بسم الله الرحمن الرحيم

Major Metabolic Pathways of Glucose

By

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Objectives:
Major Metabolic Pathways

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

- **Define a metabolic pathway.**
- **Define reactions, and rate limiting steps in a pathway**
- **Determine different regulatory mechanisms for metabolic pathways**
- **Describe the general metabolic pathways for glucose (production and utilization)**
- **briefly describe the glycogen metabolic pathway and HMP**
- **Recognize the mechanisms of glucose transport**

Metabolic Pathway

Definition

Site:

Cellular (tissue) and Subcellular

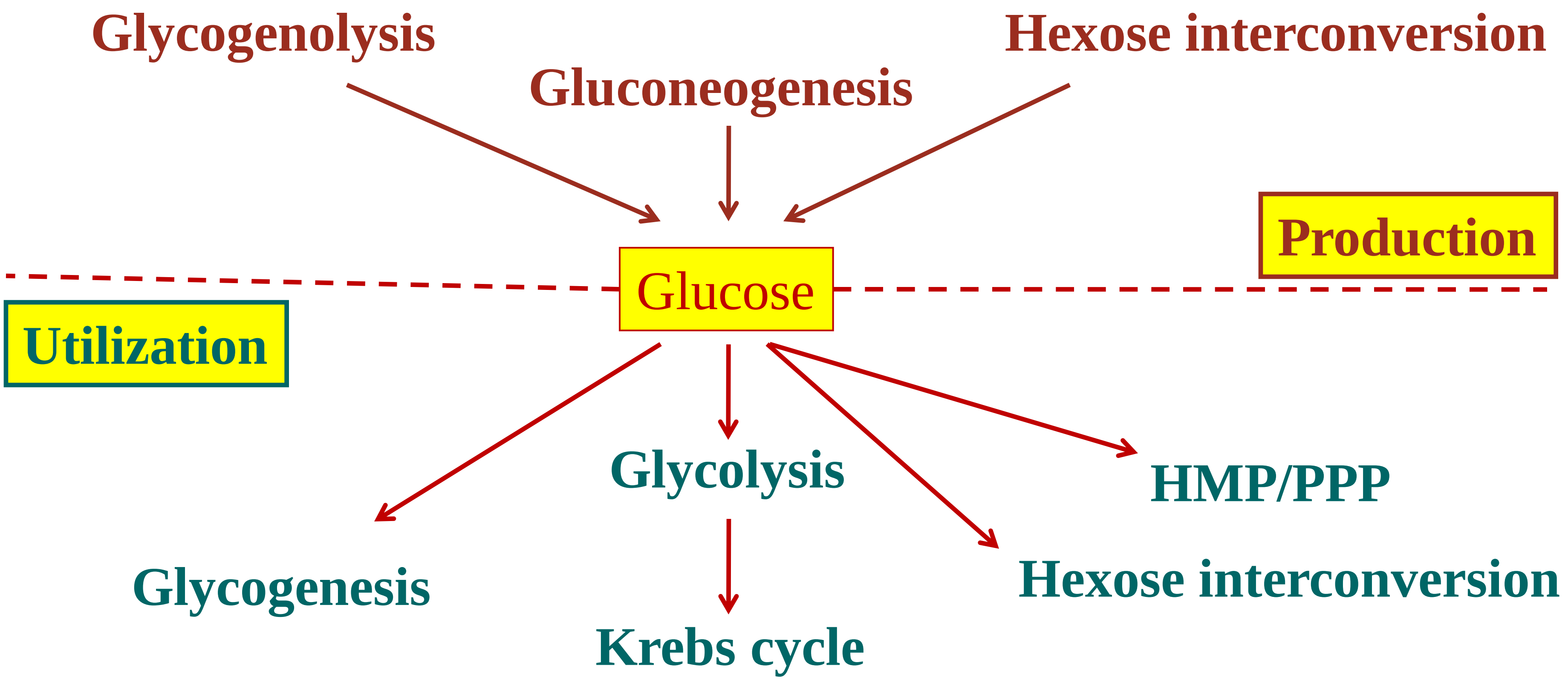
Reactions

Rate-limiting enzyme(s)

Regulatory mechanism(s):

- **Rapid, short-term**
  - **Covalent modification**
  - **Allosteric**
- **Slow, long-term**
  - **Induction/repression**

Metabolic Pathways of Glucose: Production and Utilization



Metabolic Pathways of Glucose: Catabolic and Anabolic

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

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

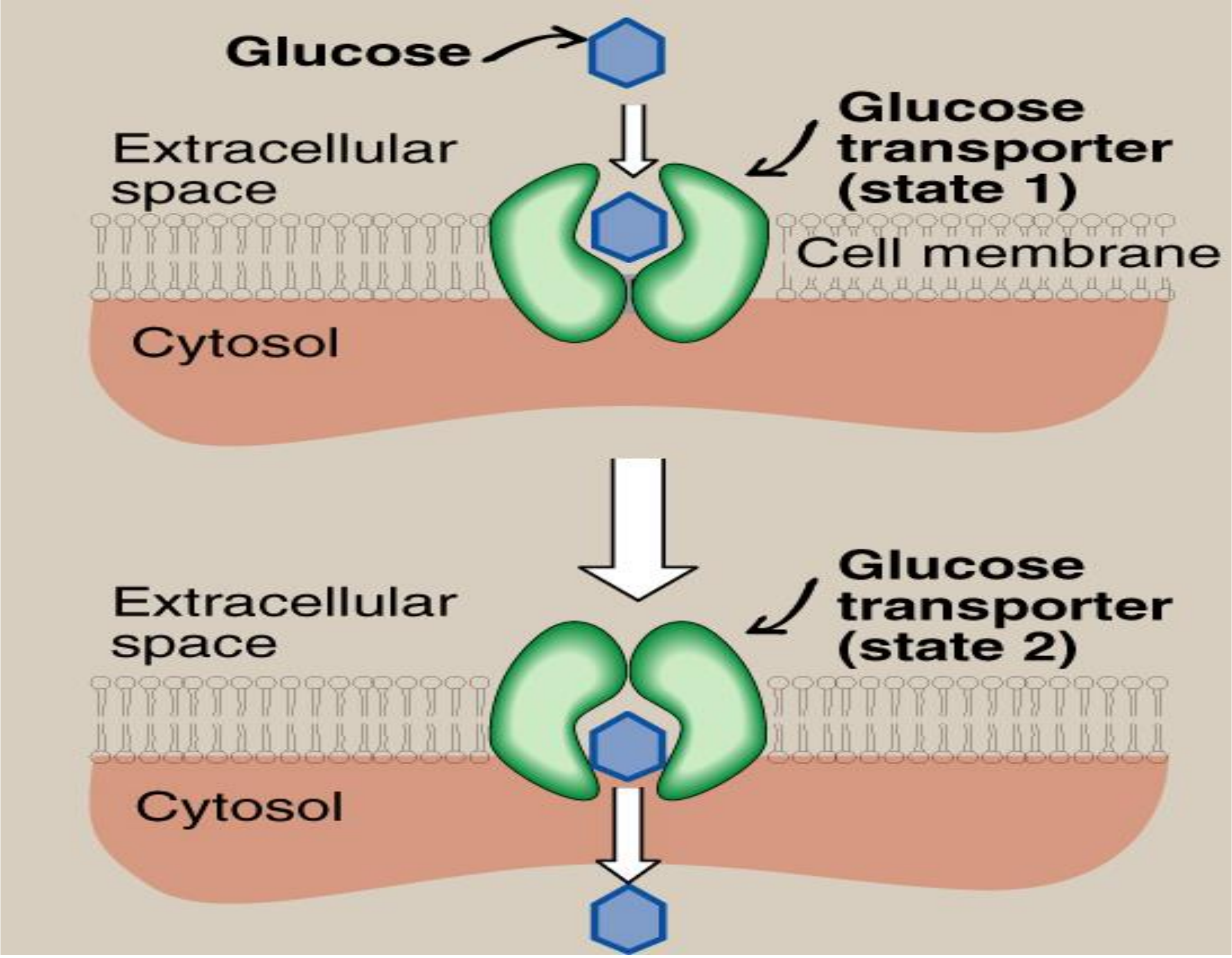
Na^+-Monosaccharide Cotransporter:

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

Na^+-Independent Facilitated Diffusion:

- 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**

Objectives: Glycolysis

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

- **Recognize glycolysis as the major oxidative pathway of glucose**
- **List the main reactions of glycolytic pathway**
- **Discuss the rate-limiting enzymes/Regulation**
- **Assess the ATP production (aerobic/anaerobic)**
- **Define 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.
- It allows tissues to survive in presence or absence of oxygen, e.g., skeletal muscle.
- RBCs, which lack mitochondria, are completely reliant on glucose as their metabolic fuel, and metabolizes it by anaerobic glycolysis.

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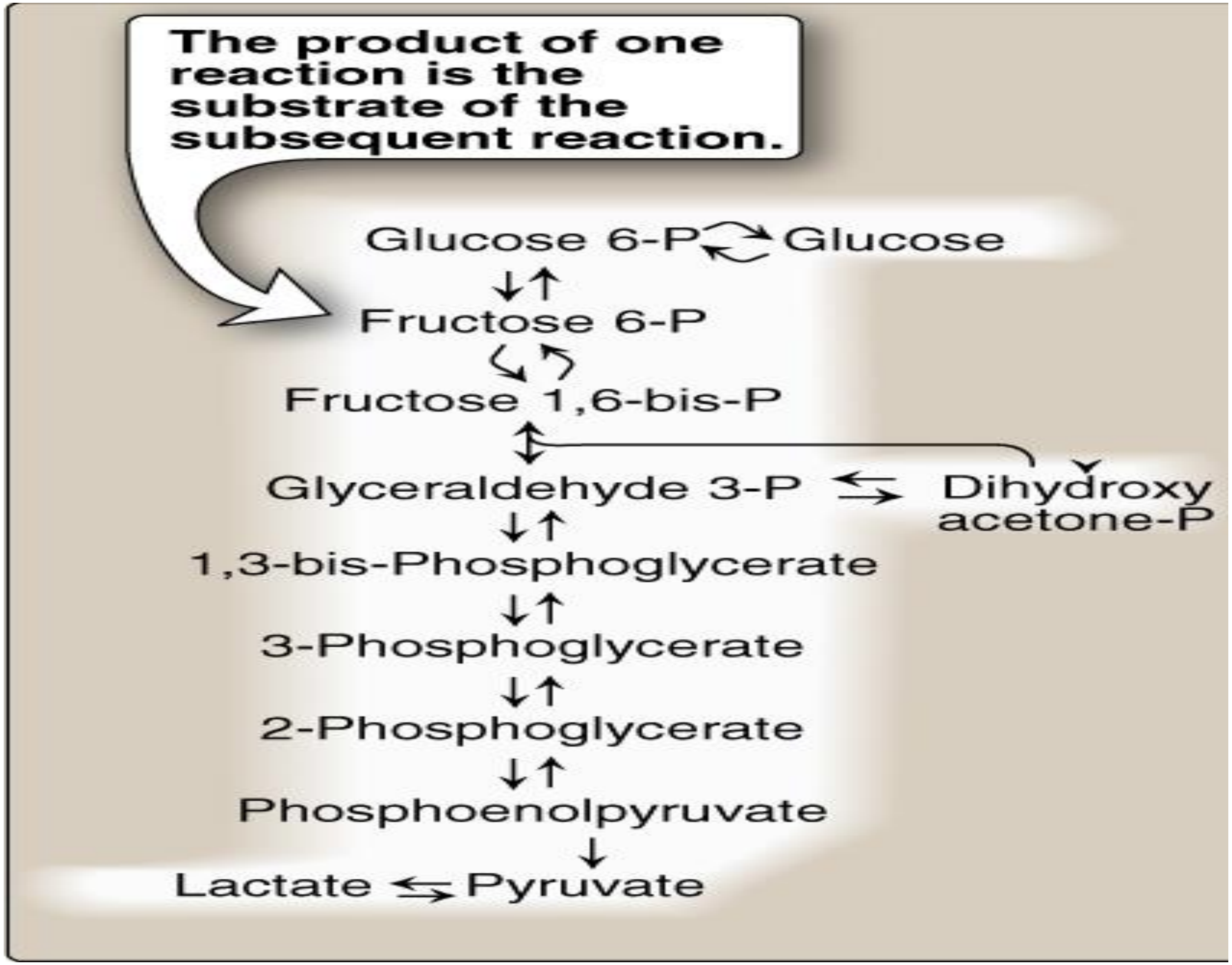
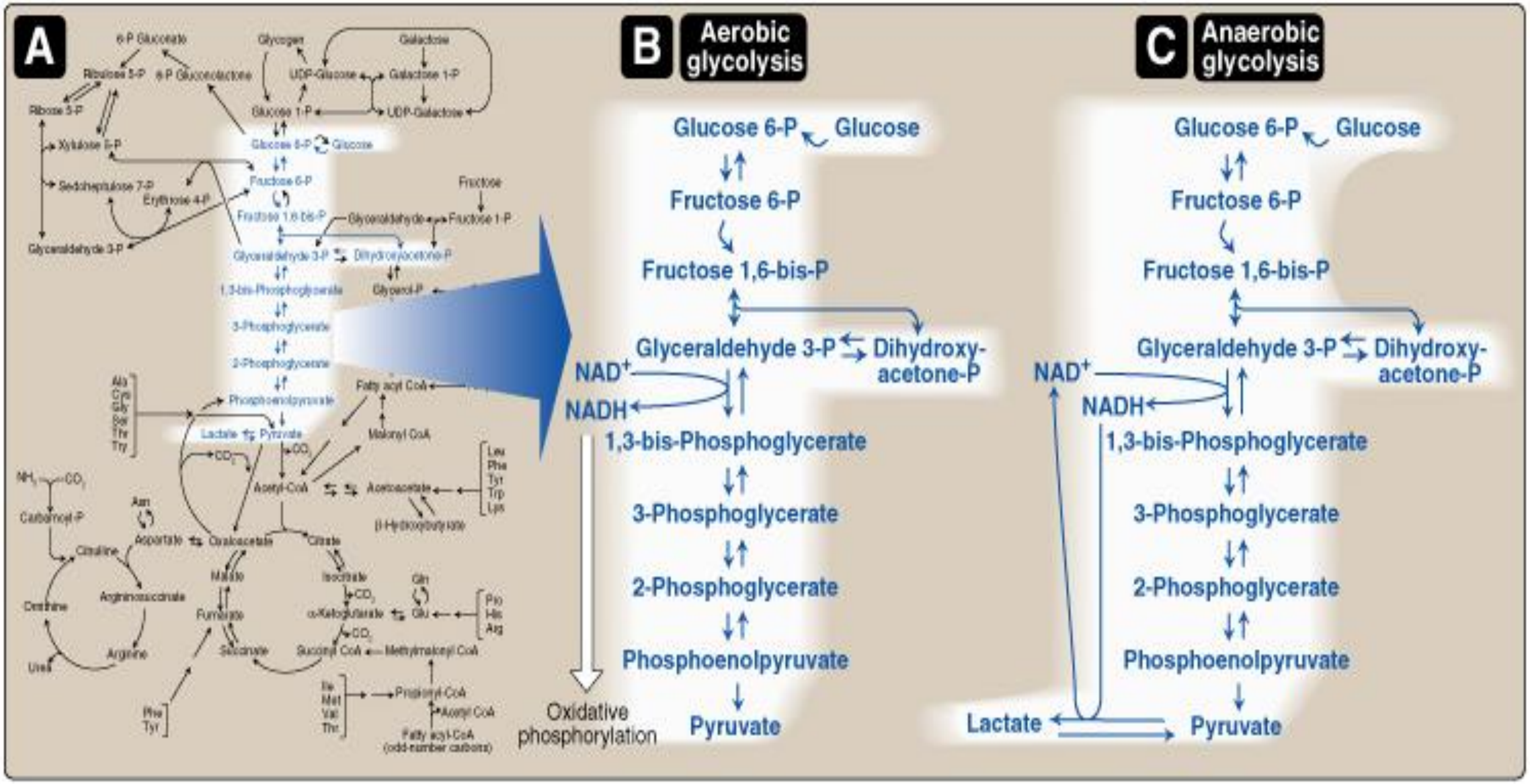
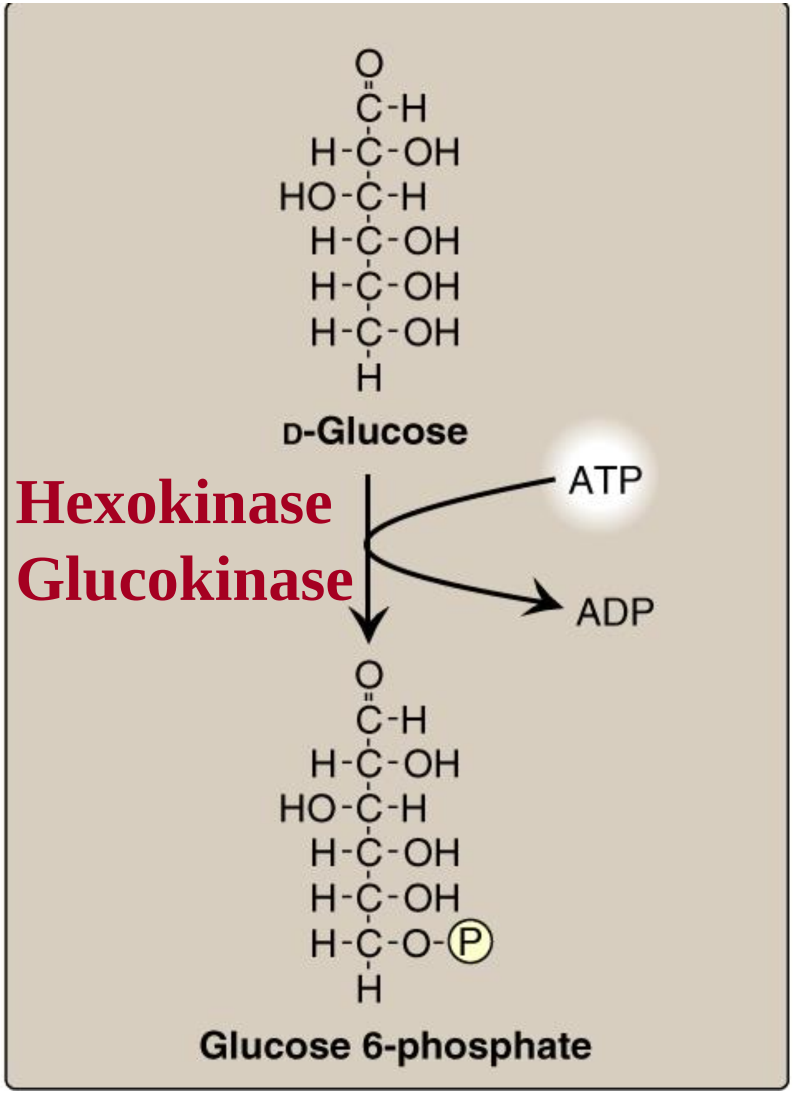
Glycolysis


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

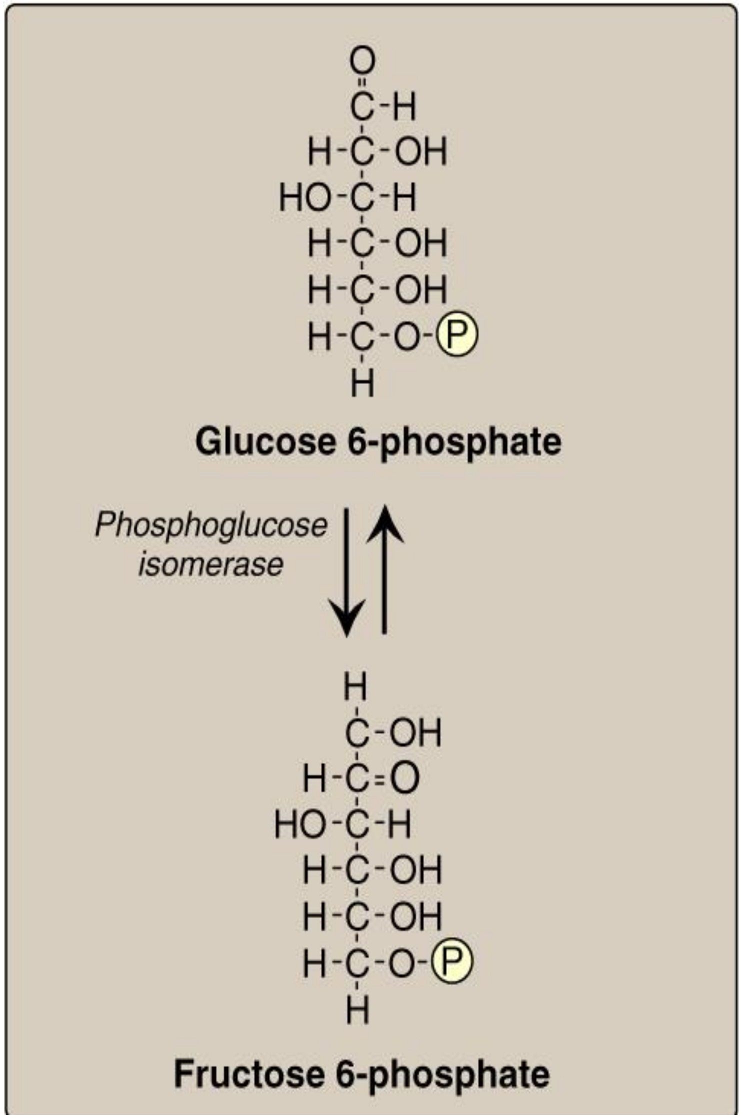
Aerobic Vs Anaerobic Glycolysis



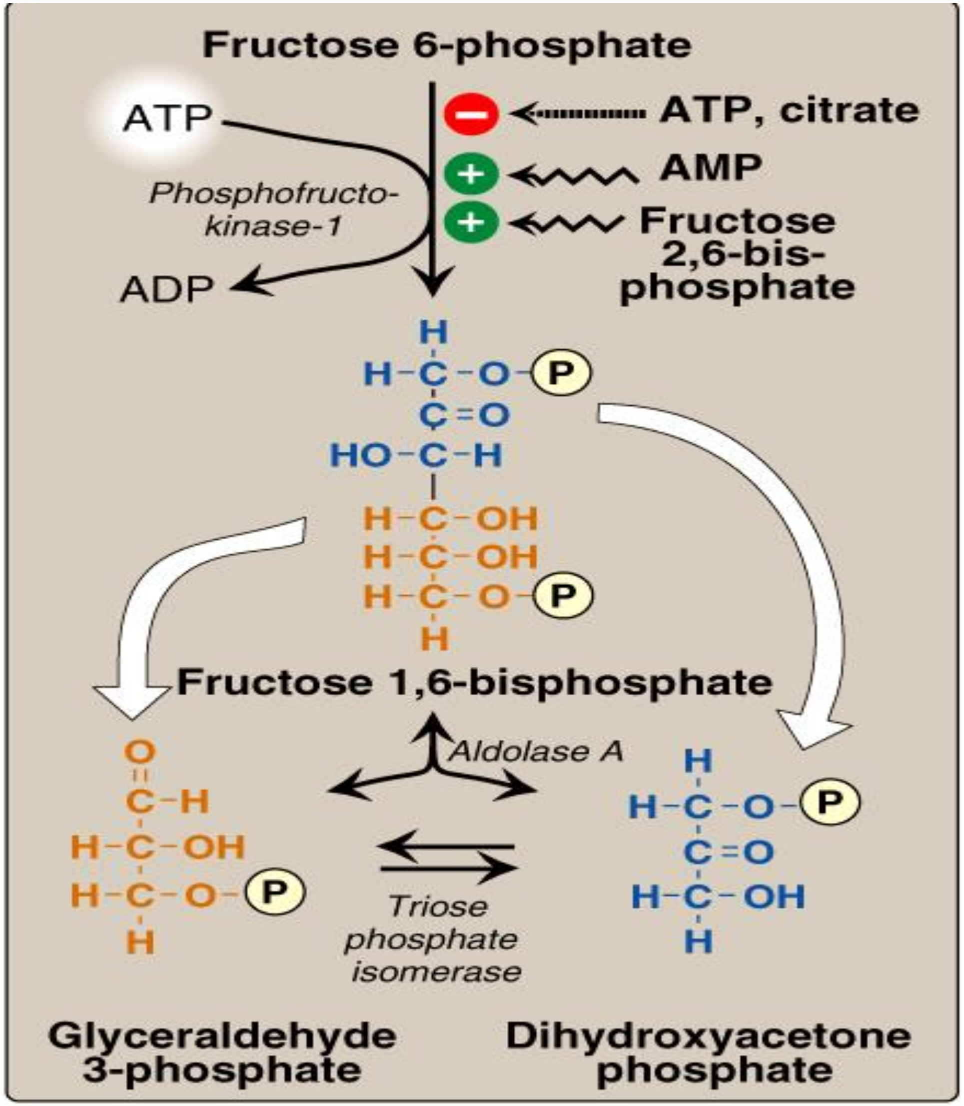
Aerobic Glycolysis-1



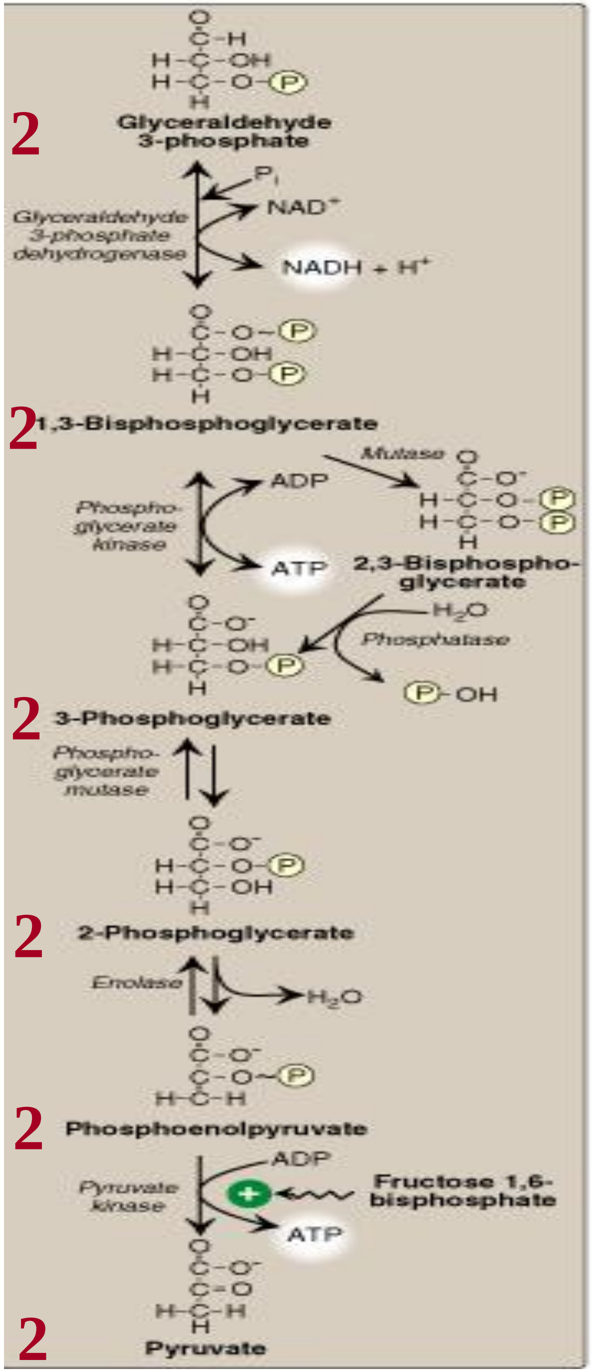
Aerobic Glycolysis-2



Aerobic Glycolysis: 3-5



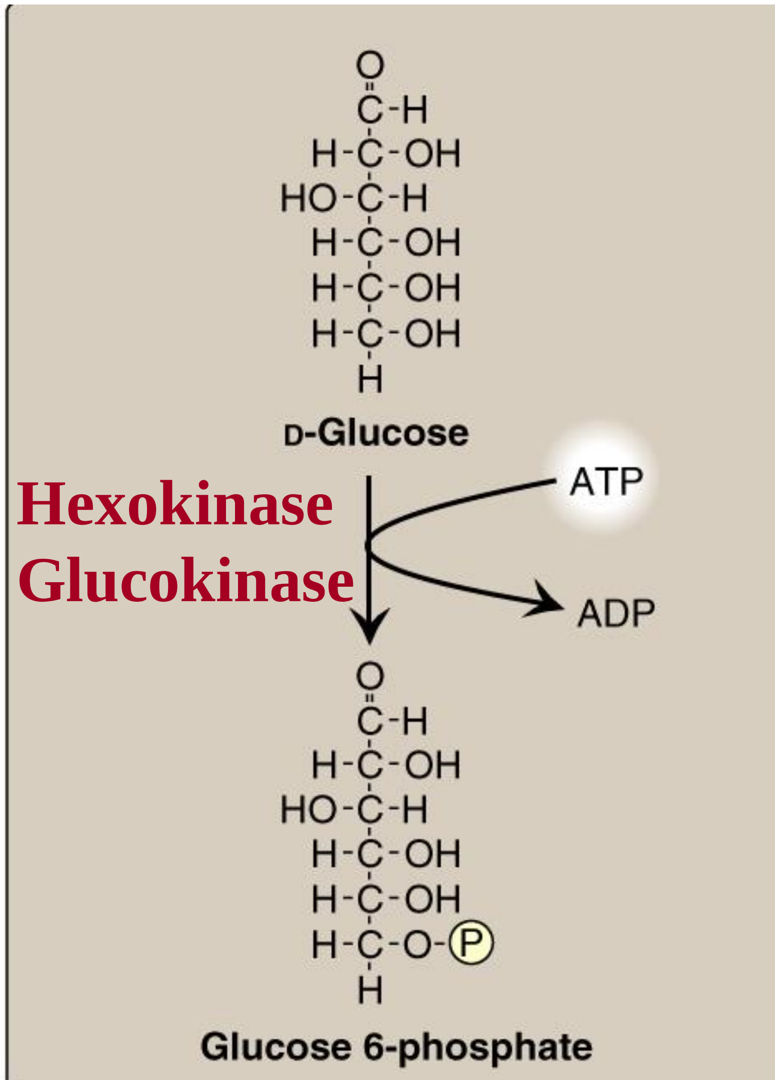
Aerobic Glycolysis: 6 -10



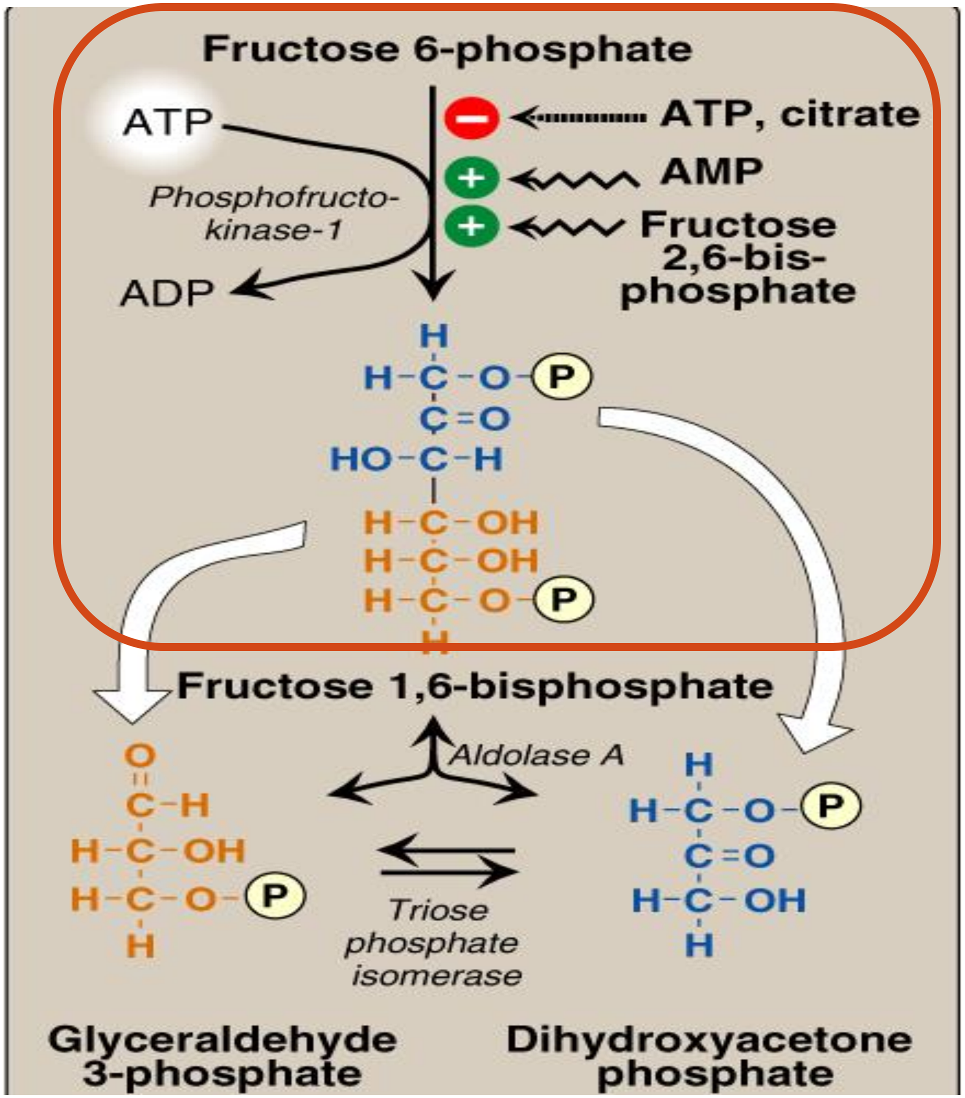
Aerobic Glycolysis-1

Hexokinase:
Most tissues

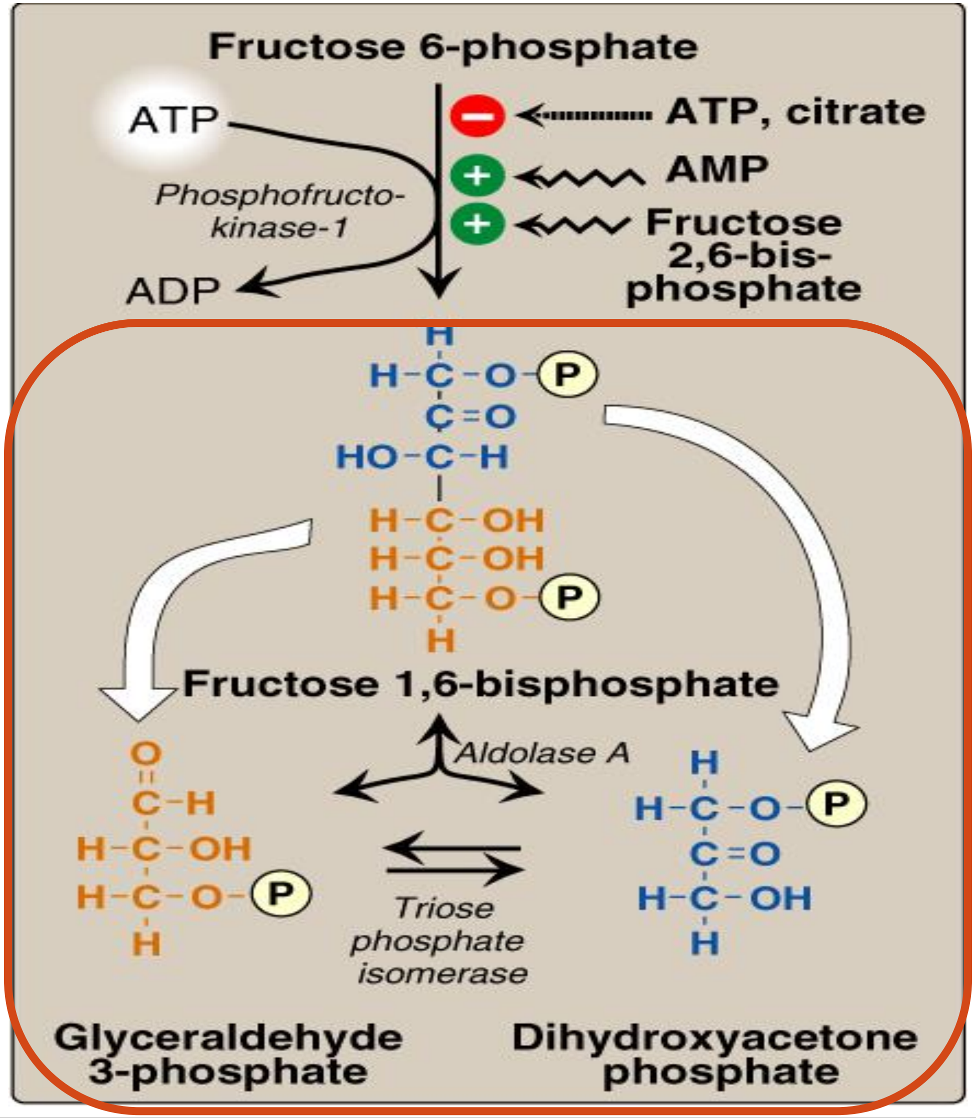
Glucokinase:
Hepatocytes



PFK-1 : Regulation

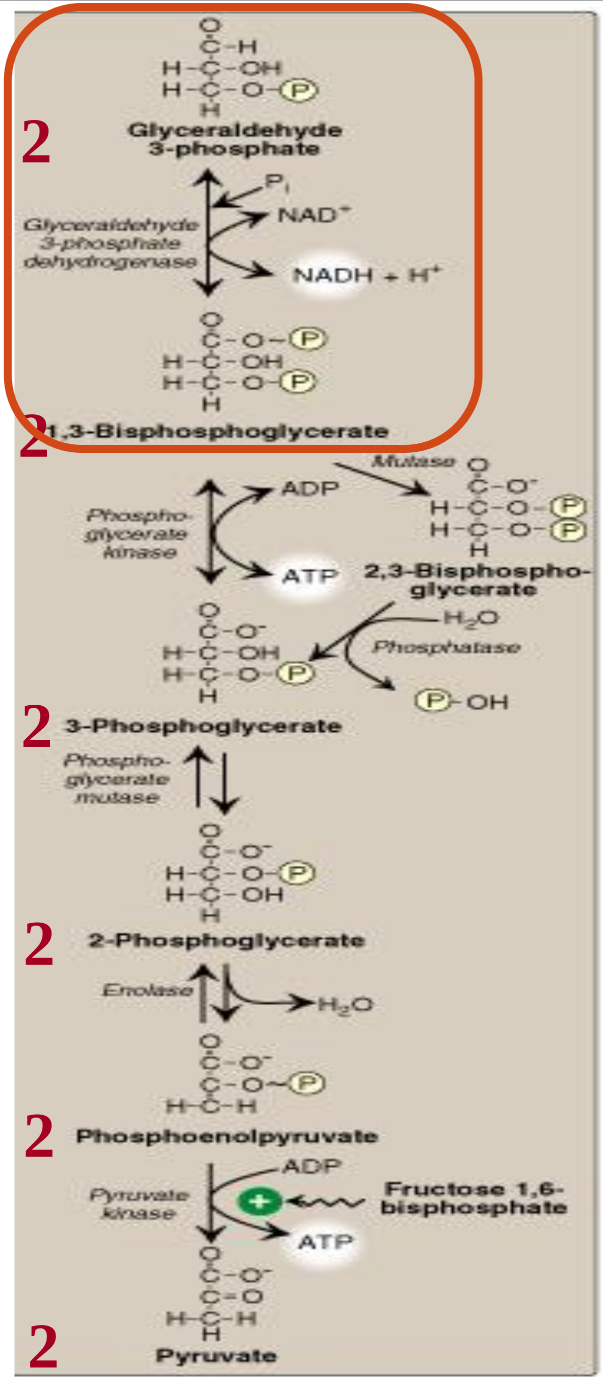


Aldolase and Triose Isomerase

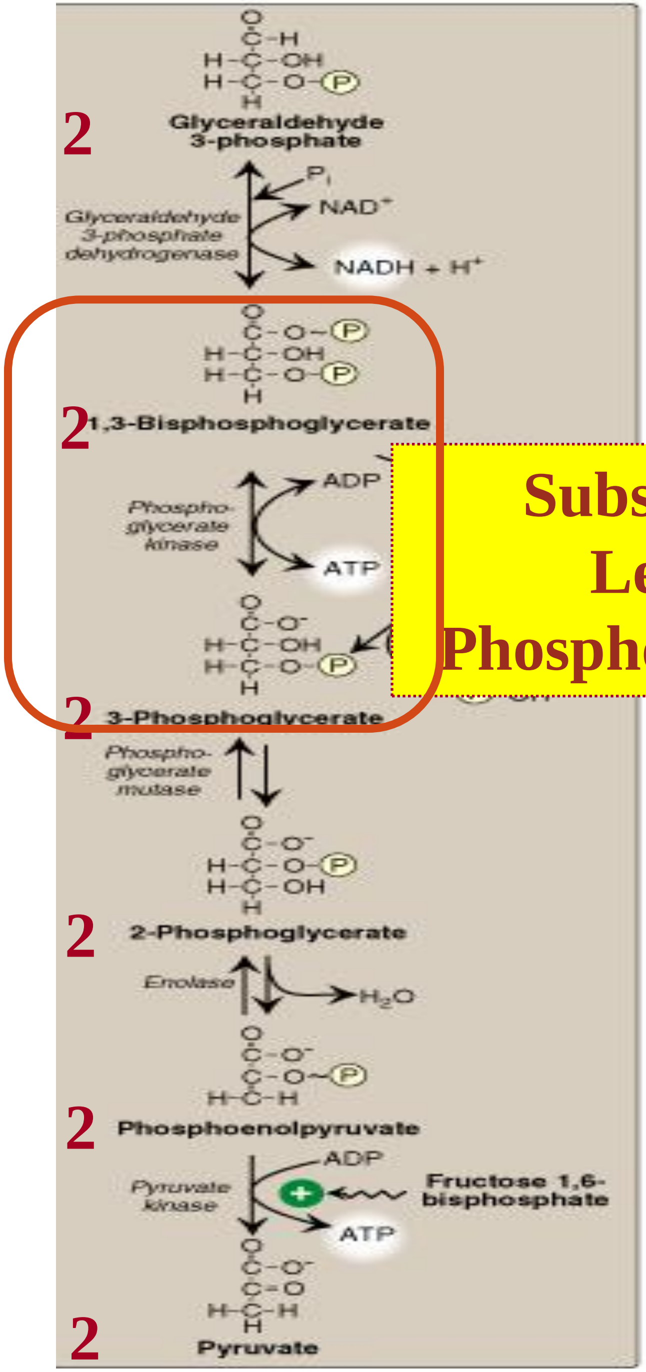


Glyceraldehyde 3-Phosphate Dehydrogenase

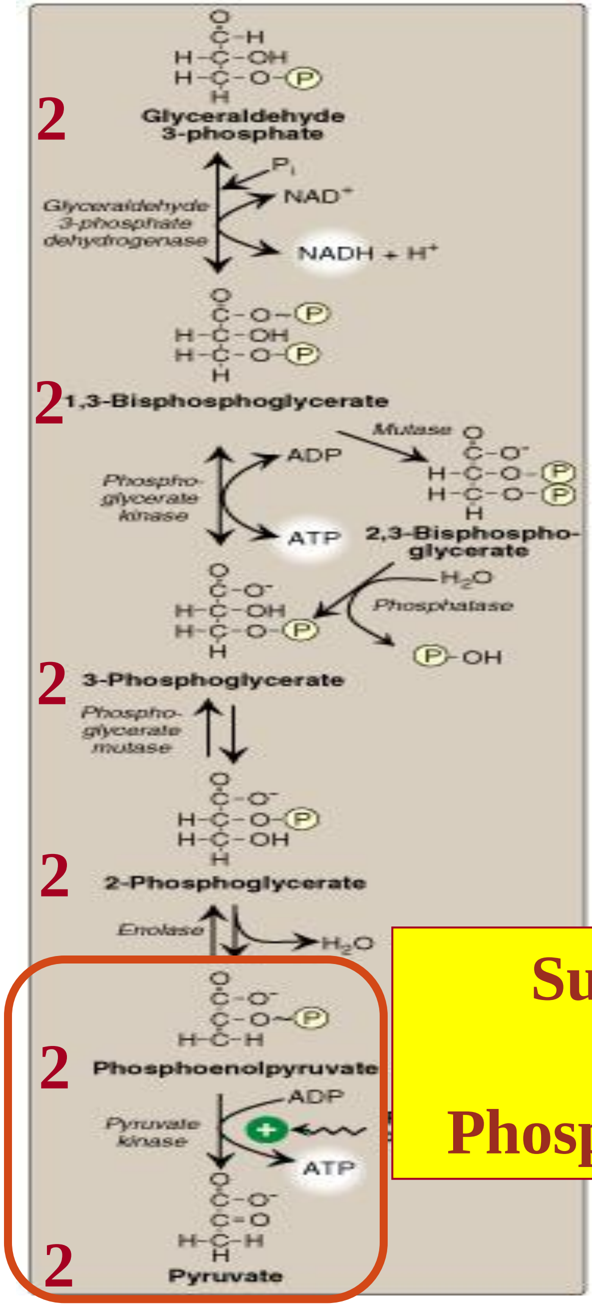
For each NADH, 3 ATP will be produced by ETC in the mitochondria i.e., 6 ATP are produced



Phospho-glycerate Kinase

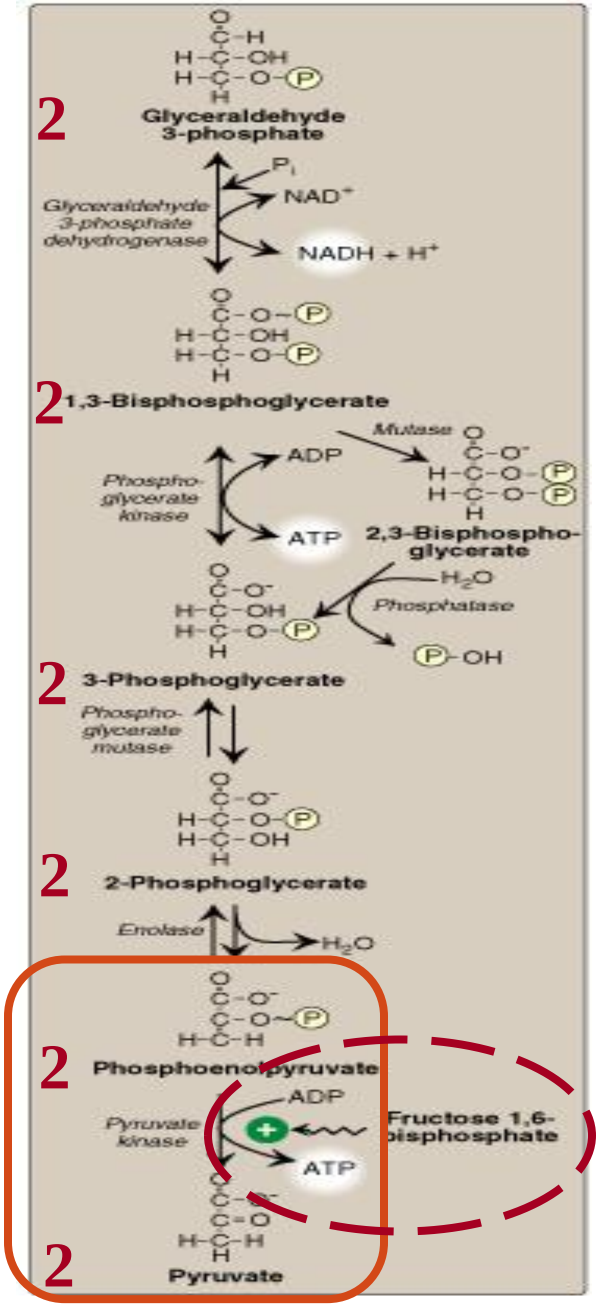


Substrate-Level Phosphorylation



Substrate-Level Phosphorylation

Pyruvate Kinase



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**

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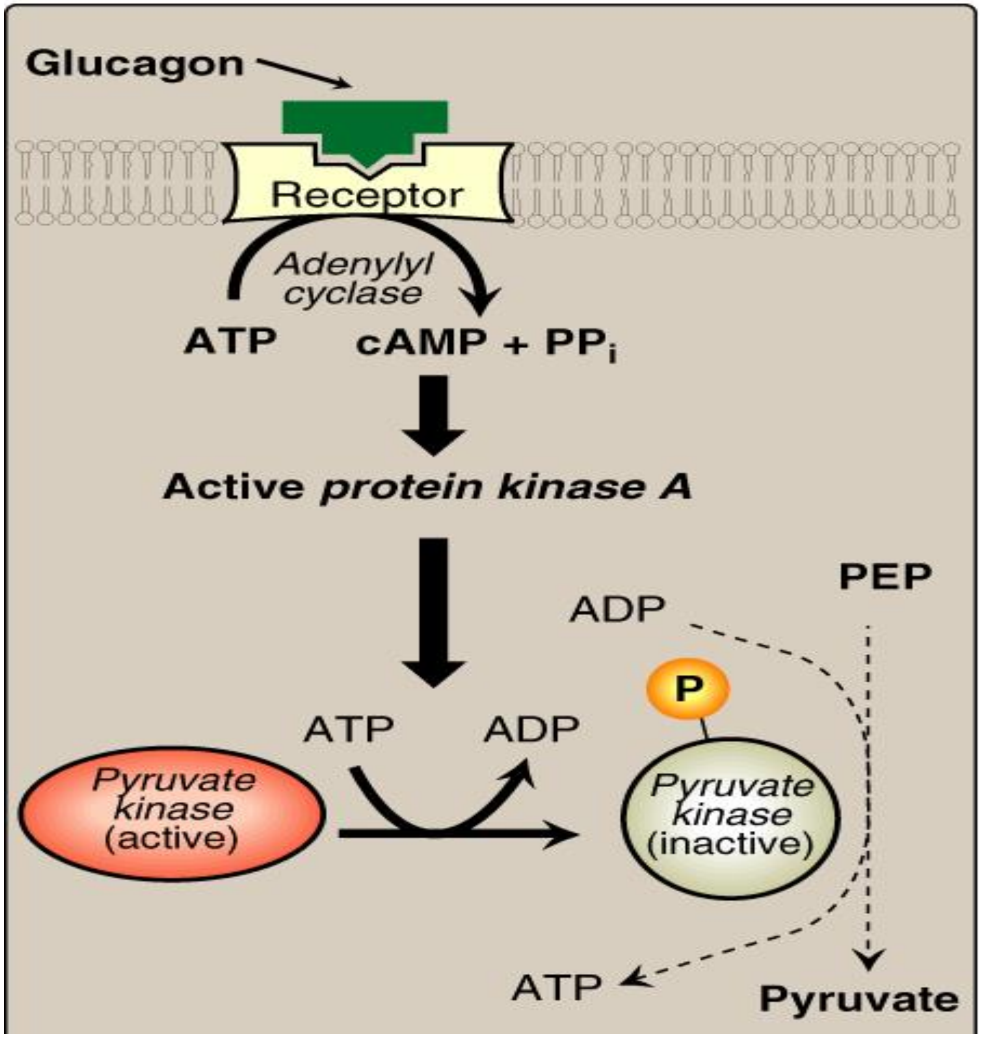
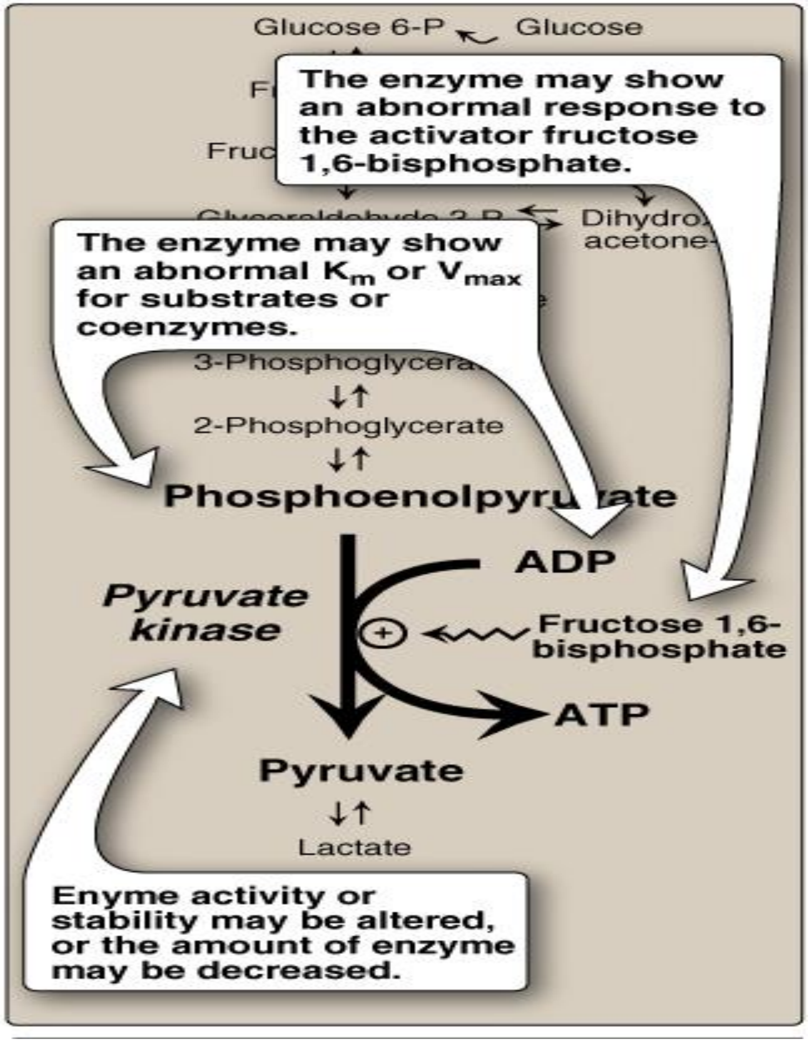
Pyruvate Kinase Covalent Modification



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