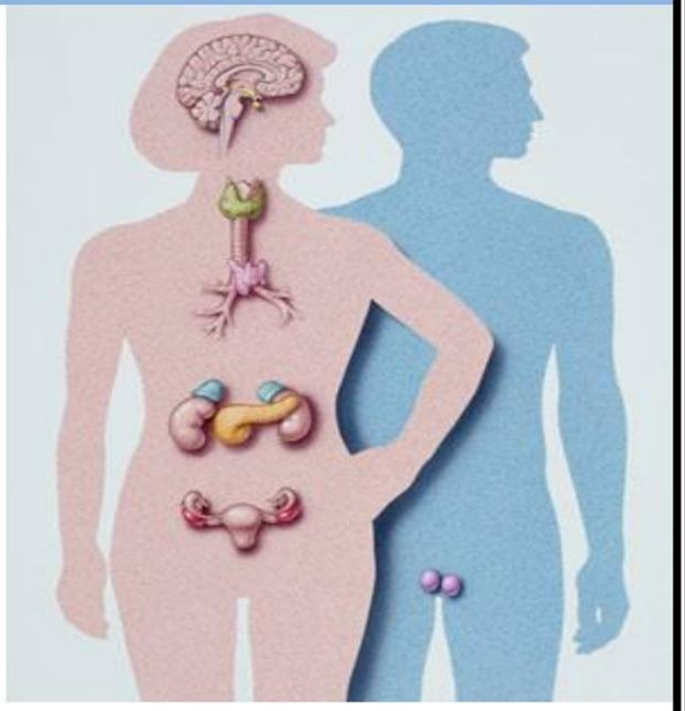
University of Jordan - Faculty of Medicine
(2013-19)

Medical Committee
The University of Jordan

Endocrine System



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

☐ Slide ■ Sheet ☐ Handout ☐ Other

Lecture #: **1**

Date:

Dr's Name: **Nafeth**

Price:

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Designed by: Zakaria W. Shkoukani

INTEGRATION OF METABOLISM: HORMONES & CELLULAR SIGNALING

It`s an easy lecture, I promise..

Before we start

Course Resources are:

1- Harper's Illustrated Biochemistry

2- Stryer's Biochemistry

3- Campbell's Biochemistry

In this sheet you will find everything that was mentioned by the doctor beside its description from the slides so there is no need to return back to the slides. Also, you might find it a long one but that because of pictures sizes which I intended to make them big and clear.

Let`s start! :D

Slide #3 Hormones: The Remote Controllers

Q. What are hormones?

A. They are chemical substances (signaling molecules) produced by glands in multicellular organisms that are transported by circulatory system to target distant organs to regulate physiology & behavior.
P.s Hormones are specific. Also they are secreted in low amounts.

Functions of Hormones:

♣ They help maintain homeostasis.

♣ Mediate responses to external stimuli.

♣ Play roles in growth and development.

Classes of Hormones:

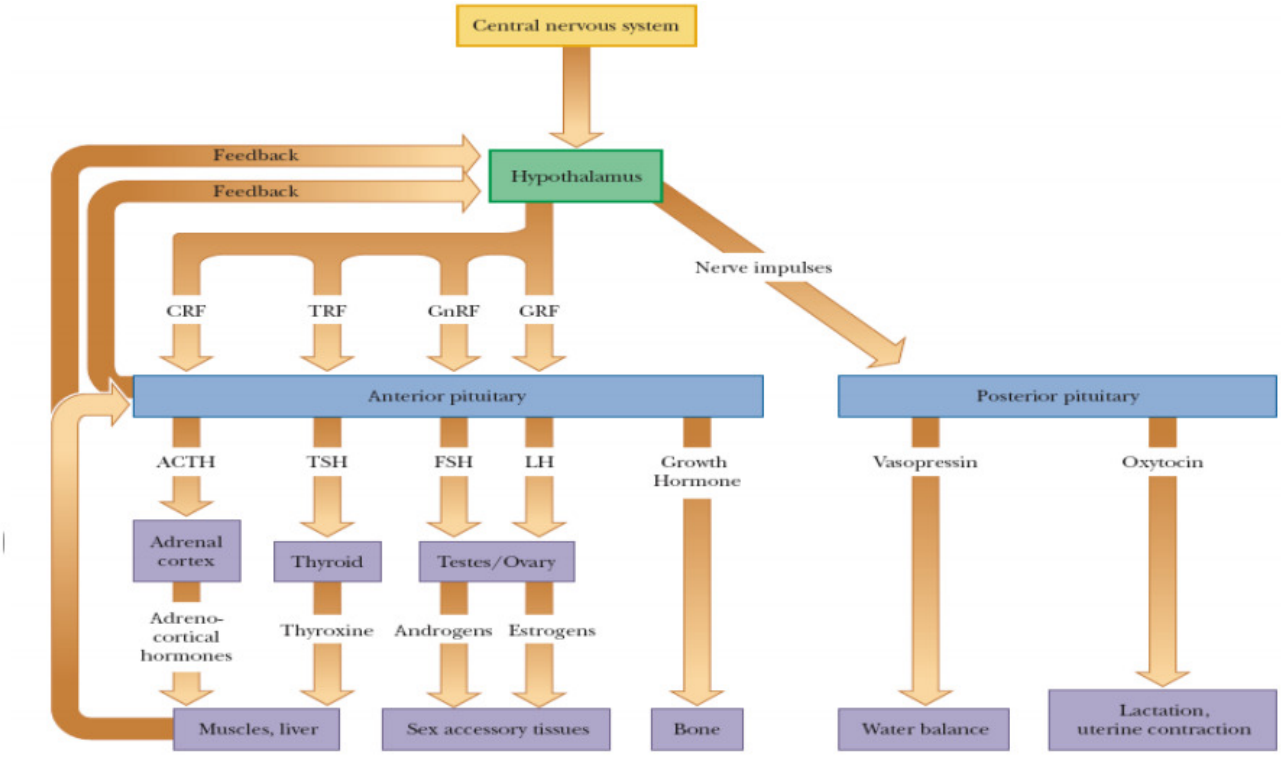
♣ Endocrine hormones: Act at distant places.

♣ Paracrine hormones: Act on nearby cells.

♣ Autocrine hormones: Affecting the same cell that has secreted them.

Slide #4 Nervous vs./ &Endocrine

Two systems act individually and together they share in regulating the whole body`s physiology.



General Notes:

- Hormones affect ALL tissues.

- We have 75 trillion cells, forming 200 types of differentiated cells.

- The integration between the Nervous system & the Endocrine system is that:

a- Endocrine system is regulated by Nervous system.

b- Nervous system gives signals to secrete hormones.

c- Some of the Endocrine system molecules resemble Neurotransmitters and some hormones are made by the Nervous system.

Slide #5 The Target Cell Concept//1

♣ 200 types of differentiated cells in humans. Only a few produce hormones! (<50 known hormones).

♣ All of the 75 trillion cells in a human are targets to one or more.

♣ One hormone → several cell types.

♣ One cell type → several hormones.

♣ One hormone → several effects.

Note: The definition of a target has been expanded to include any cell in which the hormone (ligand) binds to its receptor, regardless of the action.

Slide #6 The Target Cell Concept//2

Target cell: is the cell that will be affected by the binding hormone.

Several factors determine the response of a target cell to a hormone:

1- Factors affect the concentration of the hormone at the target cell.

2- Factors affecting the target cell response.

Let`s start with #1: Factors affect the concentration of the hormone at the target cell.

♣ The rate of synthesis and secretion of the hormone from its source

♣ The proximity of the target cell to the hormone source (dilution). When the target cell is close to the source (gland) the concentration of the hormone would be less diluted, if it was distant the concentration would be more diluted.

♣ The Kd of the hormone – receptor complex

Q. What`s Kd?

A. Dissociation constant. It tells you how much the affinity between the hormone and its target cell.

Rule: When Kd decreases, Affinity increases, so the effect will increase.

♣ The rate of conversion of inactive form to the fully active form. (Time and Amount wise)

♣ The rate of clearance from the plasma.

Slide #7 The Target Cell Concept//3

Now #2: Factors affecting the target cell response:

♣ The number, relative activity, and state of occupancy of receptors (how much these receptors are occupied be the hormone itself).

♣ The metabolism (activation / inactivation) of the hormone in the target cell

♣ The presence of factors within target cell necessary for the response. (Amount & Activity)

♣ Up- or down-regulation of the receptors upon interaction with ligand. Remember: Up = increase, down= decrease.

♣ Post-receptor desensitization of the cell; which is a down regulation

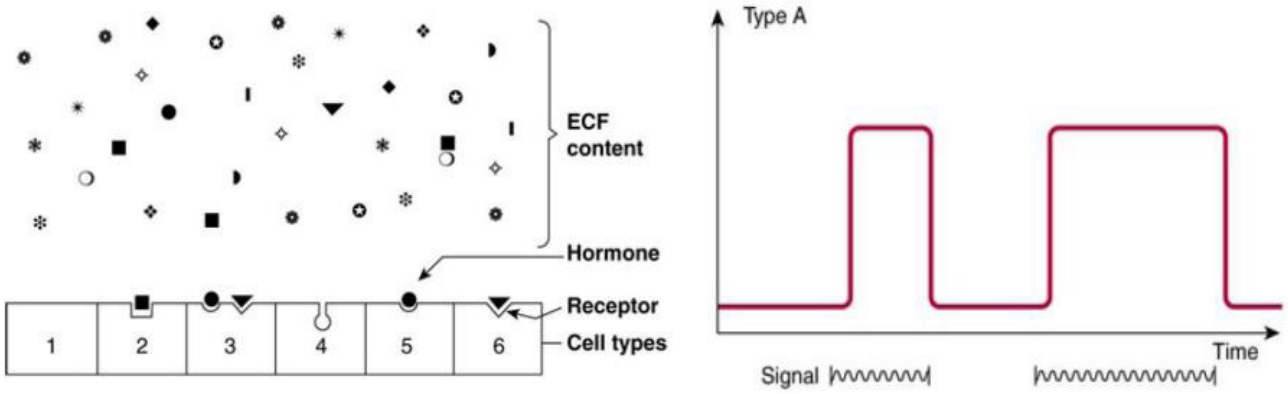
Note: within the target cell, there are other molecules which bind to the message intracellularlly, such as co-repressors, co-activators that might activate or inhibit the message and the effect in the target cell, their

presence, amounts and their activity within the cell controls the action of the hormone at cellular level.

Slide #8 Receptors Discriminate Precisely, Receptors Follow Type A Response

For a cell to bind to a hormone it faces major challenge:

♣ Concentrations of hormones in the blood and ECF is equal to (10^{-15} to 10^{-9} mol/L), these molecules are competing with structurally similar molecules; such as: sterols, amino acids, peptides, and proteins. These closely related molecules are found in higher concentration than the hormone's concentration (10^{-6} to 10^{-3} mol/L) range, so cells face this problem and the binding between the cell and the hormone has to be very specific.



Slide #9 Accordingly; Hormone- Receptor Interactions

Binding between hormone and receptor:

♣ Should be specific: displaceable by agonist (to make an effect) or antagonist (to remove the effect).

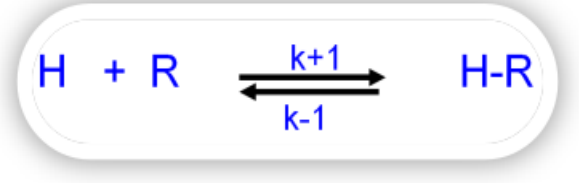
♣ Should be saturable; which means all receptors should be occupied by hormones.

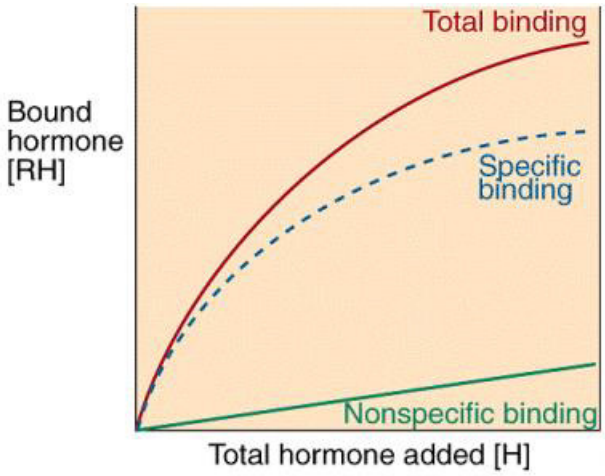
Q. We said the hormone is produced in low amounts, how would cells be saturated with these low amounts of hormones?

A. When hormone binds with the receptor chemically it produces a complex called hormone-receptor complex; there is a constant for its association and another constant for the dissociation of this complex toward its intermediates which are hormone and receptor.

Note: the type of binding between hormone and the receptor is non-covalent interaction so we could have dissociation and the binding will be reversible.

♣ Should occur within the small amount and concentration of the hormone within the ECF.





♣ Association constant Ka

♣ Dissociation constant Kd

♣ Ka = [H-R] / {[H] X [R]}

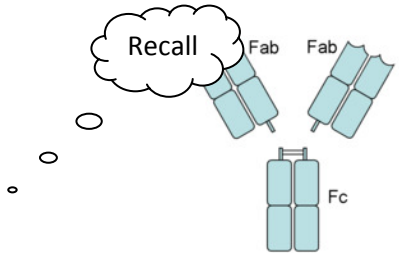
♣ Kd = {[H] X [R]} / [H-R]

♣ Kd values for many hormone range from 10^{-9} to 10^{-11} M (around 10^{-10}, it's very low which means affinity is very high between hormone and receptor). It's a small value, so high binding ability so specific, saturable…etc.

♣For receptors to be saturated with hormones, hormone's concentration should be 20X the dissociation constant (20*kd). Almost 10^{-10} which means that very small concentration of the hormone will produce saturation for the receptors.

** EXCEPTION: we said that hormones have specific bindings with receptors but a few proteins do nonspecific binding.

Slide #10 Receptor Domains



Receptors are proteins. Proteins have functional domains (domain: each part of the protein makes a special folding it order to be functional; this folding is called domain).

Receptors might be in the membrane, inside the cytoplasm, or in the nucleus.

♣ All receptors have at least two functional domains:

1- Recognition domain (hormone binding site); to recognize hormones.

2- Coupling or signal transduction domain; to transfer the signal.

Remember globulins; they have Y-shaped structure, the V shaped portion is to recognize the antigens, whereas the Fc portion transmits the signal

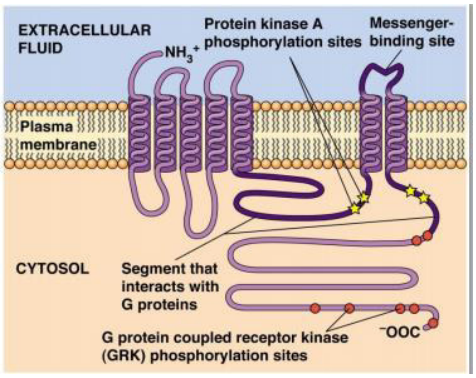
♣ Coupling occurs in two general ways:

1- Changing the activity of an enzyme (Polypeptide & catecholamines, plasma membrane)

2- Direct (steroids, retinoids, and thyroid hormones).. They directly enter the cell because they are lipid soluble. They have cytoplasmic receptors and nuclear receptors, once they bind those receptors, they can bind DNA and increase the transcription of certain genes.

♣ Steroid, thyroid, and retinoid hormone receptors: They have many binding sites:

1)Hormone binding site (to recognize the hormone); 2)DNA binding site; 3)co-regulator proteins binding site (they increase or decrease the activity of the receptor), 4)cellular trafficking proteins binding site.



So each receptor should have at least 2 domains; once for coupling and the other for recognition. Steroid hormone receptors have more domains compared to amino acids and polypeptide hormones receptors.

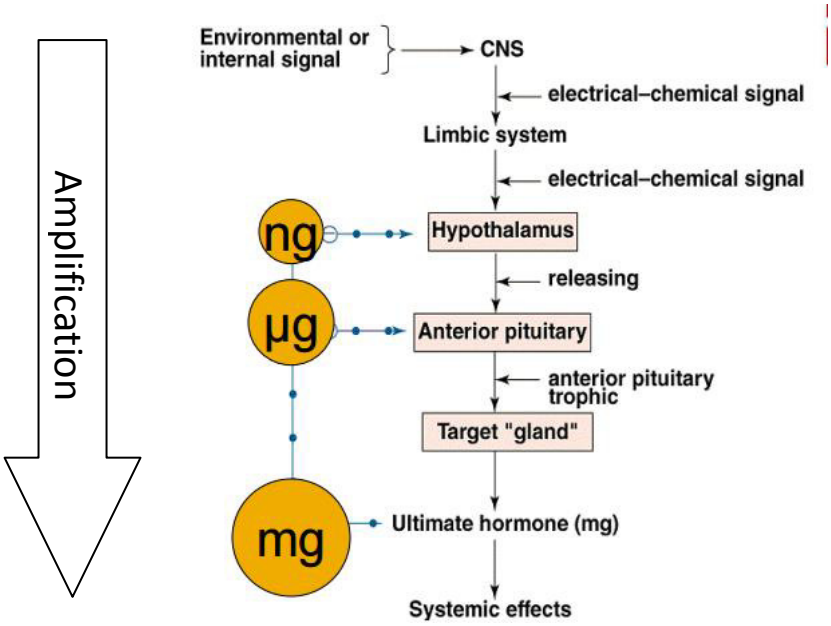
♣ Receptor–effector coupling is the first step in amplification.

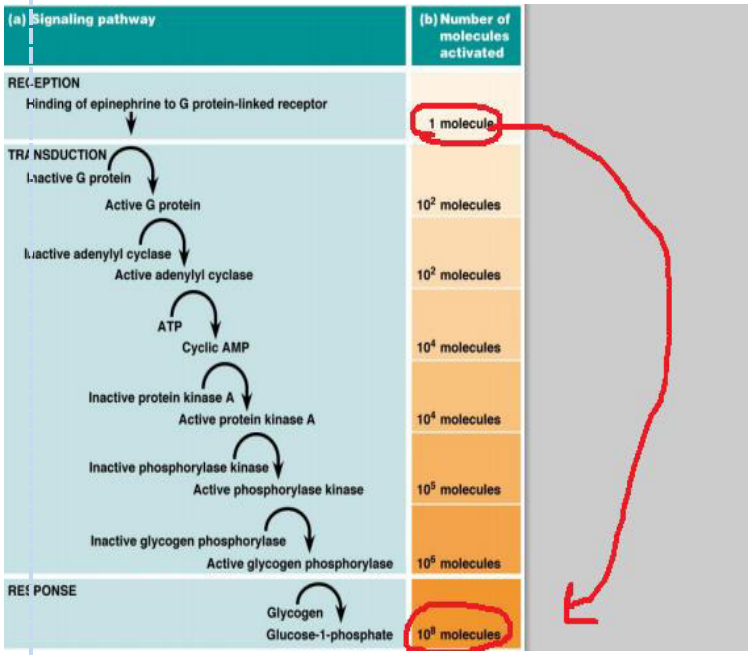
Slide #11 Signal Amplification

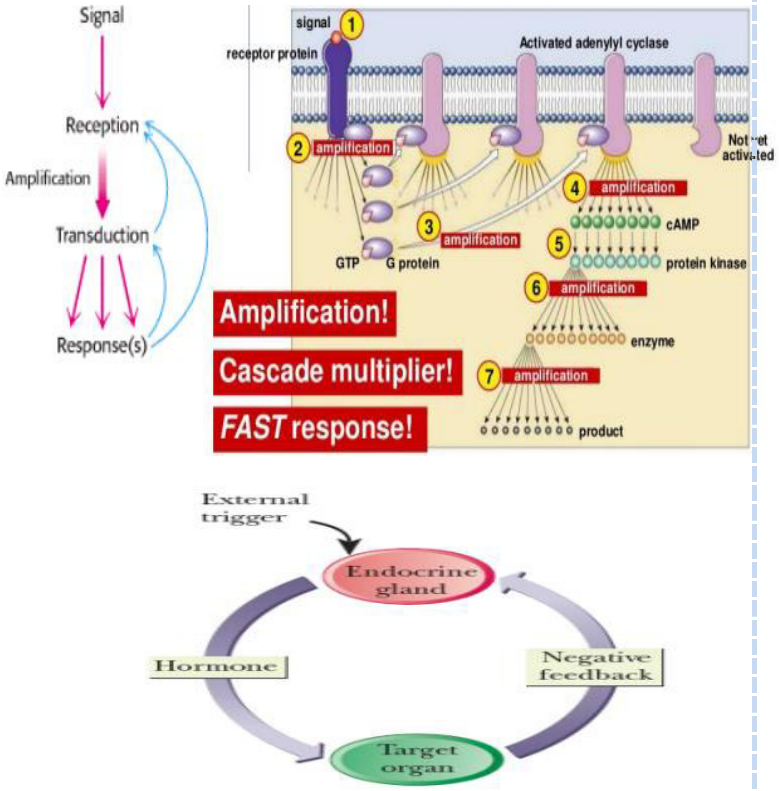
♣ Hormones amplify the action.

♣ When hormones are secreted from hypothalamus, it'll be in nanograms, those are secreted from pituitary are in micrograms, 1 molecules gives you 10, 10 give you 100, 100 give you 1000 so there's amplification, One molecule goes to 10 cells and affect those cells to produce hormones, so there must be an amplification process. Finally the hormone that reaches the cells will be in milligram concentration. To reach the target cells you will have 10^8 molecules if you started with 1 hormone. This is the amplification.

♣ Amplification means less energy use; more action and stronger response.

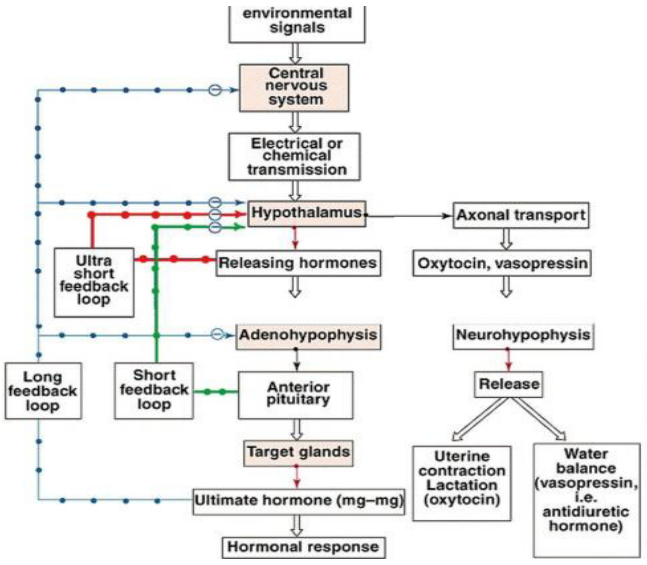






Slide #12 How The Release is Controlled?

♣ Hormones are controlled by feedback mechanism.



♣ **Feedback inhibition:**

a- Ultra short loop: affecting the gland that has secreted it.

b- Short loop: affecting the gland that has secreted the hormone that affected it.

c- Long loop: affecting the first gland which has secreted the first hormone in the series.

Slide #13 Classification of Hormones- Chemical Structure

Hormones were classified according to:

Chemical composition; solubility; location of receptors; nature of the signal used to mediate hormonal action.

According to Chemical Structure:

1- Polypeptides: ALL Pituitary hormones; Hypothalamic releasing hormones; Insulin, Glucagon, Growth factors…

2- Amino acid derivatives: Adrenalin, (dopamine, epinephrine, nor epinephrine, dopa), Thyroid hormones.

Kindly note, the ones between brackets are Tyrosine derivatives.

3- Steroids: Androgen, Estrogen..

Slide #14 Classification of Hormones, According to the Mechanism of Action (more realistic):

1- Hormones that can cross the cell membrane (lipid soluble) and bind to intracellular receptors:

♣ Steroids ♣ Thyroid hormones ♣ Calcitriol (the active form of Vitamin D) ♣retinoic acid (the active form of Vitamin A).
Kindly note all are lipid soluble.

Note: for these hormones to be transferred through the blood from their source to the target they have to be bound to proteins (cholesterol and triglycerides are transferred through blood as HDL, LDL, VLDL..), if lipids are transferred alone in the blood, atherosclerosis occurs (fat embolism), after you break a bone you will be afraid of having fat embolism, fats is coming from bone marrow through the blood, it goes to the arteries of the lungs causing death. These hormones that have intracellular receptors move through blood by transport proteins, at the same time they have

long half life and their action is slow. (they have long half life because they are bound to proteins. Their action is slow also because they are bound to proteins)

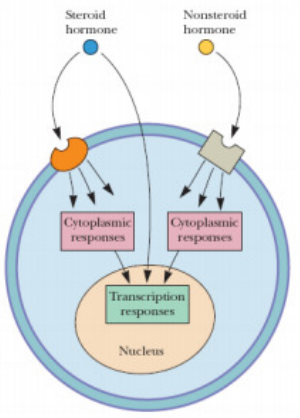
2- Hormones that bind to cell surface receptors, they cannot cross membranes and they move through blood by themselves without proteins, they transfer their messages through second messenger; the first messenger is the hormone itself

(these hormones are classified according to second messenger):

♣ cAMP (β adrenergic factor, glucagon, ACTH) ♣ cGMP (atrial natriuretic factor, Nitric oxide) ♣ Calcium or phosphatidyl inositol (oxytocin, TRH) ♣ Kinase or phosphatase cascade (insulin, GH)

Slide #15 General Features of Hormone Classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow *	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, kinase cascades, metabolites of phosphoinositols



* Because they are bounded to proteins.

Slide #16 Hormones Classes- Steroid Hormones

A- Sex hormones - are divided into 3 groups

1. Male sex hormones or Androgens

2. Female sex hormones or Estrogens

3. Pregnancy hormones or Progestines

B- Hormones of Adrenal Cortex

1. Mineralocorticoids: aldosterone. ...

2. Glucocorticoids: cortisol. ...

3. Adrenal androgens: male sex hormones mainly dehydroepiandrosterone (DHEA) and testosterone

Slide #17 Hormones Classes- Non- Steroid Hormones

A- Peptide and protein hormones : All hypothalamic, pituitary, digestive hormones. all peptide and polypeptide hormones their amino acid content is small.

ϖ All pituitary hormones are made from single (short, small) polypeptide chain EXCEPT: TSH; FSH; LH

Note: TSH, FSH & LH are big, homodimers and they are attached to glycoproteins (≈ 25 kDa).

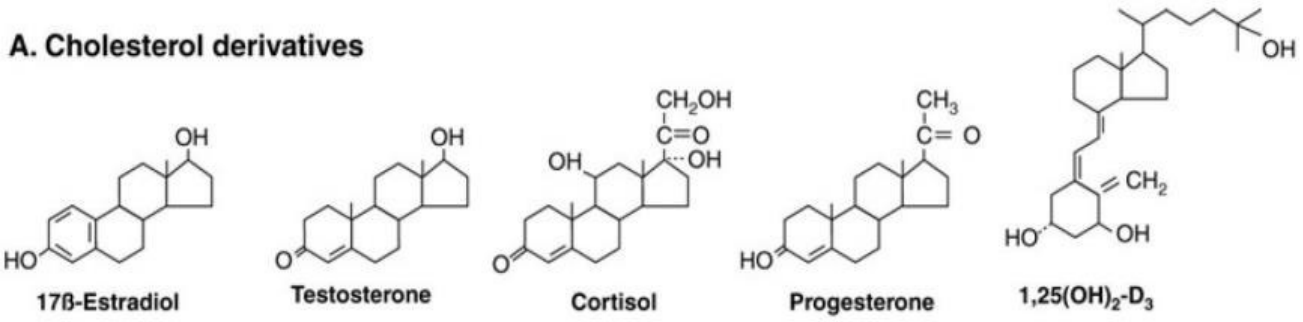
B- Amino acid derivatives

Amines - derived from tyrosine or tryptophan.

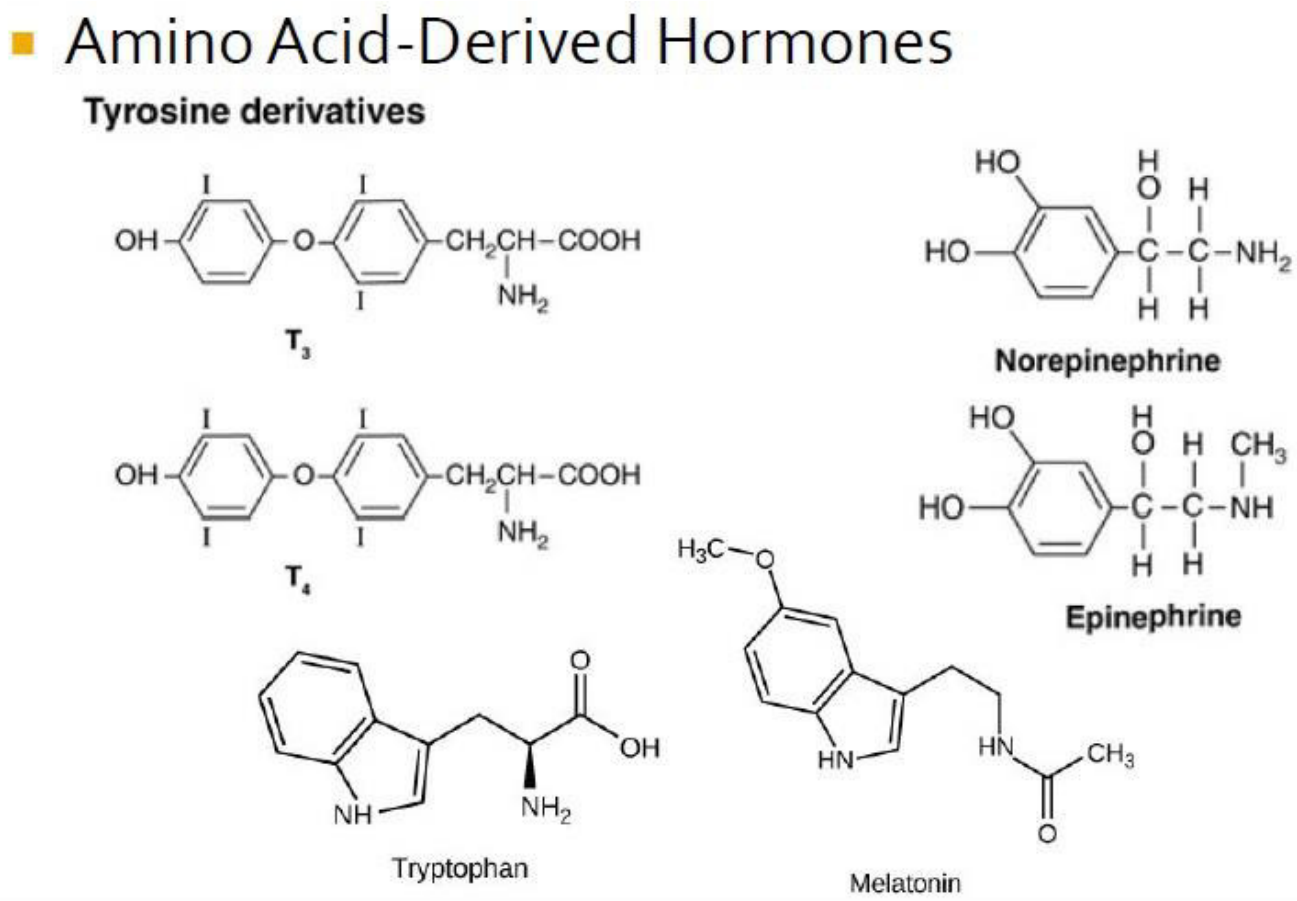
Ex: TH, dopamine, epinephrine, melatonin (melatonin controls day and night cycle. It induces sleep. But it has adaptation problem).

Slide #18 Structure of Hormones//1

Lipid – soluble hormones: Cholesterol is their origin, according to the constituent that is attached to the cholesterol ring you will have deferent steroid hormones.



Slide #19 Structure of Hormones//2



You should know the structures above.

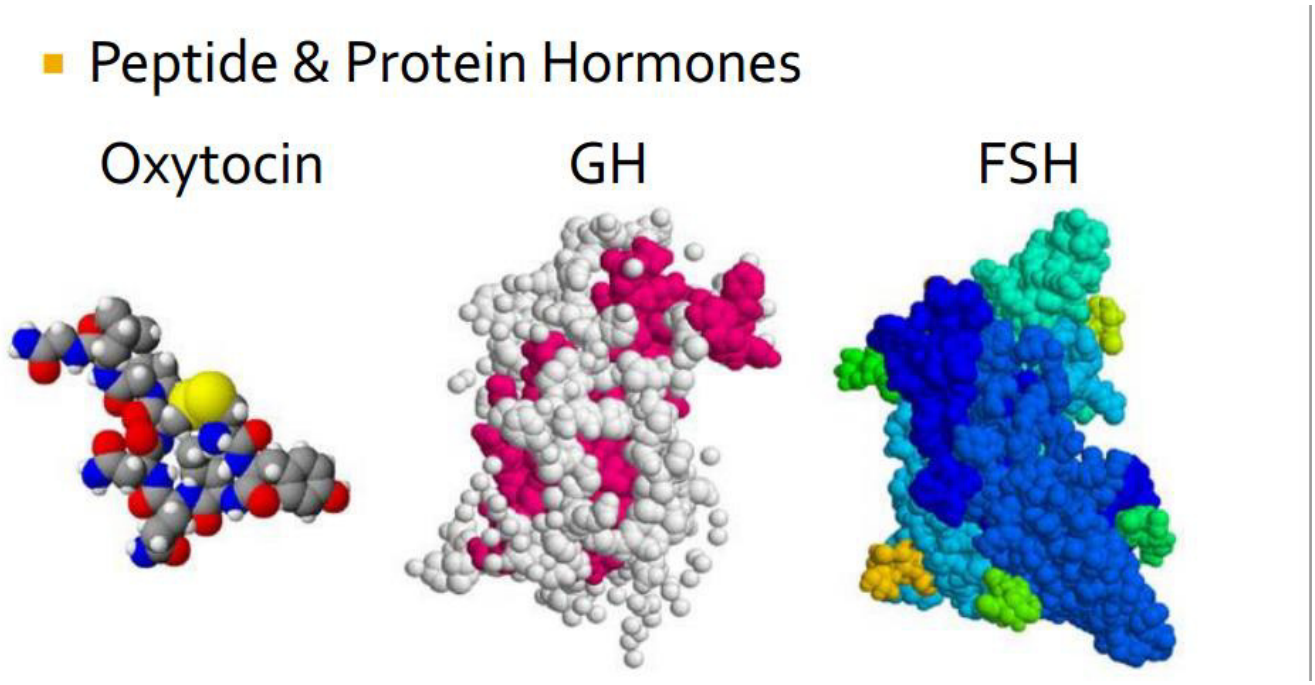
Notes:

1- Tyrosine has a ring and an OH, thyroxine has 2 rings, the second ring is attached to the first by OH and there is modification on these rings by iodine

2- Epinephrine and nor epinephrine differ from each other by the methyl group. norepinephrine has no methyl group

3- The 2 rings in the Tryptophan are called Indole Ring.

Slide #20 Structure of Hormones//3



Notes:

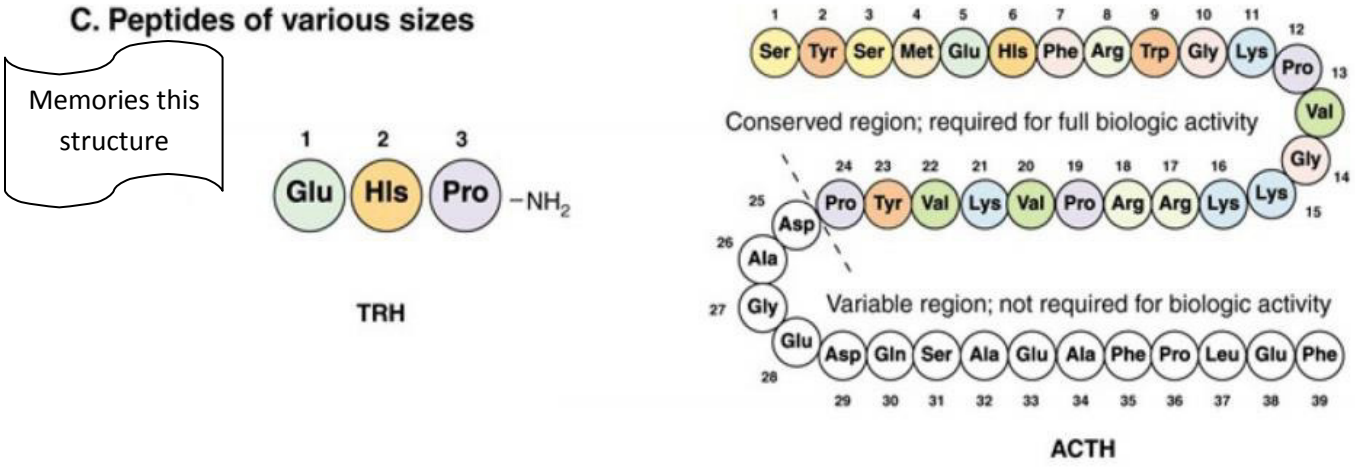
1- Oxytocin causes contractions in smooth muscles ex. Uterus and mammary glands.

2- Oxytocin has 9 small amino acids.

3- GH and FSH are big hormones. (glycoproteins), LH is also a glycoprotein

Slide #21 Structure of Hormones//4

- Peptide & Protein Hormones



Thyrotropin releasing hormone is the smallest peptide hormone, it's composed of 3 amino acids glutamic acid, histidine and proline

ACTH structure has 2 parts constant and variable

Slide #22 Structure of Hormones//5

There is a table in the slides, the only thing you need to know from it is that TRH (Thyrotropin Releasing Hormone) is the smallest hormone, consisting of 3 amino acids only. Vasopressin (ADH) prevents the excretion of water through kidneys, it's secreted from the posterior pituitary.

Slide #23 Synthesis of Peptide Hormones//1

From precursor polypeptides.

♣ One gene (is the source) may code more than one hormone (POMC)

POMC: Proopiomelanocortin

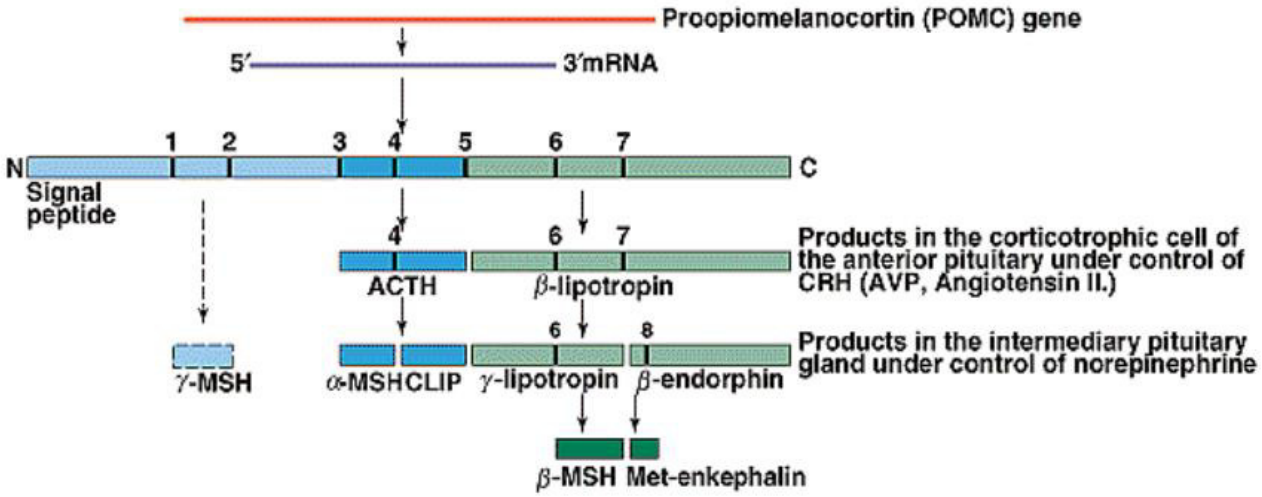
-pro: before (inactive)

-opio: opioid (anesthetic drug related to morphine)

-melano: melanin -cortine: gene

POMC gives MSH, ACTH (that gives corticosteroids of adrenal glands), lipotropin (that gives enkephalines that work as analgesics; 2 types methionine and Leucine) and endorphin.

♣ The cleavage depends on specific enzymes.



Slide #24 Synthesis of Peptide Hormones//2

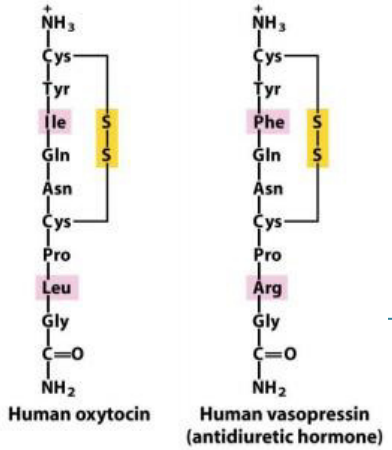
From precursor polypeptides.

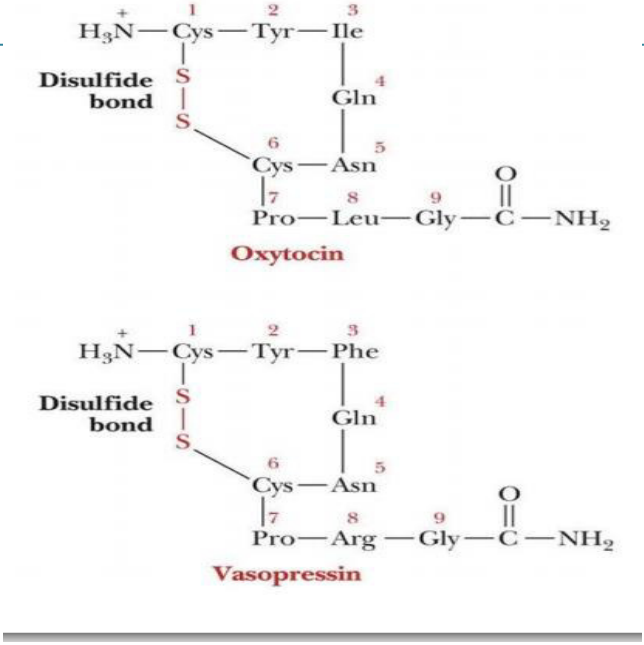
♣ Vasopressin (to retain water) and Oxytocin (smooth muscle contraction).

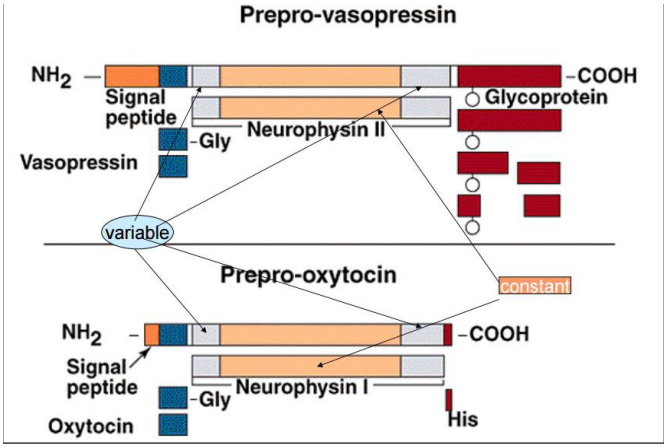
Both are secreted from the posterior pituitary gland. Also, they are composed of 9 amino acids and the same gene made them but in different locations in the posterior pituitary.

♣ Synthesis in separate cell bodies of hypothalamic neurons.

They differ at amino acid #3 & #8

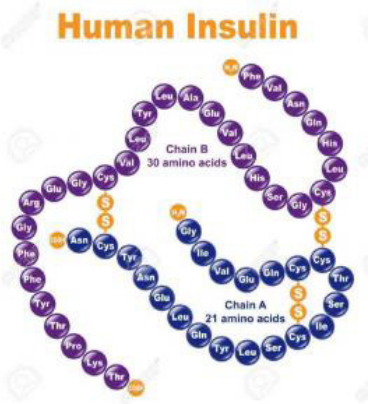






Slide #25 Synthesis of Peptide Hormones//3

Slide #26 Synthesis of Peptide Hormones//4



Sometimes you produce hormones as pre-pro-hormones, you don't want it to be active all the time, you want it to be ready to use it when it's needed without being created and produced from the beginning to save time

Like insulin, it's created as long polypeptide, then it undergoes post-translational modification, it loses the signal peptide and insulin goes outside the cell, then fragmentation occurs on one piece (c peptide), insulin loses the c

peptide then we end up with 2 polypeptide chains connected to each other through disulfide bonds.

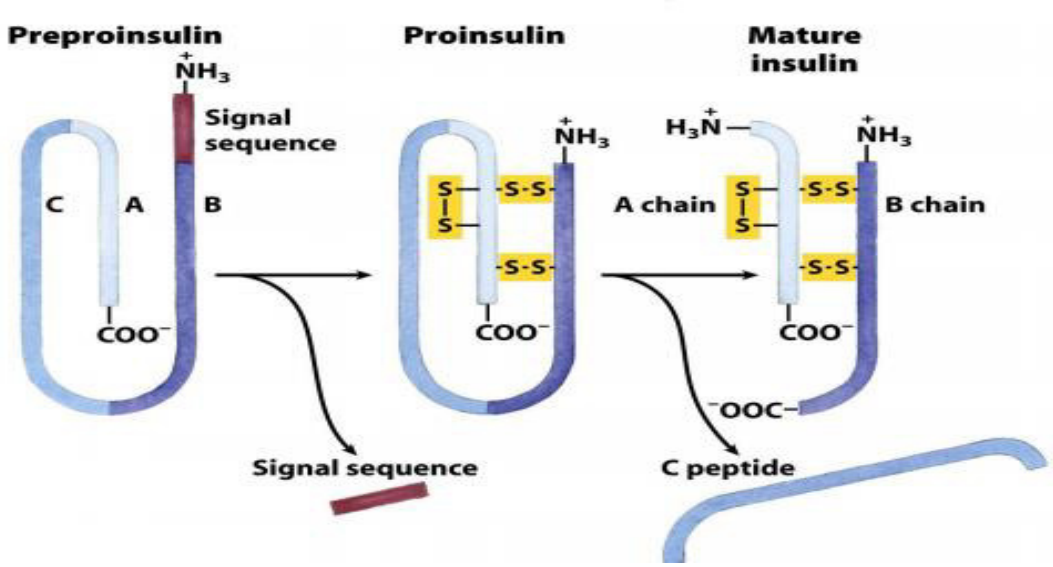
* Peptide & Protein Hormones

* From Pre-pro-hormones

* A larger precursor preproinsulin
♣ 23 aa signal sequence ♣ 3 disulfide bonds

* Pro-insulin
♣ Remove the C peptide

* Mature insulin
♣ A and B chains



Now we are done! :D
Sorry for any accidental mistakes.

Always remember that one day you will be at the place you always wanted to be.
Don`t forget me from your dua!