# Signal Transduction lec-2

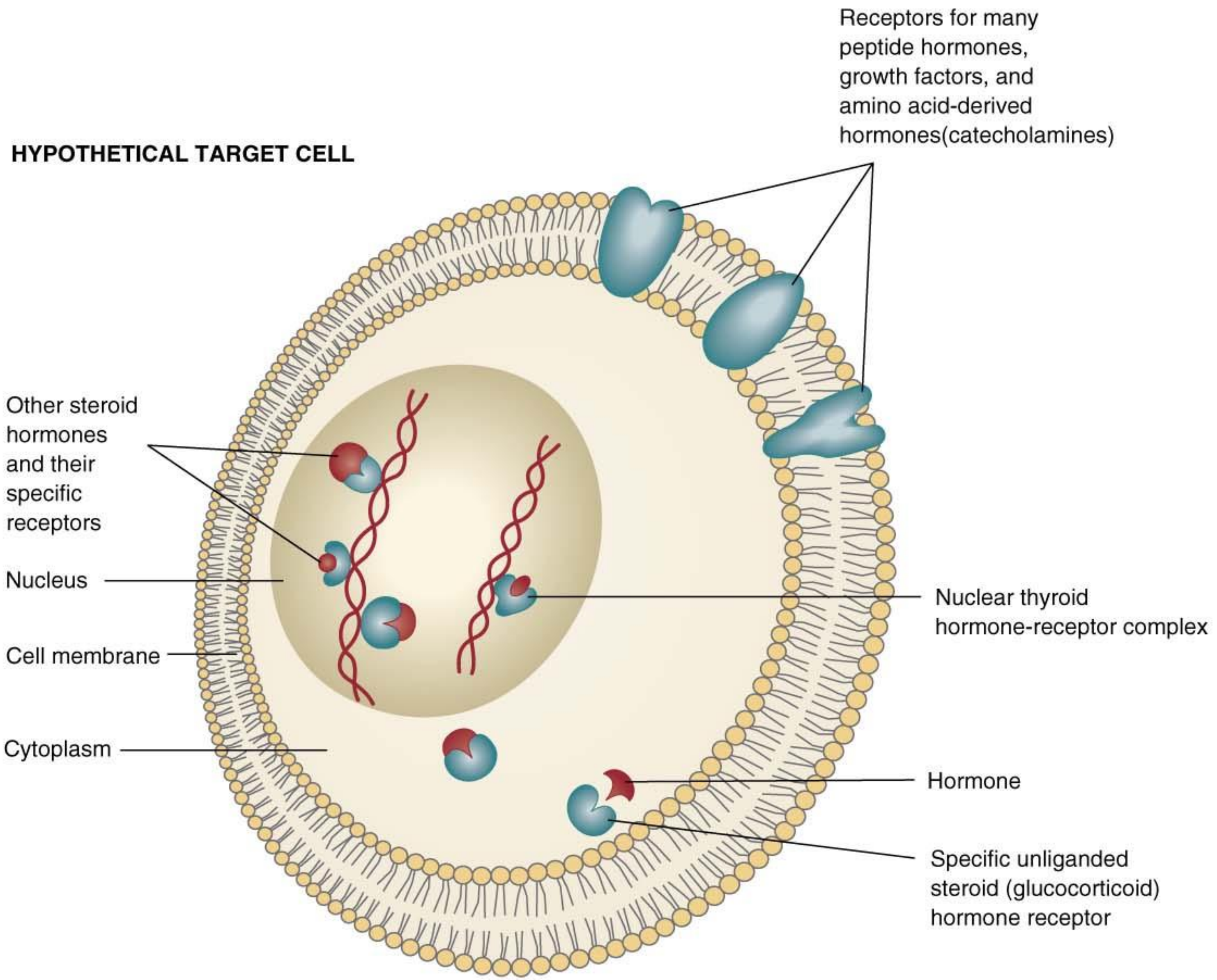
ALAA BAWANEH, MD. PH.D

# Extracellular chemical messengers bring about cell responses by signal transduction

- The term **signal transduction** refers to the process by which incoming signals (instructions from extracellular chemical messengers) are conveyed into the target cell, where they are transformed into the dictated cellular response

# Hormone Receptors

- The locations for the different types of hormone receptors are generally the following:
- 1. *In or on the surface of the cell membrane.* The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.
- 2. *In the cell cytoplasm.* The primary receptors for the different steroid hormones are found mainly in the cytoplasm.
- 3. *In the cell nucleus.* The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes



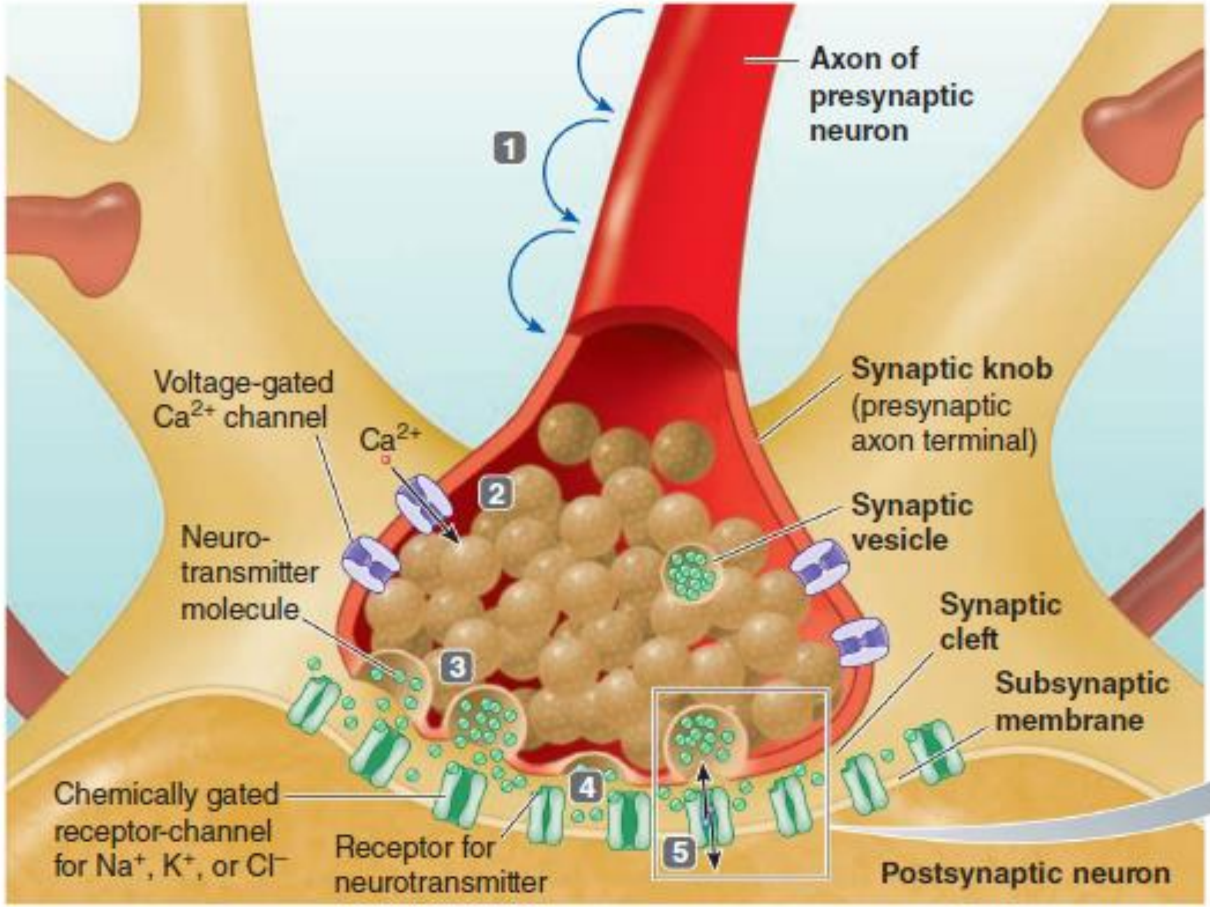

**. Diagram showing the different locations of classes of hormone receptors expressed by a target cell.**

Almost without exception, a hormone affects its target tissues by first forming a Hormone-Receptor Complex.

# Signal Transduction Pathways Used by Extracellular Chemical Messengers

- **I. Pathway used by lipid-soluble extracellular messengers that bind to intracellular receptors**
- A. Function in nucleus to change specific gene activity (ex: steroid hormones)
- **II. Pathways used by water-soluble extracellular messengers that bind to surface membrane receptors**
- A. Bind to and open or close chemically gated receptor-channels (ex: neurotransmitters)
- B. Bind to G-protein-coupled receptors (GPCRs) and activate second-messenger pathways (ex: eicosanoids and most peptide hormones)
- C. Bind to and activate receptor–enzyme complexes
- 1. Use tyrosine kinase pathway, where the receptor itself functions as an enzyme (ex: insulin, growth factors)
- 2. Use JAK/STAT pathway, where the receptor and attached enzymes function as a unit (ex: prolactin, immune cytokines)

# Ion Channel–Linked Receptors



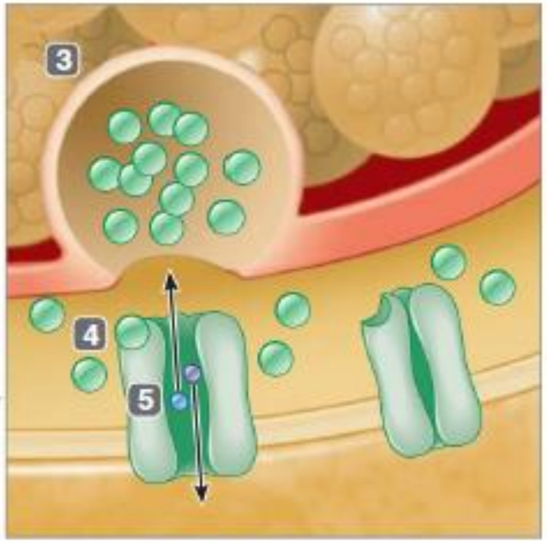

1 Action potential reaches axon terminal of presynaptic neuron.

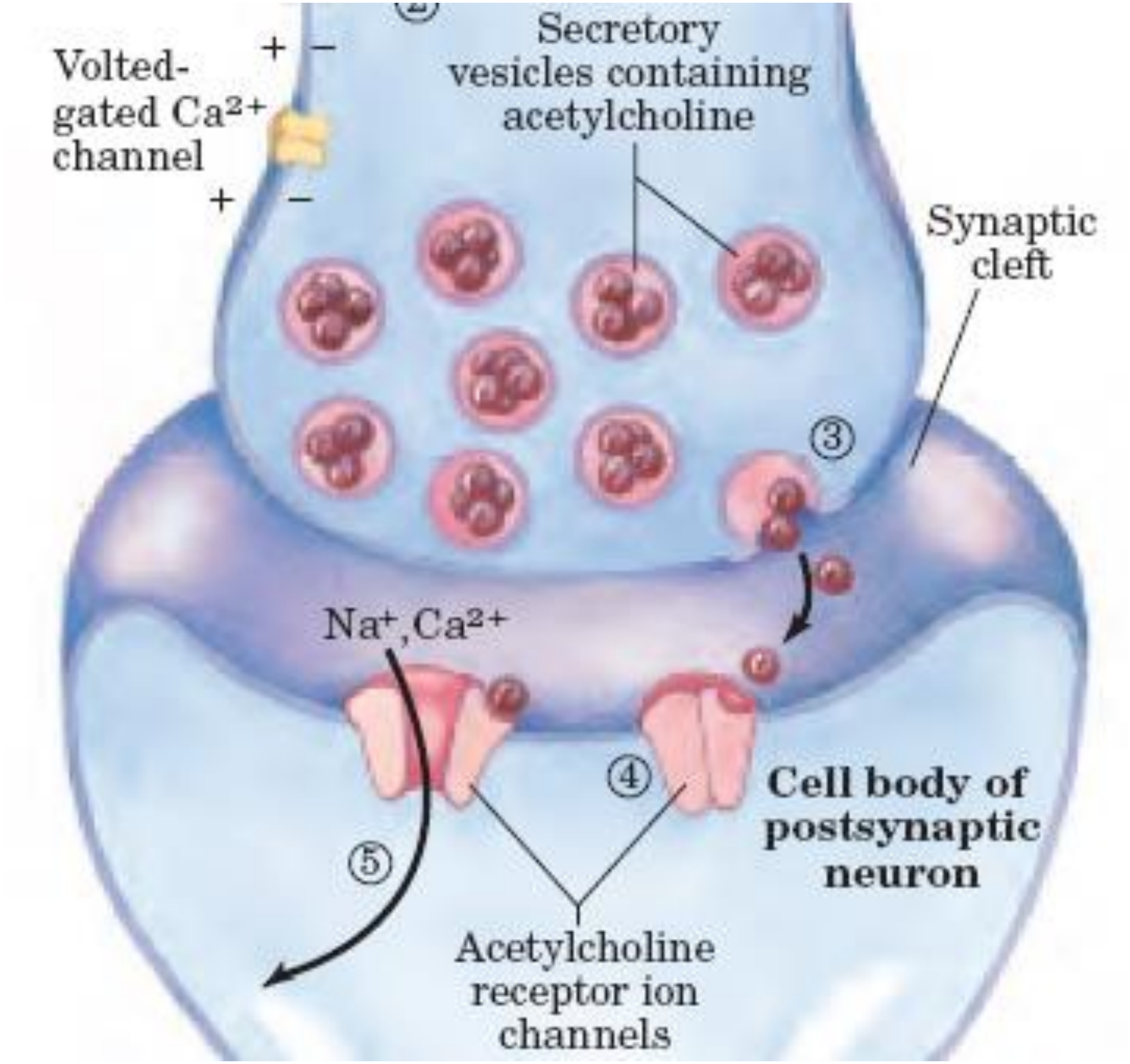
2 $Ca^{2+}$ enters synaptic knob (presynaptic axon terminal).

3 Neurotransmitter is released by exocytosis into synaptic cleft.

4 Neurotransmitter binds to receptors that are an integral part of chemically gated channels on subsynaptic membrane of postsynaptic neuron.

5 Binding of neurotransmitter to receptor-channel opens that specific channel.



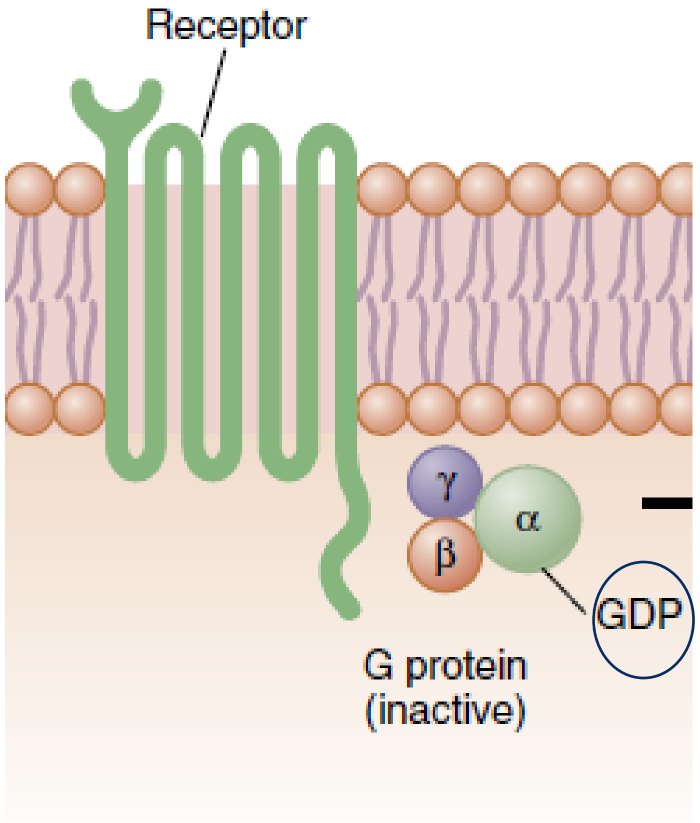


Volted-
gated Ca²⁺
channel
Secretory
vesicles containing
acetylcholine
Synaptic
cleft
③
Na⁺,Ca²⁺
④
Cell body of
postsynaptic
neuron
⑤
Acetylcholine
receptor ion
channels

# Signal Transduction Pathways Used by Extracellular Chemical Messengers

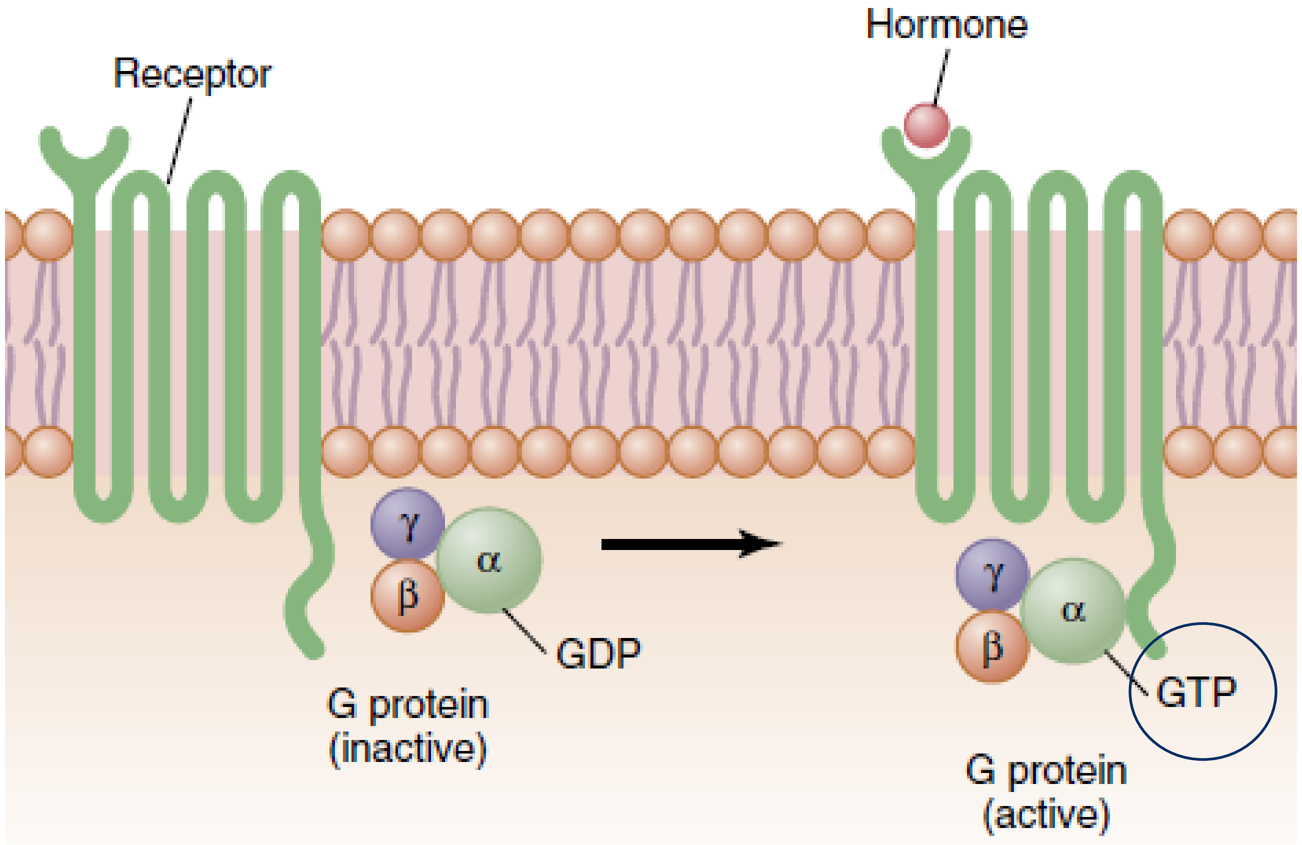
- **I. Pathway used by lipid-soluble extracellular messengers that bind to intracellular receptors**
- A. Function in nucleus to change specific gene activity (ex: steroid hormones)
- **II. Pathways used by water-soluble extracellular messengers that bind to surface membrane receptors**
- A. Bind to and open or close chemically gated receptor-channels (ex: neurotransmitters)
- B. Bind to G-protein-coupled receptors (GPCRs) and activate second-messenger pathways (ex: eicosanoids and most peptide hormones)
- C. Bind to and activate receptor–enzyme complexes
- 1. Use tyrosine kinase pathway, where the receptor itself functions as an enzyme (ex: insulin, growth factors)
- 2. Use JAK/STAT pathway, where the receptor and attached enzymes function as a unit (ex: prolactin, immune cytokines)

# G Protein–Linked Hormone Receptors



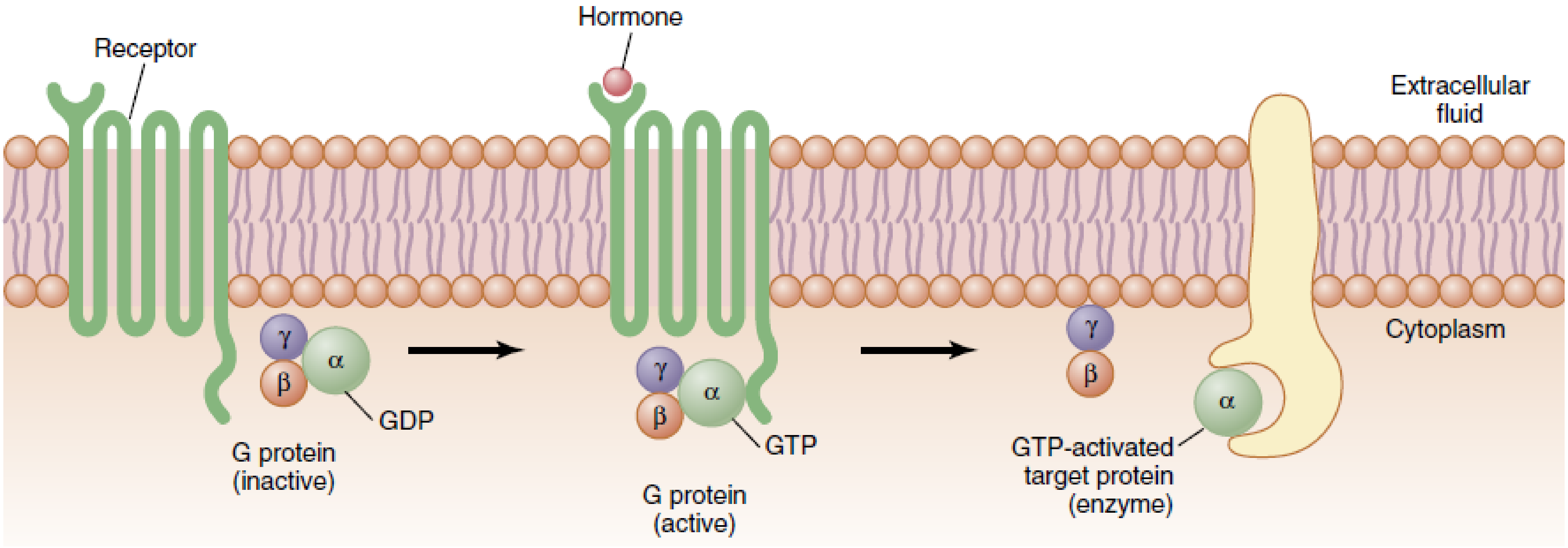

- *Heterotrimeric guanosine triphosphate (GTP)-binding proteins (G proteins)*
- Have seven transmembrane segments motifs of α helices that loop in and out of the cell membrane
- The cytoplasmic tail of the receptor are coupled to G proteins that include three (i.e.,trimeric) parts—the α, β, and γ subunits.

# G Protein–Linked Hormone Receptors




- When the ligand (hormone) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins and induces intracellular signals

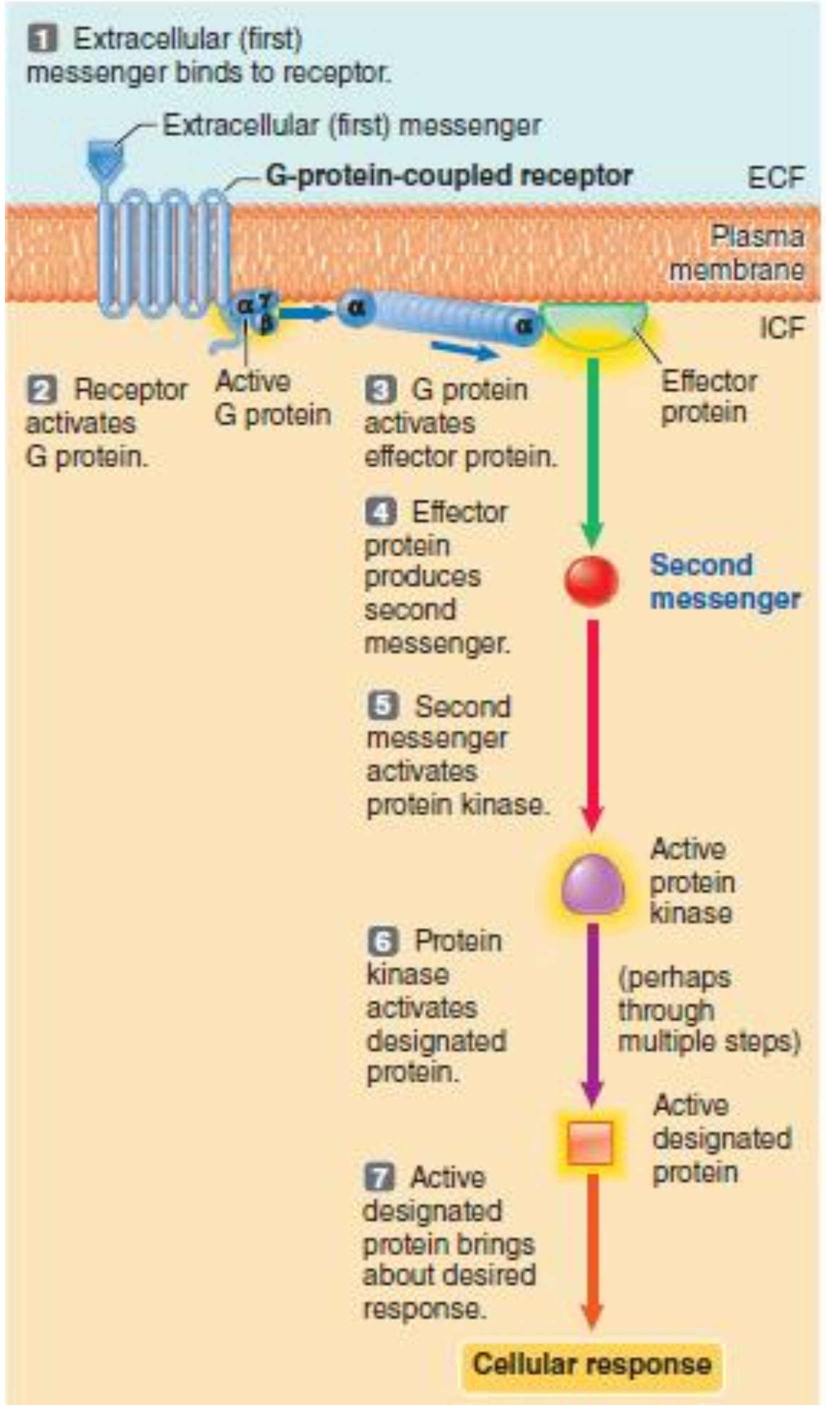
# G Protein–Linked Hormone Receptors




(1) open or close cell membrane ion channels
(2) change the activity of an enzyme in the cytoplasm of the cell
(3) activate gene transcription.

# G Protein–Linked Hormone Receptors

- Binding of the first messenger to the receptor activates the **G protein**,
- On activation, a portion of the G protein shuttles along the membrane to alter the activity of a nearby membrane protein called the **effector protein**.
- Once altered, the effector protein leads to an increased concentration of an intracellular messenger, known as the **second messenger**.
- The second messenger relays the orders through a cascade of chemical reactions inside the cell that cause a change in the shape and function of designated proteins.



# G Protein–Linked Hormone Receptors

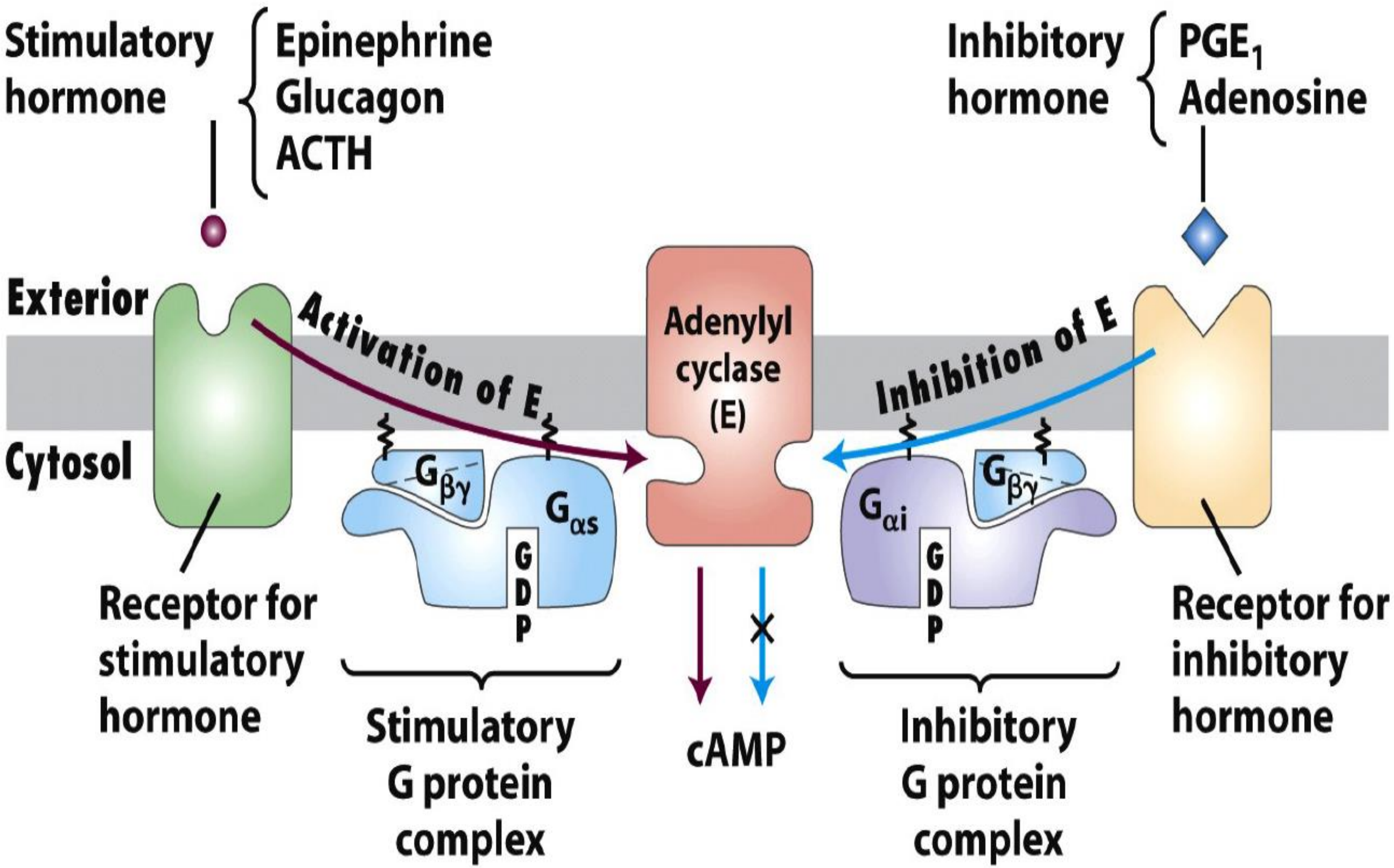



Figure 15-21

# G Protein–Linked Hormone Receptors

- **Different** isoforms of $\mathbf{G_\alpha}$ have different signal roles. E.g.:
  - The **stimulatory** $\mathbf{G_{s\alpha}}$, when it binds GTP, **activates** Adenylate cyclase.
  - An **inhibitory** $\mathbf{G_{i\alpha}}$, when it binds GTP, **inhibits** Adenylate cyclase.

**Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes.**

- The complex of $\mathbf{G_{\gamma\beta}}$ that is released when $G_\alpha$ binds GTP is itself an effector that binds to and **activates or inhibits** several other proteins.

  E.g., $\mathbf{G_{\gamma\beta}}$ **inhibits** one of several isoforms of **Adenylate Cyclase**, contributing to rapid signal turnoff in cells that express that enzyme.

# G Protein–Linked Hormone Receptors

**Turn off of the signal:**

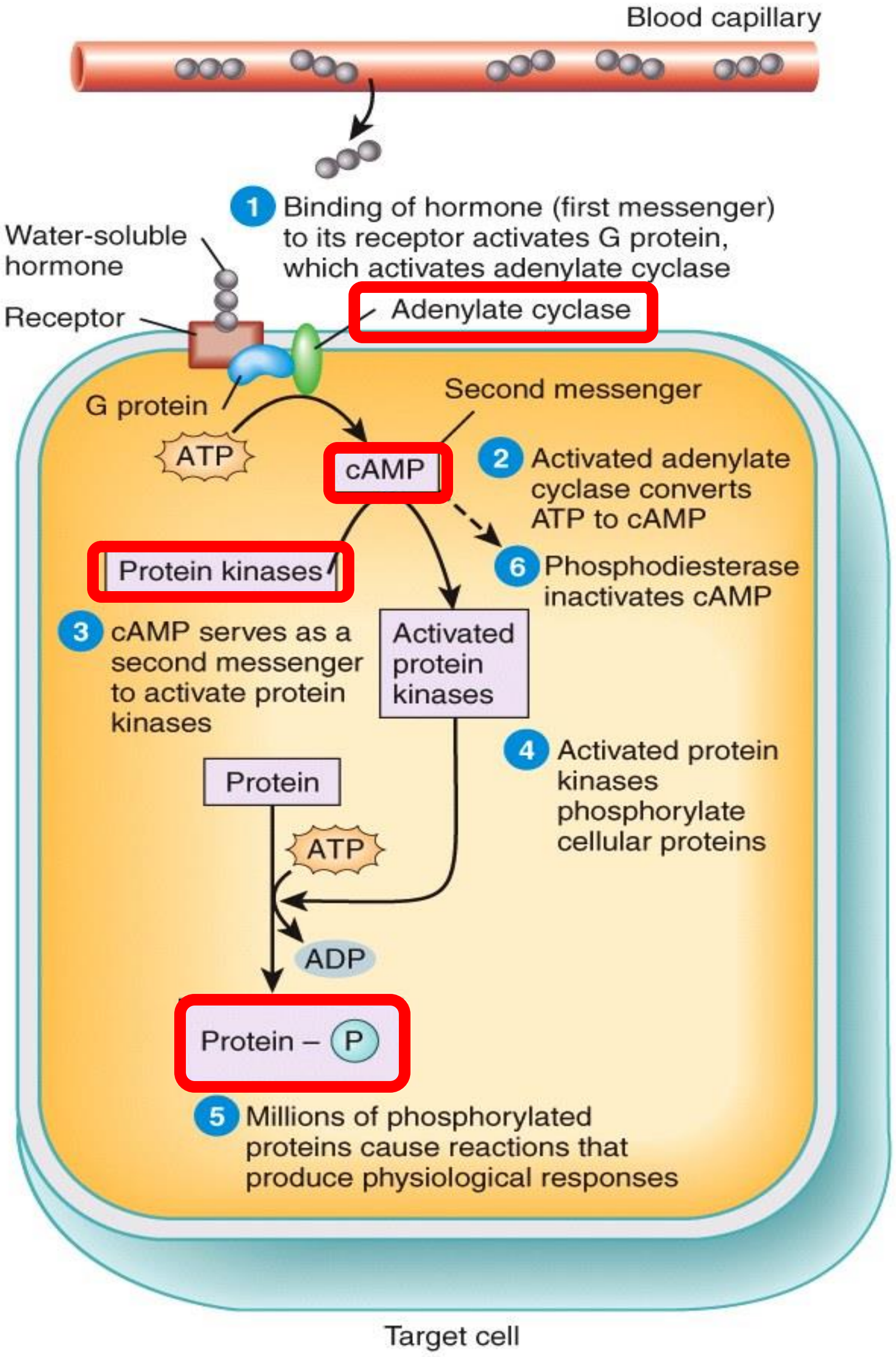
1. **Gα** hydrolyzes GTP to GDP + $P_i$. (**GTPase**).

   The presence of **GDP** on $G_\alpha$ causes it to rebind to the inhibitory ßγ complex.

   Adenylate Cyclase is no longer activated.

2. **Phosphodiesterases** catalyze hydrolysis of **cAMP → AMP**.

# Summary



Blood capillary
Water-soluble hormone
Receptor
1 Binding of hormone (first messenger) to its receptor activates G protein, which activates adenylate cyclase
Adenylate cyclase
G protein
Second messenger
ATP
cAMP
2 Activated adenylate cyclase converts ATP to cAMP
6 Phosphodiesterase inactivates cAMP
Protein kinases
3 cAMP serves as a second messenger to activate protein kinases
Activated protein kinases
4 Activated protein kinases phosphorylate cellular proteins
Protein
ATP
ADP
Protein – P
5 Millions of phosphorylated proteins cause reactions that produce physiological responses
Target cell

# Signal Transduction Pathways Used by Extracellular Chemical Messengers

- **I. Pathway used by lipid-soluble extracellular messengers that bind to intracellular receptors**
- A. Function in nucleus to change specific gene activity (ex: steroid hormones)
- **II. Pathways used by water-soluble extracellular messengers that bind to surface membrane receptors**
- A. Bind to and open or close chemically gated receptor-channels (ex: neurotransmitters)
- B. Bind to G-protein-coupled receptors (GPCRs) and activate second-messenger pathways (ex: eicosanoids and most peptide hormones)
- C. Bind to and activate receptor–enzyme complexes
- 1. Use tyrosine kinase pathway, where the receptor itself functions as an enzyme (ex: insulin, growth factors)
- 2. Use JAK/STAT pathway, where the receptor and attached enzymes function as a unit (ex: prolactin, immune cytokines)

# Enzyme-Linked Hormone Receptors

- Some receptors, when activated, function directly as enzymes or are closely associated with enzymes that they activate. These *enzyme-linked receptors* are proteins that pass through the membrane only once
- When the hormone binds to the extracellular part of the receptor, an enzyme immediately inside the cell membrane is activated
- 1. Tyrosine Kinase Pathway
- 2. JAK/STAT Pathway

**Table 75-2** Hormones That Use Receptor Tyrosine Kinase Signaling

| |
|---|
| Fibroblast growth factor |
| Growth hormone |
| Hepatocyte growth factor |
| Insulin |
| Insulin-like growth factor-1 |
| Leptin |
| Prolactin |
| Vascular endothelial growth factor |

# 1. Tyrosine Kinase Pathway

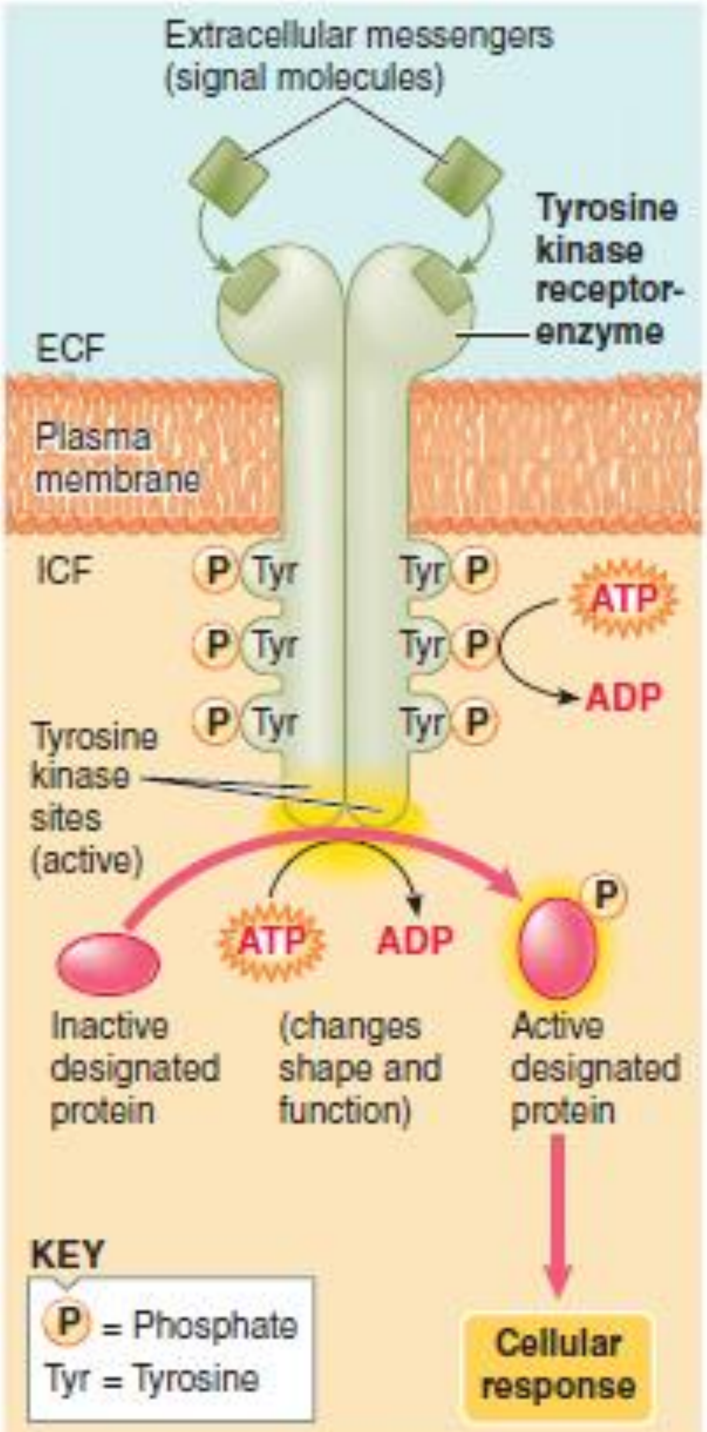
- The *receptor itself functions as an enzyme,* a so-called **receptor-enzyme**
- Has a receptor portion facing the ECF and protein kinase (tyrosine kinase) site on its portion that faces the cytosol
- **N terminal extracellular ligand-binding domain, single TM domain, cytosolic C-terminal domain with tyrosine kinase activity.**
- **Includes receptors for most growth factors (NGF, EGF. PDGF), insulin.**

1 Two extracellular messengers bind to two tyrosine kinase receptor-enzymes, which pair, activating receptor-enzyme's protein kinase (tyrosine kinase) site that faces the cytoplasm.

2 Tyrosine kinase site self-phosphorylates receptor-enzyme's tyrosines.

3 Inactive designated protein binds to phosphorylated receptor-enzyme, which phosphorylates protein, activating it.

4 Active designated protein brings about desired response.

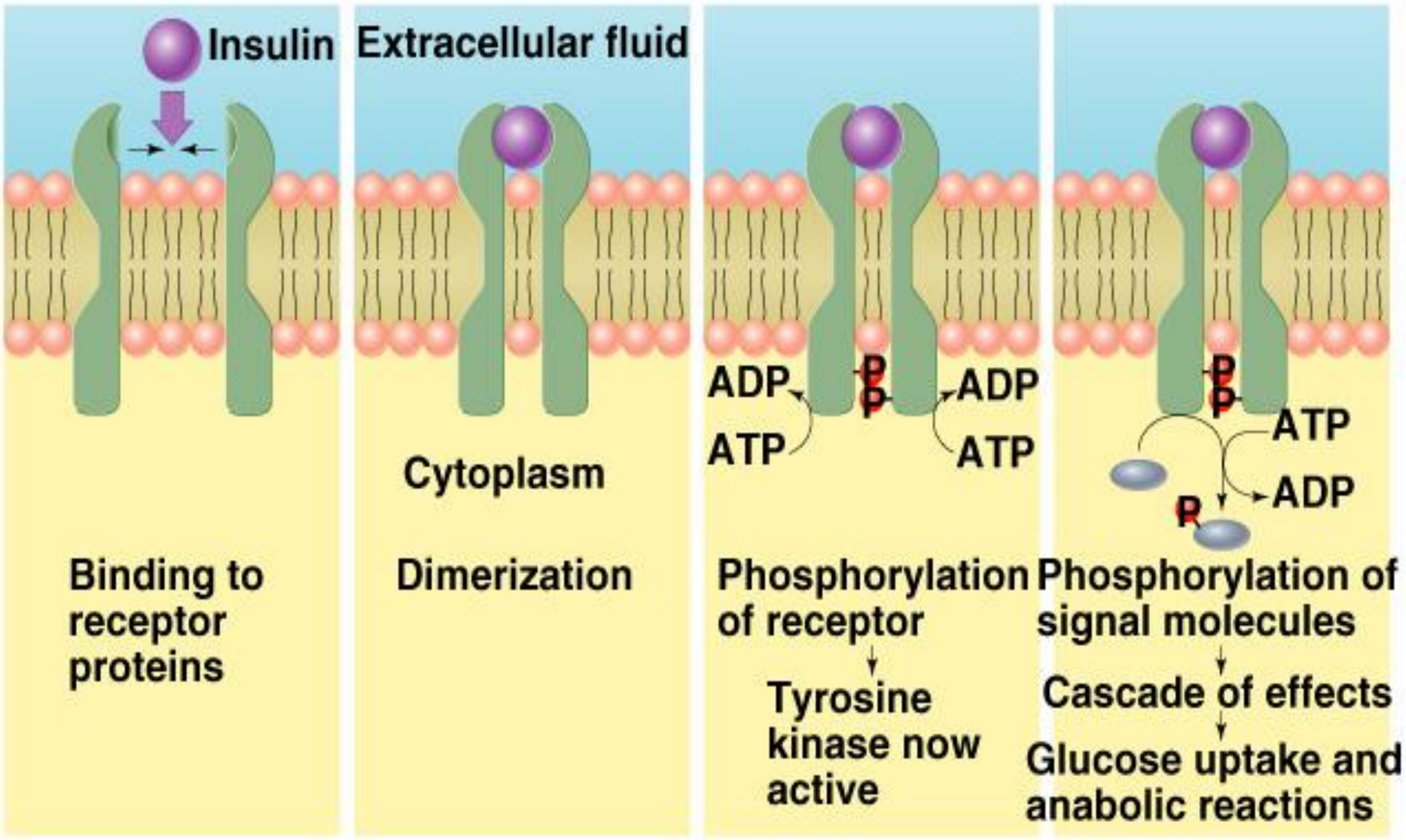


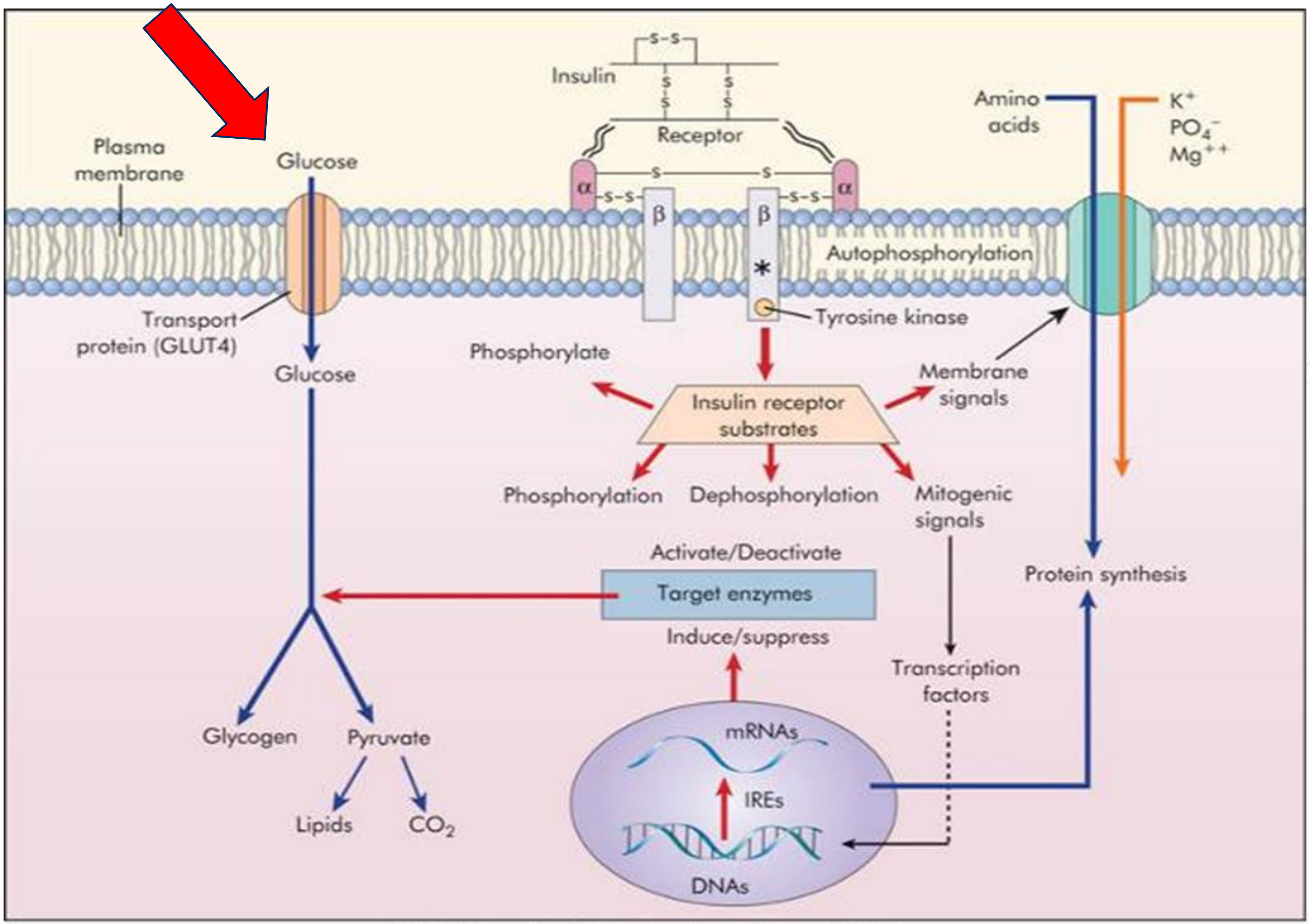
# Tyrosine Kinase Receptors

- 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 Receptor





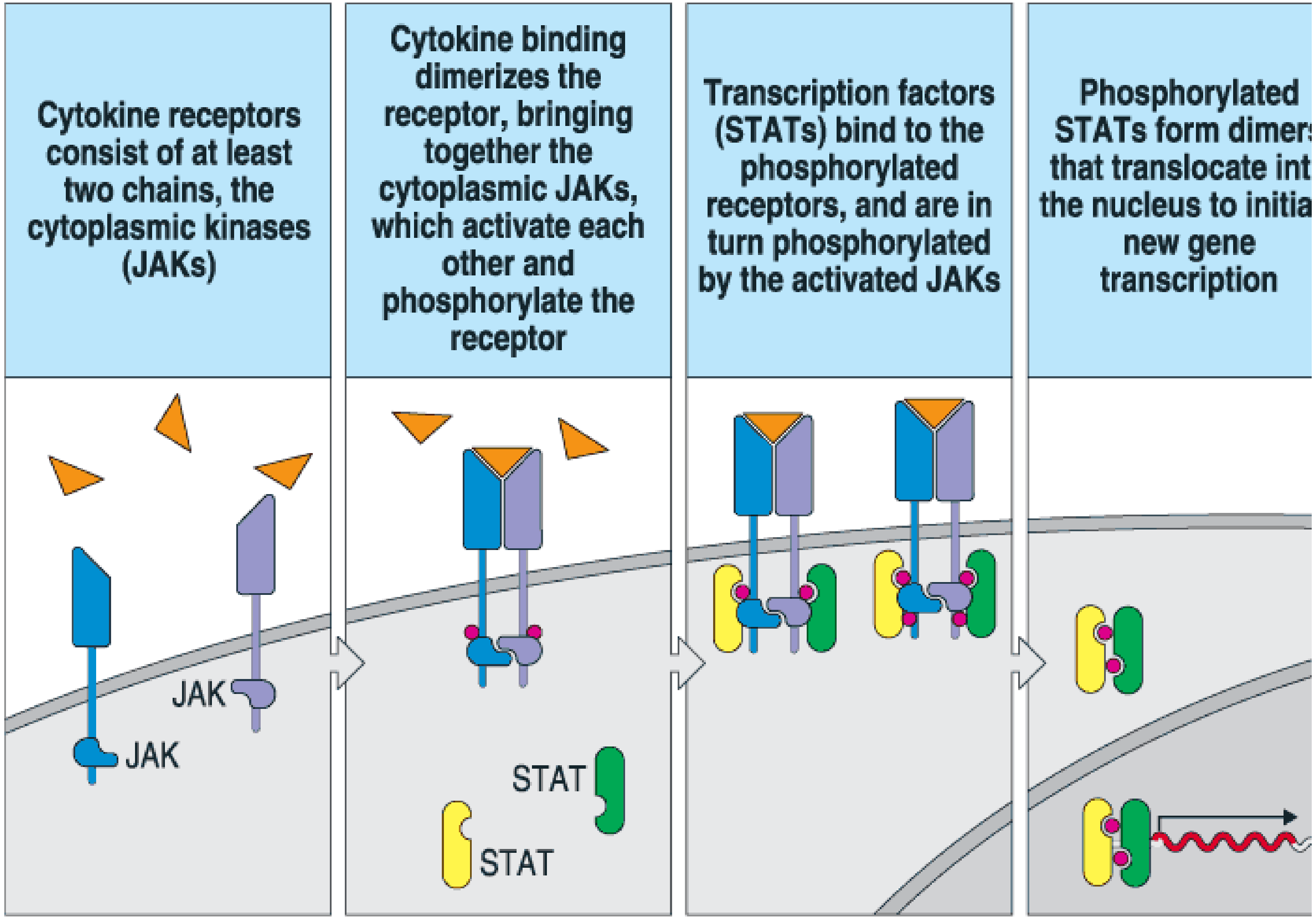



From Berne RM, Levy MN. *Principles of physiology*, ed 3, St Louis, 2000, Mosby.

# 2. JAK/STAT Pathway

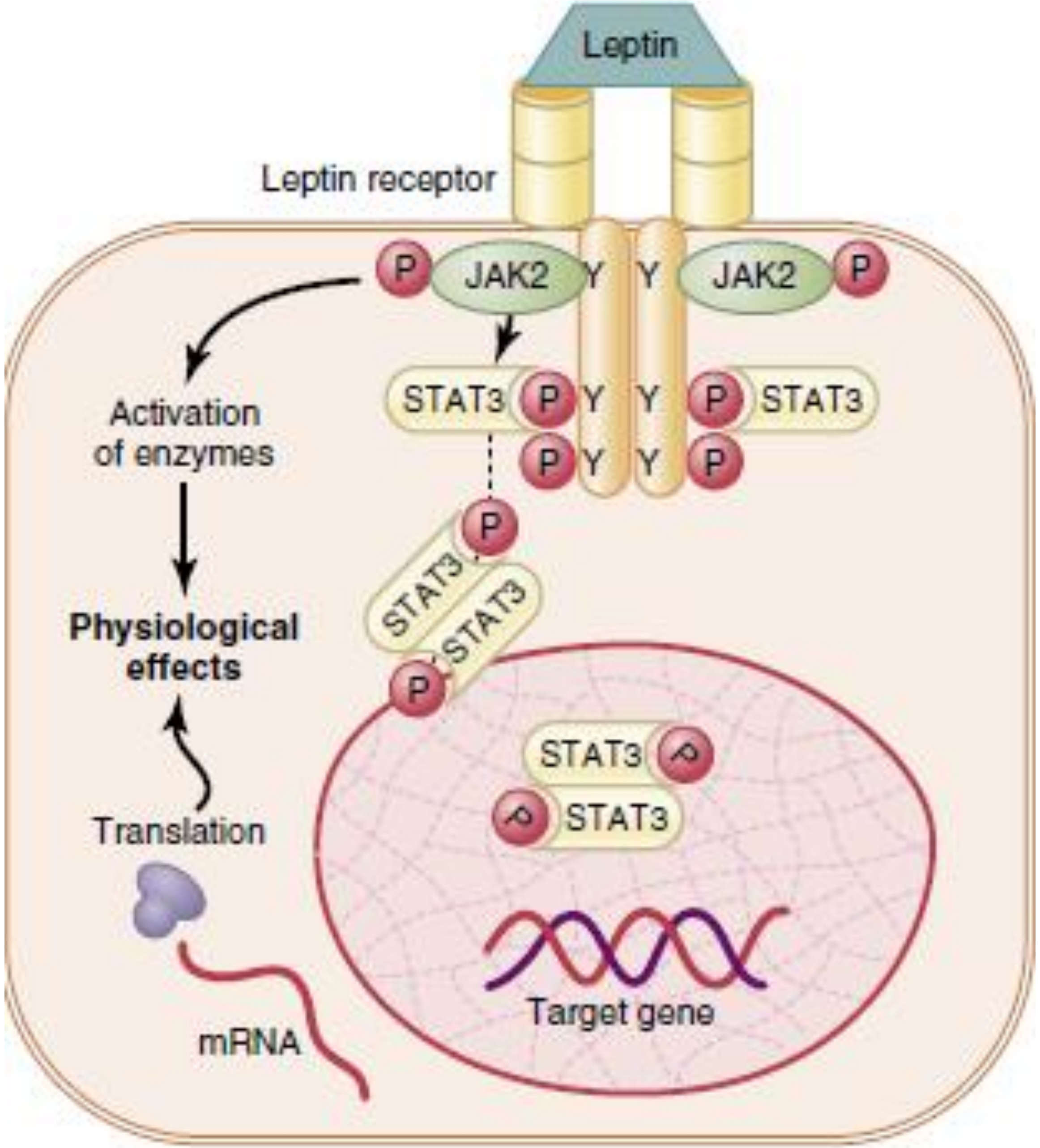
- The tyrosine kinase activity resides in a family of separate cytosolic enzymes called *Janus family tyrosine kinases,* better known as *JAKs*
- *The receptor and attached enzymes function as a unit.*
- Binding of an extracellular messenger to the receptor on the ECF side causes a conformational change in the receptor that activates the JAKs bound to the cytosolic side of the receptor.
- Activated JAKs phosphorylate *signal transducers and activators of transcription (STAT)* within the cytosol.
- Phosphorylated STAT moves to the nucleus and turns on transcription of selected genes
- Resulting in synthesis of new proteins that carry out the cellular response.

**Janus kinases (JAK) - universally required for signaling from cytokine receptors and Leptin receptor**



# 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-JAK2
- This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins
- 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



# Signal Transduction Pathways Used by Extracellular Chemical Messengers

- ✓ **I. Pathway used by lipid-soluble extracellular messengers that bind to intracellular receptors**
- A. Function in nucleus to change specific gene activity (ex: steroid hormones)
- **II. Pathways used by water-soluble extracellular messengers that bind to surface membrane receptors**
- ✓ A. Bind to and open or close chemically gated receptor-channels (ex: neurotransmitters)
- ✓ B. Bind to G-protein-coupled receptors (GPCRs) and activate second-messenger pathways (ex: eicosanoids and most peptide hormones)
- ✓ C.  Bind to and activate receptor–enzyme complexes
- ✓ 1. Use tyrosine kinase pathway, where the receptor itself functions as an enzyme (ex: insulin, growth factors)
- ✓ 2. Use JAK/STAT pathway, where the receptor and attached enzymes function as a unit (ex: prolactin, immune cytokines)

# Thank you