بسم الله الرحمن الرحيم

METABOLISM

FINAL – Lecture 1

Pentose Phosphate Pathway (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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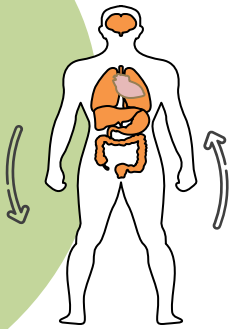

فريق دوبامين العلمي - THE SCIENTIFIC TEAM OF DOPAMINE - APPROVED 0501223 FINAL Lecture 1

Pentose Phosphate Pathway (PPP) or Hexose Monophosphate Shunt

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Pentose Phosphate Pathway (PPP) or Hexose Monophosphate Shunt

- The **pentose phosphate pathway** is named as such because it produces pentose (five-carbon) sugars and NADPH molecules (which include phosphate).

- This pathway is also referred to as the "**hexose monophosphate shunt**" because it begins with a six-carbon sugar (mainly glucose) that has a single phosphate group (monophosphate). It acts as an alternative route (shunt) , where glucose-6-phosphate does not immediately enter glycolysis but instead goes through a different pathway before eventually rejoining glycolysis at a later stage.

Functions of the PPP

1. **Production of NADPH** → **Most important**
   - ✓ 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 reduced form in the RBCs

2. **Metabolism of five-carbon sugars (Pentoses)**
   - ✓ Ribose 5-phosphate (nucleotide biosynthesis)
   - ✓ Metabolism of pentoses

SEE NEXT SLIDES FOR FURTHER EXPLANATION

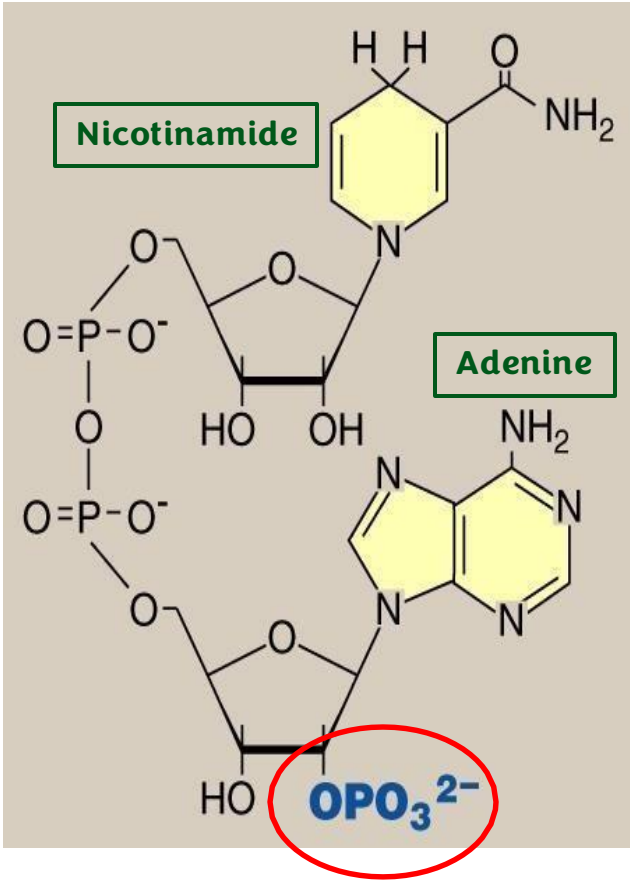
Functions of the PPP / 1

1- Production of NADPH

- In general , degradative (catabolic) pathways involve the oxidation of the main substrate and the reduction of a coenzyme. In contrast , synthetic (anabolic) pathways involve the reduction of the main substrate and oxidation of a coenzyme.
- This setup ensures that the cell is equipped (سبحان الله) with two pools of coenzymes : one predominantly in an oxidized form and the other in a reduced form. This arrangement allows the cell to carry out the needed reactions , whether it requires oxidizing or reducing the main substrate.
- For instance , in synthetic pathways such as fatty acid synthesis, steroid hormone synthesis (e.g. sex hormones) , aldosterone or cortisol , etc , the main substrate is reduced, and the coenzyme , primarily NADPH, is oxidized.
- Additionally , NADPH plays a key role in regenerating glutathione , a tripeptide that acts as an antioxidant. This regeneration is essential to maintain adequate levels of glutathione, enabling it to counteract reactive oxygen species (ROS) and protect cells from oxidative damage.

Structure of NADPH

- NADPH stands for nicotinamide adenine dinucleotide phosphate
- As shown , the connection between the two sugar molecules in NADPH is through phosphate groups
- The additional phosphate -marked in red- (which differentiates NADPH from NADH) is attached to the sugar bound to adenine.
- This phosphate group does not affect the site of oxidation-reduction reactions , as these occur at the same location in both NADH and NADPH. However, enzymes are able to distinguish between NADH and NADPH , allowing each to play distinct roles in cellular processes.



Functions of the PPP / 2

2- Metabolism of five-carbon sugars (Pentoses)

- **The second , less critical function of the pentose phosphate pathway is the production of pentose sugars , which are essential for synthesizing various nucleotides.**

- **This pathway is active when glucose levels are high (bcz it uses glucose-6-phosphate) , such as in a well-fed state. Additionally , other related anabolic pathways are generally active during this well-fed state (NADPH level is also high) .**

Pentose Phosphate Pathway (PPP)

Phases of the PPP

The pentose phosphate pathway (PPP) is composed of two phases :

- ✓ Oxidative Phase : This phase is irreversible and involves oxidation-reduction reactions.
- ✓ Non-Oxidative Phase : This phase is reversible and does not involve oxidation.

Phase One : Oxidative Phase

Begins with glucose-6-phosphate , produced when glucose is phosphorylated by either glucokinase or hexokinase. This traps glucose in the cell , diverting it into the PPP.

Step 1 :

- Oxidation Reaction : Converts the carbonyl group of glucose-6-phosphate to a carboxyl group , forming 6-phosphogluconate. (Oxidation on C1 -onate / C6 -uronate)
- The enzyme glucose-6-phosphate dehydrogenase (G-6-PDH) catalyzes this step , reducing NADP+ to NADPH.
- G-6-PDH is essential in the PPP and is associated with several common diseases.

Step 2 :

- Oxidative Decarboxylation : The removable of the carboxyl group from 6-phosphogluconate as CO_2 , and oxidation of the hydroxyl group on carbon 3 (of 6-phosphogluconate) to form a ketose (carbonyl on C2)
- This reaction produces ribulose-5-phosphate (a pentose), catalyzed by 6-phosphogluconate dehydrogenase (6-PGDH).
- Another NADP+ is reduced producing NADPH molecule.

Phase Two : Non-Oxidative Phase

Step 3 :

- Ribulose-5-phosphate is converted to ribose-5-phosphate through an isomerization reaction (ketose to aldose), catalyzed by an isomerase enzyme in a reversible reaction.
- Ribose-5-phosphate can exit the pathway for nucleotide synthesis , especially during the S phase of cell division when energy and nucleotide demand is high (during well-fed state) - or may continue the pathway-
- However , to continue the pathway , a new molecule of glucose-6-phosphate enters Phase One , producing more ribulose-5-phosphate.

✓ Any loss in carbons happens in phase one not phase two

Step 4 :

- Ribulose-5-phosphate then bypasses step 3, converting into xylulose-5-phosphate (a ketose) by an epimerization reaction , catalysed by epimerase.

✓ At this stage, we have two 5-carbon molecules : ribose-5-phosphate and xylulose-5-phosphate

- Xylulose-5-phosphate transfers two carbons to ribose-5-phosphate , forming sedoheptulose-7-phosphate and glyceraldehyde-3-phosphate.
- Sedoheptulose-7-phosphate then transfers three carbons to glyceraldehyde-3-phosphate, producing fructose-6-phosphate and erythrose-4-phosphate.
- This process is repeated with a new glucose-6-phosphate entering Phase One, converting to ribulose-5-phosphate and then to xylulose-5-phosphate , which transfers two carbons to erythrose-4-phosphate.
- This results in another fructose-6-phosphate molecule and glyceraldehyde-3-phosphate from xylulose.

End products of the PPP

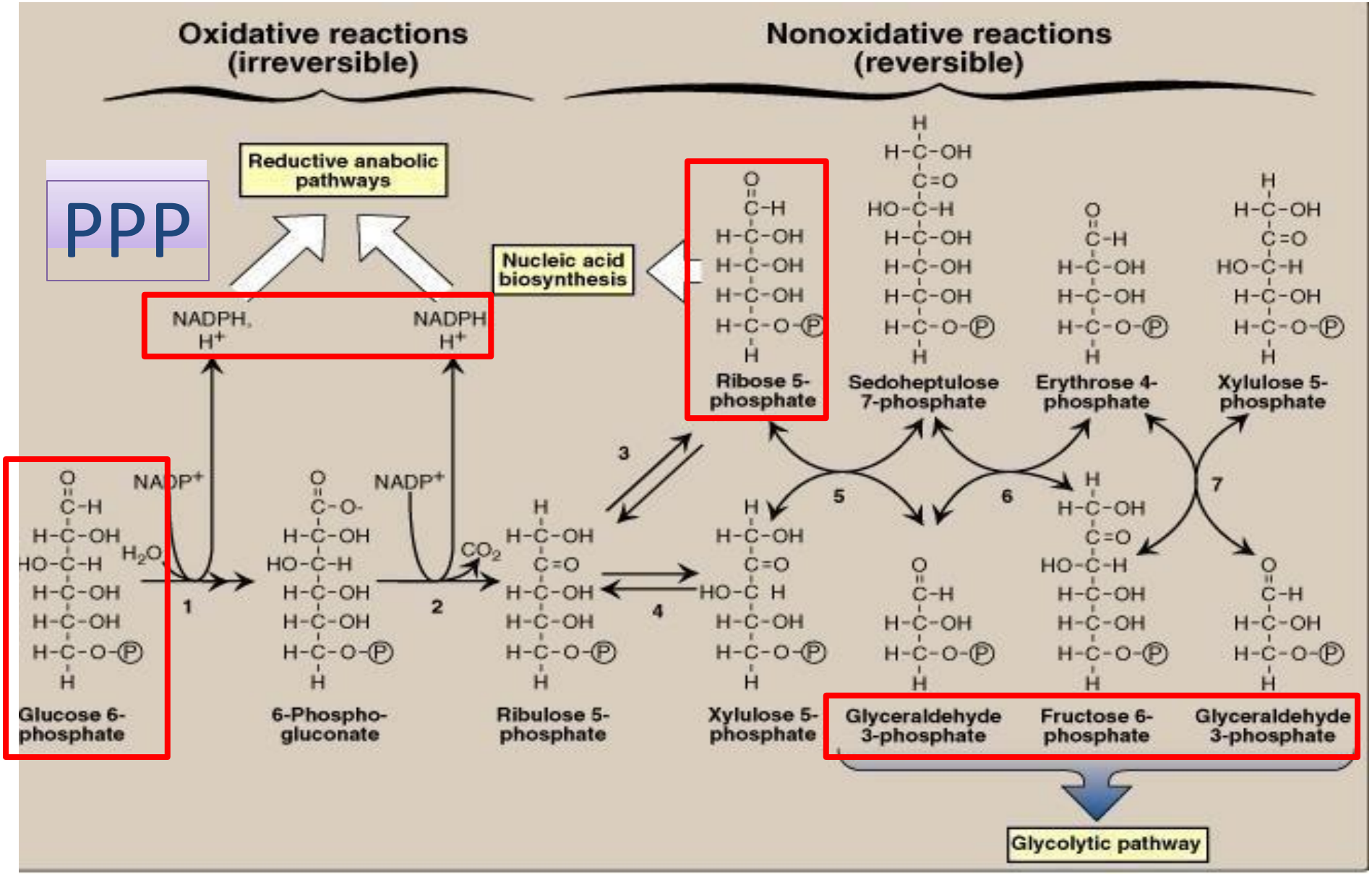
- **End of Phase One** : produces two NADPH molecules per glucose-6-phosphate molecule.

- **End of Phase Two** : produces two fructose-6-phosphate molecules and glyceraldehyde-3-phosphate , both are intermediates of glycolysis.

- **Key Outcome of the Pentose Phosphate Pathway :**

This pathway , an alternative to glycolysis , generates NADPH along with glycolytic intermediates.

- **NADPH** is critical for antioxidant function , specifically in regenerating glutathione to protect cells from reactive oxygen species (ROS)



Note: the phosphate group is always on the last carbon of the molecule

Phase	# of Step	Reaction Type	Enzyme	Reactants (Or intermediates)	Products	Coenzyme
Oxidative phase	Step 1	Oxidation - Reduction	Glucose-6-phosphate dehydrogenase	Glucose-6-phosphate	6-phosphogluconate	NADP+ → NADPH
	Step 2	Oxidative decarboxylation	6-phosphogluconate dehydrogenase	6-phosphogluconate	Ribulose-5-phosphate	NADP+ → NADPH
Non-oxidative phase	Step 3	Isomerization	Isomerase	Ribulose-5-phosphate	Ribose-5-phosphate (may exit the pathway or may continue)	
	Step 4 (Bypass step 3 for second molecule)	Epimerization	Epimerase	Ribulose-5-phosphate	Xylulose-5-phosphate	
		2-carbon transfer	Transketolase	Xylulose-5-phosphate + Ribose-5-phosphate	Sedoheptulose-7-phosphate + Glyceraldehyde-3-phosphate	
		3-carbon transfer	Transaldolase	Sedoheptulose-7-phosphate + Glyceraldehyde-3-phosphate	Fructose-6-phosphate + Erythrose-4-phosphate	
		(Cycle repeated with new molecule) 2-carbon transfer	Transketolase	Xylulose-5-phosphate + Erythrose-4-phosphate	Fructose-6-phosphate + Glyceraldehyde-3-phosphate	

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used :

Lippincott’s Illustrated Reviews:Biochemistry 8th edition

اللهم أنت ربي لا إله إلا أنت خلقتني وأنا عبدك وأنا على عهدك ووعدك ما استطعت،
أعوذ بك من شر ما صنعت، أبوء لك بنعمتك علي وأبوء بذنبي فاغفر لي فإنه لا يغفر الذنوب إلا أنت
لا إله إلا الله، وحده لا شريك له، له الملك، وله الحمد، وهو على كل شيء قدير
اللهُم صلّ وسلم وبارك على سيدنا محمد

إنّه «لا يُستطاع العِلم براحة الجسد» ، ومَن ألِفَ الرّاحة تَلِف.

الحمد لله وبعد أن طوينا صفحة امتحانات الميد بفضل الله وكرمه علينا، بكل ما حملته من جهد وتحديات وفيها الاجر والثواب ان شاء الله يعطيكم العافية جميعا. وهذا يحملنا لبذل المزيد والسعي الحثيث لاقتناص فرصة جديدة تلوح بالافق . فلنبدأ بتجديد النية وبتركيز وعزيمة، ولننظر إلى الأمام بثقة وحسن توكل على الله واحتساب العمل خالصا لله. تذكروا دائمًا أن الطب رسالة نبيلة، فلنكن على قدر المسؤولية، ولنجعل من القادم محطة نجاح وتميز وبالتوفيق جميعا!
وتذكروا قوله عليه الصلاة والسلام: "مَن سلَكَ طريقًا يلتَمِسُ فيهِ علمًا ، سَهَّلَ اللَّهُ لَهُ طريقًا إلى الجنَّةِ ".