Oxidative Decarboxylation and Krebs Cycle

- Color Index:

- Important.
- Extra Information.
- **Doctors slides.**

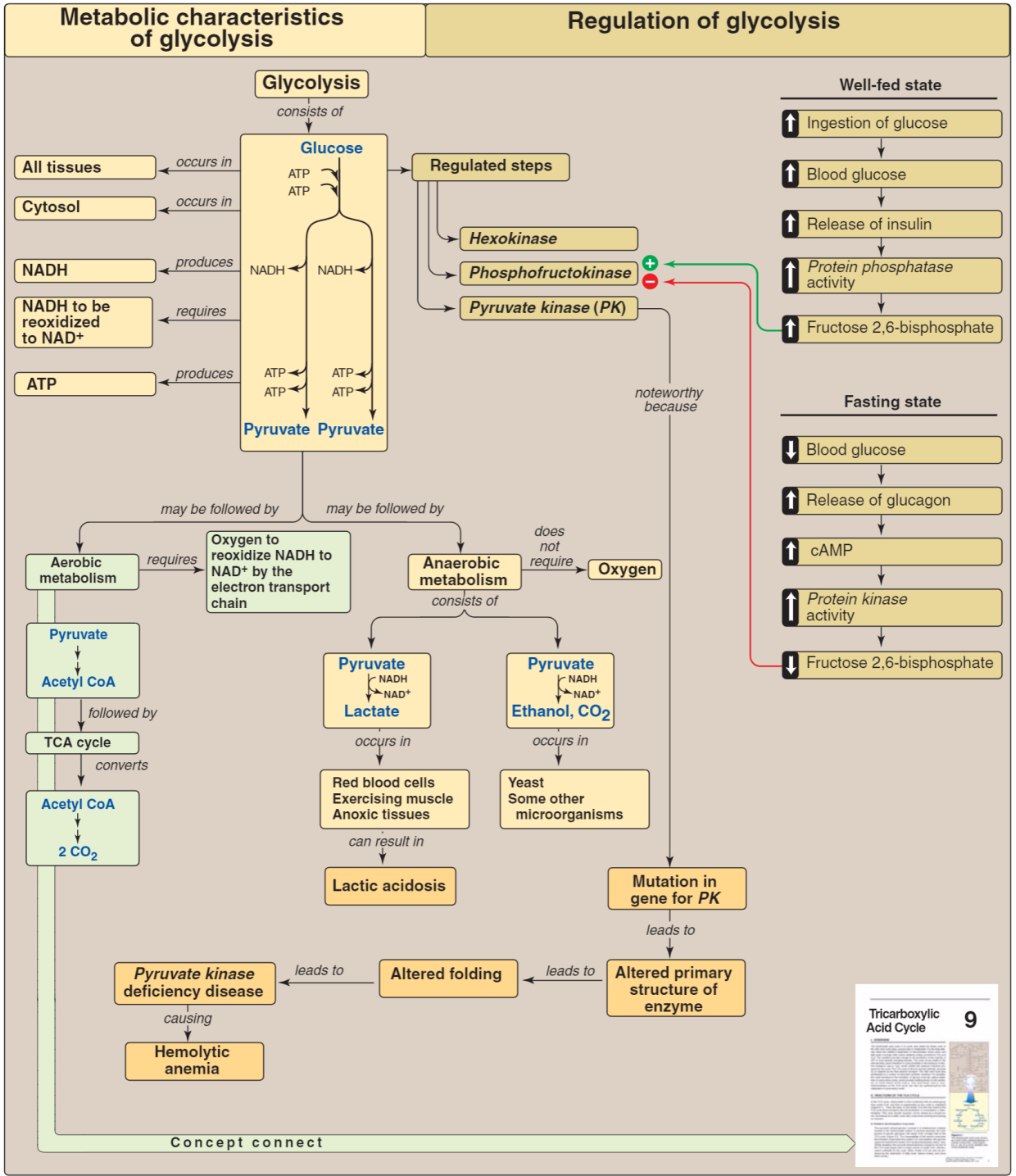
Objectives:

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



From Lippincott.
(Extra slide → to understand general concept) ☺

Overview of Krebs cycle:

The citric acid cycle – also known as the tricarboxylic acid (TCA) cycle or the Krebs cycle– is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidation of acetyl-CoA derived from carbohydrates, fats and proteins into carbon dioxide and chemical energy in the form of adenosine triphosphate. In addition, the cycle provides precursors of certain amino acids as well as the reducing agent NADH that is used in numerous other biochemical reactions. The name of this metabolic pathway is derived from citric acid (a type of tricarboxylic acid) that is consumed and then regenerated by this sequence of reactions to complete the cycle. In addition, the cycle consumes acetate (in the form of acetyl-CoA) and water, reduces NAD+ to NADH, and produces carbon dioxide as a waste byproduct. The NADH generated by the TCA cycle is fed into the oxidative phosphorylation (electron transport) pathway. In eukaryotic cells, the citric acid cycle occurs in the matrix of the mitochondrion.

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

Lactate

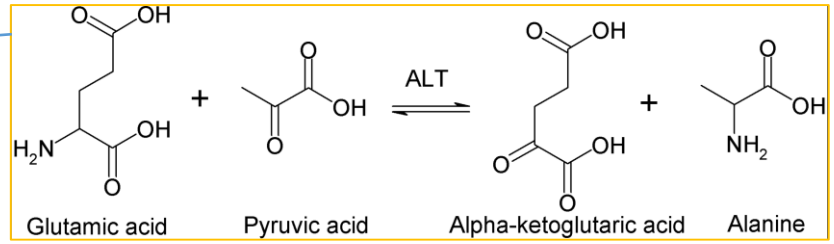
*in humans and some microorganisms “anaerobic”

Alanine

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

*Done by Alanine transaminase enzyme “ALT”

*• PLP = pyridoxal phosphate



1-Glutamine ‘donating group ‘ will give NH2 to pyruvate (pyruvic acid)
2-Glutamine will transfer into alpha-keto glutamic acid , while pyruvate will transfer into alanine

Ethanol

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

* Thiamine pyrophosphate-dependent pathway

Acetyl CoA

***in Krebs cycle**

Oxaloacetate

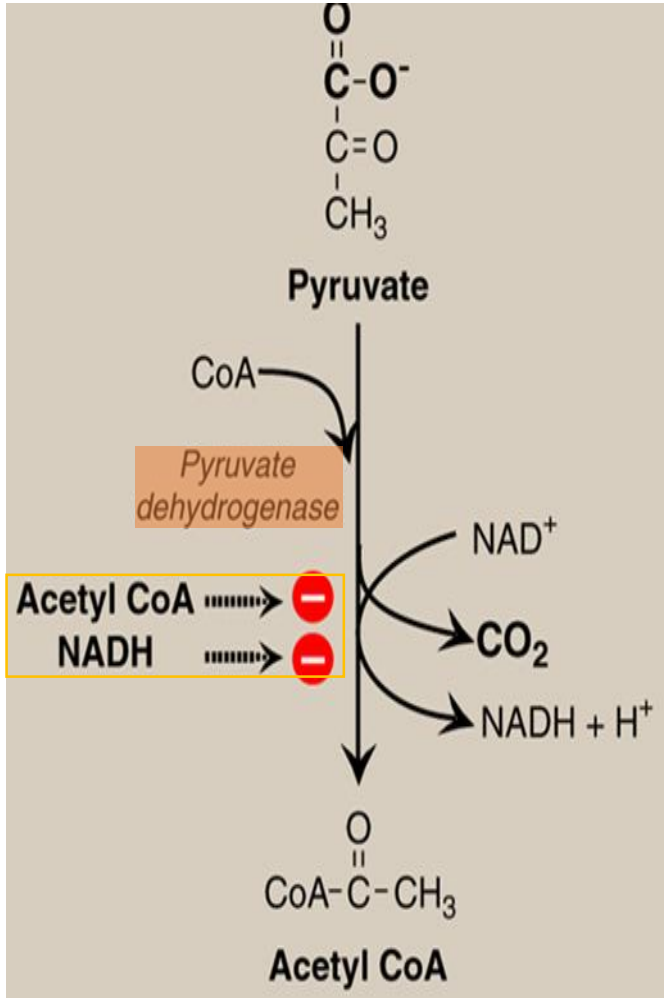
*In Krebs cycle (it’s an intermediate)

* Activated by acetyl CoA

***Importance**:

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

oxidative decarboxylation of pyruvate
'pre Krebs cycle'



- It's the process of making acetyl Co-A "mainly" & oxaloacetate from pyruvates by the enzyme: pyruvate dehydrogenase
- **Produces** 2 NADH 6 ATP
- **Regulated by** allosteric regulation of Acetyl coA and NADH

- Increased amount of Acetyl CoA and NADH **act as** "Negative Feedback" inhibitors of their respective reactions.

How?
They activate "Pyruvate dehydrogenase **kinase** which phosphorylates and **inactivates** "Pyruvate dehydrogenase"

Understanding the **pyruvate dehydrogenase complex (PDC).**
It is made of three enzymes
One of them is **Pyruvate Dehydrogenase**
The pyruvate dehydrogenase complex contributes to transforming pyruvate into acetyl-CoA by a process called pyruvate decarboxylation. Acetyl-CoA may then be used in the citric acid cycle to carry out cellular respiration, so pyruvate dehydrogenase contributes to linking the glycolysis to Krebs cycle and releasing energy via NADH.

More in the next slide

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

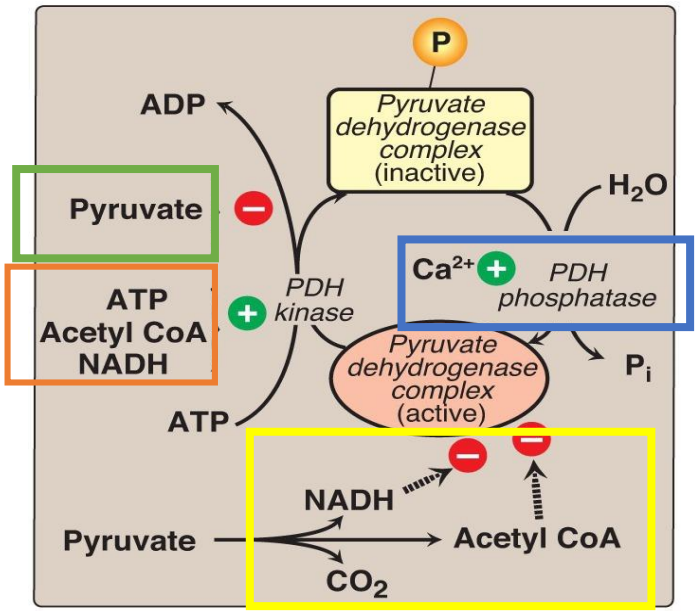
PDH : enzyme complex "3 enzymes joint together" that convert pyruvate into acetyl CoA .

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

***inactive form:** regulated by PDH kinase

***active form:** regulated by PDH phosphatase

**Those two enzymes are controlled by many factors*



Regluation of PDH kinase

↑ **pyruvates**

↓

Inactivation of PDH kinase

↓

Active form of pyruvate complex

↑ **ATP, acetyl co-A, NADH**

↓

Activation of PDH kinase

↓

Inactive form of the complex

Regulation PDH phosphatase

PDH phosphatase +Ca remove phosphates

↓

active complex

↓

↑ acetyl Co-A ,NADH ,CO_2

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

Extra info:
Thiamine: vitamin B_1, a coenzyme in the catabolism of sugars and amino acids.
Niacin,: also known as vitamin B_3 A precursor of coenzymes called NAD and NADP, which are needed in many metabolic processes.

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.

*has 8 reactions.

Properties of the cycle

Final common pathway for oxidation.

Exclusively in mitochondria

Major source for ATP

(24 ATP)

Mainly catabolic with some anabolic features

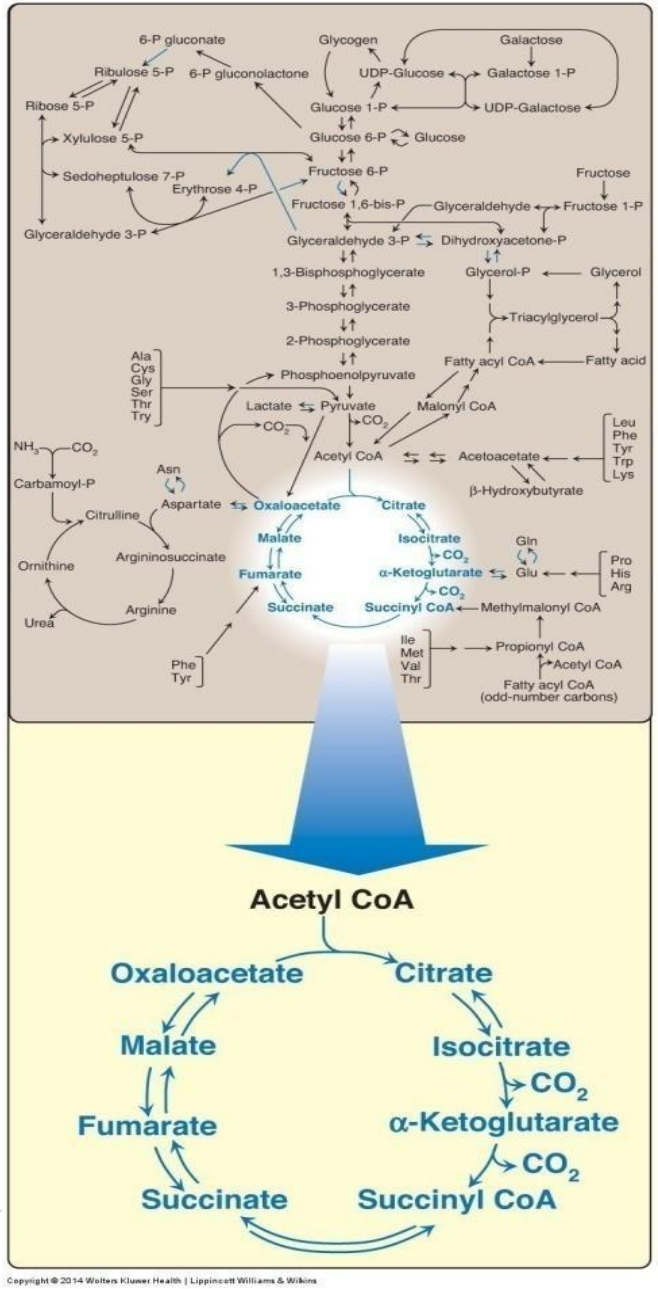
Synthetic reactions (anabolic features):

1-Glucose from amino acids

2-Nonessential amino acids

3-Fatty acids

4-Heme



CoA = coenzymeA.

Krebs Cycle Reactions (1) (1st → 3rd)

1st step:

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

Joined by condensation

Citrate synthase: H2O in CoA out

2nd step:

Citrate → iso-citrate

Aconitase

3rd step:

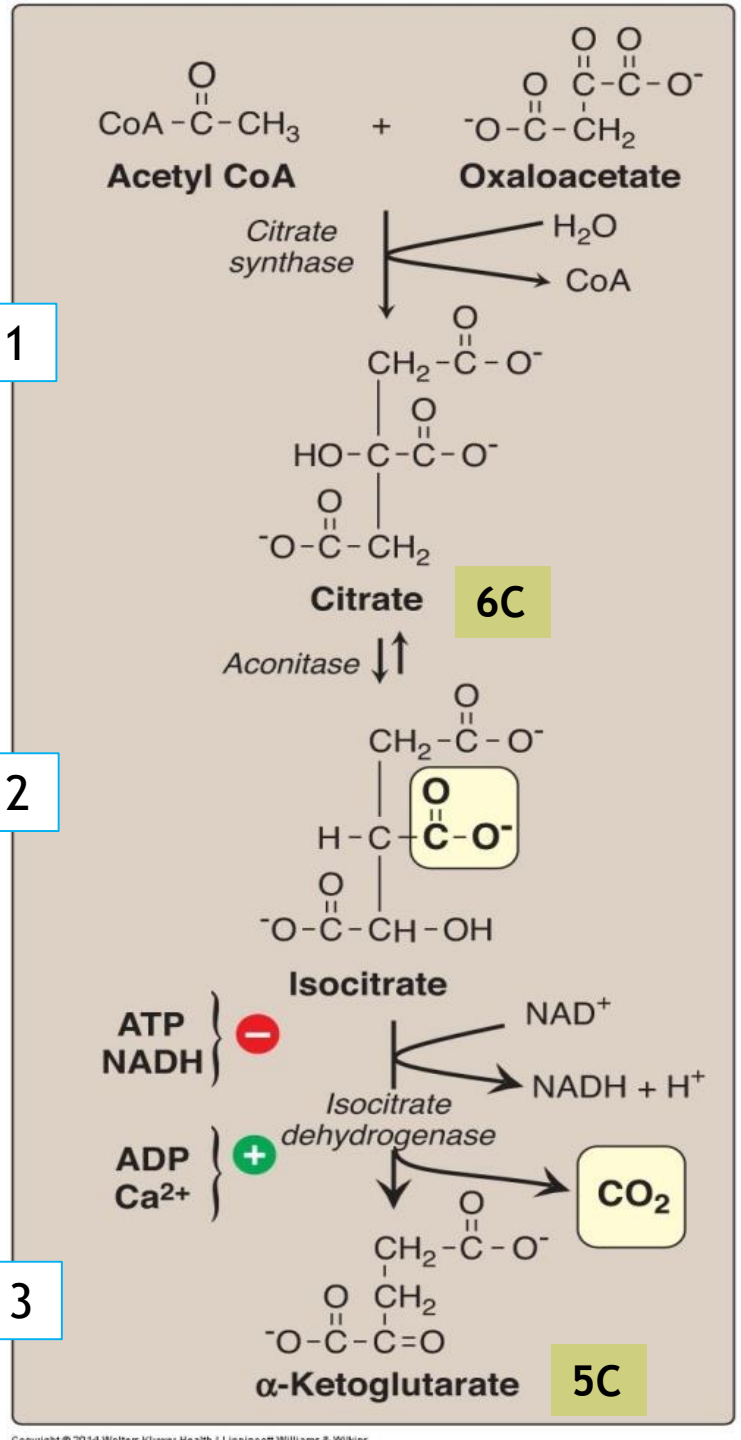
Iso-citrate → α-Ketoglutarate (5C)

Oxidized by coenzyme NAD+

IsoCitrate Dehydrogenase: NAD+ is reduced Co2 is out

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

Understanding the molecules ☺
NAD(H) = nicotinamide adenine dinucleotide
α-Ketoglutarate: It is the keto acid derivative of glutamate, and is an intermediate.



Krebs Cycle Reactions (2) (4th → 7th)

4th Step *oxidation and decarboxylation*

α-Ketoglutarate oxidized by co-enzyme NAD+

↓

α-Ketoglutarate Dehydrogenase complex

- NAD+ is reduced to NADH + H^+
- CO_2 is out
- CoA is in

↓

Succyinyl CoA

It is regulated

It is activated by: Ca2+
Inhibited by: NADH and Succinyl CoA

5th Step *oxidation and decarboxylation*

Succinyl Co-A

↓

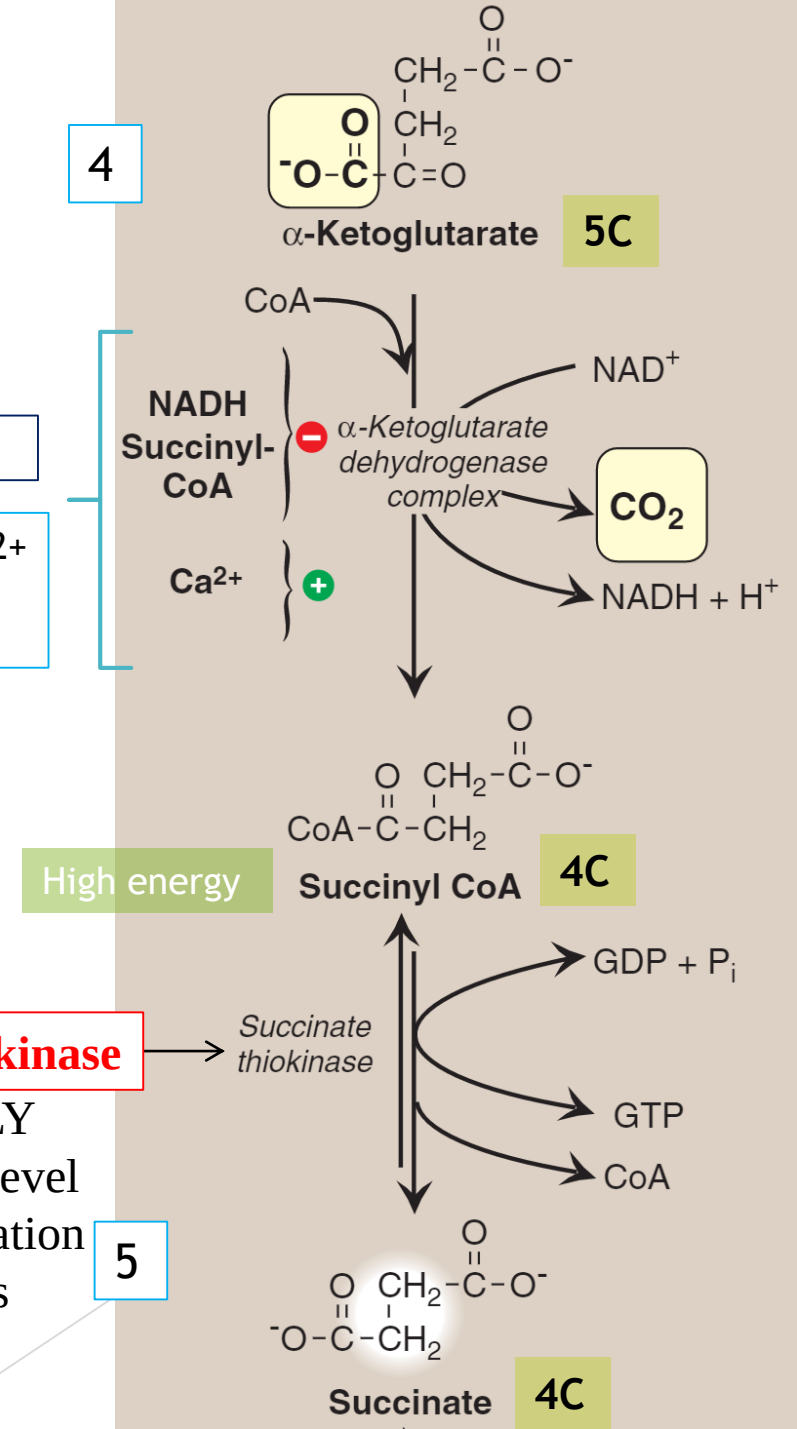
Succinate Thiokinase

- Co-A is out
- GPD+Pi → GTP

Succinate Thiokinase

The ONLY Substrate-Level Phosphorylation in Krebs

Understanding the molecules ☺
GDP = guanosine diphosphate.



6th step *oxidation of succinate to fumarate*

Succinate ⟶ Fumarate (4C)

Oxidized by co-enzyme FAD

Succinate Dehydrogenase:
- FAD is reduced

7th step *hydration of fumarate to L-malate*

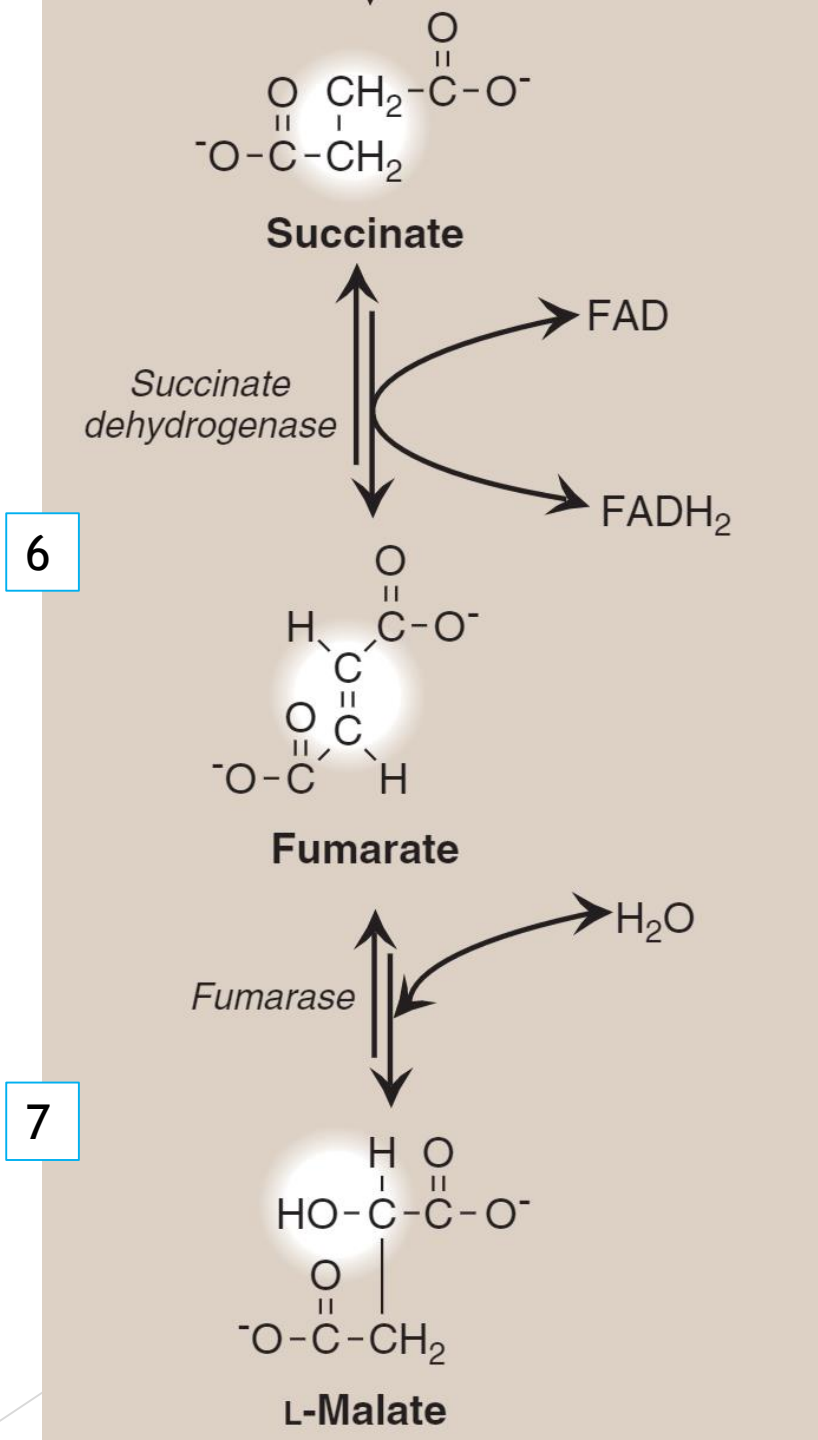
Fumarate ⟶ L-Malate (4C)

Fumarase:
- H2O is in

Understanding the molecules ☺

FAD(H_2) = flavin adenine dinucleotide.

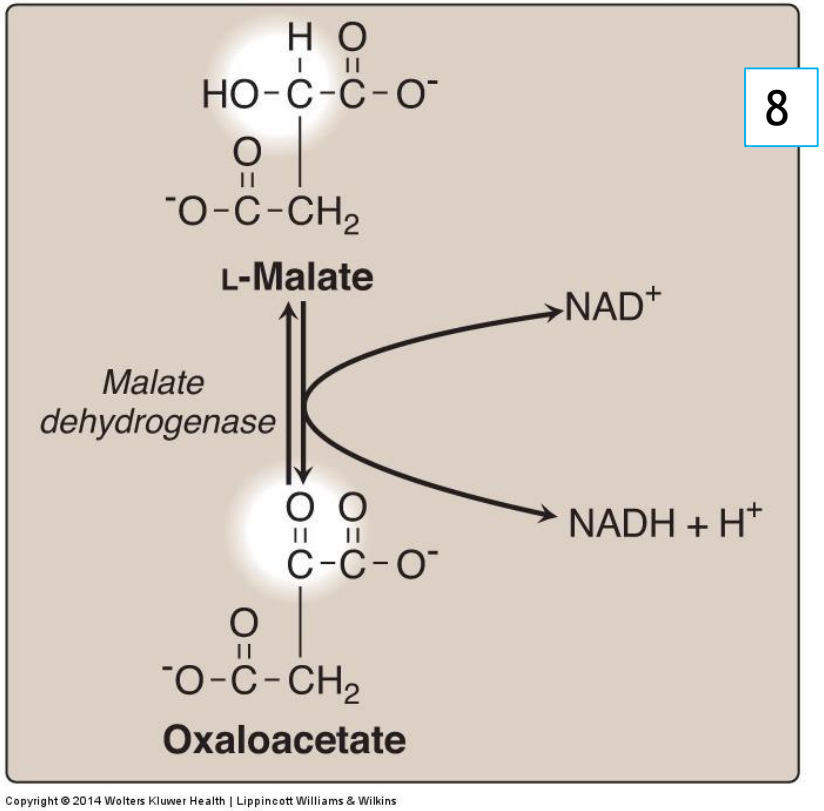
Malate: is an organic compound with the molecular formula C4H6O5. It is a dicarboxylic acid that is made by all living organisms, contributes to the pleasantly sour taste of fruits, and is used as a food additive. The malate anion is an intermediate in the citric acid cycle.



Krebs Cycle Reactions (3)

Irreversible steps:

Step1
Step 3
Step 4



8th step:

L-Malate → Oxalo-acetate (4C)

Oxidized by co-enzyme NAD+

Malate dehydrogenase:

- NAD+ is reduced

Why do we convert Succinyl CoA to Succinate to Fumarate to L- Malate to Oxaloacetate even though they all have the same number of carbons?

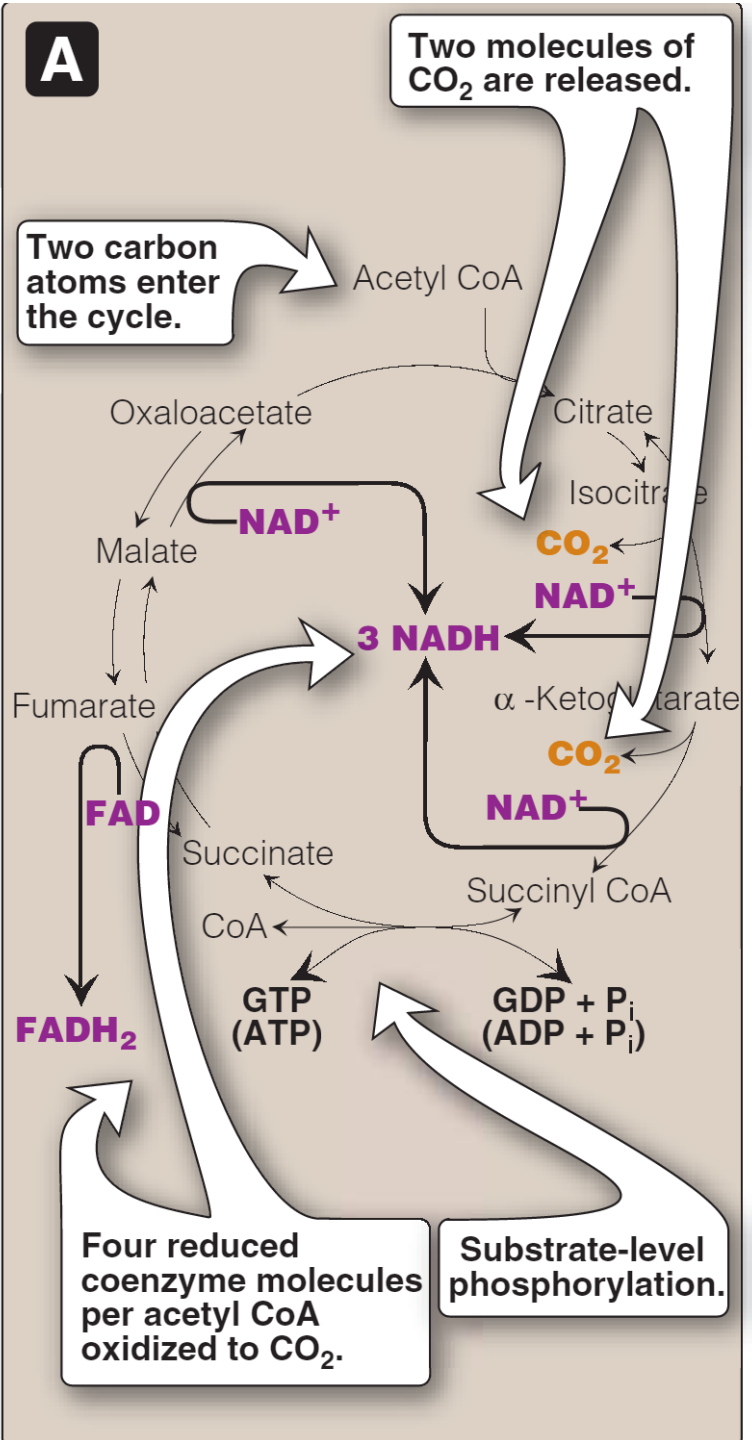
Because we want to release more energy by :

1/Substrate level phosphorylation

2/ Oxidative phosphorylation

team435

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**.

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**

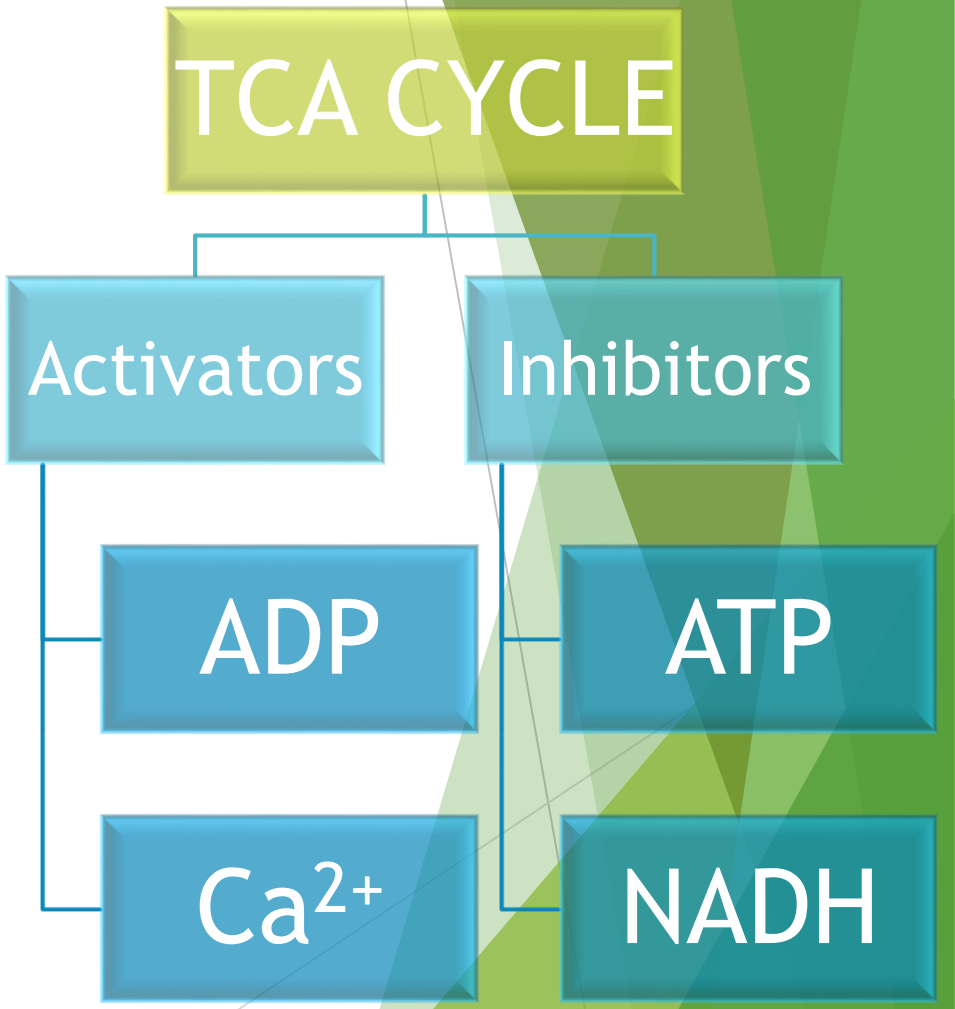
Regulation of Oxidative Decarboxylation and Krebs Cycle

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 كربس

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

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

- Girls team members:

1- هيفاء الوعيل.

2- روان الوادعي.

3- زينة الكاف.

4- نجود العنزي.

5- نورة الشبيب.

-Team leaders:

نوره السهلي.
عبدالله المانع.

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