Metabotropic Receptors

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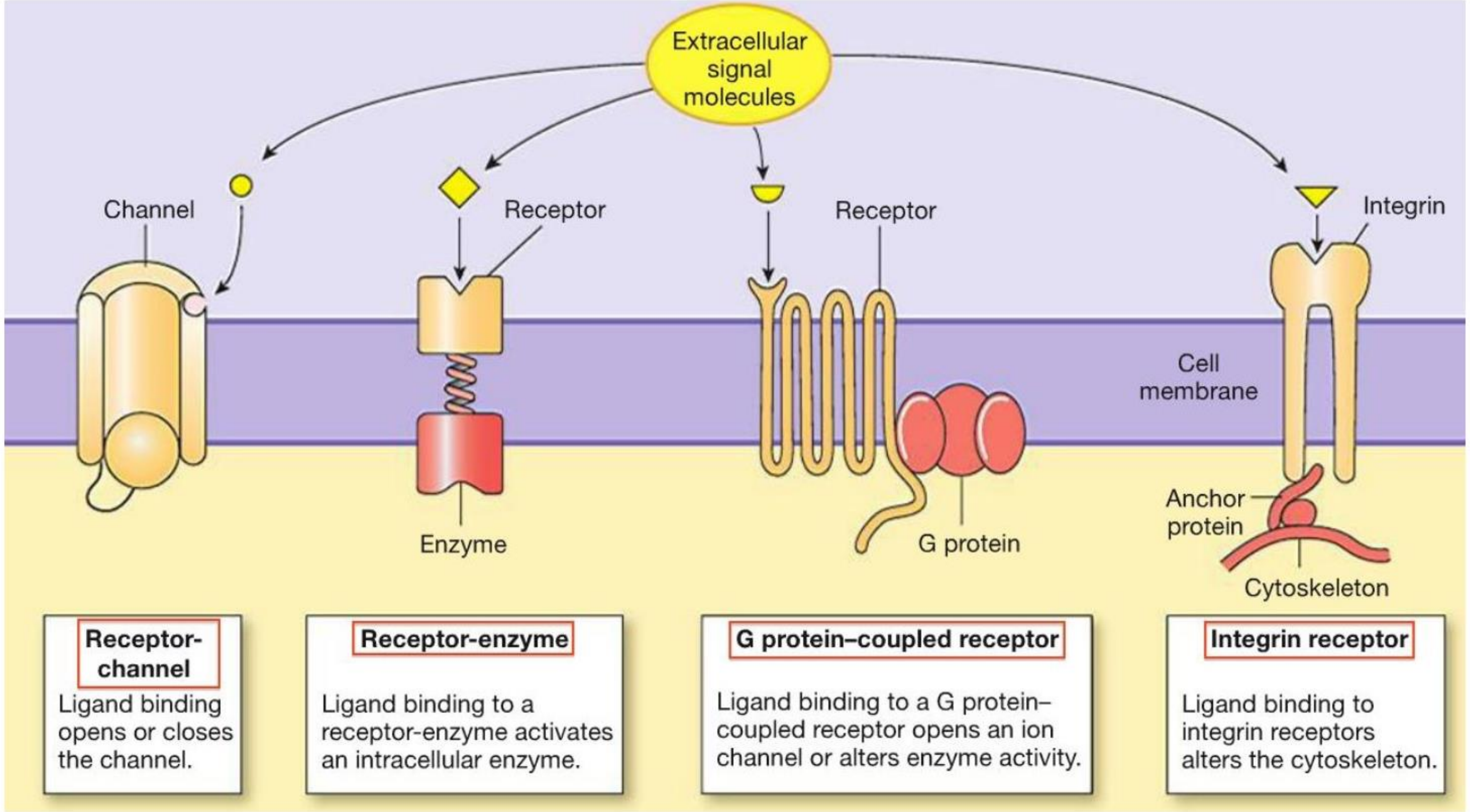

Cell-surface (or transmembrane) receptors are membrane-anchored, or integral proteins that bind to external ligand molecules.
This type of receptor spans the plasma membrane and performs signal transduction, converting an extracellular signal into an intracellular signal.

Metabotropic Receptors

The Nobel Prize in Chemistry 2012
Robert J. Lefkowitz, Brian K. Kobilka

The Nobel Prize in Chemistry 2012

Robert J. Lefkowitz

Biographical
Photo Gallery

Other Resource

Brian K. Kobilka

Photo: Stewart Waller/PR Newswire. © HHMI

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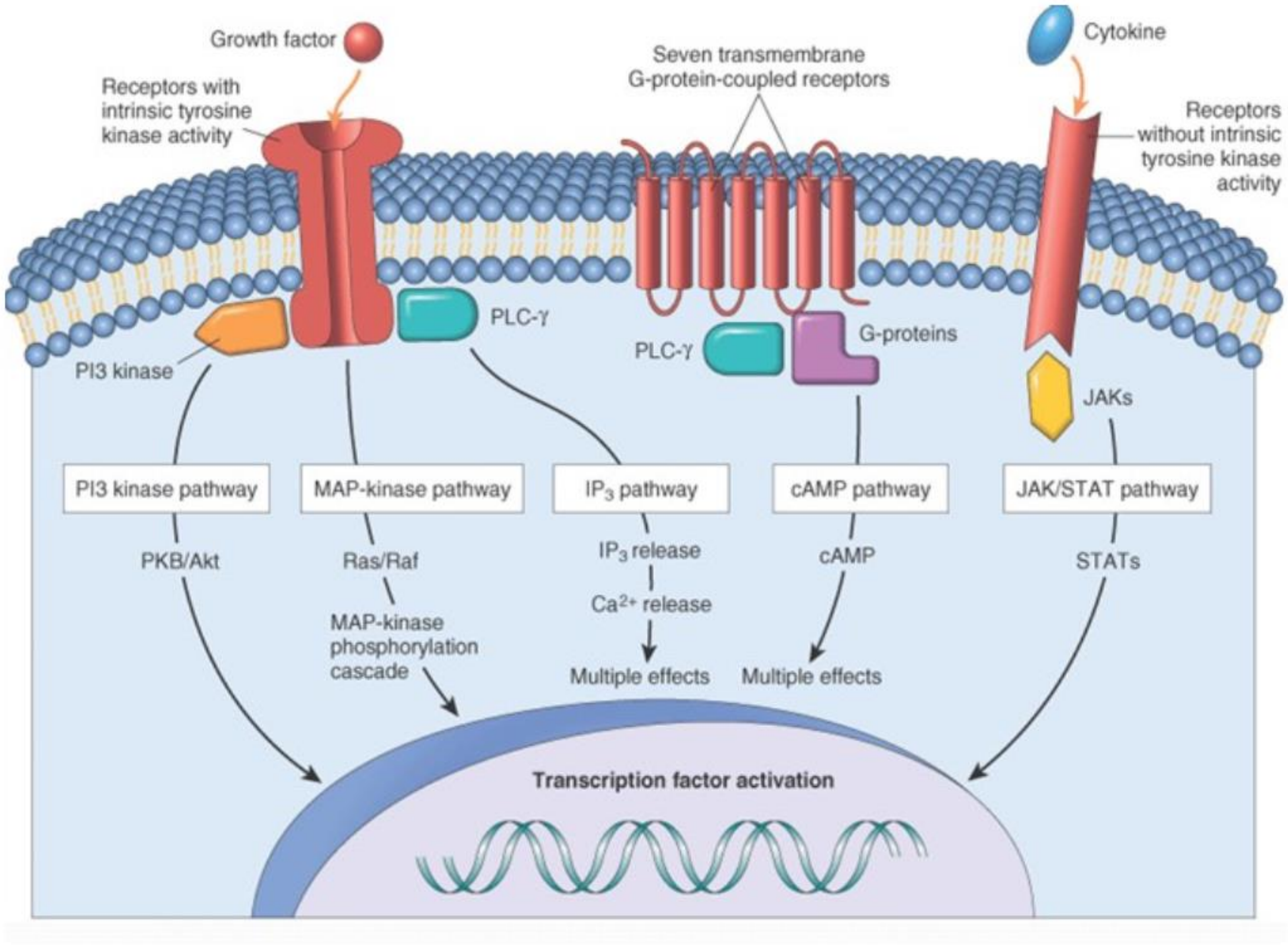
The Nobel Prize in Chemistry 2012

In our eyes, noses and mouths, we have sensors for light, odours and flavours. Within the body, cells have similar sensors for hormones and signalling substances, such as adrenalin, serotonin, histamine and dopamine. As life evolved, cells have repeatedly used the same basic mechanism for reading their environment: G-protein-coupled receptors. But they remained hidden from researchers for a long time.

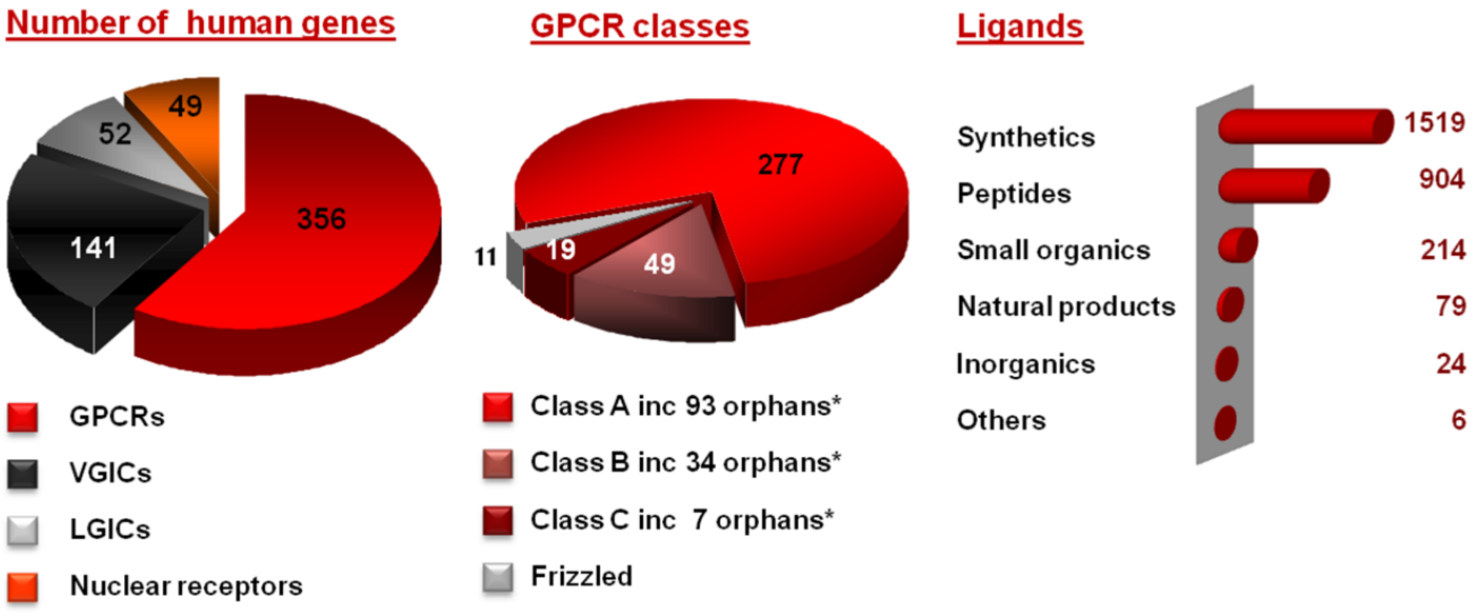
Metabotropic Receptors are Transmembrane Receptors



This large group of membrane-bound receptors comprises the 7TM or 1TM receptor families. All recruit multiple intracellular signaling cascades known as "second messengers".

G Protein-Coupled Receptors (GPCRs)

The largest and most diverse group of membrane receptors in eukaryotes.



Class A (Rhodopsin-like) most receptors binding monoamines and neurotransmitters
Class B (Secretin receptor family) binding ligands such as secretin, glucagone, calcitonin
Class C (Metabotropic glutamate/pheromone) Ca-sensitive receptors as the mGlu R

Classe D (Fungal mating pheromone receptors)
Classe E (Cyclic AMP receptors)
Classe F (Frizzled/Smoothened)

G Protein-Coupled Receptors (GPCRs)

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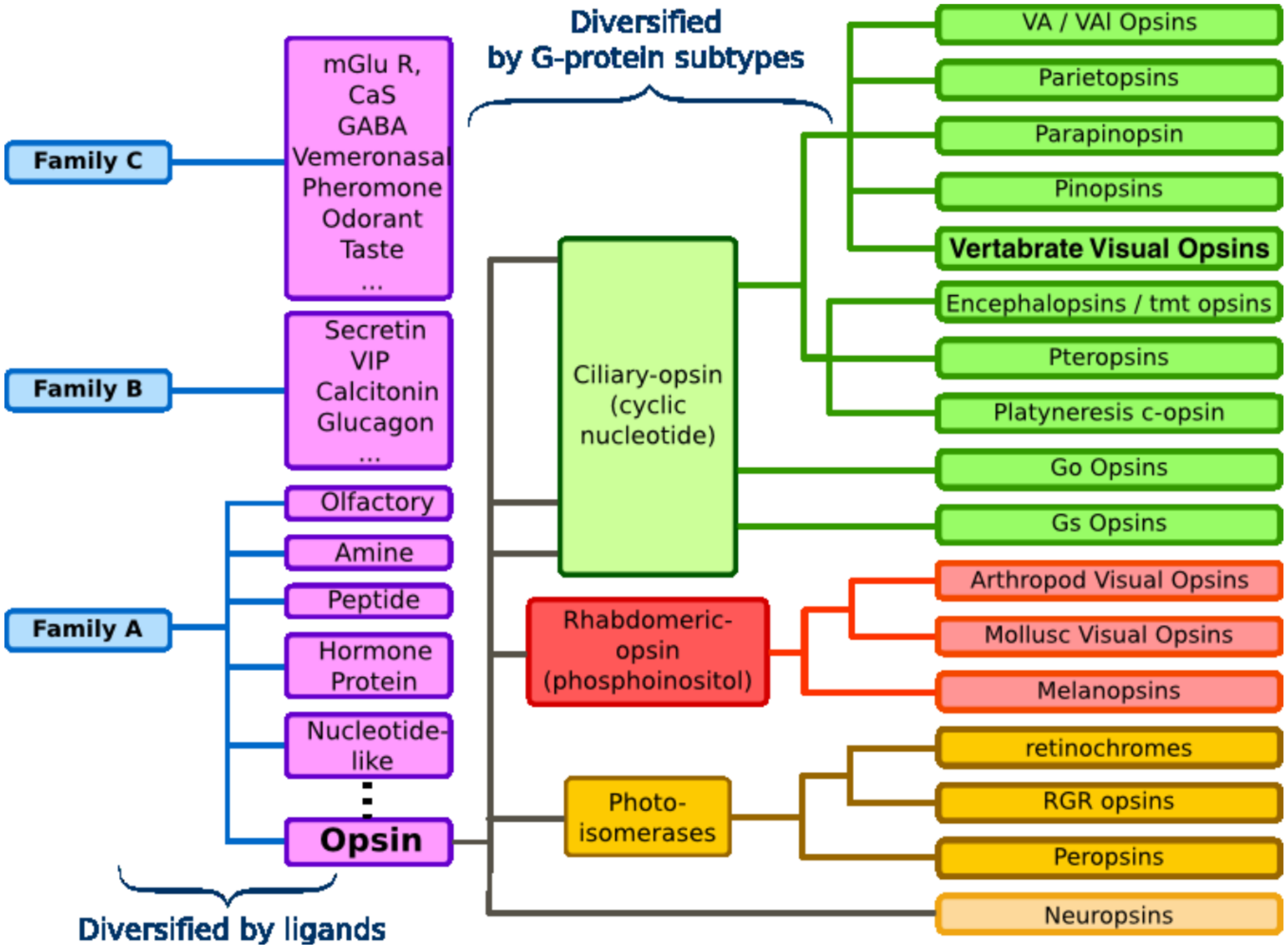
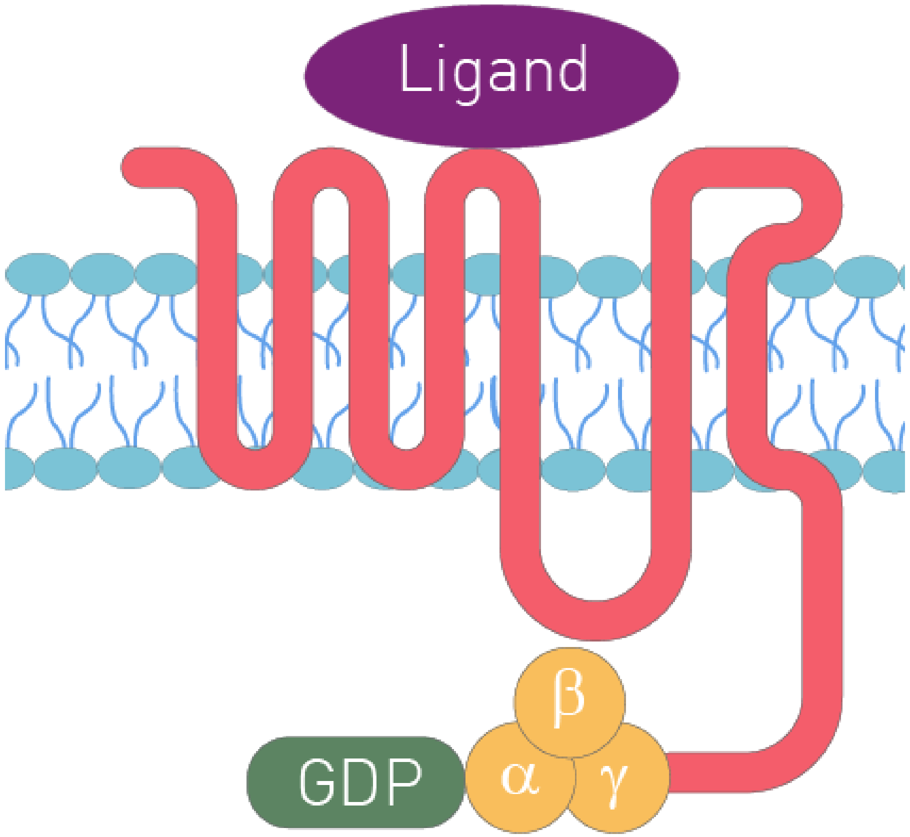


G Protein-Coupled Receptors (GPCRs)

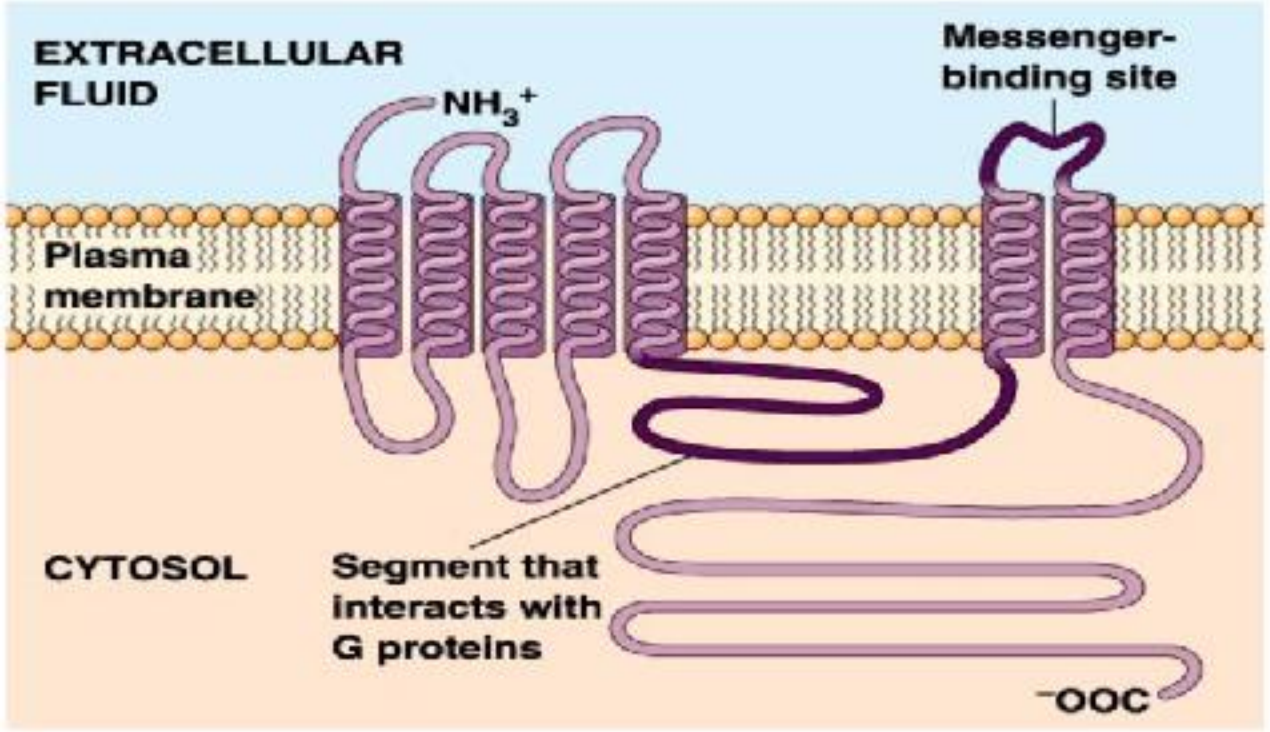
Neurotransmitters   Hormones



They sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses.

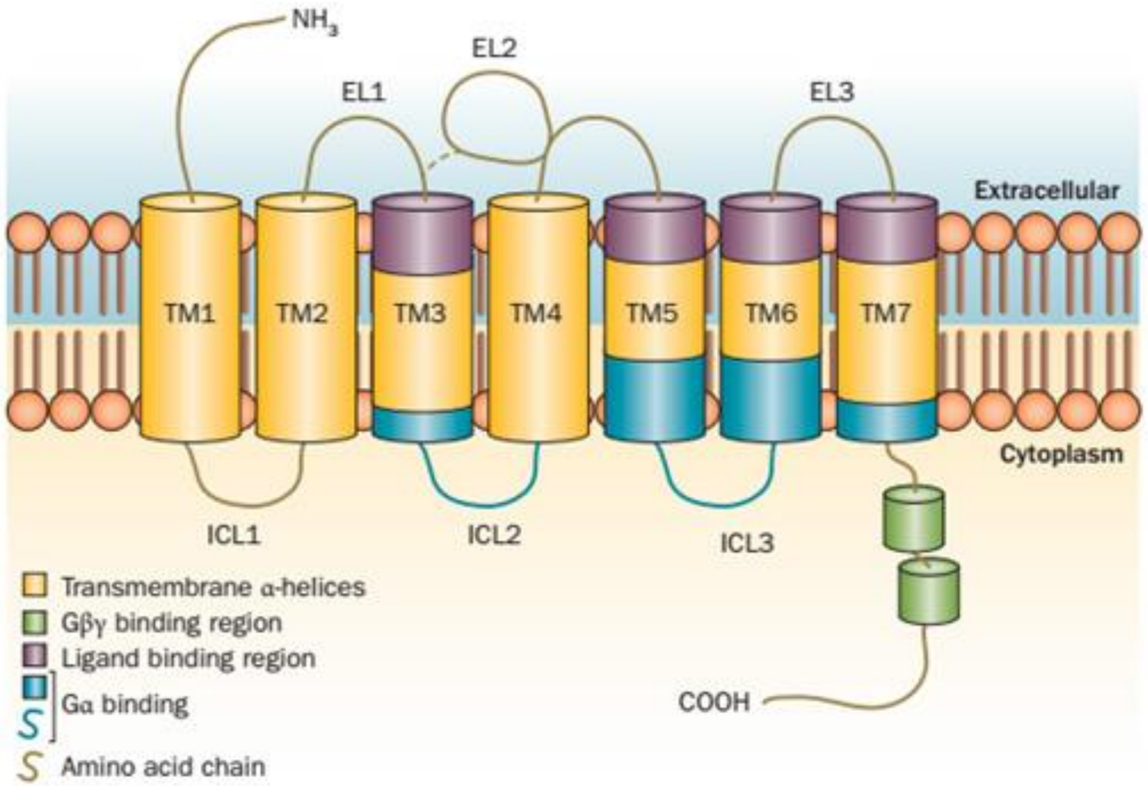
GPCRs are also known as seven-transmembrane domain receptors, 7TM receptors because they pass through the cell membrane seven times.

Structure of GPCRs



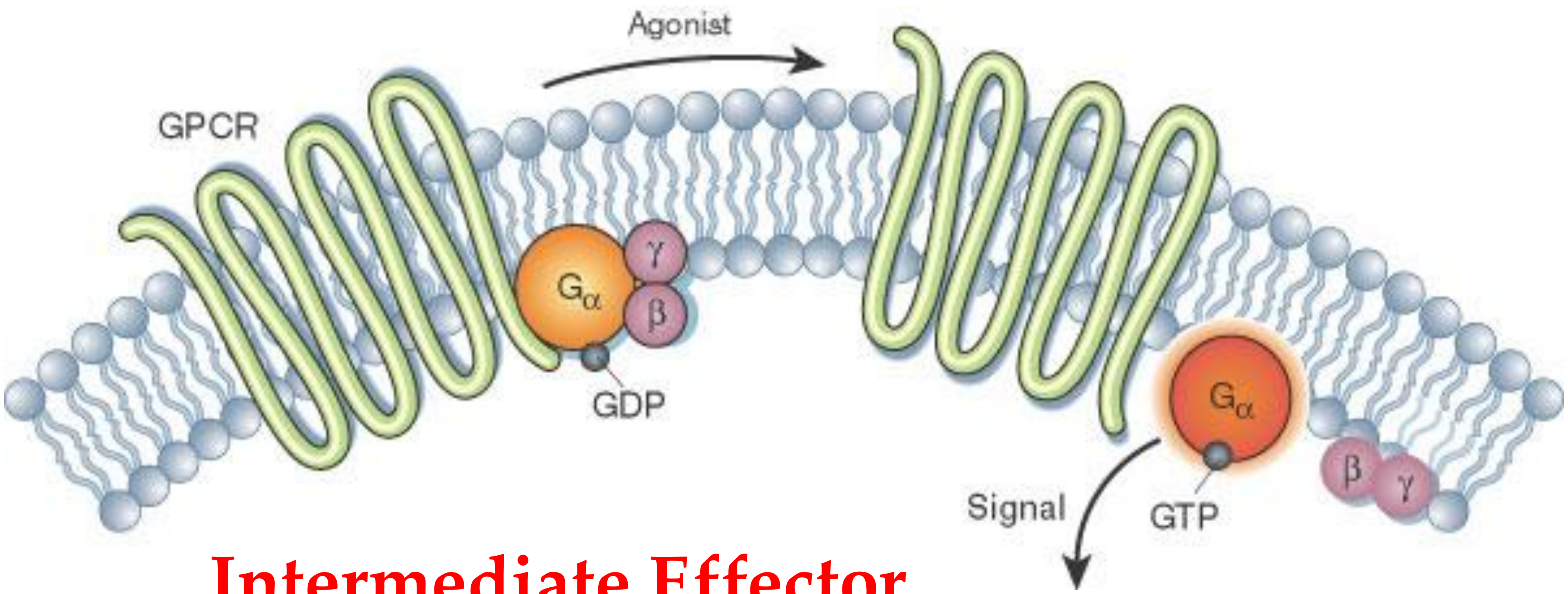
The extracellular part of the receptor (N terminal) holds the ligand binding site and can be glycosylated.
These extracellular loops also contain two highly conserved
cysteine residues that form disulfide bonds to stabilize the receptor structure.

Structure of GPCRs



The intracellular parts of the receptor can be phosphorylated. This serves as additional modulatory mechanism of activity. In addition, lipid anchoring sites allow for its membrane localization.

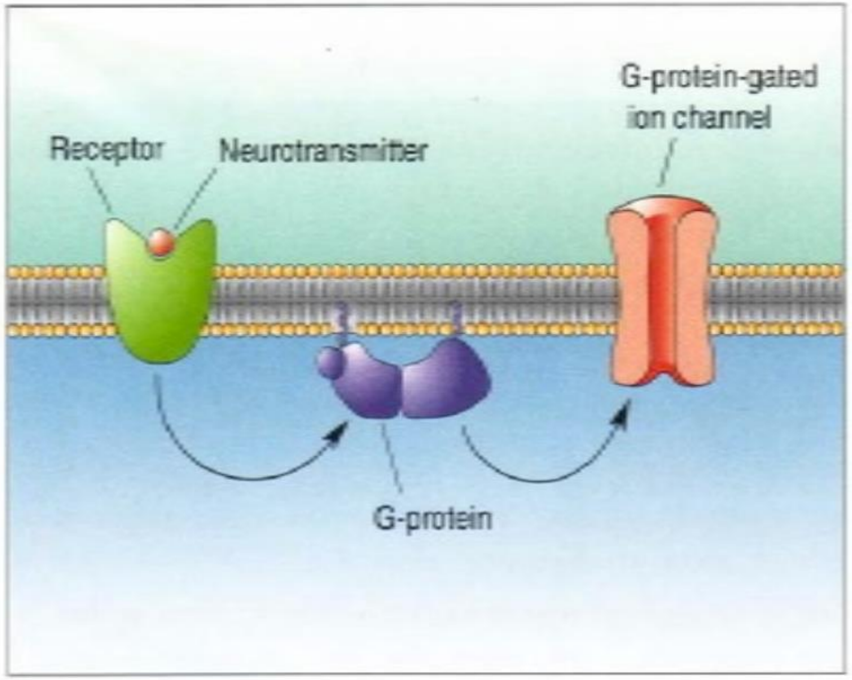
Metabotropic Receptors Activation



Intermediate Effector

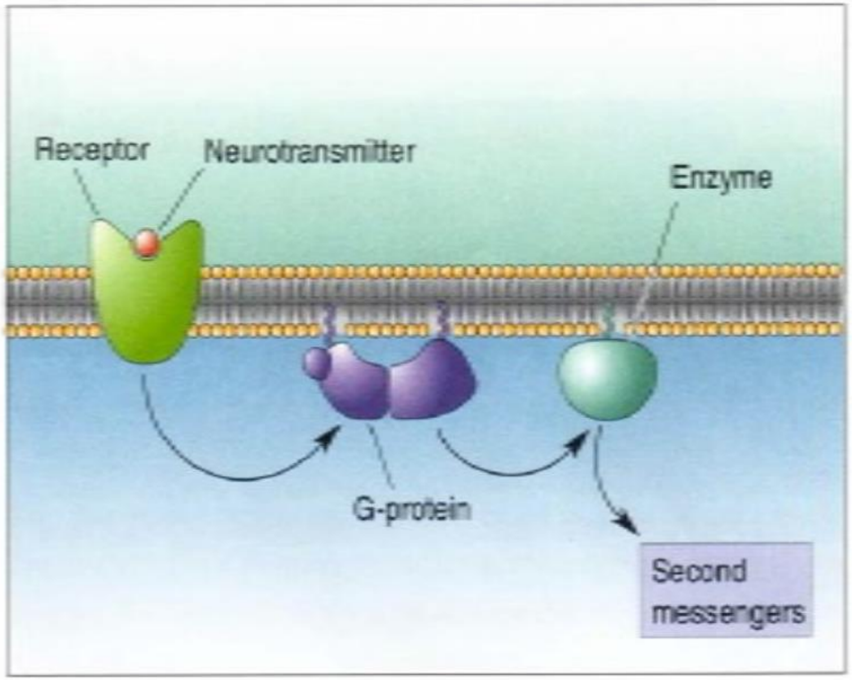
Metabotropic Receptors Activation and Effectors

1) ION CHANNELS



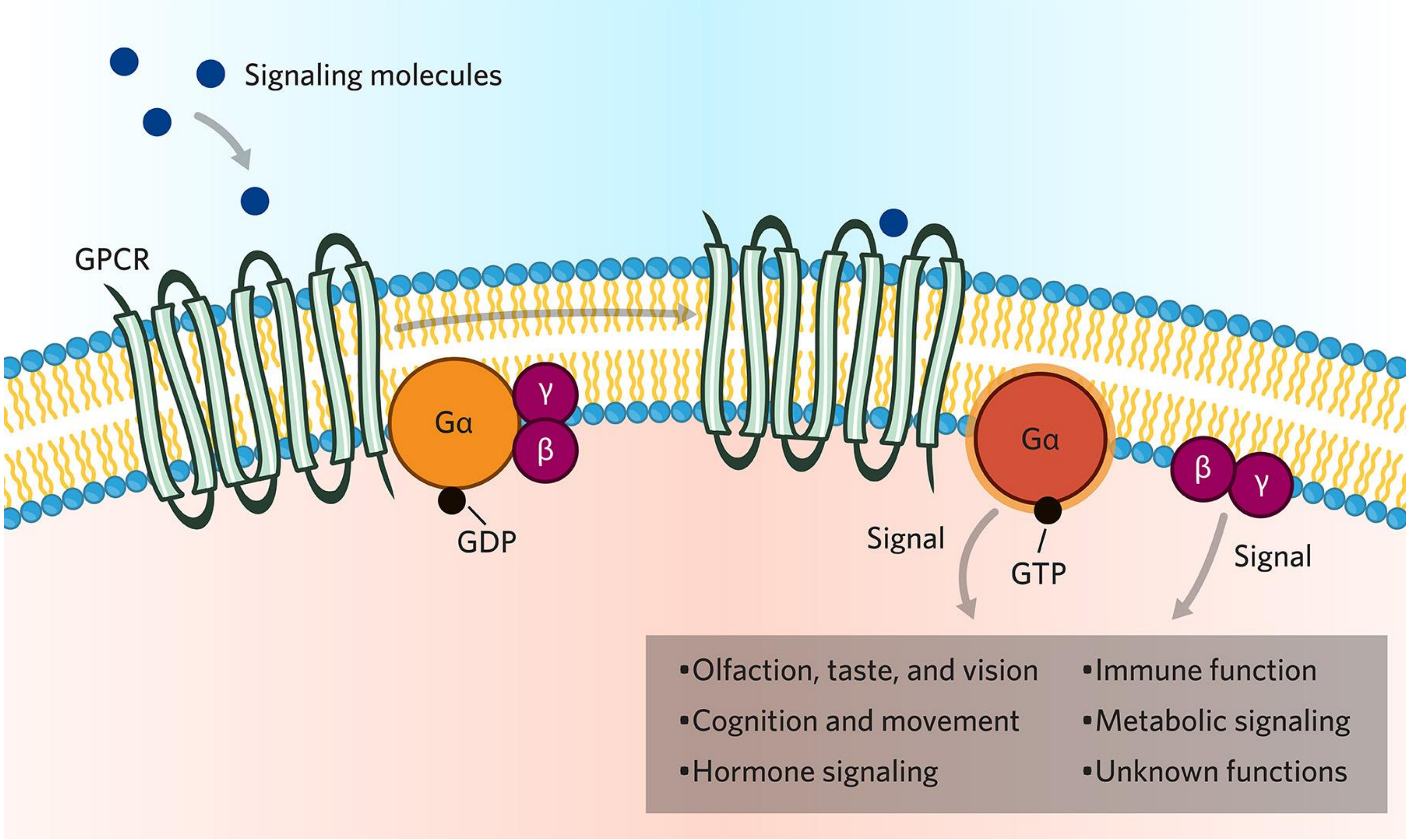
Some GPCRs, when activated, modify the intracellular ion concentration

2) ENZYMES
and second messengers



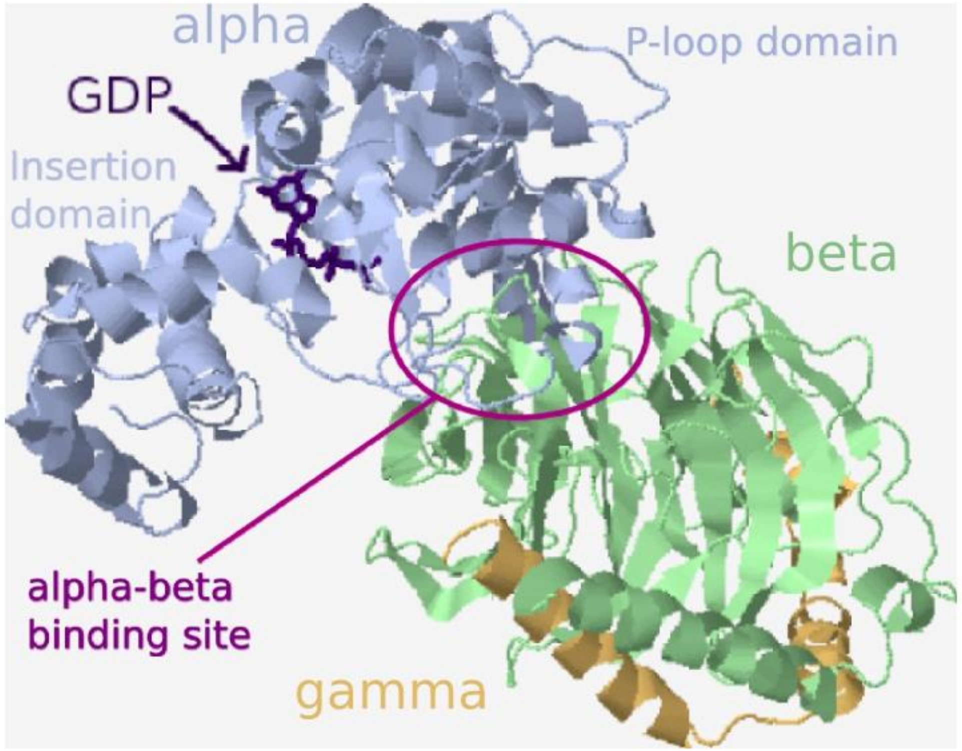
Some others amplify the signal giving raise to biologically active second messengers

G Protein-Coupled Receptors (GPCRs)



- GPCR are so called because they are bound to an intracellular G protein
- Guanine nucleotide-binding proteins (G proteins) act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli.

G Proteins



Two classes of G proteins:

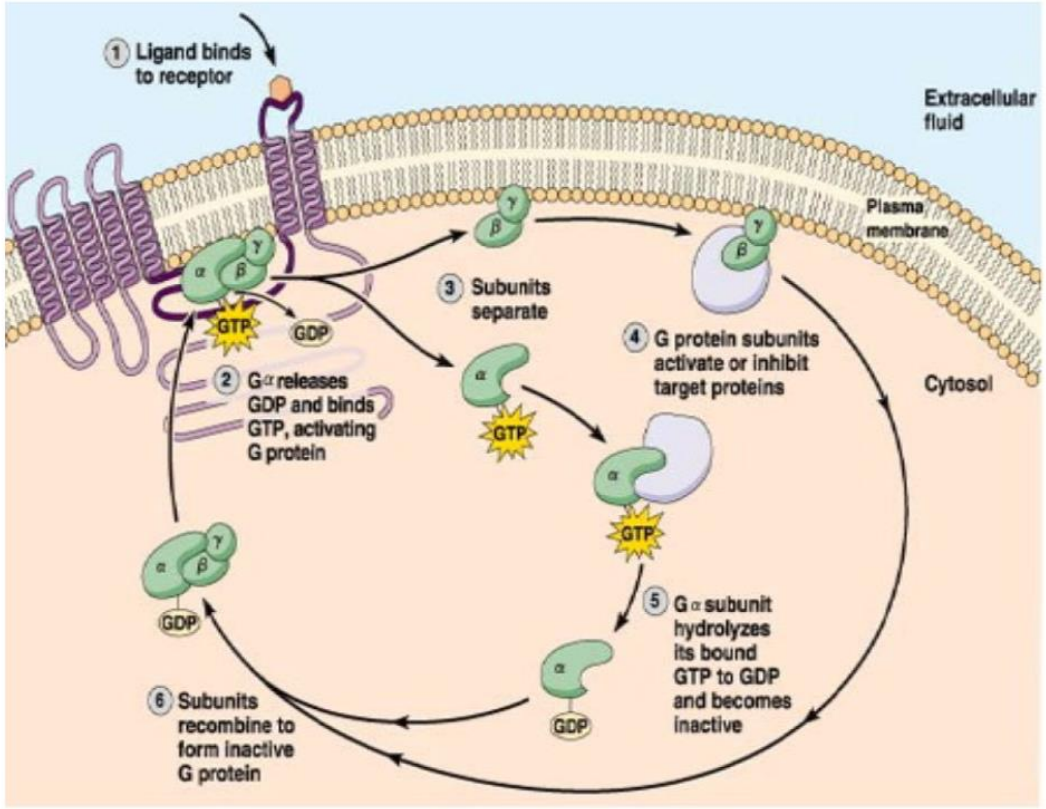
1. **Monomeric small GTPases**
2. **Heterotrimeric G protein complexes.**

- **The heterotrimeric G protein is made up of alpha (α), beta (β) and gamma (γ) subunits.**
- **The alpha (α) subunit holds the catalytic GTPase activity.**
- **The beta (β) and gamma (γ) Subunits can form a stable dimeric complex referred to as the beta-gamma complex with regulatory activity.**

Their activity is regulated by factors that control their ability to bind to and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP).

Activation/Inactivation Cycle of GPCRG Proteins

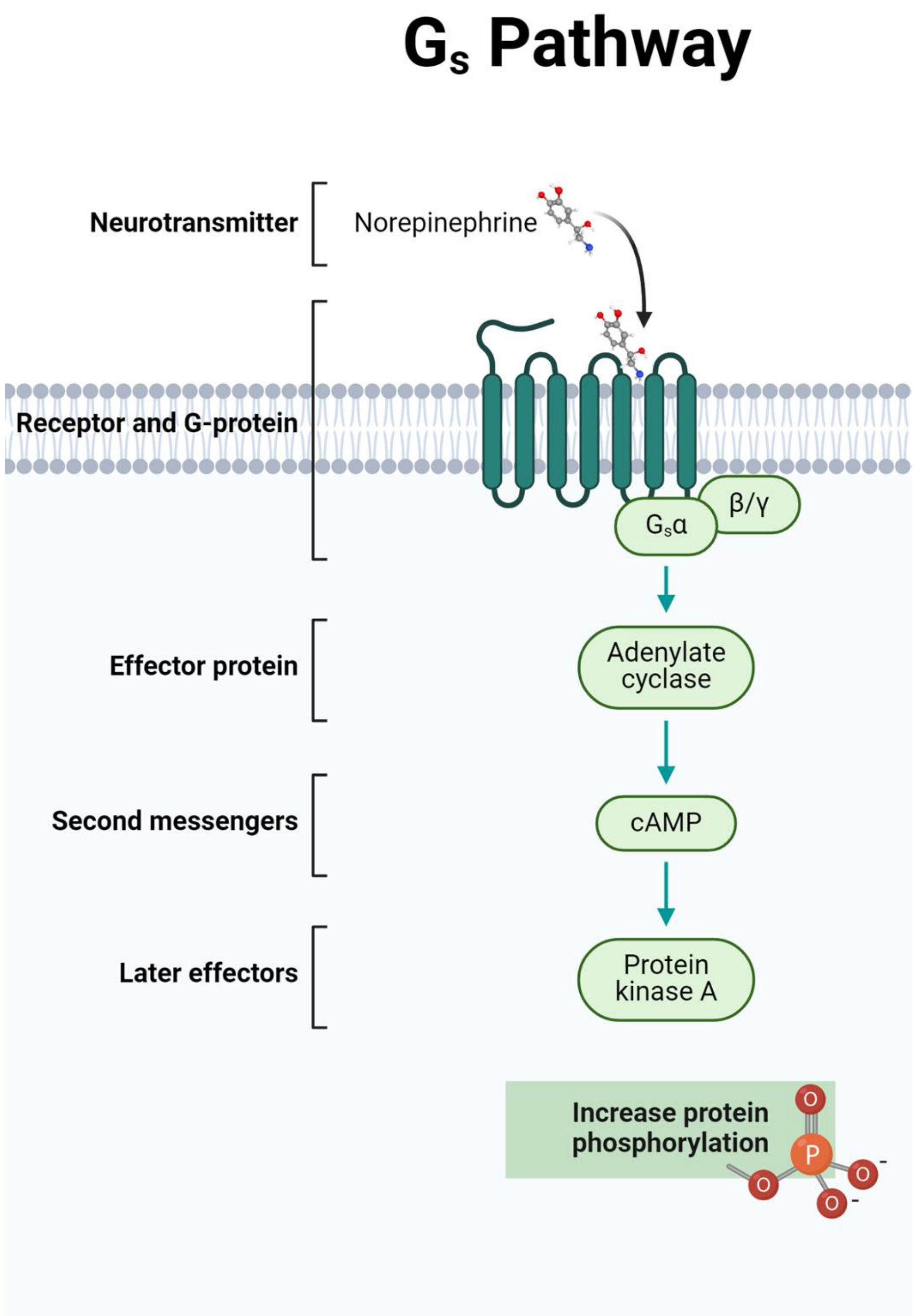
ACTIVATION: ligand binding results in G-protein exchange of GTP for GDP. The activated G-protein then dissociates into an **alpha (G-alpha)** and a **beta-gamma** complex.



- G-alpha bound to GTP is active, and diffuses along the membrane surface to activate target proteins, (often enzymes that generate **second messengers)**.

- The beta-gamma complex is also able to diffuse and activate proteins, typically affecting ion channels

INACTIVATION: it occurs because G-alpha has intrinsic **GTPase activity**. After GTP hydrolysis, G-alpha bound to GDP will reassociate with a beta-gamma complex to form an inactive G-protein that can again associate with a receptor

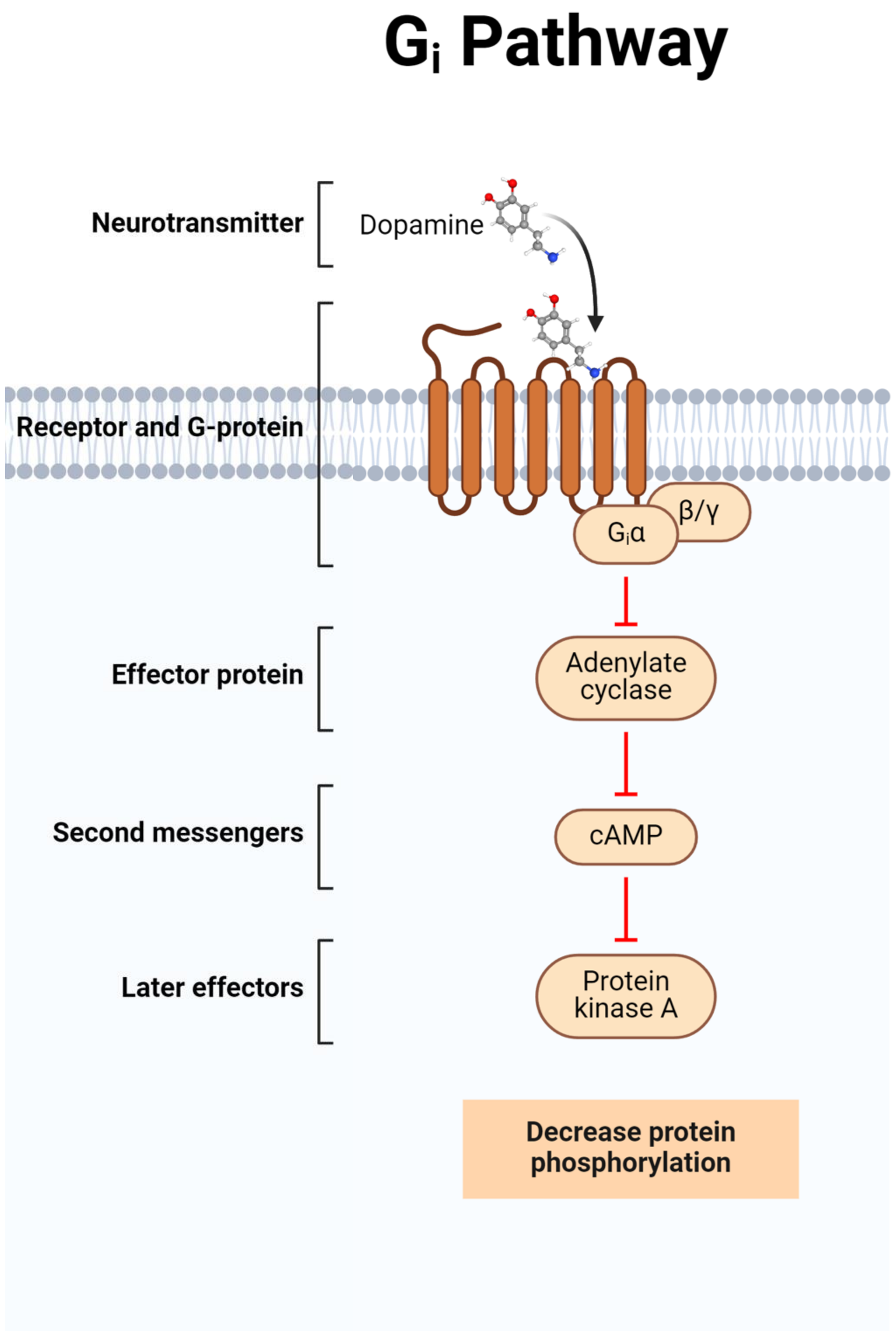


Gα subunits

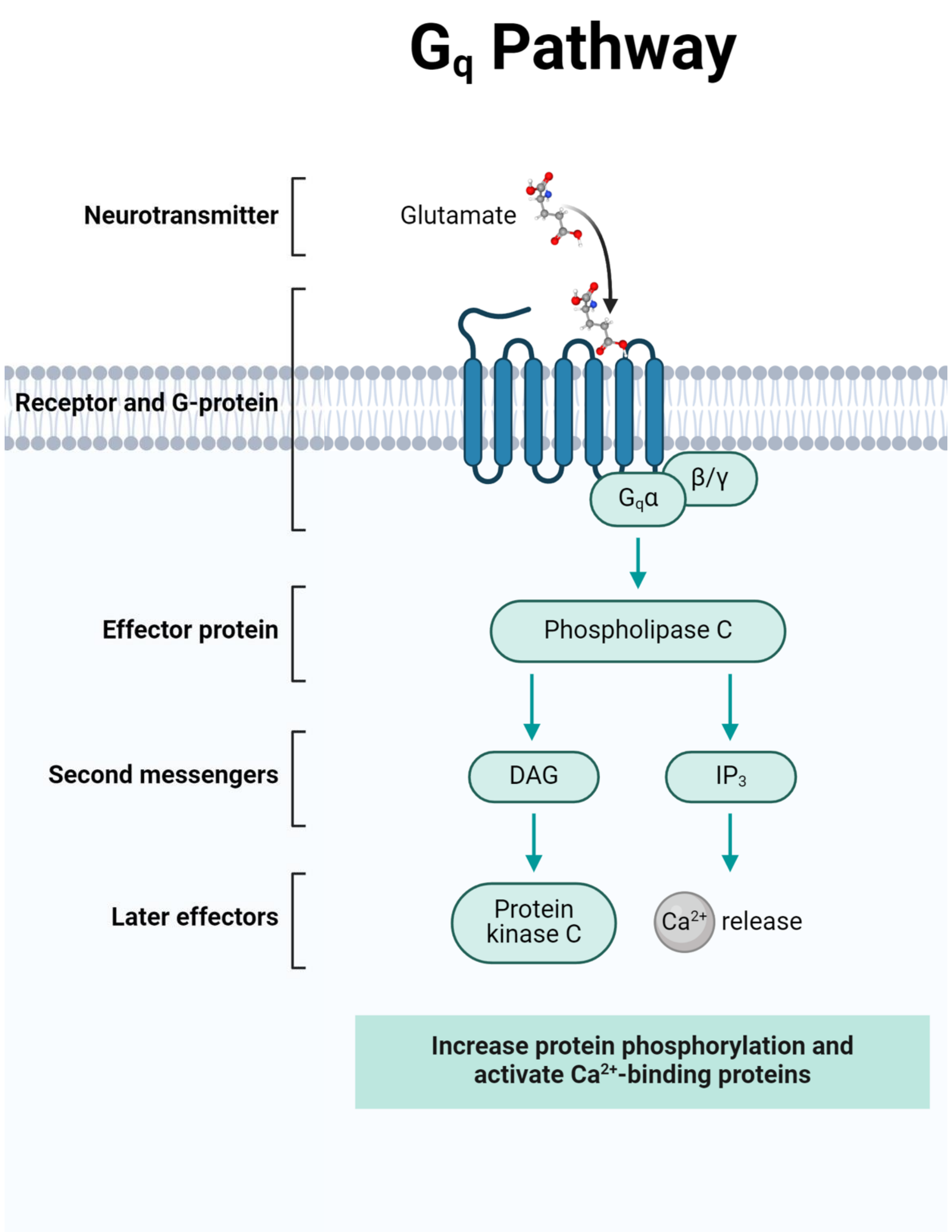
The many classes of Gα subunits behave differently in the recognition of the effector molecule, but share similar activation mechanisms.

- **Gs** activates adenylyl cyclase (AC) and increases intracellular cAMP levels. cAMP major effect is to bind to and activate cAMP- dependent kinase (PKA)

Gα subunits

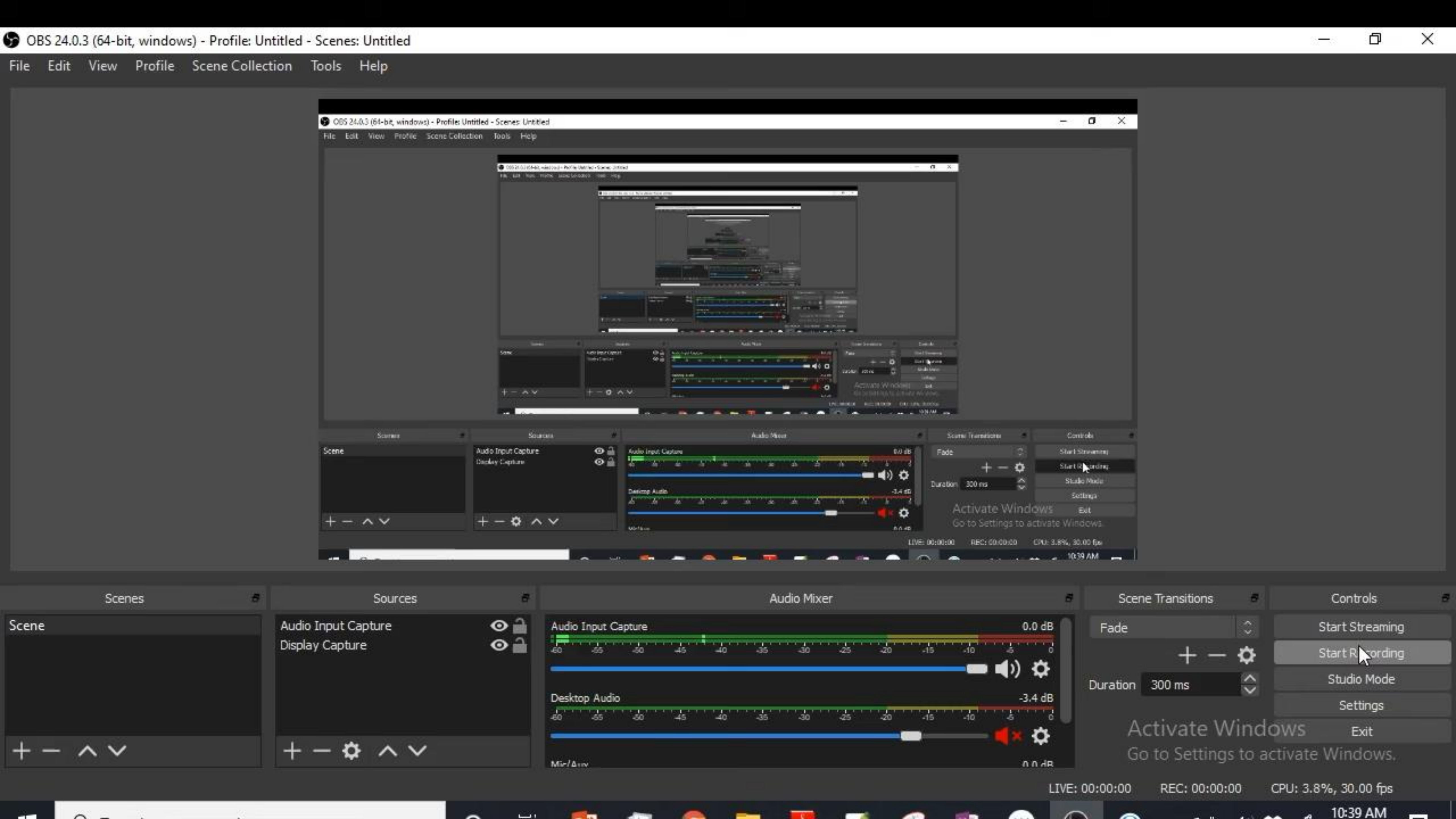


- Gi/Go inhibit adenylyl cyclase (AC), activate K+ channels or inhibit Ca2+ channels



Gα subunits

- Gq activates phospholipase C (PLC), which transforms PIP2 into InsP3 and DAG. In turn, DAG activates protein C kinase (PKC) while InsP3 increases intracellular [Ca2+].



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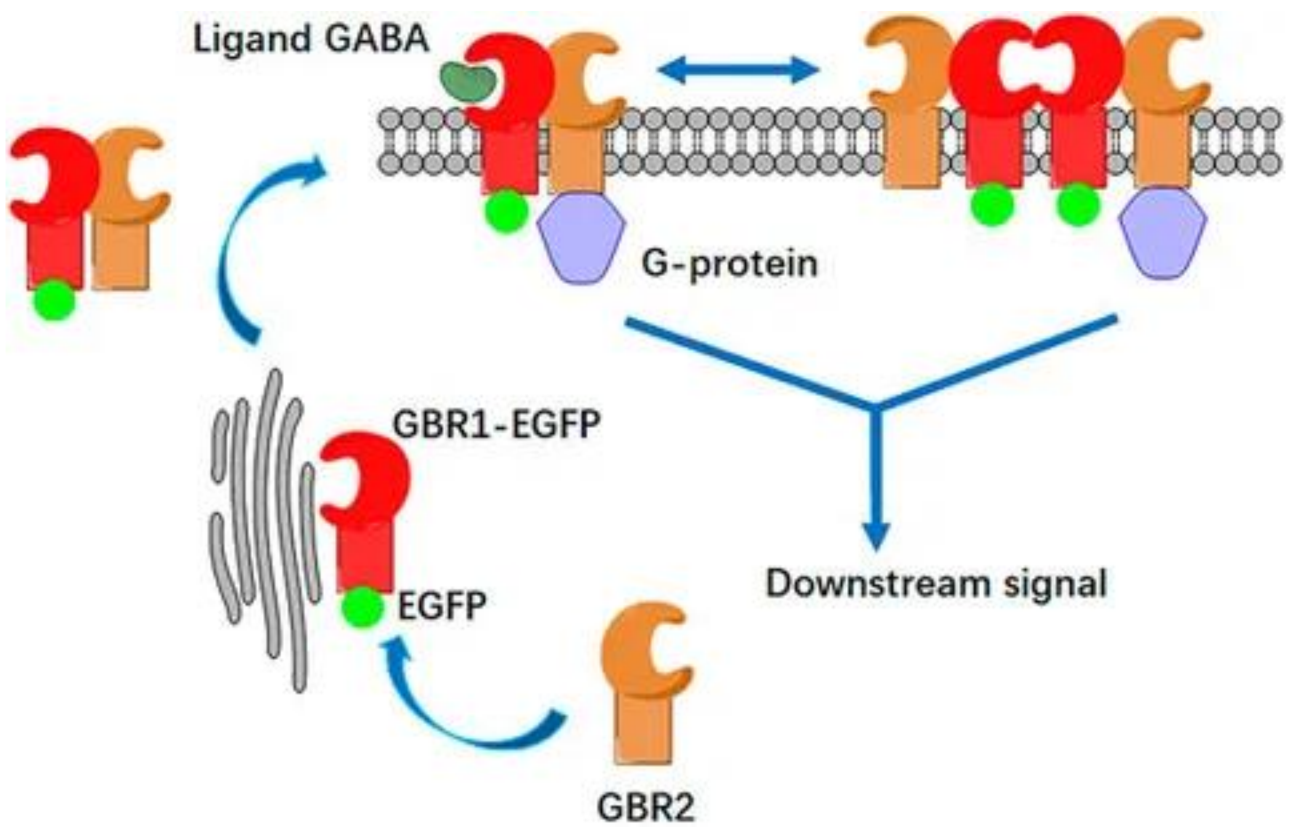
Endogenous GPCRs Ligands

α SUBUNIT	EFFECTOR	LIGANDS AND RECEPTOR TYPES
α_s	Adenylyl-cyclase (+) Canali al calcio (+)	**noradrenaline (β_1, β_2, β_3); dopamine (D_1,D_5); serotonin ($5HT_4$); ACTH, FSH, LH, TFH, GnRH, GHRH, Vasopressin, Calcitonin, Prostaciclin**
$\alpha_{i\ 1,2,3}$	Adenylyl-cyclase (-)	**noradrenaline (α_2); dopamine (D_2, D_3, D_4); serotonine ($5HT_1$); acetilcholine (M_2, M_4); somatostatin ($SSTR_{1\text{-}5}$)**
$\alpha_{i\ 3}$	Potassium channels (GIRK) (+)	**acetilcholine (M_2, M_4); dopamine (D_2,); somatostatin ($SSTR_{1,2}$)**
α_q	Phospholipase C (+)	**noradrenaline (α_1); serotonine ($5HT2_1$); TSH, TRH, GnRH, LXs, thromboxans**
$\alpha_{0\ 1,2}$	Calcium channels (-)	**noradrenaline (α_2); acetilcholine (M_2, M_4); somatostatin ($SSTR_{1,\ 2}$)**

GPCR dimerization

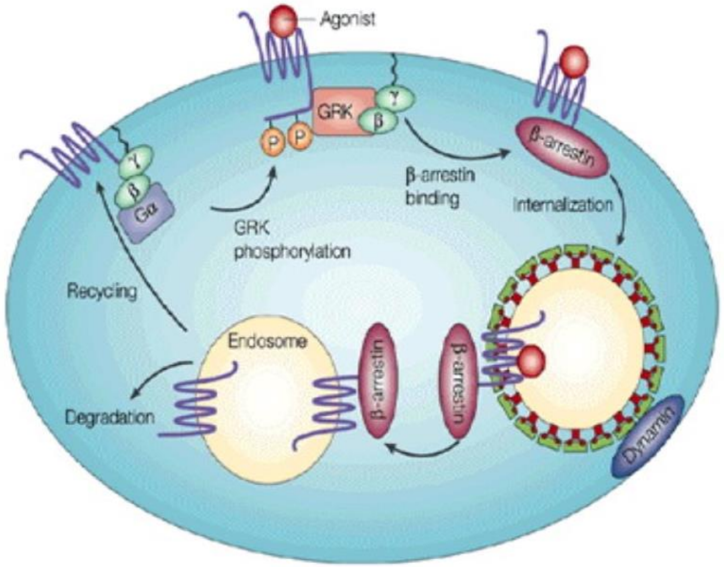


Some GPCRs undergo dimerization. This process can be a homodimerization (M3, β2, GABAB) or a more complex heterodimerization (D2/SSTR5, AT1/B2, SSTR2/μ opioid).

Constitutive	**Ligand-induced**
δ/κ opioid Adenosin A1/DopamineD1 δ opioid/β_2 adrenergic	$SSTR_5/D_2$ $GABA_B/D_5$

GPCR Desensitization

GPCRs become desensitized when exposed to their ligand for a prolonged period of time. There are two recognized forms of desensitization:

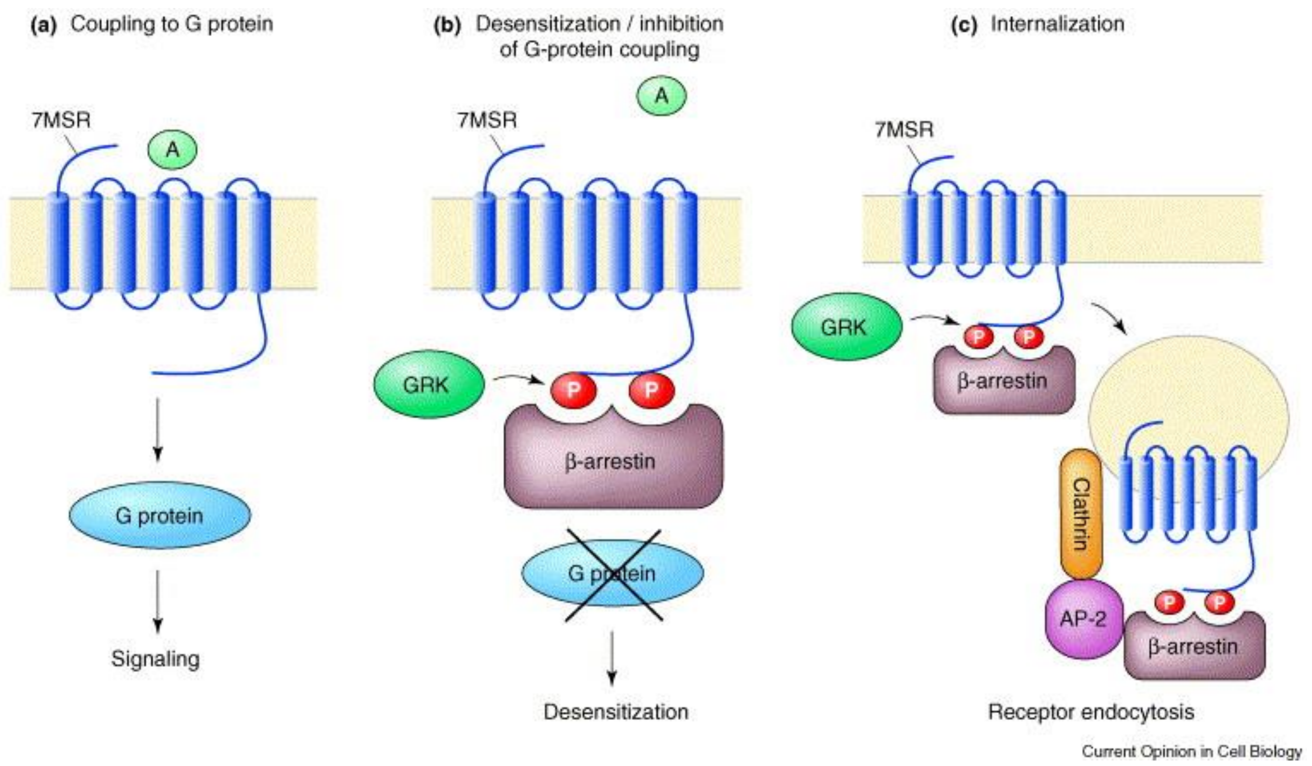


1) **homologous desensitization,** in which the activated GPCR is downregulated;

2) **heterologous desensitization,** wherein the activated GPCR causes downregulation of a different GPCR. This downregulation is regulated by protein kinase-dependent phosphorylation of the intracellular (or cytoplasmic) receptor domain.

GPCR Desensitization

When an agonist binds, the receptor is converted into a substrate for G-protein-coupled receptor kinases (GRKs). These kinases specifically phosphorylate receptors that have been activated by an agonist. Once phosphorylated, the receptor can then interact with arrestins.



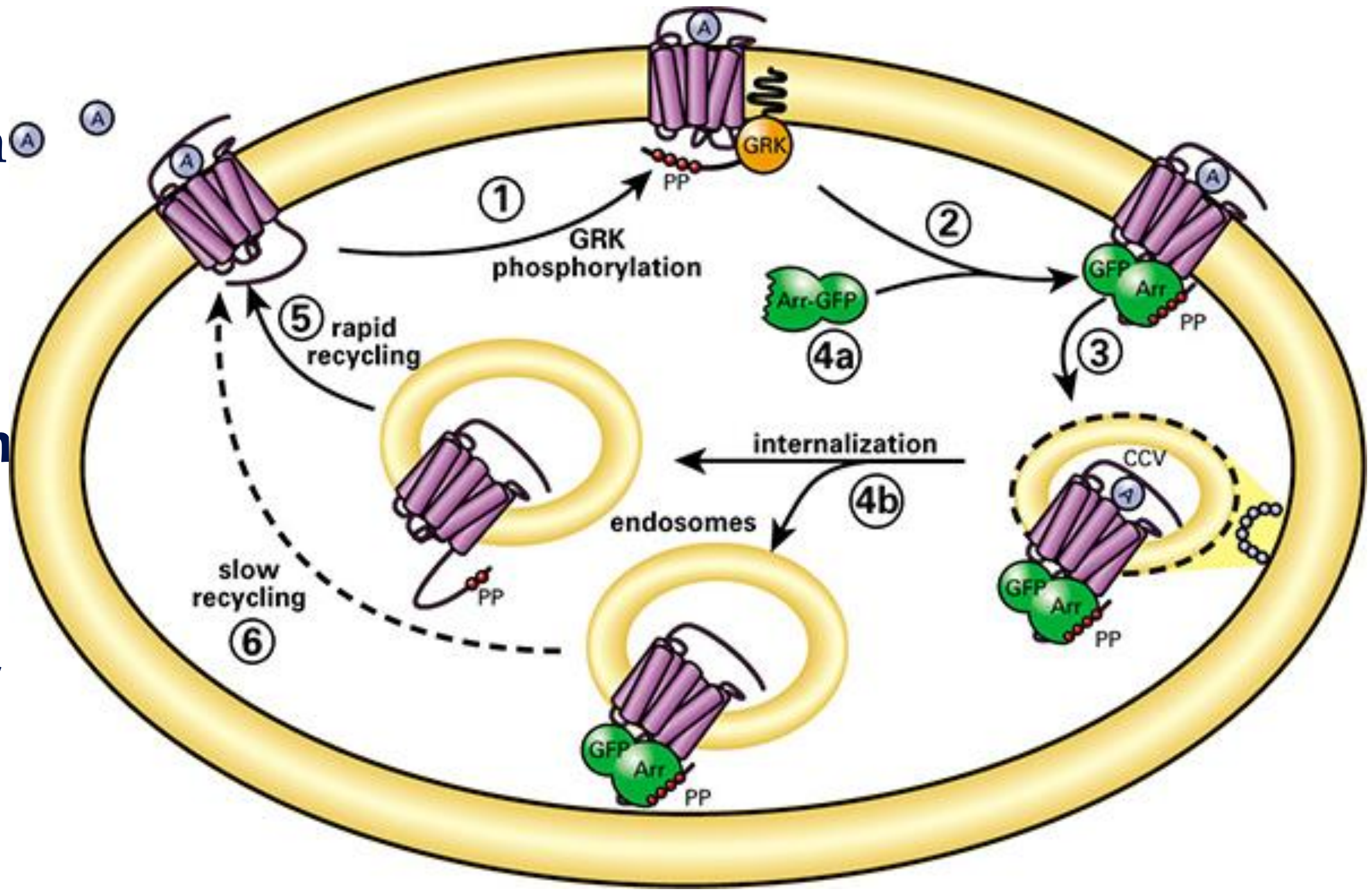
GPCR Desensitization

Arrestins: cytosolic proteins that bin agonist-activated, phosphorylated receptors

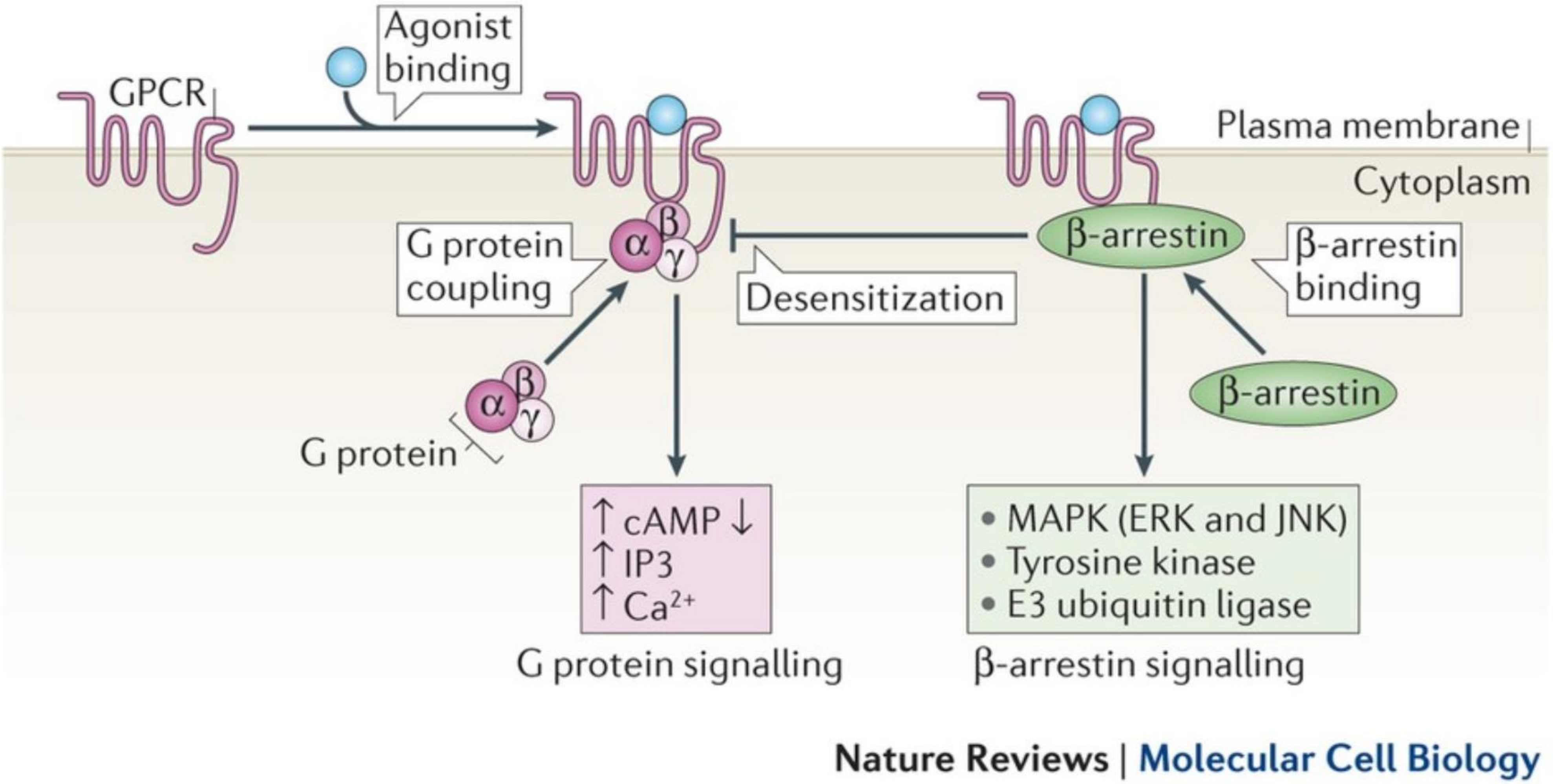
Binding → blocks G-protein couplin (desensitization)

Arrestins also interact with clathrin-coated pits

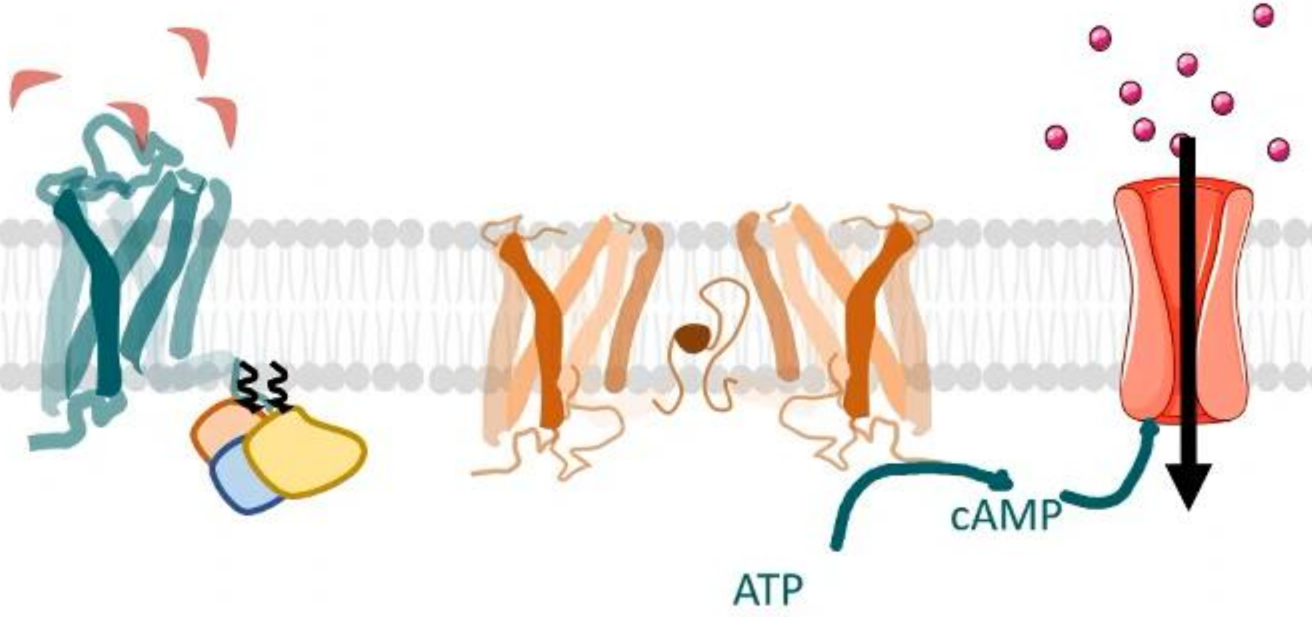
Receptor–arrestin complexes → internalized via endocytosis



GPCR Desensitization



Metabotropic receptor



Metabotropic Receptors - Examples

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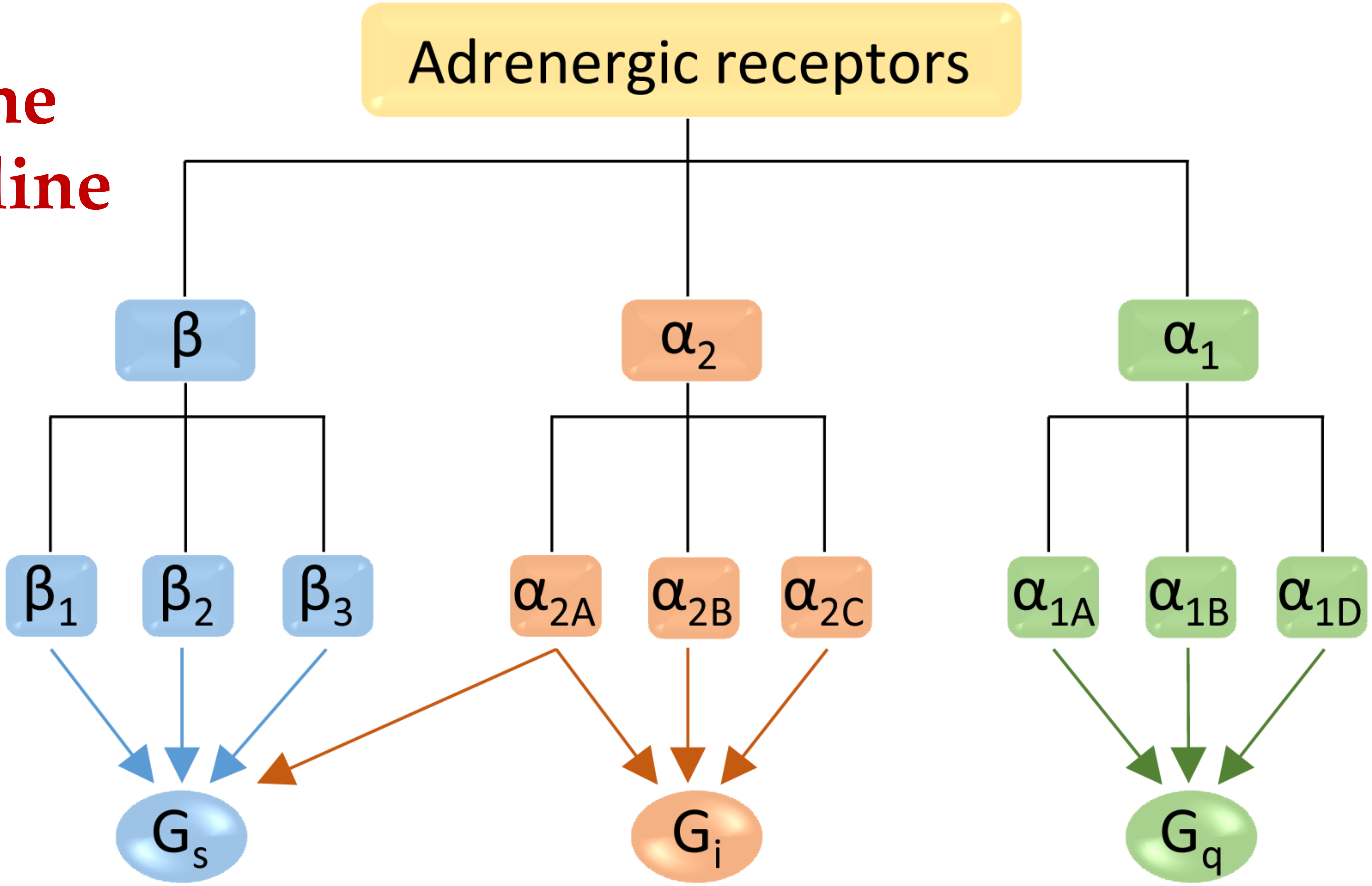
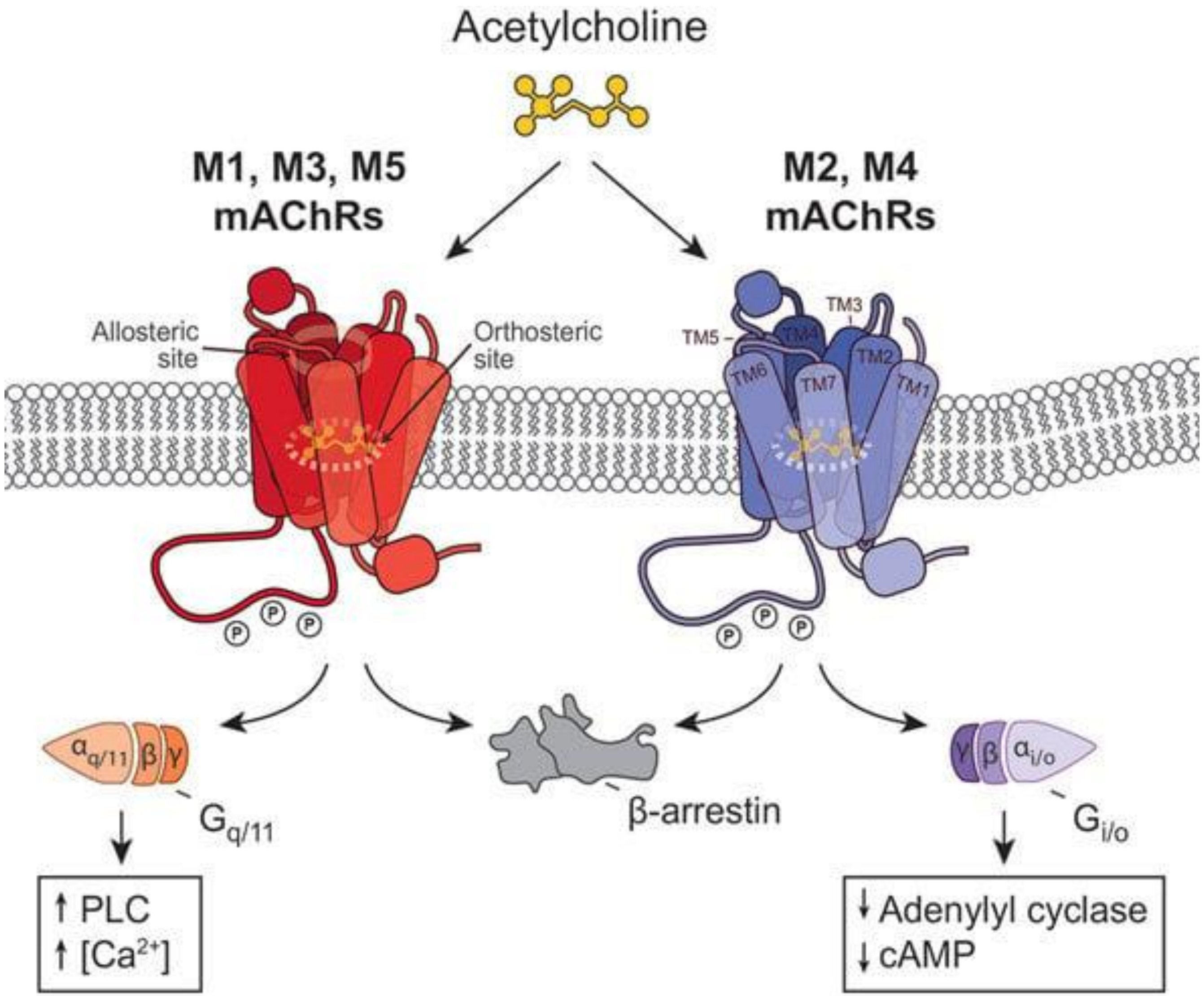
$\alpha_{0\ 1,2}$	Calcium channels (-)	**noradrenaline (α_2); acetilcholine (M_2, M_4); somatostatin ($SSTR_{1,\ 2}$)**

Adrenergic Receptors

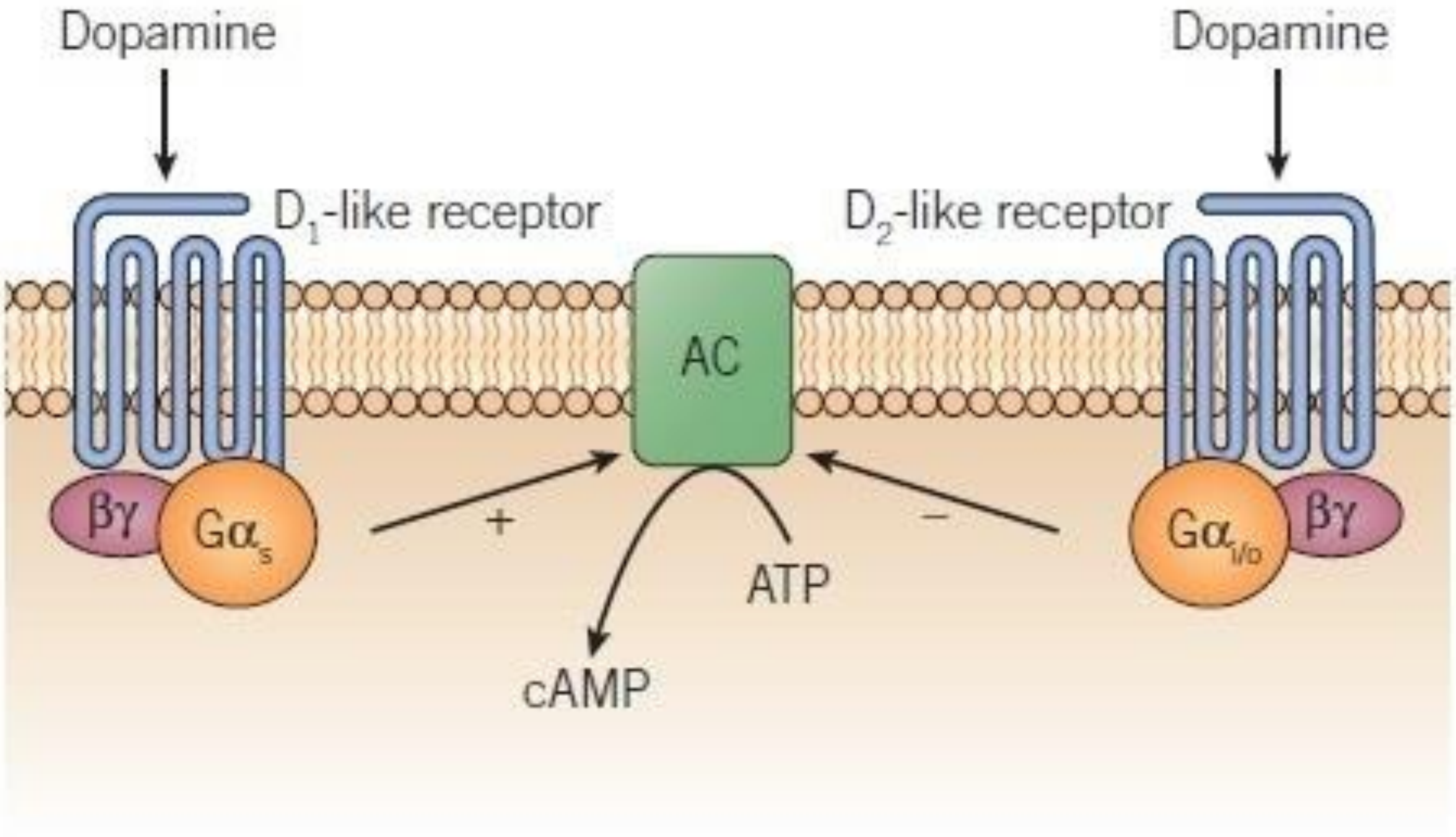
Adrenaline
Noradrenaline

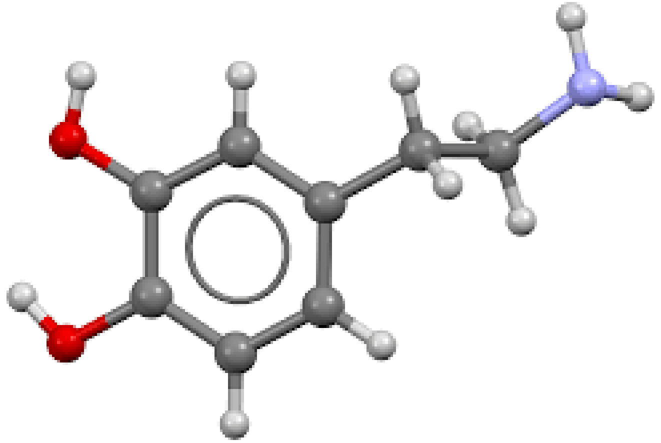


Acetylcholine Muscarinic Receptors



Dopamine Receptors





Dopamine Receptors

Dopamine Receptors: Genetics, Addiction, Mood and Schizophrenia

Dopamine Functions

Motion: Dopamine is important in how the brain controls movement, and it needs to be balanced. Too much dopamine leads to more movement – such as tics and involuntary movement. Too little dopamine leads to less movement – such as in Parkinson's.
Emotion: Dopamine is also important in emotions. Excess dopamine leads to euphoria, hallucinations, and psychosis.

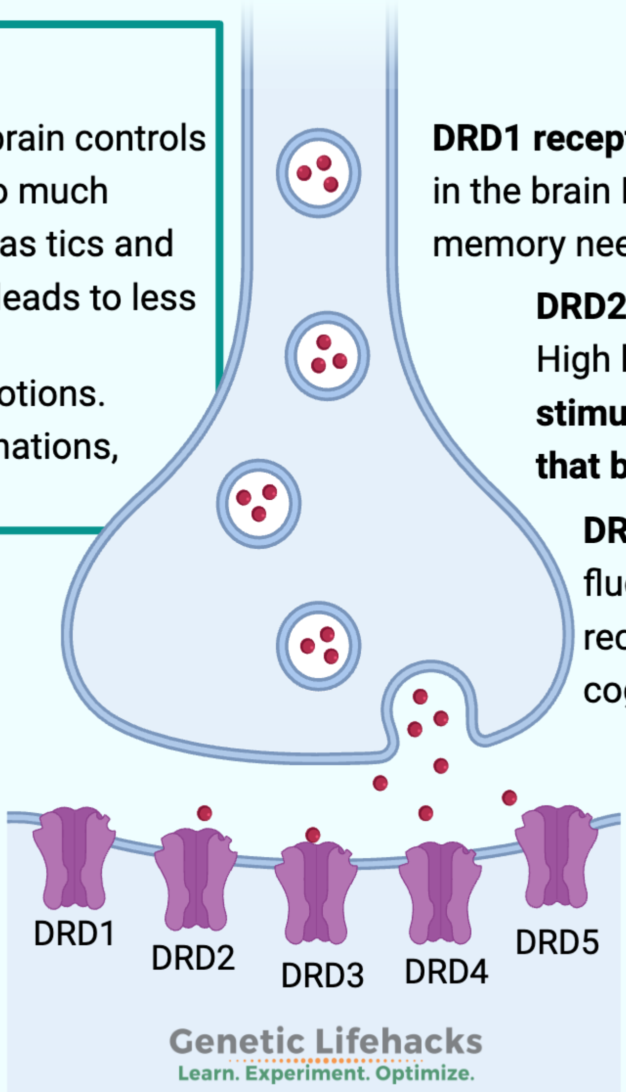
Supplements that Affect Dopamine Levels

Receptor Agonists **(stimulates the receptor)**

- **L-theanine**
- **Ginkgo biloba**
- **Bacopa**
- **Mucuna pruriens**

Receptor Antagonists **(blocks the receptor)**

- **Yohimbine**
- **Ningdong granules**



Dopamine Receptors

DRD1 receptor: Is the most abundant dopamine receptor in the brain It is involved with working memory (short-term memory needed for thinking and speaking)

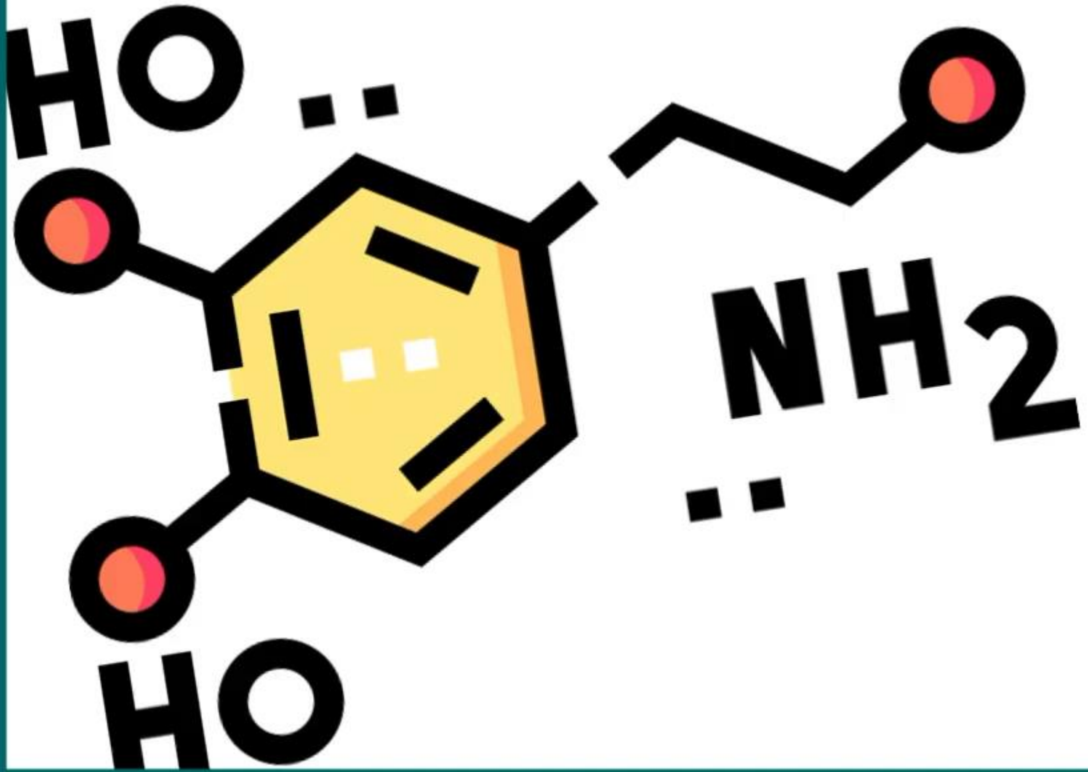
DRD2 receptor: Involved with addiction response. High levels of either an **agonist (something that stimulates the receptor)** or **antagonist (something that blocks the receptor)** alter the addictive response.

DRD3 receptor: Has the ability to change with fluctuating dopamine levels makes the DRD3 receptor critical in dopamine-related functions and cognition.

DRD4 receptor: Found in the retina, cerebral cortex, amygdala, hypothalamus, and pituitary.

DRD5 receptor: DRD5 receptor is very similar to the DRD1 receptor, and they are often located together.

Dopamine



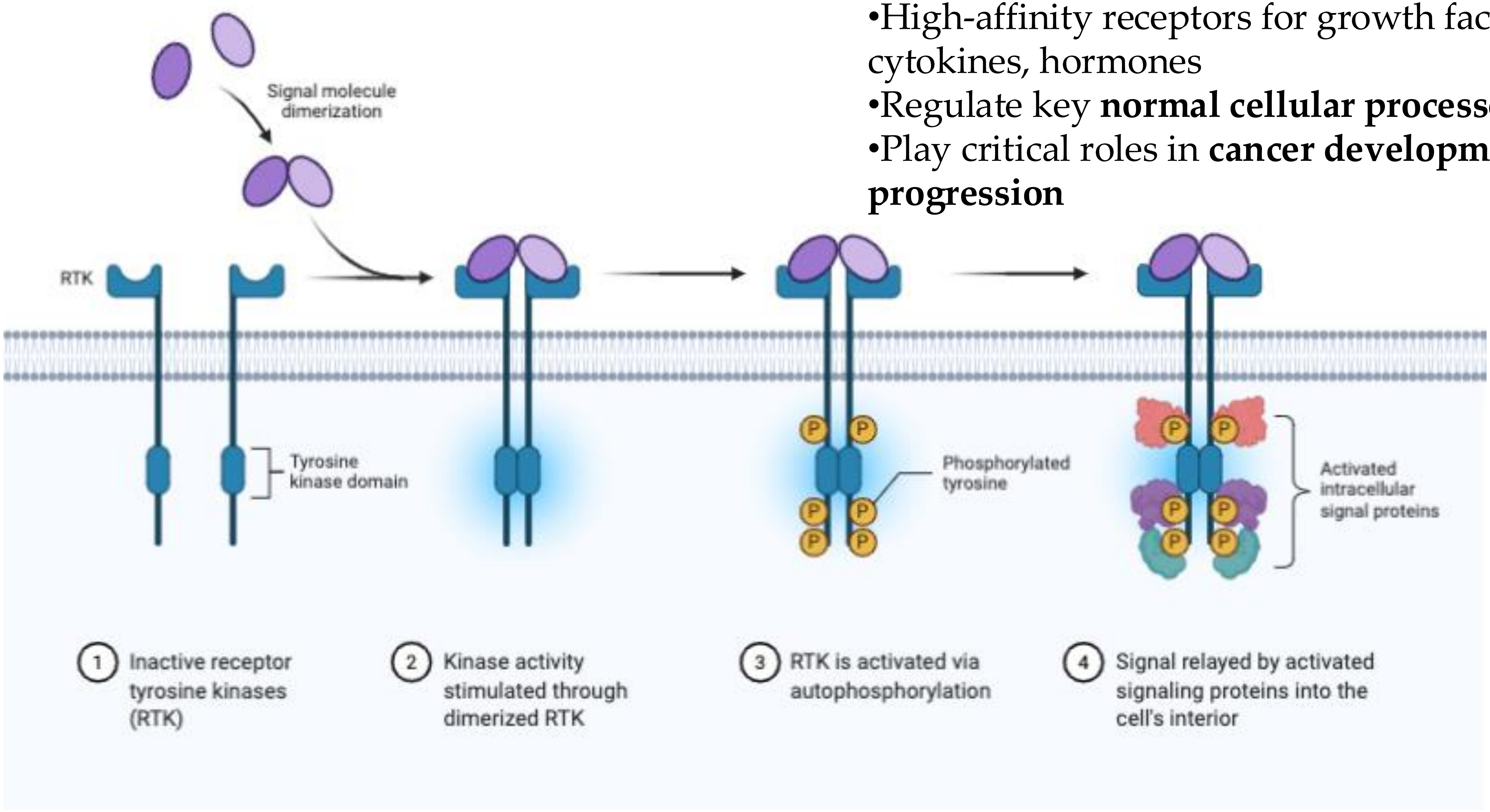
Tyrosine-Kinase Receptors (RTKs)

Receptor Tyrosine Kinases (RTKs)

•High-affinity receptors for growth factors, cytokines, hormones

•Regulate key **normal cellular processes**

•Play critical roles in **cancer development and progression**



Tyrosine-Kinase Receptors (RTKs)

Ligand binding to the extracellular domain of the TKRs causes dimerization that results in autophosphorylation and activation of the intracellular kinase domain.
The ensuing phosphorylation of docking sites on the receptor leads to the recruitment of enzymes, signal transducers and adaptor molecules activating downstream signalling pathways.
The signalling pathways regulate a diverse array
of processes including transcription, translation, metabolism, cell proliferation, survival, differentiation and motility.