بسم الله الرحمن الرحيم

Oxidative Decarboxylation and Krebs Cycle

By

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Objectives: Oxidative Decarboxylation

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

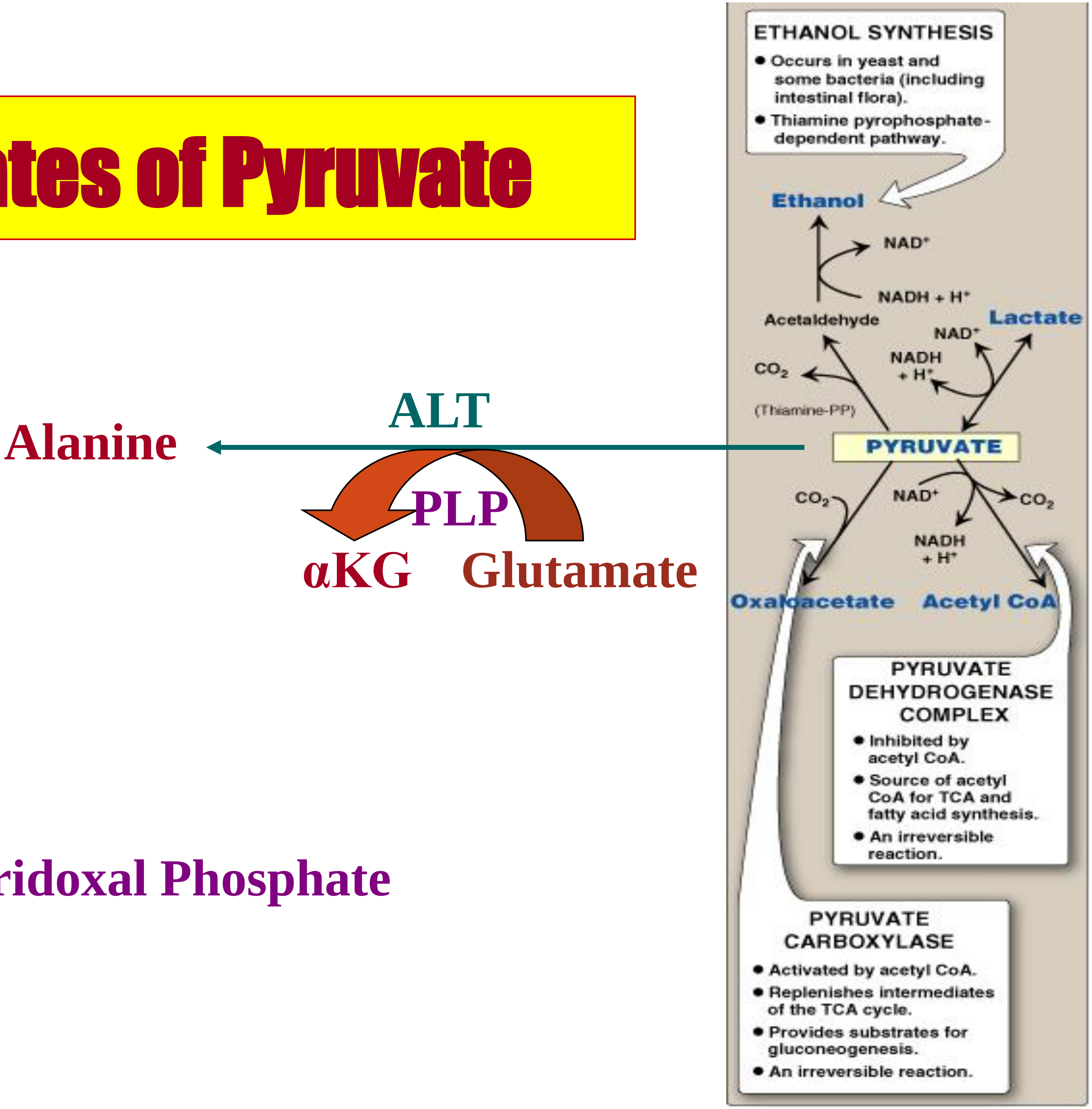
- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoA
- Discuss the major regulatory mechanisms for PDH complex
- Recognize the clinical consequence of abnormal oxidative decarboxylation reactions

Objectives: Krebs Cycle

By the end of this part of the 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

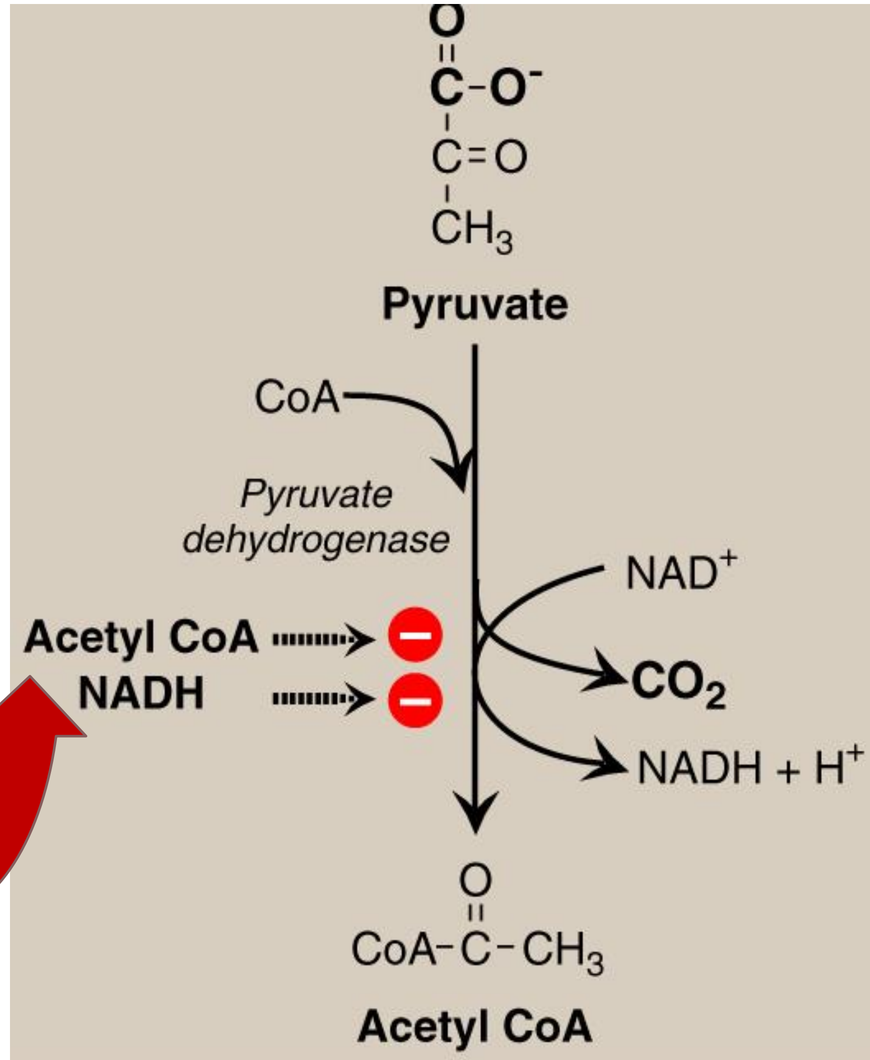
Fates of Pyruvate



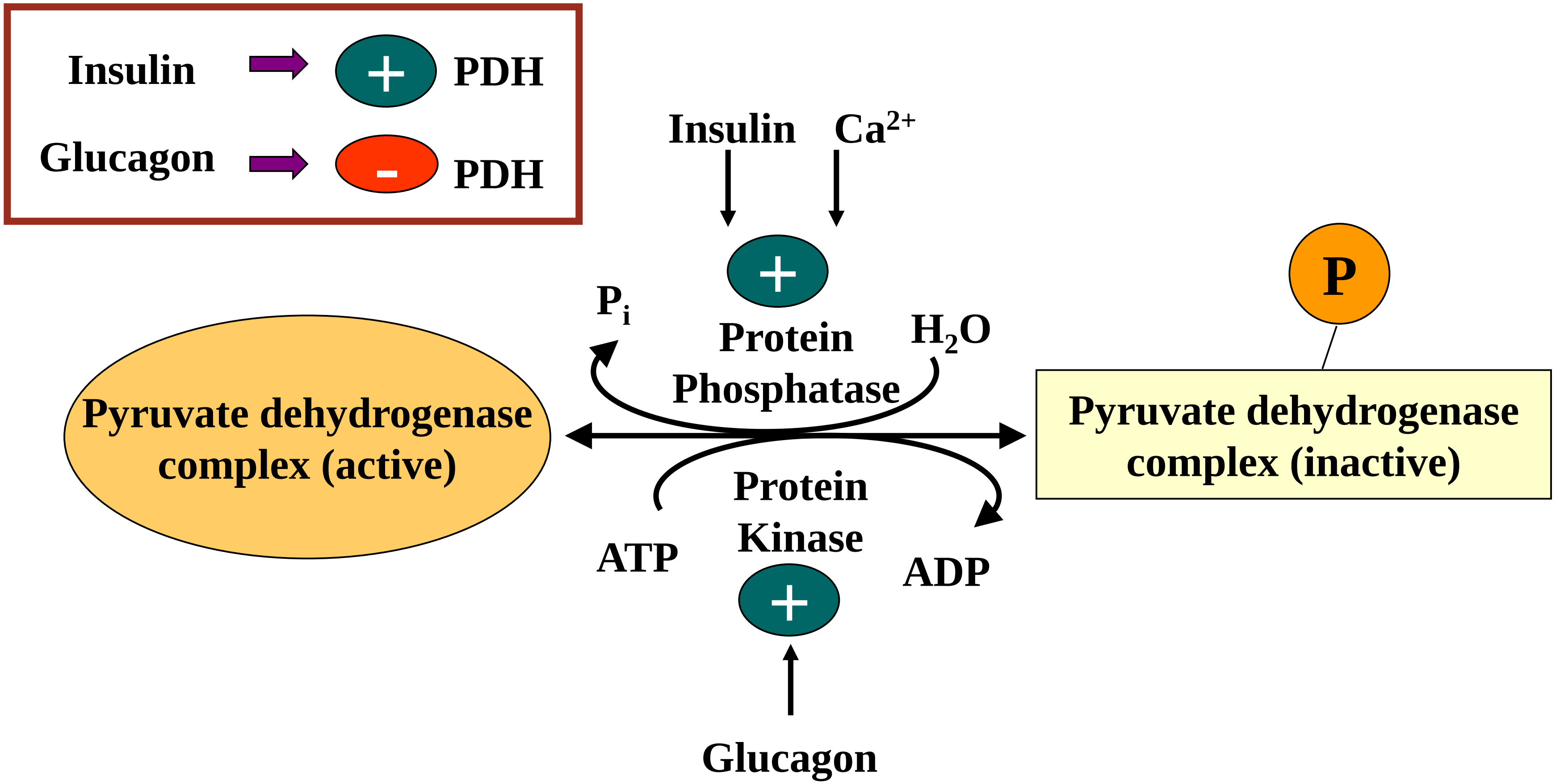
PLP = Pyridoxal Phosphate

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.

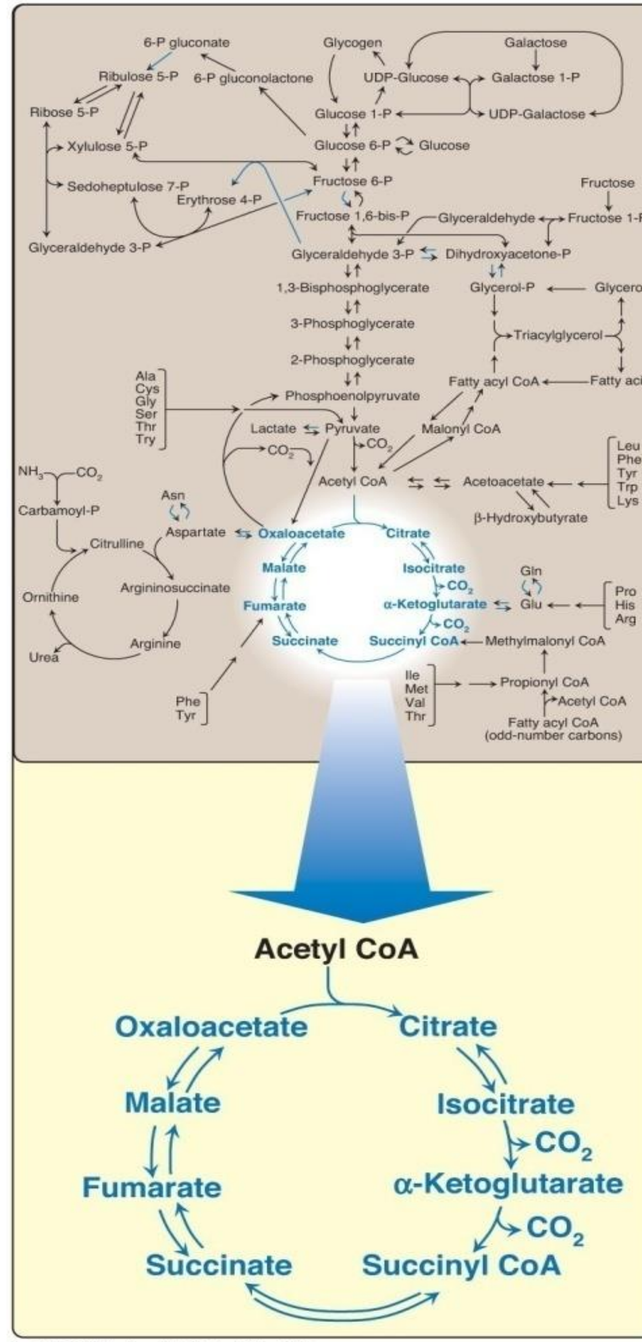
2. Wernicke-Korsakoff (encephalopathy-psychosis syndrome) due to thiamine deficiency, may be seen with alcohol abuse.

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.

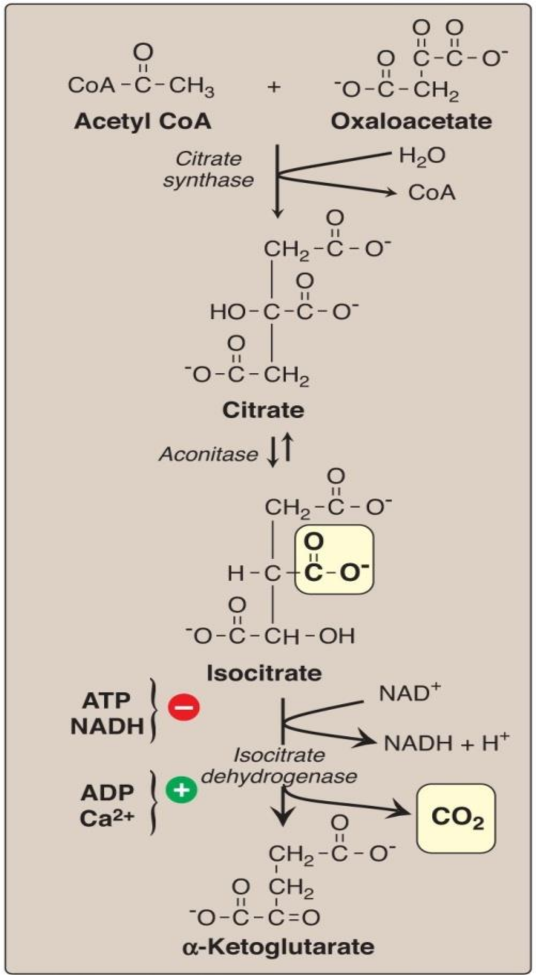
CoA = coenzyme A



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)

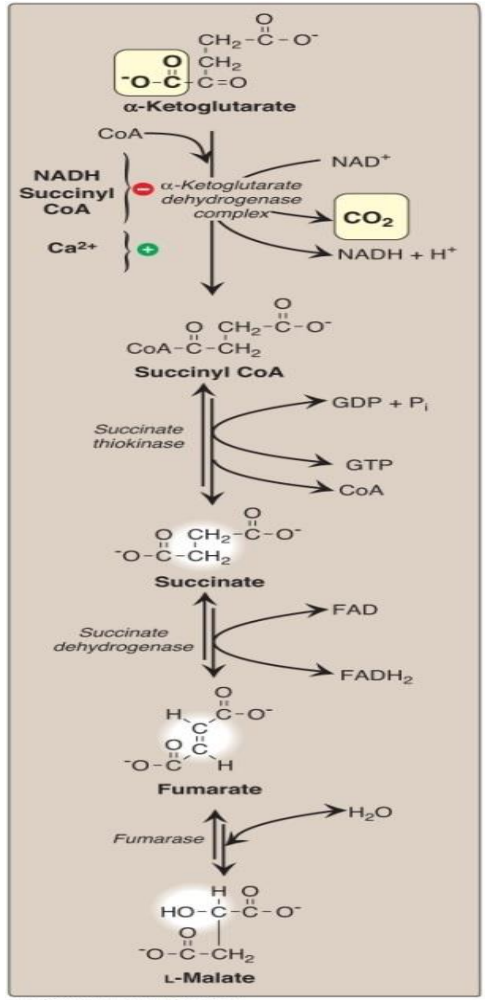


Formation of α-ketoglutarate from acetyl coenzyme A (CoA) and oxaloacetate.
NAD(H) = Nicotinamide adenine dinucleotide

Krebs Cycle Reactions (2)

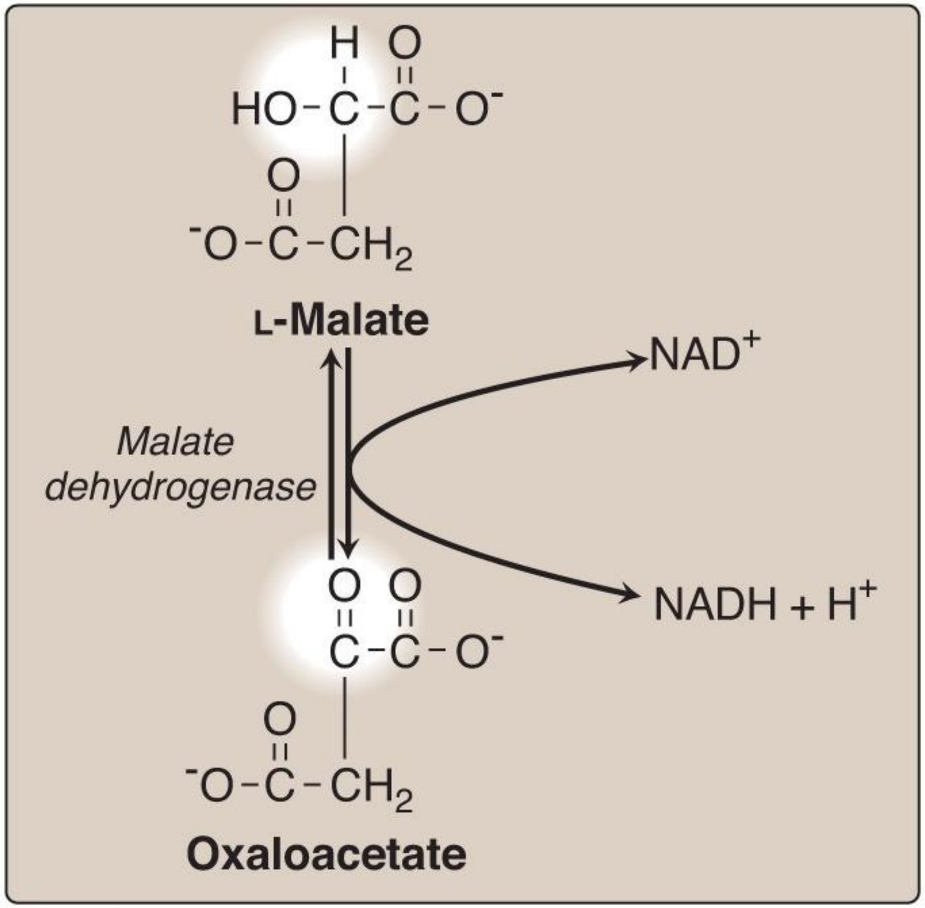
Succinate Thiokinase

Substrate-Level Phosphorylation



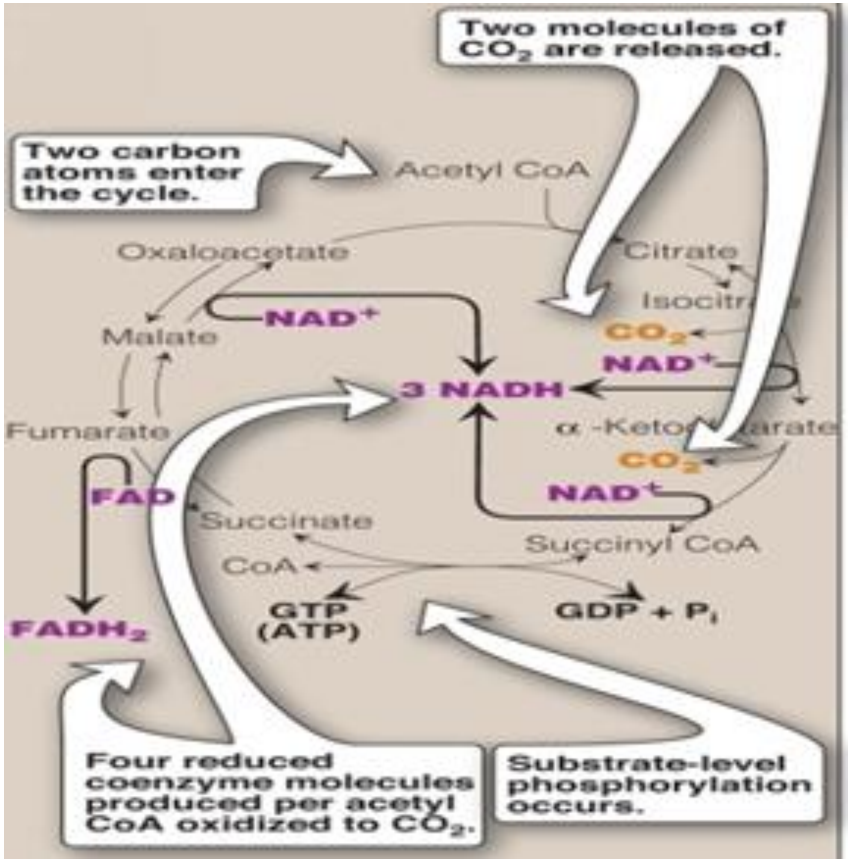
Formation of malate from α-ketoglutarate.
NAD(H) = nicotinamide adenine dinucleotide; GDP = guanosine diphosphate;
P = phosphate; CoA = coenzyme A; FAD(H_2) = flavin adenine dinucleotide.

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