Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved

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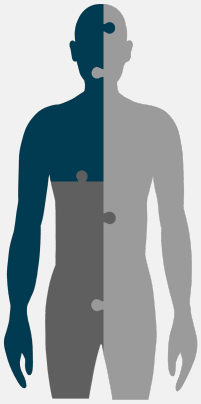


Adrenocortical Hormone

Objectives*:

Lecture 10

- The cellular arrangements and functional components of the adrenal gland.
- The hormones secreted by the medulla and cortex of the adrenal gland.
- The synthesis of the adrenocortical steroids.
- The physiological actions of aldosterone.
- The regulation of aldosterone secretion.
- The major stimuli for aldosterone secretion.

Lecture 11

- Describe the metabolism and physiological effects of glucocorticoids.
- Describe the mechanisms that regulate secretion of glucocorticoids
- Describe the main features of the diseases caused by excess or deficiency of each of the hormones of the adrenal gland.

Lecture 12

Not found

Color index:

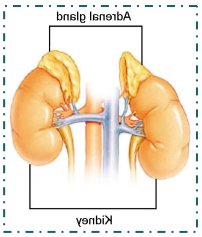
- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

L10

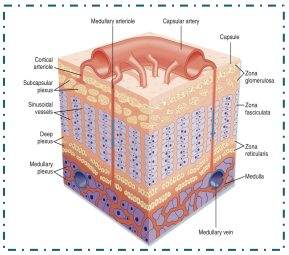
The Adrenal Gland

- Paired, small pyramidal-shaped organ atop the kidneys.
- Weigh 4/6-10 g
- Structurally and functionally, they are two glands in one
- There are two adrenal (suprarenal) glands that lie at the superior pole of the two kidneys
- Divide into two morphologically and distance regions



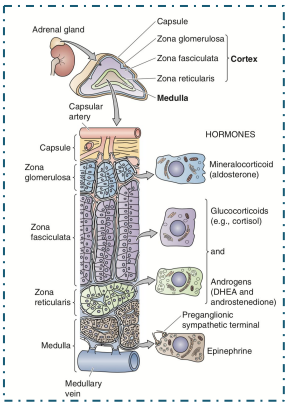
Adrenal medulla

- 10-20% formed from neural ectoderm, can be considered a modified sympathetic ganglion
- It is the central region
- 20% of the gland
- Secretes **epinephrine** and **norepinephrine** (related to sympathetic nervous system).



Adrenal Cortex

- 80%-90% glandular tissue derived from embryonic mesoderm
- Secrete group of hormones called corticosteroids
- All synthesized from the steroid cholesterol
- Have different functions.
- Synthesizes and releases steroid hormones (corticosteroids)
- Different corticosteroids are produced in each of the **three layers.**

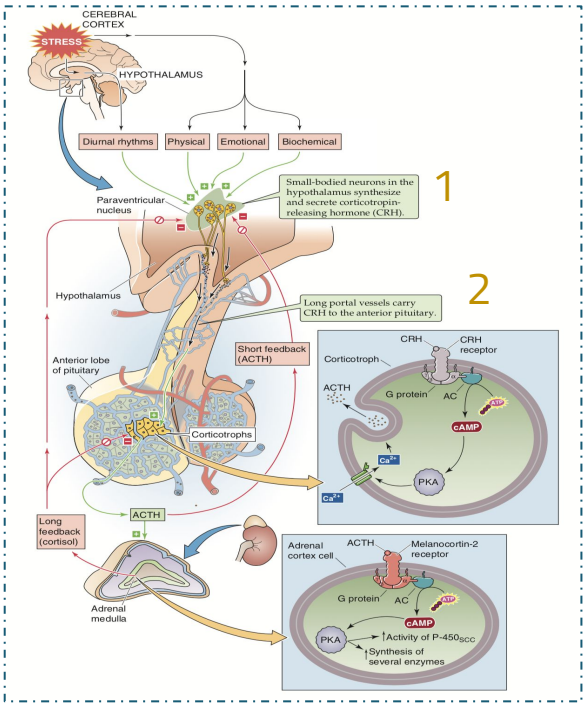


Region	Type	Hormone
Zona Glomerulosa (15%)	**Mineralo**corticoids القشريات المعدنية	○ Mainly aldosterone
Zona Fasciculata (75%)	**Gluco**corticoids القشريات السكرية + Androgens	○ Cortisol (mainly) ○ Corticosterone (Mainly) ○ Androgens (small amount) ○ Estrogens (small amount)
Zona Reticularis (10%)	**Gonado**corticoids القشريات الجنسية + glucocorticoids	○ Androgens: -DHEA "Dehydroepiandrosterone" (Mainly) -Androstenedione -Estrogen (small amount) ○ Glucocorticoids

Notice that Aldosteron can only be synthesized in the Glomerulosa whereas Cortisol, Androgens, and Estrogens can be synthesized from two layers.

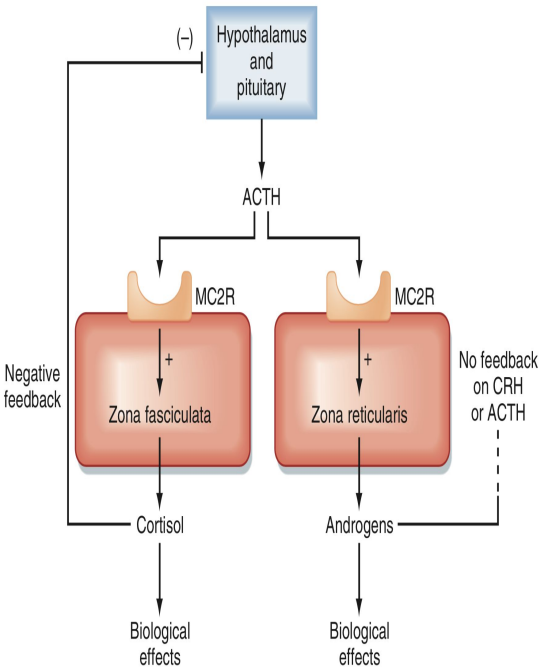
The Adrenal Gland *

Hypothalamo Pituitary Axis (HPA)



1st and 2ed step are explained above
3) CRH activates ACTH by acting on Corticotrophs in the anterior pituitary
4) ACTH is then released and travel to the adrenal cortex and stimulates Glucocorticoids mainly, and to a lesser extent Mineralocorticoid and Gonadocorticoid.

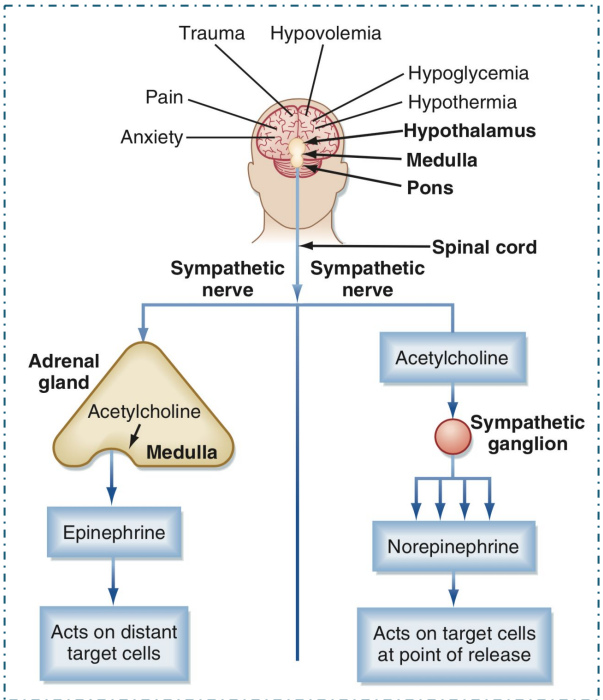
Loophole in the -ve feedback



The "loophole" in the hypothalamic-pituitary-adrenal axis: ACTH stimulates production of both cortisol and adrenal androgens, but only cortisol negatively feeds back on ACTH and CRH. Thus if cortisol production is blocked , ACTH levels increase along with adrenal androgens → androgens will be produced excessively due to absence of any negative feedback.

Stimuli that enhance catecholamine secretion

The pathway on the left shows the effect of the sympathetic nervous system on the adrenal medulla that mainly secrete epinephrine which act on distant target cells #Team 437



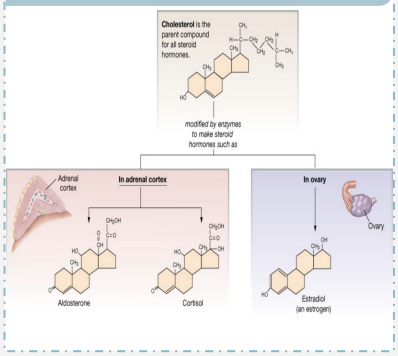
The pathway on the right shows when norepinephrine is secreted from the sympathetic neurons which then act on target cells at the point of release. #Team 437

Steroid Hormone

Synthesis*

- Steroids are derivatives of cholesterol.
- Cholesterol is from the lipid droplets in cortical cells **(cholesterol esters in LDL).**
- Removed cholesterol is replenished by cholesterol in LDL in blood or synthesized from acetate.
- Steroidogenic Acute regulatory protein **(StAR protein)** transfers cholesterol to the inner membrane of the mitochondria (mutation causes accumulation of cholesterol in the cytoplasm).
- Steroid hormones are synthesized and secreted on demand (not stored). Remember, peptide hormones are stored in vesicles.
- The first step in the synthesis of all steroid hormones is conversion of cholesterol to pregnenolone by the enzyme cholesterol desmolase (Rate limiting step) aka cholesterol side chain cleavage (SCC) enzyme.
- Newly synthesized steroid hormones are rapidly secreted from the cell.
- Following secretion, all steroids bind to some extent to plasma proteins: CBG (transcortin) and albumin.

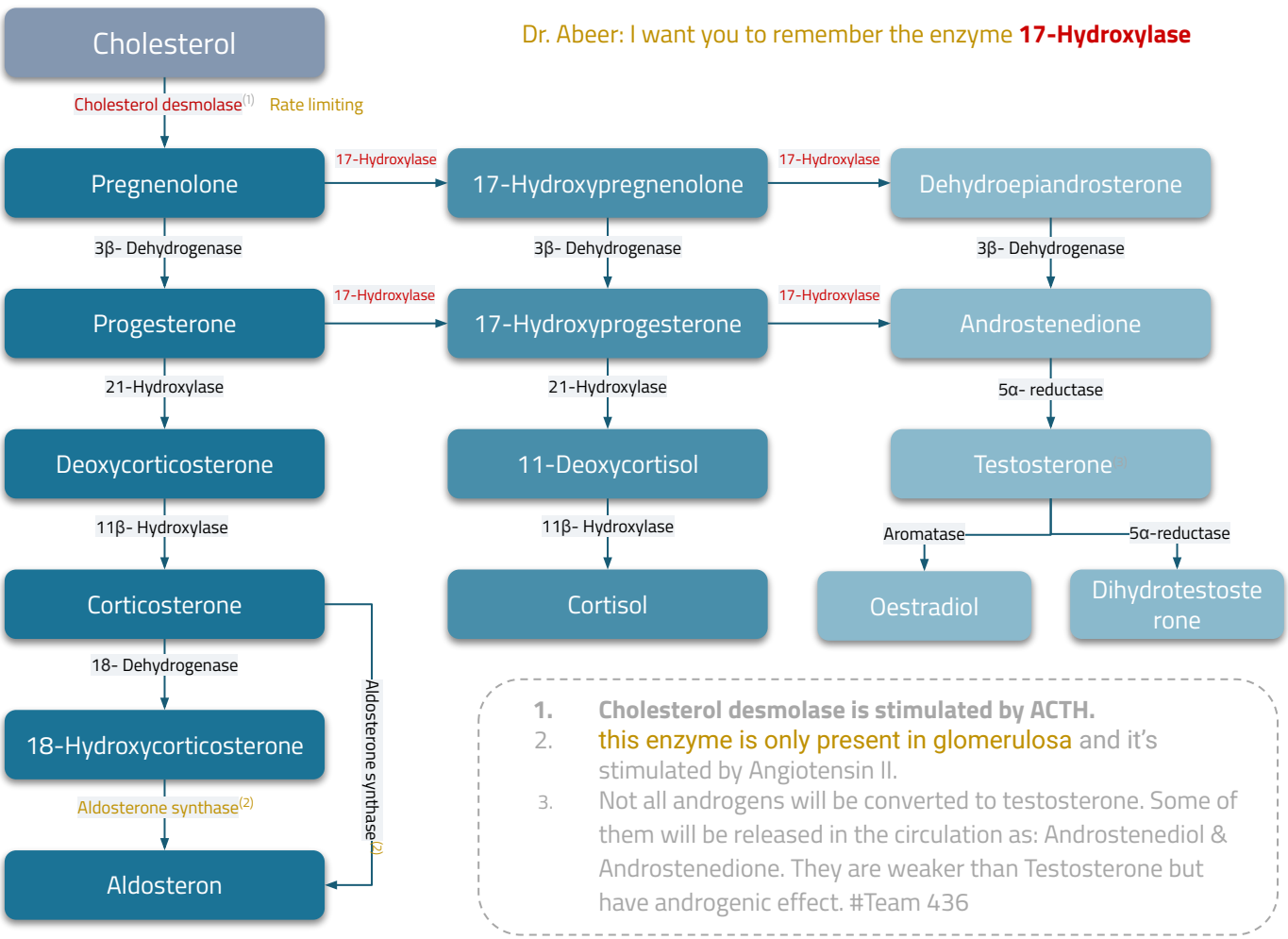
Steroid hormones structure



Steroidogenesis

Male dr said that we don't need to worry about these processes

Dr. Abeer: I want you to remember the enzyme **17-Hydroxylase**

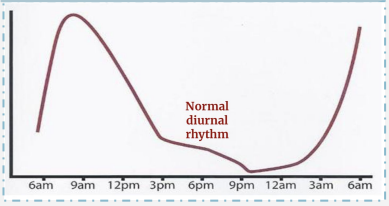


1. **Cholesterol desmolase is stimulated by ACTH.**
2. this enzyme is only present in glomerulosa and it's stimulated by Angiotensin II.
3. Not all androgens will be converted to testosterone. Some of them will be released in the circulation as: Androstenediol & Androstenedione. They are weaker than Testosterone but have androgenic effect. #Team 436

Aldosterone

- The main mineralocorticoid produced by the adrenal gland.
- A steroid hormone.
- **Essential** for life.
- Synthesized in zona glomerulosa.
- Aldosterone exerts 90% of all mineralocorticoid activity[1].
- Responsible for regulating Na+ reabsorption in the distal tubule and the cortical collecting duct.
- It also affects Na+ reabsorption by sweat,salivary and intestinal cells.
- Target cells are called "**principal (P) cell**".
- Transport: 60% of aldosterone bound to plasma protein (40% is free form) it binds to albumin and corticosteroid bind protein in blood with low affinity and therefore has a biological half-life of about 20 minutes, unlike cortisol which binds strongly giving it a longer half life.
- Metabolism: Much of the secreted aldosterone is metabolized (inactivated) by the liver and conjugated (converted) to tetrahydro-glucuronide derivative / glucuronic acid or sulfate and secreted in the bile or excreted by the kidney all steroids are eliminated this way
- Aldosterone level fluctuate diurnally:
  - Highest concentration being at 8 AM
  - Lowest at 11 PM in parallel to cortisol rhythms

Serum cortisol level



Glucocorticoids vs. Mineralocorticoids

Table 78-1 Adrenal Steroid Hormones in Adults; Synthetic Steroids and Their Relative Glucocorticoid and Mineralocorticoid Activities

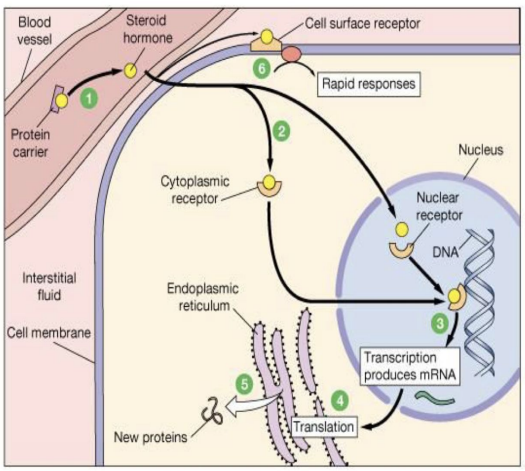
Steroids	Average Plasma Concentration (free and bound, μg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal steroids				
Cortisol	12	15	1.0	1.0
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydroepiandrosterone	175	20	—	—
Synthetic steroids				
Cortisone	—	—	0.7	0.5
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	30	—
9α-Fluorocortisol	—	—	10	125

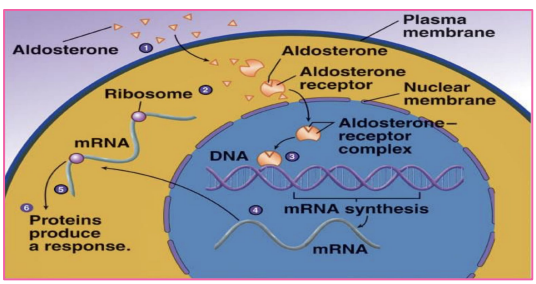
Glucocorticoid and mineralocorticoid activities of the steroids are relative to cortisol, with cortisol being 1.0.

MOA of Steroid Hormone[3]

A Repetition of the 1st lecture :)

1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into target cell.
2. Steroid hormone receptors are in the cytoplasm or nucleus.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.
4. Activated genes create new mRNA that moves back to the cytoplasm.
5. Translation produces new proteins[2] to cell processes.
6. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.





- Increases transcription of Na+/K+ pump.
- Increases **expression of apical Na+ channels and Na+/K+/Cl- cotransporter.**

1. meaning that it affects/regulate body minerals such as sodium & potassium.
2. In case of aldosterone; New protein = Na+/K pump and channels.
3. the place where this occurs in case of aldosterone is the renal tubules of kidney.

- Cortisol does have some mineralocorticoid activity, even though it's very minor compared to aldosterone, the amount of cortisol secretion can be much higher than aldosterone. So if we have very high levels of cortisol (cushings) we will see water retention

Aldosterone

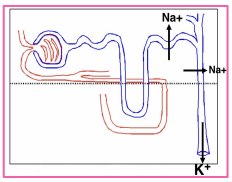
AKA salt retaining hormone

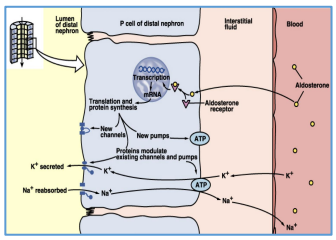
Actions of Aldosterone

- Acts mainly on the cells of the **collecting ducts** and **distal tubules** of the nephron.
- **Increase renal tubular reabsorption of Na+ and secretion of K+ and H+**
- Binds to mineralocorticoid receptor (MR).

1- Renal Actions

- Aldosterone causes Na+ to be conserved in the ECF (**water** will follow) while increasing K+ excretion in the urine.
- Increases transcription of Na+/K+ pump (basolateral). This will decrease the intracellular Na+ levels even more.
- Increases the expression of apical Na channels and Na/Cl Cotransporter (NCC). allowing Na+ to enter passively as it moves from high to low con.
- Stimulate the secretion of K+ into the tubular lumen.
- Stimulate secretion of H+ via **the H+/ATPase** by intercalated cells of the cortical collecting tubule.
- Causes secretion of H+ **in exchange for Na+** sodium-hydrogen exchanger (Na+/H+ exchanger)in the intercalated cells of the collecting tubules. (so they secrete H+ through two transporters),
- Excess aldosterone not only causes loss of K+ from ECF into urine but also stimulate transport of K+ from ECF into most cells of the body.
- Excess aldosterone increases tubular hydrogen ion secretion and causes alkalosis.
- Net effect on K^+ : Removing K^+ from ECF and plasma and moving it inside cells or excreting it through the kidneys





This Image shows that aldosterone will activate the transcription of the channel proteins

2- Circulatory Actions

- Aldosterone increases **ECF volume** and **arterial pressure** but has only a small effect on plasma Na+ concentration. (water is also absorbed, ADH is secreted).
- Higher levels of Aldosterone cause left ventricular hypertrophy and remodeling (fibrinogenic) by unknown mechanisms. So, aldosterone increases mortality of HTN.

3- Na+ Reabsorption Action

- Aldosterone has the same effects on **sweat glands**, **salivary gland** and **intestinal cells** as it has on the **renal tubules**. (reabsorption of Na+ and Cl- and excretion of K+) (stimulates synthesis of more Na/K-ATPase pumps).
- Aldosterone greatly **enhances Na+ absorption** by intestines, especially in the colon.

Aldosterone Escape*

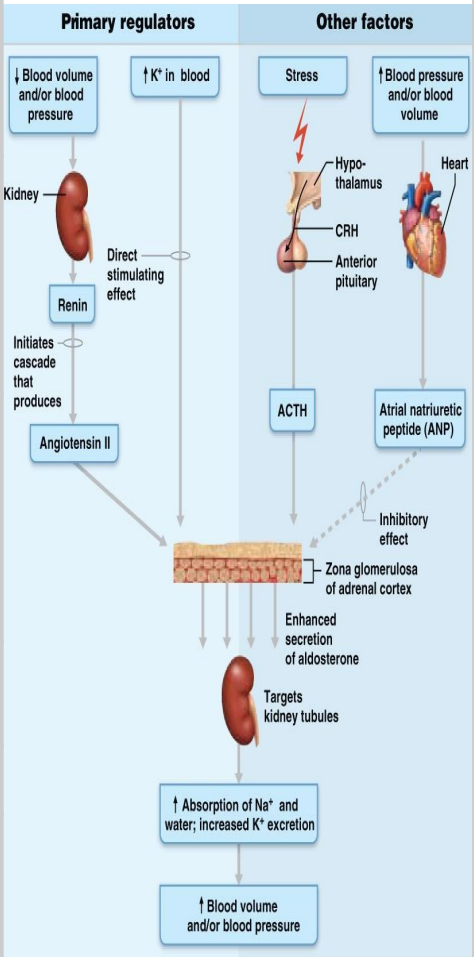
"We will not ask about this but you might need it somewhere else"

When excess amount of aldosterone are secreted:
The rise in arterial pressure increases kidney excretion of both sodium and water, called **pressure natriuresis** and **pressure diuresis**.

Aldosterone

★★★ Aldosterone secretion

Increase Aldosterone secretion (Stimulation)	**Hyperkalemia**	Increased plasma concentration of potassium directly influences zona glomerulosa cells. increased potassium concentration leads to arrhythmia. on the other hand, decreased potassium levels leads to muscle weakness and arrhythmia too.
	RAAS Very strong	The major stimulant, Activated by a decrease in blood pressure or volume (**hypovolemia** and **hypotension**) ↑ activity of RAAS (↑levels of Angiotensin II) more info in next slide.
	ACTH Very weak	Causes small increase of aldosterone during stress. However ACTH stimulation is more transient than the other stimuli and is diminished within several days
	Hyponatremia	A decrease in Na+ conc. Increases aldosterone
	Other factors	Stress, Surgery.
Decrease Aldosterone secretion	**Atrial Natriuretic peptide (ANP)**	ANP inhibits activity of the zona glomerulosa and reduces aldosterone ANP & Aldosterone antagonise each other. ↑ECF → ↑ANP → ↑Na excretion



GUYTON: Aldosterone Increases Sodium Reabsorption and Potassium Secretion. Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex, is an important regulator of sodium reabsorption and secretion of potassium and hydrogen ions by the renal tubules. *A major renal tubular site of aldosterone action is on the principal cells of the cortical collecting tubule*. The mechanism by which aldosterone increases sodium reabsorption and potassium secretion is by stimulating the sodium- potassium ATPase pump on the basolateral side of the cortical collecting tubule membrane. Aldosterone also increases the sodium permeability of the luminal side of the membrane. The cellular mechanisms of aldosterone action are discussed in

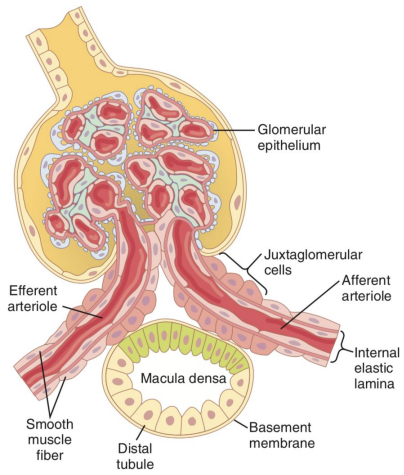
The most important stimuli for aldosterone are (1) increased extracellular potassium concentration and (2) increased angiotensin II levels, which typically occur in conditions associated with sodium and volume depletion or low blood pressure. The increased secretion of aldosterone associated with these conditions causes renal sodium and water retention, helping to increase extracellular fluid volume and restore blood pressure toward normal.

In the absence of aldosterone, as occurs with adrenal destruction or malfunction *(Addison's disease),* there is marked loss of sodium from the body and accumulation of potassium. Conversely, excess aldosterone secretion, as occurs in patients with adrenal tumors *(Conn's syndrome),* is associated with sodium retention and decreased plasma potassium concentration due, in part, to excessive potassium secretion by the kidneys. Although day-to-day regulation of sodium balance can be maintained as long as minimal levels of aldosterone are present, the inability to appropriately adjust aldosterone secretion greatly impairs the regulation of renal potassium excretion and potassium concentration of the body fluids. Thus, aldosterone is even more important as a regulator of potassium concentration than it is for sodium concentration.

Control of Aldosterone secretion through RAAS*

Renin

- An enzyme released by the kidneys when **arterial pressure falls**. Renin is synthesized and stored in the juxtaglomerular cells (JG cells) of the kidneys.
- JG cells are modified smooth muscle cells located in the walls of the afferent arterioles immediately proximal to the glomeruli.
- Renin acts on another plasma protein (angiotensinogen) to release angiotensin I which is converted to angiotensin II (in the lungs)

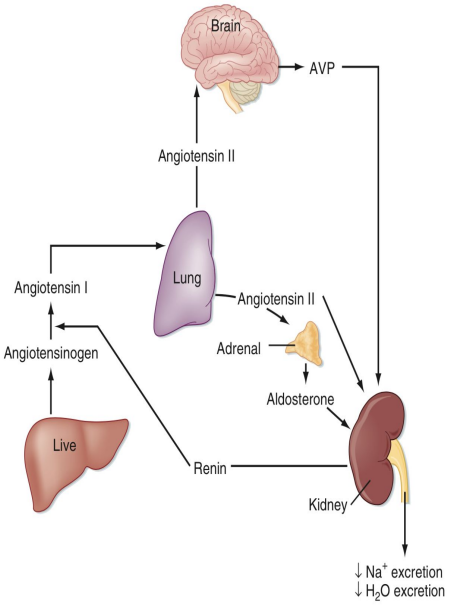


Angiotensin II

Angiotensin II increases the blood pressure through:

1. **Vasoconstriction** occurs intensely in the arterioles and less so in the veins. Constriction of the arterioles increases total peripheral resistance, thereby raising the arterial pressure.
2. **Decrease excretion of both salt and water by the kidneys.** This slowly increases ECF volume, which increases the arterial pressure during subsequent hours and days.

- Angiotensin II acts on the zona glomerulosa to **stimulate aldosterone synthesis**. Acts via increased intracellular cAMP to stimulate aldosterone synthesis.



Aldosterone abnormalities

- Complete failure to secrete aldosterone leads to **death** (dehydration, **low blood volume,** low blood pressure)
- Hyperaldosterone states contribute to hypertension associated with **increased blood volume.**
- **Primary hyperaldosteronism (conn's syndrome):** decreased plasma renin
- **Secondary hyperaldosteronism:** increased plasma renin

Hyperaldosteronism

Primary

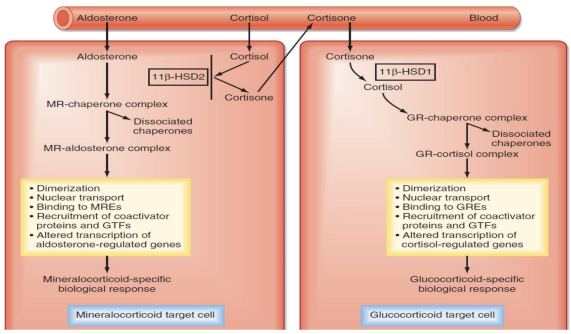
Example	**Conn's syndrome** (Increased secretion of mineralocorticoids)
Causes	Nodular hyperplasia of adrenal cortex Tumor of the **zona glomerulosa cells** (adenoma) ⟶ Secretes large amount of aldosterone.
Sign & Symptoms	Headache. Very slight increase in plasma sodium concentration. Hypokalemia, (causing muscle weakness / occasional periods of muscle paralysis). Hypernatremia. Hypervolemia.(Slight increase in ECF volume and blood volume). Almost always, **hypertension.** Metabolic alkalosis, caused by increased tubular (intercalated cells) hydrogen ion secretion. Nocturnal polyuria and polydipsia. **Decreased plasma renin concentration** (from feedback suppression of renin secretion caused by the ↑ aldosterone) or by the excess ECF volume and arterial pressure. **Neuromuscular manifestations**: weakness, paresthesia and intermittent paralysis. Hand cramping.
Treatment	Surgical (Usually) for adenoma Spironolactone, a potassium-sparing diuretic that acts as an aldosterone antagonist.

Secondary

Causes	Hyperreninism, Left Ventricular Failure, Cor Pulmonale, Cirrhosis, Ascites

Other causes*

"We will not ask about this but you might need it somewhere else"

Example	Apparent mineralocorticoid excess syndrome (AME) (cortisol binds MR) Cortisol can bind with high affinity to mineralocorticoids and cause their activity, however this is normally blocked by an enzyme called 11ß-HSD2 (11ß- hydroxysteroid dehydrogenase type-2) that converts cortisol to cortisone. And in case of deficiency or mutation of that enzyme, conversion will not happen, and so cortisol will bind to the mineralocorticoid receptors and cause their activation Some people eat liquorice (عرق سوس) during ramadan. Liquorice suppresses 11ß-HSD2 causing water and sodium retention 

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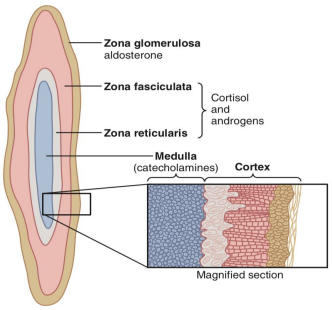
Glucocorticoids

Overview

- Produced by the fasciculata and reticularis (small amount) layers of the adrenal cortex
- Glucocorticoids (cortisol): recognized early to increase plasma glucose levels (this is the reason behind the name "Gluco") :
  - Mobilization of amino acids from proteins.
  - Enhance liver gluconeogenesis.
- Target tissues: most body tissues.
- They are catabolic as they break Glycogen (Glycogenolysis indirectly), proteins, fat (Lipolysis)



Main glucocorticoids in humans

Cortisol:

- Very **potent**.
- Account for **95%** of glucocorticoid activity.

Corticosterone:

- Account for about 4% of total glucocorticoid activity.
- Less potent than cortisol

Cortisol: Corticosterone:

- Produced in humans in a ratio 10:1

Regulation of Glucocorticoid Secretion*

CRH from hypothalamus is the major regulator of ACTH secretion

ADH is also a secretagogue for ACTH, but it's weaker than CRH

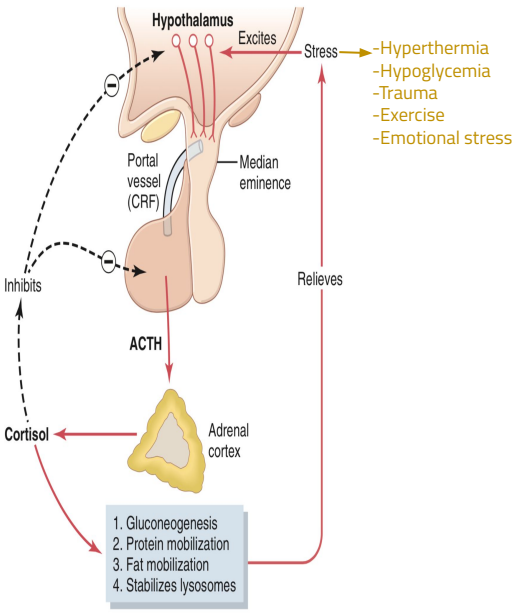
ACTH from anterior pituitary stimulates cortisol synthesis and secretion

CRH (and ACTH) are secreted in pulses

The greatest ACTH secretory activity occurs in the early morning hours and diminish late in the afternoon

Stress stimulates CRH secretion by the hypothalamus.

Cortisol has a direct negative feedback effect on both the hypothalamus and anterior pituitary



Glucocorticoids

Cortisol Transport & Metabolism *

Bound

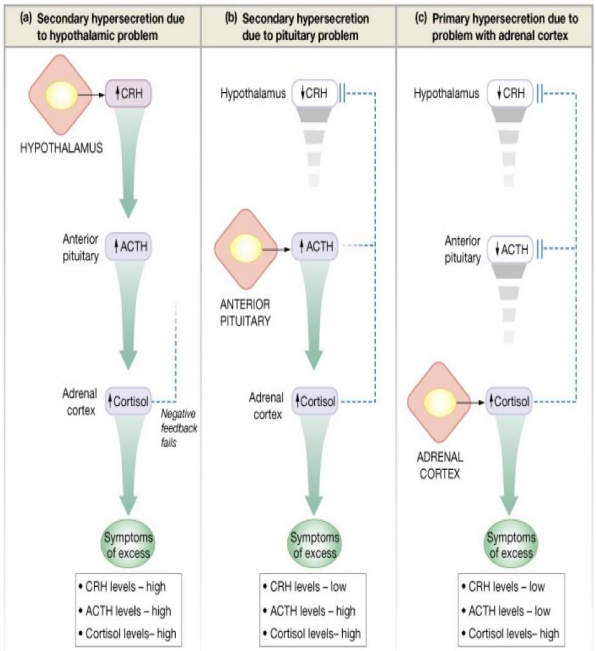
- 90-95%
- Mostly to transcortin (Cortisol Binding Globulin)
- Albumin

Free

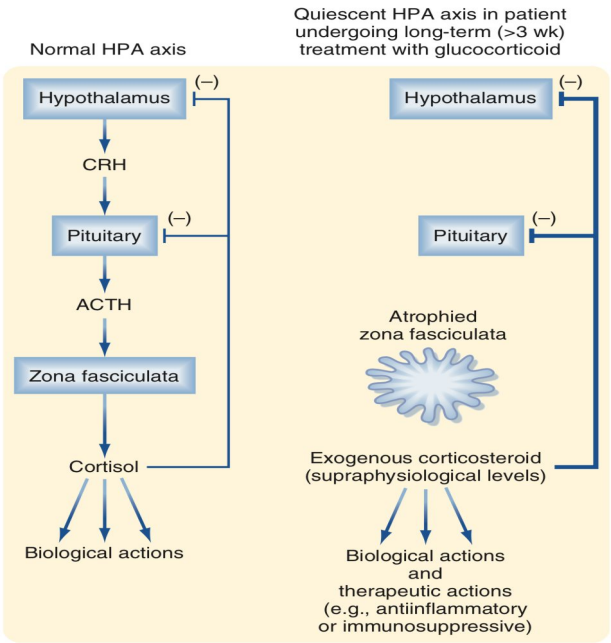
- 6%
- **Active form**

- Half life =60-90 minutes
- Metabolized in liver by reductases & conjugated to glucuronides and excreted via kidney.
- Free cortisol is secreted into urine.

Primary and secondary hypersecretion of cortisol*



Quiescent HPA axis: Long-term GC treatment*



When giving treatment of Glucocorticoid for longer than 3 week, this will negatively suppresses the hypothalamus and pituitary to produce CRH and ACTH, as a result there will be an atrophy of the zona fasciculata.
So **Withdrawal should be gradual** until the hypothalamus and the pituitary resume their normal function and until the adrenal cortex gets back to its normal size
Know that the hormones that act on the gland increase the size of the gland, so for e.g.
TSH on the thyroid → ↑Thyroid gland size
ACTH on adrenal cortex → ↑Adrenal gland size.

Glucocorticoids

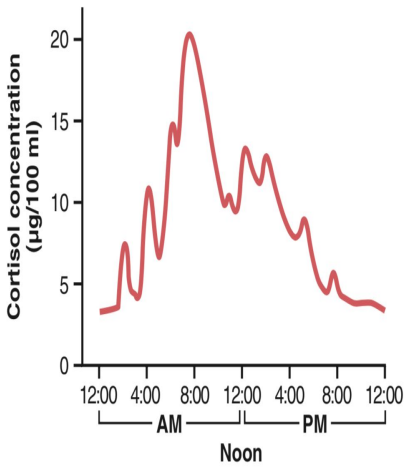
Circadian rhythm of cortisol secretion

◄ The secretory rates of CRF, ACTH, and cortisol:
- High in the early morning: the plasma cortisol level ranges between a high of about 20 µg/dl an hour before arising in the morning
- Low in the late evening: low of about 5 µg/dl around midnight.

◄ This effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.

◄ When a person changes daily sleeping habits, the cycle changes correspondingly. Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

Picture was in both slides while text is from female slides only



Actions of Glucocorticoids*

❖ Cortisol acts primarily through the **glucocorticoid receptor** (which is an intracellular receptor that is found inside almost every cell in the body)**.**

❖ Which regulates gene transcription

Metabolic response to fasting:

- Gluconeogenesis from amino acids (increased expression of the enzymes) **(PEPCK).**
- Cortisol also decreases GLUT4-mediated sensitive to glucose uptake in skeletal muscle and adipose tissue. It is the only glucose transporter that is sensitive to insulin.
- Mobilization of stored fat (activation of HSL Hormone Sensitive Lipase) and its use in β-oxidation and the production of ketone bodies

Physiological actions of cortisol

Metabolic

Carbo-hydrates

- Increase the enzyme required to convert amino acids into glucose in the liver cells (Gluconeogenesis). The required enzyme is PEPCK.
- Mobilization of amino acids from extrahepatic tissues (muscles) for gluconeogenesis.
- Antagonize insulin effects to inhibit gluconeogenesis in the liver.
- Cortisol ↑ insulin resistance in tissues → Insulin becomes less effective on moving glucose inside the cell → ↑Blood glucose levels → The increased glucose level stimulate the release of more insulin → this is similar to what happens in diabetes so this effect is known as Diabetogenic effect
- Promote glucose sparing by potentiation the effects of catecholamines on lipolysis, thereby making FFAs available as energy source.
- Adrenal diabetes. When glucocorticoids increase fasting glucose levels beyond 126g/dl, it's considered diabetes. Only happens in genetically prone patients .
- ↑↑**Glucose level in the blood by:** (can lead to hyperglycemia & DM if excess)
  1. Liver:
     - **Stimulates** gluconeogenesis (6-10 fold).
     - **Increase glycogen storage** by the liver.
  2. ↓↓**Glucose utilization** by the cells.
  3. ↓ the sensitivity of tissues to insulin. (prevents insulin action & leads to accumulation of glucose in blood, and eventually increased glucose levels)

Proteins

Males

- Mobilization of amino acids from non-hepatic tissue
- Protein Catabolic effect in all body cells except of the liver
- Decrease protein synthesis
- Decrease amino acids transport into extrahepatic tissue (muscles, lymphatic tissue)
- Protein Anabolic effect in the liver
  - Enhanced liver proteins
  - Increased plasma proteins

Females

1. Proteins:

- ↓↓ Protein stores in all body (**except the liver**).
- ↑ Catabolism of protein and Decrease protein synthesis

2. ↑ Liver and plasma proteins.

3. Amino acids:

- ↑↑ Amino acid level in the blood.
- ↓ Amino acid transport into extrahepatic cells. result will be muscle wasting if excess
- ↑ Amino acid transport into hepatic cells.

Fat

- Mobilization of fatty acid from adipose tissue, which increases the concentration of free fatty acids in the plasma/ blood
- ↑↑ Their utilization for energy.
- Excess cortisol causes obesity

Physiological actions of cortisol cont..

Stress

- Without glucocorticoids, the body cannot cope with even mild stressors.
- Fat and Glucose metabolism
- Stress include (trauma, infection, surgery, any debilitating disease, increase heat or cold).
- Cortisol causes rapid mobilization of amino acids and FFA from their cellular stores, making them immediately available both for energy & synthesis of other compounds, including glucose, needed by the different tissues in the body.
- ↑BP, ↑glycogen, prevents stress induced reaction from becoming excessive.
- Effects on CNS.
- Maintenance of the vascular response to norepinephrine.

Anti-inflammatory

- Glucocorticoids are used to alleviate inflammation.
- **Stabilize lysosomal membranes** (reduce their rupture and release of proteolytic enzymes).
- **Inhibit production of prostaglandins, leukotrienes, and thromboxane** (mediate inflammation). This occurs via inhibiting **phospholipase A2.** Cortisol induces the synthesis of **lipocortin,** an inhibitor of the enzyme phospholipase A2.
- **Decrease permeability of capillary membranes** → reducing swelling
- They also reduce the effects of histamine
- Attenuates fever mainly because cortisol reduces the release of interleukin-1 from white blood
- **Reduces degree of vasodilatation.**
- **Decreases migration of white blood cells.** (These effects probably result from the fact that cortisol diminishes formation of prostaglandins and leukotrienes that otherwise would increase vasodilation, capillary permeability, and mobility of white blood cells).
- Suppresses immune system.
- Damage to the tissues by trauma/infection almost always leads to inflammation.
- Inflammation can be more damaging than the trauma or disease itself.
- Cortisol has anti-inflammatory effects....How? By causing the stabilization of the intracellular lysosomal membranes → more difficult for these membranes to rupture → **less release of proteolytic enzymes that cause Inflammation**.
- Reduces all aspects of the inflammatory process:
  - Block the early stages of the inflammation process before inflammation even begin
  - If inflammation begun: It cause rapid resolution of the inflammation and increase rapidity of healing
  - Resolution of inflammation

Blocks the inflammatory response to allergic reaction*

GUYTON: The basic allergic reaction between antigen and antibody is not affected by cortisol, and even some of the secondary effects of the allergic reaction still occur. However, because the inflammatory response is responsible for many of the serious and sometimes lethal effects of allergic reactions, administration of cortisol, followed by its effect in reducing inflammation and the release of inflammatory products, can be lifesaving. For instance, cortisol effectively prevents shock or death as a result of anaphylaxis, a condition that otherwise kills many people

Physiological actions of cortisol cont..

Immunosuppression* Blood Cells*

- Cortisol **Increases RBC production.** by mechanisms that are unclear. When excess cortisol is secreted by the adrenal glands, polycythemia often results, and conversely, when the adrenal glands secrete no cortisol, anemia often results.
- Decreases production of T lymphocyte, eosinophils count. (decrease immunity)
- Large doses of cortisol administration: Suppresses lymphoid tissue systemically therefore decrease T cell and antibody production decreasing immunity.
- Administration of large doses of cortisol causes significant atrophy of lymphoid tissue throughout the body.
- Decrease immunity could be fetal in disease such as tuberculosis
- Decrease immunity effect is **useful in transplantation surgery in reducing organ rejection**.

Anti-allergic effects*

(In pharmacological doses):

- It decreases fibroblastic activity and local swelling
- ↓phospholipase A2
- Stabilizes lysosomal membrane
- Inhibits collagenase from breaking down proteins
- Inhibits histamine release (anti-allergic)

Circulation

Excrete water load: Cortisol levels vary with water intake.

Mineral metabolism (mineralocorticoid effect, Not as potent as aldosterone):

- Na+ reabsorption and K+ secretion.
- Anti-vitamin D effect, reduces osteoblast differentiation, reduces calcium absorption.

Vascular Effect (BP regulation & cardiovascular function):

- Maintains body fluid volumes & vascular integrity. (If excess, can lead to HTN)
- Sensitizes arterioles to action of **noradrenaline (Permissive effect)**.
- Cortisol is necessary for the maintenance of normal blood pressure and plays a permissive role in the arterioles by up-regulating α1-adrenergic receptors. In this way, cortisol is required for the vasoconstrictive response of the arterioles to catecholamines. In hypocortisolism, there is hypotension; in hypercortisolism, there is hypertension.
- Increase in GFR (vasodilation of afferent arterioles which increases renal Blood flow).
- Decreased capillary permeability.
- Cortisol stimulates erythropoietin synthesis and hence increases red blood cell production.

Others

CNS	• Decreases REM sleep • Increase slow-wave sleep • Increases awake time • Negative feedback control on release of ACTH • Modulates perception & emotion
Mineral Metabolism	anti-vitamin D effect, reduces osteoblast differentiation , reduces calcium absorption
GIT*	• Increases HCl secretion
Develop-mental*	• Permissive regulation of fetal organ maturation,required for the development of CNS, retina, skin,GI tract, and lungs. • Surfactant synthesis (phospholipid that maintains alveolar surface tension). • Inhibition of linear growth in children due to direct effects on bone & connective tissue If a child has high amounts of glucocorticoids, the linear growth will increase but the epiphyseal plates will close prematurely. This makes the kid get taller compared to others but his growth will stop premature and they will eventually be taller.

Glucocorticoids Abnormalities

1- Cushing's Syndrome

Overview

- **Increased secretion of corticosteroid**
- Cushing's syndrome results from continued high glucocorticoid levels
- 3rd - 6th decade, 4 to 1 females
- treatment based on cause
- 80% of patients have hypertension (because of the mineralocorticoid effects of cortisol)

Causes & Types

Anterior Pituitary Adenoma	Abnormal function of the hypothalamus*	ectopic secretion of ACTH	Adrenal adenoma, carcinoma.	Pharmacologic Most common
Increased ACTH When the pituitary is the cause, it's called Cushing disease.	Increased CRH	By a tumor elsewhere in the body, such as an abdominal carcinoma.	Adenomas of the adrenal cortex When Cushing's syndrome is secondary to ↑ACTH by the anterior pituitary = Cushing's disease.	When large amounts of glucocorticoids are administered over prolonged periods for therapeutic purposes. e.g. patients with chronic inflammation associated with diseases such as rheumatoid arthritis.

Effects on*

Carbs

- ↑blood glucose level (Can lead to DM)
- ↑gluconeogenesis
- ↓glucose utilization by the tissues

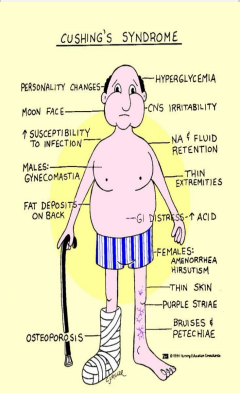
Proteins

- **Generally catabolism everywhere except in liver & plasma proteins.**
- ↓ Tissue proteins almost everywhere in the body (except liver).
- Protein loss from the muscles in particular causes severe weakness.
- Protein collagen fibers in the s.c. (loss of CT) (Leads to osteoporosis)
- Thinning of the skin
- Severely ↓ protein deposition in bones → severe osteoporosis
- Suppressed immune system.

Lipids

- **Mobilization of fat from the lower part** of the body, with concomitant extra **deposition of fat in the thoracic and upper abdominal regions**, giving rise to a buffalo torso (truncal obesity).
- The appearance of the face described as a **"moon face"**

Signs



- Fat is deposited in the body trunk (central obesity)
- Many people with excess cortisol secretion develop a peculiar type of obesity.
- Buffalo hump (excess deposition of fat in the chest and head regions of the body).
- Moon facies, rounded face (subcutaneous fat in cheeks and submandibular).
- Purple striae, (↑cortisol → ↓synthesis of collagen → Rupture of blood vessels). during pregnancy or obesity it appears white
- Blood-glucose levels rises chronically, causing adrenal diabetes.
- May cause beta cells to die.
- memory and attention dysfunctions, depression.
- Susceptibility to infections. This is why you could get sick before an exam. **Stress!**
- Hypertension. (Cortisol up-regulate alpha 1 receptors on the blood vessels→ vasoconstriction)
- Proximal muscle weakness. (break down of muscles to provide amino acids for gluconeogenesis)
- Immunosuppression. (Cortisol inhibits phosphlipase A2, IL-2 and inhibit release of histamine)
- Gluconeogenesis → ↑Glucose in the blood → more insulin is produced by the pancreas → fat storage → Moon face , truncal obesity and buffalo hump.

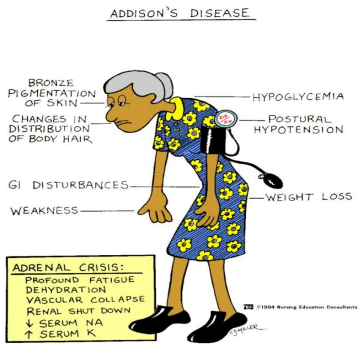
How to Differentiate between ACTH-dependent & ACTH Independent*

By administering large doses of cortisol (dexamethasone).

- In patients with↑ACTH → no suppression of ACTH secretion.
- Patients with primary adrenal overproduction of cortisol (ACTH-independent) →↓levels of ACTH.

Glucocorticoids Abnormalities

2. Addison's disease

Definition	• Failure of the adrenal cortices to produce adrenocortical hormones because of primary atrophy of adrenal cortices. • **Decrease secretion of glucocorticoids and mineralocorticoids**
Primary causes	• Autoimmune disease • Tumors • Infection • Hemorrhage • Metabolic failure • Impaired steroidogenesis • Adrenal dysgenesis • Ketoconazole (glucocorticoid antagonist activity)
Secondary causes	• Hypopituitarism • Suppression by exogenous steroids
Signs & Symptoms	• Fatigability, weakness, anorexia, nausea, weight loss. • **Hyperpigmentation** (Skin pigmentation). Due to high ACTH. • The person is allowed to eat large amounts of salt and drink large amounts of water to balance the increased urine output of salt and water • Increased excretion of sodium and water. • Reduction in ECF volume. • Tendency toward low blood pressure. • Complete absence of aldosterone, the volume depletion may be severe. • **Hypotension** • women loss of axillary and pubic hair • Poor blood glucose regulation • Patient cannot cope with stress • Adrenal crisis: asthenia, severe pains in the abdomen, **hypoglycemia, hyponatremia, hyperkalemia,** hypercalcemia, vascular collapse. 
Clinical manifestations*	• General weakness and becoming easily tired. • Darkened areas of skin (pigmentation). • Blood pressure is low & falls further when you stand which make you dizzy. • Being off your food and weight loss. • Feeling sick and vomiting from time to time. • Abdominal pain which may come and go. • Diarrhea or constipation which may come and go. • Cramps and pain in muscles. • Craving for salt, or salty foods and drinks. • Menstrual periods in women may become irregular, or stop.
Treatment	• glucocorticoid replacement, mineralocorticoid replacement. • The person is allowed to eat large amounts of salt and drink large amounts of water to balance the increased urine output of salt and water.

L12

Adrenal Androgen

Zona Reticularis*

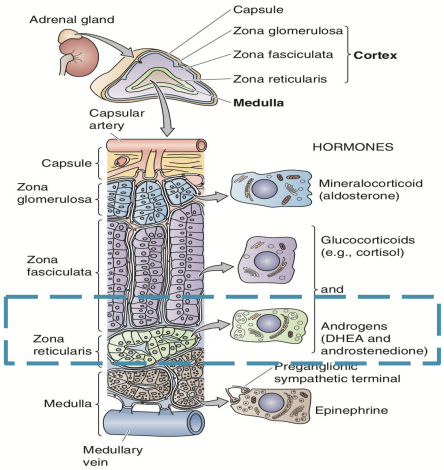
- Produce significant amounts of androgens, mostly dehydroepiandrosterone sulfate (DHEAS)

Hormone Control:

- ACTH

Target tissue:

- General body cells



Androgens

Androgens are the male hormones, they exert masculinizing effects and promote **anabolism and growth**. They include:

Testosterone (Testis)	Adrenal androgens (adrenal gland)
The major active androgen*	Have less than 20% of testosterone activity*

Androgen sources:
Females: 50% adrenal. 50% from Ovaries.
Males: Main source of androgens the Testis

Adrenal cortex

The adrenal cortex in both sexes produce small amounts of sex hormone of the opposite sex

Male sex hormone (Androgens)	Female sex hormone
Adrenal androgens include: Dehydroepiandrosterone (DHEA) Androstenedione	Estrogen Progesterone

Adrenal Androgen

Overview

Adrenal androgens have little androgenic activity, but they provide a pool of circulating precursor for peripheral conversion to more potent androgens (e.g. testosterone, T) and estrogens, (e.g. estradiol)*

- The adrenal cortex produces both androgens "male sex hormones" and estrogens or "female sex hormones". But they don't show any effect because they are produced in a very small amount.
- Produced from zona reticularis in small amounts
- Control of secretion of adrenal androgens is by **ACTH**
- Additional small amounts of sex hormones come from nonadrenal sources.
- Some testosterone in males is converted into estrogen by the enzyme aromatase found in adipose tissues.
- In females, ovaries produce androgen as an intermediate step in estrogen production. Little of this androgen is released in the blood instead of being converted into estrogen.
- Adrenal androgens account for 50% of the androgens in females.

Include

- **Dehydroepiandrosterone (DHEA):**
  - It is the most abundant adrenal androgen
  - DHEA is the primary precursor of natural estrogens.
  - Normally they exert very little masculinizing effect (weak) when secreted in normal amount (mild effect in female).
- **DHEA sulfate (DHEAS).**
- **Androstenedione:**
  - An androgenic steroid produced by the testes, adrenal cortex, and ovaries.
  - Androstenediones are converted metabolically to testosterone and to estrogens in the fat and other peripheral tissues.
  - It is an important source of estrogen in men and postmenopausal women.
  - Androstenedione were used as an athletic or body building supplement.
- **Androstenediol**
- **11β-hydroxyandrostenedione (11OHA)**
- **11β-hydroxytestosterone (11OHT)**

Binding & Metabolism*

- About 90% of adrenal androgens are bound to albumin and 3% approximately is bound to sex hormone-binding globulin (SHBG).
- DHEAS has high affinity to albumin, half-life 7-10 hours. DHEA has low affinity, 15-30 minutes.
- DHEA, DHEAS, and Androstenedione are converted to the potent androgens T and DHT in peripheral tissues.

Effects

Males	Females
• Spermatogenesis • Inhibition of fat deposition • Muscle mass • Brain: Androgen levels have been implicated in the regulation of human aggression and libido • Masculinization of the developing male fetus (including penis and scrotum formation)	• Growth of pubic and axillary hair • Pubertal growth spurt development • Androgens have potential roles in relaxation of the myometrium preventing premature uterine contractions in pregnancy • Development and maintenance of female sex drive (libido)

Adrenarche*

- It's the premature activation of the adrenal gland to send androgen.
- The onset of adrenarche in humans is a gradual process that precedes the onset of puberty (6-7 years of age in girls and 7-8 years of age in boys).

Adrenogenital Syndrome

Causes

1. **Adrenocortical tumors**
   - Secretes excessive quantities of androgens that cause intense masculinizing effects throughout the body
2. **Congenital adrenal hyperplasia (CAH)** (explained with a diagram in the next slide)
   - It is a familial disorder of adrenal steroid biosynthesis with autosomal recessive mode of inheritance.
   - The defect is expressed as adrenal enzyme deficiency.
   - Affect both boys and girls
   - Most important enzyme deficiencies:
     - **21 α-Hydroxylase** (>80% of cases).
     - 11 β-Hydroxylase (5-10% of cases)
     - 17 α-Hydroxylase (very rare)
   - The enzyme deficiency causes reduction in end products, accumulation of hormone precursors & increased ACTH production.
   - The clinical picture reflects the effects of inadequate production of cortisol & aldosterone and the increased production of androgens & steroid metabolites (steroids are diverted to become androgens).

Signs & Symptoms

In Female

Before birth*	After birth
Pseudohermaphroditism: - Before 12 weeks in female fetus - XX true female with external male genitalia Cause: - exposure of the mother to excessive androgens	- Virilization: Development of male characters in females: causes beard growth, deeper voice, masculine distribution of body hair, and growth of the clitoris to resemble a penis. Increase bulk of muscles, Hoarseness, Atrophy of the breast, Amenorrhea, increase body and facial hair, occasionally baldness.

In Males

After birth (Prepubertal Male)	Adult male *
- Early appearance of male characters - Increase musculature - Development of external genitalia organ to adult size - No spermatogenesis - rapid development of secondary sexual characters - increased growth but shorter stature because of early closure of epiphyseal plates.	the virilizing characteristics of adrenogenital syndrome are usually obscured by the normal virilizing characteristics of the testosterone secreted by the testes.

Diagnosis*

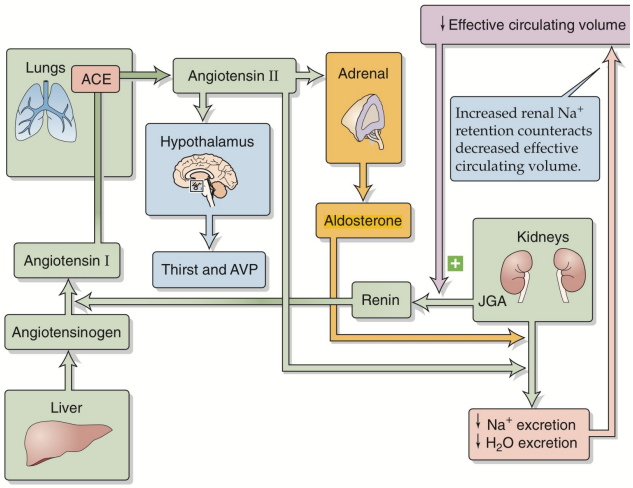
It is often difficult to make a diagnosis. However, the excretion of 17-ketosteroids (derived from androgens) in urine may be 10 to 15 times normal, used in diagnosing the disease.

Treatment*

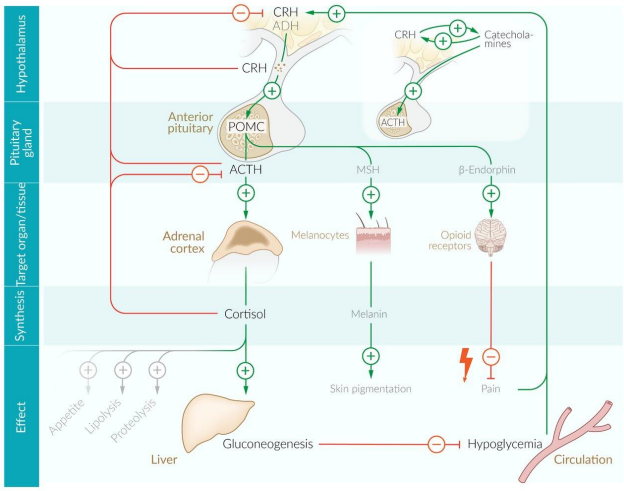
Glucocorticoids

EXTRA

L10

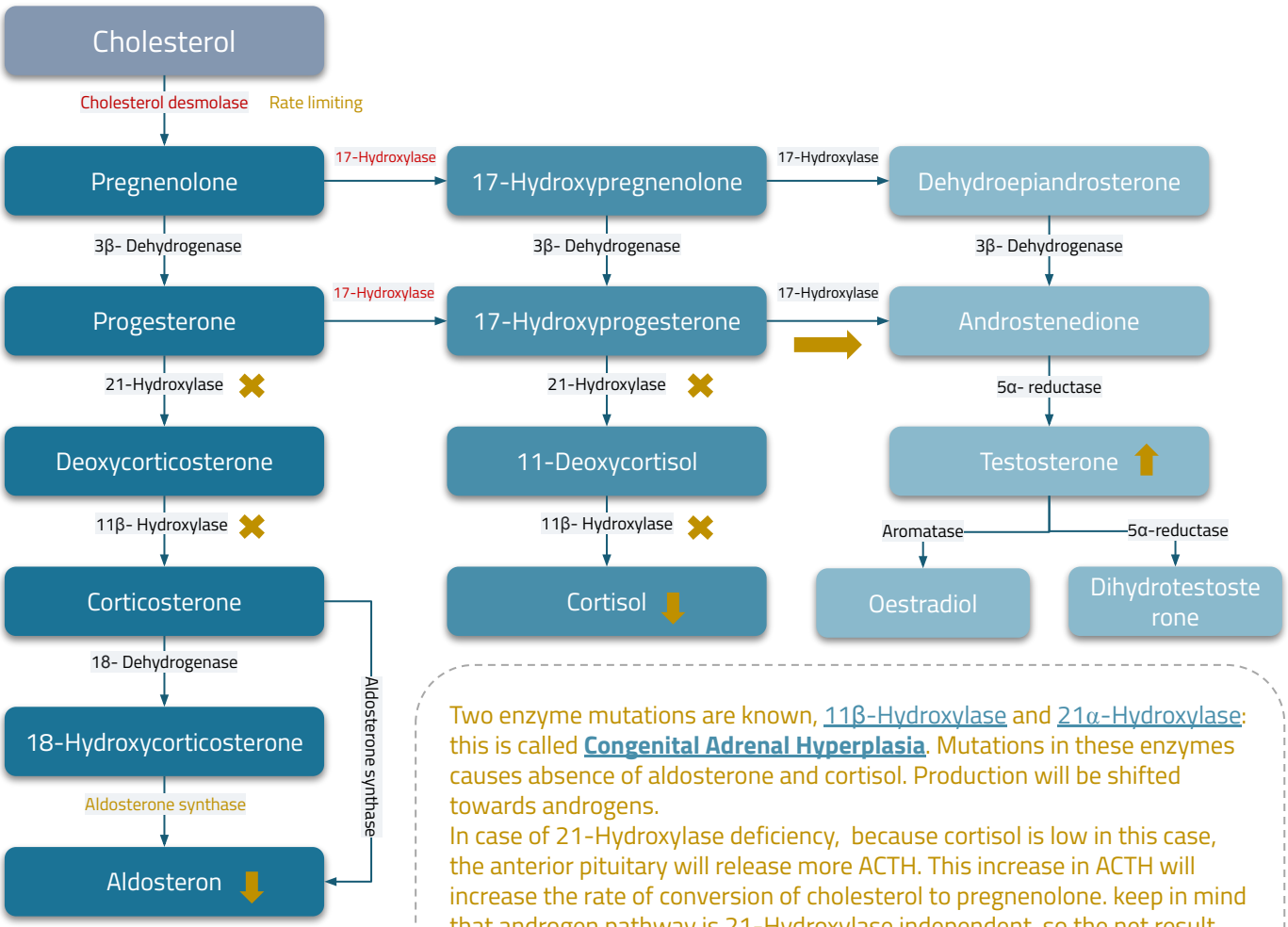


L11



L12

Congenital Adrenal Hyperplasia



Two enzyme mutations are known, 11β-Hydroxylase and 21α-Hydroxylase: this is called **Congenital Adrenal Hyperplasia**. Mutations in these enzymes causes absence of aldosterone and cortisol. Production will be shifted towards androgens.
In case of 21-Hydroxylase deficiency, because cortisol is low in this case, the anterior pituitary will release more ACTH. This increase in ACTH will increase the rate of conversion of cholesterol to pregnenolone. keep in mind that androgen pathway is 21-Hydroxylase independent, so the net result will be increased secretion of androgens.
Click on the names to learn more!

EXTRA

L11 LINDA

Table 9–12 Pathophysiology of the Adrenal Cortex

Disease	Clinical Features	ACTH Levels	Treatment
Addison disease (primary adrenocortical insufficiency)	Hypoglycemia Anorexia, weight loss, nausea, vomiting Weakness Hypotension Hyperkalemia Metabolic acidosis Decreased pubic and axillary hair in females Hyperpigmentation	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids and mineralocorticoids
Cushing syndrome (e.g., primary adrenal hyperplasia)	Hyperglycemia Muscle wasting Central obesity Round face, supraclavicular fat, buffalo hump Osteoporosis Striae Virilization and menstrual disorders in females Hypertension	Decreased (negative feedback effect of increased cortisol)	Ketoconazole Metyrapone
Cushing disease (excess ACTH)	Same as Cushing syndrome (see above)	Increased	Surgical removal of ACTH-secreting tumor
Conn syndrome (aldosterone-secreting tumor)	Hypertension Hypokalemia Metabolic alkalosis Decreased renin levels	—	Aldosterone antagonist (e.g., spironolactone) Surgery
21β-hydroxylase Deficiency	Virilization in females Early acceleration of linear growth Early appearance of pubic and axillary hair Symptoms of deficiency of glucocorticoids and mineralocorticoids	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids and mineralocorticoids
17α-hydroxylase Deficiency	Lack of pubic and axillary hair in females Symptoms of deficiency of glucocorticoids Symptoms of excess mineralocorticoids	Increased (negative feedback effect of decreased cortisol)	Replacement of glucocorticoids Aldosterone antagonist (e.g., spironolactone)

MCQ & SAQ:

Q1: Which one of the following is NOT true about aldosterone?

A. Synthesis in zona glomerulosa (in adrenal cortex)
B. Considered as mineralocorticoids
C. Highest conc. begin at 8 PM
D. The target cell is called Principle (P) cell

Q2: Which of the following is NOT an action of aldosterone?

A. Increase ECF volume and arterial pressure
B. Decrease secretion of H+ through sodium-hydrogen exchanger
C. Transport of K+ from ECF into most cells of the body
D. Enhances Na+ absorption, especially in the colon

Q3: During stressful conditions, cortisol will be released, which of the following will be an effect of cortisol:

A. Decrease amino acid level in the blood
B. Decrease blood glucose level
C. Increase Glucose utilization by the cells
D. Mobilization of FFA & amino acids from stores

Q4: Which one of the following is a sign of Addison's disease?

A. Irritability
B. Purple striae
C. hyperpigmentation
D. Moon face

Q5: What is the most common enzyme deficiency in (CAH)?

A. 23 α-Hydroxylase
B. 11 β-Hydroxylase
C. 17 α-Hydroxylase
D. 21 α-Hydroxylase

Q6: F Dr. What is the main hormone produced from Reticularis

A. Aldosterone
B. Sex hormone
C. Cortisol
D. ADH

From females dr:
What is the main hormone produced from Fasciculata?

What is the main hormone produced from Glomerulosa?

answer key: 1: 2: B 3: D 4: C 5: D 6: B

1- Compare between the regions of adrenal cortex and their hormones

2- List three mechanisms in which glucocorticoids secretion is regulated?

3- List the mechanisms that increase and decrease aldosterone secretion.

4- Enumerate four causes of Cushing's syndrome?

A1: Check table slide 8

A2: 1-CRH from hypothalamus regulate ACTH secretion, 2-ACTH from anterior pituitary stimulates cortisol synthesis and secretion, 3-ADH is a secretagogue for ACTH.

A3: Mechanisms that increase secretion: 1-RAAS(The Major stimulant), 2-Hyperkalemia, 3-ACTH
Mechanisms that decrease secretion: Atrial natriuretic peptide (ANP)

A4: 1- Adenomas of the anterior pituitary
2- Abnormal function of the hypothalamus
3- Ectopic secretion of ACTH by a tumor
4- Adenomas of the adrenal cortex

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