بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Lecture 11

Glycolysis Pt.2

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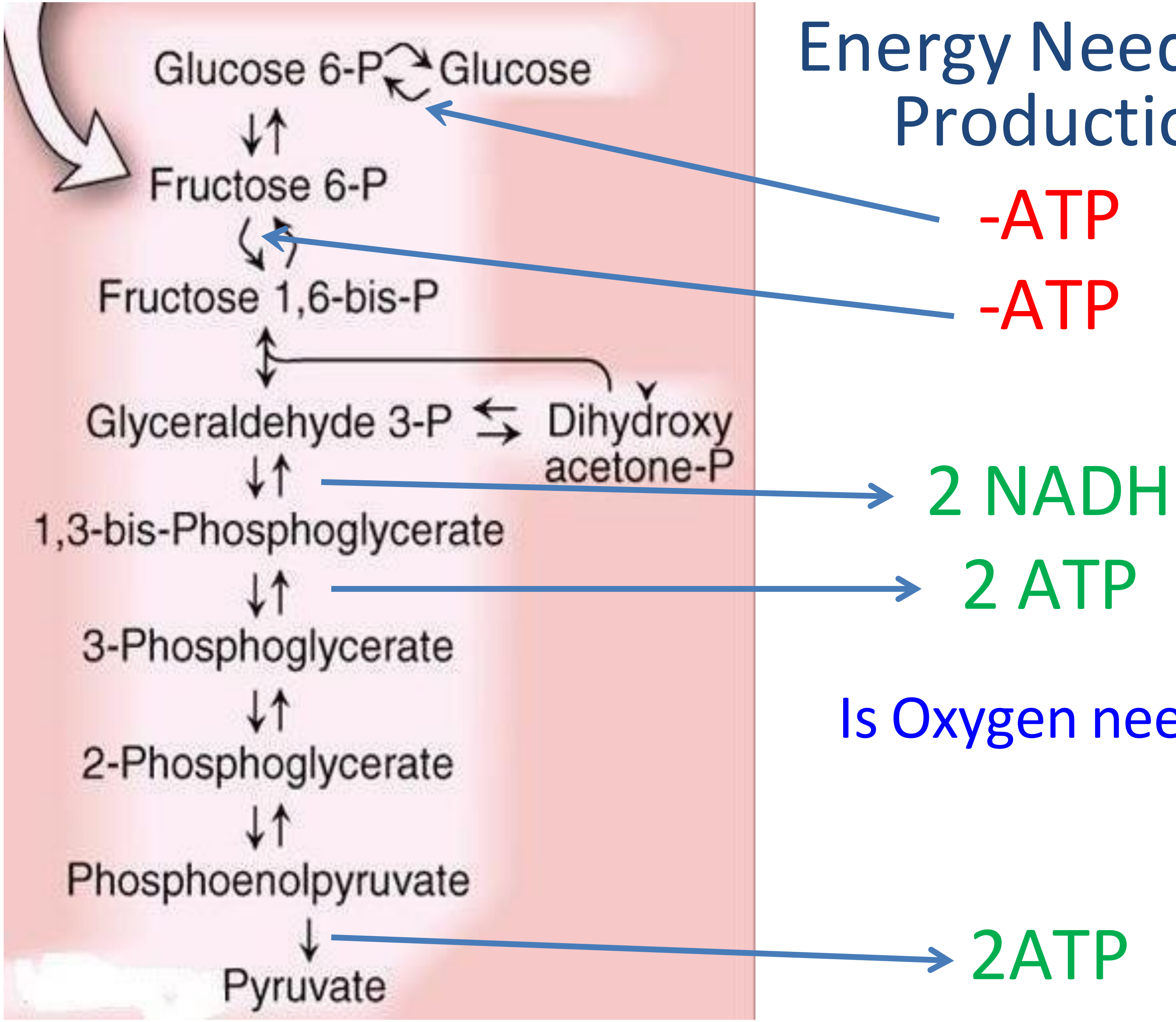
Energy Need and Production



Is Oxygen needed?

- As we can see in the first phase of glycolysis, in the preparatory phase, we had to use two ATP molecules for the two phosphorylation events that occurred.

-First phosphorylation: transforming glucose to glucose-6-phosphate (hexokinase).
-Second phosphorylation: fructose-6-phosphate to fructose-1,6-bisphosphate (phosphofructokinase-1, PFK-1).

- In the second phase, however, there will be production of two ATP per one glyceraldehyde-3-phosphate molecule that entered the second phase.

-First ATP: produced during the reaction from 1,3-bisphosphoglycerate to 3-phosphoglycerate (phosphoglycerate kinase).
-Second ATP: from PEP to pyruvate (pyruvate kinase).

- Since the second phase is repeated twice due to the presence of two glyceraldehyde-3-phosphate molecules, there will be four ATP produced per glucose. So, net ATP is 2 ATP and there is 2 NADH (produced during glyceraldehyde-3-phosphate → 1,3-bisphosphoglycerate, catalyzed by glyceraldehyde-3-phosphate dehydrogenase).

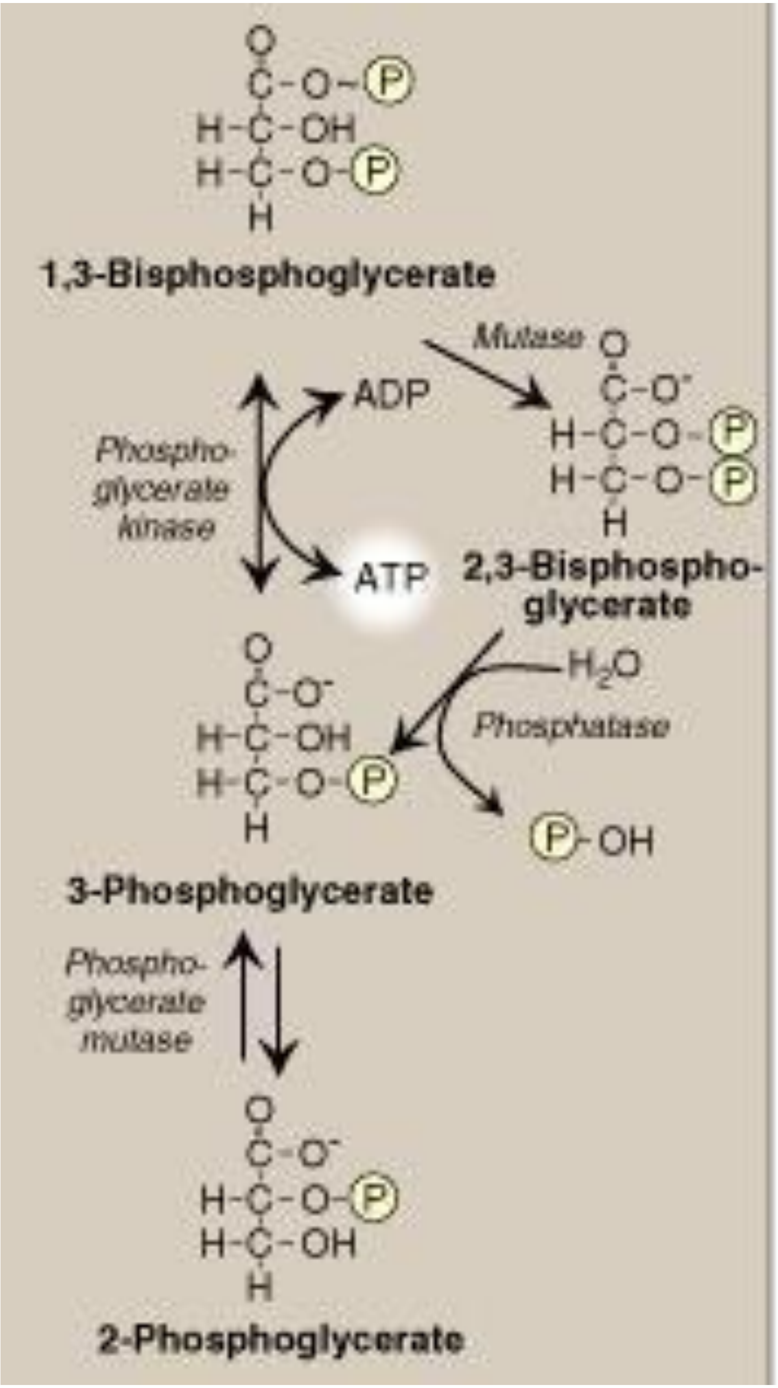
Glycolysis and Oxygen Independence

- Glycolysis does not require oxygen at any step.
- It is therefore oxygen-independent, occurring under both aerobic and anaerobic conditions.
- This universality makes glycolysis a fundamental pathway in all cells.

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

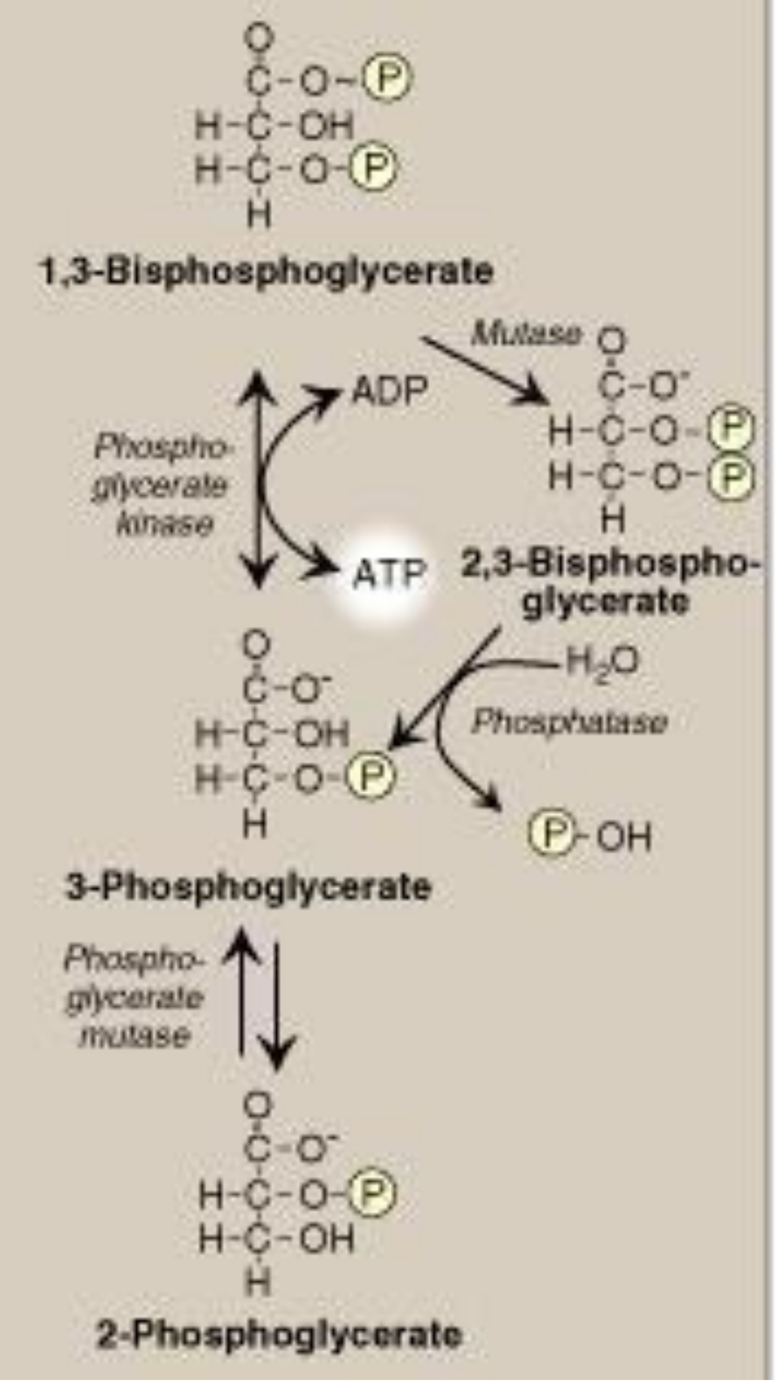


2,3-Bisphosphoglycerate Production in Red Blood Cells (RBCs)

In RBCs, a **divergent detour** occurs in glycolysis between **1,3-bisphosphoglycerate (1,3-BPG)** and **3-phosphoglycerate**, the step normally producing ATP via **phosphoglycerate kinase**.

Physiological context:

- RBCs deliver oxygen to peripheral tissues.
- After oxygen is released, it must diffuse into surrounding cells for metabolism.
- To prevent oxygen from rebinding hemoglobin prematurely, hemoglobin must be stabilized in the **T-state (tense state)**.



2,3-Bisphosphoglycerate Production in Red Blood Cells (RBCs)

Mechanism:

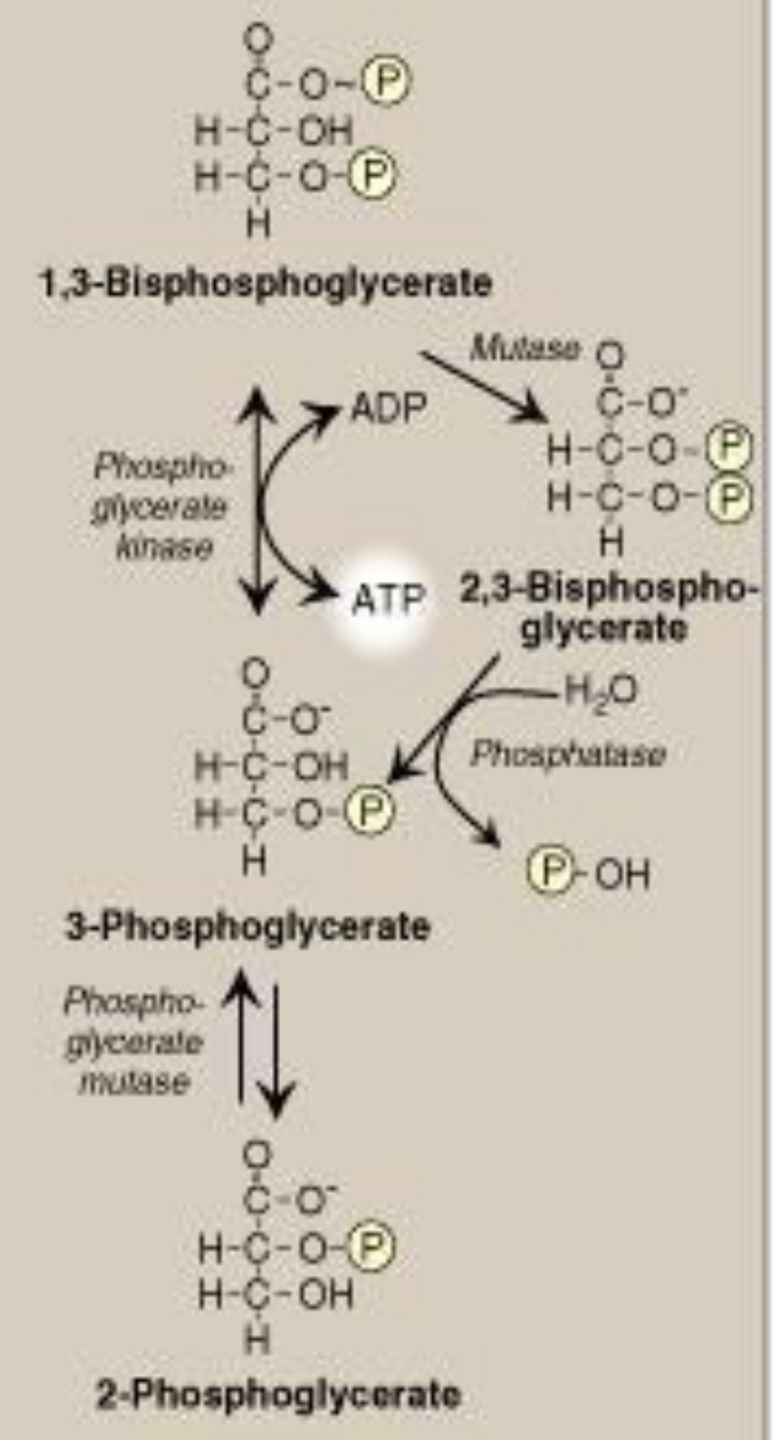
- 1,3-BPG is converted to **2,3-bisphosphoglycerate (2,3-BPG)** via a **mutase enzyme**, transferring a phosphate from carbon-1 to carbon-2.
- 2,3-BPG binds hemoglobin, stabilizing the T-state and **reducing hemoglobin's affinity for oxygen**.
- Afterward, a **phosphatase enzyme** removes a phosphate as inorganic phosphate, forming **3-phosphoglycerate**.
- Glycolysis then continues along the normal pathway.

Functional consequence:

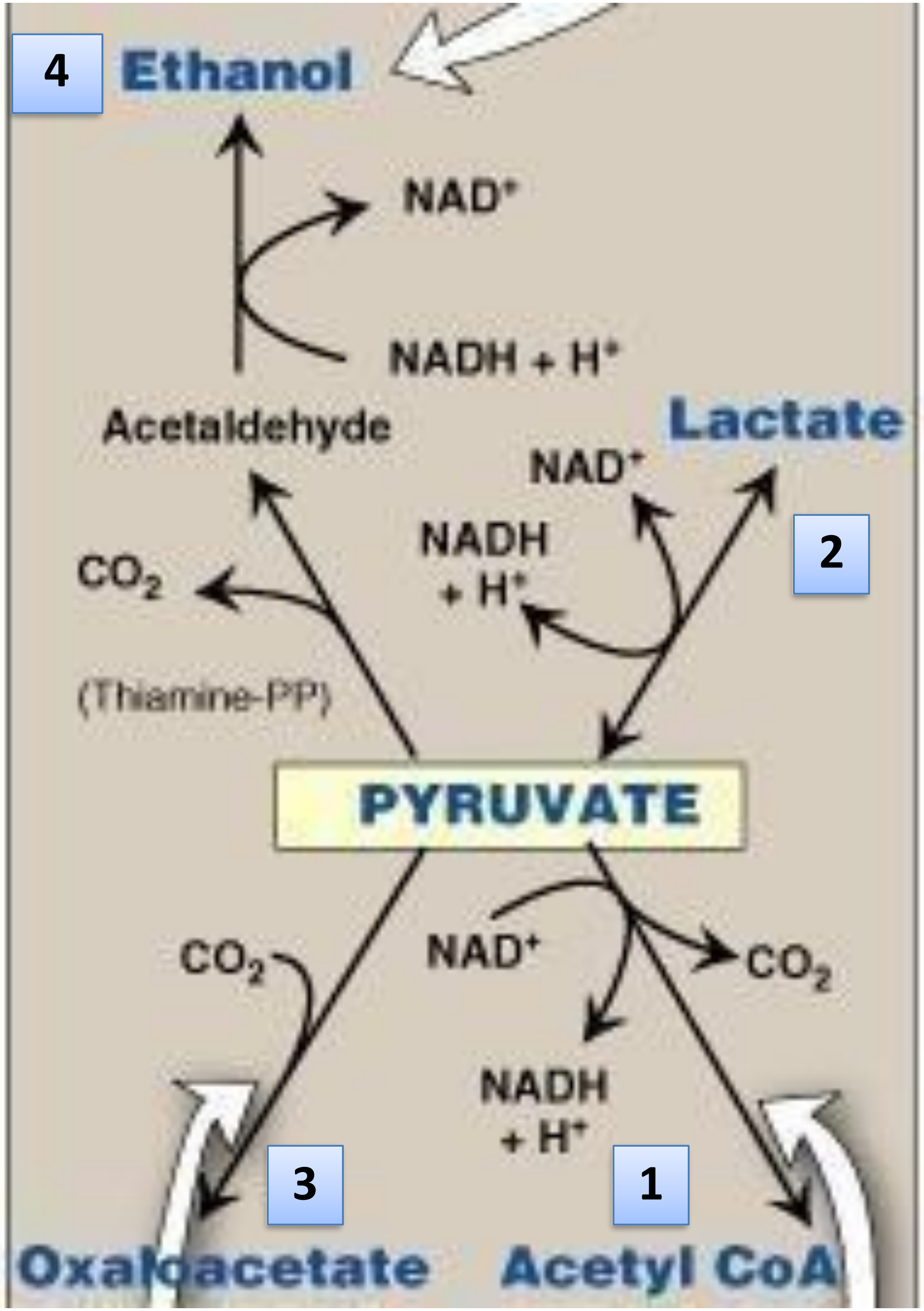
- ATP production by **phosphoglycerate kinase** is bypassed, so this detour **does not produce ATP**.
- Normally, glycolysis produces 2 ATP per glucose in RBCs; this detour temporarily reduces ATP yield to zero.
- This is a **sacrificial step** to ensure proper hemoglobin function and efficient oxygen delivery.

Physiological specificity:

- This detour occurs **only near peripheral tissues**.
- In other regions, such as blood vessels and the lungs, glycolysis proceeds normally, producing sufficient ATP for the **low energy demands of RBCs**.



Pyruvate Fates



Fates of Pyruvate

What happens to pyruvate molecules produced by glycolysis?

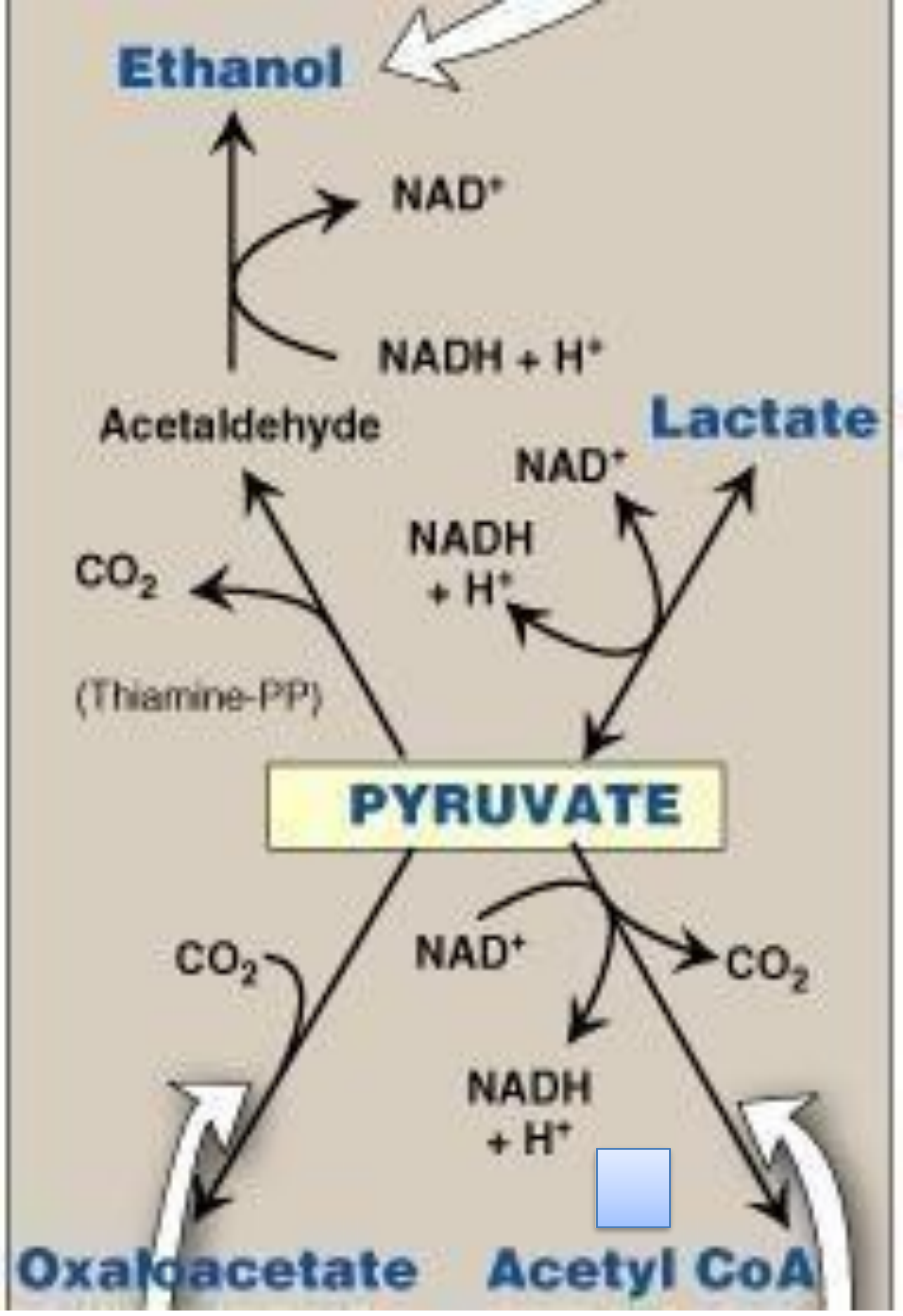
- The pyruvate molecule produced by glycolysis has multiple fates, depending on the cellular conditions.
- Pyruvate can also originate from other sources, such as the metabolism of certain amino acids—not just glycolysis.

1. Conversion to Acetyl-CoA:

- Pyruvate is converted to acetyl-CoA by the pyruvate dehydrogenase complex.
- Acetyl-CoA can then enter the Krebs cycle for aerobic energy production.

2. Conversion to Lactate:

- Under anaerobic conditions, pyruvate is reduced to lactate via lactate dehydrogenase, regenerating NAD$^+$.



Fates of Pyruvate

What happens to pyruvate molecules produced by glycolysis?

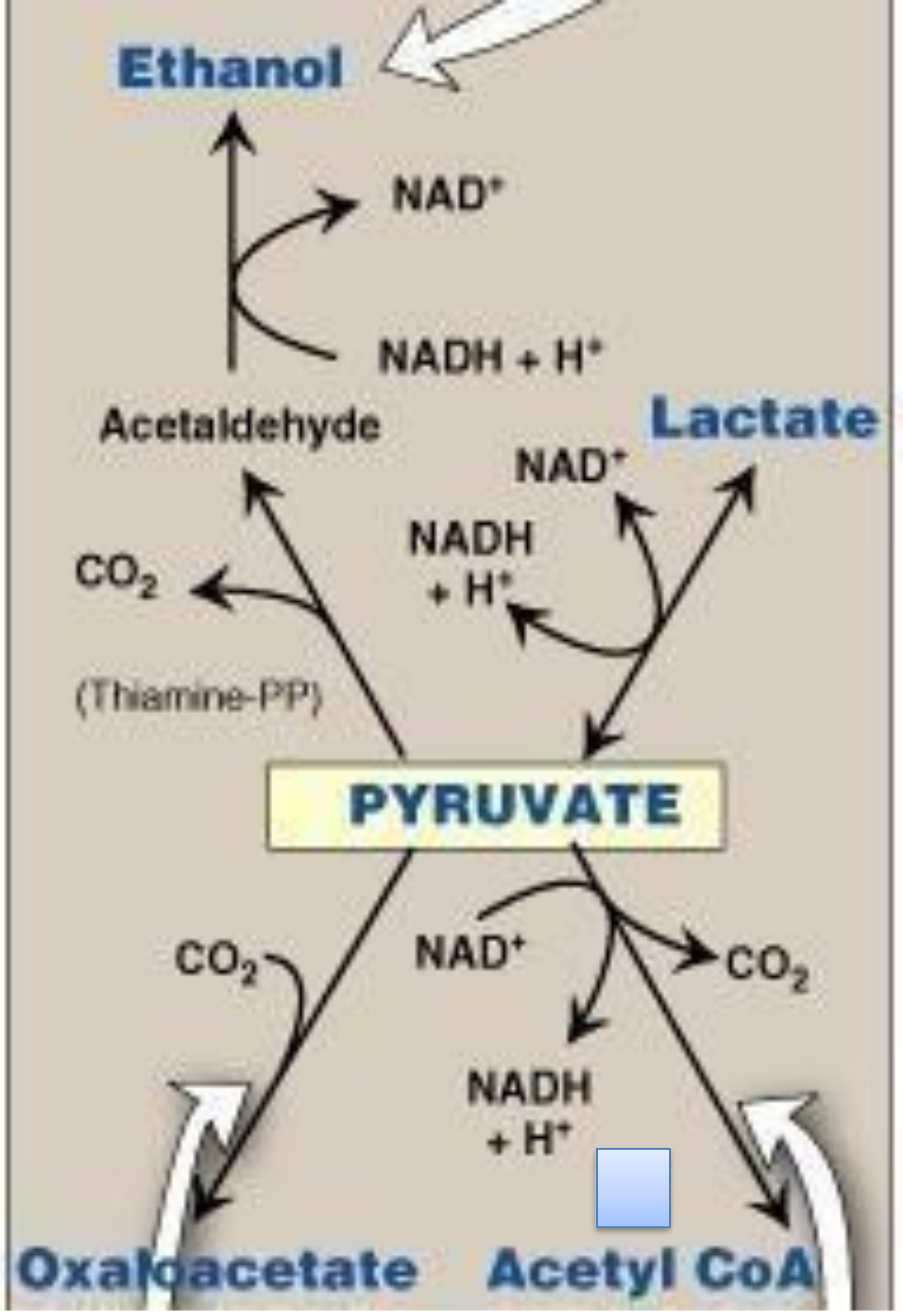
3. Conversion to Oxaloacetate:

- Pyruvate can be **carboxylated to oxaloacetate** by **pyruvate carboxylase**.
- This reaction is important for **gluconeogenesis** (synthesis of glucose).

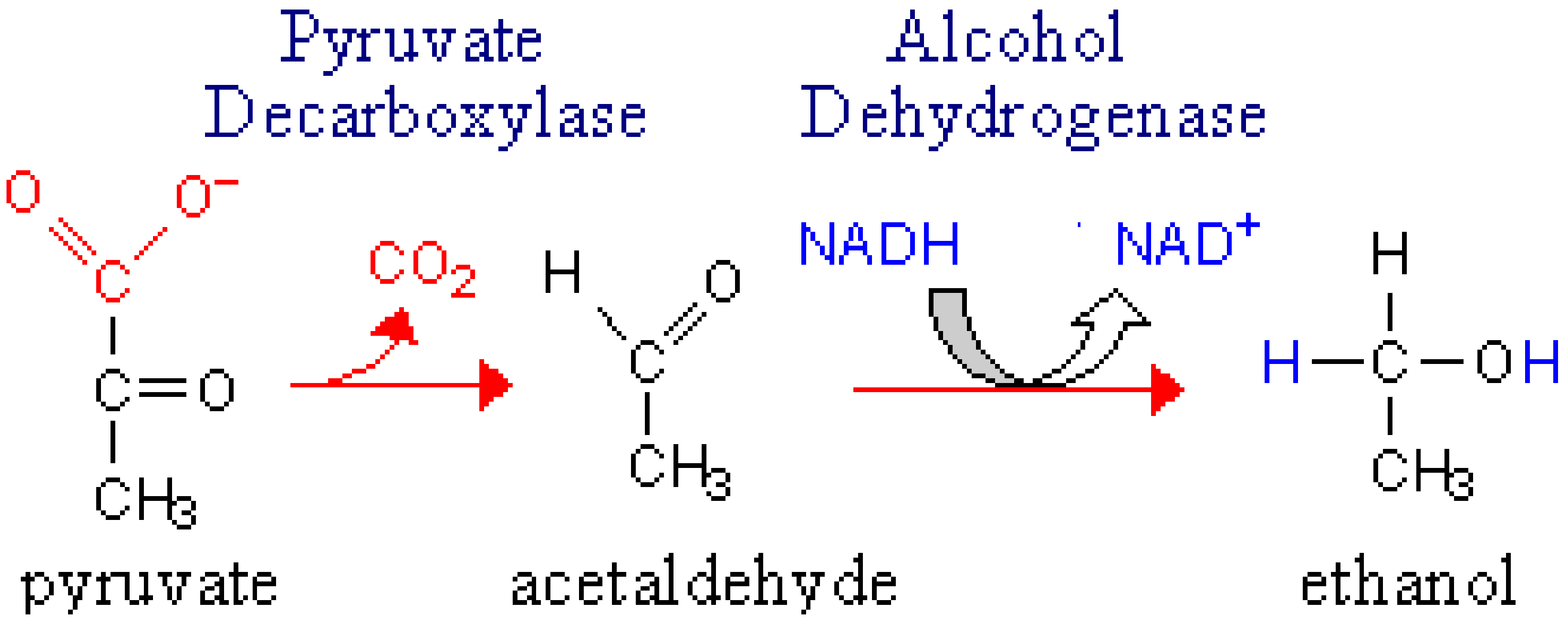
4. Conversion to Ethanol (in other organisms, e.g., yeast):

- Pyruvate is decarboxylated to **acetaldehyde** and then reduced to **ethanol**.
- This pathway does **not occur in humans** but is relevant in other cell types.
- Each of these fates depends on the **metabolic needs and oxygen availability** of the cell.

We will discuss each fate **separately**.



1. From Pyruvate to Ethanol



Conversion of Pyruvate to Ethanol (Fermentation in Yeast)

- This pathway occurs in **yeast** and involves **two steps**:

1. Decarboxylation of Pyruvate:

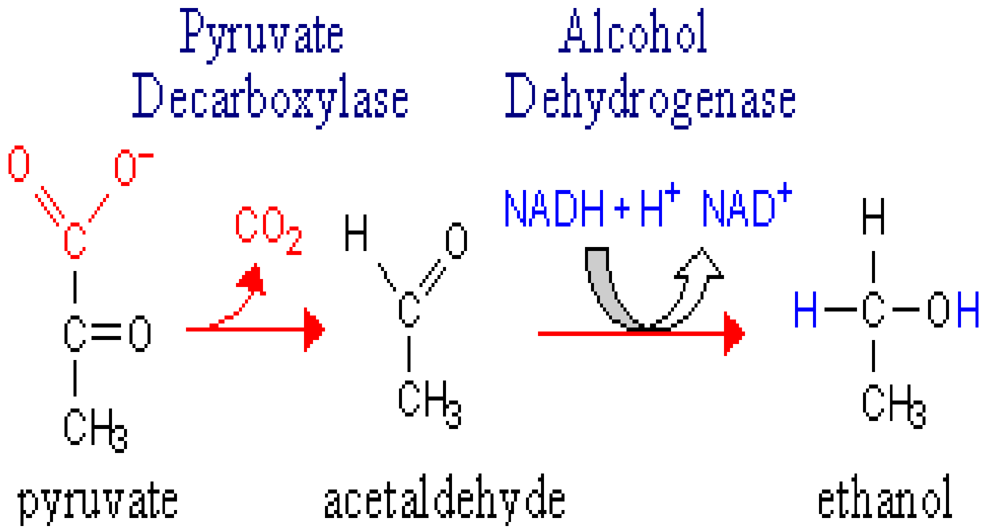
- Catalyzed by **pyruvate decarboxylase**.
- Pyruvate loses a carboxyl group, producing **acetaldehyde** and releasing **CO_2**.

2. Reduction of Acetaldehyde to Ethanol:

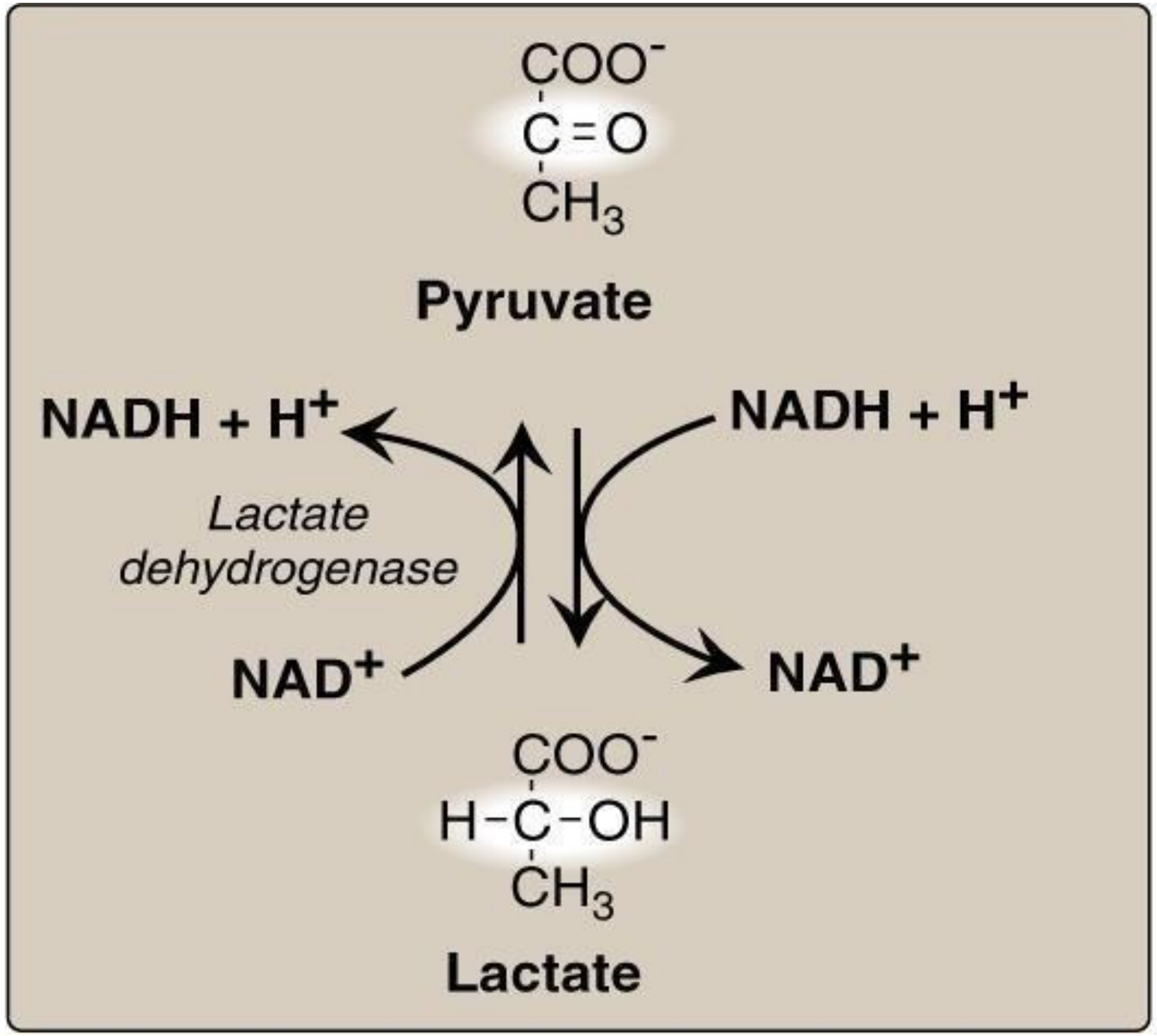
- Catalyzed by **alcohol dehydrogenase**.
- Acetaldehyde is reduced to **ethanol**, and **NADH is oxidized to NAD^+**.

Physiological relevance in baking:

- The CO_2 produced during decarboxylation causes dough to rise, making it **fluffy** and increasing its size.



2. From Pyruvate to Lactate



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

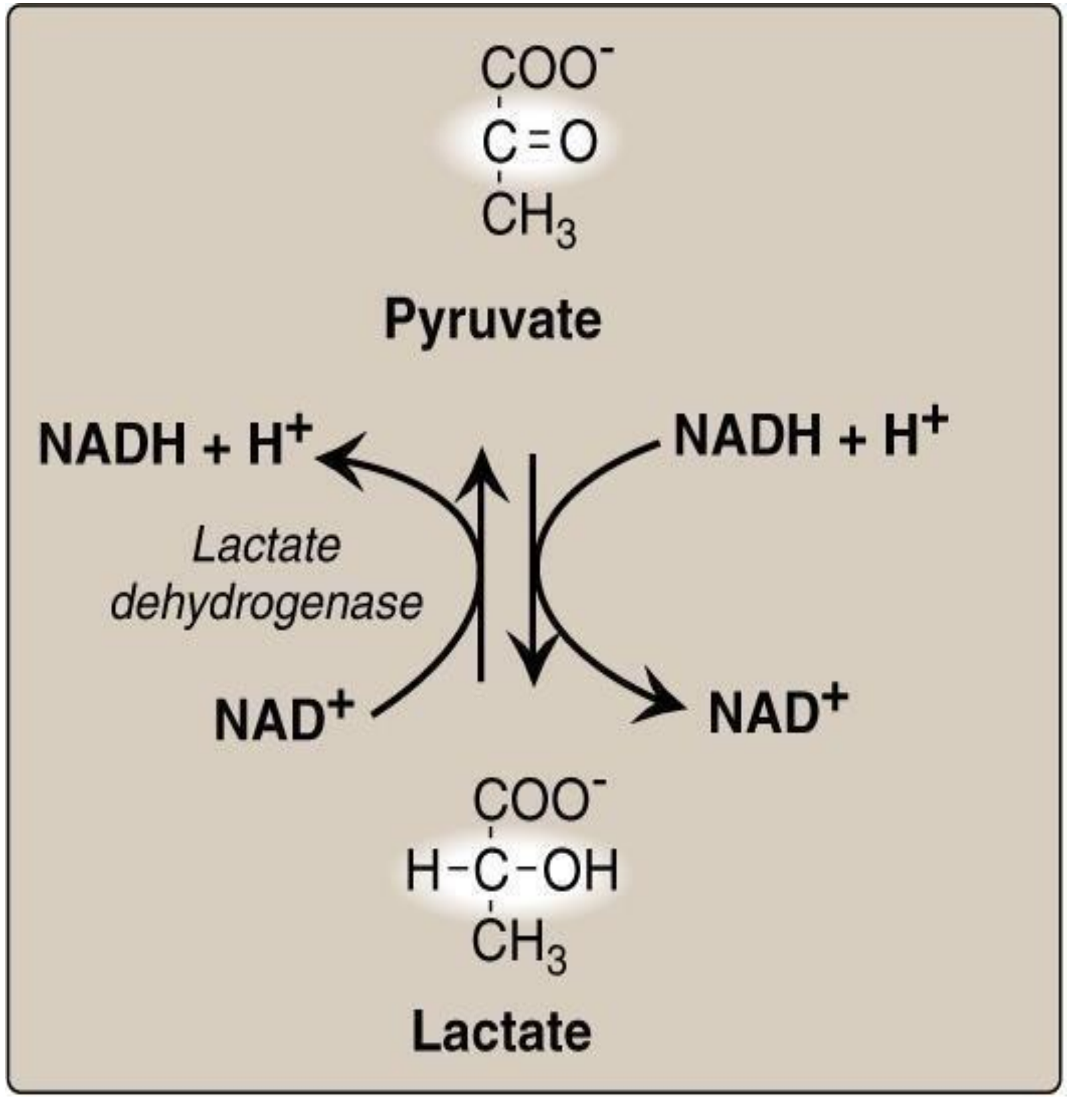
Conversion of Pyruvate to Lactate

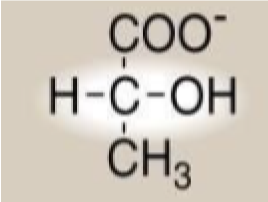
- This occurs under **anaerobic conditions**, when oxygen is insufficient.

- Pyruvate produced by glycolysis is reduced to **lactate** in an **oxidation-reduction reaction**:

1. **The carbonyl group of pyruvate** is reduced to an alcohol group.
2. **NADH is oxidized to NAD^+** during this reaction.

- The reaction is catalyzed by **lactate dehydrogenase**.
- This enzyme is **reversible**, allowing lactate to be oxidized back to pyruvate when oxygen becomes available.





Lactate

When is Lactate Produced?

Generally speaking:

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

Low amount of O_2 can affect the tissue or the whole body; it can be either **generalized** or **localized** to certain tissues.

to survive brief episodes of hypoxia

Like in RBCs, they can activate **anaerobic respiration**. RBCs, for example, **don't have mitochondria**, so they cannot use the TCA cycle or **OXPHOS** to produce ATP. Instead, they produce ATP through **glycolysis**, with pyruvate being reduced to **lactate**. In these cells, lactate **doesn't cause fatigue**; fatigue only occurs in **muscle cells**.

At the beginning, there is **dependence on aerobic respiration** to produce ATP/energy. But at some point, there may be an **inadequate amount of O_2** for the TCA cycle ETC. That's why there is a **shift toward anaerobic respiration**, producing **lactate**.

To survive episodes of hypoxia, where certain tissues, cells, or even the whole body receive low oxygen, cells become more dependent on anaerobic respiration to produce at least some energy. Although the energy yield from anaerobic respiration is much lower than with O_2, it is enough to maintain basic cellular functions during these hypoxic conditions.

Clinical Hint: Lactic Acidosis

Whenever the concentration of **lactate** increases under these conditions, it may lead to **lactic acidosis**, because lactate is acidic in nature. It contains a **carboxyl group** and an **alcohol group**, both contributing to its acidity. High lactate levels can reduce **plasma pH below 7.4**, making it one of the causes of **metabolic acidosis**.

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

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

- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
  - Impaired O_2 transport caused by respiratory failure.
  - Respiratory failure causes impaired O2 transport.
  - Uncontrolled hemorrhage which reduces hemoglobin and oxygen-carrying capacity, increasing reliance on anaerobic respiration and lactate production.

Other causes:
-**Problems** with oxidative phosphorylation.
-**Defective hemoglobin** affecting oxygen delivery.

Clinical Hint: Lactic Acidosis

- Direct inhibition of oxidative phosphorylation
- Hypoxia in any tissue
- Alcohol intoxication (high NADH/ NAD+)
- ↓ Gluconeogenesis
- ↓ Pyruvate Dehydrogenase
- ↓ TCA cycle activity
- ↓ Pyruvate carboxylase

Causes of Lactic Acidosis

Direct inhibition of oxidative phosphorylation / ETC:

- Interferes with oxygen-dependent energy production
- Increases reliance on **anaerobic respiration** to compensate

Hypoxia:

- Low oxygen availability, either **localized** (e.g., myocardial infarction, stroke) or **generalized**
- Shifts metabolism toward lactate production

Alcohol intoxication:

- Alcohol metabolized to **acetaldehyde**, reducing **NAD^+ to NADH**
- High NADH/NAD^+ ratio inhibits the **Krebs cycle**
- More dependence on anaerobic respiration → lactate accumulation

Causes of Lactic Acidosis

Reduced gluconeogenesis:
- Glucose production from non-carbohydrate precursors (e.g., lactate) is impaired
- Leads to **lactate accumulation**

Reduced pyruvate dehydrogenase activity:
- Pyruvate → Acetyl-CoA conversion is impaired
- Pyruvate accumulates and is redirected to lactate

Reduced TCA (Krebs) cycle activity:
- Enzyme mutations or deficiencies reduce aerobic ATP production
- Increases lactate production

Reduced pyruvate carboxylase activity:
- Pyruvate → Oxaloacetate conversion is impaired
- Gluconeogenesis is reduced, leading to pyruvate accumulation → lactate

Overall effect:
- Increased lactate production under various conditions → **lactic acidosis**

رسالة من الفريق العلمي:

Discipline will beat motivation every single time.

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Corrections from previous versions:

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