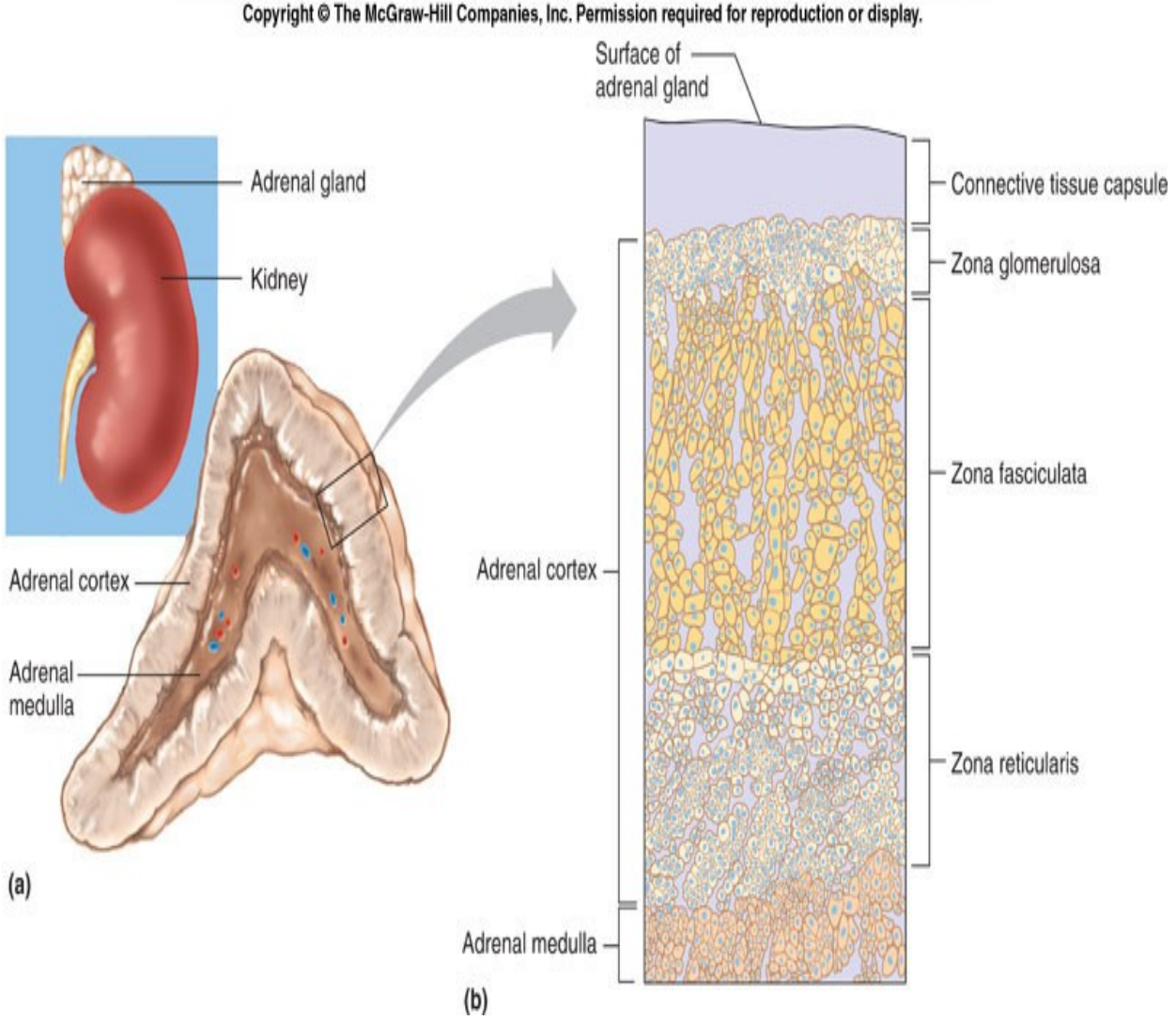
ADRENOCORTICAL HORMONES

ADRENAL GLAND

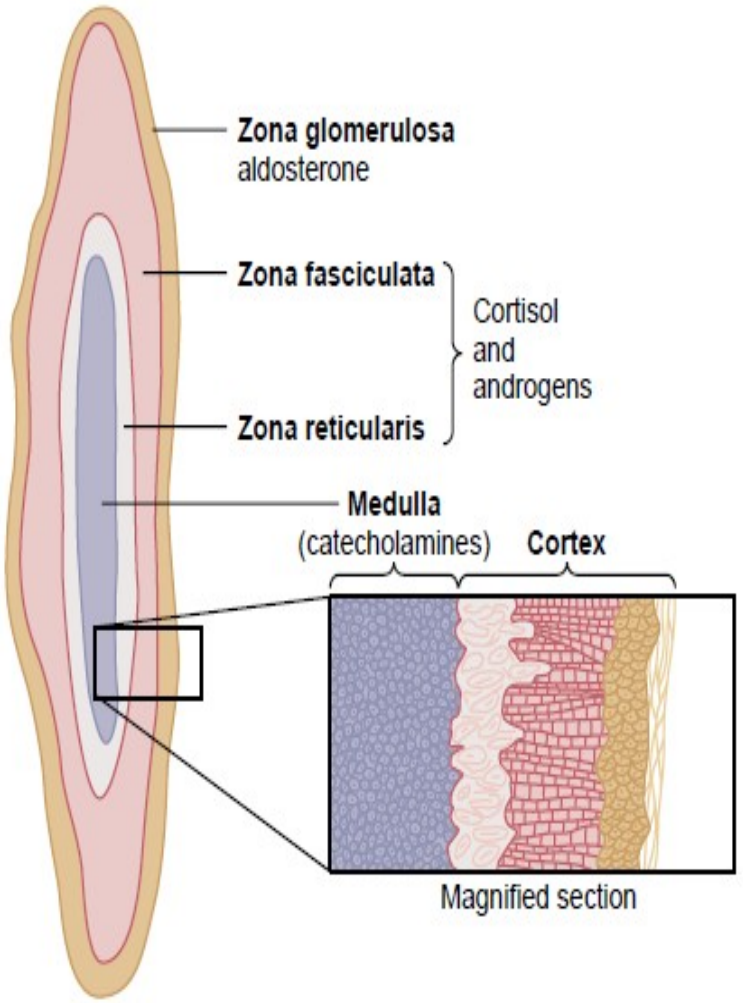


- The two ***adrenal glands***, each of which weighs about 4 grams, lie at the superior poles of the two kidneys.
- Each gland is composed of two distinct parts, the ***adrenal medulla*** and the ***adrenal cortex***.
- The adrenal medulla, the central 20 per cent of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones ***epinephrine*** and ***norepinephrine*** in response to sympathetic stimulation.
- The adrenal cortex secretes an entirely different group of hormones, called ***corticosteroids***

Hormones of the Adrenal Cortex

- 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
- 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.
- 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.

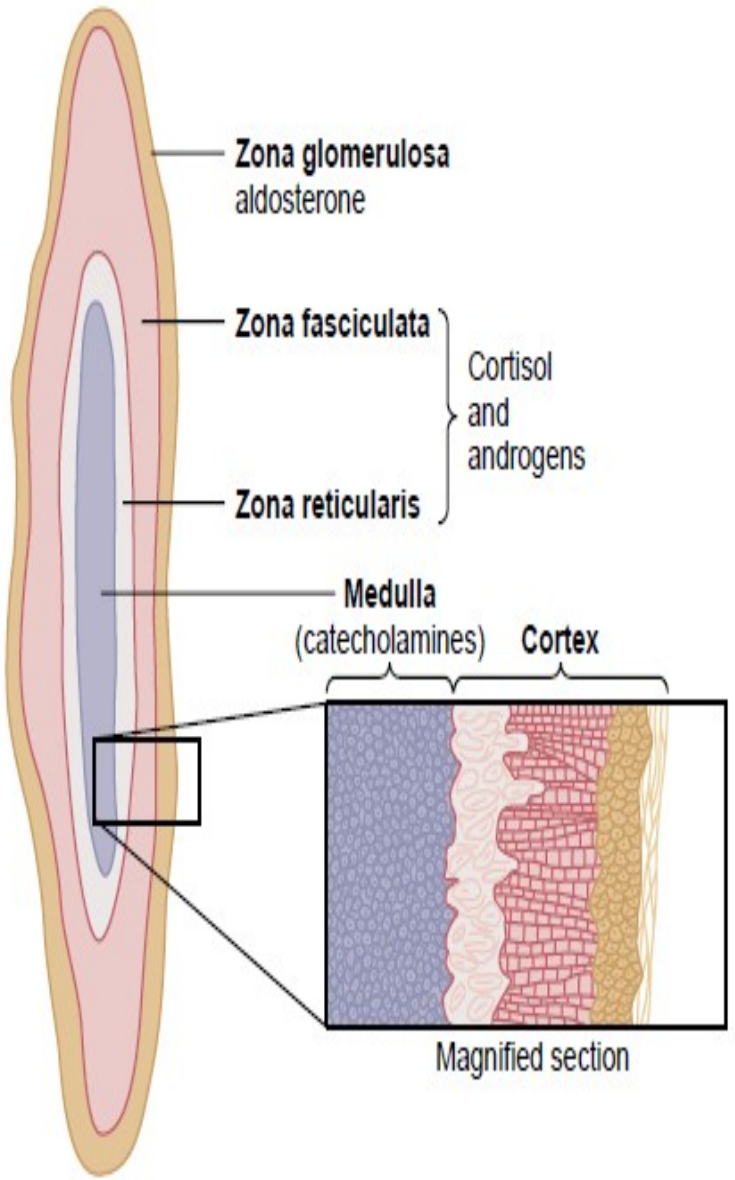
Synthesis and Secretion of Adrenocortical Hormones



❑The Adrenal Cortex Has Three Distinct Layers

❖***Zona glomerulosa***

- It is 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.



❖*Zona fasciculata*

It is 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***.

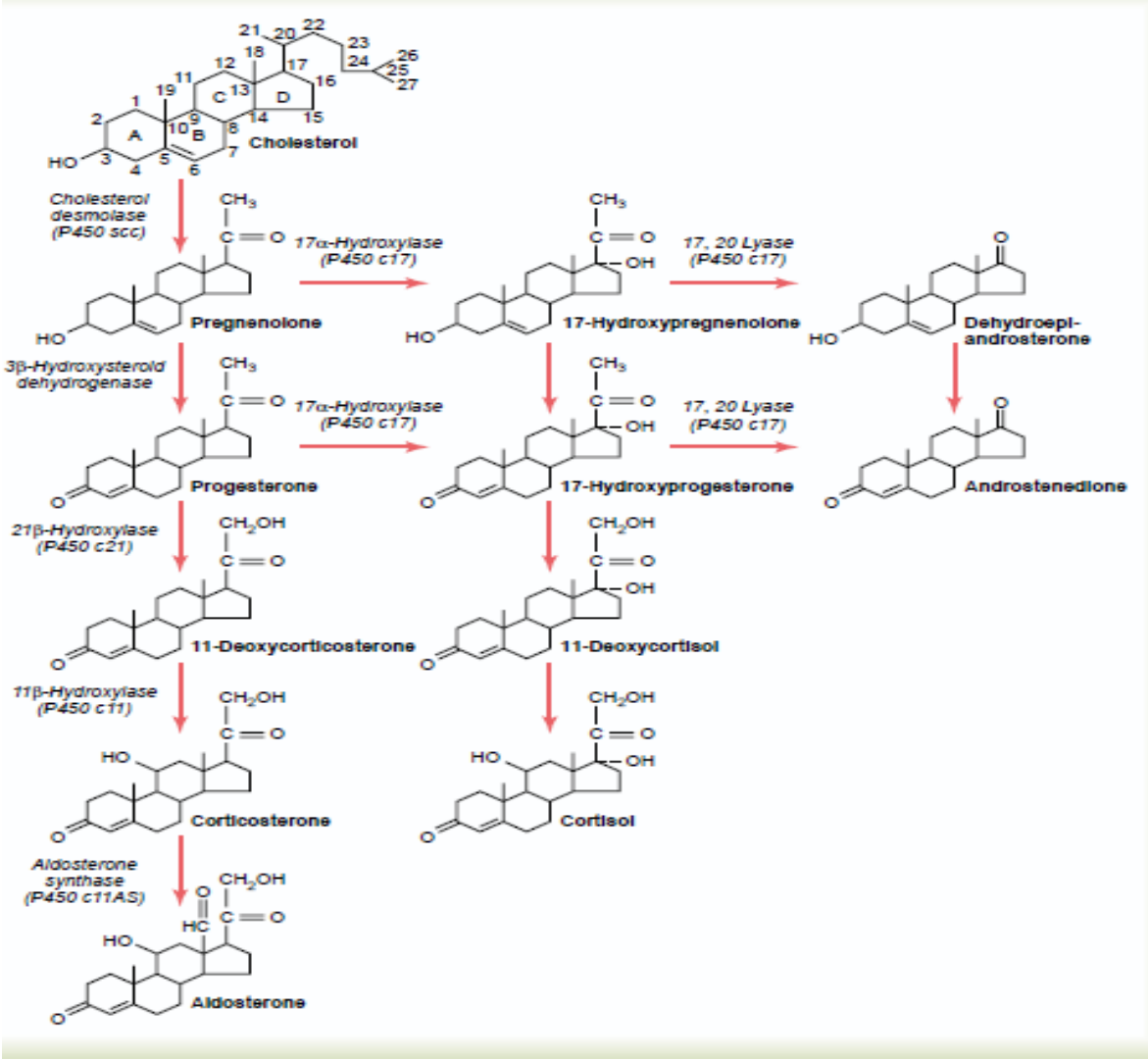
- The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via ***adrenocorticotropic hormone (ACTH).***

❖*Zona reticularis*

- It is 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.

BIOSYNTHESIS OF ADRENOCORTICAL HORMONES

- 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.



Some important corticosteroid hormones

❑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)

Transport and metabolism

- 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
- 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.

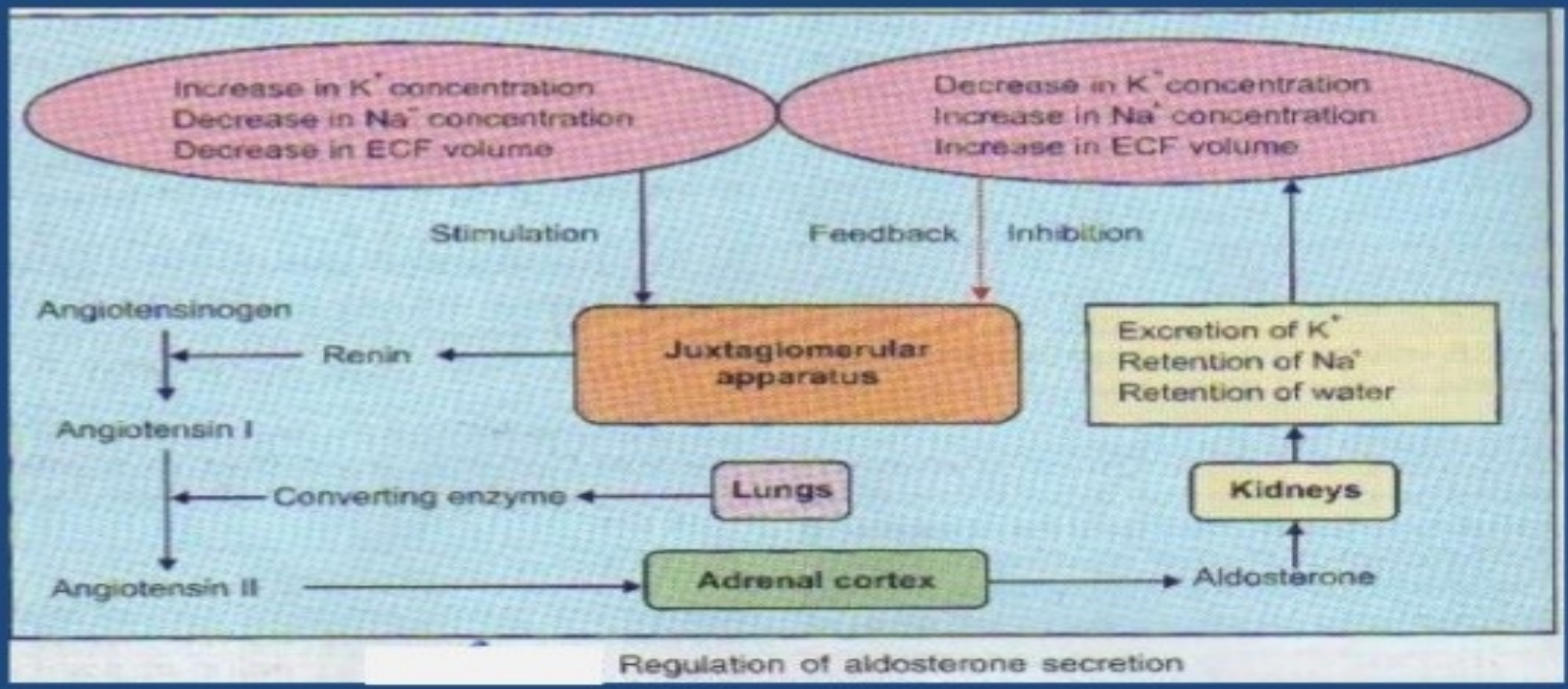
Functions of the Mineralocorticoids- Aldosterone

- Mineralocorticoid deficiency causes severe renal sodium chloride wasting and hyperkalemia.
- Aldosterone increases renal tubular reabsorption of sodium and secretion of potassium.
- Excess aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium concentration.
- Excess aldosterone causes hypokalemia and muscle weakness; too little aldosterone causes hyperkalemia and cardiac toxicity.
- Aldosterone stimulates sodium and potassium transport in sweat glands, salivary glands, and intestinal epithelial cells

Cellular Mechanism of Aldosterone Action

- 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***, 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.

Regulation of aldosterone secretion



Regulation of aldosterone secretion

Functions of the Glucocorticoids

❑**Effects of Cortisol on Carbohydrate Metabolism**

➢Stimulation of gluconeogenesis

- *Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells*
- *Cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle.*

➢Decreased Glucose Utilization by Cells

➢Elevated Blood Glucose Concentration and “Adrenal Diabetes.”

❑**Effects of Cortisol on Protein Metabolism**

➢Reduction in Cellular Protein.

➢Cortisol Increases Liver and Plasma Proteins

➢Increased Blood Amino Acids, Diminished Transport of Amino Acids into Extrahepatic Cells, and Enhanced Transport into Hepatic Cells.

❑**Effects of Cortisol on Fat Metabolism**

➢Mobilization of Fatty Acids

➢Obesity Caused by Excess Cortisol.

❑Cortisol is Important in Resisting Stress and Inflammation

❖**Anti-inflammatory Effects of High Levels of Cortisol**

✓Release from the damaged tissue cells of chemical substances that activate the inflammation process chemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes;

✓An increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called *erythema;*

✓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;*

✓Infiltration of the area by leukocytes; and

✓After days or weeks, ingrowth of fibrous tissue that often helps in the healing process

❖**Cortisol Prevents the Development of Inflammation by Stabilizing Lysosomes and by Other Effects.**

✓*Cortisol stabilizes the lysosomal membranes*

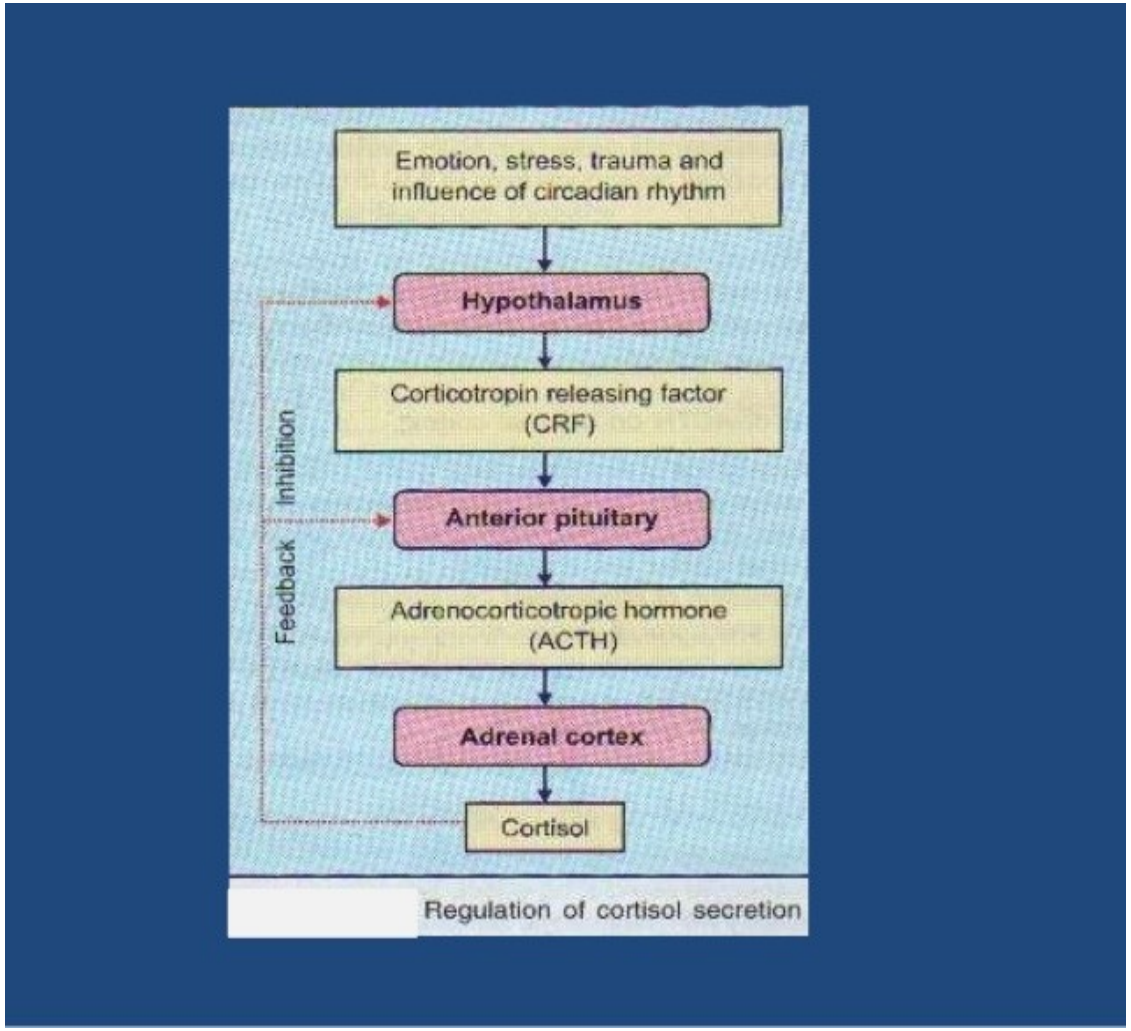
✓*Cortisol decreases the permeability of the capillaries*, probably as a secondary effect of the reduced release of proteolytic enzymes.

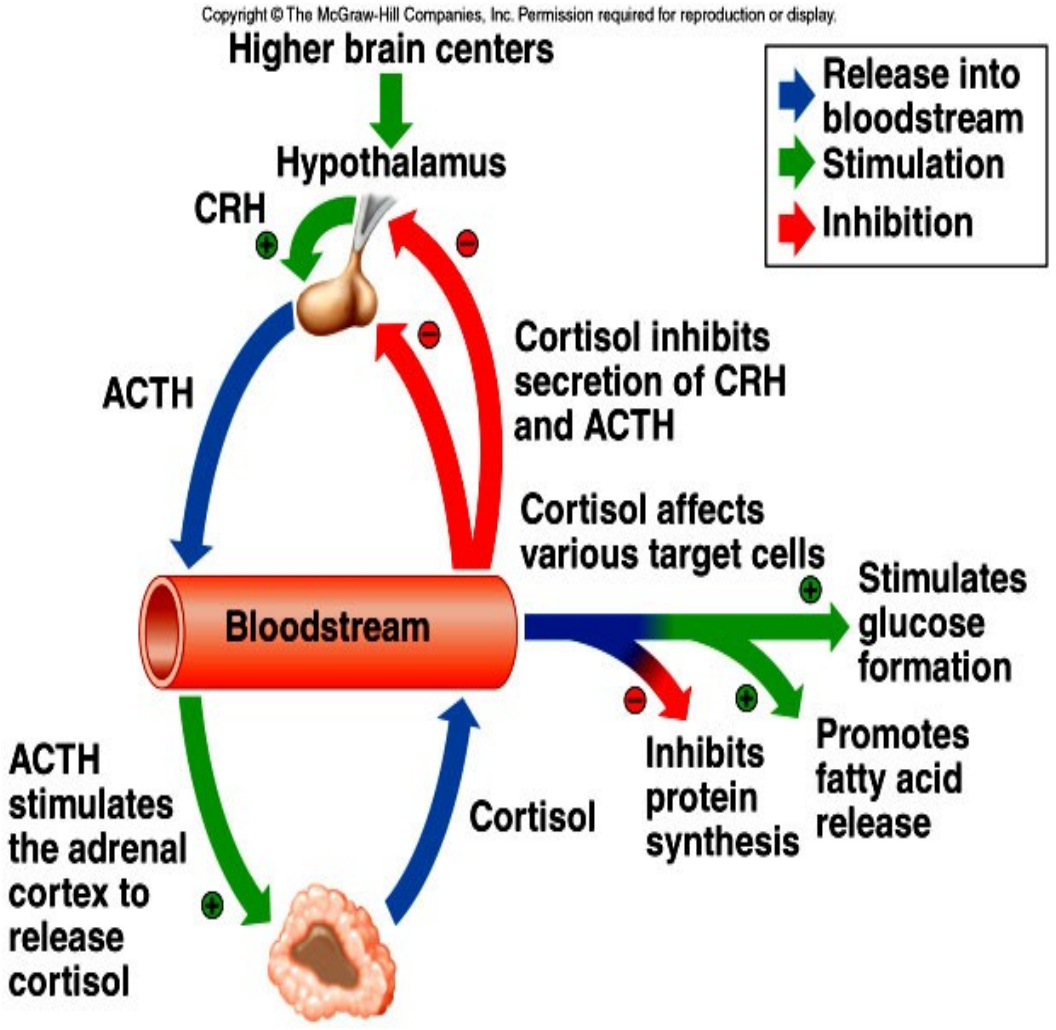
- ✓ *Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells.*
- ✓ *Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly.*
- ✓ *Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells*, which is one of the principal excitants to the hypothalamic temperature control system.
- ❖ **Cortisol blocks the inflammatory response to allergic reactions**
- ❖ **Effect on blood cells and on immunity in infectious diseases**

Cellular Mechanism of Cortisol Action

- Cortisol, like other steroid hormones, exerts its effects by first interacting with intracellular receptors in target cells.
- Because cortisol is lipid soluble, it can easily diffuse through the cell membrane. Once inside the cell, cortisol binds with its protein receptor in the cytoplasm, and the hormone-receptor complex then interacts with specific regulatory DNA sequences, called ***glucocorticoid response elements***, to induce or repress gene transcription.
- Other proteins in the cell, called ***transcription factors***, are also necessary for the hormone-receptor complex to interact appropriately with the glucocorticoid response elements
- Glucocorticoids increase or decrease transcription of many genes to alter synthesis of mRNA for the proteins that mediate their multiple physiologic effects..

Regulation of Cortisol Secretion by Adrenocorticotropic Hormone from the Pituitary Gland





Abnormalities of Adrenocortical Secretion

❑**Hypoadrenalism-Addison's Disease**

✓Addison's disease results from failure of the adrenal cortices to produce adrenocortical hormones, and this in turn is most frequently caused by *primary atrophy* of the adrenal cortices.

❖**Mineralocorticoid Deficiency**

❖**Glucocorticoid Deficiency**

❑**Hyperadrenalism-Cushing's Syndrome**

- Hypercortisolism can occur from multiple causes, including

✓Adenomas of the anterior pituitary that secrete large amounts of ACTH, which then causes adrenal hyperplasia and excess cortisol secretion;

✓Abnormal function of the hypothalamus that causes high levels of corticotropin-releasing hormone (CRH), which stimulates excess ACTH release;

✓"Ectopic secretion" of ACTH by a tumor elsewhere in the body, such as an abdominal carcinoma; and

✓Adenomas of the adrenal cortex.

❖When Cushing's syndrome is secondary to excess secretion of ACTH by the anterior pituitary, this is referred to as ***Cushing's disease.***

Abnormalities of Adrenocortical Secretion contd…

- **Primary Aldosteronism (Conn's Syndrome)**

✓ Occasionally a small tumor of the zona glomerulosa cells occurs and secretes large amounts of aldosterone; the resulting condition is called "primary aldosteronism" or "Conn's syndrome." Also, in a few instances, hyperplastic adrenal cortices secrete aldosterone rather than cortisol.

- **Adrenogenital Syndrome**

✓ An occasional adrenocortical tumor secretes excessive quantities of androgens that cause intense masculinizing effects throughout the body.

✓ If this occurs in a female, she develops virile characteristics, including growth of a beard, a much deeper voice, occasionally baldness if she also has the genetic trait for baldness, masculine distribution of hair on the body and the pubis, growth of the clitoris to resemble a penis, and deposition of proteins in the skin and especially in the muscles to give typical masculine characteristics.

THANKS FOR LISTENING