The Endocrine System

☑ Sheet ☐ Slide ☐ Handout

Number:	6
Subject:	**Synthesis and Degradation of Hormones**
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Date:

Price:

Salam alaikum

-This sheet will be the last biochemistry sheet in this system ;)

-This sheet was written according to the records of sections 1+2 and its includes everything in the slides.

Lets start^_^

Synthesis and Degradation of Hormones

As we studied before, hormones can be classified according to their mechanism of actions and other factors. some of them will bind to the cell membrane receptors , and another will get inside the cell to bind their receptors which is found either in the nucleus or within the cytoplasm.

1- steroid hormones :

steroid hormones are classified according to:**

-number of carbon units within these molecules.(the one that we are concerned about)

-mechanism of action within the cell and their function.

-their chemistry.

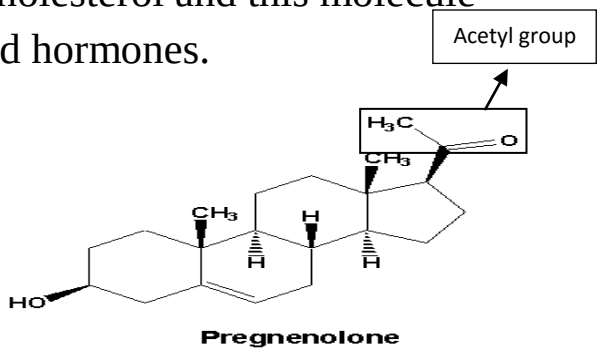
All steroid hormones are **lipid soluble

synthesis of steroid hormone :

>-Steroids are **derived from** cholesterol.

>Cholesterol molecule contain 4 rings connect to each others(*steran ring/core)*.

> **pregnenolone** is derived from cholesterol and this molecule is the parent compound for all steroid hormones.



1-First class C21:

-progesterone
-cortesol
-aldosterone

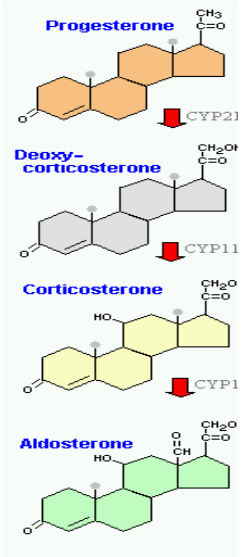
>>how progesterone is derived from pregnenolone?

The conversion of pregnenolone to progesterone takes place in two steps. **First**, the 3-hydroxyl group is oxidized to a keto group (**4**) and **second**, the double bond is moved to C-4, from C-5

NOTE: pregnenolone doesn't have great effect to our bodies ,BUT progesterone have effect to all body .

-This explain{ structure-function relationship}which mean: how can small modification change the function of molecules.

>>how cortisol and aldesterone are derived from pregnenolone?



-Aldosterone and cortisol share the first part of their biosynthetic pathways …

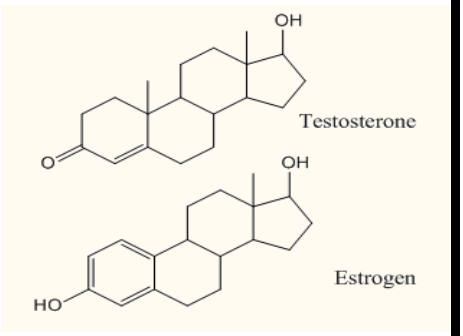
-only know that they are synthesized **<u>from progesterone</u>**

by hydroxylation process.

2-second class C19:

-Testosterone

-This hormone has a shortage of 2 carbons compared to progesterone (the difference in carbon is due to the removal of the acetyl group in testosterone).
-its **derived from** progesterone, ALSO can be derived from pregnenolone with different route.???



3 Third class C18:

-estrogen
-it can be **derived from testosterone** (the difference in carbons number is due to the removal of a methyl group)by an **enzyme** called **Aromatase.**

*****Breakdown of steroid hormones :***

*always remember cholesterol ring"steran" **can't be** metabolism within our bodies .*

Steroid hormones are broken down and released from the body through:

1- *The kidneys : they release :*
   - *The hormones metabolites*
   - *small sized unchanged hormones*
2- *The liver :*
   - *Hydroxylation and conjugation then excretion with bile .*

2- Nitric oxide:

**NO does not always work as a hormone ,only some of them work as a hormone.

****Nitric synthase** is the enzyme that responsible for NO formation.

** **Nitric synthase** has many isoform. "isozyme; multiple forms of the same enzyme in many tissue but with different function"

** **Nitric synthase isoforms are** found in :

1-Neurons (NOS-I) : neurotransmission
2-Macrophage (NOS-II) : bacteriostatic/lytic
3-endothelial cells (NOS-III) *: this one is important for the cardio vascular system* because it can cause vasodilation;; after NO bind to its receptor it will activate second messenger pathway cAMP and after it reachs the smooth muscle that surround the endothelial ,it cause vasodilation there.

Clinical case :

1- people who suffer from angina take NO "nitrates" cause it works as vasodilator which prevents myocardial infarction.

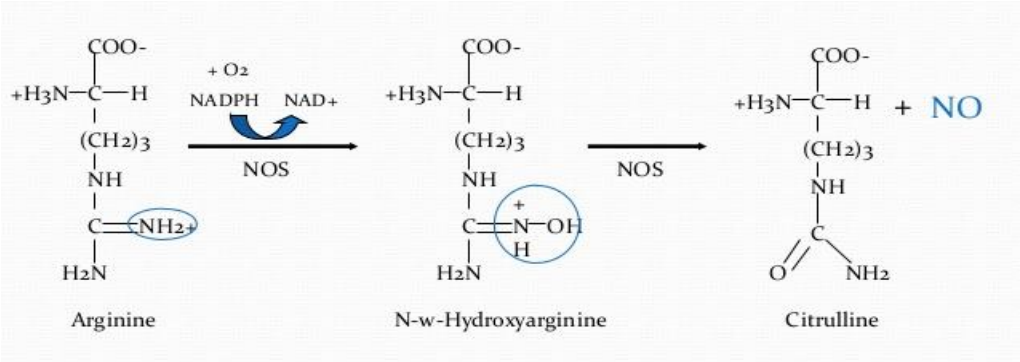
2- people who have septic shock suffer from hypotension because of the production of NO so they must be given NO synthase blocker .

**synthesizing of NO:

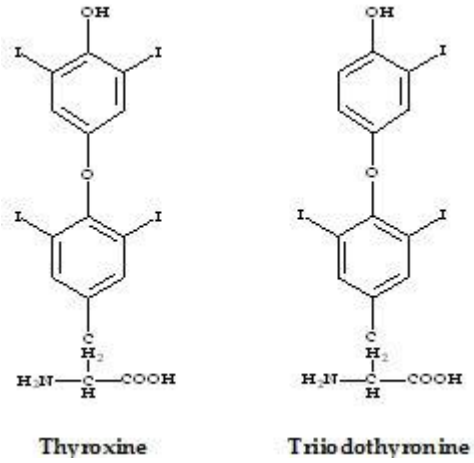
-the **substrate** of the NO-synthase is the **Arginine** (that is a basic amino acid**).**

- through the **use of NADPH** Arginine will transformed into **Citrulline** (it's a basic amino acids ,found in urea cycle).

-the enzyme(NO-synthase) will give O2 molecule : **one of the oxygen atom** will be involved in the structure of Citrulline, and the **other oxygen** atom will coupled to the nitrogen atom that was excreted from Arginine …then NO is produced.



3- Thyroid hormones :



Its is derived from **tyrosine** through the conjugation of a phenol ring to the tyrosine and then the addition of iodine , if 3 iodine atoms are added then its diiodothyronine (T3) , and if 4 are added then its thyroxine (T4) .

**this processwas explained in details in physiology lectures.

4- Catechol amines:

- **derived from** Tyrosine OR phenyl Alanine amino acids
- **Synthesis IN** adrenal medulla , nerve tissue .
- **products :** epinephrine, norepinephrene, dopamine…etc
- **catecholamine synthesis:**

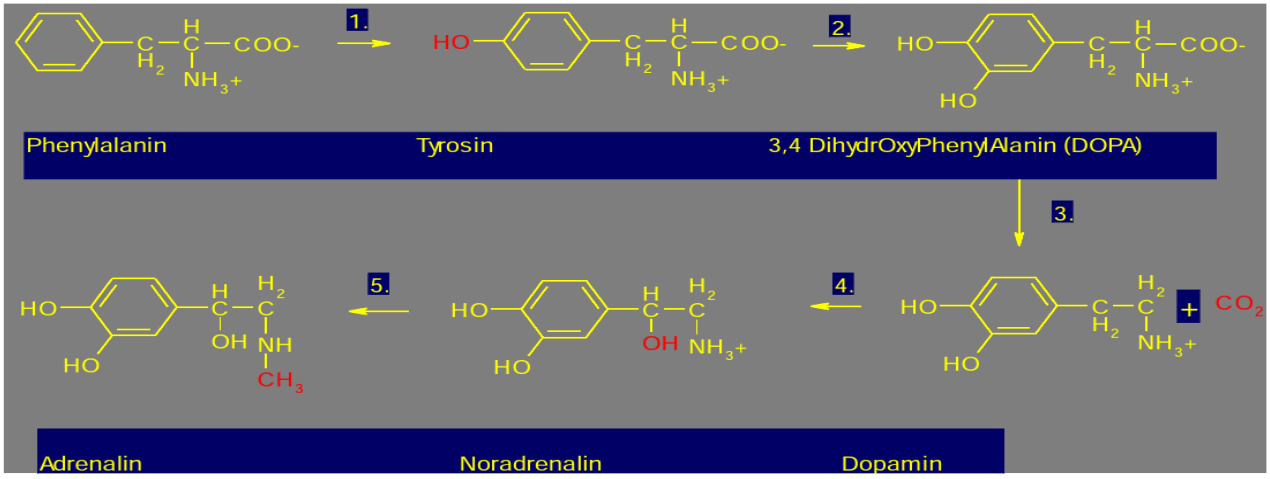
*Tyrosine as we know is a nonessential A.A ,and our body can synthesize it BY **hydroxylation** of phenyl alanine.

***Another hydroxylation** of Tyrosine will give DOPA.

*__decarboxylation__ of DOPA will give DOPAMINE.

*__Hydroxylation__ of dopamine will convert it into norepinephrine.

*__Methylation__ of the nitrogen atom of norepinephrine will form Epinephrine .



- **Breaks down of these catecholamine :**
  Occurs in the body through action of two enzyme:

  <u>1-MAO mono amino oxidase</u> :

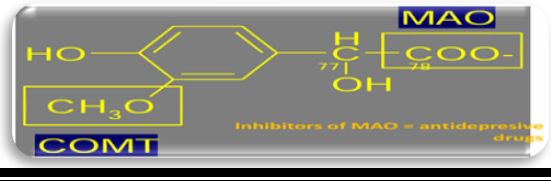
  **oxidation of amine group then break the bond so nitrogen atom get out ..so now catecholamine become inactive.

  **we can say this enzyme is responsible for breaking all a.a of the catecholamine.

  ****MAO inhibitors** "antidepressant drugs"are used in psychiatric medicine to treat depression .ex.incresing the concentration of DOPAMINE may cause mental defect **.**

  <u>2-COMT catechol oxygen methyl transferase</u> :

  -they add methyl group on the oxygen that found on the ring.



5- Proteins and Peptides :

Ex. -growth factor :IGF,CSF,EPO

-insulin and glucagon

- CNS mediators: neuropeptides ex.opioid

-hypothalamic hormones

****general steps in peptides hormones synthesize:**

-All of them will be synthesis in their inactive form as (preprohormone) then they need at least **two steps** to become active .and this happens by the action of protease enzyme that make two cleavage on the hormone :

1-the first cleavage is usually occurs on terminal peptides (the pre).

2-the second cleavage not necessarily on the terminal ; it may occur in the middle (the pro). ex. In the Insulin, cleavage occurs in the middle of the peptide .

-after the transcription ends ,the protein will be directed to the ER where the first step of activation occurs ,the splitting of the "pre" sequence ,so it produces "prohormone".

** the pre Is the signaling sequence in protein synthesis .

-then it will be directed towards Golgi apparatus where splitting of "pro" occurs so in Golgi the final modification of the structure of the hormone .

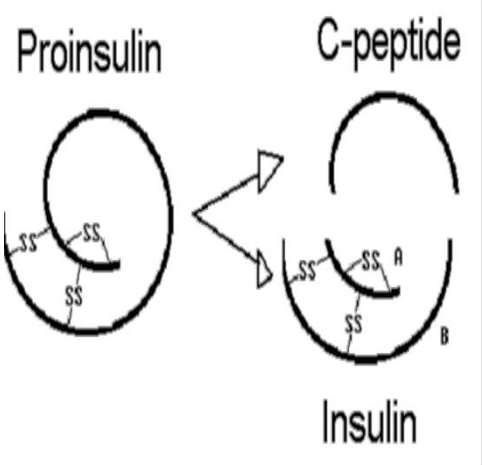
-now the hormone is in its active form .

- then it might be secreted or stored in vesicles (mainly the non-steroid hormones are stored) and released when they cells get triggered by a signal .

** Cells have internal sensors to measure the amount of hormone stored in it in order to know if synthesis/degradation is needed .

-Example on this pathway : Insulin hormone that is released from pancreas .

- **proinsulin structure** :



2 super secondary peptides wrapped around each other , connected by 3 disulfide bridges (*insulin itself has 3 s-s bonds too, two of these are between the peptides and one between the residues of one peptide -look at the figure-)*
** in Golgi proinsulin is converted to insulin by proteolytic cleavage (of the C-peptide) in the middle of it .

** Some hormones have the same precursor polypeptide:

- here the way its broken down, will determine the hormone synthesized according to cutting site.

- One gene may code more than one hormone

–The cleavage depends on specific enzymes

-examples on this :

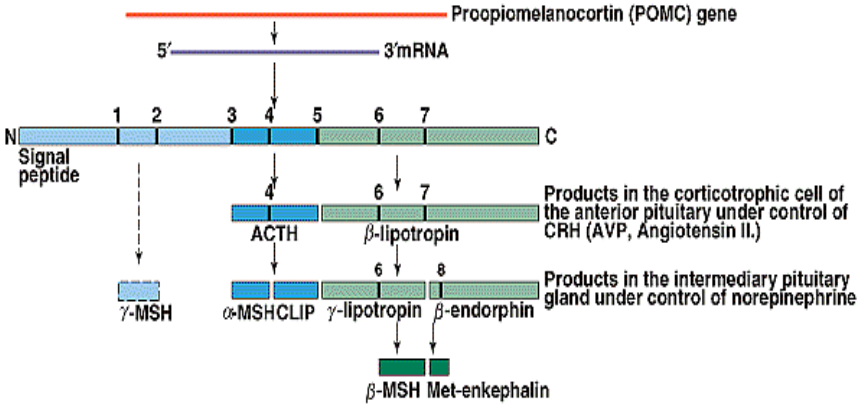
1-Proopiomelanocortin (POMC)

Pro=previous\ opio=opioids\melano=Melanotropin\cortin=Corticotropin

-it's a large precursor that when it's cleaved it gives many hormones.

-POMC can be cleaved enzymatically into the following peptides.

- *N*-Terminal Peptide of Proopiomelanocortin (NPP, or pro-γ-MSH)
- **γ-Melanotropin (γ-MSH)**
- **Corticotropin (Adrenocorticotropic Hormone, or ACTH)**
- **α-Melanotropin (α-Melanocyte-Stimulating Hormone, or α-MSH)**
- Corticotropin-like Intermediate Peptide (CLIP)
- **β-Melanotropin (β-MSH)**
- **Enkephalins and endorphins (opioids)**

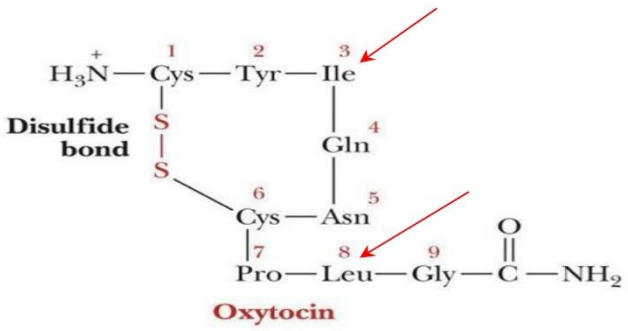


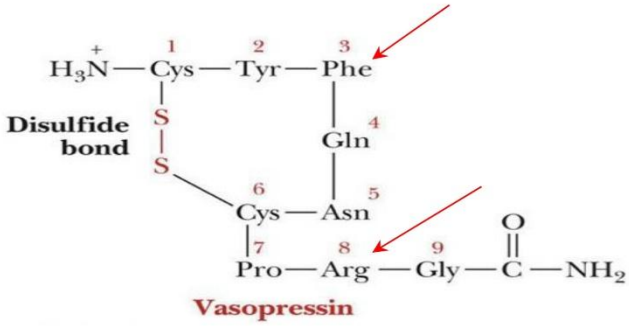
*clinical case:

(I couldn't find a real drug or case like this) المهم الفكرة:p

People who need to increase the ACTH hormone and are given POMC ,they will have an increment in the synthesis of MSH which increases the pigmentation of skin by increasing melanin production in melanocytes.(they will have high production of opioids resulting in an analgesic effect too)

2- Vasopressin and oxytocin (have the same precursor polypeptide)





–Synthesized in separate cell bodies of hypothalamic neurons .

-these two hormone have the same structure which contains 9 carbons and a ring (due to presence of two cystine a.a)'however, they differ from each other in the type of the a.a on position3 \position8.

**Degradation of peptide hormones :

-any hormone that comes from outside and binds on the surface of the cell, it will invade inside the cell as a complex "hormone and its receptors" by endocytosis, then this complex will fuse with lysosome and degraded by lysosomal enzyme .

-hormones that didn't bind to a receptor will be degraded by: **either** the hormone will go to the liver where modification (rearrangement of S-S bridges, cleavage) occurs ,then they are secreted with the bile. **OR** its directly secreted into the urine if their size is small (Renal excretion).

4- Eicosanoids:

-Derivates of arachidonic acid which is a carboxylic acid with a 20-carbon chain and 4 *cis*-double bonds.

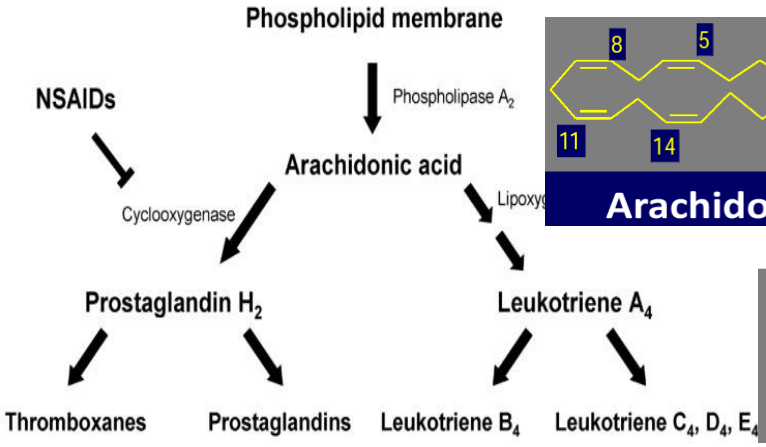
- Arachidonic acid is found in the cell membrane and it can be released by the action of phospholipase A2 enzyme .

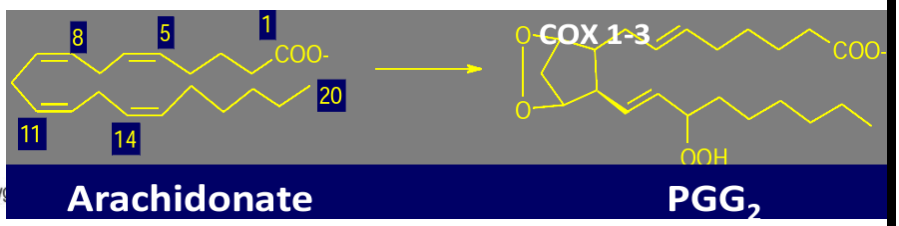
- Arachidonic acid can give many derivatives when it's cleaved inside the cytosol by these two enzyme :

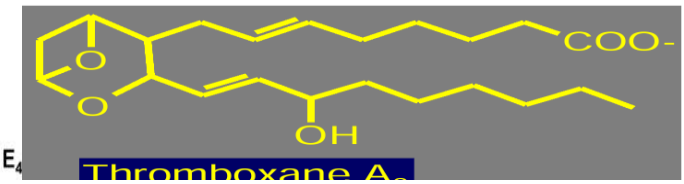
1- **Cyclooxygenase (COX) :**
-Which synthetizes prostaglandines and thromboxanes .

-these hormone not onle cause platlet aggregation ; some of them work as mediators of pains ;;so using a blockers for these enzyme as " aspiren" will reduce the pain .

2- **Lipooxygenase:**
Which synthetizes leukotrienes .







Sorry For any mistakes..

THE END