Biochemistry course

Part 02: metabolic biochemistry

Chapter 01: Carbohydrate metabolism

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Chapter 01: Carbohydrate metabolism

1/Introduction:

Carbohydrate metabolism is one of the most important metabolic processes in living cells.

It plays a central role in the capture and storage of solar energy. It also contributes to the biosynthesis of structural macromolecules found in various forms in all organisms. In addition, it is involved in the synthesis of the carbohydrate components of glycoproteins and glycolipids, which perform numerous functions in antigenicity and cellular communication.

Carbohydrates have several roles in the body, including energy production and storage, the synthesis of glycoproteins and other macromolecules, the synthesis of nucleotides (such as ribose and NADPH), detoxification of insoluble and toxic compounds, and participation in metabolic interrelationships.

2/General Principles of Metabolism

Metabolism is defined as the set of material transformations and energy exchanges that occur within the organism. It involves two fundamental, simultaneous, and opposing processes: anabolism and catabolism.

-Anabolism refers to the synthetic reactions that enable the formation of complex molecules from simple ones, leading to the formation of living matter and storage substances. These reactions require an energy input.

-Catabolism encompasses the reactions that break down complex molecules into simpler compounds, resulting in the formation of waste products and the release of energy that can be used by the organism.

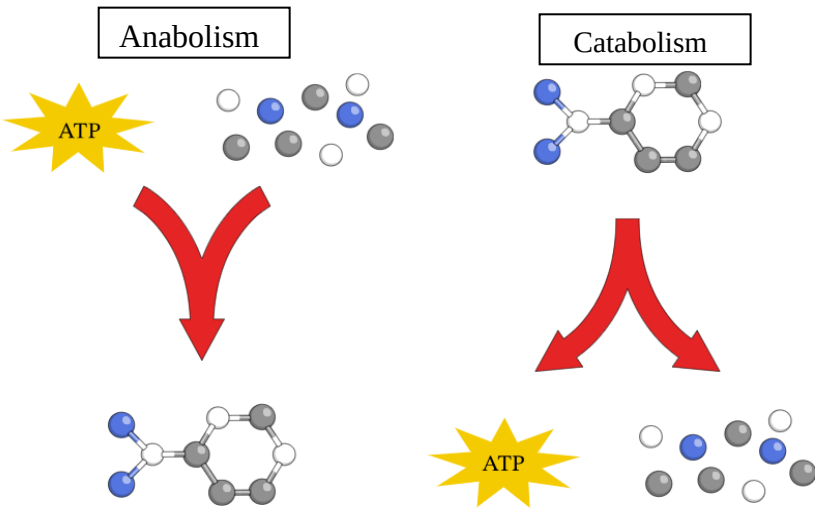


Figure .1 processes of metabolism

3/Digestion and Absorption of Carbohydrates

3.1/Carbohydrate Digestion

Carbohydrate digestion begins in the oral cavity under the action of salivary α-amylase. However, this activity is limited, as the enzyme is rapidly inactivated by the acidity of gastric juice.

Digestion then continues in the small intestine hrough the action of pancreatic α-amylase, which hydrolyzes polysaccharides into disaccharides, primarily maltose and isomaltose.

These disaccharides are then broken down into monosaccharides by enzymes of the enterocyte brush border: maltase, isomaltase, sucrase, and lactase. The resulting monosaccharides are then absorbed by enterocytes and enter the bloodstream.

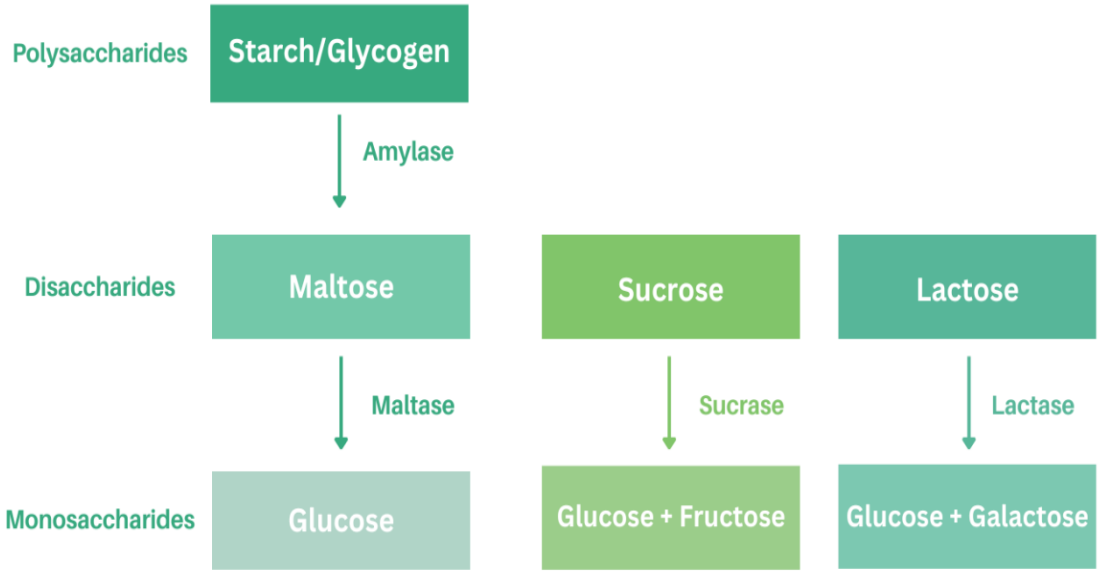


Figure 2. Carbohydrate Digestion

3.2/Absorption of monosaccharides

A) Simple diffusion

This process occurs down the concentration gradient. It is negligible for glucose, as it is hydrophilic, while the plasma membrane is hydrophobic.

B) Secondary active transport

This mechanism relies on a gradient established by another active transporter (that consumes ATP).

The SGLT (sodium–glucose transporter) family includes co-transporters that mediate the uptake of glucose along with sodium. They utilize the Na^+ gradient generated by the Na^+/K^+ ATPase pump.

C) Facilitated diffusion

The GLUT family mediates glucose transport via facilitated diffusion (which does not require ATP) and comprises 14 members.

These transporter isoforms exhibit different affinities for glucose, and their expression is tissue-specific. Some isoforms are ubiquitous, being present in all tissues, whereas others are expressed in specific tissues.

GLUT 1: primarily expressed in erythrocytes and neurons
GLUT 2: primarily expressed in hepatocytes and pancreatic β-cells of the islets of Langerhans
GLUT 3: primarily expressed in neurons
GLUT 4: primarily expressed in skeletal muscle cells and adipocytes
GLUT 5: primarily expressed in enterocytes and sperm cells
GLUT 6–14: expressed in various other tissues.

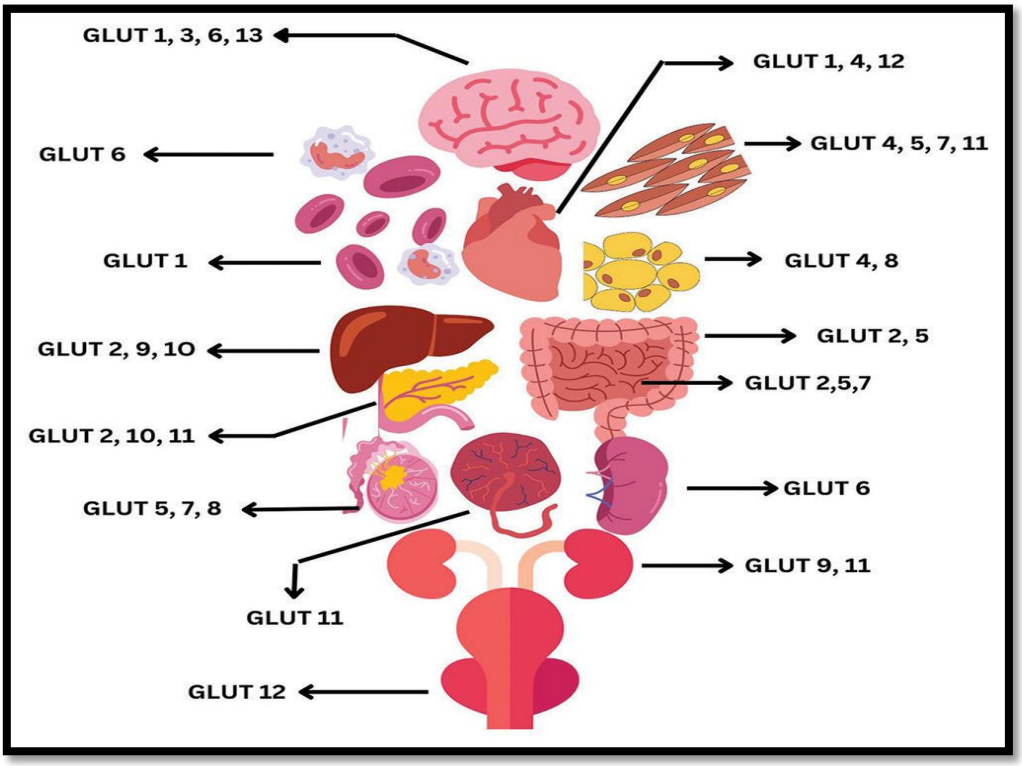


Figure 3. Expression of GLUTs in the different organs and tissues of the body.

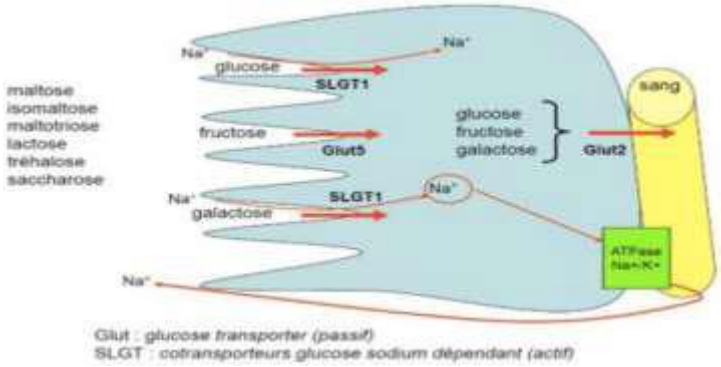


Figure 4. Carbohydrate absorption

Glycolysis

1/Defenition

Glycolysis, also known as the Embden–Meyerhof pathway, is a metabolic pathway occurring in the cytosol.

It comprises ten biochemical reactions that transform glucose into pyruvate.

The energy released during these reactions is harnessed to generate high-energy molecules, specifically adenosine triphosphate (ATP) and reduced nicotinamide adenine dinucleotide (NADH).

The overall reaction of glycolysis is as follows :

Glucose + 2 NAD^+ + 2 ADP + 2 Pi → 2 pyruvate + 2 NADH + 2 ATP + 2 H_2O + 4 H

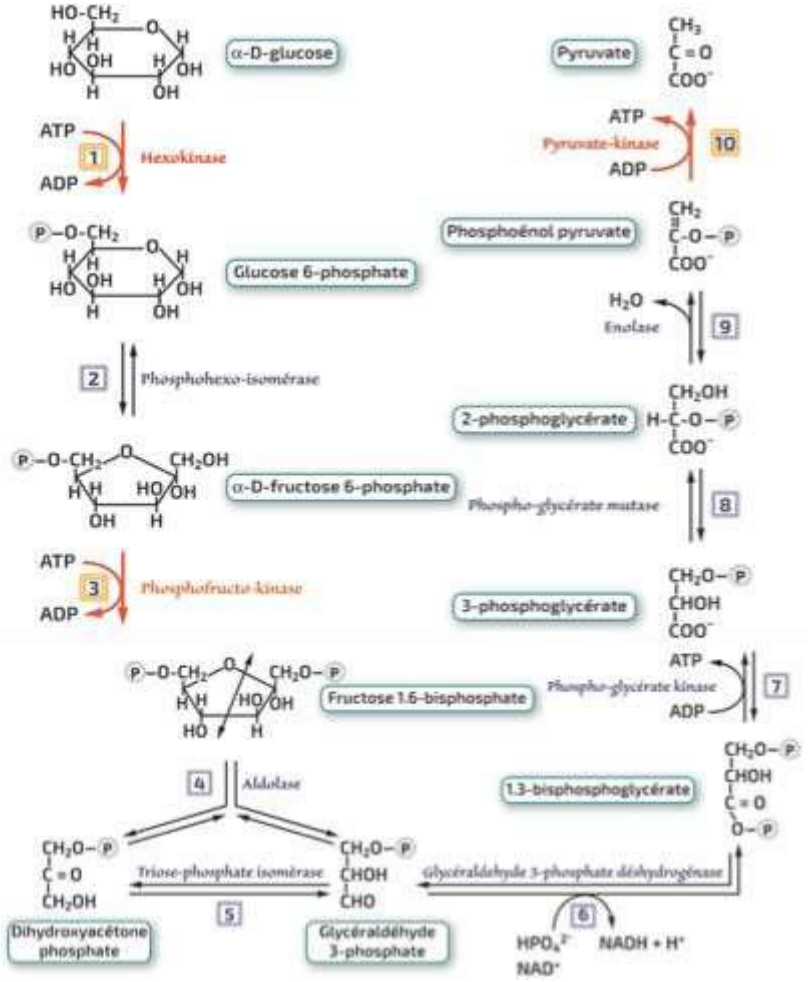


Figure 5. Enzymatic reactions of glycolysis

2/ Phases of glycolysis

Glycolysis occurs in two phases:

- In the first phase, a series of five reactions breaks down glucose into two molecules of glyceraldehyde-3-phosphate.
- In the second phase, five subsequent reactions convert these two molecules of glyceraldehyde-3-phosphate into two molecules of pyruvate.

2.1./Energy investment phase of glycolysis

1/ Phosphorylation of glucose (irreversible reaction)

This is a transphosphorylation reaction in which glucose is phosphorylated to glucose-6-phosphate.

This reaction is catalyzed by hexokinase in most extrahepatic tissues and by glucokinase in the liver.

It is accompanied by the consumption of one molecule of ATP, requires the presence of Mg^{2+}, and is irreversible. This ensures the intracellular trapping of glucose and directs it toward metabolic pathways that depend on glucose-6-phosphate (G6P)

2. Isomerization of glucose-6-phosphate

Glucose-6-phosphate undergoes a reversible isomerization reaction of the aldose–ketose type, leading to the formation of fructose-6-phosphate (F6P).

This transformation is catalyzed by phosphoglucose isomerase (also known as phosphohexose isomerase) and involves the shift of the carbonyl group from carbon 1 to carbon 2, a necessary step for the subsequent phosphorylation of the molecule.

3. Phosphorylation of fructose-6-phosphate (irreversible and regulatory step)

Fructose-6-phosphate is converted into fructose-1,6-bisphosphate (F-1,6-BP) by a second transphosphorylation reaction catalyzed by phosphofructokinase-1 (PFK-1).

This reaction consumes one molecule of ATP and constitutes the rate-limiting and committed step of glycolysis, acting as the key regulatory point of glycolytic flux in response to the cell's energy status.

4. Aldolytic cleavage of fructose-1,6-bisphosphate

Fructose-1,6-bisphosphate then undergoes a reversible aldolytic cleavage reaction catalyzed by aldolase, leading to the formation of two triose phosphates: dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (G3P).

This step marks the conversion of a six-carbon metabolite into two three-carbon intermediates.

5. Isomerization of triose phosphates

Dihydroxyacetone phosphate (DHAP), metabolically inactive in the subsequent steps of glycolysis, is reversibly converted into glyceraldehyde-3-phosphate (G3P) by triose phosphate isomerase.

This reaction ensures that the entire glycolytic flux is directed toward the formation of two molecules of G3P, which are the only molecules capable of entering the subsequent energy-yielding phase.

2.2/Energy Payoff Phase of Glycolysis

6. Oxidation and Phosphorylation of Glyceraldehyde-3-Phosphate

Glyceraldehyde-3-phosphate (G3P) is converted into 1,3-bisphosphoglycerate (1,3-BPG) through a redox reaction (oxidation-reduction) coupled with phosphorylation.

This step is catalyzed by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and requires the presence of inorganic phosphate (Pi). It is accompanied by the reduction of NAD^+ to $NADH^+ H^+$, representing the only oxidative step of glycolysis.

7. Substrate-Level Phosphorylation

1,3-bisphosphoglycerate transfers a phosphate group to ADP via a transphosphorylation reaction, leading to the formation of 3-phosphoglycerate (3-PG) and one molecule of ATP. This reaction is catalyzed by phosphoglycerate kinase and corresponds to a substrate-level phosphorylation, representing the first energy gain of glycolysis.

8. Intramolecular Rearrangement of Phosphoglycerate

3-phosphoglycerate is reversibly converted into 2-phosphoglycerate (2-PG) by an intramolecular mutation reaction, catalyzed by phosphoglycerate mutase. This transformation prepares the substrate for a subsequent high-energy dehydration (dehydration with high energetic potential).

9. Dehydration of 2-Phosphoglycerate

2-phosphoglycerate is converted into phosphoenolpyruvate (PEP) through a dehydration reaction, catalyzed by enolase, which is accompanied by the release of a water molecule (H_2O). The PEP formed is a compound with a very high phosphoryl transfer potential.

10. Formation of Pyruvate (Irreversible Reaction)

Phosphoenolpyruvate is converted into pyruvate by a transphosphorylation reaction, catalyzed by pyruvate kinase, during which the phosphate group is transferred to ADP, leading to the formation of one molecule of ATP.

This reaction is irreversible, constitutes a substrate-level phosphorylation, and represents a key regulatory step of glycolysis.

3/Molecular and Energetic Balance of Glycolysis

The oxidation of one mole of glucose into two moles of pyruvate is accompanied by a net gain of 2 ATP.

-The **first phase of glycolysis** (the Preparatory Phase), which results in the formation of two **triose phosphates**, consumes **2 moles of ATP** per mole of glucose.

-The **last phase** (the Payoff Phase), which transforms **2 moles of 1,3-bisphosphoglycerate** into 2 moles of pyruvate, produces **2 moles of ATP per mole of pyruvic acid**.

-The energy balance is straightforward:

2 × 2 − 2 = 2 ATP produced per mole of transformed glucose.

The oxidation of one mole of glucose into two moles of pyruvate is also accompanied by the **reduction of two moles of NAD+**; under **aerobic conditions**, the reoxidation of these two moles of **NADH, H+** in the **mitochondrial respiratory chain** produces an additional **6 molecules of ATP**.

4/Regulation of Glycolysis

Within metabolic pathways, enzymes catalyzing irreversible reactions serve as major control points for metabolic flux.

In glycolysis, regulation is primarily achieved through three complementary mechanisms:

- Allosteric regulation of enzymes by metabolic effectors
- Covalent modification by phosphorylation/dephosphorylation
- Regulation of gene expression of glycolytic enzymes

4.1/Key Regulatory Enzymes of Glycolysis

- Three steps of glycolysis are irreversible and play a major role in the regulation of glycolytic flux.

Hexokinase and Glucokinase

Hexokinase is subject to allosteric inhibition by its product, glucose-6-phosphate, ensuring negative feedback regulation.

In contrast, glucokinase is not inhibited by glucose-6-phosphate, and its activity is mainly regulated at the hormonal and transcriptional levels, particularly by insulin.

Phosphofructokinase-1 (PFK-1)

Allosteric inhibitors:

- ATP (signal of high energy abundance)

- Citrate (indicator of high flux through the Krebs cycle)
- Glucagon (liver)

Allosteric activators:

- AMP and ADP (signals of low energy)
- Insulin (indirectly, notably via fructose-2,6-bisphosphate)

This enzyme represents the **main control point of glycolytic flux**.

Pyruvate kinase

Allosteric inhibitors: ATP, alanine, $NADH/H^+$, and pyruvate (via feedback inhibition)

Allosteric activator: Fructose-1,6-bisphosphate (feed-forward activation)

In hepatic cells, pyruvate kinase is further regulated via **phosphorylation** by glucagon and **dephosphorylation** by insulin.

Fates of Pyruvate / Pyruvate Metabolism

The fate of pyruvate depends on the following factors:

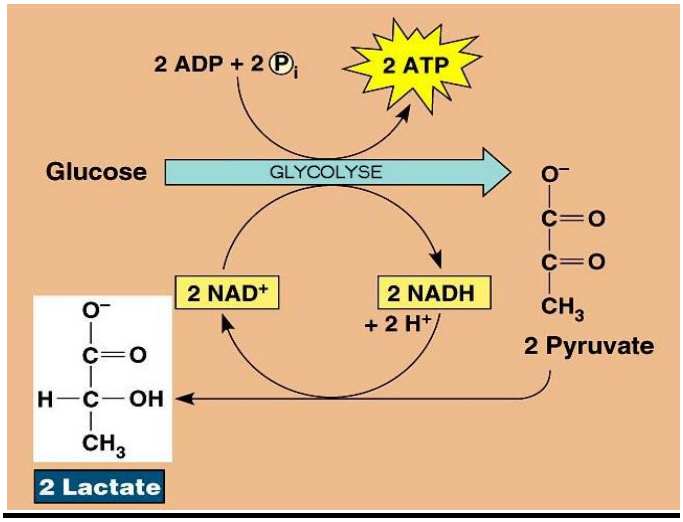
- The oxygen level in the cell's environment.
- The energy status of the cell.
- The enzymatic capacity available to the cell to oxidize $NADH/H^+$.

1/Anaerobic Conditions

Pyruvate can have different fates depending on the organism in which it is found.

1.1/Lactic Fermentation:

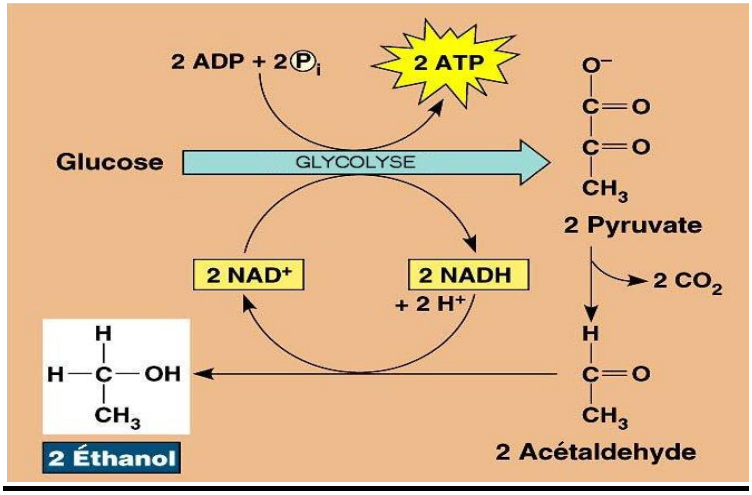
When the cell lacks mitochondria (as in red blood cells), is deprived of oxygen (anaerobiosis), or is under hypoxic conditions (e.g., contracting muscle tissue), pyruvate is reduced to lactate by **lactate dehydrogenase**. This reaction regenerates NAD^+ from $NADH/H^+$, allowing glycolysis to continue, with a net production of 2 ATP per glucose molecule.



1.2/Alcoholic Fermentation:

This conversion of pyruvate to ethanol occurs in yeast, which lack lactate dehydrogenase but possess **pyruvate decarboxylase** instead.

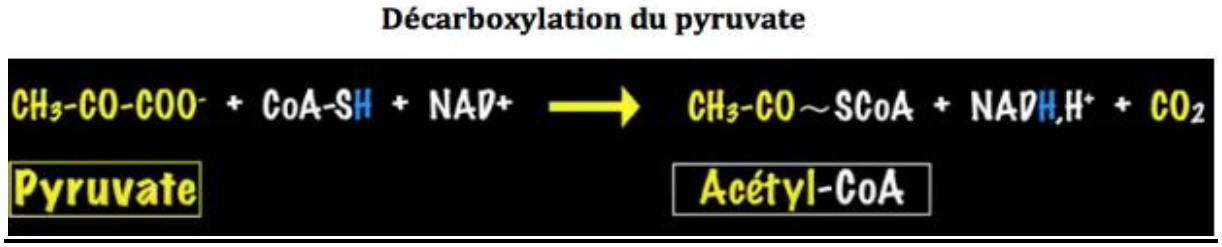
Pyruvate is decarboxylated to **acetaldehyde** by pyruvate decarboxylase. Acetaldehyde is then reduced to **ethanol** by **alcohol dehydrogenase**, regenerating NAD^+ from $NADH/H^+$ produced during glycolysis. This process allows glycolysis to continue, yielding a net production of 2 ATP per glucose molecule.



2/Aerobic Conditions

Pyruvate enters the mitochondrion to be converted into **acetyl-CoA**. This reaction occurs under aerobic conditions, with pyruvate transported into the mitochondrial matrix by a **pyruvate transporter (permease)**.

Pyruvate then undergoes an **irreversible oxidative decarboxylation** catalyzed by the **pyruvate dehydrogenase complex**, forming acetyl-CoA.



The Krebs cycle (Citric acid cycle)

1/Introduction :

Pyruvate, a product of incomplete degradation of glucose via glycolysis, continues its degradation in the mitochondria through a cycle pathway: the Krebs cycle, the gateway to aerobic metabolism allowing free energy to be recovered by transforming it into ATP.

2/Definition of the cycle:

Also known as the tricarboxylic acid cycle (TCA) or citric acid cycle. The Krebs cycle is the unique pathway of aerobic catabolism allowing the oxidation of acetyl coA into two carbon dioxide molecules.

Acetyl CoA (metabolic crossroads) comes from:

1- Oxidative decarboxylation of pyruvate

2- β oxidation of fatty acids

3- The degradation of certain amino acids into CO2

Therefore, the Krebs cycle is a common pathway for the catabolism of carbohydrates, lipids and proteins.

Among the cellular oxidation pathways, acetyl coA oxidation is the one that contributes most to ATP synthesis.

The cycle has different roles:

- ✓ Energy production; more than 90% of the energy produced in the aerobic cells come from the Krebs cycle in relation to the mitochondrial respiratory chain,
- ✓ The supply of intermediates for biosynthesis (source of precursors) (Next figure)

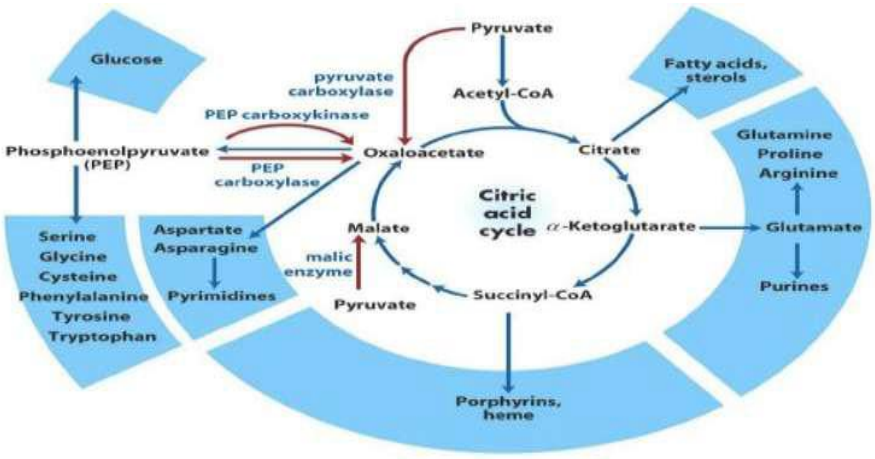


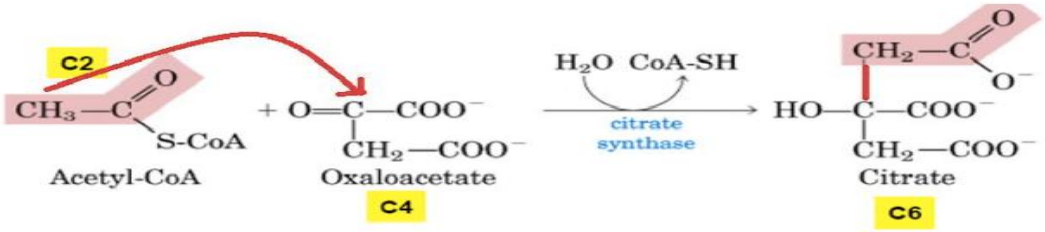
Figure 6. Biosynthetic intermediates

Red blood cells (erythrocytes) do not contain mitochondria, making them dependent on glycolysis for energy, with pyruvate ultimately converted to lactate.

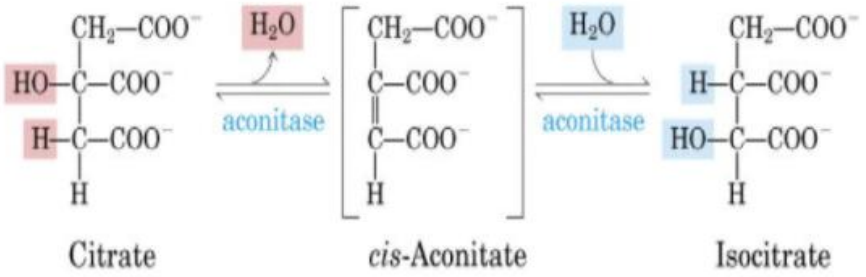
3/Different Stages of the Krebs Cycle

The Krebs cycle consists of **8 main steps**, each catalyzed by a specific enzyme:

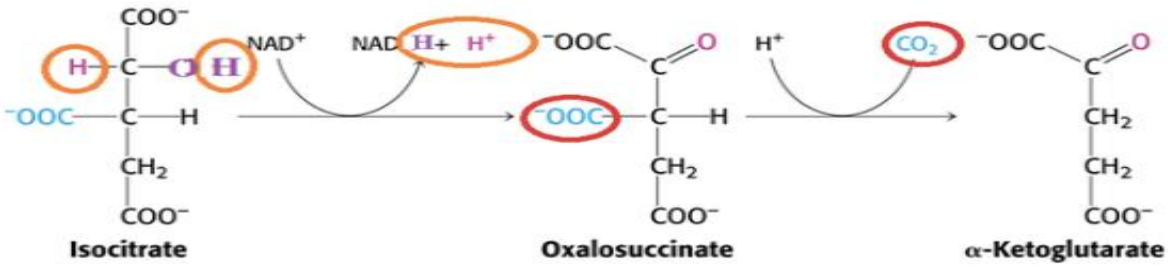
1. Condensation of acetyl-CoA and oxaloacetate to form citrate, catalyzed by **citrate synthase**. This reaction consumes one molecule of H_2O and releases CoA-SH.



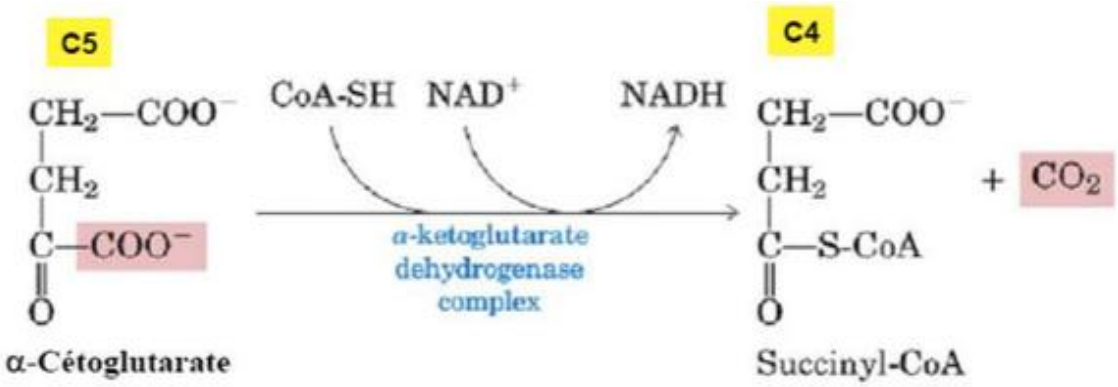
2. Isomerization of citrate to isocitrate, catalyzed by **aconitase**.



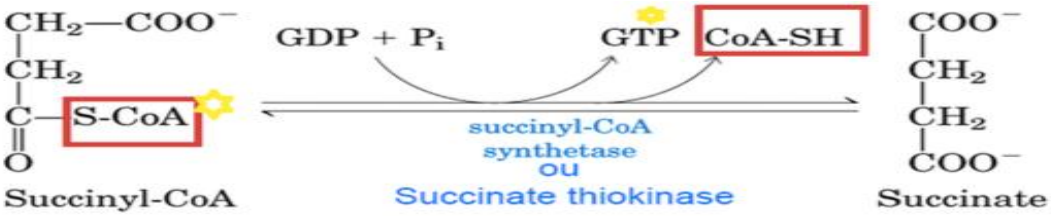
3. Dehydrogenation of isocitrate to oxalosuccinate (unstable), catalyzed by **isocitrate dehydrogenase**. This reaction produces **NADH + H^+** from NAD^+, followed by **β-decarboxylation** of oxalosuccinate to α-ketoglutarate, releasing CO_2.



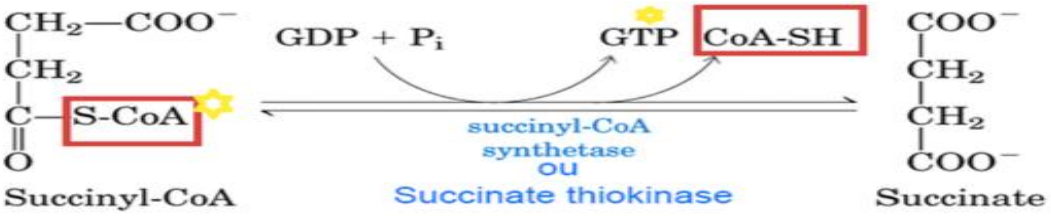
4. **α-Oxidative decarboxylation of α-ketoglutarate to succinyl-CoA**, catalyzed by **α-ketoglutarate dehydrogenase**. This step requires CoA-SH, generates **NADH + H^+**, and releases CO_2.



5. Transphosphorylation of succinyl-CoA to succinate, catalyzed by **succinate thiokinase**. This reaction consumes a phosphate group, releases CoA-SH, and produces **GTP from GDP**.

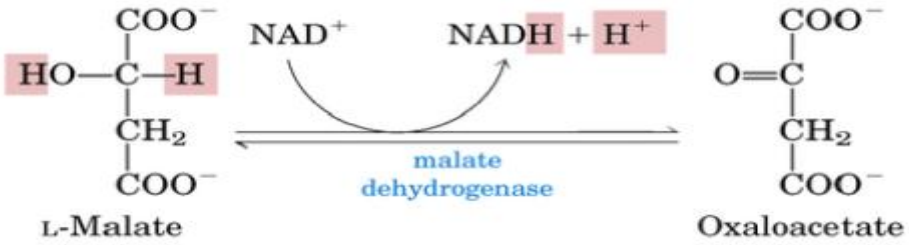


6. Dehydrogenation of succinate to fumarate, catalyzed by **succinate dehydrogenase**, forming **$FADH_2$ from FAD**.



7. Hydration of fumarate to malate, catalyzed by **fumarase**. This reaction requires one molecule of H_2O.

8. Dehydrogenation of malate to oxaloacetate, catalyzed by **malate dehydrogenase**, producing **NADH + H**$^+$ from NAD$^+$.



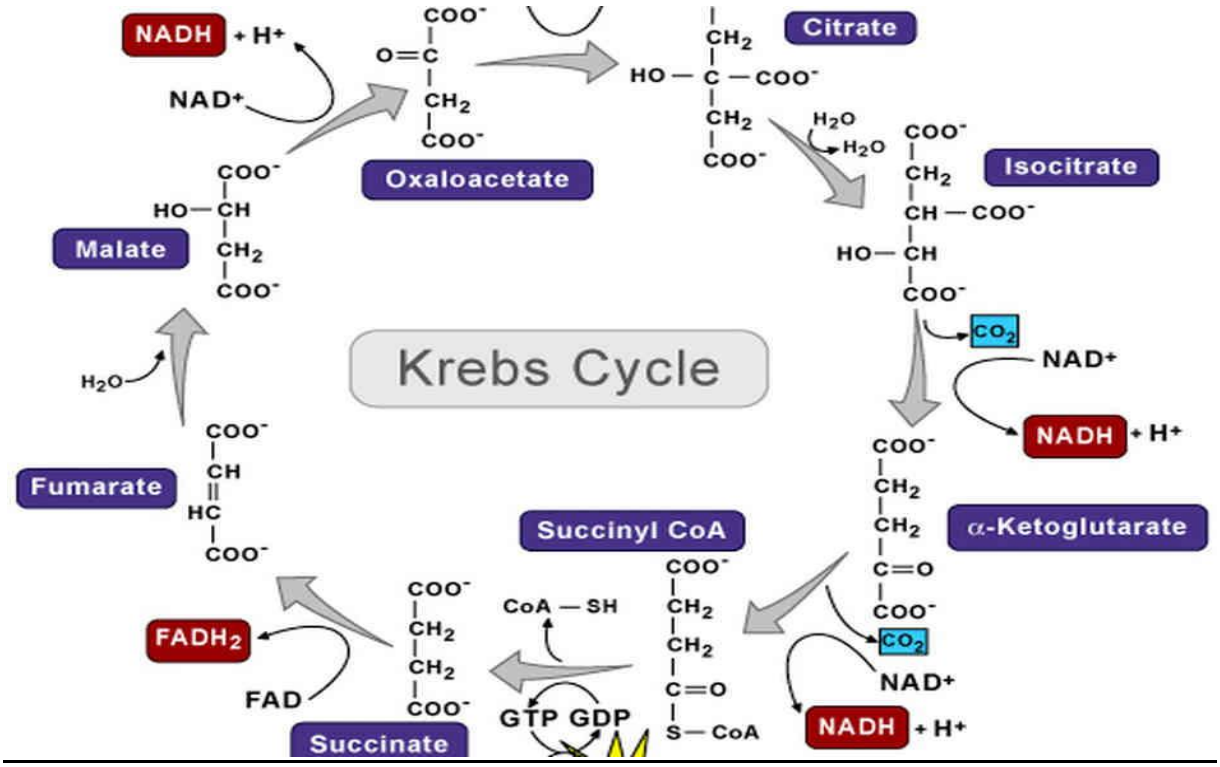


Figure 7. Enzymatic reactions of the Krebs cycle

4. Regulation of the Krebs cycle

The interest of this regulation is the adaptation of the speed of the cycle to the cellular needs in ATP. The citric acid cycle is accelerated when the cellular energy needs are not satisfied and is slowed down when they are satisfied.

The means of regulating this cycle are of two types:

- upstream regulation of the cycle, at the level of the pyruvate DSHase enzymatic complex, and internal regulation of the cycle which is carried out on the 03 irreversible reactions of the cycle catalyzed by allosteric enzymes.

➢Regulation at the level of the pyruvate DSHase enzyme complex:

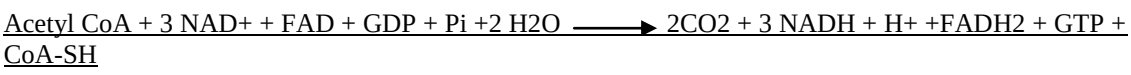
This enzyme controls the entry flux into the cycle of acetyl coA of carbohydrate origin.

Feedback inhibition; by the accumulation of ATP, acetyl coA and NADH H+ (energy needs of the cell satisfied).

Internal regulation of the Krebs cycle: Regulation occurs at the level of three irreversible reactions:

- Citrate synthase**(reaction 1)**:inhibited by citrate, ATP and activated by ADP.
- Isocitrate dehydrogenase**(reaction 3)**:inhibited by ATP and activated by ADP and calcium.
- Alpha ketoglutarate dehydrogenase**(reaction 4)**:inhibited by NADH, succinyl-COA, and activated by calcium.

5/Energy Balance of the Krebs Cycle



Per cycle turn:

- 1 GTP (equivalent to 1 ATP)
- 3 NADH + H^+ (yielding 9 ATP via oxidative phosphorylation)
- 1 $FADH_2$ (yielding 2 ATP via oxidative phosphorylation)
- **Total energy yield per cycle = 12 ATP**

6. Energy balance of carbohydrate catabolism

We will consider here the degradation of a glucose molecule by glycolysis and the Krebs cycle, without taking into account the additional pathways.

6.1. In anaerobic conditions

- **Glycolysis balance:**formation of 2 ATP and 2 NADH, H+(which will be used in the formation of lactate).

-**Assessment of pyruvate catabolism:**catabolism impossible in anaerobic conditions.

-**Krebs cycle balance:**In anaerobic conditions the Krebs cycle does not work. **Lactate**

-**formation balance:**The two pyruvate molecules formed by glycolysis are broken down into lactate, each requiring a NADH, H+(those formed during glycolysis).

The overall balance of the degradation of a glucose molecule in anaerobic conditions is therefore **2 ATP**which can be immediately mobilized.

6.2. In aerobics

-**Glycolysis assessment:**theoretical training of**6 ATP** (5 ATP in reality).

-**Assessment of pyruvate catabolism:**training of**3 ATP**per molecule of pyruvate in theory (2.5 in reality) and therefore 6 ATP in theory (5 ATP in reality) for a molecule of glucose.

-**Krebs cycle assessment:**in theory**12 ATP**per molecule of acetylcoenzyme A (10 ATP in reality) and therefore in theory**24 ATP**(20 ATP in reality) for one glucose molecule.

The overall theoretical balance of the degradation of a glucose molecule in aerobic conditions is therefore**36 ATP**(**30 ATP**in reality) which are not immediately mobilizable because the majority of ATP formed comes from oxidative phosphorylation.

It is important to clarify here that some works speak of a global theoretical assessment of **38 ATP**; This difference can be explained by the type of shuttle used: NADH, H+ in aerobic (3 ATP) or anaerobic (2 ATP).