**Cell** **Signaling:**

GPCR and Role of Second messenger:

G protein.

**G proteins**, also known as **guanine nucleotide-binding proteins**, are a [family of proteins](https://en.wikipedia.org/wiki/Protein_family) that act as [molecular switches](https://en.wikipedia.org/wiki/Molecular_switch) inside cells, and are involved in transmitting signals from a variety of stimuli outside a [cell](https://en.wikipedia.org/wiki/Cell_%28biology%29) to its interior. Their activity is regulated by factors that control their ability to bind to and hydrolyze [guanosine triphosphate](https://en.wikipedia.org/wiki/Guanosine_triphosphate) (GTP) to [guanosine diphosphate](https://en.wikipedia.org/wiki/Guanosine_diphosphate) (GDP). When they are bound to GTP, they are 'on', and, when they are bound to GDP, they are 'off'. G proteins belong to the larger group of enzymes called [GTPases](https://en.wikipedia.org/wiki/GTPase).

There are two classes of G proteins. The first function as [monomeric](https://en.wikipedia.org/wiki/Monomeric) [small GTPases](https://en.wikipedia.org/wiki/Small_GTPase) (small G-proteins), while the second function as [heterotrimeric G protein](https://en.wikipedia.org/wiki/Heterotrimeric_G_protein) [complexes](https://en.wikipedia.org/wiki/Protein_complex). The latter class of complexes is made up of [*alpha*](https://en.wikipedia.org/wiki/G_alpha_subunit) (α), *beta* (β) and *gamma* (γ) [subunits](https://en.wikipedia.org/wiki/Protein_subunit). In addition, the beta and gamma subunits can form a stable dimeric complex referred to as the [beta-gamma complex](https://en.wikipedia.org/wiki/G_beta-gamma_complex) .

Heterotrimeric G proteins located within the cell are activated by [G protein-coupled receptors](https://en.wikipedia.org/wiki/G_protein-coupled_receptor) (GPCRs) that span the cell membrane. Signal molecules bind to a domain of the GPCR located outside the cell, and an intracellular GPCR domain then in turn activates a particular G protein. Some active-state GPCRs have also been shown to be "pre-coupled" with G proteins. The G protein activates a cascade of further signal events that finally results in a change in cell function. G protein-coupled receptor and G proteins working together transmit signals from many [hormones](https://en.wikipedia.org/wiki/Hormone), [neurotransmitters](https://en.wikipedia.org/wiki/Neurotransmitter), and other signal factors. G proteins regulate metabolic [enzymes](https://en.wikipedia.org/wiki/Enzyme), [ion channels](https://en.wikipedia.org/wiki/Ion_channel), [transporter proteins](https://en.wikipedia.org/wiki/Membrane_transport_protein), and other parts of the cell machinery, controlling [transcription](https://en.wikipedia.org/wiki/Transcription_%28genetics%29), [motility](https://en.wikipedia.org/wiki/Motility), [contractility](https://en.wikipedia.org/wiki/Contractility), and [secretion](https://en.wikipedia.org/wiki/Secretion), which in turn regulate diverse systemic functions such as [embryonic development](https://en.wikipedia.org/wiki/Embryonic_development), learning and memory, and [homeostasis](https://en.wikipedia.org/wiki/Homeostasis).

GPCRs

G protein-coupled receptors (GPCRs), also known as seven-(pass)-transmembrane domain receptors, 7TM receptors, hepta helical receptors, serpentine receptors, and G protein-linked receptors (GPLR), form a large group of [evolutionarily-related proteins](https://en.wikipedia.org/wiki/Protein_family) that are [cell surface receptors](https://en.wikipedia.org/wiki/Cell_surface_receptor) that detect [molecules](https://en.wikipedia.org/wiki/Molecule) outside the [cell](https://en.wikipedia.org/wiki/Cell_%28biology%29) and activate cellular responses. Coupling with [G proteins](https://en.wikipedia.org/wiki/G_protein), they are called seven-transmembrane receptors because they pass through the [cell membrane](https://en.wikipedia.org/wiki/Cell_membrane) seven times.



Fig:GPCR

G protein-coupled receptors are found only in [eukaryotes](https://en.wikipedia.org/wiki/Eukaryote), including [yeast](https://en.wikipedia.org/wiki/Yeast), [choanoflagellates](https://en.wikipedia.org/wiki/Choanoflagellate),[[3]](https://en.wikipedia.org/wiki/G_protein-coupled_receptor#cite_note-pmid12869759-3) and animals. The [ligands](https://en.wikipedia.org/wiki/Ligand_%28biochemistry%29) that bind and activate these receptors include light-sensitive compounds, [odors](https://en.wikipedia.org/wiki/Odor), [pheromones](https://en.wikipedia.org/wiki/Pheromone), [hormones](https://en.wikipedia.org/wiki/Hormone), and [neurotransmitters](https://en.wikipedia.org/wiki/Neurotransmitter), and vary in size from small molecules to [peptides](https://en.wikipedia.org/wiki/Peptide) to large [proteins](https://en.wikipedia.org/wiki/Protein). G protein-coupled receptors are involved in many diseases.

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

* the [cAMP](https://en.wikipedia.org/wiki/Cyclic_adenosine_monophosphate) signal pathway and
* the [phosphatidylinositol](https://en.wikipedia.org/wiki/Phosphatidylinositol) signal pathway.

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](https://en.wikipedia.org/wiki/G_protein). Further effect depends on the type of G protein. G proteins are subsequently inactivated by GTPase activating proteins, known as [RGS proteins](https://en.wikipedia.org/wiki/Regulator_of_G_protein_signaling).



The [transduction of the signal](https://en.wikipedia.org/wiki/Signal_transduction) through the membrane by the receptor is not completely understood. It is known that in the inactive state, the GPCR is bound to a [heterotrimeric G protein](https://en.wikipedia.org/wiki/Heterotrimeric_G_protein) complex. Binding of an agonist to the GPCR results in a [conformational change](https://en.wikipedia.org/wiki/Conformational_change) in the receptor that is transmitted to the bound Gα subunit of the heterotrimeric G protein via [protein domain dynamics](https://en.wikipedia.org/wiki/Protein_dynamics#Global_flexibility:_multiple_domains). The activated Gα subunit exchanges [GTP](https://en.wikipedia.org/wiki/Guanosine_triphosphate) in place of [GDP](https://en.wikipedia.org/wiki/Guanosine_diphosphate) which in turn triggers the dissociation of Gα subunit from the Gβγ dimer and from the receptor. The dissociated Gα and Gβγ subunits interact with other intracellular proteins to continue the signal transduction cascade while the freed GPCR is able to rebind to another heterotrimeric G protein to form a new complex that is ready to initiate another round of signal transduction.[[](https://en.wikipedia.org/wiki/G_protein-coupled_receptor#cite_note-pmid17095603-45)

It is believed that a receptor molecule exists in a conformational [equilibrium](https://en.wikipedia.org/wiki/Dynamic_equilibrium) between active and inactive biophysical states. The binding of ligands to the receptor may shift the equilibrium toward the active receptor states. Three types of ligands exist: Agonists are ligands that shift the equilibrium in favour of active states; [inverse agonists](https://en.wikipedia.org/wiki/Inverse_agonist) 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.

## **Signaling**



 Fig G-protein-coupled receptor mechanism

If a receptor in an active state encounters a [G protein](https://en.wikipedia.org/wiki/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](https://en.wikipedia.org/wiki/Guanosine_triphosphate).

Further signal transduction depends on the type of G protein. The enzyme [adenylate cyclase](https://en.wikipedia.org/wiki/Adenylate_cyclase) is an example of a cellular protein that can be regulated by a G protein, in this case the G protein [Gs](https://en.wikipedia.org/wiki/Gs_alpha_subunit). 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](https://en.wikipedia.org/wiki/Guanosine_diphosphate)-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](https://en.wikipedia.org/wiki/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](https://en.wikipedia.org/wiki/Protein_primary_structure) and [tertiary structure](https://en.wikipedia.org/wiki/Tertiary_structure) of the GPCR itself but ultimately determined by the particular [conformation](https://en.wikipedia.org/wiki/Protein_conformation) stabilized by a particular [ligand](https://en.wikipedia.org/wiki/Ligand_%28biochemistry%29), as well as the availability of [transducer](https://en.wikipedia.org/wiki/Transducer) molecules. Currently, GPCRs are considered to utilize two primary types of transducers: [G-proteins](https://en.wikipedia.org/wiki/G-proteins) and [β-arrestins](https://en.wikipedia.org/wiki/Arrestin). Because β-arr’s have high [affinity](https://en.wikipedia.org/wiki/Affinity_%28pharmacology%29) only to the [phosphorylated](https://en.wikipedia.org/wiki/Phosphorylated) form of most GPCRs (see above or below), the majority of signalling is ultimately dependent upon G-protein activation. However, the possibility for interaction does allow for G-protein-independent signaling to occur.

Role of secondary messenger(cAMP)

**Second messenger**, molecule inside [cells](https://www.britannica.com/science/cell-biology) that acts to transmit signals from a [receptor](https://www.britannica.com/science/receptor-nerve-ending) to a target. The term second messenger was coined upon the discovery of these substances in order to distinguish them from [hormones](https://www.britannica.com/science/hormone) and other molecules that function outside the cell as “first messengers” in the transmission of biological information. Many second messenger molecules are small and therefore diffuse rapidly through the [cytoplasm](https://www.britannica.com/science/cytoplasm), enabling information to move quickly throughout the cell. As elements of signaling pathways, second messengers can serve to [integrate](https://www.merriam-webster.com/dictionary/integrate) information when multiple independent upstream inputs influence the rates of synthesis and [degradation](https://www.merriam-webster.com/dictionary/degradation) of the second messenger. In addition, second messengers can have multiple downstream targets, thereby expanding the scope of signal transmission.

A large number of second messenger molecules have been characterized, including cyclic [nucleotides](https://www.britannica.com/science/nucleotide) (e.g., cyclic adenosine monophosphate, or cAMP, and cyclic guanosine monophosphate, or cGMP), [ions](https://www.britannica.com/science/ion-physics) (e.g., Ca2+), [phospholipid](https://www.britannica.com/science/phospholipid)-derived molecules (e.g., [inositol](https://www.britannica.com/science/inositol) triphosphate), and even a gas, [nitric oxide](https://www.britannica.com/science/nitric-oxide) (NO). The [calcium](https://www.britannica.com/science/calcium) ion Ca2+ has a critical role in the rapid responses of [neurons](https://www.britannica.com/science/neuron) and muscle cells. At rest, cells maintain a low concentration of Ca2+ in the cytoplasm, expending energy to pump these ions out of the cell. When activated, neurons and muscle cells rapidly increase their cytoplasmic Ca2+ concentration by opening channels in the [cell membrane](https://www.britannica.com/science/cell-biology/Intercellular-communication#ref37365), which allow Ca2+ ions outside the cell to enter rapidly. The cyclic nucleotide [cAMP](https://www.britannica.com/science/cyclic-35-adenosine-monophosphate) is synthesized by adenylyl cyclase [enzymes](https://www.britannica.com/science/enzyme), which are downstream of heterotrimeric G-proteins ([guanine](https://www.britannica.com/science/guanine) nucleotide binding proteins) and receptors. For example, when [epinephrine](https://www.britannica.com/science/epinephrine) binds to beta-adrenergic receptors in cell membranes, G-protein activation stimulates cAMP synthesis by adenylyl cyclase. The newly synthesized cAMP is then able to act as a second messenger, rapidly [propagating](https://www.merriam-webster.com/dictionary/propagating) the epinephrine signal to the appropriate molecules in the cell. This stimulatory signaling pathway leads to the production of effects such as increasing rate and force of contraction of the [heart](https://www.britannica.com/science/heart) that are characteristic of epinephrine. [Caffeine](https://www.britannica.com/science/caffeine) also [enhances](https://www.merriam-webster.com/dictionary/enhances) the action of cAMP by [inhibiting](https://www.merriam-webster.com/dictionary/inhibiting) the [enzyme](https://www.britannica.com/science/enzyme) phosphodiesterase, which degrades cAMP; the enhancement of cAMP activity contributes to the general stimulatory action of caffeine. As a gas, nitric oxide (NO) is distinct among second messengers in being able to diffuse across cell membranes, which allows signal information to cross into neighbouring cells.



The cAMP signal transduction contains 5 main characters: stimulative [hormone](https://en.wikipedia.org/wiki/Hormone) receptor (Rs) or inhibitory [hormone receptor](https://en.wikipedia.org/wiki/Hormone_receptor) (Ri); stimulative regulative G-protein (Gs) or inhibitory regulative G-protein (Gi); [adenylyl cyclase](https://en.wikipedia.org/wiki/Adenylyl_cyclase); [protein kinase A](https://en.wikipedia.org/wiki/Protein_kinase_A) (PKA); and cAMP [phosphodiesterase](https://en.wikipedia.org/wiki/Phosphodiesterase).

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

Adenylyl cyclase is a 12-transmembrane glycoprotein that catalyse ATP to form cAMP with the help of cofactor Mg2+ or Mn2+. The cAMP produced is a second messenger in cellular metabolism and is an allosteric activator of protein kinase A.

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.

These signals then can be terminated by cAMP phosphodiesterase, which is an enzyme that degrades cAMP to 5'-AMP and inactivates protein kinase A.

## **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](https://en.wikipedia.org/wiki/Opsin) use a [photoisomerization](https://en.wikipedia.org/wiki/Photoisomerization) reaction to translate [electromagnetic radiation](https://en.wikipedia.org/wiki/Electromagnetic_radiation) into cellular signals. [Rhodopsin](https://en.wikipedia.org/wiki/Rhodopsin), for example, uses the conversion of [*11-cis*-retinal](https://en.wikipedia.org/wiki/Retinal) to [*all-trans*-retinal](https://en.wikipedia.org/wiki/Retinal) for this purpose.

The gustatory sense (taste): GPCRs in taste cells mediate release of [Gustducin](https://en.wikipedia.org/wiki/Gustducin) in response to bitter-, umami- and sweet-tasting substances.

1. The sense of smell: Receptors of the [olfactory epithelium](https://en.wikipedia.org/wiki/Olfactory_epithelium) bind odorants (olfactory receptors) and pheromones (vomeronasal receptors)
2. Behavioural and mood regulation: Receptors in the [mammalian](https://en.wikipedia.org/wiki/Mammal) [brain](https://en.wikipedia.org/wiki/Brain) bind several different [neurotransmitters](https://en.wikipedia.org/wiki/Neurotransmitter), including [serotonin](https://en.wikipedia.org/wiki/Serotonin), [dopamine](https://en.wikipedia.org/wiki/Dopamine), [histamine](https://en.wikipedia.org/wiki/Histamine), [GABA](https://en.wikipedia.org/wiki/Gamma-aminobutyric_acid), and [glutamate](https://en.wikipedia.org/wiki/Glutamate)
3. Regulation of [immune system](https://en.wikipedia.org/wiki/Immune_system) activity and [inflammation](https://en.wikipedia.org/wiki/Inflammation): [chemokine](https://en.wikipedia.org/wiki/Chemokine) receptors bind ligands that mediate intercellular communication between cells of the immune system; receptors such as [histamine receptors](https://en.wikipedia.org/wiki/Histamine_receptor) bind [inflammatory mediators](https://en.wikipedia.org/wiki/Inflammatory_mediators) and engage target cell types in the [inflammatory response](https://en.wikipedia.org/wiki/Inflammation). GPCRs are also involved in immune-modulation, e. g. regulating interleukin induction or suppressing [TLR](https://en.wikipedia.org/wiki/Toll-like_receptor)-induced immune responses from T cells.
4. Autonomic nervous system transmission: Both the [sympathetic](https://en.wikipedia.org/wiki/Sympathetic_nervous_system) and [parasympathetic](https://en.wikipedia.org/wiki/Parasympathetic_nervous_system) 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
5. Cell density sensing: A novel GPCR role in regulating cell density sensing.
6. Homeostasis modulation (e.g., water balance).
7. Involved in growth and [metastasis](https://en.wikipedia.org/wiki/Metastasis) of some types of [tumours](https://en.wikipedia.org/wiki/Tumor).
8. Used in the endocrine system for peptide and amino-acid derivative hormones that bind to GCPRs on the cell membrane of a target cell. This activates cAMP, which in turn activates several kinases, allowing for a cellular response, such as transcription.