Chapter

Adrenal Cortex Hormones

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Abstract

Over 50 different steroids, including precursors to other steroid hormones, are secreted by the adrenal glands, which are located directly above the kidneys. Aldosterone and hydrocortisone, however, are the two most significant hormonal steroids created by the adrenal cortex. Since aldosterone is too expensive to produce commercially, other semi-synthetic analogues are now used to treat Addison's disease in its place. Fludrocortisone, for example, greatly increases both salt retention and anti-inflammatory activity when combined with hydrocortisone. The kidneys' ability to reabsorb sodium is increased by aldosterone. Increased blood volume will follow an increase in plasma sodium concentration. Additionally, aldosterone boosts potassium ion excretion. Addison's disease is brought on by inconsistency. Glycogen storage synthesis is induced by the synthesis of glycogen synthase, and gluconeogenesis (the production of glucose from glucose) is induced in the liver.

Keywords: steroid hormones, adrenal glands, synthesis, metabolism, structure-activity relationship, mechanism and activity

1. Introduction

Over 50 different steroids, including precursors to other steroid hormones, are secreted by the adrenal glands, which are located directly above the kidneys. Aldosterone and hydrocortisone, however, which are the most significant hormonal steroids produced by the adrenal cortex, are only used to treat Addison's disease [1]. An 11-OH and an 18-CHO in the naturally occurring hormone aldosterone naturally bridge to form a hemiacetal.

Because aldosterone is too expensive to produce commercially, other semi-synthetic analogues are now used to treat Addison's disease instead [1].

Fludrocortisone, for example, greatly increases both salt retention and anti-inflammatory activity when added to hydrocortisone [2, 3].

They also secrete a number of vital hormones that are crucial for maintaining a healthy immune system, metabolic rate, and salt and water balance in the body (**Tables 1**–5).

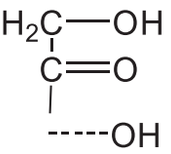
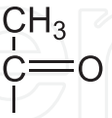
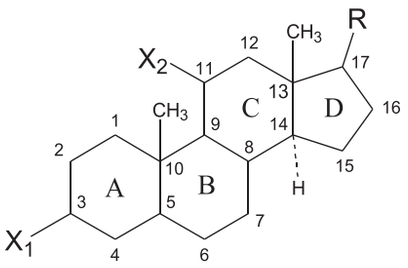
Group of hormones	Double bond	Substitutes		
		X_1	X_2	R
Corticosteroids	en-4 Dien- 1,4	=O	-H -OH =O	
Gestogens	en-4	=O	-H	
Androgens	en-4	=O	-H	-OH
Estrogens	Trien-1,3,5 (No C-19)	-OH	-H	-OH =O

Table 1.
Chemical structure of steroid hormones [3].



Medicinal substances	Color of solution	Florescence
Dezoxycortone acetate	Yellow (after addition of water becomes violet)	Green-yellow color with red florescence (after addition of ethanol)
Cortisone acetate	Red (after heating to 80–90°C becomes orange) "within 2 minutes"	Yellow (within 5 minutes under UV lamp)
Hydrocortisone	Yellow transferred into red (within 5 minutes)	Yellow green transferred into green (after addition of water)
Prednisolone	Green transferred into red	Not available (absent)

Table 2.
Results of the reaction between corticosteroids with conc. H_2SO_4 [3–5].

Medicinal substances	Solvent	Max. absorption (nm)	Refractive index
Dezoxy cortone acetate	Ethanol	241	430–450
Cortisone acetate	Ethanol	238	390
Hydrocortisone acetate	Ethanol	241	395
Prednisolone	Methanol	242	400–430

Table 3.
Conditions of spectrophotometric determination of corticosteroids) [3–5].

Clinical antirheumatic enhancement factors			
Functional group	**Factor**	**Functional group**	**Factor**
1-Dehydro	2.8	16 α-Methyl	1.6
6-Dehydro	0.9	6 β-Methyl	1.3
6 α-Methyl	0.9	16 α, 17 α-Isopropylidenedioxy	0.6
6 α-Fluoro	1.9	17 α-Acetoxy	0.3
9 α-Fluoro	4.9	21-Deoxy	0.2
16 α-Hydroxy	0.3	21-Methyl	0.3

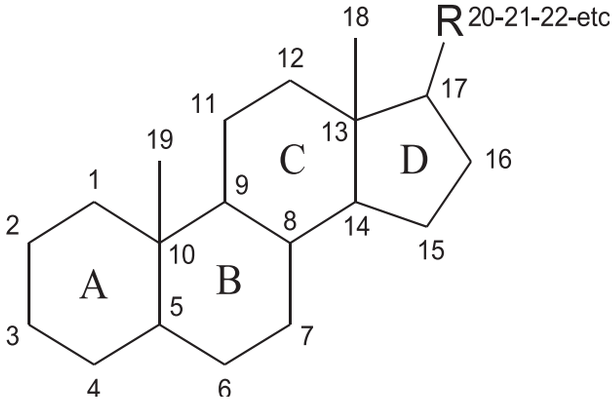
Table 4.
Effects of substituents on glucocorticoid activity.

Functional group	Glycogen deposition	Anti-inflammatory activity	Effects on urinary sodium
9 α-Fluoro	10	7–10	+ + +
9 α-Chloro	3–5	3	+ +
9 α-Bromo	0.4		+
12 α-Fluoro	6–8		+ +
12 α-Chloro	4		
1-Dehydro	3–4	3–4	—
6-Dehydro	0.5–0.7		+
2 α-Methyl	3–6	1–4	+ +
6 α-Methyl	2–3	1–2	—
16 α-Hydroxy	0.4–0.5	0.1–0.2	—
17 α-Hydroxy	1–2	4	—

Table 5.
Enhancement factors for various functional groups of corticosteroids.

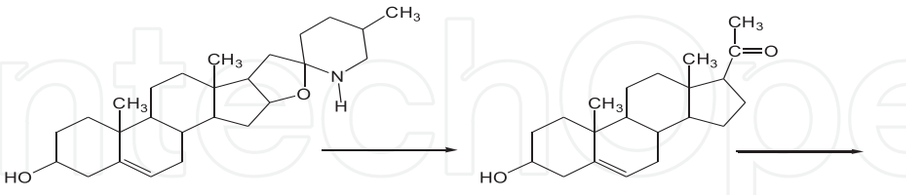
2. Chemistry of steroid hormones

The general formula for the basic structure of the steroid compounds may be represented as follows [3].



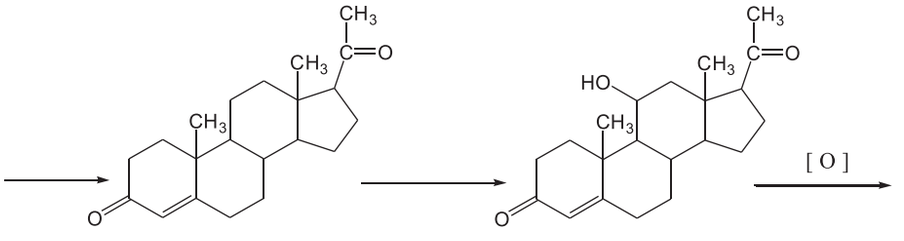
2.1 General steroid formula

In 1956, N.N. Suvoroviy with his colleagues (Allunion Scientific Research of Chemical and Physical Institute) were shown the ability of obtaining cortisone from solasodine from the plant *Solanum* [3, 4]

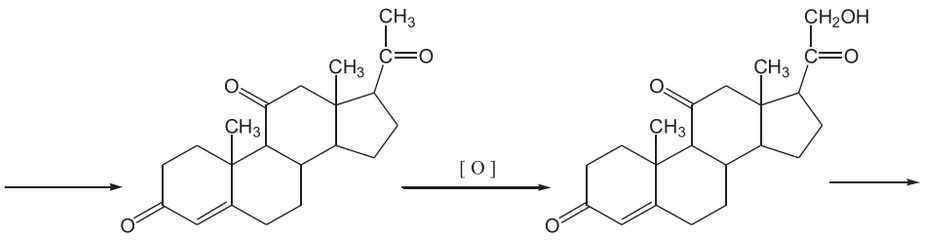


Solasodine Pregnenolone

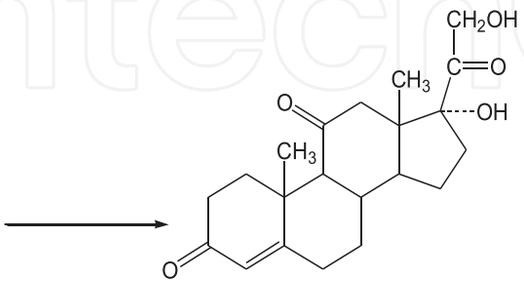
aviculare, family of *Solanaceae*.



Progesterone 11- α -oxy progesterone



11- dihydrocorticosterone

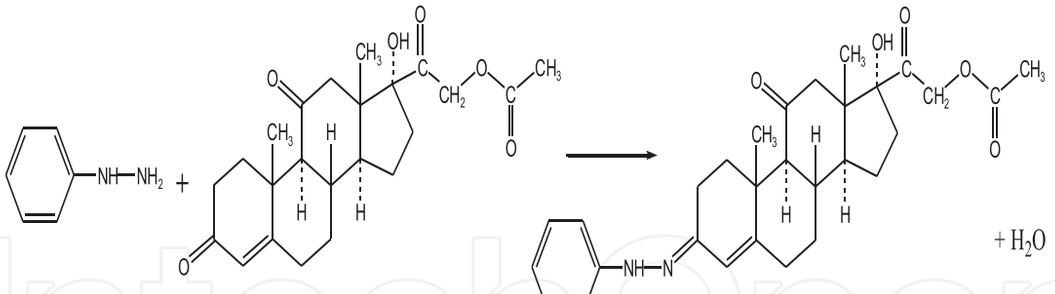


Cortisone

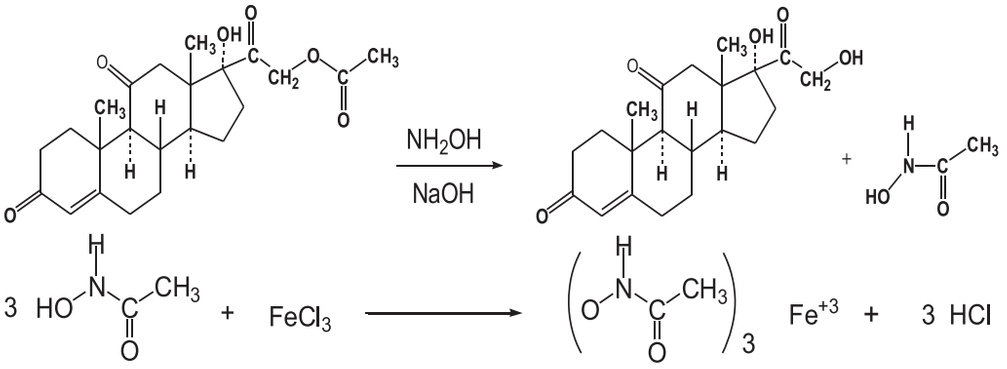
Corticosteroids may be differentiated from each other by reaction on this or other functional groups. [3].

By heating on water bath, spiritus solutions of corticosteroids with phenylhydrazine solution formed yellow color. This reaction occurred with ketonic group, for example [3].

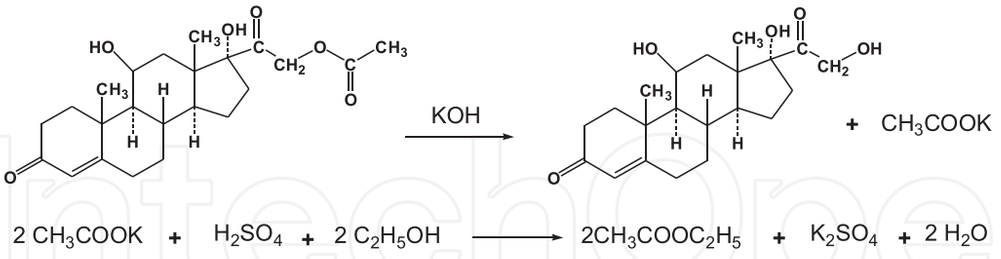
DOI: http://dx.doi.org/10.5772/intechopen.106785



Reaction for obtaining acetohydroxamic acid which reacts with iron salts (III) formed compounds colored in dark cherry (cortisone acetate) or red-brown color (dezoxycortone acetate) [3].



Acetyl group may be detected after hydrolysis of cortisone and hydrocortisone acetate in spiritus solution of hydroxid potassium and subsequent addition of conc. Sulfuric acid which forms ethyl acetate with characteristic odor. For identification of hydrocortisone acetate: [3].



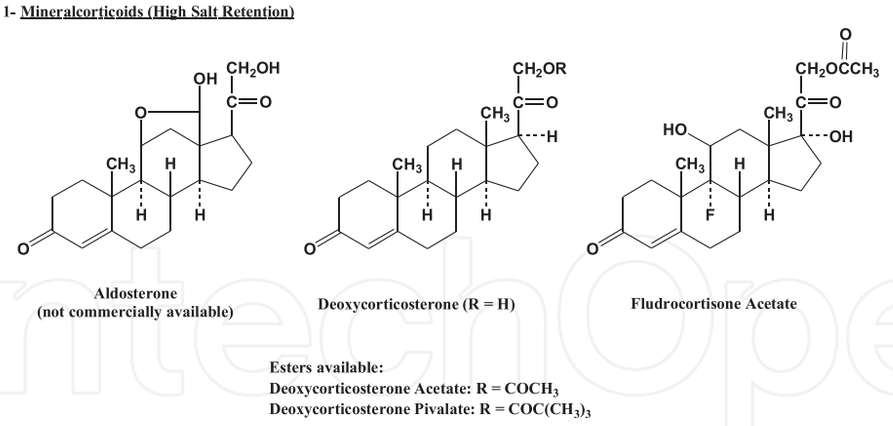
The adrenal glands (which lie just above the kidneys) secrete over 50 different steroids, including precursors to other steroid hormones. However the most important hormonal steroids produced by the adrenal cortex are aldosterone and hydrocortisone [6–11].

2.2 Mineralocorticoids

They are used only for treatment of Addison's disease. The naturally occurring hormone aldosterone has an 11 β-OH and an 18-CHO that naturally bridge to form a hemiacetal. [7–13].

Aldosterone is too expensive to produce commercially; therefore other semisynthetic analogues have taken its place for treatment of Addison's disease [12].

Adding a 9 α-halogen to hydrocortisone (e.g. Fludrocortisone) greatly increases both salt retention and anti-inflammatory activity [2, 3].



The following table summarizes the relative effect of various substituents on salt retention and glucocorticoid activity. The salt-retaining actions are approximately additive. For example, a 9 α-fluoro group's + + + increase in salt retention can be eliminated by 6 α-methyl's - - - . [2, 14–16]

2.3 Glucocorticoids with Moderate to Low Salt Retention

The glucocorticoids with moderate to low retention include cortisone, hydrocortisone, and their 1-enes prednisolone and prednisone [2, 14–16].

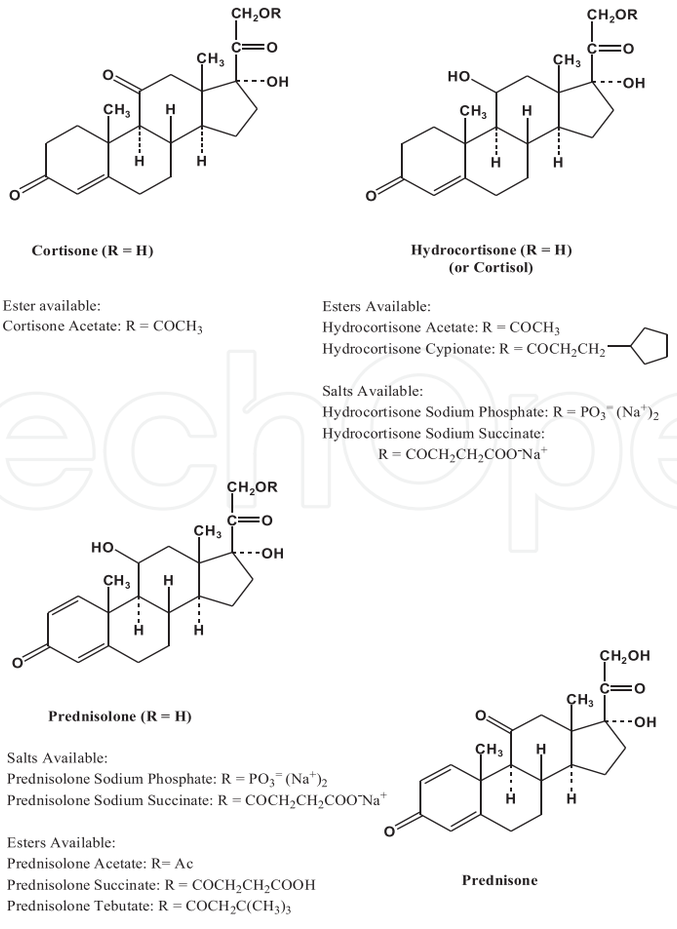


Fig... Natural and semisynthetic adrenal cortex hormones

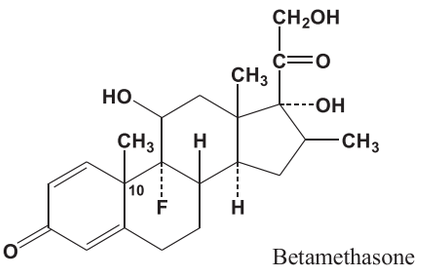
DOI: http://dx.doi.org/10.5772/intechopen.106785

An 11-OH maintains good topical anti-inflammatory activity, but 11-ones have little or none [2, 3, 14–16].

The 1-ene of prednisolone and prednisone increases anti-inflammatory activity by about a factor of 4 and somewhat decreases salt retention [2, 3, 14–16] (**Figures 1–13**).

The 11 β-OH of hydrocortisone is believed to be of major importance in binding to the receptors. Cortisone may be reduced in vivo to yield hydrocortisone as the active agent [2, 3, 14–16, 19–22].

Introduction of fluoro (F) to C6α and C9α positions increase both mineralocorticoid and glucocorticoid activity due to the electron-withdrawing inductive effect on the 11β-OH making it more acidic, therefore, better able to form noncovalent bonds with the receptor. A 9α-halo substituent also reduces oxidation of the 11 β-OH to the less active 11-one [2, 3, 14–16, 19–22].



Betamethasone
(C10 β- methyl)

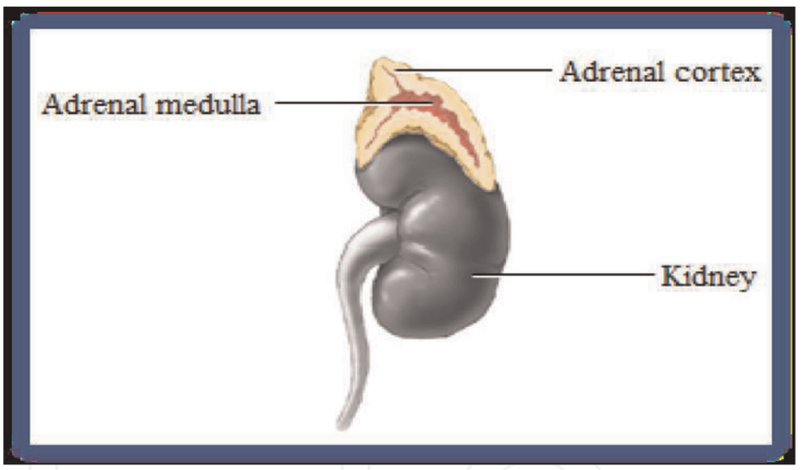


Figure 1.
Structure of adrenal gland.

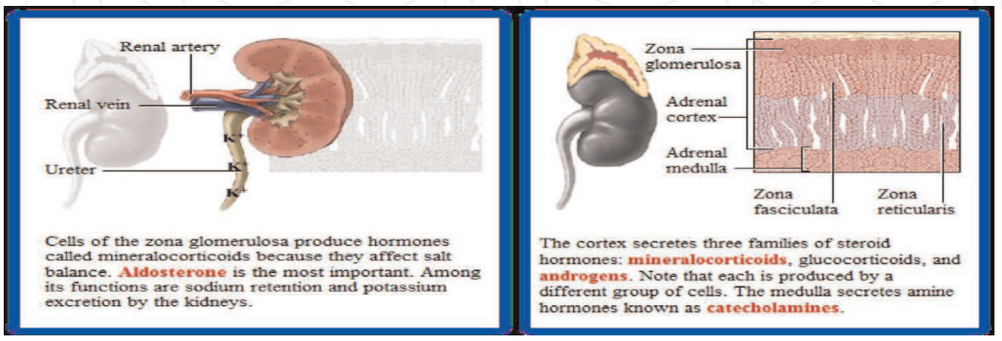


Figure 2.
(Left) Cells of the zona glomerulosa produce hormones called mineralocorticoids because they affect salt balance. ***Aldosterone*** *is the most important. Among its functions are sodium retention and potassium excretion by the kidneys. (Right) The cortex secretes three families of steroid hormones:* ***mineralocorticoids****, glucocorticoids, and* ***androgens****. Note that each is produced by a different group of cells. The medulla secretes amine hormones known as* ***catecholamines****.*

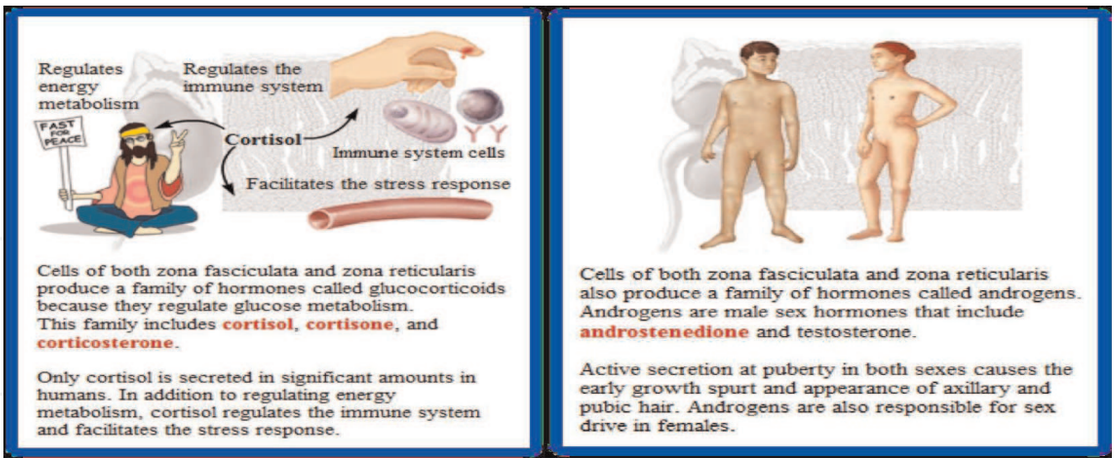


Figure 3.
(Left) Cells of both zona fasciculata and zona reticularis produce a family of hormones called glucocorticoids because they regulate glucose metabolism. This family includes ***cortisol, cortisone****, and* ***corticosterone****. Only cortisol is secreted in significant amounts in humans. In addition to regulating energy metabolism, cortisol regulates the immune system and facilitates the stress response. (Right) Cells of both zona fasciculate and zona reticularis also produce a family of hormones called androgens. Androgens are male sex hormones that include* ***androstenedione*** *and testosterone. Active secretion at puberty in both sexes causes the early growth spurt and appearance of axillary and pubic hair. Androgens are also responsible for sex drive in females.*

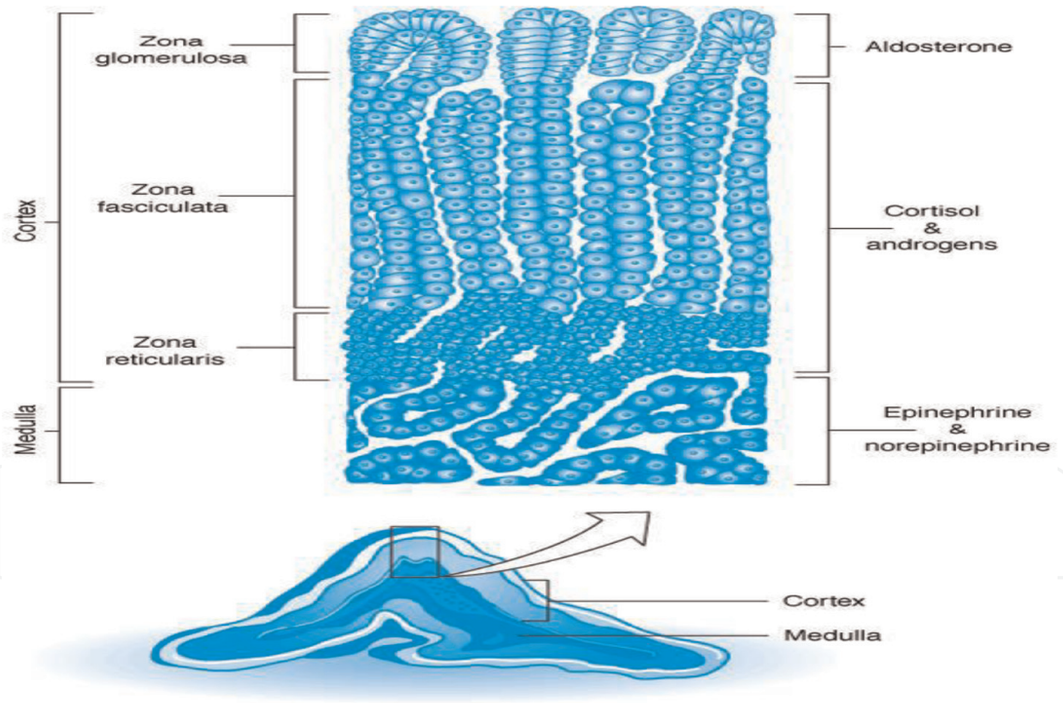


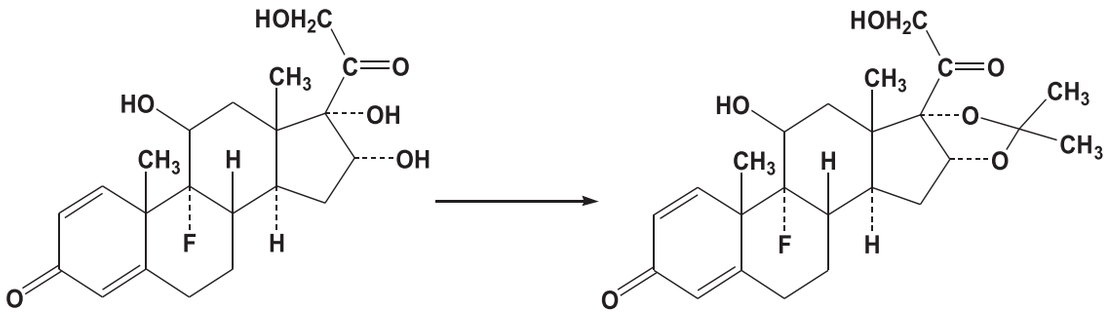
Figure 4.
Functional Anatomy and Zonation.

2.4 Glucocorticoids with very little or no salt retention

They include 16 α-hydroxy (Triamcinolone); 16 α-, 17 α-ketal; (Amcinolone, Desonide, Flunisolide, Triamcinolone acetonide, Flucinolone acetonide, Flurandrenolide) [2, 14–16, 23].

Common Name	Previous Form	Current Form	Gene
Cholesterol side-chain cleavage enzyme	$P450_{SCC}$	CYP11A1	*CYP11A1*
3β-Hydroxysteroid dehydrogenase	3β-HSD	3β-HSD II	*HSD3B2*
17α-Hydroxylase	$P450_{C17}$	CYP17	*CYP17*
21-Hydroxylase	$P450_{C21}$	CYP21A2	*CYP21A2*
11β-Hydroxylase	$P450_{C11}$	CYP11B1	*CYP11B1*
Aldosterone synthase	$P450_{C11AS}$	CYP11B2	*CYP11B2*

Figure 5.
Synthesis of the adrenal cortical hormones.



Triamcinolone — Triamcinolone Acetonide

Triamcinolone is converted to acetonide derivative (ketal) by reaction of acetone in the presence of strong acid. The latter is used only locally (topically) [2, 14–16].

They include also 6 α-methyl (methyl prednisolone); 16 α-methyl (Dexamethasone, Alclomethasone, Flumethasone) and 16 β-methyl (Betamethasone, Diflorasone, Paramethasone, Beclomethasone) [2, 3, 14–16, 23].

Other substituents have been found to significantly increase both glucocorticoid and mineralocorticoid activities: 1-ene; 2 α-methyl; 9 α-fluoro; 9 α-chloro; and 21-hydroxy [2, 3, 14–16].

In every case a 16-hydroxy or methyl (to eliminate salt retention) has been combined with another substituent to increase glucocorticoid or anti-inflammatory activity [2, 3, 14–16].

A primary goal of these highly anti-inflammatory drugs has been to increase topical potency [6, 7, 12].

2.5 Risk of systemic absorption

Except for fludrocortisones, the topical corticosteroids do not cause absorption effects when used on small areas of intact skin [6, 7, 12].

The adrenocortical steroids are contraindicated or should be used with great caution in patients having: [2, 3, 6–8, 10–12, 24, 25].

1. Peptic ulcer (in which the steroids may cause hemorrhage)

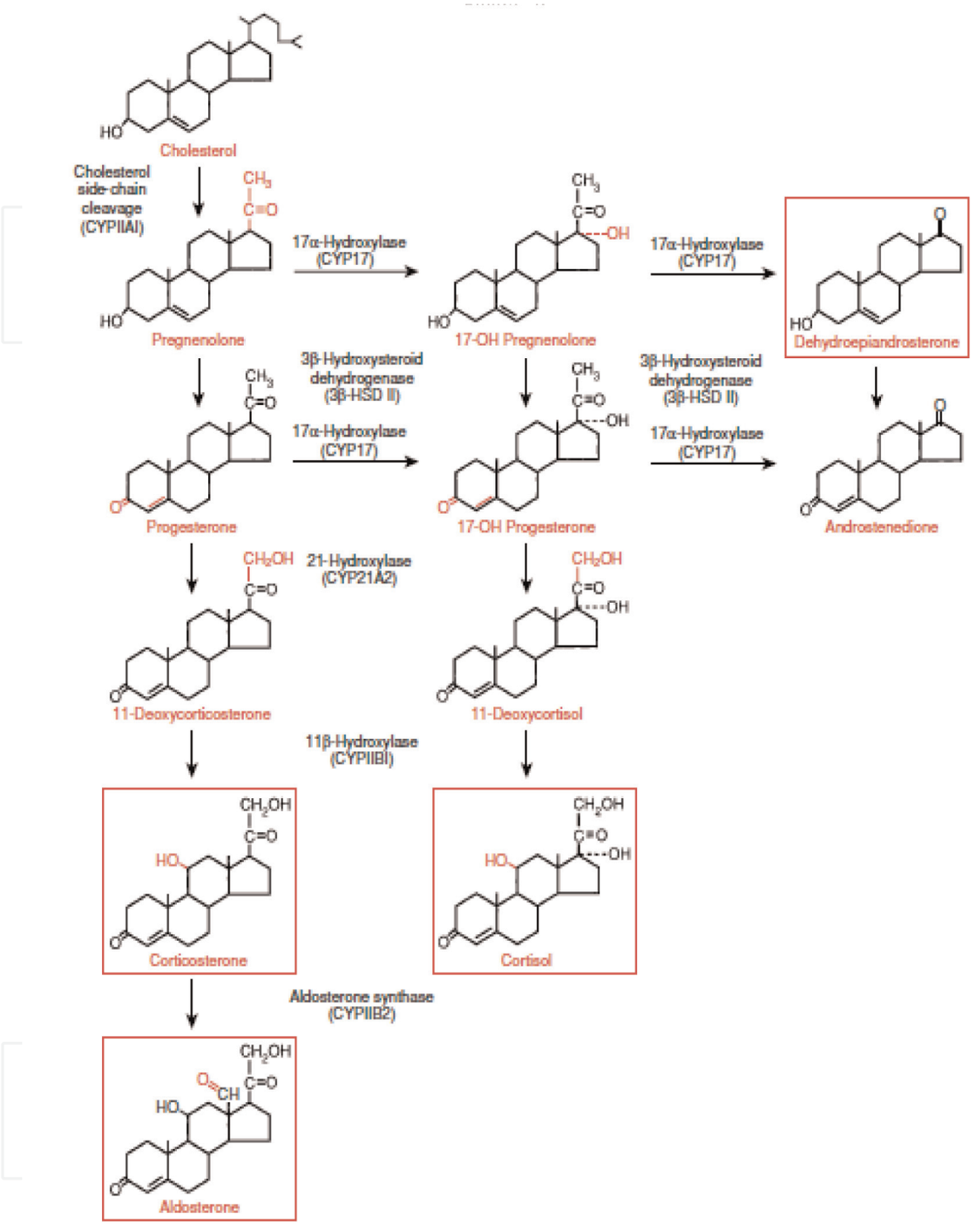


Figure 6.
The synthesis of steroids in the adrenal cortex.

2. Heart disease

3. Infections (the glucocorticoids suppress the body's normal infection-fighting processes)

4. Psychosis (since behavioral disturbances may occur during steroid therapy)

5. Diabetes (the glucocorticoids increase glucose production, so more insulin may be needed)

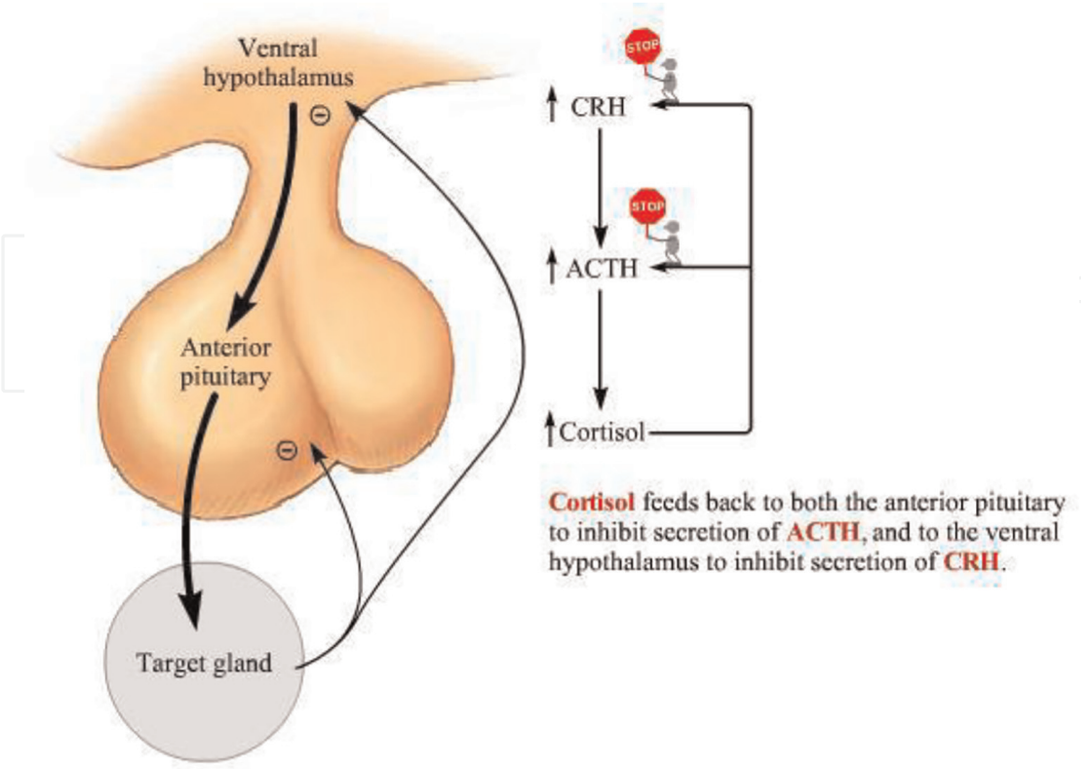


Figure 7.
Cortisol *feeds back to both the anterior pituitary to inhibit secretion of* ***ACTH****, and to the ventral hypothalamus to inhibit secretion of* ***CRH****.*

6. Glaucoma

7. Osteoporosis

8. Herpes simplex involving the cornea

When glucocorticoids are topically administrated, their anti-inflammatory action can mask symptoms of infection.

If absolutely necessary to use the glucocorticoids topically during pregnancy, they should be limited to small areas of intact skin and used for a limited time.

3. The adrenal glands

3.1 Introduction

Pyramid-shaped organs in pairs.

Placed on each kidney's upper poles.

3–5 cm in length on average, weighing 1.5–2.5 gm.

The outer cortex, which is composed primarily of mesodermal tissue and makes about 90% of the weight of the adrenals [26].

The inner medulla (derived from a subpopulation of neural crest).

The adrenal gland is made up of the cortex and medulla. The cortex produces steroid hormones including glucocorticoids, mineralocorticoids, and adrenal

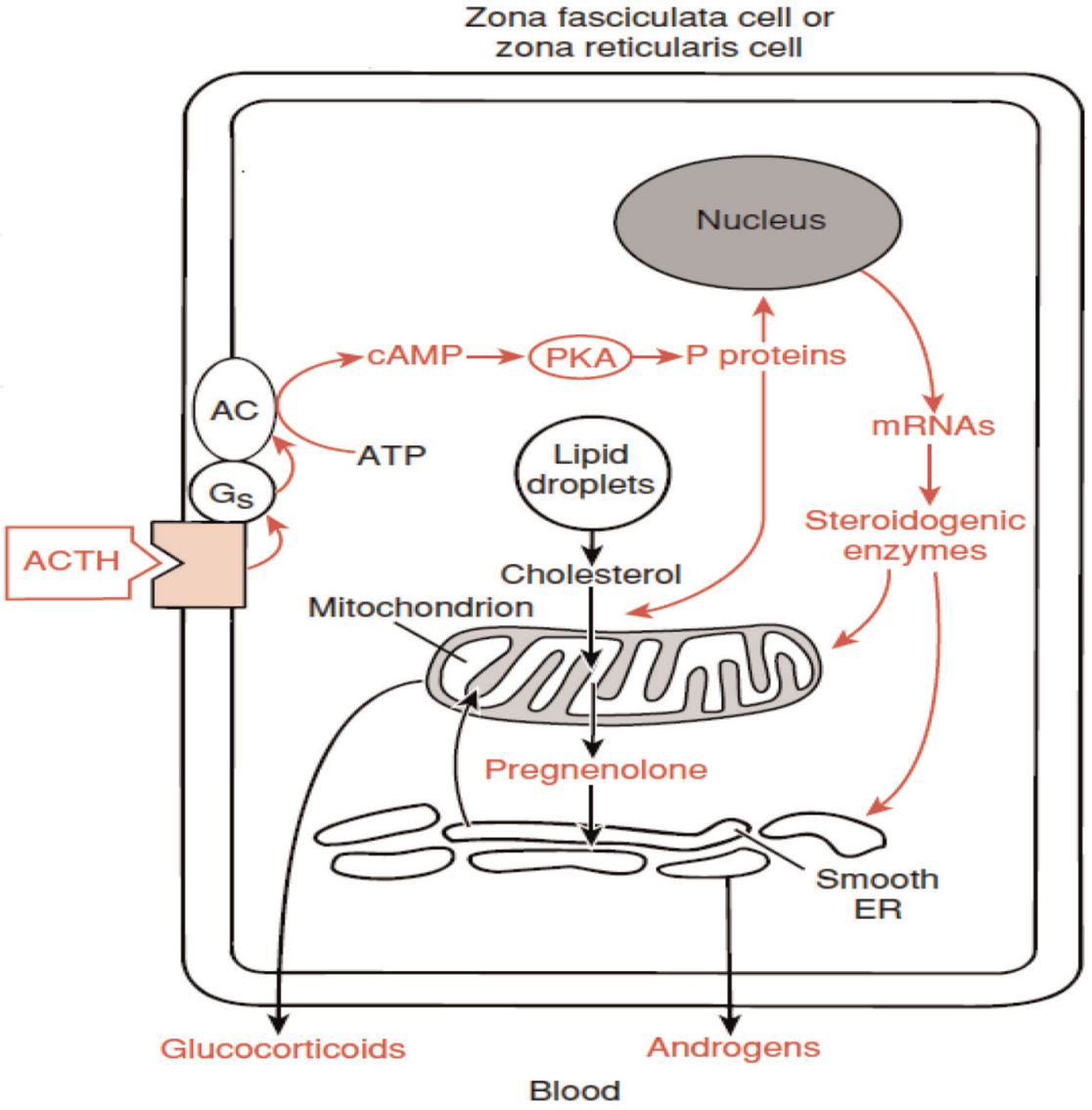


Figure 8.
ACTH's primary effects on steroidogenesis.

androgens, and the medulla produces the catecholamines, epinephrine, and norepinephrine [26].

The body's adaptive response to stress is regulated by the adrenal glands' role in maintaining homeostasis in maintaining the balance of Na and K in the body's water blood pressure regulation [26].

3.2 The main hormones

1. The hormones called steroid (glucocorticoids, mineralocorticoids, androgens).

2. Secondly, catecholamines (norepinephrine, epinephrine).

The two different embryologic origins of the AG have an impact on the mechanisms that each of the two components uses to regulate the production of hormones [17, 26].

DOI: http://dx.doi.org/10.5772/intechopen.106785

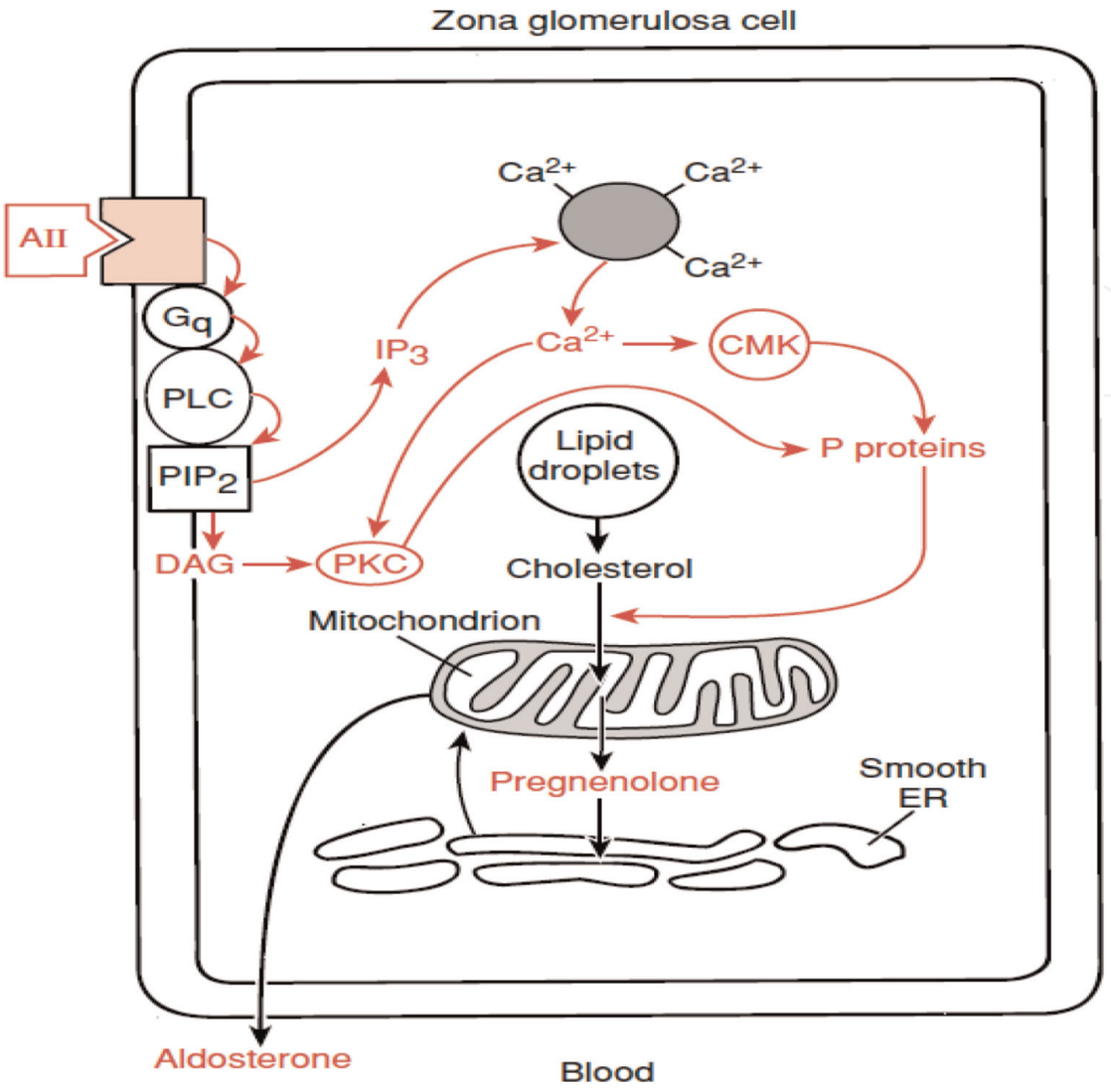


Figure 9.
The impact of angiotensin II on the production of aldosterone.

3.3 Functional Anatomy and Zonation

Three histologically distinct zones can be found in the adrenal cortex, arranged from outside to inside [27]:

- zona glomerulosa.
- zonafasciculata.
- zonareticularis.

The adrenal cortex secretes the following hormones:

- glucocorticoids.
- aldosterone.

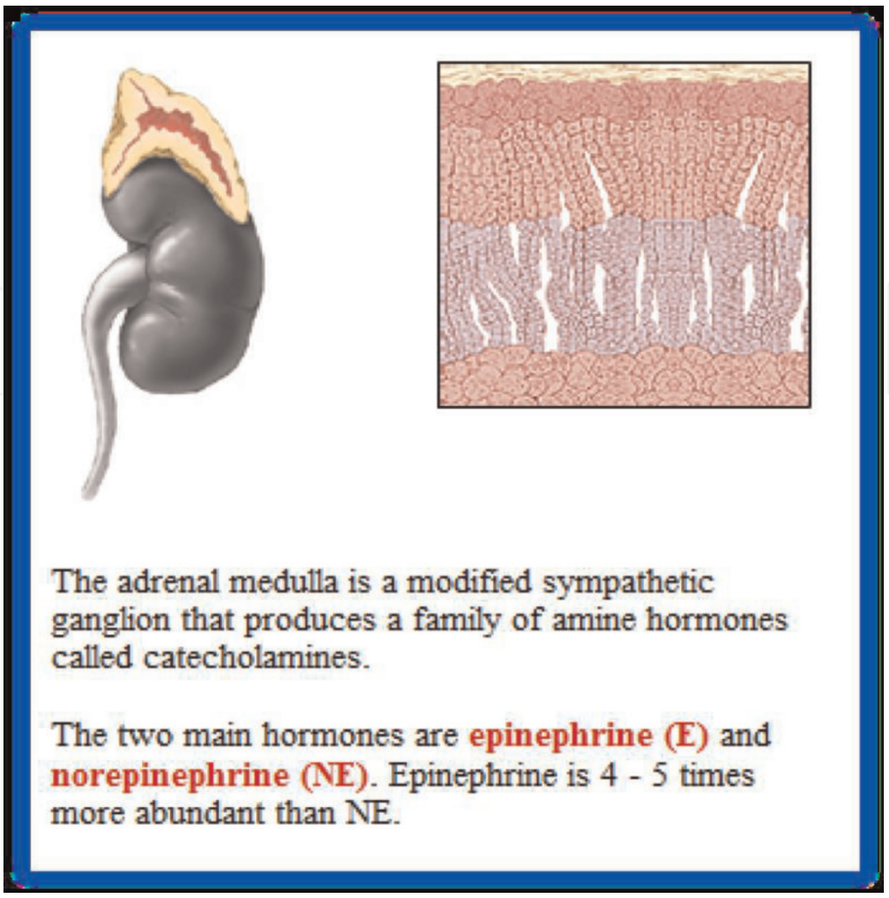


Figure 10.
The adrenal medulla is a modified sympathetic ganglion that produces a family of amine hormones called catecholamines. The two main hormones are epinephrine (E) and norepinephrine (NE). Epinephrine is 4-5 times more abundant than NE. The adrenal medulla [17, 18].

α-Adrenergic mediated	β-Adrenergic mediated
Vasoconstriction	Vasodilation
Iris dilation	Cardioacceleration
Intestinal relaxation	Increased myocardial strength
Intestinal sphincter contraction	Intestinal and bladder wall relaxation
Pilomotor contraction	Uterus relaxation
Bladder sphincter contraction	Bronchodilation
Bronchoconstriction	Calorigenesis
Uterine smooth muscle contraction	Glycogenolysis
Cardiac contractility	Lipolysis
Hepatic glucose production	

Figure 11.
Catecholamine physiologic effects [17, 18].

Liver	Stimulation of glycogenolysis
	Stimulation of gluconeogenesis
Skeletal muscle	Simulation of glycogenolysis
Adipose tissue	Simulation of glycogenolysis
	Stimulation of triglyceride lipolysis
Pancreatic islets	Inhibition of insulin secretion by beta cells
	Stimulation of glucagon secretion by alpha cells

Figure 12.
Catecholamine-Mediated Responses to Hypoglycemia [17, 18].

effect	epinephrine	norepinephrine
peripheral resistance	-	+++
systolic BP	++	+++
diastolic BP	0-	+++
cardiac output	++	-
vasodilation	-	0
glycogenolysis	+++	+
lipolysis	+++	+++
bronchodilation	++	0

Figure 13.
Effects of epinephrine vs. norepinephrine [17, 18]. "–" negative inhibitory effect; "+" positive stimulatory effect; and "0" no effect.

3.4 Zonation

The adrenal cortex's zonafasciculata and zonareticularis are where the glucocorticoids cortisol and corticosterone, as well as the androgen dehydroepiandrosterone, are synthesized [27].

The zonaglomerulosa of the adrenal cortex is where mineralocorticoid aldosterone is made [27].

3.5 Synthesis of the adrenal cortical hormones

Four CYP enzymes (cytochrome P450 enzymes = a large family of oxidative enzymes with a maximum 450 nm absorbance when complexed with carbon monoxide) convert cholesterol into adrenal steroid hormones [28]. Cholesterol esters stored in the cells are used to synthesize the adrenal cortical hormones. [28].

LDL particles in the blood are the main source of stored cholesterol, but the AG can also produce it entirely from scratch using acetate [28].

The first step in the synthesis of all adrenal steroids, which happens in each of the three zones of the cortex, is the conversion of cholesterol to pregnenolone in mitochondria. Enzymes that produce steroids [28].

3.6 Genetic defects in adrenal steroidogenesis

Can result in either relative or absolute deficiencies in the enzymes necessary for the biosynthesis of steroid hormones [29].

Changes in the types and quantities of steroid hormones secreted by the adrenal cortex are the direct results of these defects. In the end, disease results [29].

The majority of steroidogenic enzyme-related genetic flaws hinder cortisol production [29].

A decrease in blood cortisol levels prompts the release of ACTH, which has a growth-promoting effect on the adrenal cortex, causing either congenital adrenal hyperplasia or adrenal hypertrophy [29].

3.7 Transport of adrenal steroids in blood

A steroid hormone is prevented from being absorbed by cells or from being excreted in the urine by binding to a circulating protein molecule [18].

The blood is cleared of circulating steroid hormone molecules that are not bound to plasma proteins because they are free to interact with cell receptors [18].

Bound hormone separates from its binding protein and adds more free hormone to the system [18].

The half-lives of adrenal steroid hormones in the body are very long (from many minutes to hours) [18].

3.8 Metabolism of adrenal steroids

After being structurally altered to reduce their hormone activity and increase their water solubility, adrenal steroid hormones are primarily excreted from the body through the urine (primarily in the liver) [29]. Adrenal steroids are primarily metabolized in the liver where they are conjugated to glucuronic acid and eliminated in the urine [29].

3.9 Control over the production of adrenal steroids

By increasing intracellular cAMP, ACTH increases glucocorticoid and androgen synthesis in the zonafasciculata and zonareticularis of the adrenal cortex (cAMPactivates protein kinase A, which phosphorylates proteins that regulate steroidogenesis) [18].

On these cells, ACTH also has a trophic effect [18].

Angiotensin II increases cytosolic calcium and activates protein kinase C in the cells of the zonaglomerulosa to stimulate aldosterone synthesis [18].

ACTH's primary effects on steroidogenesis [18].

When ACTH binds to plasma membrane receptors, stimulatory G proteins connect those receptors to adenylyl cyclase (AC) (Gs).

Protein kinase A (PKA) is activated by cAMP in the cells, which phosphorylates specific proteins (PProteins). The expression of the genes for steroidogenic enzymes is stimulated and steroidogenesis is presumably started by these proteins.

The expression of the genes for steroidogenic enzymes is stimulated and steroidogenesis is presumably started by these proteins [18].

The impact of angiotensin II on the production of aldosterone [18].

Angiotensin II (AII) binds to receptors on the plasma membrane of zonaglomerulosa cells. Phospholipase C (PLC), which is connected to the angiotensin II receptor by G proteins, is activated as a result (Gq) [18].

In the plasma, PLC hydrolyzes phosphatidylinositol 4,5 bisphosphate (PIP2) membrane, resulting in the production of IP3 and diacylglycerol (DAG) [18].

3.10 Intracellularly bound Ca2 is moved by IP3

Protein kinase C (PKC) and calmodulin-dependent protein kinase are both activated by an increase in Ca2 and DAG (CMK) [18]. These enzymes phosphorylate the proteins (P-Proteins) that start the synthesis of aldosterone [18].

4. Process of action

Target cells' cytosol contains glucocorticoid receptors, which glucocorticoids bind to [18]. The glucocorticoid-bound receptor moves to the nucleus where it attaches to DNA glucocorticoid response elements to alter the transcription of particular genes. [18]. The body must have access to glucocorticoids in order to adjust to stress, injury, and fasting [18].

Glucocorticoids

Very powerful and responsible for about 95% of all glucocorticoid activity is cortisol [18].

About 4% of the total glucocorticoid activity is provided by corticosterone, which is significantly less potent than cortisol [18].

Cortisone, which is nearly as potent as cortisol [18].

Synthetic, four times as potent as cortisol, prednisone [18].

Synthetic methylprednisone, which has five times the potency of cortisol [18] (Synthetic, 30 times more potent than cortisol) Dexamethasone [18].

Glucocorticoids' effects [18].

Catabolic, anti-anabolic, and diabetogenic effects on metabolism.

Glucocorticoids' Anti-Inflammatory Properties.

The Immune System's Impact.

Protection of the Norepinephrine-Induced Vascular Response.

Stress Glucocorticoids.

Glucocorticoid Secretion Control.

Glucocorticoids Are Involved in the Responses to Injury, Stress, and Fasting [18].

Effects of cortisol on the metabolism of carbohydrates: [18]

Stimulation of Gluconeogenesis - Cortisol increases the enzymes needed in the liver cells to convert amino acids into glucose [18].

Cortisol causes the extrahepatic tissues, primarily muscle, to release amino acids [18].

Cells' Utilization of Glucose is Reduced [18].

"Adrenal Diabetes" and Increased Blood Glucose Concentration [18].

Cortisol's Impact on Protein Metabolism [18].

Protein Cellular Reductionin.

Plasma and Liver Protein Levels are Raised by Cortisol a rise in blood amino acids, a decline in amino acid transport into extrahepatic cells, and an improvement in transport into hepatic cells.

Cortisol's Impact on Fat Metabolism [18].

Mobilization of Fatty Acids Excess Cortisol Leads to Obesity.

Cortisol Helps the Body Fight Stress and Inflammation.

Effects of High Cortisol Levels on Inflammation.

Cortisol Prevents the Development of Inflammation through Other Effects and Lysosome Stabilization.

Cortisol Leads to Inflammation Healing.

The Inflammatory Response to Allergic Reactions is Blocked by Cortisol.

Effects of cortisol in reducing inflammation.

The lysosomal membranes are stabilized by cortisol.

Capillary permeability is lessened by cortisol.

White blood cell migration into the inflamed area and phagocytosis of the aged cells are both decreased by cortisol.

Cortisol significantly reduces lymphocyte production by suppressing the immune system.

Cortisol reduces interleukin-1 release from white blood cells, which is the primary mechanism by which it lowers fever.

Mineralocorticoids [18].

Aldosterone (very potent, accounts for about 90 percent of all mineralocorticoid activity).

Deoxycorticosterone (1/30 as powerful as aldosterone, but secreted in very small amounts).

Corticosterone (slight mineralocorticoid activity).

9α-Fluorocortisol (synthetic, slightly more potent than aldosterone).

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

Cortisone (slight mineralocorticoid activity).

Mineralocorticoids' effects [18].

Aldosterone stimulates sodium reabsorption in the kidneys by the distal tubule and collecting duct of the nephron and promotes the excretion of potassium and hydrogen ions, according to its physiological action.

Since potassium directly affects zona glomerulosa cells, an increase in the concentration of potassium in extracellular fluid stimulates aldosterone secretion.

Aldosterone Secretion Control.

The extracellular fluid's increased potassium ion concentration significantly boosts aldosterone secretion.

Aldosterone secretion is also significantly increased by an increase in the extracellular fluid's angiotensin II concentration.

Aldosterone secretion is very slightly reduced when the extracellular fluid's sodium ion concentration rises.

Aldosterone secretion requires ACTH from the anterior pituitary gland, but it has little impact on regulating the rate of secretion in most.

The catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline).

Four adrenergic receptors (alpha 1, 2, beta 1, 2) interact with catecholamines to mediate the effects of the hormones on cells.

Catecholamines have immediate and extensive effects.

DOI: http://dx.doi.org/10.5772/intechopen.106785

Catecholamines are released from the chromaffin cells as a result of impulses generated in the cholinergic preganglionic fibers that innervate them by stimuli like injury, rage, pain, cold, strenuous exercise, and hypoglycemia.

Catecholamines promote the production of glucose in the liver, the release of lactate from muscle, and the breakdown of fat in adipose tissue to combat hypoglycemia.

5. Conclusion

The body's defense mechanisms depend heavily on the adrenal glands.

They trigger physiological adjustments that are required to combat changes in the environment outside the body. They also secrete a number of vital hormones that are crucial for maintaining a healthy immune system, metabolic rate, and salt and water balance in the body. Additionally protecting the body from stress. High levels of glucocorticosteroid production in response to stress can result in a 95 percent reduction in thymus gland size. It has not yet been completely determined how glucocorticoid stimulation protects against stress.

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