جامعة الملك سعود
King Saud University

MED437
KING SAUD UNIVERSITY

BIO TEAM

# Oxidative Decarboxylation and Krebs Cycle

437 Biochemistry Team

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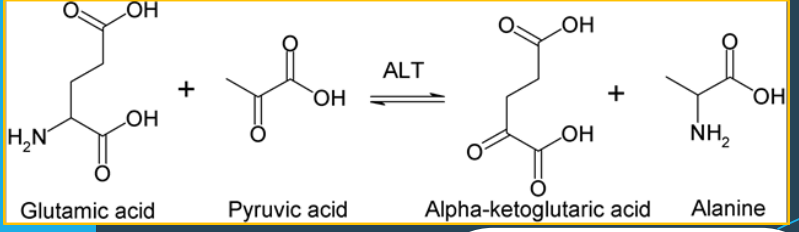
# Objectives:

## Of Oxidative Decarboxylation:

- 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

## Of Krebs Cycle:

- 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




## Acetyl CoA

***in Krebs cycle**

## Alanine

Synthesis of non-essential amino acid using pyruvate + glutamine "essential"

*Done by Alanine transaminase enzyme "ALT"

• PLP = pyridoxal *phosphate

## Oxaloacetate

*In Krebs cycle (it's an intermediate)

* Activated by acetyl CoA

***Importance**:

1. Replenishes intermediates of the TCA cycle.
2. Provide substrates for gluconeogenesis
3. An irreversible reaction

Fates of Pyruvates

## Ethanol

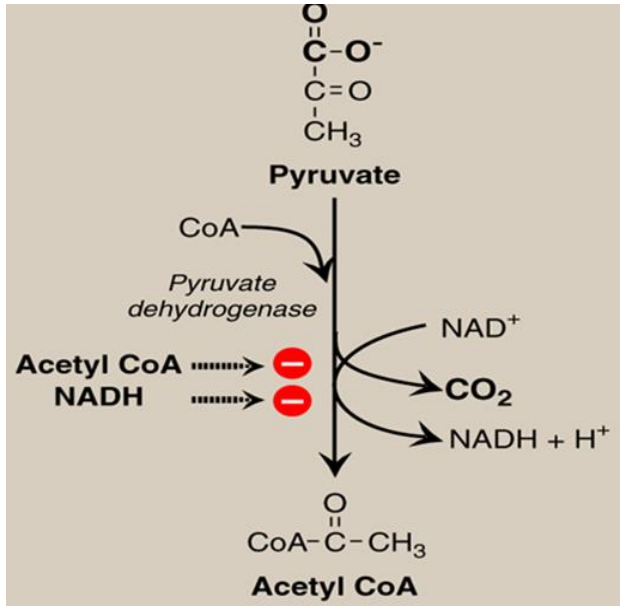
*It occurs in yeast and some Bactria (including intestinal flora)(Anaerobic)

* Thiamine pyrophosphate-dependent pathway

## Lactate

*in humans and some microorganisms "anaerobic"

(Remember: Pyruvate is the end product of glycolysis)




# Oxidative Decarboxylation of Pyruvate

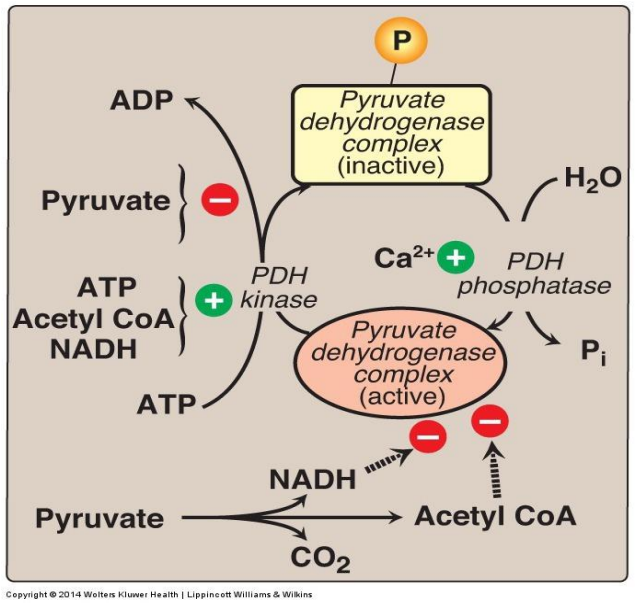
**making** acetyl Co-A from pyruvate by pyruvate dehydrogenase

- **Produces** 2 NADH=6 ATP
- **Regulated by** allosteric regulation of Acetyl coA and NADH
- **Inhibtors :**Increased amount of Acetyl CoA and NADH **act as** "Negative Feedback" inhibitors of their respective reactions.

## PDH Complex: Covalent Regulation

*Pyruvate dehydrogenase complex (PHD) has two forms active and inactive. Regulated by co-enzymes.

***inactive form:** regulated by PDH kinase (adds phosphate)
***active form:** regulated by PDH phosphatase (removes phosphate)





- ↑ **pyruvate , Inactivation** of PDH kinase (leading to activate acetyl CoA)
- ↑ **ATP, acetyl co-A, NADH , Activation** of PDH kinase (leading to inhibit making acetyl CoA)

**Ca+2 activates** PDH phosphate , which activates the enzyme pyruvate dehydrogenase, making more acetyl CoA -

**-NADH, Acetyl CoA inhibits** PDH phosphate which inhibits making of acetyl CoA

شرح مبسط:

اذا زاد البيروفيت وصار متواجد بكميات كبيرة بديهيا نحتاج نتخلص منه ونحوله الى استيل كو أي ف رح نثبط انزيم الكينيز اللي وظيفته اساسا تثبيط عملية تحويل البيروفيت الى استيل كو اي والناتج من هذي العملية جزئ الطاقة, الحين اذا كان زايد عندك جزئ الطاقة والاستيل كو أي نفسه رح تحتاج تسوي عكس العملية اللي فوق وهي انك تحفز انزيم الكينيز اللي بوظيفته يثبط عملية التحويل

# PDH Reaction: Clinical application

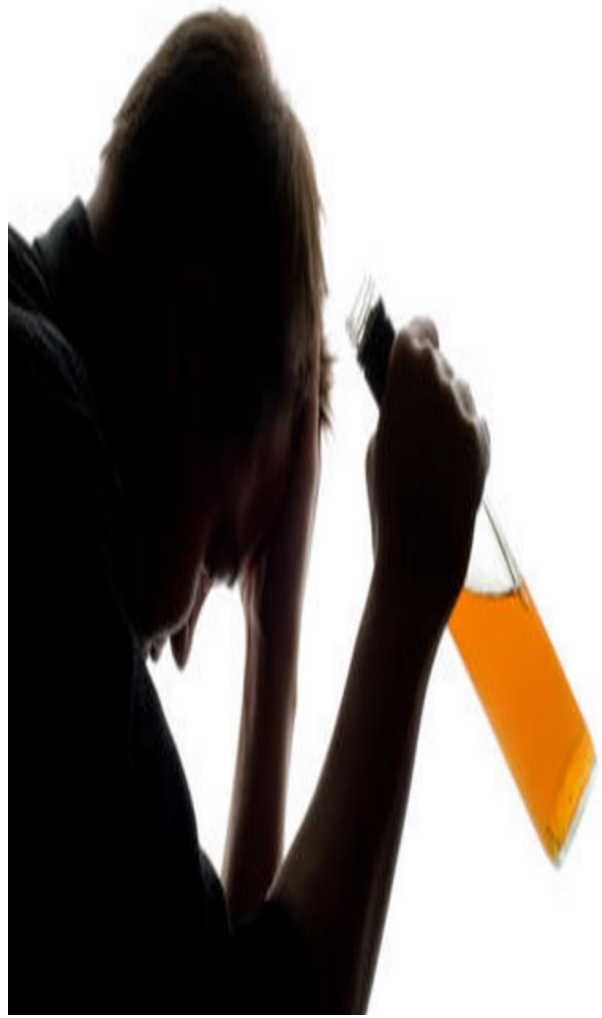
PDH complex plays a important role in CNS

## How?

Brain cells are unable to produce sufficient ATP if the PDH complex is inactive 'no production of acetyl coA thus, no krebs cycle thus, no ATP'

*Thiamine and niacin are co-factors that helps PDH complex

*Deficiencies of them can cause serious CNS problems



**congenital lactic acidosis**

**PDH complex deficiency is the most common biochemical cause.**

'too many pyruvates leads to the use of anaerobic respiration which make lactate accumulate'

**Wernicke-Korsakoff (encephalopathy-psychosis syndrome):**

due to thiamine deficiency, may be seen especially with alcohol abuse.

# Tricarboxylic Acid Cycle: Krebs Cycle

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

CoA = coenzyme A.

- Final common pathway for oxidation
- Exclusively in mitochondria
- Major source for ATP
- Mainly catabolic with some anabolic features
- Synthetic reactions (anabolic features):

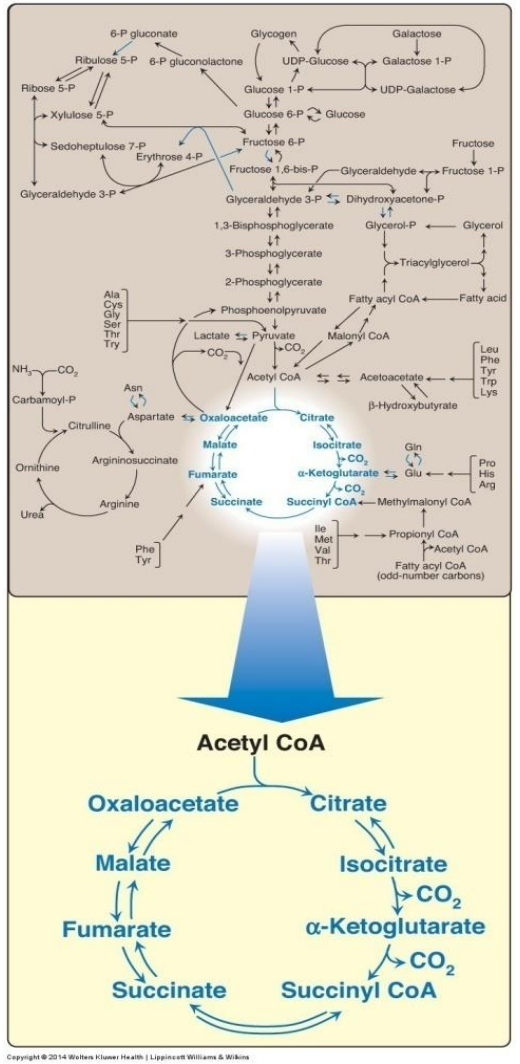
  Glucose from amino acids

  Nonessential amino acids

  Fatty acids

  Heme

Please click to watch video before proceeding



# Krebs Cycle Reactions (1)

**Formation of α-Ketoglutarate from acetyl CoA and oxaloacetate**

Acetyl Co-A + Oxaloacetate

↓

citrate (6C)

**Citrate synthase:** H2O in CoA out

Citrate

↓

iso-citrate

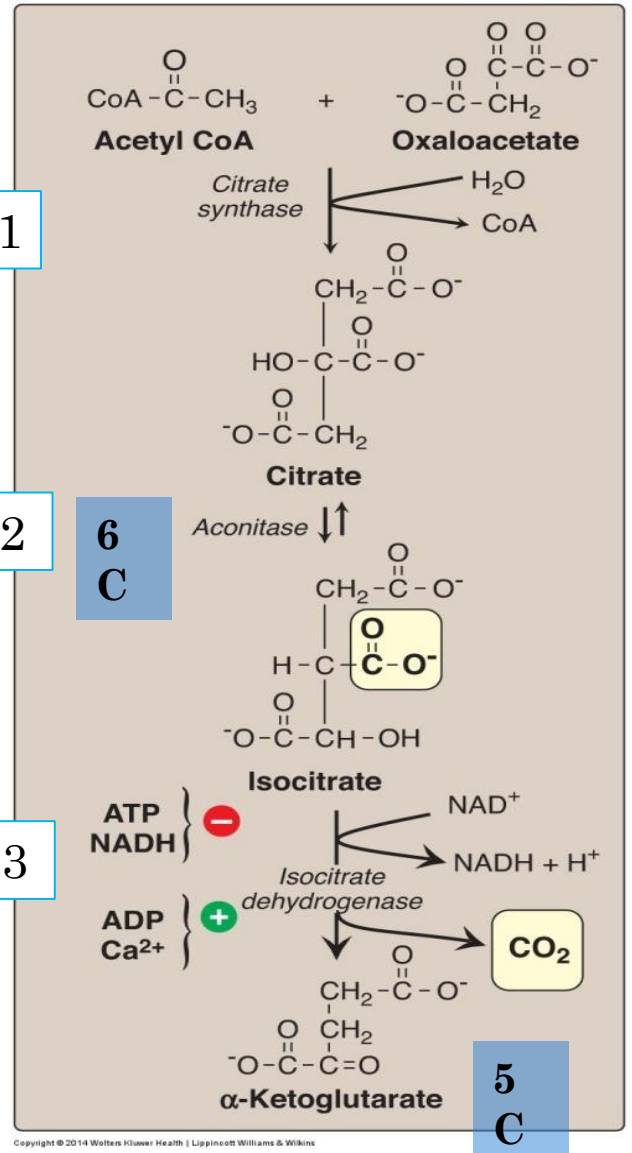
**Aconitase**

Iso-citrate

↓

α-Ketoglutarate (5C)

**IsoCitrate Dehydrogenase:** NAD+ is reduced Co2 is out




Step (3) regulation:

Isocitrate dehydrogenase is :

1- activated by ADP – CA+2

2- inhibited by ATP- NADH

# Krebs Cycle Reactions (2)

**Formation of malate from α-ketoglutarate.**

**α-ketoglutarate.**

↓

**α-ketoglutarate dehydrogenase** → Regulation:
1- inhibited by NADH – succinyl CoA
2-activated by CA+2

↓

**Succynyl CoA**

↓

Succinate thiokinaze → GTP generation

↓

**Succinate**

↓

Succinate dehydrogenase → FADH generation

↓

**Fumarate**

↓

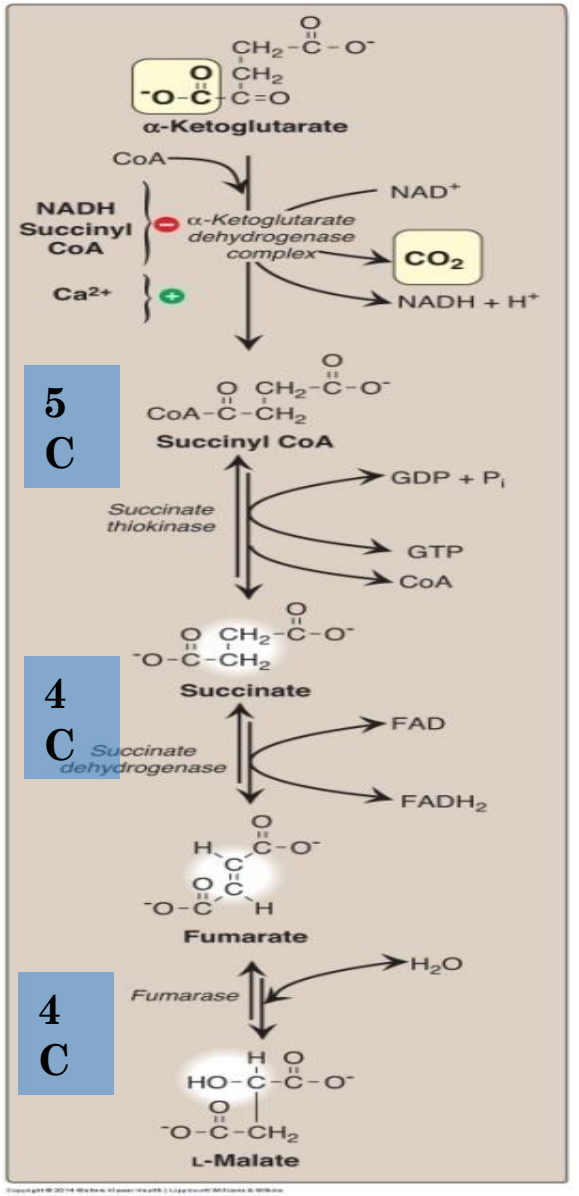
**fumarase**

↓

**L-malate**

Succinate Thiokinase

Substrate-Level Phosphorylation



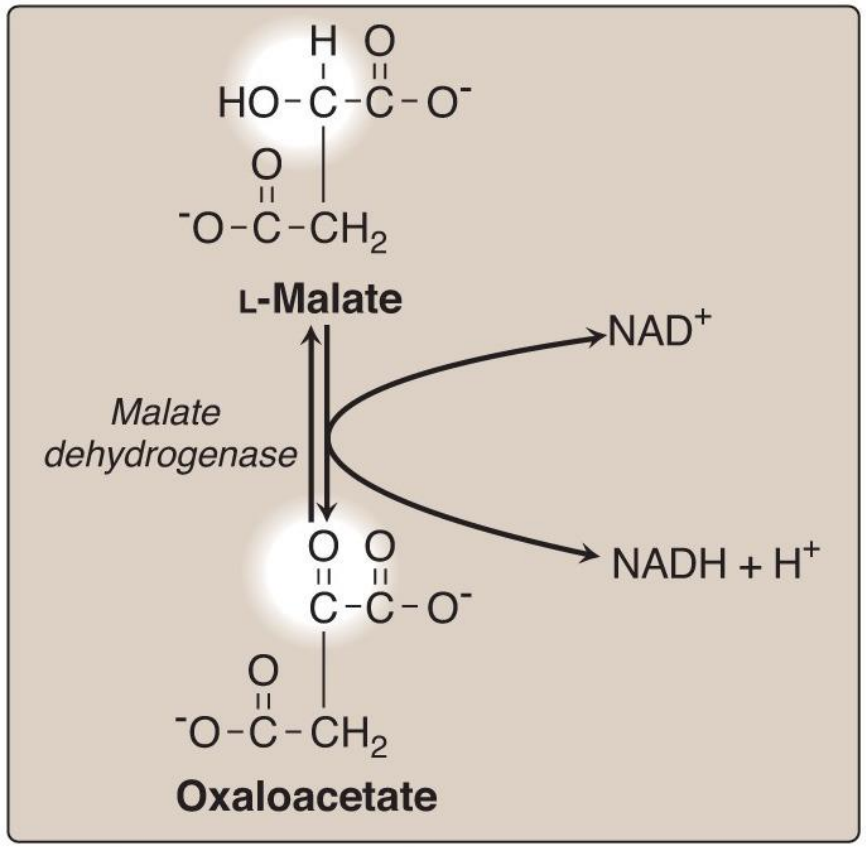

NAD(H) = nicotinamide adenine dinucleotide
GDP = guanosine diphosphate;
P = phosphate
FAD($H_2$) = flavin adenine dinucleotide.

**Irreversible steps:**

Step1
Step 3
Step 4

# Krebs Cycle Reactions (3)

L-Malate → Oxalo-acetate (4C)

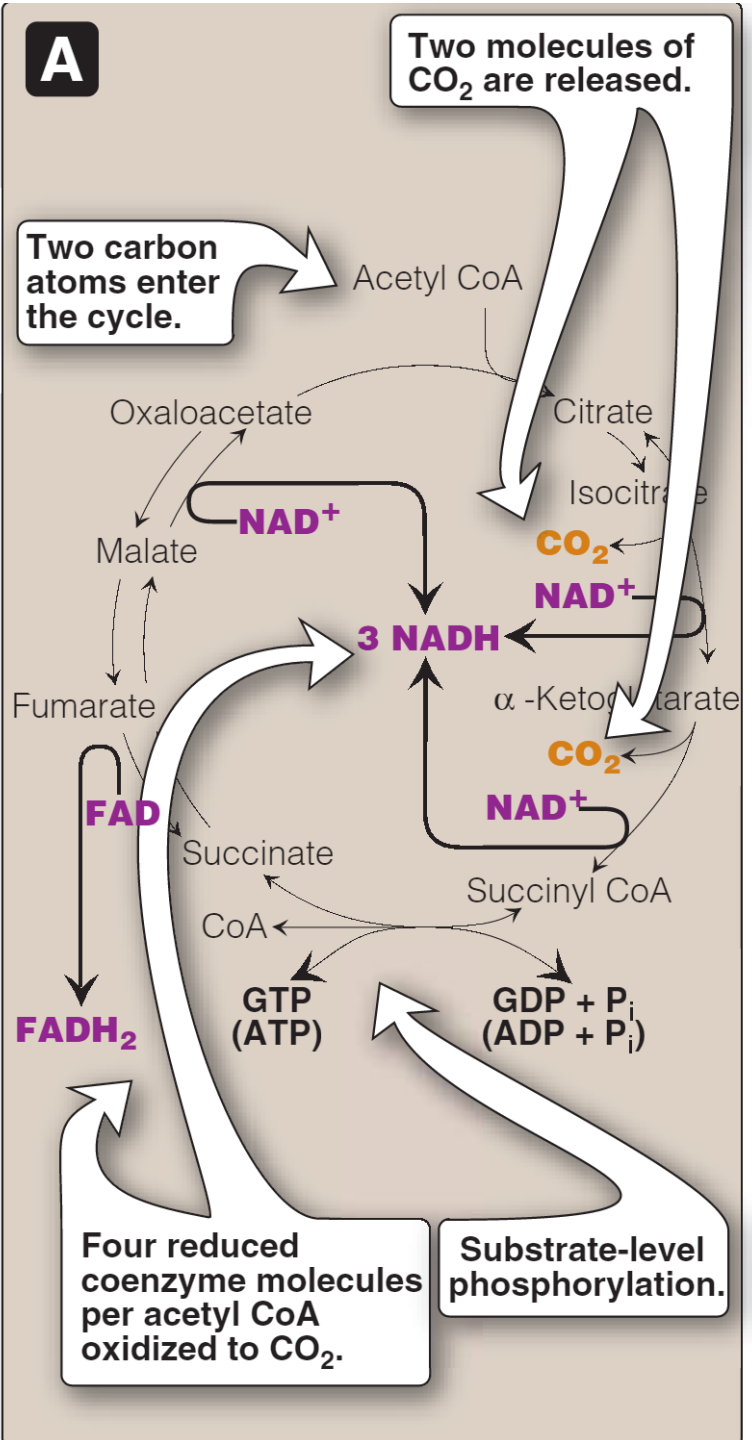





**Formation (regeneration) of oxaloacetate from malate.**

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.

**We get 3 NADH from:**
Isocitrate → α-Ketoglutarate
α-Ketoglutarate → Succinyl CoA
Malate → Oxaloacetate

**We get 1 FADH from:**
Succinate → Fumarate

| 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 |

Succinyl CoA "high energy compound" breaks down which leads to a substrate level phosphorylation of **GDP to GTP**, which means **1 ATP**.

**NADH = 3 ATP**
**FADH = 2 ATP**
**GTP = 1 ATP**

Krebs **energy** outcome

So, we get 24 ATP from 2 Acetyl CoA

Other outcome

**We get 2 $CO_2$ from:**
Isocitrate → α-Ketoglutarate
α-Ketoglutarate → Succinyl CoA

## 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** |

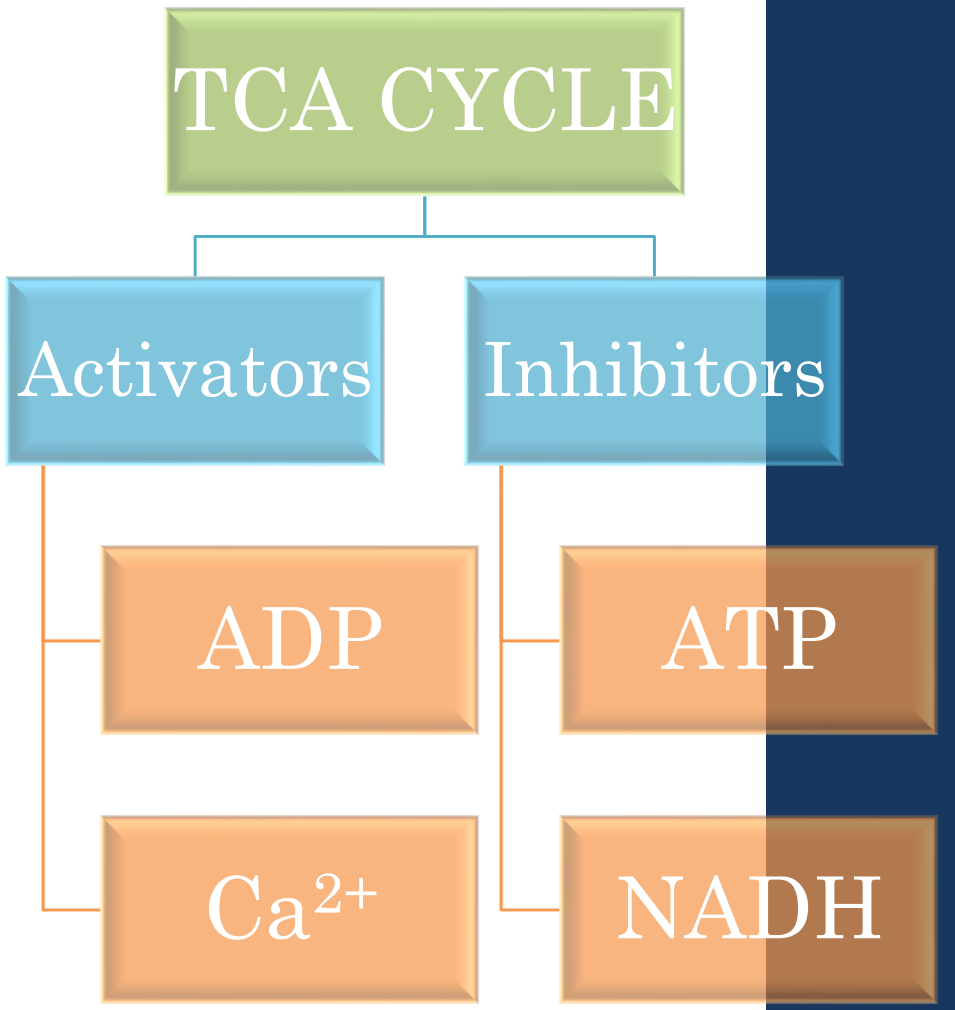
## Regulation of Oxidative Decarboxylation and Krebs Cycle

PDH complex and the TCA cycle are both **up-regulated** in response to a **decrease in the ratio** of

- **ATP : ADP**
- **NADH : $NAD^+$**

PDH complex & TCA: make ATP & NADH IN LOW ENERGY CONDITIONS

PDH: The Pyruvate Dehydrogenase  TCA: Tricarboxylic Acid



# videos

- Krebs cycle made simple
- Krebs cycle حلقة كريس

# MCQs

1\ Allosteric regulation in oxidative decarboxylation of pyruvate is done by:
A- Acetyl CoA
B- NADH
C- ATP
D- A & B

2\ PDH kinase is inhibited by:
A- Acetyl CoA
B- Pyruvate
C- ATP
D- ADP

3\ deficiencies of thiamine or niacin can cause serious problems in:
A- liver
B- kidney
C- CNS
D- GIT

4\ ADP AND Ca 2+ are:
A- TCA inhibitors
B- TCA activators

5\ net ATP production by oxidative decarboxylation is:
A- 8 ATP
B- 24 ATP
C- 6 ATP
D- 38 ATP

6\ net ATP production by complete glucose oxidation is:
A- 38 ATP
B- 24 ATP
C- 6 ATP
D- 8 ATP

1- D
2- B
3- C
4- B
5- C
6- A

# 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**

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