

# **Glucose Metabolism (Glycolysis)**

# Objectives

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*By the end of this 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
- Discuss the unique nature of glycolysis in RBCs.

# Glycolysis: An Overview

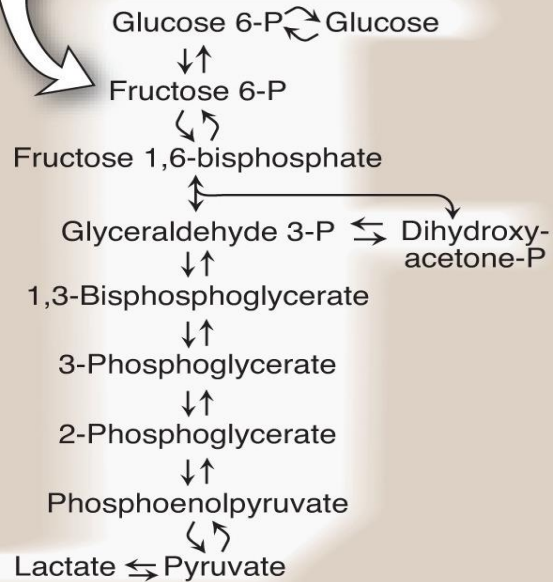
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- ❖ Glycolysis, the major pathway for glucose oxidation, occurs in the cytosol of all cells.
- ❖ It is unique, in that it can function either aerobically or anaerobically, depending on the availability of oxygen and intact mitochondria.
- ❖ It allows 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.

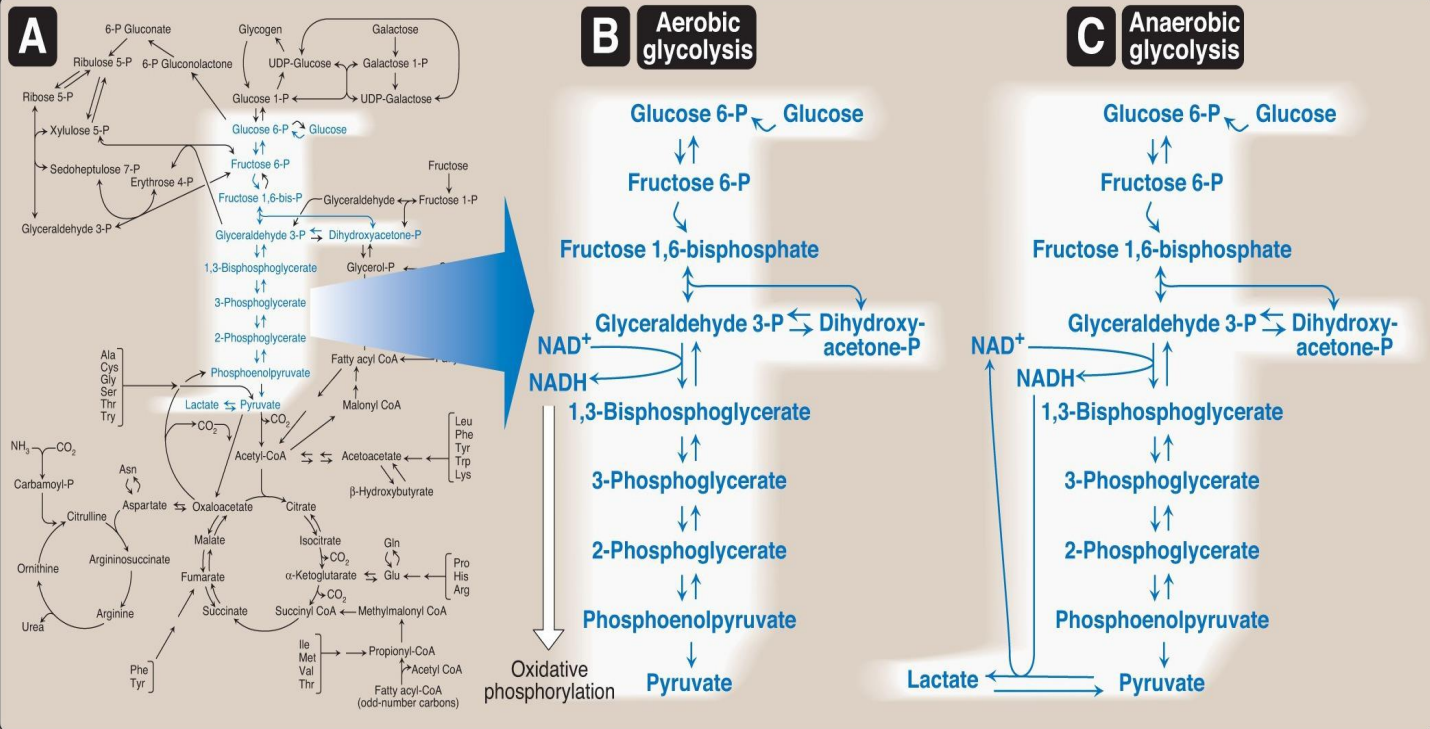


# Glycolysis

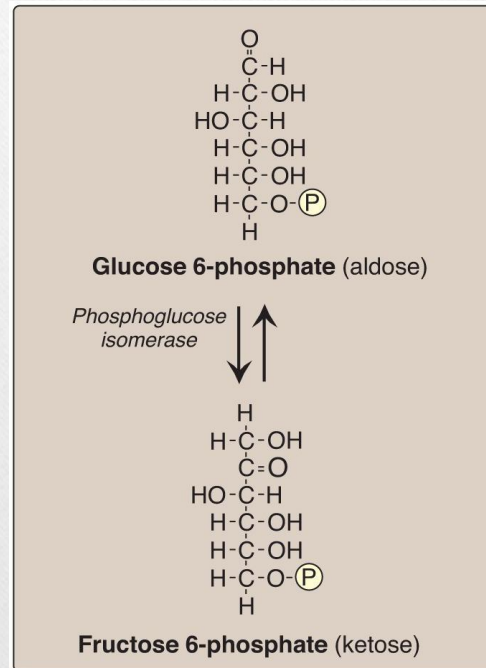
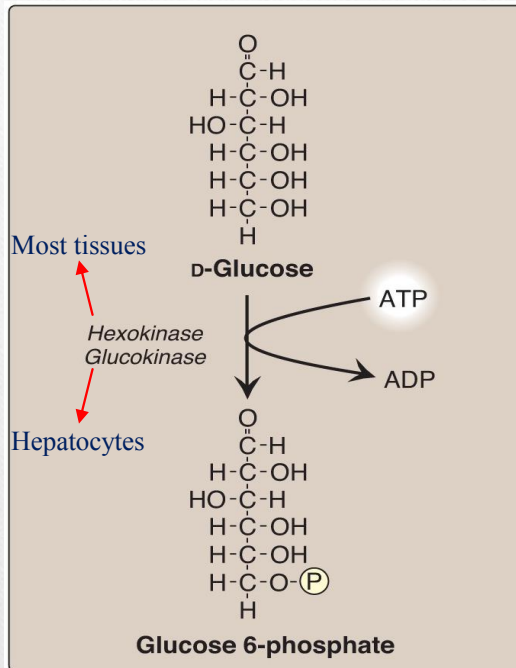
The product of one reaction is the substrate of the subsequent reaction.



# Aerobic Vs Anaerobic Glycolysis



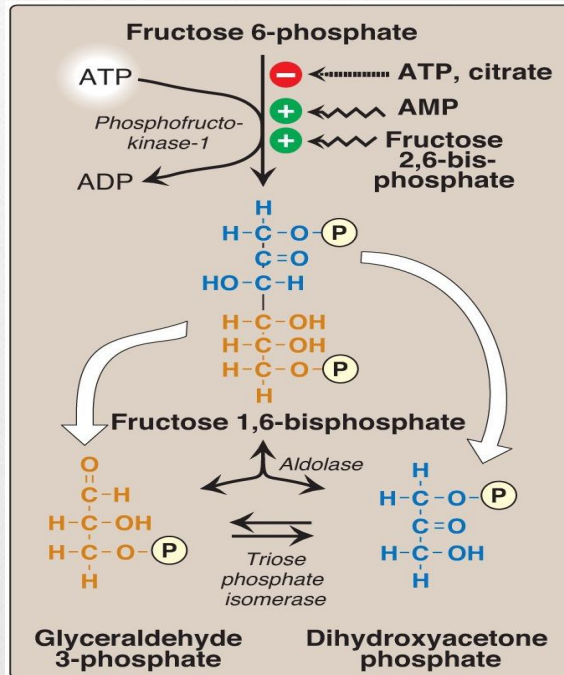
# Aerobic Glycolysis (1<sup>st</sup> and 2<sup>nd</sup> reactions)





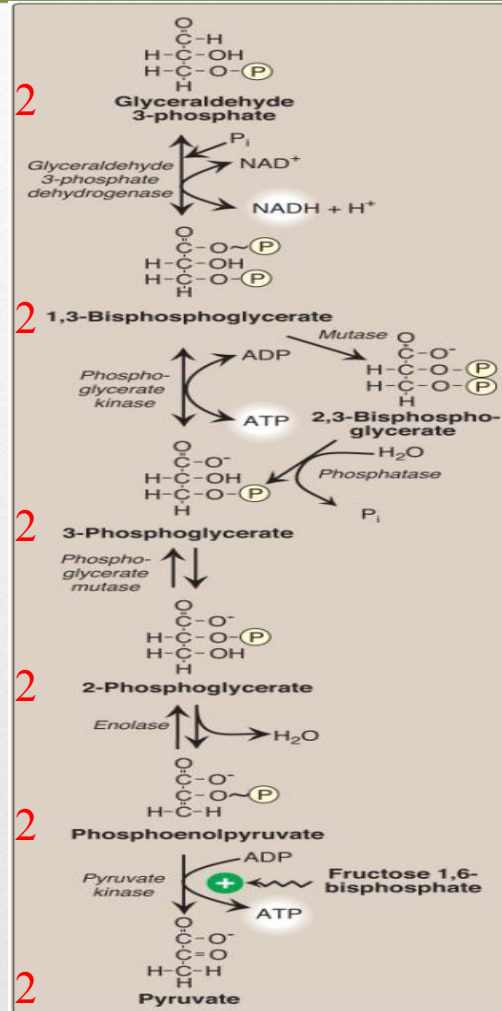
# Aerobic Glycolysis

## (Reactions: 3<sup>rd</sup> – 5<sup>th</sup>)



# Aerobic Glycolysis

(Reactions: 6<sup>th</sup> – 10<sup>th</sup>)





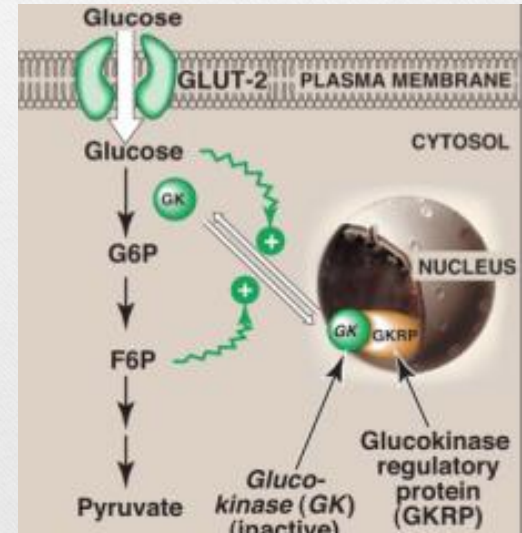
# Regulation: Glucokinase/Hexokinase

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- **Hexokinase** – it is inhibited by the reaction product, glucose-6-P which accumulates when further metabolism of this hexose is reduced
- **Glucokinase** – It is inhibited indirectly by Fructose-6-P and is indirectly stimulated by glucose

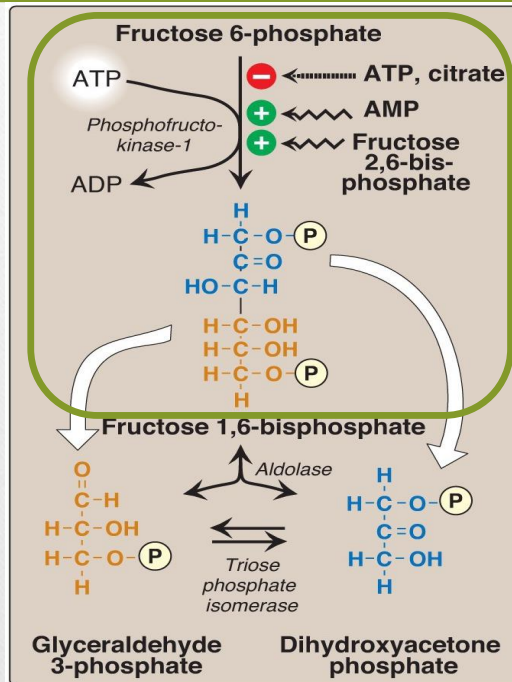
# Glucokinase (GK) Regulation

- In the presence of high fructose-6-phosphate, GK translocates and binds tightly to **GKRP** (glucokinase regulatory protein) in the nucleus, making it inactive
- When glucose levels are high in blood and hepatocytes (GLUT-2), GK is released from GKRP and enters the cytosol



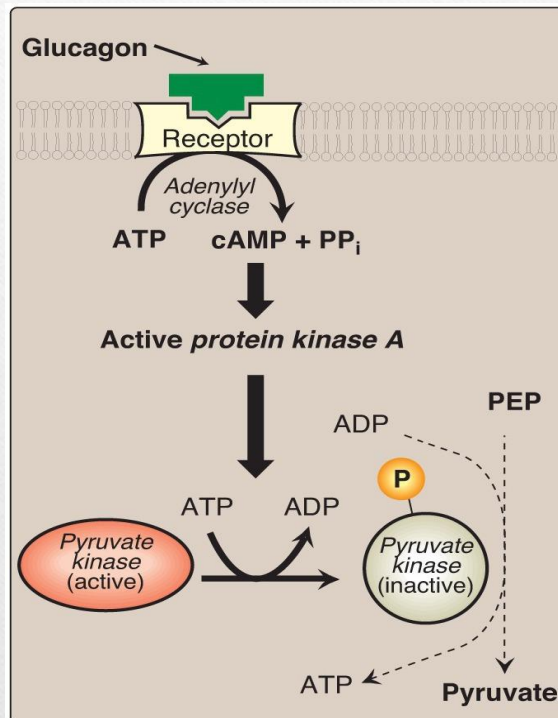


# Regulation: PFK-1





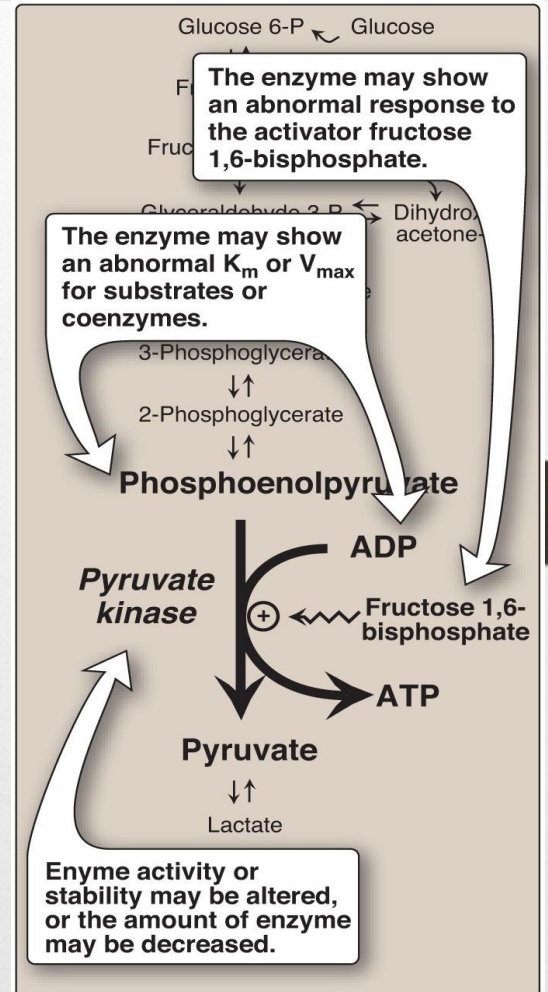
# Pyruvate Kinase Covalent Modification



# Pyruvate Kinase Deficiency Hemolytic Anemia

**PK Mutation may lead to:**

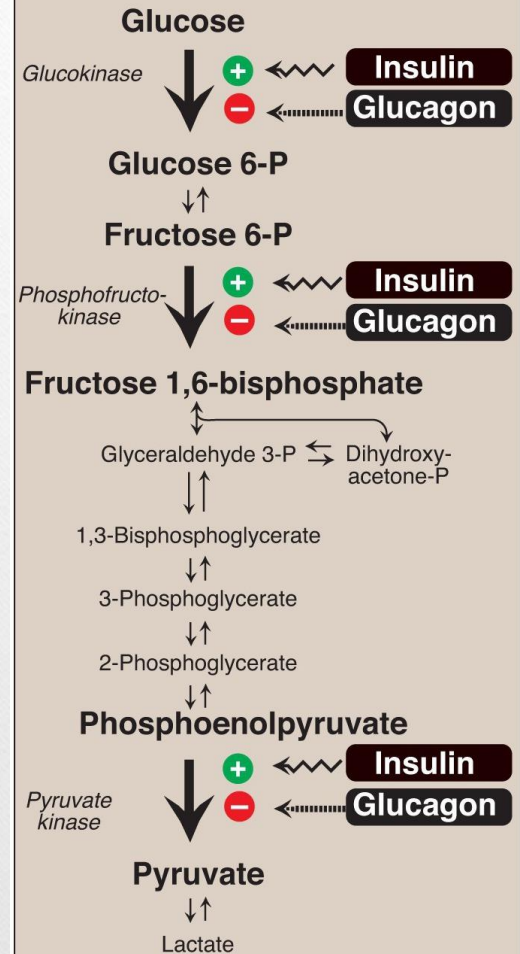
1. Altered Enz. Kinetics.
2. Altered response to activator.
3. Decreased the amount of the Enz. or its stability



# Long-Term Regulation of Glycolysis

**Insulin:** Induction

**Glucagon:** Repression





# Summary

## (Regulation of Glycolysis)

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### **Regulatory Enzymes (Irreversible reactions):**

Glucokinase/hexokinase

PFK-1

Pyruvate kinase

### **Regulatory Mechanisms:**

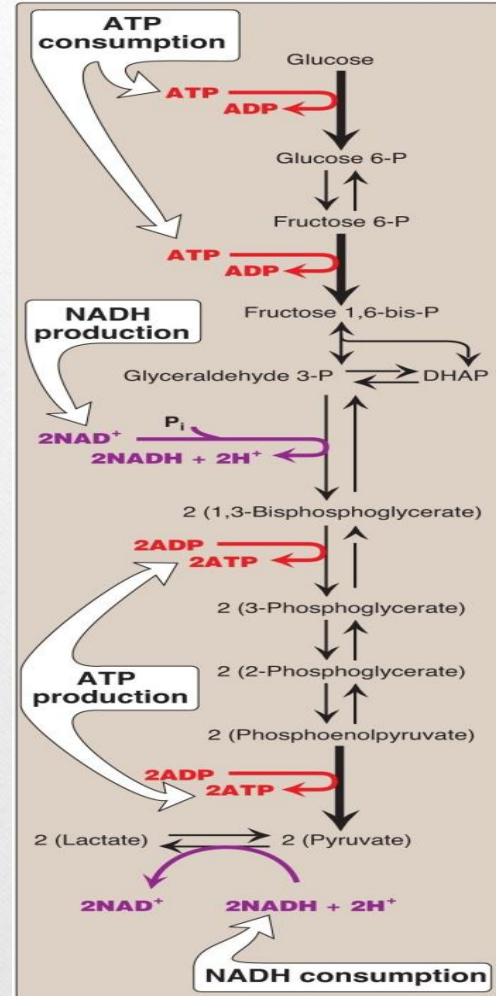
**Rapid, short-term:** Allosteric, Covalent modifications

**Slow, long-term:** Induction/repression

Apply the above mechanisms for each enzyme where applicable

# Glycolysis

For each NADH, 3 ATP will be produced by ETC in the mitochondria





# Substrate-level phosphorylation vs. Oxidative phosphorylation

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- **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



# Aerobic Glycolysis

## (Net ATP produced)

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### ATP Consumed:

2      ATP

### ATP Produced:

Substrate-level       $2 \times 2 = 4$       ATP

Oxidative-level       $2 \times 3 = 6$       ATP

Total      10      ATP

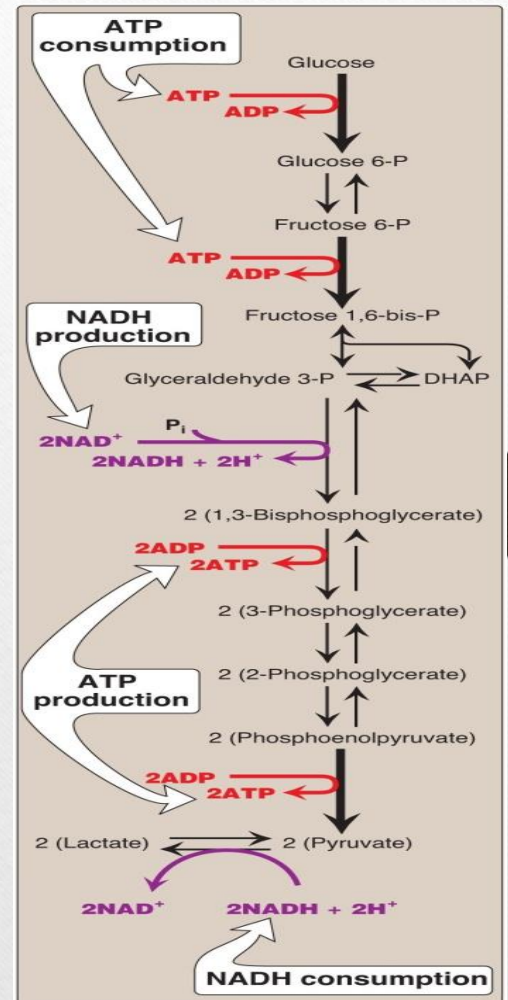
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Net:       $10 - 2 = 8$       ATP

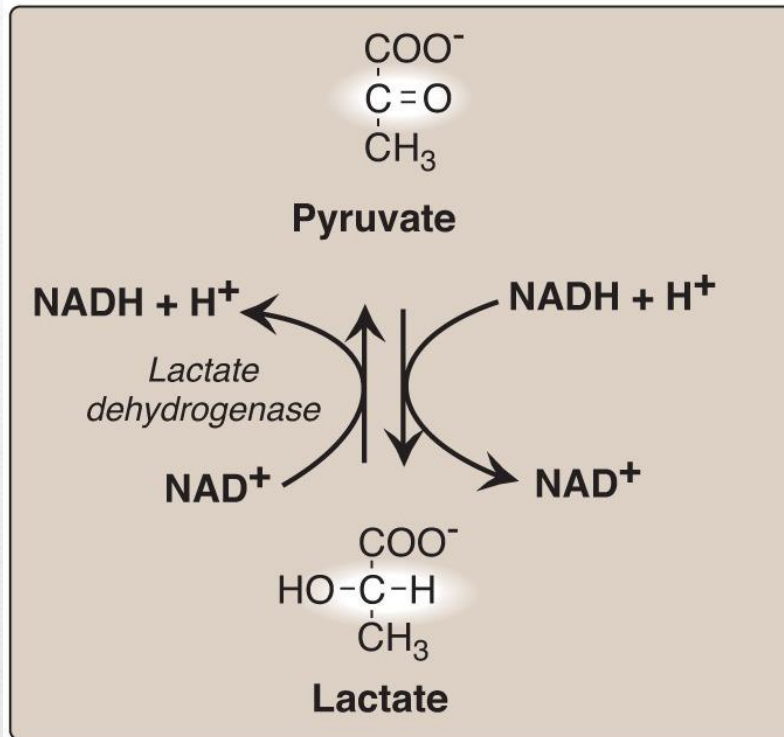
# Anaerobic Glycolysis

- **NADH produced** cannot be used by ETC for ATP production.  
(No O<sub>2</sub> and/or No mitochondria)
- **Less ATP production**, as compared to aerobic glycolysis.
- **Lactate is an obligatory end product, Why?**

*Because if not formed, All cellular NAD<sup>+</sup> will be converted to NADH, with no means to replenish the cellular NAD → Glycolysis stops → death of the cell*



# Lactate Dehydrogenase





# Anaerobic Glycolysis

## (Net ATP produced)

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### ATP Consumed:

2      ATP

### ATP Produced:

Substrate-level       $2 \times 2 = 4$       ATP

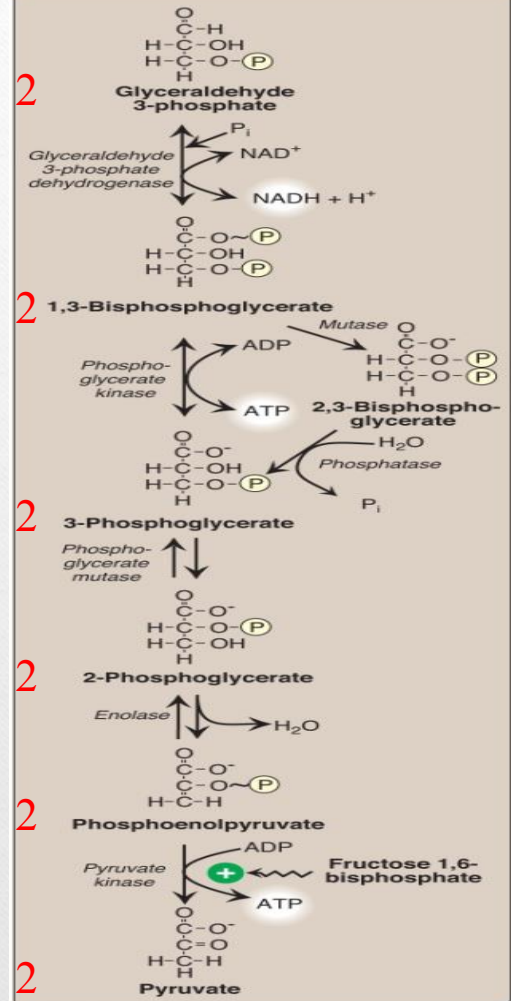
Oxidative-level       $2 \times 3 = 6$       ATP

Total      4      ATP

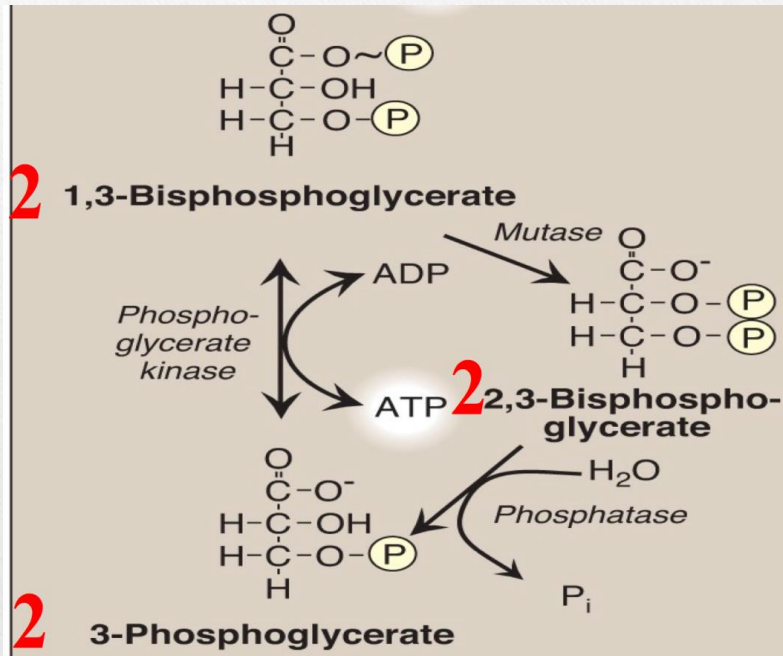
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Net:       $4 - 2 = 2$       ATP

# Anaerobic Glycolysis in RBCs (2,3-BPG Shunt)



# Anaerobic Glycolysis in RBCs (2,3-BPG Shunt)





# Glycolysis in RBCs

## (Net ATP produced)

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### ATP Consumed:

2 ATP

### ATP Produced:

Substrate-level	or	$2 \times 2 = 4$	ATP
		$1 \times 2 = 2$	
Oxidative-level		$2 \times 3 = 6$	ATP
Total		4 or 2	ATP

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Net:		$4 - 2 = 2$	ATP
		$2 - 2 = 0$	ATP

# Glycolysis in RBCs

## (Summary)

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### **End product:**

Lactate

No net production or consumption of NADH

### **Energy yield:**

If no 2,3-BPG is formed: 2 ATP

If 2,3-BPG shunt occurs: 0 ATP

### **PK Deficiency hemolytic anemia depends on:**

Degree of PK Deficiency

Compensation by 2,3-BPG

# Take Home Messages

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- ❑ 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
- ❑ 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



# Take Home Messages

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❑ **Net energy produced in:**

Aerobic glycolysis: 8 ATP

Anaerobic glycolysis: 2 ATP

❑ **Net energy produced in glycolysis in RBCs:**

Without 2,3 BPG synthesis: 2 ATP

With 2,3 BPG synthesis: 0 ATP

# Reference

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Lippincott Illustrated Review of Biochemistry, 6<sup>th</sup> edition, 2014, Unit 2, Chapter 8, Pages 91-108.