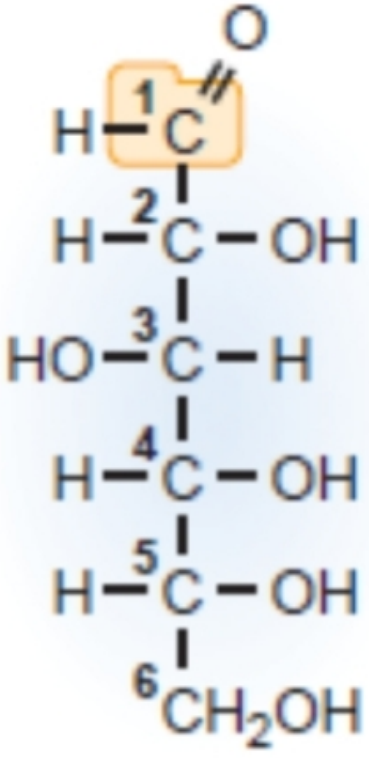
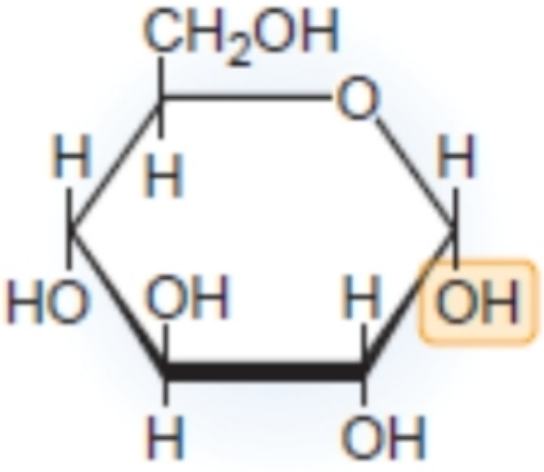
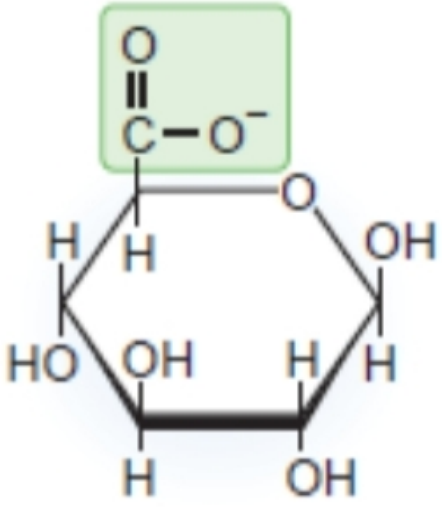
Oxidized Sugars



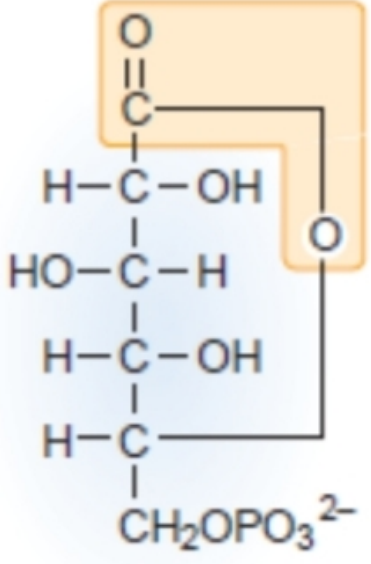
D-glucose

D-glucose

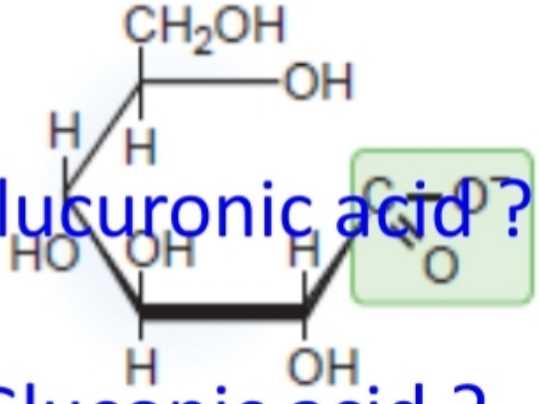




β-D-glucuronate



6-Phosphoglucono-δ-lactone

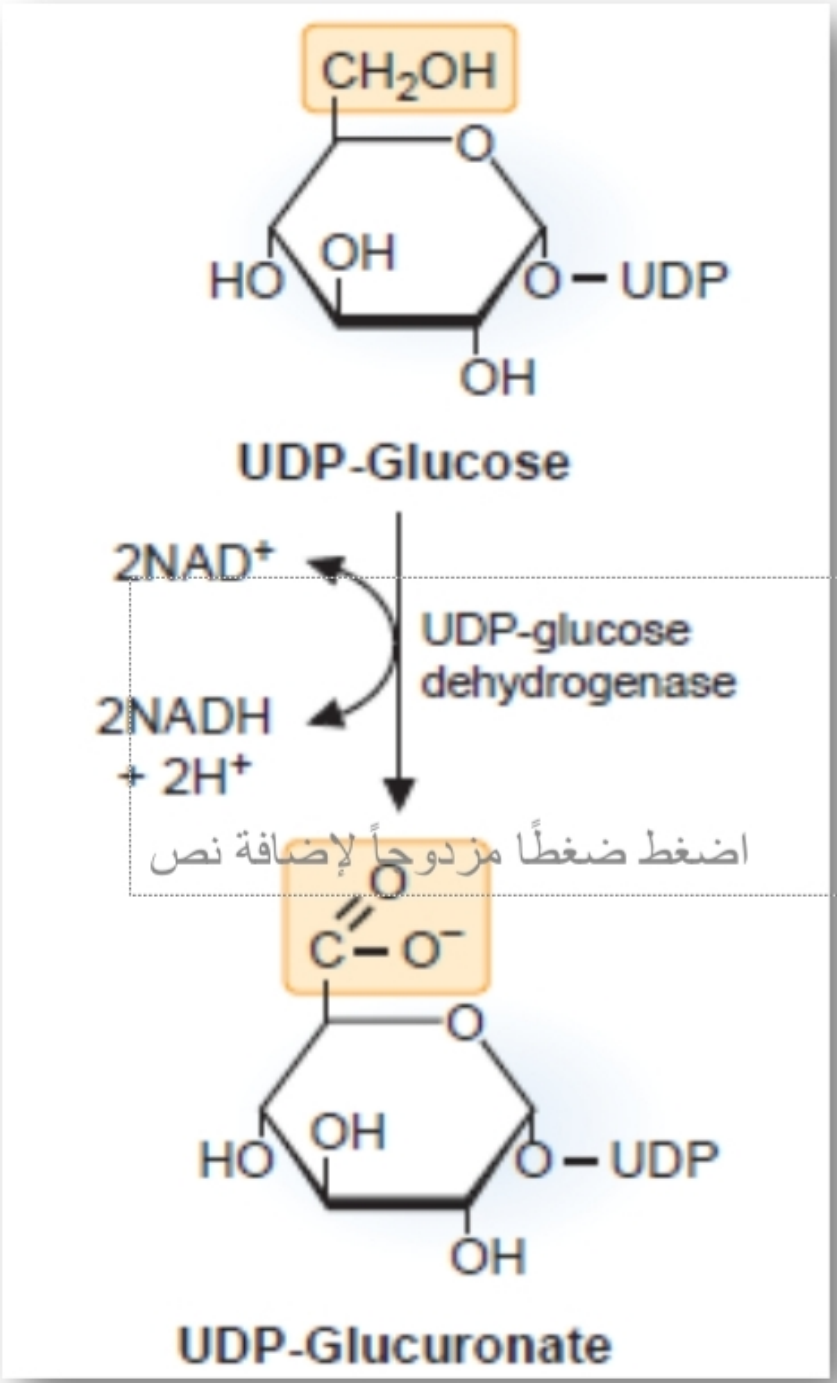


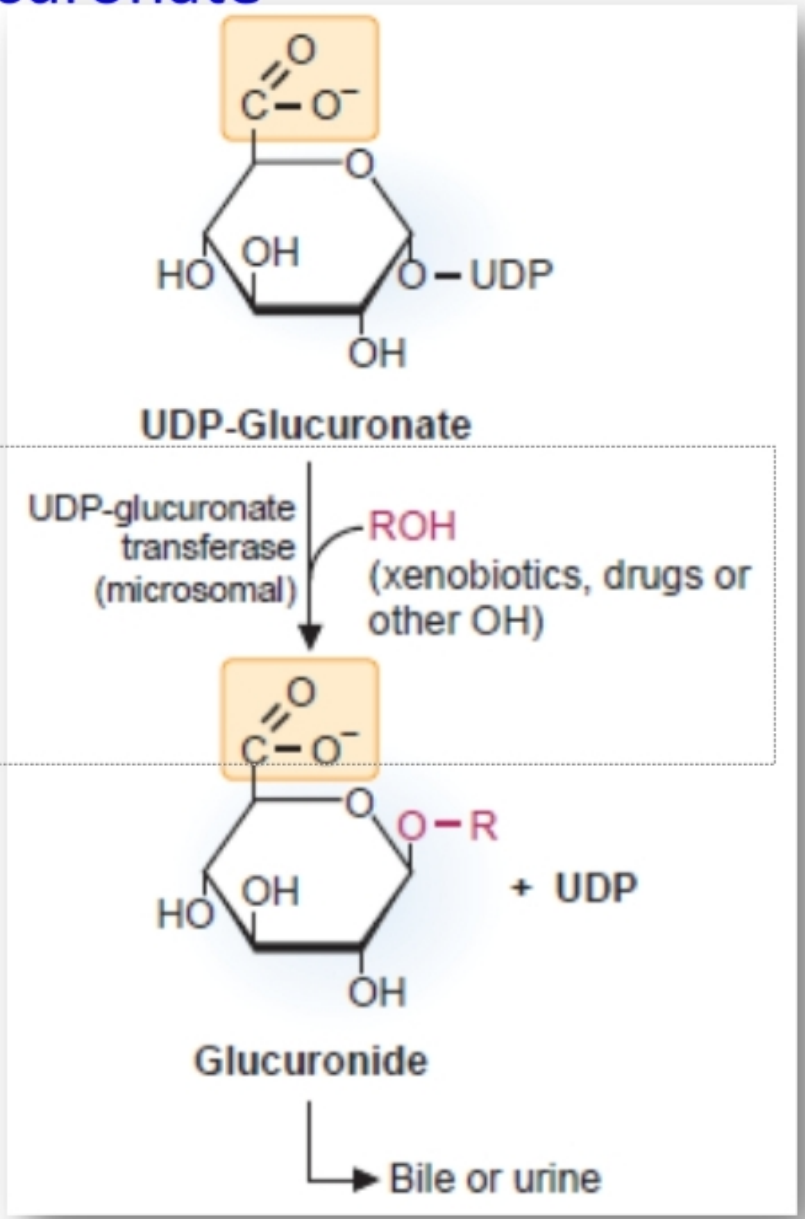
D-gluconate

Glucuronic acid ?

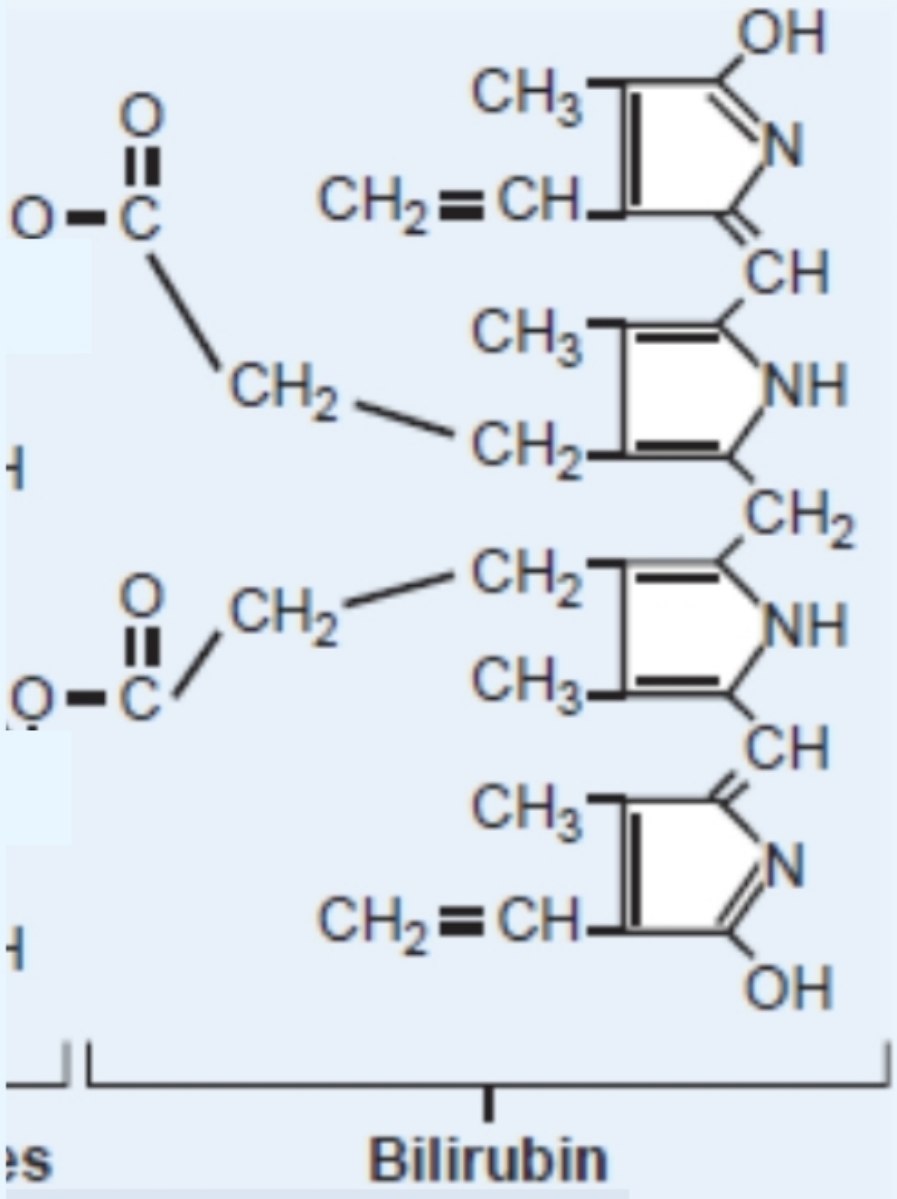
Gluconic acid ?

Formation and uses of glucuronate

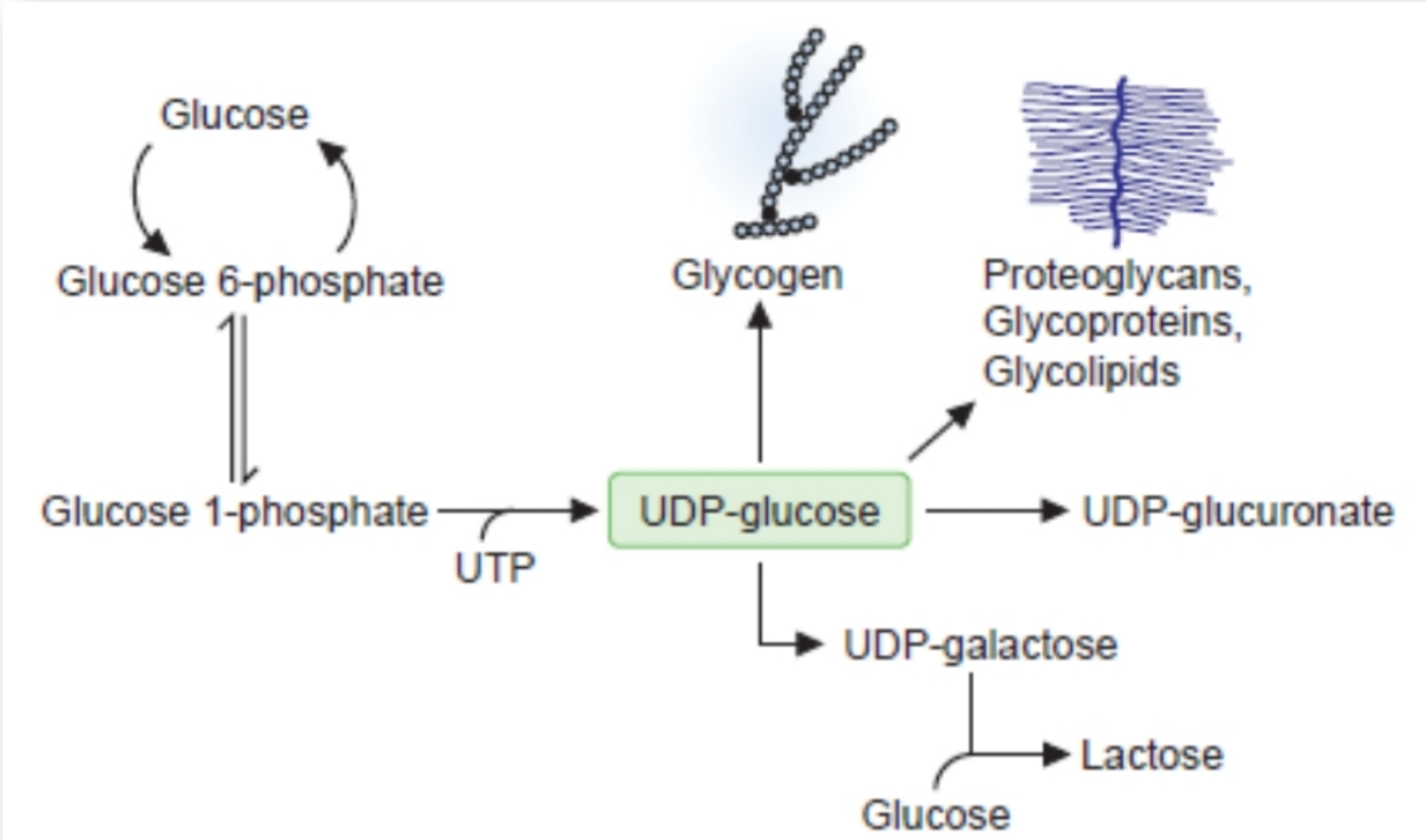




اضغط د


OH
CH3
N
O
C
CH2
CH
CH
CH3
NH
CH2
CH2
CH2
CH2
O
C
O
CH3
NH
CH3
CH
CH3
N
CH2
CH
OH
Bilirubin

The Role of UDP-Glucose in Metabolism

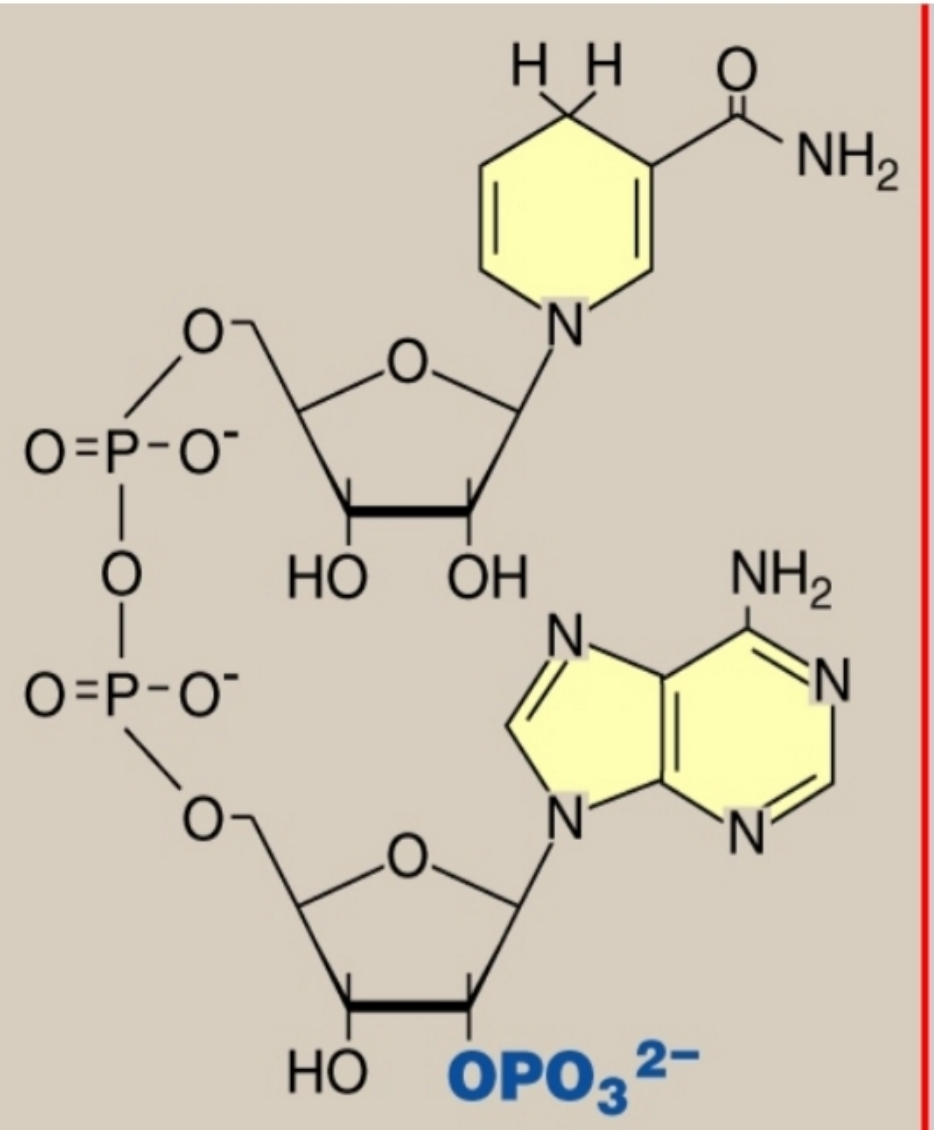


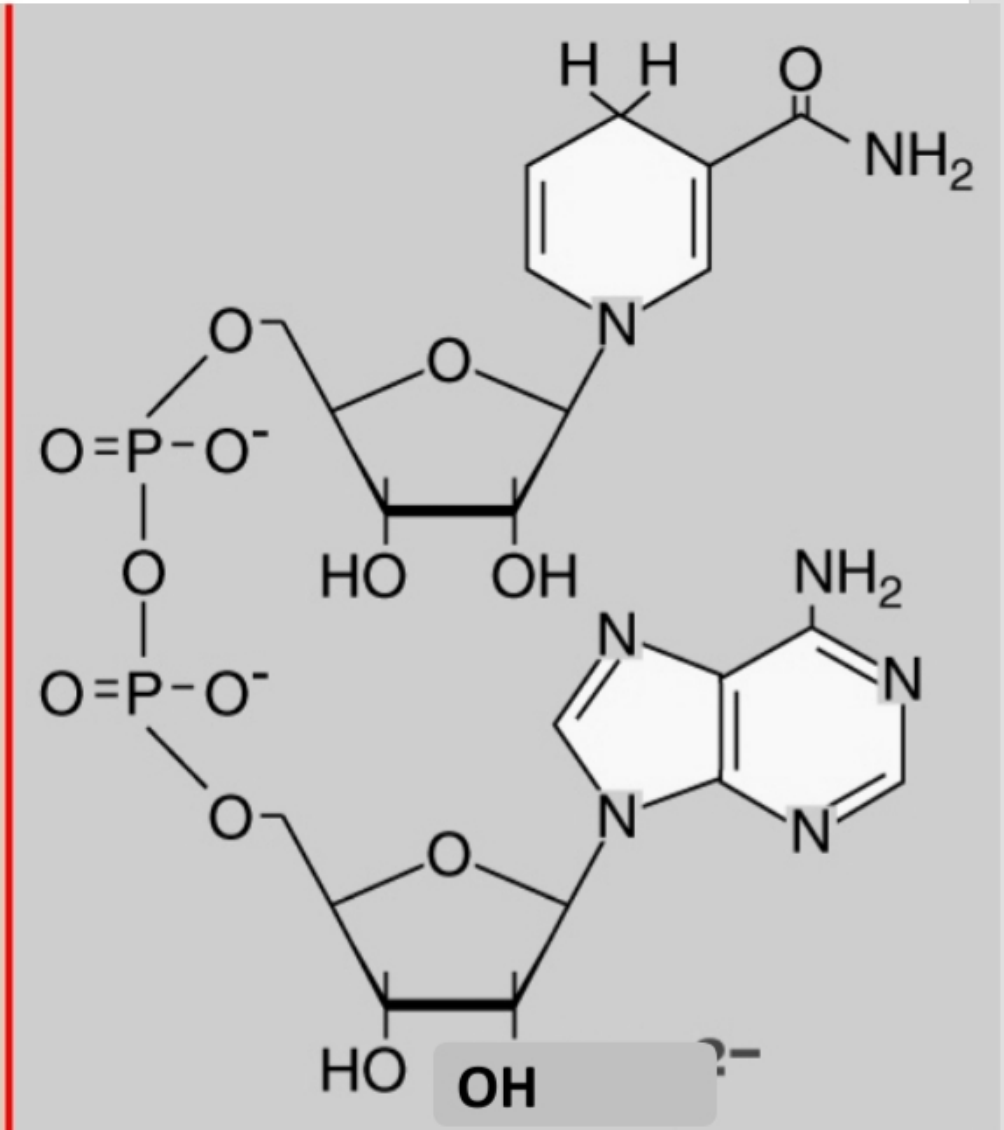
Pentose Phosphate Pathway (PPP)
or
Hexose Monophosphate Shunt

Lippincott's Chapter 13

Functions of the PPP

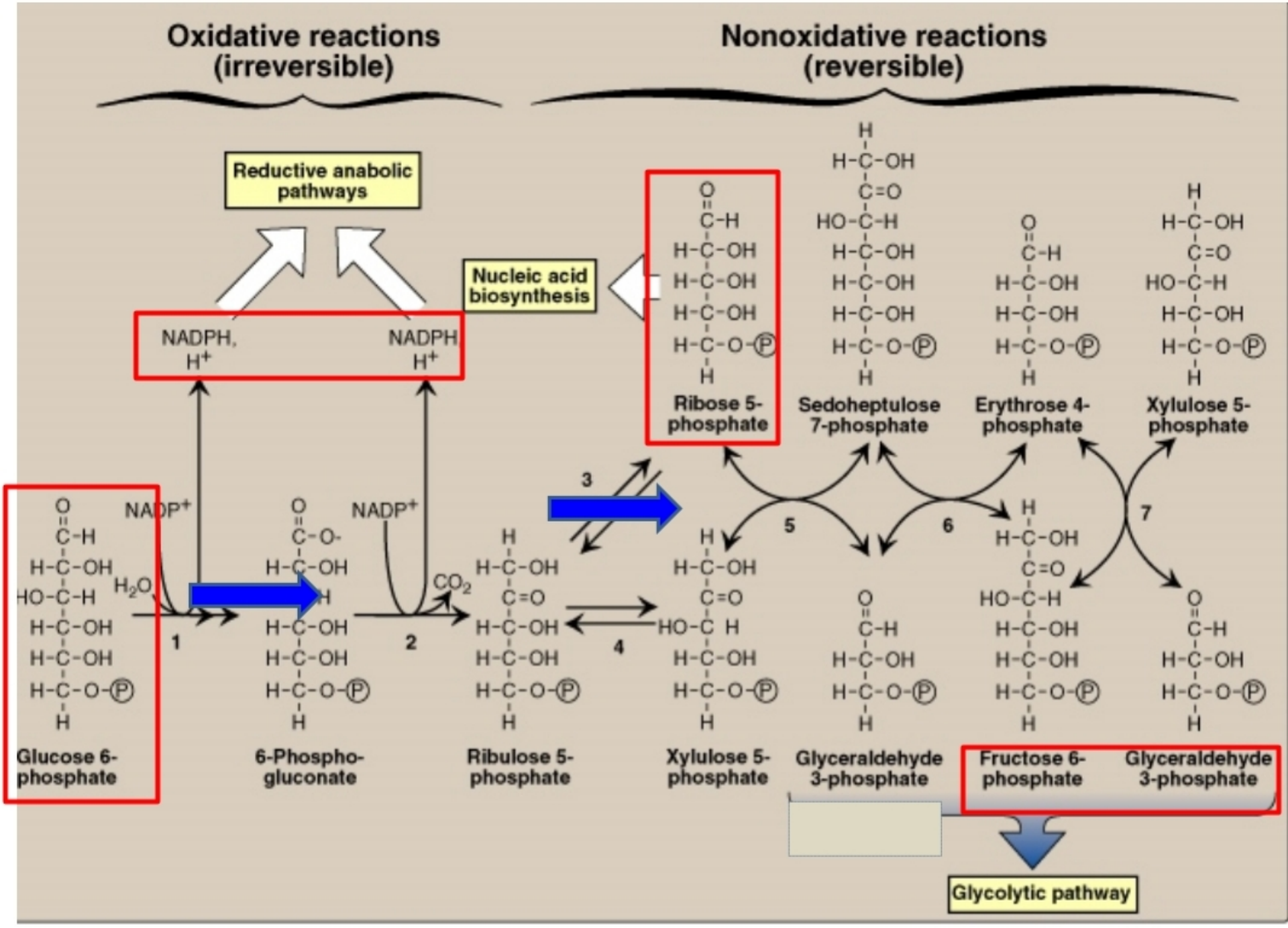
- Production of NADPH



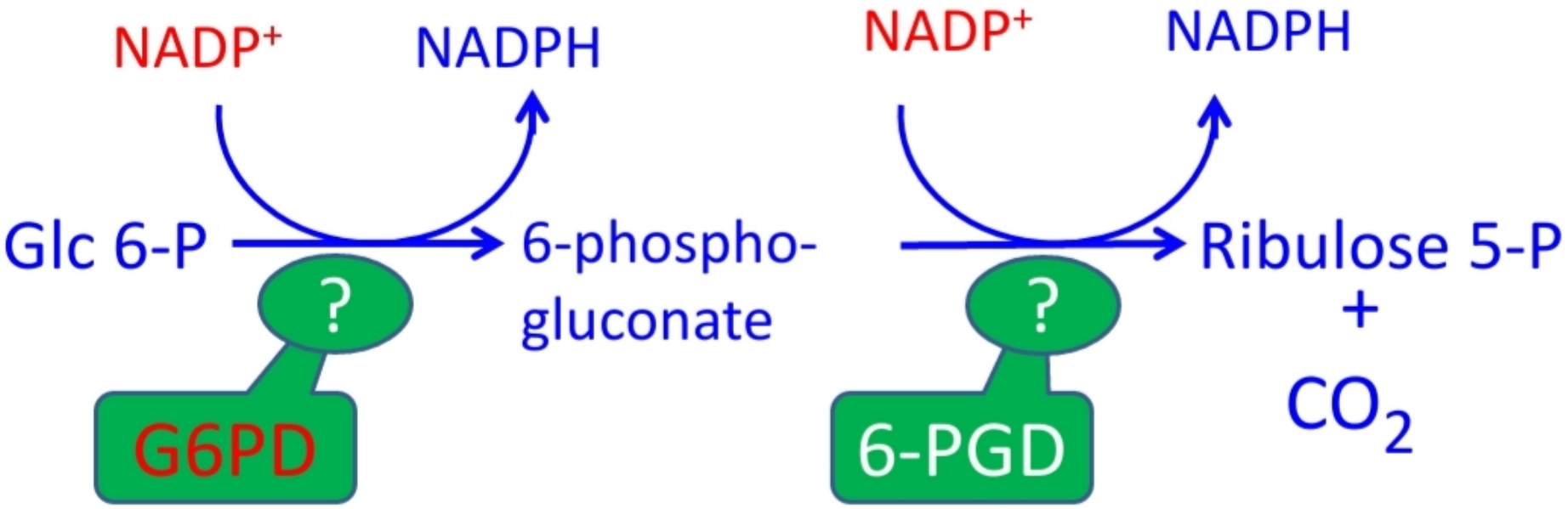


Functions of the PPP

- Production of NADPH
  - NADPH dependent biosynthesis of fatty acids
    - Liver, lactating mammary glands, adipose tissue
  - NADPH dependent biosynthesis of steroid hormones
    - Testes, ovaries, placenta, and adrenal cortex
  - Maintenance of Glutathione (GSH) in the reuced form in the RBCs
- Metabolism of five-carbon sugars (Pentoses)
  - Ribose 5-phosphate (nucleotide biosynthesis)
  - Metabolism of pentoses


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

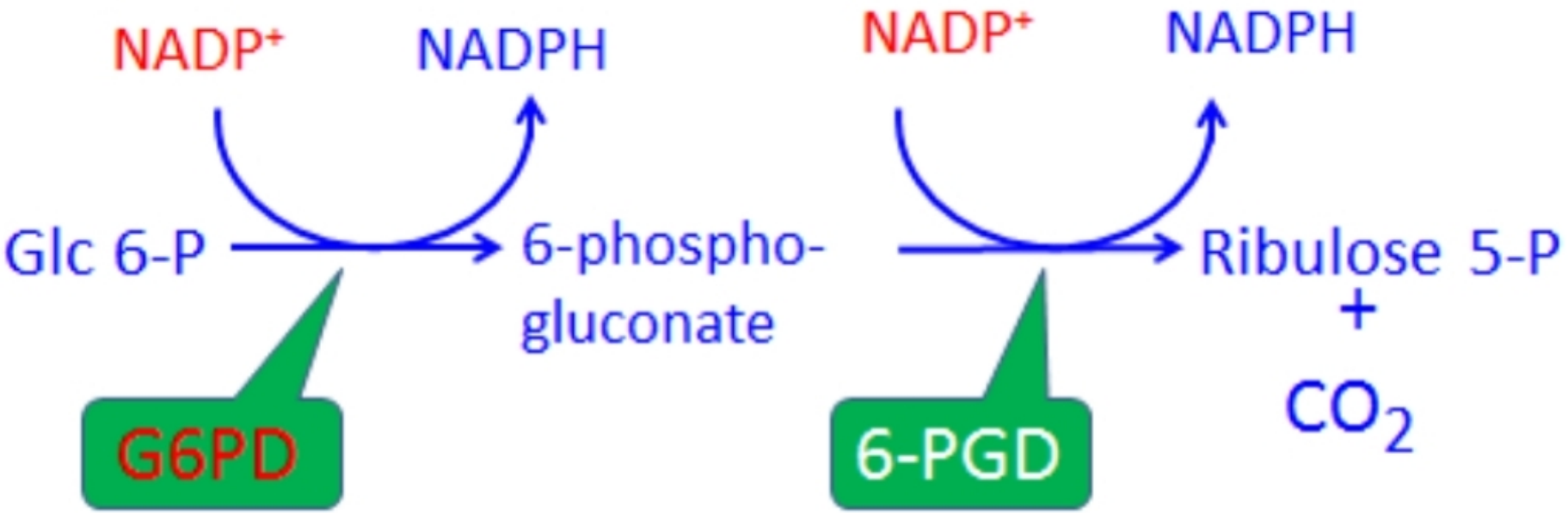
The Pentose Phosphate Pathway
The Oxidative Phase (irreversible)



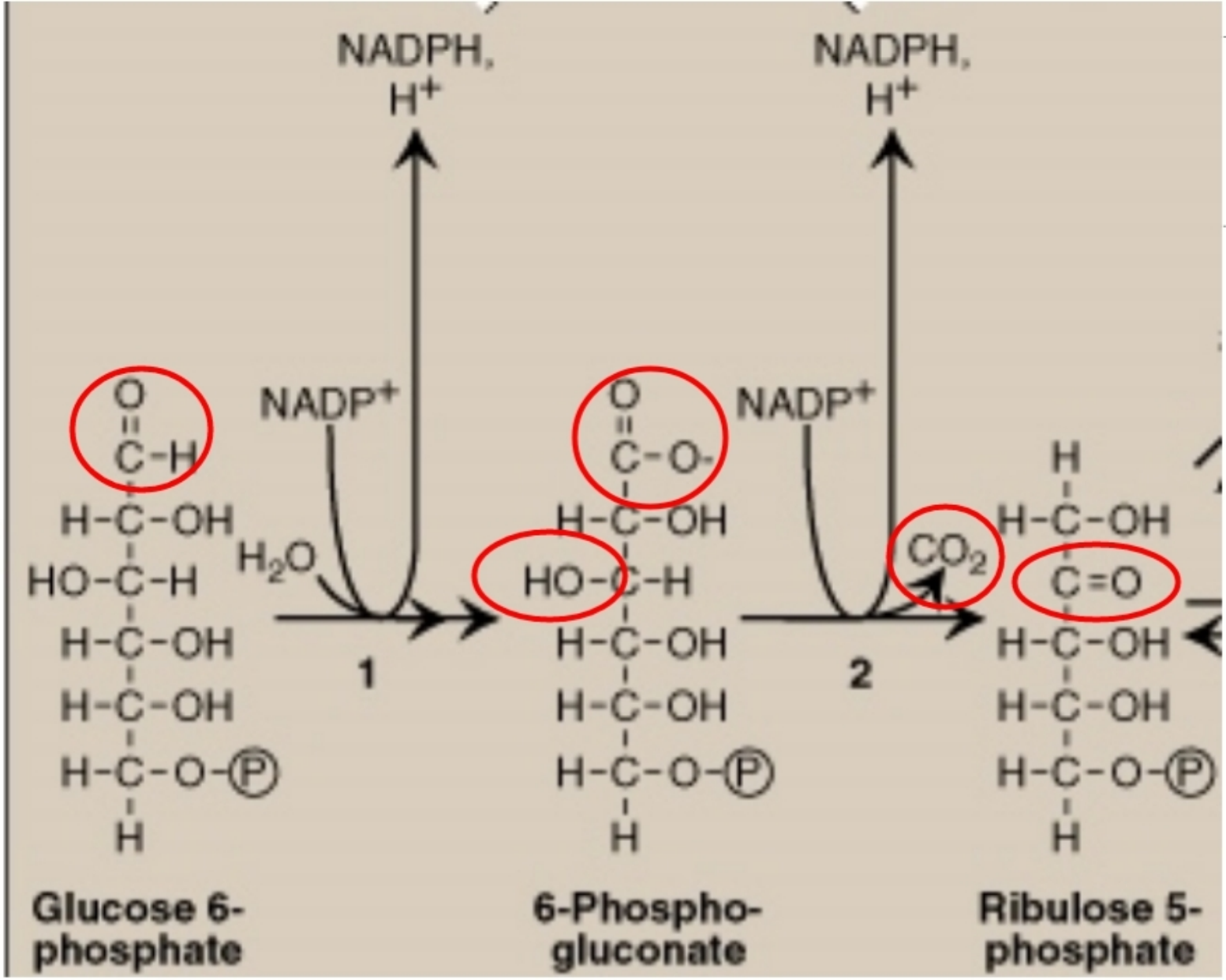
G6PD: Glucose 6-Phosphate Dehydrogenase

6-PGD: 6-phosphogluconate Deydrogenase

The Pentose Phosphate Pathway
The Oxidative Phase (irreversible)



G6PD: Glucose 6-Phosphate Dehydrogenase
6-PGD: 6-phosphogluconate Deydrogenase

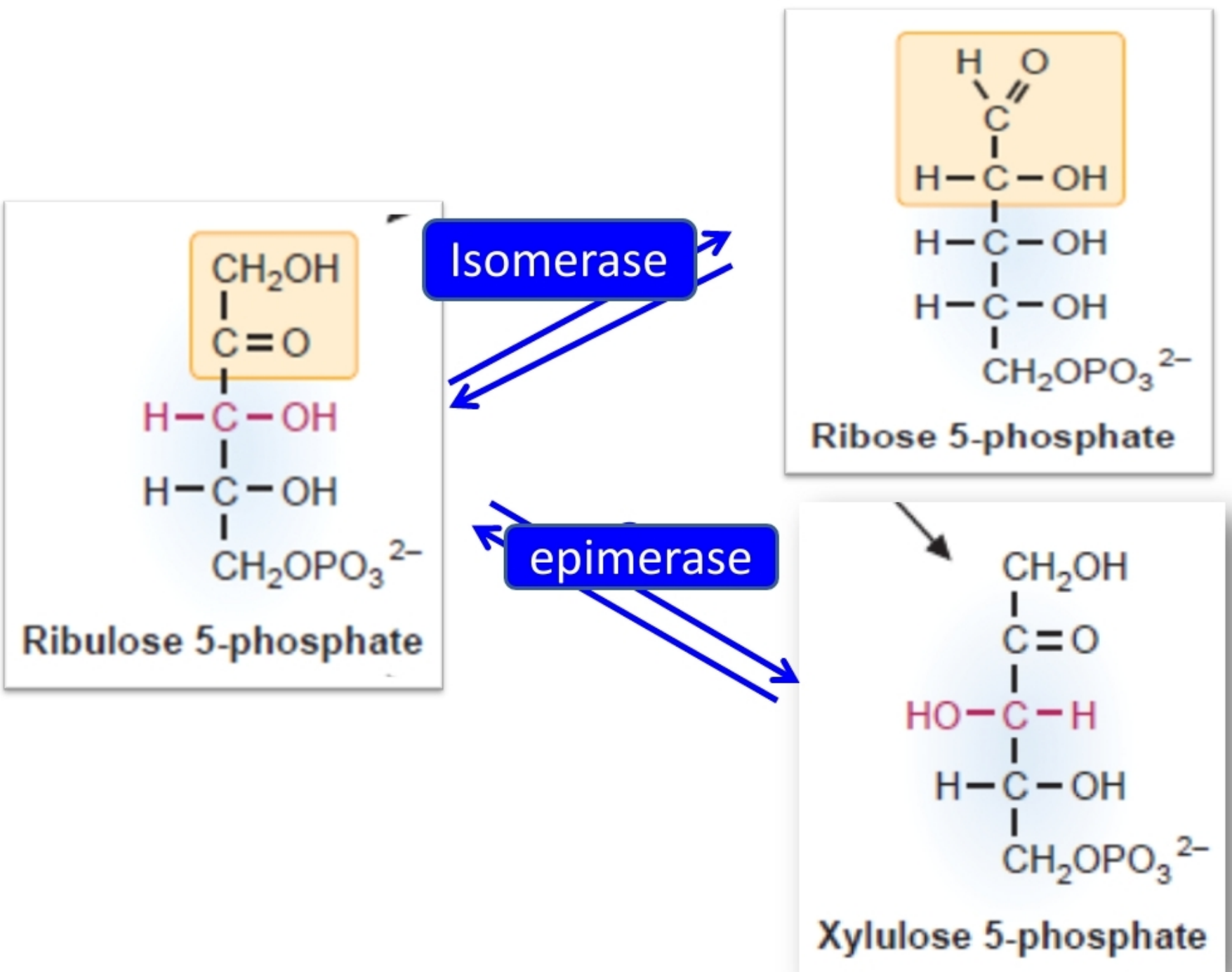


Glc. 6 Phosph. +2 $NADP^+$ ⟶ Ribulose 5-Phosph. + CO_2 + 2 NADPH

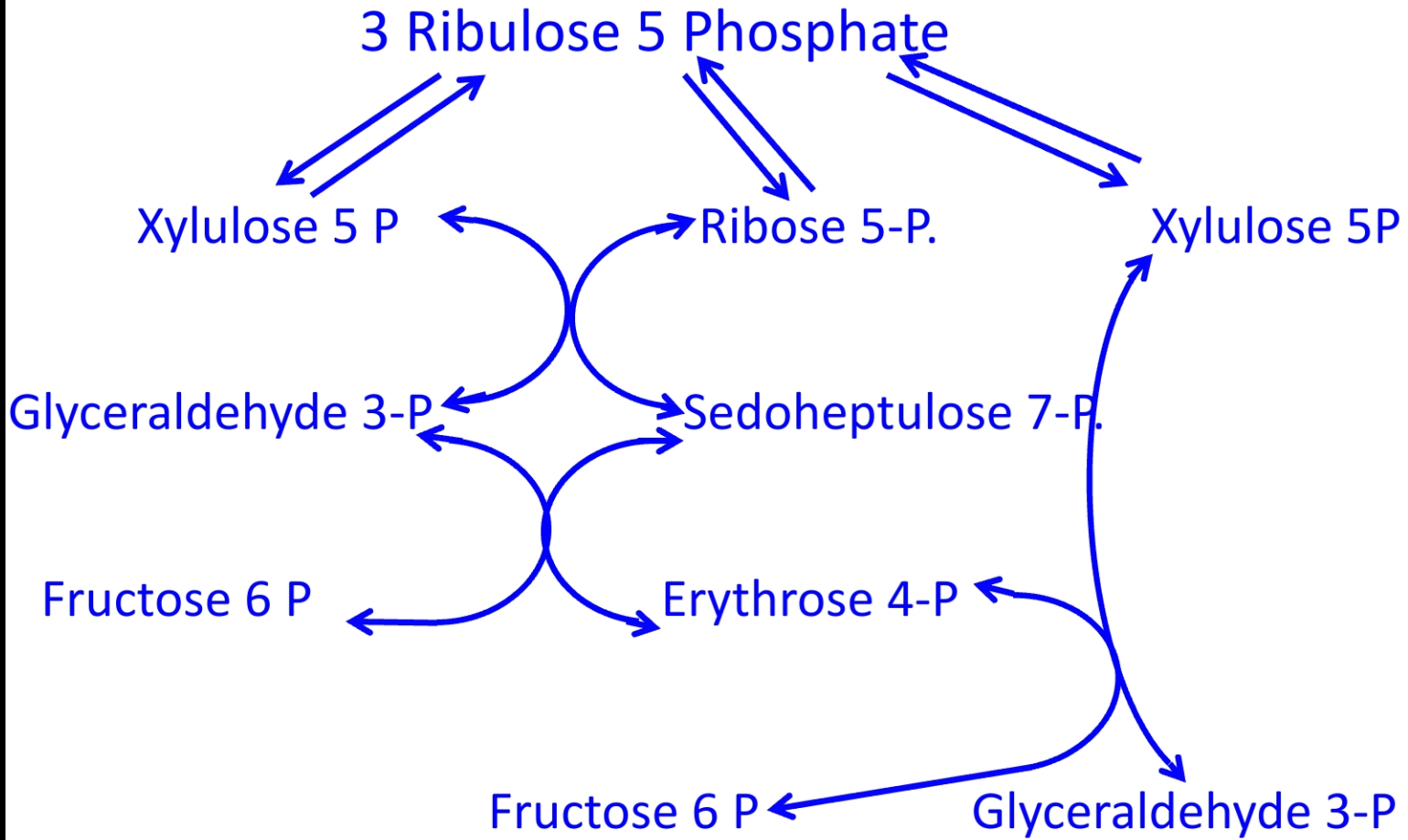
Summary of the non-oxidative reactions

- Reversible reactions
- Transfer of 2 or 3 carbon fragment
- Transketolase (2C), Transaldolase (3C)
- Ketose + aldose $\rightleftharpoons$ ketose + aldose
- From ketose to aldose

- Rearrangment of sugars
- 3 pentose phosph.. $\rightleftharpoons$ { 2 hexose phosph + 1 triose phosph. }


Isomerase
epimerase
Ribulose 5-phosphate
Ribose 5-phosphate
Xylulose 5-phosphate

The Non-oxidative Phase (reversible)

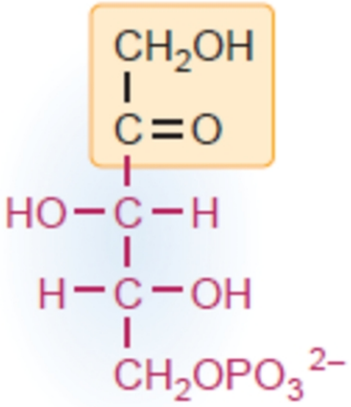


Ketose + Aldose ⇌ Aldose + Ketose

C5 + C5 ⇌ C3 + C7

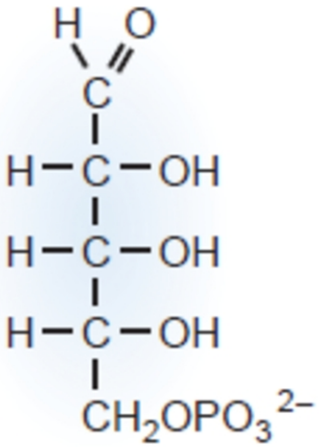
C7 + C3 ⇌ C4 + C6

C5 + C4 ⇌ C3 + C6

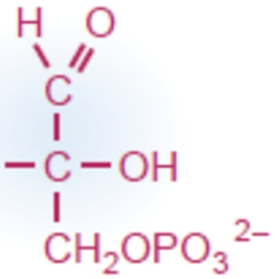


Xylulose 5-phosphate

+

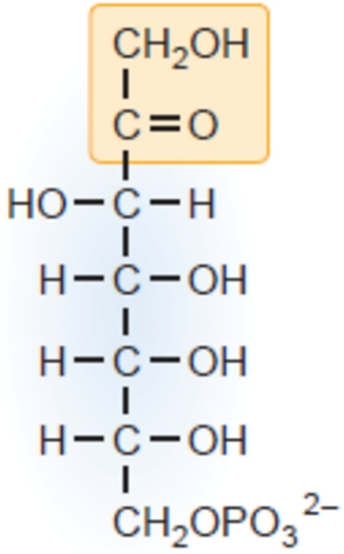


Ribose 5-phosphate

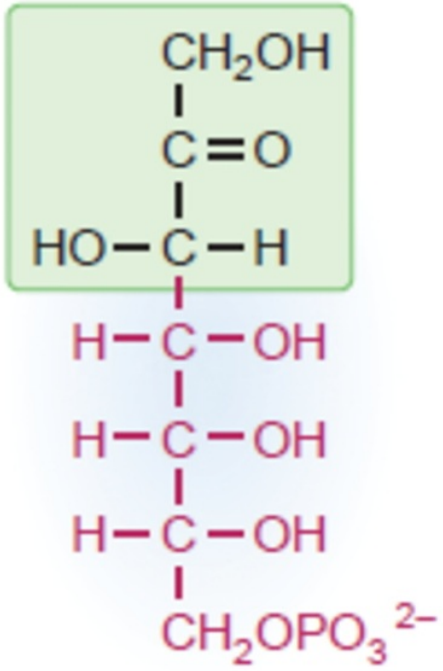


Glyceraldehyde 3-phosphate

+

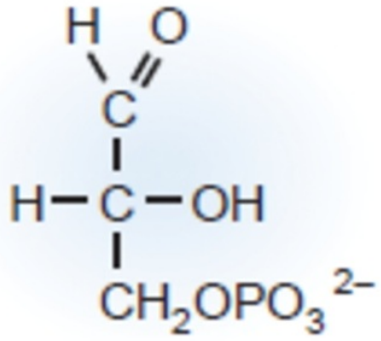


Sedoheptulose 7-phosphate

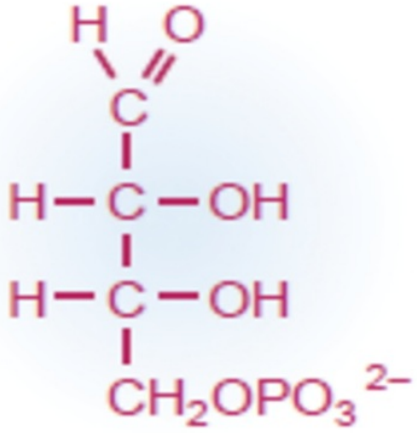


Sedoheptulose 7-phosphate

+

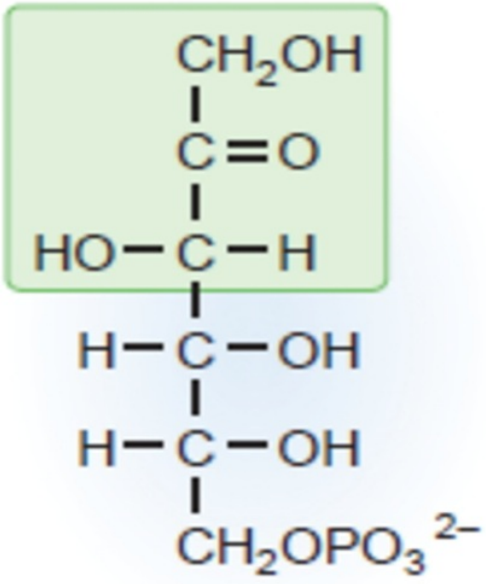


Glyceraldehyde 3-phosphate

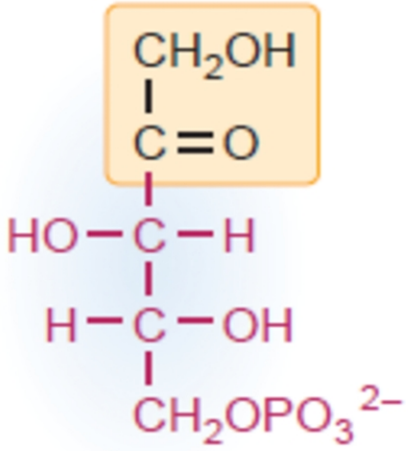


Erythrose 4-phosphate

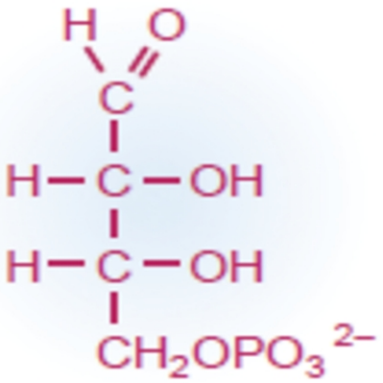
+



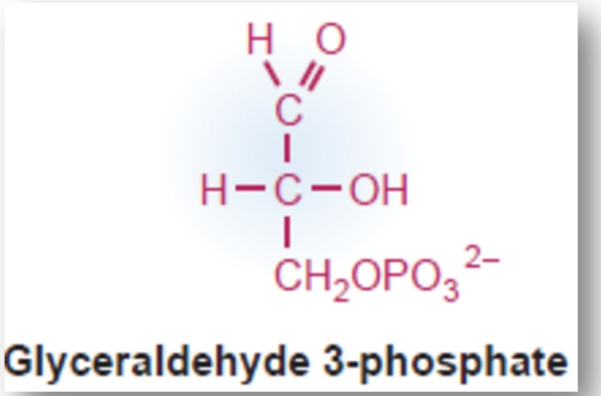
Fructose 6-phosphate



Xylulose 5-phosphate

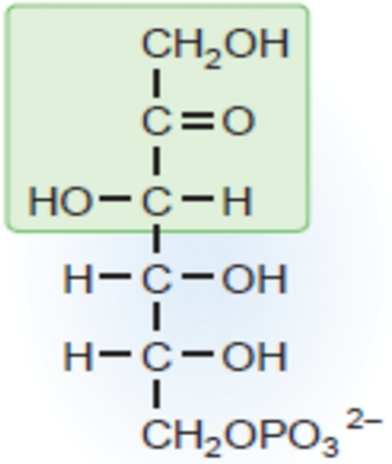


Erythrose 4-phosphate



Glyceraldehyde 3-phosphate

+



Fructose 6-phosphate

Ketose + Aldose ⇌ Aldose + Ketose

C5 + C5 ⇌ C3 + C7

C7 + C3 ⇌ C4 + C6

C5 + C4 ⇌ C3 + C6

The net non-oxidative reaction

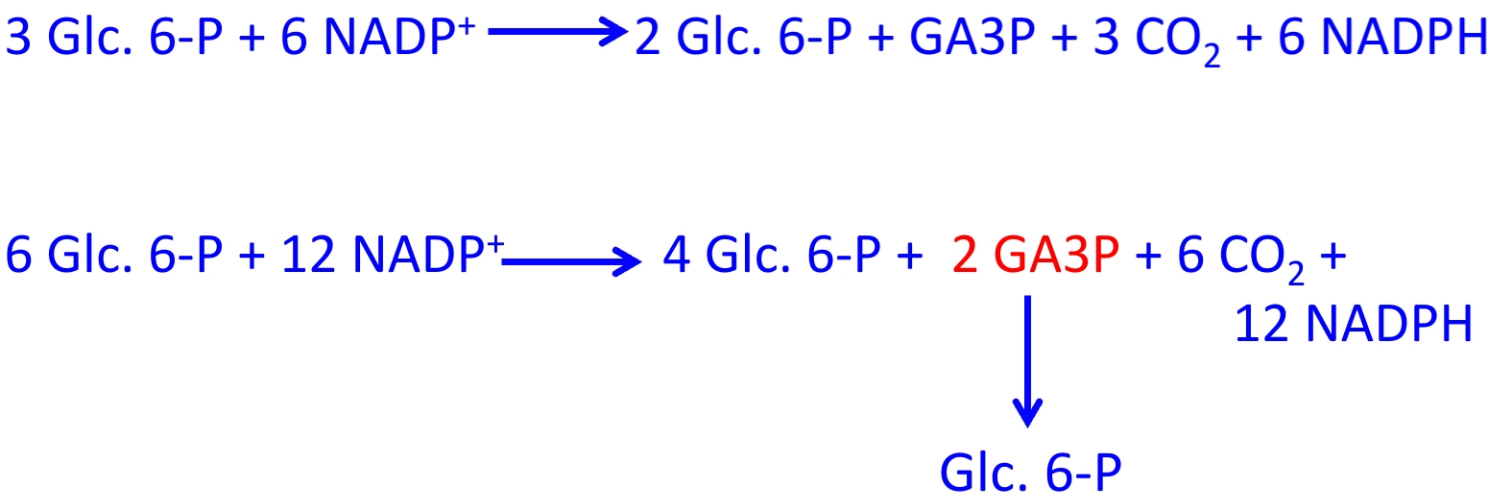
- 3 Ribulose 5-phosph. ⇌ { 2 Fructose 6-phosph. + Glyceraldehyde 3-phosph. }
- Multiply by 2
- 6 Ribulose 5-phosph. ⇌ { 4 Fructose 6-phosph. + 2 Glyceraldehyde 3-phosph. }

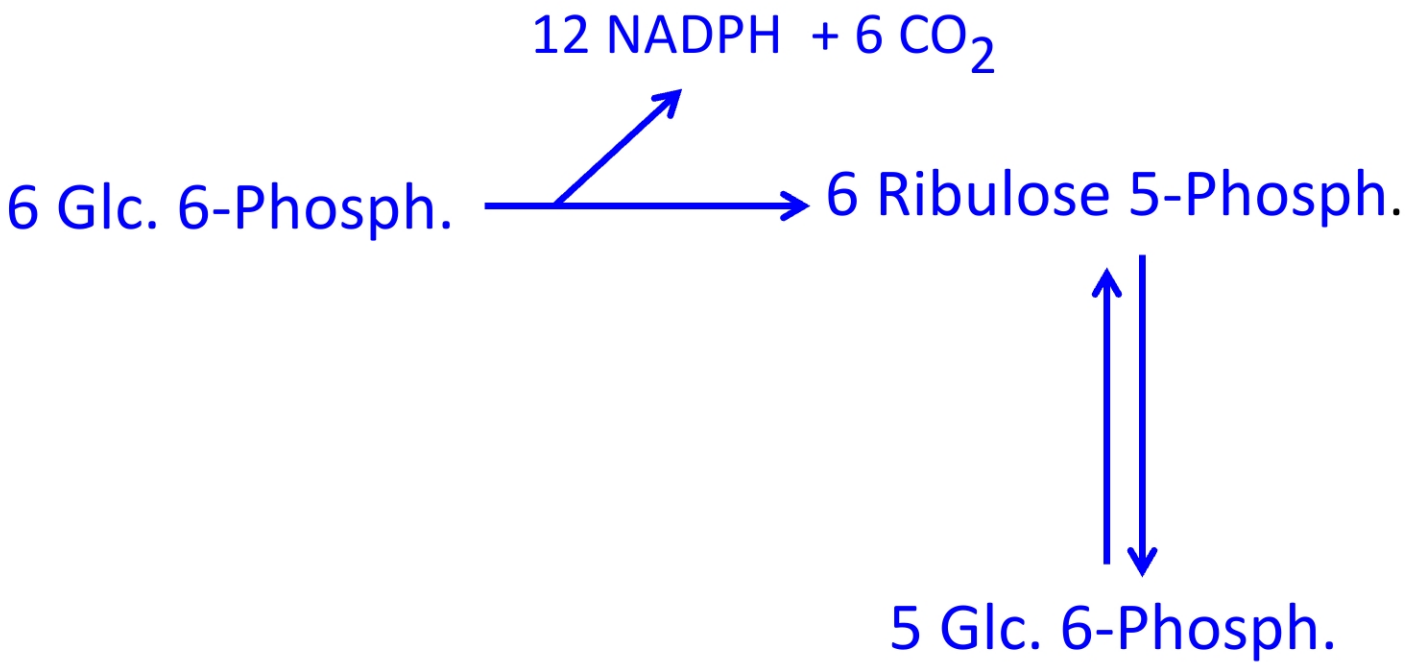
↓

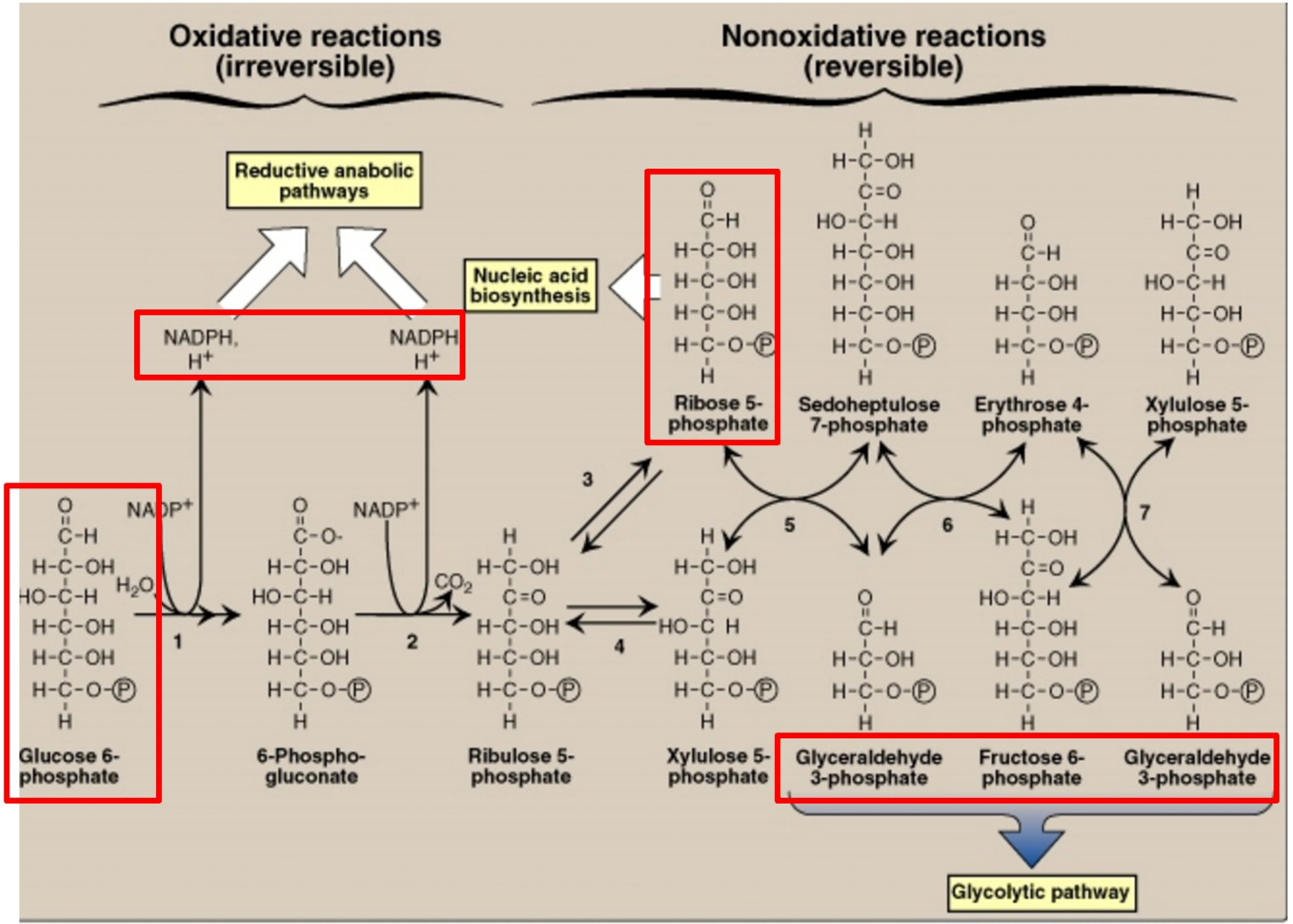
↓

↓

5 Fructose. 6-Phosph.

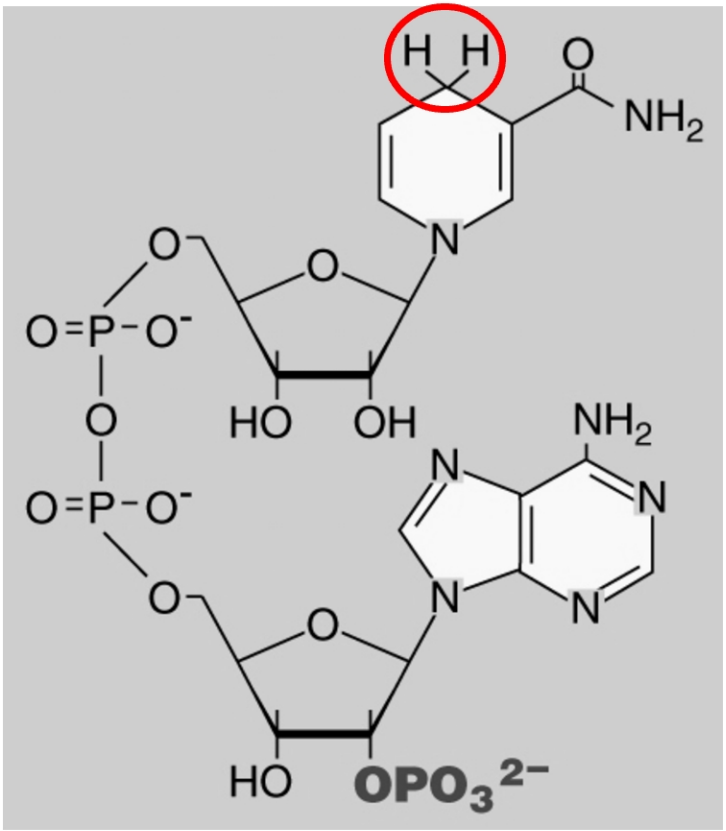

3 Glc. 6-P + 6 NADP+ → 2 Glc. 6-P + GA3P + 3 CO2 + 6 NADPH
6 Glc. 6-P + 12 NADP+ → 4 Glc. 6-P + 2 GA3P + 6 CO2 + 12 NADPH
Glc. 6-P
6 Glc. 6-P + 12 NADP+ → 5 Glc. 6-P + 6 CO2 + 12 NADPH


12 NADPH + 6 CO_2
6 Glc. 6-Phosph.
6 Ribulose 5-Phosph.
5 Glc. 6-Phosph.

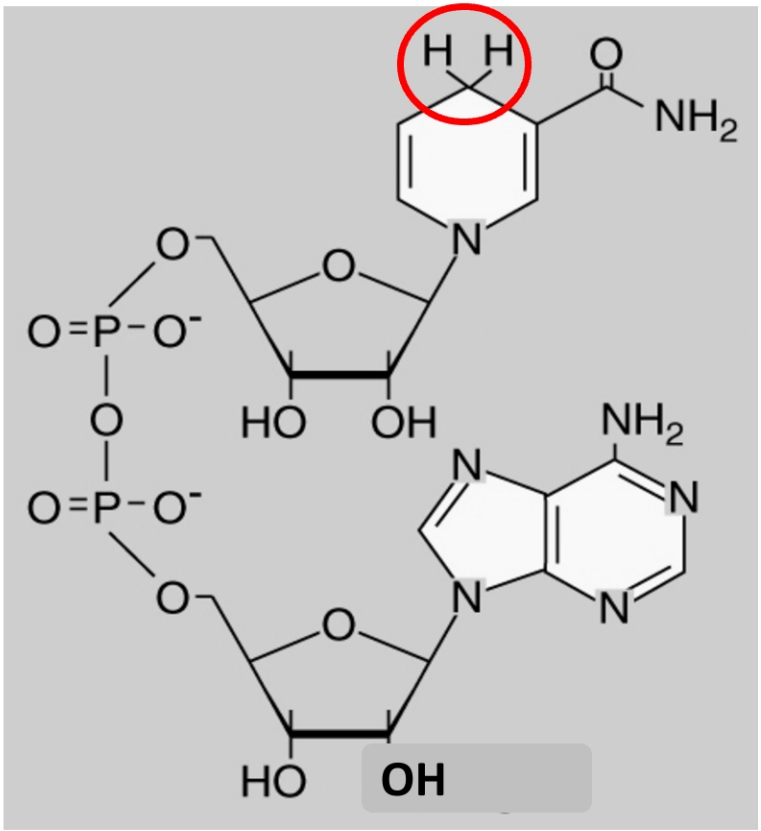

Oxidative reactions
(irreversible)
Nonoxidative reactions
(reversible)
Reductive anabolic pathways
Nucleic acid biosynthesis
NADPH, H+
NADPH H+
NADP+
NADP+
H2O
CO2
1
2
3
4
5
6
7
Glucose 6-phosphate
6-Phospho-gluconate
Ribulose 5-phosphate
Xylulose 5-phosphate
Ribose 5-phosphate
Sedoheptulose 7-phosphate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

Uses of NADPH

NADPH



NADH



Why NADPH and NADH

- Enzymes can specifically use one NOT the other
- NADPH and NADH have different roles
- NADPH exists mainly in the reduced form (NADPH)
- NADH exists mainly in the oxidized form (NAD^+)
- In the cytosol of hepatocyte
  - $NADP^+/NADPH \approx 1/10$
  - $NAD^+/NADH \approx 1000/1$

Uses of NADPH
Reductive Biosynthesis

- Some biosynthetic reactions require high energy electron donor to produce reduced product
- Examples: Fatty acids, Steroids …
- 8 CH_3COO ➔ $C_{15}H_{33}COO$

Uses of NADPH
Reductive Biosynthesis

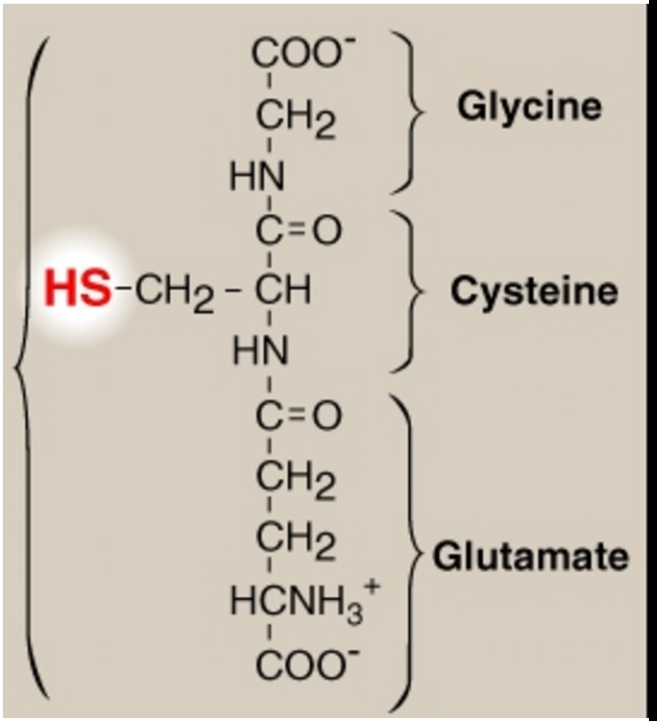
- Some biosynthetic reactions require high energy electron donor to produce reduced product
- Examples: Fatty acids, Steroids …
- 8 CH_3COO ➔ $C_{15}H_{33}COO$

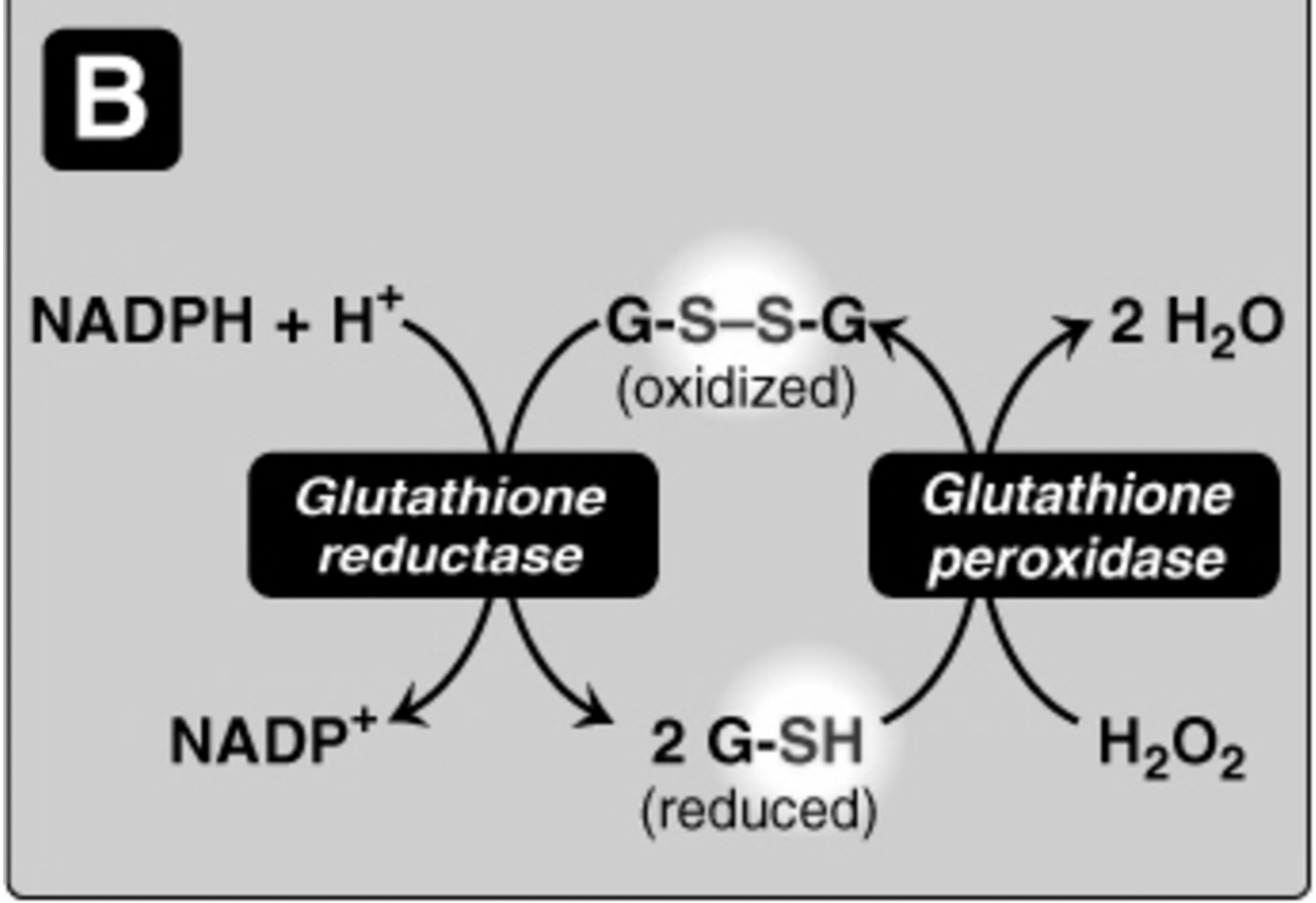
Uses of NADPH
Reduction of Hydrogen Peroxide

- H_2O_2 one of a family of compounds known as Reactive Oxygen Species (**ROS**)
- Other: Super oxide, hydroxyl radical,
- Formed continuously
  - As by products of aerobic metabolism
  - Interaction with drugs and environmental toxins
- Can cause chemical damage to proteins, lipids and DNA ➔ cancer, inflammatory disease, cell death

Enzymes that catalyze antioxidant reactions

- Glutathione peroxidase
- Glutathione is a reducing agent
- Tripeptide
- GSH is the reduced form
- Oxidation ➔two molecules joined by disulfide (GSSG)
- 2 GSH ⟶ GSSG





Glutathione peroxidase is Selenium requiring Enzyme

RBCs are totally dependent on Pentose Phosphate Pathway for NADPH production

G6PD Deficiency

- Common disease
- characterized by hemolytic anemia
- 200 – 400 millions individuals worldwide
- Highest prevalence in Middle East, S.E. Asia, Mediterranean
- X-linked inheritance
- > 400 different mutations
- Deficiency provides resistance to falciparum malaria

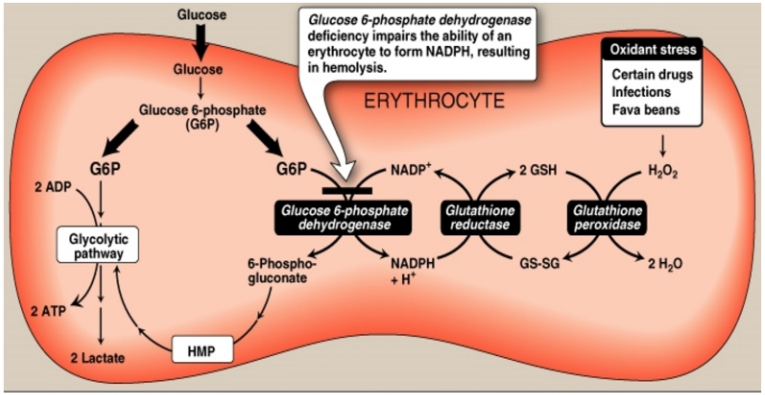
Role of G6PD in red blood cells

$$H_2O_2 + GSH \longrightarrow G\text{-}S\text{-}S\text{-}G + 2H_2O$$

$$G\text{-}S\text{-}S\text{-}G + NADPH \longrightarrow 2GSH + NADP+$$

GSH helps maintain the SH groups in proteins in the reduced state

Oxidation ➔ denaturation of proteins and rigidity of the cells



Precipitating Factors inG6PD Deficiency

- Oxidant drugs
  - Antibiotics e.g. Sulfomethxazole
  - Antimalaria Primaquine
  - Antipyretics Acetanalid
- Favism
- Infection
- Neonatal Jaundice

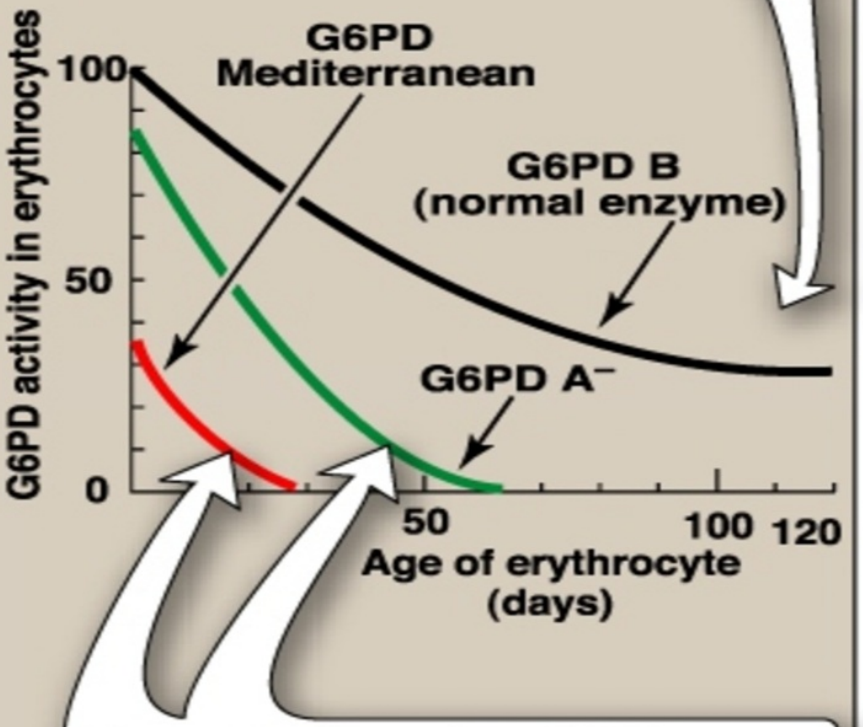
G6PD Deficiency Variants

- Wild type B
- Mediterranean Variant B^- (Class II) : 563C → T
- African Variant A^- (Class III); two point mutation
- African Variant A; Normal activity 80%
- Very severe deficiency (Class I)
- Majority missense mutation point mutation
- Large deletions or frame shift; Not Observed

Classification of G6PD Deficiency Variants

Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	> 60%

Although the activity of the normal enzyme declines as red cells age, even the oldest cells have a sufficient level of activity to provide protection against oxidative damage and hemolysis.



By contrast, very few *G6PD Mediterranean* red cells have sufficient enzyme activity to prevent oxidative damage, whereas a substantial fraction of young *G6PD A⁻* red cells are able to provide protection.

Enzymes that catalyze antioxidant reactions

- Super oxide dismutase (**SOD**)

$$2O_2\bullet^- + 2H^+ \longrightarrow O_2 + H_2O_2$$

- Catalase

$$2H_2O_2 \longrightarrow O_2 + 2H_2O$$

Anti oxidant chemicals

- Vitamin E, Vitamin C, Carotenoids

Sources of ROS in the cell

- Oxidases

  e- + O_2

Most oxidases produce H_2O_2 (peroxidase)

Oxidases are confined to sites equipped with protective enzymes

- Oxygenases
  - Mono oxygenases (hydroxylases)
  - Dioxygenases in the synthesis of prostaglandins, Thromboxans, leucotrienes
- Coenzyme Q in Respiratory chain

Sources of ROS in the cell

- Respiratory Burst (during phagocytosis)

  O_2^- H_2O_2 $OH^\bullet$ NO HOCl

- Ionizing Radiation

  $OH^\bullet$

Cytochrome P450 Mono oxygenase

- Mixed function oxygenase
- Super family of structurally related enzymes

Mitochondrial system

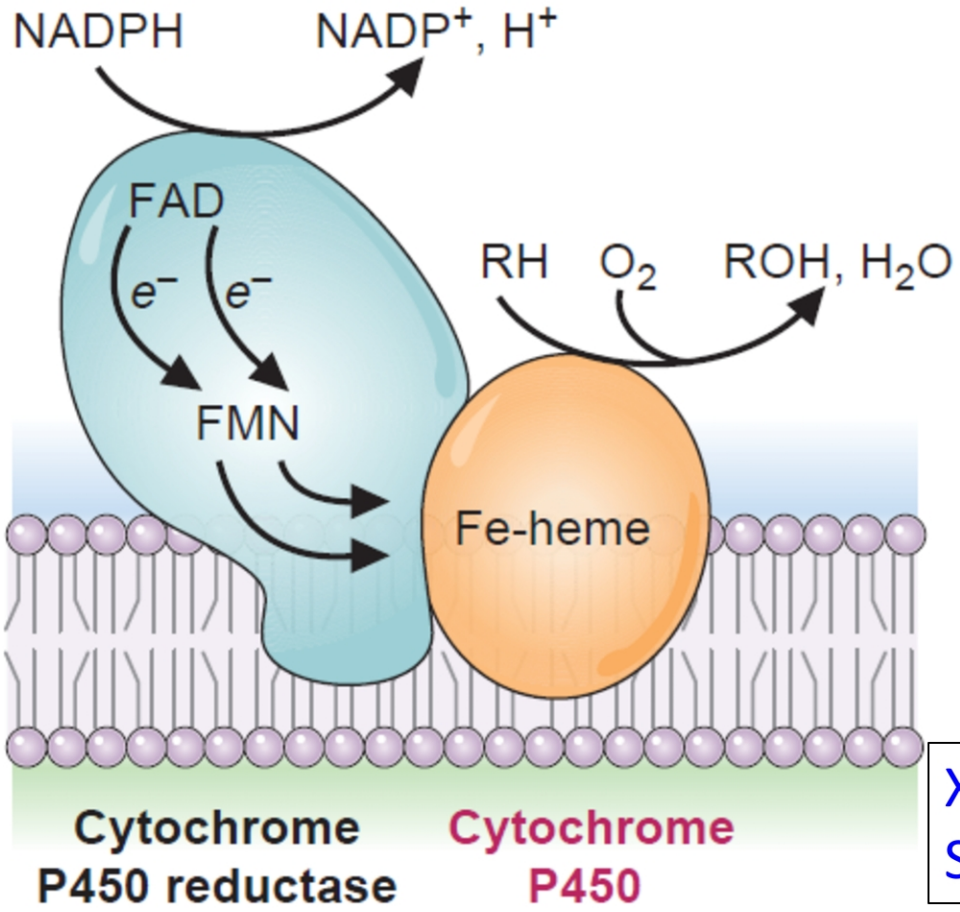
Hydroxylation of steroids, bile acids, active form of Vit. D

Microsomal system

Detoxification of foreign compounds

activation or inactivation of Drugs

solublization



Accidental release of free radical intermediates may occur

XH2: electron donor
S: substrate

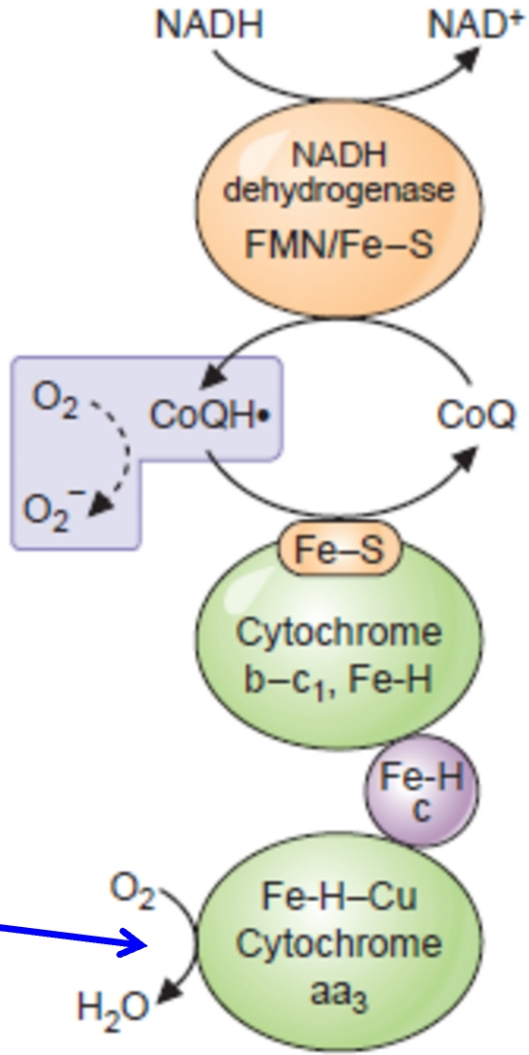
$$O_2 + S + XH_2 \longrightarrow H_2O + SOH + X$$

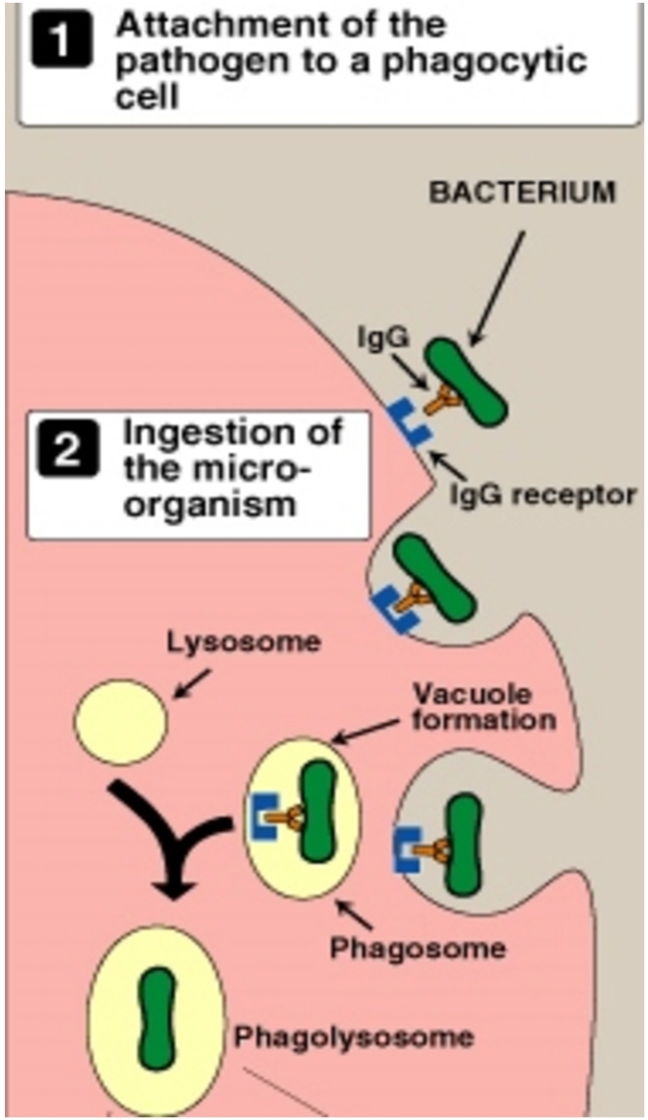
Generation of O_2^- by respiratory chain

Accidental non-specific interaction

Major source of free radicals

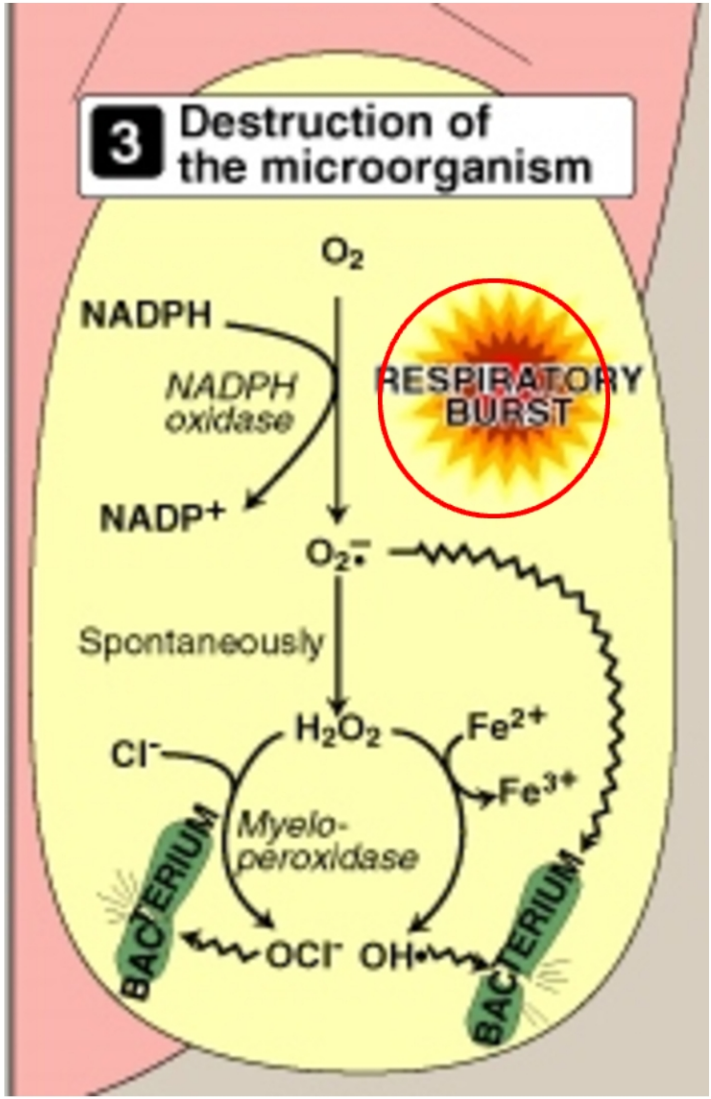
Binuclear center prevents release of free O_2 radicals





Phagocytosis; the oxygen dependant pathway of microbial killing by White Blood Cells (WBC)

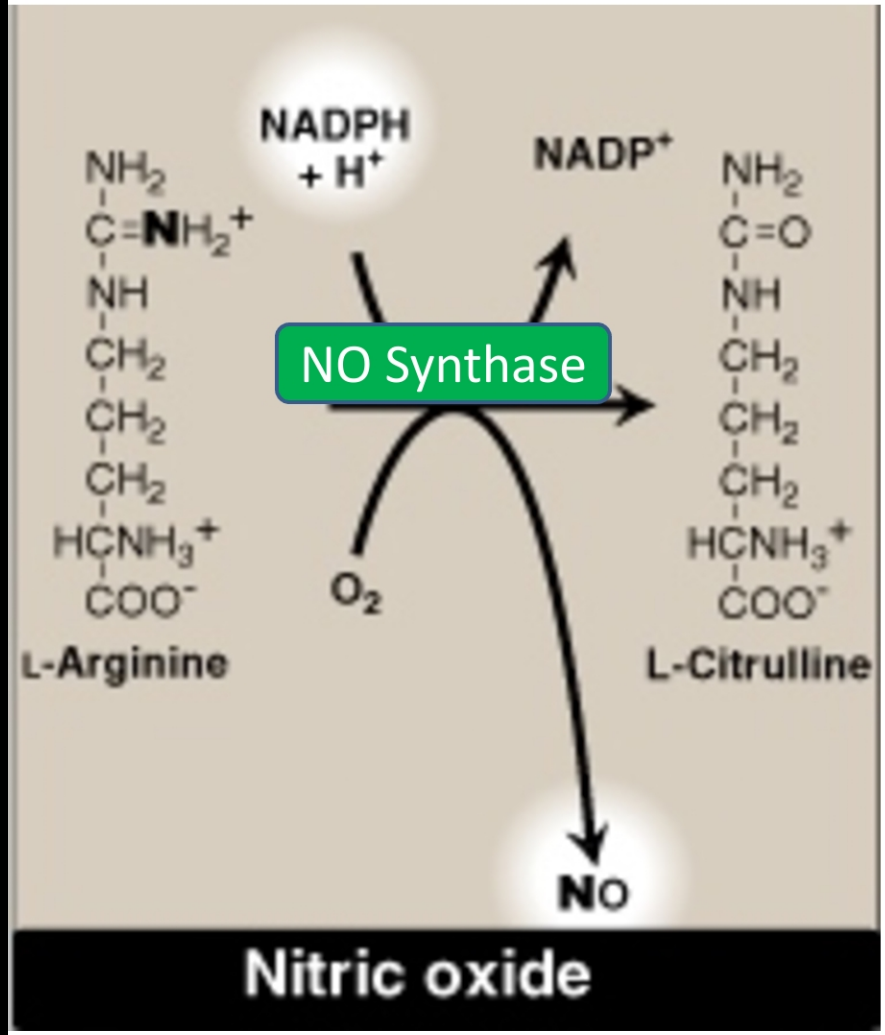
Rapid consumption of O^2 that accompanies superoxide formation



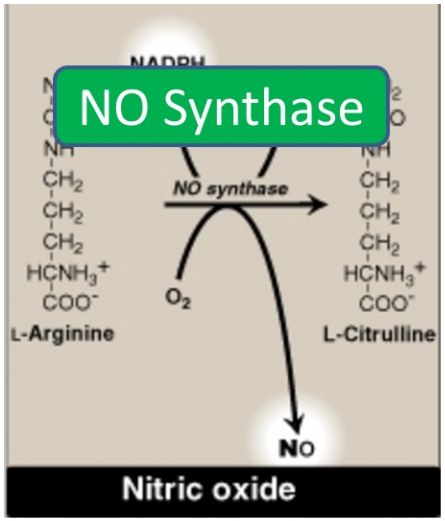
NO and Reactive Nitrogen Oxygen Spciese (RNOS)

- Free radical diffuses readily
- Essential for life and toxic
- Neurotransmitter , vasodilator
- ↓Platelet aggregation
- At high concentration combines with $O_2\bullet^-$ or O_2 to form **RNOS**
- **RNOS** are involved in neurodegenerative diseases and inflammatory diseases

NO Synthesis



NO Synthesis



NO Synthase

Three isoforms

nNOS neural

eNOS endothelial

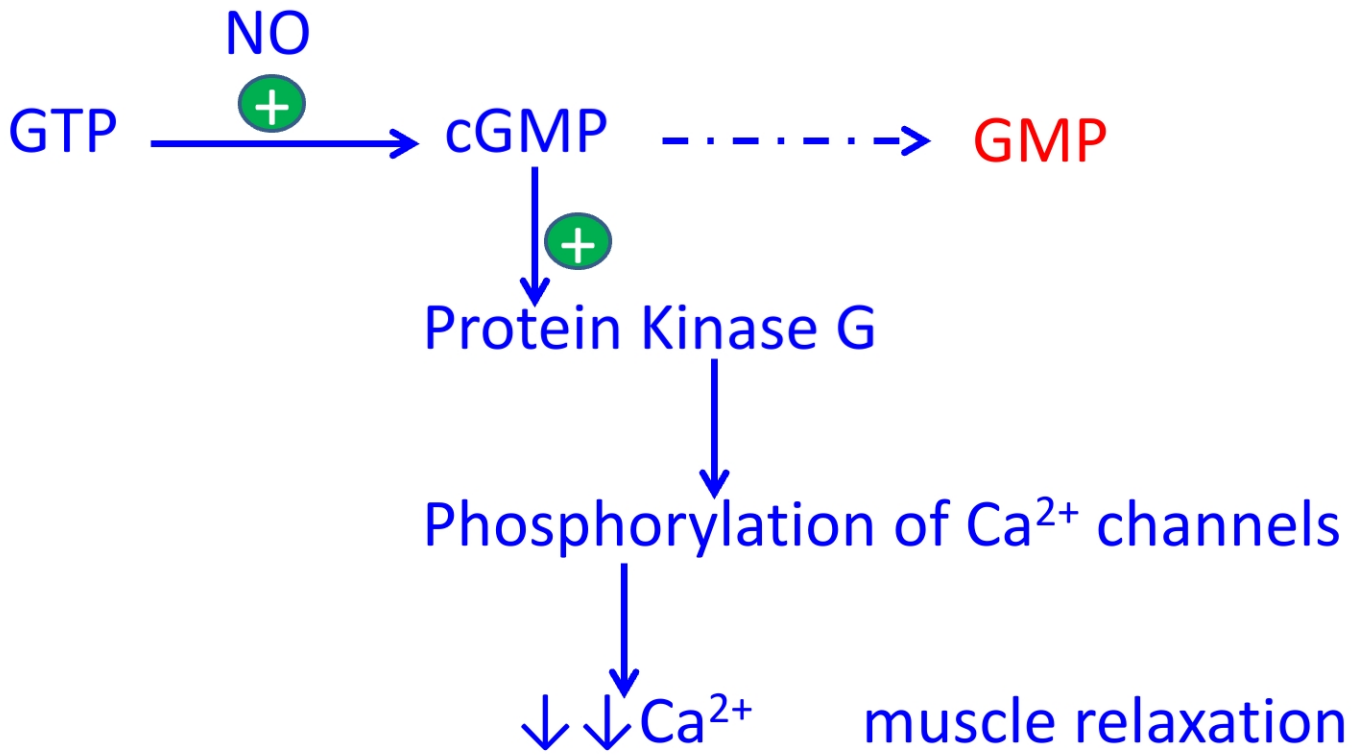
Both are constitutive

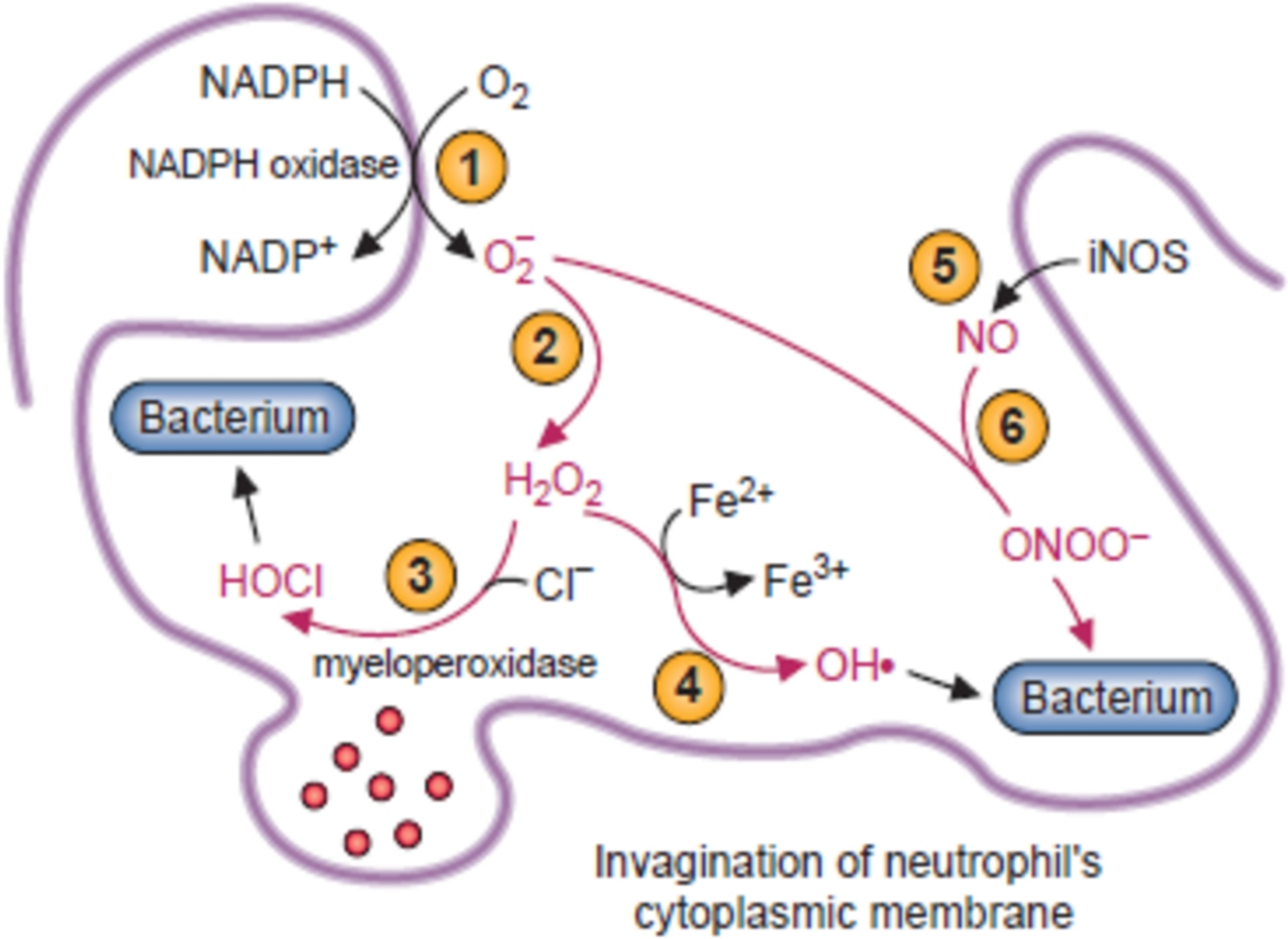
iNOS inducible

Induction of transcription in many cells of immune system → ↑↑ NO → RNOS to kill invading bacteria

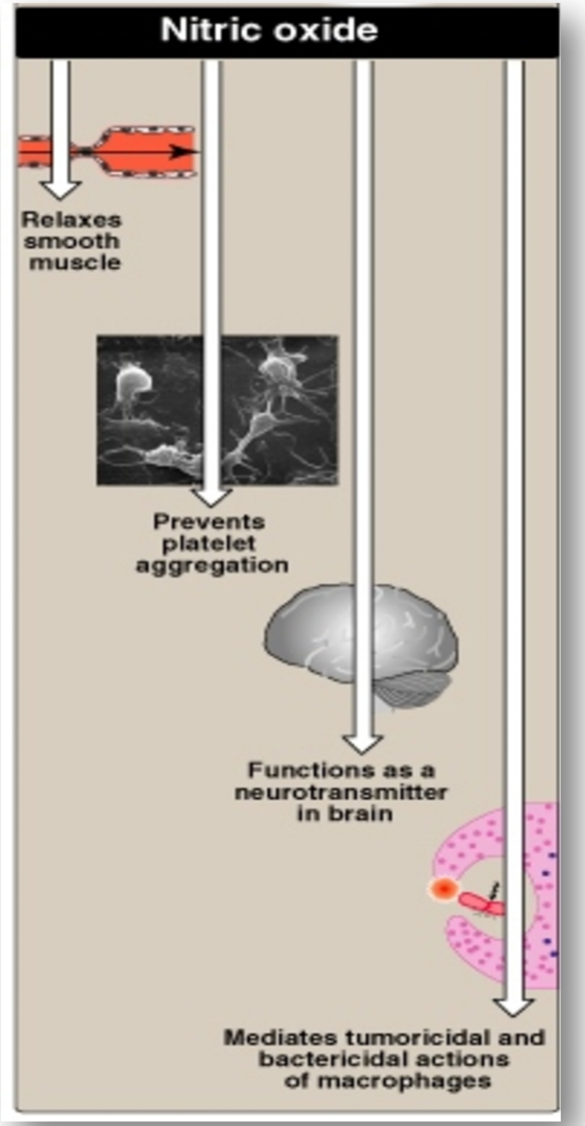
Action of NO on vascular endothelium

Synthesis by endothelia cells → smooth muscle

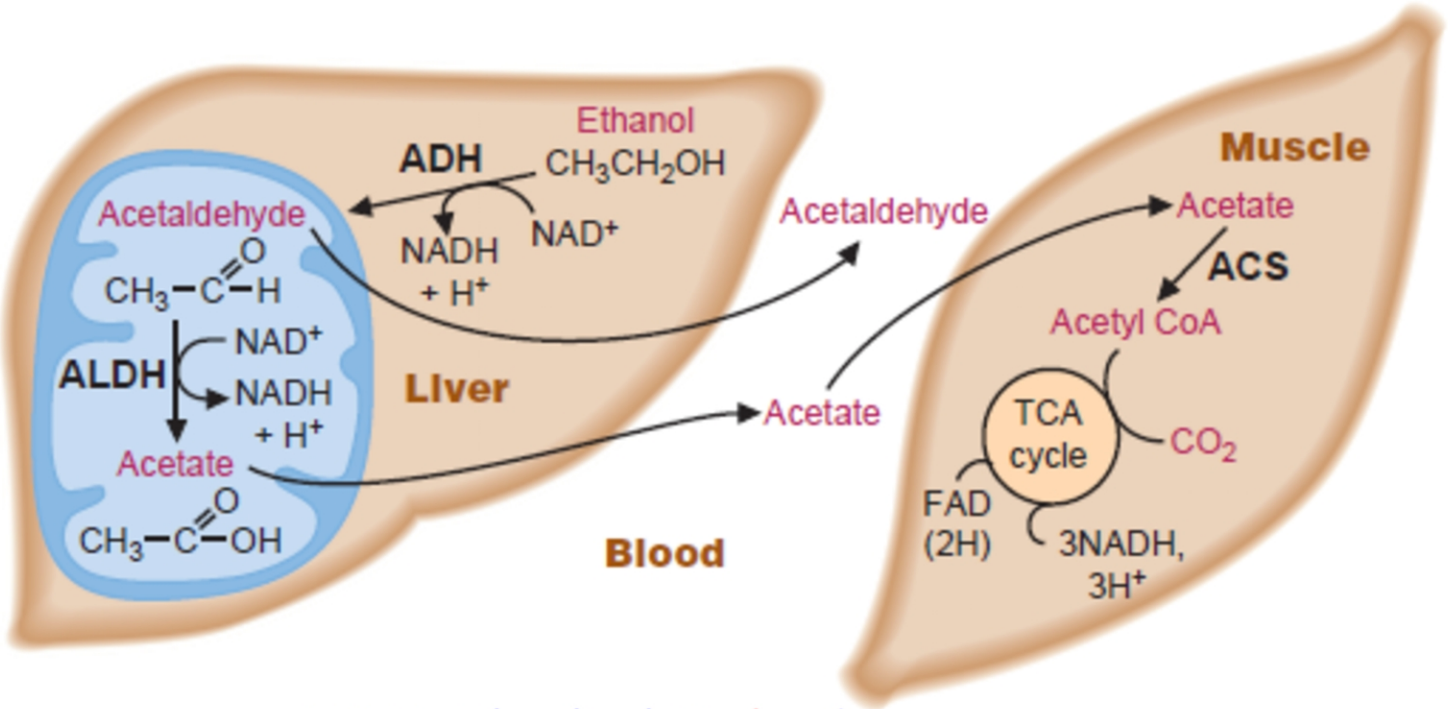




Hypoclorous acid


Nitric oxide
Relaxes smooth muscle
Prevents platelet aggregation
Functions as a neurotransmitter in brain
Mediates tumoricidal and bactericidal actions of macrophages

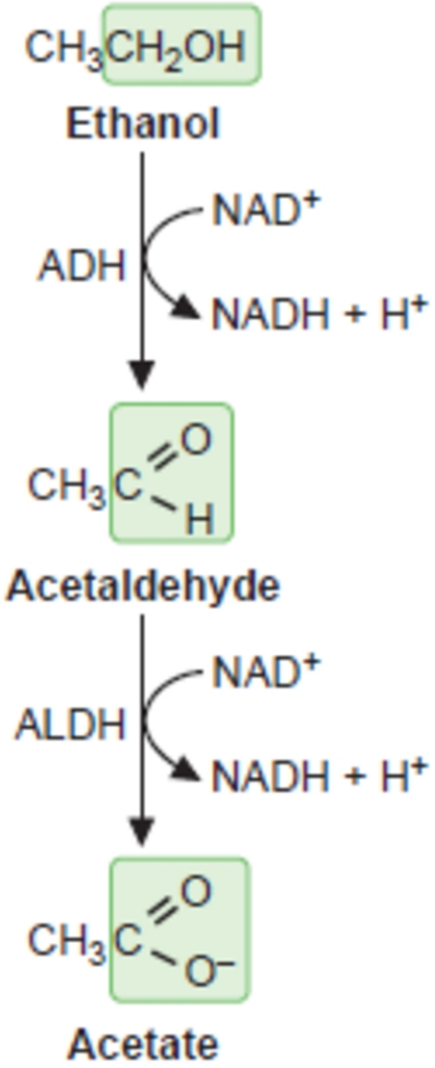
Metabolism of Alcohol

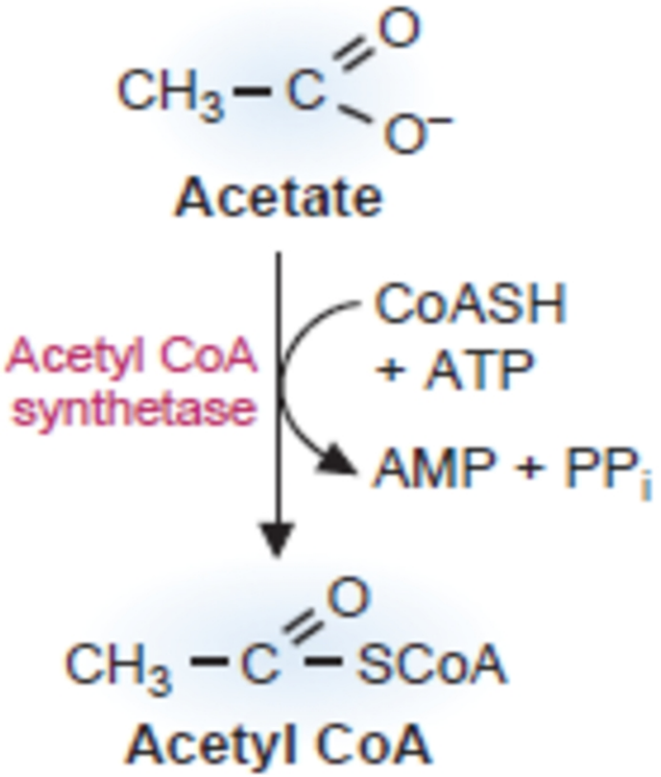


ADH: Alcohol Dehydrogenase

ALDH: Acetaldehyde Dehydrogenase

ACS: Acetyl CoA Synthetase





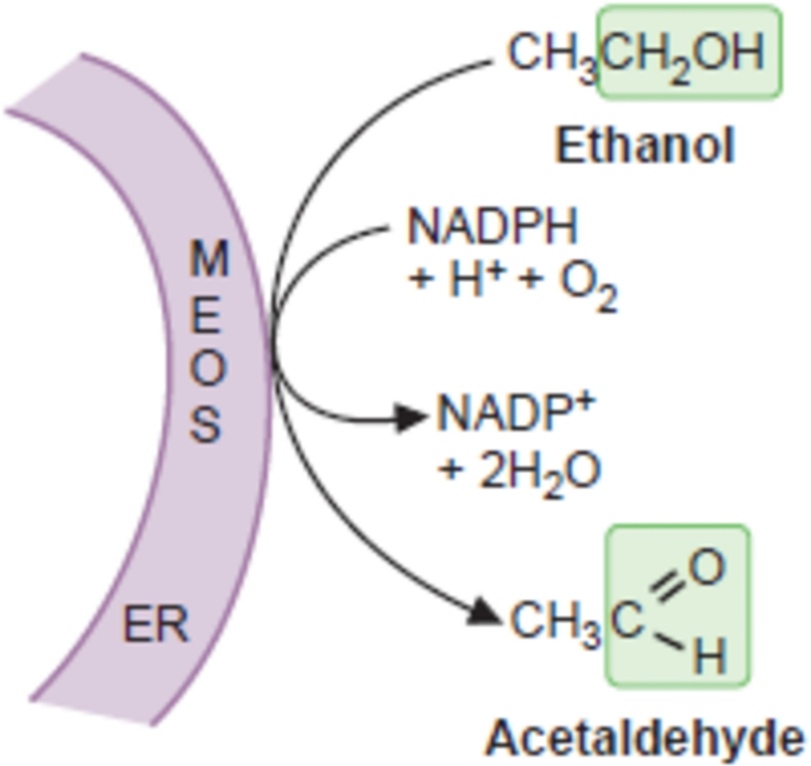
High NADH/NAD+

Inhibition of FA oxidation

Inhibition of gluconeogenesis

Lactic acidosis

MEOS: Microsomal Oxidizing System

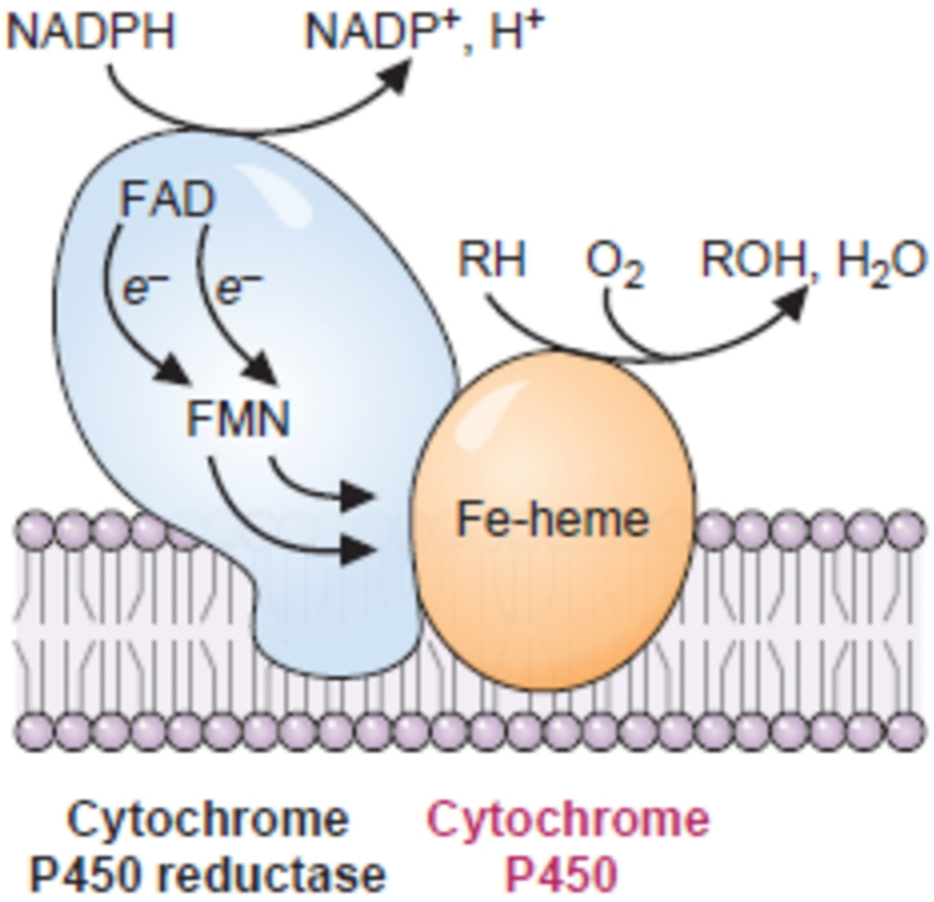


10-20% of the ingested ethanol

Cytochrome P450 (CYP2E1)

High K_m for ethanol

Inducible by ethanol


NADPH
NADP+, H+
FAD
e−
e−
FMN
RH
O2
ROH, H2O
Fe-heme
Cytochrome P450 reductase
Cytochrome P450