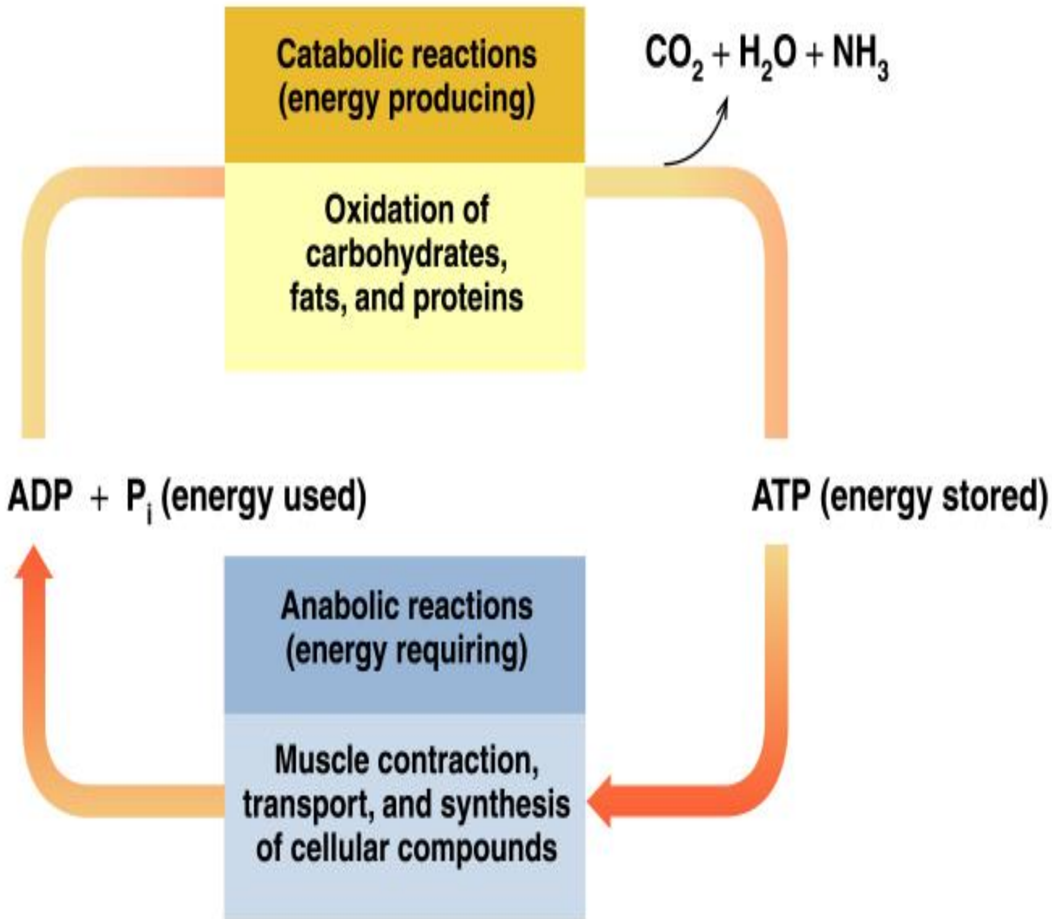
METABOLISM

Biosynthetic Pathways

Metabolism

Metabolism involves :

- Catabolic reactions that break down large, complex molecules to provide energy and smaller molecules.
- Anabolic reactions that use ATP energy to build larger molecules.



Stages of Metabolism

Catabolic reactions are organized as :

Stage 1: Digestion and hydrolysis break down large molecules to smaller ones that enter the bloodstream.

Stage 2: Degradation breaks down molecules to two- and three-carbon compounds.

Stage 3: Oxidation of small molecules in the citric acid cycle and electron transport provide ATP energy.

Stages of Metabolism

Catabolic reactions:

Stage 1: Digestion and hydrolysis

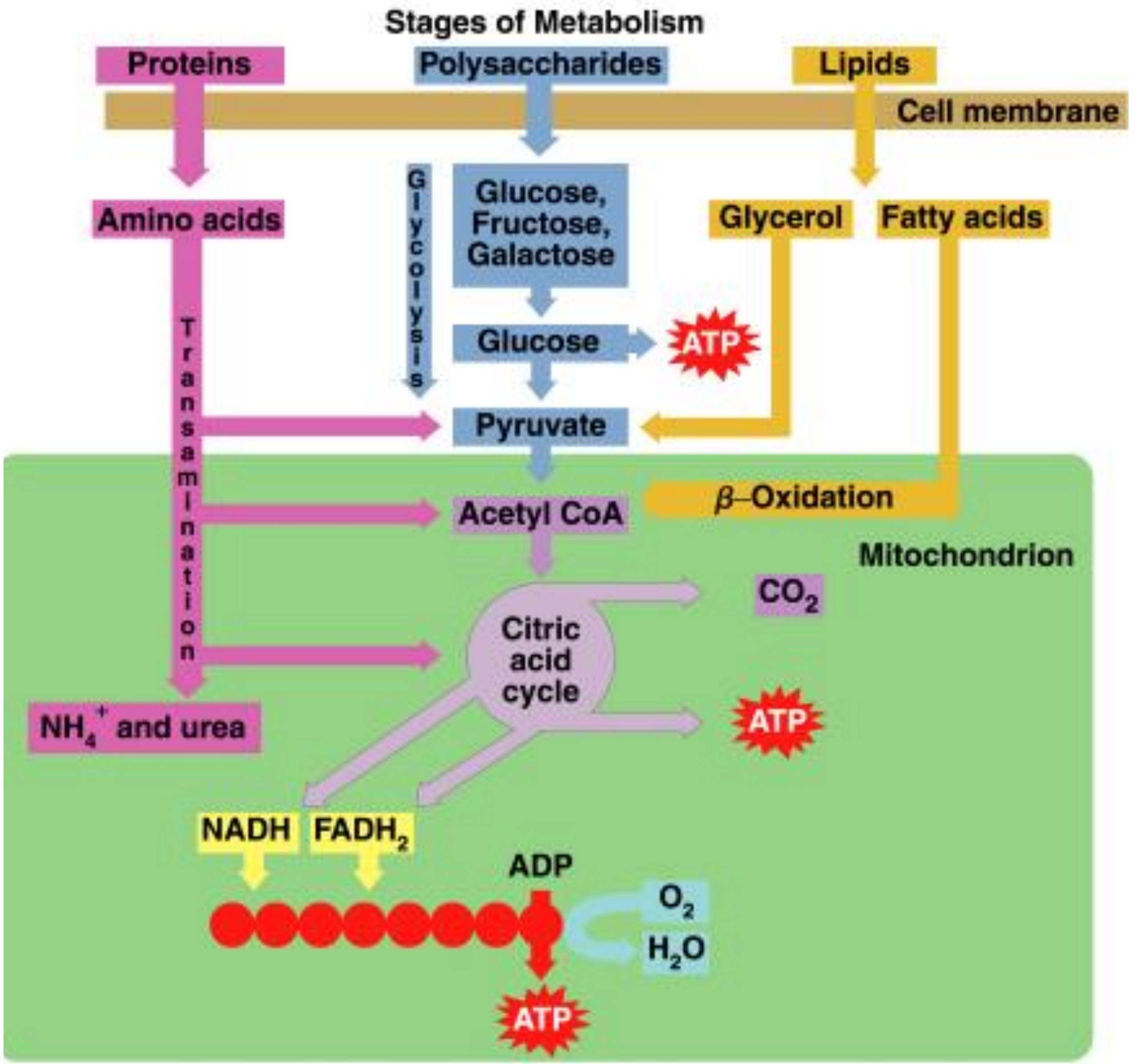
break down large molecules to smaller ones that enter the bloodstream.

Stage 2: Degradation

Further breaking and some oxidation of molecules to 2 & 3-carbon compounds.

Stage 3: Oxidation

of small molecules to CO_2 & H_2O in the citric acid cycle and electron transport provides energy for ATP synthesis.



Metabolism

Catabolic reactions: -

Complex molecules → Simple molecules + Energy

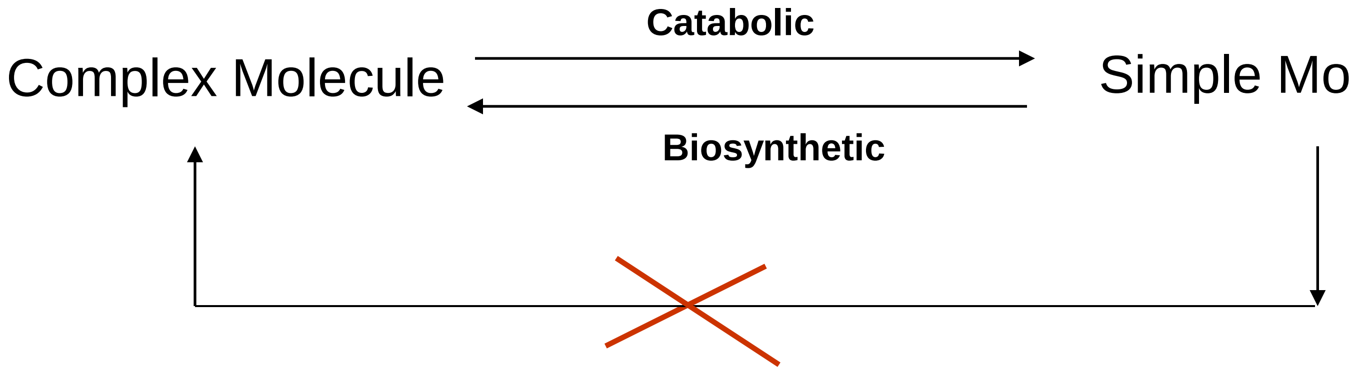
Anabolic reactions: - Biosynthetic reactions

Simple molecules + Energy (in cell) → Complex molecules

Biosynthetic pathways

Anabolic and catabolic reactions have different pathways.

1. Flexibility: if a normal biosynthetic pathway is blocked, the organism can often use the reverse of the catabolic pathway for synthesis.



Biosynthetic pathways

2. Overcoming Le Chatelier's principle:

> If a dynamic equilibrium is disturbed by changing the conditions, the position of equilibrium moves to counteract the change.

$$\underset{\text{Glycogen}}{(\text{Glucose})_n} + P_i \underset{}{\overset{\text{phosphorylase}}{\rightleftharpoons}} \underset{\substack{\text{Glycogen} \\ \text{(one unit smaller)}}}{(\text{Glucose})_{n-1}} + \text{Glucose 1-phosphate}$$

$$(\text{Glucose})_{n-1} + \text{UDP-glucose} \longrightarrow \underset{\substack{\text{Glycogen} \\ \text{(one unit larger)}}}{(\text{Glucose})_n} + \text{UDP}$$

Biosynthetic pathways

Anabolic and catabolic reactions need different energy.

Anabolic and catabolic reactions take place in different locations.

Catabolic reactions ⟶ Mitochondria

Anabolic reactions ⟶ Cytoplasm

Biosynthetic pathways

1. Biosynthesis of Carbohydrates

2. Biosynthesis of Lipids
   - Biosynthesis of Fatty acids
   - Biosynthesis of Membrane Lipids

3. Biosynthesis of Amino acids

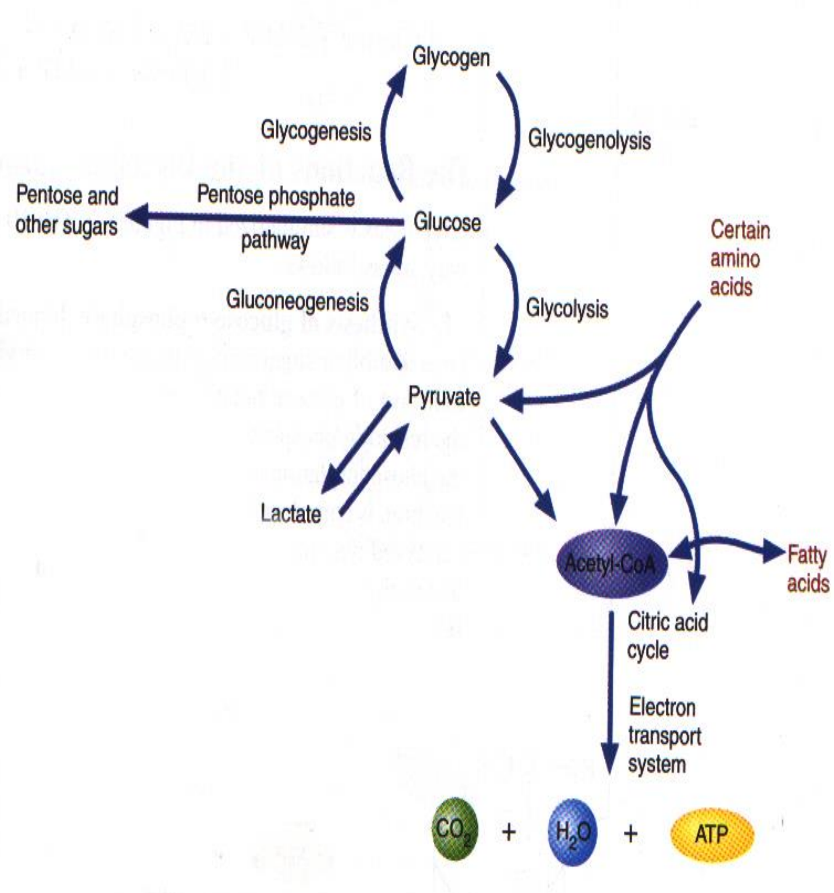
Carbohydrate Metabolism

Major Pathways of CHO Metabolism

CHO metabolism in mammalian cells can be classified into:

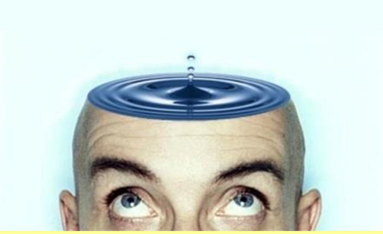
1. **Glycolysis**: Oxidation of glucose to pyruvate (aerobic state) or lactate (anaerobic state)
2. **Krebs cycle:** After oxidation of pyruvate to acetyl CoA, acetyl CoA enters the Krebs cycle for the aim of production of ATP.
3. **Hexose monophosphate shunt:** Enables cells to produce ribose-5-phosphate and NADPH.
4. **Glycogenesis:** Synthesis of glycogen from glucose, when glucose levels are high
5. **Glycogenolysis**: Degradation of glycogen to glucose when glucose in short supply.
6. **Gluconeogenesis:** Formation of glucose from noncarbohydrate sources.

Glucose is the major fuel of most organisms. The major pathways of CHO metabolism either begin or end with glucose.



Steps for metabolic pathways

- Definition :
- Site of reaction : (tissue site and/or intracellular site)
- Starting material :
- End product :
- Regulation of pathway : (Inhibitor/Activator)
- Energetics :
- Clinical significance :



Learning Objectives

By the end of this topic you should be able to:

- Outline the three stages of glycolysis.
- Describe the steps of glycolysis between glucose and pyruvate and recognize all the intermediates and enzymes and the cofactors that participate in the reactions.
- Mention ATP-generating reactions.
- Illustrate the regulation of glycolysis.

Glycolysis (Embden-Meyerhof Pathway)

[glycolysis: from the Greek *glyk* - sweet, and *lysis* -splitting]

Glycolysis occurs in all human cells. Glycolysis is believed to be among the oldest of all the biochemical pathways.

Aerobic: Glucose → Pyruvate

Anaerobic: Glucose → Lactate (or ethanol & acetic acid)

Glycolysis (10 reactions in 3 stages in 2 phase, all in cytoplasm)

1) Priming stage: D-Glucose + 2ATP → D-fructose 1,6-biphosphate + 2ADP + $2H^+$

2) Splitting stage : D-Fructose 1,6-biphosphate → 2 D-Glyceraldehyde 3-phosphate

3) Oxidoreduction – Phosphorylation stage:

2 D-Glyceraldehyde 3-phosphate + 4ADP + 2Pi + 2H+ → 2 Lactate + 4ATP

Sum:

Glucose + 2ADP + 2Pi ----- 2 Lactate + 2ATP + 2H2O (Anaerobic)

Glucose + 2ADP + 2Pi + $2NAD^+$ ---- 2 pyruvate + 2ATP + 2NADH + $2H^+$ + $2H_2O$

(Aerobic)

Glycolysis

- **Definition** :

  - Glycolysis breakdown (oxidation) of glucose for energy.

- **Site of reaction :**

  1. **Tissue site** : All the tissues of body
  2. **Intracellular site**: Cytosol

- **Starting material :** Glucose

- **End product :**

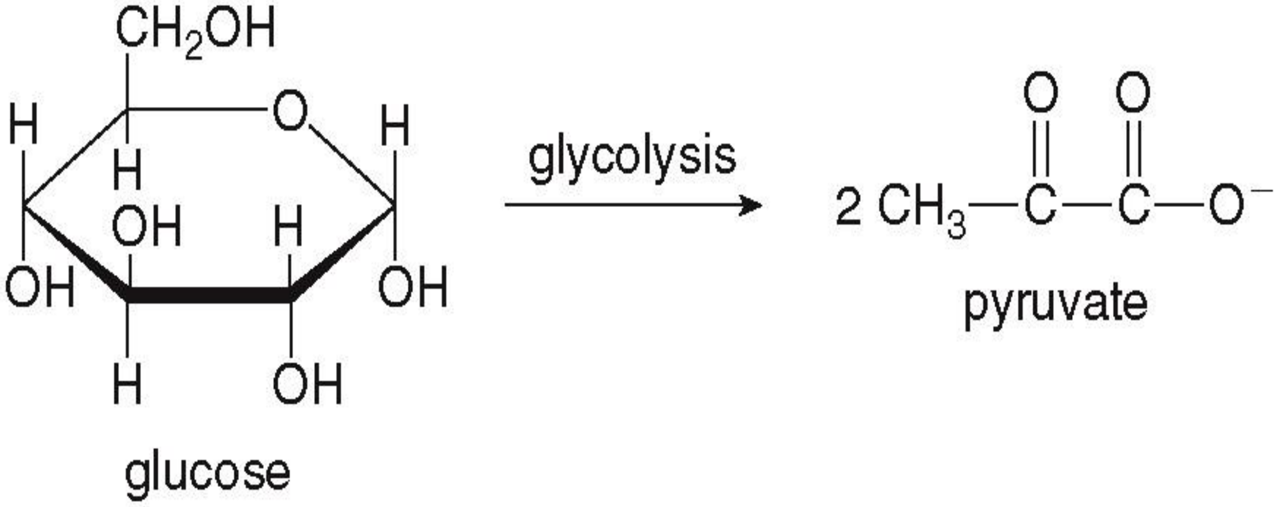
  1. Pyruvate (**Aerobic** – oxygen present)

  2. **Lactate** (**Anaerobic-** without oxygen)

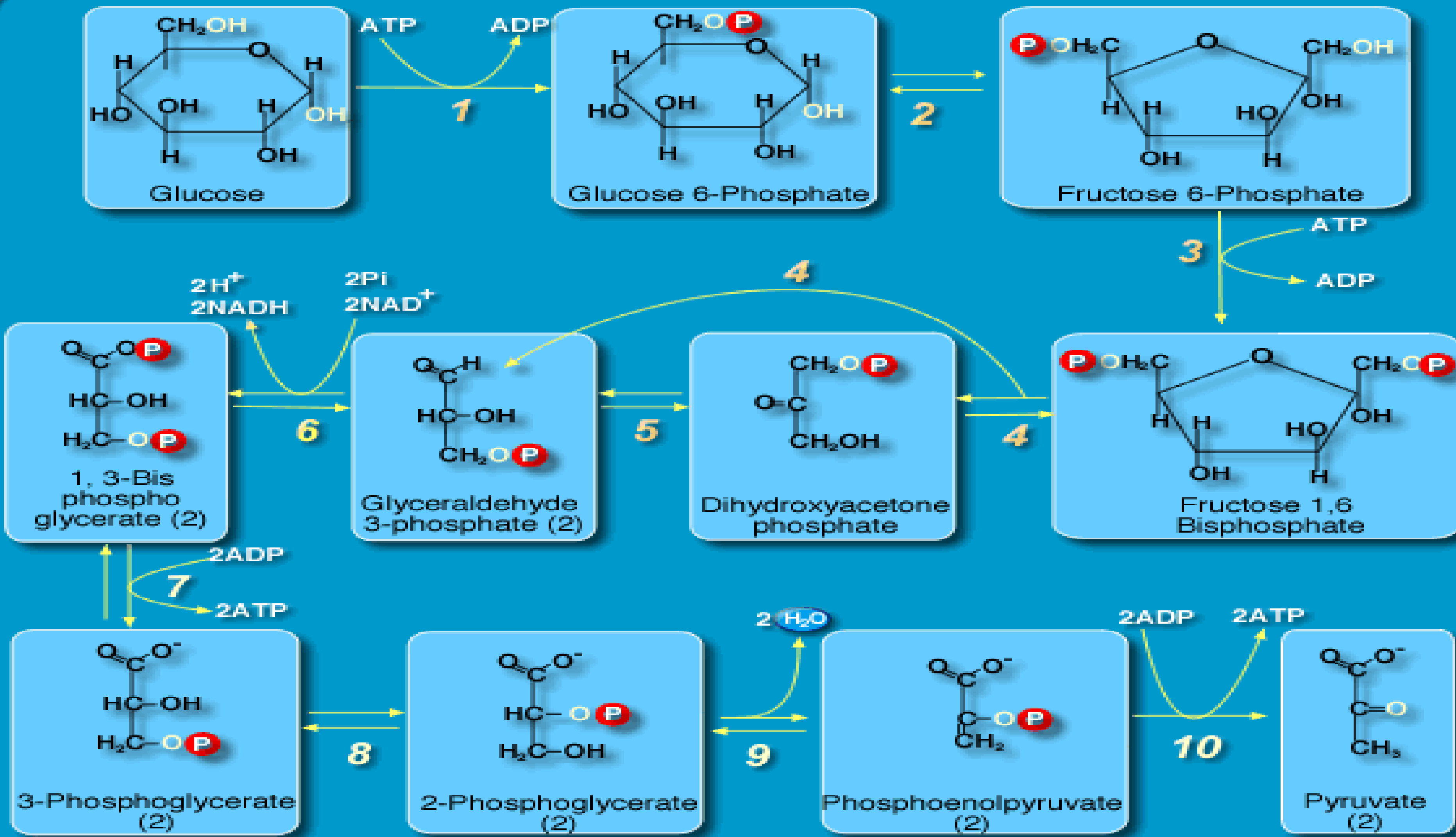
Glycolysis

Glucose is converted to two molecules of pyruvate.

An anaerobic reaction in cytoplasm.



10 Reactions

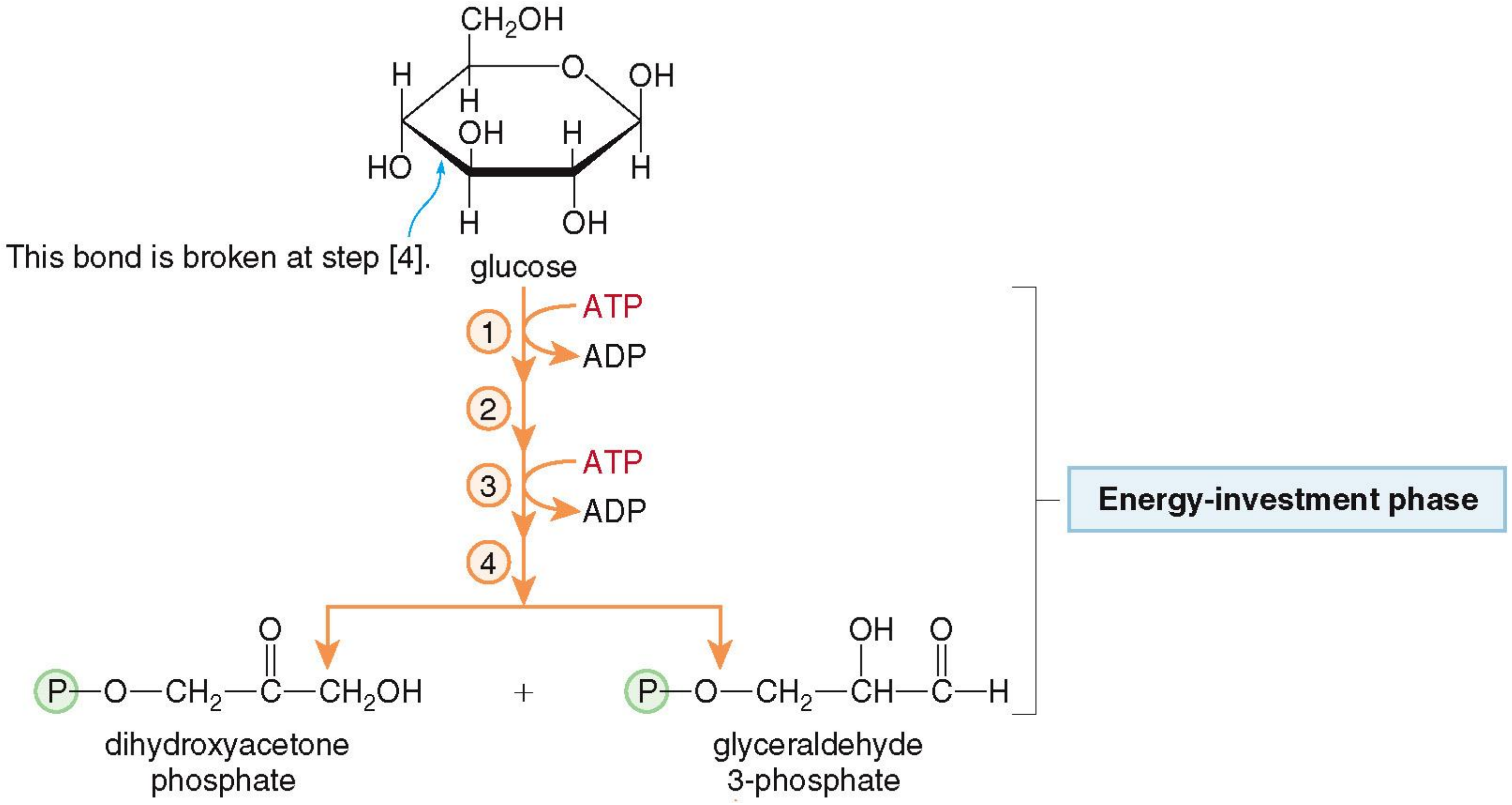


ENZYMES — Preparatory phase — Payoff phase

1. Hexokinase
2. Glucose Phosphate Isomerase
3. Phosphofructokinase
4. Fructose diphosphate aldolase
5. Triose phosphate Isomerase
6. Glyceraldehyde Phosphate Dehydrogenase
7. Phosphoglycerate Kinase
8. Phosphoglyceromutase
9. Enolase
10. Pyruvate Kinase

Glycolysis

Steps [1] – [5] energy investment phase:

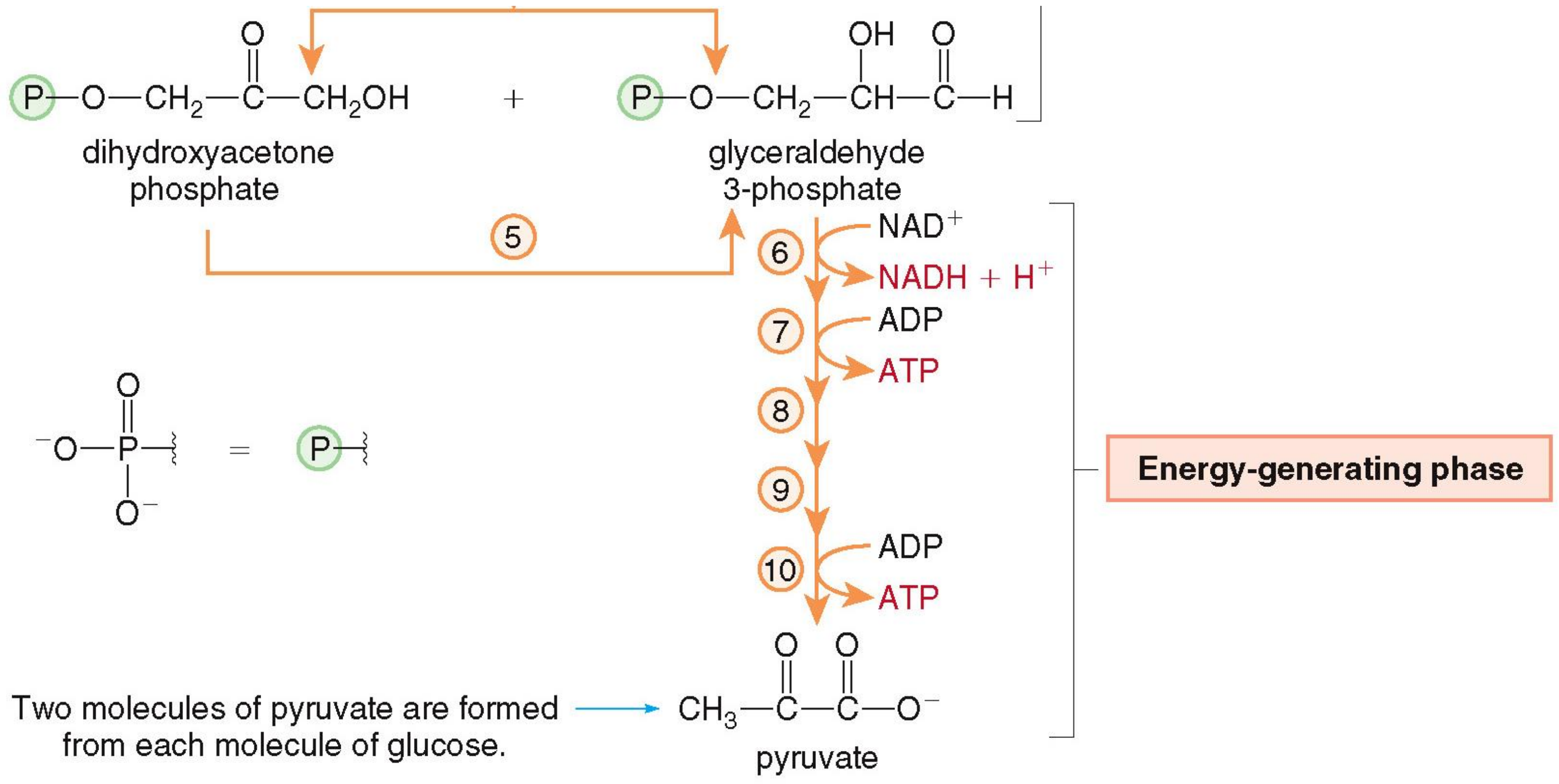


2 ATP molecules are hydrolyzed.

The 6-carbon glucose molecule is converted into two 3-carbon segments.

Glycolysis

Steps [6] – [10] energy-generating phase:



producing 1 NADH and 2 ATPs for each pyruvate formed.

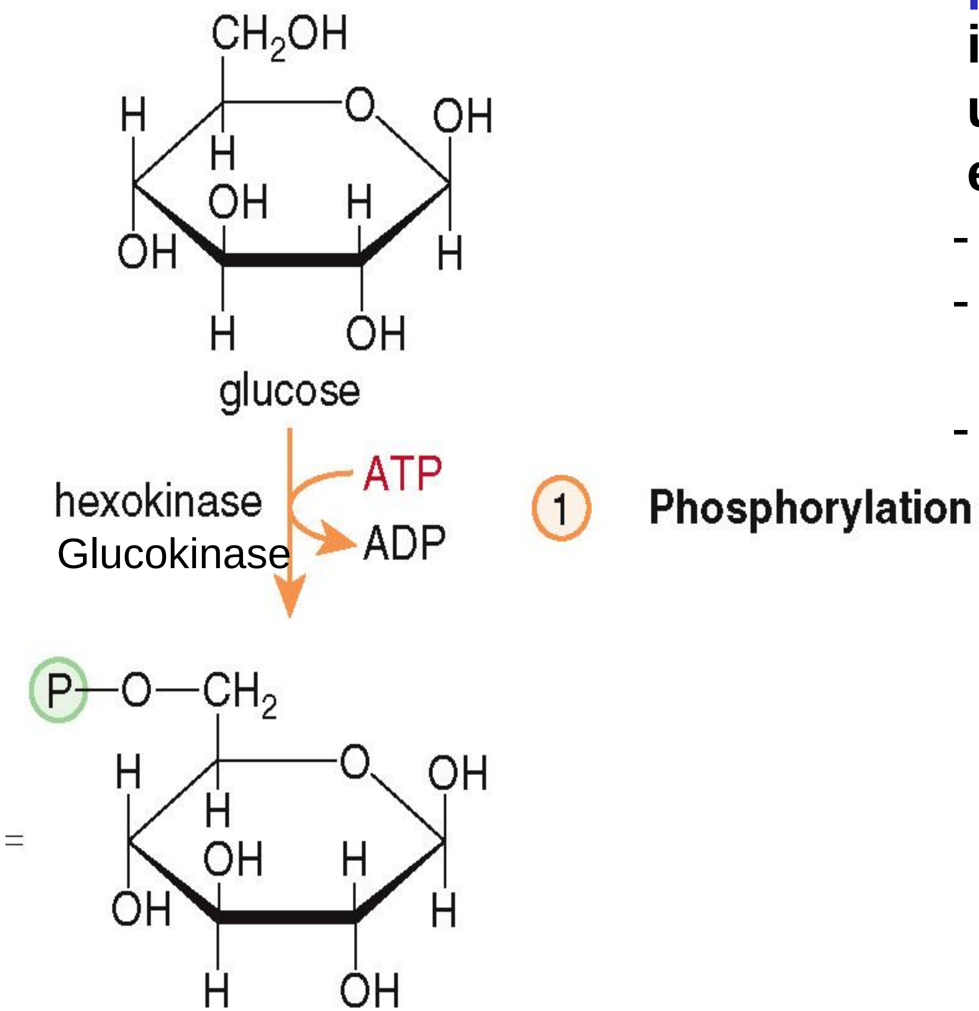
Glycolysis

Enzymes:

TABLE 24.1 Common Enzymes in Metabolism

Type of Enzyme	Type of Reaction
Carboxylase	Addition of a carboxylate ($-COO^-$)
Decarboxylase	Removal of carbon dioxide (CO_2)
Dehydrogenase	Removal of two hydrogen atoms
Isomerase	Isomerization of one isomer to another
Kinase	Transfer of a phosphate

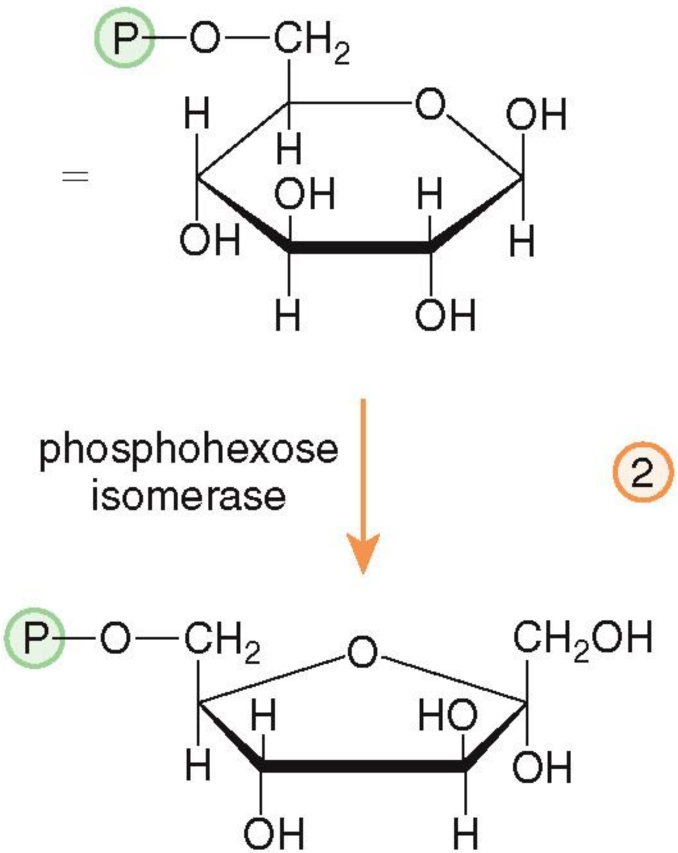
Glycolysis



Step [1] begins with the phosphorylation of glucose into glucose 6-phosphate, using an ATP , and a kinase (Mg+) enzyme.

- Irreversible and regulatory step
- *Hexokinase* **(all tissues) inhibited by G6P.**
- *Glucokinase* **(liver only) cannot inhibited**

Glycolysis

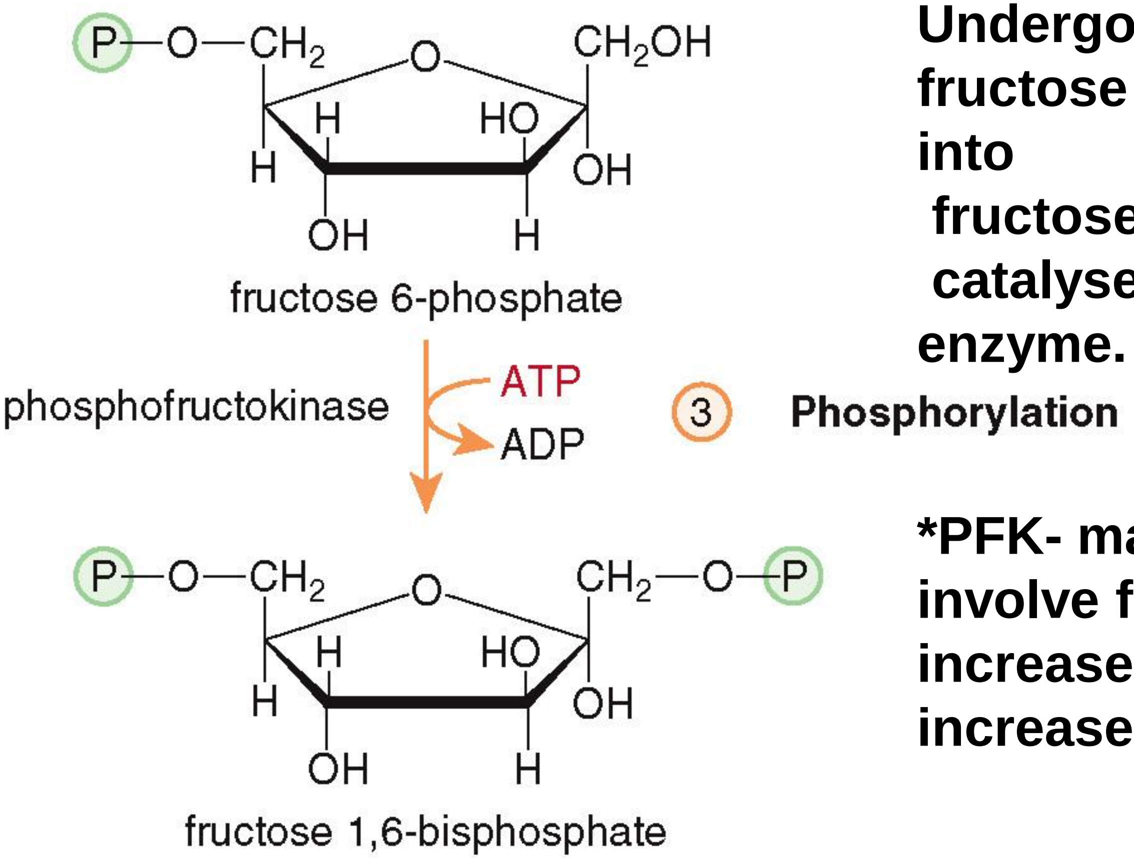


fructose 6-phosphate

2 **Isomerization**

Step [2] isomerizes glucose 6-phosphate to fructose 6-phosphate with an isomerase enzyme.

Glycolysis



Step [3] formation of F-6-P to F-1,6-bisphosphate:

Undergoes phosphorylation fructose 6-phosphate converted into fructose 1,6-bisphosphate catalysed by kinase (Mg+) enzyme. ATP again used.

***PFK- main regulatory enzyme and involve feedforward reaction ie F6P increases activity of enz lead increase product formation.**

Glycolysis

Overall, the first three steps of glycolysis:

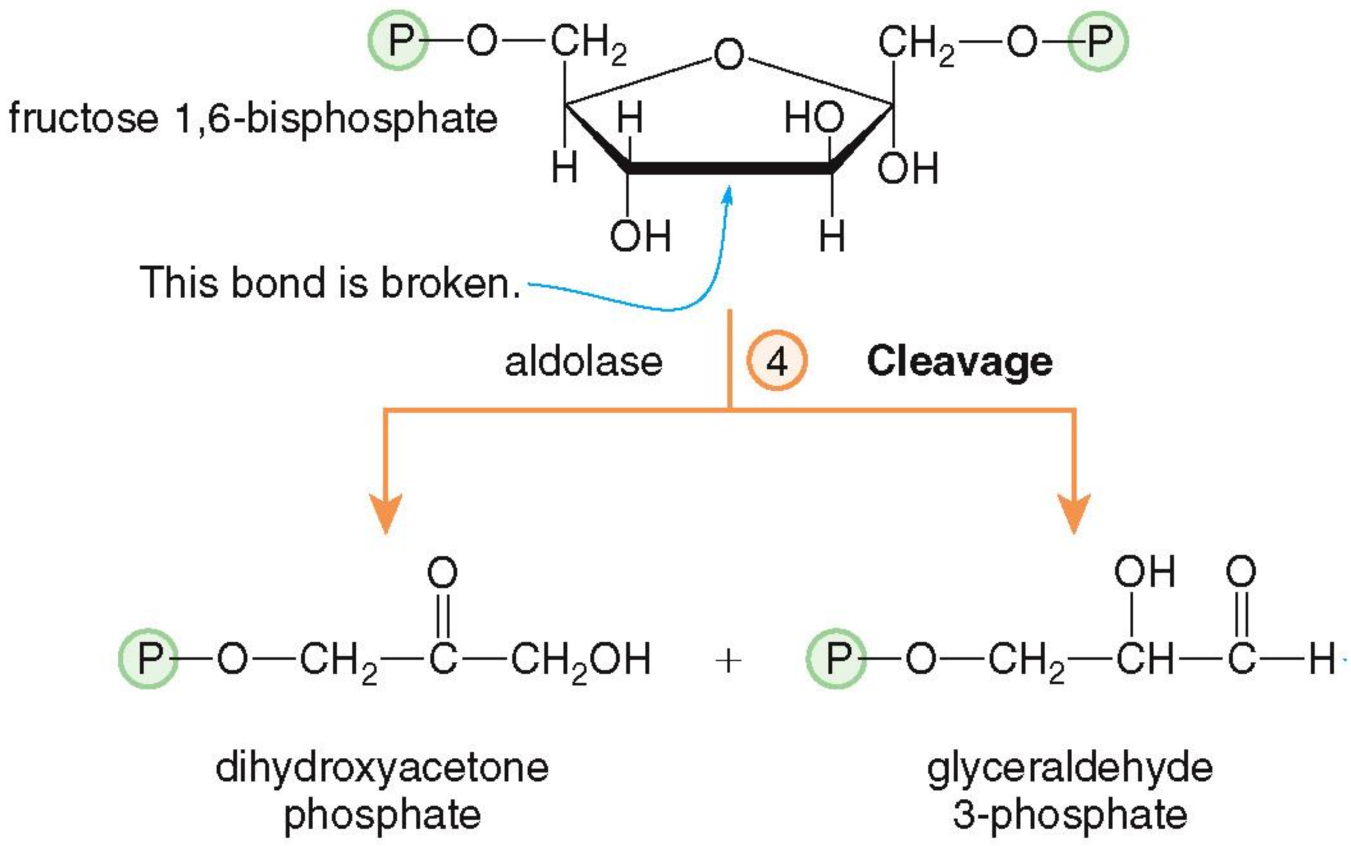
1. 2 phosphate groups is added.

2. A 6-membered glucose ring is isomerized into a 5-membered fructose ring.

3. The energy stored in 2 ATP molecules is utilized to modify the structure of glucose

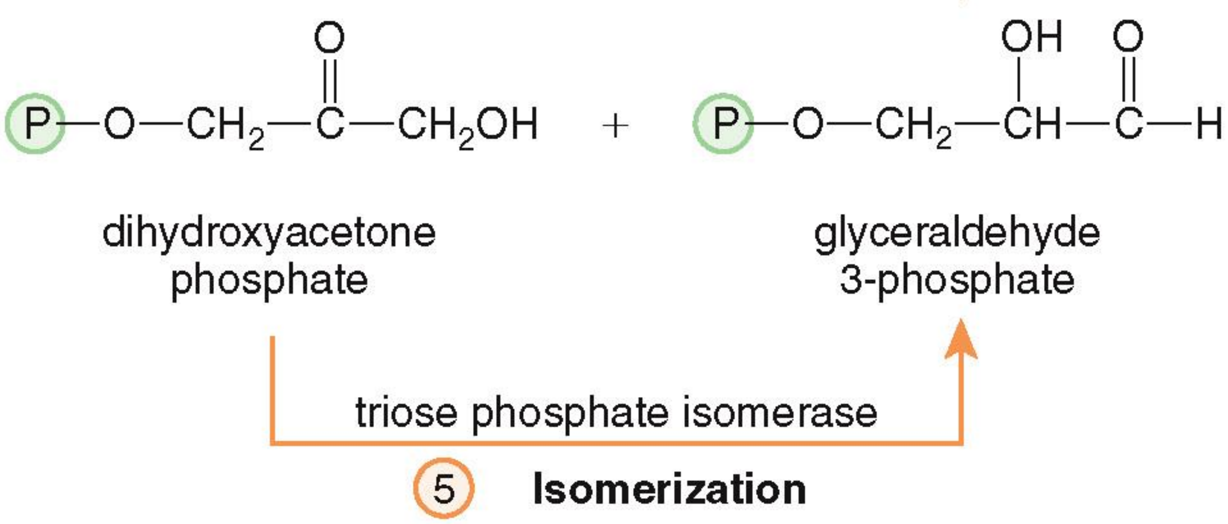
Glycolysis

Step [4] Formation of 2 triose :cleaves the fructose ring into a dihydroxy-acetone phosphate (DHAP) and a glyceraldehyde 3-phosphate (Gly-3-P) by an enzyme aldolase which is irreversible reaction.



Glycolysis

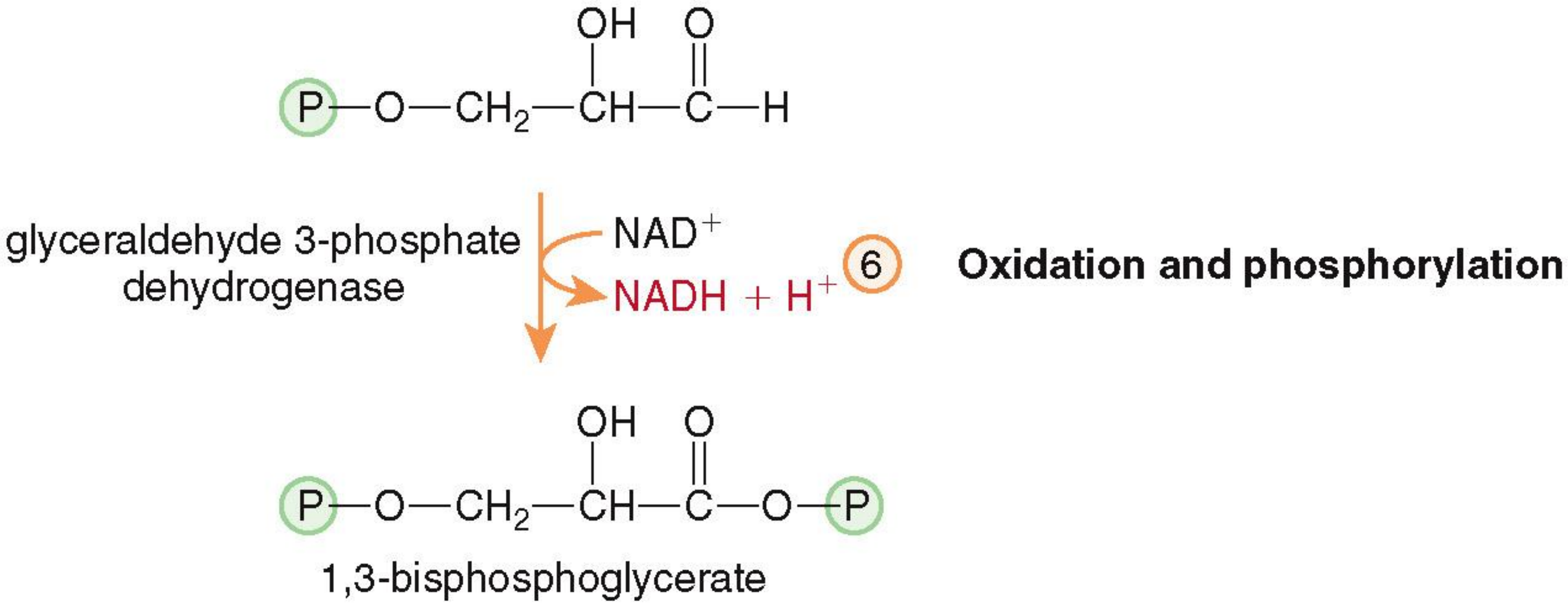
Step [5] isomerizes the dihydroxyacetone phosphate into another glyceraldehyde 3-phosphate undergoes isomerization by enzyme. Now each triose is metabolised into the end product : 2-pyruvate and 2-lactate. This happen bcoz two triose are interconvertible



Thus, the first phase of glycolysis converts glucose into 2 glyceraldehyde 3-phosphate units and 2 ATP is used.

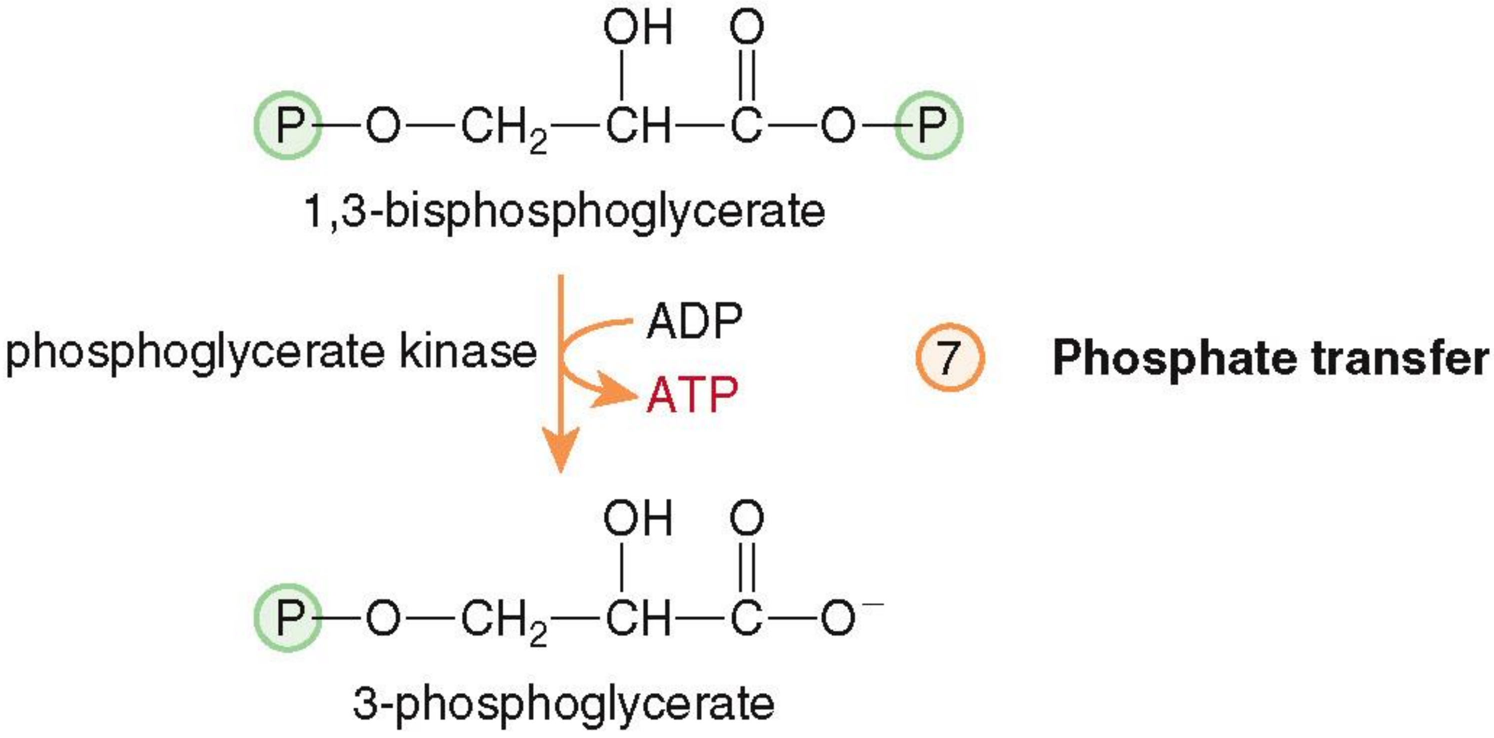
Glycolysis

In step [6] the aldehyde end of the molecule is oxidized and phosphorylated by a dehydrogenase enzyme and NAD^+; this produces 1,3-bisphospho-glycerate and NADH.



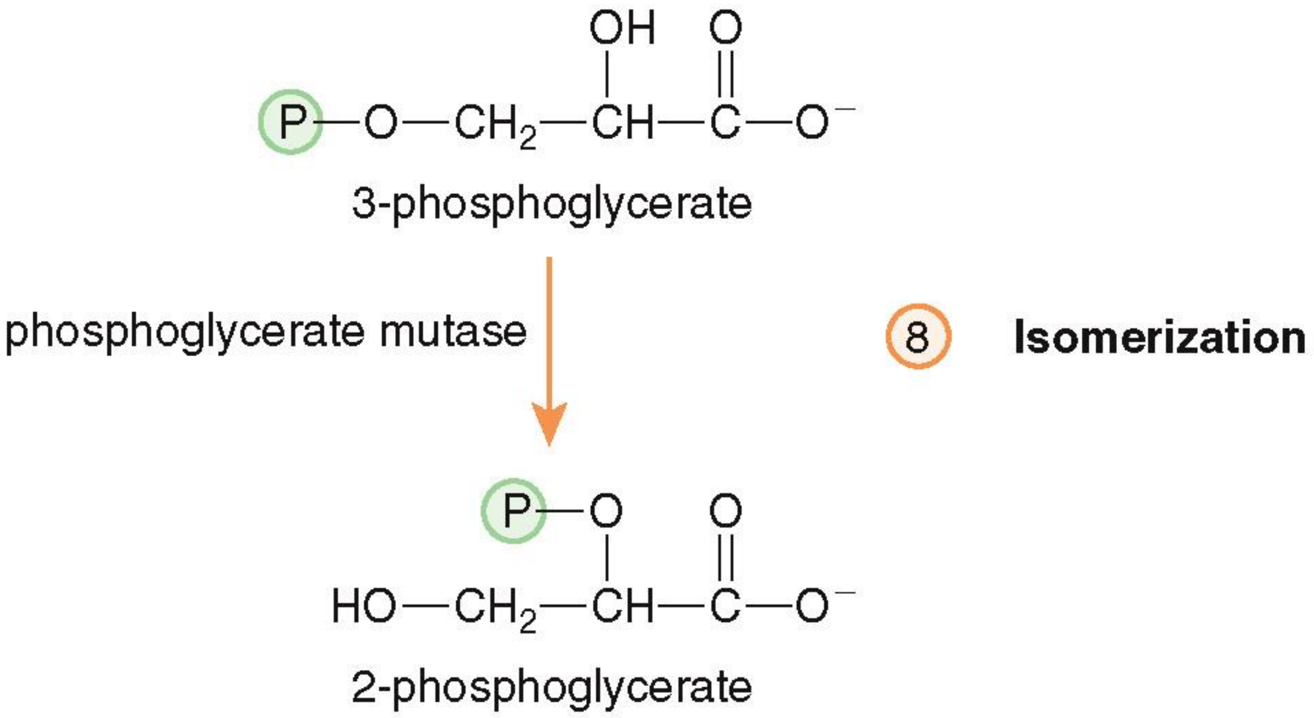
Glycolysis

In step [7], the phosphate group is transferred onto an ADP with a kinase enzyme, forming 3-phosphoglycerate and ATP.



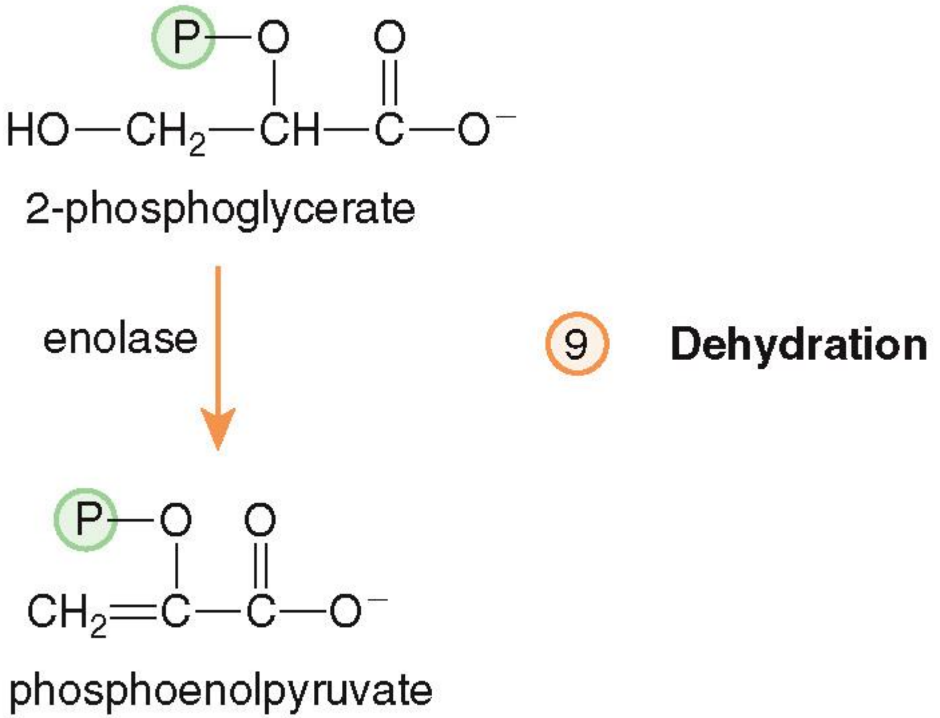
Glycolysis

In step [8], the phosphate group is isomerized to a new position in 2-phosphoglycerate.



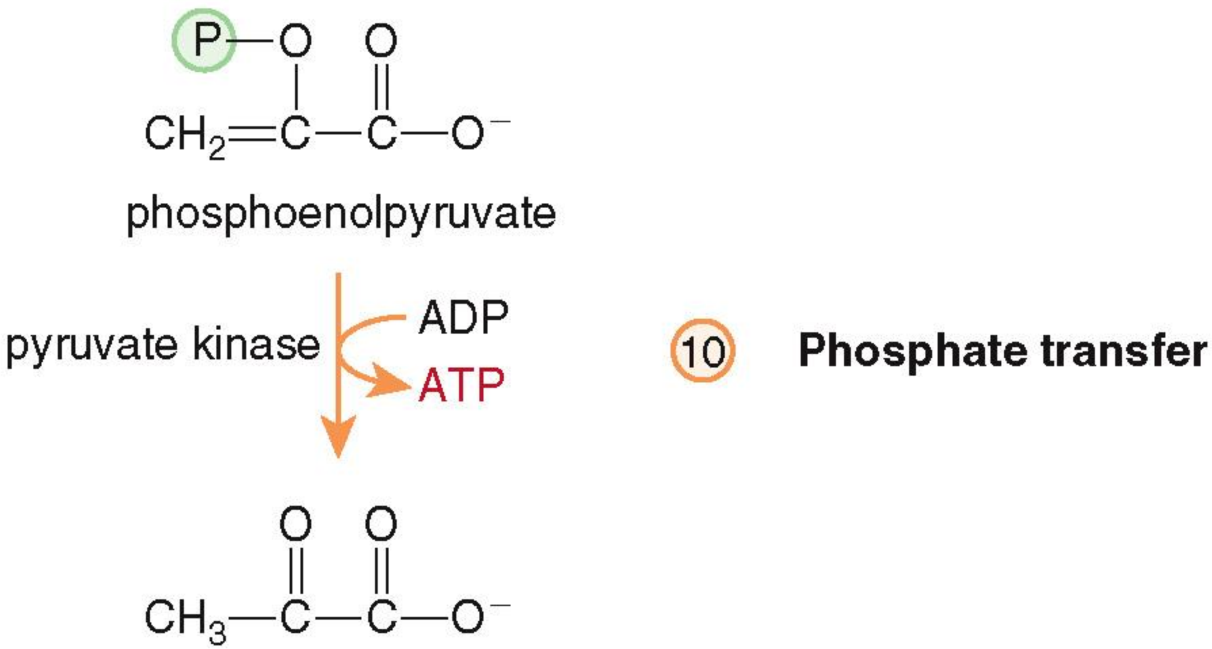
Glycolysis

In step [9], water is lost to form phosphoenol-pyruvate.



Glycolysis

In step [10], the phosphate is transferred to an ADP, yielding pyruvate and ATP with a kinase enzyme.



Glycolysis

The 2 glyceraldehyde 3-phosphate units are converted into 2 pyruvate units in phase two of glycolysis.

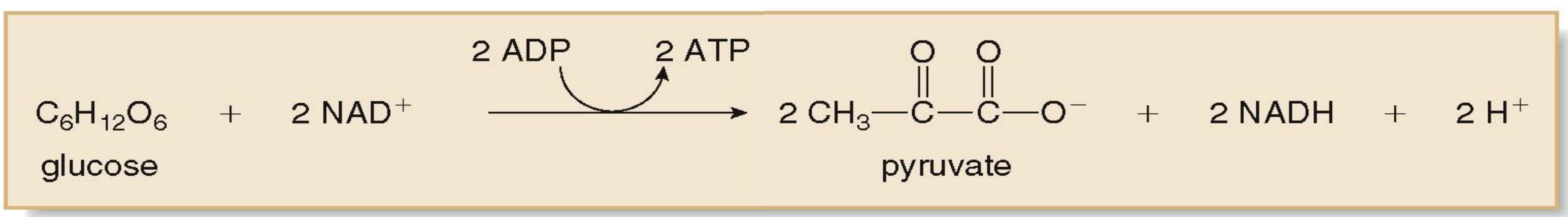
Overall, the energy-generating phase forms 2 NADHs and 4 ATPs.

Glycolysis

2 ATPs are used in phase one of glycolysis, and 4 ATPs are made in phase two of glycolysis.

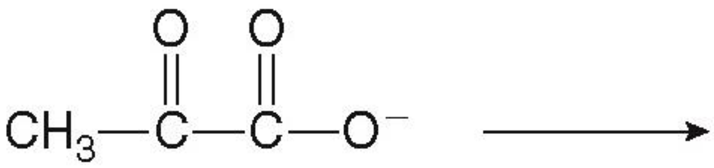
The net result is the synthesis of 2 ATPs from glycolysis.

The 2 NADHs formed are made in the cytoplasm and must be transported to the mitochondria to join the electron transport chain and make ATP.

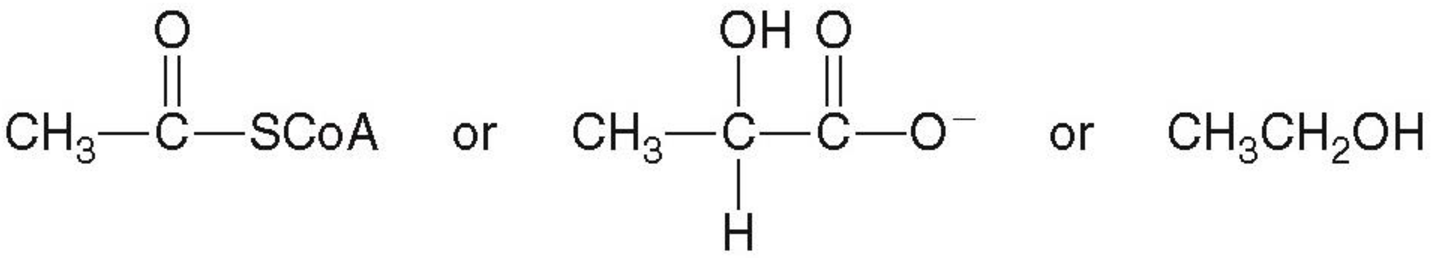


Overall of glycolysis

The fate of pyruvate



pyruvate



acetyl CoA | lactate | ethanol

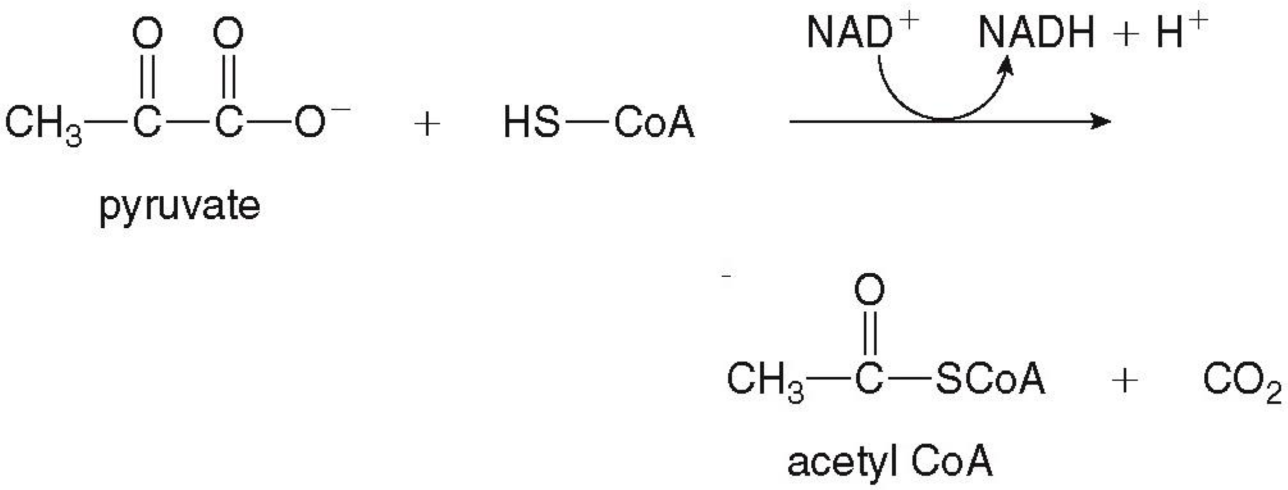
under aerobic conditions

under anaerobic conditions

in fermentation by microorganisms

Aerobic conditions

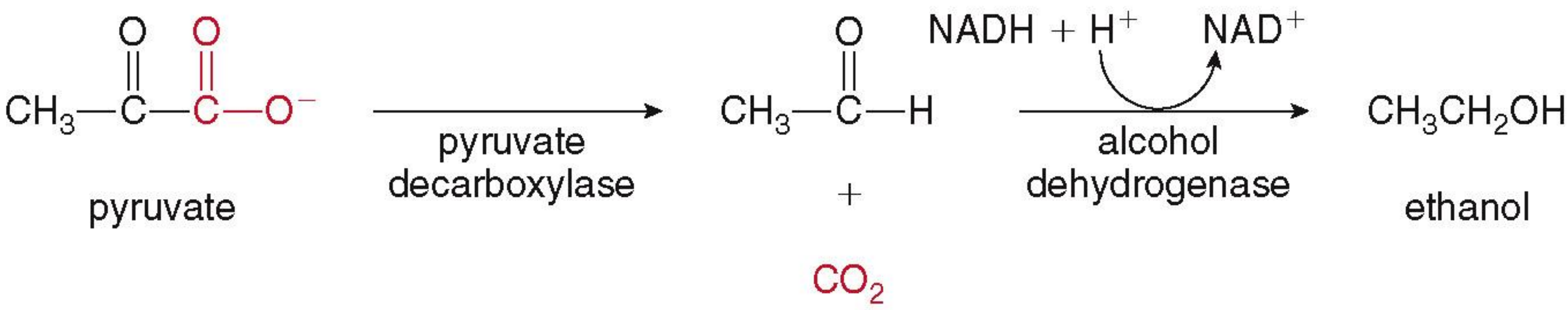
Pyruvate must diffuse across the outer and inner membrane of mitochondria into the matrix.



The NADH formed needs O_2 to return to NAD^+, so without O_2 no additional pyruvate can be oxidized.

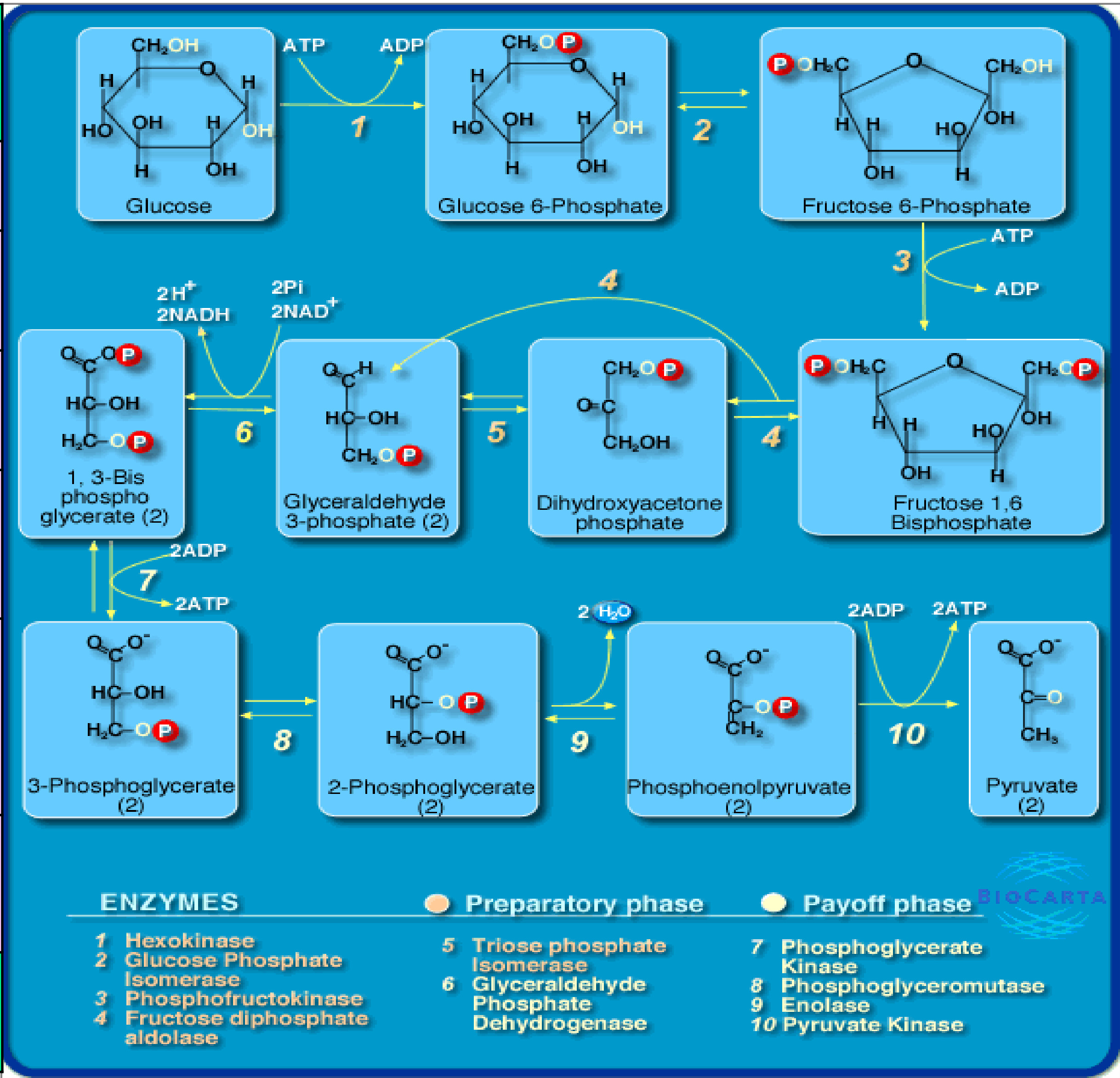
Fermentation

Fermentation is the anaerobic conversion of glucose to ethanol and CO_2 by yeast and other microorganisms.



Overall pathway of Glycolysis & ATP Formation

Number of ATP generated from glycolysis		
Enzyme	Aerobic	Anaerobic
Hexokinase	-1 ATP	-1 ATP
PFK-1	-1 ATP	-1 ATP
G-3-P dehydrog.	+6 ATP	----
Phospho-glycerate kinase	+2 ATP	+2 ATP
Pyruvate kinase	+2 ATP	+2 ATP
Sum	+8 ATP	+2 ATP



Regulation of Glycolysis

- <u>PFK-1</u> is the major regulatory enzyme of glycolysis. In the <u>liver only</u>, PFK-1 is activated by **<u>fructose-2,6-diphosphate</u> (F-2,6-DP)**.
- **<u>PFK-2</u>**, the enzyme that synthesize the activator F-2,6-DP, is itself a regulatory enzyme. It is inhibited by citrate & ATP and by phosphorylation. The reverse reaction is catalyzed by **<u>fructose-2,6-diphosphatase</u>(F-2,6-DPase).**
- **<u>Hormones</u>** also regulate glycolysis e.g., glucagon inhibits glycolysis by repressing the synthesis of F-2,6-DP. Insulin promotes glycolysis by stimulating the synthesis of F-2,6-DP.

Rate of glycolysis is controlled primarily by allosteric regulation of the 3 key enzymes (irreversible steps), hexokinase, PFK-1, and pyruvate kinase.

Enzyme	Activator	Inhibitor
Hexokinase	AMP, ADP, Pi	G-6-P
PFK-1	F-6-P, AMP, F-2,6-DP (liver only)	NADH, H^+, citrate, ATP
Pyruvate kinase	AMP, F-1,6-DP	ATP, acetyl CoA, phosphorylation