Major Metabolic Pathways of Glucose and Glucose Transport

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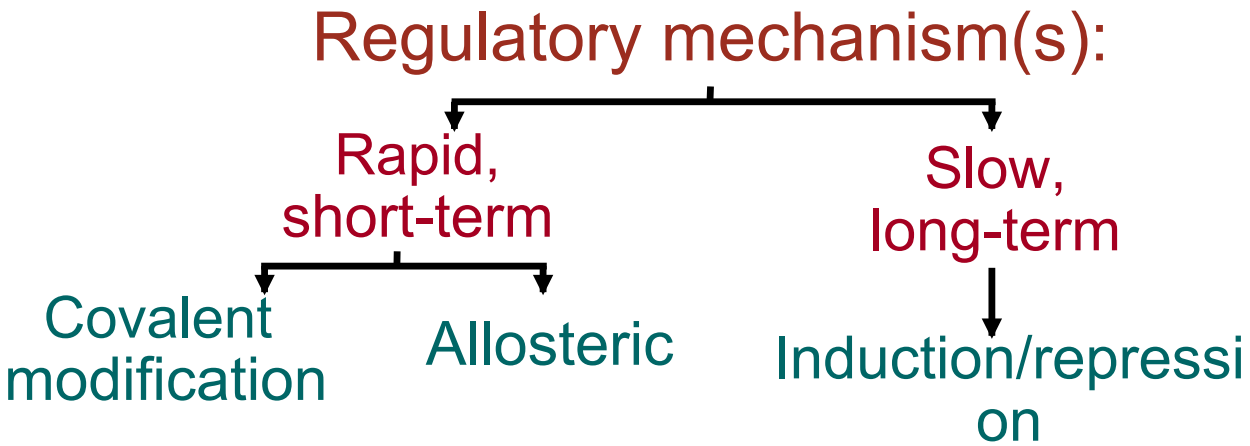
Objectives

By the end of the lecture, students are expected to:

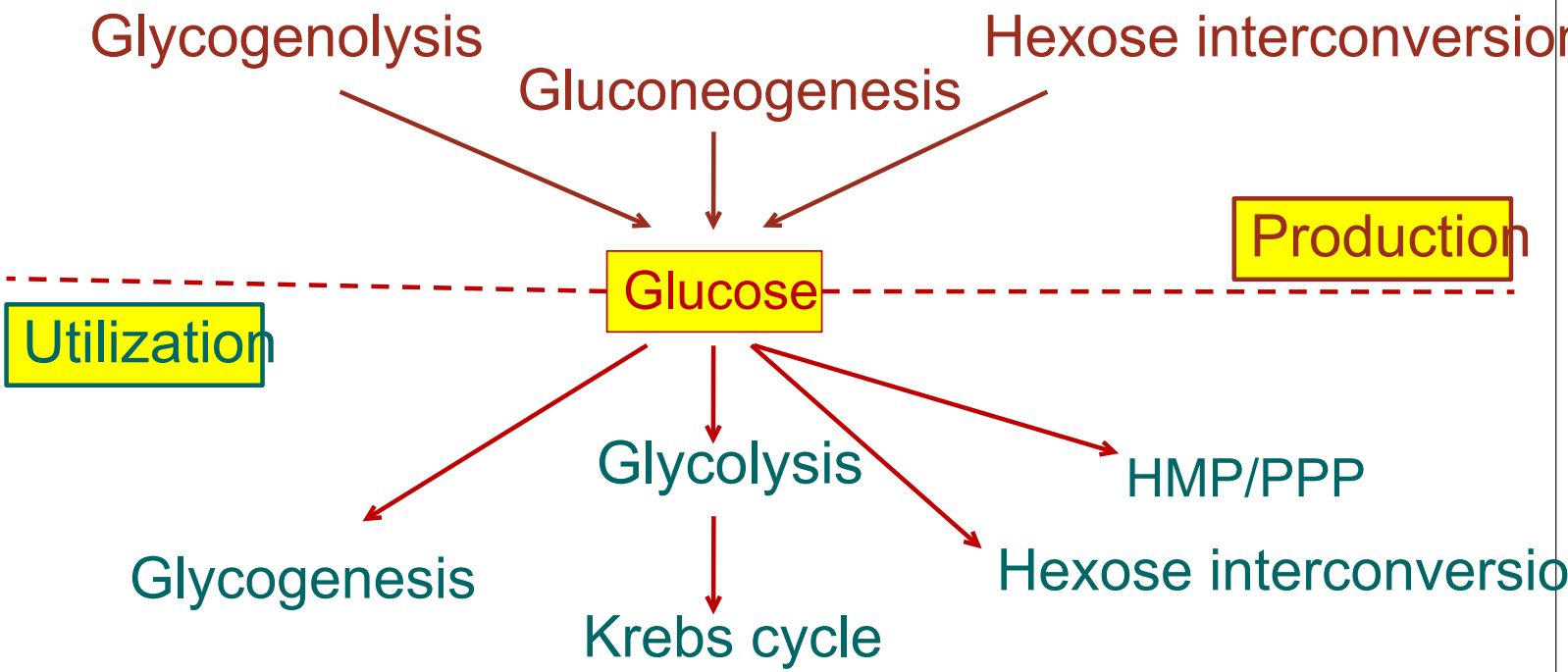
- Define a metabolic pathway.
- Describe the general metabolic pathways for glucose (production and utilization)
- Briefly describe the HMP
- Recognize the mechanisms of glucose transport

Metabolic Pathway

Definition
Site:
    Cellular (tissue) and Subcellular
Reactions
Rate-limiting enzyme(s)



Metabolic Pathways of Glucose-production and utilization



Metabolic Pathways of Glucose- catabolic and anabolic

Catabolic cycles
- Glycolysis (Mainly)
- Krebs (Mainly)
- Glycogenolysis
- HMP

Anabolic cycles
- Gluconeogenesis
- Glycogenesis

Glycolysis

Oxidation of glucose to provide energy.
Pyruvate is the end product of glycolysis in cells with mitochondria and an adequate supply of oxygen- aerobic glycolysis
In absence of oxygen and in cells that lack mitochondria, the end product is lactate- anaerobic glycolysis

Glycogenesis and Glycogenolysis

Glycogenesis:

Synthesis of glycogen from glucose

Mainly liver and muscle, Cytosol

Glycogenolysis

Degradation of glycogen into glucose

Mainly liver and muscle, Cytosol

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
Liver and kidney

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

HMP shunt is an alternative pathway of glucose oxidation
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 upto 30%

Biomedical Importance

It has two main functions-

1. Provides NADPH which is required for –
   - synthesis of fatty acids, steroid and some amino acids
   - Detoxification of drugs by cytochrome p450
   - In scavenging the free radicals
2. Provides Pentoses
   - This pentose and its derivatives are useful in the synthesis of
     - Nucleic acids (DNA and RNA)
     - Nucleotides (ATP, NAD, FAD and CoA)

Tissue Distribution

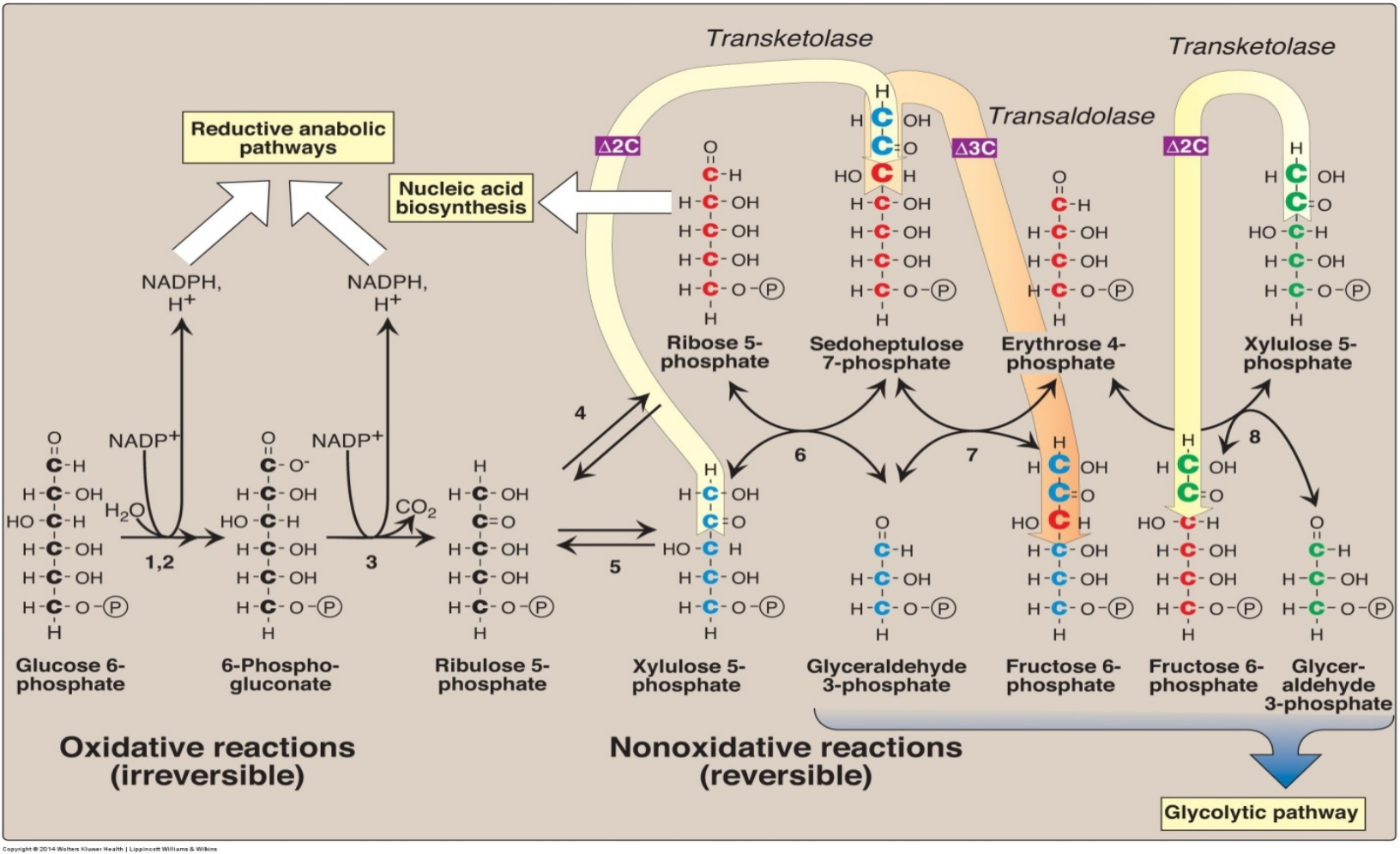
Location- Cytosol

- Liver
- Lactating mammary gland
- Adrenal cortex
- Gonads
- Adipose tissue
- Erythrocytes to reduce glutathione
- Lens and cornea

Phases of HMP Shunt

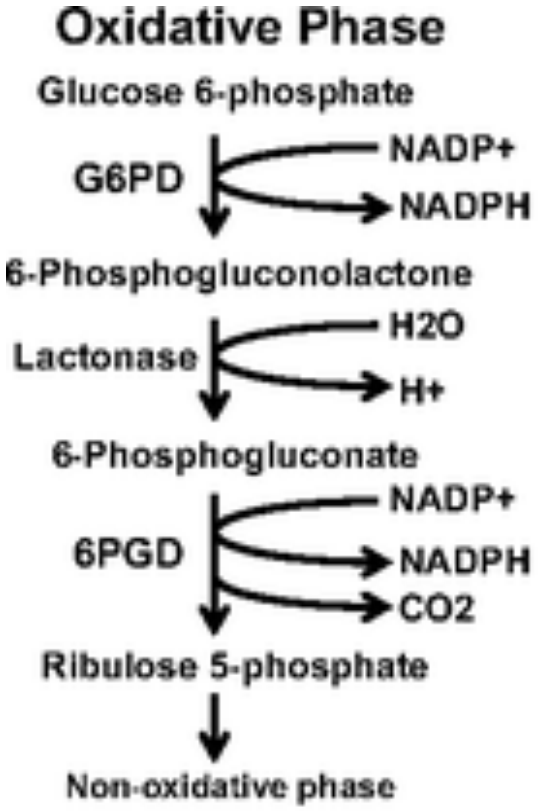
It has two phases-

- Oxidative phase
- Non-oxidative phase



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.

Phase 1- Oxidative pathway



G6PD- Glucose 6-Phosphate Dehydrogenase

Lactonase- 6 phosphogluconolactone hydrolase

6PGD- 6 phosphogluconate dehydrogenase

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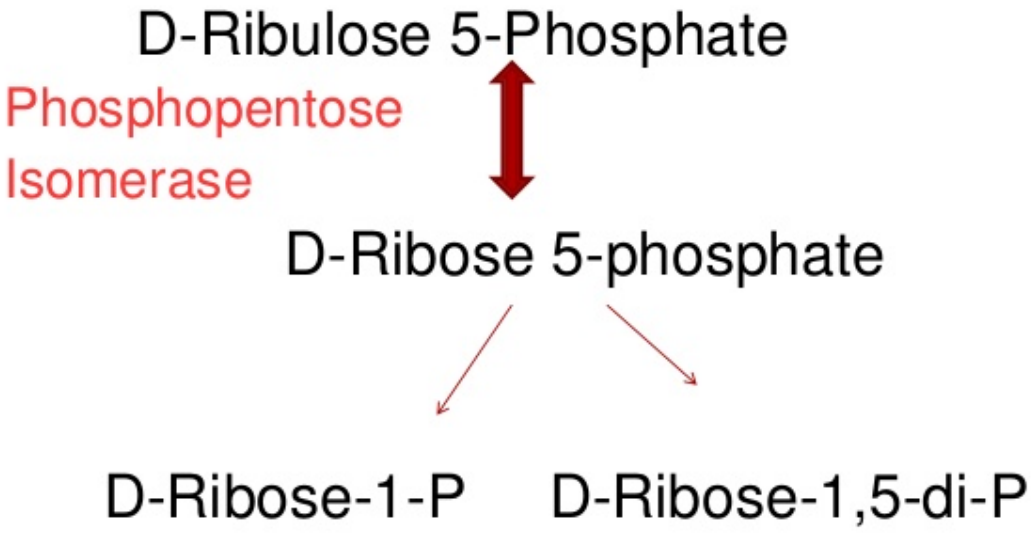
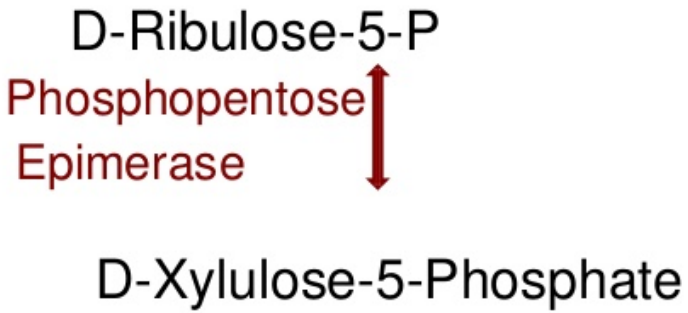
Phase 2- Non-oxidative

a) Interconversion of pentoses



Phase 2- Non-oxidative



Phase 2- Non-oxidative

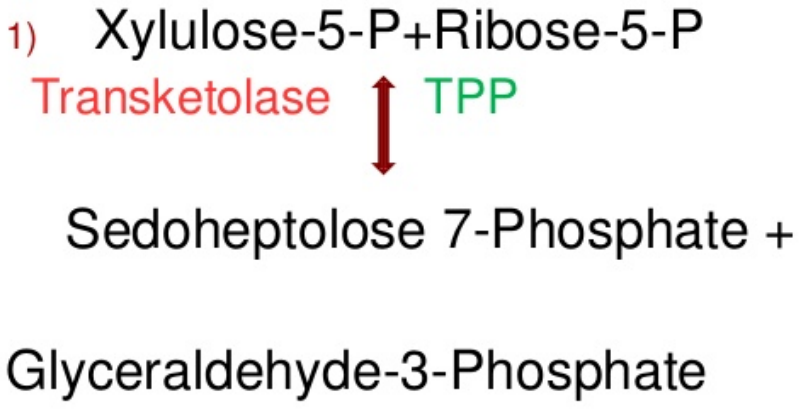
a) Conversion of pentose phosphate to hexose phosphates

➡ 2 Particular Enzymes are required:

1) TRANSKETOLASE

2) TRANSALDOLASE

Transketolation



Transaldolation

Sedoheptolose 7-P+G3P

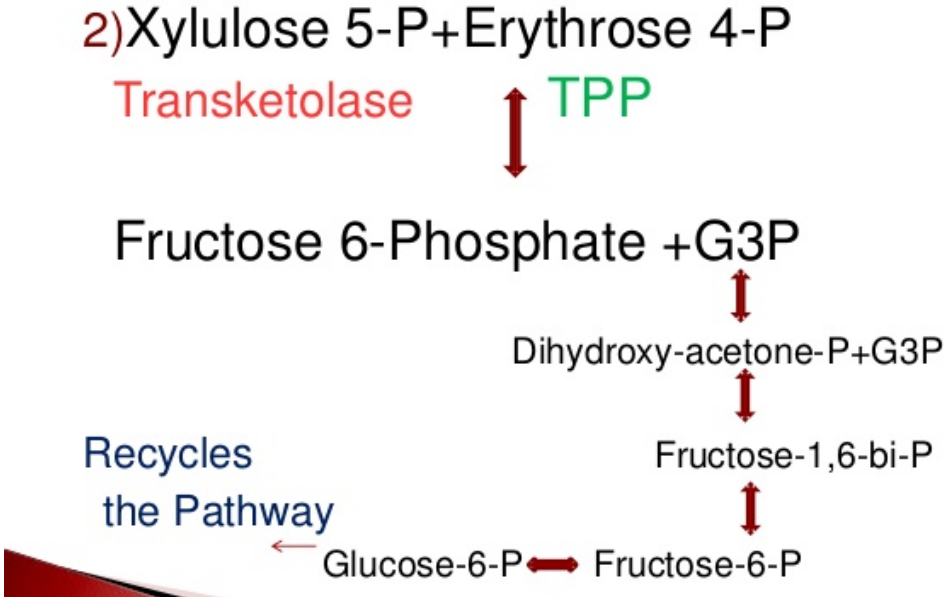
Transaldolase 

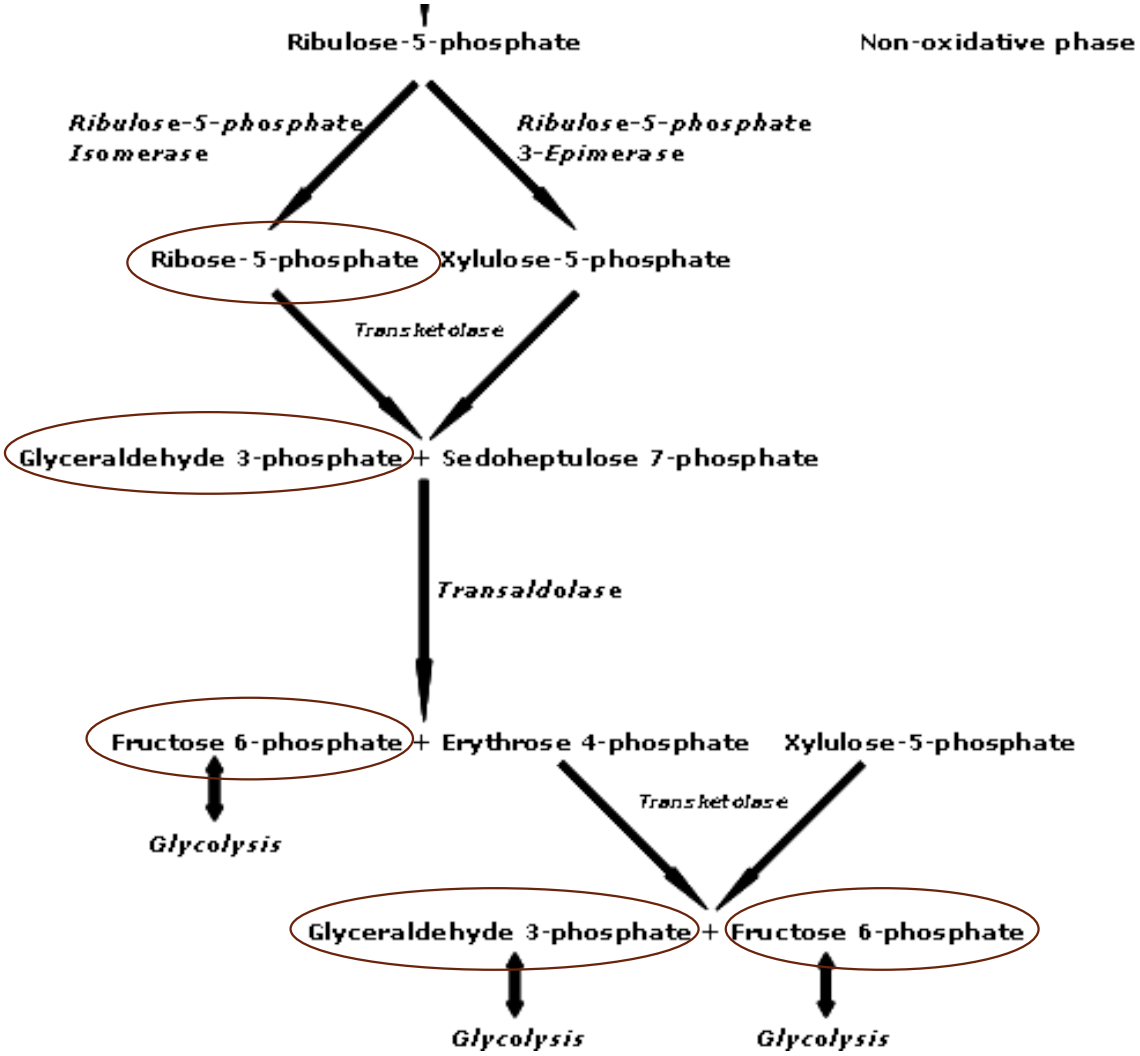
Fructose 6-Phosphate

+

Erythrose 4-Phosphate

Transketolation





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Clinical Correlations

G-6-PD deficiency results in:

- Heamolytic Aneamia
- Neonatal Jaundice
- Kidney failure

Glucose Transport

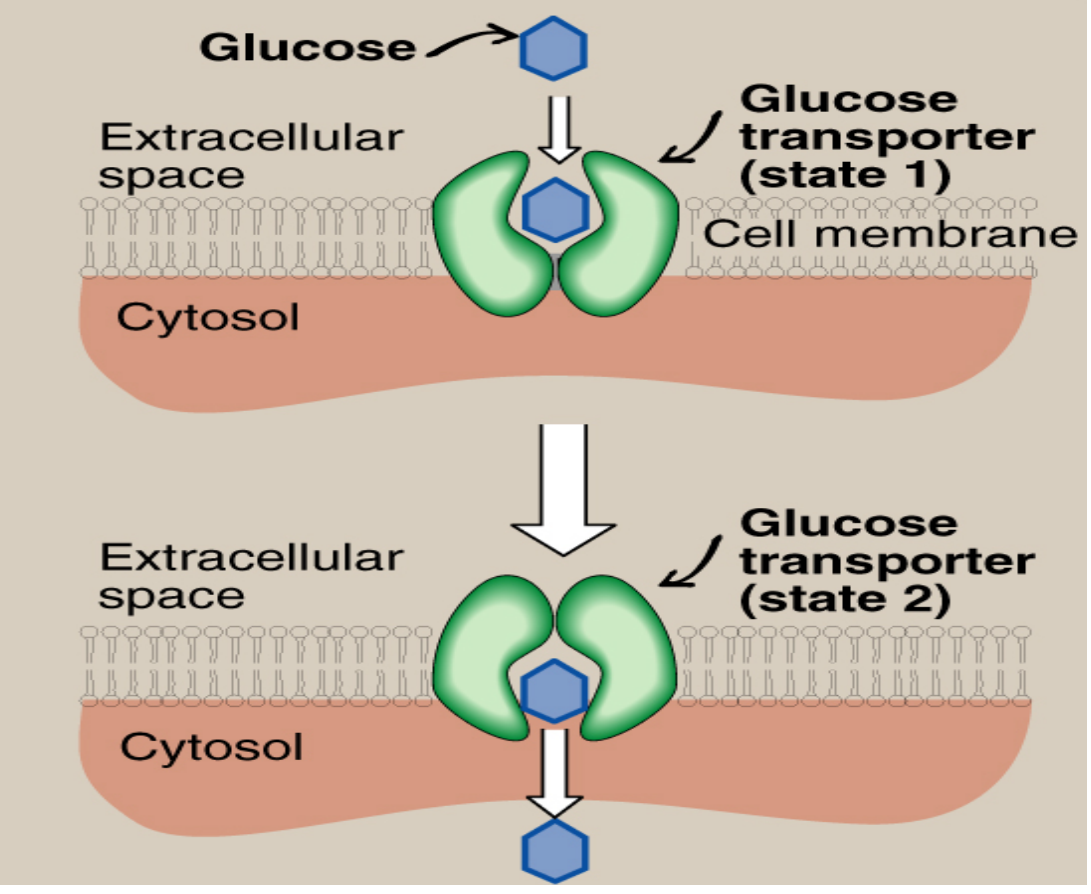
Na+-Monosaccharide Cotransporter:

- Against concentration gradient
- Energy dependent
- Carrier-mediated
- Coupled to Na+ transport
- Small intestine, renal tubules & choroid plexus

Na+-Independent Facilitated Diffusion:

- Down the concentration gradient
- Energy Independent
- Glucose Transporters (GLUT 1-14)

Glucose Transport: Facilitated Diffusion



Glucose Transporters

- Tissue-specific expression pattern

GLUT-1	RBCs and brain
GLUT-2	Liver, kidney & pancreas
GLUT-3	Neurons
GLUT-4	Adipose tissue & skeletal muscle
GLUT-5	Small intestine & testes
GLUT-7	Liver (ER-membrane)

- Functions:

GLUT-1, 3 & 4	Glucose uptake from blood
GLUT-2	Blood & cells (either direction)
GLUT-5	Fructose transport

Take Home Messsage

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

Take Home Messsage - HMP

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

References

Lippincott's Illustrated Reviews- Biochemistry 6th Edition- pages: 96-97,117,126,128,145-147
http://www.biochemden.com/the-hexose-monophosphate-shunt/