بسم الله الرحمن الرحيم

Physiology | Final 6

Signal Transduction 2

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Signal Transduction lec-2

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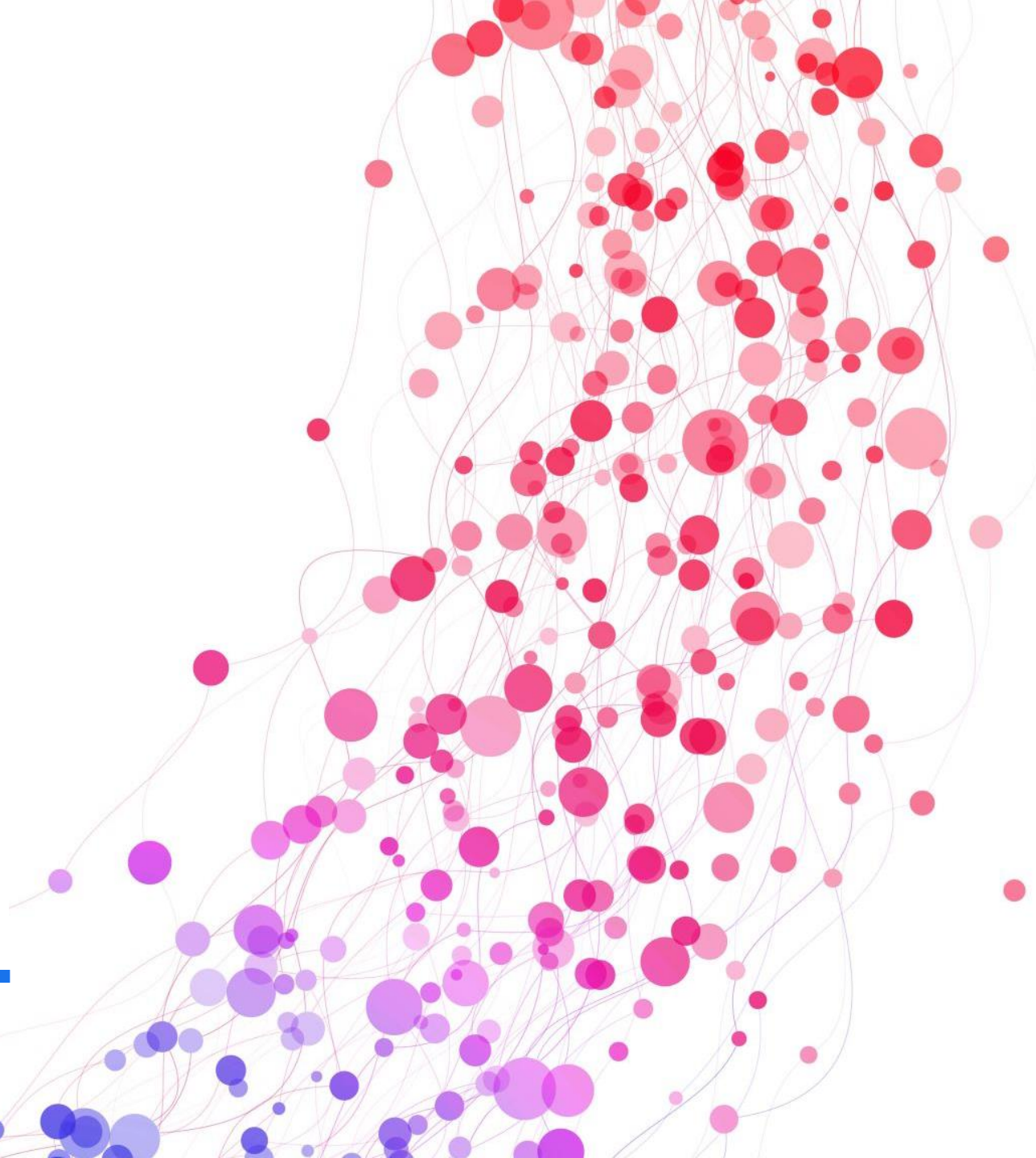


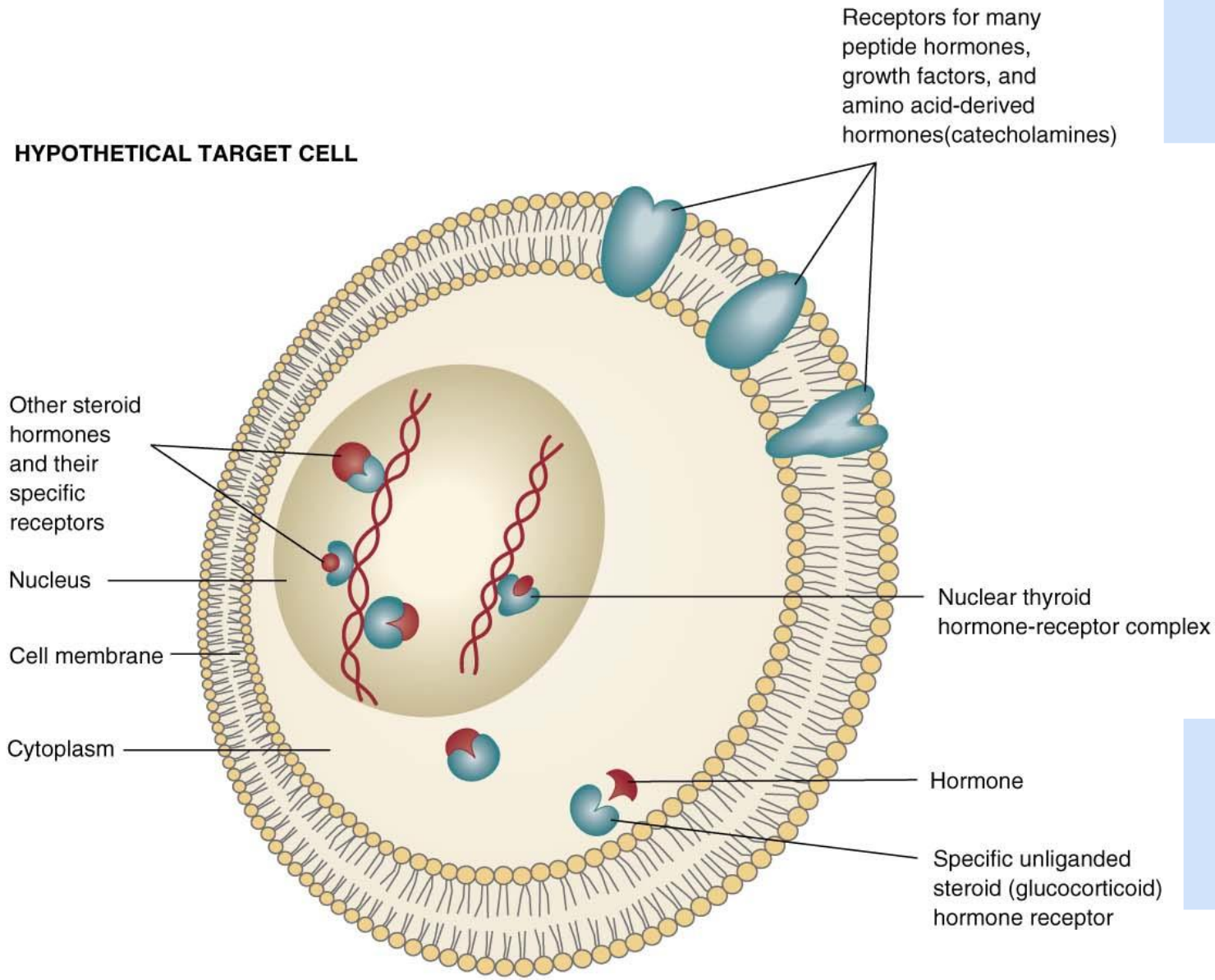
Extracellular chemical messengers bring about cell responses by signal transduction

- 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. (water soluble)
- 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

In plasma membrane



In nucleus

In cytoplasm

. 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**.

(there must be connection)

Signal Transduction Pathways Used by Extracellular Chemical Messengers

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- 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)
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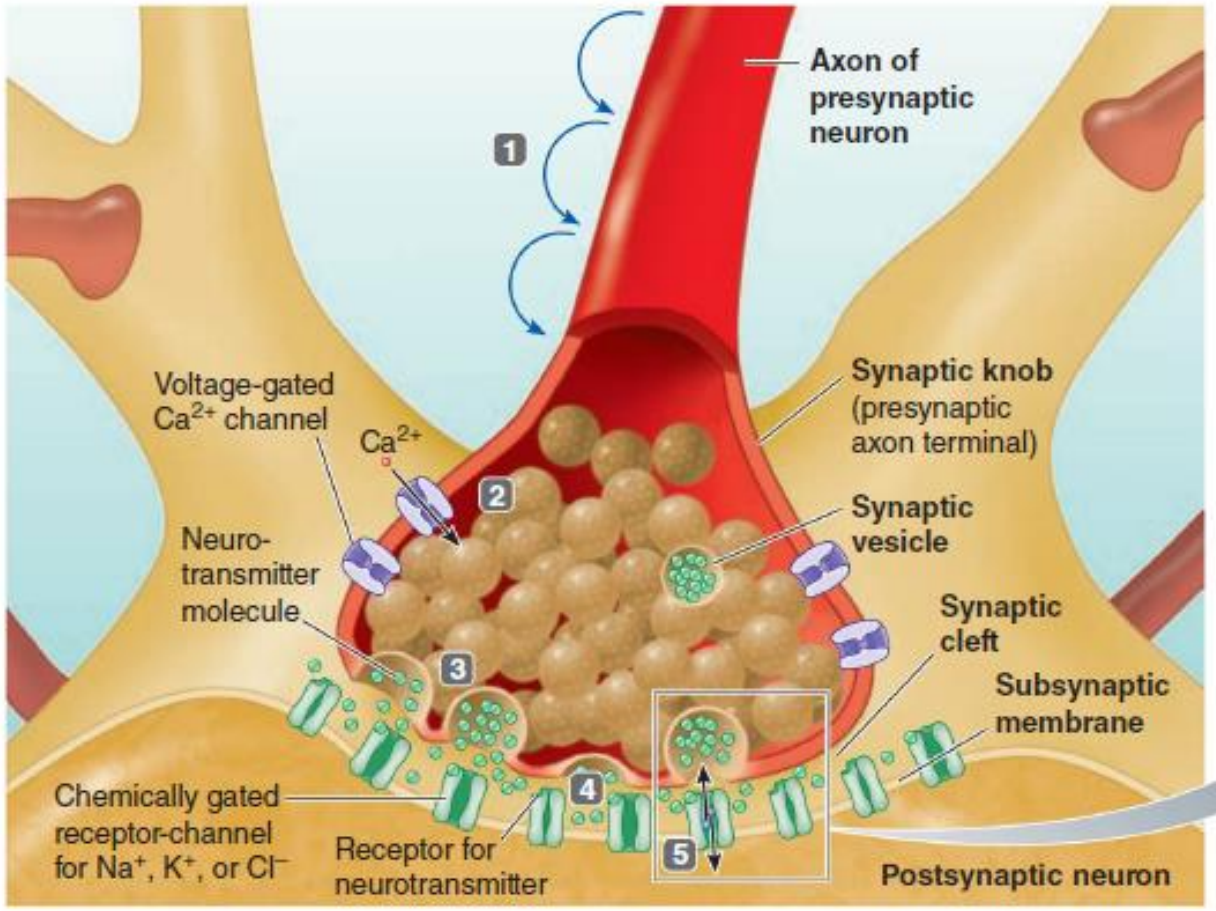
Ion Channel–Linked Receptors



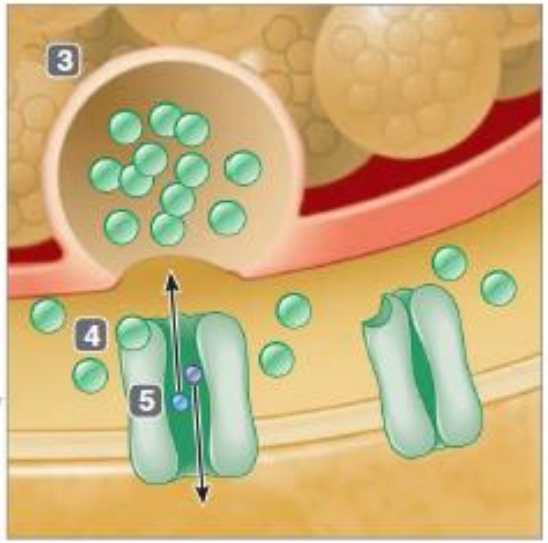
1 Action potential reaches axon terminal of presynaptic neuron.

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

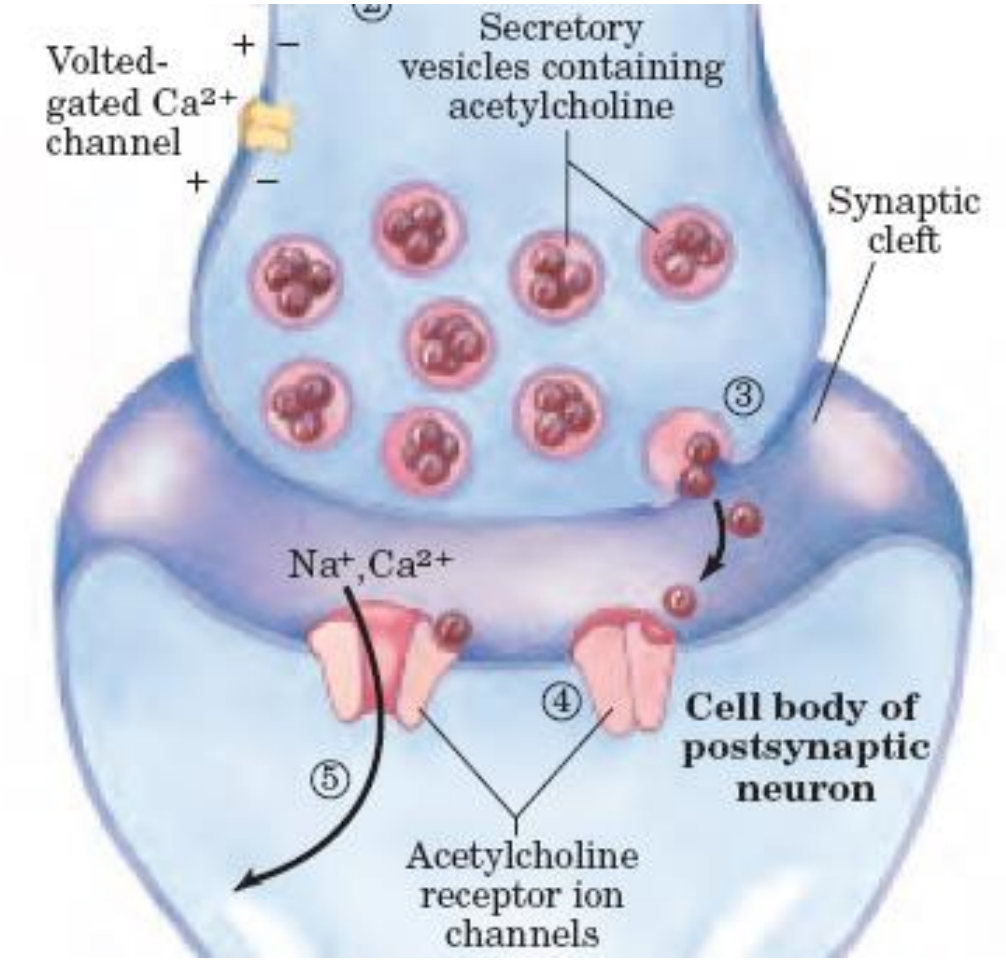
3 Neurotransmitter is released by exocytosis into synaptic cleft.

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.



- As taught previously, synapses at synaptic cleft is a great example of ion channel linked receptor , presynaptic neuron meets postsynaptic neuron at ▪ synaptic cleft , when action potential fires at presynaptic neuron ,calcium gated channels open , which will introduce neurotransmitter(Acetylcholine, the class 1 main neurotransmitter) via exocytosis into synaptic cleft , then from synaptic cleft into postsynaptic neuron ,acetylcholine will bind through postsynaptic neuron ligand gated ion channels , when these channels have a ligand on their surface , they will go under conformational change , thus making them open, and neurotransmitter to pass.



As we see here, neurotransmitter is released into synaptic cleft , binded to ligand ion channel , but it will not pass through, it will just open it, in order Na to pass , thus initiating depolarization.

NOTE: Although a few hormones may exert some of their actions through activation of ion channel receptors,

***Most hormones that open or close ions channels do this indirectly by coupling with G protein-linked or enzyme-linked receptors

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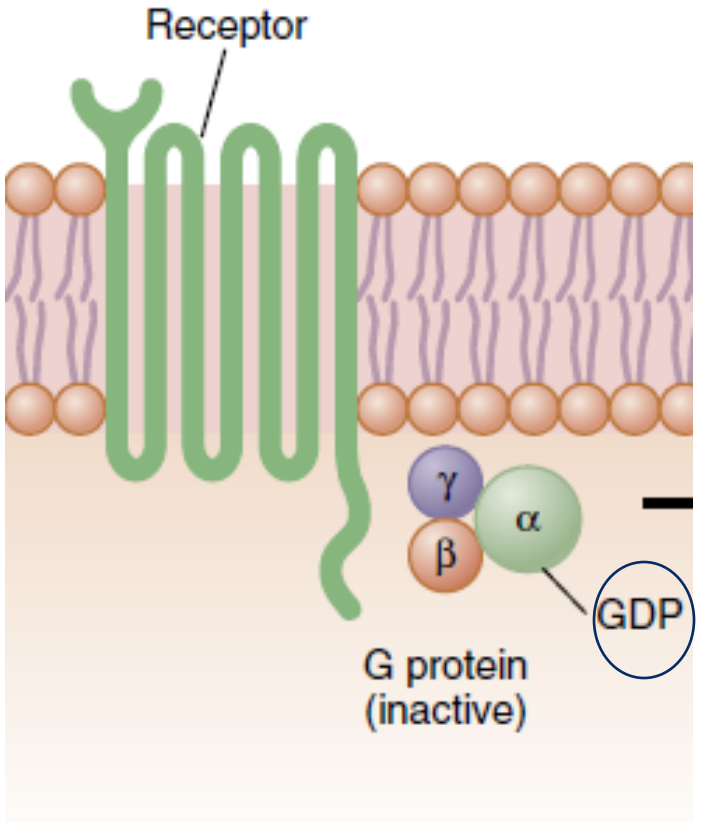
G Protein–Linked Hormone Receptors (named according to the protein it binds to)



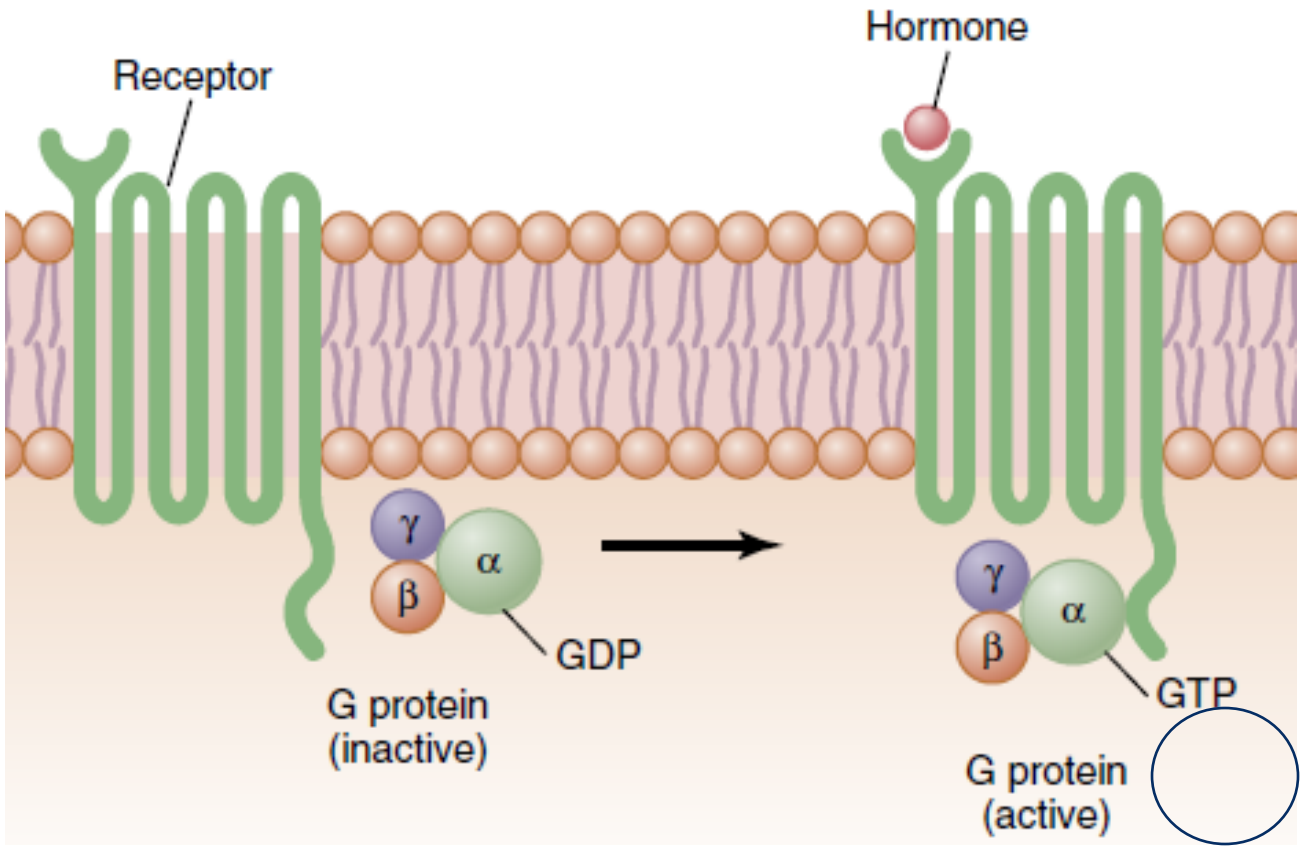
- ***Heterotrimeric guanosine triphosphate (GTP)****-binding proteins (G proteins)*
- Have ***seven*** transmembrane segments motifs of ***α*** helices that **loop** in and out of the cell membrane.
- The cytoplasmic tail of the receptor are coupled to G proteins that include three (i.e., trimeric) parts—the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

G-protein has both extracellular(receptor) and intracellular cytoplasmic (G-protein) parts.

Trimeric part(Alpha,Beta,Gamma), can be in active and inactive forms.

NOTE: The trimeric G proteins are named for their ability to bind *guanosine nucleotides.*
In their inactive state, theα, β, and γ subunits of G proteins form a complex that binds *guanosine diphosphate* (GDP)

G Protein–Linked Hormone Receptors

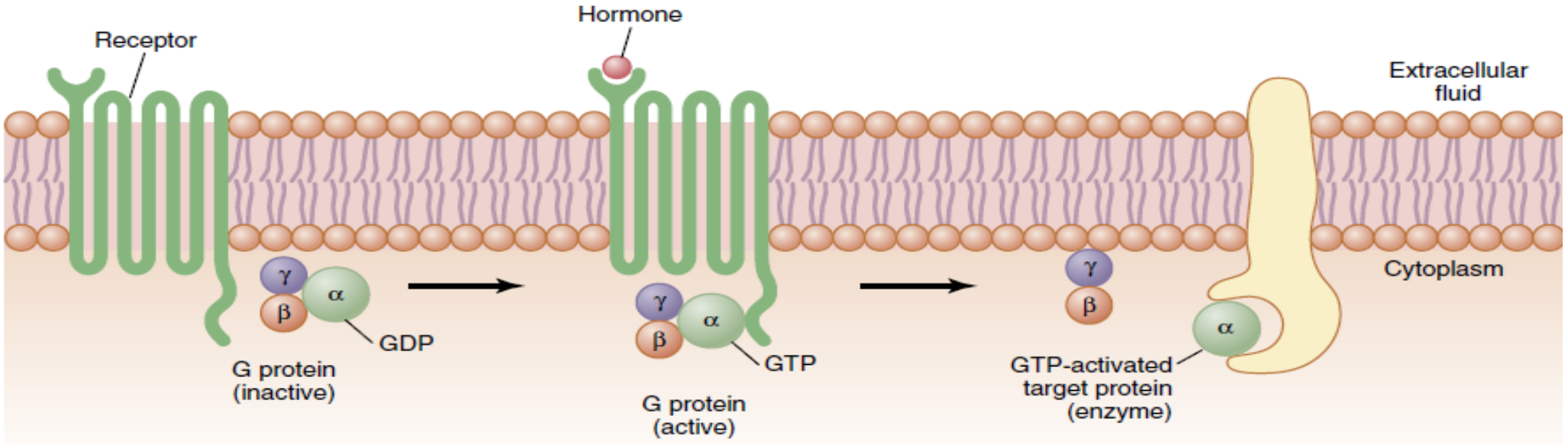


- When the **ligand (hormone)** binds to the extracellular part of the receptor, a **conformational change** occurs in the receptor that **activates the G proteins** and induces intracellular signals

Here trimeric part is transferred from inactive form(Gdp) to active form(Gtp).

NOTE:When the receptor is activated, it undergoes a conformational change that causes the GDP-bound trimeric G protein to associate with the cytoplasmic part of the receptor and to exchange GDP for GTP.

G Protein–Linked Hormone Receptors



It frees the alpha subunit, Thus activating the effector protein

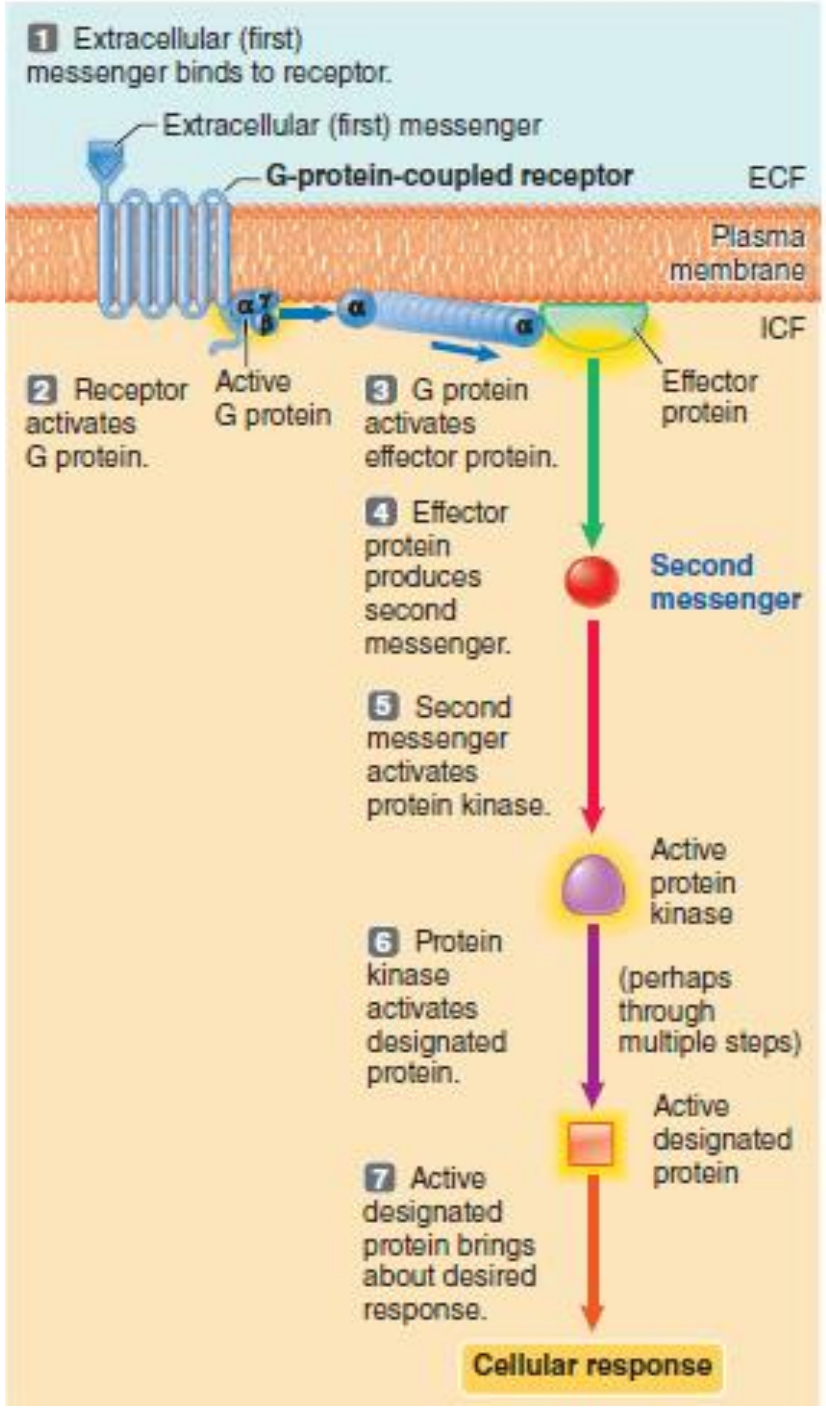
(1) open or close cell membrane ion channels
(2) change the activity of an enzyme in the cytoplasm of the cell
(3) activate gene transcription.

NOTE: Displacement of GDP by GTP causes the α subunit to dissociate from the trimeric complex and to associate with other intracellular signaling proteins; these proteins, in turn, alter the activity of ion channels or intracellular enzymes such as *adenylyl cyclase* or *phospholipase C,* which alter cell function.

The signaling event is terminated when the hormone is removed and the α subunit inactivates itself by converting its bound GTP to GDP; then the α subunit once again combines with the β and γ subunits to form an inactive, membrane-bound trimeric G protein

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 (cellular responses, protein kinases)** inside the cell that cause a change in the shape and function of designated proteins.



G Protein–Linked Hormone Receptors

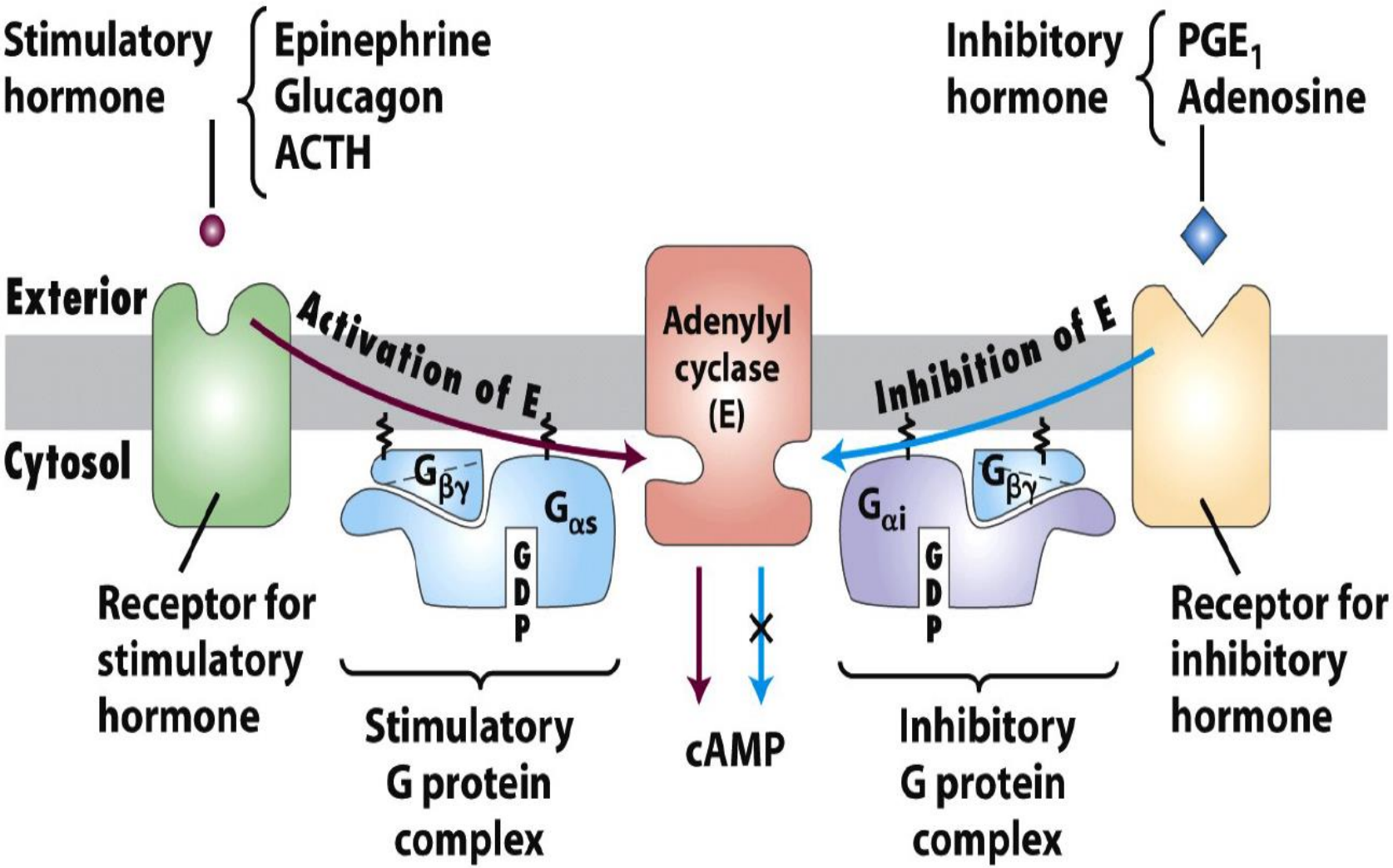


Figure 15-21

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_{α} 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:

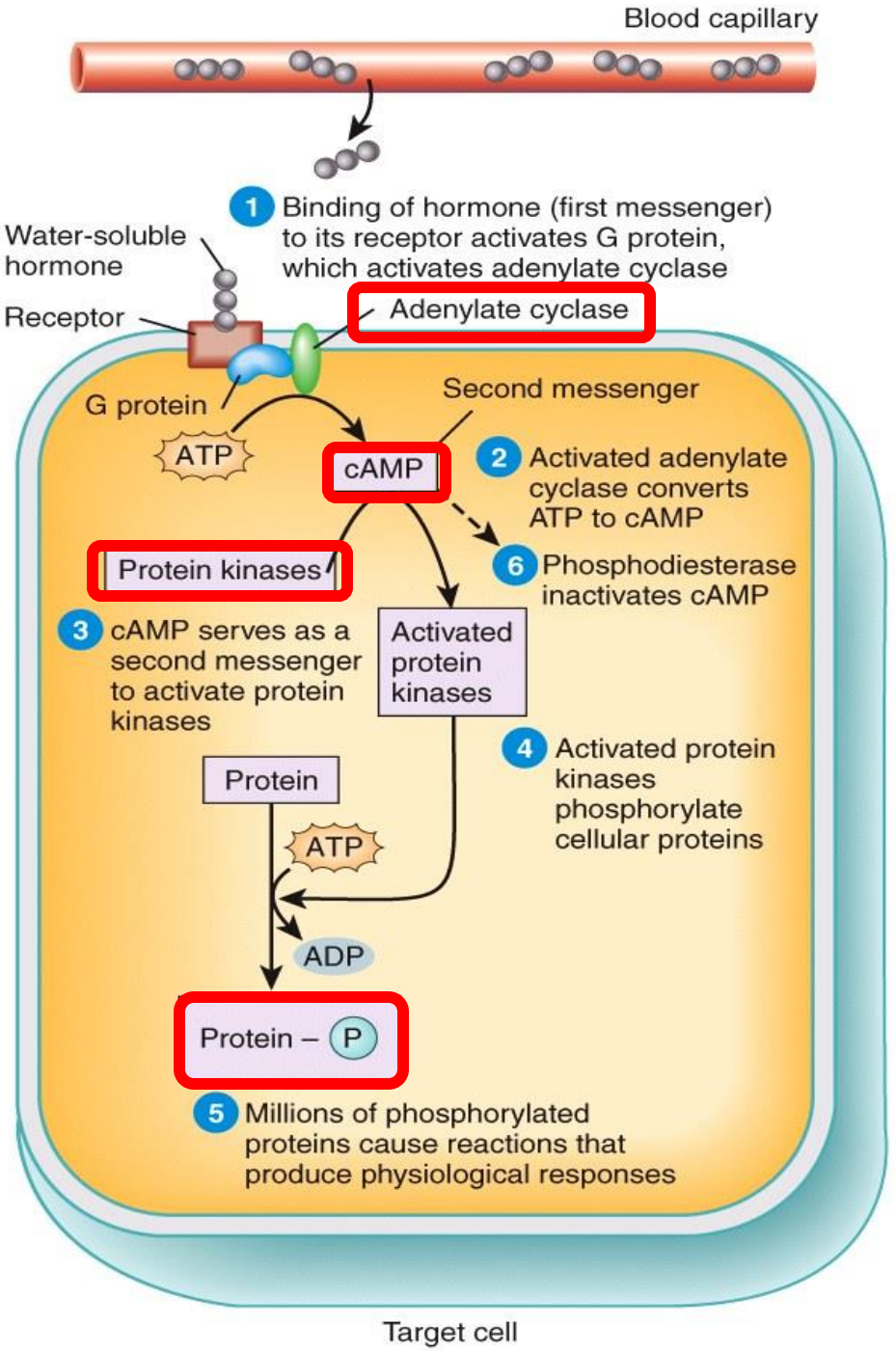
1. **Gα** hydrolyzes GTP to GDP + P_i. (**GTPase**).

   The presence of **GDP** on G_α 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
1 Binding of hormone (first messenger) to its receptor activates G protein, which activates adenylate cyclase
Water-soluble hormone
Receptor
Adenylate cyclase
G protein
ATP
Second messenger
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

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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

NOTE: The hormone-binding site on the outside of the cell membrane and their catalytic or enzyme-binding site on the inside

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

Leptin, Prolactin: Activate JAK/STAT

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.**

Transmembrane

- **Includes receptors for most growth factors (NGF, EGF. PDGF), insulin.**

NOTE: NGF, EGF *nerve growth factor* and *epidermal growth factor*
Platelet derived growth factor pdgf

Autophosphorylation

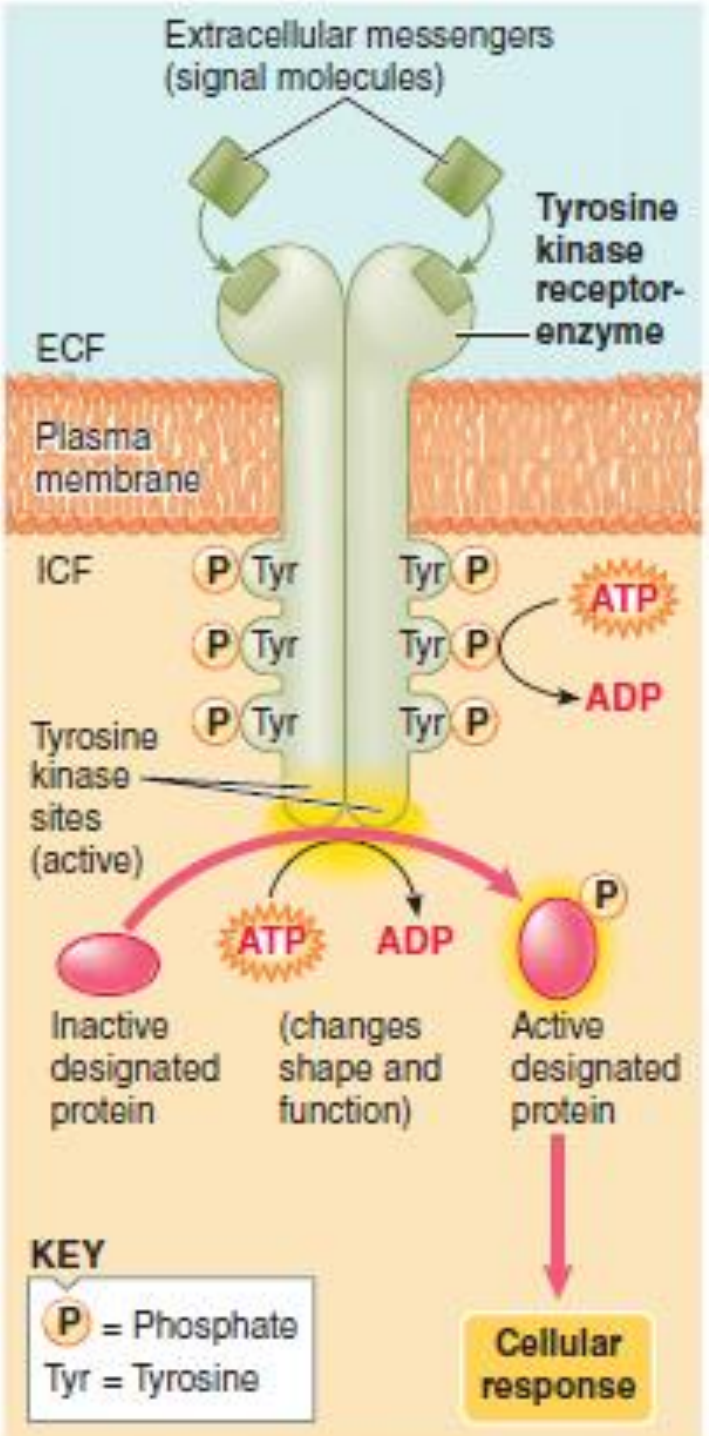
Every tyrosine will activate the next tyrosine
At the end, inactive designated protein will be activated

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.

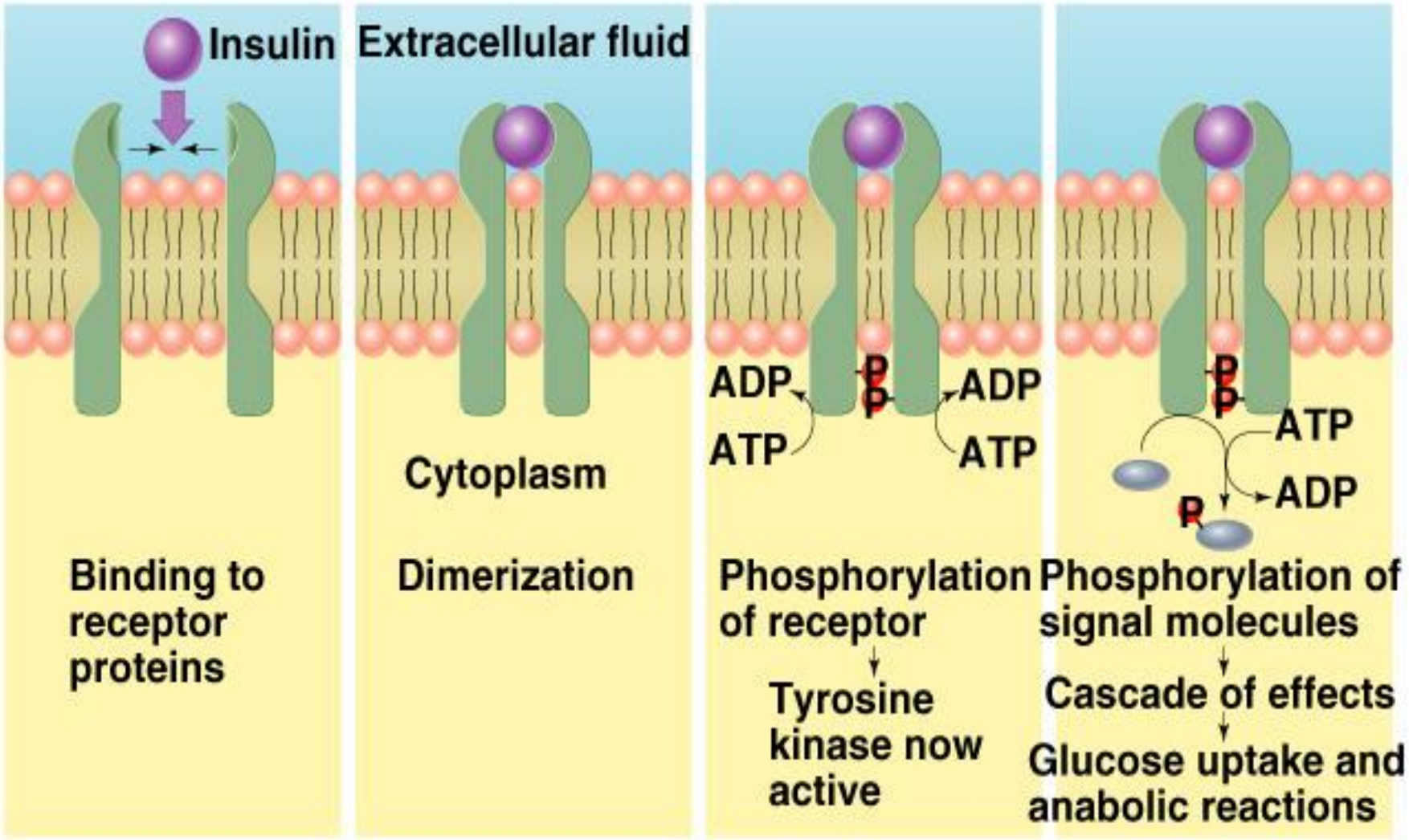


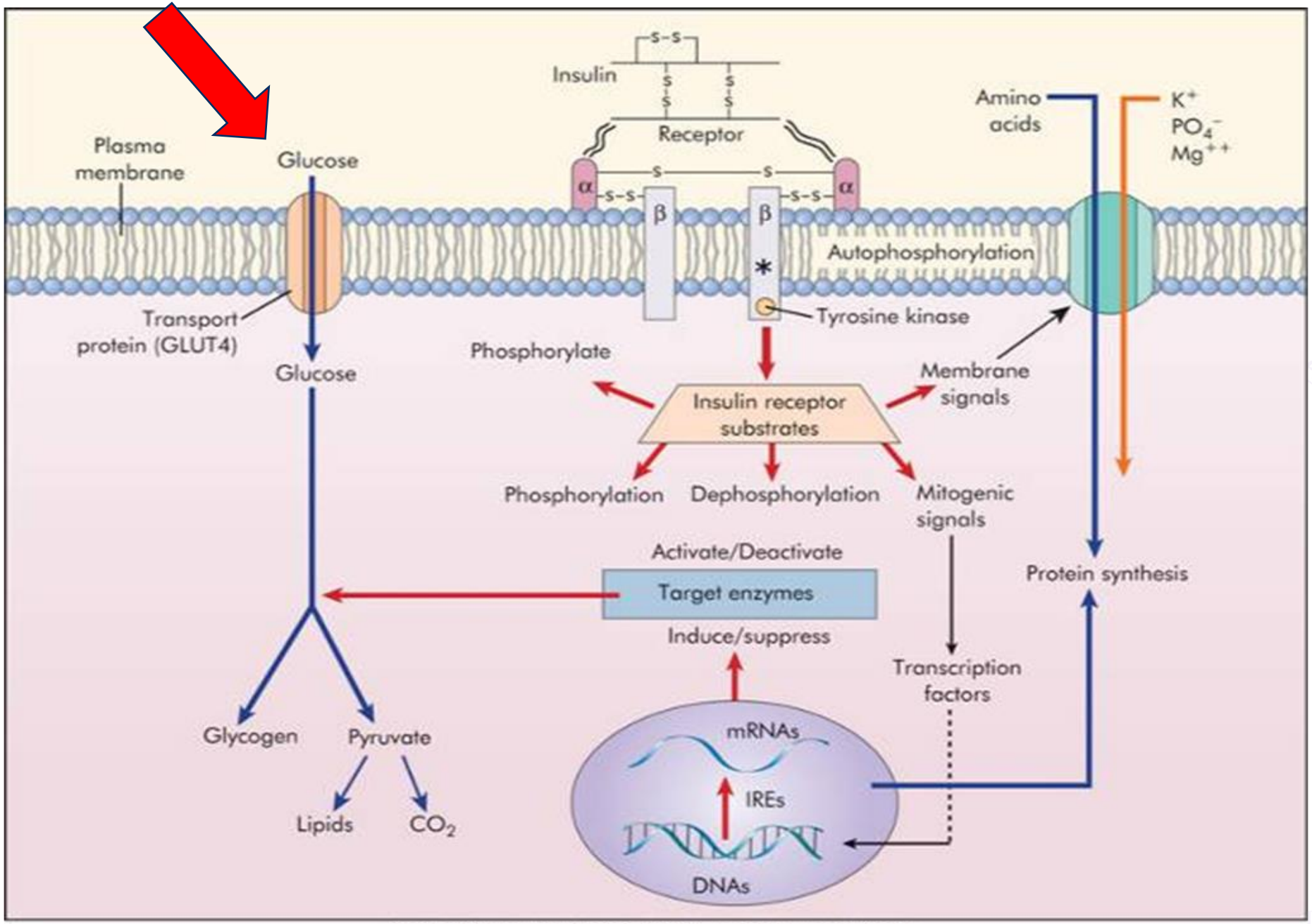
Tyrosine Kinase Receptors

- 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.

It will do the function of insulin by stimulating the uptake of glucose and amino acids into cells which increases protein, glycogen and GLUT4 (glucose carriers) on the cell surface, which enhances glucose uptake

Tyrosine Kinase Receptor





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

Insulin binds to its dimeric receptor, and this activates the tyrosine kinase domain through autophosphorylation.

This leads to phosphorylation and dephosphorylation of target proteins within the cytoplasm, resulting in increased amino acid uptake and enhanced protein synthesis.

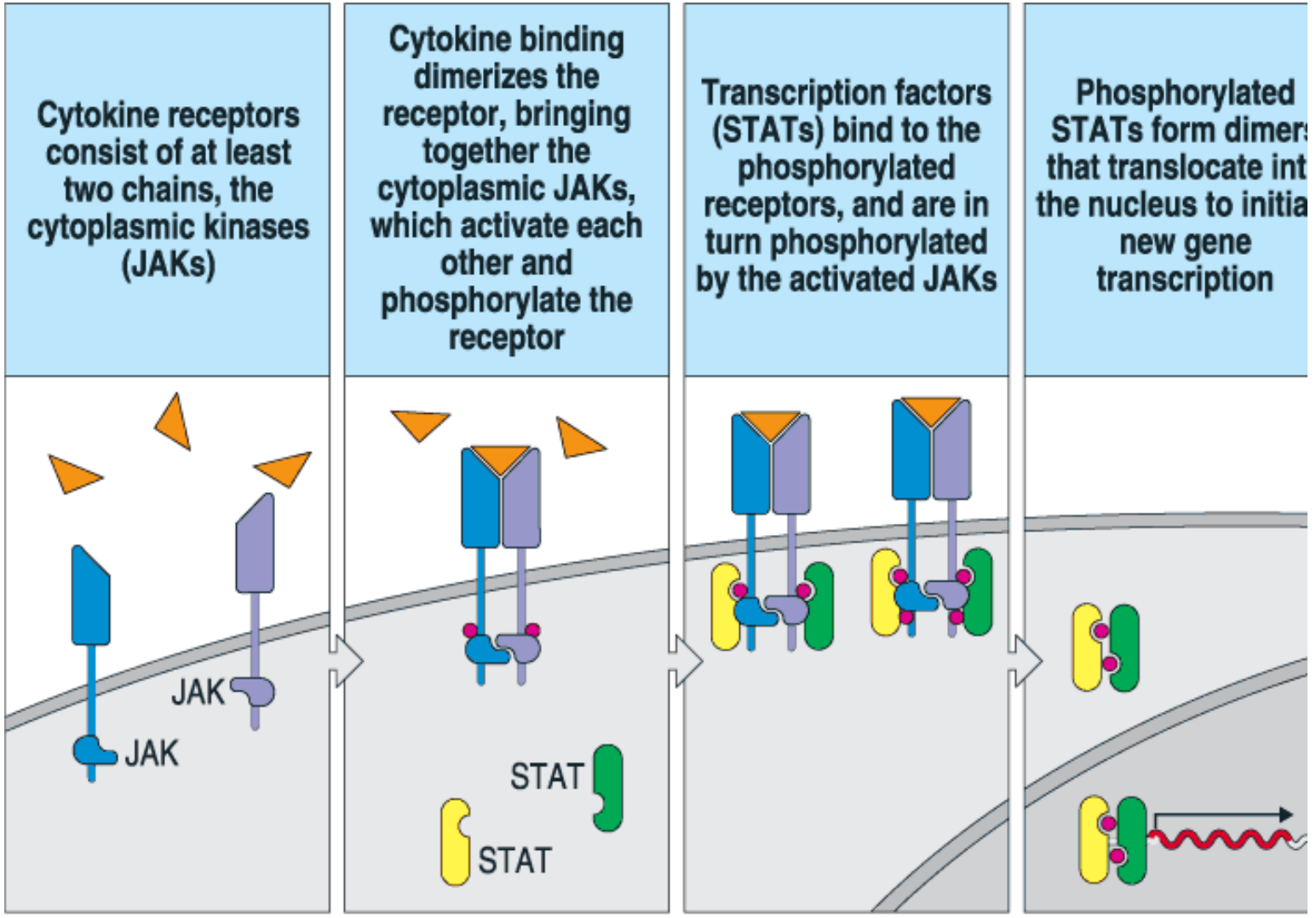
Insulin also triggers mitogenic signal transduction that serves as transcription factors within the nucleus, stimulating mRNA production and synthesis of new proteins.

Also,it stimulates GLUT4 transporter activation that encourages glucose uptake and glycogen storage. This anabolic effect is through the tyrosine kinase signal pathway.

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

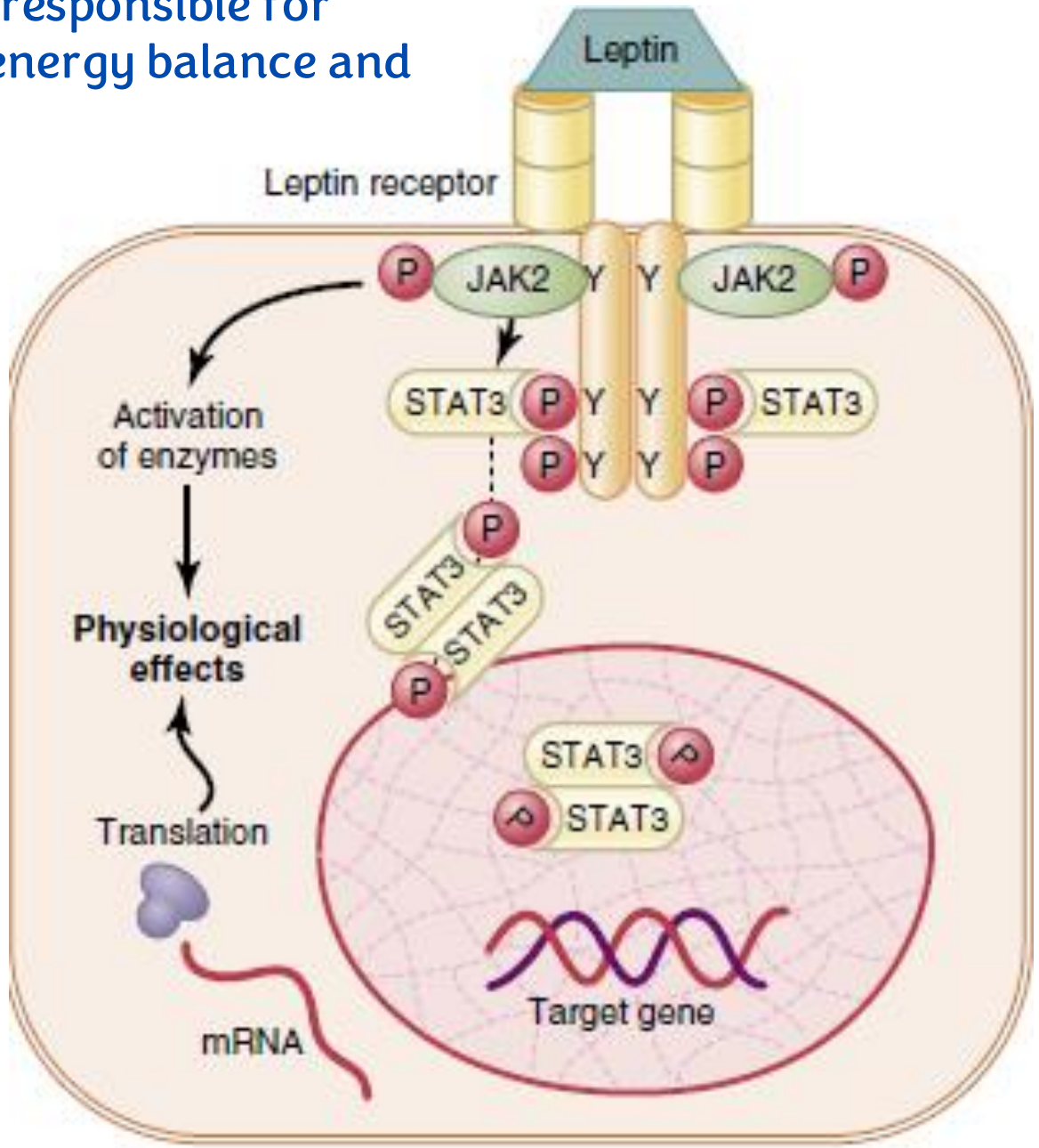


Enzyme-linked receptor (the leptin receptor)

Leptin is a hormone secreted by fat cells that is responsible for regulating energy balance and appetite.

- 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

NOTE: Leptin is a hormone secreted by fat cells and has many physiological effects, but it is especially important in regulating appetite and energy balance



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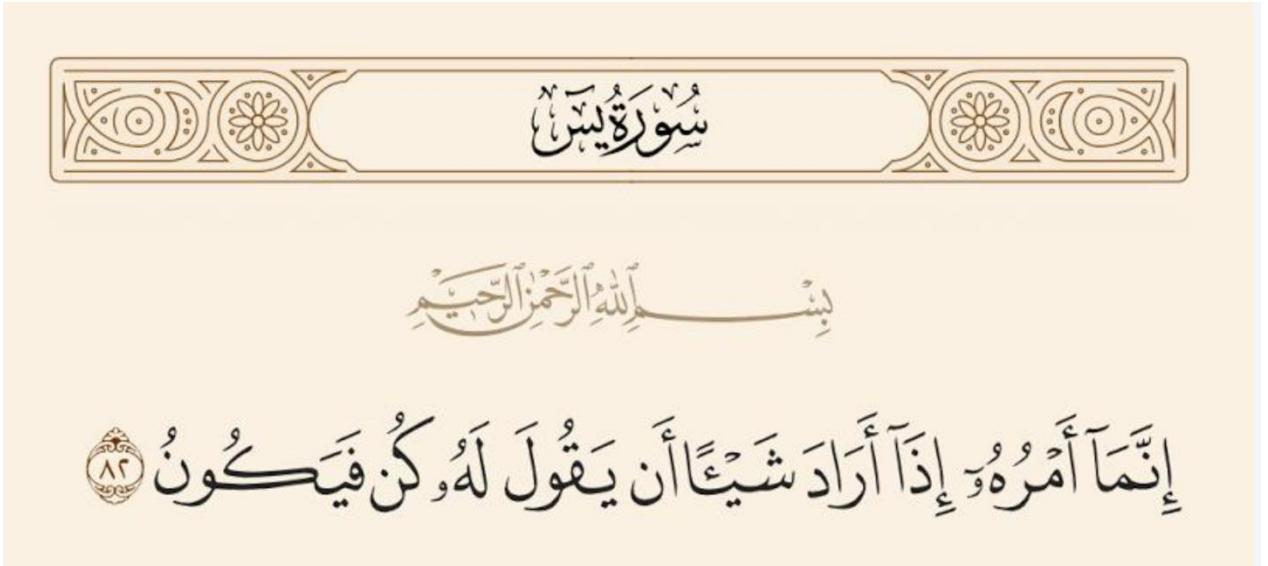
Thank you

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	**25**	It will do the function of insulin by stimulating the uptake of glucose and amino acids into cells which increases protein, glycogen and GLUT4 (glucose **receptors**) on the cell surface, which enhances glucose uptake	It will do the function of insulin by stimulating the uptake of glucose and amino acids into cells which increases protein, glycogen and GLUT4 (glucose **carriers**) on the cell surface, which enhances glucose uptake
V1 → V2	**10** **12** **13** **15** **22** **24** **32**		Note added Note added Note added Slide added Note added Note added Note added

رسالة من الفريق العلمي:


سُورَةُ يٰسٓ

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

إِنَّمَآ أَمْرُهُۥٓ إِذَآ أَرَادَ شَيْـًٔا أَن يَقُولَ لَهُۥ كُن فَيَكُونُ ﴿٨٢﴾

حين تتلاشى الحيلة وتنقطع الأسباب، يبقى أمر الله هو السر الأعلى...
لا يحتاج إلى زمن، ولا إلى وسائل، فقط إذا أراد شيئًا، قال له: كن، فيكون.