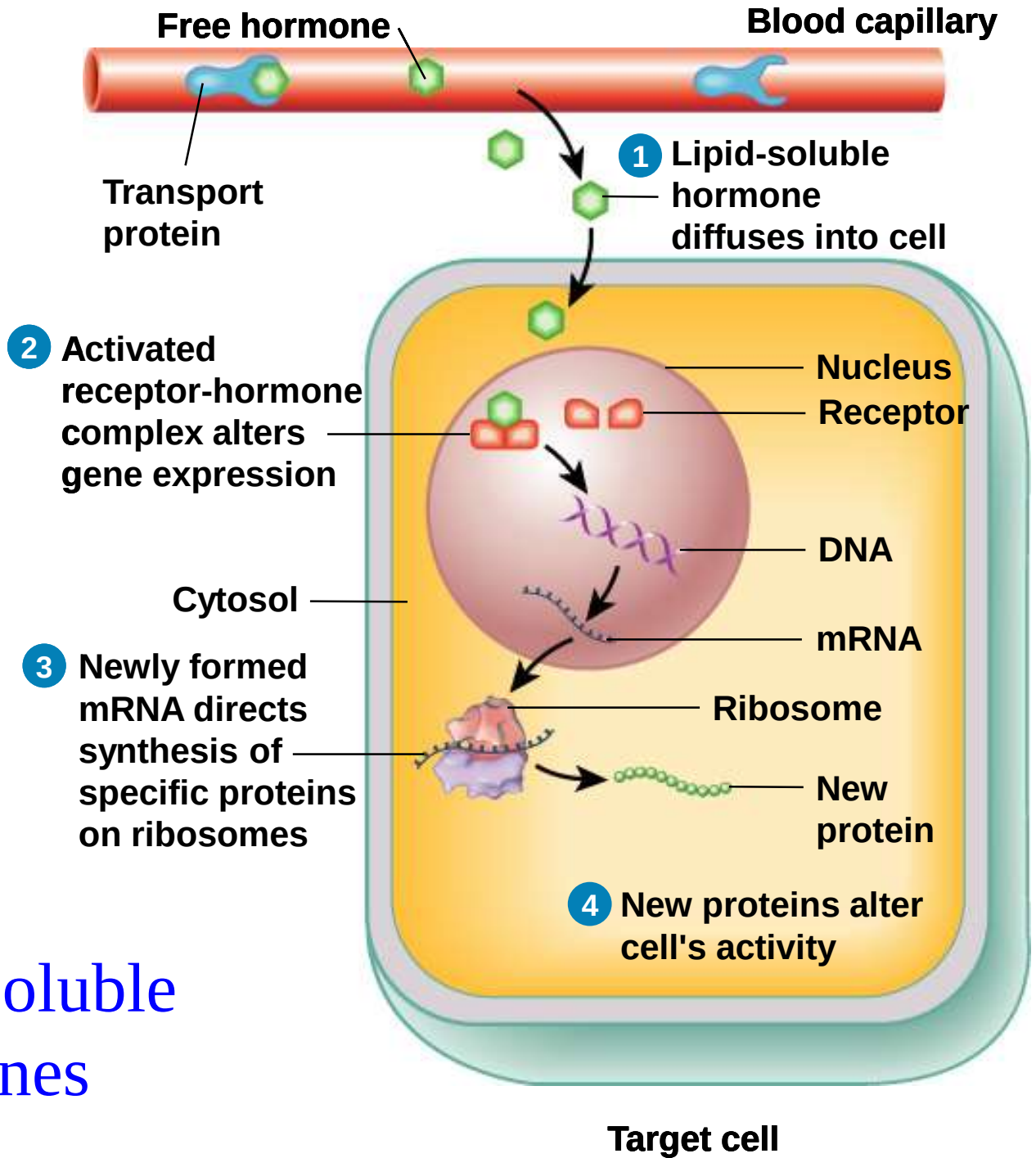
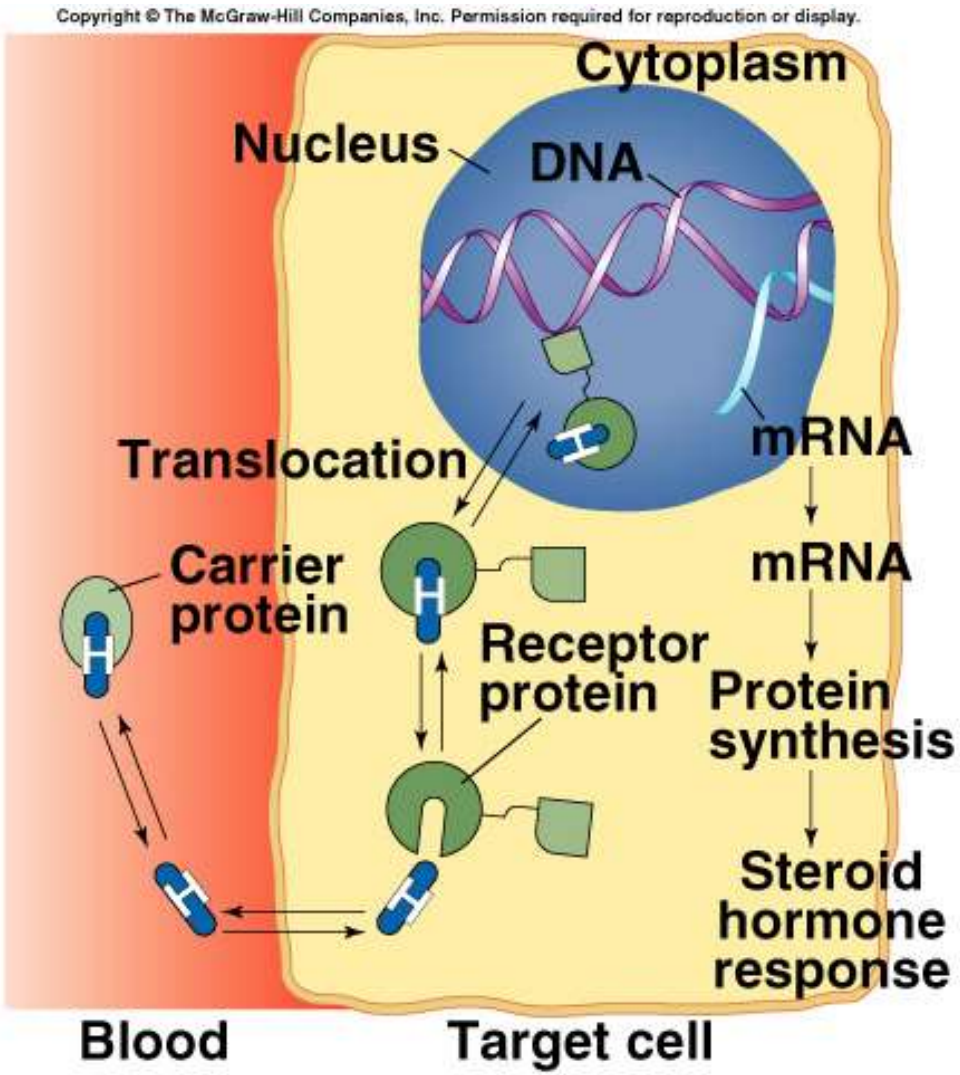
# Lipid-soluble Hormones



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

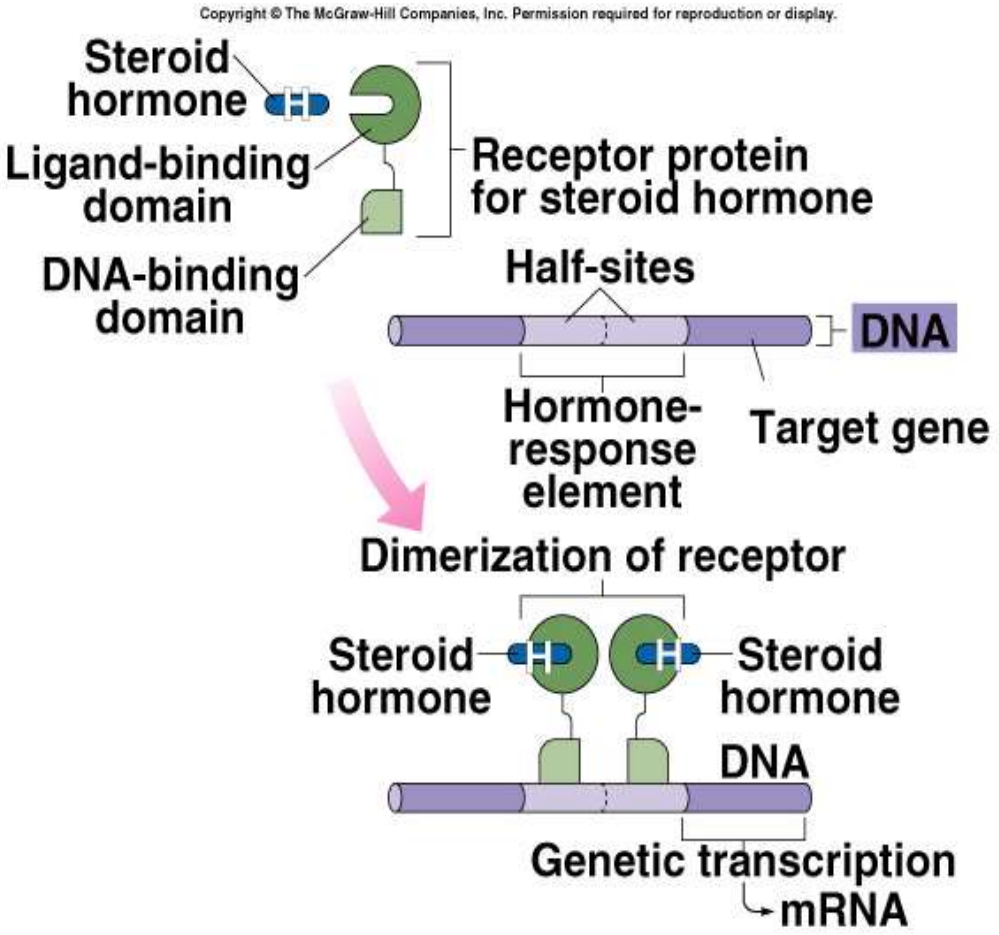


# Nuclear Hormone Receptors

- 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).
  - Located adjacent to gene that will be transcribed.

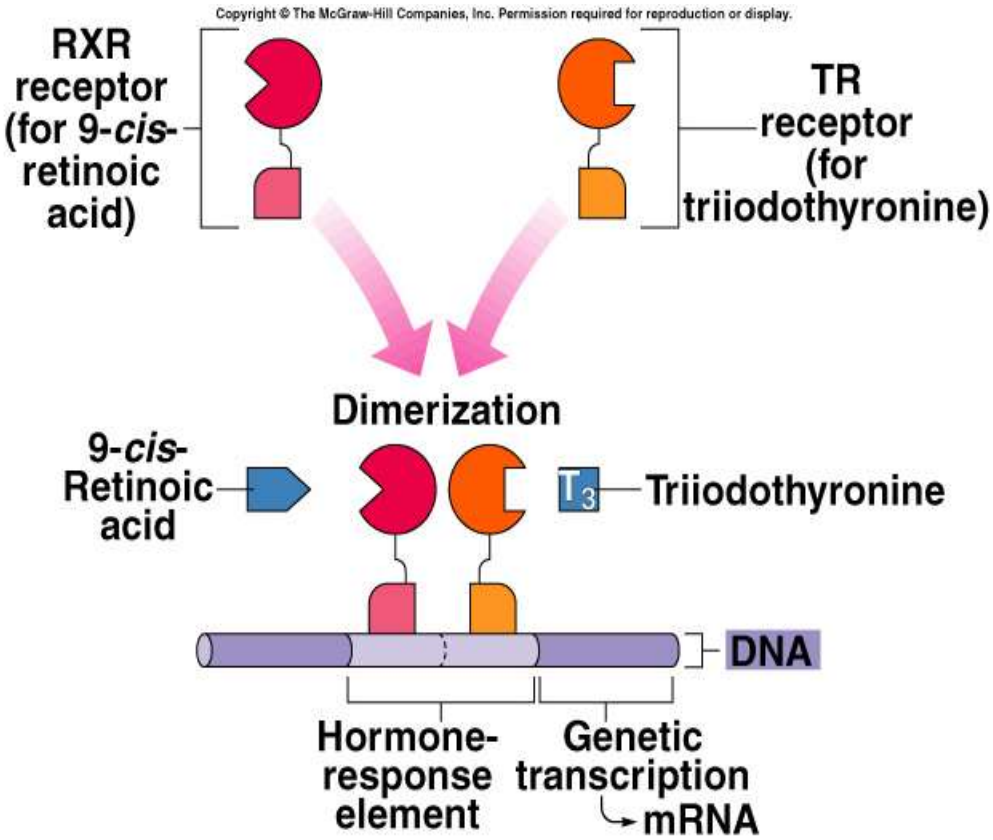
# Mechanisms of Steroid Hormone Action

- Cytoplasmic receptor binds to steroid hormone.
- Translocates to nucleus.
- DNA-binding domain binds to specific HRE of the DNA.
- Dimerization occurs.
  - Process of 2 receptor units coming together at the 2 half-sites.
- Stimulates transcription of particular genes.

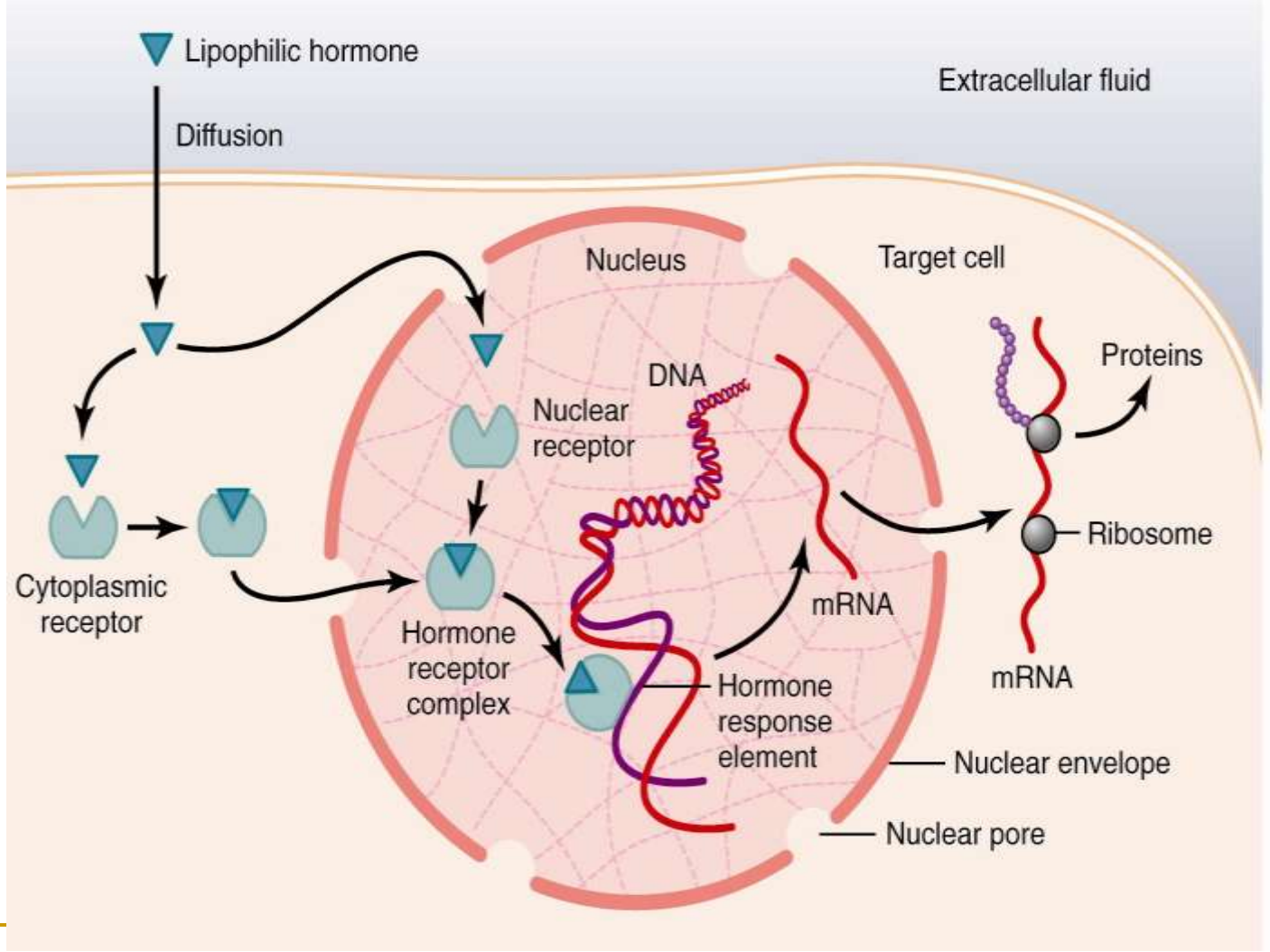


# Mechanism of Thyroid Hormone Action

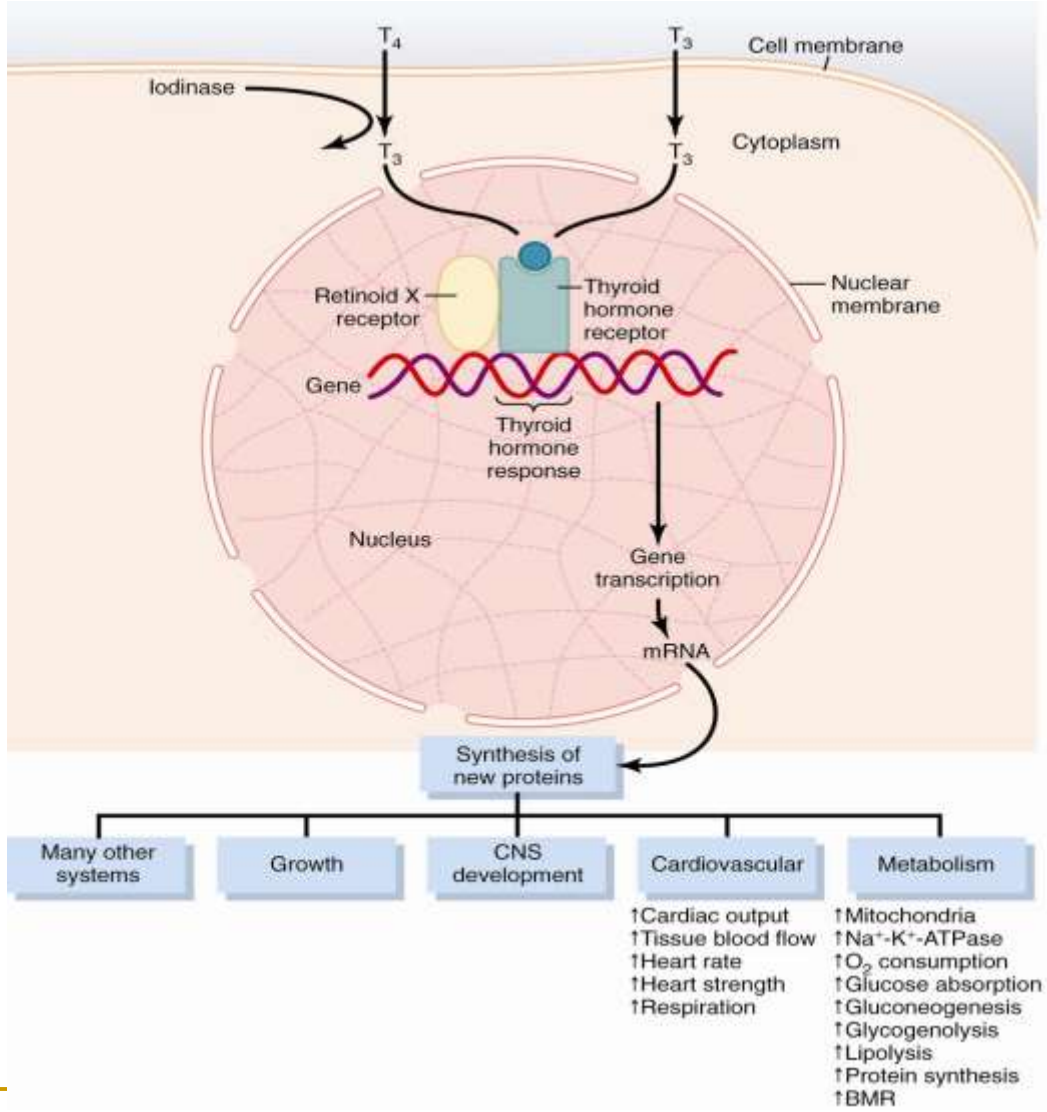
- $T_4$ passes into cytoplasm and is converted to $T_3$.
- Receptor proteins located in nucleus.
  - $T_3$ binds to ligand-binding domain.
  - Other half-site is vitamin A derivative (9-cis-retinoic) acid.
    - DNA-binding domain can then bind to the half-site of the HRE.
  - Two partners can bind to the DNA to activate HRE.
    - Stimulate transcription of genes.



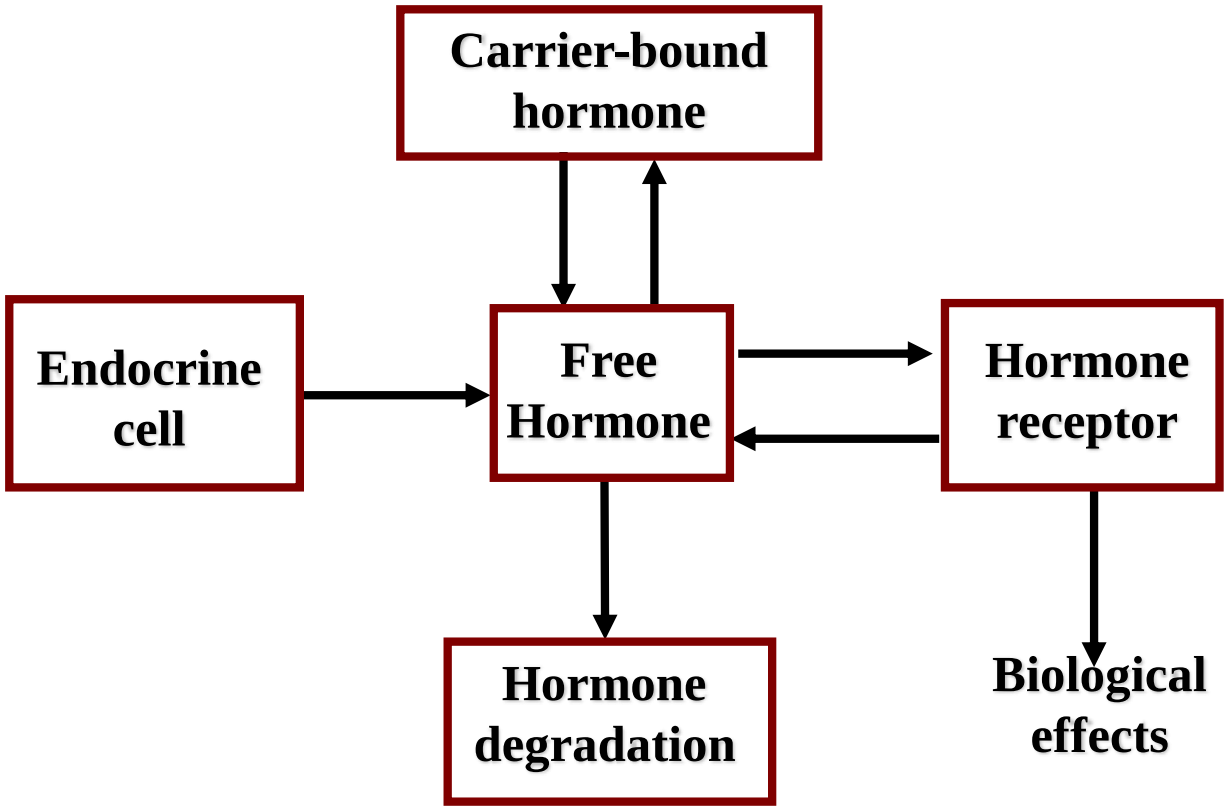
# Steroid & Thyroid Hormones - Mechanism of Action



# Actions of Thyroid Hormones



# Determinants of Free Hormone Receptor Binding



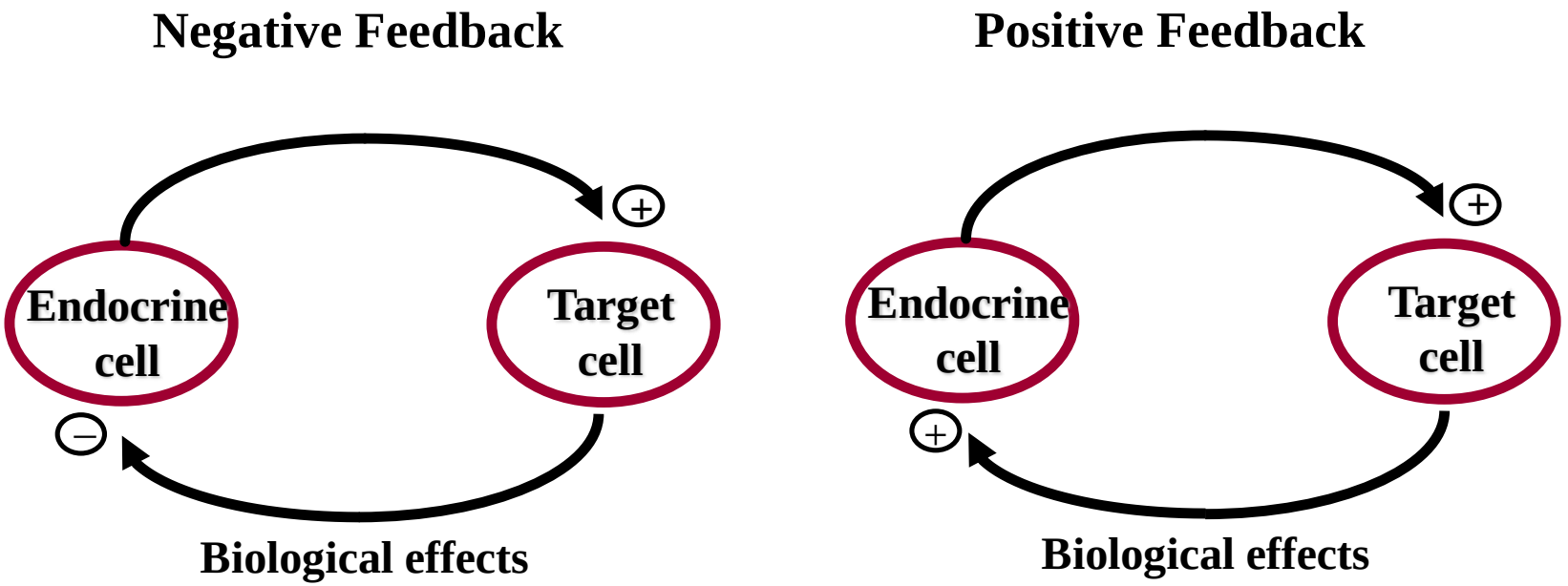
# Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

| 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 |

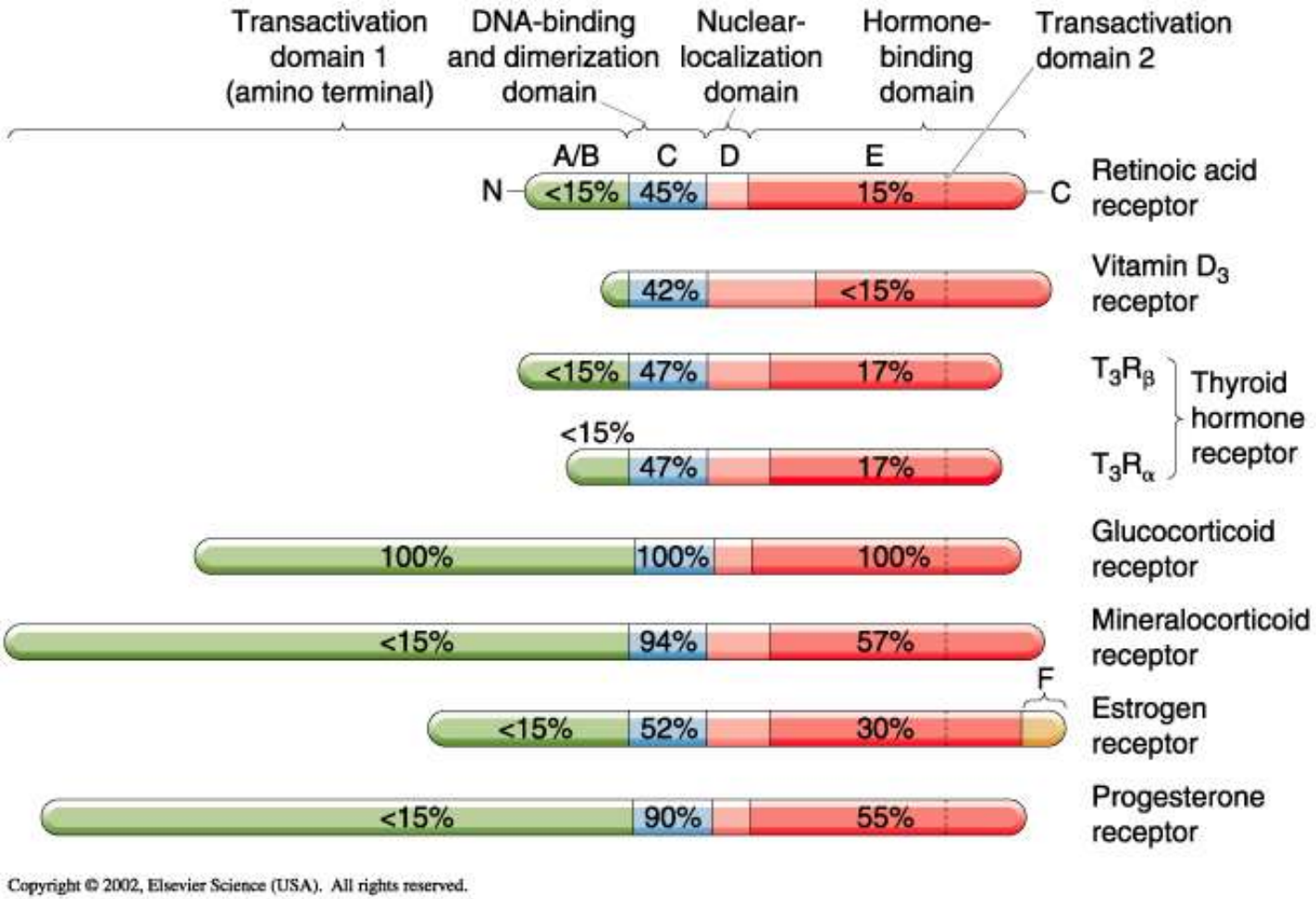
# Circulating Transport Proteins

| 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 |

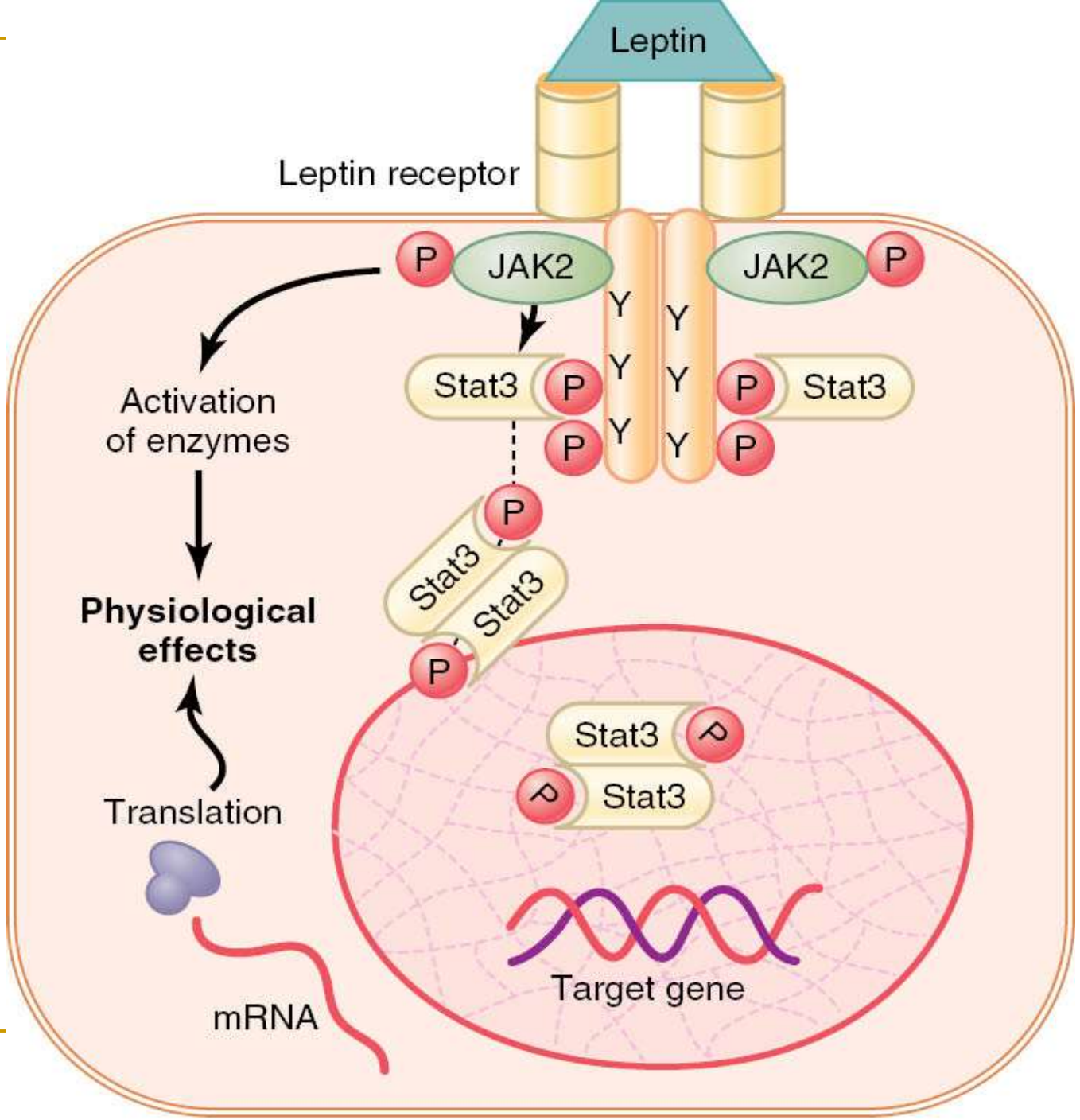
# Feedback Mechanisms



# Steroid & Thyroid Hormones - Receptors



Enzyme-linked Receptor (the Leptin receptor)
JAK= Janus Kinase
STAT= Signal Transducer and Activator of Transcription



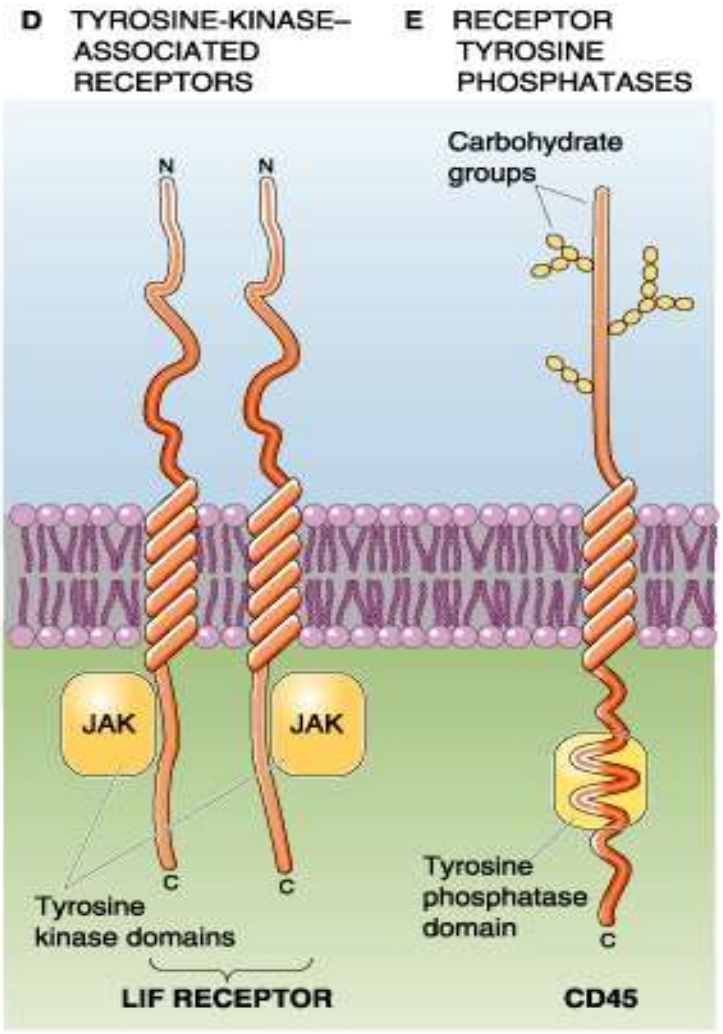
# Enzyme-linked receptor (the leptin receptor)

- 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
- This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins

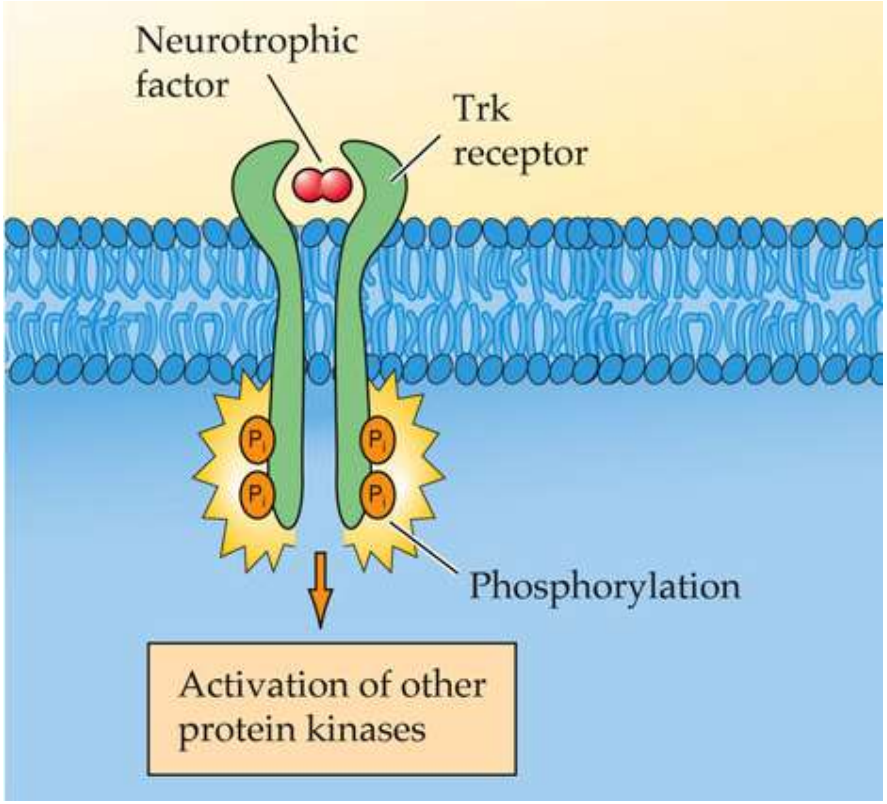
# Enzyme-linked receptor (the leptin receptor)….cont

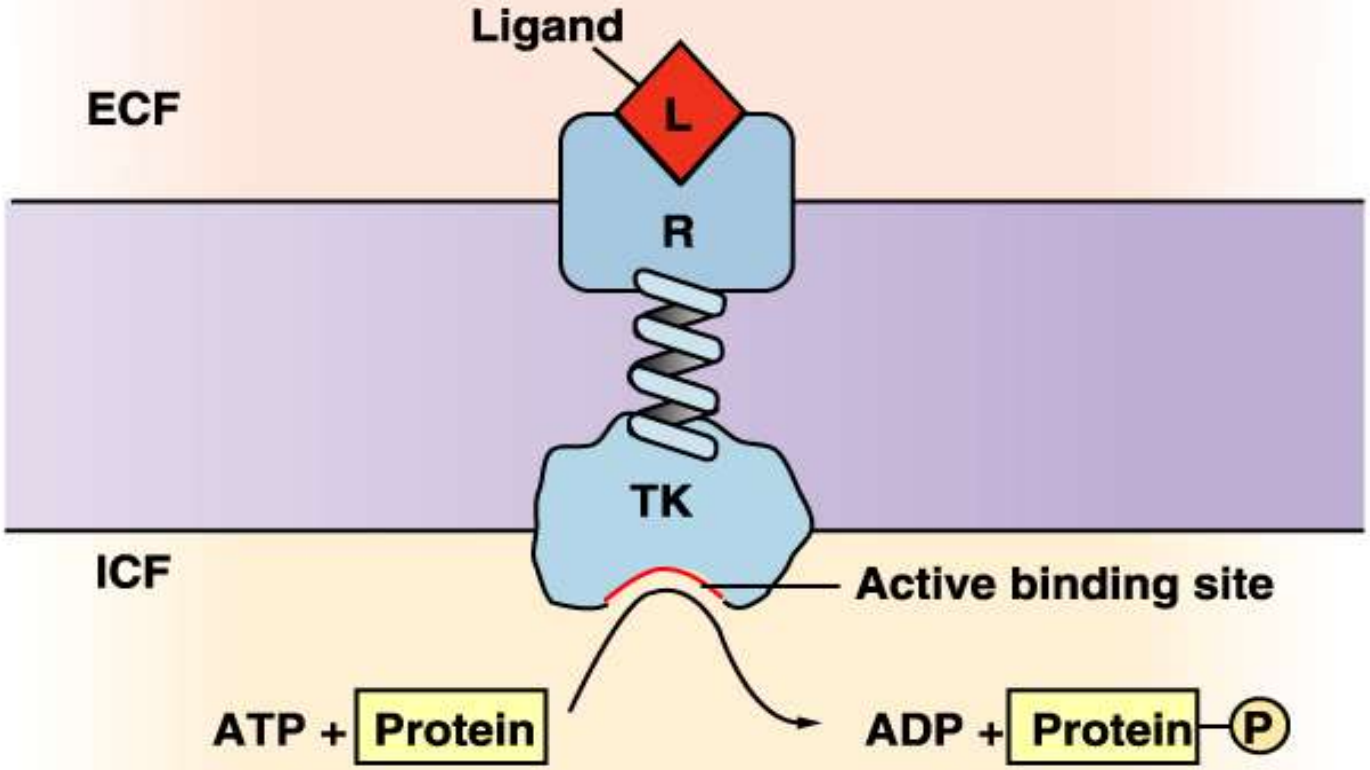
- This then activates the transcription of target genes and synthesis of proteins
- JAK 2 phosphrylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin

# Tyrosine Kinase



# Tyrosine Kinase Receptors:



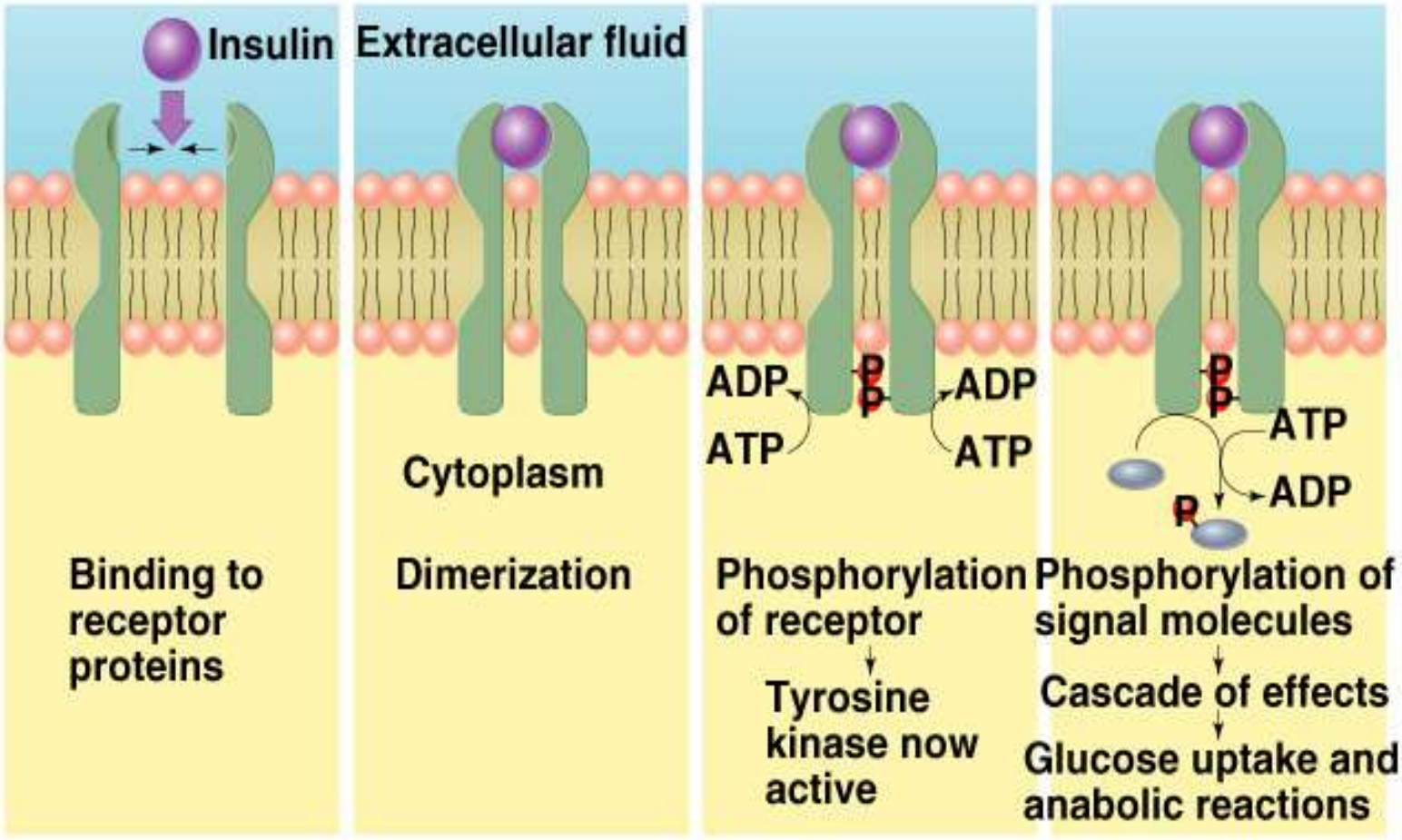

Ligand
L
ECF
R
TK
ICF
Active binding site
ATP + Protein
ADP + Protein
P

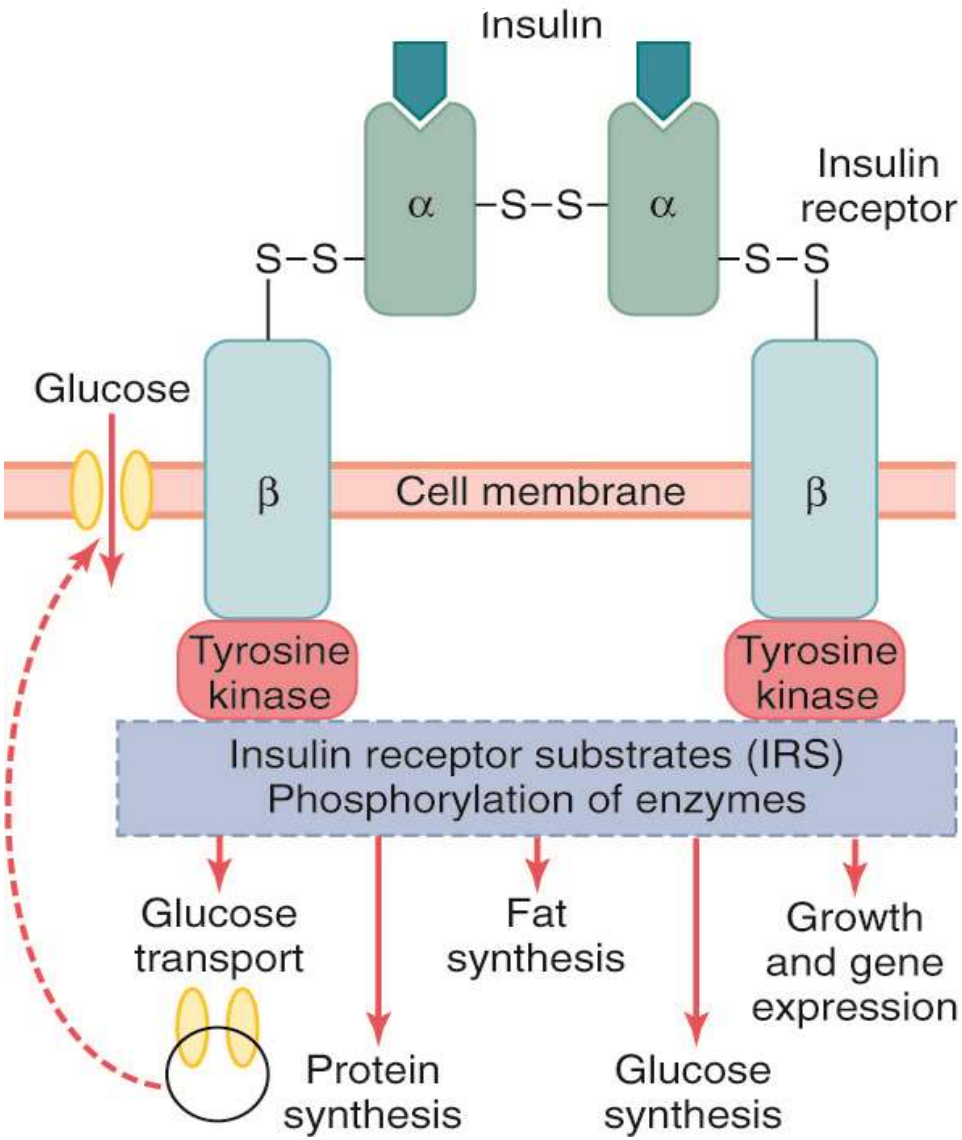
# Tyrosine Kinase

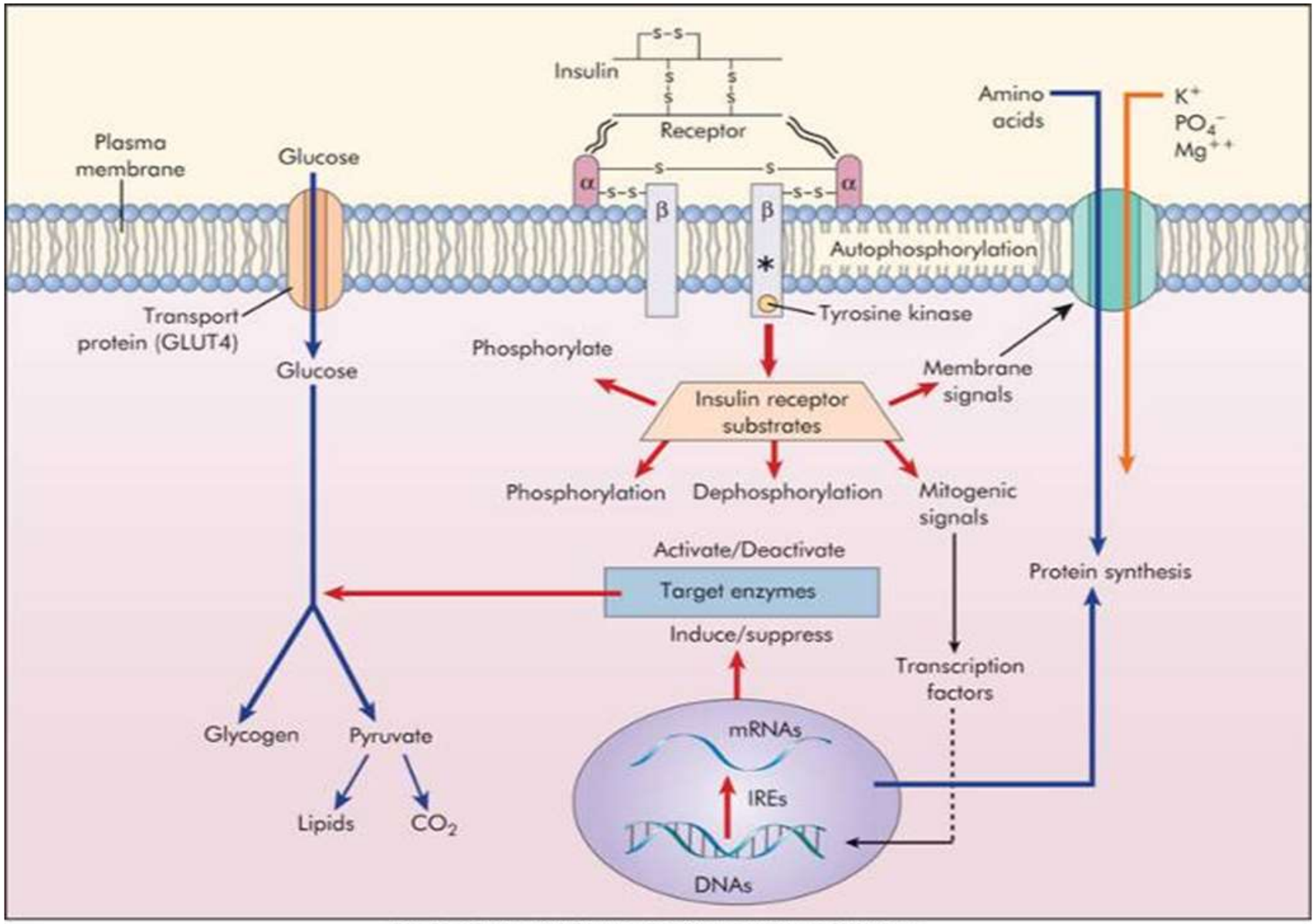
- Insulin receptor consists of 2 units that dimerize when they bind with insulin.
  - Insulin binds to ligand–binding site on plasma membrane, activating enzymatic site in the cytoplasm.
- Autophosphorylation occurs, increasing tyrosine kinase activity.
- Activates signaling molecules.
  - Stimulate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

# Tyrosine Kinase (continued)



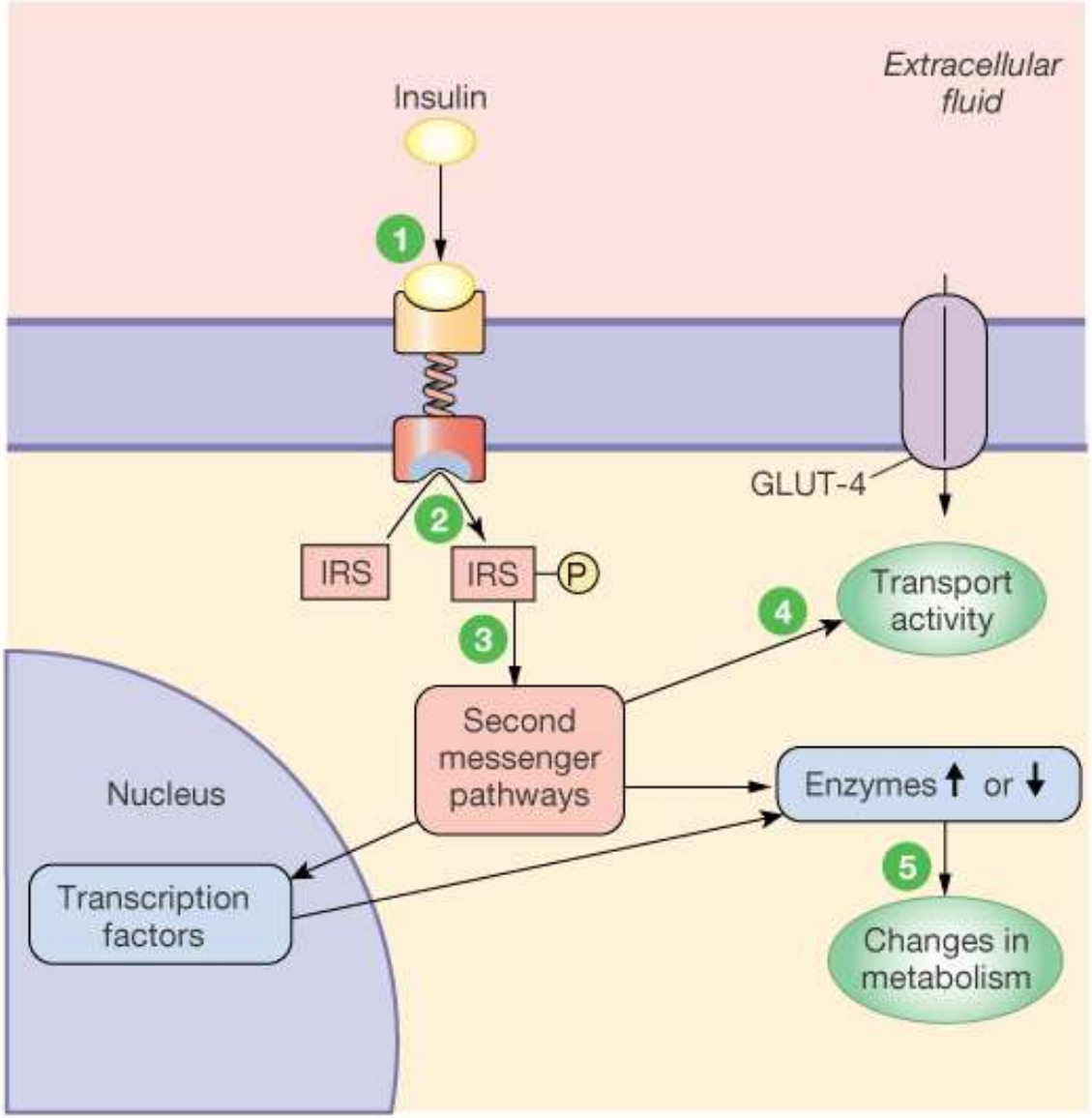



Insulin
α
S–S
α
Insulin receptor
S–S
S–S
Glucose
β
Cell membrane
β
Tyrosine kinase
Tyrosine kinase
Insulin receptor substrates (IRS)
Phosphorylation of enzymes
Glucose transport
Protein synthesis
Fat synthesis
Glucose synthesis
Growth and gene expression

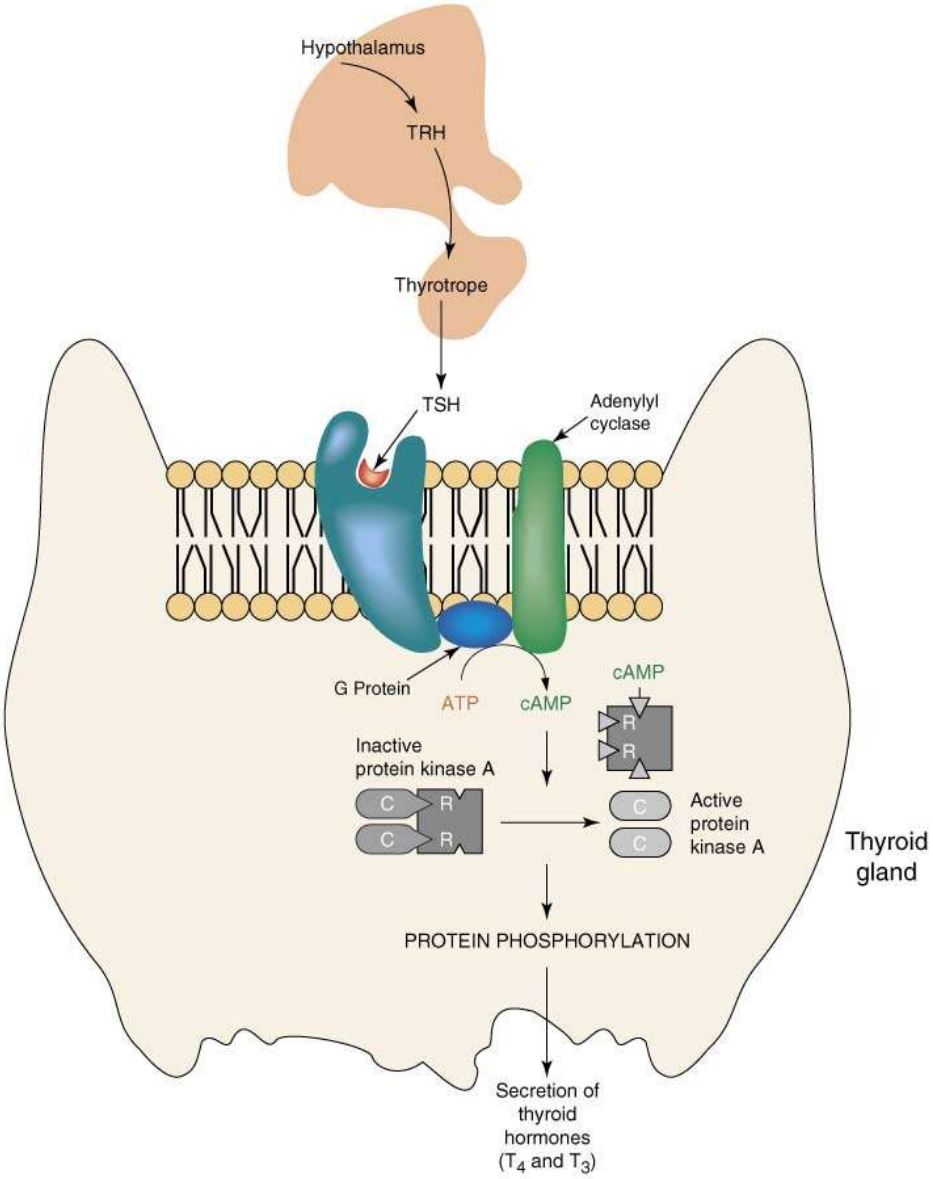



From Berne RM, Levy MN: *Principles of physiology*, ed 3, St Louis, 2000, Mosby.

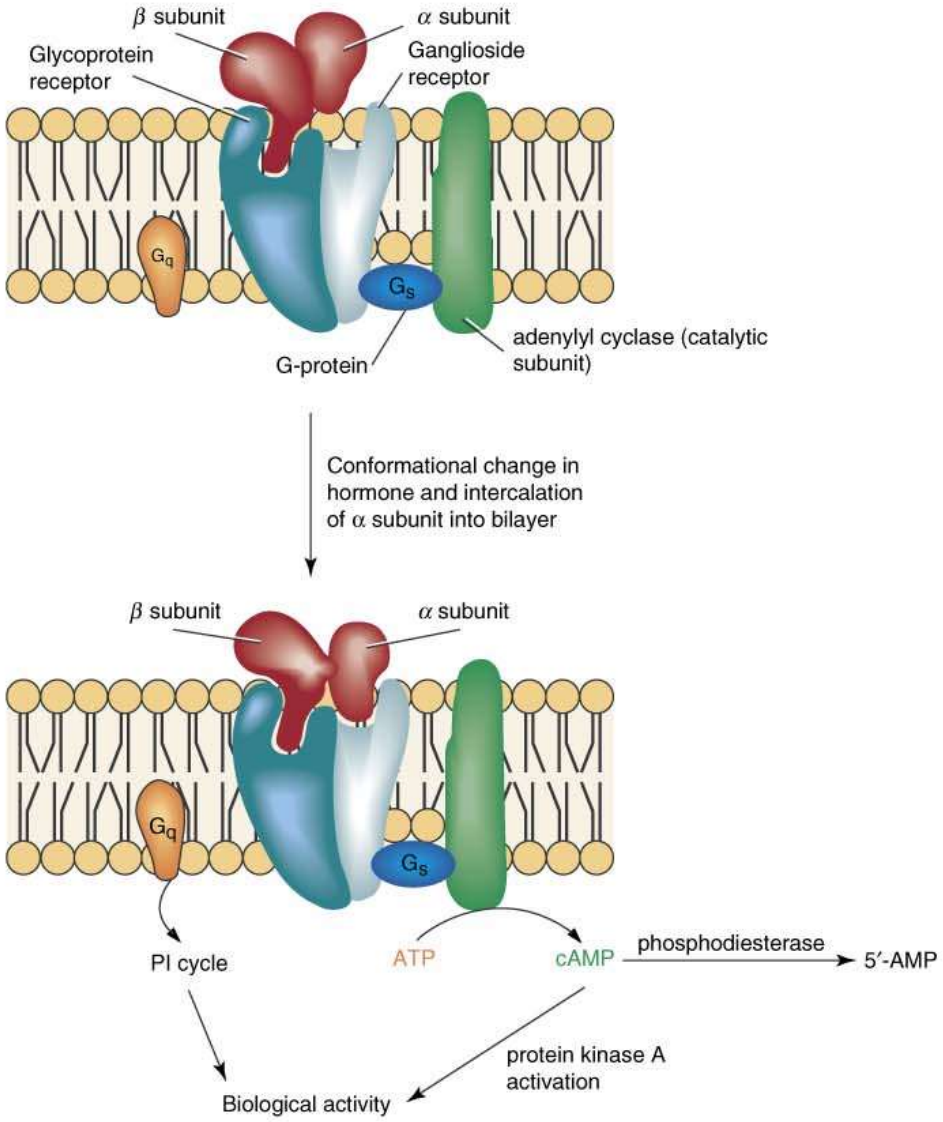
# Insulin Action on Cells:



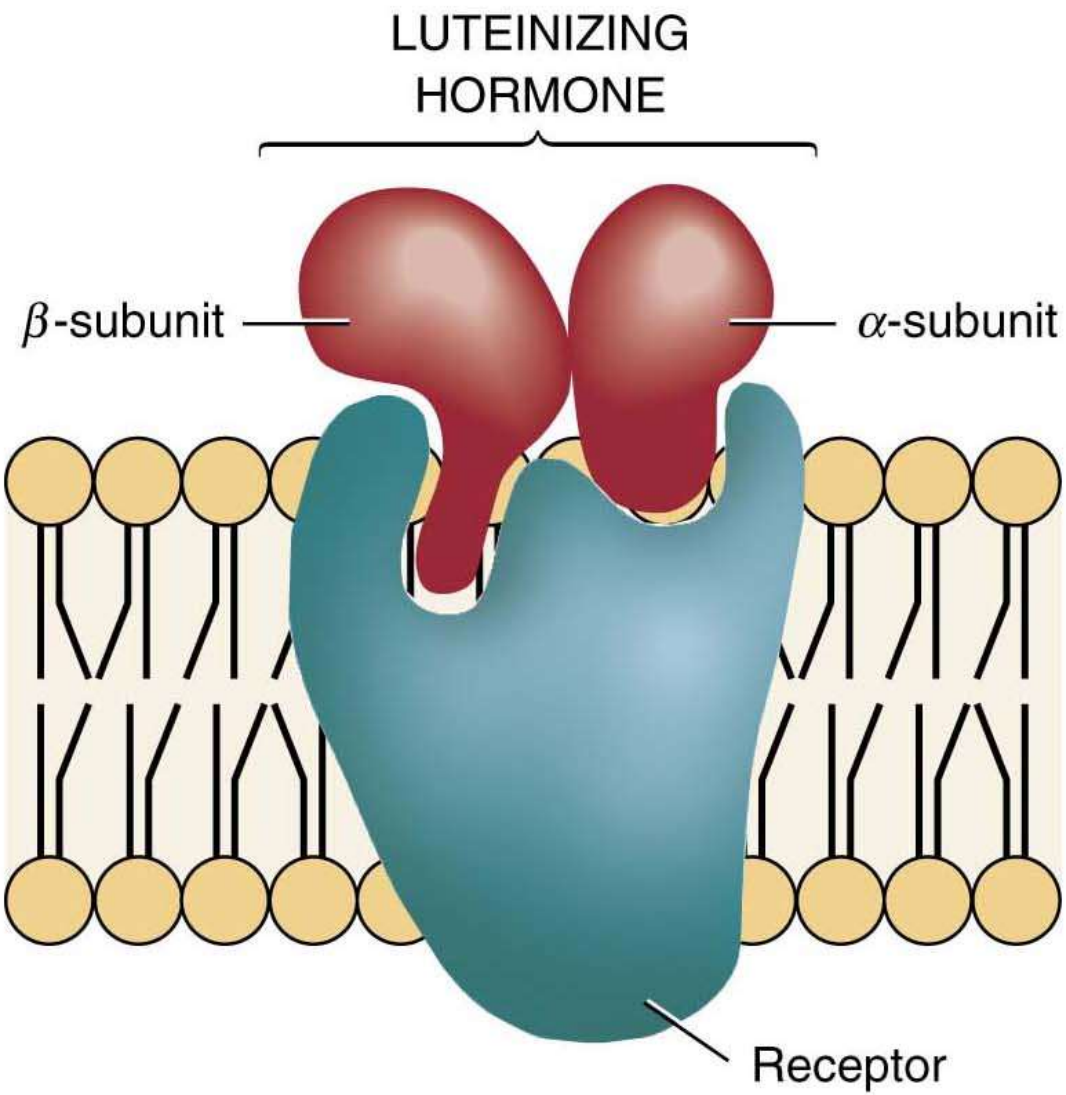

1. Insulin binds to tyrosine kinase receptor.
2. Receptor phosphorylates insulin-receptor substrates (IRS).
3. Second messenger pathways alter protein synthesis and existing proteins.
4. Membrane transport is modified.
5. Cell metabolism is changed.



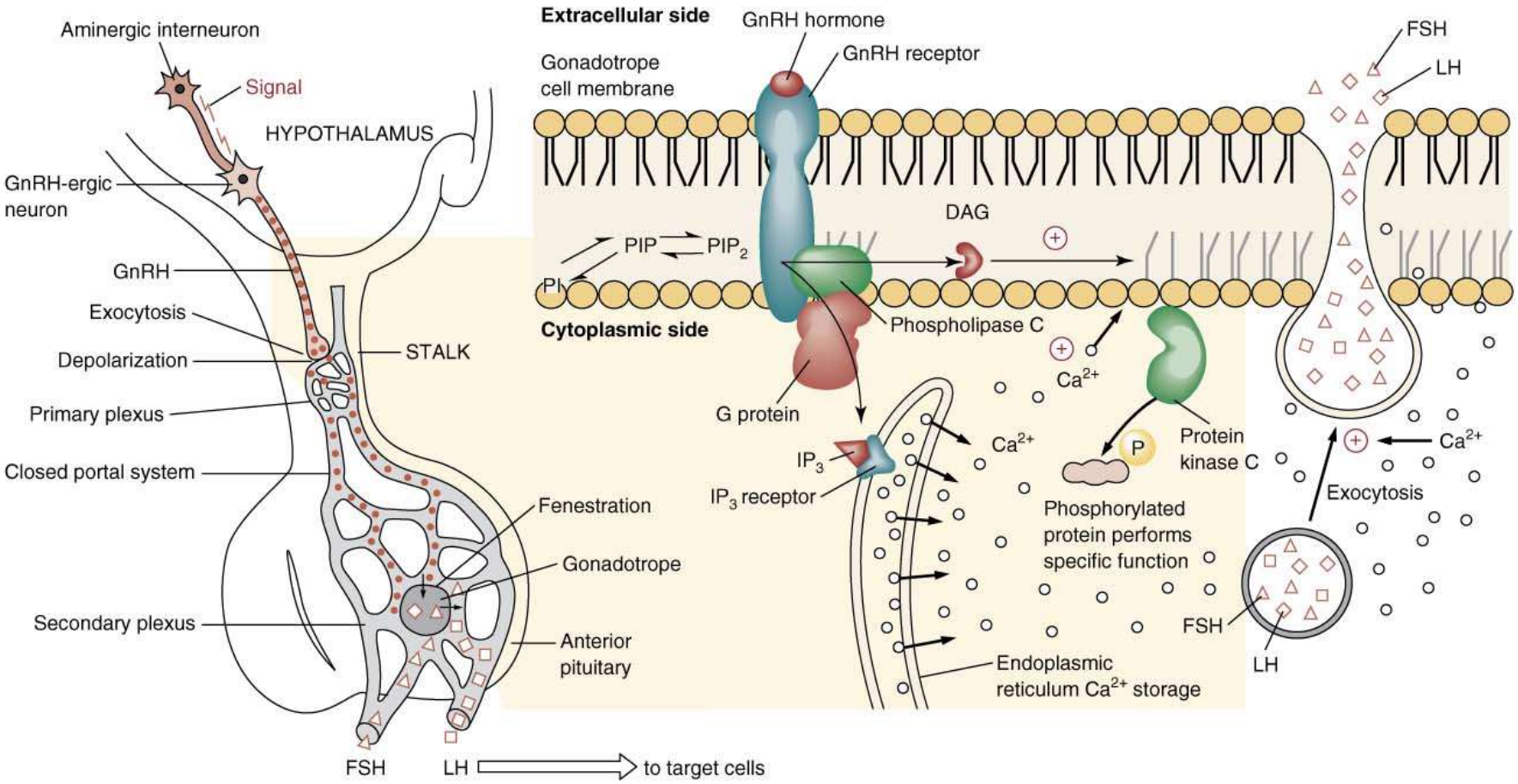

**Effect of TSH on secretion of thyroid hormone.**



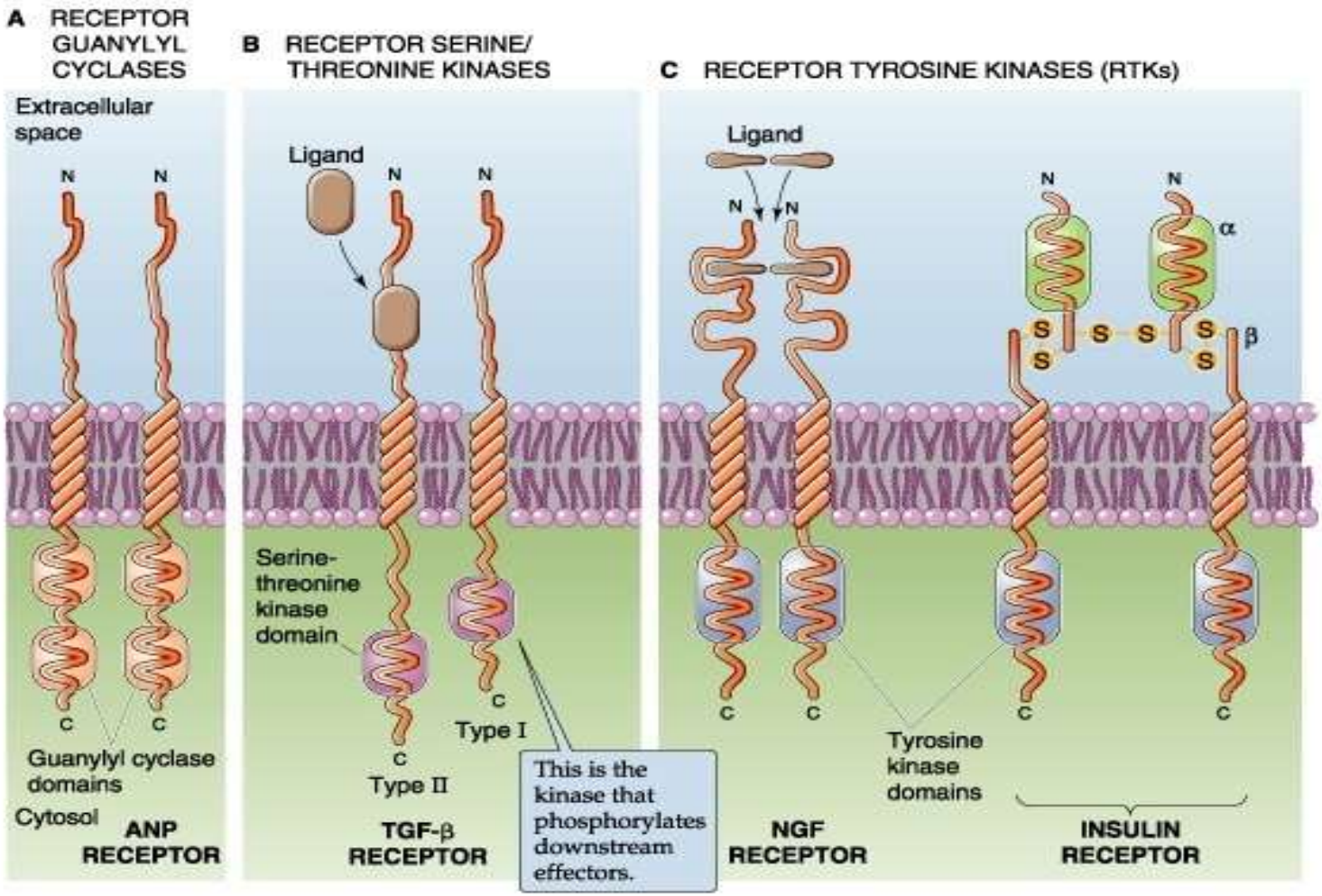

**Model of TSH receptor.** Adapted with modifications from Kohn, L. D., et al. In: G. Litwack (Ed.), *Biochemical Actions of Hormones*, Vol. 12. New York: Academic Press, 1985, p. 466.

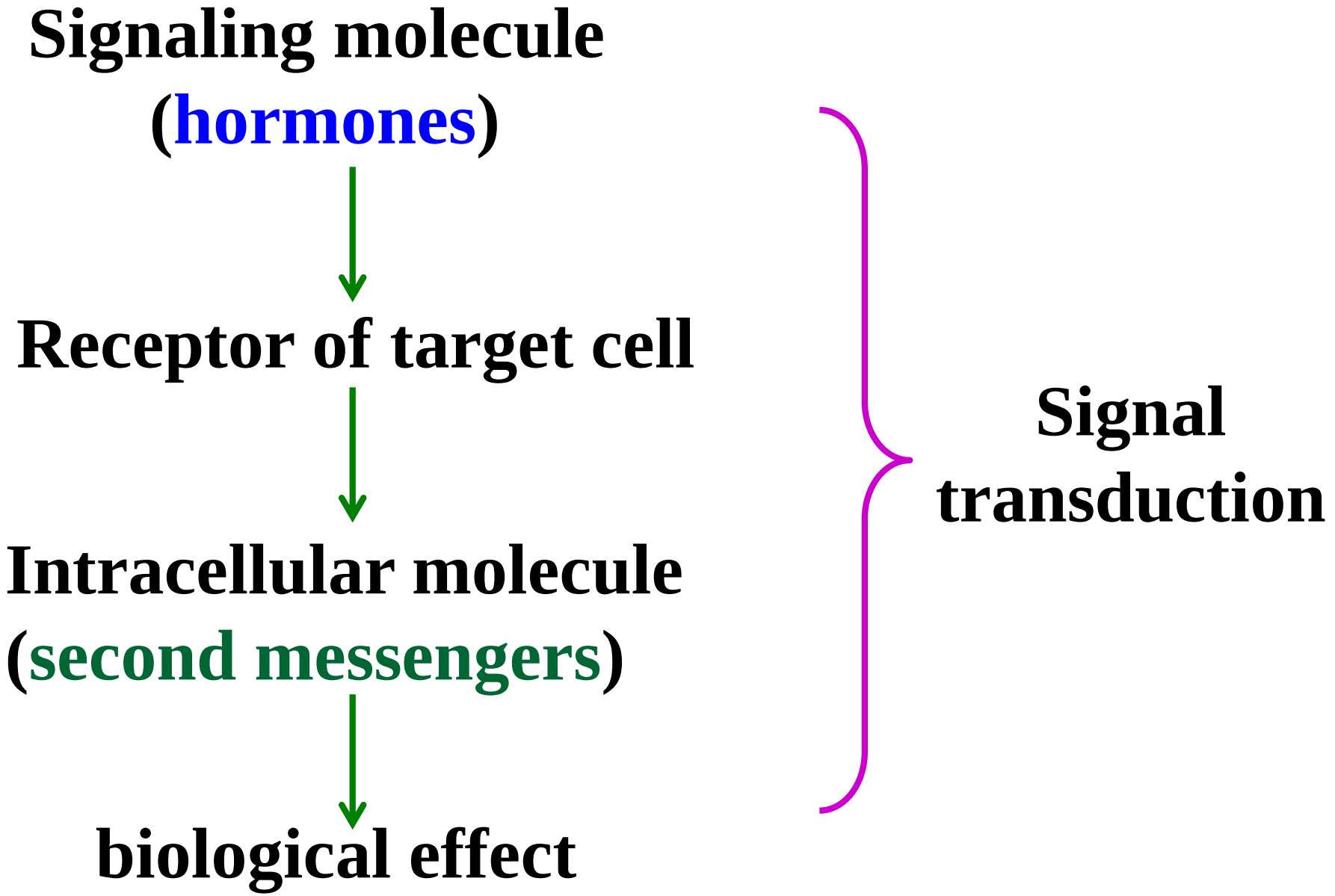



**The interaction of α and β subunits of LH with LH receptor of rat Leydig cells.** Adapted from Alonoso-Whipple, C., Couet, M. L., Doss, R. Koziarz, J., Ogunro, E. A., and Crowley, W. E. Jr. *Endocrinology* 123:1854, 1988.



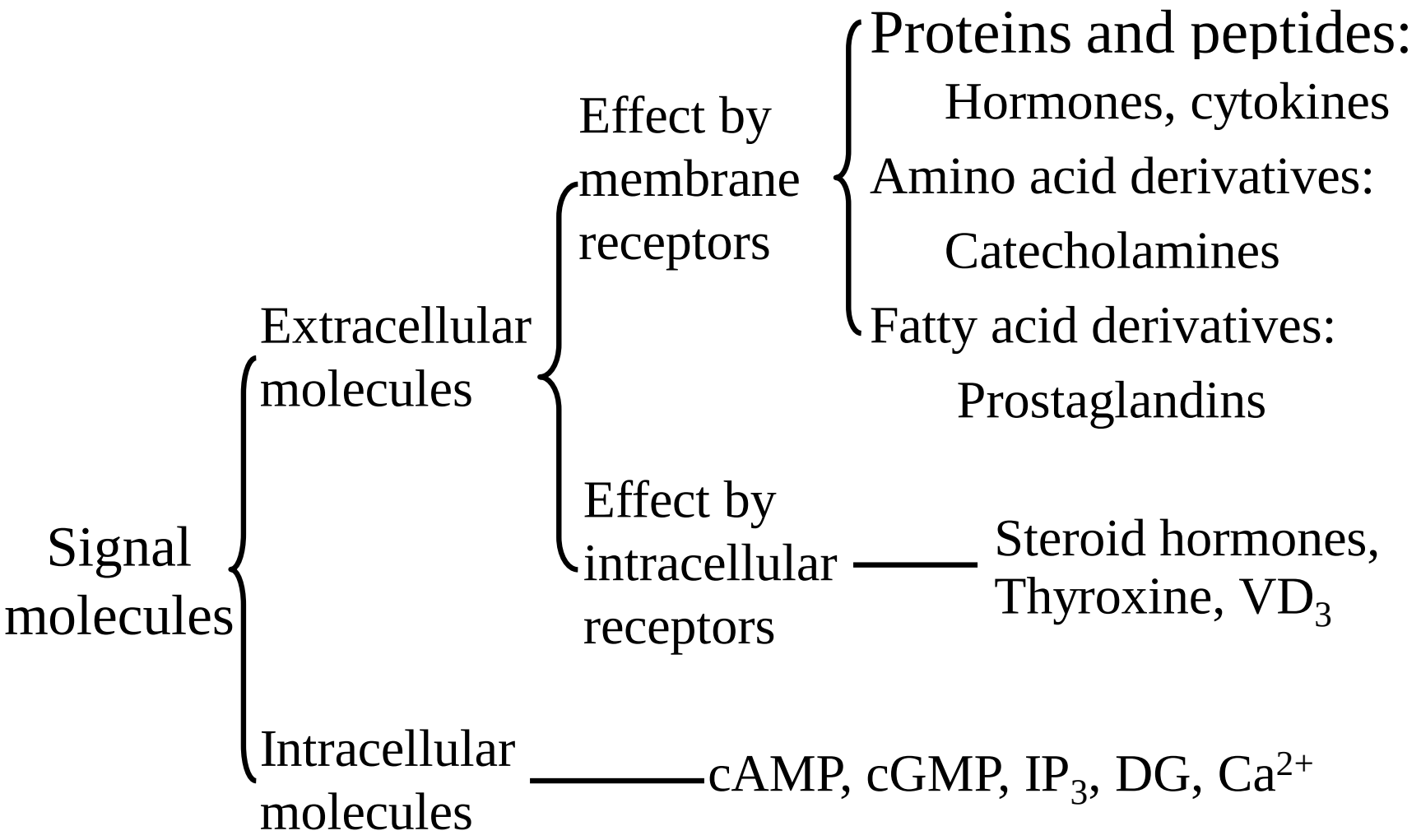

**Regulation of secretion of LH and FSH by protein kinase C.**




Signaling molecule
(hormones)
Receptor of target cell
Intracellular molecule
(second messengers)
biological effect
Signal
transduction

# Third messengers:

**Third messengers are the molecules which transmit message from outside to inside of nucleous or from 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
Effect by intracellular receptors
Steroid hormones, Thyroxine, VD3
Intracellular molecules
cAMP, cGMP, IP3, DG, Ca2+


THANK YOU