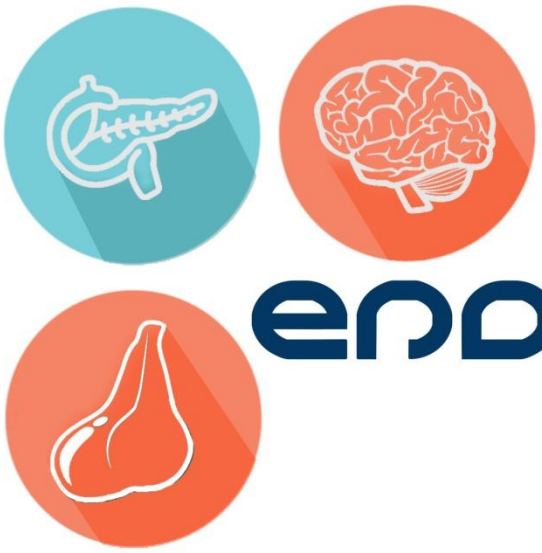


endocrine system

physiology

Sheet Slide

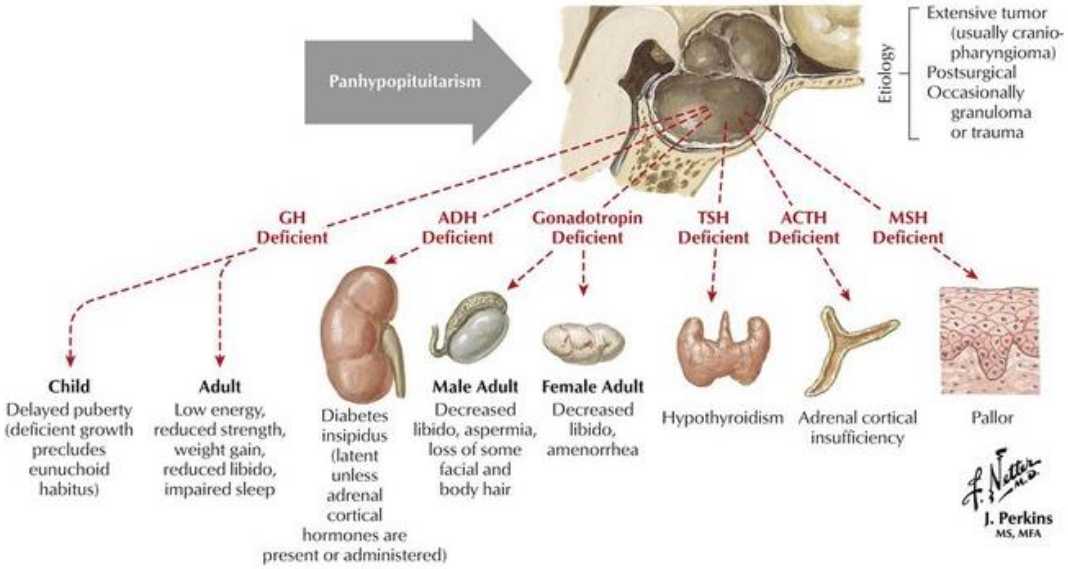
number	3
Done by	Ola Al-juneidi
Correction	Abdullah Nimer
Doctor	Salim Khraisha

Pituitary Gland

Pathophysiology

1. Panhypopituitarism:

Pan means all; panhypopituitarism is the deficiency of ALL pituitary hormones (hormones of the anterior pituitary and posterior pituitary).



[We can know the features from the functions of the hormones]

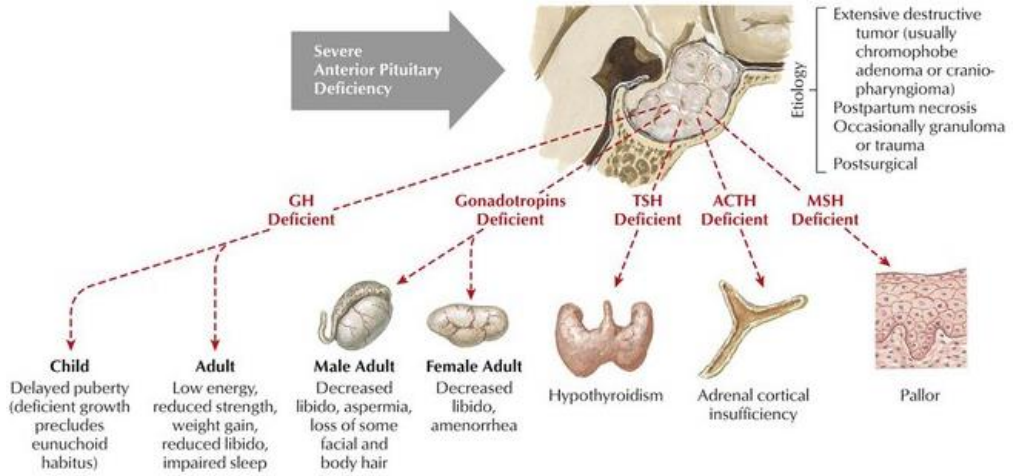
- **Hormones of the posterior pituitary:**
  - **ADH (Anti diuretic hormone):** it causes water reabsorption through kidney tubules. So, when it's deficient, water will **not** be reabsorbed into the blood (it is excreted). Thus the patient will have a disease called ***diabetes insipidus***. It is like diabetes mellitus but the color of the urine is pale and the taste is different.
  - **Oxytocin:** In the deficiency of oxytocin, delivery occurs but it'll be much more **difficult**. Also, milk production is **not much** affected.
- **Hormones of the anterior pituitary:**
  - **Gonadotropins (FSH & LH):** both testes and ovaries are affected. Their deficiency causes:
    In **male** adults → decreased libido (sexual desire), aspermia, loss of facial hair
    In **children** → delayed puberty

In **female** adult → decreased libido, amenorrhea (no menstrual cycle)

- **TSH:** When it is deficient, the function of thyroid gland is deficient (***hypothyroidism***).
- **ACTH:** This hormone functions on the **adrenal cortex**. Therefore, its deficiency affects the secretion of the adrenal cortical hormones (***adrenal cortical insufficiency***).
- **MSH (Melanocyte Stimulating Hormone):** its deficiency causes **pallor** (paleness).
- **Growth Hormone (somatotropin):** Its deficiency causes children to become **dwarfs** (short stature) but usually mentally normal. The mentality or sexuality might be **sometimes** affected; they are sometimes infertile.

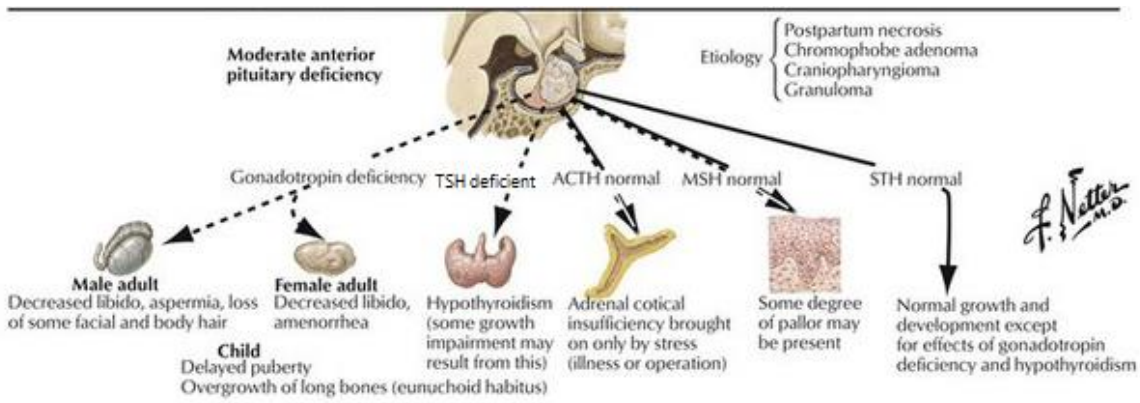
2. Severe anterior pituitary deficiency:

Similar to panhypopituitarism except that the hormones of the **posterior** pituitary are **normal**. All hormones of the **anterior** pituitary are **deficient**.



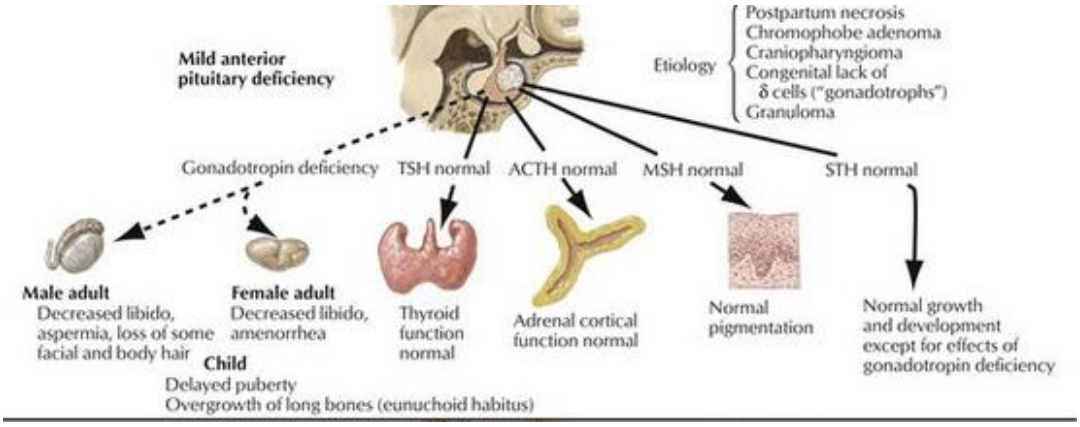
3. Moderate anterior pituitary deficiency:

GH is **normal**. ACTH is **partially normal**. TSH and gonadotropins are **deficient (abnormal).**



4. Mild anterior pituitary deficiency:

All the hormones of the anterior pituitary are normal **except gonadotropins (FSH & LH).**



***note that gonadotropins are affected either in mild or severe conditions.**

5. Oversecretion of GH (Growth hormone):

- **Gigantism:** If GH producing cells/tumor occurs <u>before adolescence</u>, all body tissues will grow rapidly **<u>including bones</u>** because the ends **(epiphysis) of long bones have not fused with the shafts yet**. Therefore:
  1. Their height is 8-9 feet (1 foot=30.5cm); they are more than 2.5m tall.
  2. They have **hyperglycemia*** and **10% develop diabetes mellitus.**
  3. If the giants remained without treatment, they will develop **panhypopituitarism**.

  Their extremities have **normal proportions** but they are **very tall**.

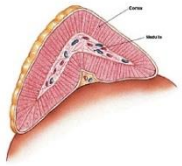
- **Acromegaly:** If the tumor occurred <u>after adolescence</u> (after the fusion of long bones), the person **cannot grow taller** but the <u>soft tissues</u> can continue to grow and the <u>bones can grow in thickness</u>. Features:
  1. **Enlargement** marked in the **small bones** of the hand and feet, the cranium, nose, forehead, supraorbital ridges, the lower jaw bones and the vertebrae.
  2. Many **soft tissues or organs** like the liver, tongue, and kidneys become greatly **enlarged**.

*Remember: GH increases the glucose level in blood

00:00-10:00

Adrenal Glands

- The adrenal glands are located <u>above the kidneys</u>. They are very important as indicated by the blood supply to those glands since their blood supply comes from the <u>aorta directly</u>.
  The adrenal gland has **two parts**: the <u>cortex</u> and the <u>medulla</u>. These two parts are different in their embryology, histology, and physiology. Their total weight is 6-10g.

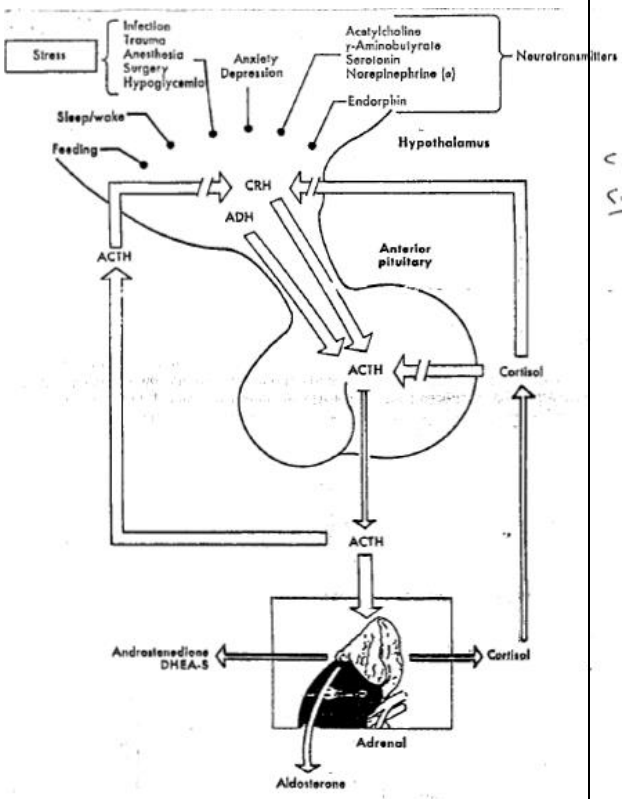


  The adrenal cortex is essential for life because it:
  - Controls Na^+, k^+ and H_2O metabolism
  - Controls carbohydrate, fat and protein metabolism and mobilization for energy.
  - Participates in responses of stresses of various kinds.

  - **ACTH (Adrenocorticotropic hormone)**, an anterior pituitary hormone, stimulates growth of the **adrenal cortex** and the **synthesis and secretion of its hormones**. The most important target hormone of ACTH is **cortisol**. ACTH stimulates **desmolase** enzyme that converts cholesterol to pregnenolone thus increasing the synthesis of cortisol.

- Fetus ACTH synthesis and secretion <u>begins just before the development of the adrenal cortex</u>.

- The **regulation** of ACTH secretion is among the most complex of all the pituitary hormones. Although the mechanisms for each form of control are not completely clear, the **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.
- ACTH has **extra-adrenal actions** like: lipolysis and MSH-like action.



- As we said, the adrenal gland is composed of <u>cortex (80%)</u> and <u>medulla (20%)</u>. The adrenal medulla functions in the production of catechol amines. The adrenal cortex is composed of **three zones**:

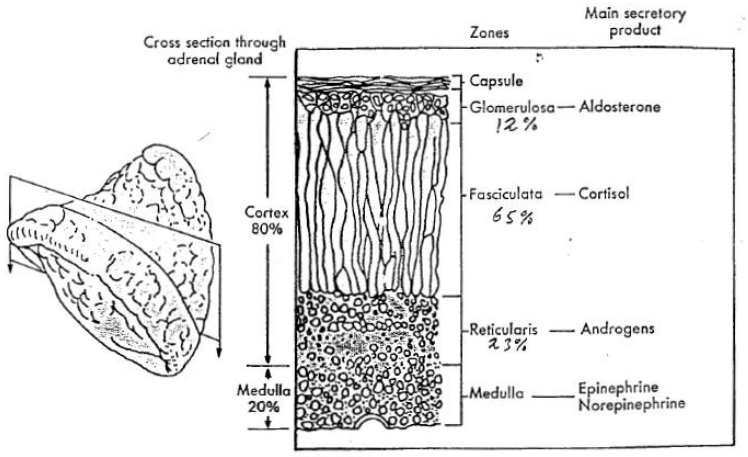


FIGURE 41-1 Schematic representation of the adrenal gland and its main secretory products.

- <u>Glomerulosa</u> (12%): It produces a number of 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**.

- <u>Fasciculata</u> (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 amount of androgens and estrogens.

- <u>Reticularis</u> (23%): It mainly produces ***androgens*** and ***estrogens***, but it also produces small amount of cortisol.

The adrenal reticularis does not develop properly until the age of 6-8yrs. In the adult, the cells of the **glomerulosa migrate down to the reticularis** and they change their **shape and function while migrating**.

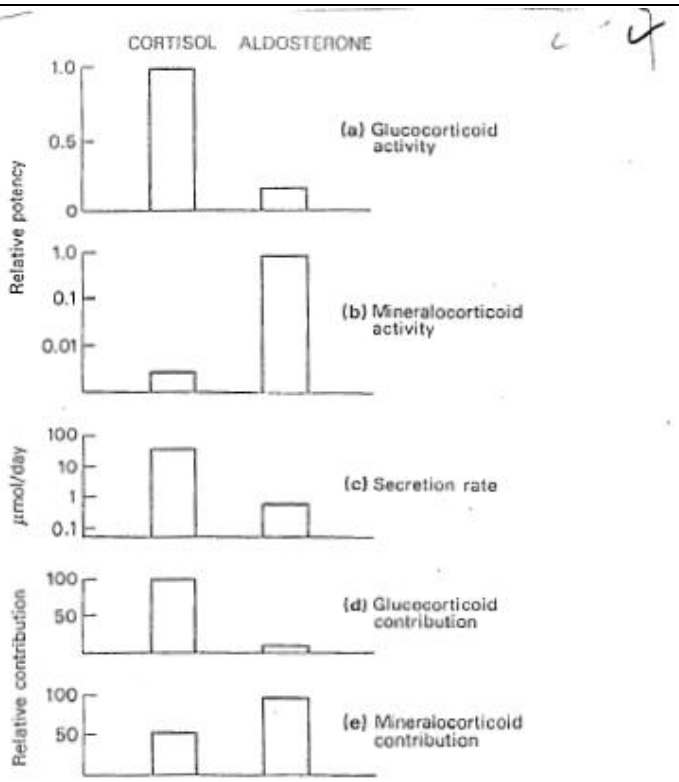


Fig. 3.5 A comparison of cortisol and of aldosterone. Glucocorticoid activity was measured as ability to increase glycogen in the liver: cortisol is very potent in this assay. Mineralocorticoid effects were measured in terms of the ability to reduce the ratio of the excretion of sodium to the excretion of potassium in urine; aldosterone is much more potent. However, since the rate of secretion of cortisol is much higher, it can have significant mineralocorticoid effects (see d and e).

(a) **Glucocorticoid activity:** even aldosterone (a mineralocorticoid) plays a role

(b) **Mineralocorticoid activity:** In addition to aldosterone, cortisol (a glucocorticoid) plays a role in the metabolism of minerals

(c) **Secretion rate:** the secretion rate of cortisol is higher

(d) **The contribution of glucocorticoid activity:** aldosterone has some contribution

(e) **Mineralocorticoid contribution:** cortisol also contributes in mineralocorticoid activity.

But when comparing the glucocorticoid contribution of aldosterone with the mineralocorticoid contribution of cortisol we notice that the relative contribution of cortisol is much more than that of aldosterone because it has a higher secretion rate (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 aldosterone is secreted in very high amounts. Note that cortisol itself can bind the receptor with a very low affinity. **

** Highlighted notes are added from 2014's sheet for clarification.

Rhythm of ACTH and cortisol throughout the day

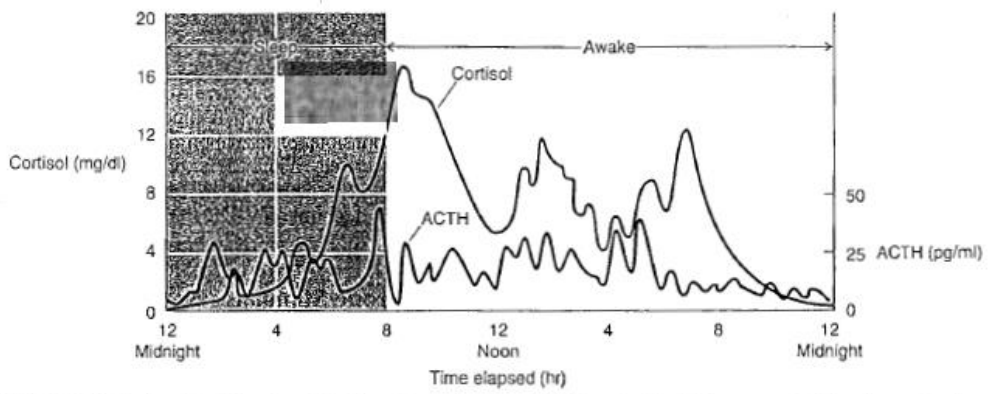


FIGURE 49–5. Rhythm of ACTH and cortisol. The corticotrophs release ACTH in a circadian rhythm, greater in the early morning hours and less late in the afternoon and early evening. Superimposed on the circadian rhythm is the effect on the corticotrophs of the pulsatile secretion of CRH by the hypothalamus. Thus, ACTH levels exhibit both circadian and pulsatile behavior. Notice that, although both ACTH and cortisol are secreted episodically, the duration of the ACTH bursts is briefer, reflecting the shorter half-life of ACTH in plasma. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. (Data from Wilson JD et al: Williams Textbook of Endocrinology. Philadelphia, WB Saunders, 1998.)

Recall: the main target hormone of ACTH is **cortisol; when ACTH level changes, cortisol level changes.*

- Cortisol is relatively high in the morning but low in the afternoon and early evening.
- ACTH and cortisol show circadian rhythm as well as pulsatile rhythm.

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.
- When these hormones, are produced they are released immediately into the blood. This means that any need requires new synthesis.

10:00-20:00

Actions of Adrenocortical Steroids

1) Glucocorticoid Hormones (cortisol)

- 90% of cortisol binds the **corticosteroid-binding protein (CBP)**, **6% binds albumin** and the rest (4%) is the functional portion (free).
- Cortisol acts 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. Increase the response of blood vessels to catecholamines.
4. Modulate CNS function.

Actions of Glucocorticoids
Increase gluconeogenesis
Increase proteolysis (catabolic)
Increase lipolysis
Decrease glucose utilization
Decrease insulin sensitivity
Anti-inflammatory
Immunosuppression
Maintain vascular responsiveness to catecholamines
Inhibit bone formation
Increase GFR
Decrease REM sleep

Tissue	Effects
Central nervous system	Taste, hearing, and smell ↑ in acuity with adrenal cortical insufficiency and ↓ in Cushing's disease
	↓ Corticotropin-releasing hormone (see text)
	↓ ADH secretion
Cardiovascular system	Maintain sensitivity to epinephrine and norepinephrine
	↑ Sensitivity to vasoconstrictor agents
	Maintain microcirculation
Gastrointestinal tract	↑ Gastric acid secretion
	↓ Gastric mucosal cell proliferation
Liver	↑ Gluconeogenesis
Lungs	↑ Maturation and surfactant production during fetal development
Pituitary	↓ ACTH secretion (acute) and synthesis (chronic)
Kidney	↑ GFR
	Needed to excrete dilute urine
Bone	↑ Resorption
	↓ Formation
Muscle	↓ Fatigue (probably secondary to cardiovascular actions)
	↑ Protein catabolism
	↓ Glucose oxidation
	↓ Insulin sensitivity
	↓ Protein synthesis
Immune system (see text)	↓ Mass of thymus and lymph nodes
	↓ Blood concentrations of eosinophils, basophils, and lymphocytes
	↓ Cellular immunity
Connective tissue	↓ Activity of fibroblasts
	↓ Collagen synthesis

- Cortisol has a **permissive** action with **glucagon**. Cortisol **doesn't** *cause* **glycogenolysis**. Rather, it **facilitates** the action of glucagon.

- The most important function of cortisol is that <u>it facilitates the production of glucose from non-carbohydrate sources</u>. This makes cortisol essential for life for humans and animals especially during fasting; it has a role in the defense against <u>hypoglycemia</u>.

- Cortisol binds to the receptor of aldosterone but there is an enzyme in the kidney that inactivates cortisol so it won't function too much.

- Cortisol is a **magic drug** that is used in many diseases; from 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.

- Cortisol is important even **during fetal life**. It is essential for the normal development of the fetus; it is involved in:

    1. **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.
    2. Development of **hypothalamic function** and of the **thyroid-pituitary axis.**
    3. The sequential changes of **placental structure** and in the ionic composition of amniotic and allantoic fluids during development.
    4. They are most important in the initiation of the **endocrine changes** of the fetus and mother which are responsible for **parturition**.
    5. The development of **hepatic enzymes**, including those involved in gluconeogenesis.
    6. Induction of **thymic involution**.

- There is natural as well as synthetic **glucocorticoids**:

    - Cortisol: very potent, accounts for about 95% of all glucocorticoid activity.
    - Corticosterone: provides about 4 per cent of total glucocorticoid activity but much less potent than cortisol. Any problem in the last step of the synthesis of cortisol, **corticosterone level increases**.
    - Cortisone: **synthetic**, almost as potent as cortisol.
    - Methyl prednisone: **synthetic**, five times as potent as cortisol.
    - Dexamethasone: **synthetic**, 30 times as potent as cortisol.

2) Mineralocorticoids (represented by aldosterone)

- Mineralocorticoids function on mineral metabolism; **they normalize Na^+ and K^+** level and **consequently water volume in the body**.
- They are produced from cholesterol.

Actions of Mineralocorticoids
Increase Na^+ reabsorption
Increase K^+ secretion
Increase H^+ secretion

- 20% of aldosterone is bound to CBP (also called transportin) and 40% is bound to albumin. Thus, 40% of aldosterone is free/functional (the functional portion of aldosterone is more than that of cortisol).

- There are natural and synthetic **mineralocorticoids**:
  - Flourocortisol
  - Cortisol
  - Cortisone
  - Aldosterone
  - Deoxycorticosterone
  - Corticosterone

- Aldosterone is a steroid, so it binds its receptor inside the cell. It **increases the reabsorption of Na^+** through the luminal and the basal membrane into the interstitial spaces then into the capillaries.

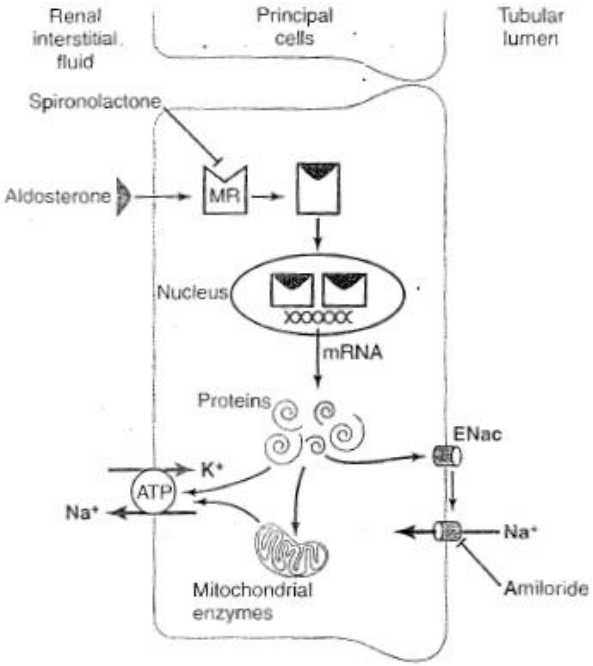


Figure 77-4 Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

20:00-30:00

- **Regulation of aldosterone secretion:**

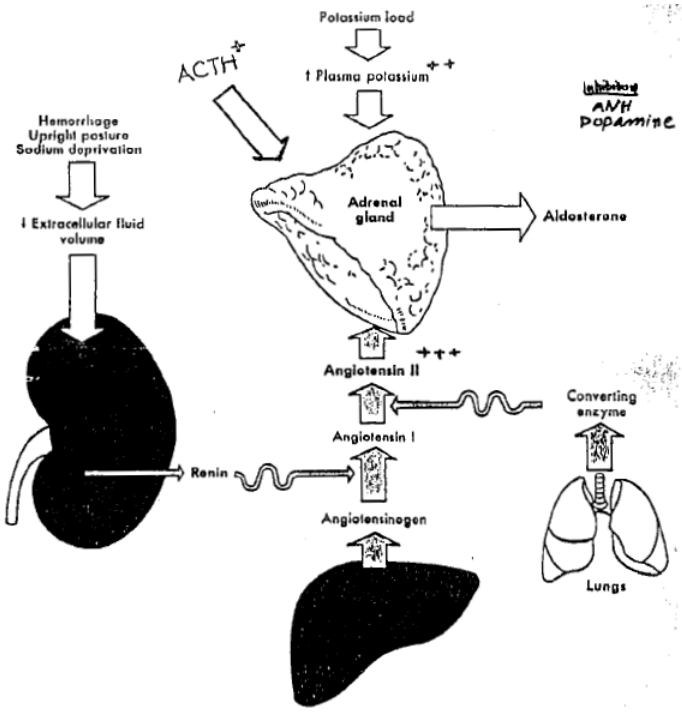
  - We said that the main target hormone of ACTH is **cortisol**. This means that the main stimulus for aldosterone is different (other than ACTH).

  - Hemorrhage or any change in the volume of the blood will affect the **kidney**. Juxtaglomerular apparatus' cells in the kidney produce a

hormone called **renin**. This hormone produces **angiotensin I from angiotensinogen in the liver**. **Angiotensin I** produces **angiotensin II** under the effect of an enzyme from the lungs. **Angiotensin II** is the **<u>main stimulus</u>** for the secretion of aldosterone.

- **Stimuli** for aldosterone secretion:

  1. Angiotensin II: **<u>the main stimulus</u>**
  2. Increase in K^+ level
  3. ACTH



- **Angiotensin II** also has a direct and an indirect effect on **Na^+ reabsorption:**

1. **Direct effect:** reabsorption of Na^+ through the luminal and basal membranes.

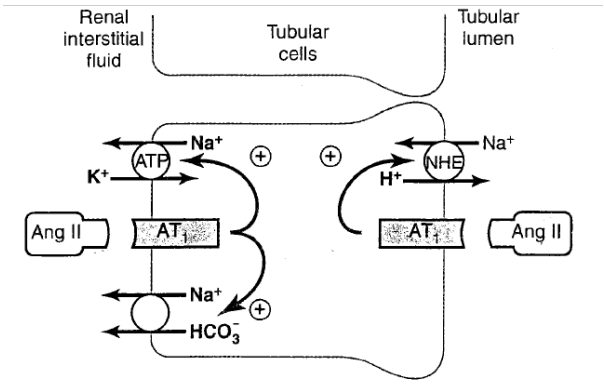
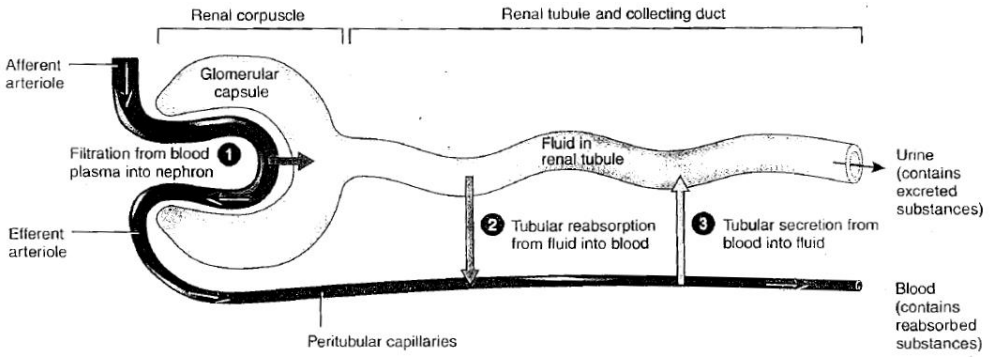


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. 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.

Notice*: the receptor of angiotensin II is on the **plasma membrane because it is not a steroid

2. **Indirect effect:** The **afferent arteriole** brings blood into the nephron (renal corpuscle), and it leaves through the **efferent arteriole**. Angiotensin II **vasoconsrticts the efferent arteriole** resulting in:

- Decreasing **the hydrostatic** pressure inside the peritubular capillary
- Increasing **the colloidal osmotic** pressure in the peritubular capillary



-This results in the **<u>reabsorption of Na^+ and water</u>**

Angiotensin III is similar to Angiotensin II but its level is low; it is said that they have the same potency.

- Aldosterone **does not only** function on **renal tubules**; it also functions on **salivary gland, intestine and sweating gland**.

3) Androgens and estrogens

- The **reticularis zone** produces <u>androgens</u> and <u>estrogens</u> as well as a small portion of cortisol.

- 2 weak androgens are produced: **dehydroepiandrosterone** and **androstenedione**. These androgens produce **testosterone**, the most potent androgen. Testosterone then produces **estradiol** and androstenedione produces **estrol**.

- Androgens and estrogens are **not** that important in males. However, they are very important in females in **all stages of life especially after menopause.**

- **Actions** of Adrenal Androgens:
    - In Females: presence of pubic hair; libido.
    - In Males: same as testosterone.
- If any abnormality occurs in the synthesis of cortisol **not only** the level of corticosterone increases, but also the level of **androgens** increase.