بسم الله الرحمن الرحيم

METABOLISM

MID – Lecture 12

GLYCOLYSIS(pt.2)

﴿ وَإِن تَتَوَلَّوۡاْ يَسۡتَبۡدِلۡ قَوۡمًا غَيۡرَكُمۡ ثُمَّ لَا يَكُونُوٓاْ أَمۡثَٰلَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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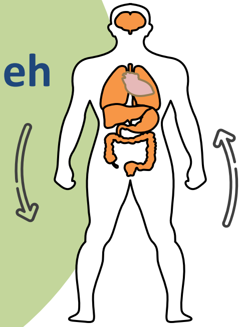

- فريق دوبامين العلمي -
THE SCIENTIFIC TEAM OF DOPAMINE
APPROVED
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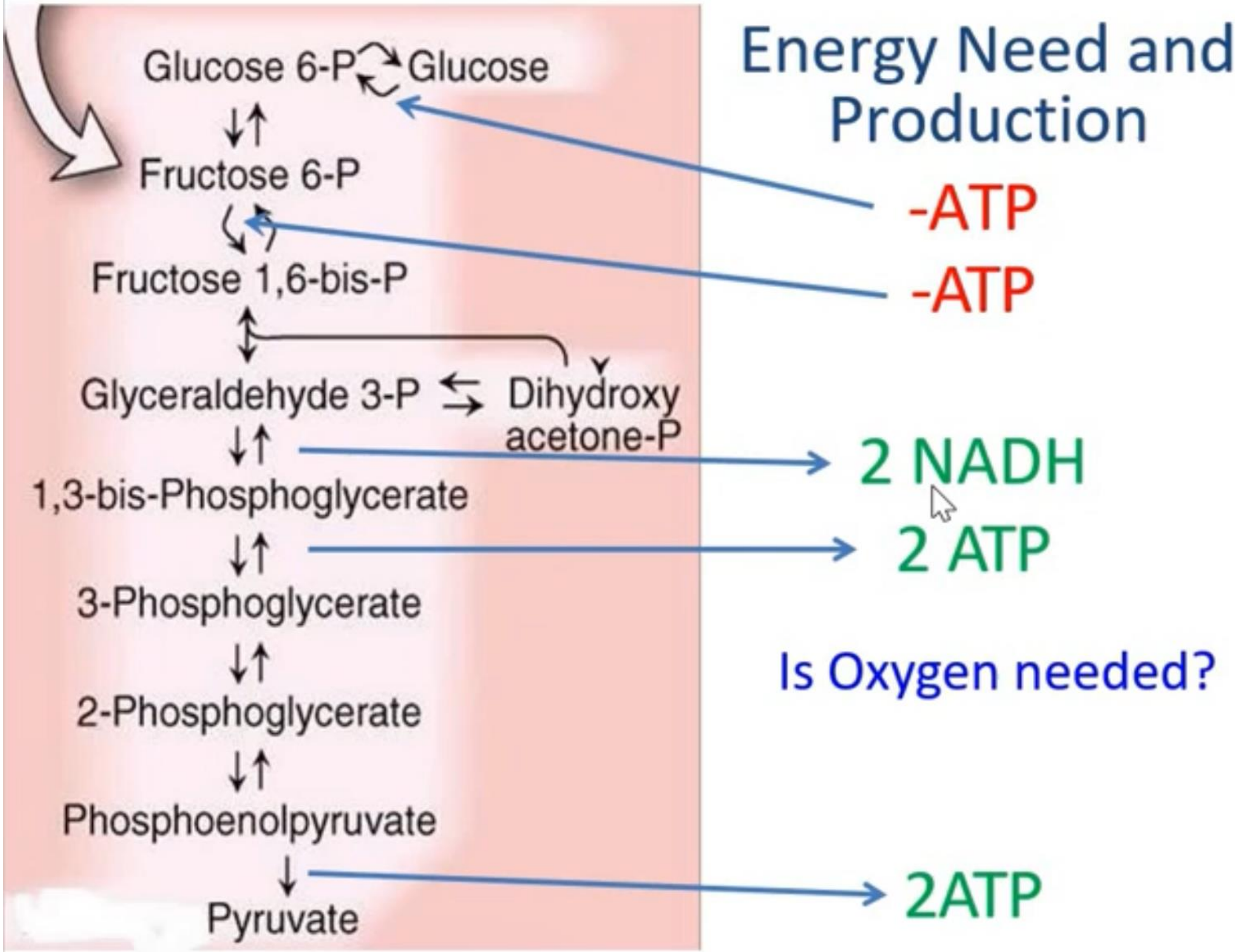
Lecture 12


Energy Need and Production
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Pyruvate
-ATP
-ATP
2 NADH
2 ATP
Is Oxygen needed?
2ATP

Energy Need and Production

1. Preparation Phase (first phase):

Two ATP molecules are consumed in these two phosphorylation steps:

Glucose → Glucose-6-Phosphate

Fructose-6-Phosphate → Fructose-1,6-Bisphosphate

2. Second phase :

- Two ATP molecules are produced per glyceraldehyde-3-phosphate in these two steps:

1,3-Bisphosphoglycerate → 3-Phosphoglycerate. (+ATP)

Phosphoenolpyruvate → Pyruvate. (+ATP via pyruvate kinase)

-Since each glucose molecule generates two molecules of glyceraldehyde-3-phosphate, the reactions in the second phase are repeated twice, leading to a total of 4 ATP molecules.

3. Net ATP production:

2 ATP per glucose molecule (4 ATP produced - 2 ATP consumed).

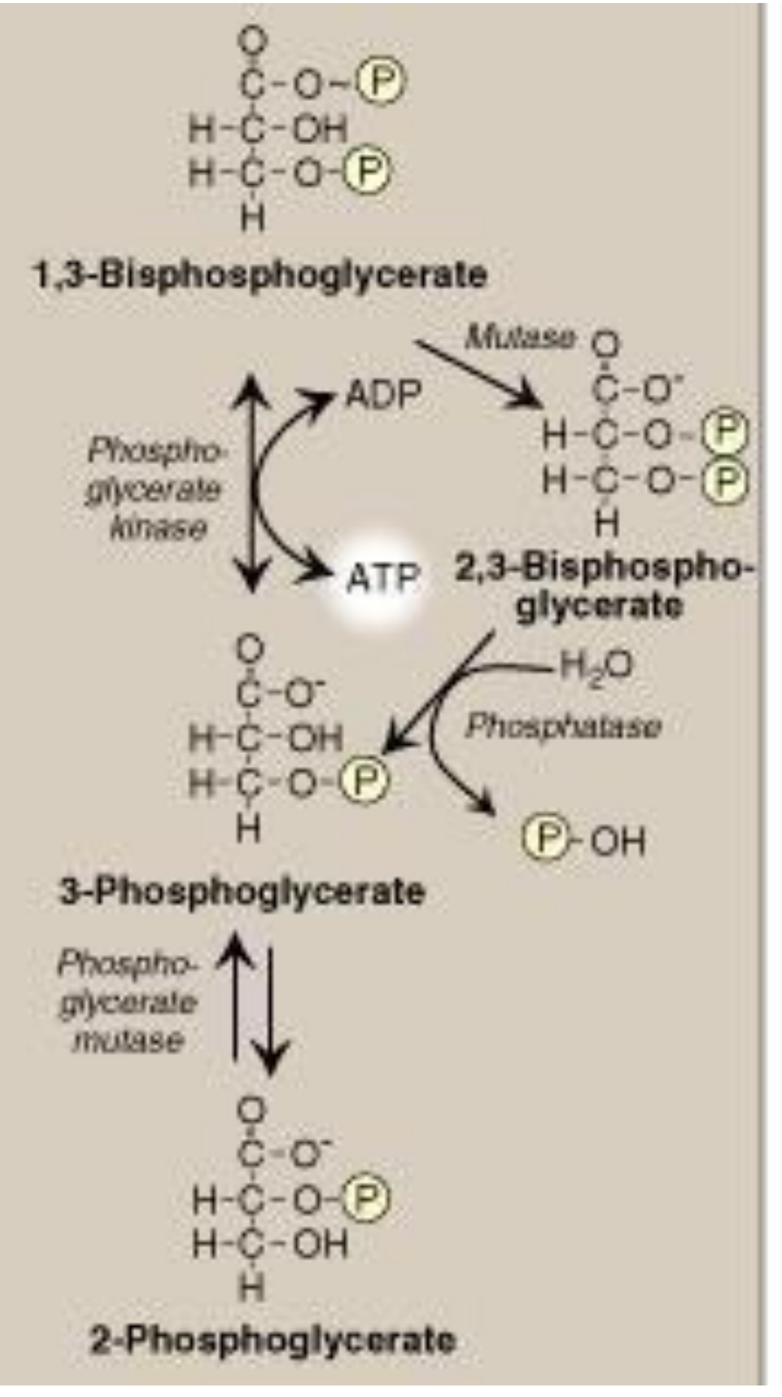
+ 2 NADH for each Glucose molecule that passes through glycolysis.

4. This pathway does not require oxygen and can operate in both aerobic and anaerobic conditions.

Synthesis of 2,3 bisphosphoglycerate in RBC

↑↑Oxygen delivery to tissues

By binding to deoxyhemoglobin reducing its affinity to O2 and increasing O2 release to tissues



Synthesis of 2,3-bisphosphoglycerate in RBC

- A diversion occurs specifically in red blood cells at the step between 1,3-bisphosphoglycerate and 3-phosphoglycerate, where ATP is normally produced via phosphoglycerate kinase (PGK). In RBCs near peripheral tissues, oxygen is released to supply these tissues, spreading to different cell types to meet their metabolic needs without needing to bind back to hemoglobin.

-By producing a molecule called 2,3-bisphosphoglycerate (2,3-BPG), which binds to hemoglobin, it stabilizes hemoglobin in the T-state (tense state), preventing it from re-binding to oxygen. This intermediate is not produced in standard glycolysis; however, red blood cells near peripheral tissues can go through a detour of the glycolytic pathway to produce it. Here, 1,3-bisphosphoglycerate is isomerized to 2,3-BPG by transferring a phosphate group from carbon number one to carbon number two via a mutase enzyme.

-They form 2,3-bisphosphoglycerate, which binds to hemoglobin to stabilize the T-state and reduce the return of oxygen and its binding again to hemoglobin. Then, its phosphate will be removed by a phosphatase enzyme as inorganic phosphate, producing 3-phosphoglycerate, and the pathway will continue until the end, just like the normal steps in glycolysis.

-In this case, the step that produces ATP is bypassed by this alternative path. As a net result, there would be no direct production of ATP because we typically produce two ATP per glucose molecule; this time, two ATP will be lost through this reaction that occurs twice for each glucose molecule. This is a big sacrifice to guarantee the proper performance of hemoglobin and red blood cells.

-This process doesn’t occur all the time; it happens near peripheral tissues. For example, glycolysis in other areas, such as in blood vessels and the lungs, will happen normally, producing energy sufficient for the low energy demands of blood cells.

To sum up :

1) 1,3-bisphosphoglycerate is converted to 2,3-bisphosphoglycerate by a mutase enzyme.

2)Then, 2,3-bisphosphoglycerate binds to hemoglobin, preventing it from re-binding to oxygen and stabilizing it in the T-state.

3) After fulfilling its function, the phosphate group is removed, producing 3-phosphoglycerate, which re-enters the glycolytic pathway to continue.

4) This process occurs in peripheral tissues.

5) The ATP production step is bypassed.

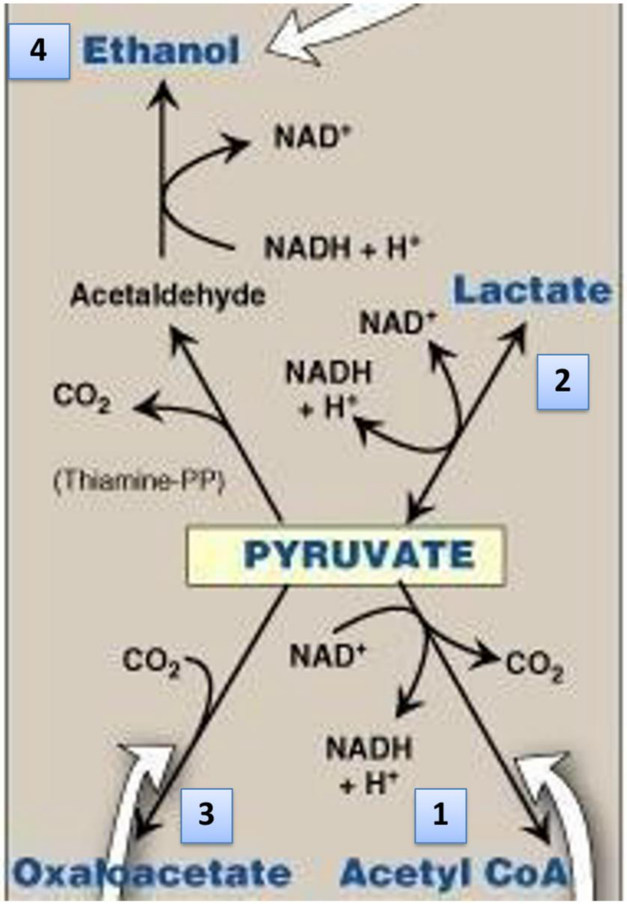
Pyruvate Fates

1)Conversion to Acetyl CoA ;Pyruvate is converted to acetyl CoA by the <u>pyruvate dehydrogenase complex,</u> allowing it to enter the Krebs cycle.

2)Anaerobic Respiration ;Pyruvate can enter anaerobic respiration, producing lactate.

3) Carboxylation to Oxaloacetate; Pyruvate can be carboxylated to oxaloacetate, which occurs during the synthesis of glucose.

4) Decarboxylation to Ethanol;Pyruvate can undergo decarboxylation to acetaldehyde, which is then reduced to ethanol; this process occurs in organisms like yeast but not in humans.

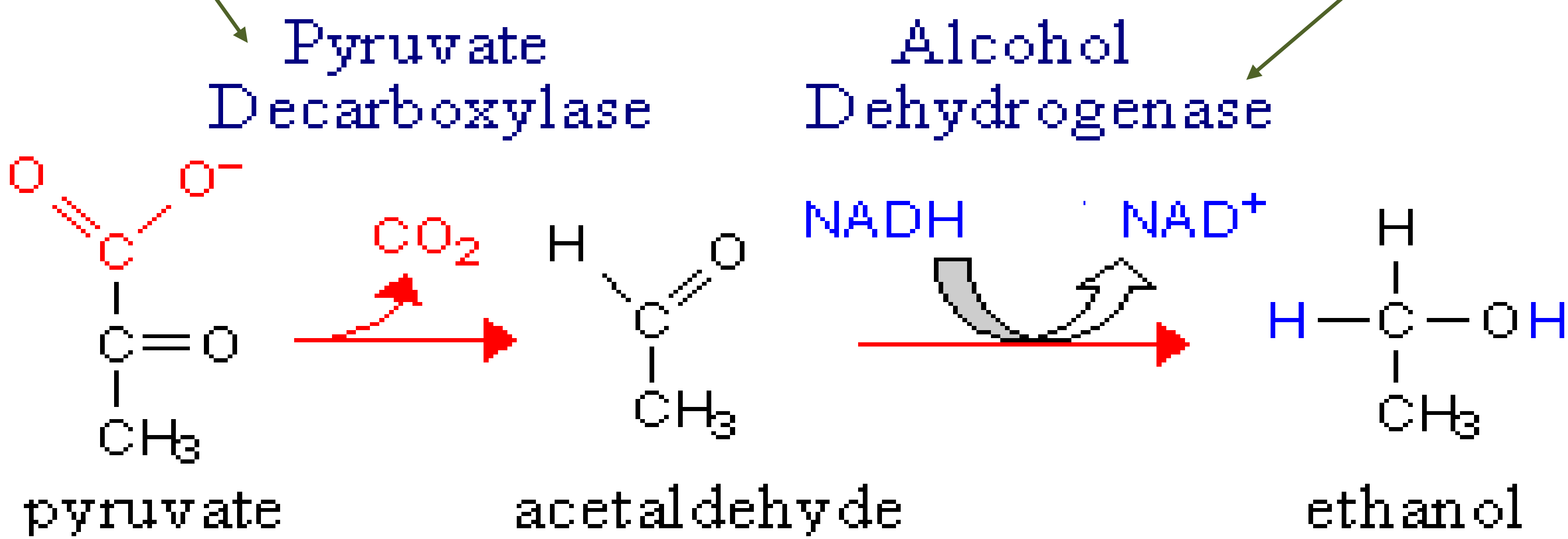


Note:
These fates can come from pyruvate produced by glycolysis or other pathways, including the metabolism of some amino acids(depending on the condition of the cell).

1. From Pyruvate to Ethanol

Decarboxylation: The first step is the conversion of pyruvate to acetaldehyde, catalyzed by pyruvate decarboxylase. In this reaction, a carboxyl group is lost from pyruvate, releasing carbon dioxide (CO_2).

Reduction to Ethanol: In the second step, acetaldehyde is reduced to ethanol (converting an aldehyde to an alcohol) by alcohol dehydrogenase. During this process, NADH is oxidized to NAD^+.



Role in Yeast Fermentation

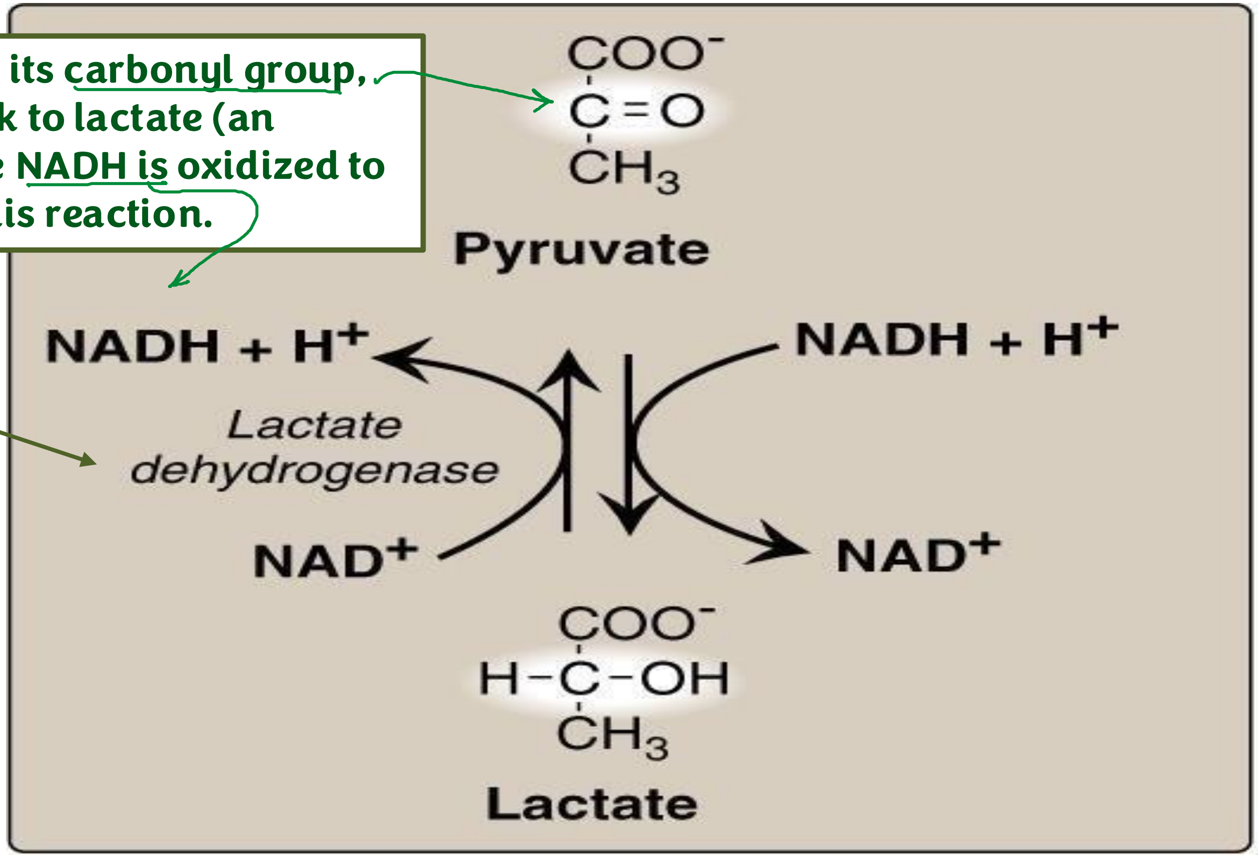
This process occurs in yeast and is an example of how yeast functions in dough. The decarboxylation reaction releases CO_2, which causes the dough to rise and increases its size, making it fluffy.

2. From Pyruvate to Lactate

When there is an inadequate amount of oxygen, anaerobic respiration is activated, allowing pyruvate produced by glycolysis to be converted into lactate.

Pyruvate, with its carbonyl group, is reduced back to lactate (an alcohol), while NADH is oxidized to NAD^+ during this reaction.

This reaction is catalyzed by lactate dehydrogenase, which can also catalyze the reverse reaction, oxidizing lactate back to pyruvate when oxygen is available.



Pyruvate + NADH $\rightleftharpoons$ Lactate + NAD^+

When is Lactate Produced?

- **Cells with low energy demand**

-Cells with low energy demand, like red blood cells, can activate anaerobic respiration since they lack mitochondria and cannot rely on the Krebs cycle and oxidative phosphorylation to produce ATP.
-Instead, they produce ATP through glycolysis followed by anaerobic respiration to produce lactate.
-In red blood cells, lactate does not cause fatigue.

- **To cope with increased energy demand in rigorously exercising muscle, lactate level is increased 5 to 10 folds**

- During exercise, muscle cells initially rely on aerobic respiration to produce energy.
-When oxygen becomes insufficient for the Krebs cycle and electron transport chain, muscle cells shift to anaerobic respiration, producing lactate.
-In muscle cells, lactate buildup can cause fatigue

- **Hypoxia**

to survive brief episodes of hypoxia

-In cases of hypoxia, where oxygen supply is low, either to specific tissues or the entire body, cells depend on anaerobic respiration to generate some energy.
- Although anaerobic respiration produces less energy than aerobic respiration, it can maintain essential functions during hypoxic conditions.

Clinical Hint: Lactic Acidosis

- ↓ pH of the plasma

High lactate concentrations can lead to lactic acidosis. A reduction in blood plasma pH below 7.4 contributes to metabolic acidosis.

Lactate is acidic due to its carboxyl group and alcohol group, which can release protons and lower pH

- The most common cause of metabolic acidosis
  - ↑ Production of lactic acid
  - ↓ utilization of lactic acid

$$\text{Pyruvate} + \text{NADH} \rightleftharpoons \text{Lactate} + \text{NAD}^+$$

Disruptions in oxidative phosphorylation or the electron transport chain reduce aerobic respiration, leading to a shift to anaerobic respiration and increased lactate production.

- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
  - Impaired O_2 transport

Hemoglobin Disorders: Problems with hemoglobin's ability to carry oxygen also increase reliance on anaerobic respiration, leading to higher lactate levels.

  - Respiratory failure
  - Uncontrolled hemorrhage

Conditions that impair oxygen transport, such as respiratory failure, reduce oxygen availability and lead to greater lactate production.

Significant blood loss reduces the amount of hemoglobin available for oxygen transport, resulting in a shift to anaerobic respiration and increased lactic acid production.

Please note that the prof. emphasized the concept of lactic acidosis in both the previous slide and the following ones

Clinical Hint: Lactic Acidosis

- **Direct inhibition of oxidative phosphorylation**

  Any inhibition in these oxygen-dependent pathways reduces energy production, causing a shift to anaerobic respiration and increased lactate production.

- **Hypoxia in any tissue**

  Whether localized or generalized, reduced oxygen levels force cells to rely on anaerobic respiration, leading to higher lactate production.

- **Alcohol intoxication (high NADH/ NAD+)**

  Excessive alcohol intake increases NADH levels, which interferes with the Krebs cycle and promotes a shift to anaerobic respiration, raising lactate levels.

- **↓ Gluconeogenesis**

  If gluconeogenesis is reduced, lactate—normally used as a substrate for glucose production—accumulates, contributing to lactic acidosis.

Clinical Hint: Lactic Acidosis

In each of these conditions, anaerobic respiration increases as the body compensates for reduced aerobic energy production, resulting in elevated lactate and lactic acidosis.

- **↓ Pyruvate Dehydrogenase**

Lowered activity of this enzyme prevents pyruvate from entering the Krebs cycle, redirecting it toward lactate formation.

- **↓ TCA cycle activity**

Mutations or deficiencies in TCA cycle enzymes decrease energy production, shifting metabolism toward anaerobic respiration and increasing lactate output.

- **↓ Pyruvate carboxylase**

Reduced activity of this enzyme leads to pyruvate buildup(it's important for converting pyruvate into oxaloacetate-> curial substrate in gluconeogenesis), **pushing it toward lactate production, which contributes to lactic acidosis.**

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Removed slide 7		
V1 → V2			

Additional Resources:

https://youtu.be/BO0zL03CtDs?si=INd5xRjIIKhEMGRr

https://youtu.be/Nt_r8Ey1i-E?si=_oLAR6nxZmz_I4tU

https://youtu.be/DMoFq3b2Lis?si=9vs5om0IqYKMneZ4

رسالة من الفريق العلمي:

عن عليّ بن أبي طالب رَضِيَ اللَّهُ عَنهُ قال، قال رَسُول اللَّه صلى اللّه عليه وسلم ﷺ :

("الْبخِيلُ مَنْ ذُكِرْتُ عِنْدَهُ، فَلَم يُصَلِّ علَيَّ.")