HEXOSE MONOPHOSPHATE SHUNT

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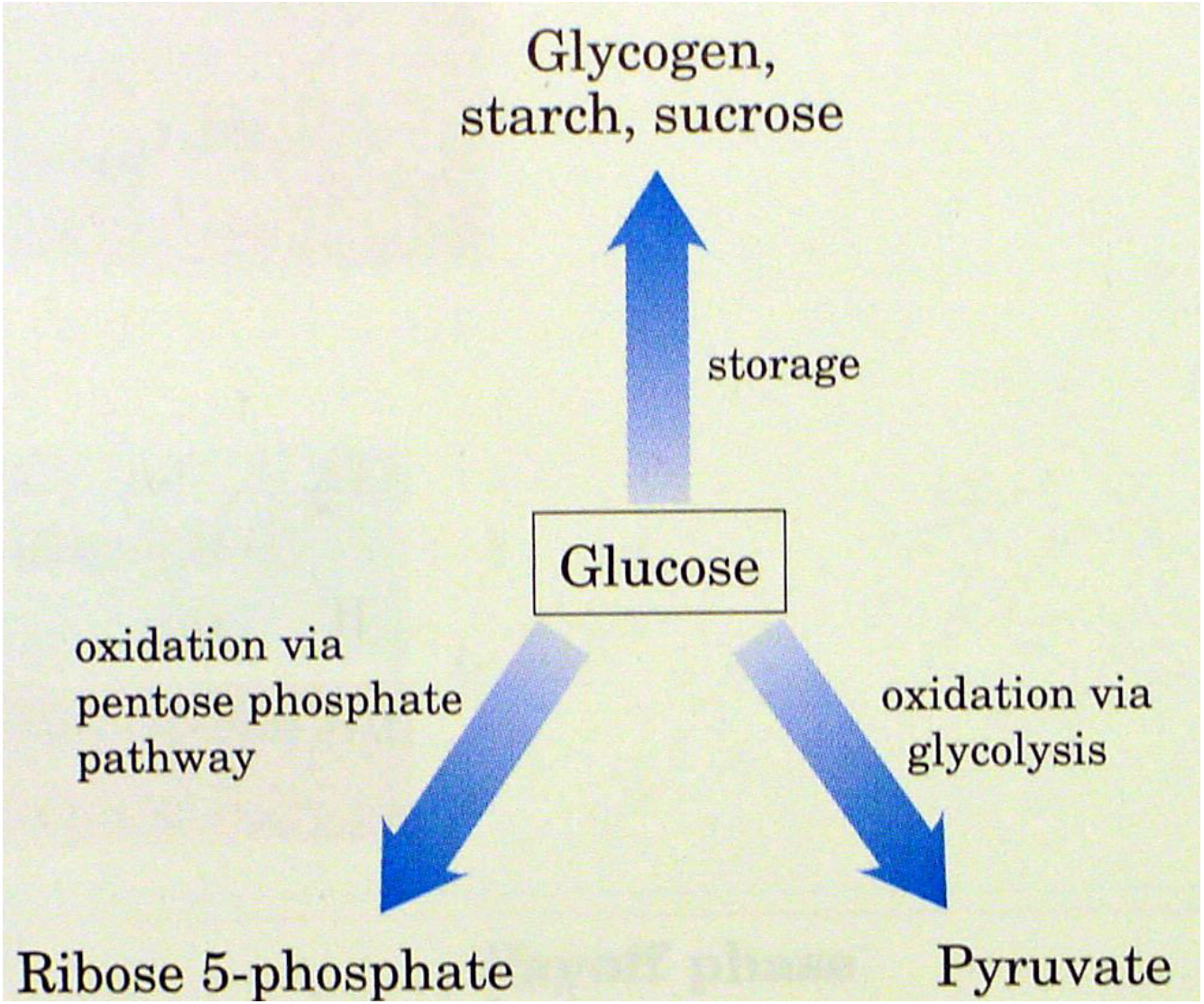
INTRODUCTION:

- Hexose Monophosphate pathway or HMP Shunt is also called pentose phosphate pathway or phosphogluconate pathway.

- This is an alternative pathway to glycolysis and TCA Cycle for the oxidation of glucose.

- However, HMP shunt is more anabolic in nature, since it is concerned with the biosynthesis of NADPH and pentoses.


Glycogen,
starch, sucrose
storage
Glucose
oxidation via
pentose phosphate
pathway
oxidation via
glycolysis
Ribose 5-phosphate
Pyruvate

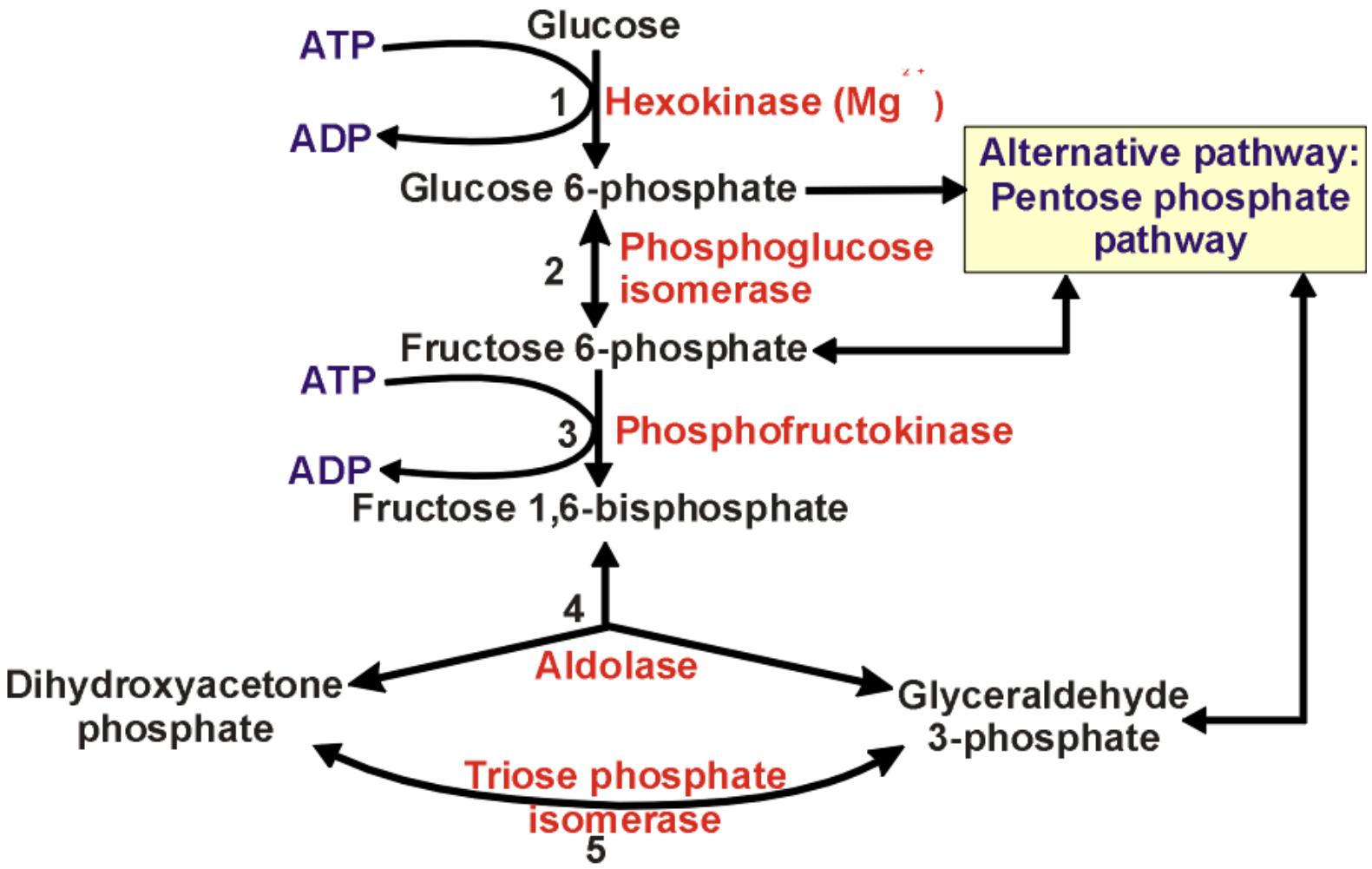
It is also known as "Pentose Phosphate Pathway", "Shunt Pathway' or "Phosphogluconate oxidative pathway".

Instead of glucose going through the glycolytic pathway, it is shunted through this pathway; so it is known as the shunt pathway.

In the glycoysis there are a few bisphosphate intermediates; but in this pathway, there are monophosphates only; Hence this is called hexose monophosphate (HMP) pathway.

The reactions involve the intermediate formation of pentose phosphates; hence this is also called pentose phosphate pathway.

It's a shunt


Glucose
ATP
1
Hexokinase (Mg++)
ADP
Glucose 6-phosphate
Alternative pathway: Pentose phosphate pathway
2
Phosphoglucose isomerase
Fructose 6-phosphate
ATP
3
Phosphofructokinase
ADP
Fructose 1,6-bisphosphate
4
Aldolase
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
Triose phosphate isomerase
5

About 10% of glucose molecules per day are entering in this pathway.

The liver and RBC metabolise about 30% of glucose by this pathway.

The major purpose of this pathway is generation of reduced NADPH and pentose phosphates for nucleotide synthesis.

Location of the Pathway:

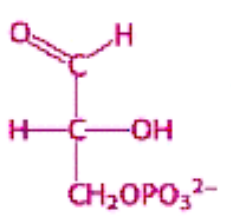
The enzymes of HMP shunt are located in the cytosol.

The tissues such as liver, adipose tissue, adrenal gland, erythrocytes, testes and lactating mammary gland, are highly active in HMP shunt.

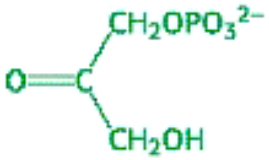
Most of these tissues are involved in the biosynthesis of fatty acids and steroids which are dependent on the supply of NADPH.

Biological systems utilize a variety of simple sugars which must be synthesized by the cell.

These sugars range in carbon number from C_3 to C_7:

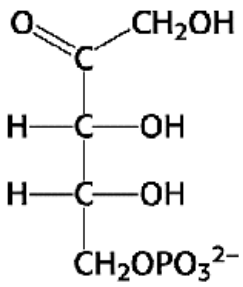


Glyceraldehyde 3-phosphate

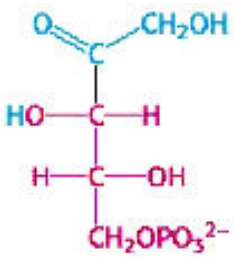


Dihydroxyacetone phosphate

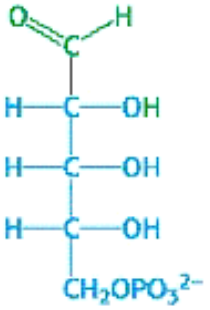
C_3



Ribulose 5-phosphate

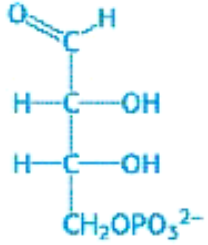


Xylulose 5-phosphate



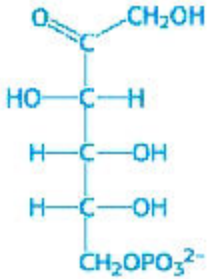
Ribose 5-phosphate

C_5



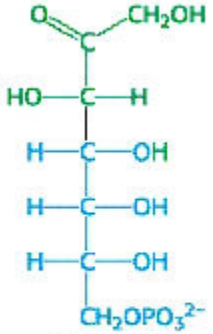
Erythrose 4-phosphate

C_4



Fructose 6-phosphate

C_6



Sedoheptulose 7-phosphate

C_7

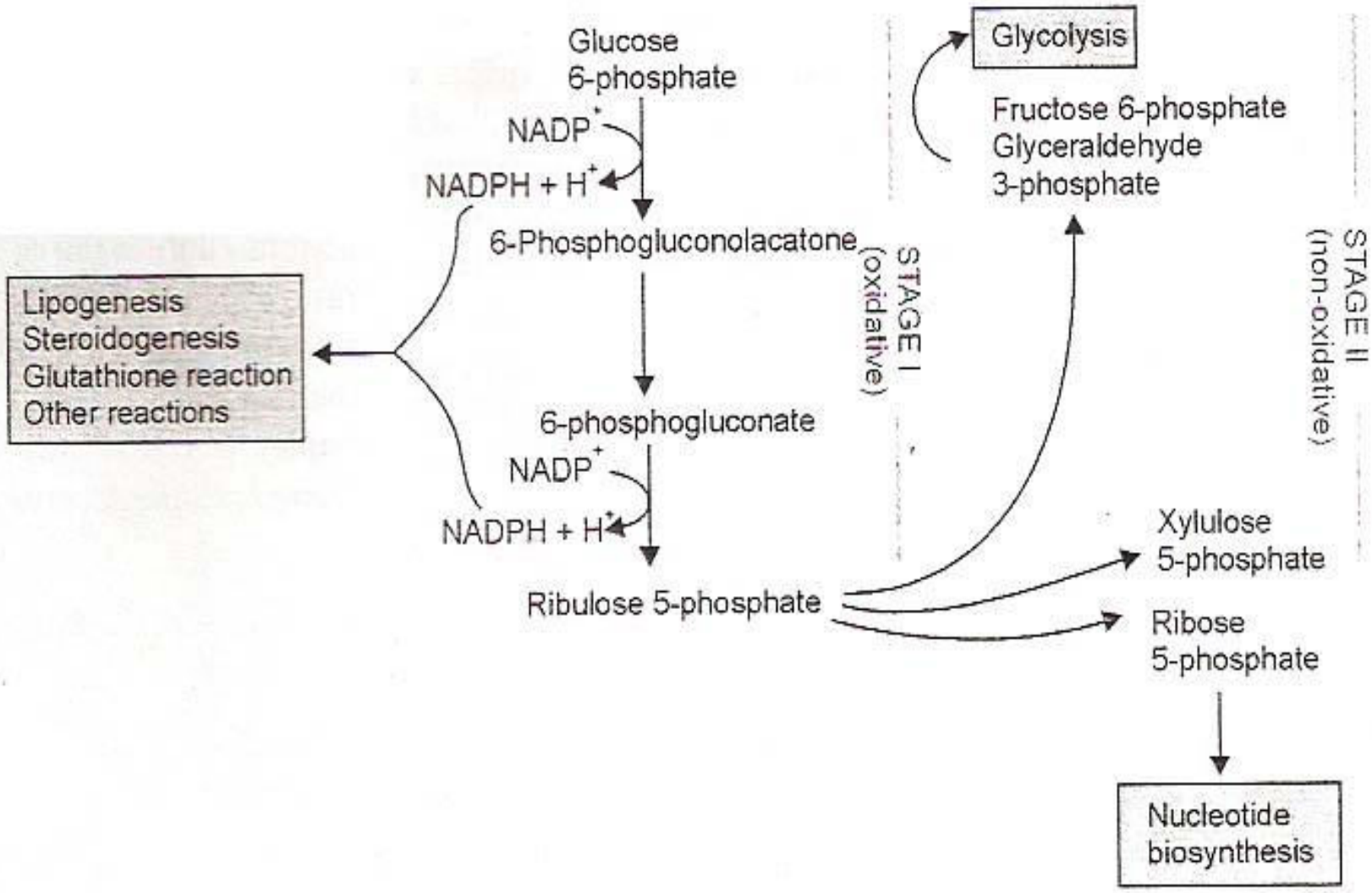
Overview of the Shunt Pathway:

The HMP Shunt Pathway has

1. oxidative and
2. non-oxidative phases.

During the oxidative phase, glucose-6-phospate is oxidized with the generation of 2 molecules of NADPH, and one molecule of pentose phosphate, with the liberation of one molecule of CO_2.

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



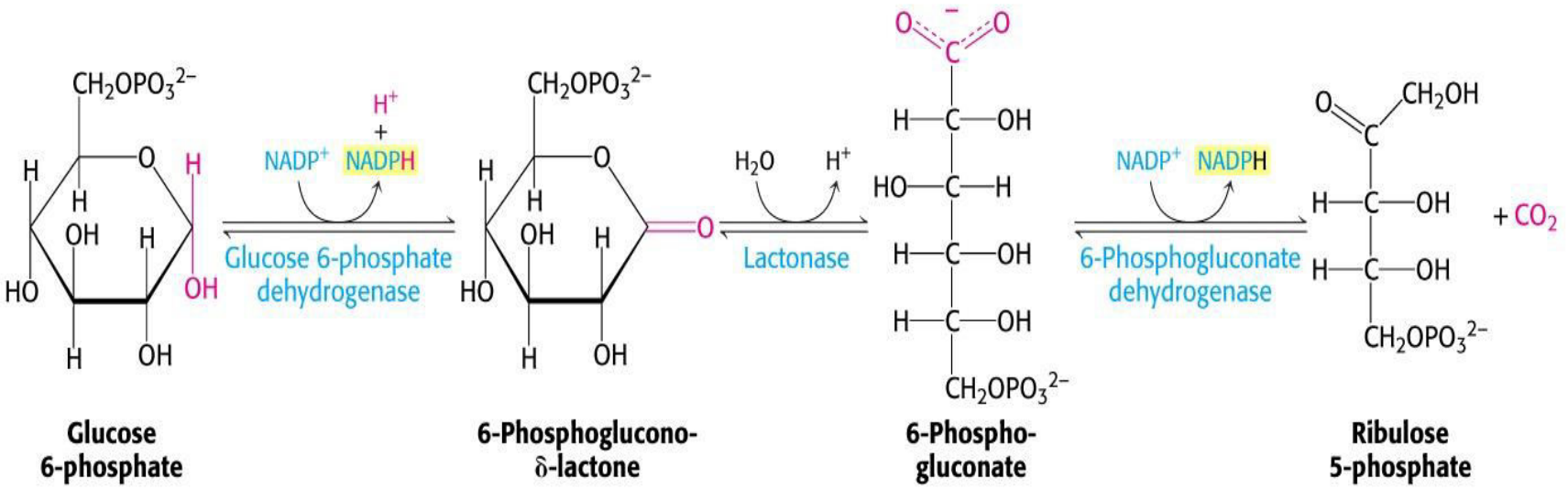
Overview of the pentose phosphate pathway.

A. Oxidative Phase:

When PFK (the controlling enzyme for glycolysis) is inactive, glucose 6-phosphate is diverted or “shunted” into this pathway.

It is first oxidized to a lactone (cyclic ester) and then opened to form 6-phosphogluconate. This is followed by an oxidative decarboxylation to form ribulose 5-phosphate (a five-carbon sugar):

Two molecules of NADPH and one CO_2 are formed for every molecule of glucose 6-phosphate that enters this pathway.



Step 1 of HMP Pathway:

Glucose-6-phosphate is oxidized by NADP+ dependent Glucose-6-phosphate dehydrogenase (GPD).

6-phospho glucono lactone is formed.

One molecule of NADPH is formed in the reaction.

This is the rate-limiting step.

Regulation is effected by this enzyme.

Step 2 of HMP Pathway:

- The lactone is hydrolysed by glucono-lactone hydrolase to form 6-phospho-gluconic acid

Step 3, NADPH is again Generated

This is an oxidative step coupled with decarboxylation.

The enzyme is 6-phospho-gluconate dehydrogenase.

The 6-phospho-gluconic acid is dehydrogenated to 3-keto-6-phospho-gluconate.

It is a transient compound and spontaneously undergoes decarboxylation to form ribulose-5-phosphate.

The carbon of CO2 is derived form COOH group of gluconic acid.

In this step a second molecule of NADPH is generated.

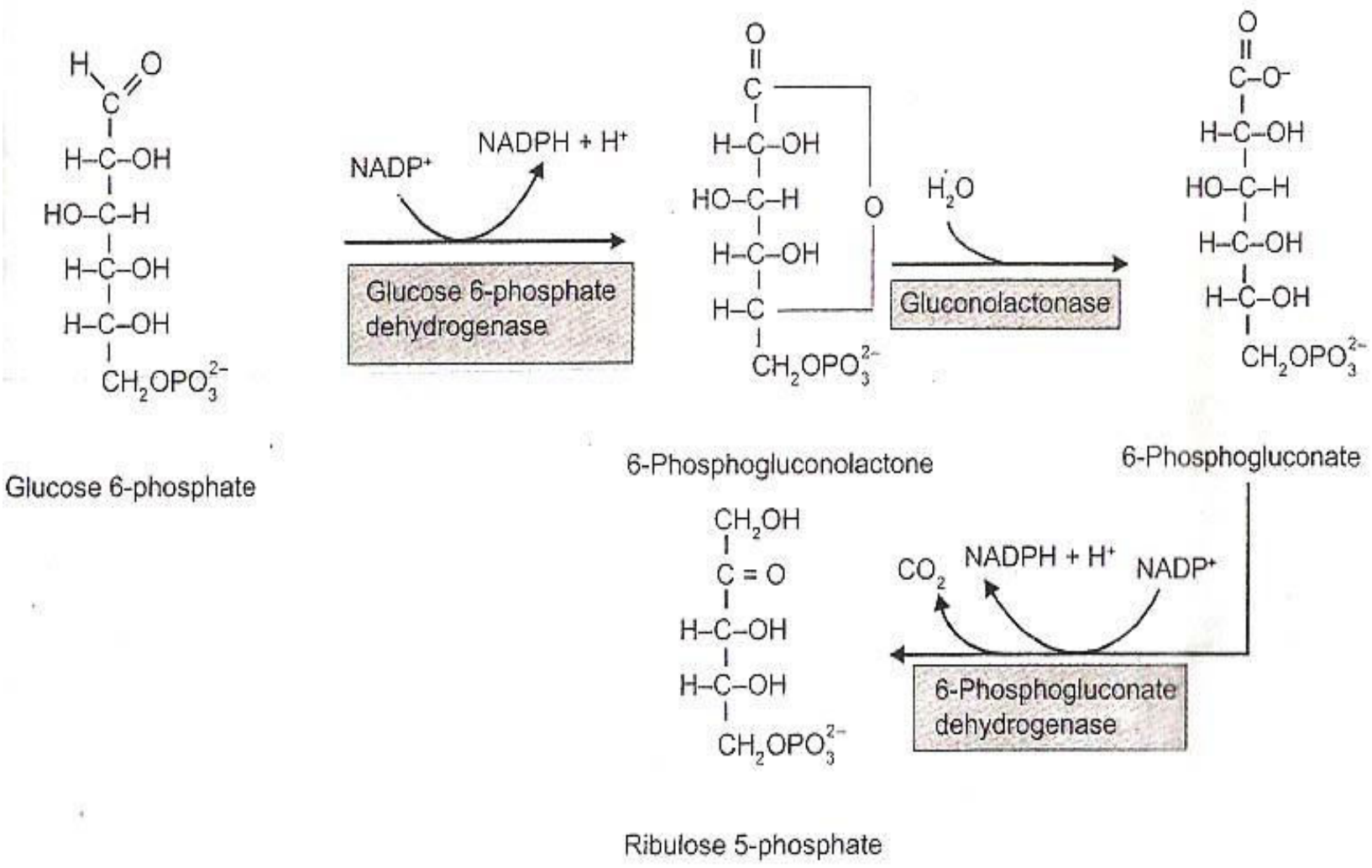
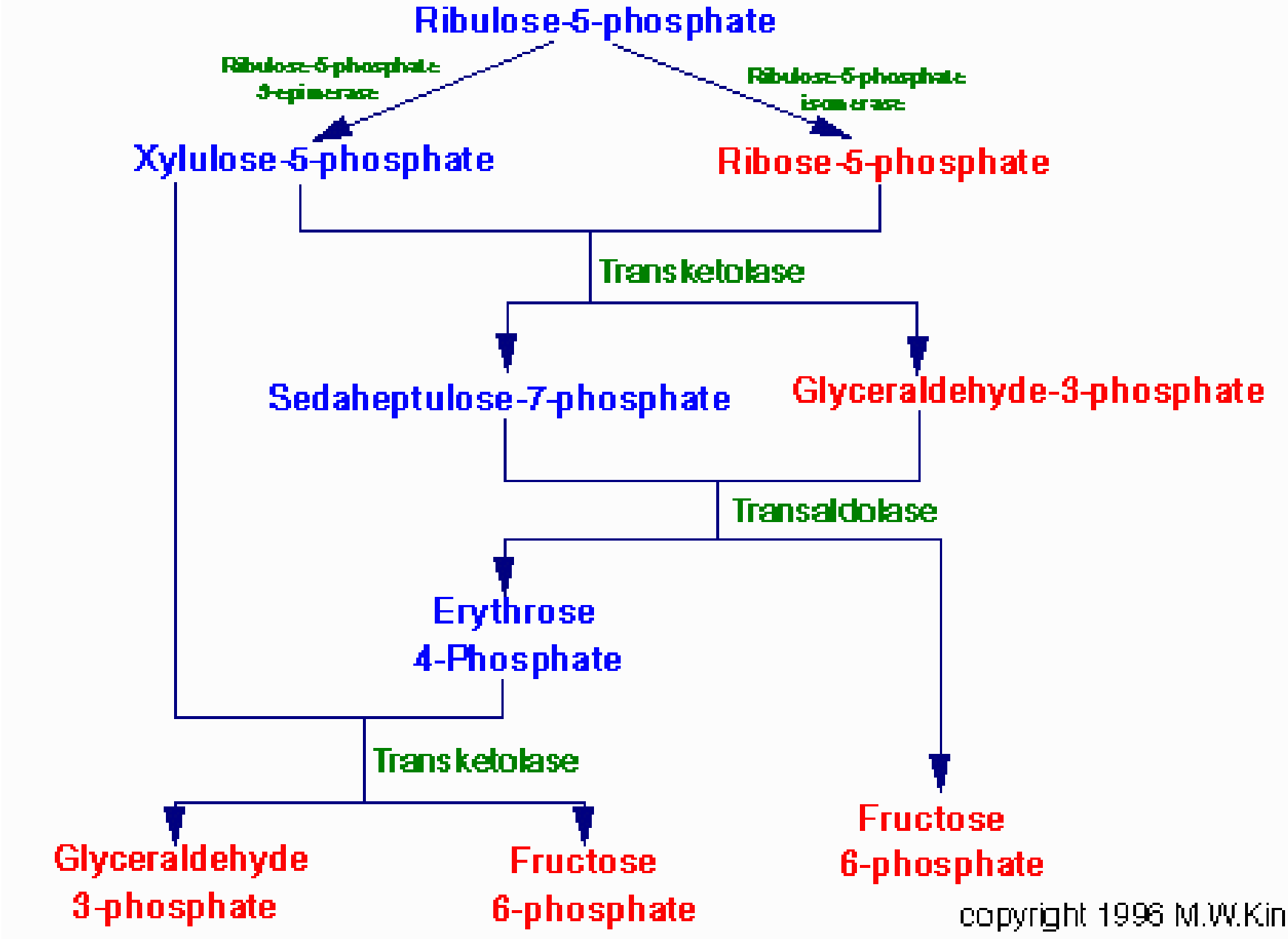


Fig. 10.2. The oxidative reactions of pentose phosphate pathway.

Non-Oxidative Stage of Pentose Phosphate Pathway



B.Non-Oxidative Phase

Step 4: Isomerisation

The ribulose-5-phosphate is then isomerised to ribose-5-phosphate or epimerised to xylulose-5-phosphate.

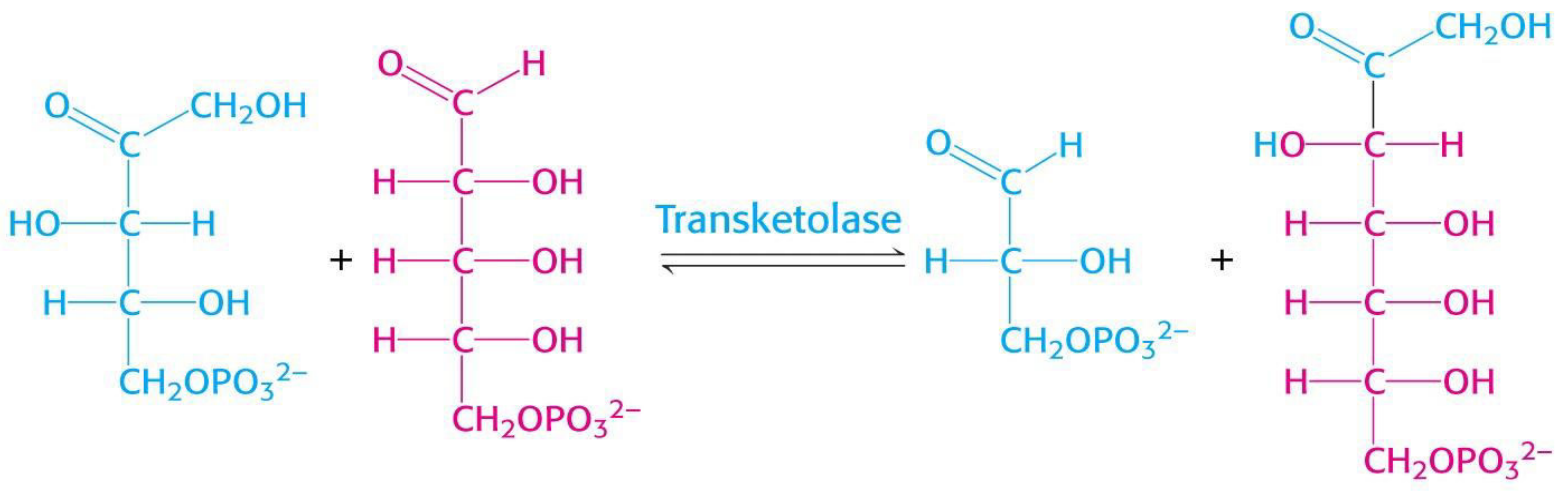
Step 5: Transketolase Reaction

Transketolase is a thiamine pyrophosphate (TPP) dependent enzyme.

It transfers two-carbon unit (with keto group) from xylulose-5-phosphate to ribose -5-phosphate to form a 7 carbon sugar, sedoheptulose-7-phosphate and glyceraldehyde-3-phosphate.

Transketolase enzyme will transfer the group form a donor ketose to an aldose acceptor.

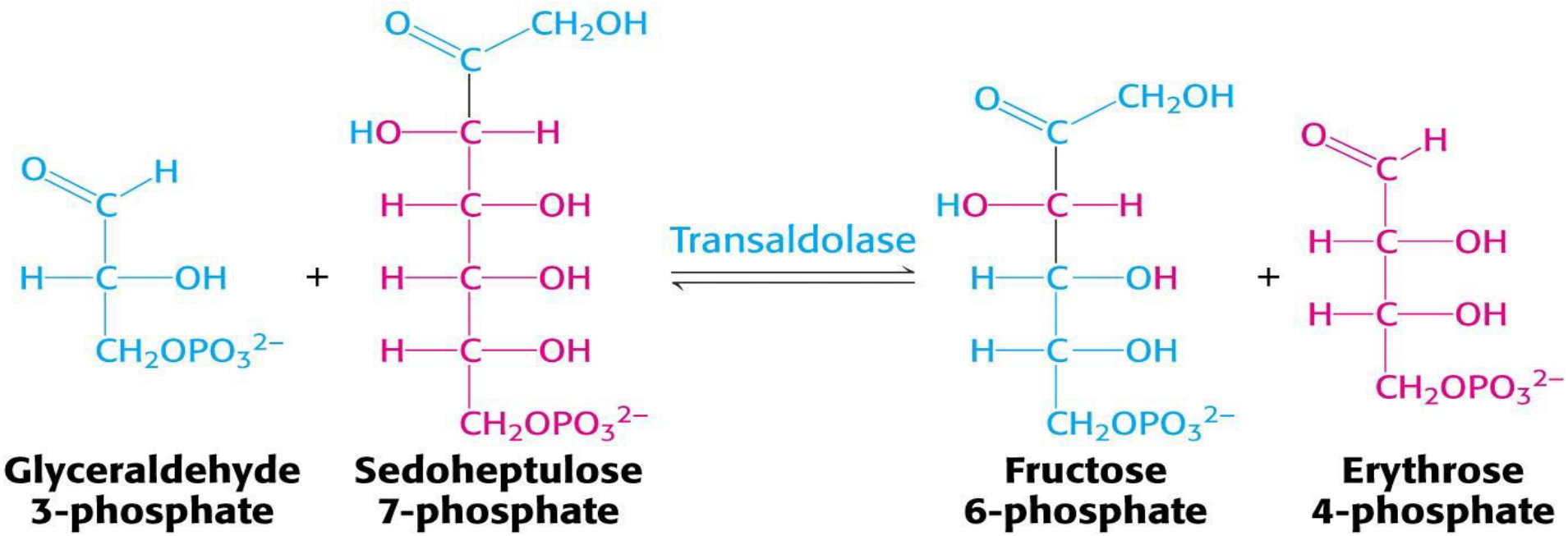
In thiamine deficiency transketolase activity is decreased.



Step 6: Transaldolase Reaction

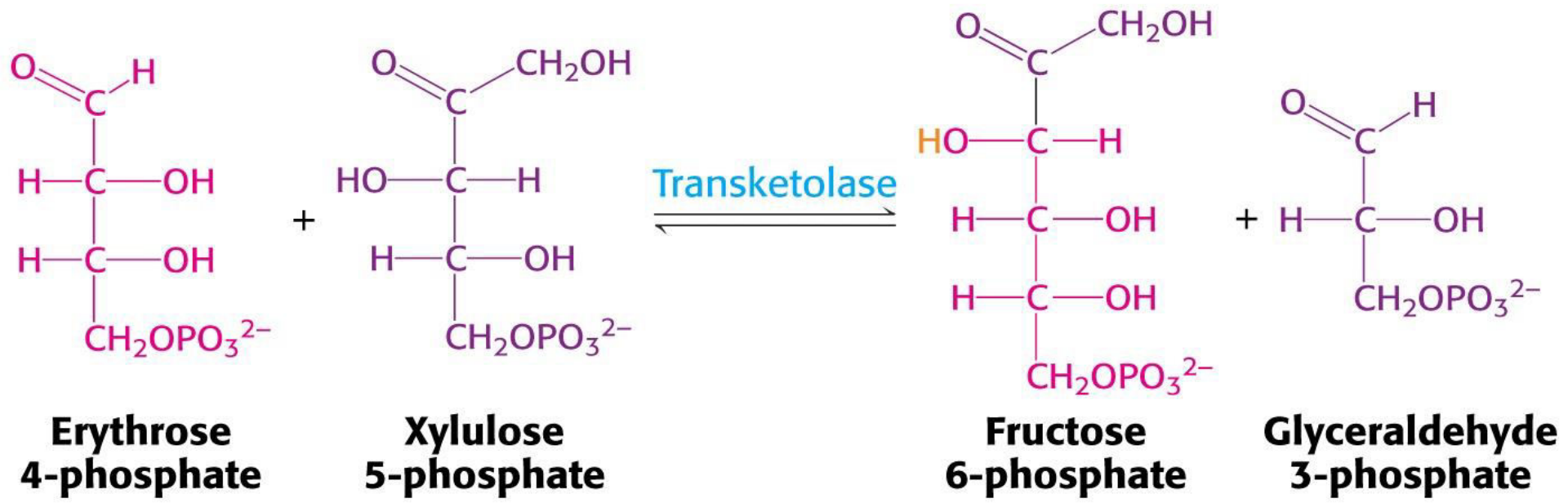
These two products (C_3 & C_7) can further react, transferring a C_3 unit from sedoheptulose-7-P back to glyceraldehyde-3-P forming fructose-6-P and erythrose-4-P. This C_3-transfer is catalyzed by *transaldolase*.

Here also the donor is a ketose and acceptor is an aldose



Step 7: Second Transketolase Reaction

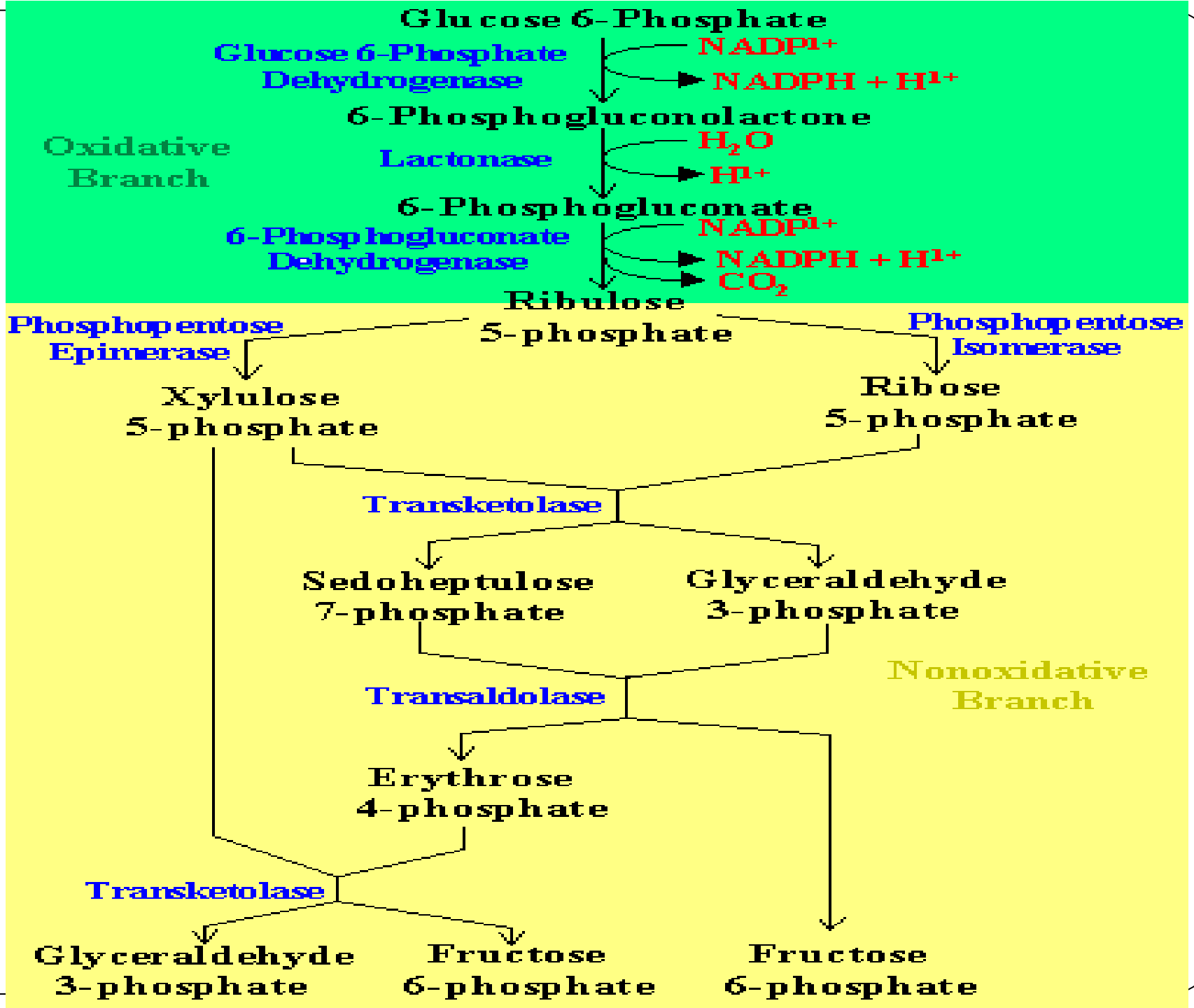
- Finally, in another transketolase-catalyzed transfer of a C2-unit from a second molecule of xylulose-5-P to erythrose-4-P, another fructose-6-P is formed together with another glyceraldehyde-3-P.
- These products are all part of the glycolytic pathway.
- Hence, the relatively few reactions in this hexose monophosphate shunt, provide for a variety of sugars with 3, 4, 5, 6, and 7 carbons.



Step 8: Regeneration of Glucose-6-phosphate

Two molecules of glyceraldehyde-3-phosphate formed in step 7 are condensed to form one fructose-6-phosphate (reversal of step 4 of glycolysis).

Fructose-6-phosphate is then converted to glucose-6-phosphate (reversal of step 2 of glycolysis).


Glucose 6-Phosphate
Glucose 6-Phosphate Dehydrogenase
NADP1+
NADPH + H1+
6-Phosphogluconolactone
Oxidative Branch
Lactonase
H2O
H1+
6-Phosphogluconate
6-Phosphogluconate Dehydrogenase
NADP1+
NADPH + H1+
CO2
Ribulose 5-phosphate
Phosphopentose Epimerase
Phosphopentose Isomerase
Xylulose 5-phosphate
Ribose 5-phosphate
Transketolase
Sedoheptulose 7-phosphate
Glyceraldehyde 3-phosphate
Nonoxidative Branch
Transaldolase
Erythrose 4-phosphate
Transketolase
Glyceraldehyde 3-phosphate
Fructose 6-phosphate
Fructose 6-phosphate

Regulation of HMP Shunt Pathway

The pathway is mainly regulated by the level of NADP+.

The first reaction catalysed by GPD is the rate-limiting step and it 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.

Summary of Shunt Pathway

The overall reaction may be represented as

6 Glucose 6-phosphate +12 NADP+ +6H_2O → 6CO_2 + 12NADPH + 12H+ + 5 Glucose 6-phosphate.

Suppose, 6 molecules of glucose (6x6=36 carbons) are entering in this pathway.

The first carbon atom of all 6 glucose molecules are removed as 6 molecules of CO2.

(This is equivalent to complete oxidation of 1 molecule of glucose).

In this process, 12 NADPH are generated.

The remaining 6 molecules of 5-carbon pentoses (6x5=30) are interchanged in such a way that 5 molecules of glucose (5x6=30C) are regenerated.

Significance of HMP shunt

HMP shunt is unique in generating two important products –

1. pentoses and

2. NADPH- needed for the biosynthetic reactions and other functions.

Importance of pentoses

In the HMP shunt, hexoses are converted into pentoses, the most important being ribose-5-phosphate.

This pentose or its derivatives are useful for the synthesis of nucleic acids (RNA and DNA) and many nucleotides such as ATP, NAD^+, FAD and CoA.

Skeletal muscle is capable of synthesizing pentoses, although only the first few enzymes of HMP shunt are active.

It, therefore, appears that the complete pathway of HMP shunt may not be required for the synthesis of pentoses.

Physiological Significance of the Pathway

1. Pathway is operating in following organs:
   i. Liver,
   ii. Adipose tissue,
   iii. Adrenal cortex,
   iv. Mammary glands,
   v. Testes and ovaries,
   vi. RBCs,
   vii. Lens of eye

A. The oxidative phase of the pathway is seen in the above organs, where NADPH generation is required for lipid synthesis or steroid synthesis.

B. The non-oxidative phase is present in all tissues, and so synthesis of ribose is possible in all tissues of the body.

2. Generation of Reducing Equivalents

The major metabolic role of the pathway is to provide cytoplasmic NADPH for reductive biosynthesis of fatty acids, cholesterol and steroids.

3. Free Radical Scavenging

Free radicals (super oxide, hydrogen peroxide) are continuously produced in all cells.

These will destroy DNA, proteins, fatty acids and all biomolecules, and in turn cells are destroyed.

The free radicals are inactivated by enzyme systems containing super-oxide dismutase (SOD), peroxidase (POD) and glutathione reductase (GR).

Reduced GSH is regenerated with the help of NADPH.

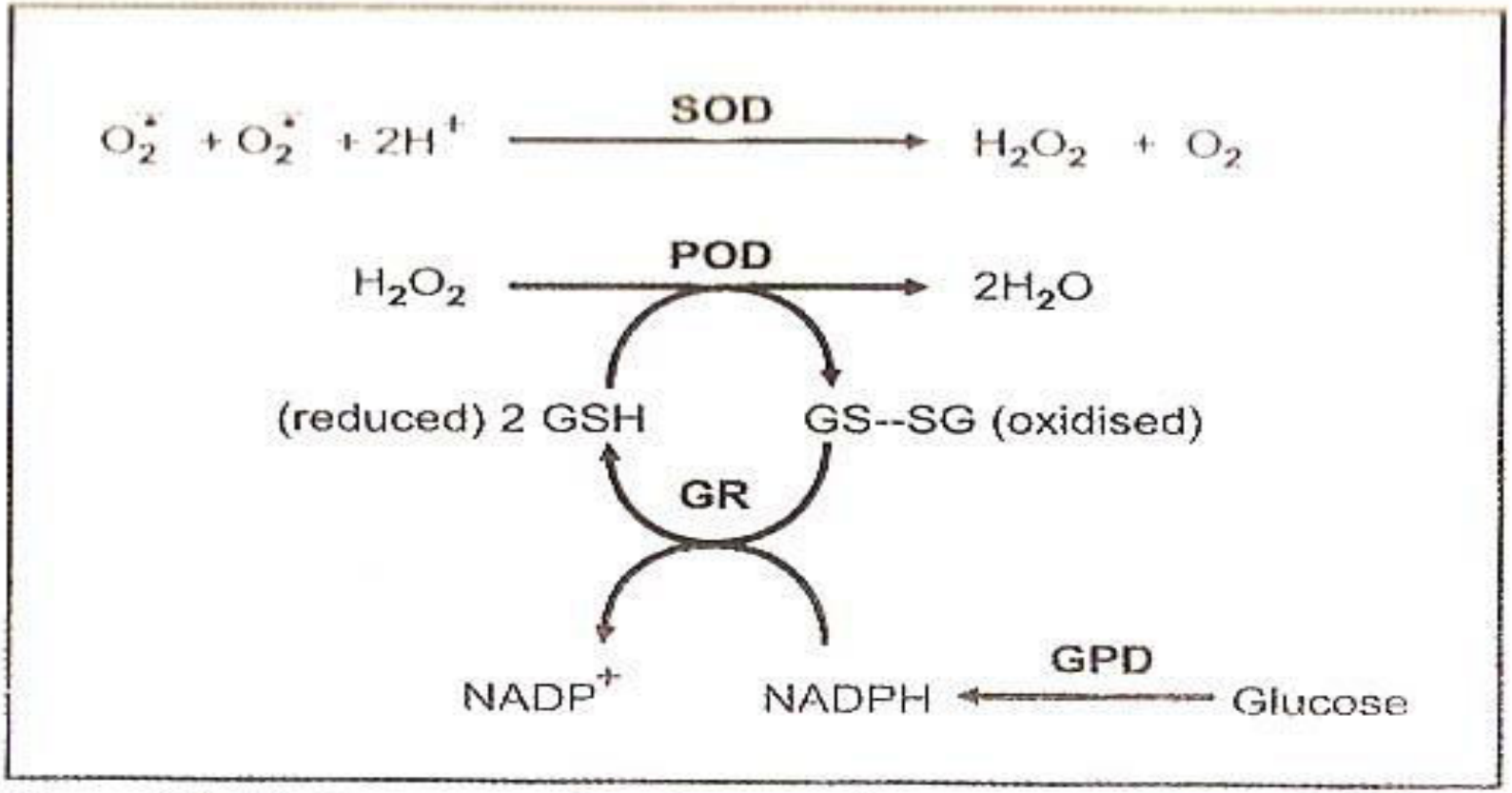


Fig. 11.5. Free radical scaving enzymes. SOD = super oxide dismutase. POD = glutathione peroxidase. GSH = glutathione. GR= glutathione reductase. GPD = glucose-6-phosphate dehydrogenase

4. Erythrocyte Membrane Integrity

NADPH is required by the RBC to keep the glutathione in the reduced state. In turn, reduced glutathione will detoxify the peroxides and free radicals formed within the RBC. So, NADPH, glutathione and glutathione reductase together will preserve the integrity of RBC membrane.

5. Prevention of Met-Hemoglobinemia

NADPH is also required to keep the iron of hemoglobin in the reduced (ferrous) state and to prevent the accumulation of met-hemoglobin.

Met-hemoglobin cannot carry oxygen.

6.Detoxification of Drugs

Most of the drugs and other foreign substances are detoxified by the liver microsomal P450 enzymes, with the help of NADPH.

Monooxygenases (mixed function oxidases) incorporate one atom from molecular oxygen into a substrate (creating a hydroxyl group), with the other atom being reduced to water.

In the cytochrome P450 monooxygenase system, NADPH provides the reducing equivalents required by this series of reactions.

The overall reaction catalyzed by a cytochrome P450 enzyme is:

$$R\text{-}H + O_2 + NADPH + H^+ \rightarrow R\text{-}OH + H_2O + NADP^+$$

Where R may be a steroid, drug, or other chemical.

7. Lens of Eye

Maximum concentration of NADPH is seen in lens of eye. NADPH is required for preserving the transparency of lens.

8. Macrophage bactericidal activity

NADPH is required for production of reactive oxygen species (ROS) (Superoxide anion radical) by macrophages to kill bacteria.

10. Availability of Ribose

Ribose and deoxy-ribose are required for DNA and RNA synthesis. Ribose is also necessary for nucleotide co-enzymes.

Reversal of non-oxidative phase is present in all tissues, by which ribose could be made available.

Thank you