CONCEPT: G PROTEIN COUPLED RECEPTORS

Structure and Signaling

● G Protein Coupled Receptors are the largest family of cell surface receptors (700+) and signal through _____ proteins

□ GPCRs are composed of a single polypeptide chain that snakes back and forth through the bilayer seven times

- Three extracellular loops that bind ligands

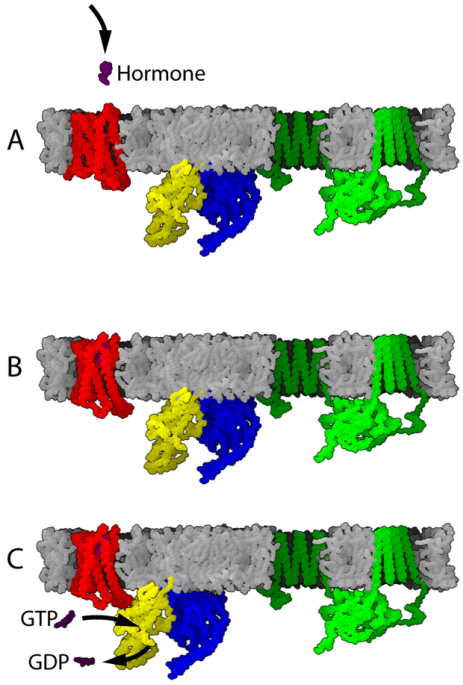
- Three intracellular loops that bind signaling proteins

□ The cytosolic side of the GPCR is bound to a *G protein* which acts as a molecular _____

- **G protein** is a trimeric protein (three subunits) activated upon GTP binding and inactivated with GDP

- When activated a G protein can couple ligand/receptor binding to other enzymes or ion channels

EXAMPLE: G protein activation through GPCRs



● Regulation of GPCR signaling involves regulating the G protein

□ Signaling can be effected by proteins that effect GTP _____

□ **Desnsitation** is a process that blocks active receptors from activating G proteins

- *G protein coupled receptor kinase 2 (GRK2)* bind to GPCRs and compete for binding

□ The GPCR can be regulated via receptor inactivation, sequesteriation, or down-regulation

Common GPCR Signaling Pathways

● Cyclic AMP (cAMP) concentration is regulated by G protein _____

□ cAMP is a signaling molecule present in every cell that has been studied

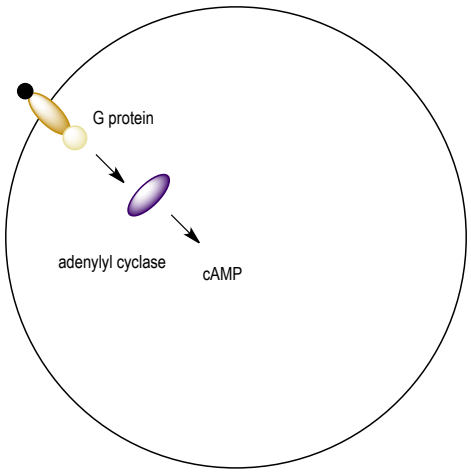
□ cAMP is kept at a low concentration in the cell

- Extracellular signals can cause a huge increase in intracellular concentration

□ cAMP is made by the enzyme **adenylyl cyclase** and degraded by phosphodiesterase

- G proteins can stimulate or inhibit adenylyl cyclase which therefore controls cAMP levels

EXAMPLE: cAMP signaling pathway



● Calcium is an important intracellular signaling molecule

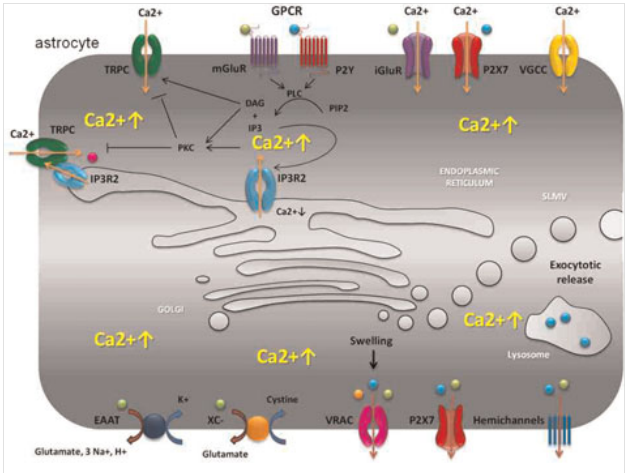
□ G proteins can trigger _____ in cytosolic calcium concentration

□ Calcium effects many other enzymes and proteins

- *CaM kinases* are protein kinases that phosphorylate proteins that inhibit and activate gene transcription

□ **Calmodulin** is a protein which mediates animal cell responses to calcium

EXAMPLE: Various methods of calcium signaling



● Inositol phospholipid signaling pathways are _____ by GPCRs

□ G protein G_q activated adenylyl cyclase – which in this pathway cleaves a lipid called PIP2

□ This cleavage creates two molecules: IP3 and DAG which are both second messengers

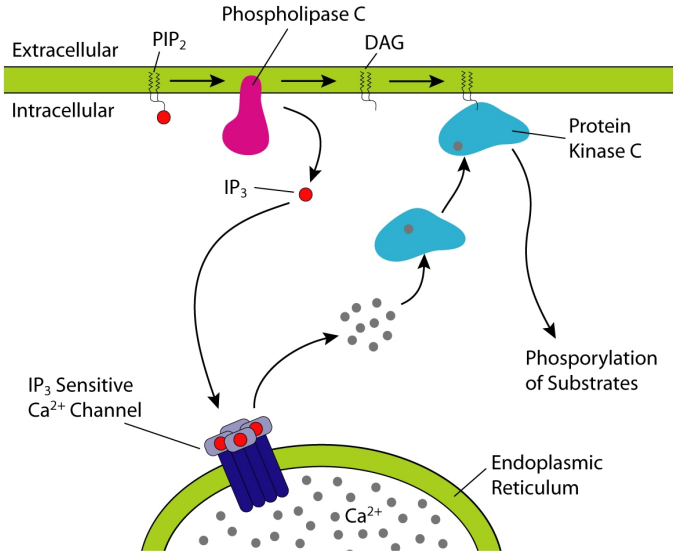
- IP3: Binds to ER and opens calcium channels

- DAG: Acts in a variety of signaling pathways

□ **Calmodulin** is a protein which mediates animal cell responses to calcium

- Binds calcium, undergoes conformational change, binds to other proteins and influences their functions

EXAMPLE: Inositol phospholipid signaling pathway



PRACTICE:

1. Which of the following is true regarding G-protein coupled receptors?
    a. It contains three transmembrane sections
    b. The G protein binds the intracellular side of the G protein coupled receptors
    c. There are four intracellular and extracellular loops
    d. G proteins respond only to calcium

2. True or False: cAMP levels are kept at high levels in the cell.
    a. True
    b. False

3. Calmodulin is an important signaling molecule because it does what?
    a. Cleaves PIP_2 into IP3 and DAG
    b. Creates cAMP
    c. Mediates the animal cell response to calcium
    d. Blocks GPCR activation