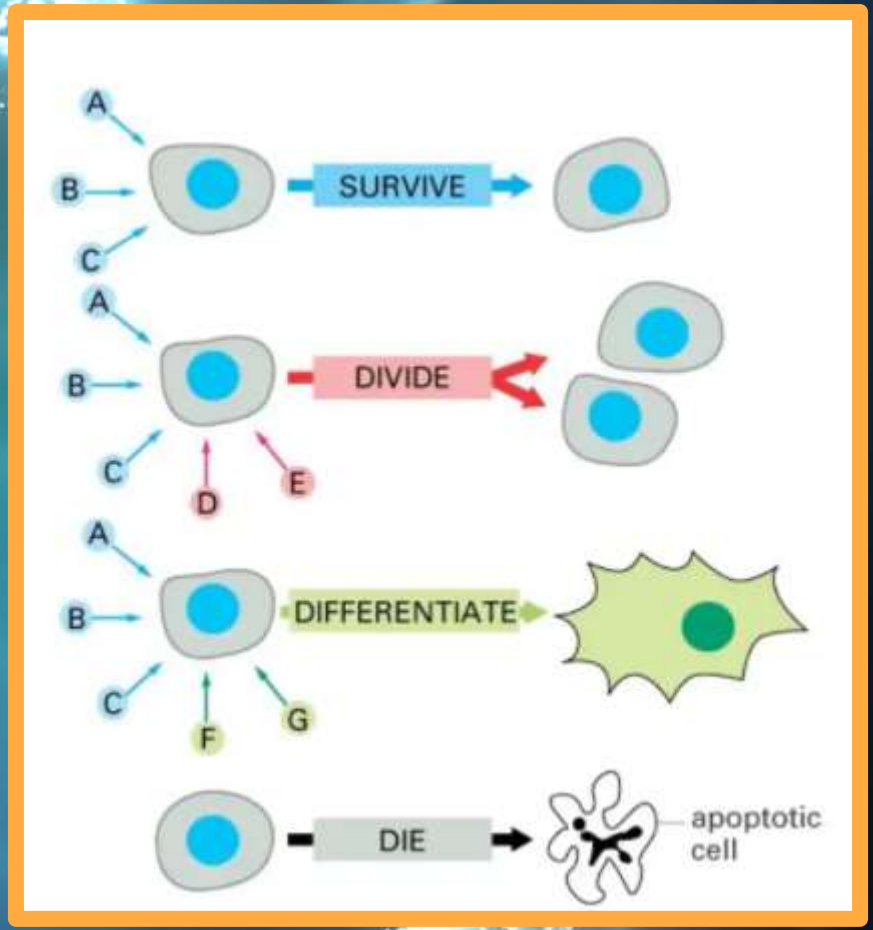
Cell signaling



Types of cell signalling

1. Paracrine signaling

Often, cells that are near one another communicate through the release of chemical messengers (ligands that can diffuse through the space between the cells). This type of signaling, in which cells communicate over relatively short distances, is known as paracrine signaling.

2. Synaptic signaling

One unique example of paracrine signaling is synaptic signaling, in which nerve cells transmit signals. This process is named for the synapse, the junction between two nerve cells where signal transmission occurs.

3. Autocrine signaling

In autocrine signaling, a cell signals to itself, releasing a ligand that binds to receptors on its own surface (or, depending on the type of signal, to receptors inside of the cell). This may seem like an odd thing for a cell to do, but autocrine signaling plays an important role in many processes

4. Endocrine signaling

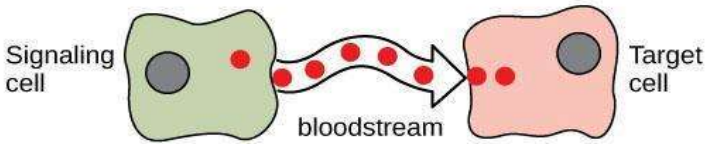
When cells need to transmit signals over long distances, they often use the circulatory system as a distribution network for the messages they send. In long-distance endocrine signaling, signals are produced by specialized cells and released into the bloodstream, which carries them to target cells in distant parts of the body.

5. Signaling through cell-cell contact

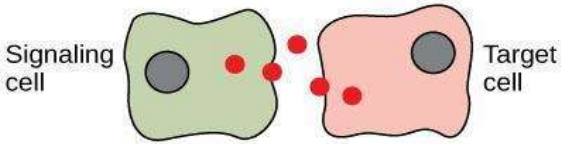
Gap junctions in animals and plasmodesmata in plants are tiny channels that directly connect neighboring cells. These water-filled channels allow small signaling molecules, called intracellular mediators, to diffuse between the two cells. Small molecules and ions are able to move between cells, but large molecules like proteins and DNA cannot fit through the channels without special assistance.

Forms of Chemical Signaling

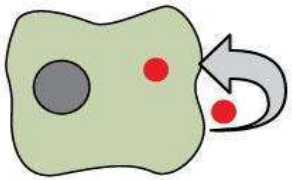
Endocrine	A cell targets a distant cell through the bloodstream.



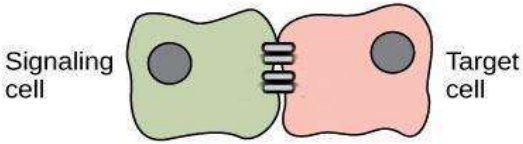
Paracrine	A cell targets a nearby cell.



Autocrine	A cell targets itself.



Contact-Dependent	Cells must physically interact to initiate signaling



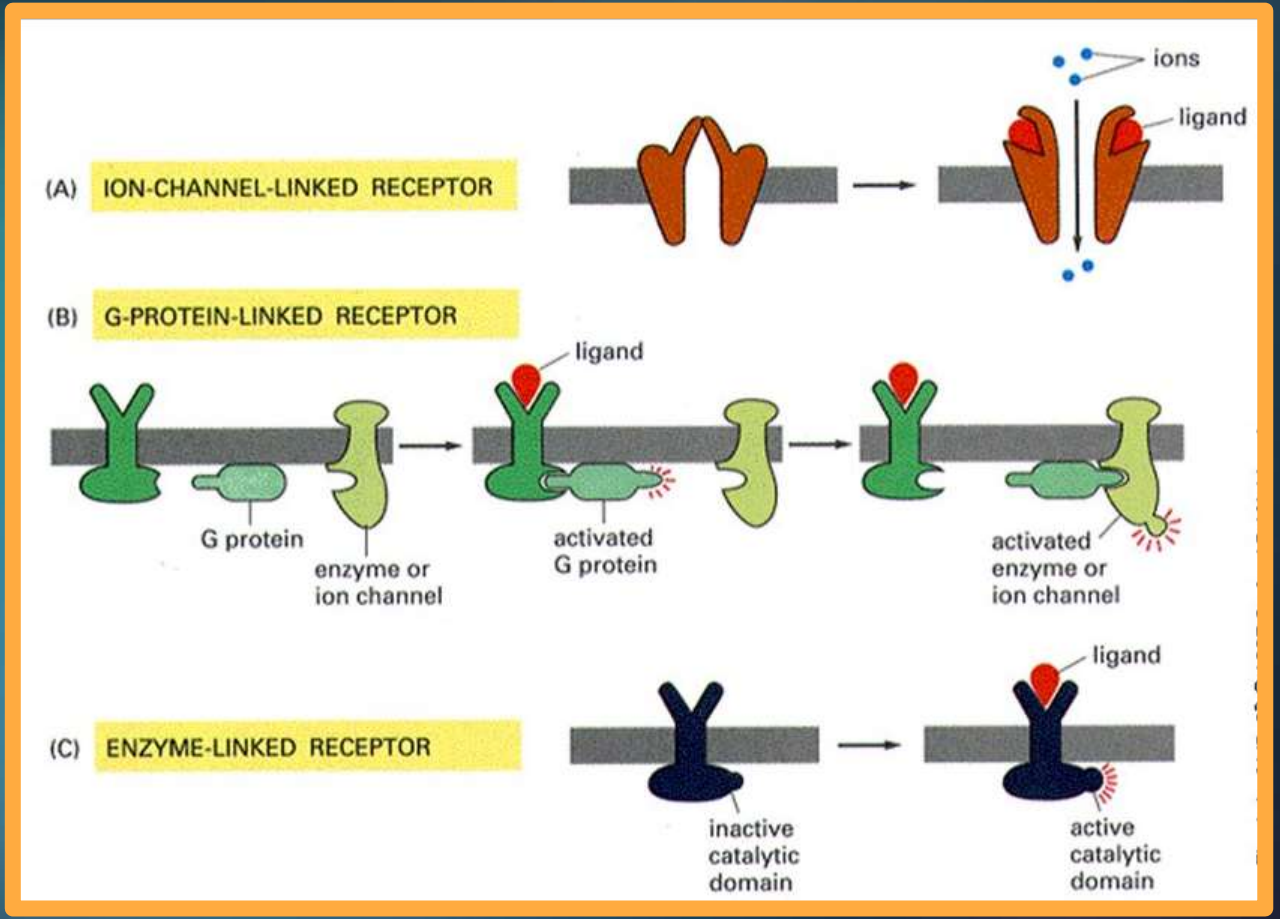
Type of Receptors

- Cell-surface receptors, also known as transmembrane receptors, are cell surface, 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.

- Ion channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through. To form a channel, this type of cell-surface receptor has an extensive membrane-spanning region. In order to interact with the phospholipid fatty acid tails that form the center of the plasma membrane, many of the amino acids in the membrane-spanning region are hydrophobic in nature.

Major classes of surface receptor of signaling

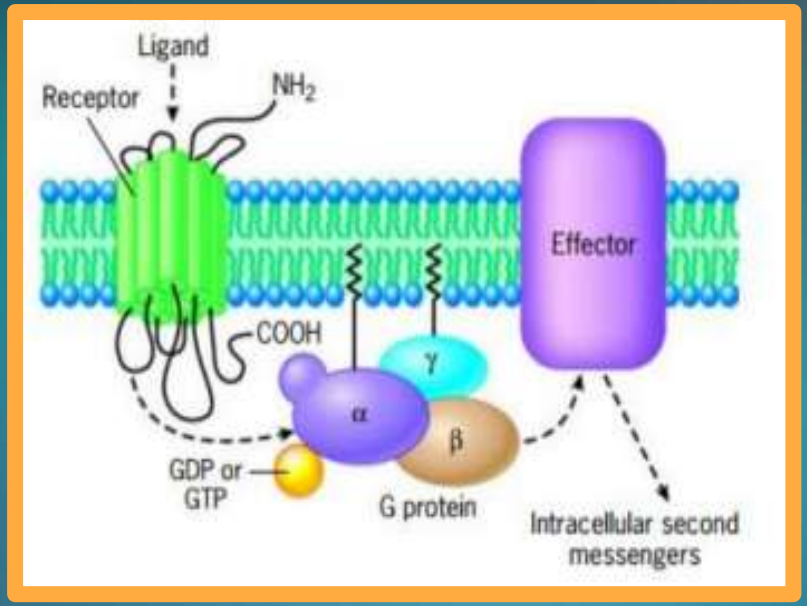
- **Cell Surface Receptors** :- Cell surface receptors, also known as transmembrane receptors, are cell surface, membrane-anchored, or integral proteins that bind to external ligand molecules, including cytokine receptors and growth factor receptors.
- **Ion channel-linked receptors** bind a ligand and open a channel through the membrane that allows specific ions to pass through. To form a channel, this type of cell surface receptor has an extensive membrane spanning region.
- **G protein-coupled receptors** are the largest family of cell surface receptors and are structurally and functionally related proteins characterized by seven membrane-spanning α helices.
- **Enzyme-linked receptors** include receptor tyrosine kinases (RTKs), receptor serine/threonine kinases, receptor-like tyrosine phosphatases, histidine kinase associated receptors and receptor guanylyl cyclases. Disorders of cell growth, proliferation, differentiation, survival and migration are fundamental to cancer

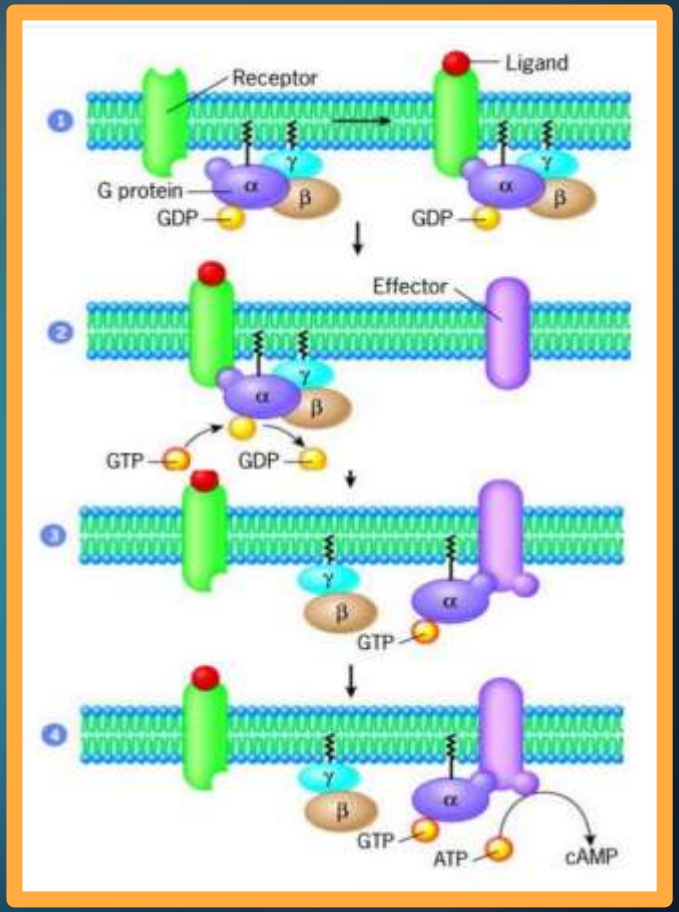

(A) ION-CHANNEL-LINKED RECEPTOR
ions
ligand
(B) G-PROTEIN-LINKED RECEPTOR
ligand
G protein
enzyme or
ion channel
activated
G protein
activated
enzyme or
ion channel
(C) ENZYME-LINKED RECEPTOR
ligand
inactive
catalytic
domain
active
catalytic
domain

G Protein – Coupled Receptors

- G-protein-coupled receptors (GPCRs) are the largest and most diverse group of membrane receptors in eukaryotes. These cell surface receptors act like an inbox for messages in the form of light energy, peptides, lipids, sugars, and proteins.

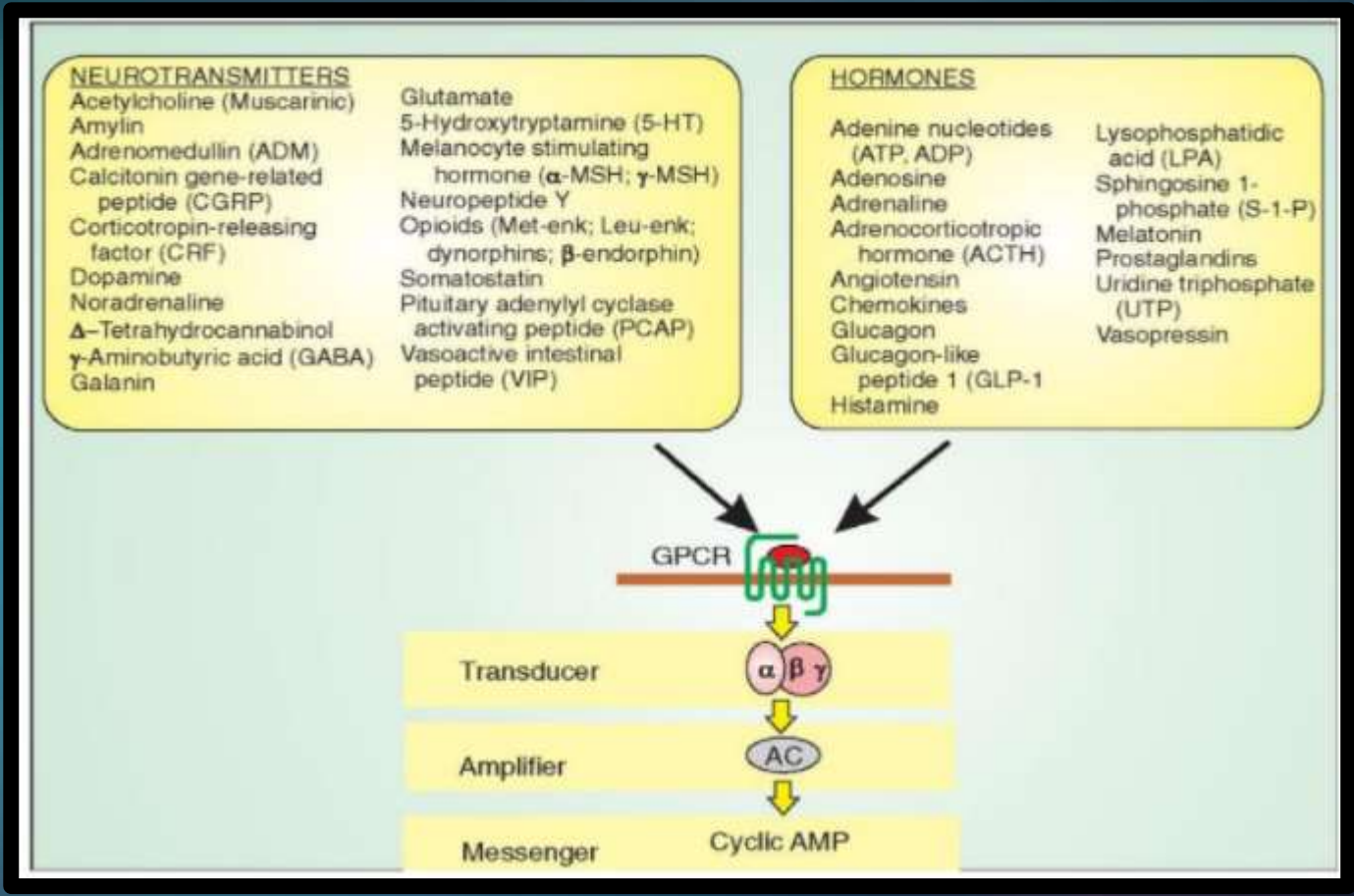
- When a GPCR binds a ligand (a molecule that possesses an affinity for the receptor), the ligand triggers a conformational change in the seven-transmembrane region of the receptor. This activates the C-terminus, which then recruits a substance that in turn activates the G protein associated with the GPCR.


Ligand
Receptor
NH2
COOH
Effector
γ
α
β
GDP or
GTP
G protein
Intracellular second
messengers


Receptor
Ligand
G protein
GDP
GDP
Effector
GTP
GDP
GTP
GTP
ATP
cAMP

Ligands that used Gpcr

Stimulus	Receptor	Effector	Physiologic response
Epinephrine	β-Adrenergic receptor	Adenylyl cyclase	Glycogen breakdown
Serotonin	Serotonin receptor	Adenylyl cyclase	Behavioral sensitization and learning in *Aplysia*
Light	Rhodopsin	cGMP phosphodiesterase	Visual excitation
IgE–antigen complexes	Mast cell IgE receptor	Phospholipase C	Secretion
f-Met Peptide	Chemotactic receptor	Phospholipase C	Chemotaxis
Acetylcholine	Muscarinic receptor	Potassium channel	Slowing of pacemaker activity


NEUROTRANSMITTERS
Acetylcholine (Muscarinic)
Amylin
Adrenomedullin (ADM)
Calcitonin gene-related peptide (CGRP)
Corticotropin-releasing factor (CRF)
Dopamine
Noradrenaline
Δ–Tetrahydrocannabinol
γ-Aminobutyric acid (GABA)
Galanin
Glutamate
5-Hydroxytryptamine (5-HT)
Melanocyte stimulating hormone (α-MSH; γ-MSH)
Neuropeptide Y
Opioids (Met-enk; Leu-enk; dynorphins; β-endorphin)
Somatostatin
Pituitary adenylyl cyclase activating peptide (PCAP)
Vasoactive intestinal peptide (VIP)
HORMONES
Adenine nucleotides (ATP, ADP)
Adenosine
Adrenaline
Adrenocorticotropic hormone (ACTH)
Angiotensin
Chemokines
Glucagon
Glucagon-like peptide 1 (GLP-1
Histamine
Lysophosphatidic acid (LPA)
Sphingosine 1-phosphate (S-1-P)
Melatonin
Prostaglandins
Uridine triphosphate (UTP)
Vasopressin
GPCR
Transducer
α β γ
Amplifier
AC
Messenger
Cyclic AMP

G Proteins

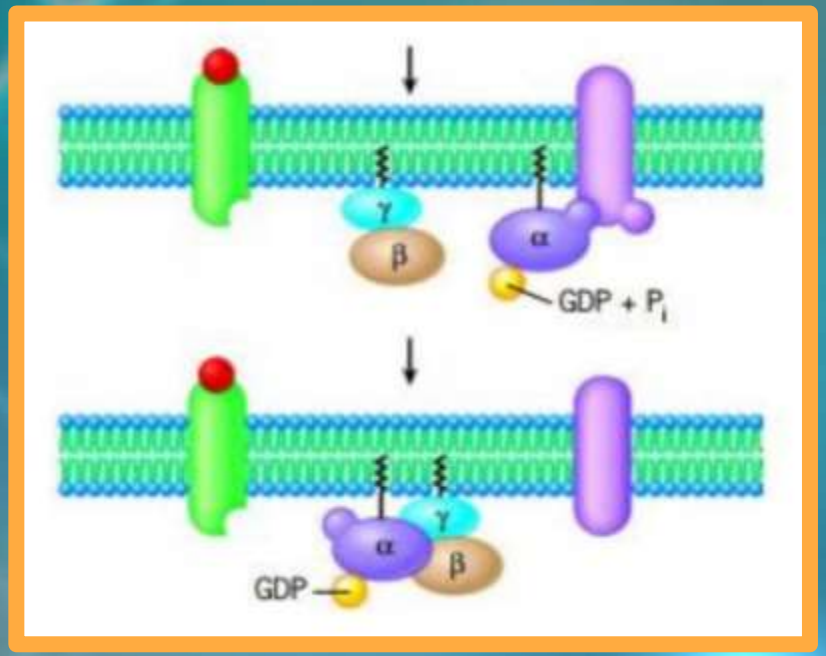
- G proteins, also known as guanine nucleotide-binding proteins, are a family of proteins that act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli outside a cell to its interior.
- G proteins belong to the larger group of enzymes called GTPases
- G proteins are commonly used in signal transduction pathways in animal cells in response to diverse stimuli such as light, odorants, hormones, neurotransmitters and chemoattractants. They consist of heterotrimers of an α-subunit, a β-subunit and a γ-subunit.

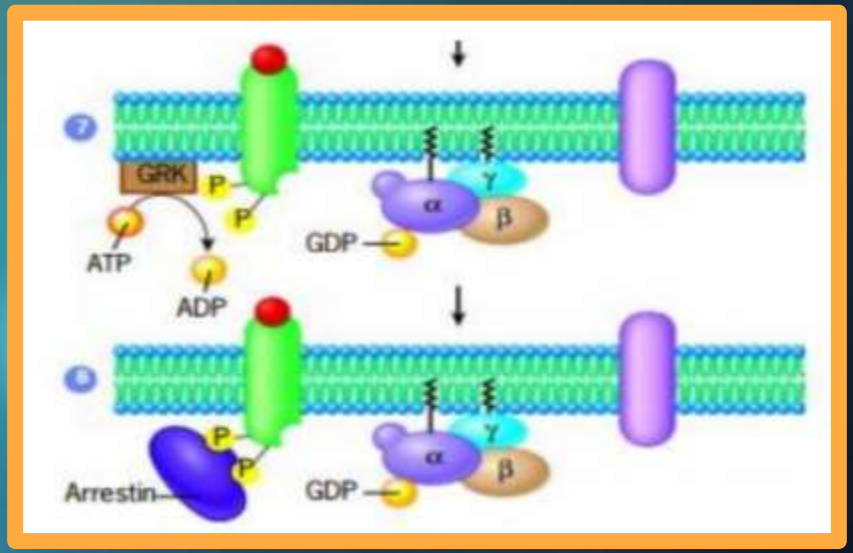
Types of G Proteins

Three Major Families of Trimeric G Proteins*

FAMILY	SOME FAMILY MEMBERS	ACTION MEDIATED BY	FUNCTIONS
I	G_s	α	activates adenylyl cyclase; activates Ca^{2+} channels
	G_{olf}	α	activates adenylyl cyclase in olfactory sensory neurons
II	G_i	α	inhibits adenylyl cyclase
		βγ	activates K^+ channels
	G_o	βγ	activates K^+ channels; inactivates Ca^{2+} channels
		α and βγ	activates phospholipase C-β
	G_t (transducin)	α	activates cyclic GMP phosphodiesterase in vertebrate rod photoreceptors
III	G_q	α	activates phospholipase C-β

Termination Of GPCR Response

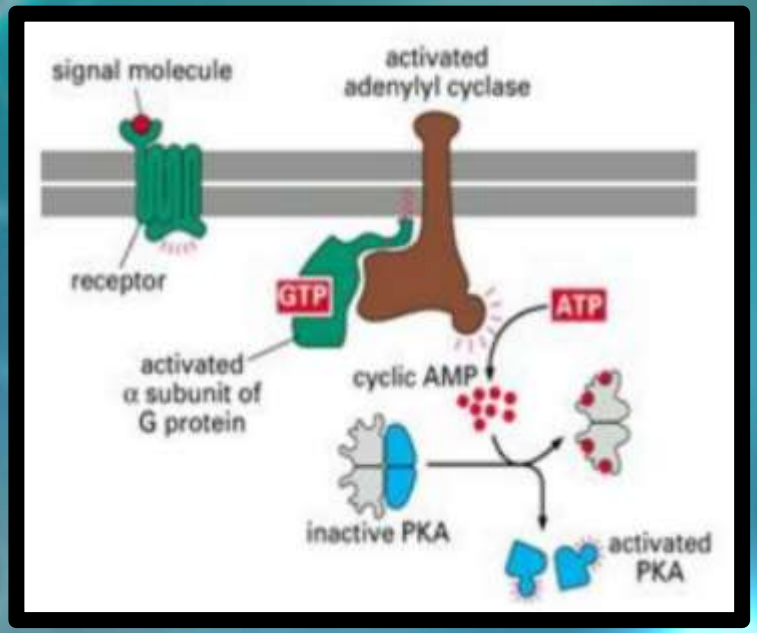


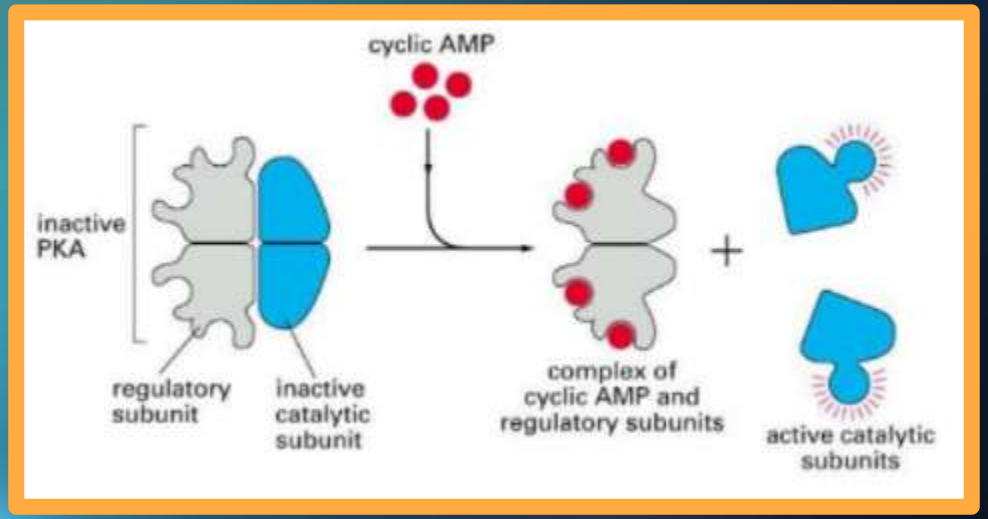


Secondary messenger

- Second messengers are small molecules and ions that relay signals received by cell-surface receptors to effector proteins.
- These messengers then diffuse rapidly from the source and bind to target proteins to alter their properties (activity, localization, stability, etc.) to propagate signaling.
- Example:- DAG, NO, Oxygen

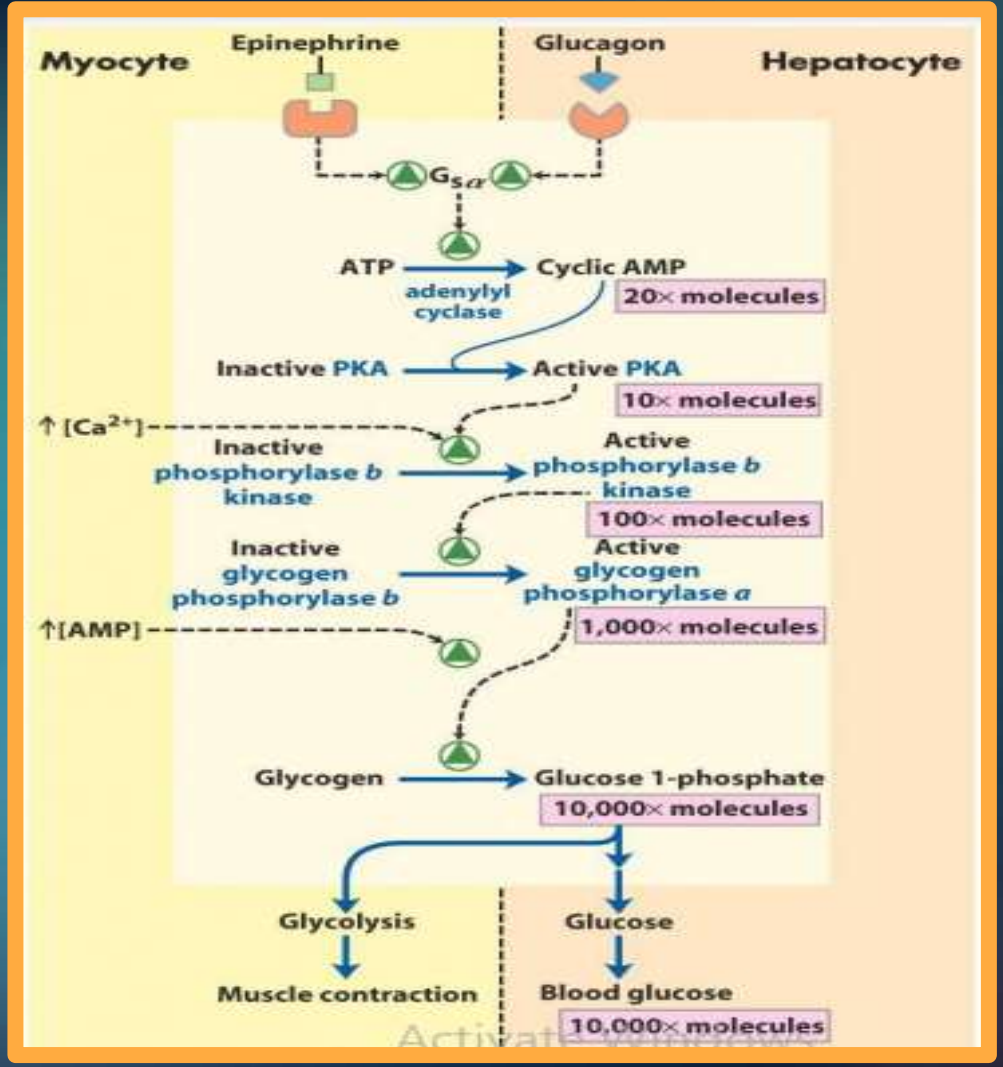
Cyclic AMP Pathway





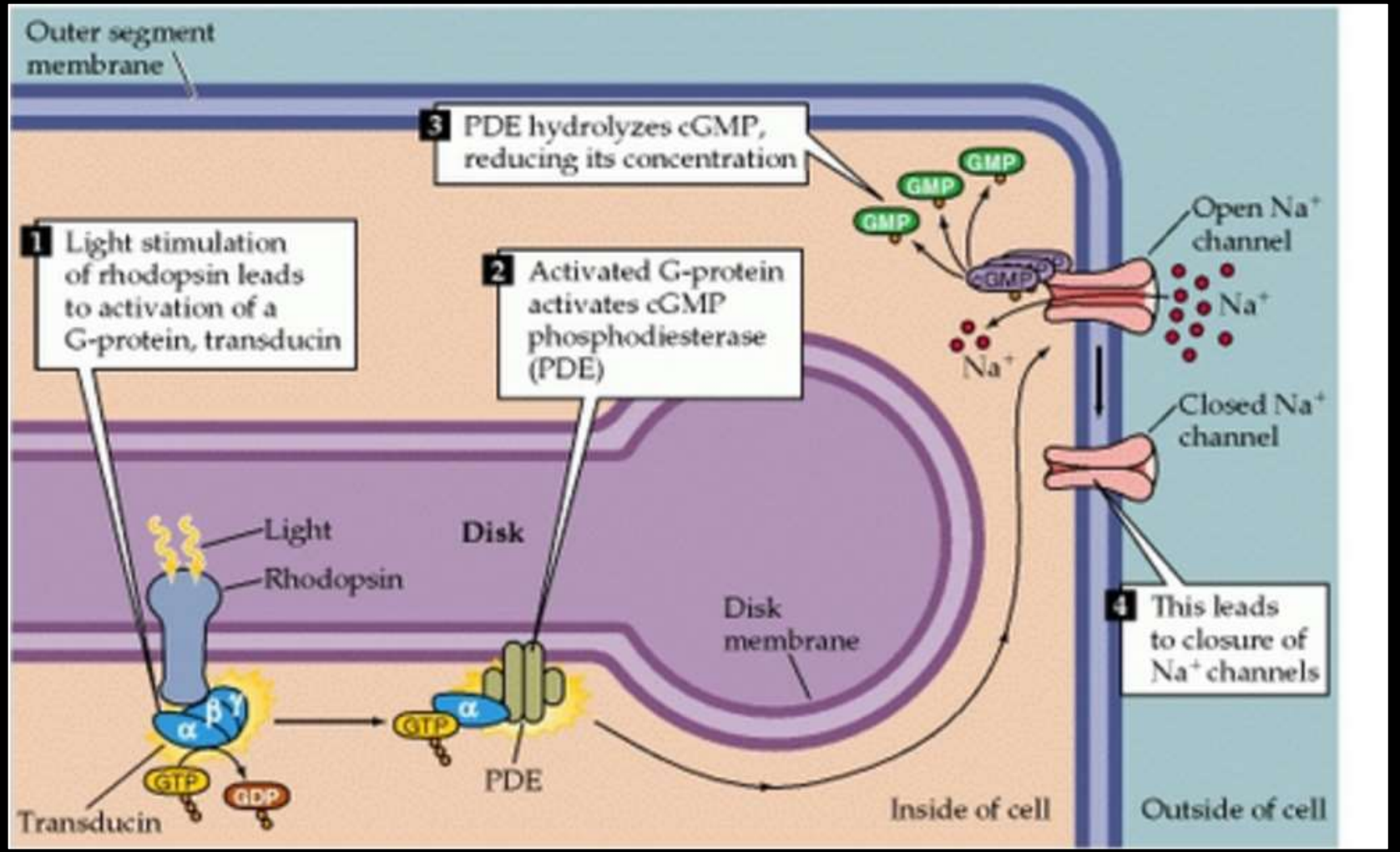
CAMP – pKA pathway

- The level of cAMP is regulated by AC and PDE.
- During the process, AC is activated by a type of G-alpha, which in turn induces the conversion of adenosine triphosphate (ATP) into cAMP.
- The stimulated adenylyl cyclase can produce numerous cAMP molecules to intensify the signal.
- As the figure shows, cAMP acts directly on three main targets: protein kinase A (PKA), the exchange protein activated by cAMP (Epac), and cyclic nucleotide-gated ion channels (CNGCs).
- PKA modulates a number of cellular substrates via phosphorylation, including transcription factors, ion channels, transporters, exchangers, intracellular Ca2+-handling proteins, and the contractile machinery.
- Epac proteins, as guanine nucleotide exchange factors (GEFs) for both Rap1 and Rap2, have a series of effector proteins, involving adaptor proteins implicated in modulation of the actin cytoskeleton, regulators of G proteins of the Rho family, and phospholipases, relay signaling downstream from Rap.


Myocyte
Epinephrine
Glucagon
Hepatocyte
$G_{s\alpha}$
ATP
adenylyl cyclase
Cyclic AMP
20× molecules
Inactive PKA
Active PKA
10× molecules
↑ [Ca^{2+}]
Inactive phosphorylase b kinase
Active phosphorylase b kinase
100× molecules
Inactive glycogen phosphorylase b
Active glycogen phosphorylase a
↑[AMP]
1,000× molecules
Glycogen
Glucose 1-phosphate
10,000× molecules
Glycolysis
Glucose
Muscle contraction
Blood glucose
10,000× molecules

CGMP

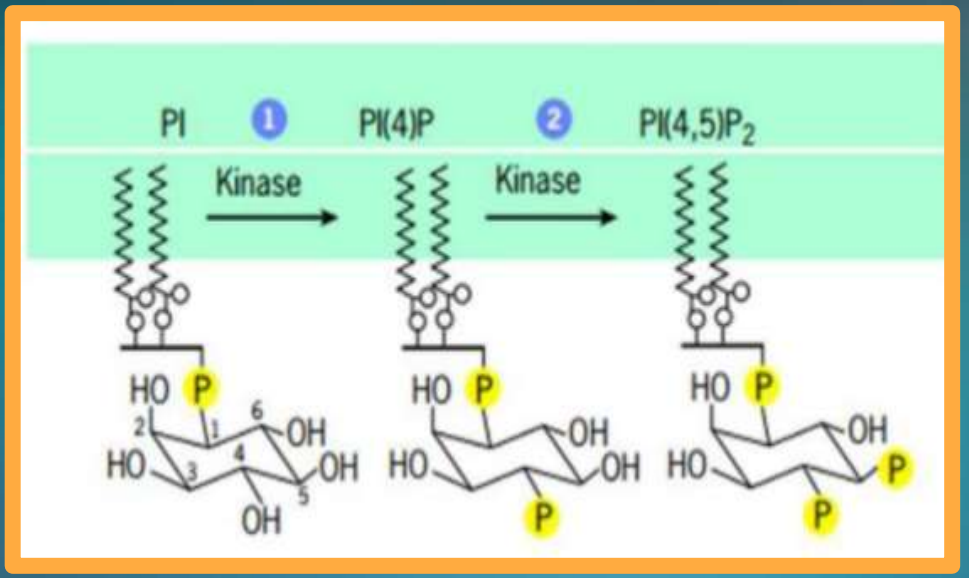
- cGMP is a common regulator of ion channel conductance, glycogenolysis, and cellular apoptosis.
- It also relaxes smooth muscle tissues. In blood vessels, relaxation of vascular smooth muscles lead to vasodilation and increased blood flow.
- cGMP is a secondary messenger in phototransduction in the eye.
- In the photoreceptors of the mammalian eye, the presence of light activates phosphodiesterase, which degrades cGMP.
- The sodium ion channels in photoreceptors are cGMP-gated, so degradation of cGMP causes sodium channels to close, which leads to the hyperpolarization of the photoreceptor's plasma membrane and ultimately to visual information being sent to the brain.

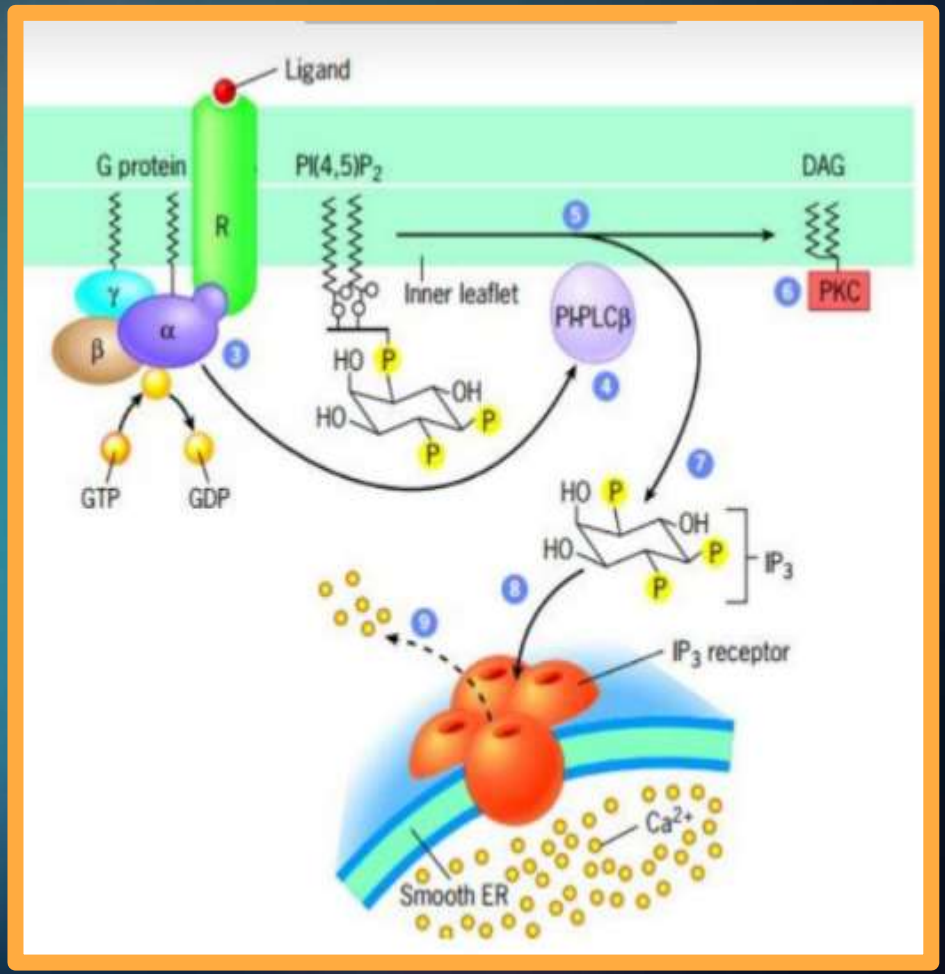

Outer segment membrane
3 PDE hydrolyzes cGMP, reducing its concentration
GMP
GMP
GMP
GMP
Open Na+ channel
Na+
Na+
1 Light stimulation of rhodopsin leads to activation of a G-protein, transducin
2 Activated G-protein activates cGMP phosphodiesterase (PDE)
Closed Na+ channel
Light
Rhodopsin
Disk
Disk membrane
4 This leads to closure of Na+ channels
α
β
γ
GTP
GDP
Transducin
α
GTP
PDE
Inside of cell
Outside of cell

Phodphotidylinositol – Derived Secondary Messenger

- The phosphatidylinositol (PI) system is another second messenger system. PI is a minor component of membrane lipids.

- This molecule serves as a source of second messenger compounds. PI has three parts
- The first part of PI consists of two fatty acids esterified to a glycerol. One of the fatty acids is the unsaturated fatty acid arachidonic acid (20:4), bound to carbon 2 of the glycerol. The other fatty acid is usually stearate (18:0).
- The combination of two fatty acids esterified to glycerol is called diacylglycerol, abbreviated DAG.
- Another component of PI is a carbohydrate, phosphoinositol,which a phosphate diester binds to the third position of the glycerol. The inositol is usually phosphorylated at two positions.


PI
1
PI(4)P
2
PI(4,5)P2
Kinase
Kinase
HO
P
OH
P


Ligand
G protein
R
γ
α
β
GTP
GDP
PI(4,5)P2
Inner leaflet
PI-PLCβ
DAG
PKC
IP3
IP3 receptor
Ca2+
Smooth ER

Inositol 1,4,5 – triphosphate (IP_3)

- Inositol trisphosphate or inositol 1,4,5-trisphosphate abbreviated InsP3 or Ins3P or IP3 is an inositol phosphate signaling molecule.
- It is made by hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2), a phospholipid that is located in the plasma membrane, by phospholipase C (PLC).
- Together with diacylglycerol (DAG), IP3 is a second messenger molecule used in signal transduction in biological cells.
- While DAG stays inside the membrane, IP3 is soluble and diffuses through the cell, where it binds to its receptor, which is a calcium channel located in the endoplasmic reticulum.
- When IP3 binds its receptor, calcium is released into the cytosol, thereby activating various calcium regulated intracellular signals.

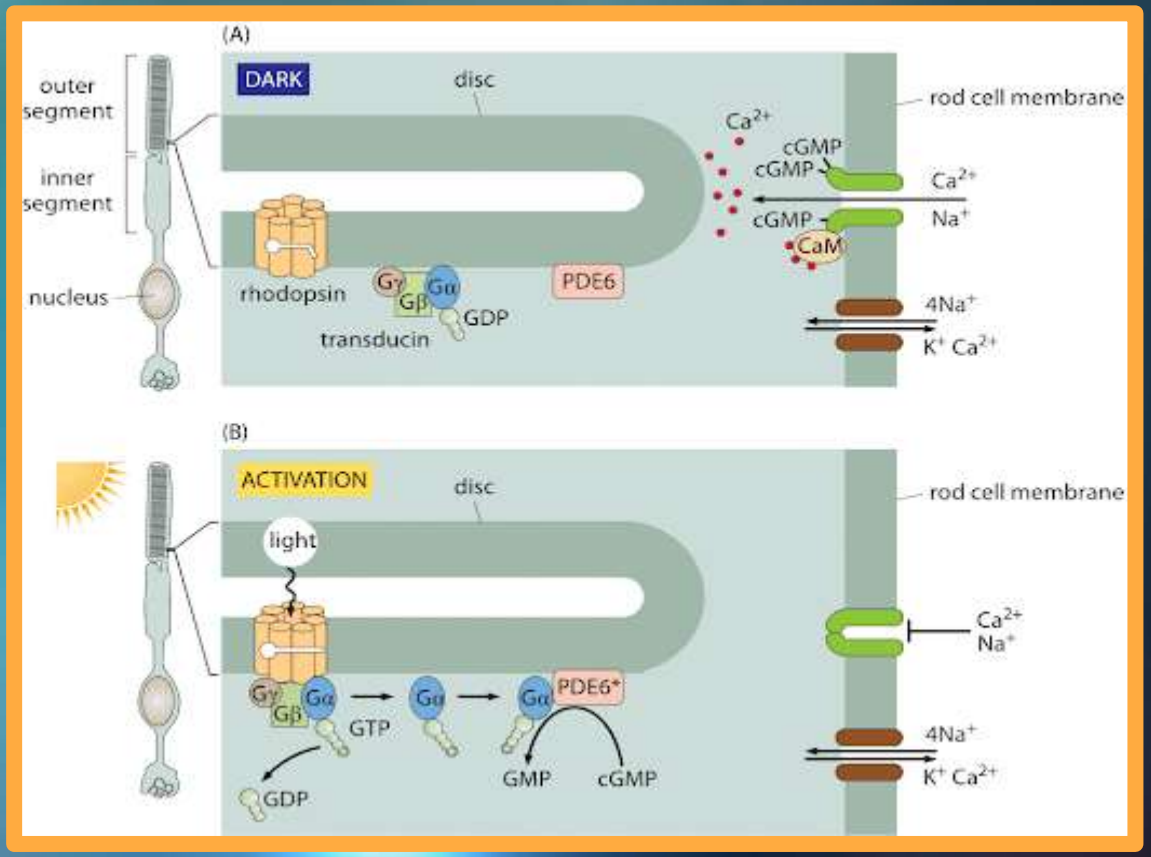
DAG

- Diacylglycerol (DAG) is a key secondary lipid messenger for transducing signals downstream of many receptors expressed by hematopoietic cells.
- DAG has shown to be important in driving the activation, proliferation, migration, and effector function of adaptive and innate immune cells

Nitric oxide (NO)

- NO is synthesized by nitric oxide synthase (NOS) which oxidizes a guanidine nitrogen of L-arginine releasing nitric oxide in the form of a free radical and citrulline.
- The neuronal enzyme (NOS-1) and the endothelial isoform (NOS-3) are calcium-dependent and produce low levels of gas as a cell signaling molecule.

Rhodopsin pathway



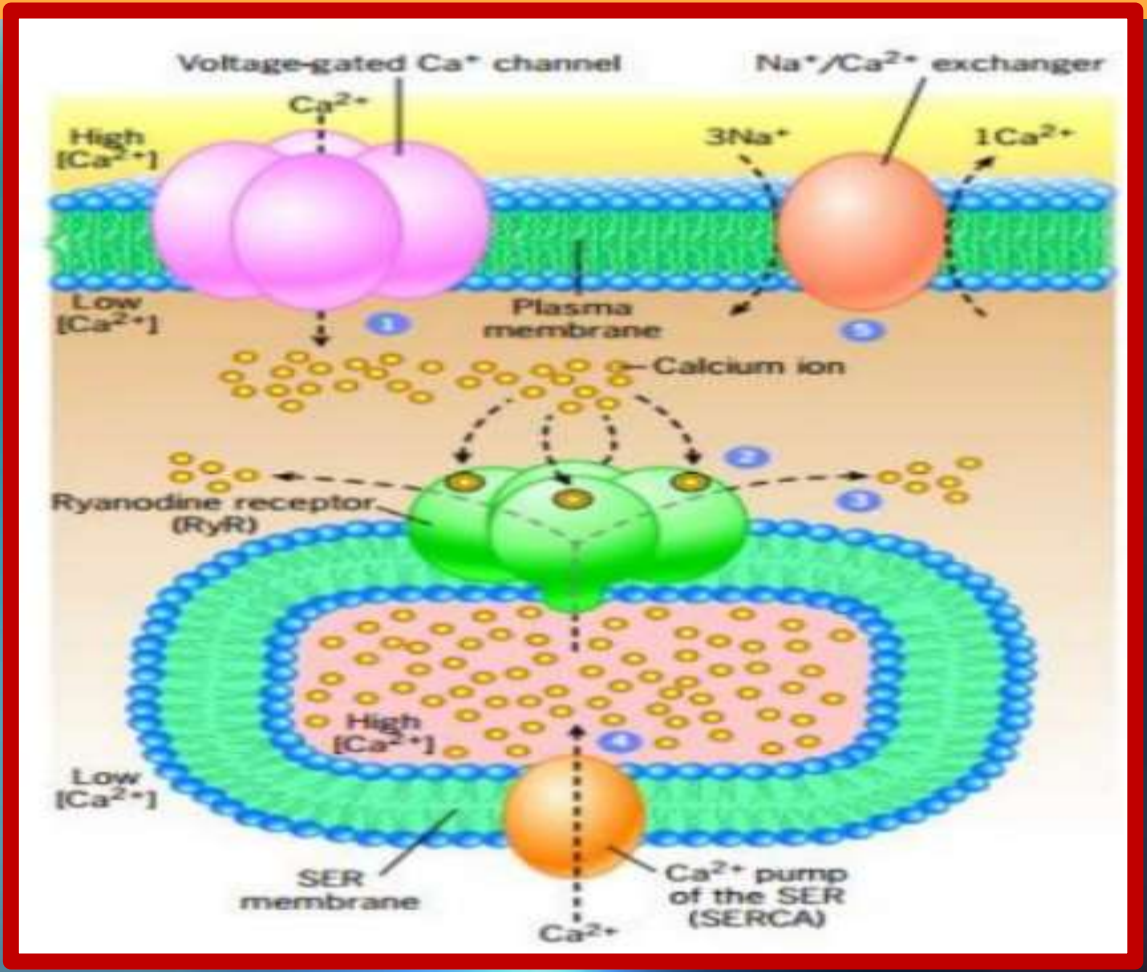
Rhodopsin pathway

- Rhodopsin is a membrane protein that detects light in the rod photoreceptor cell.
- Like other G protein-coupled receptors (GPCRs), rhodopsin exists in equilibrium between its activated and inactivated forms in vivo.
- In the presence of light, retinal is photoisomerized to the all-trans form, which activates rhodopsin.
- Rhodopsin is the photoreceptor in rod cells; it mediates vision in dim light and is coupled to the retinal G protein transducin (Gt). Photoexcited rhodopsin catalyzes the activation of Gt, which in turn triggers a biochemical cascade of reactions (phototransduction), eventually leading to a visual signal.

Rhodopsin pathway

- When rhodopsin is activated by light the protein couples with the G protein transducin which is the first step in the signal cascade.
- Rhodopsin must undergo several conformational changes before being able to bind transducin. Rhodopsin is initially converted to metarhodopsin II which is the active form of rhodopsin.

calcium


Voltage-gated Ca⁺ channel
Na⁺/Ca²⁺ exchanger
Ca²⁺
High [Ca²⁺]
3Na⁺
1Ca²⁺
Low [Ca²⁺]
Plasma membrane
Calcium ion
Ryanodine receptor (RyR)
High [Ca²⁺]
Low [Ca²⁺]
SER membrane
Ca²⁺ pump of the SER (SERCA)
Ca²⁺

The second messenger cAMP, synthesised by adenylyl cyclase transduces a wide variety of physiological signals in various cell types in mammalian cells. Most of the diverse effects of cAMP are mediated through activation of protein kinase A (PKA), also called cAMP dependent protein kinase. Which of the following statements regarding PKA is **NOT** correct?

1. Inactive PKA is a tetramer consisting of two regulatory (R) subunits and two catalytic (C) subunits.
2. Each R subunit binds the active site in a catalytic domain and inhibits the activity of the catalytic subunits.
3. Each R subunit has two distinct cAMP binding sites and binding of cAMP occurs in a cooperative fashion.
4. Binding of cAMP to R subunit causes a conformational change resulting in binding to site other than catalytic site causing strengthening of binding to C subunit activating its kinase activity.

91. G-protein coupled receptors (GPCR) consist of three protein subunits α, β and γ. In unstimulated state, α subunit is GDP bound and GPCR is inactive. When GPCR gets activated, it acts like guanine nucleotide exchange (GEF) factor and induces α-subunit to release its bound GDP allowing GTP to bind in its place. In order to regulate G-protein activity by regulating GDP/GTP concentration, α subunit acts as

1. GTPase
2. GDP kinase
3. cGMP-specific phosphodiesterase
4. cAMP-specific phosphodiesterase