جامعة الملك سعود
King Saud University

Biochemistry team 436

Major Metabolic Pathways of Glucose & Glucose Transport

- Color Index:

Important. ▪

Extra Information. ▪

Doctors slides. ▪

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Objectives:

- Define a metabolic pathway.
- Describe the general metabolic pathways for glucose (production and utilization).
- Briefly describe the HMP.
- Recognize the mechanisms of glucose transport

Metabolic pathways

Pathway: Series of chemical reactions that have one goal.
Reaction: Substrate+Substrate Product.

Definition

Pathway for glucose happens in almost every cell, starting by oxidation of glucose and ending with pyruvate (or lactate).

Regulatory mechanism(s)

1- Rapid short-term
-Covalent modification
-Allosteric
2- Slow long-term (hormone)
-Induction\repression

Reaction

Few are rate-limiting enzymes (They are found only in irreversible pathways).

Site

- Cellular tissue (tissue)
- Subcellular Inside the cell (Mitochondrial)

Metabolic pathways of glucose

Production

Glycogen**olysis** (Catabolic)

Gluco-**neo**-**genesis** (Anabolic)

Hexose interconversion

Catabolic Cycles	Anabolic Cycles
• Glycolysis & Kreb (mainly) • Glycogenolysis • HMP	Gluconeogenesis Glycogenesis

To understand ☺
You DON'T have to know this

Prefix:
Glyco-: glucose
Glycogeno-: glycogen
*except in synthesis of glycogen: we say **glycogensis** instead of saying glycogeno-genesis.

To differentiate: the synthesis of glucose is **glucoNEOgenesis***

Utilization

HMP / PPP
Catabolic

Glyco-**lysis**
Catabolic

Krebs cycle
Catabolic

Hexose interconversion

Glyco**genesis**
Anabolic

Suffix:
-genesis: process of producing
-lysis: breaking down.

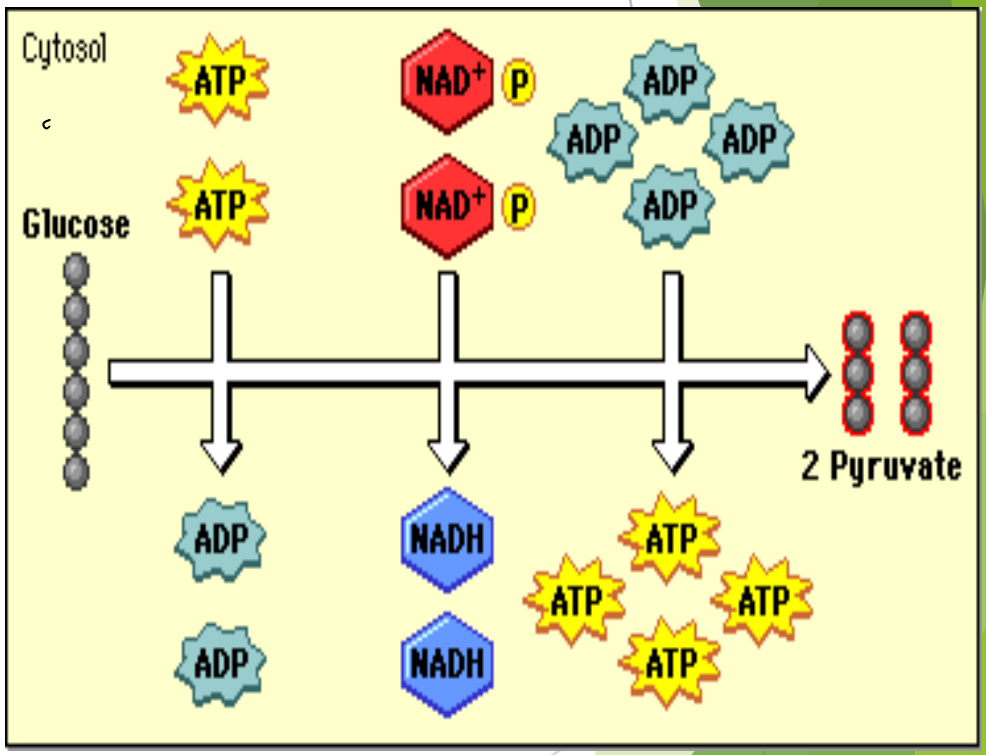
*Aerobic: with oxygen
*Anaerobic: without oxygen

GLYCOLYSIS

- Oxidation (breaking down) of glucose to provide energy

	Anaerobic glycolysis	Aerobic glycolysis
When	In absence of oxygen , cells that lack mitochondria	If there is enough(adequate supply) oxygen, Cells that has mitochondria
End product	Lactate + 2 ATP	Pyruvate(s) + 8 ATP

Aerobic glyclolysis



Glycogenesis and Glycogenolysis

Glycogenesis

- Occurs when glucose and ATP are present in relatively high amounts (This process is: storage)
- Synthesis of glycogen from glucose

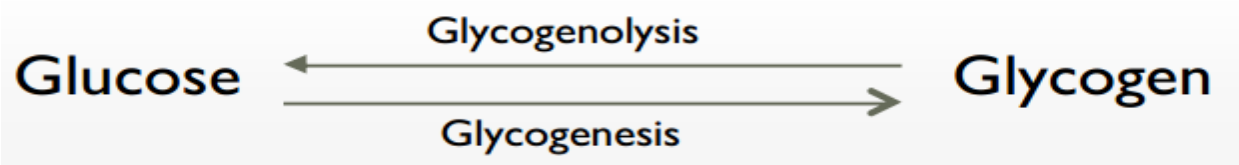
(اذا زاد الجلوكوز في الجسم و كانت الطاقة موجودة يتم تخزين الجلوكوز على شكل جلايكوجين عشان يحرقه و يستخدمه بعدين)

Glycogenolysis

- Occurs in response to hormonal and neural signals
- Degradation (تكسير) of glycogen into glucose

(اذا احتاج الجسم يرسل اشارت كهربائية او هرمونات لتكسير الجلايكوجين و تحويله لجلوكوز)

Both the same location: Mainly in **liver** and **muscle**→ Cytosol



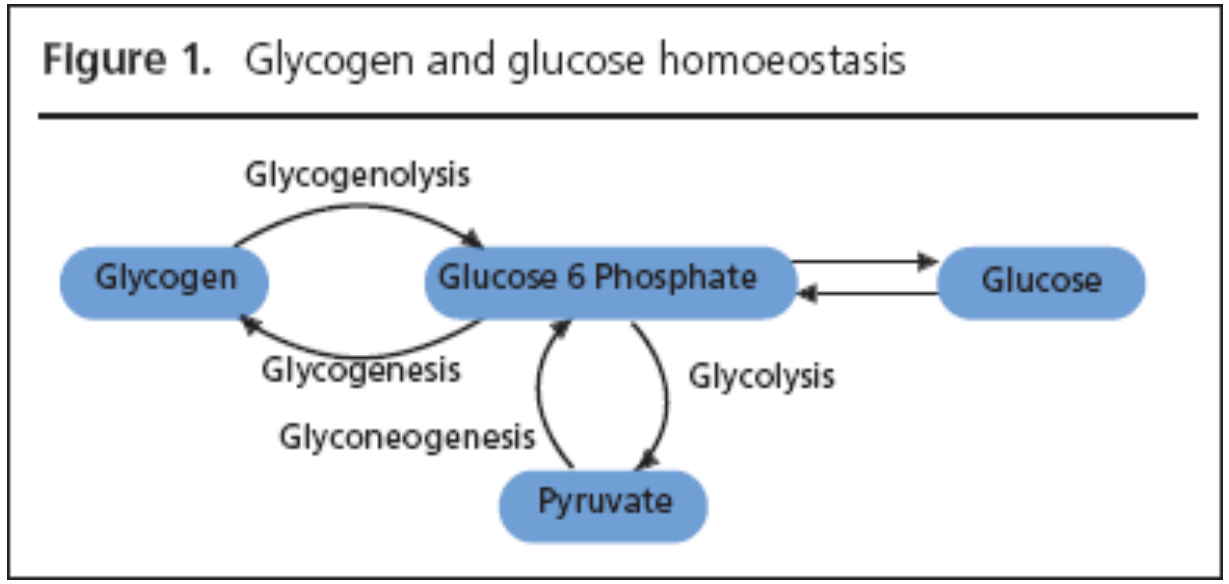
Gluconeogenesis

- Synthesis of glucose from non-carbohydrate precursors

صناعة الجلوكوز من مواد غير الكربوهيدرات

Precursor: is a chemical that is transformed into another compound

- The precursors could be **lactate** (anaerobic), **pyruvate** (aerobic), **glycerol** and **alpha-keto acids**
- It requires **mitochondria** and **cytosolic enzymes**
- Occurs in **Liver** and **kidney**



Glycerol: is a part of the triacylglycerol molecule which is the main constituent of body fat.

Keto acids: are organic compounds that contain a carboxylic acid group and a ketone group. The alpha-keto acids are especially important in biology as they are involved in the Krebs citric acid cycle and in glycolysis.

cytosolic enzymes: present in cytosol.

Hexose MonoPhosphate shunt (HMP)
Also known as Pentose Phosphate Pathway (PPP)

Note: Oxidation of glucose, also known as glycolysis, is the process which releases energy stored in **glucose** by combining it with oxygen.

- HMP shunt is an **alternative** (another) pathway of glucose oxidation.
- Has the same regulatory mechanism's as glucose (rapid short-term and slow long-term)
- it is **not** involved in the generation of energy unlike glycolysis
- Around 10% of glucose (that all the body makes) is entered in this pathway.
- In liver and kidney→ this percentage is up to 30%
- Occurs in many places such as the **cytosol** of the liver, adipose tissue (to produce fatty acids from glucose)
- Has two main functions and two phases →

1- Oxidative phase
2- Non-oxidative phase

↓

1-Provides NADPH
2- Provides Pentoses

YouTube

فيديو يلخّص لك

Biomedical Importance of (HMP) & (PPP)

A source of NADPH

NADPH is required for:

1. Synthesis of fattyacids, steroid and some amino acids.
2. Detoxification of drugs by (cytochrome P450) .
3. In scavenging (remove) the free radicals .

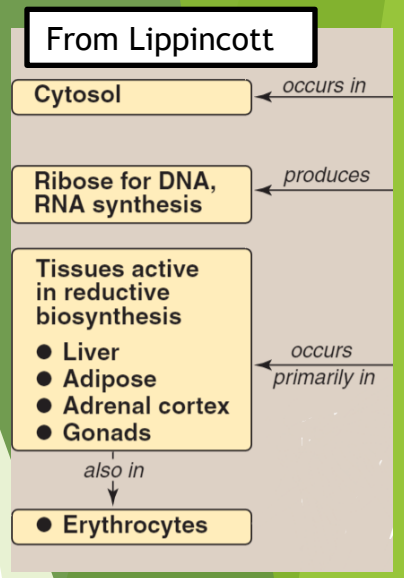
Note: **Cytochrome P450:** enzymes also function to metabolize potentially toxic compounds, including drugs and products of endogenous metabolism such as bilirubin

Provides Pentoses for: (Pentose and its derivatives are useful in the synthesis of:)

1. Nucleic acids (DNA and RNA)
2. Nucleotides (ATP , NAD ,FAD and CoA)

Tissue Distribution

Location of HMP: in the Cytosol of the following locations:			
Liver	Lactating mammary glands	Adrenal cortex	Gonads
Adipose Tissue	Erythrocytes(RBC) to reduce glutathione	Lens	Cornea



Phases of HMP Shunt

Oxidative phase
-which provides NADPH-

Non-Oxidative phase
-which provides pentoses-

Oxidative phase

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Non-Oxidative phase

Notes ☺

Glutathione: antioxidant capable of preventing damage caused by reactive oxygen species. (Free Radicals)

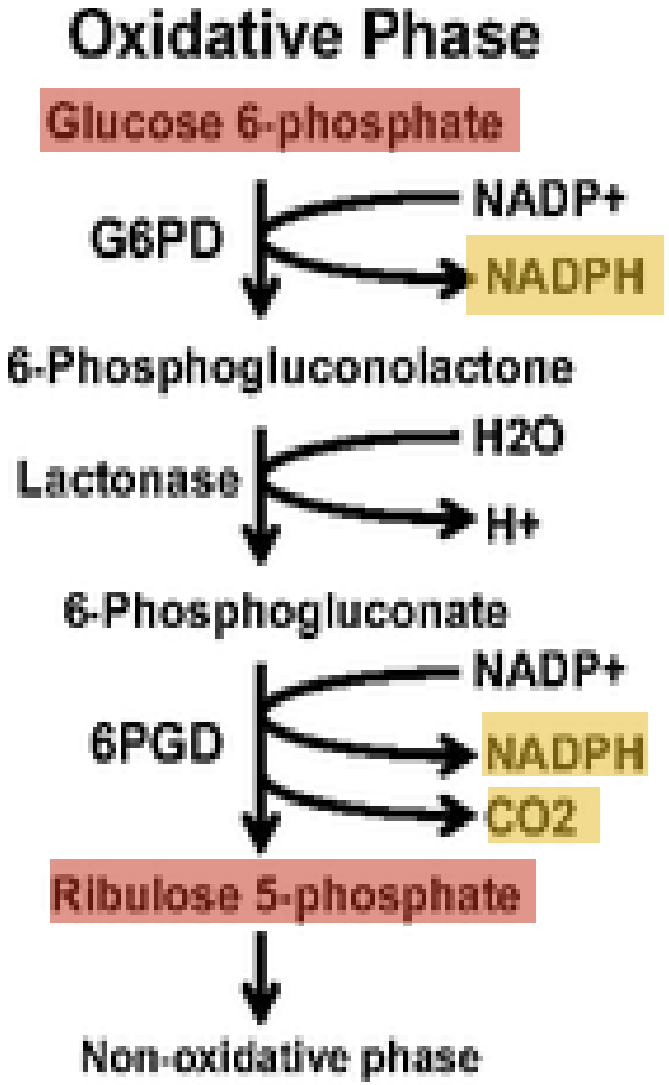
Cornea: the transparent layer forming the front of the eye.

The adrenal cortex: the outer part of the adrenal gland.

Gonads: an organ that produces gametes; a testis or ovary.

Colors are for your understanding ☺

Phase1: oxidative pathway



The purpose of this phase is to :

1- provide **2 NADPH**

2- convert **Glucose6-phosphate** to **Ribulose 5-phospate** which is an important molecule to start the next phase.

Note ☺
We start with Glucose-6-Phosphate $C_6H_{13}O_9P$
We end with Ribulose 5-phosphate $C_5H_{11}O_8P$

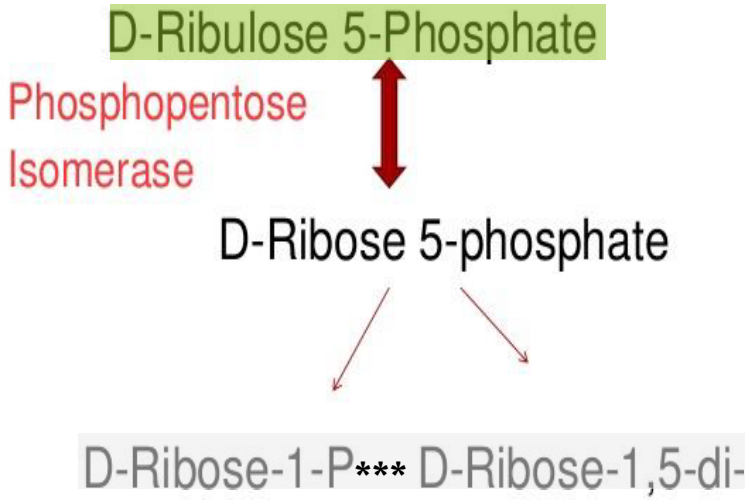
Ribose: aldose sugar
Ribulose: Ketone sugar

Phase2: non oxidative
A) Interconversion of pentose

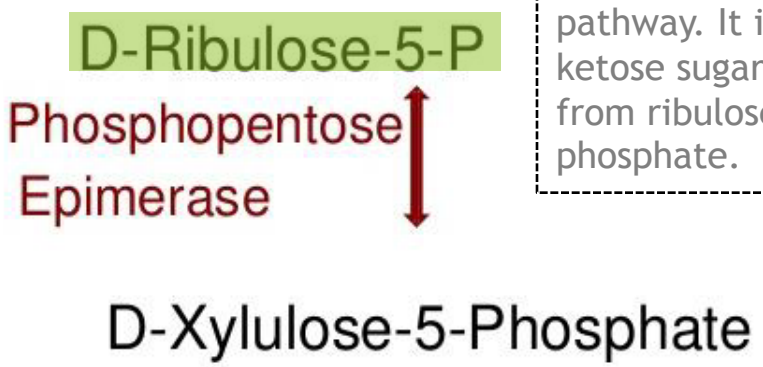
***girls doctor said skip it

- **Ribulose** 5 phosphate
- يتحول الى:
- **Ribose** 5 phosphate

These non-oxidative **reversible** reactions permit ribulose 5-phosphate to be converted either to ribose 5-phosphate (needed for nucleotide synthesis) **or** to intermediates of glycolysis—fructose 6-phosphate and glyceraldehyde 3-phosphate.



الهدف منه
سكر خماسي
وسداسي



Xylulose-5P: an intermediate in the pentose phosphate pathway. It is a ketose sugar formed from ribulose-5-phosphate.

#للرّبط: تنطق "زي اللوز"

Remember that 2 important enzymes are needed in non-oxidative reactions :

- **1- Transketolase**, an enzyme always associated with TPP (Thiamine pyrophosphate)

•TPP: a prosthetic group (is a Coenzyme associated permanently) for the **Transketolase enzyme.**

- It is important to activate the enzyme.

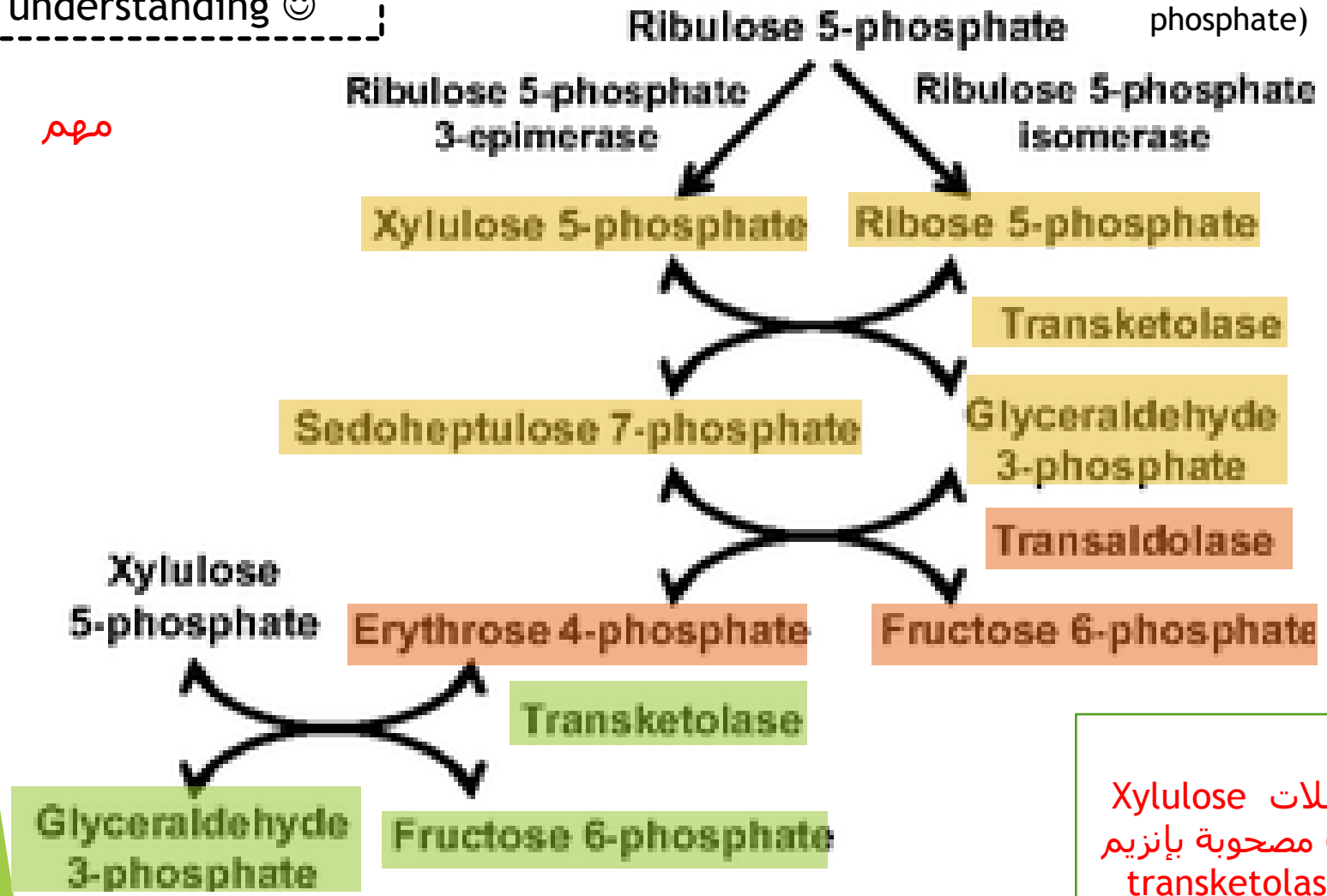
- **2- Transaldolase**.

Colors are for your understanding ☺

Non-Oxidative Phase

(Conversion of pentose phosphate to hexose phosphate)

مهم



Note: both Glyceraldehyde and fructose are intermediates of glycolysis

Non Oxidative

التفاعل الاول

تحويل ribose الى ribulose

التفاعل الثاني

Ribose + xylulose (this reaction is catalyzed by Transketolase with TPP). And will give us 2 new sugar molecules : Sedoheptolose (7C) AND glyceraldehyde (3C)

التفاعل الثالث

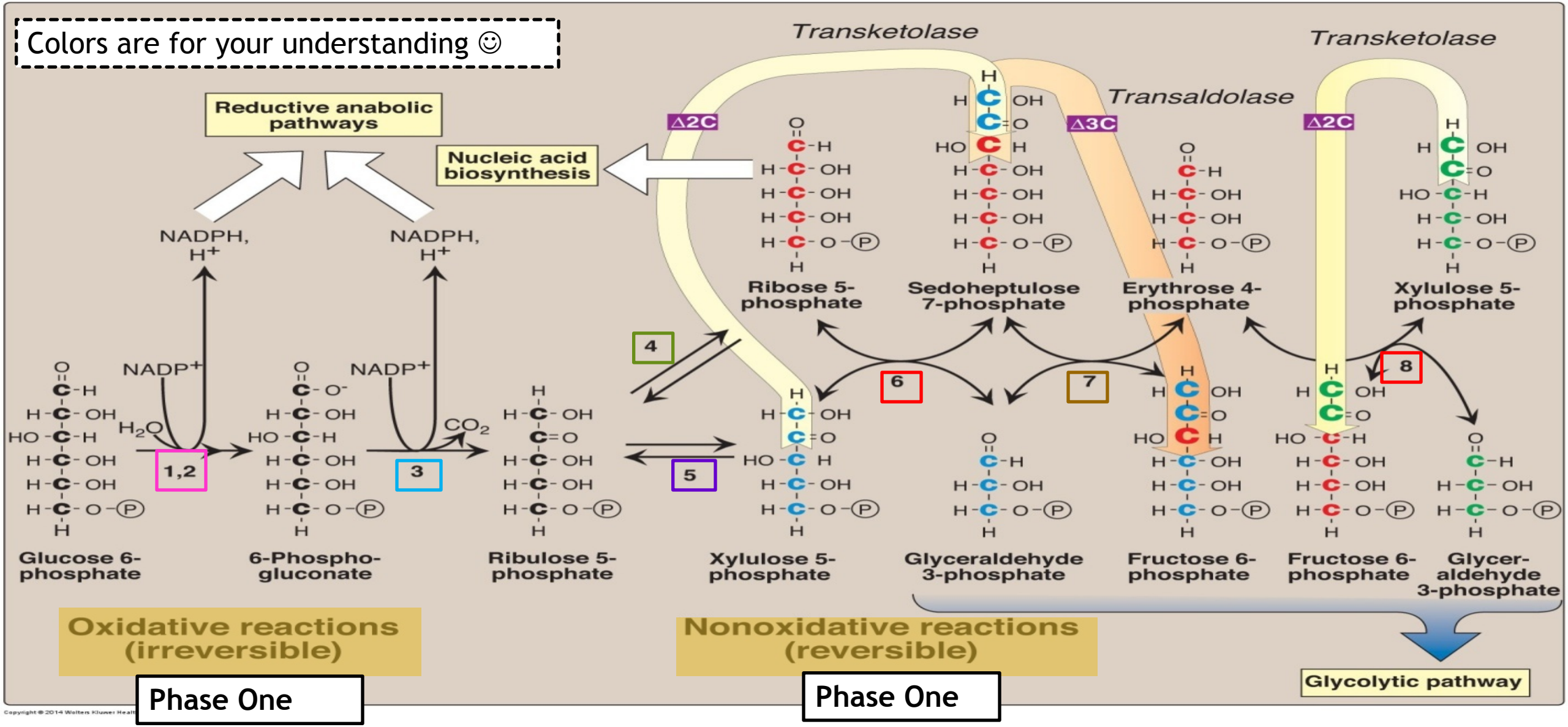
Sedoheptolose +glyceraldehyde (this reaction is catalyzed by Transaldolase) And will give us 2 new sugar molecules : fructose (6C). And erythrose (4C).

تفاعلات Xylulose تكون مصحوبة بإنزيم transketolase .
وزي ماقلنا هالإنزيم دايما يكون معاه TPP

التفاعل الأخير

Xylulose5-P+Erythrose4-P (this reaction is catalyzed by Transketolase with TPP. And will give us 2 sugar molecules : Fructose 6-P AND Glyceraldehyde 3-P .

Colors are for your understanding ☺



Phase One

Phase One

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.

Extra explanation: From Lippincott

I. OVERVIEW

The pentose phosphate pathway (also called the hexose monophosphate pathway, or 6-phosphogluconate pathway) occurs in the cytosol of the cell. It includes two, irreversible oxidative reactions, followed by a series of reversible sugar–phosphate interconversions (Figure 13.1). No ATP is directly consumed or produced in the cycle. Carbon 1 of glucose 6-phosphate is released as CO_2, and two NADPH are produced for each glucose 6-phosphate molecule entering the oxidative part of the pathway. The rate and direction of the reversible reactions of the pentose phosphate pathway are determined by the supply of and demand for intermediates of the cycle. The pathway provides a major portion of the body's NADPH, which functions as a biochemical reductant. It also produces ribose 5-phosphate, required for the biosynthesis of nucleotides (see p. 293), and provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or the degradation of structural carbohydrates in the body.

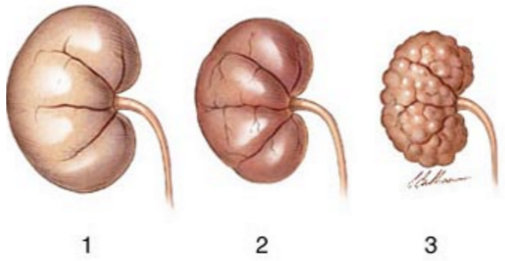
Clinical Correlations

G-6-PD deficiency results in :

Heamolytic Aneamia

Neonatal Jaundice

Kidney failure



Notes ☺

Glucose-6-phosphate dehydrogenase deficiency

The condition is characterized by abnormally low levels of glucose-6-phosphate dehydrogenase, an enzyme involved in the pentose phosphate pathway that is especially important in the red blood cell. G6PD deficiency is the most common human enzyme defect

Hemolytic anemia: relating to or involving the rupture or destruction of red blood cells.

Neonata: relating to newborn children

Glucose Transport

Na+ Monosaccharide Co-transporter:	Na-Independent Facilitated Diffusion
1. Against concentration gradient 2. Energy dependent 3. Carrier-mediated 4. Coupled to Na+ transport	1. Down the concentration gradient 2. Energy-Independent 3. Glucose Transporters (GLUT 1-14)

Boys doctor mentioned that now it 20 Glucose transporters

Note : GLUT-4 is insulin sensitive, because it needs insulin to work.

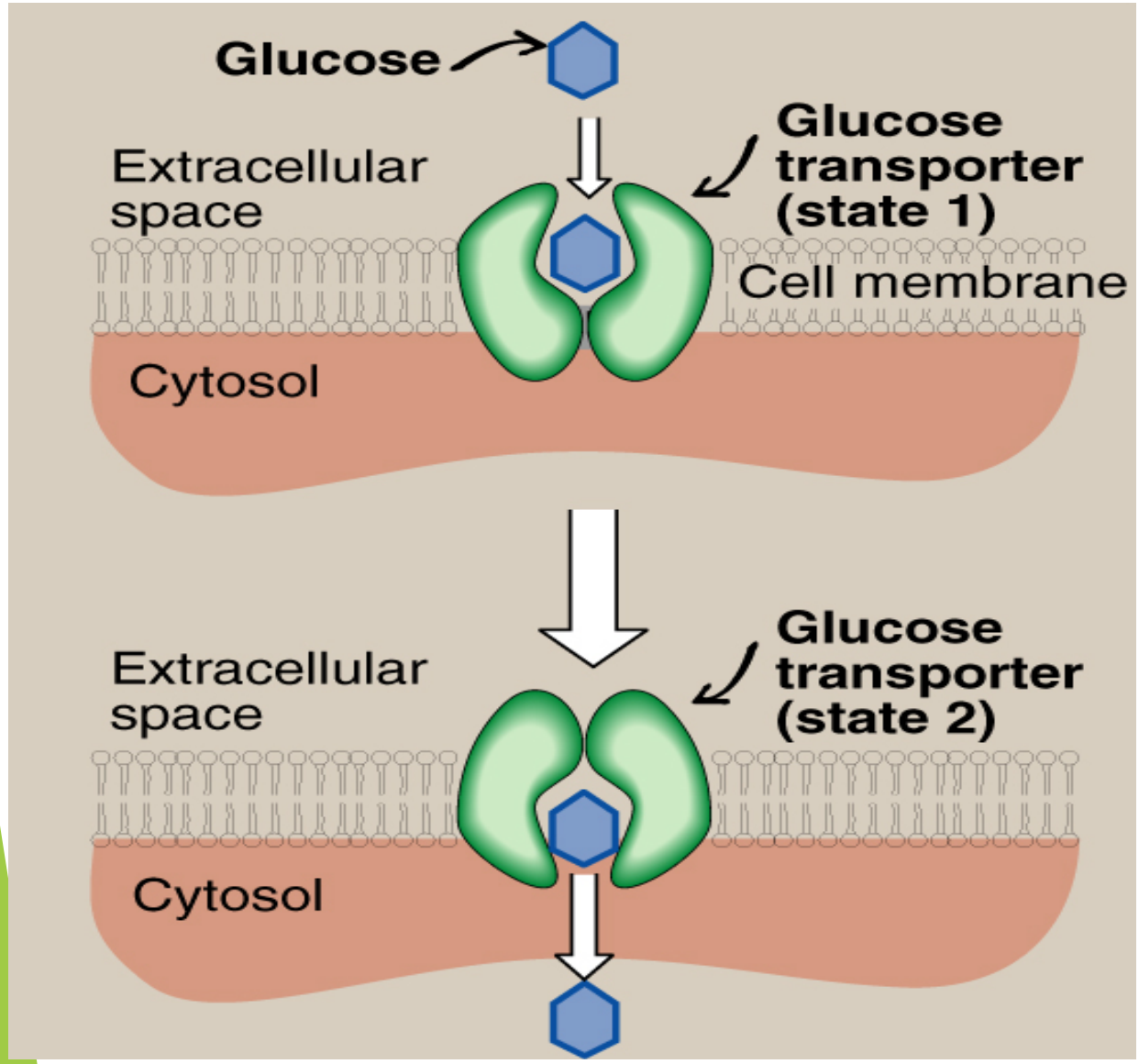
(GLUT 1-14)	• Tissue-specific expression pattern
1. GLUT-1	RBCs and brain (blood-brain barrier)
2. GLUT-2	Liver, kidney & pancreas
3. GLUT-3	Neurons
4. GLUT-4	Adipose tissue & skeletal muscle
5. GLUT-5	Small intestine & testes
6. GLUT-7	Liver (ER-membrane

GLUT-1, 3 & 4: Uptake of glucose from the blood.

GLUT-2: Blood, cells it's a bidirectional transporter, allowing glucose to flow in 2 directions.

GLUT-5: Fructose transport .

Glucose Transport: Facilitated Diffusion



435 Teamwork:

- الجلوكوز لا يستطيع أن ينتشر خلال الخلية , لأنه مركب هايدروفيلك \ محب للماء .
- لذلك فهو يحتاج إلى طريقة أخرى , فإما أن يدخل مع الصوديوم عن طريق الكو ترانسبورت الذي سبق أن تعرفنا عليه بالفسيولوجي.
- أو أنه يدخل عن طريق كارير بروتينز خاصة به بطريقة الفاسيليتد دفيوجن والتي أيضا سبق التعرف عليها بالفسيولوجي. (مثل الصورة)

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Revision

Metabolic Pathways of Glucose

Production

Glycogenolysis *Catabloic*

- Degradation of glycogen into glucose
- Mainly liver and muscle, Cytosol

Gluconeogenesis *Anabolic*

Note : Producing of glucose from non-carbohydrates sources
e.g. : amino acids, glycerol & lactate

Hexose interconversion

Note : converting of other hexoses into glucose

Utilization

HMP/PPP *Catabolic*

1- Important source for NADPH
Which is used in reductive syntheses.

2- Source for metabolically active ribose
Which is used for production of nucleotides:

- For nucleic acids.
- For co-enzymes.

Hexose interconversion

Note : Converting glucose into other hexoses

Glycolysis *catabolic*

Krebs cycle

Glycogenesis *Anabolic*

- Synthesis of glycogen from glucose
- Mainly liver and muscle, Cytosol

Catabolic cycles	Anabolic cycles
Glycolysis (Mainly) Krebs (Mainly) Glycogenolysis HMP	Gluconeogenesis Glycogenesis

Glucose ⟵ Glycogenolysis
Glycogen ⟶ Glycogenesis

Take home messages

- There are multiple pathways for glucose that can be grouped in to catabolic (utilizing glucose) or anabolic (producing glucose)
- Glycolysis is the major metabolic pathway of glucose breakdown to provide energy

- Alternative pathway for glucose oxidation but not meant for producing energy
- Has two phases- oxidative and non-oxidative
- During oxidative phase, glucose-6-P is oxidized with generation of 2 moles of NADPH, and one mole of pentose phosphate, with liberation of CO2
- During non-oxidative phase, pentose phosphate is converted to intermediates of glycolysis

QUIZ

Boys team members:

1- حمد الحسون.
2- محمد حكمي.
3- خالد القحطاني.
4- حمد الحميدان.
5- محمد حبيب.
6- خالد الراجح.
7- فهد العتيبي.
8- طلال الطخيم.

Girls team members:

نورة الشبيب

-Team leaders:

عبدالله المانع.
نوره السهلي.

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