Glucose Metabolism(Glycolysis)

- Color Index:
  - Original slides.
  - Original slide : for enzyme
  - Important.
  - 436 Notes
  - 438 notes
  - Extra information

رابط التعديل:
https://docs.google.com/document/d/1WvdeC1atp7J-ZKWOUSukSLsEcosjZ0AqV4z2VcH2TA0/edit?usp=sharing

Reviewed by Razan AlRabah & Khalid Alkhani

Biochemistry team 438

Objectives:

- Recognize glycolysis as the major oxidative pathway of glucose
- List the main reactions of glycolytic pathway

(there are 10 reactions)

- 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.

Dr's Notes:
You must know:
- location: cytosol
- Net yield
- Substrates & products

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.

Reversible =

Irreversible =

Glycolysis

Aerobic

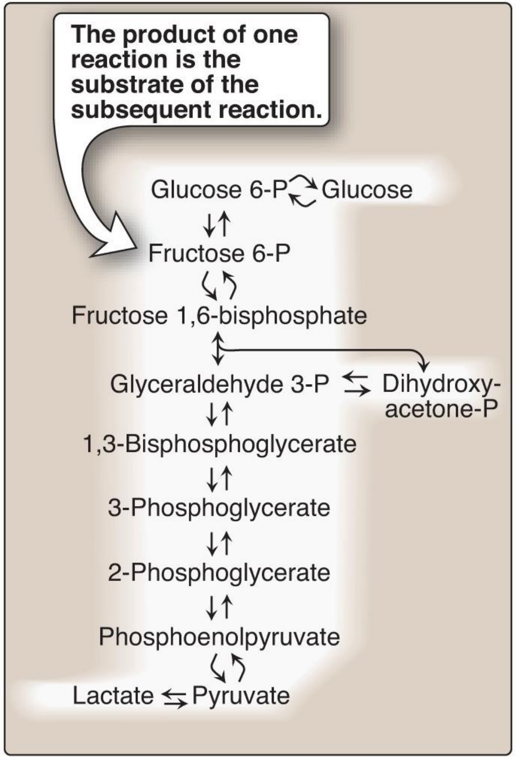
Available both : O2 & MITOCHONDRIA

End product: Pyruvate

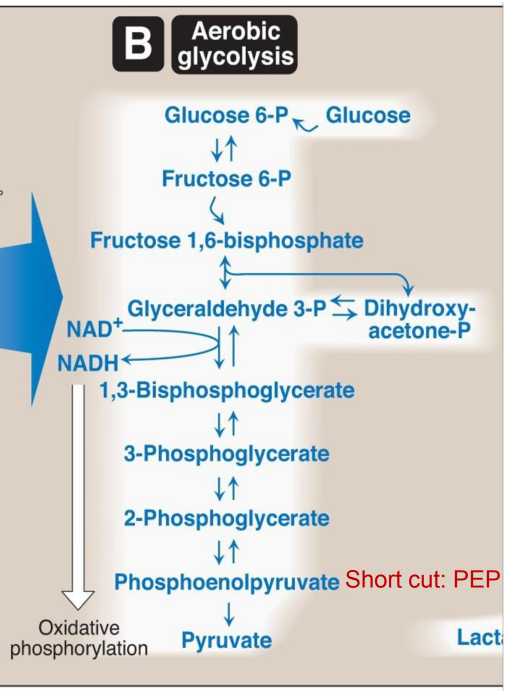
Anaerobic

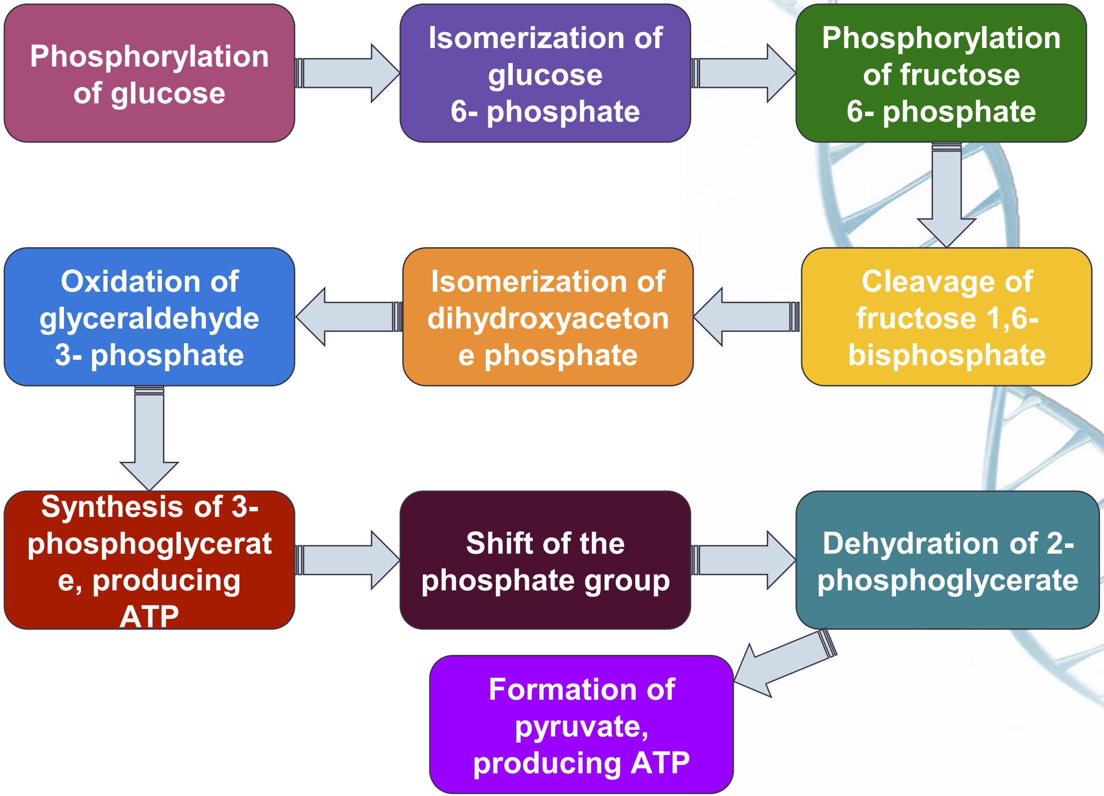
Absence of O2 or mitochondria or both of them

End product: Lactate



Aerobic

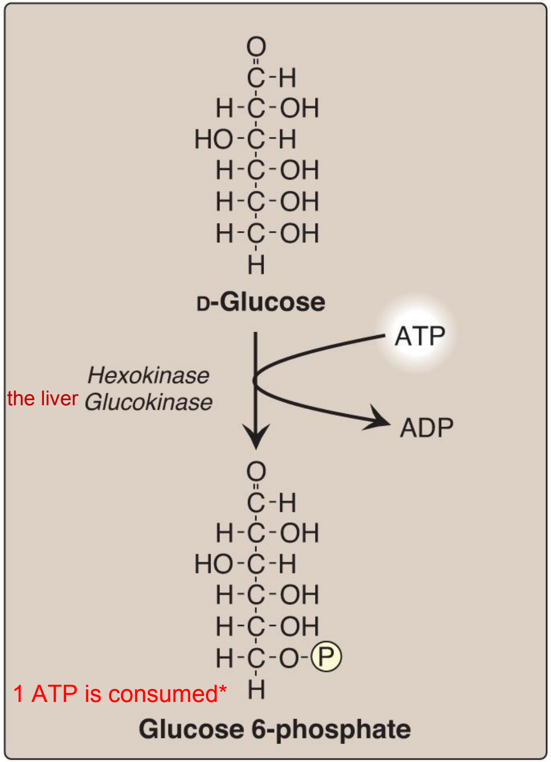

B
Aerobic glycolysis
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bisphosphate
Glyceraldehyde 3-P
Dihydroxy-acetone-P
NAD+
NADH
1,3-Bisphosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Short cut: PEP
Oxidative phosphorylation
Pyruvate
Lact


Phosphorylation of glucose
Isomerization of glucose 6- phosphate
Phosphorylation of fructose 6- phosphate
Cleavage of fructose 1,6-bisphosphate
Isomerization of dihydroxyacetone phosphate
Oxidation of glyceraldehyde 3- phosphate
Synthesis of 3-phosphoglycerate, producing ATP
Shift of the phosphate group
Dehydration of 2-phosphoglycerate
Formation of pyruvate, producing ATP

1st reaction

Phosphorylation of glucose

In the liver

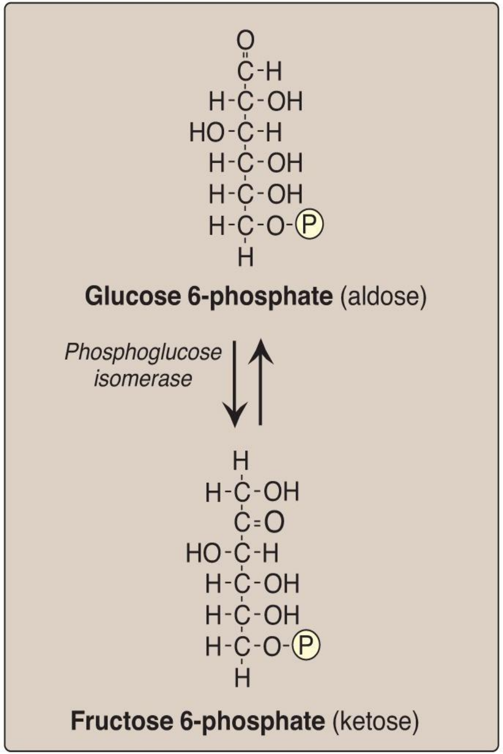


1-ACTION :
Adding of phosphate group to glucose

Enzymes :
Hexokinase: Most tissues
Glucokinase: Hepatocyte

2nd reaction

Isomerization of glucose 6-phosphate



2-ACTION :
Isomerization
1 ATP is consumed*
of glucose 6-phosphate to fructose 6-phosphate

Enzyme :
Phosphoglucose isomerase

Regulation: Glucokinase/Hexokinase

Hexokinase isoforms
(4 isoforms)

3 Hexokinase

In tissues

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

1 Glucokinase

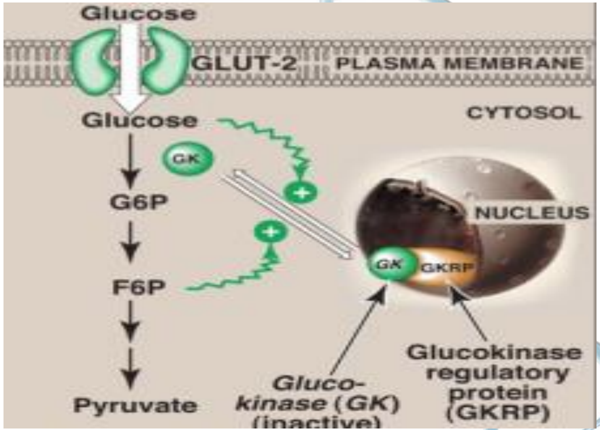
In liver & pancreas

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

Glucokinase (GK) Regulation

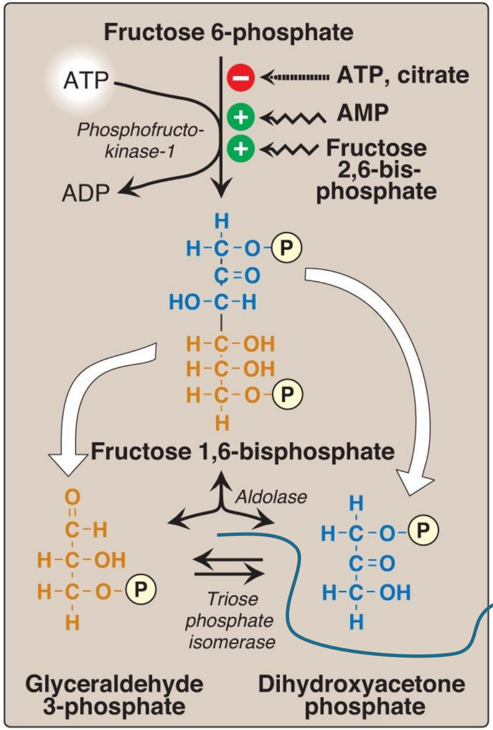
- In the presence of high fructose-6-phosphate, GK translocates and binds tightly to GKRP (glucokinase regulatory protein) in the nucleus, making it inactive

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



Phosphorylation of fructose 6-phosphate

1 ATP is consumed*



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 .

It's a rate limiting enzyme

(PFK-1) and its regulation

- Allosteric Regulation

Inhibited by: ATP & citrate
Stimulated by: AMP & Fructose2,6-bisphosphate

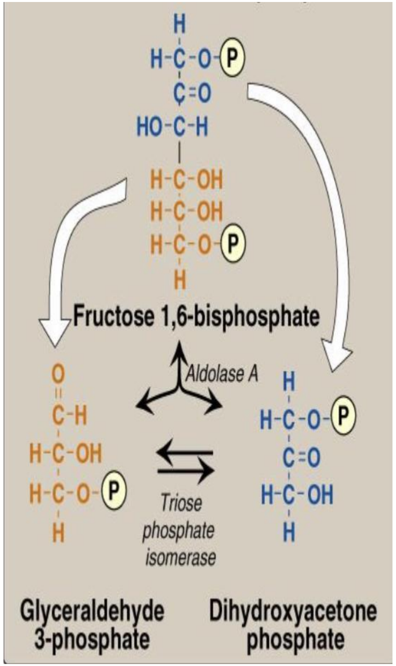
- Induction/Repression

Induced by: insulin
Repressed by: glucagon

ممكن يأخذ الجسم ثنين من واحد منهم
يعني؟؟ يحول واحدة منهم لثاني لان هذا تفاعل رجعي
او ينتج ثنين اللي هو محتاجه بيسويه
بس حنا ندرس لما يكون
2 Glyceraldehydes

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 phos- phate (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 2 molecules of the each next reactions

(Reactions: 6th – 10th)

الانزيمات في التفاعلات 6-10 لا نحبذ التحدث بها كعيال

Oxidation of glyceraldehyde 3- phosphate

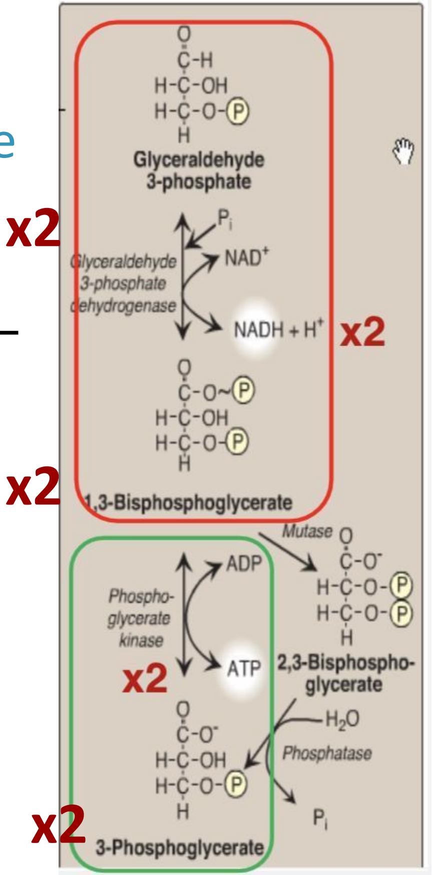
(Oxidative level)

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

(Reactions: 6th – 10th)
"last 3"

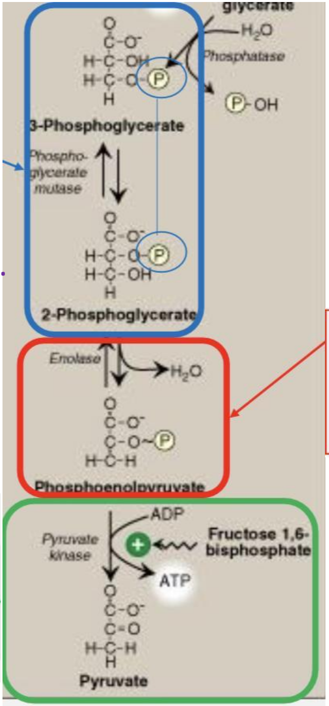
Shift of the phosphate group

الانزيمات في التفاعلات 10-6 لا نحبذ التحدث بها كعيال

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.



Outcomes :2 ATP

Dehydration of 2-phosphoglycerate

ACTION :
Phosphoglycerate change to phosphoenolpyruvate by remove water .

Enzyme: Enolase

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

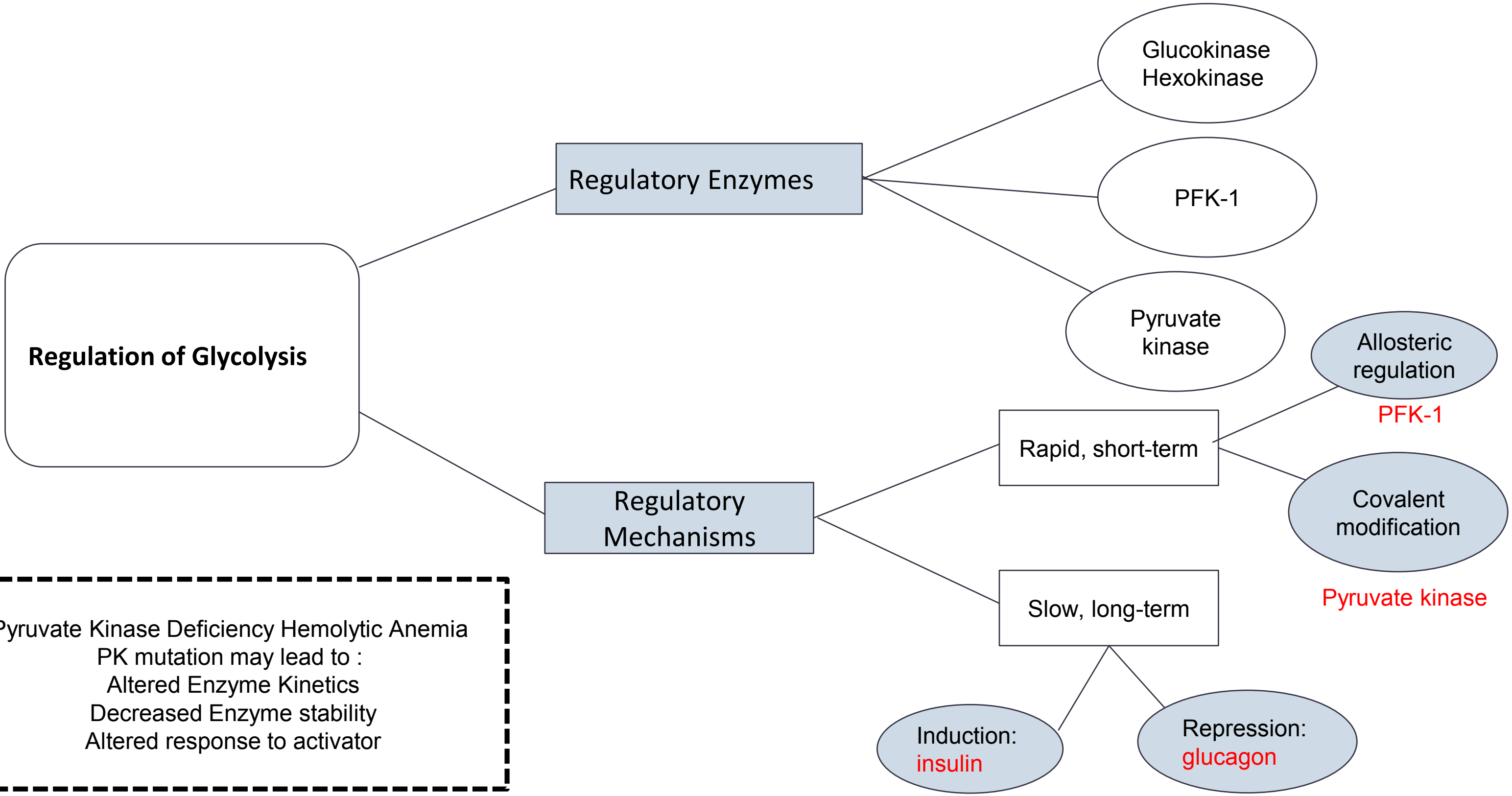
This slide is important
it may come in SAQ

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

This slide is important



Pyruvate Kinase Deficiency Hemolytic Anemia
PK mutation may lead to :
Altered Enzyme Kinetics
Decreased Enzyme stability
Altered response to activator

Aerobic Glycolysis: ATP Production

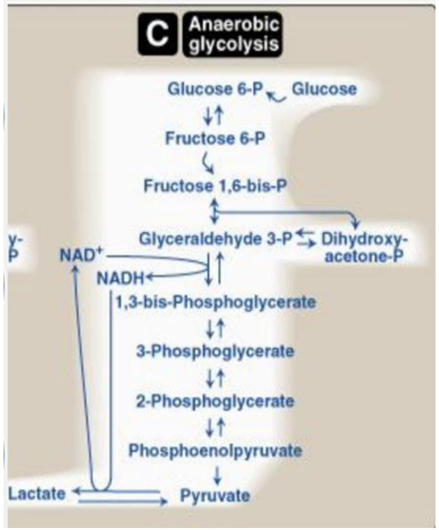
ATP Consumed: 2 ATP

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=8ATP

Anaerobic



- 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

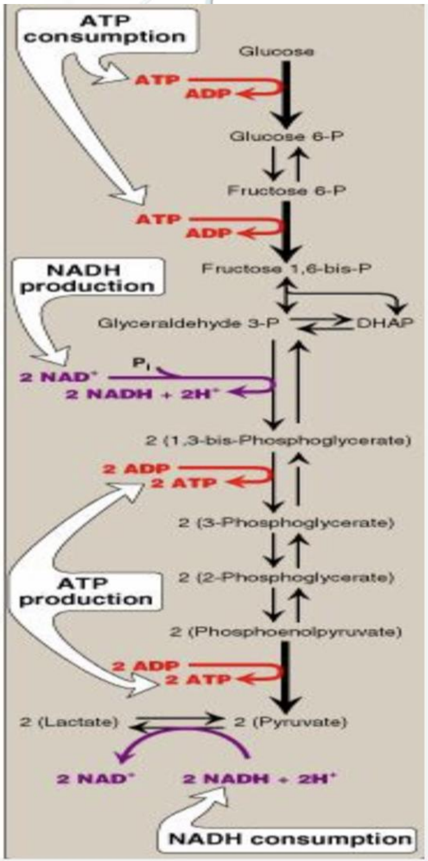
Phosphorylation of glucose → **Isomerization of glucose 6- phosphate** → **Phosphorylation of fructose 6- phosphate** → **Cleavage of fructose 1,6-bisphosphate** → **Isomerization of dihydroxyaceton e phosphate** → **Oxidation of glyceraldehyde 3- phosphate** → **Synthesis of 3-phosphoglycerat e, producing ATP** → **Shift of the phosphate group** → **Dehydration of 2-phosphoglycerate** → **reduction of pyruvate, formation of lactate**

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

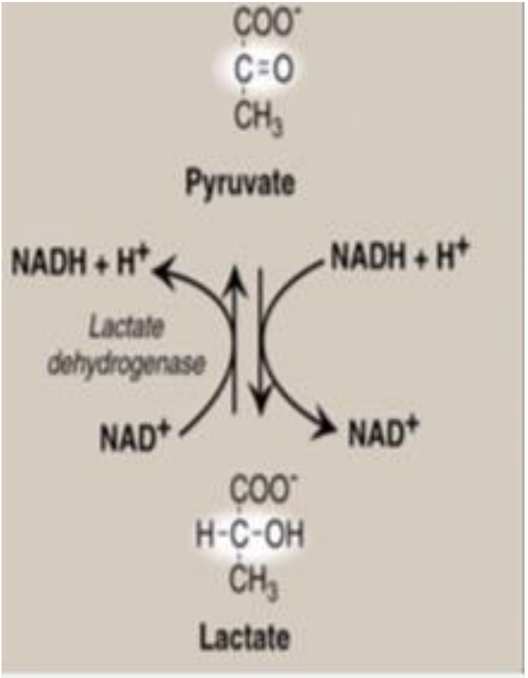
ACTION :

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



The enzyme used the NADH

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

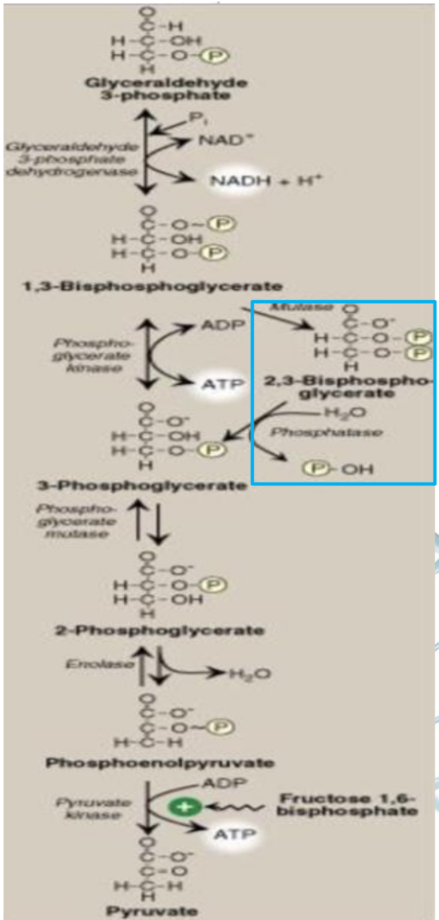
Total: 4 ATP

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.

Function of: 2,3-BPG: delivery of oxygen



Importance of mutase enzyme

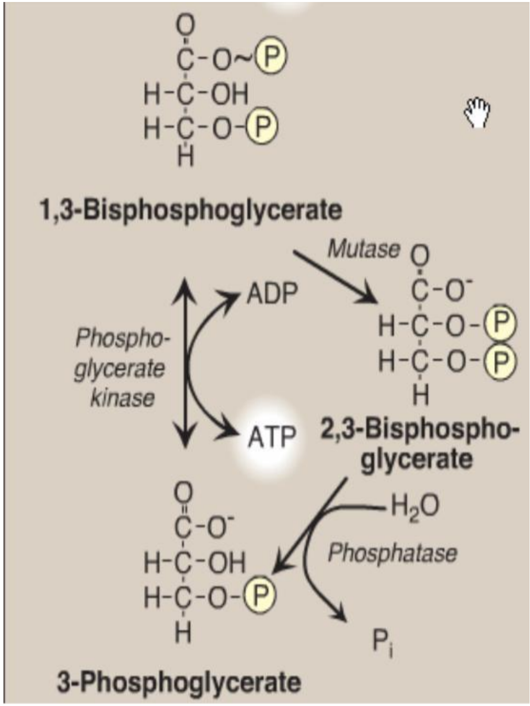
- It is important for association and dissociation between O2 and hemoglobin.
- Increase in "2,3-BPG" will help to loss of association between O2 and hemoglobin and will release more O2.
- It usually occurs with people who live in high altitude.

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 if the is 2,3-BPG

Total : 4 ATP

Net : 4-2= 2 ATP

Or 2-2= 0 ATP if the is 2,3-BPG

Glycolysis in RBCs: Summary

End product

- Lactate
- No net production or consumption of NADH

Energy yield

Without 2,3 BPG: 2 ATP

With 2,3 BPG shunt: 0 ATP

PKD haemolytic anaemia depend on

Degree of PKD

Compensation by 2,3-BPG

This slide is important

Glycolysis net yield

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

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
- Net energy produced in:
  Aerobic glycolysis: Anaerobic glycolysis:
  8 ATP 2 ATP
- Net energy produced in glycolysis in RBCs:
  Without 2,3 BPG synthesis: With 2,3 BPG synthesis:
  2 ATP 0 ATP

Review

Glycolysis is a type of anaerobic (does not directly require oxygen) cellular respiration that breaks glucose down into two ATP molecules and pyruvic acid (also called pyruvate) and releases electrons. Glycolysis happens in the cytoplasm of the cell. The electrons that are released in the process are picked up by NAD+ molecules and carried to another part of the cell for another reaction called the electron transport system. Glycolysis is the first step of a series of steps that produces ATP for cellular energy. The pyruvic acid produced by glycolysis is then transferred into another process called the krebs cycle where even more ATP is made.

MCQs

Q1; Which of the following biochemical pathways does NOT require oxygen?

A-glycolysis
B-krebs cycles
C-electron transport system

Q2; Where does glycolysis take place?

A-The mitochondria
B-The chloroplast
C-The cytoplasm

Q3; What is the overall end product of the proccess of glycolysis?

A-Two extra ADP
B-four extra ATP
C-Two extra ATP

Q4; Which 3-carbon molecule is one of the final products of glycolysis?

A- glucose
B- pyruvate
C-ATP

Answer key:

1-A
2-C
3-C
4-B

SAQs

Q1- What is the net production of ATP, pyruvate, and NADH when one molecule of glucose undergoes glycolysis?

2 ATP, 2 NADH and 2 pyruvate

Q2- what is the Glycolysis?

Glycolysis is a type of anaerobic (does not directly require oxygen) cellular respiration that breaks glucose down into two ATP molecules and pyruvic acid (also called pyruvate) and releases electrons. Glycolysis happens in the cytoplasm of the cell.

❖ Girls team:

- أجيد آل رشود
- الوتين البلوي
- إيلاف المسيحل
- جود الخليفة
- جود العتيبي
- ريم القرني
- سارة الهلال
- شهد السلامه
- طيف العتيبي
- عبير الخضير
- غيداء البريثن
- لينا العصيمي
- نورة التركي
- نورة المزروع
- نوف الحميضي
- هيفاء الوايلي

❖ Boys team:

- بدر الشهري
- حميد حميد
- سهيل باسهيل
- عمر الغامدي
- مهند القرني
- نايف السبر

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