BAU-Medicine

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دعاء إلى روح زميلنا رشيد الهواملة

اللهم يمّن كتابه، ويسر حسابه، و ثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنّات, في جوار نبيك و مصطفاك صلى الله عليه وسلّم، اللهم اجعل قبره روضةً من رياض الجنة. اللهم افسح له في قبره مدّ بصره، وافرُش قبره من فراش الجنة .

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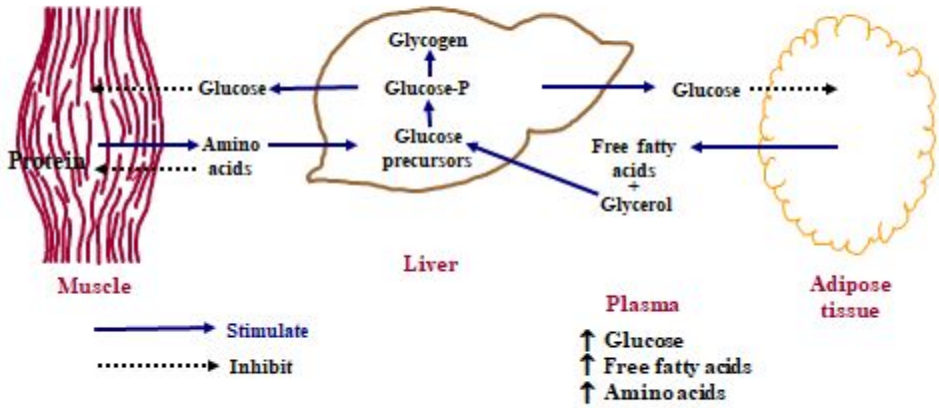
Quick recap, from the previous lecture.

- ★ ACTH is the regulator for glucocorticoids which is secreted by the zona fasciculata.
- ★ The effect of ACTH on the adrenal gland is to stimulate the production of cortisol
- ★ Low ACTH, zona fasciculata will regress
- ★ More ACTH, zona fasciculata will increase in size and secrete more cortisol.
- ★ The width of zona fasciculata depends on the stimulation of ACTH.
- ★ When there's NO cortisol we don't have negative feedback, so there's an increase in ACTH, lead to the production of more intermediates (androgen and mineralocorticoids)
- ★ Cortisol is essential to regulate ACTH and ACTH is essential to regulate zona fasciculata.

Metabolic Effects of Cortisol



- The main goal of glucocorticoid is to maintain glucose concentration
- From where we get glucose?
    1. Gluconeogenesis (from the released amino acids from muscle and the released glycerol from stored fat)
    2. Protein mobilization (to release AA)
    3. Fat mobilization (to release FFA)
    4. Less influx of glucose to the fat and muscle cells (antagonize the effect of insulin)
- there is less utilization of glucose by cells (weak effect) whereas growth hormone has a great effect
    - ➔ So the plasma level of glucose will go high
    - ➔ Due to less intracellular glucose level, the cell undergoes an alternative pathway of metabolism, energy supply for the citric acid cycle is mainly provided by Amino acid and fatty acid.
    - ➔ To sum up the effect of glucocorticoid :
        - Less utilization of glucose
        - Store more glycogen
        - Less formation of fat and protein
        - More mobilization of fat and protein
        - More plasma FFA, AA & glucose
        - Less intracellular glucose.

Effect on CHO

↑Gluconeogenesis

- ↑amino acid mobilization to liver
- ↑conversion of aa to glucose in the liver (not in other tissues)
- antagonize insulin in the liver→↓glycogenesis & ↑gluconeogenesis

↓Glucose utilization ↓influx of glucose to muscles

Net effect: ↑ PLASMA GLUCOSE

★ So we have glycogen in the liver and glucose in the plasma but there's intracellular deficiency of glucose

★ But the cells need energy and the insulin effect is antagonized (insulin is present but the effect is absent),

Effect on Proteins

- ↓ Protein synthesis & ↑protein catabolism in most tissues

if there's protein destruction of the bone	lead to less mass of the bone, weaker and easily fractured
destruction of blood vessels	Weak blood vessel
Protein destruction of skin	Weak skin
Protein destruction of the muscle	Weaker and smaller muscle

- ↑ Plasma amino acids
- ↑ protein synthesis in the liver & subsequently plasma proteins & Gluconeogenesis plasma protein

Increase the synthesis of proteins produced by the liver normally and synthesize plasma proteins, not muscle, skin, or other proteins

Effect on Fats

- ↑mobilization of fatty acids
- ↑ Plasma fatty acids & subsequent effects:

Cortisol release More free fatty acid in the plasma and (as we said) the intracellular level of carbohydrates is low, so fatty acid accumulates in the form of ketone bodies

FFA → acetoacetic acid → ketone bodies → acidosis

Other effects of cortisol

- Resisting stress and inflammation
  - Stabilizes lysosomal membranes (one of the defense processes that some microbes have)

- Decreases capillary permeability
- Decreases migration of white blood cells into the inflamed area and phagocytosis of the damaged cells
- (net effect is to) Suppresses the immune system

- Reduces the release of interleukin-1 from white blood → attenuate fever
- Resolution of Inflammation
- Blocks the Inflammatory Response to Allergic Reactions
- Mood effect (unknown mechanism, called the feeling of well-being)

- Foreign molecules that enter the body may be infectious or noninfectious.
  - ➔ local defenders (tissue macrophage system) cause an increase in capillary permeability and more infiltration of plasma proteins & WBC, and lysosomes destroy this foreign material, this what happen in the inflammatory process.
  - ➔ Cortisol will suppress all this
  - ➔ cortisol is beneficial in noninfectious inflammatory reactions to defend against rejection esp; in organ transplant.
  - ➔ But the usage of cortisol may be harmful if it is used during the infectious inflammatory process.
- cortisol suppress Fibrous tissue formation; by preventing the Inflammatory reaction of joints and bone and reducing the post-fibrous reaction that may cause limitation in the function

★ **the effect of cortisol on the mood,**
- This figure shows that the peak concentration of cortisol is at 8 AM after waking in the morning and the people (almost all people after having enough sleep) will have a good mood
- In the evening he will be low- mood.

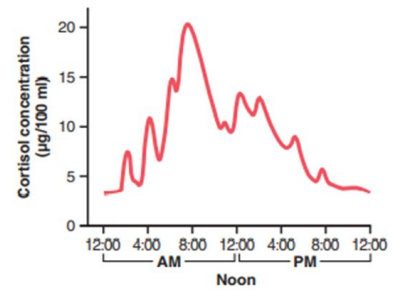
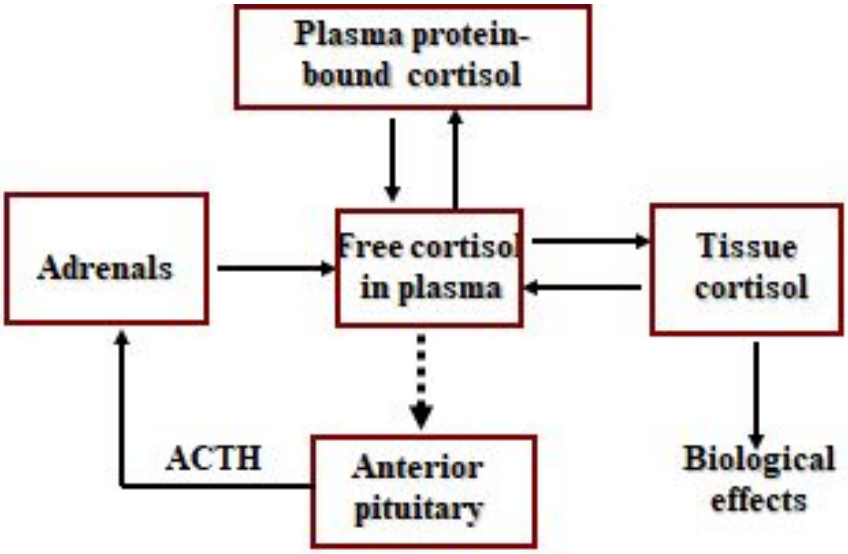


Figure 78-8. Typical pattern of cortisol concentration during the day. Note the oscillations in secretion, as well as a daily secretory surge an hour or so after waking in the morning.

This guy has excess glucocorticoid
- Fluid accumulation and water retention
- lipid deposition
- Weak skin
- Varicose veins; protein destruction leads to weaker vessels, blood applies pressure on the walls of bv and may lead to sth similar to varicose veins or causing rupture.

Interrelationships Between Free & Bound Cortisol



"the functional portion of the hormone is the free pat (not bound) in the plasma"

- Thyroid hormones, steroid hormones, aldosterone all have the same principle but they differ in the carrier protein.
- Albumin is the common binding protein of almost all hormones

Corticosteroids & Their Relative Glucocorticoid & Mineralocorticoid Activities

Steroids	Average Plasma Concentration (free and bound, µg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal Steroids				
Cortisol	12	15	1	1
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydropiandrosterone	175	20	—	—
Synthetic Steroids				
Cortisone	—	—	0.7	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasome	—	—	30	—
9α-fluorocortisol	—	—	10	125

Just focus on red and green boxes, we are going to understand something from these numbers. Of course, you don't have to save them. Please don't bother with this excessive explanation

The purpose of this slide is To compare cortisol and aldosterone and to notice <u>their cross binding to their receptors</u>

- **Aldosterone** has glucocorticoid activity (minimal activity)
- And also has a mineralocorticoid activity of 3000.
- **Cortisol** has mineralocorticoid activity that is lower than aldosterone (1/3000) but, wait don't rush to judge

Notice that the plasma concentration of cortisol is 2000x higher than aldosterone.

** So actually cortisol has good mineralocorticoid activity, but there's an enzyme in the tissue that breaks down cortisol and will reduce its activity.

★ However, if there is any disorder in this enzyme, there will be a strong mineralocorticoid activity of cortisol, and strong reabsorption of sodium ions will occur, although aldosterone concentration is normal.

★ Corticosterone has a small amount and low secretion rate and has minimal activity

★ **In conclusion,** cortisol may have a very strong mineralocorticoid activity

- you have to look at the whole picture not to focus on a certain point of the view
- there's overlap in the function of steroid hormones because of the similarities in the structure of them
- You may see hypertensive patients that aldosterone level is normal but they have abnormal enzymes that destroy the mineralocorticoid activity of the cortisol
- An abnormally high concentration of cortisol in the plasma will rise the mineralocorticoid activity many folds ⇒ this lead to the accumulation of more fluid in the face and body and water retention (look at the two pictures on page 4)

We will discuss the effect of excess adrenocortical excess:

Obesity: it is found that they have an accumulation of fat in the center of the body (around the neck) although they have fat removal (mobilization of fat from one area to another)

hypertension: due to more water and sodium retention

Weakness: discussed earlier

Cushing's Syndrome
(Adrenocortical excess)

Signs and symptoms	Incidence (%)
Moon facies	88
Obesity	86
Hypertension	85
Menstrual disorders	77
Hirsutism (in females)	73
Weakness	67
Violaceous striae, bruisability	60
Osteoporosis	58
Ankle edema	57
Buffalo hump	54
Acne	54

This will be discussed more in pathology

In certain cases, there is excess ACTH and normal enzyme system of cortisol so there will be more cortisol.

- More cortisol will make feedback inhibition on ACTH

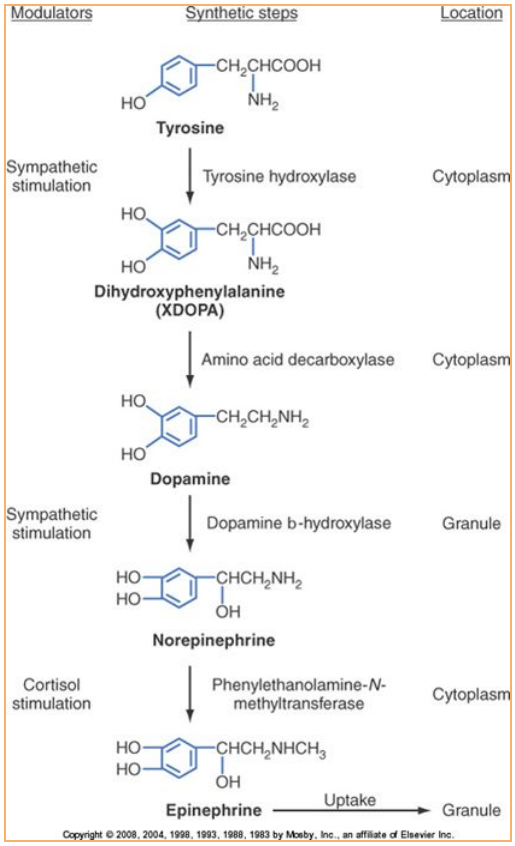
But in uncontrolled ACTH secretion (such as a tumor) ⇒ (more cortisol, more ACTH) indicates that there's a central abnormality

➔ ACTH may increase due to a failure in the production of cortisol (due to many pathologies) (excess ACTH → thick cortex) and if there's an enzyme deficiency in its pathway there will be an alternate pathway that leads to excessive production of androgens and aldosterone

ADRENAL MEDULLA

Modified sympathetic ganglion, produces epinephrine and norepinephrine

- Epinephrine and norepinephrine are synthesized from tyrosine (single amino acid) the same precursor of thyroid hormones.
- Modified sympathetic means: that postganglionic neurons' axons don't exist from the adrenal medulla so Epi and NE are secreted inside the medulla.
- Most of the secretions of the adrenal medulla are epinephrine (80%)
- Differ from the sympathetic system neurons which mostly secrete norepinephrine
- (EPI & NE) are called hormones here because they are transported in the blood and each one bind with their receptor but there are similarities in the receptors
- Norepinephrine is a vasoconstrictor of the muscles of blood vessels but its concentration is low
- Whereas the effect of epinephrine on blood vessel muscle is lower than NE but its effect on the heart is high (on the metabolic process)



The effect of the autonomic nervous system

★ There are alpha and beta-adrenergic receptors ...

★ But the wanted function occur during facing stress... **sympart of the sympathetic response**

★ Sympathetic Responses

- Stress... ↑ sympathetic system ↑ fight-or-flight response (in addition to exercise).
  1. production of ATP (bcz of the need to a huge amount of energy) mainly from carbohydrates (glycogenolysis) after that from fat, note that we don't use protein in these conditions because it is used after weeks to months of starvation.
  2. Dilation of the pupils.
  3. ↑ heart rate and blood pressure.
  4. Dilation of the airways. (beta receptors for epi in the bronchial tree) To increase the amounts of oxygen that gets into the lung and thereby in the blood.

5. Constriction of blood vessels that supply the kidneys and gastrointestinal tract. The effect of norepinephrine in these tissues is preferred to decrease the blood utilized by them and transported to the muscles
6. ↑ blood supply to the skeletal muscles, cardiac muscle, liver, and adipose tissue
7. ↑ glycogenolysis ↑ blood glucose.
8. ↑ lipolysis.

- During fight and flight response we mainly need energy and ATP for muscle cells so we need more blood coming to the muscles.
- During sympathetic stimulation (exercise), the adrenal gland secretes epinephrine more than norepinephrine because norepinephrine effect is less preferred on muscles and we need vasodilation of bv and more blood to flow to the muscle cells so epinephrine works on the heart to pump more blood to go mainly to the muscles
- And muscles have local regulators that antagonize the effects of norepinephrine

➢ When the cardiac output increases 4-5 folds, muscle cell blood flow increases 20-25 folds; because of the dilation of blood vessels in the muscles and vasoconstriction in other tissues.

ADRENAL GLAND

PREPARING THE BODY TO FACE STRESS

- Mineralocorticoids are the acute "lifesaving" portion of the adrenocortical hormones.

- Glucocorticoids Allow the person to resist the destructive effects of life's intermittent physical and mental "stresses," with the help of epinephrines.

- Catecholamines help the body within sympathetic system response

Refer to chapter 61 of Guyton and Hall textbook to read about adrenal medulla; Dr. Mohammad Shaban.