SIGNAL TRANSDUCTION

Signal transduction is the process by which a chemical or physical signal is transmitted through a cell as a <u>series of molecular events</u>, most commonly <u>protein phosphorylation</u>

catalysed by protein kinases, which ultimately results in a cellular response.

 Any process occurring within cells that convert one kind of signal/stimulus into another type.

SIGNAL TRANSDUCTION

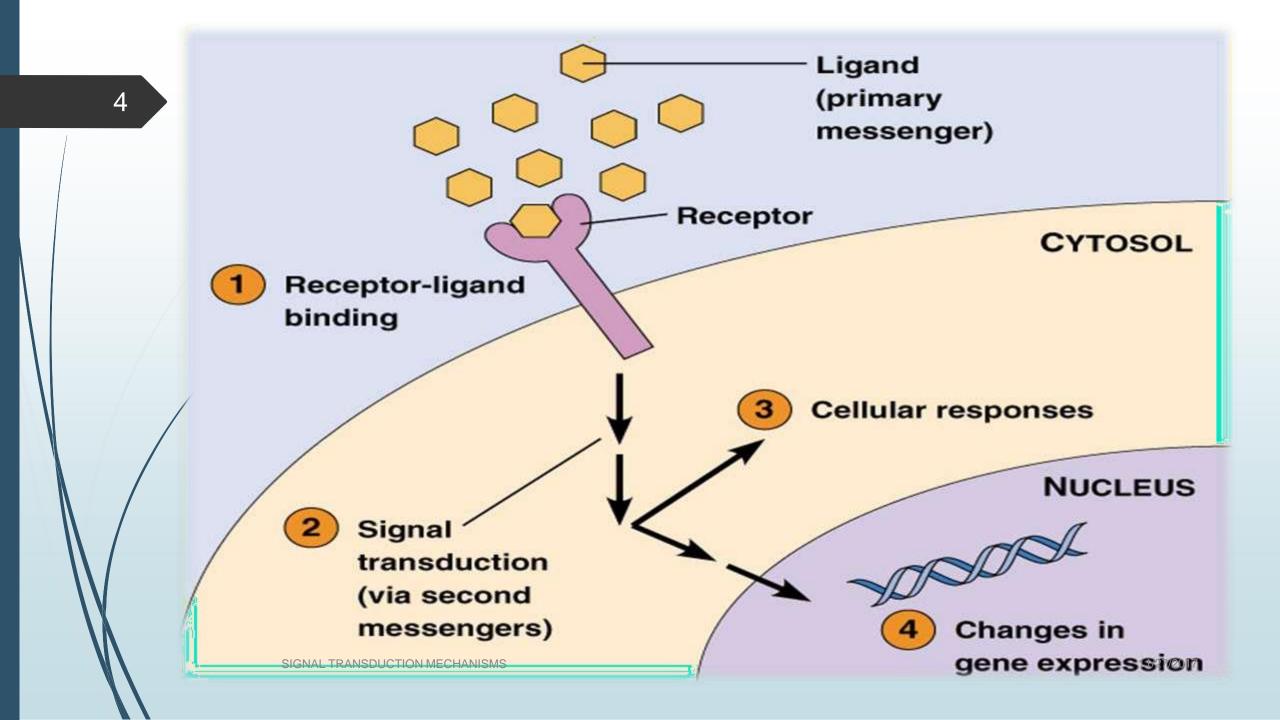
- It also known as cell signaling in which the transmission of molecular signals from a cell's exterior to its interior.
- Signals received by cells must be transmitted effectively into the cell to ensure an appropriate response. This step is initiated by cell-surface receptors which triggers a biochemical chain of events inside the cell, creating a response.

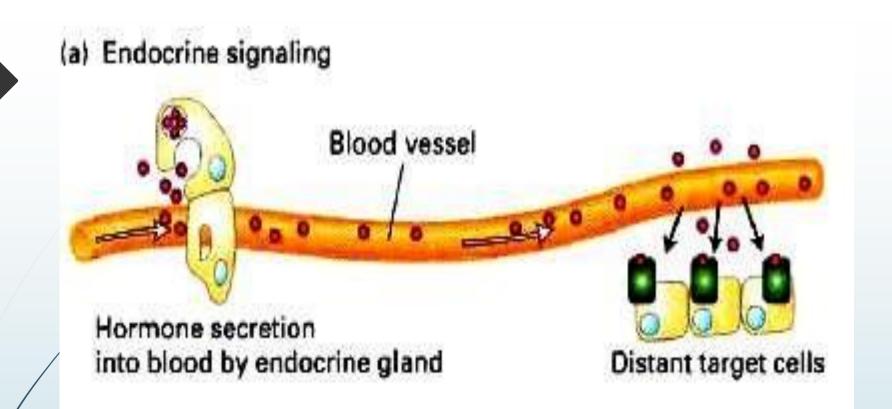
3 Proteins responsible for detecting stimuli are generally termed as <u>receptors</u>.

The ligand is signalling molecules that binds to receptors that trigger events inside the cell & they are *primary messenger*.

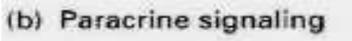
As the result of binding the ligand to receptor, other molecules or **second messengers** are produced within the target cell.

Second messengers relay the signal from one location to another (such as from plasma membrane to nucleus) leading to cascade of events/changes within a cell.

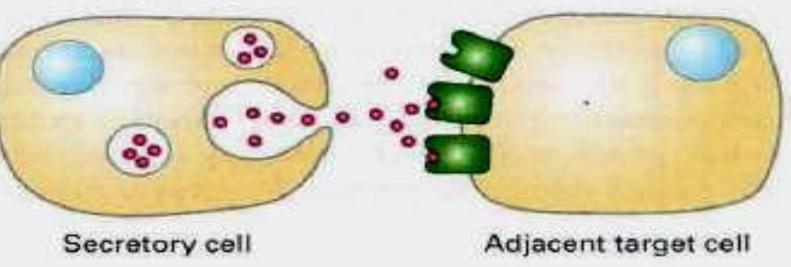




In endocrine signaling, the signaling molecules are synthesized and secreted by signaling cells (for example, those found in endocrine glands), transported through the circulatory system of the organism, and finally act on target cells distant from their site of synthesis.



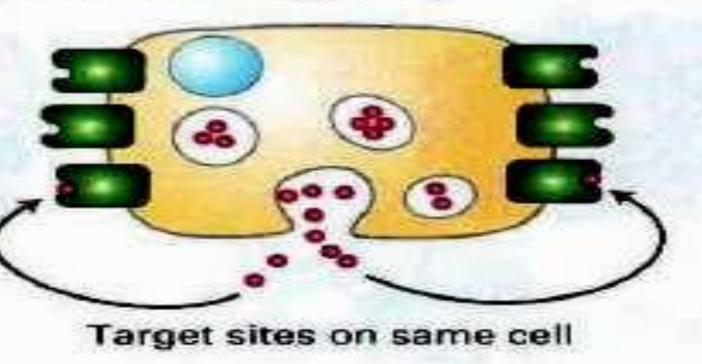
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In paracrine signaling, the signaling molecules released by a cell affect only those target cells in **close proximity**. Anerve cell releasing a neurotransmitter (e.g., acetylcholine) that acts on an adjacent nerve cell or on a muscle cell (inducing or inhibiting muscle contraction) is an example of paracrine signaling.

SIGNAL TRANSDUCTION MECHANISMS

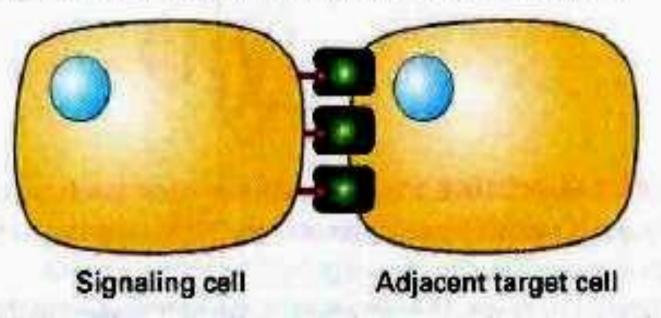
(c) Autocrine signaling



In autocrine signaling, cells respond to substances that they themselves release. Some growth factors act in this fashion, and cultured cells often secrete growth factors that stimulate their own growth and proliferation.

SIGNAL TRANSDUCTION MECHANISMS

(d) Signaling by plasma-membrane-attached proteins



Proteins attached to the plasma membrane of one cell can interact directly with cell-surface receptors on adjacent cells.

Integral membrane proteins located on the cell surface also play an important role in signaling . In some cases, such membrane-bound signals on one cell bind receptors on the surface of an adjacent target cell, triggering its differentiation.

RECEPTORS

Seceptors can be roughly divided into two major classes: *intracellular* receptors and *extracellular* receptors.

EXTRACELLULAR RECEPTORS

- Extracellular receptors are integral transmembrane proteins and make up most receptors.
- They span the plasma membrane of the cell, with one part of the receptor on the outside of the cell and the other on the inside.
- Signal transduction occurs as a result of a ligand binding to the outside region of the receptor (the ligand does not pass through the membrane).

10 Various Extracellular Receptors

G protein-coupled receptors.

Receptors with Kinase activity.

Integrin receptors.

Toll gate receptors.

Ligand-gated ion channel receptors.

SIGNAL TRANSDUCTION MECHANISMS

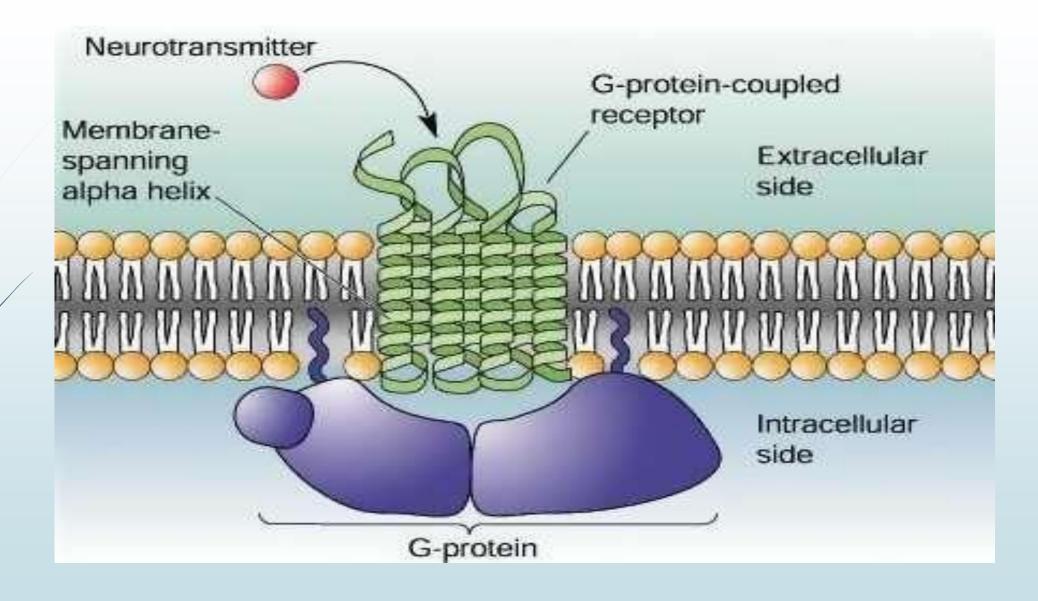
G PROTEIN_COUPLED RECEPTORS (GPCRs)

Also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors, and G protein–linked receptors (GPLR).

These constitute a large protein family of receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses.

Coupling with G proteins, they are called seven-transmembrane receptors because they pass through the cell membrane seven times.

SIGNAL TRANSDUCTION MECHANISMS



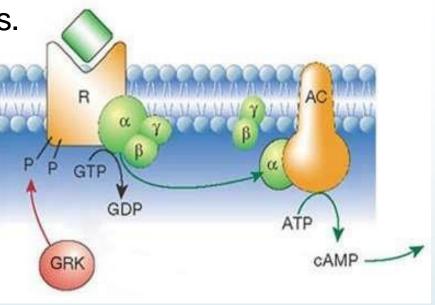
G proteins, also known as guanine nucleotide-binding proteins, are a family of proteins that act as molecular switches inside cells, and are involved in transmitting signals from a variety of stimuli outside a cell to its interior.

When they are bound to GTP, they are 'on', and, when they are bound to GDP, they are 'off'.

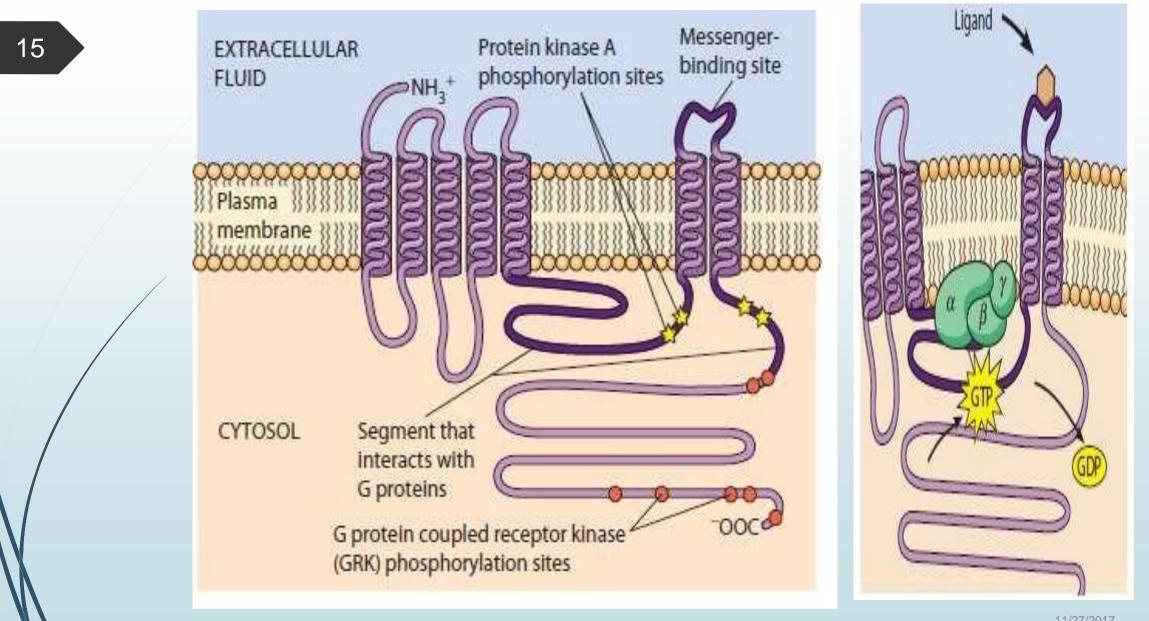
G proteins belong to the larger group of enzymes called GTPases

 There are two classes of G proteins.
The first function as monomeric small *GTPases*.

The second form and function as heterotrimeric G protein complexes.



Heterotrimeric class of complexes is made up of alpha (α), beta (β) and gamma (γ) subunits. The beta and gamma subunits can form a stable dimeric complex referred to as the beta-gamma complex while alpha subunit dissociates on activation.



There are two principal signal transduction pathways involving the G protein-coupled receptors:

□ A. the *cAMP signal pathway* and

B. the phosphatidylinositol signal pathway.

A. CAMP-DEPENDENT PATHWAY

It is also known as the adenylyl cyclase pathway.

In a cAMP-dependent pathway, the activated G_s alpha subunit binds to and activates an enzyme called *adenylyl cyclase*, which, in turn, catalyzes the conversion of ATP into cyclic adenosine monophosphate (cAMP).

Μ

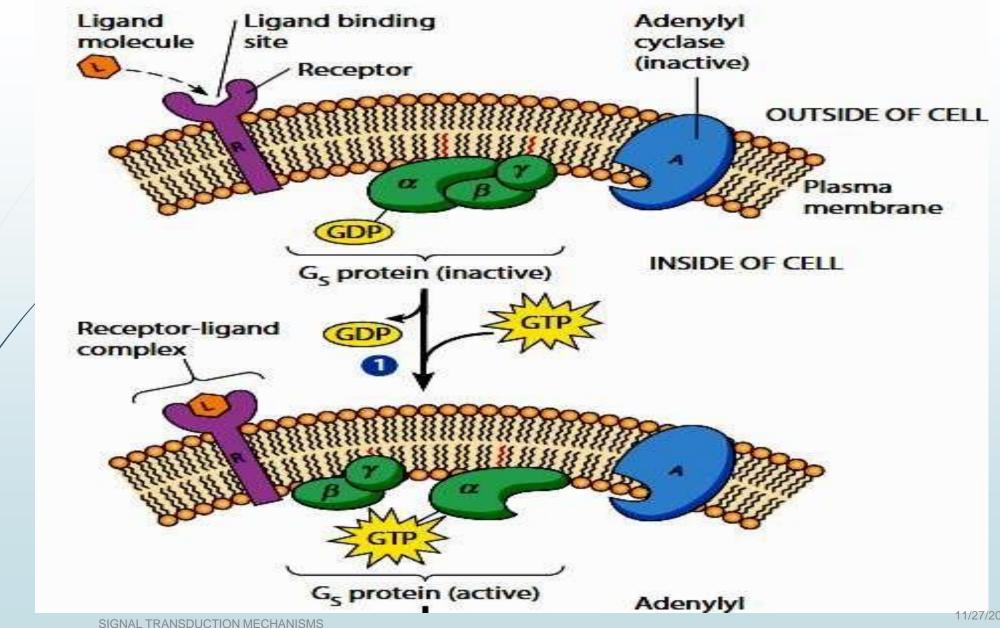
 It is known that in the inactive state, the GPCR is bound to a heterotrimeric G protein complex.

Binding of primary messenger to the GPCR results in a conformation change in the receptor that is transmitted to the bound G_{α} subunit of the heterotrimeric G protein.

The activated G_{α} subunit exchanges GTP in place of GDP which in turn triggers the dissociation of G_{α} subunit from the $G_{\beta\gamma}$ dimer and from the receptor.

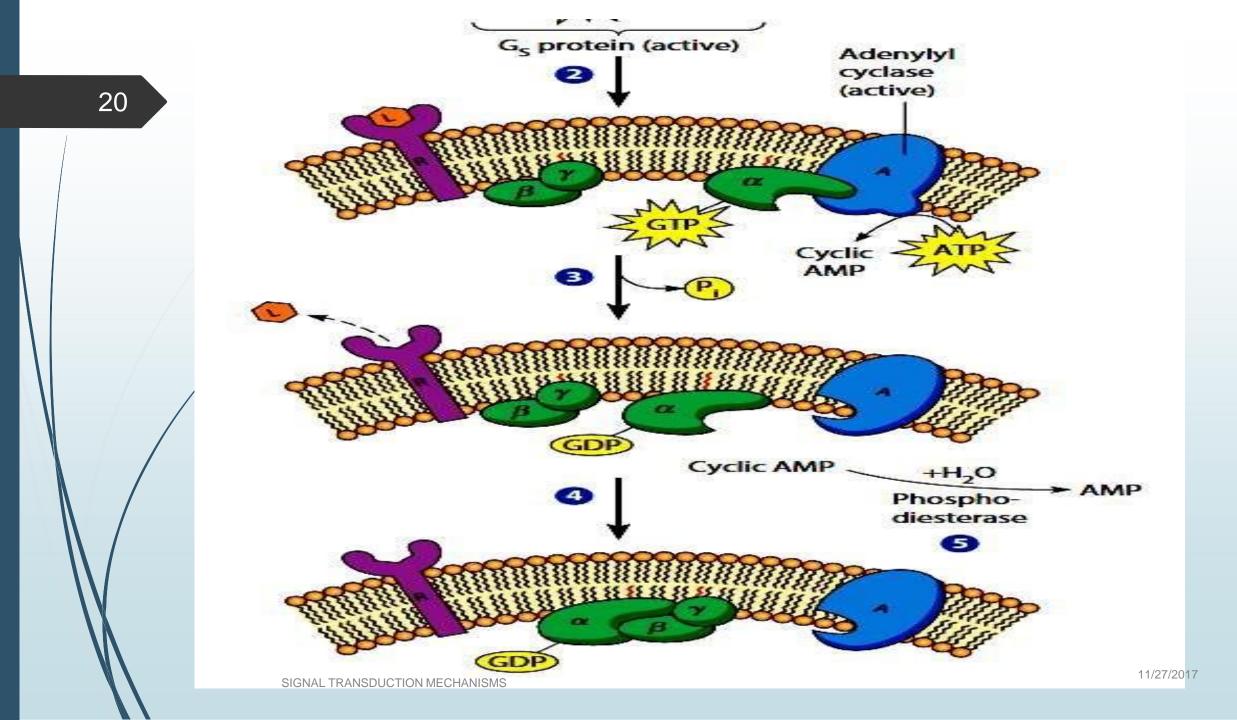
The dissociated G_{α} and $G_{\beta\gamma}$ subunits interact with other intracellular proteins to continue the signal transduction cascade.

While the freed GPCR is able to rebind to another heterotrimeric G protein to form a new complex that is ready to initiate another round of signal transduction.



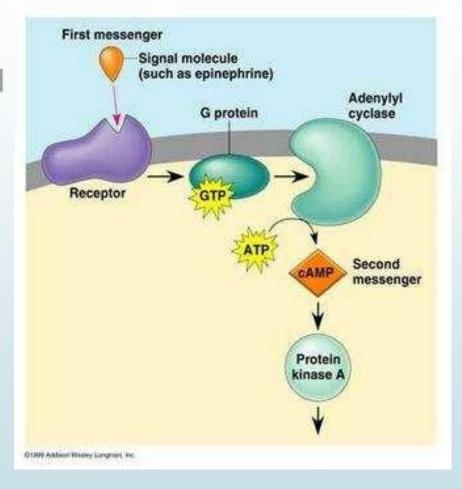
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- In the inactive state, and subunits a represent as a complex, with GDP bound to the subunit. When a ligand (L) binds its receptor, it binds and activates a Gs protein.
- When a receptor is activated by ligand binding, the receptor-ligand complex associates with the Gs protein, causing the displacement of GDP by GTP and the dissociation of the Gsa-GTP complex.
- The GTP-Gsa complex then binds to and activates membrane-bound adenylyl cyclase, which synthesizes cAMP.
- Activation ends when the ligand leaves the receptor, the GTP is hydrolyzed to GDP by the GTPase activity of the Gsa subunit, and the Gsa dissociates from adenylyl cyclase.
- Adenylyl cyclase then reverts to the inactive form, the Gsa re-associates with the Gsbg complex, and cAMP molecules in the cytosol are hydrolyzed to AMP by the phosphodiesterase.

- Increases in concentration of the second messenger cAMP may lead to the activation of:
- □ cyclic nucleotide-gated ion channels
- exchange proteins activated by cAMP (EPAC).
 - an enzyme called protein kinase A (PKA).



The PKA enzyme is also known as cAMP-dependent enzyme because it gets activated only if cAMP is present. Once PKA is activated, it phosphorylates a number of other proteins including:

enzymes that convert glycogen into glucose

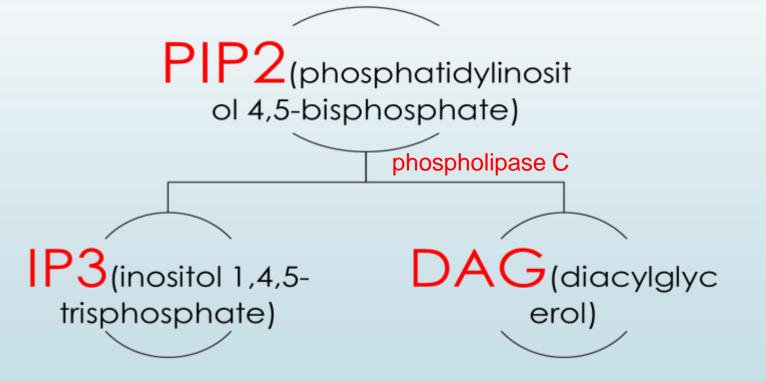
transcription factors, which regulate gene expression

DEACTIVATION

- The G_s alpha subunit slowly catalyzes the hydrolysis of GTP to GDP, which in turn deactivates the G_s protein, shutting off the cAMP pathway.
- The pathway may also be deactivated downstream by directly inhibiting adenylyl cyclase or dephosphorylating the proteins phosphorylated by PKA.
- Molecules that inhibit the cAMP pathway include:
- cAMP phosphodiesterase dephosphorylates cAMP into AMP, reducing the cAMP levels.
 - G_i protein, which is a G protein that inhibits adenylyl cyclase, reducing cAMP levels.

B. PHOSPHATIDYLINOSITOL SIGNAL PATHWAY;

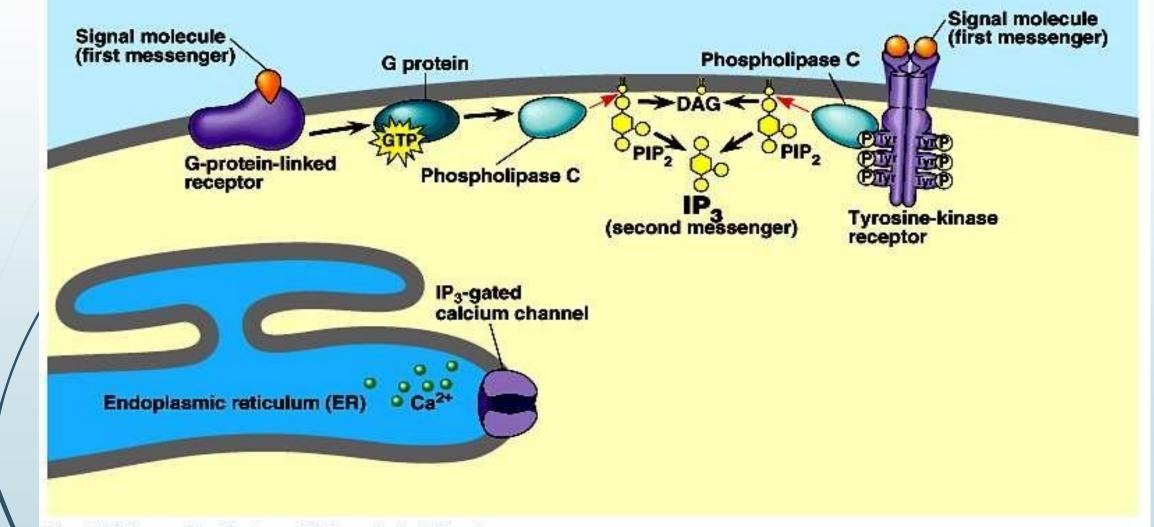
In the phosphatidylinositol signal pathway, the extracellular signal molecule binds with the G-protein receptor (G_q) on the cell surface and activates secondary messenger phospholipase C, which hydrolyzes PIP2.



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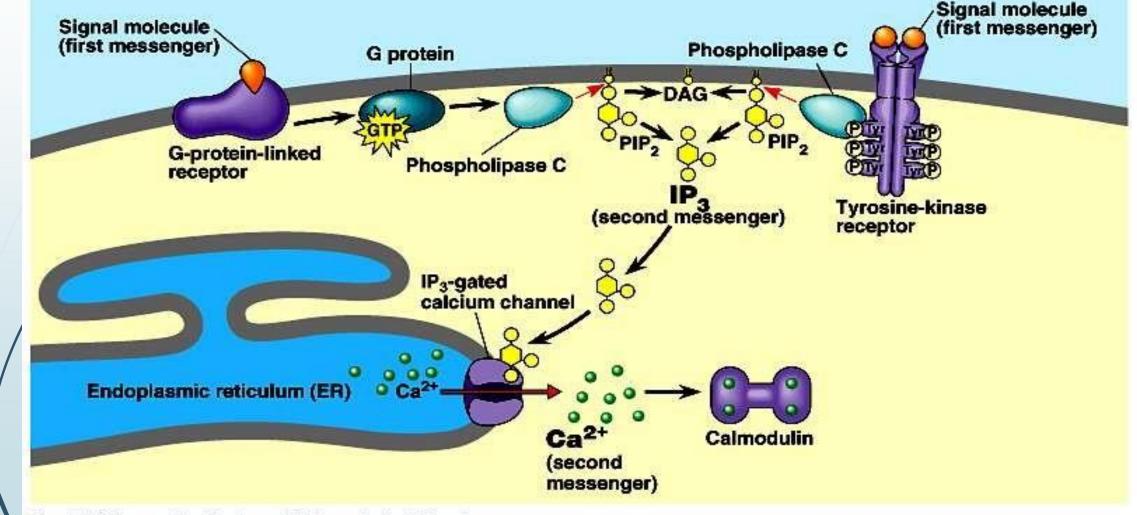
 IP3 binds with the IP3 receptor in the membrane of the smooth endoplasmic reticulum and mitochondria to open Ca²⁺ channels.

DAG helps activate protein kinase C (PKC), which phosphorylates many other proteins, changing their catalytic activities, leading to cellular responses. During signal transduction, calcium can be released into the cytoplasm: Perception



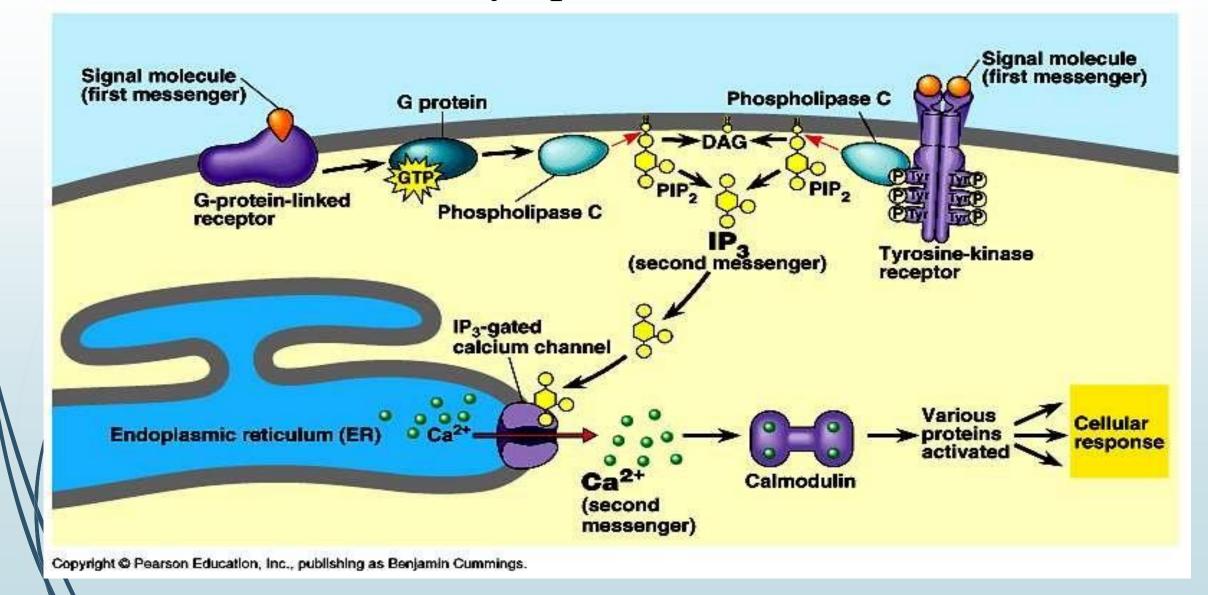
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During signal transduction, calcium can be released into the cytoplasm: Transduction



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During signal transduction, calcium can be released into the cytoplasm



The effects of Ca²⁺ are also remarkable:

It cooperates with DAG in activating PKC and can activate the CaM kinase pathway, in which calcium-modulated protein calmodulin (CaM) binds Ca²⁺, undergoes a change in conformation, and activates CaM kinase.

The kinase then phosphorylates target enzymes, regulating their activities. The two signal pathways are connected together by Ca²⁺-CaM, which is also a regulatory subunit of adenylyl cyclase and phosphodiesterase in the cAMP signal pathway.

A wide variety of cellular effects have been linked to the activation of protein kinase C, including the stimulation of cell growth, the regulation of ion channels, changes in the cytoskeleton, increases in cellular pH, and effects on secretion of proteins and other substances.

5. INTRACELLULAR RECEPTORS

Intracellular receptors are receptors located inside the cell rather than on its cell membrane.

Examples are:

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Class of nuclear receptors located in the cell nucleus and cytoplasm

 \square IP₃ receptor located on the endoplasmic reticulum.



SIGNAL TRANSDUCTION MECHANISMS

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