Pentose Phosphate Pathway and NADPH

The pentose phosphate pathway also called

- hexose monophosphate pathway
- 6-phosphogluconate pathway

occurs in the cytosol of the cell. It includes two reactions

1. irreversible oxidative reactions
2. reversible sugar–phosphate interconversions.

The pathway provides

1. a major portion of the body's NADPH, which functions as a biochemical reductant.
2. produces ribose 5-phosphate, required for the biosynthesis of nucleotides.
3. provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or the degradation of structural carbohydrates in the body.

1) IRREVERSIBLE OXIDATIVE REACTIONS

The irreversible oxidative portion of the pentose phosphate pathway consists of three reactions that lead to the formation of ribulose 5-phosphate, CO_2, and two molecules of NADPH for each molecule of glucose 6-phosphate oxidized. This portion of the pathway is particularly important in the liver, lactating mammary glands, and adipose, which are active in the NADPH-dependent biosynthesis of fatty acids, in the testes, ovaries, placenta and adrenal cortex,

which are active in the NADPH-dependent biosynthesis of steroid hormones, and in erythrocytes, which require NADPH to keep glutathione reduced .

A. Dehydrogenation of glucose 6-phosphate

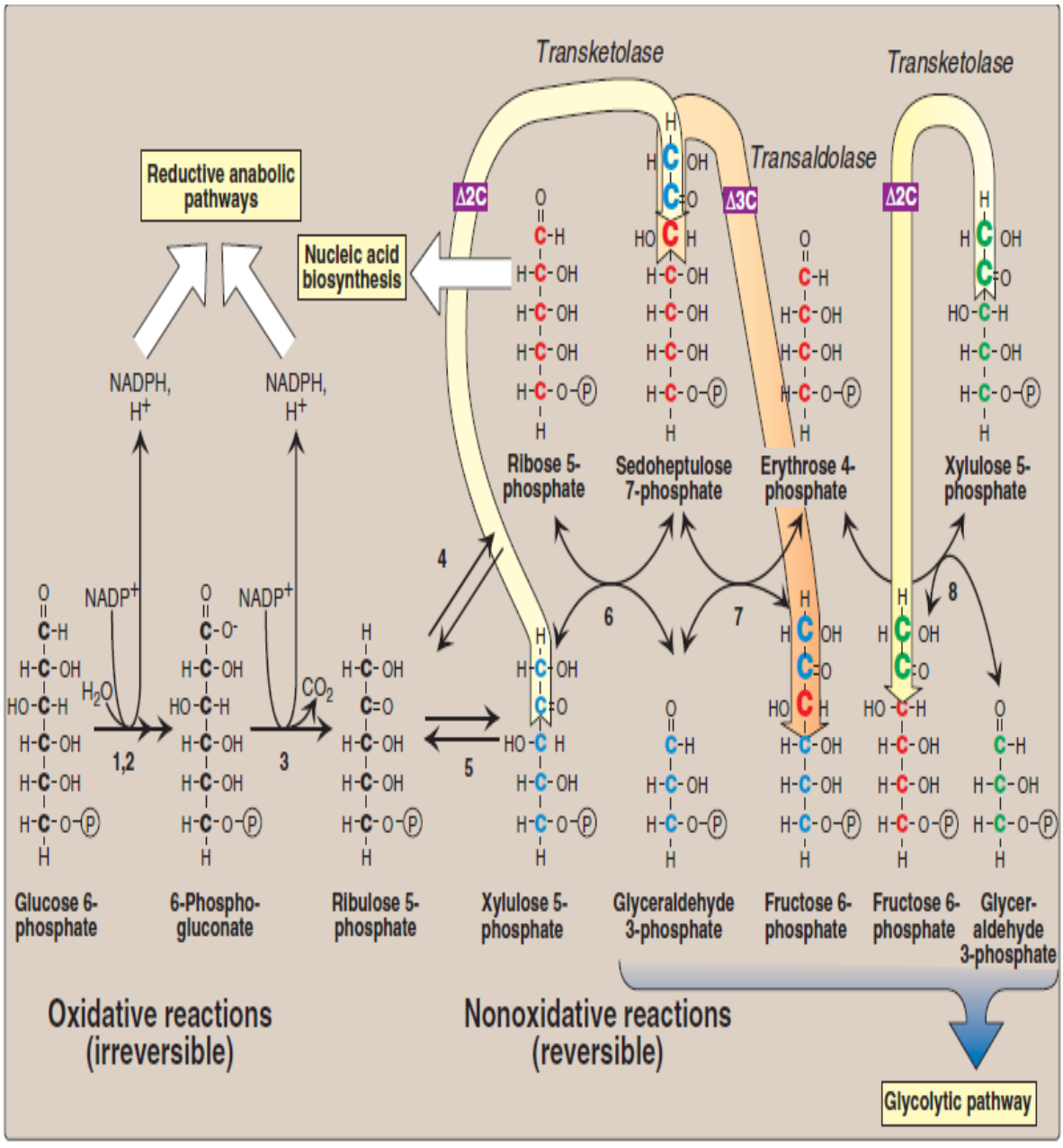
Glucose 6-phosphate dehydrogenase (G6PD) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone in a reaction that is specific for NADP+ as its coenzyme.

B. Formation of ribulose 5-phosphate

6-Phosphogluconolactone is hydrolyzed by 6-phosphogluconolactone hydrolase. The reaction is irreversible and not rate-limiting. The oxidative decarboxylation of the product, 6-phosphogluconate is catalyzed by 6-phosphogluconate dehydrogenase. This irreversible reaction produces a pentose sugar–phosphate (ribulose 5-phosphate), CO2 (from carbon 1 of glucose), and a second molecule of NADPH.

2) REVERSIBLE NONOXIDATIVE REACTIONS

The nonoxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids.

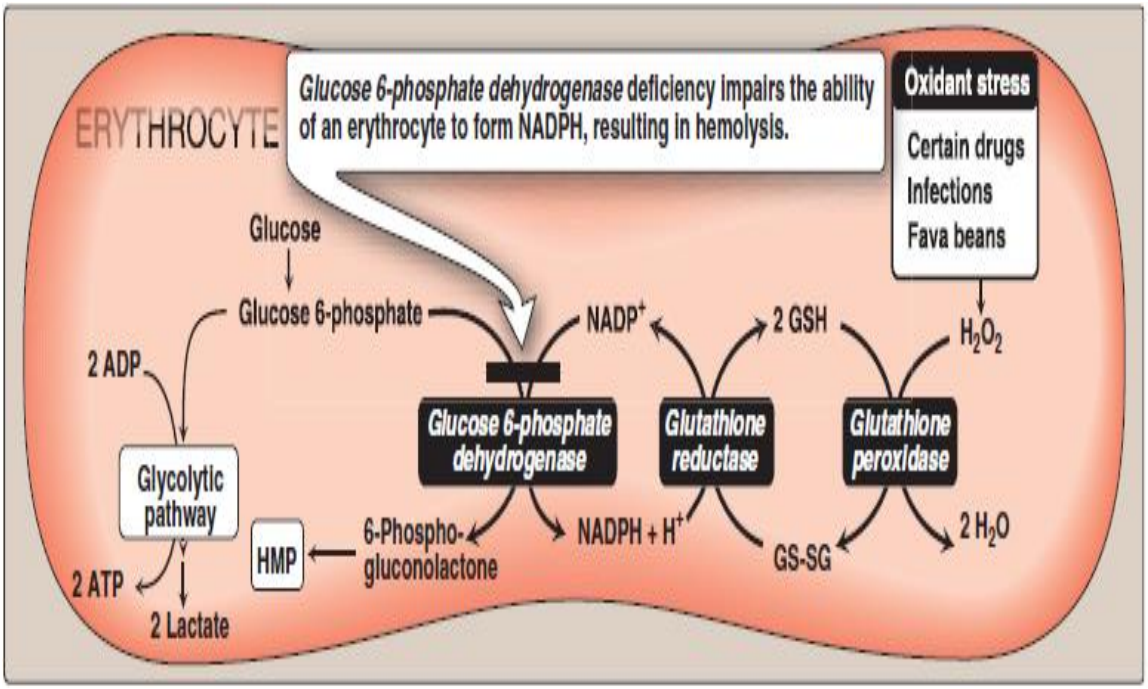

Transketolase
Transketolase
Transaldolase
Reductive anabolic pathways
Nucleic acid biosynthesis
Δ2C
Δ3C
Δ2C
NADPH, H+
NADPH, H+
NADP+
NADP+
H2O
CO2
1,2
3
4
5
6
7
8
Ribose 5-phosphate
Sedoheptulose 7-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate
Glucose 6-phosphate
6-Phospho-gluconate
Ribulose 5-phosphate
Xylulose 5-phosphate
Glyceraldehyde 3-phosphate
Fructose 6-phosphate
Fructose 6-phosphate
Glycer-aldehyde 3-phosphate
Oxidative reactions (irreversible)
Nonoxidative reactions (reversible)
Glycolytic pathway

GLUCOSE 6-P DEHYDROGENASE DEFICIENCY

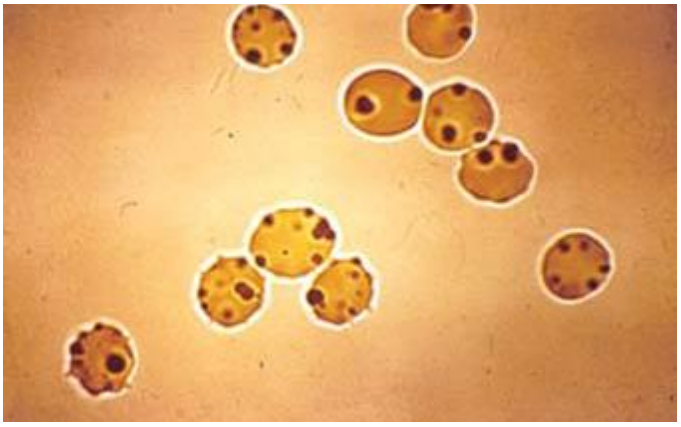
Glucose 6-phosphate dehydrogenase (G6PD) deficiency is an inherited disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents. G6PD deficiency is the most common disease-producing enzyme abnormality in humans .

Role of G6PD in red blood cells:

Diminished G6PD activity impairs the ability of the cell to form the NADPH that is essential for the maintenance of the reduced
glutathione pool. This results in a decrease in the cellular detoxification of free radicals and peroxides formed within the cell. Glutathione also helps maintain the reduced states of sulfhydryl groups in proteins, including hemoglobin. Oxidation of those sulfhydryl groups leads to the formation of denatured proteins that form insoluble masses (called Heinz bodies) that attach to the red cell membranes. Additional oxidation of membrane proteins causes the red cells to be rigid (less deformable)and they are removed from the circulation by macrophages in the spleen and liver.



Pathways of glucose 6-phosphate metabolism in the erythrocyte. HMP = hexose monophosphate pathway



Heinz bodies in erythrocytes of a patient with *G6PD* deficiency.

Precipitating factors in G6PD deficiency

1. Oxidant drugs: Commonly used drugs that produce hemolytic anemia in patients with G6PD deficiency are best remembered from the mnemonic AAA—Antibiotics.

2. Favism: Some forms of G6PD deficiency, are particularly susceptible to the hemolytic effect of the fava (broad) bean, a dietary staple in the Mediterranean region. Favism, the hemolytic effect of ingesting fava beans, is not observed in all individuals with G6PD deficiency, but all patients with favism have G6PD deficiency.

3. Infection: Infection is the most common precipitating factor of hemolysis in G6PD deficiency. The inflammatory response to infection results in the generation of free radicals in macro phages, which can diffuse into the red blood cells and cause oxidative damage.