

Biochemistry lec. 2nd stage

by

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Glycolysis

Definition: Oxidation of **glucose** or **glycogen** to pyruvate and lactate is called glycolysis. It is called also EM pathway "Embden Meyerhof pathway".

It occurs virtually in **all tissues**. **Erythrocytes** and **nervous tissues** drive its energy mainly from **glycolysis.**

Glycolysis occurs in the cytosol of all cells of the body. There are two phases of glycolysis:

1- Aerobic phase (with oxygen)

2- Anaerobic phase (without oxygen)

Aerobic phase (with oxygen)

This series of **ten** reactions is called aerobic glycolysis **because oxygen** is required to reoxidize the NADH formed during the oxidation of glyceraldehydes – 3 – phosphate. Aerobic glycolysis sets the stage for the oxidative phosphorylation of pyruvate to acetyl CoA, a major fuel of the **citric acid cycle.**

Anaerobic phase (without oxygen):

Glucose can be converted to **pyruvate** which is reduced by **NADH** to form **lactate. This conversion of glucose to lactate is called anaerobic pathway** because it can occur without the participation of oxygen. Anaerobic glycolysis allows the continued production of ATP in tissues that lack mitochondria, like red blood cells, or in cells deprived of sufficient oxygen.

- **The anaerobic phase of glucose metabolism occurs whether O2 is present or not.**

B. Reactions of glycolysis (Figure 5-17)

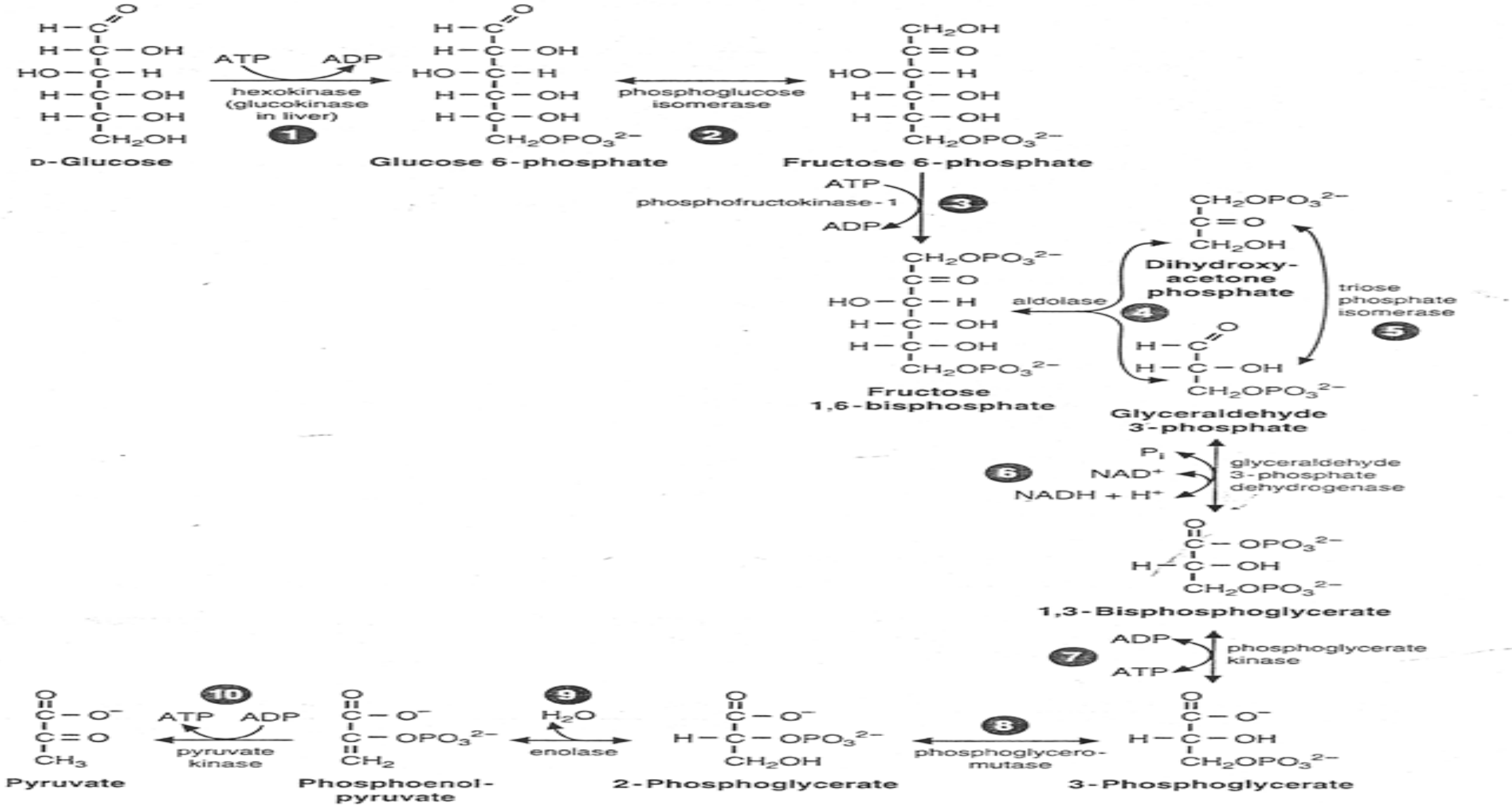


Figure 5-17. The reactions of glycolysis. The numbers correspond with those in V B in the text. These reactions occur in the cytosol.

Reactions of glycolysis:

1- **Phosphorylation of glucose:** glucose is converted to glucose – 6 – phosphate in a reaction that uses **ATP** and produce **ADP**. The reaction is catalyzed by specific enzyme **(glucokinase)** in liver cells and by non – specific **(hexokinase)** in liver and extra hepatic tissues. Both of these enzymes are subject to regulatory mechanisms.

2- Isomerization of glucose-6- phosphate to fructose–6 – phosphate.

3- Phosphorylation of fructose – 6 – phosphate to fructose 1,6 – bis – phosphate : This reaction is phosphorylated by ATP by the enzyme phosphofructokinase – 1 (PFK-1) is the most important control point and the rate – limiting step of glycolysis. This enzyme is activated by AMP and F-2, 6 – P and inhibited by ATP and citrate.

4- Cleavage of fructose 1, 6 – bisphosphate, to form the triose phosphate: glyceraldehyde 3 – phosphate and dihydroxyacetone phosphate (DHAP).

5- Isomerization of DHAP and formation of glyceraldehydes-3-P.

6- Oxidation of glyceraldehydes – 3 – phosphate to 1, 3 – Bisphosphoglycerate.

7- Synthesis of 3-phospoglycerate producing ATP

8- Shift of the phosphate group from carbon 3 to carbon 2 and form 2-phosphoglycerate.

9- Dehydration of 2 – phosphoglycerate and form (PEP) phosphoenol pyruvate.

10- Formation of pyruvate producing ATP: The conversion of PEP to pyruvate is catalyzed by pyruvate kinase, the third irreversible reaction of glycloysis , pyruvate kinase is activated by F-1,6-p and inhibited by alanine and by phosphorylation in the liver during fasting.

Differences between hexokinase and glucokinase:

Hexokinase	Glucokinase
1. **1**-Non – specific, can phosphorylate any of the hexoses.	**1**- specific, can phosphorylated glucose only.
2- Found almost in all tissues.	**2**- Found only in liver.
3- Found in foetal as well as in adult liver.	**3**- Found in adult liver, not in foetal liver.
4- More stable.	**4**- Physiologically more labile.
5- Allosteric inhibition by G-6-P.	**5**- Not inhibited by G-6-P.
6-Km is low = 0.1mM, hence high affinity for glucose.	**6**- Km is high = 10Mm, low affinity for glucose.
7-Not very much influenced by diabetic state or fasting.	**7**-Depressed in fasting and in diabetes. Glucokinase is deficient in patients of DM.
8- No change with glucose feeding.	**8**- Increased by feeding of glucose after fasting.
9- Inhibited by glucocorticoids and GH, insulin doesn't affect it.	**9**- Inhibited by glucocorticoids and GH. Synthesis is induced by insulin.
10- Main function to make available glucose to tissues for oxidation at lower blood glucose level.	**10- Main function is to clear glucose from blood after meals and at blood levels greater than 100 mg/dl.**

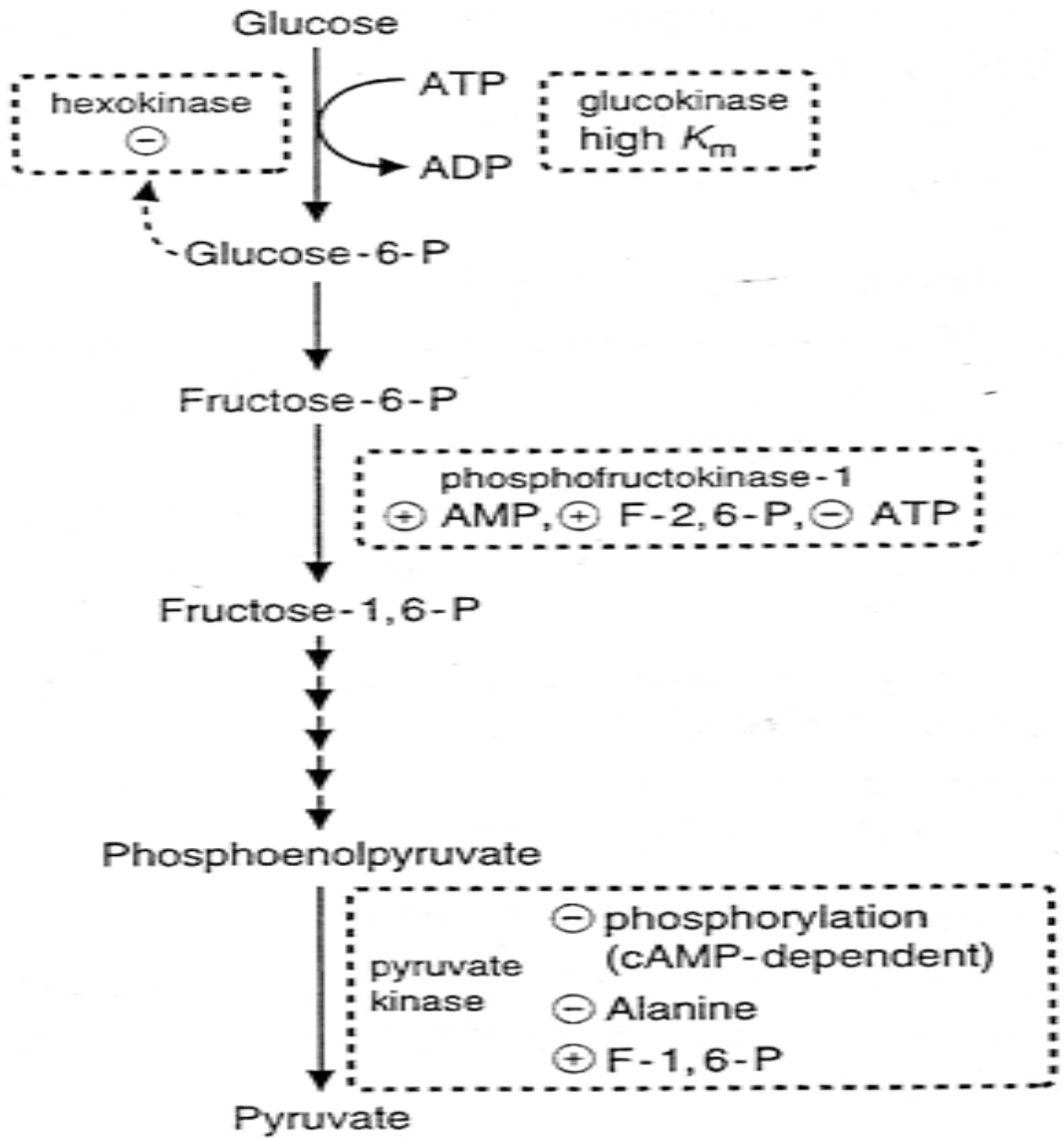


Figure 5-18. Regulation of glycolysis. In muscle, PFK1 is the key enzyme. It is activated (⊕) by AMP and inhibited (⊖) by ATP and citrate. In liver, glucokinase, PFK1 (activated by fructose 2,6-bisphosphate [F-2,6-P]), and pyruvate kinase are the key enzymes.

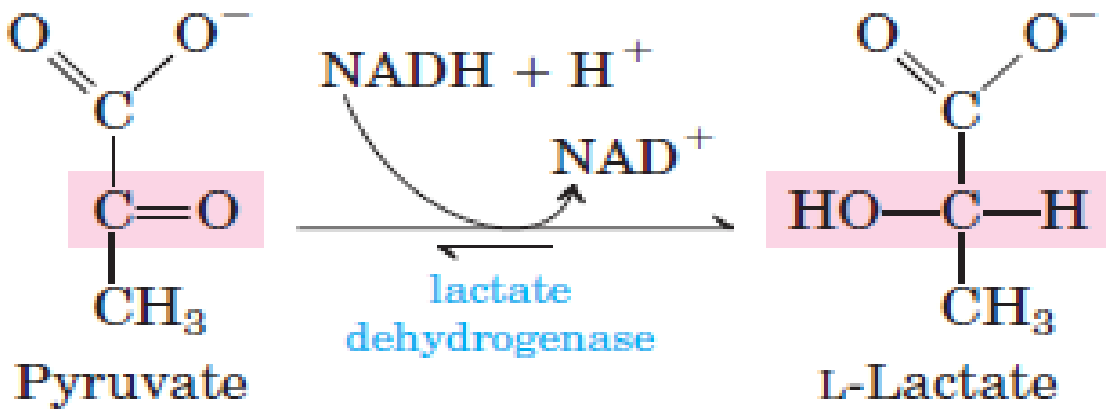
Energy yield per glucose molecule oxidation

A – In Glycolysis in presence of O2 (Aerobic phase).

Reaction Catalyzed by	ATP production
(phosphorylation)	
1- Hexokinase/Glucokinase reaction	- 1 ATP
2- Phosphofructokinase	- 1 ATP
(Oxidation of 2 NADH in electron transport chain)	
3- Glyceraldehyde - 3 - P dehydrogenase	+ 6 ATP
(Substrate level phosphorylation)	
4- Phosphoglycerate kinase	+ 2 ATP
5- Pyruvate kinase	+ 2 ATP
*** (1 NADH → 3 ATP)** **Net gain**	= 10 – 2
	= **8 ATP**

B-In Glycolysis in the absence of O2 (Anaerobic phase)

This is achieved by re-oxidation of NADH by conversion of pyruvate to lactate (without producing ATP) by the enzyme lactate dehydrogenase.



4 – 2 = 2 ATP will be produced

Clinical Importance of anaerobic glycolysis :

- Tissues that function under hypoxic circumstances will produce lactic acid from glucose oxidation, producing local acidosis. If lactate production is more it can produce metabolic acidosis.
- Whether O2 is present or not, glycolysis in erythrocytes always terminates in pyruvate and lactate.
- Vigorously contracting skeletal muscle will produce relative anaerobiosis and glycolysis will produce lactic acid.
- Inhibitor of Lactate Dehydrogenase (LDH) is Oxamate: it competitively inhibits lactate dehydrogenase and prevents the reoxidation of NADH.

The Biomedical Importance of Glycolysis

This pathway is meant for provision of energy.

- It has importance in **skeletal muscle** as glycolysis provides **ATP** even in absence of O2
- **Heart muscle:** as compared to skeletal muscle, heart muscle is adapted for aerobic performance. It has relatively poor glycolytic activity and poor survival under conditions of ischemia.
- **Role in cancer therapy:** **In fast- growing cancer cells, rate of glycolysis is very high**. Producing more pyruvic acid than TCA cycle can handle. Accumulation of pyruvic acids leads to excessive formation of lactic acid producing local lactic acidosis.
- **Hemolytic anemia:** inherited enzyme deficiencies like **hexokinase deficiency** and **pyruvate kinase deficiency** in glycolytic pathway enzymes, can produce **hemolytic anemia.**