Glucose Metabolism (Glycolysis)

Objectives

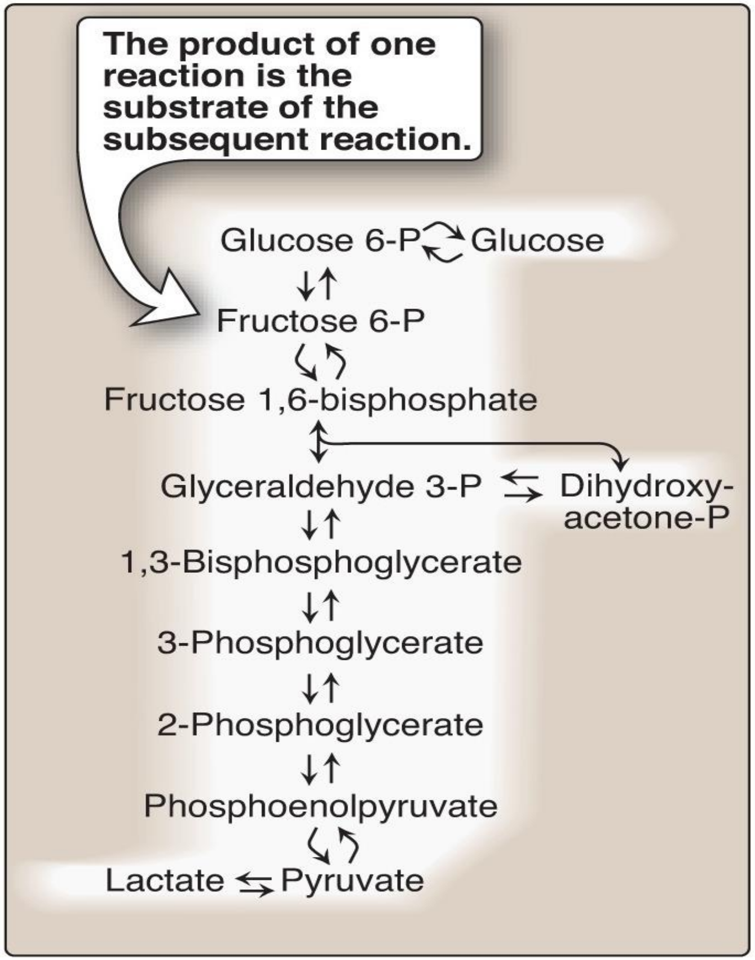
By the end of this lecture, students are expected to:

- 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

- 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



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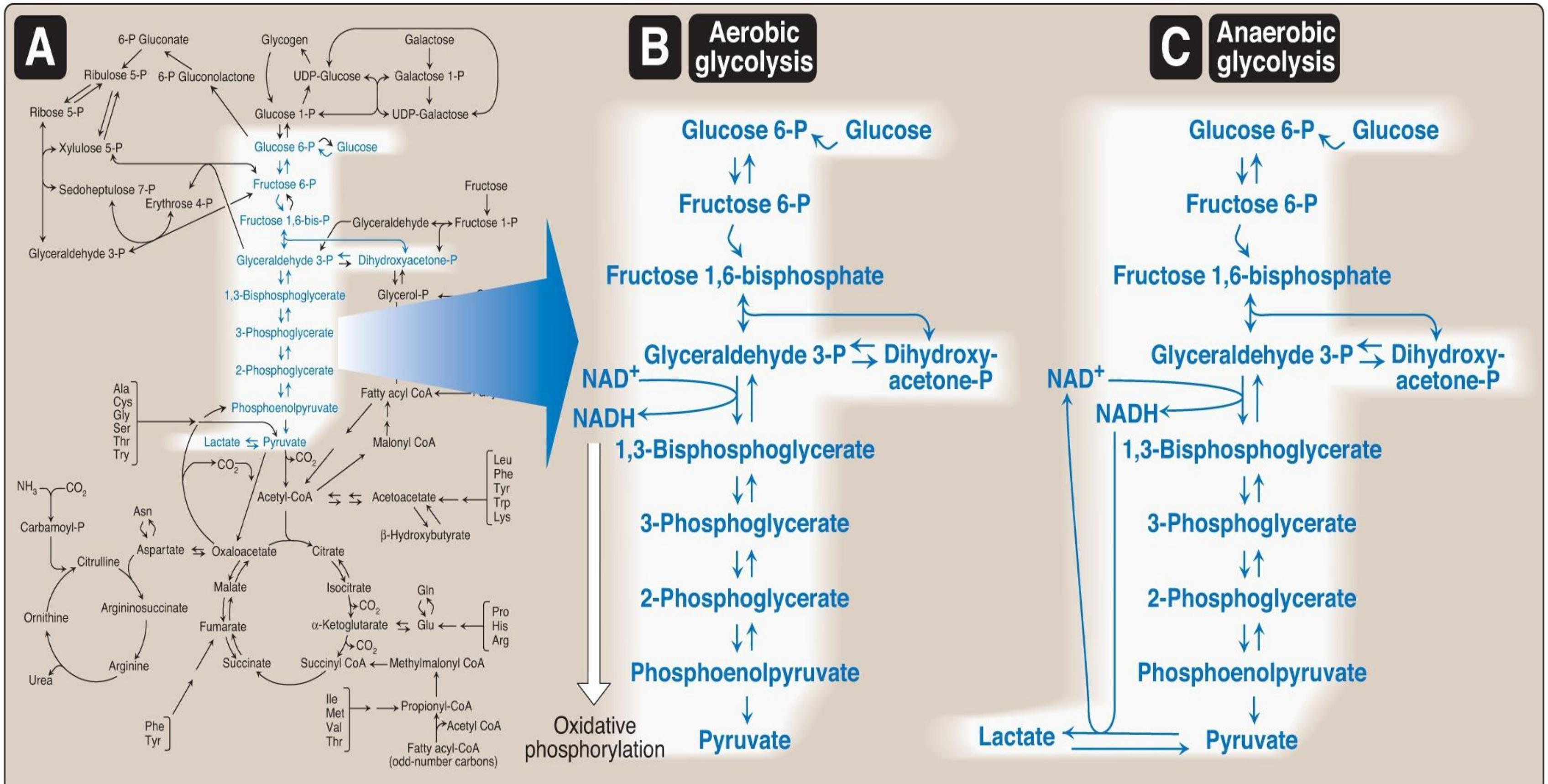
Aerobic Vs Anaerobic Glycolysis



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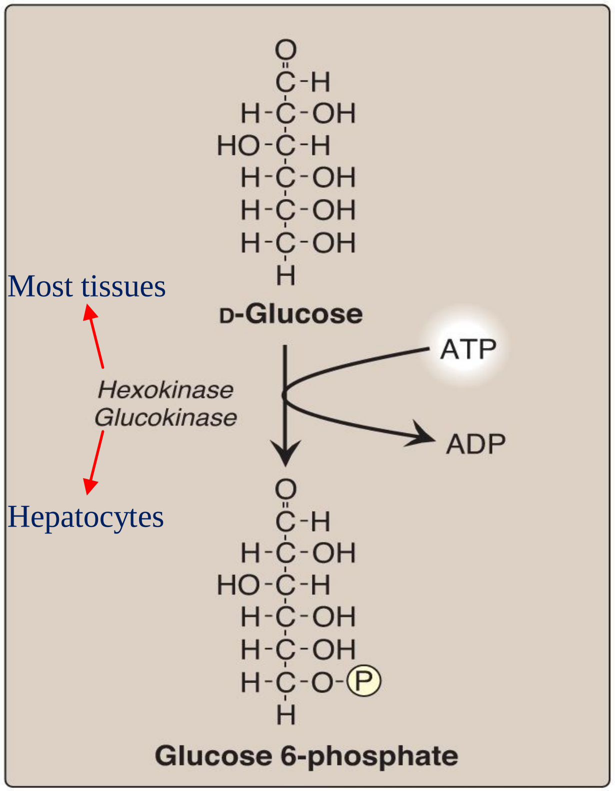
Aerobic Glycolysis

(1st and 2nd reactions)



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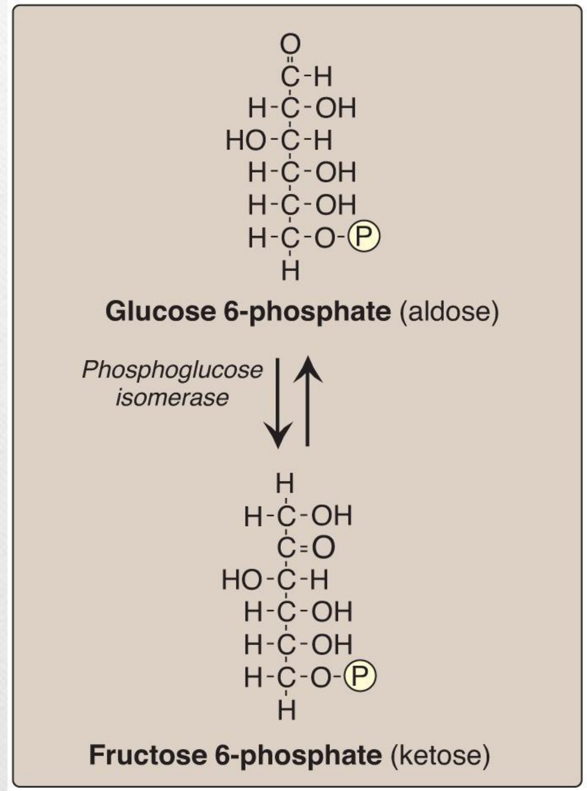

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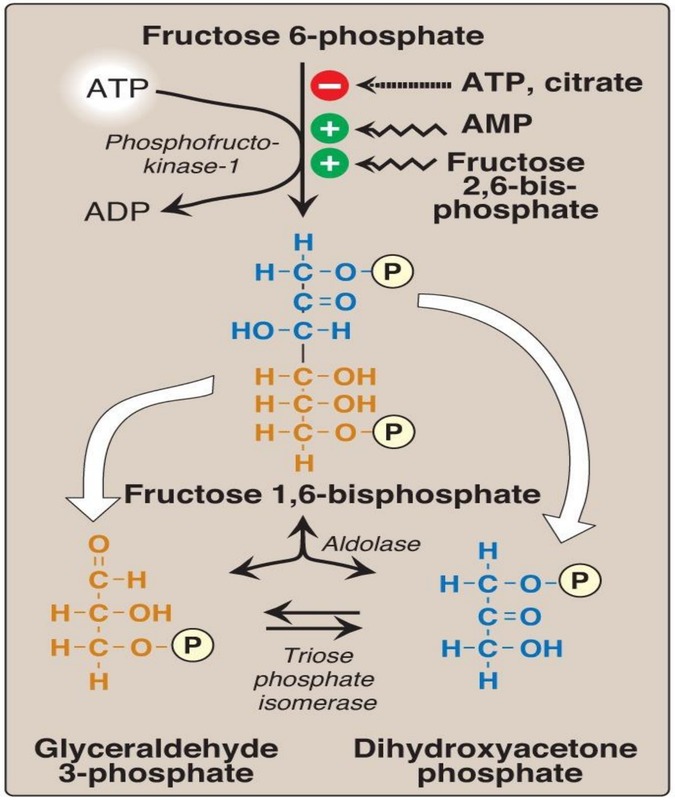
Aerobic Glycolysis
(Reactions: 3rd – 5th)



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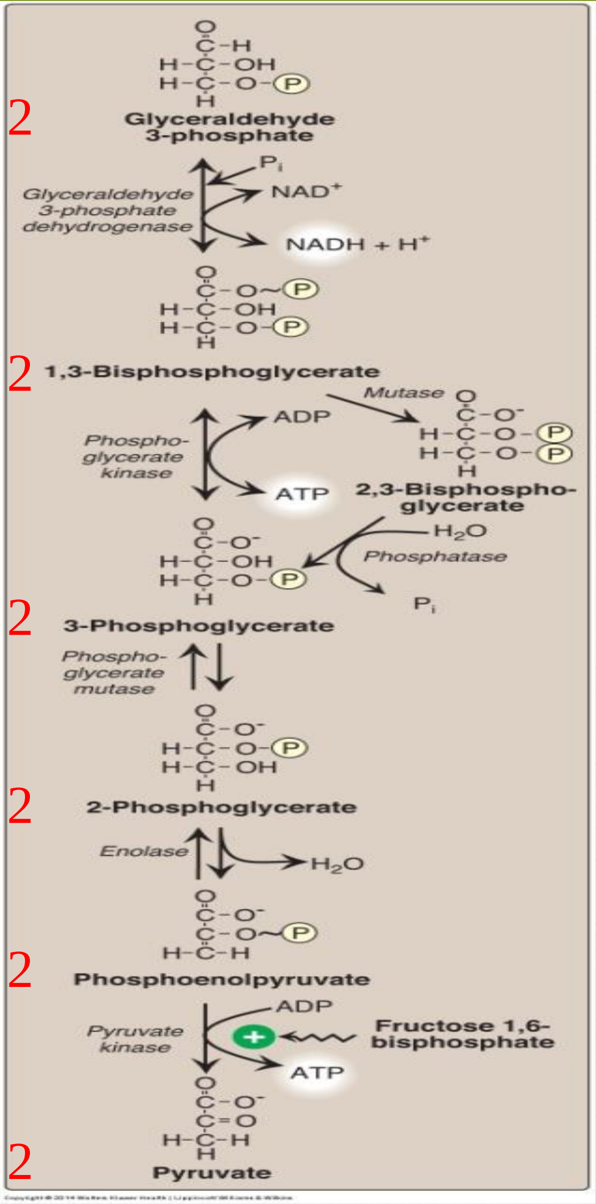
Aerobic Glycolysis
(Reactions: 6th – 10th)



Regulation: Glucokinase/Hexokinase

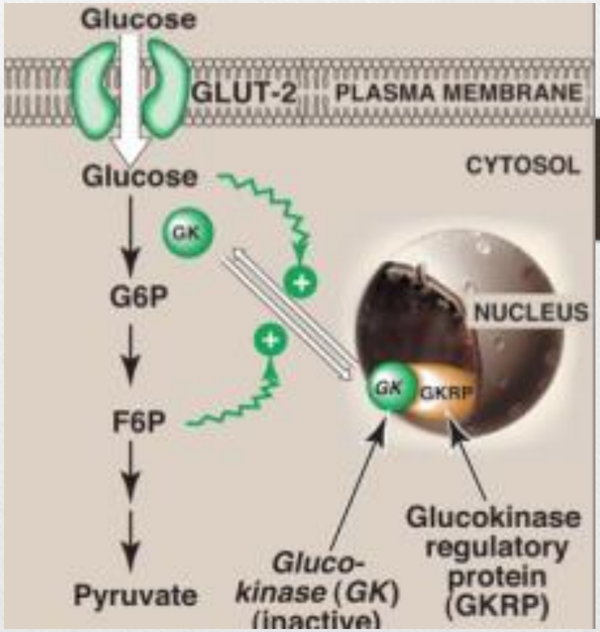
- Hexokinase – it is inhibited by the reaction product, glucose-6-P which accumulates when further metabolism of this hexose is reduced

- Glucokinase – It is inhibited indirectly by Fructose-6-P and is indirectly stimulated by glucose

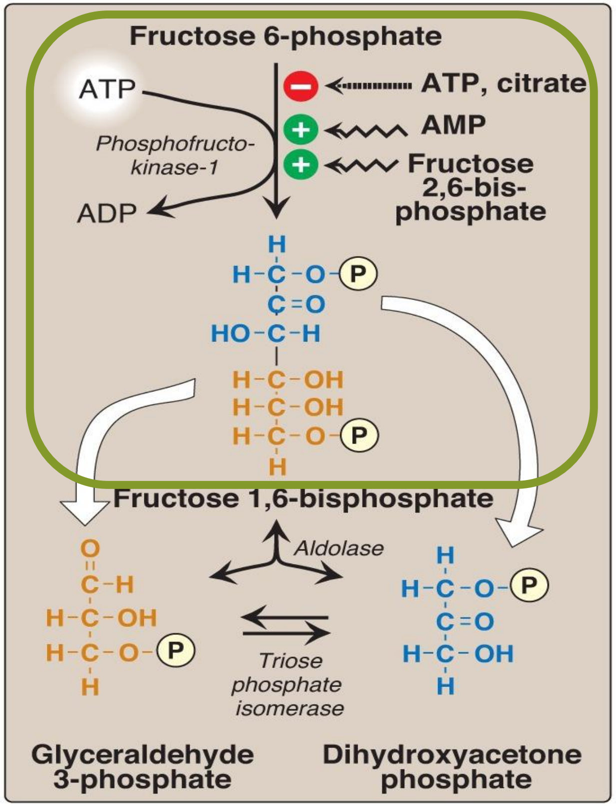
Glucokinase (GK) Regulation

- 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



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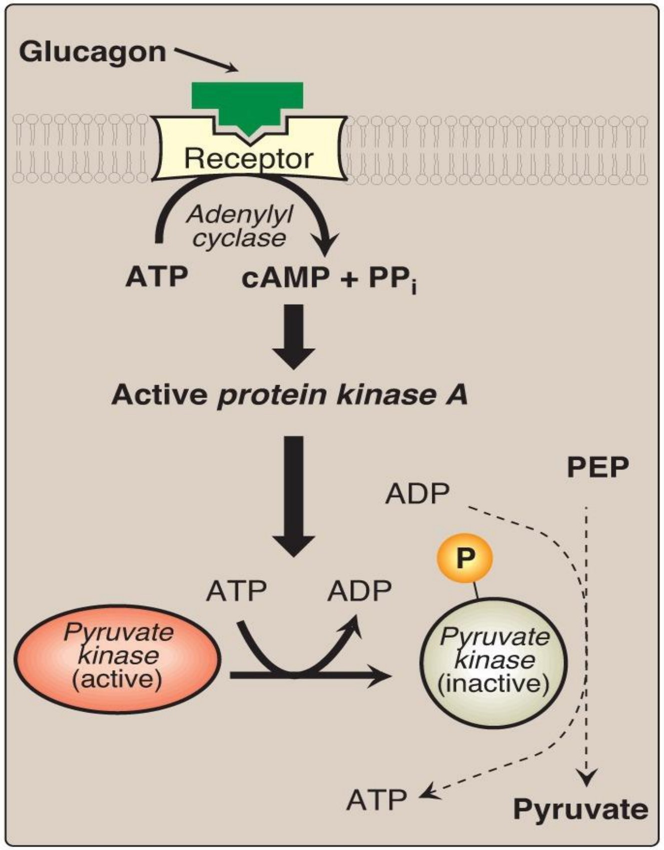
Pyruvate Kinase Covalent Modification



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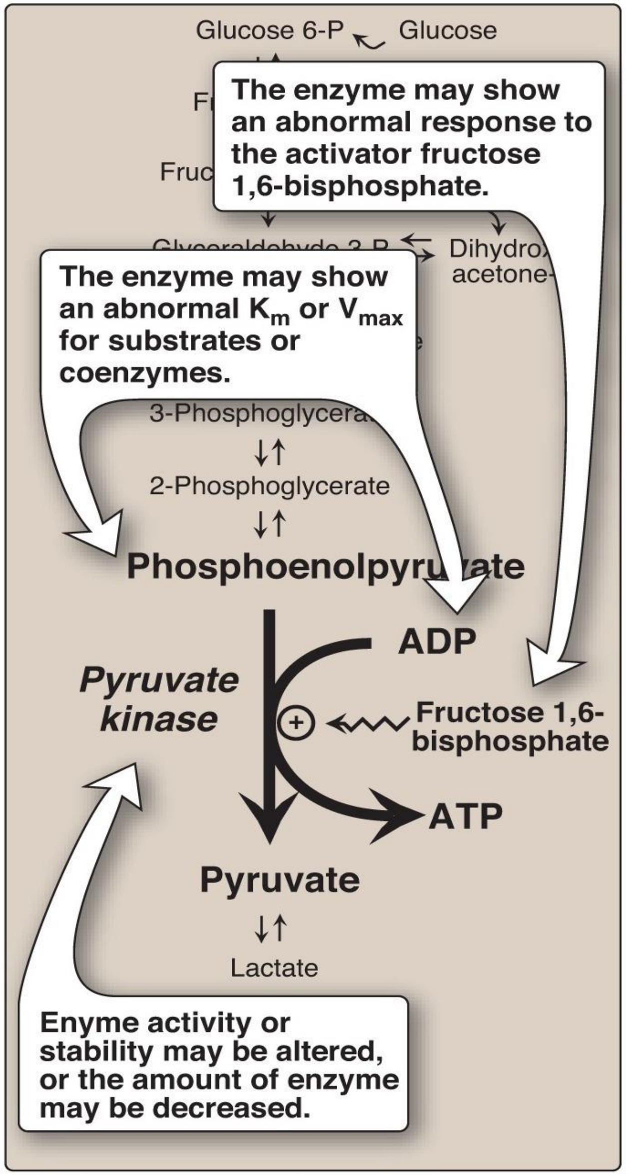
Pyruvate Kinase Deficiency Hemolytic Anemia

PK Mutation may lead to:

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



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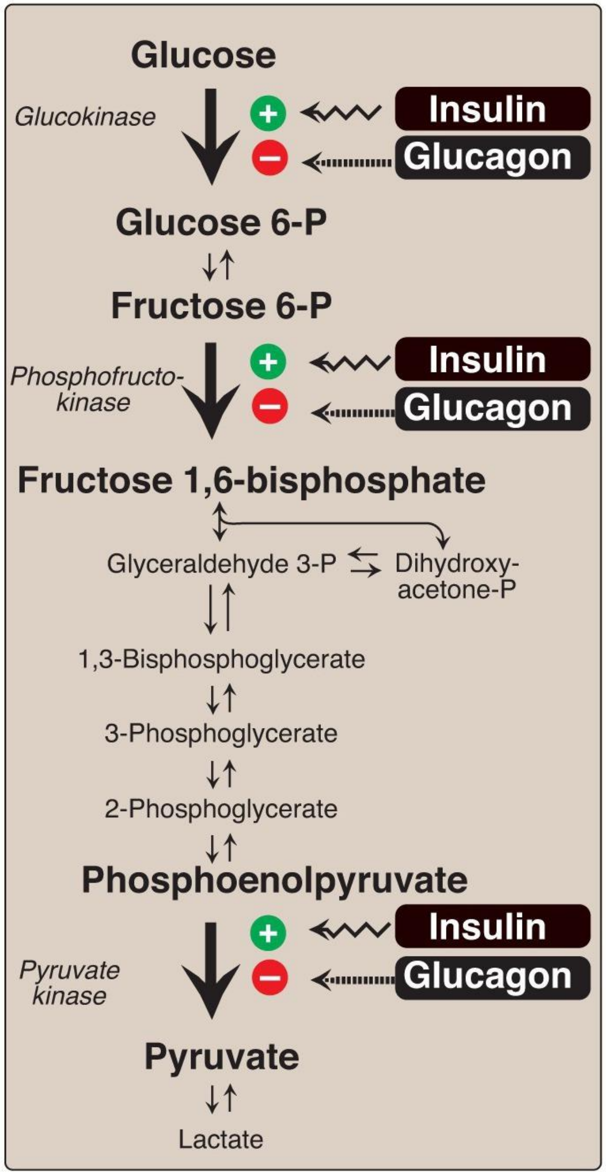
Long-Term Regulation of Glycolysis

Insulin: Induction

Glucagon: Repression



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Summary
(Regulation of Glycolysis)

Regulatory Enzymes (Irreversible reactions):

- Glucokinase/hexokinase
- PFK-1
- Pyruvate kinase

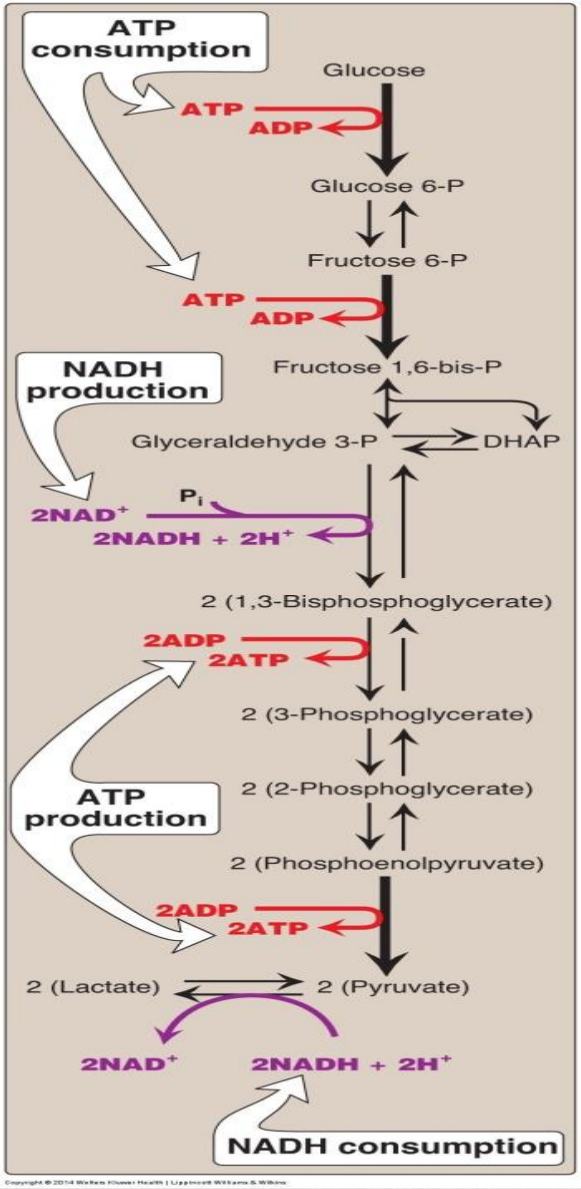
Regulatory Mechanisms:

- **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

- 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)

ATP Consumed:

		2	ATP

ATP Produced:

Substrate-level	2 X 2 =	4	ATP
Oxidative-level	2 X 3 =	6	ATP
Total		10	ATP

Net: 10 – 2 = 8 ATP

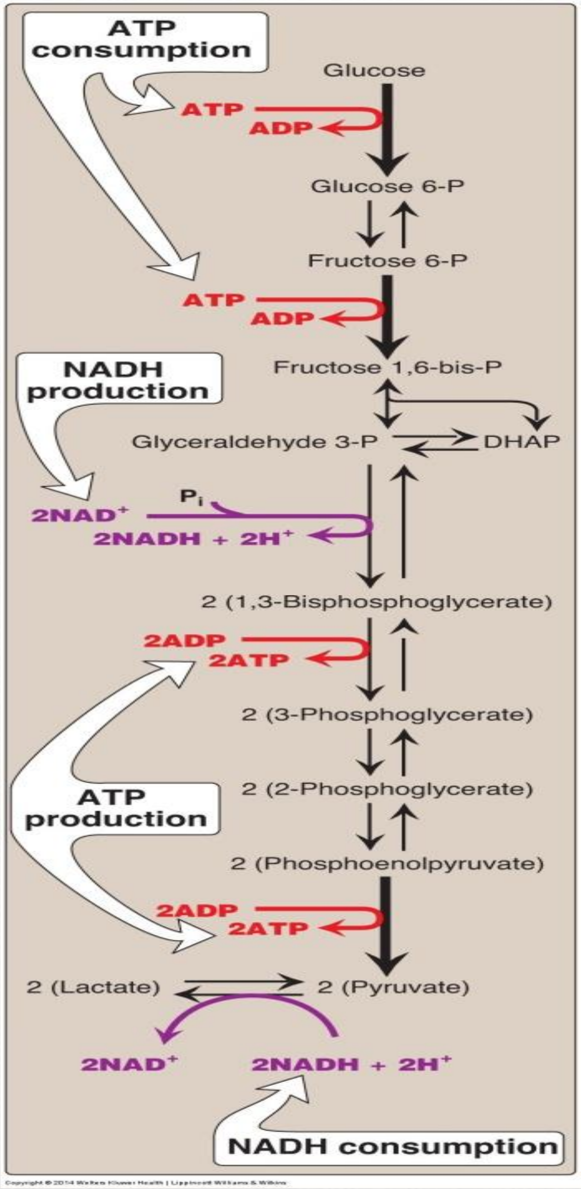
Anaerobic Glycolysis

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

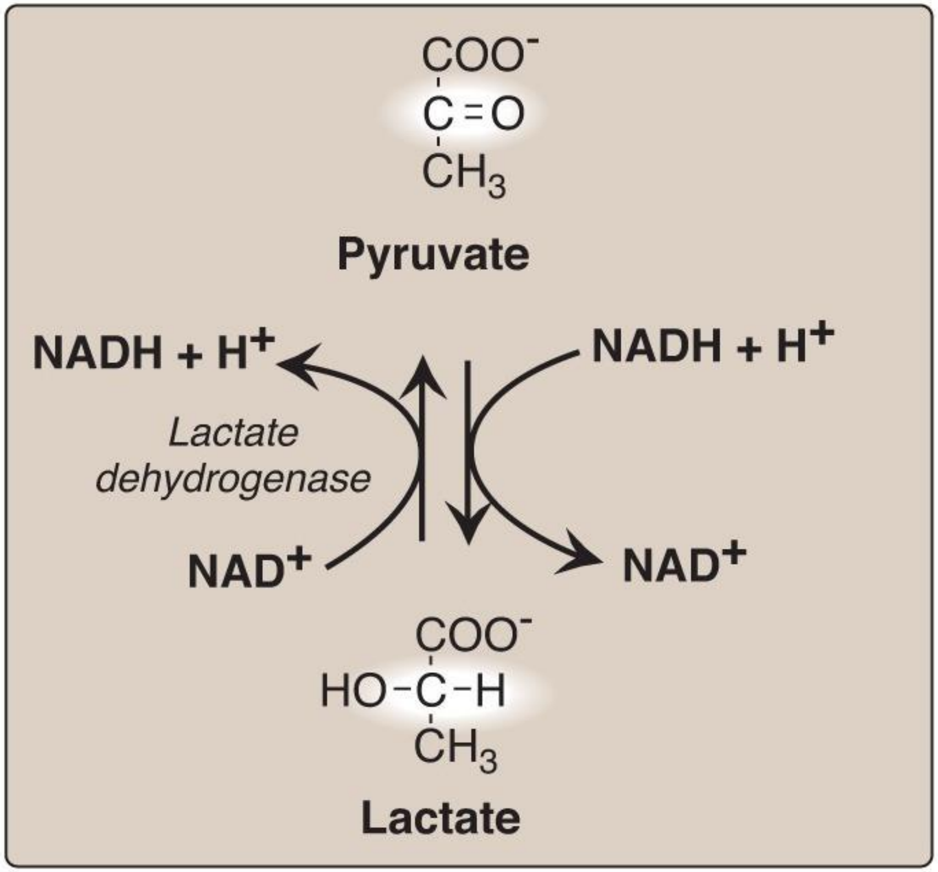
- Less ATP production, as compared to aerobic glycolysis.

- Lactate is an obligatory end product, **Why?**

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



Lactate Dehydrogenase



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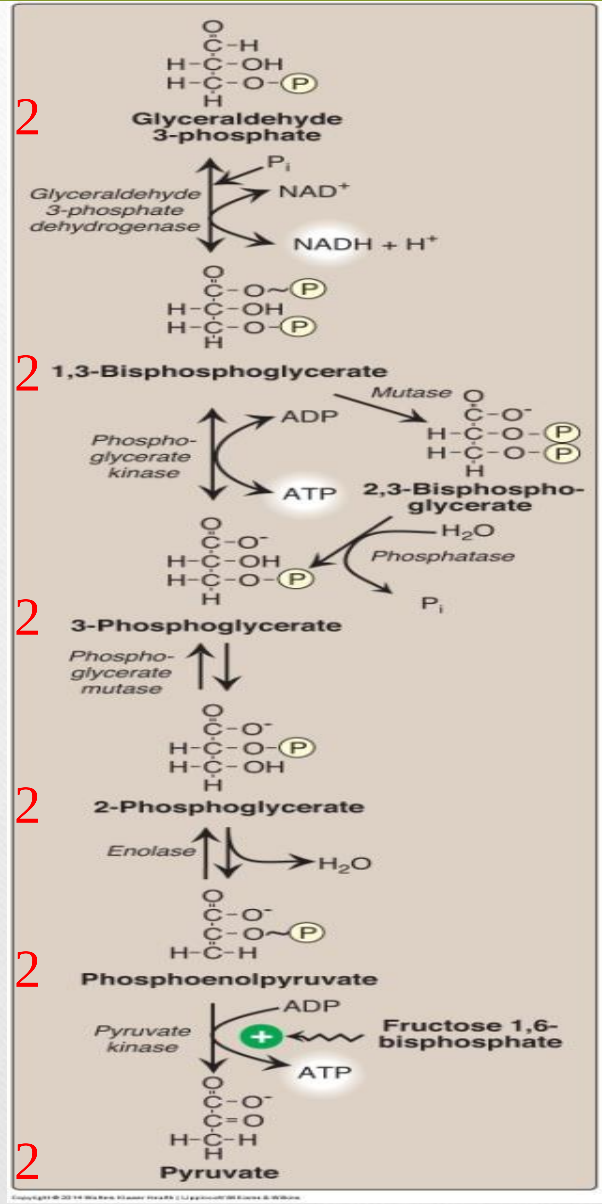
Anaerobic Glycolysis
(Net ATP produced)

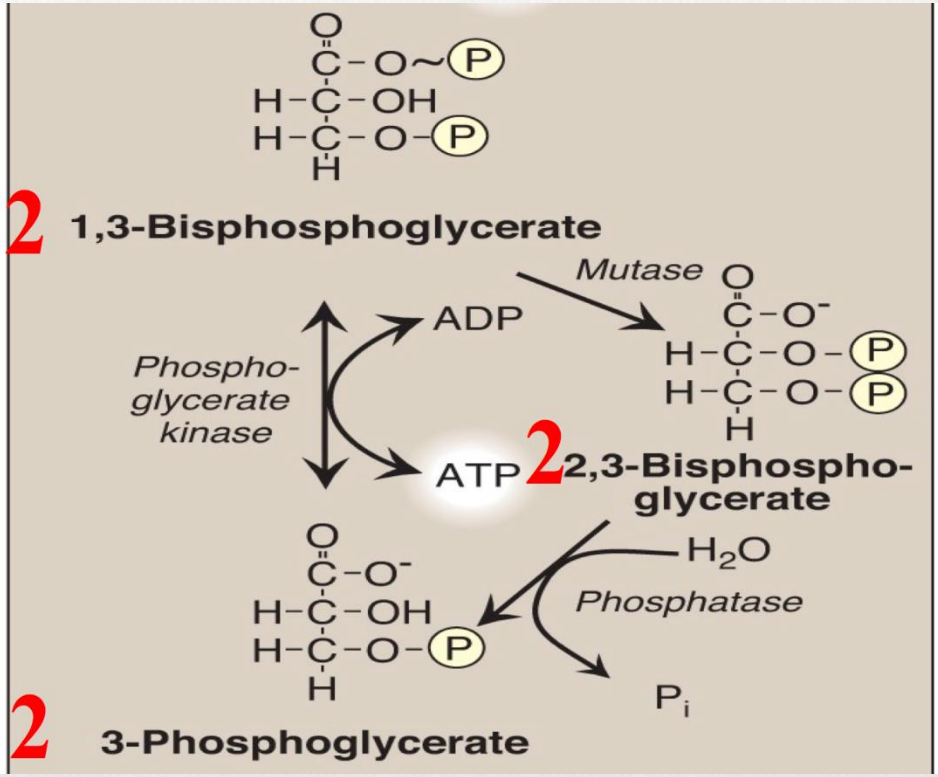
ATP Consumed:			
		2	ATP
ATP Produced:			
Substrate-level	2 X 2 =	4	ATP
Oxidative-level	2 X 3 =	6	ATP
Total		4	ATP
Net:	4 – 2 =	2	ATP

Anaerobic Glycolysis in RBCs

(2,3-BPG Shunt)



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



Glycolysis in RBCs
(Net ATP produced)

ATP Consumed:

			2	ATP
ATP Produced:				
	Substrate-level	or	2 X 2 = 4	ATP
			1 X 2 = 2	
	Oxidative-level		2 X 3 = 6	ATP
	Total		4 or 2	ATP
Net:			4 – 2 = 2	ATP
			2 – 2 = 0	ATP

Glycolysis in RBCs
(Summary)

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

- 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

- **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

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