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

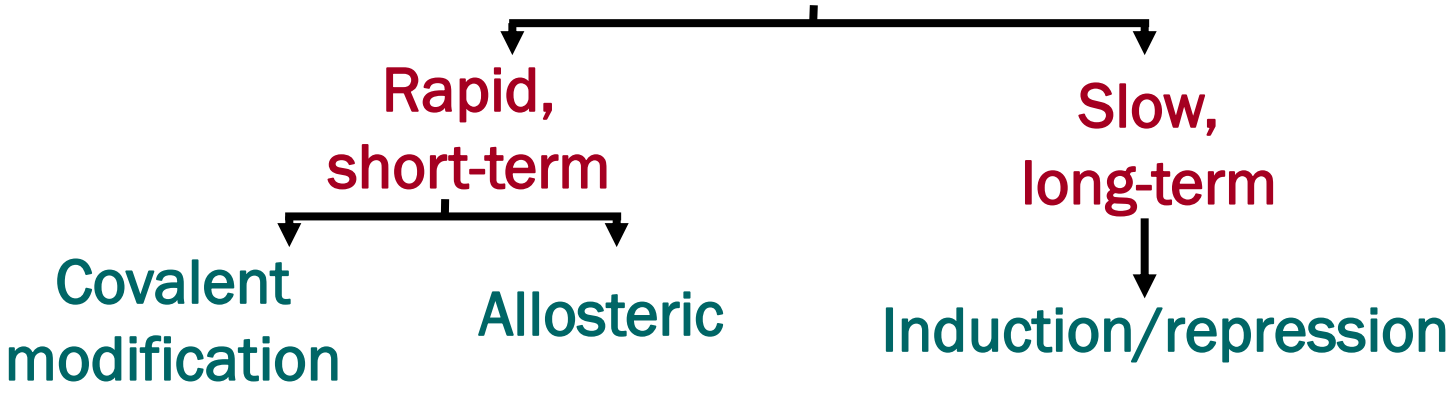
Site:

Cellular (tissue) and Subcellular

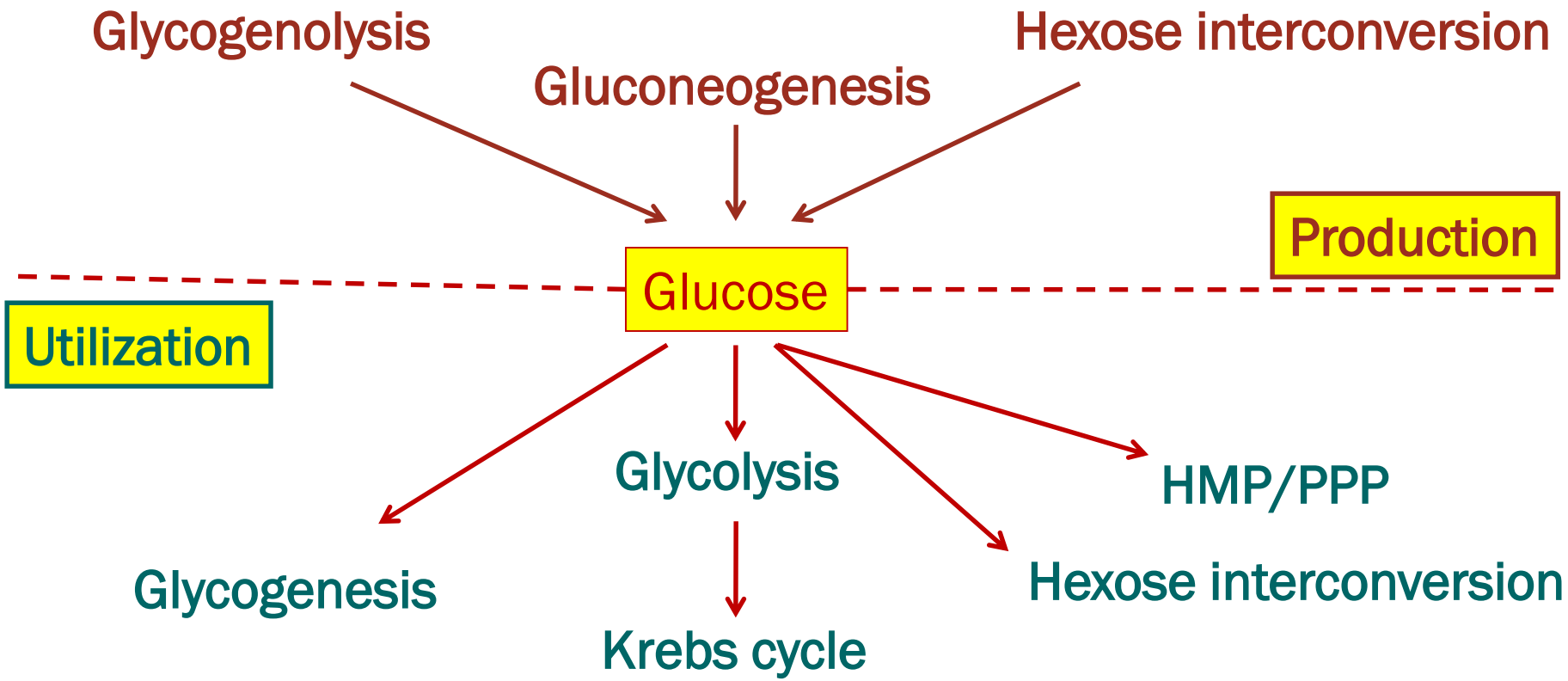
Reactions

Rate-limiting enzyme(s)

Regulatory mechanism(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)

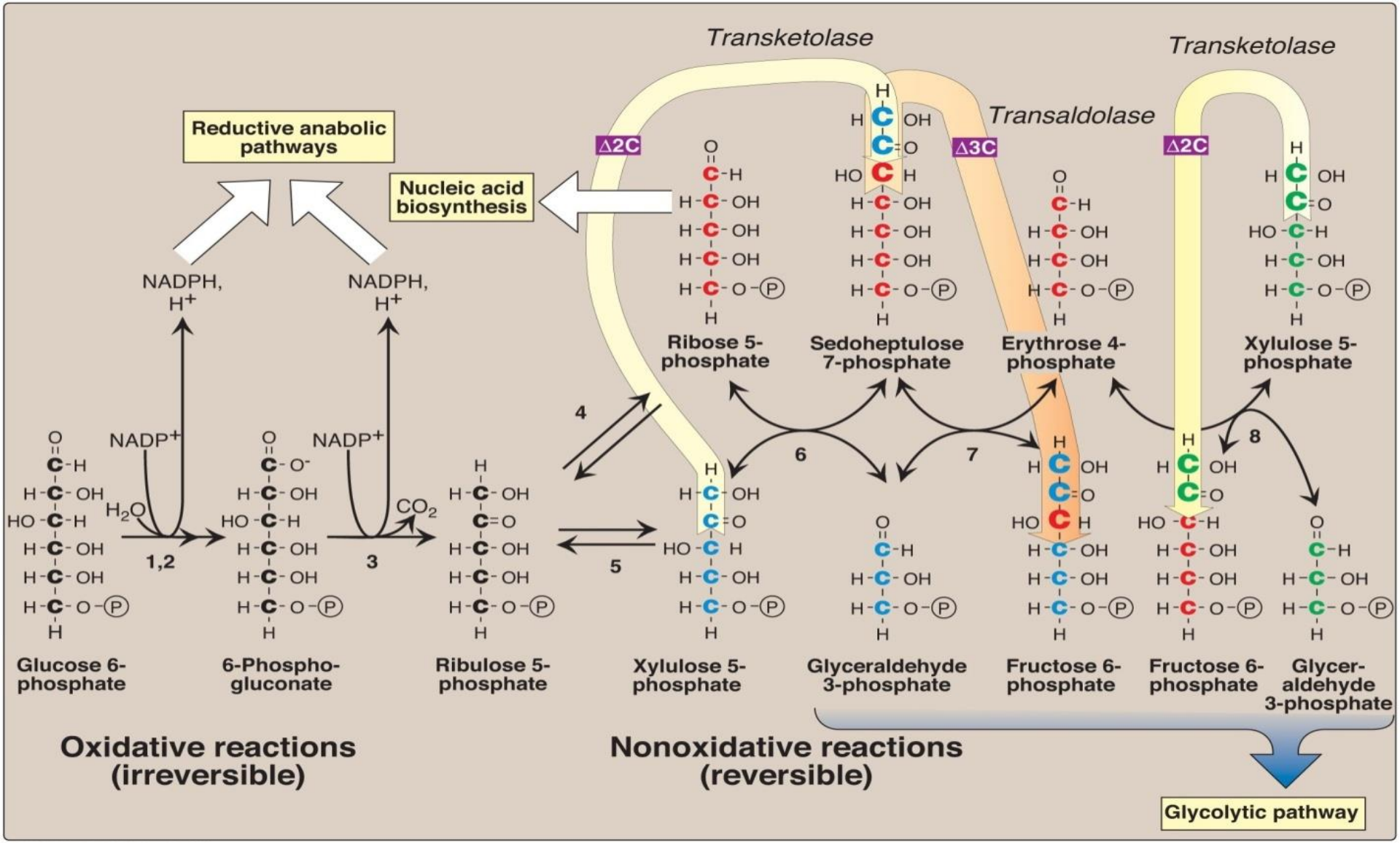
Tissue Distribution

Location- Cytosol

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

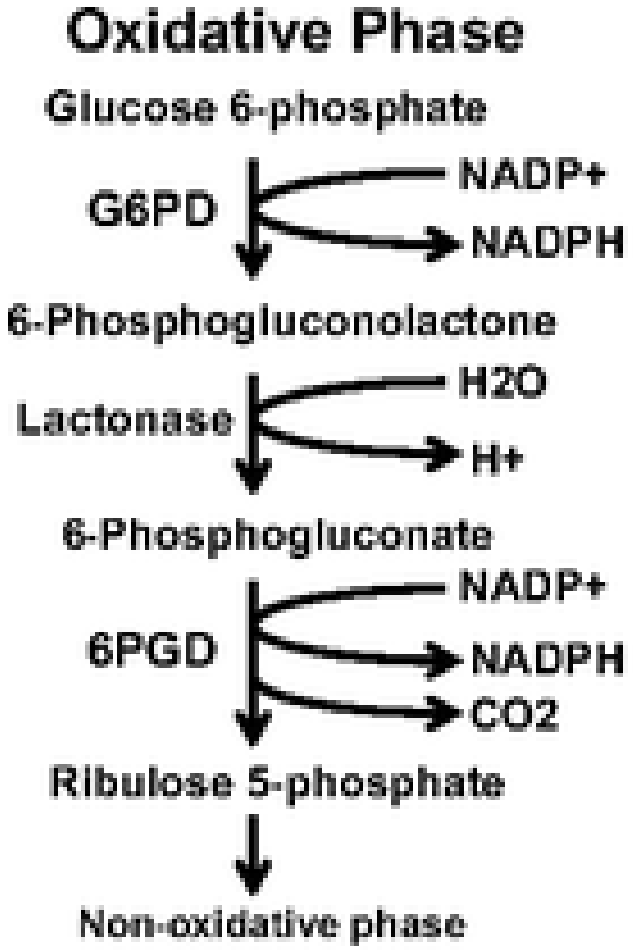
Phases of HMP Shunt

- 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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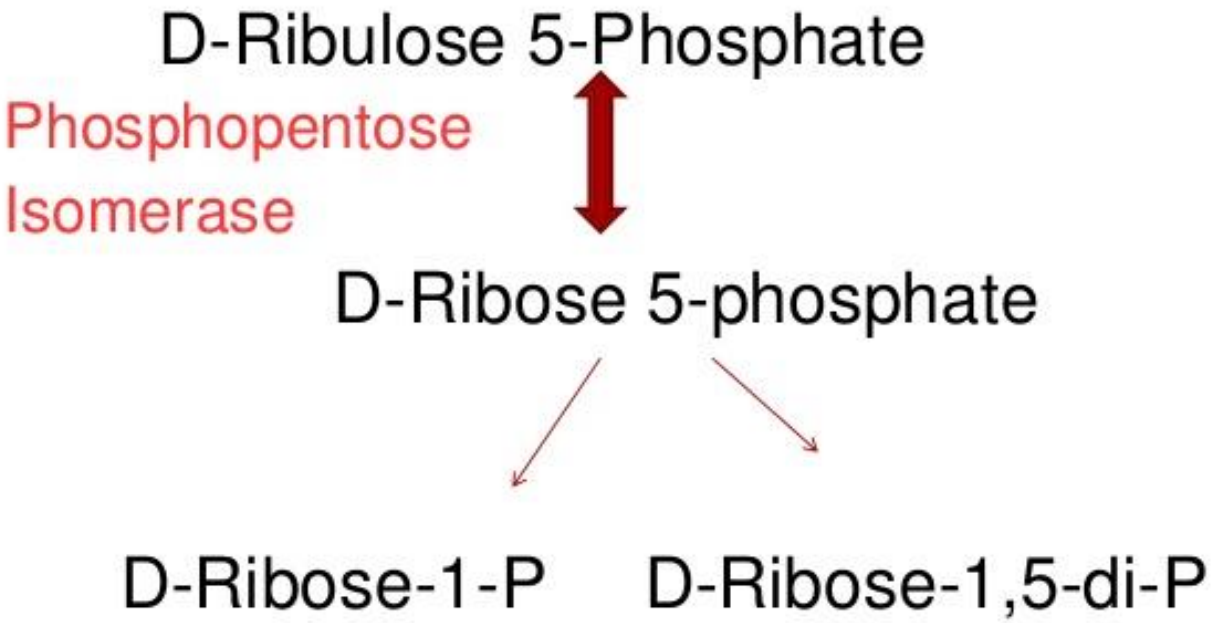
Phase 2- Non-oxidative

a) Interconversion of pentoses



Phase 2- Non-oxidative

D-Ribulose-5-P

D-Xylulose-5-Phosphate

Phase 2- Non-oxidative

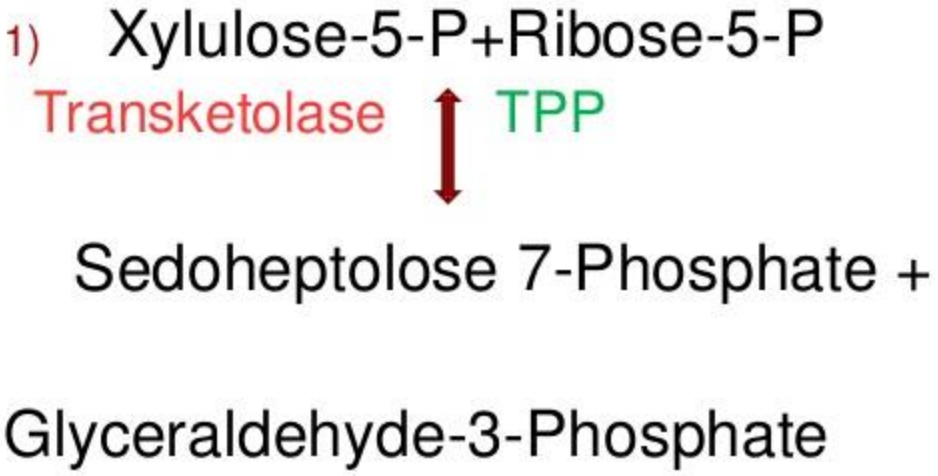
a) Conversion of pentose phosphate to hexose phosphates

➡ 2 Particular Enzymes are required:

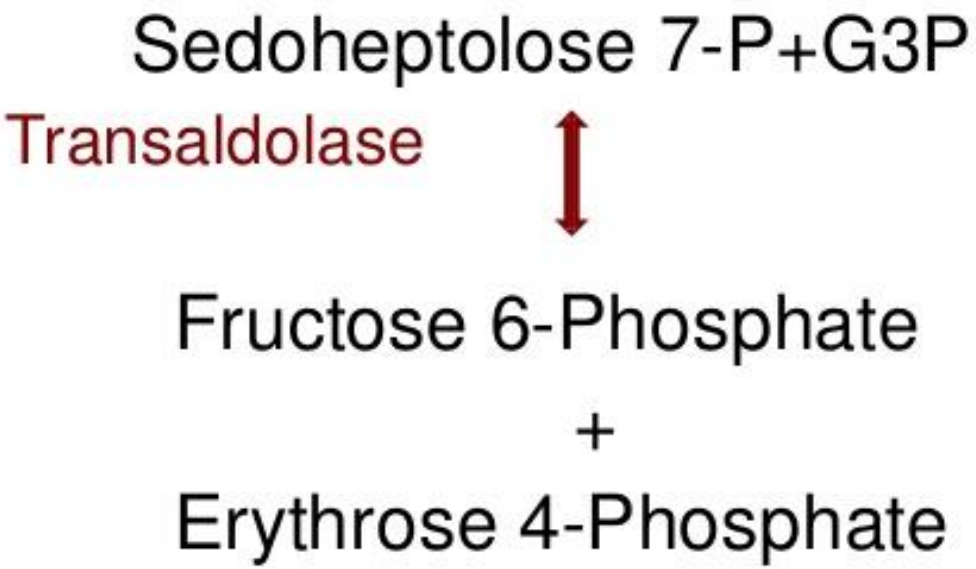
1) TRANSKETOLASE

2) TRANSALDOLASE

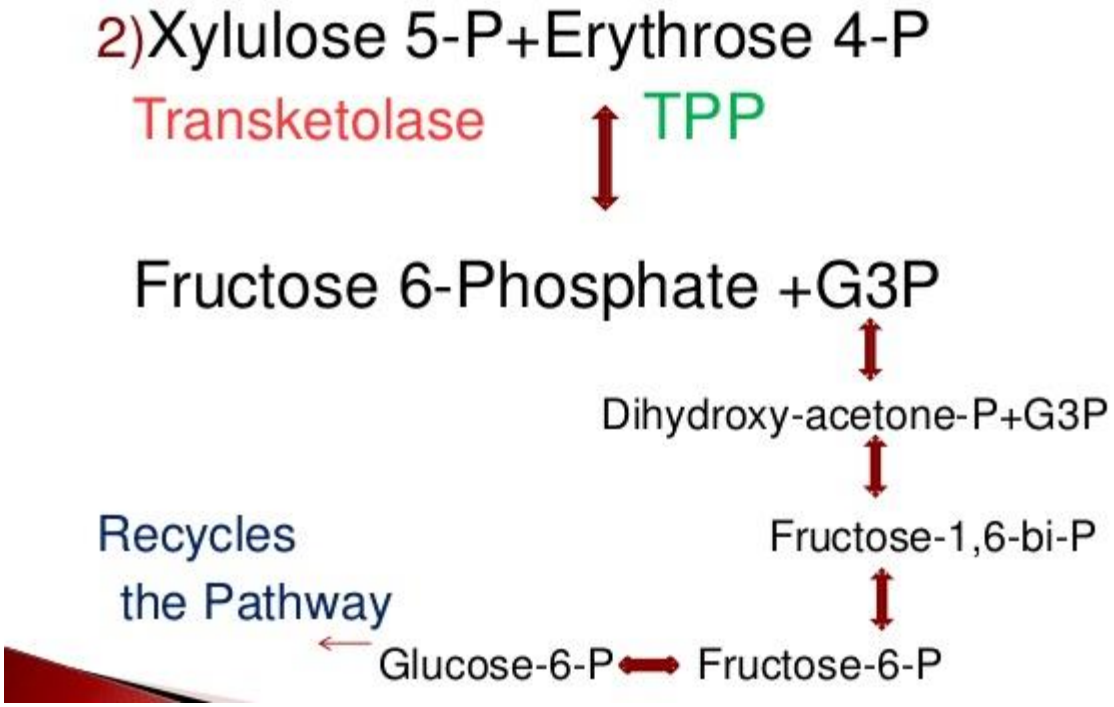
Transketolation

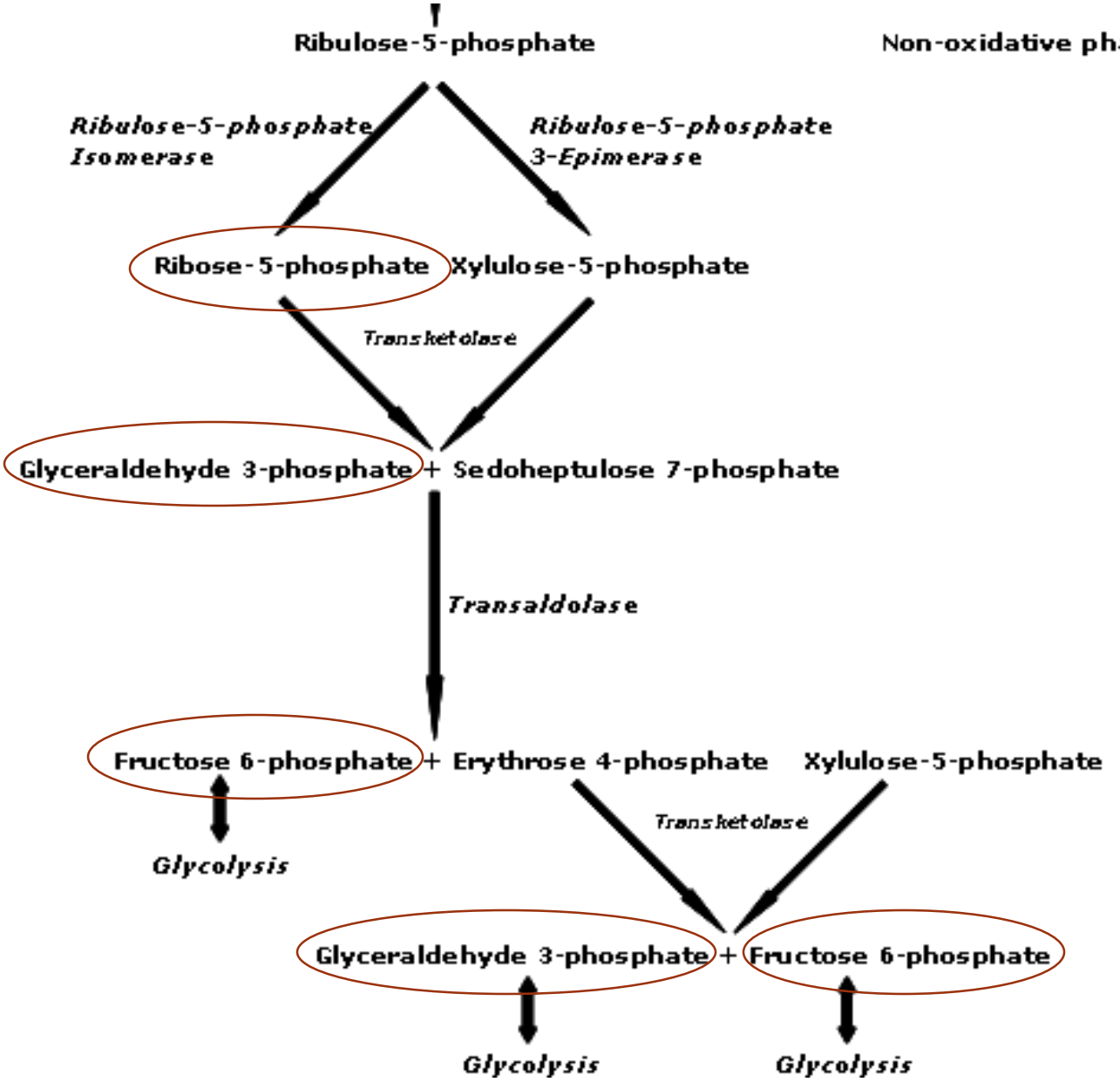


Transaldolation



Transketolation





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Clinical Correlations

G-6-PD deficiency results in:

- Heamolytic Aneamia
- Neonatal Jaundice
- Kidney failure

Glucose Transport

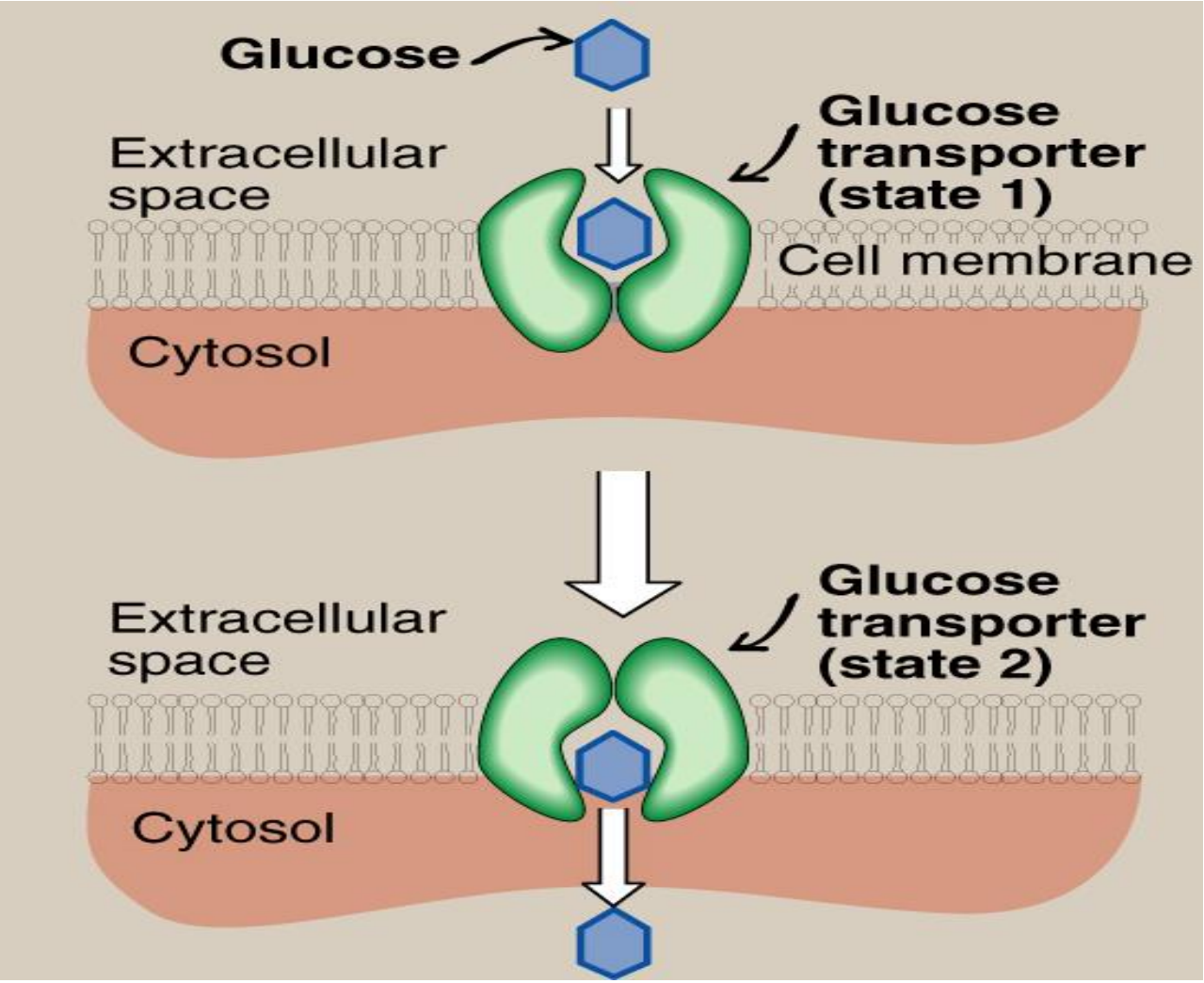
Na^+-Monosaccharide Cotransporter:

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 CO2
- 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/