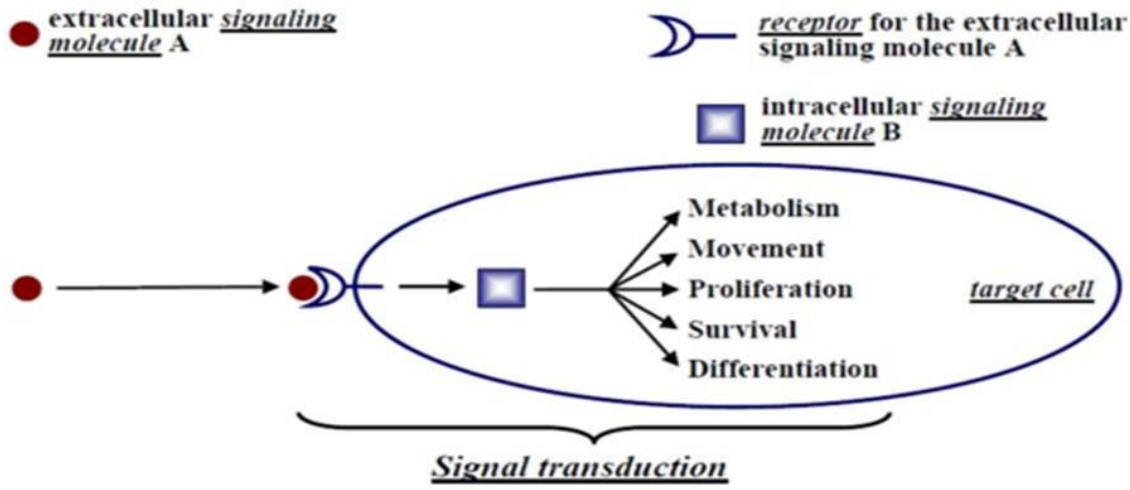
Mechanism of

Signal transduction

Introduction

No cell lives in isolation; Cells lie n the form of groups in diverse tissues and cells. Therefore, cell to cell communication network is needed to coordinate the growth, differentiation and metabolism of the cells. Cellular communication is a fundamental property of all cells and shapes the function and abilities of every living organism. But cells communicating over large distances need extra cellular products which act as signals. These extra cellular products are synthesized and released by signaling cells and then they move towards the other cells and induce

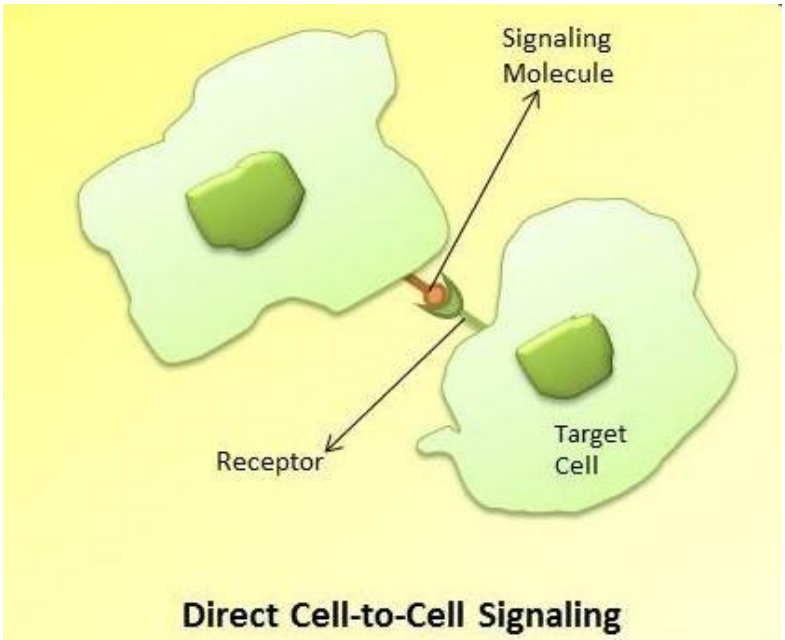
response on the target cells that have receptors for signal molecules. Receptors are usually present on cell surface but sometimes they are present inside the cell as well. Even single-celled organisms have the ability to communicate with each other or other organisms. Eukaryotic microorganisms, such as yeasts, slime molds, and protozoans, use secreted molecules called pheromones to coordinate the aggregation of free-living cells for sexual mating or differentiation under certain environmental conditions. Yeast mating-type factors are a well-understood example of pheromone-mediated cell to-cell signalling.



Cell signaling: is the transmission of signal from one cell to another cell so that the response generated subsequently in the target cell may lead to the biological processes like metabolic activities within the cell and thereby in the body.

Cell signalling can lead to:

- Muscle contraction
- Changes in transcription/translation
- Changes in protein secretion and protein activity
- Apoptosis or cell division
- Hormones, neurotransmitters, environmental change result in changes within the cell itself that are mediated by signal transduction (cell signalling).



Signaling molecules are the molecules that are responsible for transmitting information between cells in your body. signaling molecules are basically chemicals (like nitric oxide etc.) or proteins (hormones etc.) which are secreted or expressed on the surface of the cell. They then bind to receptors which are present on the other cell (these cells are called target cell) or sometimes even present on the same cell; thereby coordinating the functions of various cells. The binding of these signaling molecules on the receptor creates a series of reactions that regulates various methods/systems like movement, metabolism, survival, differentiation etc. Chemical signals are released by signaling cells in the form of small, usually volatile or soluble molecules called ligands. A ligand is a molecule that binds another specific molecule, in some cases, delivering a signal in the process. Ligands can thus be thought of as signaling molecules. Ligands interact with proteins in target cells, which are cells that are affected by chemical signals; these proteins are also called receptors. Ligands and receptors exist in several varieties; however, a specific ligand will have a specific receptor that typically binds only that ligand.More important in plants and animals are extracellular signaling molecules that function within an organism to control metabolism of sugars, fats' and amino acids, the growth and differentiation of tissues, the synthesis and secretion of proteins, and the composition of intracellular and extracellular fluids. Animals also respond to many signals from their environment, including light, oxygen, odorants, and tastants in food.

Some signaling molecules are able to cross the plasma membrane and bind to intracellular receptors in the cytoplasm or nucleus, whereas others bind to receptors expressed on the target cell surface. The signalling molecule or ligand can be **water soluble** or **hydrophobic.** Water-soluble ligands are polar and therefore cannot pass through the plasma membrane unaided; sometimes, they are too large to pass through the membrane at all. Instead, most water-soluble ligands bind to the extracellular domain of cell-surface receptors. This group of ligands is quite diverse and includes small molecules, peptides, and proteins. Small Hydrophobic Ligands can directly diffuse through the plasma membrane and interact with internal receptors. Important members of this class of ligands are the steroid hormones.

The signalling is based on (3 factors)

1. The distance over which the signal molecule acts

2. The speed the signal molecule is delivered to target cell

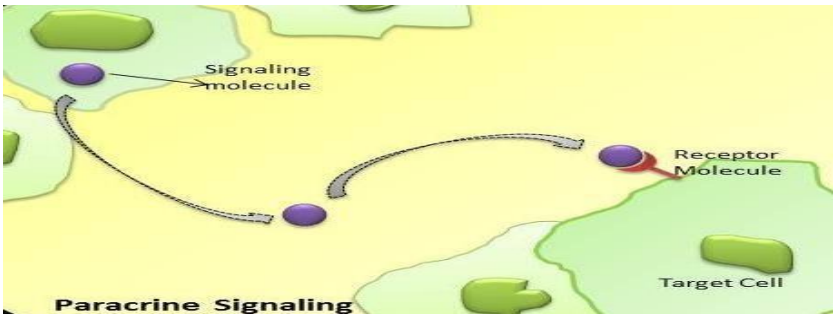
3. Selectivity with which the signal molecule is delivered to its target cell

Types of Signalling

Cells communicate by means of exrtracellular signalling molecules that are produced and released by signalling cells. These molecules recognize and bind to receptors on the surface of target cells where they cause a cellular response by means of a signal transduction pathway. Depending on the distance the signal molecules has to travel, there are four categories of chemical signaling found in multicellular organisms: paracrine signaling, endocrine signaling, autocrine signaling, and direct signaling across gap junctions. The main difference between the different categories of signalling is the distance that the signal travels through the organism to reach the target cell. Not all cells are affected by the same signals.

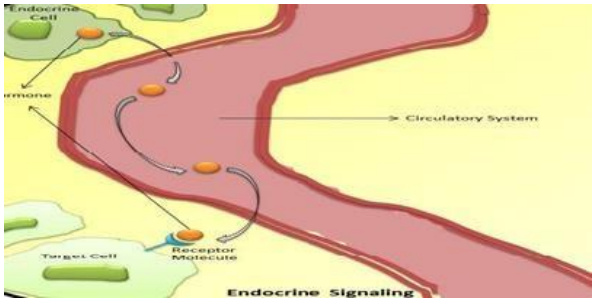
1. Paracrine Signalling

Signals that act locally between cells that are close together are called paracrine signals. Paracrine signals move by diffusion through the extracellular matrix. These types of signals usually elicit quick responses that last only a short amount of time.



2. Endocrine Signalling

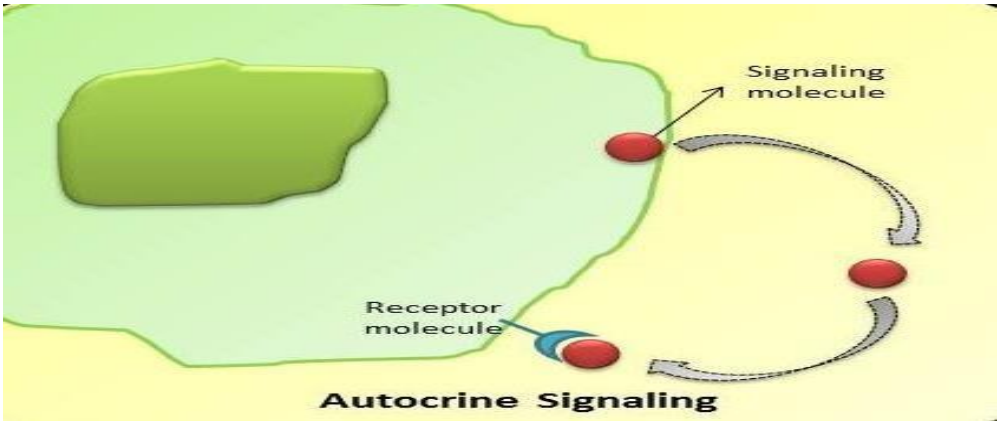
Signals from distant cells are called endocrine signals, and they originate from endocrine cells. (In the body, many endocrine cells are located in endocrine glands, such as the thyroid gland, the hypothalamus, and the pituitary gland, different source of plant hormone) These types of signals usually produce a slower response but have a longer-lasting effect.



In both plant and animal, the ligands/signal molecules released in the form of signalling cells are called hormones, signalling molecules that are produced in one part of the body but affect other body regions some distance away.

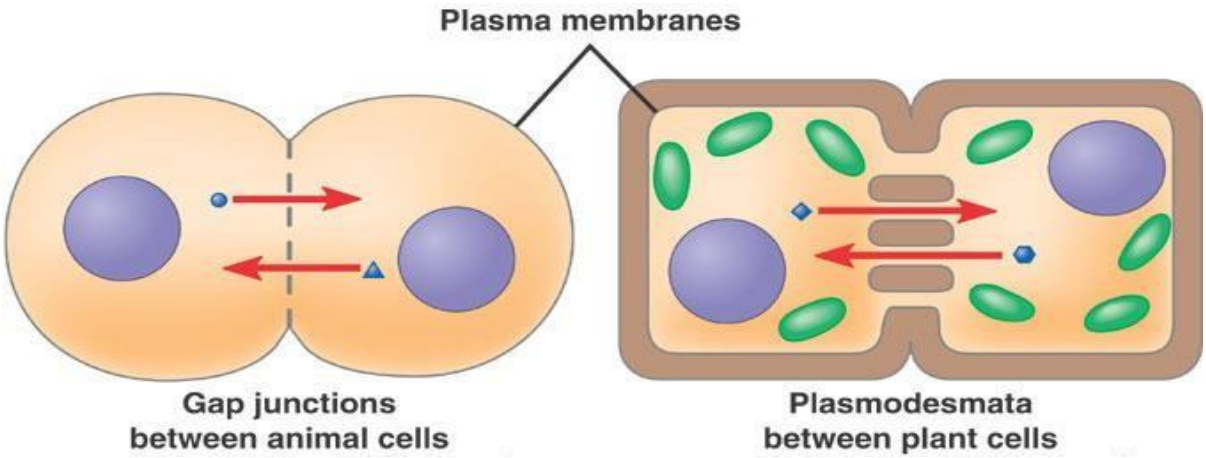
3. Autocrine Signalling

Autocrine signals are produced by signalling cells that can also bind to the ligand that is released. This means the signalling cell and the target cell can be the same or a similar cell (the prefix auto- means self, a reminder that the signalling cell sends a signal to itself). This type of signaling often occurs during the early development of an organism to ensure that cells develop into the correct tissues and take on the proper function.



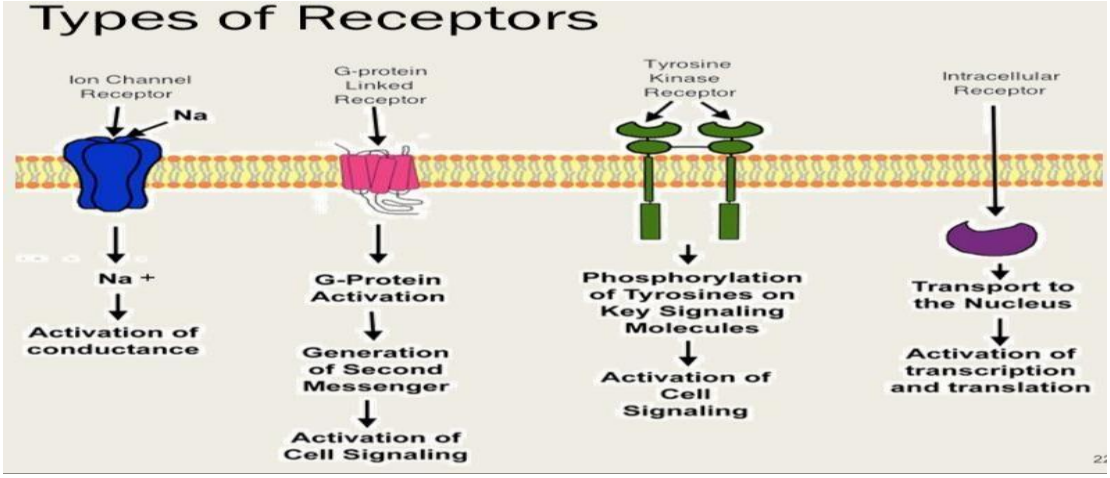
4. Direct Signalling Across Gap Junctions

Gap junctions in animals and plasmodesmata in plants are connections between the plasma membranes of neighbouring cells. These water-filled channels allow small signalling molecules, called intracellular mediators, to diffuse between the two cells. Small molecules, such as calcium ions (Ca2+), are able to move between cells, but large molecules like proteins and DNA cannot fit through the channels. In plants, plasmodesmata are ubiquitous, making the entire plant into a giant, communication network.



Signaling receptors

Receptors are protein molecules in the target cell or on its surface that bind ligand. There are two types of receptors, internal receptors and cell-surface receptors. Once the signalling molecule binds to its receptor, it causes a conformational change in it that result in a cellular response. The same ligand can bind to different receptors causing different responses (acetylcholine). On the other hand different ligands binding to different receptors can produce the same cellular response (Glucagon, Epinephrine).



Internal receptors

Internal receptors, also known as intracellular or cytoplasmic receptors, are found in the cytoplasm of the cell and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane. Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis (transcription) to mediate gene expression. When the ligand binds to the internal receptor, a conformational change is triggered that exposes a DNA-binding site on the protein. The ligand-receptor complex moves into the nucleus, then binds to specific regulatory regions of the chromosomal DNA and promotes the initiation of transcription.

Cell-Surface receptors

Cell-surface receptors, also known as transmembrane receptors, are cell surface, membrane-anchored (integral) proteins that bind to external ligand molecules. This type of receptor spans the plasma membrane and performs signal transduction, in which an extracellular signal is converted into an intercellular signal. Ligands that interact with cell-surface receptors do not have to enter the cell that they affect. Cell-surface receptors are also called cell-specific proteins or markers because they are specific to individual cell types.

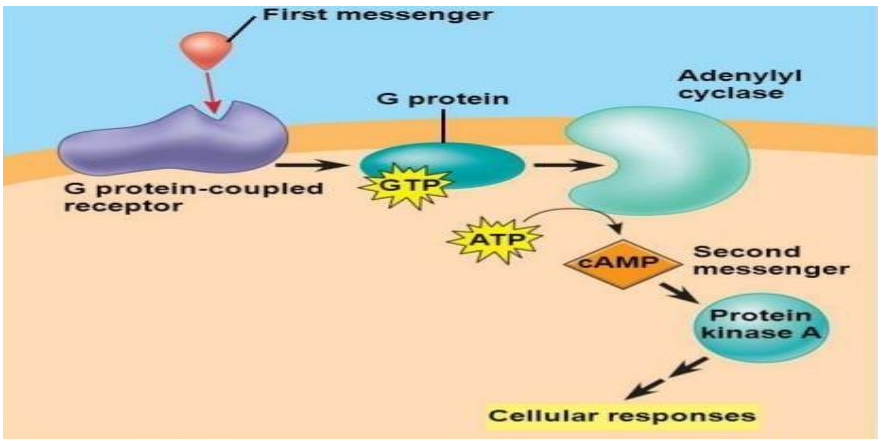
Cell-surface receptors are involved in most of the signaling in multicellular organisms. There are three general categories of cell-surface receptors: ion channel-linked receptors, G-protein-linked receptors, and enzyme-linked receptors.

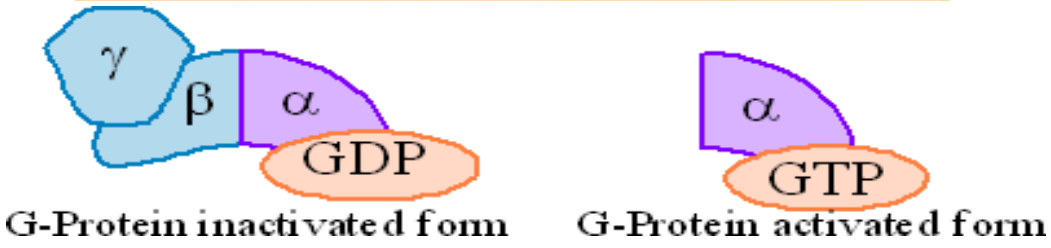
Ion channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through. To form a channel, this type of cell-surface receptor has an extensive membrane-spanning region.

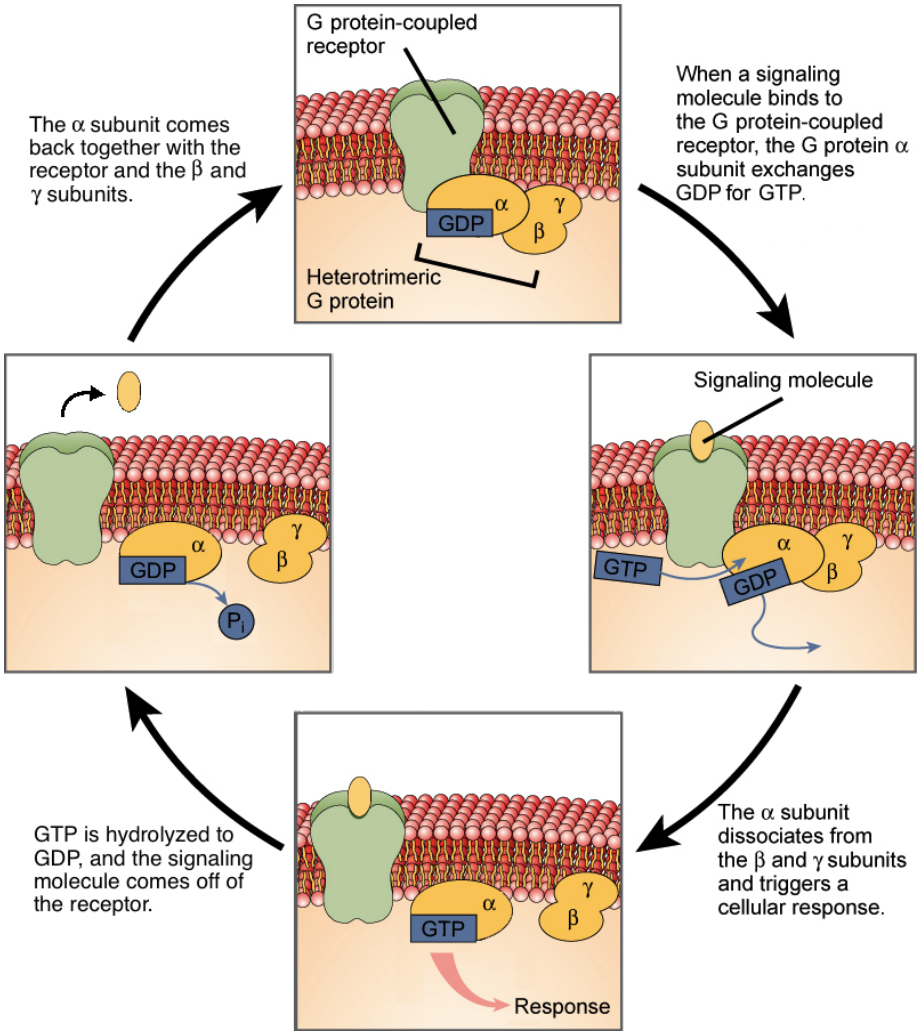
When a ligand binds to the extracellular region of the channel, there is a conformational change in the proteins structure that allows ions such as sodium, calcium, magnesium, and hydrogen to pass through.

G-protein-linked receptors bind a ligand and activate a membrane protein called a G-protein. The activated G-protein then interacts with either an ion channel or an enzyme in the membrane. All G-protein-linked receptors have seven transmembrane domains, but each receptor has its own specific extracellular domain and G-protein-binding site.

Cell signaling using G-protein-linked receptors occurs as a cyclic series of events. Before the ligand binds, the inactive G-protein can bind to a newly revealed site on the receptor specific for its binding. Once the G-protein binds to the receptor, the resultant shape change activates the G-protein, which releases GDP and picks up GTP. The subunits of the G-protein then split into the α subunit and the βγ subunit. One or both of these G-protein fragments may be able to activate other proteins as a result. After a while, the GTP on the active α subunit of the G-protein is hydrolyzed to GDP and the βγ subunit is deactivated. The subunits reassociate to form the inactive G-protein and the cycle begins anew.



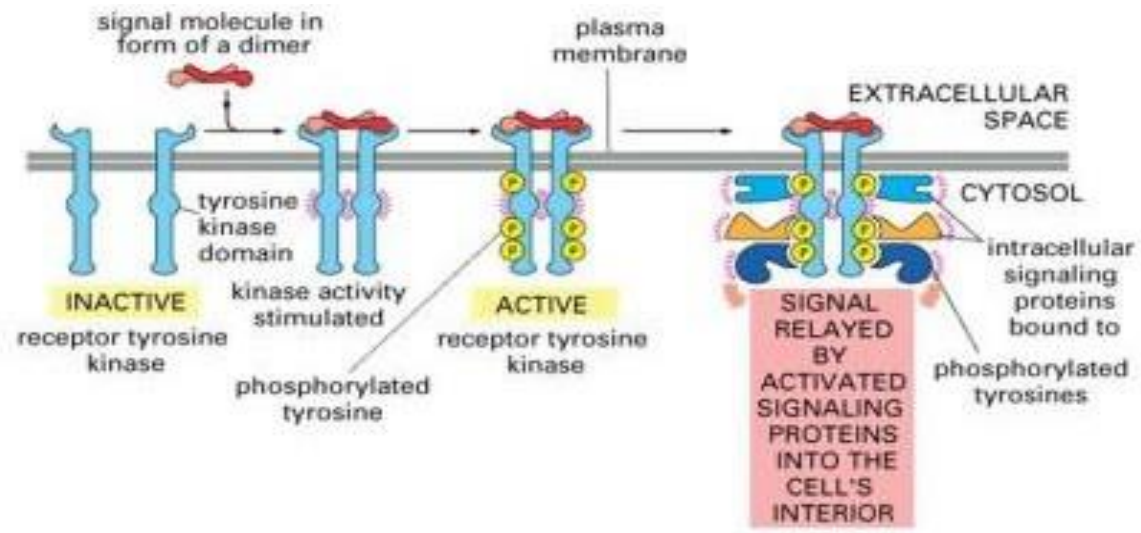




In cholera, for example, the water-borne bacterium *Vibrio cholerae* produces a toxin, choleragen that binds to cells lining the small intestine. The toxin then enters these intestinal cells, where it modifies a G-protein that controls the opening of a chloride channel and causes it to remain continuously active, resulting in large losses of fluids from the body and potentially fatal dehydration as a result

Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme. In some cases, the intracellular domain of the receptor itself is an enzyme. The enzyme-linked receptors normally have large extracellular and intracellular domains, but the membrane-spanning region consists of a single alpha-helical region of the peptide strand. When a ligand binds to the extracellular domain, a signal is transferred through the membrane, activating the enzyme. Activation of the enzyme sets off a chain of events

within the cell that eventually leads to a response. One example of this type of enzyme-linked receptor is the tyrosine kinase receptor. A kinase is an enzyme that transfers phosphate groups from ATP to another protein. The tyrosine kinase receptor transfers phosphate groups to tyrosine molecules (tyrosine residues). First, signaling molecules bind to the extracellular domain of two nearby tyrosine kinase receptors. The two neighboring receptors then bond together, or dimerize. Phosphates are then added to tyrosine residues on the intracellular domain of the receptors (phosphorylation). The phosphorylated residues can then transmit the signal to the next messenger within the cytoplasm



Cell signaling can be divided into 3 stages.

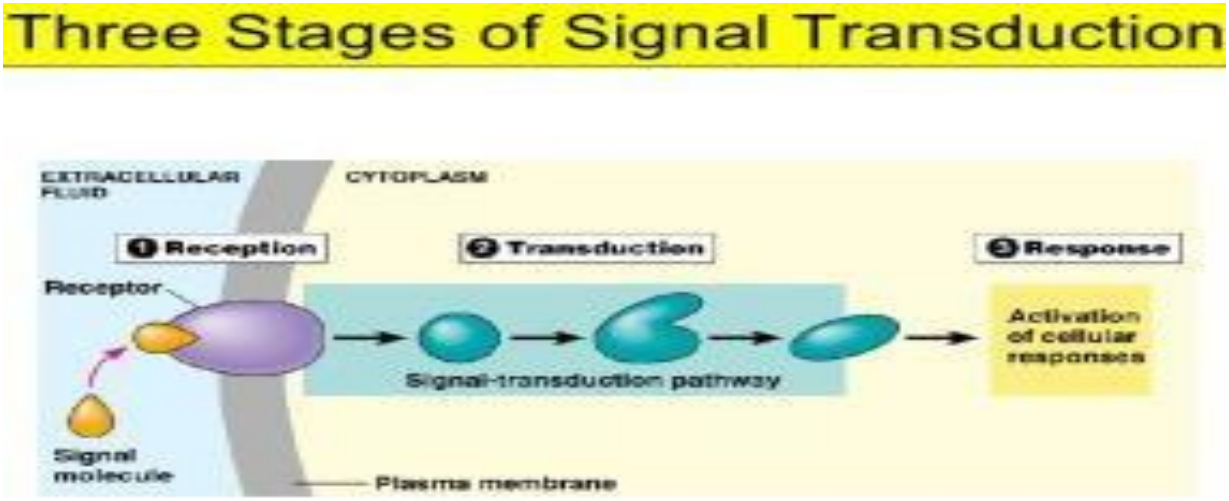
1. **Reception**: A cell detects a signaling molecule from the outside of the cell. A signal is detected when the chemical signal (also known as a ligand) binds to a receptor protein on the surface of the cell or inside the cell.
2. **Transduction**: When the signaling molecule binds the receptor it changes the receptor protein in some way. This change initiates the process of transduction. Signal transduction is usually a pathway of several steps. Each relay molecule in the signal transduction pathway changes the next molecule in the pathway.
3. **Response**: Finally, the signal triggers a specific cellular response.

Reception:

Reception refers to when a signal molecule binds to its receptor, most commonly either an integral membrane protein at the plasma membrane or a cytosolic receptor. In order to respond to changes in their immediate environment, cells must be able to receive and process signals

that originate outside their borders. Individual cells often receive many signals simultaneously, and they then integrate the information they receive into a unified action plan. But cells aren't just targets. They also send out messages to other cells both near and far.Once bound and activated by the signal molecule, the activated receptor can initiate a cellular response, such as a change in gene expression. Different receptors are specific for different molecules. In fact, there are hundreds of receptor types found in cells, and varying cell types have different populations of receptors. Receptors are generally transmembrane proteins, which bind to signaling molecules outside the cell and subsequently transmit the signal through a sequence of molecular switches to internal signaling pathways.

Once a receptor protein receives a signal, it undergoes a conformational change, which in turn launches a series of biochemical reactions within the cell. These intracellular signaling pathways, also called **signal transduction cascades**, typically amplify the message, producing multiple intracellular signals for every one receptor that is bound.



Transduction

Signal transduction is phenomenon which involves in the transfer of signal from extracellular to intracellular environment through the cell surface receptor protein that stimulate intracellular target enzymes, which may be either directly linked or indirectly coupled to receptors by G proteins. These intracellular enzymes serve as downstream signalling elements that propagate and amplify the signal initiated by ligand binding. Thus, signal transduction pathway allows cells to respond to extracellular environmental signals. Cells often use a multi-step pathway that transmits the signal quickly, while amplifying the signal to numerous molecules at each step.

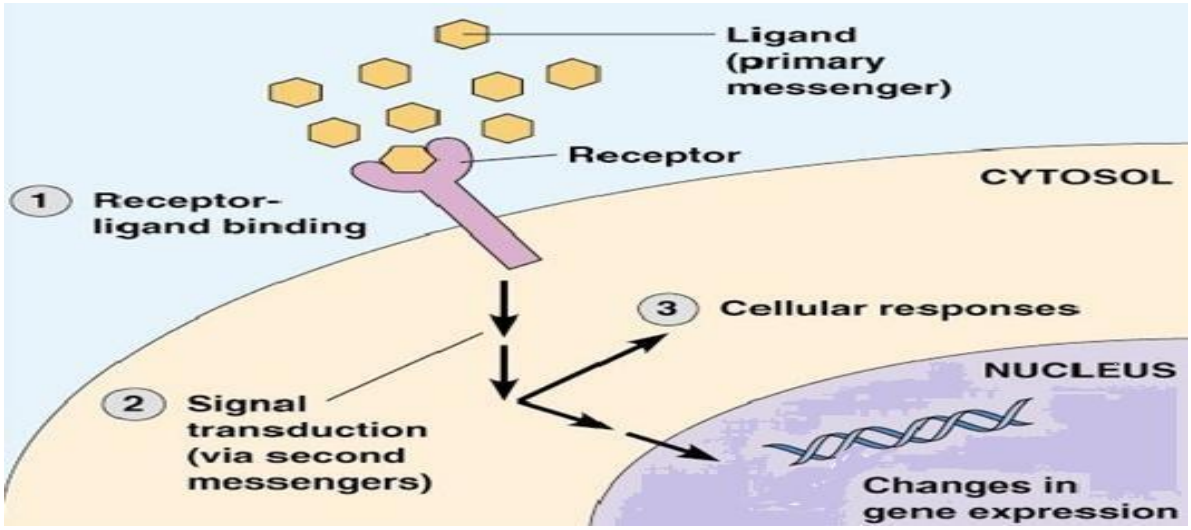
Steps in the signal transduction pathway often involve the addition or removal of phosphate groups which results in the activation of proteins. Enzymes that transfer phosphate groups from ATP to a protein are called **protein kinases**. Many of the relay molecules in a signal transduction pathway are protein kinases and often act on other protein kinases in the pathway. Often this creates a **phosphorylation cascade**, where one enzyme phosphorylates another, which then phosphorylates another protein, causing a chain reaction. Kinases are not the only tools used by cells in signal transduction. Small, nonprotein, water-soluble molecules or ions called **second messengers** (the ligand that binds the receptor is the first messenger) can also relay signals received by receptors on the cell surface to target molecules in the cytoplasm or the nucleus. Examples of second messengers include cyclic AMP (cAMP) and calcium ions. Each step in the cascade further amplifies the initial signal, and the phosphorylation reactions mediate both short- and long-term responses in the cell.

Also important to the phosphorylation cascade are a group of proteins known as protein phosphatases. **Protein phosphatases** are enzymes that can rapidly remove phosphate groups from proteins (dephosphorylation) and thus inactivate protein kinases.

Protein phosphatases are the "off switch" in the signal transduction pathway. Turning the signal transduction pathway off when the signal is no longer present is important to ensure that the cellular response is regulated appropriately. Dephosphorylation also makes protein kinases available for reuse and enables the cell to respond again when another signal is received.

Response

It is the third stage of cell signaling where the transduced signal finally triggers a specific cellular response. This response may be in the form of cellular activity–such as catalysis by an enzymeCell signaling ultimately leads to the regulation of one or more cellular activities. Regulation of gene expression (turning transcription of specific genes on or off) is a common outcome of cell signaling. A signaling pathway may also regulate the activity of a protein, for example opening or closing an ion channel in the plasma membrane or promoting a change in cell metabolism such as catalyzing the breakdown of glycogen. Signaling pathways can also lead to important cellular events such as cell division or apoptosis (programmed cell death).



Second messengers

Second messengers are molecules that relay signals received at receptors on the cell surface such as hormones, growth factors, etc. to appropriate target molecules in the cytosol and/or nucleus. In addition to their job as relay molecules, second messengers serve to amplify the strength of the signal. Binding of a ligand to a single receptor at the cell surface may end up causing massive changes in the biochemical activities within the cell.

Role of second messenger in Transduction

The use of second messengers has several consequences:

a) The second messengers are able to diffuse frequently into other compartment of the cell such as nucleus where they can influence gene expression and other process.

b) Generation of second messengers leads to amplification of signal. Each signaling molecule is involved in the generation of several second messengers in the cell. Thus, a low concentration of signal in the environment, even as little as a single molecule, can yield a large intracellular signal and response

c) Since common second messengers generate in different signaling pathway, thus the coordination of signal transduction is driven by interaction between these pathways. Multiple signaling pathways create both opportunities and potential problems. Interactions between signaling pathways enables the cell to process and interpret multiple inputs differently in different contexts leading to cross-talk. Cross talk between second messengers cause oscillation of various second messengers and also creates biostability between two steady states. Thus

cross talk more precisely involves in regulation of cell activity than individual independent pathways without cross talk. However, inappropriate cross-talk can cause second messengers to be misinterpreted.

There are 3 major classes of second messengers:

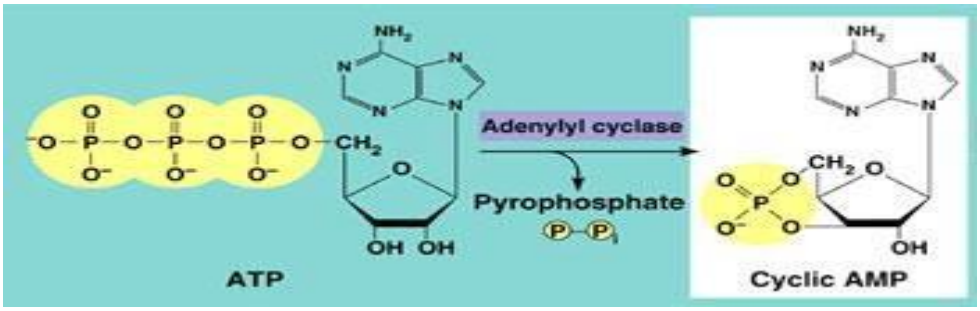
1. Cyclic nucleotides (cAMP and cGMP)

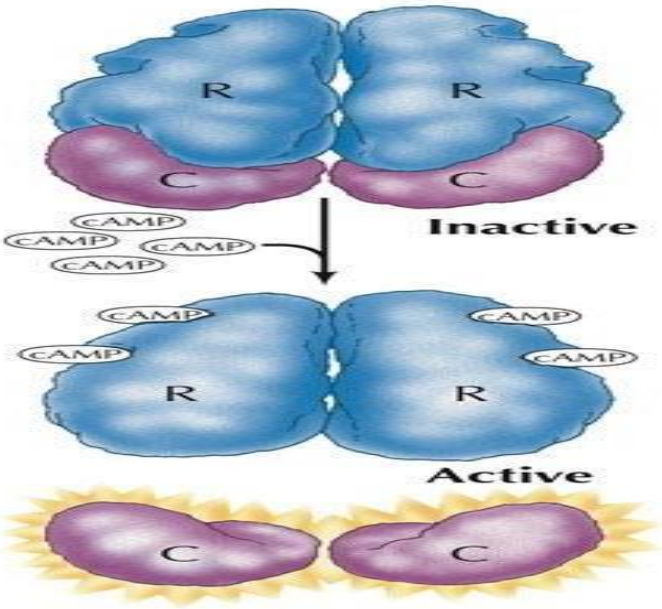
2. Inositol trisphosphate (IP3) and diacylglycerol (DAG)

3. Calcium ions (Ca2+)

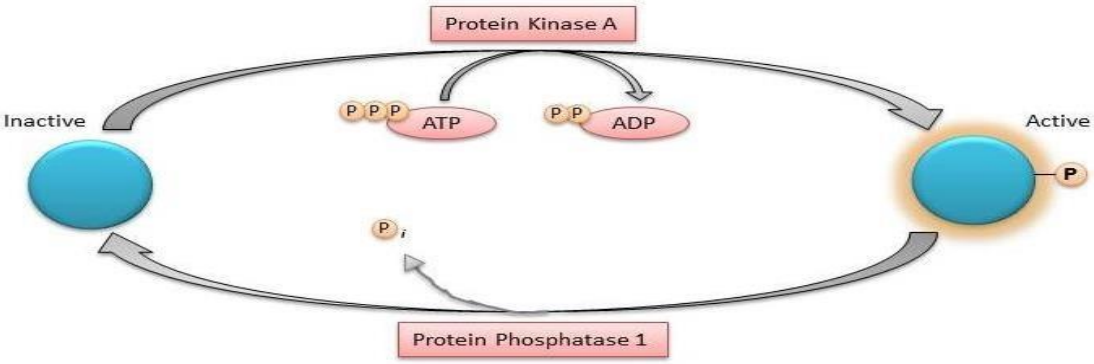
Cyclic adenosine monophosphate (cAMP)

cAMP stands for *c*yclic-*a*denosine *m*ono*p*hosphate. The concept as to why cAMP is the secondary messenger was first discovered by **Earl Sutherland** in 1958, when he discovered that the action of hormone, epinephrine, was mediated by an increase in the concentrations of cAMP. cAMP is an important second messenger used by a major class of G proteins and involved in biological roles by regulating various metabolic process and mediating the effects of many hormones that binds to a specific receptor on the cell membrane of target cells. Binding of the hormone to its receptor activates a G protein which, in turn, activates adenylyl cyclase which is embedded in the plasma membrane with the enzymatic activity in the cytoplasm.. The activation of adenylyl cyclase can result in the manufacture of hundreds or even thousands of cAMP molecules. The resulting rise in cAMP turns on the appropriate response in the cell by either (or both): changing the molecular activities in the cytosol, often using Protein Kinase A (PKA) — a cAMP-dependent protein kinase that phosphorylates target proteins; turning on a new pattern of gene transcription. Protein kinase A is found primarily in inactive form in the cell in which it consists of two regulatory (R) and two catalytic (C) subunits together. Binding of cAMP to the regulatory subunits induces a conformational change that leads to dissociation of the catalytic subunits, which elicits formation of enzymatically active form of protein kinase A, and are now able to phosphorylate Ser and Thr residues on their target proteins. cAMP is broken down by an enzyme called phosphodiesterase.





Regulation of protein kinase



Regulation of Phosphorylation by Protein Kinase A and Protein Phosphatase 1

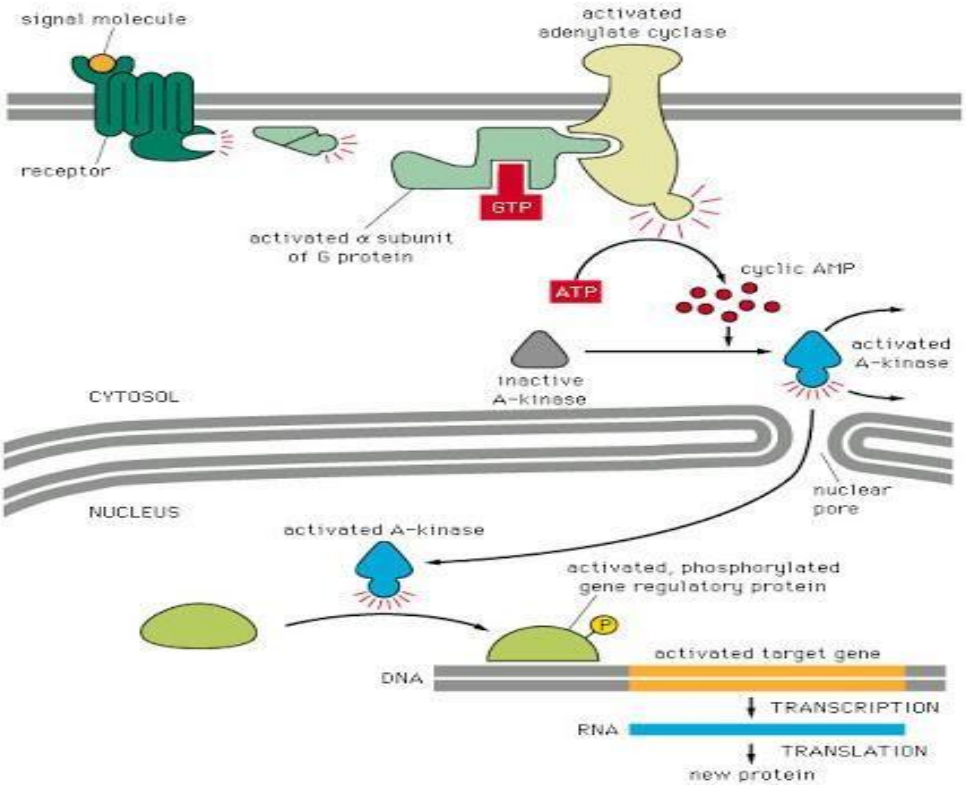


Fig: cAMP pathway

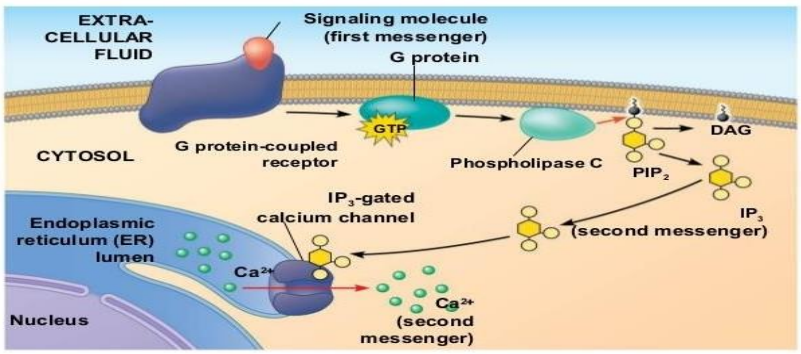
IP3 and DAG Pathway

IP3 Pathway

One of the most widespread pathways of intracellular signaling is based on the use of second messengers derived from the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2). PIP2 is a minor component of the plasma membrane, localized to the inner leaflet of the phospholipid bilayer. There are two important types of receptors whose availability is identified and transduced. They are the G protein coupled receptors (GPCRs) and receptor tyrosine kinases. These two receptors activate the isoforms of phospholipase C through various mechanisms which extends into the cytosol adjacent to the membrane, can be reversibly phosphorylated at several positions by the combined actions of various kinases and phosphatases. These intracellular enzymes perform as downstream signaling components that generate and amplify the signals originated from the binding of ligand molecules. The targets of this intracellular signaling pathway include transcription factors that help in the control of gene expression.

It is noteworthy that the hydrolysis of PIP_2 is activated downstream of both G protein-coupled receptors and protein-tyrosine kinases. This occurs because one form of phospholipase C (PLC-β) is stimulated by G proteins, whereas a second (PLC-γ) contains SH2 domains that mediate its association with activated receptor protein-tyrosine kinases. This interaction localizes PLC-γ to the plasma membrane as well as leading to its tyrosine phosphorylation, which increases its catalytic activity. A variety of hormones and growth factors stimulate the hydrolysis of PIP2 by phospholipase C—a reaction that produces two distinct second messengers, diacylglycerol and inositol 1, 4, 5-trisphosphate (IP3). Diacylglycerol and IP3 stimulate distinct downstream signaling pathways (protein kinase C and Ca2+ mobilization, respectively), so PIP2 hydrolysis triggers a two-armed cascade of intracellular signaling.

Whereas diacylglycerol remains associated with the plasma membrane, the other second messenger produced by PIP2 cleavage, IP3, is a small polar molecule and is a negatively charged water-soluble molecule that is released into the cytosol, to bind with IP3 receptor where it acts to signal the release of Ca2+ from intracellular stores). The cytosolic concentration of Ca2+ is maintained at an extremely low level (about 0.1 μM) as a result of Ca2+ pumps that actively export Ca2+ from the cell. Ca2+ is pumped not only across the plasma membrane, but also into the endoplasmic reticulum, which therefore serves as an intracellular Ca2+ store. IP3 acts to release Ca2+ from the endoplasmic reticulum by binding to receptors that are ligand-gated Ca2+ channels. As a result, cytosolic Ca2+ levels increase to about 1 μM, which affects the activities of a variety of target proteins, including protein kinases and phosphatases. For example, some members of the protein kinase C family require Ca2+ as well as diacylglycerol for their activation, so these protein kinases are regulated jointly by both arms of the PIP2 signaling pathway.



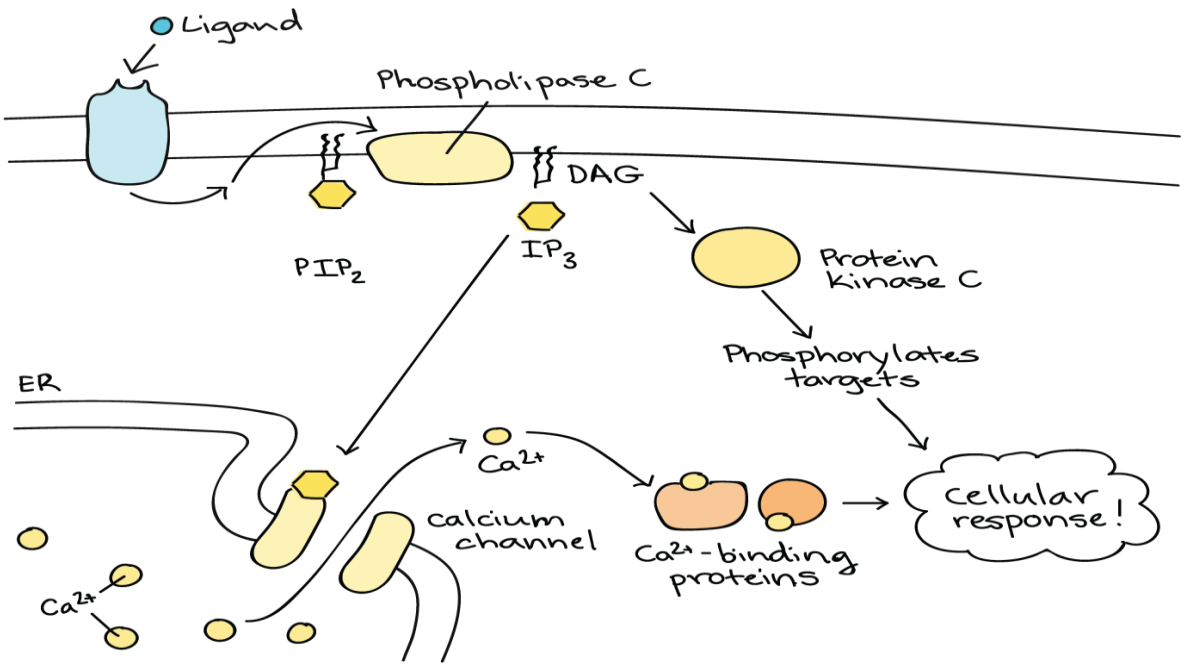
DAG Pathway:

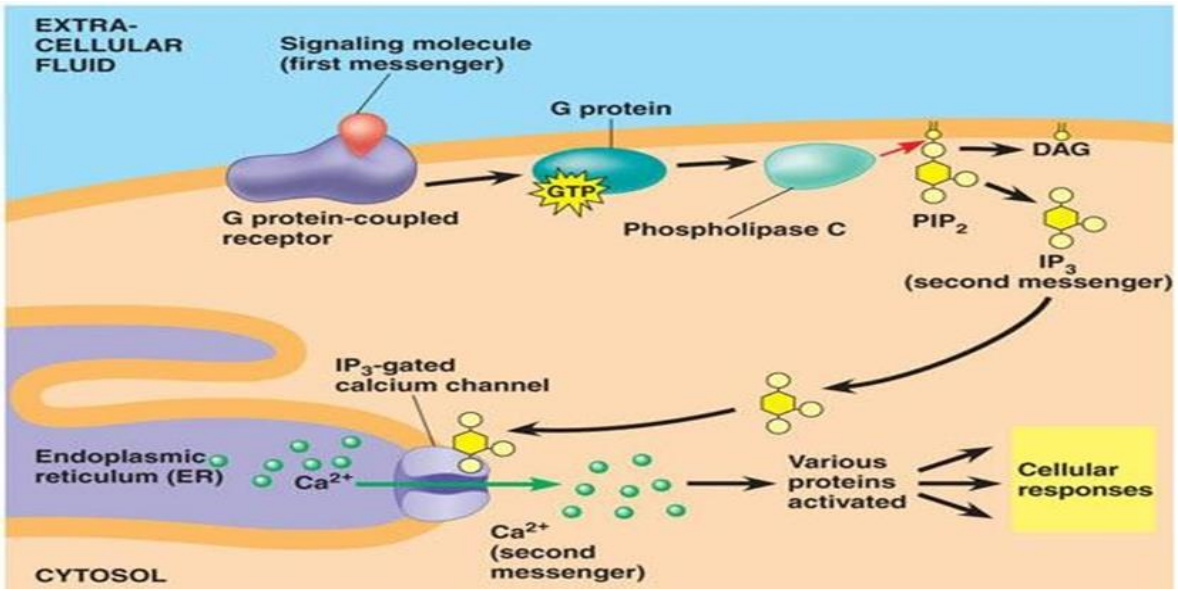
The diacylglycerol produced by hydrolysis of PIP2 activates protein-serine/threonine kinases belonging to the protein kinase C family, many of which play important roles in the control of cell growth and differentiation. Protein kinase C then activates other intracellular targets, including a cascade of protein kinases known as the MAP kinase pathway, leading to transcription factor phosphorylation, changes in gene expression, and stimulation of cell proliferation.

Calcium ion as second messenger

Calcium ion is a widely used second messenger. The free concentration of calcium ions (Ca2+) within a cell is very low because ion pumps in the plasma membrane continuously use adenosine-5′-triphosphate (ATP) to remove it. For signaling purposes, Ca2+ is stored in cytoplasmic vesicles, such as the endoplasmic reticulum, or accessed from outside the cell. When signaling occurs, ligand-gated calcium ion channels allow the higher levels of Ca2+ that are present outside the cell (or in intracellular storage compartments) to flow into the cytoplasm, which raises the concentration of cytoplasmic Ca2+. The response to the increase in Ca2+ varies, depending on the cell type involved. For example, in the β-cells of the pancreas, Ca2+ signaling leads to the release of insulin, and in muscle cells, an increase in Ca2+ leads to muscle contractions. The principles of Ca2+ signaling, from changes in protein conformations driven by Ca2+ to the mechanisms that control Ca2+ levels in the cytoplasm and organelles. The highly localized nature of Ca2+-mediated signal transduction and its specific roles in excitability, exocytosis, motility, apoptosis, and transcription. Normally, cytosolic calcium [Ca2+] ions is kept very low (10-7 M) by the action of Ca2+ pumps in the ER, mitochondria and plasma membrane. Hormonal, neural, or other stimuli cause either an influx of Ca2+ into the cell through specific Ca2+ channels in the plasma membrane or the release of sequestered Ca2+ from the ER or mitochondria, in either case raising the cytosolic [Ca2+] and triggering a cellular response. Ca2+ can readily bind to proteins and cause conformational changes. Ca2+ is attracted to the negatively charged oxygen atoms in the side chains of glutamate and asparagines, and the uncharged oxygen in both the side chains and main chains of glutamine and asparagine. Ca2+ is readily able to cause large conformational changes due to the fact that it can form ligand with up to eight oxygen atoms. This can lead to cross linking of amino acids

in a protein that did not exist before Ca2+ was introduced. Protein function is governed by shape and charge. Ca2+ binding triggers changes in protein shape and charge. Similarly,

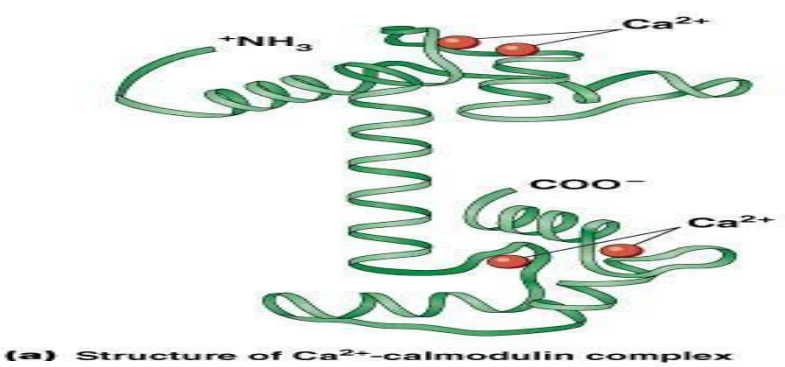




phosphorylation imparts a negative charge, altering protein conformations and their interactions. Protein kinases, comprising ~2% of eukaryotic genomes, remove phosphate from ATP and covalently attach it to the free hydroxyl groups of serine, threonine, or tyrosine residues. The abilities of Ca2+ and phosphate ions to alter local electrostatic fields and protein conformations are the two universal tools of signal transduction.

Calmodulin

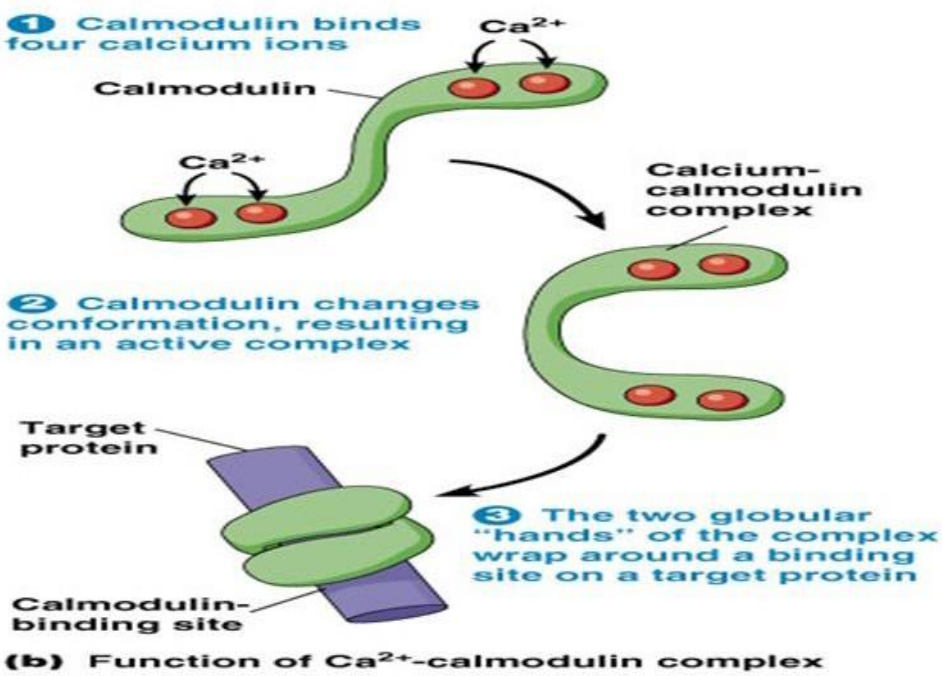
Calmodulin, or **CaM**, is a polypeptide that is ubiquitous in all eukaryotic cells. Calmodulin (CaM) (Mr 17,000) is an acidic protein with four high-affinity Ca2+- binding sites. When intracellular [Ca2+] rises to about 10-6 M (1 μM), the binding of Ca2+ to calmodulin drives a conformational change in the protein. This protein is known as calmodulin because it is a **cal**cium-**mod**ulated prote**in** that plays a vital role in the process of calcium signal transduction. Calcium signal transduction is the process through which the interactions between calcium ions and numerous proteins mediate communication between cells. calmodulin's function, therefore, is necessary in all eukaryotic cells, and some of the tasks that it helps to accomplish are nerve signaling, skeletal muscle movement, and memory. By sensing calcium ions in the environment, calmodulin activates and subsequently acts as an intermediate, initiating the binding of important proteins such as kinases, assisting our cells in basic and sophisticated function. Calmodulin associates with a variety of proteins and, in its Ca2+-bound state, modulates their activities. The protein itself is 148 amino acids in length with two globular regions containing 2 **EF-hand motifs** each, which are characteristic sites of calcium-mediated polypeptides. When activated, calmodulin houses 4 Ca^{2+} ions that drastically change the shape of the protein.



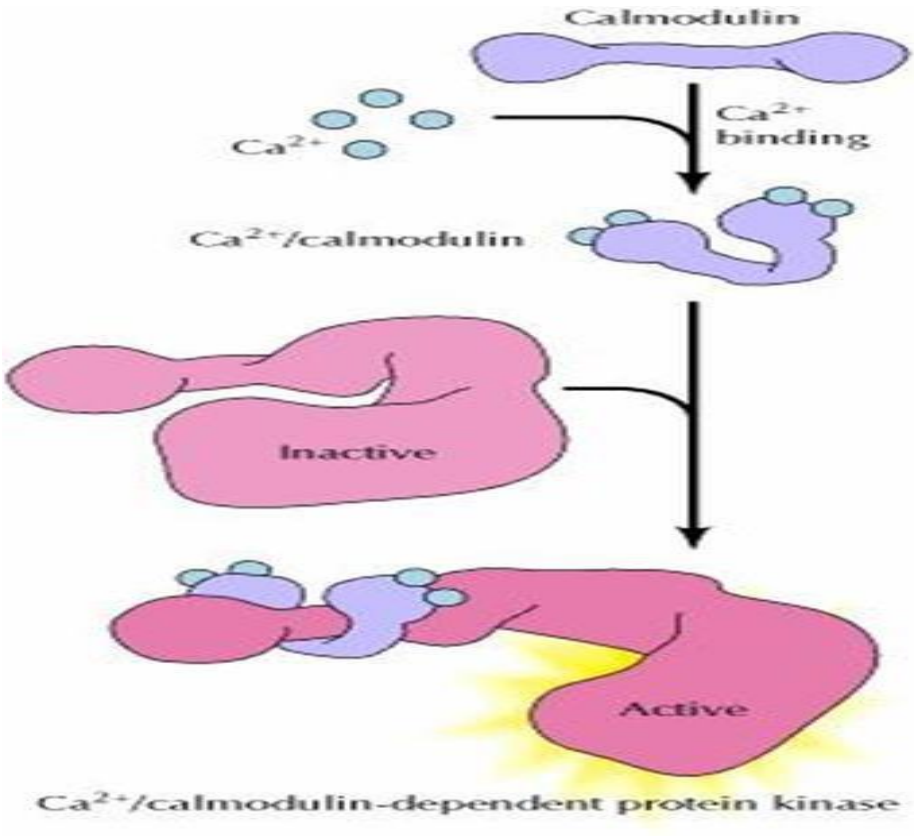
(a) Structure of Ca^{2+}-calmodulin complex

When calmodulin binds with the calcium ions, the protein opens from its apo form to its

halo form, exposing an alpha helix that is known as the linker or central tether region. Coined for its flexibility, the central tether region is the location of the protein on which partner proteins bind and contribute to the cascade that is the secondary messaging of calcium. Within in the cell, calcium signaling is accompanied by a temporary increase in the concentration of calcium ions, which is sensed by proteins such as calmodulin (Bertini et. al., 636). This calcium surge could be due to intracellular G-proteins that induce the rough and smooth reticulum to release calcium, or the calcium ions could be brought in from the extracellular space. In the case of calmodulin, it is usually responding to calcium being brought into the cell from the outside, which occurs during processes such as nerve signaling (Bertini et. al. 637). Before the concentration of calcium is momentarily raised, the concentration within the cell is usually between 10-100 nm, whereas during the brief influx of ions, the concentration increases to 1,000-100,000 nm. The change in concentration causes the calmodulin to sense the calcium ions, bind them, and initiate further signal transduction (Bertini et. al., 635). When intracellular [Ca2+] increases in response to some stimulus, calmodulin binds Ca2+, undergoes a change in conformation, and activates the CaM kinase. The kinase then phosphorylates a number of target enzymes, regulating their activities.



Calmodulin, based on its structure and the composition of its vital bonding site, plays an integral part of innumerable processes carried out by eukaryotic cells. Through the accepting and binding of calcium ions in signal transduction, calmodulin acts as a pivotal component of basic and high-level functioning in organisms such as humans. Calmodulin is also a regulatory subunit of phosphorylase b kinase of muscle, which is activated by Ca2+. Thus Ca2+ triggers ATP-requiring muscle contractions while also activating glycogen breakdown, providing fuel for ATP synthesis. Many other enzymes are also known to be modulated by Ca2+ through calmodulin.



What is a G-protein?

A G-protein is a protein that can interact with a G-protein linked receptor. The name G-protein comes from the fact that it is a protein that can bind a guanine nucleotide (either GTP or GDP). There are various sorts of G-proteins, all of which have a characteristic structure (please note that not all proteins that can bind guanine nucleotides are G-proteins, only those that have the classic three-part structure described below, and that interact with the G-protein linked

receptors).

Structure of a G-protein

All G-proteins have a similar structure- they are composed of three subunits called alpha, beta and gamma. Because of this, they are sometimes called heterotrimeric G proteins (hetero=different, trimeric= having three parts). The alpha subunit of such proteins can bind GDP or GTP. In the unstimulated state of the cell, the G-proteins are found in the trimeric form (alpha-beta-gamma bound together) and the alpha subunit has a GDP molecule bound to it. The binding of a signal molecule by the extracellular part of the G-protein linked receptor causes the receptor to interact with, and alter the conformation of, a G-protein that is associated with the cytosolic side of the plasma membrane.

When the G-protein's conformation is altered:

1. The alpha subunit of the G-protein loses its GDP and binds a GTP instead.

2. The G-protein breaks up into the GTP-bound alpha part and the beta-gamma part.

These two parts can diffuse freely along the membrane and act upon their targets, which in turn may relay the signal to yet another part of the cell.

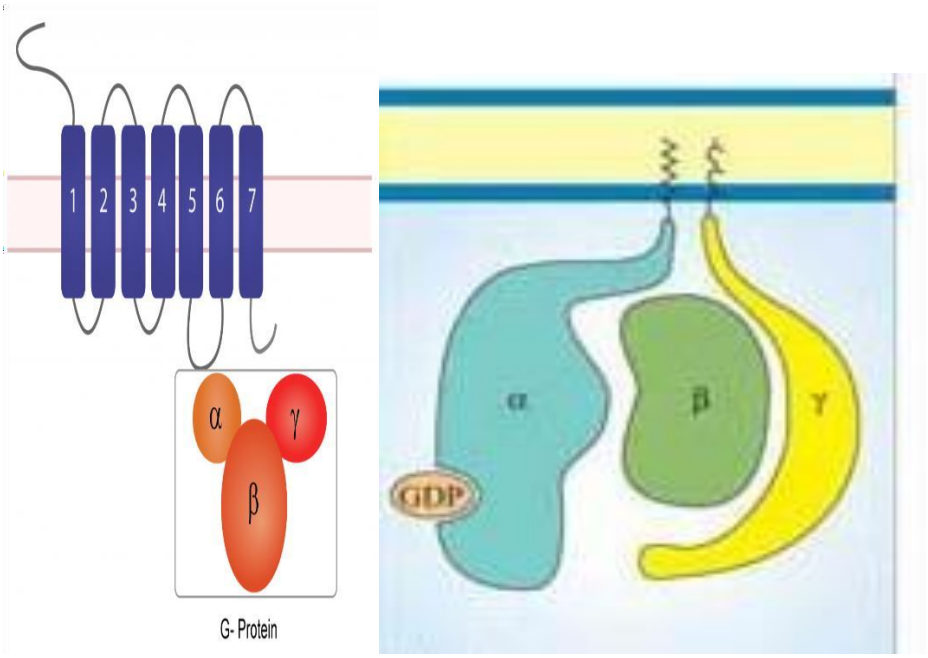


Fig: Structure of G-Protein