بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

PHYSIOLOGY

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

Final | Lecture #

Receptors' Functions and Signal Transduction L4

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Hamza Saraireh

Reviewed by : Ahmad Mohy

Color coding used in the modified:

- *Black: the original slides*
- *Blue: the doctor's explanation/words*
- *Gray: additional information and explanation*
- *Red: important information*

Receptors Functions and Signal Transduction- L4- L5

Faisal I. Mohammed, MD, PhD

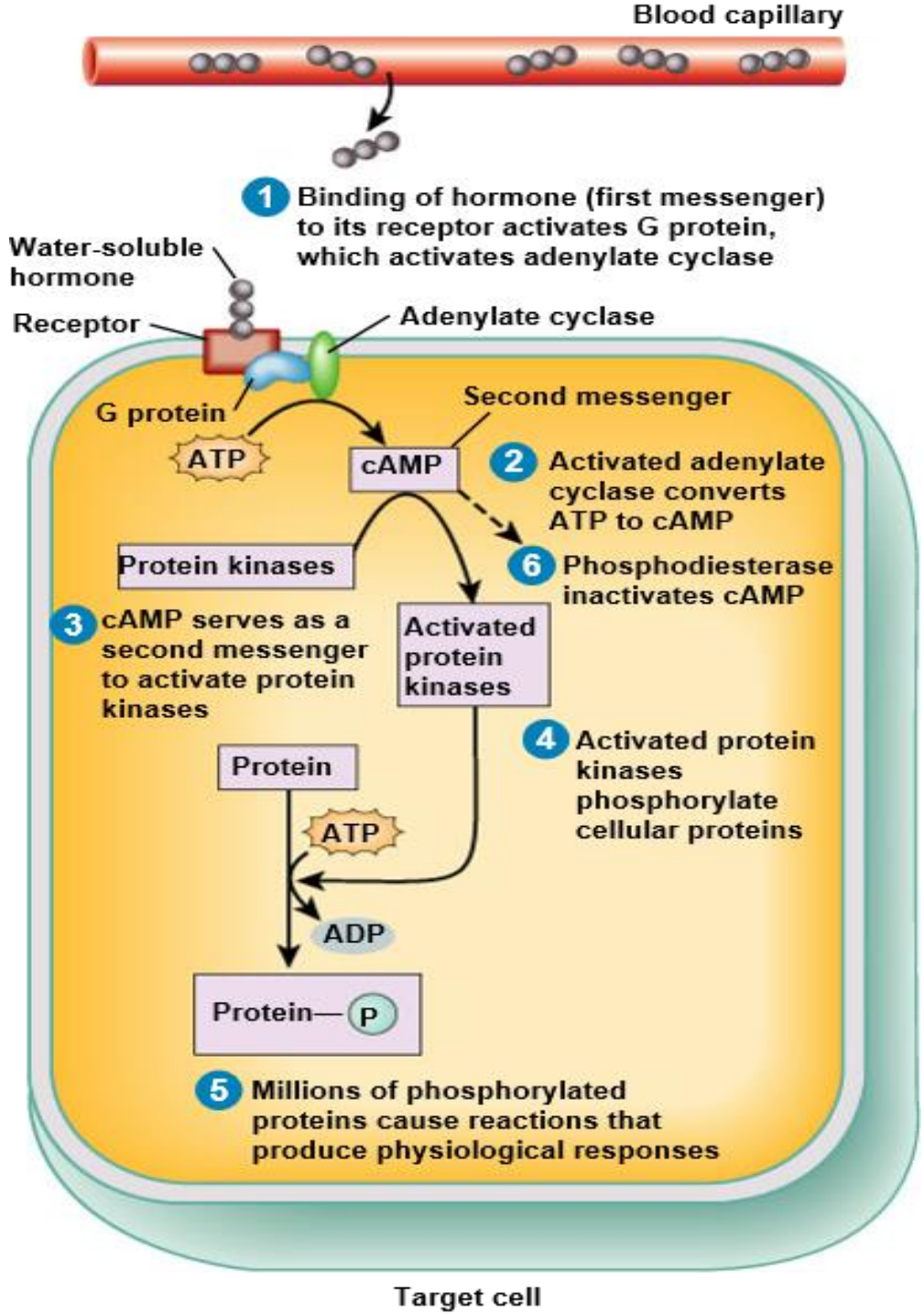
- **Receptors superfamilies:**
- Ionotropic receptors (ligand-gated channels)
- Metabotropic receptors (G protein-coupled receptors)
- Tyrosine Kinase

TABLE 3.2 Comparison of Ionotropic and Metabotropic Receptors

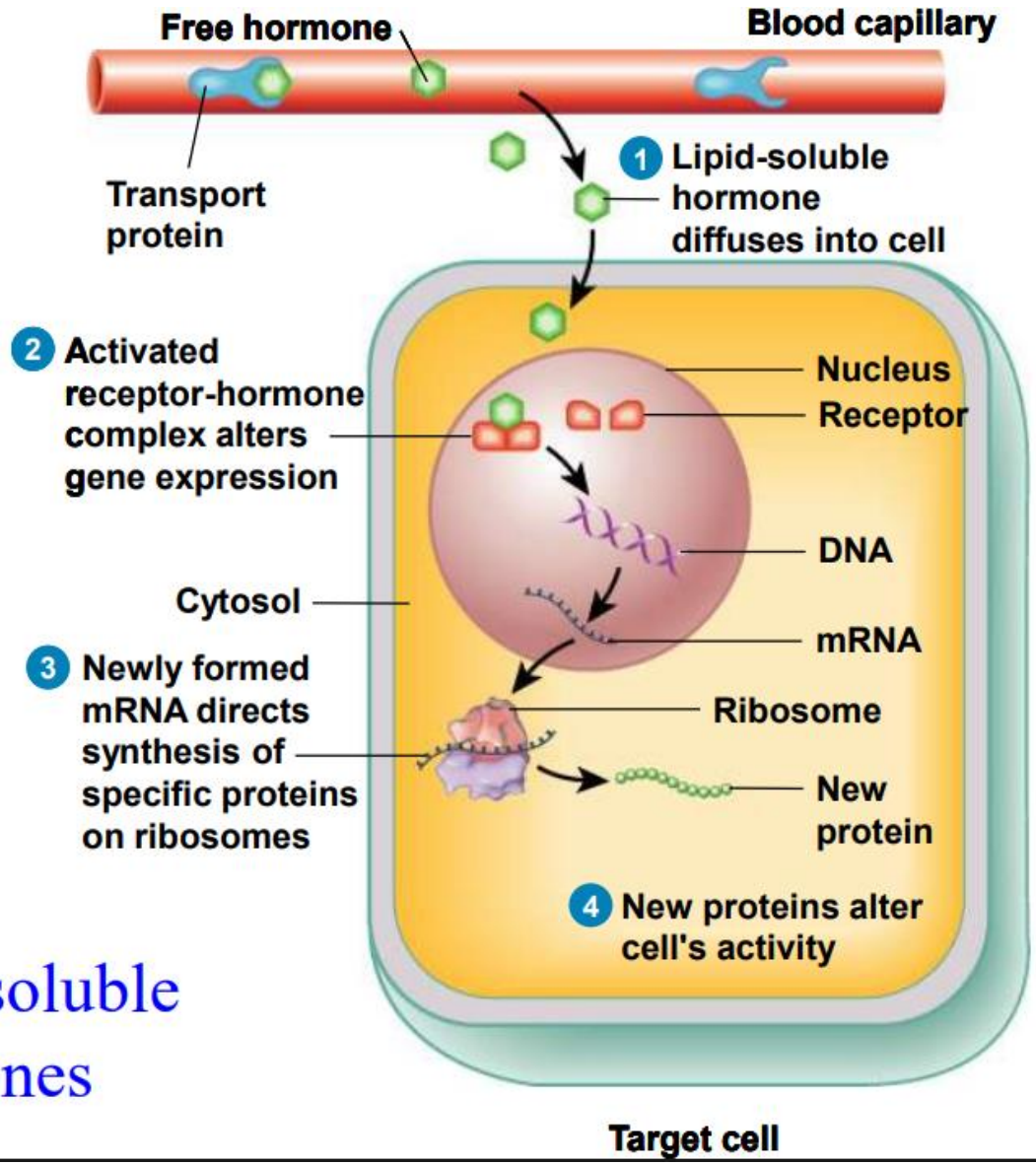
Characteristics	Ionotropic receptors	Metabotropic receptors
Structure	4 or 5 subunits that assemble in the cell membrane	1 subunit
Mechanism of action	Contain an intrinsic ion channel that opens in response to neuro-transmitter or drug binding	Activate G proteins in response to neurotrans-mitter or drug binding
Coupled to second messengers?	No	Yes
Speed of action	Fast	Slower

Almost all neurotransmitters discovered so far have more than one kind of receptor -- called **receptor subtypes.**

Water-soluble Hormones



Phosphorylation of a protein can either activate it or inactivate it



Lipid-soluble Hormones

Transported in the plasma by binding to a carrier protein (either specific like steriod-binding globulin and steriod-binding testosterone and thyroxine or non-specific like or albumin.

They diffuse through the membrane and bind to their receptor in the cytoplasm or nucleus but at the end they always reach the nucleus and bind to a specific area in the DNA called Hormone Responsive Element, leading to formation of new protein(could be enzyme or receptor ....etc.)
The work of insulin in the end forms a transporter(glucose transporter)

1-Inactive G-protein
2-Hormone activates the receptor
3- the activation of the receptor causes a substution of GTP(is now bound to alpha subunit) for GDP(which was bound to alpha subunit) which activates the G-protein
4- G-protein alpha subunit dissociate
5-Alpha subunit stimulate a membrane bound protein (usually enzyme)

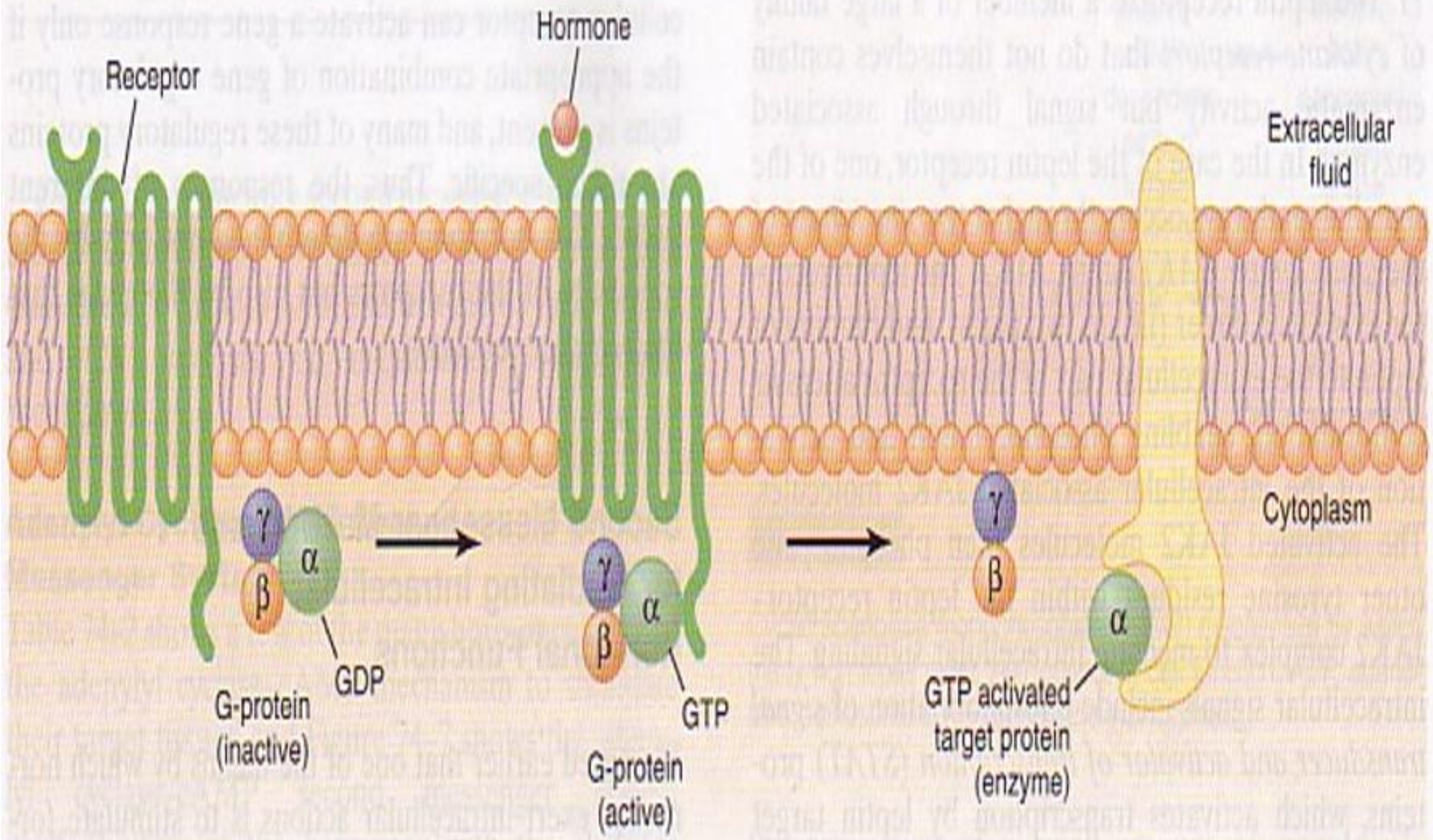
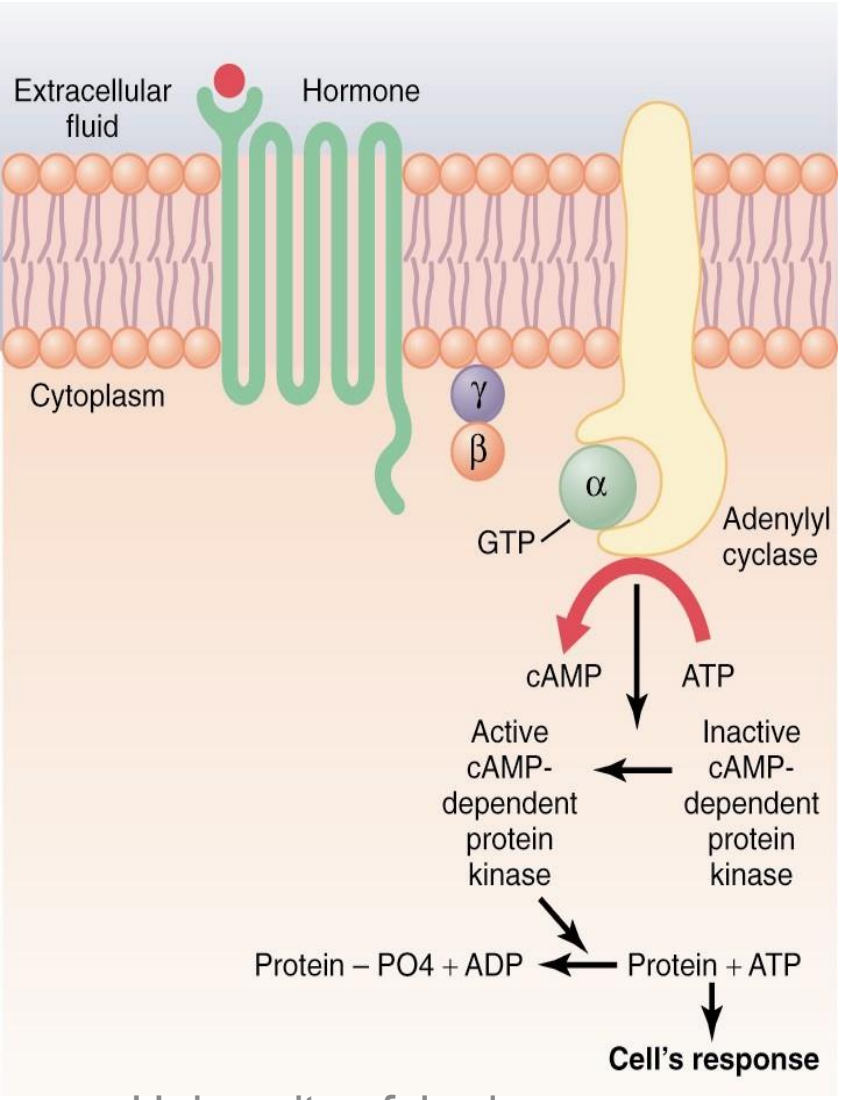


Figure 74-4

Mechanism of activation of a G protein-coupled receptor. When the hormone activates the receptor, the inactive α, β, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit (to which the GTP is bound) to dissociate from the β and γ subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

Cyclic Monophasphate (cAMP) Second Messenger Mechanism



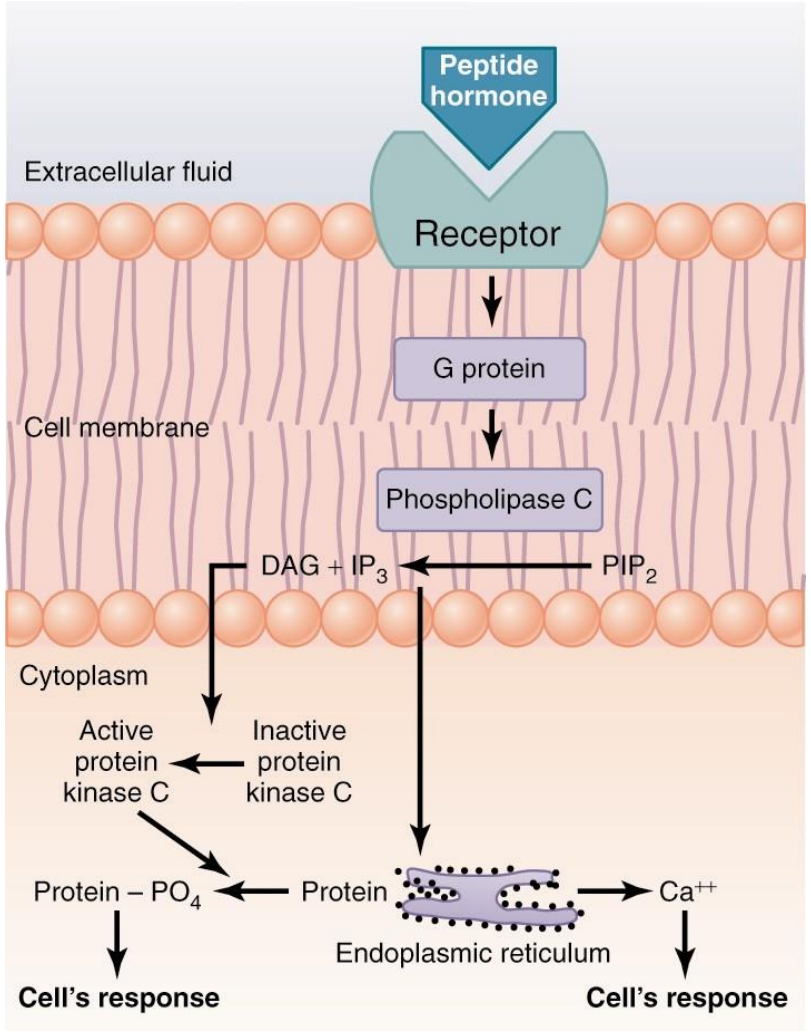
1-hormone activates G-protein alpha subunit dissociate

2- Alpha subunit stimulates adenylate cyclase which converts ATP to cAMP

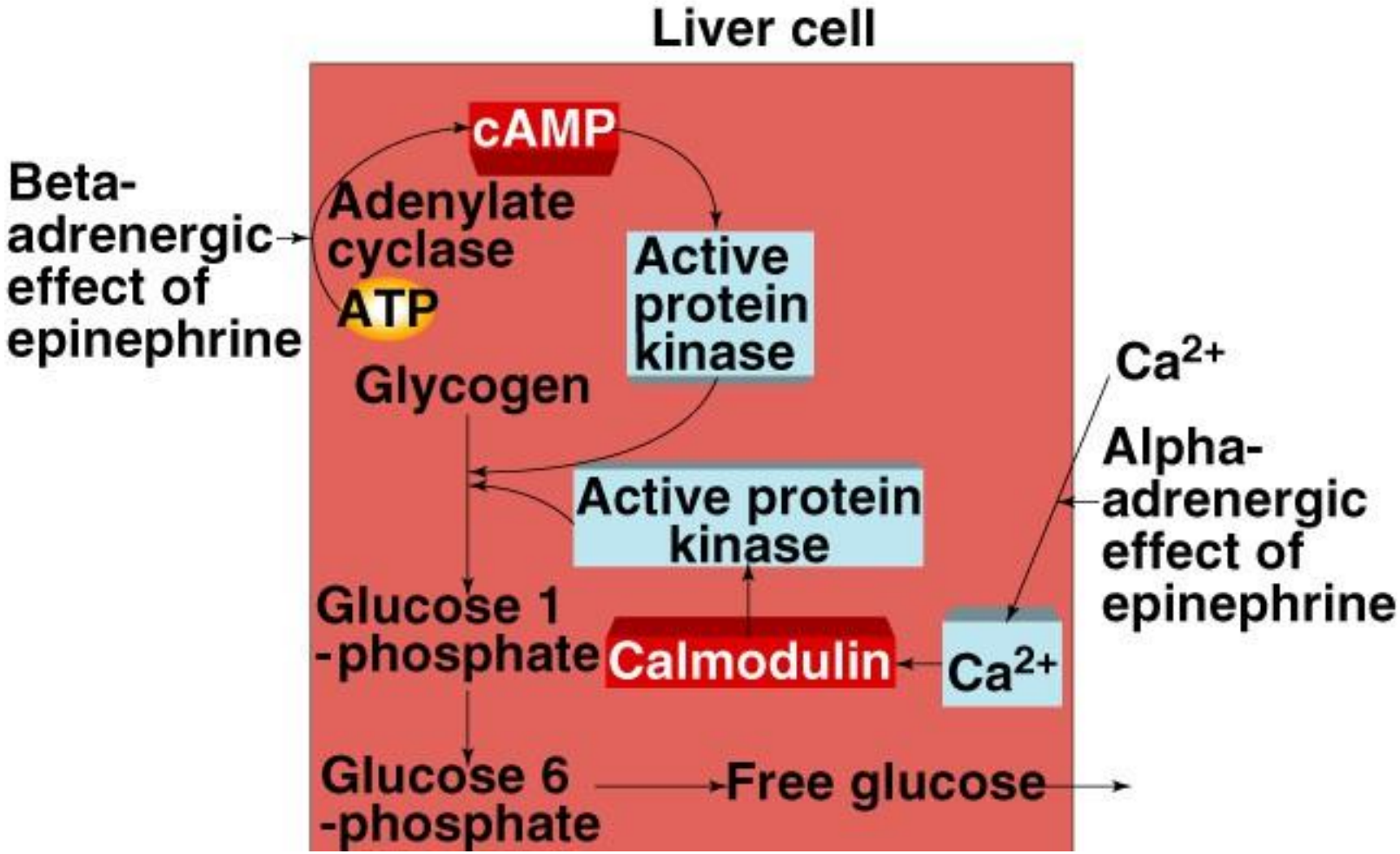
3- cAMP acts like a second messenger to activate protein kinases

4- protein kinases phosphorylate another protein which cause cell response

Cell Membrane Phospholipid Second Messenger System



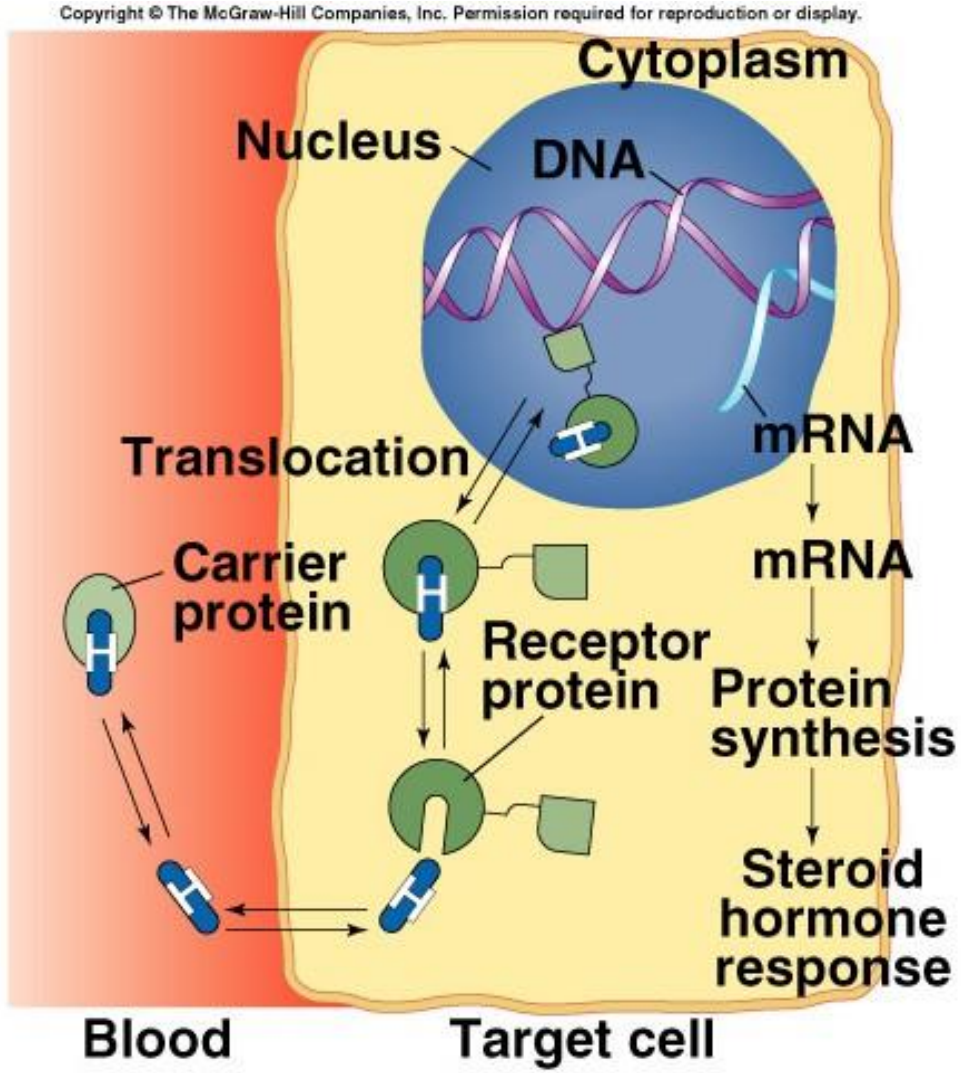
Epinephrine Can Act Through Two 2nd Messenger Systems



Hormones That Bind to Nuclear Receptor Proteins

These receptors have two domains for binding: one for binding with DNA and other for hormone binding . Whenever it binds to its hormone, the receptor is translocated with the hormone to the nucleus and specifically to the hormone responsive element

- 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.
- Receptors for the lipophilic hormones are known as **nuclear hormone receptors.**

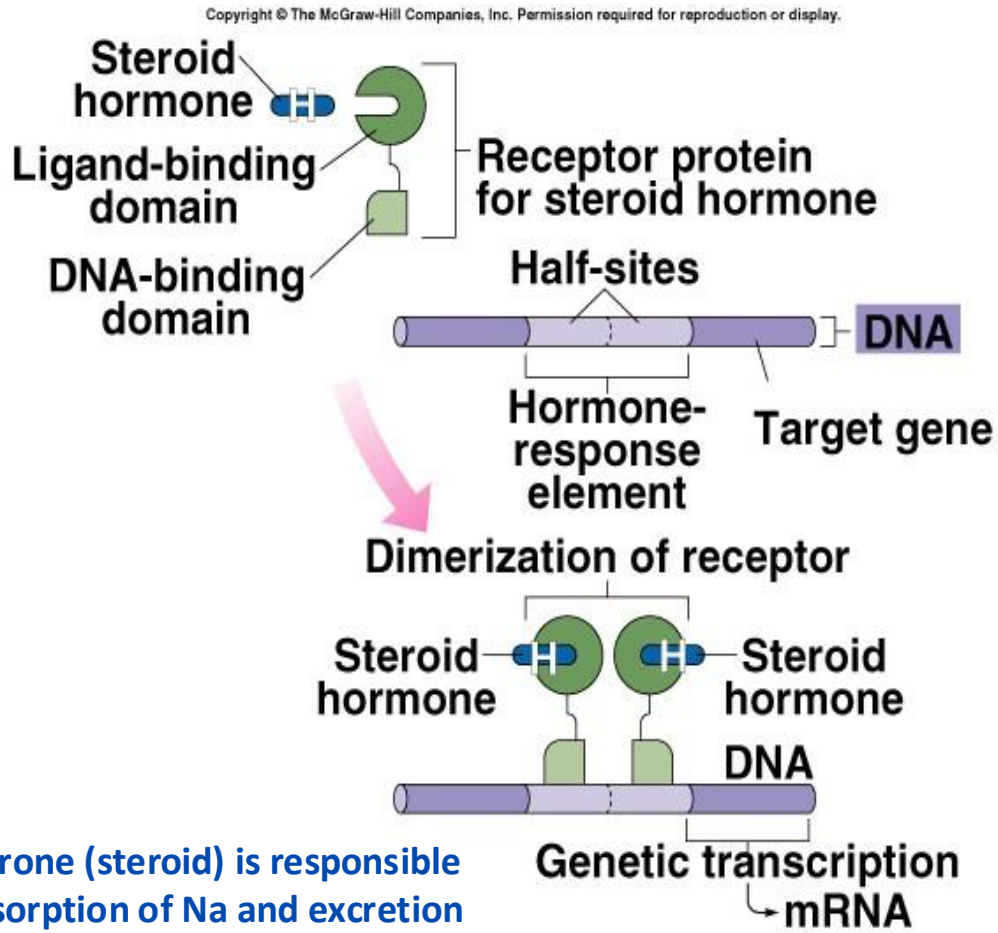


Nuclear Hormone Receptors

- Steroid receptors are located in cytoplasm and in the nucleus.
- Function within cell to activate genetic transcription.
- Messenger RNA directs synthesis of specific enzyme proteins that change metabolism.
- Each nuclear hormone receptor has 2 regions: A
- ligand (hormone)-binding domain.
- DNA-binding domain.
- Receptor must be activated **by binding to hormone before binding to** specific region of DNA called **HRE** (hormone responsive element).
- **HRE is located adjacent to gene that will be transcribed.**

Mechanisms of Steroid Hormone Action

- Cytoplasmic receptor binds to steroid hormone.
- Translocate to nucleus.
- DNA-binding domain binds to **specific** HRE of the DNA. **Because of that, specific protein is synthesized**
- **Dimerization** occurs.
  Process of 2 receptor units coming together at the 2 half-sites.
- Stimulates transcription of particular genes.



Aldosterone (steroid) is responsible of reabsorption of Na and excretion of K at distal tubules of nephron, so the synthesized proteins are transporters.

Mechanism of **Thyroid Hormone** Action

Each half-site bind to a different substance one to the hormone and the other to a (vitamin a) derivative (at least one of this two sites should bind to the hormone or the two of them)

T4 passes into cytoplasm and is converted to T3. 4 to 5 times More active than T4

Receptor proteins located in nucleus.

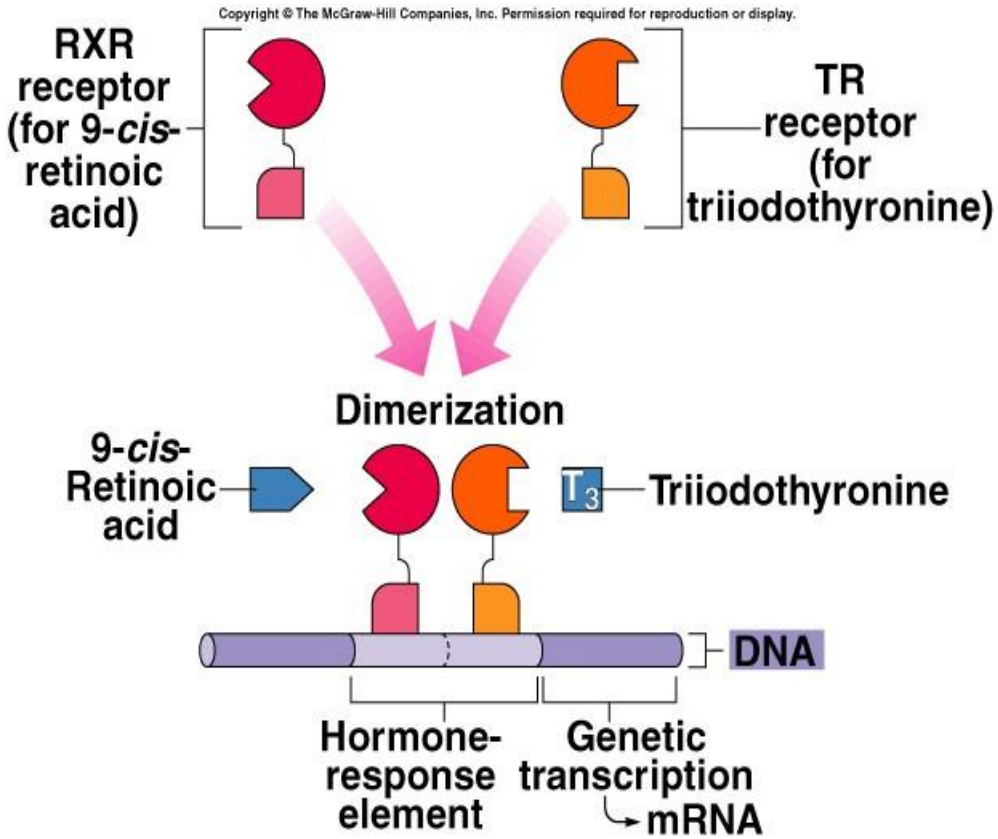
T3 binds to ligand-binding domain.

Other half-site is vitamin A derivative (9-cis-retinoic) acid.

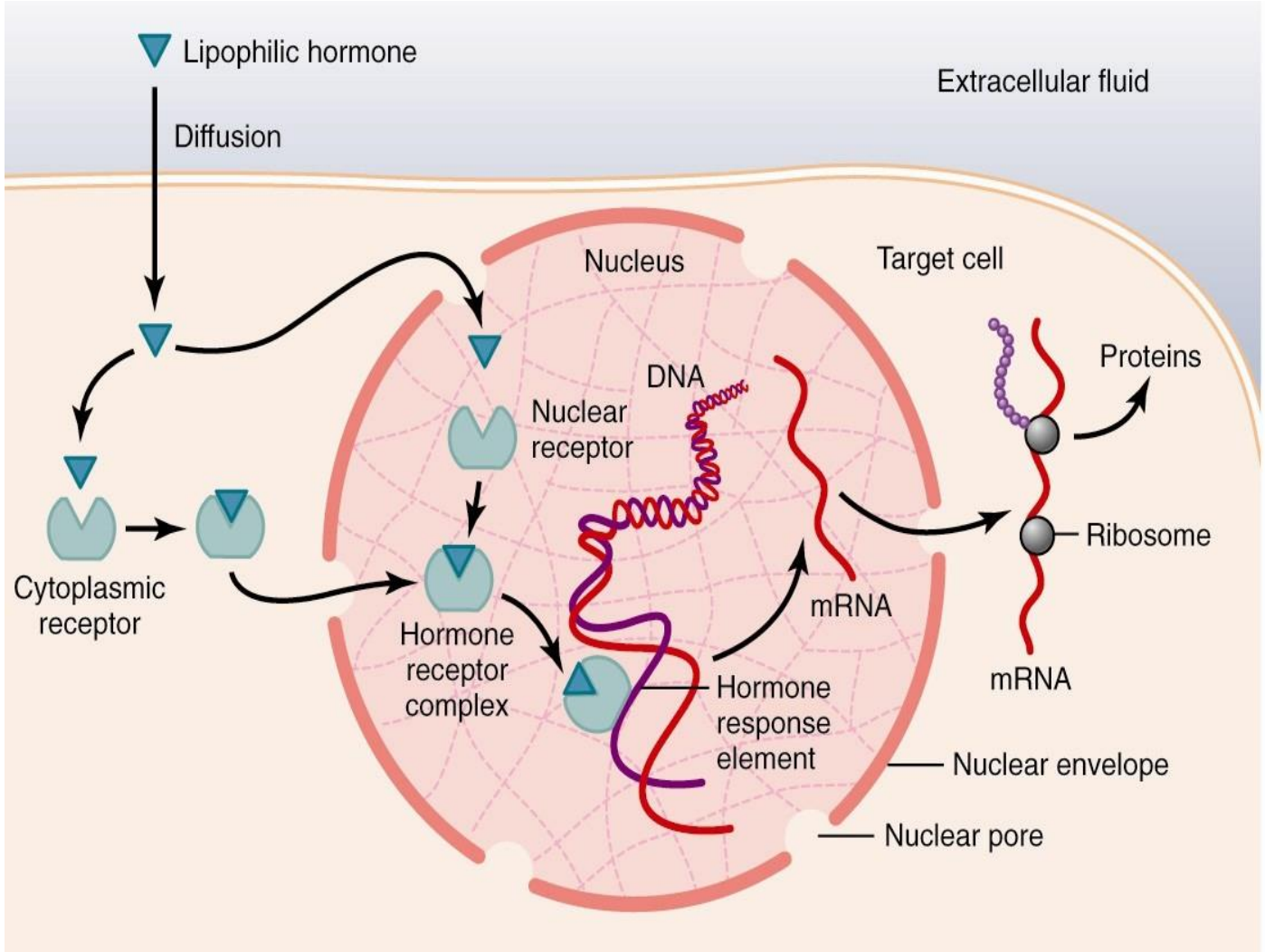
DNA-binding domain can then bind to the half- site of the HRE.

Two partners can bind to the DNA to activate HRE.

Stimulate transcription of genes.

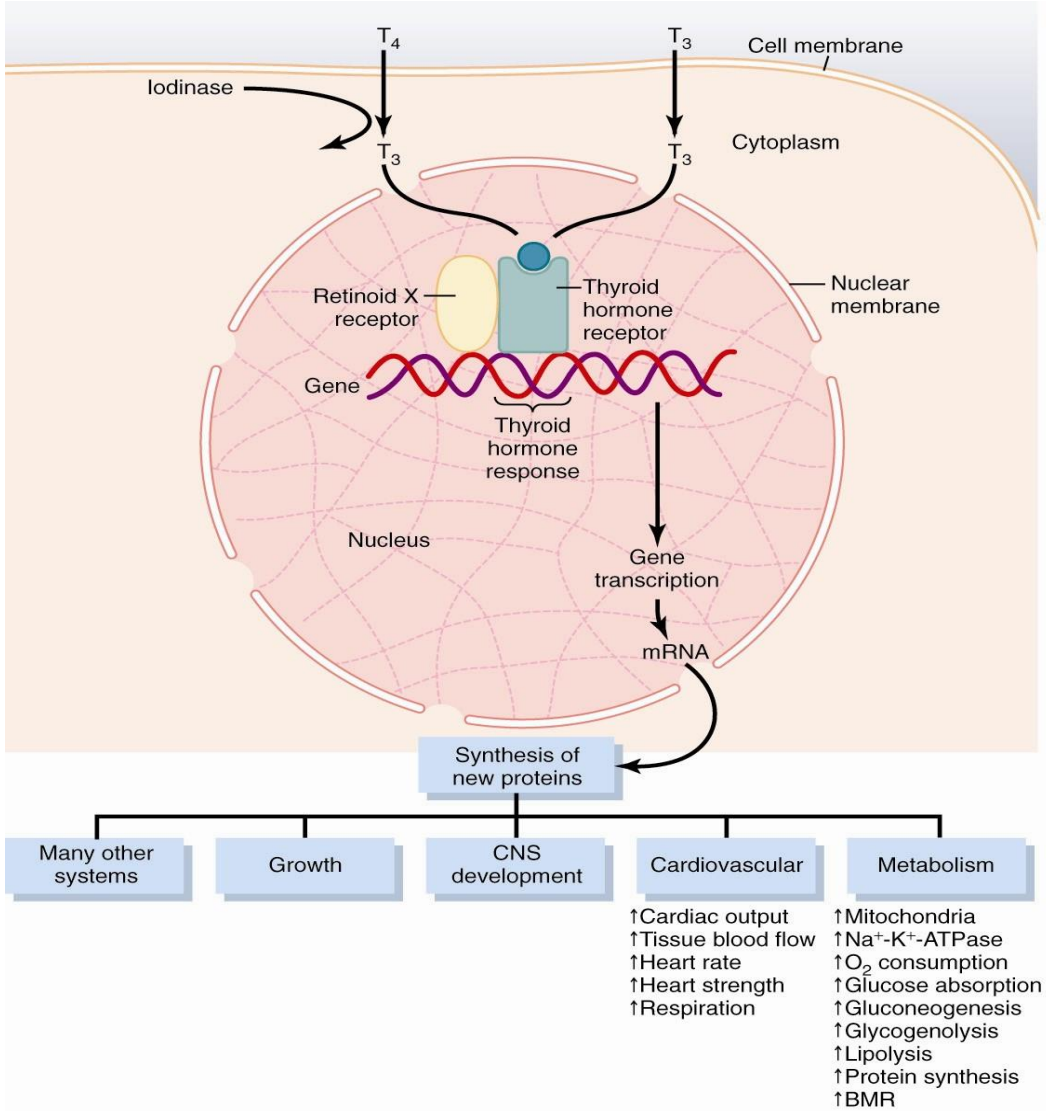


Steroid & Thyroid Hormones - Mechanism of Action



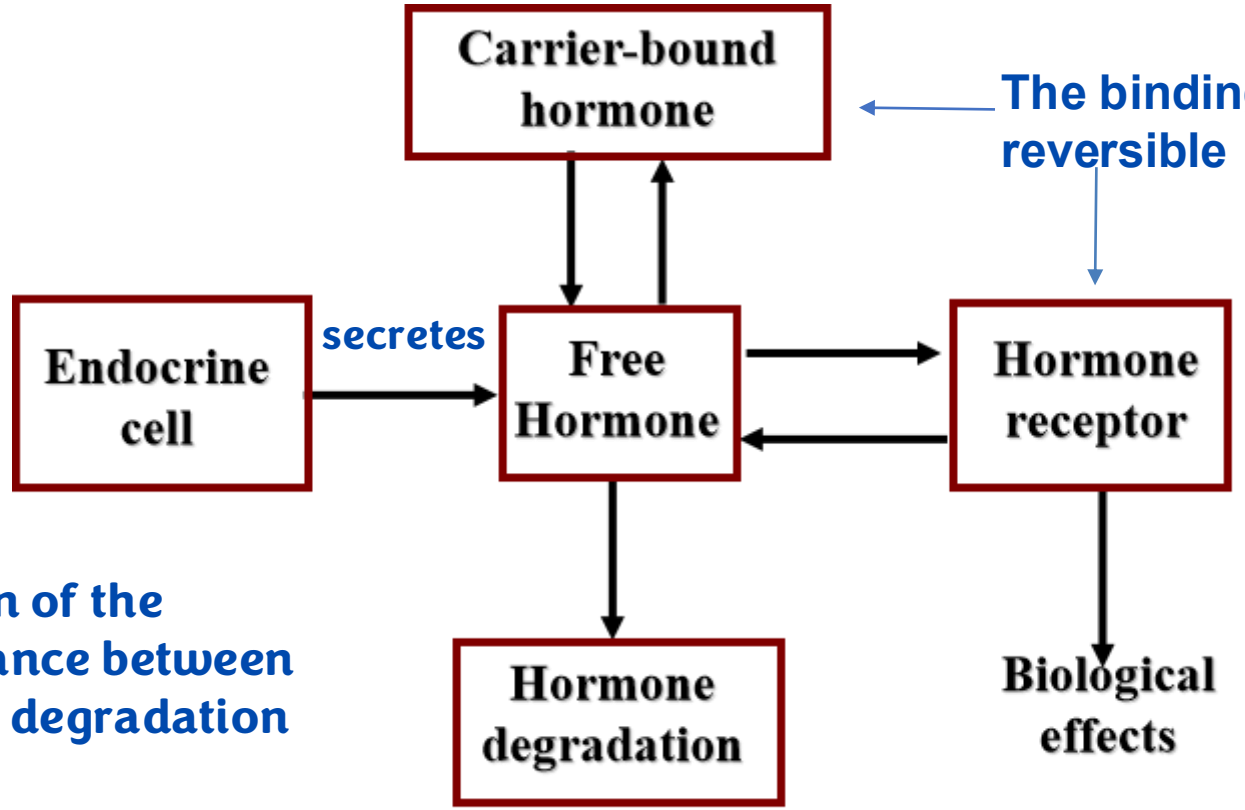
Actions of Thyroid Hormones

The doctor will not ask about the effects of thyroid hormone (will be taken in the endocrine system)



Congenital **hypothyroidism** lead to short stature(the height is less than normal). Also **hypopituitarism** lead to short stature with mental retardation together.
(Short stature **do not mean** there's hypothyroidism.

Determinants of Free Hormone Receptor Binding



The concentration of the hormone is a balance between the secretion and degradation

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

The half life is directly proportional to protein binding

The half life is inversely proportional to the metabolic clearance

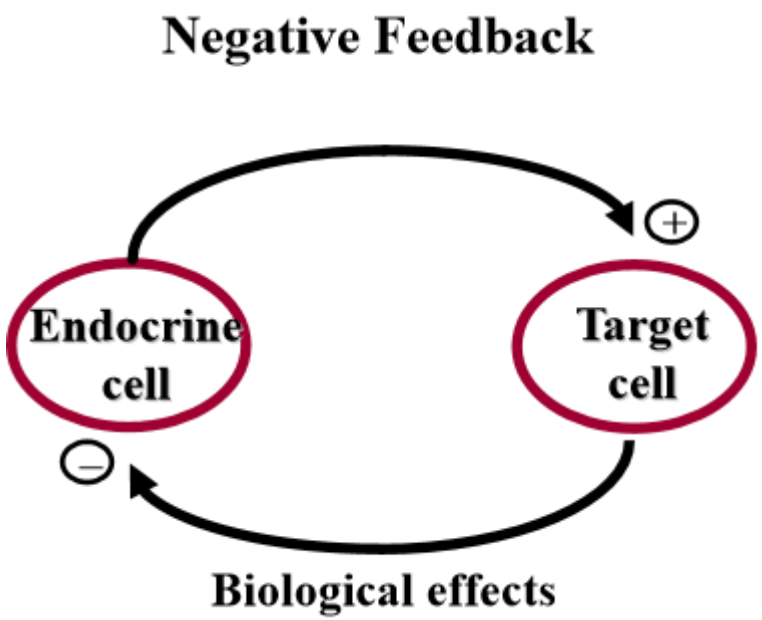
The half-life of lipid soluble hormones is more than it in the water-soluble hormones due to the protein binding in the lipid-soluble hormones (we talk about carriers in the plasma here)

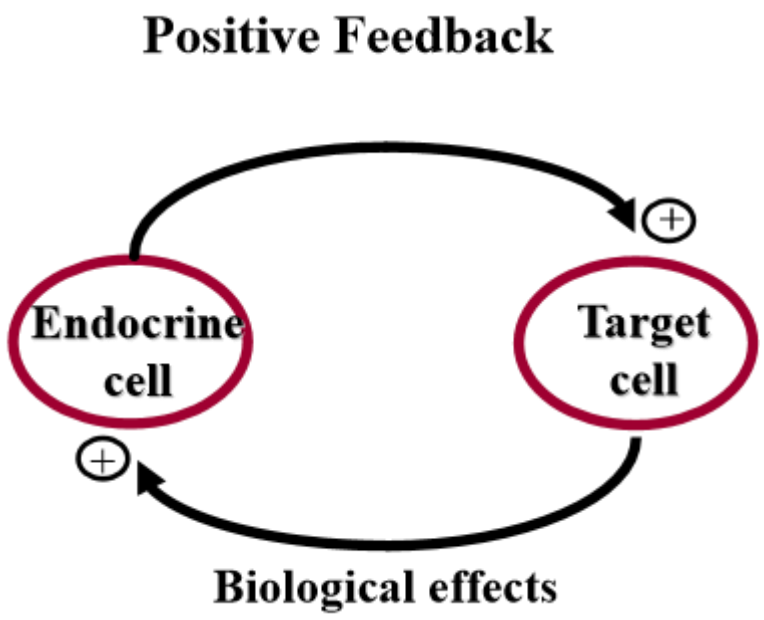
Circulating Transport Proteins

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

Feedback Mechanisms

Usually, the hormones are controlled by negative feedback



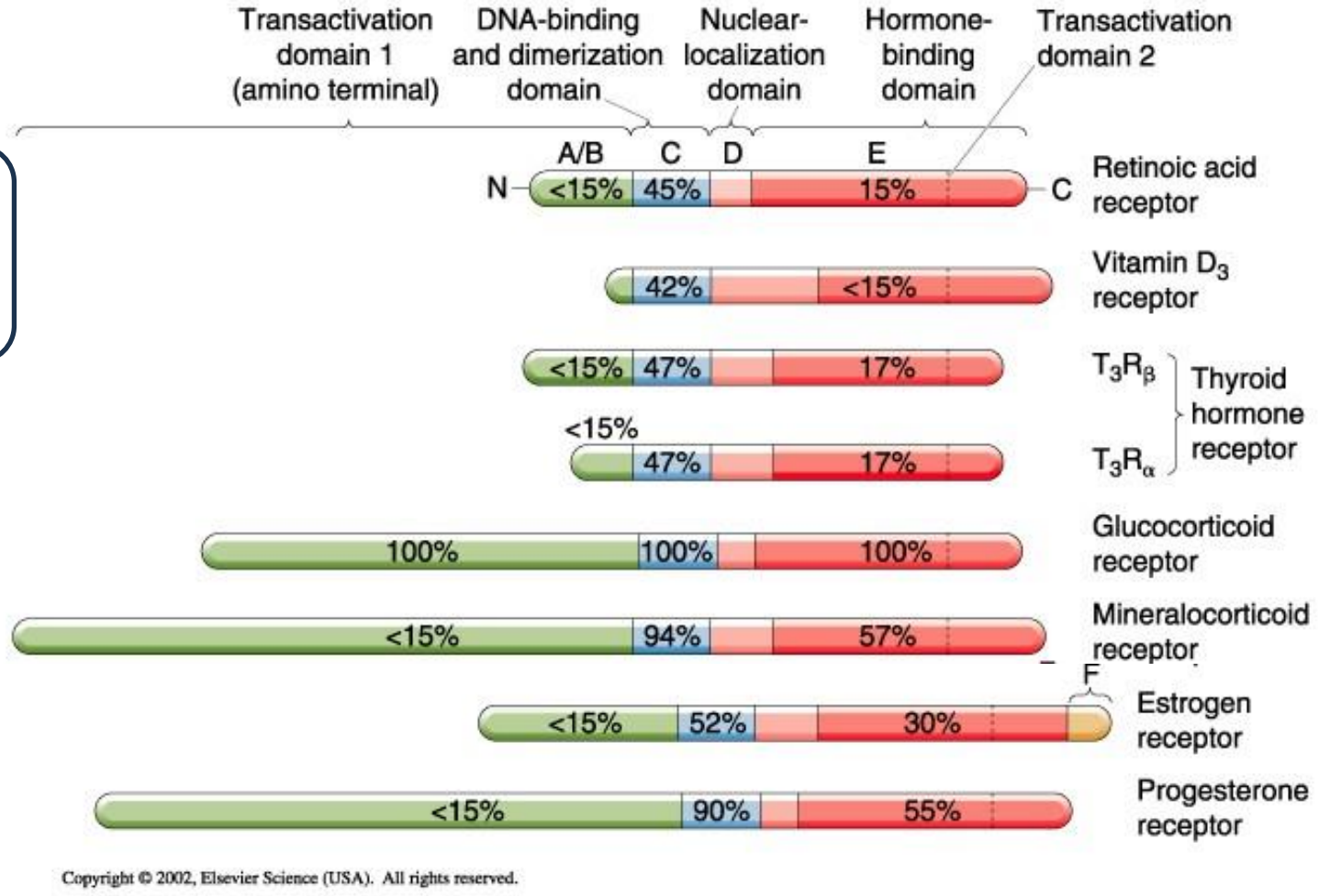


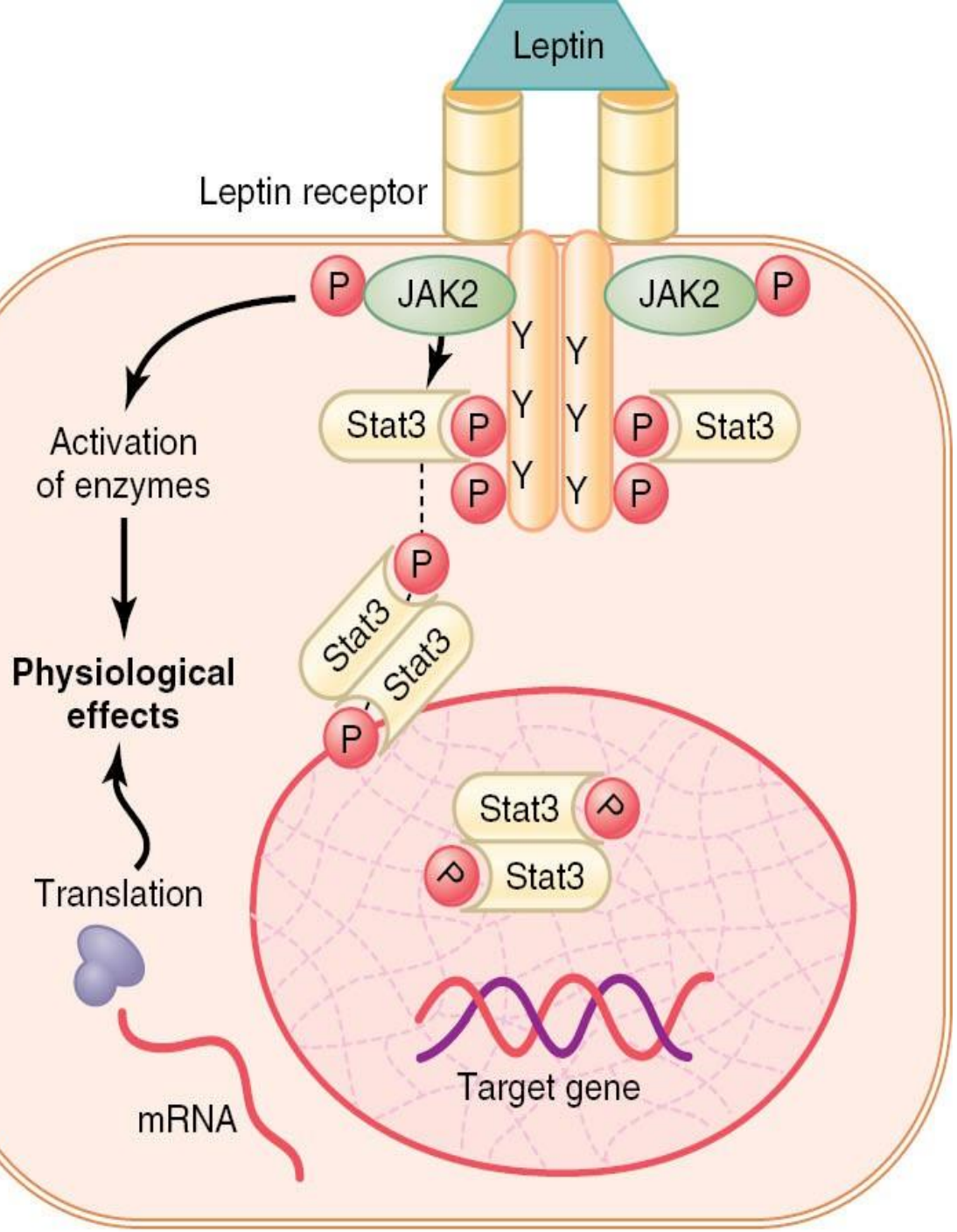
It is used for the amplifying of the secretion

Steroid & Thyroid Hormones - Receptors

NOT FOR MEMORIZATION

Receptors are proteins and glycoprotein





Specific mechanism that works throw kinase JAK kinase (just another kinase)=Janus kinase .
Leptin is a peptide secreted by adipocytes when it binds to its receptor on the membrane it stimulates JAK kinase which phosphorylates STAT3 (signal transducer and activator of transcription) ,STAT3 then moves to the nucleus and leads to gene transcription .
JAK kinase can phosphorylate an enzyme which causes physiological effect (Translation)

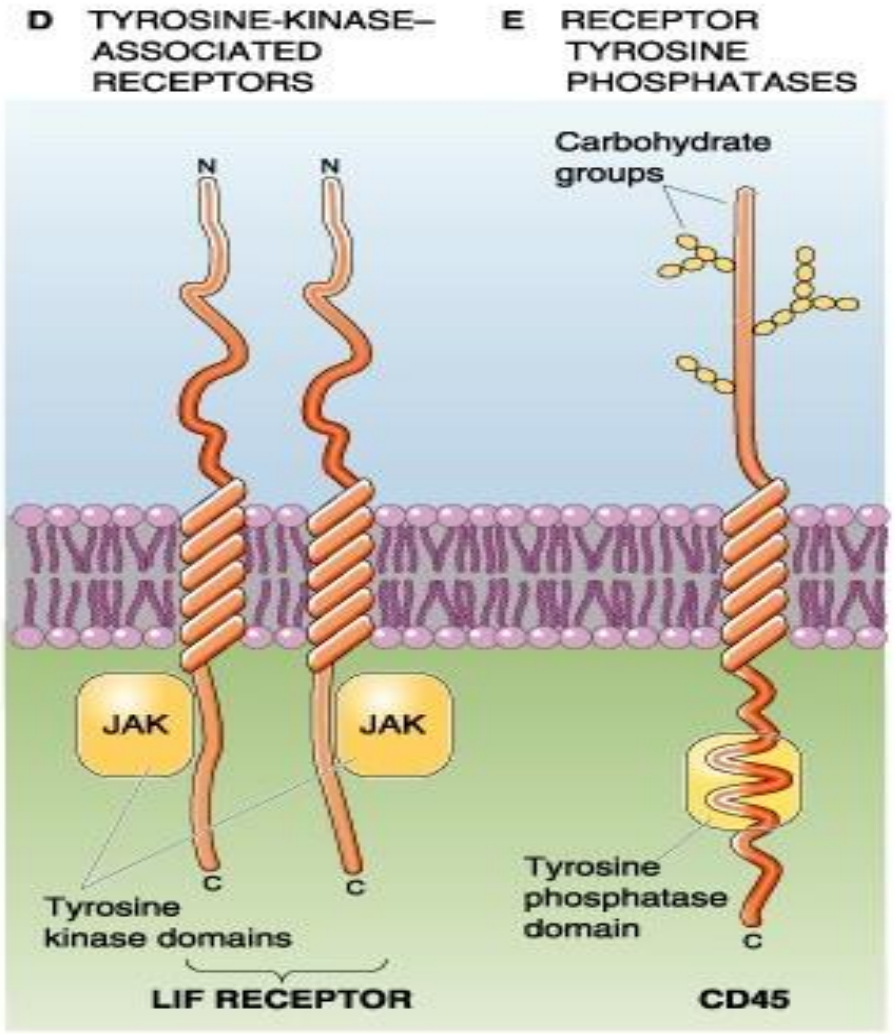
Enzyme-linked receptor (the leptin receptor)

- The receptor exists as a homodimer (two identical parts)
- Leptin binds to the extracellular part of the receptor
- This causes activation of the intracellular associated Janus kinas 2 (just another kinase)
- This causes phosphorylation of signal transducer and activator of transcription (STAT3) proteins

Enzyme-linked receptor (the leptin receptor)….cont

- This then activates the transcription of target genes and synthesis of proteins
- JAK 2 phosphorylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin

Tyrosine Kinase

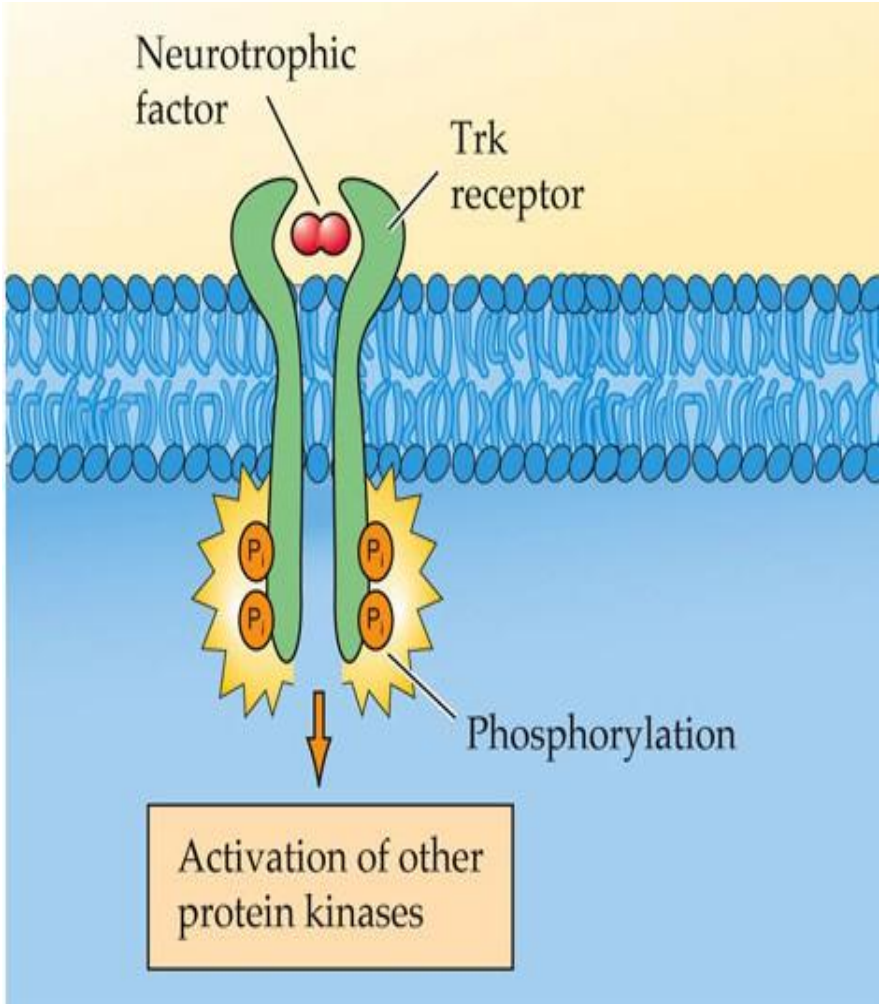


Tyrosine Kinase receptors :

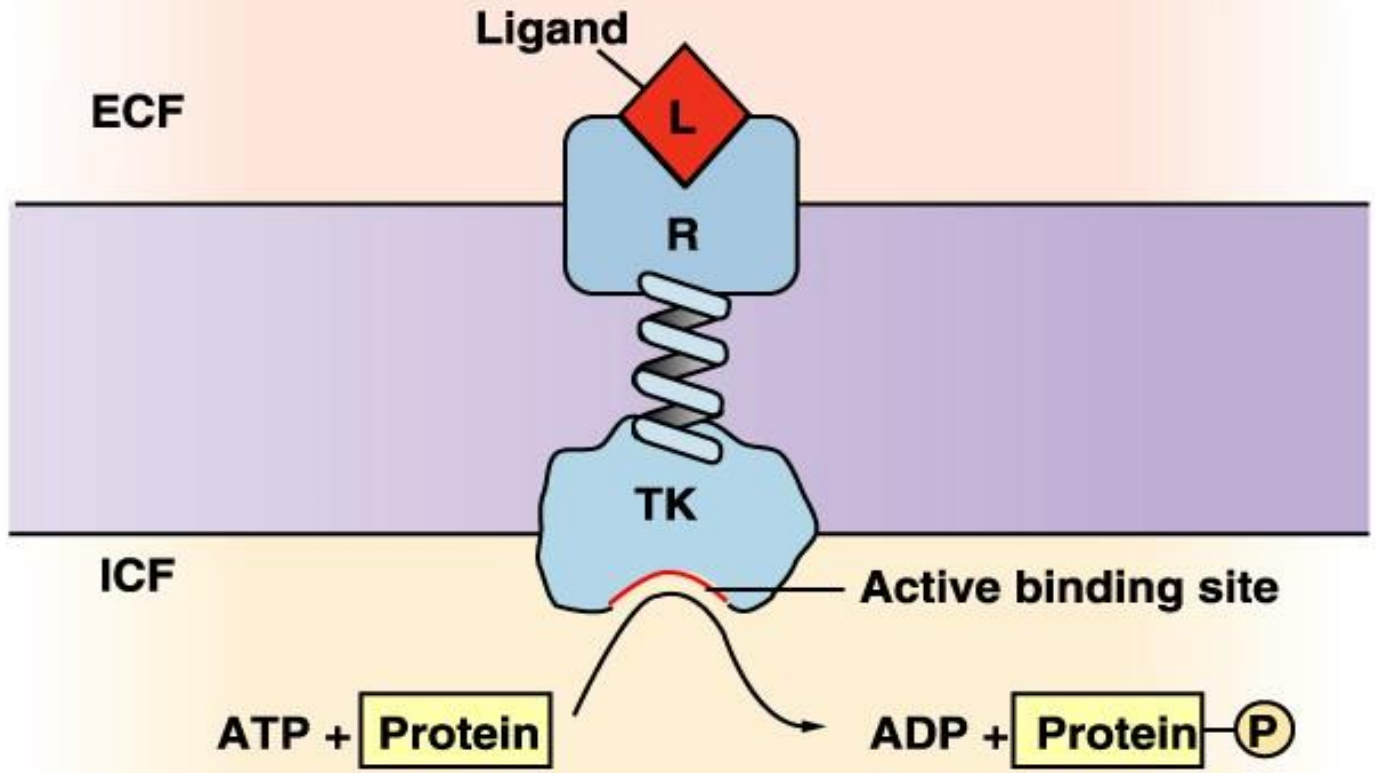
1- Tyrosine kinase-associated receptor that binds with JAK kinase .

2- Tyrosine receptor that contains tyrosine phosphatase domain

Tyrosine Kinase Receptors:



The neurotrophic factor when it binds to the extracellular part of the receptor it causes autophosphorylation in the intercellular part activating the kinase .

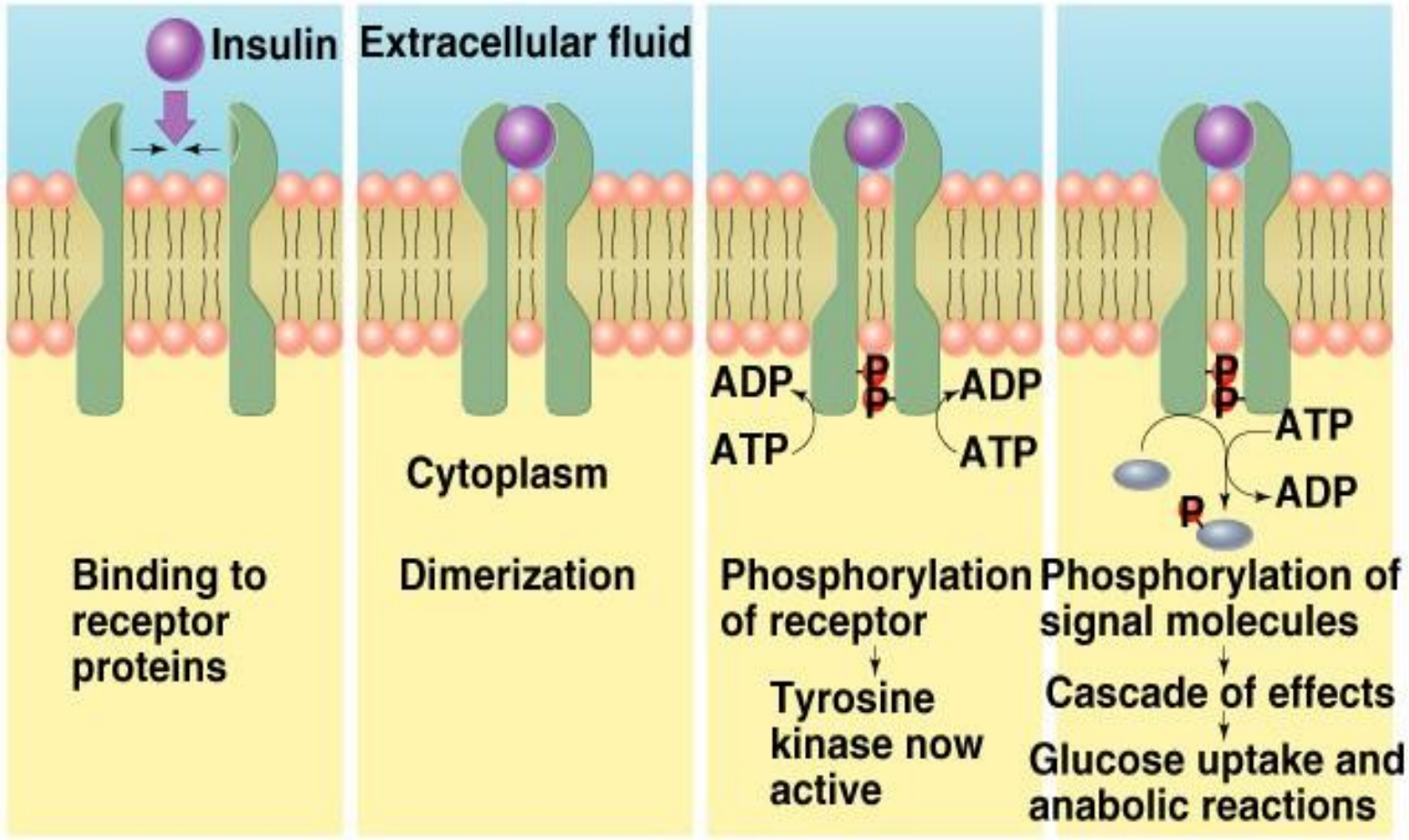


This type of receptors is called enzyme-linked receptor. When the ligand attach with the receptor it activates tyrosine kinase that phospholerate a specific protein .

Tyrosine Kinase

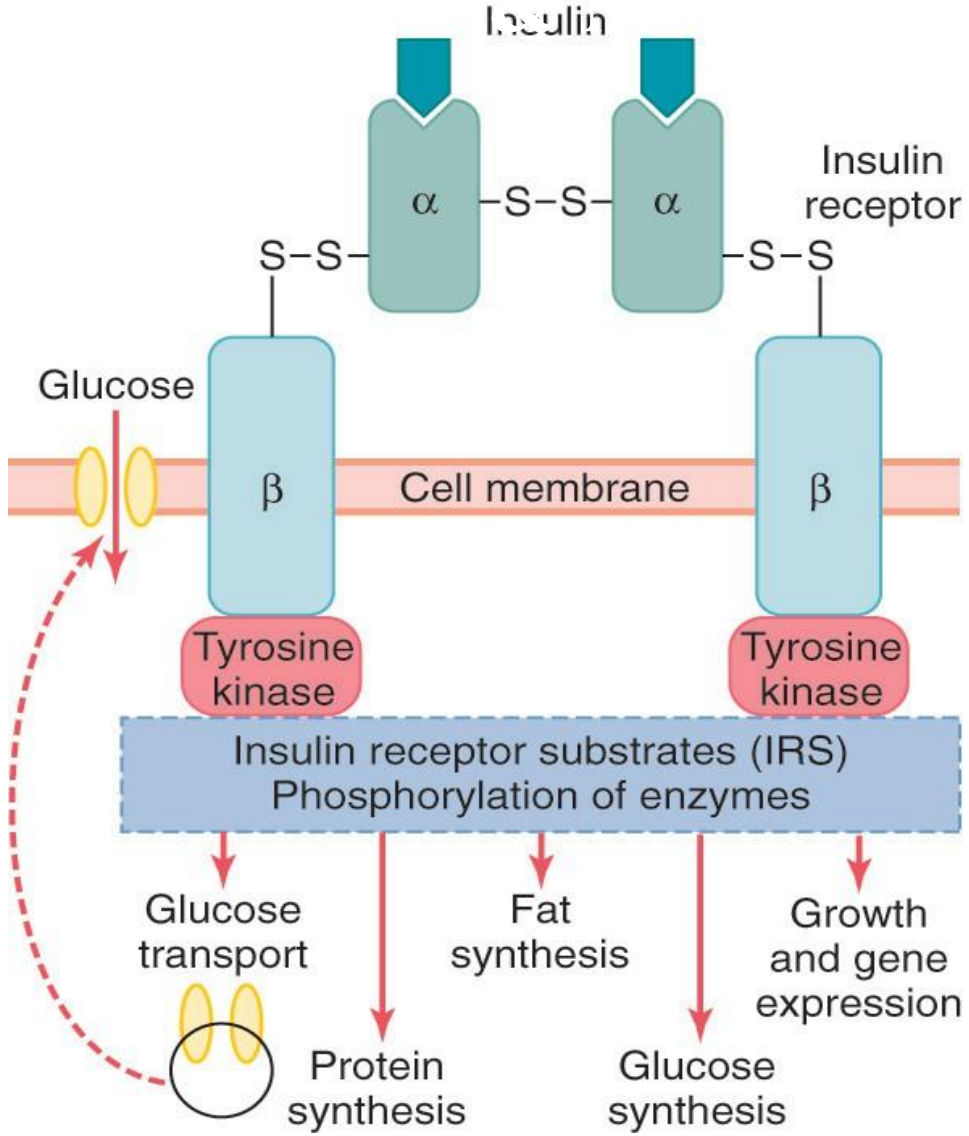
- Insulin receptor consists of 2 (alpha and beta)units that dimerize when they bind with insulin.
  - Insulin binds to ligand-binding site on plasma membrane, activating enzymatic site in the cytoplasm.
  - Autophosphorylation occurs, increasing tyrosine kinase activity.
  - Activates signaling molecules.
  - Stimulate glycogen, fat and protein synthesis. Stimulate insertion of GLUT-4 carrier proteins. In the membrane

Tyrosine Kinase (continued)

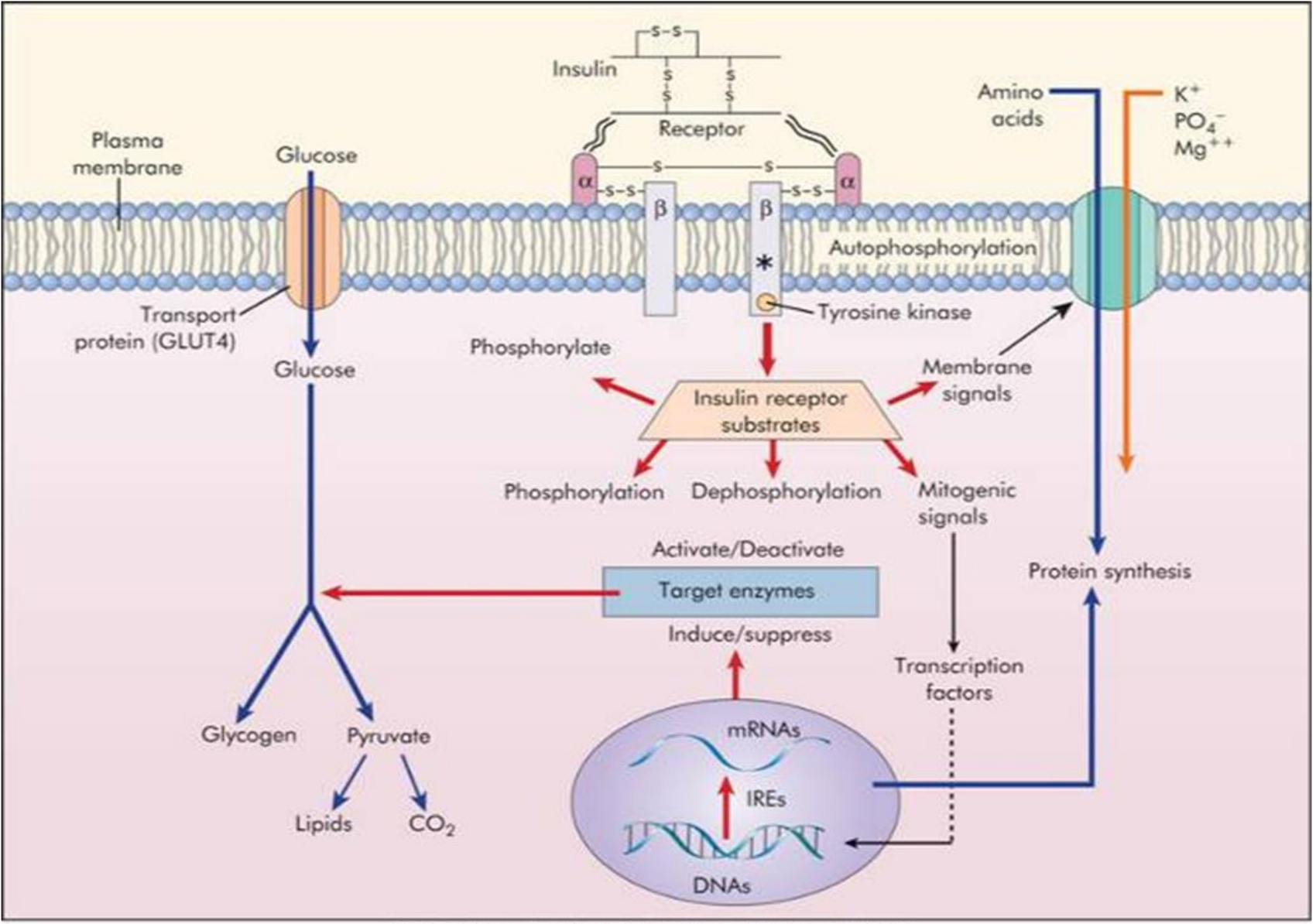


Beta subunits are tyrosine kinase receptors.

Insulin binds to the alpha subunits (extracellular) activating the beta subunits (tyrosine kinase) which undergo autophosphorylation activating kinase.



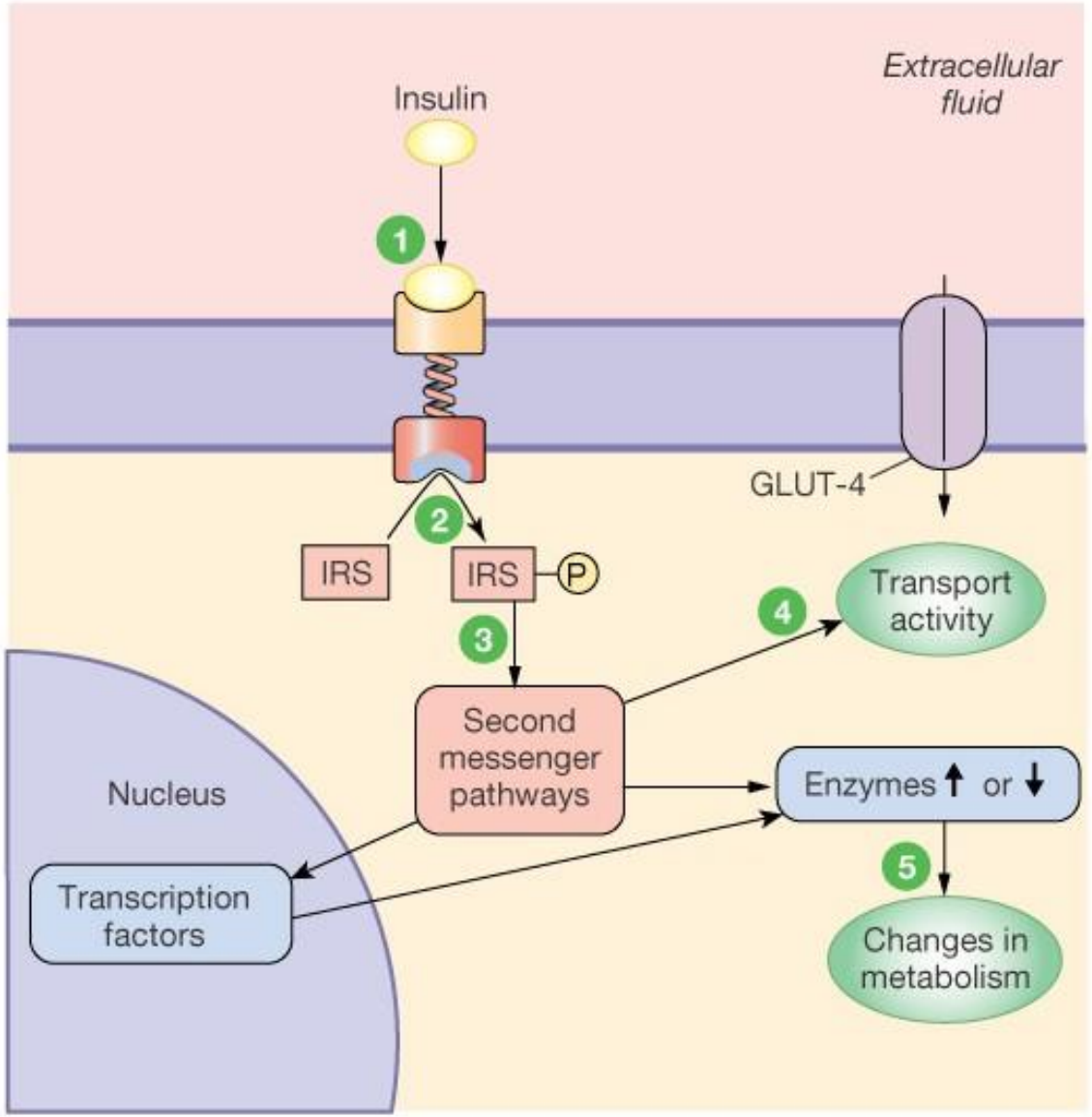
Insulin is secreted when there is hyperglycemia to reduce glucose level in blood (causes hypoglycemia) through this mechanisms.



From Berne RM, Levy MN. *Principles of physiology*, ed 3, St Louis, 2000, Mosby.

Insulin receptor activation sends signals that increase uptake of k+ and amino acids. K+ is transported inside the cell (against its concentration gradient) , so in some cases when we have high K+ levels (very toxic) we may use insulin although it causes hypoglycemia.

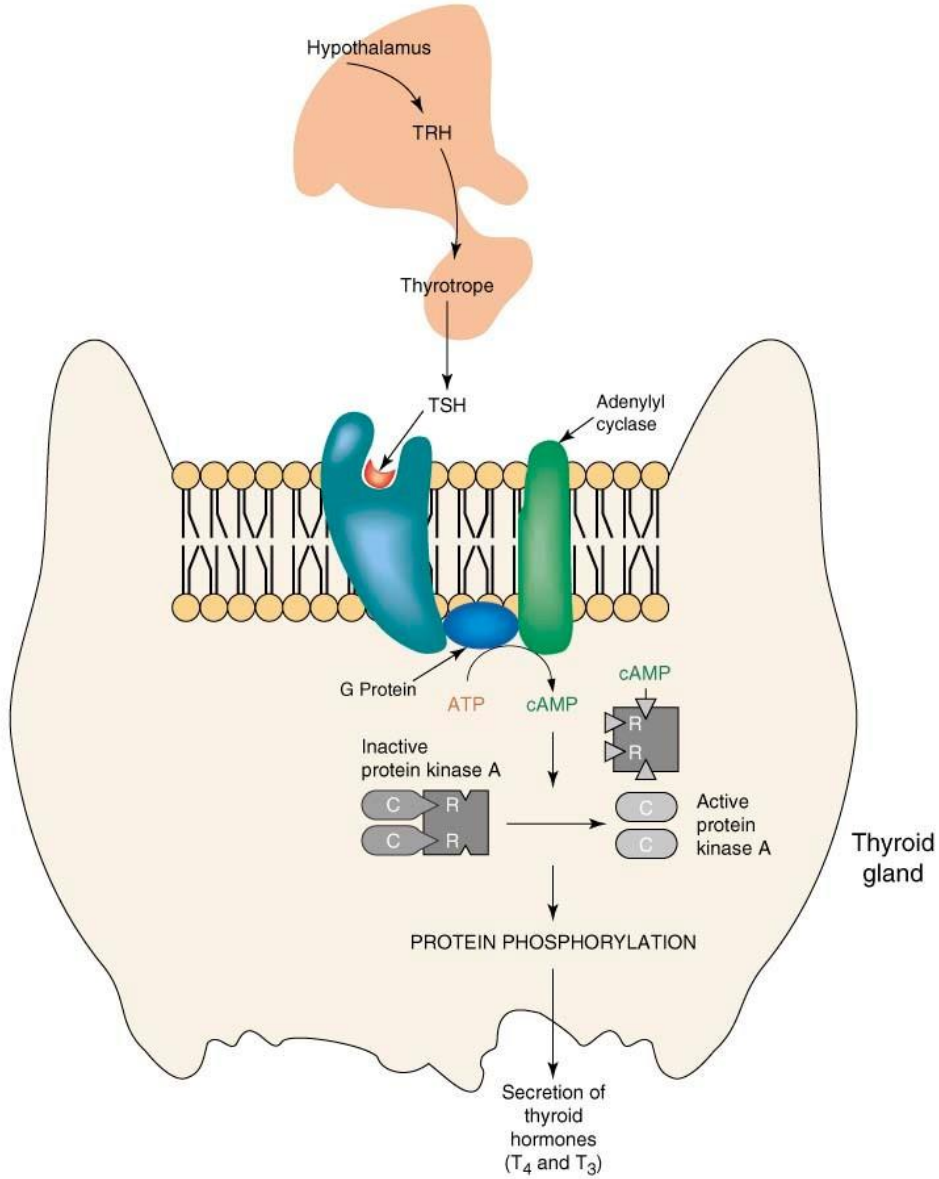
Insulin Action on Cells:



1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
3. Second messenger pathways alter protein synthesis and existing proteins.
4. Membrane transport is modified.
5. Cell metabolism is changed.

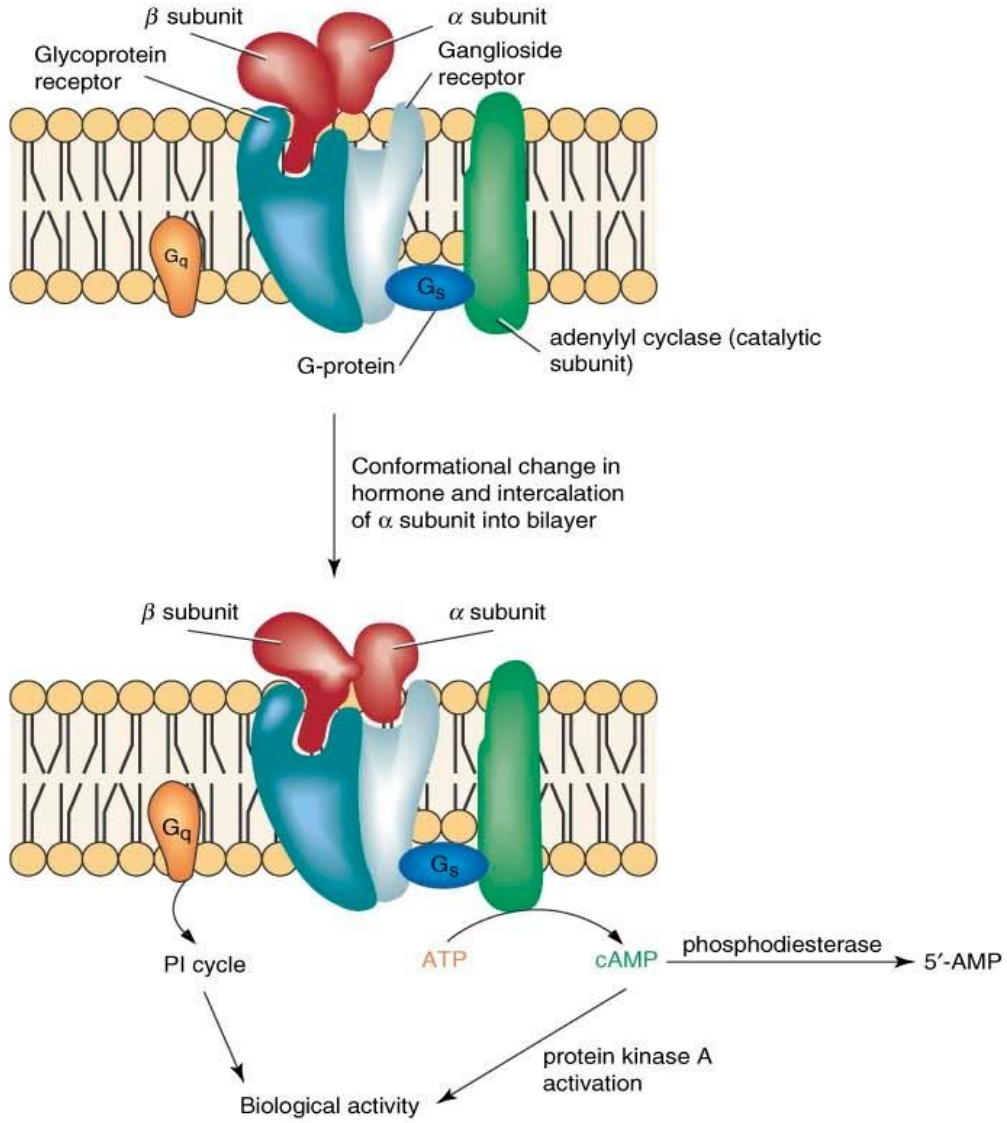
TRH: Thyrotropin-Releasing Hormone simple peptide (3 amino acids).

Hypothalamus releases TRH which stimulates thyrotrope in the pituitary gland to release TSH,TSH is a glycoprotein binds to G-protein that has an alpha and beta subunits .



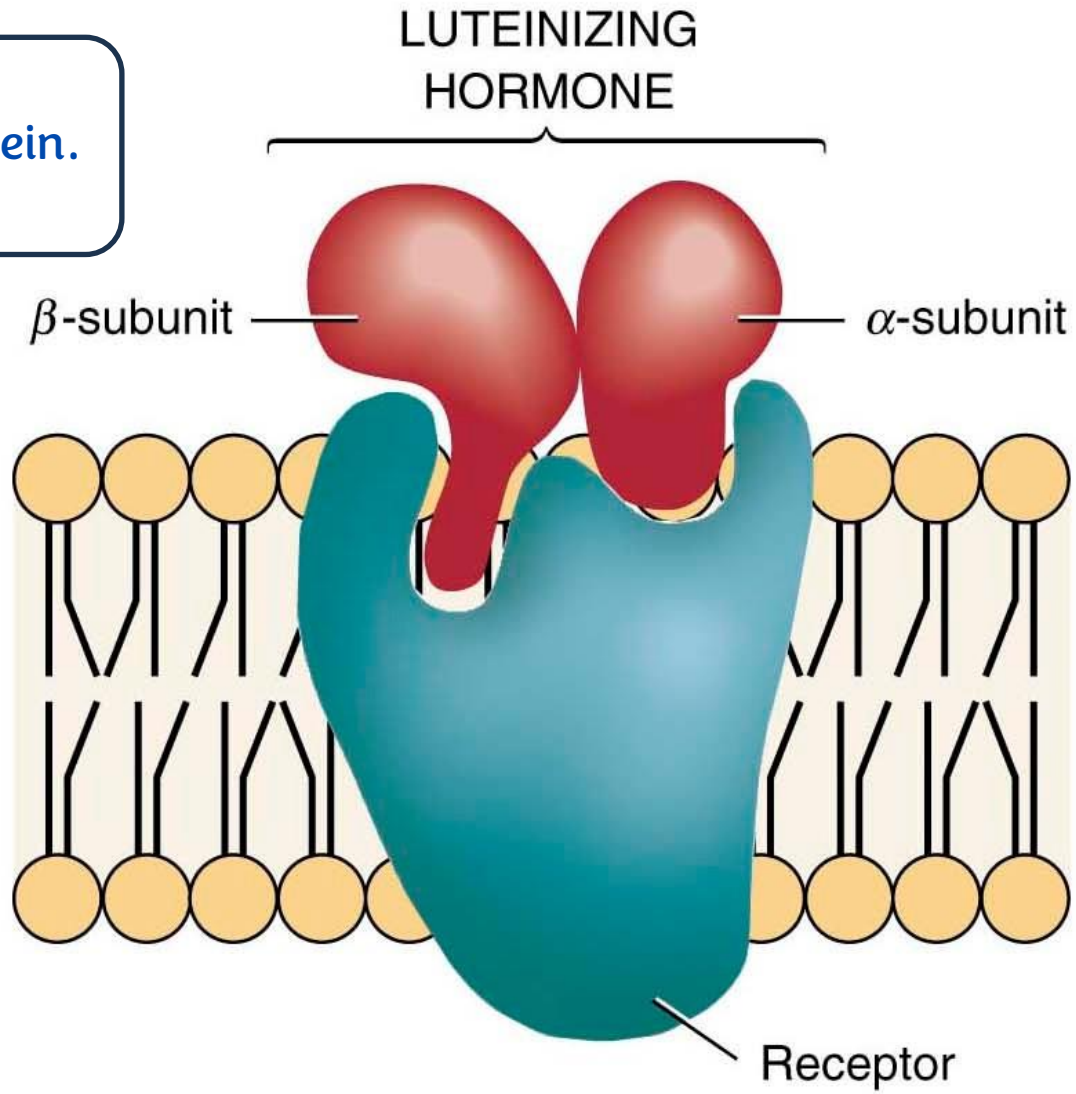
Effect of TSH on secretion of thyroid hormone.

TSH (alpha + beta) subunits beta subunit activates G-protein.

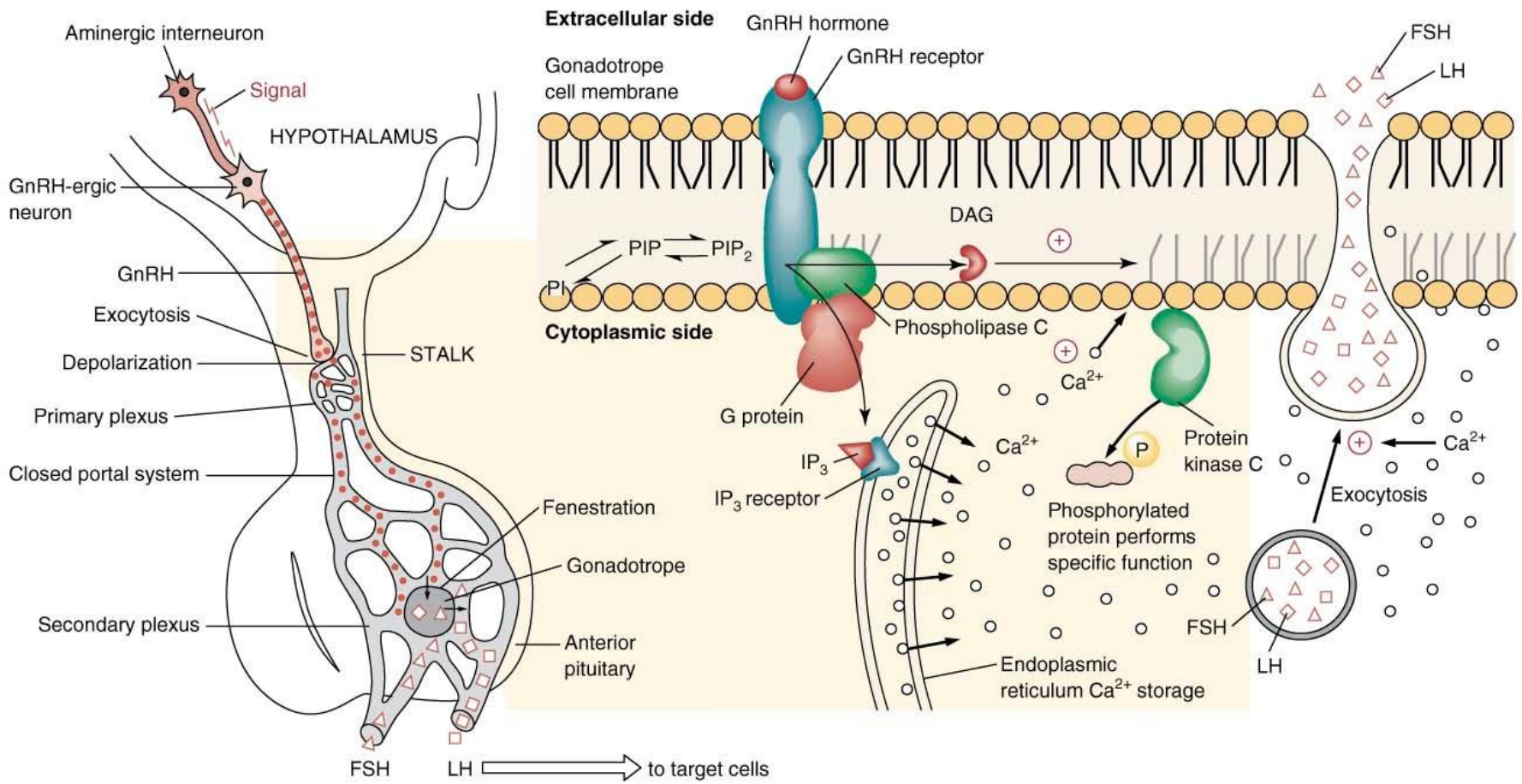


Model of TSH receptor. Adapted with modifications from Kohn, L. D., et al. In: G. Litwack (E
Biochemical Actions of Hormones, Vol. 12. New York: Academic Press, 1985, p. 466.

Beta. Subunit activates G-protein.

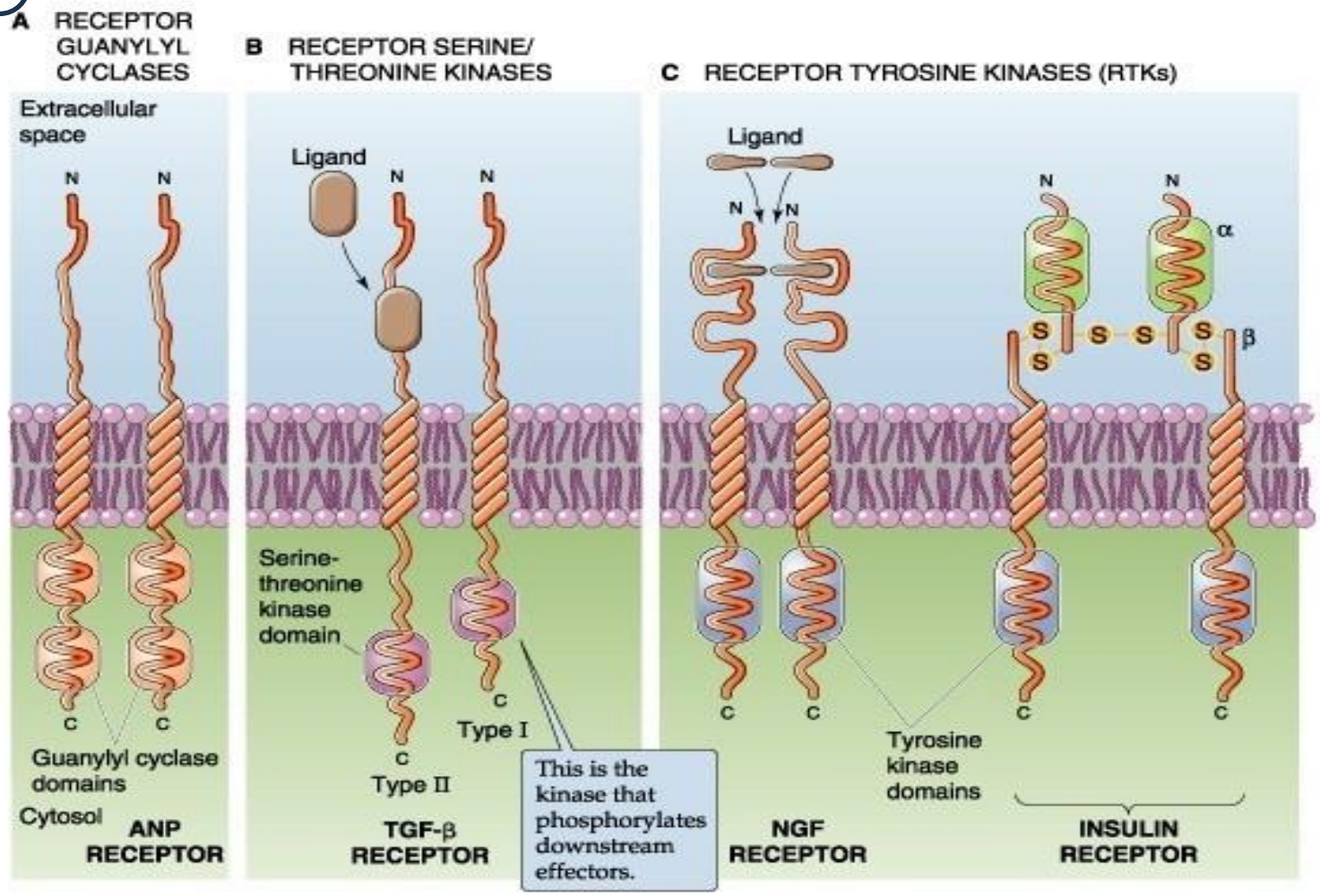


The interaction of α and β subunits of LH with LH receptor of rat Leydig cells. Adapted from Alonoso-Whipple, C., Couet, M. L., Doss, R. Koziarz, J., Ogunro, E. A., and Crowley, W. E. Jr. *Endocrinology* 123:1854, 1988.



Regulation of secretion of LH and FSH by protein kinase C.

NOT FOR MEMORIZATION.



Signaling molecule
(hormones)

↓

Receptor of target cell

↓

Intracellular molecule
(second messengers)

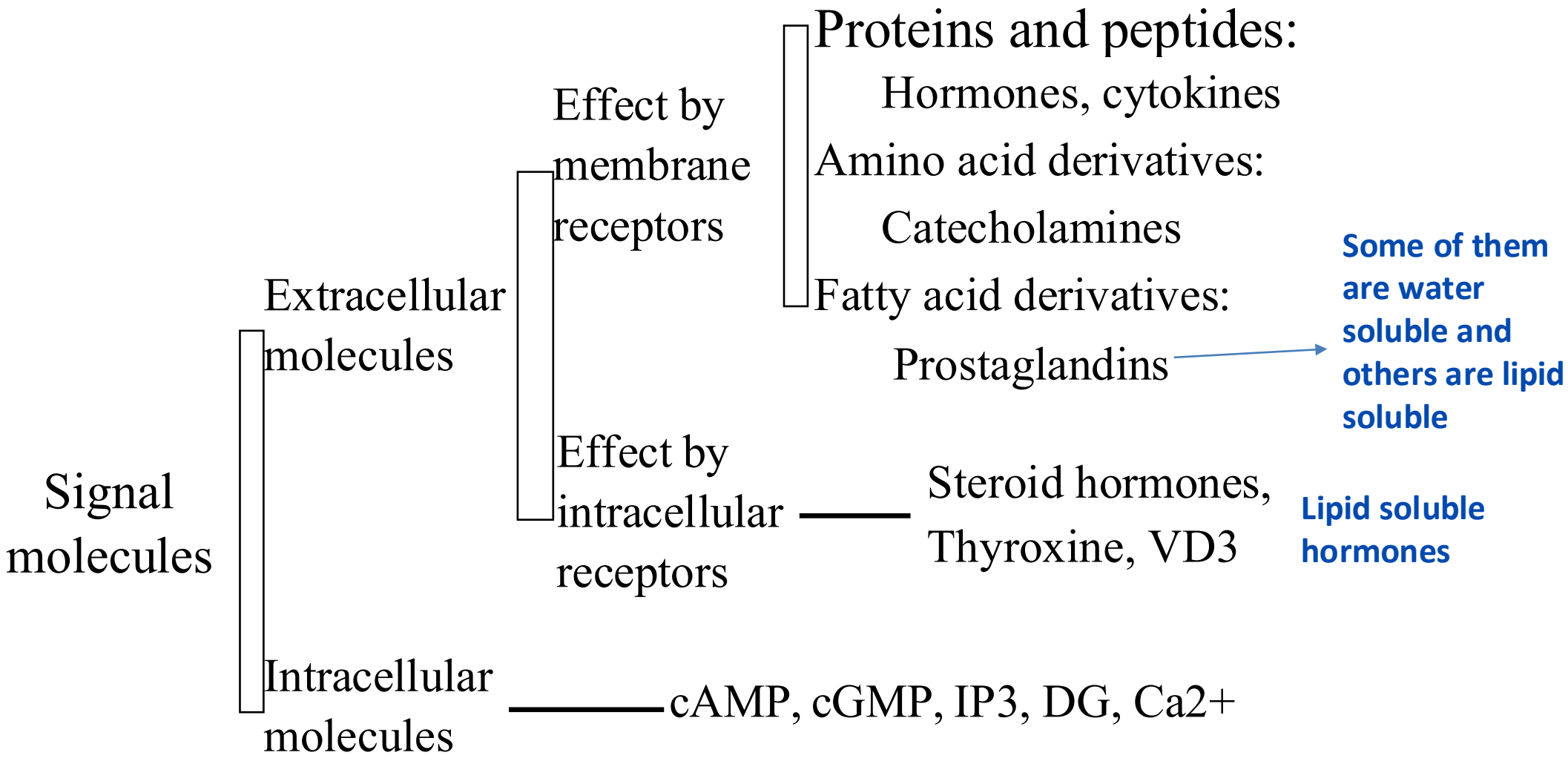
↓

biological effect

Signal transduction

Third messengers:

Third messengers are molecules which transmit message from outside to inside of nucleous or inside to outside of nucleous , also called DNA binding protein.


Signal molecules
Extracellular molecules
Effect by membrane receptors
Proteins and peptides:
Hormones, cytokines
Amino acid derivatives:
Catecholamines
Fatty acid derivatives:
Prostaglandins
Some of them are water soluble and others are lipid soluble
Effect by intracellular receptors
Steroid hormones, Thyroxine, VD3
Lipid soluble hormones
Intracellular molecules
cAMP, cGMP, IP3, DG, Ca2+


THANK YOU
WELLS FARGO
We're on Track For a Cure

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Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

Dr. Faisal lecture 4

إذا غامَرْتَ في شَرَفٍ مَرُومِ

فَلا تَقنَعْ بما دونَ النّجومِ

فطَعْمُ المَوْتِ في أمْرٍ حَقِيرٍ

كطَعْمِ المَوْتِ في أمْرٍ عَظيمِ

أبو الطيب المتنبي