Homeostasis and Cell Signalling

* **Homeostasis** refers to the **maintenance of a stable internal environment independent of fluctuations in the external environment** by **self-regulating** & **negative feedback** mechanisms so that the **organism** can **function optimally**.
  Self-regulation: where a **corrective mechanism is triggered** by the very **entity which is to be regulated**
  (e.g. control of blood glucose levels is triggered by changes in blood glucose levels)
  Negative feedback: a mechanism which brings about **increasing stability of a system** i.e. it **removes any deviations from the set point**
  i.e. a change in a variable triggers a response that counteracts the initial change.
  (e.g. when blood glucose level goes higher than set point, insulin is secreted to return glucose levels to set point).
* **Hormones:**
  → secreted by **endocrine** glands (ductless glands) **directly** into the **bloodstream**
  → effective in **small quantities** (as signal amplification, that occurs during signal transduction, will lead to the production of a strong cellular response)
  → act on specific **target cells** which have **specific cell surface receptors**
  → each type elicits **different cellular responses** & after having served their function, are rapidly broken down
  → e.g. insulin & glucagon are **hydrophilic peptide** hormones that bind to the **specific receptors on the cell membrane (**e.g. **RTK & GPCR)**

* **Pancreas:**
  → is an organ that is both an **endocrine** (**islets of Langerhans**) gland & an exocrine (acinar cells) gland
  → the **islets of Langerhans** contain **alpha** cells which secrete **glucagon** and **beta** cells which secrete **insulin** into the bloodstream
  (insulin and glucagon (which are protein in nature) are secreted constantly and work in an **antagonistic** fashion; it is their relative concentrations and not their actual levels that are critical to maintain normal blood glucose levels at the set point which is **90mg/dL**)

* **Glucose:**
  → key **respiratory substrate**
* **Glycogen:**
  → stored in **liver** and **muscles**
* Insulin **triggers** the conversion of glucose to glycogen
* Glucagon **triggers** the conversion of glycogen to glucose
  (It is incorrect to say that insulin converts glucose to glycogen as insulin binds to the insulin receptor which triggers a signal transduction pathway that eventually leads to the conversion of glucose to glycogen in the cell. Likewise, it is incorrect to say that glucagon converts glycogen to glucose.)
* A **deviation from the set point i.e. stimulus (e.g. high blood glucose levels)**
  → is detected by **detectors (e.g. beta cells in islets of Langerhans)** (N.B. Sometimes detectors are referred to as receptors)
  → which secretes an appropriate **signal** (**e.g. insulin**)
  → which binds to the **cell surface receptors** of the cell** (e.g. **cell surface insulin receptor, RTK**) of the **effector** (e.g. **liver/muscle cells**)
  → which brings about an appropriate **response** that **restores the condition to the set point** (e.g. **blood sugar levels return to set point**)
  → this serves as **negative feedback** to detectors (e.g. beta cells) to decrease secretion of signal (e.g. insulin)

* Cell signaling (3 stages) and role of kinases and phosphatases in signal amplification:

1) Ligand-receptor interaction:
→ **ligand/signal/first messenger** binds to a specific, **ligand-binding site** (which is **complementary in shape and charge** to the ligand) on the **extracellular domain** of the **cell-surface receptor** to form a **ligand-receptor complex.**

2) Signal transduction & amplification:
→ where binding of the ligand/signal to the protein receptor causes a **conformational change** in the **intracellular domain** of the protein receptor which **<u>initiates</u>** the signal transduction. i.e. the signal is converted to a form that can bring about a specific cellular response.
→ signal transduction usually occurs in a series of **multiple catalytic steps** in a **signal transduction pathway**
→ the multiple catalytic steps allow **amplification** of the signal, where the number of activated molecules increases with each subsequent step.(Hence signal amplification occurs during signal transduction.)
→ the signal transduction pathway is mediated by intracellular signaling proteins (e.g. kinases) or small molecules (e.g. cAMP) or ions.
→ **kinases phosphorylate** and **activate proteins** and are involved in multiple **catalytic** steps in a signal transduction pathway. Hence kinases allows **amplification** of the signal
→ **phosphatases dephosphorylate** and **inactivate proteins** and are involved in multiple **catalytic** steps in a signal transduction pathway. By dephosphorylating and inactivating proteins, they can inhibit signal transduction.

3) Cellular response:
→ where the transduced signal triggers specific changes in cellular function, metabolism, or development by **changing gene expression** by **targeting proteins** such as gene regulatory proteins, ion channels, components of a metabolic pathway etc.

* Advantages of a cell signaling pathway:

1) Facilitates **amplification** of signal
   → **small number of signal molecules** binding to the receptors can produce a **large cellular response** as the **number of activated molecules increases with each catalytic step** in the pathway
2) One signal molecule can trigger many signal transduction pathways **in a cell** and elicit **many different cellular responses**
   → when blood glucose levels are high, insulin can bind to the RTK and increase rate of glycolysis, glycogenesis, protein and lipid synthesis etc.)
3) Provides **many checkpoints for regulation** as cellular responses can be **terminated/regulated** at
   (i) **<u>At Reception</u>**:
   → extracellular first messenger can be **degraded by enzymes** in the extracellular space
   → **endocytosis of cell surface receptors** to prevent ligand-receptor interaction can prevent signal transduction
   → **endocytosis of the entire ligand-receptor complex** can prevent signal transduction
   (ii) **<u>During Signal Transduction Pathway</u>**
   → production of phosphatases dephosphorylate & inactive the relay proteins → inhibit further signal transduction
   → production of inhibitors that bind to the intracellular domain of the ligand-receptor complex and /or any of the intracellular signal proteins in the signal transduction pathway to prevent transduction of the signal.
4) One type of signal can allow the **coordinated activation of many different cells** simultaneously (e.g. insulin can bind to receptors on liver and muscle cells and trigger signal transduction pathways in the cell.)
5) Ensures **specific reactions** are triggered as a **specific signal** will bind to a **specific receptor** and will elicit specific reactions in specific cell types.
6) A signal molecule can **activate genes in nucleus** upon binding to cell surface receptor **without the need to move into nucleus**.

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

	INSULIN	GLUCAGON
A **stimulus**	An **increase** in **blood sugar level above 90 mg/dL**	A **decrease** in **blood sugar level below 90 mg/dL**
↓ is detected by a **detector/receptor** (which is a cell that detects the change)	↓ is detected by the **beta cells** of islets of Langerhans of pancreas	↓ is detected by the **alpha cells** of islets of Langerhans of pancreas
↓ which releases a **ligand/signal** (e.g. insulin/glucagon)	↓ which secretes **insulin (1st messenger)**	↓ which secretes **glucagon (1st messenger)**
↓ which recognises and binds to **cell surface receptors** (e.g. RTK / GPCR)	↓ which recognises and binds to cell surface receptors known as **insulin receptors (a receptor tyrosine kinase, RTK)** which exist as **linked dimers**	↓ which recognises and binds to cell surface receptors known as **glucagon receptors (a G-protein coupled receptor, GPCR)**
↓ on the **effector** (which is a cell where the cellular response occurs).	↓ on the **liver** (or muscle) cell	↓ on the **liver** cell
↓ Ligand-binding causes a **conformational change** in the **intracellular**,**cytoplasmic domain** of the receptor, activating it This **initiates signal transduction**.	↓ Ligand-binding causes RTK to undergo **changes in conformation** in its **intracellular, cytoplasmic domain**	↓ Ligand-binding causes GPCR to undergo **changes in conformation** in its **intracellular**, **cytoplasmic domain**
↓ The signal is **further transduced** and **amplified**.	↓ This conformational change **activates tyrosine kinases** in each of the subunits of the receptor and triggers **crossphosphorylation / autophosphorylation** of tyrosine residues i.e. where **kinases on 1 subunit cross-phosphorylates tyrosine residues on the other subunit**	↓ This conformational change causes an **inactive G protein to bind to the GPCR**, and **release** its bound **GDP** and allow **GTP to bind** in its place. GTP binding causes a **conformational change** in **the G protein, activating it.**
	↓ Phosphorylated tyrosine residues serve as **docking sites** for other relay proteins	↓ Activated G protein dissociates from the receptor and translocates along the **cytoplasmic side** of the cell membrane to bind to and activate an enzyme, **adenylyl cyclase**
	↓ Relay proteins activated by binding or via phosphorylation by RTK	↓ Adenylyl cyclase converts ATP to **cAMP (2nd messenger)** which activates **Protein Kinase A**
	↓ Relay proteins may be kinases which can go on to phosphorylate other proteins when activated	↓ Activated Protein Kinase A can phosphorylate other proteins
	↓ a phosphorylation cascade ↓	
↓ which results in the following **cellular responses**	Phosphorylation activates protein kinases in a cascade which eventually activates **glycogen synthase** which catalyses **glycogen synthesis from glucose**. (i.e. increase **glycogenesis** in liver & muscle) Other cellular responses: e.g. 1) **Translocation of glucose transporters from the membrane of cytoplasmic vesicles to the cell membrane.** This **increases glucose intake** into cells e.g. 2) Increased **rate of glycolysis** e.g. 3) Increased lipid & protein synthesis	Protein kinase A activates phosphorylase kinase which activates **glycogen phosphorylase** which catalyses the **breakdown of glycogen to glucose** (i.e. **glycogenolysis** in liver & muscle cells) Other cellular responses: e.g. 1) Increased **gluconeogenesis** (synthesis of glucose from non-carbohydrate sources)
↓ which eliminates the stimulus, ↓ resulting in a diminished response.	↓ Blood glucose levels **decreases** ↓ This is detected by the receptor (detector, i.e. beta cells) which then **decreases insulin production**	↓ Blood glucose level **increases** ↓ This is detected by the receptor (detector, i.e. alpha cells) which then **decreases glucagon production** (Note: G protein has **intrinsic GTPase activity** which can hydrolyse GTP to GDP and inactivate the G protein, terminating the cellular response.)

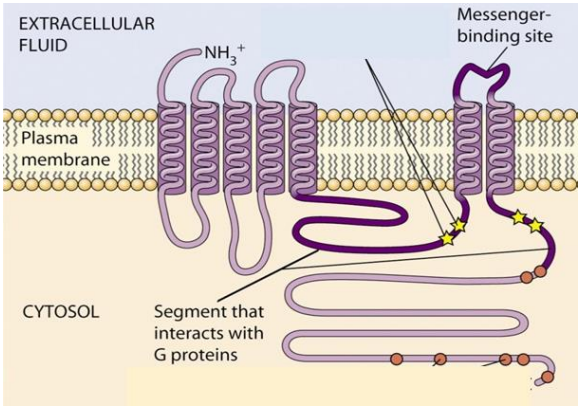
∗ **Explain the role and nature of second messengers (including cAMP):**

→ small, non-protein, water-soluble molecules or ions

→ can readily spread throughout the cell by diffusion and activate cellular proteins

→ can participate in pathways initiated by both **GPCR** and **RTK**.
e.g. cAMP → synthesised from ATP by adenylyl cyclase
→activates protein kinase A which phosphorylate other proteins hence in a signal transduction pathway
(Note: First messenger is the ligand/signal molecule that binds to membrane receptor e.g. insulin, glucagon etc.)

Describe the molecular structure of the G-protein linked receptor and explain how its structure is related to the function it plays.



1. G protein coupled receptor (GPCR) is **cell surface receptor** that will bind to specific signal molecule and initiates the process of ***signal transduction*** which converts the information in the signal from the outside of the cell into a **cellular response** within the cell**.**
2. GPCRs consist of a **single polypeptide** with an **extracellular N-terminus**, and an **intracellular C-terminus**.
3. GPCR is a **globular, seven pass transmembrane protein** with a **tertiary** structure.
4. GPCR consists **of *7 α-helices*** connected by three intracellular and three extracellular peptide loops.
5. As a transmembrane protein that is embedded in a cell's plasma membrane, it is folded such that its amino acid residues with **hydrophobic R groups** are interacting with the **hydrophobic core** of the **phospholipid bilayer** of the plasma membrane and
6. its amino acids with **hydrophilic R groups** are arranged **within the interior of the protein** and also **interact with the aqueous interior and exterior of the cell as well as the hydrophilic phosphate heads of phospholipid bilayer.**
7. The **extracellular** loops have a **ligand binding site** at which a **specific** signaling molecule (e.g. glucagon) can bind to the GPCR.
8. The **intracellular domain** of GPCR has a **G protein binding site** that allows binding of a heterotrimeric G protein complex.
9. When a ligand binds to the ligand binding site at the extracellular side of a GPCR it causes a **conformational change** of the **intracellular domain** at the cytoplasmic side of the GPCR,
10. The activated GPCR can then **activate** an associated **G protein by exchanging its bound GDP for a GTP.**