7.1: Pentose phosphate pathway

The pentose phosphate pathway (PPP — also known as the hexose monosphosphate shunt) is a cytosolic pathway that interfaces with glycolysis. In this pathway, no ATP is directly produced from the oxidation of glucose 6-phosphate; instead the oxidative portion of the PPP is coupled to the production of NADPH. In addition to generating NADPH, which is essential for detoxification reactions and fatty acid synthesis, it also produces five-carbon sugars required for nucleotide synthesis.

Oxidative and nonoxidative functions

There are two parts of the pathway that are distinct and can be regulated independently. The first phase, or oxidative phase, consists of two irreversible oxidations that produce NADPH. As noted above, NADPH is required for reductive detoxification and fatty acid synthesis. (NADPH is not oxidized in the ETC.) In the red blood cell, this is extremely important as the PPP pathway provides the only source of NADPH. NADPH is essential to maintain sufficient levels of reduced glutathione in the red blood cell. Glutathione is a tripeptide commonly used in tissues to detoxify free radicals and reduce cellular oxidation.

The nonoxidative phase of the pathway allows for the conversion of ribulose 5-phosphate into ribose 5-phosphate, which is needed for nucleotide synthesis (figure 7.1). All of these interconversions in the nonoxidative pathway are reversible and use the enzymes transketolase or transaldolase to move two-carbon or three-carbon units on to other sugar moieties to generate a variety of sugar intermediates. Transketolase requires thiamine pyrophosphate (TPP) as a cofactor. This is of clinical relevance as TPP levels can be measured by addressing the activity of transketolase in a blood sample. A reduction in transketolase activity is an indicator of a thiamine deficiency.

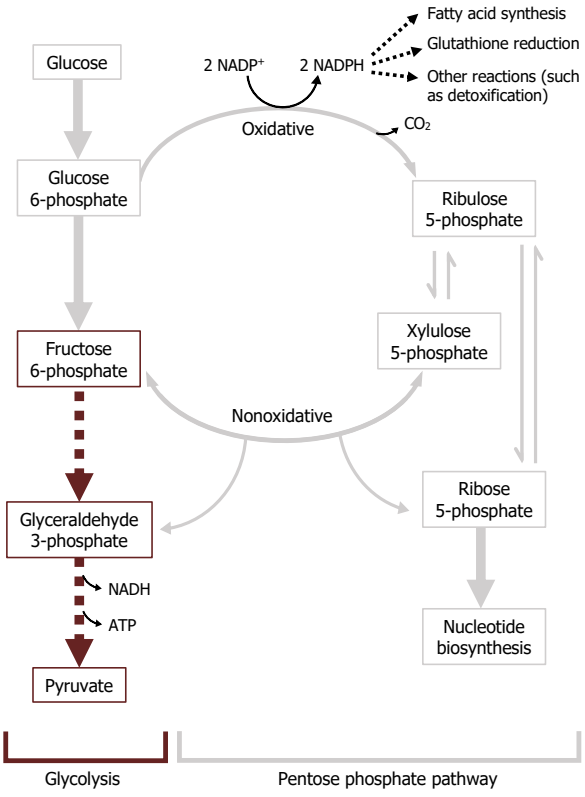

Figure 7.1: Overview of the pentose phosphate pathway and its interface with glycolysis.

Any compounds unused by the nonoxidative pathway will eventually be converted to fructose 6-phosphate or glyceraldehyde 3-phosphate, both of which will re-enter the glycolytic pathway (figures 7.1 and 7.2).

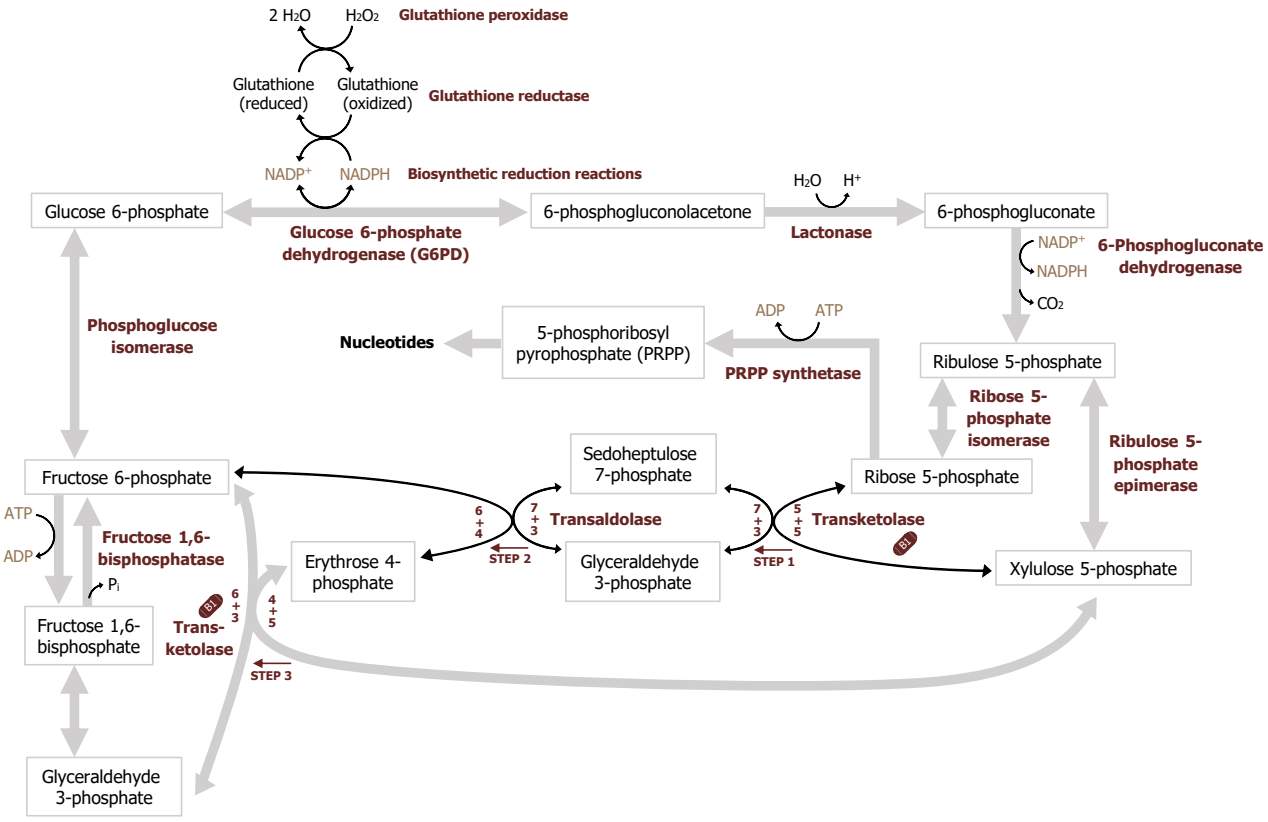

Figure 7.2: Pentose phosphate pathway and its connection to glycolysis and glutathione synthesis.

Regulation of the pentose phosphate pathway

The key regulatory enzyme for the pentose phosphate pathway is within the oxidative portion. Glucose 6-phosphate dehydrogenase oxidizes glucose 6-phosphate to 6-phosphogluconolactone, and is regulated by negative feedback. In this two-step reaction NADPH is also produced, and high levels of NADPH will inhibit the activity of glucose 6-phosphate dehydrogenase. This ensures NADPH is only generated as needed by the cell; this is the primary regulatory mechanism within the pathway.

The nonoxidative phase is not regulated; however, in conditions where there is a high demand for nucleotide production (such as in the case for highly proliferative cells), the nonoxidative part of the pathway can function independently of the oxidative phase to produce ribose 5-phosphate from the glycolytic intermediates fructose 6-phosphate and glyceraldehyde 3-phosphate (figure 7.2).

Requirement of the pentose phosphate pathway in RBCs

The two essential products of this pathway are NADPH and ribose 5-phosphate. NADPH is a high-energy compound often used for reductive biosynthesis as it cannot be oxidized in the ETC. It is also used by many tissues to scavenge (and detoxify) reactive oxygen species (ROS) before causing cellular damage. This is especially important in red blood cells; RBCs lack malic enzyme, making this the only pathway that can generate NADPH. A lack of NADPH in RBCs (such as due to a glucose 6-phosphate dehydrogenase deficiency) can cause excessive hemolysis, leading to the clinical presentation of jaundice (figure 7.3).

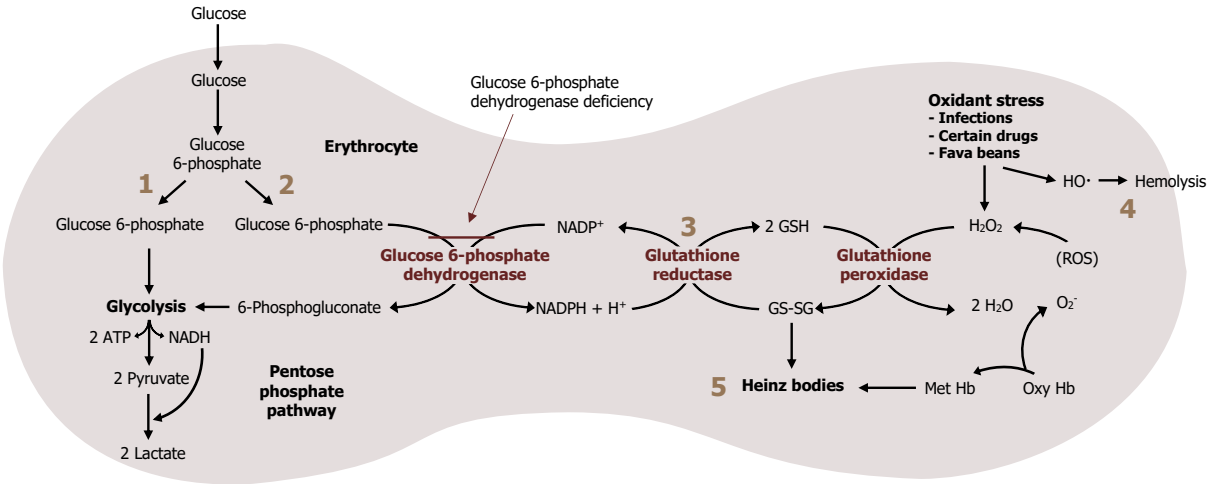

Figure 7.3: NADPH in the red blood cell as a means of reducing glutathione.

Glutathione (GSH) is a tripeptide compound consisting of glutamate, cysteine, and glycine. It plays a key role in scavenging reactive oxygen species (ROS), which cause both DNA and cellular/protein damage. Reduction of GSH in the red blood cell is done exclusively through a series of oxidation reduction reactions using NADPH. The loss of NADPH in RBCs therefore increases ROS and can lead to hemolysis (figure 7.3).

Summary of pathway regulation

Metabolic pathway	Major regulatory enzyme	Allosteric effectors	Hormonal effects
Pentose phosphate pathway	Glucose 6-phosphate dehydrogenase	NADPH (-)	None

Table 7.1: Summary of pathway regulation.

References and resources

Text

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Le, T., and V. Bhushan. *First Aid for the USMLE Step 1*, 29th ed. New York: McGraw Hill Education, 2018, 35–37, 79.

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Figures

Grey, Kindred, Figure 7.2 Pentose pathway and its connection to glycolysis and glutathione synthesis. 2021. https://archive.org/details/7.2_20210926. CC BY 4.0.

Lieberman M, Peet A. Figure 7.1 Overview of the pentose phosphate pathway and its interface with glycolysis. Adapted under Fair Use from Marks' Basic Medical Biochemistry. 5th Ed. pp 543. Figure 27.1 Overview of the pentose phosphate pathway. 2017.

Lieberman M, Peet A. Figure 7.3 NADPH in the red blood cell as a means of reducing glutathione. Adapted under Fair Use from Marks' Basic Medical Biochemistry. 5th Ed. pp 549. Figure 27.7 Hemolysis caused by reactive oxygen species (ROS). 2017.

Gluconeogenesis

Gluconeogenesis is the metabolic process by which organisms produce sugars (namely glucose) for catabolic reactions from non-carbohydrate precursors. Glucose is the only energy source used by the brain (with the exception of ketone bodies during times of fasting), testes, erythrocytes, and kidney medulla. In mammals this process occurs in the liver and kidneys.

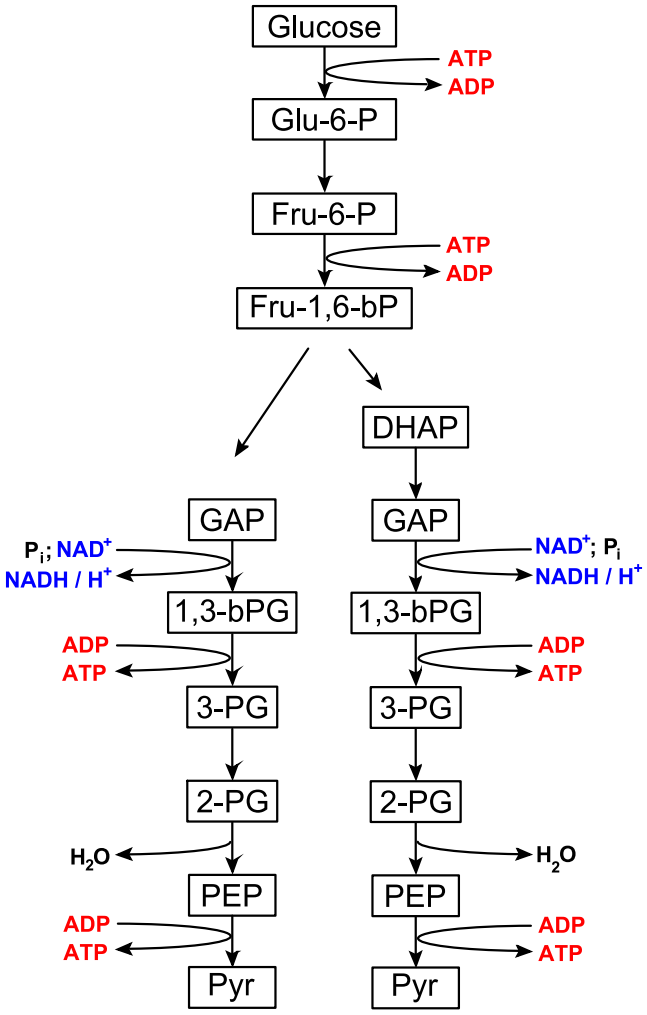
Introduction

The need for energy is important to sustain life. Organisms have evolved ways of producing substrates required for the catabolic reactions necessary to sustain life when desired substrates are unavailable. The main source of energy for eukaryotes is glucose. When glucose is unavailable, organisms are capable of metabolizing glucose from other non-carbohydrate precursors. The process that coverts pyruvate into glucose is called gluconeogenesis. Another way organisms derive glucose is from energy stores like glycogen and starch.

Overview

Gluconeogenesis is much like glycolysis only the process occurs in reverse. However, there are exceptions. In glycolysis there are three highly exergonic steps (steps 1,3,10). These are also regulatory steps which include the enzymes hexokinase, phosphofructokinase, and pyruvate kinase. Biological reactions can occur in both the forward and reverse direction. If the reaction occurs in the reverse direction the energy normally released in that reaction is now required. If gluconeogenesis were to simply occur in reverse the reaction would require too much energy to be profitable to that particular organism. In order to overcome this problem, nature has evolved three other enzymes to replace the glycolysis enzymes hexokinase, phosphofructokinase, and pyruvate kinase when going through the process of gluconeogenesis:

1. The first step in gluconeogenesis is the conversion of pyruvate to phosphoenolpyruvic acid (PEP). In order to convert pyruvate to PEP there are several steps and several enzymes required. Pyruvate carboxylase, PEP carboxykinase and malate dehydrogenase are the three enzymes responsible for this conversion. Pyruvate carboxylase is found on the mitochondria and converts pyruvate into oxaloacetate. Because oxaloacetate cannot pass through the mitochondria membranes it must be first converted into malate by malate dehydrogenase. Malate can then cross the mitochondria membrane into the cytoplasm where it is then converted back into oxaloacetate with another malate dehydrogenase. Lastly, oxaloacetate is converted into PEP via PEP carboxykinase. The next several steps are exactly the same as glycolysis only the process is in reverse.
2. The second step that differs from glycolysis is the conversion of fructose-1,6-bP to fructose-6-P with the use of the enzyme fructose-1,6-phosphatase. The conversion of fructose-6-P to glucose-6-P uses the same enzyme as glycolysis, phosphoglucoisomerase.
3. The last step that differs from glycolysis is the conversion of glucose-6-P to glucose with the enzyme glucose-6-phosphatase. This enzyme is located in the endoplasmic reticulum.



Glycolysis

Regulation

Because it is important for organisms to conserve energy, they have derived ways to regulate those metabolic pathways that require and release the most energy. In glycolysis and gluconeogenesis seven of the ten steps occur at or near equilibrium. In gluconeogenesis the conversion of pyruvate to PEP, the conversion of fructose-1,6-bP, and the conversion of glucose-6-P to glucose all occur very spontaneously which is why these processes are highly regulated. It is important for the organism to conserve as much energy as possible. When there is an excess of energy available, gluconeogenesis is inhibited. When energy is required, gluconeogenesis is activated.

1. The conversion of pyruvate to PEP is regulated by acetyl-CoA. More specifically pyruvate carboxylase is activated by acetyl-CoA. Because acetyl-CoA is an important metabolite in the TCA cycle which produces a lot of energy, when concentrations of acetyl-CoA are high organisms use pyruvate carboxylase to channel pyruvate away from the TCA cycle. If the organism does not need more energy, then it is best to divert those metabolites towards storage or other necessary processes.
2. The conversion of fructose-1,6-bP to fructose-6-P with the use of fructose-1,6-phosphatase is negatively regulated and inhibited by the molecules AMP and fructose-2,6-bP. These are reciprocal regulators to glycolysis' phosphofructokinase. Phosphofructosekinase is positively regulated by AMP and fructose-2,6-bP. Once again, when the energy levels produced are higher than needed, i.e. a large ATP to AMP ratio, the organism increases gluconeogenesis and decreases glycolysis. The opposite also applies when energy levels are lower than needed, i.e. a low ATP to AMP ratio, the organism increases glycolysis and decreases gluconeogenesis.
3. The conversion of glucose-6-P to glucose with use of glucose-6-phosphatase is controlled by substrate level regulation. The metabolite responsible for this type of regulation is glucose-6-P. As levels of glucose-6-P increase, glucose-6-phosphatase

increases activity and more glucose is produced. Thus glycolysis is unable to proceed.

References

1. Garrett, H., Reginald and Charles Grisham. Biochemistry. Boston: Twayne Publishers, 2008.
2. Raven, Peter. Biology. Boston: Twayne Publishers, 2005.

Problems

1. How many enzymes are unique to Gluconeogenesis?
2. What is reciprocal regulation and why is it important to Glycolysis and Gluconeogenesis?
3. Where does the activity of glucose-6-phosphatase occur?
4. Why is it necessary for gluconeogenesis to incorporate other enzymes in its pathway that are different from glycolysis?
5. Draw glycolysis and Gluconeogenesis side by side with the products, reactants and enzymes for each step.

Contributors

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