormones to be formed. Long-term stimulation of the adrenal cortex by ACTH not only increases secretory activity but also causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculate and zona reticularis, where cortisol and the androgens are secreted.

Physiologic Stress Increases ACTH and Adrenocortical Secretion

As pointed out earlier in the chapter, almost any type of physical or mental stress can lead within minutes to greatly enhanced secretion of ACTH and consequently cortisol as well, often increasing cortisol secretion as much as 20-fold. This effect was demonstrated by the rapid and strong adrenocortical secretory responses after trauma

Pain stimuli caused by physical stress or tissue damage are transmitted first upward through the brain stem and eventually to the median eminence of the hypothalamus, as shown in Figure 77–6. Here CRF is secreted into the hypophysial portal system. Withinminutes the entire control sequence leads to large quantities of cortisol in the blood.

Mental stress can cause an equally rapid increase in ACTH secretion. This is believed to result from increased activity in the limbic system, especially in the region of the amygdala and hippocampus, both of which then transmit signals to the posterior medial hypothalamus.

Inhibitory Effect of Cortisol on the Hypothalamus and on the Anterior Pituitary to Decrease ACTH Secretion.

Cortisol has direct negative feedback effects on

(1) the hypothalamus to decrease the formation of CRF and

(2) the anterior pituitary gland to decrease the formation of ACTH. Both of these feedbacks help regulate the plasma concentration of cortisol.That is, whenever the cortisol concentration becomes too great, the feedbacks automatically reduce the ACTH toward a normal control level.

Adrenal Androgens

Several moderately active male sex hormones called *adrenal androgens* (the most important of which is *dehydroepiandrosterone*) are continually secreted by the adrenal cortex, especially during fetal life, Also progesterone and estrogens, which are female sex hormones, are secreted in minute quantities.

Normally, the adrenal androgens have only weak effects in humans. It is possible that part of the early development of the male sex organs results from childhood secretion of adrenal androgens. The adrenal androgens also exert mild effects in the female, not only before puberty but also throughout life. Much of the growth of the pubic and axillary hair in the female results from the action of these hormones.

In extra-adrenal tissues, some of the adrenal androgens are converted to testosterone, the primary male sex hormone, which probably accounts for much of their androgenic activity.