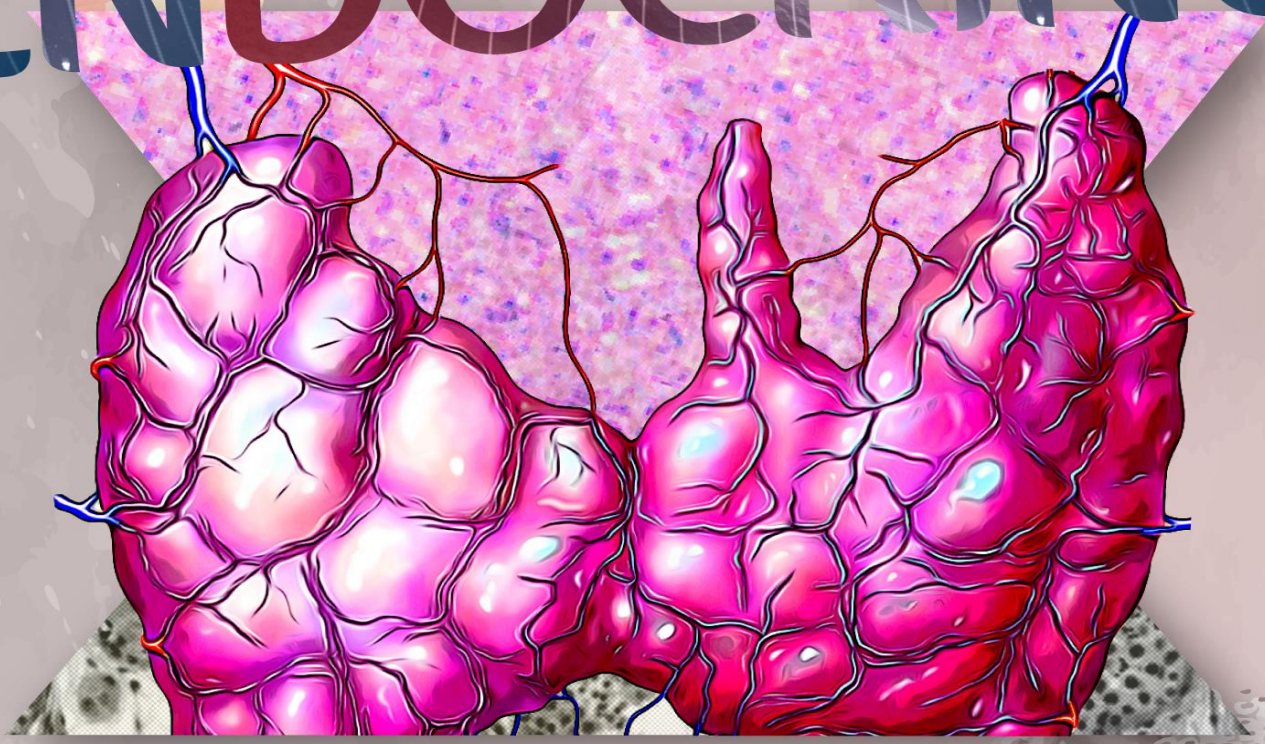
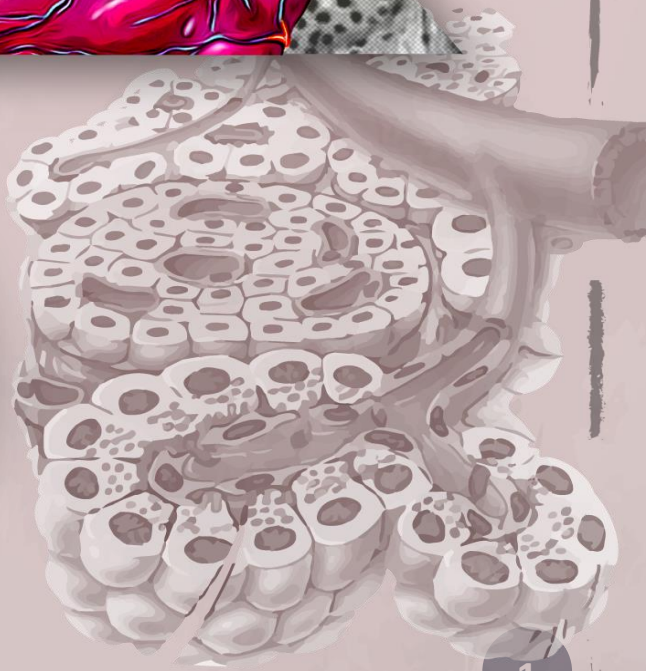
4

ENDOCRINE





SUBJECT: Physiology

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Over Secretion of Growth Hormone

- **Giantism** *(Gigantism)*: is a condition characterized by **excessive growth** and **height** above average, caused by over-production of growth hormone. It is a rare disorder resulting from **increased** levels of growth hormone **before** the fusion of the growth plate which usually occurs at some point **after puberty**. Characteristics include:

  1- Their height is 8-9 feet(1 foot=30.5m); they are more than 2.5m tall.

  2- Their extremities have **normal** proportions compared to their height.

  3- Giants have **hyperglycemia** *(GH increases the glucose level in blood)*, 10% develops diabetes mellitus.

> ***Extra Note:*** *Since Giantism causes **hyperglycemia**, the beta cells of the islets of Langerhans in the pancreas become **hyperactive** and thus they become prone to **degeneration**. Beta cells produce **insulin**, and diabetes is due to the pancreas **not** producing enough insulin, therefore, by the degeneration of beta cells, **not** enough insulin will be produced and **diabetes mellites** may develop.*

- If patients with Giantism remain **without** treatment, they will develop **panhypopituitarism**; that is because gigantism is usually caused by a **tumor** of the **pituitary gland** that grows until the gland is destroyed.

- Gigantism should not be confused with **Acromegaly**, the adult form of the disorder, characterized by enlargement specifically in the **extremities** and **face**. Since Acromegaly occurs **after** puberty, i.e. after the fusion of the growth plate, it **doesn't** cause excessive **height**. Characteristics include:

  1- Enlargement marked in the **small bones** of the hands, feet, and in the **membranous bones**, including the cranium, nose, forehead, supraorbital ridge, the lower jaw bones, and portions of the vertebrae.

  2- Many **soft tissues** or organs like the liver, tongue, and especially the kidneys become greatly enlarged.

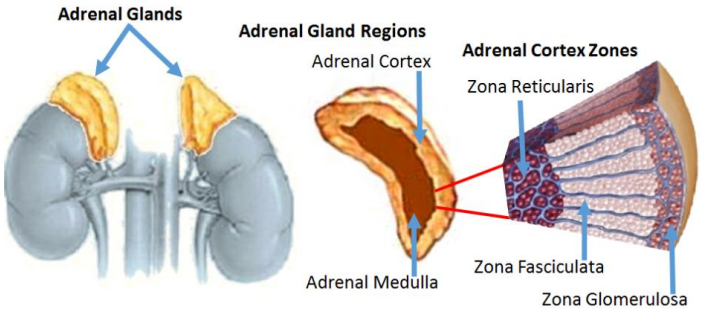
  ⇨ **Gigantism** occurs when the growth hormone over-secretion occurs **before** puberty *(adolescence)*, while in **Acromegaly,** over-secretion occurs **after** puberty.

Adrenal Glands

- There are **two** adrenal glands *(suprarenal glands)*, left and right. They lie in the **superior** pole of the two kidneys, their total weight is 6-10g. The blood supply of these glands comes **directly** from the **aorta**, which indicates the importance of these glands.
- The adrenal glands have the **greatest** blood supply rates per gram of tissue compared to all other organs. If we remove **both** adrenal glands, the person does **not** survive, but **one** gland alone is **sufficient**.
- The adrenal gland is composed of **two** major parts, these parts **differ** in their embryology, histology, and physiology:

  1- The Adrenal medulla (20%): it the **central** part of the gland and is functionally related to the **sympathetic** nervous system. It secretes the hormones **epinephrine** and **norepinephrine** *(catecholamines)* in response to sympathetic stimulation.

  2- The Adrenal cortex (80%): secretes an entirely different group of hormones called **corticosteroids**, these hormones are synthesized form **steroid cholesterol**. *'our main topic'*



- The **adrenal cortex** is composed of 3 zones, and each zone produces specific hormones:

  1- Glomerulosa (12%): It produces several hormones collectively known as **mineralocorticoids**. The most potent hormone of these is **aldosterone**. From their name, these hormones only function on the **metabolism of minerals**.

  2- Fasciculata (65%): This zone produces a group of hormones called **glucocorticoids** which function on **glucose metabolism**. The most potent glucocorticoid is **cortisol**. This zone also produces a small number of androgens and estrogens.

  3- Reticularis (23%): It mainly produces **androgens** and **estrogens**, but it also produces small amounts of cortisol.

- The **zona reticularis** does not differentiate fully until the age of 6-8yrs. In the adult gland, the cells of the **glomerulosa** migrate down through the zona fasciculata to the zona Reticularis, changing their secretory pattern, shape, and function as they migrate. The functional significance of this migration is not yet clear.

Note 1: ***Mineralcorticoids*** *(aldosteron) secretion from zona* ***glomerulosa*** *is controlled by* ***angiotensin II and potassium****, while* ***glucocrticoids*** *(cortisol) secretion froma zona* ***fasciculata*** *and adrenal* ***androgens*** *secretion from zona* ***reticularis*** *are contolled by* ***ACTH****.*

Note 2: *Notice that zona* ***fasciculata*** *which secrets* ***cortisol*** *account 65% of the adrenal cortex while zona* ***glomerulosa*** *which secretes* ***aldosteron*** *accounts for only 12%, for this reason cortisol secretion rate is much* ***higher*** *than aldosteron secretion rate.*

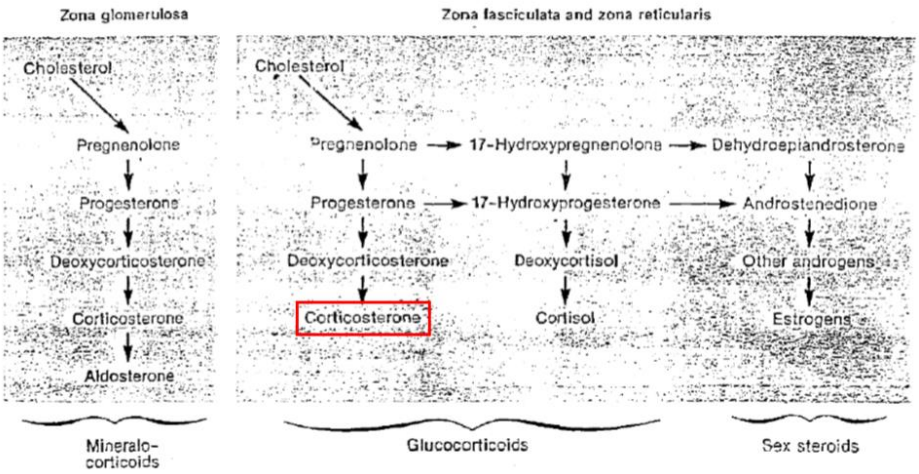
- The adrenal cortex hormones are essential for life because they:
  1- Control Na+, k+ and H2O metabolism.
  2- Control carbohydrate, fat and protein metabolism and mobilization for energy.
  3- Participates in responses of stresses of various kinds.

The Synthesis of the Adrenal Cortical Hormones

- All the adrenal cortical hormones are **steroids** and are synthesized from **cholesterol**. They are synthesized in many steps; many enzymes are needed and then secreted by the **cortex** of the adrenal gland.

Note: *Steroid hormones are Adrenocortical hormones, sex hormones in both females and males and vitamin D.*

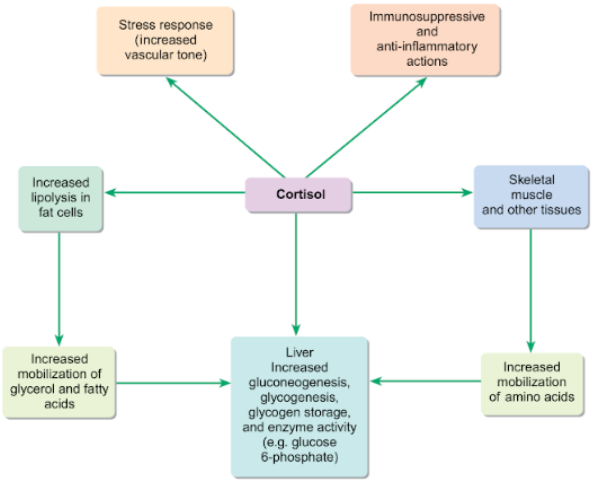
- The adrenal cortex produces steroids that regulate:
  1- Na+ and k+ balance (Mineralocorticoids).
  2- Glucose balance (glucocorticoids).
  3- Small amounts of sex steroid hormones.



- Sometimes there is a problem in the last step of **cortisol** production which leads to an **increase** in the level of **corticosterone**.
- When the adrenal cortex hormones are produced, they are **not stored** in the gland, rather they are **released immediately** and this means that in any need of new hormones, i.e. new synthesis of these hormones is **required** because there are no hormones stored in the adrenal cortex.

Glucocorticoids (Cortisol)

- Cortisol is a **steroid** hormone, in the **glucocorticoid** class of hormones. It is produced mainly by the zona **fasciculata** of the adrenal **cortex** within the adrenal gland.
- Being a steroid allows the Cortisol to act on **all** the systems of the body. The main Functions of cortisol are:



1- Production of glucose from non-carbohydrate sources.
2- Facilitates fat mobilization.
3- Increases the response of blood vessels to catecholamines.
4- Modulates CNS function.

- The most important function of cortisol is that it facilitates the production of **glucose** from non-carbohydrate sources. This makes cortisol **essential** for life for humans and animals especially **during fasting**; it has a role in the **defense** against **hypoglycemia**; meaning that humans and animals cannot fast in case of cortisol deficiency.

  ⇨ **Hypoglycemia** occurs because of the **deficiency** of **cortisol**, hypoglycemia is a kind of stress (danger).

- **Cortisol** has a **permissive** interaction with **glucagon** in the process of **glycogenolysis** *(the presence of one hormone is required in order for another hormone to exert its full effects)*, i.e. Cortisol facilitates the action of glucagon in glycogenolysis, this is similar to the permissive relation between adrenaline and thyroxin on the fat cell 'recall sheet 2, page 5'.
- **Cortisol** binds very well to the **aldosterone** receptors to produce **mineralocorticoid activity**. But there is an **enzyme** in the kidney that **inactivates** cortisol. In this case, cortisol does **not** function as **effective** as aldosterone in producing a **mineralocorticoid activity**.

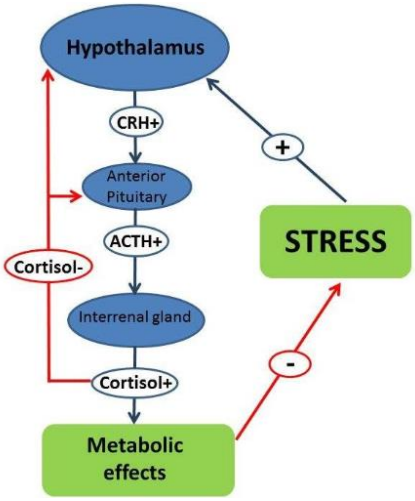
- Cortisol is important even during **fetal life**. It is essential for the normal development of the fetus; it is involved in the production of **surfactant from type II cells** of the alveoli of the lung -a lack of which leads to the respiratory distress syndrome in newborn infants.
- Cortisol is considered as a magical drug since it works on **all** body systems and is used in many diseases; from the skin to cardiovascular diseases. However, it sometimes does not function in some people. If it finds the receptor it functions, if not it doesn't function.
- People who have cortisol as the drug they look **obese** because it **retains minerals** and **increases appetite**.
- There are natural as well as synthetic glucocorticoids:

  1- **Cortisol**: **natural**, very potent accounting for about 95% of all glucocorticoid activity.
  2- **Corticosterone**: **natural**, provides about 4 percent of total glucocorticoid activity but much less potent than cortisol. Any problem in the last step of the synthesis of cortisol causes increased levels of corticosterone.
  3- **Cortisone**: **synthetic**, almost as potent as cortisol.
  4- **Methylprednisone**: **synthetic**, five times as potent as cortisol.
  5- **Dexamethasone**: **synthetic**, 30 times as potent as cortisol.

Adrenocorticotropic Hormone (ACTH) in Regulating Cortisol

- Adrenocorticotropic hormone ACTH, an **anterior pituitary hormone** that stimulates the **growth** of the **adrenal cortex** and the **synthesis** and **secretion** of **all** its hormones. Its main effects are increased production and release of **cortisol** by the cortex of the adrenal gland and its growth.
- ACTH stimulates **desmolase** enzyme that converts **cholesterol** to **pregnenolone** thus increasing the synthesis of **cortisol**. Foetus ACTH synthesis and secretion begins just before the development of the adrenal cortex.
- ACTH has extra-adrenal actions like lipolysis and MSH-like action.

The hypothalamus-pituitary-adrenal axis (HPA axis):

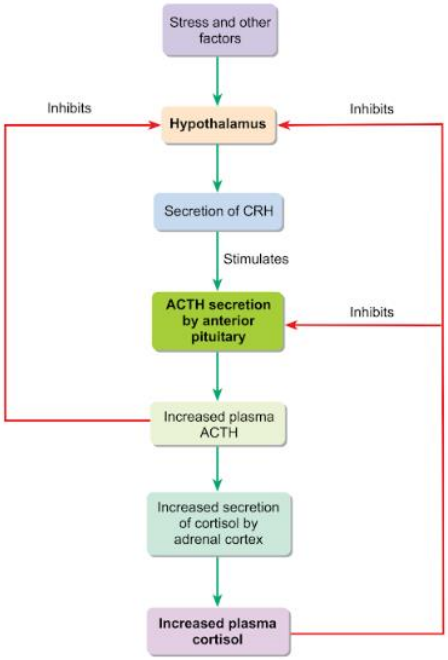


- HPA axis is a complex set of direct influences and feedback interactions among three components: the **hypothalamus**, the **pituitary gland**, and the **adrenal glands.** It has a major role in **regulation cortisol secretion**.

  Corticotropin-releasing hormone (**CRH**) from the **hypothalamus** controls the secretion of **ACTH**. **ACTH**, from the **anterior** pituitary gland, stimulates **cortisol** secretion from the adrenal gland.

- **CRH** and **ADH** are the main stimuli for **ACTH secretion**. ACTH secretion responds most strikingly to **stressful** stimuli of **all** types, a response that is critical for survival:

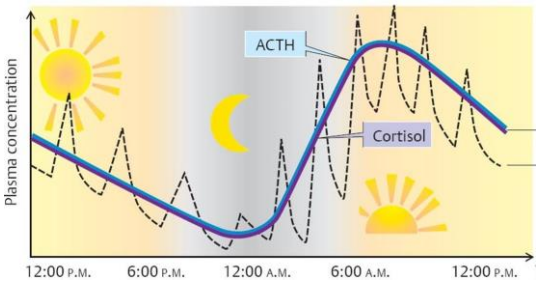
  ⇨ **Pain stimuli** caused by physical stress or tissue damage are transmitted first upward through the brain stem and eventually to the median eminence of the hypothalamus and then carried to the anterior pituitary gland where it **induces ACTH secretion**.



  The main effect of **ACTH** on the adrenocortical cells is to activate **adenylyl cyclase** in the cell membrane. This induces the formation of **cAMP**, which activates intracellular enzymes that causes the formation of **adrenocortical** hormones. One of the most important intracellular enzymes to be activated is the **desmolase**, which causes the conversion of cholesterol to pregnenolone raising the serum level of **cortisol**. This conversion is the **rate-limiting step** for all the adrenocortical hormones synthesis.

  Cortisol produced in the adrenal cortex will **negatively** feedback to inhibit both the **hypothalamus** and the **pituitary gland** if the pain persists, causing **cortisol** serum levels to **fall** below normal.

The rhythm of ACTH and cortisol throughout the day (Diurnal Rhythm):



- Recall that the **main** target hormone of **ACTH** is **cortisol**, thus when ACTH level changes, cortisol level changes as well.
- Cortisol is relatively **high** in the **morning** but **low** in the **afternoon** and **early evening**.
- ACTH and cortisol are also related to the **circadian rhythm** *(sleep-wake cycle)* in many organisms, as well as having a **pulsatile** type of secretion.

Mineralocorticoids (Aldosterone)

- **Mineralocorticoids** are a class of **corticosteroids**, which in turn are a class of **steroid** hormones. Mineralocorticoids are produced by the adrenal **cortex** of the adrenal gland. The primary mineralocorticoid is **aldosterone**.
- As for all adrenocortical hormones, mineralocorticoids are synthesized from **cholesterol** *'page 4'*.
- Mineralocorticoids **influence salt and water balances**, they have gained this name because they affect the **electrolytes** (minerals) of the **extracellular fluids** (ECF), especially **sodium** and **potassium**.
- Important mineralocorticoids, including the synthetic ones, are:
  1- **Aldosterone**: very potent; accounts for about 90% of all mineralocorticoid activity.
  2- **Deoxycorticosterone**: 1/30 as potent as aldosterone, but very small quantities are secreted.
  3- **Corticosterone**: slight mineralocorticoid activity.
  4- **9-α-Fludrocortisone**: synthetic; slightly more potent than aldosterone.
  5- **Cortisol**: very slight mineralocorticoid activity, but a large quantity is secreted.
  6- **Cortisone**: slight mineralocorticoid activity.
- **Aldosterone**, which is the principal mineralocorticoid and the **most potent**, is synthesized by a thin layer of cells in Zona **glomerulosa** of the adrenal cortex, these cells are the only ones in the adrenal gland capable of secreting **significant** amounts of aldosterone because they contain the enzyme **aldosterone synthase**, which is necessary for synthesis of aldosterone.
- ECF concentrations of **angiotensin II** and **potassium**, both of which stimulate aldosterone secretion, are the **most potent regulators** of **aldosterone secretion**, the other two factors are:
  1- **Increased sodium ion** concentration in the ECF slightly **decrease aldosterone secretion**.
  2- **ACTH** from the anterior pituitary is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions.

- Functions of the mineralocorticoids (aldosterone): to maintain **normal body fluid volume**, **blood volume,** and **blood pressure** mainly by controlling the concentration of **sodium** and **potassium** in the body. Any **decrease** in blood volume and pressure induces the **renin-angiotensin system**.

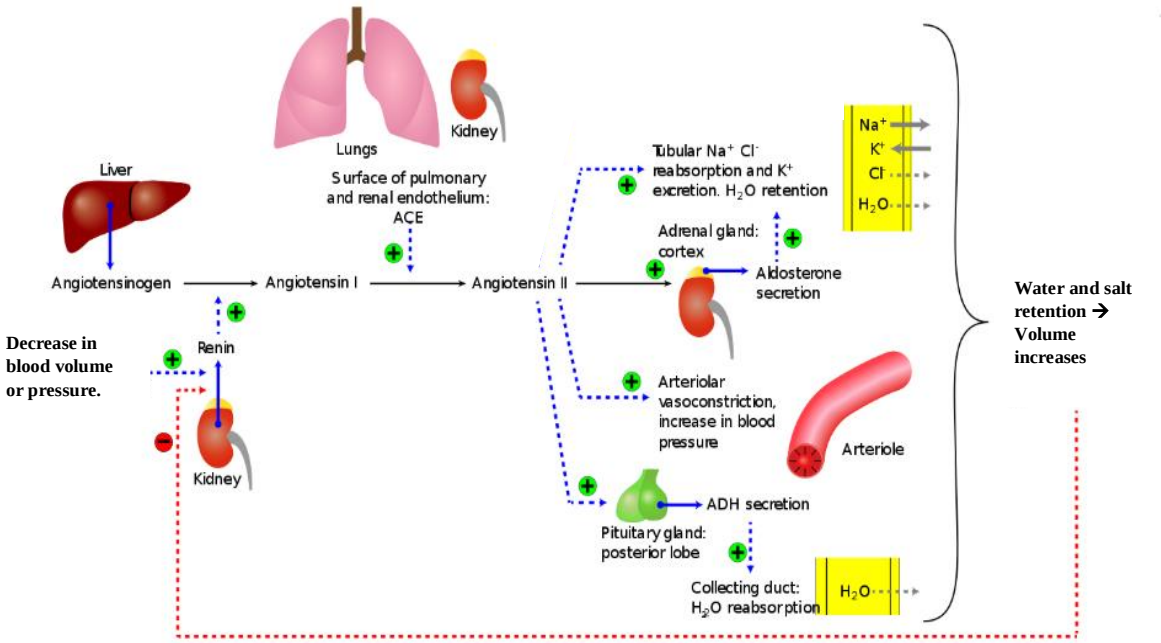
The Renin-Angiotensin System (RAS):

1- RAS is a hormone system that regulates blood pressure and fluid balance. When renal blood flow is **reduced**, juxtaglomerular cells in the kidneys convert the precursor – **prorenin**, already present in the blood, into **renin** and secrete it **directly** into the **circulation**.

2- Plasma renin then carries out the conversion of **angiotensinogen**, released by the **liver**, into **Angiotensin I**. Angiotensin I is subsequently converted to **angiotensin II** by the angiotensin-converting enzyme (**ACE**) found in the **lungs**.

3- Angiotensin II is a **potent vasoconstrictive** peptide that causes blood vessels to narrow, resulting in **increased blood pressure**. Angiotensin II also **stimulates** the secretion of the hormone **aldosterone** from the adrenal cortex.

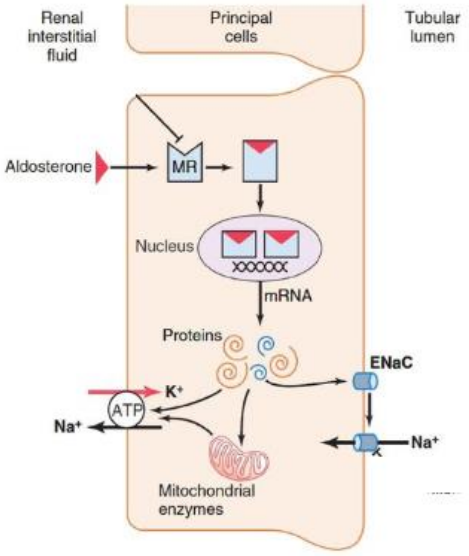
4- Aldosterone causes the renal tubules to **increase the reabsorption of sodium and water** into the blood, while at the same time causing the **excretion of potassium'** in order to maintain electrolyte balance. This increases the volume of ECF in the body, which also **increases** blood pressure.



Now to discuss the role of Aldosterone and Angiotensin II in details:

Aldosterone mechanism of action 'understand':

- **Aldosterone** 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 ducts of the kidney.



  1- Aldosterone is **lipid soluble**, thus it **diffuses** readily to the interior of the renal tubular epithelial cells.

  2- In the cytoplasm of the tubular cells, aldosterone combines with a highly specific cytoplasmic **mineralocorticoid receptor** (MR) protein.

  3- The **aldosterone-MR complex** diffuses into the **nucleus**, inducing one or more specific portions of the DNA to form one or more types of **mRNA** related to the process of **sodium** and **potassium transport**.

  4- The **mRNA** diffuses back into the **cytoplasm** causing protein formation, the proteins formed are a mixture of one or more **enzymes** and membrane **transport proteins** that, all acting together, are required for sodium, potassium and hydrogen transport through cell membranes.

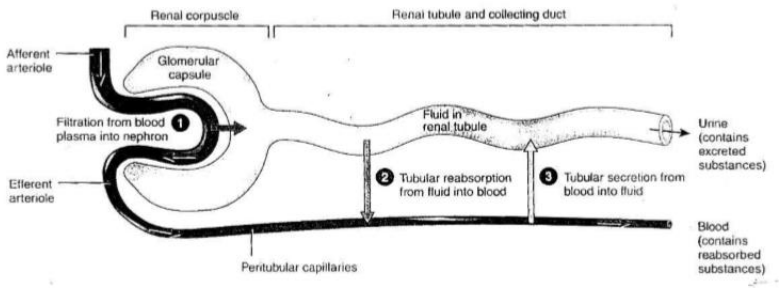
- The most important produced enzyme is **sodium-potassium adenosine triphosphates** associated with the pump for **Na and K exchange** at the **basolateral** membranes of the renal tubular cells.
- Additional important produced protein are **sodium channel proteins**, inserted to the **luminal** membrane of the same tubular cells allowing **rapid** diffusion of **sodium** ions from the lumen into the cells, sodium is then pumped by the Na^+/K^+ pump into the interstitial fluid then into the blood.

Angiotensin II mechanism of action:

- Angiotensin acts by **increasing reabsorption of NaCl, H_2O**, and **increasing the secretion of H^+.** By regulating these factors, angiotensin maintains **normal** blood pressure and ECF volume when they decrease. The three main effects of Angiotensin are:

  1- Angiotensin II stimulates **aldosterone secretion** which in turn **increases sodium** reabsorption as discussed before.

2- It **constricts** the **efferent arterioles**, which has two effects on peritubular capillary dynamics that **increase** sodium and water reabsorption:



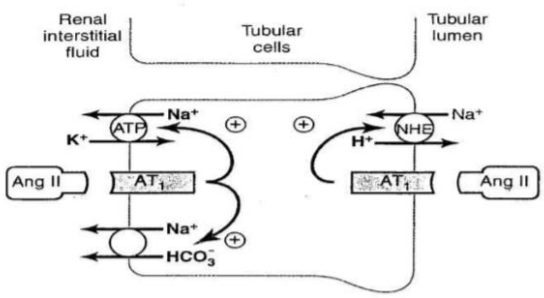
Indirect Effect:

a- Efferent arteriolar constriction **reduces** peritubular capillary **hydrostatic pressure**, which **increases** net tubular **reabsorption**, especially from the proximal tubules.

b- Efferent arteriole constriction **reduced** renal **blood flow**, thus **increasing** the concentration of proteins and the **colloid osmotic pressure** in the peritubular capillaries; this increases the **reabsorptive** force at the peritubular capillaries and **raises** tubular reabsorption of **sodium** and **water**.

Direct Effect:

c- Angiotensin II directly **stimulates sodium reabsorption** by stimulating the sodium-potassium **ATPase pump** on the tubular epithelial cell basolateral membrane of the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules.



d- It also stimulates **sodium-hydrogen** exchange in the luminal membrane, especially in the proximal tubule.

3- Angiotensin II stimulates **sodium-bicarbonate co-transport** in the basolateral membrane.

- Controlling blood pressure and blood volume is mainly stimulated by **angiotensin** which controls **aldosterone**. Aldosterone does not only function on renal tubules; it also functions on the salivary gland, intestine and sweating gland.
- There are 3 types of angiotensin, **angiotensin III** is similar to angiotensin II in potency, but it is released in **smaller amounts**.
- The **synthesis** of **angiotensin II** is **inhibited** by using **angiotensin II converting enzyme inhibitors**, this will we inhibit the formation of angiotensin II from angiotensin I, thus angiotensin I concentration will increase. These inhibitors are usually **safe** drugs, but they don't work on every individual so we have to depend on other drugs that may have some side effects.

Comparison Between Cortisol and Aldosterone

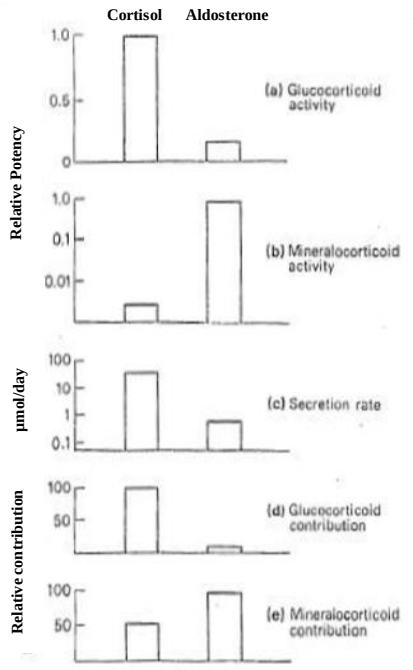
Graphs Explanation:

a) **Glucocorticoid activity** shows which one is more potent as a glucocorticoid, which is **cortisol**. However, even **aldosterone** (a mineralocorticoid) plays a role, especially in glucose metabolism.

b) **Mineralocorticoid activity** means which one is more potent as a mineralocorticoid, which is **aldosterone**. **Cortisol** (a glucocorticoid) can also play a minor role in the metabolism of minerals.

c) **Secretion rate**: Here, the rate of secretion was compared and it was found that **cortisol** is secreted at a much **higher** rate than **aldosterone**, as mentioned in note 2, page 4.

d) **Glucocorticoid contribution** means how much both, cortisol and aldosterone contribute in the activity of glucocorticoids. **Cortisol** was found to have a higher contribution, i.e. the amount of cortisol that works as a glucocorticoid is higher than the amount of aldosterone that works as a glucocorticoid.



e) **Mineralocorticoids contribution** shows that the amount of **Aldosterone** that works as a mineralocorticoid is higher than the amount of Cortisol that works as a mineralocorticoid. However, the **relative contribution** of **cortisol** as a mineralocorticoid is much **more** than that of **aldosterone** as a glucocorticoid; because **cortisol** has a **higher secretion rate**.

⇨ The contribution of **cortisol** in **mineralocorticoid activity** is relatively much **more** than the contribution of **aldosterone** in **glucocorticoid activity**; that is because it is secreted in a **much higher rate** (more than 200 folds) so its levels will always be much greater than aldosterone's levels.

***Note**: In "**contribution**" we take the **secretion rate** into consideration, not only the **potency** like in "**activity**".*

Stimulation:

- **Angiotensin II** and **potassium** stimulate **aldosterone** secretion, while **cortisol** is stimulated through **ACTH**.

Steroid Hormones in the bloodstream:

- 90% of cortisol is bound to Corticosteroid-binding protein, while 6% binds with albumin. Therefore, free cortisol is the physiologically active form of the hormone and its normal percentage is ≈ **4%.**

Table 5.4.2 Plasma protein binding of corticosteroids

	Cortisol (%)	Aldosterone (%)
Corticosteroid-binding protein (CBG)	90	20
Albumin	6	40

- As for Aldosterone, about **40%** is in the free form (functional), the other 60% combines with plasma proteins; where 20% are bound to cortisol-binding globulin (CBG), also called transcortin, and the other 40% is bound to serum albumin.

> ***Note:*** *The high degree of binding (94%) of **cortisol slows** the rate of elimination thus it has a **long** half-life. Unlike **aldosterone** where relatively **low** degrees of binding (60%) has a **short** half-life.*

In this sheet, we discussed the adrenal glands, their parts (medulla and cortex), and what each part secretes. The doctor focused on hormones produced by the adrenal cortex, discussing their mechanism of action and regulators; the mineralocorticoids (Aldosterone) and the glucocorticoids (Cortisol).

In addition to these hormones, small amounts of sex hormones are secreted, especially androgens and estrogens which will be discussed further in the next sheet.

Contact me upon difficulties and sorry for any mistake.

Good Luck