Glycolysis

Lecture #

Color Index

- Girls' slides
- Boys' slides
- Doctors' notes
- Important
- Extra info

Editing File

Biochemistry 442

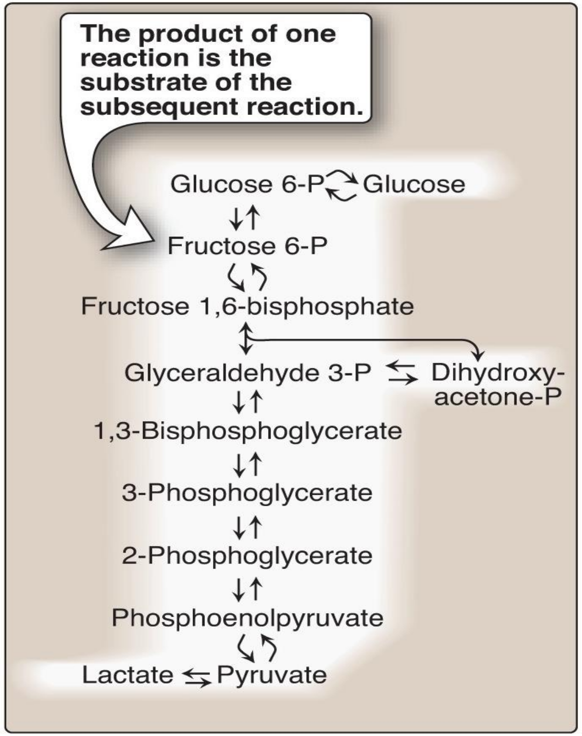
Objectives

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

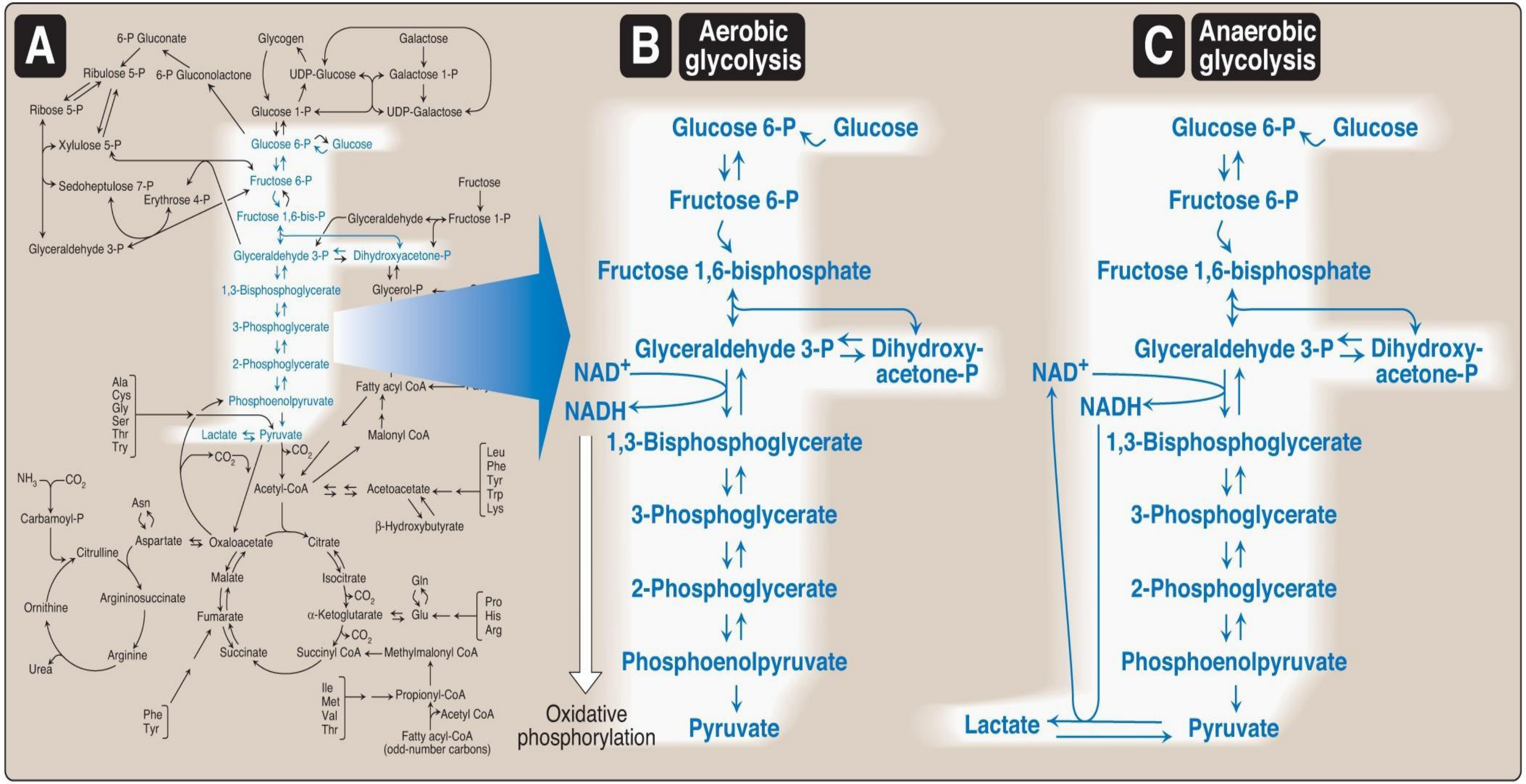
- Recognize glycolysis as the major oxidative pathway of glucose.
- List the main reactions of glycolytic pathway.
- Discuss the rate-limiting enzymes/Regulation.
- Assess the ATP production (aerobic/anaerobic).
- Define pyruvate kinase deficiency hemolytic anemia.
- Discuss the unique nature of glycolysis in RBCs.

Glycolysis

- **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**.

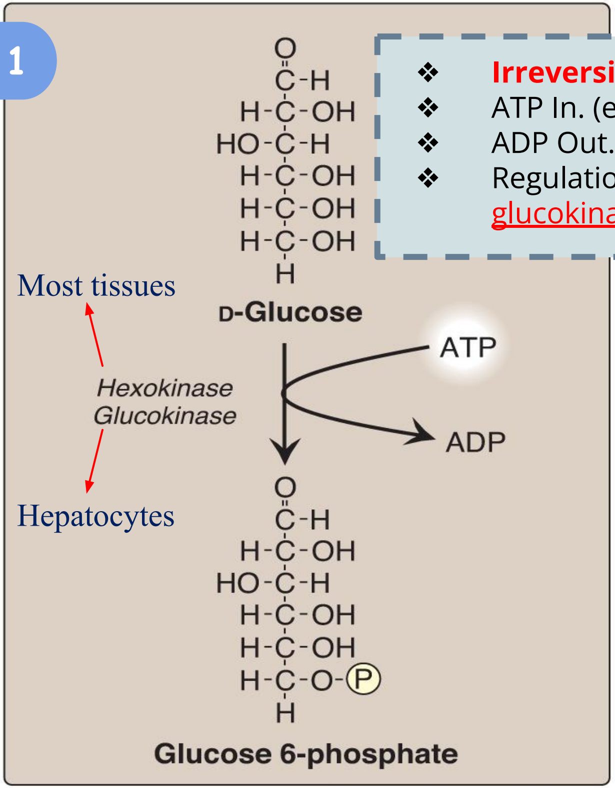


Aerobic Vs. Anaerobic Glycolysis overview



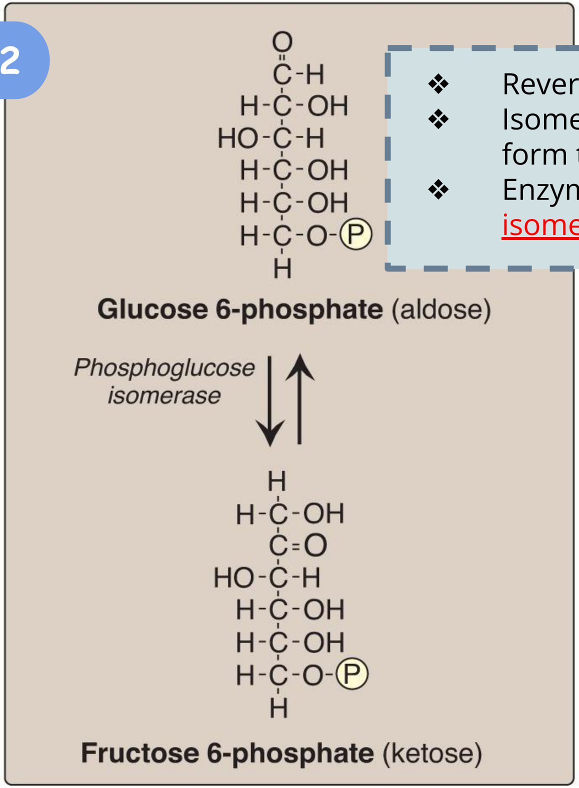
Aerobic Glycolysis 1

1



- **Irreversible**.
- ATP In. (energy consuming)
- ADP Out.
- Regulation of hexokinase and glucokinase.

2



- Reversible.
- Isomerization from aldose form to ketos form.
- Enzyme: Phosphoglucose isomerase

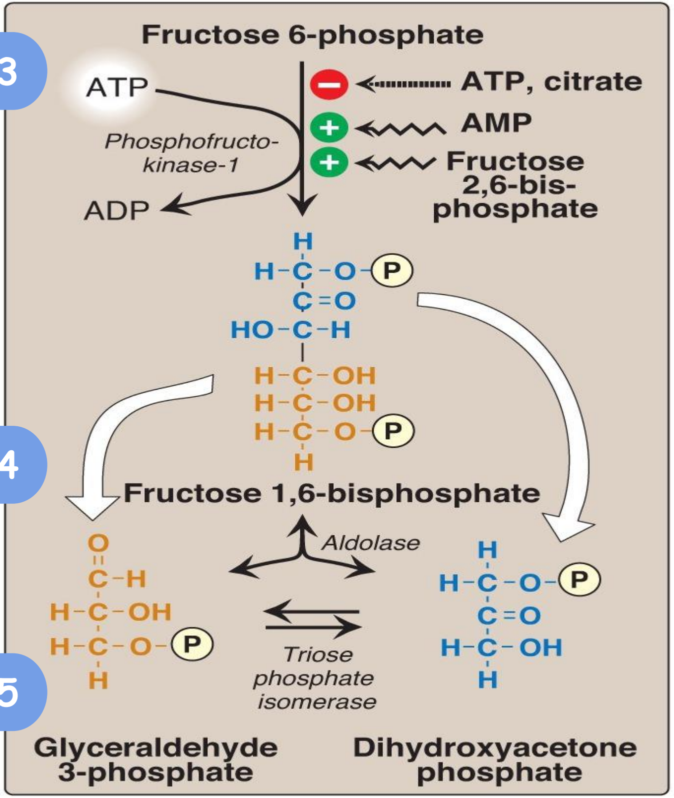
Aerobic Glycolysis 2

3

4

5

×2



- **Irreversible**
- ATP in (energy consuming)
- ADP out
- Can be regulated :
  - Activated + AMP and Fructose 2,6-bisphosphate.
  - Inhibited - ATP and citrate.
- Enzyme: Phosphofructokinase-1 (PFK-1)

- Aldolase breaks down carbon-carbon bond.
- Enzyme: Aldolase

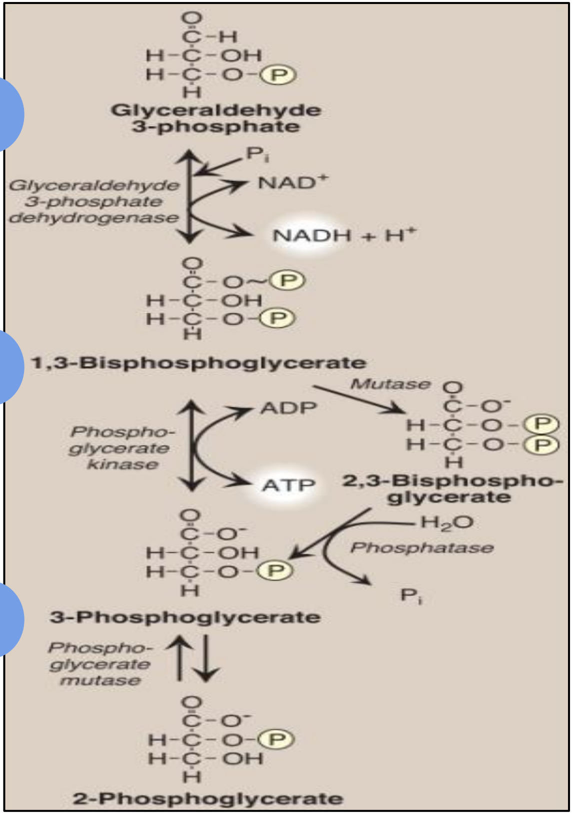
- Isomerization from ketos form to aldose from.
- Enzyme: Triose phosphate isomerase

Aerobic Glycolysis 3

×2 6

×2 7

×2 8



- 2x Pi and NAD+ in.
- 2x NADH and H+ out
- Enzyme: Glyceraldehyde 3-phosohate dehydrogenase

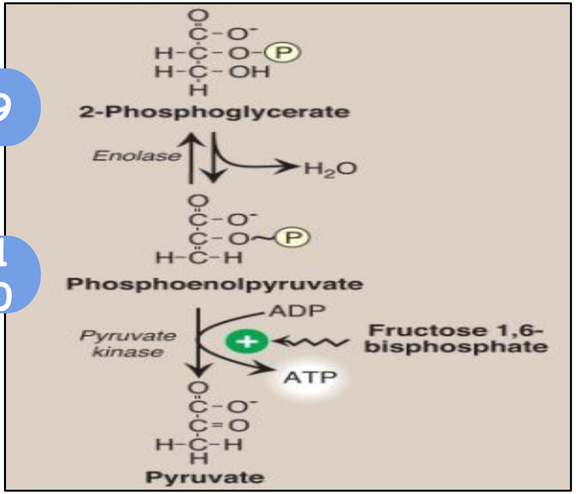
- 2xADP in.
- 2xATP out.
- Enzyme: Phosphoglycerate kinase

- **Team441** position of phosphate group is changed.
- Enzyme: Phosphoglycerate mutase

Aerobic Glycolysis 4

×2 9

×2 10



- 2x H2O out.
- Enzyme: Enolase

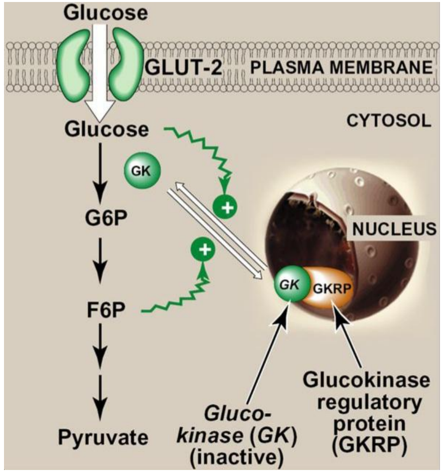
- 2x ADP in.
- 2x ATP out.
- Can be regulated (activated) :
  - Fructose 1,6-Bisphosphate .
- Regulation of pyruvate kinase A
- Enzyme: Pyruvate kinase

Regulation of enzymes: Glucokinase/Hexokinase

Regulation of: hexokinase (in most cells) and glucokinase (in liver or we can say hepatocyte).

- **Hexokinase**: it is **inhibited** by the reaction product, glucose-6-P (**1st** reaction) which accumulates when further metabolism of this hexose is reduced.
- **Glucokinase** (GK): It is **inhibited** indirectly by Fructose-6-P (**2nd** reaction) and is indirectly **stimulated** by glucose.
  - In the presence of high fructose-6-phosphate, Glucokinase (GK) translocates and binds tightly to GKRP (glucokinase regulatory protein) in the **nucleus**, making it **inactive** (by translocation into the nucleus).
  - When glucose levels are high in blood and hepatocytes (GLUT-2), GK is released from GKRP and enters the **cytosol**.

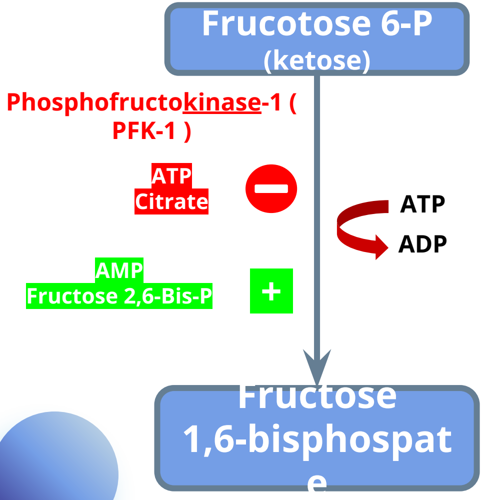
	Hexokinase	Glucokinase
Site	All tissues	hepatocytes
Inhibited by	glucose-6-Phosphate	Fructose-6-Phosphate (indirectly)
Stimulated by	-	Glucose



Regulation of enzymes: PFK-1 & Pyruvate Kinase

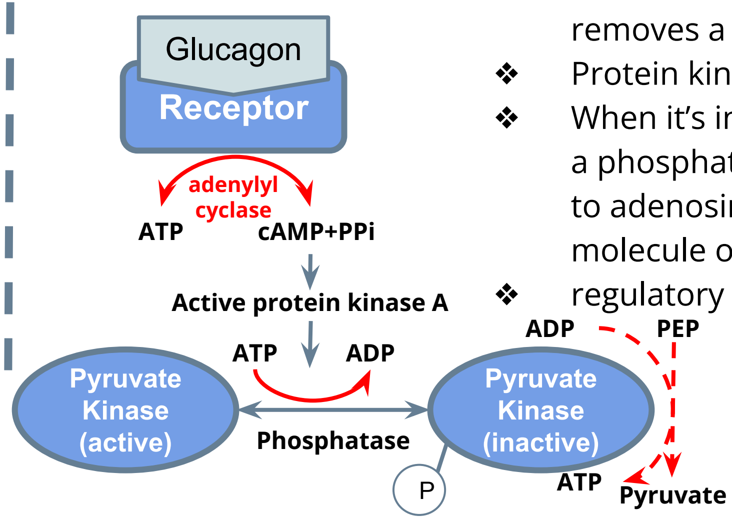
Phosphofructokinase-1 (PFK-1) enzyme:

- ❖ Rate limiting enzyme
- ❖ Reaction number 3 in glycolysis , is Irreversible reaction
- ❖ Can regulate glycolysis through allosteric regulation.
- ❖ + Activated by AMP and Fructose 2,6-bisphosphate.
- ❖ - Inhibited by ATP and citrate.
- ❖ regulatory mechanism : rabid , short term.



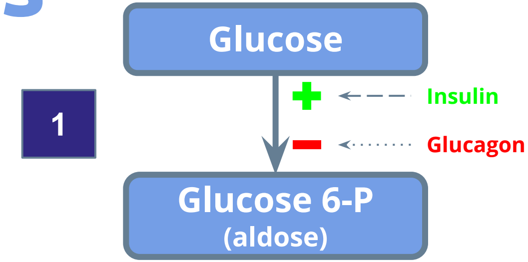
Pyruvate Kinase covalent modification

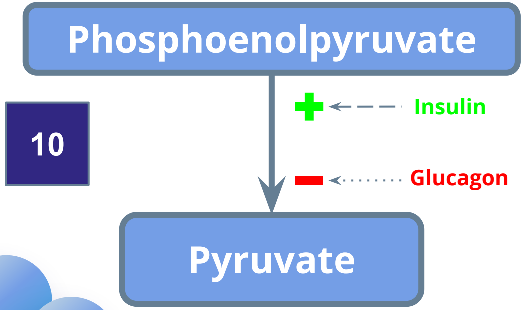
- ❖ Reaction number 10 in glycolysis , Irreversible reaction.
- ❖ Once glucagon (hormone) bind to the receptor it will activate the adenylyl cyclase that will produce cAMP which will activate protein kinase A. This protein will inhibit pyruvate kinase by adding P group to it (phosphorylation).
- ❖ + Activation of enzyme can be done by phosphatase (removes a phosphate group)
- ❖ Protein kinase A is cAMP dependent
- ❖ When it's in the active form It catalyzes the transfer of a phosphate group from phosphoenolpyruvate (PEP) to adenosine diphosphate (ADP), yielding one molecule of pyruvate and one molecule of ATP.
- ❖ regulatory mechanism : rabid , short term

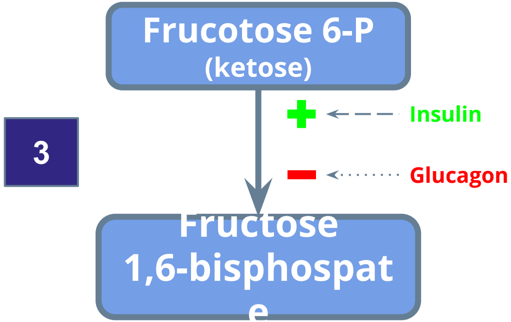


Long-Term Regulation of Glycosis

Long term regulation of glycolysis in reactions
1, 3 and 10: (irreversible, Rate limiting enzymes).
Insulin: Induction (increase the transcarbtion).
Glucagon: Repression (decrease the transcarbtion).







Summary

[Regulation of glycolysis]

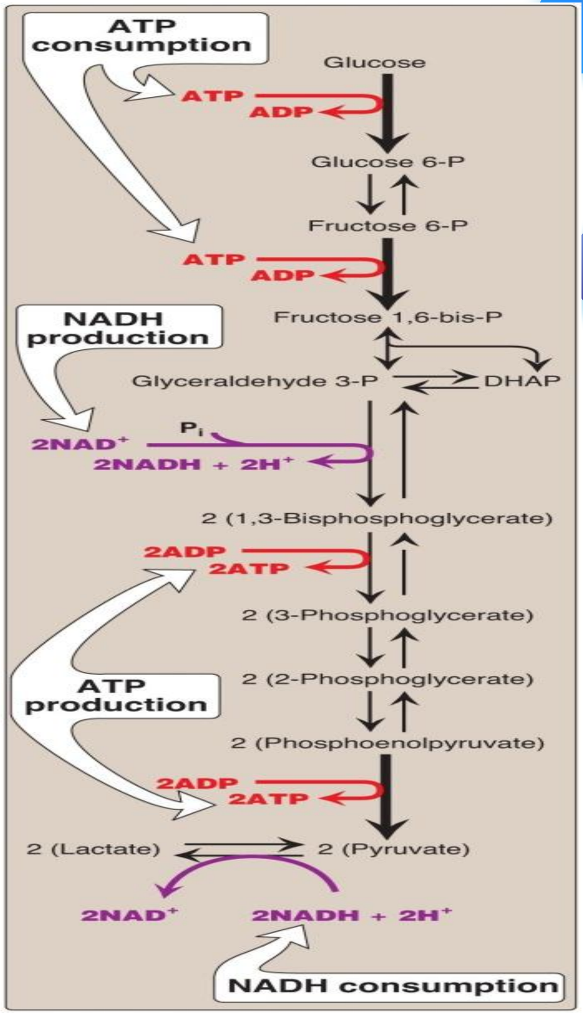
Regulatory enzymes
[irreversible reactions]

1-Glucokinase [in the liver] / hexokinase [other tissue]
2- PFK-1 [phosphofrctukinase
3- Pyruvate kinase

Regulartory Mechanism

- **Rapid, short-term:** Allosteric, Covalent modifications
- **Slow, long-term:** Induction/repression

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

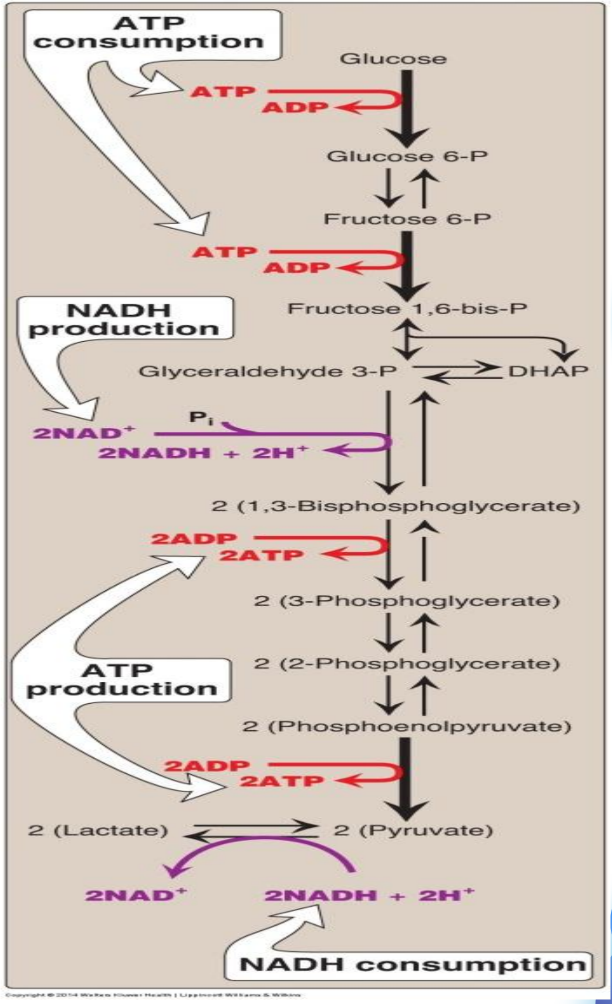
Anaerobic glycolysis

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

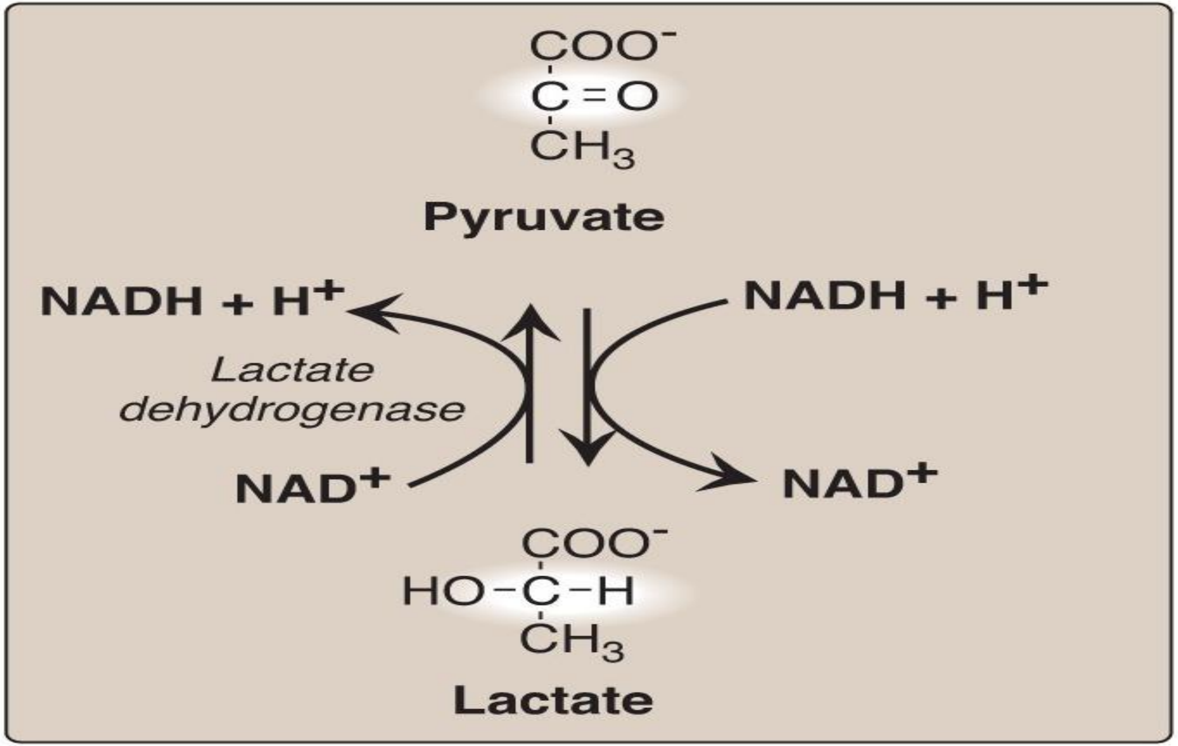
- Less ATP production, as compared to aerobic glycolysis.

Text

- 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

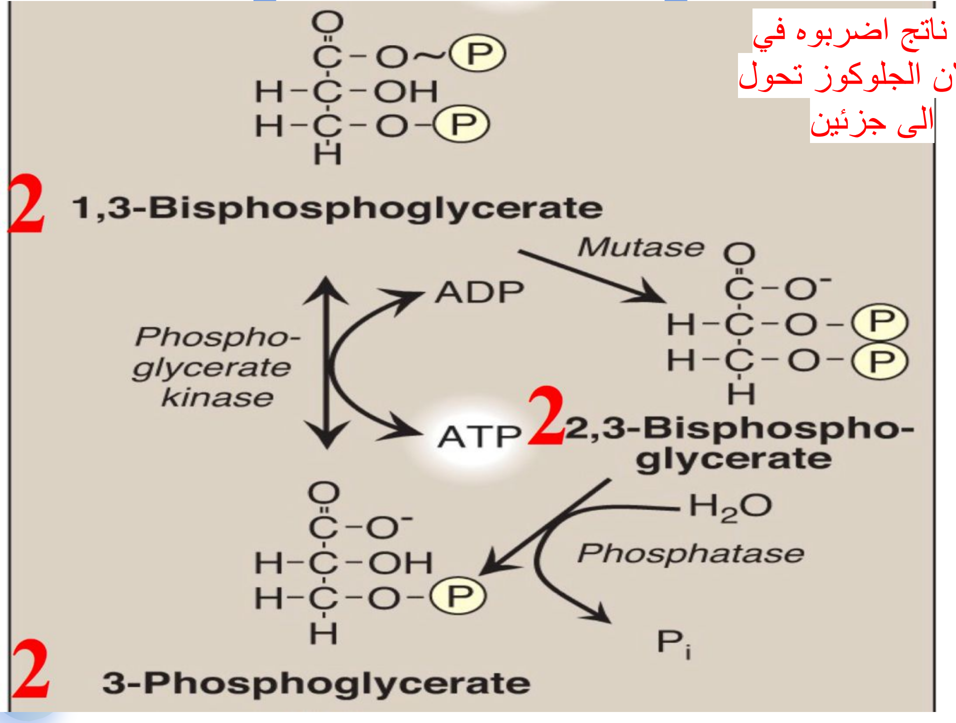
ATP Produced:

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]



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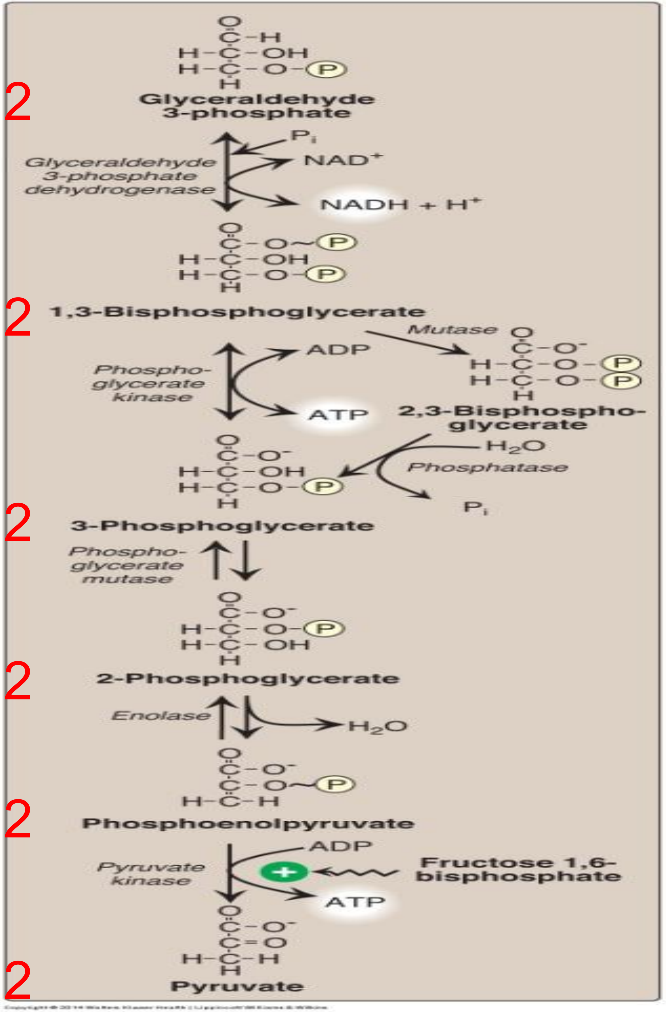

Glycolysis in RBCs
{ Net ATP produced }

ATP Consumed:

2 ATP

ATP Produced:

Substrate-level	2 X 2 = 4 ATP
	or 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 Message

- ❖ 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

❑ **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

Quiz

What is the net energy produced in the Aerobic glycolysis ?			
A- 8 ATP	B- 12ATP	C- 4ATP	D- 2ATP
Any of these enzymes converts Fructose6_phosphate into Fructose 1,6bis phosphate			
A-enoloose	B- lactase	C-phospho fructoKinase	D-glucase
Glucokinase work in			
A-liver cell	B-muccel cells	C-WBC	D-blood cells
Any of these are in irreversible reactions?			
A-APFK-3	B-PFK-1	C-PkF-1	D-PPP
In this reaction (glucose into glucose 6-phospat) what is happen with ATP?			
ATP TO AMP	B-NADH TO NAD+	C-AMP TO ADP	D-ATP TO ADP

1A 2C 3A 4B 5D

SAQ

Q1:what are PFK-1 inhabitors and activator ?

Q2:what is the enzyme's name involves in glycolysis and has an important role in hemolytic anemia? And what are the types of its mutations?

ANSWERS:

1-The activators are AMP and Frucose 2,6-bisphosphat and the inhabitors are ATP and citrate.

2-Pyruvate kinase,

-Partial deficiency {Altered enzyme kinetic. mutation in allosteric binding site}

-complete deficiency {Altered response to activator. mutation in active site}

-Decrease amount of the enzyme or its stability

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