The Endocrine System

PHYSIOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	4
Subject:	Cortisol / aldosterone/ androgens and estrogens
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Date: 00/0/2016

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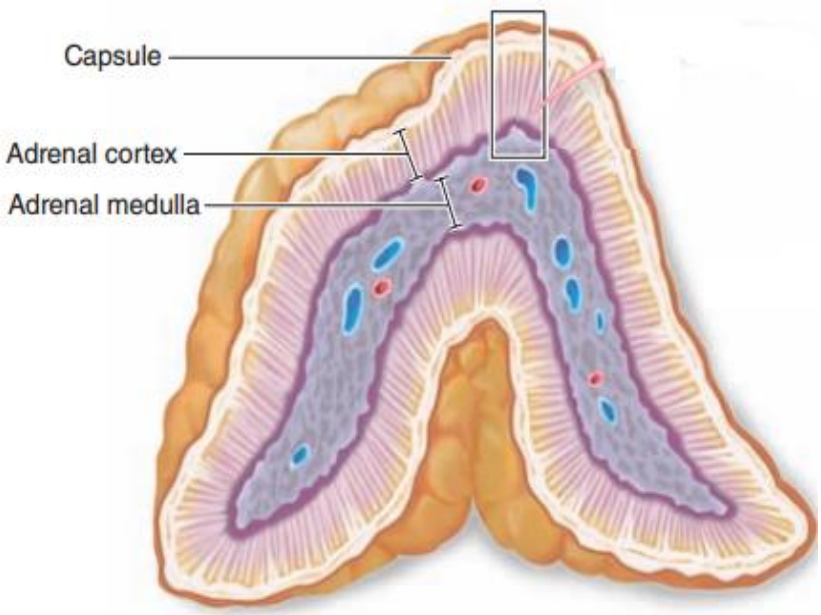
Adrenocorticotropic hormone (ACTH)

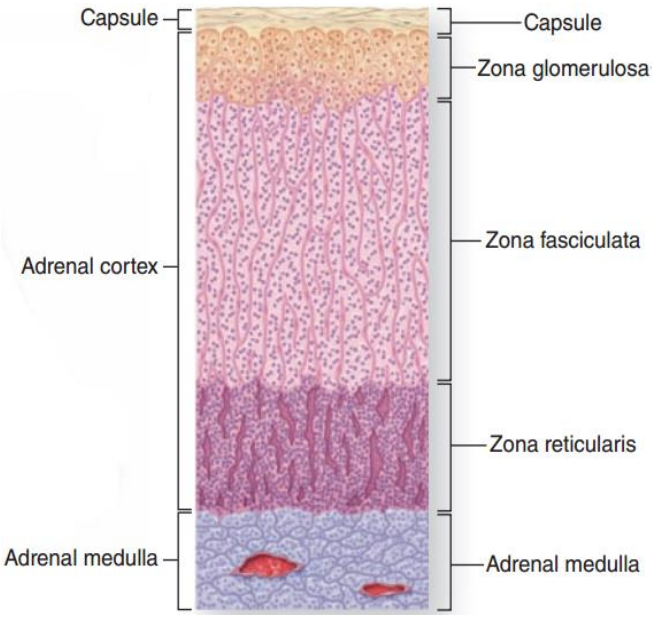
- ACTH is a **peptide** hormone secreted from the **anterior** pituitary.
- Its secretion in the fetus begins very **early** in uterine life, before the development of the adrenal cortex .
- It stimulates the growth and secretions of hormones from the adrenal **cortex** (the main targeted hormone is cortisol)
- Its secretion is stimulated by
    - **CRH** (corticotropin releasing hormone) from the **hypothalamus**.
    - **ADH** (antidiuretic hormone) from the **posterior pituitary**.



- Each adrenal gland is composed of 2 parts; the adrenal medulla and adrenal cortex.

- They are very different in their histology, function, and embryological origin.

- Each weighs **3-5** grams.



This section shows the capsule of the gland, adrenal cortex and the adrenal medulla.

There are 3 zones of the adrenal cortex:

Zona glomerulosa (12%)

Zona fasciculata (65%)

Zona reticularis (23%)

Zona glomerulosa

- Just underneath the capsule.
- Cells of this zone secrete steroid hormones called **mineralocorticoids**.
- The most potent is **aldosterone**.

Zona fasciulata

- Cells of this zone secrete steroid hormones called **glucocorticoids** in addition to small amounts of **androgens**.
- The most potent of these glucocorticoids is **cortisol**.

Zona reticularis

- Cells of this zone secrete **androgens** and small amounts of cortisol.
- They don't differentiate until age 8.
- In adults, cells of the zona glomerulosa **migrate** down to reach the zona reticularis. While they are migrating down, their shape and function change

	Glucocorticoid activity	Mineralocorticoid activity	Plasma concentration	Secretion rate(mg/day)
Cortisol	**1**	**1**	**12**	**15**
Aldosterone	**0.3**	**3000**	**0.006**	**0.15**

- Note that cortisol is an **active** mineralocorticoid beside its glucocorticoid activity.
- Aldosterone is a relatively **inactive** glucocorticoid; it **only** has an important mineralocorticoid activity.
- Secretion rate of cortisol is much higher than secretion rate of aldosterone

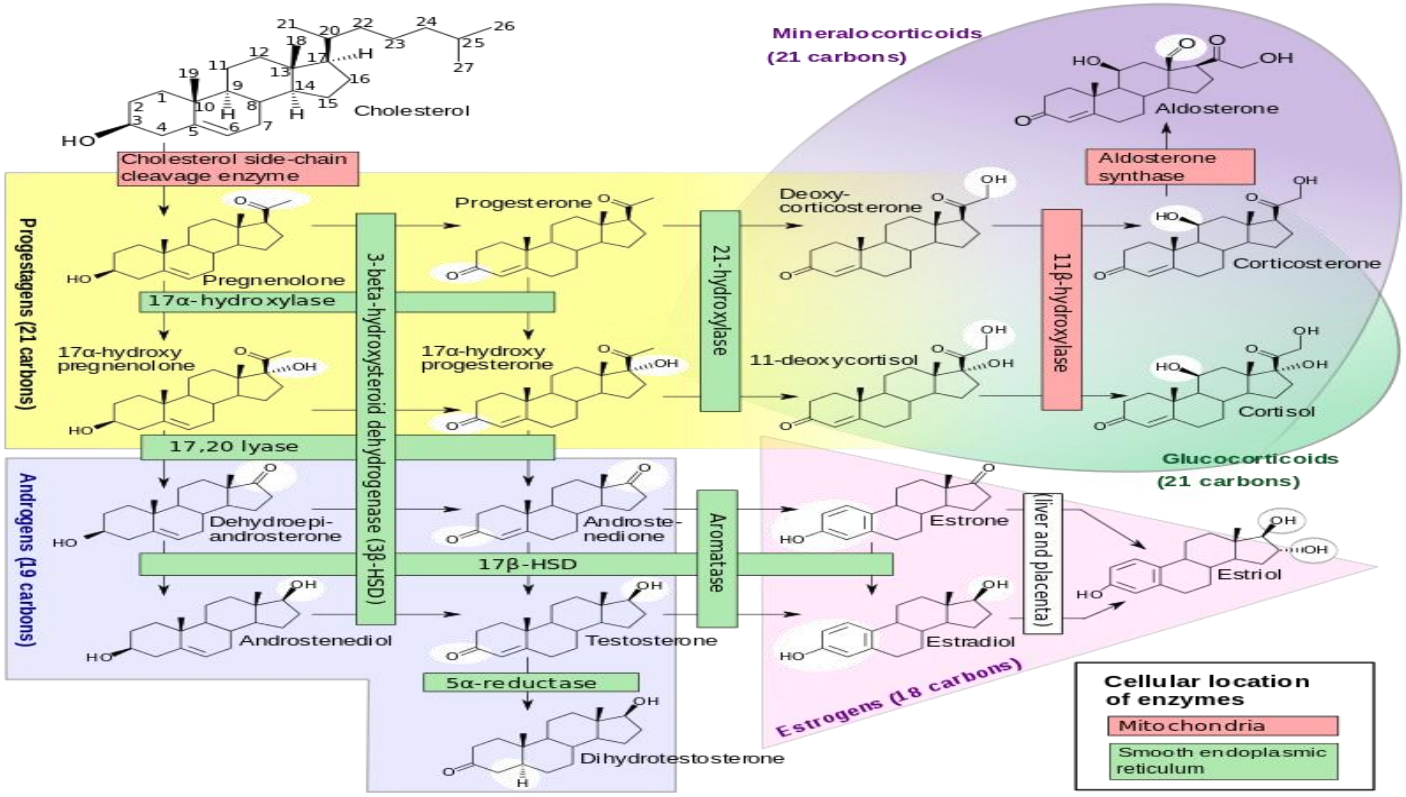
From the table, we can obtain each hormone's glucocorticoid and mineralocorticoid activity **contribution** in the body.

	Glucocorticoid contribution (glucocorticoid activity X plasma concentration)	Mineralocorticoid contribution (mineralocorticoid activity X plasma concentration)
Cortisol	**12**	**12**
Aldosterone	**0.018**	**18**

- Note that aldosterone contribution to the glucocorticoid activity is **negligible**.

- Important: as seen, cortisol contribution to the mineralocorticoid activity is **significant**. This is **not true** in our bodies because the epithelial cells of the kidney which contain aldosterone receptor, express an **enzyme** which **immediately inactivates** cortisol upon entry into the cell preventing it from binding the receptor. A **deficiency** of this enzyme allows cortisol to contribute **significantly** to the mineralocorticoid activity as if **alodosterone** is secreted in very high amounts. Note that cortisol itself can bind the receptor with a very low affinity.

- Most of the cortex secretion is **cortisol** (mainly from zona fasciculata)
- **ACTH** targets this zone; it stimulates these cells to release cortisol.
- Cortisol, like other cortex hormones, is a steroid synthesized from cholesterol.



A change in even a single enzyme that catalyzes a single step causes vastly different types and relative **proportions** of hormones to be formed.

For example, deficiency in the enzyme that catalyzes the last step of the synthesis of cortisol:

1. Increases the levels of **deoxycortisol**, **11-deoxycorticosterone** and **androgens**(dehydroepiandrosterone and androstenedione**)**
2. Decreases the levels of **aldosterone** and **corticosterone**.

(All the doctor mentioned was that this enzyme deficiency increases the level of corticosterone which doesn't make sense since corticosterone production requires the deficient enzyme as seen in the figure.)

In many mammals, including **rats**, **corticosterone** is the main glucocorticoid with cortisol being absent.

Adrenal cortex cells don't store hormones. Once stimulated, they synthesize the hormones and **immediately** secrete them.

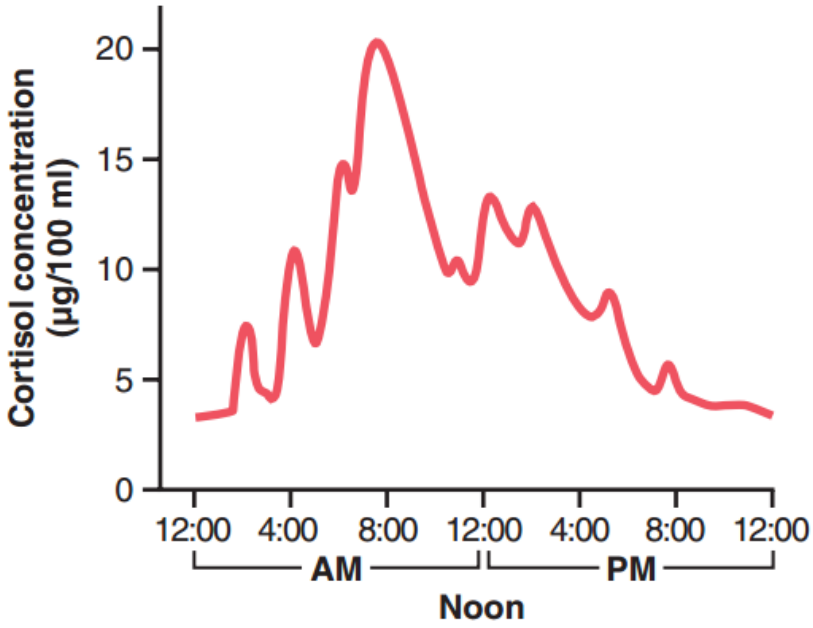
Cortisol

Being **lipid** soluble, it's **bound** to plasma proteins in the blood:

- **90%** of cortisol is bound to cortisol binding globulin (**transcortin**).
- **6%** of cortisol is bound to albumin.
- **4%** of cortisol is free to diffuse into cells.
- An **equilibrium** is maintained between free and bound cortisol.
- Only the **free** cortisol is the functional cortisol.
- Half-life: **60** to **90** min.

Cortisol is **essential** to life, especially while **fasting**, because glucose level decreases and **glucagon** has to act to return it to its normal level.

Diurnal rhythm of cortisol



Effects of cortisol

1) Alter metabolic activities

Carbohydates

1. **Stimulates gluconeogenesis:**
   It doesn't stimulate gluconeogenesis itself; it just has a **permissive** action to glucagon. (Without cortisol, glucagon fails to stimulate gluconeogenesis).
2. **Decreases glucose utilization by cells**

Proteins

1. **Decreases amino acids uptake by cells.**
   These amino acids diffuse to the liver which in turn uses them as **substrates** for gluconeogenesis and synthesizes **plasma proteins**.
2. **Increase mobilization of proteins from nonhepatic tissues**

Fats

1. **Promotes mobilization of fatty acids by adipocytes**
   This causes the cells to utilize energy from Fatty acids rather than glucose in times of starvation or other stresses. This in turn**conserves** glycogen stores.

2) **Suppresses immunity and inflammation (anti-inflammatory)**
3) **Responds to stresses**
4) **Modulates the functions of the nervous system.**

Cortisol is also essential in fetal life:

1) **Production of surfactants from type 2 cells of the alveoli.**
   Surfactants lack causes respiratory distress syndrome.
   Injection of minute quantities of cortisol in new born babies who lack surfactants stimulates their production immediately and they start to breathe properly within minutes.
2) **Development of hypothalamic function and of the thyroid pituitary axis**
3) **Causes the sequential changes of the placental structure and the composition of the amniotic and allantoic fluids.**
4) **Very important in the initiation of parturition.**
5) **Formation of the hepatic enzymes including those involved in gluconeogenesis.**
6) **Induction of thymic involution**

- Cortisol and its derivatives are used as effective medications in most diseases especially those with no known reasons and medications "The magic drug". This is because they are steroids so they can enter all cells and affect those which have its receptor**.**

Some glucocorticoids:

- Cortisol: Natural , provides 95% of the total glucocorticoid activity.
- Corticosterone: Natural, provides 4% of the total glucocorticoid activity.
- Cortisone : Synthetic .
- Prednisone : Synthetic. The **most** commonly used.
- Methylprednisone : Synthetic .
- Dexamethasone: Synthetic . The most potent (**30** times as cortisol).

Aldosterone

These hormones control **minerals** metabolism (Na^+, K^+), **water** reabsorption, blood **volume** and consequently, blood **pressure**.

Aldosterone is **essential** to life; its absence causes death within days.

Excess aldosterone greatly increases blood pressure (hypertension) which eventually causes kidney failure.

Being lipid soluble, it's bound to plasma proteins in the blood:

- **20%** is bound to corticosteroid-binding globulin (transcortin).
- **40%** is bound to albumin.
- **40%** is free to diffuse into cells. (high compared to others)
- An **equilibrium** is maintained between free and bound aldosterone.
- Only the **free** aldosterone is the functional aldosterone.
- Half-life: relatively **short**. **20** min

The main stimulants of its secretion are 1)angiotensin 2, 3 and 2)K^+ concentrations. 3) ACTH only slightly stimulates its secretion.

> Additional Info: Small amount of ACTH is enough to **permit** the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion.
>
> Therefore, ACTH plays **permissive** role in regulation aldosterone secretion

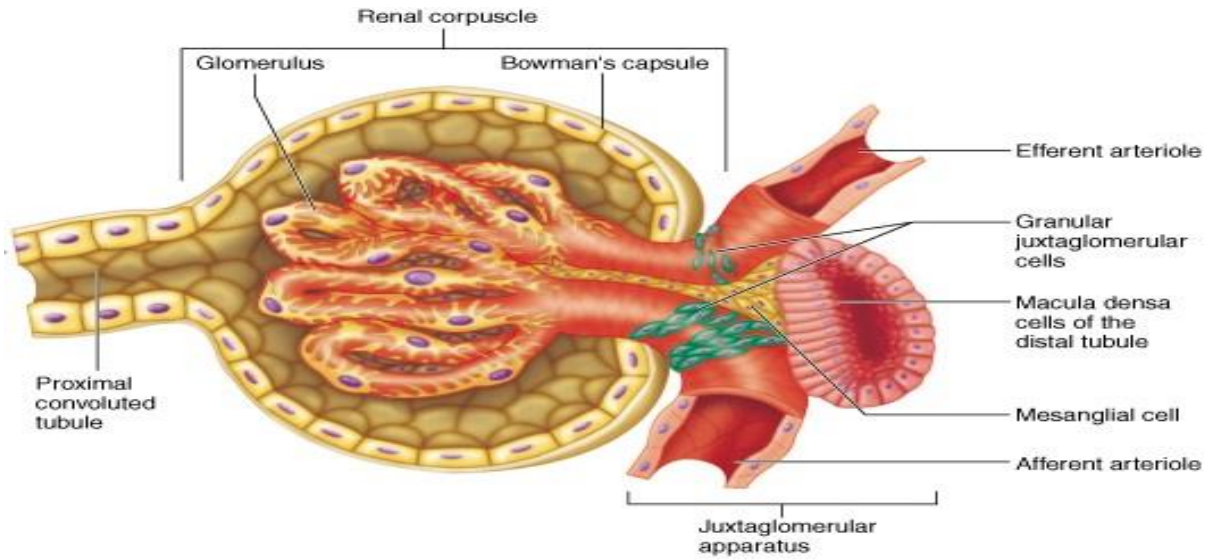
Renin-Angiotensin 2 system

1) Decreased blood pressure, plasma volume, Na^+concentration stimulates
2) Juxtaglomerular apparatus of the kidney produces renin enzyme .Renin cleaves **angiotensinogen** (a protein secreted by the liver) to form **angiotensin 1** which is further cleaved by **angiotensin-converting enzyme (ACE)** to form **angiotensin 2**.

** **ACE** inhibitors drugs are **commonly** used to reduce blood pressure because they are very **safe** drugs with no side effects.

3) Angiotensin 2 has:

- **Indirect** effect in stimulating **aldosterone** secretion.
- **Direct** effect in increasing **Na^+**reabsorption.
  Blood enters **Bowman's** capsule in the afferent arteriole and leaves through the efferent arteriole.
- Angiotensin 2 constricts the efferent arteriole.
- The fluid in the peritubular capillaries is reduced while protein concentration remains the same
- This indirectly increases the colloidal osmotic pressure and water is reabsorbed followed by Na^+.



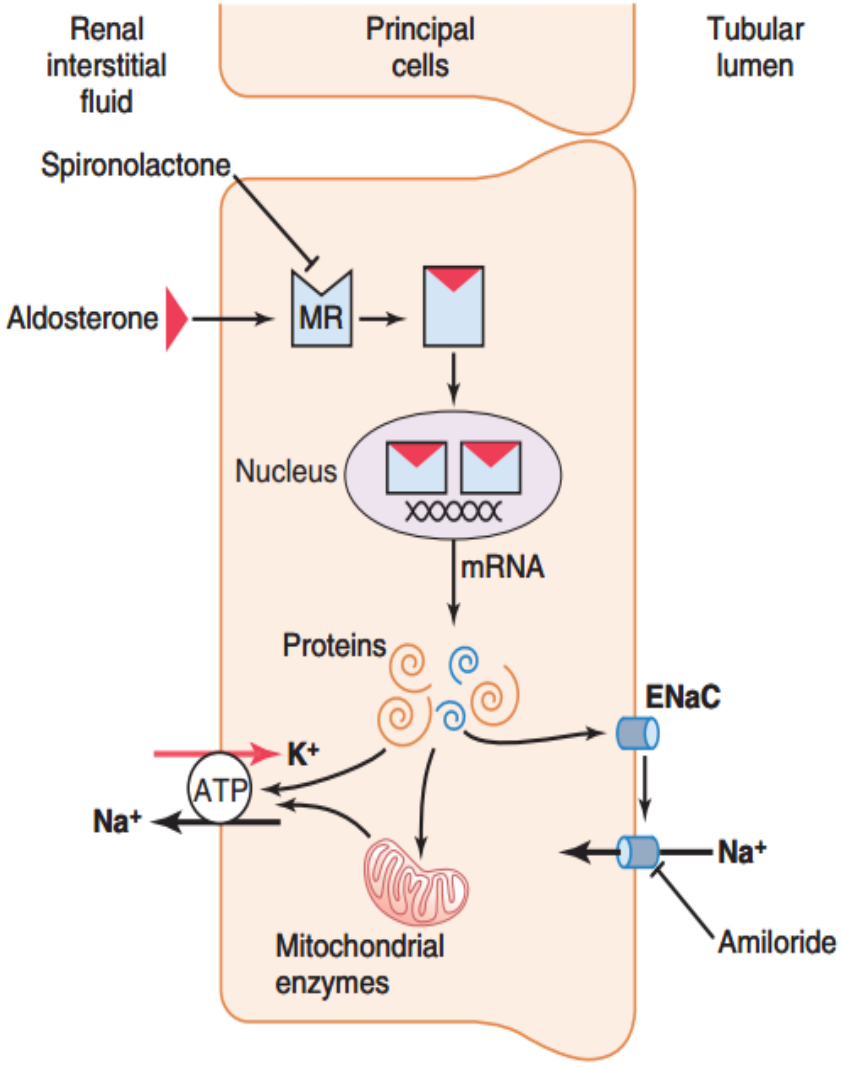
- Angiotensin 3 and 4 do the same effects as angiotensin 2 but with **lower** potencies.

- Aldosterone also stimulates retention of water from **intestines**, **salivary** and **sweat** glands.

Other mineralocorticoids include:

deoxycorticosterone, corticosterone, flurocortisone, cortisol and cortisone. Cortisol is used as a medication.

Mechanism of action of aldosterone



1) Aldosterone enters the cell and binds a specific **cytoplasmic** mineralocorticoid receptor (**MR**)

2) This complex enters the nucleus and induces **transcription** of DNA.

3) Proteins are produced to increase Na^+ reabsorption:
1. Na^+ / K^+ ATPase , at the basolateral membrane of the renal tubular cell.

2. Epithelial Na^+ channel (ENaC) inserted into the luminal membrane.

Note: The **filtrate** is in the tubular **lumen**. Along its way to form urine, **reabsorption** of materials occurs at the luminal (**apical**) membrane of the epithelial cells. Reabsorbed materials are then transported from the **basolateral** membrane of the cells to the interstitial fluid and eventually the **blood**. Na^+ diffuses from the tubules to the epithelial cells through **ENaC** and actively transported from the cell to the interstitial fluid in exchange with **K^+**. Aldosterone increases transcription of both **ENaC** protein and **Na^+/K^+ ATPase** enzyme.

Note: increased **K^+**concentration in the interstitial fluid itself **stimulates** the secretion of aldosterone.

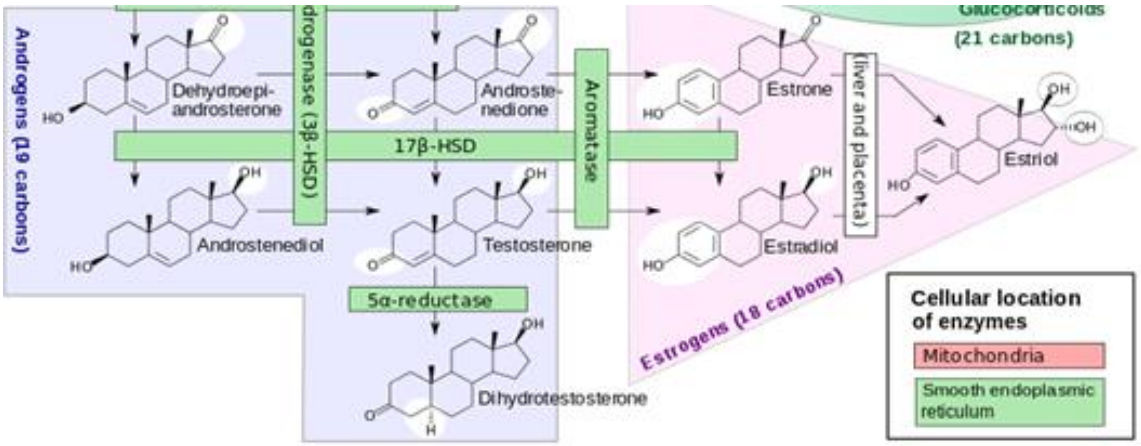
Spironolactone blocks MR receptor, amiloride blocks ENaC. Both drugs reduce blood pressure

Androgens and Estrogens

The main androgen produced is **d**e**h**ydro**e**pi**a**ndrosterone (**DHEA**)which is converted into **androstenedione**. Both are **weak** androgens.

They are converted into **testosterone**. It is the **most potent** androgen.

Androstenedione is converted into **estrone** and testosterone is converted into **estradiol**. Both are estrogens



Function of androgens

Presence of pubic and axillary hair and libido(sexual desire)

They are **not** important in **males** in any stage of life. However, their **over-secretion** in childhood causes rapid development of male sexual organs (**adrenogenital syndrome**)

They are **important** in **females** in all stages of life, especially after **menopause,** when the ovaries stop secreting hormones and the adrenal cortex becomes their **only** source.