

Hexose MonoPhosphate (HMP) shunt pathway

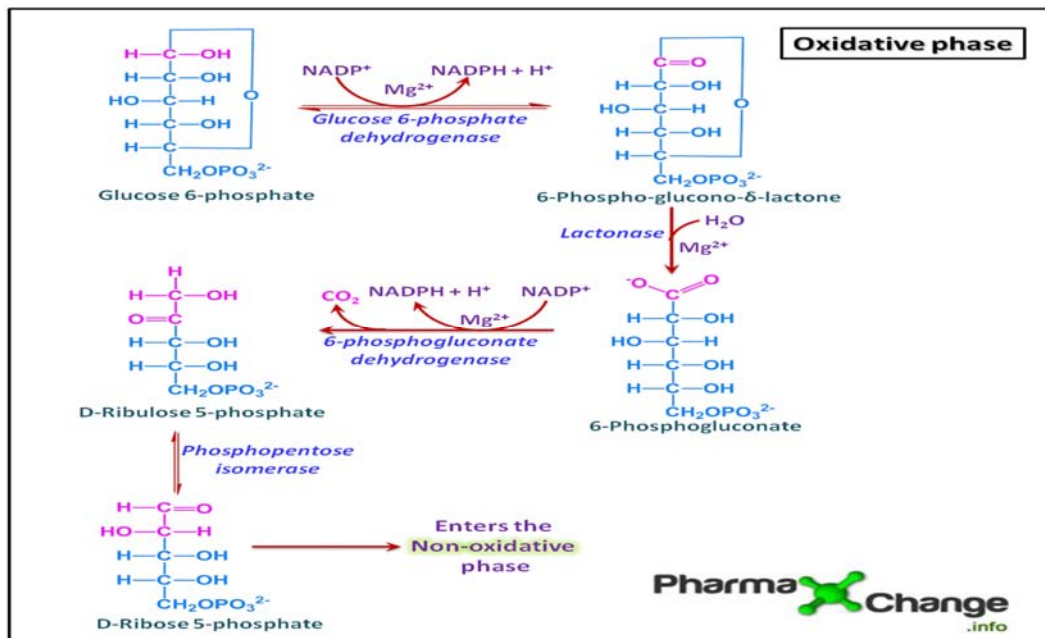
It is also known as "pentose phosphate pathway-PPP" because the reactions involve formation of pentose phosphates. It occurs in the cytosol of the cell. Instead of glucose going through the glycolytic pathway, it is shunted through this pathway; so it is known as the shunt pathway. Since the first carbon atom of glucose is liberated as CO₂, it is called the direct oxidative pathway of glucose metabolism. About 10% of glucose molecules per day are entering in this pathway. The major purpose of this pathway is generation of NADPH and pentose phosphates. No ATP is directly consumed or produced in this pathway.

Overview of the Shunt Pathway

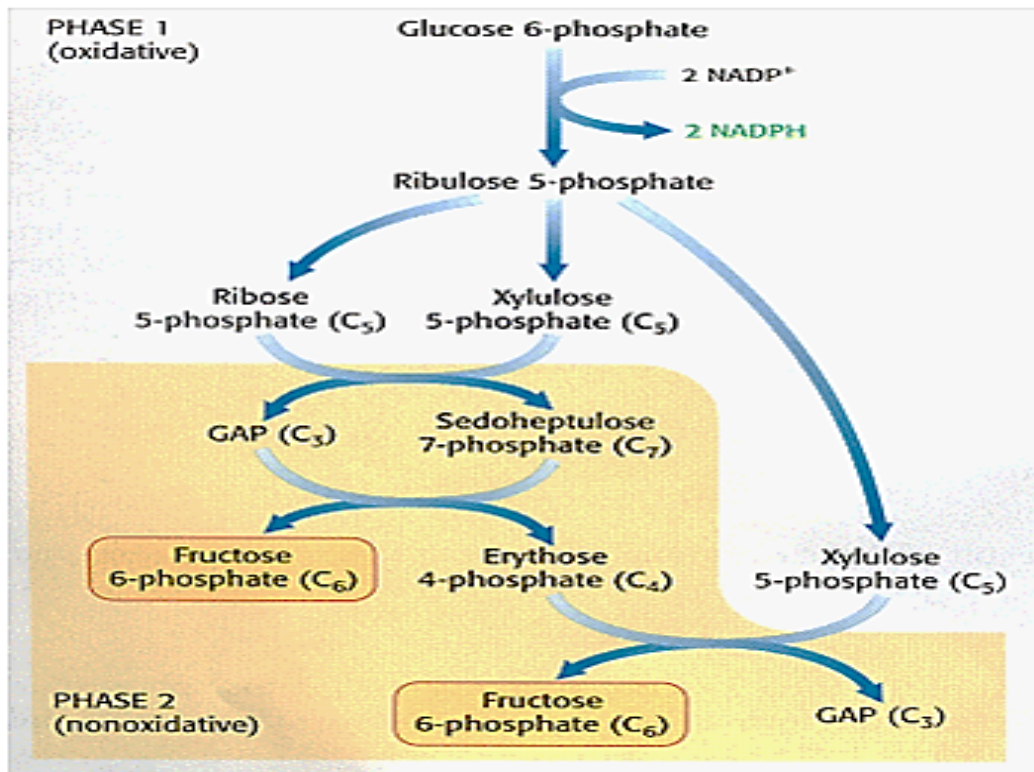
The HMP shunt pathway consists of two phases; oxidative and non-oxidative.

- During the oxidative phase, glucose-6-phosphate is oxidized with the generation of 2 molecules of NADPH, and one molecule of pentose phosphate, with the liberation of one molecule of CO₂.

- Overall equation of 1st phase is:



- During the non-oxidative phase, the pentose phosphate is converted to intermediates of glycolysis.



Regulation of HMP Shunt Pathway

The first reaction of HMP Shunt catalyzed by NADP⁺ dependent Glucose-6-phosphate dehydrogenase (GPD). This is the rate-limiting step, Regulation is affected by this enzyme. The pathway is mainly regulated by the level of NADP⁺. GPD is inhibited by NADPH. The oxidative phase is therefore controlled by the level of NADP⁺ and non-oxidative phase by the requirement of pentoses. Insulin will induce GPD and therefore will increase the overall pathway.

Use and Importance of HMP Shunt Pathway

The hexose monophosphate pathway is used for production of NADPH from NADP. The NADPH is required for biosynthetic reactions that require reducing power such as fatty acid synthesis, cholesterol synthesis, drug reduction, and as a cofactor for some non-synthetic enzymatic reactions. In addition, HMP is used for the production of ribose for nucleotide and nucleic acid synthesis. The hexose monophosphate pathway also allows the entry of some carbohydrates into the glycolytic

pathway, and therefore acts as a connection route between different pathways. NADPH plays two critical roles in red blood cells, both of these roles are related to the oxygen-transport function of the red blood cell. The first role is related to glutathione: erythrocytes require NADPH to maintain their levels of reduced glutathione. Oxygen is toxic without reduced glutathione (Peroxides that spontaneously formed from molecular oxygen would oxidize the lipid components of the red blood cell membranes, oxidized membranes are significantly less flexible than normal membranes, and result in damage to the red blood cells when the cells attempt to transit capillaries. In addition, peroxides tend to damage hemoglobin, resulting in precipitation of the protein. Insoluble aggregates of hemoglobin have severely impaired oxygen carrying capacity. Two enzymes are required to deal with the peroxides. First; Glutathione peroxidase uses reduced glutathione to convert the peroxide to an alcohol. Second Glutathione reductase uses NADPH to regenerate the reduced glutathione).

The second role of NADPH in red blood cells is related to hemoglobin (Oxygen tends to oxidize the hemoglobin iron from Fe +2 to the more stable Fe +3 state resulting in methemoglobin. This is a problem: the Fe +3 state of heme iron binds oxygen very poorly which disturb RBCs function. NADPH is used to supply reducing equivalents to methemoglobin reductase, the enzyme that returns the hemoglobin to the Fe +2 oxidation state.

Clinical Significance of Shunt Pathway

G6PD Deficiency

Glucose 6-phosphate dehydrogenase (G6PD) deficiency is an inherited X-linked disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents. The deficiency is manifested only when exposed to certain drugs or toxins. In G6PD deficient cells, the level of NADPH is low; hence further production of peroxides will lead to cell lysis. In some forms of G6PD deficiency, persons are particularly susceptible to the hemolytic effect of the fava bean, this condition called (favism).