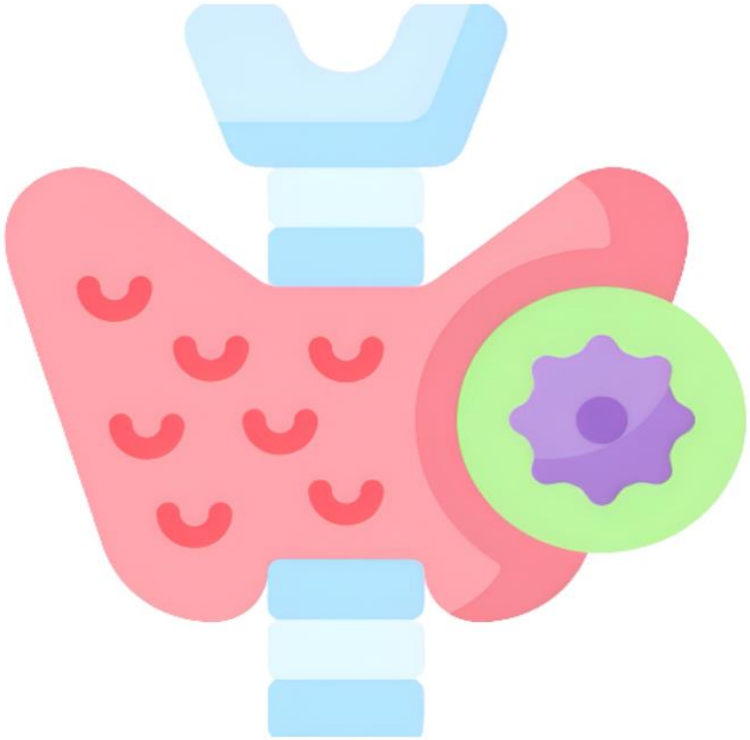
Endocrine system 4

physiology



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The adrenal glands

The adrenal glands are located in the retroperitoneal cavity above each kidney. The adrenal glands are actually two separate glands, the **adrenal medulla** and the **adrenal cortex** (whose secretion are essential for life). They have the highest blood flow directly from the aorta. One adrenal gland is sufficient but without both of them (specially the cortex), humans can't survive.

- ✓ The adrenal gland is 6-10 g, and it is composed of **two major parts**, these parts differ in their embryology, histology, and physiology.

1. **The adrenal medulla**: which is in the inner zone of the gland, composes approximately 20% of the tissue and secretes the catecholamines (epinephrine and norepinephrine) in response to sympathetic stimulation.

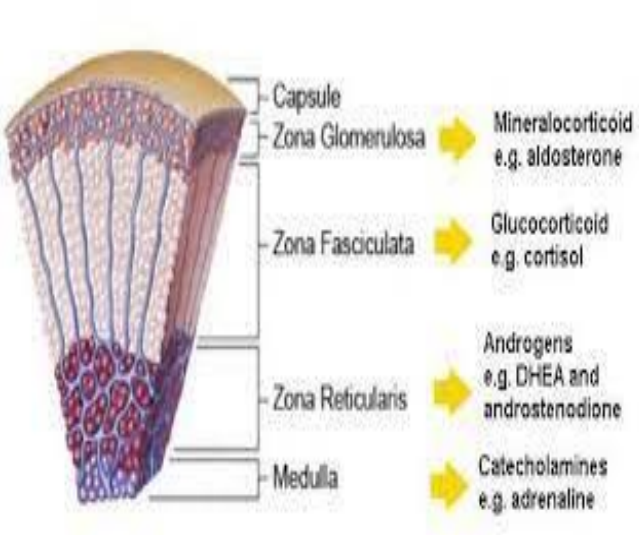
2. **The adrenal cortex**: which is in the outer zone of the gland and has three distinct layers. It composes 80% of the adrenal tissue and secretes adrenocortical steroid hormones, these hormones are synthesized from **cholesterol**.

❖ The adrenal cortex (which is the main topic of the lecture) is composed of 3 zones, each zone produces specific hormones:

A. **zona reticularis** (23%): the innermost zone of the cortex, it mainly produce androgens and estrogens and small amounts of cortisol (glucocorticoid).

B. **Zona fasciculata** (65%): the middle and the widest zone of the cortex, synthesize and secrete glucocorticoids (mainly cortisol) which function in metabolism of glucose, and small amounts of adrenal androgens.

C. **zona glomerulosa** (12%): the outermost zone of the cortex, secretes mineralocorticoids (mainly aldosterone), they control the metabolism of minerals.



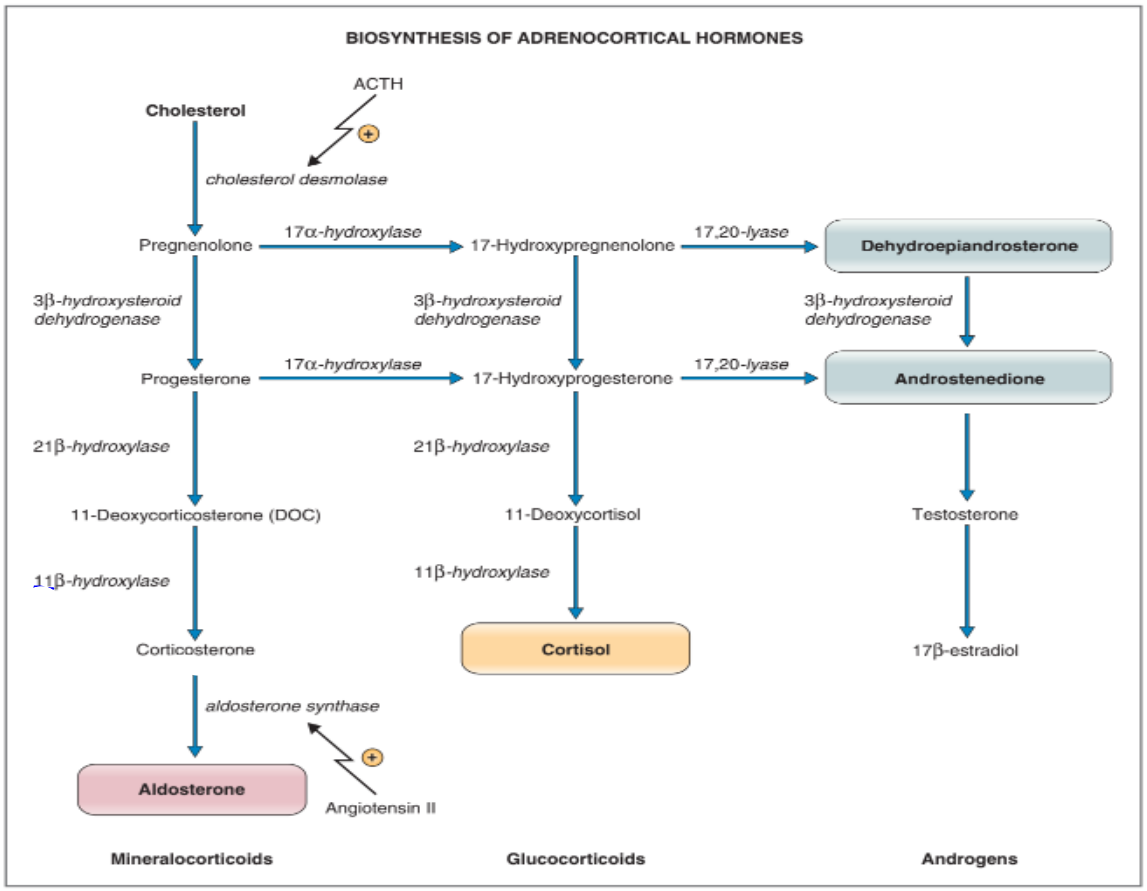
The **zona reticularis** does not differentiate fully until the age of 6-8 yrs (because it secretes androgens and estrogens which are not needed before the age of 6). In the adult gland, the cells of the glomerulosa migrate down through the zona fasciculata to the zona reticularis, changing their secretory pattern, shape, and function as they migrate. The functional significance of this migration is not yet clear.

- The adrenal cortex hormones are essential for life because they:

1- Control Na+, k+ and H2O metabolism (ECF volume).
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

The precursor for all adrenocortical steroids is **cholesterol**, the layers of the adrenal cortex are specialized to synthesize and secrete particular steroid hormones: either glucocorticoids and androgens or mineralocorticoids, the basis for this specialization is the presence or absence of the enzymes that catalyze various modifications of the steroid nucleus.



The adrenal cortex produces steroids that regulate:

1. Na+ and k+ balance (Mineralocorticoids). 2. Glucose balance (glucocorticoids). Small amounts of sex steroid hormones.

Note: If there is a problem in the last step of cortisol production that will lead to an increase in the level of corticosterone.

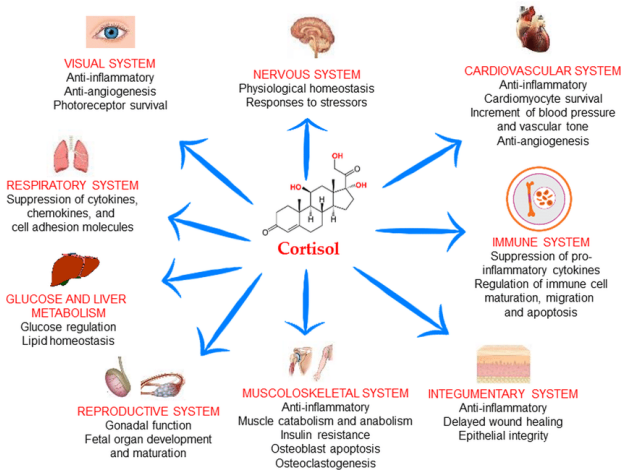
When the adrenal cortex hormones are produced, they are **not stored in the gland**, rather they are released immediately and this means, in any need of new hormones, new synthesis of these hormones is required because there are **no hormones stored in the adrenal cortex**.

Glucocorticoids (Cortisol)

The major glucocorticoid produced in humans is cortisol (hydrocortisone), which is synthesized in the zona fasciculata (mainly) and zona reticularis (minorly). Thus, these zones contain all of the enzymes required to convert cholesterol to cortisol.

Being a steroid allows the cortisol to enter all the systems of the body, it is called a magic drug because it is used for any disease with unknown medication,specifically cardiovascular diseases.

- The **main Functions of cortisol** are: (others are in the figure)
  1- Production of glucose from non-carbohydrate sources (gluconeogenesis).
  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 of 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.

Note: cortisol can induce glycogenolysis by facilitating the effect of glucagon, it means that glucagon can't do its function unless cortisol is present (***permissive effect***).

- Cortisol binds very well to the aldosterone receptors to produce mineralocorticoid activity, but there is an enzyme in the kidney "**hydroxysteroid dehydrogenase**" 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 deficiency of cortisol leads to Rispiratory distress syndrome in newborns. (from 017)

☒ Cortisol is either:

90% >> bound to corticosteroid-binding proteins.

6% >> bound to albumin.

4% >> "free" >> This is the only amount that is functional

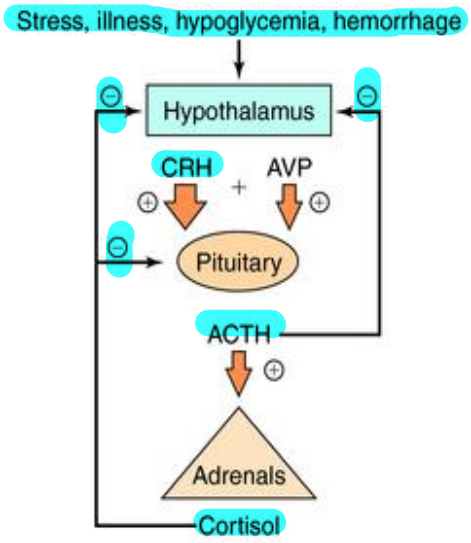
☒ There are **natural** as well as **synthetic** glucocorticoids:

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 increase the production and release of cortisol by the cortex of the adrenal gland and its growth.

'Extra' the synthesis of all adrenocortical hormones started with converting the cholesterol to pregnenolone by the enzyme **"cholesterol desmolase"**, this enzyme is stimulated by ACTH. Since this enzyme is present in the three pathways, ACTH stimulate the release of all adrenocortical hormones but **its main effect is on cortisol.**



- **CRH** and **ADH** are the main stimuli for ACTH secretion; corticotropin-releasing hormone (CRH) from the hypothalamus controls the secretion of ACTH from the anterior pituitary gland, ACTH stimulates cortisol secretion from the adrenal gland, while the mechanism of ADH is not well-understood yet.
- ACTH secretion responds most strikingly to stressful stimuli of all types ,a response that is critical for survival. (e.g. hypoglycemia).
- Fetus ACTH synthesis and secretion begins just before the development of the adrenal cortex.
- ACTH has extra-adrenal actions like **lipolysis** and **MSH-like action**.

Mineralocorticoids (Aldosterone)

The major mineralocorticoid in the body is **aldosterone**, which is synthesized **only in the zona glomerulosa**. As for all adrenocortical hormones, mineralocorticoids are synthesized from cholesterol, in addition to the enzyme that catalyzes the last step which is "***aldosterone synthase***" that only exists in zona glomerulosa.

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 which are important in having normal blood pressure.

- ✓ Aldosterone is either:

20% >> bound to corticosteroid binding proteins (transcortin).

40% >> bound to albumin.

40% >> free

The amount of free aldosterone is **relatively high** in comparison to cortisol (4%) because aldosterone controls our blood pressure.

- ✓ Also, there are synthetic and natural mineralocorticoid hormones;
    1. **Aldosterone:** (natural) very potent; accounts for about 90% of all mineralocorticoid activity.
    2. **Deoxycorticosterone:** (natural) 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.
- The cortisol plays a role in the metabolism of minerals, as we said because it binds very well to aldosterone receptors, but it gets inactivated as soon as it binds (minimal effect).

Factors affecting the excretion of Aldosterone

The main function of aldosterone is **controlling the balance of water and salts in the kidney** by keeping sodium in and releasing potassium from the body and finally **increasing the blood pressure**.

blood

increase the water in blood
(increase the blood volume)

Factors that stimulate the release of aldosterone from adrenal cortex:

1. Angiotensin II from the renin angiotensin system. (the strongest effect) decrease in bp
2. High potassium & low sodium in blood.
3. ACTH from the anterior pituitary gland (the weakest effect).

The Renin Angiotensin System (RAS)

The renin angiotensin system is activated when the blood pressure drops down, it tries to raise the pressure back to normal by reabsorption of water and electrolytes (mainly sodium). water follow the Na+

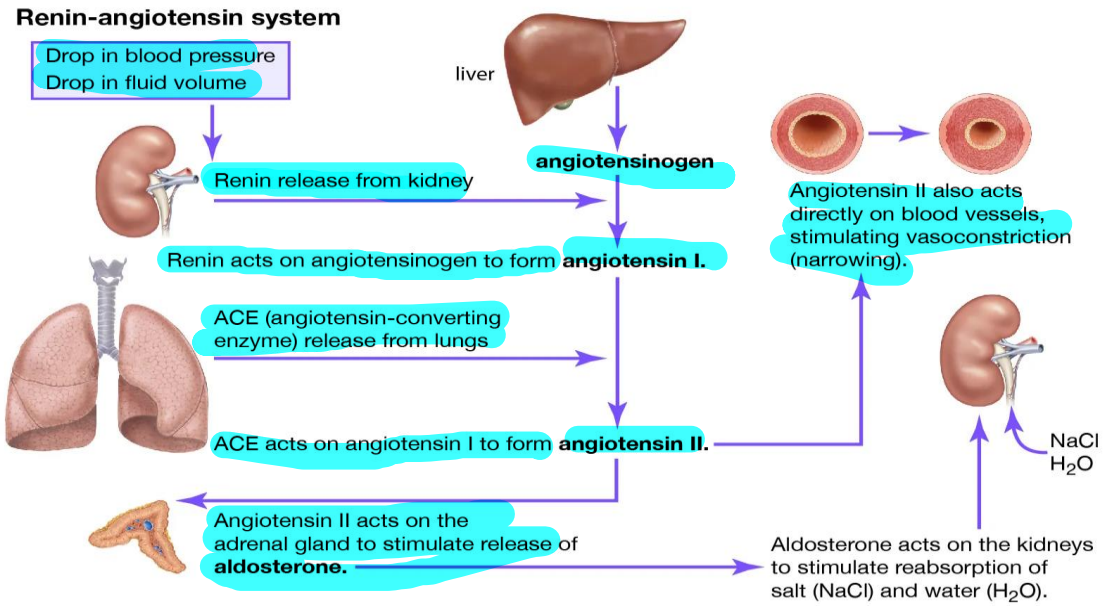
1. when renal blood flow is reduced, juxtaglomerular cells in the kidneys convert the precursor prorenin, already present in the blood, into renin and secrete it directly into the circulation.

2. Plasma renin then carries out the conversion of angiotensinogen (released by the liver) into Angiotensin I.

3. Angiotensin I is subsequently converted to angiotensin II by the angiotensin converting enzyme (ACE) found in the lungs.

4. Angiotensin II is a potent vasoconstrictor, 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.

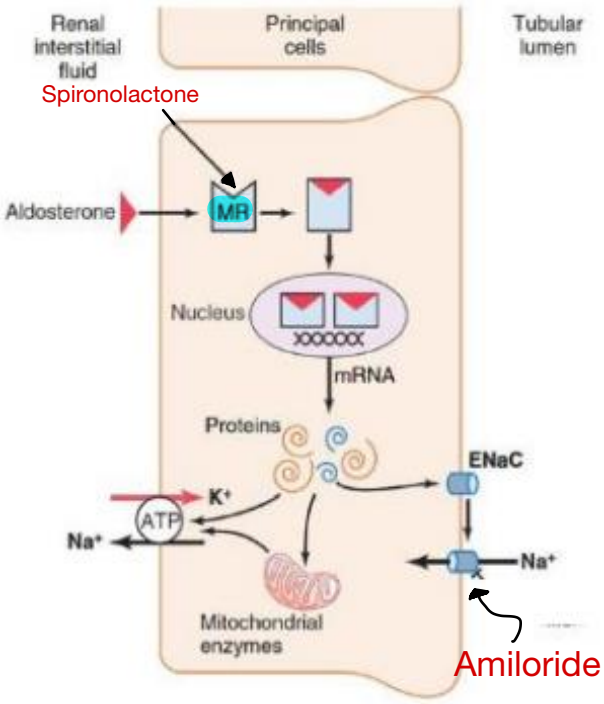
5. Aldosterone causes the renal tubules to increase the reabsorption of sodium and water into the blood, while at the same time causing the excretion of potassium, in order to maintain electrolyte balance. This increases the volume of ECF in the body, which also increases blood pressure.



Aldosterone mechanism of action

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.



To sum up: Aldosterone induces the transcription of new membrane transport proteins (Sodium channels, potassium channels and sodium potassium pumps), all these contribute to enhance the secretion of potassium from the blood to the urine, and enhances the reabsorption of sodium from urine back to the blood. Water will follow the concentration of the sodium (to the blood), so the final result will be an **increase in blood pressure**.

- There are drugs that inhibit the action of aldosterone, causing more release of water and sodium to the urine, these drugs are known as diuretic drugs. Examples are; **Amiloride** (inhibit the reabsorption of sodium from sodium channels) **Spironolactone** (bind to MR protein).

The mechanism of action of Angiotensin II

In addition to the effect of angiotensin II on aldosterone, it also increases sodium and water reabsorption from the renal tubules, these other effects can be **direct** or **indirect**.

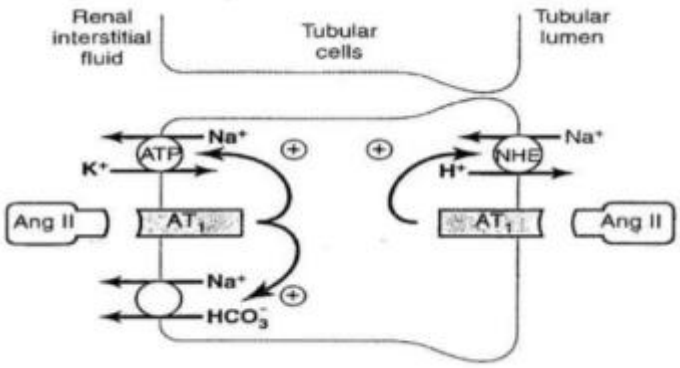
Note: the effect of angiotensin II on sodium reabsorption is more potent than aldosterone effect.

1. **DIRECT effect** on renal tubules by:

   A. 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.

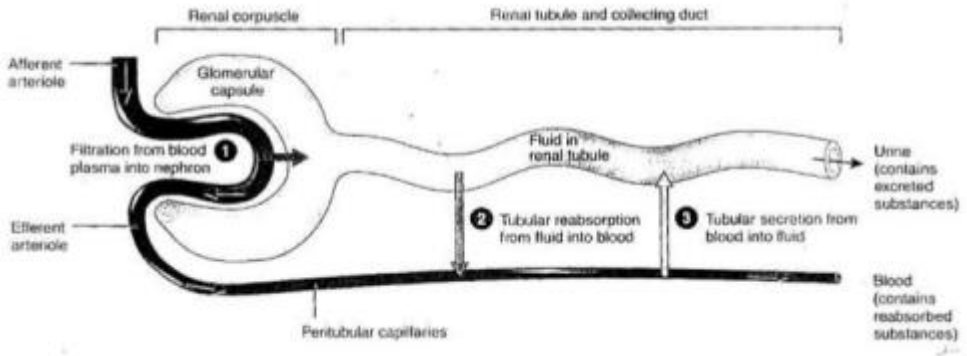
   B. It also stimulates **sodium-hydrogen exchange** in the luminal membrane, especially in the proximal tubule.

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



2. **INDIRECT effect** on renal tubules by constriction of the **peritubular capillaries:**

As you can see in the next figure, this is a nephron, there is an afferent arteriole that supplies the glomerulus, then blood leaves through the efferent arteriole. Angiotensin II is a vasoconstrictor for the <u>efferent arterioles</u>, this causes the **colloid osmotic pressure to increase** and the **hydrostatic pressure to decrease** (in the area pointed as 2), and as a result of these changes, reabsorption of sodium and water occurs.

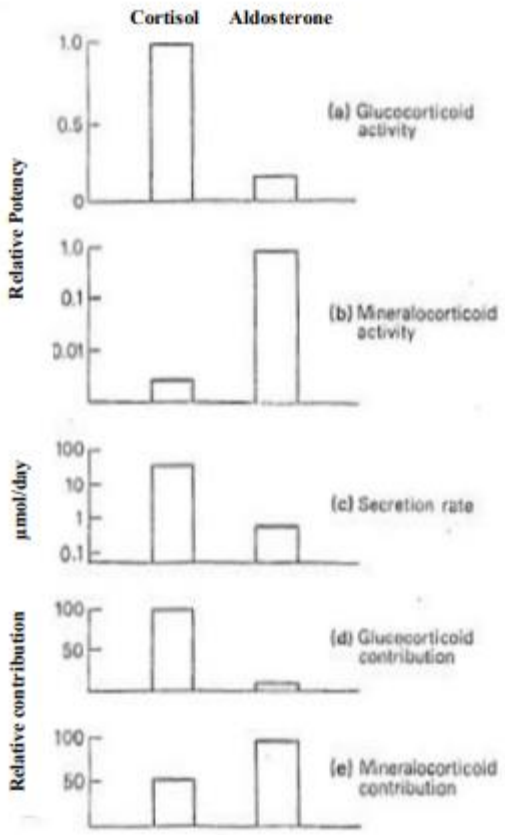


There is also **Angiotensin III** that is produced from angiotensin II, it is as potent as Angiotensin II but is present in low amounts.

Aldosterone functions are *not on the renal tubules only* but also on other glands like salivary glands, intestines, as well as on the sweat glands, so it reabsorbs sodium in all these organs.

Comparison between aldosterone and cortisol

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, because 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.

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 high degree of binding of cortisol (94%) slows the rate of elimination thus, it has a long half-life. Unlike Aldosterone where relatively low degree of binding (60%) has a short half-life.

The End