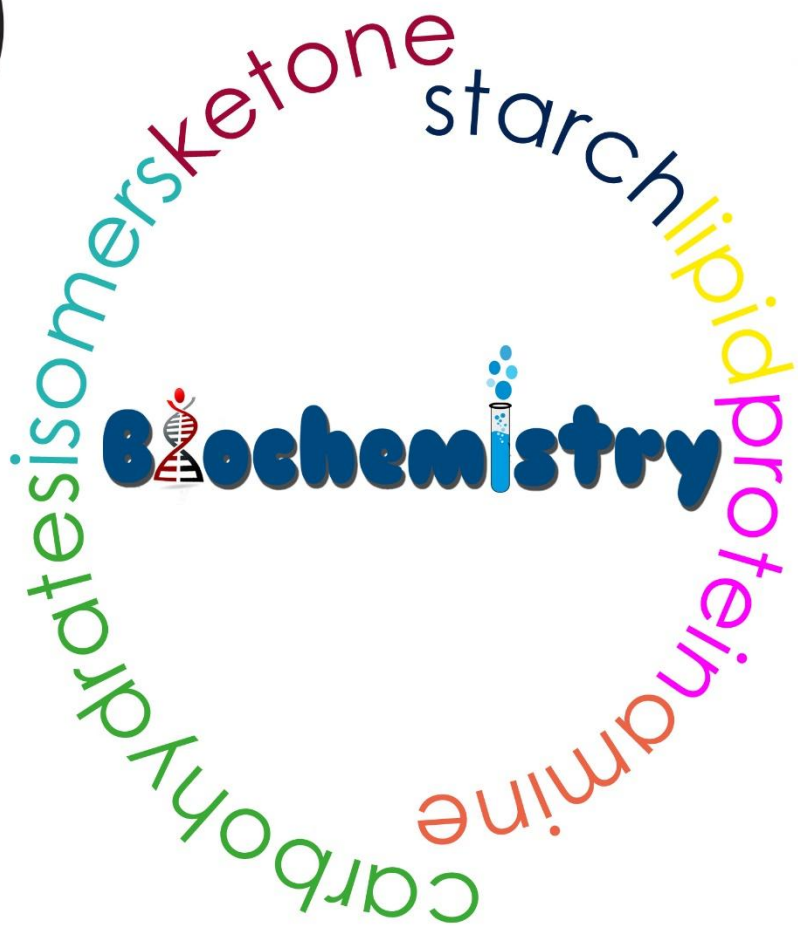


Sheet Slides

Subject :	**Monosaccharides Metabolism**
Done by :	**Joud Baki**
Corrected by :	**Abdullah AlZibdeh**
Number :	**16**

In this sheet, we will continue talking about metabolism of monosaccharides but before that let's remember what we said last time.

Fructose is first phosphorylated to fructose 1-phosphate by fructokinase and then cleaved by aldolase B to dihydroxyacetone phosphate and glyceraldehyde. DHAP is converted into glyceraldehyde 3-phosphate which can continue in the glycolytic pathway.

We also talked about disorders in fructose metabolism which can result from the deficiency of the enzyme **fructokinase**. This results in the accumulation of fructose causing ***essential fructosuria*** and it is a benign condition.

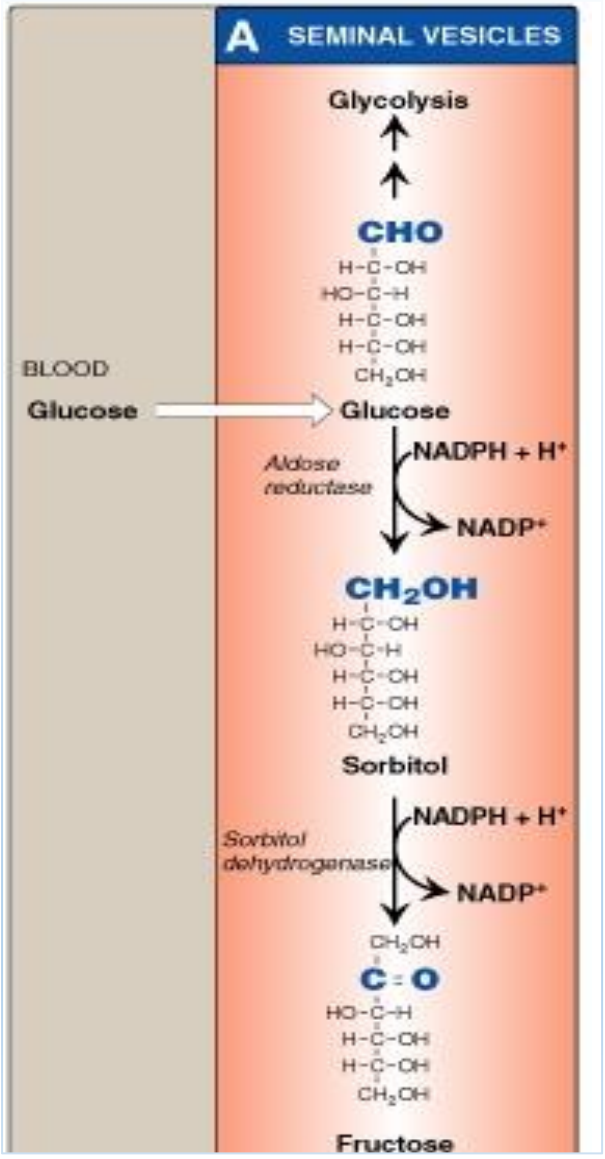
Also, the deficiency of the enzyme aldolase B which cleaves fructose 1-phosphate leads to the accumulation of fructose 1-phosphate, which eventually decreases the rate of ATP synthesis because phosphate is trapped by fructose 1-phosphate. So, the production of ATP becomes impaired causing the inhibition of gluconeogenesis. As a result, protein synthesis decreases leading to hyperuricemia. This is actually the cause of **fructose intolerance** or **fructose poisoning.** *(End of revision)*

Conversion of glucose into fructose via sorbitol:

***This will be the last part in fructose metabolism.*

As you can see in the picture below, there is glucose and sorbitol, a sugar alcohol. Sorbitol pathway can be explained in these two points:

1- The reduction of the aldehyde group "CHO" in glucose to a hydroxyl group by the enzyme **aldose reductase** forms Sorbitol.



Sorbitol is **a sugar alcohol** as the name indicates (ends with –ol), it has 6 carbons with 6 hydroxyl groups.

As a rule, whenever a sugar is reduced at the aldehyde or the ketone group, the result will be a polyalcohol (also called sugar alcohol). Sorbitol is a common sweetener used in food, especially in gum. Notice that this reduction of glucose to sorbitol requires NADPH to be converted to NADP+ (oxidation of NADPH).

2-The next step is the **<u>oxidation</u>** of sorbitol which occurs at **<u>carbon number 2</u>** to produce fructose by an enzyme called ***sorbitol dehydrogenase***, reducing NADP+ into NADPH in the process. (Be careful guys; there is a mistake in the picture in this step, the arrow should indicate that NADP+ is reduced into NADPH and NOT the opposite, please be aware).

As we can see, by these two reactions above we can get fructose from glucose.

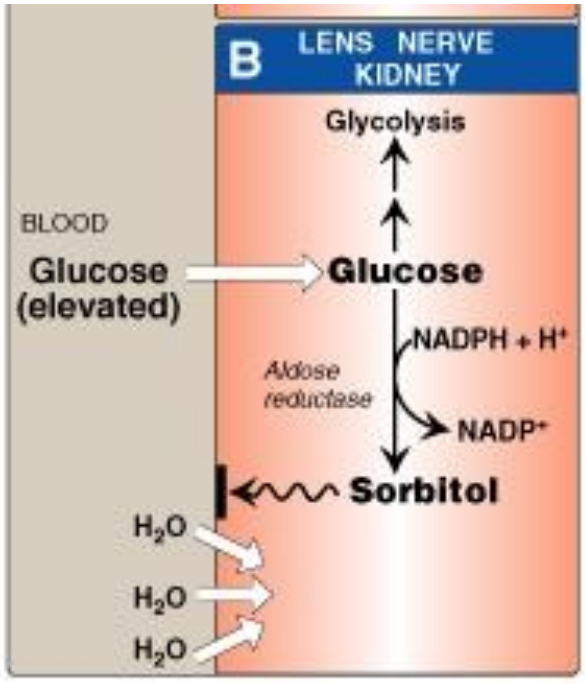
The enzyme ***aldose reductase*** is found in many tissues including liver, kidney, retina, ovaries, seminal vesicles, Schwann cells, lens, placenta, and red blood cells, while ***sorbitol dehydrogenase*** is found in the liver, ovaries and the seminal vesicles. Why in the seminal vesicles? Because fructose is the major energy source for sperm cells, that's why seminal vesicles produce fructose by these 2 reactions.

The last thing we're going to say before moving to another subject is that the reduction of glucose to sorbitol occurs in the lens, nerve cells,

kidney cells, and the other cells we mentioned above, *where aldose reductase can be found but not sorbitol dehydrogenase.*

If glucose was elevated in these tissues (hyperglycemia; in uncontrolled diabetes), something wrong happens:

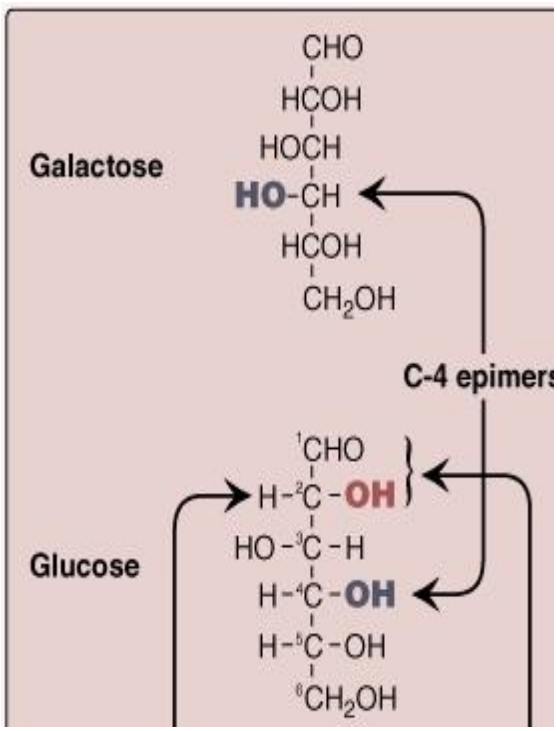
- High level of glucose → accumulation of sorbitol in retina, Schwann cells, lens and kidney (highly soluble small molecules and hardly released from the cells) → high osmotic pressure and more H_2O molecules enters the cell → the cell swells → formation of complication such as nephropathy, peripheral neuropathy, retinopathy and cataract (cataract is a medical condition in which the lens of the eye becomes opaque leading to blurred vision. We call it مي بيضا or الساد). These complications can be seen in uncontrolled diabetic cases. In addition to that, NADPH is consumed in the reaction, so the use of NADPH as a defense against free radicals is affected.



Glacatose Metabolism:

What is galactose?

- Galactose, a monosaccharide, is a C-4 epimer of glucose. Remember that carbohydrate isomers that differ in configuration around only one specific carbon (except the carbonyl carbon) are defined as epimers of each other.

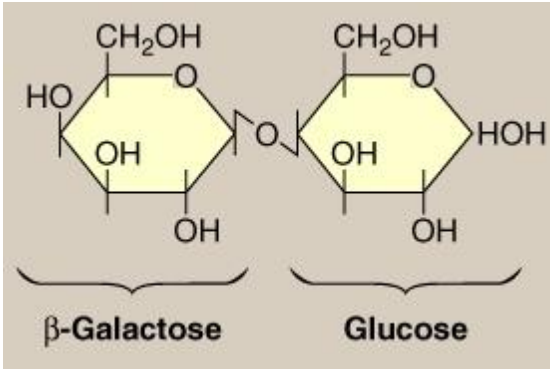


At C-4, the hydroxyl group is on the left side of galactose whereas in glucose, it's on the right.

Despite the similarity in their structures, the enzyme which uses glucose as a substrate does not use galactose and vice versa.

Sources of galactose:

The most important source of galactose is lactose, a sugar found in milk. Glucose and galactose are the components of lactose.

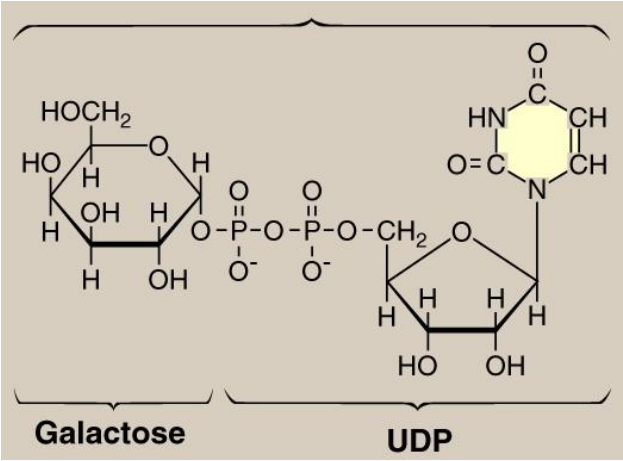


Galactose is also found in glycolipids and glycoproteins which are found in the plasma membrane of the cell.

UDP Galactose; an intermediate in Galactose Metabolism

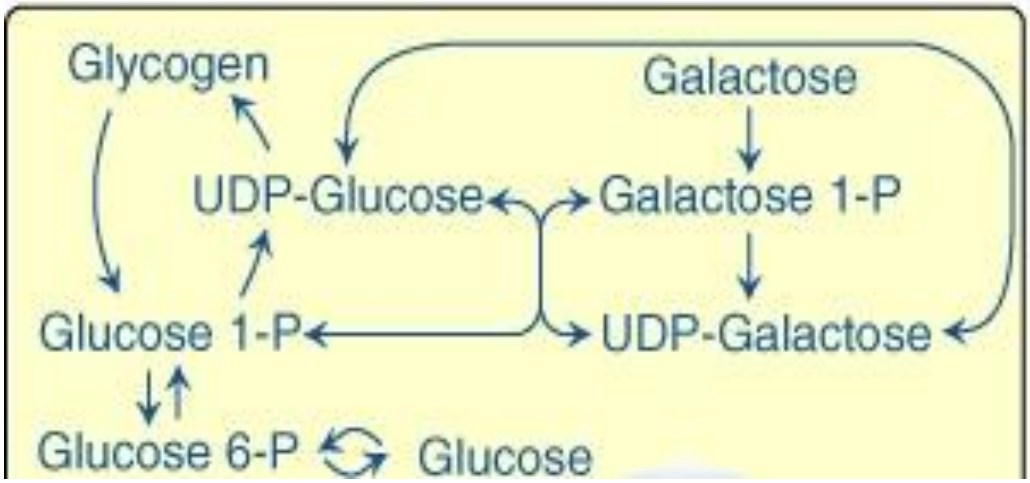
Remember that the uptake of galactose is insulin independent, just like fructose uptake. Also remember that we talked about UDP glucose in glycogen metabolism, now we have UDP galactose which is an intermediate in galactose metabolism.

Structure of Uracil diphosphate galactose (UDP galactose)



Galactose Metabolism

-



-The first step in galactose metabolism is the phosphorylation of galactose at carbon number 1 to produce galactose 1-phosphate by the enzyme *galactokinase.*

Galactose + ATP → Galactose 1-P + ADP

-The second step is the conversion of galactose 1-P to UDP-Galactose which can be achieved by the exchange of glucose and galactose from the UDP. But how?

- In this reaction, UDP-glucose reacts with galactose 1-phosphate, producing UDP-galactose and glucose 1-phosphate. So, galactose 1-P becomes glucose 1-P and UDP-glucose becomes UDP-galactose, thus we

call the *transferase* enzyme which catalyzes this reaction Galactose 1-Phosphate Uridyl transferase (GALT).

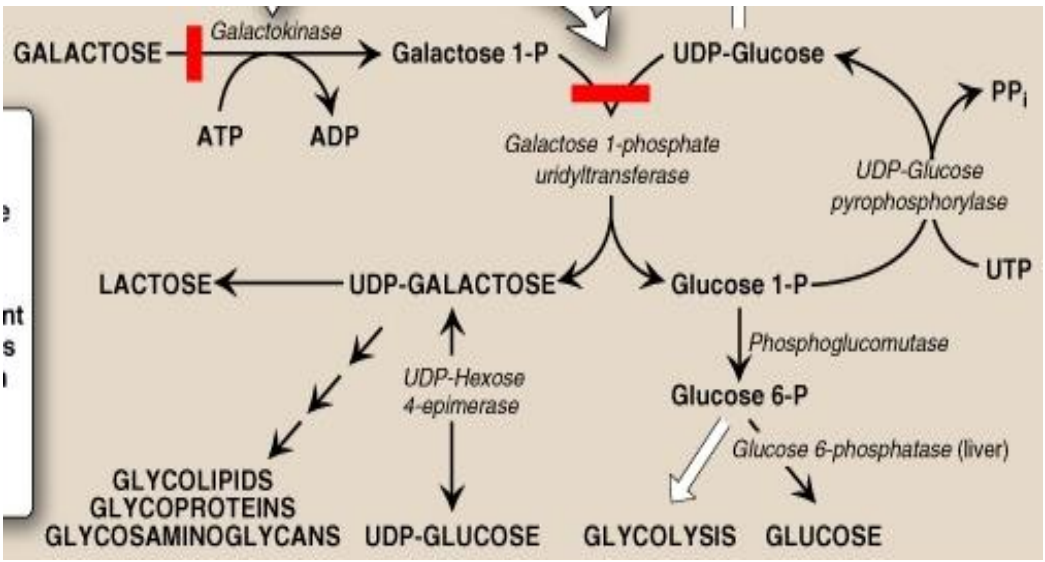
Galactose 1-P + UDP-glucose ⇌ glucose 1-P + UDP-galactose

The outcome of this pathway can be used in many other reactions, such as:

1- UDP-galactose can be converted back to UDP-glucose by an isomerization reaction using the enzyme UDP-hexose 4-epimerase (reversible isomerization). This enzyme binds the cofactor NAD^+.

UDP-Galactose ⇌ UDP-Glucose

2- UDP-glucose can give glucose 1-P which can be used to build up glycogen, converted to glucose 6-phosphate which can go through glycolysis, or converted to glucose in the liver by glucose 6-phosphatase.
3- As we will see later, UDP-galactose is used in lactose synthesis and many other pathways "see the figure".



The picture above is a summary of the galactose metabolism. You have to know the following notes:

- As usual, any enzyme can become deficient. Mutations result in the deficiency of enzymes .If the enzyme essential to life, this would lead to death.
- But if the deficiency of an enzyme is compatible with life, it would result in problems and disorders later on, and that exactly what might happen in galactose metabolism.

Deficiency of galactokinase or GALT (the transferase enzyme) may lead to disorders and problems.

- UDP- Galactose is required for the synthesis of glycolipids, glycoproteins and glycoaminoglycans (GAGs) by donating galactose to them (exactly like UDP-glucose donating glucose in glycogen synthesis).
- UDP-Galactose is also the **donor** when lactose is produced. But why is UDP-galactose added to glucose to make lactose and not UDP-glucose added to galactose? Simply because in Lactose, carbon number one of galactose binds with glucose so we use UDP-Galactose.

Disorders of galactose metabolism:

Deficiency of GALT → Accumulation of Galactose 1-Phosphate and galactose → Classic Galactosemia

So the deficiency of the galactose 1-Phosphate Uridyl transferase (GALT) does not only lead to the accumulation of its substrate (Galactose 1-P), but also the accumulation of the molecule giving this Galactose 1-P from the earlier reaction (which is Galactose).These consequences are similar to those in fructose intolerance. This leads to liver damage, severe intellectual disability, and cataract. Treatment of such deficiency is to remove galactose and "lactose" from diet.

Deficiency of galactokinase "very rare" →Accumulation of galactose →Galacticol accumulation →galactosemia and galactosuria (similar of what we've talked about in fructose metabolism.)

Aldose reductase is an enzyme which reduces galactose to galacticol (sugar alcohol). This reaction is of no importance unless galactose levels are high (as in galactosemia). It is present in the kidney, liver, seminal vesicles, retina, nerve tissue, lens, and ovaries. So when galacticol is elevated it can also cause **cataract**.

- Note that glalactosemia can result from deficiencies in GALT, galactokinase and epimerase, but GALT deficiency accounts for most cases, and so it is called classical galactosemia.

Lactose Synthesis:

Lactose is Galactosyl β (1→4) glucose, which means that it is formed from the binding of carbon 1 in galactose to carbon 4 in glucose.

The bond formed in Galactosyl β (1→4) glucose can be found in glycolipids and glycoproteins as well.

Lactose synthesis reaction:

UDP-Galactose + Glucose→ Lactose + UDP

The enzyme: *Lactose synthase.*

Lactose synthase is a complex of 2 proteins:

1- Galactosyl transferase (Protein A) 2- α-lactalbumin (Protein B)

1-Galactosyl transferase (Protein A): it is present in BOTH males and females and is found in different tissues (liver, muscle …). It is needed in glycolipids synthesis as you can see in this reaction:

UDP-Galactose + N-acetyl glucosamine→ N-acetyllactosamine

-The enzyme: *Galactosyl transferase (protein A)*
-The product N-acetyllactosamine is found in glycolipids and glycoproteins.

2-α-lactalbumin (Protein B): it is present ONLY in lactating mammary glands ("lact" means milk). Its synthesis is stimulated by the hormone *prolactin*.

TOGETHER Protein A and Protein B make the enzyme Lactose synthase.

-We all know that in order to make lactose, glucose must be added to galactose, so the enzymes will be working on glucose as a substrate.

-But why doesn't Galactosyl transferase (Protein A) produce lactose without the presence of protein B? Because this enzyme has an EXTREMELY **high Km** for **Glucose** as a substrate (low affinity) so it does not recognize glucose alone, it actually recognizes N-acetyl glucosamine as well.

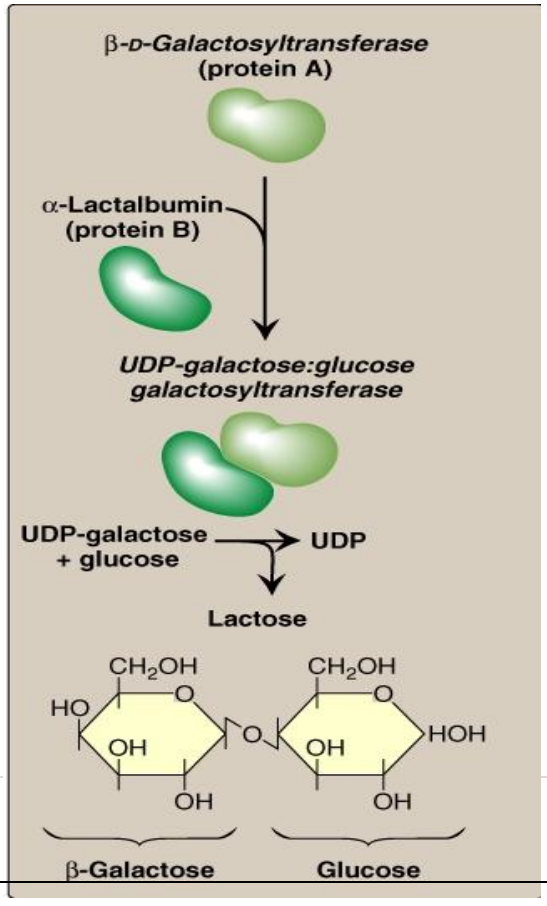
Whereas in the presence of **lactalbumin**, the protein-protein interaction greatly decreases Km, leading to a change in specificity, so Glucose can be recognized alone.

Production of Milk (Lactose):

1- The pituitary gland (الغدة النخامية) produces the hormone Prolactin after giving birth directly.

2- Prolactin goes to the mammary gland to make this gland produce lactalbumin

3- Together Protein A (galactosyltransferase) and Protein B (lactalbumin) make up the lactose synthase, which is the enzyme in the lactose synthesis reaction :
UDP-Galactose + Glucose→ Lactose + UDP



Pentose Phosphate Pathway (PPP)
Or
Hexose Monophosphate Shunt

As the name indicates, Pentose phosphate pathway (PPP) is the metabolic pathway of sugars composed of (five carbons + one phosphate group). This pathway is also called *Hexose Monophosphate Shunt.*

Functions of Pentose Phosphate pathway (PPP):

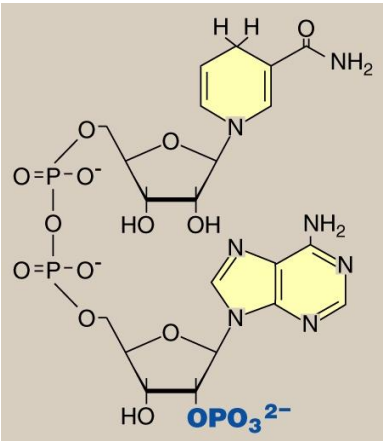
a-The Production of NADPH:

1- NADPH dependent biosynthesis of fatty acids, as in the: Liver, lactating mammary glands, adipose tissue.

2- NADPH dependent biosynthesis of steroid hormones as in the: testes, ovaries, placenta, and adrenal cortex.

3- Maintenance of Glutathione (GSH) in the reduced form in the RBCs.

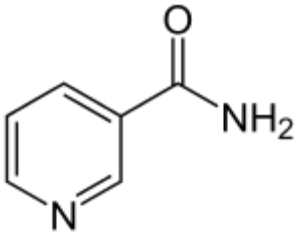
Nicotinamide adenine dinucleotide phosphate (NADPH):



** This is the structure of NADPH (Nicotinamide adenine dinucleotide phosphate).

So it composed of adenine +dinucleotide (two nucleotides) + phosphate + nicotinamide.

The single nucleotide is composed of ribose + phosphate group + nitrogenous base (the coloured rings are the nitrogenous bases).

**This is nicotinamide 

NADH vs. NADPH:

* Both have similar structures, but NADPH has an additional phosphate group on the ribose.

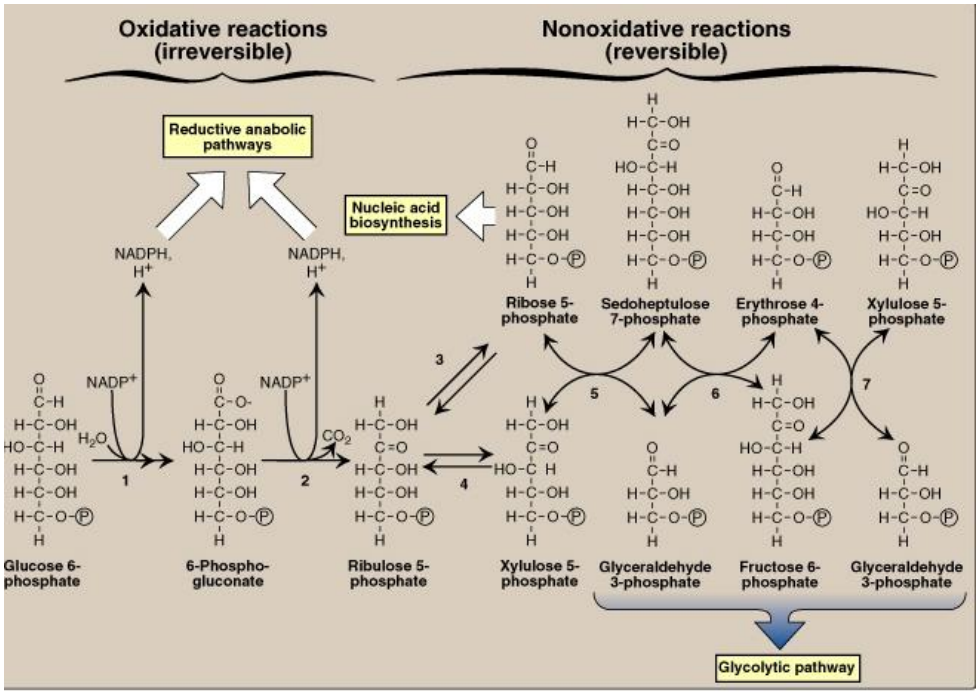
* NADH uses the high energy electrons for energy production, whereas NADPH uses high energy electrons for reductive biosynthetic pathways and for oxidants' reduction.

b- Production and metabolism of pentoses.

Metabolism of five-carbon sugars (pentoses):

-Why do we need Pentoses such as Ribose? We need them to synthesize RNA and DNA.

-So the metabolism of five-carbon sugars such as Ribose is required for nucleotide biosynthesis, and these pentoses can result from RNA degradation.



This figure shows the Pentose Phosphate pathway. It surely does frighten you in the very beginning, but it is so simple if you just try to divide it and understand each part. Now follow me step by step.

First of all, pentose phosphate pathway is composed of TWO branches (TWO kinds of reactions) which are:

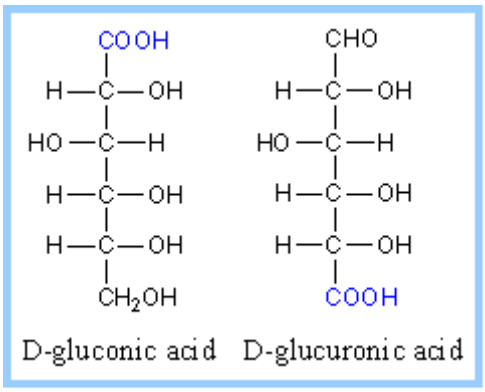
a. Oxidative reactions ,which are <u>IRREVERSIBLE</u>
b. Nonoxidative reactions ,which are <u>REVERSIBLE</u>

a. Oxidative reactions*:*

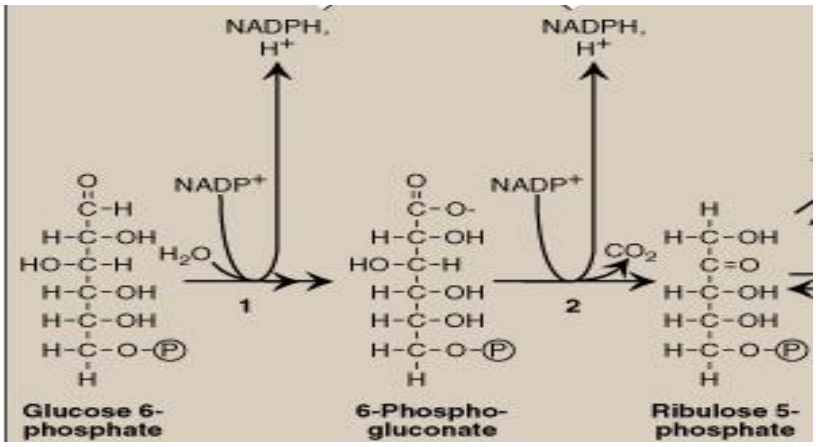
1- Starting with oxidative reactions, **Glucose 6-Phosphate** is oxidized by the enzyme *Glucose 6-Phosphate Dehydrogenase (G6PD)* , which means the aldehyde group in glucose 6-P is oxidized to carboxyl group (remember oxidation of aldehydes gives carboxylic acids) resulting in **6-Phosphogluconate** . At the same time, NADP+ is reduced to NADPH. This reaction is the rate limiting and the regulated reaction, and it is inhibited by NADPH "feedback inhibition".
This step consists actually of 2 reactions:

- Glucose 6-phosphate + $NADP^+$ = 6-phosphogluconolactone + NADPH + H^+ (enzyme: glucose 6-phosphate dehydrogenase).
- Hydrolysis of 6-phosphogluconolactone to 6-phosphogluconic acid (enzyme: 6-phosphogluconolactone hydrolase).

*Remember: gluconic acid "carboxyl group at C1" vs. glucuronic acid "carboxyl group at C6"



2- **In 6-Phosphogluconate**, the Hydroxyl group on <u>carbon number 3</u> will be oxidized to Ketone group (remember that oxidation of primary alcohols gives aldehydes and oxidation of secondary alcohols gives ketones) AND <u>carbon number 1</u> in this compound will be released in the form of **CO2**, so what just happened in this step is ***Oxidation + Decarboxylation***, resulting in a Ketose called Ribulose 5-Phosphate (Rib**ul**ose is the isomer of Ribose and it is a ketose as the name indicates "**ul**"), and reduction of NADP+ to NADPH occurs here as well. This reaction is catalyzed by 6-phosphogluconate dehydrogenase.



<u>To summarize oxidative reactions :</u>

Glucose 6 Phosphate +2 NADP+ → Ribulose 5-Phosphate + CO_2 + 2NADPH

- So if we have six Glucose 6-P molecules for example, how many NADPH molecule are they going to give? The answer is 12.

**It is an IRREVESIBLE reaction because of the Decarboxylation (the release of CO2).

This portion of the pathway is particularly important in the liver, lactating mammary glands, and adipose tissue, which are active in the NADPH-dependent biosynthesis of fatty acids; in the testes ovaries, placenta, and adrenal cortex, which are active in the NADPH-dependent biosynthesis of steroid hormones; and in red blood cells (RBCs), which require NADPH to keep glutathione reduced.

b- Nonoxidative reactions

And now moving to the other part of the pentose phosphate pathway, where pentoses react in nonoxidative reactions. The nonoxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids.

First of all, **Ribulose 5-Phosphate** will be converted to **Ribose 5-Phosphate** by an *isomerase*, OR it can be converted to **Xylulose 5-Phosphate** (a ketose) by an *epimerase* (Xylulose 5-P and Ribulose 5-P are isomers).

- Seven simple rules you need to know about nonoxidatvie reactions:

1- Nonoxidative reactions in the (PPP) are ONLY **rearrangements** of sugars, which means that there won't be any CO2 release or ATP production or oxidation or reduction.
2- Three pentose phosphates will eventually give two hexose phosphates and one triose phosphate.
   -Three pentoses =15 carbon atom
   -Two hexoses +one triose =15 carbon atom
   Same number of carbon atoms; that's why we said it's only rearrangement of sugars.

3 pentose phosphate ⇌ 2 hexose phosphate +1 triose phosphate

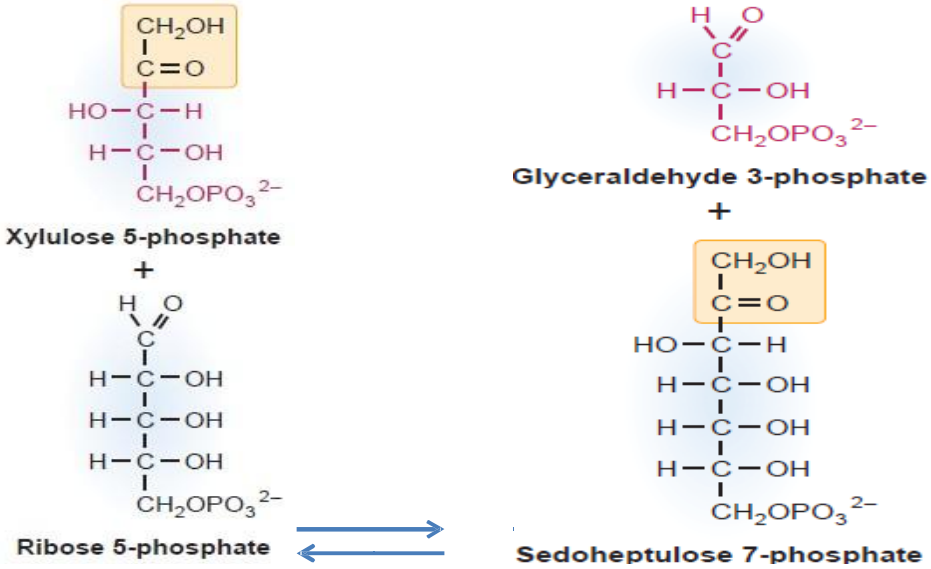
3- They are REVERSIBLE reactions.
4- Transfer of 2 or 3 carbon fragment from sugar to sugar.
5- **Transketolase** transfer 2 carbons and **Transaldolase** transfer 3 carbons.
6- **Ketose + Aldose ⇌ Ketose + Aldose** ….. and this reaction is reversible as we said .

7- The transfer always occurs from *Ketose* to *Aldose* (the donor is the Ketose and the acceptor is the aldose).

Now let's start with the nonoxidative reactions and see if these rules are applicable or not.

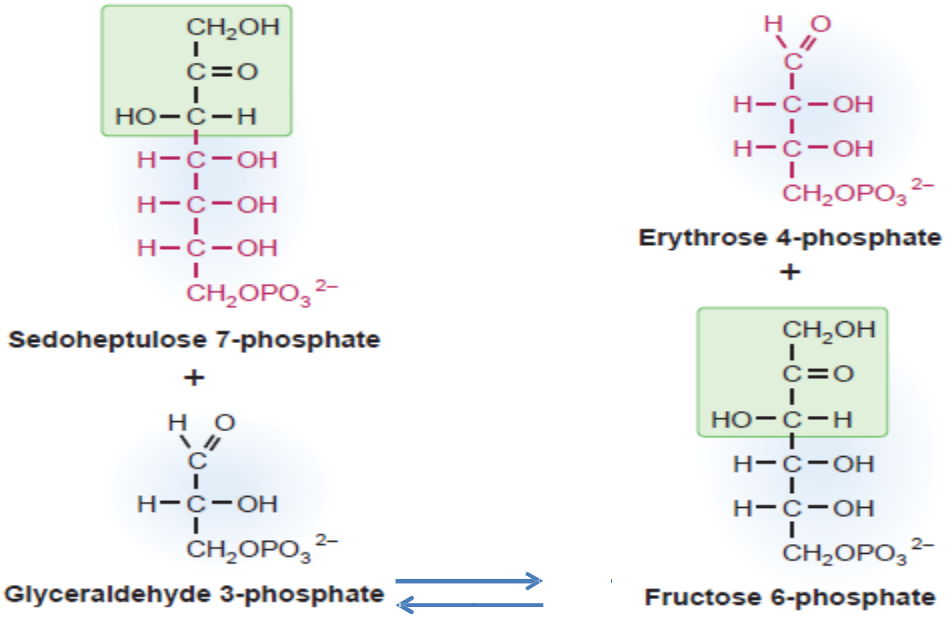
The first reaction:

Two carbons are transferred from Xylulose 5-Phosphate (ketose) to Ribose 5-Phosphate (aldose), turning the Xylulose 5-P into a triose called glyceraldehyde 3-phosphate (aldose composed of 3 carbons), and the Ribose 5-P turns into Sedoheptulose 7-Phosphate (ketose composed of 7 carbons, hept=seven, ul=ketose). This reaction is catalyzed by transketolase (coenzyme: thiamine pyrophosphate).



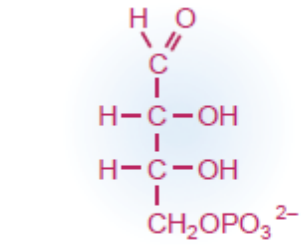
The second reaction:

Three carbons are transferred from sedoheptulose 7-Phosphate (ketose) to Glyceraldehyde 3-phospate (aldose), turning the sedoheptulose 7-P into a tetrose called Erythrose 4-Phosphate (aldose composed of 4 carbons), and the Glyceraldehyde 3-P into fructose 6-Phosphate (a ketose hexose). This reaction is catalyzed by transaldolase.



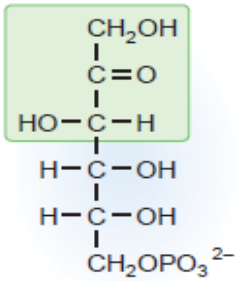
The third reaction:

Erythrose 4-P will accept a new fragment (2 carbons) from Xylulose 5-phosohate "which is produced from ribulose 5-p by the enzyme phosphopentose epimerase" to give fructose 6-phosohate, whereas xylulose 5-phosphate becomes glyceraldehyde 3-phosphate. This reaction is catalyzed by transketolase (coenzyme: thiamine pyrophosphate).



Erythrose 4-phosphate

+



Fructose 6-phosphate

Ok.. So?! What is the idea beyond all these reactions??
Let's see, the NET nonoxidative reaction is:

3 Ribulose 5-Phosphate ⇌2 fructose 6-phosphate + 1 Glyceraldehyde 3-Phosphate

- The net equation for the whole pathway:
3G6P + 6NADP$^+$ = 2F6P (=2G6P) + 6NADPH + GA3P + 3CO_2 +6H^+

-The idea is that our body can make ribose and ribulose by nonoxidative reactions in the pentose phosphate pathway.
How?? Using intermediates of glycolysis such as Fructose 6-phosphate and Glyceraldehyde 3-phosphate to make ribose 5-phosphate or ribulose 5-phosphate.

-Another thing is that our body can actually make intermediates of glycolysis and gluconeogensis by using nonoxidative reactions as well.
How?? We'll see. By multiplying the NET nonoxidative reaction by 2 we get:

6 Ribulose 5-Phosphate ⇌4 fructose 6-phosphate + 2 Glyceraldehyde 3-Phosphate

Remember : fructose 6-phosphate and glyceraldehyde 3-phosphate are intermediates in gluconeogenesis so they can be converted to ***glucose 6-phosphate .***
So 4 fructose 6-p and 2 glyceraldehyde 3-p can give 5 glucose 6-p

-Notice that the number of carbons in this reaction has stayed the same (30 carbons) … because it is ONLY a rearrangement reaction.

FINALLY, we can simply say that: Pentose Phosphate Pathway (PPP) produces NADPH and Pentoses.

Three important points :

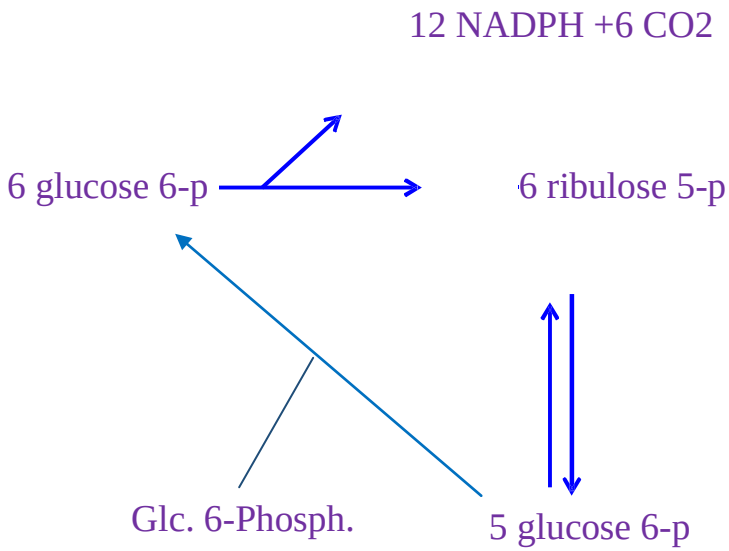
1-Suppose a cell (like RBC) needs only NADPH (but without pentoses) , the whole pentose phosphate pathway will happen (oxidative and non oxidative reactions will occur) giving 12 NADPH molecules , and that's because we started by 6 glucose 6-p and ended with 5 glucose 6-p ; so adding another molecule of glucose 6-p to the 5 gluc 6-p (that we ended with) will ultimately give us again 6 gluc 6-p (the same number of molecules we started with) , which means there was only NADPH production but NO pentoses .

2-Suppose we only need sugars like pentoses, we can simply use the second part of the reaction (nonoxidative reactions which are reversible), where 5 glucose 6-p can give 4 fructose 6-p and 2-glyceraldehyde 3-p which will give 6 ribulose 5-p (the pentose we need) .

3-Suppose we need both NADPH and pentoses (like ribulose), then ONLY oxidative reactions will occur , giving 12 NADPH and releasing 6 CO2 , and eventually making 6 ribulose 5-p (which is a pentose) .

*Please check the figure below to understand these three points

(Multiplied by 6)



I know you guys wanted a shorter sheet, and I wanted that too! But the lecture was long, sorry for mistakes and good luck all ☺

The End