Major Metabolic Pathways of Glucose

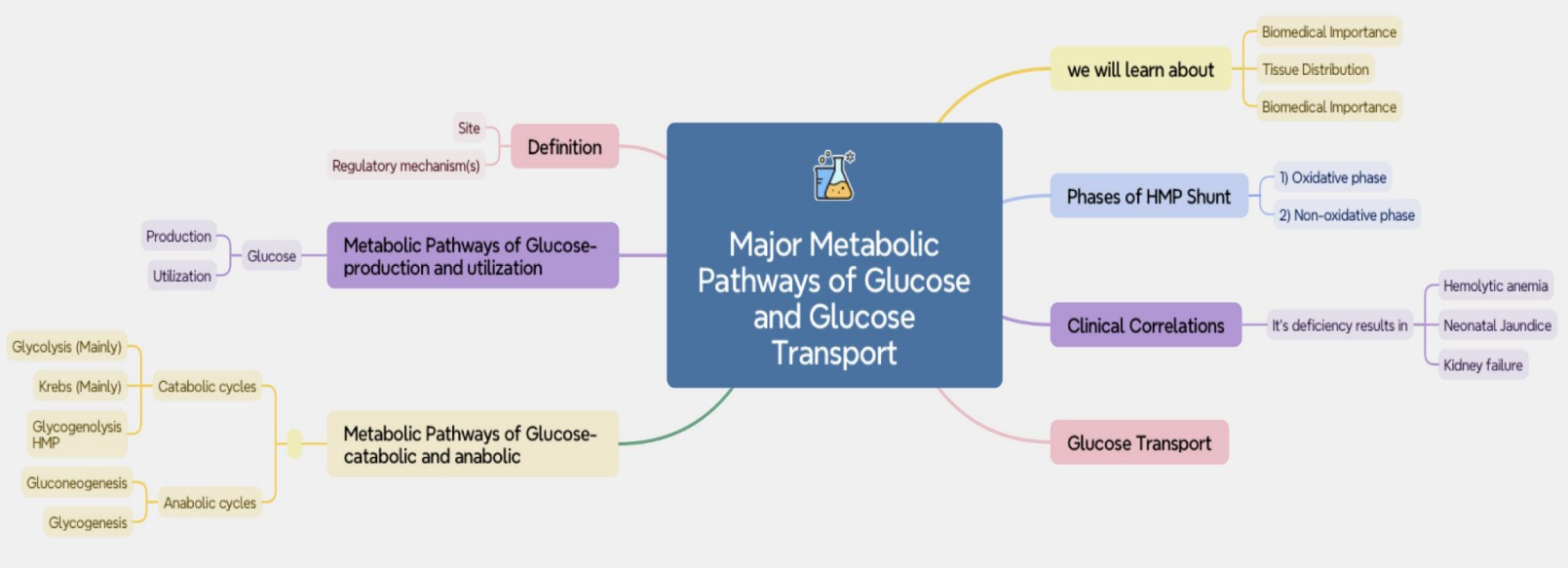
Editing File

Color Index:
- Main Text (black)
- Female Slides (Pink)
- Male Slides (Blue)
- Important (Red)
- Dr's Notes (Green)
- Extra Info (Grey)

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

Quick summary of the lecture



Metabolic Pathways

Definitions

Metabolism: A group of reactions including catabolism and anabolism

Pathway: Series of chemical reactions that have one goal

Sites:

1. Cellular (Tissue): signaling between cells
2. Subcellular: reactions inside the cell

Reactions: reversible & irreversible

Rate-limiting enzymes: Enzymes that control the rate of the reaction, and without them the reaction can't complete the cycle

There is at least one Rate-limiting enzyme

Regulatory mechanisms

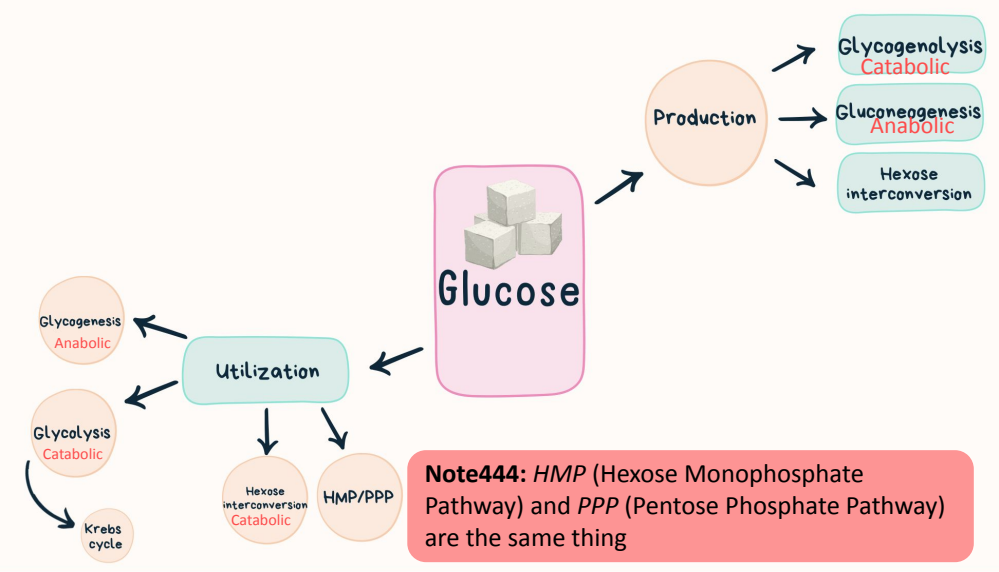
Rapid/Short-term

- Covalent modification (e.g. Adding phosphate group)
- Allosteric (A molecule that can bind noncovalently at a site other than the active site of an enzyme and affect its activities "either activation or inhibition" without being involved in the reaction)

Slow/Long-term

Induction (e.g. Insulin)
Repression (e.g. Glucagon)

Metabolic Pathways of Glucose- production and utilization



For a better understanding:

- **Prefixes:**

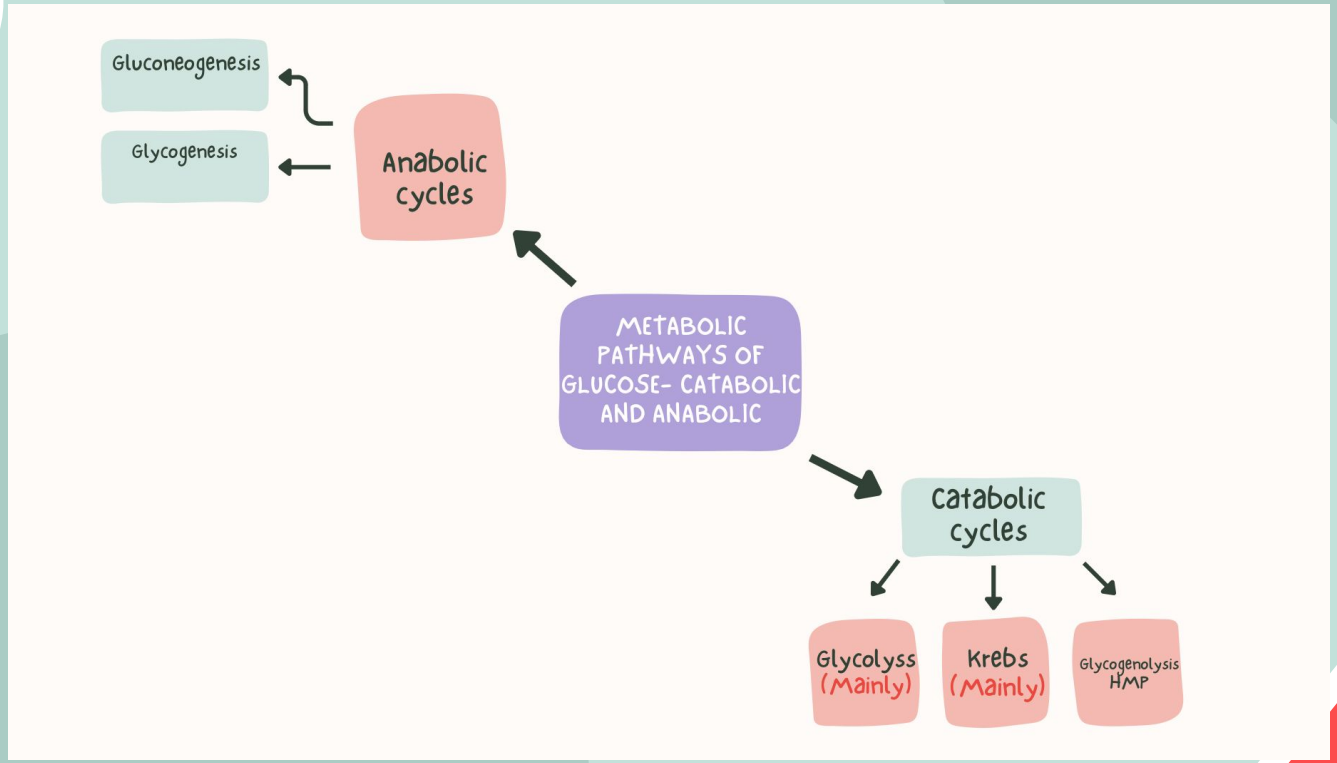
1. *Glyco-* = glucose (e.g. glycolysis)
2. *Glycogeno-* = glycogen (except in synthesis of glycogen we say Glycogenesis instead of saying Glycogeno-genesis)

Exception: the synthesis of glucose is Gluconeogenesis

- **Suffixes:**

1. *-genesis* = process of producing (synthesis)
2. *-lysis* = breaking down

Metabolic Pathways of Glucose: Catabolic and Anabolic



Glycolysis

Definition: Oxidation (breakdown) of glucose to provide energy.

	Anaerobic glycolysis	Aerobic glycolysis
Occurs when?	In absence of oxygen and in cells that lack mitochondria	In adequate supply of oxygen and in cells with mitochondria
End product	Lactate	Pyruvate

Glycogenesis and Glycogenolysis

Glycogenesis:

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

Both occur *mainly* in the liver, muscle, and cytosol

Glycogenolysis

- Degradation of glycogen into glucose
- Occurs in response to hormonal and neural signals.
-

Gluconeogenesis and HMP/PPP

Gluconeogenesis:

- Synthesis of glucose from **non-carbohydrate precursors**
- The precursors could be lactate, pyruvate, glycerol and alpha-keto acids.
- It requires both **mitochondria** and **cytosolic enzymes**
- Occurs (mainly) in the liver and kidneys

Hexose Monophosphate shunt(HMP) or Pentose Phosphate Pathway (PPP):

- HMP shunt is an alternative pathway of glucose oxidation. (main pathway is glycolysis)
- It is not involved in the generation of energy.
- Around 10% of glucose is entered in this pathway (in liver and kidney, this percentage is up to 30%)

Biomedical importance of HMP/PPP:

1- *Provide NADPH* which is required for :

- Synthesis of fatty acid, steroids, and amino acids.
- Detoxification of drugs, cytochrome P450.
- Scavenging the free radicals

2- *Provide pentoses* " The most important pentose is ribose ":

- Pentose and its derivatives are useful in the synthesis of:
  Nucleic acids (DNA and RNA) & Nucleotides (ATP, NAD, FAD, CoA).

- NADH : in the electron transport chain as energy molecule.
- NADPH: cofactor in the glutathione system

Tissue Distribution

(Location of HMP in the cytosol of the following reaction)

1. Liver
2. Lactating mammary gland
3. Adrenal cortex
4. Gonads
5. Adipose tissue
6. Erythrocytes to reduce glutathione
7. Lens and cornea

Phases of HMP shunt

Helpful video!

Oxidative	Non-oxidative
• Generates NADPH • Irreversible	• Generates pentoses • Reversible

This picture summarizes everything (very important)

HMP Shunt

Helpful video!

Points you need to know:

Oxidative reactions: you need to know everything except the structure

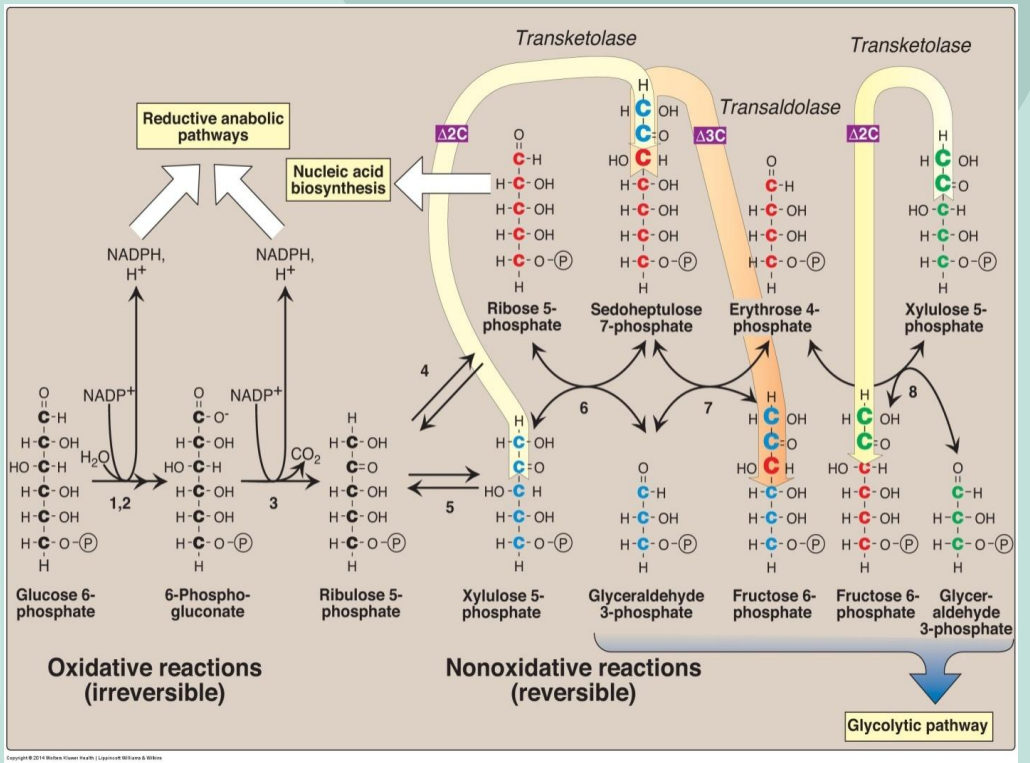
Nonoxidative reactions: 3 points

1-Glycolysis metabolites
. glyceraldehyde 3-phosphate
. Fructose 6-phosphate

2-transketolase transfer 2C and needs coenzyme thiamine pyrophosphate(TPP)

3-transaldolase transfer 3C

4- TTP is derived from vitamin B1 (thiamin)



Oxidative Pathway

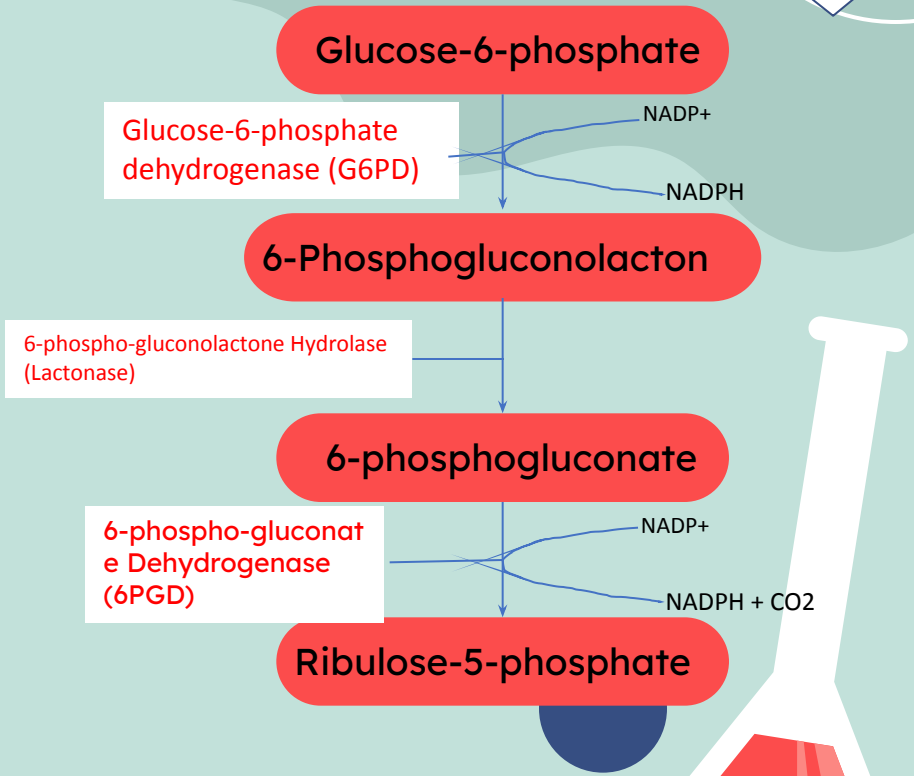
It's important to remember the enzymes.

- Oxidation of Glucose-6-phosphate to 6-Phosphogluconolacton by using an enzyme called Glucose-6-phosphate dehydrogenase (G6PD) and NADP+ is reduced to NADPH.

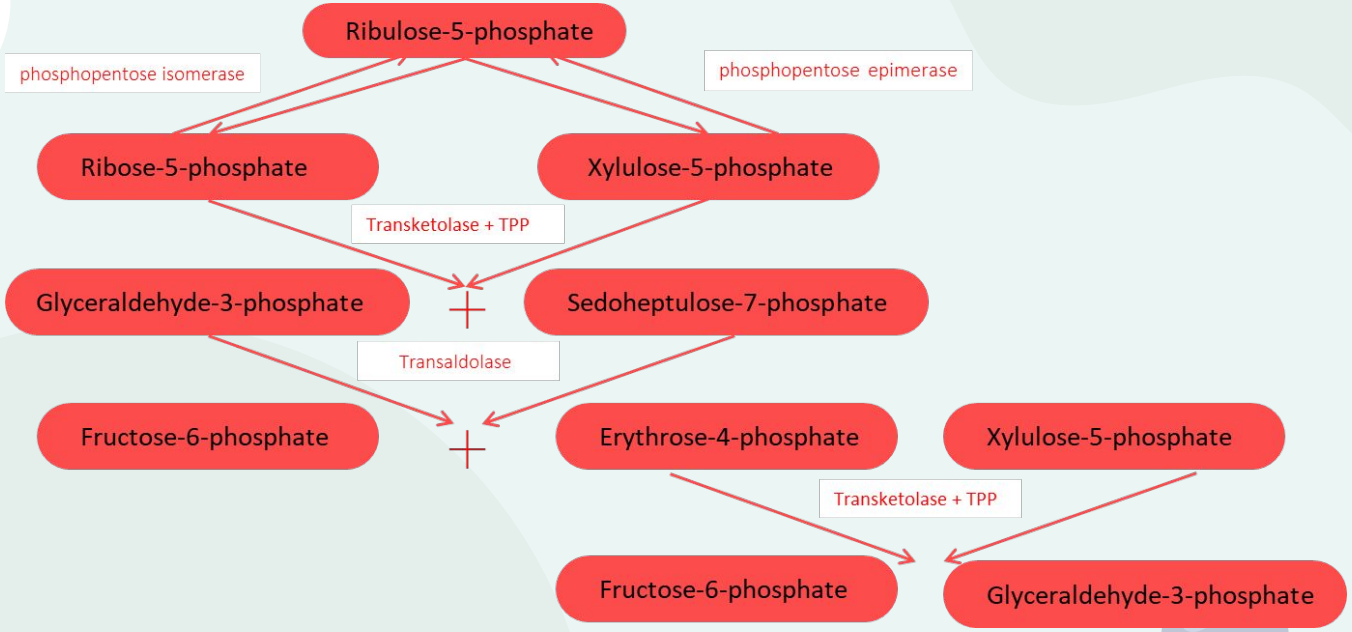
- Hydrolysis of 6-phosphogluconolactone to 6-phosphogluconate by 6-phospho-gluconolactone Hydrolase (Lactonase)

- Oxidation of 6-Phosphogluconate to Ribulose-5-phosphate by 6-phospho-gluconate Dehydrogenase (6PGD) and NADP+ is reduced to NADPH

The final products of this phase are 2NADPH and CO_2



Phase 2: Non-Oxidative Pathway



HMP SHUNT

PHASES	• Oxidative: (irreversible): from Glucose-6-phophate to Ribulose-5-phosphate • Non-Oxidative : (reversible): from Ribulose-5-phosphate till the end of pathway
MAJOR OUTCOMES	• NADPH : synthesis of fatty acids, steroid, amino acid • Ribose : synthesis of DNA, RNA, ATP, FAD, NAD
ENZYMES	Dehydrogenase - Hydrolase - Dehydrogenase Epimerase - isomerase - transketolase - transaldolase (acronym to help you remember: DHD Eitt)

Notes

Transketolase: needs help from coenzyme TPP. this enzyme will take 2 carbon from Ribose 5-phosphate and put them on Xylulose
5-phosphate to form Sedoheptulose 7-phosphate and the rest 3 carbon from Ribose 5-phosphate will form Glyceraldehyde 3-phosphate.

Transaldolase: this enzyme now will take 3 carbon from Sedoheptulose 7-phosphate and put them on Glyceraldehyde 3-phosphate to form
Fructose 6-phosphate
and also the rest 4 carbon atoms from Sedo 7-phosphate will form Erythrose 4-phosphate

Oxidative	Non-Oxidative
• RATE LIMIT ENZYME FOR ALL THIS PATHWAY IS Glucose 6-phosphate dehydrogenase (G6PD) . how? because without this enzyme, all the pathway won't occur, this enzyme has The ability to switch on/off the pathway "extremely important" • From oxidative phase we will get TWO NADPH . one from reaction 1, another from reaction 3 • All oxidative reactions are irreversible	• The precursor for this phase is Ribulose 5-phosphate • From non-oxidative phase we will get a Ribose 5-phosphate "pentose sugar" • All non-oxidative reactions are reversible • Transketolase requires an important co-factor which is thiamine pyrophosphate (TPP) to be activated "extremely important"

Clinical correlations

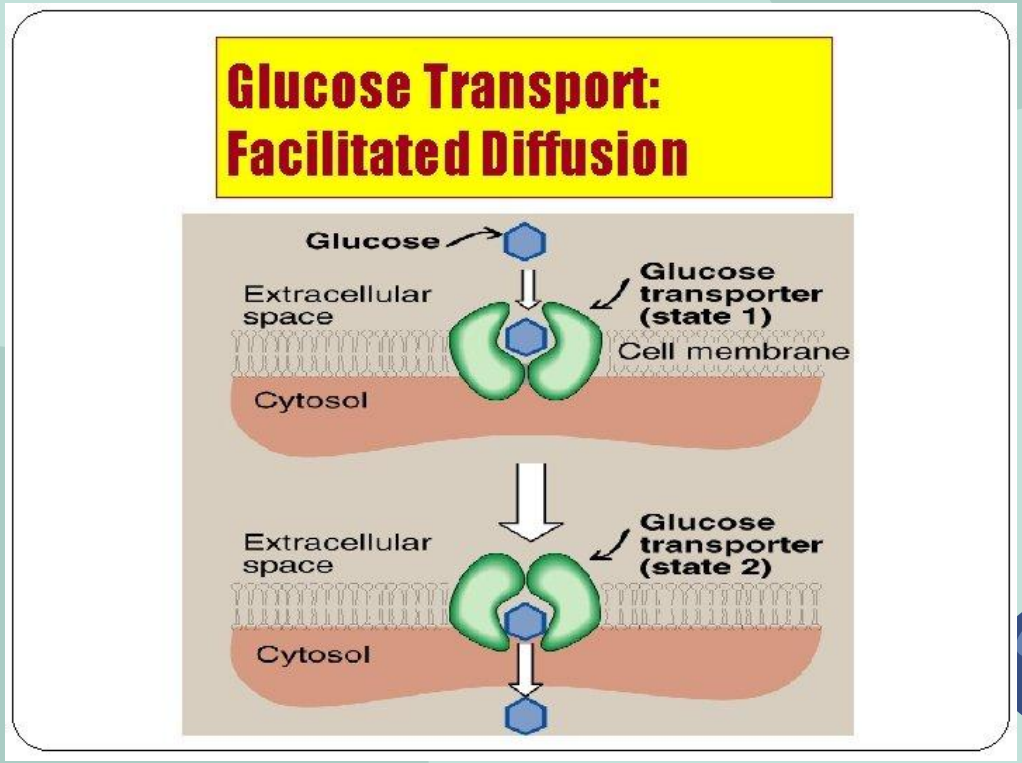
Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency:
The condition is characterized by abnormally low levels of glucose-6- phosphate dehydrogenase, an enzyme involved in the pentose phosphate pathway that is especially important in the red blood cell. G6PD deficiency is the most common human enzyme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

- Neonatal jaundice
- kidney failure
- hemolytic anemia

Glucose Transport

	Na+ Monosaccharide Co-transporter	Na+ - Independent Facilitated diffusion
About	Glucose is hydrophobic molecule that's why it cannot pass easily inside the cell so it needs another way to go inside the cell either by co-transporter which will take Na+ and glucose together to go inside the cell or by Facilitated diffusion which mean it has a specific carrier to it	
Movement of glucose	Against concentration gradient	Down the concentration gradient
Energy need	Needs energy (Energy dependent)	(Energy independent) doesn't need energy
	It's Carrier-mediated and Coupled to Na+ transport	Glucose Transporters (GLUT 1-14)
Location	Small intestine, renal tubules & choroid plexus	-

Glucose Transport: Facilitated Diffusion



Glucose Transporters

Very very important

Transporter	Location	Function
GLUT-1	RBCs & Brain	Glucose uptake from blood
GLUT-2	Liver & Kidney & Pancreas	Blood & cells (either direction)
GLUT-3	Neurons	Glucose uptake from blood
GLUT-4	Adipose tissues & skeletal muscles	Glucose uptake from blood
GLUT-5	small intestine & testes	Fructose uptake from blood
GLUT-7	Liver (ER membrane)	-

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 CO_2
- During non-oxidative phase, pentose phosphate is converted to intermediates of glycolysis.

MCQs

1. Which coenzyme dose transketolase needs to transfer 2C ?			
A) (TPP)	B) (G6PD)	C) ATP	D) Tranaldolase
2. Which of the following transporters (GLUT) is found in small intestine and testes?			
A) GLUT-1	B) GLUT-2	C) GLUT-8	D) GLUT-5
3. Deficiency in Glucose 6-phosphate dehydrogenase causes all the below except?			
A) Aplastic anemia	B) Kidney failure	C) Hemolytic anemia	D) Neonatal jaundice
4. GLUT-2 is found in			
A) Liver	B) Brain	C) Neurons	D) RBCs

4-A
3-A
2-D
1-A

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