بسم الله الرحمن الرحيم

Oxidative Decarboxylation and Krebs Cycle

By

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Objectives: Oxidative Decarboxylation

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

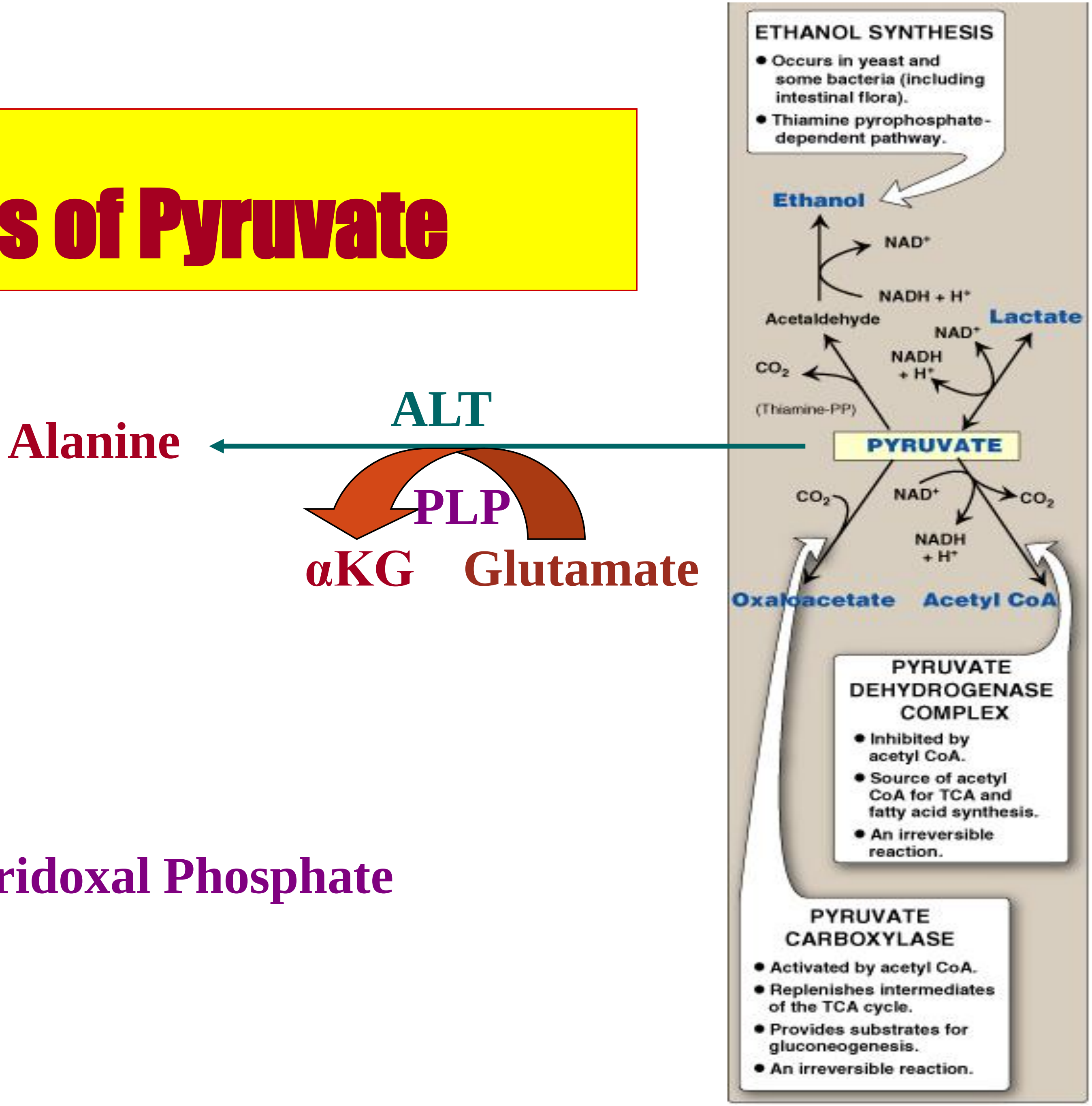
- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoA
- Discuss the major regulatory mechanisms for PDH complex
- Recognize the clinical consequence of abnormal oxidative decarboxylation reactions

Objectives: Krebs Cycle

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

- Recognize the importance of Krebs cycle
- Identify various reactions of Krebs cycle
- Define the regulatory mechanisms of Krebs cycle
- Assess the energy yield of PDH reaction and Krebs cycle's reactions

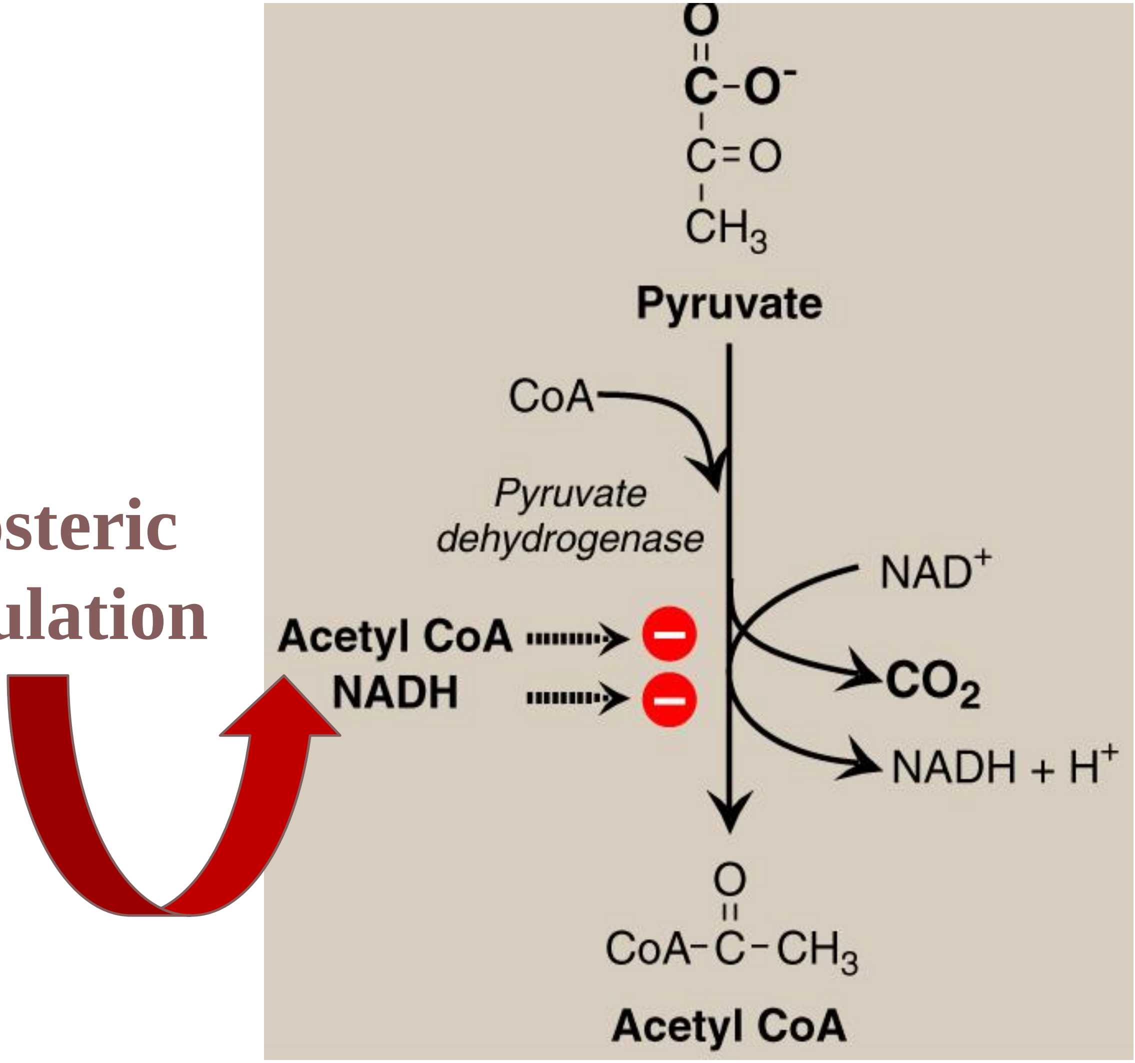
Fates of Pyruvate



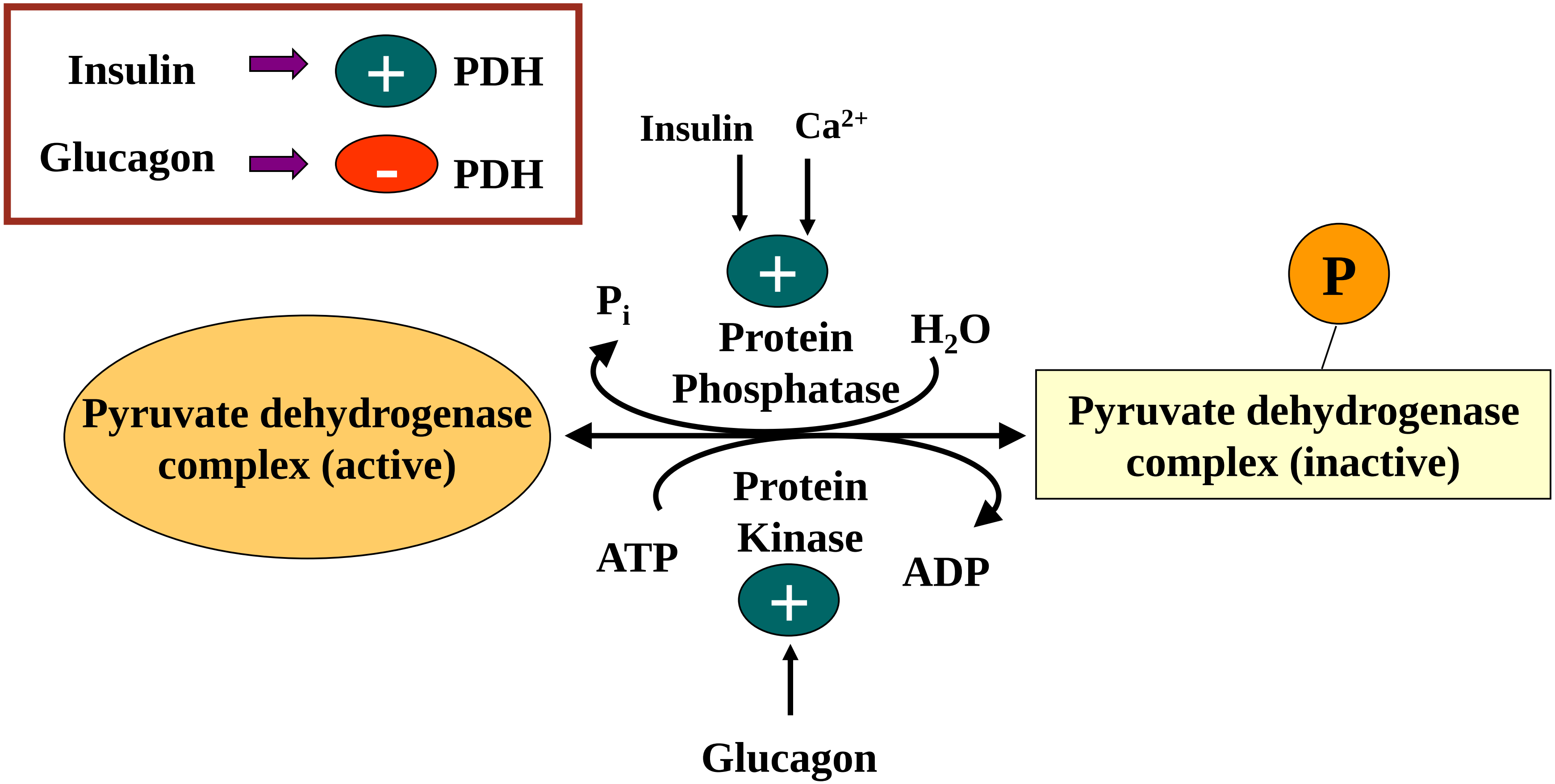
PLP = Pyridoxal Phosphate

Oxidative Decarboxylation of Pyruvate

Allosteric Regulation



PDH Complex: Covalent Regulation



PDH Reaction: Clinical application

1. Deficiencies of thiamine or niacin can cause serious CNS problems. WHY?
   - Brain cells are unable to produce sufficient ATP if the PDH complex is inactive.

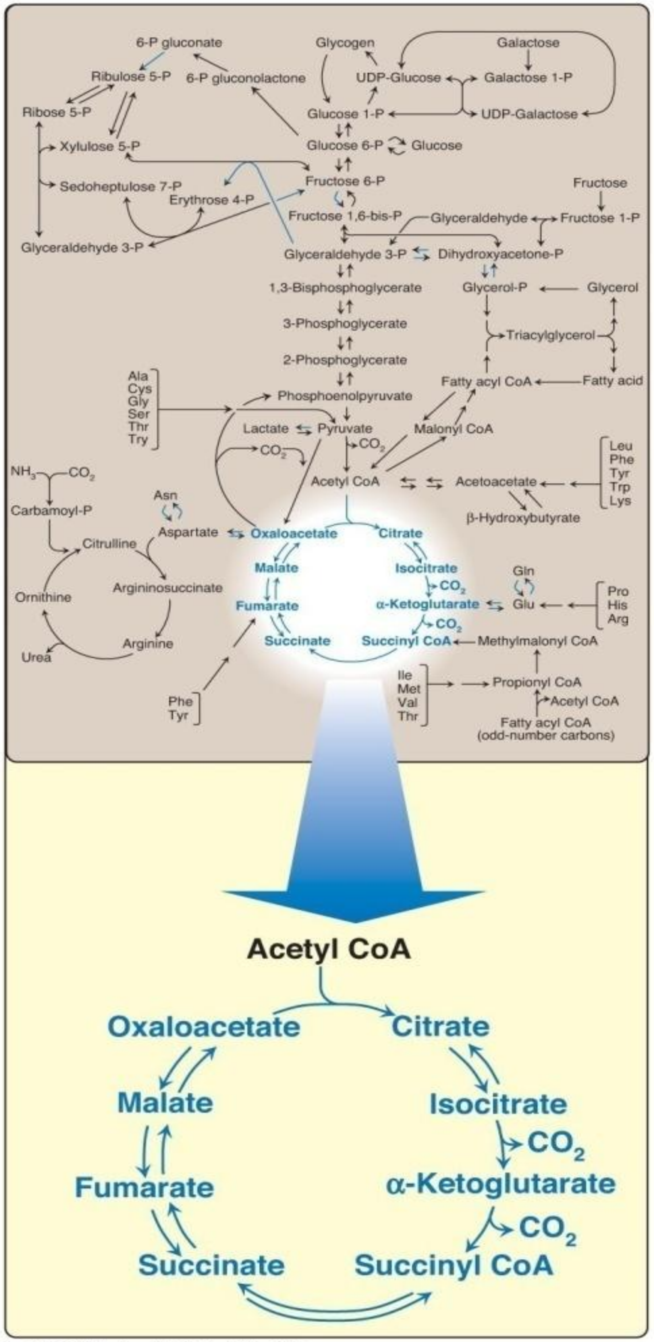
2. **Wernicke-Korsakoff** (encephalopathy-psychosis syndrome) due to thiamine deficiency, may be seen especially with alcohol abuse.

3. PDH complex deficiency is the most common biochemical cause of **congenital lactic acidosis.**

Krebs Cycle

The tricarboxylic acid cycle (Krebs) shown as a part of the essential pathways of energy metabolism.

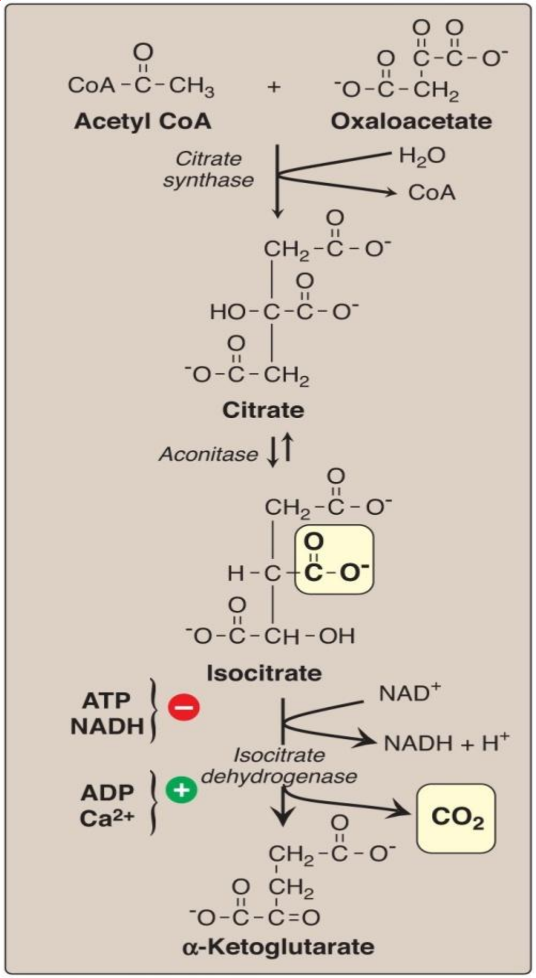
CoA = coenzyme A.



Tricarboxylic Acid Cycle: Krebs Cycle

- Final common pathway for oxidation
- Exclusively in mitochondria
- Major source for ATP
- Mainly catabolic with some anabolic features
- Synthetic reactions (anabolic features):
  - Glucose from amino acids
  - Nonessential amino acids
  - Fatty acids
  - Heme

Krebs Cycle Reactions (1)

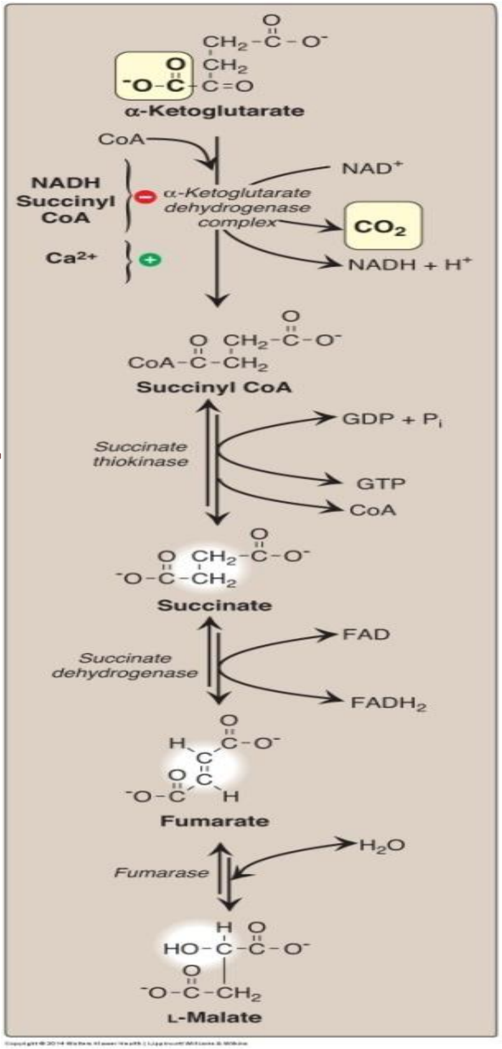


Formation of α-ketoglutarate from acetyl coenzyme A (CoA) and oxaloacetate. NAD(H) = Nicotinamide adenine dinucleotide.

Krebs Cycle Reactions (2)

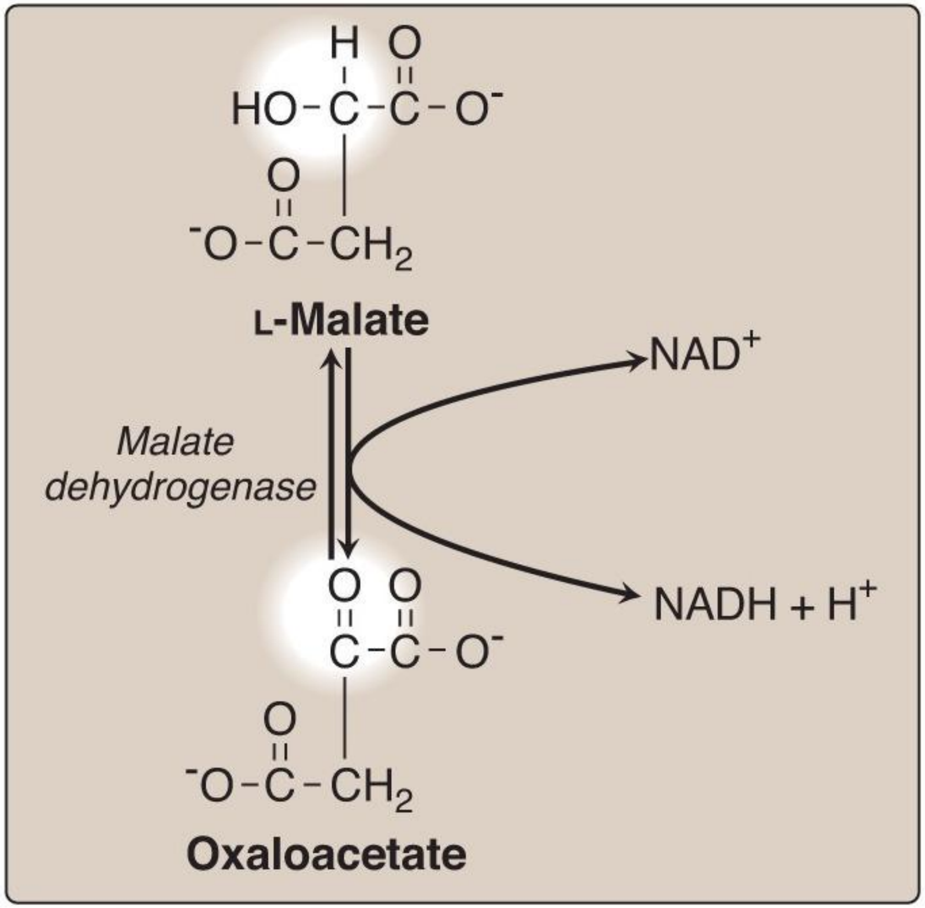
Succinate Thiokinase

Substrate-Level Phosphorylation



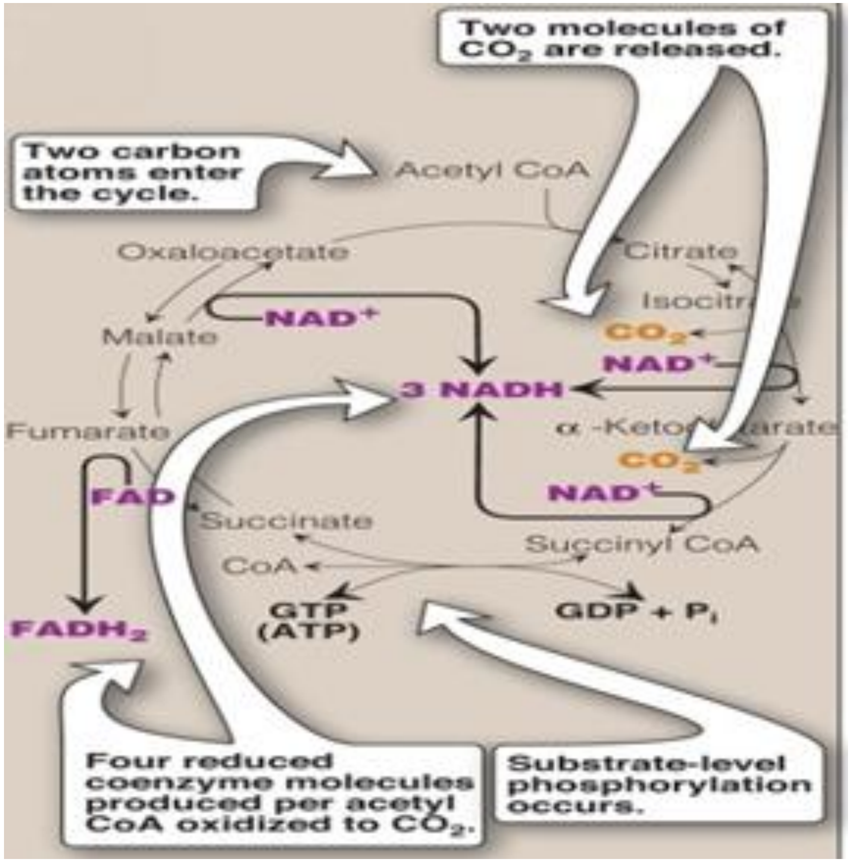
Formation of malate from α-ketoglutarate.
NAD(H) = nicotinamide adenine dinucleotide; GDP = guanosine diphosphate;
P = phosphate; CoA = coenzyme A; FAD(H_2) = flavin adenine dinucleotide.

Krebs Cycle Reactions (3)



Formation (regeneration) of oxaloacetate from malate.
NAD(H) = nicotinamide adenine dinucleotide

Krebs Cycle: Energy Yield



Number of ATP molecules produced from the oxidation of one molecule of acetyl coenzyme A (CoA) using both substrate-level and oxidative phosphorylation.

Krebs Cycle: Energy Yield

Energy-producing reaction	Number of ATP produced
3 NADH ⟶ 3 NAD^+	9
$FADH_2$ ⟶ FAD	2
GDP + P_i ⟶ GTP	1
	12 ATP/acetyl CoA oxidized

Number of ATP molecules produced from the oxidation of one molecule of acetyl coenzyme A (CoA) using both substrate-level and oxidative phosphorylation.

Net ATP Production by Complete Glucose Oxidation

Aerobic glycolysis:		**8 ATP**
Oxidative decarboxylation:	**2 X 3 =**	**6 ATP**
Krebs cycle:	**2 X 12 =**	**24 ATP**
Net:		**38 ATP**

Regulation of Oxidative Decarboxylation and Krebs Cycle

- PDH complex and the TCA cycle are both **up-regulated** in response to a **decrease in the ratio** of
  - ATP:ADP
  - NADH:NAD^+
- TCA cycle activators are:
  - ADP
  - Ca^{2+}
- TCA cycle inhibitors are:
  - ATP
  - NADH

Take Home Message

- **Pyruvate is oxidatively decarboxylated by PDH to acetyl CoA inside the mitochondria**
- **Krebs cycle:**
  - **Final common pathway for the oxidation of carbohydrates, fatty acids and amino acids**
  - **occurs in the mitochondria**
  - **Aerobic**
  - **Mainly catabolic, with some anabolic reactions**
- **The complete oxidation of one glucose molecule results in a net production of 38 ATP molecules**

Thank you