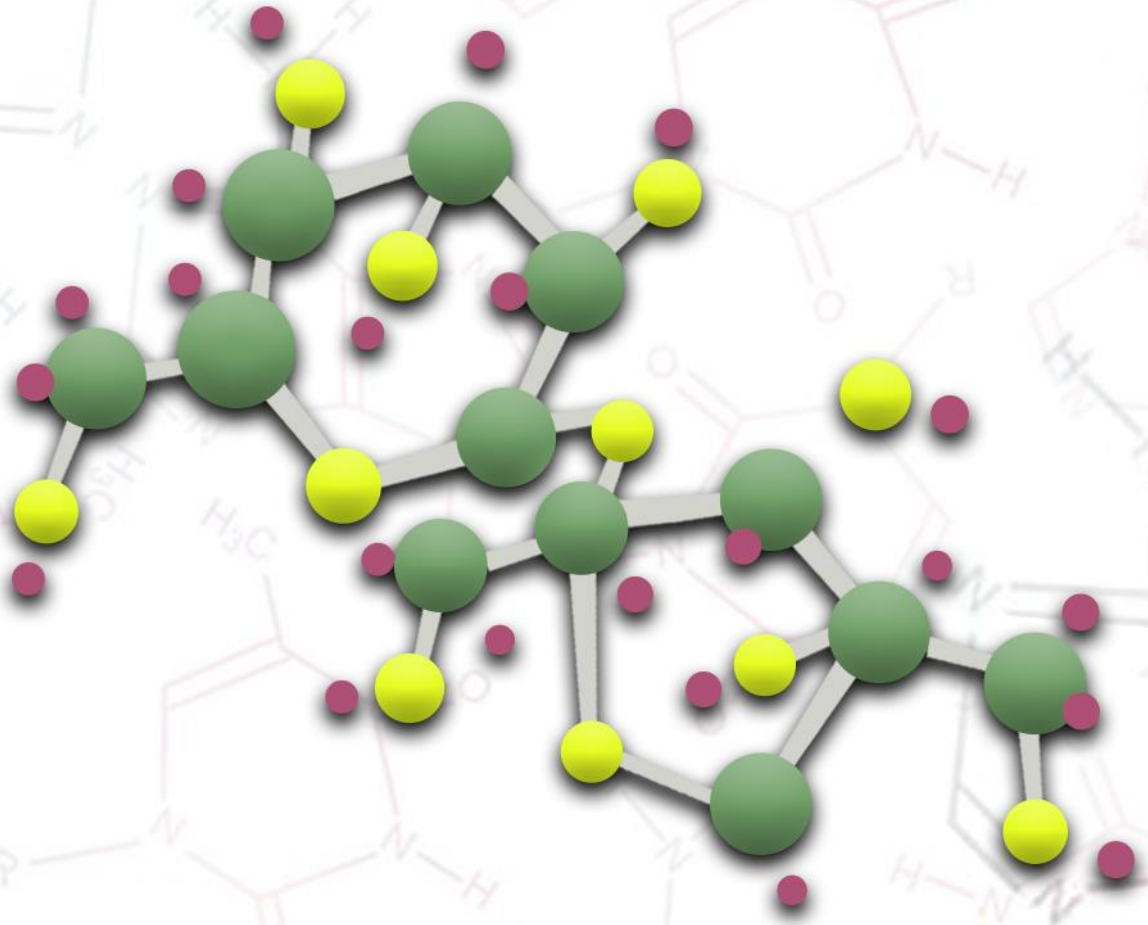
BIOCHEMISTRY

Second material



DONE BY :

Osama Alomour

LECTURE :

Signal transduction

01

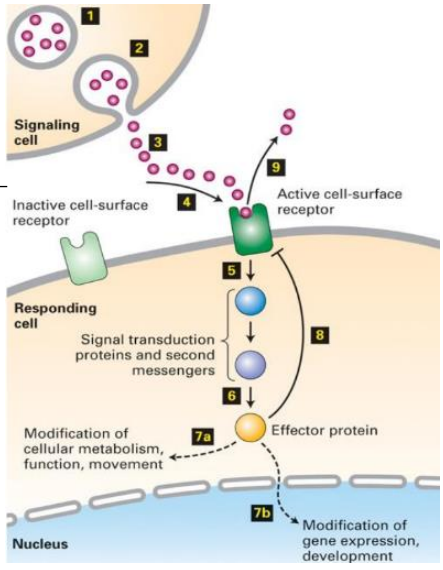
Signal transduction

Signal transduction overview

- **Signal**: is the mechanism one cell uses to **communicate** and **influence the behavior** of another cell.
- **Signal transduction**: a process of **converting extracellular signal into an intracellular response** (the chemical reactions that occur inside the cells in response to a specific signal)
- **Metabolism**: is the chemical changes that take place in the cell that produce energy and basic materials needed for important life processes (it's both **catabolic** and **anabolic** reactions)
- Metabolism occurs in a millions of cells inside multiple organs (liver, adipose, heart, brain) with a thousand enzymes (that activate metabolism steps) in a various condition (fed, fasted, exercise, stress). So we need signal transduction **to regulate all these processes**
- How cells communicate? One cell synthesis an extracellular signal (signals example is **hormones** such as **insulin**) → release → transport → detection by target cell → **changes in metabolism of the target cell**
- In this lecture we will talk about the mechanisms that is used by cells to communicate and then we will talk about the **role of insulin hormone** in signaling and how insulin affects the **glycogen synthesis** inside the hepatic and muscle cells

Hormones

- Hormones are the major signals that is used to regulate metabolism (anabolism or catabolism)
- Hormones can be classified into:
  1) Anabolic hormones
     - Hormones that are used **to build (anabolic) macromolecules** (proteins, lipids and carbohydrate) in the body from simple monomers (amino acids, fatty acids and monosaccharides)
     - They are elevated in the body **during well fed state** (because in the well fed state you will have a lot of monomers to synthesis macromolecules)
     - Important example is **Insulin** (released from β-cells of the pancreas)
  2) Catabolic – stress hormones
     - Hormones that are used **to degrade (catabolic) macromolecules** to simple monomers
     - They are elevated **during fasting or stress** to use the monomers as an energy source
     - Important examples are **Glucagon** (released from α-cells of the pancreas), **Cortisol** (released from adrenal cortex) and **Epinephrine**
     - They are called counter regulatory hormones (**counter the effect of insulin**)



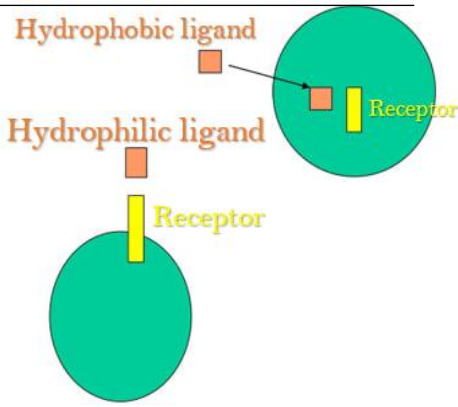
General principles of signal transduction

- As we said Signal transduction refers to the overall process of converting extracellular signals into intracellular responses.
- Key players in signal transduction are **signaling molecules**, **receptors**, **signal transduction proteins** and **second messengers**, and **effector proteins**.
- Cells respond to signals by changing the activity of existing enzymes (fast) and/or the levels of expression of enzymes (slower) by gene regulation (Steps 7a & 7b).

Regulatory function of Insulin

- Insulin can do its effect either in short term or in long term
  1) Short term
     - Insulin can **increase glucose transport into the cells of extrahepatic tissue** by **increasing the glucose transporters on the surface of the cells** (after the meal → high glucose (monomers) level in the blood → increase insulin level → insulin increase glucose transporter on the cell surface → glucose translocate from the blood into the cells)
     - Insulin also can **stimulate lipogenesis, decrease lipolysis and increase amino acid transport into the cells to synthesis proteins**
  2) Long term (the effect of insulin on enzyme synthesis)
     - Insulin can **Modulates transcription** (the conversion of DNA to mRNA) so insulin can **change the mRNA level and there for affect the level of enzymes**
     - Insulin can **stimulate growth** (remember insulin is anabolic), **DNA synthesis and cell replication**

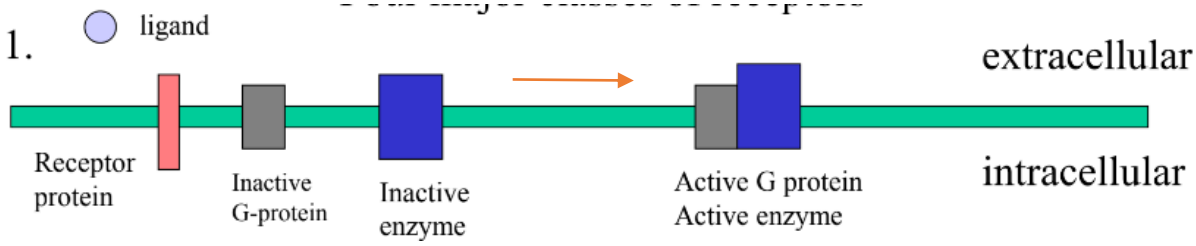
Ligands and receptors binding



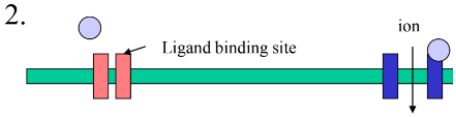
- Receptors can be mainly divided into 2 main subtypes based on their location:
  1) **Intracellular receptors**: located inside the cell, they can bind to a **hydrophobic ligand** such as **testosterone**
  2) **Extra cellular (cell surface) receptors**: located on the cell surface, they can bind to **hydrophilic ligands** such as **Insulin**
- Binding of ligands to receptors elicit a variety of cellular changes that affect the cell

Types of extracellular cell surface receptor

- Before we talk about the types you have to remember that the **phosphorylation of a protein (or enzyme) can make it active or inactive**
  - **Kinases** is an enzyme that phosphorylates proteins
  - **Phosphatase** is an enzyme that dephosphorylate proteins, and counter act the effect of kinases
- There are 3 major subgroups of extracellular receptor
  1) G-protein coupled receptor (GPCR)
     - They are an integral membrane protein
     - Binding of a ligand to the receptor will lead to activate the G protein (multisubunits).
     - G protein will activate a certain enzyme that will initiate a response inside the cell

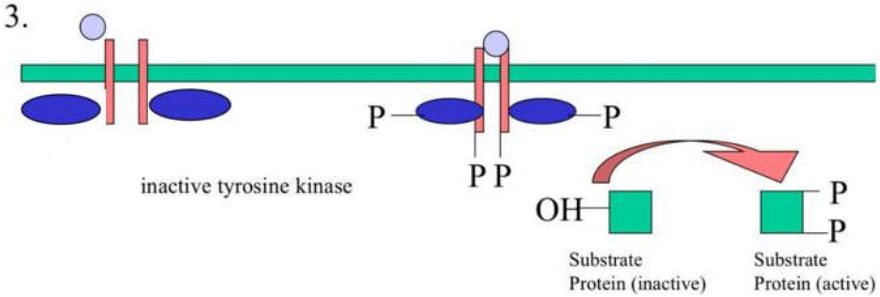


  2) Ion-channel receptors
     - Binding of a ligand to the receptor will lead to **open the ion channel**



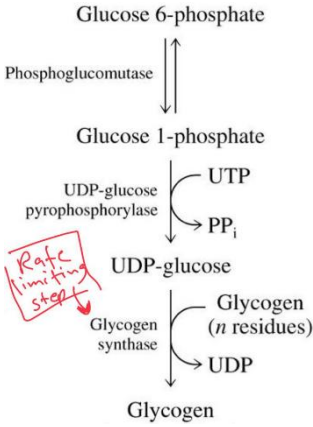
- Ions will enter the cell and will change the cell response

3) Tyrosine kinase linked receptor (Insulin receptor)
   - These receptors intracellular domains have **tyrosine kinase activity** that is inactive
   - When the ligand bind, the 2 tyrosine kinases **become active** and will cross **phosphorylate each other and the tyrosine residues on the intracellular domains of the receptor**
   - The phosphorylated receptor will **phosphorylate a substrate protein and activate a cellular response**

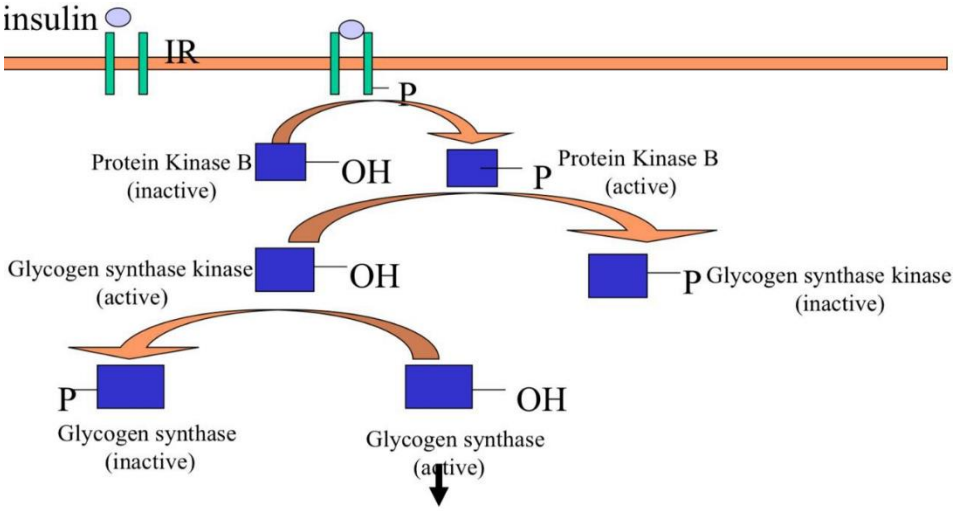


Role of signal transduction in carbohydrate metabolism

- Eating a carbohydrate rich meal (**well fed state**)→ high glucose plasma concentration → this will **induce the release of insulin** from pancreatic β cells → insulin **increase glucose transporter** on the cell surface → glucose **will shift from plasma to inside the cells** → inside the cells, **insulin will induce the utilization and storage of glucose as glycogen** → any excess glucose **will be converted to lipids (lipogenesis)** by insulin as well
- The figure to the right is a glycogen synthesis pathway and as you can notice that **glycogen synthase** is the **rate limiting step**
   - Insulin **will activate glycogen synthase** (rate limiting step) so our cells can convert glucose to glycogen for storage, but how can insulin (which is an **extracellular** ligand) activate glycogen synthase (which is an intracellular enzyme)?



   - ➢ Insulin bind to its extracellular receptor → activation of the intrinsic tyrosine kinase of the receptor → tyrosine kinase will phosphorylate the tyrosine residues of the receptor → **protein kinase B will be phosphorylated and activated** → active protein kinase B will **phosphorylate and inhibit glycogen synthase kinase** → inhibited glycogen synthase kinase **will not phosphorylate and will not inhibit glycogen synthase** → glycogen synthase **will stay active and synthesis glycogen**
   - ➢ **Glucagon** (one of the counter regulatory hormones) **act the exact opposite of insulin** so it will lead to **inhibition of glycogen synthase and inhibition of glycogen synthesis**
   - ➢ You have to remember that when glycogen synthase kinase and glycogen



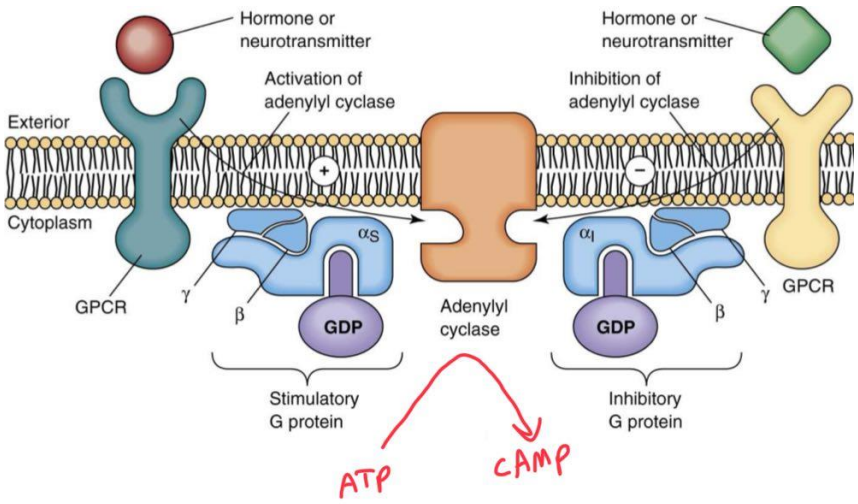
synthase are **phosphorylated they are inhibited**

- Note: signaling is involved in so many functions of the body such as Vision, Sense of smell, Behavioral and mood regulation (GPCRs in brain bind to neurotransmitter), Regulation of immune system, Autonomic nervous system (GPCRs regulate autonomic functions like blood pressure, heart rate and digestive system).
  Orphan receptor: are **GPCRs whose ligands aren't known**

Second messenger

- They are molecules that **intervene** between the **chemical signaling** (ligand such as hormone) and the **intracellular response**. We will talk about cAMP and Ca^{+2} as a second messengers

1) **cAMP**
   - It's a second messenger **for GPCRs**
   - As we said binding the ligand to GPCRs will activate the G protein
   - G proteins can be **stimulatory or inhibitory**
   - Stimulatory G protein will **activate the adenylate (adenylyl) cyclase** → adenylate cyclase will **convert ATP to cAMP** → cAMP will affect the response of the cell
   - Inhibitory G protein **will inhibit the adenylate (adenylyl) cyclase** → adenylate cyclase **will not convert ATP to cAMP** → cAMP will decrease



2) **Ca^{+2}**
   - Ca^{+2} is a versatile second messenger
   - All eukaryotes use Ca^{+2} signaling
   - Regulates many processes
   - Ca^{+2} levels are controlled by release and removal from its storage in the cell