Cell Signalling

1. Introduction

The study of cell communication focuses on how a cell gives and receives messages with its environment and with itself. Cells do not live in isolation. In fact, their survival hinges on receiving and processing information from the external environment.

In multicellular organisms, cell communication takes the form of cell signalling. Cell signalling is the fundamental process by which specific information is transferred from the cell surface to the cytosol and ultimately to the nucleus, leading to changes in gene expression. As such, cell signalling allows for specialisation of groups of cells. Multiple cell types can then join together to form tissues such as muscle, blood, and brain tissue.

Disruption of cell signalling processes can have significant impacts on cell physiology. Alteration of cell signalling by neurotoxicants may be linked to transient functional impairment or to long-term changes, resulting in permanent behavioural impairments.

2. Learning Outcomes

3 (m) Outline the main stages of cell signaling:

i. Ligand-receptor interaction
ii. Signal transduction (phosphorylation cascade and signal amplification)
iii. Cellular response (change in gene expression)
(Knowledge of intracellular receptors is not required)

3 (n) Explain the roles and nature of second messengers (including cyclic AMP)

3 (o) Explain the role of kinases and phosphatases in signal amplification.

3 (p) Outline how insulin and glucagon regulate the concentration of blood glucose through the respective tyrosine kinase receptor and G-protein linked receptor. (The outline should be limited to describing how the ligand induces a conformational change in a membrane-bound receptor to trigger downstream signalling pathways that elicit physiological changes in blood glucose concentration. Details of different second messengers and specific kinases activated in the pathway are not required.)

Students should be able to use the knowledge gained in this section in new situations or to solve related problems.

3. References

- Campbell, N.A. and Reece, J.B. (2008). Biology, 8th edition. Pearson.
- Sherwood, Fundamental of Human Physiology, 4th edition
- Brooker *et al.*, Biology, McGraw-Hill
- Ho YK (2003) A-level course in Biology – Core syllabus, Longman

4. Organisation of Lecture Content

5. Overview of Cell Signaling

- Cells in multicellular organisms usually communicate by **releasing chemical messengers** targeted for cells that are not immediately adjacent.

- Some messengers travel only short distances to influence the cells in their vicinity, while other messengers travel greater distances via the circulatory system.

A Types of Cell Communication

- There are two types of cell-to-cell communication:
  1. **Direct communication** which involves **physical contact** between interacting cells.
  2. **Indirect communication** which involves **extracellular chemical messengers or signal molecules** that bind to **receptors**.

- The study of indirect communication has led to the identification of many signalling systems.

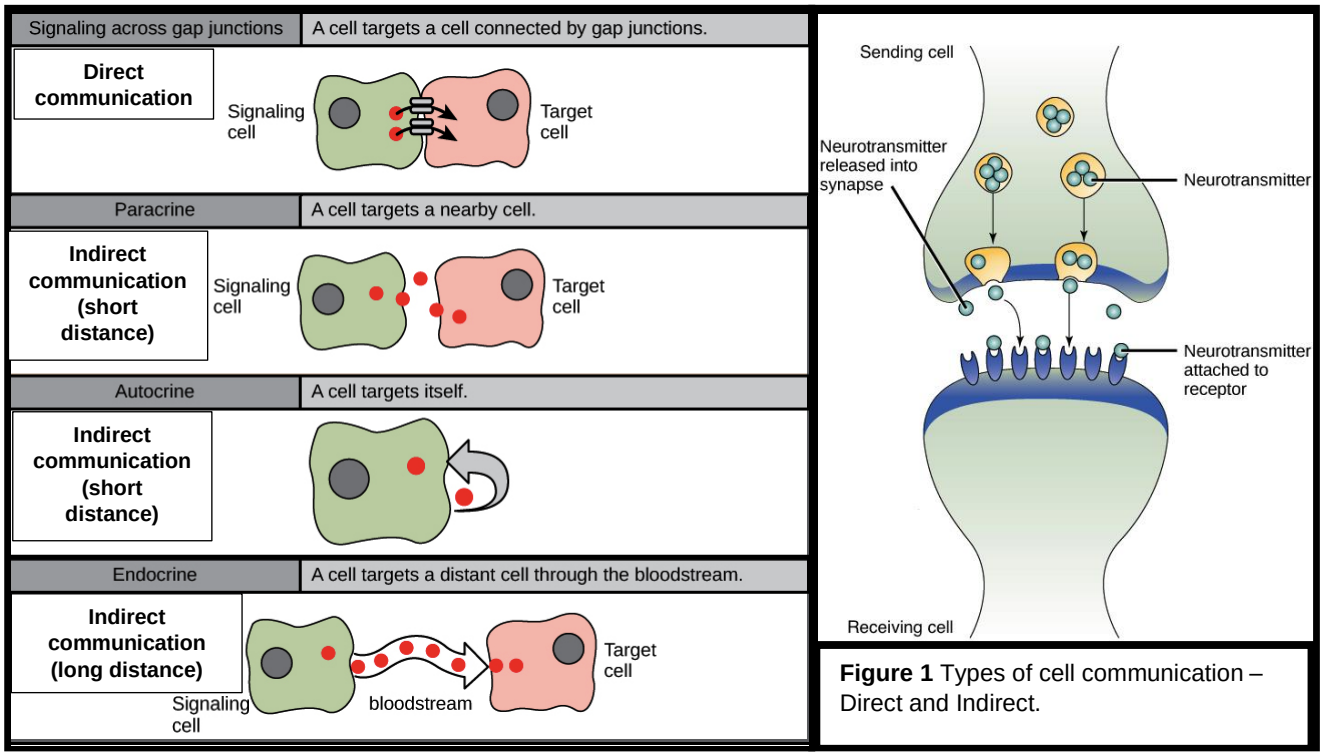

Figure 1 Types of cell communication – Direct and Indirect.

B Overview of the Stages of Cell Signalling

- Cell signalling systems consists of three stages as illustrated in Fig. 2:
  - Stage 1: **Reception**
  - Stage 2: **Signal Transduction**
  - Stage 3: **Cellular Response**

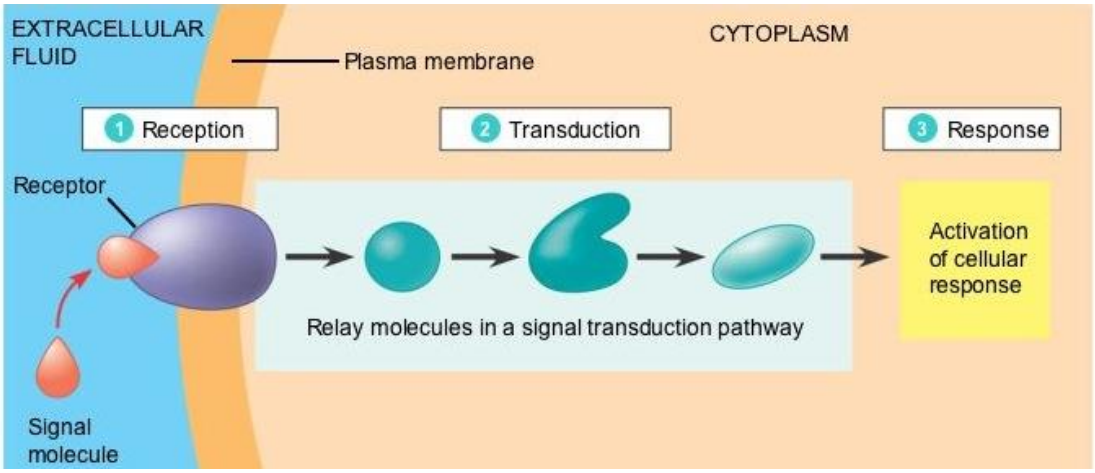

Figure 2: Diagram showing the three stages involved in cell signalling: 1. Reception 2. Signal Transduction 3. Response

Reception: Ligand-receptor Interaction

- Cell signalling begins with an extracellular signalling molecule (e.g. hormones, growth factors) called a **ligand.**
- Ligand (signal molecule) **binds** to a **specific ligand-binding site** of a **protein receptor** to form a **ligand-receptor complex.**

Signal Transduction & Signal Amplification

- Binding of ligand to protein receptor causes a **conformational change** in the protein receptor which **initiates signal transduction**.
- In signal transduction, the **signal is converted** to a form that can bring about a **specific cellular response**. Transduction can occur in a single step, or in a series of multiple steps in a **signal transduction pathway**.
- **Signal transduction pathway** is mediated by **intracellular signalling proteins** such as **kinases (that carry out phosphorylation)**, or small molecules and ions such as **cAMP (secondary messengers)**.
- **Multiple steps** in a signal transduction pathway results in an **amplification** of the signal with each subsequent step.

Cellular Response

- Cellular response occurs through specific changes in cellular function, metabolism, or development (e.g. gene expression) by **targeting proteins** such as gene regulatory proteins, ion channels, components of a metabolic pathway, parts of cytoskeleton.

Figure 3: Flow chart giving the summarised details for the three stages involved in cell signalling.

- **Ligand** – a signal molecule that binds specifically to another molecule, usually a receptor
  - Known as extracellular chemicals/ **first messengers**

- **Receptor** – proteins that bind and transduce the message of the signal molecule into a cellular response.

- **Signal transduction** – a series of steps by which signals are conveyed into the target cell where they are transformed into a cellular response

6. Mechanisms of Cell Signaling

Notes to self

(m) Outline the main stages of cell signaling:
i. ligand-receptor interaction
ii. signal transduction (phosphorylation cascade and signal amplification)
iii. cellular response (change in gene expression)

I. STAGE 1: Ligand- Receptor Interaction (RECEPTION)

- A specific ligand binds to the **extracellular ligand-binding site** of the **specific receptor**. This is known as **reception** or **ligand –receptor interaction.**

- **Ligand binding** generally causes a **receptor protein** to **undergo a change in conformation.**

i. For *many receptors (e.g.* ***G protein coupled receptor****)*, this **conformation change directly activates** the **receptor** so that it can interact with another cellular molecule.

ii. For *other kinds of receptors (e.g.* ***receptor tyrosine-kinase****)*, the immediate effect of ligand binding is more limited, mainly causing the **dimerisation** of two or more receptor subunits.

Question
Why is ligand-receptor interaction specific?

- There are **two** types of receptors that are classified based on their location in a cell:
  - **i. Cell surface receptors (focus of the syllabus)**
    - Located on the plasma membrane.
    - Bind to **large, polar or hydrophilic** signal molecules that cannot diffuse readily across the phospholipid bilayer of the plasma membrane.
  - **ii. Intracellular receptors (not in syllabus)**
    - Located in the cytoplasm or nucleus.
    - Bind to **small, non-polar or hydrophobic** signal molecules (e.g. steroid horomes) that can diffuse through the hydrophobic core of the phospholipid bilayer of the plasma membrane.

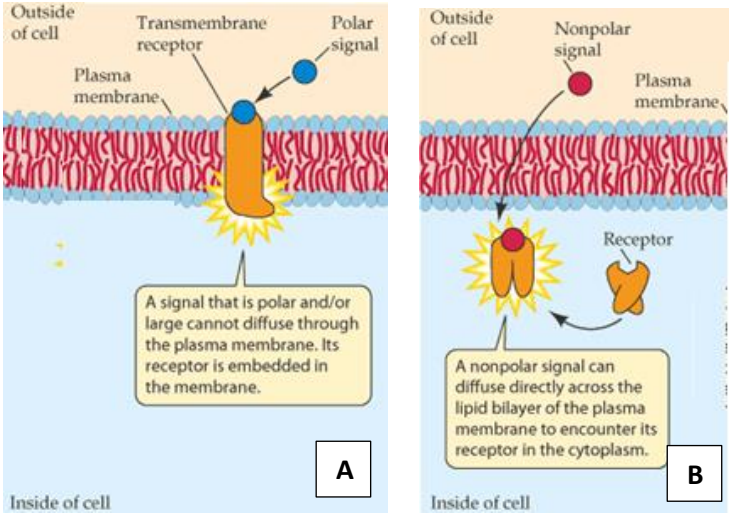

Figure 4: Types of receptors: A – Cell surface receptors; B – Intracellular receptors (not in syllabus)

Intracellular receptors (not in syllabus, for information only)

- Intracellular receptors may be located in the cytoplasm or in the nucleus.
- They are bound by small, hydrophobic molecules that can easily diffuse across the hydrophobic core of the phospholipid bilayer to enter the target cell.
- Upon activation, receptors may function as transcription factors or gene regulators (e.g. receptors for steroid hormones such as estrogen and progesterone).
- Signal transduction is usually a 1-step process: binding of signal molecule causes a conformational change that allows the receptor protein to function as a transcription factor.
  - No signal amplification is involved.

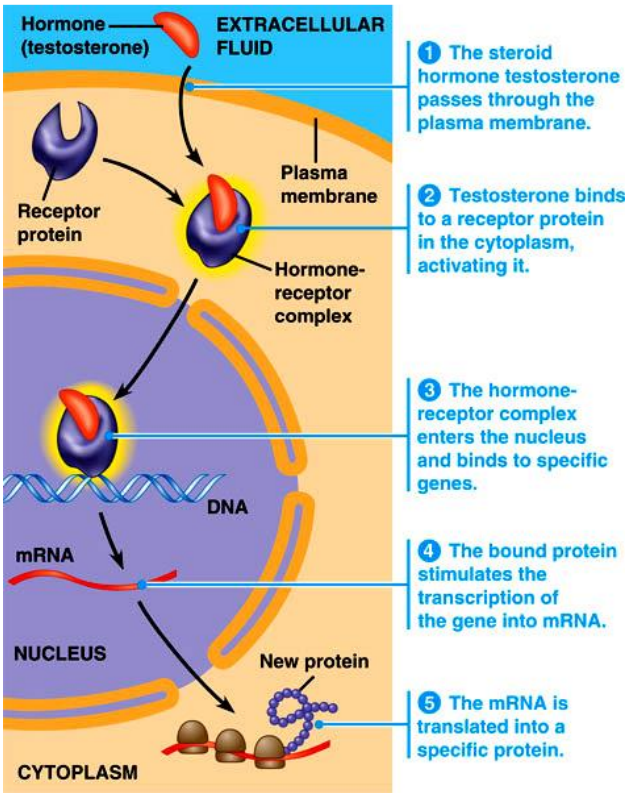

Figure 5: Intracellular receptors and signalling mechanism (not in syllabus)

II. STAGE 2: Signal Transduction (TRANSDUCTION)

Notes to self

- Signal transduction refers to the series of changes in cellular proteins that converts an **extracellular chemical signal** to a **specific intracellular response**. The function of a signal transduction pathway is to change the behaviour of a cell.

- Signal transduction pathway starts after reception.
  - During reception (previous stage), a signal molecule binds to the extracellular ligand-binding site of receptor protein. This now causes a **conformational change** in the **intracellular domain of receptor protein**. It activates the receptor protein, enabling it to interact with other cellular molecules.
  - As a result, other proteins, known as **relay proteins**, are activated as well.

- Signal transduction pathway involves:
  1. **Multiple steps**
     - activated receptor activates another relay protein, which activates another relay protein molecule and so on until the final protein that produces cellular response is activated.
     - involving specific molecular interactions.

  2. **Phosphorylation** cascade
     - A phosphorylation cascade is a sequence of events where one enzyme phosphorylates another, causing a chain reaction leading to the phosphorylation of thousands of proteins
     - **Phosphorylation** and **dephosphorylation** are ways of changing these proteins and they involve the addition or removal of phosphate groups respectively

  3. **Signal amplification**
     - each step **increases the proportion** of proteins that make up a cell i.e., or the **activities** of cellular proteins.

1. Phosphorylation Cascade

- **Protein phosphorylation is a major mechanism of signal transduction**.

- When initially synthesized, many proteins are **inactive** and **require modification** to be **activated**. Conversely, some proteins that are produced active might require modification for deactivation.

- Protein phosphorylation/ dephosphorylation is a type of **post-translational modification** that helps to regulate protein function (covered during Organisation and Control of Prokaryotic and Eukaryotic Genome).

- **Protein phosphorylation:**

  - Refers to the **addition of phosphate groups to proteins**.
  - Most proteins are **activated** by phosphorylation.
  - Phosphorylation is carried out by the enzyme **kinase** which **adds phosphate** groups from **ATP to the protein**.

- **Protein dephosphorylation:**
  - Refers to the **removal of phosphate groups from proteins**.
  - Most proteins are **deactivated** by dephosphorylation.
  - Dehosphorylation is carried out by the enzyme **phosphatase** which **removes phosphate** groups from **proteins** by **hydrolysis**.

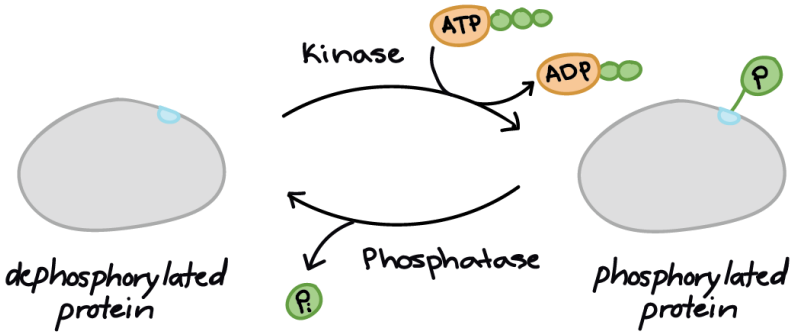

Figure 6: Diagram showing the functions of protein kinase and protein phosphatase enzymes respectively.

- Many of the **relay molecules** in signal-transduction pathways are **protein kinases**.
- A signal-transduction pathway may involve a **phosphorylation cascade**, in which a series of protein kinases **successively** add a phosphate group to the next one in line, activating it. Hence, **sequential phosphorylation occurs in the cascade**.
- In the absence of the extracellular signal, the signal-transduction pathway is **turned off by protein phosphatases**. Thus, shutting down the signalling pathway and cellular response.

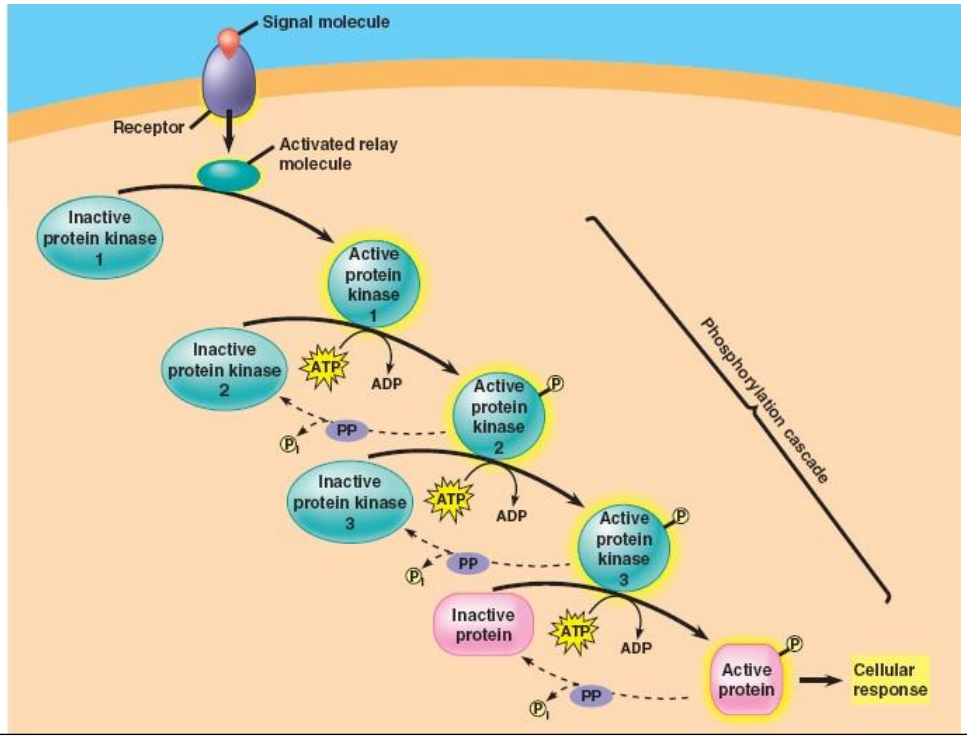

Figure 7: Phosphorylation cascade involving 3 different protein kinases (labelled 1 to 3).

2. Signal Amplification

- **Signal amplification** produces **a large number** of an intracellular mediator from a relatively small number of extracellular signals.
    - When a few of the molecules in a pathway transmit the signal to multiple molecules of the next component in the series, the result can be a **larger number of activated molecules** at the end of the pathway.
    - **Protein kinases** are usually involved as when these enzymes are activated, they catalysed the **phosphorylation** of several other specific proteins in the next step thus activating these proteins.
    - Each step increases the proportion of the molecule. In other words, a **small number of extracellular signal molecules** can produce a **large cellular response** in a signal transduction pathway. Starting with 1 signalling molecule, one cell surface receptor can trigger the production of 10^8 copies of the final product.
    - **Protein phosphatases** serve to terminate the responses initiated by receptor activation of protein kinases.

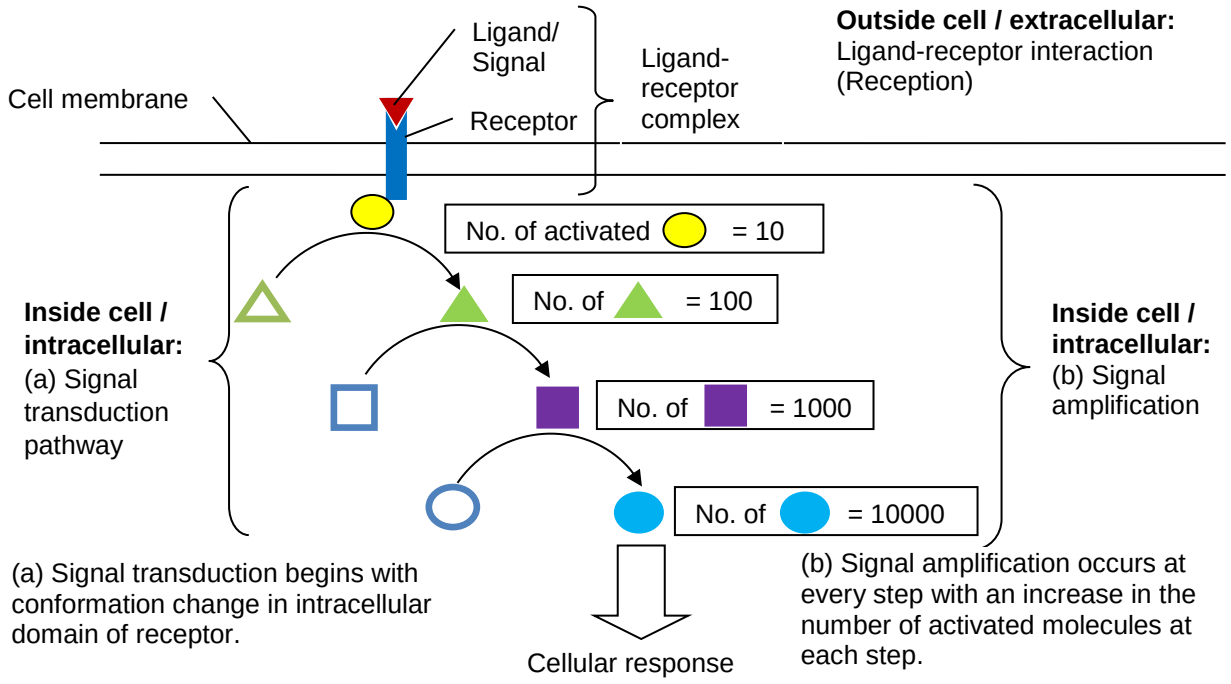

Figure 8: Cell signalling highlighting signal transduction and signal amplification. Receptor shown here is located on the cell membrane (cell surface receptor).

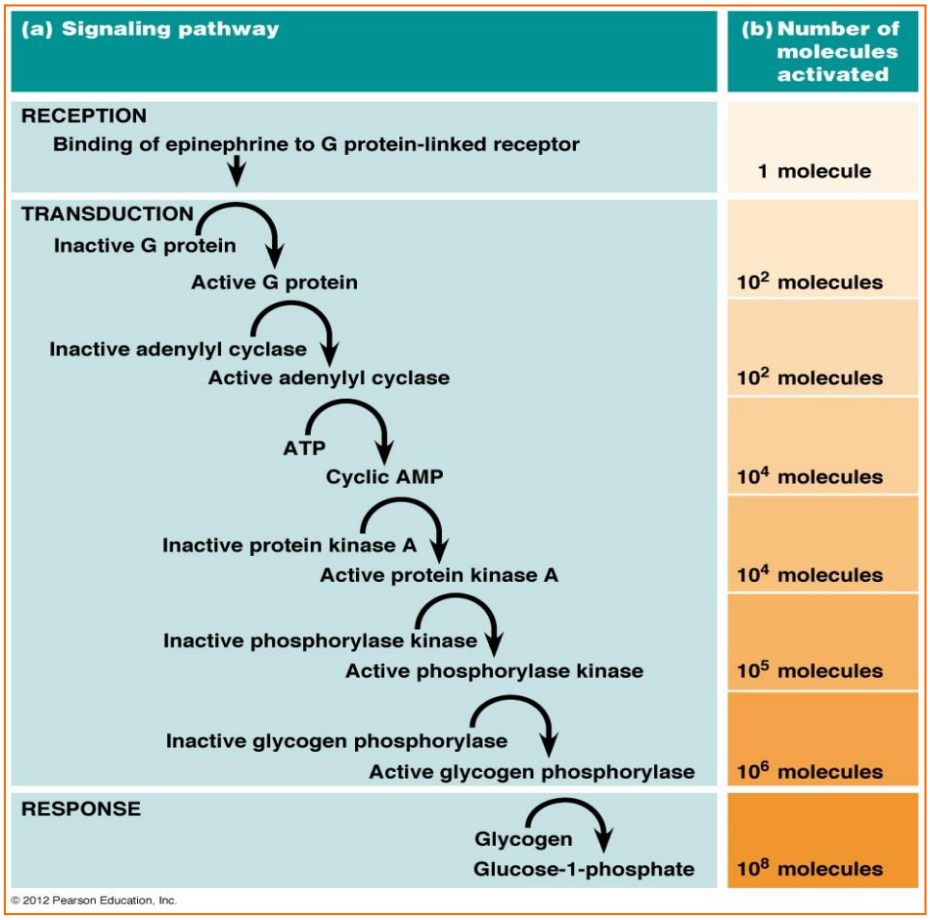

Figure 9: Signal Amplification – the number of activated molecules at each step of the signal transduction pathway increases.

Think about these!

a. What is the basis of signal amplification?

At each step, one molecule acts on many other molecules, in this way it produces a large amount of the final product.

This allows signal transduction to proceed even with very little amount of signal molecules / receptors at the start.

b. Why is amplification of signal required?

As there may not be enough receptors to yield the appropriate responses, signal amplification will help with converting the signals to appropriate cellular responses

c. With reference to Fig. 9, which transduction step/s does not result in signal amplification? Explain.

III. STAGE 3: Cellular Response (RESPONSE)

- The transduced signal will eventually produce an appropriate cellular response in the cells, for example:
  - **Regulation of gene expression**
    (a gene may be upregulated or downregulated by the activation of transcription factors)
  - **Regulation of metabolic pathways**
    (through the activation or inhibition of enzymes)
  - **Changes in cytoskeleton**
    (e.g. assembly of microtubules for movement of vesicles to plasma membrane).

- Not all signals give rise to the same cellular responses in different cell types. This is termed as **the specificity of cell signalling.** In fact, the following are observed when it comes to cellular responses:

  (a) different cell types can have different responses to the same signal
  - e.g. in liver cells, insulin will increase permeability to glucose, and stimulate conversion of glucose to glycogen. In adipose cells, insulin will inhibit breakdown of triglycerides.

  (b) same cells can have the same response to different signals
  - e.g. liver cells can be stimulated by both glucagon and adrenaline (sometimes known as epinephrine) to mobilise glucose. These different signals act by the same transduction pathway to stimulate the breakdown and inhibit the synthesis of glycogen.

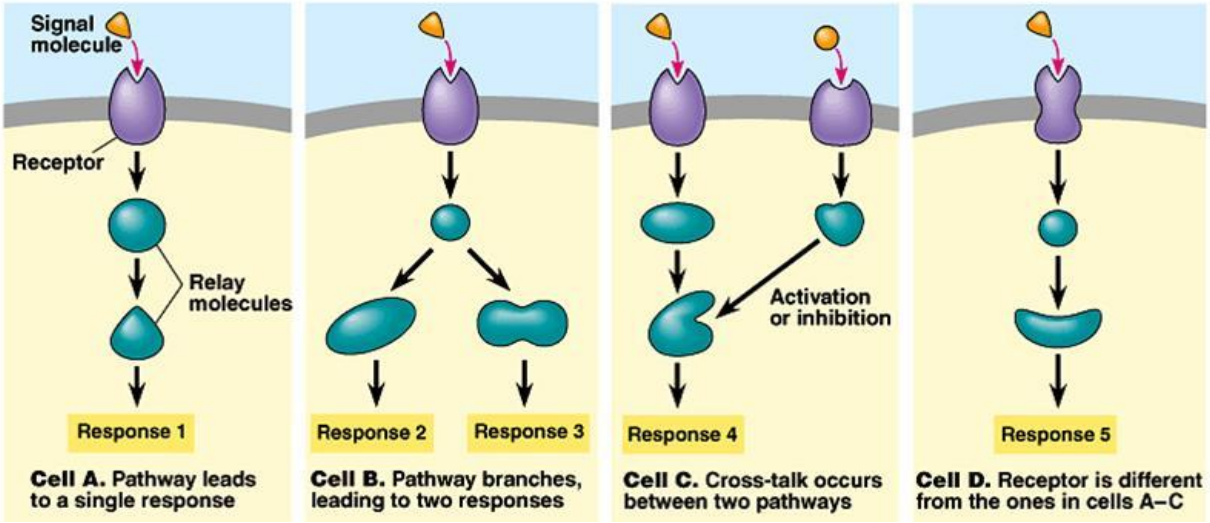

Figure 10: The specificity of cell signalling
The 4 different cells respond to the same signal molecule in different ways.
Cells A, B and C all use the same receptor protein for the signal molecule (represented by a triangle); differences in other proteins account for their differing responses.
Cell B - a pathway triggered by a single kind of signal diverges to produce 2 responses.
Cell C - 2 pathways triggered by separate signals (represented by a triangle and a circle) converge to modulate a single response.
Cell D - same signal molecule recognises a different receptor molecule which transduces the signal via a different pathway, producing a different cellular response.

Question
Even though the ligand and receptor may be the same, different responses may be elicited from different cells. Why?
In different kind of cells, different sets of genes are expressed thus resulting in the presence of **different collections of relay molecules and signal pathways** in different cells.

Termination of Cellular Response

- Cellular responses can be **terminated** at 2 points:
  (a) Reception
    - Extracellular first messenger can be **degraded by enzymes** in the extracellular space.
    - **Note**: It is important to remove a bound ligand after a cellular response has been triggered. This is so that signal transduction will not continue permanently, leading to excessive cellular responses. E.g. if a ligand is a growth factor that leads to cell growth as the cellular response, a permanently bound ligand would likely cause tumour formation.

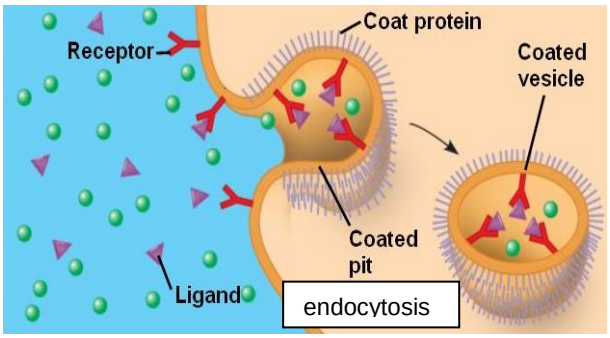

Figure 11: Ligand binds to receptor on cell surface to form a ligand-receptor complex, which then enters the cell by endocytosis.

    - **Endocytosis of ligand-receptor complex** prevents signal transduction from continuing.

  (b) During signal transduction pathway
    - Increased activity of **phosphatases** function to dephosphorylate proteins, thus inactivate the relay molecules. This results in the inhibition of signal propagation.
    - Production of inhibitors that bind to the ligand-receptor complex and/or any of the intracellular signal proteins in the signal transduction pathway to prevent transduction of the signal.

Advantages of signal transduction:

1. Facilitate signal amplification
   - only a small number of signal molecules needed to solicit a large response from cell

2. Multiple responses to 1 signal molecule (ligand) because 1 signal molecule (ligand) can trigger multiple signal transduction pathways to elicit different responses;
   - E.g. insulin binding to liver cell triggers increase GLUT 4 transporters at cell membrane to increase glucose uptake from blood, results in activation of enzymes for increased glucogenesis, glycolysis and decreased gluconeogenesis.

3. Provides multiple checkpoints for regulation
   - Several steps in the signaling pathway can be regulated and controlled.
     E.g. activation/ inactivation of G protein, activation of adenyl cyclase and amount of cAMP produced. This will eventually regulate the cellular response of the pathway.

4. Ensures specificity because the specific signal molecule (ligand) binds to a specific receptor to elicit specific reaction via specific pathway in each cell type;

5. Ability of a signal molecule (ligand) to activate genes in nucleus upon binding to cell surface receptor without the need to move into nucleus;

7. Types of Receptors

p) Outline how insulin and glucagon regulate the concentration of blood glucose through the respective tyrosine kinase receptor and G-protein linked receptor.

- There are three main types of cell surface receptors (Syllabus focuses on i and ii):
  i. **G-protein-coupled receptors** (e.g. glucagon receptor)
  ii. **enzymatic receptors** (e.g. receptor tyrosine kinase) such as insulin receptor
  iii. **chemically-gated ion channels** (not in syllabus)

1. G-protein-coupled Receptor

- The G protein system comprises of 3 components – **G protein-coupled receptor, G protein and another protein (usually an enzyme).**

- **G-protein-coupled receptor (GPCR):**
  - is a **cell surface receptor**
  - consists of 7 alpha-helices spanning the membrane
  - has an **extracellular ligand –binding site** that ligand binds to
  - and an **intracellular/ cytoplasmic side** that associates with a G-protein

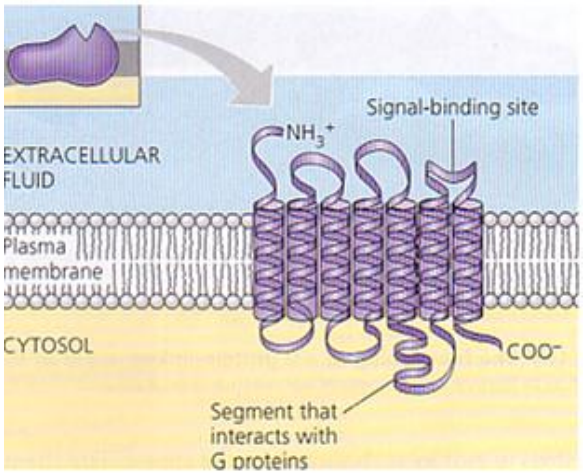

Figure 12: Structure of a G-protein coupled receptor (GPCR). This is one of 3 components in the G protein system.

- **G proteins:**
  - Are found on the cytoplasmic side of the membrane.
  - Are complexes made up of 3 subunits, namely **alpha (α), beta (β) and gamma (γ) subunits**
  - Are GTP-binding proteins
  - Alternate between 2 states:
    i. **Inactive** state – **bound to GDP**
    ii. **Active** state – **bound to GTP**
  - Has intrinsic **GTPase activity,** thus can hydrolyse GTP to GDP

- **Reception and Initiation of transduction**
  - The following steps show how a chemical signal activates the entire G protein system.
  - **G protein system in inactive form**
  - (Fig. 13a) In the absence of extracellular signal molecules specific to the receptor, all 3 proteins are in inactive form. Inactive G protein has a GDP molecule bound to it.

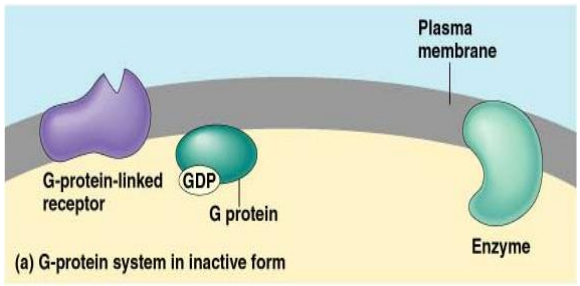

Figure 13a: The G protein system when G protein is inactive.

- **G protein system in action (activated)**
  1. When a signal molecule binds to receptor, the receptor changes conformation in such a way that it binds to an inactive G protein.
  2. A molecule of GTP displaces GDP on the inactive G protein. This activates the G protein.
  3. The active G protein dissociates from the receptor and moves along the cytoplasmic side of the cell membrane.
  4. It binds to and activates the enzyme (usually **adenylate cyclase**) which
  5. triggers the next step in the pathway leading to cellular response (Fig. 13b)

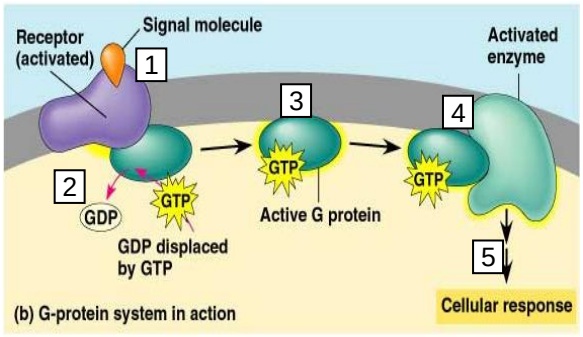

Figure 13b: The G protein system when G protein is activated.

- **G protein system returns to inactive form**
- Due to **intrinsic GTPase activity**, it catalyses the hydrolysis of its GTP to GDP, returning the G protein to an inactive state.
- Once inactivated, G protein dissociates from the enzyme and becomes available for reuse (Fig. 13c).

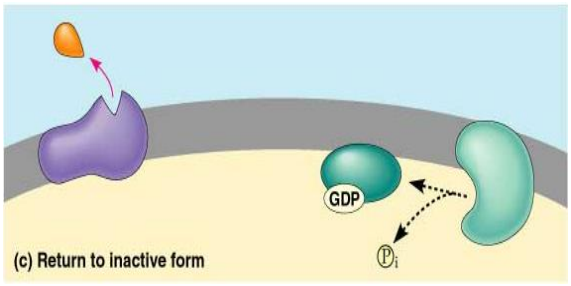

Figure 13c: Return to inactive G protein

- **Examples of G-protein-coupled receptors** are the receptor for the hormone **glucagon and adrenaline**.

- Once G protein is activated, it can activate 2 enzymes in the signal transduction pathway:

  a. **Adenylate cyclase**:
  Catalyses the conversion of ATP to cAMP (**secondary messenger**) which triggers a series of biochemical events within the cell to bring about the response dictated by the signal molecule.

  b. phospholipase C (not in syllabus).

(n) Explain the roles and nature of second messengers (including cyclic AMP)

1.1 Secondary Messengers

- Both G protein-coupled receptors (GPCR) and receptor tyrosine kinase (RTK)-initiated pathways involve second messengers.

- The **extracellular signal molecule/ ligand** that binds to the membrane receptor is a pathway's **first messenger**.

- Many signalling pathways also involve **small, non-protein, water-soluble molecules or ions**, called **second messengers.** Being small and water-soluble molecules, they readily spread throughout the cell by diffusion and hence are able to function effectively in the cytoplasm. (Note: Not all components of signal-transduction pathways are proteins.)

- Secondary messengers help to activate cellular proteins.

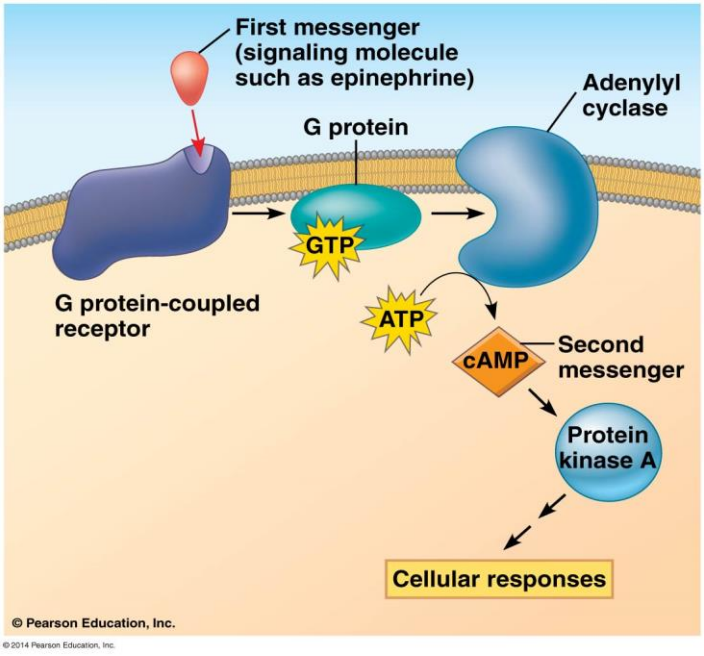

Figure 14: cAMP is the second messenger in a GPCR initiated pathway. **Once its function is completed, it will be converted to AMP to ensure that cellular response does not persist permanently**.

- Second messenger in G protein-coupled receptors/ GPCR-initiated pathway:

  - **cAMP**
    - cAMP are produced by **breakdown of ATP** by **activated adenylyl cyclase**
    - Signal molecule is the 1st messenger, which activates a G-protein-coupled receptor, which activates a specific G-protein.
    - In turn, G-protein **binds and activates adenylate cyclase** (enzyme) which catalyses the **conversion of ATP to cAMP**.
    - cAMP acts as a **second messenge**r. Its concentration is increased and it binds and activates another protein, usually protein kinase A.
    - **Protein kinase A** starts a **phosphorylation cascade** leading to cellular responses.

- Other second messengers include **Ca^{2+}**, **IP_3** and **DAG** etc. (Syllabus does not require you to know how these work.)

2. Receptor Tyrosine Kinase (RTK)

- Some cell surface receptors that bind to extracellular ligands either act as enzymes themselves or are linked to enzymes. These enzymes are necessary to activate a cellular response.

- **R**eceptor **T**yrosine **K**inase (**RTK**) is a group of cell surface receptors that also functions as an enzyme.

- Each receptor protein consists of an **extracellular ligand-binding site**, a single alpha-helix spanning the membrane, and **an intracellular domain** with **several tyrosine residues** (Fig. 9a).

- Part of the receptor protein that **extends into the cytoplasm** functions as an enzyme called **tyrosine kinase**, which phosphorylates specific tyrosine residues. Hence, RTKs are said to have intrinsic kinase activity. (A protein kinase is a class of enzymes that adds phosphate groups from ATP to proteins.)

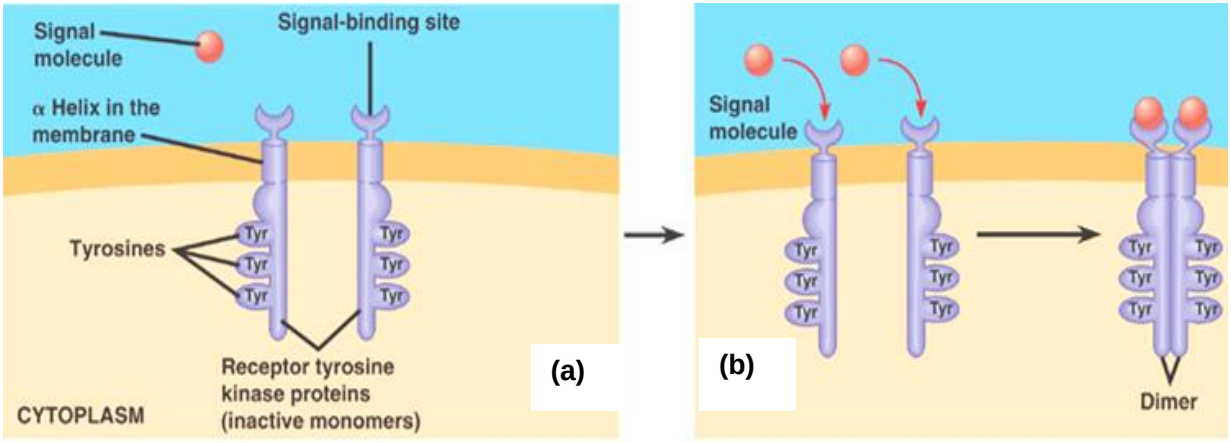

Figure 14. (a) Structure of receptor tyrosine kinase. Before the signal molecule binds, the receptors exist as individual polypeptides.

Figure 14 (b) Dimerisation of receptor, Upon binding of ligand to each receptor, 2 receptor molecules dimerises.

- RTKs exists as two separate subunits (Fig. 14a) or as a linked dimer.

- The binding of a signal molecule to such a receptor **does not cause enough of a conformational change to activate** the cytoplasmic side of the protein directly. Instead, **receptor activation** occurs in 2 steps:

  1. **Dimerisation**

     - When **ligands bind** to each of the 2 receptor subunits, the subunits **aggregate**, forming a **dimer** (a protein consisting of 2 polypeptides).

2. **Phosphorylation of receptor**

   - This aggregation **activates** the **tyrosine-kinase** activity of both subunits, each tyrosine kinase catalyses the attachment of a **phosphate** to **specific tyrosine residues** on the intracellular domain of the other subunit, to become a **phosphorylated dimer**. This is known as **cross-phosphorylation)**

- The fully-activated receptor protein dimer will be recognized by **specific relay proteins** inside the cell.

- Each relay protein **binds** to a **specific phosphorylated tyrosine**, resulting in a **conformation change** and thus **activation of the bound relay protein**.

- Each **activated tyrosine kinase dimer** may now **activate ten or more different intracellular proteins simultaneously** (covered in signal amplification later) and **trigger** many **different transduction pathways** and cellular responses.

  - The tyrosine-kinase receptor system is thus **specialised** for **triggering more than one** signal-transduction pathway **at once** so that the cell can **regulate** and **coordinate** many aspects of cell growth and reproduction.

- Abnormal tyrosine-kinase receptors that **dimerise even without ligand** cause some kinds of cancer.

- **Insulin** hormone is a signal molecule that binds to a tyrosine kinase receptor.

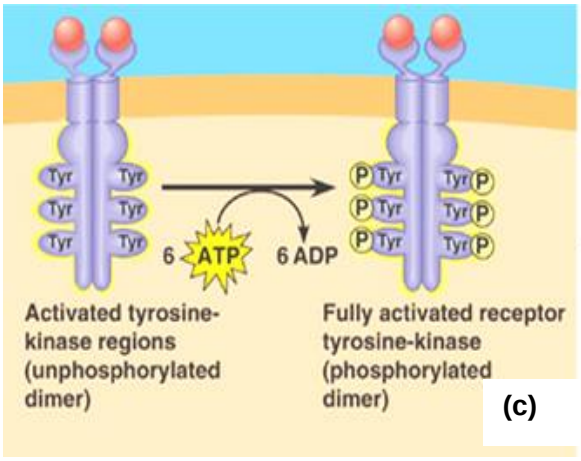

Figure 14 (c) Phosphorylation of receptor, Each tyrosine kinase adds a phosphate from ATP to a tyrosine on the intracellular domain of the other receptor sununit.

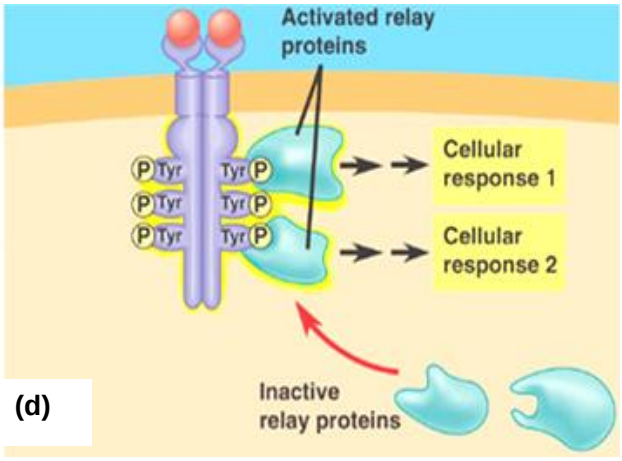

Figure 14. (d) Activated tyrosine kinase dimer. Each activated relay protein triggers a transduction pathway, leading to cellular response.

3. Ion Channel Receptor (not in syllabus)

- Ion channel receptors are **ligand-gated ion channels** that open or close in **response to a chemical signal**, allowing or blocking the flow of specific ions, such as Na^+ or Ca^{2+}.
- When a ligand (e.g. neurotransmitters) **binds** at a specific site on the extracellular side of the ion channel receptor, it **changes the conformation of receptor** and **opens the channel**.
- Specific ions flow in and rapidly change the concentration of that ion inside the cell.
- This flow of ions across cell membrane results in a temporary change in membrane potential, which can affect the activity of other membrane proteins (such as voltage-gated channels). In this way, a cellular response is triggered.

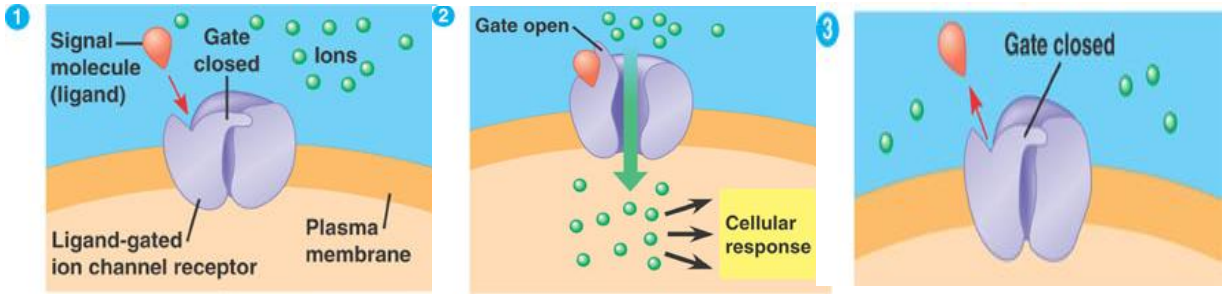

Figure 15: 1. Binding of ligand triggers; 2. The opening of the ion channel; 3. Closing of the channel when Ligand dissociates.

8. Specific examples of Receptors

1. Glucagon and G-protein signaling

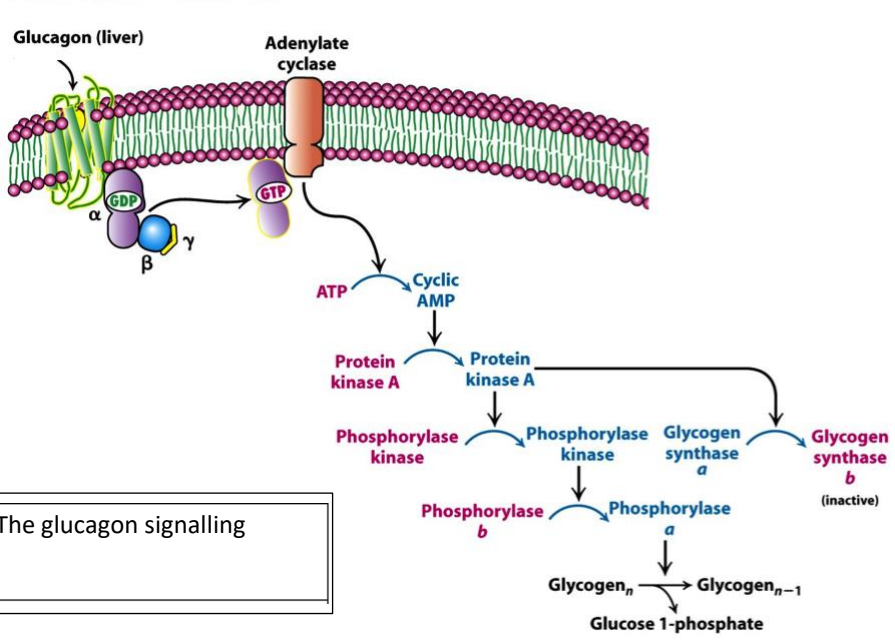

Figure 16: The glucagon signalling pathway

Notes to self

- Glucagon is a hormone which is released, from **α cells of the Islets of Langerhans** in the pancreas, in response to **low blood glucose** levels. It acts mainly on liver cells to **promote glycogen breakdown and to encourage glucose synthesis**. The net effect of glucagon signalling is an **increase** in blood glucose levels.

Ligand – receptor interaction

- The glucagon receptor on the cell surface of liver cells is a **G-protein coupled receptor (GPCR)**.
- This GPCR has two domains: an extracellular binding domain which is complementary to the shape of glucagon and an intracellular binding domain which is coupled to a G-protein.

Signal Transduction

- Upon binding of glucagon to the extracellular **ligand- binding site** of the glucagon receptor, **conformational changes** occur in the **intracellular domain** of the transmembrane receptor leading to the displacement of a GDP molecule with a GTP molecule on the G protein, thus activating the G protein.

- The **activated G protein** binds to and activates the next enzyme in the cascade, **adenylate cyclase**. The **activated adenylate cyclase** will then convert **intracellular ATP into cAMP**.
- This results in **an increase in cAMP levels** which also serves to **amplify the glucagon signal**.
- cAMP will then bind to and activate protein kinase A (PKA) which is a cAMP-dependent protein kinase. Activated PKA in turn phosphorylates and activates phosphorylase kinase, which, in turn, phosphorylates glycogen phosphorylase, converting it into the active form.
- The activated PKA will also phosphorylate and inactivate glycogen synthase enzyme.

Cellular Response

- The activated glycogen phosphorylase will function to catalyze the **breakdown of glycogen to produce glucose-1-phosphate.** The glucose-1-phosphate will be converted into glucose within the cell before it is released into the bloodstream.
- Since the activated PKA will inactivate glycogen synthase, glycogen production will be inhibited as a result.

Notes to self

2. Insulin and Receptor Tyrosine Kinase (RTK) signalling

- Insulin is the major hormone controlling critical energy functions such as glucose and lipid metabolism. Insulin functions **to increase the permeability of muscle and liver cells to increase glucose uptake**. It also stimulates **glycogenesis, lipid and protein metabolism** as well as many other cellular metabolic activities. The net effect of insulin signaling is to **decrease** the blood glucose levels.

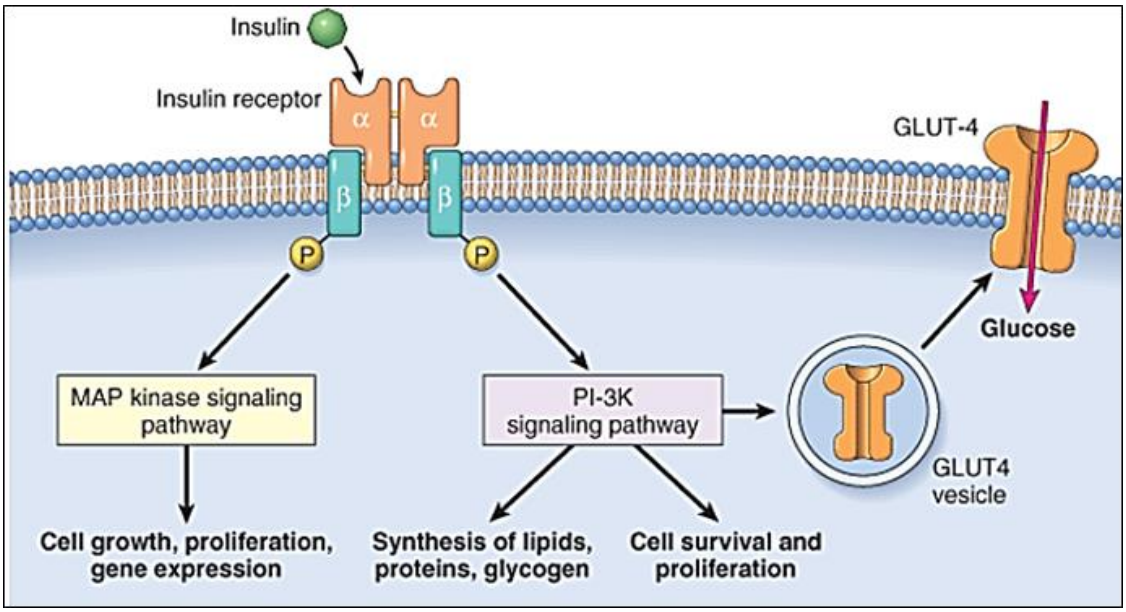

Figure 17: The insulin signalling pathway and the translocation of GLUT 4 to the plasma membrane

Ligand - Receptor interaction

- The insulin receptor is a RTK that exists as a **linked dimer**. Insulin binds to the **extracellular ligand-binding site of insulin receptor,** causing a **conformational change** in the **intracellular domain**.

Signal Transduction

- This change in conformation of the intracellular domain leads to the **cross-phosphorylation** of the **specific tyrosine residue**s on the **receptor subunits**, activating the insulin receptor..
- Different intracellular relay proteins will **bind** to **specific phosphorylated tyrosine residues** on receptor subunits. Intrinsic tyrosine kinase activity of receptor can phosphorylate these relay proteins, which can activate **different intracellular pathways**.

Cellular response

- Cellular responses of insulin include induction of glycogen synthesis via activated glycogen synthase and stimulation of glucose uptake in muscle and adipose tissues via translocation of vesicles containing GLUT4 transporters to the plasma membrane.

9. Links to other topics

Cell Signalling and Cancer

Cancer may result from defects in critical signalling molecules that regulate many cell properties, including cell proliferation, differentiation and survival.

When proto-oncogenes are mutated to form oncogenes, many of the protein products encoded by these oncogenes encode hyperactive forms of proteins that normally function in the regulation of cell proliferation.

Examples of signalling molecules that can become oncogenic span the entire signal transduction pathway. E.g. Ligands (growth factors), receptors, adapter and effector molecules and transcription factors.

Ras protein signalling pathway

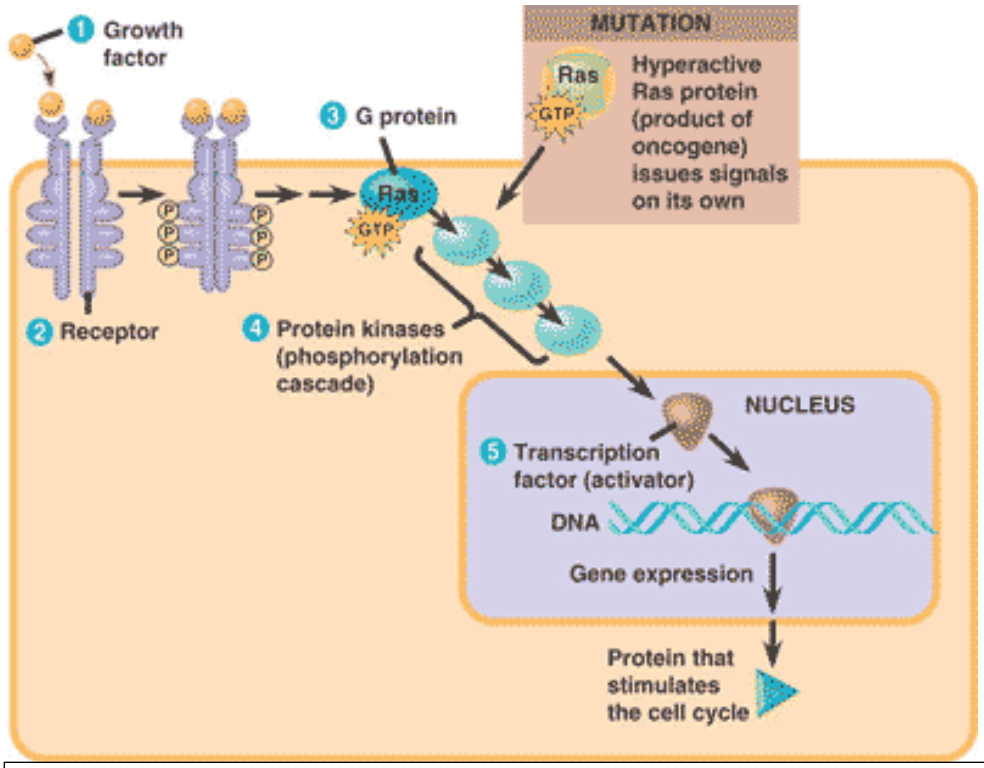

Figure 18: ras protein signalling pathway with hyperactive ras protein

One of the most common intracellular signaling pathways triggered by RTKs is known as the **mitogen-activated protein (MAP) kinase cascade.** The pathway starts with the activation of **Ras**, a small G protein anchored to the plasma membrane.

A mutation in the Ras gene can result in the Ras protein becoming **oncogenic**. This mutation causes the Ras protein to **lose its ability to hydrolyse GTP to GDP**.

Therefore, the Ras protein **remains in the active state consitutively** even with no extracellular signal molecule binding to the RTK receptor. The Ras protein then sends **continuous** signals to keep the cell cycle running with no checks and balances. The result is **excessive cell proliferation** and cancer.