Biochemistry course

Part 02: metabolic biochemistry

Chapter 01: Carbohydrate metabolism

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Pentose Phosphate Pathway (PPP)

1/DEFINITION :

The pentose phosphate pathway (also known as the phosphogluconate pathway, the Dickens–Horecker pathway, or the pentose shunt) is a major cytosolic metabolic pathway that, from glucose-6-phosphate, generates:

- **NADPH**, a reduced coenzyme required for:

  -Reductive biosynthetic reactions (fatty acid synthesis, cholesterol synthesis, and steroid hormone synthesis)

  -Antioxidant defense, particularly through the reduction of glutathione
- **Ribose-5-phosphate**, which is essential for **nucleotide synthesis**

Unlike glycolysis, its primary function is not to produce energy.

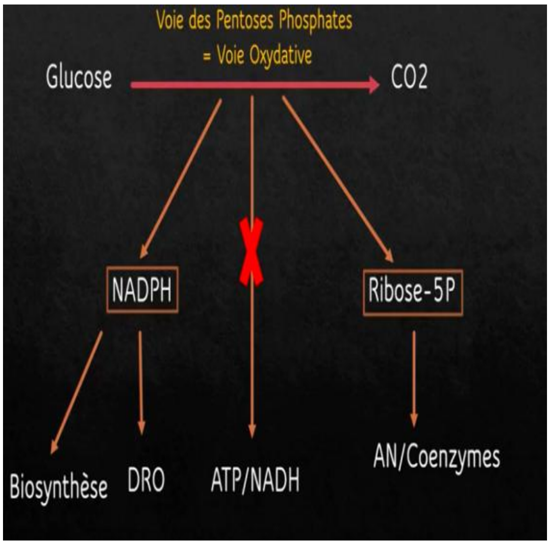


Figure.1 : Pentose Phosphate Pathway (PPP)

The substrate of the pentose phosphate pathway is **glucose-6-phosphate**. This pathway branches from glycolysis at the level of glucose-6-phosphate and rejoins it at the level of fructose-6-phosphate and triose phosphates.

2/Site of Occurrence

The pentose phosphate pathway is particularly active in:

- **The liver:** fatty acid synthesis, cholesterol synthesis, and hydroxylation reactions,
- **Adipose tissue:** fatty acid synthesis,

- **Mammary gland during lactation:** fatty acid synthesis,
- **Steroidogenic tissues** (adrenal cortex, testes, ovaries, placenta): steroid hormone synthesis,
- **And Red blood cells:** glutathione reduction (antioxidant defense).

The pathway is minimally active in muscle, where reductive biosynthesis is limited and glucose is primarily utilized for energy production.

3/Reactions of the Pentose Phosphate Pathway

The reactions of the pentose phosphate pathway occur in two phases:

- ***Oxidative phase (irreversible):***

  This phase generates ***2 molecules of NADPH + H***$^+$ and produces the first pentose of the pathway, ***ribulose-5-phosphate***.

- ***Non-oxidative phase (reversible):***

  This phase involves the ***interconversion of pentose phosphates***. Ribulose-5-phosphate can be:

  ✓ ***Isomerized*** into ***ribose-5-phosphate***, which is used for nucleotide synthesis, or

  ✓ ***Epimerized*** into ***xylulose-5-phosphate***.

It also includes ***transketolase*** and ***transaldolase reactions***, which transfer carbon units between sugars, allowing the formation of glycolytic intermediates.

3.1/Oxidative Phase

During this phase, glucose-6-phosphate (G6P) is converted into ribulose-5-phosphate, producing 2 molecules of NADPH and 1 molecule of CO_2. This process involves three key enzymatic reactions:

Glucose-6-phosphate dehydrogenase (G6PD) reaction 1:

- Oxidation of G6P to **6-phosphogluconolactone**
- Produces **1 NADPH**

6-Phosphogluconolactonase reaction 2:

- Hydrolysis of 6-phosphogluconolactone to **6-phosphogluconate**

6-Phosphogluconate dehydrogenase reaction 3:

- Oxidative decarboxylation of 6-phosphogluconate to **ribulose-5-phosphate**
- Produces **1 NADPH** and releases $\mathbf{CO_2}$

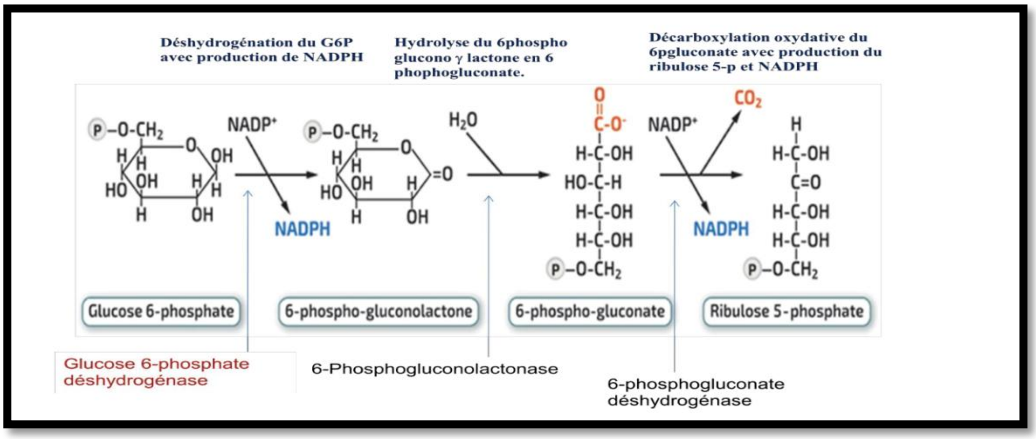


Figure .2 : Reactions 1, 2, 3 of oxidative phase of the pentose phosphate pathway

Reactions 4 and 5 : isomerization and epimerization of pentose phosphates

Ribulose-5-phosphate: substrate of two reversible reactions

- **Epimerization (ketose → ketose):**

  Ribulose-5-phosphate is **epimerized** into **xylulose-5-phosphate** by **ribulose-5-phosphate epimerase**.

- **Isomerization (ketose → aldose):**

  Ribulose-5-phosphate is **interconverted** into **ribose-5-phosphate** by **ribulose-5-phosphate isomerase**.

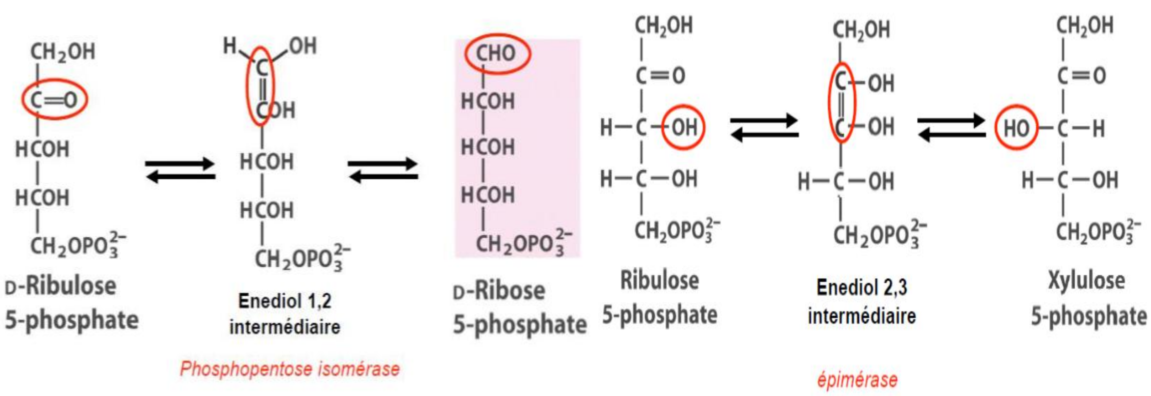


Figure .2 : Reactions 4, 5 of oxidative phase of the pentose phosphate pathway

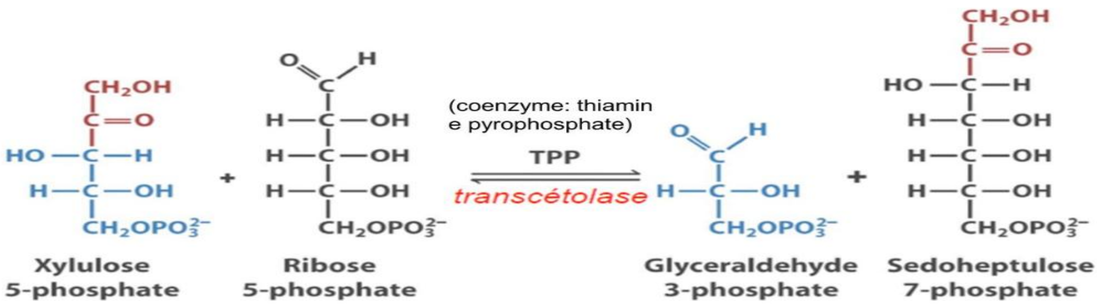
3.2/ Non Oxidative Phase

The non-oxidative phase continues with a series of **three transketolase and transaldolase reactions**, which convert pentose phosphates into **glyceraldehyde-3-phosphate** and **fructose-6-phosphate**, key intermediates of **glycolysis**.

- **Transketolase reactions (**reactions 6 and 8**):**
  Involve the transfer of a two-carbon unit from a ketose to an aldose, catalyzed by transketolases.
- **Transaldolase reaction (**reaction 7**):**
  Involves the transfer of a three-carbon unit from a ketose to an aldose, catalyzed by transaldolases.

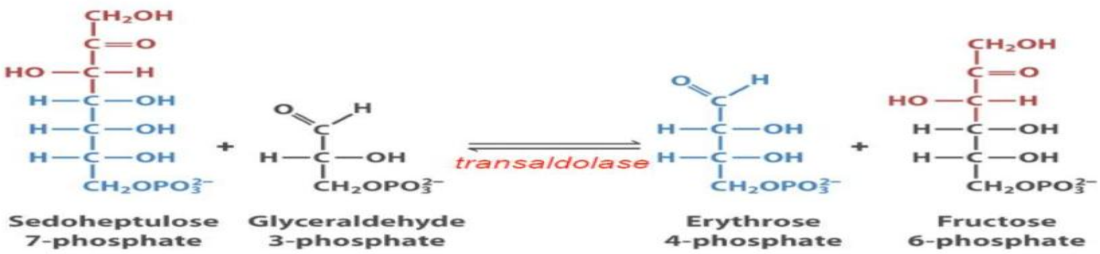
<u>Réaction 6</u>

A **transketolase** catalyzes the transfer of a **two-carbon unit** from **xylulose-5-phosphate** to **ribose-5-phosphate**, forming one molecule of **glyceraldehyde-3-phosphate (G3P)** and one molecule of **sedoheptulose-7-phosphate (S7P)**.



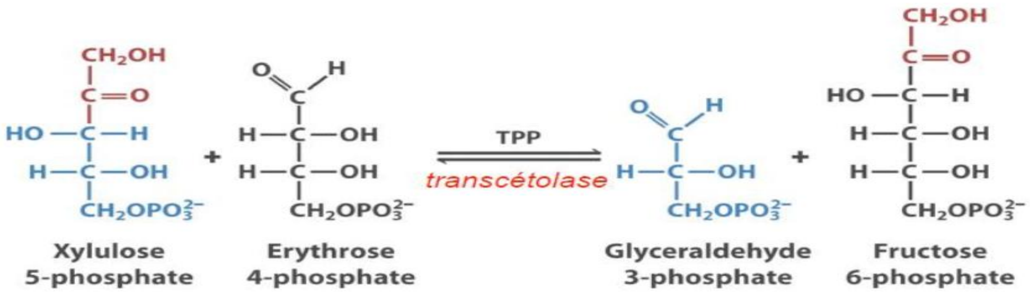
<u>Réaction 7:</u>

A **transaldolase** catalyzes the transfer of a **three-carbon unit** from **sedoheptulose-7-phosphate (S7P)** to **glyceraldehyde-3-phosphate (G3P)**, forming one molecule of **fructose-6-phosphate (F6P)**, which can be interconverted into **glucose-6-phosphate**, and one molecule of **erythrose-4-phosphate (E4P)**.



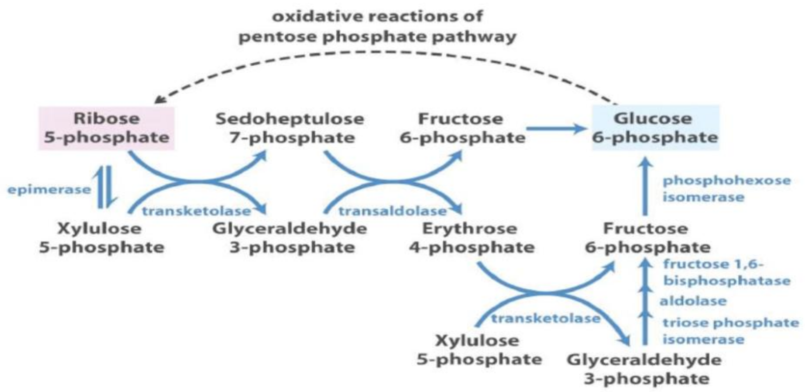
Réaction 8 :

A **transketolase** catalyzes the transfer of a **two-carbon unit** from **xylulose-5-phosphate** to **erythrose-4-phosphate**, forming one molecule of **fructose-6-phosphate (F6P)**, which can be interconverted into **glucose-6-phosphate (G6P)**, and one molecule of **glyceraldehyde-3-phosphate (G3P)**.



Interconversion of three pentose phosphates into two fructose-6-phosphate molecules and one glyceraldehyde-3-phosphate.

These intermediates can enter **glycolysis** and/or **gluconeogenesis**, depending on cellular needs.



4/Regulation of the Pentose Phosphate Pathway (PPP)

Glucose-6-phosphate (G6P) serves as a common substrate for both the pentose phosphate pathway and glycolysis**.** The distribution of G6P between these two pathways depends on the cell's immediate metabolic needs, particularly its requirements for energy (ATP) and for biosynthetic precursors such as NADPH and ribose-5-phosphate**.**

While glycolysis is inhibited when the cellular energy charge is high**,** glucose-6-phosphate dehydrogenase (G6PD) is inhibited by elevated levels of NADPH as well as by intermediates of fatty acid biosynthesis**.**

Nevertheless, depending on cellular requirements, the metabolism of glucose-6-phosphate **(G6P)** can proceed through **four different metabolic scenarios**.

<u>Situation 1: The cell requires both NADPH and ribose 5-phosphat</u>

The initial reactions of the pentose phosphate pathway are predominant.
The oxidative segment of the pentose phosphate pathway produces two molecules of NADPH and one ribulose 5-phosphate, which will be converted into ribose 5-phosphate, the main carbon product.

<u>Situation 2: The cell requires a greater quantity of ribose 5-phosphate than NADPH</u>

The oxidative segment is bypassed (or short-circuited). Glucose 6-phosphate is converted, through the glycolysis pathway, into fructose 6-phosphate and glyceraldehyde 3-phosphate.
These intermediates are then converted by transaldolase and transketolase into ribose 5-phosphate.
Two molecules of fructose 6-phosphate and one molecule of glyceraldehyde 3-phosphate produce three molecules of ribose 5-phosphate.

<u>Situation 3: The cell requires a greater quantity of NADPH than ribose 5-phosphate</u>

The oxidative segment of the PPP (Pentose Phosphate Pathway) forms NADPH and ribose 5-phosphate.
The ribose 5-phosphate is then converted by the non-oxidative phase into fructose 6-phosphate and glyceraldehyde 3-phosphate.
These intermediates will regenerate glucose 6-phosphate through gluconeogenesis.

<u>Situation 4: The cell requires NADPH and ATP but not ribose 5-phosphate</u>

This simultaneous requirement for NADPH and ATP implies that the ribose 5-phosphate, produced by the oxidative segment, is converted into fructose 6-phosphate and glyceraldehyde 3-phosphate, as in Mode 3.
However, these metabolites will follow the glycolytic pathway (and not gluconeogenesis) and will produce pyruvate and ATP.

5/Pathologies Related to the Pentose Phosphate Pathway

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Deficiency in the rate-limiting enzyme of the pentose phosphate pathway, glucose-6-phosphate dehydrogenase, is one of the most common hereditary diseases.

In the event of a G6PD enzymatic deficiency, there is a lack of NADH/H+ (specifically NADPH required for glutathione regeneration. Consequently, peroxides and oxygen free radicals damage the erythrocyte membrane (red blood cell membrane), causing the destruction of red blood cells which can lead to severe hemolytic anemia.