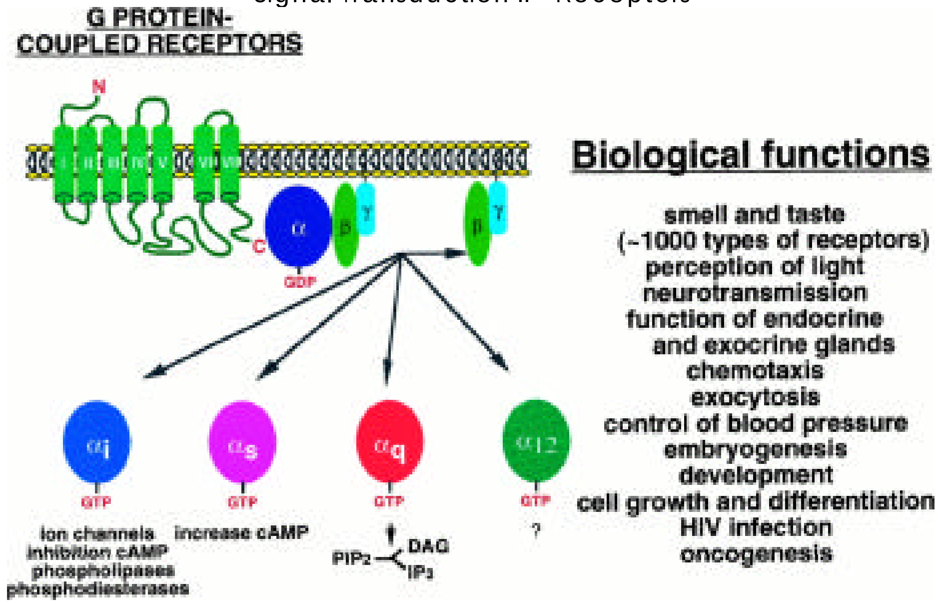
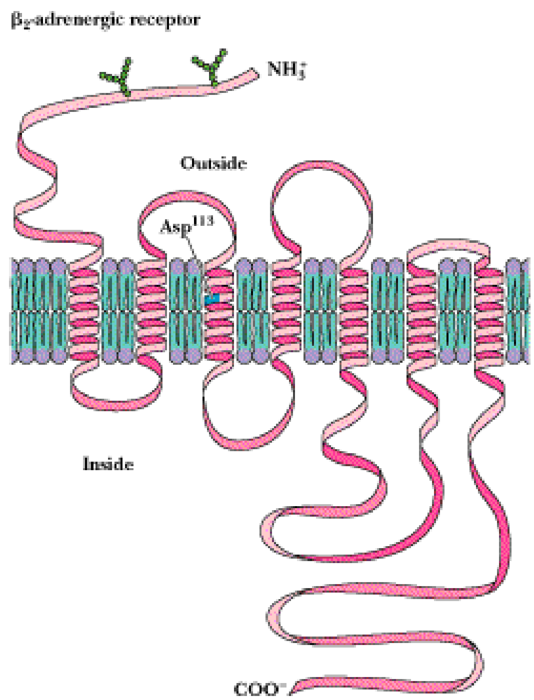
Signal Transduction II - Receptors



Three different classes of GPCR:



1. GPCRs that modulate adenylate cyclase activity. One class of adenylate cyclase modulating receptors activate the enzyme leading to the production of cAMP as the second messenger. Receptors of this class include the β-adrenergic, glucagon and odorant molecule receptors. Increases in the production of cAMP leads to an increase in the activity of PKA in the case of β-adrenergic and glucagon receptors. In the case of odorant molecule receptors the increase in cAMP leads to the activation of ion channels. In contrast to increased adenylate cyclase activity, the α-type adrenergic receptors are coupled to inhibitory G-proteins that repress adenylate cyclase activity upon receptor activation.

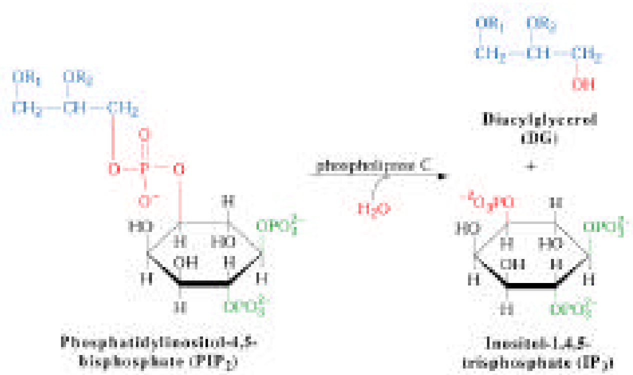


Figure 21-18. Phosphatidylinositol-4,5-bisphosphate (PIP_2) and its hydrolysis products.

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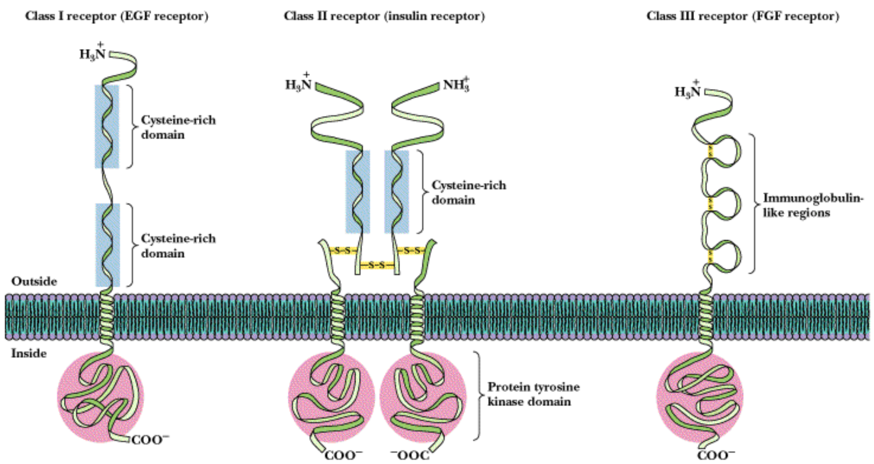
2.

GPCRs that activate PLC-β leading to hydrolysis of polyphosphoinositides (e.g, phosphatidylinositol-4,5 bisphosphate; PIP_2) generating the second messengers, diacylglycerol (DAG) and inositoltrisphosphate (IP3).

3. A novel class of GPCRs are the photoreceptors. This class is coupled to a G-protein termed transducin that activates a phosphodiesterase which leads to a decrease in the level of cGMP.
   - The drop in cGMP then results in the closing of a Na+/Ca2+ channel leading to hyperpolarization of the cell.
   - Vitamin A is key in detecting the light and initiating these changes.

Receptors with integral enzyme activity
Most receptors of this class are - single pass receptors
- guanylate cyclase (GTP -> cGMP) responsible for vasiodilation
- protein tyrosine kinase (tyrosine + ATP -> tyrosine-P + ADP)
- interlukins/immunological receptors



Each receptor has three basic domains:
1 - Extracellular domain
   - this is the ligand binding domain
   - often glycosylated
   - often heavy in cystein rich domains and immunoglobin like domains
2 - Transmembrane domain
   - usually a single alpha helix (rich in hydrophobic amino acids)
3 - Intracellular domain -
   - the intracellular portion becomes activated by tertiary structural changes
   - many times autophosphorylates intracellular domain (tyrosine-P)
   - once activated, many different proteins bind to intracellular domain

Receptor Activation – Many of these types of receptors initiate cellular growth (proliferation) or differentiation (the act of converting from one precursor cell type to a mature form).
- activated by growth factors
- The receptor itself has a tyrosine kinase activity
- other than insulin binding of hormone/growth factor ligand leads to dimerization
- leads to many changes in second messenger biological activities

Many intracellular receptor binding sites for other proteins based on Rous Sarcoma Virus
   - Src is a transforming causing protein with 3 distinct domains Src Homology
SH1 - contains tyrosine kinase of Src specific for this protein
SH2 - binds phosphotyrosine
SH3 - believed to bind to cytoskeleton or portion of plasma membrane that is high in proline amino acid residues

Therefore once the receptor is activated and phosphorylated there will be a slug of proteins recruited to the cell membrane.
   - This may result in the receptor phosphorylation of the protein (PLCy)
   - Another action is that a number of critical components are brought together where they can form a functional complex and initiate a series of events (Ras MAPK)