11.3.3

G Protein-Coupled Receptor (GPCR)

The GPCR complex is composed of two units: a receptor protein that binds to the chemical signal (the ligand) and the G protein complex associated with the inner side of the membrane (i.e., a peripheral protein complex). The GPCR has a ligand binding site on the external surface and a G protein binding site on the internal surface. The G protein complex is composed of three subunits: the alpha, beta, and gamma subunits. The alpha subunit has a site that can bind **Guanosine Triphosphate (GTP)** or **Guanosine Diphosphate (GDP)**, hence the name **G protein**. In its inactive form, the G-alpha subunit is bound to GDP, and the three subunits (alpha, beta, and gamma) are bound together. When a ligand binds to the receptor on the surface of the cell, the G protein binding site changes shape, allowing the G protein to bind to the intracellular region of the receptor. This binding causes the G protein to then change shape, and the GDP exits the binding site on the alpha subunit and is replaced by a GTP from the cytoplasm. The binding of GTP causes the alpha subunit to separate from the other two subunits (beta/gamma dimer). Once separated, the alpha subunit (and sometimes the beta/gamma dimer) can then bind to and activate other proteins inside the cell. The mechanism of action is typically mediated by one of two enzymes: **adenylate cyclase** or **phospholipase C**. Cellular responses include activation of metabolic enzymes, opening or closing ion channels, turning on transporters, initiating gene transcription, regulating motility, regulating contractility, stimulating secretion, and even controlling memory. After a short period of time, the G-alpha subunit hydrolyzes the GTP into a GDP and phosphate, allowing it to reunite with the beta/gamma dimer, turning off the signal. To date, approximately 800 genes for G protein-coupled receptors have been identified.

Adenylate cyclase

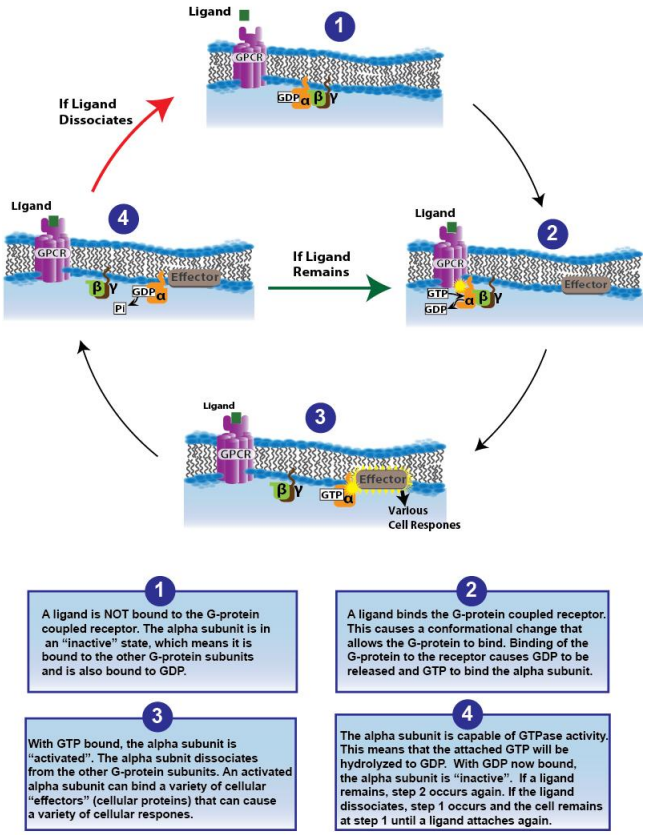
Activation of Adenylate cyclase results in the synthesis of a second messenger molecule called cyclic adenosine monophosphate (cAMP). The primary action of cAMP is to activate the enzyme protein kinase A (PKA). PKA phosphorylates serine and threonine residues of proteins which can lead to activation.

Phospholipase C

Activation of the phospholipase C results in the cleavage of a membrane phospholipid called Phosphatidylinositol bisphosphate (PIP2). This enzymatic cleavage yields two molecules: diacylglycerol (**DAG**) and inositol triphosphate (**IP3**). DAG remains in the membrane and activates another enzyme called protein kinase C (PKC) while IP3 diffuses into the cytoplasm and acts as a ligand for calcium channels on the endoplasmic reticulum.

Calcium

The ion calcium is a very common intracellular second messenger. Intracellular Ca^{++} levels are kept very low because of various secondary and primary active pumps. This is because Ca^{++} has potent effects on a variety of different protein activities. Muscle cell proteins are particularly sensitive to Ca^{++}.



Ligand Activation and G-Protein Effect. Image drawn by JS Fall 2014