Cell Signalling

Cell Signalling Pathway
General Process:

1. Ligand-receptor interaction
    - Binding of ligand which is structurally complementary in conformation to the ligand binding site in the extracellular domain of the **specific** receptor protein
2. Signal Transduction
    - Causes a conformational change in the intracellular domain of the protein receptor
    - Signal transduction is initiated when signal is converted to a form that can bring about a specific response
3. Phosphorylation cascade
    - Signal cascade mediated by kinases and phosphatases where activated kinases activate a relay protein in the next step by phosphorylating it
    - Phosphatase will inactivate kinase in preceding step to prevent constitutive transduction of signal
4. Signal amplification
    - Signal amplification occurs via a signaling cascade
    - **At each catalytic step of cascade, number of activated products is much greater than at preceding step
    - Signal amplification occurs during signal transduction
5. Cellular responses
    - Transduced signal triggers a specific cellular response
        - e.g. catalysis by an enzyme
        - e.g. rearrangement of cytoskeleton
        - e.g. activation of specific genes in nucleus
    - Cell signalling ensures activities occur in the right cells at the right time in proper coordination with other cells of the organism
        - Different cells can have different responses to the same signal
        - Same cells can have the same response to different signals

Types of Receptors:
G Protein-Coupled Receptors (GPCR) [e.g. glucagon]

- Comprises:
    1. GPCR
    2. G protein
    3. Another enzyme (Adenylyl Cyclase*/Phospholipase C)
        - All bound to the plasma membrane
            - Proximity and restriction of movement increases the chances of interaction
- Characteristics
    - Transmembrane protein that snakes through membrane 7 times

    - **Extracellular ligand-binding site and an intracellular G protein binding site which binds to inactive G protein
    - Binds to hydrophilic ligands
- G proteins
    - GTP-binding proteins
    - Found on cytoplasmic side of the membrane
    - Activated when bound to GTP
    - Inactivated when bound to GDP
    - Intrinsic GTPase activity (i.e. capable of hydrolysing GTP to GDP)
        - Ensures that GTP bound to G protein is quickly hydrolysed, returning the G protein to its inactive state, hence terminating the cellular response
        - If continued activation, cell will be unable to respond to new signals

Cell Signalling Pathway:

- Inactive Form
    - In absence of extracellular signal molecule specific for the receptor, all proteins are in inactive form
- Signal Transduction:
    - When glucagon binds to ligand binding site in the extracellular domain of the glucagon receptor, the receptor causes a conformational change in the intracellular domain of GPCR
    - This allows inactive G protein to bind to intracellular domain of receptor, causing GDP on G protein to be displaced by GTP, resulting in a conformational change in the G protein and activating it
    - Activated G protein dissociates from receptor and moves along the membrane, binding to adenylyl cyclase, altering its conformation and hence activating it
    - Adenylyl cyclase catalyses the breakdown of many ATP to many cAMP
- Secondary Messengers
    - cAMP acts as a secondary messenger
    - cAMPs are small, non-protein water-soluble molecules that are able to diffuse quickly throughout the cytosol
    - cAMP binds to and activates protein kinase A
    - Protein kinase A starts a phosphorylation cascade eventually leading to cellular responses (e.g. activation of glycogen phosphorylase involved in breaking down glycogen to glucose in the liver cells)
- Return to Inactive Form
    - Due to intrinsic GTPase activity of the G protein, it catalyses the hydrolysis of its GTP to GDP, returning the G protein to an inactive state
    - G protein dissociates from the enzyme and becomes available for reuse → Allows signalling pathway to respond to new signals

Receptor Tyrosine Kinase (RTK) [e.g. insulin]

- Characteristics:
    - Also functions as an enzyme

- Intrinsic kinase activity
- Exists as 2 individual subunits or as a linked dimer

Cell Signalling Pathway:

- Signal Transduction
  - Binding of insulin, which is complementary in shape to the extracellular ligand binding site of the insulin receptor, to the receptor
  - Causes the dimerisation of the 2 receptor subunits (if 2 individual subunits)
  - Resulting in conformational change in the intracellular domain of the receptor which activates intrinsic tyrosine kinase activity of the intracellular domain
  - Resulting in the autophosphorylation of the tyrosine residues by tyrosine kinase where the kinases on 1 subunit cross-phosphorylates the tyrosine residues on the other subunit
  - Specific relay proteins can bind to phosphorylated tyrosine residues and are in the process activated (via binding/phosphorylation)

Ligand-gated ion channels

- Specific ligand binds to ligand binding site of specific ligand-gated ion channel
- Causes the opening of the ligand-gated ion channel

Benefits of cell signalling pathway:

1. Amplify the signal to produce a stronger response
   - A small number of signal molecules can produce a large cellular response as the number of activated molecules increases with each catalytic step in the pathway
2. A single signal molecule can elicit many cellular responses through many different pathways
3. Ability to regulate and control as pathway provides many potential checkpoints for regulation
4. Co-ordinated activation of many cells simultaneously
5. Specific ligand elicits specific reaction via specific pathway in each cell type
6. Ability of a molecule reaching a cell membrane to activate genes in the nucleus

Regulation of cellular response

1. Reception
   - Inhibit conformational change of receptor when signal molecule binds
     - G protein unable to bind, remains inactive as GDP not displaced by GTP
     - No activation of adenylyl cyclase
     - No conversion of ATP to cAMP
     - No response in target cell
   - Degradation of signal molecules by enzymes in extracellular space

    - Endocytosis of ligand-receptor complex
        - Ligands hydrolysed intracellularly
2. Signal transduction pathway
    - Inhibit GTPase activity
        - G protein unable to hydrolyse GTP to GDP, GTP remains bound, G protein continuously activated
        - Continuous activation of adenylyl cyclase
        - Conversion of more ATP to cAMP
        - Continuous response in target cell
    - Bind to adenylyl cyclase to continuously activate it even in absence of signal molecule
    - Increase in activity of phosphatase that dephosphorylate proteins to inactivate the relay molecules

Secondary Messengers = small, non-protein water-soluble molecules that are able to diffuse quickly throughout the cytosol
Protein Kinase = Enzymes that take a phosphate group from one molecule and transfers it to another
Phosphorylase = Enzymes that take a free phosphate group and adds it to a molecule