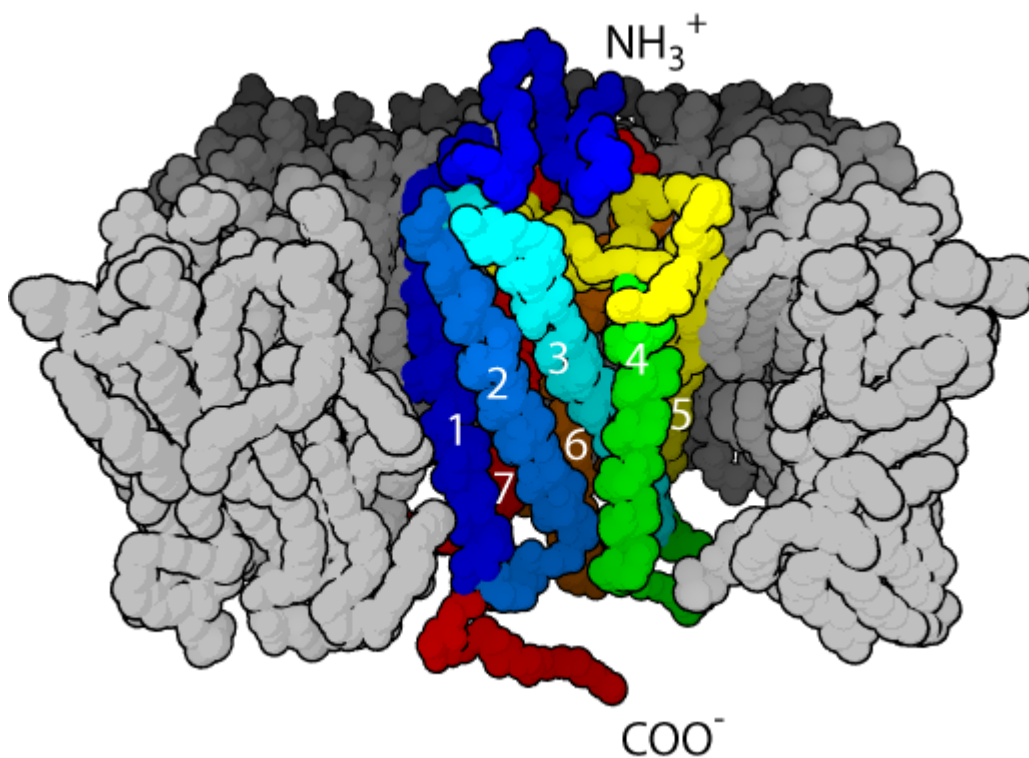


## Second Messenger Systems

[See online here](#)

**Signaling pathways are complex systems in which a single extracellular signal can elicit multiple intracellular events, some of which may also be triggered by other signaling pathways. We will discuss how this process occurs through kinase cascades and second messengers, and then apply these to processes to the regulation of protein expression and the fight or flight response, respectively.**



## Receptor Tyrosine Kinase Pathways

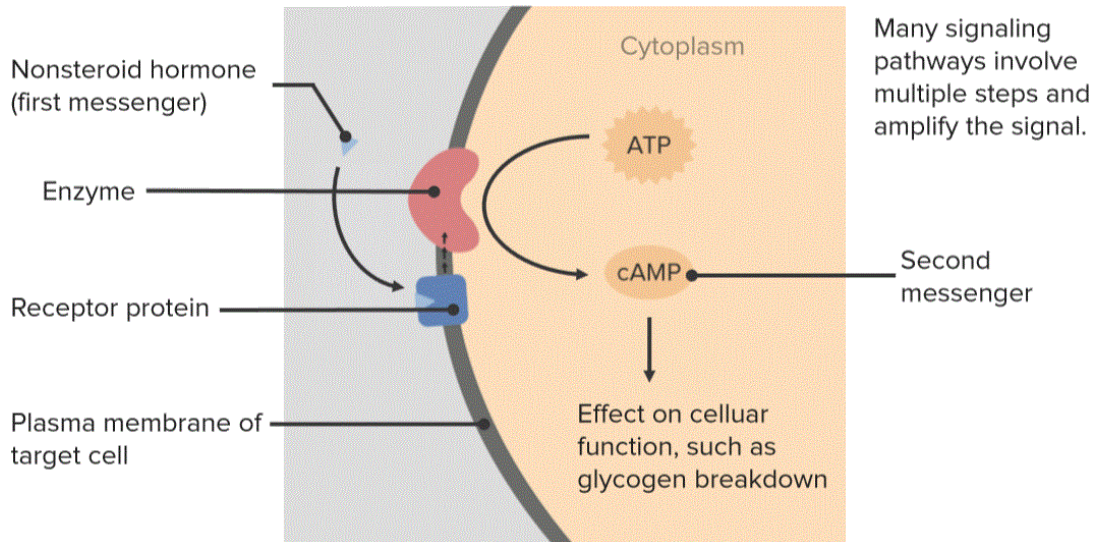
Receptor tyrosine kinases transmit signals across the membrane

**Ligand** binding to its receptor protein is the first step in all biochemical-signaling pathways. For example, **insulin** is a protein growth factor that binds to a specific receptor whose C-terminal domain has **tyrosine kinase** activity. Receptor tyrosine kinases (RTKs) such as this usually have a single transmembrane segment remain as monomers in the unliganded state.

Receptor tyrosine kinases are activated by **autophosphorylation**, which is the cross-phosphorylation that occurs between cytoplasmic protein tyrosine kinase domains

brought into close proximity of each other as RTK protein dimerizes. How does autophosphorylation activate the protein tyrosine kinase activity of the insulin receptor?

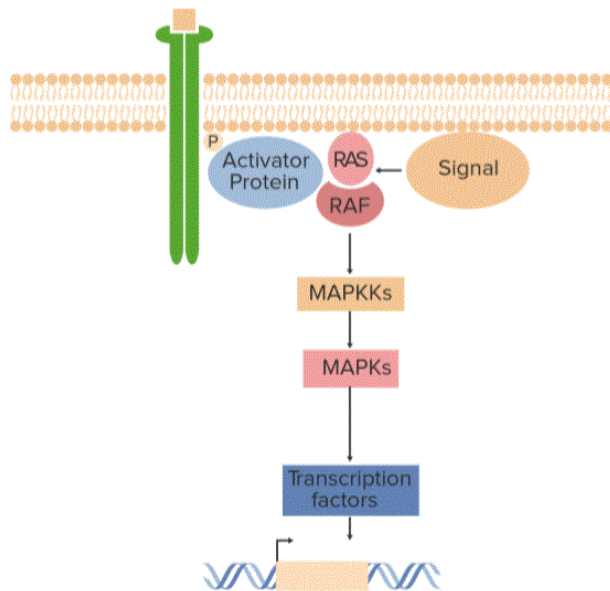
The human protein is a single 1382-residue precursor peptide that is proteolytically cleaved to give rise to a mature insulin receptor with  $\alpha$  and  $\beta$  subunits that are linked together by disulfide bridges. Insulin binds to the receptor's  $\alpha$  domains on the extracellular face of the membrane, whereas the protein tyrosine kinase  $\beta$  domains are on the intracellular side.



"Second Messenger Systems. Overview" Image created by Lecturio

## Kinase cascades relay signals to the nucleus

The advantage of a kinase cascade is that a small signal can be amplified much fold inside the cell. In the previous example, we discussed how the insulin receptor is directly activated by autophosphorylation, but many target proteins are activated through a highly diverse and sophisticated set of interconnected signaling pathways that involve cascades of associating proteins. In the case of the G protein **Ras**, which is anchored on the inner surface of the plasma membrane, is activated by growth factor binding its cognate receptor tyrosine kinase before it activates a **kinase cascade** to signal the transcriptional apparatus inside the nucleus.



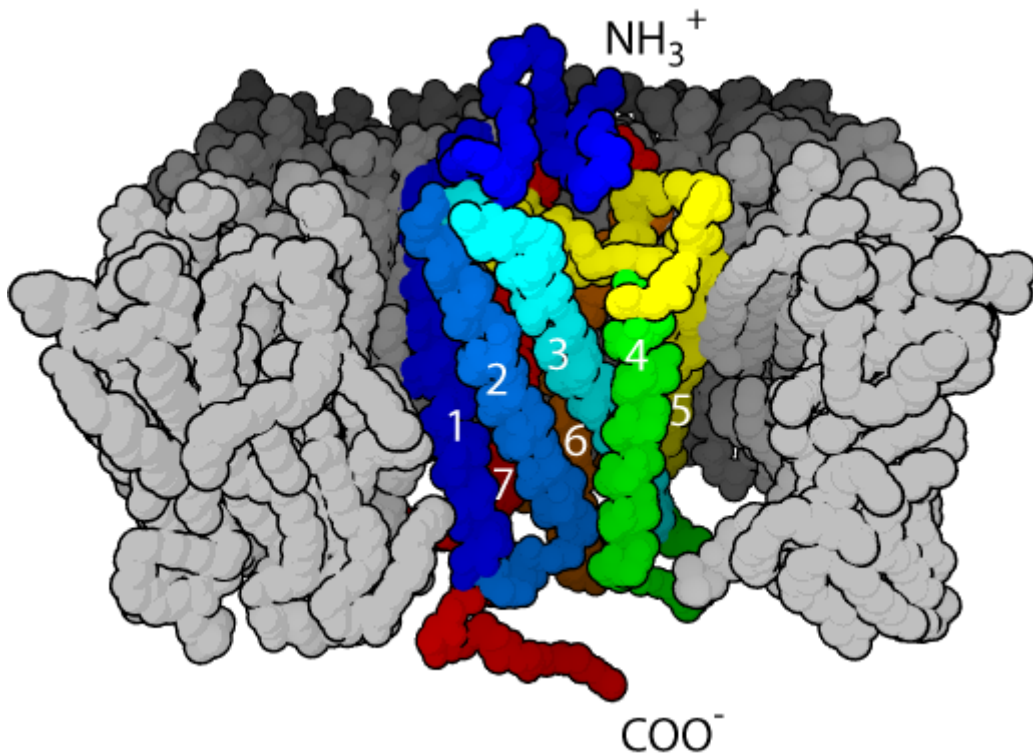
"Receptor Tyrosine Kinase Pathways" Image created by Lecturio

The binding of growth factor to its receptor tyrosine kinase leads to autophosphorylation of the receptor tyrosine kinase, which then interacts with an SH2-containing protein, whose function is to activate Ras to release bound GDP and replace it with GTP. The kinase cascade downstream of Ras completes the signaling pathway, first by the phosphorylation of either **MEK** or **MAPS kinase**, which migrate from the cytosol to the nucleus to phosphorylate a variety of protein **transcription factors**.

Transcription factors stimulate various genes to produce the effects commissioned by the extracellular presence of the growth factor that initiated the signaling cascade. When insulin activates the Ras signaling pathway, the result is an increase in protein synthesis that supports cell growth and differentiation, a response consistent with insulin's function as a signal of fuel abundance.

In addition, phosphorylation of more than one target protein can lead to the simultaneous activation of several intracellular processes, such as the **MAP Kinase** cascade. Thus, insulin signaling mediates changes in vesicle trafficking, enzyme activation, and gene expression.

## G-Protein Coupled Receptors

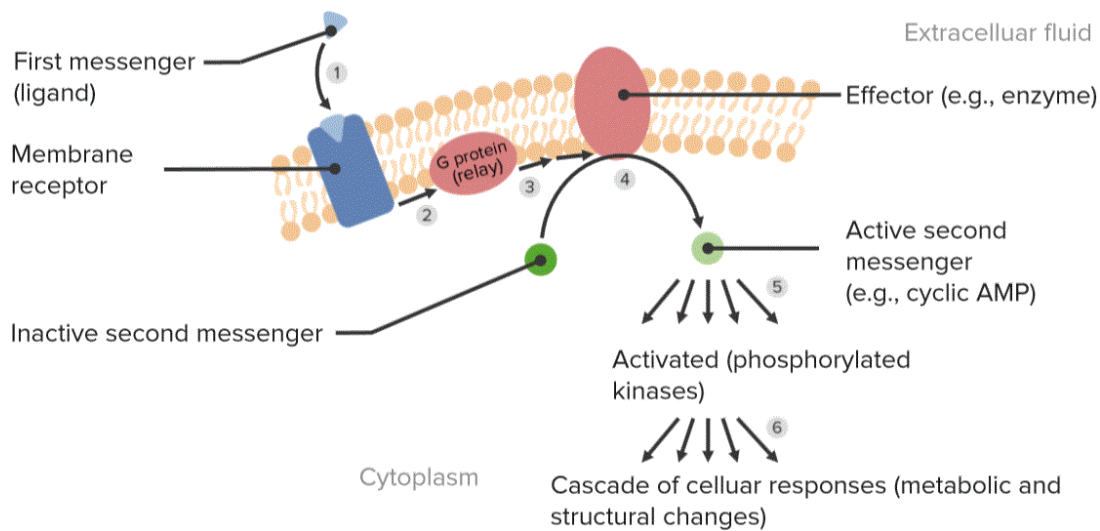


G-Protein Coupled Receptor 7TM4 (GPCR)

Another major class of signal transduction pathway involves **Heterotrimeric G proteins**, which are members of the superfamily of GTPases known as the G proteins. These proteins have the ability to bind and hydrolyze guanine nucleotides GTP and GDP. The monomeric G proteins are essential in a few key processes like signal transduction, translation, protein targeting, and the growth of actin microfilaments.

The signal transduction pathways that many G proteins participate in consist of three components depicted in. **G protein-coupled receptors (GPCRs)** are transmembrane proteins that bind hormone ligands on the extracellular side, and induce a conformation inside the cell on the cytoplasmic face of the membrane. This binding of the ligand activates the G protein to in turn activate or inhibit a transmembrane enzyme called **Adenylate cyclase (AC)**.

Activated Adenylate cyclase synthesizes a compound called **adenosine-3 ,5 -cyclic monophosphate (3', 5' -cyclic AMP or cAMP)** from ATP. cAMP, activates numerous cellular processes by binding and activating a variety of proteins. cAMP is also known as a **second messenger** because it intracellularly transmits a signal originated by an extracellular ligand.



"G Protein-coupled receptor" Image created by Lecturio

## G Protein-coupled receptors contain seven transmembrane helices

**G protein-coupled receptors (GPCRs)**, such as the  $\beta$ 2-adrenergic receptor depicted in, exists as integral membrane proteins with seven transmembrane  $\alpha$ -helices. The N- and C-terminal amino acid residues vary in sequence and participate in ligand binding on the extracellular face of the cell and confer a Heterotrimeric G protein function on the cytoplasmic side. Many of these proteins are posttranslationally modified by N-glycosylation and/or by the palmitoylation of a cysteine residue, making them lipid-linked glycoproteins.

There are few other structural similarities between GPCR binding sites other than the general location. They function much like hemoglobin, which is an allosteric protein that alternates between two discrete conformations.

## Adenylate cyclase synthesizes cAMP to activate protein kinase A

**Protein Kinase A (PKA)** is activated when it binds four molecules of cAMP, which is a polar molecule capable of acting as a freely diffusing second messenger. Protein Kinase A is an enzyme that specifically phosphorylates serine and threonine residues of many cellular proteins containing the consensus kinase-recognition sequence Arg-Arg-X-Ser/Thr-Y, where Ser/Thr is the phosphorylation site, X is any small residue, and Y is a large hydrophobic residue.

In the absence of cAMP, PKA is an inactive heterotetramer consisting of two regulatory and two catalytic subunits, R2C2. cAMP binds to the regulatory subunits to cause the dissociation of active catalytic monomers. The intracellular concentration of cAMP, therefore, determines the fraction of PKA in its active form and thus the rate at which it phosphorylates its substrates.

The targets of PKA include enzymes involved in glycogen metabolism. For example, when epinephrine binds to the  $\beta$ -adrenergic receptor of a muscle cell, the sequential activation of a heterotrimeric G protein, adenylate cyclase, and PKA leads to the activation of

glycogen phosphorylase, thereby making glucose- 6-phosphate available for glycolysis in a “fight-or-flight” response. In the end, signaling activity is limited by the destruction of the second messenger, cAMP.

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