hexose monophosphate shunt lecture 4

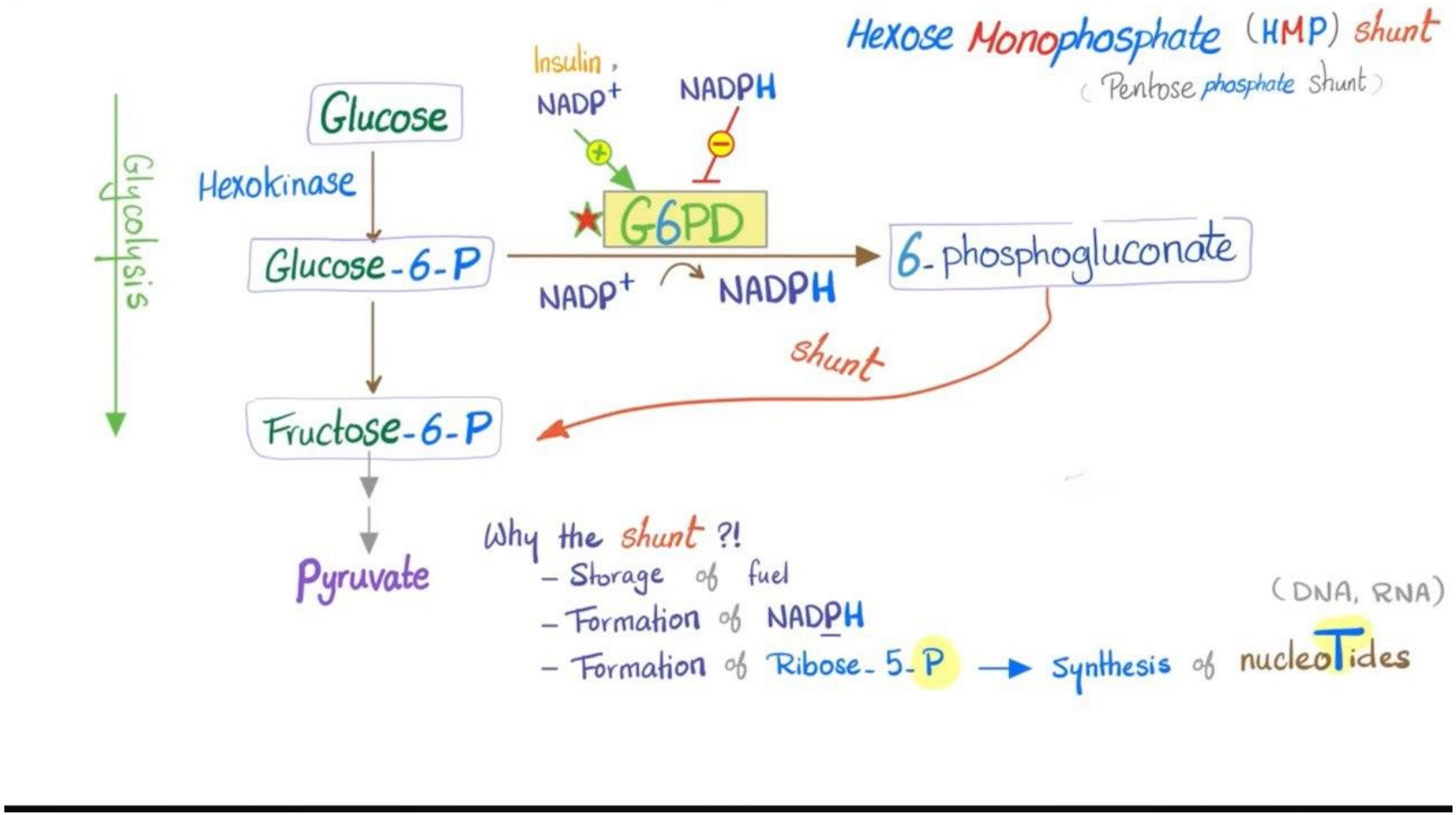
Third year-biochemistry subject – laboratory science departments -Alzahraa university college of pharmacy

Dr .Esraa Ali Almustafa **M.B.Ch.B , F.I.C.M.S /PATH**

introduction

- the hexose monophosphate shunt (HMP shunt), also known as the pentose phosphate pathway (PPP), is a metabolic pathway that operates parallel to glycolysis and is crucial for cellular metabolism
- About 10% of glucose molecules per day are entering in this pathway.
- The liver and RBC metabolise about 30% of glucose by this pathway.

- hexose monophosphate shunt overview



Purpose:

- **- The HMP shunt has two primary functions:**

1. - NADPH Production: It generates NADPH, which is act as electron donor(reducing agent) for

- **fatty acid synthesis**
- **Cholesterol synthesis**
- **reactive oxygen species**
- **maintenance of reduced glutathione for protecting against oxidative stress.**
- Ribose-5-Phosphate Production: It provides ribose-5-phosphate for nucleotide synthesis, necessary for DNA and RNA.

Pathway is Operating in Following Organs

- The HMP shunt primarily occurs in the **cytoplasm of cells**, particularly in tissues engaged in lipid synthesis and those needing rapid cell proliferation
- **I Liver**
- **ii. Adipose tissue**
- **iii. Adrenal cortex**
- **iv. Mammary glands**
- **v. Testes and ovaries**
- **vi. RBCs**
- 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.

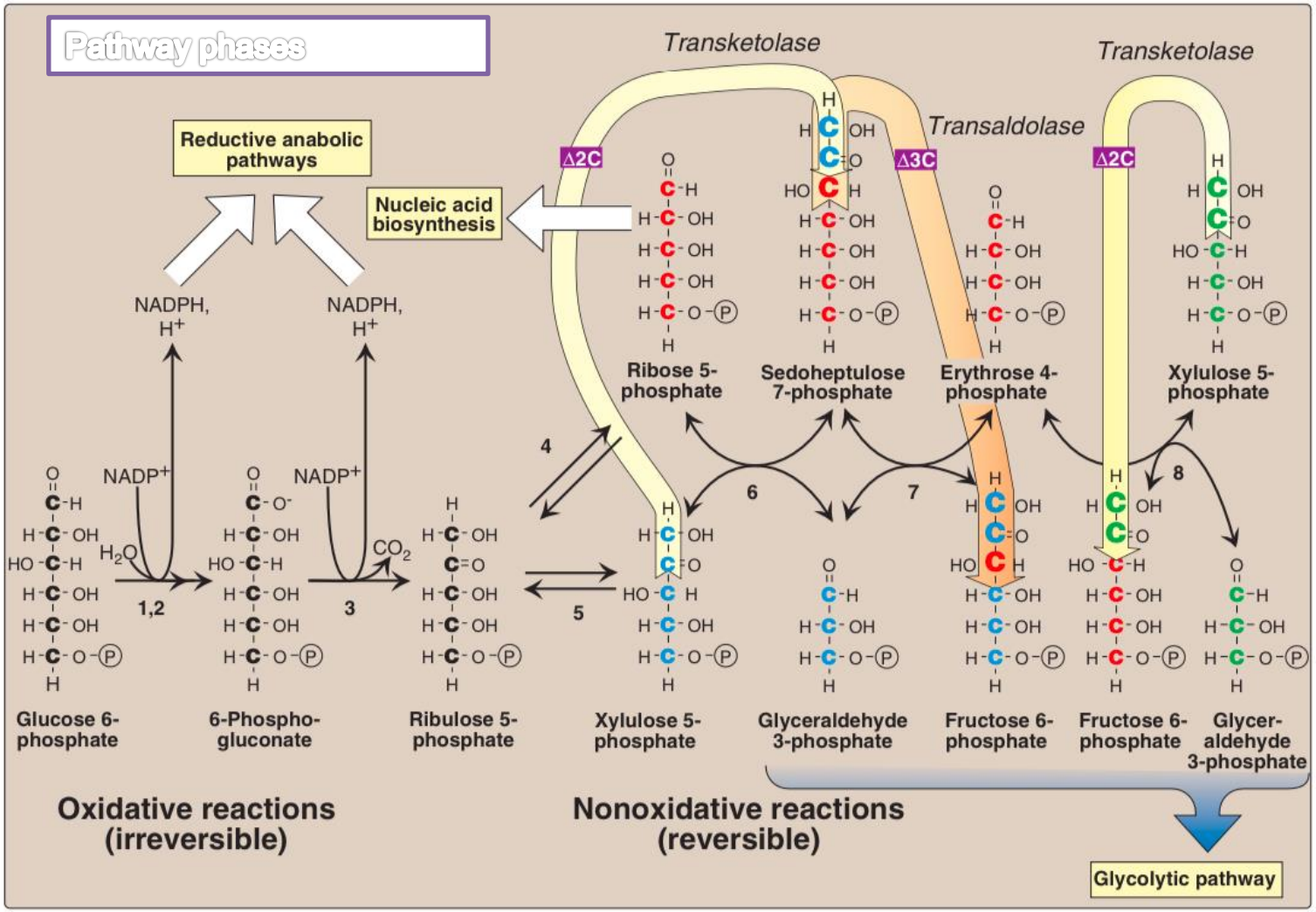


Figure 13.2
Reactions of the hexose monophosphate pathway. Enzymes numbered above are: 1,2) *glucose 6-phosphate dehydrogenase* and *6-phosphogluconolactone hydrolase*, 3) *6-phosphogluconate dehydrogenase*, 4) *ribose 5-phosphate isomerase*, 5) *phosphopentose epimerase*, 6) and 8) *transketolase* (coenzyme: thiamine pyrophosphate), and 7) *transaldolase*. Δ2C = two carbons are transferred in *transketolase* reactions; Δ3C = three carbons are transferred in the *transaldolase* reaction.

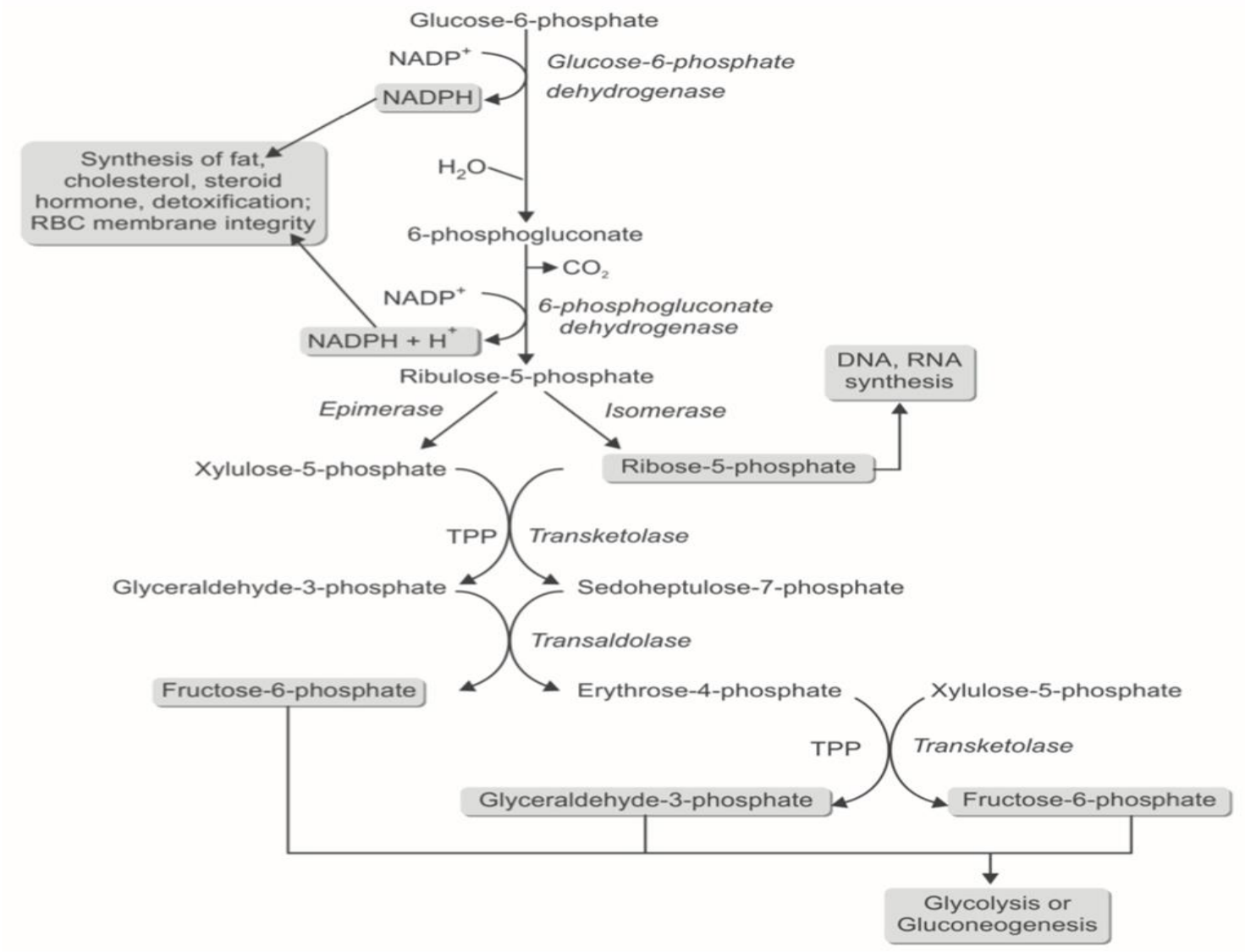


Fig. 4.14: Hexose monophosphate shunt

Pathway Phases

- The HMP shunt is divided into two phases:
- the oxidative phase and the non-oxidative phase.

- 1. Oxidative Phase
- - **This phase is responsible for the generation of NADPH and involves three key enzymatic reactions:**

❖ - Glucose-6-Phosphate Dehydrogenase (G6PD):

- - Converts glucose-6-phosphate into 6-phosphoglucono-δ-lactone while producing NADPH.
- This is the rate-limiting step. Regulation is effected by this enzyme

❖ - 6-Phosphogluconolactonase:

- - Hydrolyzes 6-phosphoglucono-δ-lactone to 6-phosphogluconate.

❖ - 6-Phosphogluconate Dehydrogenase:

- - Converts 6-phosphogluconate into ribulose-5-phosphate, producing another molecule of NADPH and releasing carbon dioxide (CO_2).

1. Oxidative Phase

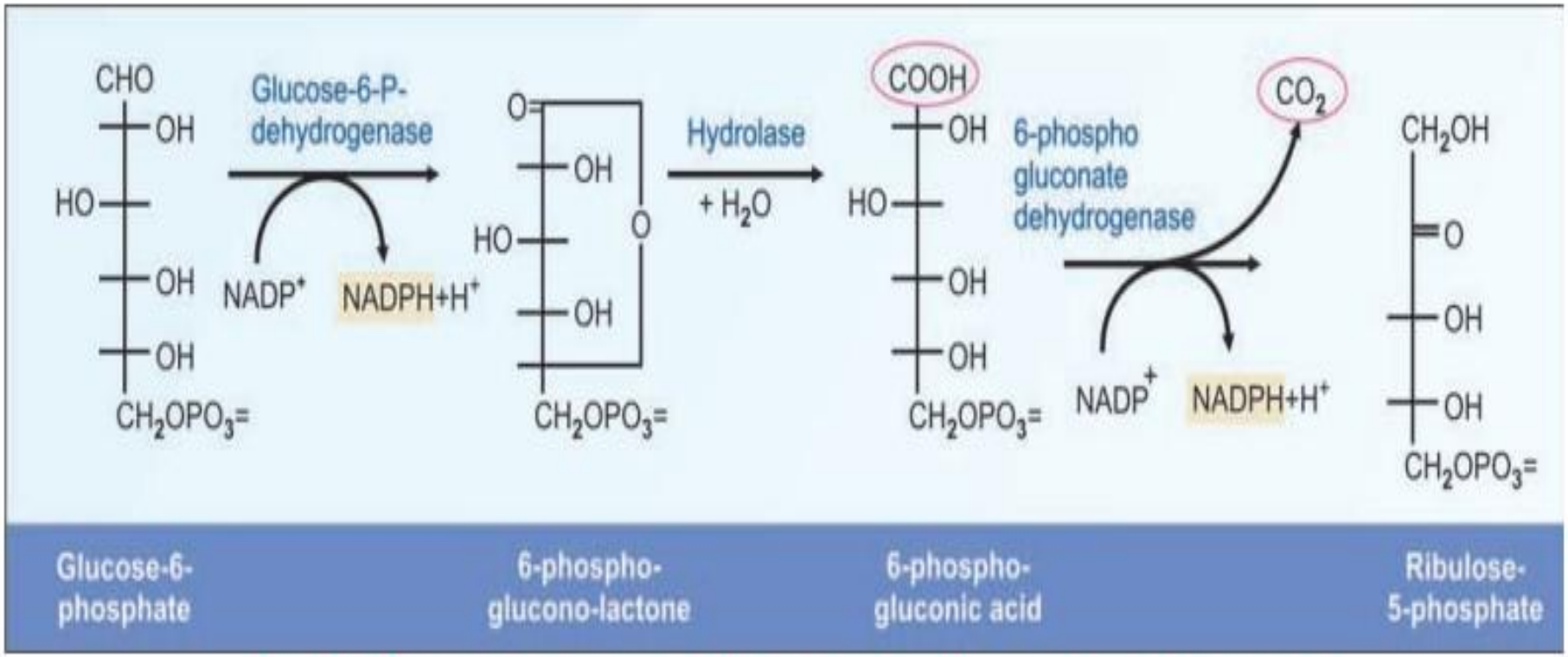


Fig. 10.1. Oxidative phase of HMP shunt pathway; Steps 1, 2 and 3

NAD vs NADP

- NAD (Nicotinamide Adenine Dinucleotide) and NADPH (Nicotinamide Adenine Dinucleotide Phosphate) are essential cofactors in cellular metabolism
- **Structural Differences**
- **NAD**: Composed of two nucleotides (one with adenine and the other with nicotinamide) linked by their phosphate groups.
- **NADPH**: Similar to NAD but has an additional phosphate group.
- **Functional Roles**
- **A. NAD**
- **Primary Function**: Electron carrier in **catabolic reactions** (energy production).
- **Oxidized Form**: NAD^+
- **Reduced Form**: NADH

❖ **B. NADPH**

- **Primary Function**: Electron carrier in **anabolic reactions** (biosynthesis and antioxidant defense).
- **Oxidized Form**: $NADP^+$
- **Reduced Form**: NADPH

❖ NADPH is not entering the electron transport chain; and NADPH will not generate ATP.

2. Non-Oxidative Phase

- - This phase interconverts various sugars and is responsible for producing **ribose-5-phosphate and other sugars**:
- Isomerization The ribulose-5-phosphate is then isomerized to ribose-5-phosphate **or** epimerised to xylulose-5- phosphate

❖ - Ribulose-5-Phosphate Isomerase:

- - Converts ribulose-5-phosphate into ribose-5-phosphate.
- A key precursor for nucleotide and nucleic acid biosynthesis.

❖ - Ribulose-5-Phosphate Epimerase:

- - Converts ribulose-5-phosphate into xylulose-5-phosphate.
- Participates in sugar interconversions.

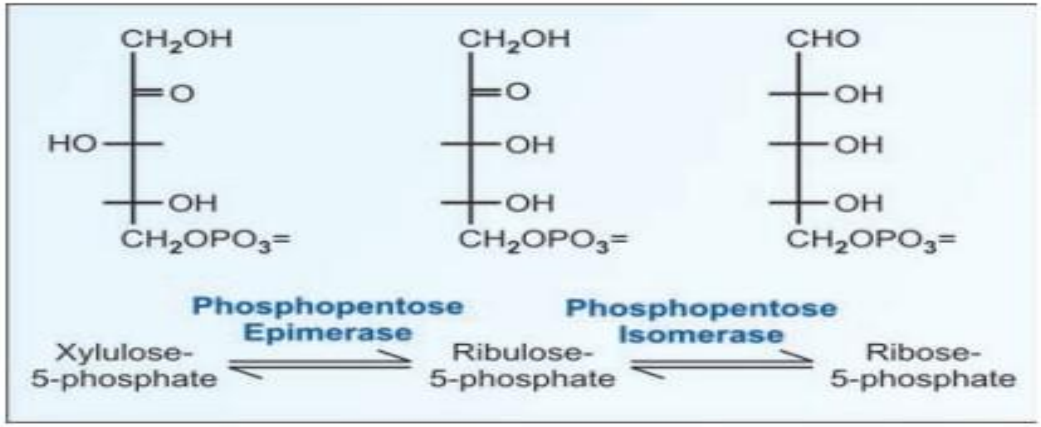


Fig. 10.2. Step 4 of HMP shunt pathway

Transketolase and Transaldolase:

- ***Transketolase and Transaldolase:***
- - These enzymes facilitate a series of reactions that convert ribose-5-phosphate and xylulose-5-phosphate into fructose-6-phosphate and glyceraldehyde-3-phosphate, which can re-enter glycolysis.

- Transketolase Reaction :- Transketolase is a thiamine pyrophosphate (TPP) dependent enzyme.

Interconnections with Other Pathways

1. - **Glycolysis**: The products of the HMP shunt, such as fructose-6-phosphate and glyceraldehyde-3-phosphate, can re-enter glycolysis, linking these pathways for energy production and biosynthetic processes.
2. **- Fatty Acid Synthesis**: NADPH produced in the HMP shunt is crucial for lipid biosynthesis, providing the reducing power required for the synthesis of fatty acids.
3. **- Nucleotide Synthesis**: Ribose-5-phosphate is essential for the synthesis of nucleotides and nucleic acids, linking the HMP shunt to cellular proliferation and growth.

Regulation

- - The HMP shunt is tightly regulated, with glucose-6-phosphate dehydrogenase being the key regulatory enzyme. Its activity is influenced by:

❖ - NADP+ Concentration: High levels activate the enzyme, driving the pathway forward.

❖ - NADPH Levels: High concentrations inhibit the enzyme, reducing the flux through the pathway.

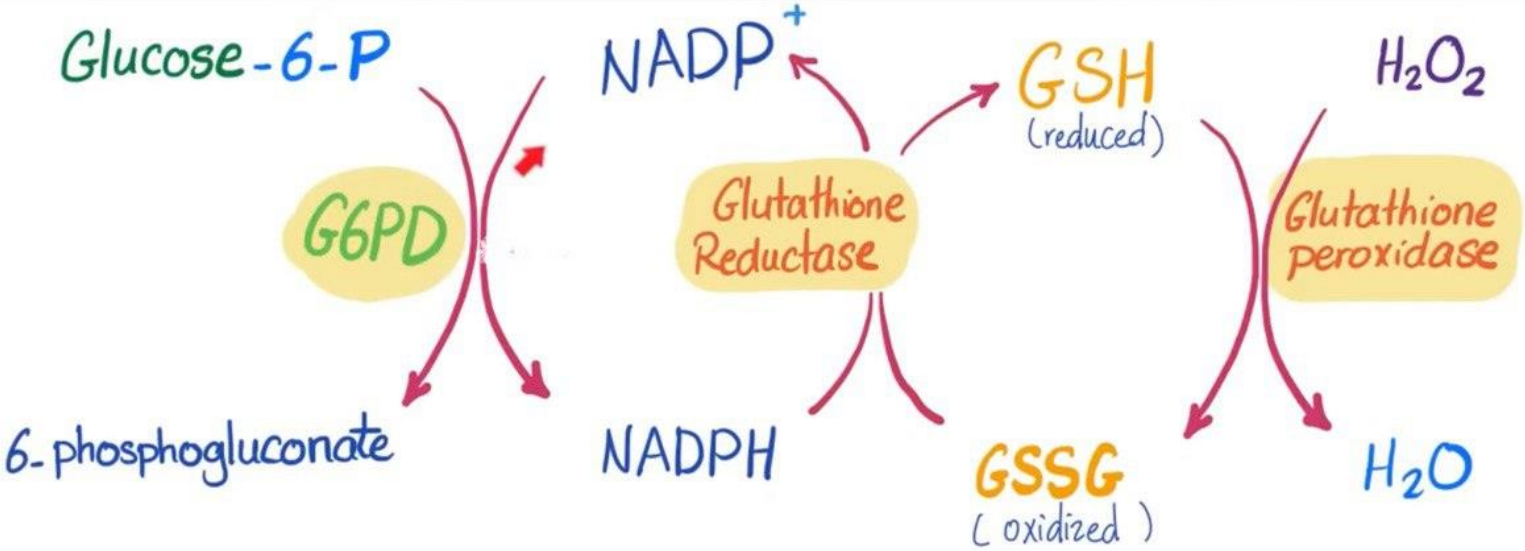
- Insulin stimulate it(the rate limiting enzyme **G6PD**)

Importance of this shunt

1- 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 glutathione reductase **(GR).**
- Reduced GR is regenerated with the help of NADPH

Free Radical Scavenging



Redox Metabolism in the Red blood Cell

ROS can
- kill bacteria (Neutrophilic oxidative burst)
- Kill our own cells (lipid peroxidation) → damages lipid

2 -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

3- Macrophage Bactericidal Activity

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

4- Availability of Ribose

- **Ribose** and deoxyribose are required for DNA and RNA synthesis
- . **What about ATP?**
- ATP is neither utilized nor produced by the HMP shunt pathway. Cells do not use the shunt pathway for energy production.

Clinical Significance of Shunt Pathway

- **1. G6PD Deficiency**

❖ **The enzyme glucose-6-phosphate dehydrogenase (G6PD) may be deficient in some persons**

❖ **It is the most common enzyme deficiency seen in clinical practice.**

❖ **The defect is transmitted as an X-linked recessive trait.**

❖ **It will lead to drug-induced hemolytic anemia.**

❖ **The deficiency is manifested only when exposed to certain drugs or toxins, e.g. intake of antimalarial drugs like primaquine. Primaquin stimulates peroxide formation inside RBC.**

❖ **In G6PD deficient cells, the level of NADPH is low; hence further production of peroxides will lead to cell lysis**

Clinical Significance

- **- Deficiency in G6PD can lead to hemolytic anemia, especially under oxidative stress, as there is insufficient NADPH to maintain reduced glutathione levels.**
- **- The pathway is also important in cancer metabolism, where rapidly dividing cells rely on NADPH for biosynthesis**.

PATIENTS with G6PD DEFICIENCY

↳ ASYMPTOMATIC until EXPOSED to an OXIDATIVE STRESSOR

SYMPTOMS

* JAUNDICE
* DARK TEA-COLORED URINE
* BACK PAIN (KIDNEY DAMAGE)
* ANEMIC SYMPTOMS
  - FATIGUE
  - HYPOTENSION
  - TACHYCARDIA
  - CONFUSION

  & OTHERS

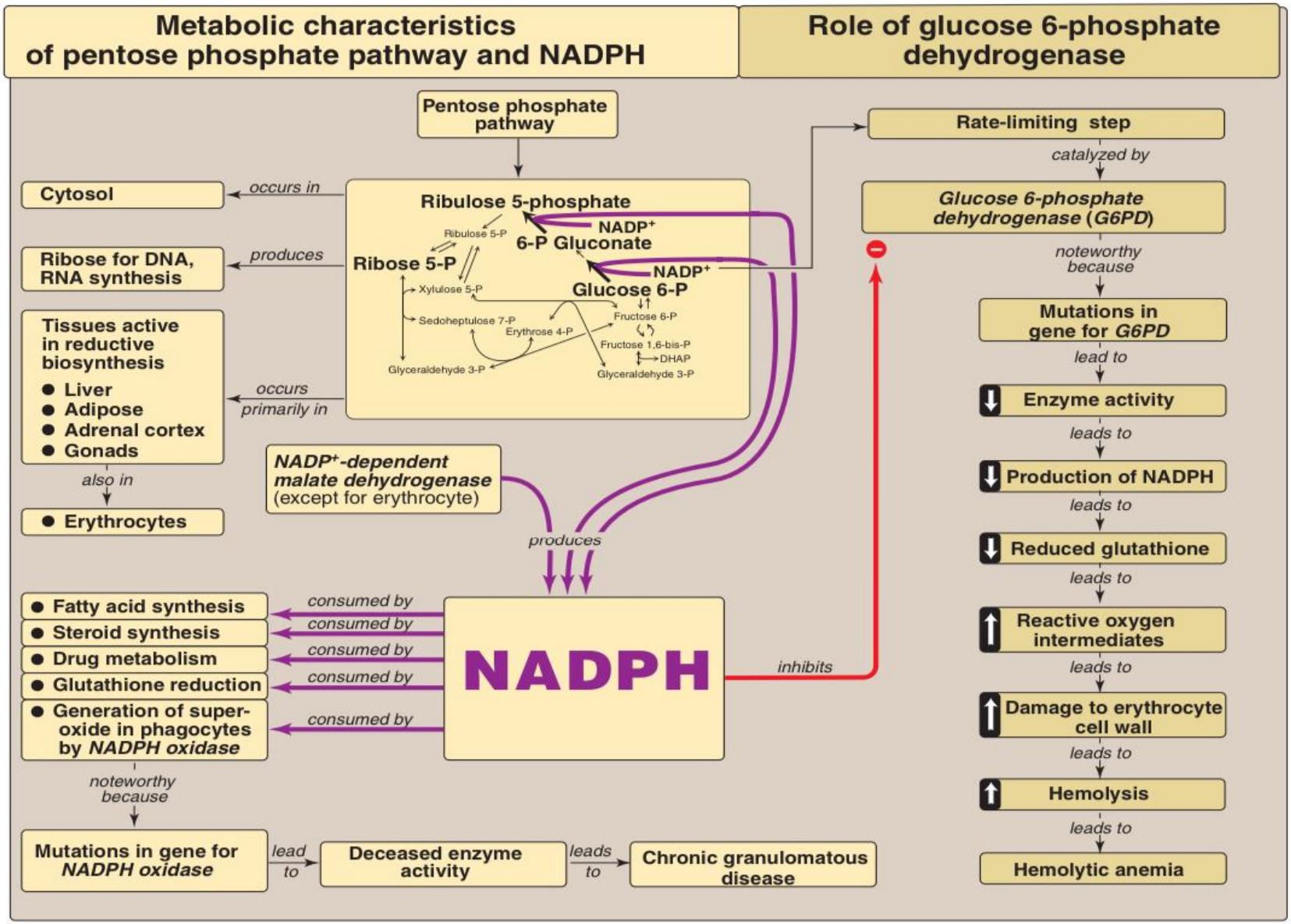


Figure 13.14
Key concept map for the pentose phosphate pathway and NADPH.

Summary of carbohydrate metabolism

- **Glycolysis** – Glucose is broken down into pyruvate, **producing ATP and NADH.**
- **Citric Acid Cycle & Oxidative Phosphorylation** – Pyruvate from glycolysis enters the mitochondria **,converted to acetyl COA then enter Citric Acid Cycle** generating ATP through the electron transport chain

- **Glycogenesis & Glycogenolysis** – Excess glucose is stored as glycogen in the liver and muscles (glycogenesis), while glycogen is broken down when energy is needed (glycogenolysis).

- **Gluconeogenesis** – The production of glucose from non-carbohydrate sources like amino acids and fats.
- **Pentose Phosphate Pathway (PPP)** – Generates NADPH and ribose-5-phosphate for biosynthesis.

Thank you

Any questions ?