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Cell signalling

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Tags	

how does Cell surface membrane facilitate cell signalling

- Describe the structure and properties of CSM
    - CSM consists of hydrophobic fatty acid tails which forms hydrophobic interactions and consists of hydrophilic phosphate heads
- Allow embedment of glucagon and insulin receptors so that insulin and glucagon are able to interact with their receptor by binding to the extra cellular ligand binding site since insulin and glucagon are large and hydrophilic, unable to pass through the hydrophobic core of the phospholipid bilayer
- CSM is fluid and allows tyrosine receptor kinase to dimerise after binding of insulin to the ligand binding site, hence cross-phosphorylation of tyrosine amino acid residues at the intracellular tails by tyrosine kinases of other receptor monomer
    - Also enables activated G protein bound to GTP to move to bind and activate adenyl cyclase so that ATP can be converted to cAMP to trigger a phosphorylation cascade in order to eventually reach effector molecules in order to elicit a cellular response

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Advantages of cell signalling pathway/ why are ligands never found within the cells/ why are receptors found on cell surface membrane and never within cells/ why should receptors span the cell membrane

- The cell surface receptor allows signal from ligand to be relayed from outside the cell into the cell, this advantageous as ligand is hydrophilic and large, has a

polar region which makes it unable to pass through the small gaps in the phospholipid bilayer of the membrane hydrophobic core of the phospholipid bilayer as it will be repelled

  - **Hence receptor outside to allow binding of ligand at the extracellular binding site**
  - **Signal can be transduced to cytoplasmic side of cell through change in intracellular domain**

- The receptor of the cell signalling pathway is specific to the ligand and this specific ligand receptor interaction will elicit specific cellular responses
- Small number of signal molecules binding to the receptors can produce a large cellular response inside the cell as the number of activated molecules increases with each catalytic step in the pathway facilitating signal amplification
- One signal molecule can trigger many signal transduction pathways **in a cell** and elicit **many different cellular responses by activating intracellular domain of receptor**
- signal molecule can **activate genes in nucleus** upon binding to cell surface receptor **without the need to move into nucleus**

How each protein kinase in the cascade is activated?/ how does a signalling cascade amplifies signal?/how release of cAMP leads to a cellular response?

- cAMP binds and activates protein kinase A
- Activation of PKA will initiate a sequential activation of kinases resulting in a phosphorylation cascade
- The active protein kinase in the previous step transfers a phosphate group from ATP to the inactive protein kinase, phosphorylating it and hence activating it, activating multiple kinases or the next step
- A signalling amplification occurs where A small number of ligand can thus rapidly produce a much greater number of final products and number of

activated products is always greater than in previous steps leading to a greater cellular response

- Eventually activates a large number of glycogen phosphorylase to break down glycogenesis to generate a high yield of glucose and decreasing rate of glycolysis

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How does insulin trigger a response inside target cell?

- Insulin has a specific 3D conformation and binds specifically to the insulin receptor, a tyrosine kinase receptor, at the ligand-binding site, which is complementary to the shape and charge of insulin,
- The binding induces a conformational change in the receptor that brings the tyrosine kinase domains closer together in a process called dimerisation
- Contact between the two adjacent RTK tails in the intracellular domain activates their tyrosine kinase function, triggering auto phosphorylation of the tyrosine residues on each tyrosine kinase domain
- This leads to a signal transduction where Activated RTK triggers assembly of relay/ adaptor proteins which will further recruit and activate other downstream relay molecules such **(relay proteins are molecules that attach to the RTK directly to cause downstream signalling)**
- Each tyrosine kinase receptor activates many phospholipase C, where each binds to phosphorylated tyrosine residues (signal amplification)
- Each phospholipase C produces many IP3 (signal amplification)
- Each IP3 open a ip3-gated calcium channel releasing many ca2+ (signal amplification)

Effects of insulin on different target cells

- **increase permeability of cells to glucose** as **more glucose transporters (GLUT4)** become **embedded in the plasma membrane**, triggering translocation of vesicles to plasma membrane and Target cells, increase uptake of glucose by the cells, decreasing blood glucose concentration

- **Increases rate of glycolysis and Increase rate** of glucose utilisation and ATP generation in the cells by **cellular respiration to break down glucose**
- Glucose uptake Stimulate **conversion of excess glucose into glycogen (glycogenesis) for storage in liver and skeletal muscle cells via a series of condensation reactions catalysed by glycogen synthase which is an enzyme activate as a Result of insulin signalling**
- Stimulate **conversion of excess glucose to fatty acids in adipose cells by various enzymes activated as a result of insulin signalling**
- **Inhibit** the **breakdown of glycogen to glucose (glycogenolysis) in liver and skeletal muscle cells**;
- **Inhibit conversion of amino acids or fats to glucose (gluconeogenesis)**;

Role of secondary messengers and why are they usually small and non-protein in nature

- Second messengers are small, non-protein, water Soo molecules/ions that relay signal in signal transduction pathway
- Bind, induce change in confrontation and activate relay protein

Compare GPCR and RTK

	GPCR	RTK
Type of structure	A protein monomer (one protein molecule)	A dimer with two protein subunits
Number of ligand binding site	One	Two
Ligand-specificity	Ligand binding site complementary to the shape and charge of insulin	Ligand binding site complementary to the shape and charge of glucagon
Intracellular binding sites	Intracellular binding site's complementary to the conformation and charge of G protein	Intracellular binding site complementary to the conformation and charge of phospholipase C

Structure of GPCR and how it is related to its function

- GPCR has 7 alpha-helices that are transmembrane connected by 3 intracellular and 3 extracellular peptide loops with the amino acids of hydrophobic R groups forming hydrophobic interactions with the fatty acid tails of the phospholipid in cell surface membrane allowing GPCR to be embedded in cell membrane
- Extra cellular loops of the GPCR has a ligand binding site with a specific conformation that its complementary to the shape and charge of the ligand, allowing binding to specific signal molecule or ligand
- Intracellular region has a G protein binding site and is weakly associated with a G protein enabling Transmission of an external signal into the cell
- Binding of ligand at ligand binding site, causes conformational change in of the intracellular domain of GPCR activates G protein associated for downstream signalling by triggering an exchange of its bound GDP for a GTP

How does glucagon trigger a response in a cell

- Binding of glucagon induces a confrontational change in the intracellular domain of the GPCR, activating it
- Activated GPCR initiates signal transduction, enabling binding to inactive G protein causing it to release its bound GDP and bind to GTP, activating the G protein
- The activated G protein will dissociate from the GPCR and translocate along the cytoplasmic side of the cell membrane, binding to inactive adenyl Cyclase and phosphorylating it in order to activate adenyl Cyclase
- Activation of one adenyl Cyclase results in the conversion of ATP to many cyclic AMP molecules (signal amplification)
- The cyclic amp molecules will then activate protein kinase A, which will also initiate a sequential activation of kinases resulting in a phosphorylation

cascade, further amplifying signal, eventually activate glycogen phosphorylase for breakdown of glycogen

Effect of glucagon On target cell

- Trigger cell surface membrane with embedded glucose transporters to Invaginate inwards to form vesicles with embedded glucose transporters to reduce the number of glucose transporters at the cell surface membrane
- Increases the hydrolysis of glycogen to glucose/ glycogenesis in the liver/ activation of glycogen phosphorylase to enable the liver cells to release more glucose into the blood circulation
- Decreases synthesis of glycogen from glucose/glycogenesis/inactivation of glycogen synthase to increase amount of blood glucose
- Increases production of glucose/gluoneogenesis from amino acids molecules or non-carbohydrate sources

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Describe cross-phosphorylation in tyrosine kinase receptor

- Tyrosine kinase add a phosphate group from an ATP molecule via phosphorylation to the other receptor at the tyrosine residues in the intracellular domain

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Role and significance of second messengers

- Small non-protein molecules
- Acts as a second messenger that relays signals inside the cell
- Is produced quickly in large quantities allowing for signal amplification
- Activates effector protein resulting in extracellular actions

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Similarities of glucagon and insulin receptors

- Both have a specific ligand binding site that is complementary to their specific ligand In shape and charge on the extracellular domain

- Cytoplasmic domain of both receptors can change their 3D conforms upon binding of ligand
- Cytoplasmic domain have binding sites for their relay proteins like G protein
- Both are globular proteins with unique 3D conformation