Membrane receptors

Membrane receptors are **specialized protein molecules attached to or integrated into the cell membrane**. Through interaction with specific ligands (e.g., hormones and neurotransmitters), the receptors facilitate communication between the cell and the extracellular environment.

Types of Receptors :

A cell within a multicellular organism may need to signal to other cells that are at various distances from the original cell (**Figure 1**). Not all cells are affected by the same signals. Different types of signaling are used for different purposes.

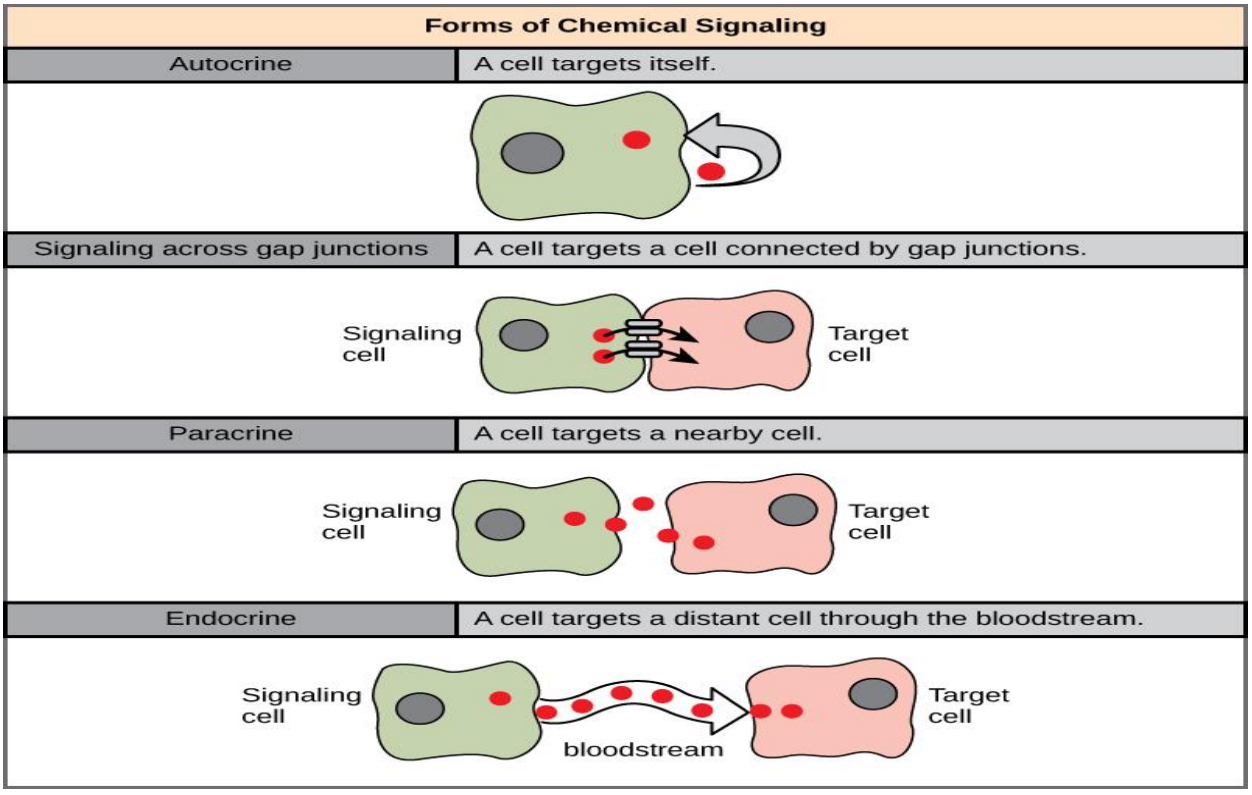

Figure 1 In chemical signaling, a cell may target itself (autocrine signaling), a cell connected by gap junctions, a nearby cell (paracrine signaling), or a distant cell (endocrine signaling). Paracrine signaling acts on nearby cells, endocrine signaling uses the circulatory system to transport ligands, and autocrine signaling acts on the signaling cell. Signaling via gap junctions involves signaling molecules moving directly between adjacent cells.

Receptors are protein molecules inside the target cell or on its surface that receive a chemical signal. 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 and receptors exist in several varieties; however, a specific ligand will have a specific receptor that typically binds only that ligand.

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. Recall that mRNA carries genetic information from the DNA in a cell's nucleus out to the ribosome, where the protein is assembled. When the ligand binds to the internal receptor, a change in shape is triggered that exposes a DNA-binding site on the receptor protein. The ligand-receptor complex moves into the nucleus, then binds to specific regions of the DNA and promotes the production of mRNA from specific genes (**Figure 2**). Internal receptors can directly influence

gene expression (how much of a specific protein is produced from a gene) without having to pass the signal on to other receptors or messengers.

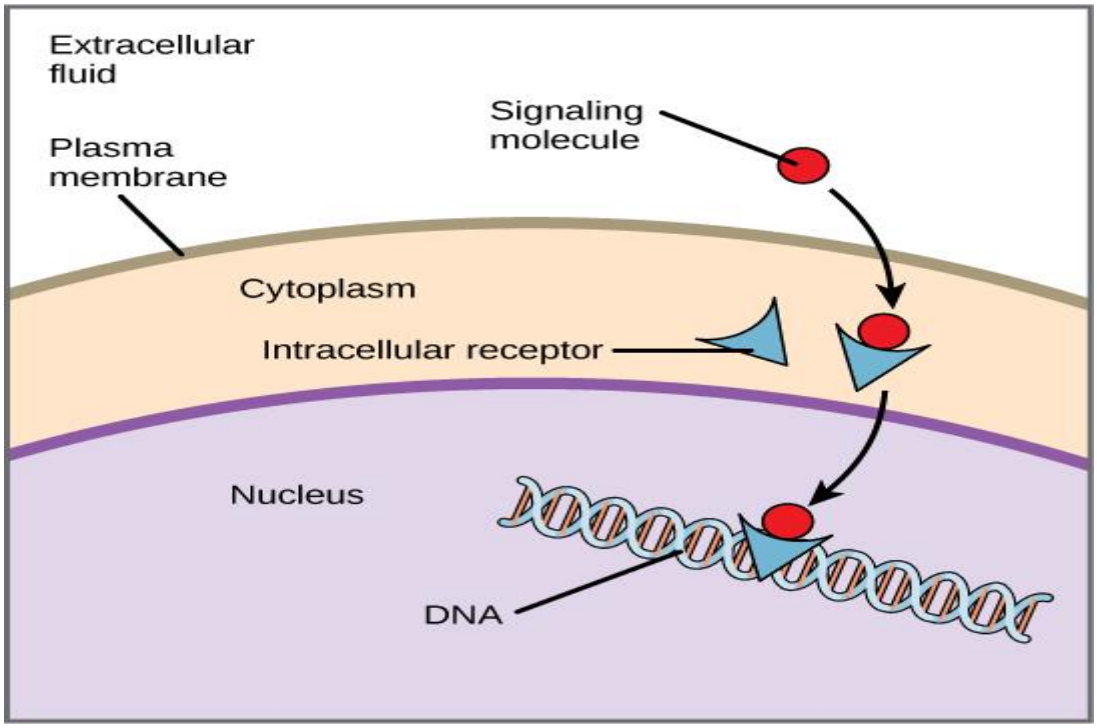

Figure 2 Hydrophobic signaling molecules typically diffuse across the plasma membrane and interact with intracellular receptors in the cytoplasm. Many intracellular receptors are transcription factors that interact with DNA in the nucleus and regulate gene expression.

Cell-surface receptors, also known as **transmembrane receptors**, are proteins that are found attached to the cell membrane. These receptors bind to external ligand molecules (ligands that do not travel across the cell membrane). 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.

Each cell-surface receptor has three main components: an external ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular domain inside the cell. The size and extent of each of these domains vary widely, depending on the type of receptor.

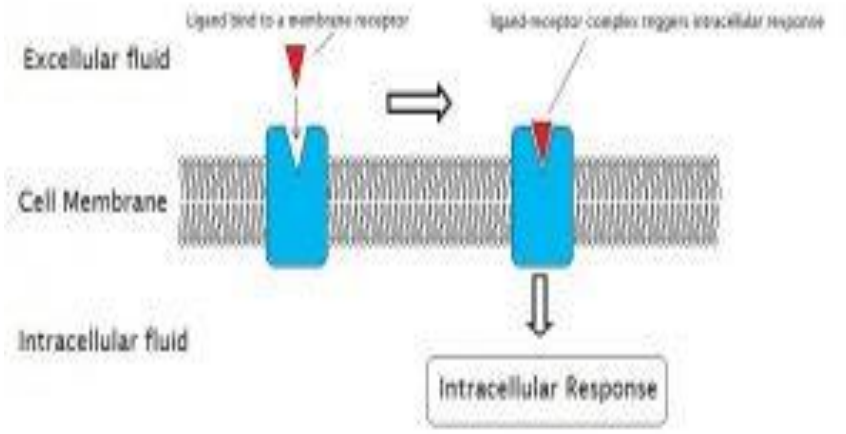

Figure 3 Cell-surface receptors function by transmitting a signal through the cell membrane. The ligand does not directly enter the cell. Photo credit Laozhengzz; Wikimedia commons.

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 (**Figure 4)**.

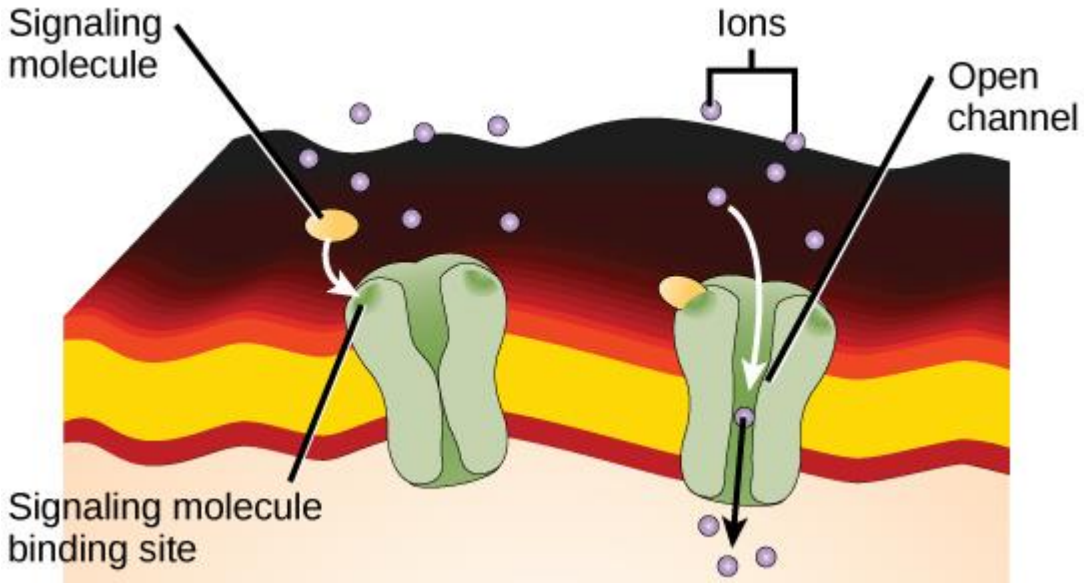

Figure 4 Gated ion channels form a pore through the plasma membrane that opens when the signaling molecule binds. The open pore then allows ions to flow into or out of the cell.

G-protein-coupled 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 (**Figure 4, 5**). Before the ligand binds, the inactive G-protein can bind to a site on a specific receptor. Once the G-protein binds to the receptor, the G-protein changes shape,

becomes active, and splits into two different subunits. One or both of these subunits may be able to activate other proteins as a result.

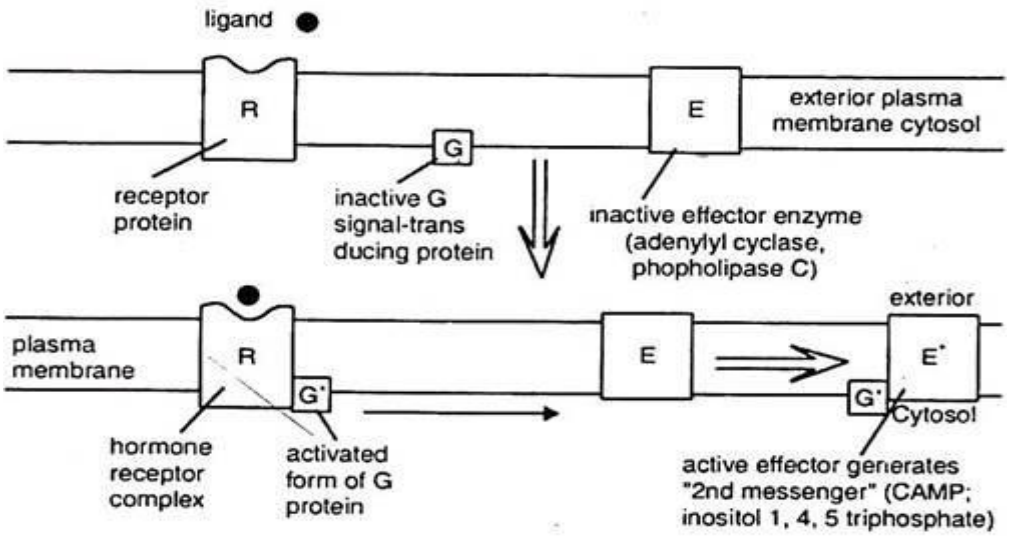

Fig. 4. G. protein coupled receptors.

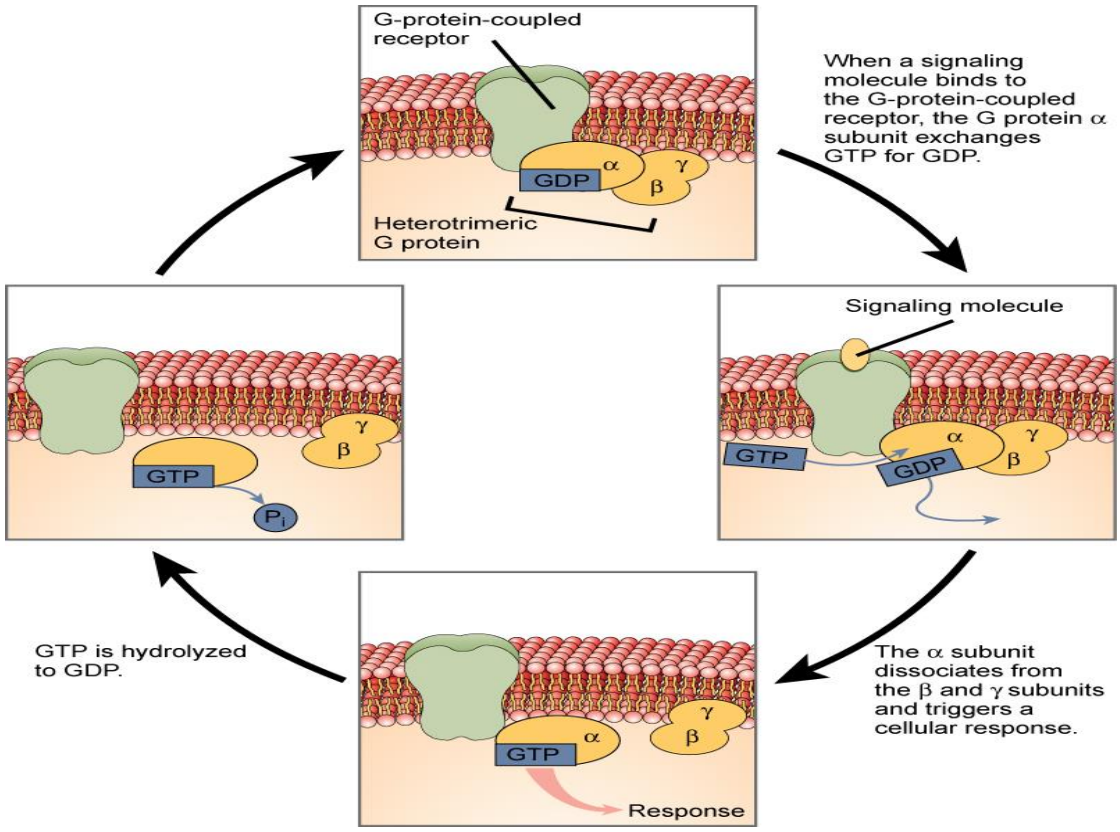

Figure 5 When a signaling molecule binds to a G-protein-coupled receptor in the plasma membrane, a GDP molecule associated with the G-protein is exchanged for GTP. The subunits come apart from each other, and a cellular response is triggered either by one or both of the subunits. Hydrolysis of GTP to GDP terminates the signal.

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

G-protein coupled receptors are a diverse family of receptors found in a huge range of tissues throughout the body. They function to respond to a wide variety of **extracellular signals**, such as hormones or neurotransmitters, and trigger **intracellular signalling cascades**, which regulate a wide range of bodily functions. This article will discuss the structure and function of GPCRs in the human body.

Structure of G-Proteins

G-protein coupled receptors are composed of a **transmembrane region** crossing the lipid bilayer seven times (hence they are also be referred to as 7-transmembrane receptors). This transmembrane region is coupled with a **G-protein**. GPCRs have no integral enzyme activity or ion channel, therefore all their downstream effects are mediated via their G-protein.

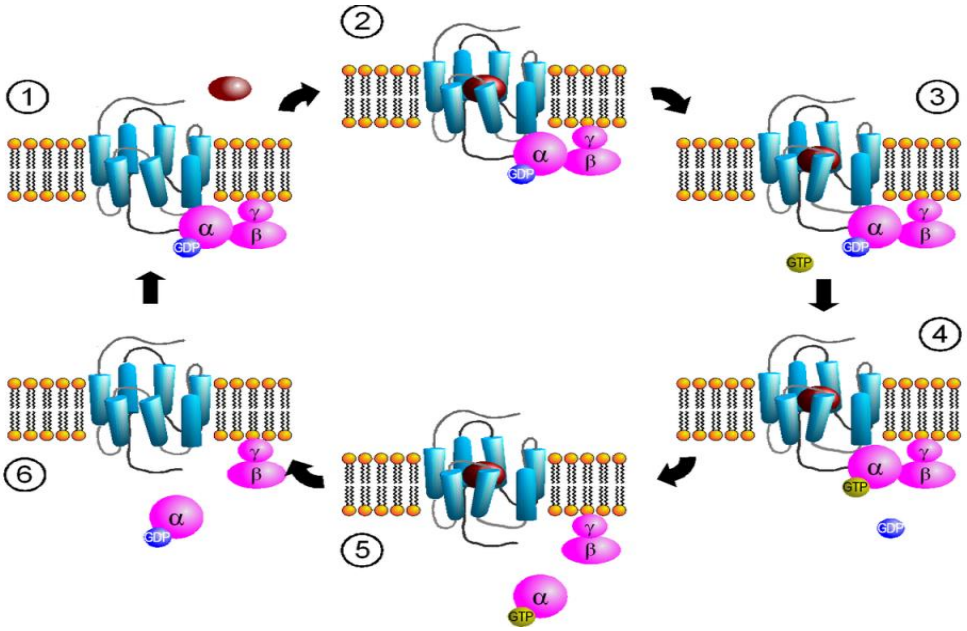

Figure 1 – G protein structure and activation cascade

The G-protein is **heterotrimeric** and is made up of three different subunits: alpha (**α**), beta (**β**) and gamma (**γ**). In its inactive state, GDP is bound to the α-subunit of the G-protein.

There are hundreds of GPCRs in the genome and their receptors are activated by many signals such as neurotransmitters, hormones, ions, peptides and even photons in the retina. Common examples of GPCRs include **adrenoreceptors**, **muscarinic** acetylcholine receptors and **opioid** receptors.

There are also many different types of α-, β- and γ-subunits. This allows for many GPCR combinations created by different receptors being coupled with G proteins comprised of different subunits. Furthermore, one GPCR can be associated with many G proteins, hence one signal can have many downstream cellular reactions.

Ligand Binding to G-Proteins

An **agonist** (ligand) is a substance which binds to a receptor and brings about a cellular response. For G-protein coupled receptors, this consists of 5 main steps.

1. Ligands bind to the extracellular portion of the G-protein coupled receptor, binding either at the N-terminus or a binding site within the transmembrane region.
2. Binding at the extracellular ligand binding site causes a **conformational change** in the GPCR, resulting in release of GDP from the α-subunit of the G-protein.
3. Released GDP is then replaced with a **GTP**
4. This activates the G-protein, causing the α-subunit and bound GTP to **dissociate** from the transmembrane portion of the GPCR and βγ-subunit.
5. These α-subunit interacts with its relevant effectors and cause **downstream effects**, e.g. ion channel opening or enzyme activity regulation.

Despite the fact that one G-protein coupled receptor only contains one α-subunit, this can interact with several **secondary messengers**, which can in turn activate multiple enzymes and catalyse many reactions. This creates a cascade response whereby one agonist binding to the GPCR can bring about the catalysis of many reactions (**signal amplification**).

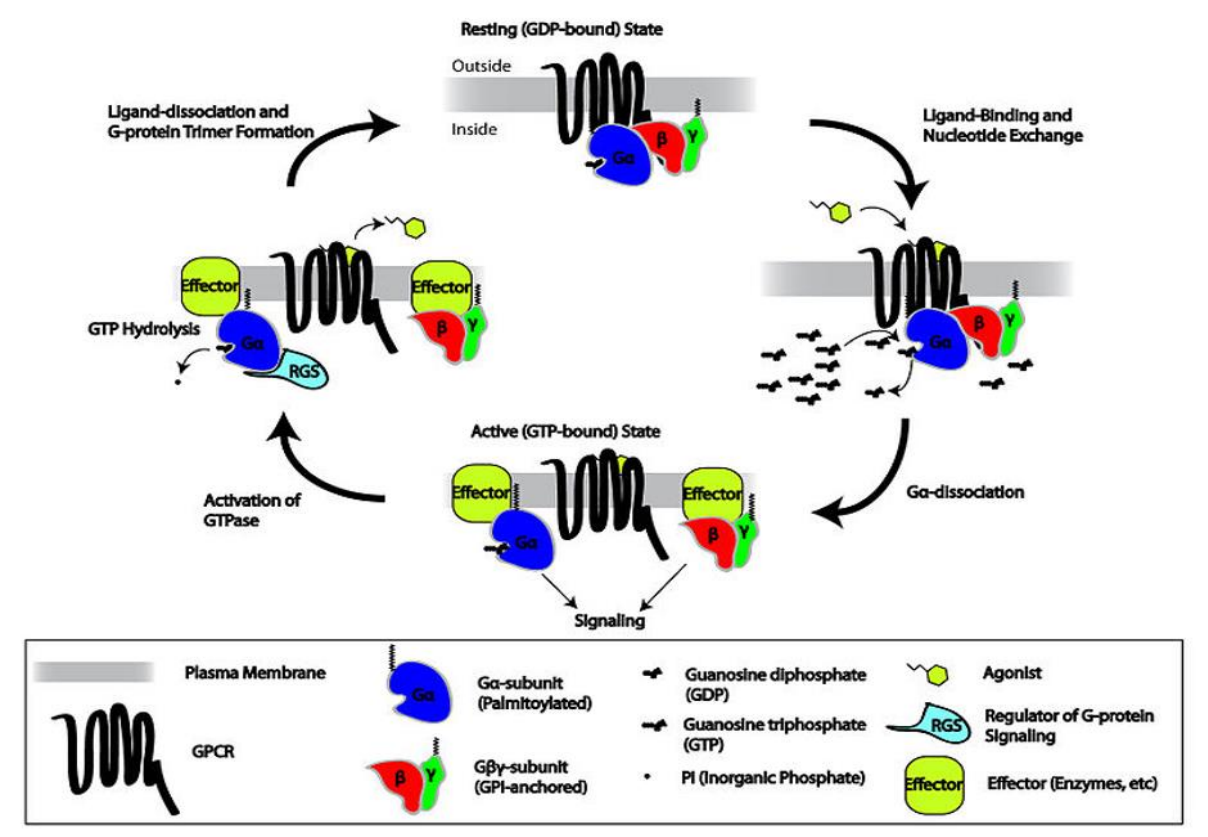

Figure 2 – Sequence following GPCR ligand binding

To prevent excess signalling, GPCR activity can be switched off. **GTPase** catalyses the breakdown of GTP on the α-subunit into **GDP + Pi**. GDP increases the α-subunit's affinity for the βγ-subunit, allowing reformation of the heterotrimeric complex of the G-protein. The G-protein then **reassociates** with the transmembrane receptor, reforming the GPCR for the next ligand binding.

Types of G-protein

There are several different types of G-protein that can be present in a GPCR, which vary based on their **α -subunit**. Each alpha-subunit stimulates an enzyme, which acts to either increase or decrease the concentration of a **secondary messenger**. This goes on to impact a **downstream effector**, which then causes a **cellular response**. The

ultimate effect of these proteins depends on the specific cell in which it is located.

Alpha subunit	Enzyme	Secondary messenger	Effector
G_S	Stimulates adenylyl cyclase, which catalyses conversion of ATP to cyclic AMP	Increases cAMP	Stimulates PKA activation (cAMP-dependent protein kinase), which goes on to phosphorylate target proteins
G_i	Inhibits adenylyl cyclase, which catalyses conversion of ATP to cyclic AMP	Reduces cAMP	Inhibits PKA activation (cAMP-dependent protein kinase)
G_Q or G_{11}	Stimulates phospholipase C, which cleaves PIP_2 in the cell membrane into IP_3 and DAG	Increases IP3 and DAG	IP3 opens calcium channels, causing a Ca^{2+} efflux into the cytoplasm DAG activates protein kinase C (PKC), which goes on to phosphorylate target proteins

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. Other enzyme-linked receptors have a small intracellular domain that interacts directly with an enzyme. 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.

Intracellular Receptors: Steroid hormones, thyroxin and retinoids are lipophilic and are transported by carrier proteins in the blood. After dissociation from these carriers, such hormones diffuse across the cell membrane and bind to specific receptors in the cytosol or nucleus. The receptor-hormone complex then acts on nuclear DNA to alter transcription of specific genes (Fig. 2).

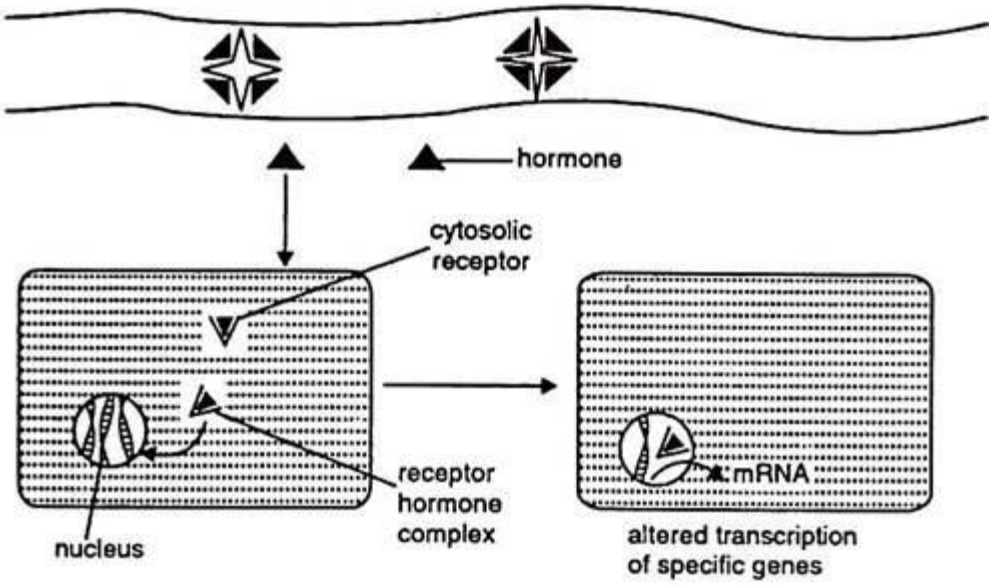

Fig. 2. Intracellular receptors.

Cell Surface Receptors: Polypeptide hormones and catecholamines, which are water soluble and prostaglandins, which are lipophilic, all bind to cell surface receptors. This binding triggers an increase or decrease in the cytosolic concentration of second messengers (cAMP, Ca), activation of protein kinases, or a change in the membrane potential (Fig. 3).

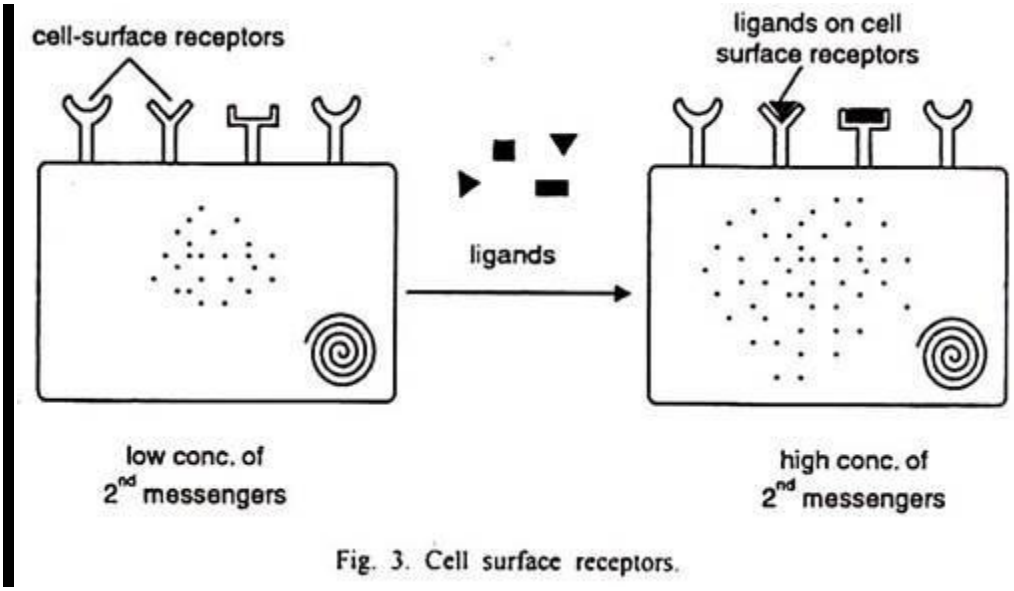

Fig. 3. Cell surface receptors.

Ion-Channel Receptors: Ligand binding changes the conformation of the receptor so that only specific ions flow through it; the resultant ion movements alter the electric potential across the cell membrane. The acetylcholine receptor at the neuro-muscular junction is an example (Fig. 5).

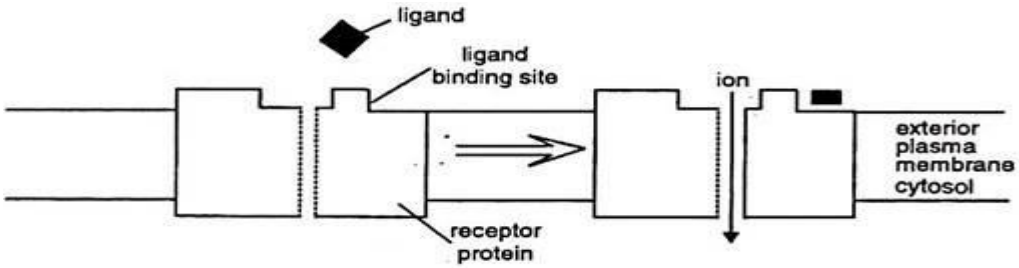

Fig. 5. Ion-channel receptors.

Tyrosine Kinase Linked Receptors: These receptors lack intrinsic catalytic activity, but ligand binding stimulates formation of a dimeric receptor, which then interacts with and activates one or more cytosolic protein tyrosinekinases. The receptors for many cytokines, the interferons and human growth factor are of this type (Fig. 6).

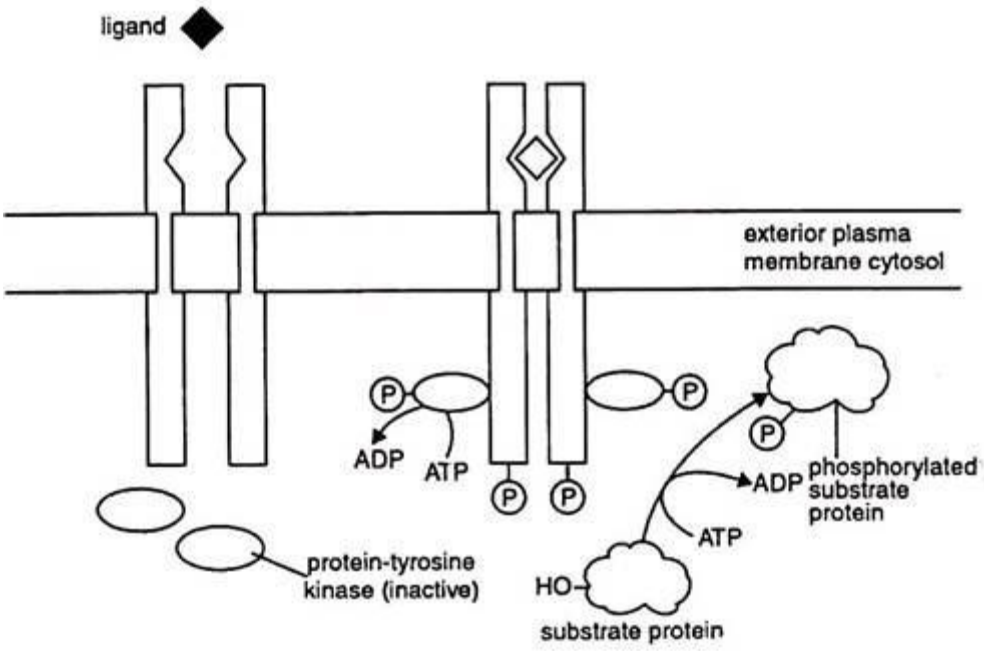

Fig. 6. Tyrosine kinase-linked receptors.