◉Sheet ○Slides

Number

24

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We were talking last time about receptors for lipid soluble hormones.The general mechanism of receptors for lipid soluble hormones:

1. Receptors of lipid soluble hormones are located in intracellular compartment.
2. Lipid-soluble hormones are found in the plasma membrane and are carried on protein transporters (because proteins are water-soluble), they travel in the blood until they reach the **target cell** then the hormone dissociates from the carrier protein to pass through lipid component of the target plasma membrane.
3. When lipid-soluble hormones bind to their receptors either in the Cytoplasm or the nucleus they will form **Hormone-receptor complexes.**
4. **Hormone-receptor complexes** will go to their target place in the DNA, exactly in a specific region of the DNA called **HRE(hormone responsive element),** located adjacent to the gene that will be transcribed.
5. Once they are bound to **HRE,** they will stimulate the transcription and translocation of particular genes forming new proteins that can change the behavior of the cell.

Hormones That Bind to Nuclear Receptor Proteins

Lipophilic steroid and **thyroid hormones** are attached to plasma carrier proteins.

Hormones dissociate from carrier proteins to pass through lipid component of the target plasma membrane.

Nuclear Hormone Receptors:

Receptors for the lipophilic hormones are known as nuclear hormone receptors.Steroid receptors are a type of nuclear hormone receptor, they are located in cytoplasm and in the nucleus. They function within the cell to activate genetic transcription.

Messenger RNA directs synthesis of specific enzyme proteins that change metabolism.

Each nuclear hormone receptor **has 2 regions**:

1- A ligand (hormone)-binding domain.
2- DNA-binding domain

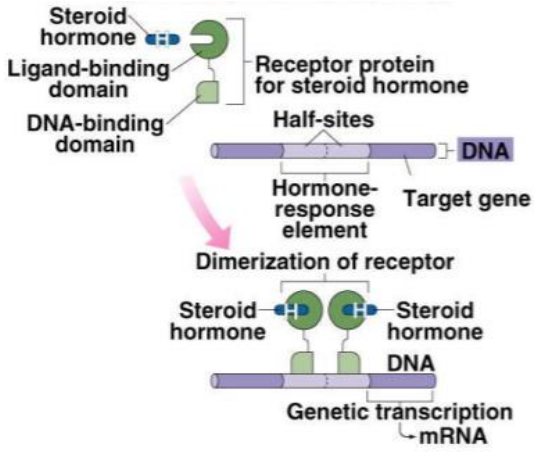
Receptors must be activated by binding to a hormone before binding to the specific region of the DNA (**HRE**)**.**

***Inactivated receptors** bind to **lipid hormones** then they bind to **HRE** to be **activated**, So Receptors and hormones don't work alone they work together.

*After the binding of receptors with lipid hormones, **Dimerization** will occur which Stimulates transcription of particular genes in the DNA to form proteins like hormones, channels, enzyme,… etc.

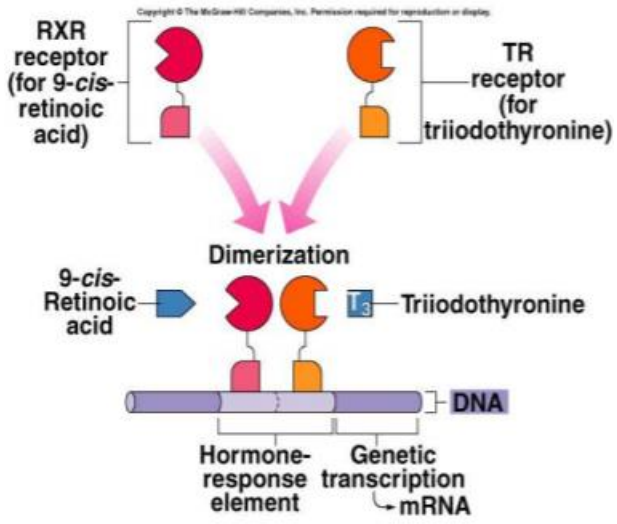
Dimerization: process of two receptor units coming together at the two half sites.

Mechanisms of Steroid Hormone Action



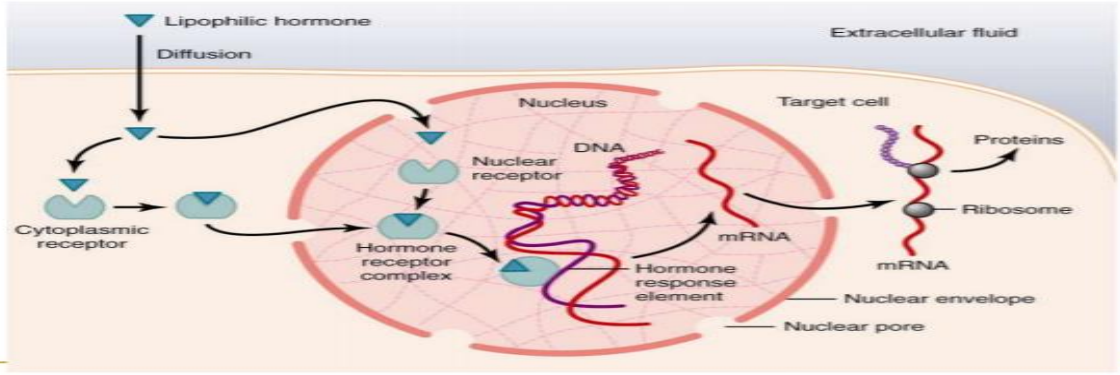
1. Cytoplasmic receptor binds to steroid hormone.2. Translocates to nucleus.3. DNA-binding domain binds to specific HRE of the DNA. 4. Dimerization occurs.5. Stimulates transcription of particular genes.

Mechanism of Thyroid Hormone Action

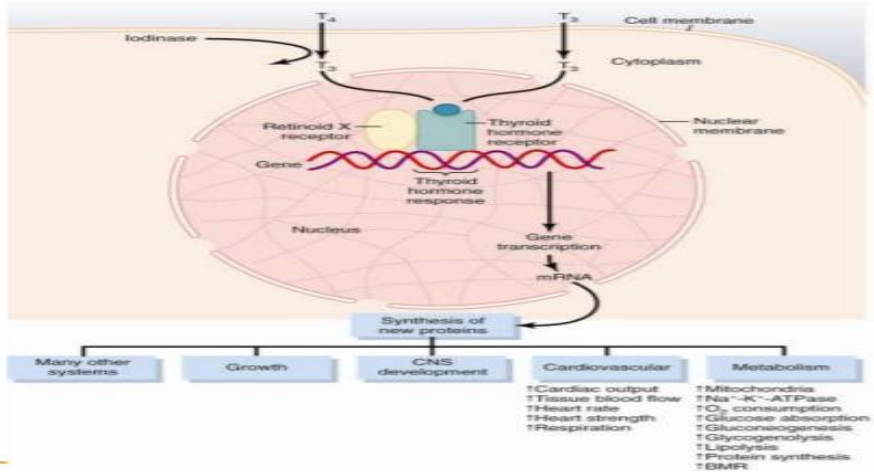


1. T4 passes into the cytoplasm and is converted to T3 (because T3 is 3 times more active than T4.) **2**. Receptor proteins located in nucleus: T3 binds to ligand-binding domain, Other half-site is vitamin A derivative (9-cis-retinoic acid). **3**. DNA-binding domain can then bind to the half-site of the HRE: Two partners bind to the DNA to activate HRE. **4**.Stimulates transcription of genes.

Steroid & Thyroid Hormones – Mechanism of Action



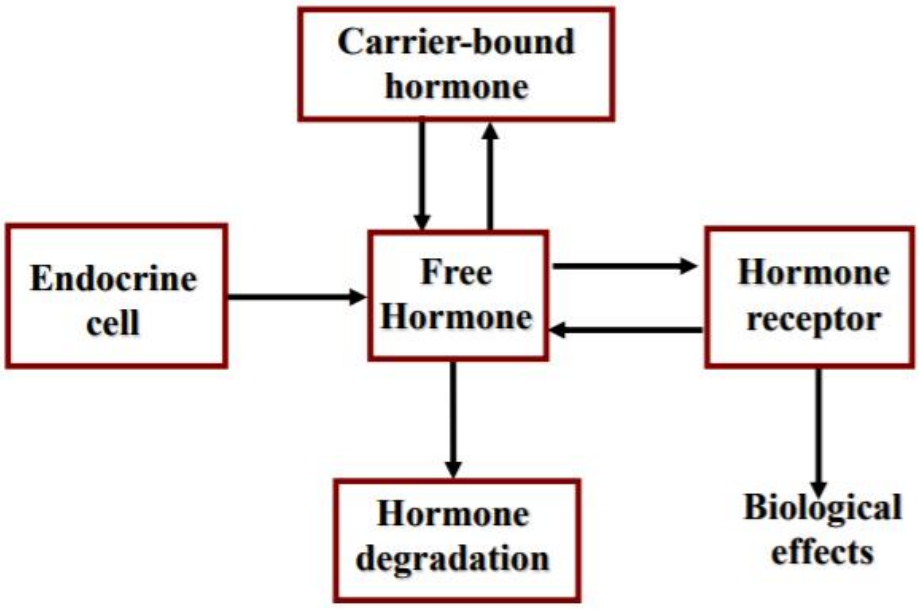
Actions of Thyroid Hormones



Free Hormones

Free hormones are *balanced* in equilibrium with bound hormones.They are secreted from Endocrine cells then bind to hormone receptors.All free hormone can be degraded, for example if the hormone is protein it can be hydrolyzed, if it is lipid it will be degraded in the liver like Testosterone.

Determinants of Free Hormone Receptor Binding



In **the Half-life** for hormones, lipid soluble hormones usually have ***longer*** half-life than protein hormones.

Note: Insulin has a short half-life that's why it is bounded with compounds to prolong its half-life in for diabetic patients.

Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

MCR = (mg/minute removed) / (mg/ml of plasma) = ml cleared/minute

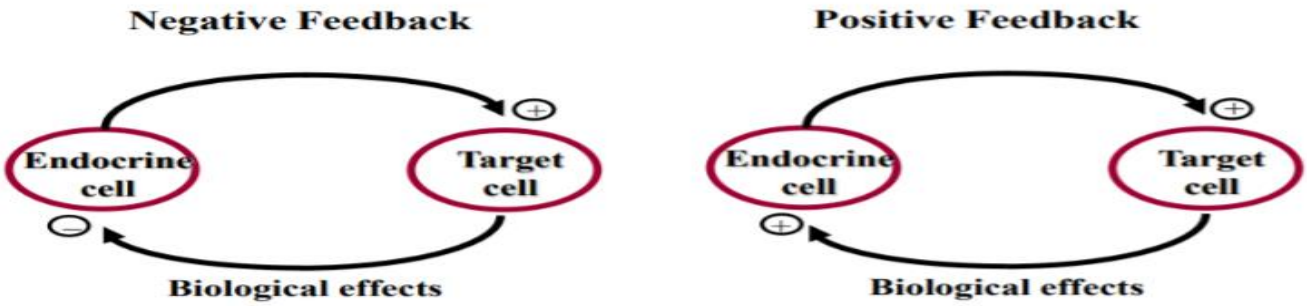
Circulating Transport Proteins

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

Transport proteins for lipid-soluble hormones could be ***specific*** or ***nonspecific***

Hormones are usually regulated by Negative Feedback.

Feedback Mechanisms



Special receptors

Enzyme linked receptors:

1- *Leptin receptors*: Leptin is a peptide which has a specific receptor on its membrane, its receptor has 2 subunits Alpha & Beta.When Leptin binds to its subunits in the extracellular part of the receptor, it causes phosphorylation and activation of kinase called (JAK2:Just Another Kinase).The activation of JAK2 causes phosphorylation of signal transducer and activation of transcription (STAT) proteins. (for more information, check the slide page126).

2- *Serine/Threonine kinases* : TGF-beta Receptor.

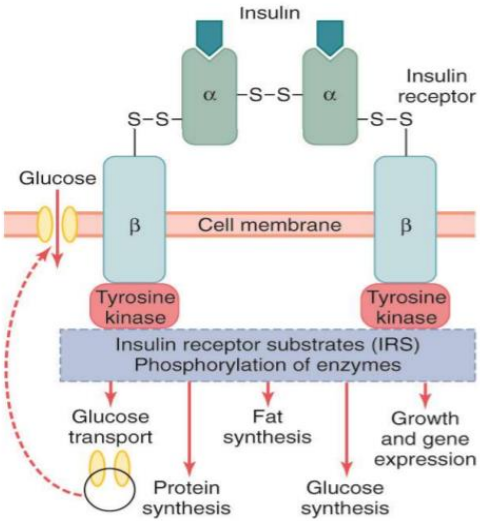
3- *Gunaylyl cyclases* : ANP Receptors, synthesize cGMP from GTP.

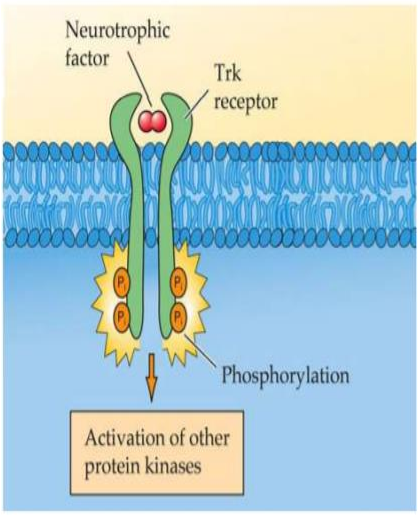
**ANP : Atrial natriuretic peptide is secreted from the heart to increase the secretion of Na+

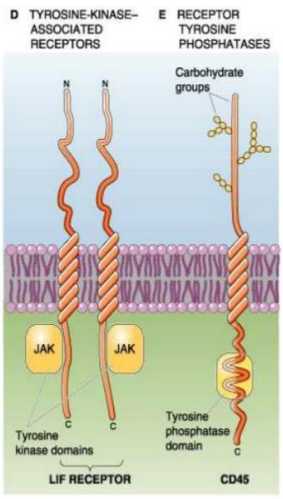
4- *Tyrosine Kinases*:

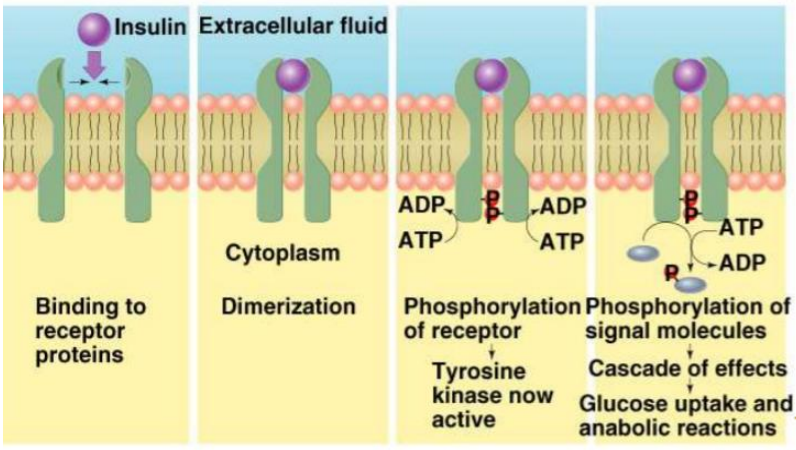
Insulin receptors and NGF receptors are examples of Receptor Tyrosine Kinases (RTKs). Insulin receptor consists of 2 units that dimerize when they bind with insulin, Insulin binds to ligand–binding site on plasma membrane, activating enzymatic site in the cytoplasm. Alpha subunit of insulin receptors is exposed to the extracellular part and they dimerize when they bind with insulin, those dimers are connected by disulfide bridges.

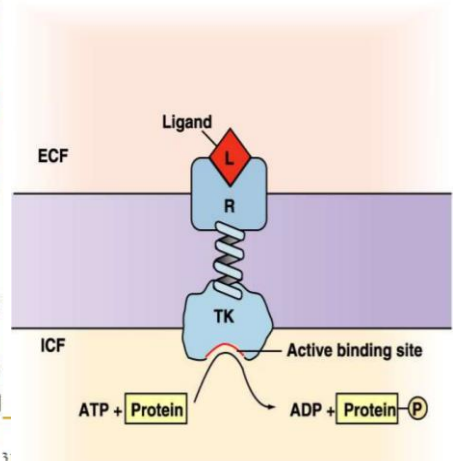
Autophosphorylation occurs to Beta subunits, increasing tyrosine kinase activity. Activates signaling molecules, stimulates glycogen, fat and protein synthesis and Stimulates insertion of GLUT-4 carrier proteins.











→ phosphorylation of insulin substrates may act on a gene to form new proteins, induce an enzyme (change in metabolism), or open a channel. Opening of channels increases K+ influx into the cell (K+ is very important for the heart, it changes membrane potential). So, we

must be very careful when giving insulin to a patient as it decreases K+ concentration in the blood .Hyperkalemia can be treated with insulin

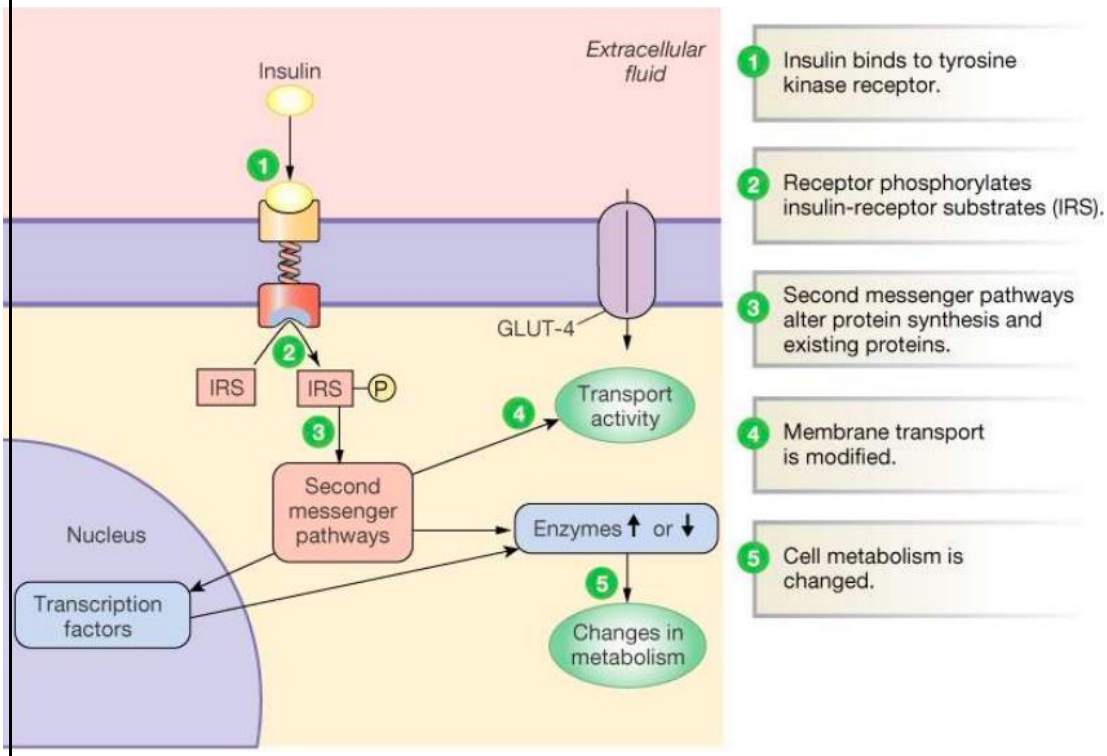
Examples on hormones that act on membrane receptors:

1- **Insulin**

Insulin has 2 peptide units; one peptide is formed of 30 amino acids and the other of 21 amino acid [51 amino acids = peptide not a protein]. Each insulin has one C peptide which is very important because it connects the alpha unit to the beta unit. C peptides are generally found in amounts equal to insulin because they are linked together when first made by the pancreas.

Measuring insulin→if a patient is taking insulin, it is important to know how much his pancreas secretes insulin "endogenous insulin". Insulin may be secreted or ingested. To measure the secreted insulin only, the level of C peptides is measured rather than the level of insulin in the body.

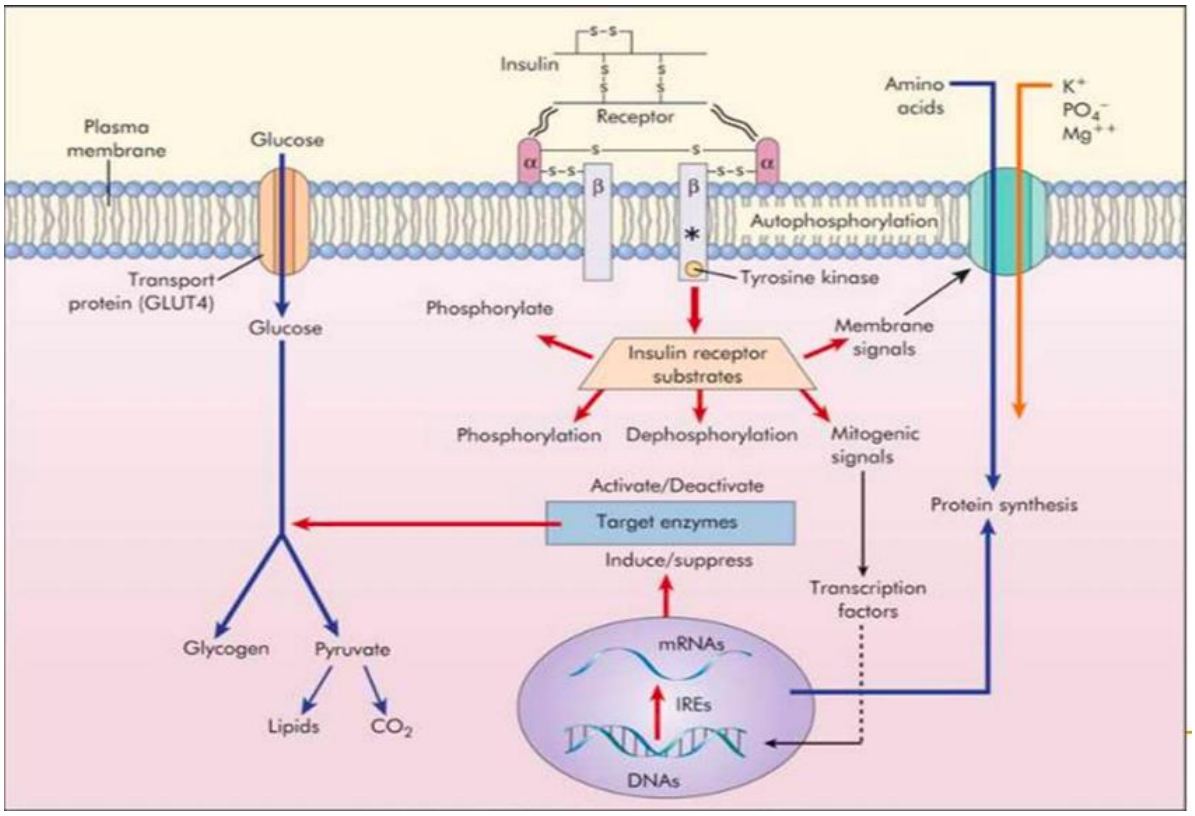
Summarizing insulin action:



growth(insulin deficiency may cause decreased growth)

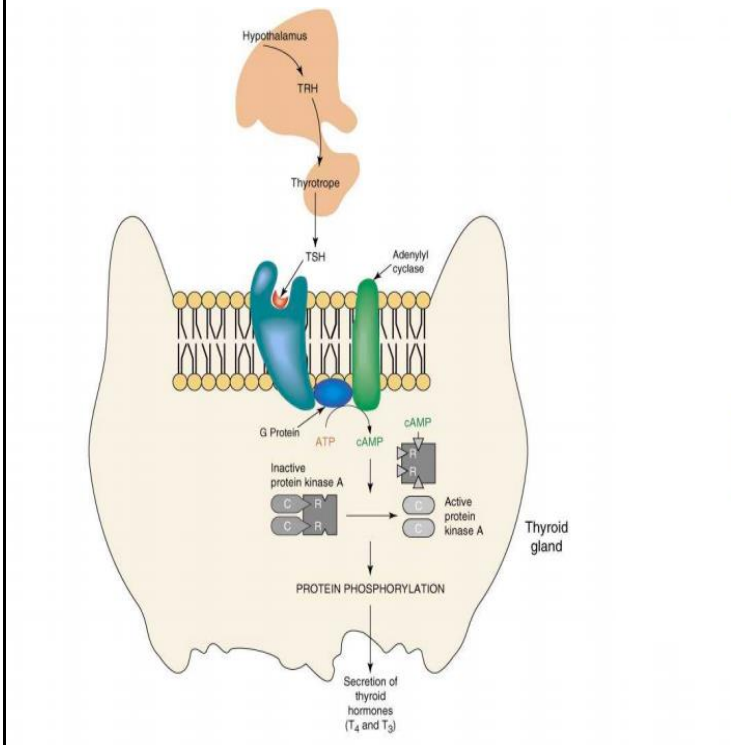
4)If hyperglycemia: increase in glucose transport into the cells

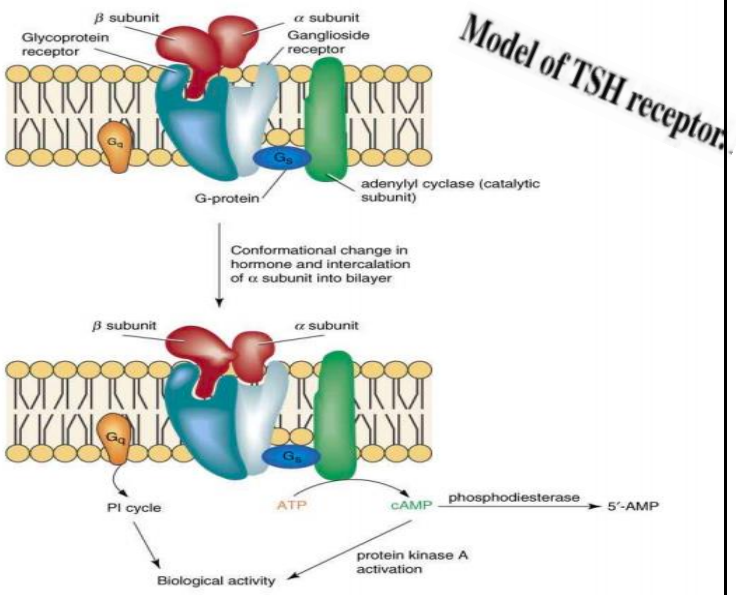
Note: insulin sometimes is called growth hormonelipo



2- TSH thyroid stimulating hormone

It is a **glycoprotein** secreted by pituitary gland, the target cells for TSH are the thyroid cells.(ALL Glycoproteins have the same alpha subunit but have different beta subunits





TSH receptor is beta receptor (not alpha), this receptor acts on G-protein which will act on adenylate cyclase in order to produce cAMP from AMP.cAMP will then activate protein

kinase A which will phosphorylate proteins causing secretion of thyroid hormone T_3 andT_4. phosphodiesterase stops the process by convertingcAMP into 5'-AMP.

3- LH luteinizing hormone

A glycoprotein (has Alpha and Beta subunits).

4- GTRH (GnRH) gonadotropin releasing hormone

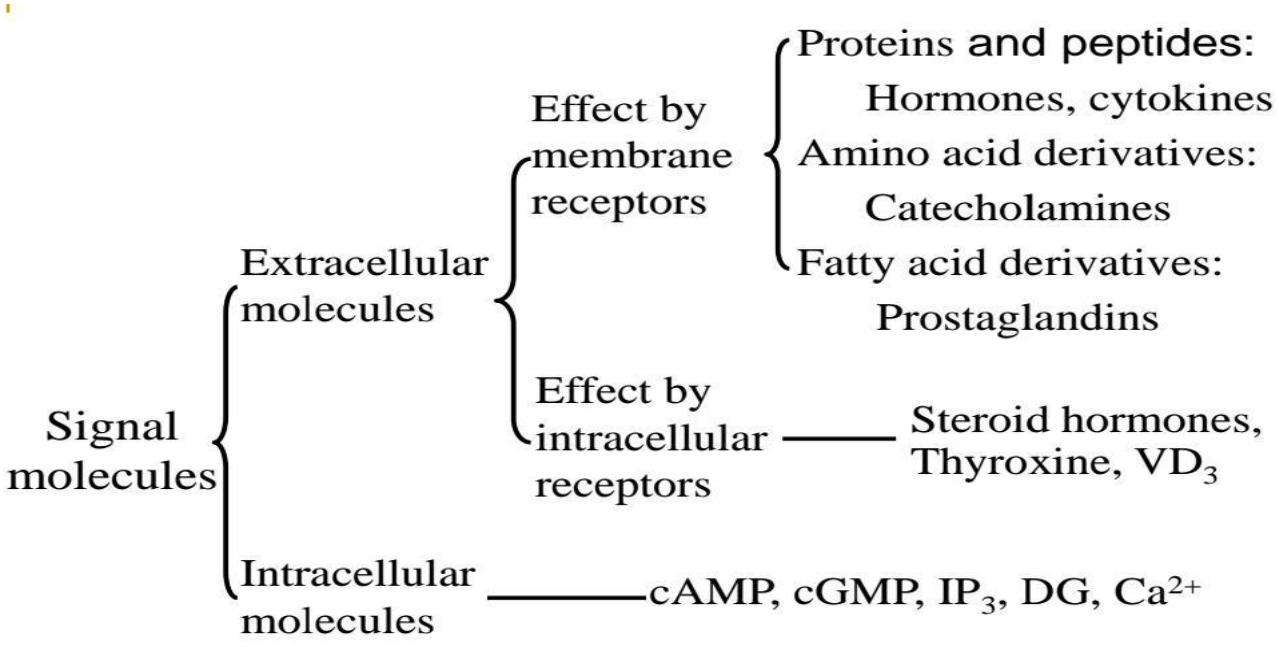
GnRH is a **deca-peptide** released by the hypothalamus, activates the secretion of Gonadotropins : FSH and LH, from the anterior pituitary.

It activates phospholipase C 》 》 converts PIP2 to IP3 + DAG 》 》 IP3 releases Ca++》 》 Ca++ and DAG activate protein kinase C.

Third messenger

molecules which transmit messages from the outside to the inside of the nucleus or from the inside to the outside of the nucleus, also called *DNA binding protein.*

The summary of signal transduction :



You might find this useful :

https://quizlet.com/127850179/mechanisms-of-lipid-and-water-soluble-hormone-action-flash-cards/

good luck