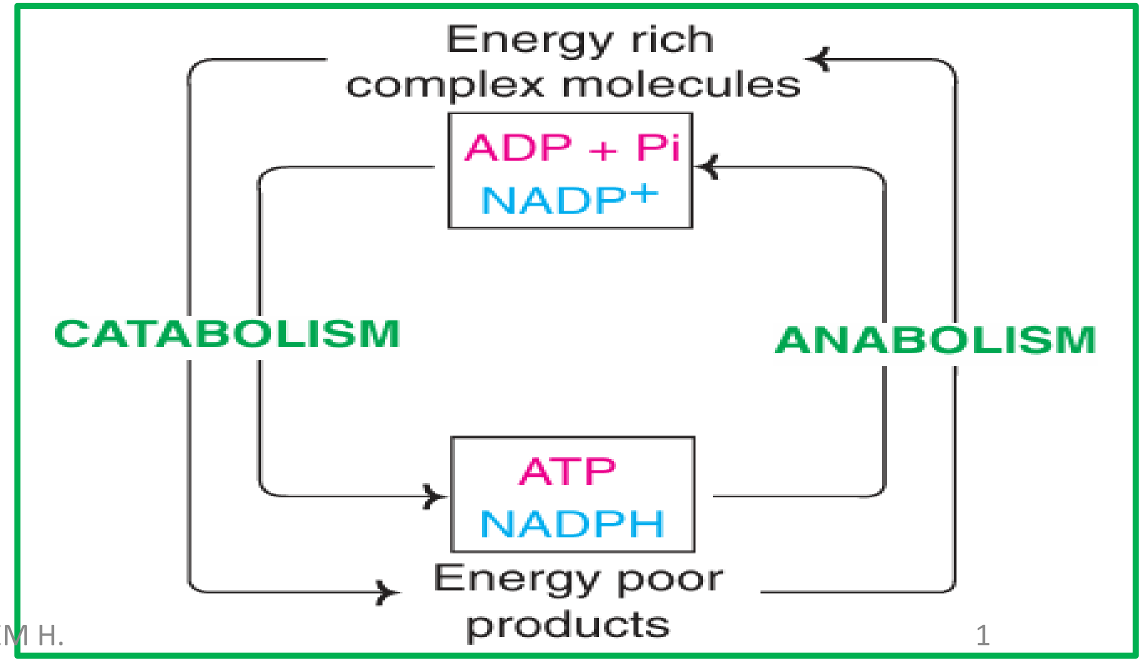
# Badji Mokhtar University of Annaba
# Faculty of Medicine
# 1st year of Medicine.
# 2025/2026

# MODULE: BIOCHEMISTRY

## CHAPTRE 1: Carbohydrates

## B- Carbohydrate Metabolism

DAROUI-MOKADDEM H.



# Table of Contents

# *Introduction*

After **digestion** and **absorption**, nutrients undergo a series of **biochemical transformations** collectively referred to as **intermediate metabolism**. This term encompasses all intracellular enzymatic reactions responsible for the **conversion**, **interconnection**, and **regulation** of molecules to maintain the cell's energetic balance.

Metabolic pathways are classified into three main types:

- **Anabolic pathways:** These include **synthetic reactions** that build **complex molecules** (**such** as **glycogen**, **lipids**, and **proteins**) from **simple precursors**. These processes require **energy** input, provided by **ATP** or **reduced coenzymes.**

- **Catabolic pathways:** These involve **oxidative degradation reactions** of energy substrates (carbohydrates, lipids, amino acids), leading to the release of **energy** in the form of **ATP, NADH,$H^+$, or $FADH_2$**. These energy carriers subsequently feed the **Electron respiratory chain (ETC).**

- Amphibolic pathways: These are dual-purpose pathways that function as **intermediates** between **anabolism** and **catabolism**. The Krebs cycle (citric acid cycle) represents the principal metabolic crossroads of this type.

***Note:*** *Understanding **normal** carbohydrate **metabolism** is essential for interpreting **metabolic disorders** associated with various **pathologies**. Diabetes mellitus is a typical example, characterized by impaired regulation of blood glucose and energy metabolism.*

# *Digestion and Absorption of Dietary Carbohydrates*

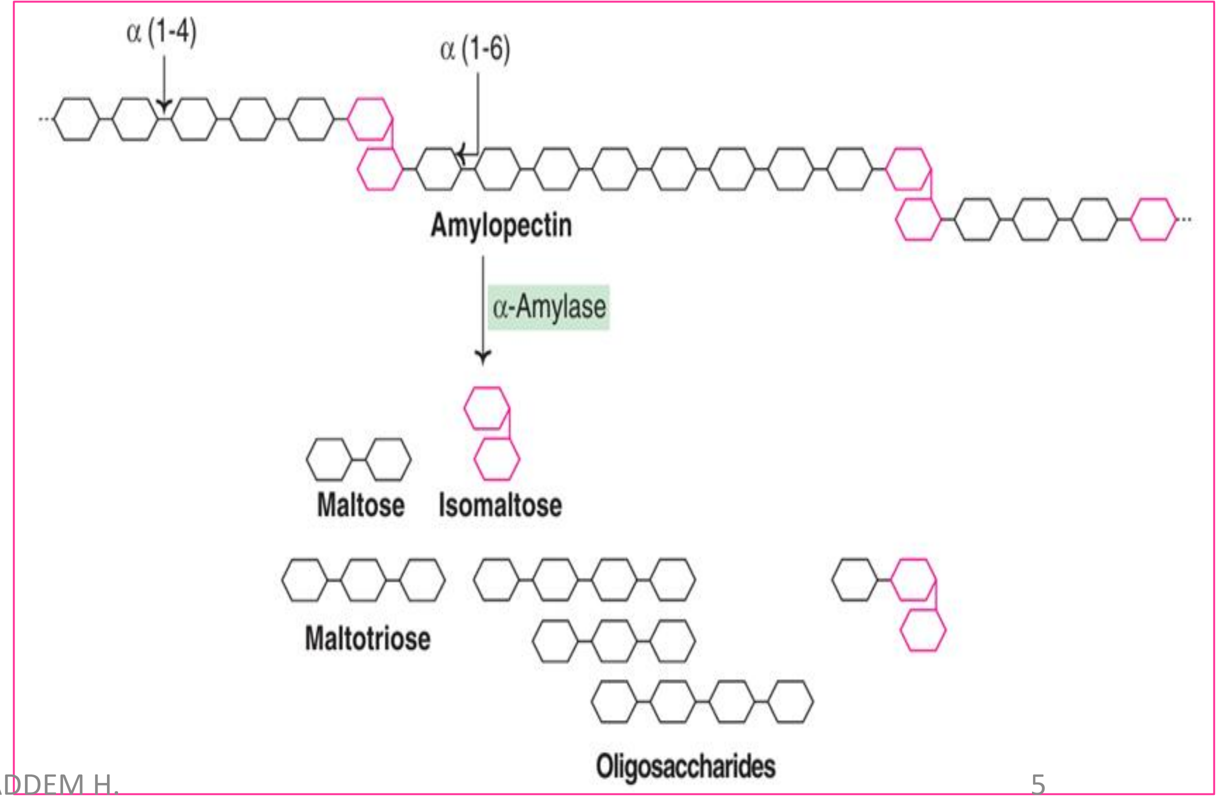
# Digestion

- The principal dietary carbohydrates are **polysaccharides** (starch, glycogen), **disaccharides** (lactose, sucrose) and, to a minor extent, **mono-saccharides** (glucose, fructose).

- The digestion of carbohydrates **begins** in the mouth and is **completed primarily** in the small **intestine.**

## *Digestion in the mouth :*

Carbohydrates are the only macronutrients whose digestion **begins** significantly in the **oral cavity**. During mastication, the enzyme salivary α-amylase (ptyalin) initiates the hydrolysis of starch by randomly cleaving **α-1,4-glycosidic bonds**. This enzymatic activity results in the formation of α-limit **dextrins** (oligosaccharides containing about eight glucose units with one or more α-1,6-glycosidic linkages), as well as smaller fragments such as **maltotriose** and **maltose**.



# Digestion

***Carbohydrates are not digested in the stomach:***

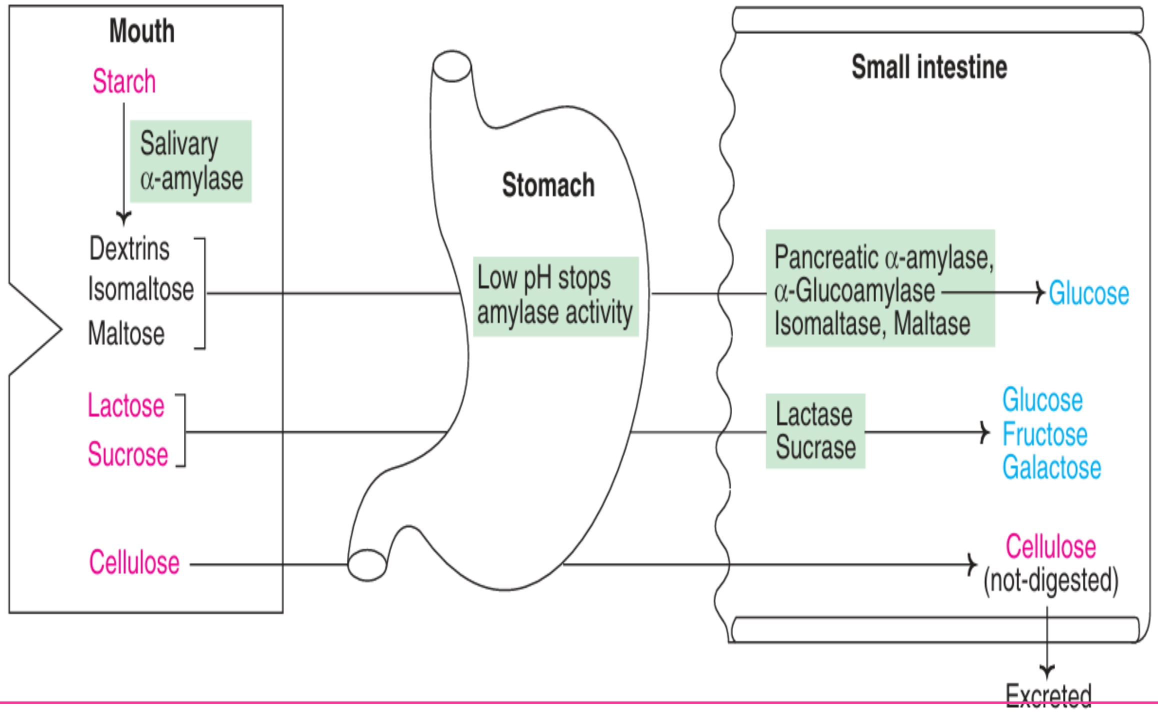
The enzyme salivary amylase is rapidly inactivated by the highly acidic environment (low pH) of the stomach. As a result, the hydrolysis of starch initiated in the mouth ceases, and no further enzymatic digestion of carbohydrates occurs in this compartment.

***Digestion in the Small Intestine***

- Upon entry into the **small intestine**, the **acidic chyme** from the stomach is **neutralized** by **bicarbonate** secreted from the **pancreas**. **Pancreatic α-amylase** then continues starch hydrolysis by cleaving α-1,4-glycosidic bonds, producing **disaccharides** (maltose, isomaltose) and **short oligosaccharides.**

- The final **breakdown** into **monosaccharides** occurs mainly at the **brush border** of the **upper jejunum**, through the action of oligosaccharidases (e.g., glucoamylase) and disaccharidases (e.g., maltase, sucrase, lactase).

- Sucrase efficiently hydrolyzes **sucrose**, whereas lactase (β-galactosidase) acts more slowly, making **lactose** digestion a rate-limiting step in carbohydrate absorption in humans.



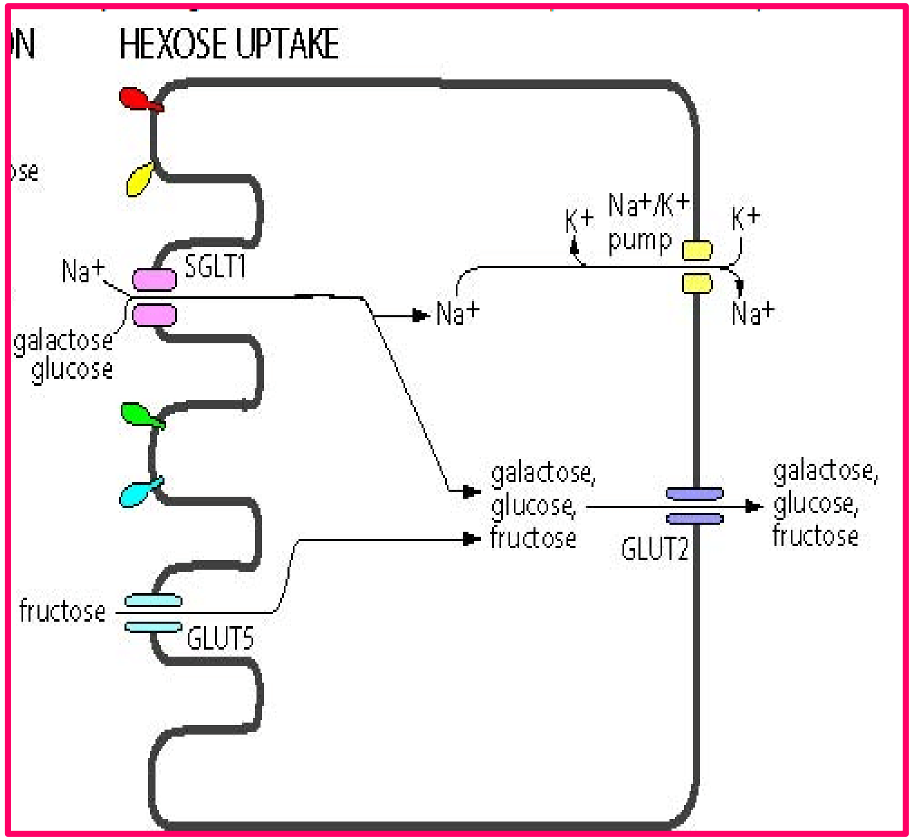

***Note:*** *Cellulose, hemicellulose, pectins, lignin and gums are not digested in the human digestive tract and constitute the main component of **dietary fiber**, playing an important role in **intestinal transit** and in the prevention of **constipation**.*

# Absorption of Monosaccharides

Carbohydrates are absorbed exclusively as **monosaccharides**. Because the enterocyte plasma membrane is **lipophilic**, monosaccharides cannot diffuse freely and require specific membrane transport proteins to facilitate their passage. Two major classes of carbohydrate transporters operate in **intestinal absorption:**

**SGLT** (Sodium–Glucose Linked Transporters): Mediate secondary active transport, driven by the sodium gradient maintained by ATP-dependent $Na^+/K^+$-ATPase.

**GLUT** (Glucose Transporters): Facilitate passive transport of monosaccharides by facilitated diffusion, without direct energy expenditure.




**At the apical border of enterocytes**, SGLT1 co-transports **glucose**, **galactose**, and **$Na^+$** ions in the same direction across the membrane.
**GLUT5**, on the other hand, specifically mediates the facilitated diffusion of **fructose** into the cell.
**At the basolateral membrane**, GLUT2 facilitates the transport of **glucose**, **fructose**, and **galactose**. This membrane protein mediates the facilitated diffusion of these three monosaccharides from the enterocyte into the bloodstream, from where they are carried to the liver via the portal vein.

*Note: Insulin increases the number and promotes the activity of* ***GLUT-4*** *in* ***skeletal muscle*** *and* ***adipose*** *tissue. In* ***type 2 diabetes mellitus****, insulin* ***resistance*** *is observed in these tissues. This is due to the* ***reduction*** *in the quantity of GLUT-4 in insulin deficiency.*

# Main Pathways of Carbohydrate Metabolism

The monosaccharides, **glucose**, **galactose**, and **fructose** resulting from the **digestion** and **absorption** of dietary carbohydrates are transported to the **liver** via the portal vein. Within hepatocytes, **fructose** and **galactose** are **converted** into **glucose**, which serves as the primary energy substrate of the body.

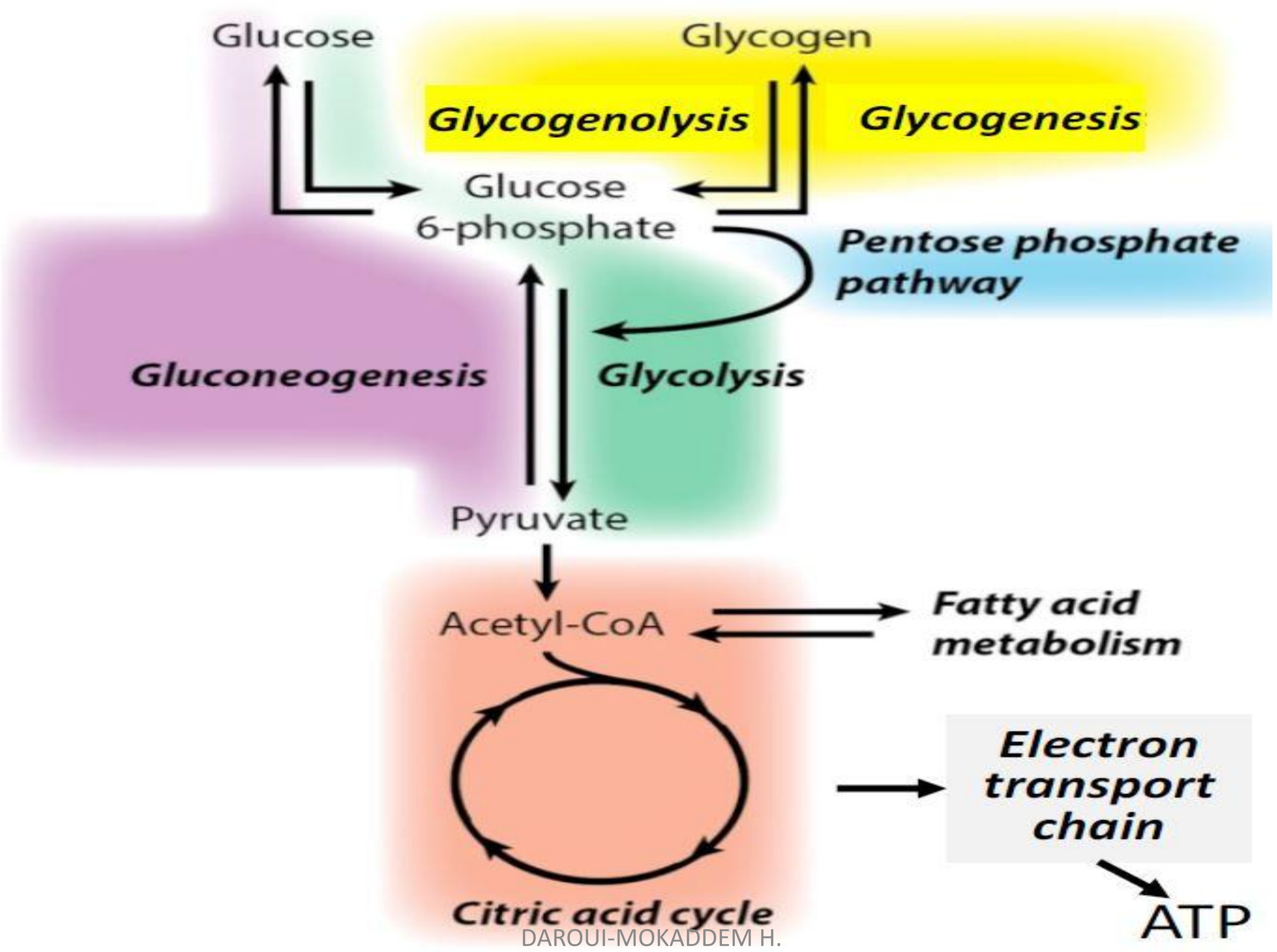
➢ **Glucose in the liver can follow several metabolic fates:**

- It may be **oxidized** to **pyruvate** through glycolysis, then enter the Krebs cycle to generate energy in the form of **ATP**.
- It may be stored as **glycogen** through the process of glycogenesis.
- Under conditions of **excess glucose**, when glycogen stores are saturated, it may be converted into **fatty acids** via lipogenesis.
- A small fraction (approximately **5–10%**) is metabolized through the pentose phosphate pathway, producing **NADPH**, which is essential for **lipogenic reactions**.

➢ **The portion of glucose not taken up by the liver** enters the systemic circulation via the hepatic veins. This circulating glucose represents a major energy source for the **brain** (which consumes about **50%** of it), **skeletal muscles** (approximately **30%**), and other **peripheral tissues**.

➢ **During periods between meals or fasting**, glucose is produced either from **glycogen** stores through glycogenolysis or by **de novo synthesis** from amino acids through gluconeogenesis.

# Main Pathways of Carbohydrate Metabolism



# *Carbohydrate Metabolism and Glucose Homeostasis*

**The primary function of carbohydrate metabolism is to maintain glucose homeostasis.**

- Glucose **homeostasis** is a vital **physiological** process that ensures the maintenance of a **stable** blood glucose concentration (glycemia), thereby providing a constant supply of glucose to body organs.

- In a **healthy adult**, fasting blood glucos**e** levels range between 0.7 and 1.1 g/L, and remain below 1.4 g/L in the **postprandial state** (after a meal).

- This **regulation** is essential to prevent the adverse effects of fluctuating glucose supply to strictly glucose-dependent organs, such as the **brain**, **blood cells**, and **kidneys**.

> ***Note:*** *In **diabetic individuals**, these regulatory mechanisms are impaired, and glucose **homeostasis** is no longer maintained.*

# *Glycolysis pathway*

# *Glycolysis pathway*

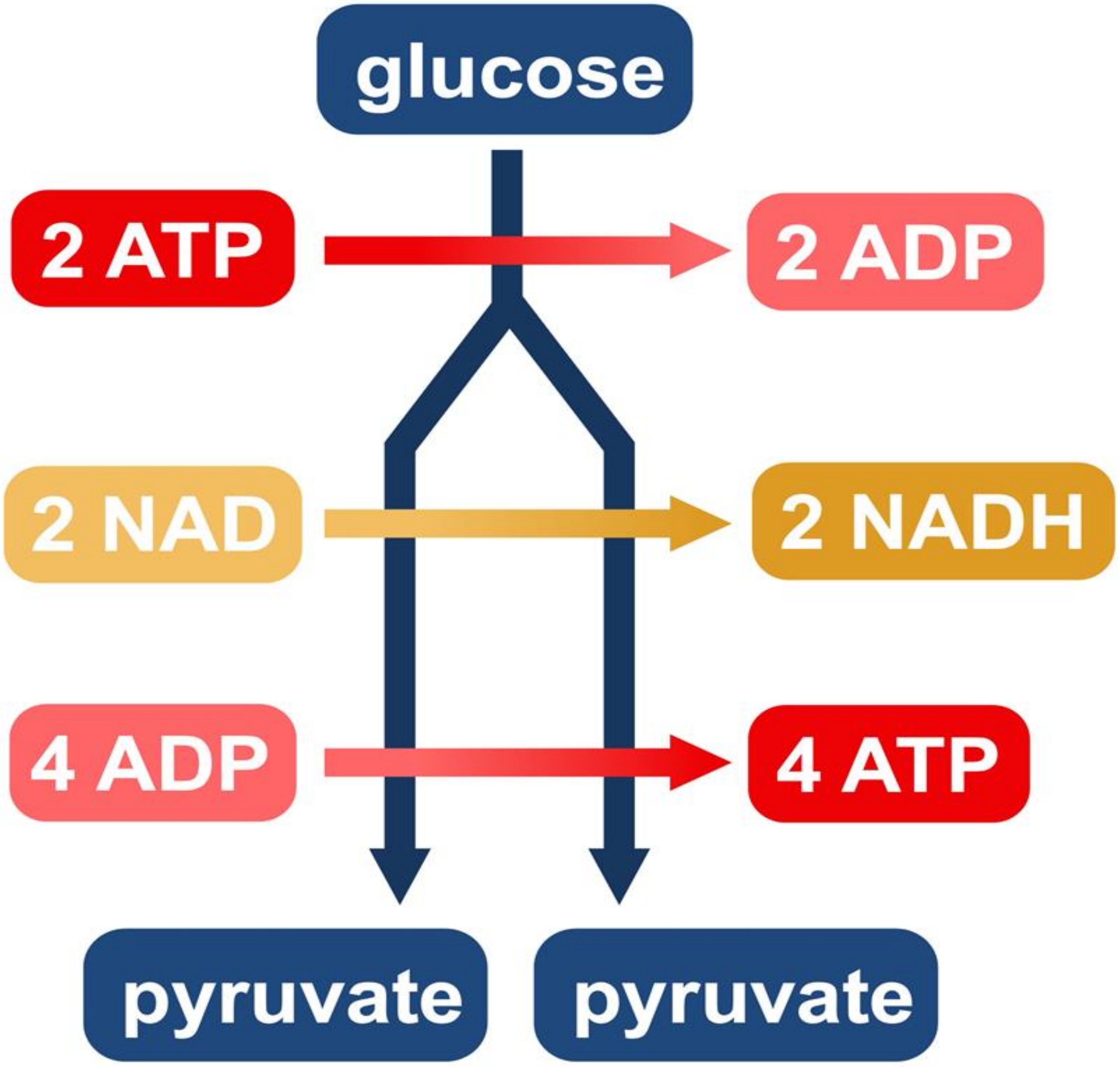
- **Glycolysis,** also known as the **Embden-Meyerhof** pathway**.**

- The process **takes place** in the cytoplasm of a cell and does not **require oxygen.**

- It occurs in both aerobic and anaerobic organisms.

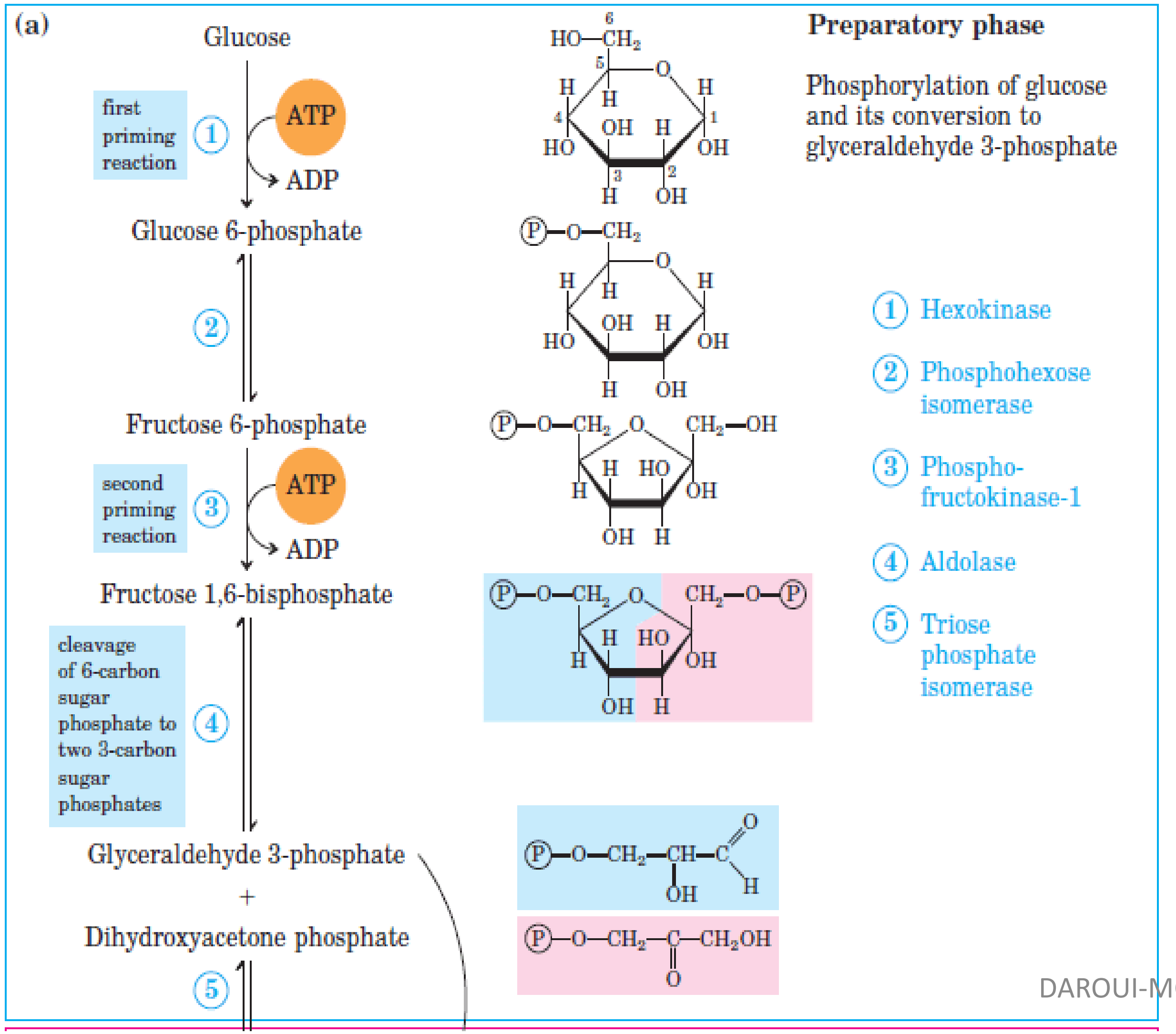
- **Glycolysis** is the process in which glucose is **broken** down to **produce energy**.

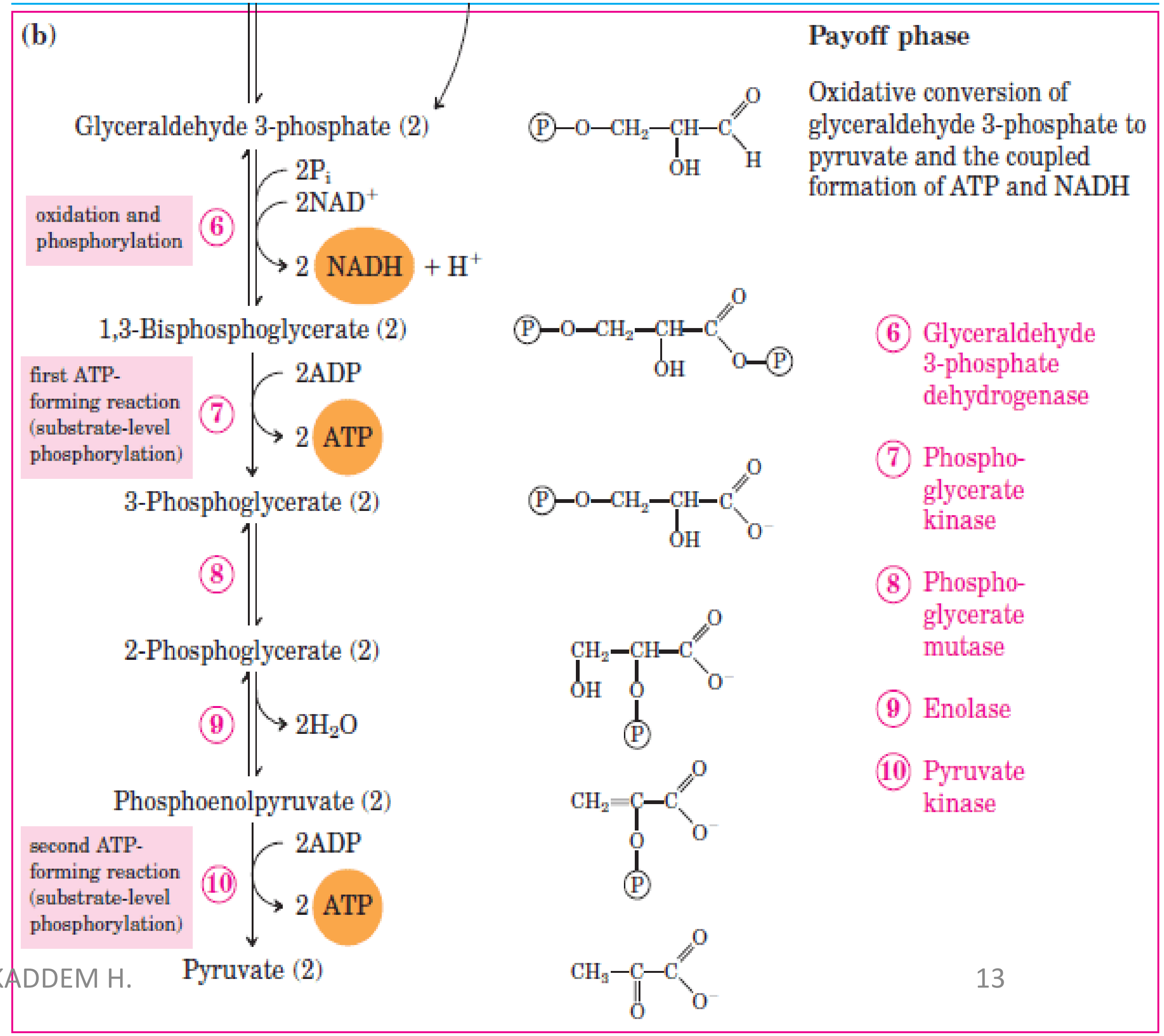
- It produces **two** molecules of pyruvate, ATP, NADH and **water**.



# glycolysis pathway

The **glycolytic pathway** consists of **ten enzymatic reactions**, all of which are reversible except for **three** key regulatory steps. These ten reactions are divided into two distinct phases: Preparatory phase (**five reactions**) and Payoffe phase (**five reactions**)



## *The intermediates of glycolysis are phosphorylated compounds.*

**The phosphoryl group plays three essential roles:**

- The **phosphate group** imparts a net **negative charge** to all intermediates between **glucose** and **pyruvate** at physiological pH (pH 7), thereby preventing their diffusion out of the cell.

- The phosphate group participates in **energy conservation**, enabling the generation of **two molecules** of **ATP** during glycolysis.

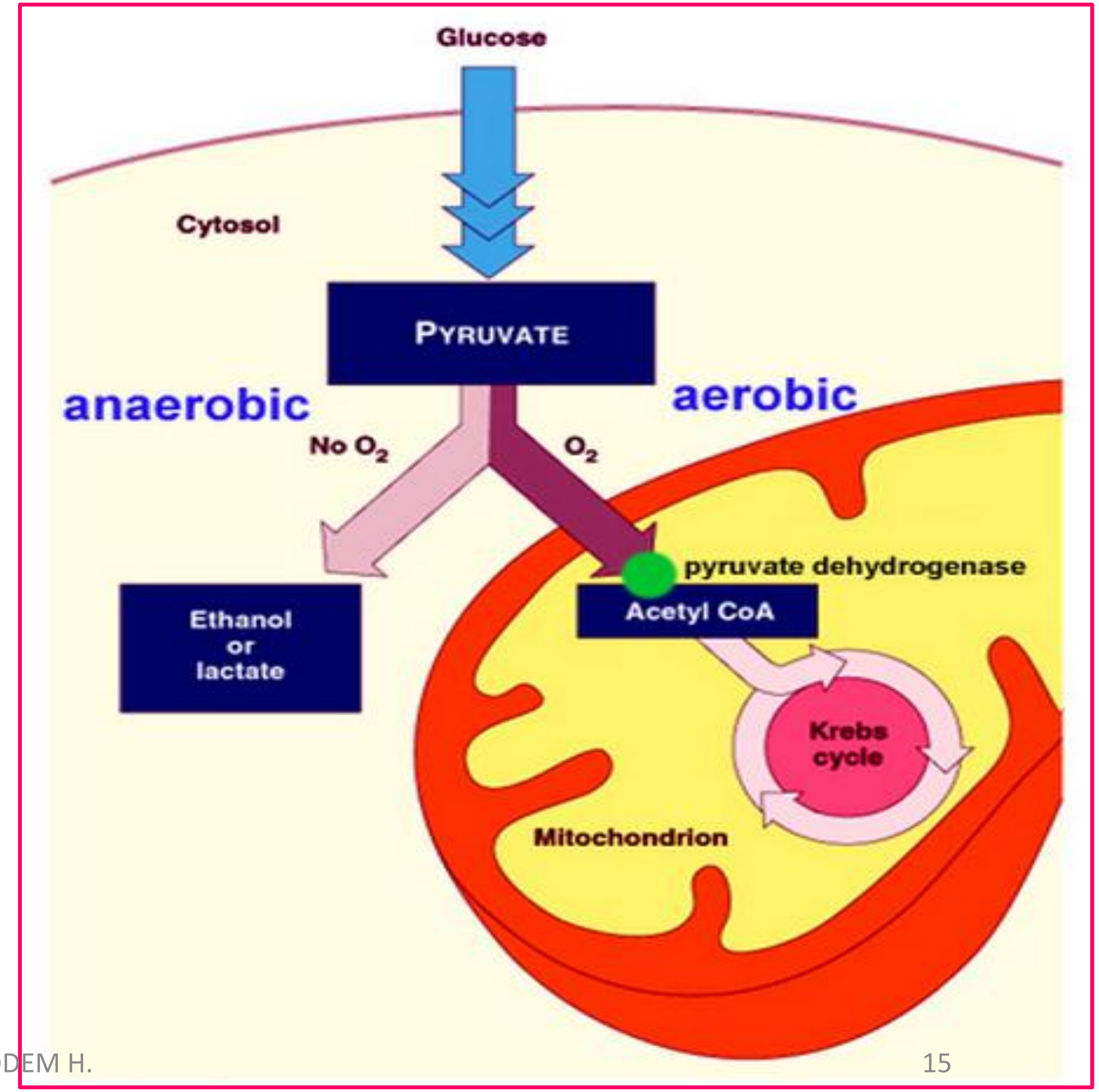
- The phosphate group also functions as a binding and **recognition element**, facilitating the formation of **enzyme- substrate** complexes.

# *Position of Glycolysis in Energy Metabolism*

- It involves the **degradation** of **glucose** with the **production** of **ATP** and **intermediate metabolites**, which can be further **utilized** in other **metabolic pathways**.

- **Aerobic glycolysis** yields 2 ATP, 2 NADH + $H^+$, and 2 pyruvate molecules.

- It therefore represents an essential stage leading to the formation of **pyruvate** and its **mitochondrial** conversion into acetyl-CoA, the key substrate fueling the Krebs cycle (tricarboxylic acid cycle). Under these conditions, glucose undergoes **complete oxidation** to $CO_2$ and $H_2O$.

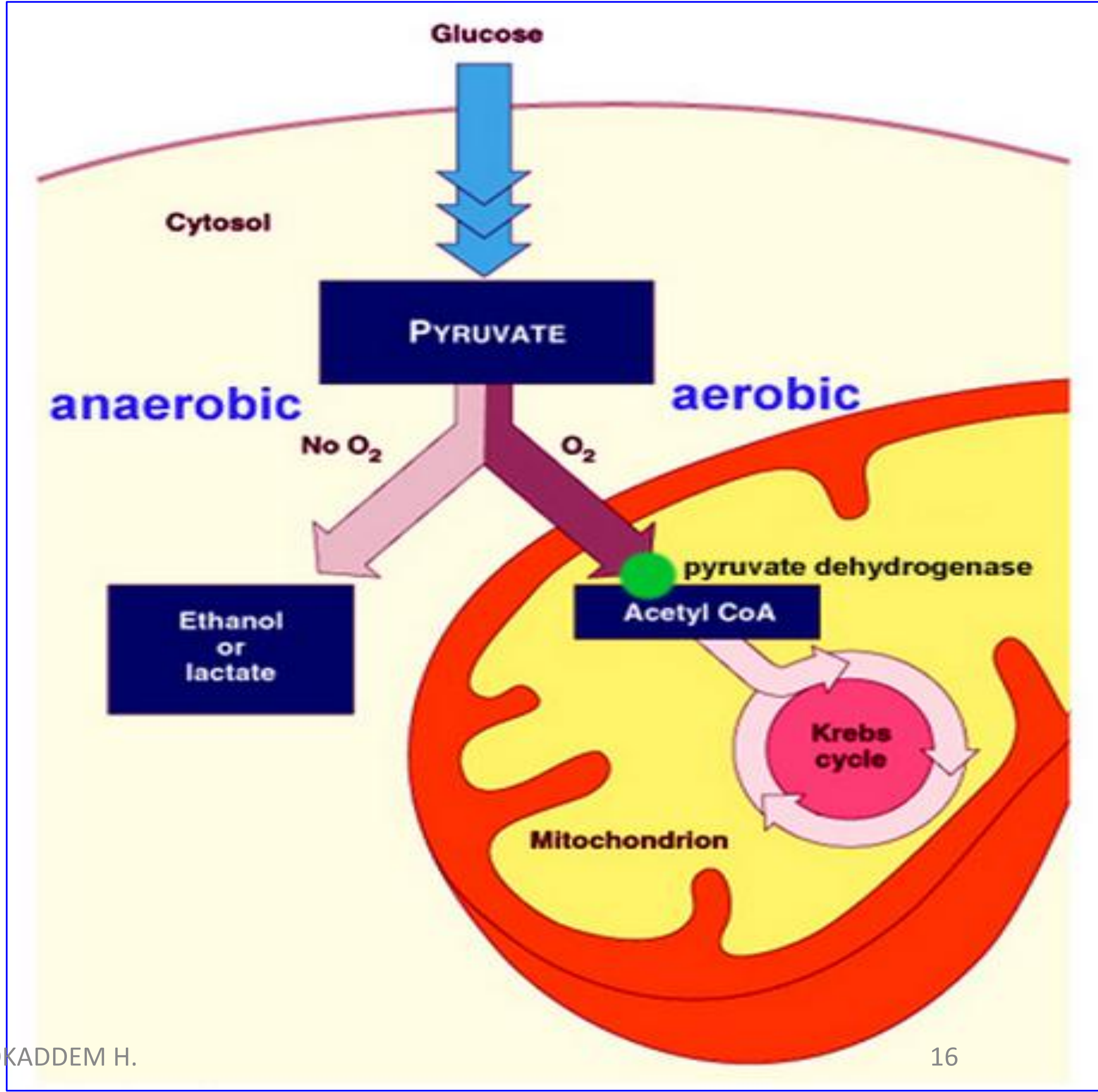


# *Position of Glycolysis in Energy Metabolism*

***Anaerobic glycolysis*** also produces 2 **ATP,** 2 N**ADH + H⁺,** and 2 **pyruvate m**olecules, which are subsequently utilized in reactions that reoxidize NADH + H⁺, leading to the formation of:

Lactate **(lactic fermentation)**: a process that provides ATP to cells **lacking mitochondria** (e.g., red b**lood cells)** and to **hypoxic tissues s**uch as rapidly contracting s**keletal muscle.**

Ethanol **(alcoholic fermentation)**: occurring in **yeasts** and certain **microorganisms.**



# *Cytoplasmic Glycolysis Balance*

**The general reaction is written as:**

**1 glucose ($C_6H_{12}O_6$) + 2 ADP + 2 Pi + 2 $NAD^+$ $\longrightarrow$ 2 pyruvates ($CH3\text{-}CO\text{-}COO^-$) + 2 ATP + 2 $H_2O$ + 2 NADH, $H^+$**

**Energy balance under anaerobic conditions (up to pyruvate):**

Two reactions consume energy: – 2 ATP

Two reactions generate energy: + 4 ATP

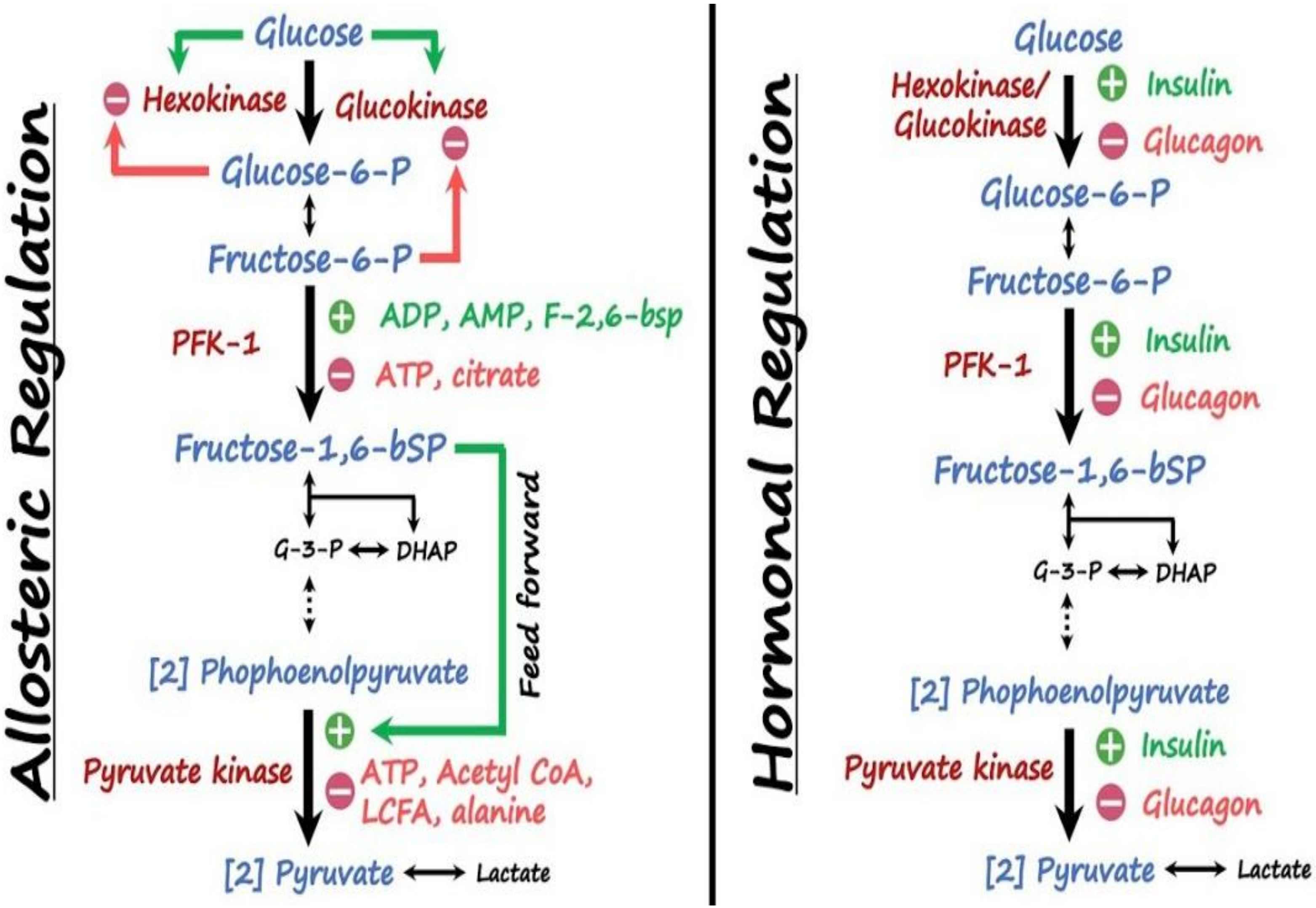
The net gain is therefore 2 ATP.

**Energy balance under aerobic conditions:**

The 2 NADH + $H^+$ produced are oxidized through the respiratory chain, yielding 3 ATP × 2 = 6 ATP.

Under **aerobic conditions**, the total energy yield is 2 + 6 = 8 ATP.

# Regulation of Glycolysis




### *Hormonal Regulation*

- In the **postprandial state** (after a meal), **insulin** increases hepatic levels of **glucokinase**, **phosphofructokinase-1** (PFK-1), and **pyruvate kinase**.

These changes result from the **activation** of **gene transcription** for the corresponding enzymes.

The **increase** in these enzyme concentrations enhances glycolytic activity.

- **Conversely**, during **fasting**, when blood **glucagon** levels are elevated, the transcription of these genes is **downregulated**, leading to a **decrease** in the **concentrations** of these **enzymes**.

Glucagon **inhibits** glycolysis, thereby preserving glucose for **glucose-dependent tissues** such as the **brain** and **kidneys**.

# *Allosteric regulation of Glycolysis*

Purpose: To adjust the rate of glycolysis according to the cell's metabolic demands:

- For energy production (ATP)
- For the supply of biosynthetic precursors

The rate of glycolysis depends on:

- The cellular availability of glucose
- The activity of the rate-limiting reactions (steps 1, 3, and 10) catalyzed respectively by *hexokinase* (or glucokinase), *phosphofructokinase-1* (PFK-1), and *pyruvate kinase*.
- The major regulatory step is **reaction 3**, catalyzed by **PFK-1**, which irreversibly commits glucose to the glycolytic pathway.

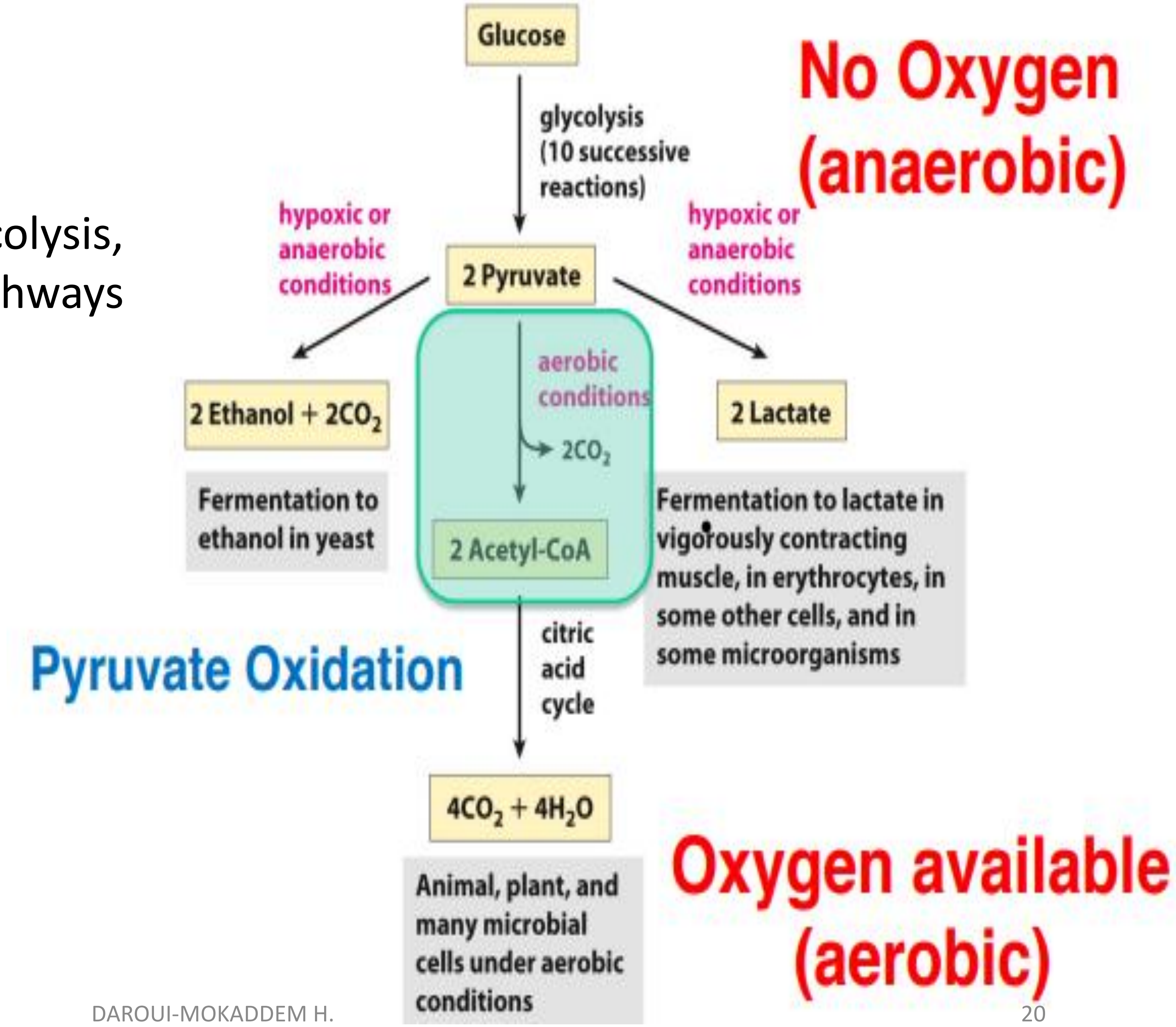
*Hexokinase*: Slightly limiting step. Allosterically inhibited by its product, glucose-6-phosphate (G6P).
*Phosphofructokinase-1* (PFK-1): **Key regulatory enzyme** and the most rate-limiting step of glycolysis. **Allosterically** regulated by several **activators** and **inhibitors**.
Activators: AMP, ADP, **Fructose-2,6-bisphosphate**, Fructose-6-phosphate
Inhibitors: ATP, Citrate
*Pyruvate Kinase*: Allosterically inhibited by ATP.

***Note:* Fructose-2,6-bisphosphate** *is derived, like fructose-1,6-bisphosphate, from fructose-6-phosphate, but it functions solely as a regulatory molecule. Its synthesis and degradation are under hormonal control.*

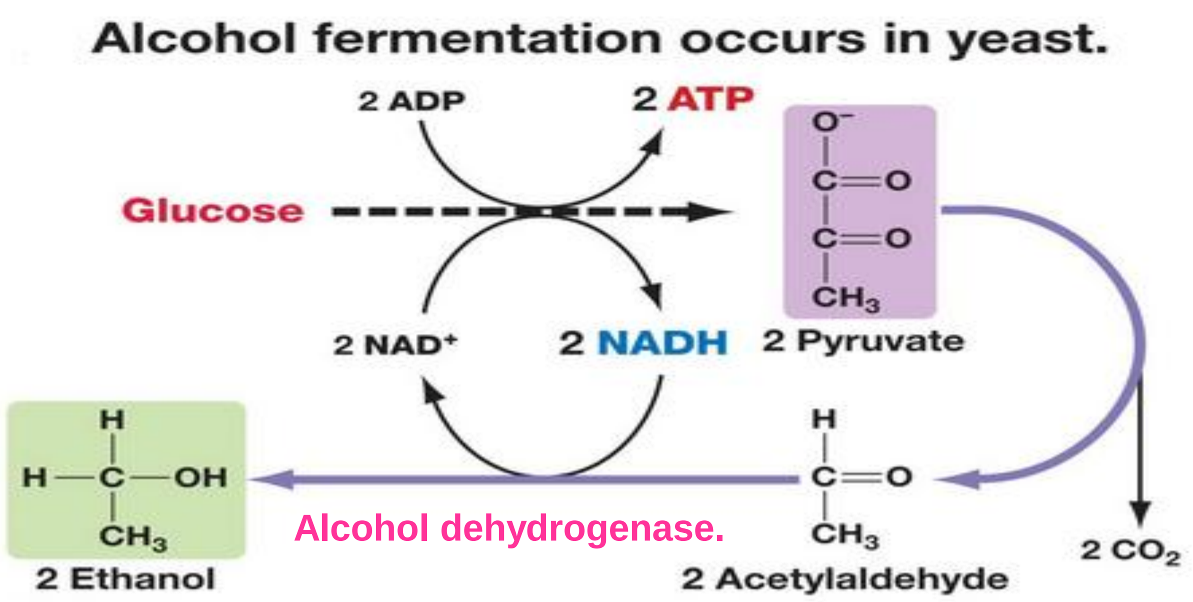
# *Fates of Pyruvate*

Pyruvate, the end product of glycolysis, can follow different catabolic pathways depending on:

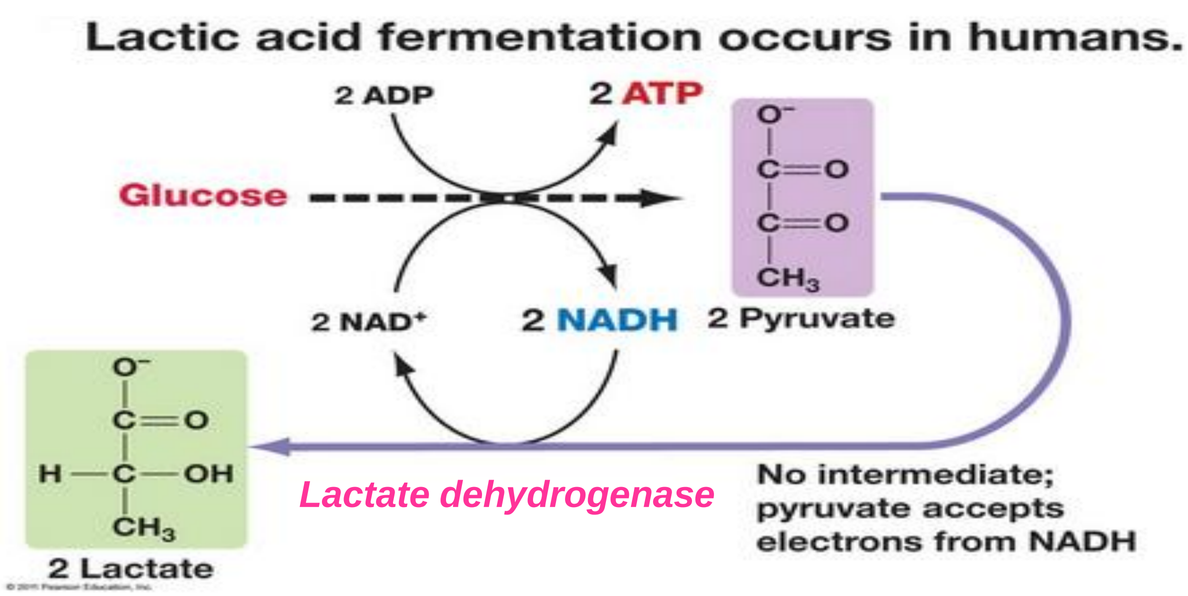
- The type of **organism**
- The **metabolic conditions**.



## Ethanol pathway




## Lactate pathway




**Alcoholic Fermentation:**

In yeasts and other microorganisms, **NADH** is **used** to **reduce** pyruvate to ethanol through the sequential action of the enzymes pyruvate decarboxylase and *alcohol dehydrogenase*.

**Lactic Fermentation:**

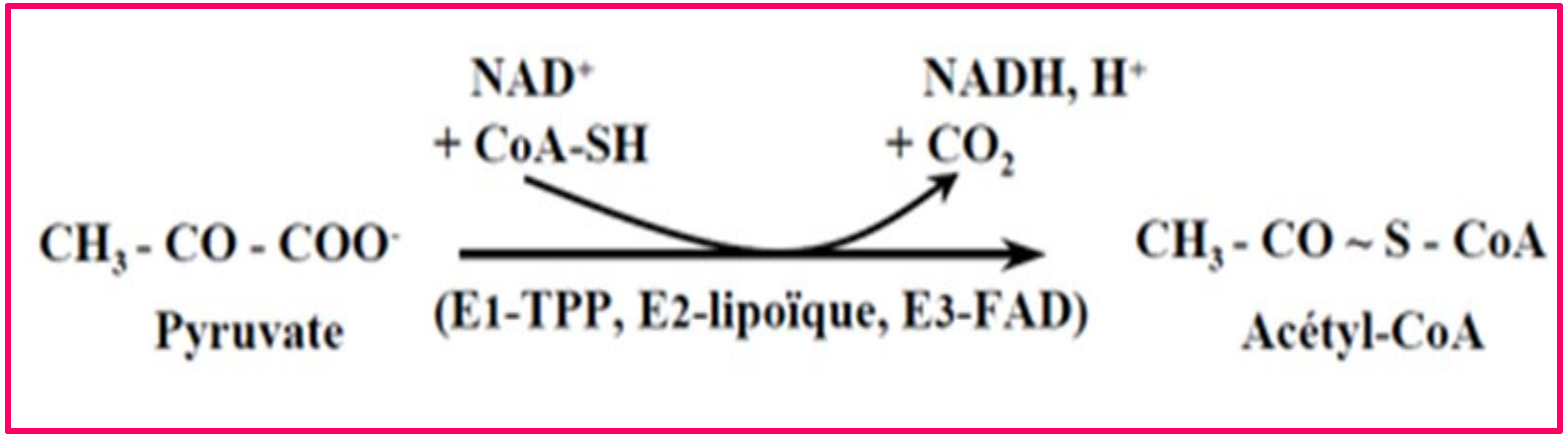
Under anaerobic conditions, the **NADH** produced during **glycolysis** cannot enter the **mitochondria** and therefore does not participate in the respiratory chain.

Instead, it is **used** to **reduce** pyruvate to lactate, a reaction catalyzed by the enzyme *lactate dehydrogenase.*

**This process occurs in:**

- Intensely contracting muscles
- Red blood cells
- Certain microorganisms.

# Oxidative decarboxylation of pyruvate into acetyl-CoA (Aerobiosis)




It is a key reaction between glycolysis and the Krebs cycle.

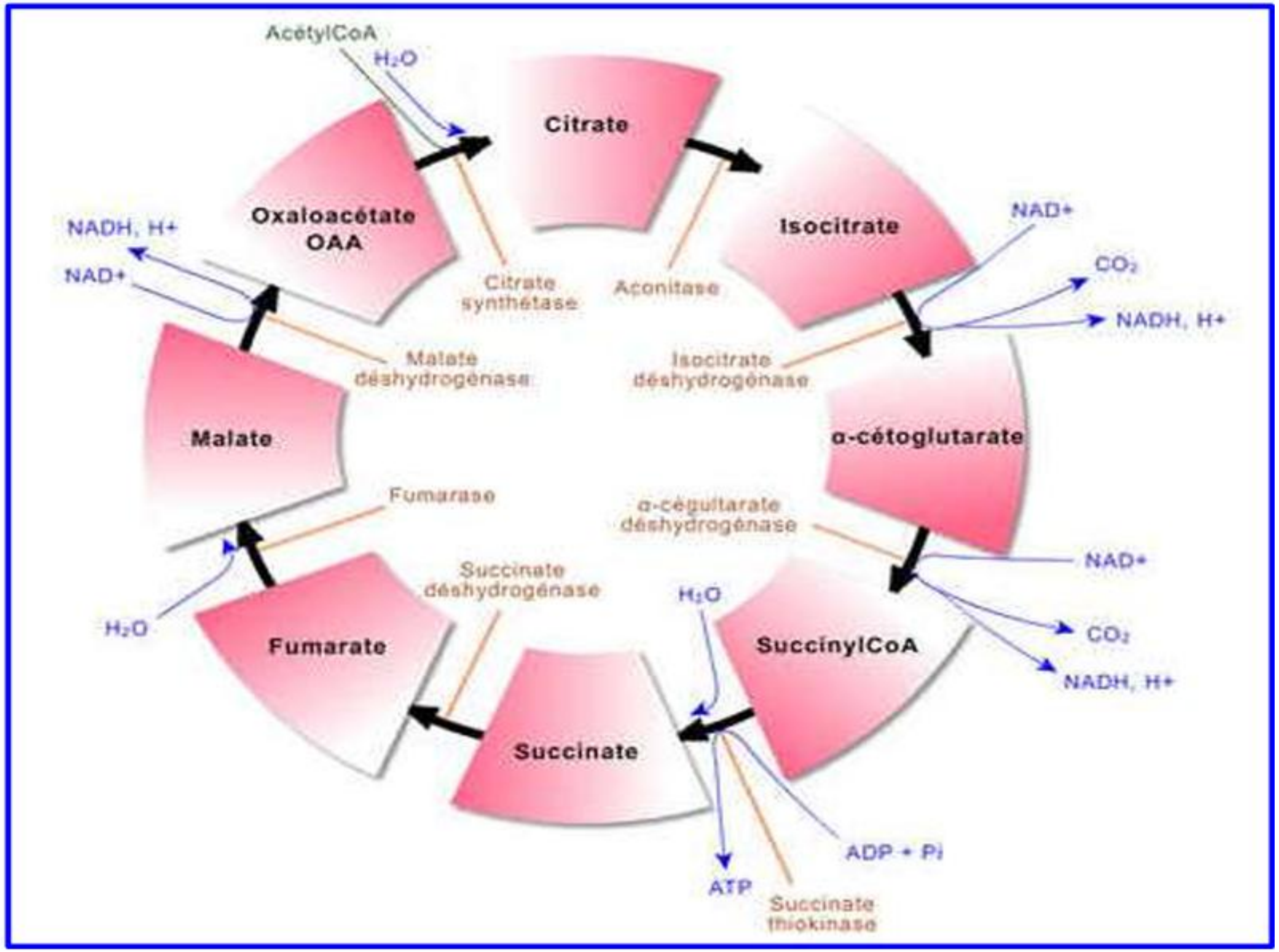
- In the **mitochondrion**, the **oxidative decarboxylation** of pyruvate into acetyl-CoA is catalyzed by *pyruvate dehydrogenase* **(PDH)**

**Required Cofactors:** Thiamine pyrophosphate (**TPP**), Lipoic acid (lipoamide), Coenzyme A (CoA-SH), FAD (flavin adenine dinucleotide), $NAD^+$ (nicotinamide adenine dinucleotide).

- This reaction is **highly exergonic** (irreversible). It leads to the formation of a high-energy **thioester** bond in acetyl-CoA and the production of **$NADH,H^+$**, which will yield **3 ATP** molecules in the **respiratory chain**.

- *Pyruvate dehydrogenase* is regulated by its substrates:
  - increased [pyruvate], $NAD^+$, CoA-SH, and AMP (**activators**);
  - NADH, acetyl-CoA, and ATP (**inhibitors**).

# *Krebs cycle (Tricarboxylic acid cycle)*



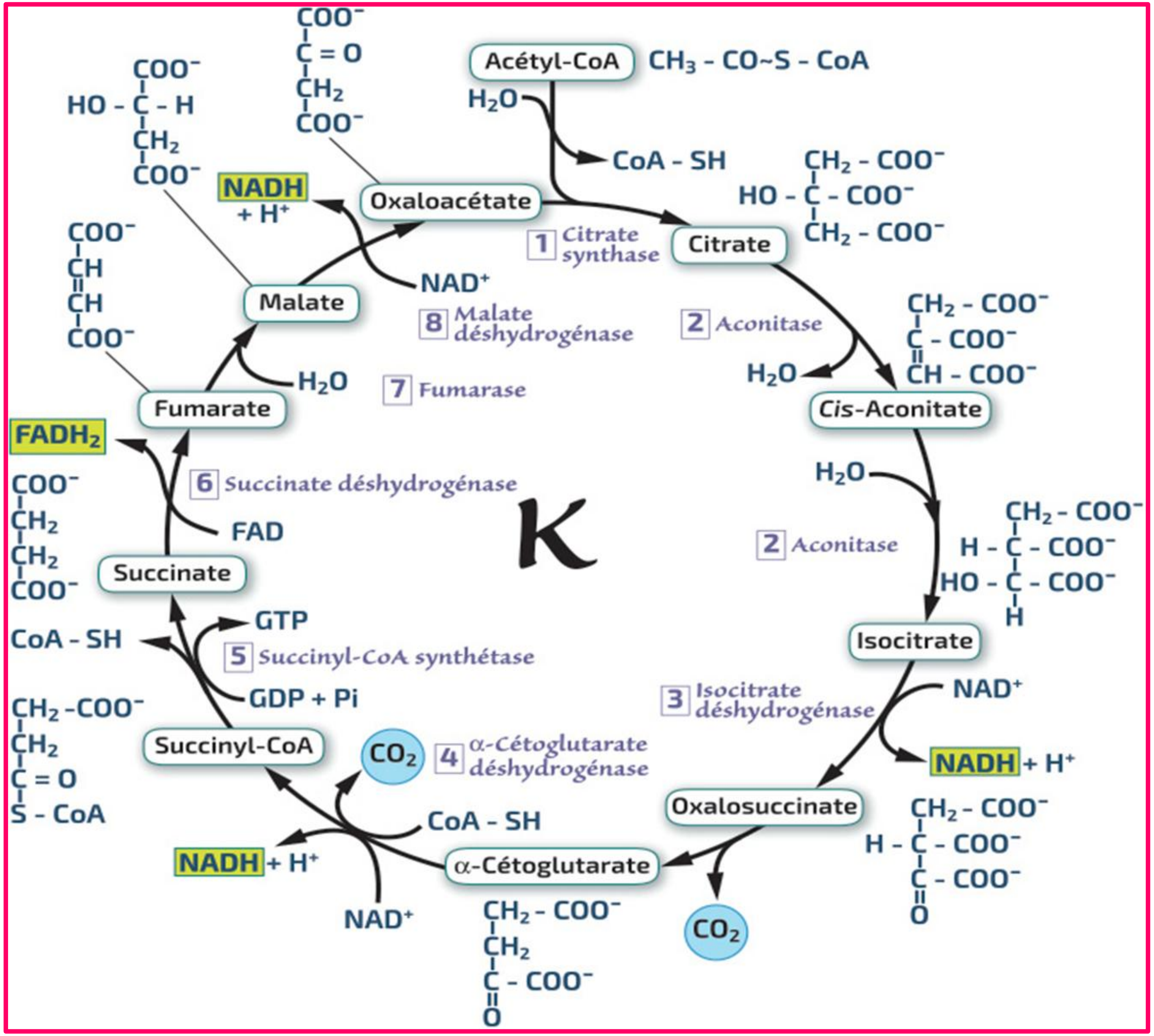
# Krebs cycle

**_Metabolic Importance:_**

The Krebs cycle is **amphibolic**, meaning that it plays a dual role:

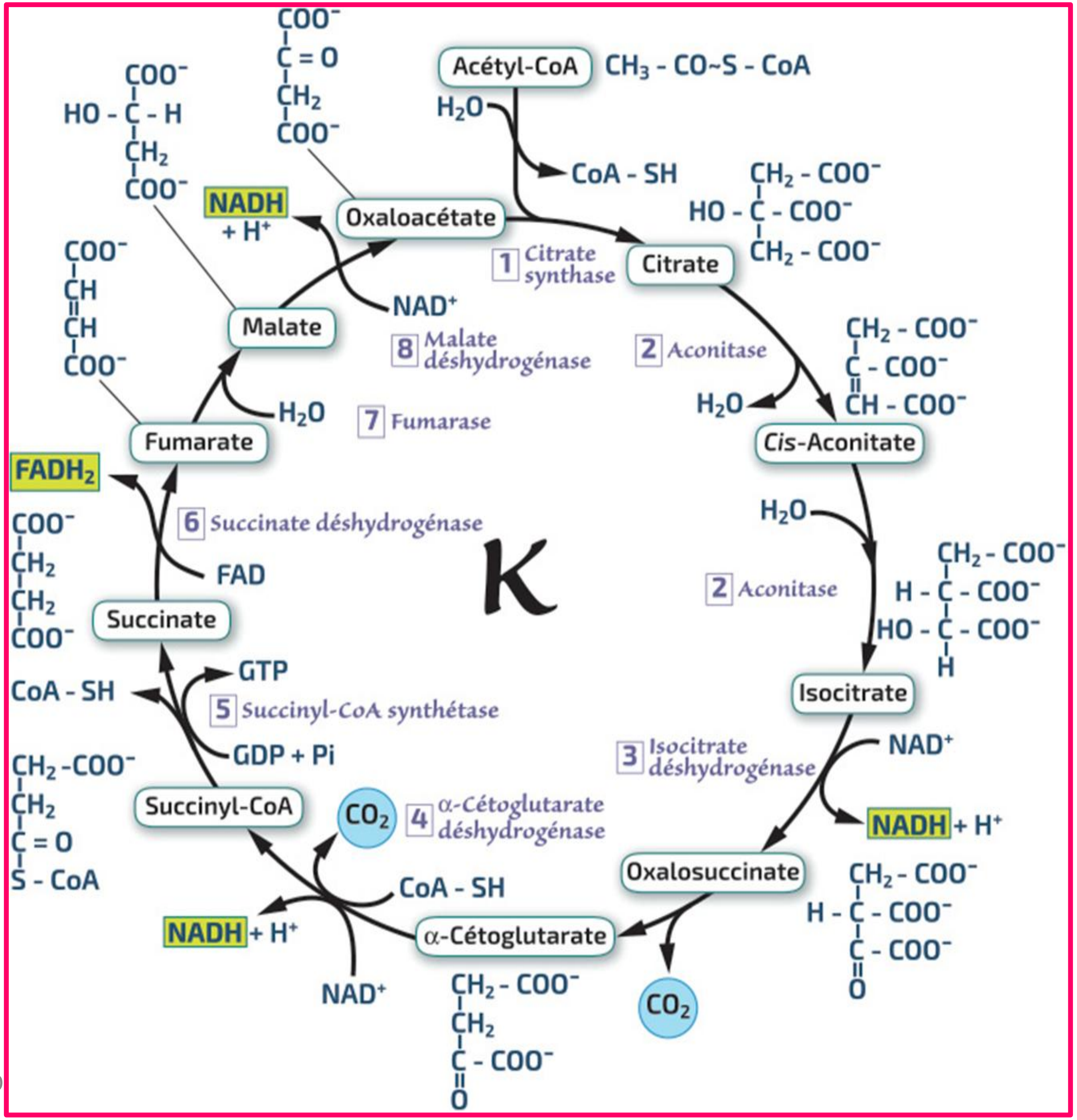
- Catabolic, by oxidizing acetyl CoA to produce energy.

- Anabolic, by providing metabolic intermediates for the biosynthesis of amino acids, purine bases, heme, and glucose (via gluconeogenesis).



# Krebs cycle

- The Krebs cycle, or citric acid cycle, takes place in the **mitochondrion** in **eukaryotic cells**.
- At each turn of the cycle, one molecule of **acetyl-CoA** (2 carbons), derived from carbohydrates, condenses with one molecule of **oxaloacetate** (4 carbons) to form **citrate** (6 carbons).
- The cycle consists of eight reactions catalyzed by **seven soluble enzymes** and one enzyme anchored in the inner mitochondrial membrane: *succinate dehydrogenase*.
- It generates **reduced coenzymes** (3 NADH + $H^+$ and 1 $FADH_2$), which will be reoxidized in the **respiratory chain**. Therefore, the **Krebs cycle** is functionally **coupled** to the respiratory chain.
- During the sequence of reactions, **two carbons** of citrate are **released** as $CO_2$, thereby allowing the regeneration of oxaloacetate.



# *Energy balance of the Krebs cycle*

➢ ***The overall reaction of the cycle***

Acetyl-CoA + 3$NAD^+$ + FAD + GDP+$P_i$ + 2$H_2O$ $\longrightarrow$ 2$CO_2$ + 3(NADH, $H^+$) + $FADH_2$ + GTP + COASH

➢ ***Each turn produces***

- 1 ATP
- 3 (NADH, $H^+$) = 3 X 3 ATP = 9 ATP
- 1 FADH2 = 2 ATP

➢ *In total, **one** molecule of **acetyl-CoA** produces **12 ATP** per cycle turn.*

# *Regulation du cycle de Krebs*

- The cycle is **regulated** by the availability of its **substrates** and by the cell's **energetic state**:

- Inhibited by **ATP**, **NADH**, and **succinyl-CoA** (high-energy state).
- Activated by **ADP** and **Ca$^{2+}$** (increased energy demand).

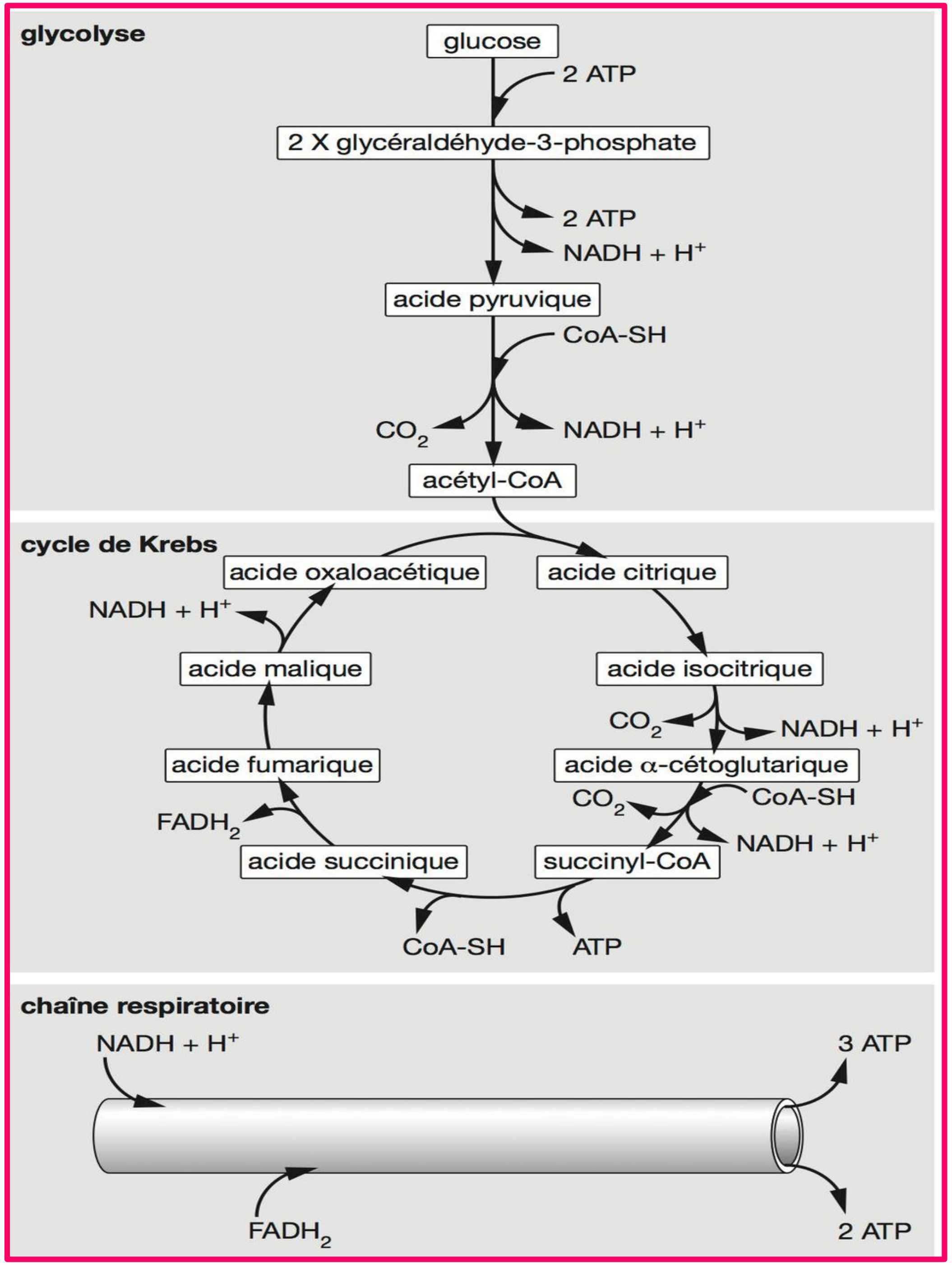
- **The main regulated enzymes are:**

- *Citrate synthase*
- *Isocitrate dehydrogenase*
- *α-Ketoglutarate dehydrogenase*.

# *Total energy yield from glucose degradation*

| | Réaction | ATP ou Coenzymes réduits formés | | ATP | |
|---|---|---|---|---|---|
| Glucose | → | Glucose 6P | - 1 ATP | - 1 | 8 |
| Fructose 6P | → | Fructose 1,6 bisP | - 1 ATP | - 1 | |
| 2 Glycéraldéhyde 3P | → | 2 1,3 bis Phospho Glycérate | 2 NADH | 6 | |
| 2 1,3 bis Phospho Glycérate | → | 2 3 Phospho Glycérate | 2 ATP | 2 | |
| 2 Phosphoénolpyruvate | → | 2 Pyruvate | 2 ATP | 2 | |
| 2 Pyruvate | → | 2 AcétylCoA | 2 NADH | 6 | 6 |
| 2 Isocitrate | → | 2 α cétoglutarate | 2 NADH | 6 | 24 |
| 2 α cétoglutarate | → | 2 SuccinylCoA | 2 NADH | 6 | |
| 2 SuccinylCoA | → | 2 Succinate | 2 GTP | 2 | |
| 2 Succinate | → | 2 Fumarate | 2 $FADH_2$ | 4 | |
| 2 L-malate | → | 2 Oxaloacétate | 2 NADH | 6 | |

**Total ATP formés : 38**




$NADH,H^+$ and $FADH_2$ are reoxidized by the respiratory chain.

# *Clinical aspect of glycolysis*

| Clinical Aspect | Description | Consequences / Manifestations |
|---|---|---|
| **Tissues Dependent on Glycolysis** | Red blood cells (lack mitochondria), brain, muscle under anaerobic conditions | Muscle fatigue, increased sensitivity to hypoglycemia, hemolysis if glycolytic enzymes are defective |
| **Cancer (Warburg Effect)** | Increased glycolytic flux even in the presence of oxygen | High glucose uptake, basis for PET imaging using 18-FDG |
| **Lactic Acidosis** | Excess lactate production or impaired lactate clearance | Decreased blood pH, respiratory distress, medical emergency |
| **Enzymatic Deficiencies** | Pyruvate kinase, phosphofructokinase (Tarui disease), hexokinase defects | Hemolytic anemia, exercise intolerance, myoglobinuria |
| **Intense Exercise** | Anaerobic glycolysis leading to elevated lactate | Muscle cramps, decreased pH, fatigue |
| **Hypoglycemia** | Insufficient glucose supply to the brain | Neurological symptoms: confusion, seizures, coma |
| **Diabetes Mellitus** | Chronic hyperglycemia causing metabolic overload | Vascular complications, increased oxidative stress |

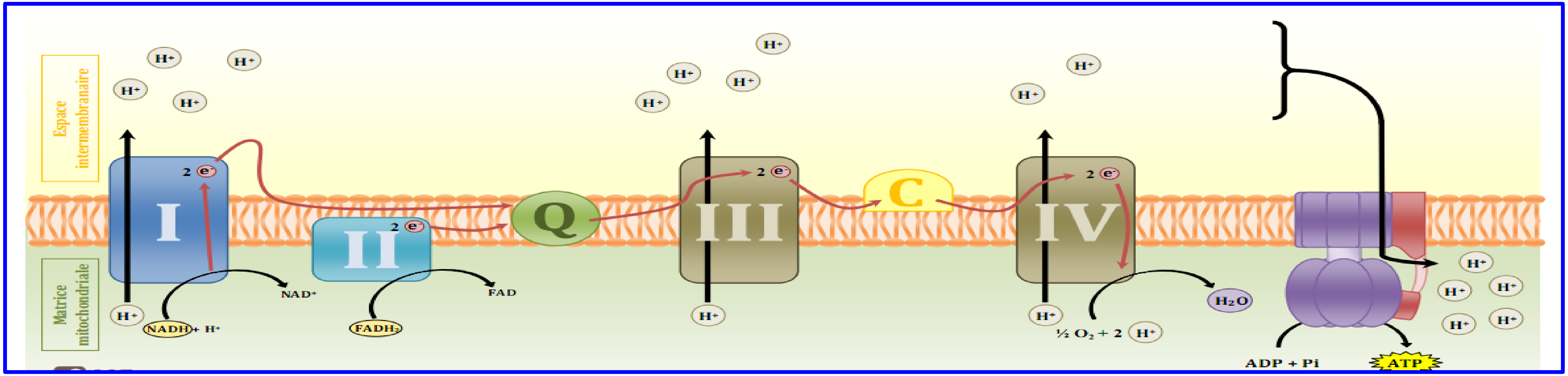
# *Clinical aspect of Krebs cycle*

- Mutations affecting Krebs cycle enzymes have profound clinical and metabolic effects. They can cause severe metabolic **encephalopathies** in infants, as well as a broad spectrum of **tumors** and **cancers** in adults.

- The underlying mechanisms include impaired **mitochondrial oxidation**, the accumulation of **oncometabolites**, and extensive **epigenetic modifications** of **DNA** and **histones**.

# *Respiratory chain*

# Respiratory chain




➢ The respiratory chain is located in the inner mitochondrial membrane. This electron transport chain consists of four protein complexes:

- Complex I: *NADH-coenzyme Q oxidoreductase,*
- Complex II: *Succinate-coenzyme Q oxidoreductase,*
- Complex III: *Coenzyme Q-cytochrome c oxidoreductase,*
- Complex IV: *Cytochrome c oxidase*.

➢ Coenzyme Q (ubiquinone) and cytochrome c are mobile electron carriers within the respiratory chain.

# *Respiratory chain*

It produces **ATP** and **water** through a **coupled process** composed of two main components:

- The **electron transport chain** generates **$H_2O$** by transferring protons ($H^+$) from the reduced coenzymes NADH,$H^+$ and $FADH_2$ to molecular oxygen, this process constitutes **cellular respiration**.

- The **phosphorylation of ADP into ATP** is driven by the energy released from the electron transport chain. The coupling of these two processes is known as **oxidative phosphorylation**.

- During this process, **ADP is phosphorylated to ATP** by the enzyme ***ATP synthase***, yielding approximately **3 ATP** per **NADH,$H^+$** and **2 ATP** per **$FADH_2$**.

- The **ADP** and inorganic phosphate (**Pi**) used for ATP synthesis originate from the cytosol.

- The control of the **respiratory chain** and **ATP synthesis** depends on the **concentration** of **ADP**. When ADP concentration increases, the **rate** of the respiratory chain **rises rapidly** and **significantly**.

## *Clinical aspect of the mitochondrial respiratory chain*

- The mitochondrial respiratory chain produces the energy required by our cells.

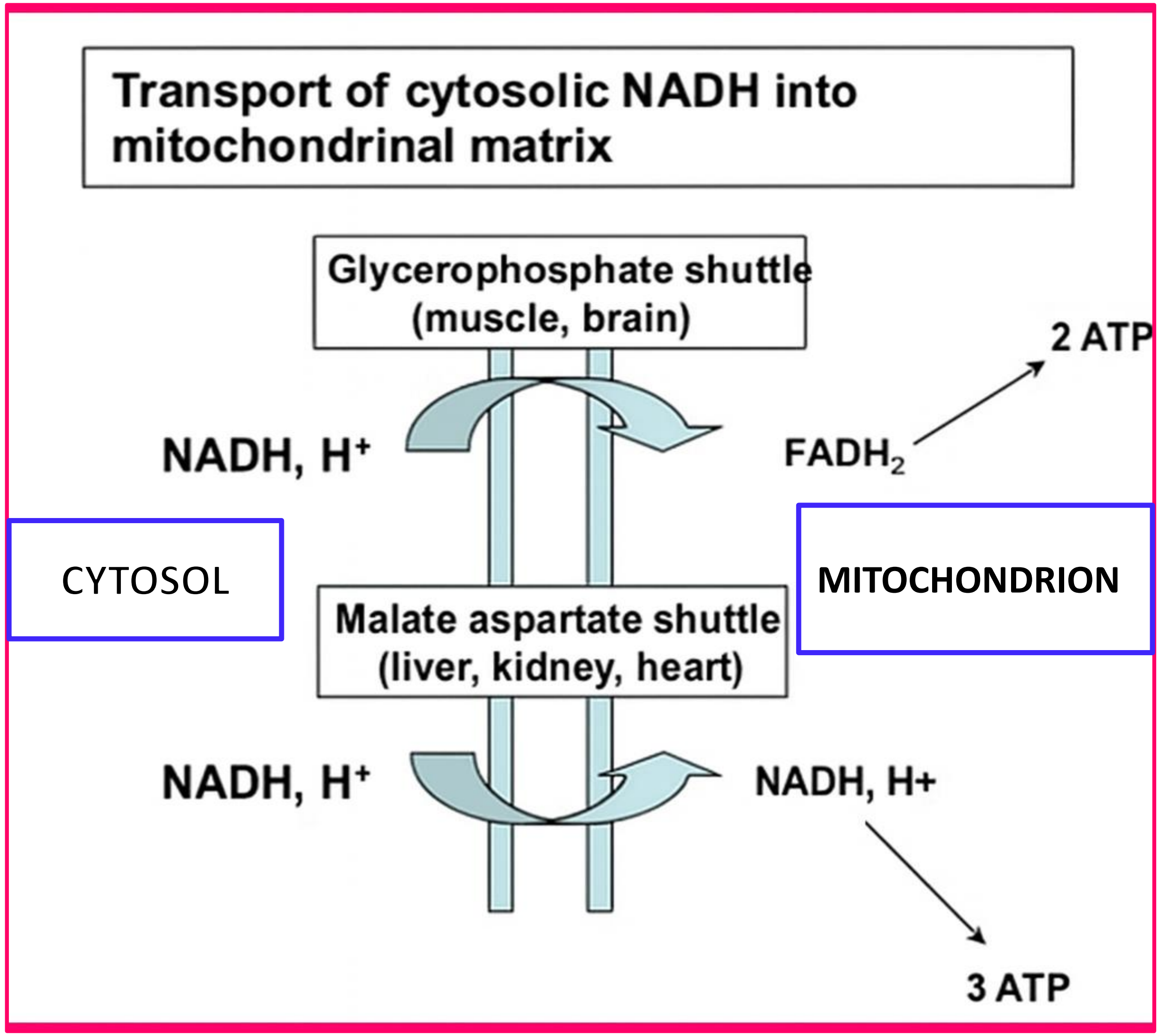
- When it is impaired, high-energy-demand organs such as the **brain** and **muscles** are particularly affected.

- Symptoms include **fatigue**, **muscle weakness**, and **neurological disorders**. Certain genetic diseases, known as **mitochondrial myopathies**, are associated with these defects.

# Shuttle system

36 or 38
ATP !

*Depending on the shuttle system used, one molecule of glucose will generate 36 or 38 molecules of ATP.*



# ***Shuttle system***

**(Transport of cytosolic NADH to the mitochondrial matrix)**

- During **glycolysis**, the **cytosolic NADH** produced in step 6 catalyzed by *glyceraldehyde-3-phosphate dehydrogenase* must be regenerated into $NAD^+$, otherwise glycolysis would stop due to insufficient $NAD^+$.

- The problem: The mitochondrial membrane is **impermeable** to cytosolic NADH.

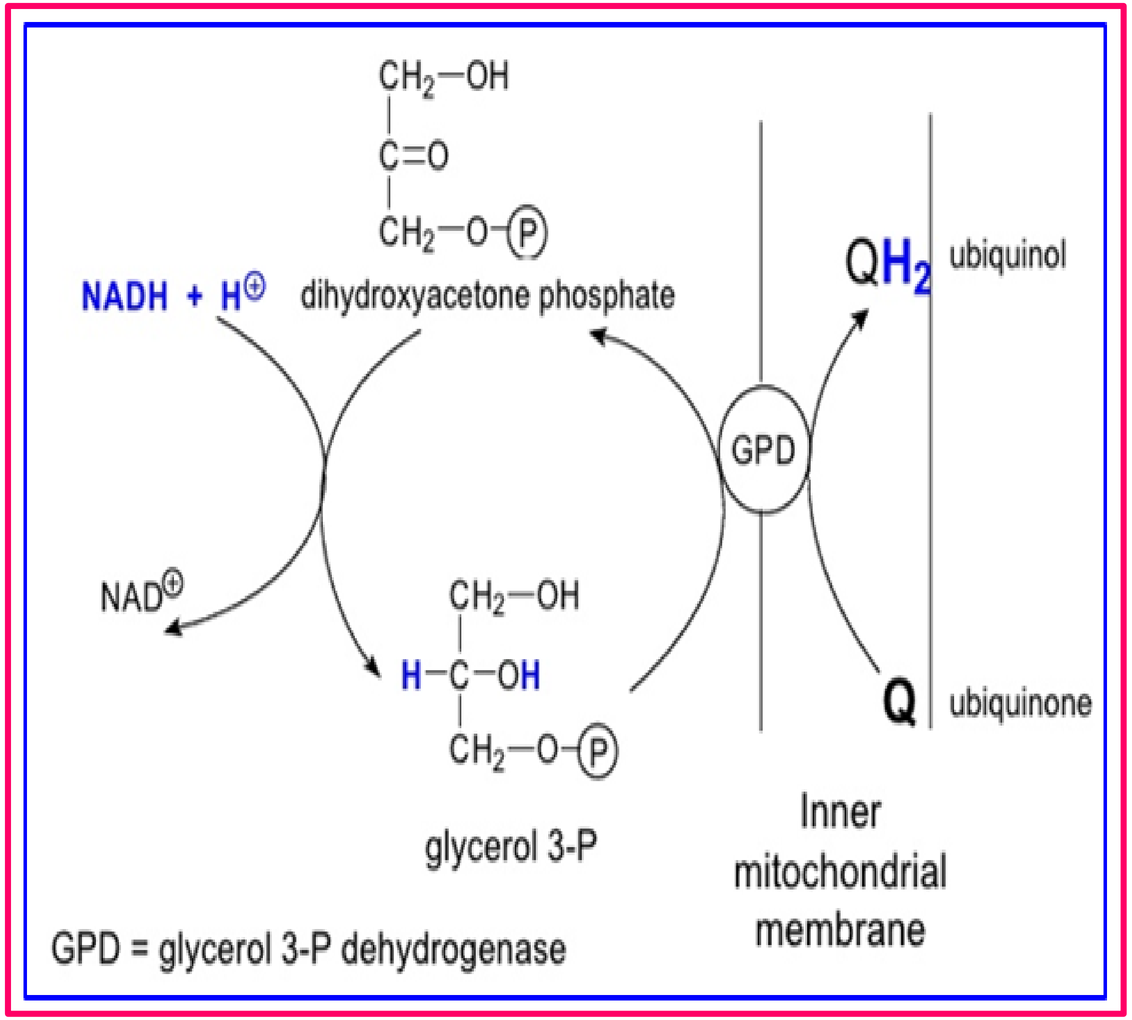
- The solution: Eukaryotic cells possess shuttle systems that **transfer** the **electrons** from **cytosolic NADH** into the **mitochondria** without the NADH molecule itself crossing the inner membrane.

- **Depending on the tissue, there are two types of shuttles:**

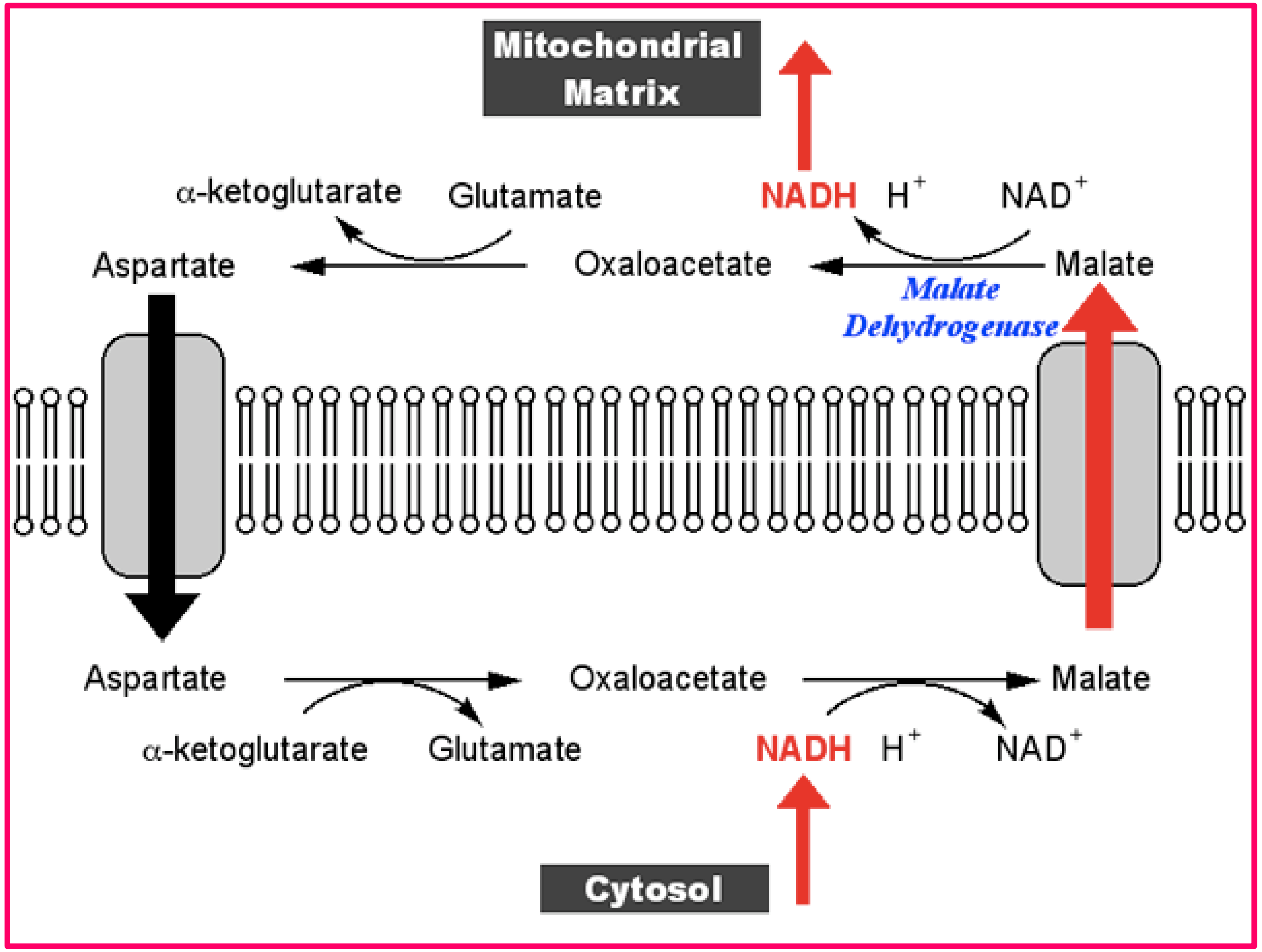
- Glycerol phosphate shuttle (muscle, brain)

- Malate–aspartate shuttle (liver, kidneys, heart)

## The glycerol phosphate shuttle




## The malate–aspartate shuttle



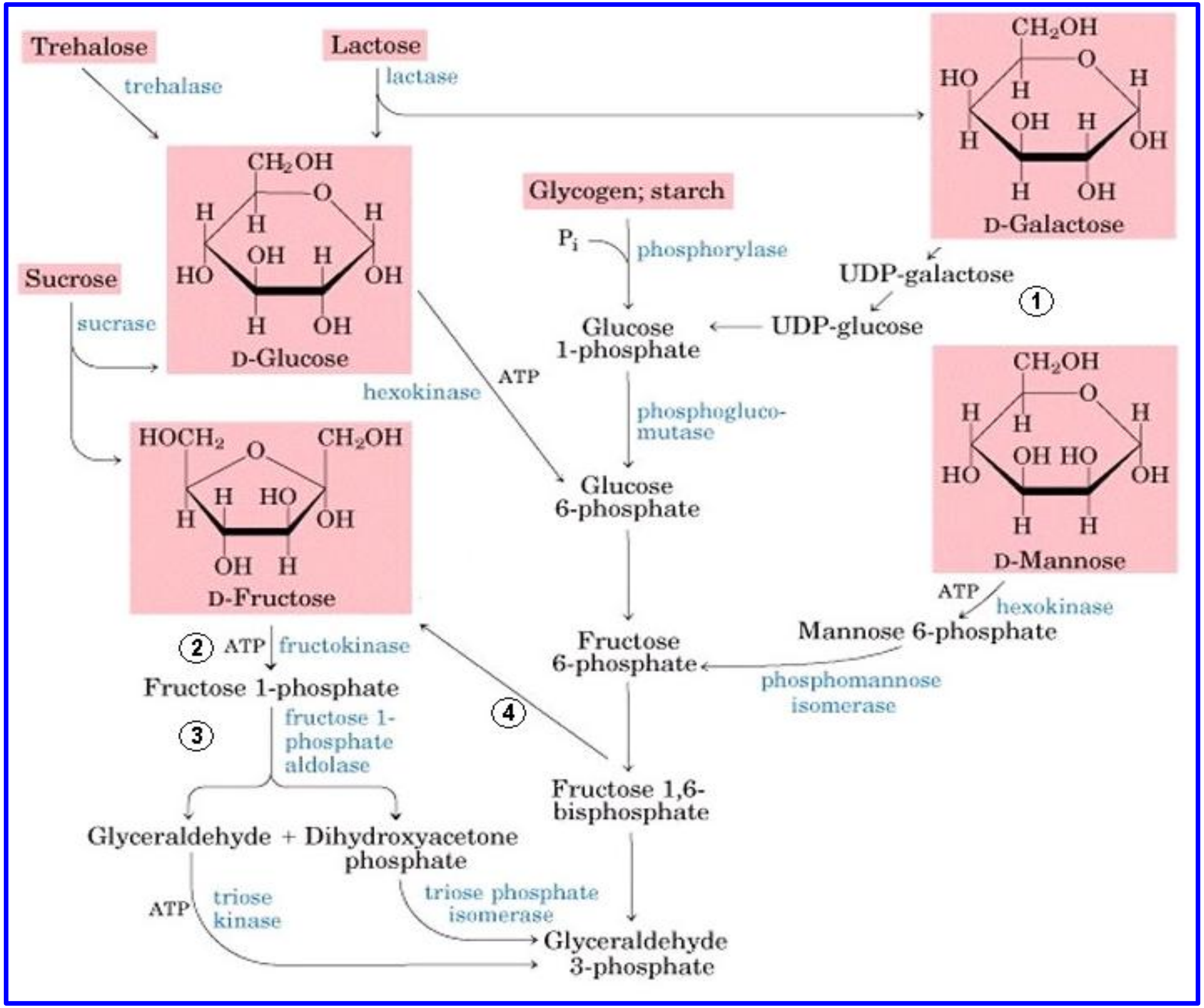
# *Gluconeogenesis from other hexoses*

-

➢ Fructose, galactose, and mannose are required for the biosynthesis of **glycoproteins**.

➢ They can also serve as **energy substrates**.

➢ Their **conversion** into glucose occurs in the **liver**. Indeed, these hexoses undergo a series of parallel reactions that allow them to enter the **glycolytic pathway** at an appropriate intermediate step.



# *Fructose Metabolism*

## Clinical aspect:

- Hepatic *fructokinase* deficiency: This results in essential fructosuria, which is generally benign and asymptomatic.

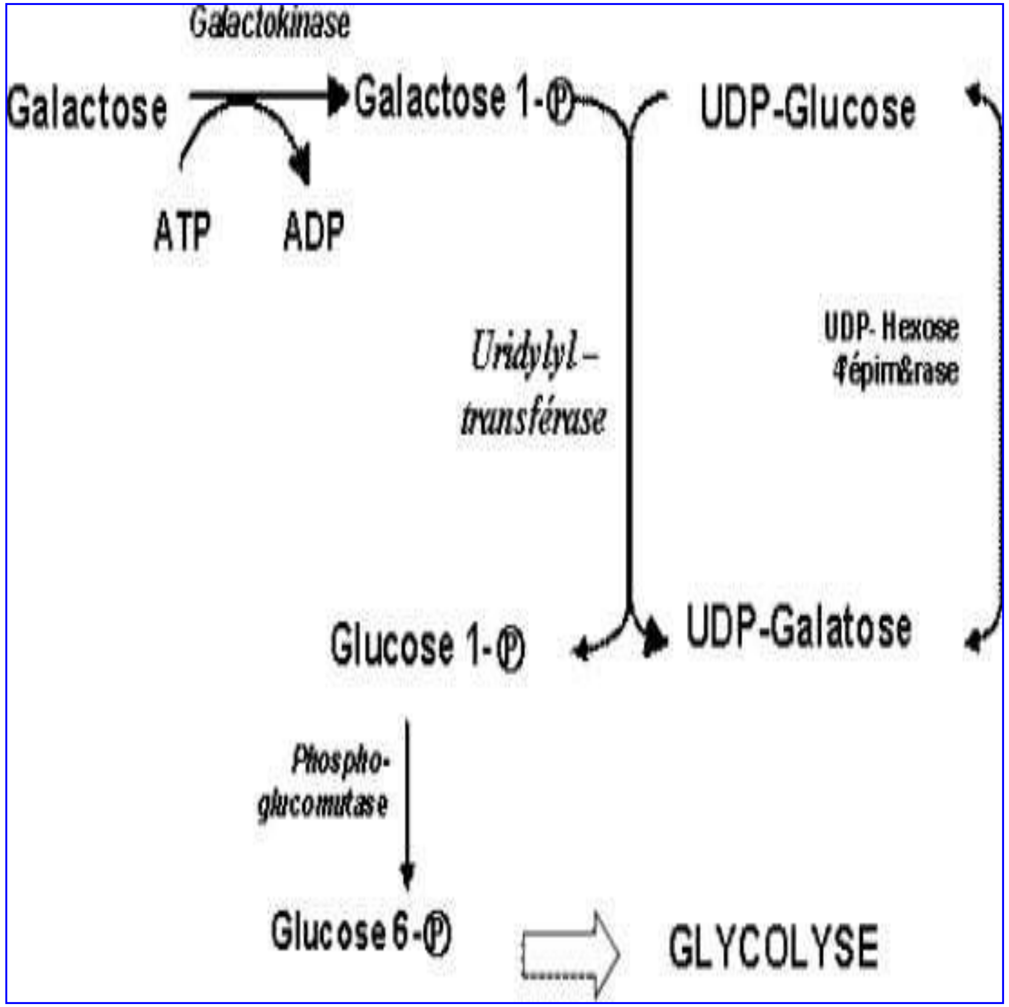
- *Aldolase B* deficiency: This leads to hereditary fructose intolerance, characterized by the accumulation of fructose-1-phosphate, leading to **hypoglycemia**, **nausea**, **vomiting**, and potential **liver damage**.

# Galactose Metabolism

***Clinical aspect:***

*Galactose-1-phosphate uridyltransferase* deficiency causes congenital galactosemia, the most common inherited disorder of carbohydrate metabolism.

- **Galactosemia** is characterized by the accumulation of **galactose** in the blood and tissues, leading, among other effects, to severe hypoglycemia and early-onset **cataracts**.
- Galactose is **reduced** by *aldose reductase* *to* galactitol, which opacifies the lens.
- Symptoms of this disease include **vomiting, diarrhea,** and **mental retardation;** a galactose-free diet prevents the manifestation of the disease. If needed, the body can synthesize **galactose** from **glucose**.




***Note**: The same enzyme, aldose reductase, reduces **glucose** to **sorbitol**, which is responsible for **cataracts** in diabetics and can contribute to liver dysfunction.*

# *Pentose Phosphate Pathway (PPP)*

# *Pentose Phosphate Pathway (PPP)*

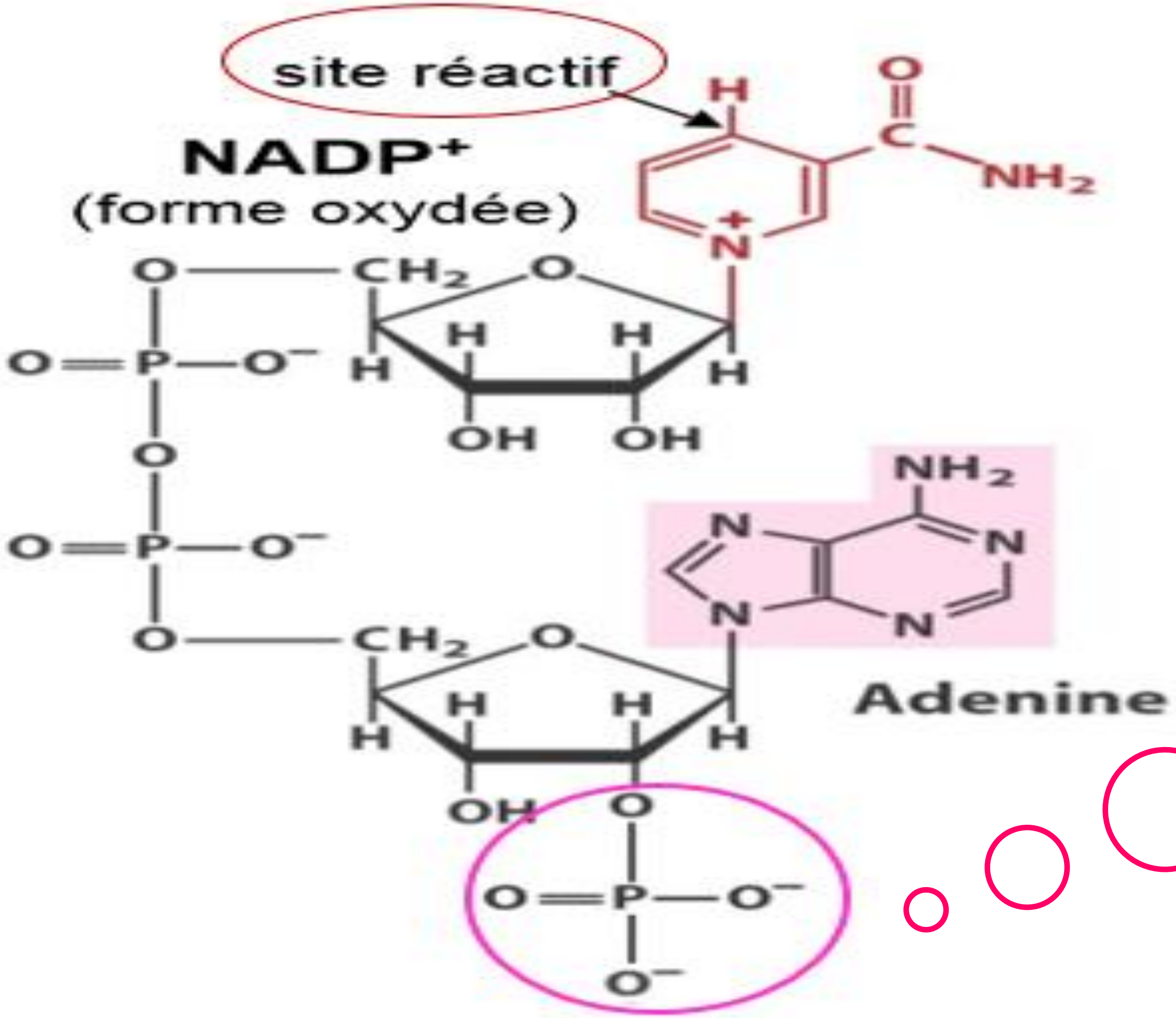
- The PPP **occurs** in the cytosol.
- Unlike **glycolysis**, this pathway does not generate energy.
- Its primary **function** is the **production** of:

• NADPH, $H^+$: This molecule plays a critical role in the **detoxification** of peroxides in **red blood cells**, as well as in the **biosynthesis** of **fatty acids**, **cholesterol**, and **steroid hormones**. NADPH, $H^+$ provides the reducing power required for numerous cellular reactions.

• Ribose-5-phosphate and its derivatives: These compounds are essential for the **synthesis** of nucleic acids (**RNA** and **DNA**) and nucleotides (such as **ATP**, **coenzyme A**, **NAD**, **FAD**, etc.). The pathway also produces erythrose-4-phosphate, which serves as a precursor for the biosynthesis of **aromatic amino acids.**

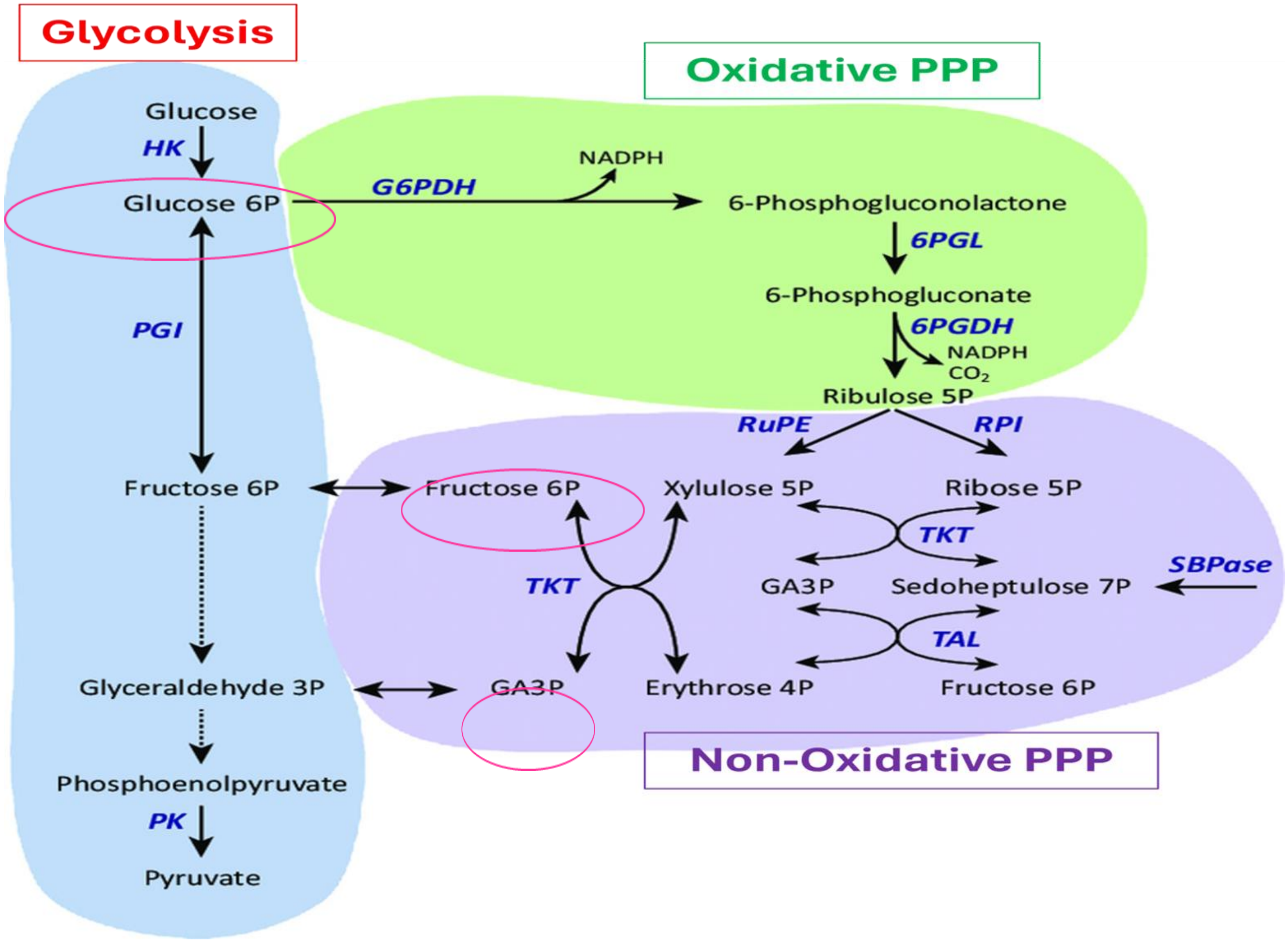
*Note: The pentose phosphate pathway is **ubiquitous** (it operates in all cells), but its **activity** varies according to the cellular requirements for **ribose** and **NADPH, $H^+$**.*

# *Chemical structure of $NADP^+$ (Nicotinamide Adenine Dinucleotide Phosphate)*




- There is a very important difference between $NADP^+$ and $NAD^+$.
- From a chemical standpoint, it is simply the presence of an additional phosphate group on the 2' position of the adenosine moiety.

# *Overview of the Pentose Phosphate Pathway*




*Note: The starting substrate is **glucose-6-phosphate**, and the final products are **fructose-6-phosphate** and **glyceraldehyde-3-phosphate**; thus, both the **initial** and **final** metabolites of the pathway are intermediates of **glycolysis**.*

# The phases of the pentose phosphate pathway

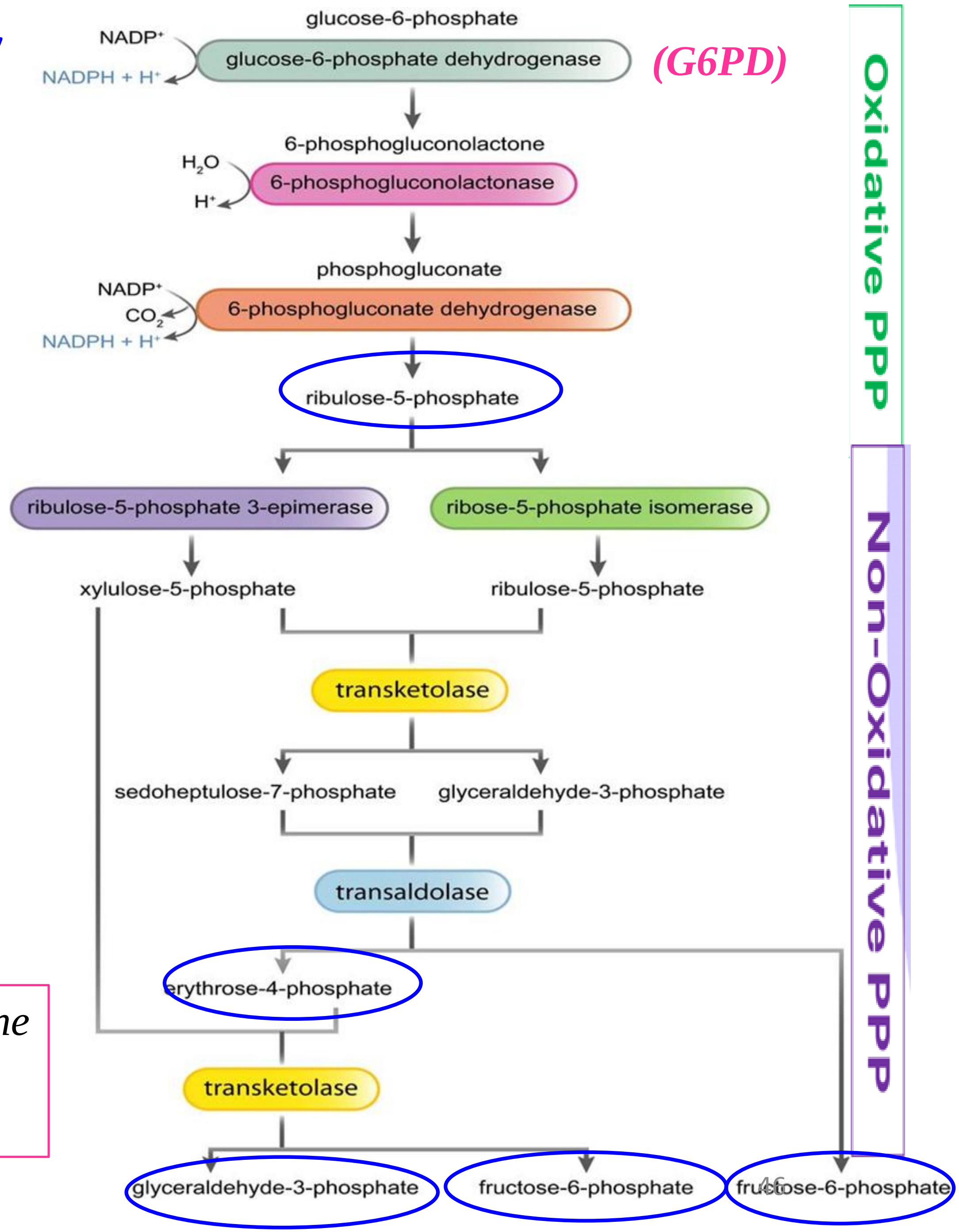
- The ribose-5-phosphate produced is utilized for the synthesis of **nucleic acids** or other nucleotides.

- In **cells** that require **only** NADPH, $H^+$, **ribose-5-phosphate** is redirected back into **glycolysis**.

- Erythrose-4-phosphate is used for the **biosynthesis** of **aromatic amino acids** (tyrosine, tryptophan, and phenylalanine), or it can be **converted** together with **xylulose-5-phosphate** into **glyceraldehyde-3-phosphate** and fructose-6-phosphate.

- The intermediates generated (glyceraldehyde-3-phosphate and fructose-6-phosphate) can eventually enter the **glycolytic pathway**, serving as **connection** points between the **pentose phosphate pathway** and **glycolysis**.

***Note:** Glucose-6-phosphate dehydrogenase (G6PD) is the **key enzyme** of the pentose phosphate pathway. The reactions of the **non-oxidative phase** are reversible and are primarily **regulated** by substrate availability.*

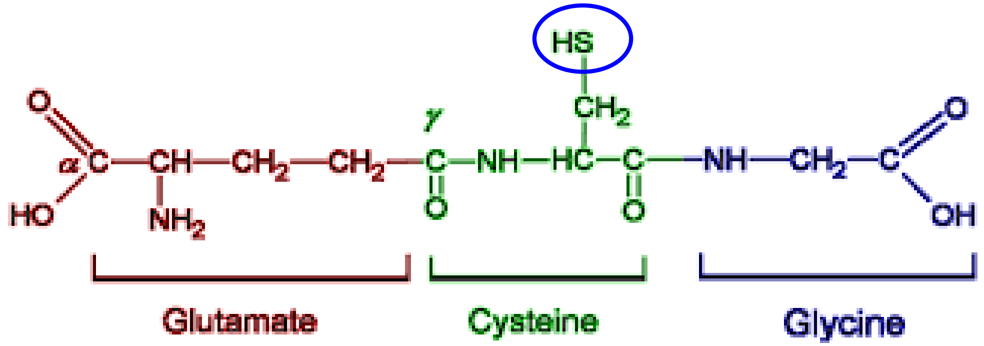


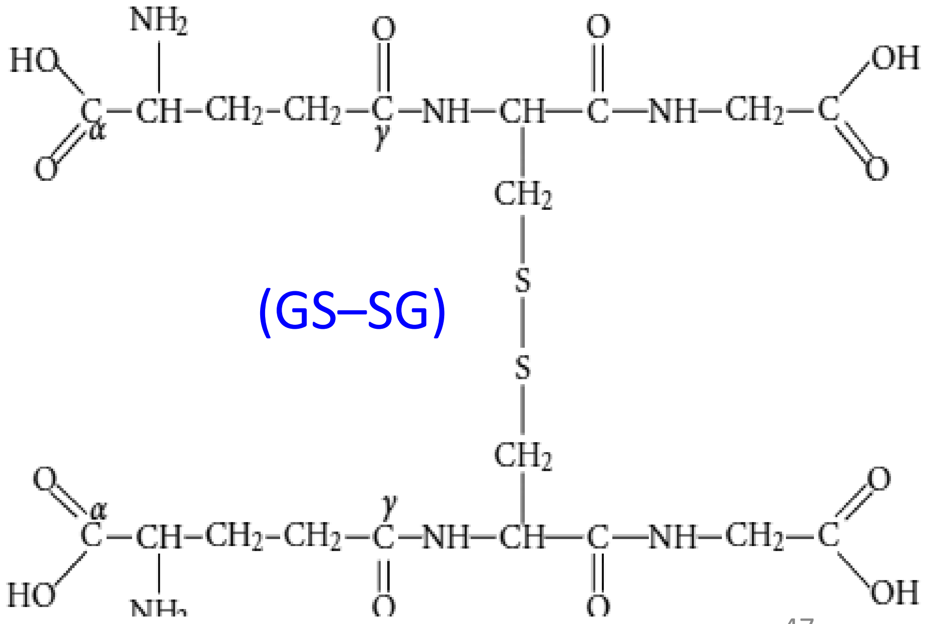
# *Role of NADPH and Glutathione in Red Blood Cells*

- The **pentose phosphate pathway** supplies **red blood cells** with NADPH, which is required to recycle **oxidized** glutathione (GS–SG) back to its **reduced** form (GSH).

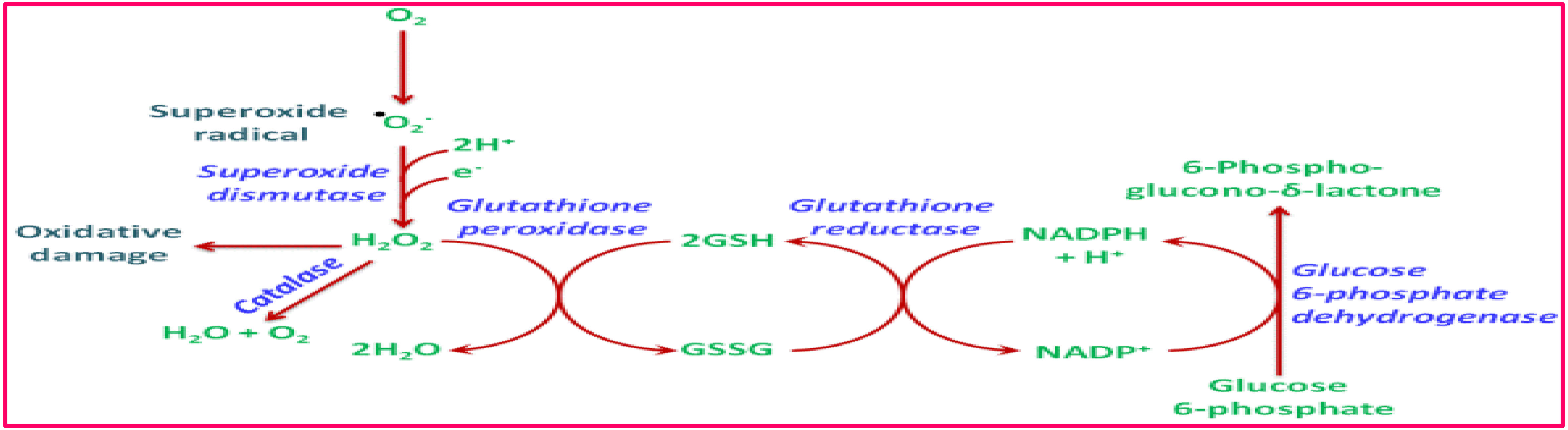
- **Reduced glutathione** protects red blood cells from damage caused by toxic oxidizing molecules, such as hydrogen peroxide ($H_2O_2$).

GLUTATHIONE (GSH)



# Role of NADPH and Glutathione in Red Blood Cells



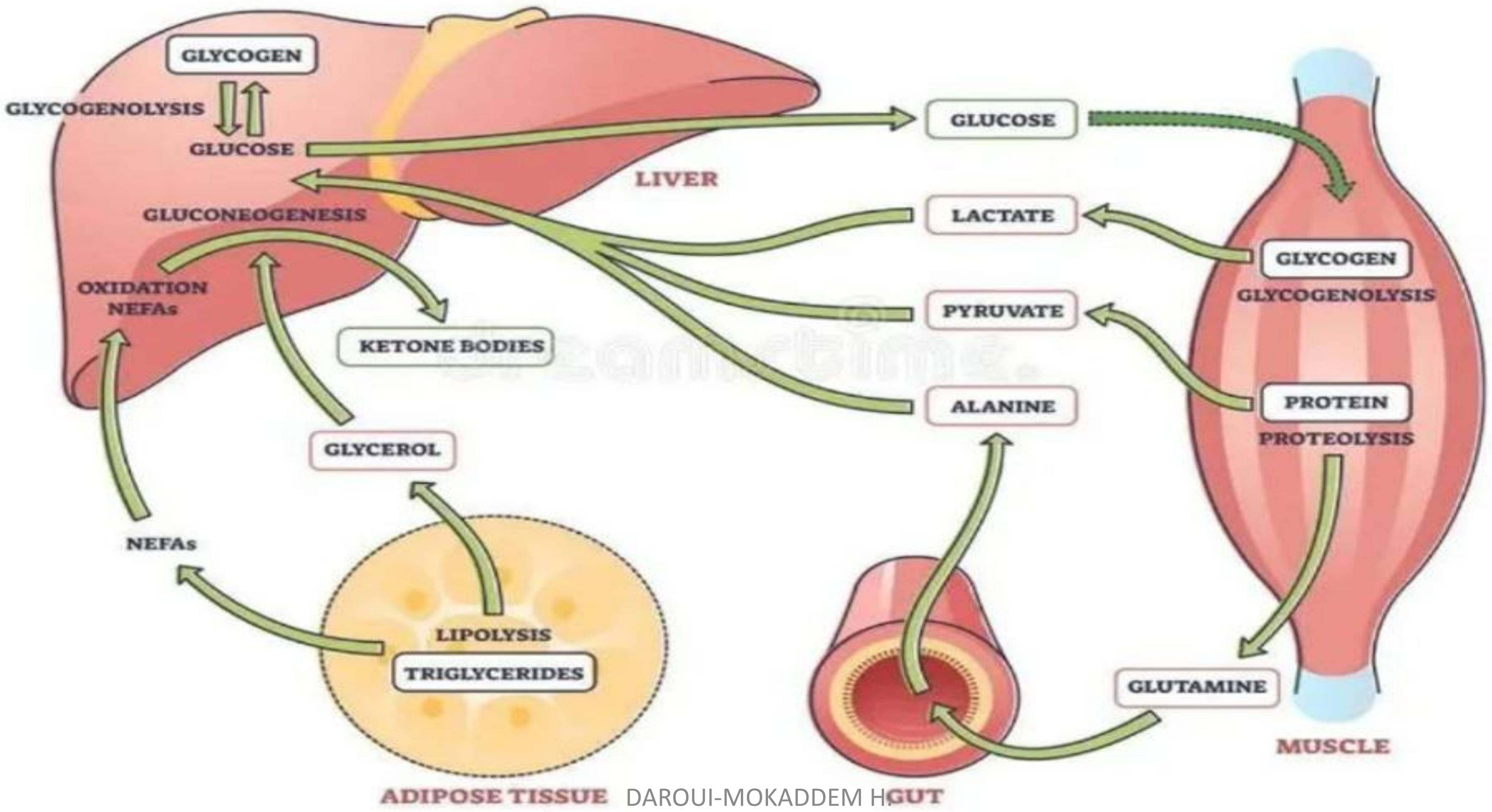

A **deficiency** in *glucose-6-phosphate dehydrogenase (G6PD)* **decreases** the efficiency of the **pentose phosphate pathway** in producing NADPH. This reduction leads to the **accumulation** of **organic peroxides**, which **deform** the **red blood cell membrane** and **oxidize** hemoglobin ($Fe^{2+} \rightarrow Fe^{3+}$) as well as **other** erythrocyte **proteins**.

***Note****: The main clinical manifestation is an acute hemolytic crisis occurring a few hours after ingestion of an oxidizing agent (e.g.,* ***fava beans****,* ***drugs*** *such as* ***aspirin*** *or* ***sulfonamides****), resulting in* ***hemolytic anemiaa*** *condition known as favism.*

# *Gluconeogenesis*

# Gluconeogenesis

**Definition**: the formation of **carbohydrate molecules**, primarily **glucose** and **glycogen**, from non-carbohydrate **precursors**.



# *Gluconeogenesis*

- Certain **tissues** (the **brain**, **red blood cells**, rapidly contracting **muscle**, etc.) require a **continuous supply** of **glucose**. The liver can fulfill this function by **mobilizing glycogen** (short-term) and through gluconeogenesis.

- **In humans, gluconeogenesis occurs primarily in:**

- The **liver**: 90% of newly synthesized glucose
- The **kidneys** and **intestinal** epithelium: 10%
- It does not occur in **muscle** or **brain** tissue.

***Note:*** *The reactions of gluconeogenesis are conserved across animals, **plants, fungi**, and **microorganisms.***

# *Precursors of gluconeogenesis*

- Pyruvate and lactate (≈ 1/3): derived from **red blood** cells and **muscle cells**.

- Alanine (≈ 1/3): an amino acid originating from **muscle cells**.

- Glycerol: derived from the **catabolism** of dietary **triglycerides**, **adipose tissue**, or circulating **lipoproteins**.

- Gluconeogenic amino acids: obtained from **dietary proteins** or **tissue proteins.**

- Propionate: derived from the **degradation** of odd-chain fatty acids.

***Note:*** *In humans and animals, **acetyl-CoA** (produced from fatty acid degradation) cannot be converted into **glucose**; therefore, **fatty acids** cannot serve as substrates for **gluconeogenesis**.*

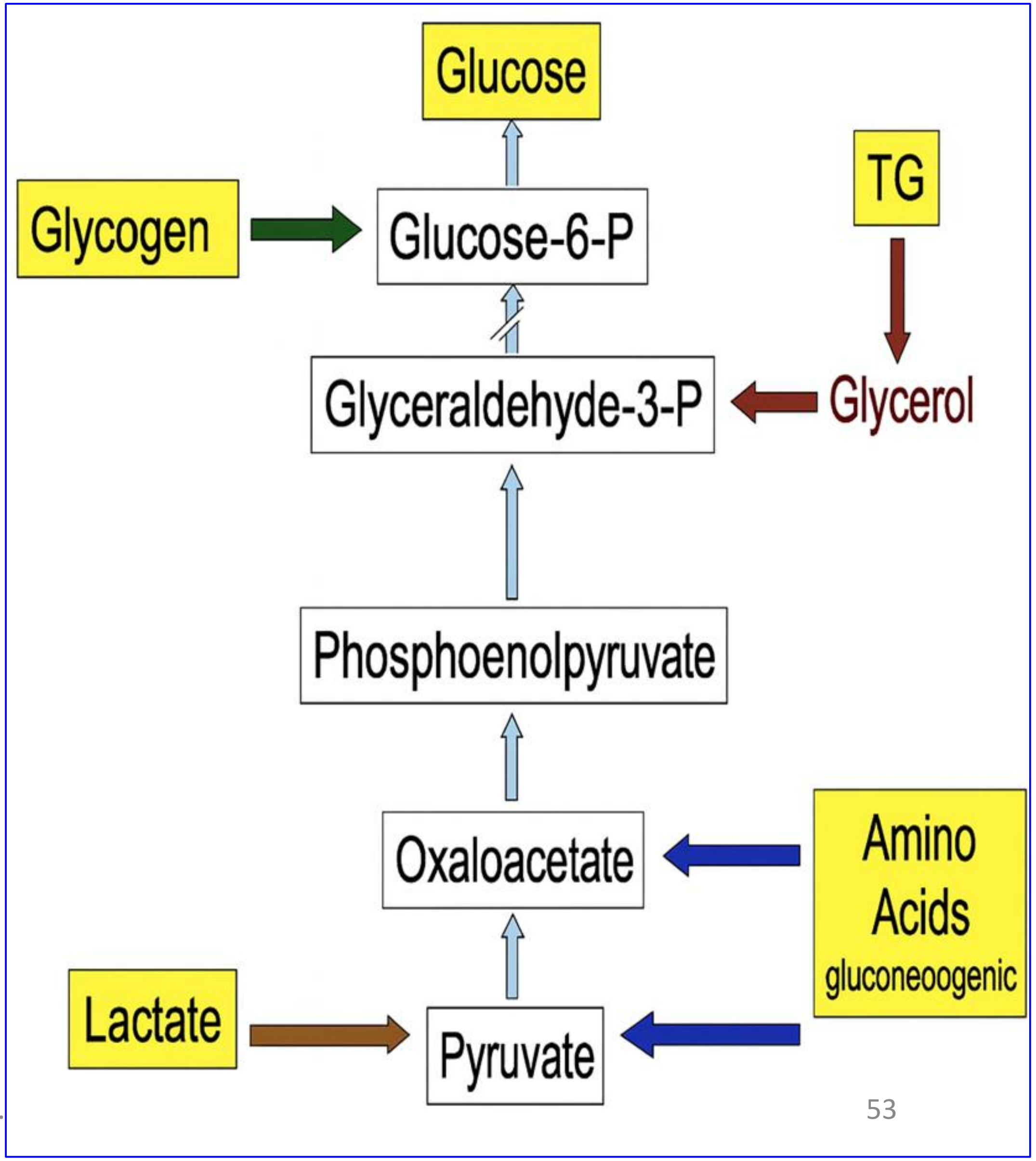
## *Entry of Precursors into Gluconeogenesis*

The three entry points of precursors into gluconeogenesis are:

- Pyruvate: for **lactate**, **alanine**, and **gluconeogenic amino acids** whose catabolism converges at pyruvate.

- Phosphoenolpyruvate (PEP): for **gluconeogenic amino acids** whose catabolism feeds into intermediates of the **Krebs cycle**.

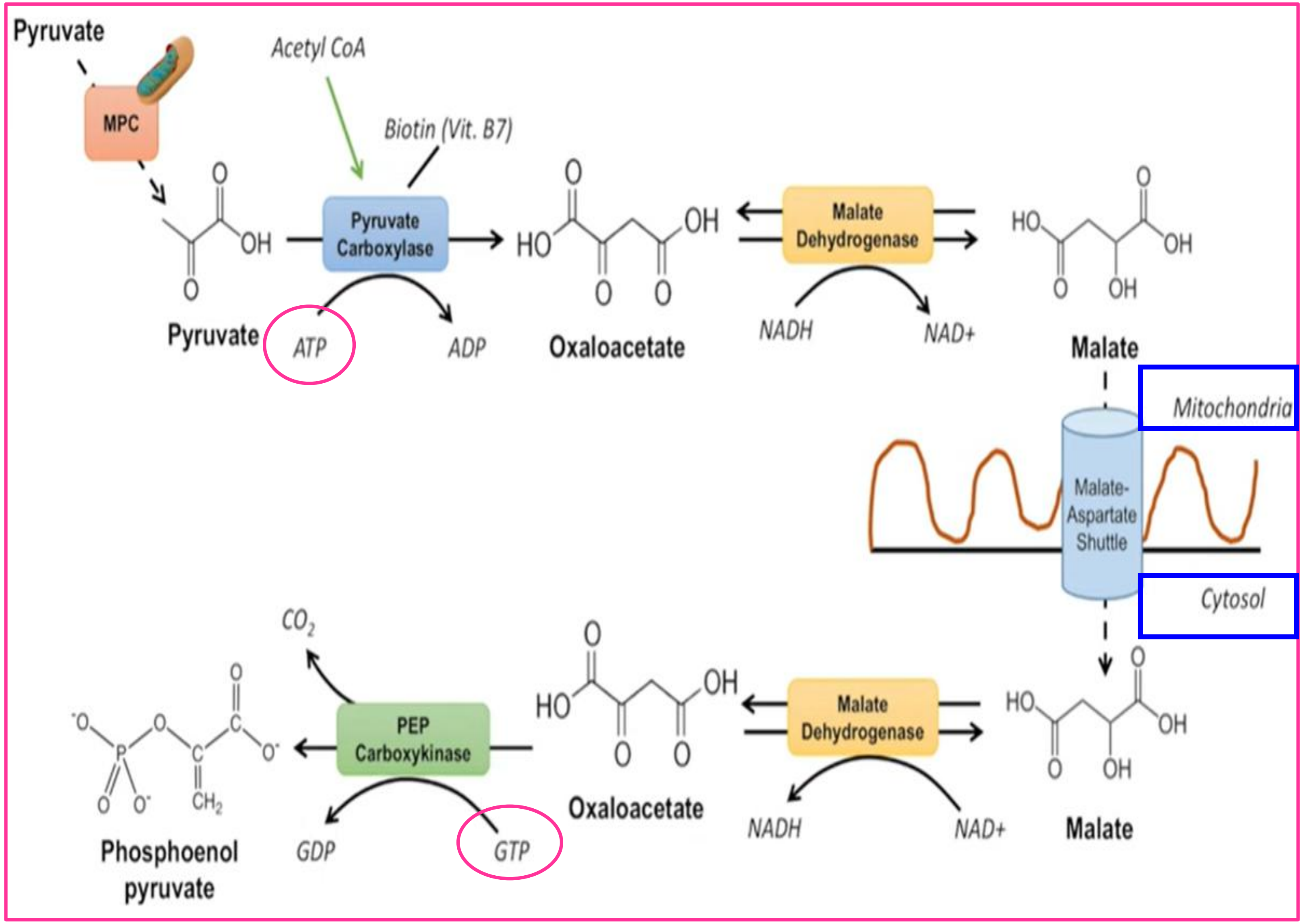
- Dihydroxyacetone phosphate (DHAP): for **glycerol**.



# *Gluconeogenesis from Pyruvate*

➢ Pyruvate is transported into the **mitochondrial** matrix and then carboxylated to oxaloacetate by *pyruvate carboxylase*, a **strictly mitochondrial enzyme** requiring the coenzyme biotin (vitamin B8). This reaction **consumes** one molecule of ATP.

➢ The phosphorylative decarboxylation of oxaloacetate to phosphoenolpyruvate (PEP) **consumes** one molecule of GTP (regenerated from ATP) and is catalyzed by *phosphoenolpyruvate carboxykinase* (PEPCK).



# *Derivation of Gluconeogenesis*

The **conversion** of **pyruvate** into **glucose** is the central pathway of gluconeogenesis. Among its ten enzymatic reactions:

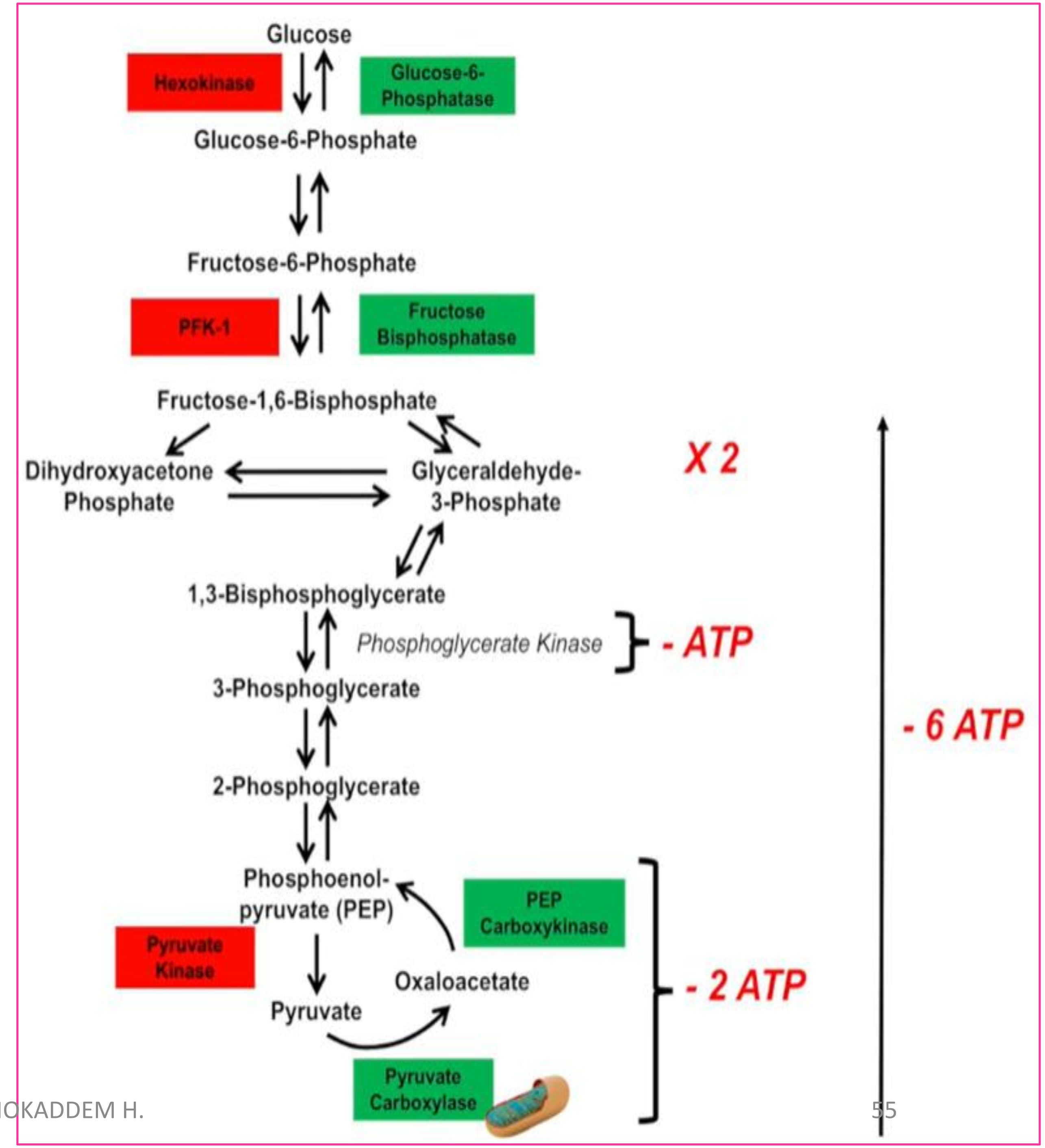
- **Seven** are the reverse reactions of **glycolysis**, and are therefore catalyzed by the same **cytosolic enzymes.**
- Three **irreversible** glycolytic reactions must be bypassed in gluconeogenesis so that glucose synthesis becomes thermodynamically favorable.

- Thus, reactions 1, 8, and 10 of **gluconeogenesis** are catalyzed by enzymes that are different from those of glycolysis:

*Pyruvate carboxylase*, which are mitochondrial enzymes,

*Fructose-1,6-bisphosphatase* (*F1*,6BPase), and

*Glucose-6-phosphatase.*

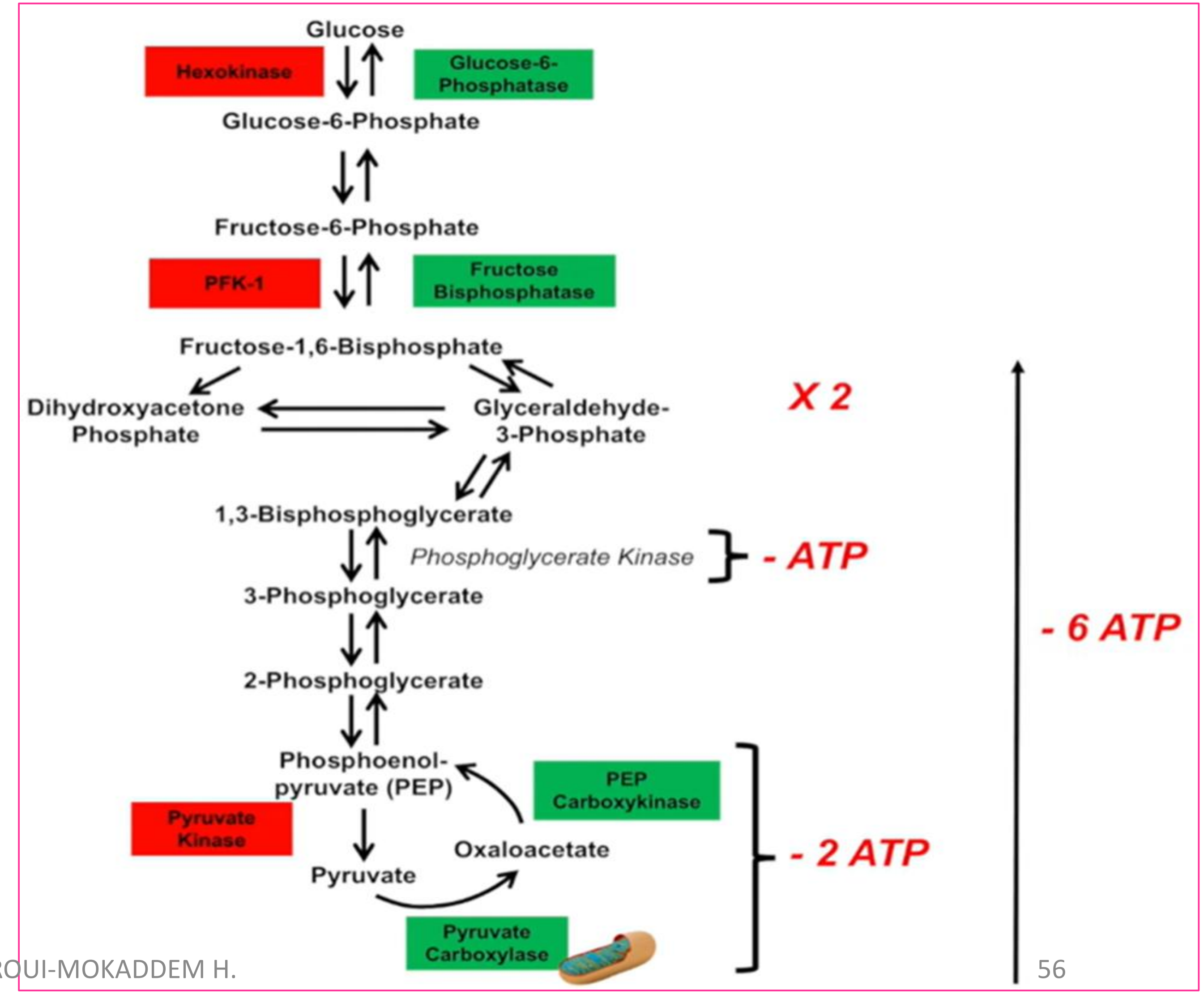


# Energetic Balance of Gluconeogenesis

**2 pyruvates + 4 ATP + 2 GTP + 2 (NADH, $H^+$) + 6 H2O $\longrightarrow$ Glucose + 4 ADP + 2 GDP + 6 Pi + 2 $NAD^+$ + 2H+**

- From **two molecules** of **pyruvate** to one molecule of glucose, 2 × 3 ATP = 6 ATP are consumed.

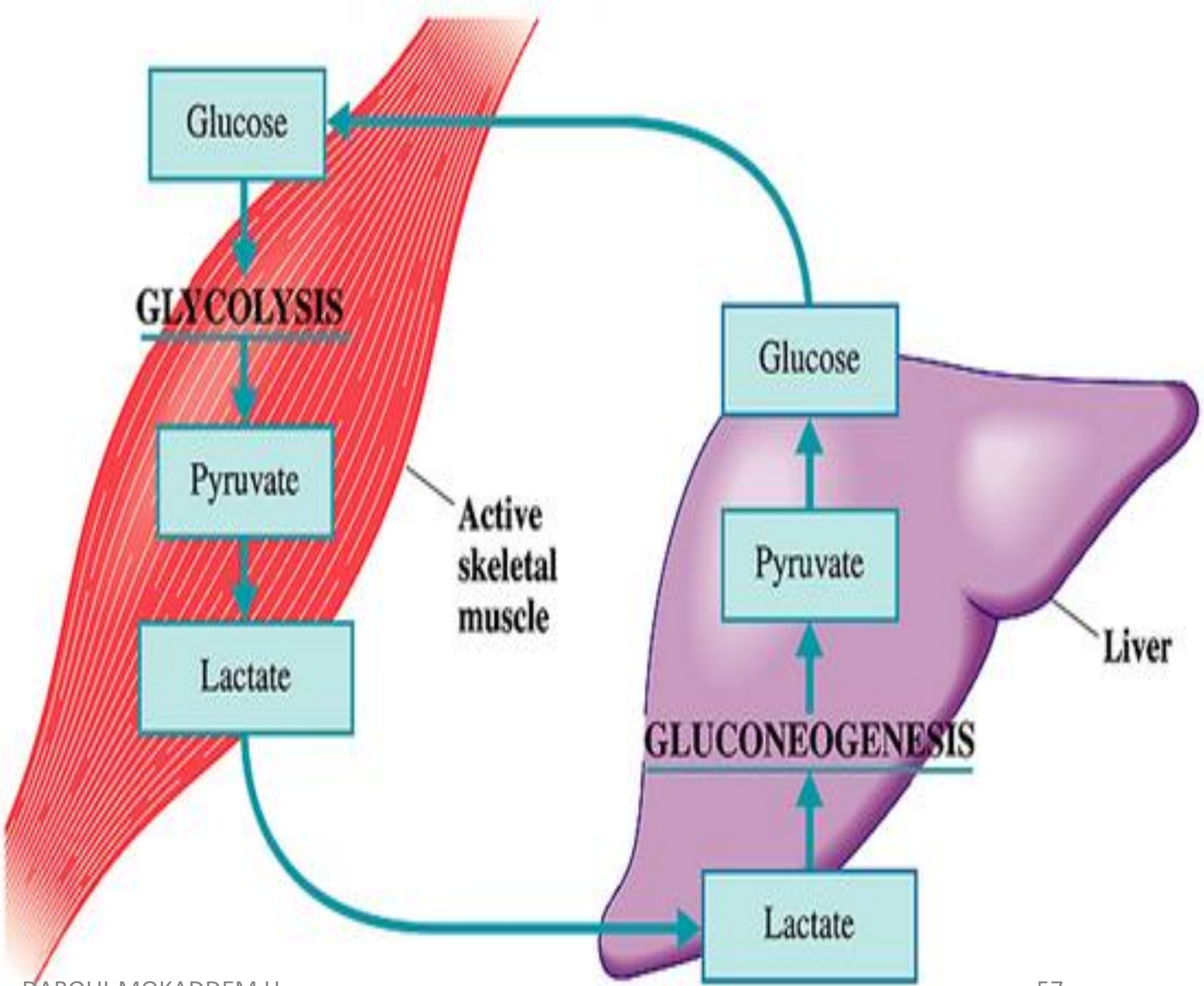
- The energetic cost of **gluconeogenesis** versus **glycolysis** (**6 ATP / 2 ATP**) reflects the price of the irreversibility of these pathways and their reciprocal regulation.



# *Gluconeogenesis from Lactate*

## Muscle-derived lactate:

- During **anaerobic** muscle activity (hypoxia), lactate is produced in the **muscles**, released into the bloodstream, and transported to the **liver**, where it is converted into glucose.
- This **glucose** is then made available again to the **muscles**.
- This **cycle** of **glucose-lactate** is known as the **Cori cycle.**



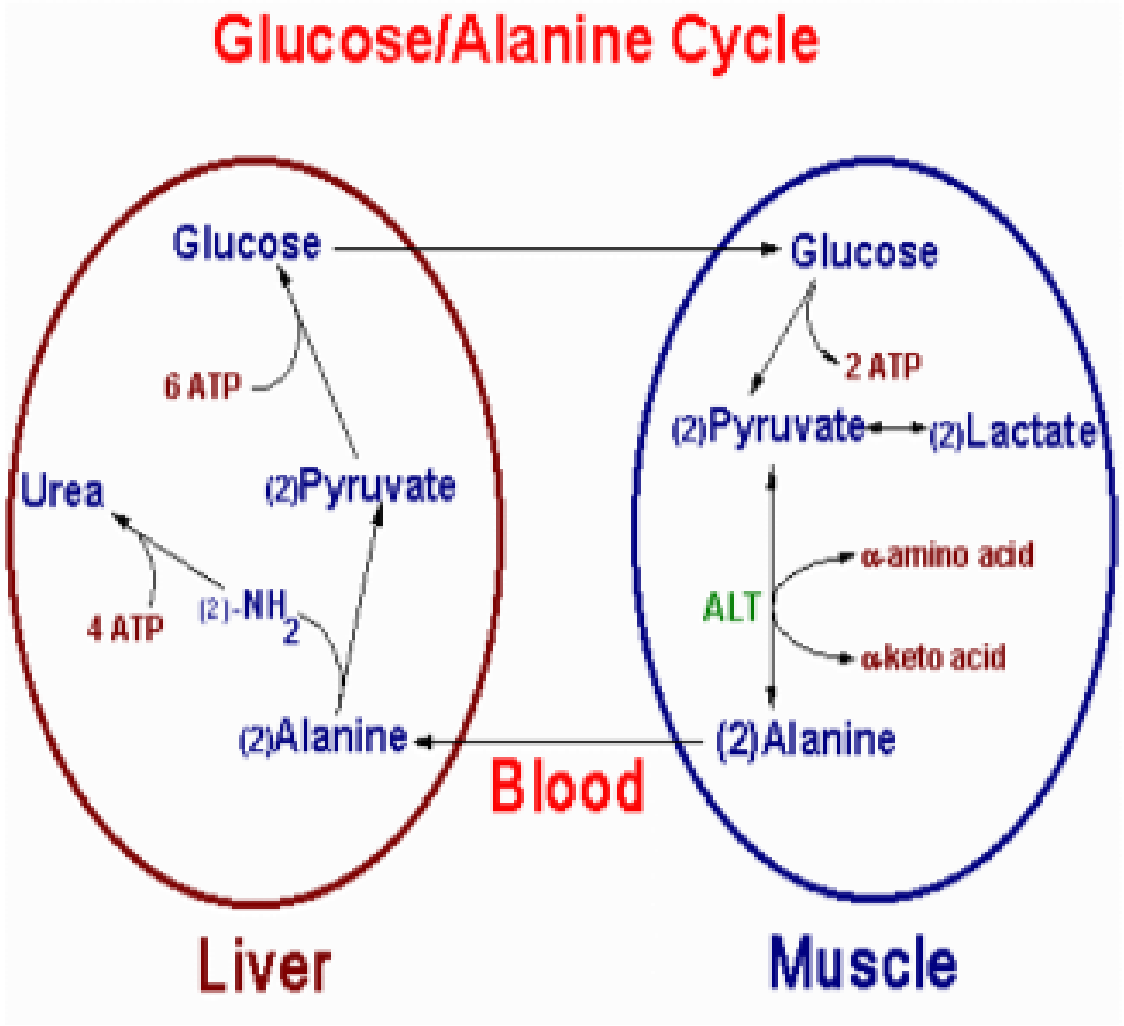
# Gluconeogenesis from Alanine of Muscular Origin

- A constant precursor of glucose during prolonged fasting, alanine originates from the **catabolism** of **muscle proteins** as well as from **glycolytic pyruvate**.

- **Pyruvate** is converted into **alanine**.

- Alanine is then released into the **bloodstream**, transported to the **liver**, and subsequently reconverted into **pyruvate**.

- This **glucose-alanine** cycle is known as the **Felig cycle**.



# Gluconeogenesis from glycerol

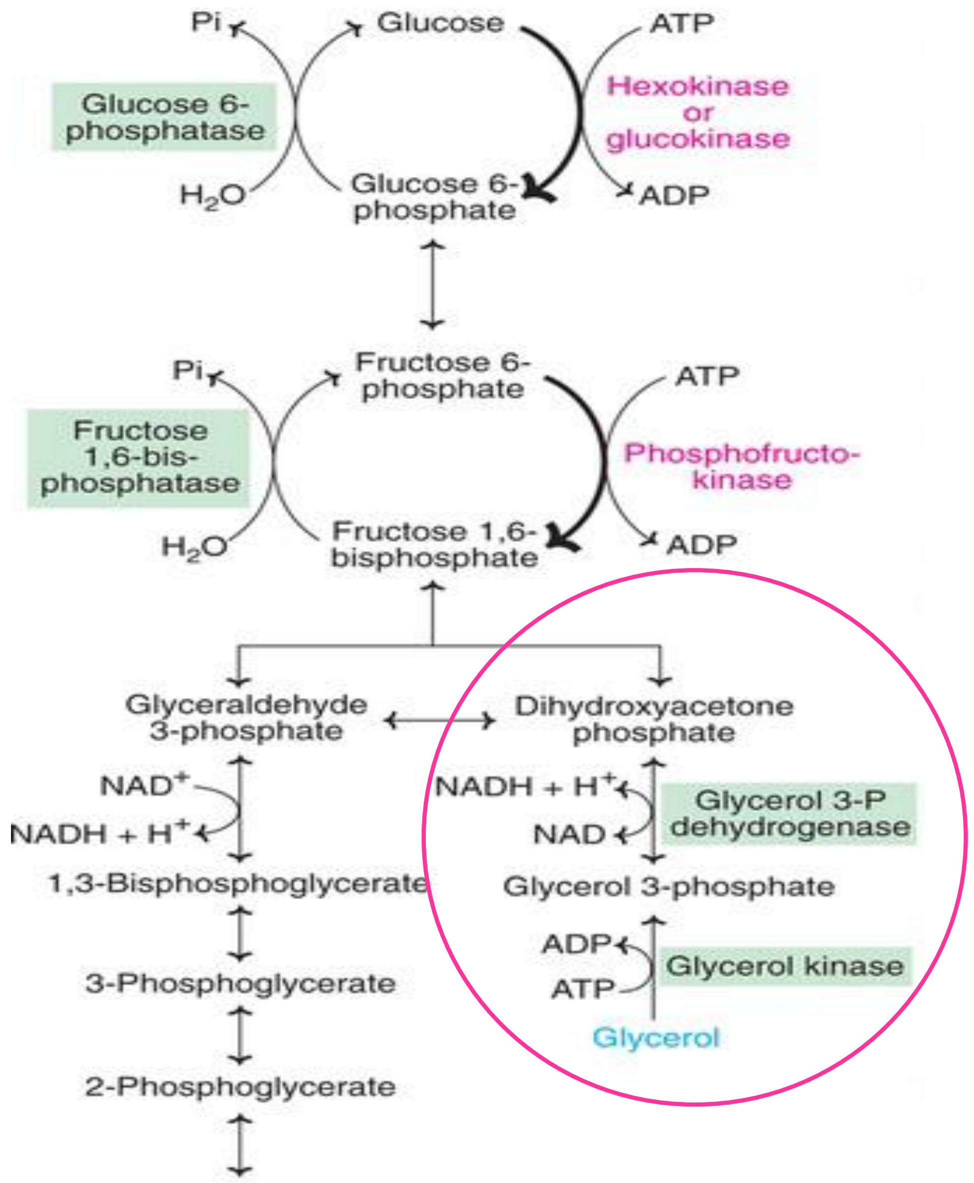
- Glycerol is the degradation product of **triglycerides** (from dietary sources, circulating lipoproteins, and adipose tissues)

- The **liver** and kidneys possess *glycerol kinase*, which phosphorylates glycerol into **glycerol-3-phosphate**.

<u>This molecule can then</u>:

- **Accept fatty acids** (to synthesize **triglycerides**)

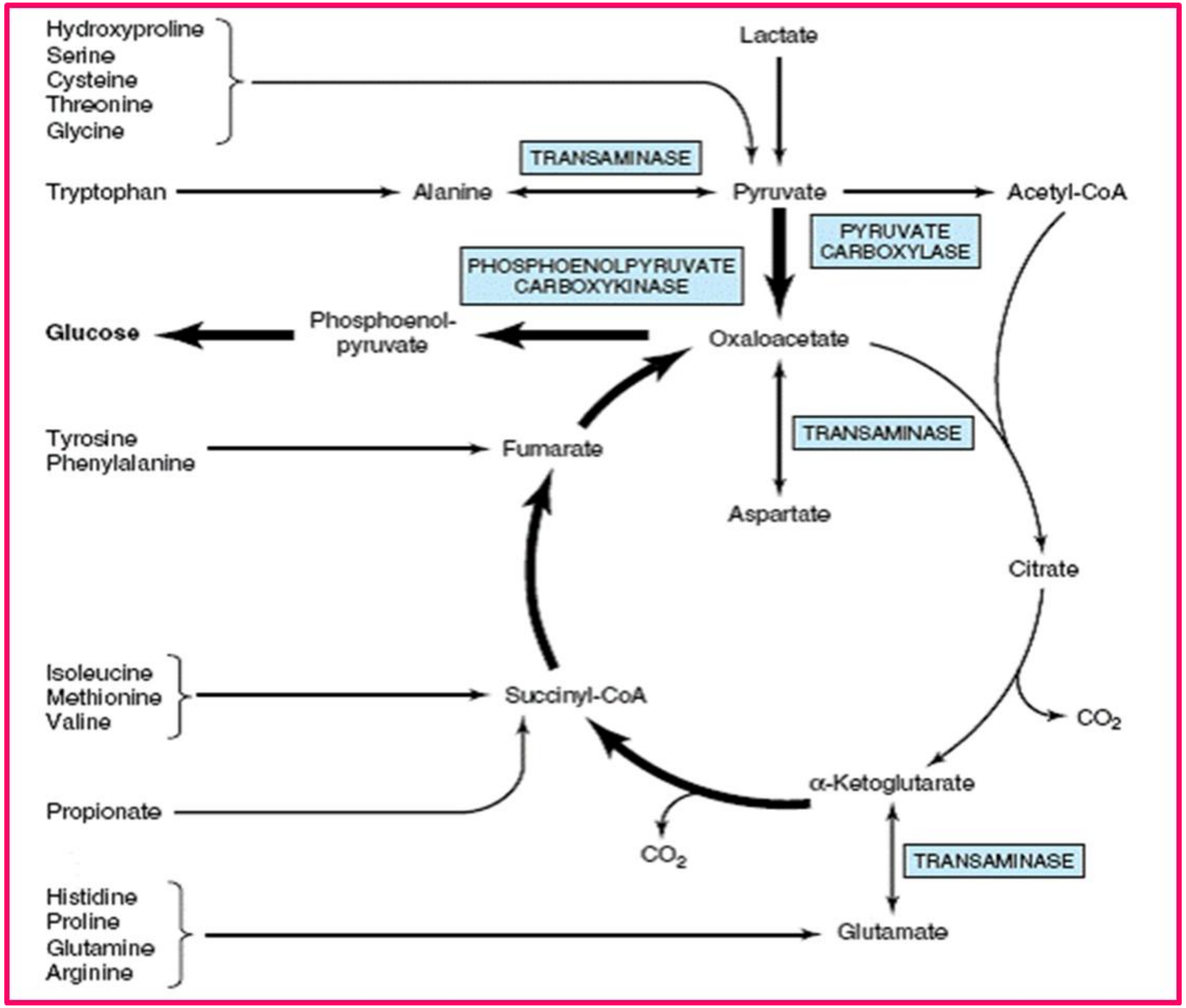
- Be **oxidized** into **dihydroxyacetone phosphate** by *glycerol-3-phosphate dehydrogenase* and enter the **gluconeogenesis** pathway.



# *Gluconeogenesis from glucogenic amino acids*

- **Amino-acids** whose carbon skeleton is converted into **pyruvate** or into one of the four intermediates of the **Krebs cycle** (α-**ketoglutarate**, **succinyl-CoA**, **fumarate**, or **oxaloacetate**) are called glucogenic.

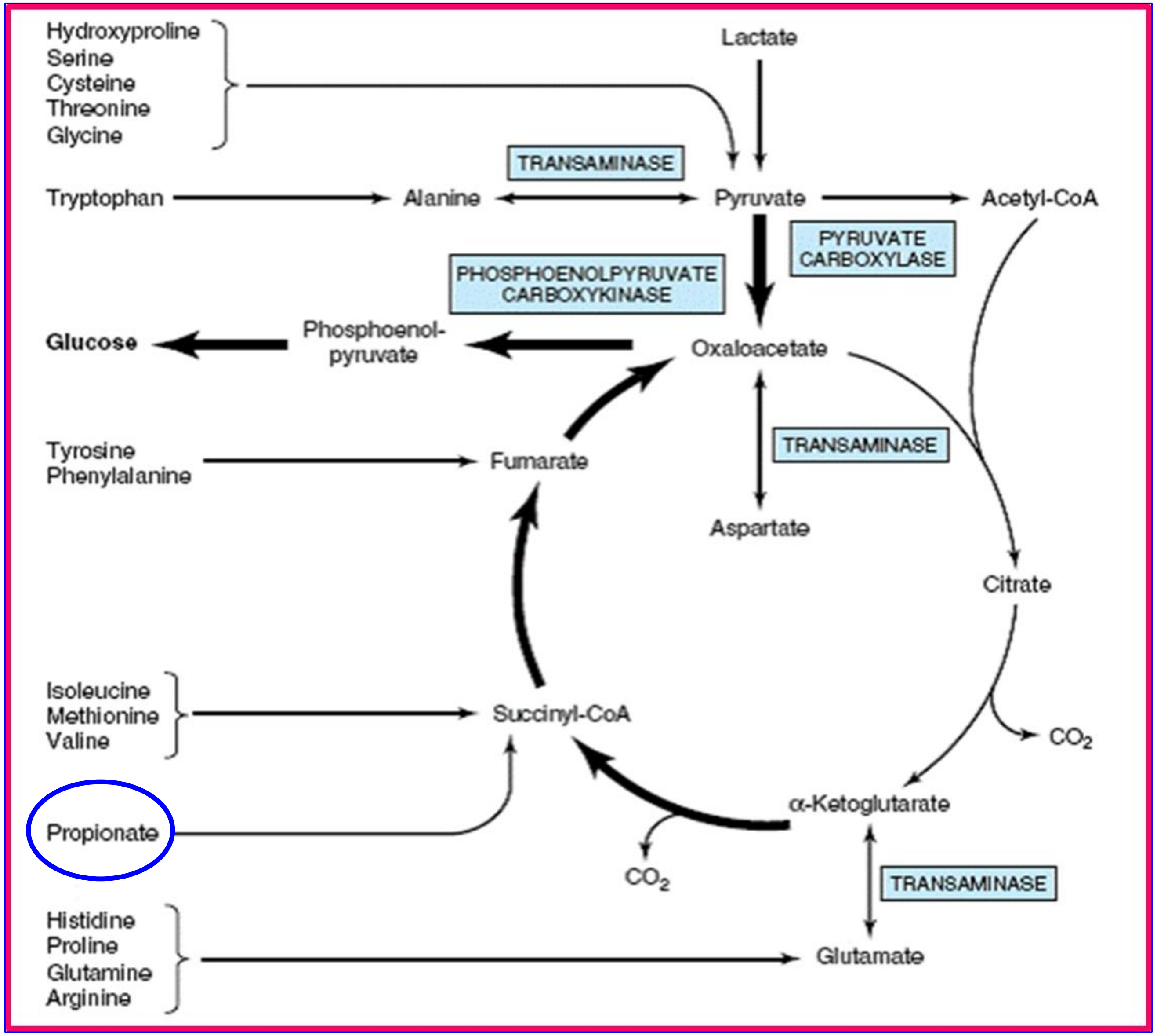
- This carbon skeleton exits at the **malate** level and proceeds toward **phosphoenolpyruvate** (PEP).



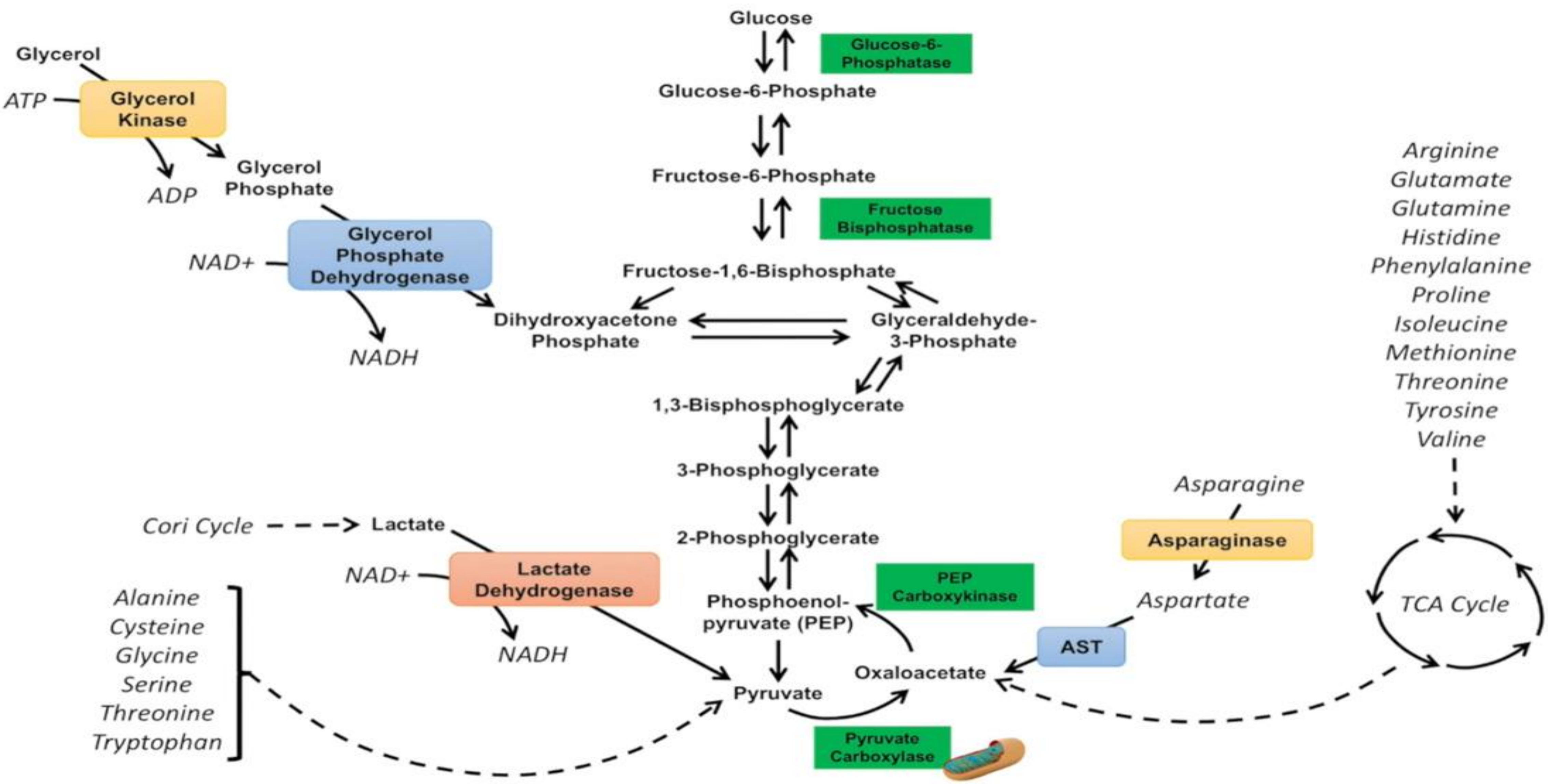
# *Gluconeogenesis from Propionate*

- **Propionate** ($CH_3–CH_2–COOH$) is the degradation product of **odd-chain fatty acids**.

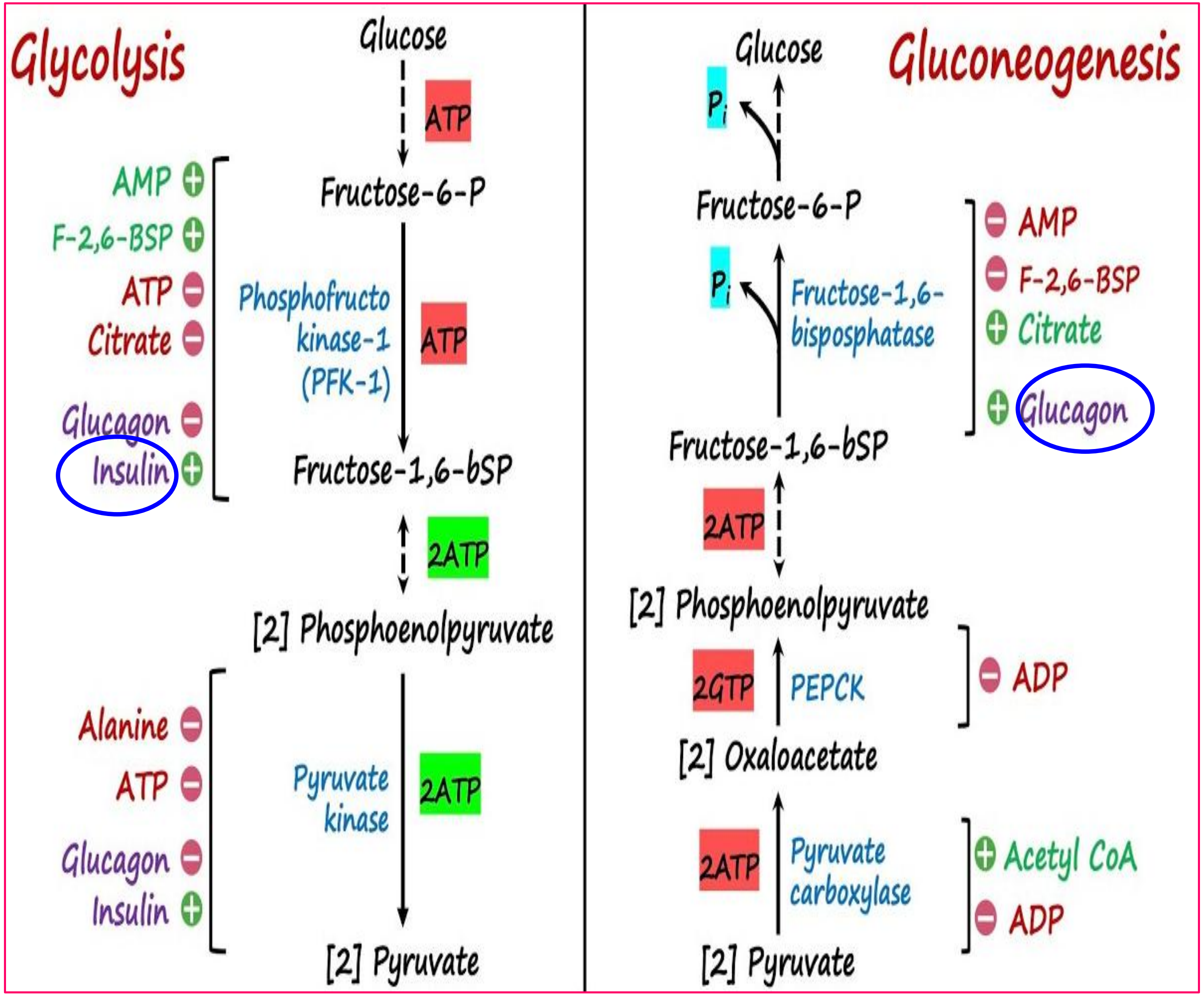
- It is **converted** into succinyl-CoA, an intermediate of the **Krebs cycle**, from which it can be directed toward the formation of **phosphoenolpyruvate** (PEP).



# Substrates and Enzymatic Steps of Gluconeogenesis



# Regulation of Gluconeogenesis




### *Hormonal Regulation*

- During fasting periods (between meals), **blood** glucose **levels** decrease, leading to the **secretion** of glucagon by the endocrine pancreas.
- **Glucagon** accelerates **gluconeogenesis** and inhibits **glycolysis**. Additionally, glucagon induces the synthesis of key gluconeogenic **enzymes**, including: *Phosphoenolpyruvate carboxykinase (PEPCK)* *Fructose-1,6-bisphosphatase (F1,6BPase).*

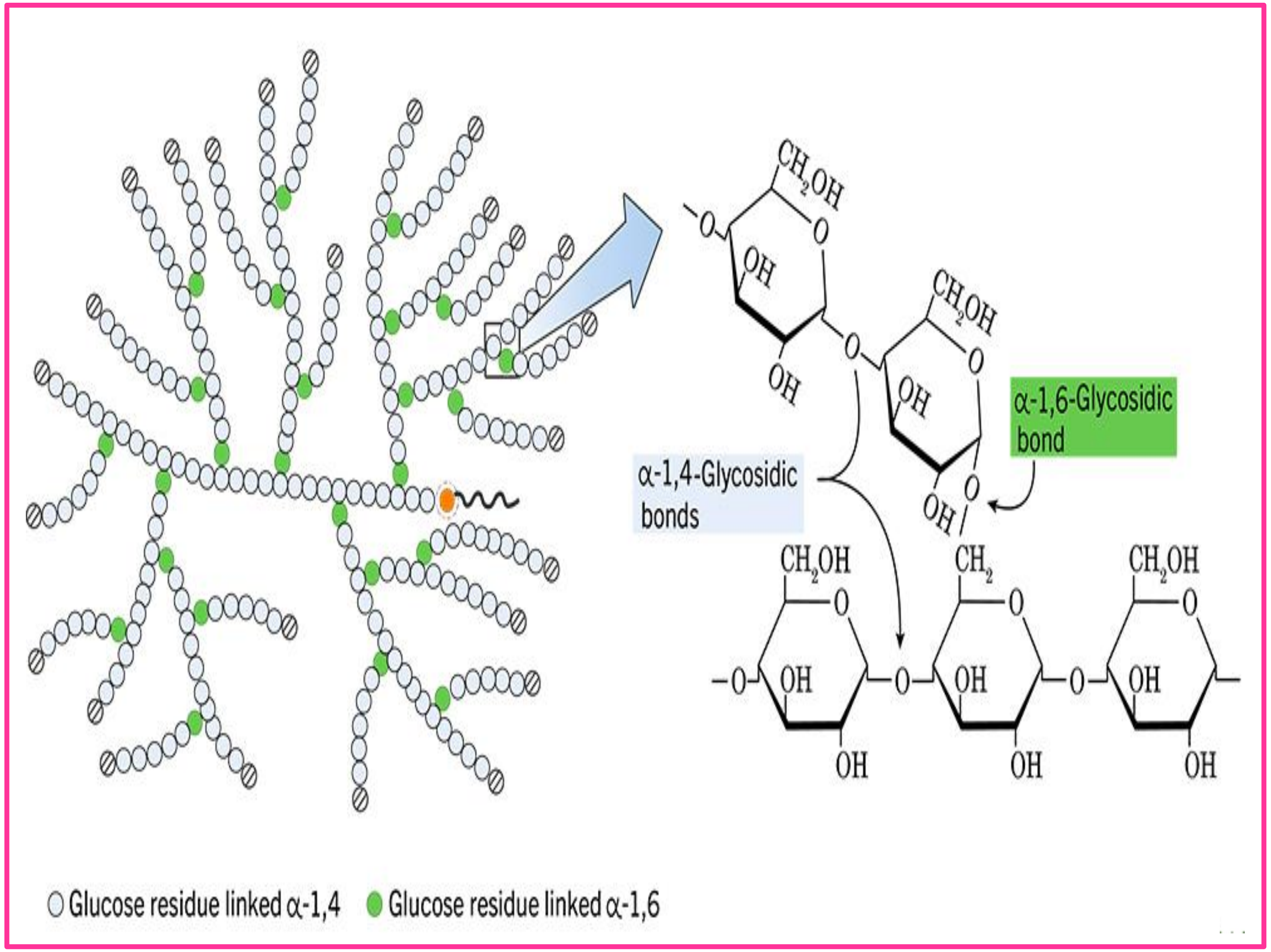
- **Conversely**, insulin has the opposite effect: during the **postprandial period** (after a meal), it slows down **gluconeogenesis** and activates **glycolysis**.

# *Glycogen Metabolism*

# *Introduction*

Glycogen metabolism, whether **synthesis** (**glycogenesis**) or **breakdown** (**glycogenolysis**), is regulated according to:

- ➤ The body’s nutritional state **(**fed or fasting)
- ➤ Cellular energy status (ATP/AMP ratio).



# *Introduction*

Glycogen **Metabolism** occurs in the **intestines**, **liver**, and **muscles**.

- **In the intestines:** During the postprandial period, the digestive catabolism of glycogen and, more importantly, dietary starch produces glucose, which is directed to:

**Storage sites**, in the form of glycogen (**liver** and **muscles**)
**Sites of consumption**, where it is used as an **energy substrate**

- **In the liver: D**uring the postprandial period, intestinal glucose and glucose produced between meals via **gluconeogenesis** are stored as **glycogen** through **glycogenesis**.

During fasting periods, glucose derived from **glycogenolysis** is exported to consuming tissues.
The hepatic glycogen store, which can be depleted within 24 hours, is considered **“public use”.**

- **In the muscles:**

At rest, **glucose** is **stored** as **glycogen** through **glycogenesis**.
During muscular activity, **glycogenolysis** provides an immediate source of **glucose**, which is used **locally** as an **energy substrate**. Muscle glycogen is considered **“private use”**.

# *Pathways of Glycogenesis and Glycogenolysis*

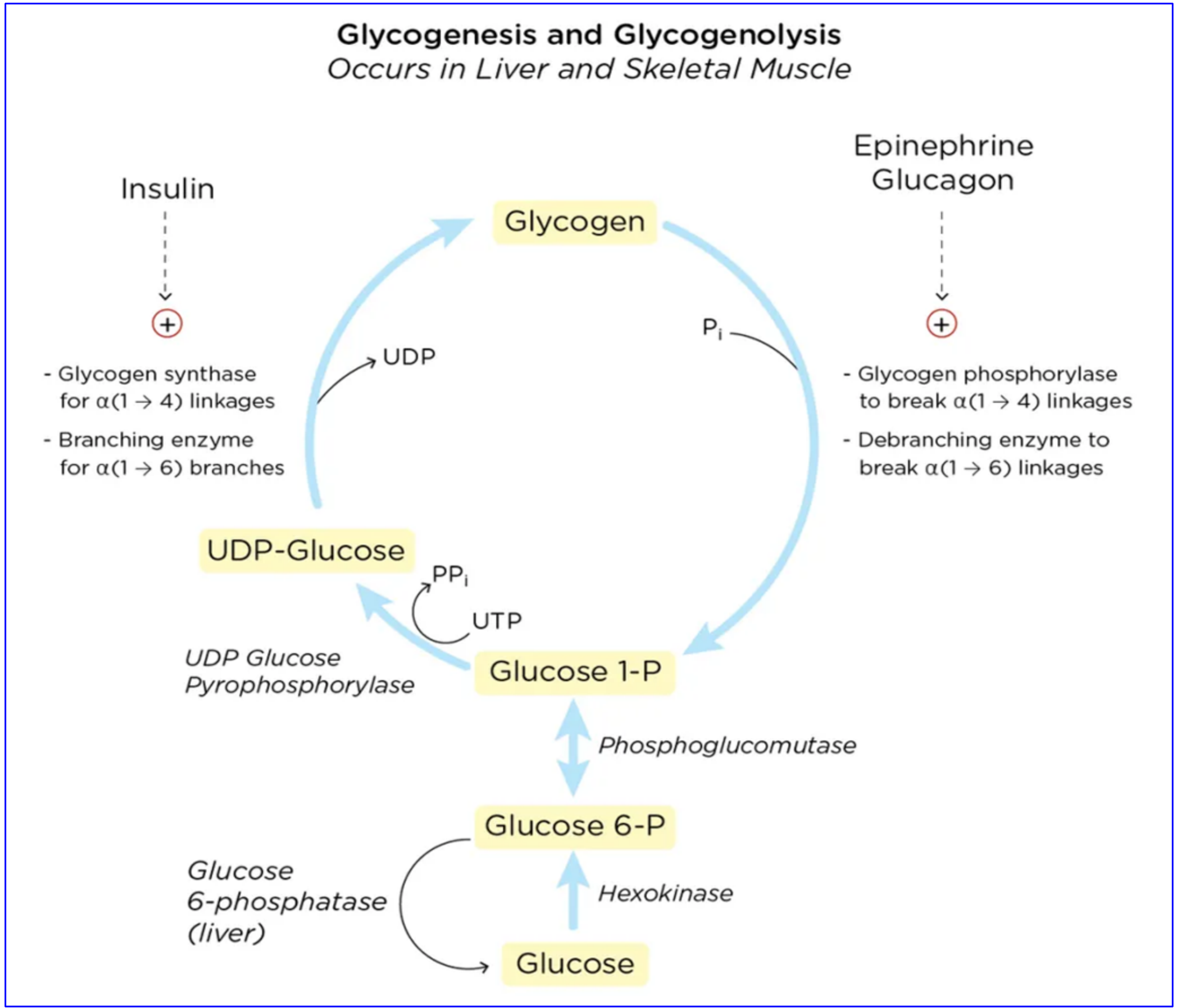
➢ Glycogenesis (Glycogen Synthesis ):

The process of **forming glycogen** from **glucose**. Catalyzed primarily by *glycogen synthase* and *branching enzyme*. **Stimulated** by **insulin** during the **postprandial period**.

➢ Glycogenolysis (Glycogen Degradation ):

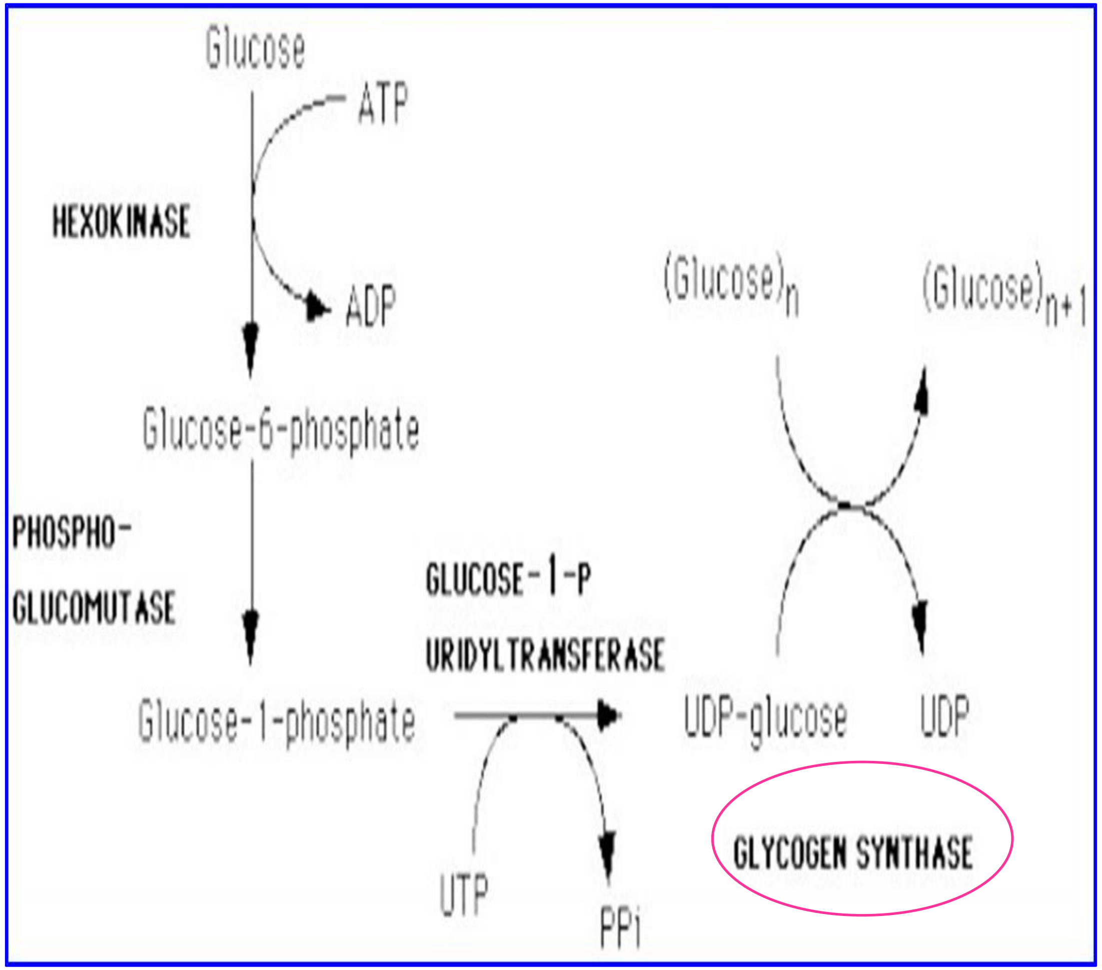
The **breakdown** of **glycogen** into **glucose-1-phosphate**, which can be converted to **glucose-6-phosphate**. Catalyzed by *glycogen phosphorylase* and *debranching enzyme*. **Stimulated** by **glucagon** (in **liver**) and **epinephrine** (in muscle) during **fasting** or **exercise**.

➢ These pathways are tightly regulated to maintain blood glucose homeostasis and provide **energy** according to the body's nutritional and energy status.



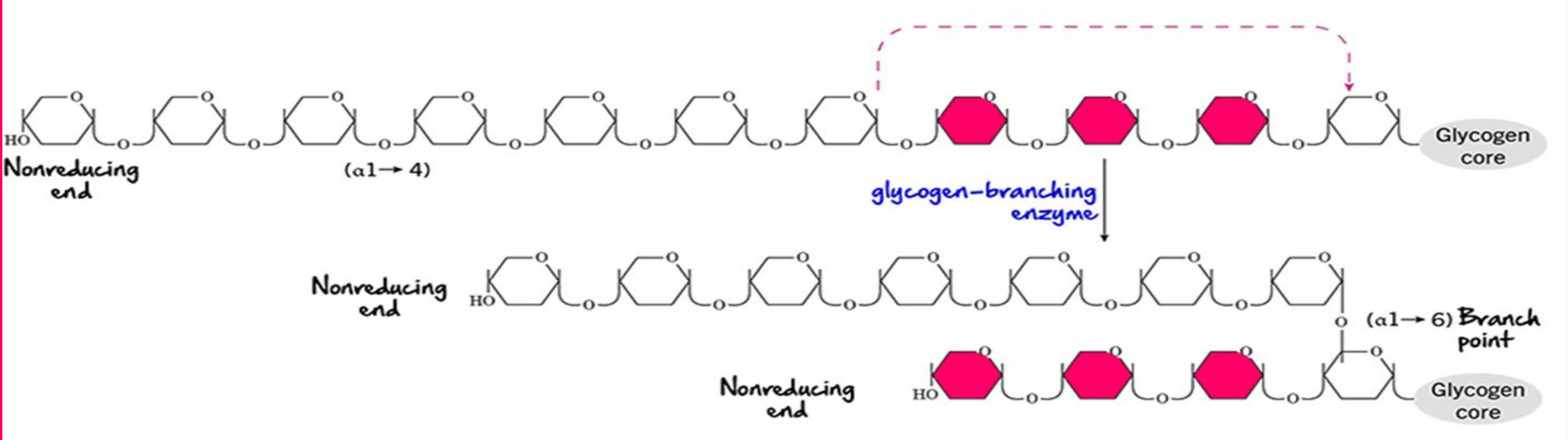
# *Glycogenesis: Glycogen Synthesis*

- The purpose of **glycogen synthesis** is to store **excess** glucose in the liver (approximately 150 g, one-third of the body's total glycogen) and muscles (approximately 300 g, two-thirds of the total glycogen).
- **Glycogen synthesis** occurs in the **cytosol**.
- The key enzyme is *glycogen synthase*.
- The precursor is **glucose-6-phosphate** (G6P).
- The synthesis process requires **energy** in the form of **ATP** and **UTP** (uridine triphosphate), consuming **two** high-energy **bonds**.

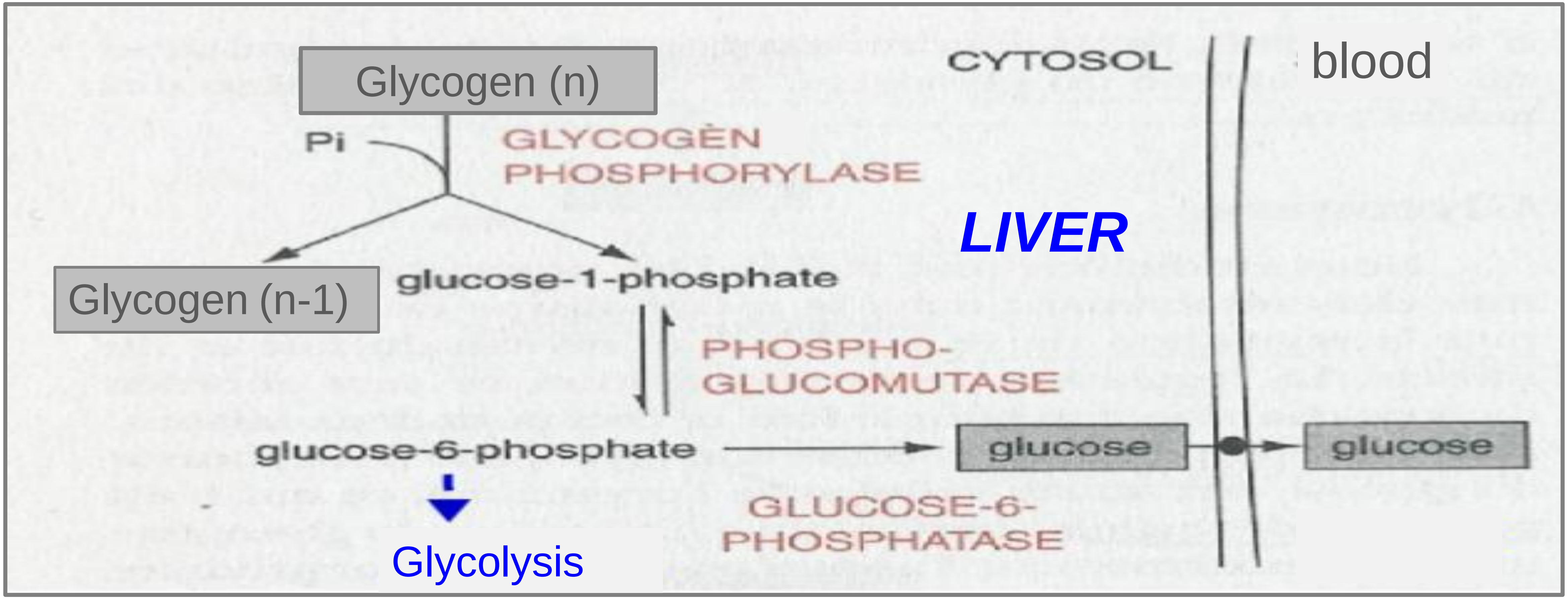


# *Branch Formation in Glycogen*

- When a **glycogen** chain elongates by at least **11 glucose residues**, the branching enzyme cleaves an α(1→4) bond and **releases** a fragment of **7 glucose residues**. This fragment is then transferred to the **C6 position** of a glucose residue on the same or another chain, forming an **α(1→6) linkage.**
- This process results in a highly branched glycogen structure, which enhances its **solubility** and provides multiple sites for rapid addition or removal of glucose units.

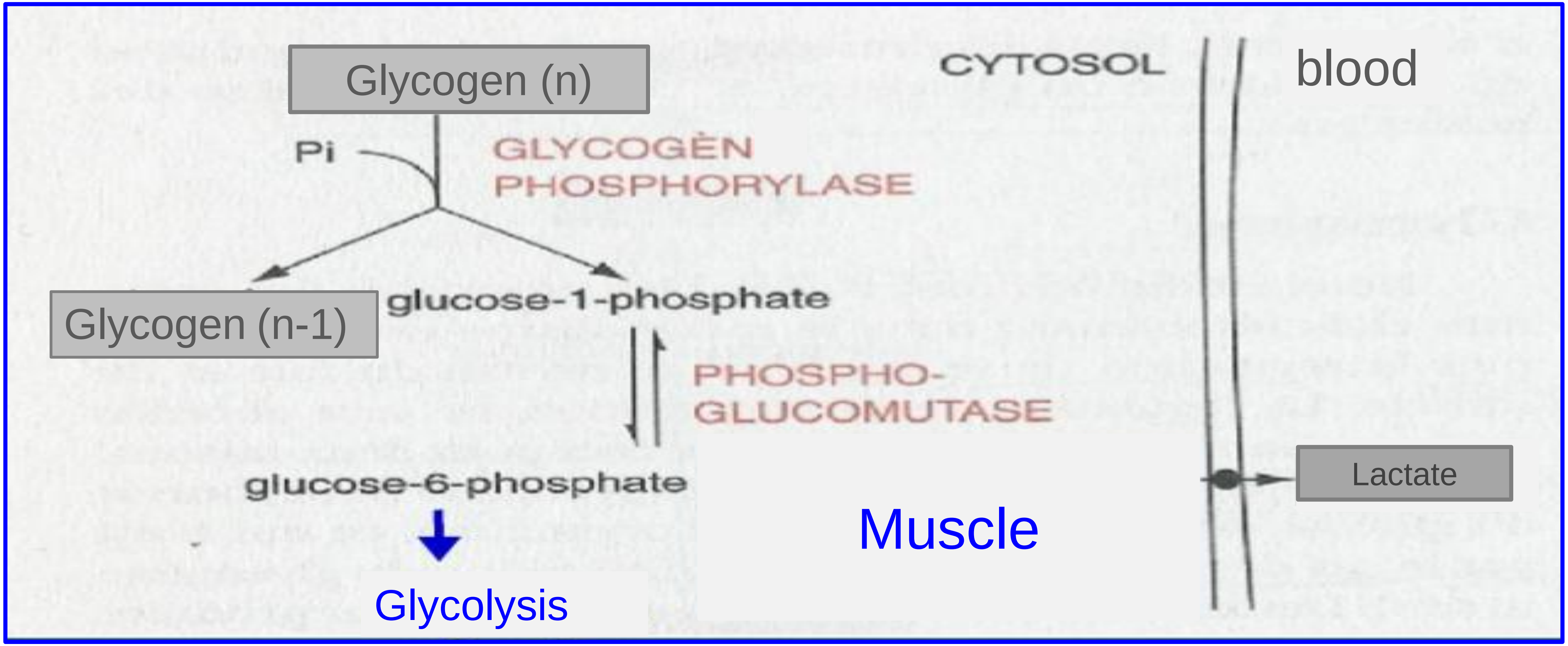


# Glycogenolysis: Glycogen Degradation (Liver)



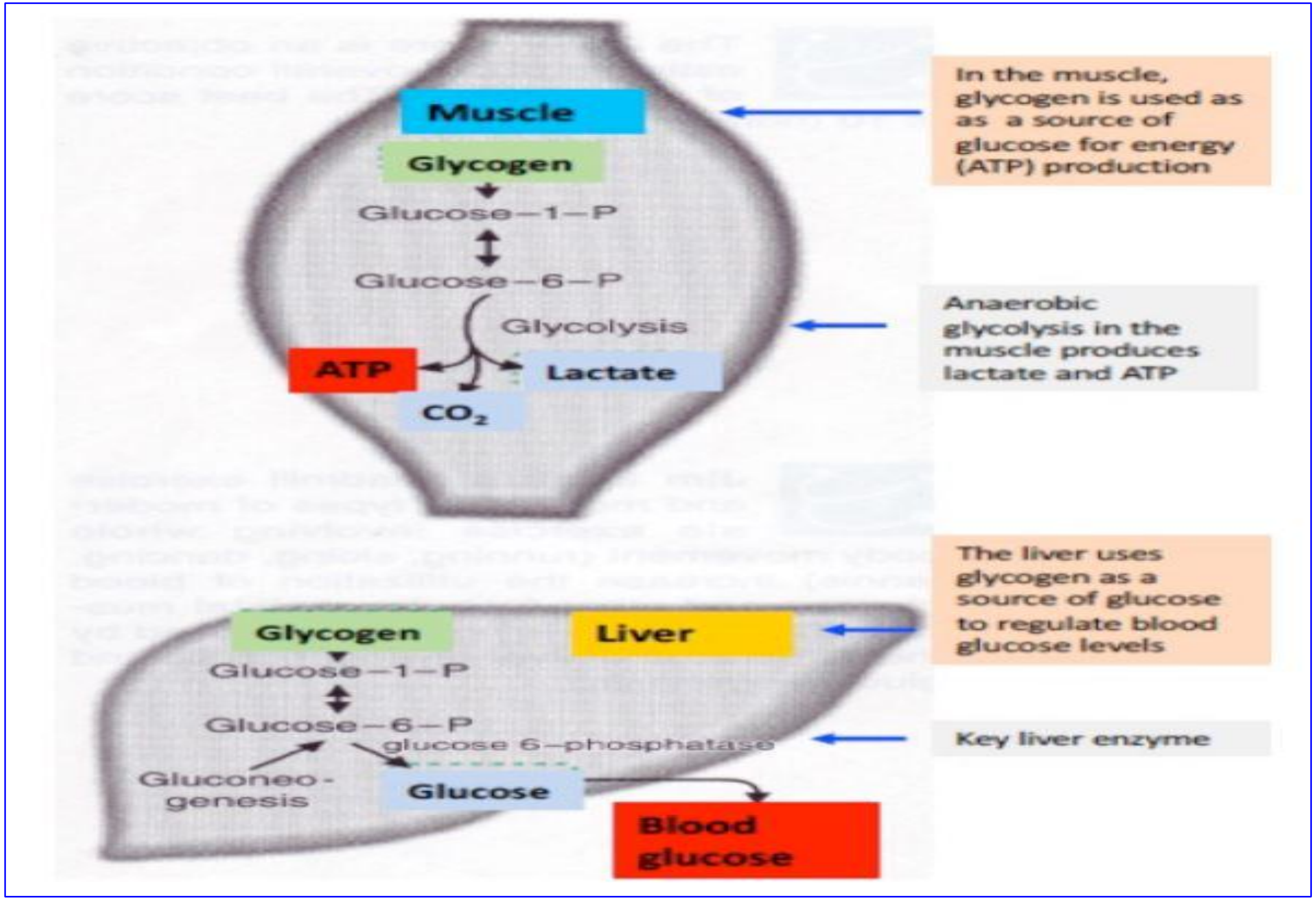

***Note:*** *Glucose-6-phosphatase is a liver-specific enzyme that hydrolyzes **glucose-6-phosphate** to free **glucose**, allowing the liver to export glucose into the bloodstream and **maintain blood glucose** homeostasis.*

# Glycogenolysis: Glycogen Degradation (Muscle)




***Note:*** *The* ***glycogen stored*** *in muscle is restricted to* ***local use****, as muscle cells do not express glucose-6-phosphatase. Therefore, glucose-6-phosphate generated from glycogen cannot be converted to free glucose and exported; it is* ***used intracellularly*** *for* ***energy production.***

# Use of Hepatic and Muscular Glycogen



# Glycogen storage diseases

| Type | Name | Enzyme | Glycogen | Prevalence | Clinical |
|---|---|---|---|---|---|
| 0 | | Glycogen synthase | None | Very rare | Hypoglycemia, ketosis |
| I | VonGierke | Glucose-6-phosphatase | Normal | 1/50000 | Severe hypoglycemia, big liver, lactic acidosis |
| II | Pompe | Lysosomal a1,4-glucosidase | Inclusion bodies with glycogen | 1/140000 | Big heart, weakness, death |
| III | Cori | Debranching enzyme (a1,6- glucosidase) | Shorter outer branches | 1/100000 | Mild hypoglycemia, big liver |
| IV | Anderson | Branching enzyme | Long chains with few branches | Very rare | Cirrhosis, hypoglycemia, death |
| V | McArdle | Muscle glycogen phosphorylase | Normal | 1/100000 | Muscle cramps, weakness, teens |
| VI | Hers | Liver glycogen phosphorylase | normal | 1/70000 | Mild hypoglycemia, cirrhosis |