Red boxes are IMPORTANT!

Krebs Cycle

Color Index:

- **Original slides.**
- Important.
- 436 Notes
- **438 notes**
- **Extra information**

رابط التعديل:
https://docs.google.com/document/d/1WvdeC1atp7J-ZKWOUSukSLsEcosjZ0AqV4z2VcH2TA0/edit?usp=sharing

Biochemistry team 438

Objectives:

Of Oxidative Decarboxylation:

Slide No.3
1. Recognize the various fates of pyruvate

Slide No.4
2. Define the conversion of pyruvate to acetyl CoA

Slide No.5
3. Discuss the major regulatory mechanisms for PDH complex

Slide No.6
4. Recognize the clinical consequence of abnormal oxidative decarboxylation reactions

Of Krebs Cycle:

1. Recognize the importance of Krebs cycle
2. Identify various reactions of Krebs cycle
3. Define the regulatory mechanisms of Krebs cycle
4. Assess the energy yield of PDH reaction and Krebs cycle's reactions

Fates of Pyruvates.(Remember: Pyruvate is the end product of glycolysis)

Dr. say the important thing to know is that pyruvate can go in 5 directions

Lactate

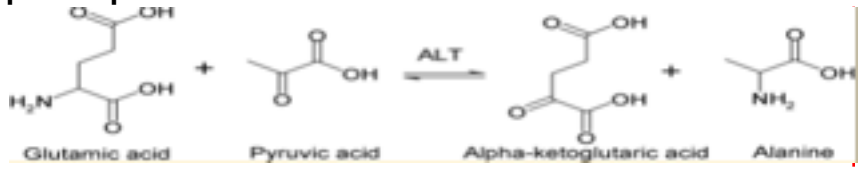
*in humans and some microorganisms

"in anaerobic conditions"

Alanine

Synthesis of nonessential amino acid using pyruvate + glutamine "essential"

*Done by Alanine transaminase enzyme "ALT" • PLP = pyridoxal *phosphate



Ethanol

*It occurs in yeast and some Bacteria (including intestinal flora)(Anaerobic) * Thiamine pyrophosphate-dependent pathway

Acetyl CoA (Pyruvate dehydrogenase complex)

***in Krebs cycle**

-inhibited by **acetyl CoA**

-source of acetyl CoA for TCA cycle and **fatty acid synthesis**

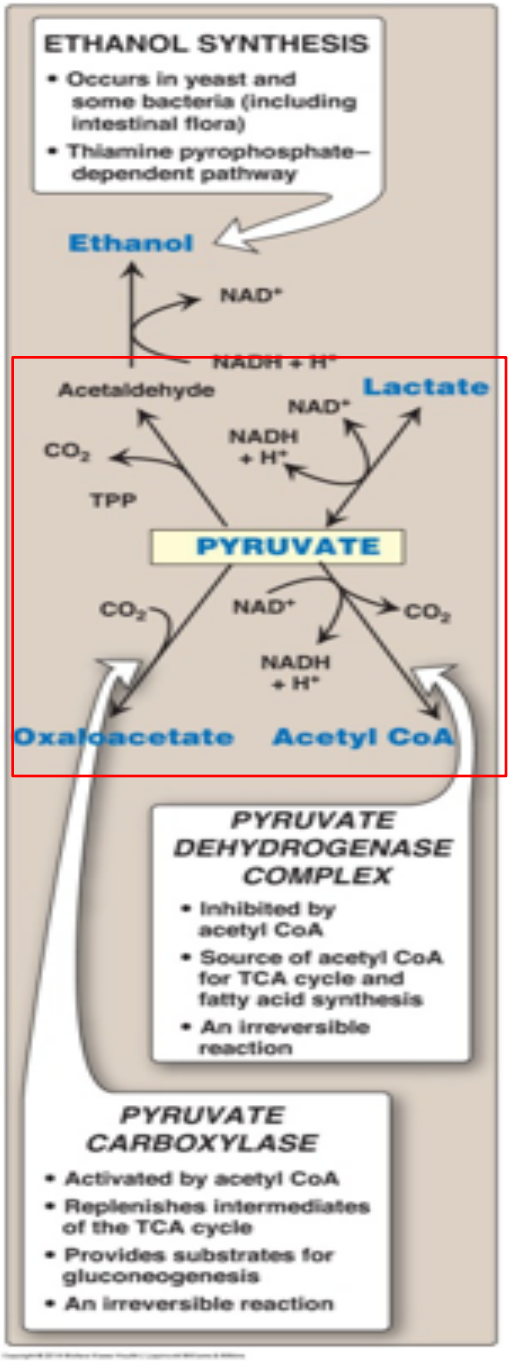
-An irreversible reaction

Oxaloacetate (Pyruvate carboxylase)

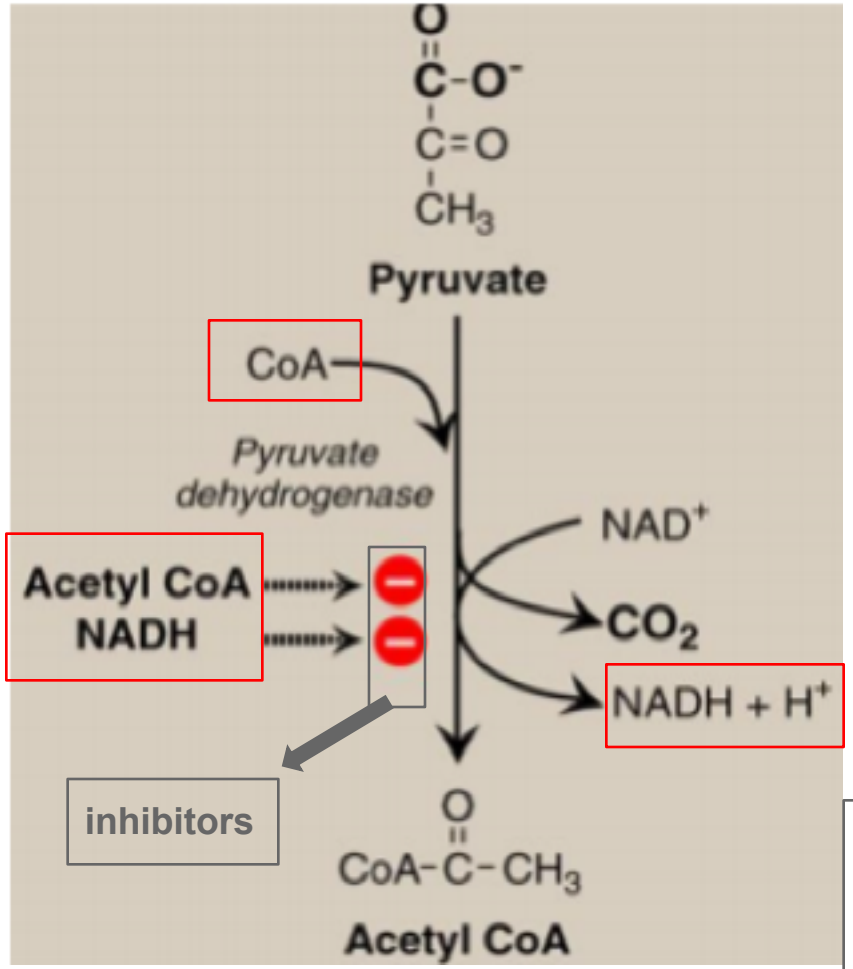
*In Krebs cycle (it's an intermediate)

* Activated by acetyl CoA *Importance:

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



Oxidative Decarboxylation of Pyruvate



- It's the process of **making <u>acetyl Co-A</u>** "mainly" & oxaloacetate from **<u>pyruvate</u>** by the enzyme: **pyruvate dehydrogenase**
- **Produces** 2 NADH 6 ATP (each NADH=3ATP)
- **Regulated by** allosteric regulation of Acetyl coA and NADH
- **Inhibitors**: Increased amount of **Acetyl CoA** and **NADH <u>act as</u>** "Negative Feedback" inhibitors of their respective reactions.

How?
They activate "Pyruvate dehydrogenase **<u>kinase</u>**" which phosphorylates and **inactivates** "Pyruvate dehydrogenase"

NOTE
Kinase= enzyme **adds** P group "phosphorylates"
Phosphatase= enzyme that **removes** P group
Note: phosphorylation can either activate or inactivate, according to the enzyme.

PDH Complex: Covalent Regulation

NOTE
Kinase= enzyme **adds** P group "phosphorylates"
Phosphatase= enzyme that **removes** P group
Note: phosphorylation can either activate or inactivate, according to the enzyme.

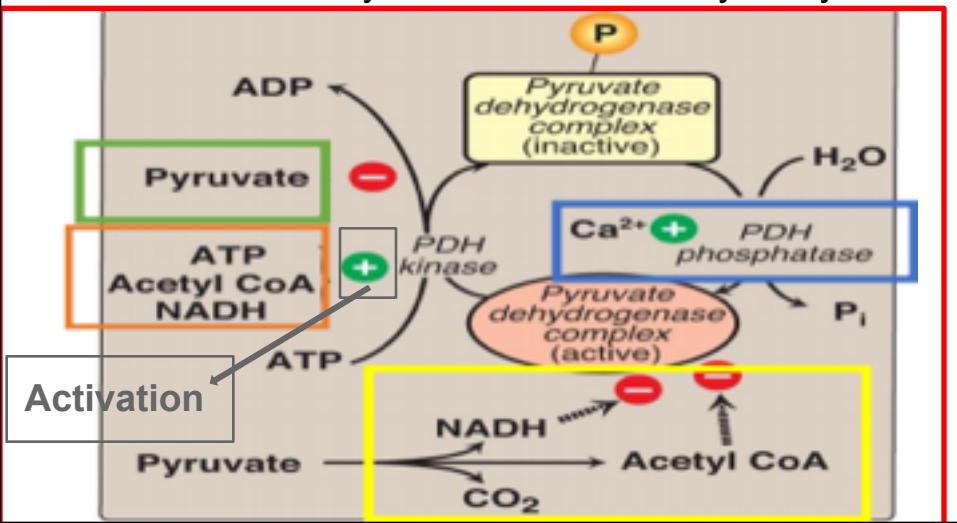
PDH : enzyme complex "3 enzymes joint together" that convert pyruvate into acetyl CoA .

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

***inactive form (with phosphate)**: regulated by PDH kinase (adds phosphate)

***active form (without phosphate)**: regulated by PDH phosphatase (removes phosphate)

*Those two enzymes are controlled by many factors



Regluation of PDH kinase

↑ pyruvates

↓

Inactivation of PDH kinase

↓

Active form of pyruvate complex

(leading to activate acetyl CoA)

Regulation PDH phosphatase

PDH phosphatase +Ca remove phosphates

↓

active complex

↓

↑ acetyl Co-A ,NADH ,CO_2

↑ ATP, acetyl co-A, NADH

↓

Activation of PDH kinase

↓

Inactive form of the complex

(leading to inhibit making acetyl CoA)

Direct regulation of the complex

↑ NADH, Co-2 and acetyl Co-A can directly inhibit the active form

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 (too much lactate)

PDH complex deficiency is the most common biochemical cause.

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

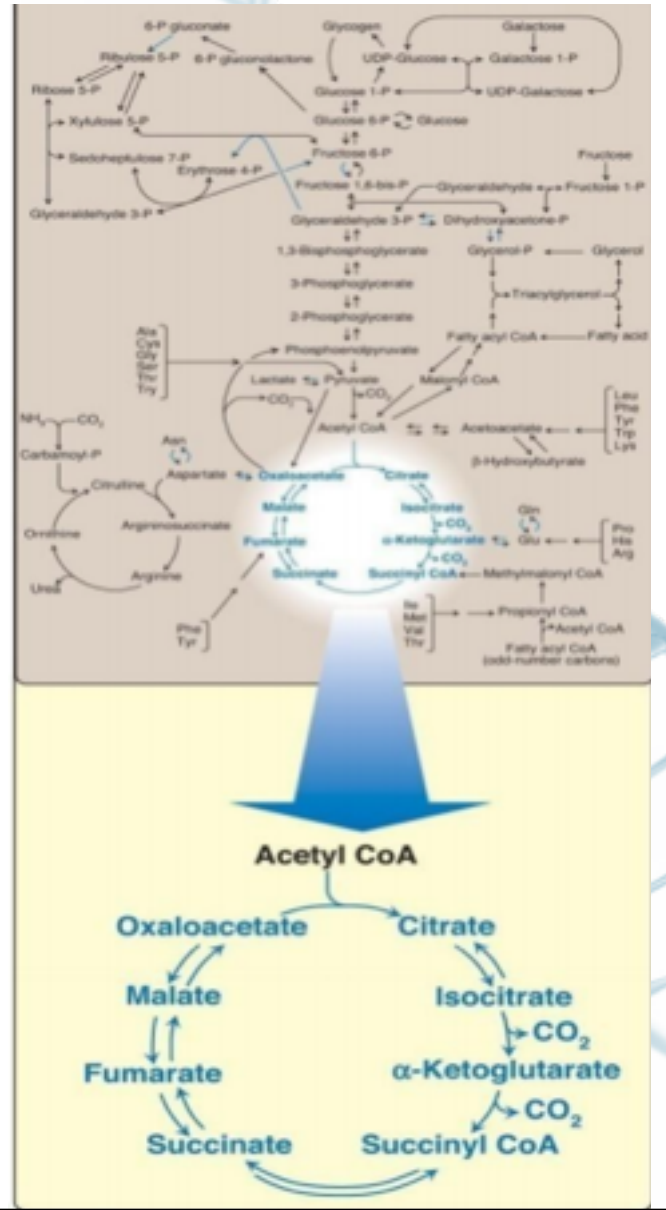
Wernicke-Korsakoff (encephalopathypsychosis syndrome):

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

Dr. Ahmad focused on the red box

Tricarboxylic Acid Cycle: Krebs Cycle

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



Properties of the cycle

- Final common pathway for oxidation
- Exclusively in mitochondria
- Major source for ATP (24 ATP)
- Mainly catabolic with some anabolic features
- Synthetic reactions (anabolic features):
  -Glucose from amino acids
  -Nonessential amino acids
  -Fatty acids
  -Heme

Dr. Ahmad focused on the red box

Krebs Cycle Reactions (1)

Formation of α-ketoglutarate from acetyl coenzyme A (CoA) and oxaloacetate.

fist step:

Acetyl Co-A + Oxaloacetate ⟶ citrate (6C)

citrate synthase:
H2O in
CoA out

second step:

Citrate ⟶ Iso-citrate

Aconitase

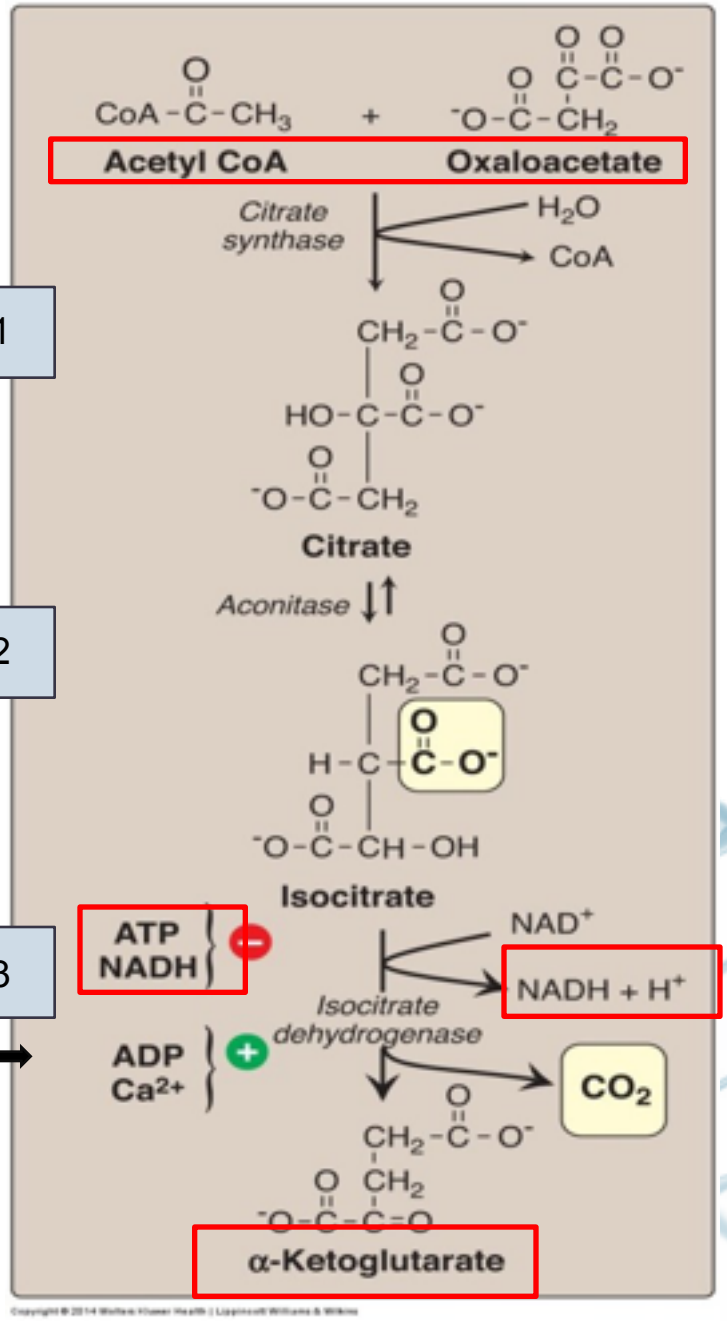
third step:

Iso-citrate ⟶ α-Ketoglutarate (5C)

Isocitrate Dehydrogenase:
NAD+ is reduced
Co2 is out

NAD(H) = Nicotinamide adenine dinucleotide.

is regulated
"can be inhibited or activated"
(+)ADP, Ca2+
(-)ATP, NADH



Krebs Cycle Reactions (2)

fourth Step *oxidation and decarboxylation*

α-Ketoglutarate oxidized by co-enzyme NAD+

α-Ketoglutarate Dehydrogenase complex → **It is regulated**

•NAD+ is reduced to NADH + H^+

•CO_2 is out

•CoA is in

•

Succyinyl CoA

It is activated by: Ca2+

Inhibited by: NADH and Succinyl CoA

fifth Step *oxidation and decarboxylation*

SucSuccinate Thiokinase → **Succinate Thiokinase**

•Co-A is out

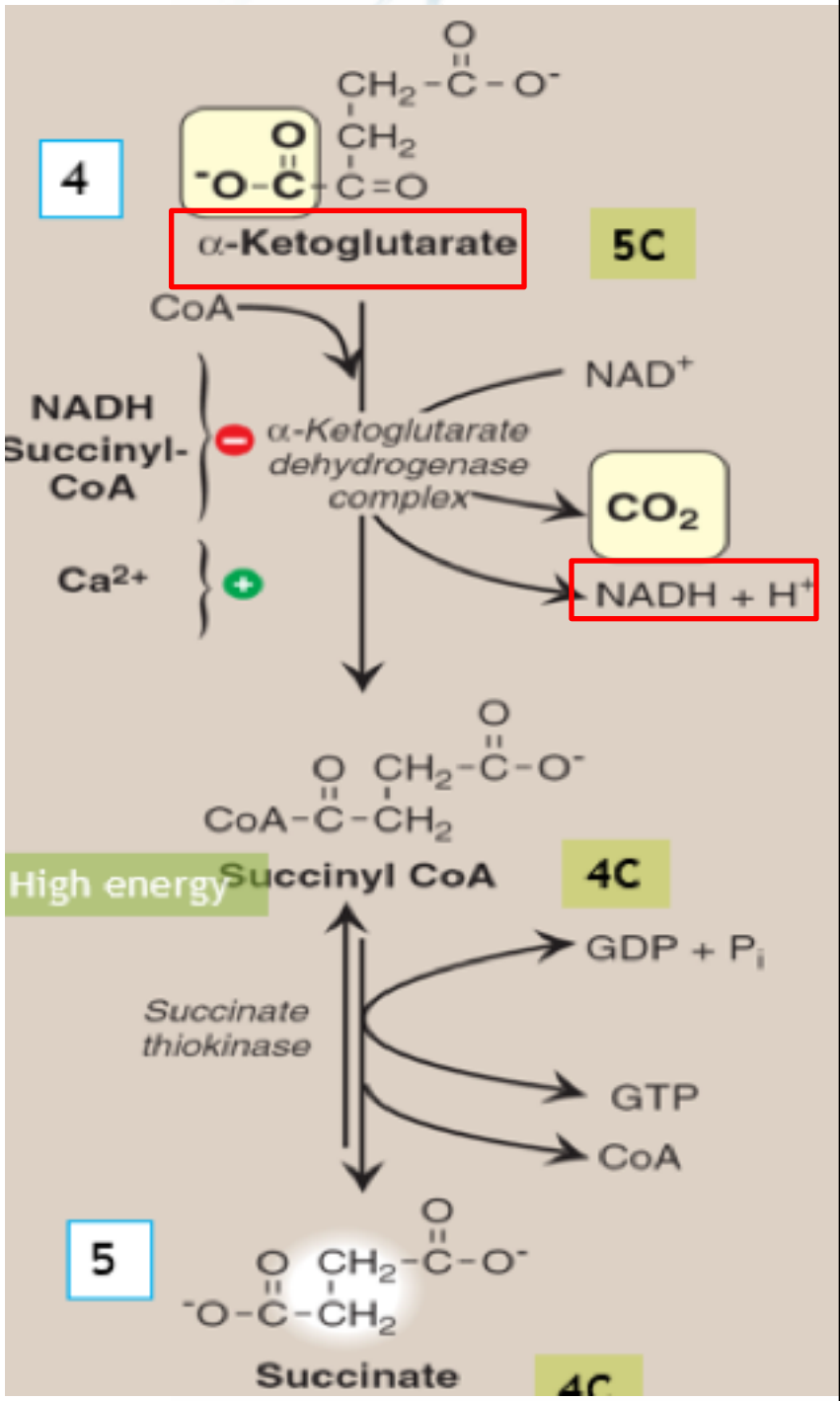
•GPD+Pi à GTP

cinyl Co-A

The ONLY Substrate-Level Phosphorylation in Krebs

Understanding the molecules J

GDP = guanosine diphosphate



sixth step *oxidation of succinate to fumarate*

Succinate ⟹ Fumarate (4C)

Oxidized by co-enzyme FAD

Succinate Dehydrogenase:
•FAD is reduced

seventh step *hydration of fumarate to L-malate*

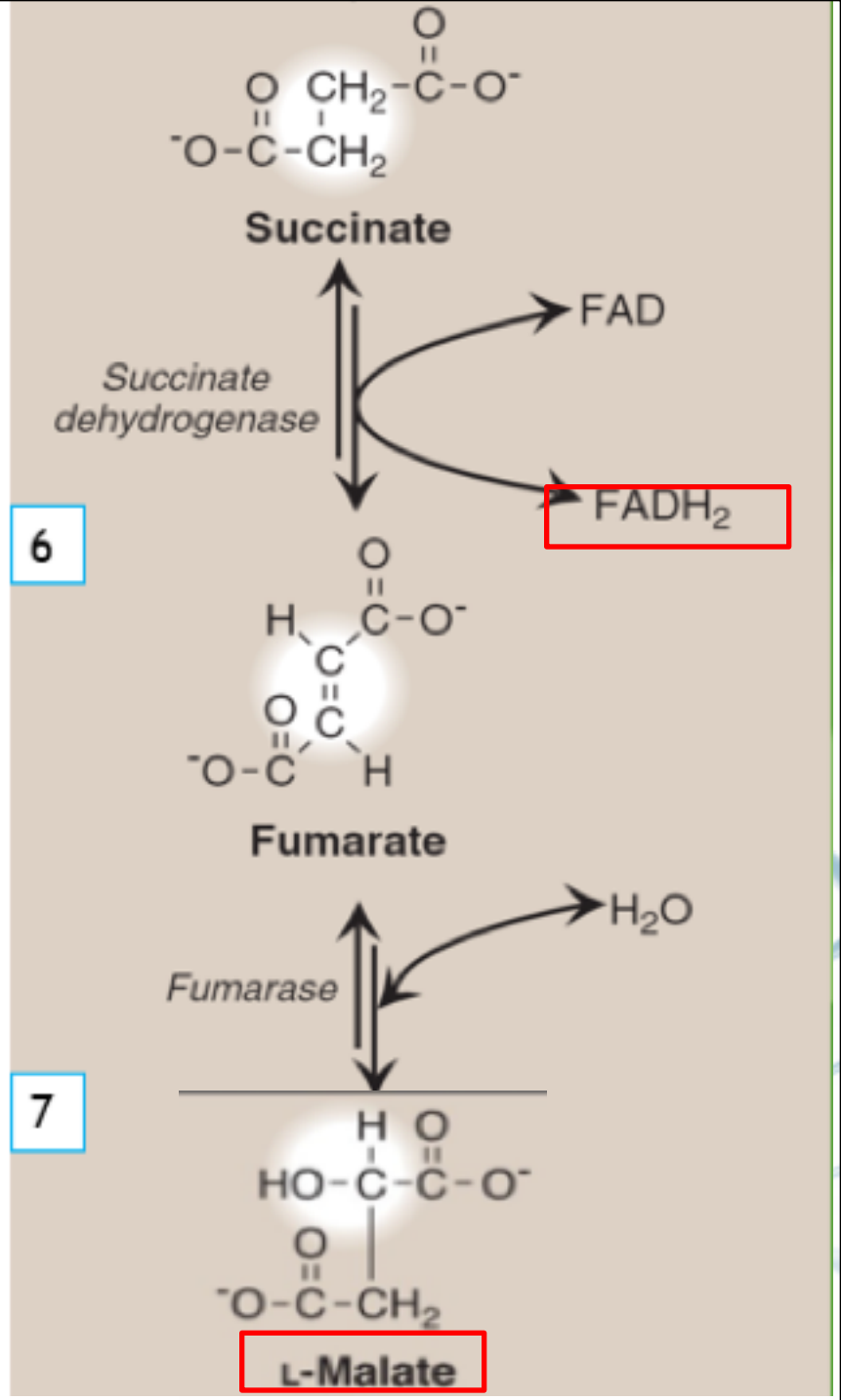
Fumarate ⟹ L-Malate (4C)

Fumarase:
•H2O is in

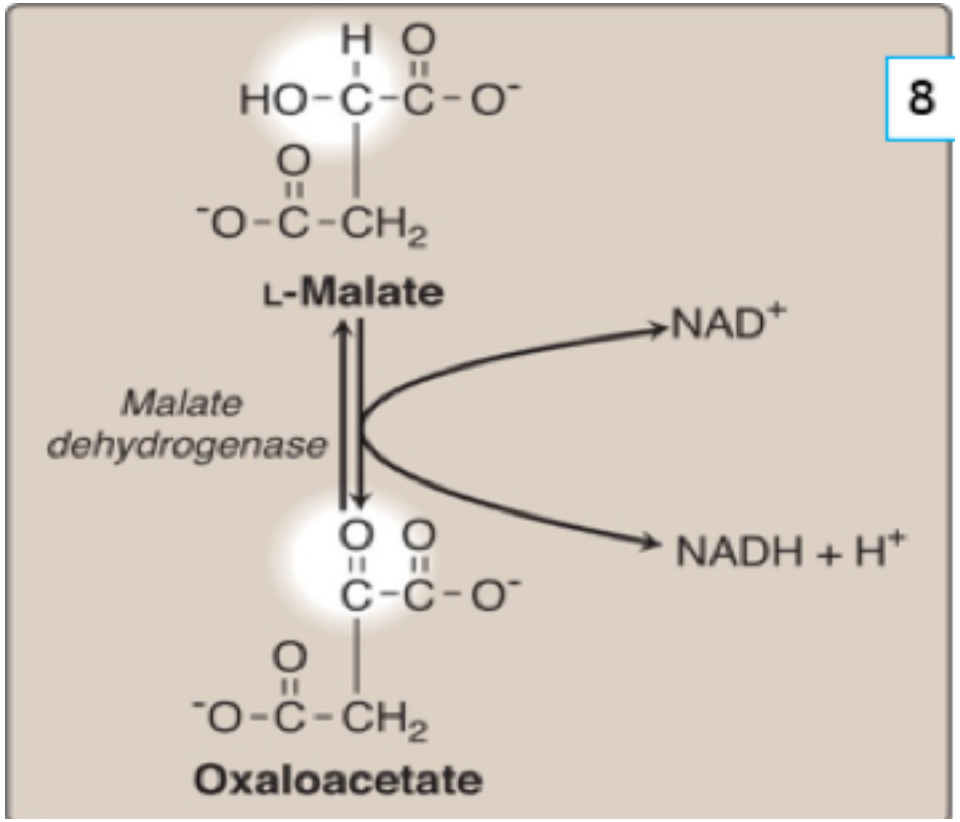
Understanding the molecules J

FAD(H_2) = flavin adenine dinucleotide.

Malate: is an organic compound with the molecular formula C4H6O5. It is a dicarboxylic acid that is made by all living organisms, contributes to the pleasantly sour taste of fruits, and is used as a food additive. The malate anion is an intermediate in the citric acid cycle.



..Krebs Cycle Reactions (3)



Eighth **step:**

L-Malate → Oxalo-acetate (4C)

Oxidized by co-enzyme NAD+

Malate dehydrogenase:
•NAD+ is reduced

Simply from:α-Ketoglutarate to L-Malate to oxaloacetate

Formation (regeneration) of oxaloacetate from malate.

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.

Krebs energy outcome

So, we get 24 ATP from 2 Acetyl CoA

Other outcome

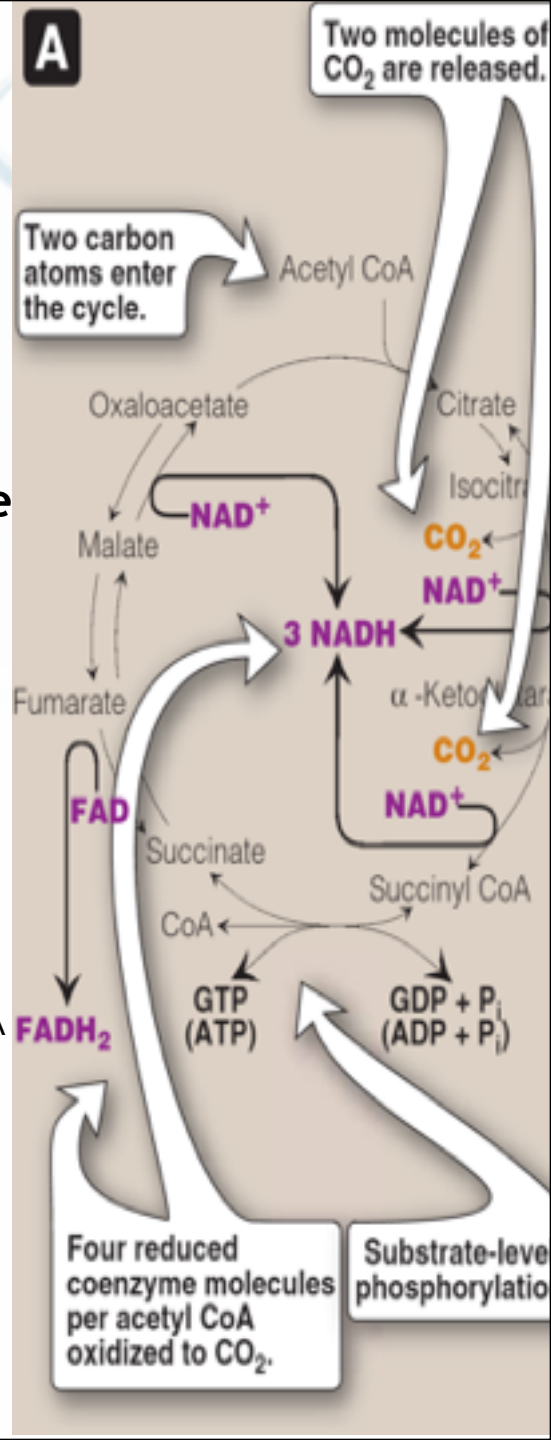
NADH = 3 ATP
FADH = 2 ATP
GTP = 1 ATP

We get 2 CO_2 from:

Isocitrate à α-Ketoglutarate
α-Ketoglutarate à 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



Important slide

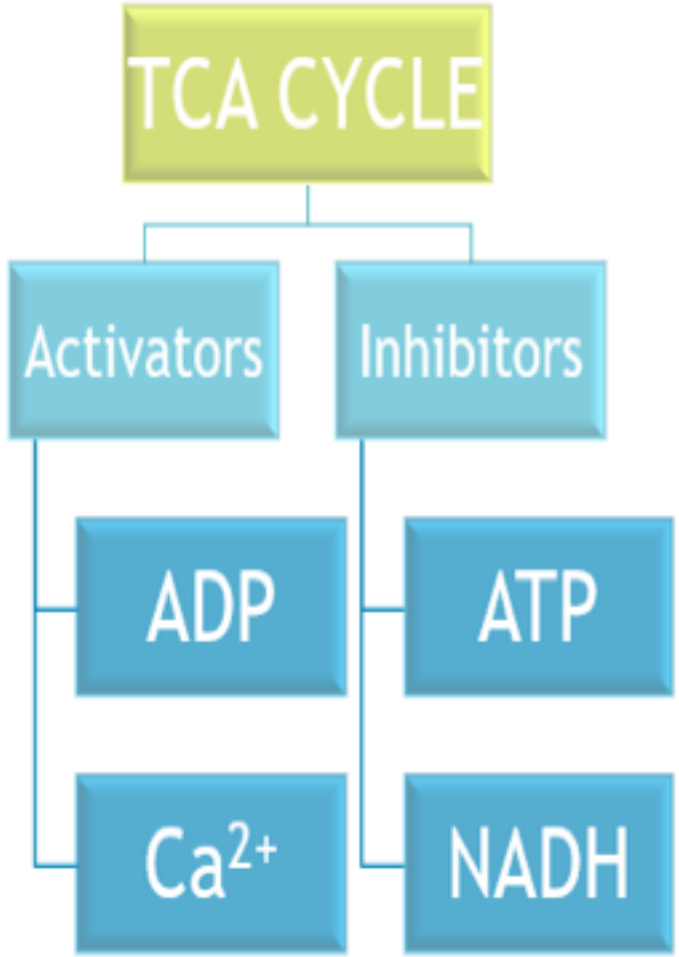
Regulation of Oxidative Decarboxylation and Krebs Cycle

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



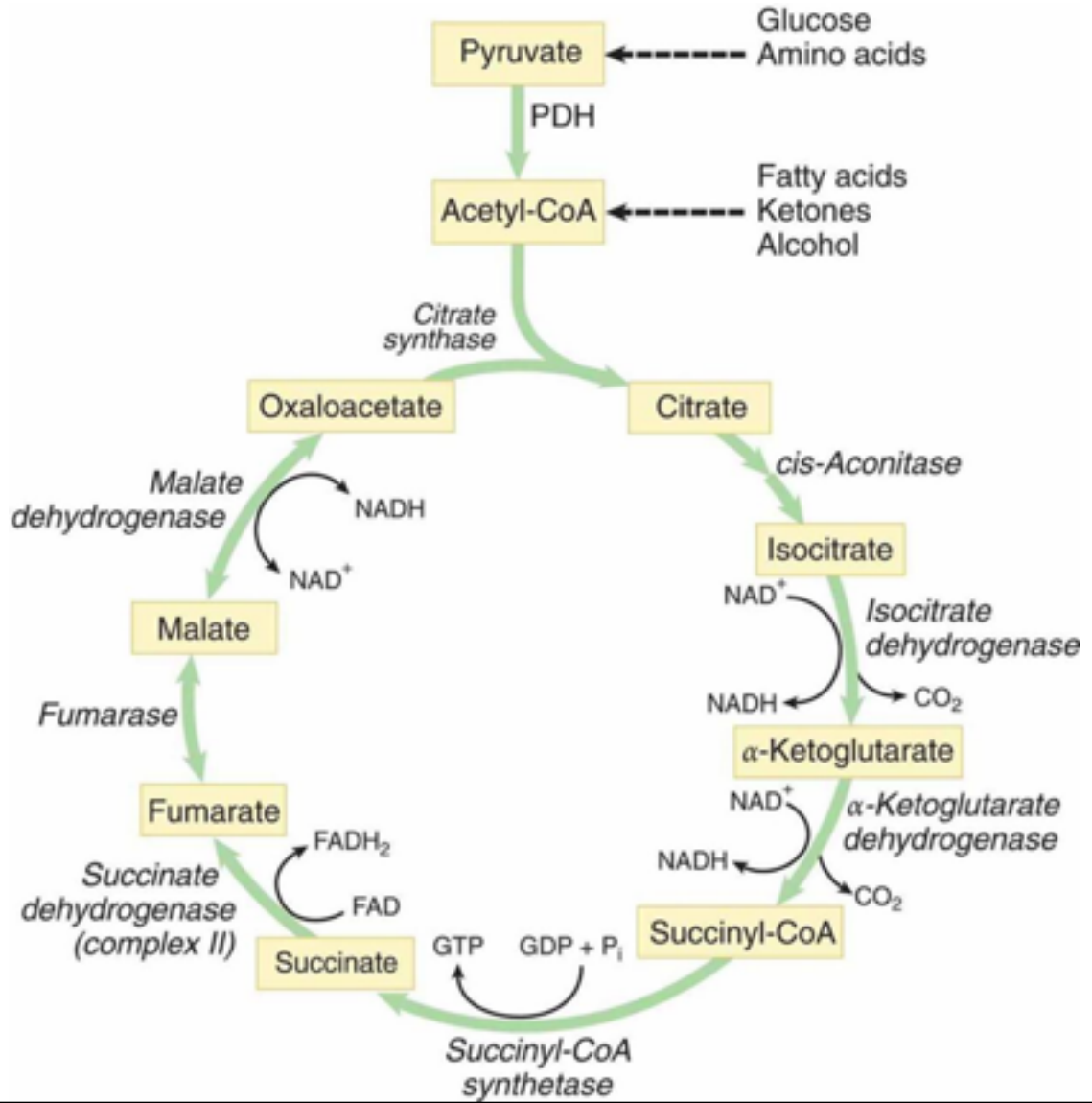
Take Home Message

- Pyruvate is oxidatively decarboxylated by PDH to acetyl CoA inside the mitochondria

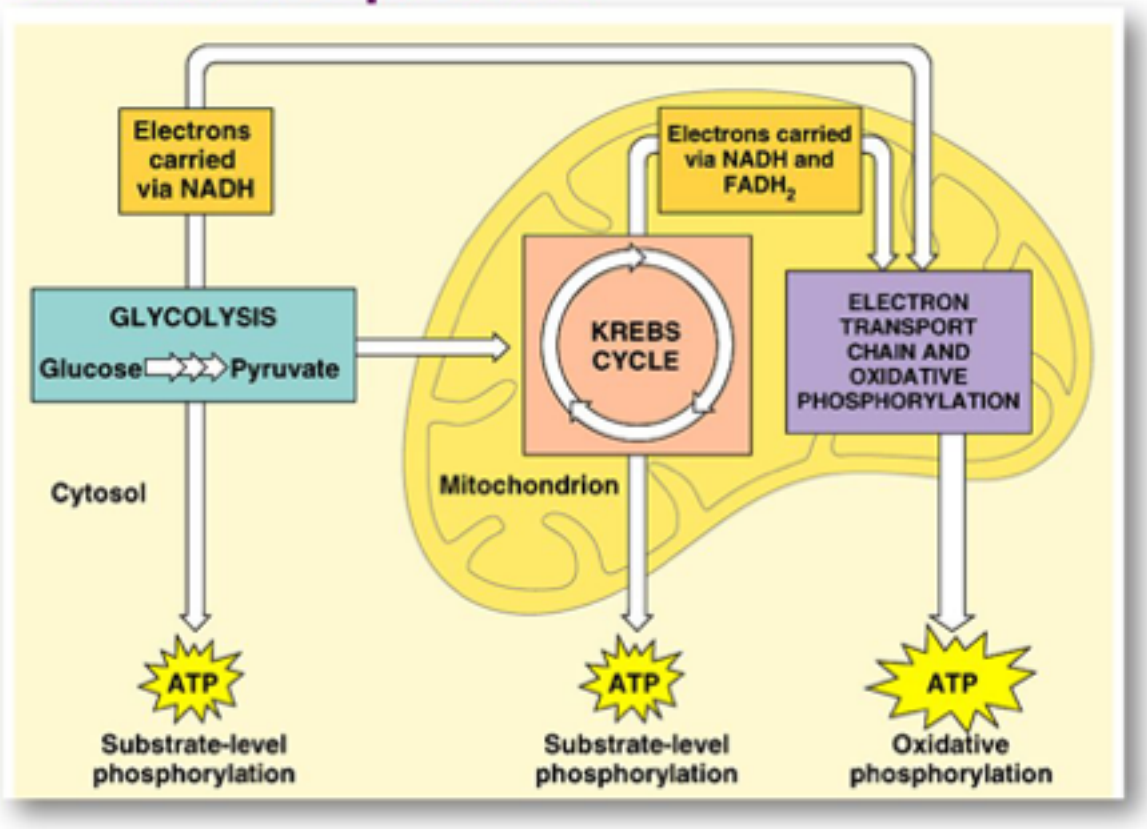
- *Krebs cycle:*
  - Final common pathway for the oxidation of carbohydrates, fatty acids and amino acids
  - Occurs in the mitochondria
  - Aerobic
  - Mainly catabolic, with some anabolic reactions

- The complete oxidation of one glucose molecule results in a net production of **38 ATP molecules**

Review



Cellular Respiration



MCQs

Q1; net ATP production by oxidative decarboxylation is:

A- 38 ATP
B- 6 ATP
C- 24 ATP
D- 8 ATP

Q2;Allosteric regulation in oxidative decarboxylation of pyruvate is done by:

A- Acetyl CoA
B- NADH
C- ATB
D- A&B

Q3; the enzyme that convert Citrate to Isocitrate is :

A- Isocitrate
B-Aconitase
C-citrate synthase

Q4; net ATP production by complete glucose oxidation is:

A-38 ATP
B-38 ADP
C-8 ATP

Answer key:

1)B
2)D
3)B
4)A

SAQs

1-what deficiencies of Thiamine and niacin can cause?

CNS problems

2- where does the Krebs cycle occur?

in mitochondria

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- جود العتيبي
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