Biochemical Pathways: The Pentose Phosphate Pathway

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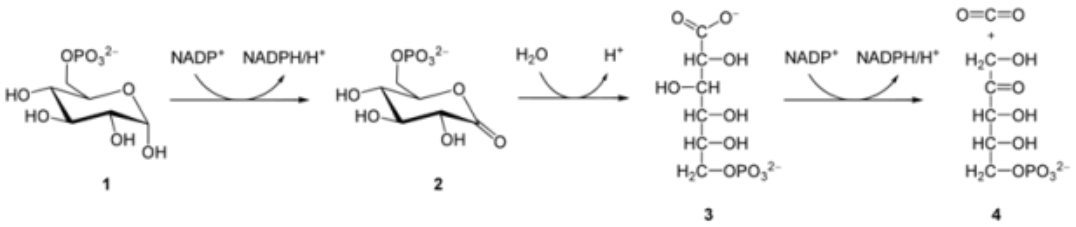
Both glycolysis and its parallel metabolic, the pentose phosphate pathway, start with the breakdown of glucose, i.e. glucose-6-phosphate. Divided into two distinct phases, the pentose phosphate pathway generates NADPH and pentoses, which can be used in other metabolic pathways. The pentose phosphate pathway is a small, but very important biochemical pathway physicians should be aware of, as, for instance, the metabolic disorder glucose-6-phosphate dehydrogenase deficiency (G6PD) may impart a distinct selective advantage against malaria.



Definition

The pentose phosphate pathway may be referred to as the pentose phosphate cycle, the phosphogluconate pathway, the hexose monophosphate cycle, or **Warburg-Dickens-Horecker shunt**. They all mean the same thing: the provision of **NADPH** and **pentoses** that can be used in other biochemical pathways.

NADPH is mainly found in tissues in which biosynthetic processes are important, which means that in those tissues, the pentose phosphate pathway is required to generate NADPH by reducing glucose. Examples are **hepatocytes and adipocytes, which synthesize fatty acids, or the ovaries, testes and the adrenal cortex, which synthesize steroids**.

In addition to the synthesis of fatty acids, NADPH is also required for the **biosynthesis of cholesterol**, the **biosynthesis of neurotransmitters and the biosynthesis of nucleotides via Phosphoribosyl-pyrophosphate (*PRPP*)**. Furthermore, NADPH-dependent reductases are involved in tissue detoxification and it is further used in the reduction of glutathione in erythrocytes. The pentose phosphate pathway can be divided into two distinct phases: a first oxidative and a second non-oxidative (reductive) phase. Both processes occur exclusively in the **cytoplasm**.

Oxidative Phase

In the first **oxidative** phase of the pentose phosphate pathway, glucose is oxidized to generate **2 molecules of NADPH**. This step is essentially irreversible and **the committing step**, as the reactions are strongly exergonic.

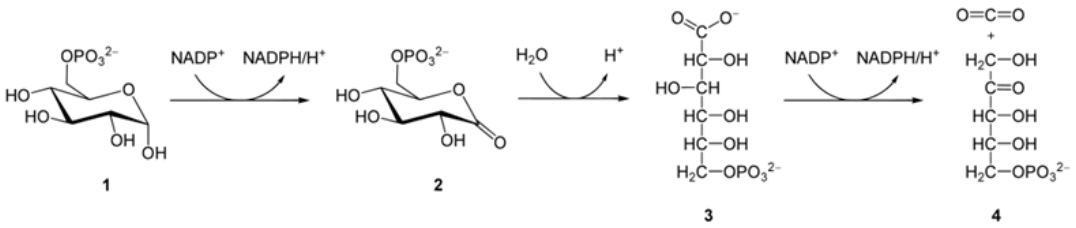


Image: “Oxidative Phase” by Yikrazuul. License: Public Domain

First Reaction

The initial metabolite of the pentose phosphate pathway is glucose-6-phosphate, 2 $NADP^+$ and H_2O. The oxidative phase starts with dehydrogenation at the C1 atom of glucose-6-phosphate, a reaction catalyzed by glucose-6-phosphate dehydrogenase. The reaction product is 6-phosphoglucono-δ-lactone. In a converse manner, $NADP^+$ is reduced to NADPH during this process.

Second Reaction

6-phosphoglucono-δ-lactone is hydrolyzed to **6-phosphogluconate** by a specific enzyme called **lactonase**.

Third Reaction

Oxidative decarboxylation of 6-phosphogluconate by **gluconate-6-phosphate dehydrogenase** yields **3-keto-6-phosphogluconate**, which converts into **ribulose-5-phosphate**, substrate for the non-oxidative reactions, and NADPH.

Non-Oxidative Phase

This second, non-oxidative phase is **reversible** and **reductive**. It yields pentoses used in the **synthesis of nucleotides** and catalyzes the interconversion of three-, four-, five-, six-, and seven-carbon sugars. This, in turn, may result in intermediates, which may enter, for example, glycolysis.

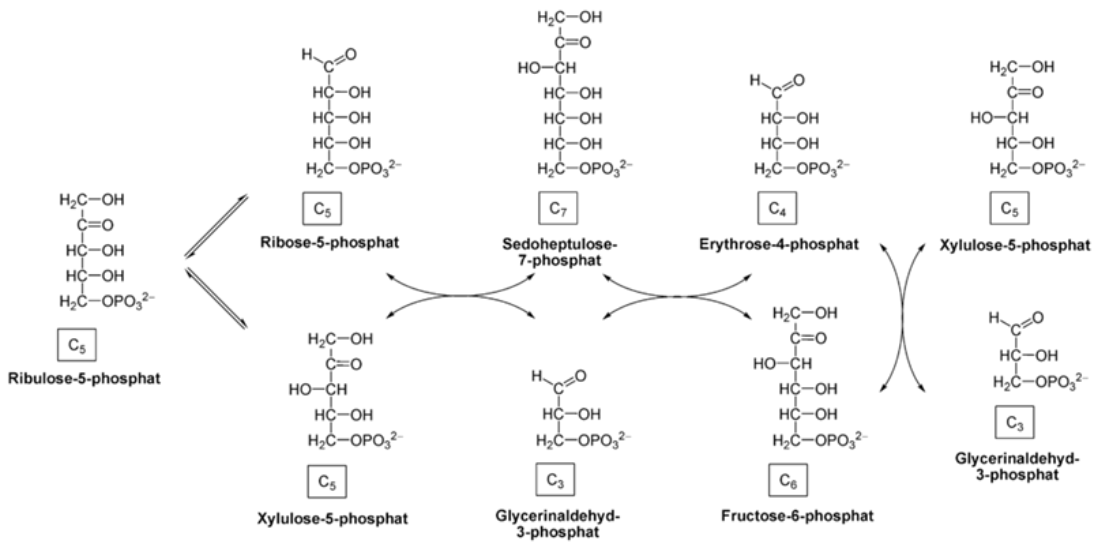


Image: “Die nichtoxidativen Schritte des Pentosephosphatweges” by Yikrazuul. License: (CC BY-SA 3.0)

First Reaction

Ribulose-5-phosphate generated in the oxidative phase is partly converted to **xylulose-5-phosphate,** catalyzed by **ribulose-5-phosphate epimerase**, and partly isomerized by means of the enzyme **phosphopentose isomerase** to **ribose-5-phosphate**.

Second Reaction

The two resulting C_5 carbohydrates are now required for the next step: xylulose-5-phosphate serves as C_2-donor. The enzyme **transketolase** transfers 2 carbon fragments to the pentose ribose-5-phosphate, which yields **glyceraldehyde-3-phosphate** and **sedoheptulose-7-phosphate**.

Third Reaction

The two products of the previous step continue to transfer carbon fragments: The enzyme **transaldolase** transfers 3 carbon atoms of sedoheptulose-7-phosphate to glyceraldehyde-3-phosphate; thus, two new carbohydrates are generated: **erythrose-4-phosphate** and **fructose-6-phopshate**.

Fourth Reaction

This step is also catalyzed by a **transketolase**: Together with erythrose-4-phosphate, generated in the third reaction, another xylulose-5-phosphate is used to generate another fructose-6-phosphate and a further glyceraldehyde-3-phosphate.

Ultimately, this means that 3 ribose-5-phosphates can generate 2 fructose-6-phosphates and 1 glyceraldehyde-3-phosphate, which may be fed into the glycolytic pathway. Furthermore, fructose-6-phosphate can convert back into glucose-6-phosphate and enter into a new pentose phosphate pathway.

Regulation Mechanisms of the Pentose Phosphate Pathway

Which part of the pentose phosphate pathway is operative and how fast depend on the demand and **availability of different reaction products, intermediates and substrates** (starting reactants) of the pathway. The most important regulatory factor is the intracellular $NADP^+$ concentration.

In a cell with low $NADP^+$ levels, the dehydrogenation of glucose-6-phosphate is inhibited, which means that hardly any NADPH is produced. **Only when NADPH is required for reductive biosynthesis reactions, the first phase of the pentose phosphate pathway is active.** It is assumed that insulin upregulates the transcription rate of glyceraldehyde-3-phosphate dehydrogenase, which amplifies the first step of the pentose phosphate pathway.

While the concentration of $NADP^+$ mainly has an effect on the first phase of the pentose phosphate pathway, the concentrations of different substrates tend to influence the second phase.

Energy Balance of the Pentose Phosphate Pathway

As the pentose phosphate pathway and the glycolytic pathway are directly connected and defined by a coordinated interplay or exchange of various molecules between them, the output of the pentose phosphate pathway is determined by the needs of the cell. In the following, four different metabolic situations are described:

If the cell, for example, requires many **nucleotides** for DNA synthesis, it has to generate a large amount of ribose-5-phosphate. For this, the cell can reverse the reactions described above and, using ATP, it can generate 3 molecules of ribose-5-phosphate from 2 fructose-6-phosphate molecules and 1 glyceraldehyde-3-phosphate.

If the cell requires both, ribose-5-phosphate and NADPH, the oxidative phase of the pentose phosphate pathway is triggered, forming two molecules of NADPH and one molecule of ribose-5-phosphate from one molecule of glucose-6-phosphate.

If the cell needs a large amount of NADPH for **reductive biosynthesis**, it will use the reaction products of the second phase of the pentose phosphate pathway, glyceraldehyde-3-phosphate and fructose-6-phosphate, converting them back to glucose-6-phosphate and feeding it into the pentose phosphate pathway. This way, 1 glucose-6-phosphate can convert 12 $NADP^+$ to NADPH.

If the cell needs both NADPH and ATP, products of the pentose phosphate pathway, namely fructose-6-phosphate and glyceraldehyde-3-phosphate, will enter the glycolytic pathway (rather than reverting to glucose-6-phosphate). Like this, 3 glucose-6-phosphates can be converted into 5 molecules pyruvate, 6 NADPH, and 8 ATP.

Pathophysiology

As mentioned above, the NADPH generated in the pentose phosphate pathway plays a key role in antioxidant defenses (**cellular detoxification**): It reduces oxidized glutathione. **Glutathione** is a tripeptide, which reduces reactive oxygen species **ROS** and thus, combats the so-called oxidative stress that causes many diseases.

If the pentose phosphate pathway is not working properly, e.g. in case of a **glucose-6-phosphate dehydrogenase deficiency** (G6PD), an insufficient amount of NADPH is generated. As the pentose phosphate pathway is the only source of reduced glutathione in erythrocytes, this leads to **cell decay**; thus, **individuals with a G6PD deficiency are at risk of hemolytic anemia**. The associated clinical presentation is called Favism.

By the way: glucose-6-phosphate dehydrogenase deficiency confers a natural protection against malaria, as the pathogenic parasites require reduced glutathione for their growth. This selective advantage explains why this genetic deficiency is widespread in sub-Saharan Africa and the Mediterranean region.

Review Questions

1. Which of the following is not a substrate or product of the pentose phosphate pathway?

A. xylulose-6-phosphate.
B. ribose-5-phosphate.
C. ribulose-5-phosphate.
D. erythrose-4-phosphate.
E. fructose-6-phosphate.

2. The non-oxidative phase of the pentose phosphate pathway…

A. …generates NADPH.
B. …converts ribulose-5-phosphate into glyceraldehyde-3-phosphate.
C. …converts xylulose-5-phosphate into glucose-6-phosphate.
D. …reduces NADPH.
E. …yields the reaction product fructose-6-phosphate.

3. The symptoms of a glucose-6-phosphate dehydrogenase deficiency are most likely characterized by…

A. …increased glycolysis.
B. …increased hemolysis.
C. …elevated levels of glucose-6-phosphate.
D. …lowered levels of fructose-6-phosphate.
E. …elevated concentrations of reduced glutathione.

References

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Correct Answers: 1A, 2E, 3B

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Notes