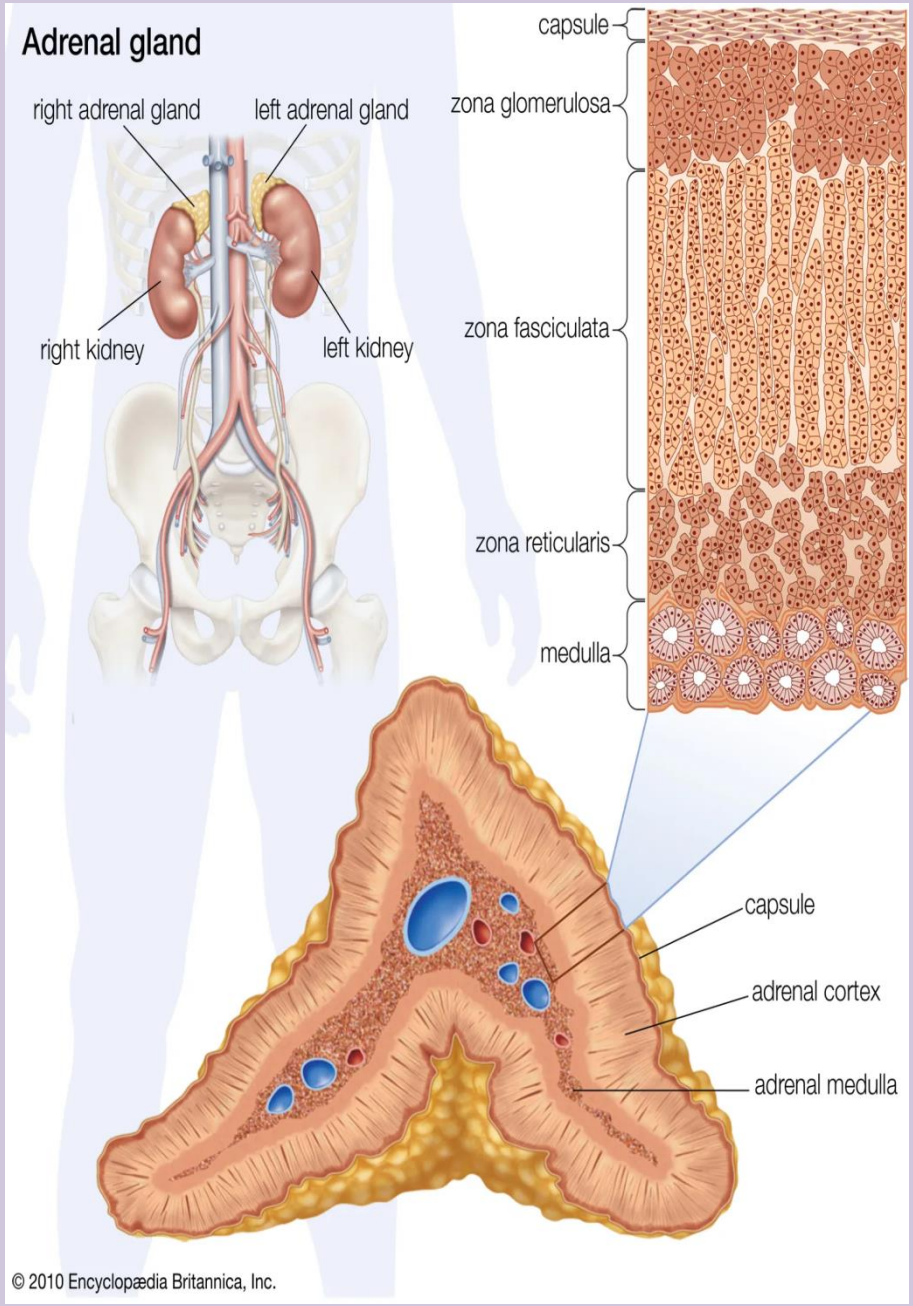
Al Mustaqbal Universty
Collage of pharmacy

The Adrenal Medulla & Adrenal Cortex

DR. IMAN GHANIM ALRAKHT

There are two endocrine organs in the adrenal gland, one surrounding the other.

The main secretions of the inner adrenal medulla are the catecholamines epinephrine, norepinephrine, and dopamine; the outer adrenal cortex secretes steroid hormones.



The adrenal cortex secretes glucocorticoids, steroids with widespread effects on the metabolism of carbohydrate and protein; and a mineralocorticoid essential to the maintenance of Na+ balance an extracellular fluid (ECF) volume.

- It is also a secondary site of androgen synthesis, secreting sex hormones such as testosterone, which can exert effects on reproductive function.

The adrenal medulla, which constitutes 28% of the mass of the adrenal gland, two cell types can be distinguished morphologically: an epinephrine-secreting type and a norepinephrine-secreting type.

In humans, 90% of the cells are the epinephrine secreting type and 10% are the norepinephrine-secreting type.

- In adult mammals, the adrenal cortex is divided into ***three*** zones ,the outer zona glomerulosa , then zona fasciculate and zona reticularis.

- All three cortical zones secrete corticosterone, but the active enzymatic mechanism for aldosterone biosynthesis is limited to the zona glomerulosa, whereas the enzymatic mechanisms for forming cortisol and sex hormones are found in the two inner zones.

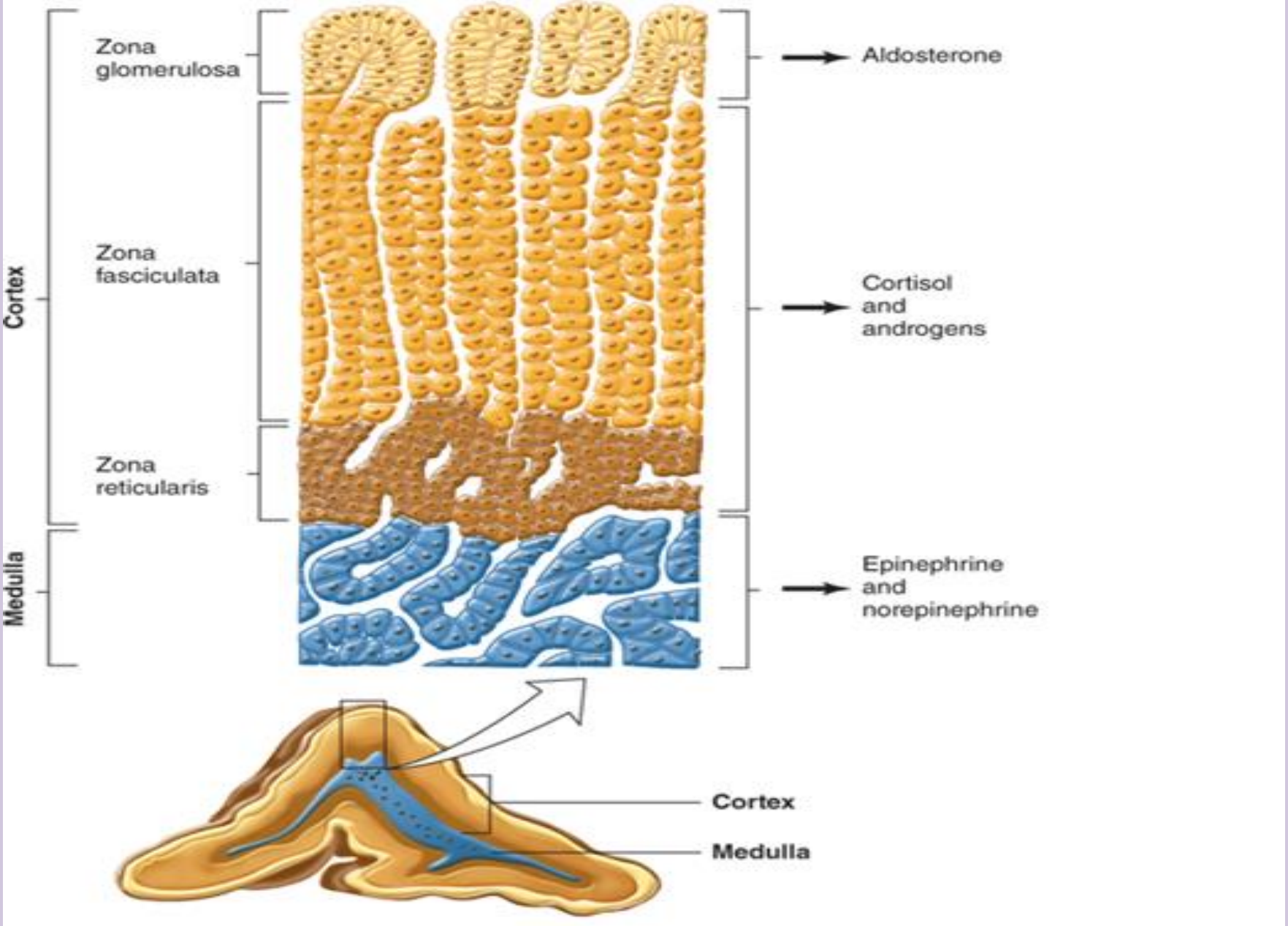


FIGURE 1: Section through an adrenal gland showing both the medulla and the zones of the cortex, as well as the hormones they secrete.

ADRENAL MEDULLA: STRUCTURE & FUNCTION OF MEDULLARY HORMONES:

CATECHOLAMINES

Norepinephrine, epinephrine, and small amounts of dopamine are synthesized by the adrenal medulla.

- Norepinephrine is formed by hydroxylation and decarboxylation of tyrosine, and epinephrine by methylation of norepinephrine.
- In plasma, about 95% of the dopamine and 70% of the norepinephrine and epinephrine are conjugated to sulfate.
- Sulfate conjugates are inactive and their function is unsettled.
- The catecholamines have a half-life of about 2 min in the circulation.

A\ EFFECTS OF EPINEPHRINE & NOREPINEPHRINE:

- The norepinephrine and epinephrine exert metabolic effects that include ***glycogenolysis*** in liver and skeletal muscle, ***mobilization*** of free fatty acids (FFA), ***increased*** plasma lactate, and ***stimulation*** of the metabolic rate.

The effects of norepinephrine and epinephrine are brought about by actions on two classes of receptors: α- and β-adrenergic receptors.

- In addition, the catecholamines **increase** the secretion of insulin and glucagon via β-adrenergic mechanisms and inhibit the secretion of these hormones via α-adrenergic mechanisms.
- Norepinephrine and epinephrine both increase the force and rate of contraction of the isolated heart. These responses are mediated by β1-receptors.
- Norepinephrine produces vasoconstriction in most if not all organs via α1-receptors, but epinephrine dilates the blood vessels in skeletal muscle and the liver via β2-receptors.

B\EFFECTS OF DOPAMINE:

The physiologic function of the dopamine in the circulation is unknown. However, injected dopamine produces renal vasodilation, probably by acting on a specific dopaminergic receptor.

It produces vasoconstriction, probably by releasing norepinephrine, and it has a positive inotropic effect on the heart by an action on β1 adrenergic receptors.

Dopamine is made in the renal cortex. It causes natriuresis and may exert this effect by inhibiting renal Na, K, ATPase.

REGULATION OF ADRENAL MEDULLARY SECRETION

- Certain drugs act directly on the adrenal medulla, but physiologic stimuli affect medullary secretion through the nervous system.

Catecholamine secretion is low in basal states, but the secretion of epinephrine and, to a lesser extent, that of norepinephrine is **reduced** even further during sleep.

Increased adrenal medullary secretion is part of the diffuse sympathetic discharge provoked in emergency situations, which Cannon called the "**emergency function of the sympathoadrenal system**." The ways in which this discharge prepares the individual for flight or fight and the increases in plasma catecholamines under various conditions.

ADRENAL CORTEX: STRUCTURE & BIOSYNTHESIS OF ADRENOCORTICAL HORMONES

CLASSIFICATION & STRUCTURE

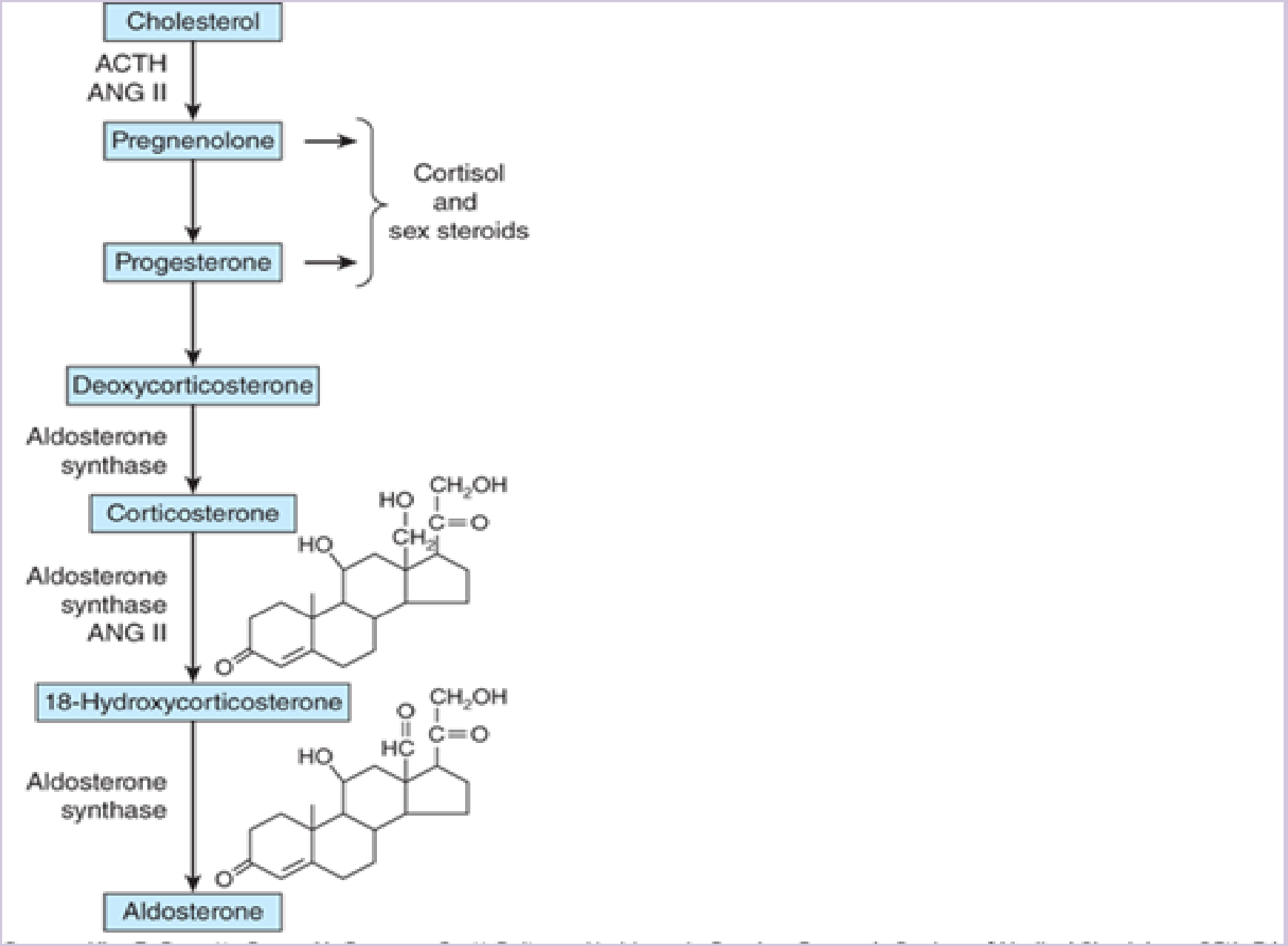
The hormones of the adrenal cortex are **derivatives** of cholesterol.

Like cholesterol, bile acids, vitamin D, and ovarian and testicular steroids, they contain the cyclopentanoperhydrophenanthrene nucleus.

SECRETED STEROIDS:

Innumerable steroids have been isolated from adrenal tissue, but the only steroids normally secreted in physiologically significant amounts are the mineralocorticoid aldosterone, the glucocorticoids cortisol and corticosterone, and the androgens dehydroepiandrosterone (DHEA) and androstenedione.

Deoxycorticosterone is a mineralocorticoid that is normally secreted in about the **same** amount as aldosterone ***but*** has only 3% of the mineralocorticoid activity of aldosterone


Cholesterol
ACTH
ANG II
Pregnenolone
Progesterone
Cortisol
and
sex steroids
Deoxycorticosterone
Aldosterone
synthase
Corticosterone
Aldosterone
synthase
ANG II
18-Hydroxycorticosterone
Aldosterone
synthase
Aldosterone
HO
CH2OH
C=O
CH2
O
HC

STEROID BIOSYNTHESIS:

- The precursor of all steroids is cholesterol.

Some of the cholesterol is synthesized from acetate, but most of it is taken up from LDL in the circulation.

- ***Cholesterol ester hydrolase*** catalyzes the formation of free cholesterol in the lipid droplets.

- The cholesterol is transported to mitochondria by a sterol carrier protein. In the mitochondria, it is converted to pregnenolone.

- Pregnenolone moves to the smooth endoplasmic reticulum, where some of it is dehydrogenated to form progesterone.
- ACTH binds to high-affinity receptors on the plasma membrane of adrenocortical cells. This activates adenylyl cyclase via Gs.
- The resulting reactions lead to a prompt increase in the formation of pregnenolone and its derivatives.
- Over longer periods, ACTH also increases the synthesis of the P450s involved in the synthesis of glucocorticoids.

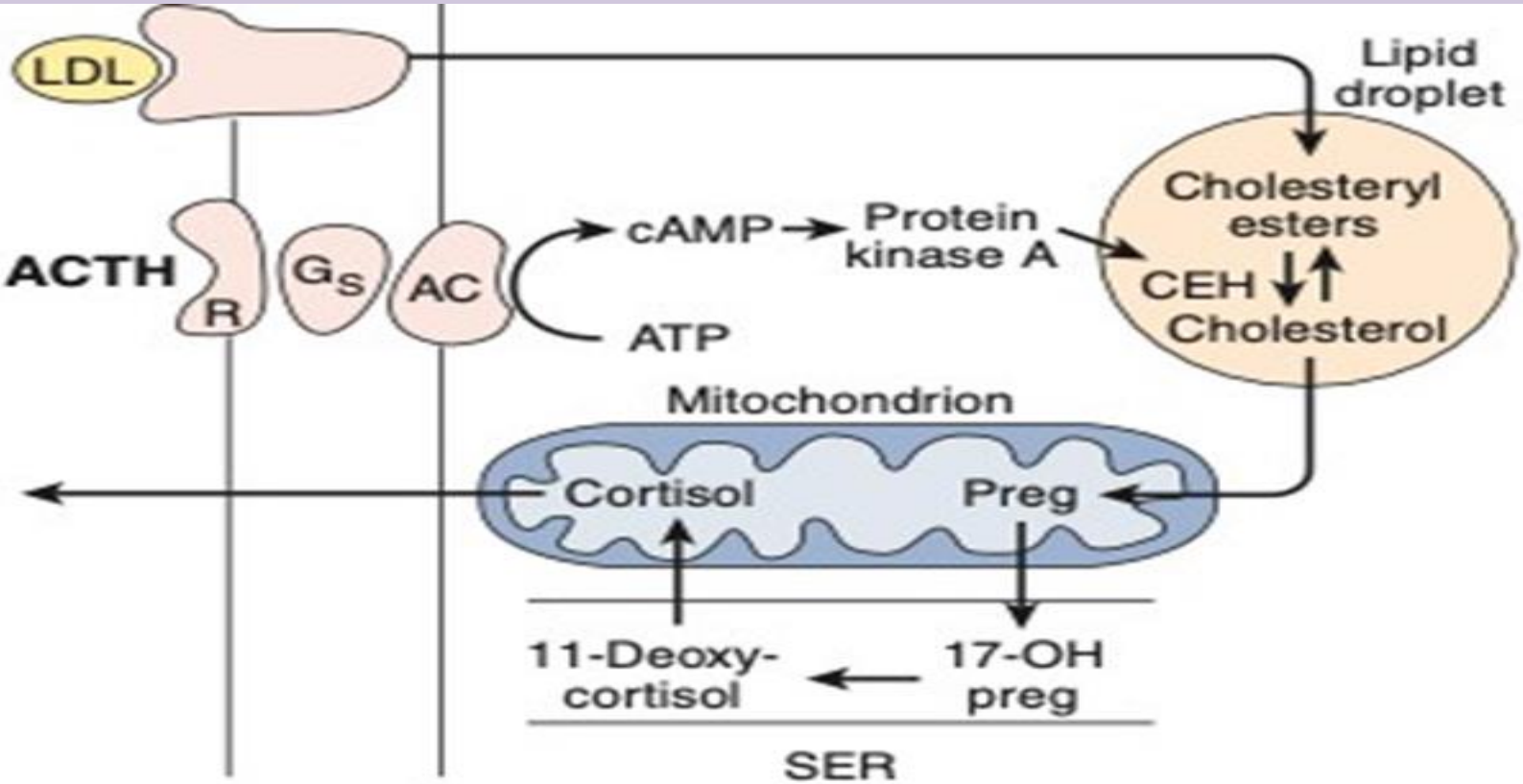


FIGURE 20–9 Mechanism of action of ACTH on cortisol-secreting cells in the inner two zones of the adrenal cortex. When ACTH binds to its receptor (R), adenylyl cyclase (AC) is activated via Gs. The resulting increase in cAMP activates protein kinase A, and the kinase phosphorylates cholesteryl ester hydrolase (CEH), increasing its activity. Consequently, more free cholesterol is formed and converted to pregnenolone. Note that in the subsequent steps in steroid biosynthesis, products are shuttled between the mitochondria and the smooth endoplasmic reticulum (SER). Corticosterone is also synthesized and secreted.

TRANSPORT, METABOLISM, & EXCRETION OF ADRENOCORTICAL HORMONES

GLUCOCORTICOID BINDING

Cortisol is bound in the circulation to an α globulin called ***transcortin*** or ***corticosteroid-binding globulin (CBG***). CBG is synthesized in the liver and its production is increased by estrogen.

CBG levels are elevated during pregnancy and depressed in cirrhosis, nephrosis, and multiple myeloma. When the CBG level rises, more cortisol is bound, and initially the free cortisol level drops. This stimulates ACTH secretion, and more cortisol is secreted. Changes in the opposite direction occur when the CBG level falls.

- A minor degree of binding to albumin also takes place.
- The half-life of cortisol in the circulation is therefore longer (about 60–90 min).
- Bound steroids are physiologically inactive. In addition, relatively little free cortisol & corticosterone are found in the urine because of protein binding.
- The bound cortisol functions as a circulating reservoir of hormone that keeps a supply of free cortisol available to the tissue.

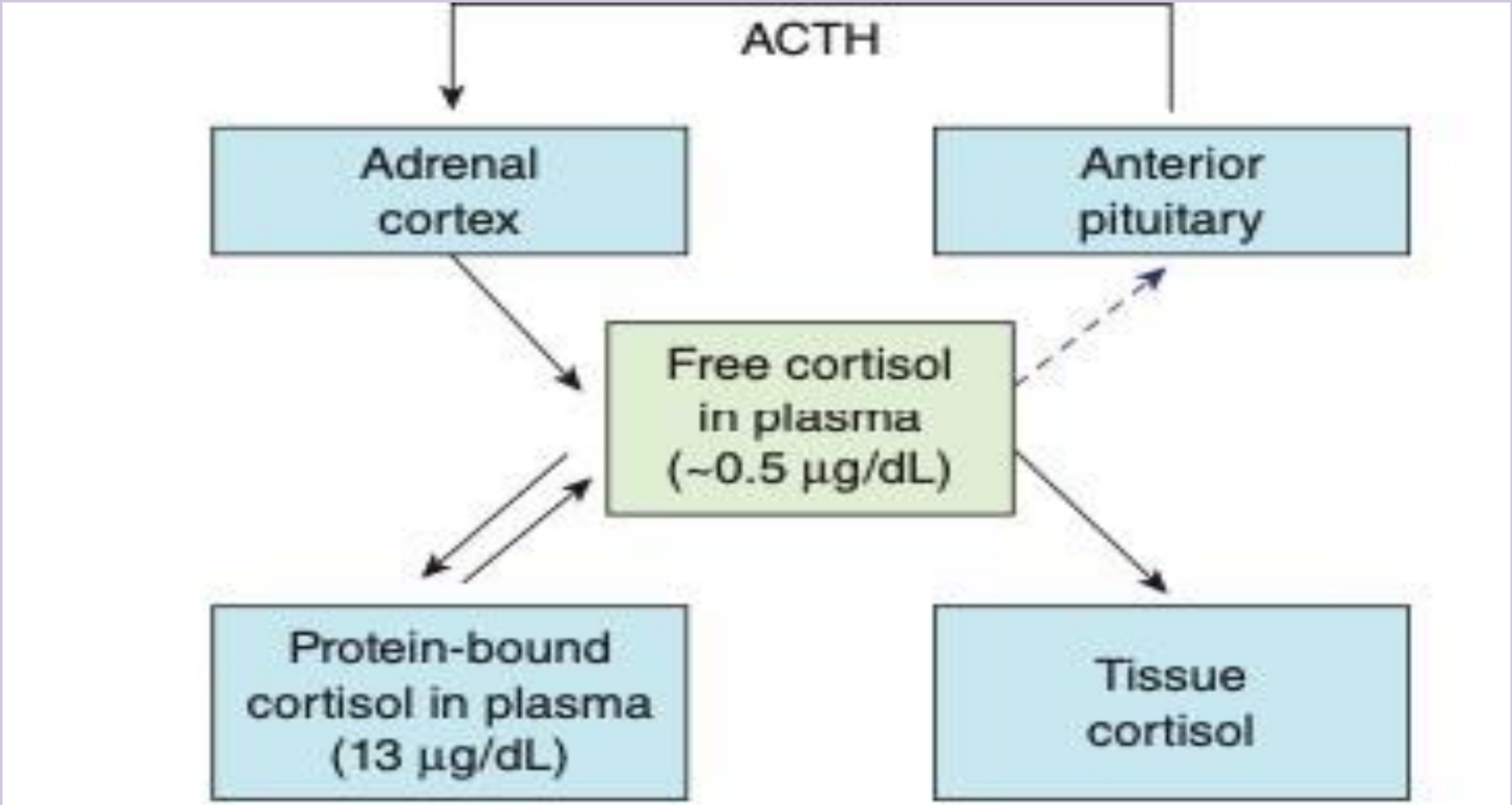


FIGURE 20–10 The interrelationships of free and bound cortisol. The dashed arrow indicates that cortisol inhibits ACTH secretion. The value for free cortisol is an approximation; in most studies, it is calculated by subtracting the protein-bound cortisol from the total plasma cortisol.

METABOLISM & EXCRETION OF GLUCOCORTICOIDS

Cortisol is metabolized in the liver, which is the principal site of glucocorticoid catabolism. Most of the cortisol is reduced to dihydrocortisol and then to tetrahydrocortisol, which is conjugated to glucuronic acid .

Cortisone is an active glucocorticoid because it is converted to cortisol, and it is well known because of its extensive use in medicine. It is not secreted in appreciable quantities by the adrenal glands.

Little, if any, of the cortisone formed in the liver enters the circulation, because it is promptly reduced and conjugated to form tetrahydrocortisone glucuronides.

ALDOSTERONE

Aldosterone is bound to protein to only a slight extent, and its half-life is short (about 20 min). The amount secreted is small when compared with a cortisol level (bound and free).

Much of the aldosterone is converted in the liver to the tetrahydroglucuronide derivative, but some is changed in the liver and in the kidneys to an 18-glucuronide.

17-KETOSTEROIDS

The **major** adrenal androgen is the 17-ketosteroid dehydroepiandrosterone, although androstenedione is also secreted.

The 11-hydroxy derivative of androstenedione and

the 17-ketosteroids formed from cortisol and cortisone by side chain cleavage in the liver. Testosterone is also converted to a 17-ketosteroid.

Because the daily 17 ketosteroid excretion in normal adults is 15 mg in men and 10 mg in women, about two-thirds of the urinary ketosteroids in men are secreted by the adrenal or formed from cortisol in the liver and about one-third are of testicular origin.

EFFECTS OF ADRENAL ANDROGENS & ESTROGENS

ANDROGENS

Androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth. Testosterone from the testes is the most active androgen and the adrenal androgens have less than 20% of its activity. Secretion of the adrenal androgens is controlled acutely by ACTH and not by gonadotropins.

In normal males, so it is clear that these hormones exert very little masculinizing effect when secreted in normal amounts. However, they can produce appreciable masculinization when secreted in excessive amounts.

In adult males, excess adrenal androgens merely accentuate existing.

ESTROGENS

The adrenal androgen androstenedione is converted to testosterone and to estrogens (aromatized) in fat and other peripheral tissues. **This is an important source of estrogens in men and postmenopausal women.**

PHYSIOLOGIC EFFECTS OF GLUCOCORTICOIDS

MECHANISM OF ACTION

The multiple effects of glucocorticoids are triggered by binding to glucocorticoid receptors, and the steroid–receptor complexes act as transcription factors that promote the transcription of certain segments of DNA.

EFFECTS ON INTERMEDIARY METABOLISM

They include increased protein catabolism and increased hepatic ***glycogenesis*** and ***gluconeogenesis***.

Glucose-6-phosphatase activity is increased, and the plasma glucose level rises. Glucocorticoids exert an anti-insulin action in peripheral tissues and make diabetes worse.

However, the brain and the heart are spared, so the increase in plasma glucose provides extra glucose to these vital organs. In diabetics, glucocorticoids raise plasma lipid levels and increase ketone body formation.

EFFECTS ON ACTH SECRETION

Glucocorticoids inhibit ACTH secretion, which represents a negative feedback response on the pituitary

EFFECTS ON THE NERVOUS SYSTEM

Changes in the nervous system in adrenal insufficiency that are reversed only by glucocorticoids include the appearance of electroencephalographic waves slower than the normal β rhythm, and personality changes. The latter, which are mild, include irritability, apprehension, and inability to concentrate.

EFFECTS ON WATER METABOLISM

Adrenal insufficiency is characterized by an inability to excrete a water load, causing the possibility of water intoxication. Only glucocorticoids repair this deficit. In patients with adrenal insufficiency who have not received glucocorticoids, glu- cose infusion may cause high fever (“glucose fever”) followed by collapse and death.

EFFECTS ON THE BLOOD CELLS & LYMPHATIC ORGANS:

- Glucocorticoids decrease the number of circulating eosinophils by increasing their sequestration in the spleen and lungs.
- Glucocorticoids also lower the number of basophils in the circulation and increase the number of neutrophils, platelets, and red blood cells .

RESISTANCE TO STRESS

The term ***stress*** as used in biology has been defined as any change in the environment that changes or threatens to change an existing optimal steady state.

Most, **if not all**, of these stresses activate processes at the molecular, cellular, or systemic level that tend to restore the previous state, that is, they are homeostatic reactions.

Some, but not all, of the stresses stimulate ACTH secretion.

The increase in ACTH secretion is essential for survival when the stress is severe. Most of the stressful stimuli that increase ACTH secretion also activate the sympathetic nervous system, and part of the function of circulating glucocorticoids may be maintenance of vascular reactivity to catecholamines.

It should also be noted that the increase in ACTH, which is beneficial in the short term, becomes harmful and disruptive in the long term, causing among other things, the abnormalities of Cushing syndrome.

PHARMACOLOGIC & PATHOLOGIC EFFECTS OF GLUCOCORTICOIDS

CUSHING SYNDROME

The clinical picture produced by prolonged increases in plasma glucocorticoids was described by Harvey Cushing and is called Cushing syndrome . Patients with Cushing syndrome are protein-depleted as a result of excess protein catabolism. The skin and subcutaneous tissues are therefore thin and the muscles are poorly devel- oped. The hair is thin and scraggly.

- Many patients with the disease have some increase in facial hair and acne, but this is caused by the increased secretion of adrenal androgens and often accompanies the increase in glucocorticoid secretion.
- Body fat is redistributed in a characteristic way.
- The extremities are thin, but fat collects in the abdominal wall, face, and upper back, where it produces a “buffalo hump.”

The salt and water retention plus the facial obesity cause the characteristic plethoric, rounded “moon-faced” appearance, and there may be significant K+ depletion and weakness. About 85% of patients with Cushing syndrome are hypertensive.

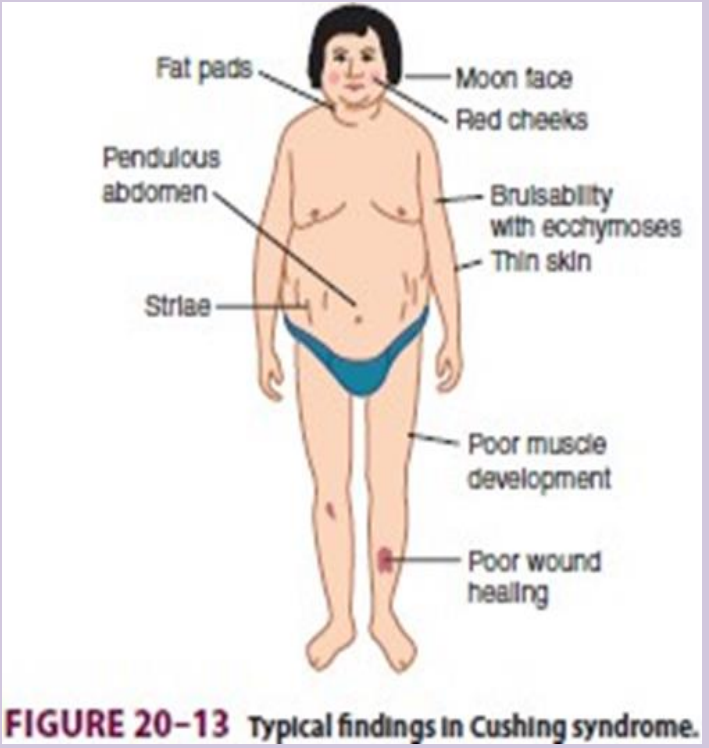


FIGURE 20–13 Typical findings in Cushing syndrome.

The hypertension may be due to increased deoxycorticosterone secretion, increased angiotensinogen secretion, or a direct glucocorticoid effect on blood vessels .

ANTI-INFLAMMATORY & ANTI-ALLERGIC EFFECTS OF GLUCOCORTICOIDS

Glucocorticoids inhibit the inflammatory response to tissue injury. The glucocorticoids also suppress manifestations of allergic disease that are due to the release of histamine from mast cells and basophils. Both of these effects require high levels of circulating glucocorticoids and cannot be produced by administering steroids without producing the other manifestations of glucocorticoid excess.

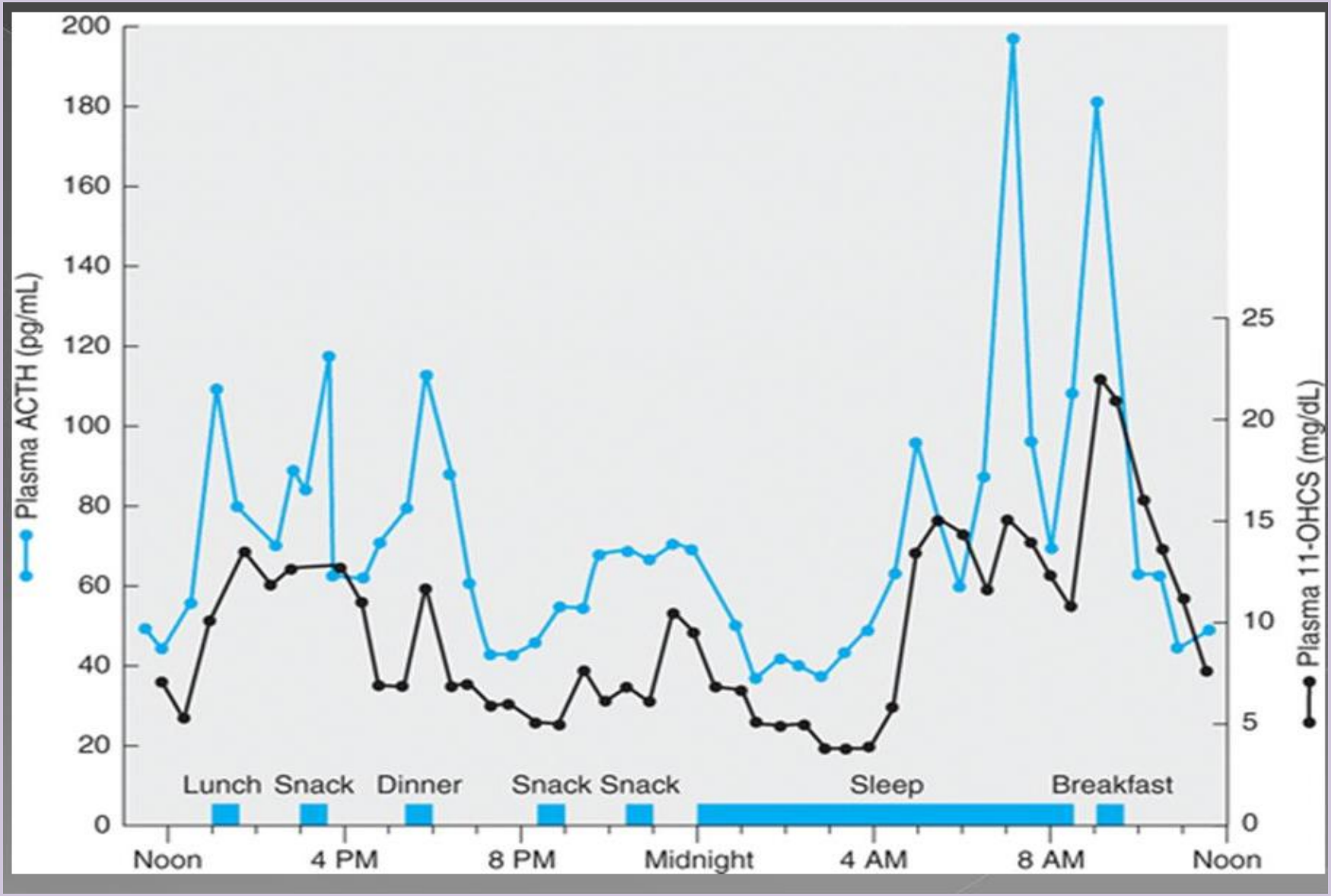
REGULATION OF GLUCOCORTICOID SECRETION

ROLE OF ACTH

Both basal secretion of glucocorticoids and the increased secretion provoked by stress depend on ACTH from the anterior pituitary, its half-life in the circulation in humans is about 10 min. ACTH not only produces prompt increases in glucocorticoid secretion but also increases the sensitivity of the adrenal to subsequent doses of ACTH. ACTH are necessary to restore normal adrenal responses to ACTH.

CIRCADIAN RHYTHM

ACTH is secreted in irregular bursts throughout the day and plasma cortisol tends to rise and fall in response to these bursts . In humans, the bursts are most frequent in the early morning, and about 75% of the daily production of cortisol occurs between 4:00 AM and 10:00 AM. The bursts are least frequent in the evening. This diurnal (circadian) rhythm in ACTH secretion is present in patients with adrenal insufficiency receiving constant doses of glucocorticoids


Plasma ACTH (pg/mL)
200
180
160
140
120
100
80
60
40
20
0
Plasma 11-OHCS (mg/dL)
25
20
15
10
5
0
Lunch
Snack
Dinner
Snack
Snack
Sleep
Breakfast
Noon
4 PM
8 PM
Midnight
4 AM
8 AM
Noon

GLUCOCORTICOID FEEDBACK

Free glucocorticoids inhibit ACTH secretion, and the degree of pituitary inhibition is proportional to the circulating glucocorticoid level. The inhibitory effect is exerted at both the pituitary and the hypothalamic levels. A drop in resting corticoid levels stimulates ACTH secretion, and in chronic adrenal insufficiency the rate of ACTH synthesis and secretion is markedly increased.

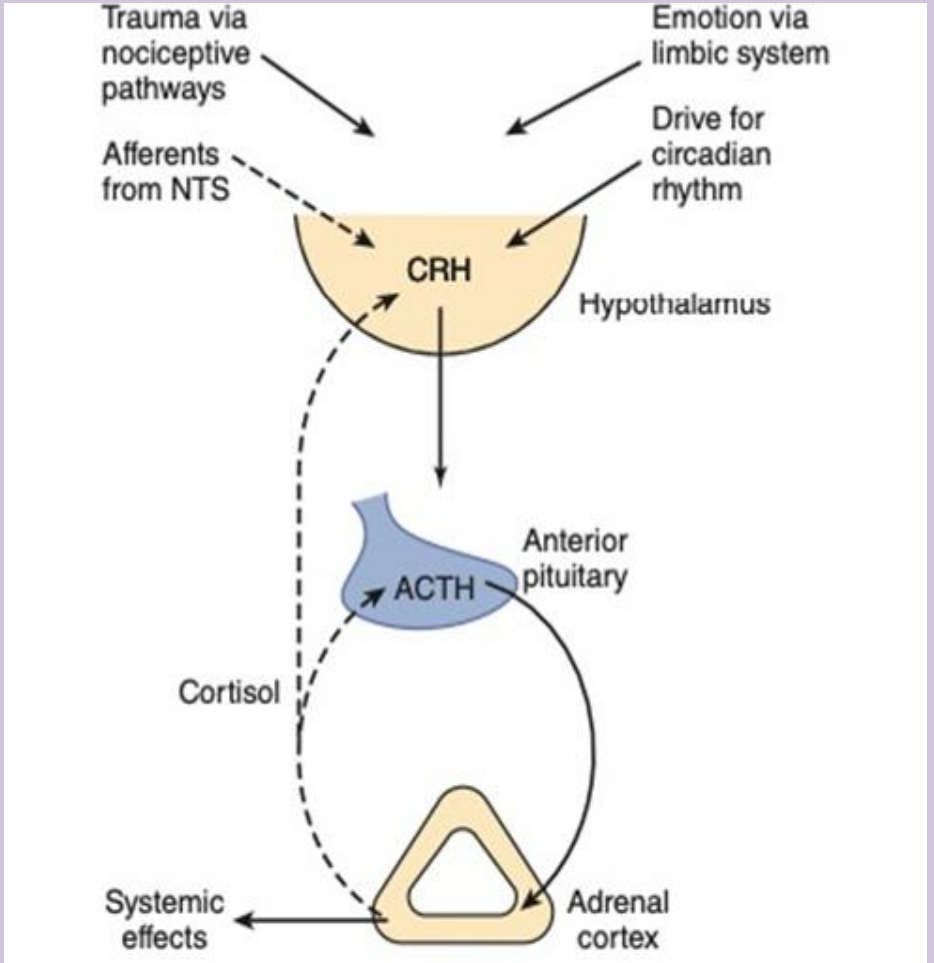


FIGURE 20–17 **Feedback control of the secretion of cortisol and other glucocorticoids via the hypothalamic-pituitary-adrenal axis.** The dashed arrows indicate inhibitory effects and the solid arrows indicate stimulating effects. NTS, nucleus tractus solitarius.

EFFECTS OF MINERALOCORTICOIDS:

ACTIONS

Aldosterone and other steroids with mineralocorticoid activity increase the reabsorption of Na^+ from the urine, sweat, saliva, and the contents of the colon. Thus, mineralocorticoids cause retention of Na^+ in the ECF. This expands ECF volume. Under the influence of aldosterone, increased amounts of Na^+ are in effect

exchanged for K^+ and H^+ in the renal tubules, producing a K^+ diuresis and an increase in urine acidity.

MECHANISM OF ACTION

Like many other steroids, aldosterone binds to a cytoplasmic receptor, and the receptor–hormone complex moves to the nucleus where it alters the transcription of mRNAs. The aldosterone-stimulated proteins have two effects—a **rapid** effect, to increase the activity of epithelial sodium channels (ENaCs) by increasing the insertion of these channels into the cell membrane from a cytoplasmic pool; and a **slower** effect to increase the synthesis of ENaCs.

REGULATION OF ALDOSTERONE SECRETION STIMULI

The principal conditions that increase aldosterone secretion are summarized in Table 20–6. Some of them also increase glucocorticoid secretion; others selectively affect the output of aldosterone. The primary regulatory factors involved are ACTH from the pituitary, renin from the kidney via angiotensin II, and a direct stimulatory effect on the adrenal cortex of a rise in plasma K+ concentration.

TABLE 20–6 Conditions that increase aldosterone secretion.

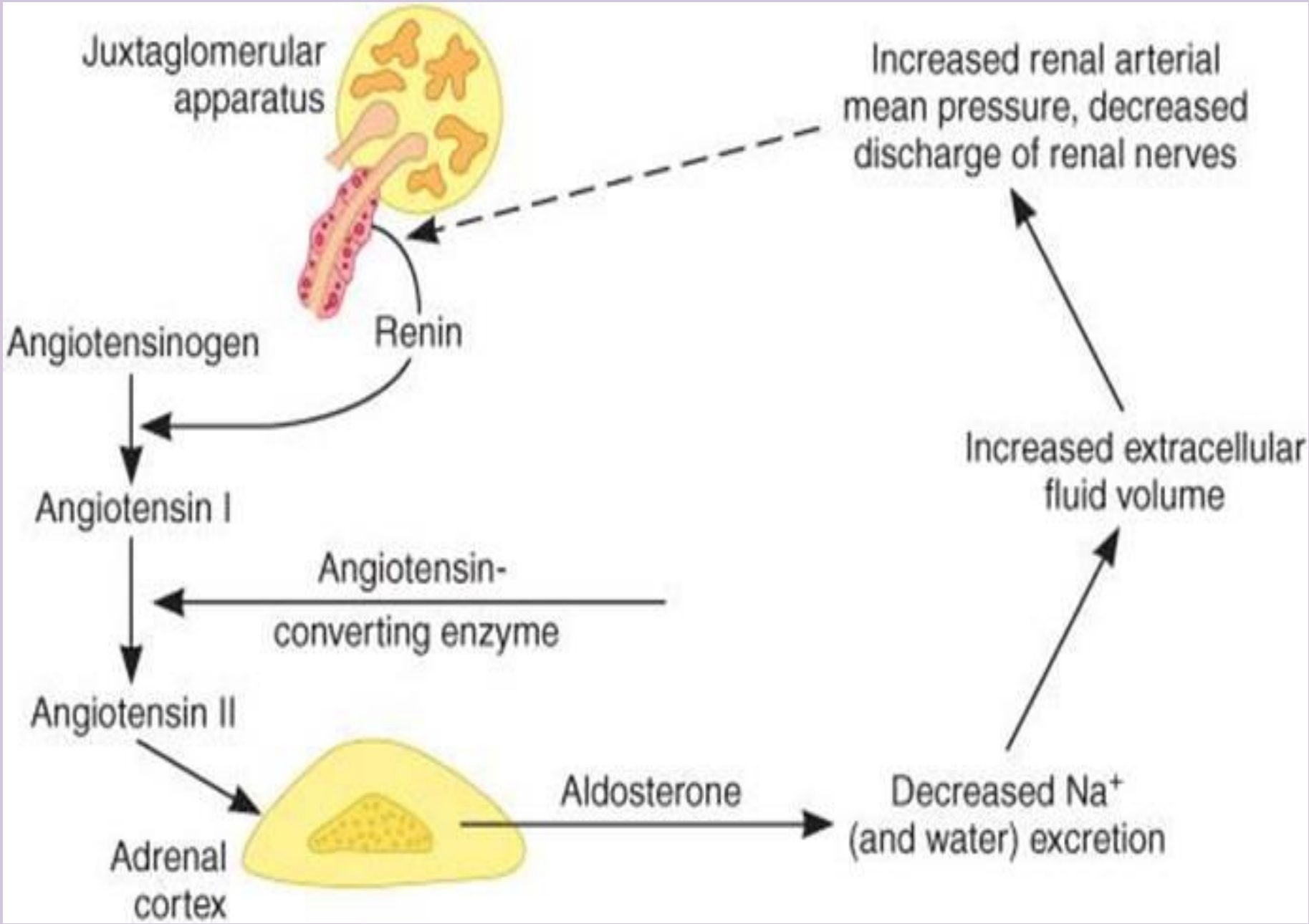
Glucocorticoid secretion also increased
Surgery
Anxiety
Physical trauma
Hemorrhage
Glucocorticoid secretion unaffected
High potassium intake
Low sodium intake
Constriction of inferior vena cava in thorax
Standing
Secondary hyperaldosteronism (in some cases of heart failure, cirrhosis, and nephrosis)

EFFECT OF ACTH

When first administered, ACTH stimulates the output of aldosterone as well as that of glucocorticoids and sex hormones. Although the amount of ACTH required to increase aldosterone output is somewhat greater than the amount that stimulates maximal glucocorticoid secretion.

EFFECTS OF ANGIOTENSIN II & RENIN

The angiotensin II is formed in the body from angiotensin I, which is liberated by the action of renin on circulating angiotensinogen. Injections of angiotensin II stimulate adrenocortical secretion and, in small doses, affect primarily the secretion of aldosterone. Hemorrhage stimulates ACTH and renin secretion. Like hemorrhage, standing and constriction of the thoracic inferior vena cava decrease intrarenal arterial pressure. Dietary sodium restriction also increases aldosterone secretion via the renin–angiotensin system .Such restriction reduces ECF volume, but aldosterone and renin secretion are increased before any consistent decrease in blood pressure takes place.


Juxtaglomerular apparatus
Increased renal arterial mean pressure, decreased discharge of renal nerves
Angiotensinogen
Renin
Angiotensin I
Increased extracellular fluid volume
Angiotensin-converting enzyme
Angiotensin II
Aldosterone
Decreased Na+ (and water) excretion
Adrenal cortex

ROLE OF MINERALOCORTICOIDS IN THE REGULATION OF SALT BALANCE

Variations in aldosterone secretion is only one of many factors affecting Na+ excretion. Other major factors include the glomerular filtration rate, ANP, the presence or absence of osmotic diuresis, and changes in tubular reabsorption of Na+ independent of aldosterone. It takes some time for aldosterone to act. When one rises from the supine to the standing position, aldosterone secretion increases and Na+ is retained from the urine. However, the decrease in Na+ excretion develops too rapidly to be explained solely by increased aldosterone secretion. The primary function of the aldosterone-secreting mechanism is the defense of intravascular volume, but it is only one of the homeostatic mechanisms involved in this regulation.