University of Jordan - Faculty of Medicine
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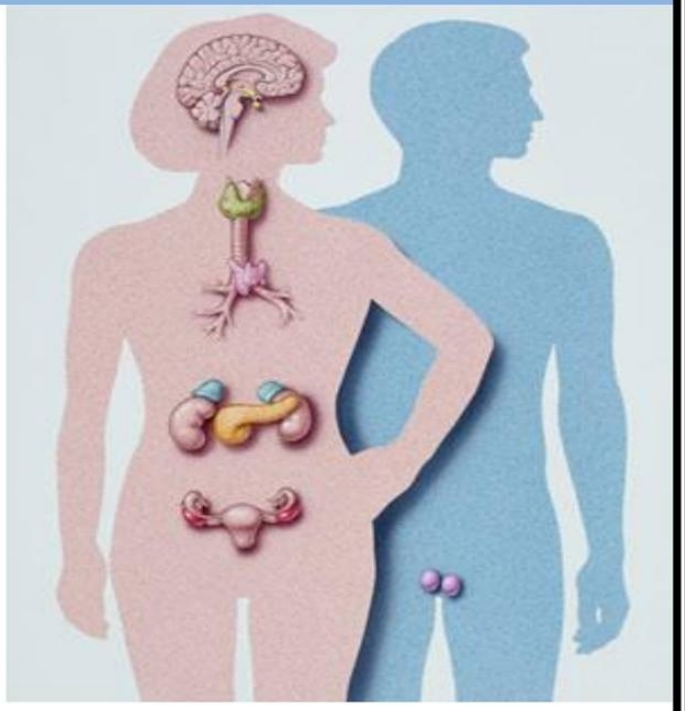
Medical Committee
The University of Jordan

Endocrine System



- ☐ Anatomy/Embryology/Histology
- ☐ Biochemistry
- ■ Physiology
- ☐ Pharmacology
- ☐ Pathology
- ☐ PBL

☐ Slide ■ Sheet ☐ Handout ☐ Other

Lecture #: **3**

Date:

Dr's Name: **saleem**

Price:

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Designed by: Zakaria W. Shkoukani

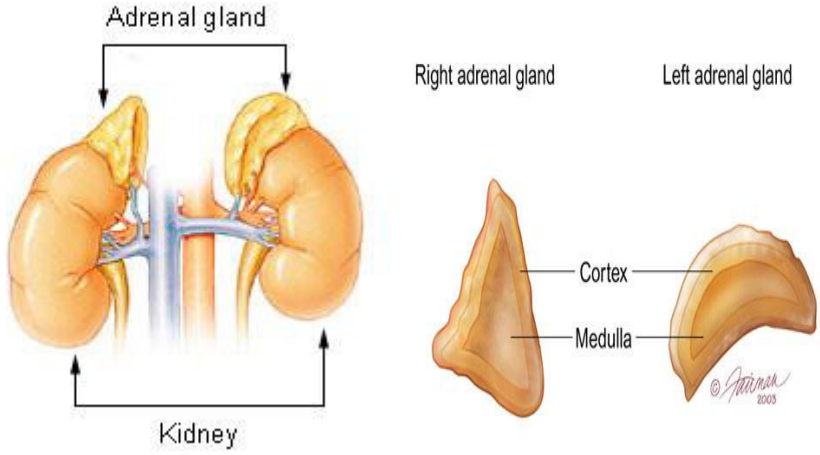
PHYSIOLOGY OF ADRENAL GLANDS

(AKA SUPRARENAL GLANDS)

Introduction:

Suprarenal glands (adrenal glands) are two endocrine glands that are located above the two kidneys. They are supplied by arteries that originate directly from the aorta; this fact reflects the great importance of the adrenal glands, they are essential for life. If the adrenal glands are removed, the individual dies!

Adrenal Gland



Two notes from sheet writer :

1) The dr. said that adrenal glands are supplied by arteries that originate DIRECTLY from the aorta . He means that the origin of adrenal glands' blood supply is the aorta . Remember that the adrenal glands are supplied by three arteries : superior , middle and inferior suprarenal arteries . The one which originates directly from the aorta is the middle suprarenal artery , while the superior and inferior arteries are branches of inferior phrenic and renal arteries respectively . The latter two arteries originate from the aorta so we conclude that superior and inferior suprarenal arteries originate indirectly from the aorta .

2) Actually , removal of the adrenal cortex is of disastrous consequences , whereas removal of the adrenal medulla can be tolerated .

Adrenal gland is composed of two parts: adrenal cortex and adrenal medulla. We already know that the adrenal medulla is related to the autonomic nervous system (ANS) embryologically and functionally , that's why it'll be discussed later in the ANS course . In this course we are going to discuss the adrenal cortex .

Control of the adrenal cortex :

The anterior pituitary secrets adrenocorticotropic hormone (ACTH) – a polypeptide hormone - which is responsible for activating the adrenal cortex . Indeed, ACTH regulates the growth of the adrenal cortex as well as secretion of hormones from it .

The adrenal cortex secretes three main hormones : cortisol , aldosterone and androgens . The target hormone for ACTH is cortisol . This doesn't mean that other hormones (aldosterone and androgens) are not stimulated by ACTH , in fact they are stimulated by ACTH but its effect on them is very little compared to that on cortisol . Thus we can conclude that there must be some other stimuli for aldosterone and androgens .

In the fetus , ACTH synthesis and secretion processes begin just before the development of the adrenal cortex (makes sense as ACTH will control the adrenal cortex) . Glucocorticoids in the fetus are involved in a number of important processes .The doctor emphasizes again that production of ACTH is very important for the secretion of aldosterone , cortisol and androgens.

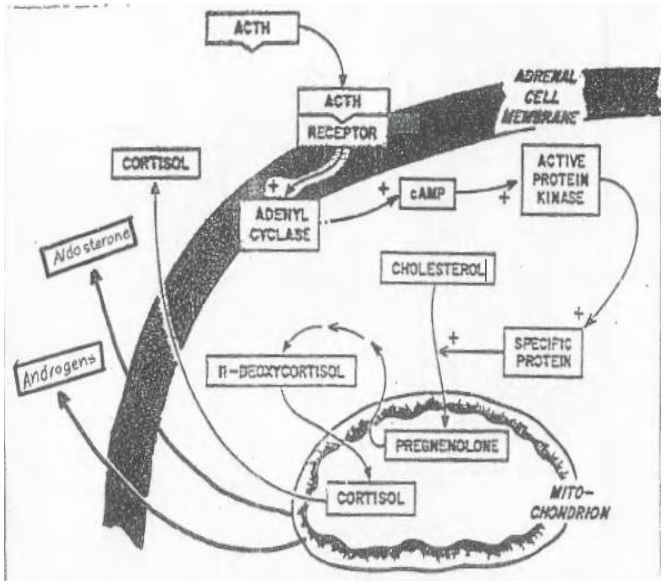
We know that pituitary hormones are very well regulated .
Regulation of ACTH secretion is considered one of the most complicated regulatory processes that control pituitary hormones .

Now after knowing that ACTH is the controller of adrenal cortex hormones , let us see how this controller is controlled !
The main stimuli for the secretion of ACTH are :
* CRH (corticotropin – releasing hormone)
* ADH (antidiuretic hormone) .

The doctor now is reading this from the slides :
" ACTH secretion responds most strikingly to stressful stimuli , a response that is critical to survival . "

ACTH has extra-adrenal actions like lipolysis and MSH-like action (MSH = Melanocyte stimulating hormone) .

The doctor described briefly some steps that are involved in cortisol synthesis and here is what he said (notice the figure) :



ACTH stimulates production of cAMP .cAMP activates other enzymes - kinases - (notice the cascade of actions in the figure) . Then an enzyme catalyzes the conversion of cholesterol to pregnenolone . This step is the most important step in the production of cortisol and the other adrenal cortex hormones(aldosterone and androgens) .

Adrenal cortex (a deeper look) :

As we said previously, the adrenal gland is made up of two distinct parts (the cortex (80%) and the medulla (20%)) . These two parts differ in their anatomy, histology, embryology and physiology .

Adrenal glands are relatively small glands (6 – 10 grams) .

We also said that the adrenal cortex is essential for life , let us see why :
** It controls sodium , potassium and water metabolism and thus fluid volume in the body (blood volume) and therefore it controls blood pressure .

** It controls carbohydrate , fat and protein metabolism (i.e. energy metabolism).

** It participates in responses to stress of various kinds .

Removal of the adrenal cortex from both sides ⟶ The individual dies .

The adrenal cortex is composed of three zones :
** **Glomerulsoa**(12%)
** **Fasciculata** (65%)
** **Reticularis**(23%)

Each zone produces specific hormones :
** First zone ; glomerulosa , produces specific hormones that are called collectively **mineralcorticoids** ("mineral" because they affect minerals metabolism) .The master of mineral corticoids , the most potent and the most important one , is **aldosterone** .

** Second zone ; fasciculata , produces specific hormones that are called collectively **glucocorticoids** (" gluco" because they affect glucose metabolism). The representative of this group is cortisol . Zona fasciculata also produces small amounts of androgens .

** Third zone ; reticularis , produces androgens and estrogens as well as small amount of cortisol . this zone does not develop properly until the age of eight .

In the adult , the cells of the first zone ; glomerulosa , migrate down through the 2nd and the 3rd zones . While they migrate , they change their shape and function (the reason behind this is unknown) .

The doctor now is showing a figure that compares cortisol and aldosterone , this is the figure and the doctor's comments about it :

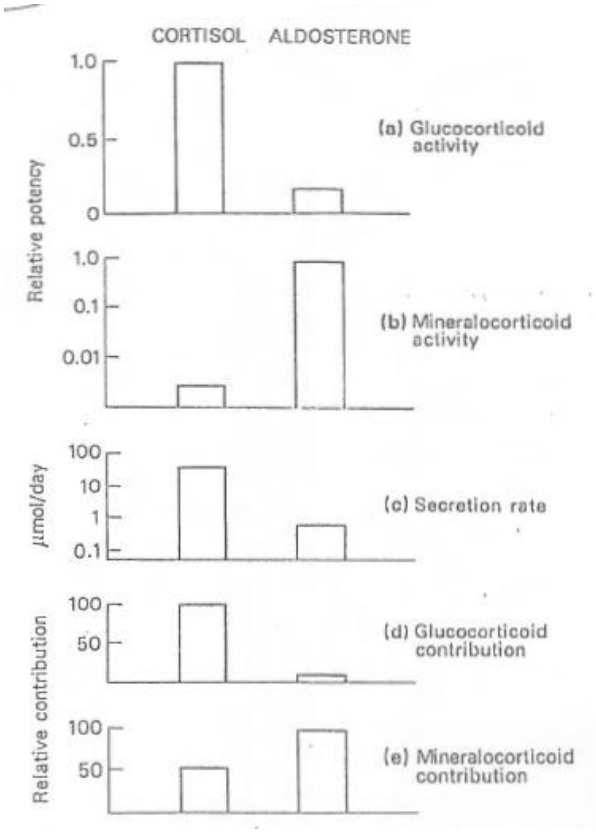


Diagram (a) : Even though aldosterone is a mineralcorticoid , it has a glucocorticoid activity (minimal role) .

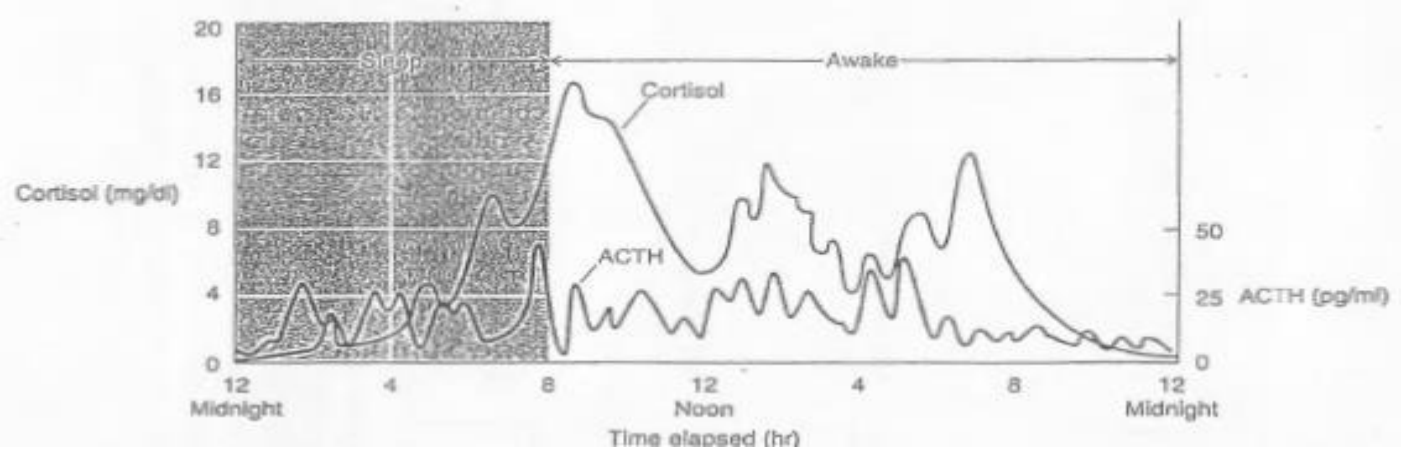
Diagram (b) : Similarly , cortisol plays a minimal role in mineralcorticoid activity .

Diagram (c) : Regarding secretion rate , it is for cortisol much more than that for aldosterone .

Diagram (d) : The role of aldosterone in glucocorticoid activity is very little .

Diagram (e) : The role of cortisol in mineralcorticoid activity is much higher than the role of aldosterone in glucocorticoid activity (shown in diagram (d)) and this is because secretion rate of cortisol is higher than aldosterone's secretion rate (shown in diagram(c)) so that the relatively high secretion rate of cortisol compensates its low amount of contribution in the aspect of mineralcorticoid activity .

This figure shows the variation of cortisol secretion during the day . The variation in cortisol secretion is parallel to the variation in ACTH level . Notice the high level of cortisol during daytime and not during midnight .



Let's get back to adrenal cortex hormone synthesis .

In a previous lecture , we mentioned that adrenal cortex hormones are steroids (i.e. they are synthesized from cholesterol). The process of their synthesis involves many steps that are catalyzed by many enzymes .Sometimes , cortisol synthesis is blocked ; in this case , corticosterone level increases in blood .

(Sheet writer's note : the doctor means here blockage at the last step of synthesis , see the star in the figure below) .

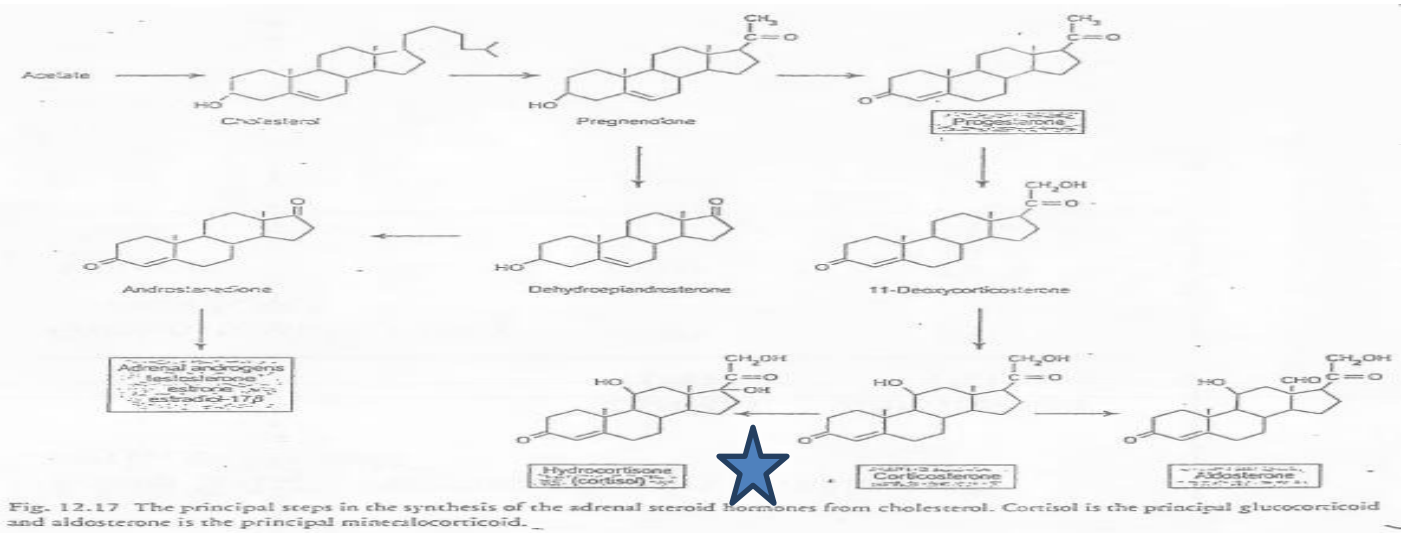


Fig. 12.17 The principal steps in the synthesis of the adrenal steroid hormones from cholesterol. Cortisol is the principal glucocorticoid and aldosterone is the principal mineralocorticoid.

**Important : When adrenal cortex hormones are synthesized , they are released immediately . They are not stored in the adrenal cortex .Therefore , any need for one of these hormones requires new synthesis .

Cortisol :

** 90% of it is bound to corticosteroid-binding protein, sometimes this hormone is called transportin especially in pharmacology .
**6% is bound to albumin . The left 4% represents the free (not bound) portion.

Cortisol has many effects on almost all body systems including the NS , the CVS and others . These are some of these effects (the most important ones) :
note : The doctor mentioned them randomly , here I have rearranged them according the level of importance (from the highest to the lowest):

** **1st : Production of glucose from non-carbohydrate sources .**

** 2nd : Modulation of CVS function : maintains sensitivity to vasoconstrictive agents and maintains microcirculation .

** 3rd : Increases the mobilization of glycerol and fatty acids from adipose tissue.

** 4th : Modulation of CNS function : maintains sensitivity to epinephrine and norepinephrine .

Cortisol affects glycogenolysis . It aids in breaking glycogen down but not directly, it facilitates the action of another hormone (glucagon) → Permissive action .

Remember :
Glycogenolysis is the breakdown of glycogen (n) to glucose-6-phosphate and glycogen (n-1). Thus it is important when glucose levels drop since it provides glucose (e.g. : during fasting) . Imagine if a human being or an animal has been fasting for a long period and there is no cortisol in their body , they'll die ! Cortisol is essential for life .

Conclusion : Cortisol plays a role in the defense against hypoglycemia by two ways :

1- production of glucose from non-carbohydrate sources .

2- The permissive effect in glycogenolysis along with glucagon .

** Cortisol is capable of binding to the receptors of aldosterone . Although this , the effect of cortisol on mineral metabolism is not similar to aldosterone's effect on it . This is because there are enzymes in the kidney that inactivate (modulate) cortisol action .

** Even in the fetus , cortisol plays a very important role (The dr. just read the following points so I'll just put them as they are with few comments beside) :

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.

** Regarding the first point : Babies who are born with respiratory distress syndrome are injected with cortisol . Within minutes , they will breathe properly .

** Regarding the fourth point :"parturition " means "delivery ".

** There are natural and synthetic glucocorticoids :
Cortisol : Natural , provides 95% of glucocorticoid activity , very potent .

Corticosterone : Natural , provides 4% of total glucocorticoid activity , less potent than cortisol .

Cortisone : Synthetic .

Prednisone : Synthetic .

Methylprednisone : Synthetic .

Dexamethasone : Synthetic .

** Cortisol and its derivatives are widely used in medicine . According to the doctor's point of view , these drugs are magic drugs that can be used for many diseases in the body and work properly .

Note : the effect of these drugs follows personalized medicine rules . In some patients these drugs do not function , while in others they work efficiently .

Now think ! Why do these drugs treat diseases that are related to almost all body systems ? Because they can get into all types of cells since they are steroids (They are capable of passing through plasma membrane) . After getting to the cell and binding to their receptor , they start to do their job in curing the patient . They are used to treat diseases related to blood , skin , GIT , CVS & CNS .

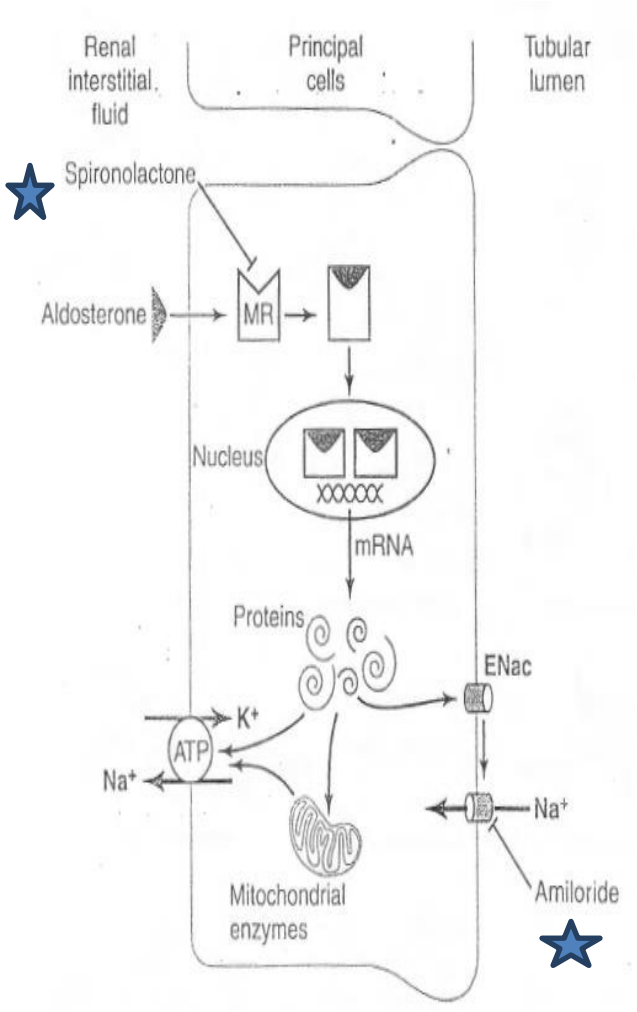
Aldosterone :

One of the mineralcorticoid hormones . Its main function is to regulate sodium/potassium balance in the body consequently regulate normal volume of the extracellular fluid consequently regulate blood volume consequently regulate blood pressure .

** 20% of aldosterone is bound to corticosteroid binding protein or transportin , 40% is bound to albumin and the left 40% represents the free portion . The free part of aldosterone (40%) is much more than the free part of cortisol (only 4%) .

** Mineralcorticoid hormones are : Aldosterone , deoxycorticosterone , corticosterone , flurocortisone , cortisol and cortisone (some are natural and some are synthetic).

Sheet writer's note :Remember that we classified cortisol and its derivatives as glucocorticoids . I think that the doctor means here that they have some mineralcorticoid activity as we mentioned previously .



The main function of aldosterone is to normalize Na+ level in the body **. It causes Na+ reabsorption through renal tubules .**

Notice in the figure beside : the principal cells , the tubular lumen and aldosterone activating the epithelial sodium channels in order to reabsorb Na+.

Amiloride , a chemical that serves as diuretic drug , opposes aldosterone (it inactivates Na+ reabsorption by inactivating Na+ channels) .

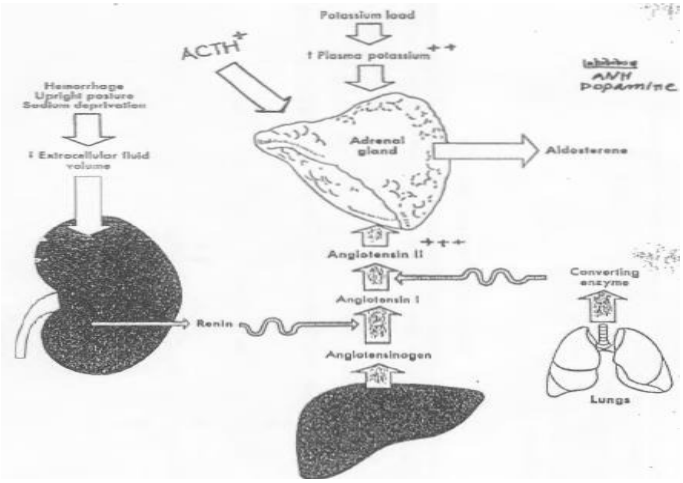
Aldosterone is a steroid , it crosses cell membrane and binds to its receptor inside the nucleus . **Spironolactone** opposes (inhibits) aldosterone binding to its receptor . It is also a diuretic .

** Conclusion :

Amiloride and aldosterone are two diuretics that oppose aldosterone function which is Na+ reabsorption . Thus these two chemicals keep Na+ in the urine to be excreted .

** Aldosterone secretion is stimulated mainly by angiotensin 2. **Hyperkalemia** (It seems that the doctor said hypokalemia but this is wrong . It must be hyperkalemia which is increased K+ levels in blood)**or low blood pressure** causes the release of the hormone (**renin**) from the **kidneys** . Renin produces angiotensin 1 from its precursor ; angiotensinogen in **the liver** . Angiotensin 1 produces angiotensin 2 under the effect of converting enzymes in **the lungs** .

Sheet writer's note : hyperkalemia (increased K+ levels) is equivalent to hyponatremia (decreased Na+ levels) and they are related to low blood pressure.



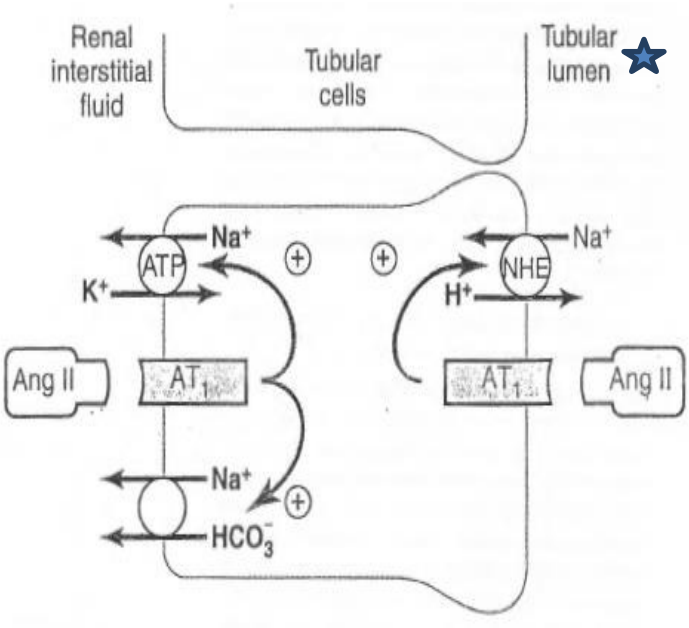
* To sum up : Stimuli for aldosterone secretion:

** The main stimulus is angiotensin 2 .
** Increased plasma K+ levels (decreased Na+ levels) .
** ACTH .

** Angiotensin 3 , potent stimulator for aldosterone secretion .

** Angiotensin 2 causes the secretion of aldosterone which causes Na+ reabsorption (indirect way by which angiotensin 2 causes Na+ reabsorption and thus elevates blood pressure) .

** Angiotensin 2 can also cause Na+ reabsorption directly through renal tubules in the exchange with K+ and parallel to HCO3- (This occurs on the basolateral membrane) . On the luminal membrane , exchange with H+ occurs .
(The doctor mistakenly said them the other way round so be careful , notice the figure beside) .



Now let us know how angiotensin 2 increases blood pressure indirectly via vasoconstriction of renal efferent arterioles .

In the figure beside , notice the nephron , the renal corpuscle and the glomerular capsule .

Afferent arteriole brings blood into the renal corpuscle .

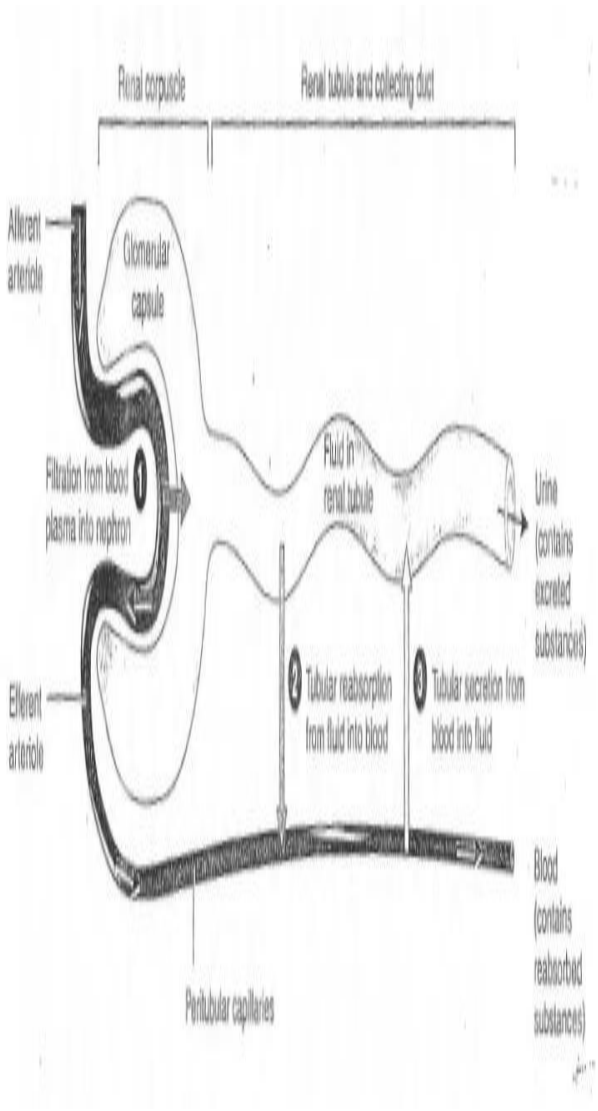
Blood leaves the renal corpuscle through the efferent arteriole .

Angiotensin 2 causes vasoconstriction of the efferent arteriole ,when this happens , fluid (plasma) in the peritubular capillary decreases . This leads to two events :
** Hydrostatic pressure in the peritubular capillary **decreases .**

** Colloid osmotic pressure (oncoticpressure) in the peritubular capillary **increases** .

These two effects cause Na+ reabsorption and thus elevation in blood pressure .

(Be careful if you hear the record or write note s during the lecture that the dr. said at first that osmotic pressure decreases and this wrong , then he corrected it and said that it increases .)



** Aldosterone doesn't cause Na+ reabsorption through renal tubules only . It does the same and by the same mechanism of Na+ reabsorption through salivary glands , intestines and sweat glands .

*** Sheet writer's note :*

Remember : Hydrostatic pressure is related to fluid volume (plasma volume in our example) , whereas colloid osmotic pressure is exerted by proteins in a blood vessel's plasma .

** **ACE inhibitors :** (ACE = Angiotensin Converting Enzyme)

In order to keep normal blood pressure , ions concentration in plasma (especially Na+) must be normal , and for this to happen , angiotensin 2 and aldosterone levels must also be normal .

One suggested treatment for those who suffer from hypertension is to inhibit production of angiotensin 2 from angiotensin 1 since angiotensin 2 stimulates secretion of aldosterone and causes Na+ reabsorption directly and indirectly as we explained . These processes elevate blood pressure so blocking them by blocking aldosterone 2 production leads to reduction in blood pressure .

The drugs that do this are called angiotensin converting enzyme inhibitors (ACE inhibitors) since they inhibit the enzyme that produces angiotensin 2 from angiotensin 1 .

The doctor then read this about these drugs :

→ ACE inhibitors have been available for many years and are among the safest and best-tolerated of all antihypertensive medications. The first to be marketed in the United States was captopril, but many others, with longer half-lives that allow once-daily administration, are now available. These drugs also improve the quality of life and survival of patients with heart failure. More recently, drugs have been developed that specifically block the AT_1 receptor. These drugs offer a good alternative for those patients who cannot tolerate ACE inhibitors, usually because of a chronic cough, the most common side effect of these drugs.

Reticularis hormones :

The third zone (reticularis) produces androgens , estrogens and little amount of cortisol . It produces two weak androgens :Dehydroepiandrosterone and Androstenedione . These two hormones produce the most potent male androgen ; testosterone . They also produce the estrogens Estrone and Estradiol .

*** Sheet writer's note : Testosterone is mostly produced in the testes and a small amount is produced by the adrenal glands .*

** The main functions of androgens :
In females : presence of pubic hair and axillary hair , libido .

In males : same as testosterone .

** When cortisol synthesis is blocked at the last step , the previously mentioned two weak androgens levels increase . These two weak androgens are not important in males in any stage of life because there is a strong male androgen that's produced by the testes which is testosterone . The doctor says that they may be important for males only in one case , at late childhood and beginning of puberty , they have a role in expressing male characteristics (e.g. growth of beard) and that's why their levels increase during this period . However , in females , they are important in all life stages especially after menopause (explanation : after menopause , ovaries stop functioning so that adrenal cortex becomes the only source for androgens and estrogens) .

That's it for today's lecture .

Good luck everyone and Ramadan Kareem ☺

Written by :Doa'a S. Dahboor

Dedicated to my mother .