Pentose Phosphate Pathway / phosphogluconate pathway/ hexose monophosphate pathway.

1) Convert hexoses into pentoses (which are essential components of ATP, CoA, $NADP^+$, FAD, RNA, and DNA).

2) Enable the complete oxidative degradation of pentoses by converting them into hexoses & trioses which can then enter the glycolytic pathway.

3) Provide the cell with NADPH (electron donor in reductive biosynthesis):

a) provide reducing power for biosynthetic reactions.

b) as the electron source for reduction of ribo- to deoxyribonucleotidesfor DNA synthesis.

c) serve as a biochemical reductant (e.g., maintain glutathione levels).

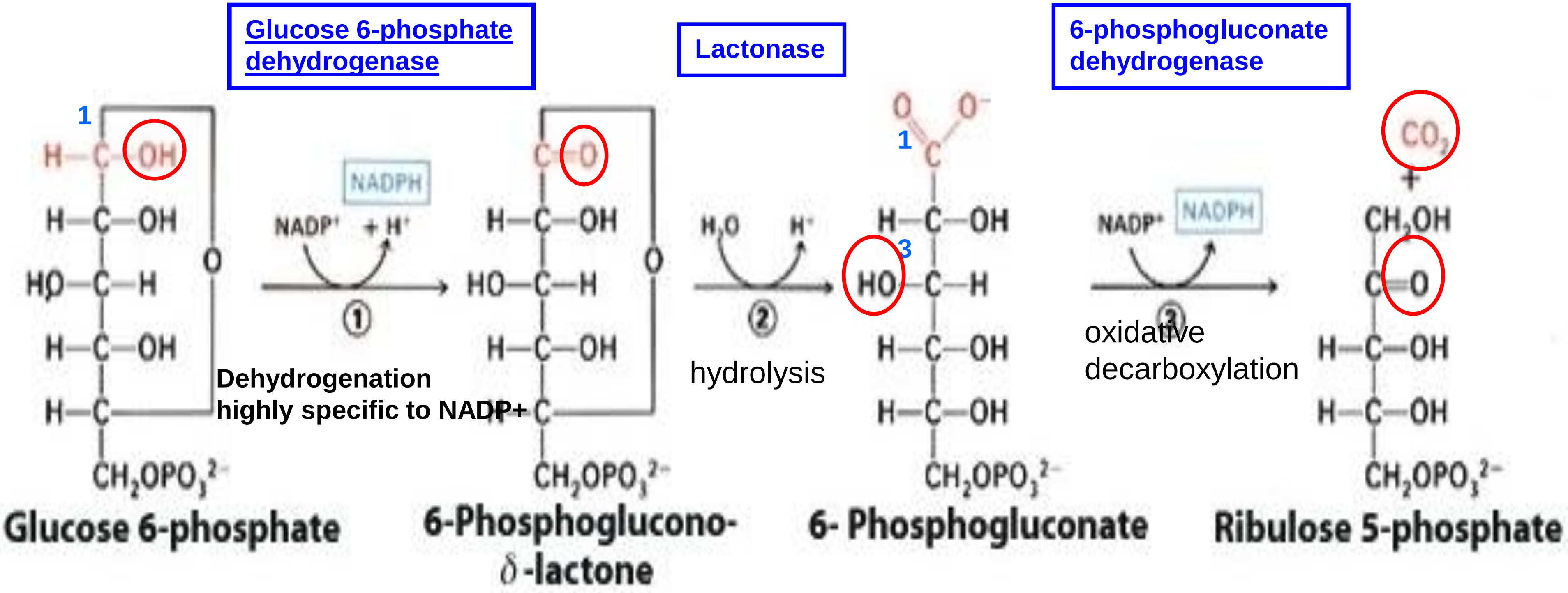
Stages of the Pentose Phosphate Pathway

Stage 1:
consists of the oxidative portion of the pathway in which two oxidative reactions provide NADPH & a hexose is decarboxylated to a pentose.

Stage 2: consists of two reversible isomerization reactions.

Stage 3: consists of the nonoxidative portion of the pathway in which via a series of interconversions of three-, four-, five-, six- & seven-carbon sugars, excess pentoses are converted to hexoses & trioses which can enter the glycolytic pathway.

Stage 1: **Three reactions two of which are oxidative & generate NADPH. Stage 1 is linked to biosynthetic reactions since NADPH & a pentose are produced.**

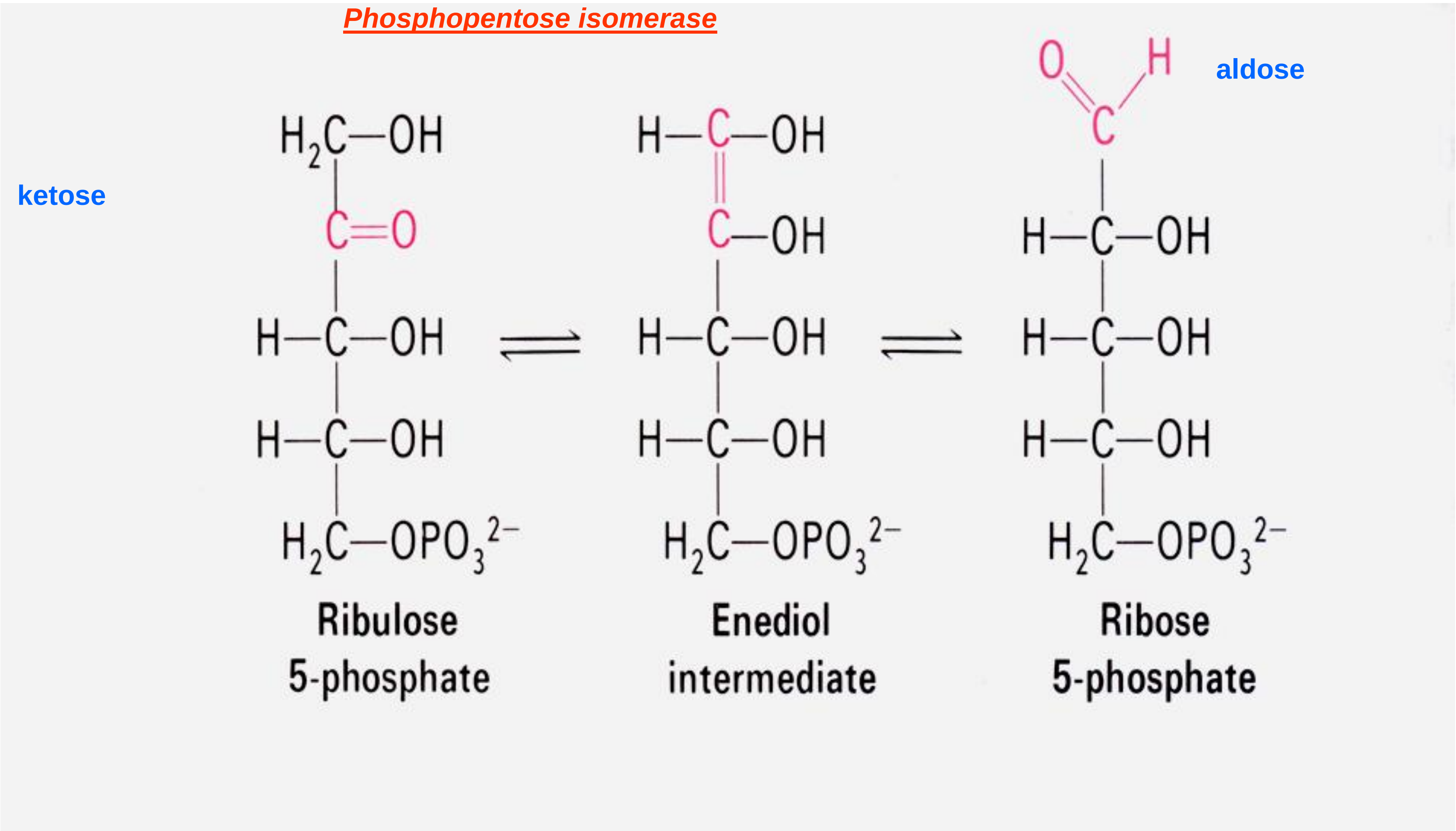


The reactions of stage 1 can be summarized as follows:

$$\text{Glucose 6-phosphate} + 2\ NADP^+ + H_2O \longrightarrow \text{ribulose 5-phosphate} + 2\ NADPH + 2\ H^+ + CO_2$$

Thus two of the three functions of the pentose phosphate pathway are accomplished : generation of NADPH and conversion of a hexose to a pentose.

<u>Stage 2</u> consists of reversible isomerization reactions which convert ribulose 5-phosphate into ribose 5-phosphate



Note: Enediol =Common intermediate in ketose-aldose isomerizations

= alkene enol with a hydroxyl group attached to both carbon atoms of the carbon double bond.

The <u>Stage 1</u> + <u>Stage 2</u> reactions yield 2 NADPH & 1 ribose 5-phosphate for each glucose 6-phosphate oxidized.

However, cells often need NADPH reducing power more than they need ribose 5-phosphate for nucleotide biosynthesis.

In these cases, ribose 5-phosphate is further converted into glyceraldehyde 3-phosphate & fructose 6-phosphate by the enzymes *transketolase & transaldolase.*

<u>These enzymes create a reversible link between the pentose phosphate pathway & glycolysis</u>.

Stage 3 consists of non-oxidative reactions which link the pentose phosphate pathway with glycolysis.

This stage allows:

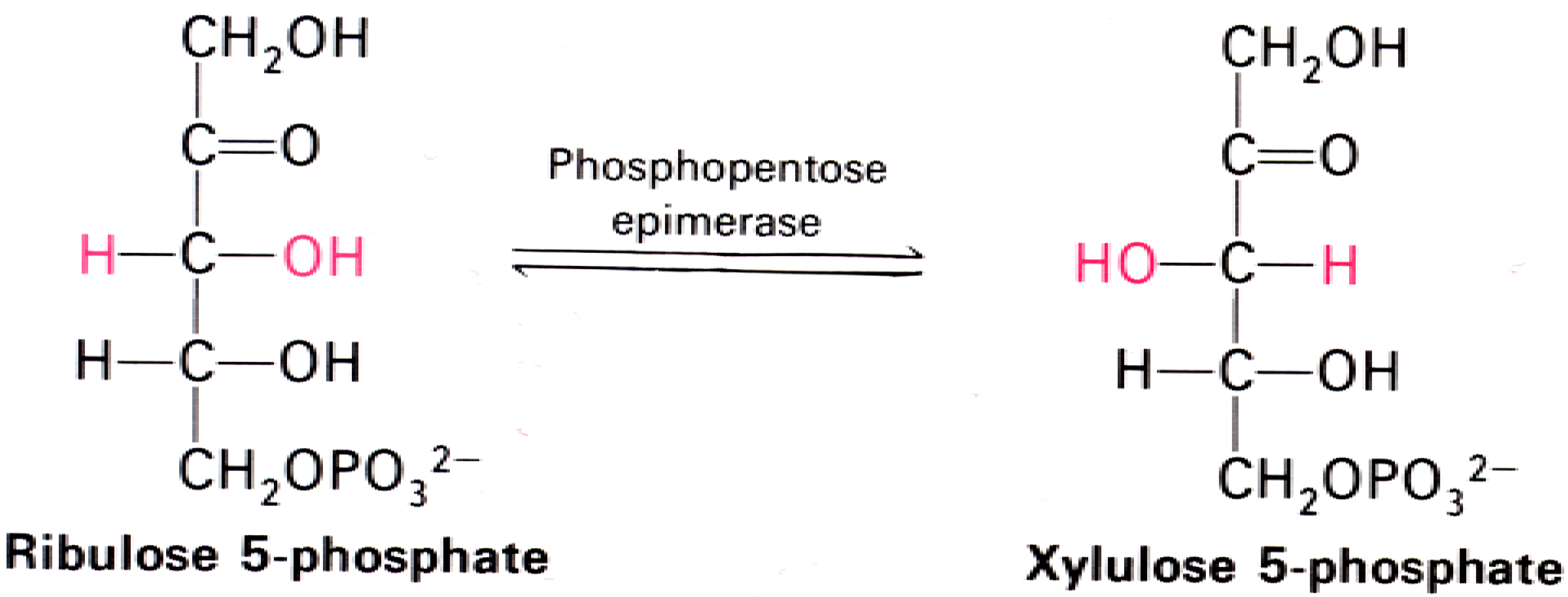
1) excess pentoses to be converted to hexoses & trioses which can then enter glycolysis;

2) hexoses to be converted to pentoses, thereby allowing pentose production without concomitant production of NADPH.

Two enzymes – *transketolase and transaldolase* – catalyze a series of three reactions which convert 3 pentoses into 2 hexoses & 1 triose.

These reactions involve interconversions of 3, 4, 5, 6 & 7-carbon sugars.

Ribulose 5-phosphate converted to xylulose 5-phosphate via *phosphopentose epimerase.*



Glyceraldehyde 3-phosphate

transketolase

$$C_5 + C_5 \rightleftharpoons C_3 + C_7$$

Fructose 6-phosphate

transaldolase

$$C_7 + C_3 \rightleftharpoons C_4 + C_6$$

transketolase

$$C_5 + C_4 \rightleftharpoons C_3 + C_6$$

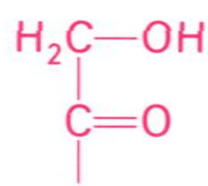
$$\text{Net: } 3\,C_5 \rightleftharpoons 2\,C_6 + 1\,C_3$$

Donor always a ketose, acceptor aldose.

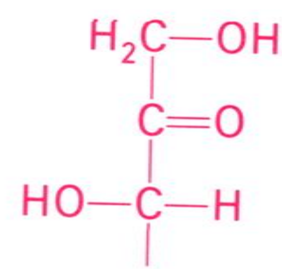
Transketolase transfers a 2-C fragment.

Transketolase require TPP.

Transaldolase transfers a 3-C fragment.



Transferred by transketolase

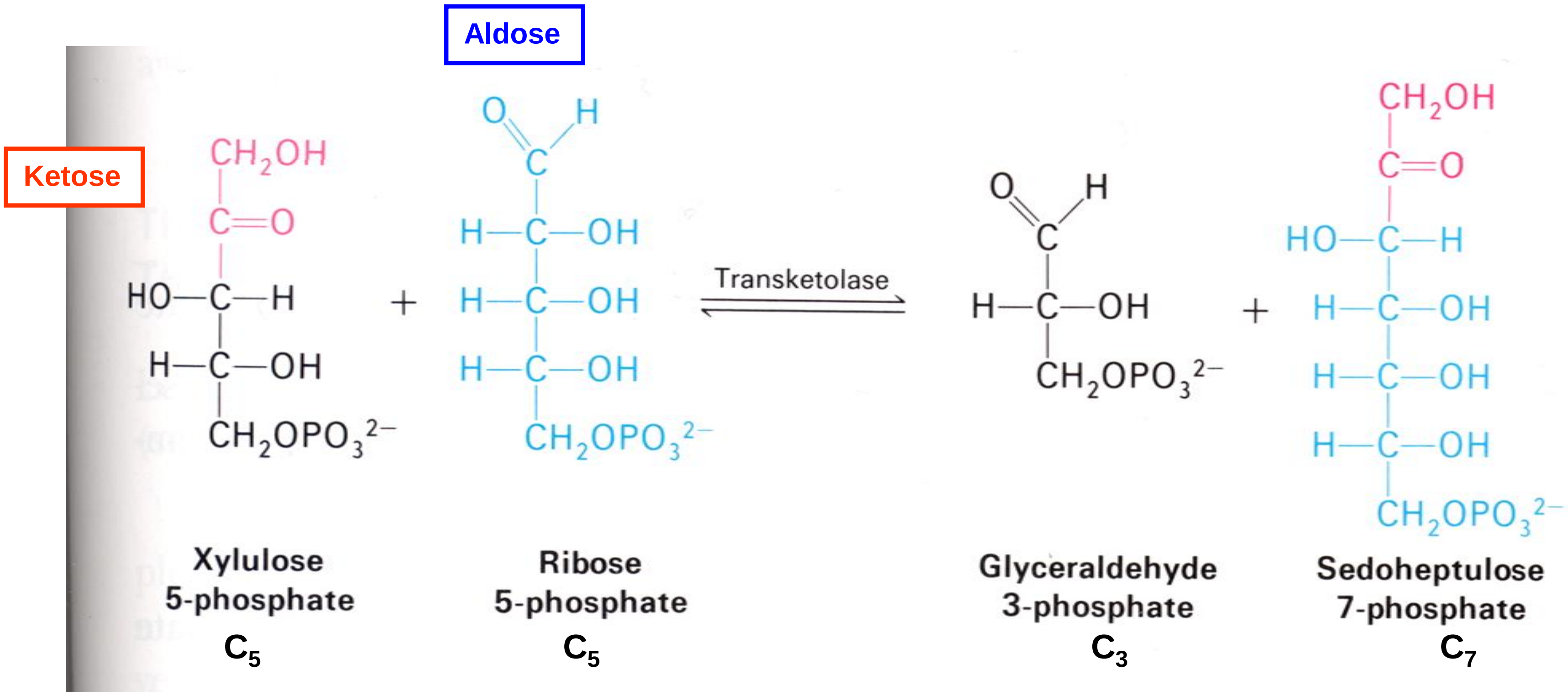


Transferred by transaldolase

Reaction 1

Two pentoses are required: ribose 5-phosphate & xylulose 5-phosphate.

A 2 carbon fragment is transferred from the ketose to the aldose. Catalyzed by transketolase.

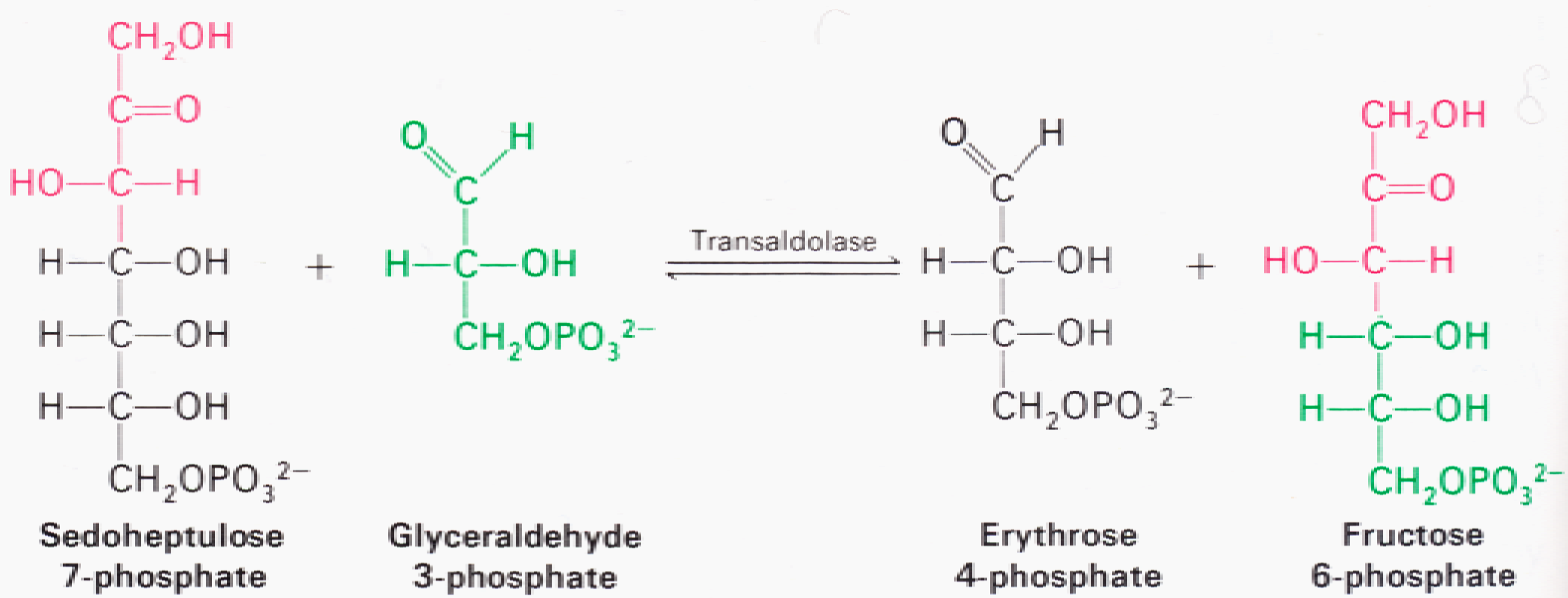


Wernicke Kosakoff Syndrome is an autosomal recessive neuropsychiatric disorder caused by an alteration in transketolase which reduces its affinity for TPP (prosthetic group important for PDH & α-ketoglutarate dehydrogenase, both are normal). Symptoms paralysis of eye movement, disorientation, impaired memory only develop if individual suffers from a moderate thiamine deficiency B1.

<u>**Reaction 2**</u>

The products of Reaction 1 (i.e., glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate) are the substrates for Reaction 2.

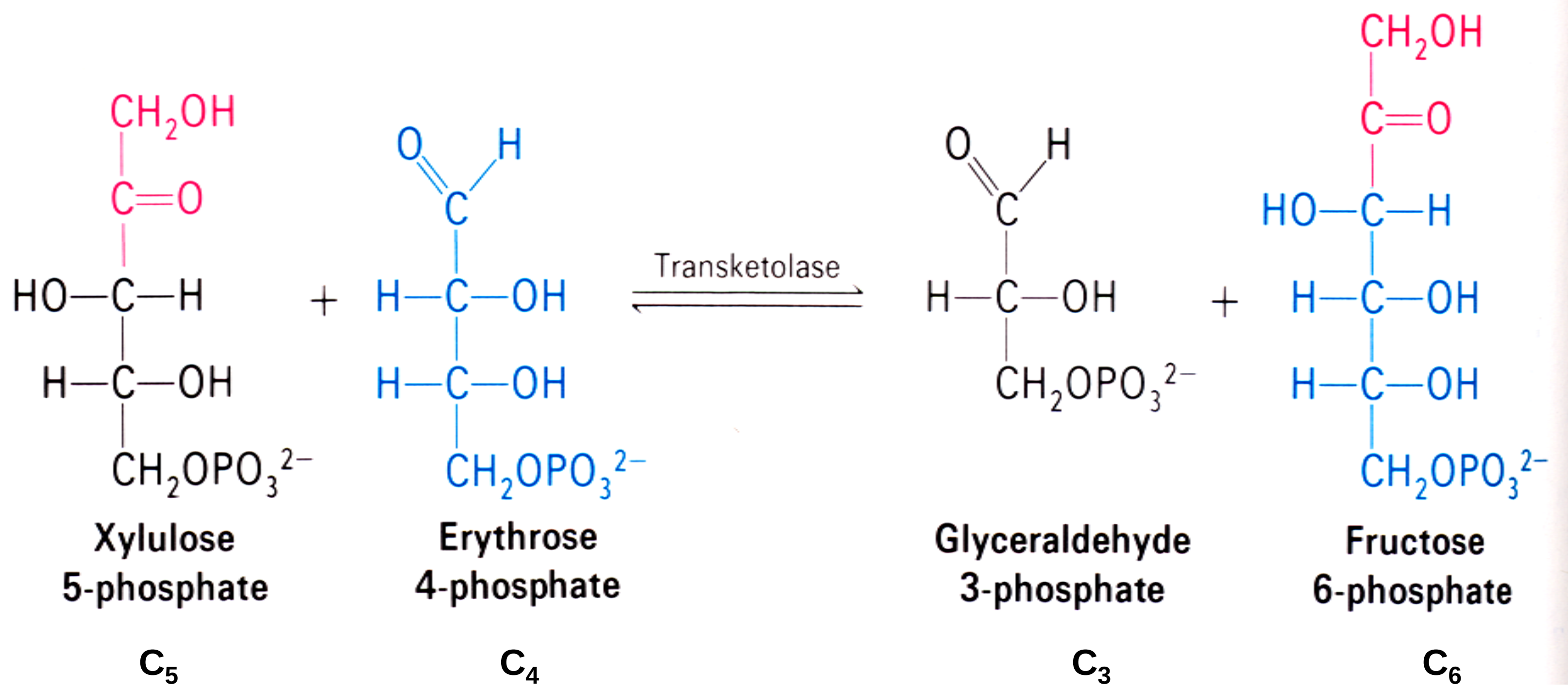
A 3-carbon unit is transferred from the ketose to the aldose by the enzyme *transaldolase.*



C7 C3 C4 C6

Transketolase **is also utilized for the third reaction.**

A 2-C unit is transferred from xylulose 5-phosphate (a ketose) to erythrose 4-phosphate (an aldose)



<u>Note:</u> the products of this reaction, glyceraldehyde 3-phosphate and fructose 6-phosphate, are both intermediates of the glycolytic pathway.

The sum of the Stage 3 reactions is:

2 Xylulose 5-phosphate + ribose 5-phosphate ⟶

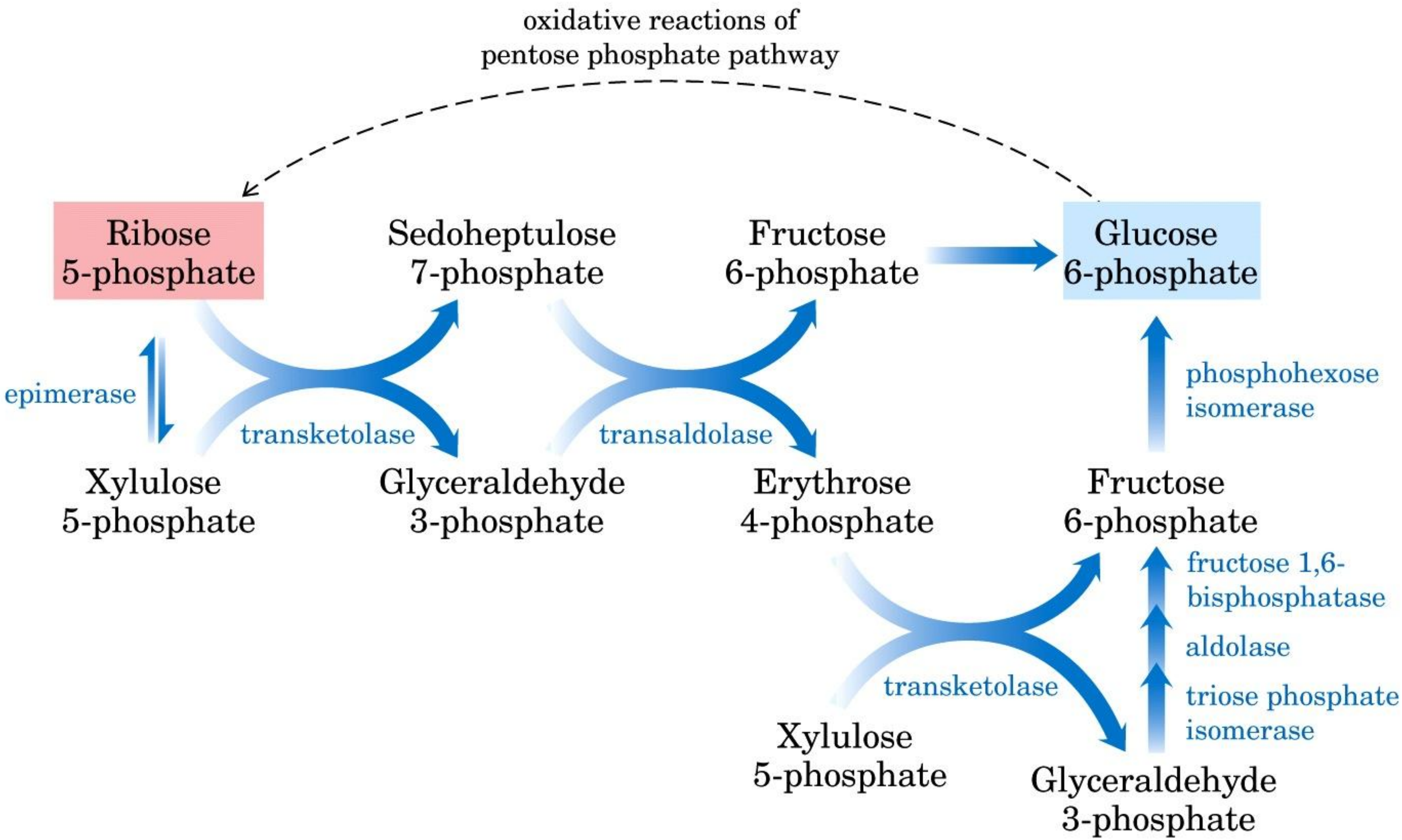
2 fructose 6-phosphate + glyceraldehyde 3-phosphate

If we include the Stage 2 isomerization reactions, the net reaction is:

3 Ribose 5-phosphate ⟶

2 fructose 6-phosphate + glyceraldehyde 3-phosphate

The important point is that excess ribose 5-phosphate formed by the pentose phosphate pathway can be completely converted into glycolytic intermediates.



oxidative reactions of
pentose phosphate pathway
Ribose
5-phosphate
Sedoheptulose
7-phosphate
Fructose
6-phosphate
Glucose
6-phosphate
epimerase
transketolase
transaldolase
phosphohexose
isomerase
Xylulose
5-phosphate
Glyceraldehyde
3-phosphate
Erythrose
4-phosphate
Fructose
6-phosphate
fructose 1,6-
bisphosphatase
aldolase
transketolase
triose phosphate
isomerase
Xylulose
5-phosphate
Glyceraldehyde
3-phosphate

(a)

The Rate Limiting Step of the Pentose Phosphate Pathway

The 1st reaction in oxidative branch of pentose phosphate pathway catalyzed by glucose 6-phosphate dehydrogenase, is the rate limiting step under physiological conditions.

NADPH is a potent competitive inhibitor of the enzyme. Thus, the ratio of $NADP^+$/NADPH regulates the pathway.

As $NADP^+$ level rises, the flux through the pathway increases.

Note:
The nonoxidative branch of the pathway is regulated primarily by substrate availability.

The Percentage of Glucose Metabolized by the Pentose Phosphate Pathway Varies for Different Tissues

Since, a main purpose of this pathway is to supply NADPH for reductive syntheses, it is prominent in tissues that actively carry out the reductive synthesis of fatty acids and/or steroids from acetyl CoA.

Adipose Tissue: 30 – 50% of glucose metabolized by pentose phosphate pathway.

Liver: 5-10%

Erythrocytes: 10% (need NADPH to maintain *reduced* glutathione)

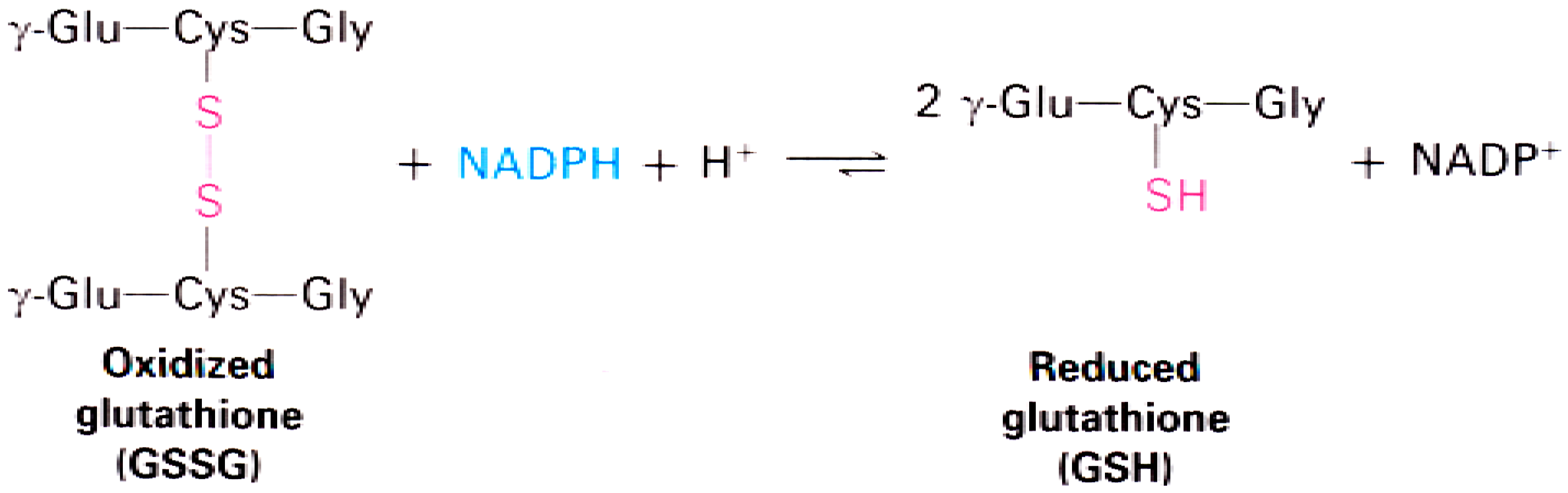
Thyroid gland, kidney, and brain: 3 – 5%

Muscle: activity is extremely low.

Role of Glucose 6-phosphate Dehydrogenase in Red Blood Cell

In RBC, glucose serves as the primary energy source. RBC's lack mitochondria & thus lack the enzymes of the citric acid cycle.
Therefore, glucose is metabolized exclusively by the glycolytic pathway (90%) & the pentose phosphate pathway (10%).

The most important function of the pentose pathway in RBC is to maintain tripeptide glutathione in a reduced state.
Oxidized glutathione is reduced by *glutathione reductase* in a reaction which utilizes NADPH:



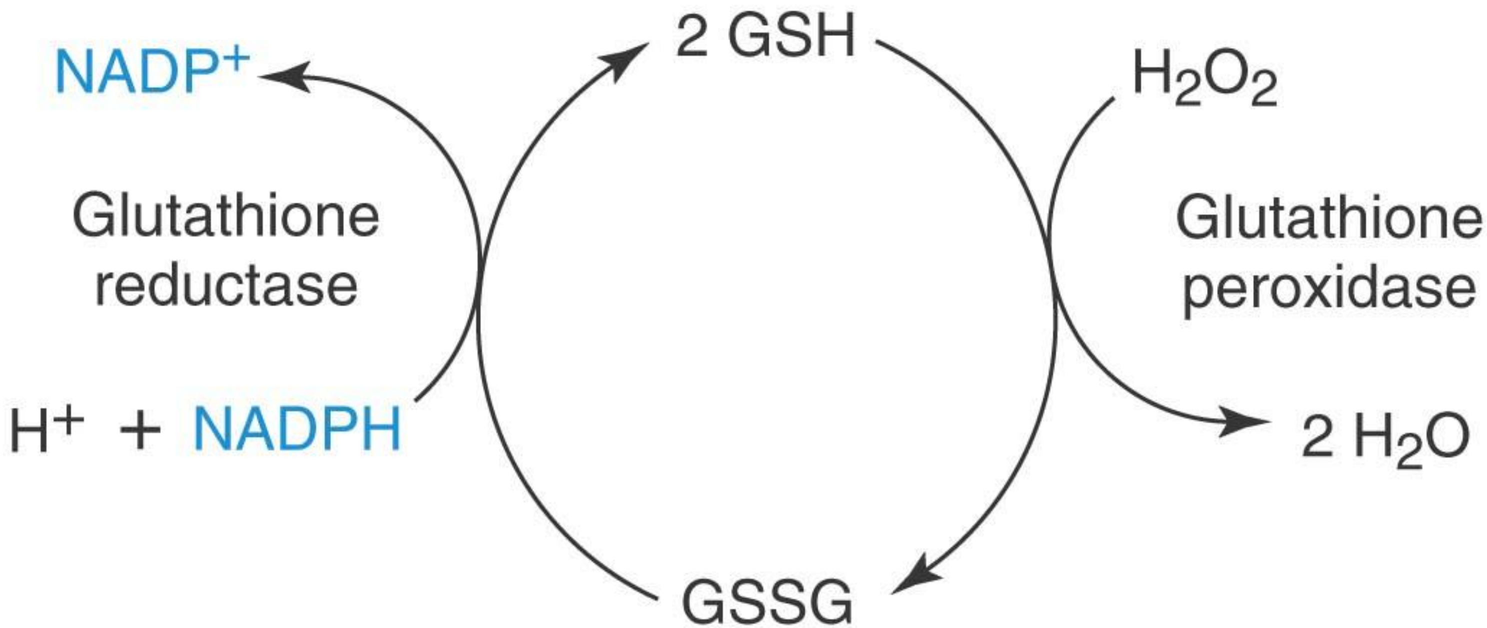
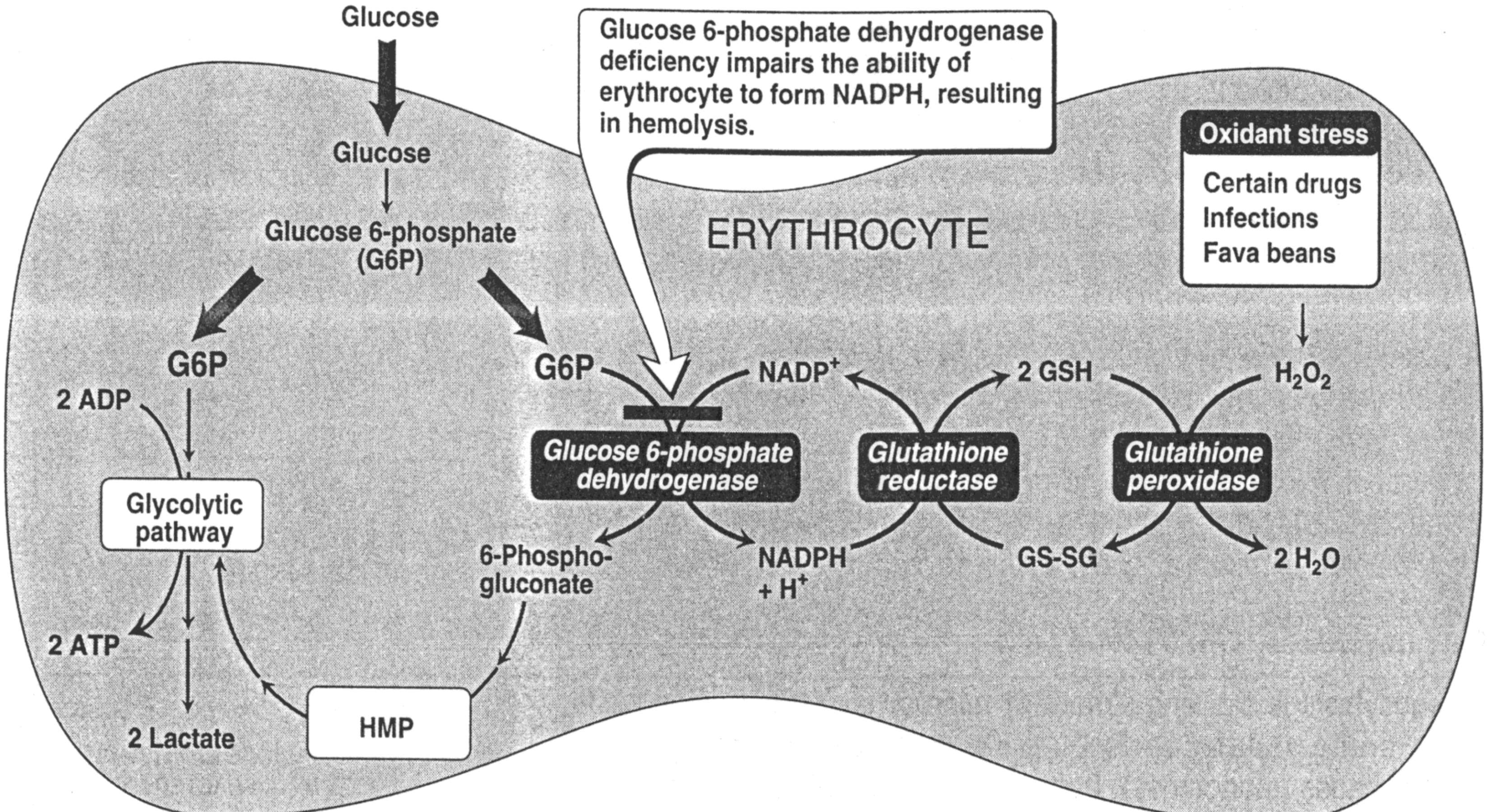


Figure 15.5. Destruction of H_2O_2 depends on reduction of oxidized glutathione by NADPH generated by pentose phosphate pathway.


Glucose
Glucose 6-phosphate dehydrogenase deficiency impairs the ability of erythrocyte to form NADPH, resulting in hemolysis.
Glucose
Glucose 6-phosphate (G6P)
ERYTHROCYTE
Oxidant stress
Certain drugs
Infections
Fava beans
G6P
2 ADP
G6P
$NADP^+$
2 GSH
H_2O_2
Glucose 6-phosphate dehydrogenase
Glutathione reductase
Glutathione peroxidase
Glycolytic pathway
6-Phosphogluconate
NADPH + H^+
GS-SG
2 H_2O
2 ATP
HMP
2 Lactate

TPP

- **Vitamin B1 (thiamine) deficiency :**
  - **Dry beriberi**: peripheral neuropathy (demyelination)
  - **Wet beriberi:** High output cardiac failure
  - **Wernicke's encephalopathy:** Confusion , Ataxia Ophtalmoplegia , Nystagmus.
  - **Korsakoff's psychosis:** Inability to remember new and old memory .
  - **WERNICKE-KORSAKOFF SYNDROME :** it is symptom complex of Wernicke disease and the Korsakoff's psychosis .
  - **Management :** 50 to 200 mg thiamine .

- Causes of deficiency:

poor diet

alcoholism

polished rice

TPP a coenzyme for :

Pyruvate dehydrogenase complex

a-ketoglutarate dehydrogenase complex

Transketolase