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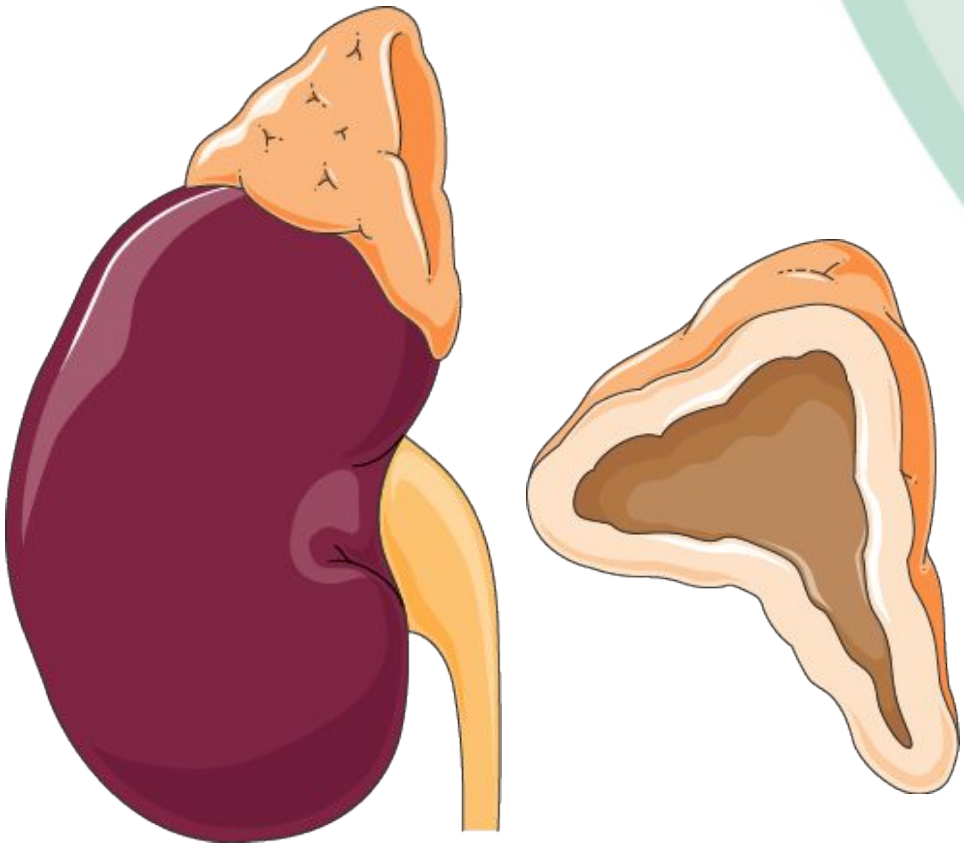


Adrenocortical Hormone

ENDO Physiology

Editing File

Color Index :

- Main Text
- Important
- Girls Slides
- Boys Slides
- Notes
- Extra

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 regulation of secretion of adrenocortical steroids.
- The physiological actions of aldosterone.
- Explain how negative feedback regulates aldosterone secretion
- Discuss regulation of aldosterone secretion.
- List the major stimuli for aldosterone secretion.

Lecture 11

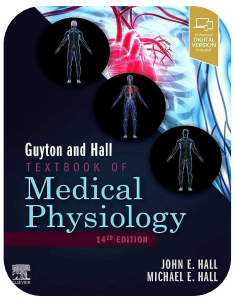
- Describe the metabolism and physiological effects of glucocorticoids.
- Describe the mechanisms that regulate secretion of glucocorticoids
- Describe the main features of the diseases caused by excess or deficiency of each of the hormones of the adrenal gland.

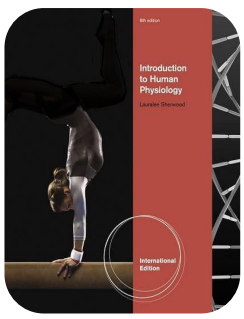
Lecture 12

- Not found.

Resources

Only ENDO chapters included





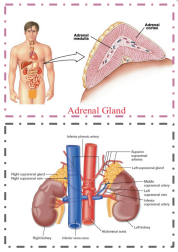
sherwood-human-physiology

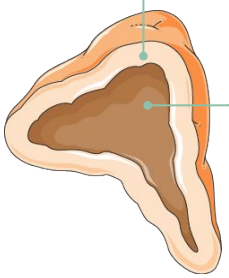
This lecture was presented by:
Dr. Abeer AlGhumlas - Dr. Khalid AlRegaiey

Adrenal (Suprarenal) Gland

Introduction

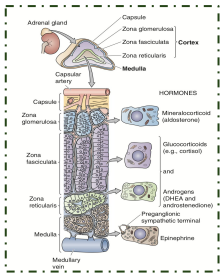
- There are two adrenal (suprarenal) glands that lie at the superior pole of the two kidneys.
- Paired, small pyramidal-shaped organ atop the kidneys.
- Weigh 4/6-10 g
- Structurally and functionally, Divide into two morphologically and distance regions they are two glands in one : **Adrenal cortex,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





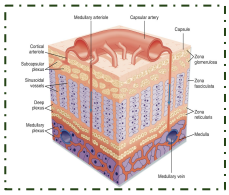
Adrenal Cortex

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



Adrenal medulla

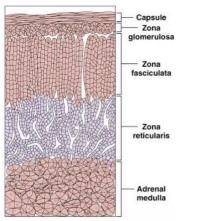
- 10-20% formed from **neural ectoderm**, can be considered a modified sympathetic ganglion
- It is the central region
- 20% of the gland Secretes **epinephrine** and **norepinephrine** (related to sympathetic nervous system).

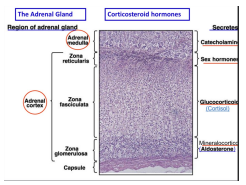


How did they get their names? **Mineralo**: mainly acts on electrolytes **Gluco**:-mainly acts on glucose

Both release glucocorticoids and androgens but in different amounts

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



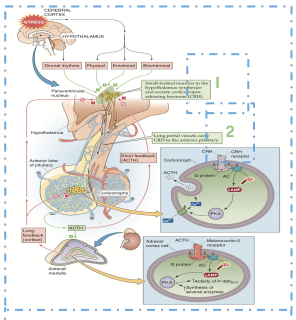


Notice that Aldosteron can only be synthesized in the Glomerulosa whereas Cortisol, Androgens, and Estrogens can be synthesized from two layers.
Mnemonic: GFR - glomerulosa, fasciculata, reticularis

DHEA: "Dehydroepiandrosterone"

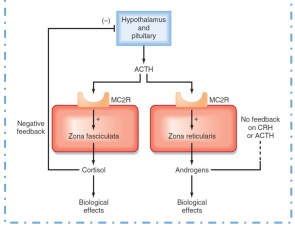
HPA Axis and Loophole in the -ve feedback

Ist 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.



The "loophole" in the hypothalamic-pituitary-adrenal axis: ACTH stimulates production of both cortisol and adrenal androgens, but only cortisol negative feedback 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. The targeted organs will get hyperplasia.

Congenital Adrenal Hyperplasia: production of cortisol, aldosterone, or both is impaired because of an autosomal recessive genetic defect in one of the adrenal enzymes involved in synthesizing adrenal steroid hormones from cholesterol This can cause the negative feedback loophole (above).
Overview of Congenital Adrenal Hyperplasia - Pediatrics - MSD Manual Professional Edition (msdmanuals.com)

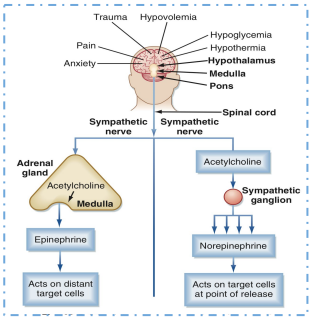


Steroid Hormone

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

GH **decreases** with age, Cortisol **increases** with age (facing more stress with time)

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

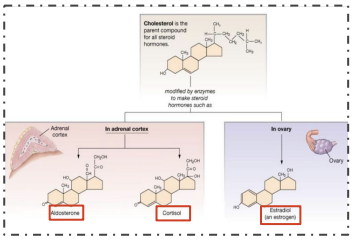


Steroid Hormones Synthesis

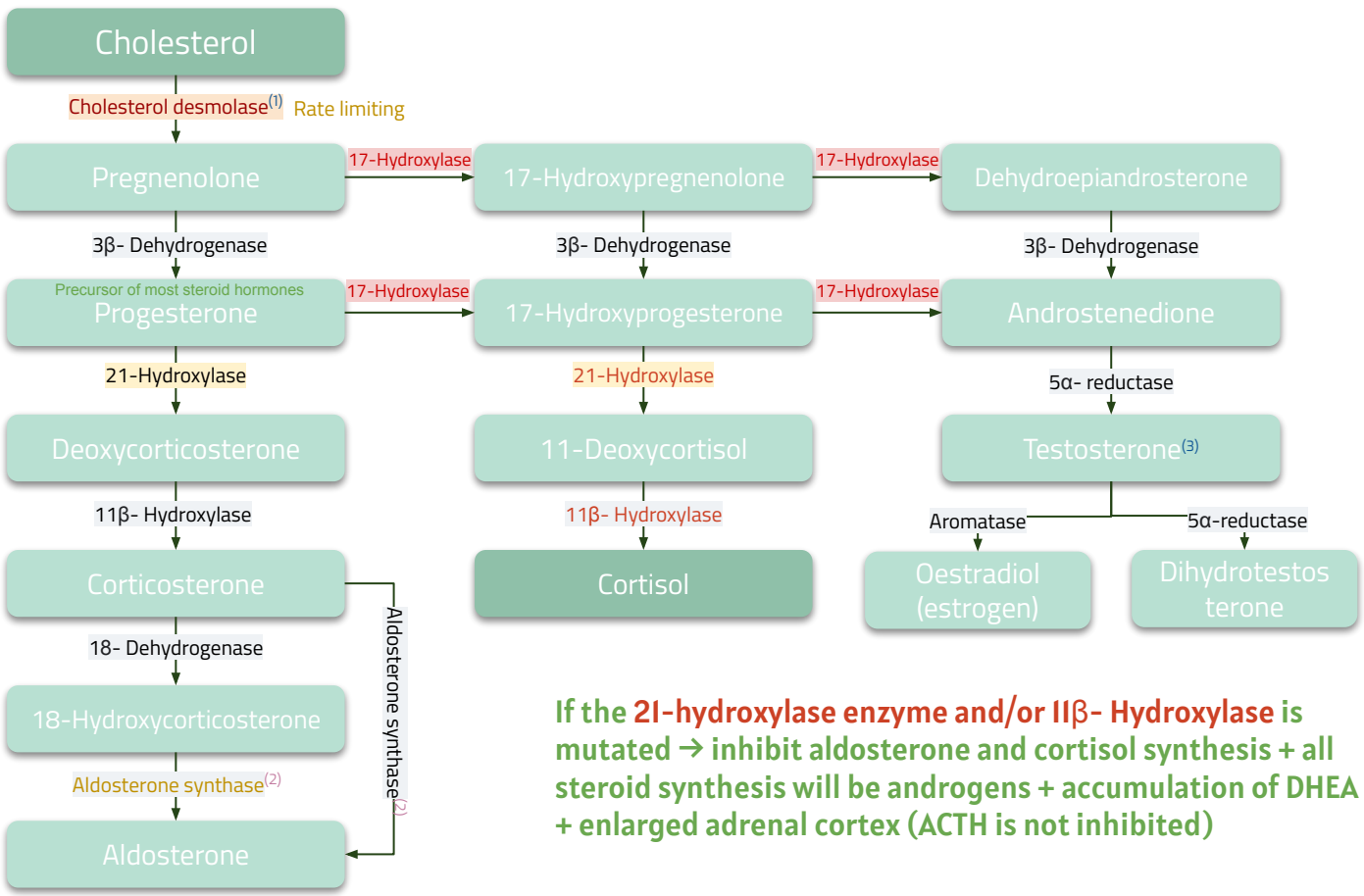
Male slides

- 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) e.g.Aldosterone
- The first step in the synthesis of all steroid hormones is conversion of cholesterol to **pregnenolone** by the enzyme cholesterol desmolase (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 Hormone : Structure



Synthetic Pathways for Adrenal Steroids (Steroidogenesis)



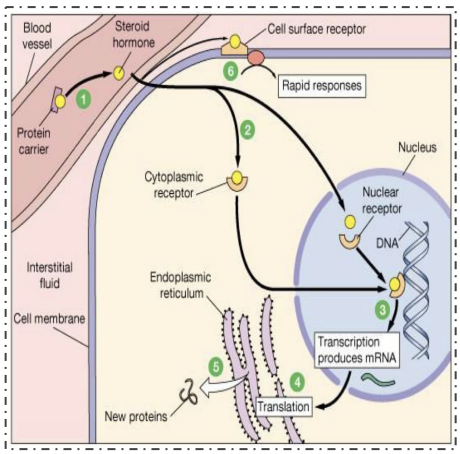
If the 21-hydroxylase enzyme and/or 11β- Hydroxylase is mutated → inhibit aldosterone and cortisol synthesis + all steroid synthesis will be androgens + accumulation of DHEA + enlarged adrenal cortex (ACTH is not inhibited)

Steroid hormones

A Repetition of the Ist lecture :)

Steroid Hormones: Action/ Cellular Mechanism of Aldosterone Action

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 (5) 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 the expression of apical Na channels and an Na/K/Cl cotransporter



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.

Aldosterone

Aka salt retaining hormone

Introduction

- A steroid hormone. • Essential for life. •Synthesized in zona glomerulosa
- 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.**
- Aldosterone exerts the 90% of the mineralocorticoid activity.
- Target cells are called "principal (P) cell".
- 60% of aldosterone bound to plasma protein, 40% is free form.
- Half life: 20 min
- The main mineralocorticoid produced by the adrenal gland

Aldosterone Secretion Is Stimulated By:

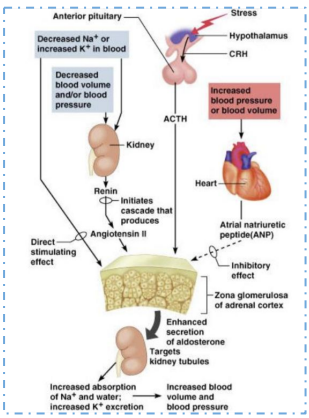
Male slides

- Decreasing blood volume or pressure (renin-angiotensin system) is the major stimulant
- ACTH
- Rising blood levels of K+ (**hyperkalemia**)

The Four Mechanisms of Aldosterone Secretion

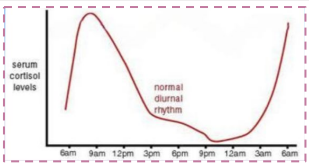
Male slides

- **Renin-Angiotensin System(RAS)**, hypovolemia
- **Hyperkalemia**: Plasma Concentration Of potassium directly influences the zona glomerulosa cells
- **ACTH**–causes small increase of aldosterone during stress
- Atrial Natriuretic Peptide(ANP)–inhibits activity of the zona glomerulosa and reduces aldosterone



Transport and metabolism

- Aldosterone binds to albumin and corticosteroid- binding protein in blood with low affinity and therefore has a biological half-life of about 20 minutes.
- Stimulates synthesis of more Na/K-ATPase pumps.
- Much of secreted Aldosterone is metabolized/inactivated by the liver and converted to tetrahydroglucuroind derivative and conjugated to a glucuronic acid or sulfate and secreted in bile/feces or excreted by the kidney/urine



Aldosterone levels fluctuate diurnally—highest concentration being at 8 AM, lowest at 11 PM, in parallel to cortisol rhythms.

Actions of aldosterone

- Increase renal tubular reabsorption of Na+ and secretion of K+ and H+
- Binds to mineralocorticoid receptor (MR).

Na reabsorption action

- This Action Acts mainly on the cells of the collecting ducts and distal tubules.
- 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

Renal action

Circulatory Actions of Aldosterone

- This action Acts mainly on the cells of the collecting tubules. and lesser in distal tubules and collecting ducts.
- Excess Aldosterone increases **ECF volume** and **arterial pressure** (maintain extracurricular volume) but has only a small effect on plasma Na+ concentration. (water is also absorbed, ADH is secreted).

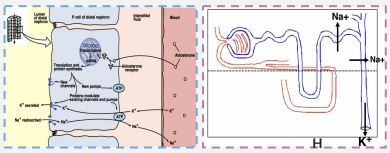
Aldosterone

Actions of aldosterone

- Increase renal tubular reabsorption of Na+ and secretion of K+ and H+
- Binds to mineralocorticoid receptor (MR).

Na reabsorption action | Renal action | Circulatory Actions of Aldosterone

- This action Acts mainly on the cells of the collecting tubules. and lesser in distal tubules and collecting ducts.
- Aldosterone causes Na+ to be conserved in the ECF (water will follow) while increasing K+ excretion in the urine.
- Stimulates **sodium reabsorption** by distal tubule and collecting duct of the nephron and promotes **potassium and hydrogen ion excretion** by:
  - 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.
  - Stimulate secretion of H+ in exchange for k+ by intercalated cells of collecting tubule.



- Causes secretion of H+ in exchange for K+ in the intercalated cells of the collecting tubules
- (so they secrete H+ through two transporters),
- 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

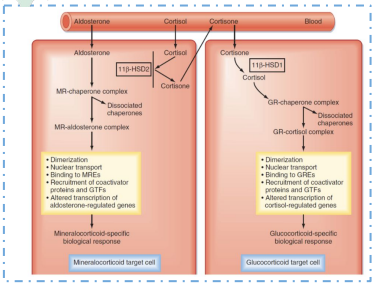
Aldosterone Escape

Male slides

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.** Moreover, ANP is released causing sodium excretion.
- (no edema in primary hyperaldosteronism).
- In hyperaldosteronism: Aldosterone escape and ANP help with reducing edema

AME



AME: "Apparent mineralocorticoid excess syndrome"

Female slides | Important

Regulation of Aldosterone

Increase Aldosterone secretion (Stimulation)

Hyperkalemia

Hyperkalemia→ increases activity of cortical cells → increased aldosterone

- Increased plasma (ECF) 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 & hypotension)**↑ activity of RAAS (↑levels of Angiotensin II) more info in next slide.

ACTH very weak

- ACTH also stimulates aldosterone synthesis. However the ACTH stimulation is more transient than the other stimuli and is diminished within several days
- 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 in the ECF —>Increases aldosterone (not significant)
- Hypovolemia
- Hypotension

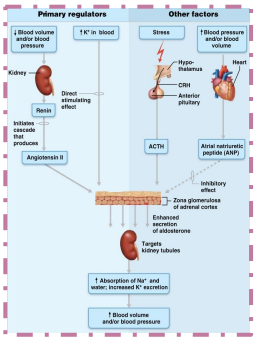
Other factors

- 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.

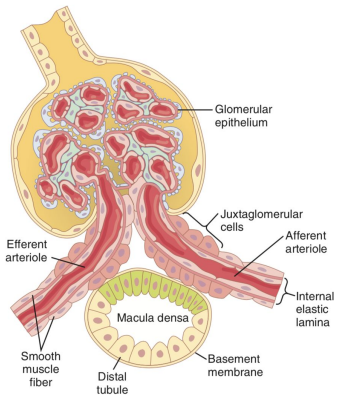
Control of Aldosterone secretion through RAAS

Female slides

- Renin
- Angiotensin II

1 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)

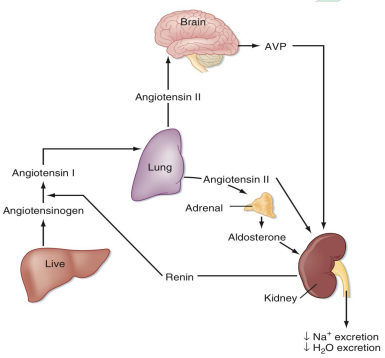


2 Angiotensin II

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.
- Inhibition of angiotensin converting enzyme causes hypotension



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)** increase secretion of mineralocorticoids : decreased plasma renin (Hypokalemia, hypernatremia, hypertension) .
- **Secondary hyperaldosteronism:** increased plasma renin

Hyperaldosteronism

Primary (decreased renin) — Important

Example	**Conn's syndrome** (Increased secretion of mineralocorticoids)
Causes	❖ Nodular hyperplasia of adrenal cortex or zona glomerulosa ❖ Tumor of the **zona glomerulosa cells** (adenoma) ⟶ Secretes large amount of aldosterone.
Sign & Symptoms	❖ Headache. ❖ Hypertension ❖ Very slight increase in plasma sodium concentration, Mild Hypernatremia. ❖ **Hypokalemia,** (causing muscle weakness / occasional periods of muscle paralysis caused by the hypokalemia). ❖ **Hypervolemia.**(Slight increase in ECF volume and blood volume). ❖ Almost always, **hypertension.** ❖ **Mild 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 -intermittent paralysis. -Hand cramping.
Treatment	• Surgical (Usually) for adenoma • Spironolactone, a potassium-sparing diuretic that acts as an aldosterone antagonist.

Secondary (increased renin)

Causes	- Cirrhosis - Hyperreninism - Cor pulmonale - Ascites - Left ventricular failure

Other causes*

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 IIß-HSD2 (IIß- 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 IIß-HSD2 causing water and sodium retention

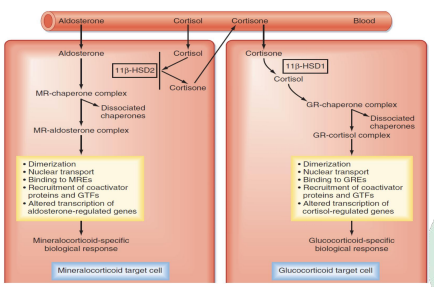


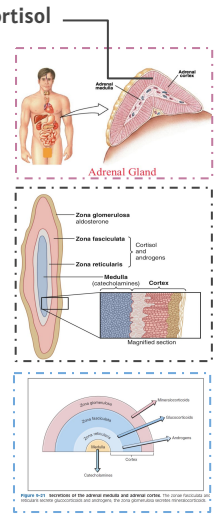
TABLE 43.3 Relative Glucocorticoid and Mineralocorticoid Potency of Natural Corticosteroids and Some Synthetic Analogues in Clinical Use[a]

	Glucocorticoid	Mineralocorticoid
Corticosterone	0.5	1.5
Prednisone (1.2 double bond)	4	<0.1
6α-Methylprednisone (Medrol)	5	<0.1
9α-Fluoro-16α-hydroxyprednisolone (triamcinolone)	5	<0.1
9α-Fluoro-16α-methylprednisolone (dexamethasone)	30	<0.1
Aldosterone	0.25	500
Deoxycorticosterone	0.01	30
9α-Fluorocortisol	10	500

[a]All values are relative to the glucocorticoid and mineralocorticoid potencies of cortisol, which have each been arbitrarily set at 1.0. Cortisol actually has only 1/500 the potency of the natural mineralocorticoid aldosterone.

From 438's team

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)

Female slides

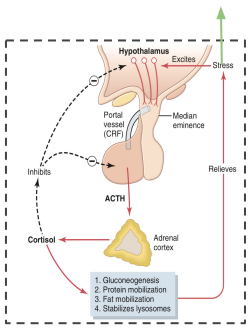
Main glucocorticoids in humans

Cortisol	• Known as hydrocortisone • 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

-Hyperthermia
-Hypoglycemia
-Trauma
-Exercise
-Emotional stress

Important

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**

Cortisol Transport & Metabolism

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

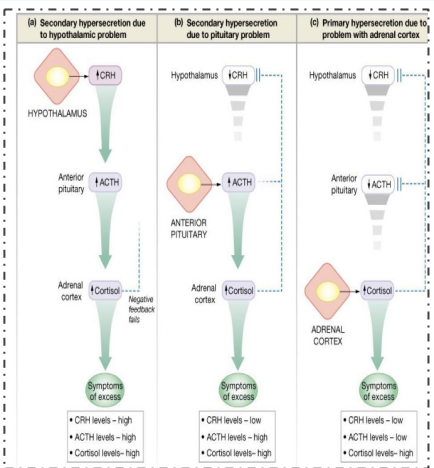
Bound

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

Free

6%
- **Active form**

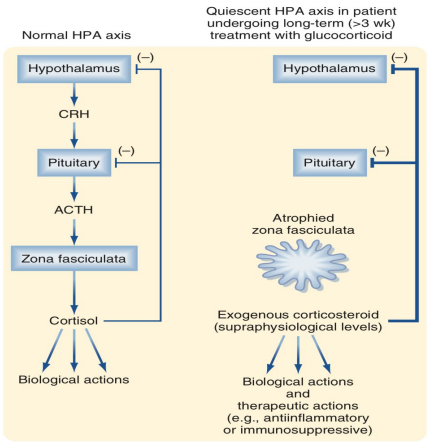
Primary and secondary hypersecretion of cortisol:



Glucocorticoids

Quiescent HPA axis: Long-term GC treatment:

Med442: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.



Actions of Glucocorticoids: Male slides

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.

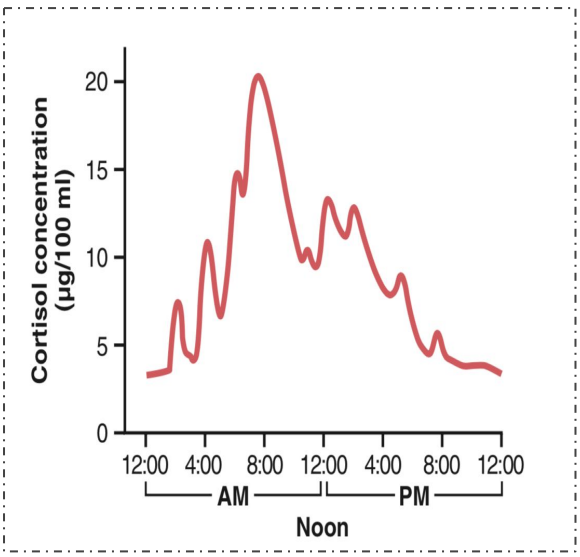
Circadian rhythm of cortisol secretion: Female slides Important

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

Physiological actions of cortisol

Metabolic — Important

Carbo-hydrates

- Increase the enzyme required to convert amino acids into glucose in the liver cells (Gluconeogenesis). Anti-insulin effect. The required enzyme is PEPCK.
- Cortisol also decreases GLUT4-mediated glucose uptake in skeletal muscle and adipose tissue.
- Mobilization of amino acids from extrahepatic tissues (muscles) for gluconeogenesis.
- Antagonize insulin effects to inhibit gluconeogenesis in the liver.
- Promote glucose sparing by potentiation the effects of catecholamines on lipolysis, thereby making FFAs available as energy source.
- Adrenal diabetes. (cortisol has anti-insulin effect so it causes insulin resistance which increases blood glucose levels, happens in predisposed patients). When glucocorticoids increase fasting glucose levels beyond 126g/dl, it's considered diabetes. Only happens in genetically prone patients .
- **↑↑Glucose level in the blood (Adrenal Diabetes)** by: (can lead to hyperglycemia & DM if excess)

1. Liver:
   - Stimulates gluconeogenesis (6-10 fold).
   - Increase glycogen storage by the liver cells (such as insulin. some glycogen will be released to general circulation and some will remain in 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)

GUYTON EXTRA: Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. For reasons that are not entirely clear, high levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilization.

Proteins

Males slides:

- Mobilization of amino acids from non-hepatic tissue.
- Proteocatabolic effect in all body cells except of the liver.
- Decrease protein synthesis. Opposite to insulin effect
- Decrease amino acids transport into extrahepatic tissue (muscles, lymphatic tissue). Opposite to insulin effect, which increases AA transport
- Proteoanabolic effect in the liver:
  - Enhanced liver proteins.
  - Increased plasma proteins. important stress response

Females slides:

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 the main source of fat (cholesterol, FFA. triglycerides...etc) in plasma is the liver not what you eat, which has little effect, so patients with high cholesterol always advised that **Stress** is the main contributor.
- ↑↑ Their utilization for energy.
- Excess cortisol causes obesity: excess deposition of fat in the chest and head regions of the body, giving a buffalo-like torso and a rounded "moon face."

Physiological actions of cortisol cont

- Metabolic
- Stress
- Anti-inflammatory
- Immunosuppression Blood Cells
- Anti-allergic effects
- Circulation
- Other (Cns, GIT…ets)

Physiological actions of cortisol

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.

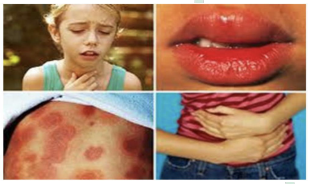
Anti-inflammatory :

- Glucocorticoids are used to alleviate inflammation. By the following:
  - 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 inhibit the secretion of histamine from mast cells
  - Attenuates fever mainly because cortisol reduces the release of interleukin-I from WBC.
  - 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.
  - After cortisol administration the inflammation caused by the disease subside with 24 hours, Prevent the damaging effect of the inflammatory process.
- 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?
  - Causes 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.

Blocks the inflammatory response to allergic reaction

Female slides

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 prevents shock and death** as a result of **anaphylaxis**, a condition that otherwise kills many people.



Physiological actions of cortisol cont

- Metabolic
- Stress
- Anti-inflammatory
- Immunosuppression Blood Cells
- Anti-allergic effects
- Circulation
- Other (Cns, GIT...ets)

Physiological actions of cortisol

- **Immunosuppression/ Blood Cells :**
- **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** (heart-kidney, liver) **in reducing organ rejection.**

- **Anti-inflammatory & 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.
- Vascular Effect :
  - Maintains **body fluid volumes** & vascular integrity. (If excess, can lead to HTN)
  - BP regulation & cardiovascular function:
    - Sensitizes arterioles to action of noradrenaline/norepinephrine **(Permissive effect).** (vasoconstriction by alpha-I, vasodilation by beta-2) **(Permissive effect,** without cortisol they will not function very well).
    - Cortisol is necessary for the maintenance of normal blood pressure and plays a permissive role in the arterioles by up-regulating αI-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. Squeezes spleen (which contains a lot of blood) causes vasoconstriction to release RBCs from spleen. in stress and exercise you need RBCs and glucose and oxygen delivery for organs that are involved like brain. Skeletal muscles, heart and lungs.

CNS	-Decreases REM sleep. - Increase slow-wave sleep . - Increases awake time. -Negative feedback control on release of ACTH. - Modulates perception & emotion. Chronic stress and chronic increase in cortisol might be damaging to neurons, and might be involved in the deterioration of cognitive functions in aging
Mineral metabolism	❖ Anti-vitamin D effect, reduces osteoblast differentiation, reduces calcium absorption. ❖ Inhibit bone formation by decreasing the synthesis of type I collagen, the major component of bone matrix.
GIT	❖ Increases HCl secretion. Decrease mucus layer, NSAIDS are contraindicated in patients with ulcers
Developmental	❖ 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

Cushing's syndrome (Hypercortisolism)

Overview:

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

Causes and types

Anterior pituitary adenoma Cushing disease	Abnormal function of hypothalamus	Ectopic secretion of ACTH	Adrenal adenoma, carcinoma	Pharmacological
Increased ACTH. When Cushing's syndrome is secondary to ↑ACTH by the anterior pituitary = Cushing's disease. 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 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.

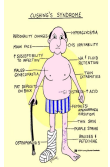
Female slides

Effects on, manifestation

Carbs metabolism	↑blood glucose level (Can lead to DM) ↑gluconeogenesis ↓glucose utilization by the tissues
Protein metabolism	Generally catabolism everywhere except in liver & plasma proteins. ↓ Tissue proteins almost everywhere in the body (except liver and plasma proteins). Protein loss from the muscles, causes severe weakness. In subcutaneous tissues, loss of collagen fibers (loss of C.T.) → thinning of the skin → Striae (Leads to osteoporosis). Severely ↓ protein deposition in bones → severe osteoporosis Suppressed immune system: ↓ lymphoid tissue protein.
Lipids	Abnormal fat redistribution: 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/-like torso (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 upregulate alpha I receptors on the blood vessels→ vasoconstriction)
- Proximal muscle weakness. (break down of muscles to provide amino acids for gluconeogenesis)



How to Differentiate between ACTH-dependent & ACTH Independent Cushing's syndrome?

Female slides

- By administering large doses of cortisol (dexamethasone).
- In patients with↑ACTH → will be there suppression of ACTH secretion.
- Patients with primary adrenal overproduction of cortisol (ACTH-independent) → no suppression of ACTH secretion (usually Cushing syndrome have low or undetectable levels of ACTH)

Abnormalities
Adrenal insufficiency: Addison's disease

Addison's disease

Female slides

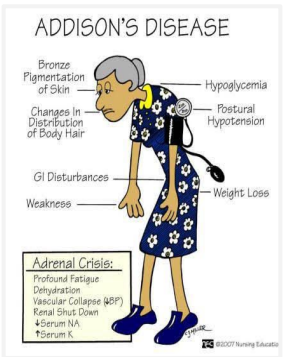
- First discovered by Thomas Addison in 1855, and described as an infection of the adrenal gland- most commonly TB
- Now instead of infection, it's most commonly characterized by an autoimmune destruction of adrenal glands

It's **failure of the adrenal cortices to produce adrenocortical hormones** because of primary atrophy of adrenal cortices → hypoadrenalism
Decrease secretion of glucocorticoids and mineralocorticoids

Causes

Primary	Secondary
• autoimmune disease • tumors • infection • bleeding / hemorrhage • impaired steroidogenesis \ metabolic failure • adrenal dysgenesis • ketoconazole (glucocorticoid antagonist activity)	• hypopituitarism • suppression by exogenous steroids

Clinical manifestation



Important

Clinical manifestation

Mineralocorticoid Deficiency:

- Increased excretion of sodium and water → hyponatremia
- **Reduction in ECF volume** → Tendency toward low blood pressure (hypotension).
- complete absence of aldosterone →Severe volume depletion and shock
- hyperkalemia
- Severe volume depletion and shock
- Mild acidosis , Hypercalcemia
- 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.

Glucocorticoid Deficiency:

- Reduced cortisol results in:
  Poor blood glucose → can't maintain normal blood glucose level between meals → **hypoglycemia**

Melanin Pigmentations:

- **Skin pigmentation** (elbow,knee, nail beds, nipples and scars) and mucus membranes

Other sign and symptoms:

- **Weakness**, anorexia, women loss of axillary and pubic hair
- Patient cannot cope with stress
- Adrenal crisis: asthenia, severe pains in the abdomen, hypoglycemia, hyponatremia hyperkalemia, hypercalcemia,vascular collapse.
- Nausea & vomiting → dehydration → ↓BP
- **Fatigability**, weight loss, postural hypotension

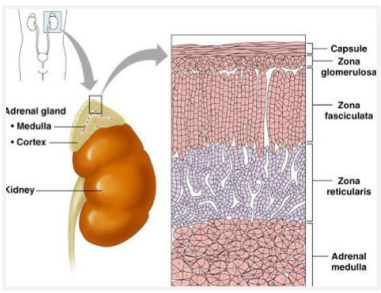
Treatment

glucocorticoid replacement, mineralocorticoid replacement.

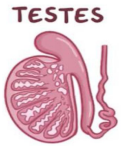
Adrenal Androgen

Androgens

Androgens are the male hormones that exert **masculinizing** (ذكوريه) effects and they promote anabolism and growth

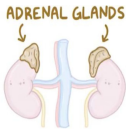


Androgen sources



Testosterone
(Testis)

The major active, significant,and more abundant testicular androgen



Adrenal androgens
(Adrenal gland)

Have little activity which is less than 20% of testosterone 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)

1. Normally they exert very little masculinizing effect (weak) when secreted in normal amount. (mild effect in female).

2. Produced: From Zona **reticularis** in significant \ small amounts هذا اللي مكتوب والله
mostly dehydroepiandrosterone (DHEA) , (DHEAS), some estrogens and cortisol
DHEA may be converted into estrogens.

3. - **Hormone Control**: of secretion of adrenal **androgens** is by -
ACTH -cortical androgen-stimulating hormone
   - Serum level of DHEA change with age.
   - Target tissue: general body cells

Adrenal cortex

- The adrenal cortex in **both** sexes produces small amounts of sex hormone of the opposite sex (androgens "male sex hormones" and estrogens or "female sex hormones")
- Additional small amounts of sex hormones come from non adrenal source
- 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 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

Adrenal Androgen

Androgens (male sex hormones)

- Male sex hormones, which are secreted by the testes and collectively called androgens, including: - testosterone - dihydrotestosterone - androstenedione.
- Adrenal androgens include:
  - Dehydroepiandrosterone (DHEA)
  - DHEA sulfate (DHEAS)
  - Androstenedione
  - Androstenediol
  - IIβ-hydroxyandrostenedione (IIOHA)
  - IIβ-hydroxytestosterone (IIOHT)

Female sex hormones:
- Estrogens
- Progesterone

- Testosterone is so much more abundant than the others that one can consider it to be the significant testicular hormone.
- Much, if not most, of the testosterone is eventually converted into the more active hormone dihydrotestosterone in the target tissues.

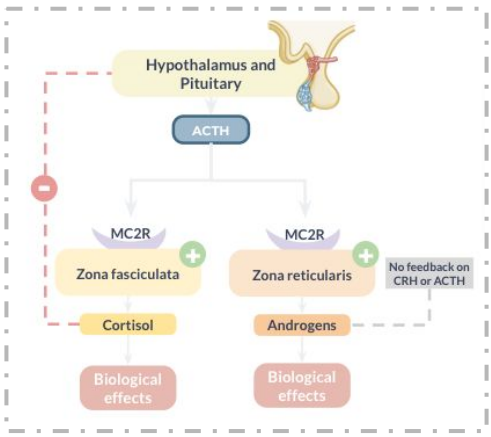
Binding & metabolism

Male slides

- 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 low affinity, 15-30 minutes
- DHEA, DHEAS, and Androstenedione are converted to the potent androgens T and DHT in peripheral tissues.

The "loophole" in the hypothalamic-pituitary-adrenal axis

Special thanks to 441 team for the AMAZING graph



Adrenarche

Male slides

The onset of adrenal androgens 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)
(It's the premature activation of the adrenal gland to send androgen)

Role of Androgens

♂ Male	Female slides	♀ Female
• Spermatogenesis • Inhibition of fat deposition • Muscle mass • Brain: androgen levels have been implicated in the of regulation 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)

Adrenogenital Syndrome

Excessive adrenal androgens secretion

Causes

Adrenocortical tumors

Secretes excessive quantities of androgens that cause intense masculinizing effects throughout the body

Congenital adrenal hyperplasia (CAH)

- It is a familial disorder of adrenal steroid biosynthesis with autosomal recessive mode of inheritance.
- The defect is expressed as adrenal enzyme deficiency.
- 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, lead to excess production of adrenal androgens
- The clinical picture reflects the effects of inadequate production of cortisol & aldosterone and the increased production of androgens & steroid metabolites

Adrenogenital Syndrome

In females

Before birth	After birth
• Pseudohermaphroditism (خنثى): - 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, much deeper voice, masculine distribution of body hair ,baldness, atrophy of the breast, amenorrhea, acne, increase bulk of muscle, growth of the clitoris to resemble a penis.

In males

After birth (Prepubertal Male)	Adult male
• Precocious puberty • Early appearance of male characters • Increase musculature • Development of external genitalia organ to adult size • a virilizing adrenal tumor causes the same characteristics as in the female plus rapid development of the male sexual organ. • 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

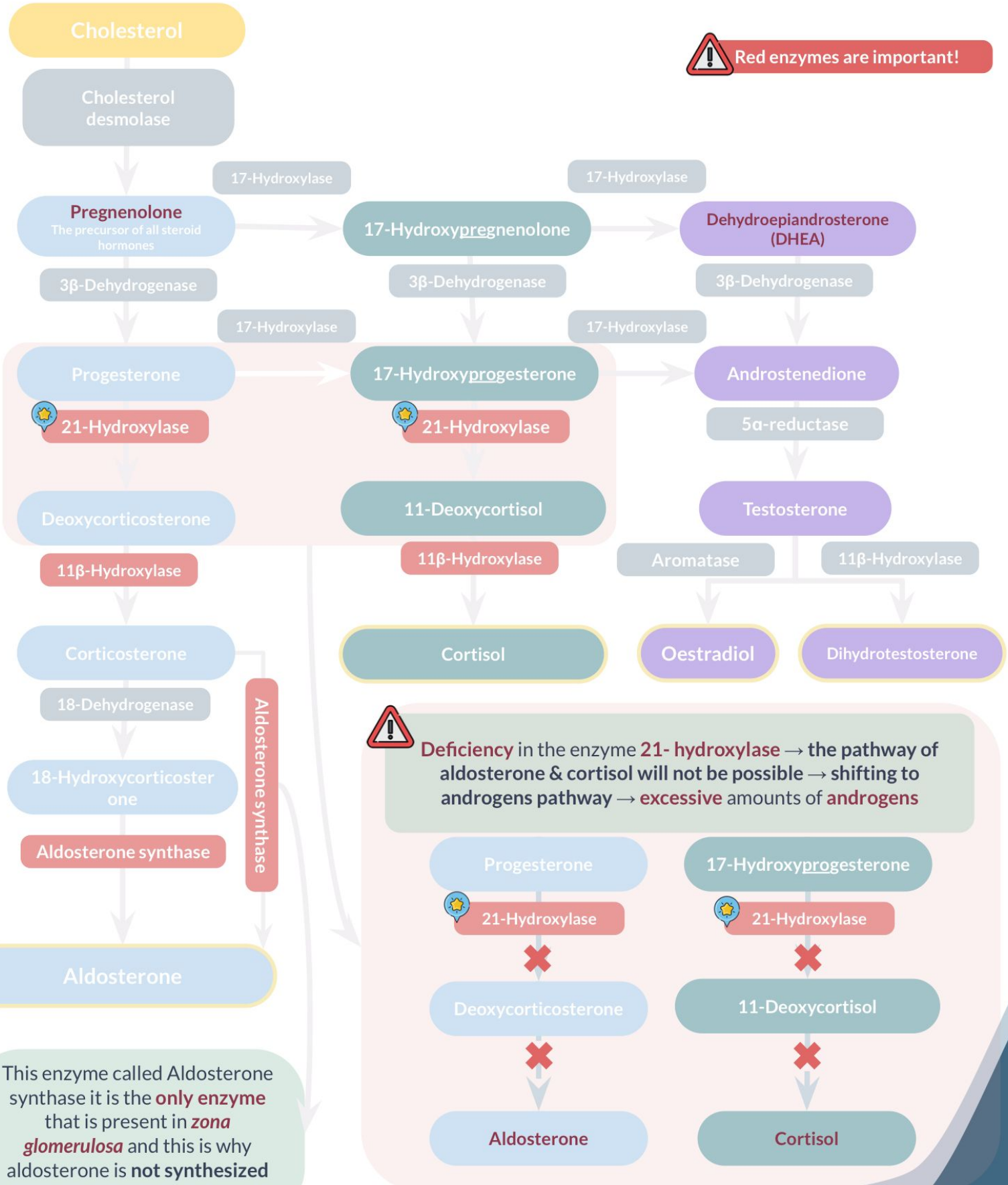
Treatment

Glucocorticoids

Special thanks to the amazing physiology team 44I!!

Steroid synthesis (steroidogenesis)

This map was used for Congenital Adrenal Hyperplasia explanation



MCQs:

Q1: Which one of the following is produced by adrenal cortex ?

A. androgens	B.estrogens	C. Both A&B	D. Catecholamine.

Q2: what is the precursor for all steroid hormones?

A.Pregnenolone	B.vit D	C.Preganglionic.	D.aldosterone

Q3:The adrenal cortex in both sexes produces small amounts of sex hormone of the ....

A.Same sex	B. opposite sex	C. Female sex	D.sex hormones

Q4: which of the following is mostly affected by ACTH deficiency?

A. Androgens	B.ALDOSTERONE	C. Hydrolyse	D. Cortisol

Q5: cortisol and growth hormone are dissimilar in which one of the following

A.Protein metabolism in muscle	B.Mobilization of triglycerides	C. Glucose concentration in blood.	D. Glucose uptake by peripheral tissue.

Q6:Hormones that have permissive effect?

A.Cortisol and norepinephrine	B.Thyroid and growth hormone	C. Thyroid and ACTH	D. A&B

Q7: Which of the following is false about cortisol?

A. It's bound to plasma protein	B. Injections lead to rise in arterial pressure	C. Is inactivated in the liver and excreted in the bile	D. Is inactivated in the kidney and excreted in the urine

Q8. which one of the following androgens was used as a body building supplement?

A. Testosterone	B. Androstenedione	C. DHEA	C. Insulin

Q9: What enzyme converts testosterone into estrogen ?

A hydroxylase	B.Peroxidase	C.aromatase	C.dehydrogenase.

SAQ :

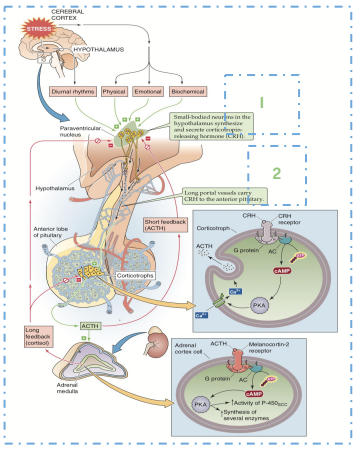
1. Write the pathway for aldosterone synthesis?
2. How does the cortisol response to fasting?
3. List 3 abnormal type of fat redistribution in Cushing Syndrome?
4. What is the secretory rate of CRF, ACTH and cortisol?
5. What will happen to a female fetus when the mother is exposed to excessive androgens before 12 weeks of pregnancy?

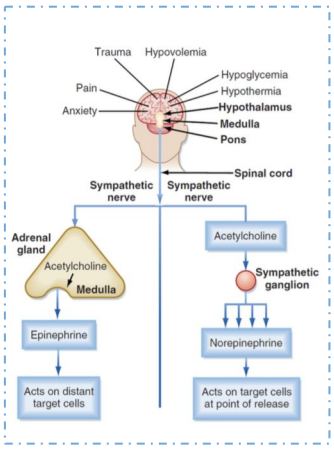
1-C,2-A,3-B,4- D, 5- A, 6- D, 7-B, 8-B,9-C

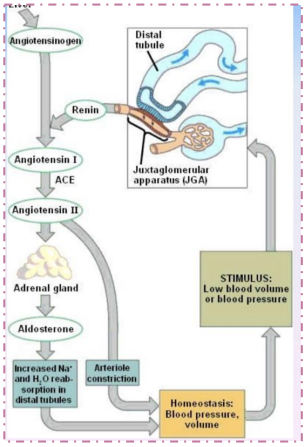
Q1 : Cholesterol > Pregnenolone > Progesterone > Deoxycorticosterone > Corticosterone > 18-Hydroxycorticosterone > Aldosterone.
Q2: Increases the expression of PEPCK enzyme which increase gluconeogenesis & decreases GLUT4-mediated glucose uptake in skeletal muscle and adipose tissue & Increases the mobilization of stored fat by activating the hormone-sensitive lipase enzyme.
Q3: -Buffalo torso (truncal obesity). -Buffalo hump (neck). -Moon face.
Q4: It's high in the early morning (20µg/dL) while it's low in the late evening (5µg/dL), this effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.
Q5: Pseudohermaphroditism, XX true female with external male genitalia.

pictures in slide

HPA Axis and Loophole in the -ve feedback

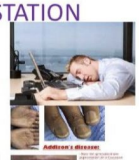


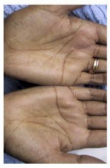


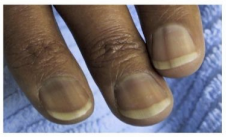


CLINICAL MANIFESTATION

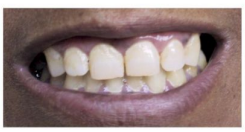
- General weakness and becoming easily tired.
- Darkened areas of skin ('pigmentation').
- Blood pressure is low and falls further when you stand which can make you dizzy.
- Being off your food and weight loss.
- Feeling sick and vomiting from time to time.
- Abdominal pains which may come and go.
- Diarrhoea or constipation which may come and go.
- Cramps and pains in muscles.
- Craving for salt, or salty foods and drinks.
- Menstrual periods in women may become irregular, or stop.





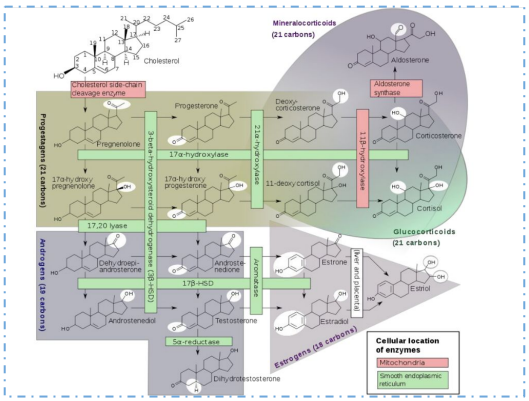


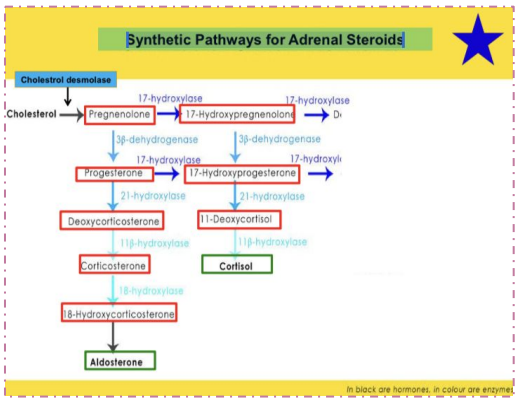
Addison's disease:



- Note the generalised skin pigmentation (in a Caucasion patient) but especially the deposition in the palmer skin creases, nails and gums.
- She was treated many years ago for pulmonary TB. What are the other causes of this condition?

Synthetic Pathways for Adrenal Steroids (Steroidogenesis)





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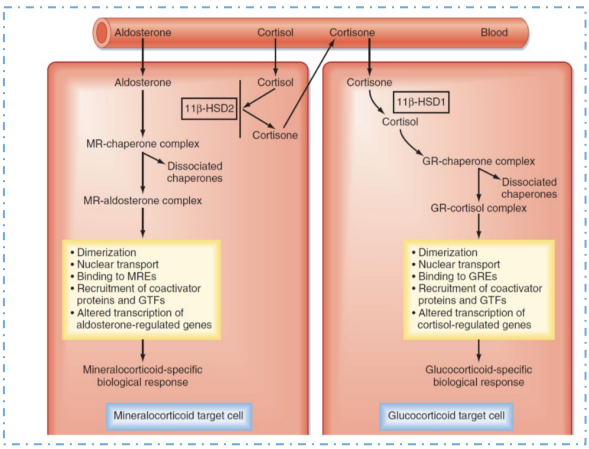
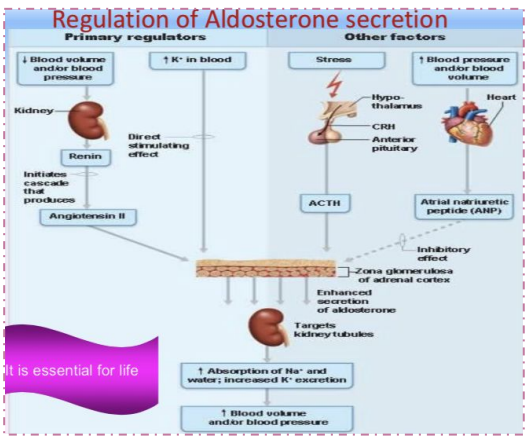
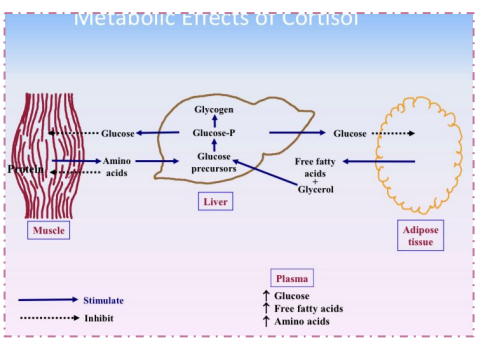
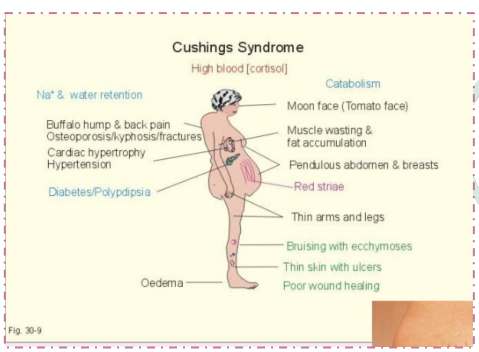






COMMON DISORDERS OF ADRENOCORTICAL FUNCTION

Conn's *(Primary Hyperaldosteronism)*	Aldosterone ↑	Hypertension, hypokalemia, alkalosis
Secondary Hyperaldosteronism	Aldosterone ↑ Renin ↑	Hypertension, hypokalemia, alkalosis
Cushing's	Cortisol ↑ ACTH ↑ or ↓ (depending on aetiology)	Altered appearance, bruising, muscle wasting, hypertension, diabetes, hypokalemia
Addison's	Cortisol ↓ Aldosterone ↓ or ⇔	Hypoglycemia, hyponatremia, hyerkalemia and raised urea **Acute:** abdominal pain, vomiting, dehydration and hypotension **Chronic:** fatigue, pigmentation, anorexia, weight loss and postural hypotension



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