G protein-coupled receptor

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G protein-coupled receptors (**GPCRs**), also known as **seven-transmembrane domain receptors**, **7TM receptors**, **heptahelical receptors**, **serpentine receptor**, and **G protein-linked receptors** (**GPLR**), constitute a large protein family of receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. They are called transmembrane receptors because they pass through the cell membrane, and furthermore, they are called seven-transmembrane receptors because they pass through the cell membrane seven times.

G protein-coupled

GPCR

The human k-opioid receptor in complex with JDTic[1]

Identifiers

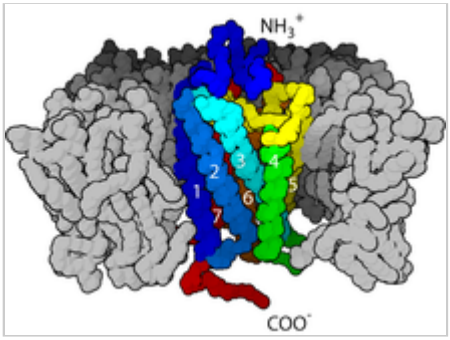
Symbol	7tm_1
Pfam	PF00001 (http://pfam.sanger.ac.uk/family?acc=PF00001)
InterPro	IPR000276 (http://www.ebi.ac.uk/interpro/entry/IPR000276)
PROSITE	PDOC00210 (http://www.expasy.org/cgi-bin/prosite-search-ac?PDOC00210)
OPM superfamily	6 (http://opm.phar.umich.edu/families.php?superfamily=6)
OPM protein	1gzm (http://opm.phar.umich.edu/protein.php?search=1gzm)

Available protein structures:

Pfam	structures (http://pfam.sanger.ac.uk/family/PF00001?tab=pdbBlock)
PDB	RCSB PDB (http://www.rcsb.org/pdb/search/smartSubquery.do?smartSearchSubtype=PfamIdQuery&pfamID=PF00001); PDBe (http://www.ebi.ac.uk/pdbe-srv/PDBeXplore/pfam/?pfam=PF00001); PDBj (http://pdbj.org/searchFor?query=PF00001)

receptors are found only in eukaryotes, including yeast, choanoflagellates,[2] and animals. The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to peptides to large proteins. G protein-coupled receptors are involved in many diseases, and are also the target of approximately 40% of all modern medicinal drugs.[3][4] The 2012 Nobel Prize in Chemistry was awarded to Brian Kobilka and Robert Lefkowitz for their work that was "crucial for understanding how G-protein–coupled receptors function."[5]

PDBsum	structure summary (http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPfamStr.pl?pfam_id=PF00001)



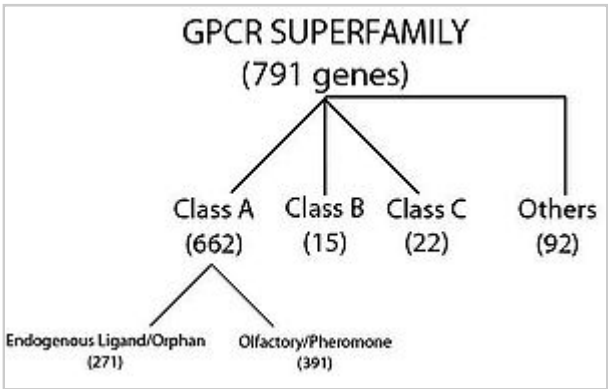
The seven-transmembrane α-helix structure of a G protein-coupled receptor

There are two principal signal transduction pathways involving the G protein-coupled receptors: the cAMP signal pathway and the phosphatidylinositol signal pathway.[6] When a ligand binds to the GPCR it causes a conformational change in the GPCR, which allows it to act as a guanine nucleotide exchange factor (GEF). The GPCR can then activate an associated G-protein by exchanging its bound GDP for a GTP. The G-protein's α subunit, together with the bound GTP, can then dissociate from the β and γ subunits to further affect intracellular signaling proteins or target functional proteins directly depending on the α subunit type ($G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q/11}$, $G_{\alpha 12/13}$).[7]:1160

Contents

Classification

The exact size of the GPCR superfamily is unknown, but nearly 800 different human genes (or ≈4% of the entire protein-coding genome) have been predicted from genome sequence analysis.[8] Although numerous classification schemes have been proposed, the superfamily is classically divided into three main classes (A, B, and C) with no detectable shared sequence homology between classes. The largest class by far is class A, which accounts for nearly 85% of the GPCR genes. Of class A GPCRs, over half of these are predicted to encode olfactory



Classification Scheme of GPCRs. Class A (Rhodopsin-like), Class B (Secretin-like),Class C (Glutamate Receptor-like), Others (Adhesion (33), Frizzled (11), Taste type-2 (25), unclassified (23)).[8]

receptors, while the remaining receptors are liganded by known endogenous compounds or are classified as orphan receptors. Despite the lack of sequence homology between classes, all GPCRs have a common structure and mechanism of signal transduction.

In all, GPCRs can be grouped into 6 classes based on sequence homology and functional similarity:[9][10][11][12]

- Class A (or 1) (Rhodopsin-like)
- Class B (or 2) (Secretin receptor family)
- Class C (or 3) (Metabotropic glutamate/pheromone)
- Class D (or 4) (Fungal mating pheromone receptors)
- Class E (or 5) (Cyclic AMP receptors)
- Class F (or 6) (Frizzled/Smoothened)

The very large rhodopsin A group has been further subdivided into 19 subgroups (A1-A19).[13] More recently, an alternative classification system called GRAFS (Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2, Secretin) has been proposed.[8]

The human genome encodes thousands of G protein-coupled receptors,[14] about 350 of which detecting hormones, growth factors, and other endogenous ligands. Approximately 150 of the GPCRs found in the human genome have unknown functions.

Some web-servers[15] and bioinformatics prediction methods[16][17] have been used for predicting the classification of GPCRs according to their amino acid sequence alone, by means of the pseudo amino acid composition approach.

Physiological roles

GPCRs are involved in a wide variety of physiological processes. Some examples of their physiological roles include:

1. The visual sense: The opsins use a photoisomerization reaction to translate electromagnetic radiation into cellular signals. Rhodopsin, for example, uses the conversion of *11-cis*-retinal to *all-trans*-retinal for this purpose
2. The gustatory sense (taste): GPCRs in taste cells mediate release of gustducin in response to bitter- and sweet-tasting substances.
3. The sense of smell: Receptors of the olfactory epithelium bind odorants (olfactory receptors) and pheromones (vomeronasal receptors)

4. Behavioral and mood regulation: Receptors in the mammalian brain bind several different neurotransmitters, including serotonin, dopamine, GABA, and glutamate
5. Regulation of immune system activity and inflammation: Chemokine receptors bind ligands that mediate intercellular communication between cells of the immune system; receptors such as histamine receptors bind inflammatory mediators and engage target cell types in the inflammatory response
6. Autonomic nervous system transmission: Both the sympathetic and parasympathetic nervous systems are regulated by GPCR pathways, responsible for control of many automatic functions of the body such as blood pressure, heart rate, and digestive processes
7. Cell density sensing: A novel GPCR role in regulating cell density sensing.
8. Homeostasis modulation (e.g., water balance).[18]
9. Involved in growth and metastasis of some types of tumors.[19]

Receptor structure

GPCRs are integral membrane proteins that possess seven membrane-spanning domains or transmembrane helices.[20][21] The extracellular parts of the receptor can be glycosylated. These extracellular loops also contain two highly conserved cysteine residues that form disulfide bonds to stabilize the receptor structure. Some seven-transmembrane helix proteins (channelrhodopsin) that resemble GPCRs may contain ion channels, within their protein.

Similar to GPCRs, the adiponectin receptors 1 and 2 (ADIPOR1 and ADIPOR2) also possess 7 transmembrane domains. However, ADIPOR1 and ADIPOR2 are orientated oppositely to GPCRs in the membrane (i.e., extracellular N-terminus, cytoplasmic C-terminus) and do not associate with G proteins.[22]

Early structural models for GPCRs were based on their weak analogy to bacteriorhodopsin, for which a structure had been determined by both electron diffraction (PDB 2BRD (http://www.rcsb.org/pdb/explore/explore.do?structureId=2BRD), 1AT9 (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1AT9))[23][24] and X ray-based crystallography (1AP9 (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1AP9)).[25] In 2000, the first crystal structure of a mammalian GPCR, that of bovine rhodopsin (1F88 (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1F88)), was solved.[26] While the main feature,

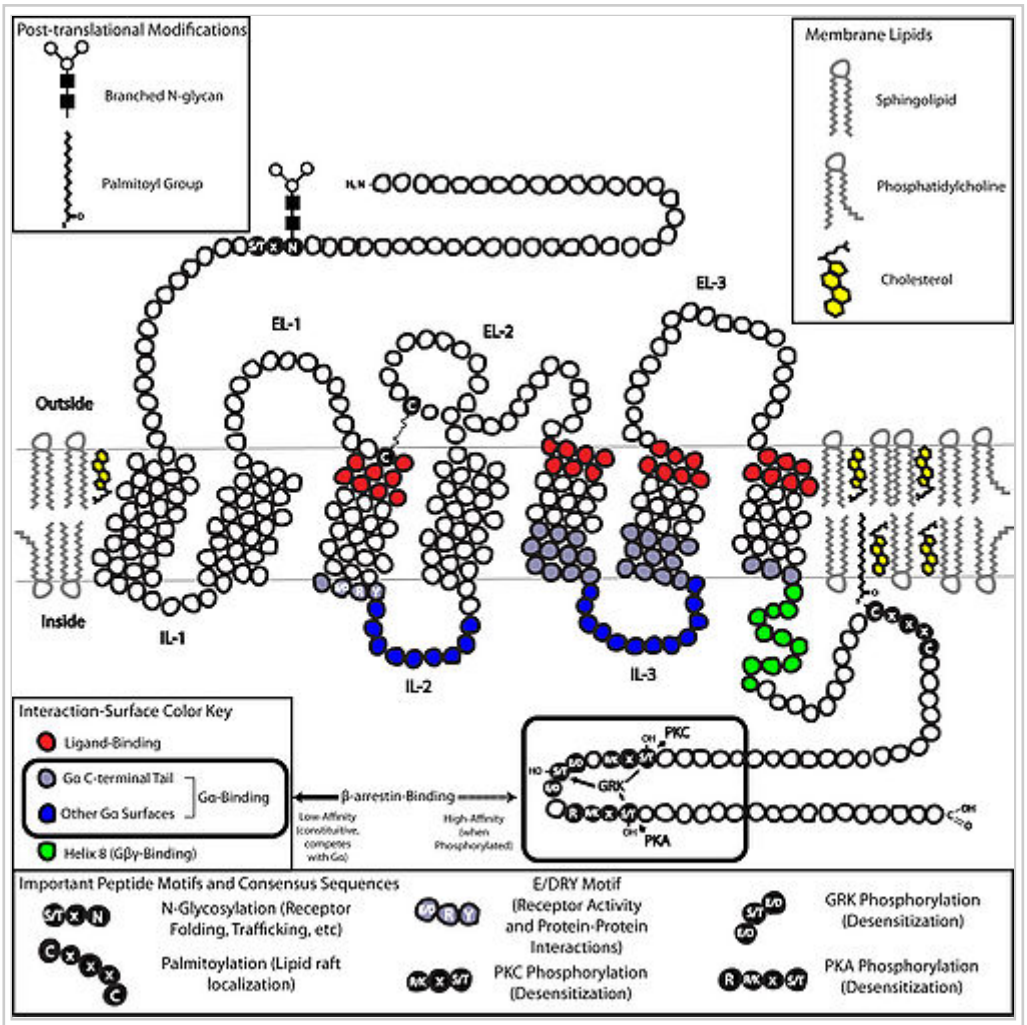
the seven-transmembrane helices, is conserved, the relative orientation of the helices differ significantly from that of bacteriorhodopsin. In 2007, the first structure of a human GPCR was solved (2R4R (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2R4R), 2R4S (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=2R4S)).[27] This was followed immediately by a higher resolution structure of the same receptor (2RH1 (http://www.rcsb.org/pdb/cgi /explore.cgi?pdbId=2RH1)).[28][29] This human β_2-adrenergic receptor GPCR structure, proved highly similar to the bovine rhodopsin in terms of the relative orientation of the seven-transmembrane helices. However, the conformation of the second extracellular loop is entirely different between the two structures. Since this loop constitutes the "lid" that covers the top of the ligand binding site, this conformational difference highlights the difficulties in constructing homology models of other GPCRs based only on the rhodopsin structure.

The structures of activated and/or agonist-bound GPCRs have also been determined.[30][31][32][33] These structures indicate how ligand binding at the extracellular side of a receptor leads to conformational changes in the cytoplasmic side of the receptor. The biggest change is an outward movement of the cytoplasmic part of the 5th and 6th transmembrane helix (TM5 and TM6). The structure of activated beta-2 adrenergic receptor in complex with G_s confirmed that the Gα binds to a cavity created by this movement.[34]

Structure-function relationships

In terms of structure, GPCRs are characterized by an extracellular N-terminus, followed by seven transmembrane (7-TM) α-helices (TM-1 to TM-7) connected by three intracellular (IL-1 to IL-3) and three extracellular loops (EL-1 to EL-3), and finally an intracellular C-terminus. The GPCR arranges itself into a tertiary structure resembling a barrel, with the seven transmembrane helices forming a cavity within the plasma membrane that serves a ligand-binding domain that is often covered by EL-2. Ligands may also bind elsewhere, however, as is the case for bulkier ligands (e.g., proteins or large peptides), which instead interact with the extracellular loops, or, as illustrated by the class C metabotropic glutamate receptors (mGluRs), the N-terminal tail. The class C GPCRs are distinguished by their large N-terminal tail, which also contains a ligand-binding domain. Upon glutamate-binding to an mGluR, the N-terminal tail undergoes a conformational change that leads to its interaction with the residues of the extracellular loops and TM domains. The eventual

effect of all three types of agonist-induced activation is a change in the relative orientations of the TM helices (likened to a twisting motion) leading to a wider intracellular surface and "revelation" of residues of the intracellular helices and TM domains crucial to signal transduction function (i.e., G-protein coupling).



Two-dimensional schematic of a generic GPCR set in a Lipid Raft. Click the image for higher resolution to see details regarding the locations of important structures.

Inverse agonists and antagonists may also bind to a number of different sites, but the eventual effect must be prevention of this TM helix reorientation.

The structure of the N- and C-terminal tails of GPCRs may also serve important functions beyond ligand-binding. In particular, the C-terminus often contains serine (Ser) or threonine (Thr) residues that, when phosphorylated, increase the affinity of the intracellular surface for the binding of scaffolding proteins called β-arrestins (β-arr).[35] Once bound, β-arrestins both sterically prevent G-protein coupling and may recruit other proteins, leading to the creation of signaling complexes involved in extracellular-signal regulated kinase (ERK) pathway activation or receptor endocytosis (internalization). As the phosphorylation of these Ser and Thr residues often occurs as a result of GPCR activation, the β-arr-mediated G-protein-decoupling and internalization of GPCRs are important mechanisms of

desensitization.[36]

A final common structural theme among GPCRs is palmitoylation of one or more sites of the C-terminal tail or the intracellular loops. Palmitoylation is the covalent modification of cysteine (Cys) residues via addition of hydrophobic acyl groups, and has the effect of targeting the receptor to cholesterol- and sphingolipid-rich microdomains of the plasma membrane called lipid rafts. As many of the downstream transducer and effector molecules of GPCRs (including those involved in negative feedback pathways) are also targeted to lipid rafts, this has the effect of facilitating rapid receptor signaling.

GPCRs respond to extracellular signals mediated by a huge diversity of agonists, ranging from proteins to biogenic amines to protons, but all transduce this signal via a mechanism of G-protein coupling. This is made possible by virtue of a guanine-nucleotide exchange factor (GEF) domain primarily formed by a combination of IL-2 and IL-3 along with adjacent residues of the associated TM helices.

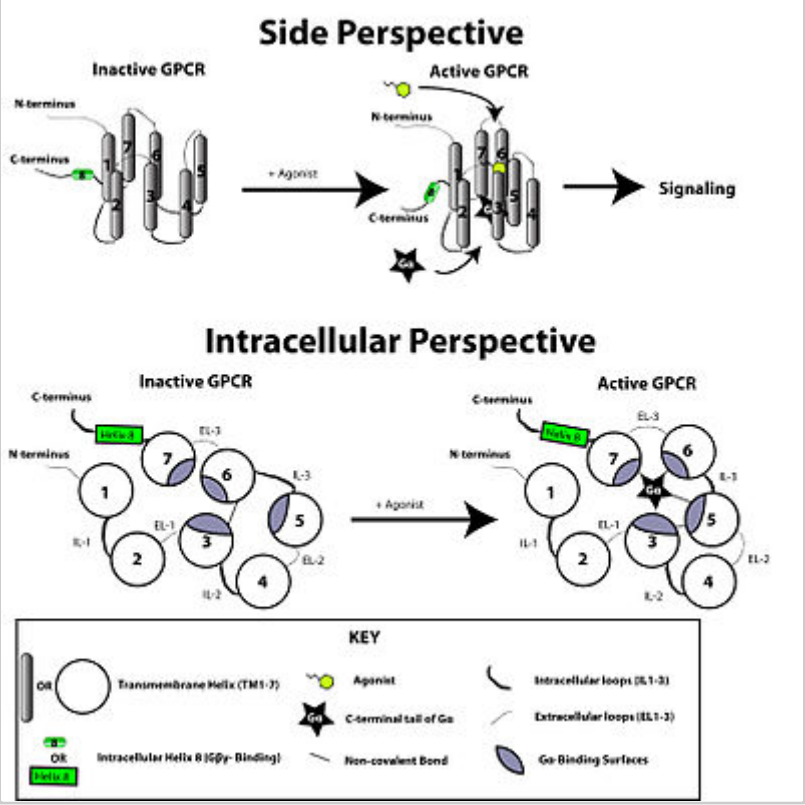
Mechanism

The G protein-coupled receptor is activated by an external signal in the form of a ligand or other signal mediator. This creates a conformational change in the receptor, causing activation of a G protein. Further effect depends on the type of G protein.

Ligand binding

GPCRs include receptors for sensory signal mediators (e.g., light and olfactory stimulatory molecules); adenosine, bombesin, bradykinin, endothelin, ɣ-aminobutyric acid (GABA), hepatocyte growth factor (HGF), melanocortins, neuropeptide Y, opioid peptides, opsins, somatostatin, GH, tachykinins, members of the vasoactive intestinal peptide family, and vasopressin; biogenic amines (e.g., dopamine, epinephrine, norepinephrine, histamine, glutamate (metabotropic effect), glucagon, acetylcholine (muscarinic effect), and serotonin); chemokines; lipid mediators of inflammation (e.g., prostaglandins, prostanoids, platelet-activating factor, and leukotrienes); and peptide hormones (e.g., calcitonin, C5a anaphylatoxin, follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), neurokinin, thyrotropin-releasing hormone (TRH), cannabinoids, and oxytocin). GPCRs that act as receptors for stimuli that have not yet been identified are known as orphan receptors.

However, in other types of receptors that have been studied, wherein ligands bind externally to the membrane, the ligands of GPCRs typically bind within the transmembrane domain. However, protease-activated receptors are activated by cleavage of part of their extracellular domain.[38]



Cartoon depicting the basic concept of GPCR Conformational Activation. Ligand binding disrupts an ionic lock between the E/DRY motif of TM-3 and acidic residues of TM-6. As a result, the GPCR reorganizes to allow activation of G-alpha proteins. The side perspective is a view from above and to the side of the GPCR as it is set in the plasma membrane (the membrane lipids have been omitted for clarity). The intracellular perspective shows the view looking up at the plasma membrane from inside the cell.[37]

Conformational change

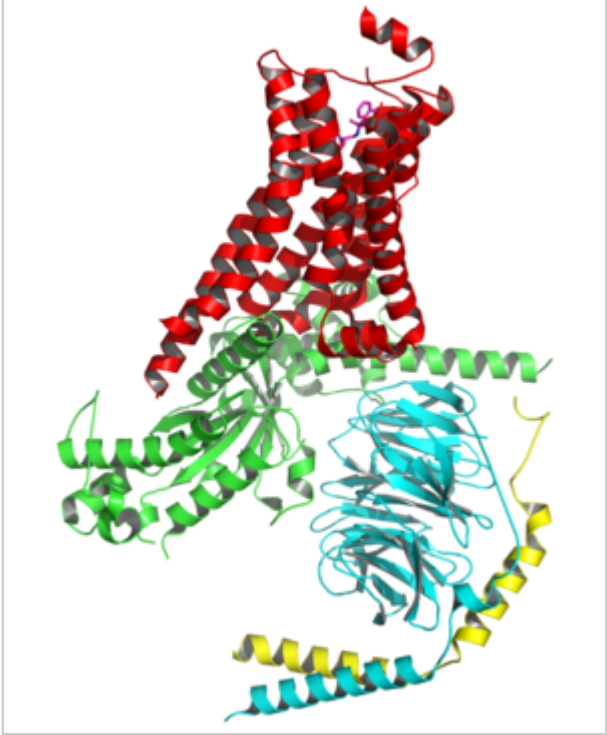
The transduction of the signal through the membrane by the receptor is not completely understood. It is known that the inactive G protein is bound to the receptor in its inactive state. Once the ligand is recognized, the receptor shifts conformation and, thus, mechanically activates the G protein, which detaches from the receptor. The receptor can now either activate another G protein or switch back to its inactive state. This is an overly simplistic explanation but suffices to convey the overall set of events.

It is believed that a receptor molecule exists in a conformational equilibrium between active and inactive biophysical states.[39] The binding of ligands to the receptor may shift the equilibrium toward the active receptor states.[40] Three types of ligands exist: Agonists are ligands that shift the equilibrium in favour of active states; inverse agonists are ligands that shift the equilibrium in favour of inactive states; and neutral antagonists are ligands that do not affect the equilibrium. It is not yet known how exactly the active and inactive

states differ from each other.

G-protein activation/deactivation cycle

See also: G protein

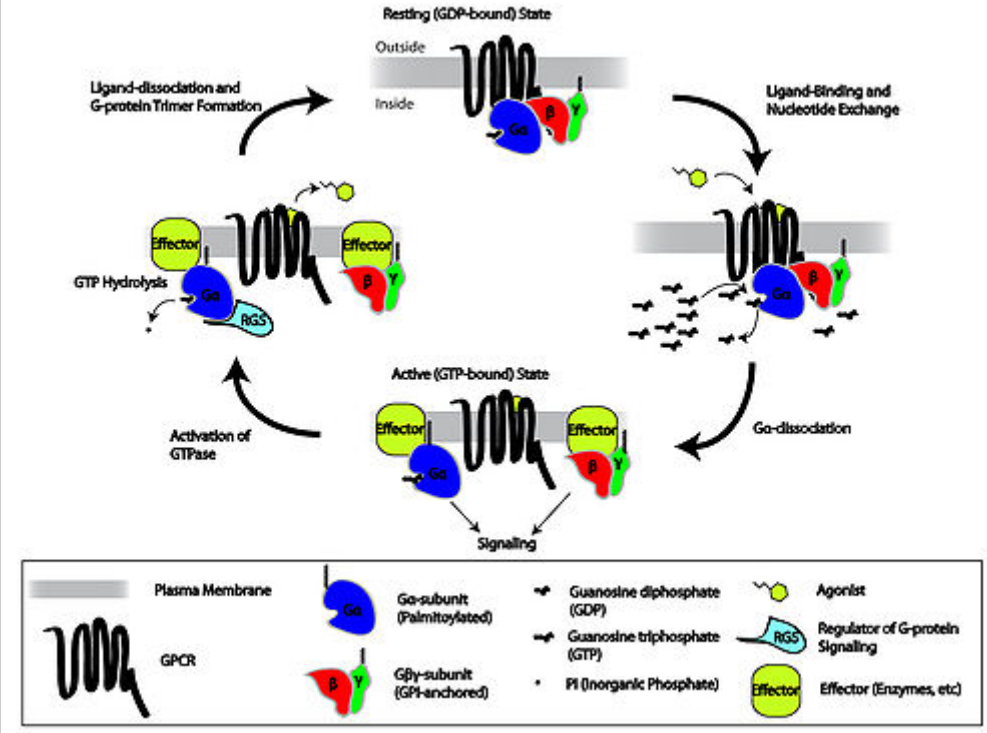


Crystal structure of activated beta-2 adrenergic receptor in complex with G_s(PDB entry 3SN6 (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3SN6)). The receptor is colored red, Gα green, Gβ cyan, and Gγ yellow. The C-terminus of Gα is located in a cavity created by an outward movement of the cytoplasmic parts of TM5 and 6.

When the receptor is inactive, the GEF domain may be bound to an also inactive α-subunit of a heterotrimeric G-protein. These "G-proteins" are a trimer of α, β, and γ subunits (known as Gα, Gβ, and Gγ, respectively) that is rendered inactive when reversibly bound to Guanosine diphosphate (GDP) (or, alternatively, no guanine nucleotide) but active when bound to Guanosine triphosphate (GTP). Upon receptor activation, the GEF domain, in turn, allosterically activates the G-protein by facilitating the exchange of a molecule of GDP for GTP at the G-protein's α-subunit. The cell maintains a 10:1 ratio of cytosolic GTP:GDP so exchange for GTP is ensured. At this point, the subunits of the G-protein dissociate from the receptor, as well as each other, to yield a Gα-GTP monomer and a tightly interacting Gβγ dimer, which are now free to modulate the activity of other intracellular proteins. The extent to which they may diffuse, however, is limited due to the palmitoylation of Gα and the presence of an isoprenoid moiety that has been covalently added to the C-termini of Gγ.

Because Gα also has slow GTP→GDP hydrolysis capability, the inactive form of the α-subunit (Gα-GDP) is eventually regenerated, thus allowing reassociation with a Gβγ dimer to form the "resting" G-protein, which can again bind to a GPCR and await activation. The rate of GTP hydrolysis is often accelerated due to the actions of another family of allosteric modulating proteins called Regulators of G-protein Signaling, or RGS proteins, which are a type of GTPase-Activating Protein, or GAP. In fact, many of the primary effector

proteins (e.g., adenylate cyclases) that become



Cartoon depicting the Heterotrimeric G-protein activation/deactivation cycle in the context of GPCR signaling

activated/inactivated upon interaction with Gα-GTP also have GAP activity. Thus, even at this early stage in the process, GPCR-initiated signaling has the capacity for self-termination.

Crosstalk

GPCRs downstream signals have been shown to possibly interact with integrin signals, such as FAK.[41] Integrin signaling will phosphorylate FAK, which can then decrease GPCR Gαs activity.

Proposed downstream interactions between integrin signaling and GPCRs. Integrins are shown elevating Ca^{2+} and phosphorylating FAK, which is weakening GPCR signaling.

GPCR signaling

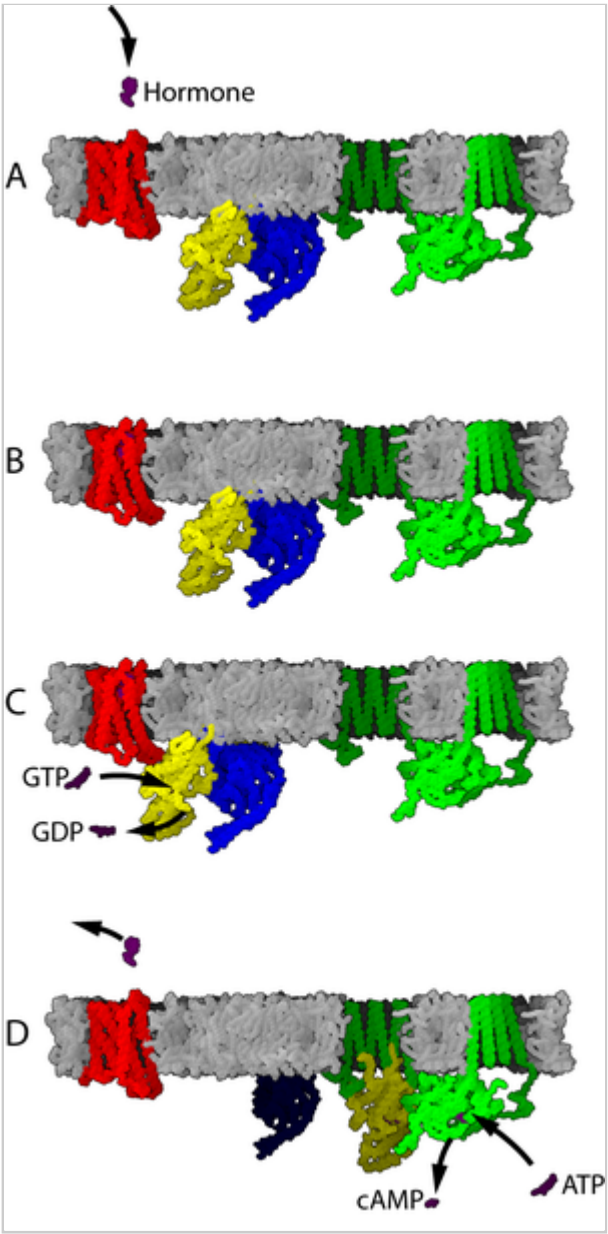
If a receptor in an active state encounters a G protein, it may activate it. Some evidence suggests that receptors and G proteins are actually pre-coupled. For example, binding of G proteins to receptors affects the receptor's affinity for ligands. Activated G proteins are bound to GTP.

Further signal transduction depends on the type of G protein. The enzyme adenylate cyclase is an example of a cellular protein that can be regulated by a G protein, in this case the G protein G_S. Adenylate cyclase activity is activated when it binds to a subunit of the activated G protein. Activation of adenylate cyclase ends when the G protein returns to the GDP-bound state.

Adenylate cyclases (of which 9 membrane-bound and one cytosolic forms are known in humans) may also be activated or inhibited in other ways (e.g., Ca2+/Calmodulin binding), which can modify the activity of these enzymes in an additive or synergistic fashion along with the G proteins.

The signaling pathways activated through a GPCR are limited by the primary sequence and tertiary structure of the GPCR itself but ultimately determined by the particular conformation stabilized by a

particular ligand, as well as the availability of transducer molecules. Currently, GPCRs are considered to utilize two primary types of transducers: G-proteins and β-arrestins. Because β-arr's have high affinity only to the phosphorylated form of most GPCRs (see above or below), the majority of signaling is ultimately dependent upon G-protein activation. However, the possibility for interaction does allow for G-protein-independent signaling to occur.



G-protein-coupled receptor mechanism

G-protein-dependent signaling

There are three main G-protein-mediated signaling pathways, mediated by four sub-classes of G-proteins distinguished from each other by sequence homology ($G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q/11}$, and $G_{\alpha 12/13}$). Each sub-class of G-protein consists of multiple proteins, each the product of multiple genes and/or splice variations that may imbue them with differences ranging from subtle to distinct with regard to signaling properties, but in general they appear reasonably grouped into four classes. Because the signal transducing properties of the various possible βγ combinations do not appear to radically differ from one another, these classes are defined according to the isoform of their α-subunit.[7]:1163

While most GPCRs are capable of activating more than one Gα-subtype, they also show a preference for one subtype over another. When the subtype activated depends on the ligand that is bound to the GPCR, this is called functional selectivity (also known as agonist-directed trafficking, or conformation-specific agonism). However, the binding of any single particular agonist may also initiate activation of multiple different G-proteins, as it may be capable of stabilizing more than one conformation of the GPCR's GEF domain, even over the

course of a single interaction. In addition, a conformation that preferably activates one isoform of Gα may activate another if the preferred is less available. Furthermore, feedback pathways may result in receptor modifications (e.g., phosphorylation) that alter the G-protein preference. Regardless of these various nuances, the GPCR's preferred coupling partner is usually defined according to the G-protein most obviously activated by the endogenous ligand under most physiological and/or experimental conditions.

Gα signaling

1. The effector of both the $G_{\alpha s}$ and $G_{\alpha i/o}$ pathways is the cyclic-adenosine monophosphate (cAMP)-generating enzyme adenylate cyclase, or AC. While there are ten different AC gene products in mammals, each with subtle differences in tissue distribution and/or function, all catalyze the conversion of cytosolic adenosine triphosphate (ATP) to cAMP, and all are directly stimulated by G-proteins of the $G_{\alpha s}$ class. In contrast, however, interaction with Gα subunits of the $G_{\alpha i/o}$ type inhibits AC from generating cAMP. Thus, a GPCR coupled to $G_{\alpha s}$ counteracts the actions of a GPCR coupled to $G_{\alpha i/o}$, and vice versa. The level of cytosolic cAMP may then determine the activity of various ion channels as well as members of the ser/thr-specific protein kinase A (PKA) family. Thus cAMP is considered a second messenger and PKA a secondary effector.
2. The effector of the $G_{\alpha q/11}$ pathway is phospholipase C-β (PLCβ), which catalyzes the cleavage of membrane-bound phosphatidylinositol 4,5-biphosphate (PIP2) into the second messengers inositol (1,4,5) trisphosphate (IP3) and diacylglycerol (DAG). IP3 acts on IP3 receptors found in the membrane of the endoplasmic reticulum (ER) to elicit Ca^{2+} release from the ER, while DAG diffuses along the plasma membrane where it may activate any membrane localized forms of a second ser/thr kinase called protein kinase C (PKC). Since many isoforms of PKC are also activated by increases in intracellular Ca^{2+}, both these pathways can also converge on each other to signal through the same secondary effector. Elevated intracellular Ca^{2+} also binds and allosterically activates proteins called calmodulins, which in turn go on to bind and allosterically activate enzymes such as Ca^{2+}/calmodulin-dependant kinases (CAMKs).
3. The effectors of the $G_{\alpha 12/13}$ pathway are three RhoGEFs (p115-RhoGEF, PDZ-RhoGEF, and LARG), which, when bound to $G_{\alpha 12/13}$ allosterically activate the cytosolic small GTPase, Rho. Once

bound to GTP, Rho can then go on to activate various proteins responsible for cytoskeleton regulation such as Rho-kinase (ROCK). Most GPCRs that couple to $G_{\alpha 12/13}$ also couple to other sub-classes, often $G_{\alpha q/11}$.

Gβγ signaling

The above descriptions ignore the effects of Gβγ–signalling, which can also be important, in particular in the case of activated $G_{\alpha i/o}$-coupled GPCRs. The primary effectors of Gβγ are various ion channels, such as G-protein-regulated inwardly rectifying K^+ channels (GIRKs), P/Q- and N-type voltage-gated Ca^{2+} channels, as well as some isoforms of AC and PLC, along with some phosphoinositide-3-kinase (PI3K) isoforms.

G-protein-independent signaling

Although they are classically thought of working only together, GPCRs may signal through G-protein-independent mechanisms, and heterotrimeric G-proteins may play functional roles independent of GPCRs. GPCRs may signal independently through many proteins already mentioned for their roles in G-protein-dependent signaling such as β-arrs, GRKs, and Srcs. In addition, further scaffolding proteins involved in subcellular localization of GPCRs (e.g., PDZ-domain-containing proteins) may also act as signal transducers. Most often the effector is a member of the MAPK family.

Examples

In the late 1990s, evidence began accumulating to suggest that some GPCRs are able to signal without G proteins. The ERK2 mitogen-activated protein kinase, a key signal transduction mediator downstream of receptor activation in many pathways, has been shown to be activated in response to cAMP-mediated receptor activation in the slime mold *D. discoideum* despite the absence of the associated G protein α- and β-subunits.[42]

In mammalian cells, the much-studied β_2-adrenoceptor has been demonstrated to activate the ERK2 pathway after arrestin-mediated uncoupling of G-protein-mediated signaling. Therefore, it seems likely that some mechanisms previously believed related purely to receptor desensitisation are actually examples of receptors switching their signaling pathway, rather than simply being switched off.

In kidney cells, the bradykinin receptor B2 has been shown to interact

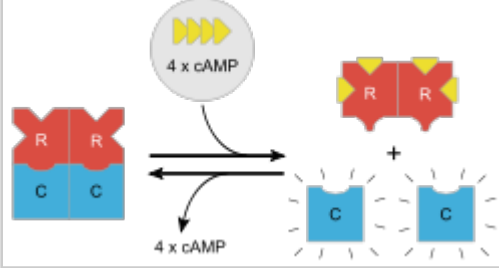
directly with a protein tyrosine phosphatase. The presence of a tyrosine-phosphorylated ITIM (immunoreceptor tyrosine-based inhibitory motif) sequence in the B2 receptor is necessary to mediate this interaction and subsequently the antiproliferative effect of bradykinin.[43]

GPCR-independent signaling by heterotrimeric G-proteins

Although it is a relatively immature area of research, it appears that heterotrimeric G-proteins may also take part in non-GPCR signaling. There is evidence for roles as signal transducers in nearly all other types of receptor-mediated signaling, including integrins, receptor tyrosine kinases (RTKs), cytokine receptors (JAK/STATs), as well as modulation of various other "accessory" proteins such as GEFs, Guanine-nucleotide Dissociation Inhibitors (GDIs) and protein phosphatases. There may even be specific proteins of these classes whose primary function is as part of GPCR-independent pathways, termed Activators of G-protein Signalling (AGS). Both the ubiquity of these interactions and the importance of Gα vs. Gβγ subunits to these processes are still unclear.

Details of cAMP and PIP2 pathways

There are two principal signal transduction pathways involving the G protein-linked receptors: cAMP signal pathway and Phosphatidylinositol signal pathway.[6]



Activation effects of cAMP on Protein Kinase A

cAMP signal pathway

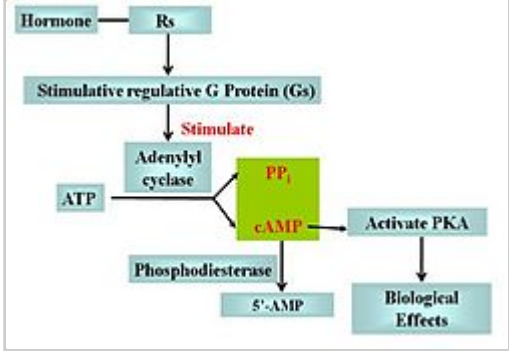
> *Main article: cAMP-dependent pathway*

The cAMP signal transduction contains 5 main characters: stimulative hormone receptor (Rs) or inhibitory hormone receptor (Ri); stimulative regulative G-protein (Gs) or inhibitory regulative G-protein (Gi); Adenylyl cyclase; Protein Kinase A (PKA); and cAMP phosphodiesterase.

Stimulative hormone receptor (Rs) is a receptor that can bind with stimulative signal molecules, while inhibitory hormone (Ri) is a receptor that can bind with inhibitory signal molecules.

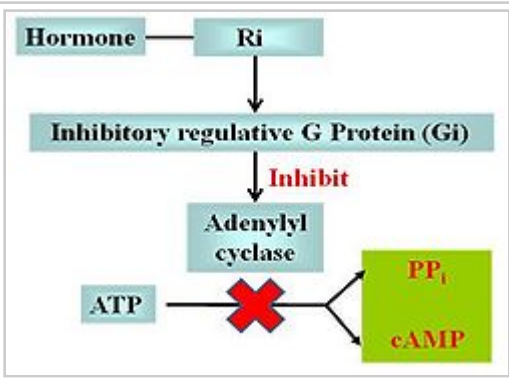
Stimulative regulative G-protein is a G protein-linked to stimulative

hormone receptor (Rs) and its α subunit upon activation could stimulate the activity of an enzyme or other intracellular metabolism. On the contrary, inhibitory regulative G-protein is linked to an inhibitory hormone receptor and its α subunit upon activation could inhibit the activity of an enzyme or other intracellular metabolism.



The effect of Rs and Gs in cAMP signal pathway

The Adenylyl cyclase is a 12-transmembrane glycoprotein that catalyzes ATP to form cAMP with the help of cofactor Mg^{2+} or Mn^{2+}. The cAMP produced is a second messenger in cellular metabolism and is an allosteric activator to Protein kinase A.



The effect of Ri and Gi in cAMP signal pathway

Protein kinase A is an important enzyme in cell metabolism due to its ability to regulate cell metabolism by phosphorylating specific committed enzymes in the metabolic pathway. It can also regulate specific gene expression, cellular secretion, and membrane permeability. The protein enzyme contains two catalytic subunits and two regulatory subunits. When there is no cAMP, the complex is inactive. When cAMP binds to the regulatory subunits, their conformation is altered, causing the dissociation of the regulatory subunits, which activates protein kinase A and allows further biological effects.

cAMP phosphodiesterase is an enzyme that can degrade cAMP to 5'-AMP, which terminates the signal.

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 phospholipase C, which is located on the plasma membrane. The lipase hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into two second messengers: Inositol 1,4,5-trisphosphate (IP3) and Diacylglycerol (DAG). IP3 binds with the receptor in the membrane of the smooth endoplasmic reticulum and mitochondria, help open the Ca^{2+} channel. DAG helps activate Protein

Kinase C (PKC), which phosphorylates many other proteins, changing their catalytic activities, leading to cellular responses. The effects of Ca^{2+} is also remarkable: It cooperates with DAG in activating PKC and can activate CaM kinase pathway, in which calcium-modulated protein calmodulin (CaM) binds Ca^{2+}, undergoes a change in conformation, and activates CaM kinase II, which has unique ability to increase its binding affinity to CaM by autophosphorylation, making CaM unavailable for the activation of other enzymes. The kinase then phosphorylates target enzymes, regulating their activities. The two signal pathways are connected together by Ca^{2+}-CaM, which is also a regulatory subunit of adenylyl cyclase and phosphodiesterase in cAMP signal pathway.

Receptor regulation

GPCRs become desensitized when exposed to their ligand for a prolonged period of time. There are two recognized forms of desensitization: 1) homologous desensitization, in which the activated GPCR is downregulated; and 2) heterologous desensitization, wherein the activated GPCR causes downregulation of a different GPCR. The key reaction of this downregulation is the phosphorylation of the intracellular (or cytoplasmic) receptor domain by protein kinases.

Phosphorylation by cAMP-dependent protein kinases

Cyclic AMP-dependent protein kinases (protein kinase A) are activated by the signal chain coming from the G protein (that was activated by the receptor) via adenylate cyclase and cyclic AMP (cAMP). In a *feedback mechanism*, these activated kinases phosphorylate the receptor. The longer the receptor remains active the more kinases are activated and the more receptors are phosphorylated. In β_2-adrenoceptors, this phosphorylation results in the switching of the coupling from the G_s class of G-protein to the G_i class.[44] cAMP-dependent PKA mediated phosphorylation can cause heterologous desensitisation in receptors other than those activated.[45]

Phosphorylation by GRKs

The G protein-coupled receptor kinases (GRKs) are protein kinases that phosphorylate only active GPCRs. G-protein-coupled receptor kinases (GRKs) are key modulators of G-protein-coupled receptor (GPCR) signaling. They constitute a family of seven mammalian

serine-threonine protein kinases that phosphorylate agonist-bound receptor. GRKs-mediated receptor phosphorylation rapidly initiates profound impairment of receptor signaling and desensitization. Activity of GRKs and subcellular targeting is tightly regulated by interaction with receptor domains, G protein subunits, lipids, anchoring proteins and calcium-sensitive proteins.[46]

Phosphorylation of the receptor can have two consequences:

1. *Translocation*: The receptor is, along with the part of the membrane it is embedded in, brought to the inside of the cell, where it is dephosphorylated within the acidic vesicular environment[47] and then brought back. This mechanism is used to regulate long-term exposure, for example, to a hormone, by allowing resensitisation to follow desensitisation. Alternatively, the receptor may undergo lysozomal degradation, or remain internalised, where it is thought to participate in the initiation of signalling events, the nature of which depending on the internalised vesicle's subcellular localisation.[45]
2. *Arrestin linking*: The phosphorylated receptor can be linked to *arrestin* molecules that prevent it from binding (and activating) G proteins, in effect switching it off for a short period of time. This mechanism is used, for example, with rhodopsin in retina cells to compensate for exposure to bright light. In many cases, arrestin's binding to the receptor is a prerequisite for translocation. For example, beta-arrestin bound to β_2-adrenoreceptors acts as an adaptor for binding with clathrin, and with the beta-subunit of AP2 (clathrin adaptor molecules); thus, the arrestin here acts as a scaffold assembling the components needed for clathrin-mediated endocytosis of β_2-adrenoreceptors.[48][49]

Mechanisms of GPCR signal termination

As mentioned above, G-proteins may terminate their own activation due to their intrinsic GTP→GDP hydrolysis capability. However, this reaction proceeds at a slow rate (≈.02 times/sec) and, thus, it would take around 50 seconds for any single G-protein to deactivate if other factors did not come into play. Indeed, there are around 30 isoforms of RGS proteins that, when bound to Gα through their GAP domain, accelerate the hydrolysis rate to ≈30 times/sec. This 1500-fold increase in rate allows for the cell to respond to external signals with high speed, as well as spatial resolution due to limited amount of second messenger that can be generated and limited distance a G-protein can diffuse in .03 seconds. For the most part, the RGS

proteins are promiscuous in their ability to activate G-proteins, while which RGS is involved in a given signaling pathway seems more determined by the tissue and GPCR involved than anything else. In addition, RGS proteins have the additional function of increasing the rate of GTP-GDP exchange at GPCRs, (i.e., as a sort of co-GEF) further contributing to the time resolution of GPCR signaling.

In addition, the GPCR may be desensitized itself. This can occur as:

1. a direct result of ligand occupation, wherein the change in conformation allows recruitment of GPCR-Regulating Kinases (GRKs), which go on to phosphorylate various serine/threonine residues of IL-3 and the C-terminal tail. Upon GRK phosphorylation, the GPCR's affinity for β-arrestin (β-arrestin-1/2 in most tissues) is increased, at which point β-arrestin may bind and act to both sterically hinder G-protein coupling as well as initiate the process of receptor internalization through clathrin-mediated endocytosis. Because only the liganded receptor is desensitized by this mechanism, it is called homologous desensitization
2. the affinity for β-arrestin may be increased in a ligand occupation and GRK-independent manner through phosphorylation of different ser/thr sites (but also of IL-3 and the C-terminal tail) by PKC and PKA. These phosphorylations are often sufficient to impair G-protein coupling on their own as well.[*citation needed*]
3. PKC/PKA may, instead, phosphorylate GRKs, which can also lead to GPCR phosphorylation and β-arrestin binding in an occupation-independent manner. These latter two mechanisms allow for desensitization of one GPCR due to the activities of others, or heterologous desensitization. GRKs may also have GAP domains and so may contribute to inactivation through non-kinase mechanisms as well. A combination of these mechanisms may also occur.

Once β-arrestin is bound to a GPCR, it undergoes a conformational change allowing it to serve as a scaffolding protein for an adaptor complex termed AP-2, which in turn recruits another protein called clathrin. If enough receptors in the local area recruit clathrin in this manner, they aggregate and the membrane buds inwardly as a result of interactions between the molecules of clathrin, in a process called opsonization. Once the pit has been pinched off, the plasma membrane due to the actions of two other proteins called amphiphysin and dynamin, it is now an endocytic vesicle. At this point, the adapter molecules and clathrin have dissociated, and the receptor is either trafficked back to the plasma membrane or targeted to lysosomes for

degradation.

At any point in this process, the β-arrestins may also recruit other proteins—such as the non-receptor tyrosine kinase (nRTK), c-SRC—which may activate ERK1/2, or other mitogen-activated protein kinase (MAPK) signaling through, for example, phosphorylation of the small GTP-ase, Ras, or recruit the proteins of the ERK cascade directly (i.e., Raf-1, MEK, ERK-1/2) at which point signaling is initiated due to their close proximity to one another. Another target of c-SRC are the dynamin molecules involved in endocytosis. Dynamins polymerize around the neck of an incoming vesicle, and their phosphorylation by c-SRC provides the energy necessary for the conformational change allowing the final "pinching off" from the membrane.

GPCR cellular regulation

Receptor desensitization is mediated through a combination phosphorylation, β-arr binding, and endocytosis as described above. Downregulation occurs when endocytosed receptor is embedded in an endosome that is trafficked to merge with an organelle called a lysosome. Because lysosomal membranes are rich in proton pumps, their interiors have low pH (≈4.8 vs. the pH≈7.2 cytosol), which acts to denature the GPCRs. In addition, lysosomes contain many degradative enzymes, including proteases, which can function only at such low pH, and so the peptide bonds joining the residues of the GPCR together may be cleaved. Whether or not a given receptor is trafficked to a lysosome, detained in endosomes, or trafficked back to the plasma membrane depends on a variety of factors, including receptor type and magnitude of the signal. GPCR regulation is additionally mediated by gene transcription factors. These factors can increase or decrease gene transcription and thus increase or decrease the generation of new receptors (up- or down-regulation) that travel to the cell membrane.

Receptor oligomerization

Main article: GPCR oligomer

G-protein-coupled receptor oligomerisation is a widespread phenomenon. One of the best-studied examples is the metabotropic $GABA_B$ receptor. This so-called constitutive receptor is formed by heterodimerization of $GABA_BR1$ and $GABA_BR2$ subunits. Expression of the $GABA_BR1$ without the $GABA_BR2$ in heterologous systems leads to retention of the subunit in the endoplasmic reticulum. Expression of

the $GABA_BR2$ subunit alone, meanwhile, leads to surface expression of the subunit, although with no functional activity (i.e., the receptor does not bind agonist and cannot initiate a response following exposure to agonist). Expression of the two subunits together leads to plasma membrane expression of functional receptor. It has been shown that $GABA_BR2$ binding to $GABA_BR1$ causes masking of a retention signal[50] of functional receptors.[51]

Origin and diversification of the superfamily

Signal transduction mediated by the superfamily of GPCRs dates back to the origin of multicellularity. Mammalian-like GPCRs are found in fungi, and have been classified according to the GRAFS classification system based on GPCR fingerprints.[52] Identification of the superfamily members across the eukaryotic domain, and comparison of the family-specific motifs, have shown that the superfamily of GPCRs have a common origin.[53] Characteristic motifs indicate that three of the five GRAFS families, *Rhodopsin*, *Adhesion*, and *Frizzled*, evolved from the *Dictyostelium discoideum* cAMP receptors before the split of Opisthokonts. Later, the *Secretin* family evolved from the *Adhesion* GPCR receptor family before the split of nematodes.

Dictyostelium discoideum

A novel GPCR containing a lipid kinase domain has recently been identified in *Dictyostelium discoideum* that regulates cell density sensing.[54]

See also

- G protein-coupled receptors database
- Metabotropic receptor
- Orphan receptor
- Pepducins, a class of drug candidates targeted at GPCRs
- Receptor activated solely by a synthetic ligand, a technique for control of cell signaling through synthetic GPCRs

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External links

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Further reading

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