Glucose Metabolism (Glycolysis)

Objectives

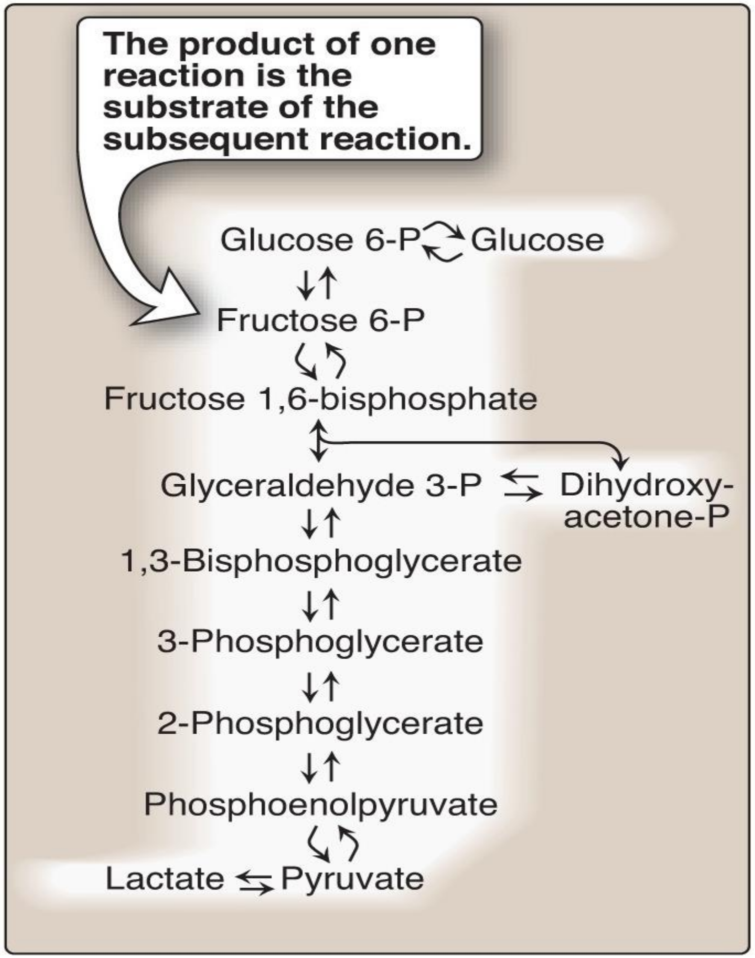
By the end of this lecture, students are expected to:

- ❑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

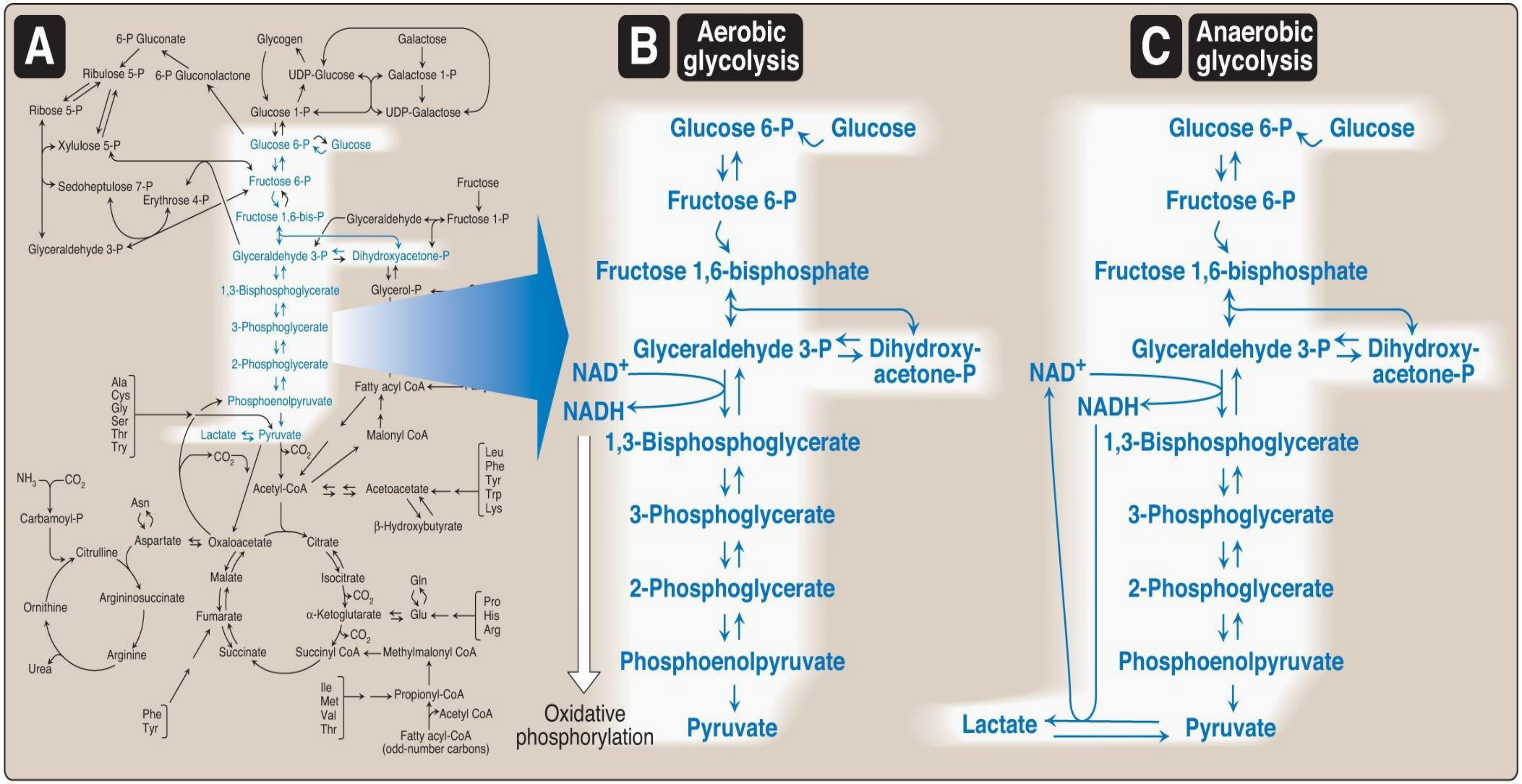
- Glycolysis, the major pathway for glucose oxidation, occurs in the cytosol of all cells.
- It is unique, in that it can function either aerobically or anaerobically, depending on the availability of oxygen and intact mitochondria.
- It allows tissues to survive in presence or absence of oxygen, e.g., skeletal muscle.
- RBCs, which lack mitochondria, are completely reliant on glucose as their metabolic fuel, and metabolizes it by anaerobic glycolysis.

Glycolysis

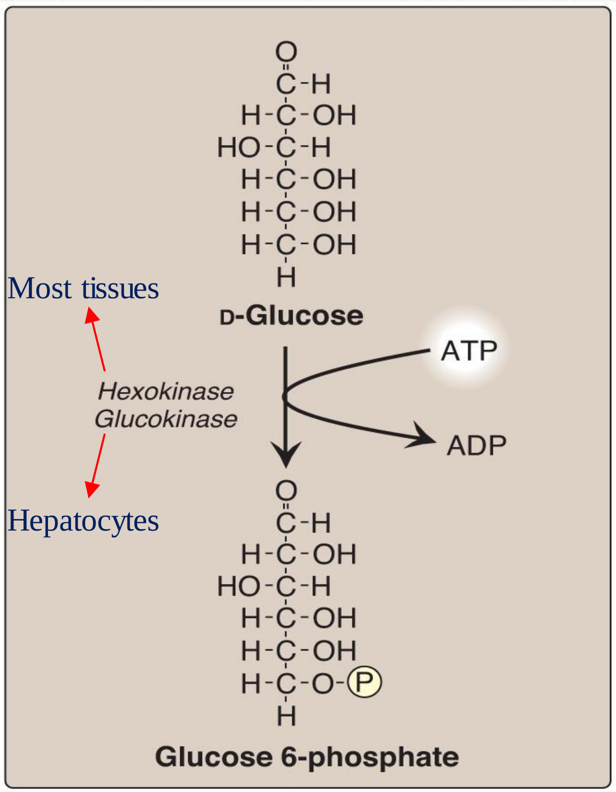


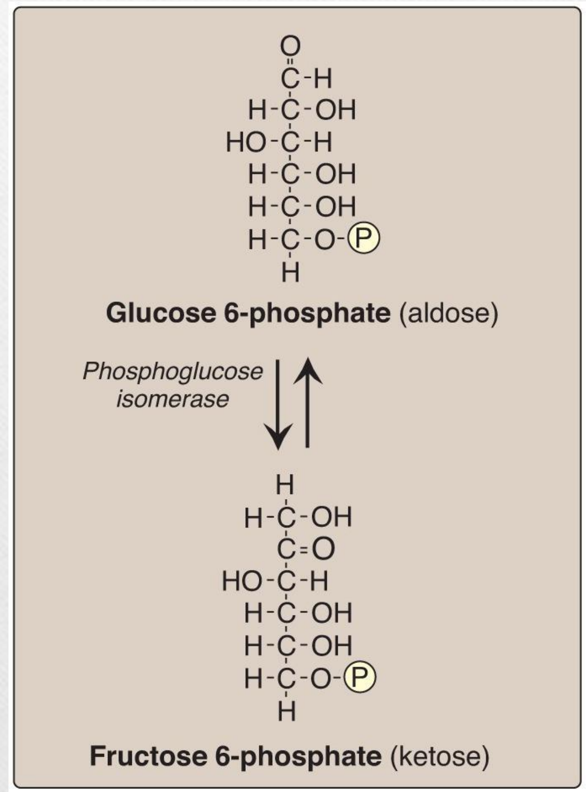
The product of one reaction is the substrate of the subsequent reaction.
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bisphosphate
Glyceraldehyde 3-P
Dihydroxy-acetone-P
1,3-Bisphosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Lactate
Pyruvate

Aerobic Vs Anaerobic Glycolysis

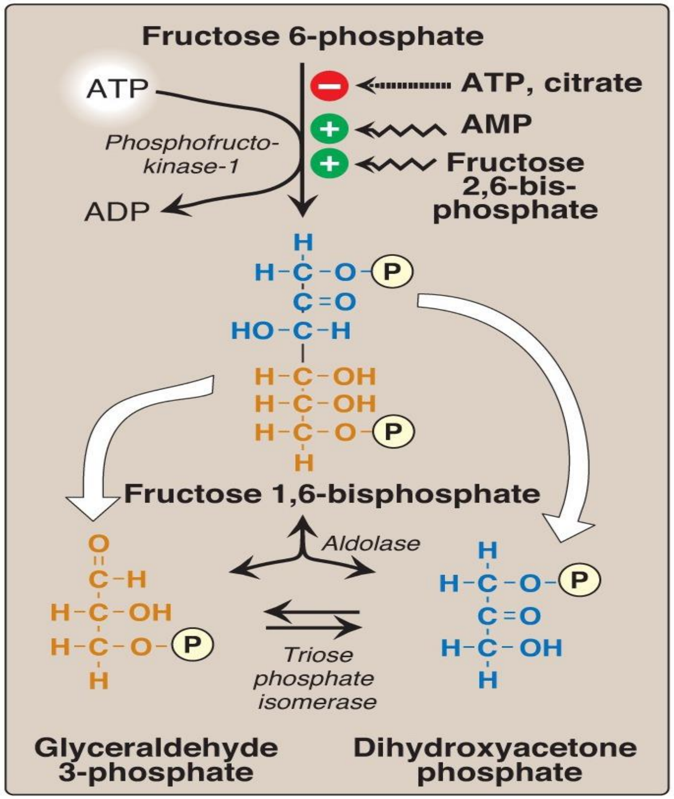


Aerobic Glycolysis
(1st and 2nd reactions)



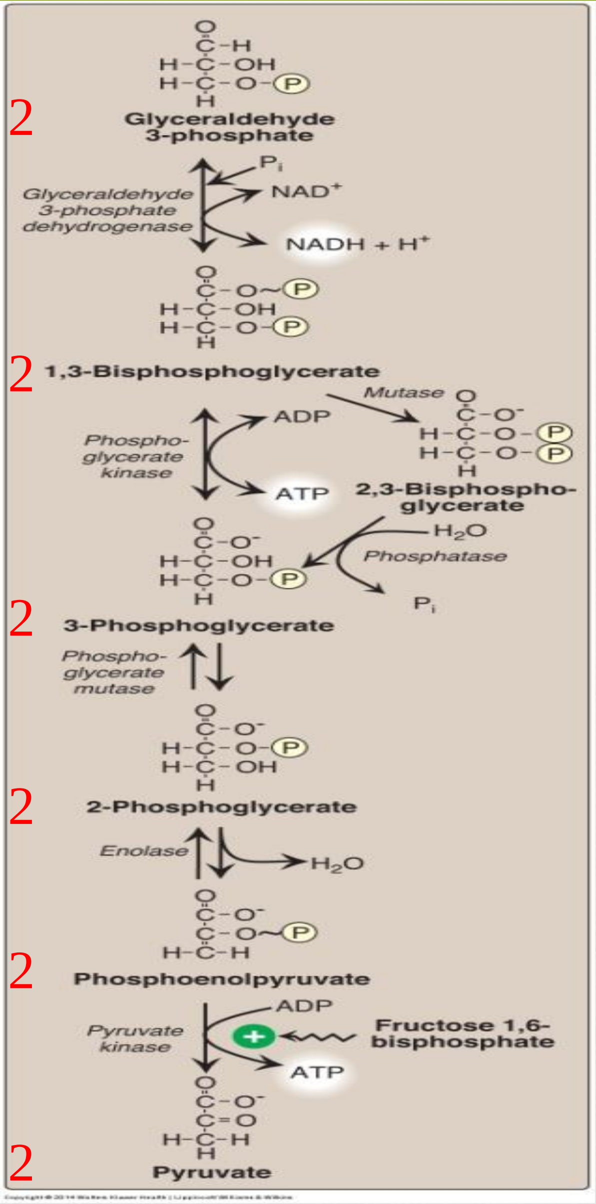


Aerobic Glycolysis
(Reactions: 3rd – 5th)



Aerobic Glycolysis

(Reactions: 6th – 10th)

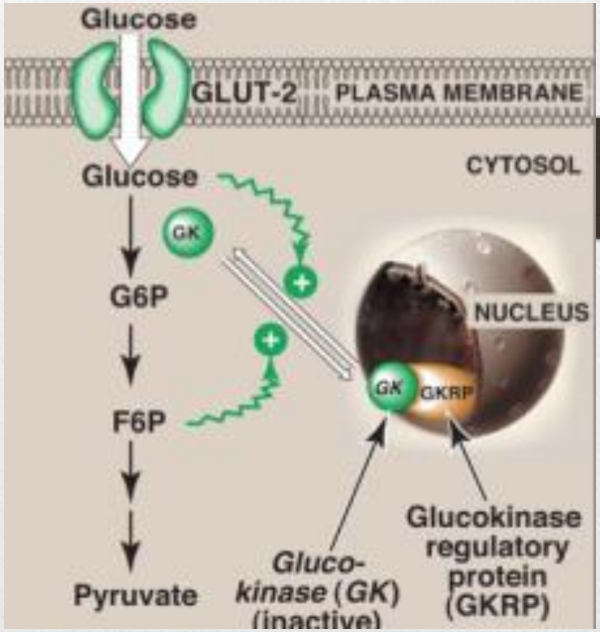


Regulation: Glucokinase/Hexokinase

- 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

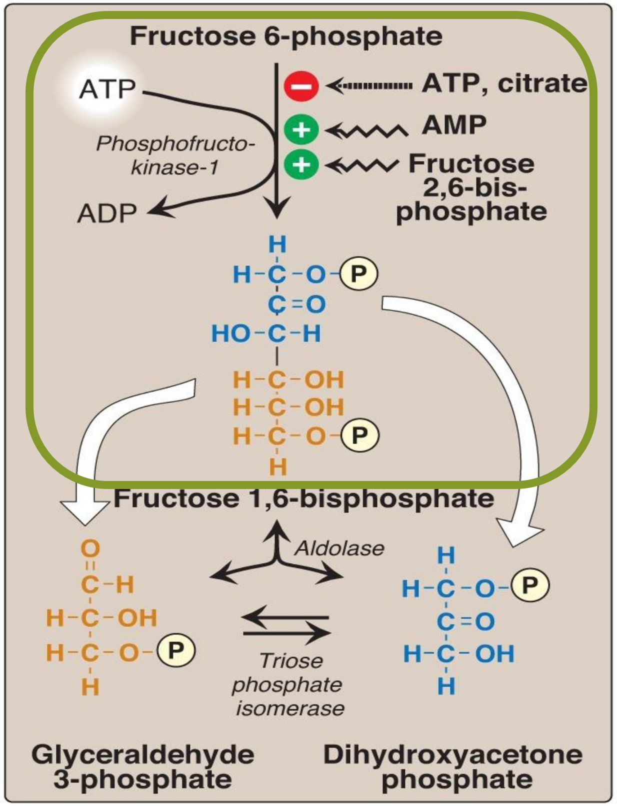
Glucokinase (GK) Regulation

- In the presence of high fructose-6-phosphate, GK translocates and binds tightly to GKRP (glucokinase regulatory protein) in the nucleus, making it inactive

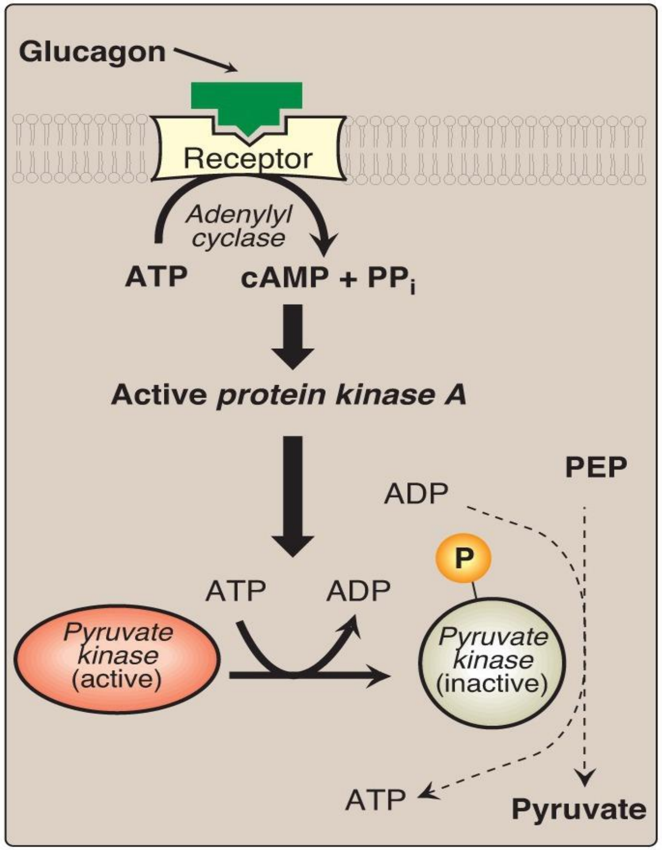


- When glucose levels are high in blood and hepatocytes (GLUT-2), GK is released from GKRP and enters the cytosol

Regulation: PFK-1



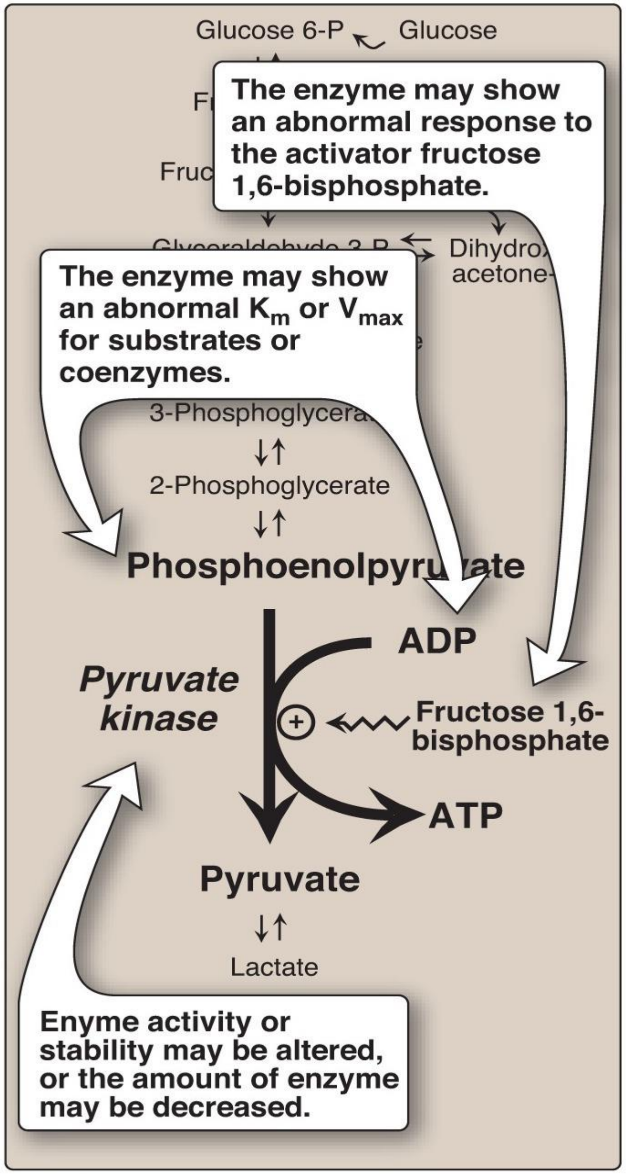
Pyruvate Kinase Covalent Modification



Pyruvate Kinase Deficiency Hemolytic Anemia

PK Mutation may lead to:

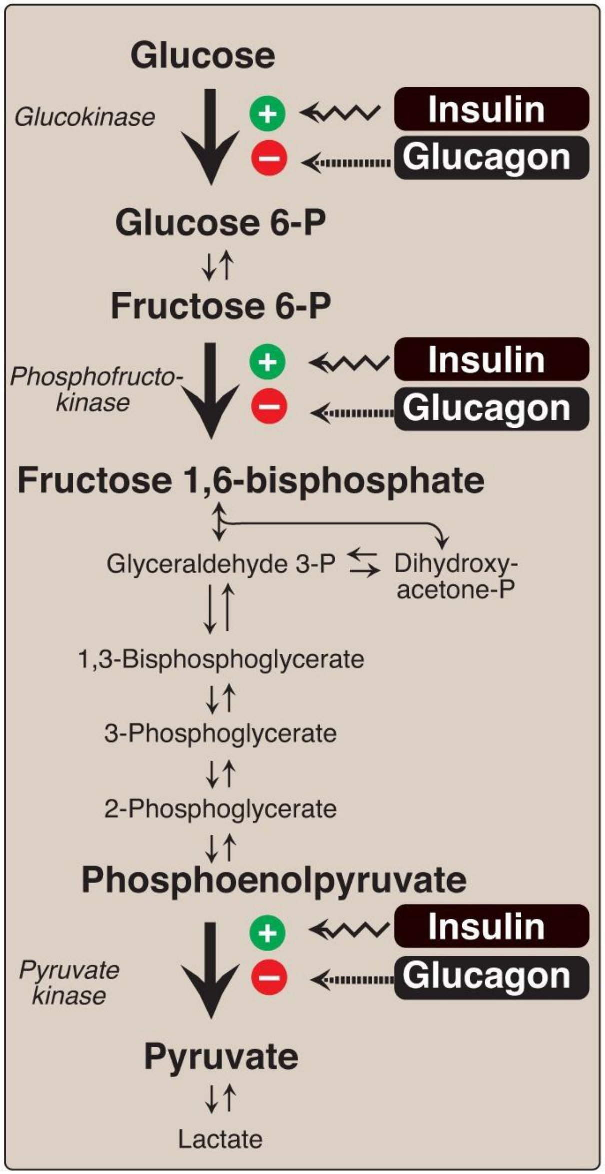
1. Altered Enz. Kinetics.
2. Altered response to activator.
3. Decreased the amount of the Enz. or its stability



Long-Term Regulation of Glycolysis

Insulin: Induction

Glucagon: Repression



Summary
(Regulation of Glycolysis)

Regulatory Enzymes (Irreversible reactions):

Glucokinase/hexokinase
PFK-1
Pyruvate kinase

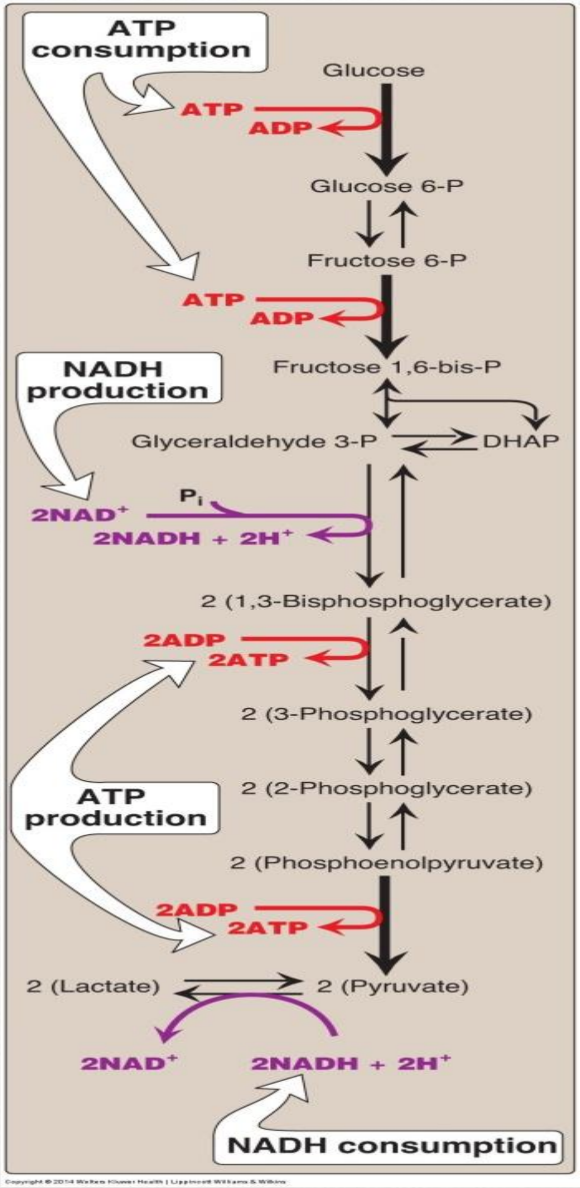
Regulatory Mechanisms:

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

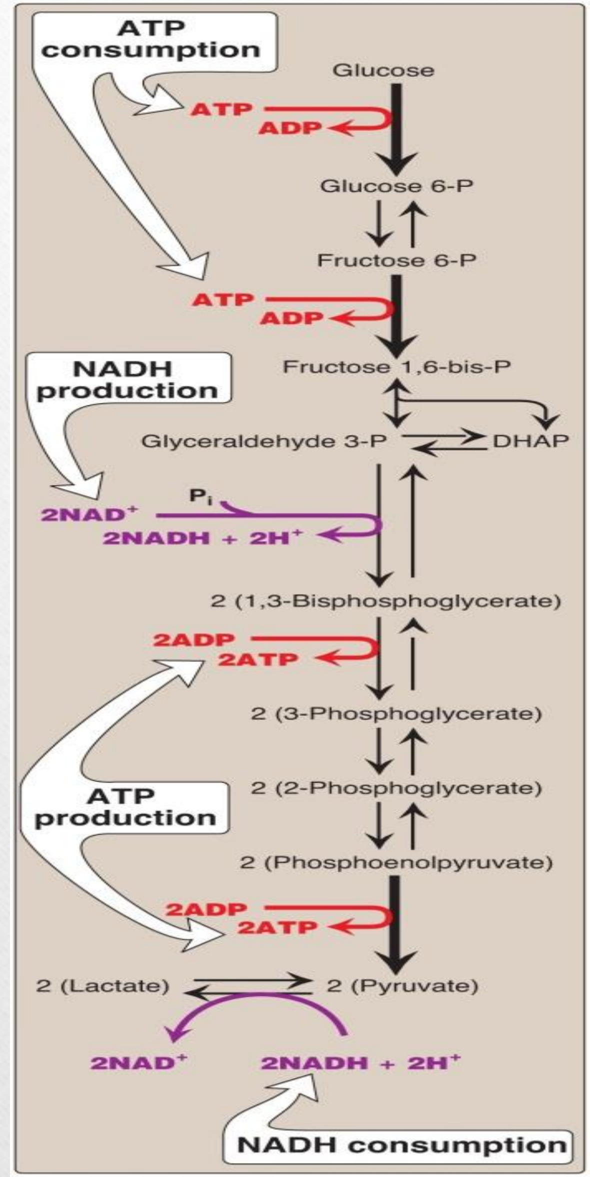
Anaerobic Glycolysis

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

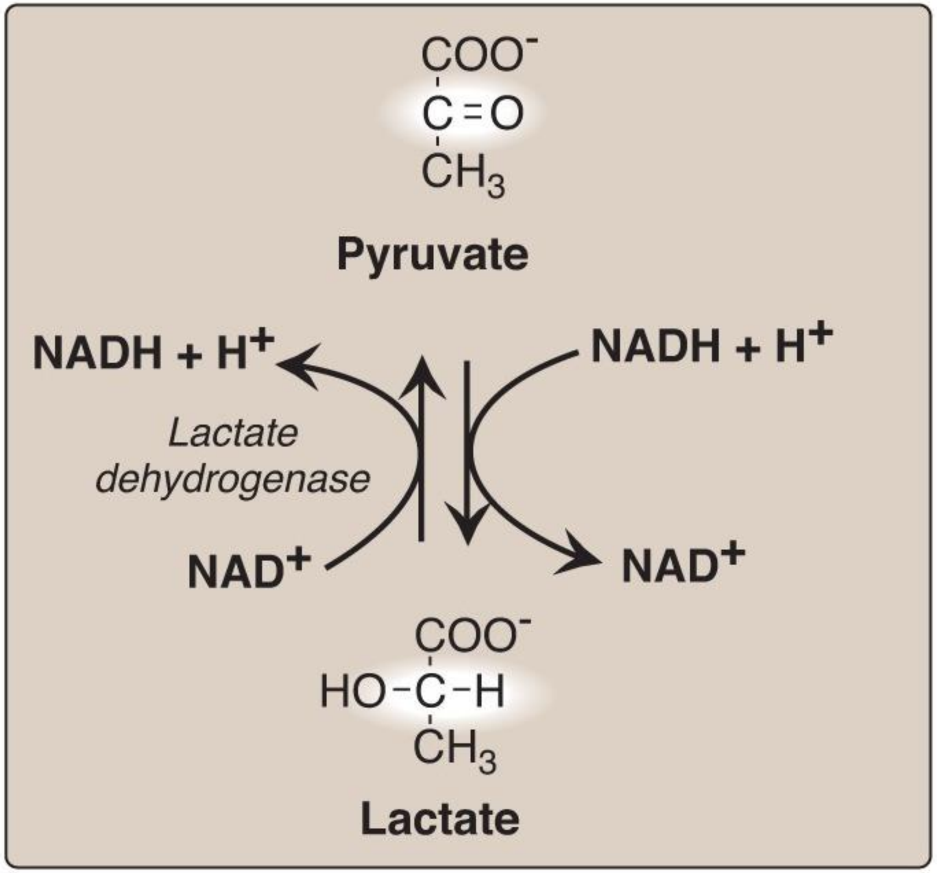
- Less ATP production, as compared to aerobic glycolysis.

- 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



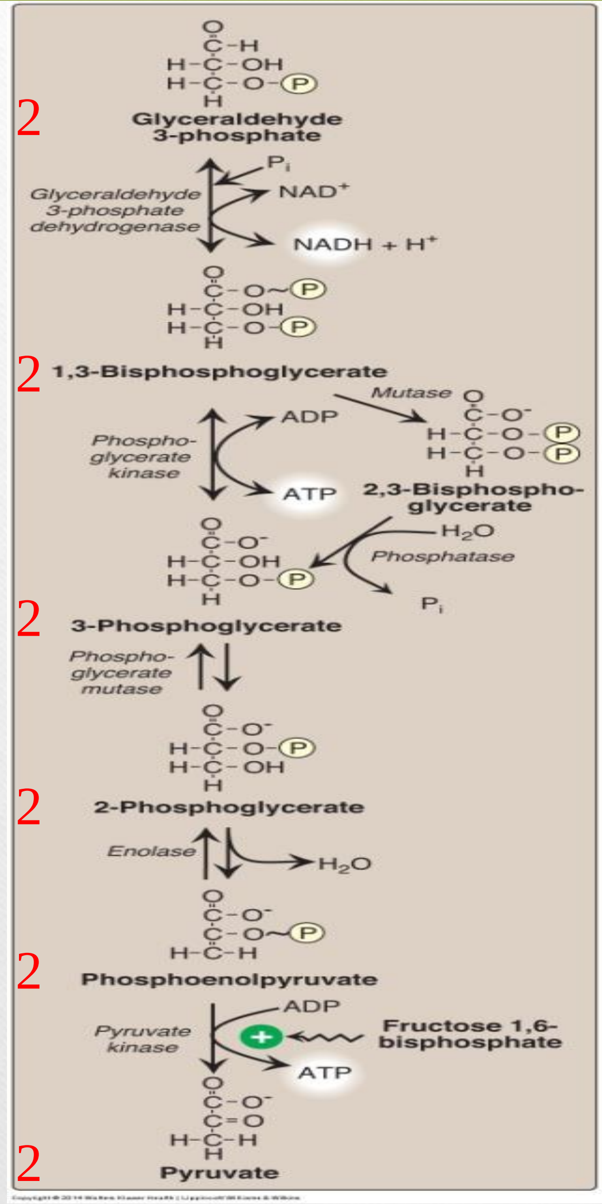
Lactate Dehydrogenase



Anaerobic Glycolysis
(Net ATP produced)

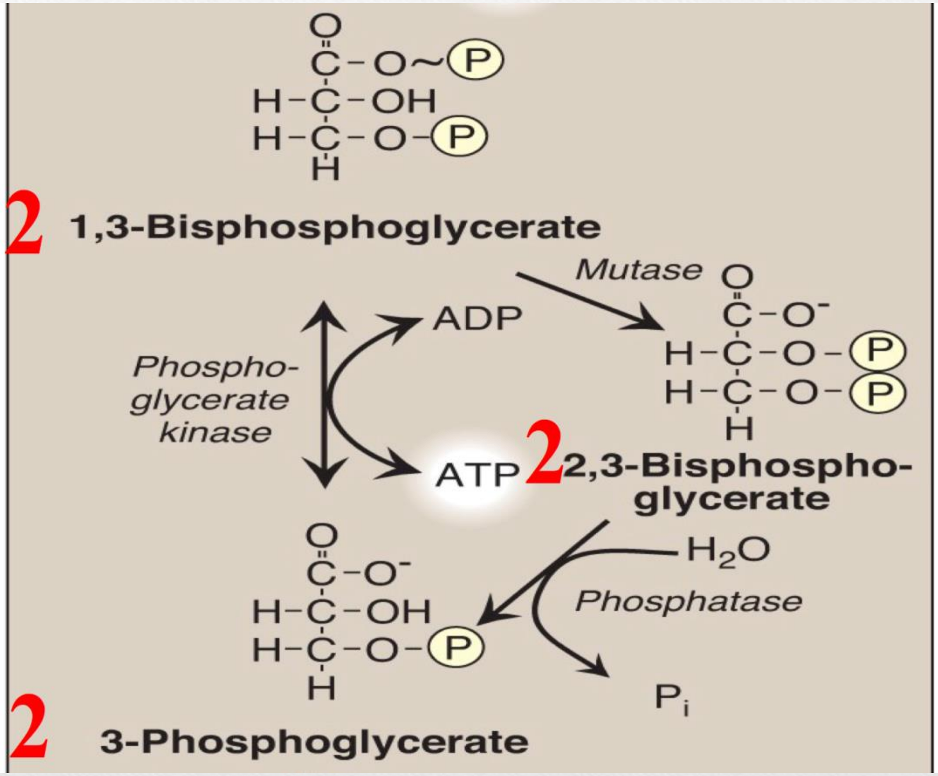
ATP Consumed:				
			2	ATP
ATP Produced:				
	Substrate-level	2 X 2 =	4	ATP
	~~Oxidative-level~~	~~2 X 3 =~~	~~6~~	~~ATP~~
	Total		4	ATP
Net:		4 – 2 =	2	ATP

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 1 X 2 = 2	ATP
~~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.