THE ADRENAL (SUPRARENAL) GLANDS

They are two glands, present above the kidneys. One adrenal gland is sufficient for human beings/mammals (example: we also have two kidneys but one is sufficient).

The Adrenal glands receive their blood supply from the aorta directly and hence they are essential for life, if we remove these glands from the embryo it will not survive. Their total weight is 6-10 g.

Each Adrenal gland is made up of two parts -two distinct organs- which differ in their histology, embryology, and functions (physiology):

1- **Adrenal Cortex - 80%**
2- **Adrenal Medulla - 20%**

The adrenal cortex is essential for life (since it controls Na, K and water metabolism) and not the adrenal medulla (since its hormones e.g. adrenaline can be produced by other organs like the sympathetic nervous system.)

In physiology of the endocrine system we will only discuss the adrenal cortex (we'll take the adrenal medulla later when we take the autonomic nervous system.)

Adrenal cortex secretes 3 main hormones:

1- *Glucocorticoids* (Cortisol - the main **target** for ACTH)
2- *Mineralocorticoids* (Aldosterone) - ACTH has a minor effect on them
3- *Androgens* (Sex hormones) - ACTH has a minor effect on them

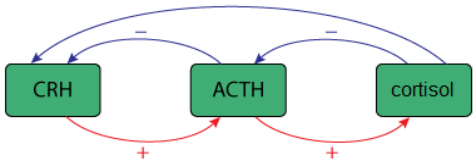
Control of adrenal cortex secretion:

The Anterior pituitary gland secretes ACTH which regulates the **growth** of adrenal cortex cells in addition to the **synthesis** and **secretion** of its hormones. Fetal ACTH synthesis and secretion by the anterior pituitary gland begins just before the development of the adrenal cortex. The adrenal cortex is essential even for the development of the fetus. The extra-adrenal actions of ACTH include lipolysis and MSH-like actions.

Regulation of ACTH is among the most complicated of all the pituitary hormones. The following regulate the secretion/synthesis of ACTH (Adrenocorticotropic hormone)**:**

1- CRH (corticotropin-releasing hormone) – most important, it is a hypothalamic hormone.
2- ADH : exhibits the same action as CRH
3- Neurotransmitters
4- Anxiety
5- Depression
6- All kinds of stress (infection, trauma, anesthesia, surgery…)

ACTH secretion responds most strikingly to stressful stimuli: a response that is critical to survival**.**



- Extra note:

- Cortisol provides negative feedback to the hypothalamus to inhibit CRH secretion and to the anterior pituitary gland to inhibit ACTH directly.
- ACTH provides negative feedback to the hypothalamus to inhibit CRH secretion.

The <u>functions</u> of the adrenal cortex - essential for life; include:

1- Controls Na^+, K^+, and H_2O metabolism.
2- Controls carbohydrate, fat and protein metabolism and mobilization for energy.
3- Participates in the response to stresses of various kinds.

The adrenal cortex is divided into <u>three zones of cells</u>:

- **Zona Glomerulosa – 12%**
- Produces: *<u>Mineralocorticoids</u>* – represented by *Aldosterone*. Those control the metabolism of minerals and water.
- **Zona Fasciculata - 65%**
- Produces: *<u>Glucocorticoids</u>* – represented by *Cortisol* as well as small amounts of *Androgens*. Function: glucose metabolism.
- **Zona Reticularis - 23%**
- Produces: *<u>Androgens</u>* as well as small amounts of *Cortisol*. This zone doesn't differentiate fully until between 6 and 8 of years of age.

In adults, zona glomerulosa cells continuously migrate down to reticularis through fasciculata, they change their morphology, function and secretory pattern as they go.

Now we will clarify the meaning of **<u>mineralocorticoid and glucocorticoid activity</u>** and the role of *Aldosterone and Cortisol* in each one:

♣**Mineralocorticoid activity**: measured in terms of the ability of the hormone to reduce the ratio of excretion of sodium to the ratio of excretion of potassium in urine. (In other words: the ability to retain Na^+ and excrete K^+.)

♣**Glucocorticoid activity**: measured as the ability of the hormone to increase glycogen concentration in the liver and increase glucose concentration in blood.

♣**In terms of potency:**

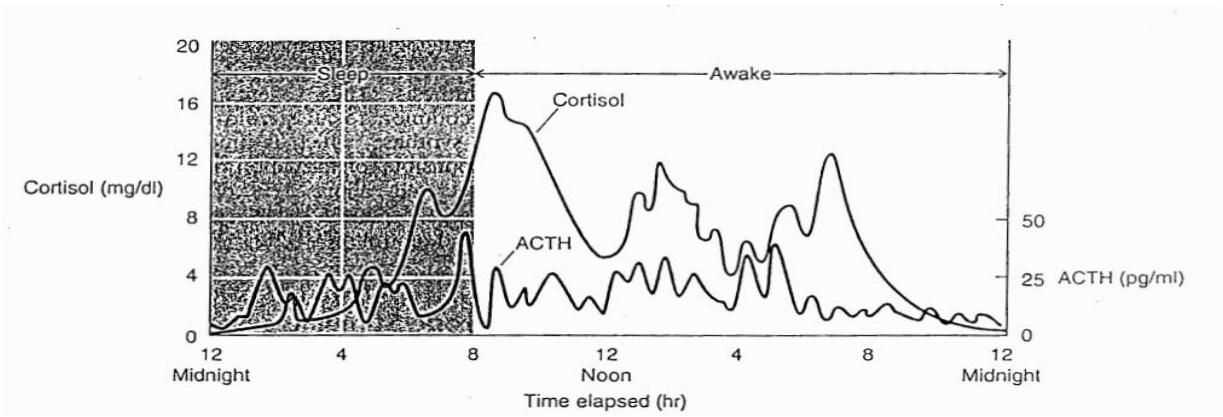
1- **Aldosterone** accounts for 90% of all meneralocorticoid activity while **Cortisol** has very slight mineralocorticoid activity.

2- **Cortisol** accounts for 95% of all glucocoticoid activity while **Aldosterone** has very slight glucocorticoid activity.

♣**In terms of actual participation**: Cortisol's mineralocorticoid contribution is greater than aldosterone's glucocorticoid contribution. This is due to the secretion rate: the adrenal cortex produces more cortisol than aldosterone and this compensates for the weakness in its potency toward mineralocorticoid activity.

	potency in meneralocorticoid activity	potency in glucocrticoid activity	rate of secretion	real participation in meneralocorticoid activity	real participation in glucocrticoid activity
aldosterone	very potent	weak	less	very potent	weak
Cortisol	**Weak**	very potent	**more**	**potent**	very potent

The *change in **ACTH** concentration is parallel to change in **Cortisol** concentration:* as ACTH increases Cortisol increases as well. ACTH release is greater in the early morning hours.



Remember that steroid hormones are divided into: sex hormones and adrenal cortex hormones. Both are synthesized from cholesterol. The **production of Steroid hormones** involves many reactions and many steps and each reaction requires its own enzyme:

♣ As we know, the production of *cortisol* is mainly in the *fasciculata*. When cortisol production decreases or is blocked due to many factors (like enzyme deficiency), the concentration of *Corticosterone* hormone will **increase**. *(The doctor didn't say the reasons but I think it is due to the absence of the main negative feedback inhibitor which is cortisol as we said previously.)* In rats there is only corticosterone and no cortisol.

♣ Adrenal cortex hormones are released immediately upon synthesis and they are not stored. When there is an immediate need for new hormones new synthesis is required.

90% of cortisol **binds** to CBG "corticosteroid –binding protein" and 6% binds to albumin. The active form which is the free form of cortisol is 4%.

The main functions of <u>Cortisol</u>: it functions on almost all the organs. Those are the main ones.

1- Production of glucose from protein by gluconeogenesis.
2- Fat mobilization.
3- Supports the vascular response.
4- Modulates CNS functions.

Also:

- Acts on fat cells: increases lipolysis.
- Skeletal muscles: Increases amino acid mobilization.
- Immunosuppressive.
- Stress response – Increased vascular response
- Affects the liver:

♣ When there is a decrease in glycogen in the liver and there is a deficiency of cortisol → the human will die of hypoglycemia (low blood glucose). Remember that cortisol is **responsible** for the synthesis of glucose from protein (**gluconeogenesis**). Cortisol is essential for life especially for fasting human beings and animals.

♣Cortisol **doesn't** promote **glycogenolysis**. It facilitates the action of glucagon. This is called permissive hormone interaction**.**

♣Cortisol can bind very well to aldosterone receptors, but there is an enzyme called **hydroxysteroid dehydrogenase** which continuously inactivates cortisol and hence the actions of aldosterone and cortisol are <u>not</u> similar. In the absence of this enzyme their actions become similar the human being can't survive because everything in the body will be degenerated.

<u>The Adrenal glands are unique during the fetal life</u> especially after four months of pregnancy. They are unique in their **size** and **function**:

♣ **Size**: The size of adrenal glands in the fetus after 4 months of pregnancy is larger than the size of kidneys

♣ **Function**: Both parts -the adrenal cortex and medulla- function properly during the fetal life. **Cortisol** particularly has very <u>important functions during the fetal life</u>:

1- Production of surfactant from type 2 cells of the alveoli of the lung, a lack of surfactant which leads to the respiratory distress syndrome in newborns. If the newborn doesn't breathe properly we give him cortisol and after a few minutes he will start breathing.

- It is called the magic drug: Cortisol diffuses into every cell in body with a nucleus. Cortisol treats and cures many diseases (Heart, skin, lung…etc). The strange thing is that sometimes it could cure one patient completely but have no effect on another, no one knows why, although some believe it could be due to a lack of receptor, a blood disease, or a genetic condition.

2- Development of hypothalamic function and development of the thyroid-pituitary axis.
3- The sequential changes of the 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.

Natural and synthetic Glucocorticoids:

- Natural:
- Cortisol
- Corticosterone

- Synthetic: more potent

- Cortisone
- Prednisone
- Methylprednisone
- Dexamethasone