18

Bio chemistry
Doctor 2017 | Medicine | JU

carbohydratesisomersketone starchlipidproteinamine

◉ Sheet ○ Slides

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Contributed in the Grammatical Correction

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Doctor

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Pentose Phosphate Pathway (PPP)

- ✓ **It is also called the "Hexose Monophosphate Shunt".**
- ✓ **It occurs in the cytosol of the cell.**
- ✓ **It includes an irreversible oxidative phase, followed by a series of reversible sugar–phosphate interconversions (reversible non-oxidative reactions).**
- ✓ **It starts with a hexose (glucose 6-phosphate) and ends with a hexose (glucose 6-phosphate or fructose 6-phosphate). This is why the PPP is also called "Hexose Monophosphate Shunt".**
- ✓ **No ATP is directly consumed or produced in this pathway.**

Functions of the PPP

I. Production of NADPH (It is the major function of the PPP).

- NADPH carries electrons for reductive biosynthesis of fatty acids in the liver, lactating mammary glands, and adipose tissue.
- Also, NADPH is an electron carrier for biosynthesis of steroid hormones in the testes, ovaries, placenta, and adrenal cortex.
- NADPH maintains Glutathione (GSH) and other scavengers in the reduced form. Scavengers are reducing agents that undergo oxidation to protect macromolecules in the cell from destruction.
- **RBC's are totally dependent on Pentose Phosphate Pathway for NADPH production.** In other cells, the PPP is the major source of NADPH production, but other reactions also take place to produce NADPH (the reactions are discussed later in lipid metabolism). So, if there is NADPH depletion the RBC's are the first cells to be affected; they will be damaged leading to hemolysis so the patient will suffer from hemolytic anemia.

II. Metabolism and production of five-carbon sugars (Pentoses).

- Forms Ribose 5-phosphate (involved in nucleotide biosynthesis).
- Metabolism of pentoses.

For each sugar in these steps you have to know its name, if it is a ketose or an aldose, and its number of carbon atoms.

The steps of PPP:

As a summary (before you start):

Glucose 6-phosphate is involved in oxidation and decarboxylation. For each glucose 6-phosphate molecule entering the irreversible oxidative part of the pathway, one CO_2

molecule and two NADPH molecules are produced. The produced sugar is Ribulose 5-phosphate. After that 3 molecules of ribulose 5-phosphate enter the reversible non-oxidative reactions to be interconverted to one glyceraldehyde 3-phosphate molecule and two fructose 6-phosphate molecules.
Two molecules of glyceraldehyde 3-phosphate and four molecules of fructose 6-phosphate can be rearranged into five molecules of glucose 6-phosphate.

The Oxidative Irreversible Reactions:

1) Dehydrogenation (Oxidation of the aldehyde group):

- Carbon 1 in glucose 6-phosphate has an aldehyde group. This aldehyde group is oxidized (and hydrolyzed**) to a carboxyl group in 6-phosphogluconate, and $NADP^+$ is reduced into NADPH.
- It is catalyzed by *glucose 6-phosphate dehydrogenase*, which is competitively inhibited by NADPH. So, this reaction is the committed, rate-limiting, and regulating step of the PPP.

**More details from the book: This dehydrogenation step actually takes place in two steps. At first, 6-phosphogluconolactone is produced by oxidation, which is a cyclic form of 6-phosphogluconate, and it is then hydrolyzed to open the cycle and become a 6-phosphogluconate by the enzyme *6-phosphogluconolactone hydrolase.*

- In Gluconic Acid, the carboxyl group is carbon 1. While in Glucoronic Acid, the carboxyl group is carbon 6. (You have to be careful with the names!!!)

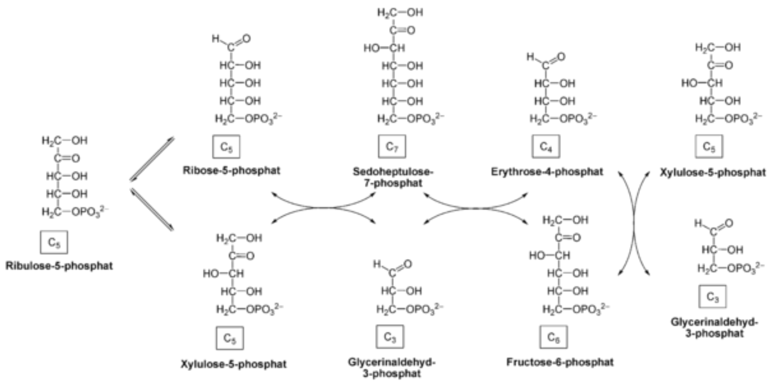
2) Formation of ribulose 5-phosphate (Decarboxylation and Oxidation of the hydroxyl group):

- The carboxyl group of 6-phosphogluconate is eliminated in the form of CO_2. The hydroxyl group on Carbon 3 in 6-phosphogluconate is oxidized into a ketone group, and $NADP^+$ is reduced into NADPH.
- It is catalyzed by *6-phosphogluconate dehydrogenase*. This irreversible reaction produces a pentose sugar–phosphate (ribulose 5-phosphate), CO_2 (from carbon 1 of glucose), and a second molecule of NADPH.

Glucose 6-Phosphate + 2 $NADP^+$ $\rightarrow$ Ribulose 5-Phosphate + CO_2 + 2 NADPH

The Non-Oxidative Reversible Reactions:

If the cell doesn't need Ribulose 5-phosphate (meaning that it was only produced in order to form NADPH), many conversions occur between sugar intermediates containing three to seven carbons, that ends eventually with reforming hexoses.
The pentoses and hexoses are interconvertible depending on the needs of the cell. If the cell requires pentoses, the reaction shifts to the left side of the process, illustrated in the photo below, forming more pentoses. The same occurs for hexoses (the process is reversible).



1) Ribulose 5-phosphate is converted either to ribose 5-phosphate by *isomerase*, or to xylulose 5-phosphate by *epimerase*.
2) Carbon units are transferred between the intermediated sugars to convert them into fructose 6-phosphate and glyceraldehyde 3-phosphate in many steps which are catalyzed by *Transketolases* and *Transaldolases*.

Transketolases transfer two-carbon units, while *Transaldolases* transfer three-carbon units.

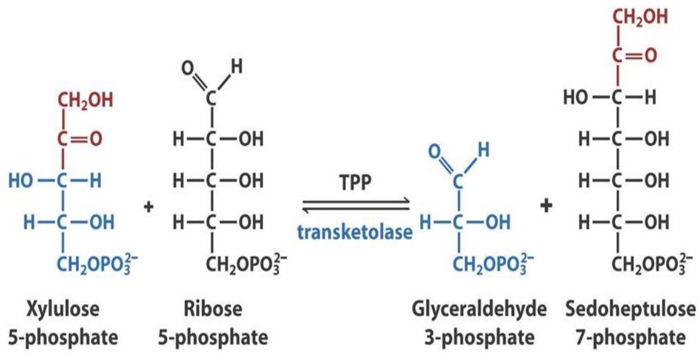
If we have sugar A (an aldose) and sugar B (a ketose), they can react by transferring carbon units to produce sugar C (a ketose) from sugar A and sugar D (an aldose) from sugar B. This reaction is catalyzed by *Transketolase* and *Transaldolase*.

Aldose + Ketose ←→ Ketose + Aldose

Sugar A + **Sugar B** ⟷ Transketolase/Transaldolase ⟷ **Sugar C** + **Sugar D**

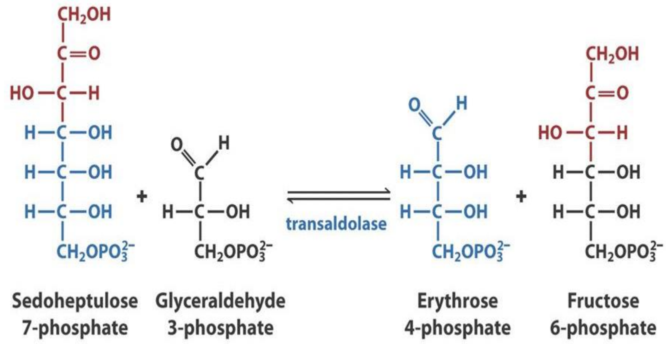
The interconversions occur in three steps:

PPP Transketolases transfer 2 Carbon units



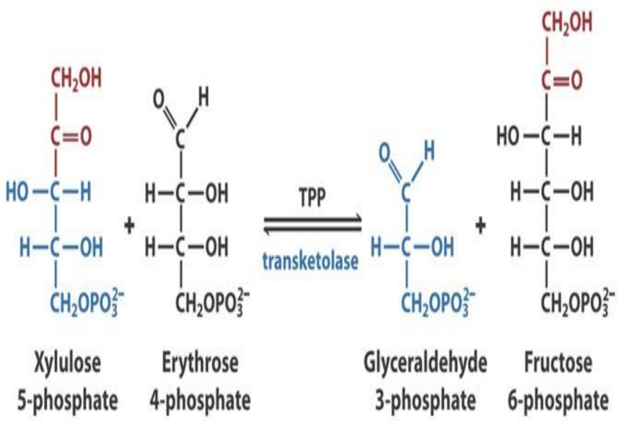
A. *Transketolase* catalyzes transferring of two-carbon units from **Xylulose 5-phosphate** to **Ribose 5-phosphate** to form **Glyceraldehyde 3-phosphate** and **Sedoheptulose 7-phosphate** (a seven-carbon sugar).

PPP Transaldolases transfer 3 Carbon units



B. *Transaldolase* catalyzes transferring of three carbon units from **Sedoheptulose 7-phosphate** to **Glyceraldehyde 3-phosphate** to form **Erythrose 4-phosphate** and **Fructose 6-phosphate.**

C. Another *Transketolase* catalyzes transferring of two-carbon units from **Xylulose 5-phosphate** to **Erythrose 4-phosphate** to form **Glyceraldehyde 3-phosphate** and **Fructose 6-phosphate.**



Summary of the non-oxidative phase:

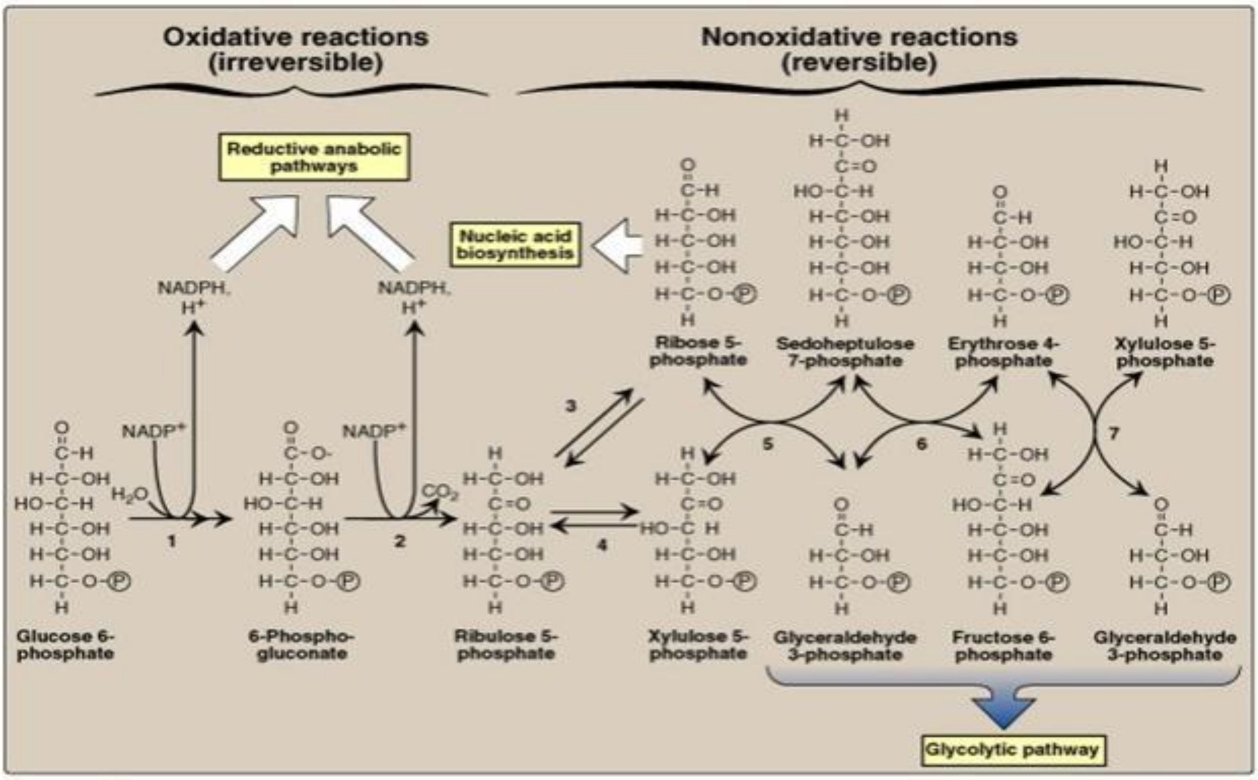
- **3 pentose 5-phosphate → 2 hexose 6-phosphate + 1 triose 3-phosphate.**
- **Reversible reactions that involve transferring of 2 or 3 carbon fragments.**
- **Ketose + aldose → ketose + aldose (ketose forms aldose and vice versa).**

- $C_5 + C_5 \longrightarrow C_3 + C_7$ **(Transketolase)**
- $C_3 + C_7 \longrightarrow C_6 + C_4$ **(Transaldolase)**
- $C_5 + C_4 \longrightarrow C_6 + C_3$ **(Transketolase)**

- The products are 1 triose 3-phosphate and 2 Hexoses 6-fructose which are intermediates in glycolysis, so 5 glucose 6-phosphate can be easily reformed from 2 triose 3-phosphate and from 4 hexoses 6-phosphate.

I. 6 Glucose 6-phosphate + 12 $NADP^+$ → 12 NADPH + 6 CO_2 + 6 Ribulose 5-Phosphate.
II. 6 Ribulose 5-Phosphate ← → 4 fructose 6-phosphate + 2 glyceraldehyde 3-phosphate ← → 5 Glucose 6-phosphate.

So, we need 3 Ribulose 5-Phosphate to form 2 xylulose 5-phosphate and 1 ribose 5-phosphate which are rearranged into 2 fructose 6-phosphate and 1 glyceraldehyde 3-phosphate.



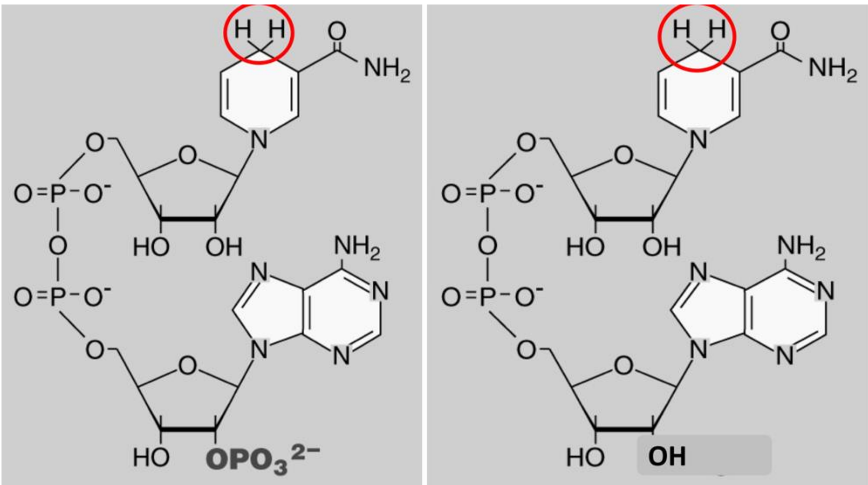
Why NADPH and NADH?

- NADPH and NADH have different roles.
- The coenzyme $NADP^+$ differs from NAD^+ only by the presence of a phosphate group on one of the ribose units. This seemingly small change in structure allows $NADP^+$ to interact with $NADP^+$-specific enzymes that have unique roles in the cell.
- Enzymes can specifically use one NOT the other.

- NADPH exists mainly in the reduced form (NADPH). NADH exists mainly in the oxidized form (NAD^+). For instance, in the cytosol of the hepatocyte:

I. $NADP^+/NADPH \approx 1/10$. So, the cell favors the use of NADPH in reductive biosynthetic reactions.

II. $NAD^+/NADH \approx 1000/1$. So, the cell favors an oxidative role for NAD^+.



The circled H's are the reducing electrons.

Uses of NADPH

1- **Reductive Biosynthesis: Some biosynthetic reactions require a high-energy electron donor to produce a reduced product. For example, Fatty acids synthesis and steroids biosynthesis.**
example: 8 CH3COO ➔ C15H33COO

2- **Reduction of Hydrogen Peroxide.**

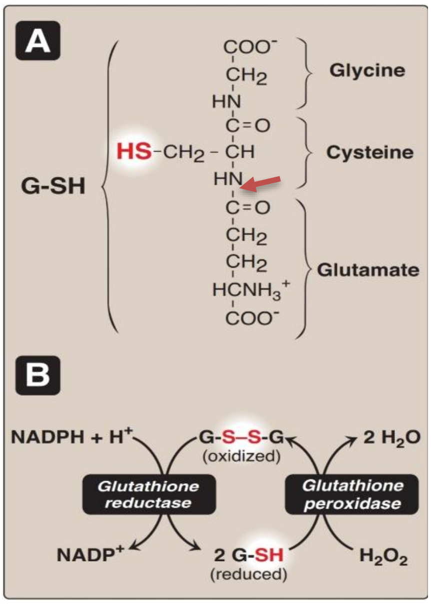
Reactive Oxidant Species

- ✓ Hydrogen peroxide (H_2O_2), Super oxide (O_2^-), hydroxyl radical ($\bullet OH^-$) are compounds known as Reactive Oxygen Species (ROS).
- ✓ They are formed continuously as by-products of aerobic metabolism in considerable amounts.
- ✓ Reactive oxygen species are excessively produced due to interaction with drugs, chemicals, environmental toxins, pollution, and smoking.
- ✓ They can cause chemical damage to our proteins, lipids, and DNA leading to cancer, inflammatory diseases, and cell death.
- ✓ They are either the direct cause of many diseases that affect any of the body's systems, or they could be by-products of diseases' complications.

Enzymes that catalyze antioxidant reactions:

They work as defense against ROS. (remove oxidants)

a. Glutathione peroxidase



- Glutathione is a reducing agent which neutralizes ROS in your body.
- Glutathione is the major antioxidant compound especially in RBC's.
- Glutathione contains three amino acids (tripeptide) which are glycine, cysteine and glutamate. Notice that the glutamate forms the peptide linkage through the γ-carboxyl group instead of the (expected) α-carboxyl group in typical peptide bonds.
- GSH is the reduced form, and GSSG is the oxidized form.
- *Glutathione Peroxidase* is a Selenium-requiring enzyme. Selenium is a metal cofactor; hence it can be taken as a supplement.
- During Oxidation, two molecules of GSH are joined by a disulfide bond: 2 GSH → GSSG.
- Glutathione is reduced back to its reduced form by *Glutathione Reductase* using NADPH.

b. Super oxide dismutase (SOD)

SOD neutralizes superoxide ion and converts it to hydrogen peroxide.

$$2(O_2^-) + 2H \rightarrow O_2 + H_2O_2.$$

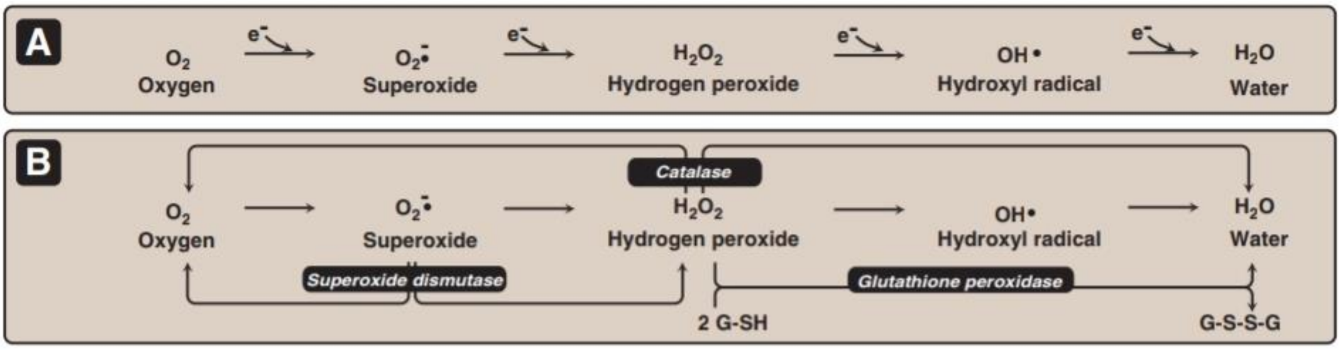
c. Catalase

It neutralizes hydrogen peroxide.

$$2H_2O_2 \rightarrow O_2 + 2H_2O$$

- A diluted solution of hydrogen peroxide is used as an antiseptic and disinfectant to kill bacteria.

- When you use this solution on your skin, oxygen bubbles arise because your tissues neutralize H_2O_2 by catalase.



Anti-oxidant chemicals: Vitamin E, Vitamin C, and Carotenoids.

These vitamins are found in healthy food and many supplements, therefore everyone must be aware to eat healthily. People above 40 years must be very careful about eating vegetables, drinking green tea, and taking antioxidant supplements in order to protect themselves from reactive oxygen species.

Good Luck!