The Adrenal Medulla & Adrenal Cortex

20

First Part

OBJECTIVES

After reading this chapter, you should be able to:

- Name the three catecholamines secreted by the adrenal medulla and summarize their biosynthesis, metabolism, and function.
- List the stimuli that increase adrenal medullary secretion.
- Differentiate between C_{18}, C_{19}, and C_{21} steroids and give examples of each.
- Outline the steps involved in steroid biosynthesis in the adrenal cortex.
- Name the plasma proteins that bind adrenocortical steroids and discuss their physiologic role.
- Name the major site of adrenocortical hormone metabolism and the principal metabolites produced from glucocorticoids, adrenal androgens, and aldosterone.
- Describe the mechanisms by which glucocorticoids and aldosterone produce changes in cellular function.
- List and briefly describe the physiologic and pharmacologic effects of glucocorticoids.
- Contrast the physiologic and pathologic effects of adrenal androgens.
- Describe the mechanisms that regulate secretion of glucocorticoids and adrenal sex hormones.
- List the actions of aldosterone and describe the mechanisms that regulate aldosterone secretion.
- Describe the main features of the diseases caused by excess or deficiency of each of the hormones of the adrenal gland.

The Adrenal Medulla & Adrenal Cortex	• adrenal medulla: structure & function of medullary hormones • regulation of adrenal medullary secretion • adrenal cortex: structure & biosynthesis of adrenocortical hormones • transport, metabolism, & excretion of adrenocortical hormones • effects of adrenal androgens & estrogens • physiologic effects of glucocorticoids • pharmacologic & pathologic effects of glucocorticoids • regulation of glucocorticoid secretion • effects of mineralocorticoids • regulation of aldosterone secretion • role of mineralocorticoids in the regulation of salt balance

- **Adrenal endocrine organs**: The **medulla** and the **cortex** (one surrounding the other)
- The **inner** adrenal **medulla**: Mainly secretes **catecholamines epinephrine**, **norepinephrine**, and **dopamine**
- **The outer adrenal cortex**: Mainly secretes **steroid** hormones which are:
  1. **Glucocorticoids**: Widespread effects on the **metabolism** of **carbohydrate** and **protein**
  2. **Mineralocorticoids**: essential to the **maintenance** of **Na+ balance** and extracellular fluid (**ECF**) volume.
  3. **Androgens** (as secondary site): **Sex hormones** such as **testosterone**, which can exert effects on **reproductive** function.
- **Mineralocorticoids** and the **glucocorticoids** are **necessary** for **survival**

- Adrenal medulla (28% of adrenal mass) compose of
  1. Epinephrine secreting cells (90%)
  2. Norepinephrine secreting cells (10%)

- Adrenal cortex (72% of adrenal mass) compose of:
  1. Zona **glomerulosa** (secrete **aldosterone** and little cortisol and androgens)
  2. Zona **fasciculata** (secrete **cortisol** and little androgens)
  3. Zona **reticularis** (secrete **androgens** and little cortisol)
- All the 3 zones secrete corticosterone **BUT** only the **grlomerulosa** contain **enzymatic** mechanism for **aldosterone** biosynthesis)

The Adrenal Medulla & Adrenal Cortex

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 and 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. Mineralocorticoids and the glucocorticoids are necessary for survival.

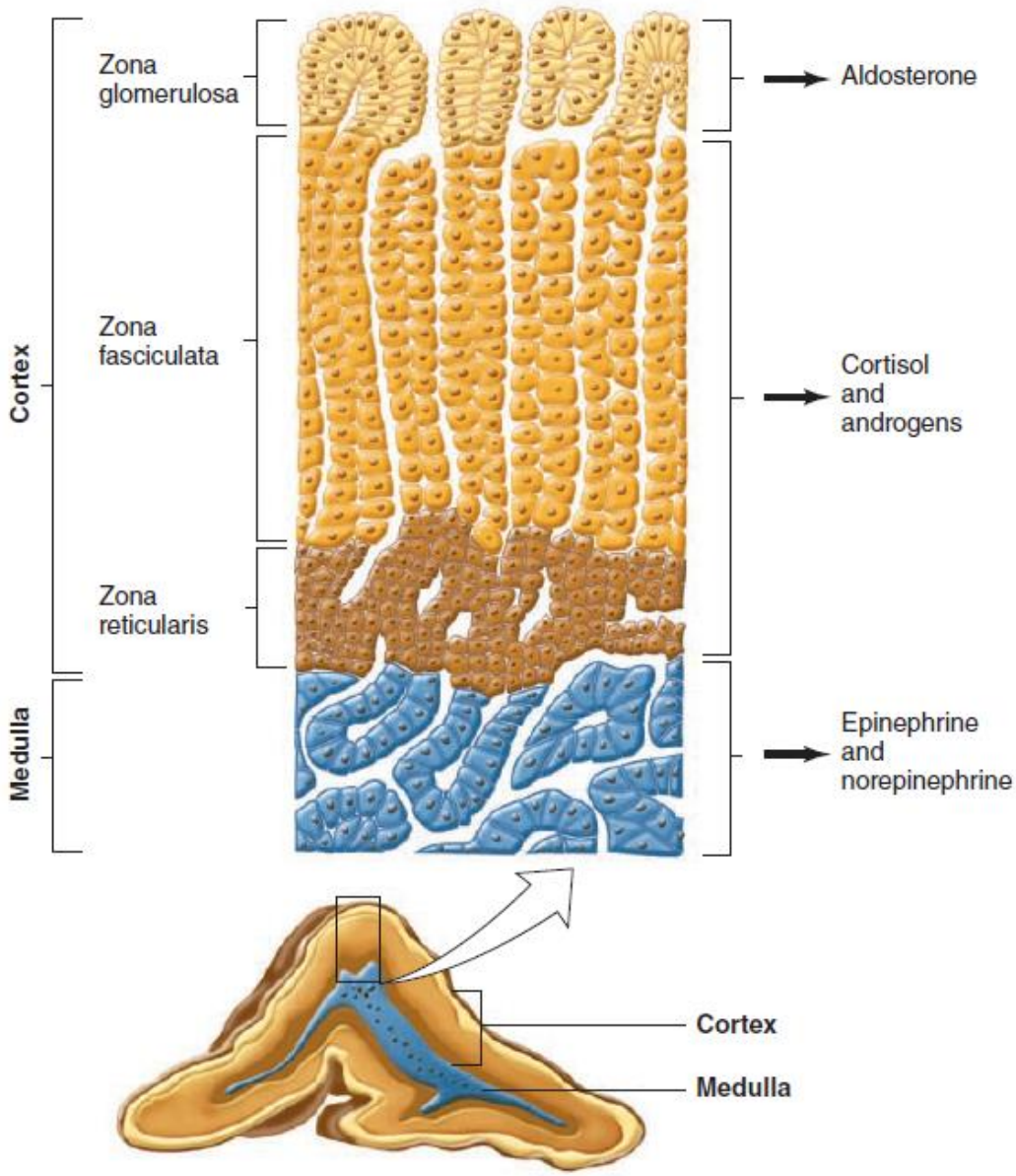
ADRENAL MORPHOLOGY

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 and 10% are the norepinephrine-secreting type.

In adult mammals, the adrenal cortex is divided into three zones (Figure). The outer **zona glomerulosa** then the **zona fasciculata**, and the **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.


Cortex
Medulla
Zona glomerulosa
Zona fasciculata
Zona reticularis
Aldosterone
Cortisol and androgens
Epinephrine and norepinephrine
Cortex
Medulla

ADRENAL MEDULLA: STRUCTURE & FUNCTION OF MEDULLARY HORMONES

- Norepinephrine, epinephrine & dopamine are synthesized by adrenal medulla
- All are synthesized from tyrosine
- Tyrosine hydroxylation and decarboxylation give norepinephrine
- Norepinephrine methylation give epinephrine
- Metabolism: by sulfate conjugation in liver (inactive)
- Dopamine 95% conjugated
- Norepinephrine & epinephrine 70% are conjugated
- All have a half-life in circulation ~ 2min

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.

EFFECTS OF DOPAMINE

- The physiologic **function** in the **circulation** is **unknown**.
- **On renal vessels**: via specific dopaminergic receptors it produce renal **vasodilation**
- **On other blood vessels**: via releasing norepinephrine it produce **vasoconstriction**
- **On heart**: via β1- adrenergic receptors it produce **positive inotropic** effect
- **On renal tubules**: local release of dopamine by renal cortex causes **natriuresis** and may exert this effect by **inhibiting** renal **Na, K, ATPase**.

EFFECTS OF EPINEPHRINE & NOREPINEPHRINE

EFFECTS OF EPINEPHRINE & NOREPINEPHRINE

- **Metabolic effects**: α- and β-adrenergic receptor actions
  1. **Glycogenolysis** in liver and skeletal muscle
  2. **Mobilization** of free fatty acids (**FFA**)
  3. Increased **plasma lactate**
  4. **Stimulation** of the **metabolic rate**

Action on insulin and glucagon:

- Via **β-adrenergic** stimulation: **increase insulin** and **glucagon** secretion
- Via **α-adrenergic** stimulation: **Inhibit insulin** and **glucagon** secretion

Action on heart:

- Via **β1-receptor** activation: **Both increase** the **force** and **rate** of contraction of the **isolated heart**.

Action on blood vessels:

- **Norepinephrine** produces **vasoconstriction** in most if not all organs via **α1-receptors**
- **Epinephrine dilates** the blood vessels in skeletal muscle and the liver via **β2-receptors**.

- Certain **drugs** act **directly** on **adrenal medulla** to change catecholamine secretion
- **Physiologic stimuli** affect adrenal medulla **indirectly** by stimulation of **nervous system** (sympathetic autonomic division)
- **During basal states**: the **secretion is low**
- **During sleep**: the secretion is **reduced** to **lesser extent**
- **Emergency situations (Emergency function of sympathoadrenal system) provoke sympathetic discharge** to prepare an individual for **Fight** or **Flight in part** by **increase adrenal medullary secretion**

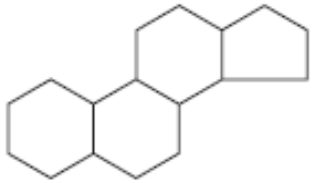
REGULATION OF ADRENAL MEDULLARY SECRETION

NEURAL CONTROL

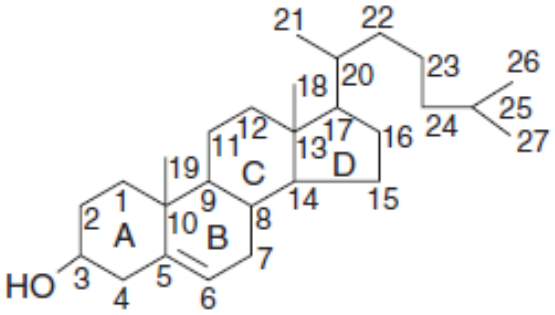
Certain drugs act directly on the adrenal medulla, but physiologic stimuli affect medullary secretion through the nervous system. Catecholamine secretion is low in basal states, but the secretion of epinephrine and, to a lesser extent, that of norepinephrine is reduced even further during sleep.

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." This discharge prepares the individual for flight or fight

- Adrenal cortex hormones are derivatives of **cholesterol (27 C)**
- **Contain Cyclopenanoperhydrophenanthrene nucleus (17 C)**



Cyclopentanoperhydrophenanthrene nucleus



Significantly secreted steroids of adrenal cortex hormones

- **Aldosterone** (**mineralocorticoid**)
- **Cortisol** and corticosterone (**glucocorticoids**)
- **DHEA** and androstenedione (**androgens**)
- **Deoxycorticosterone** (**mineralocorticoid**) has only 3% of aldosterone activity (BUT with the same secretion amount)

ADRENAL CORTEX: STRUCTURE & BIOSYNTHESIS OF ADRENOCORTICAL HORMONES

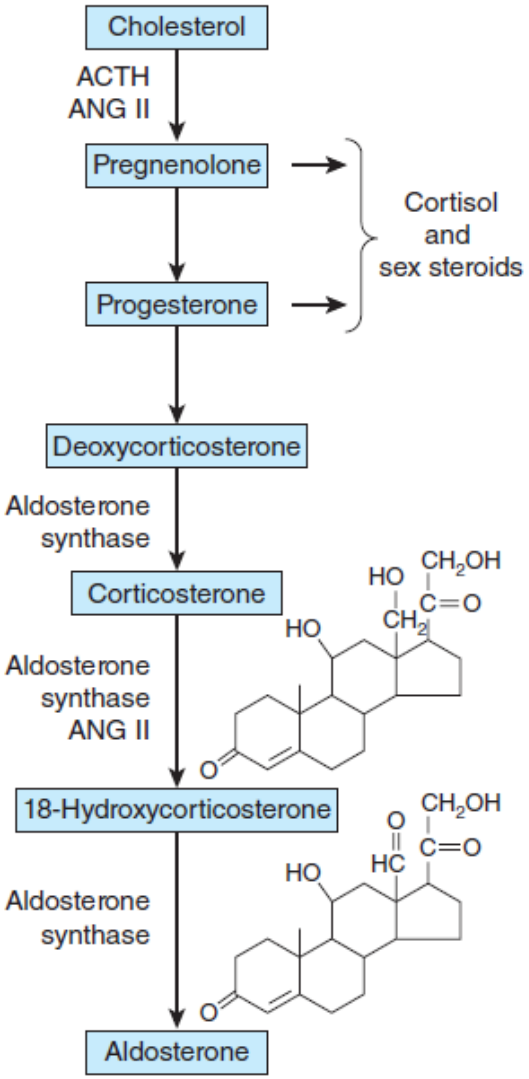
CLASSIFICATION & STRUCTURE

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** (Figure).

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.



Hormone synthesis in the zona glomerulosa. The zona glomerulosa lacks 17α-hydroxylase activity, and only the zona glomerulosa can convert corticosterone to aldosterone because it is the only zone that normally contains aldosterone synthase. ANG II, angiotensin II.

- **Precursor**: newly synthesized or esterified LDL- cholesterol
- **First step: LDL is taken up by adrenal cells**
- **Next step:** the **esterified** LDL-cholesterol is **freeing** by **cholesterol ester hydrolase**
- **Next step** : free cholesterol is **transported** by a **carrier** protein into the **mitochondria**
- **Next step :** cholesterol is converted to **pregnenolone**
- **Next step : Some of pregnenolone is converted into** progesterone

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 droplets in the circulation.

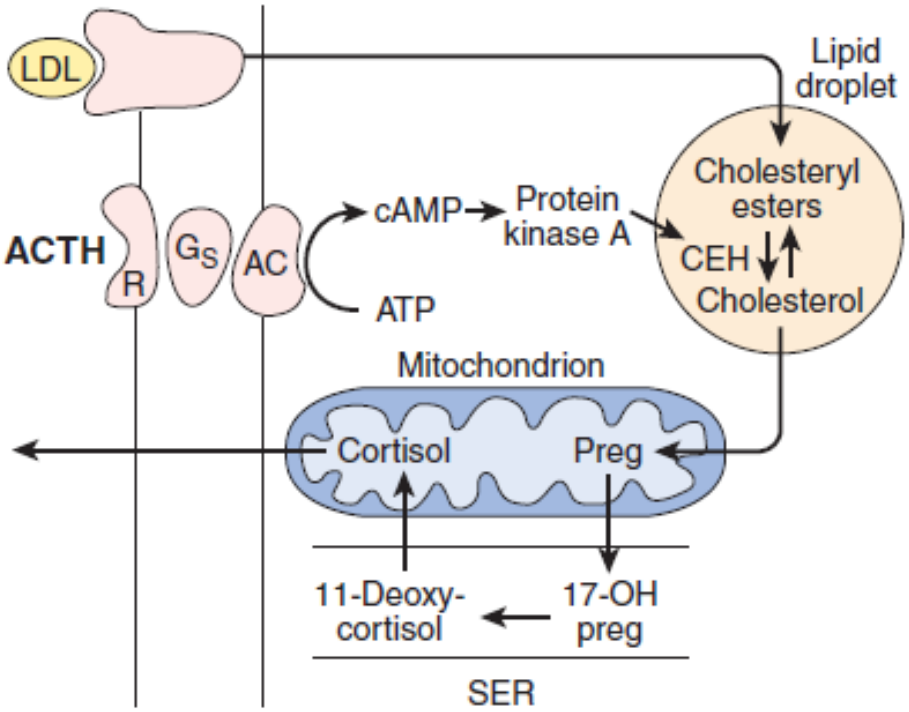
Cholesterol ester hydrolase catalyzes the formation of free cholesterol in the lipid droplets . The cholesterol is transported to mitochondria by a sterol carrier protein. In the mitochondria, it is converted to pregnenolone

Pregnenolone moves to the smooth endoplasmic reticulum, where some of it is dehydrogenated to form progesterone

- **ACTH receptors:** membrane bound **stimulatory GPCR** linked to **cAMP system**
- **cAMP enhance cholesterol ester hydrolysis** in lipid droplets and thus **increase pregnenolone** formation
- **On long period** of stimulation ACTH **increases P450** synthesis involved in **glucocorticoid synthesis**

ACTION OF ACTH

ACTH binds to high-affinity receptors on the plasma membrane of adrenocortical cells. This activates adenylyl cyclase via G_s. 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.



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

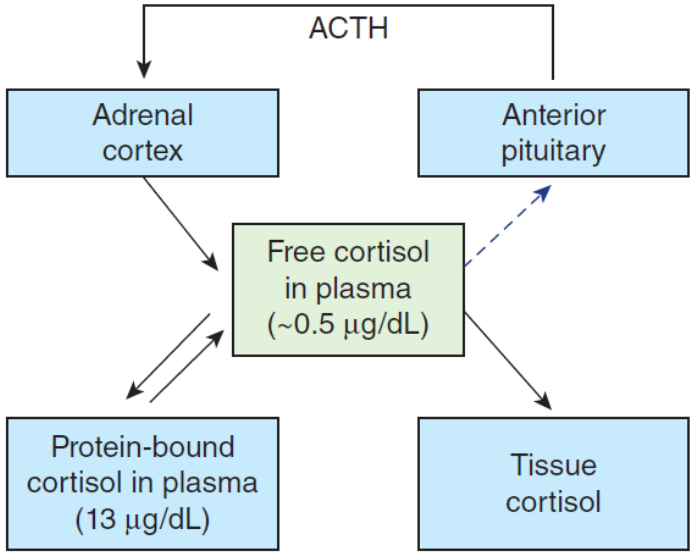
GLUCOCORTICOID BINDING

- **CGB:** Corticosteroid-binding globulin (also called **Transcortin**)
- **CGB synthesized by liver**
- Level **increase** during **pregnancy** (by **estrogen**)
- Level **decreased** by liver **cirrhosis**, **nephrosis** and **multiple myeloma** (B lymphocyte tumor)
- **When** CBG level increase; sequential effects involve
  - ✓ **More cortisol** is **bound**, **then**
  - ✓ Initial **fall** in **free cortisol**, **then**
  - ✓ **Stimulate ACTH** secretion, **then**
  - ✓ **More cortisol** is **secreted**
- **When** CBG kevel decrease; the opposite direction occurs

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



- **Site of metabolism of glucocorticoids** : Liver
- **Metabolic pathway**: Reduction and conjugation
- **Cortisol**: reduced to dihydrocortisol and THEN to tetrahydrocortisol

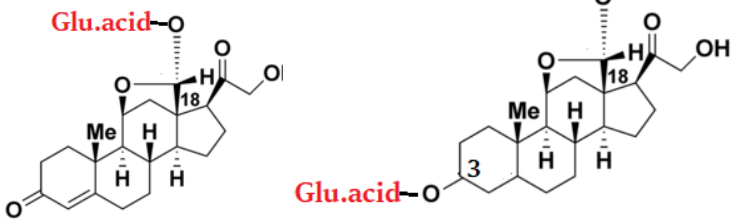
- **Cortisone**: **active** glucocorticoid because it is **converted** to **cortisol**
- **Secreted** in **small** amount by **adrenal** gland (not appreciable quantities)
- **Reduced** to **tetrahydrcortisone** and then **conjugated** with **glucuronides** (Thus little if any enter the circulation)

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 glucuronide.

- **Aldosterone** plasma protein binding is **slight** (t/2= **20min**)
- Amount secreted is compared to cortisol
- small (free + bound)
- Metabolic site: liver
- Metabolic pathway:
- reduction to tetrahydroaldosteron and subsequent glucuronide conjugation
- Some changed in the liver and kidney to 18-glucuronide



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 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.

Adrenal androgens

Dehydroepiandrostenedione "DHEA"

Chemistry: 17-ketosteroid

Source adrenal cortex and testes

- 2/3 amount from adrenal Cortisol and Cortisone by hepatic side cleavage to DHEA
- 1/3 amount from testicular testosterone by hepatic conversion

Secretion rate:

- 15mg/day in man
- 10mg/day in woman

Excretion: urine

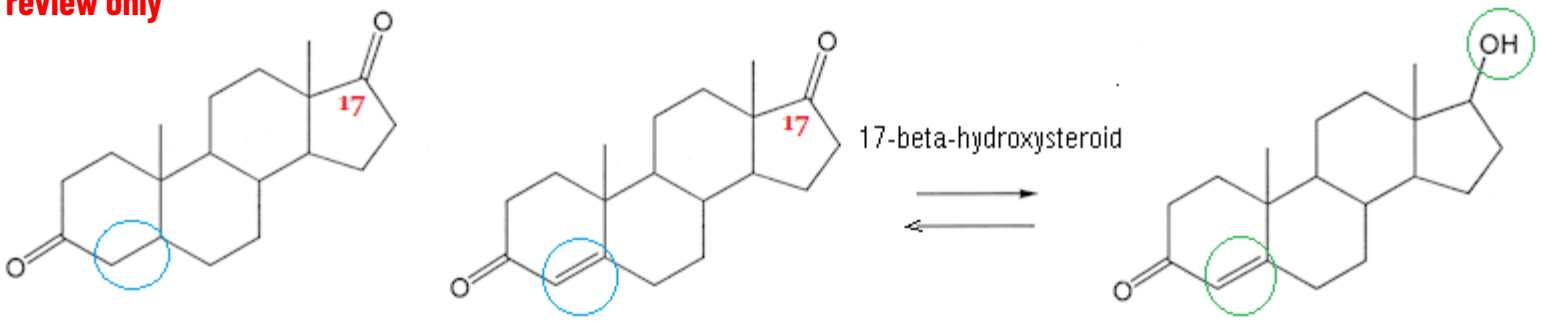
Note: DHEA is the major 17-ketosteroid although androstenedione is also secreted

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.

For review only



DHEA Androstenedione Testosterone