بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Lecture 10

Carbohydrates Metabolism pt.2 & Glycolysis pt.1

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Rawan Okour

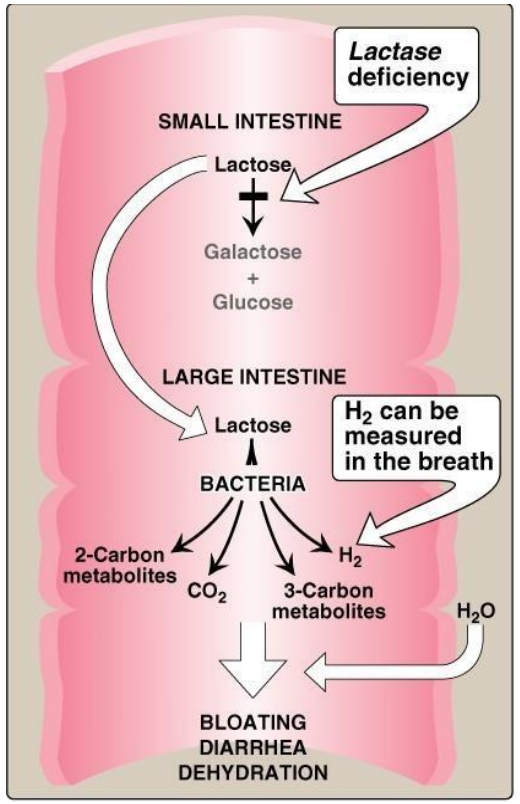
Reviewed by : Hashem Alhalalmeh

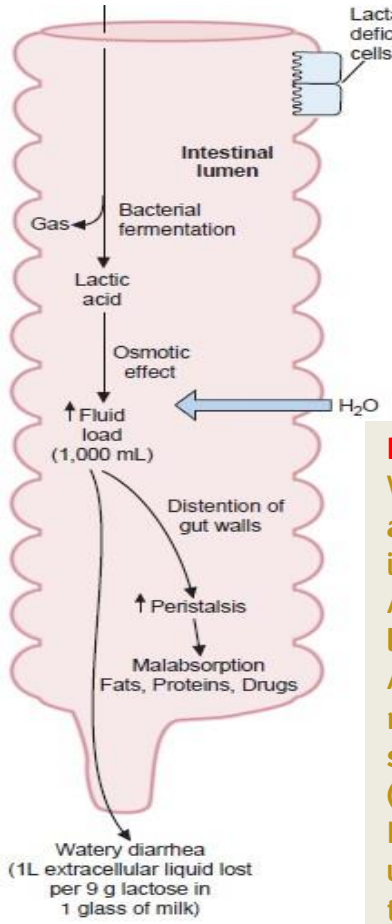
Clinical Hint: Abnormal Degradation of disaccharides

وَمَا تَوْفِيقِيٓ إِلَّا بِٱللَّهِ
عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ

2. Lactase deficiency: ½world's population

- ✓ Lactase reached maximal activity @ 1 month of age
- ✓ Declines ----- >> adult level at 5 to 7 year of age
- ✓ 10 % of infant level
- ✓ 1 cup of milk (9 grams of lactose) → loss of 1 liter of extracellular fluid , which is a significant amount.





At birth, newborns have active lactase enzyme levels that increase until they reach a maximum around **one month of age**, since **milk is their only source of sugar**.
After infancy, lactase activity gradually declines – beginning around **six years of age** – until it reaches the **adult level**, because the diet becomes more diversified and less dependent on milk.

In some individuals, **lactase enzyme activity decreases** over time more than in others. This leads to **inefficient lactose digestion**.
Approximately **50% of the world's population** has some degree of lactase deficiency.

Mechanism of lactose intolerance
When lactose is not completely digested, it **accumulates in the small intestinal lumen**, increasing **osmotic pressure**.
As a result, **water is drawn into the intestinal lumen**, leading to **osmotic diarrhea**.
Additionally, **intestinal bacteria (normal flora)** metabolize the excess lactose, producing **gases such as methane (CH_4) and carbon dioxide (CO_2)** – causing **bloating and discomfort**.
Note: Newborns rarely have lactase deficiency unless caused by a **rare genetic mutation**; typically, it develops **gradually with age**

Some people can consume dairy products without symptoms because **fermentation or enzymatic treatment (during dairy processing)** reduces lactose content in products like cheese or yogurt.

Drinking more milk **does not solve the problem**, as the enzyme itself is lacking.
Milk provides **calcium and vitamin D**, but to meet vitamin D needs through milk alone, one would have to drink **about 10 liters per day**, which is unrealistic & inefficient.
People with intolerance can use **lactose-free products**, **lactase enzyme supplements**, or **avoid milk** altogether.
Missing nutrients such as **calcium (Ca^{2+})** and **vitamin D** can be compensated by **dietary supplements** or **increased exposure to sunlight**.

To have the needed amount of vitamin D you would drink 10 L per day which is impossible … you don't even drink this amount of water

Lactose intolerance vs. milk allergy

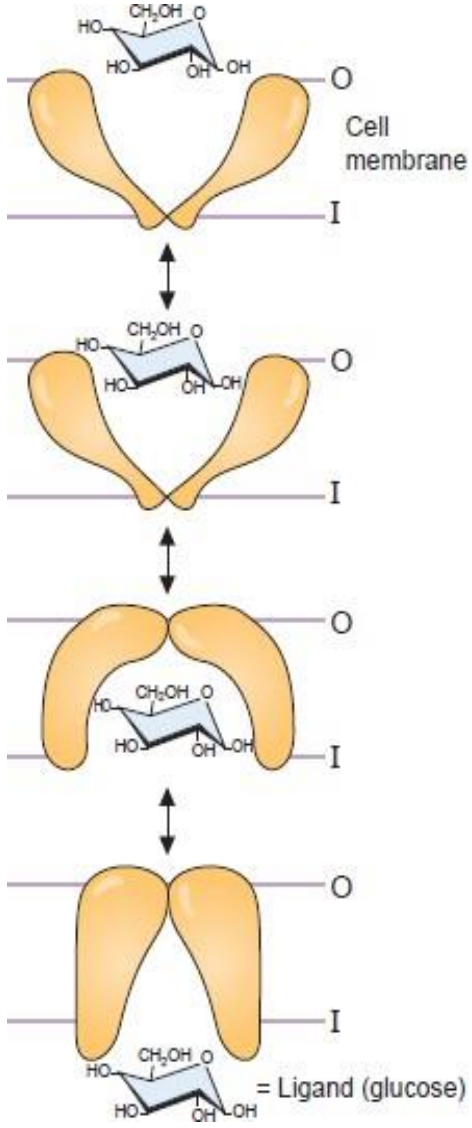
- **Lactose intolerance:** due to **enzyme deficiency** (lactase).
- **Milk allergy:** an **immune reaction** to one or more **proteins\ components** in milk, not related to lactose

Diagnosing milk allergy in newborns is difficult, so doctors often use **elimination diets** (for the mother so, her milk composition will change) or **special formulas** for allergic infants .
Some children **outgrow** this allergy, while others may **remain allergic for life**.

Absorption of Sugars

- ✓ Polar molecules cannot diffuse
- ✓ Na^+-independent facilitated diffusion transport → Carrier or transporter no energy need
- ✓ GLUT 1-----GLUT 14 each found in different tissues and specialized for certain sugars, and they are not exclusive to glucose
- ✓ Glc. Movement follows concentration gradient

- ✓ Two conformational states
- ✓ **Glucose transporter inhibitors** are used to decrease sugar transport detected in many types of cancer because the expression of these transporters in upregulated in cancer.



After digestion

By the end of carbohydrate digestion, all polysaccharides and disaccharides are broken down into monosaccharides – mainly **glucose, galactose, fructose,** and **mannose.**

These monosaccharides are absorbed into intestinal epithelial cells through **specific transport proteins** located on the cell membrane.

- Transport occurs **down the concentration gradient** (from high to low concentration).
- When the sugar concentration in the **intestinal lumen** is higher than inside the cell, glucose moves **into the cell**.
- If the gradient reverses (higher glucose inside the cell), **the direction of transport can also reverse** until equilibrium is reached.
- **No energy (ATP) is required** for this process.

Absorption of Sugars

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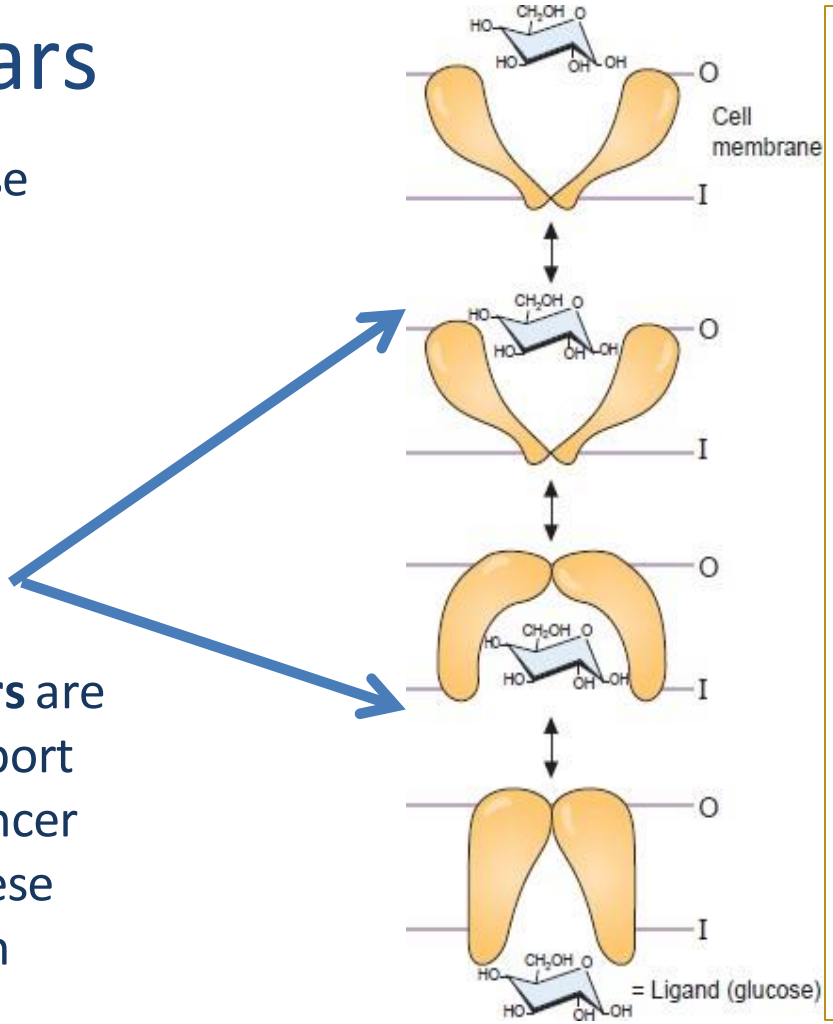

Conformational States of GLUT Transporters

- GLUT transporters function through **two alternating conformations**:
- **Outward-open state:** faces the **intestinal lumen**. The transporter binds to a sugar molecule when it encounters one.
- **Inward-open state:** after sugar binding, a **conformational change** occurs – the lumen side closes while the **cytosolic side opens**, releasing the sugar into the cell.
- After releasing the sugar, the transporter returns to its **original (outward-open)** form, ready to bind another molecule.
- This process follows a **dynamic model**, where the transporter continuously shifts between the two states depending on sugar concentration and binding orientation.
- GLUT transporters can mediate **both influx and efflux** of sugars, depending on the concentration gradient, rather than only importing sugars into cells.

- **Cancer cells** are often referred to as **metabolically opportunistic** because they have an **increased demand for glucose** to support rapid growth and metabolism.
- They achieve this by **overexpressing GLUT transporters** on their surface, allowing them to **take up large amounts of glucose** for energy production and biosynthesis.
- **GLUT inhibitors** block glucose entry into cells.
- These inhibitors affect **all body cells**, but their effect is **stronger on cancer cells** due to the higher number of GLUTs on their membranes.
- As a result, GLUT inhibitors are being studied as **potential anti-cancer therapies** that target the enhanced glucose metabolism of tumor cells.

Table 27.5 Properties of the GLUT 1 to GLUT 5 Isoforms of the Glucose Transport Proteins

Transporter	*Tissue Distribution*	*Comments*
GLUT 1	Human erythrocyte Blood–brain barrier Blood–retinal barrier Blood–placental barrier Blood–testis barrier	Expressed in cell types with barrier functions; a high-affinity glucose transport system
GLUT 2	Liver Kidney Pancreatic β-cell Serosal surface of intestinal mucosa cells	A high-capacity, low-affinity transporter May be used as the glucose sensor in the pancreas
GLUT 3	Brain (neurons)	Major transporter in the central nervous system; a high-affinity system
GLUT 4	Adipose tissue Skeletal muscle Heart muscle	Insulin-sensitive transporter. In the presence of insulin, the number of GLUT 4 transporters increases on the cell surface; a high-affinity system
GLUT 5	Intestinal epithelium Spermatozoa	This is actually a fructose transporter
GLUT 7	Glucogenic tissues	at endoplasmic reticulum membrane

Highly expressed in barriers. Barriers are made of tight junctions between endothelium cells.

Glucose, galactose and fructose

(Basolateral surface)

Fructose

Na independent

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The blood–brain barrier, with its tight junctions between endothelial cells, forms a selective barrier preventing the free flow of molecules from the blood to the brain, thus maintaining its independence. Although not found in neurons, GLUT1 plays a vital role in transporting glucose across this barrier, as sugars are the main source of energy for the brain, without which brain death may occur.

The most common and most metabolic pathways are specifically designed to handle it but that doesn't mean they can't process others.

GLUT 1 can transport sugars other than glucose, but glucose is the preferred and physiologically relevant substrate.

Glucose, galactose and fructose

Non- specific

(Basolateral surface)

When there is a high concentration of glucose, this transporter is activated by the presence of insulin. As insulin increases, it binds to its receptor, activating a signaling pathway. One of the responses activates the transcription factor that activates the expression of a specific target, GLUT4.

Not for energy but for absorption

Specific for Fructose

Na independent

GLUT 7

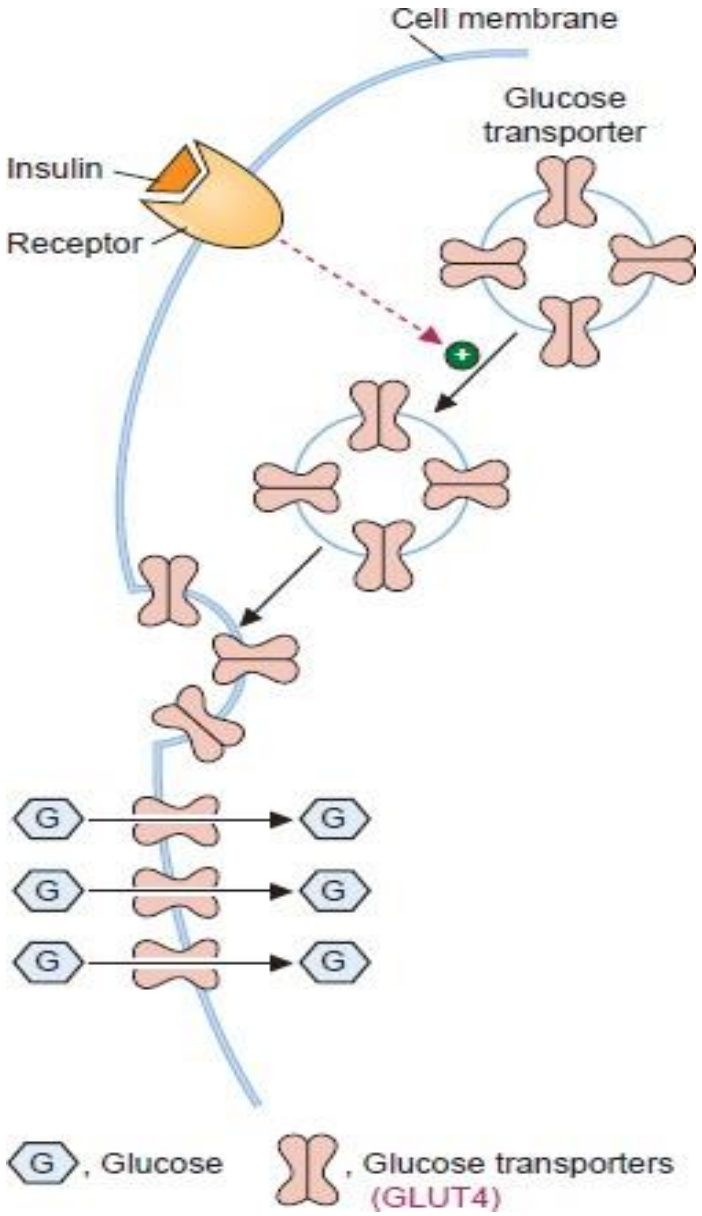
Glucogenic tissues

at endoplasmic reticulum membrane

facilitates the final step of glucose synthesis (gluconeogenesis) in the endoplasmic reticulum, allowing the produced glucose to exit to the cytosol.

Sperms Depends on fructose rather than glucose, even if there's only glucose it will be converted to fructose

(signal → vesicles → fusion → uptake → internalization).



Insulin stimulates transport of glucose into muscle and adipose tissues

- **Insulin** binds to its **receptor** on the cell membrane of **skeletal muscle** and **adipose tissue**.
- This activates a **signal transduction pathway** inside the cell.
- The signaling cascade stimulates **GLUT4-containing vesicles** to **move toward and fuse with the plasma membrane**.
- Fusion of these vesicles increases the **number (or concentration) of GLUT4 transporters** on the cell surface.
- As a result, the **rate of glucose uptake** into the cell rises.
- When insulin levels decrease, **GLUT4 transporters are internalized** again, reducing glucose entry.

Na^+ monosaccharide cotranspoerter system (SGLT)

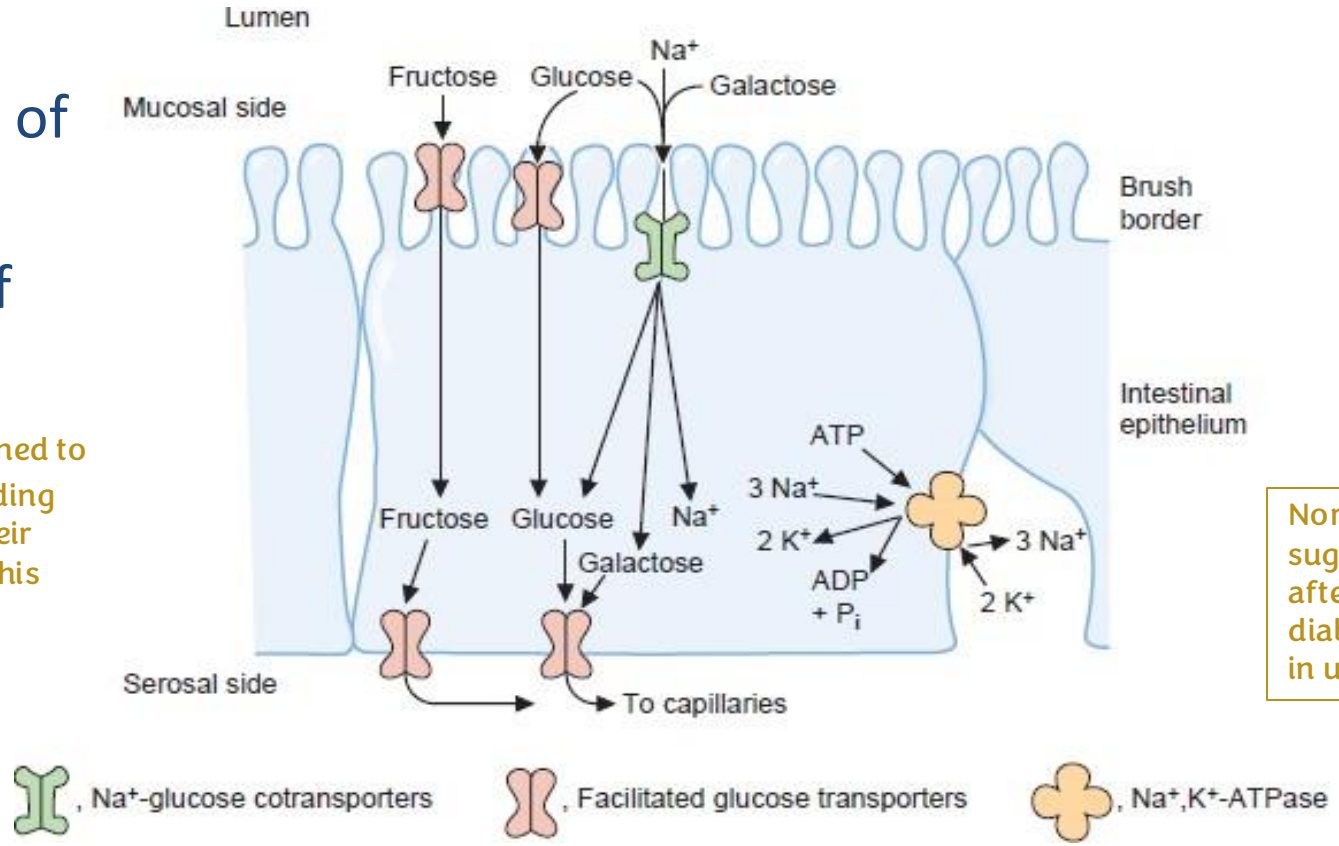
Why?
To ensure efficient glucose absorption; as most of glucose inside the cells is transported by GLUT4

- Against concentration gradient (requires energy).

* Small intestine:

Active uptake from lumen of intestine.

- Kidney: reabsorption of glucose in proximal tubule.(The fluid in the kidney destined to become urine contains substances, including sugar, that are **reabsorbed** even when their concentration is lower than in the cells. This **requires SGLT transporters**.)
- For glucose and galactose absorption



GLUTs are widely distributed and expressed in different cell types While SGLTs are limited (inside the small intestine and kidney)

Normal person won't have sugar in their urine (very little) after urine analysis test , but diabetic person will have sugar in urine

- SGLT inhibitors (**gliflozins or flozins)**, are a class of antidiabetic agents that promote renal glucose excretion independently of insulin.

They're made to treat diabetes , when we inhibit SGLT; more sugar in urine, so the sugar levels in blood decrease

The observed repurposing of SGLT inhibitors for cancer treatment yielded promising results, paving the way for this approach to cancer therapy. It also shortened the extensive scientific research process, which usually takes a long time before a drug gains approval and becomes widely available.

1. Intestinal Cell Polarity: Apical surface faces lumen (nutrient absorption); Basolateral surface faces blood/lymph (export); Transporters restricted to respective surfaces to maintain directional absorption.

2. GLUT (pink transporter): Facilitates diffusion of glucose, fructose, and other monosaccharides; Present on both apical and basolateral surfaces; Works down concentration gradient; Early absorption can rely on GLUT alone.

3. SGLT (green transporter): Sodium-glucose co-transporter (Na^+-dependent); Only on apical surface (brush border); Transports glucose against concentration gradient; Coupled with Na^+, which can disturb membrane charge; Linked to Na^+/K^+ pump (exports Na^+, ATP used indirectly; energy not in SGLT itself).

4. Transport Flow: Glucose enters cell via SGLT (active) or GLUT (passive, early stage); Exits via GLUT (basolateral) into blood/lymph; SGLT ensures full absorption when luminal glucose drops.

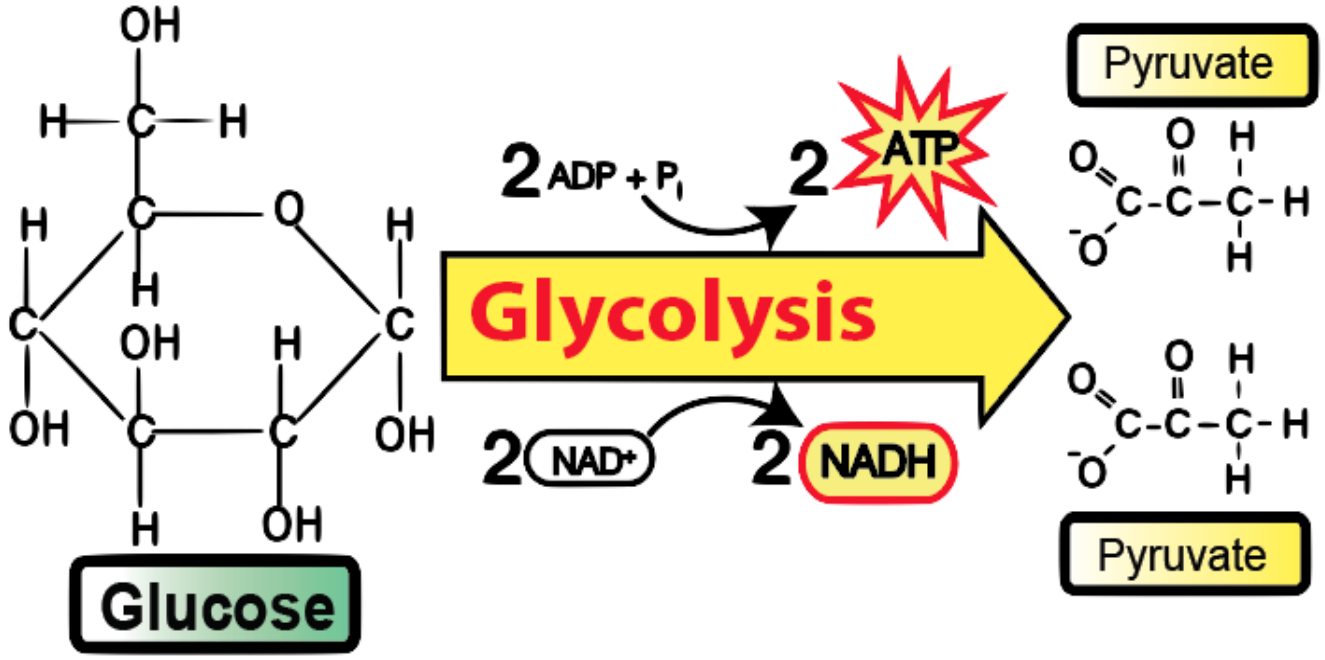
5. Functional Rationale: Apical SGLT absorbs glucose against low lumen concentration; Basolateral GLUT exports efficiently; Na^+ gradient maintenance is critical for SGLT function.

Urine Findings in Nephrotic Syndrome:

In nephrotic syndrome, kidney damage causes the filtration barrier to become abnormally permeable, allowing large molecules such as proteins to pass into the urine. Proteinuria (the presence of protein in urine) is therefore a key diagnostic feature and is typically much more significant than the presence of glucose. **Glycosuria** (glucose in urine) may occur, but it is usually associated with uncontrolled diabetes mellitus rather than nephrotic syndrome. In contrast, **elevated creatinine levels** in blood tests reflect impaired kidney filtration and help assess the degree of renal dysfunction. Overall, proteinuria is the most characteristic urinary finding in nephrotic syndrome.

وَإِن تَعُدُّوا نِعْمَةَ اللَّهِ لَا تُحْصُوهَا

Glycolysis
Reactions and Regulation



Dr. Diala Abu-Hassan

sciencemusicvideos

General Stages of Metabolism

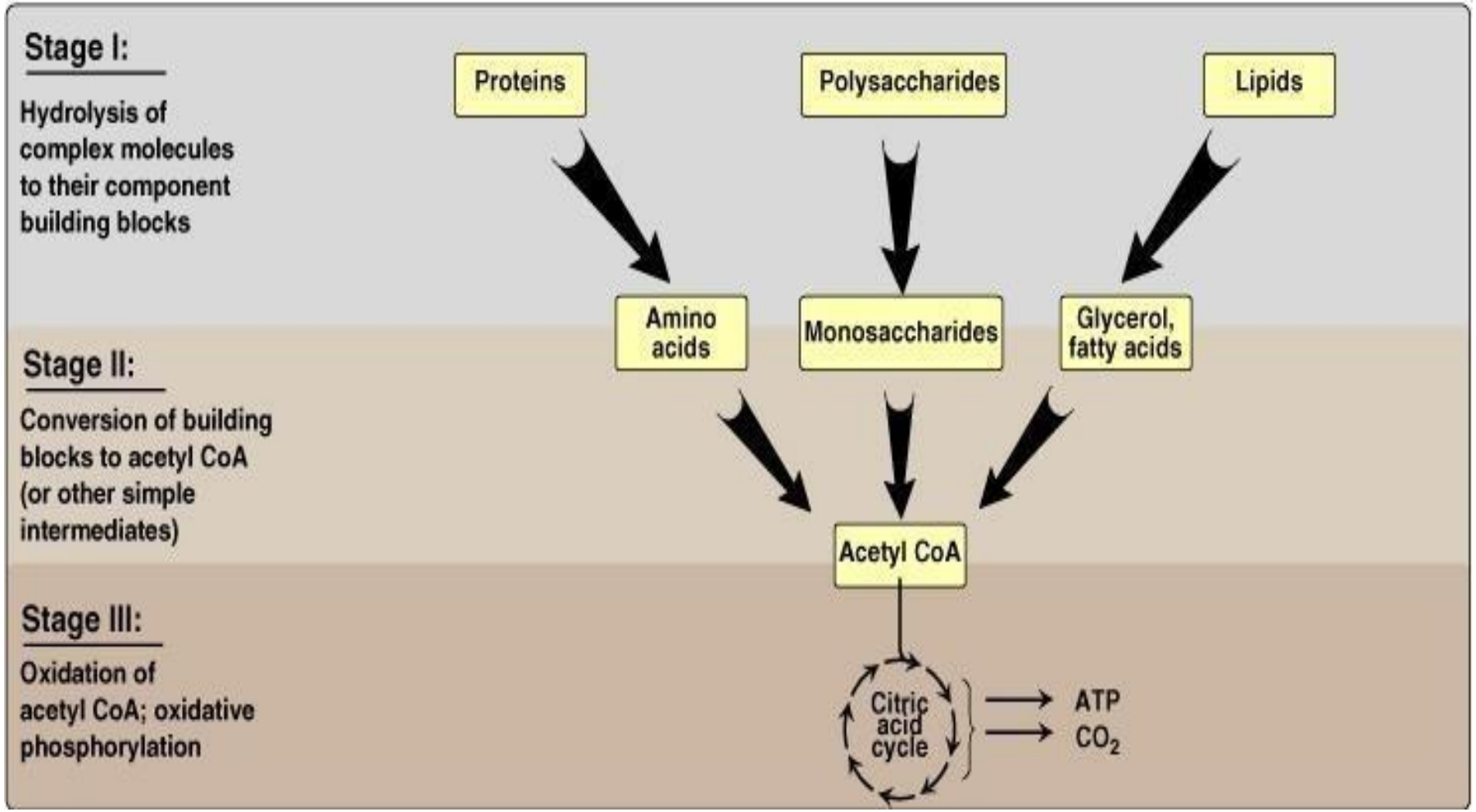
What is the difference between digestion & metabolism?

- **Metabolism** is a general term that contains the **Catabolic** (Breaking down) and **anabolic** reactions (building up).

- **Digestion** means the breaking down of molecules coming **from diets.**

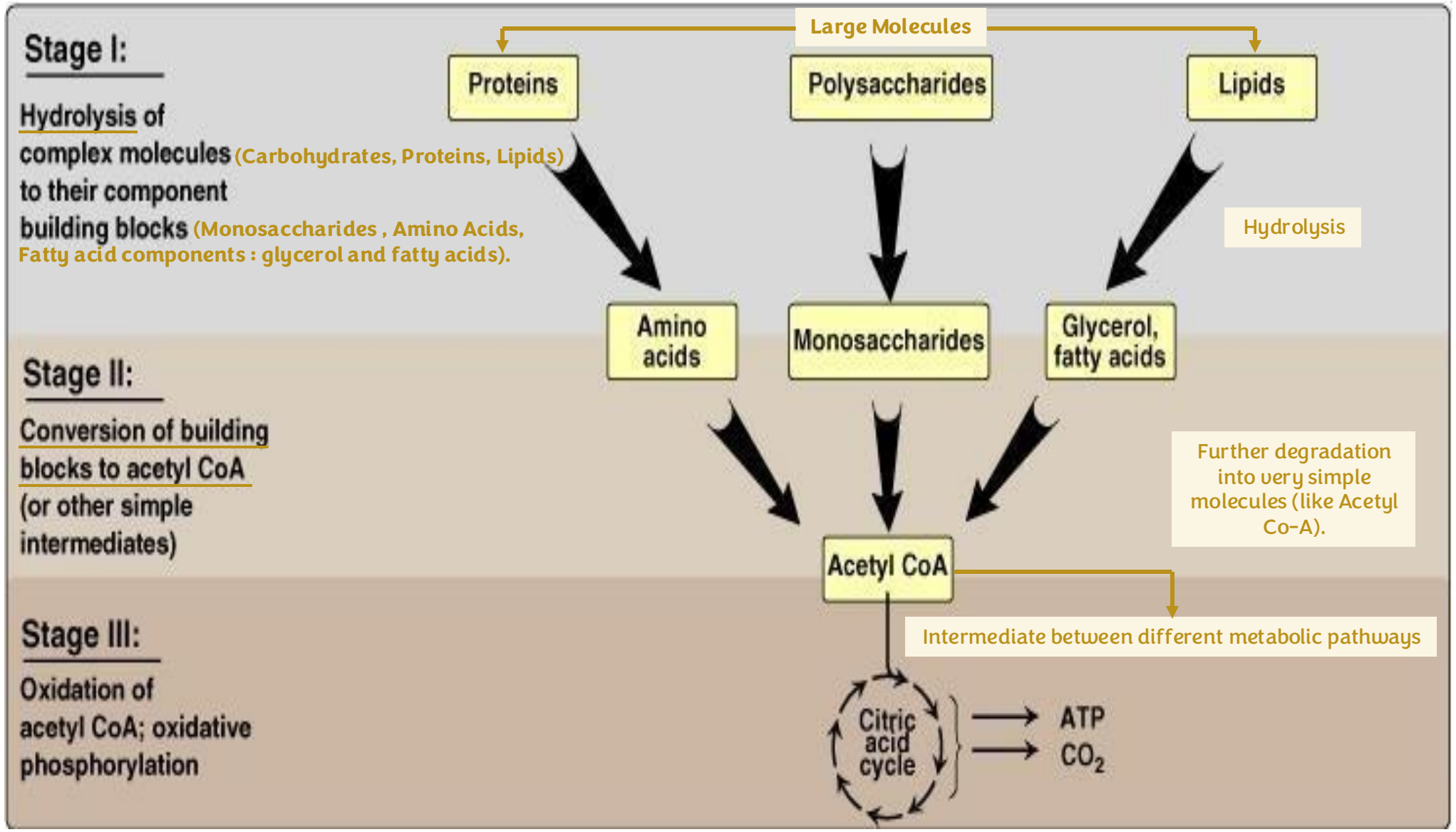
- In **metabolism catabolic reaction** we could break down molecules and substances **that are not from diets** (molecules that have been **synthesised within our body).**

- The goal of **digestion** is to simplify the molecules coming from diets into an **absorbable form.**



- The goal of **metabolism catabolic pathways** is to **break down** molecules into a **non-degradable molecules (like CO2,H2O,etc).**

General Stages of Metabolism



Glycolysis – The Central Energy Pathway

1. Universal Role

- Occurs in **all cells** to produce energy.
- **Primary energy source:** carbohydrates are metabolized first;
- lipids and proteins are used only when carbohydrates are absent.

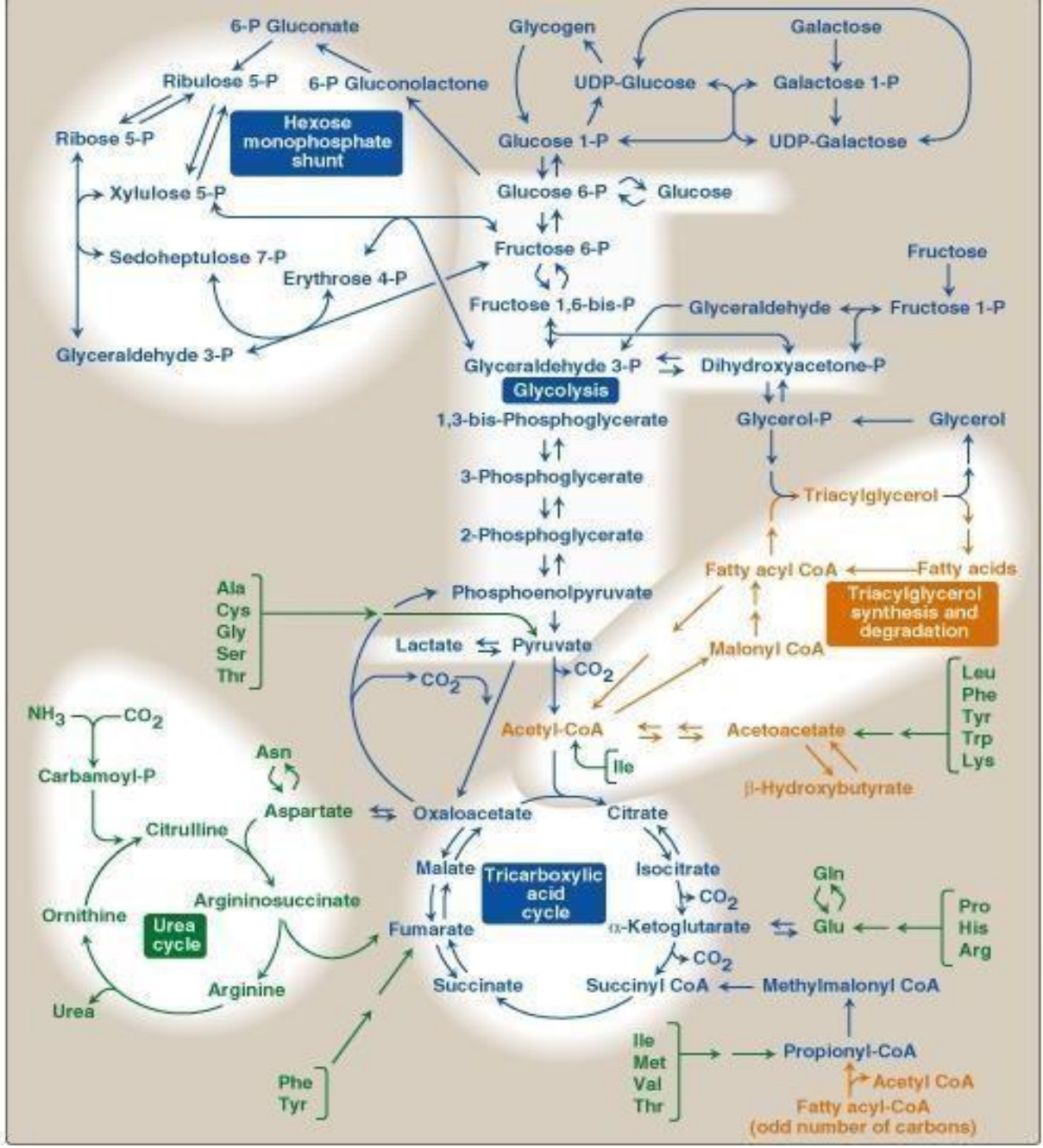
2. Glycolysis as a Metabolic Hub

- Acts as an **intersection point** connecting multiple pathways.
- Interacts with:
- **Other monosaccharides:** fructose, galactose metabolism feeds into glycolysis.
- **Glycogen metabolism:** breakdown and synthesis of glycogen are linked to glycolytic intermediates.
- **Pentose phosphate pathway (hexose monophosphate shunt):** produces NADPH and pentose sugars; glycolysis provides intermediates.
- **Lipid metabolism:**
- Fatty acids → acetyl-CoA → TCA cycle
- (Separate from glycolysis; lipid carbons enter TCA directly via acetyl-CoA)
- **Amino acid metabolism:**
- Some amino acids → acetyl-CoA or TCA intermediates
- Links to the **urea cycle** (ammonia → urea), it can interact with the amino acids metabolized in this cycle

3. Key Concept

- **Metabolic integration:** glycolysis is not isolated; it connects carbohydrates, lipids, amino acids, and nucleotide metabolism.

What's important to understand is that all these pathways are deeply integrated. They communicate through shared intermediates—molecules present in more than one pathway—allowing one pathway to influence another. This crosstalk ensures that metabolism is flexible and coordinated, adjusting to the cell's energy and biosynthetic needs. We will study each pathway in detail later, but the key takeaway now is that metabolism is a complex, interconnected network rather than isolated processes.



Metabolic pathways intersect to form network of chemical reactions

- The Metabolic pathways are **complex** and **integrated with each** other.

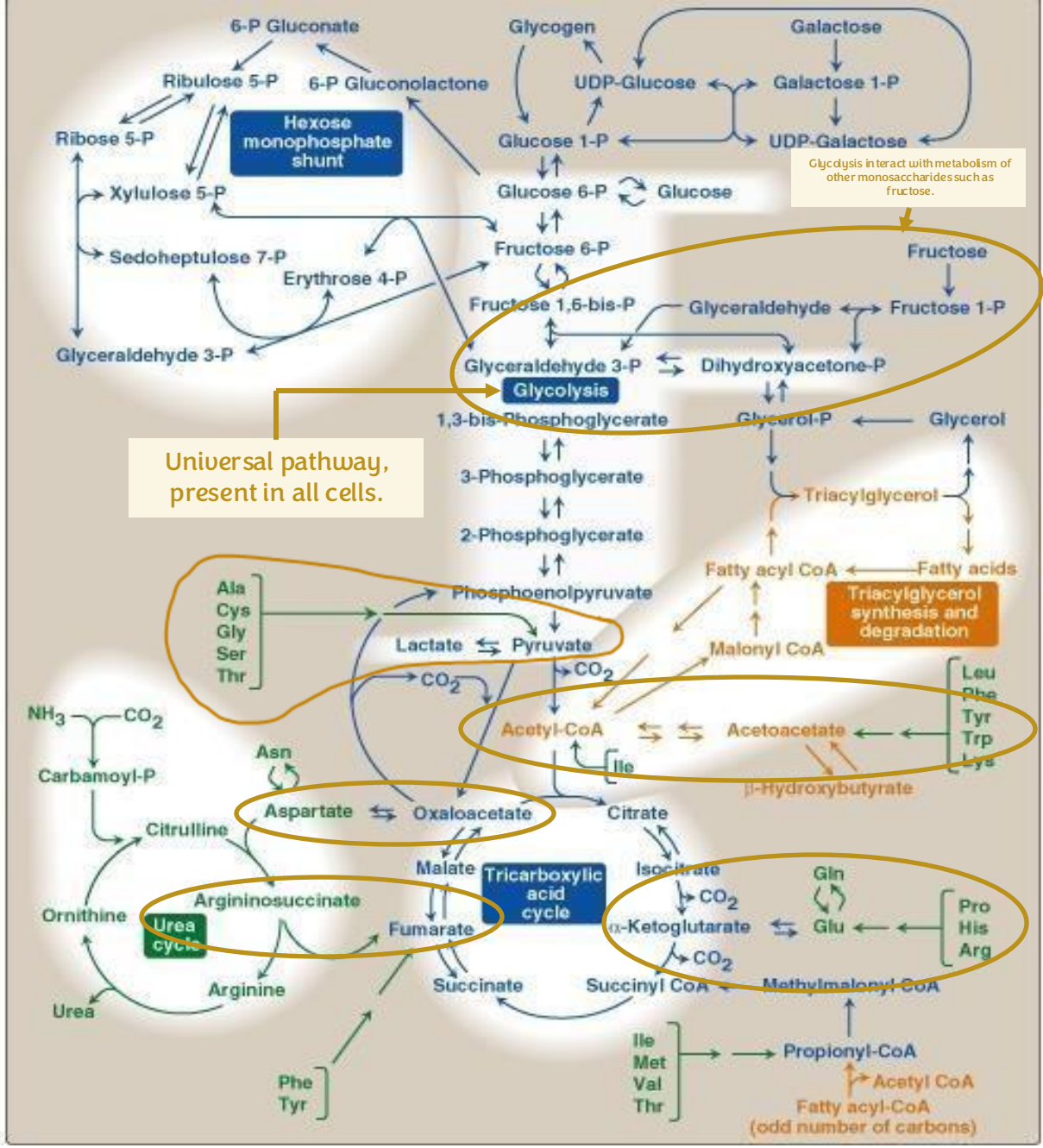
➢Examples of integration between different pathways:

⑩Excess **citrate** from the TCA cycle can be used for **fatty acid synthesis** in lipid metabolism.

⑩Excess **oxaloacetate** from the TCA cycle can contribute to the formation of **aspartate**, an amino acid used in protein synthesis.

⑩Excess **fumarate** from the TCA cycle can participate in the synthesis of **arginine**, another amino acid used in protein synthesis.

- If we have excess amounts of **glucose (glycolysis metabolic pathway)**, it can participate in the formation of **glycogen (glycogenesis metabolic pathway)**.



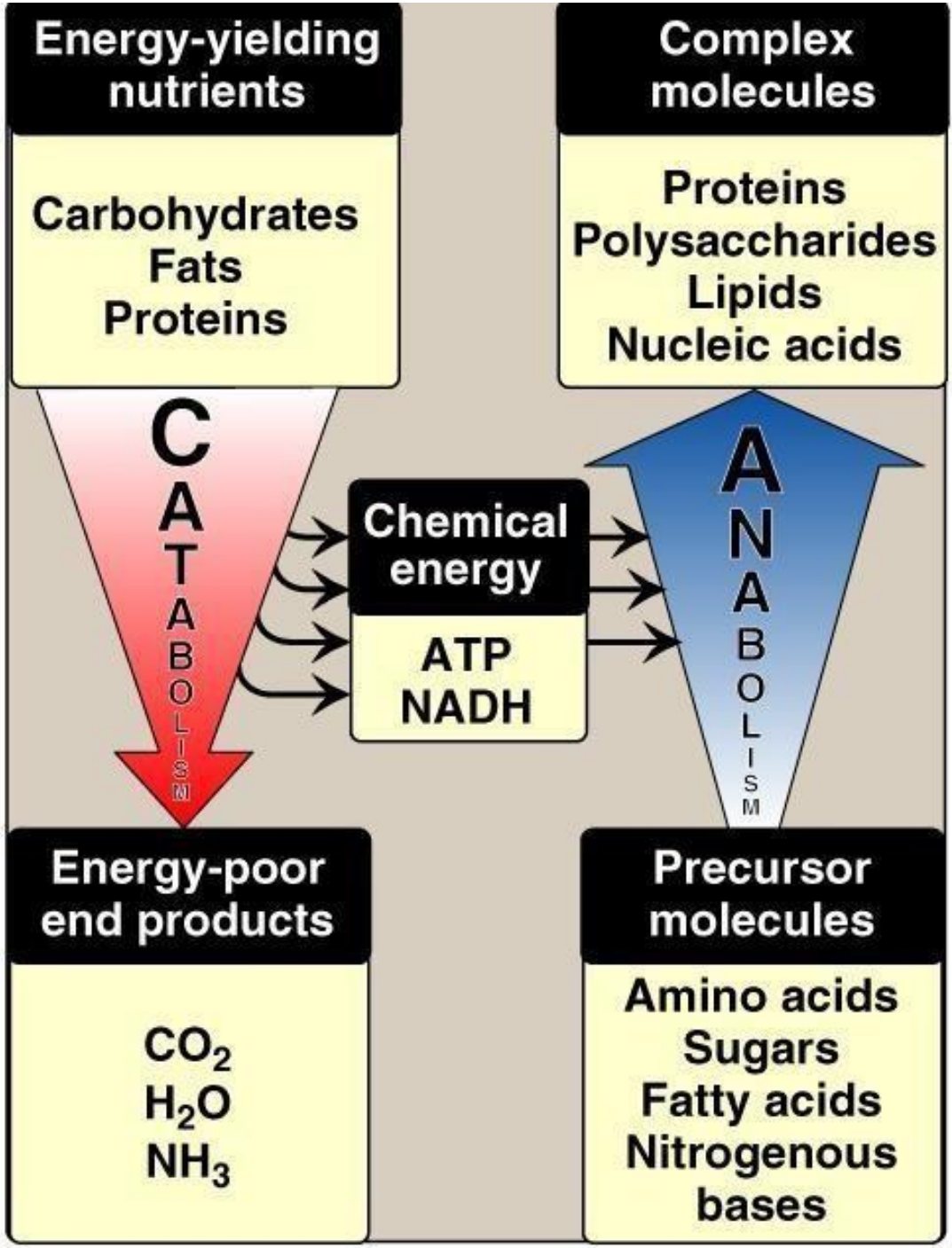
Types of Metabolic Pathways

- **Catabolic pathways :** are oxidation-reduction pathways that include the oxidation of the molecules (energy yielding nutrients) with the reduction of Coenzymes (usually NAD+), and the production of energy.

- The final products of catabolic pathway are poor in terms of energy.

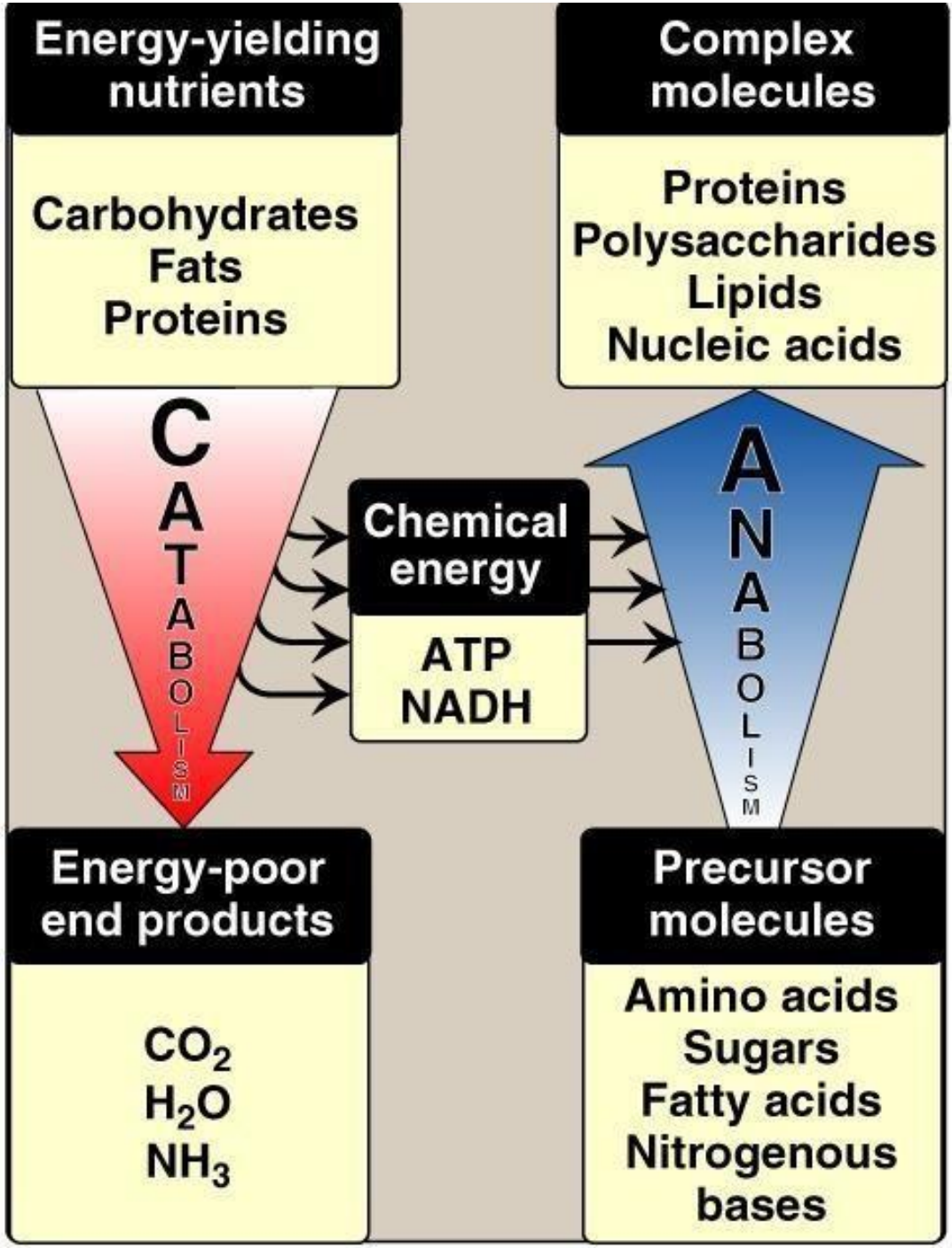
- **Anabolic pathways :** are oxidation-reduction reactions that include the oxidation of the Coenzymes and the reduction of the molecules (opposite to catabolic pathways) it involves the usage of energy to build up more complex mol from simpler ones, and mainly NADH isn't used here but rather NADPH.

- The final product of the anabolic pathways are more complex molecules.



Catabolism is the process of breaking down large molecules into smaller ones. During this breakdown, the chemical energy stored in the bigger molecules is released and captured in the form of ATP, which cells use directly for energy, and in molecules like NADH, which carry electrons and can later be used to generate more ATP through the electron transport chain. Essentially, catabolism is the body's way of extracting usable energy from complex molecules.

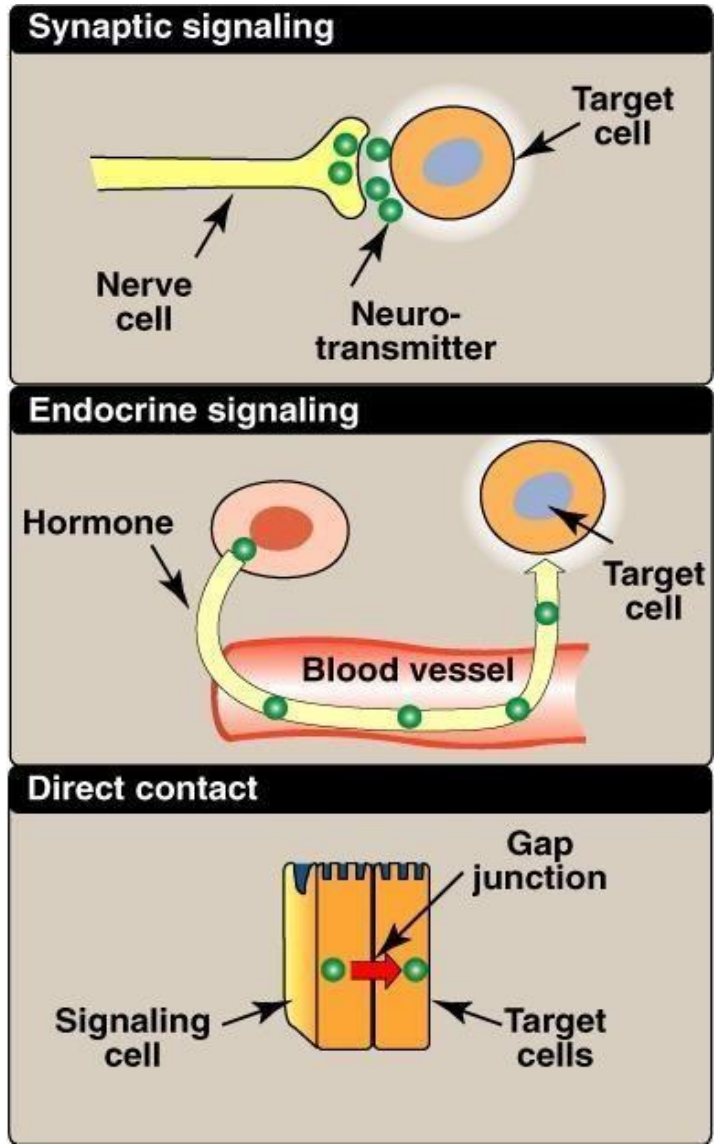
Anabolism is essentially the opposite of catabolism. It's the process of building larger, complex molecules from smaller ones, such as forming proteins from amino acids or glycogen from glucose. This process requires energy, which comes from ATP and reducing power carried by molecules like NADPH. Anabolism allows the cell to grow, repair, and store energy, turning the energy harvested from catabolism into new cellular structures and macromolecules.



Regulation of Metabolism

➢ **The regulation of the metabolism be from :**

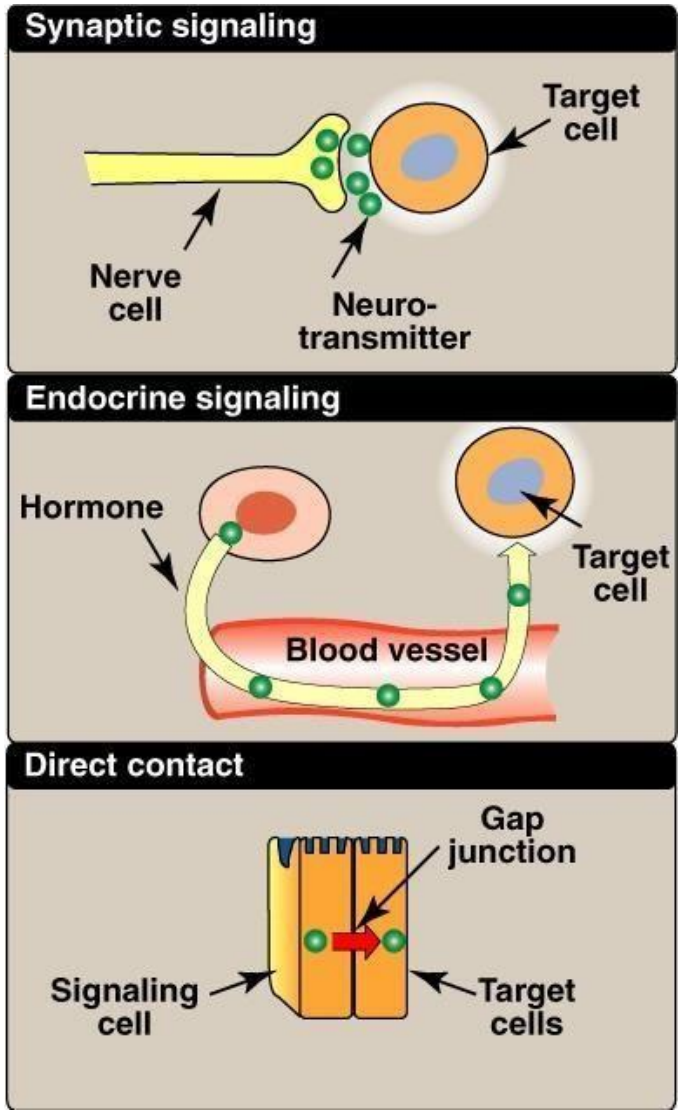
- Signals from within the cell :
  - Concentration and activation of the enzyme, substrate availability and concentration, product inhibition, allosteric & non-allosteric regulation (inhibition and activation).
  - Properties: Rapid response, moment to moment.



Commonly used mechanisms of communication between cells

Regulation of Metabolism

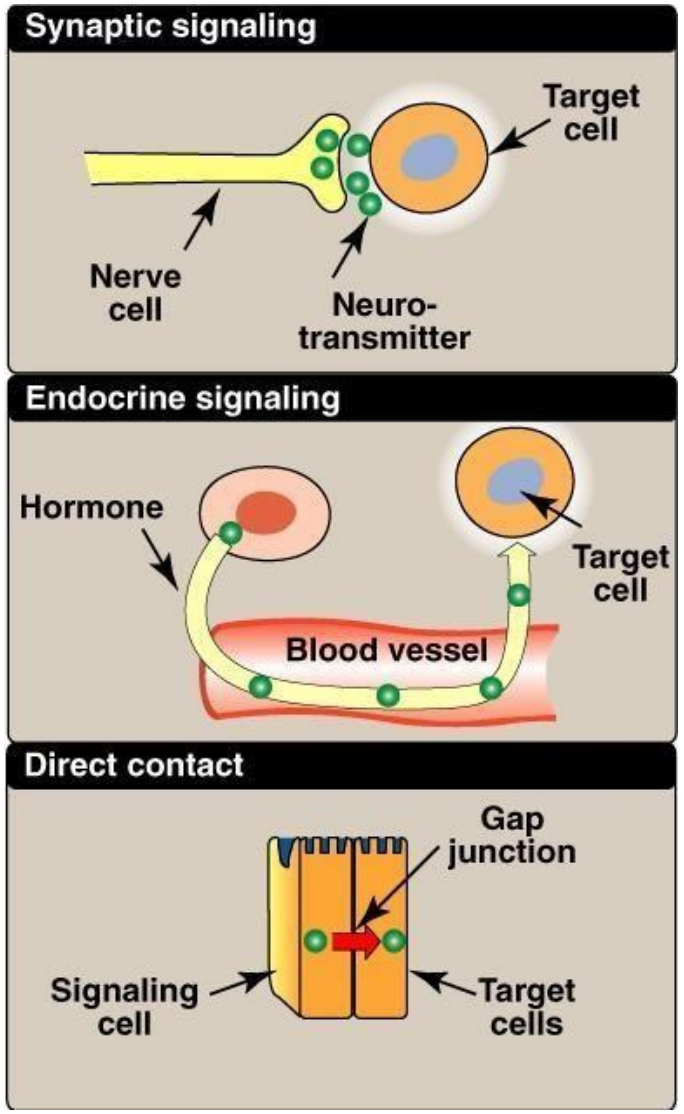
- Communication between cells (intercellular) :
  - **Synaptic signals** : Neurotransmitters released at synapses can stimulate anabolic or catabolic processes, affecting energy production or consumption, it might be a signal inducing cell movement which requires energy (glucose degradation).
  - **Endocrine signalling** : hormones that are secreted by endocrine glands and are transmitted to the target cell through the blood stream, once it binds to a target cell receptor it induces a response that affects metabolism.
  - **Direct contact:** Direct contact via **gap junctions** connecting adjacent cells, more abundant in epithelial cells, gap junctions only allow small molecules to be transferred (1000 Dalton at max), like H2O, gases or amino acids
  - Properties : Slower response, longer range integration.



Commonly used mechanisms of communication between cells

Regulation of Metabolism

- Second messenger :
  - Some extracellular signals bind surface receptors but require a second messenger to transmit the signal to intracellular effectors and induce a response.
  - We need a **polar** molecule that can go and **transmit** the signals from the membrane to the effector and induce the response. (this molecule is called **The Second Messenger**). The first messenger is the **hormone** or the ligand itself.
  - Ca^{2+} / phosphatidylinositol system (Second messengers : IP3 & DAG, each one of them is a second messenger for a different pathway).
  - Adenyl cyclase system (Second messenger : cAMP).



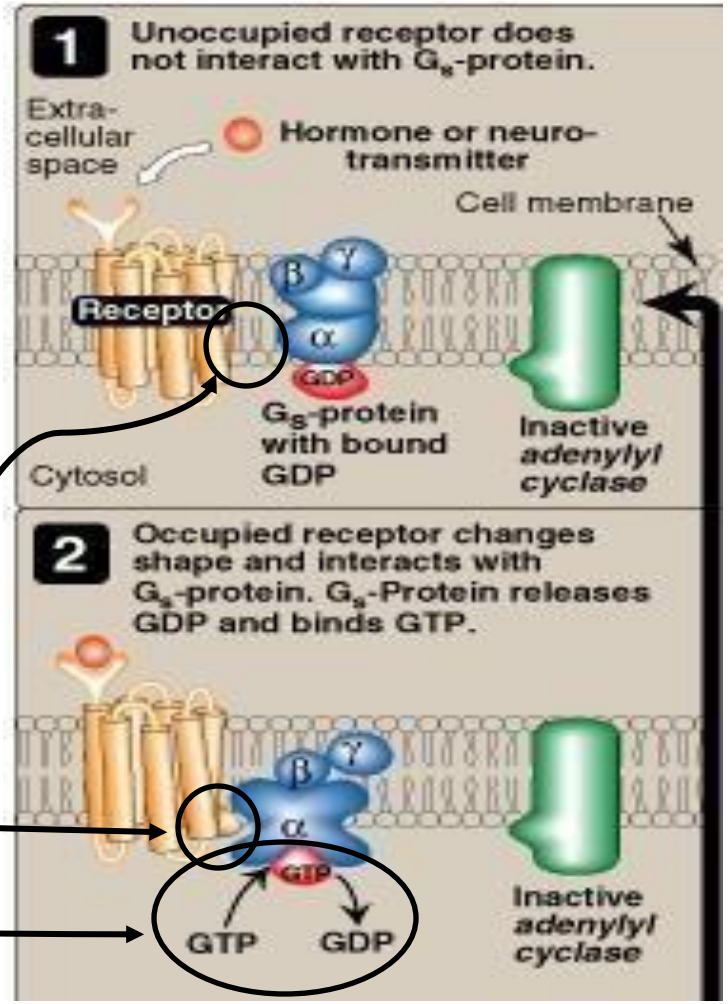
Commonly used mechanisms of communication between cells

Communication between cells through G-Protein Coupled Receptors (GPCRs)

1-The Receptor has an **Intracellular domain** (7 alpha helices bind to G protein) & an **extracellular domain** (Contains the ligand binding site).

2-The ligand binds to the ligand binding site inducing a **conformational change.**

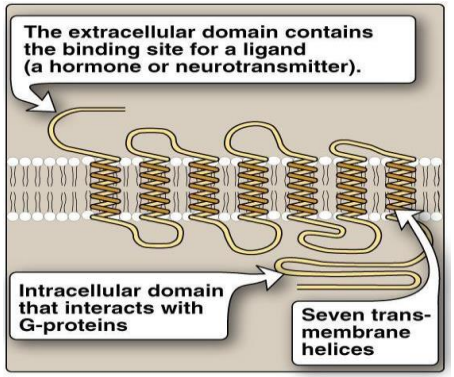
3-The conformational change results in the **activation of the G protein** by **exchanging GDP with GTP.**



conformational change.

اللهم صل على سيدنا محمد وسلم

Communication between cells through G-Protein Coupled Receptors (GPCRs)

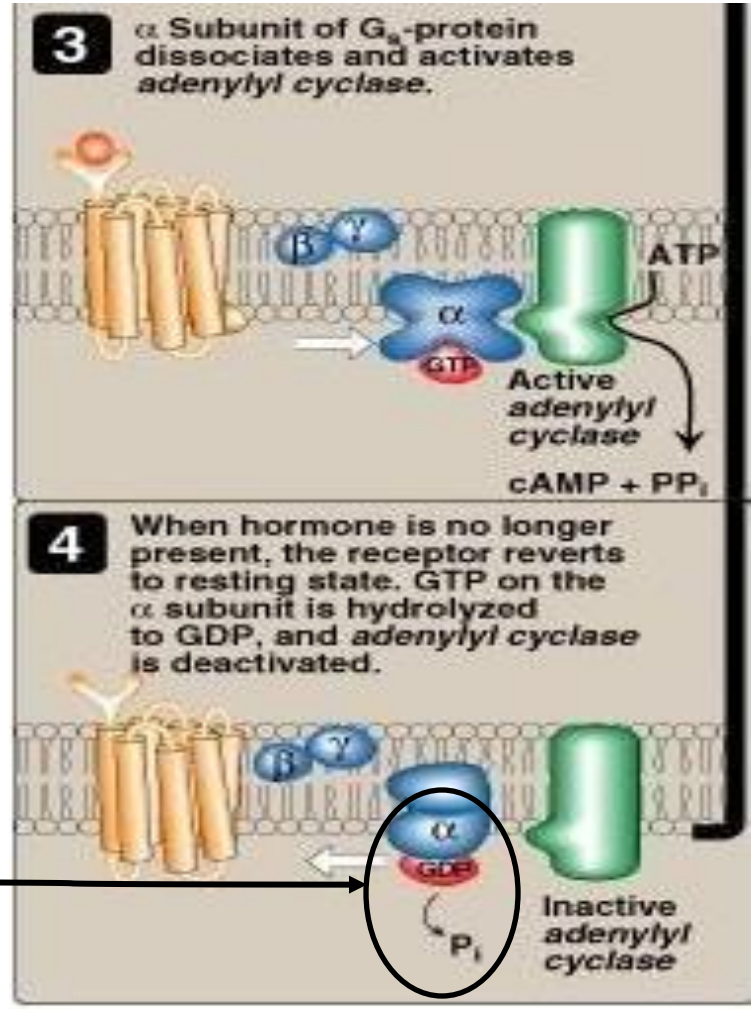


4-Effector activation:

- The **α-GTP subunit** dissociates from the βγ complex and activates a downstream enzyme.
- Example: **Gs α-subunit activates adenylyl cyclase** to produce cAMP (the 2nd messenger).

5-Termination / Reset:

- The **α-subunit hydrolyzes GTP to GDP**, inactivating itself.
- The α-GDP reassociates with the βγ complex, reforming the inactive G protein.
- The receptor returns to its **resting state** once the ligand dissociates.



GTP hydrolysis to GDP

biochem

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. DST modified
2. Marks' Basic Medical Biochemistry A
   Clinical Approach 4th Edition book pages(517-520)

Extra References for the Reader to Use:

1. https://youtu.be/LW_3Ji0mlEc?si=rro6AI8lBjYfsQKj

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			