Pentose Phosphate Pathway

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- The pentose phosphate pathway is an alternate route for the oxidation of glucose **without** direct consumption or generation of **ATP**

- The pentose phosphate pathway takes place entirely within the cytoplasm (because $NADP^+$ is used as a hydrogen acceptor) and is also known as the hexose monophosphate shunt or phosphogluconate pathway

- Is basically used for the synthesis of NADPH and D-ribose.

Pathway Questions

2. What are the key enzymes in the pentose phosphate pathway?

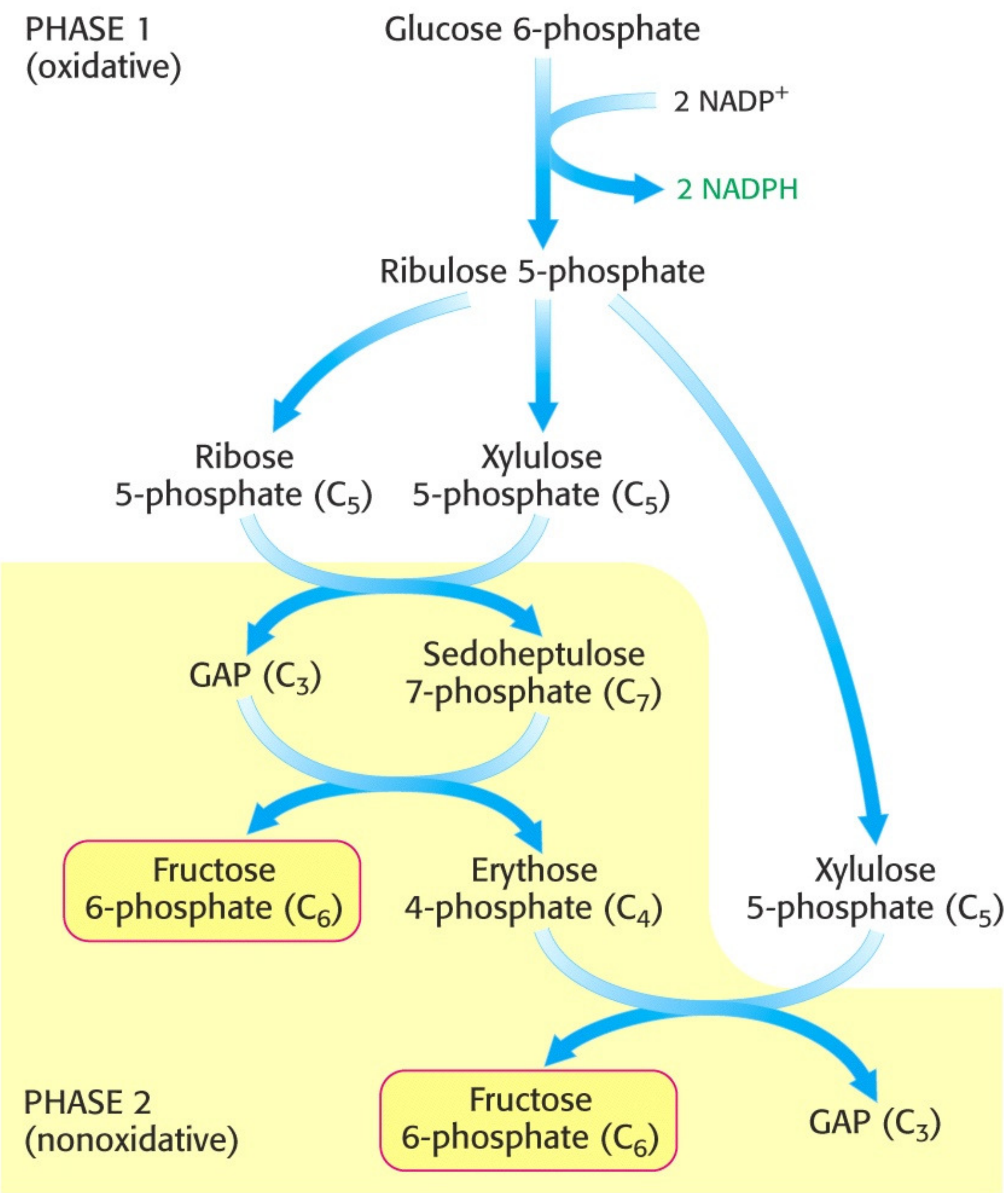
Glucose-6P dehydrogenase (G6PD)–This reaction is the commitment step in the pathway and is feedback-inhibited by NADPH

Transketolase and Transaldolase - together these two enzyme catalyze the reversible "carbon shuffle" reactions of the nonoxidative phase of the pathway

The PPP can be divided into two phases

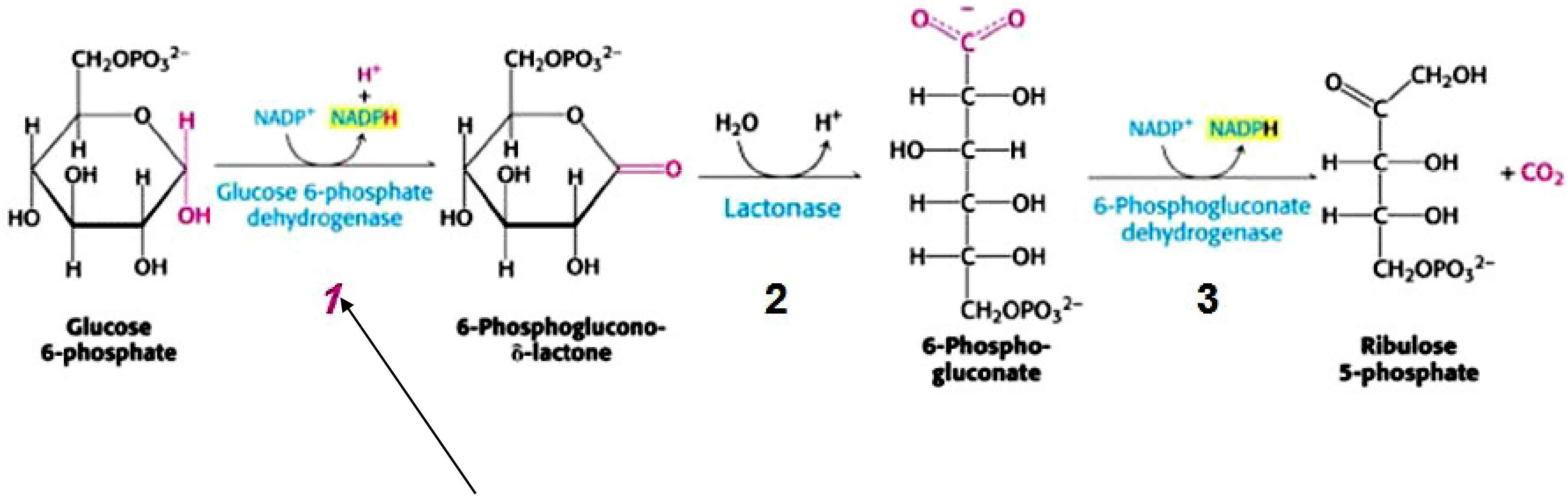
- **The oxidative phase** **generates NADPH** which is required for many biosynthetic pathways and for detoxification of reactive oxygen species.

- **The nonoxidative phase** interconverts C_3, C_4, C_5, C_6 and C_7 monosaccharides to produce **ribose-5P for nucleotide synthesis**, and also to **regenerate glucose-6P** to maintain NADPH production by the oxidative phase.

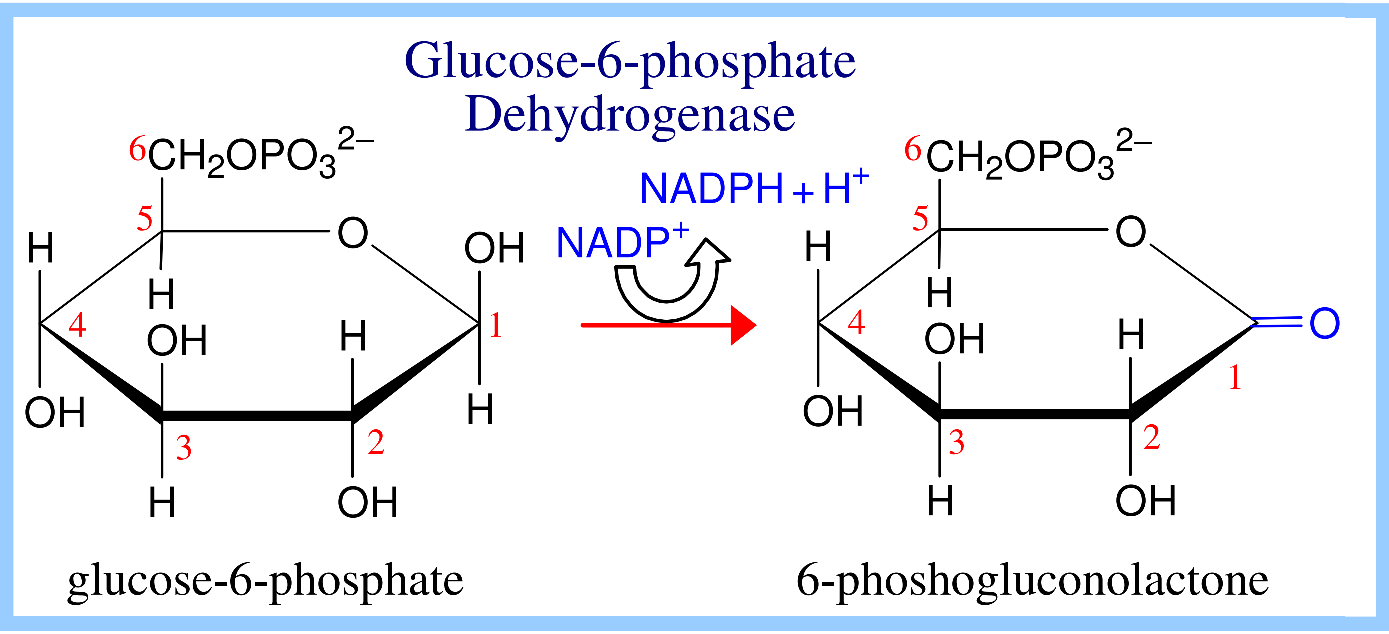


The irreversible oxidative phase

- Glucose-6-P is converted to ribulose-5-P with production of 2 molecules of NADPH and CO_2
- **Three enzymatic reactions in the oxidative phase**



G6PD is the committed step in the Pentose Phosphate Pathway because 6-Phosphogluconon-d-lactone has no other metabolic fate except to be converted to 6-phosphogluconate.



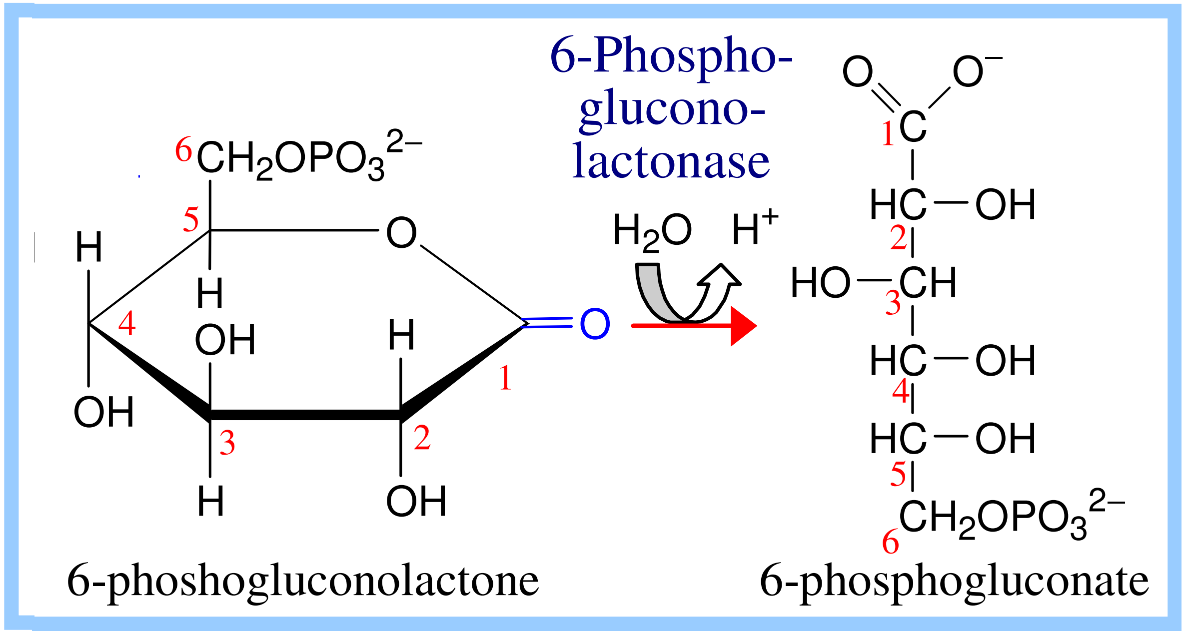
➢ **Glucose-6-phosphate Dehydrogenase** catalyzes **oxidation** of the aldehyde at **C1** of glucose-6-phosphate, to a **carboxylic acid**

➢This enzyme requires **Mg^{2+}** et **$NADP^{+}$** (serves as electron acceptor) as coenzymes

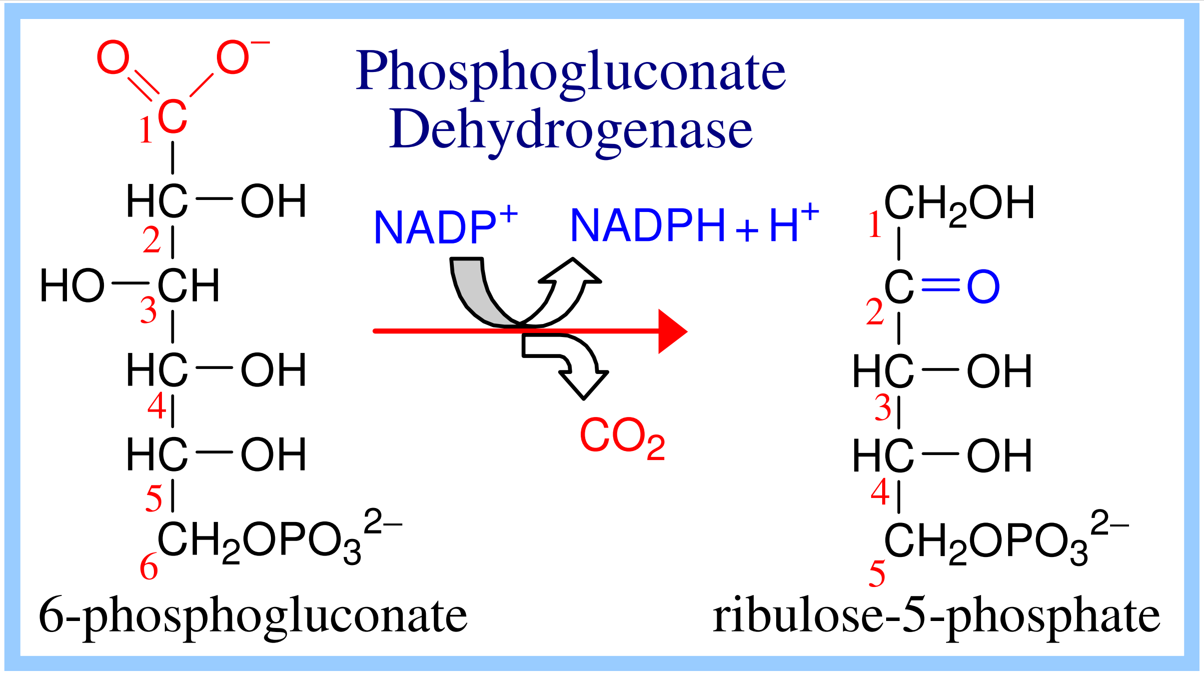
➢ NADPH is a potent competitive inhibitor of this enzyme

NADPH/NADP+ increase → inhibits the reaction

NADPH/NADP+ decrease→ stimulate the reaction



- **6-Phosphogluconolactonase** catalyzes hydrolysis of 6-phosphogluconolactone
- The product is **6-phosphogluconate**.
- It is irreversible but not rate-limiting



- **Phosphogluconate Dehydrogenase** catalyzes **oxidative decarboxylation** of 6-phosphogluconate, to yield the **5-C** ketose **ribulose-5-phosphate**
- The **OH** at C**3** (C**2** of product) is oxidized to a **ketone**
- This promotes loss of the carboxyl at C**1** as **CO_2**
- **$NADP^+$** serves as oxidant

The reversible non-oxidative phase

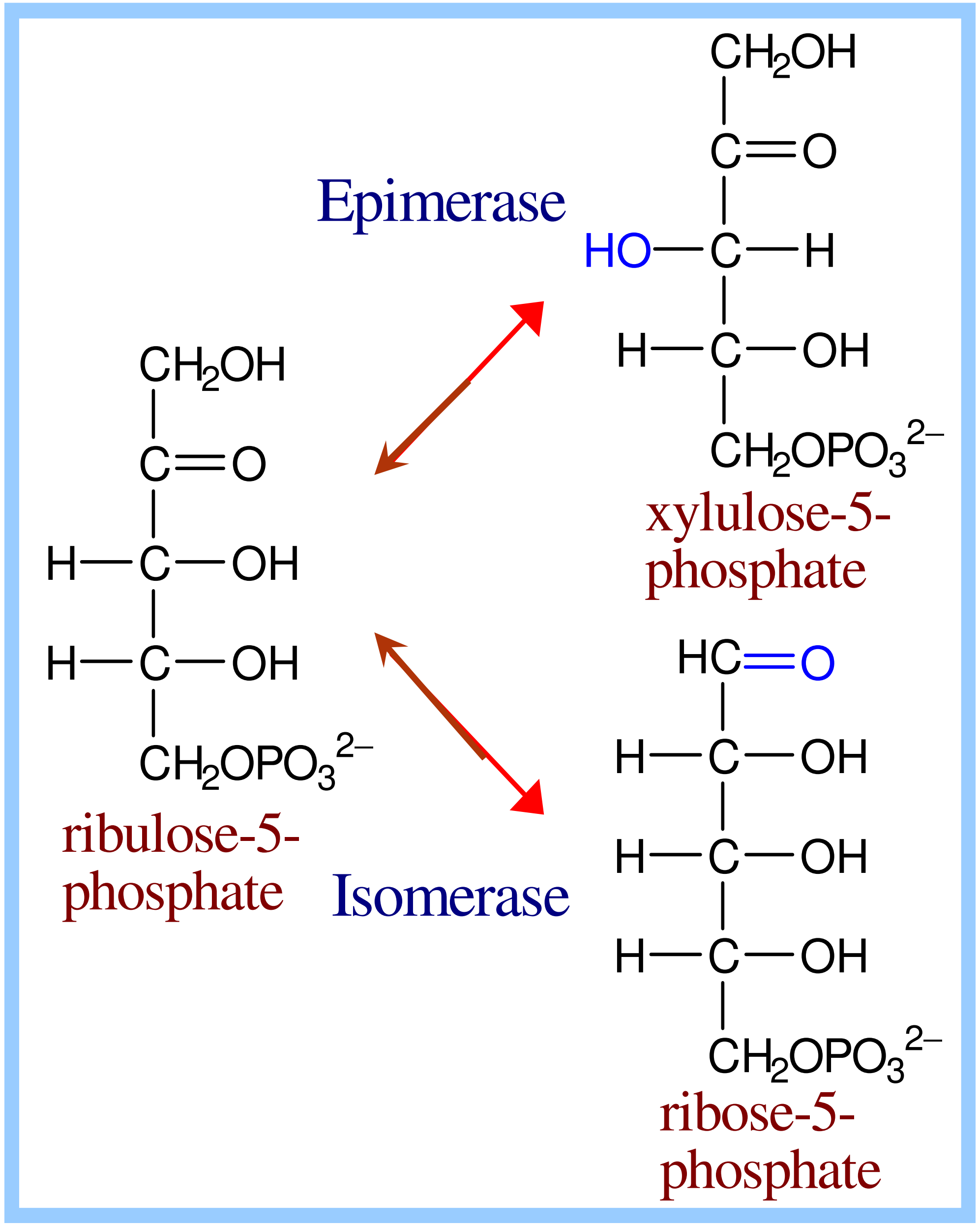
- In nonoxidative phase, **ribulose 5-P is converted back to G-6-P** by a series of reactions involving especially two enzymes

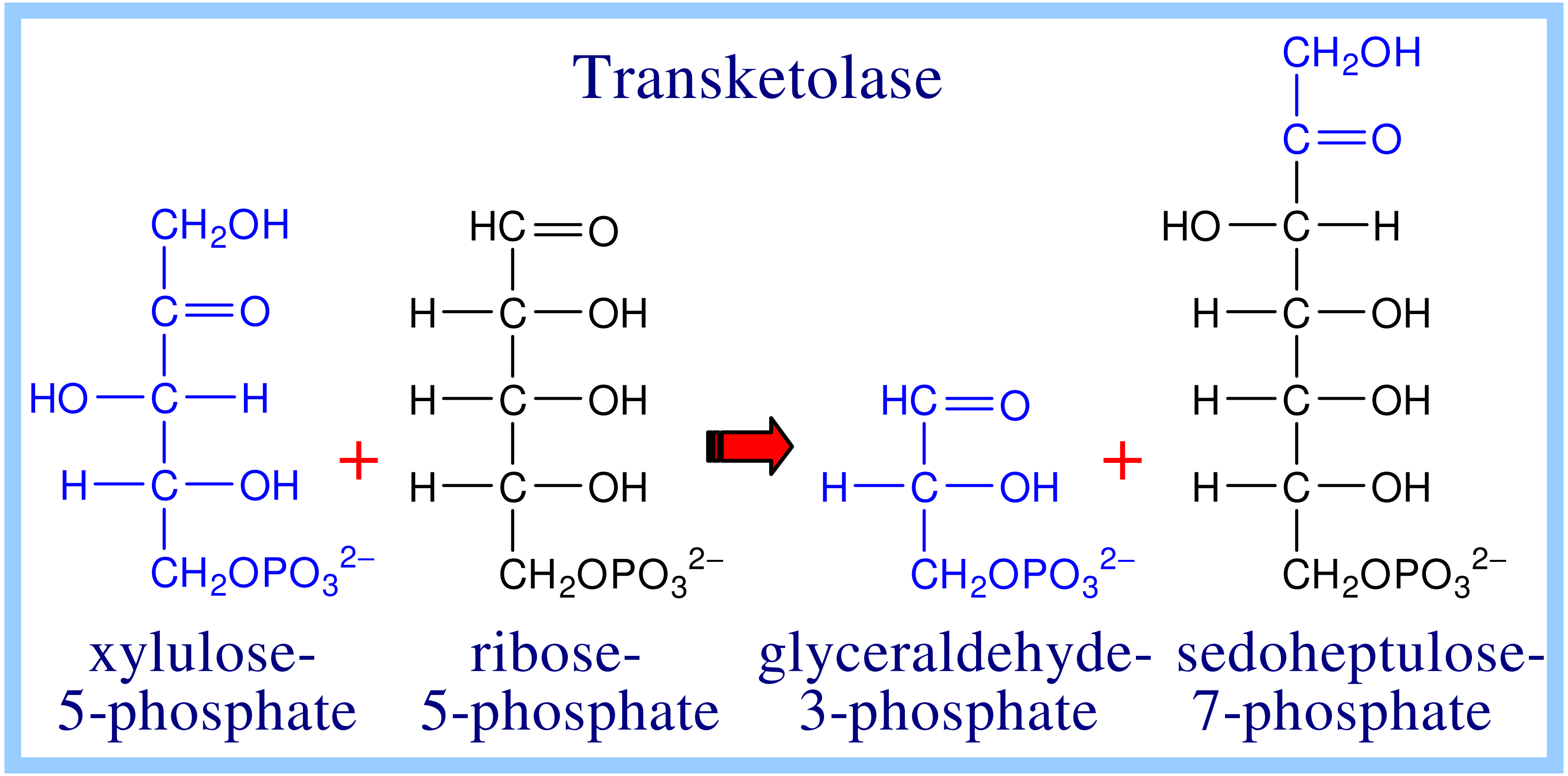
    1. Transketolase
    2. Transaldolase

- **Epimerase** inter-converts stereoisomers ribulose-5-P and xylulose-5-P

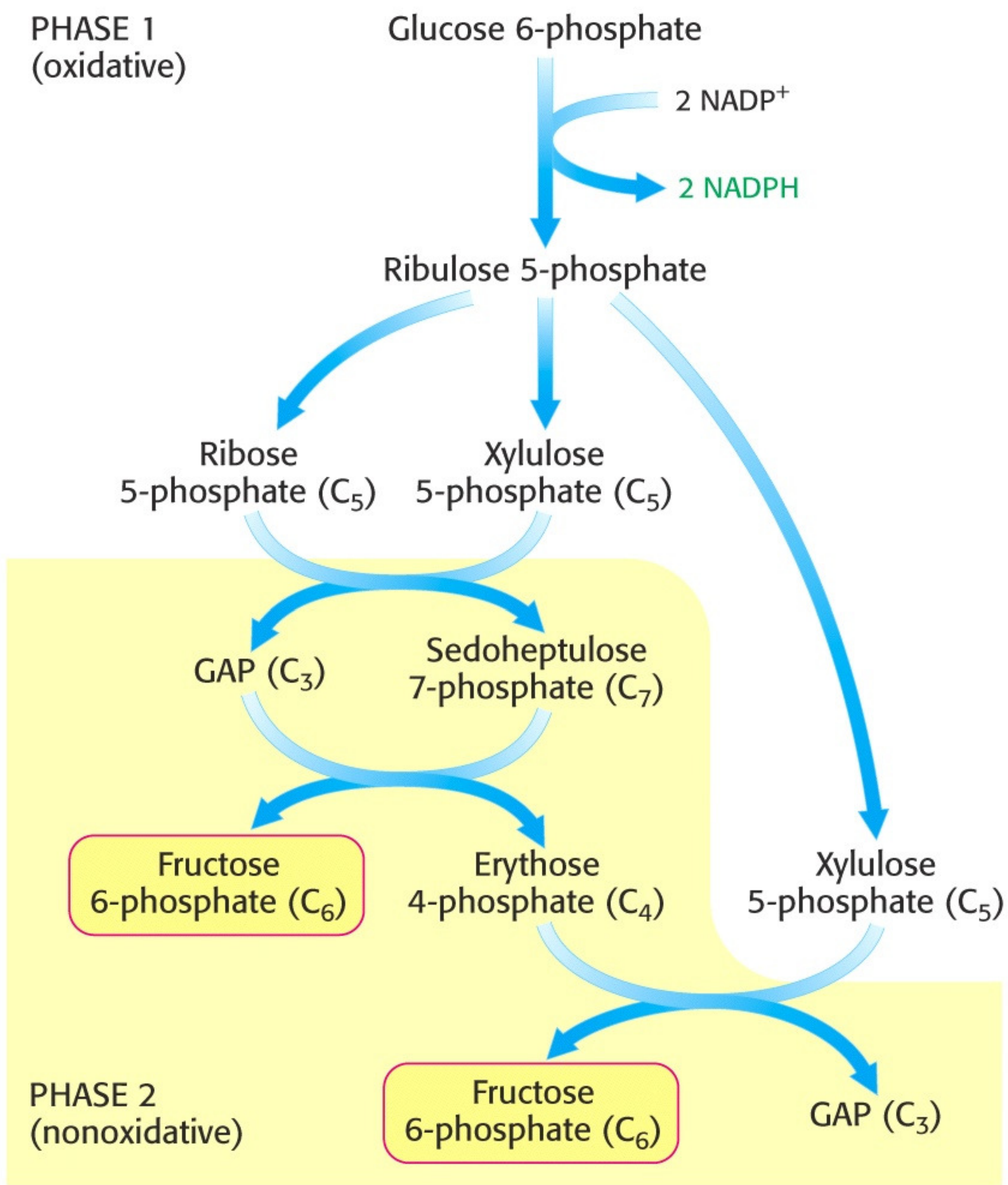
- **Isomerase** converts the ketose ribulose-5-P to ribose-5-P which is used in nucleotide, nucleic acid biosynthesis

Both reactions are reversible

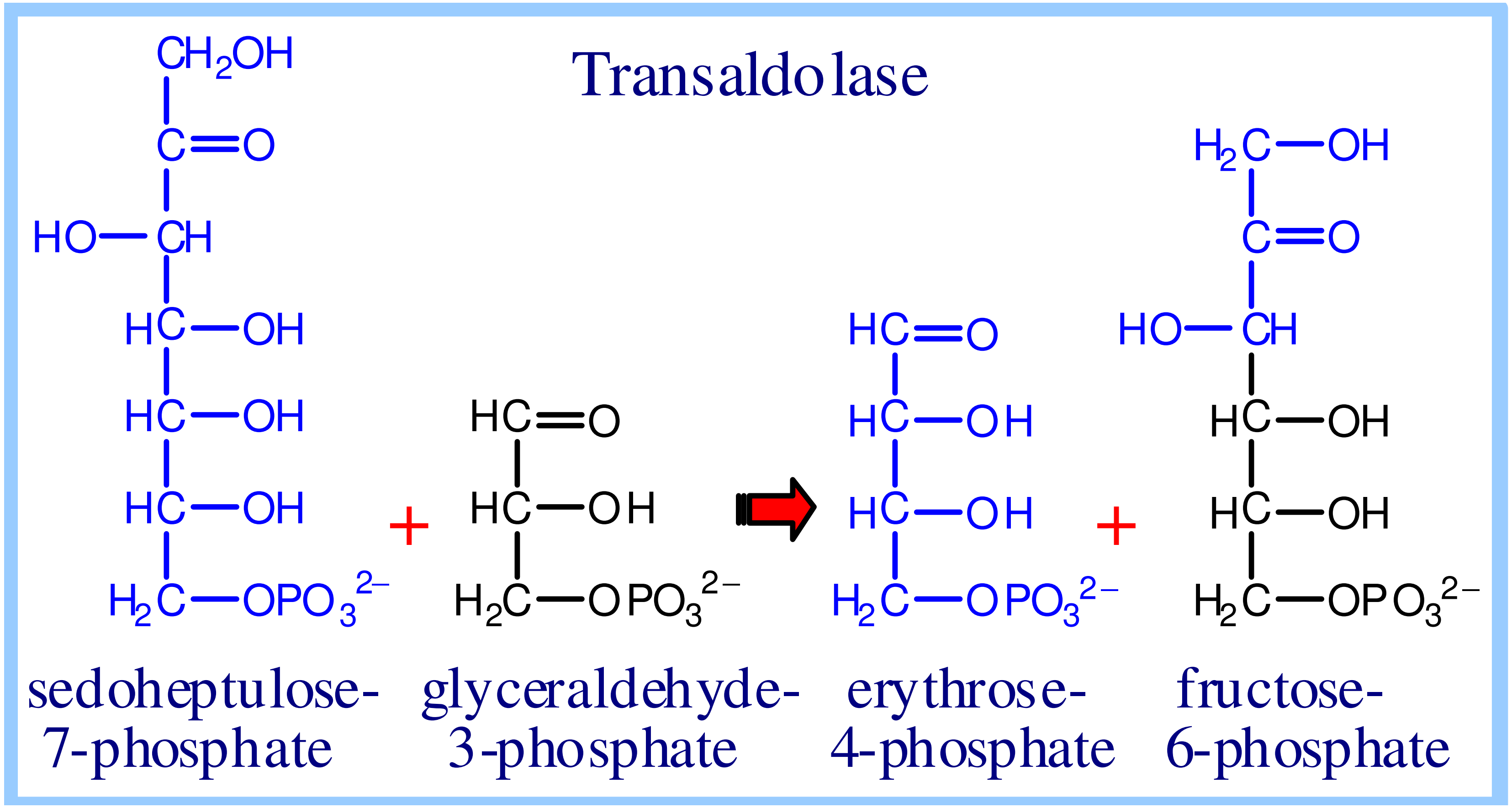




- **Transketolase** transfers a **2-C fragment** containing ketone group from xylulose-5-P to ribose-5-P.
- Transketolase requires **thiamine pyrophosphate (TPP)**, a derivative of **vitamin B_1** as coenzyme and Mg^{2+} as cofactor
- Transfer of the 2- C fragment to the 5-C ribose-5-P yields sedudoheptulose-7-P and glyceraldehyde-3-P.



PHASE 1
(oxidative)
Glucose 6-phosphate
2 NADP+
2 NADPH
Ribulose 5-phosphate
Ribose
5-phosphate (C5)
Xylulose
5-phosphate (C5)
GAP (C3)
Sedoheptulose
7-phosphate (C7)
Fructose
6-phosphate (C6)
Erythose
4-phosphate (C4)
Xylulose
5-phosphate (C5)
PHASE 2
(nonoxidative)
Fructose
6-phosphate (C6)
GAP (C3)

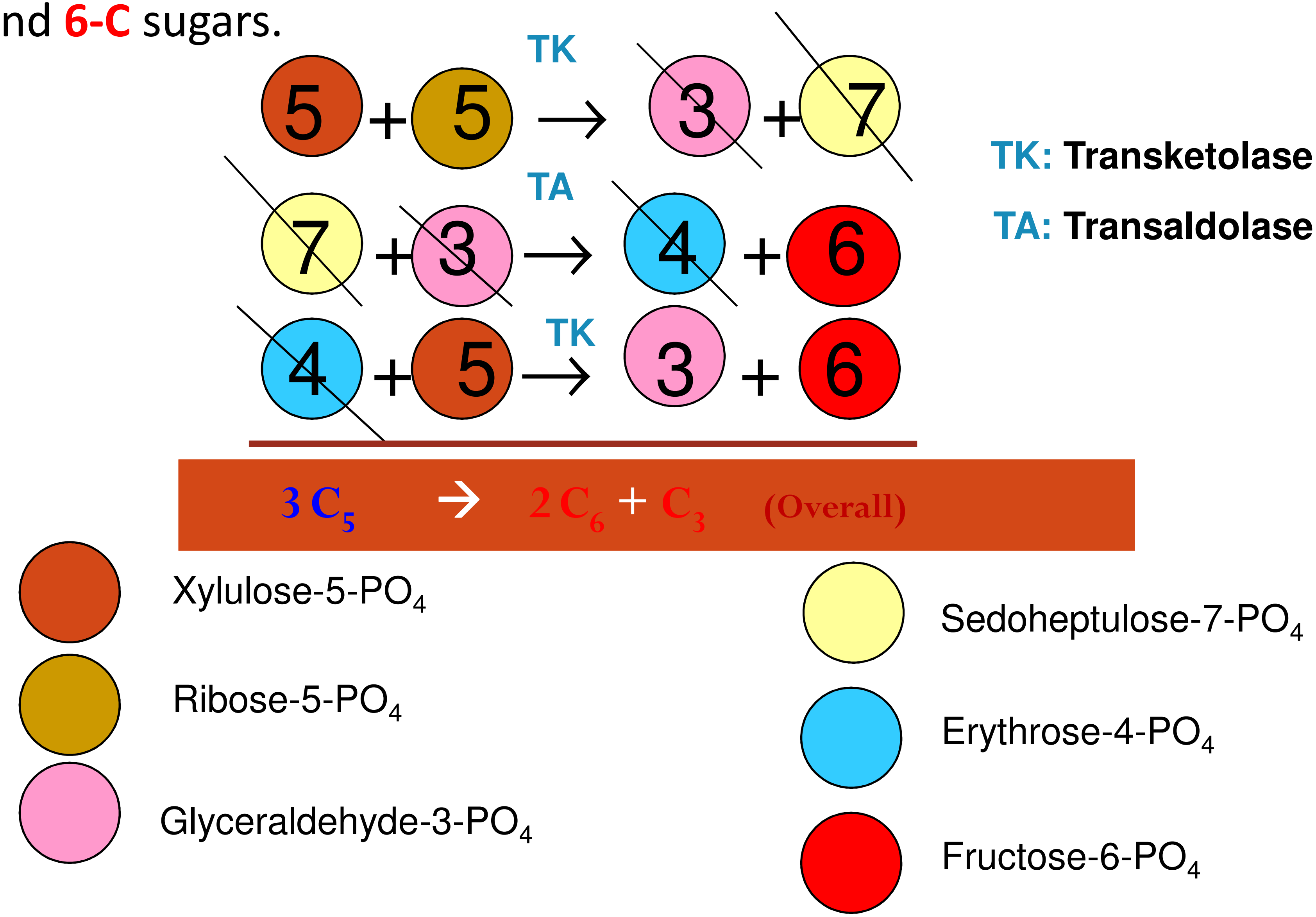


Transaldolase catalyzes transfer of a **3-C** from sedoheptulose-7-phosphate to glyceraldehyde-3-phosphate to form erythrose-4 P and fructose- 6-p.

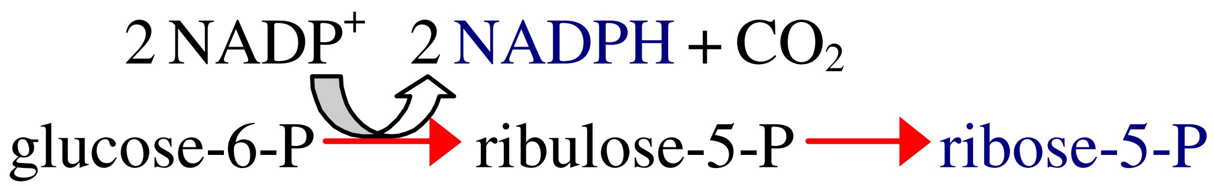
- **Transketolase** Transfer of the 2-C fragment (containing ketone group) from xylulose-5-P to erythrose-4-Pto yields **fructose-6-P and glyceraldehyde-3-P.**

  - **Xylulose-5-P + erythrose-4-P → fructose-6-P + glyceraldehyde-3-P**

SUMMARY: The **balance sheet** below summarizes flow of 15 **C** atoms Through PPP reactions by which **5-C** sugars are converted to **3-C** and **6-C** sugars.



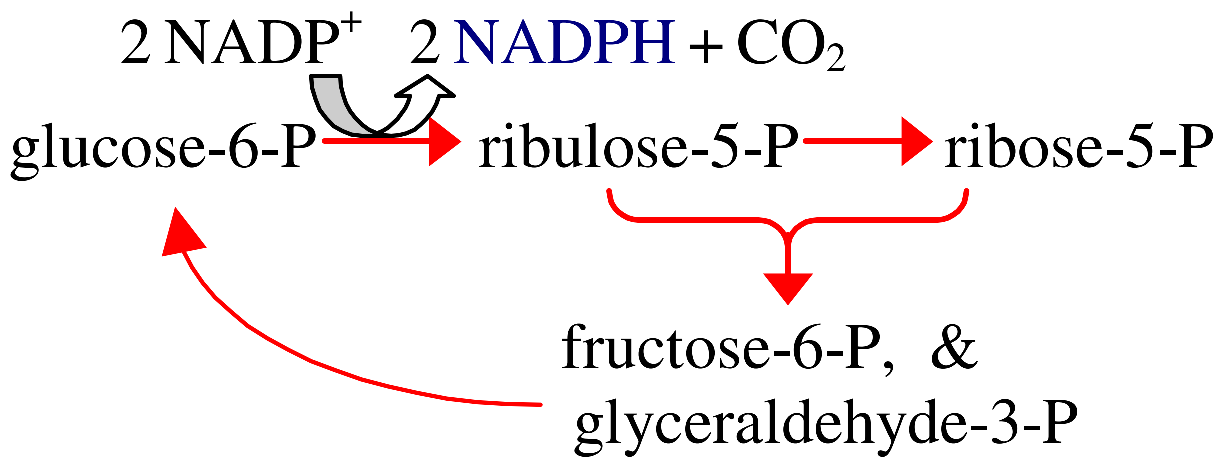
Importance of Pentose Phosphate Pathway



Pentose Phosphate Pathway producing NADPH and ribose-5-phosphate

- Ribulose-5-P may be converted to **ribose-5-phosphate**, a substrate for synthesis of **nucleotides,** nucleic acids and coenzymes
- The pathway also produces some **NADPH**

<u>NB:</u> PPP is the only way of ribose-5-P production in our body due to absence of ribokinase enzyme



Pentose Phosphate Pathway producing maximum NADPH

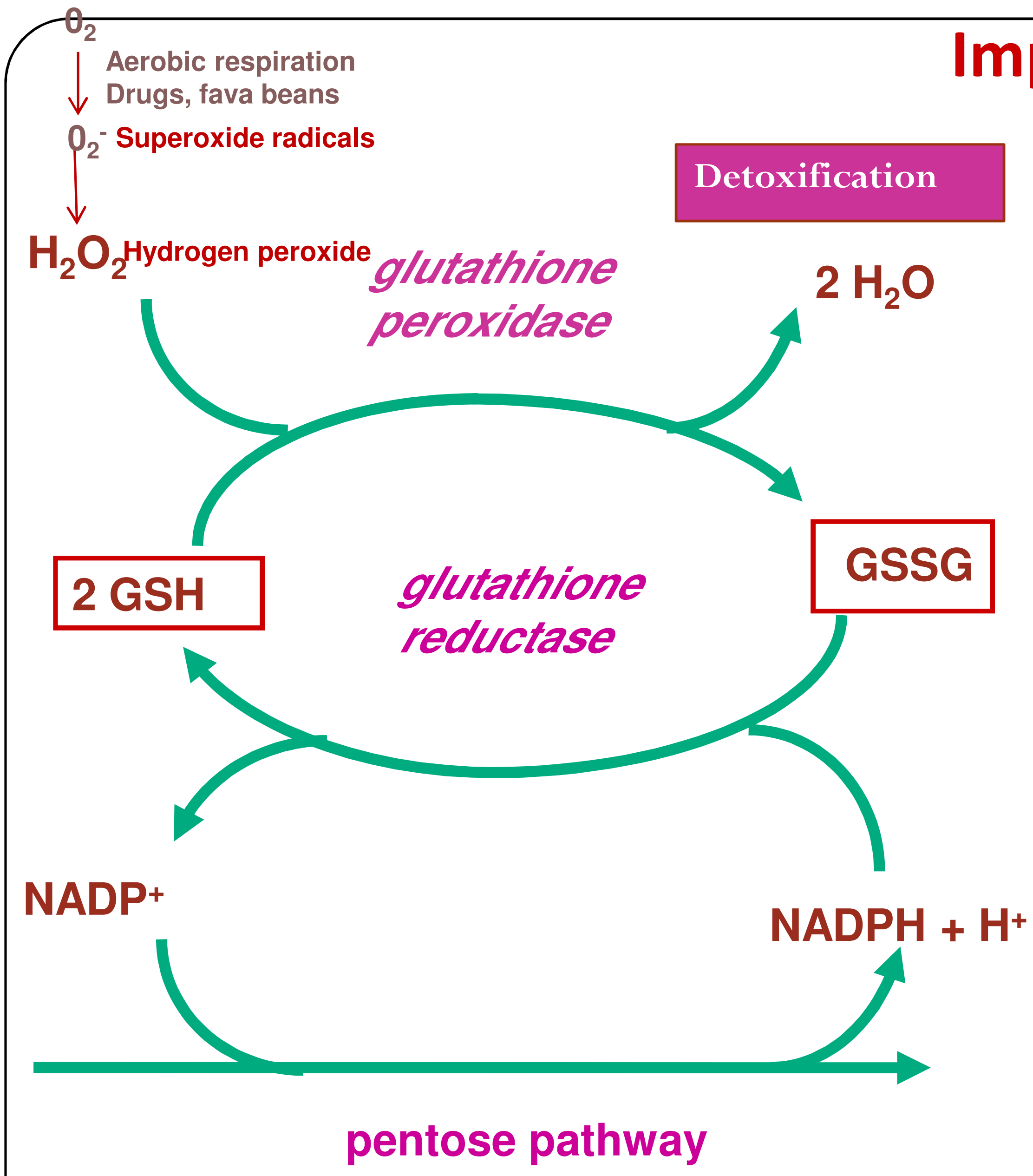
- Glyceraldehyde-3-P and fructose-6-P may be converted to **glucose-6-P,** via enzymes of gluconeogenesis, for reentry to Pentose Phosphate Pathway, maximizing formation of **NADPH,** which is need for reductive biosynthesis.

- **3-C** Glyceraldehyde-3-P and **6-C** fructose-6-P, formed from 5-C sugar phosphates, may enter **Glycolysis** for **ATP** synthesis.

- **5-C Ribose-1-phosphate** generated during **catabolism of nucleosides** also enters Glycolysis in this way, after first being converted to ribose-5-phosphate

  - Thus the Pentose Phosphate Pathway serves as an **entry into Glycolysis** for both 5-carbon & 6-carbon sugars.

Importance of PPP in RBC



- When erythrocytes are exposed to chemicals that generate high levels of superoxide radicals, **GSH** **(<u>Reduced Glutathione</u>)** is required to reduce these damaging compounds

- **Glutathione Peroxidase** catalyzes degradation of organic hydroperoxides by reduction, as two glutathione molecules are oxidized to a disulfide **GSSG**

- The PPP is responsible for maintaining high levels of NADPH in red blood cells for use as a **reductant** in the glutathione reductase reaction.

- **The major role PPP in RBCs is the production of NADPH which protect these cells from oxidative damage by providing GSH for removal of H_2O_2**

Importance of PPP (the main generator of NADPH):

- **NADPH is needed for reductive biosynthesis:**

- 1- Synthesis of fatty acids, cholesterol, steroid hormones& sphingosine.

  Thus it is active in lactating mammary gland, liver, gonads, adipose tissue& adrenal cortex.
- 2- Hydroxylation reactions in metabolism of phenylalanine and tryptophan.

- 3- synthesis of nitric oxide (NO):
- Arginine + O2 + NADPH + H+

$\longrightarrow$ NADP + NO + citrulline

NO is

- Laughing gas
- Used as ansthetic
- Casuses relaxtion of vascular smooth muscles.
- In macrophages, NO is effective against viral, fungal, protozoal infections.
- Potent inhibitor of platelet aggregations.
- Neurotransmitter in brain.

Importance of PPP

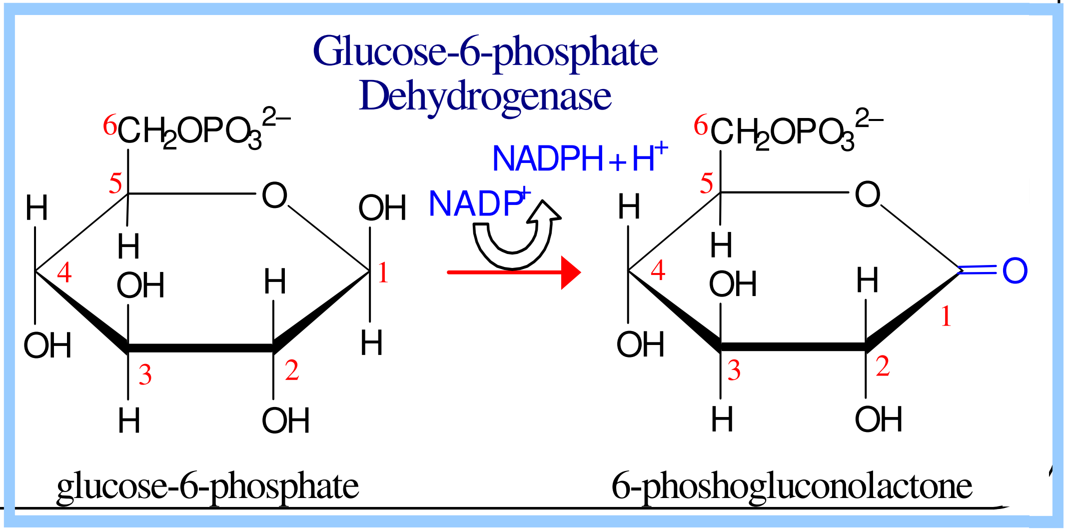
- It provides a way for oxidation of glucose by other than TCA cycle with no production of energy.

- It provides the cell with ribose -5-P which is needed for nucleosides, nucleotides, nucleic acids& coenzymes biosynthesis.

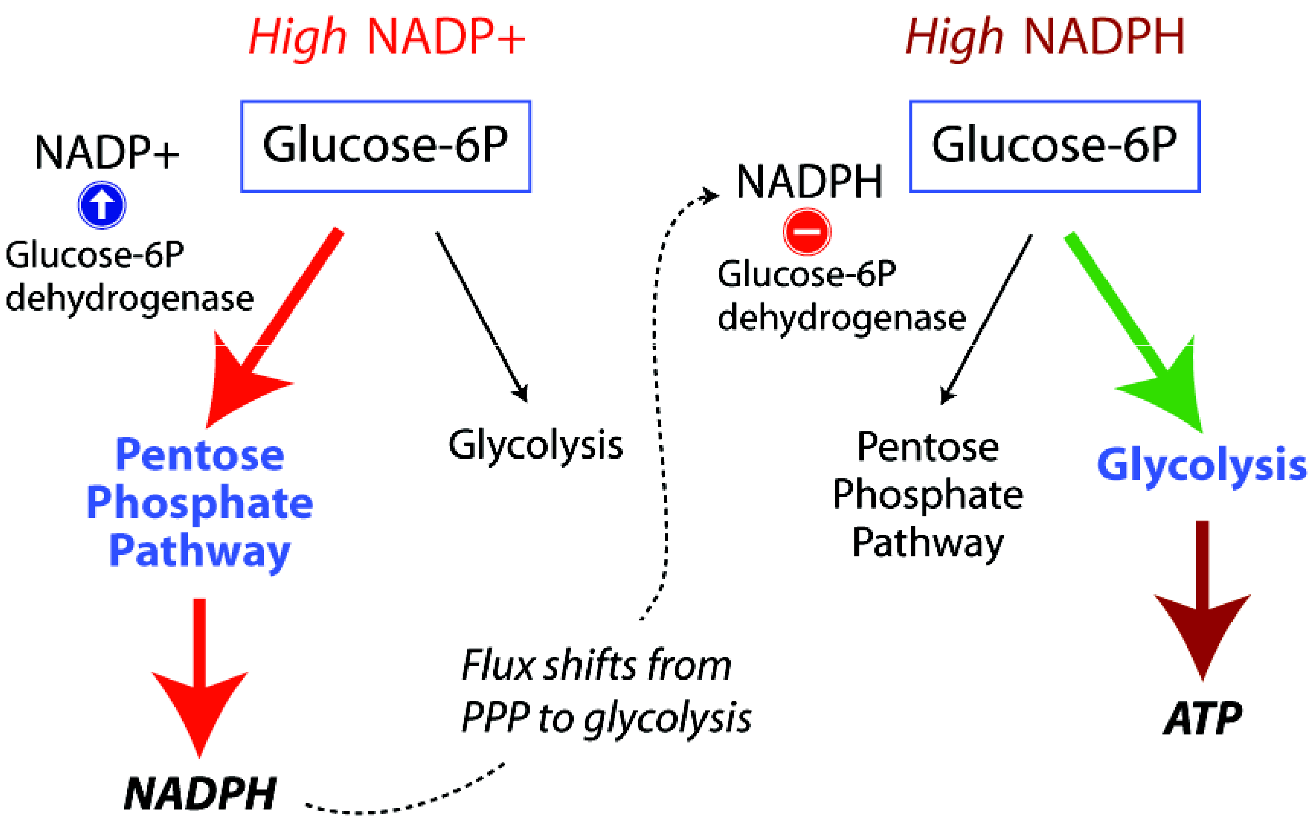
Regulation of pentose phosphate pathway

- The entry of glucose 6-phosphate into the pentose phosphate pathway is controlled by the cellular concentration of NADPH
- NADPH is a **strong inhibitor** of glucose 6-phosphate dehydrogenase (Rate Limiting Reaction)
- As NADPH is used in various pathways, inhibition is relieved, and the enzyme is accelerated

  to produce more NADPH



Regulation of the G6PD activity controls flux through the glycolytic pathway and pentose phosphate pathways



Regulation of pentose phosphate pathway

- The synthesis of glucose 6-phosphate dehydrogenase is **induced** by the increased insulin/glucagon ratio after a high carbohydrate meal
- **Insulin**, which secreted in response to hyperglycemia, **induces** the synthesis of G6P dehydrogenase and 6-phosphogluconate dehydrogenase → **increasing the rate of glucose oxidation by PPP**
- The synthesis of glucose 6-phosphate dehydrogenase is **repressed** during fasting

Glucose-6-phosphate dehydrogenase deficiency causes hemolytic anemia

- Mutations present in some populations causes a deficiency in glucose 6-phosphate dehydrogenase, **with consequent impairment of NADPH production**

- Detoxification of H_2O_2 is inhibited, and cellular damage results - lipid peroxidation leads to erythrocyte membrane breakdown and hemolytic anemia.

- Most G6PD-deficient individuals are asymptomatic - only in combination with certain environmental factors (sulfa antibiotics, herbicides, antimalarials, *divicine) do clinical manifestations occur.

*toxic ingredient of fava beans