GPCR and its Functions

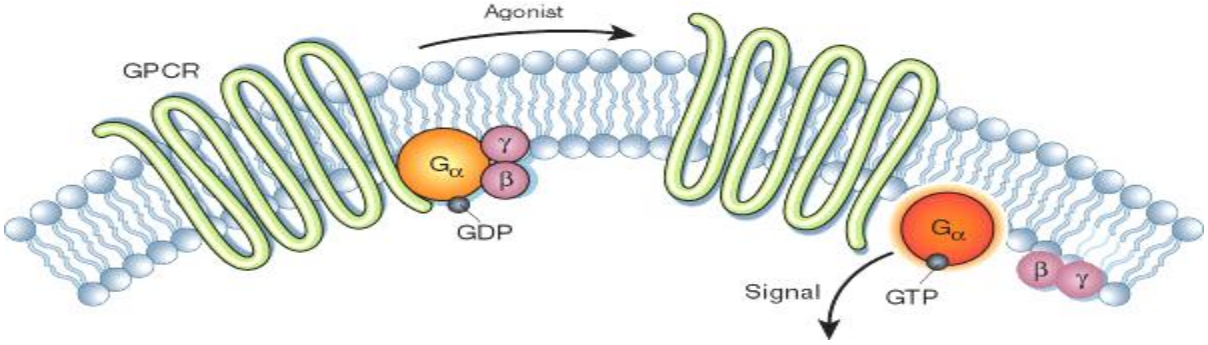
G Protein-Coupled Receptor (GPCR)

G protein-coupled receptor (GPCR), also called **seven-transmembrane receptor** or **heptahelical receptor**, protein located in the cell membrane

G-protein-coupled receptors (GPCRs) are the largest and most diverse group of membrane receptors in eukaryotes.

GPCR binds extracellular ligands and transmits signals from these substances to an intracellular molecule called a G protein (guanine nucleotide-binding protein).

GPCRs are found in the cell membranes of a wide range of organisms, including mammals, plants, microorganisms, and invertebrates.



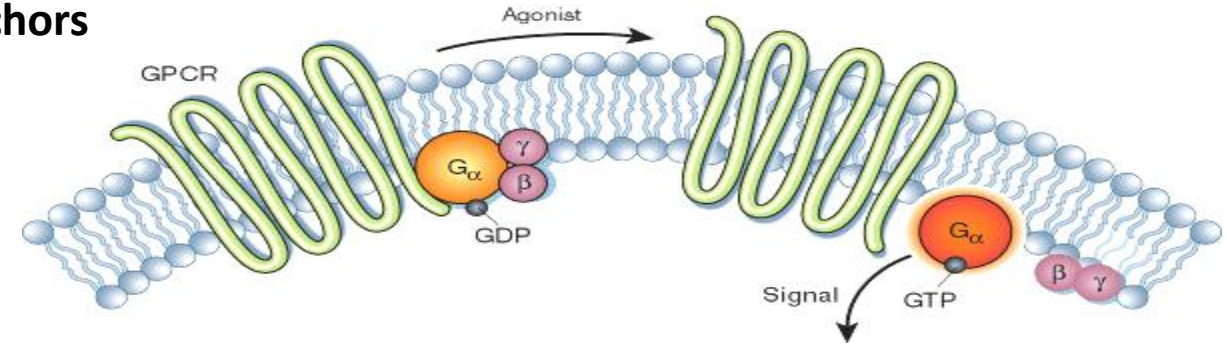
G proteins

G proteins are specialized proteins with the ability to bind the nucleotides guanosine triphosphate (GTP) and guanosine diphosphate (GDP).

Some G proteins, such as the signaling protein Ras, are small proteins with a single subunit.

The G proteins that associate with GPCRs are heterotrimeric, meaning they have three different subunits: an alpha subunit, a beta subunit, and a gamma subunit.

Two of these subunits — alpha and gamma — are attached to the plasma membrane by lipid anchors



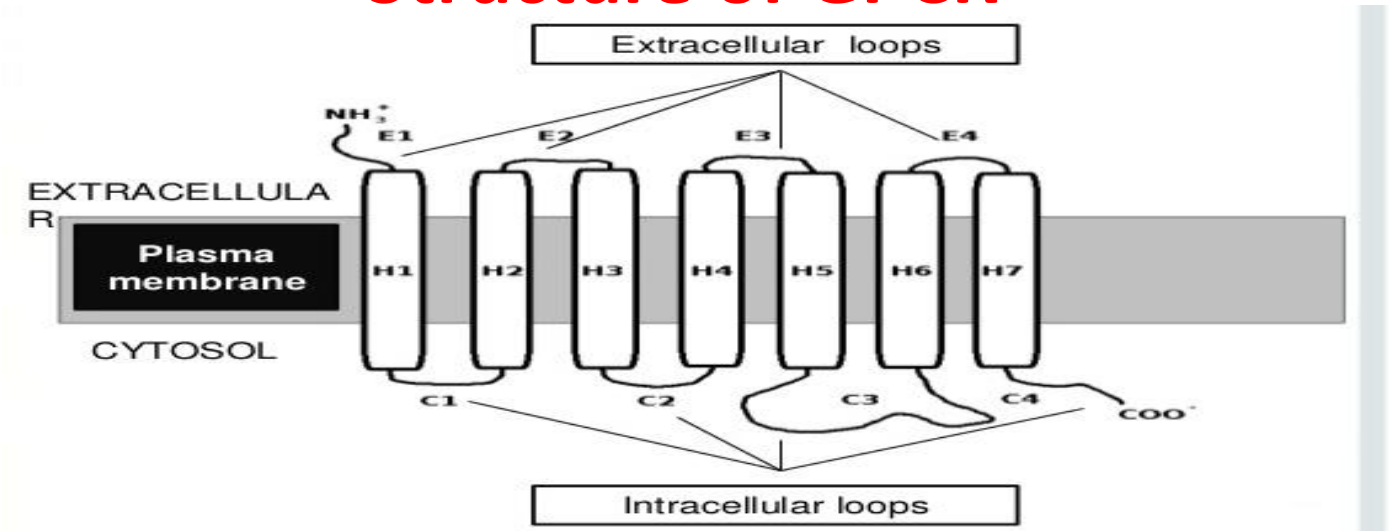
GPCRs has evolutionary conserved structure and bind a variety of signaling molecules.

Animals, plants, fungi, and protozoa — rely on these receptors to receive information from their environment.

For example, simple eukaryotes such as yeast have GPCRs that sense glucose and mating factors.

Humans alone have nearly 1,000 different GPCRs, and each one is highly specific to a particular signal.

Structure of GPCR



GPCRs consist of a single polypeptide that is folded into a globular shape and embedded in a cell's plasma membrane.

Seven segments of this molecule span the entire width of the membrane — therefore called seven-transmembrane receptors — and the intervening portions loop both inside and outside the cell.

The extracellular loops (EL) form part of the pockets at which signaling molecules bind to the GPCR. The internal loops (IL) interacts with the G-proteins.

How GPCR works

As their name implies, GPCRs interact with G proteins in the plasma membrane.
When an external signaling molecule binds to a GPCR, it causes a conformational change in the GPCR. This change then triggers the interaction between the GPCR and a nearby G protein.

A G protein alpha subunit binds either GTP or GDP depending on whether the protein is active (GTP) or inactive (GDP).

In the absence of a signal, GDP attaches to the alpha subunit, and the entire G protein-GDP complex binds to a nearby GPCR.

A change in the conformation of the GPCR activates the G protein, and GTP physically replaces the GDP bound to the alpha subunit.

As a result, the G protein subunits dissociate into two parts: the GTP-bound alpha subunit and a beta-gamma dimer.

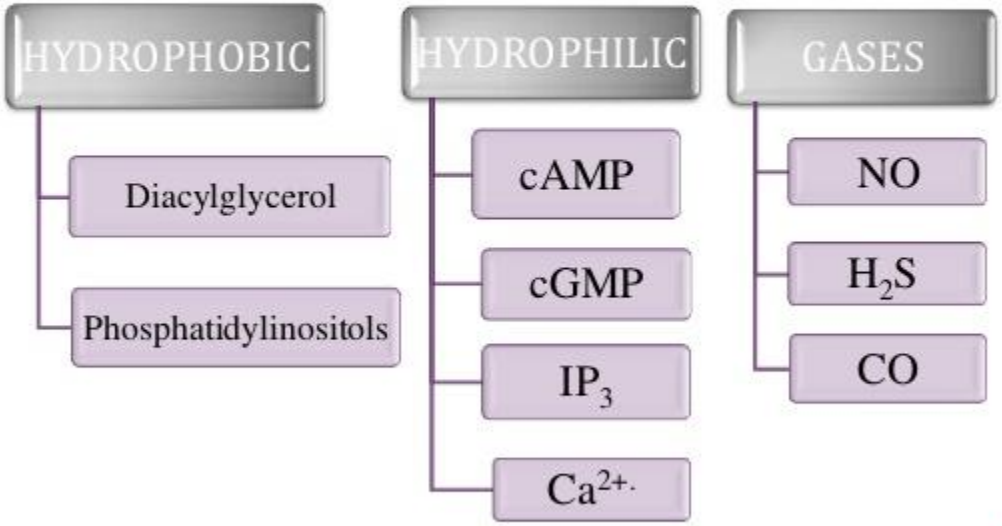
Both parts remain anchored to the plasma membrane, but they are no longer bound to the GPCR, so they can now diffuse laterally to interact with other membrane proteins.

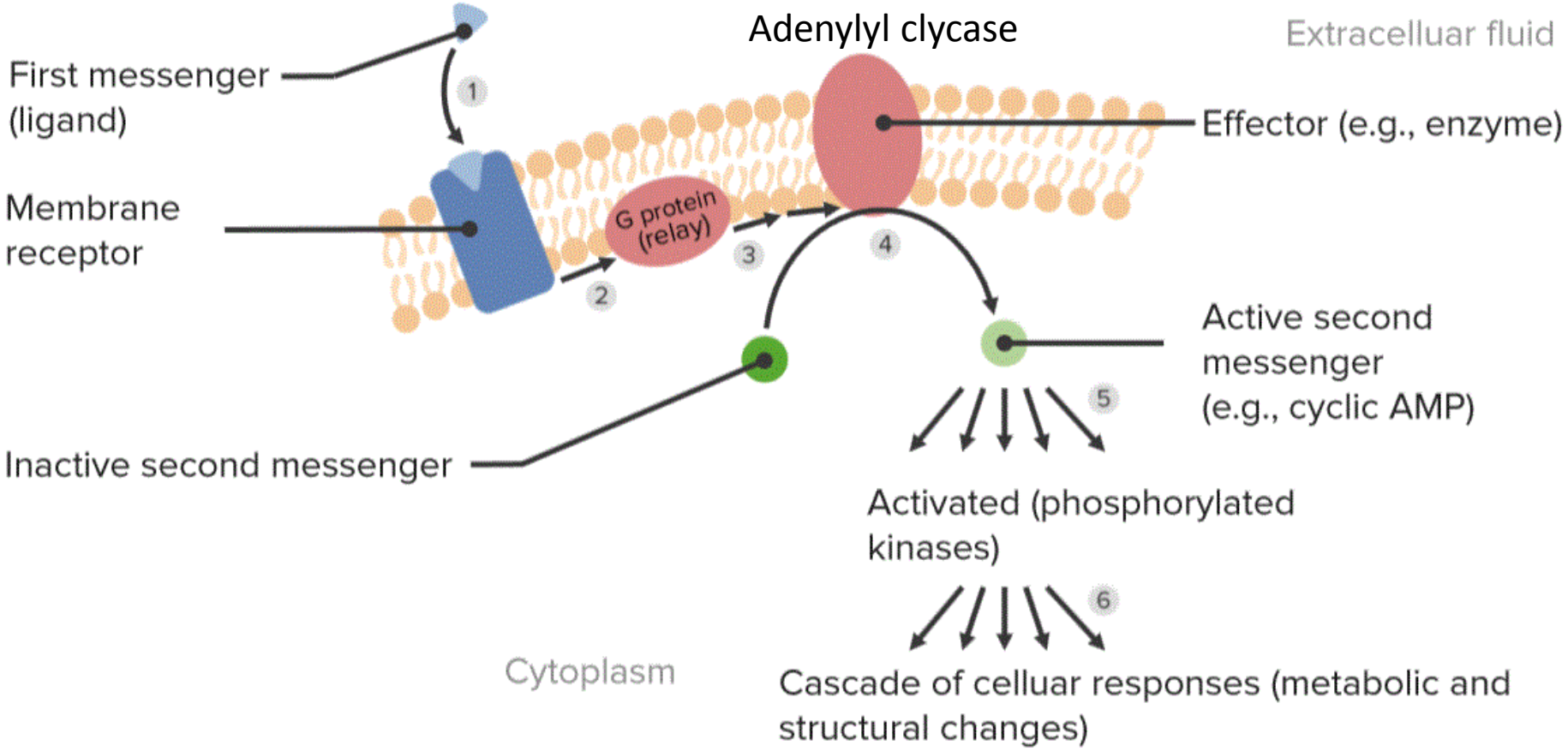
G proteins work like a switch — turned on or off by signal-receptor interactions on the cell's surface.

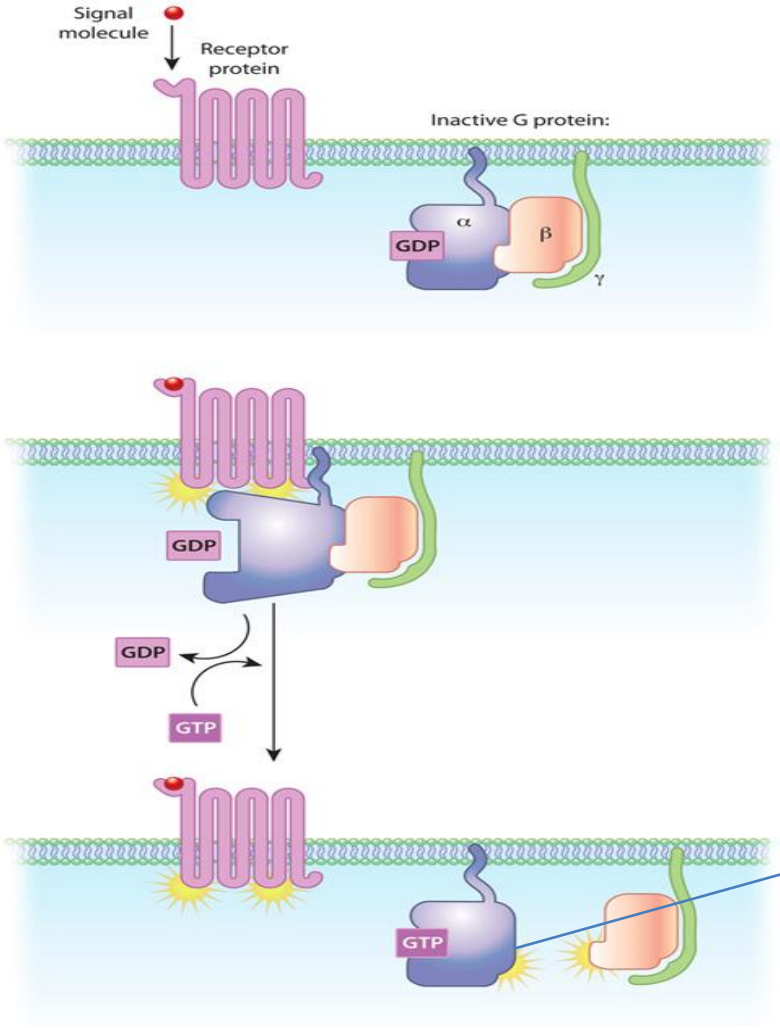
G proteins remain active as long as their alpha subunits are joined with GTP.

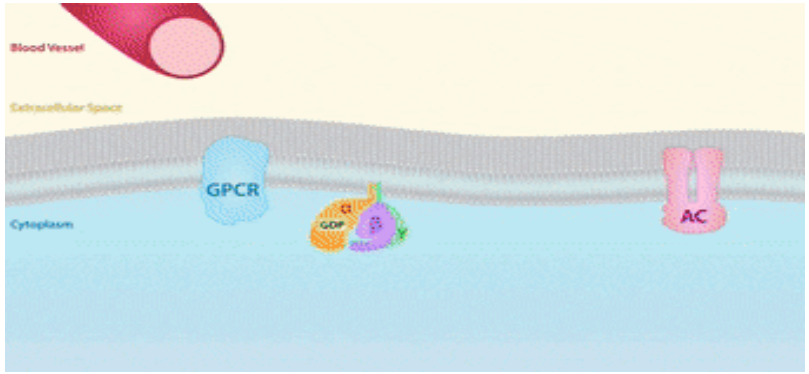
when this GTP is hydrolyzed back to GDP, the subunits once again assume the form of an inactive heterotrimer, and the entire G protein reassociates with the now-inactive GPCR

TYPES OF SECOND MESSENGERS




Adenylyl clycase
Extracelluar fluid
First messenger
(ligand)
1
Effector (e.g., enzyme)
Membrane
receptor
G protein
(relay)
2
3
4
Active second
messenger
(e.g., cyclic AMP)
5
Inactive second messenger
Activated (phosphorylated
kinases)
6
Cytoplasm
Cascade of celluar responses (metabolic and
structural changes)





Adenylyl clycase

Second Messenger

ATP

cAMP

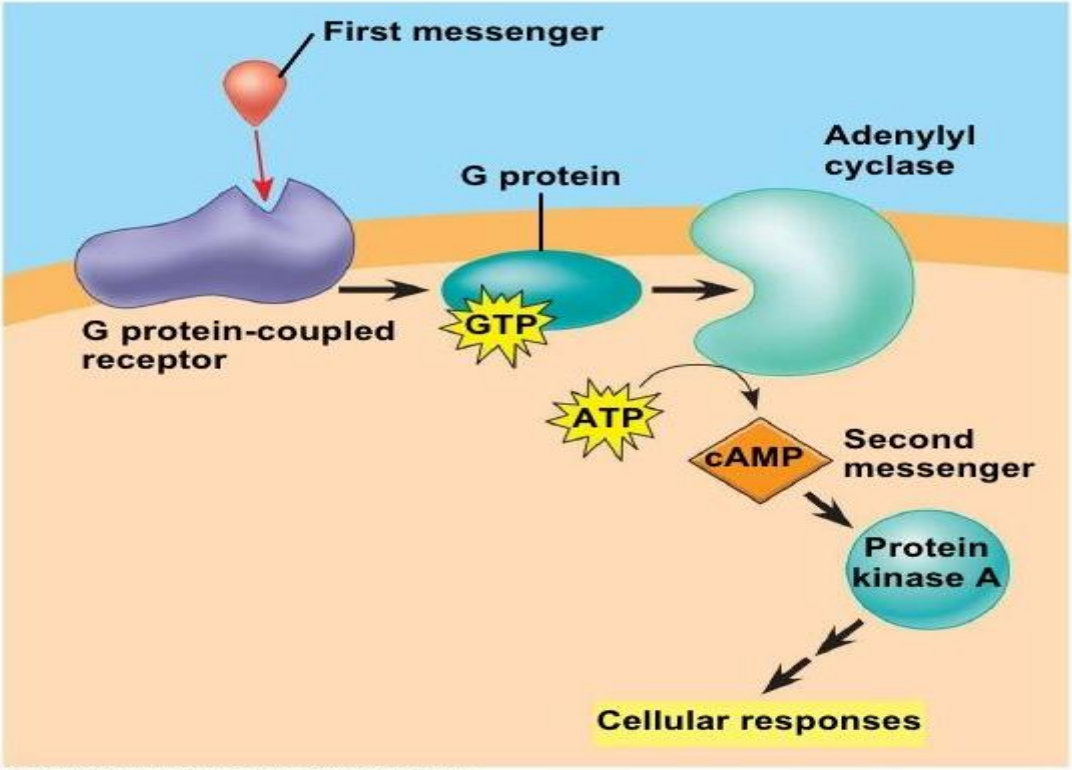
Protein Kinase A(PKA)

Activation of a single G protein can affect the production of hundreds or even thousands of second messenger molecules.

such as cyclic AMP [cAMP], diacylglycerol [DAG], and inositol 1, 4, 5-triphosphate [IP3]

One common target of activated G proteins is adenylyl cyclase, a membrane-associated enzyme that, when activated by the GTP-bound alpha subunit, catalyzes synthesis of the second messenger cAMP from molecules of ATP.

In humans, cAMP is involved in responses to sensory input, hormones, and nerve transmission, among others.



Functions of GPCR

G-protein-coupled receptors (GPCRs) constitute a large and diverse family of proteins whose primary function is to transduce extracellular stimuli into intracellular signals.

G-protein coupled receptors (GPCRs) are the targets of over half of all prescribed drugs today.

The G-protein coupled receptors (GPCRs) are the largest class of molecules involved in signal transduction across membranes and constitute ~1–2% of the human genome.

GPCRs have emerged as major targets for the development of novel drug candidates in all clinical areas due to their involvement in the generation of multitude of cellular responses.

GPCR play a crucial role in physiology by facilitating cell communication through recognition of diverse ligands, including bioactive peptides, amines, nucleosides, and lipids.

Conclusion

GPCRs are a large family of cell surface receptors that respond to a variety of external signals.

Binding of a signaling molecule to a GPCR results in G protein activation, which in turn triggers the production of any number of second messengers.

Through this sequence of events, GPCRs help regulate an incredible range of bodily functions, from sensation to growth to hormone responses.