Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved
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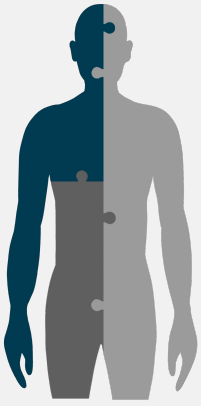


Dr. Khalid Revision

Dr. Khalids comments on the exam:

- On average you'll have 2 questions per lecture, rarely 3 qs.
- The questions are hopefully easy.
- We wouldn't ask you about physiological or clinical numbers, for example you wont get: "what are the normal plasma calcium levels?"
    - PLEASE note that the doctor did not teach us the pancreas and DM lectures, in those please memorize the normal and abnormal values of glucose tests.
- Physiology is about the function, so these are the types of questions you might get, even in cases of diseases or abnormalities, you'll be asked about the function.
- Treatments are not important.
- No SAQ or MCQ on posterior pituitary lecture.

★ The Chairperson: No MCQ questions from Med lectures.

Important

★ Very important

This file is completely a personal effort, it is not by any mean a primary source to study and prepare for the exam, study your slides or the team work first then check this file

L9

Introduction Of **Bone Composition**

Bone composition*

Organic matrix 30%

What is bone **Resorption/ Reabsorption**?
When osteoclast dissolve the bone, so that the calcium will dissolve from the bone to the ECF(blood).

Cells 2%

1. **Osteoblasts.** (bone/collagen forming cells)
2. **Osteocytes.** (osteoblasts trapped/ surrounded by calcified matrix)
3. **Osteoclasts.** bone eroding/dissolving Cell (resorping) (phagocytic)

Remodeling of Bone Bone is continually being deposited by osteoblasts, and it is continually being resorbed where osteoclasts are active

matrix 98%

Components:
-Collagen Fibers (95%)
-Ground Substance (5%): (ECF, Proteoglycans)

Provide:
Tensile force (قوة شد) provided by collagen.
If there was no collagen → the bone will break easily

Think of **collagen** like iron (in buildings) → **Tensile force**

Think of **calcium** like cement (in buildings) → **Compressional force**

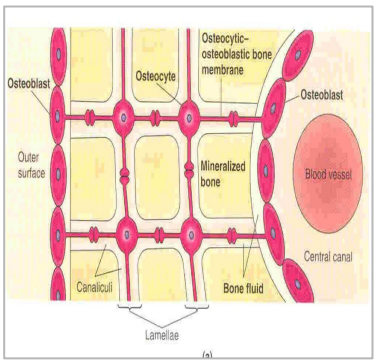
Inorganic matrix (Mineral salts) 70%

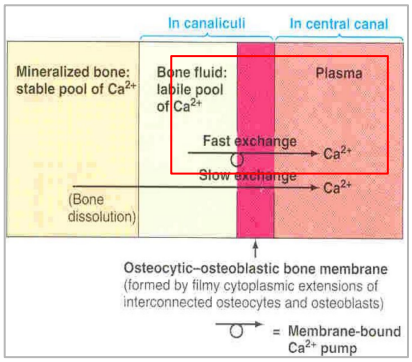
Components:
1. Salts of Ca++ & PO4- In the form of **Hydroxyapatite crystals** (99%): [In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$]
2. **Mg, Na, K, Carbonate ions**
3. **Amorphous salts:**
   A type of exchangeable calcium
   Play role in rapid **regulation** of ionized Ca++ level in ECF
   0.4-1% of total bone Ca++ always in equilibrium with Ca in ECF

Provide:
Compressional force
If there was no salt → the bone will bend easily

Mechanical Stress (Wolff's Law):*

- States that bone in a healthy person or animal will adapt to the loads under which it is placed. If loading on a particular bone increases, the bone will remodel itself over time to become stronger to resist that sort of loading.
- For example, the bones of athletes become considerably heavier than those of nonathletes. Also, if a person has one leg in a cast but continues to walk on the opposite leg, the bone of the leg in the cast becomes thin and as much as 30% decalcified within a few weeks, whereas the opposite bone remains thick and normally calcified.
- Patients who have been in hospital beds for weeks can develop hypercalcemia due to bone decalcification from the absence of mechanical stress



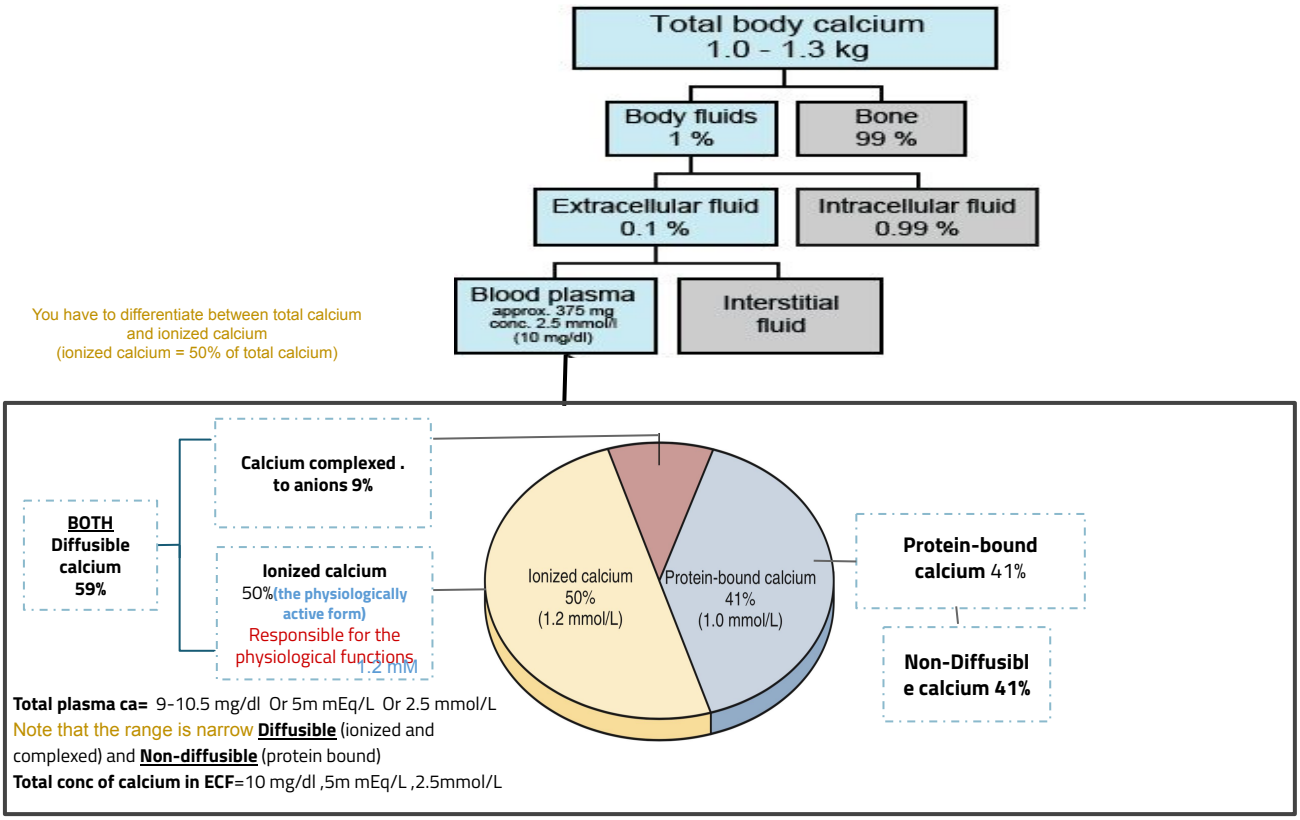


If plasma calcium levels decrease, the **very first line** response will be releasing Amorphous salts from bony fluid canaliculi to **quickly** restore normal levels. |||| If that was insufficient to restore normal levels, other mechanism that involve dissolving **Hydroxyapatite crystals** from mineralized bone will start (**slower** response)

And if plasma calcium levels increased on the other hand, the first response will be precipitating the excess calcium as amorphous salts ||||| If it was insufficient, precipitation as Hydroxyapatite crystals will start.

If none of these mechanisms was sufficient to establish homeostasis, other mechanisms will kick in (hormonal.. etc).

Distribution of Ca++ in Body



Protein-bound calcium:

- Most of this calcium is bound to **albumin** & much smaller fraction is bound to **globulin**
- Binding of calcium to albumin is **pH-dependent**
- Acute respiratory alkalosis increases calcium binding to protein thereby decreases ionized calcium level:
  Alkalosis ⇒ ↓Ionized Ca^{2+}
  Acidosis ⇒↑Ionized Ca^{2+}

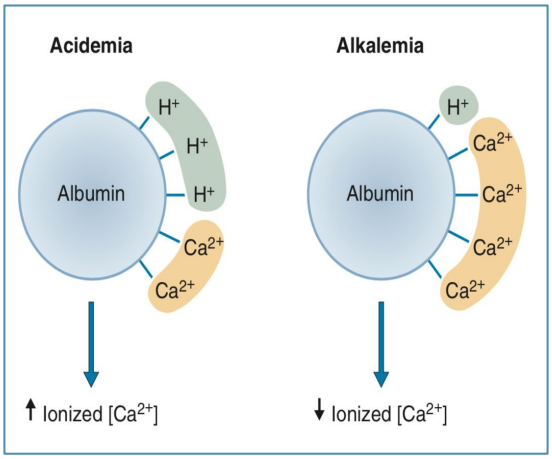
Acidemia:
We have high plasma hydrogen ion levels (low pH). These protons displace protein bound Calcium and move it to the blood causing an **increase in Ionized calcium**

Alkalemia:
We have low plasma hydrogen ion levels (high pH). Albumin will have room for more calcium to bind to it which will take away the ionized calcium in the blood. **Decreasing Ionized calcium.**

- **In both conditions, if we measure the Total Ca++ levels, it will be similar,** however the ionized Ca++ won't be the same
  - ↑Albumin levels → ↓Ionized Ca++

Phosphate*

- Approximately 85 % of the body's phosphate is stored in bones,14-15 % is in the cells.
- Less than 1% is in the extracellular fluid.
- Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.



Calcium*

Physiological importance

(all maintained by **ionized** calcium)

Calcium salts in bone provide structural integrity of the skeleton .
Calcium ions in extracellular and cellular fluids is essential to normal function for the biochemical processes :
–Neuromuscular excitability – Hormonal secretion – Enzymatic regulation
– Blood coagulation – Second messenger

Remember GIT: calcium was an important cofactor in several steps of the coagulation cascade (e.g. conversion of prothrombin to thrombin). In hospital laboratories, we prevent clotting of blood samples by adding coagulation inhibitors (such as Citrate) to the test tube (Citrate will bind to calcium and precipitate it. This will prevent it from facilitating the coagulation cascade). If calcium levels in someone's body are low (as low as 5mg/dl), he will bleed to death (because no calcium = no coagulation).

Source

- Milk ,dairy products ,Fish

Daily Requirement

- Infants & adults: 12.5 -25 mmol/day will be doubled in pregnancy & after menopause.
- Pregnancy, lactation ,after menopause: 25-35 mmol/day

Absorption

- Duodenum: active transport In general, calcium is poorly absorbed from GIT
- Small intestine: concentration gradient

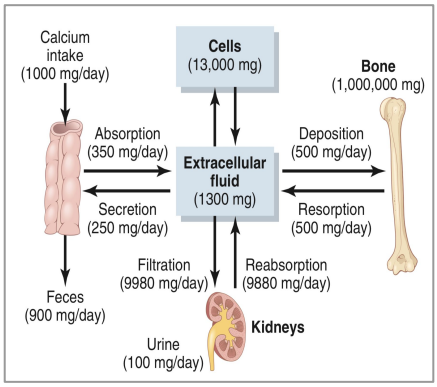
Metabolism

- 1000-350=650

الفكرة الرئيسية هنا أن تركيز الكالسيوم في ECF يكون ثابت

▪ Calcium metabolism:

- 1000mg a day intake(equals calcium amount in 1L of milk), **350** absorbed and **650** lost (depending on Vit D). Out of the 350mg, 250 secreted.
-**Total excretion =900mg (250+650) | Total absorption =100mg.**
- Cellular and extracellular calcium is constantly exchanging
- Kidney: the filtered calcium is the diffusible kind (ionized and anions bound) 60% of total Ca, 99% will be reabsorbed and 1% is excreted **(100mg)**.
- Total excretion (urine 100) + (feces 900) equals the intake (1000).
Imp Female Dr: these are the only numbers that you need to memorize
- 500mg deposited and reabsorbed in bones is due to constant remodeling of bones. This process depends on calcium,Vit D, PTH levels in the blood.
- In case of deficiency or increased Ca levels, the kidney will selectively increase/decrease its filtration to compensate.



Regulation

- ➢ Changes in Plasma Concentrations of Free Calcium
- ➢ Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations
- ➢ [Ca2+] < 9-10.5 mg/dl → **Tetany** + seizures + **excitation** of the nervous system
- ➢ [Ca2+] > 9-10.5 mg/dl → **Renal stones** + **depression** of the nervous system

- Decrease in **intracellular/Endoplasmic reticulum** calcium = decrease in contractility (as u might have known from previous blocks).
- However, in this case, we are talking about **extracellular** calcium; decrease in its levels will lead to increase Na permeability & influx inside the cells → more tissue excitability = tetany!
- Vice versa.. Increase in extracellular calcium → less Na permeability & influx → less excitability = depression of CNS.

Regulated by

Phosphate

Phosphorus is an essential mineral necessary for ATP and cAMP second messenger systems

- Phosphate plasma concentration is around 4 mg/dL.
- Forms: - Ionized (diffusible) around 50% of total (The functional form)
- Un-ionized (non-diffusible) and protein- bound (50%)
- **Calcium is tightly regulated with Phosphorus in the body.**

Hormones

- Parathyroid hormone(from p
- Calcitonin*
- Vitamin D

*no physiological importance, It's more important in children and pregnant ladies. (Thyroidectomy patients don't need calcitonin replacement)

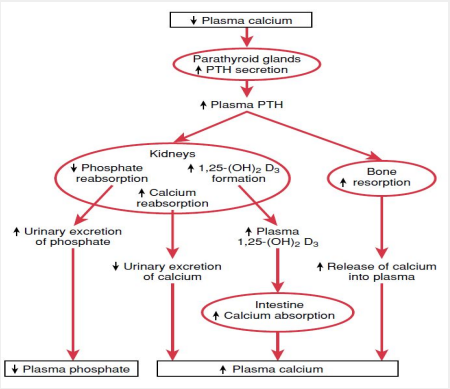
Hormones regulate Ca^{++}

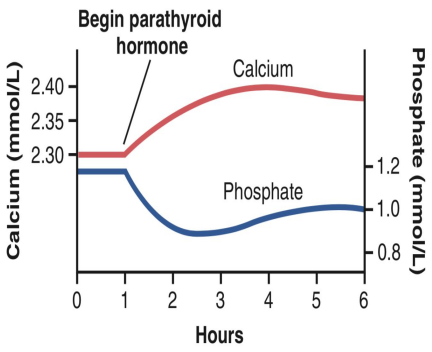
	Parathyroid hormone	Calcitonin	Vitamin D
Source	Secreted by chief cells of parathyroid gland	Secreted by the parafollicular cells (C cells) of the thyroid gland.	1--Sunlight: (7-Dehydrocholesterol > **Vit D3** aka; **cholecalciferol**) inactive 2--Dietary intake: Vit D3 (fish, meat). Vit D2(supplements) **Liver** take up the Vit D forms> converted to **25-hydroxyvitamin D3** By 25α-hydroxylase **Kidneys** take up 25-hydroxyvitamin D3 and is converted into **1-25 dihydroxyvitamin D3** (active form) by the enzyme **1α-hydroxylase** (this enzyme is activated by **parathyroid hormone**)
General	Main regulatory hormone for Ca	- Stimulus for secretion: Increased plasma calcium concentration.	
Mechanisms of action	Acts via 2nd messenger mechanism utilizing cAMP Operates in tissues via GPCR	Decrease blood Ca++ level very rapidly within minutes. Opposite effect to PTH	
Site of action	Bone, Kidney and Intestine	Bone and Kidney	Bone, kidney and Intestinal tract
Function (actions)	- **increases** calcium levels in blood - **decreases** phosphate levels ماشين عكس بعض **-On bone:** 1. Stimulates the Formation of new osteoclasts. 2.Increases Calcium and Phosphate Absorption from the Bone 3.. Activation of osteoclasts (because it causes resorption of bone and release of Ca to blood) 4.. Depression of Osteoblastic activity **-On kidney** 1. ↓phosphate reabsorption from the proximal convoluted tubules (phosphaturic action). Which leads to ↑Phosphate excretion in the urine and ↓ plasma phosphate concentration 2. ↑ Ca++ & Mg ions reabsorption from the distal convoluted tubules, collection ducts and ascending loop of Henle.important to prevent bone deterioration 3. ↑ Formation of 1,25 vit D3 in the Kidney. **-On intestine:** ↑ absorption of calcium and phosphate indirectly through stimulating formation of 1,25 – (OH)2-D3 in kidney(Increases Calcium and Phosphate Absorption from the Bone • Existing osteocytes stimulated (minutes to hours) to transport calcium - calcium pumps • Existing osteoclasts activated and new osteoclasts formed (days to weeks) to digest bone and release calcium and phosphate Stimulated indirectly by osteoblasts: osteoblasts express RANKL which binds to RANK on osteoclasts leading to its activation.)	- **decrease** calcium levels in blood **On bone:** 1.↑Ca++ deposition of bone (decrease it in blood) (Effect to decrease calcium is not permanent) 2. Inhibits Bone resorption by inhibition of osteoclasts. ↓ formation of osteoclasts. 3. Causes reduced bone turnover. **On kidney:** ↓↓ Ca++ reabsorption and ↑↑ Ca++ excretion (in addition to phosphate) (Effect to decrease calcium is transitory Causes reduced bone turnover Has weak effect in kidney and intestines)	- **increases** calcium levels in blood - **increases** phosphate levels ماشين بنفس الاتجاه Vitamin D in the form of **1,25 Dihydroxycholecalciferol** increases calcium blood level by: **-on Bone &** Its Relation to **Parathyroid Hormone Activity.** -Vitamin D in smaller quantities : promotes bone calcification (by↑calcium and phosphate absorption from the intestine and enhances the mineralization of bone) - The administration of extreme quantities of vitamin D causes absorption of bone: • by facilitating PTH action on bones. • number & activity of osteoclasts. **-On Intestinal tract.** has a potent effect to increase calcium **and** phosphate absorption. (increases synthesis of calcium binding proteins) **-On kidney:** ↑Renal calcium and phosphate absorption. **-On immunity**: stimulates differentiation of immune cells
Abnormalities	Hypoparathyroidism Hyperparathyroidism	Osteomalacia Osteoporosis	
			Control of vit D: 1- low Ca++ ions 2- prolactin 3- PTH All stimulate renal **1,alpha hydroxylase**.

cont...

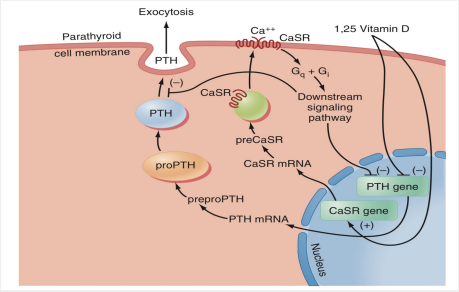
Hormones regulate Ca^{++}

Effect of PTH on Calcium level





▪ PTH: increases excretions of Phosphate and increases reabsorption of calcium (decreasing excretion) Among the diffusible calcium, 60% is reabsorbed in PCT, 30% in loop of Henle, and 10% in rest of the kidney. PTH works mainly on DCT and to a lesser extent Ascending loop of henle. PTH adjusment of reabsorption is very small because we need fine adjustment of Ca levels PTH Decreases Phosphate reabsorption in PCT ▪ In Hyperparathyroidism we see Hypercalcemia and Hypophosphatemia

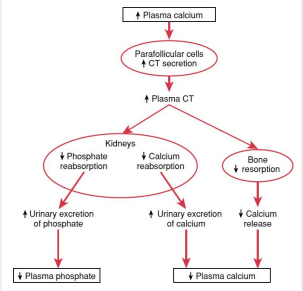


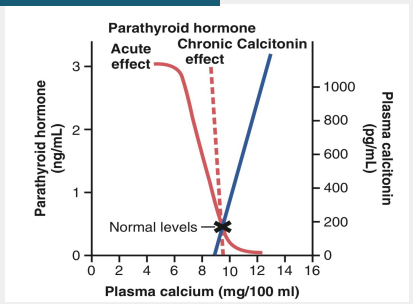
CaSR is Calcium sensing receptor, It suppresses PTH Gene expression.

-Low Serum Ca → CaSR is inactivated → PTH gene is no longer suppressed →Increased PTH production and secretion →Increase resorption in bones by activating osteoclasts. + Activate Vit D in kidneys by activating 1α-hydroxylase.

-Vit D enters parathyroid gland →Increase CaSR gene expression → increased production of CaSR (Negative feedback for Vit D activation).
-Vit D Suppress PTH gene (negative feedback for Vit D activation)

Effect of calcitonin on Calcium level

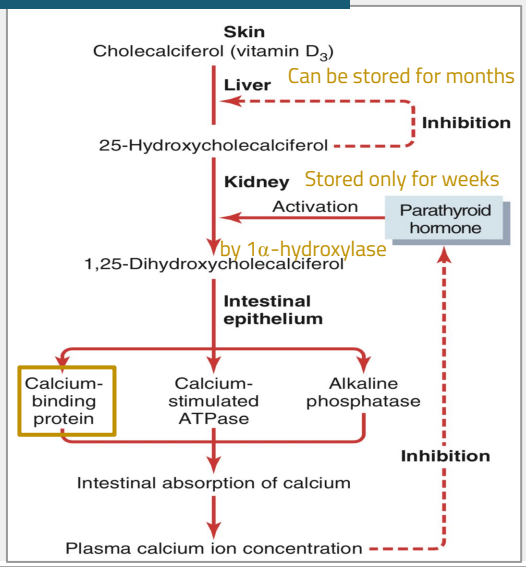




Normally Ca should be around 9.5 Ca> 9, Calcitonin secretion. Ca <9, PTH secretion.

Effect of Vit D on calcium level

Trigger of PTH → low Ca
Trigger of Vit D → PTH



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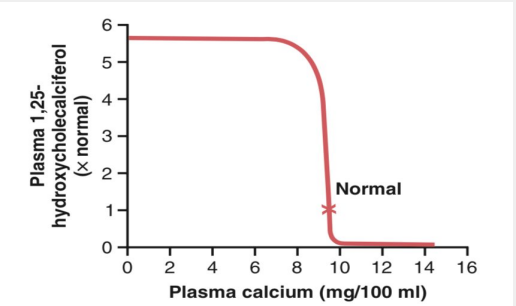
Main mechanism

Important mechanism because Ca cannot be absorbed without its binding protein



Vit D decreases dramatically when calcium is around 8-9 mg / dl

Disorders of **Bones**

Disease name	**Rickets** لين العظام / الكساح	**Osteomalacia** Adult Rickets (Rare)	***Osteoporosis**
Cause	• Lack of vitamin D **leading** to calcium/phosphate deficiency in ECF • Occurs In the spring (because vitamin D levels decreased in winter)	Poor absorption of vitamin D and calcium	• lack of physical stress • malnutrition • lack of vitamin C •postmenopausal lack of estrogen (one of estrogen function is depressing the osteoclastic activity) • old age •Cushing's syndrome
General*	positive Chvostek's sign is facial nerve irritability/spasms elicited by tapping the nerve	• serious deficiencies of both vitamin D and calcium occasionally occur as a result of **steatorrhea** (failure to absorb fat) Almost never proceeds to the stage of tetany but often is a cause of severe bone disability	• Osteoporosis is the most common of all bone diseases in adults, especially **in old age.**
Features	• Low plasma calcium and phosphate • Weak bones • Tetany (only shows in late stages due to the effect of compensating mechanisms) Normal formation of the collagen matrix BUT Incomplete mineralization (poor calcification), lead to Soft Bones , CLINICALLY: Bone Deformity	Problem in bone slats **No compression force** demineralization (poor calcification) of preexisting bones which leads to more susceptibility to fractures	Results from equal loss of both organic bone **matrix and minerals** resulting in loss of total bone mass and strength. The cause of the diminished bone: • the osteoblastic activity in the bone is usually less than normal so the rate of bone osteoid deposition is depressed. • excess osteoclastic activity.
Treatment **Not important**	• supplying adequate calcium and phosphate in the diet and, administering large amounts of vitamin D	-	-

	Tetany in rickets **Early stage**	**Osteomalacia** ***Renal Rickets (Rare)**	
	Early stage: no tetany • (PTH stimulate osteoclastic absorption of bone) • ECF Calcium level is normal When the bones finally become exhausted of calcium Calcium level falls rapidly. blood level of calcium falls below 7 mg/dl → signs of tetany: (positive Chvostek's sign) →Death: tetanic respiratory spasm	It is a type of Osteomalacia due to **prolonged kidney disease** • **Failure of the damaged kidney to form alpha hydroxylase enzyme**	-

Bone composition

Hyperparathyroidism Hypercalcemia

1

-**primary Hyperparathyroidism**
mainly tumors

causes:
● Adenoma (90%)● Multiple gland enlargement (10%)
● Familial hyperparathyroidism● Carcinoma (<1%)
● Familial benign hypercalcemia (FBH).

Manifestations:
● Hypercalcemia (↑Ca2+), Hypercalciuria.
● Hypophosphatemia (↓PO-4), Hyperphosphaturia(Parathyroid hormone causes phosphaturia and a decrease in serum phosphate)
● Demineralization of bone forming multiple bone cysts (osteitis fibrosa cystica).
● Broken bones.
● ↑ Alkaline phosphatase.
● CNS depressed and peripheral nervous system depressed.
● Muscle weakness.
● Constipation, abdominal pain, peptic ulcer & decrease appetite.
● Depressed relaxation of the heart during systole.
● Calcium containing stones in kidney.
● **Parathyroid poisoning**: Precipitation of calcium in soft tissues occur when Ca2+ → >17 mg/dl → lead to death.
● Most serious complication is the deposition of calcium in the kidney tubules resulting in impaired renal function.

Common causes of hypercalcemica
▪ PTH mediated
▪ Primary hyperparathyroidism ▪ Non-PTH mediated
▪ Parathyroid hormone–related peptide (PTHrP): certain tumors
secrete high levels of PTHrP, which causes hypercalcemia of malignancy.
▪ Vitamin D intoxication, granulomatous disorders, osteolytic bone
metastases, malignancy
▪ Immobility ▪ Dehydration ▪ Medications
▪ Lithium, thiazide diuretics

Clinical Manifestations of Hypercalcemia

▪ Nausea, vomiting ▪ Anorexia, weight loss ▪ constipation ▪ Lethargy and Fatigue ▪ Confusion, stupor, coma ▪ Impaired concentration and memory ▪ Depression & anxiety ▪ Reduced neuromuscular excitability and muscle
weakness ▪ Easy fatigability and muscle weakness more common in
hyperparathyroidism than other hypercalcemic conditions ▪ Cardiac arrhythmias ▪ Vascular calcification ▪ shortening of the QT interval.

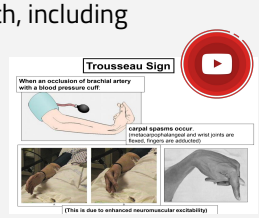
Hypoparathyroidism hypocalcemia

causes:

● Injury to the parathyroid glands (surgery).
● Autoimmune.
● Magnesium deficiency.
● PTH resistance (pseudohypoparathyroidism): Normal PTH levels but deficient receptors.
● Vitamin D deficiency or resistance.
● Lack of 1α hydroxylase, no vit D3 activation.
● Other: renal failure, pancreatitis, tumor lysis.

symptoms: (due to hypocalcemia)

● Tingling in the lips, fingers, and toes.
● convulsions
● Dry hair, brittle nail, and dry coarse skin.
● Muscles cramps and pain in the face, hand, legs, and feet.
● Cataracts of the eyes.
● Malformation of the teeth, including weakened tooth enamel.
● Loss of memory.
● Headaches.



Signs:

● Tetany can be overt or latent.
● **Positive Chvostek's sign** (facial muscle twitch): tapping the facial nerve as it emerge from the parotoid gland in front of the ear causes contraction of facial muscles.
● **Positive Trousseau's sign** (carpal spasm): arresting (stopping) blood flow to the forearm for few minutes (e.g. by sphygmomanometer), causes flexion at the wrist, thumb, and metacarpophalangeal joints.
● Delayed cardiac repolarization with prolonged of the QT interval. (arrhythmia)
● Paresthesia.

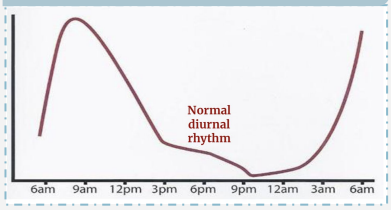
Treatment:
● Calcium carbonate and vitamin D supplements.

L10

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

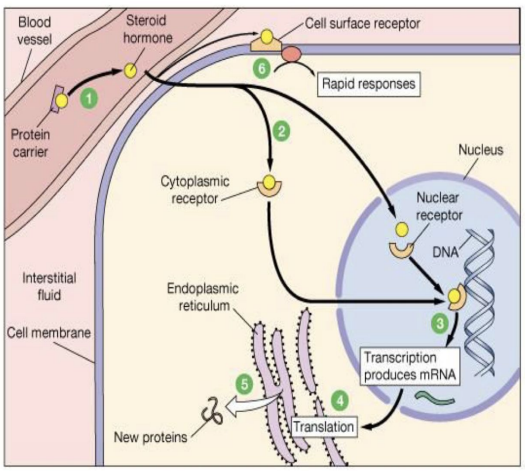
Steroids	Average Plasma Concentration (free and bound, μg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal steroids				
Cortisol	12	15	1.0	1.0
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydroepiandrosterone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

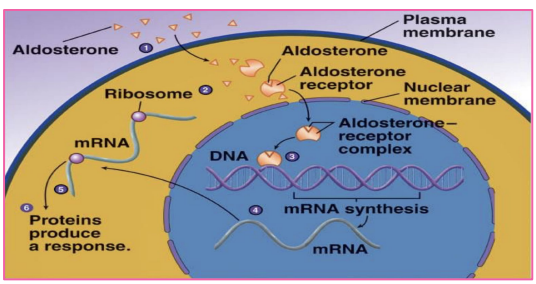
Glucocorticoid and mineralocorticoid activities of the steroids are relative to cortisol, with cortisol being 1.0.

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

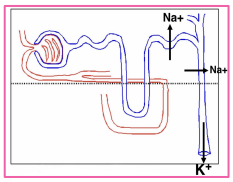
Actions of Aldosterone

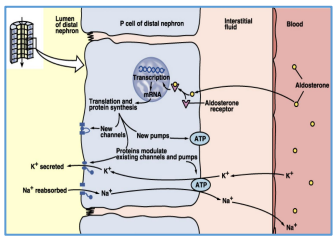
- Acts mainly on the cells of the **collecting ducts** and **distal tubules** of the nephron.
- **Increase renal tubular reabsorption of Na+ and secretion of K+ and H+**
- Binds to mineralocorticoid receptor (MR).

Increase of aldosterone → Hypokalemia + Alkalosis

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*

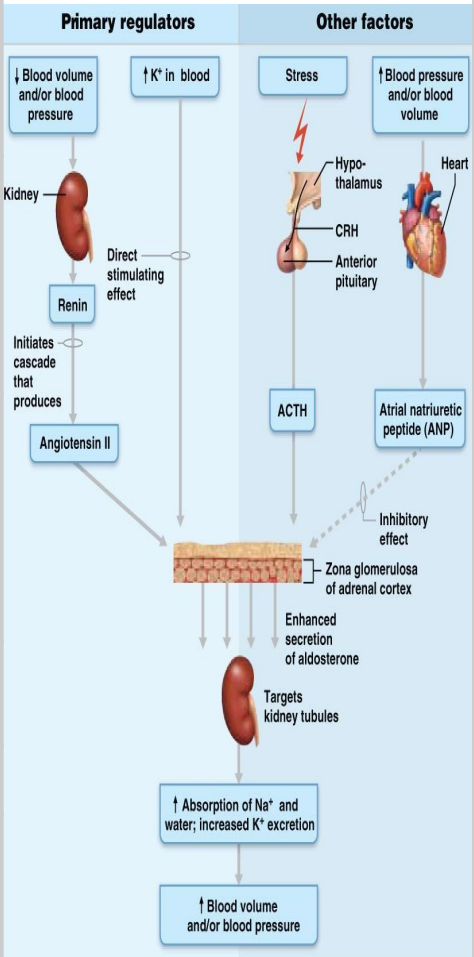
"We will not ask about this but you might need it somewhere else"

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

Main regulation of aldosterone release is by: **Hyperkalemia and RAAS**	**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.
Increase Aldosterone secretion (Stimulation)	**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.

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

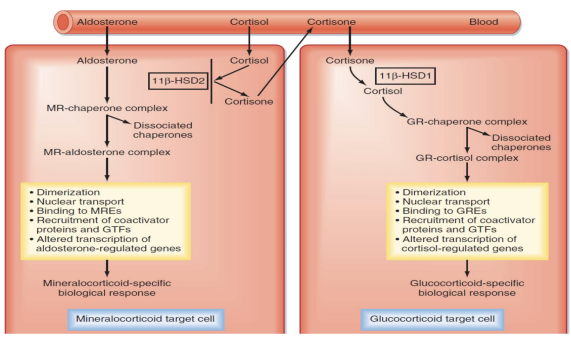
Primary

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. In the revision: the doctor said that Hypernatremia won't occur because we're also reabsorbing water 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.

Secondary

Causes	Hyperreninism, Left Ventricular Failure, Cor Pulmonale, Cirrhosis, Ascites "We will not ask about this but you might need it somewhere else"

Other causes*

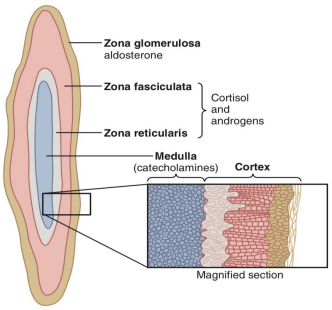
Example	Apparent mineralocorticoid excess syndrome (AME) (cortisol binds MR) Cortisol can bind with high affinity to mineralocorticoids and cause their activity, however this is normally blocked by an enzyme called 11ß-HSD2 (11ß- hydroxysteroid dehydrogenase type-2) that converts cortisol to cortisone. 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 

L11

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

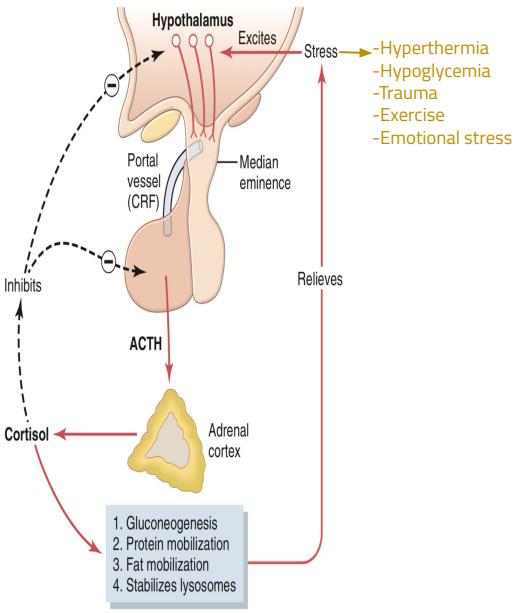
ACTH from anterior pituitary stimulates cortisol synthesis and secretion

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

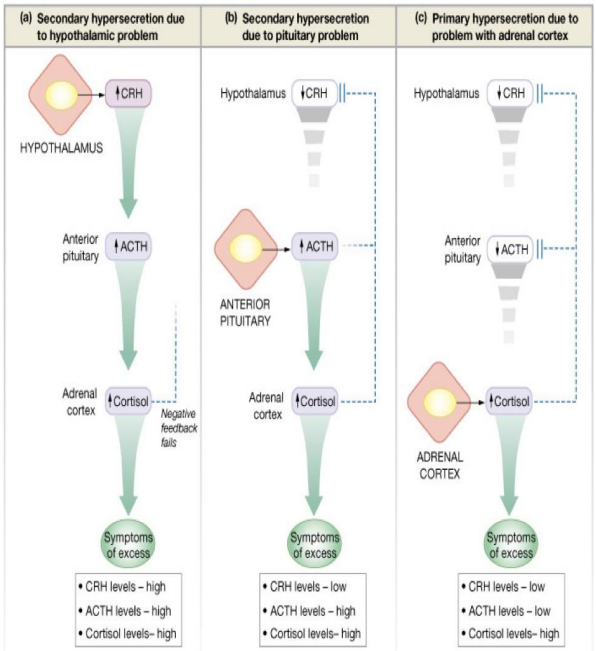
- 90-95%
- Mostly to transcortin (Cortisol Binding Globulin)
- Albumin

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.

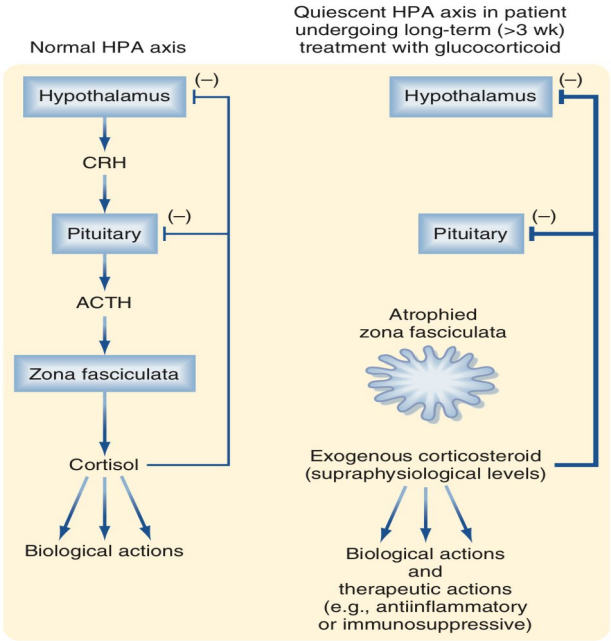
Primary and secondary hypersecretion of cortisol*



Cushing Disease
When the problem is at the level of the pituitary gland

Cushing syndrome
When the problem is at the level of the adrenal gland

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

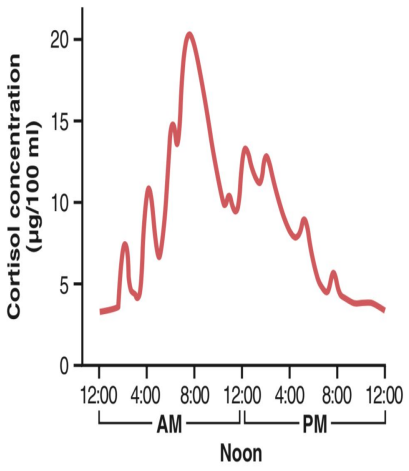
Circadian rhythm of cortisol secretion

◄ 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 antagonize insulin action.

- 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)

Revision: Glucocorticoids increase Glycogen storage in the liver, and at the same time it potentiate epinephrine action which cause Glycogenolysis, so the net effect is glycogen degradation → release more glucose into the circulation. (dr. just for your info.)

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. (Potentiate catecholamine on blood vessels)

★ 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

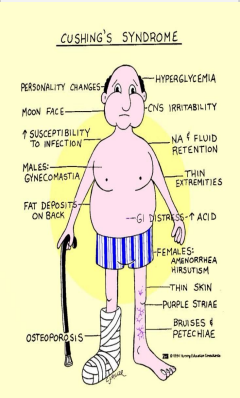
Proteins

- **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.

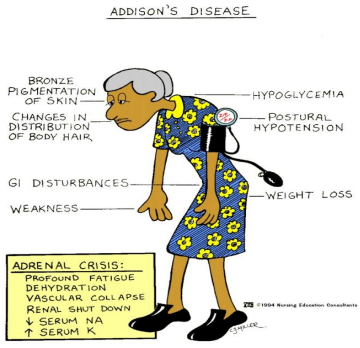
How to Differentiate between ACTH-dependent & ACTH Independent*

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) Any disease that cause an increase in ACTH→ you might expect **hyperpigmentation**. For example: Addison's and cushing disease
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 not important	• 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*

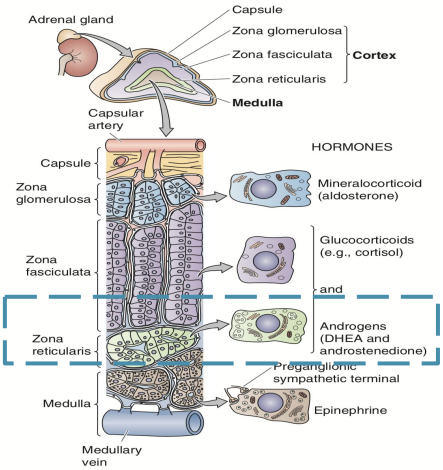
- Produce significant amounts of androgens, mostly dehydroepiandrosterone sulfate (DHEAS)

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*

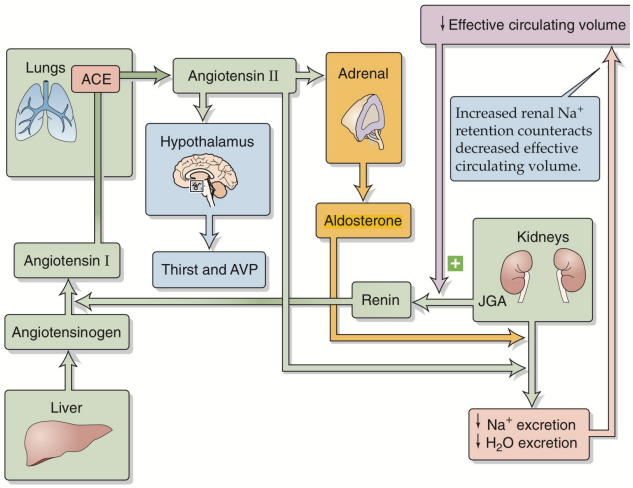
It is often difficult to make a diagnosis. However, the excretion of 17-ketosteroids (derived from androgens) in urine may be 10 to 15 times normal, used in diagnosing the disease.

Treatment*

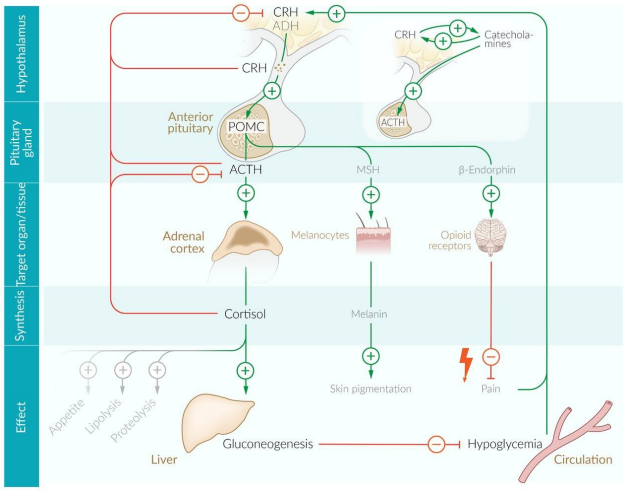
Glucocorticoids

EXTRA

L10



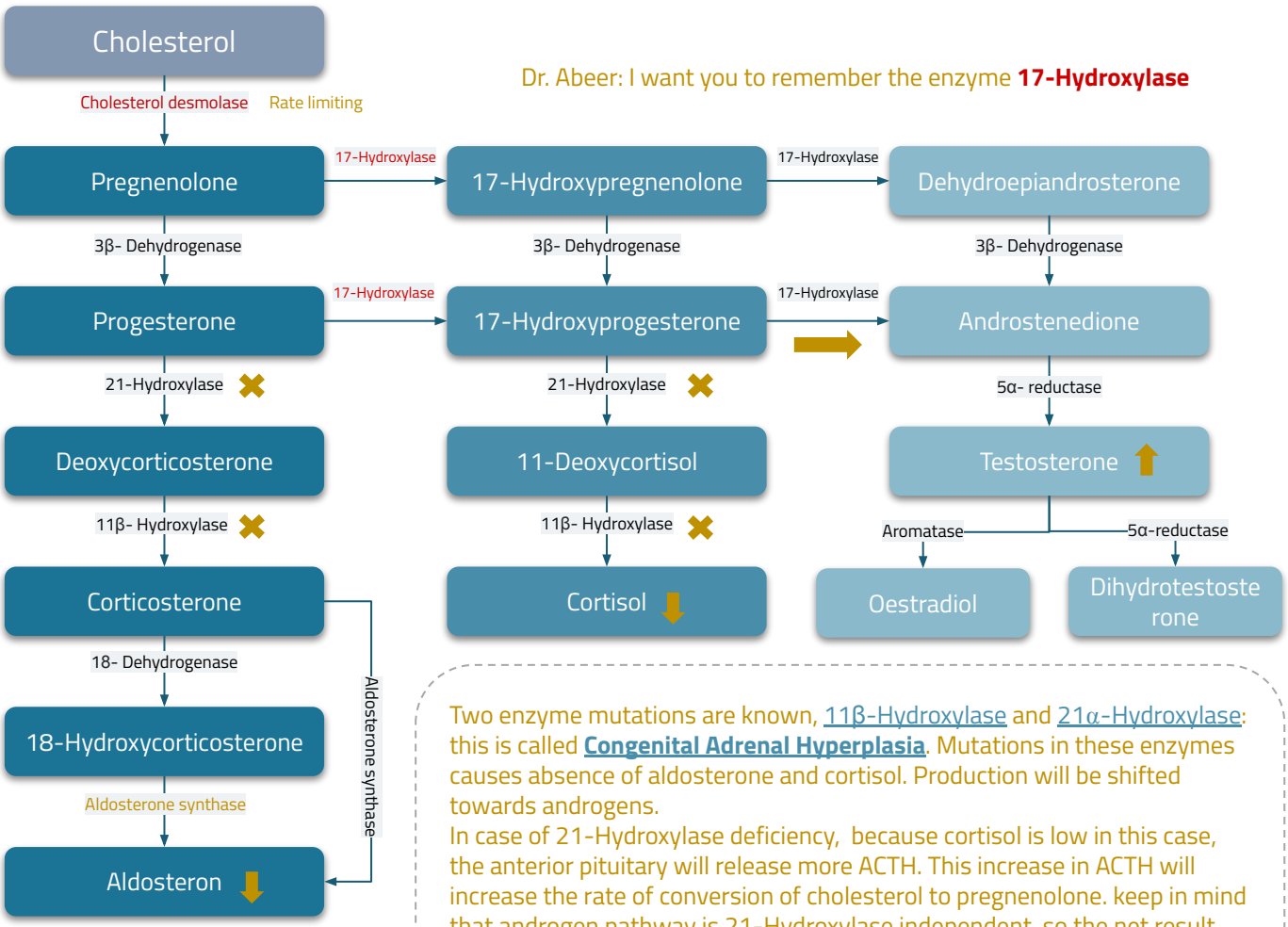
L11



L12

Congenital Adrenal Hyperplasia

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



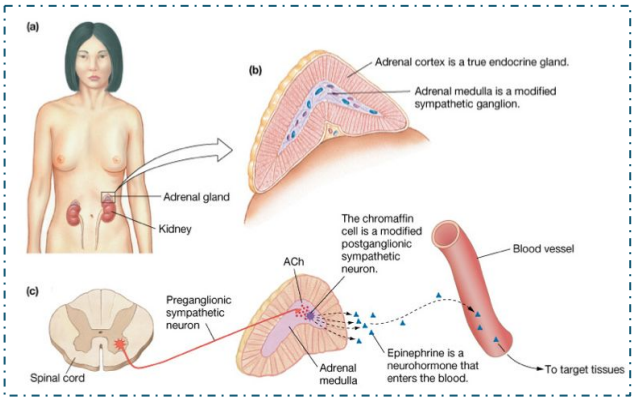
Two enzyme mutations are known, 11β-Hydroxylase and 21α-Hydroxylase: this is called **Congenital Adrenal Hyperplasia**. Mutations in these enzymes causes absence of aldosterone and cortisol. Production will be shifted towards androgens.
In case of 21-Hydroxylase deficiency, because cortisol is low in 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!

Adrenal Medulla

Overview:

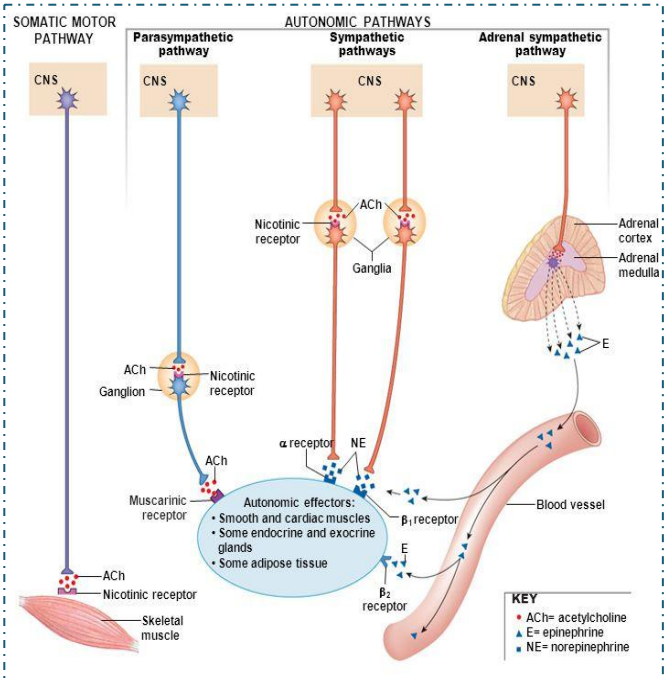
- The adrenal medulla is the inner part or core of each adrenal gland.
- It is considered as part of **sympathetic nervous system**.
- The adrenal medulla is functionally integral part (تعتبر جزء لا يتجزأ) of the sympathetic system.
- Medullary cells are derived from the embryonic neural crest, simply modified neurons (Chromaffin cells, also pheochromocytes).
- Innervated by cholinergic preganglionic sympathetic neurons.
- They synthesize the catecholamine secrete epinephrine, and 20% secrete norepinephrine . The neurotransmitter **norepinephrine** is from tyrosine.
- However, high levels of cortisol that drain into the medulla from the adrenal cortex induce expression of the enzyme **phenylethanolamine N-methyl transferase (PNMT)**, which converts norepinephrine to **epinephrine**.
- Phenylethanolamine N-methyltransferase (PNMT) is an enzyme found in the adrenal medulla that converts norepinephrine (noradrenaline) to epinephrine (adrenaline).

In the sympathetic nervous system norepinephrine is more produced **but from the adrenal medulla it's mostly epinephrine.** The reason for that is Cortisol.
Epinephrine is acting as a hormone released into the circulation participating in the Fight of flight response.



Review of Efferent Pathways: Motor and Autonomic

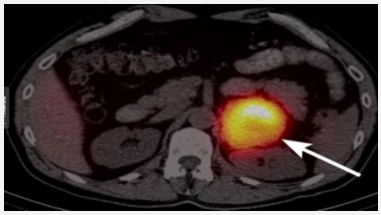
Sympathetic pathway: consists of preganglionic Neuron and postganglionic neuron preganglionic Neuron originates in CNS and has axonal fibers that terminate on a second postganglionic neurons that peripherally located, and terminate in the effector organ, and will release norepinephrine and epinephrine to specific receptors called adrenergic receptors.
Adrenal sympathetic pathway: has preganglionic neuron and Axon, But the postganglionic Neuron are modified Sympathetic Neuron (chromaffin cells).
The difference between them: that the adrenal sympathetic pathway don't have axonal fibers that terminate in the effector organ. If stimulated by preganglionic, it will release neurotransmitters directly into the Blood = Systemic Effect.



Pheochromocytoma

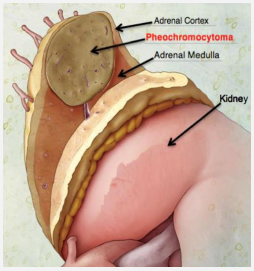
A case study?

"James" a 35-year-old husband and father of three children, has been experiencing:
headaches and palpitations of increasing frequency and severity over the past six months.
In addition, he has had periods of intense anxiety and panic attacks.



Pheochromocytoma

- **Pheochromocytoma** is a relatively rare (800-1000 cases in the us per year) tumor of the adrenal medulla or of similar specialized cells outside of the adrenal glands.
- Most often occurs in middle age.*
- Originates from the chromaffin cells (arise from neural crest) along the paravertebral sympathetic chain extending from pelvis to base of skull
- Secretes excessive amounts of epinephrine and norepinephrine.* because it isn't supplied well with cortisol like normal tissue. Epinephrine conversion will be impared
- About 10% of pheochromocytomas are malignant.*
- Most tumors secrete epinephrine, NE, and dopamine and can cause episodic hypertension.*
- Associated with neurofibromatosis 1.*
- It can occur in combination with other tumors, conditions and in some familial (inherited) syndromes.* MEN2 and von hippel-lindau syndrome
- >95% are abdominal*
- >90% in adrenal medulla*
- 80% occur unilateral*
- Surgically correctable forms of hypertension*
- It can be life threatening if not recognized & not treated.*



Clinical Features:

- Chest pain*
- Anxiety*
- Glucose intolerance*
- Increased metabolic rate
- Fast heartbeat are typical symptoms, usually associated with markedly high blood pressure.*
- **P**alpitations
- **H**eadache
- **E**pisodic Sweating (diaphoresis)

Classic Triad
PHEochromocytoma
3 most common symptoms

Pheochromocytoma Cont..

Resistant Hypertension (95%): often severe, occasionally malignant, and may be resistant to treatment with standard antihypertensive drugs. Levels could be 220/180
Classical symptoms : episodic hypertension.

Paroxysms or Crisis: frequent or sporadic,occurring at intervals as long as weeks or months. With time, the paroxysms usually increase in frequency, duration, and severity*

Other Distinctive Clinical Features:*

- Increased metabolic rate, such as profuse sweating and mild to moderate weight loss.
- Sinus tachycardia, sinus bradycardia, supraventricular arrhythmias, and ventricular premature contractions have all been noted.
- Angina and acute myocardial infarction.
- Headache 80%
- Perspiration 71%
- Palpitation 64%
- Pallor 42%

★ Diagnosis:

- The diagnosis is established by the demonstration of:
  - Increased production of catecholamines.
    Or
  - Increased catecholamine metabolites:
    Metanephrine and vanillylmandelic acid VMA (a breakdown product of norepinephrine) in plasma and/or urine.
- The diagnosis can usually be made by the analysis of a **single 24-h urine** sample, provided the patient is hypertensive or symptomatic at the time of collection.
- Imaging: CT, MRI