University of Basrah
Al-Zahraa College of Medicine

Ministry of higher Education
and Scientific Research

Academic year 2023-2024/S3

MEMBRANES AND RECEPTORS MODULE

SESSION : 6 LECTURE: 1 DATE: 05 / 11 / 2023

RECEPTORS IN CELL SIGNALLING & RECEPTOR STRUCTURE

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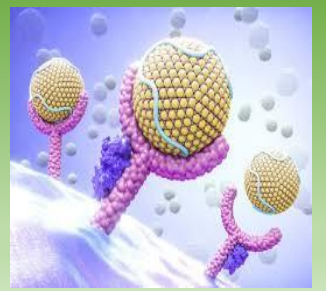
- **2016_Guyton_and_Hall_Textbook of Medical Physiology**
- **Koeppen, B.M. & Stanton, B.A. Berne & Levy: Principles of Physiology, 6th Edition, 2006**
- **Netters Essential Physiology 2009**
- **Pictures are downloaded from a common distributive source.**



➢ Learning objectives

•**LO1: The principles of communication between cells via chemical messengers in the endocrine and nervous systems.**

•**LO2: The role of receptors in transducing the information carried by an extracellular hydrophilic signaling molecule across a hydrophobic cellular membrane bilayer**

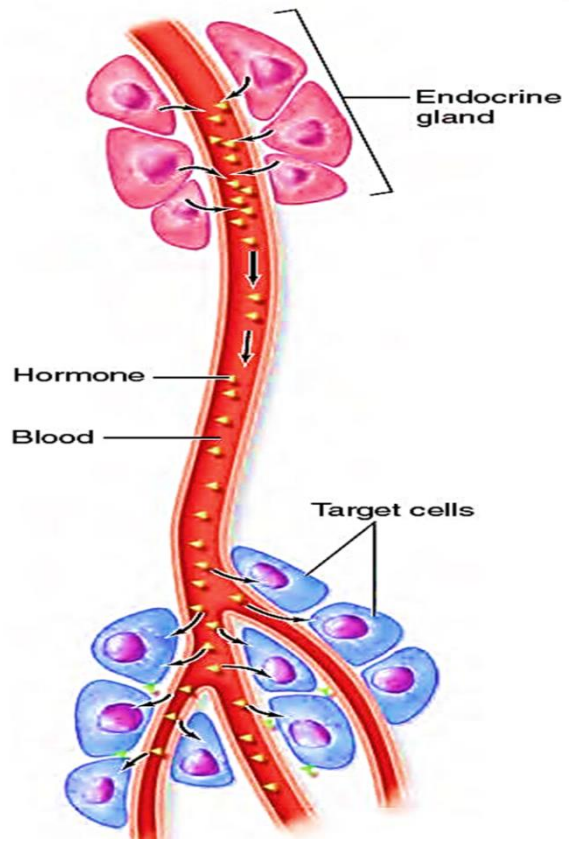
•**LO3: The concept of receptor super-families, based on common structural motifs, and the structure of the four major classes of receptors involved in cellular signaling via hormones, local mediators and neurotransmitters**

SIGNALLING

LO1

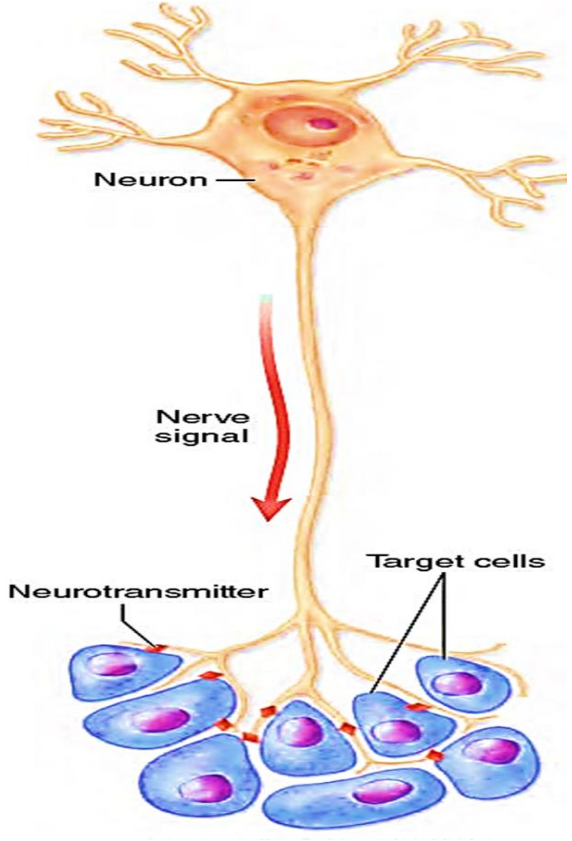
Endocrine system

Nervous system



chemical messengers

Target cells



Chemical signals (ligands) may be classified according to LO1 their functions:

1- Hormones: Signaling between cells in different tissues via the circulation. (Endocrine gland secrete hormones in the blood)

2- Neurotransmitters: signaling at synapses in the nervous system

3- Local chemical mediators: signaling between adjacent cells in the same local area.

LO1

A single molecule may fall into more than one of these categories depending on where it is synthesized and released and its site of action.

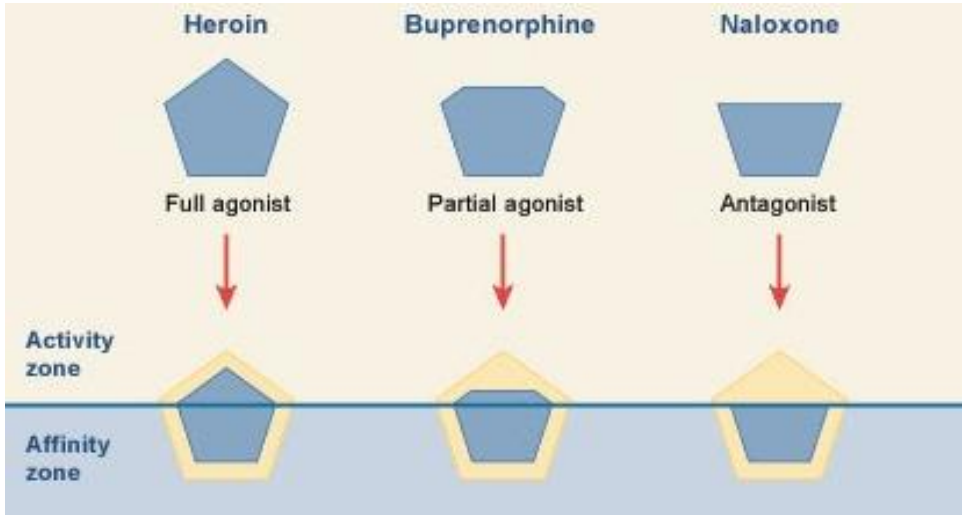
Norepinephrine:
a neurotransmitter and hormone

LIGAND (signaling molecule)

LO1

Binds specifically to a receptor site

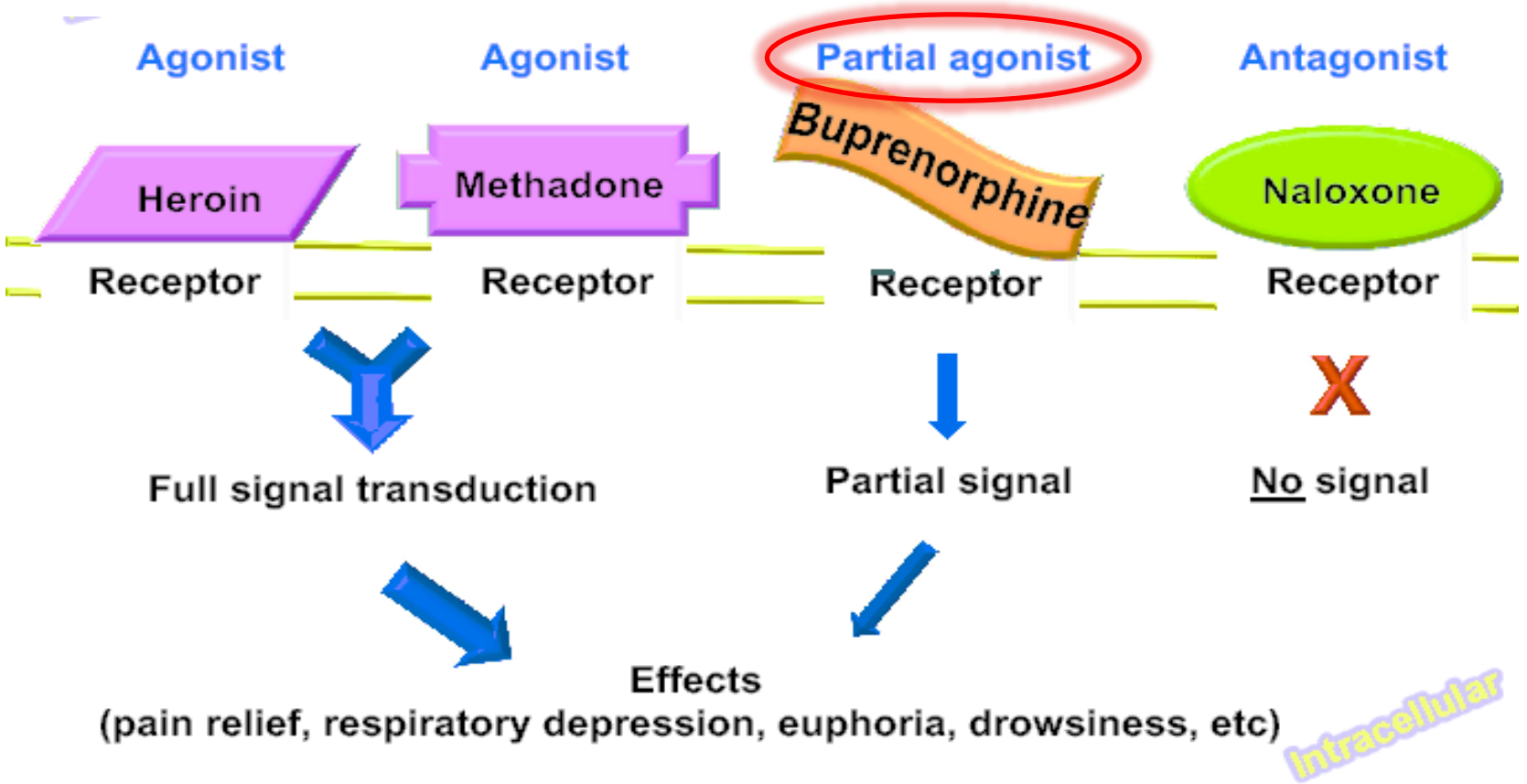
Full activation	No activation	Partial activation
Agonist	Antagonist	Partial Agonist



3- Partial agonists:

LO1

Agonists which stimulate a receptor but are unable to elicit the maximum cell response possible.



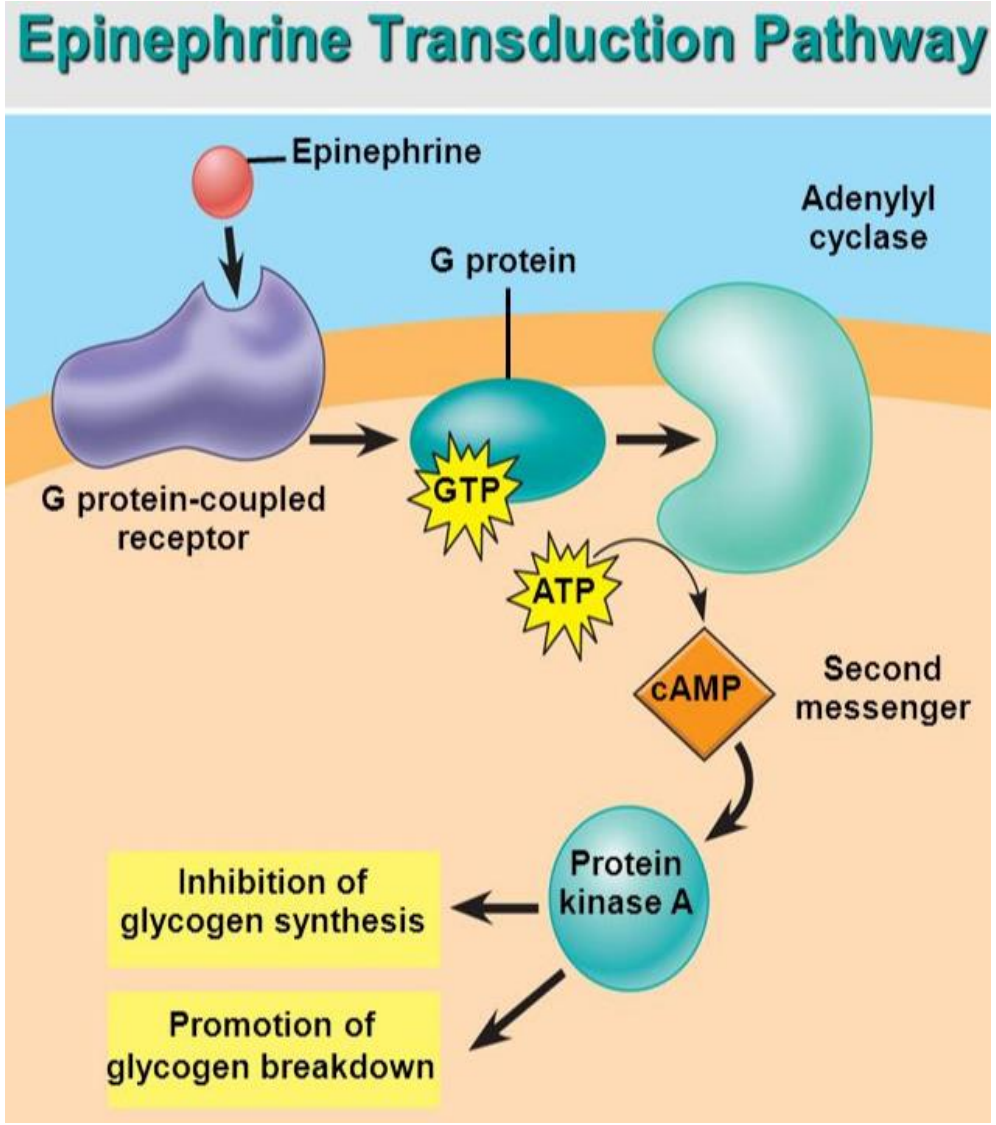
Receptors:

LO2

- A receptor is a molecule that recognizes specific a ligand or family of ligands.
- Binding of ligand to receptor ⟶ regulation of cellular process.
- In the unbound state ⟶ a receptor is functionally silent.

- Ex: catecholamine (e.g. adrenaline) binding to adrenergic receptor (adrenoceptor) brings about the activation of the enzyme, adenylyl cyclase, and a cascade of signaling events in the cell.

LO2


Epinephrine Transduction Pathway
Epinephrine
Adenylyl cyclase
G protein
G protein-coupled receptor
GTP
ATP
cAMP
Second messenger
Protein kinase A
Inhibition of glycogen synthesis
Promotion of glycogen breakdown

Acceptors:

LO2

- Molecules whose activities are modified by the binding of small chemicals including drugs
- are not strictly receptors under this definition
- Their basic function can occur without the interaction of a ligand and in the Absence of any signaling molecule, acceptors are Not functionally silent.

LO2

The enzyme dihydrofolate reductase operates normally in the absence of methotrexate

This enzyme is inhibited by the binding to methotrexate, so referred to as the Methotrexate receptor.

LO2

- **The voltage gated Na+ channel opens in response to an electrical event, but can be modulated by the binding of local anesthetic agents.**
- **Voltage gated Sodium channels are consider as receptors to local anesthetic.**
- **More accurately, these molecules should be referred to as "acceptor" molecules because their basic function can occur without the interaction of a ligand.**

SPECIFICITY OF RESPONSE

LO2

For a cell to respond to any chemical messenger it must produce specific receptor proteins

hydrophilic molecule

↓

can not cross cell membrane

↓

the receptor must be present on the cell membrane

hydrophobic molecule

↓

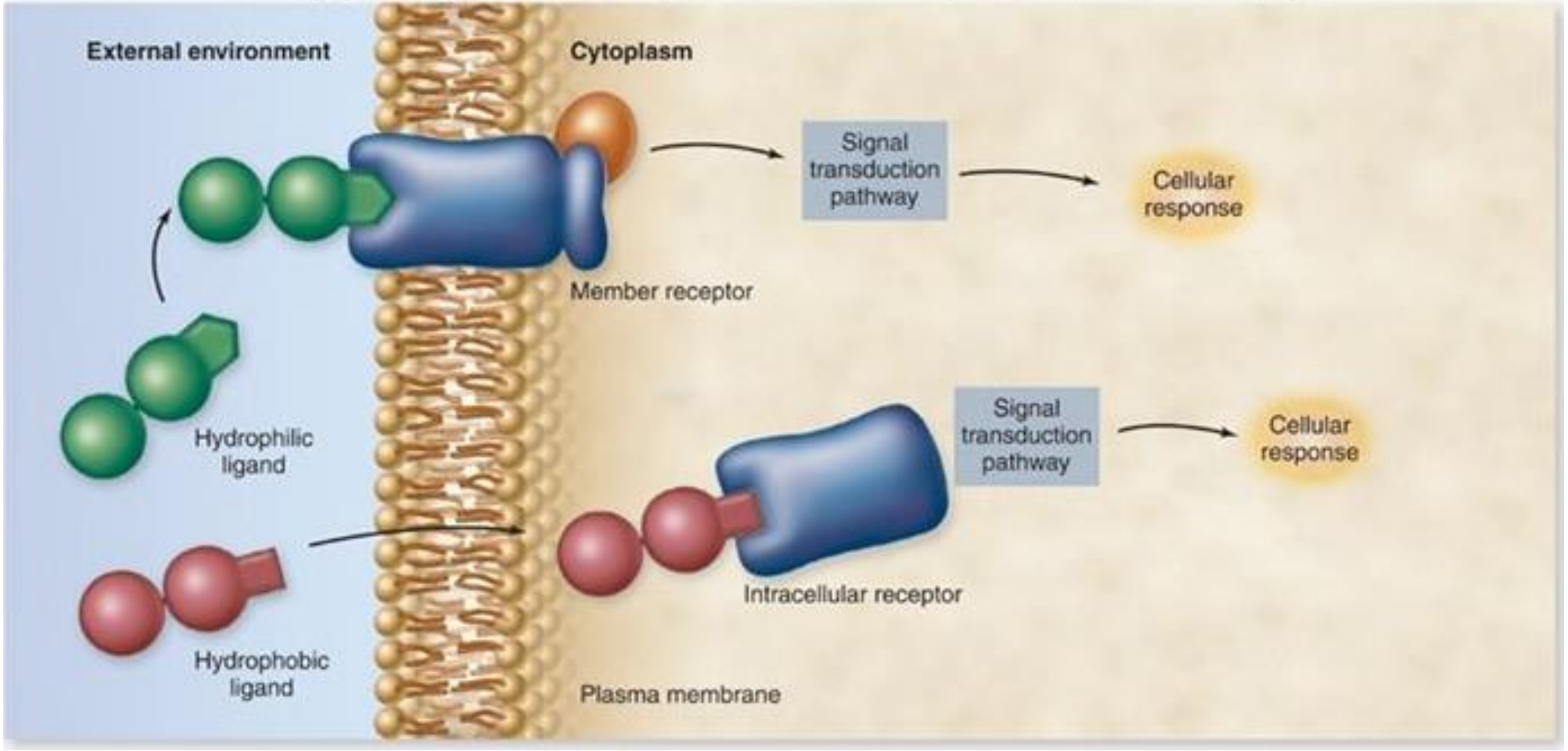
can cross cell membrane

↓

the receptor will be intracellular receptor

SPECIFICITY OF RESPONSE

LO2



LO2

PROPERTIES OF RECEPTOR BINDING SITES

- **Similarities between receptor binding sites and the active sites and regulatory sites (allosteric site) of enzymes (Acceptors).**

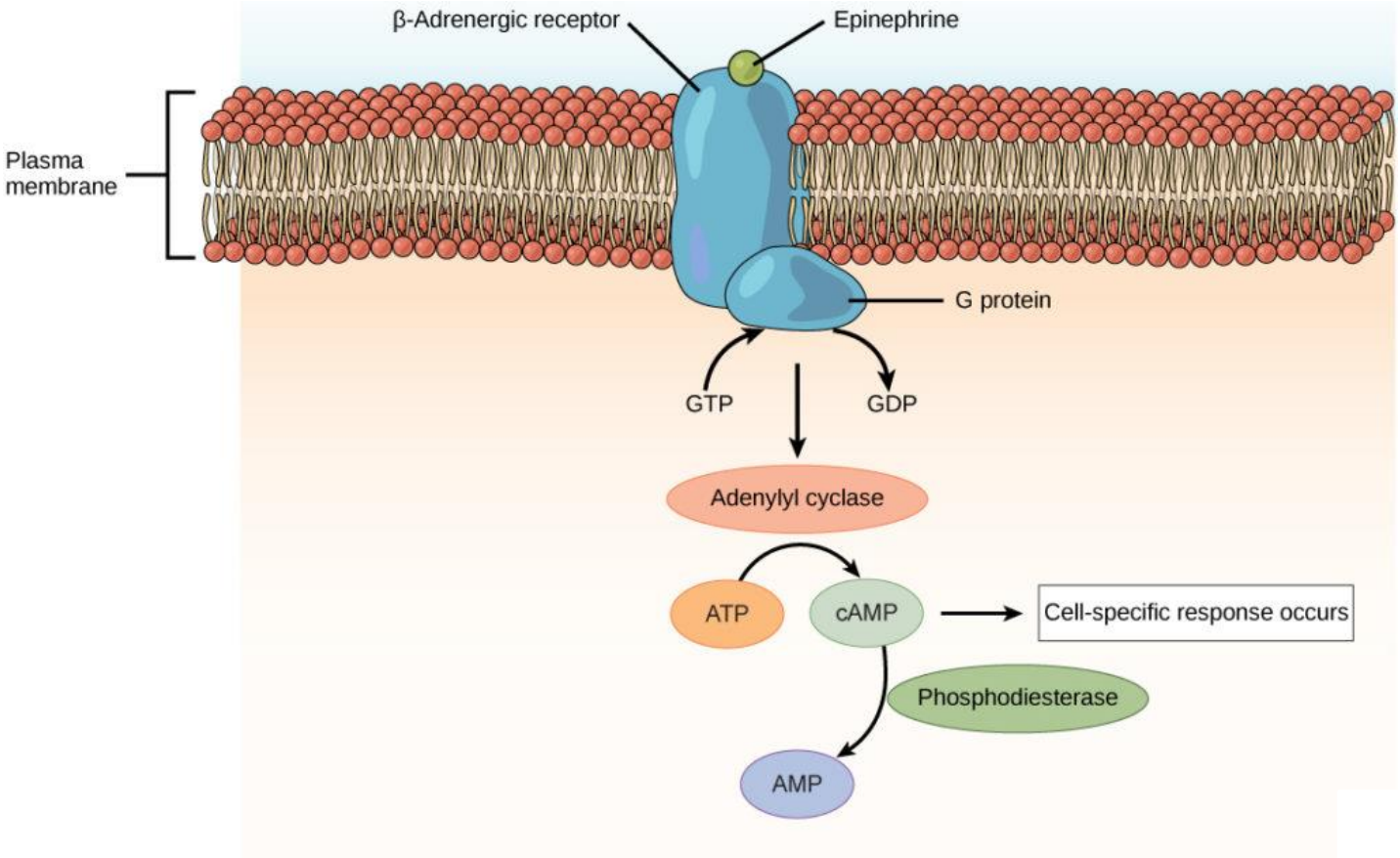
1- Specificity: The Binding on both receptor sites and enzyme sites is specific. The binding specificity is governed by the shape of the binding cleft in the receptor or enzyme site.

2- Reversibility: The Binding to both receptors and enzymes is most often reversible.

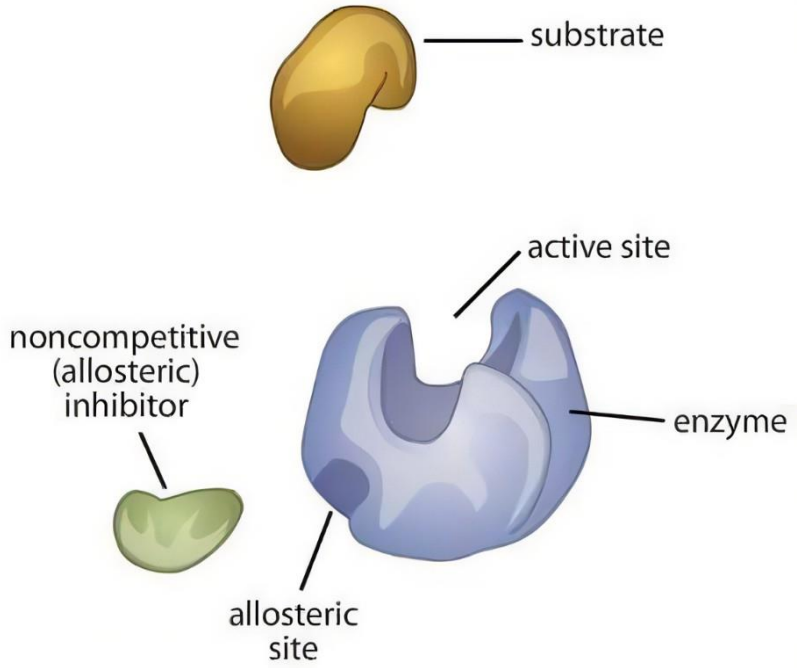
Properties of Receptor and enzyme sites

LO2

Receptor



Enzyme



LO2

3- Conformational changes: receptor and enzyme allosteric sites undergo conformational changes and a change in their activity

4- No chemical modification in receptor binding sites or enzyme regulatory sites.

LO2

PROPERTIES OF RECEPTOR BINDING SITES

- **Differences between receptor binding sites and the active sites and regulatory sites (allosteric site) of enzymes (Acceptors).**

1- The affinity of ligand binding at receptor sites is generally higher than the binding of substrates and regulators to enzyme sites.

2- The ligand bound to a receptor site is not modified chemically, whereas substrate bound in an enzyme active site is modified in a chemical reaction catalyzed by the active site.

LO2

ROLE OF RECEPTORS IN CELLULAR PHYSIOLOGY

Examples include such processes as:

- **Signaling by hormones and local chemical mediators**
- **Neurotransmission**
- **Control of gene expression (steroids, thyroid hormones)**
- **Release of intracellular calcium stores**
- **Cell growth, proliferation, metabolism and regulate cell communication**

SIGNAL TRANSDUCTION:

LO2

Most signaling molecules are hydrophilic molecule

The receptor must be present on the cell membrane (e.g. insulin)

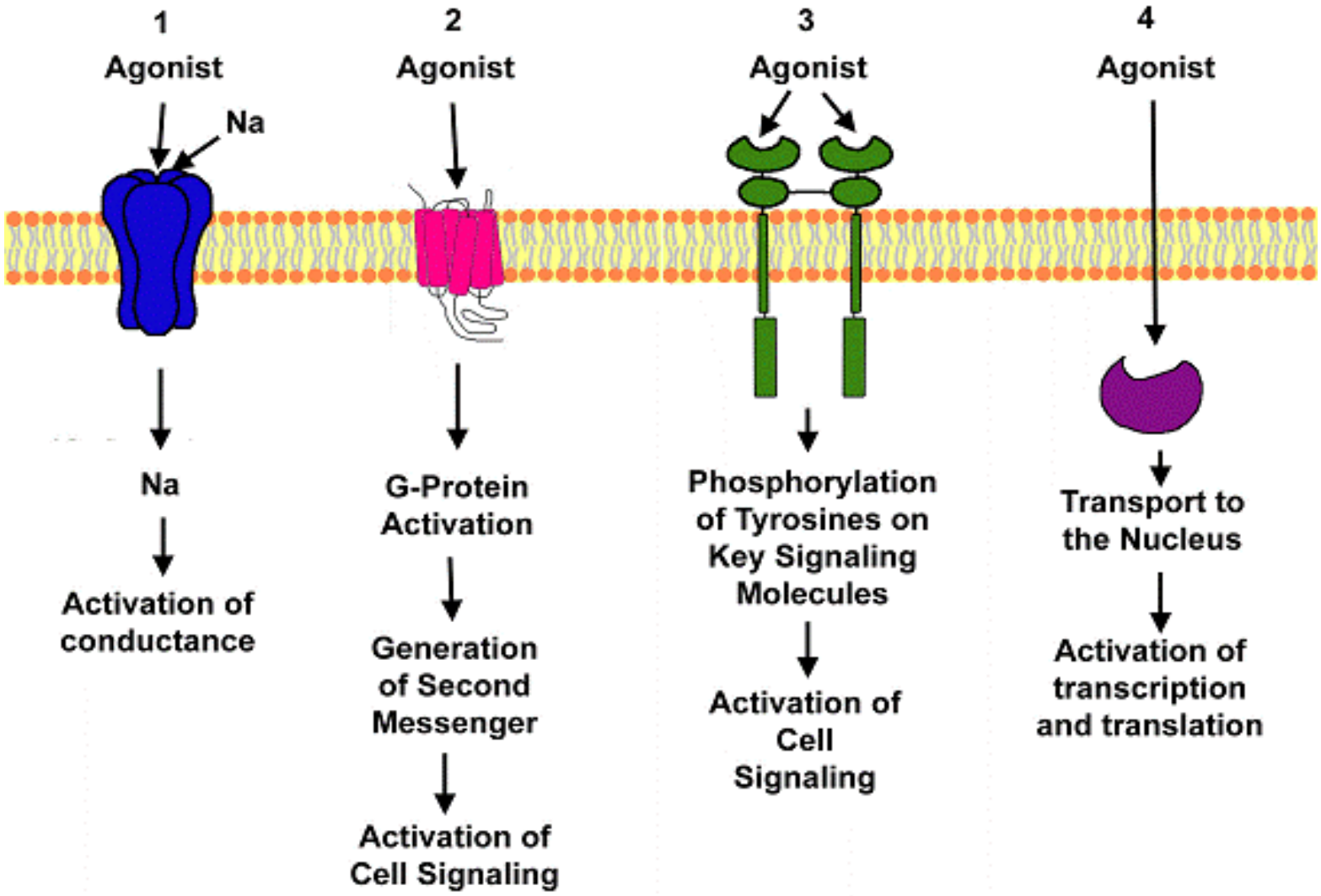
hydrophobic molecule

The receptor will be intracellular receptor (e.g. steroid and thyroid hormones)

- **Common mechanisms to transduce an <u>extracellular</u> <u>hydrophilic</u> <u>signal</u>:**
  1. **Membrane-bound receptors with integral ion channels.**
  2. **Membrane-bound receptors with integral enzyme activity.**
  3. **Membrane-bound receptors which couple to effectors through transducing proteins.**

Receptor super-families

LO2 & 3



LO2 & 3

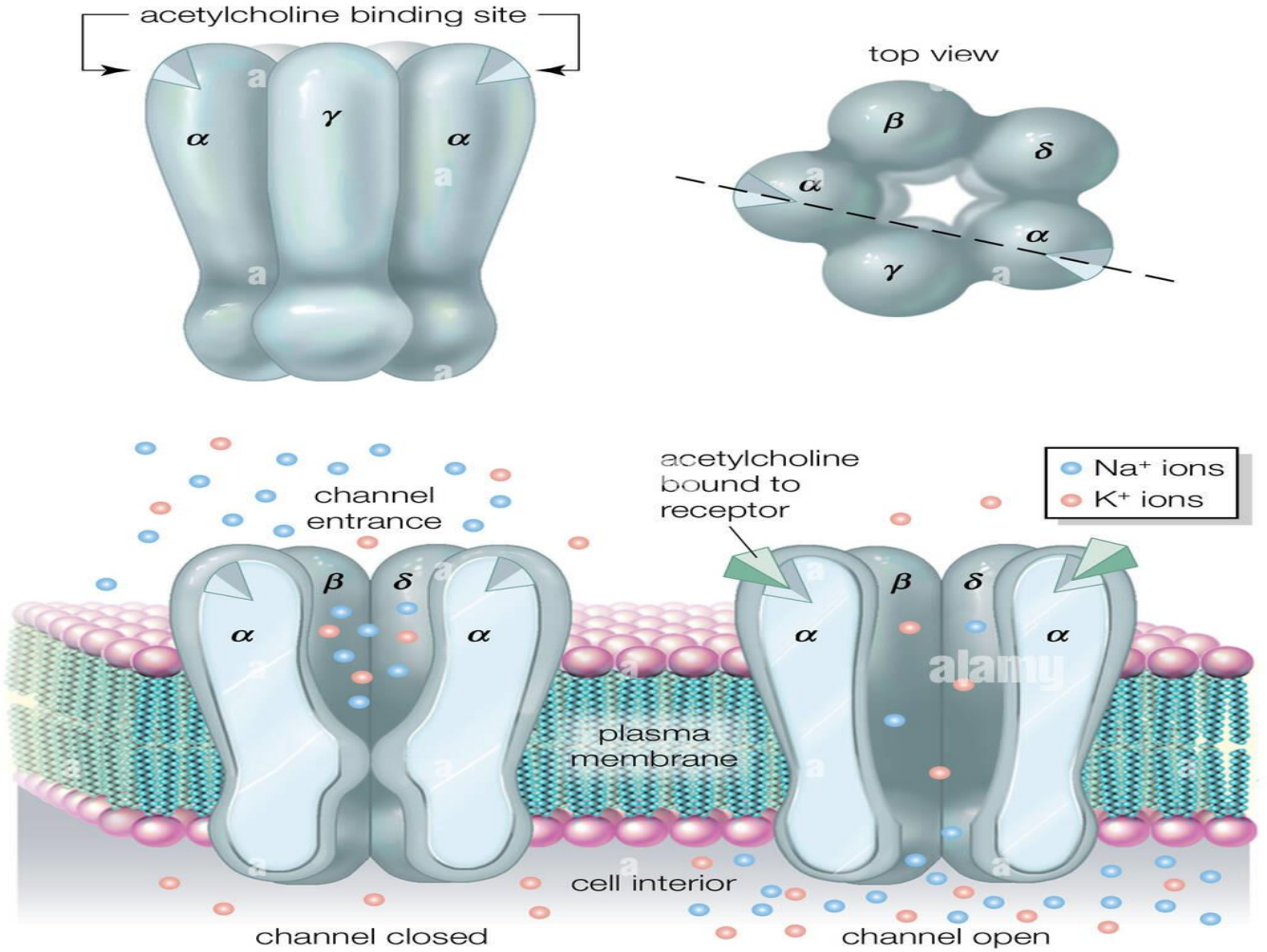
1- Membrane-Bound Receptors with Integral Ion Channels (Ligand-Gated Ion Channels):

- **Agonist binding to ligand-gated ion channels results in a change in conformation and opening of a gated channel which permits the flow of ions down an electrochemical gradient**

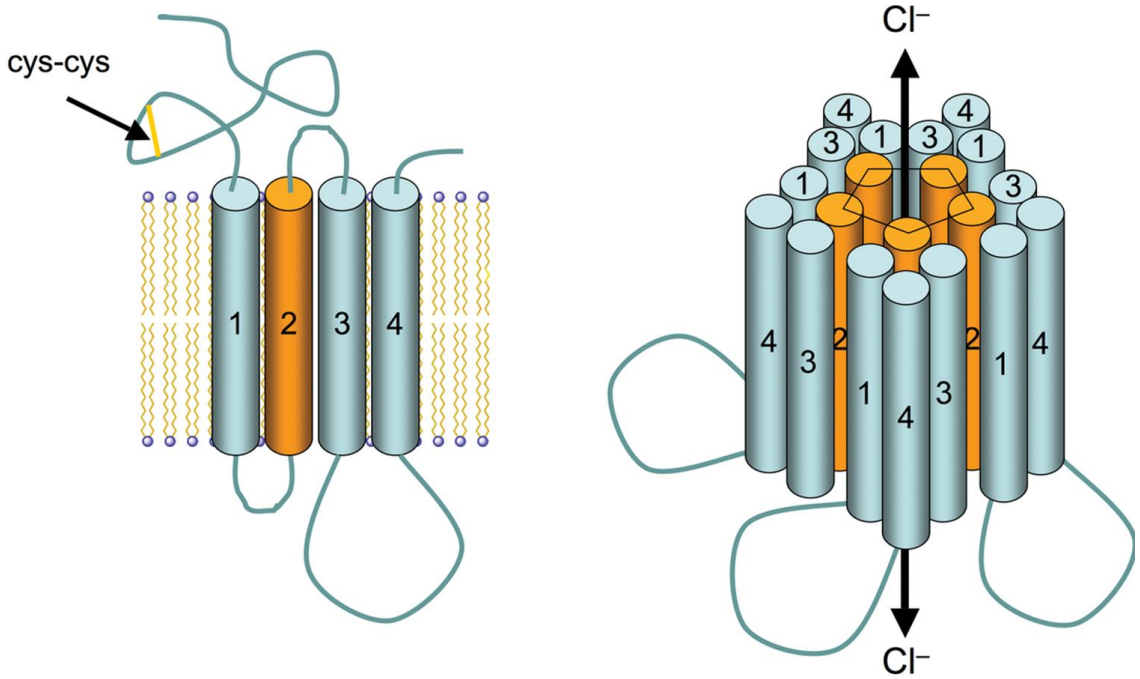
The structure → have similar pentameric subunit structures. Each one of these subunits have four transmembrane domains

LO2 & 3

1- Membrane-Bound Receptors with Integral Ion Channels (Ligand-Gated Ion Channels):



1- Membrane-Bound Receptors with Integral Ion Channels (Ligand-Gated Ion Channels): LO2 & 3



Examples:

1- Nicotinic acetylcholine receptors (nAChR)

2- Gamma aminobutyric acid receptors (GABAR)

3- Glycine receptors (GlyR).

LO2 & 3

2- Membrane-Bound Receptors with Integral Enzyme Activity:

Agonist binding extracellular domain

↓

Conformational change

↓

Activates a protein kinase activity (enzyme) in the cytoplasmic domain

↓

Auto-phosphorylates

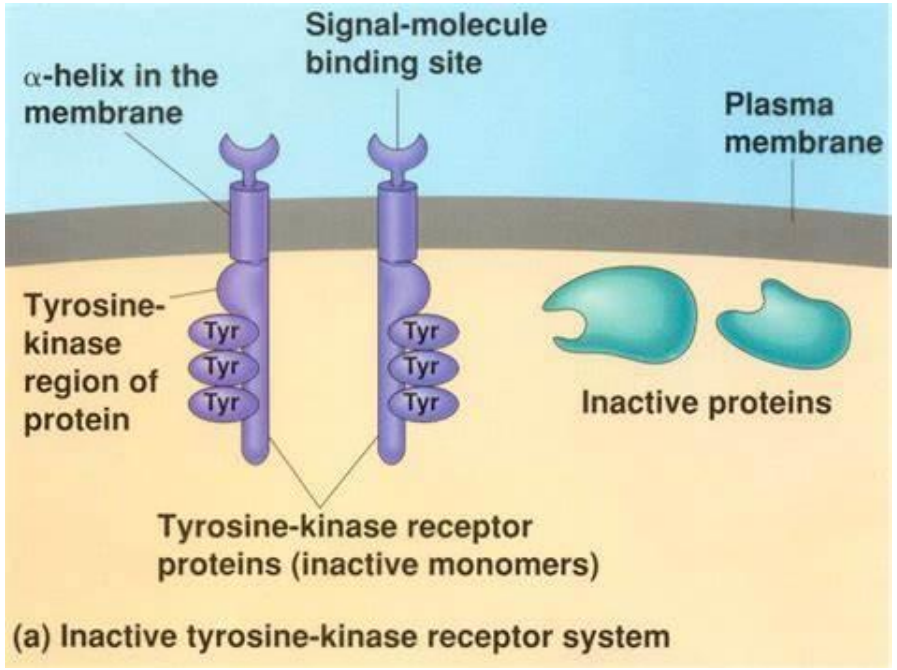
LO2 & 3

2- Membrane-Bound Receptors with Integral Enzyme Activity are 2 types:

A- Tyrosine kinase-linked receptors:

growth factor receptors such as

- ✓ **receptors for insulin,**
- ✓ **epidermal growth factor (EGF)**
- ✓ **platelet derived growth factor (PDGF).**



B- Guanylyl Cyclase-linked receptors: such as

- ✓ **atrial natriuretic peptide (ANP) receptor.**

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3. G-protein-coupled receptor (GPCR) family:

- **Seven trans-membrane domain receptors (7TMDR) couple to effector molecules via a transducing molecule (GTP-binding regulatory protein (G-protein).**

- **Effectors may be**
  - ✓ **enzymes, e.g. adenylyl cyclase (ATP to cAMP)**
  - ✓ **phosphatidylinositol 4,5bisphosphatase**
  - ✓ **ion channels e.g. Ca2+ channels and K+ channels.**

- **Receptor binding results in a conformational change which activates GDP/GTP exchange in GTP-binding regulatory proteins which transduce the message on to an enzyme or channel in the membrane.**

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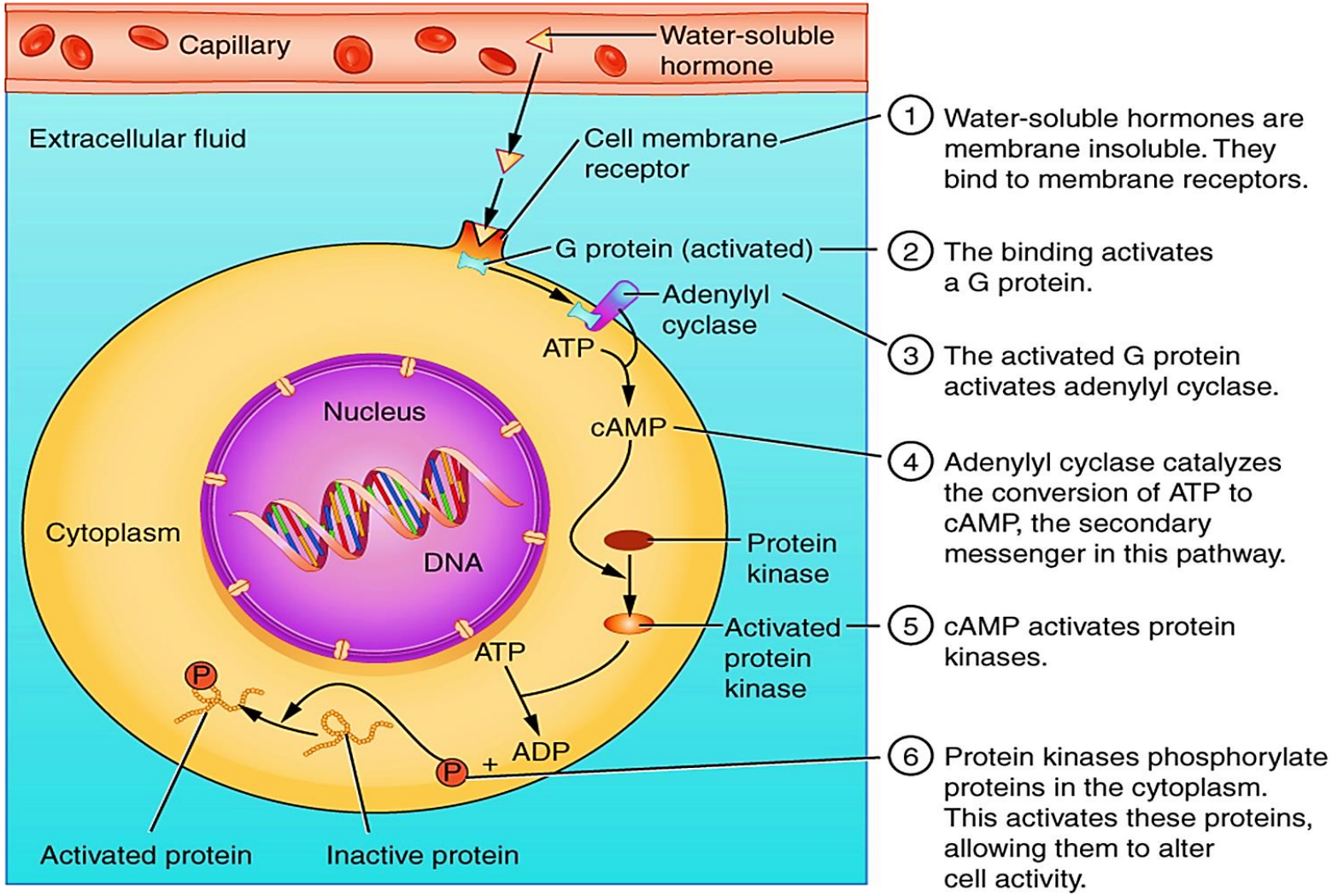
3. G-protein-coupled receptor (GPCR) family:



Example:

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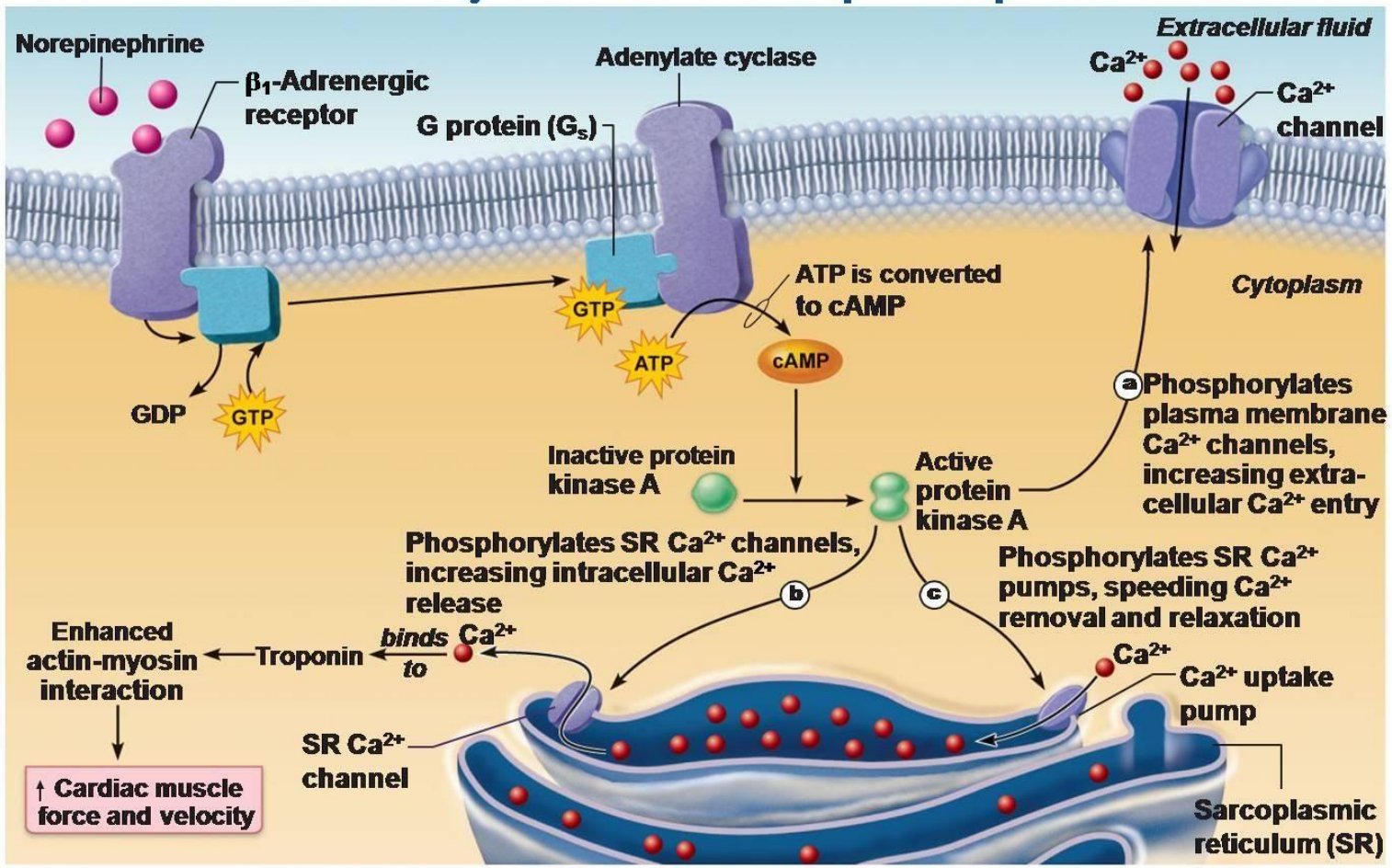
Contractility and Norepinephrine



- Sympathetic stimulation releases norepinephrine and initiates a cyclic AMP second-messenger system

Figure 18.21

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Examples:

- 1- muscarinic acetylcholine receptor
- 2- adrenoceptors
- 3- dopamine receptors
- 4- 5-hydroxytryptamine (5-HT) receptors
- 5- opioid receptors
- 6- peptide receptors (e.g. substance P, angiotensin)
- 7- purine receptors (e.g. ATP)
- 8- light receptors (rhodopsin), smell and taste receptors and many others.

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4. Intracellular Receptors:

- Monomeric receptors in the cytoplasm or nucleus.
- For hydrophobic ligands
- In the resting state these receptors are stabilized by association with heat shock or chaperone proteins.
- In activation, dissociates from the chaperone protein and translocate to the nucleus where it binds to control regions in DNA (regulating gene expression).
- The effects of intracellular receptor activation are relatively slow in onset as transcription and translation are required

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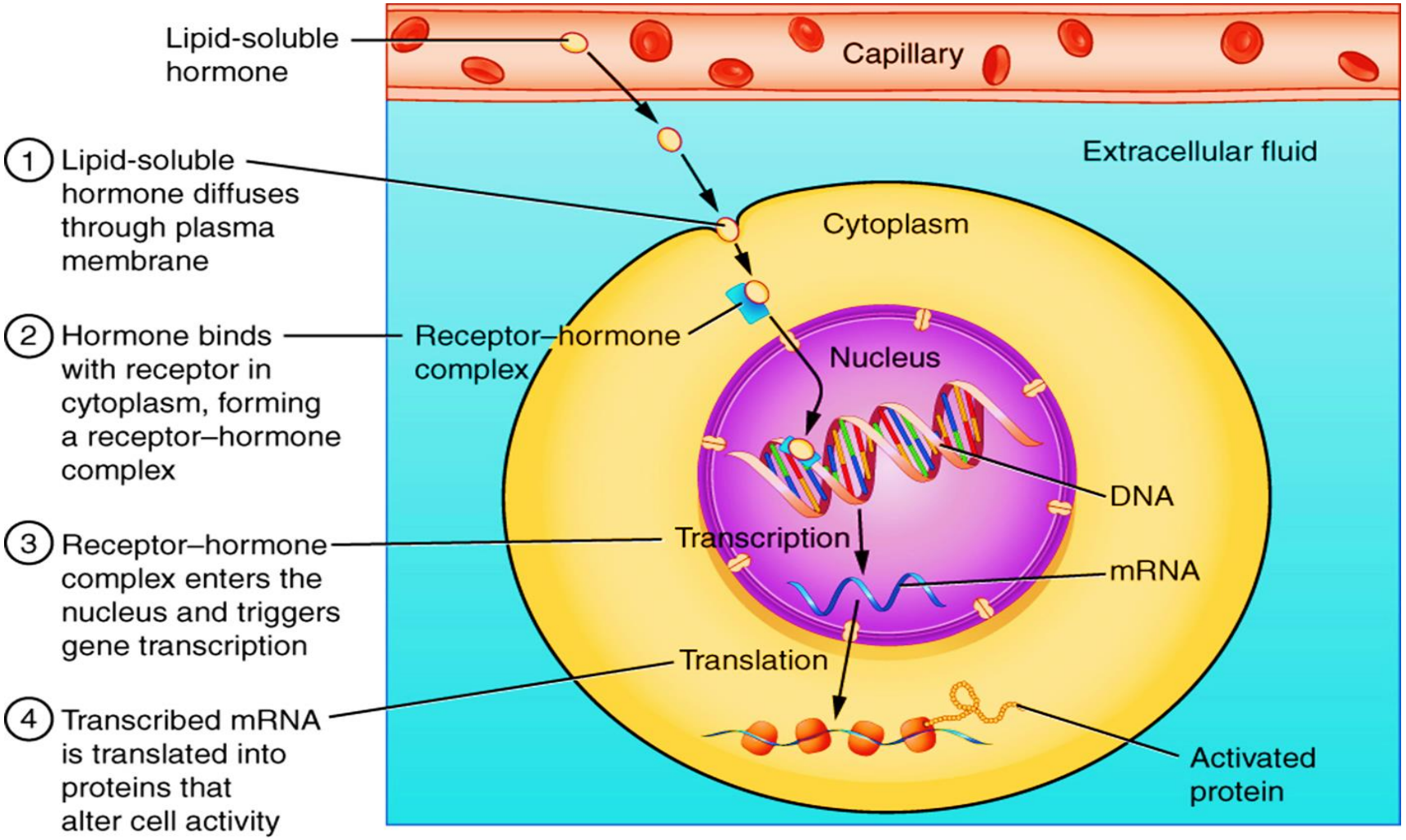
4. Intracellular Receptors:



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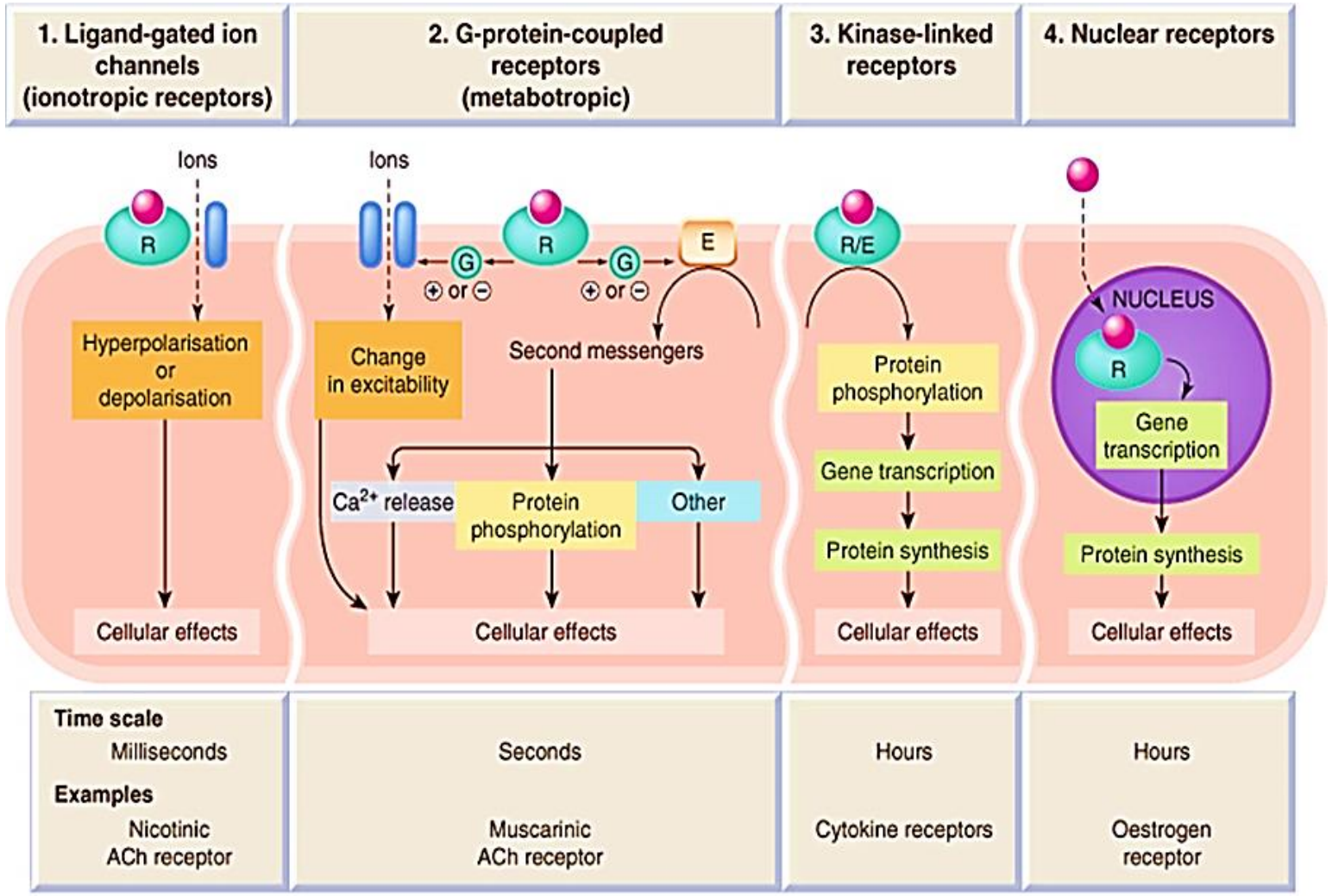
Summary of Receptors super families



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•Cellular Activation and Inhibition:

Responses to receptor activation can lead to cellular activation or inhibition depending on the receptor. For example

- in cardiac pacemaker cells noradrenaline acting on ß1-adrenoceptors produces an increased heart rate, while acetylcholine acting on M2 muscarinic receptors produces a slowing of heart rate.

- hepatocytes→ insulin stimulates the synthesis of glycogen from glucose, while glucagon stimulates glycogen breakdown


thank
you