بسم الله الرحمن الرحيم

Major Metabolic Pathways of Glucose

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Metabolic Pathway

Definition

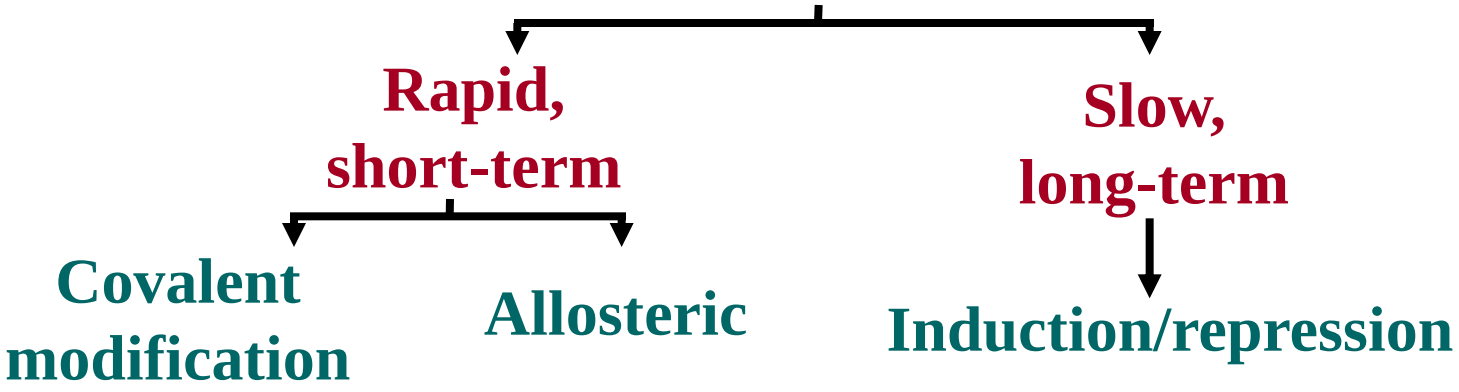
Site:

Cellular (tissue) and Subcellular

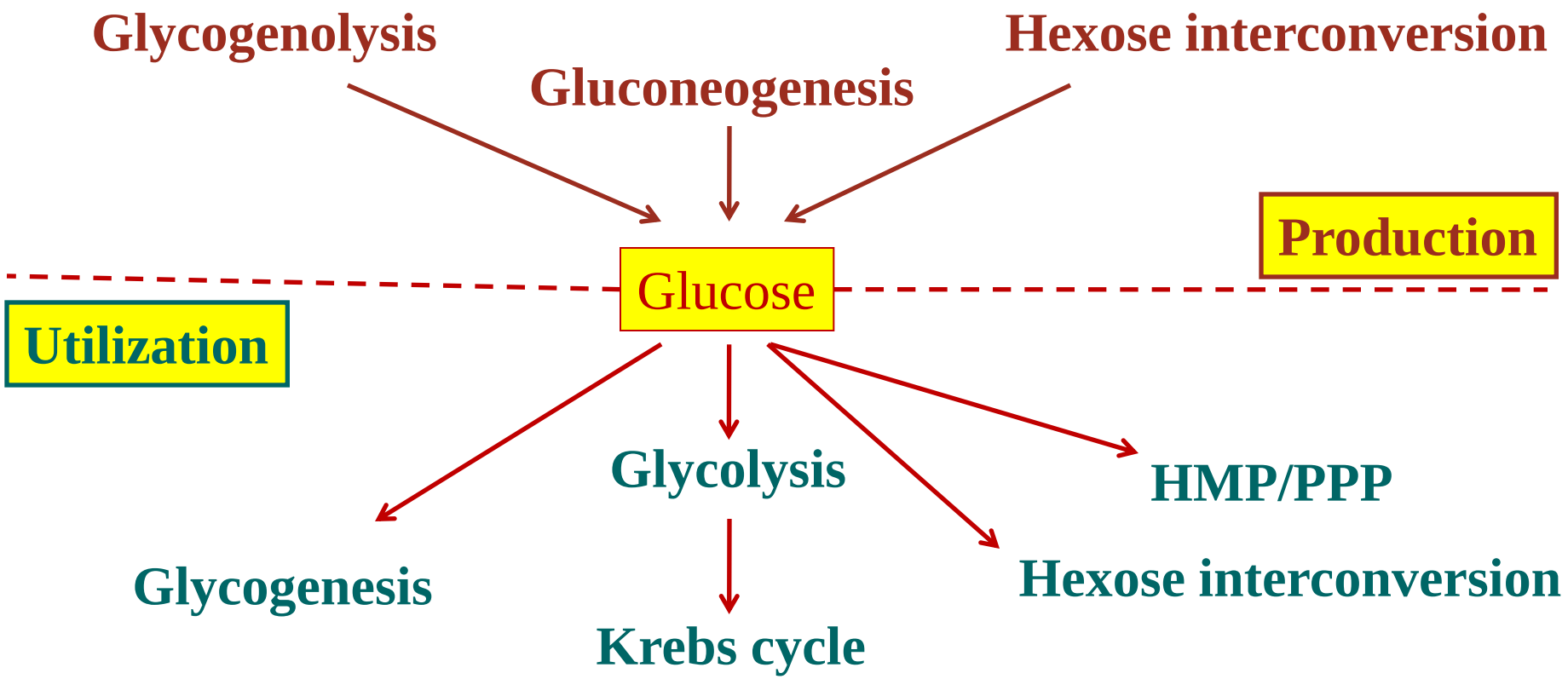
Reactions

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

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

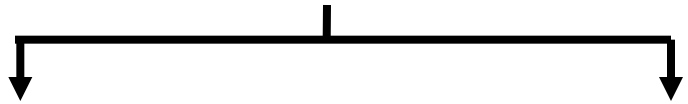
Hexose Monophosphate Pathway (HMP) or Pentose Phosphate Pathway (PPP)

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

Glucose Transport

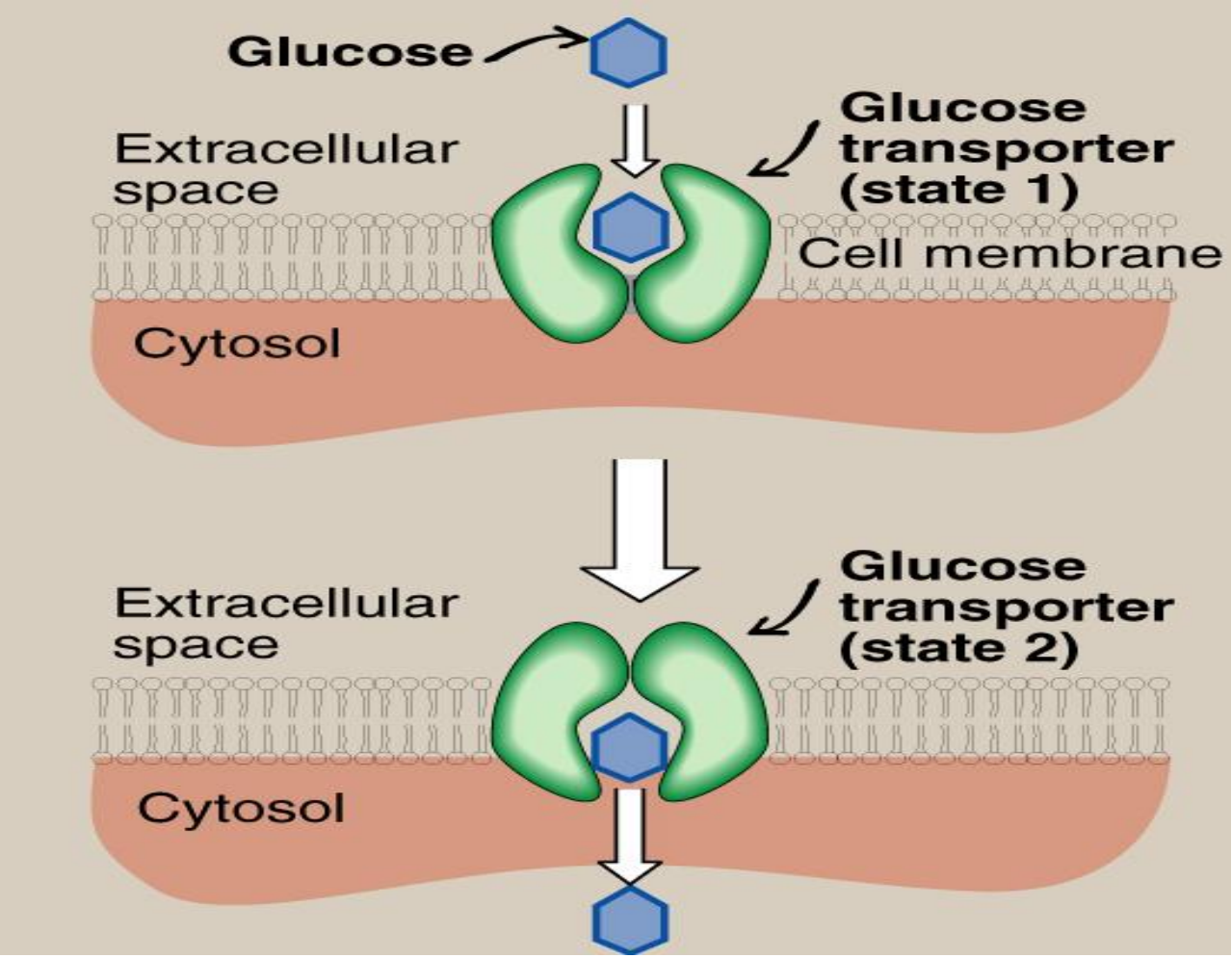
Na^+-Monosaccharide Cotransporter:

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

Na^+-Independent Facilitated Diffusion:

- With 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**

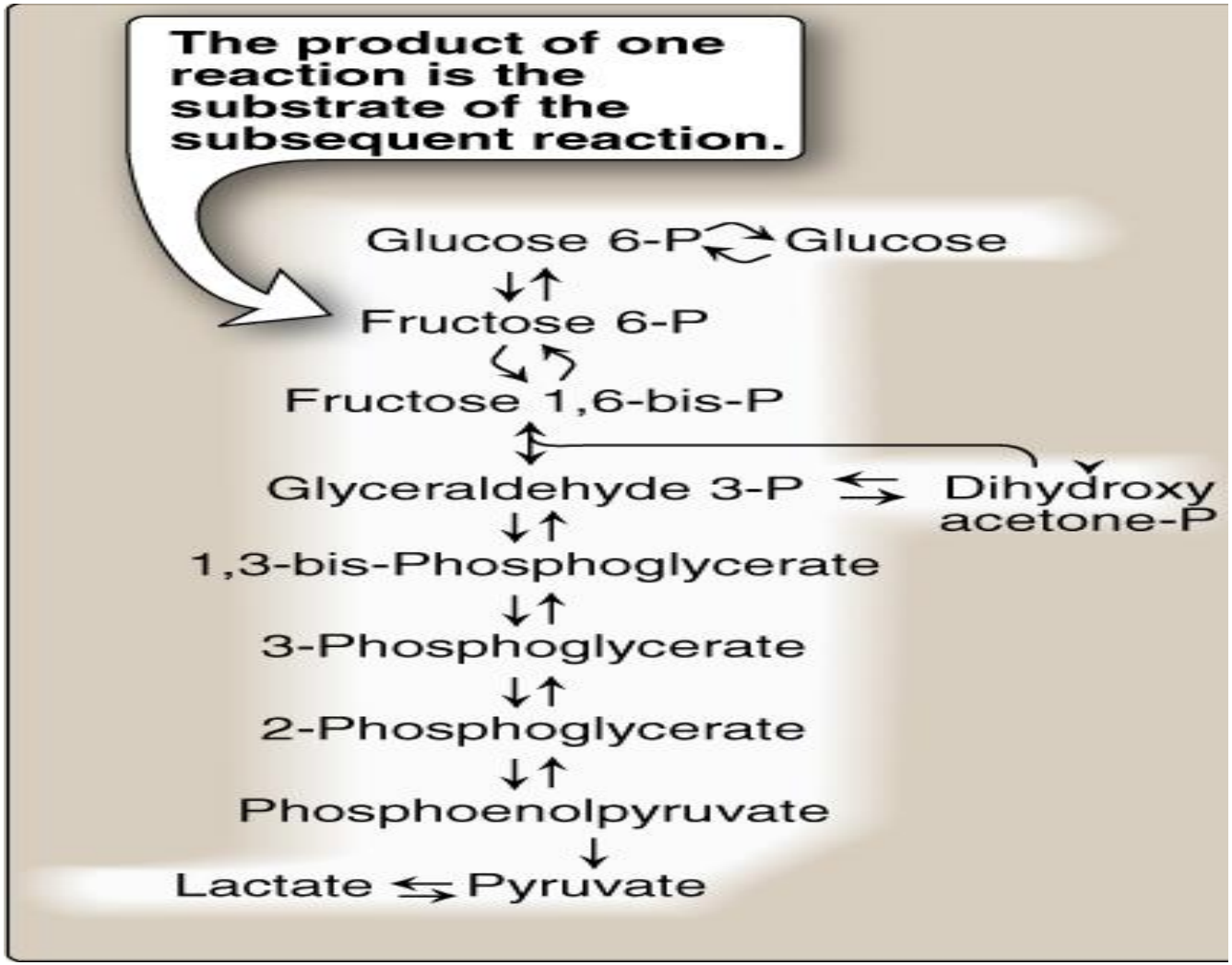
Glycolysis: Objectives

- Glycolysis as a major oxidative pathway of glucose
- The main reactions of glycolytic pathway
- The rate-limiting enzymes/Regulation
- ATP production (aerobic/anaerobic)
- Pyruvate kinase deficiency hemolytic anemia

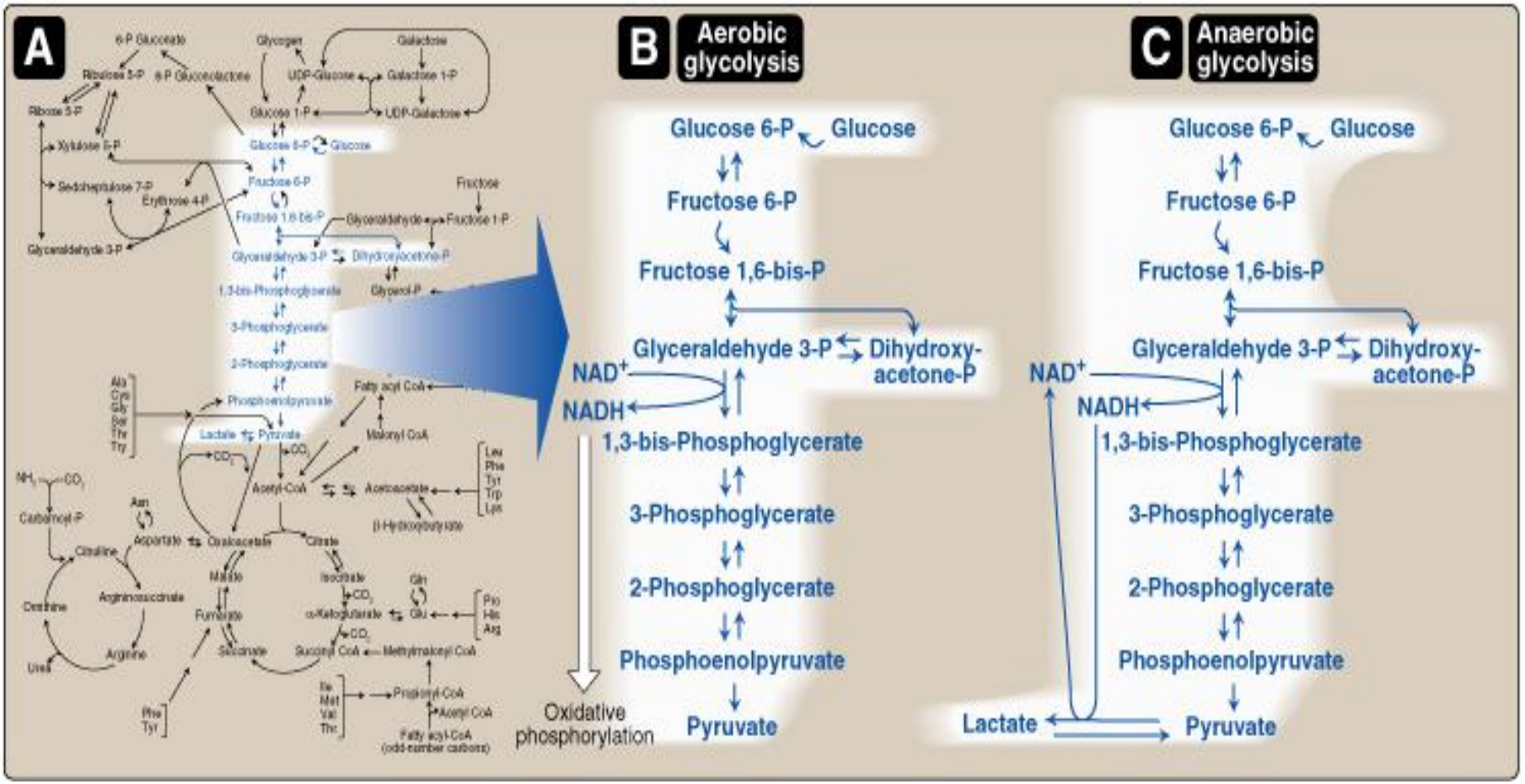
Glycolysis: An Overview

- Glycolysis, the major pathway for glucose oxidation, occurs in the cytosol of all cells.
- It is unique, in that it can function either aerobically or anaerobically, depending on the availability of oxygen and intact mitochondria.
- RBCs, which lack mitochondria, are completely reliant on glucose as their metabolic fuel, and metabolizes it by anaerobic glycolysis.
- It allows tissues to survive in presence or absence of oxygen, e.g., skeletal muscle.

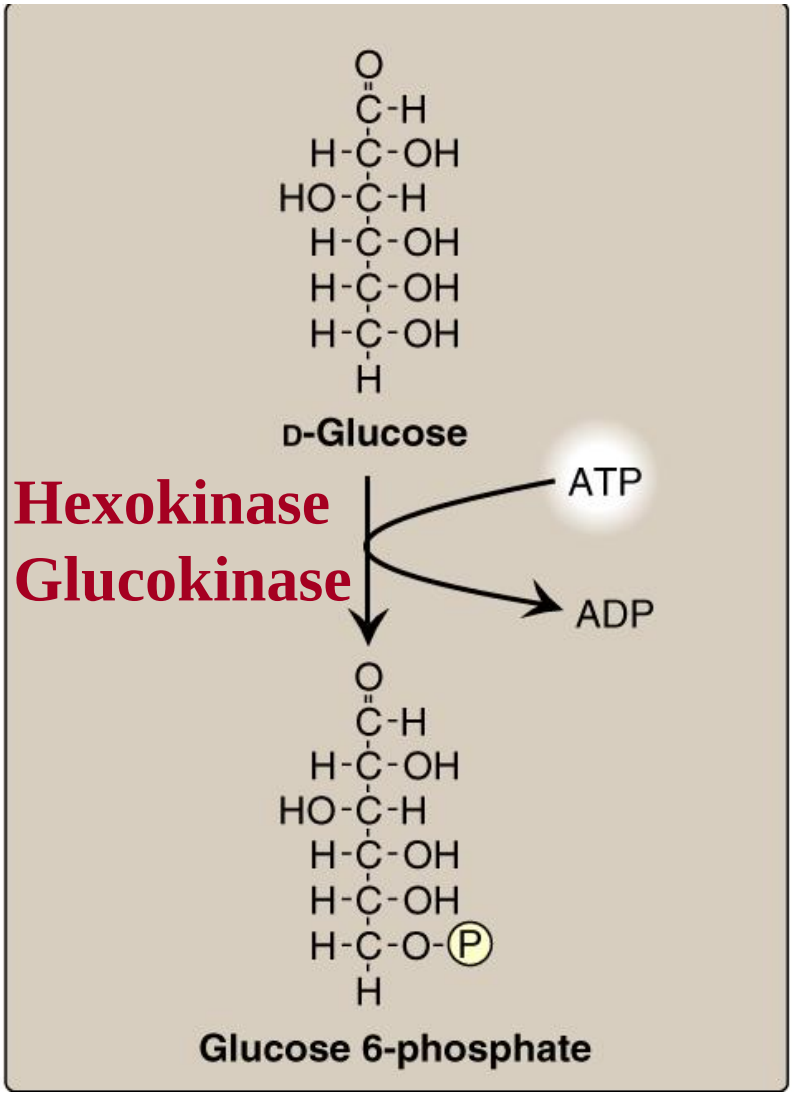
Glycolysis


The product of one reaction is the substrate of the subsequent reaction.
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate

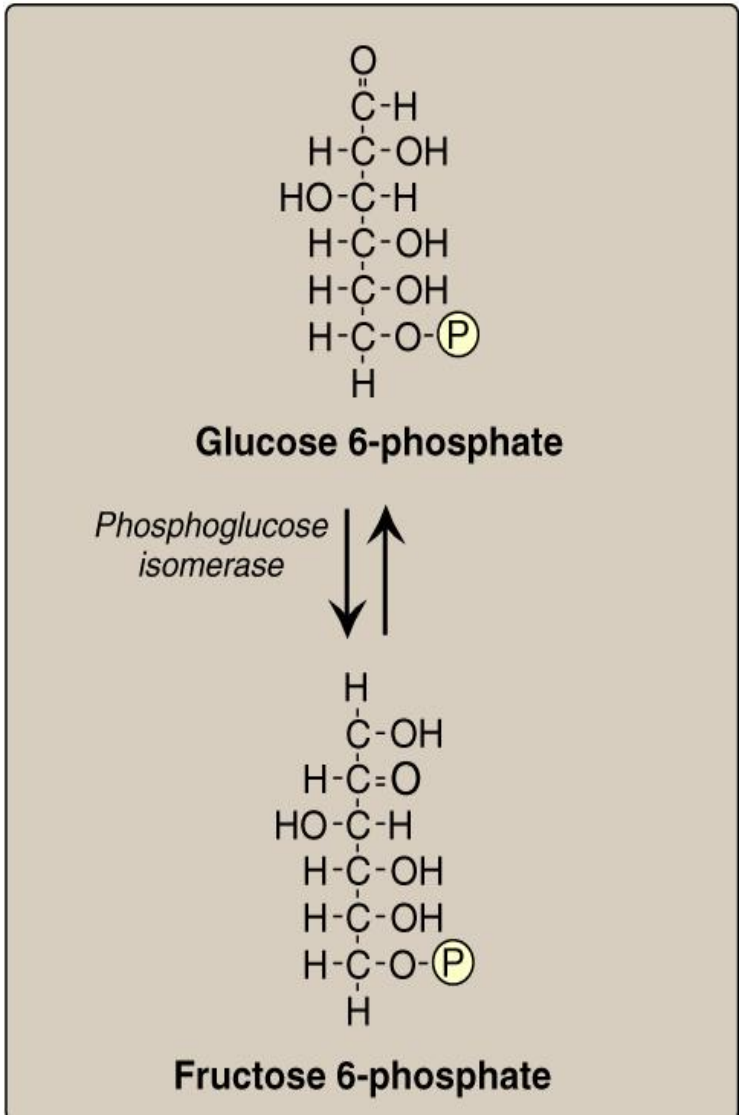
Aerobic Vs Anaerobic Glycolysis



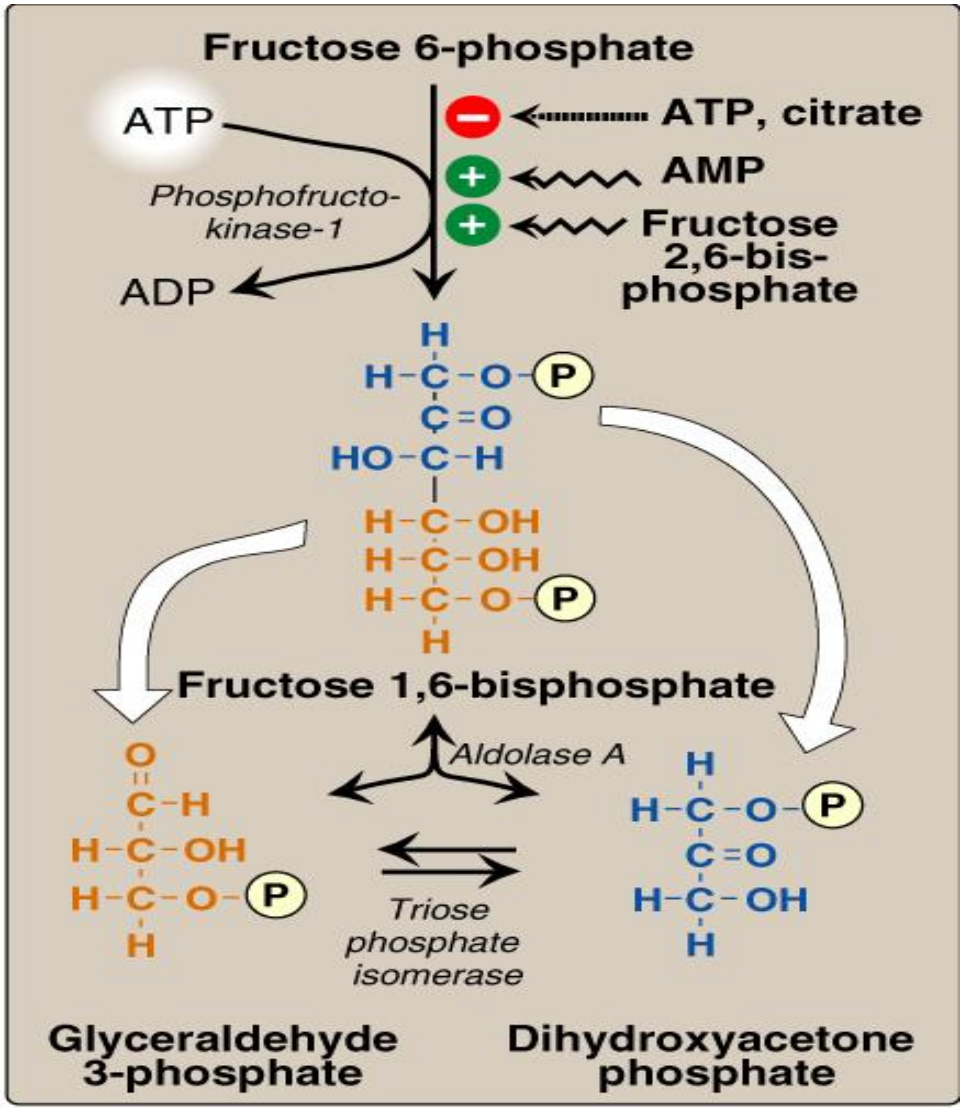
Aerobic Glycolysis-1



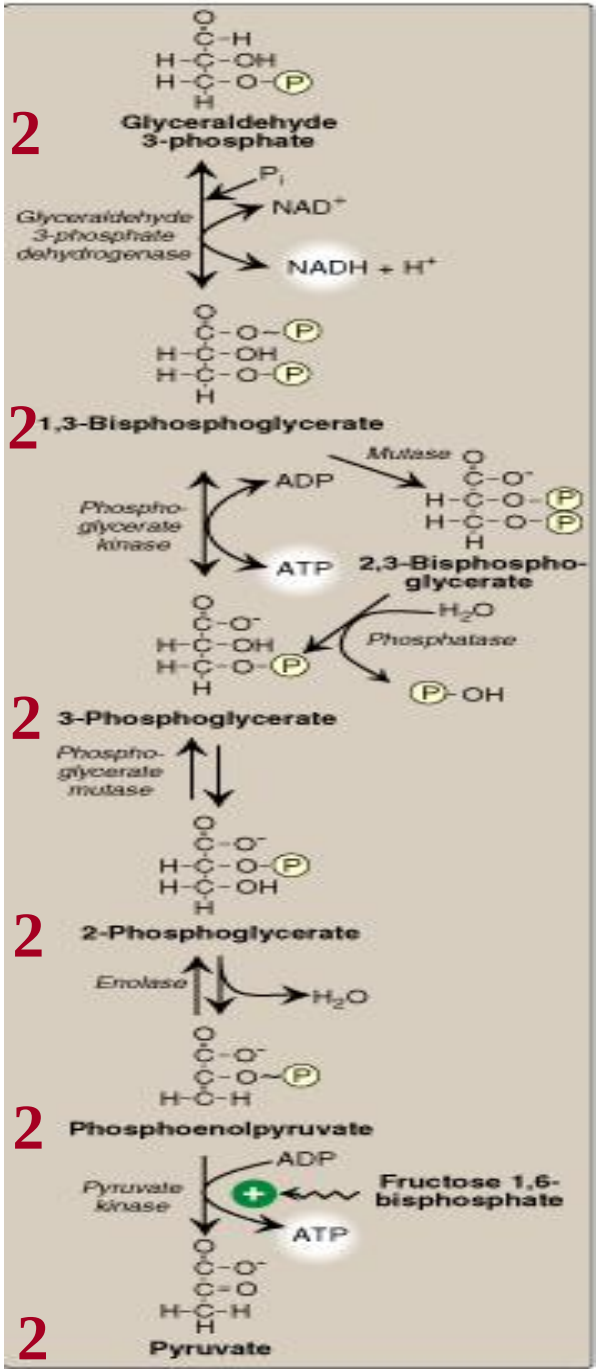
Aerobic Glycolysis-2



Aerobic Glycolysis: 3-5



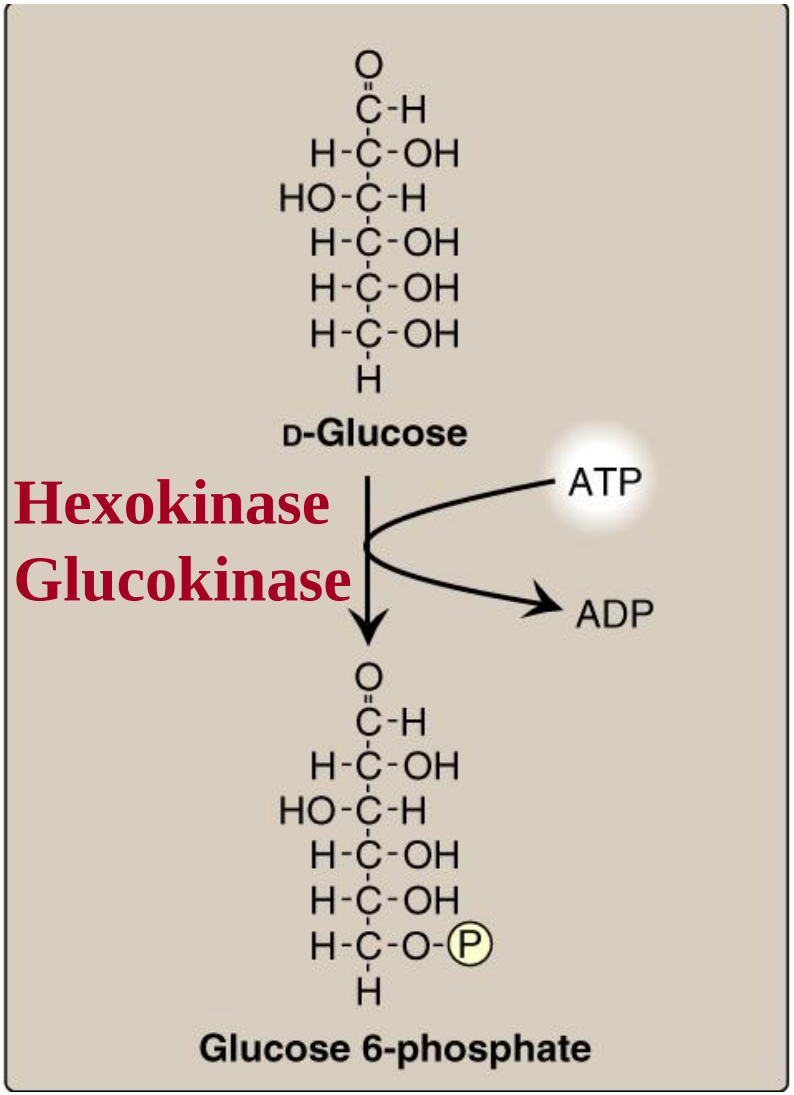
Aerobic Glycolysis: 6 -10



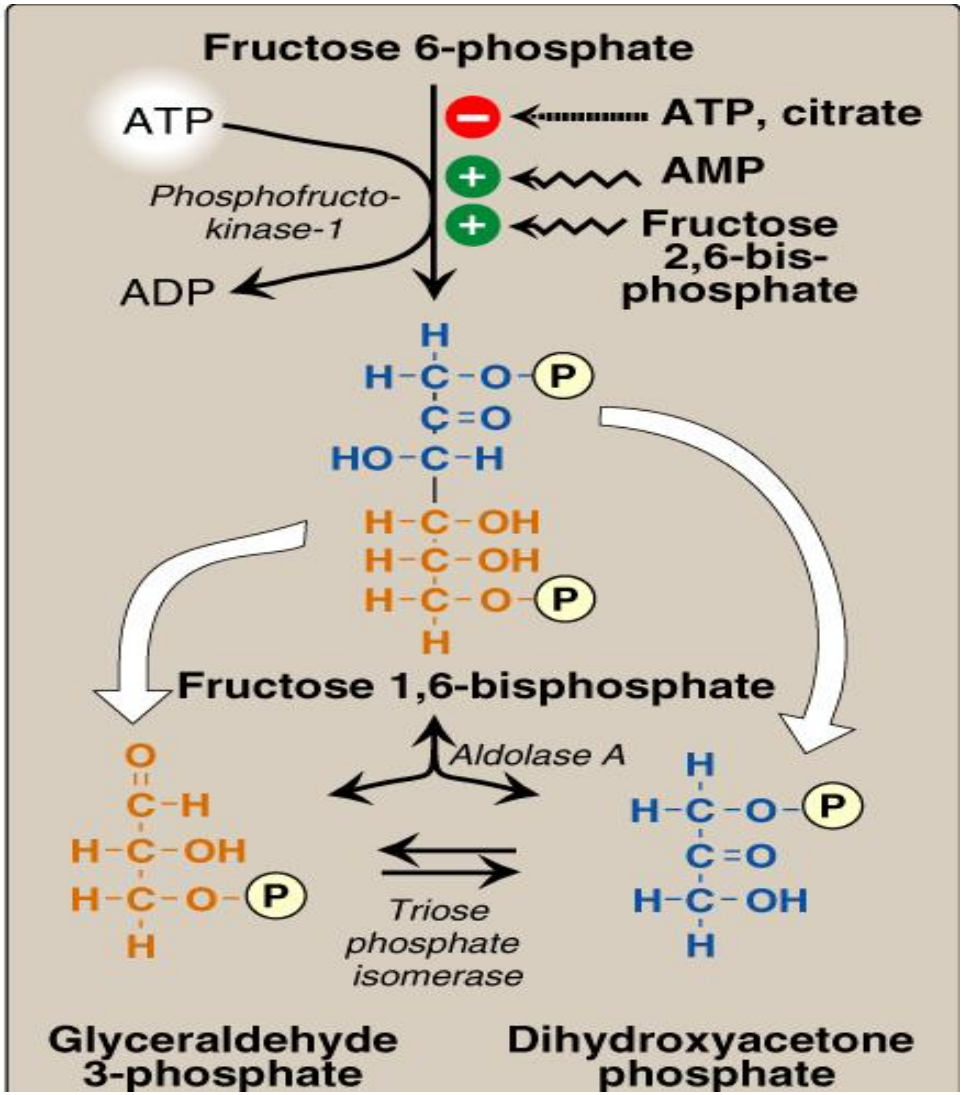
Aerobic Glycolysis-1

Hexokinase:
Most tissues

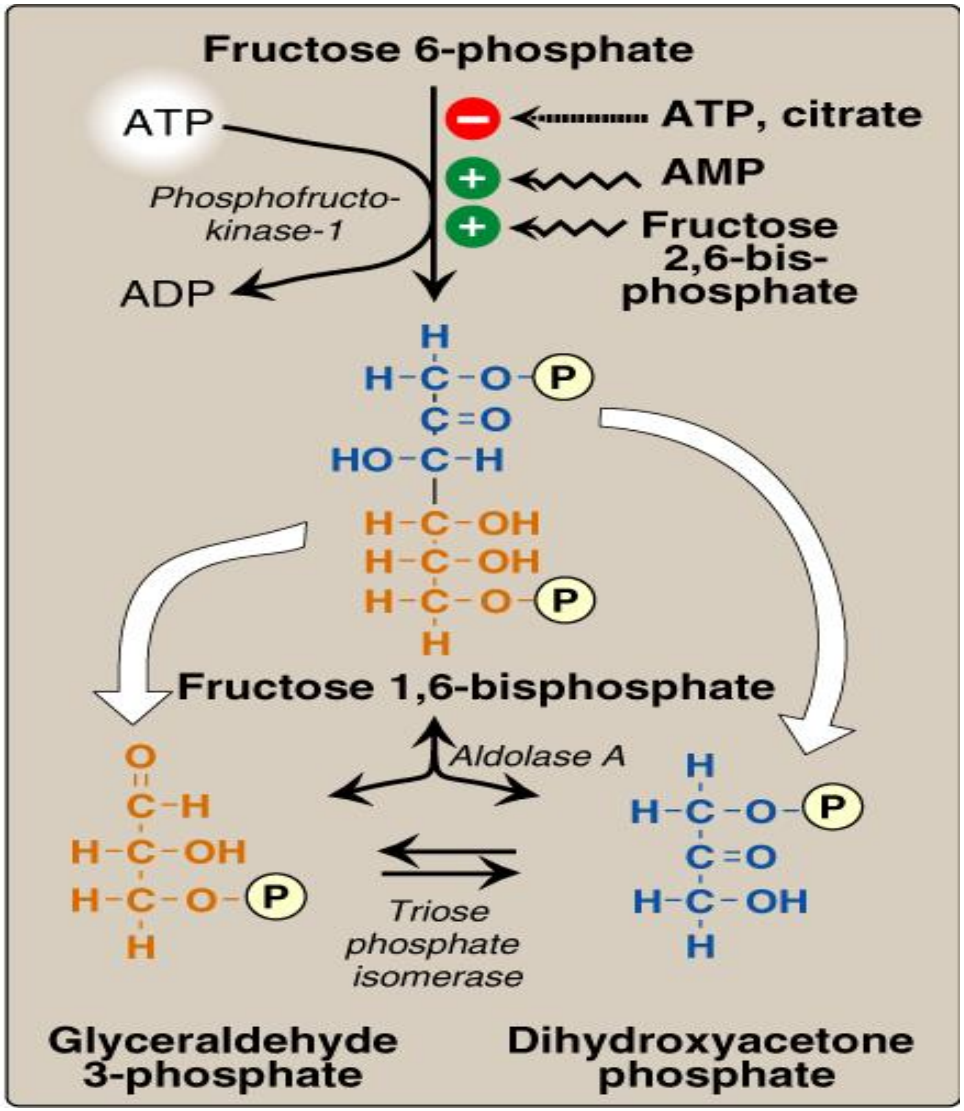
Glucokinase:
Hepatocytes



PFK-1 : Regulation

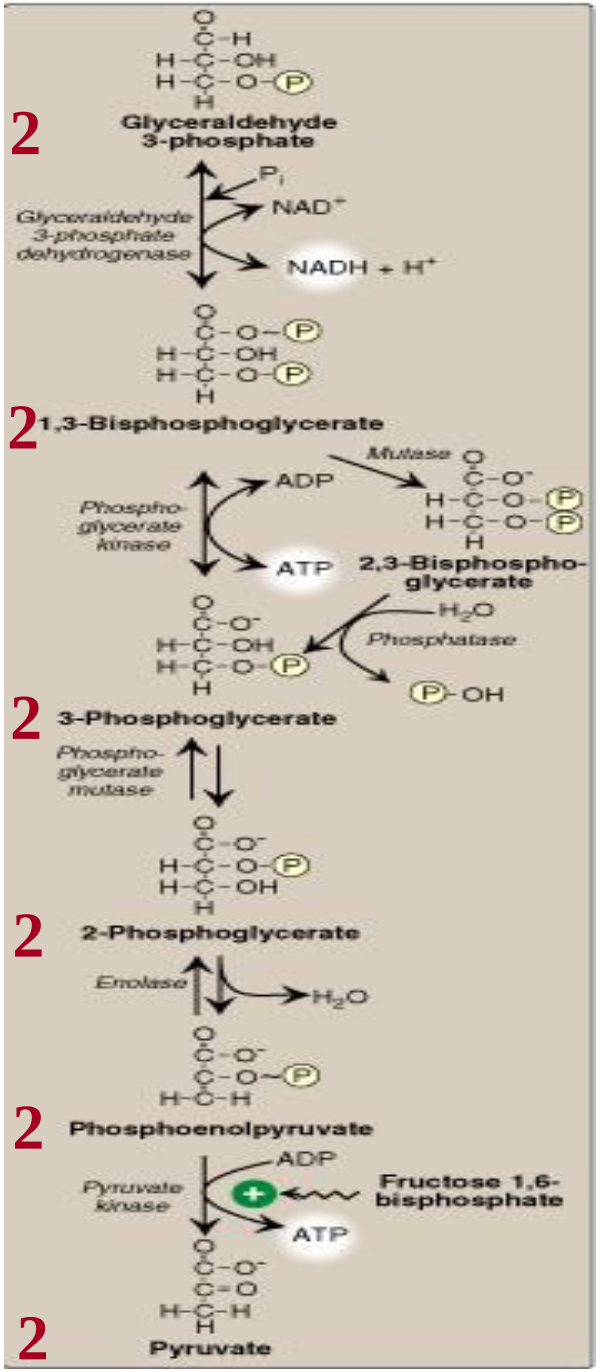


Aldolase and Triose Isomerase

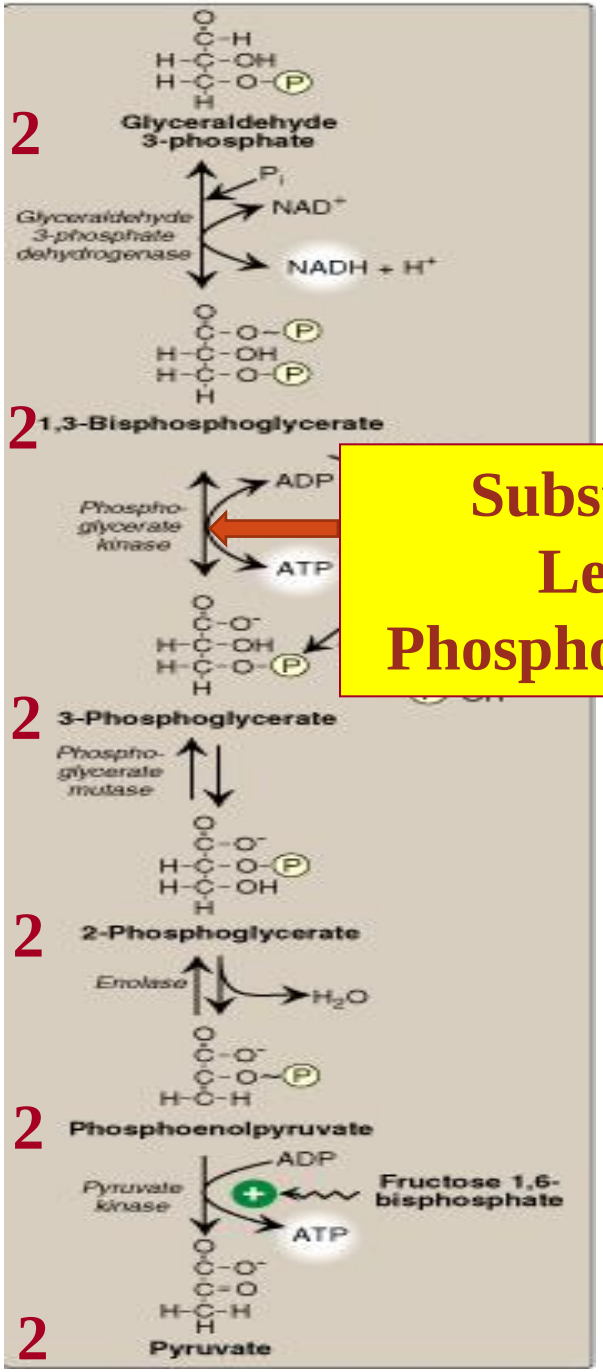


Glyceraldehyde 3-Phosphate Dehydrogenase

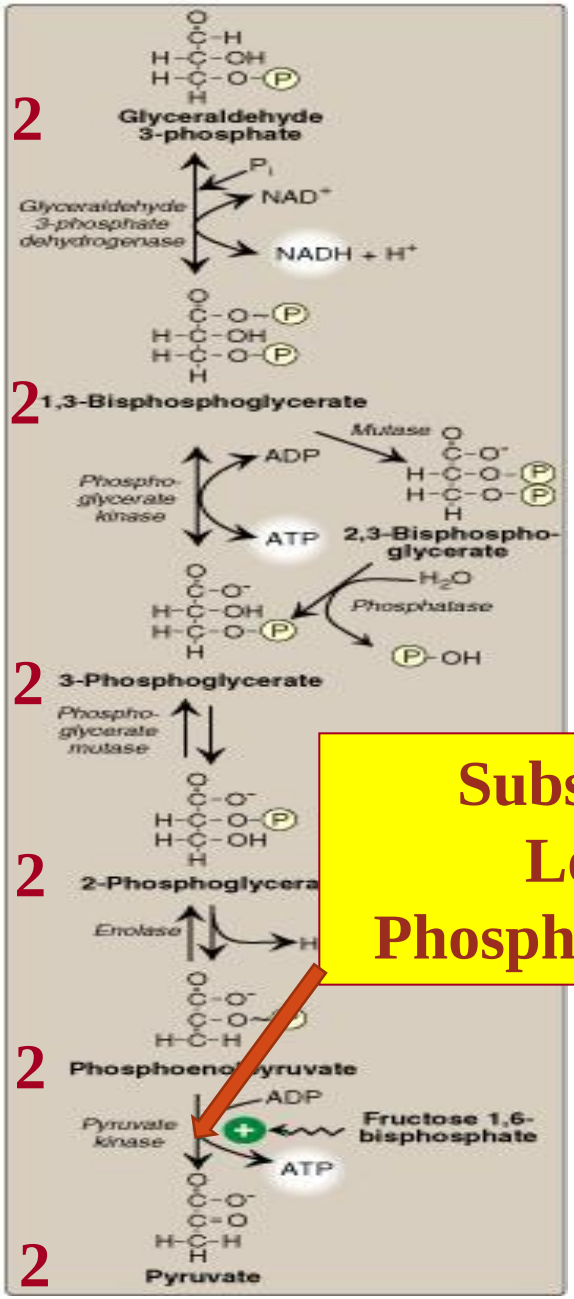
For each NADH, 3 ATP will be produced by ETC in the mitochondria i.e., 6 ATP are produced



Phospho-glycerate Kinase



Substrate-Level Phosphorylation



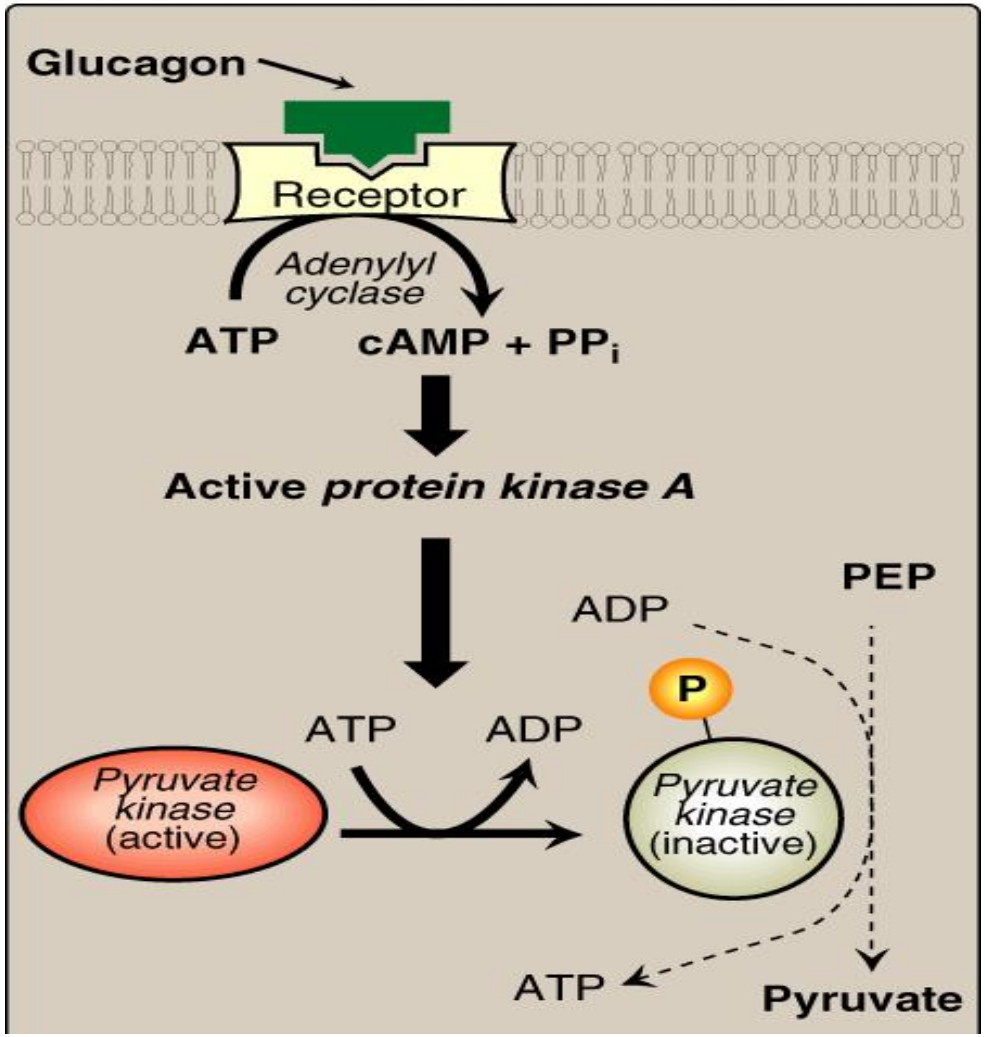
Substrate-Level Phosphorylation

Pyruvate Kinase

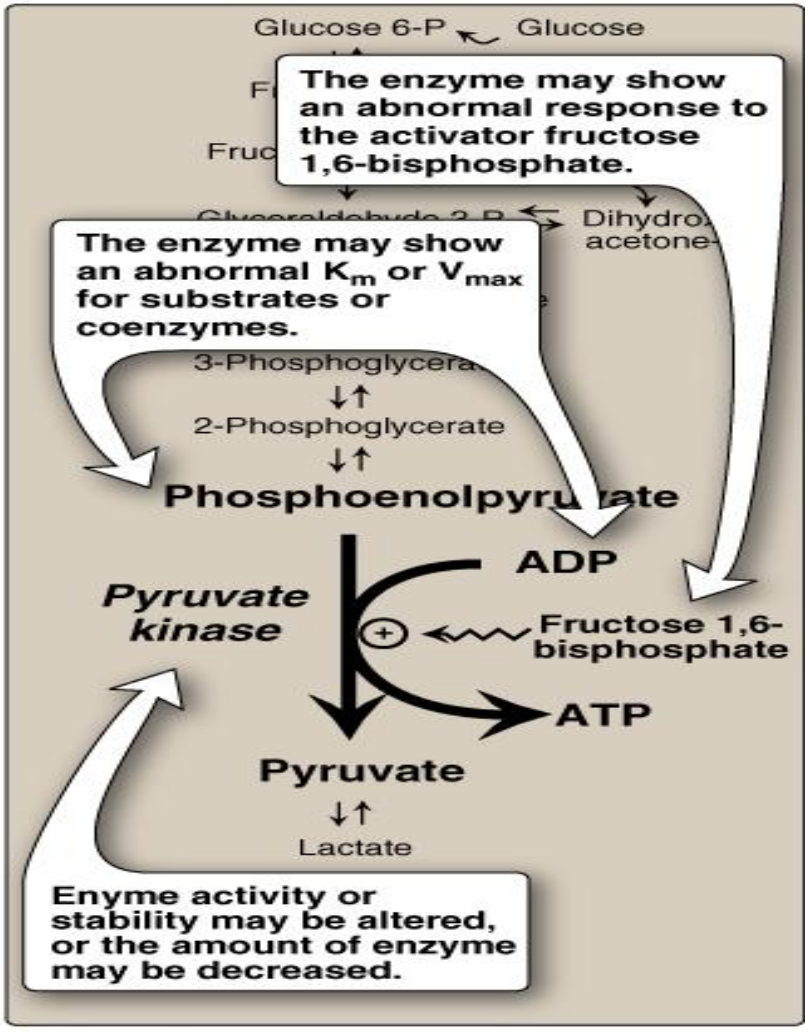
Substrate-level phosphorylation Vs. Oxidative phosphorylation

- **Phosphorylation** is the metabolic reaction of introducing a phosphate group into an organic molecule.
- **Oxidative phosphorylation:** The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP **coupled to** the transfer of electrons from reduced coenzymes to molecular oxygen via the electron transport chain (ETC); it occurs in the mitochondria.
- **Substrate-level phosphorylation:** The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP (or GDP to GTP) **coupled to** cleavage of a high-energy metabolic intermediate (substrate). It may occur in cytosol or mitochondria

Pyruvate Kinase
Covalent Modification



Pyruvate Kinase Deficiency Hemolytic Anemia



Summary: Regulation of Glycolysis

Regulatory Enzymes (Irreversible reactions):

- Glucokinase/hexokinase
- PFK-1
- Pyruvate kinase

Regulatory Mechanisms:

- Rapid, short-term:
  - Allosteric
  - Covalent modifications
- Slow, long-term:
  - Induction/repression

Apply the above mechanisms for each enzyme where applicable

Aerobic Glycolysis: ATP Production

ATP Consumed:

		2	ATP

ATP Produced:

Substrate-level	2 X 2 =	4	ATP
Oxidative-level	2 X 3 =	6	ATP
Total		10	ATP

Net:	10 – 2 =	8	ATP

Take Home Message

- **Glycolysis is the major oxidative pathway for glucose**
- **Glycolysis is employed by all tissues**
- **Glycolysis is a tightly-regulated pathway**
- **PFK-1 is the rate-limiting regulatory enzyme**

Take Home Message

- Glycolysis is mainly a catabolic pathway for ATP production, But it has some anabolic features (amphibolic)
- Pyruvate kinase deficiency in RBCs results in hemolytic anemia

THANK YOU