# 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

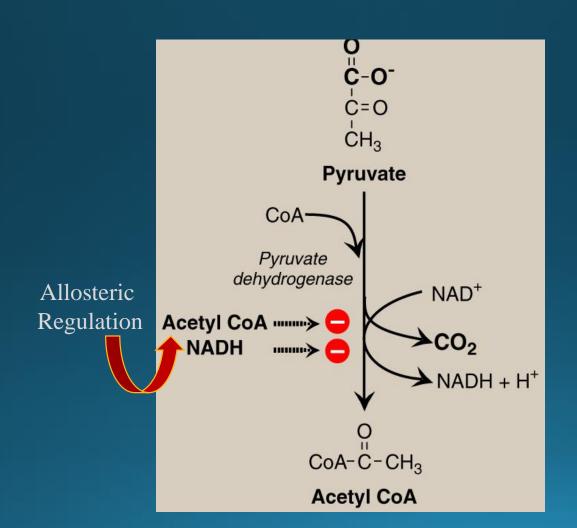
#### **Fates of Pyruvate**

**ALT** Alanine Glutamate aKG

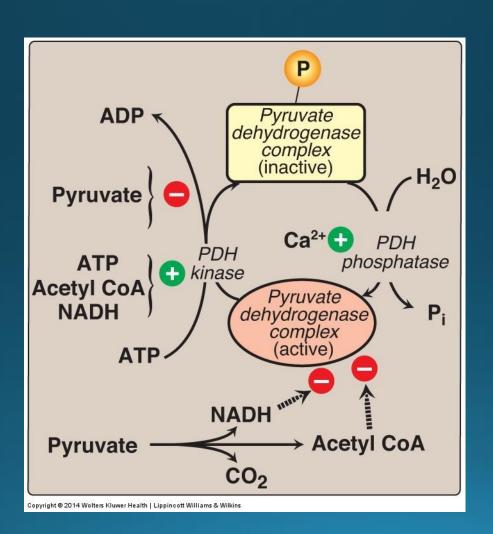
ETHANOL SYNTHESIS · Occurs in yeast and some bacteria (including intestinal flora) · Thiamine pyrophosphatedependent pathway Ethanol NAD+ NADH + H+ Lactate Acetaldehyde NAD+ NADH TPP **PYRUVATE** NAD+ CO >co, NADH + H+ Oxalgacetate **Acetyl CoA** PYRUVATE **DEHYDROGENASE** COMPLEX · Inhibited by acetyl CoA Source of acetyl CoA for TCA cycle and fatty acid synthesis An irreversible reaction **PYRUVATE** CARBOXYLASE Activated by acetyl CoA Replenishes intermediates of the TCA cycle · Provides substrates for gluconeogenesis An irreversible reaction

**PLP = Pyridoxal Phosphate** 

## Oxidative Decarboxylation of Pyruvate



#### PDH Complex: Covalent Regulation



#### PDH Reaction: Clinical application

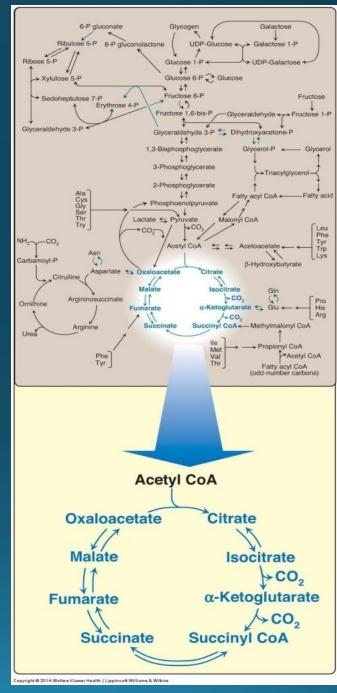
- 1. Deficiencies of thiamine or niacin can cause serious CNS problems. WHY?
  - Brain cells are unable to produce sufficient ATP if the PDH complex is inactive.
- 1. Wernicke-Korsakoff (encephalopathy-psychosis syndrome) due to thiamine deficiency, may be seen especially with alcohol abuse.
- 2. PDH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



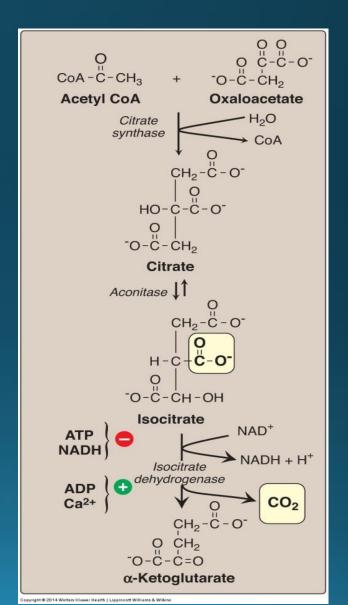
#### Tricarboxylic Acid Cycle: Krebs Cycle

- 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 \_\_\_\_

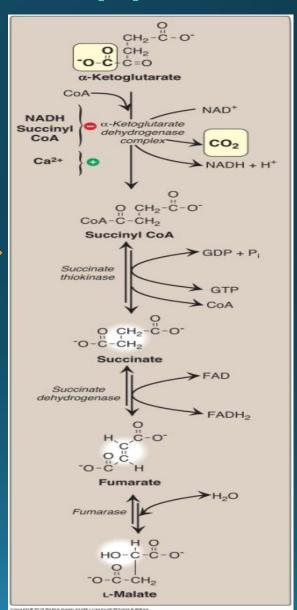
Substrate-Level Phosphorylation

#### Formation of malate from $\alpha$ -ketoglutarate.

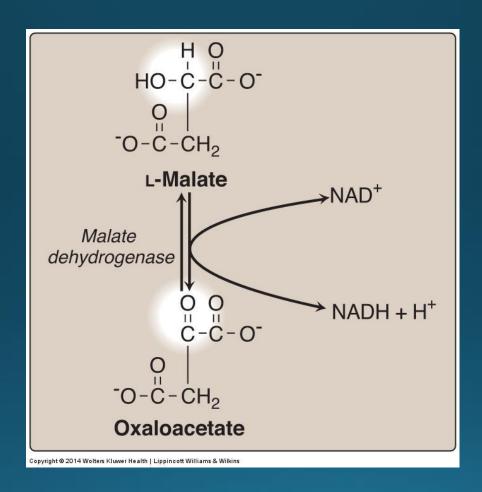
NAD(H) = nicotinamide adenine dinucleotide GDP = guanosine diphosphate; P = phosphate

P = phosphate

 $FAD(H_2)$  = flavin adenine dinucleotide.



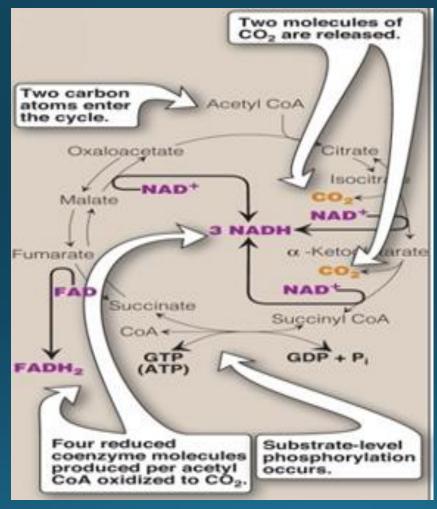
### Krebs Cycle Reactions (3)



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 <sup>+</sup>	9
$FADH_2 \longrightarrow FAD$	2
$GDP + P_i \longrightarrow GTP$	1
	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

<b>Aerobic glycolysis:</b>	8 ATP

Oxidative decarboxylation:  $2 \times 3 = 6 \text{ ATP}$ 

Krebs cycle:  $2 \times 12 = 24 \text{ ATP}$ 

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:
  - $\bullet$  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

#### Reference

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