Biochemistry Team 435

King Saud University

GLYCOLYSIS

- Very Important
- extra explanation

"STAY FOCUSED TO STAY ALIVE"

OBJECTIVES OF GLYCOLYSIS

- 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

- هذه رؤوس أقلام من أجل التذكير بمحتوى النقاط المذكورة فى العرض الأساسى :

Glycolysis: overview

- It is the major pathway for glucose oxidation, in the cytosol .
- It works 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 relate completely on glucose as their metabolic fuel "merabolised by anaerobic glycolysis .

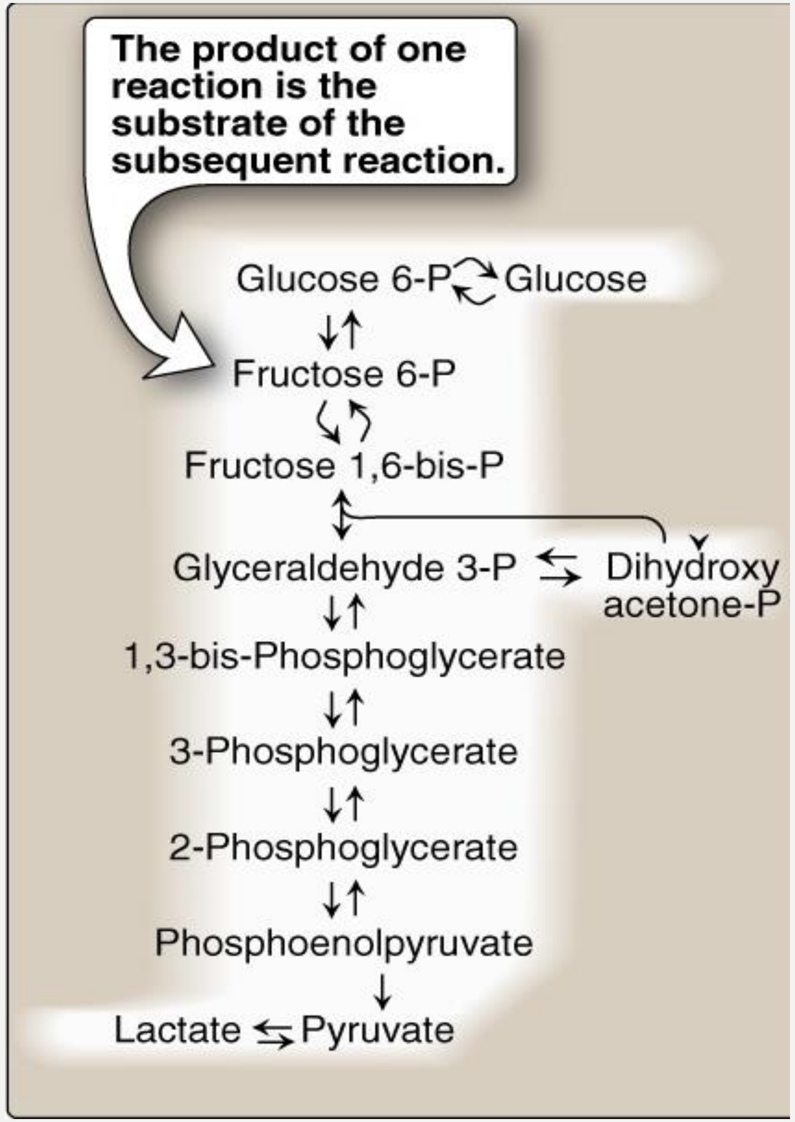
ملحوظة : جميع أسماء الإنزيمات و المواد المتفاعلة و الناتجة مطلوبة

Reversible = ↓↑

Irreversible = ↓

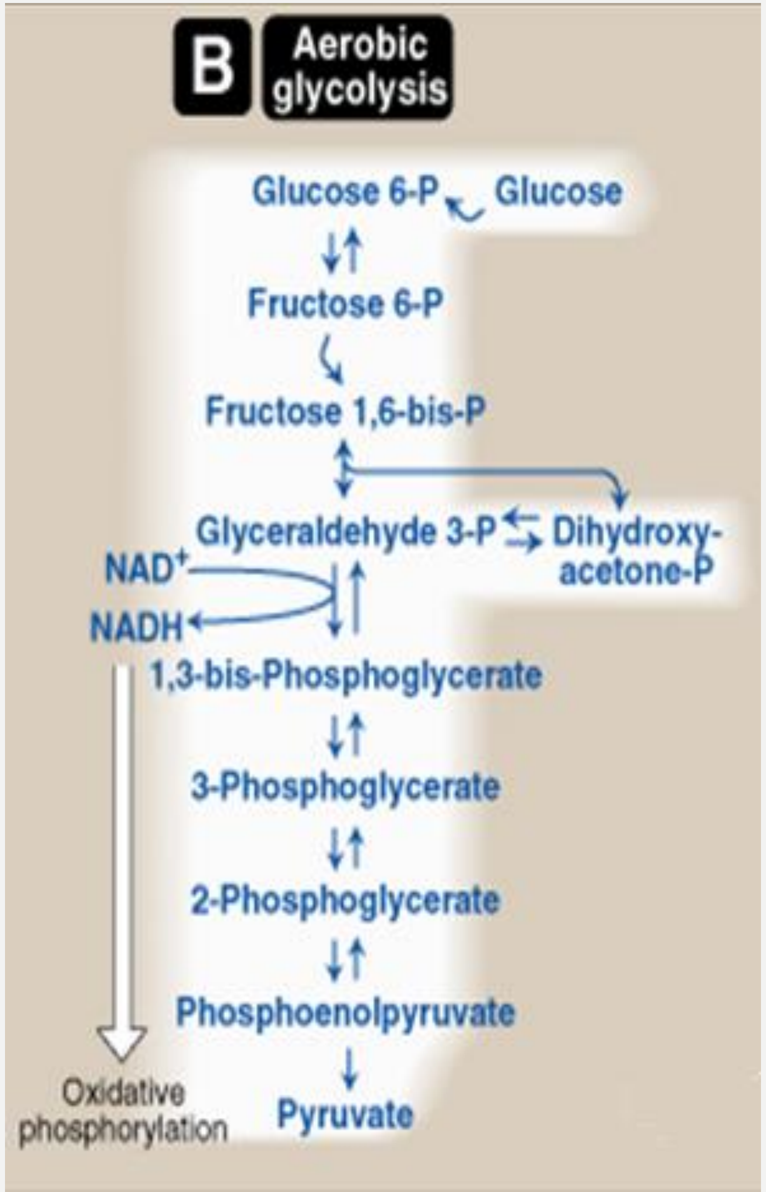
Glycolysis

- Aerobic
  - Available both : O2 & MITOCHONDRIA
- Anaerobic
  - Absence of O2 or mitochondria or both of them



Biochemistry Team 435

Aerobic Glycolysis



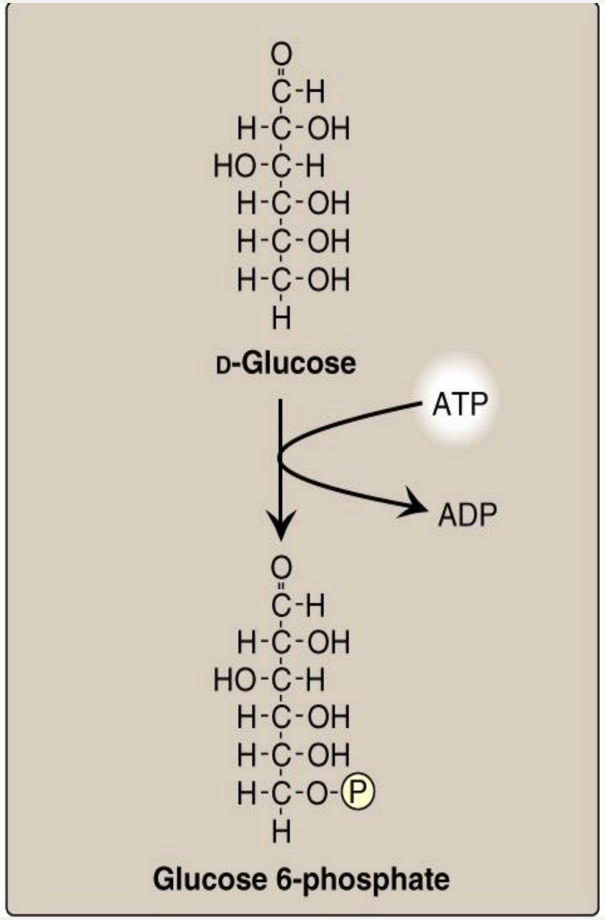
1. Phosphorylation of glucose
2. Isomerization of glucose 6-phosphate
3. Phosphorylation of fructose 6-phosphate
4. Cleavage of fructose 1,6-bisphosphate
5. Isomerization of dihydroxyacetone phosphate
6. Oxidation of glyceraldehyde 3-phosphate
7. Synthesis of 3-phosphoglycerate, producing ATP
8. Shift of the phosphate group
9. Dehydration of 2-phosphoglycerate
10. Formation of pyruvate, producing ATP

Phosphorylation of glucose

ACTION :
Adding of phosphate group to glucose

Enzymes :

- **Hexokinase:** Most tissues
- **Glucokinase:** Hepatocyte
  " خلية كبدية"



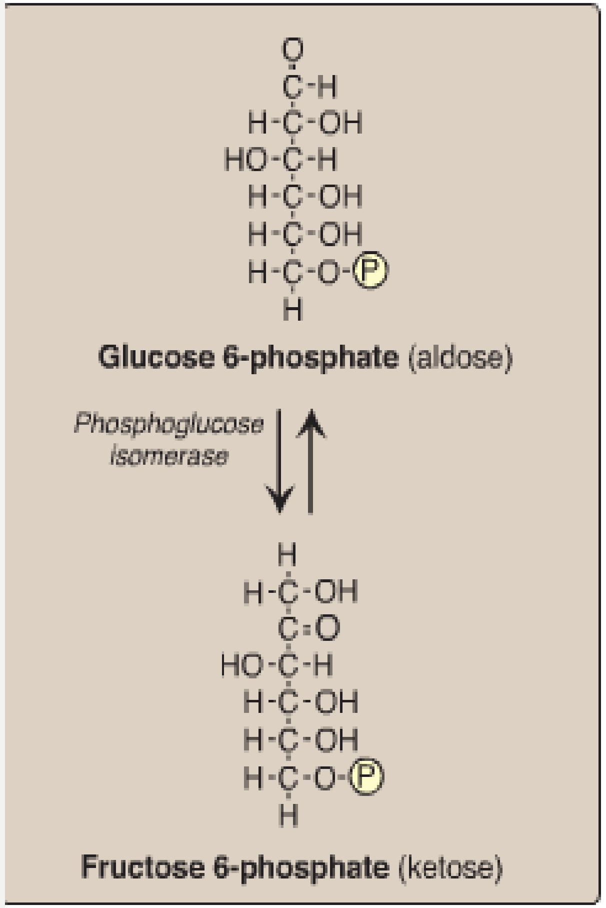
1 ATP is consumed*

Isomerization of glucose 6-phosphate

ACTION :
Isomerization of glucose 6-phosphate to fructose 6-phosphate

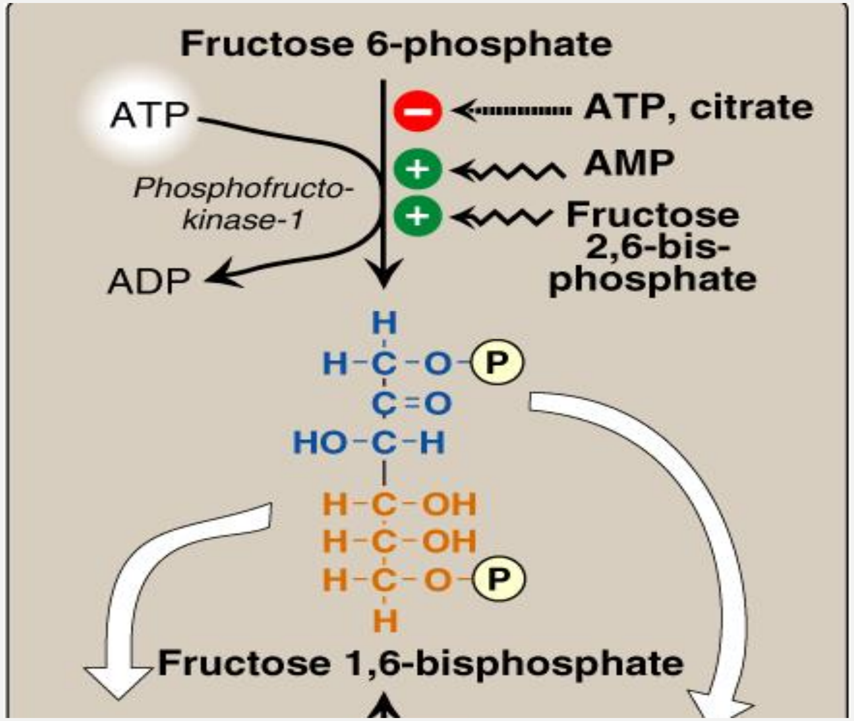
Enzyme :

- Phosphoglucose isomerase



Phosphorylation of fructose 6-phosphate

ACTION :
Adding phosphate group to fructose 6-phosphate



Enzyme :
- Phospho-fructokinase-1 (PFK-1)

Phospho-fructokinase-1 (PFK-1) is the most important regulatory enzyme in glycolysis .

1 ATP is consumed*

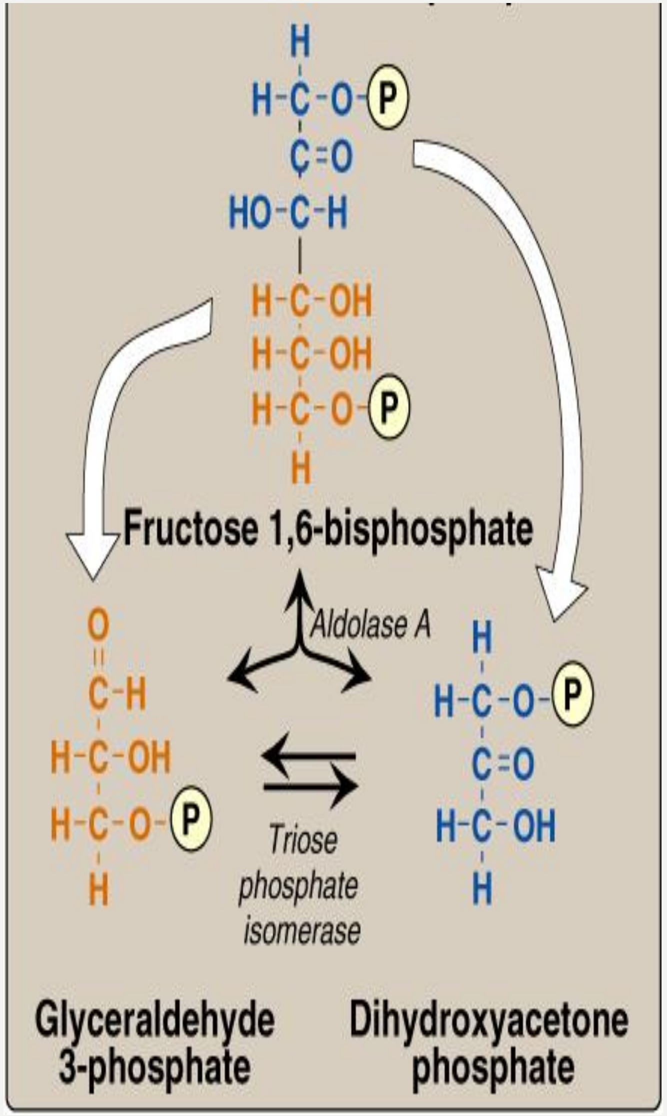
(PFK-1) and its regulation

- Allosteric Regulation
  - Inhibited by: ATP & citrate زيادة عدد جزيئات ATP , Citrate تثبط عمل الإنزيم
  - Stimulated by: AMP & Fructose2,6-bisphosphate
- Induction/Repression
  - Induced by: insulin
  - Repressed by: glucagon

Cleavage of fructose 1,6-bisphosphate

ACTION :
Cleaving fructose 1,6-bisphosphate to dihydroxyacetone phosphate and glyceraldehyde 3-phosphate

Enzyme:
- Aldolase A



Isomerization of dihydroxyacetone phosphate

ACTION :
Interconverting dihydroxyacetone phosphate (DHAP) into glyceraldehyde 3-phosphate

Enzyme:
- Triose phosphate isomerase

- To complete glycolytic pathway (DHAP) should be converted to glyceraldehyde 3-phosphate , so we will have 2 molecules of glyceraldehyde 3-phosphate
- After this point there will be <u>2 molecules</u> of the each next reactions

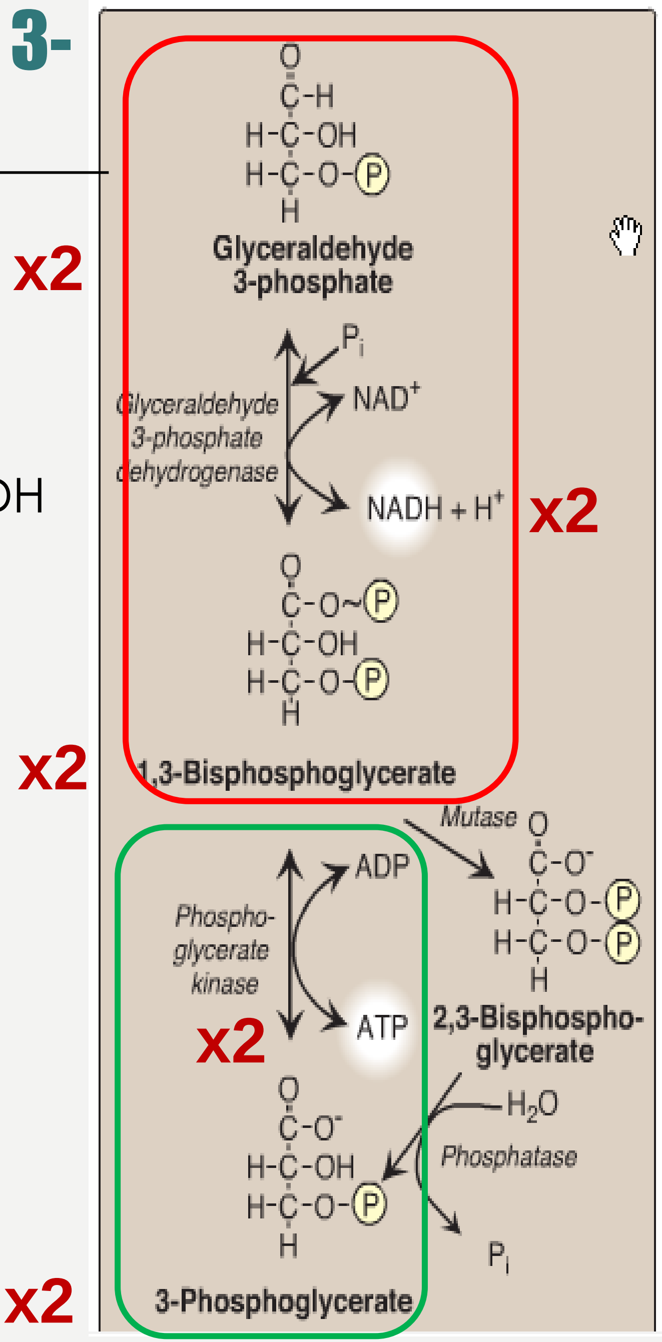
Oxidation of glyceraldehyde 3-phosphate
(Oxidative level)

ACTION :
Oxidation to the molecule NAD+ → NADH , this reaction used to add Phosphate group to the molecule.

Enzyme :
- Glyceraldehyde 3-Phosphate Dehydrogenase

Outcomes :
2 NADH = 6 ATP will be produced by ETC in the mitochondria

TOTAL : 6ATP



Synthesis of 3-phosphoglycerate, producing ATP
(Substrate–level)

ACTION :
Phosphate group add to ADP to become ATP.

Enzyme :
- Phosphoglycerate kinase

Outcomes :2 ATP

Shift of the phosphate group

ACTION
It is isomer and what change is : The P group change position from O in carbon-3 to O in carbon-2 by

Enzyme :

- phosphoglycerate mutase.

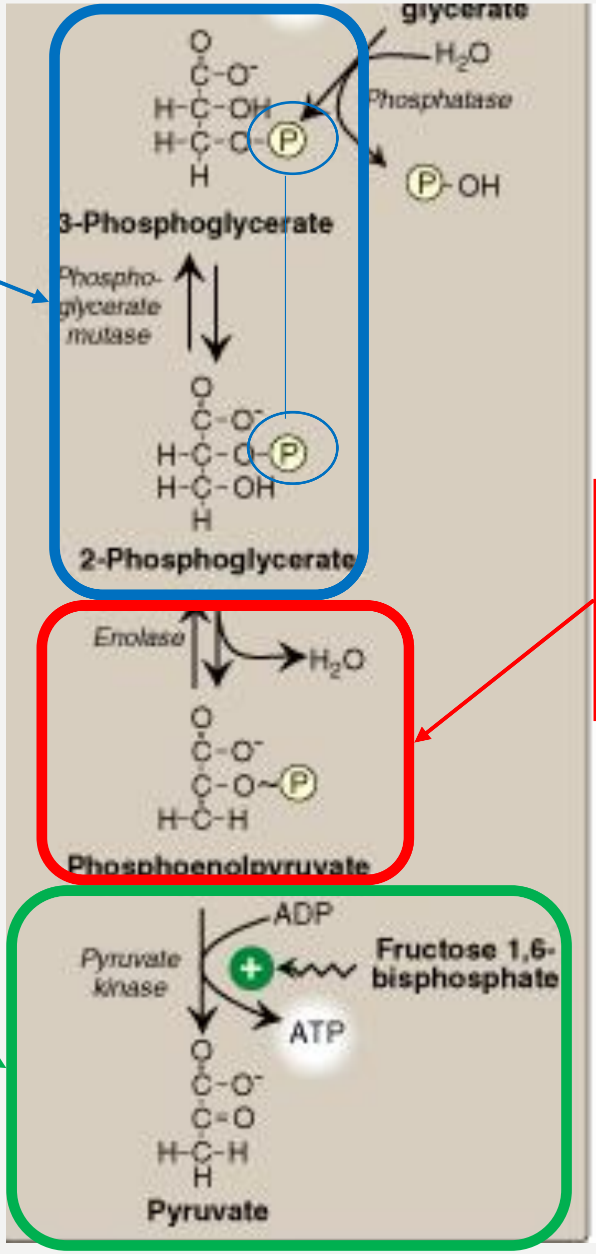
Formation of pyruvate, producing ATP
(Substrate–level)

phosphoenolpyruvate → pyruvate

Fructose 1,6-bisphosphate formed in 3rd step , it will go to the last step (it is Allosteric)

Enzyme :

- Pyruvate kinase



Outcomes :2 ATP

Dehydration of 2-phosphoglycerate

ACTION :
Phosphoglycerate change to phosphoenolpyruvate by remove water .

Enzyme :

- Enolase

Substrate-level phosphorylation Vs. Oxidative phosphorylation

- **Phosphorylation** is the metabolic reaction of introducing a phosphate group into an organic molecule.

Oxidative phosphorylation	Substrate-level phosphorylation
The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP	The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP (or GDP to GTP)
the transfer of electrons from reduced coenzymes to molecular oxygen by ETC	cleavage of a high-energy metabolic intermediate (substrate).
mitochondria	cytosol or mitochondria

- Regulation of Glycolysis
  - Regulatory Enzymes
    - Glucokinase hexokinase
    - PFK-1
    - Pyruvate kinase
  - Regulatory Mechanisms
    - Rapid, short-term
      - Allosteric Regulation
      - Covalent Modification
    - Slow, long-term
      - Induction : Insulin
      - Repression: Glucagon

Pyruvate Kinase Deficiency Hemolytic Anemia

PK mutation maybe lead to :

- Altered Enzyme Kinetics
- Decreased Enzyme stability
- Altered response to activator

Aerobic Glycolysis: ATP Production

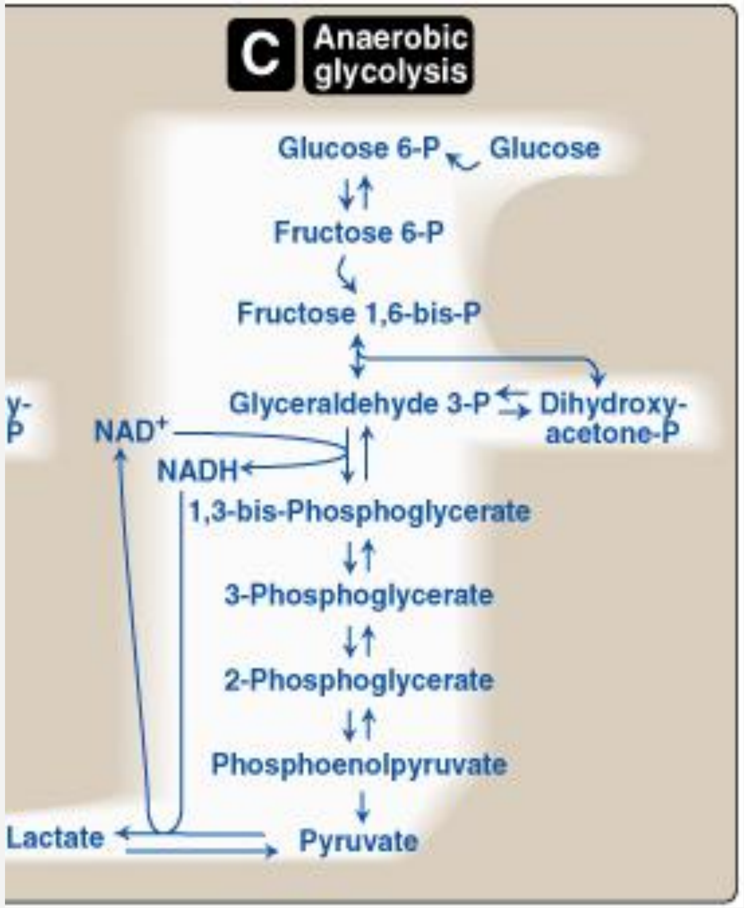
- ATP Consumed: 2 ATP

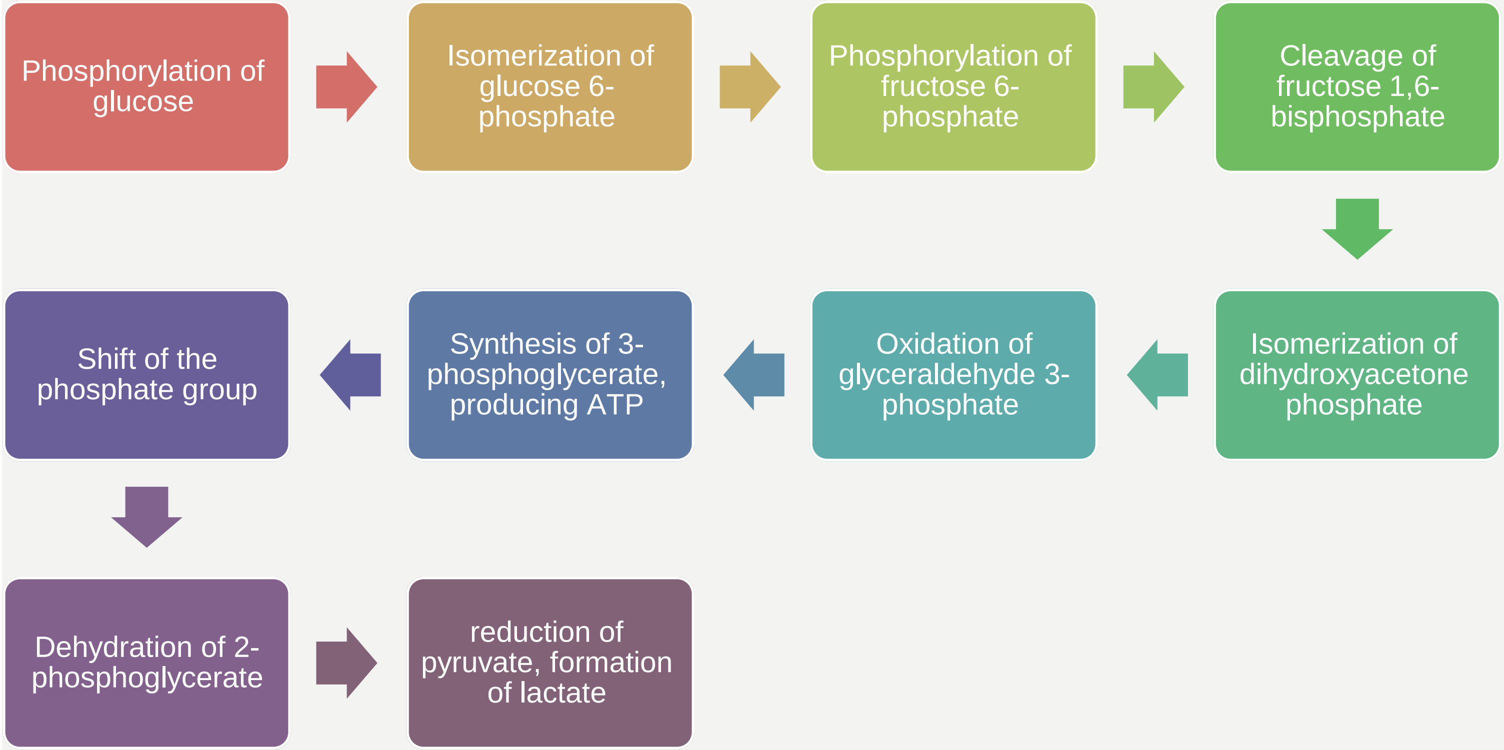
- ATP Produced:
- Substrate-level: 2 X 2 = 4 ATP
- Oxidative-level: 2 X 3 ATP (each NADH = 3 ATP will be produced)= 6 ATP

- Total: 10 ATP
- Net: 10–2=8 ATP

Anaerobic glycolysis

- The final product of anaerobic glycolysis is lactate
- transforming Glyceraldehyde 3-P to 1,3-bisphosphoglycerate in anaerobic glycolysis they go to transform pyruvate into lactate by the help of lactate dehydrogenase





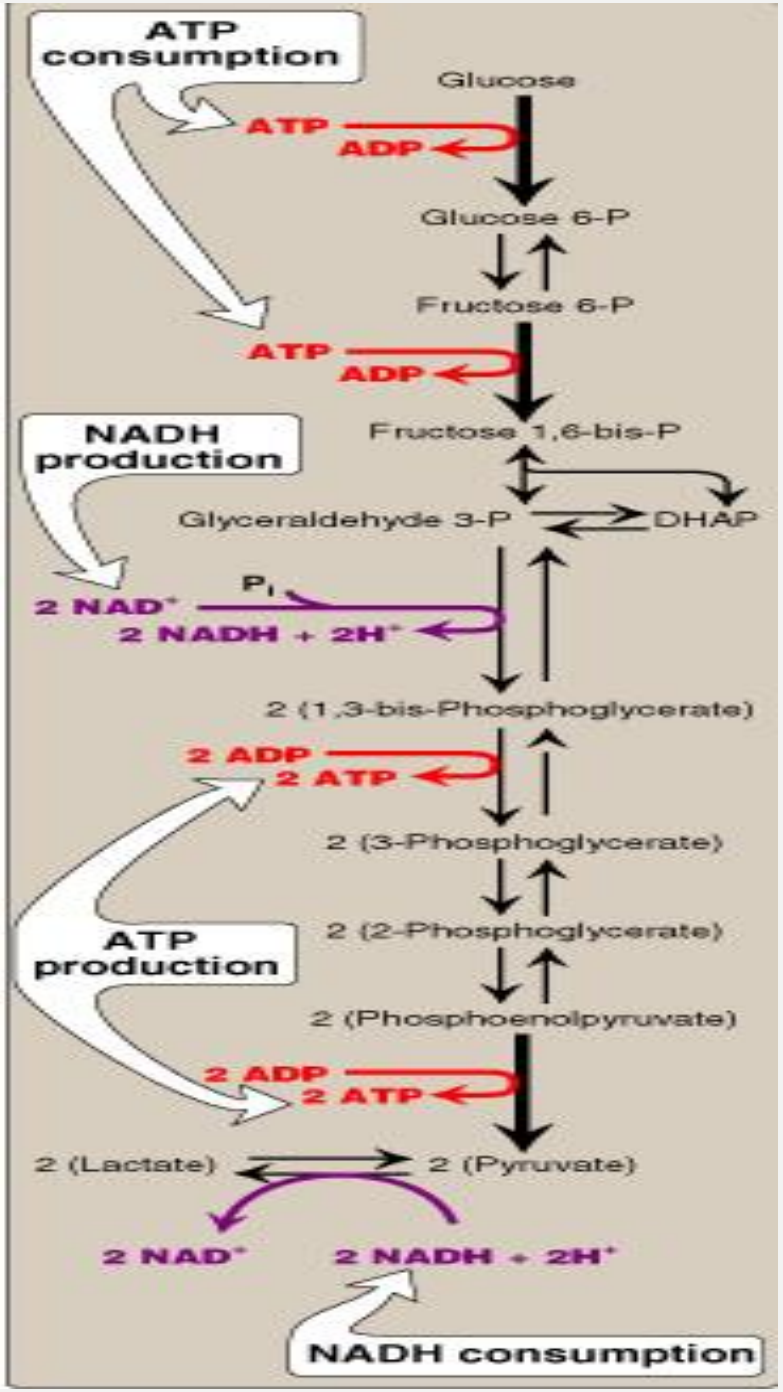
Anaerobic glycolysis

- NADH produced cannot be used by ETC for ATP production (No O_2 and/or No mitochondria)

- Less ATP production, as compared to aerobic glycolysis

- Lactate is an obligatory end product, Why?

Because the cell has limited amount of NAD+. So NAD+ is needed to transform Glyceraldehyde 3-P to 1,3-bisphosphoglycerate and NADH molecules are produced. Therefore, they need to be regenerated to NAD+ otherwise glycolysis stops .

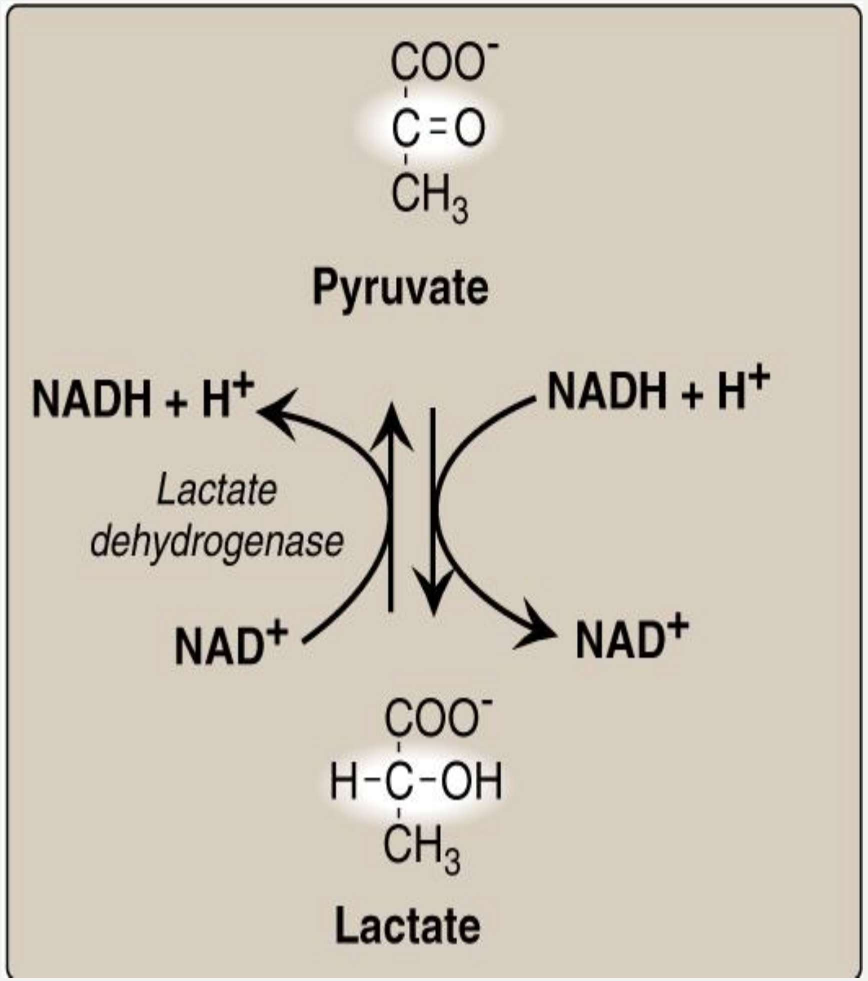


Lactate dehydrogenase

ACTION :
Pyruvate → lactate

Enzyme :
- Lactate dehydrogenase

This reaction is reversible. However, the enzyme for both directions is lactate dehydrogenase even though the reaction in the forward direction gains hydrogen



Anaerobic Glycolysis: ATP production

- **ATP Consumed: 2 ATP**

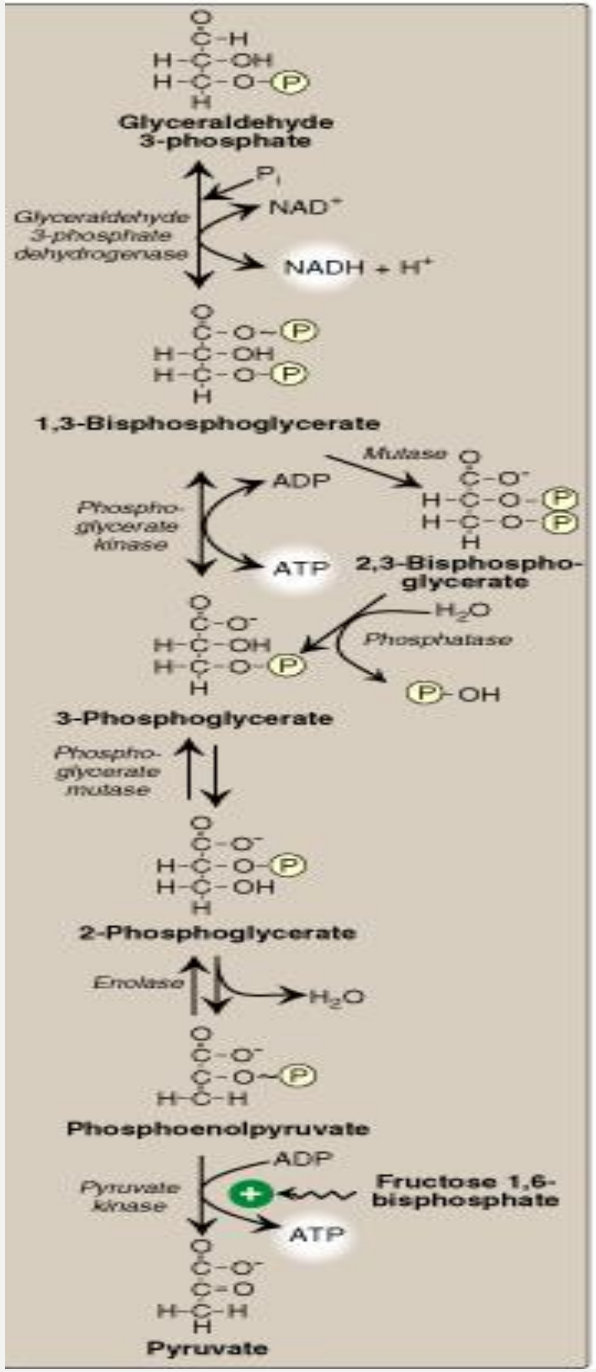
- **ATP Produced:**
  - **Substrate-level: 2 X 2 = 4 ATP**
  - ~~**Oxidative-level: 2 X 3 = 6 ATP**~~

Oxidative phosphorylation is cancelled because the NADH molecules don't go to ETC to produce ATP in anaerobic glycolysis but they go to help in lactate production

- **Total: 4 ATP**
- **Net: 4 – 2 = 2 ATP**

Anaerobic Glycolysis in RBCs

- All the steps are the same with other anaerobic glycolysis except "**2,3-BPG Shunt**" in sometimes.



Importance of Mutase enzyme

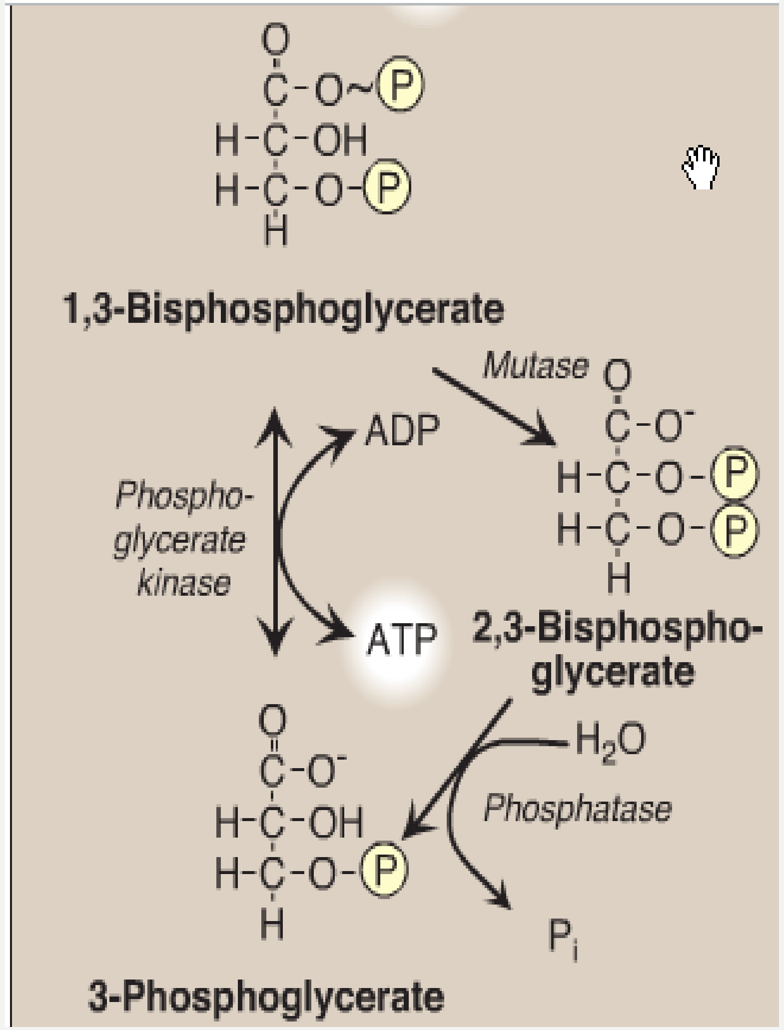
- It is important for association and dissociation between O2 and hemoglobin.
- Increase in "2,3-BPG" will help to loss of association between O2 and hemoglobin and will release more O2.
- It usually occurs with people who live in high altitude.

ACTION :
1,3-bisphosphoglycerate→ 2,3-bisphospoglycerate

Enzyme :
- Mutase

ACTION :
2,3-bisphospoglycerate → 3-phospoglycerate , by adding water molecule and removing phosphate group

Enzyme :
- phosphatase



Remember:
1- No production of ATP in formation of "2,3-BPG".
2- "2,3-BPG" comes back to "3-Phosphoglycerate" by Phosphatase enzyme

Glycolysis in RBCs: ATP Production

ATP consumed :	2 ATP
ATP produced :	
Substrate-level	2X2= 4 ATP
	Or 1X2= 2 ATP
Total	4 ATP
Net :	4 – 2 = 2 ATP
	Or 2 – 2 = 0 ATP

Glycolysis in RBCs: Summary

End product

- Lactate
- No net production or consumption of NADH

Energy yield

- without 2,3 BPG: 2 ATP
- with2,3 BPG shunt: 0 ATP

PKD haemolytic anaemia depend on

- Degree of PKD
- Compensation by 2,3-BPG

Glycolysis summary

Glycolysis	
Aerobic glycolysis	8 ATP
Anaerobic glycolysis	2 ATP

Glycolysis in RBCs	
Without 2,3 BPG synthesis	2 ATP
With 2,3 BPG synthesis	0 ATP

REMEMBER

- Glycolysis is <u>*the major oxidative*</u> pathway for glucose
- Glycolysis is employed by all tissues
- Glycolysis is tightly-regulated pathway
- PKF-1 is the rate-limiting regulatory enzyme (PFK-1=PhosphoFructoKinase-1)
- Glycolysis is mainly a catabolic pathway for ATP production, but it has some anabolic features (amphibolic) :
  - Synthesis of triacylglycerol from dihydroxyacetone phosphate
  - Synthesis of 2,3 BPG
- Pyruvate kinase deficiency in RBCs results in hemolytic anemia

*Amphibolic: it means both anabolic and catabolic reactions .

Biochemistry Team

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- نوره القحطاني.
- بدور جليدان.
- علا النهير.
- أفنان المالكي.
- فاطمه الدين.
- جوهره المالكي.
- خوله العريني.
- لجين السواط.
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