

Oxidative Decarboxylation and Krebs Cycle

Objectives: Oxidative Decarboxylation

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

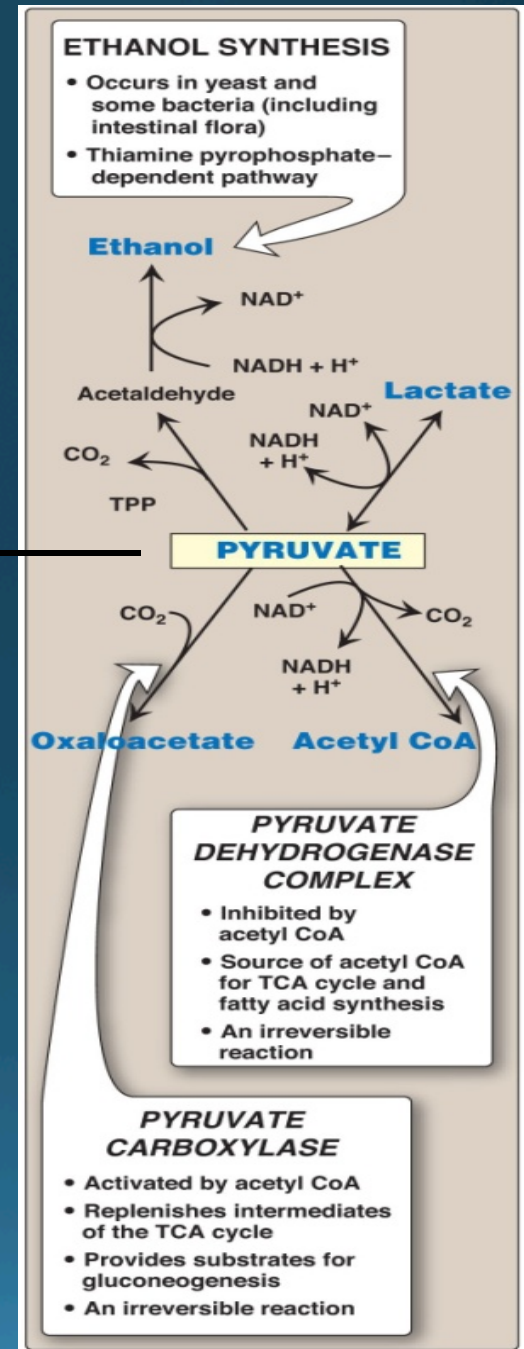
- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoA
- Discuss the major regulatory mechanisms for PDH complex
- Recognize the clinical consequence of abnormal oxidative decarboxylation reactions

Objectives: Krebs Cycle

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

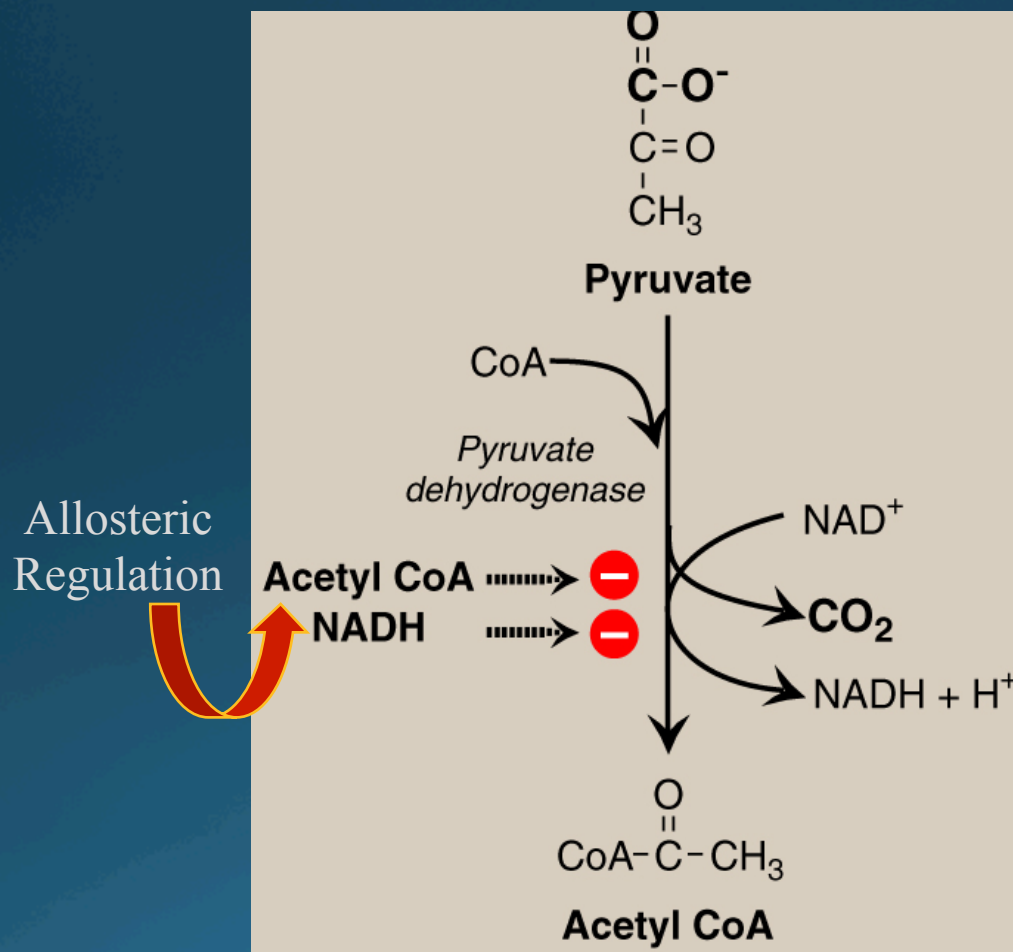
- Recognize the importance of Krebs cycle
- Identify various reactions of Krebs cycle
- Define the regulatory mechanisms of Krebs cycle
- Assess the energy yield of PDH reaction and Krebs cycle's reactions

Fates of Pyruvate

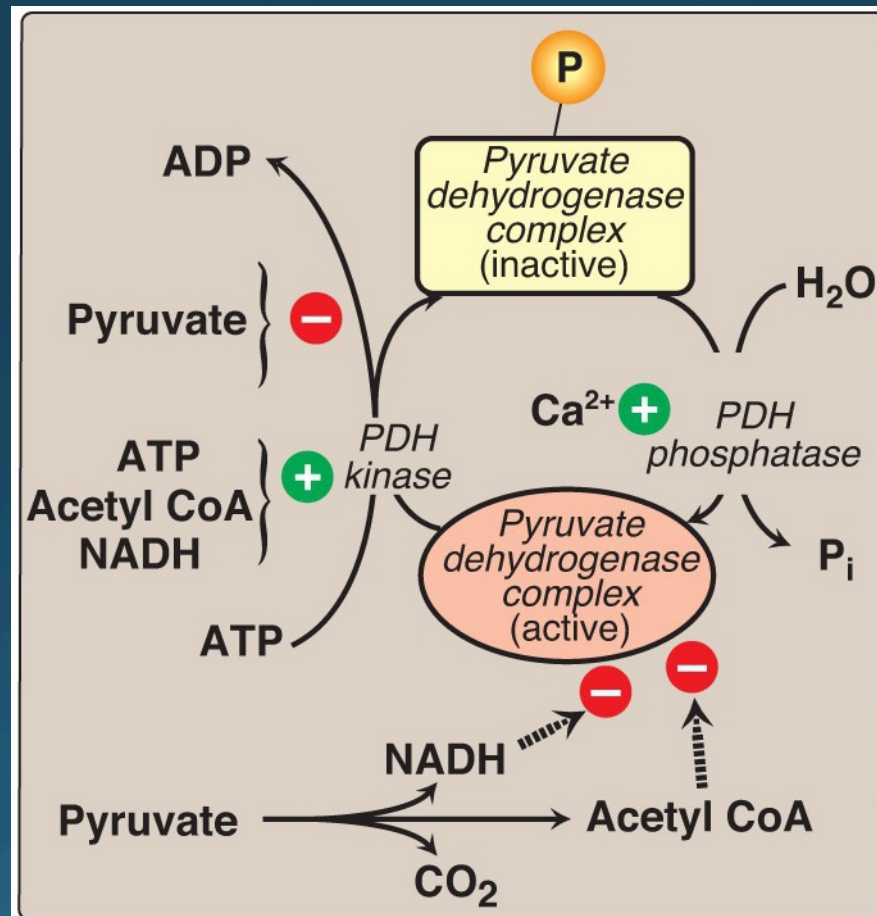


PLP = Pyridoxal Phosphate

Oxidative Decarboxylation of Pyruvate



PDH Complex: Covalent Regulation



PDH Reaction: Clinical application

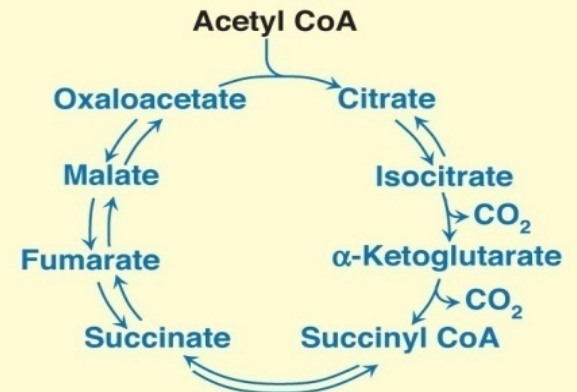
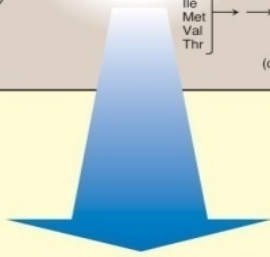
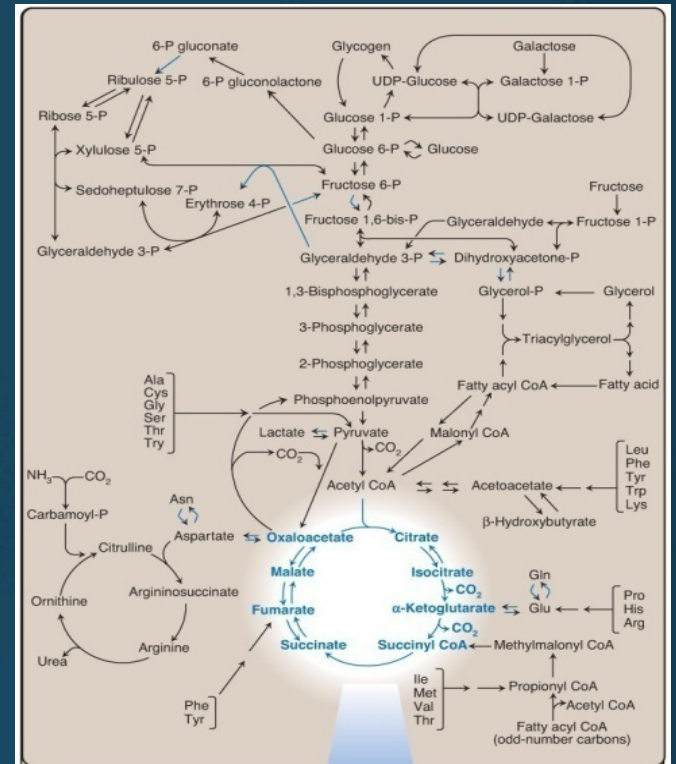
1. Deficiencies of thiamine or niacin can cause serious CNS problems. **WHY?**
 - Brain cells are unable to produce sufficient ATP if the PDH complex is inactive.
2. **Wernicke-Korsakoff** (encephalopathy-psychosis syndrome) due to thiamine deficiency, may be seen especially with alcohol abuse.
3. PDH 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

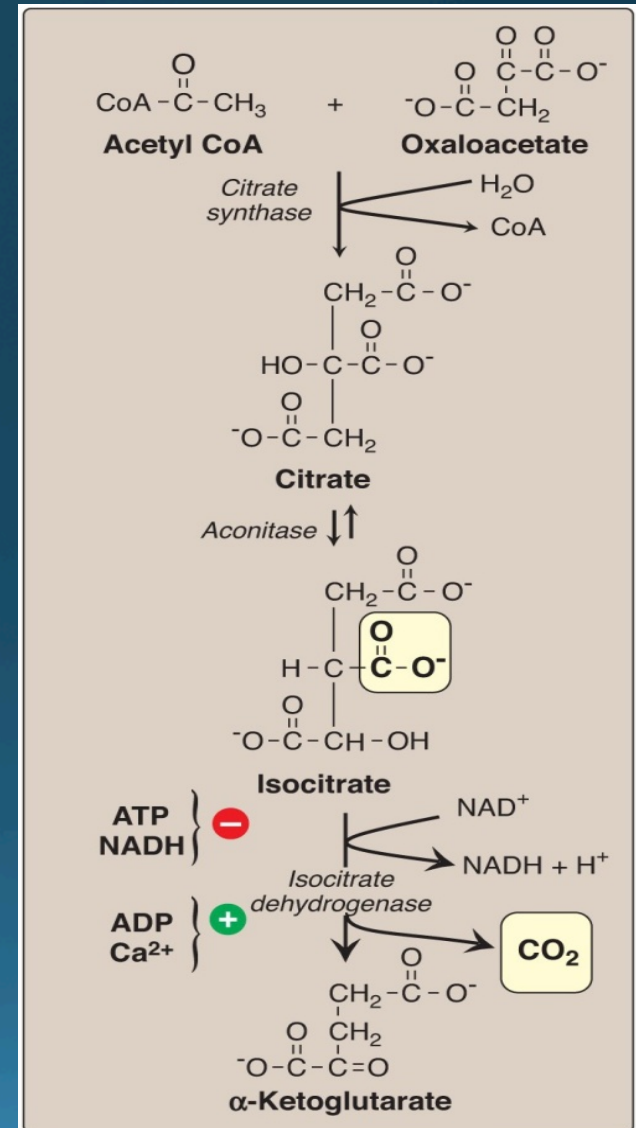
Nonessential amino acids

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

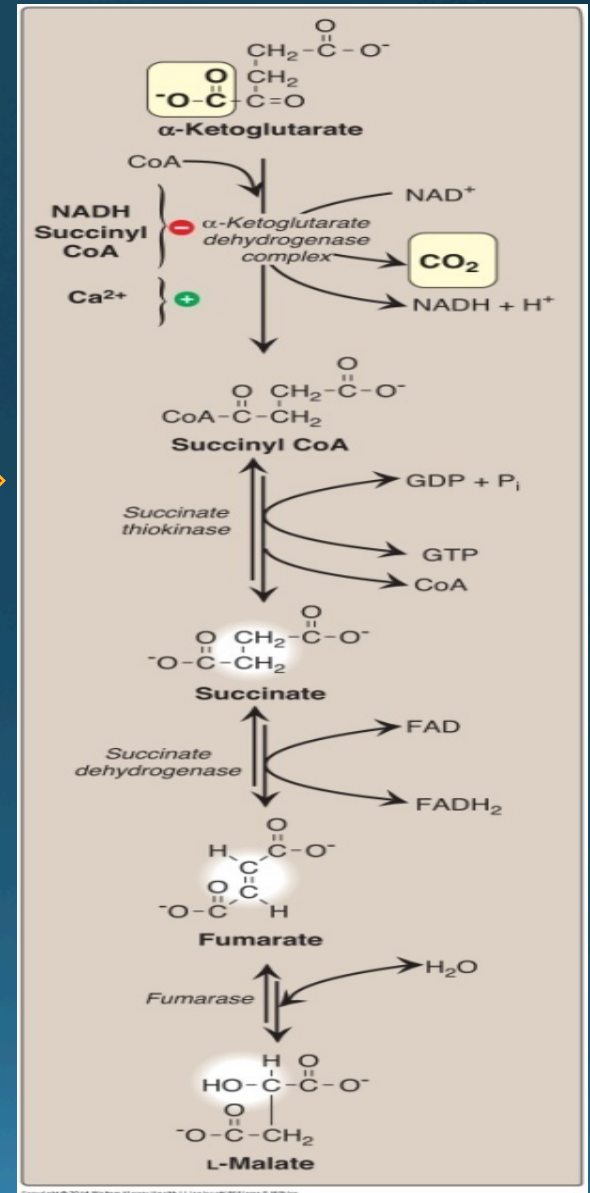
Formation of malate from α -ketoglutarate.

NAD(H) = nicotinamide adenine dinucleotide

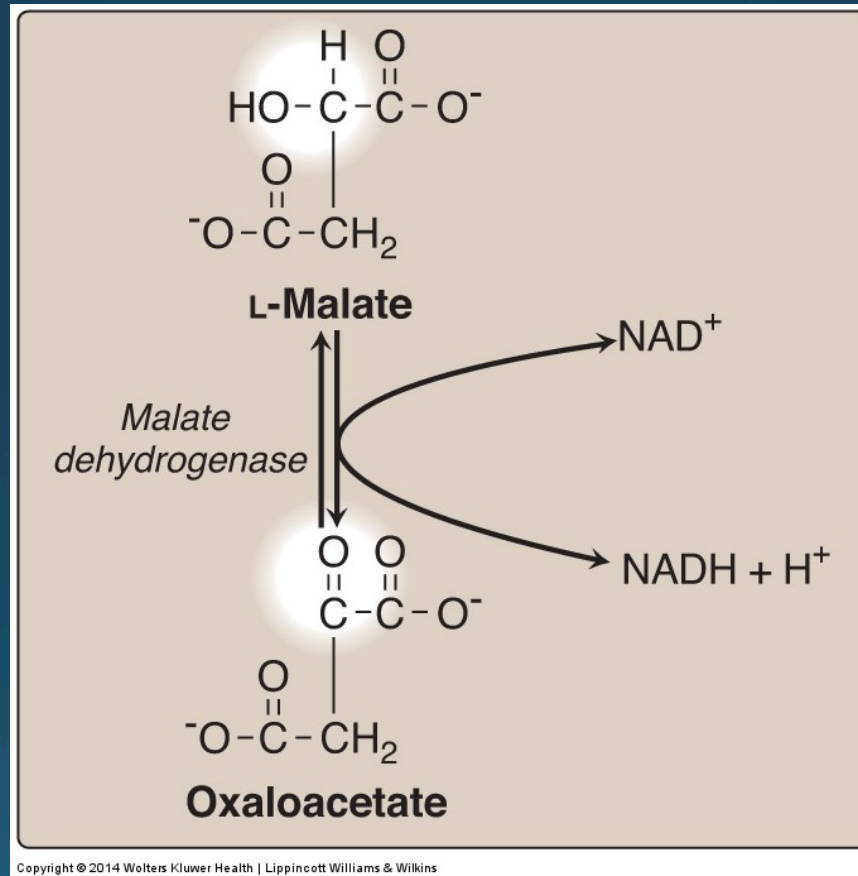
GDP = guanosine diphosphate;

P = phosphate

FAD(H₂) = flavin adenine dinucleotide.



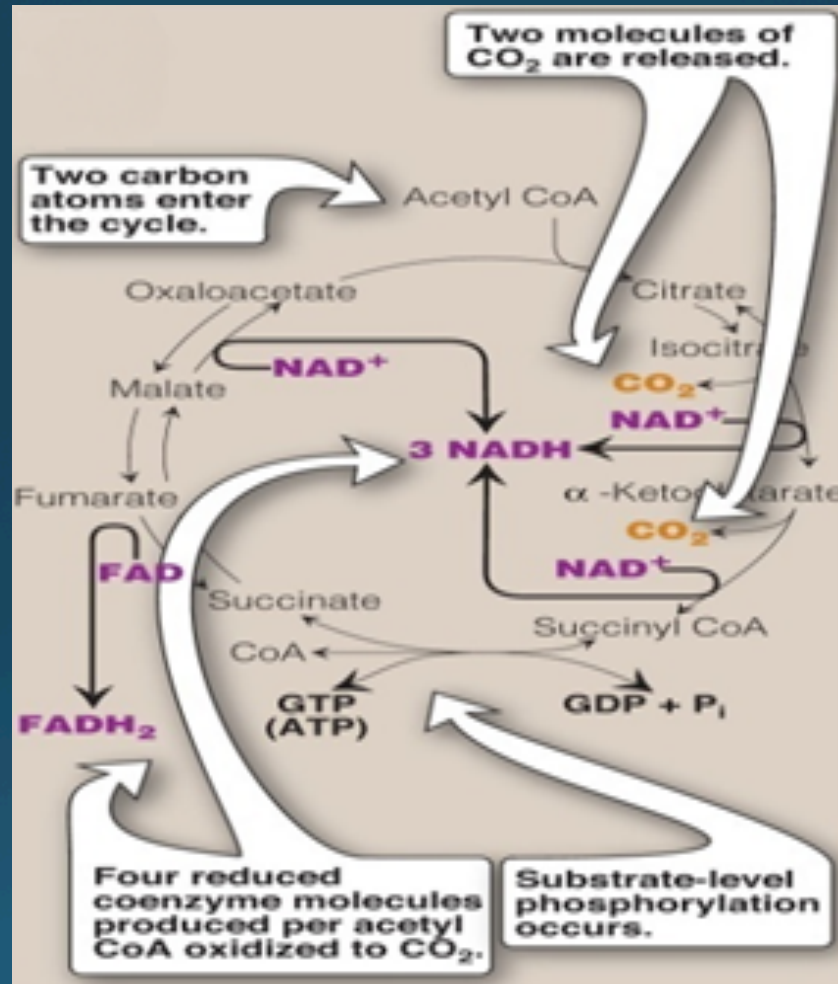
Krebs Cycle Reactions (3)



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
$3 \text{ NADH} \longrightarrow 3 \text{ NAD}^+$	9
$\text{FADH}_2 \longrightarrow \text{FAD}$	2
$\text{GDP} + \text{P}_i \longrightarrow \text{GTP}$	1
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	12 ATP/acetyl CoA oxidized

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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:	$2 \times 3 =$	6 ATP
Krebs cycle:	$2 \times 12 =$	24 ATP
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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
 - Ca²⁺
- 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

Reference

Lippincott Illustrated Review of Biochemistry, 6th edition, 2014,
Unit 2, Chapter 9, Pages 109-116.