

Lecture 9

Discipline: Bioorganic Chemistry

Lecturer: Associate Professor, Dr. Gulnaz Seitimova

Title: Glycolysis of Glucose

Objective: The aim of this lecture is to explain the biochemical pathway of glycolysis, its key enzymes, intermediates, regulatory mechanisms, and physiological significance under both aerobic and anaerobic conditions, as well as its clinical relevance.

Main Questions: General definition, localization, and biological importance of glycolysis. Stages of glycolysis: preparatory (investment) and payoff (energy-yielding) phases. Key intermediates and enzymes involved in glucose breakdown. ATP generation mechanisms: substrate-level phosphorylation. Fates of pyruvate: aerobic oxidation vs. anaerobic reduction. Regulation of glycolysis: hexokinase, phosphofructokinase-1, pyruvate kinase. Energetics of glycolysis: ATP balance under aerobic and anaerobic conditions. Clinical and biochemical aspects related to glycolysis.

Key Notes and Theses

General Characteristics of Glycolysis

Glycolysis is the central metabolic pathway for glucose catabolism found in almost all organisms. It occurs in the cytosol and converts glucose into pyruvate, producing ATP and NADH. It functions under both aerobic and anaerobic conditions and serves as a primary energy source for tissues with low mitochondrial density (e.g., erythrocytes, retina, cancer cells).

Glycolysis consists of 10 enzyme-catalyzed reactions, divided into two phases.

Preparatory (Investment) Phase

This phase consumes 2 ATP molecules to activate glucose.

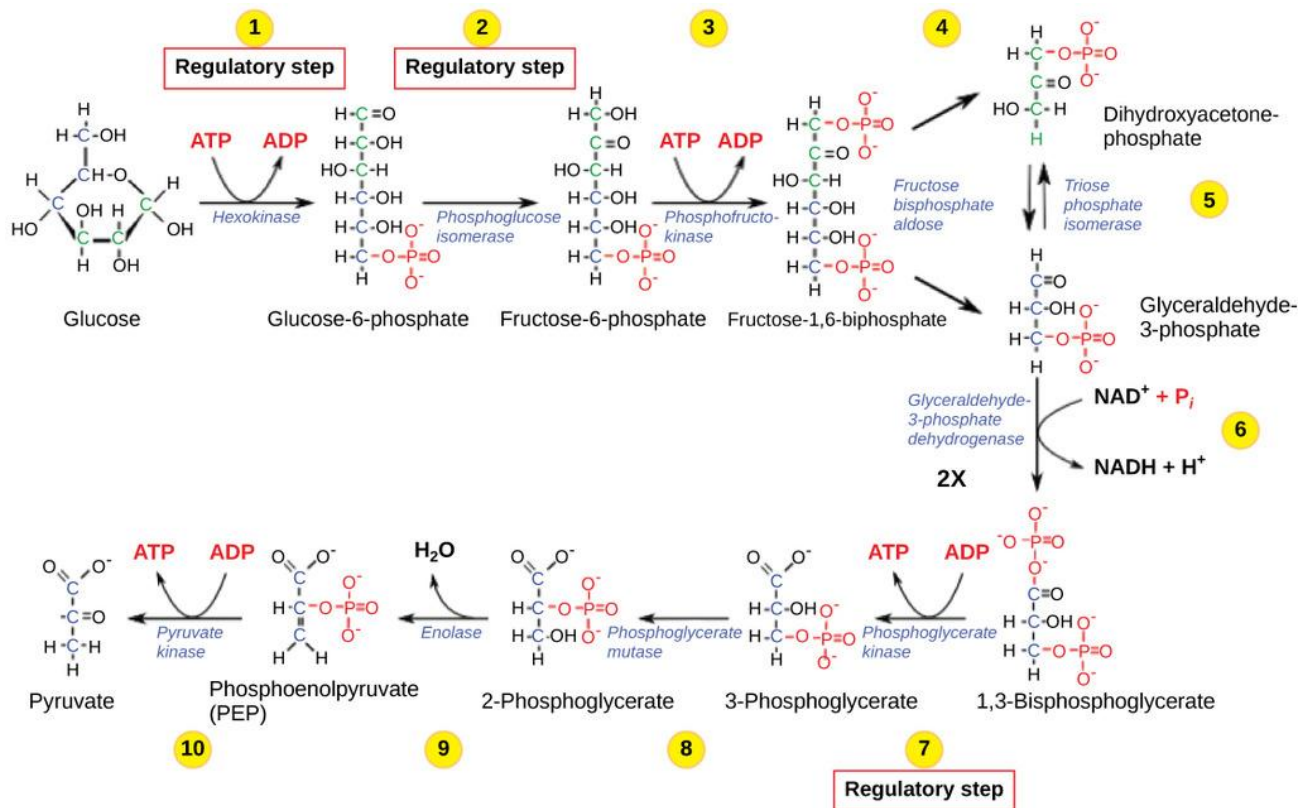
1. Glucose $\rightarrow$ Glucose-6-phosphate
 - Enzyme: Hexokinase (or glucokinase in liver).
 - Irreversible step; traps glucose inside the cell.
2. Glucose-6-phosphate $\rightarrow$ Fructose-6-phosphate
 - Enzyme: Phosphoglucose isomerase.
3. Fructose-6-phosphate $\rightarrow$ Fructose-1,6-bisphosphate
 - Enzyme: Phosphofructokinase-1 (PFK-1).
 - Major rate-limiting and highly regulated step in glycolysis.
4. Fructose-1,6-bisphosphate $\rightarrow$ DHAP + G3P
 - Enzyme: Aldolase.
5. DHAP $\rightleftharpoons$ G3P
 - Enzyme: Triose phosphate isomerase.
 - Two molecules of G3P proceed to the payoff phase.

Payoff (Energy-Yielding) Phase

This phase generates 4 ATP molecules (net gain: 2 ATP) and 2 NADH.

6. G3P $\rightarrow$ 1,3-bisphosphoglycerate
 - Enzyme: G3P dehydrogenase.

- Produces NADH.
- 7. 1,3-BPG $\rightarrow$ 3-phosphoglycerate
 - Enzyme: Phosphoglycerate kinase.
 - First substrate-level phosphorylation $\rightarrow$ ATP.
- 8. 3-PG $\rightarrow$ 2-PG
 - Enzyme: Phosphoglycerate mutase.
- 9. 2-PG $\rightarrow$ Phosphoenolpyruvate (PEP)
 - Enzyme: Enolase.
- 10. PEP $\rightarrow$ Pyruvate
 - Enzyme: Pyruvate kinase.
 - Second substrate-level phosphorylation $\rightarrow$ ATP.



Fates of Pyruvate

Aerobic Conditions

Pyruvate enters mitochondria and is converted to acetyl-CoA by pyruvate dehydrogenase $\rightarrow$ enters the TCA cycle.

NADH transfers electrons to the electron transport chain $\rightarrow$ generates ~ 2.5 ATP per NADH.

Anaerobic Conditions

NADH is reoxidized to NAD⁺ by converting pyruvate into lactate:

- Enzyme: Lactate dehydrogenase.

This allows glycolysis to continue in the absence of oxygen.

Regulation of Glycolysis

Key regulatory enzymes:

1. Hexokinase – inhibited by glucose-6-phosphate.
2. PFK-1 – main control point.
 - Activated by AMP, ADP, fructose-2,6-bisphosphate.
 - Inhibited by ATP and citrate.
3. Pyruvate kinase – inhibited by ATP and alanine; activated by fructose-1,6-bisphosphate.

Regulation ensures glycolysis adapts to cellular energy needs.

Energetics of Glycolysis

Condition	ATP Produced	ATP Consumed	Net ATP
Aerobic	4 ATP + 5 ATP from NADH	2 ATP	7 ATP per glucose
Anaerobic	4 ATP	2 ATP	2 ATP per glucose

Physiological and Clinical Significance

- Erythrocytes rely entirely on glycolysis (no mitochondria).
- In muscles, anaerobic glycolysis provides rapid ATP during intense exercise.
- Cancer cells show increased glycolysis (Warburg effect).
- Deficiency of glycolytic enzymes (e.g., pyruvate kinase deficiency) leads to hemolytic anemia.

Questions for Knowledge Assessment

1. What is glycolysis and where does it occur in the cell?
2. Describe the two phases of glycolysis.
3. Which steps of glycolysis are irreversible?
4. What are the main regulatory enzymes of glycolysis?
5. Explain the difference between aerobic and anaerobic fates of pyruvate.
6. How many ATP molecules are produced and consumed during glycolysis?
7. What is substrate-level phosphorylation?
8. Why is PFK-1 considered the key regulatory enzyme?
9. What is the role of NAD⁺ in glycolysis?
10. Why is glycolysis important in erythrocytes and cancer cells?

Recommended Literature

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