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PROGRAM	**FOR PhD STUDENTS**
SUBTOPIC NAME	**Signal transduction : Basics of signaling, G- protein coupled receptors**
CONTENT TYPE	**PDF**
SEARCH KEYWORDS	**cell signaling, receptors, GPLR, cAMP, G proteins**

Cell Signaling

Objectives:

To acquaint the students about:

i) components of cell signaling

ii) types of cell signaling

iii) cell signaling molecules

iv) nuclear receptors

v) G-Protein coupled receptors

vi) Signal transduction by G-proteins

vii) Adenylate cyclase signaling and

viii) Phospholipase C Signaling.

Extracellular Signal Molecules Bind to Specific Receptors

- All living organisms continuously receive and interpret diverse kinds of signals from environment. Thus cells communicate with one another with the help of signaling molecules produced by the cells.

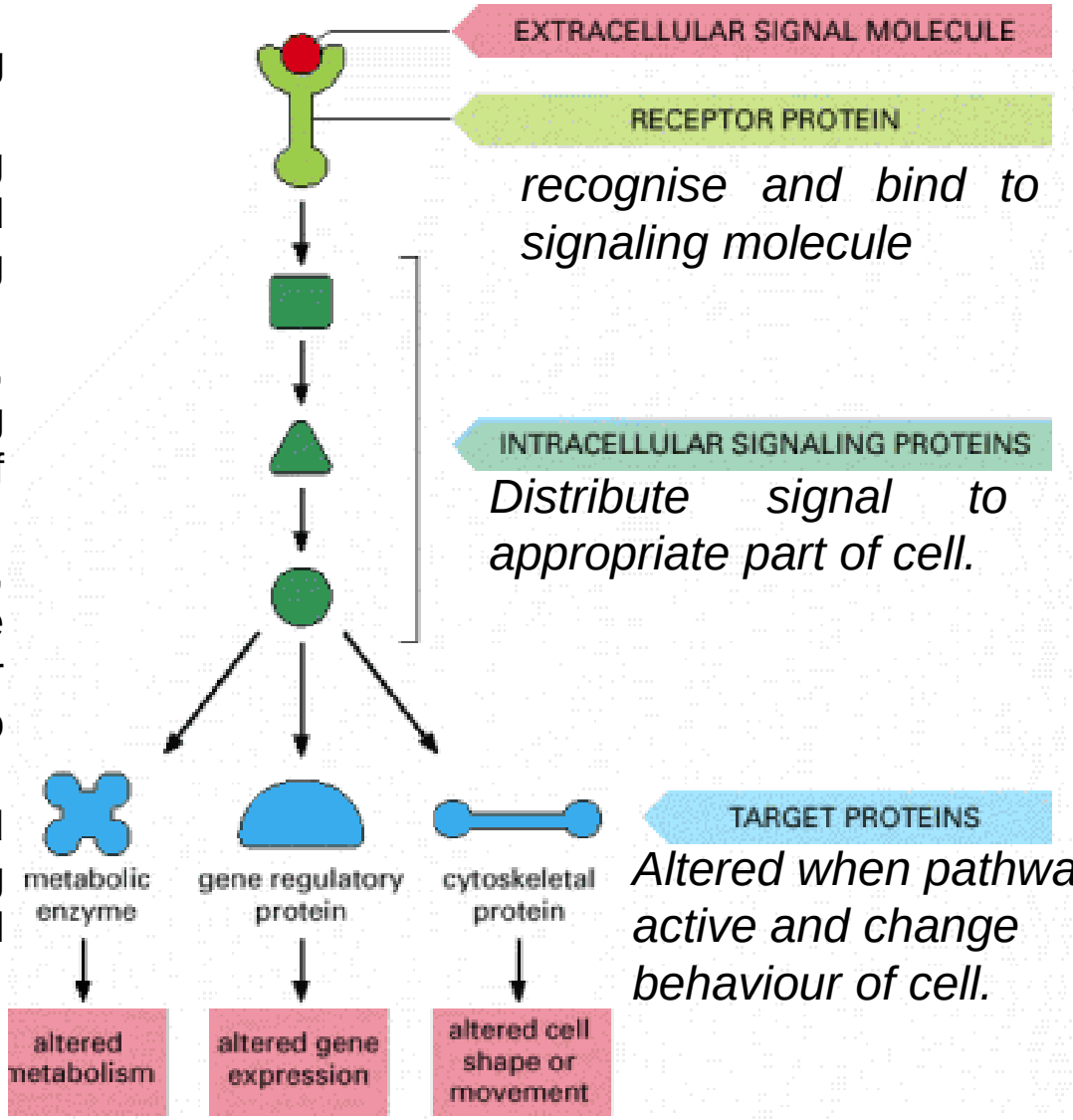
- These signals include proteins, small peptides, amino acids, nucleotides, steroids, retinoid, fatty acid derivatives and dissolved gases such as nitric oxide and carbon monoxide. These signalling molecules produced by signaling cells bind to receptors present on surface of target cells and their recognition by receptors triggers changes in activity or metabolism of a cell by a process of cellular communication referred to as **signal transduction**.

- Most of these signal molecules are secreted from the *signalling cell into the* extracellular space by exocytosis. Others are released by diffusion through plasma membrane (PM) and some are exposed to the extracellular space while remaining tightly bound to the signalling cell's surface.

- The *target cell responds to signal by means of a* specific protein called a **receptor**, which specifically binds signal molecule and then initiates a response in target cell. The extracellular signal molecules often act at very low concentrations (typically 10^{-8} M), and the receptors that recognize them usually bind them with high affinity (affinity constant $K\alpha$ - 10^{8} litters/mole).

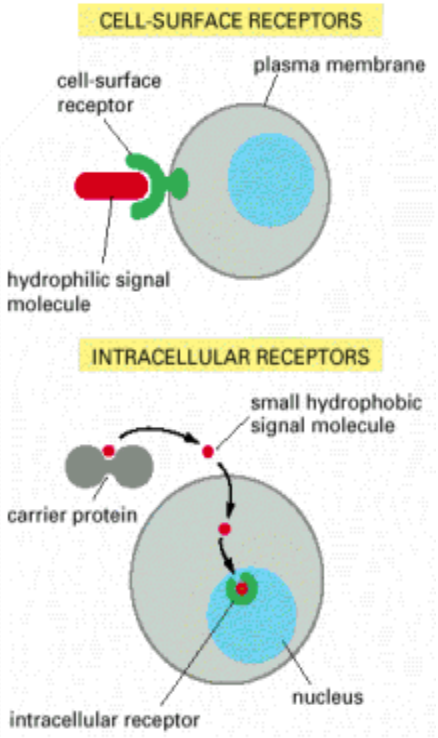
The cellular communication signaling requires 4 important components:

1. An extracellular **signaling molecule** produced by a cell and capable of travelling to neighbouring cells;
2. Cell surface **receptor proteins**, which recognise and bind to signaling molecule and are capable of communicating inward into cell;
3. **Intracellular signaling proteins**, which are activated by binding of the signal molecule to the receptor protein and distribute signal to appropriate part of cell; and
4. **Target proteins**, which are altered upon activation of a signaling pathway and causes changes in cell like activating gene transcription

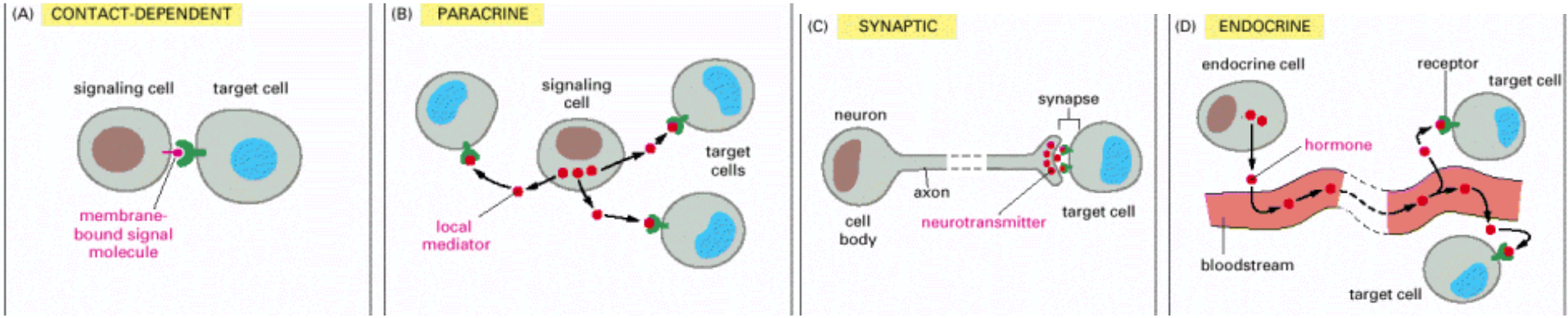


An intracellular signaling pathway activated by extracellular signal molecule. The signal molecule binds to a receptor protein (usually embedded in plasma membrane), thereby activating an intracellular signaling pathway that is mediated by a series of signaling proteins. Finally, one or more of these intracellular signaling proteins interacts with a target protein, altering target protein so that it helps to change behaviour of cell.

The binding of extracellular signal molecule to cell surface or intracellular receptors.

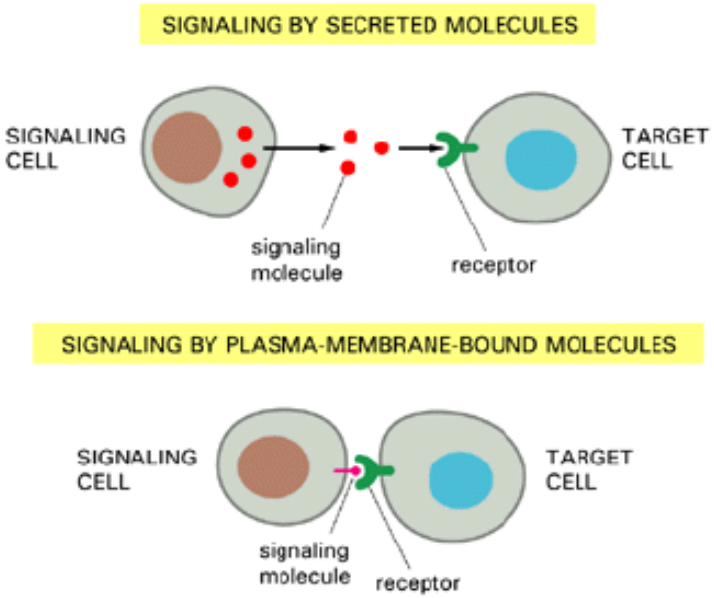


- **Cell surface receptors**: Mostly, the receptors are transmembrane proteins on target cell surface. When they bind an extracellular signal molecule *(a ligand), they become activated and generate a* cascade of intracellular signals that alter the behaviour of cell.
- **Intracellular receptors**: In other cases, the receptors are inside target cell, and signal molecule has to enter cells to activate them: thus signal molecules must be sufficiently small and hydrophobic to diffuse across the PM

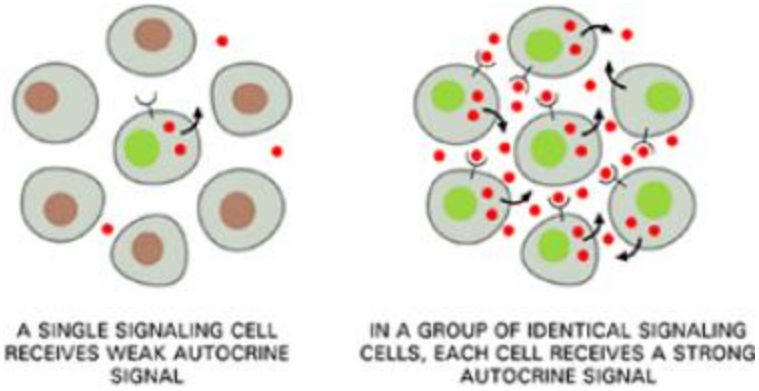


Forms of intercellular signaling. (A) ***Contact-dependent*** signaling requires cells in direct contact. (B) **Paracrine** signaling depends on signals released into extracellular space and act locally on neighbouring cells. (C) **Synaptic** signaling is by neurons that transmit signals electrically along axons and release neurotransmitters at synapses, located far from cell. (D) **Endocrine** signaling depends on endocrine cells, that secrete hormones into bloodstream that are then distributed widely throughout the body.

Many signal molecules remain bound to the surface of the signaling cell and influence only cells that contact it. Such **contact-dependent signaling** is especially important during development and in immune responses. In most cases, however, signal molecules are secreted. The secreted molecules may be carried far afield to act on distant targets, or they may act as local mediators, affecting only cells in immediate environment of signaling cell.



Autocrine signaling: Autocrine signals are produced by and affect target cell itself after their secretion and binding to receptors. Such autocrine signals may also target other similar cells in the surrounding. For example immune cells. Autocrine signaling is most effective when performed simultaneously by neighboring cells of same type, and is likely to be used to encourage groups of identical cells to make the same developmental decisions.



Second messengers: Second messengers act as intermediate molecules that relay signals from receptors on cell surface to target molecule inside cells, cytoplasm or nucleus. These are intracellular second messenger including cAMP, cGMP, Ca^{++}, IP3, DAG :

1. Second messengers can diffuse frequently into other compartment of the cell such as nucleus, and can influence gene expression.
2. Generation of second messengers leads to amplification of signal. Each signaling molecule is involved in the generation of several second messengers in cell, thus each single molecule in the environment can yield a large intracellular signal and response.

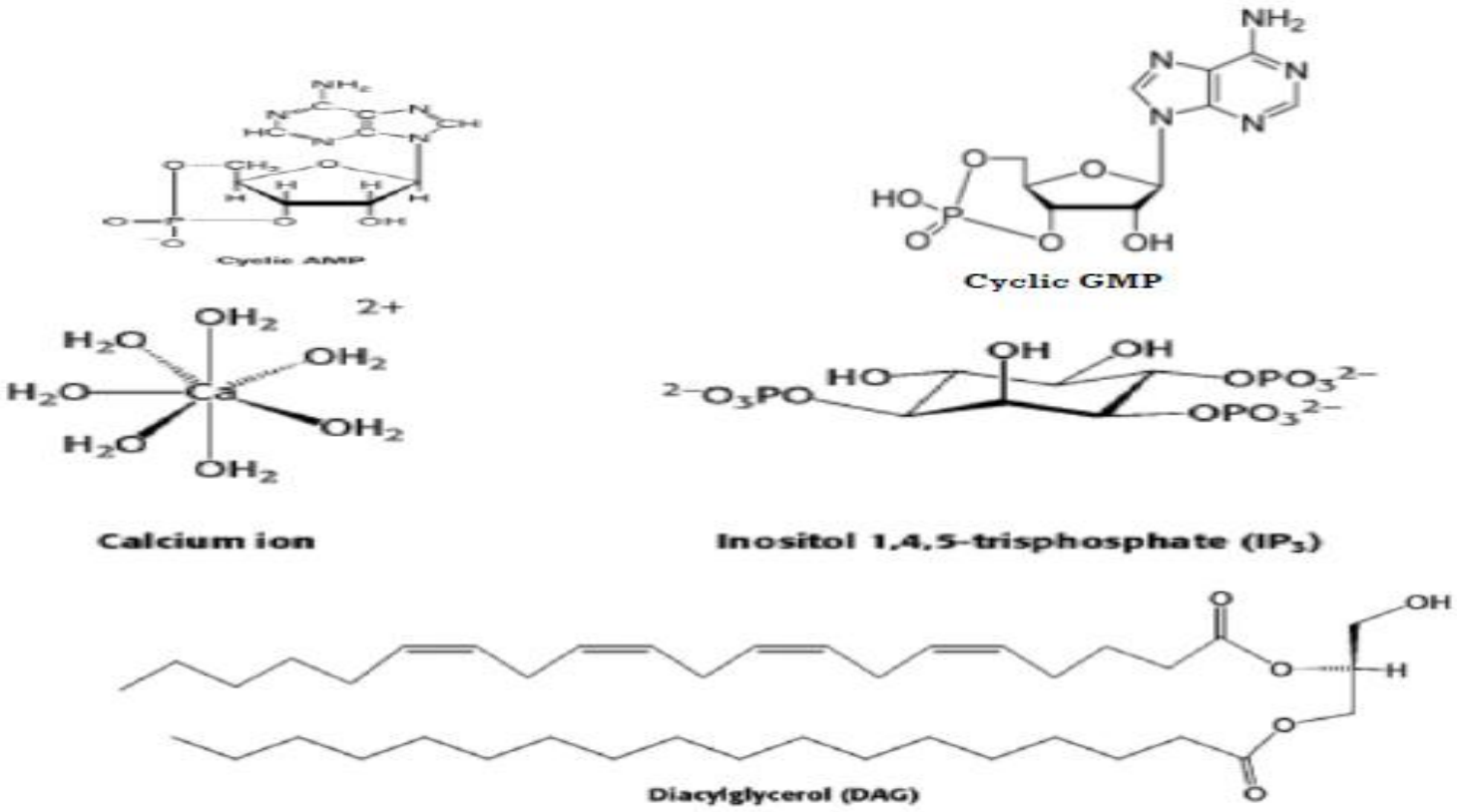


Figure 4: Common second messengers

Second messengers

Molecular mediators of signal transduction. Cells carefully, and rapidly, regulate the intracellular concentrations. Second messengers can be used by multiple signaling networks (at the same time).

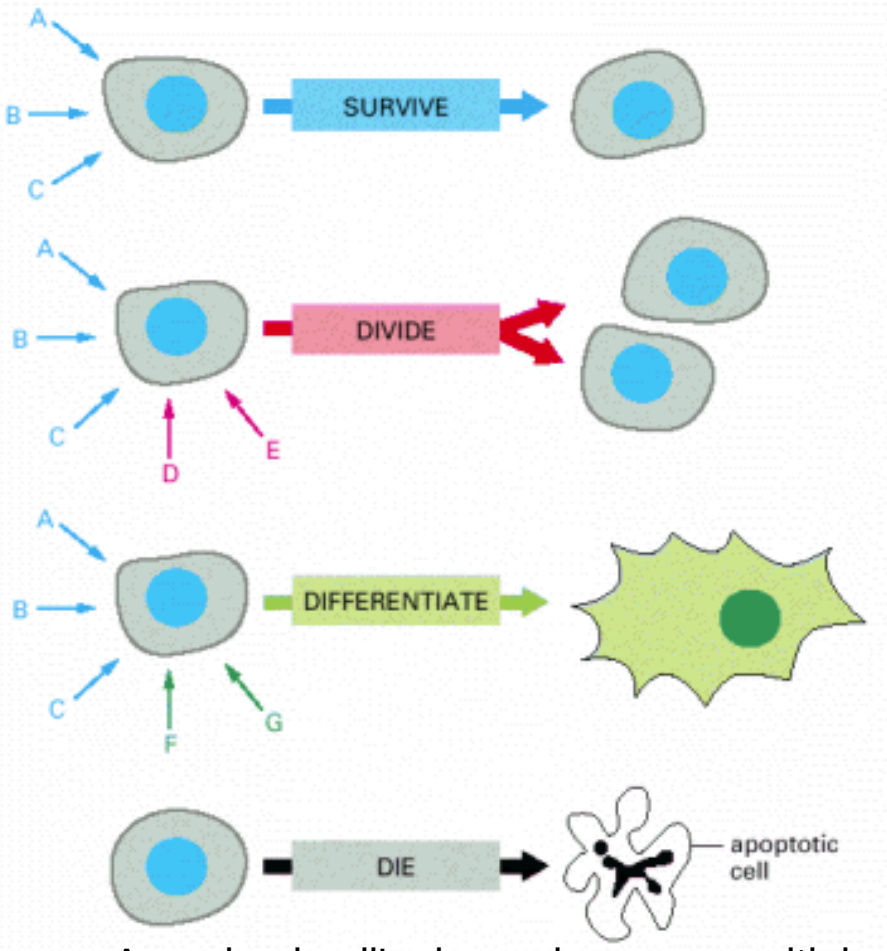
- Cyclic nucleotides: cAMP, cGMP
- Inositol phosphate (IP)
- Diacylglycerol (DAG)
- Calcium
- Nitric oxide (NO)

Each Cell Is Programmed to Respond to Specific Combinations of Extracellular Signal Molecules

A typical cell in a multicellular organism is exposed to hundreds of different signals in its environment. These signals may be soluble, bound to extracellular matrix or neighboring cell, and may act in many millions of combinations

A cell may be programmed to respond to a combination of signals by differentiating, to another combination by multiplying or by performing another function as contraction or secretion.

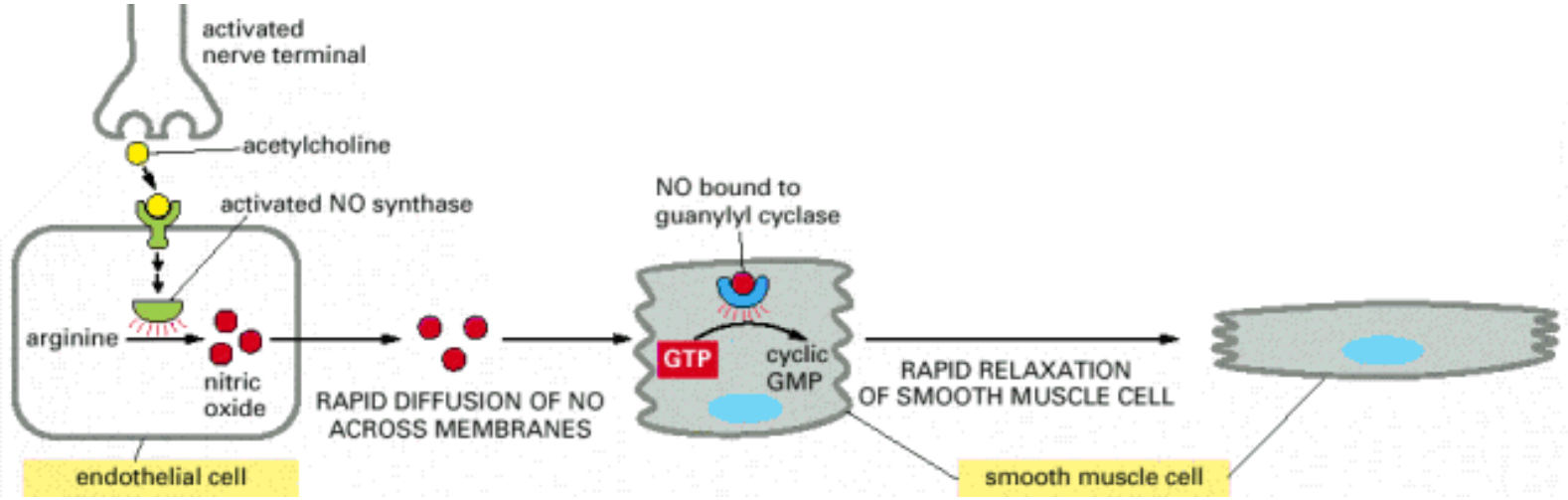
In principle, hundreds of signal molecules that animals make can be used to create an almost unlimited number of signaling combinations to control cell behavior in highly specific ways by using a limited diversity of signal molecules.



An animal cell's dependence on multiple extracellular signals.

Nitric Oxide Gas Signals by Binding Directly to an Enzyme Inside the Target Cell

- NO gas is made by deamination of amino acid arginine, by enzyme *NO synthase.*
- *Since it passes readily across membranes,* dissolved NO rapidly diffuses out of cell and into neighboring cells. It acts locally as it has a short half-life about 5-10 seconds in extracellular space before it is converted to nitrates and nitrites by O_2 and water.
- In many target cells, including endothelial cells, NO binds to iron in active site of enzyme *guanylyl cyclase, stimulating* it to produce intracellular mediator *cyclic GMP*.
- The effects of NO can occur within seconds, as the normal rate of turnover of cyclic GMP is high: a rapid degradation to GMP by a phosphodiesterase constantly balances cyclic GMP production from GTP by guanylyl cyclase.



The role of nitric oxide (NO) in smooth muscle relaxation in a blood vessel wall.

• Acetylcholine released by nerve terminals in blood vessel wall activates NO synthase in endothelial cells lining blood vessel, causing endothelial cells to produce NO. NO diffuses out of endothelial cells and into underlying smooth muscle cells, where it binds to and activates guanylyl cyclase to produce cyclic GMP. Cyclic GMP trigger response causing relaxation of smooth muscle cells, enhancing blood flow in blood vessel.

•The gas nitric oxide (NO) acts as a signal molecule in both animals and plants.

•In mammals, it functions to regulate smooth muscle contraction. Acetylcholine, for example, is released by autonomic nerves in blood vessel walls, and acts indirectly by inducing nearby endothelial cells to make and release NO, that signals underlying smooth muscle cells to relax. This explains the mechanism of action of nitroglycerine, (used for ~100 years to treat patients with angina) as nitroglycerine releases NO, which relaxes blood vessels, reducing workload on heart and O_2 requirement of heart muscle.

•NO is produced by activated macrophages and neutrophils and kill invading microbes.

•In plants, NO is involved in the defensive responses to injury or infection.

Carbon monoxide (CO) *is another gas that is used as an intercellular signal.*

It can act in the same way as NO, by stimulating guanylyl cyclase.

These gases are not the only signal molecules that can pass directly across the target-cell plasma membrane.

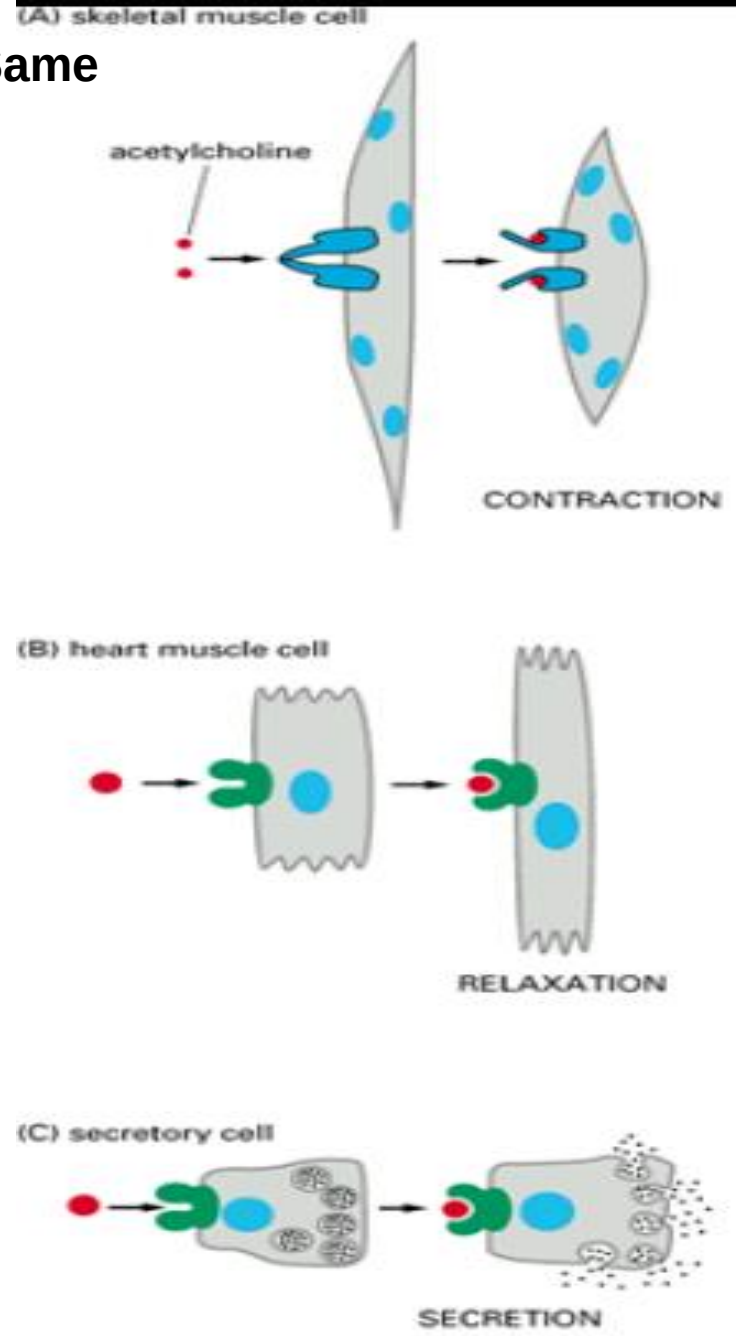
Different Cells Can Respond Differently to the Same Extracellular Signal Molecule

The specific way in which a cell reacts to its environment varies according to:

1. The set of receptor proteins a cell has, determining the particular subset of signals it can respond to, and
2. Intracellular machinery by which the cell integrates and interprets the signals it receives.

Thus, a single signal molecule often has different effects on different target cells. For example neurotransmitter acetylcholine stimulates contraction of skeletal muscles, but decreases rate and force of contraction in heart muscles due to presence of different acetylcholine receptor proteins on these cells.

Alternatively, sometimes, same signal molecule binds to identical receptor proteins, yet gives different responses in different target cells, reflecting differences in the internal machinery to which the receptors are coupled.

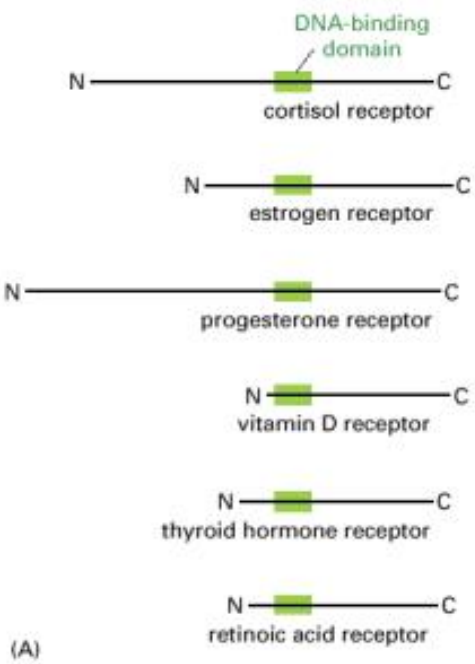


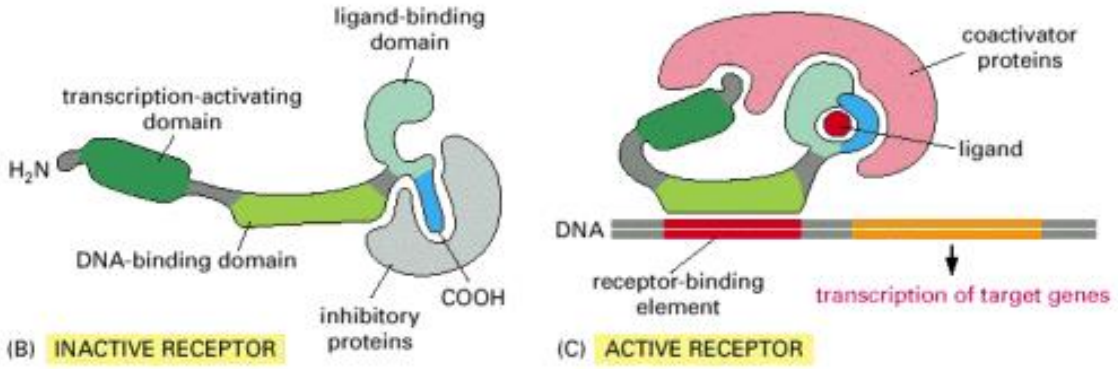
The same signaling molecule can induce different responses in different target cells.

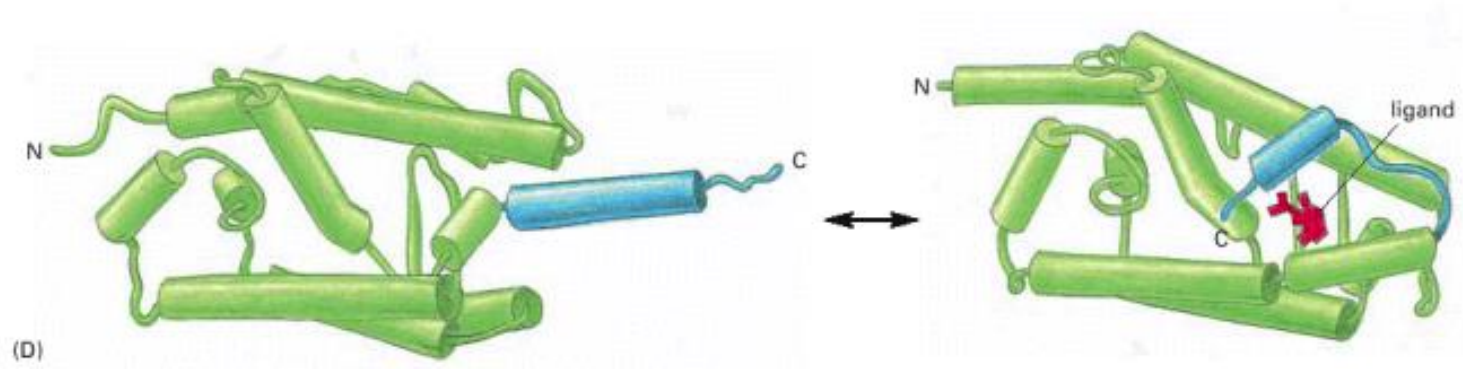
Nuclear Receptors: Ligand-activated gene regulatory proteins

- Some small hydrophobic signal molecules as *steroid hormones, thyroid hormones, retinoids,* and *vitamin D* diffuse directly across the PM of target cells & bind to intracellular receptor proteins.
- The intracellular receptors for these signals bind to specific DNA sequences adjacent to the genes the ligand regulates.
- Some receptors, such as those for cortisol, are located primarily in the cytosol and enter the nucleus after ligand binding; others, such as thyroid and retinoid receptors, are bound to DNA in nucleus even in the absence of ligand.
- In either case, the inactive receptors - bound to inhibitory protein complexes, and ligand binding alters the conformation of receptor protein, causing the inhibitory complex to dissociate.
- *Although they differ greatly from one another in both chemical* structure and function, they all act by a similar mechanism.
- ***When these signal molecules bind to their receptor proteins, they activate the receptors, which bind to DNA to regulate transcription.*** Ligand binding also causes receptor to bind to coactivator proteins - induce transcription of specific genes.
- These receptors belong to the nuclear receptor superfamily. Some receptor proteins that are activated by intracellular metabolites rather than by secreted signal mols. Many family members identified by DNA sequencing only, and their ligand is not yet known; these proteins are therefore referred to as *orphan nuclear receptors.*

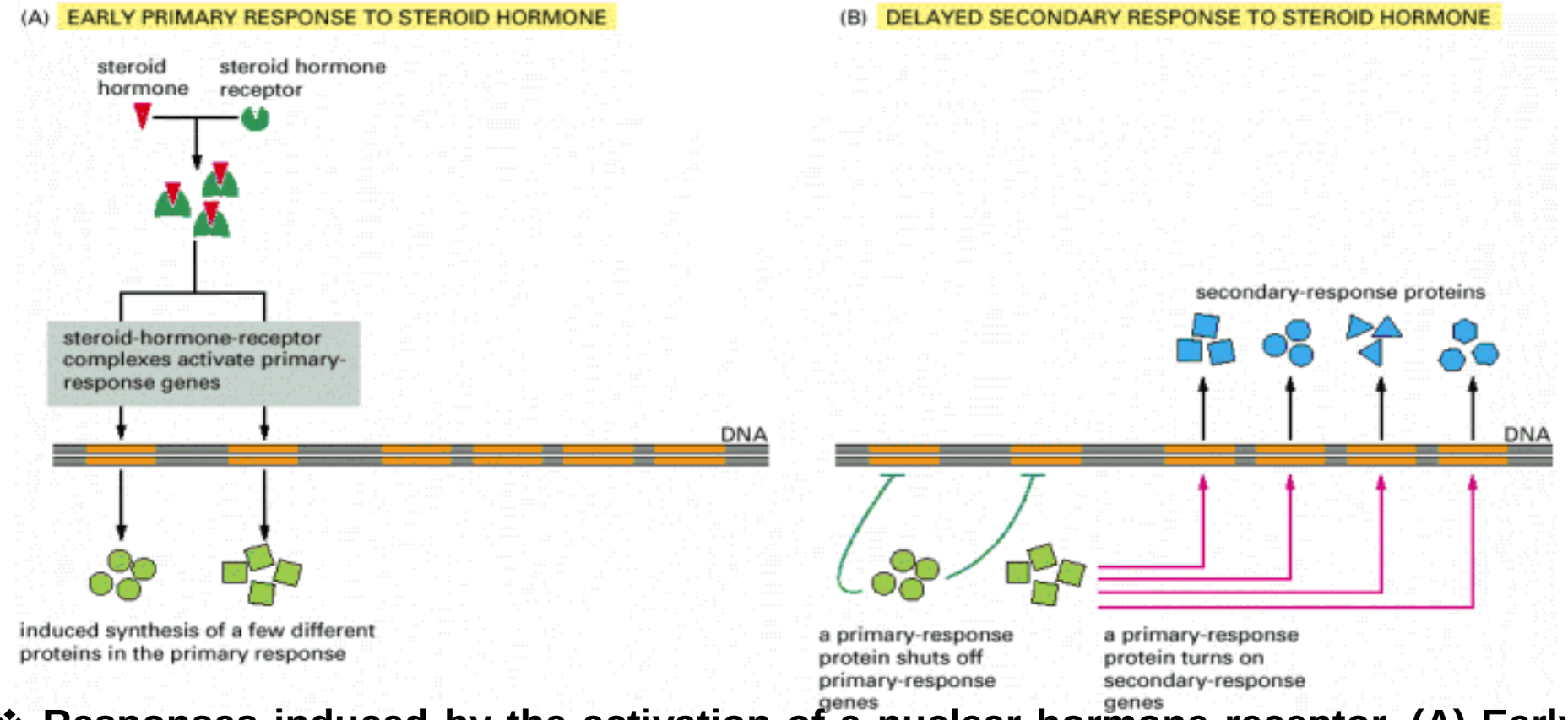
All nuclear hormone receptors bind to DNA.
(A) The receptors have a related structure with a short DNA binding domain in each. *(B) A receptor protein in its inactive state is bound to inhibitory proteins.* (C) The binding of ligand to receptor causes the ligand-binding domain of the receptor to clamp shut around the ligand, the inhibitory proteins to dissociate, and coactivator proteins to bind to the receptor's transcription-activating domain, thereby increasing gene transcription. (D) *blue α helix acts as a lid that snaps shut when the* ligand (shown in *red) binds, trapping the ligand in place.*







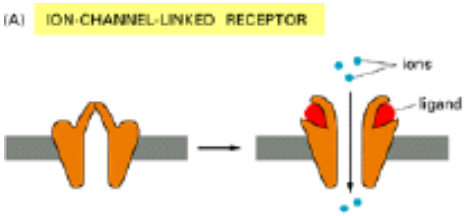
❖ The transcriptional response usually takes place in successive steps: the direct activation of a small number of specific genes occurs within about 30 minutes and constitutes the *primary response; the* protein products of these genes in turn activate other genes to produce a delayed, *secondary response; and so on. In this way, a simple hormonal trigger* can cause a very complex change in the pattern of gene expression



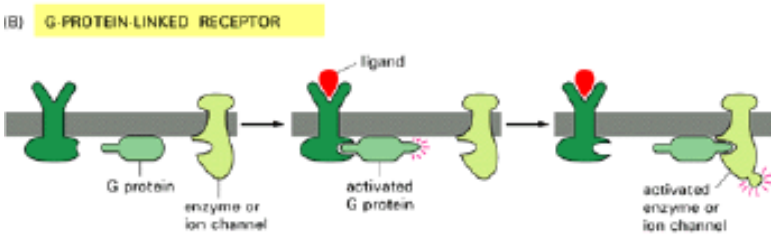
❖ **Responses induced by the activation of a nuclear hormone receptor. (A) Early primary response and (B) delayed secondary response**. Some of the primary-response proteins turn on secondary-response genes, whereas others turn off the primary-response genes.

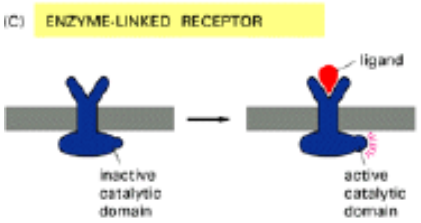
Cell surface receptors - Three types

1. **Ion-channel-linked receptors =** *transmitter-gated ion channels or ionotropic receptors, involved* in rapid synaptic signalling between electrically excitable cells.
   - ➢ Signalling by these receptors is mediated by a small number of neurotransmitters that transiently open/close an ion channel formed by protein to which they bind, briefly changing the ion permeability of PM and thus the excitability of the postsynaptic cell.
   - ➢ Homologous, multipass transmembrane proteins.



2. ***G-protein-linked receptors*** *indirectly regulate the activity of a separate PM*-bound target protein, either an *enzyme or an ion channel*.
   - ➢ Interaction between receptor and target protein is mediated by a *Trimeric GTP-binding protein (G protein)*.
   - ➢ Target protein activation changes the concentration of
     -intracellular mediators (if target protein is enzyme), or
     -ion permeability of PM (if target protein is ion channel)
   - ➢ The intracellular mediators in turn alter the behaviour of yet other signalling proteins in the cell.
   - ➢ Homologous, seven-pass transmembrane proteins.





3. ***Enzyme-linked receptors****, when activated, either function directly as enzymes* or are directly associated with enzymes that they activate.
   - ➢Single-pass transmembrane proteins that have their ligand binding site outside cell and their catalytic or enzyme-binding site on cytosolic side of PM.

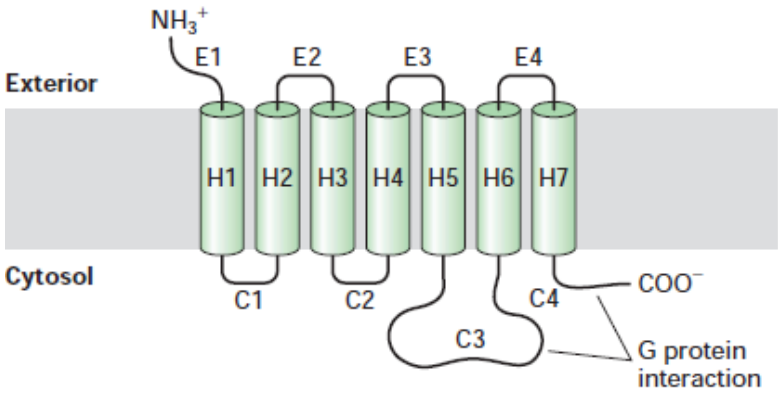
G Protein–Coupled Receptor (GPCR)

- Largest form of cell surface receptors.
- Present in all eukaryotes from yeast to higher organisms.

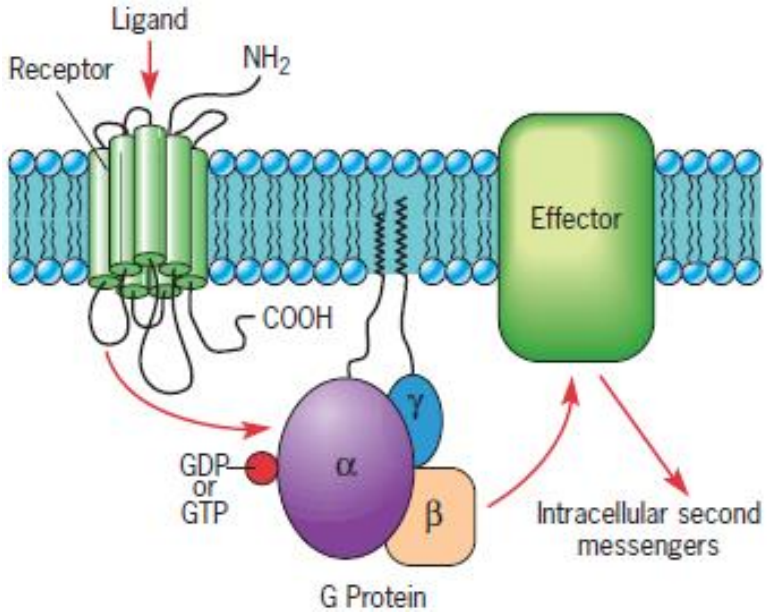
- Thousands of different GPCRs - related with sense of smell, mediate response.
- Respond to diverse signals (ligands)- including hormones (both plant and animal) as epinephrine or glucagon, neurotransmitters, odorants and tastants (molecules detected by olfactory and gustatory receptors Coupled to signal transducing Trimeric G-Proteins.

- Structure: Single polypeptide chain – contains
- Seven membrane-spanning α-helical regions (H1-H7),
- 4 extracellular (E1-E4) and
- 4 cytosolic (C1-C4) segments.

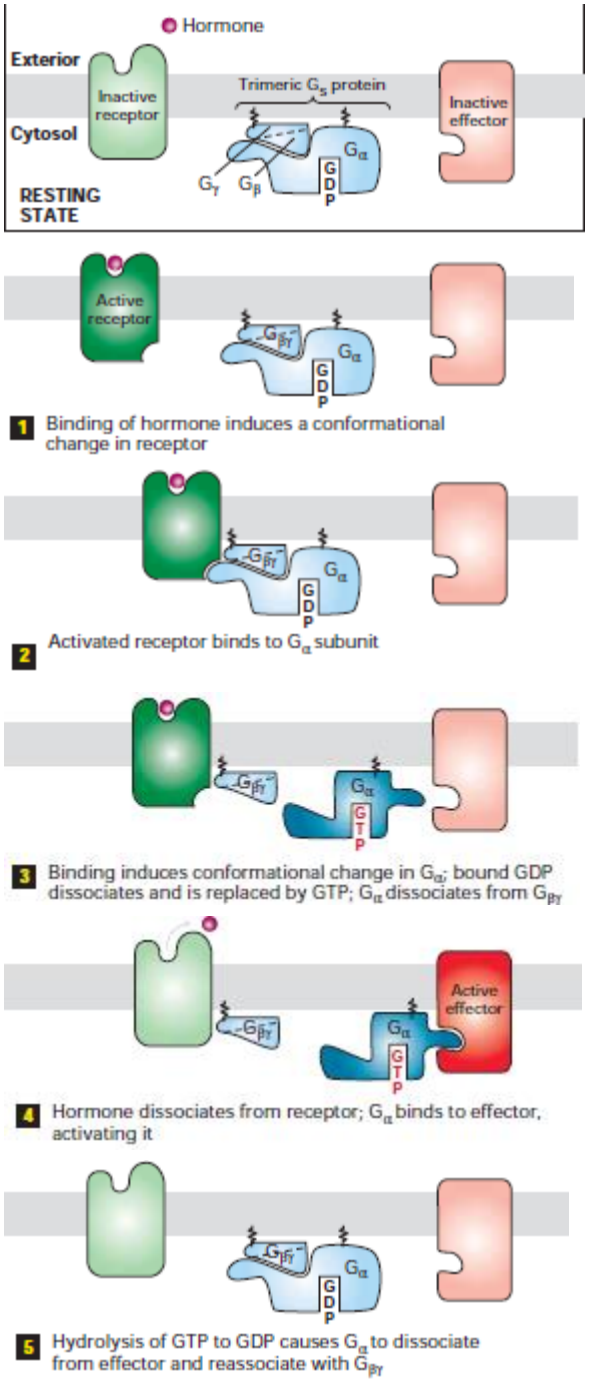
- When *GPCRs* bind to their ligand, the receptor interacts with a Trimeric G protein (GTP binding protein), which activates an effector, such as adenylyl cyclase.



7 membrane-spanning regions with N-terminus on exoplasmic face and C-terminus on the cytosolic face.



Membrane-bound machinery for transducing signals by GPCR and a heterotrimeric G protein.



- G proteins were discovered by **Alfred G. Gilman and Martin Rodbell** when investigating stimulation of cells by adrenaline

- **How are GPCR signals transduced to an effector protein?** Trimeric G protein disassembles to *relay signals* from GPCRs.

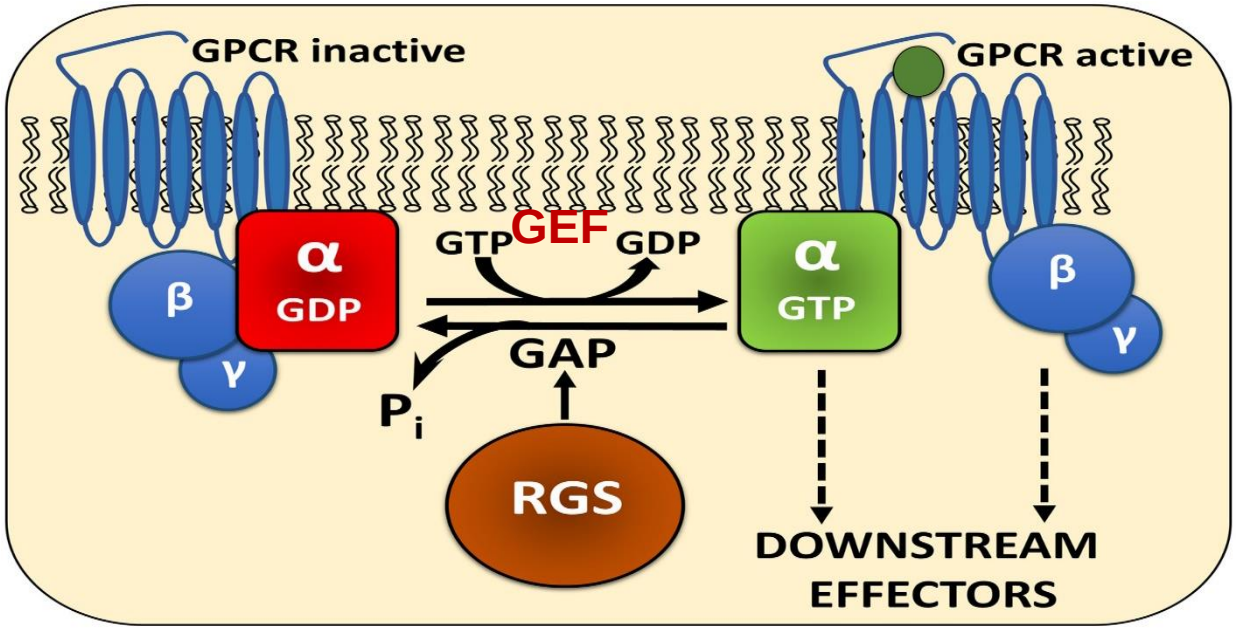
- All effector proteins, are either membrane-bound ion channels or enzymes that catalyse formation of second messengers (e.g., cAMP, DAG and IP-3).
- The human genome encodes 27 different G_α, 5 G_β, and 13 G_γ subunits.

The Gα Subunit of G Proteins Cycles Between Active and Inactive Forms.

In resting state, α subunit - GDP bound

In stimulated state α subunit - GTP bound (=GTPase)

- GTPase activity of α subunit – increased by binding of **Regulator of G-Protein Signalling (RGS)** =
  --These are GTPase activating proteins.
  – Play crucial role in shutting off G-Protein mediated responses. (human genome has 25 RSG proteins).



- Activation of α-subunit of G-Protein is regulated by the **GEF (Guanosine Exchange Factor),** that hydrolyze the bound **GDP** and activate Gα protein. Deactivation is regulated by the **GAP** (**GTPase Activator Protein)** that promotes the hydrolysis of bound GTP into GDP.

Other intracellular GTP binding proteins are:

- Ran – involved in import/export of protein from nucleous.
- Rab - involved in vesicular targeting and fusion.
- Ras - involved in regulating cell growth through serine/threonine kinases.
- Arf - involved in vesicle formation from Golgi membranes or plasma membrane.

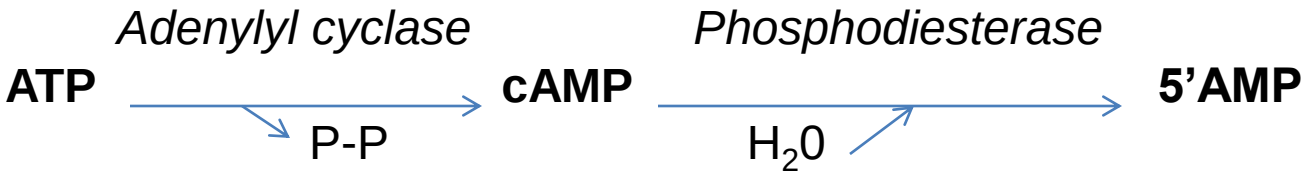
Some G-Proteins signal by regulating cAMP production

• Cyclic AMP (cAMP)- 1st identified as a small intracellular mediator in 1950s.

•Normal intracellular concentration = ~ 10^{-7} M, extracellular signal can cause cAMP levels to increase by >20 fold in seconds.

•Synthesized from ATP by a PM bound enzyme ***Adenylyl cyclase***.

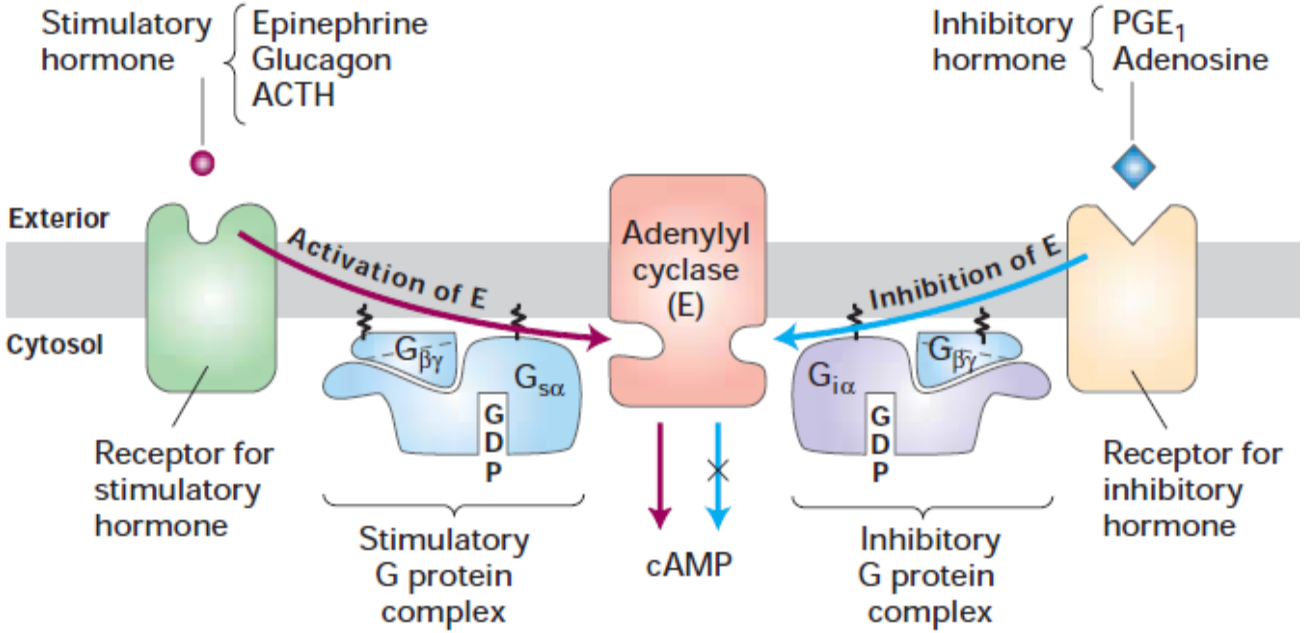
•Rapidly destroyed by phosphodiesterase



Adenylyl cyclase – is a large multipass transmembrane protein with catalytic domains on cytosolic side of PM.

Eight isoforms of adenylyl cyclase are reported to exist in mammals.

Activation and inhibition of adenylyl cyclase



Hormone-induced activation and inhibition of adenylyl cyclase in adipose cells. Ligand binding to G_s-coupled receptors cause activation of adenylyl cyclase, whereas ligand binding to G_i-coupled receptors causes enzyme inhibition. The $G_{\beta\gamma}$ subunit in both stimulatory and inhibitory G proteins is identical; the G_α subunits and their corresponding receptors differ. Ligand-stimulated formation of active $G_\alpha \cdot GTP$ complexes occurs by same mechanism in both G_s and G_i proteins. However, Gs·GTP and Gi·GTP interact differently with adenylyl cyclase, so that one stimulates and the other inhibits its catalytic activity.

All receptors which act via cAMP are coupled to stimulatory G-protein (Gs)
→ Activates adenylyl cyclase and increase intracellular cAMP levels.

The inhibitory G-protein (Gi) → Inhibits adenylyl cyclase, and mainly acts by directly regulating ion channels, rather than decreasing increase intracellular cAMP levels.

cAMP dependent Protein Kinase A (PKA) mediates most of the effects of cAMP

• cAMP directly activates some ion channels in PM of specific cells.
• But in most animal cells, its effects – exerted mainly by activating cAMP dependent Protein kinase A (PKA).
• *PKA catalyzes transfer of tertiary $P0_4$ group from ATP to Serine/Threonine of specific target proteins*.
• Substrates differ in different cell types, therefore, effects vary with respect to cell types.

• Effects of cAMP – may be slow or rapid

i. Phosphorylates enzymes in ***glycogen metabolism*** and increases amount of glucose available to muscle cells within seconds.

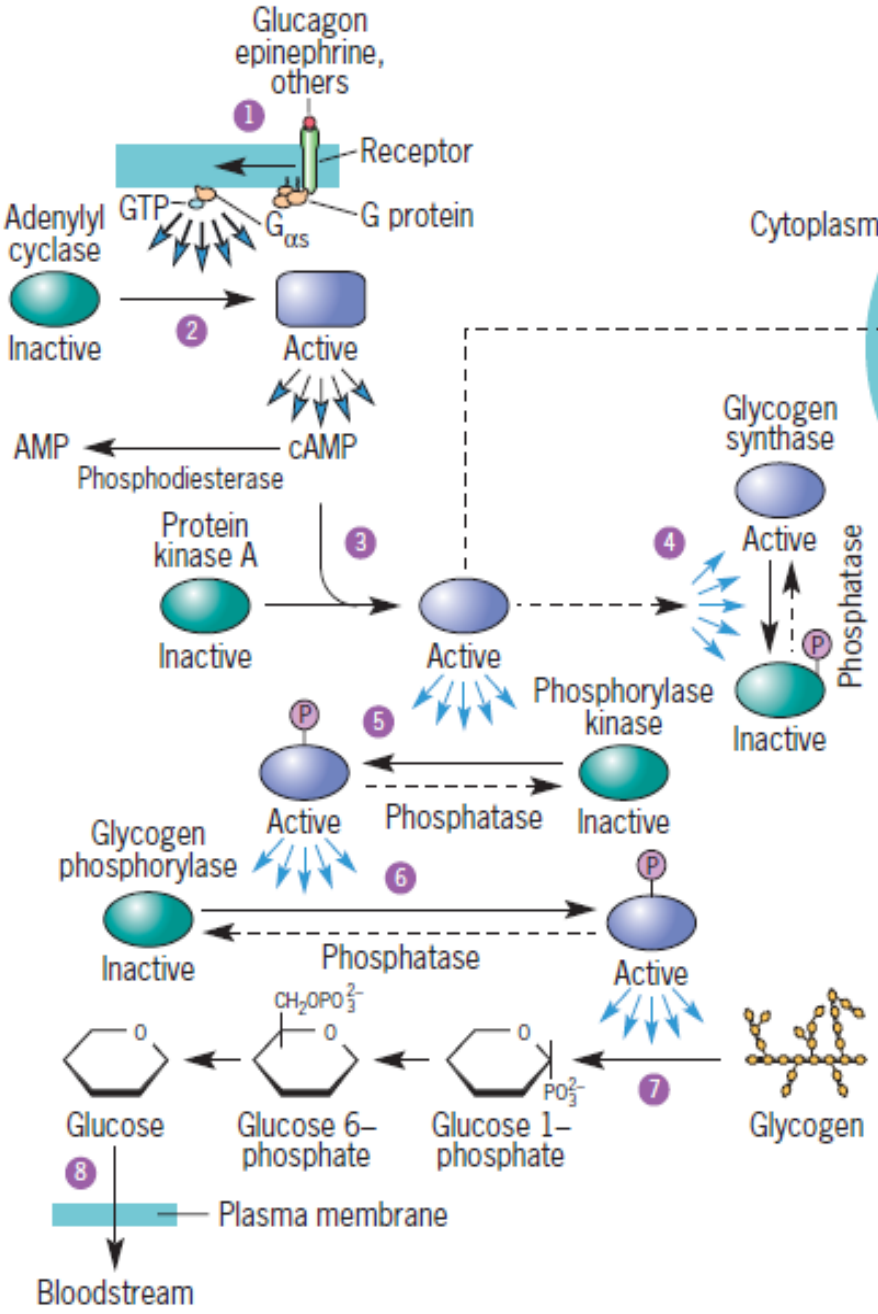
ii. Activates gene transcription

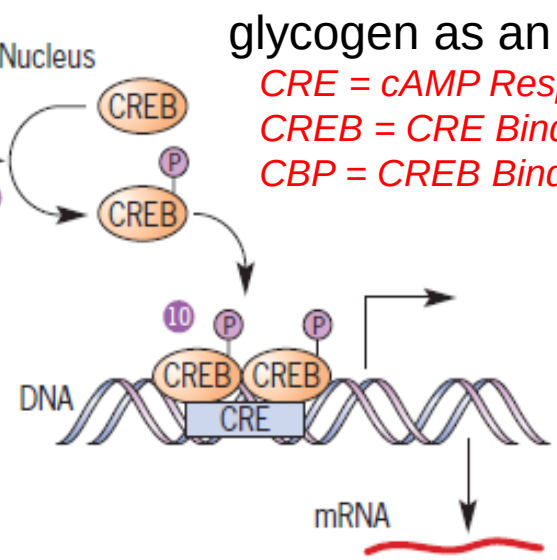
- Regulates downstream DNA region (such as for somatostatin gene) through a DNA region called as – **cAMP response element (CRE)**

- **<u>CRE</u> <u>B</u>inding protein (CREB)**- recognizes this CRE sequence

- When ***CREB is phosphorylated by PKA*** on serine residue, it recruits a transcriptional co-activator **<u>C</u>**REB-**B**inding **<u>P</u>rotein** (**CBP**) and stimulates transcription of genes.

- Protein phosphatases make effects of PKA and other Protein kinases transitory.



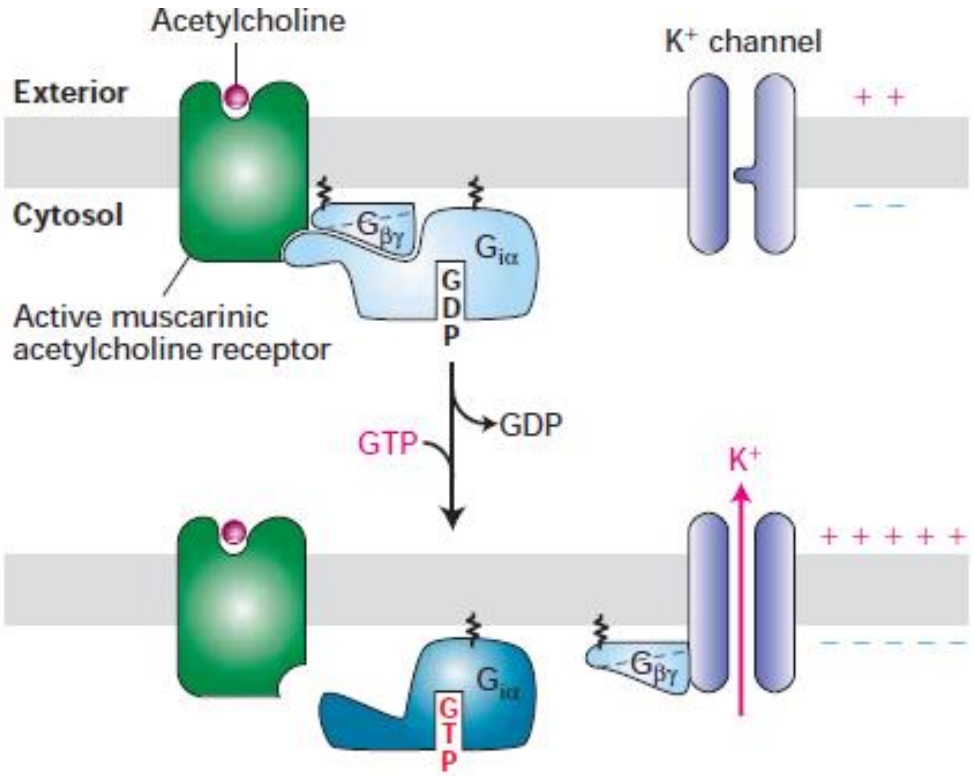


Here cAMP is the second messenger, using epinephrine stimulated degradation of glycogen as an example.

CRE = cAMP Response Element
CREB = CRE Binding Protein
CBP = CREB Binding Protein

The response by a liver cell to glucagon or epinephrine. The steps in the response to hormonal stimulation that lead to glucose mobilization. Many of the steps in the reaction cascade are accompanied by a dramatic amplification of the signal.

Cardiac Muscarinic Acetylcholine Receptors in the heart muscle plasma membrane Activate a G Protein That Opens K^+ Channels



Muscarinic acetylcholine receptors - linked via a trimeric G protein to K^+ channels. Binding of acetylcholine triggers activation of Giα subunit and its dissociation from $G_{\beta\gamma}$ subunit. In this case, the released $G_{\beta\gamma}$ subunit (rather than Giα·GTP) binds to and opens associated effector, a K^+ channel. The increase in K^+ permeability hyperpolarizes membrane, which reduces the frequency of heart muscle contraction. The activation is terminated when the GTP bound to Giα is hydrolyzed to GDP and Giα·GDP recombines with G$\beta\gamma$.

NaOUT

KIN

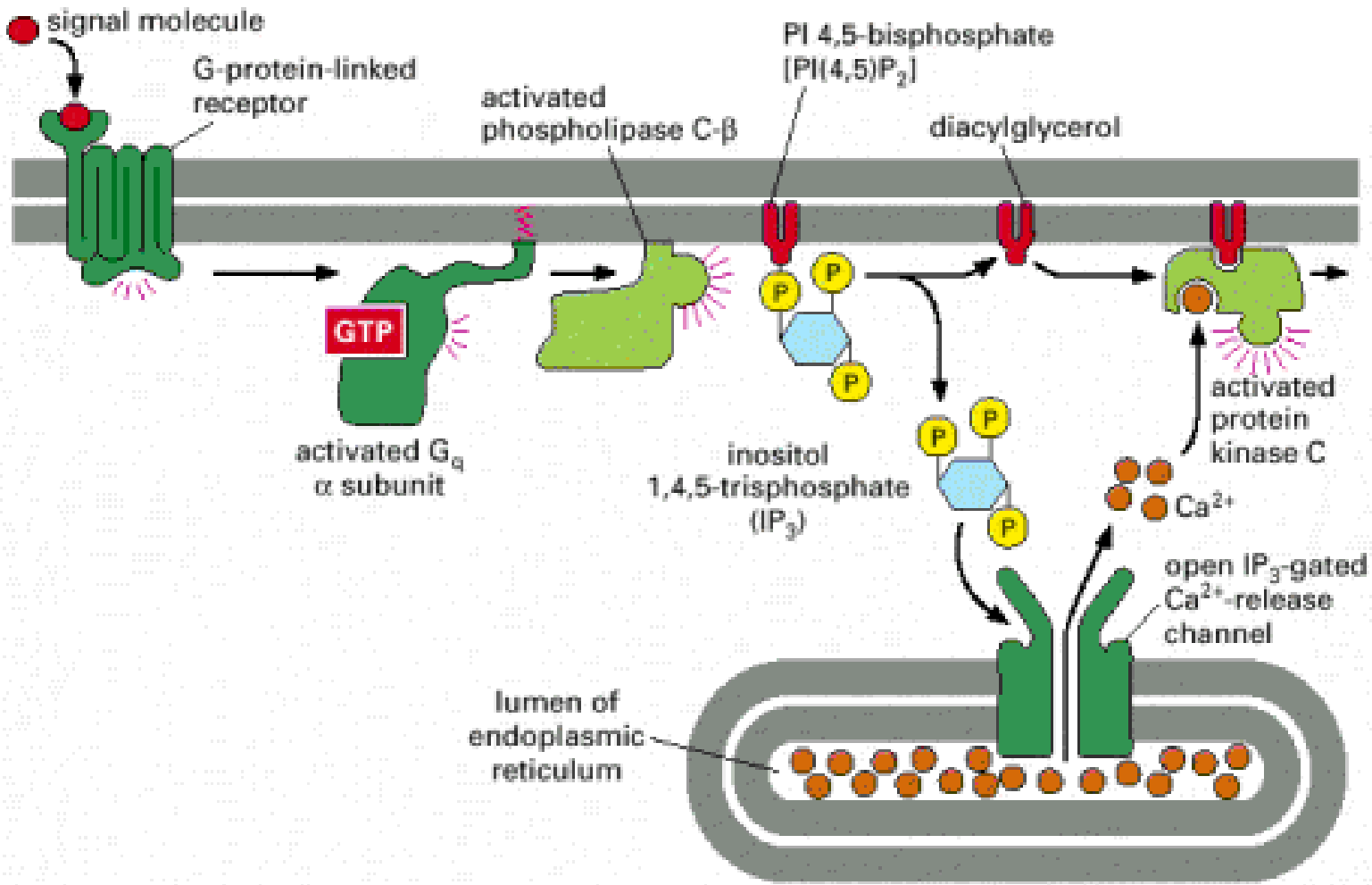
Some G Proteins induce Inositol Phospholipid signalling pathway by Activating Phospholipase C

- Phospholipase C- a PM bound enzyme- acts on Inositol Phospholipid - Phosphatidyl inositol 4, 5-bis PO_4 [$PI(4,5)P_2$].
- $PI(4,5)P_2$ – present in small amounts in inner half of PM lipid layer.
- Receptors which operate through Inositol Phospholipid pathway- activate **Gq** protein, which activates Phospholipase C.
- Activated Phospholipase C cleaves $PI(4,5)P_2$ into Inositol 1,4,5 tri-PO4 (IP3) and Diacylglycerol (DAG).
- **IP3** – small, water soluble molecule, leaves PM and diffuses rapidly through cytosol to E.R., binds to and opens IP3 gated Ca2+ release channels in E.R. membrane
- Stored Ca in ER is released through open channels- quickly raising Ca^{2+} concentration in cytosol.

DAG- Diacylglycerol remains embedded in membrane, where it has 2 signaling roles. 1st, it can be further cleaved to release arachidonic acid, which can either act as a messenger or be used in synthesis of other small lipid messengers called *eicosanoids. Eicosanoids, such as prostaglandins,* participate in pain and inflammatory responses, and most anti-inflammatory drugs (as aspirin, ibuprofen, and cortisone) act in part, at least by inhibiting their synthesis.

2^{nd} function of DAG is to activate a serine/threonine protein kinase called **protein kinase C (PKC), so** named because it is Ca2+-dependent. The initial rise in cytosolic Ca2+ induced by IP3 alters the PKC so that it translocates from cytosol to the cytoplasmic face of PM and is activated by the combination of Ca2+, diacylglycerol, and the negatively charged membrane phospholipid Phosphatidylserine.

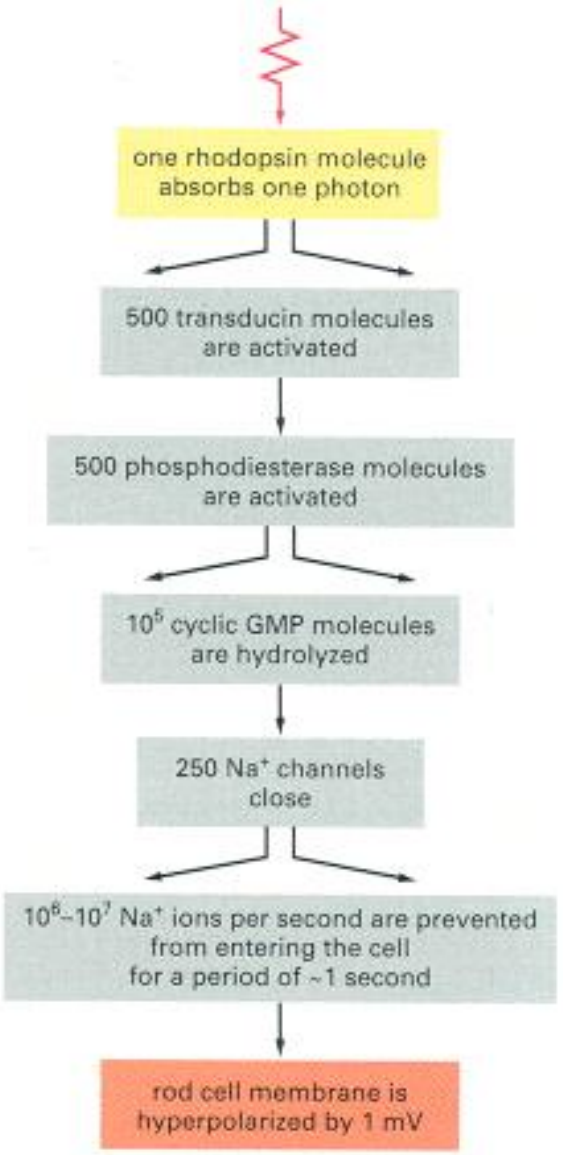
Inositol 1,4,5 Triphosphate (IP-3) Triggers Release of Ca2+ from the ER



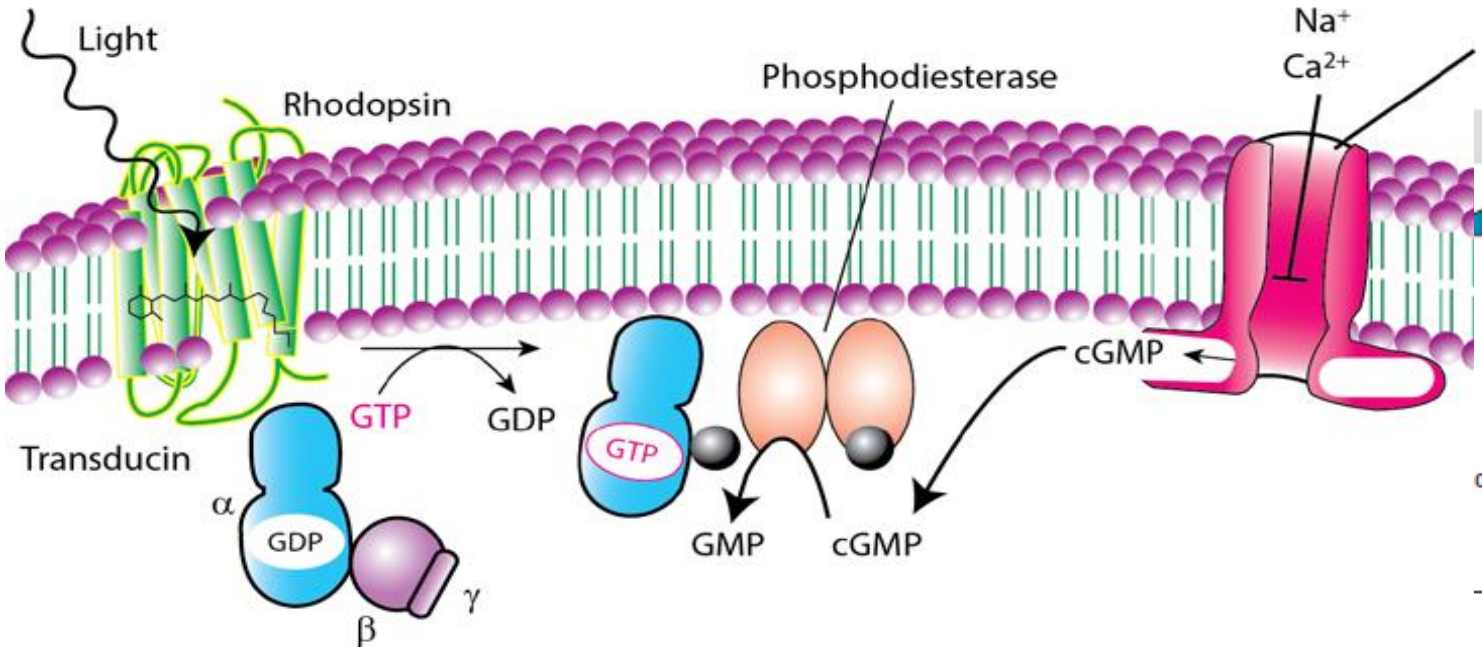
Most intracellular Ca^{2+} ions are sequestered in the mitochondria and in ER lumen and other vesicles. Cells employ various mechanisms for regulating the concentration of Ca^{2} ions in the cytosol, which usually is kept below 0.2 M. A small rise in cytosolic Ca^{2} induces a variety of cellular responses, and thus the cytosolic concentration of Ca^{2} is carefully controlled.

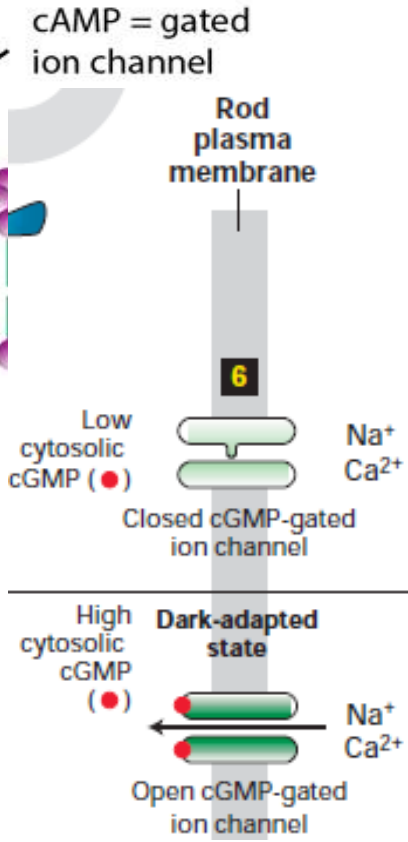
The Role of GPCRs in Sensory Perception of Light

- *Rhodopsin is the* light-sensitive GPCR present in rods of retina (photoreceptor cells responding to low light intensity) and providing black-and-white picture of our environment at night or in dark. Several closely related GPCRs are present in cones of retina, providing color vision under bright light.
- Absorption of a single photon of light induces a conformational change in the rhodopsin molecule, which transmits a signal to a heterotrimeric G protein (called *transducin), which activates a coupled effector.*
- The effector in this case is the enzyme cGMP phosphodiesterase, which hydrolyzes the cyclic nucleotide cGMP, a second messenger.
- cGMP plays an important role in visual excitation in the rod cells of the retina.
- In the dark, cGMP levels remain high and thus capable of binding to cGMP-gated sodium channels in the plasma membrane, keeping the channels in an open configuration.
- Activation of cGMP phosphodiesterase results in lowered cGMP levels, leading to the closure of sodium channels.
- This unusual response, triggered by a decrease in the concentration of a second messenger, may lead to the generation of action potentials along the optic nerve.



Amplification in the light-induced catalytic cascade in vertebrate rods.





- Photo transduction: - Rod Cell – High sensitive to light, less sensitive to color.
  - Cone Cell- High sensitive to color, less sensitive to light.
- cGMP - in the vertebrate eye, 2nd messenger that converts visual signals received as light to nerve impulses. The photoreceptor in rod cells of retina is a GPCR called rhodopsın .
- Rhodopsin interact with transducin G-transducin hetermeric G protein. In dark G transducin found inactive state and all subunit combined to each other.
- When light falls on the extracellular side of rhodopsin, then some conformational changes occurs in it by which its bounded chromophore 11-cis retinal is converted to all-trans retinal form, ultimately rhodopsine's catalytic cytoplasmic side gets exposed which interacts with the G protein transducin and activates them by replacement of GDP by GTP on its α- subunit. The activated Gα then activates cGMP phosphodiesterase, which converts all cGMP into 5' GMP. Due to this cGMP level gradually decreases, the cGMP dependent Na ion-channel becomes closed. This channel is also entry site of calcium ions so Ca^{++} levels also decrease.
- This critical situation created in the cell is called **hyperpolarisation**. But after decreasing Ca++ level, guanylyl cyclase is activated and again cGMP synthesis starts.
- Thus we can summarize the whole phenomenon as, *change in cGMP level in retinal rod cells is translated to a nerve impulse by a direct effect of cGMP on ion channels in PM*.

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

* Families are determined by amino acid sequence relatedness of the α subunits. Only selected examples are shown. About 20 α subunits and at least 4 β subunits and 7 γ subunits have been described in mammals.

(Note: All the original contributors of the concept and findings published elsewhere are gratefully acknowledged while preparing the E-content for the purpose of student reading material in convenient form for biochemistry and allied discipline).

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