PHYSIOLOGY

Sheet number 12

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THE ADRENAL GLANDS

- Two glands above kidneys
- One gland is sufficient
- The adrenal gland is an essential gland; if we remove it the human being dies!
- It is supplied by blood through the aorta.
- It's composed of two-parts (two different glands): the **adrenal cortex which secretes 80%** of secretions **AND** the **adrenal medulla which secretes 20%** of secretions, they differ from each other in physiology and histology.

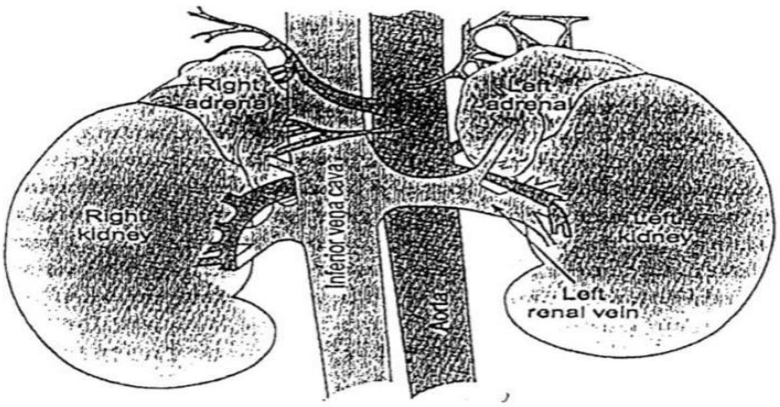
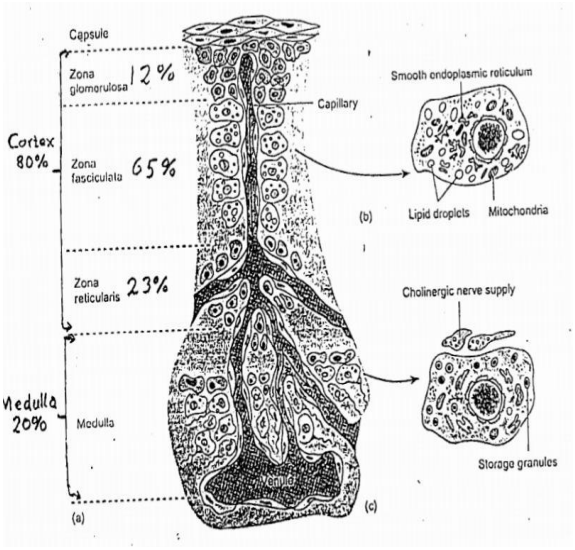


Fig. 12.15 The anatomic location of the adrenal glands and the organization of their blood supply. Note that the arterial supply is via many small arteries which originate from the aorta. The venous drainage is via a large central vein that empties into the inferior vena cava.

- The adrenal cortex is made up of three zones, each of which secretes special hormones with specific functions. It is the one essential for life not the medulla.
- The adrenal medulla secretes 20% of total secretion of the gland: catecholamines like adrenaline and noradrenaline ***it is important but not that much, why??**

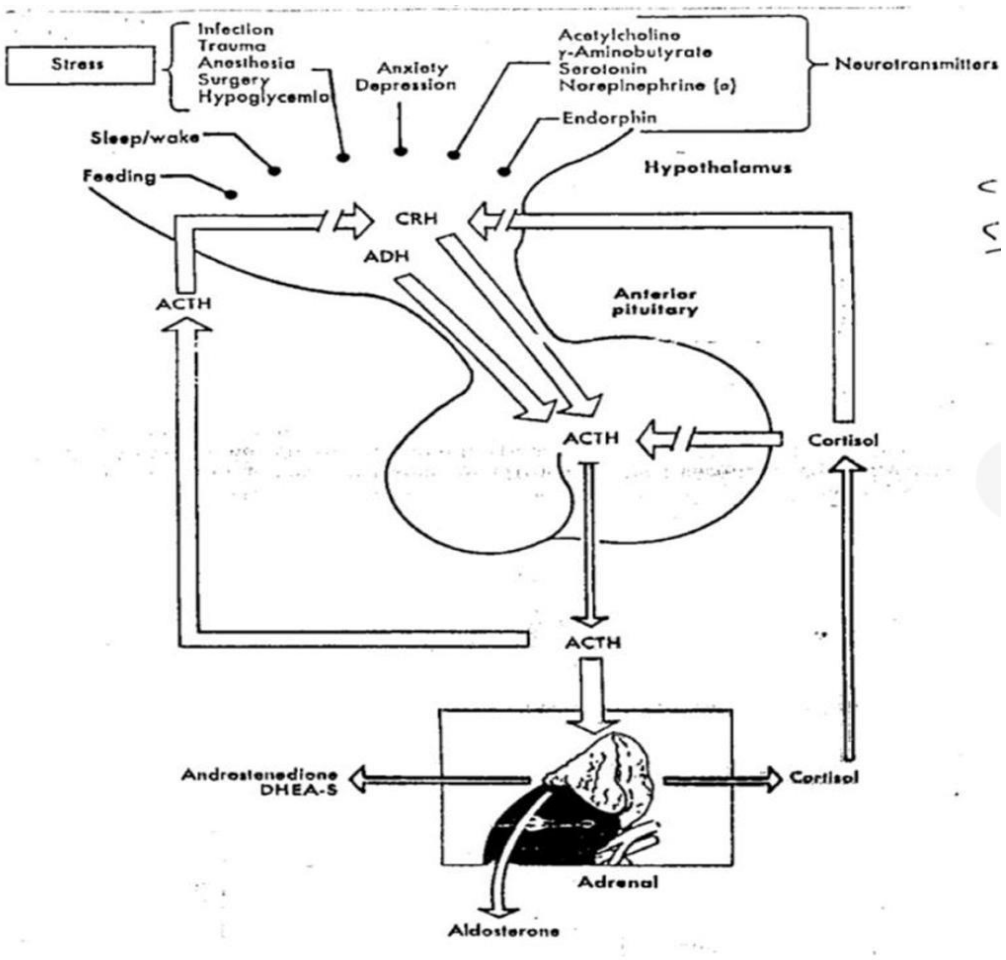
Because the sympathetic nervous system produces adrenaline noradrenaline so there is the second source of these hormones.

- Total weight is 6-10g
- The adrenal gland is very important because it controls sodium, potassium, and water metabolism. It also controls the metabolism of carbohydrates, fats , and proteins and mobilization of energy. It also participates in response to the stress of various kinds.



- The adrenal cortex is made up of three zones:

Zona Glumerulosa	Zona Fasciculata	Zona Reticularis
Produces hormones collectively called **mineralocorticoids** (secrete many hormones, these hormones control the mineral metabolism (**represented by the aldosterone hormone *the effective one*)**	Produces hormones collectively called **glucocorticoids** affect the glucose metabolism **(represented by cortisol *the effective one*)** And little secretion of androgens	Produce androgens (male hormones), estrogens and small amounts of cortisol.

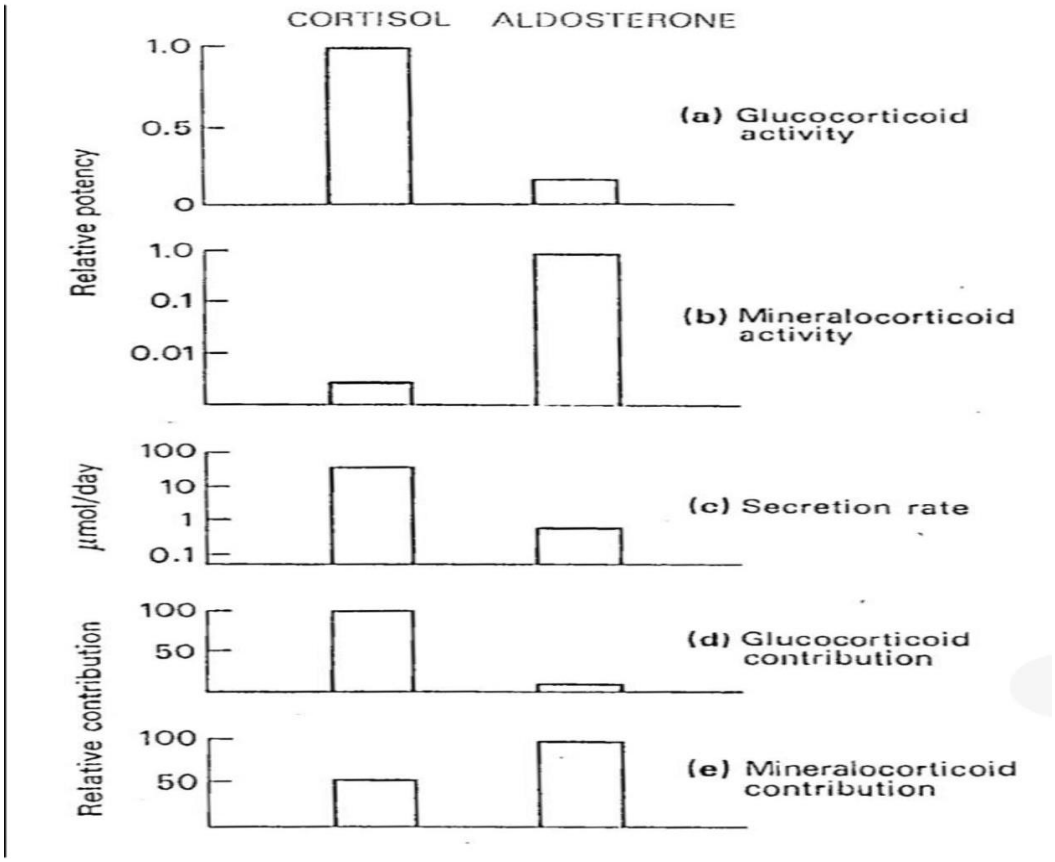


- As we know, **ACTH** (adrenocorticotropic hormone) is produced by the anterior pituitary gland.
- **ACTH** controls the growth of the adrenal cortex as well as the synthesis and secretion of its hormones (**especially cortisol which is the main target hormone**).
- **ACTH** is affected by **CRH** from the hypothalamus. So **CRH** affects **ACTH, and ACTH** affects the synthesis and secretion of hormones especially **cortisol**.
- **Fetus ACTH** synthesis and secretion begins just before the development of the adrenal cortex .

- The regulation of ACTH secretion is the most complicated among all pituitary gland hormones and is affected by all these hormones and conditions.
- The main stimulus is **CRH** from the hypothalamus
- ADH also shows the same pattern of stimulation of ACTH.
- ACTH secretion responds most strikingly to stressful stimuli, a response that is critical to survival .
- Extra-adrenal action of ACTH is also present, ex: **lipolytic** and **MSH-like action**
- Again the ACTH stimulate growth,synthesis,and secretion of the adrenal cortex (**the main target hormone is cortisol**). **ACTH affected or stimulated by CRH** and **ADH.**

- Again the **glomerulosa cells** produce **mineralocorticoids** but these cells in the adult migrate down into the reticularis, and while they are migrating down, they change their shape and function but we don't know why!
- The **Reticularis cells** don’t develop or differentiate properly until age 6-8! And that makes sense because we need them from this age and above **(the androgens and estrogens**).
- **Glucocorticoids** activity is mainly **cortisol** but even **aldosterone** plays a role in glucose metabolism (little effects).
- **Mineralocorticoids** activity is mainly **aldosterone** but even the **cortisol** plays a role (little affect). But here the role of cortisol is more than the role of aldosterone in glucocorticoid activity.

- Look at the secretion rate :



Notice that the secretion rate mainly cortisol compared to aldosterone in the **glucocorticoids**. (Contribution of cortisol is more than aldosterone because the secretion rate is higher).
When ACTH changes, cortisol also changes (because cortisol is the main target of ACTH).

- The special point about adrenal cortex hormones, is that they're considered steroid hormone so they are lipid-soluble. They are produced from lipids in many steps, therefore many enzymes are needed to produce them.
- When the adrenal cortex hormones are produced they are not stored, they are released immediately. Any need is met by new synthesis.

CORTISOL

- If a defect in the production of cortisol occurs, corticosteroids synthesis increases.
- Cortisol is either:

90% >> bound to corticosteroid-binding proteins.

6% >> bound to albumin.

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

- Cortisol circulates in the blood binding with proteins.
- **Cortisol affects almost all the systems in the body**, why??

Because it is lipid-soluble, it can enter every cell in the body if it binds with the receptor it can function, therefore it is used in medicine against many diseases and some times functions.

- **Cortisol functions:**
  1. Main function of cortisol is the production of glucose from non-carbohydrate sources (gluconeogenesis), which is essential for survival in fasting.
  2. Fat mobilization.
  3. Supports vascular response.
  4. Regulates CNS function.

- Cortisol itself doesn't directly affect glycogenolysis but it has **permissive action** to support the function of glucagon (it facilitates the action of glucagon, and glucagon doesn't function properly in the absence of cortisol). The relationship between Cortisol and glucagon (**permissive**

interaction) is similar to the relationship between adrenaline and thyroxine.

- Cortisol playing an important role in defense against hypoglycemia.
- Cortisol binds with the receptors of aldosterone but doesn't function similarly to aldosterone because there is an enzyme produced by the kidney that inactivates the cortisol.
- There is natural cortisol and synthetic cortisol:
    1. Cortisol (natual)
    2. Corticosterone (natural)
    3. Cortisone >> synthetic, almost as potent as cortisol
    4. Prednisone >> synthetic, four times as potent as cortisol.
    5. Methyl prednisone >> synthetic, five times as potent as cortisol.
    6. Dexamethasone >> synthetic, 30 times as potent as cortisol
- The production of aldosterone is similar to the production of cortisol (both are lipids) but the main function of aldosterone is to maintain the extracellular fluid volume, and consequently the blood pressure.

ALDOSTERONE

- **Aldosterone is either**:

1. 20% bound to corticosteroid binding proteins.
2. 40% bound to albumin.
3. 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)
2. Desoxycorticosterol as potent as aldosterone but very small quantities secreted (natual)

3. Corticosterone, slight mineralocorticoid activity
4. Fluorocortisol, (synthetic)
5. Cortisol
6. Cortisone, (synthetic)

So the cortisol plays a role in the metabolism of minerals.

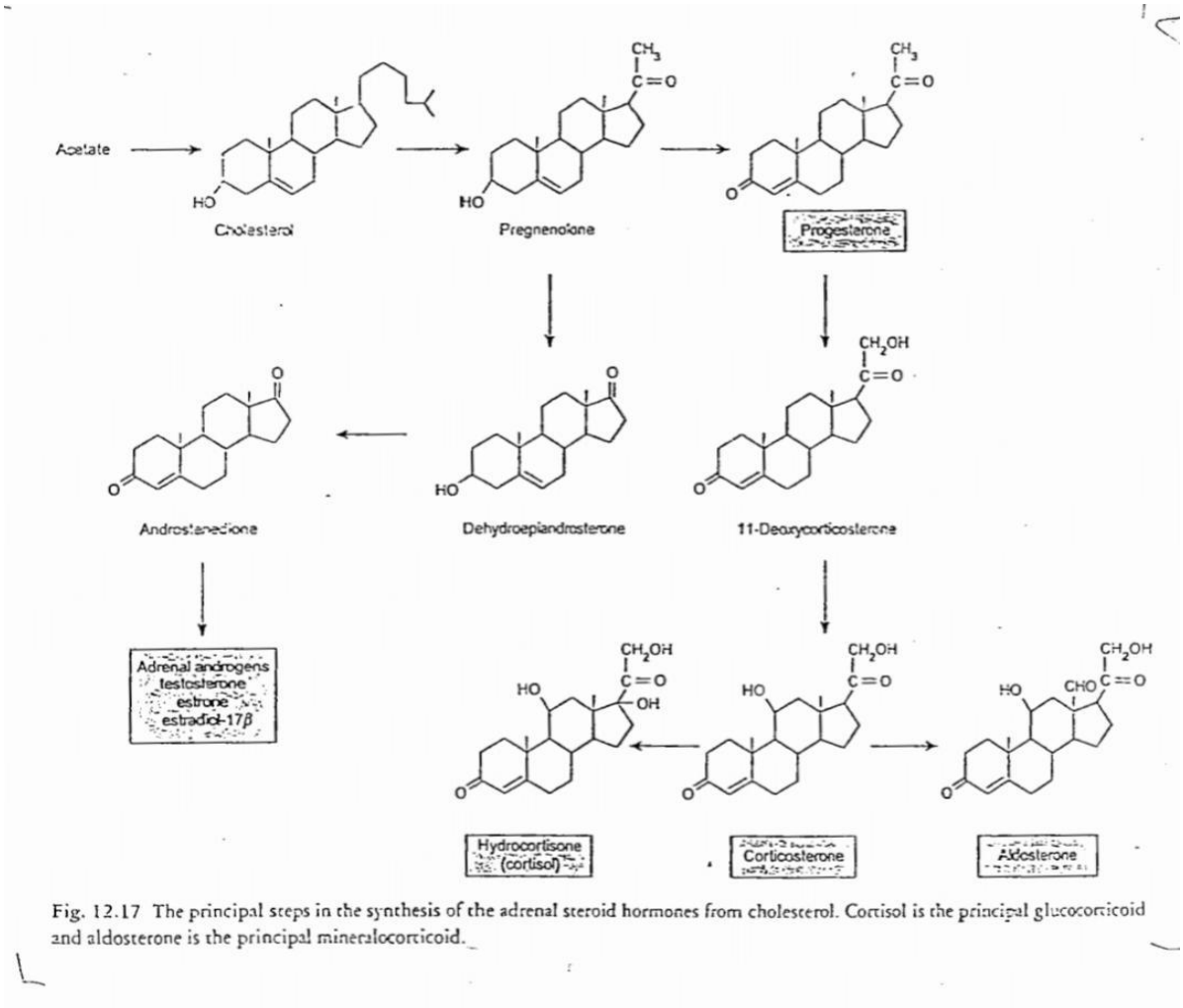


Fig. 12.17 The principal steps in the synthesis of the adrenal steroid hormones from cholesterol. Cortisol is the principal glucocorticoid and aldosterone is the principal mineralocorticoid.

ALDOSTERONE

- The first and main stimulus of aldosterone is **angiotensin 2,** not ACTH.

- How is angiotensin 2 produced??

When body fluid changes (decreases), renin is produced from kidney (juxtaglomerular apparatus), the renin converts the angiotensinogen liver protein into angiotensin 1, this angiotensin1 produces angiotensin 2 under the effect of enzyme or hormone from the lungs, angiotensin 2 then stimulates the production of aldosterone from the adrenal cortex.

This is the main stimulus for aldosterone. The second stimulus is changes in plasma potassium. The third stimulus is ACTH.

- Now we know that angiotensin 2 stimulates the secretion of the aldosterone and also affects the reabsorption of sodium directly and indirectly.

a) Directly :

Increases the reabsorption of sodium through two mechanisms:

1) Sodium potassium pump
2) Along with HCO3 .

It's even more effective than aldosterone.

When the sodium increases it means normalizing or increasing body fluid volume consequently blood volume consequently blood pressure.

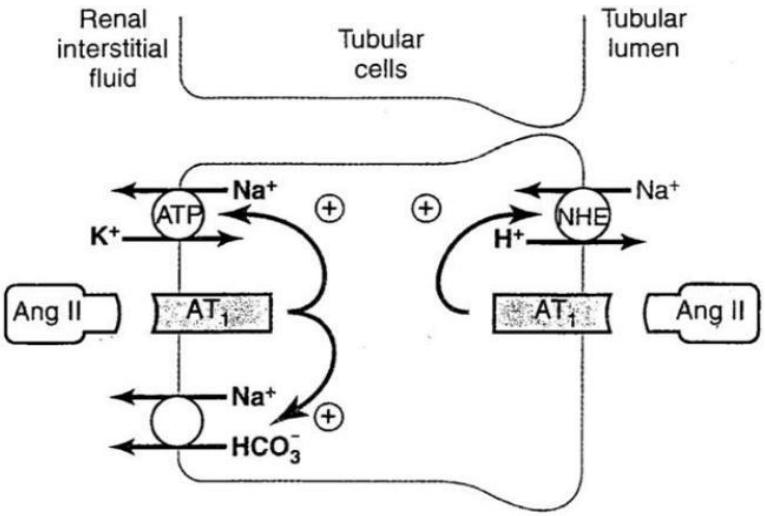
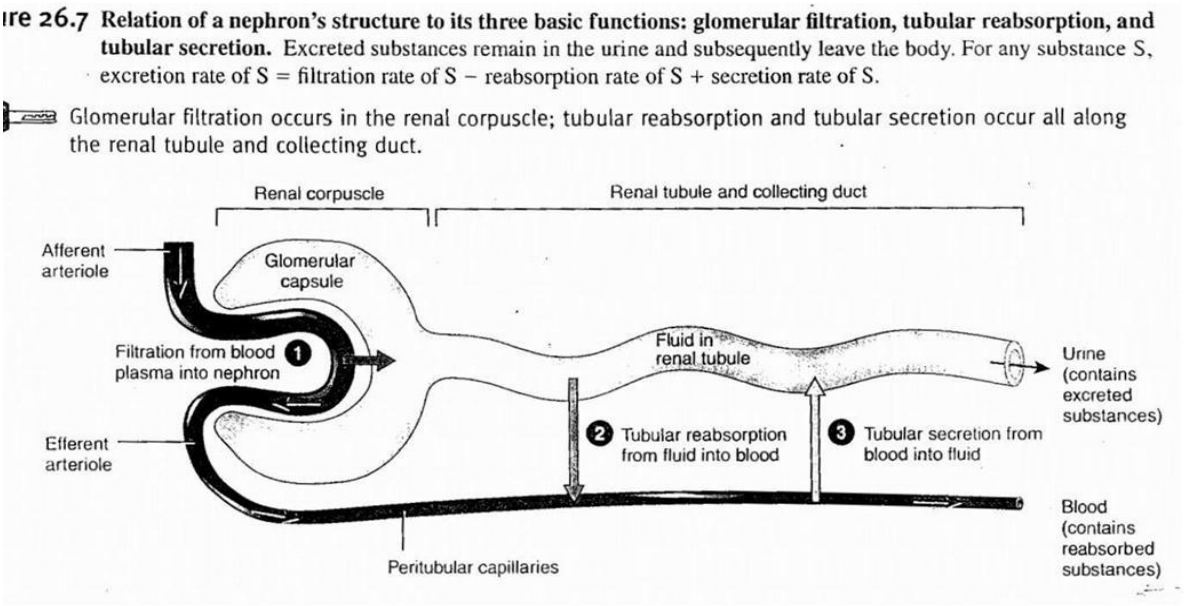


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. These same effects of Ang II likely occur in several other parts of the renal tubule, including the loop of Henle, distal tubule, and collecting tubule.

b) Indirectly: by stimulating aldosterone as well as vasoconstriction 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 2 is a vasoconstrictor for the efferent arterioles, this causes the colloid osmotic pressure to increase (in the area pointed as 2) because plasma in that area decreases. When colloid osmotic pressure increases, reabsorption of sodium occurs.



ıre 26.7 Relation of a nephron's structure to its three basic functions: glomerular filtration, tubular reabsorption, and tubular secretion. Excreted substances remain in the urine and subsequently leave the body. For any substance S, excretion rate of S = filtration rate of S − reabsorption rate of S + secretion rate of S.

Glomerular filtration occurs in the renal corpuscle; tubular reabsorption and tubular secretion occur all along the renal tubule and collecting duct.

There is also Angiotensin 3, it is as potent as Angiotensin 2, 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 sweatglands, so it reabsorbs sodium in all these organs.

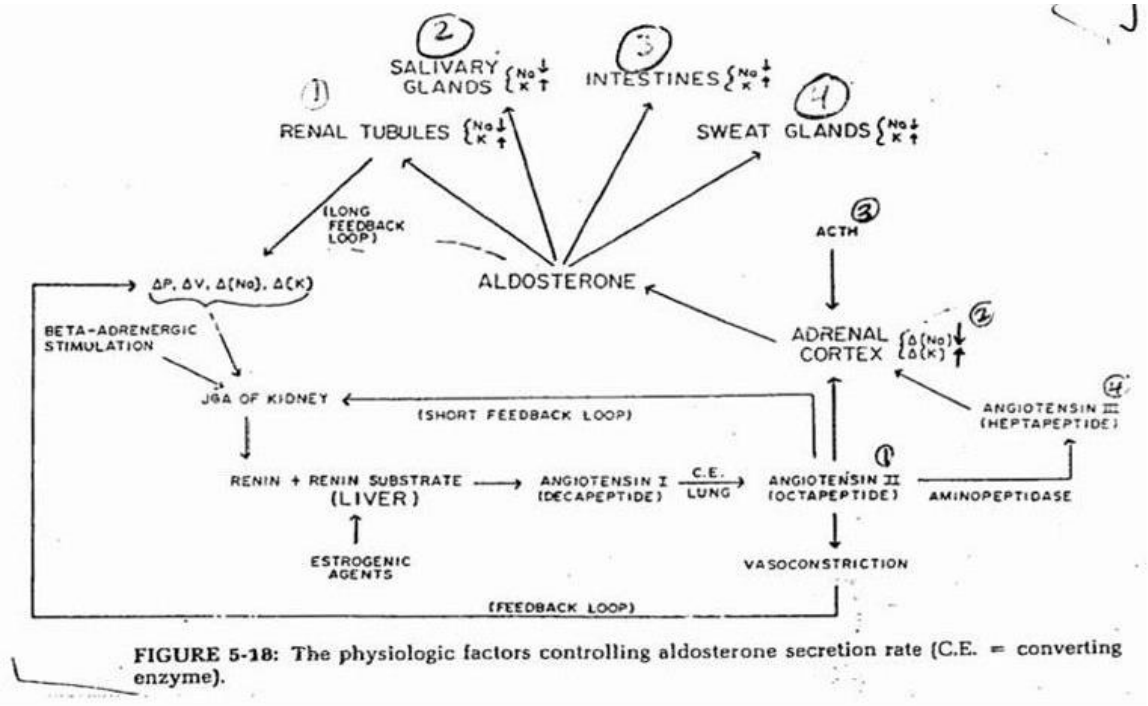


FIGURE 5-18: The physiologic factors controlling aldosterone secretion rate (C.E. = converting enzyme).

ANDROGENS AND ESTROGENS

We will talk about the third zone (Zona Reticularis) that produces the androgens, estrogens and small amounts of cortisol.

- Androgens and Estrogens are hormones produced by zona reticularis in the adrenal cortex.
- Two weak androgens are produced from the reticularis; Dehydroepiandrosterone and Androstenedione.
- These two weak androgens produce the potent androgen called Testosterone. Androstenedione produces Estrone. Dehydroepiandrosterone produces Estradiol.
- Androgens and Estrogens are very important in all stages of females' life, especially after menopause (when the ovaries stop functioning).
- They are not important normally in all stages of males' life; because there are other hormones produced by the testis.

- Actions of Adrenal Androgens:
  Females: The presence of pubic and axillary hair and libido.
  Males: same as Testosterone.

- **Metabolism of Androgens and Estrogens:**

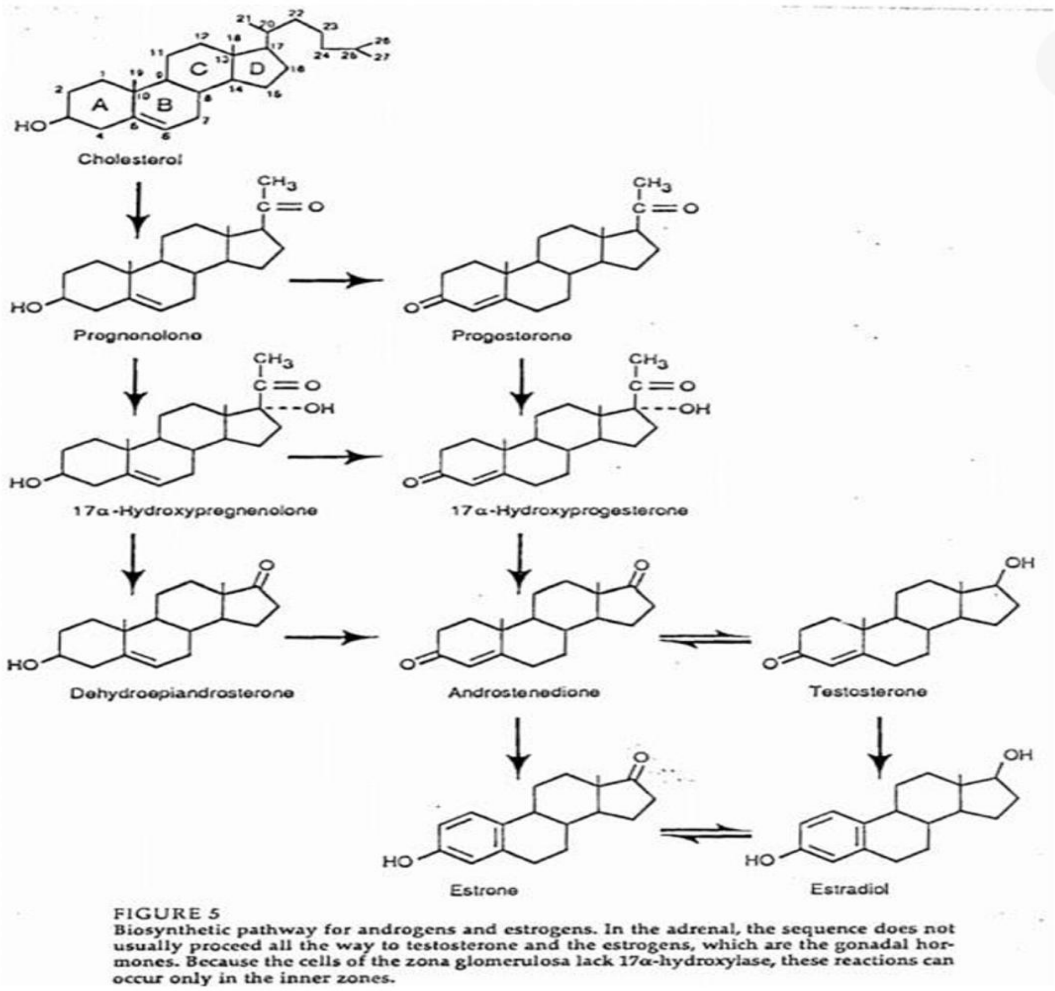


FIGURE 5
Biosynthetic pathway for androgens and estrogens. In the adrenal, the sequence does not usually proceed all the way to testosterone and the estrogens, which are the gonadal hormones. Because the cells of the zona glomerulosa lack 17α-hydroxylase, these reactions can occur only in the inner zones.

- Defected cortisol production increases corticosterone, also deficiencies in other enzymes increase concentrations of the two weak androgens in the deficiency of cortisol synthesis
- When there is a problem in the synthesis of cortisol the corticosteroid increases, and also when one of the steps of biochemistry is blocked, these two androgens will also increase .