Stimulation of G-Protein-linked Receptors Activates G-Protein Subunits

When extracellular signal molecule binds to a seven-pass transmembrane receptor, the receptor protein undergoes a conformational change that enables it to activate a G protein located on the underside of the plasma membrane. There are several varieties of G proteins. Each is specific for a particular set of receptors and particular set of downstream target proteins.

The G-protein α subunit switches itself off by hydrolyzing its bound GTP

When an activated α subunit encounters and binds its target, it turns on its protein partner (or in some cases inactivates it, not shown) for as long as the two remain in touch. Within seconds, the GTP on the α subunit is hydrolyzed to GDP by the α subunit’s intrinsic GTPase activity. This loss of GTP inactivates the α subunit, which dissociates from its target protein and reassociates with a βγ complex to re-form an inactive G protein. The G protein is now ready to couple to another receptor. Both the activated α subunit and the free βγ complex can regulate target proteins.
Some G Proteins Regulate Ion Channels

The target proteins for G-protein subunits are either ion channels or membrane bound enzymes. Different targets are affected by different types of G proteins, and these various G-proteins are themselves activated by different classes of cell surface receptor. In this way, binding of an extracellular signal molecule to a G-protein-linked receptors leads to effects on a particular subset of the possible target proteins, eliciting a response that is appropriate for that signal and that type of cell.

G proteins couple receptor activation to the opening of K+ channels in the plasma membrane of heart muscle cells.

(A) Binding of the neurotransmitter acetylcholine to its G-protein–linked receptor on heart muscle cells results in the dissociation of the G protein into an activated complex and an activated α subunit. (B) The activated αβγ complex binds to and opens a K+ channel in the heart cell plasma membrane. (C) Inactivation of the α subunit by hydrolysis of bound GTP causes it to reassociate with the βγ complex to form an inactive G protein, allowing the K+ channel to close.

Some G-proteins Activate Membrane-bound Enzymes

The most frequent target enzymes for G proteins are adenyl cyclase, the enzyme responsible for production of the small intracellular signal molecule cyclic AMP, and phospholipase C, the enzyme responsible for production of the small intracellular signaling molecules inositol(1,4,5)trisphosphate and diacylglycerol.
The Cyclic AMP Pathway Can Activate Enzymes and Turn On Genes

Many extracellular signals acting via G-protein-linked receptors affect the activity of adenylyl cyclase and thus alter the concentration of the messenger molecule cAMP inside the cell. The activated G-protein alpha subunit switches on the adenylyl cyclase, causing a dramatic and sudden increase in the synthesis of cAMP from ATP; this G protein is called Gs. To help eliminate the signal, a second enzyme called cAMP phosphodiesterase, rapidly converts cAMP to ordinary AMP.

<table>
<thead>
<tr>
<th>Extracellular Signal Molecule*</th>
<th>Target Tissue</th>
<th>Major Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>heart</td>
<td>increase in heart rate and force of contraction</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>muscle</td>
<td>glycogen breakdown</td>
</tr>
<tr>
<td>Adrenaline, ACTH, glucagon</td>
<td>fat</td>
<td>fat breakdown</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenal gland</td>
<td>cortisol secretion</td>
</tr>
</tbody>
</table>

*Although all of the signal molecules listed here are hormones, some responses to local mediators and to neurotransmitters are also mediated by cyclic AMP.
A rise in intracellular cyclic AMP can activate gene transcription

Binding of a signal molecule to its G-protein–linked receptor can lead to the activation of adenylyl cyclase and a rise in the concentration of intracellular cyclic AMP. In the cytosol, cyclic AMP activates PKA, which then moves into the nucleus and phosphorylates specific gene regulatory proteins. Once phosphorylated, these proteins stimulate the transcription of a whole set of target genes. This type of signaling pathway controls many processes in cells, ranging from hormone synthesis in endocrine cells to the production of proteins involved in long-term memory in the brain. Activated PKA can also phosphorylate and thereby regulate other proteins and enzymes in the cytosol.

cAMP exerts these various effects mainly activating the enzyme cyclic-AMP-dependent protein kinase (PKA). This enzyme is normally held inactive in a complex with another protein. The binding of cAMP forces a conformational change that unleashes the active kinase. Activated PKA then catalyzes the phosphorylation of particular serines and threonines on certain intracellular proteins, thus altering their activity.

The Inositol Phospholipids Pathway Triggers a Rise in Intracellular Ca²⁺

Some extracellular signal molecules exert their effects via a type of G-protein that activates the membrane-bound enzyme phospholipase C instead of adenylyl cyclase. Some cell responses mediated by phospholipase C activation can be seen in below.
Mechanism of signal transduction mediated by phospholipase C

Ca\(^{2+}\) Triggers Many Biological Processes

Ca\(^{2+}\) has such an important and widespread role as an intracellular messenger. The effects of Ca\(^{2+}\) in the cytosol are largely indirect; they are mediated through the interaction of Ca\(^{2+}\) with various transducer proteins known as Ca\(^{2+}\)-binding proteins. The most widespread and common of these is the Ca\(^{2+}\)-responsive protein called calmodulin.
**ENZYME-LINKED RECEPTORS**

Enzyme-linked receptors are membrane bound proteins that display their ligand binding domains on the outer surface of the plasma membrane. Instead of associating with a G protein, however, the cytoplasmic domain of the receptor acts as an enzyme or forms a complex with another protein that acts as an enzyme. Enzyme-linked receptors play major role in cell differentiation, growth, and cell survival. They are also mediate direct, rapid reconfigurations of the cytoskeleton, controlling the way a cell moves and changes its shape.

**Activated Receptor Tyrosine Kinase Assemble a Complex of Intracellular Signaling Proteins**

To do its job as a signal transducer, an enzyme-linked receptor has to switch on the enzyme activity of its intracellular domain when external signal molecule binds its extracellular domain. Enzyme-linked receptors usually have one transmembrane domain. Basic mechanism of enzyme linked receptor is outlined in figure below.

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**Figure 19-30** *Essential Cell Biology, 2nd, © 2004 Garland Science*

**Example 1: Receptor tyrosine kinases activate the GTP-binding protein RAS.**

**Figure 19-31** *Essential Cell Biology, 2nd, © 2004 Garland Science*
Not all enzyme-linked receptors trigger complex signaling cascades that require the cooperation of sequence of protein kinases to carry a message to the nucleus.