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CARBOHYDRATE METABOLISM – PENTOSE PHOSPHATE PATHWAY

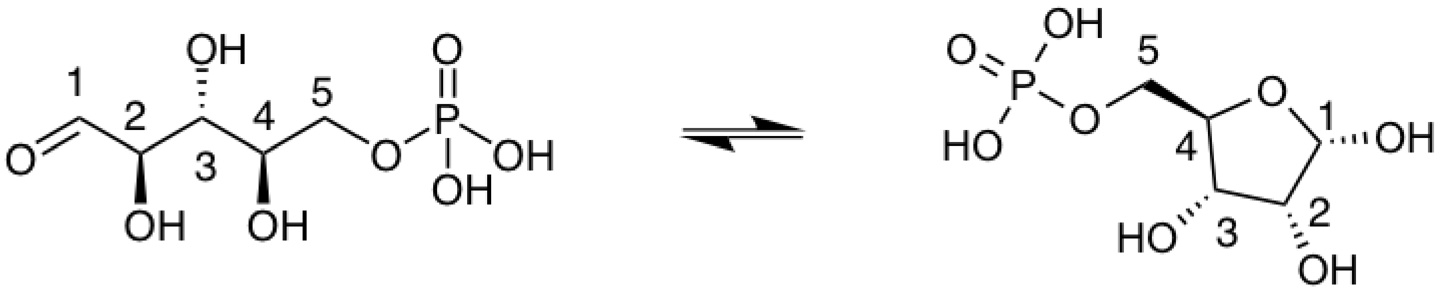
Prof. Michele Di Foggia

Dipartimento di Scienze Biomediche e Neuromotorie – DIBINEM – via Irnerio 48, Bologna

PENTOSE PHOSPHATE PATHWAY

The main products are **NADPH** and **ribose-5-phosphate**

- **NADPH** is an electron donor
  - used in biosynthesis (fatty acids, cholesterol, steroids)
  - repair of oxidative damage (reduced glutathione)
- **Ribose-5-phosphate** is a biosynthetic precursor of nucleotides
  - used in DNA and RNA synthesis
  - used in the synthesis of some coenzymes



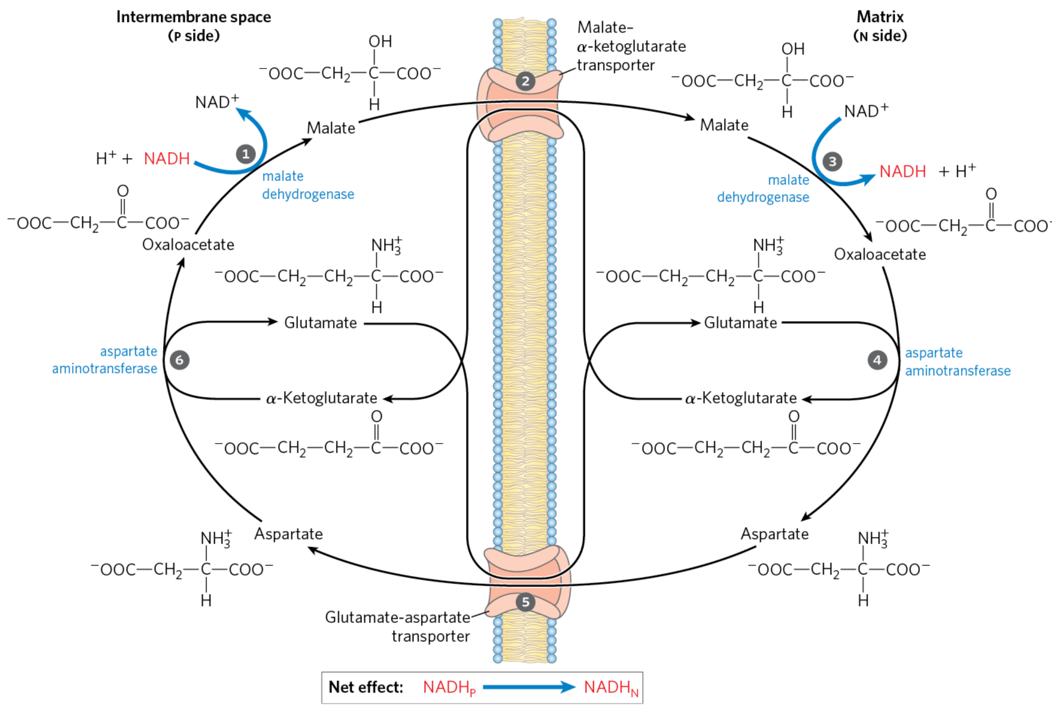
NADH vs NADPH

- **NADPH/NADP$^+$ ratio kept high**

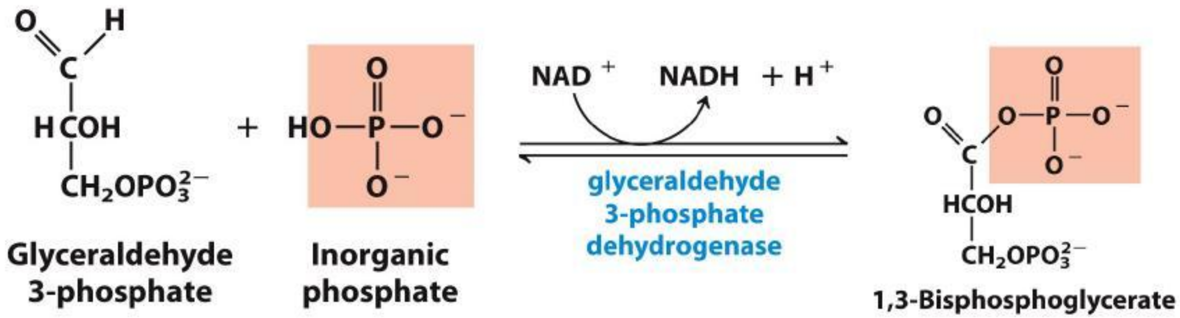
  - reflects role in biosynthesis and cellular protection from oxidation

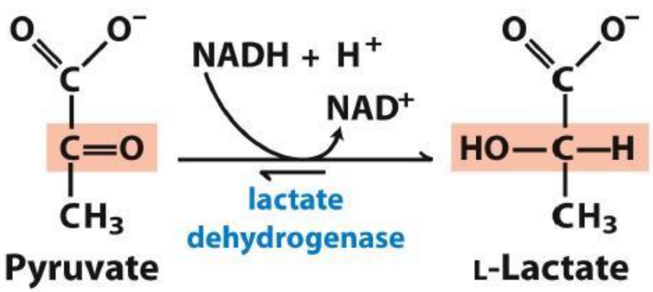
- **NADH/NAD$^+$ ratio kept low**

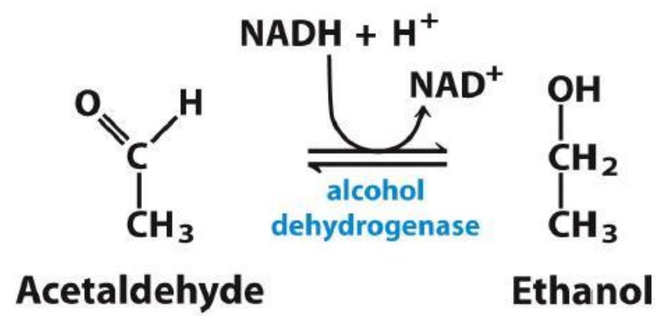
  - NADH used in respiration, much of it in mitochondria

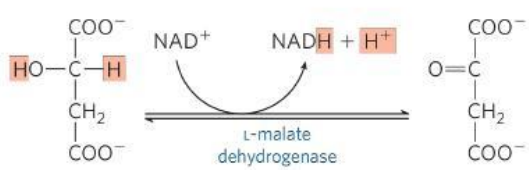


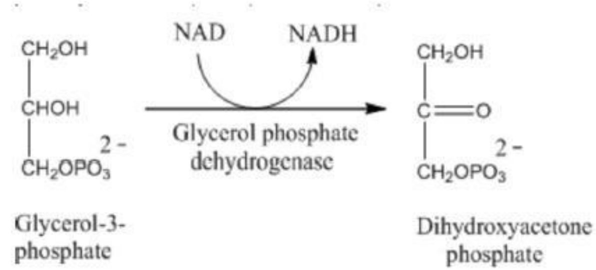
NADH vs NADPH





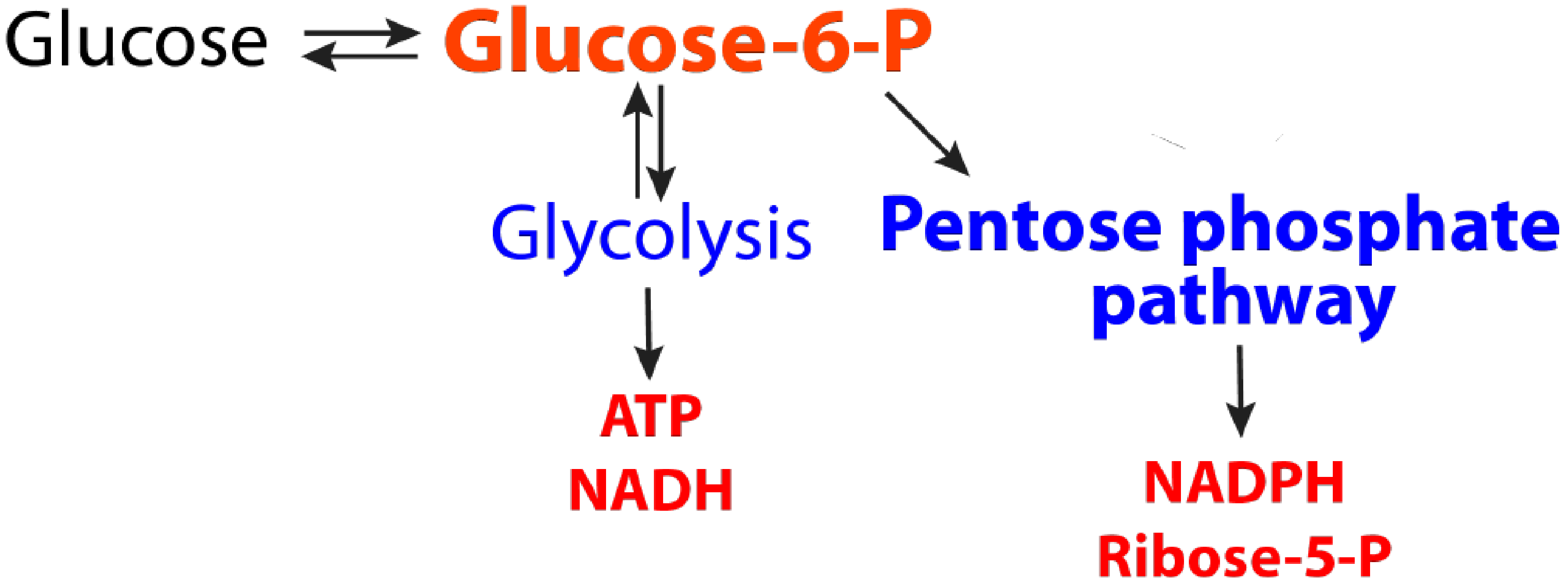






PENTOSE PHOSPHATE PATHWAY

Alternative pathway of **glucose oxidation**.

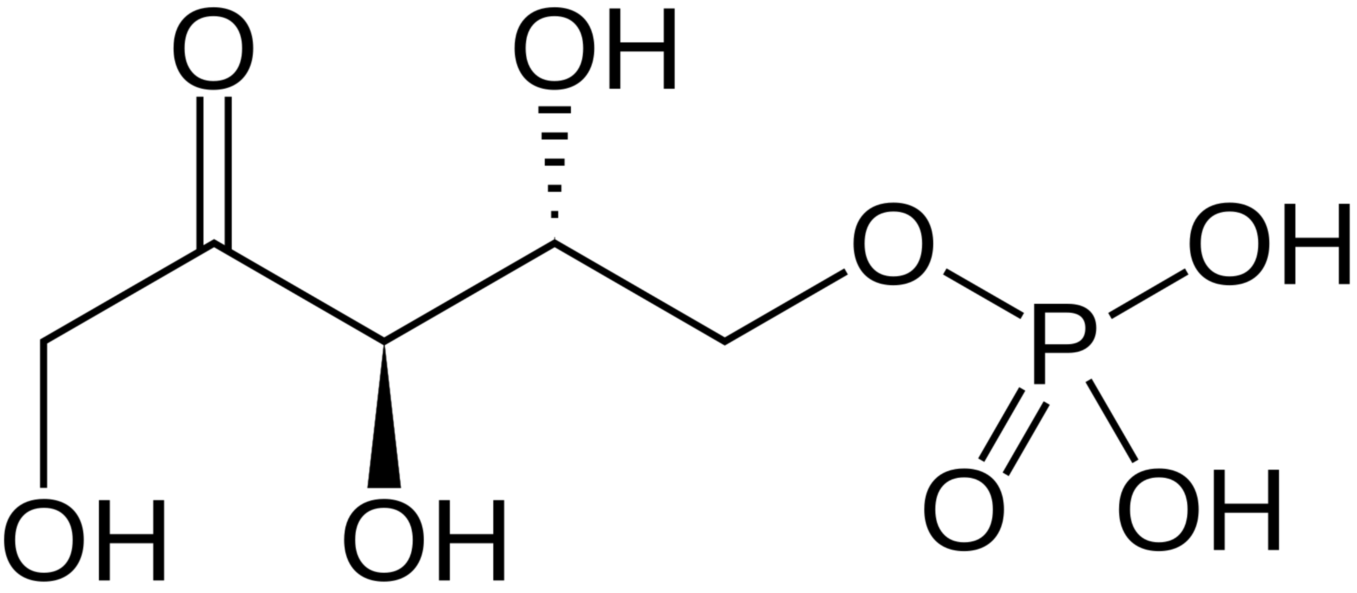


PENTOSE PHOSPHATE PATHWAY

Alternative pathway of **glucose oxidation**.

Two phases:

- Oxidative phase, irreversible (up to ribulose-5-P)
- Non-oxidative phase, reversible (interconversions)



PENTOSE PHOSPHATE PATHWAY

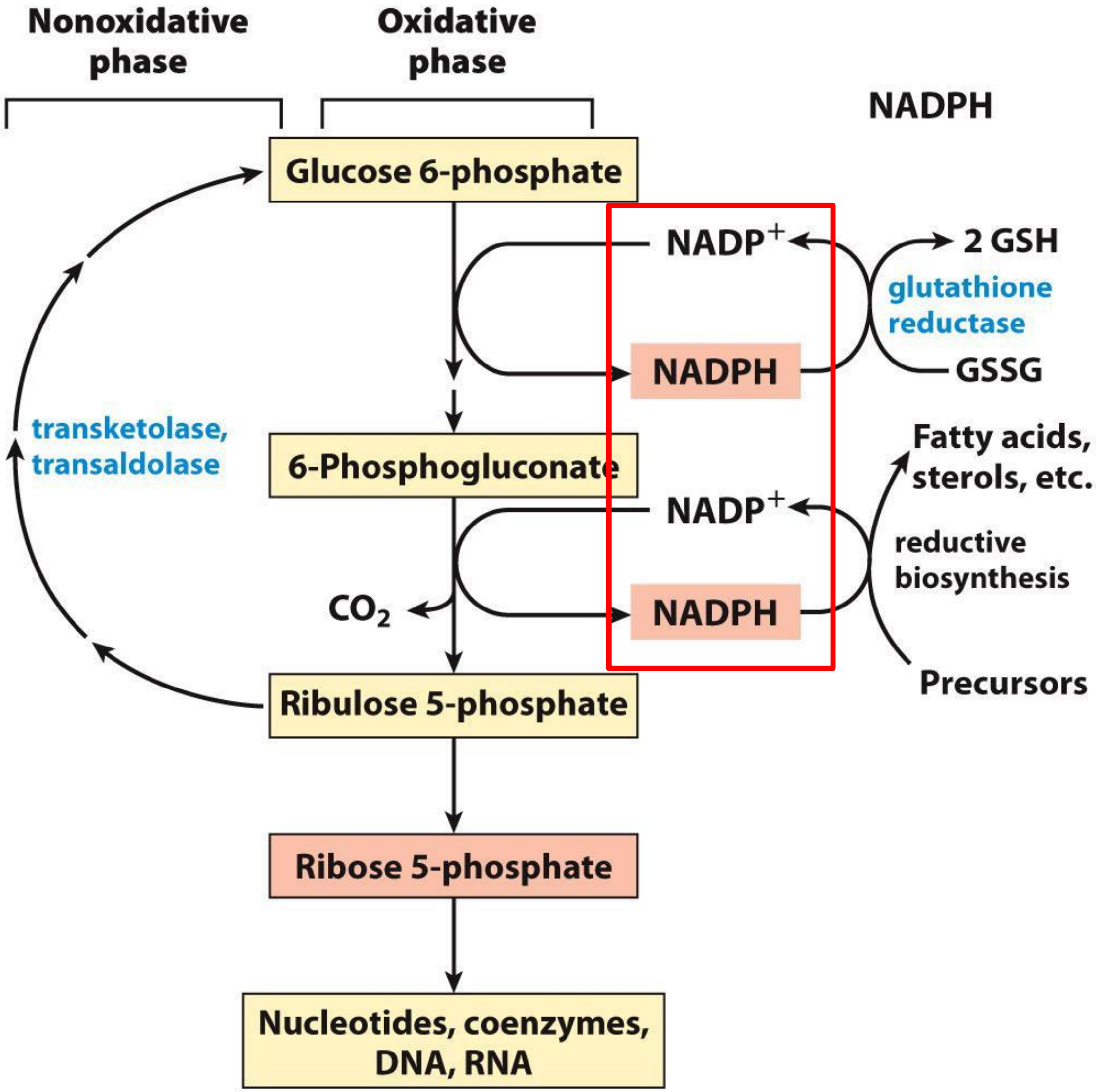


Figure 14-21
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PENTOSE PHOSPHATE PATHWAY

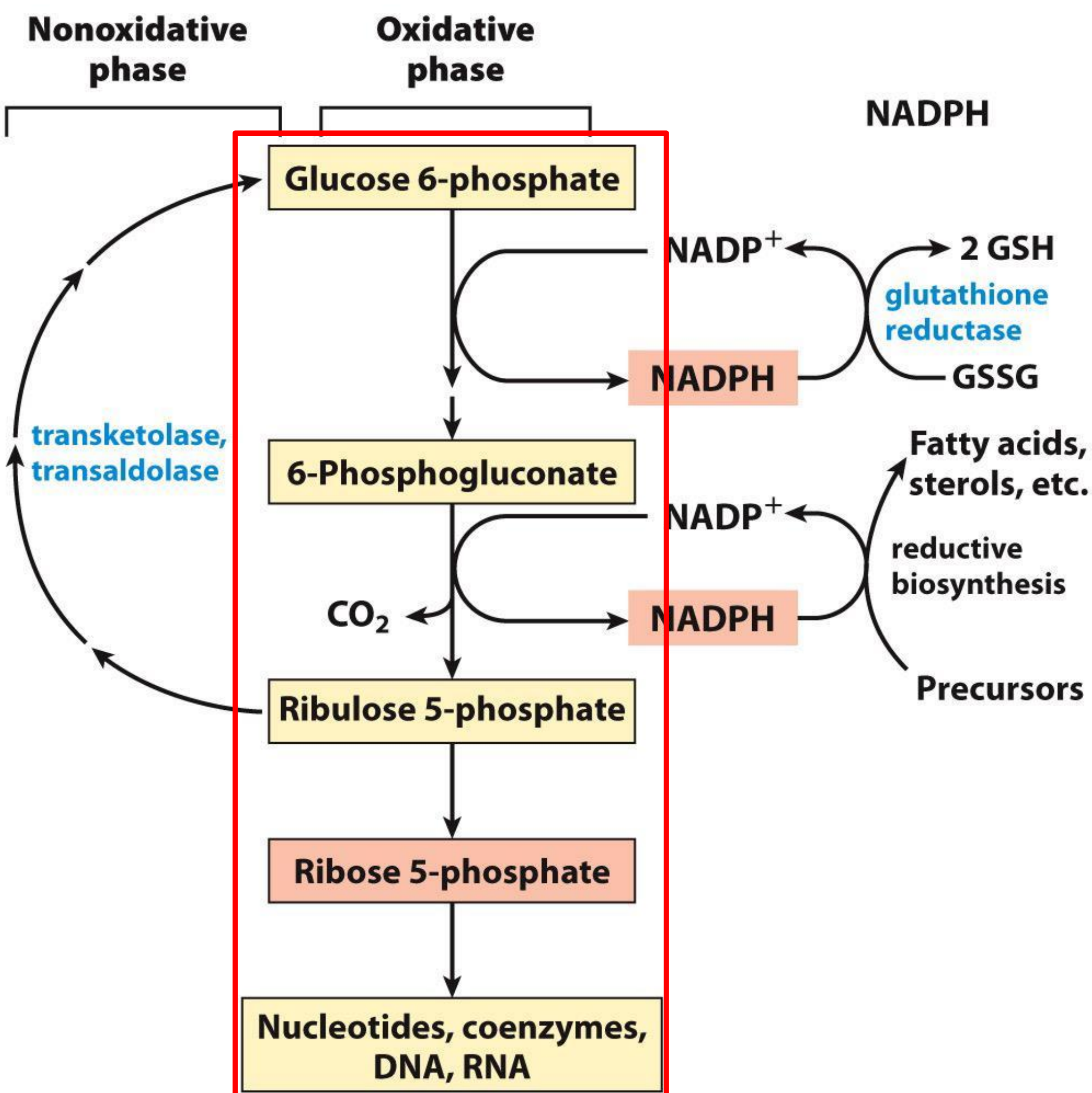

Figure 14-21
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PENTOSE PHOSPHATE PATHWAY

General Scheme

Glyceraldehyde 3-phosphate (G3P)

&

Fructose 6-phosphate (F6P)

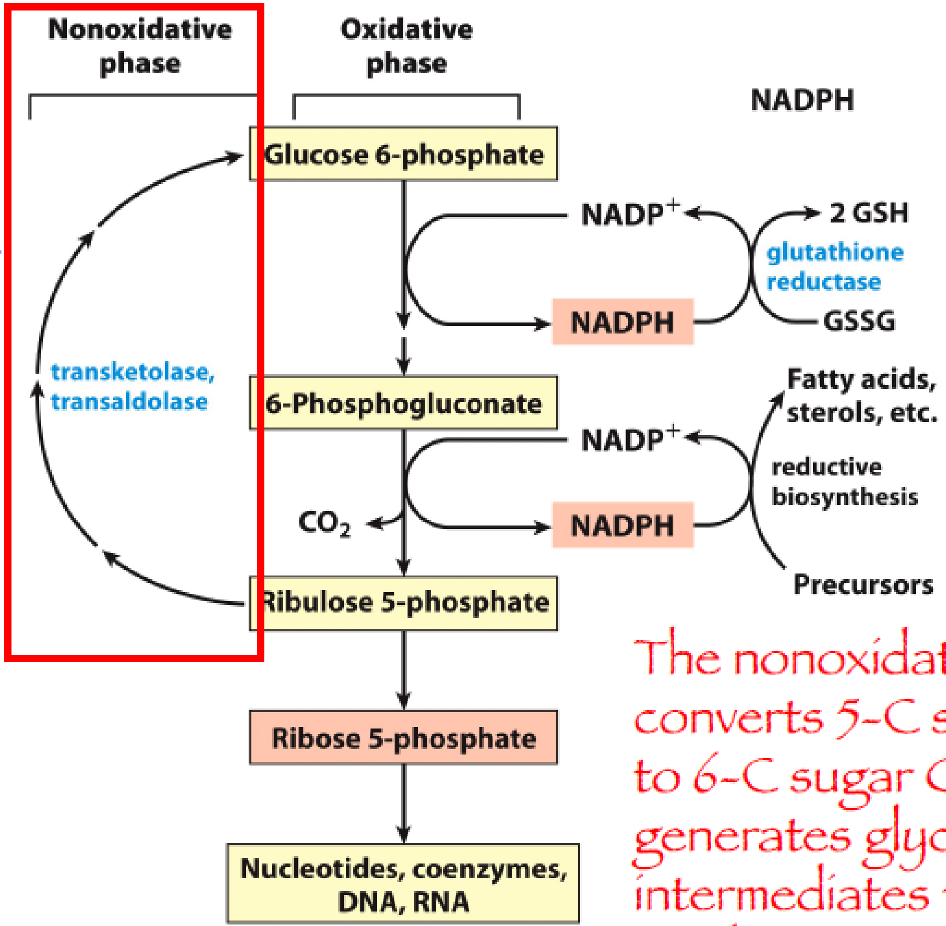

Figure 14-21
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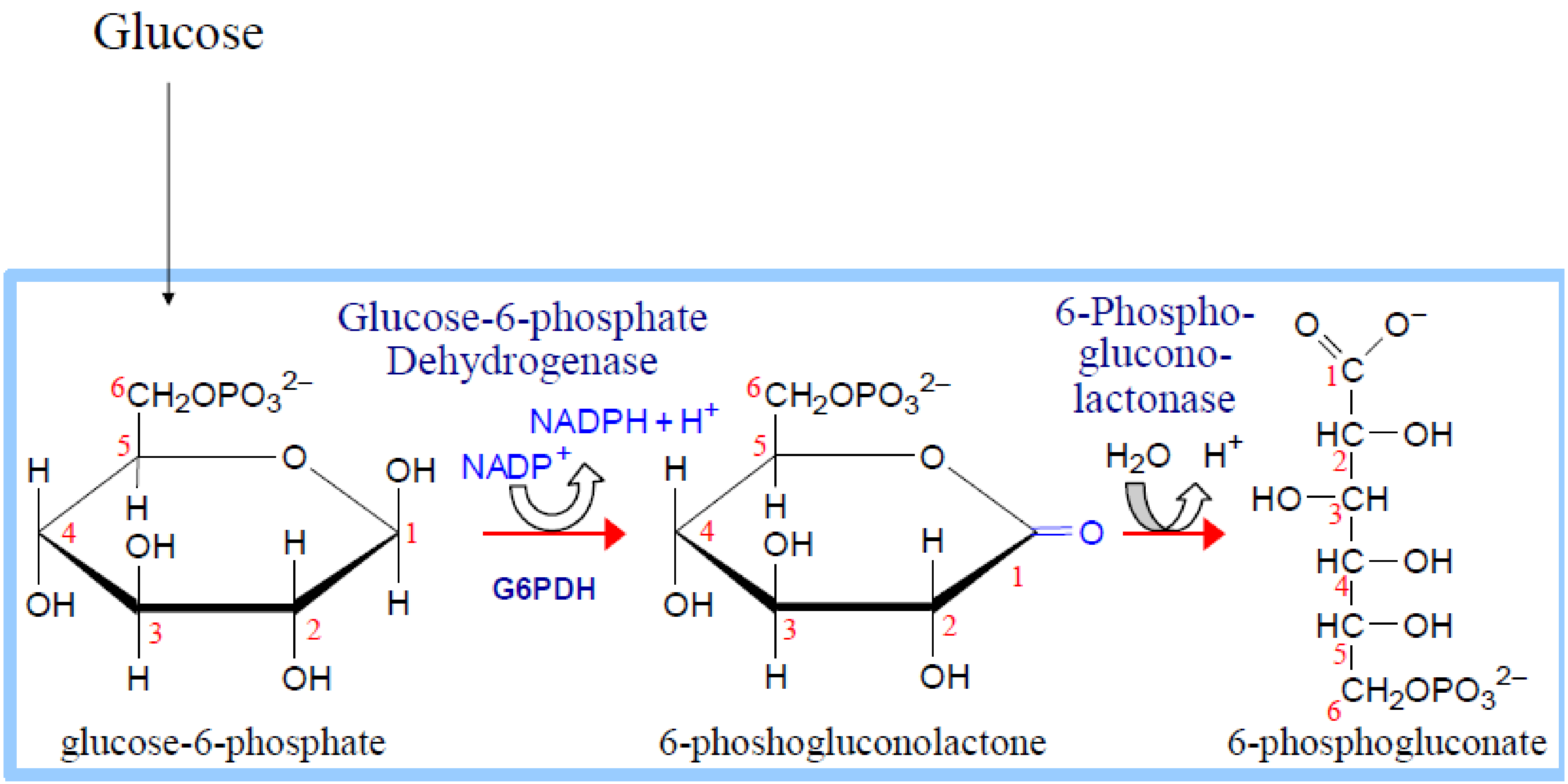
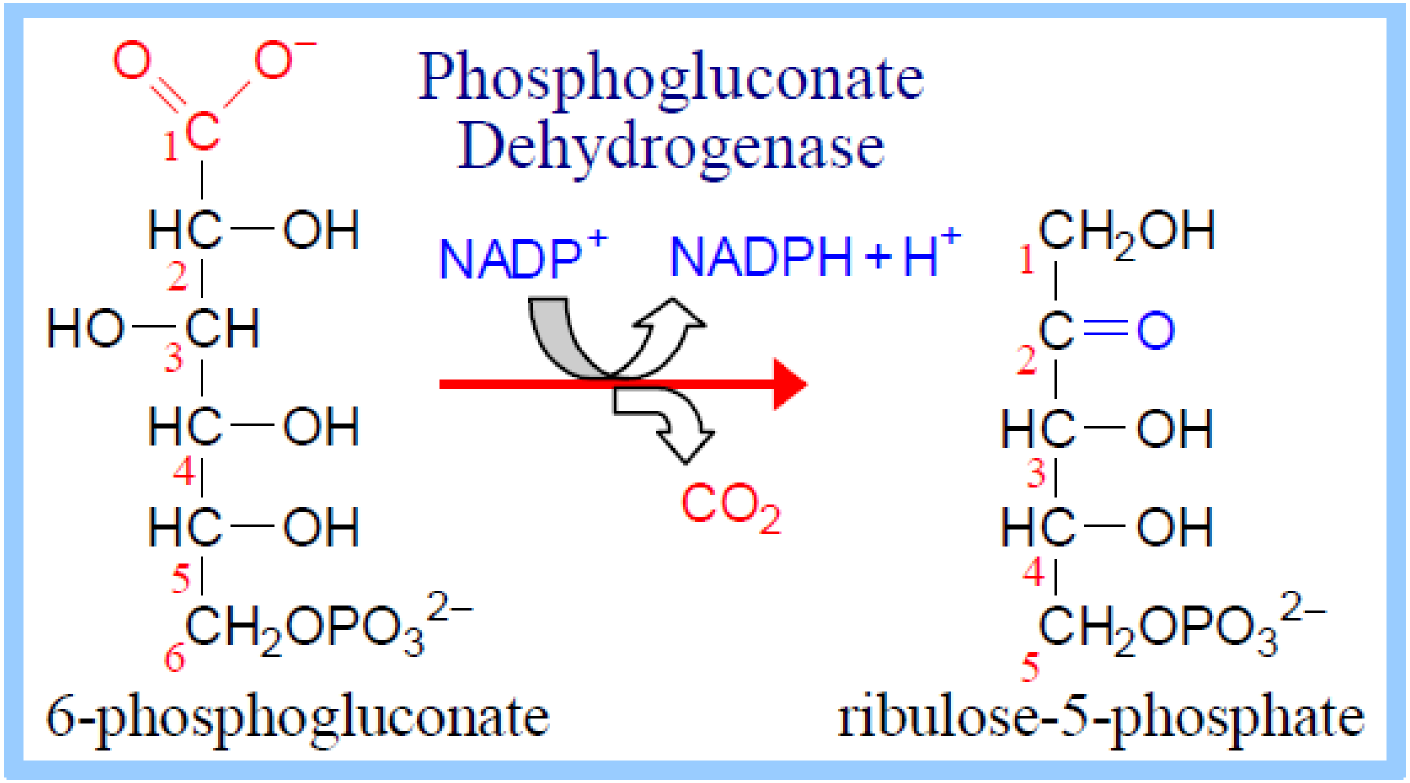
The nonoxidative phase converts 5-C sugars back to 6-C sugar OR generates glycolysis intermediates for ATP synthesis.

PENTOSE PHOSPHATE PATHWAY



PENTOSE PHOSPHATE PATHWAY



PENTOSE PHOSPHATE PATHWAY

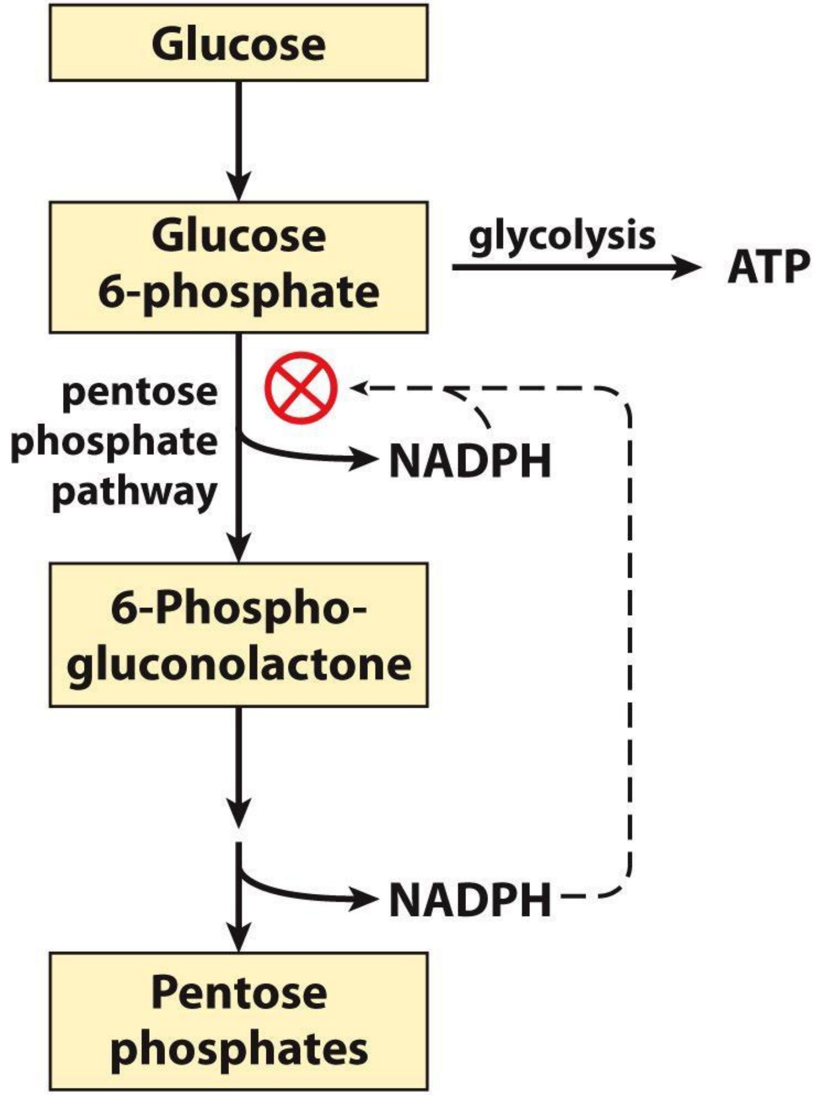


Figure 14-28
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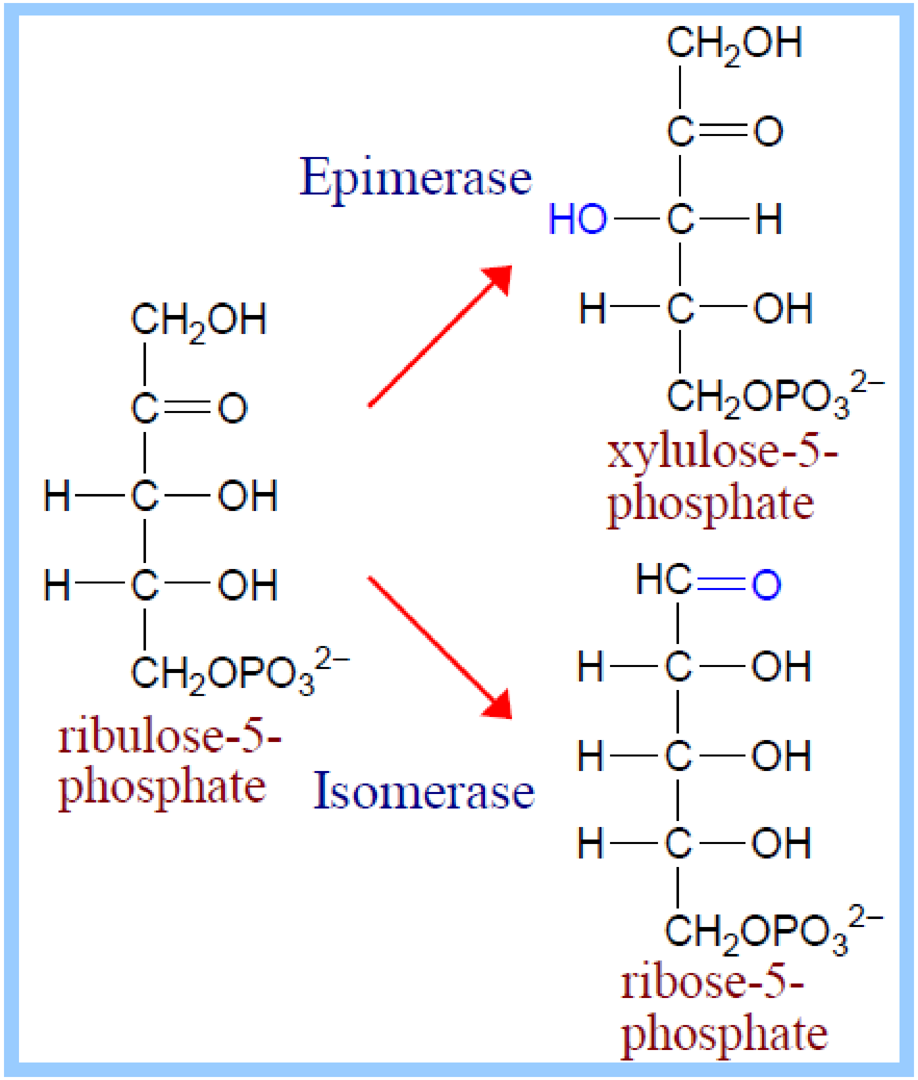
PENTOSE PHOSPHATE PATHWAY

Non-oxidative phase 2:

First reaction



PENTOSE PHOSPHATE PATHWAY

Non-oxidative phase 2:

First transketolase reaction (transfer of 2C units frome a ketose to an aldose)

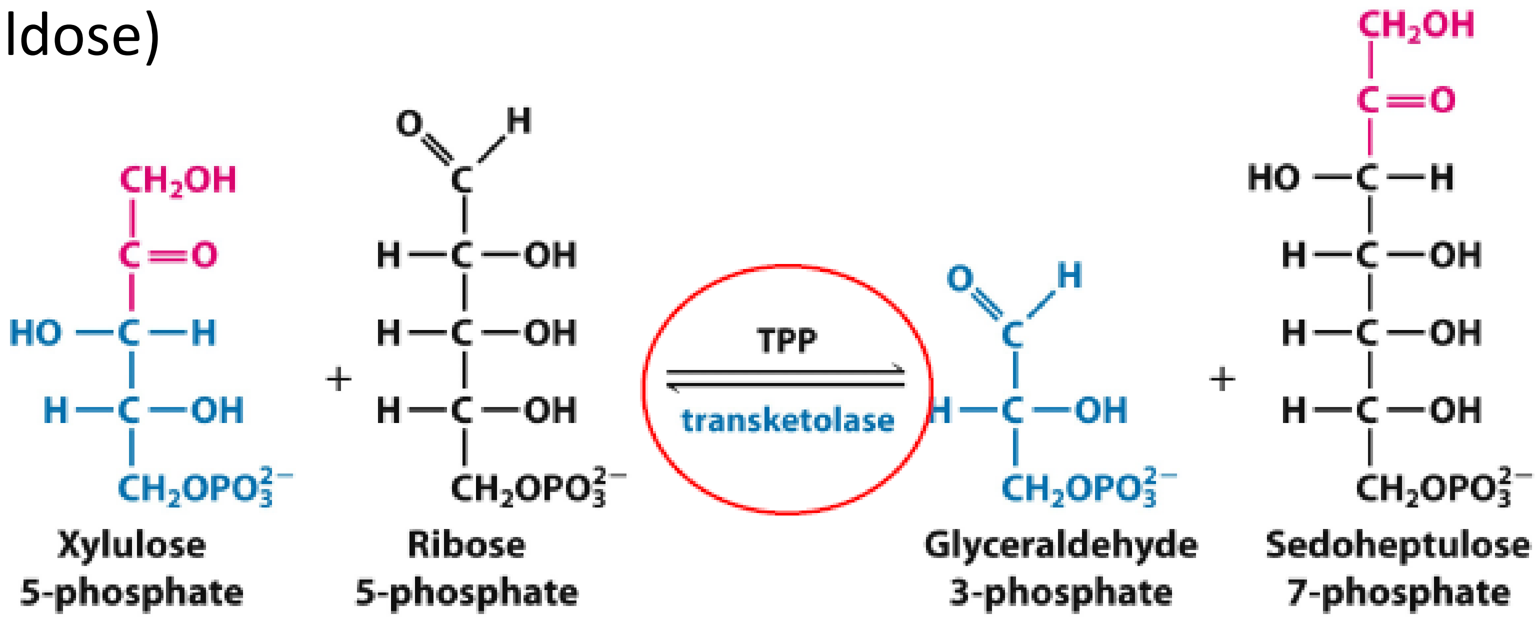


Figure 14-24b
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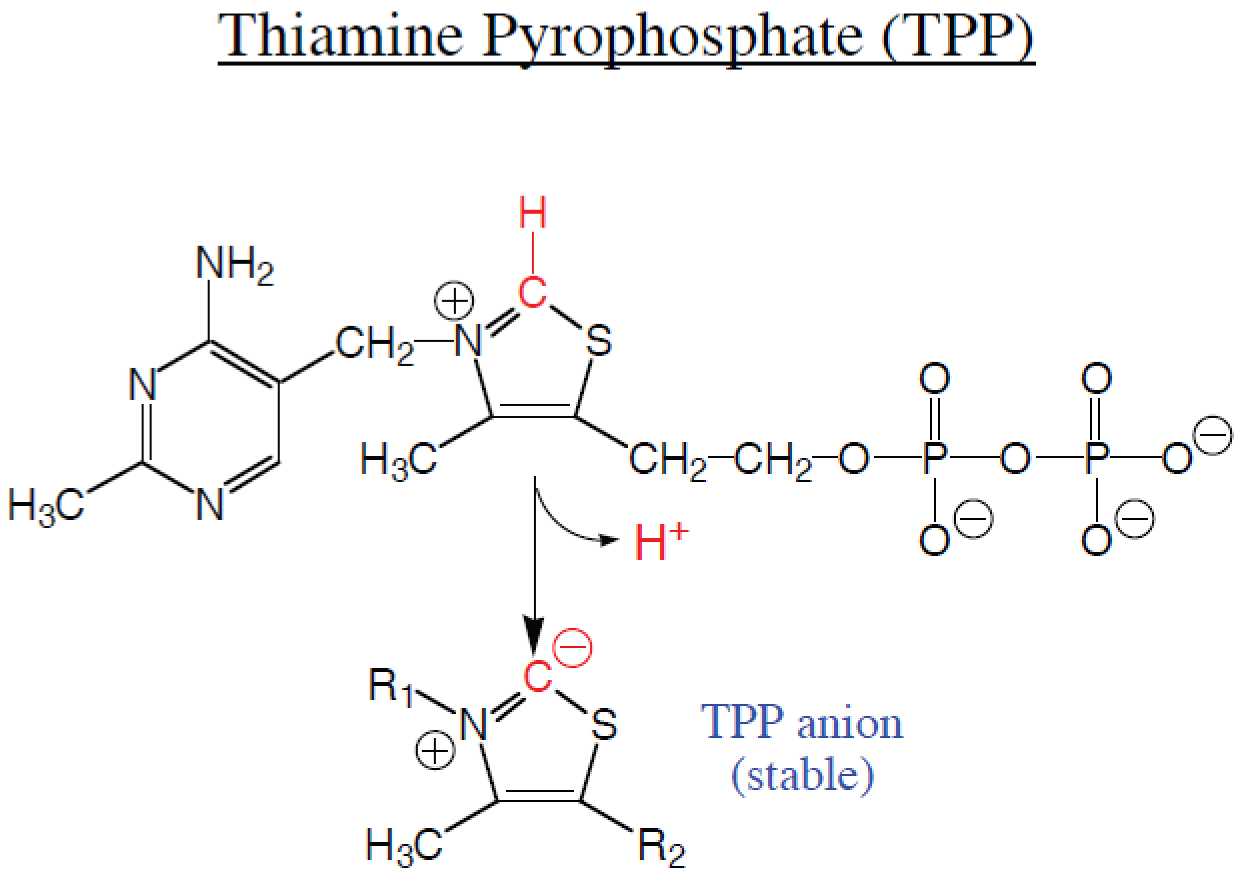
5c + 5c 3c + 7c

PENTOSE PHOSPHATE PATHWAY

Non-oxidative phase 2:

Mechanism: nucleophilic attack by TPP carbanion to carbonyls



PENTOSE PHOSPHATE PATHWAY

Non-oxidative phase 2: reaction 3

Transaldolase reaction (transfer of a 3C unit

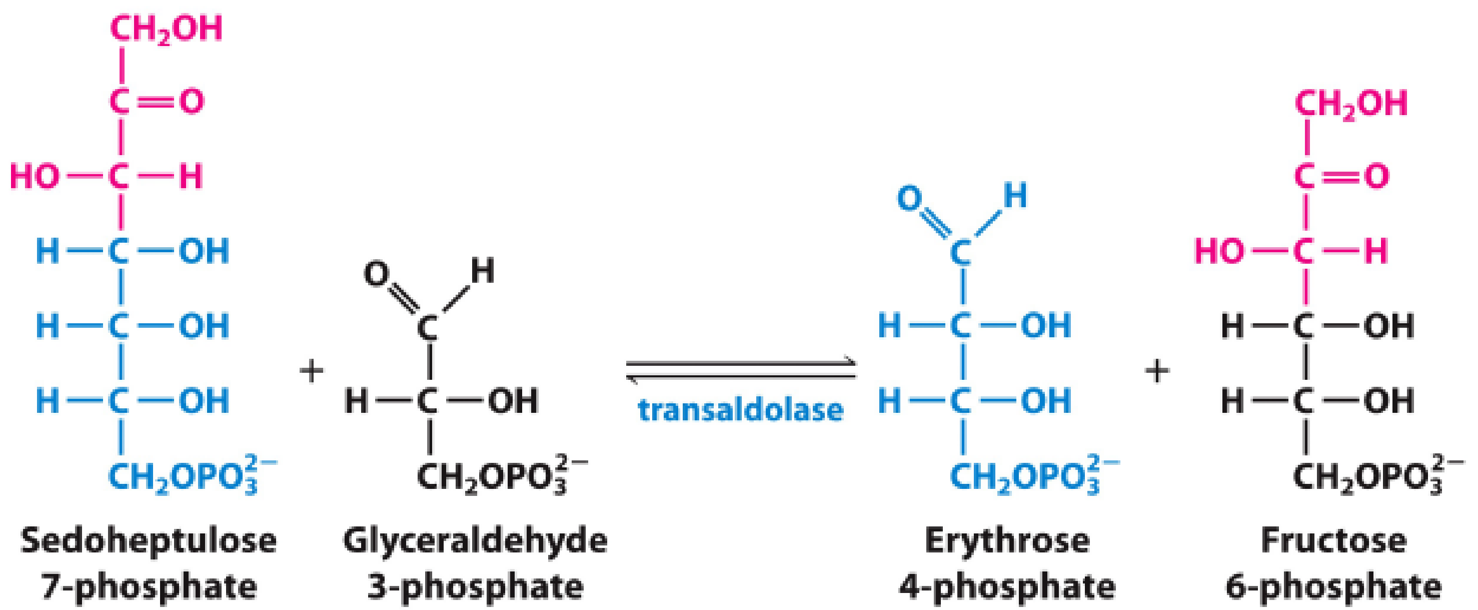


Figure 14-25
Lehninger Principles of Biochemistry, Sixth Edition

To glucose 6-phosphate <u>or</u> glycolysis

7c + 3c 4c + 6c

PENTOSE PHOSPHATE PATHWAY

Non-oxidative phase 2: reaction 4

Second transketolase reaction

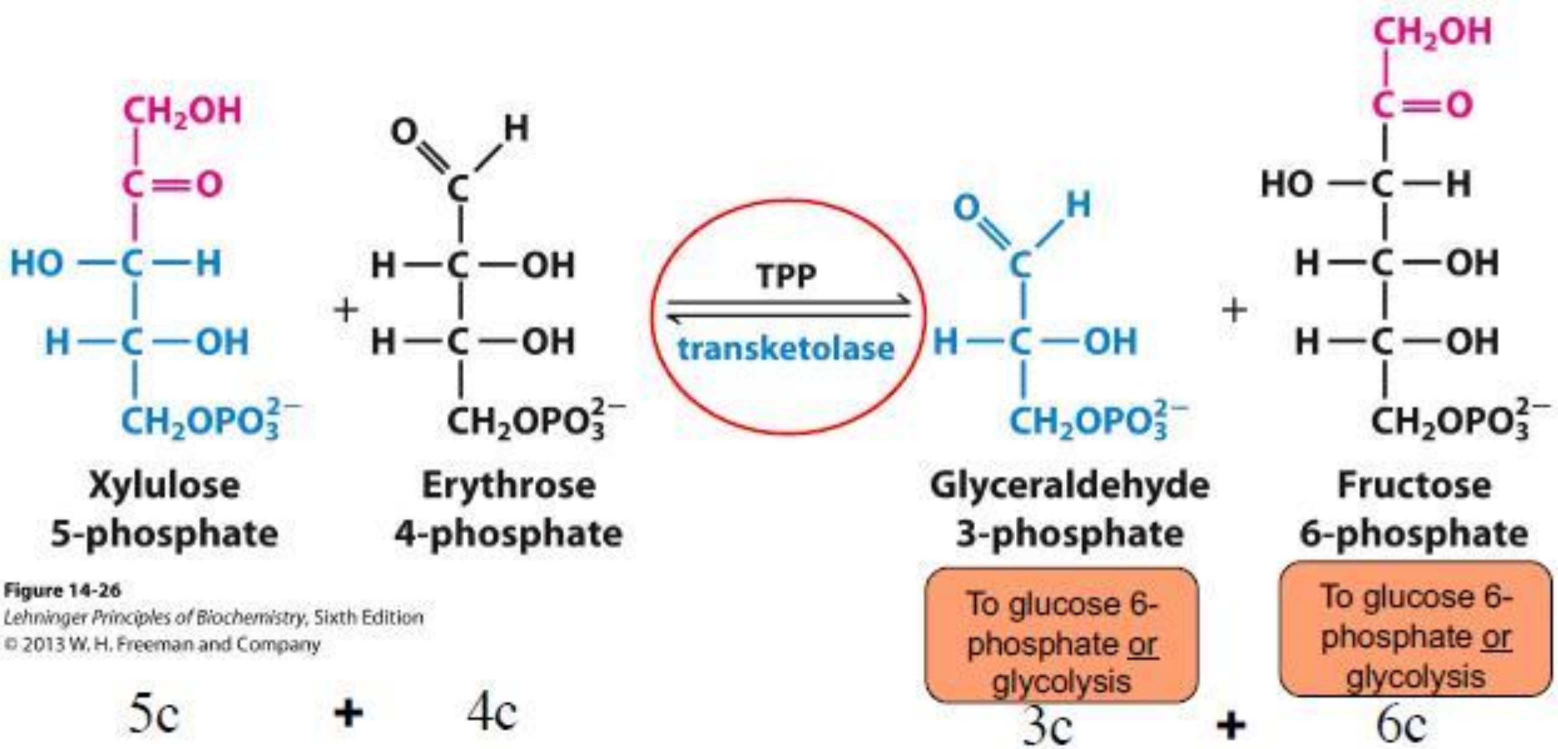


Figure 14-26
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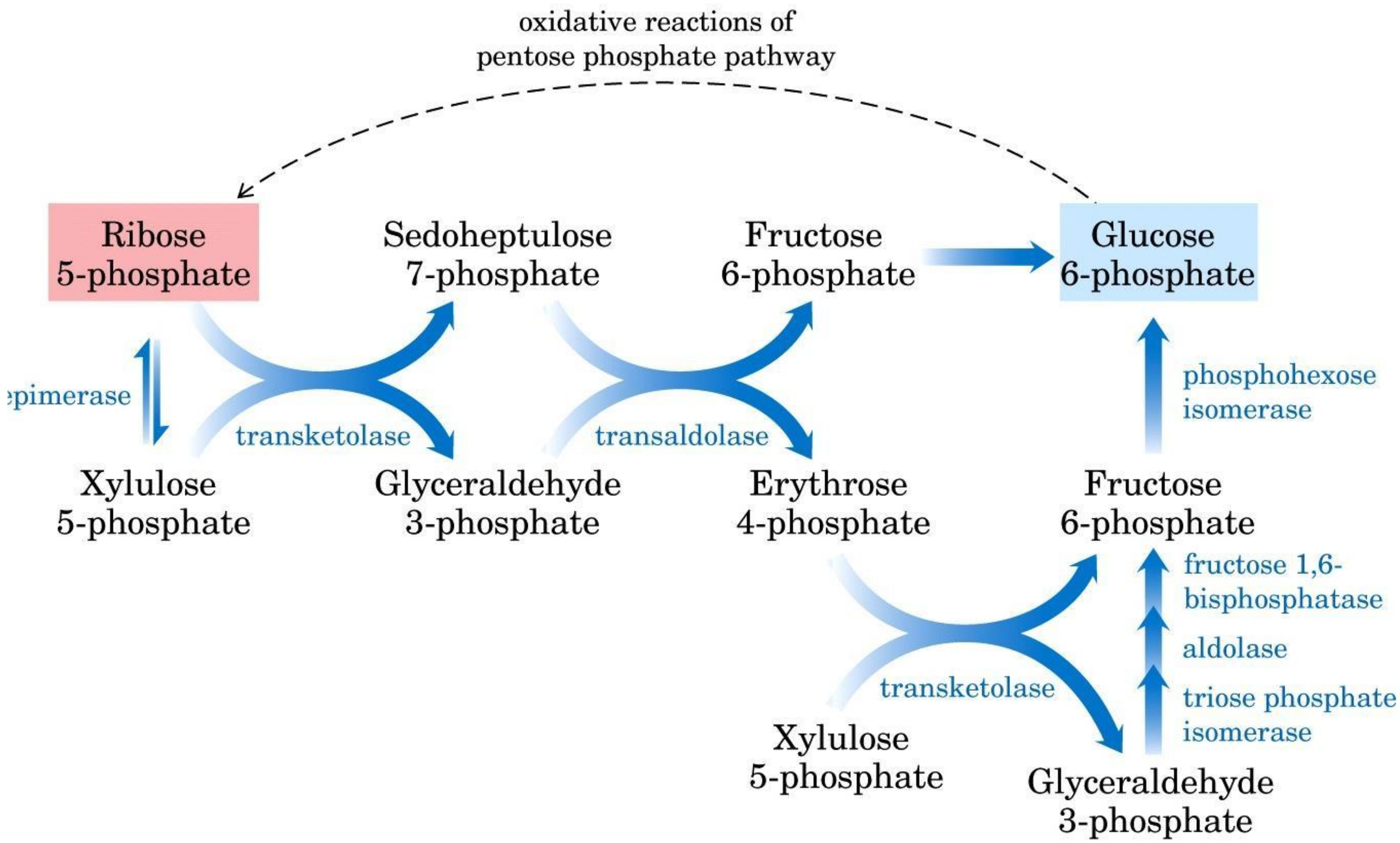
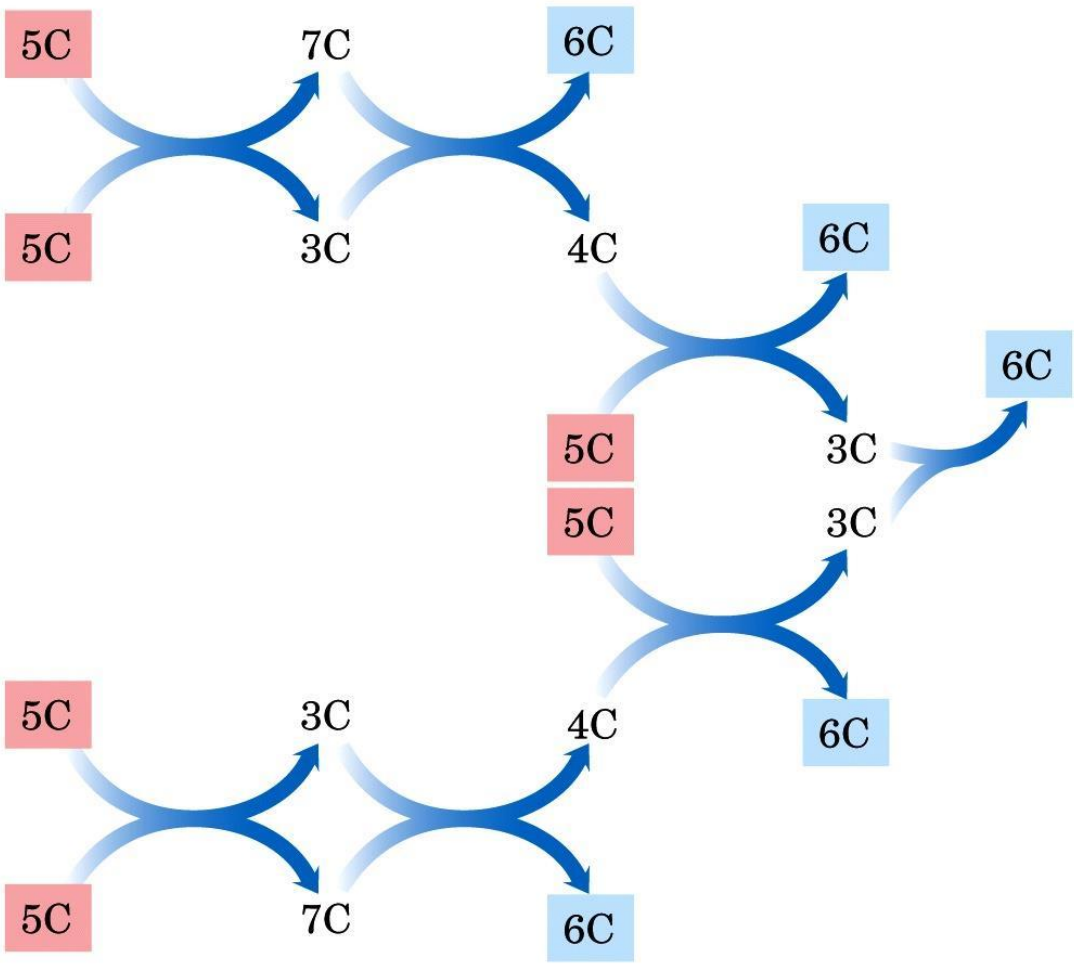
PENTOSE PHOSPHATE PATHWAY

To get this result, we need 3 ribulose-P to be converted into 1 ribose-P and 2 xylulose-P: Result: 2 fructose-P and 1 glyceraldehyde-P



PENTOSE PHOSPHATE PATHWAY

6 C5 → 5 C6



PENTOSE PHOSPHATE PATHWAY

Interconversion in the shunt:

2 Xyl-P (5) + 2 Rib-P (5) → **2 F6P** (6) + 2 Er-P (4)

2 Xyl-P (5) + 2 Er-P (4) → 2 GAP (3) + **2 F6P** (6)

2 GAP (3) → F-1,6 BP

F-1,6-BP + H_2O → **F6P** (6) + P_i

Total 6 C5 + H_2O → 5 C6 + P_i

PENTOSE PHOSPHATE PATHWAY

The nonoxidative phase regenerates G6P from R5P

It is used in tissues requiring more NADPH than R5P, such as the liver and adipose tissue.

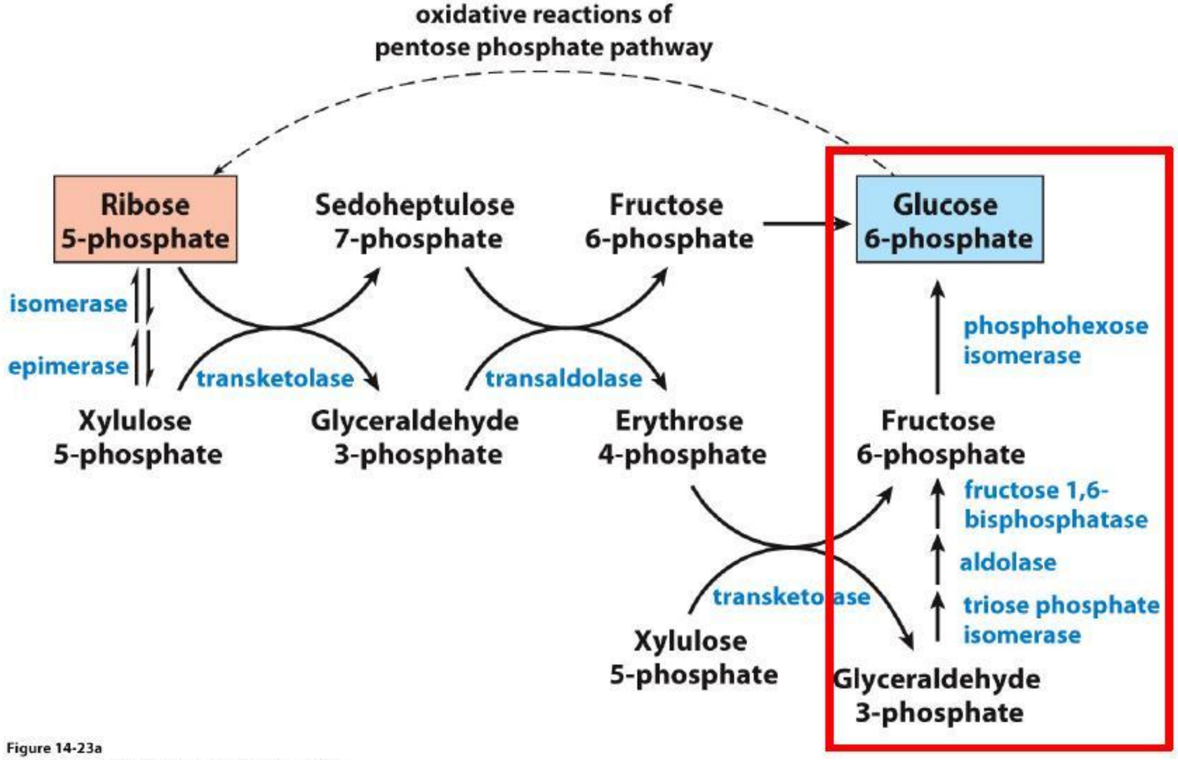


Figure 14-23a
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PENTOSE PHOSPHATE PATHWAY

Alternative sources of NADPH

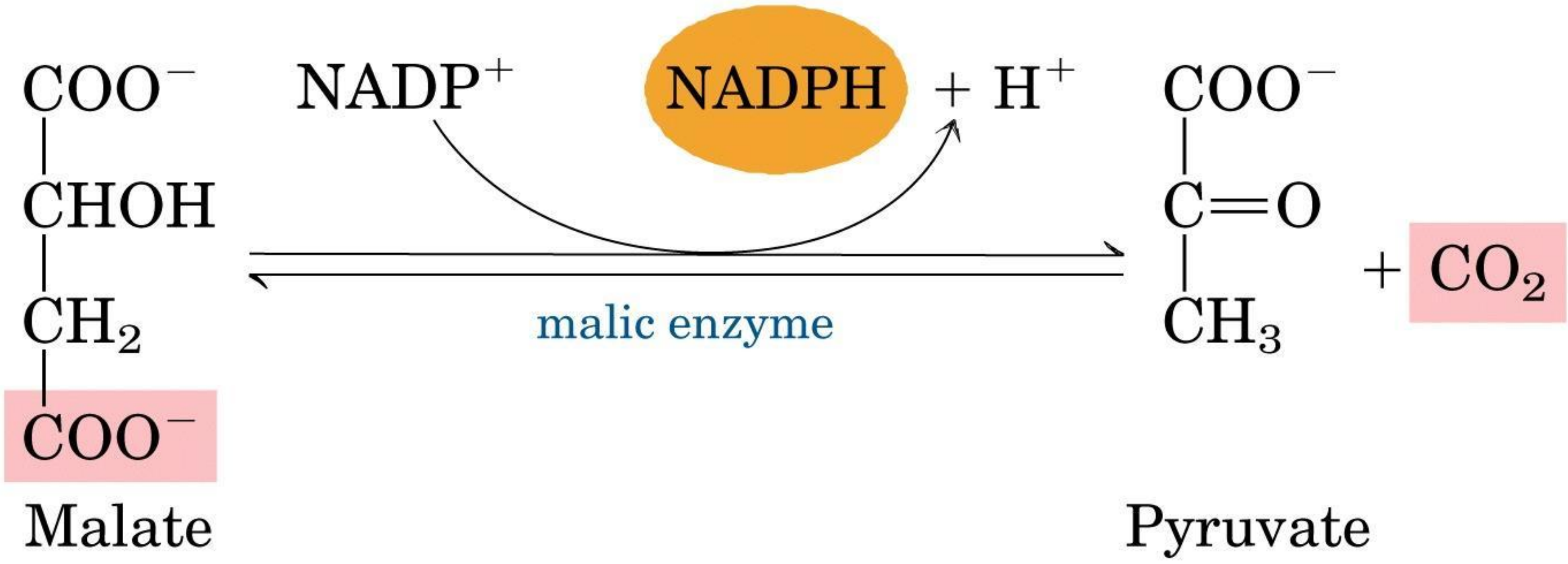
- Residual activity of **glucose-6-P dehydrogenase**:
- **Cytosolic isocitrate dehydrogenase** requires NADP and produces NADPH
- **Nicotinamide nucleotide transhydrogenase**, a mitochondrial enzyme focused on intramitochondrial oxidation:

$$NAD(H) \leftrightarrow NADP(H)$$

PENTOSE PHOSPHATE PATHWAY

Alternative sources of NADPH:

- **Malic enzyme**



PENTOSE PHOSPHATE PATHWAY

Which oxidative decarboxylations require TPP?

- ONLY oxidative decarboxylation of α-ketoacids:

  - pyruvate DH, α-ketoglutarate DH, branched chain α-ketoacid DH

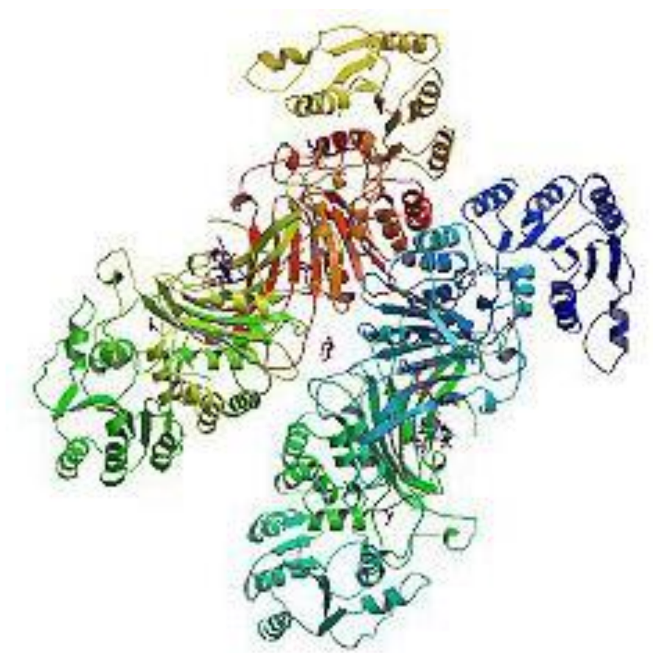
- NOT oxidative decarboxylation of hydroxy acids:

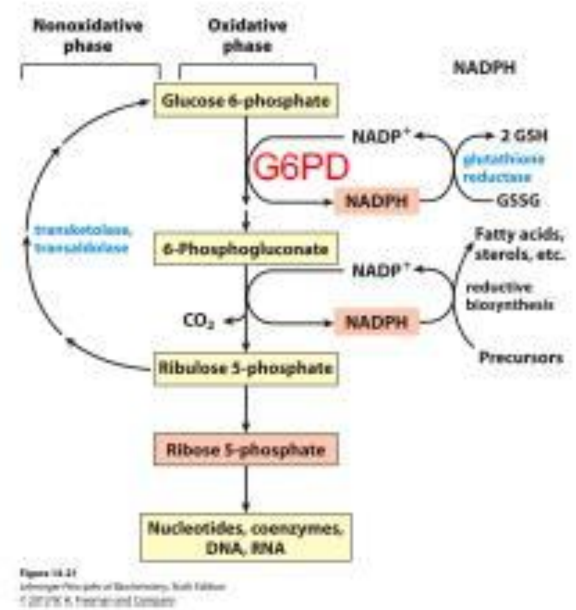
  - malic enzyme, isocitrate dehydrogenase, 6-P-gluconate DH

REGULATION OF PENTOSE PHOSPHATE PATHWAY

Rate-limiting step: Glucose-6-phosphate dehydrogenase (oxidative phase)

The rate is controlled by substrate availability: $NADP^+$ allosterically regulates glucose-6-phosphate dehydrogenase.





HORMONES & PENTOSE PHOSPHATE PATHWAY

Mainly act by gene expression

Insulin induces PPP enzymes (G6P dehydrogenase)

Glucagon represses PPP enzymes

By activating fatty acid and cholesterol biosynthesis that use NADPH, insulin decreases the $NADPH/NADP^+$ ratio, thus activating G6P dehydrogenase.

FUNCTIONS OF PENTOSE PHOSPHATE PATHWAY

Only oxidative phase: reducing power and pentoses

$$Glucose\text{-}6\text{-}P + 2\ NADP^+ + H_2O \rightarrow Ribose\text{-}5\text{-}P + CO_2 + 2\ (NADPH + H^+)$$

Oxidative + non-oxidative phase: reducing power

$$6\ glucose\text{-}6\text{-}P + 12\ NADP^+ + 7\ H_2O \rightarrow 6\ CO_2 + 5\ glucose\text{-}6\text{-}P + P_i + 12\ (NADPH + H^+)$$

That is:

$$glucose\text{-}6\text{-}P + 12\ NADP^+ + 7\ H_2O \rightarrow 6\ CO_2 + P_i + 12\ (NADPH + H^+)$$

Only non-oxidative phase (backwards): pentoses

$$5\ glucose\text{-}6\text{-}P + ATP \rightarrow 6\ ribose\text{-}5\text{-}P + ADP$$

Only non-oxidative phase (forward): pentose catabolism

$$Ribose\text{-}5\text{-}P \rightarrow glycolytic\ intermediates$$

USE OF NADPH

Reducing power for biosynthesis (fatty acids, cholesterol).

Hydroxylation reactions (several biosynthetic processes; catabolism of xenobiotics).

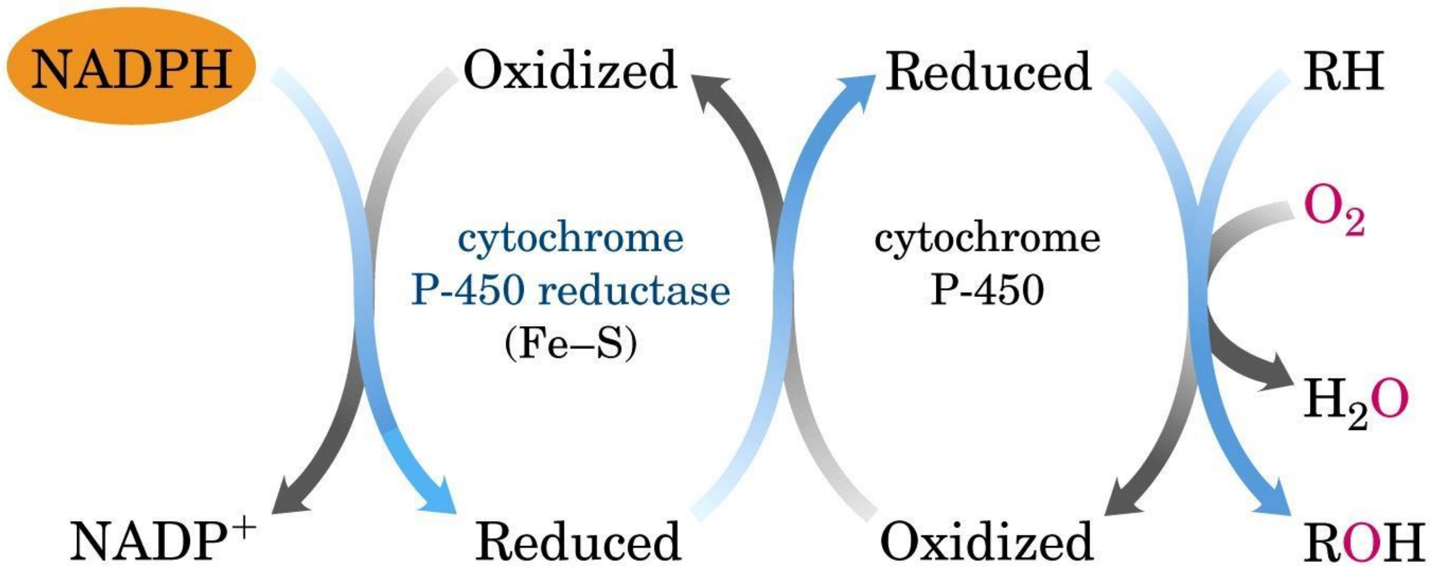
Reduction of glutathione for detoxification of hydroperoxides.

USE OF NADPH

Hydroxylation reactions (mono-oxygenase).

Other reductants:

- α-ketoglutarate (proline hydroxylation)
- tetrahydrobiopterin (catecholamines hydroxylation)



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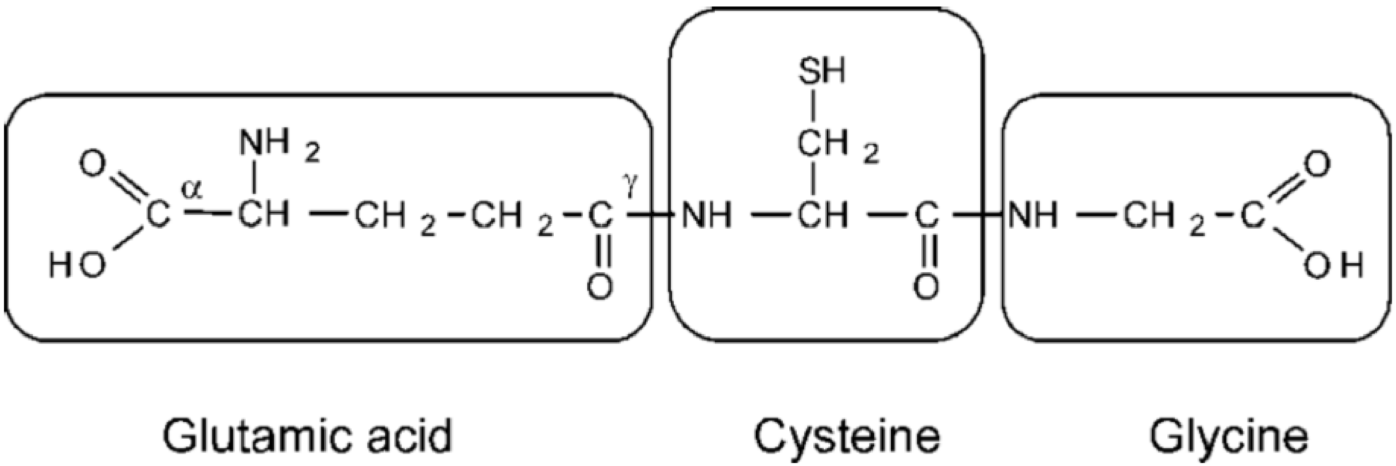
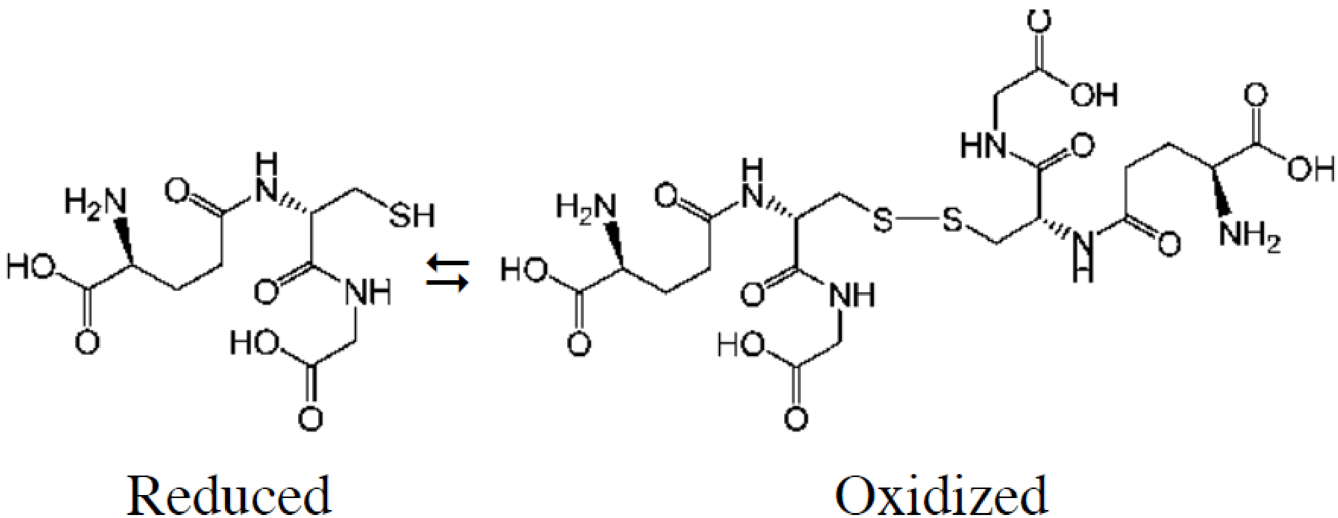
USE OF NADPH

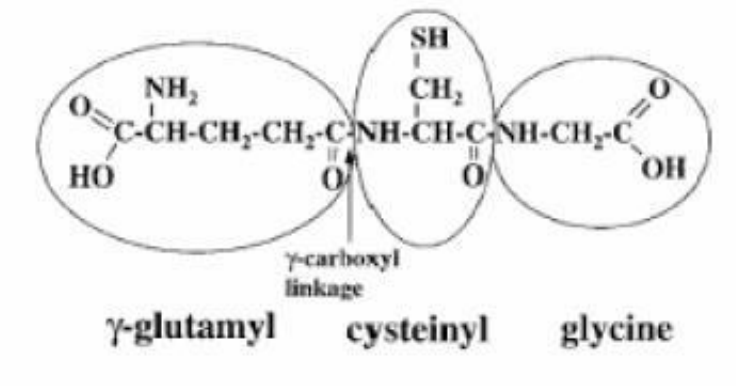
Glutathione

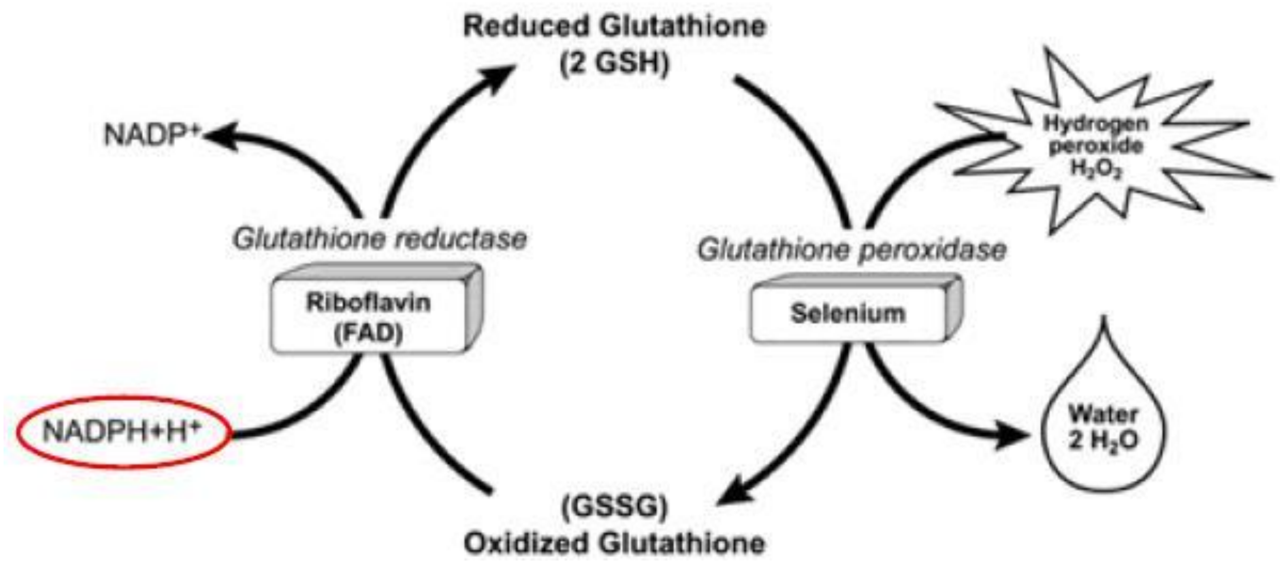




USE OF NADPH

Glutathione





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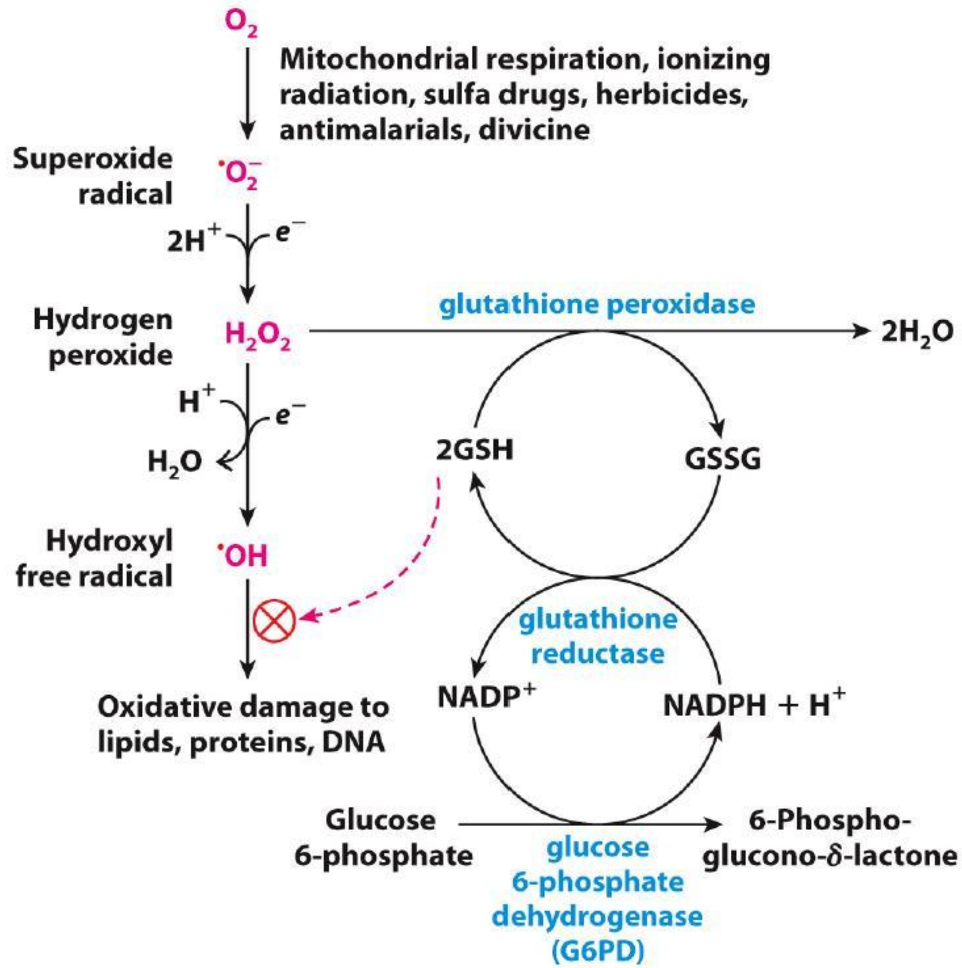
USE OF NADPH

Glutathione: especially important in erythrocytes and brain.



Box 14-4 Figure 1
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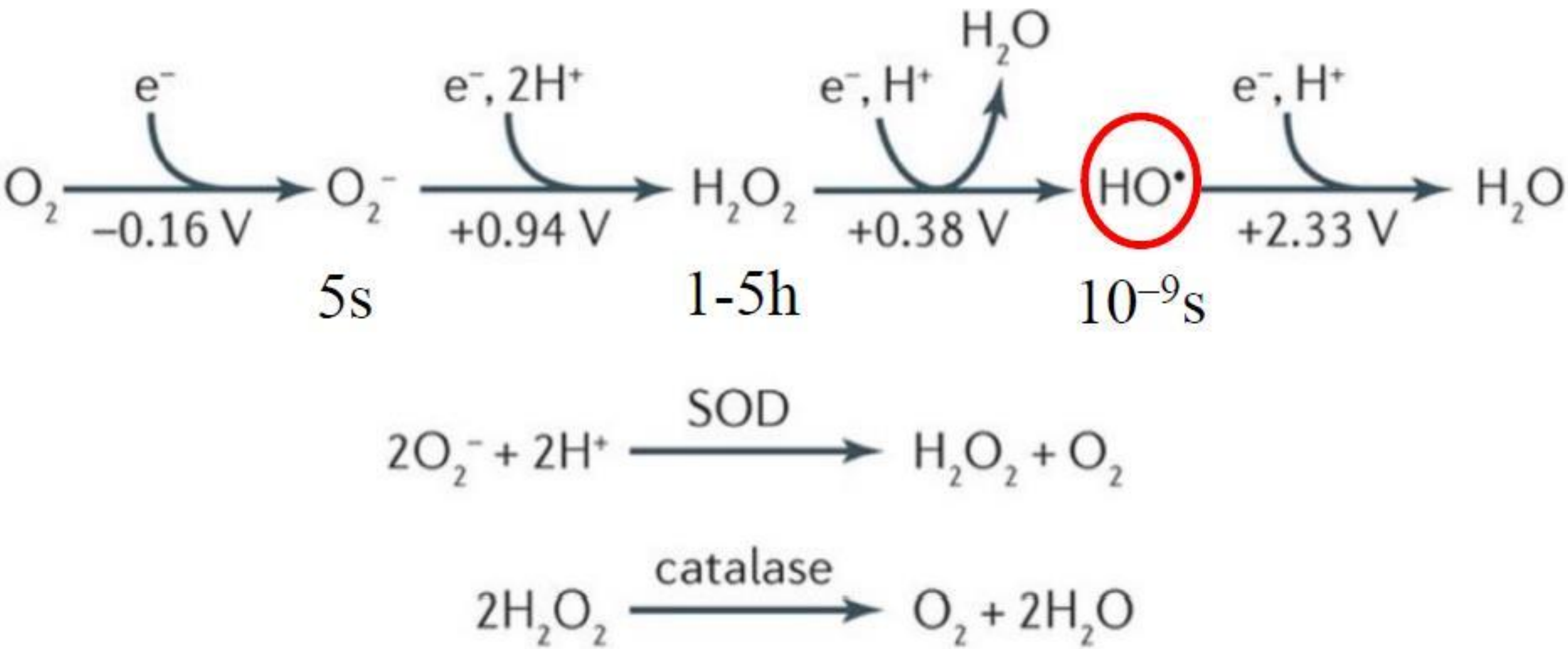
USE OF NADPH

Glutathione: defence against ROS.



USE OF NADPH

Glutathione

- Erythrocytes: full of iron and oxygen

Fenton reaction:

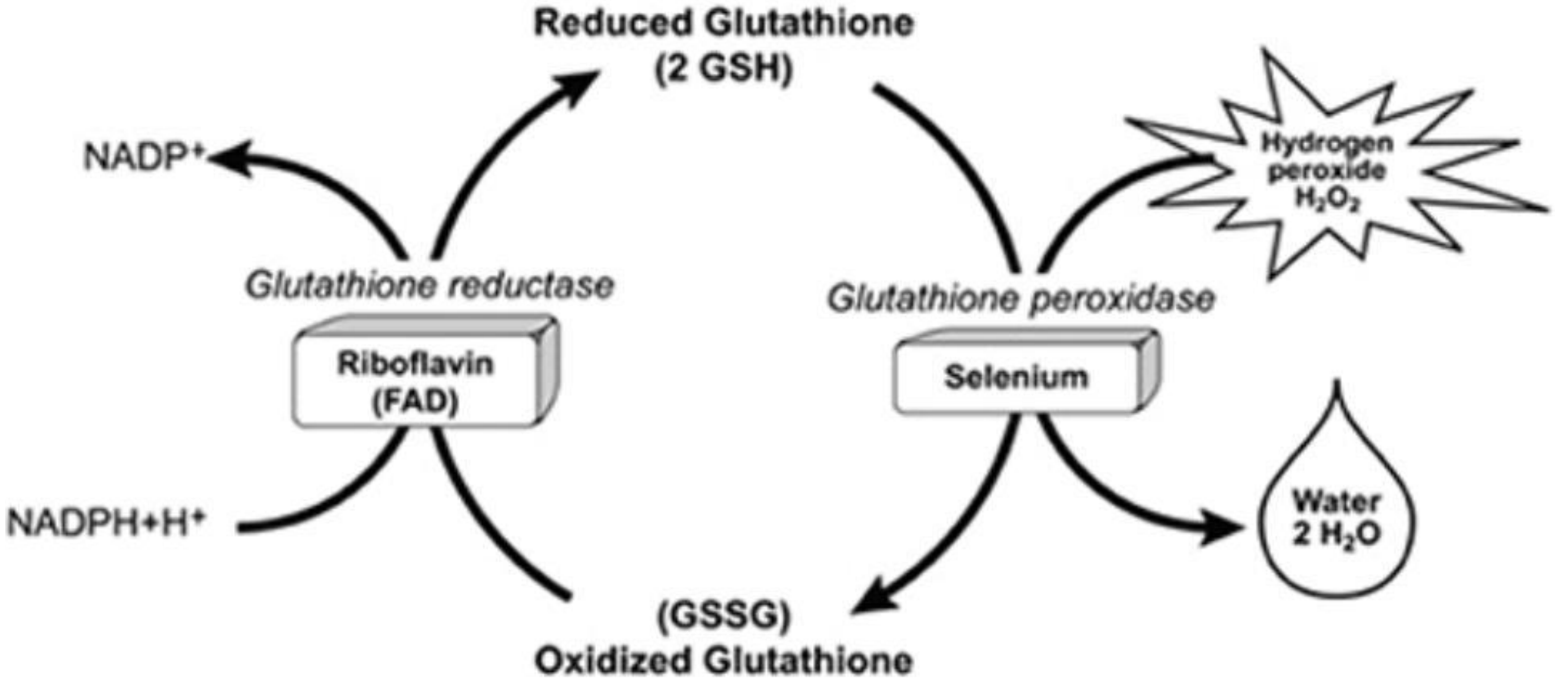
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$$

${}^{\bullet}OH$ (hydroxyl radical) most damaging of the ROS

- Brain is the tissue most active in aerobic metabolism. ROS may make important contributions to Alzheimer's disease.

USE OF NADPH

Glutathione: defence against ROS.



selenocysteine

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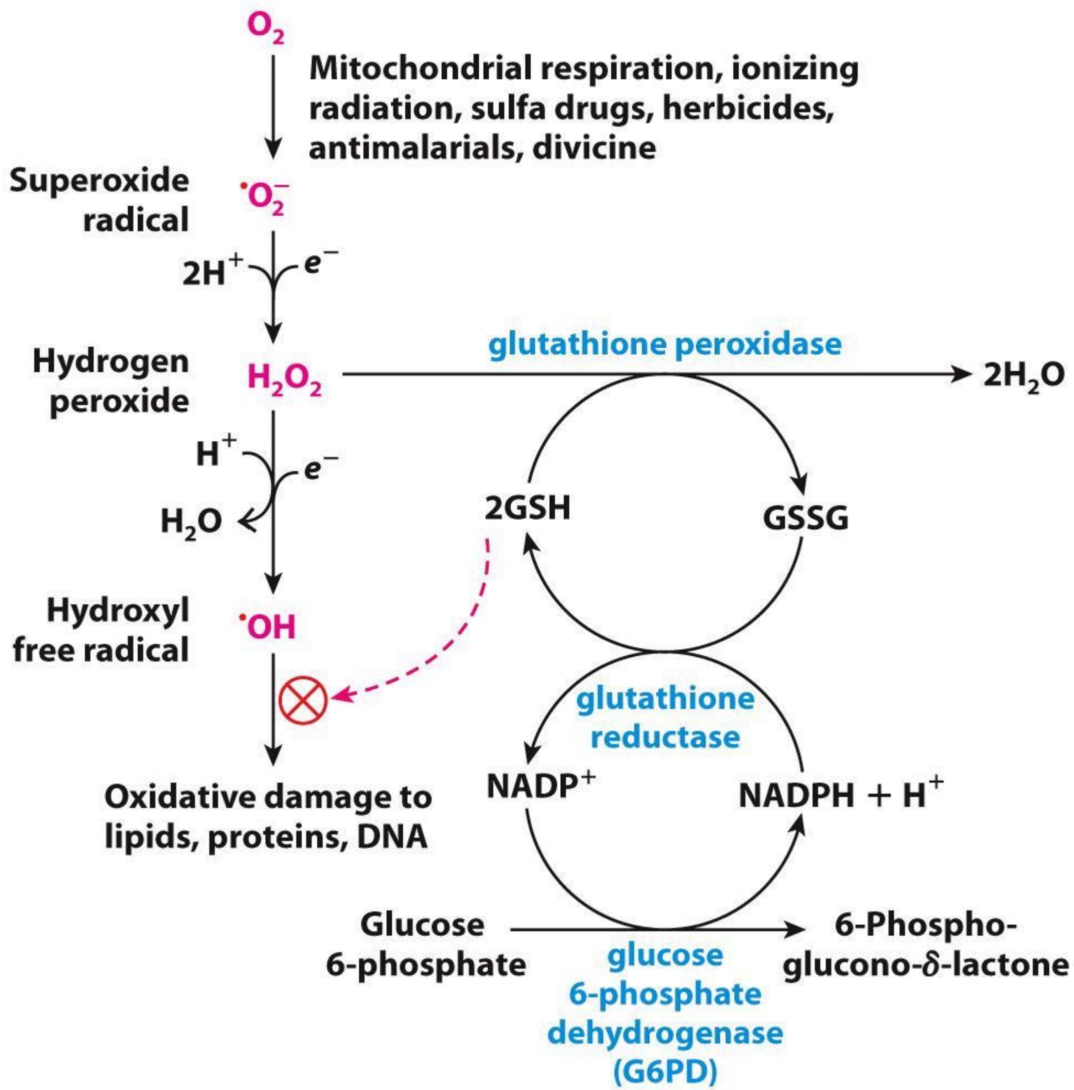
GLUCOSE6P DEHYDROGENASE DEFICIENCY



Box 14-4 Figure 1
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GLUCOSE6P DEHYDROGENASE DEFICIENCY

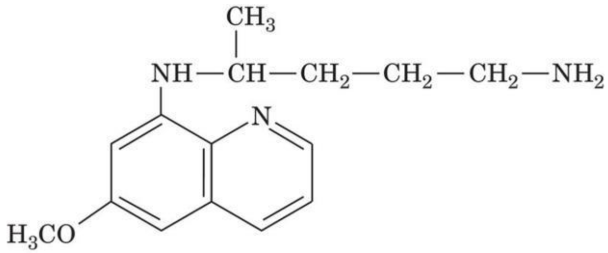
Erythrocytes:

- Formed in bone marrow; exist for 90-120 days; the old ones removed by liver and spleen.
- Role is to transport oxygen.
- Have no nuclei or mitochondria; cannot make or replace enzymes.
- Limited metabolism based on glycolysis and pentose phosphate pathway to produce energy.
- Glutathione important to deal with reactive oxygen species. NADPH important to replenish reduced glutathione.

GLUCOSE6P DEHYDROGENASE DEFICIENCY

Hemolytic anemia: red blood cells destroyed, often by oxidative processes

- Active hemoglobin (Fe^{2+}; ferrous) oxidized to inactive methemoglobin (Fe^{3+}; ferric)
- Increase in reactive oxygen species leads to depletion of reduced glutathione.
- Erythrocytes may lyse, releasing contents in bloodstream.
- Oxidation can be triggered by anti-malarial drugs (primaquine etc), fava beans.
- Can be treated with transfusions.



Primaquine

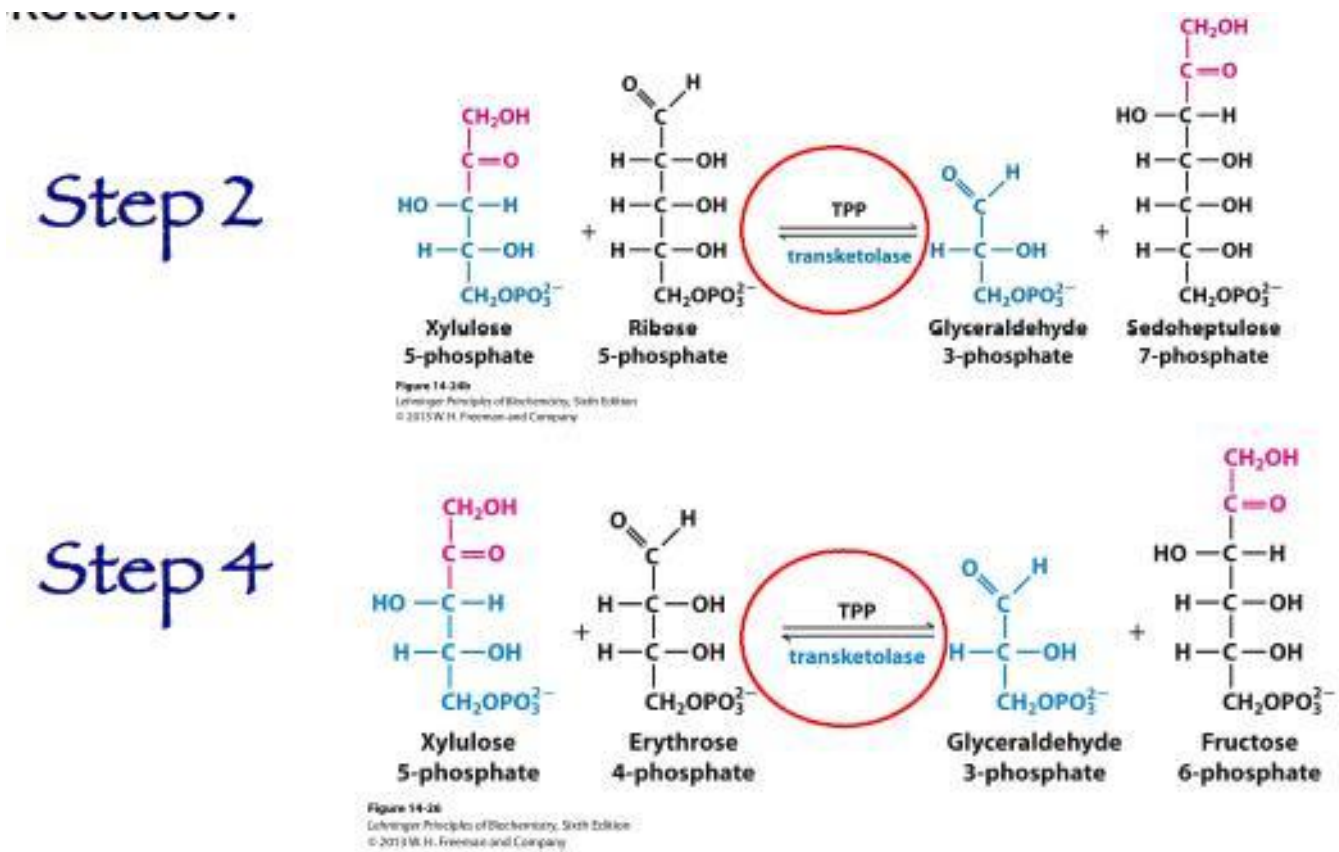
GLUCOSE6P DEHYDROGENASE DEFICIENCY

Most common human genetic deficiency:

- Affects ~400,000,000 people worldwide
- G6PD deficiency emerged > 10,000 years ago
- > 300 mutations known that decrease enzyme activity
- Sex-linked (X chromosome). Males affected most often
- Incidence coincides closely with regions affected by malaria
- Lowered activity of G6PD confers some protection from malaria
- Reduces suitability for hosting malarial parasite
- Carriers are very sensitive to anything that triggers increased oxidation in erythrocytes

PPP AND HUMAN DISEASES

Wernicke-Korsakoff syndrome results from a severe deficiency of thiamine, a component of the cofactor for transketolase



PPP AND HUMAN DISEASES

Wernicke-Korsakoff syndrome:

- PPP is slowed, attenuating NADPH production
- symptoms include memory loss, mental confusion and partial paralysis
- common in alcoholics: ethanol inhibits thiamine (vitamin B1) uptake

SYNTHESIS OF POLYSACCHARIDES

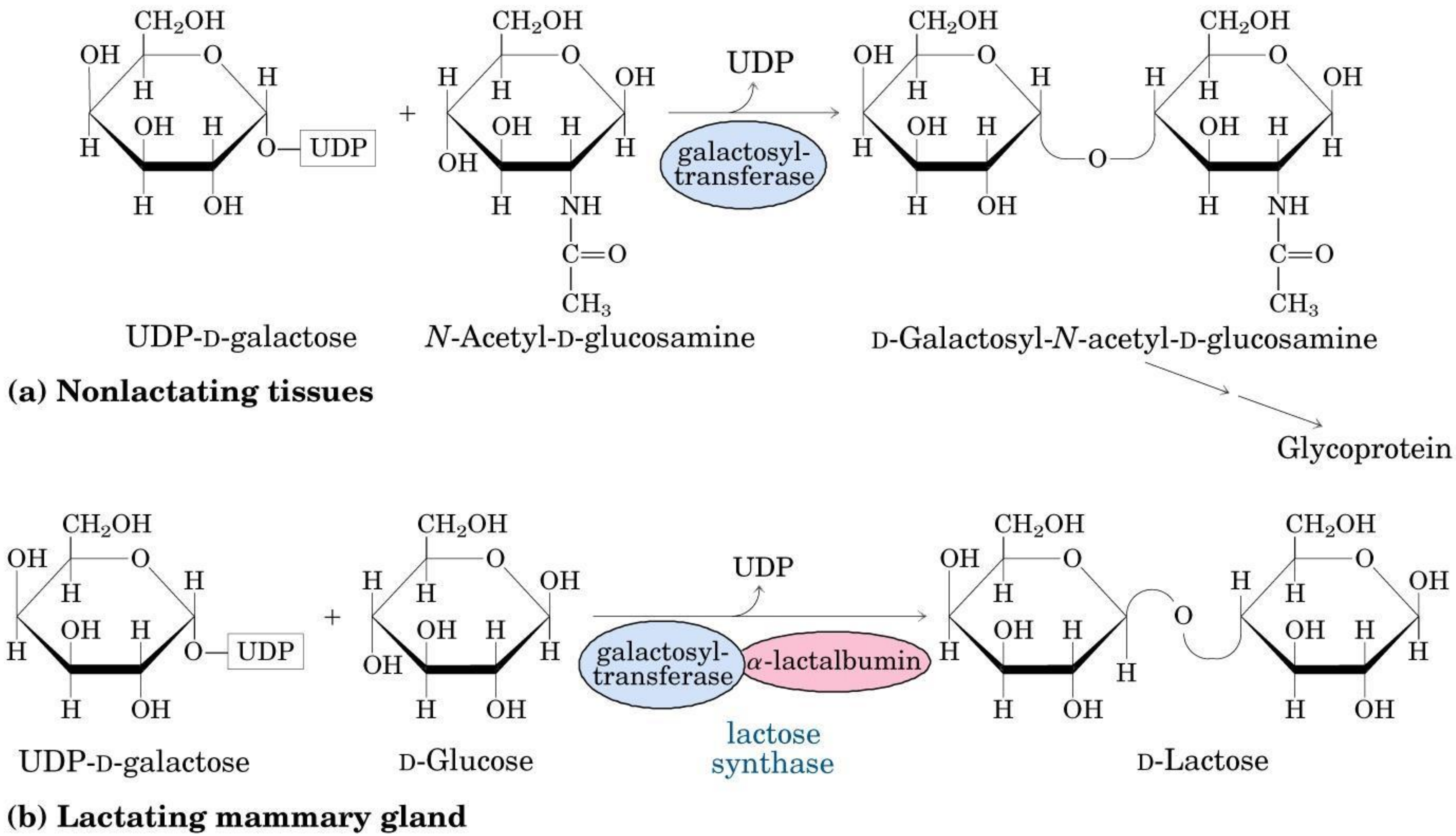
Synthesis of **mucopolysaccharides** (Hyaluronic acid, chondroitin sulfate)

Containing glucuronic acid, N-acetyl glucosamine or galactosamine etc.

Glycosyl transferases and UDP sugars are involved.

Synthesis of **glycoproteins** (Isoprenoid lipid dolichol transfers oligosaccharide chains to protein)

SYNTHESIS OF POLYSACCHARIDES



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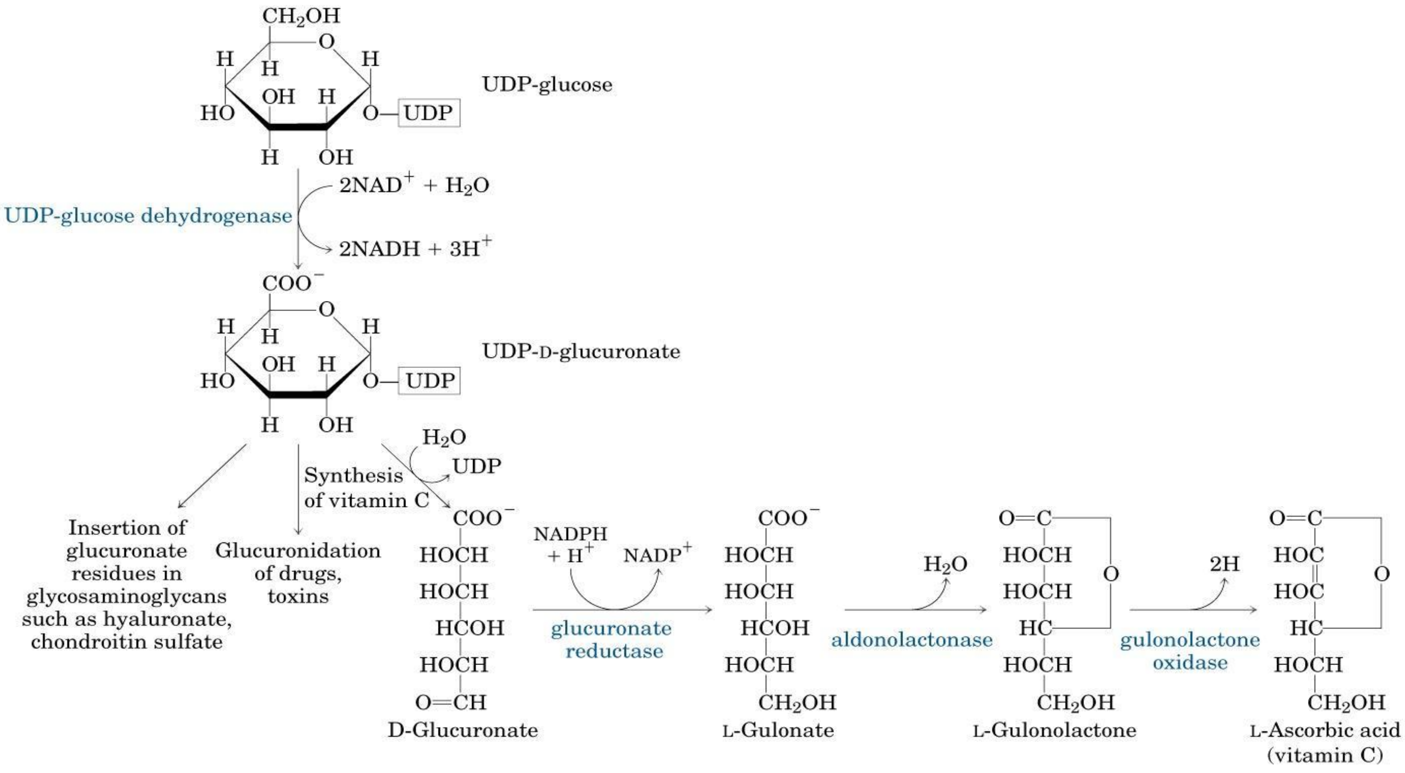
GLUCURONIC ACID

Component of mucopolysaccharides, as hyaluronic acid (= polymer of glucuronic acid + N-acetyl glucosamine).

Involved in the detoxification of physiological or xenobiotic compounds (e.g. bilirubin from heme catabolism).



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Credits:

Prof. Michele Di Foggia

Dipartimento di Scienze Biomediche e Neuromotorie – Sezione di Biochimica
via Irnerio 48
Telephone: +39 051 2094281

michele.difoggia2@unibo.it