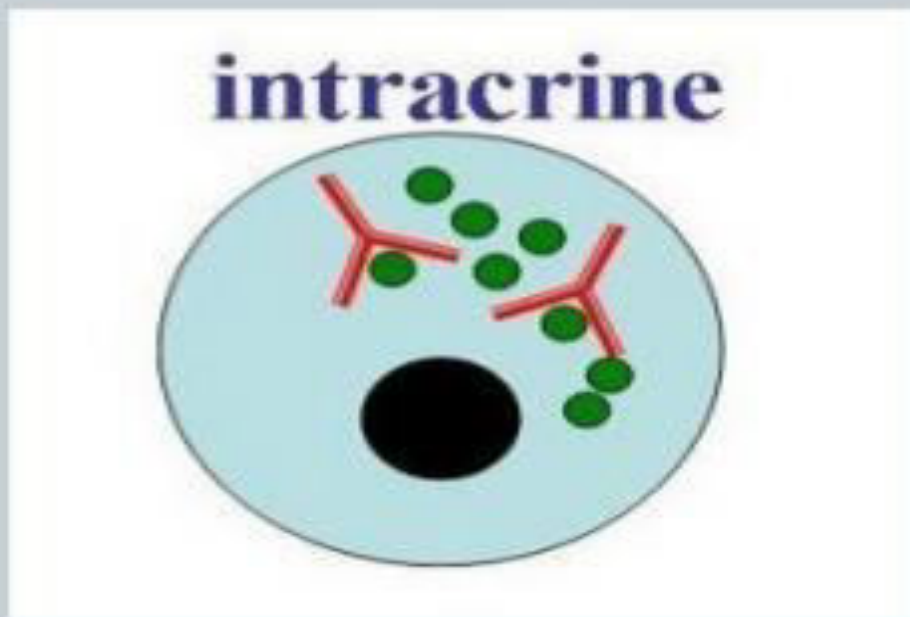
PAPER- III
CELL SIGNALLING AND CELL SURFACE RECEPTORS
UNIT II

Signalling molecules

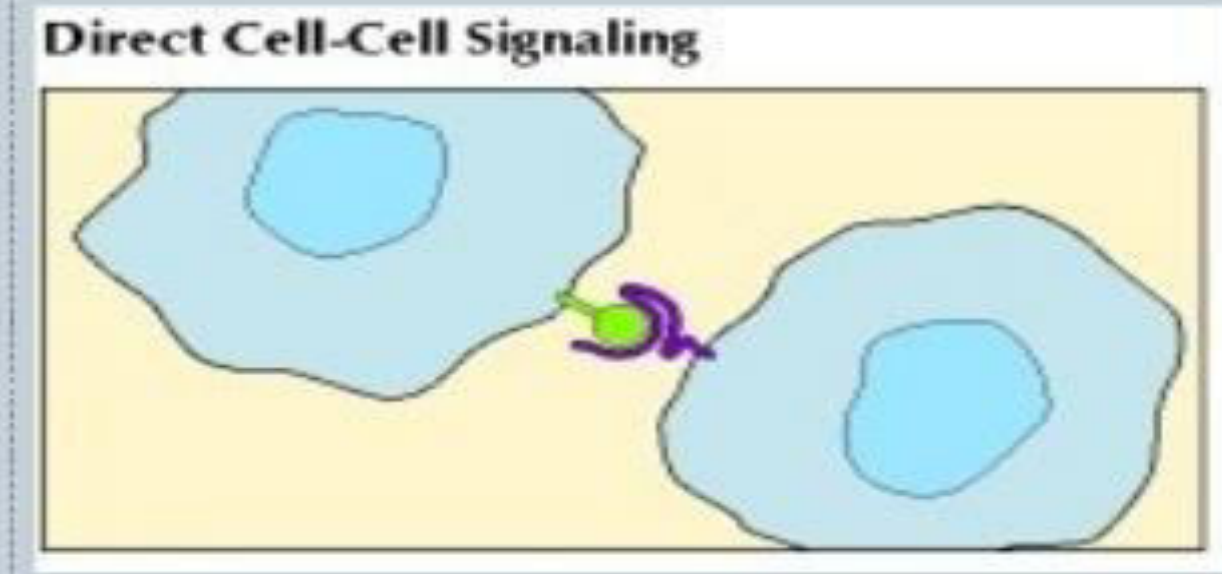
- Chemicals and other molecules
- Act as ligands
- Bind to receptor
- Vary in size, shape and structure
- Some are capable of carrying signal over large distances

Modes of signalling

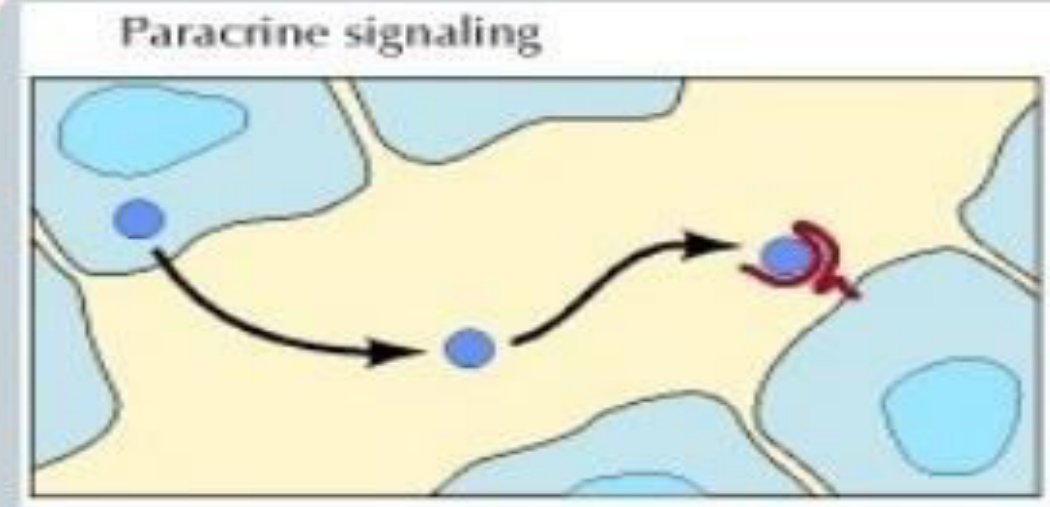
- Intracrine
  - Any hormone or ligand acting inside a cell
  - For example if they act through nuclear receptors.

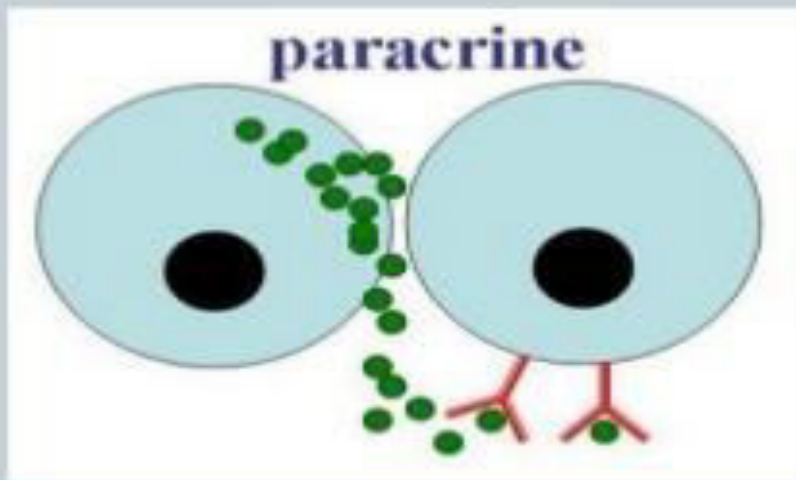


- Juxtacrine signalling
  - Also known as contacct dependant signalling.
  - Proximity between cells is mandatory for signalling to take place.

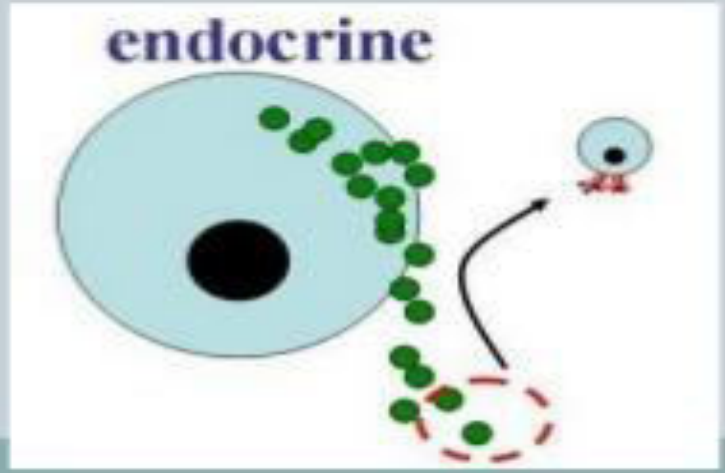


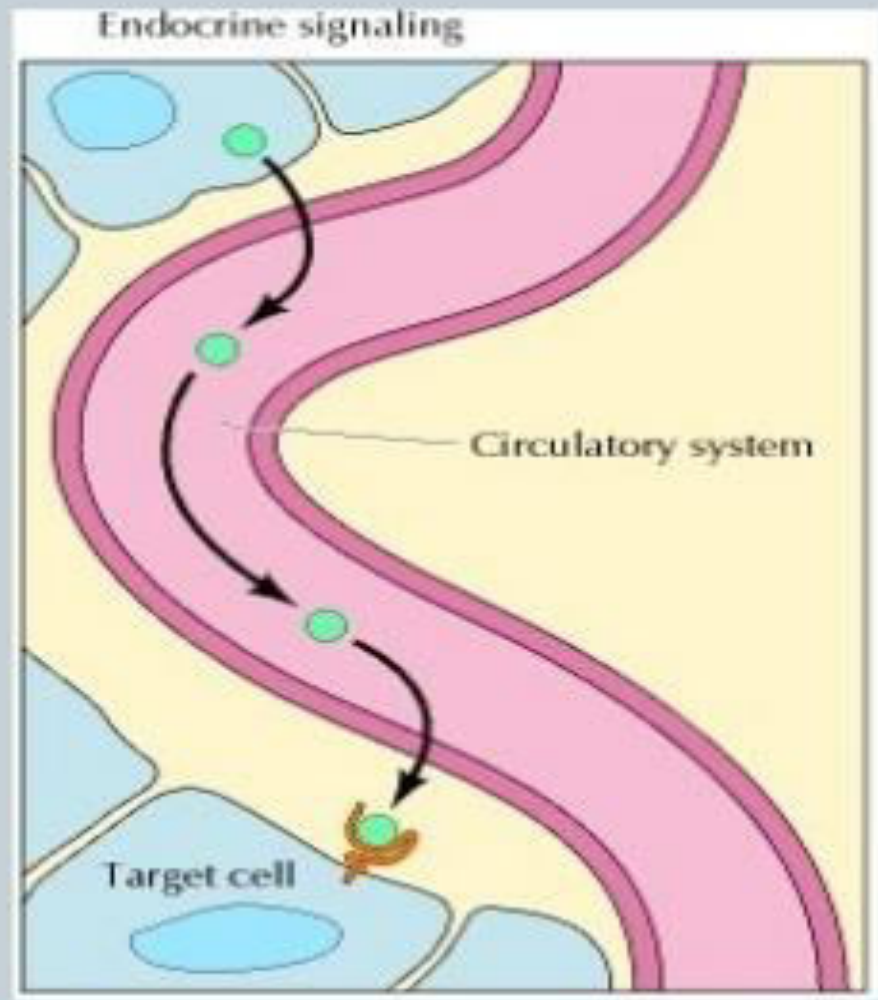
- Paracrine signalling
  - Cell to cell interaction
  - Signal is produced for adjacent cells
  - Ex: neurotransmitters in neurons





- Endocrine signalling
  - For hormone
  - For signals that need to travel over distances
  - Signals are carried by the blood stream
  - Reaches target cell with receptors





Signalling Molecules

- Messengers of cells
- For communication
- They can be compounds like peptides, amino acids, steroids or even gases.
- Secreted by signalling cell.
- Carried out by exocytosis while some by simple diffusion.

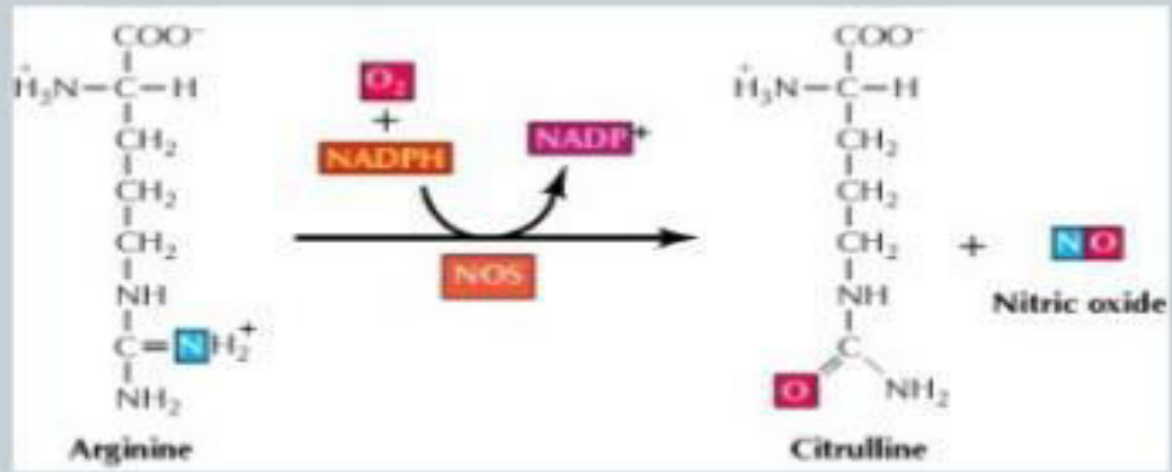
Types

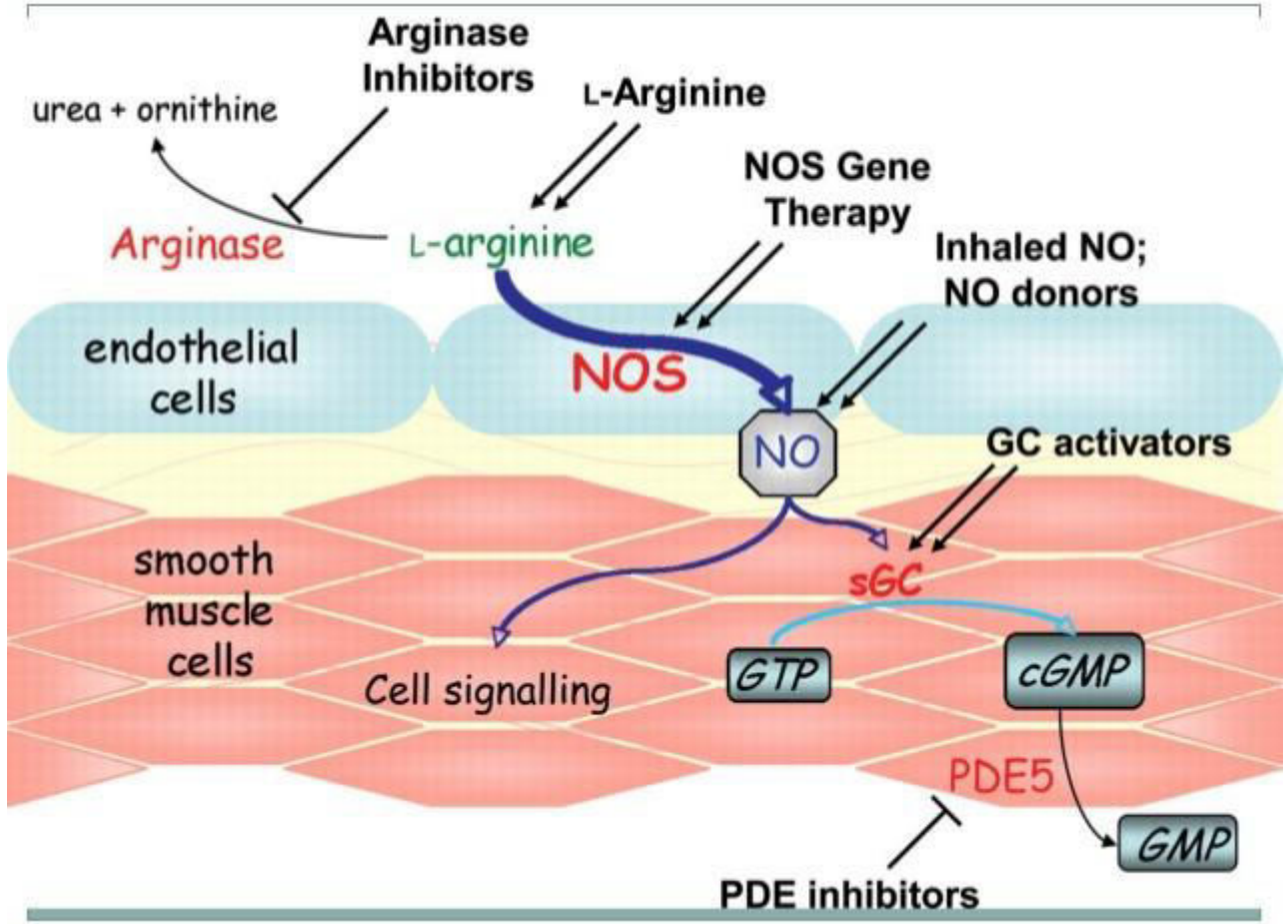
- NO gas
- Steroids
- Neurotransmitters
- Peptide hormones and growth factors

- *Second messengers*

NO: Nitric oxide

- Major paracrine signalling molecule.
- In nervous system, immune system and circulatory systems.
- Diffuses easily across plasma membrane.
- It ultimately alters the activity of intracellular target enzyme.
- NO has a very short half life.
- Its toxic.
- Therefore, it functions over short distances.
- Induces relaxation and vaso dilation.


Arginine
O2
+
NADPH
NADP+
NOS
Citrulline
+
NO
Nitric oxide

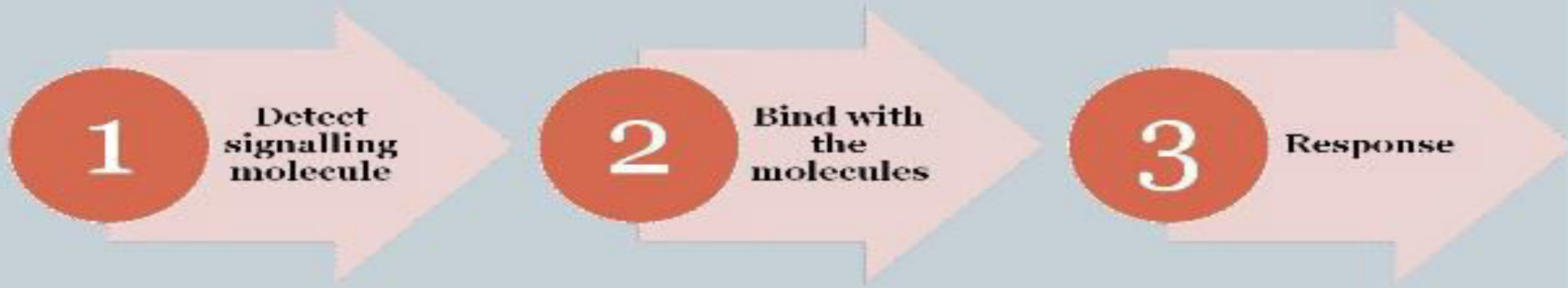

Arginase Inhibitors
L-Arginine
urea + ornithine
NOS Gene Therapy
Arginase
L-arginine
Inhaled NO; NO donors
endothelial cells
NOS
NO
GC activators
smooth muscle cells
sGC
Cell signalling
GTP
cGMP
PDE5
GMP
PDE inhibitors

NO

- NO is also helps macrophages and neutrophils to kill microorganisms.
- CO, carbon monoxide is also used as a signal.
- It acts same as NO i.e, by stimulating guanylyl cyclase.
- It's a neurotransmitter.

Cell surface receptors

- Stuctures on the plasma membrane
- Each one has unique way of reacting to different molecules to perform functions.



Forms of receptors

- Steroid receptor
- G protein coupled receptors
- Tyrosine kinase receptors
- Cytokine superfamily receptor

Steroid receptors

- Found in cytosol, plasma membrane and the nucleas.
- Usually have nuclear receptors.
- Lead to change in gene expression causing alteration in the transcriptional activity.
- Some receptors are always bound to the DNA even when the hormone is not present. Eg: Thyroid hormone receptor.
- Some can bind only when the hormone is there. Eg: Estrogen and glucocorticoid receptors.

Historical background

- **Robert Lefkowitz** and **Brian Kobilka:** the 2012 Nobel Prize in Chemistry for groundbreaking discoveries that reveal the inner workings of an important family of receptors: **G-protein–coupled**

G – Protein coupled receptors

- Known as 7TM receptor or seven transmembrane domain receptors.
- They pass through the plasma membrane 7 times forming many extracellular loops
- They have highly conserved cysteine residues forming disulfide bonds for stability.
- They extracellular regions may be glycosylated.
- The also have trimeric protiens: α, β and γ protiens which dissociate during the activation of the receptor.

G Protein - Coupled Receptors (GPCRs);

- GPCRs constitute the largest gene family in the human genome (~950 genes), ~500 of which are sensory.

Constitutes > 1% of the human genome.

- Comprises receptors for a diverse array of molecules: neurotransmitters, odorants, lipids, neuropeptides, large glycoprotein hormones.

- They are the target of the majority of best-selling drugs (40%-50% of all prescription pharmaceuticals on the market). Examples:

  • Zyprexa (bipolar disorder & schizophrenia, Eli Lilly)
  •Zantac (treat and prevent ulcers in the stomach and intestines; histamine receptor antagonists, GlaxoSmithKline)

Diversity (of physiological responses to GPCR stimulation)

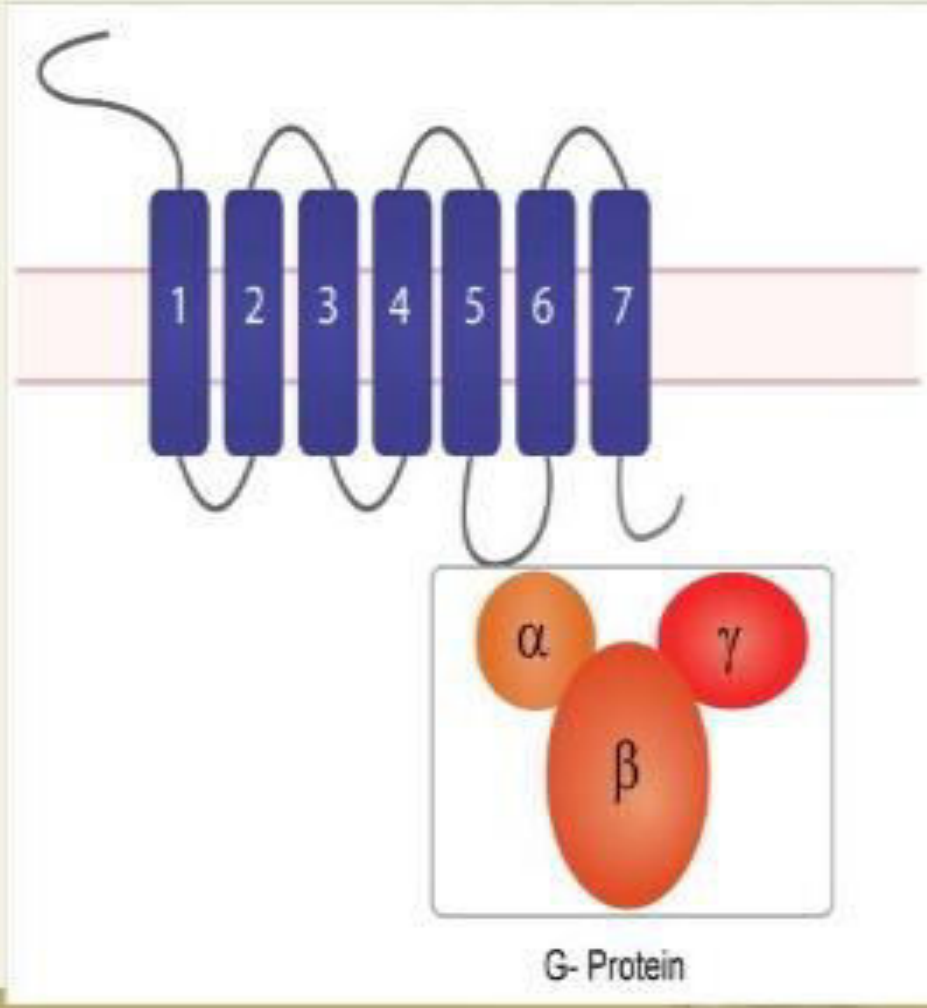
TARGET TISSUE	HORMONE	MAJOR RESPONSE
Thyroid gland	thyroid-stimulating hormone (TSH)	thyroid hormone synthesis and secretion
Adrenal cortex	adrenocorticotrophic hormone (ACTH)	cortisol secretion
Ovary	luteinizing hormone (LH)	progesterone secretion
Muscle	adrenaline	glycogen breakdown
Bone	parathormone	bone resorption
Heart	adrenaline	increase in heart rate and force of contraction
Liver	glucagon	glycogen breakdown
Kidney	vasopressin	water resorption
Fat	adrenaline, ACTH, glucagon, TSH	triglyceride breakdown

[redacted]

TARGET TISSUE	SIGNALING MOLECULE	MAJOR RESPONSE
Liver	vasopressin	glycogen breakdown
Pancreas	acetylcholine	amylase secretion
Smooth muscle	acetylcholine	contraction
Blood platelets	thrombin	aggregation

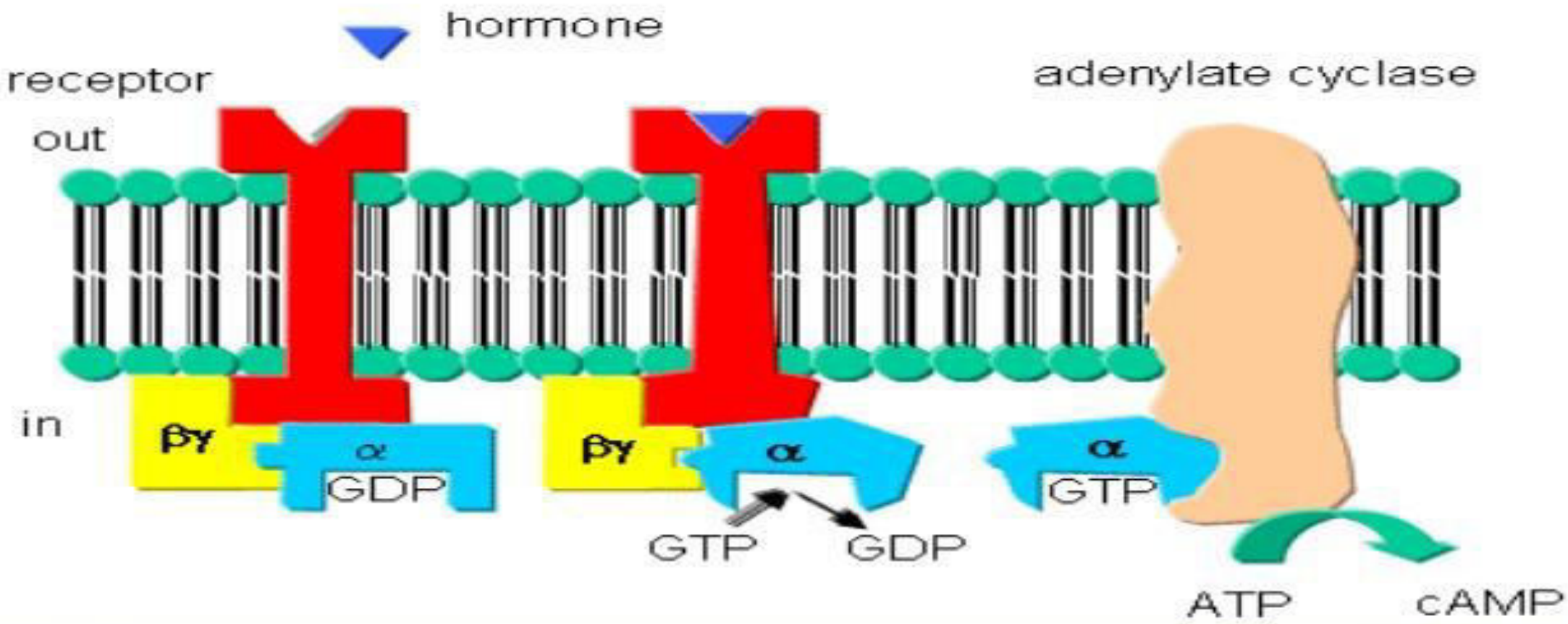
- G protein complexes are Made up of alpha (α), beta (β) and gamma (γ) subunits.

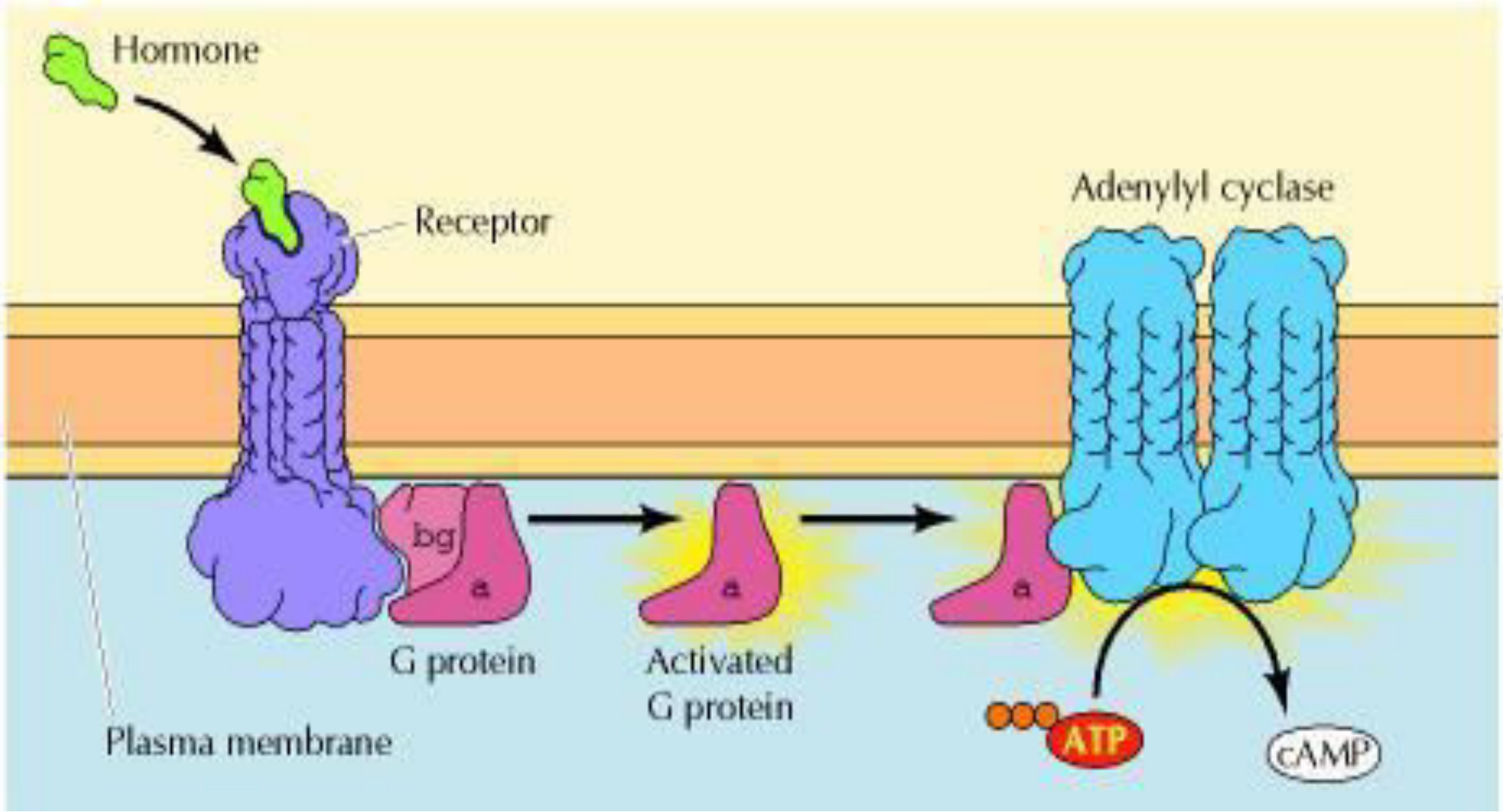
- Beta and gamma subunits can form a stable dimeric complex referred to as the beta-gamma complex.

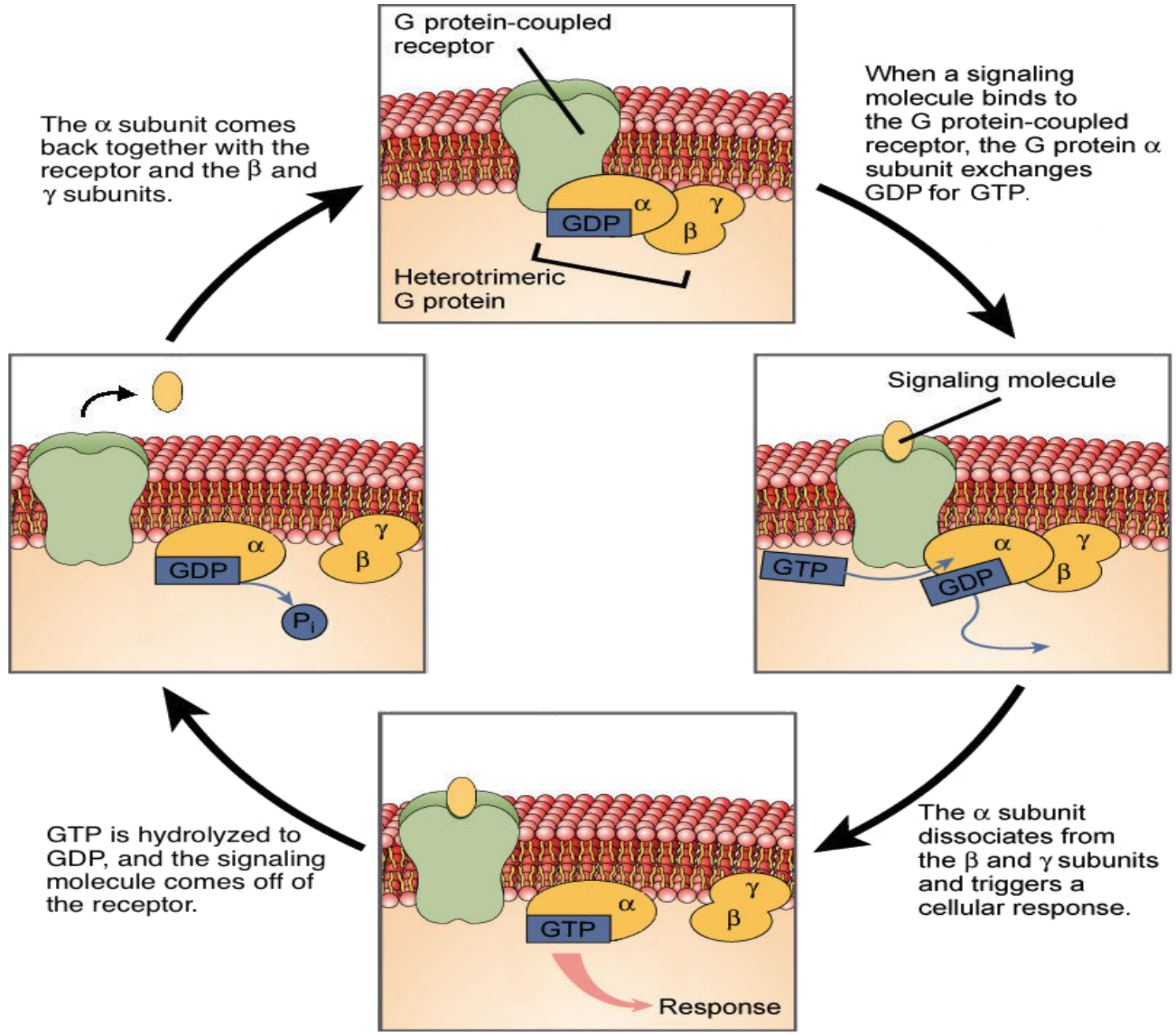


G- Protein

G protein activation of adenylate cyclase




Hormone
Receptor
Adenylyl cyclase
bg
α
G protein
α
Activated
G protein
α
ATP
cAMP
Plasma membrane


G protein-coupled receptor
When a signaling molecule binds to the G protein-coupled receptor, the G protein α subunit exchanges GDP for GTP.
GDP
α
γ
β
Heterotrimeric G protein
Signaling molecule
GTP
GDP
The α subunit dissociates from the β and γ subunits and triggers a cellular response.
GTP
Response
GTP is hydrolyzed to GDP, and the signaling molecule comes off of the receptor.
GDP
P_i
The α subunit comes back together with the receptor and the β and γ subunits.

Families of GPCR

3 Families:

- **A – Rhodopsin** family
- **B - Secretin/Glucagon** receptor family

eg. Peptide hormones.

- **C - Metabotropic Glutamate** family

eg. $GABA_B$, Glutamate.

GPC Receptors

G Protein	Receptors	Signaling Pathway
G_S	Beta adrenergic receptors, glucagon, histamine, serotonin	Increase CAMP Excitatory effects
G_i	$Alpha_2$ adrenergic receptors, mAchR, opioid, serotonin	Decrease CAMP Cardiac K^+ channel open- decrease heart rate
G_q	mAchR, H1, α1, Vasopressin type 1, $5HT_{1C}$	PLC- IP_3 , DAG Increase Cytoplasmic Ca
G_t	Rhodopsin and colour opsins in retinal rod and cone cells	Increase cGMP phosphodiesterase. Decrease cGMP

Rhodopsin Receptor Family

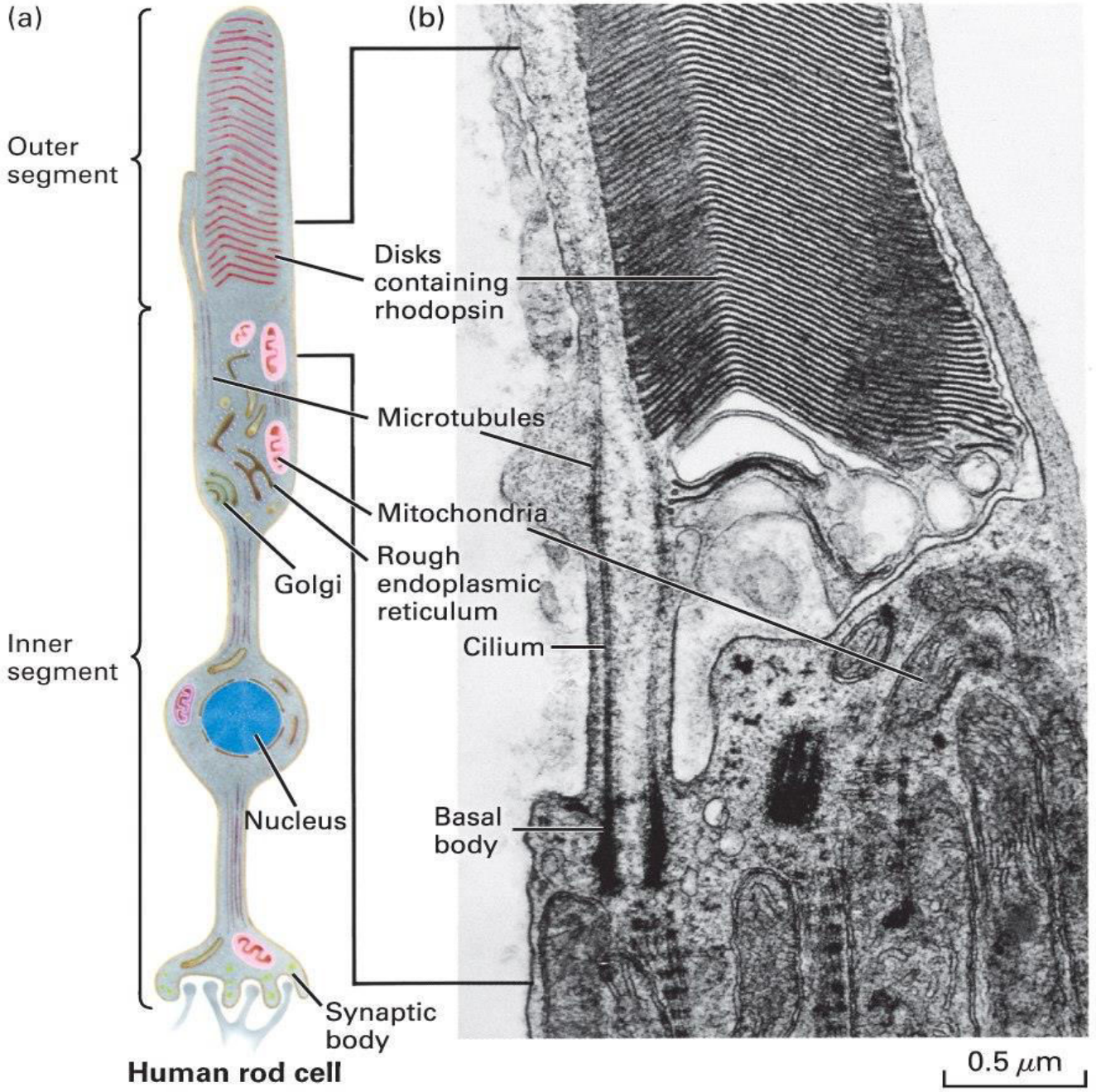
RLR are a family of proteins comprise of G protein-coupled receptors and are extremely sensitive to light. It activates the G protein transducin (G_t) to activate the visual phototransduction pathway.

Mutation of the rhodopsin gene is a major contributor to various retinopathies.

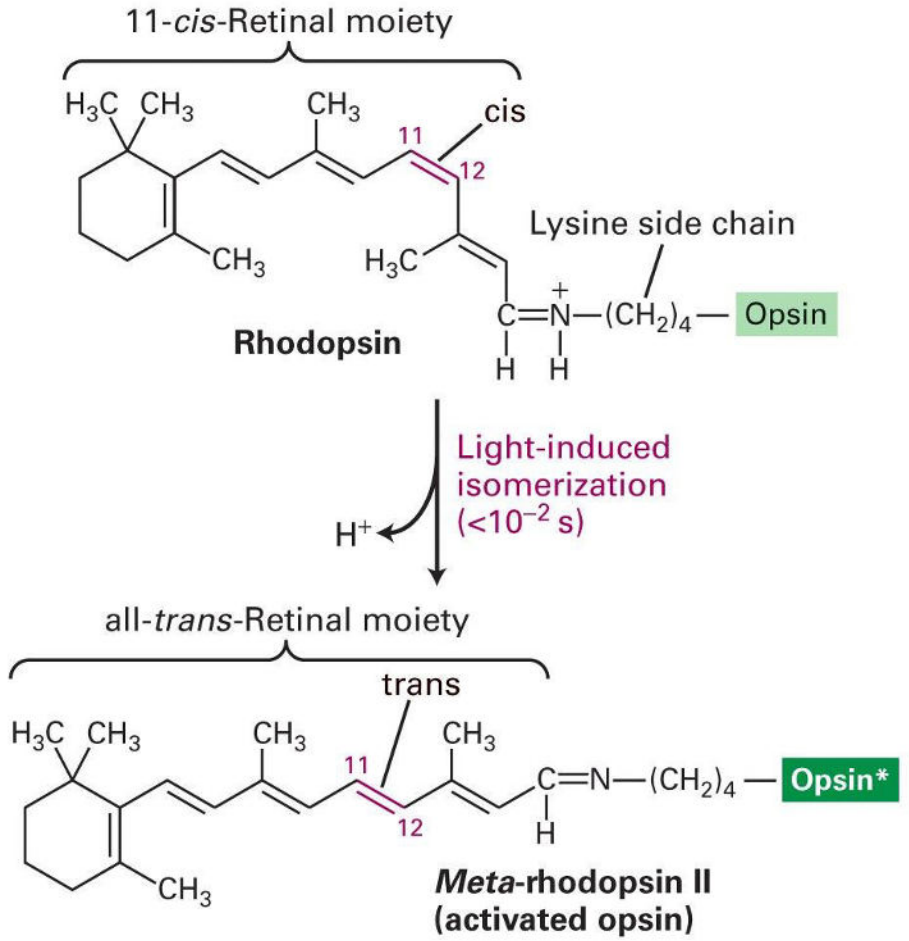
Rhodopsin is a light-activated GPCR found in the rod cells of the eye. Rhodopsin molecules are located within membrane disks in the outer segments of rod cells

About 10^7 copies of rhodopsin occur per cell. Rod cells are important in capture of low intensity light having a broad range of wavelengths.

Closely related color pigment receptors that respond to more limited regions of the visual spectrum (i.e., blue, green, & red light) are present in cone cells



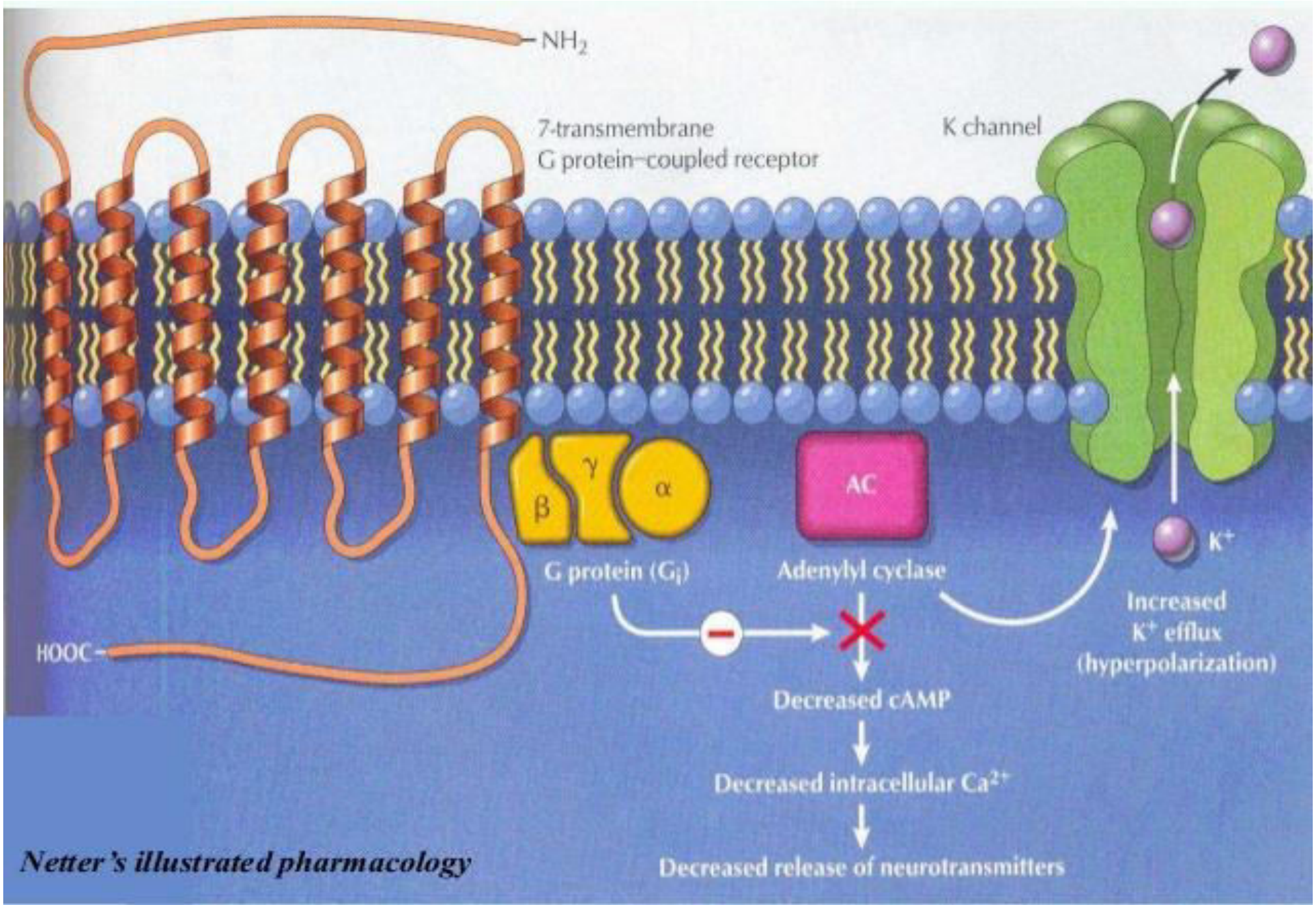
Rhodopsin consists of the protein opsin bound to the visual pigment, 11-*cis*-retinal. Like other GPCR family members, rhodopsin is a 7-transmembrane segment protein. Rhodopsin signaling is initiated when the retinal chromophore absorbs a photon of light. Light absorption causes an electronic rearrangement and isomerization from 11-*cis*- to all-*trans*-retinal . The isomerization triggers a conformational change in opsin, leading to activation of a bound G protein known as transducin (G_t). All-*trans*-retinal is released and recycled to 11-*cis*-retinal which later recombines with opsin.



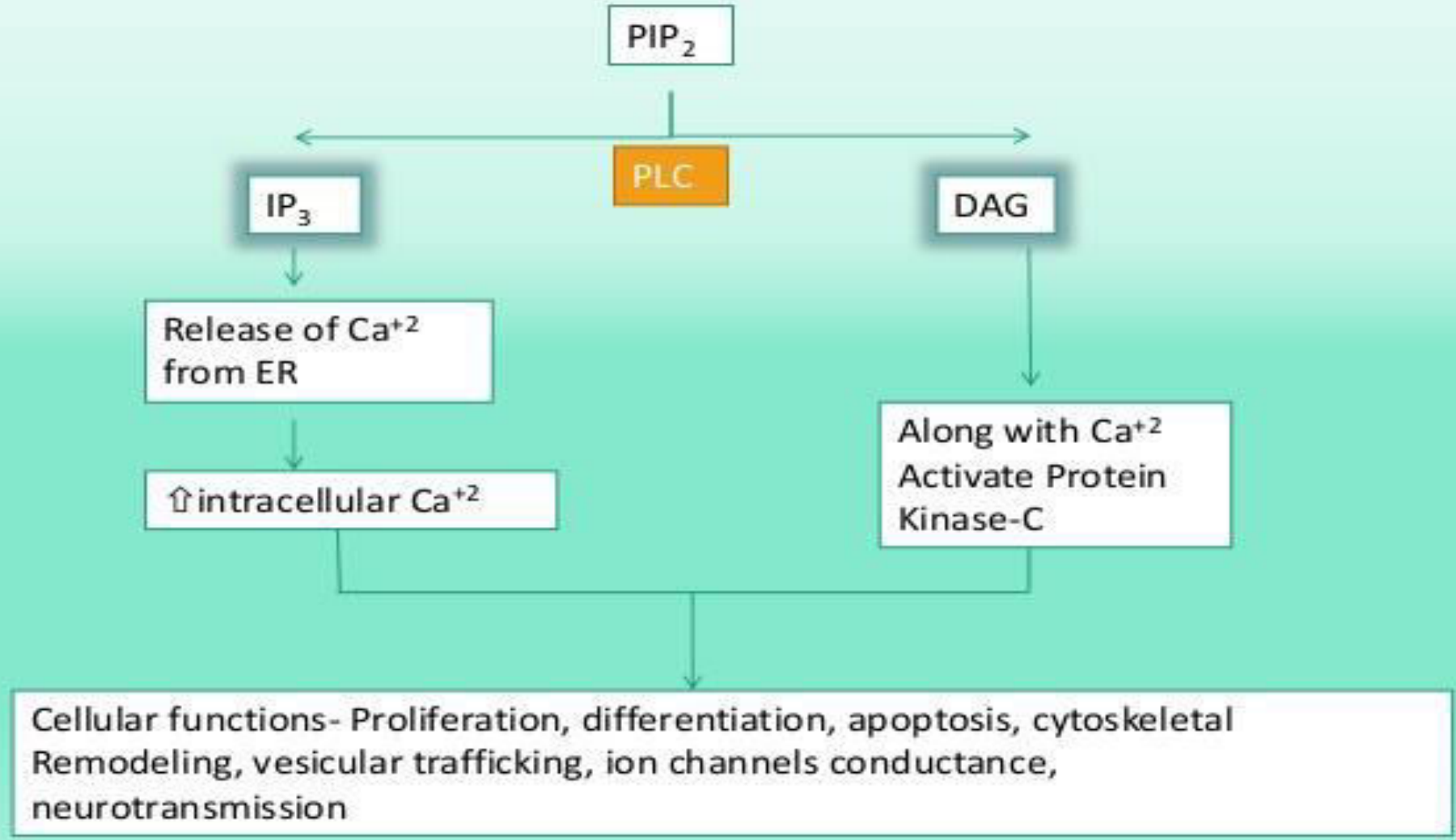
Some G Protein directly regulate ion channels

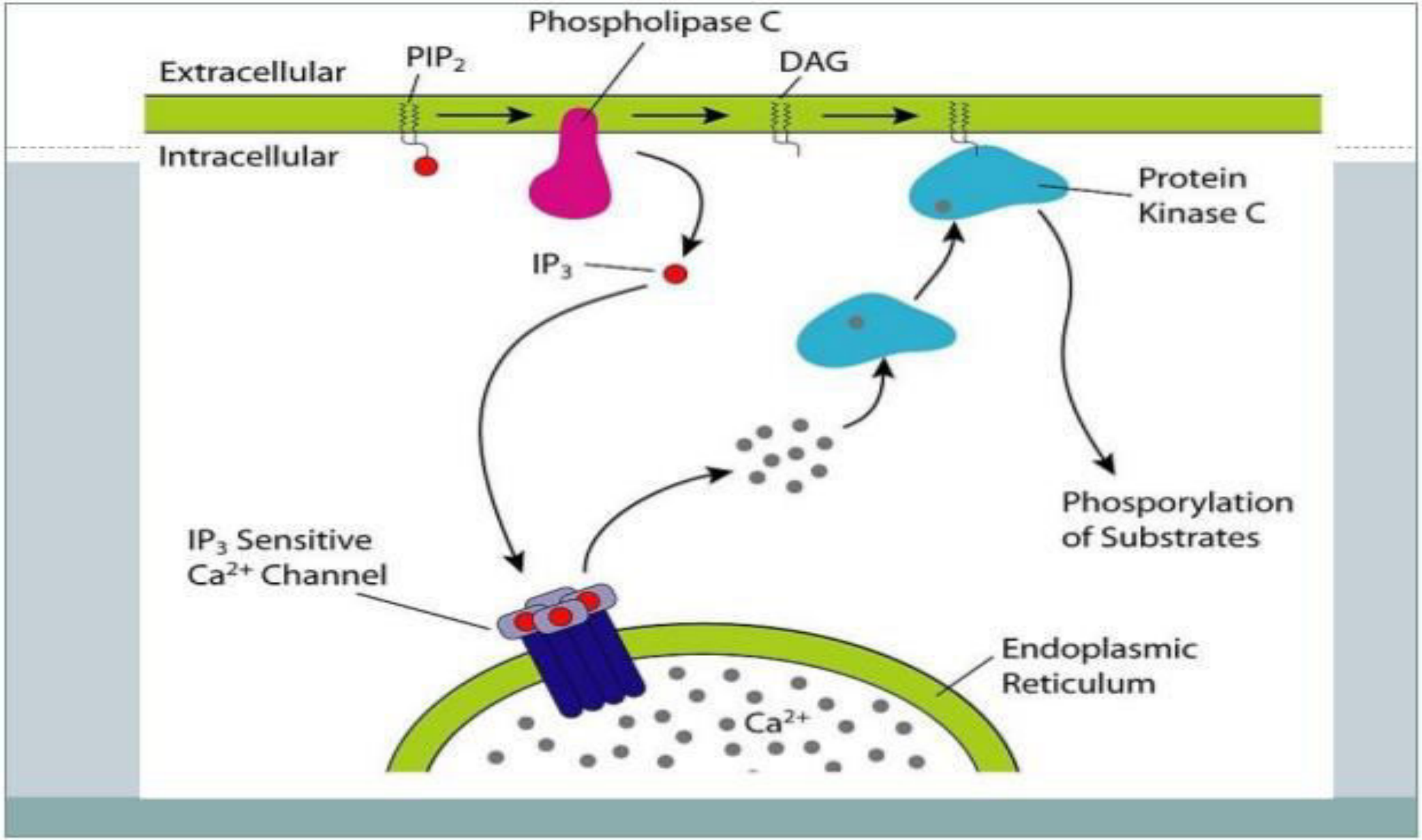
ex: Acetylcholine receptor present on Heart Muscle cells.

- This G protein is designated as Gi.
- i as the alpha subunit inhibits adenylyl cyclase.
- The Beta gamma subunit act directly open K+ channels in the plasma membrane.
- This effects in slowing in heart muscle contraction.


NH2
7-transmembrane
G protein–coupled receptor
K channel
β
γ
α
AC
G protein (Gi)
Adenylyl cyclase
K+
Increased
K+ efflux
(hyperpolarization)
HOOC
Decreased cAMP
Decreased intracellular Ca2+
Decreased release of neurotransmitters
Netter's illustrated pharmacology

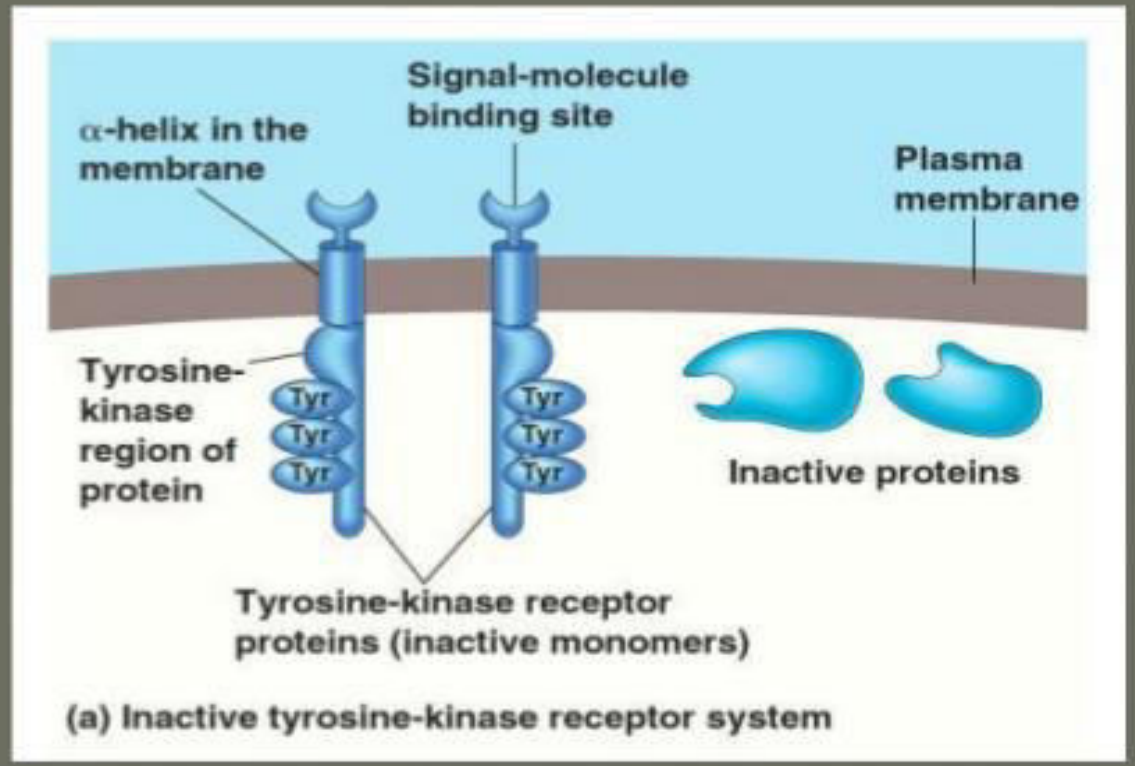
Phospholipase-c signaling system

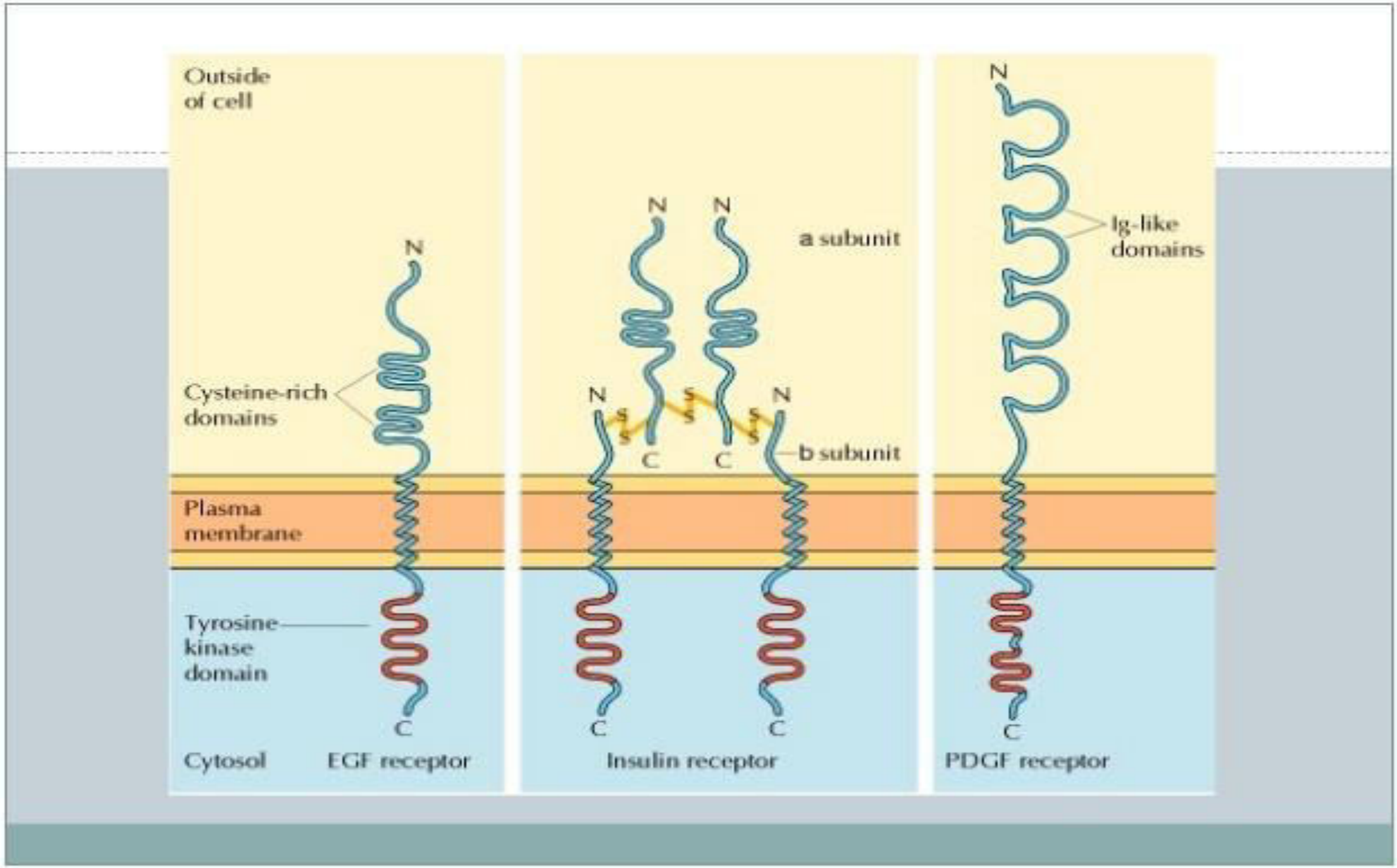


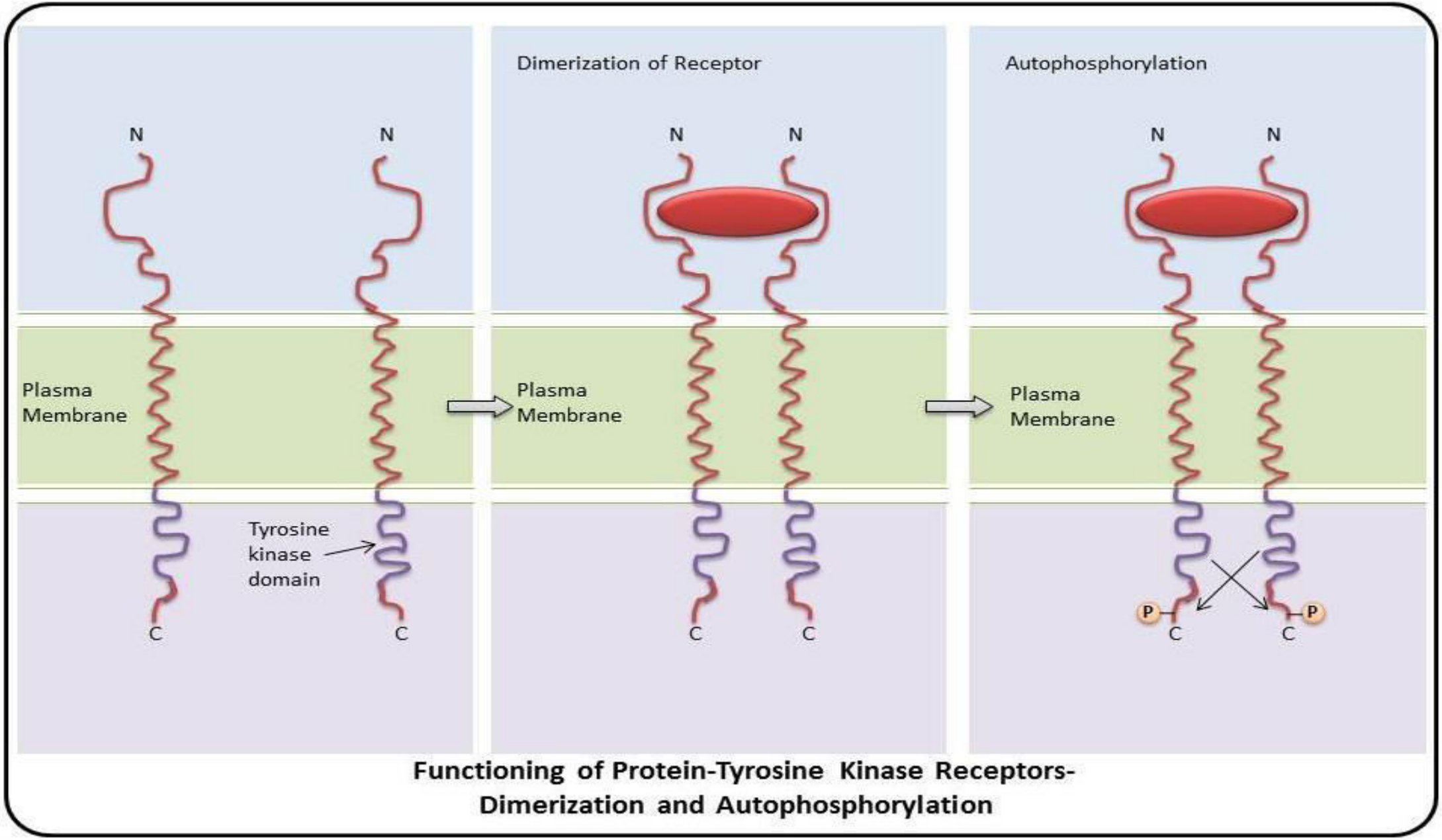

Phospholipase C
Extracellular
PIP2
DAG
Intracellular
Protein
Kinase C
IP3
Phosporylation
of Substrates
IP3 Sensitive
Ca2+ Channel
Endoplasmic
Reticulum
Ca2+

Tyrosine Kinase Receptors

- Extracellular ligand-binding domain.
- Cytosolic domain with tyrosine kinase (tk) enzyme activity.

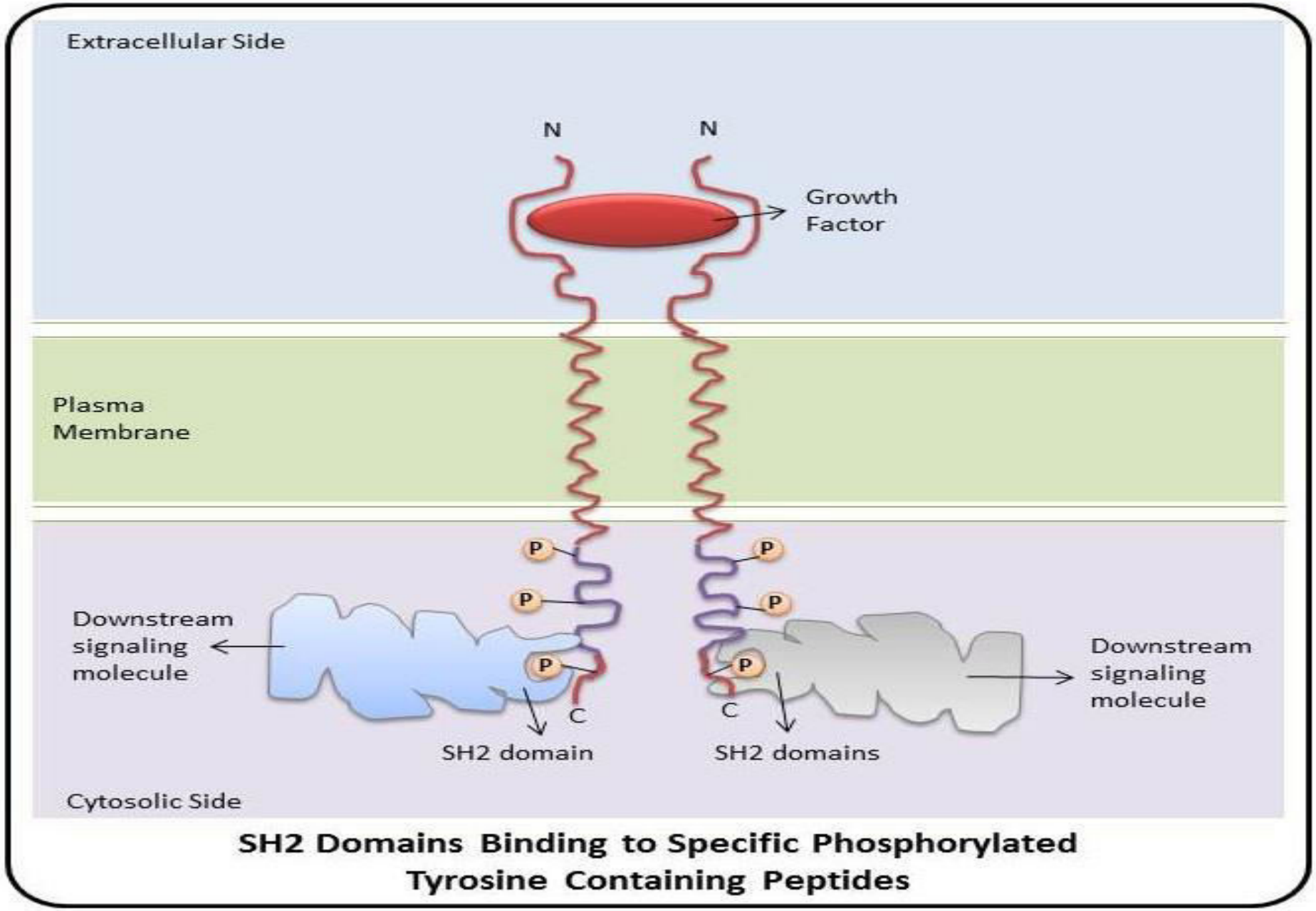



Outside of cell
N
Cysteine-rich domains
Plasma membrane
Tyrosine kinase domain
C
Cytosol
EGF receptor
N
N
a subunit
N
S
S
S
S
S
S
N
C
C
b subunit
C
C
Insulin receptor
N
Ig-like domains
C
PDGF receptor



Functioning of Protein-Tyrosine Kinase Receptors- Dimerization and Autophosphorylation

Namrata Heda

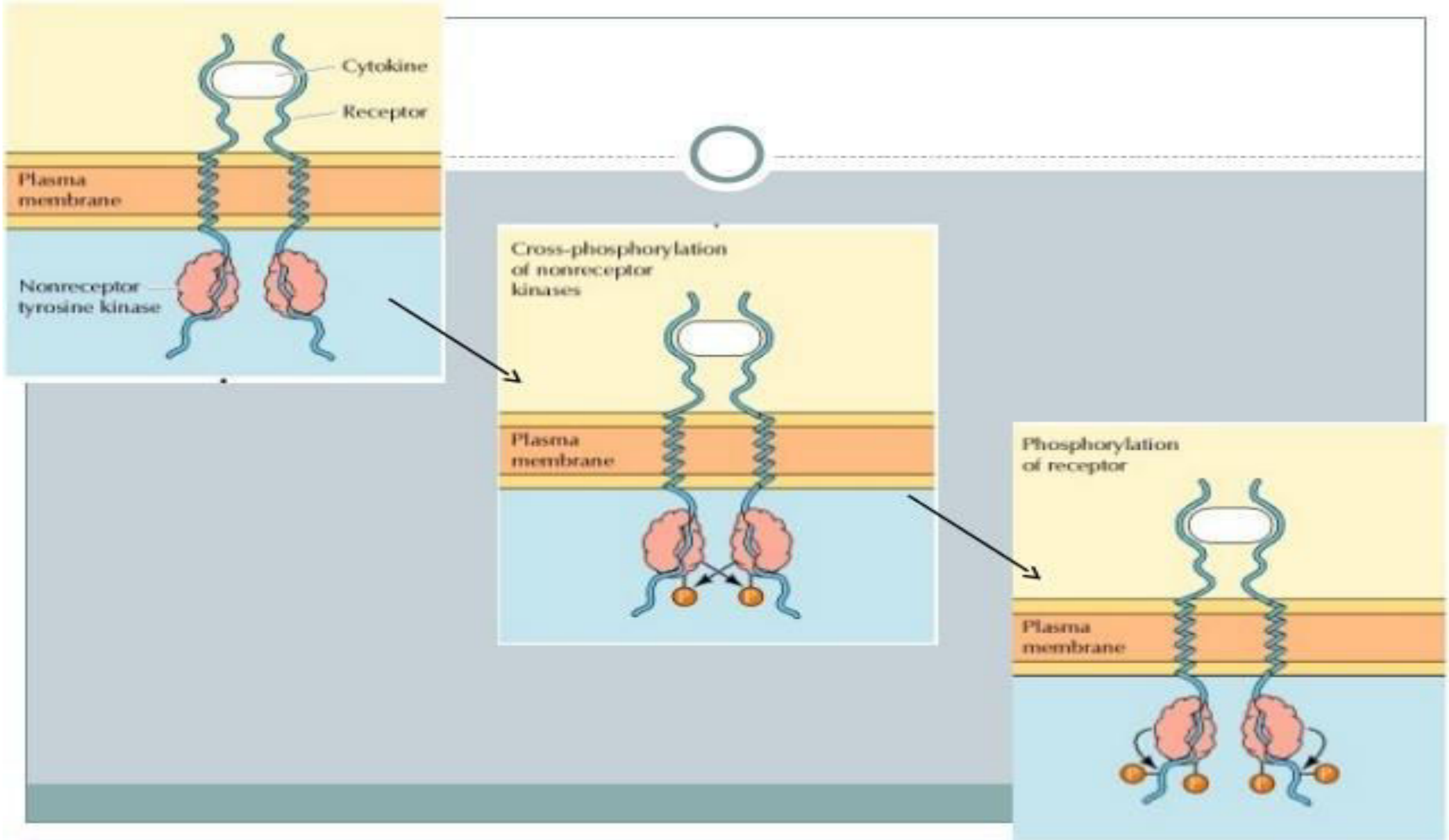


SH2 Domains Binding to Specific Phosphorylated Tyrosine Containing Peptides

Namrata Heda

Cytokine Receptors

- called the cytokine receptor superfamily.
- includes the receptors for most cytokines like interleukin2 and erythropoietin and for some polypeptide hormones (growth hormone)
- Associated with non-receptor protein kinases (protein tyrosine kinases) which get activated on ligand binding.


Cytokine
Receptor
Plasma membrane
Nonreceptor tyrosine kinase
Cross-phosphorylation of nonreceptor kinases
Plasma membrane
Phosphorylation of receptor
Plasma membrane

Cytokine -mediated effects

- Cell growth.
- Cell differentiation.
- Cell death.
- Induce non-responsiveness to other cytokines/cells.
- Induce responsiveness to other cytokines/cells.
- Induce secretion of other cytokines.

Cytokine Receptors

- Cytokine receptors are receptors that bind cytokines.
- Binding to specific receptors is essential for cytokines to carry out their functions.
- Cytokine receptors may be both membrane-bound and soluble.
- Soluble cytokine receptors are extremely common regulators of cytokine function.

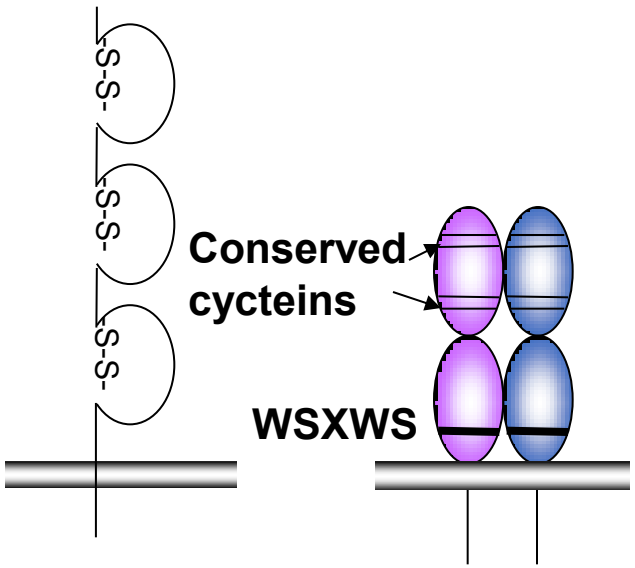
Cytokine Receptors

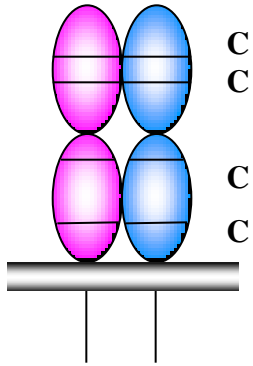
- **Type I cytokine receptors (Hematopoietin)**
- **Type II cytokine receptors**
- **Ig superfamily**
- **TNF receptors**
- **Seven-transmembrane α-helical receptors**

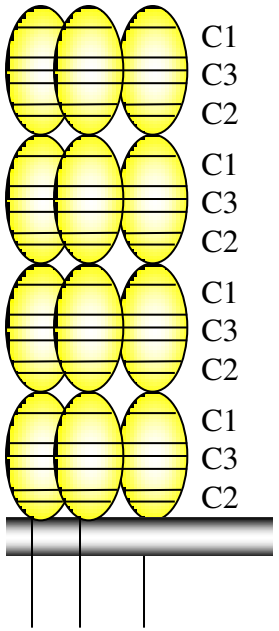
*Classification of cytokine receptors based on structural homologies among the extracellular cytokine-binding domain.

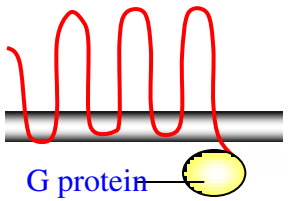
Cytokine receptor families and ligands

Ig superfamily	Type I cytokine-R	Type II cytokine-R	TNF-R	Chemokine-R









IL-1 M-CSF C-kit	IL-2 IL-3 IL-4 IL-5 IL-6 IL-7 IL-9 IL-11 IL-12 IL-13 IL-15 OSM GM-CSF G-CSF EPO	IFN-α IFN-β IFN-γ IL-10	TNF-α TNF-β CD40L NGF FASL	IL-8 RANTES MIP-1 PF4

SECOND MESSENGERS

- **Second messenger**, molecule inside cells that acts to transmit signals from a receptor to a target.

- The term *second messenger* was coined upon the discovery of these substances in order to distinguish them from hormones and other molecules that function outside the cell as “first messengers” in the transmission of biological information.

- Many second messenger molecules are small and therefore diffuse rapidly through the cytoplasm, enabling information to move quickly throughout the cell. As elements of signaling pathways, second messengers can serve to integrate information when multiple independent upstream inputs influence the rates of synthesis and degradation of the second messenger.

- In addition, second messengers can have multiple downstream targets, thereby expanding the scope of signal transmission.

Cells respond to the environment:

Signal Transduction

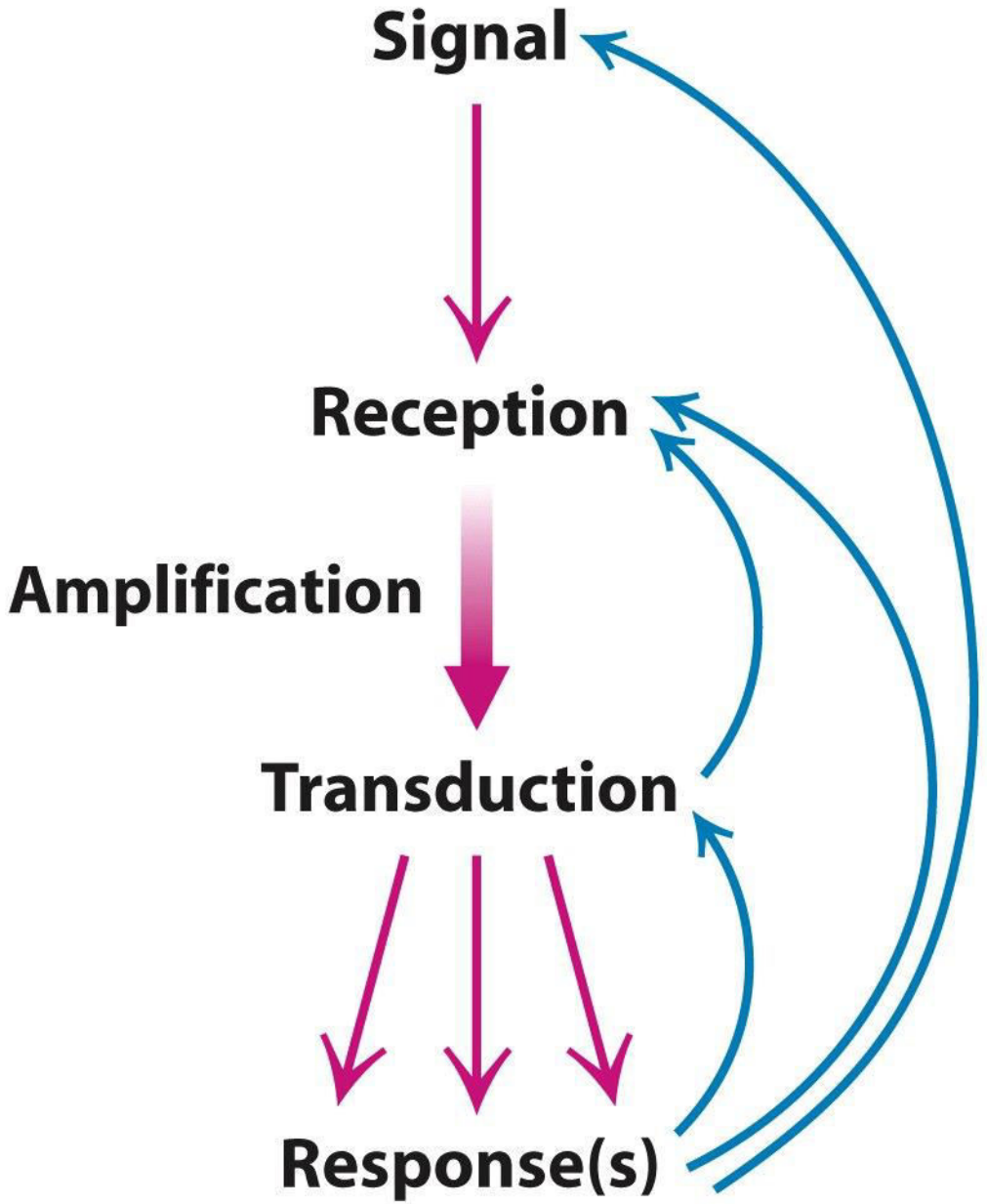
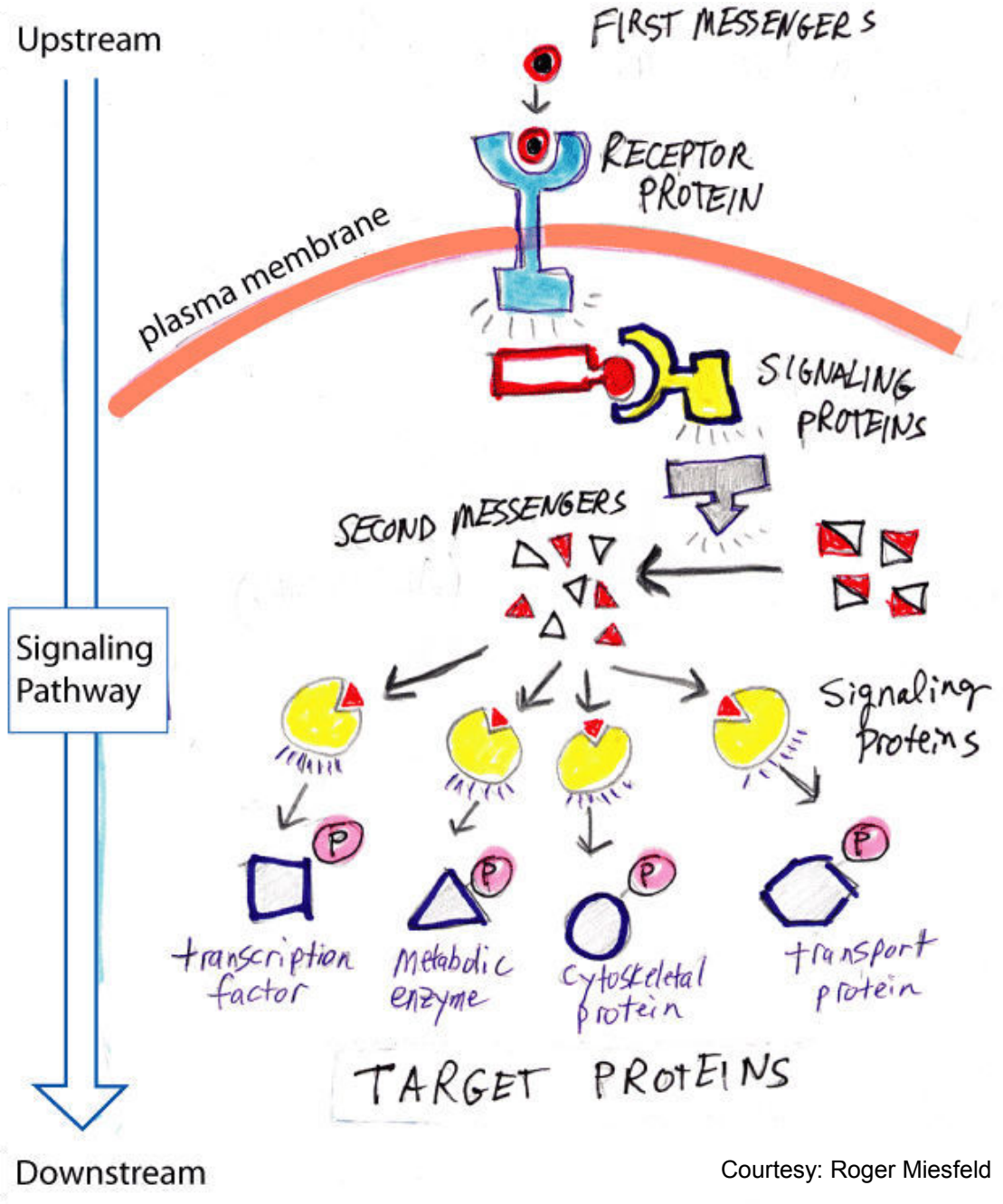


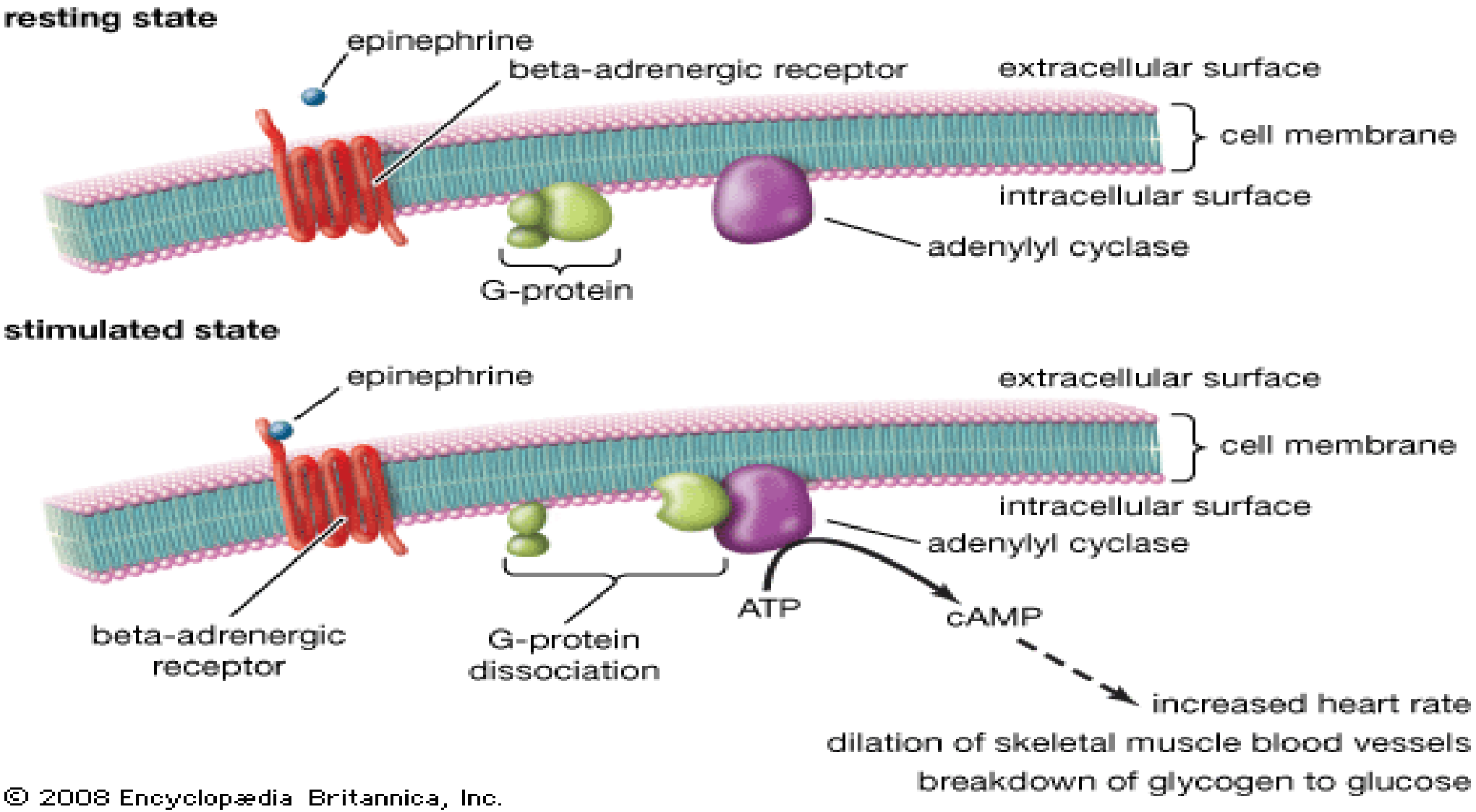
Figure 14-2
Biochemistry, Sixth Edition

The term **signal transduction** refers to the biochemical mechanism responsible for “transmitting” extracellular signals inside the cell, which ultimately lead to the activation of target proteins that control metabolic pathways or regulate gene expression.

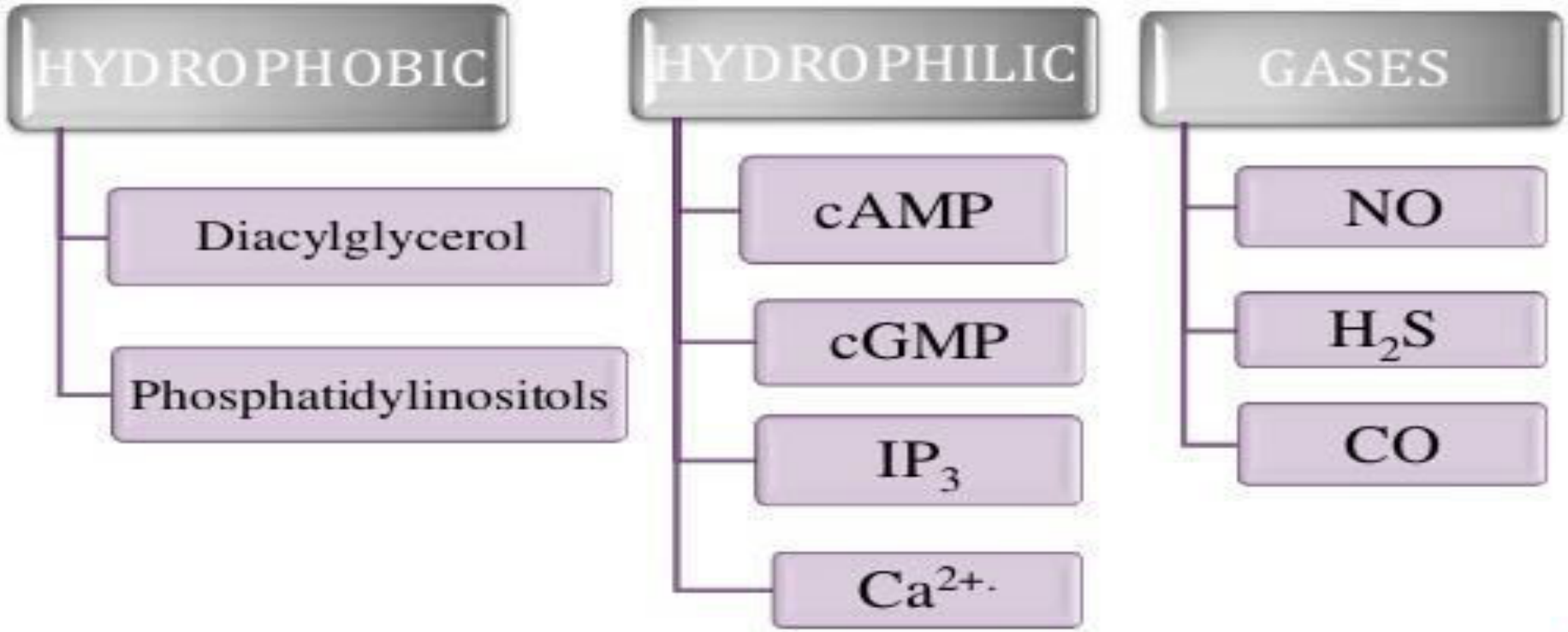


Courtesy: Roger Miesfeld

Epinephrine-stimulated cAMP synthesis



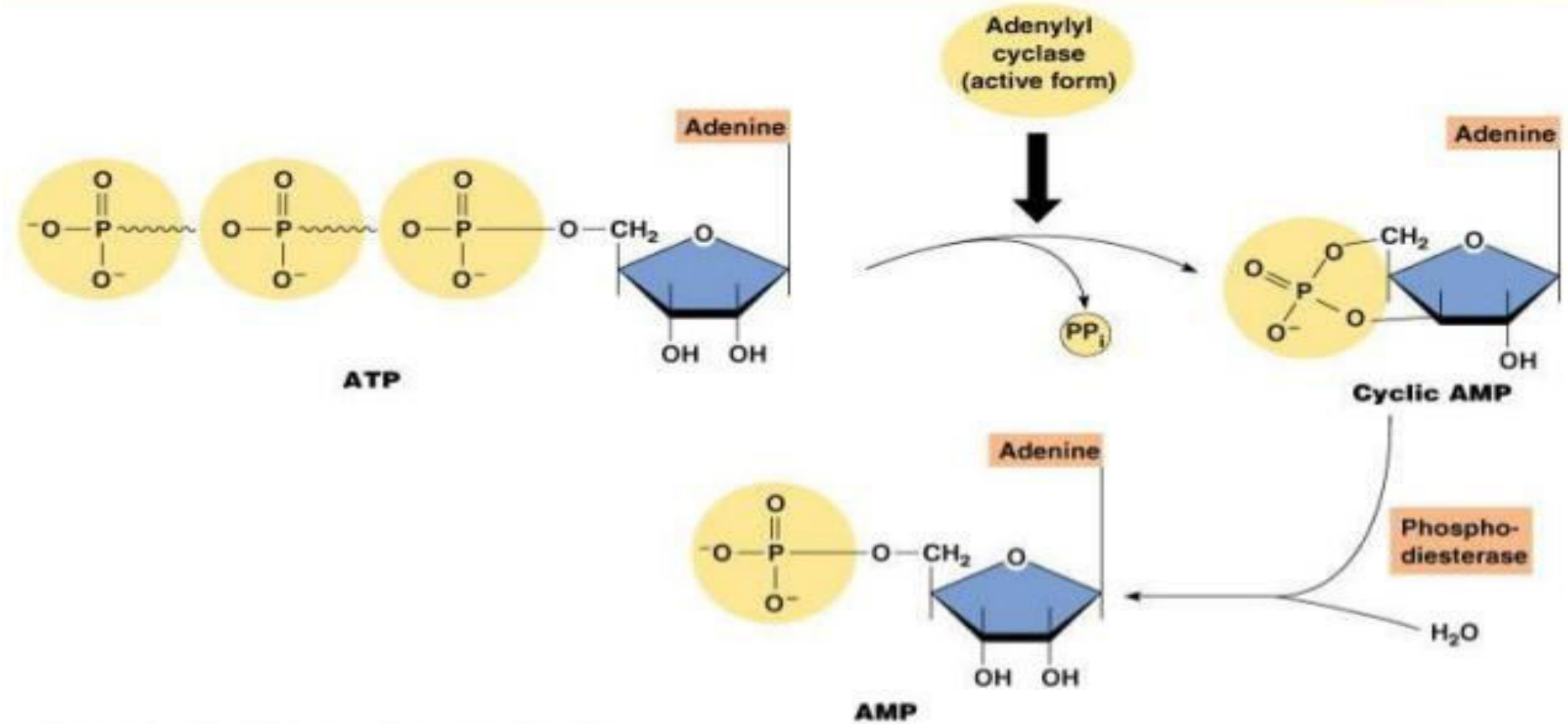
TYPES OF SECOND MESSENGERS



CYCLIC AMP

- cAMP is a second messenger that is synthesized from ATP by the action of the enzyme **adenylyl cyclase**.
- Binding of the hormone to its receptor activates a **G protein** which, in turn, activates adenylyl cyclase.
- Leads to appropriate response in the cell by either (or both):
  - using **Protein Kinase A (PKA)** — a c**A**MP-dependent protein kinase that phosphorylates target proteins;
  - cAMP binds to a protein called **CREB (cAMP response element binding protein)**, and the resultant complex controls transcription of genes.
- Eg.of cAMP action - adrenaline, glucagon, LH

Cyclic AMP



ATIVATE ADENYLYL CYCLASE

- Epinephrine (β_1, β_2)
- Norepinephrine
- Glucagon
- CRH
- ACTH
- MSH
- TSH
- hCG
- LH
- FSH
- LPH
- PTH
- CALCITONIN
- AVP/ADH

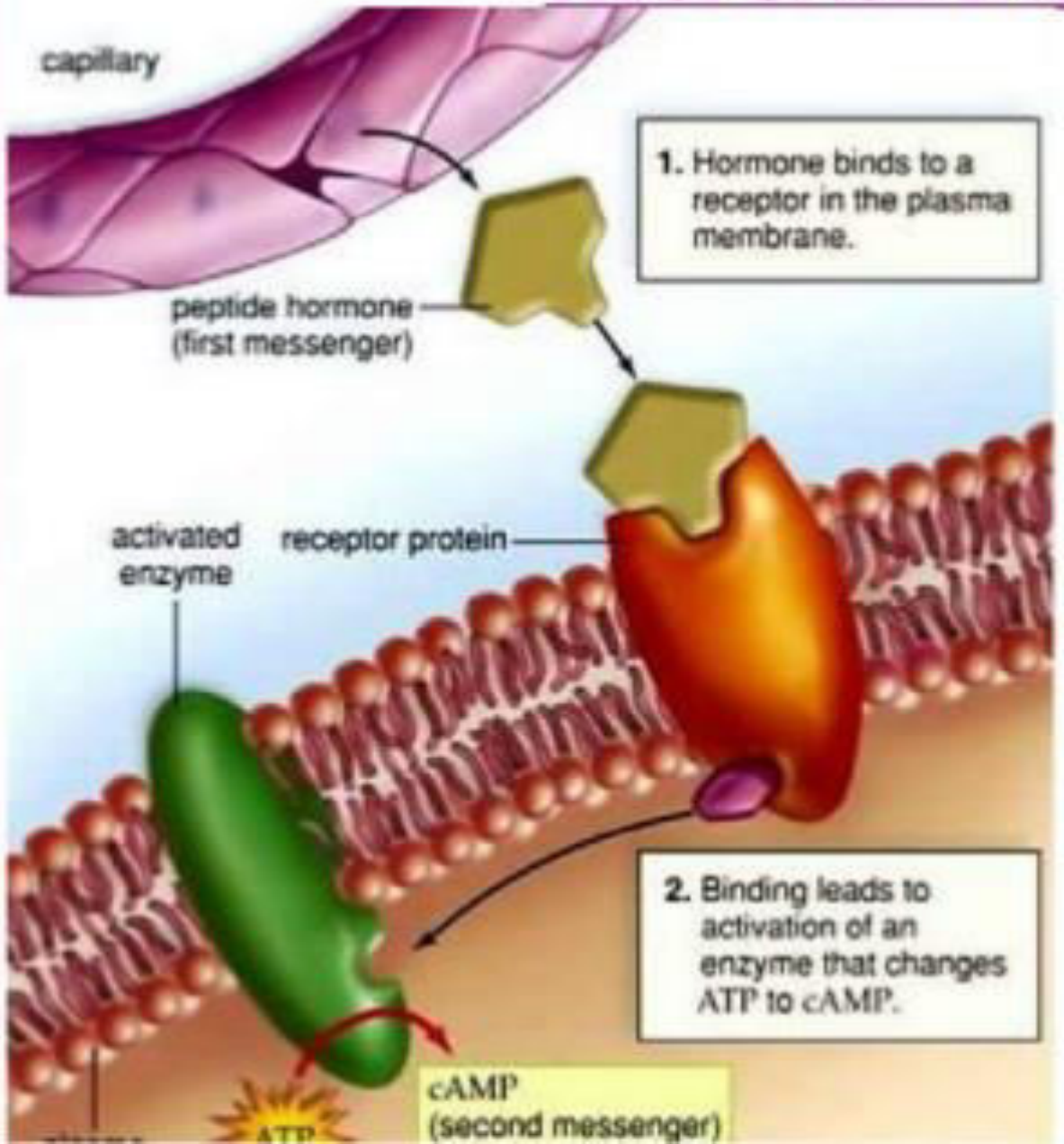
INHIBIT ADENYLYL CYCLASE

1. Somatostatin
2. Acetylcholine M_2
3. Angiotensin II
4. Epinephrine α_2

EFFECTS OF CYCLIC AMP

1. ALTERED GLYCOGEN METABOLISM BY ENZYME REGULATION
2. ALTERED GENE TRANSCRIPTION
3. HORMONE ESTRADIOL SECRETION
4. ALTERED ION TRANSPORT - HCL SECRETION IN STOMACH
5. WATER REABSORPTION BY ANTI DIURETIC HORMONE
6. CAFFEINE – PHOSPHODIESTERASE INHIBITORS
7. DRUGS – SALBUTAMOL , THEOPHYLLINE

Glucose Mobilization: An Example of a Response Induced by cAMP

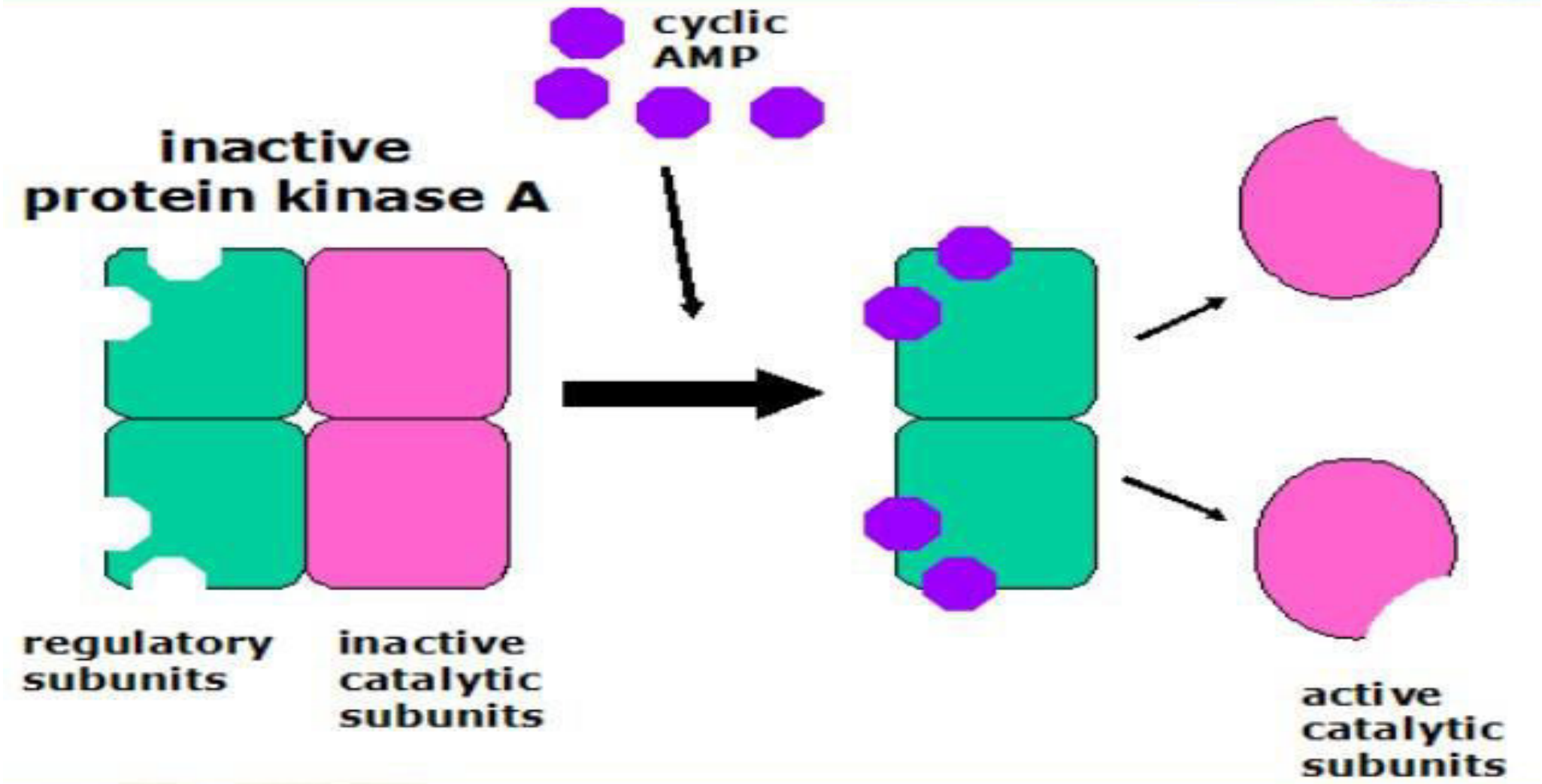


- Binding of hormone
- Activation of enzyme and formation of cAMP.
- cAMP binds to PKA & activates it.
- PKA phosphorylates

  2 enzymes:

  1. **Phosphorylase kinase** – phosphorylates glycogen phosphorylase- stimulates glycogen breakdown.
  2. **Glycogen synthetase** – inhibition – prevents conversion of glucose to glycogen.

PROTEIN KINASE A - ACTIVATION



ENZYME REGULATION

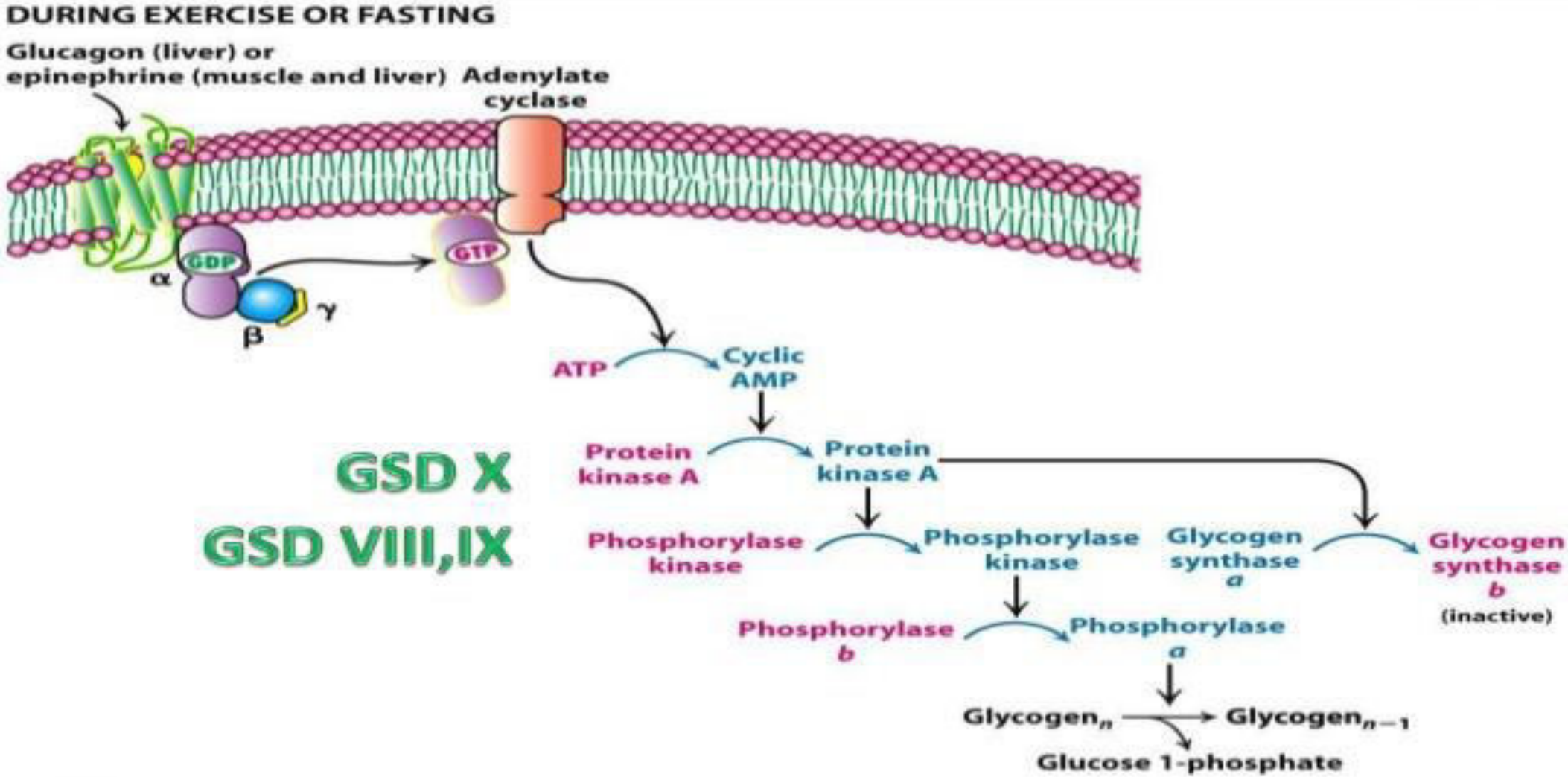
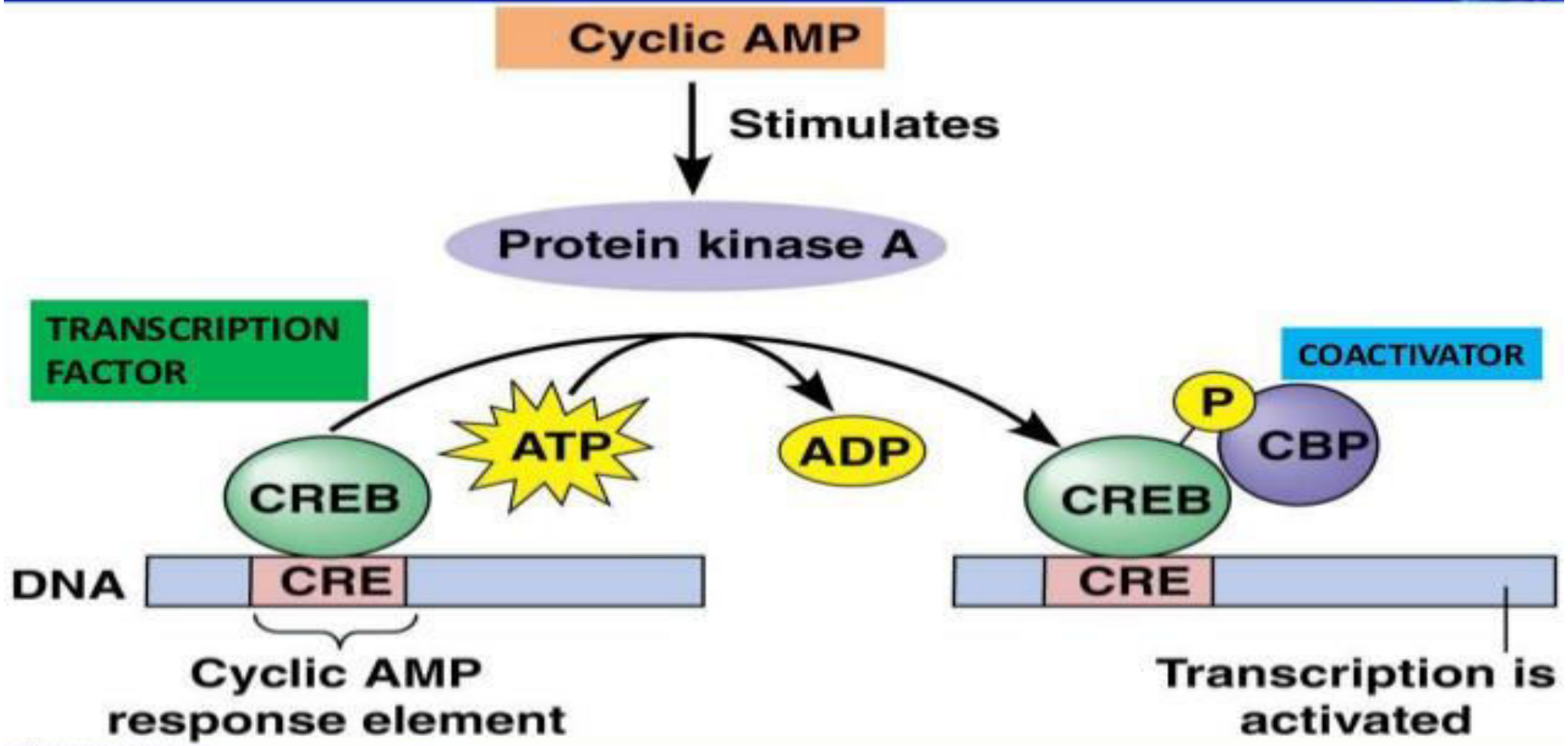
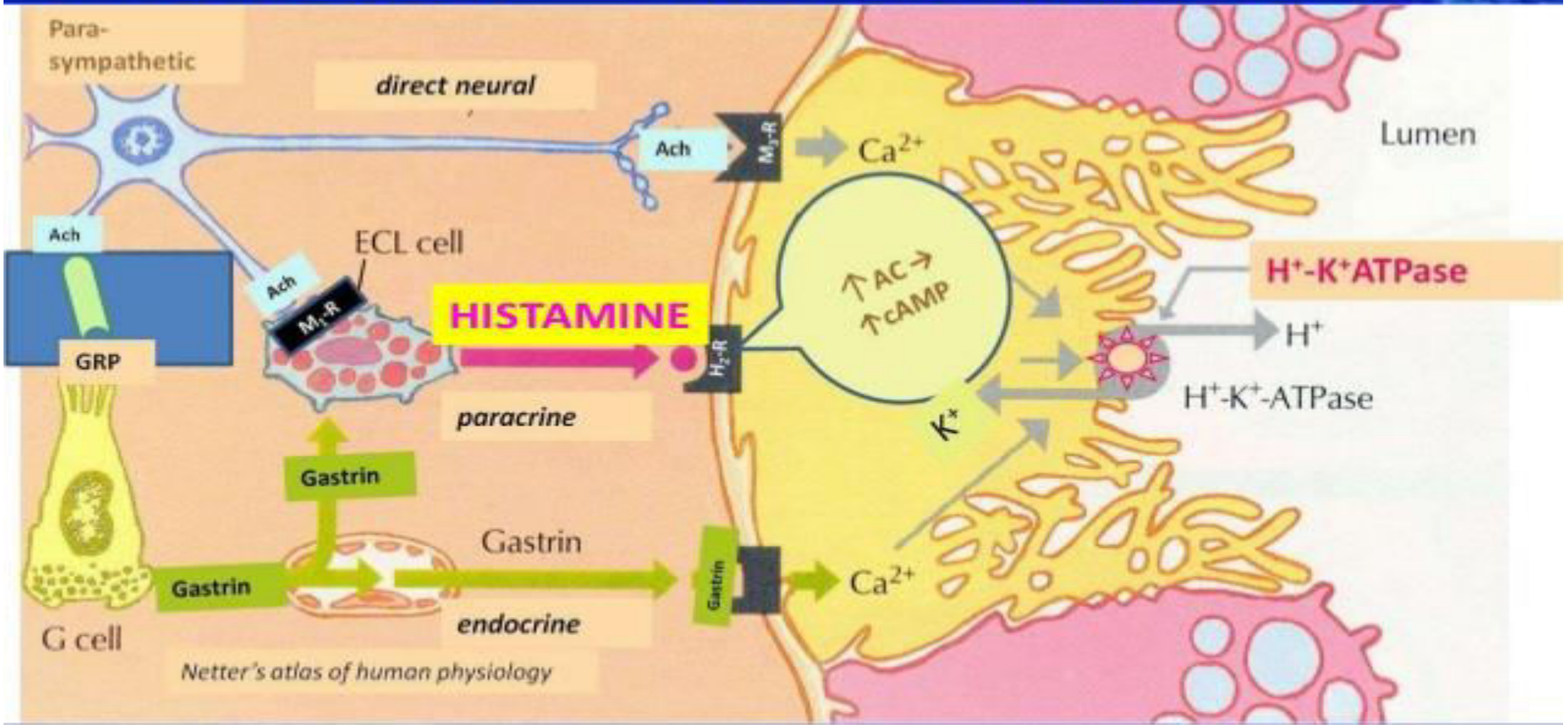


Figure 21.19
Biochemistry, Seventh Edition

GENE TRANSCRIPTION



STOMACH - HCL SECRETION



- Activation of histamine through H_2 receptor cause increase in intracellular cAMP level while Ach through M_3 receptor and gastrin through CCK2 receptor increases intracellular calcium level. These receptors are present on basolateral side of membrane.

- Increased cAMP level results in increased protein kinase A. Protein kinase A phosphorylates proteins involved in the transport of H^+/K^+ ATPase from the cytoplasm to the cell membrane. This causes resorption of K^+ ions and secretion of H^+ ions. The pH of the secreted fluid can fall by 0.8.

GMP

The cGMP Signal Transduction Pathway:

Two forms of guanylate cyclase:

1) Membrane-bound (particulate; pGC)

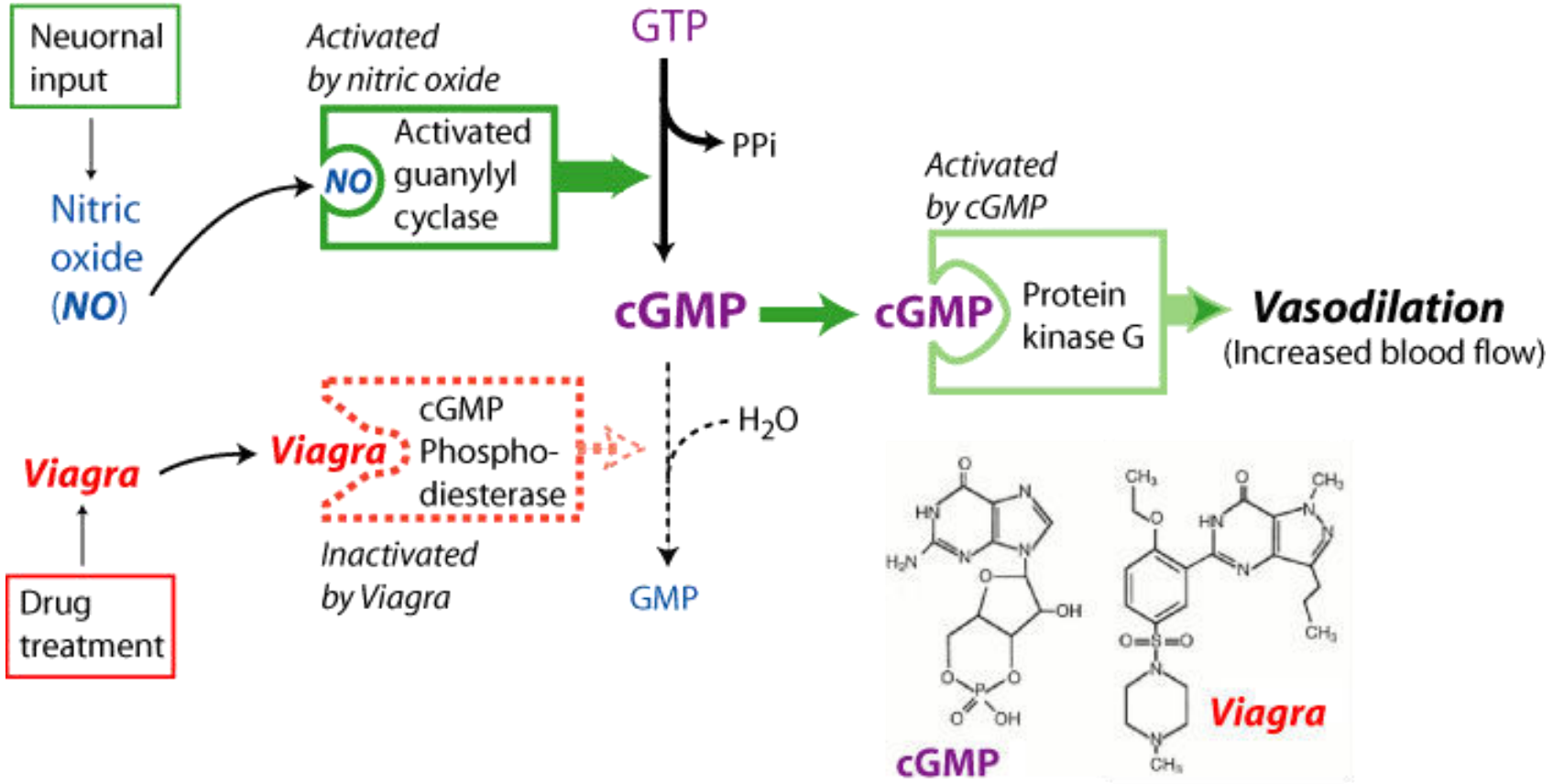
- Activated by ANF (atrial natriuretic factor)
  - ANF released when BP elevated

2) Cytosolic (soluble; sGC)
   - Activated by nitric oxide
   - NO produced from arginine by NO synthase

Nitroglycerine slowly produces NO, relaxes cardiac and vascular smooth muscle, reduces angina.

Another second messenger important in signal transduction is cyclic GMP (cGMP)

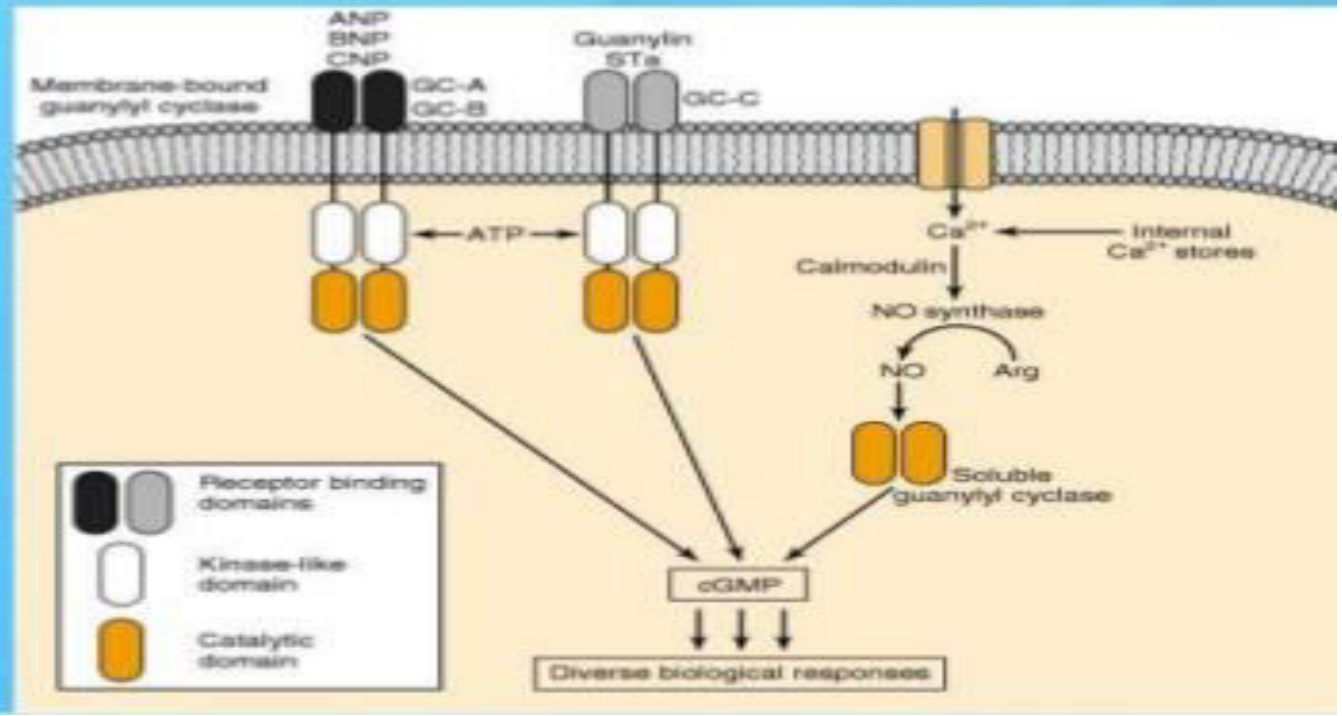
Produced from GTP by the enzyme guanylyl cyclase. The cGMP analog Sildenafil, also know as **Viagra**, is used to treat sexual dysfunction by inhibiting the activity of cGMP phosphodiesterase (PDE). The molecular structure of sildenafil is similar to cGMP and binds tightly to cGMP PDE.



Courtesy: Roger Miesfeld

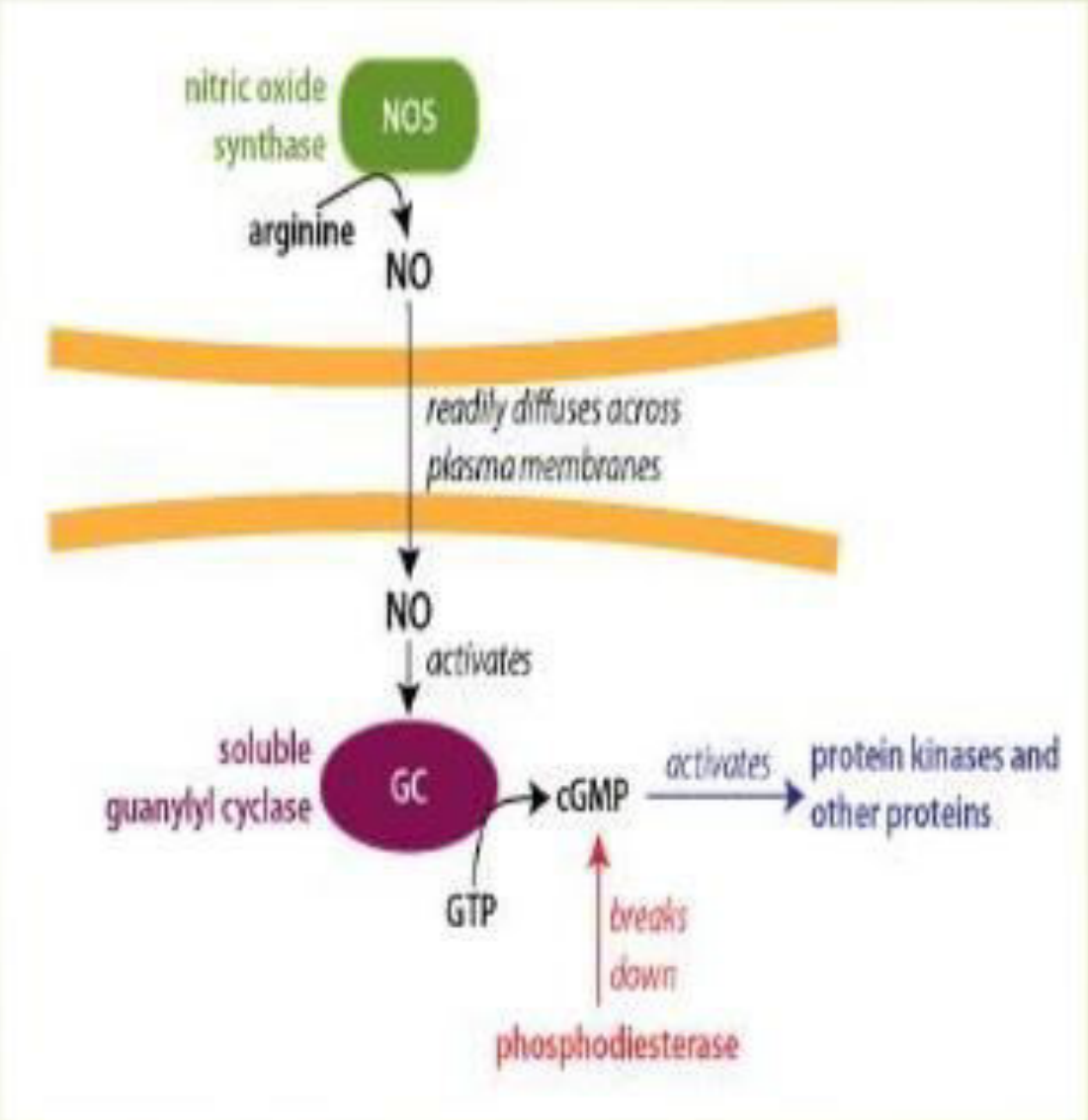
Guanylate Cyclase:

- ✓ Membrane-bound (type 1) & soluble (type 2) forms
- ✓ Membrane bound⟶ activated by ligands
- ✓ Soluble⟶ activated by NO
- ✓ Catalyzes reaction of GTP to cGMP

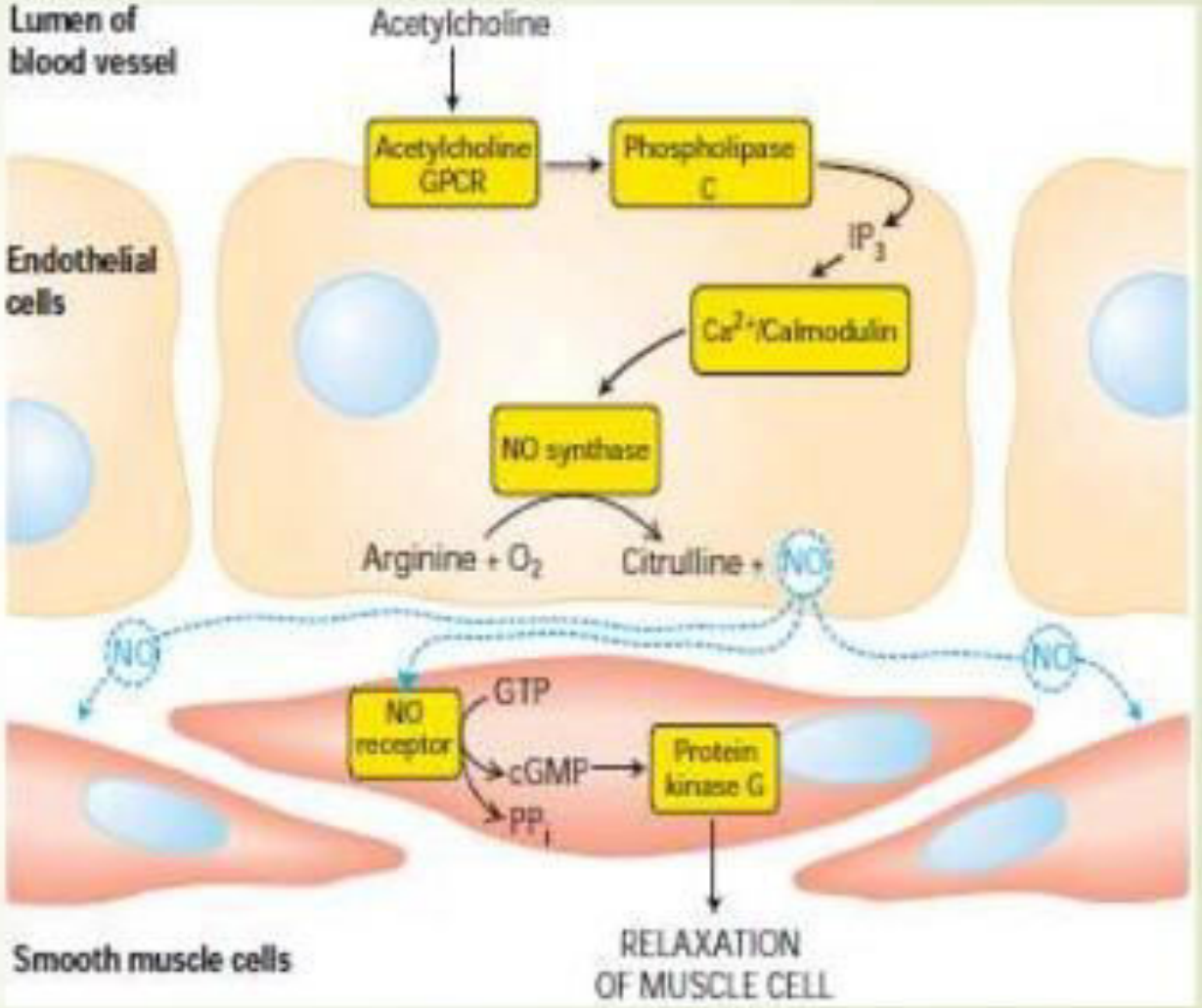


Nitric Oxide

- **Nitric oxide** (NO) is a **gas**, diffuse through the plasma membrane and affect nearby cells.
- Synthesized from **arginine** and **oxygen** by the **NO synthase**.
- NO then activate soluble guanylyl cyclase, to produce **cGMP**.



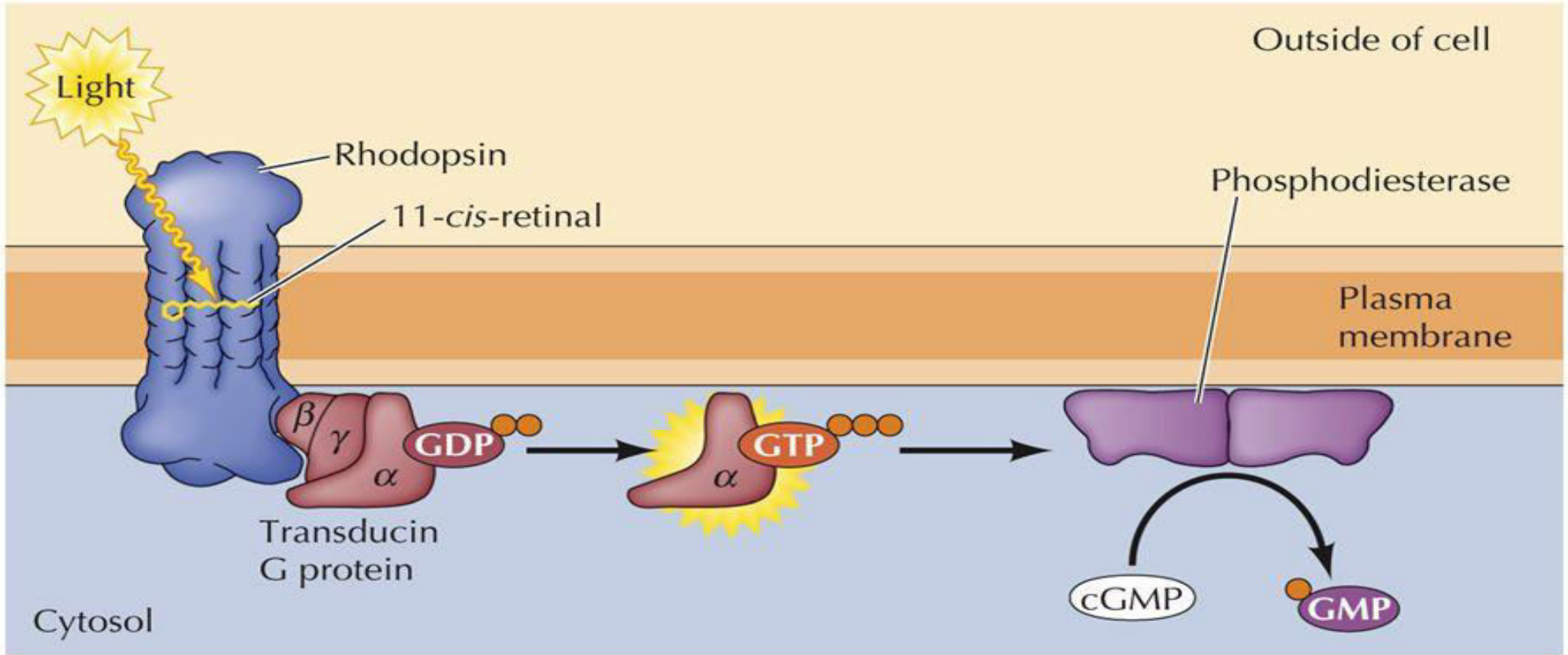
- The function of NO is the **dilation of blood vessels.**
- The **acetylcholine** (neurotransmitter) acts on **endothelial cells** to stimulate NO synthesis.
- NO, diffuses to **neighboring smooth muscle** cells where it interacts with the **guanylyl cyclase**.
- This increase enzymatic activity resulting in the synthesis of **cGMP**.
- The **cGMP** then **induces muscle relaxation** and **blood vessel dilation**.



Downstream reactions of cGMP:

- Activation of Protein Kinase G
- cGMP gated ion channels
- cGMP-modulated Phosphodiesterase

Figure 16.19 Role of cGMP in photoreception

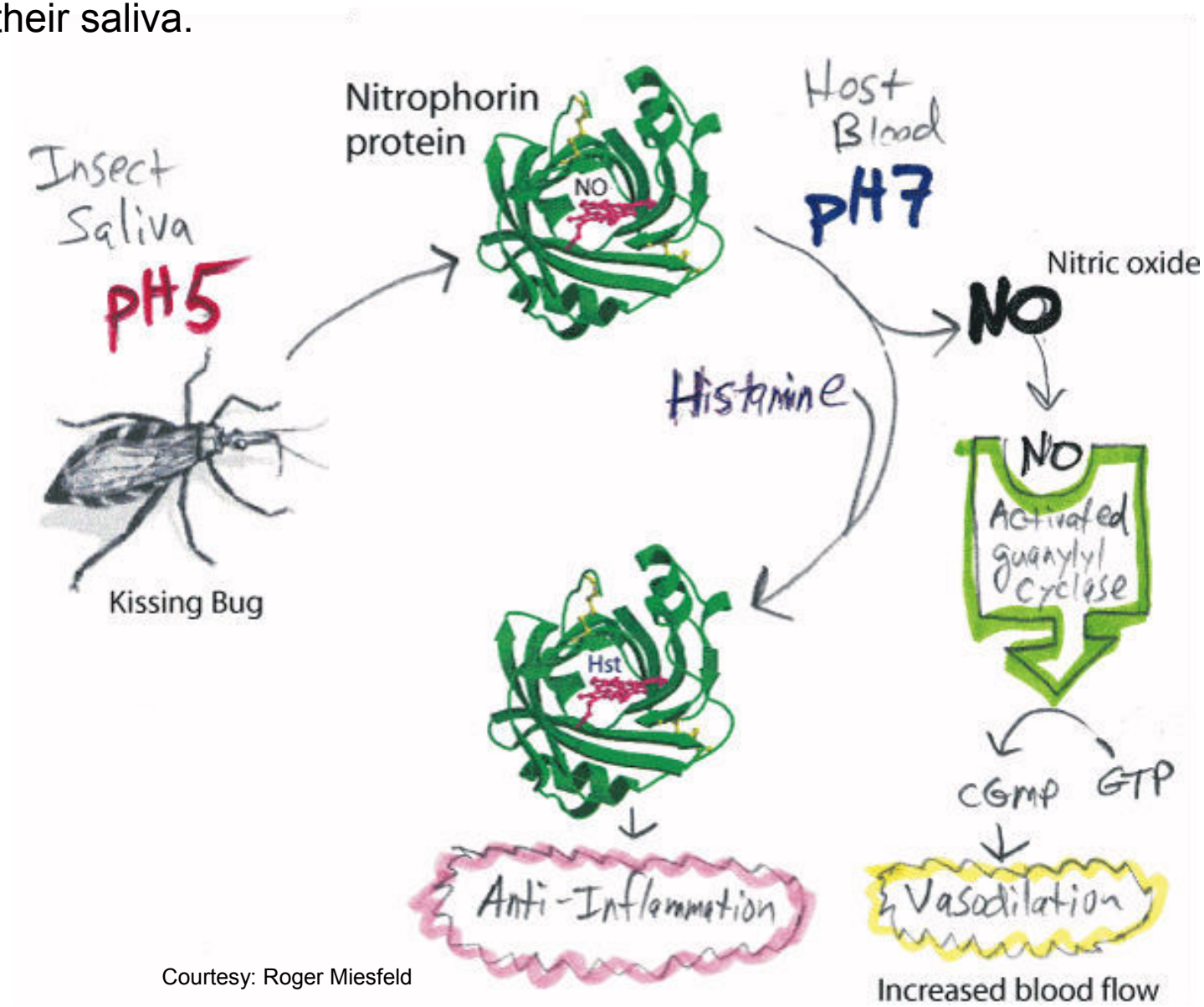


THE CELL: A MOLECULAR APPROACH 7e, Figure 16.19

- ✓ Nitric Oxide Synthase (NOS) exists as 4 isoforms

- ➢ neuronal type I isoform (**nNOS**)
- ➢ inducible type II isoform (**iNOS**)
- ➢ endothelial type III isoform (**eNOS**)
- ➢ mitochondrial isoform (**mtNOS**)

The Kissing Bug, *Rhodnius prolixus*, delivers NO to their victims by injecting heme-containing proteins called nitrophorins that carry NO into the wound along with their saliva.

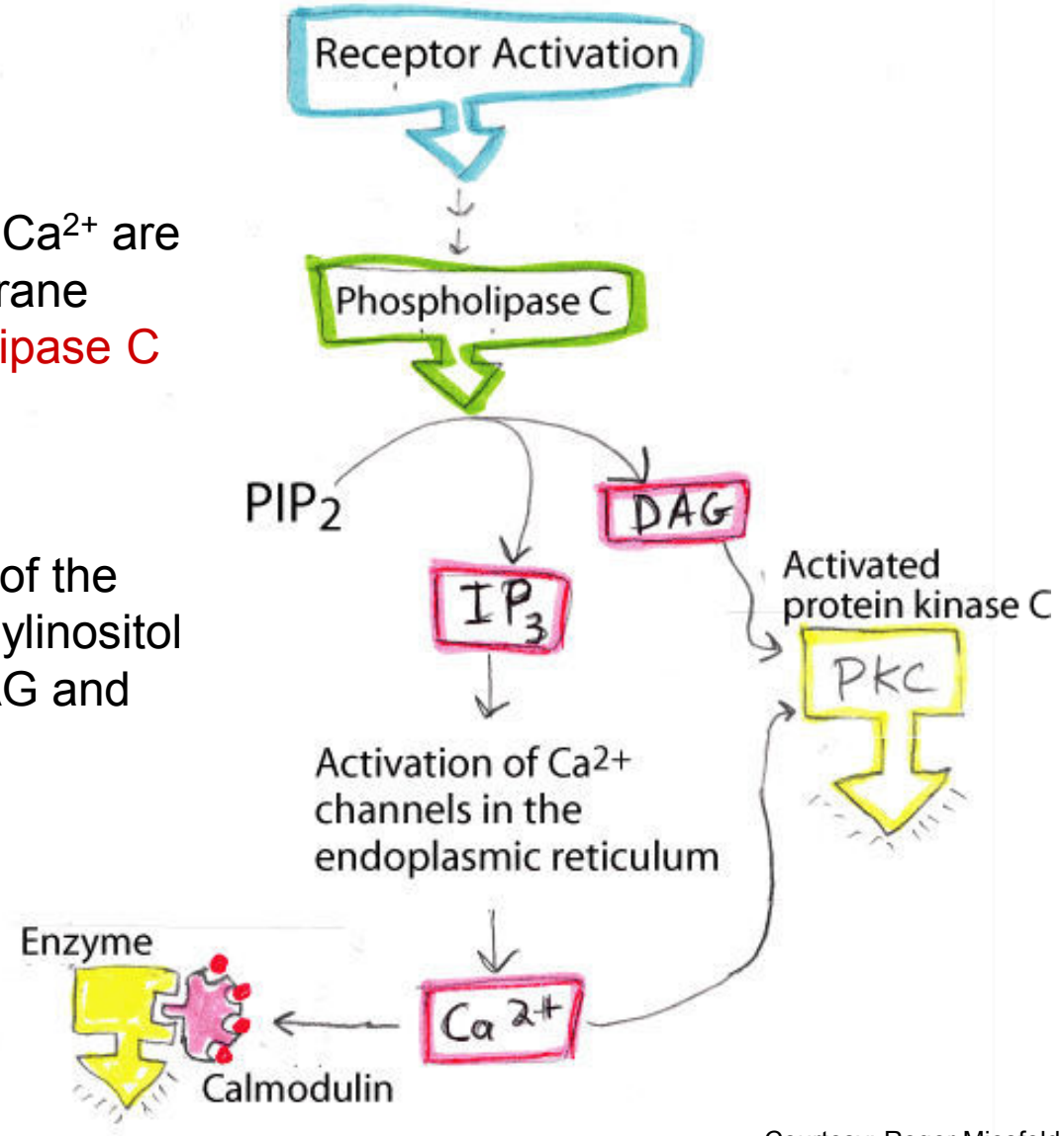


Courtesy: Roger Miesfeld

Some Other Second Messengers: diacylglycerol (DAG), inositol 1,4,5-trisphosphate (IP3) and calcium ion (Ca2+).

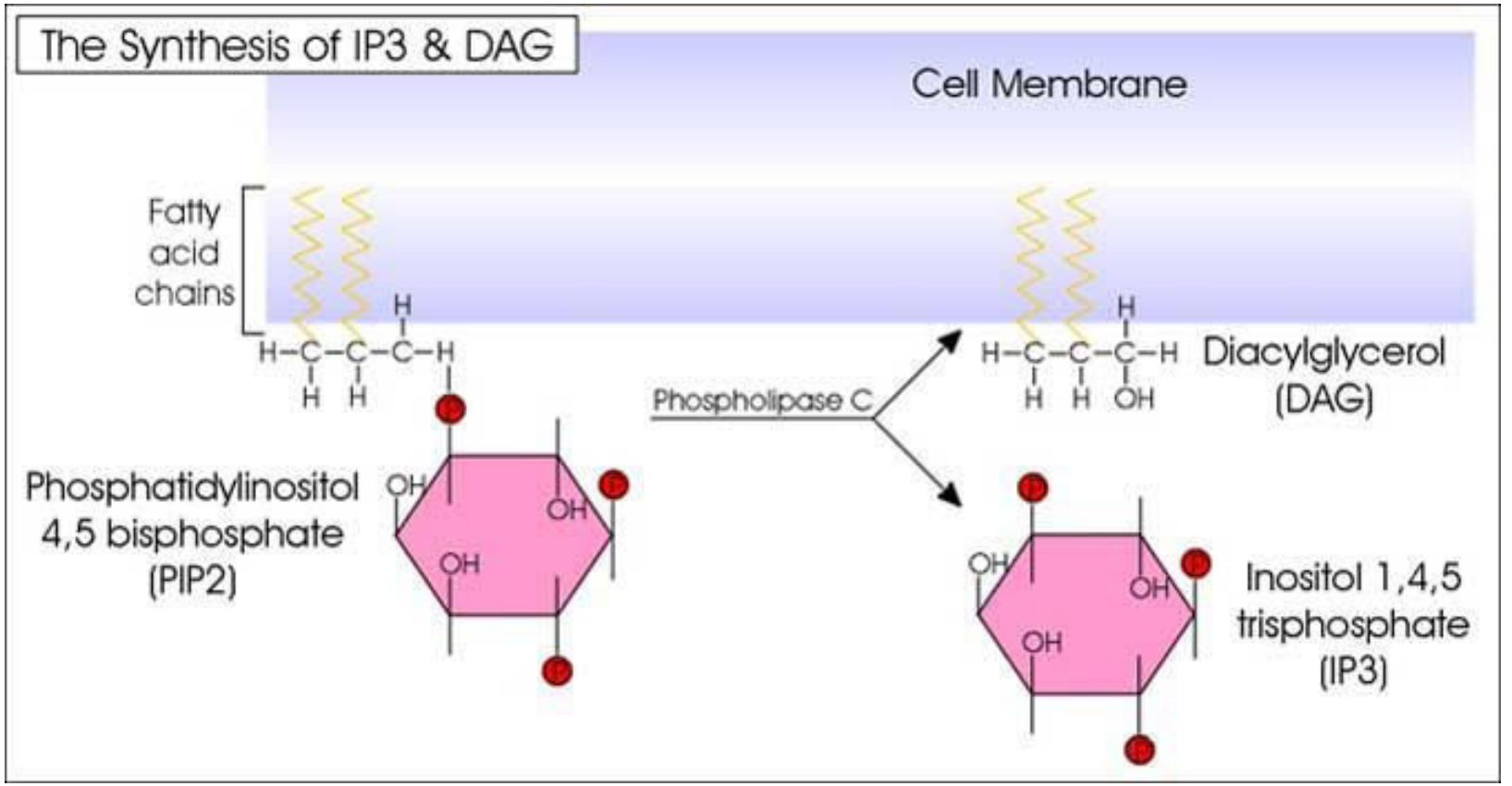
Intracellular levels of DAG, IP3 and Ca^{2+} are controlled by the activity of a membrane associated enzyme called phospholipase C (PLC).

Receptor-mediated activation of phospholipase C leads to cleavage of the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) to form DAG and IP3.



Courtesy: Roger Miesfeld

PLC produces second messengers DAG and IP3



Function of second messengers IP3 & DAG

IP3 binds to calcium channels on the endoplasmic reticulum

- causes a rapid increase in intracellular Ca^{2+} levels.

Released Ca^{2+} binds to protein kinase C (PKC)

- stimulates its association with DAG at the plasma membrane resulting in activation of the PKC kinase function

Ca^{2+} binds to calmodulin, activating:

phosphorylase kinase
calmodulin dependent kinase

PKC and calmodulin dependent kinase

phosphorylate and inactivate glycogen synthase

Calmodulin-activated phosphorylase kinase stimulates glycogen degradation by activating glycogen phosphorylase

Calcium as a second messenger

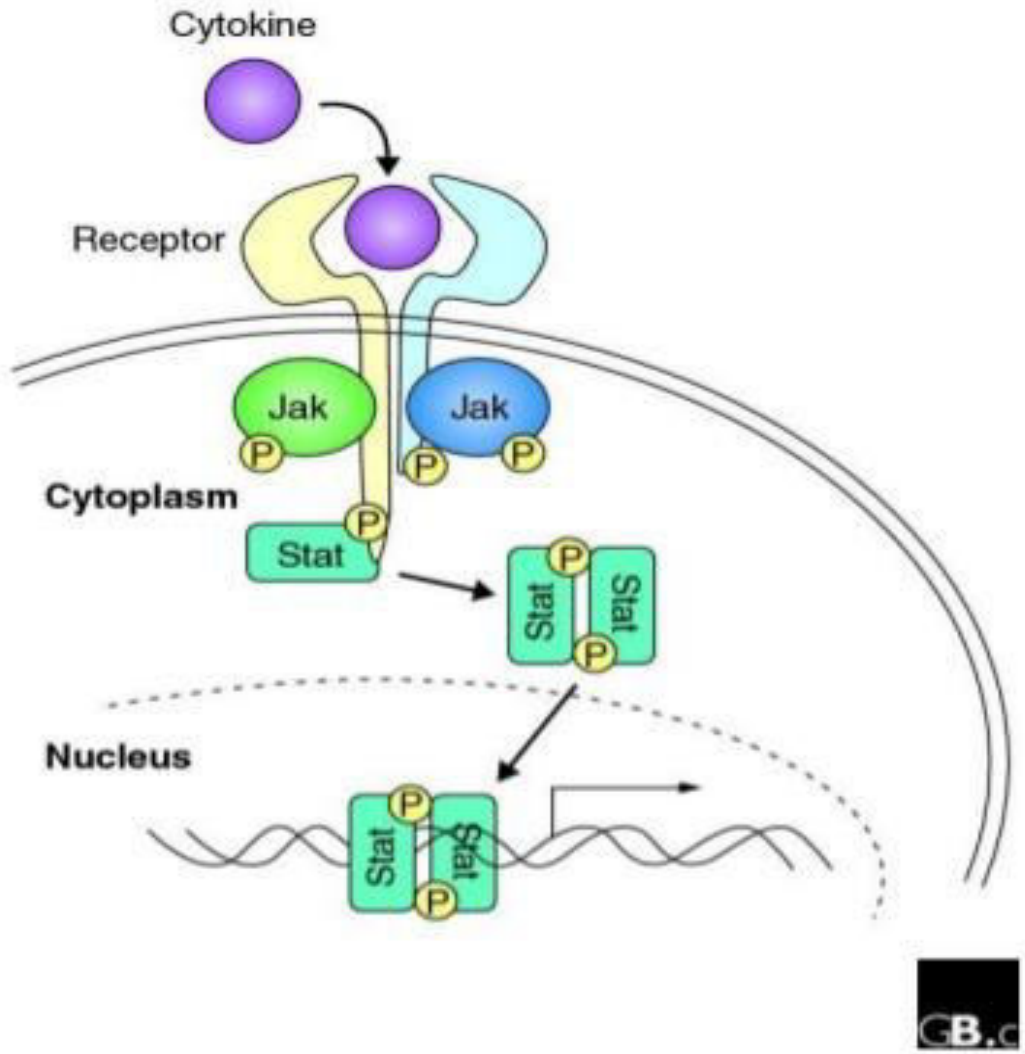
- **Calcium** ions are important for **cellular signalling**, as once they enter the cytosol of the cytoplasm they exert allosteric regulatory effects on many enzymes and proteins. Calcium can act in signal transduction resulting from activation of ion channels or as a second messenger caused by indirect signal transduction pathways such as G protein-coupled receptors.

- The resting concentration of Ca^{2+} in the cytoplasm is normally maintained around 100 nM.
- To maintain this low concentration, Ca^{2+} is actively pumped from the cytosol to the extracellular space, the endoplasmic reticulum (ER), and sometimes into the mitochondria.
- Specific signals can trigger a sudden increase in the cytoplasmic Ca^{2+} level up to 500–1,000 nM by opening channels in the endoplasmic reticulum or the plasma membrane. The most common signaling pathway that increases cytoplasmic calcium concentration is the phospholipase C pathway.
-

- Calcium (as Ca^{2+}) is a ubiquitous second messenger with wide-ranging physiological roles:
- These include muscle contraction,
- neuronal transmission as in an excitatory synapse,
- cellular motility (including the movement of flagella and cilia),
- fertilization, cell growth or proliferation,
- neurogenesis
- , learning and memory as with synaptic plasticity,
- and secretion of saliva.[
- High levels of cytoplasmic calcium can also cause the cell to undergo apoptosis.
- Other biochemical roles of calcium include regulating enzyme activity, permeability of ion channels, activity of ion pumps, and components of the cytoskeleton.[12]
- Many of Ca^{2+}-mediated events occur when the released Ca^{2+} binds to and activates the regulatory protein calmodulin.
- Calmodulin may activate calcium-calmodulin-dependent protein kinases, or may act directly on other effector proteins.(Myosin).
- Besides calmodulin, there are many other Ca^{2+}-binding proteins that mediate the biological effects of Ca^{2+}.

Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway

- JAK- Family of cytoplasmic **non-receptor tyrosine kinases** which get activated after the binding of a cytokine to the cell-surface cytokine receptor.
- STAT- Family of transcription factors that become activated when one of the tyrosine residues is phosphorylated by JAK.
- STAT3 dimers then translocate from the cytoplasm into the nucleus – bind to **Interferon-stimulated Response Elements**.
- Cellular responses to dozens of **cytokines** and **growth factors** are mediated by the evolutionarily conserved.


Cytokine
Receptor
Jak
Jak
P
P
P
P
Cytoplasm
Stat
Stat
Stat
P
P
Nucleus
Stat
Stat
P
P

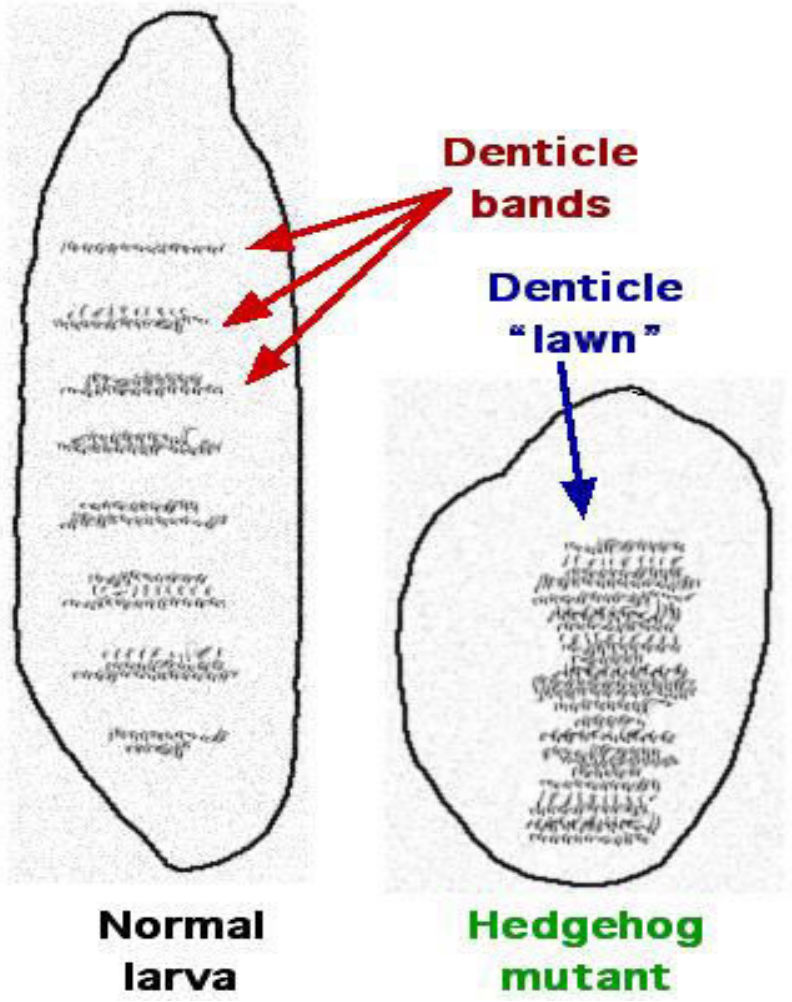
- Responses include proliferation, differentiation, migration, apoptosis, and cell survival.
- Essential for numerous developmental and homeostatic processes, including **hematopoiesis, immune cell development, stem cell maintenance, organismal growth, and mammary gland development**.
- Human JAK mutations cause numerous diseases, including SCID, hyper IgE syndrome, certain **leukemias**, polycythemia vera, and other myeloproliferative disorders.
- Small molecular weight cell membrane-permeable drugs that target this pathways have been developed for leukemia therapy. (JAK Inhibitors)

Hedgehog signaling pathway

The **Hedgehog signaling pathway** is a signaling pathway that transmits information to embryonic cells required for proper cell differentiation.
Different parts of the embryo have different concentrations of hedgehog signaling proteins. The pathway also has roles in the adult.

The Hedgehog signaling pathway is one of the key regulators of animal development and is present in all bilaterians.
The pathway takes its name from its polypeptide ligand, an intercellular signaling molecule called Hedgehog (*Hh*) found in fruit flies of the genus Drosophila.

Hh is one of Drosophila's segment polarity gene products, involved in establishing the basis of the fly body plan. Larvae without *Hh*, are short and spiny, resembling the hedgehog animal. The molecule remains important during later stages of embryogenesis and metamorphosis.
Mammals have three Hedgehog homologues, Desert (DHH), Indian (IHH), and Sonic (SHH), of which Sonic is the best studied. T



In the late 1970s Christiane Nüsslein-Volhard and Eric Wieschaus isolated mutations in genes that control development of the segmented anterior-posterior body axis of the fly;
They discovered a group of genes involved in the development of body segmentation, helping to found the field of evolutionary developmental biology.
In 1995, they shared the Nobel Prize with Edward B. Lewis for their work studying genetic mutations in *Drosophila* embryogenesis.

The *Drosophila* hedgehog (*hh*) gene was identified as one of several genes important for creating the differences between the anterior and posterior parts of individual body segments.

Rather than the normal pattern of denticles, hedgehog mutant larvae tend to have "solid lawns" of denticles (Figure 1). The appearance of the stubby and "hairy" larvae inspired the name 'hedgehog'.

Hedgehog signaling pathway

- Indian hedgehog: expressed in gut and chondrocytes
- Desert hedgehog: expressed in sertoli cells of the testes
- Sonic hedgehog: Involved in many developmental processes. Best characterized