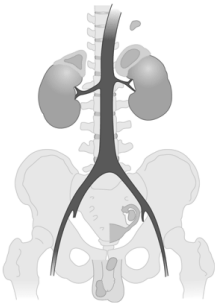
ENDOCRINOLOGY

ADRENAL CORTEX MINERALCORTICOIDS



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OBJECTIVES

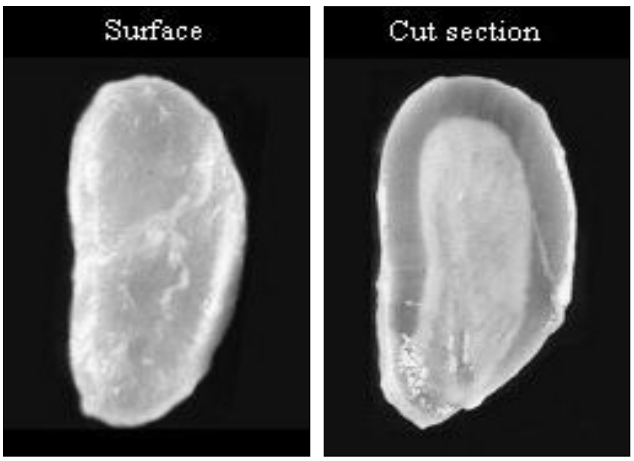
At the end of this lecture you should be able to:

- Identify and describe the structure of adrenal cortex consisting o f the zona glomerulosa, zona fasciculate and zona reticularis and list the adrenal corticoid hormones secreted by zones.
- Characterize the chemical nature of the hormones.
- Identify and describe the mineralocorticoids and the effects of aldosterone on renal functions, body fluid and cardiovascular dynamics and also sweat and salivary glands and intestinal absorption.
- Describe how Aldosterone Increases Renal Tubular Reabsorption of Sodium and Secretion of Potassium.
- Identify and describe the control of secretion of aldosterone.
- Describe clinical correlates of Addison's diseases and Conn's syndrome.

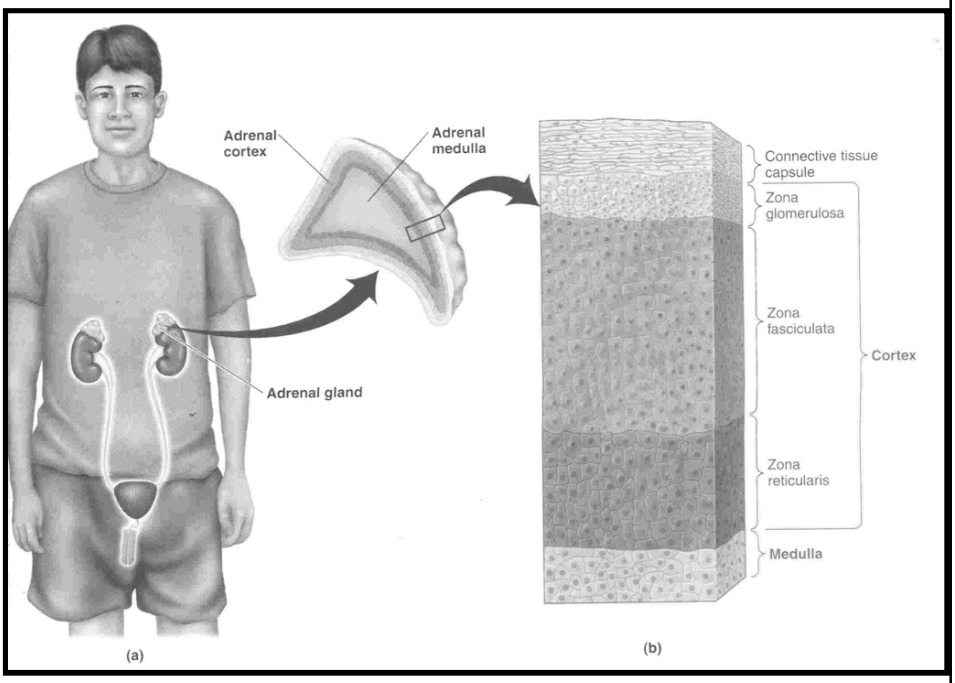
Adrenal Glands

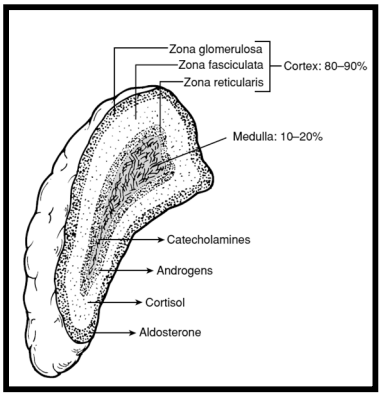
- Paired organs that cap the kidneys.
- Each gland consists of an outer cortex and inner medulla.
- Adrenal medulla:
  - Derived from embryonic neural crest ectoderm (same tissue that produces the sympathetic ganglia).
  - Synthesizes and secretes:
    - Catecholamines (mainly Epi but some NE).

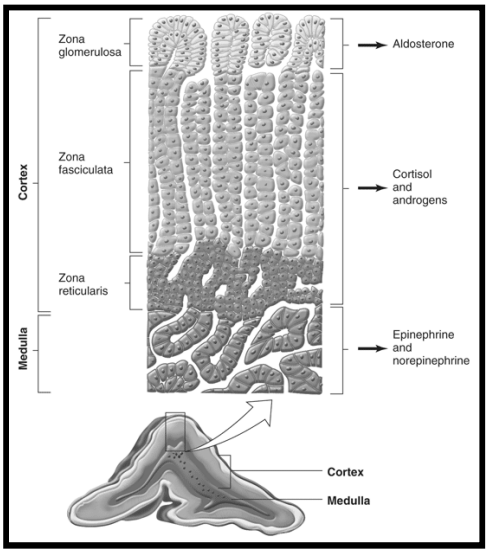
ADRENALS



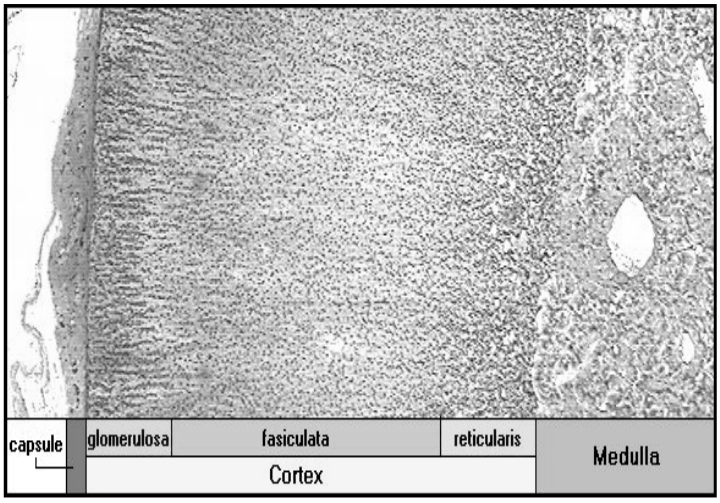
4 cm long, 3 cm wide, 4 to 6 g


Adrenal cortex
Adrenal medulla
Adrenal gland
Connective tissue capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Cortex
Medulla
(a)
(b)


Zona glomerulosa
Zona fasciculata
Zona reticularis
Cortex: 80–90%
Medulla: 10–20%
Catecholamines
Androgens
Cortisol
Aldosterone

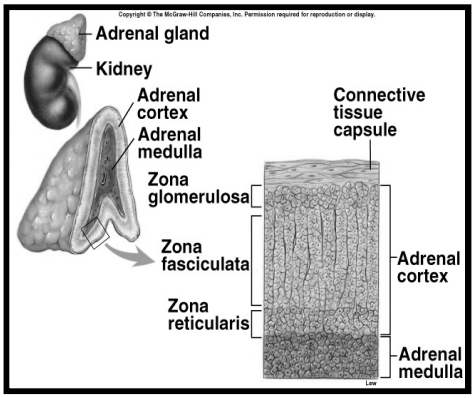

Zona glomerulosa
Zona fasciculata
Zona reticularis
Cortex
Medulla
Aldosterone
Cortisol and androgens
Epinephrine and norepinephrine
Cortex
Medulla

HISTOLOGY



Adrenal Glands (continued)

- **Adrenal cortex:**
  - **Does not receive neural innervation.**
  - **Must be stimulated hormonally (ACTH).**
- **Consists of 3 zones:**
  - **Zona glomerulosa.**
  - **Zona fasciculata.**
  - **Zona reticularis.**
- **Secretes corticosteroids.**



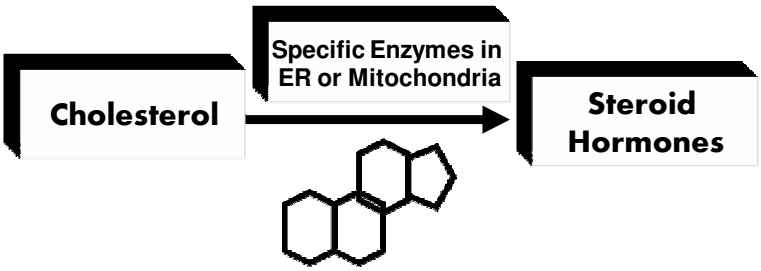
Functions of the Adrenal Cortex

- **Zona glomerulosa:**
  - **Mineralcorticoids (aldosterone):**
    - **Stimulate kidneys to reabsorb Na^+ and secrete K^+.**
- **Zona fasciculata:**
  - **Glucocorticoids (cortisol):**
    - **Inhibit glucose utilization and stimulate gluconeogenesis.**
- **Zona reticularis**
  (Dehydroepiandrosterone: DHEA):
  - **Sex steroids:**
    - **Supplement sex steroids.**

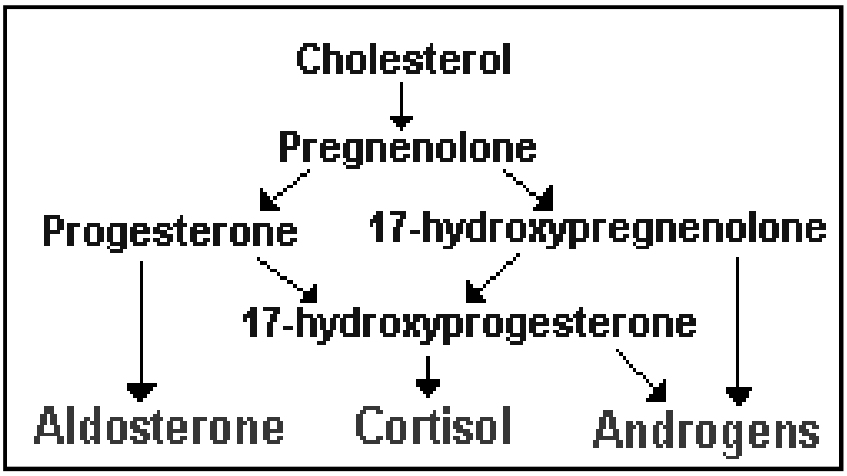
DIFFERENCES

	CORTEX	MEDULLA
Percent Mass	80 %	20 %
Origin	Mesoderm	Ectoderm (neural crest)
Regeneration Capacity	Yes	No
Zones	3 concentric zones	Chromaffin cell
Hormones	Glucocorticoids Mineralocoricoids	Ep and NE
Organelles	Large Smooth ER	Relatively Smaller

SYNTHESIS OF STEROIDS



TWO TO THREE DOZEN



Pregnenolone itself is not a hormone, but is the immediate precursor for the synthesis of all of the steroid hormones

Common name	"Old" name	Current name
Side-chain cleavage enzyme; desmolase	$P450_{SCC}$	CYP11A1
3 beta-hydroxysteroid dehydrogenase	3 beta-HSD	3 beta-HSD
17 alpha-hydroxylase/17,20 lyase	$P450_{C17}$	CYP17
21-hydroxylase	$P450_{C21}$	CYP21A2
11 beta-hydroxylase	$P450_{C11}$	CYP11B1
Aldosterone synthase	$P450_{C11AS}$	CYP11B2
Aromatase	$P450_{aro}$	CYP19

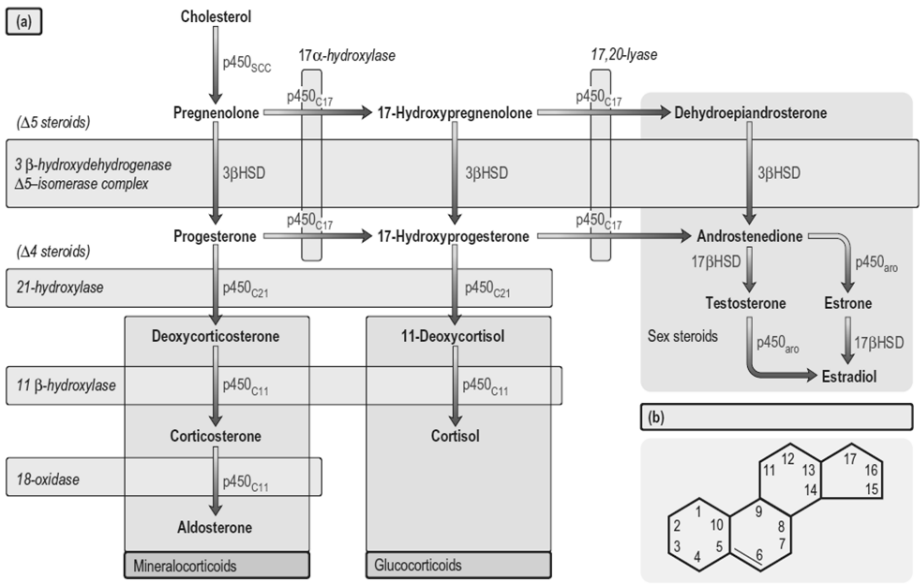
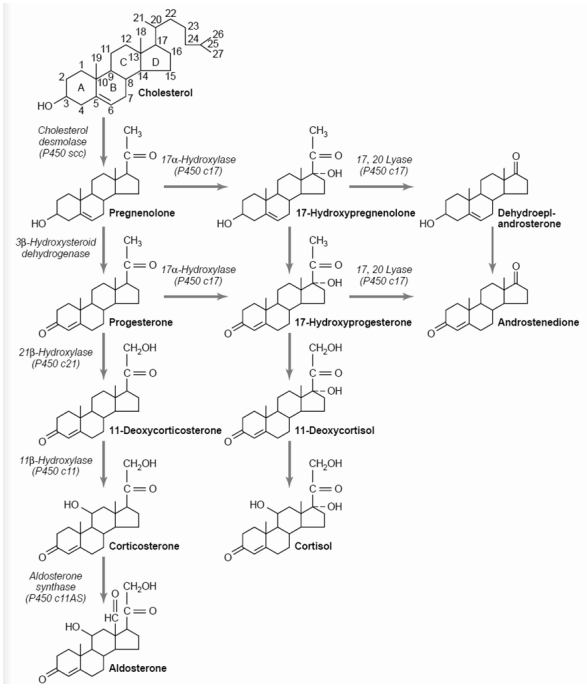
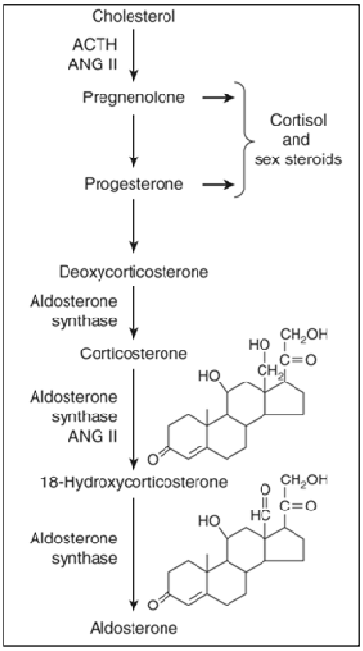
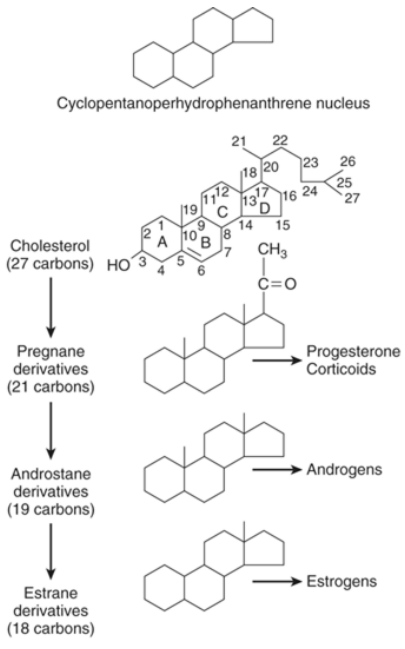
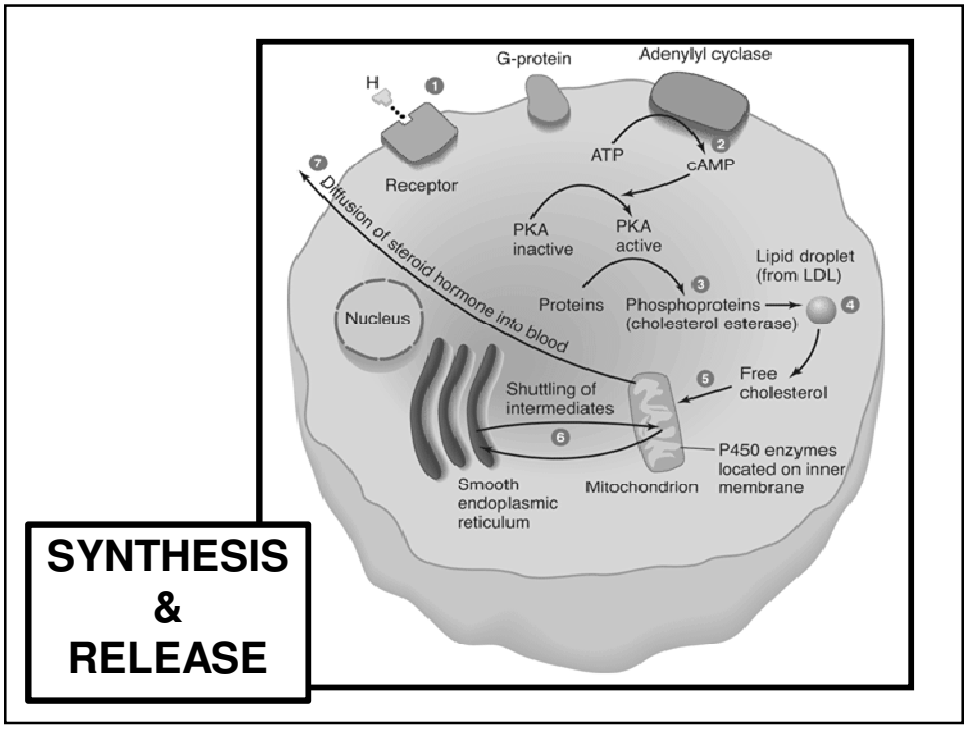


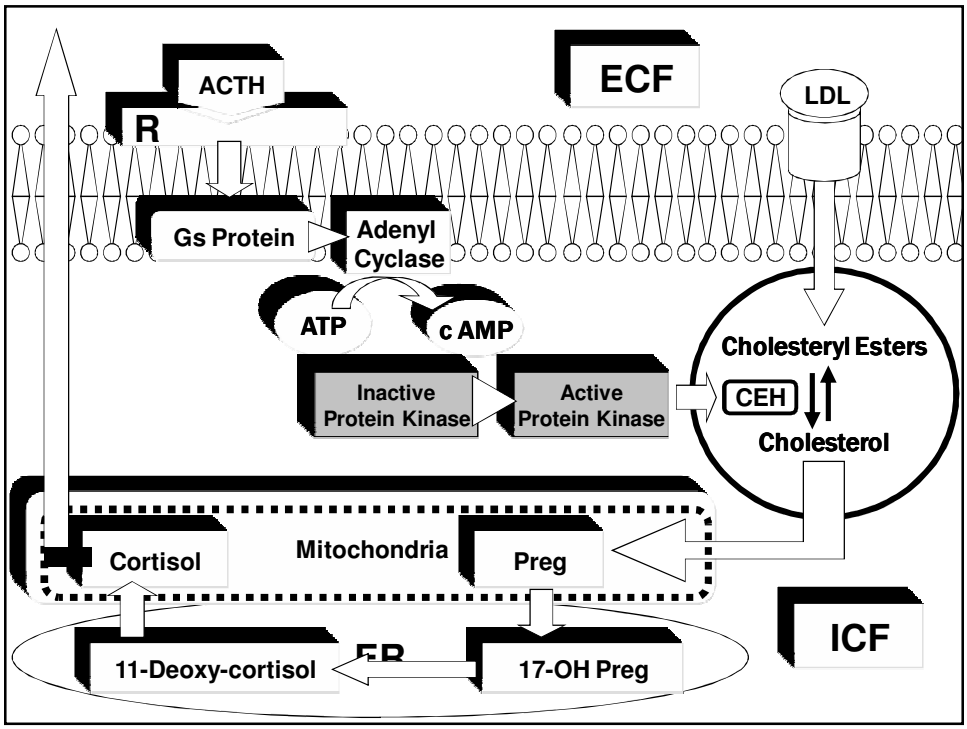
Fig. 18.22 **(a) The major steroid biosynthetic pathways.** Steroid hormones are synthesized in adrenal and gonads from the initial substrate cholesterol via a series of interconnected enzymatic steps. The reactions catalysed are shown by shaded boxes with italic labels. The molecular identity of the enzymes is shown in red – some catalyse more than one reaction. p450 enzymes are in mitochondria, 3βHSD (hydroxysteroid dehydrogenase) in cytoplasm. 17βHSD and $p450_{aro}$ (aromatase) are found mainly in gonads. **(b) The steroid molecule.**


Cholesterol
Cholesterol desmolase (P450 scc)
Pregnenolone
17α-Hydroxylase (P450 c17)
17-Hydroxypregnenolone
17, 20 Lyase (P450 c17)
Dehydroepi-androsterone
3β-Hydroxysteroid dehydrogenase
Progesterone
17α-Hydroxylase (P450 c17)
17-Hydroxyprogesterone
17, 20 Lyase (P450 c17)
Androstenedione
21β-Hydroxylase (P450 c21)
11-Deoxycorticosterone
11-Deoxycortisol
11β-Hydroxylase (P450 c11)
Corticosterone
Cortisol
Aldosterone synthase (P450 c11AS)
Aldosterone


Cholesterol
ACTH
ANG II
Pregnenolone
Progesterone
Cortisol and sex steroids
Deoxycorticosterone
Aldosterone synthase
Corticosterone
Aldosterone synthase ANG II
18-Hydroxycorticosterone
Aldosterone synthase
Aldosterone


Cyclopentanoperhydrophenanthrene nucleus
Cholesterol (27 carbons)
Pregnane derivatives (21 carbons)
Progesterone Corticoids
Androstane derivatives (19 carbons)
Androgens
Estrane derivatives (18 carbons)
Estrogens


SYNTHESIS
&
RELEASE
G-protein
Adenylyl cyclase
H
Receptor
ATP
cAMP
PKA
inactive
PKA
active
Lipid droplet
(from LDL)
Proteins
Phosphoproteins
(cholesterol esterase)
Nucleus
Diffusion of steroid hormone into blood
Free
cholesterol
Shuttling of
intermediates
P450 enzymes
located on inner
membrane
Smooth
endoplasmic
reticulum
Mitochondrion


ACTH
R
ECF
LDL
Gs Protein
Adenyl
Cyclase
ATP
c AMP
Inactive
Protein Kinase
Active
Protein Kinase
Cholesteryl Esters
CEH
Cholesterol
Cortisol
Mitochondria
Preg
ICF
11-Deoxy-cortisol
17-OH Preg

Principal Adrenocortical Hormones in Adult Humans

Name	Plasma Concentration (Free and Bound)[a] (g/dL)	Amount Secreted (mg/24 h)
Cortisol	13.9	10
Corticosterone	0.4	3
Aldosterone	0.0006	0.15
Deoxycorticosterone	0.0006	0.20
Dehydroepiandrosterone sulfate	175.0	20

Relative Potencies of Corticosteroids Compared with Cortisol

TABLE 34.2 Comparison of Shared Activities of Adrenal Cortical Hormones

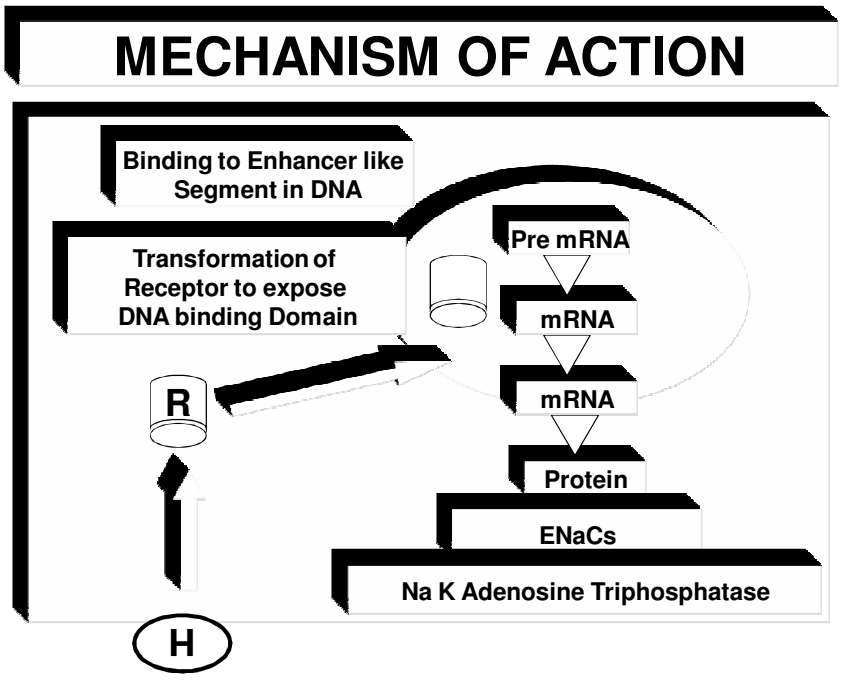
Hormone	Glucocorticoid Activity[a]	Mineralocorticoid Activity[b]
Cortisol	100	0.25
Corticosterone	20	0.5
Aldosterone	10	100

[a]Percentage activity, with cortisol being 100%
[b]Percentage activity, with aldosterone being 100%

ALDOSTERONE

- **Source Zona Glomerulosa**
- **Chemistry Steroid**
- **Half Life 20 min**
- **Plasma basal levels:** 0.006 ug/dL (**6.0 ng/dl**)
- **Daily Output 150-250 mg/24 Hours**
- **Fate Conjugated in Liver and then Excreted in urine or bile.**
- **Transport Only about 40% free & 60 % bound to Albumin**

MECHANISM OF ACTION



WHAT ARE THE TARGETS OF ALDOSTERONE?

ALDOSTERONE TARGETS

- Renal tubules
- Sweat Glands
- Salivary glands
- Gastrointestinal Tract

Increases Na Epithelial channels

ALDOSTERONE EFFECTS

Renal tubules

Aldosterone acts on collecting duct principal cells

(1)increase the Na permeability of the luminal plasma membrane
(2)increase the number and activity of basolateral plasma membrane Na/K-ATPase pumps
(3)increase the luminal plasma membrane K permeability,
(4)increase cell metabolism.
All of these changes result in increased K secretion.

Functions of the Mineralocorticoids

2- EFFECTS ON SWEAT GLANDS AND SALIVARY GLANDS

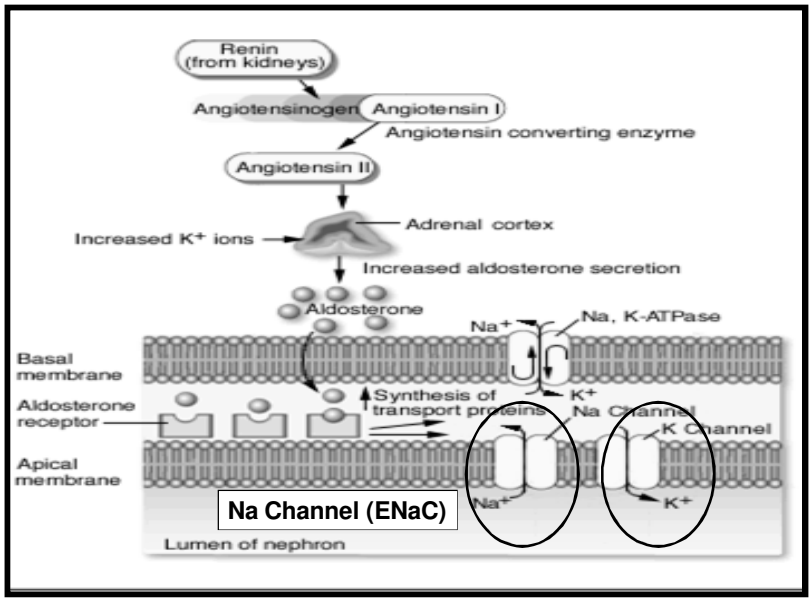
- ✓Aldosterone greatly increases the reabsorption of NaCl and the secretion of K^+ by the ducts of sweat glands and salivary glands.
- ✓The effect on the **sweat glands** is important to conserve body salt in hot environments,
- ✓The effect on the **salivary glands** is necessary to conserve salt when excessive quantities of saliva are lost.

Functions of the Mineralocorticoids

3- EFFECTS ON INTESTINAL EPITHELIAL CELLS

- ✓ Aldosterone enhances Na^+ absorption by the intestines, especially in the colon, which prevents loss of Na^+ in the stools.
- ✓ In the absence of aldosterone, Na^+ absorption can be poor, leading to failure to absorb Cl- and other anions and water as well.
- ✓ The unabsorbed NaCl and water then lead to diarrhea, with further loss of salt from the body.

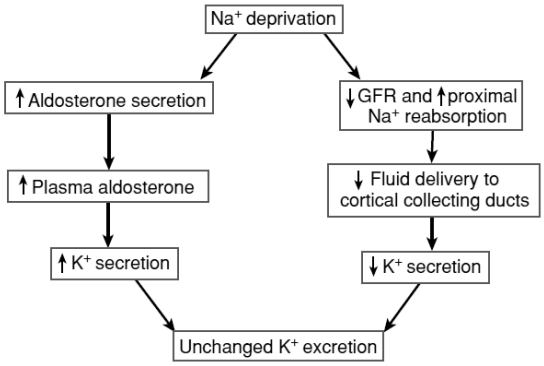
Effect Of Aldosterone On Cortical Collecting Duct



WHY NA DEPLETION DOES NOT LEAD TO ENHANCED K EXCRETION?

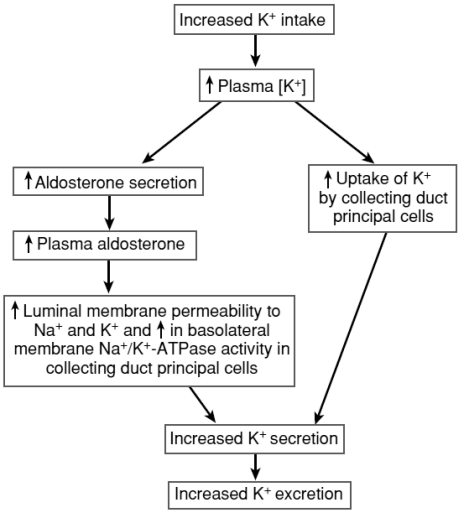
In cases of decreased dietary K intake or K depletion, the activity of the luminal plasma membrane H/K-ATPase found in -intercalated cells is increased. This promotes K reabsorption by the collecting ducts.

The collecting ducts can greatly diminish K excretion, but it takes a couple of weeks for K loss to reach minimal levels.



EFFECT OF INCREASED DIETARY K INTAKE ON K EXCRETION

K directly stimulates aldosterone secretion and leads to an increase in cell [K] in collecting duct principal cells. Both of these lead to enhanced secretion and, hence, excretion, of K.



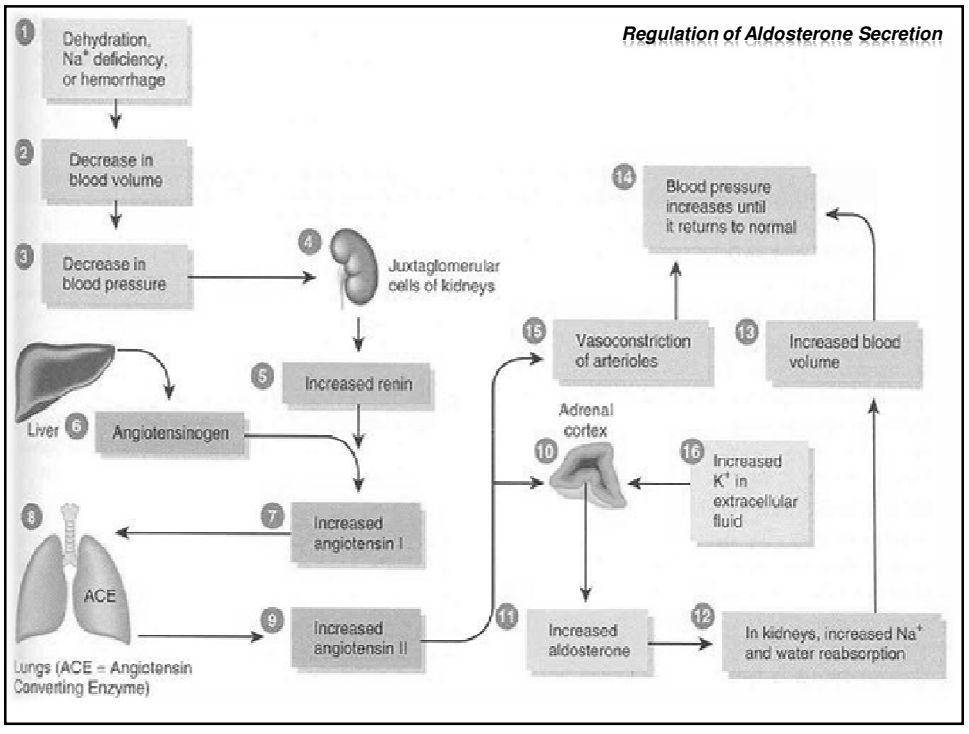
MINERALOCORTICOID ESCAPE

Large doses of a potent mineralocorticoid result in "escape" from the salt-retaining action of the steroid

The fact that the person will not continue to accumulate Na and water is due to the existence of numerous factors that are called into play when ECF volume is expanded; these factors promote renal Na excretion and overpower the salt-retaining action of aldosterone.

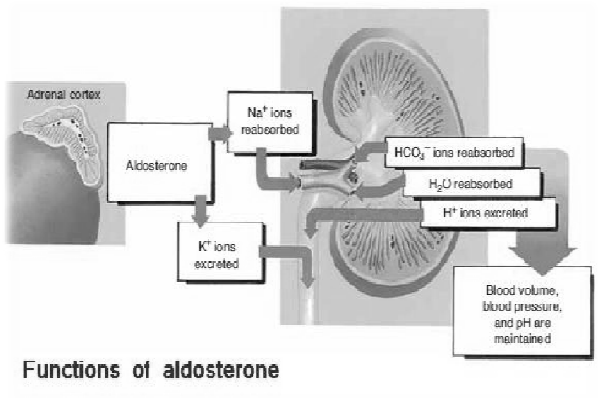
Factors Affecting Aldosterone Secretion

Stimulatory agents
Angiotensin II
Adrenocorticotropic hormone
High potassium
Sodium deficiency
Inhibitory agents
Atrial natriuretic hormone
High sodium concentration
Potassium deficiency

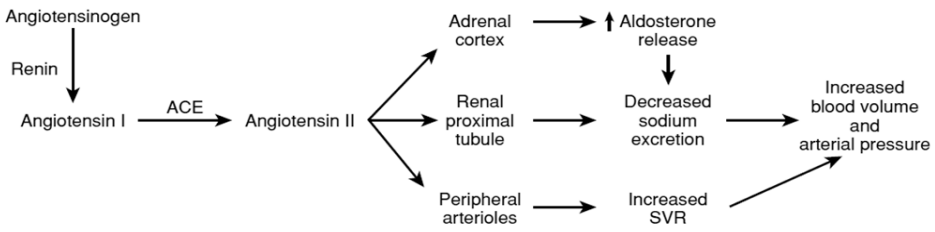

Regulation of Aldosterone Secretion
1 Dehydration, Na^+ deficiency, or hemorrhage
2 Decrease in blood volume
3 Decrease in blood pressure
4 Juxtaglomerular cells of kidneys
5 Increased renin
Liver
6 Angiotensinogen
7 Increased angiotensin I
8
ACE
9 Increased angiotensin II
Lungs (ACE = Angiotensin Converting Enzyme)
10
Adrenal cortex
11 Increased aldosterone
12 In kidneys, increased Na^+ and water reabsorption
13 Increased blood volume
14 Blood pressure increases until it returns to normal
15 Vasoconstriction of arterioles
16 Increased K^+ in extracellular fluid

Four factors are known to play essential roles in the regulation of aldosterone.

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.**



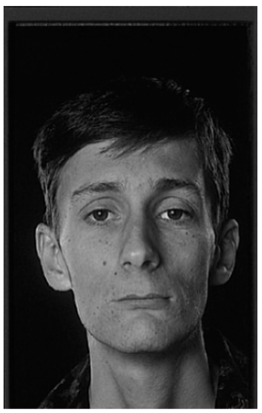
Functions of aldosterone



Primary Hypoadrenalism Addison's disease

Symptoms

Weight loss
Anorexia
Malaise
Weakness
Fever
Depression
Impotence/amenorrhoea
Nausea/vomiting
Diarrhoea
Confusion
Syncope from postural hypotension
Abdominal pain
Constipation
Myalgia
Joint or back pain



Signs

Pigmentation, especially of new scars and palmar creases
Buccal pigmentation
Postural hypotension
Loss of weight
General wasting
Dehydration
Loss of body hair
(Vitiligo)

Fig. 18.24 **Primary hypoadrenalism (Addison's disease) – symptoms and signs.** Bold type indicates signs of greater discriminant value.

Mineralocorticoid Deficiency. Lack of Aldosterone secretion

Greatly decreases renal tubular sodium reabsorption and consequently allows sodium ions, chloride ions, and water to be lost into urine in great profusion. The net result is a greatly decreased extracellular fluid Volume.

Hyponatremia, hyperkalemia, and mild acidosis develop because of failure of potassium and hydrogen ions to be secreted in exchange for Sodium reabsorption.

As the extracellular fluid becomes depleted, plasma volume falls, red blood cell concentration rises markedly, cardiac output decreases, and the patient dies

In shock, death usually occurring in the untreated patient 4 days to 2 weeks after cessation of mineralocorticoid secretion.

PRIMARY ALDOSTERONISM (CONN'S SYNDROME)

Small tumor of the zona glomerulosa cells

- **Hypokalemia,**
- **Slight increase in extracellular fluid volume and blood volume,**
- **Very slight increase in plasma sodiu concentration**
- **Hypertension.**
- **Occasional periods of muscle paralysis……hypokalemia.**

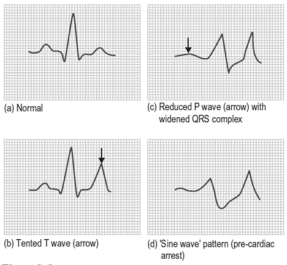


Fig. 12.9 **Progressive ECG changes with increasing hyperkalaemia.**

One of the diagnostic criteria of primary aldosteronism is a decreased plasma renin concentration. This results from feedback suppression of renin secretion caused by the excess aldosterone or by the excess extracellular fluid volume and arterial pressure resulting from the aldosteronism.