Biochemistry Team 435

جامعة الملك سعود
King Saud University

OXIDATIVE DECARBOXYLATION AND KREBS CYCLE

"EITHER YOU RUN THE DAY, OR THE DAY RUNS YOU"

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.

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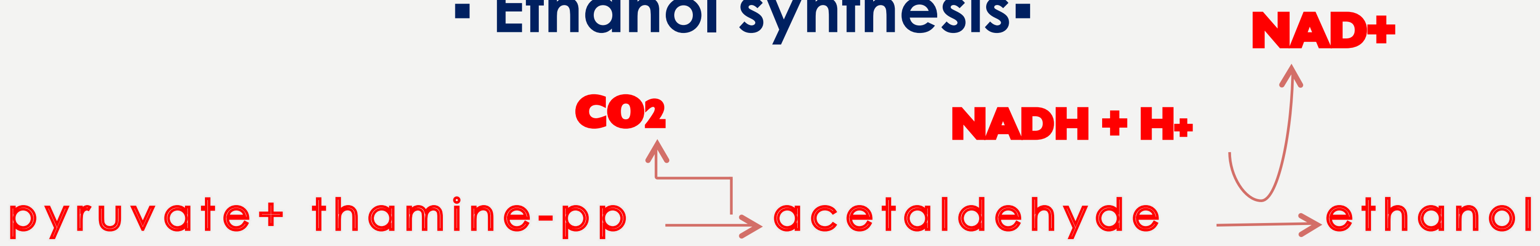
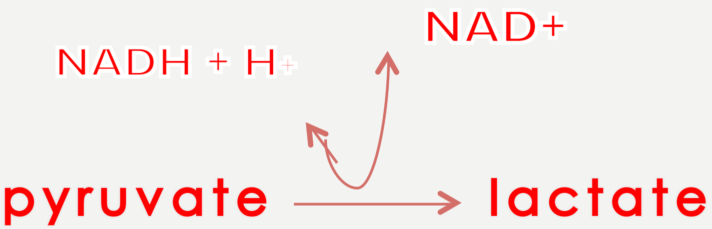
▪ Ethanol synthesis▪



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

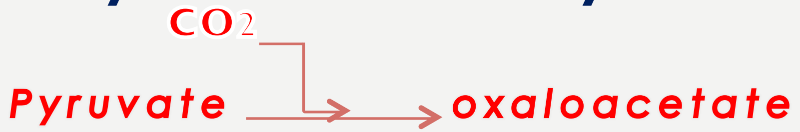
FATES OF PYRUVATE

▪ Reduction of pyruvate to lactate ▪



- **Enzyme:** lactate dehydrogenase.
- We talked about it in the previous lecture

▪ Pyruvate carboxylase ▪



- **Activated by** acetyl CoA

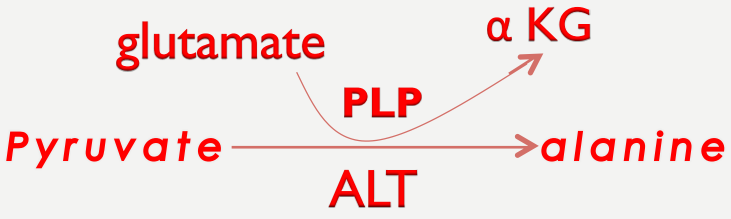
- **Important :**

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

FATES OF PYRUVATE

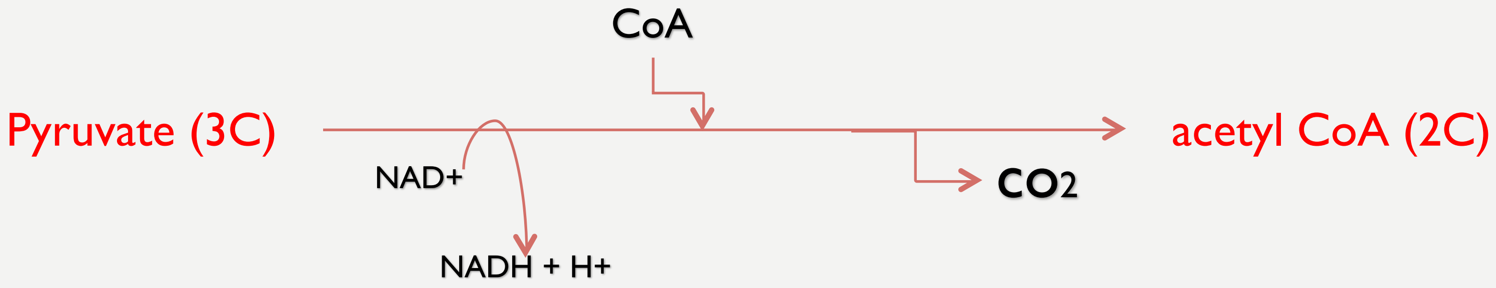
Oxidative decarboxylase of pyruvate

(next slide)



- PLP = pyridoxal phosphate

OXIDATIVE DECARBOXYLASE OF PYRUVATE



Enzyme: pyruvate dehydrogenase (PDH)

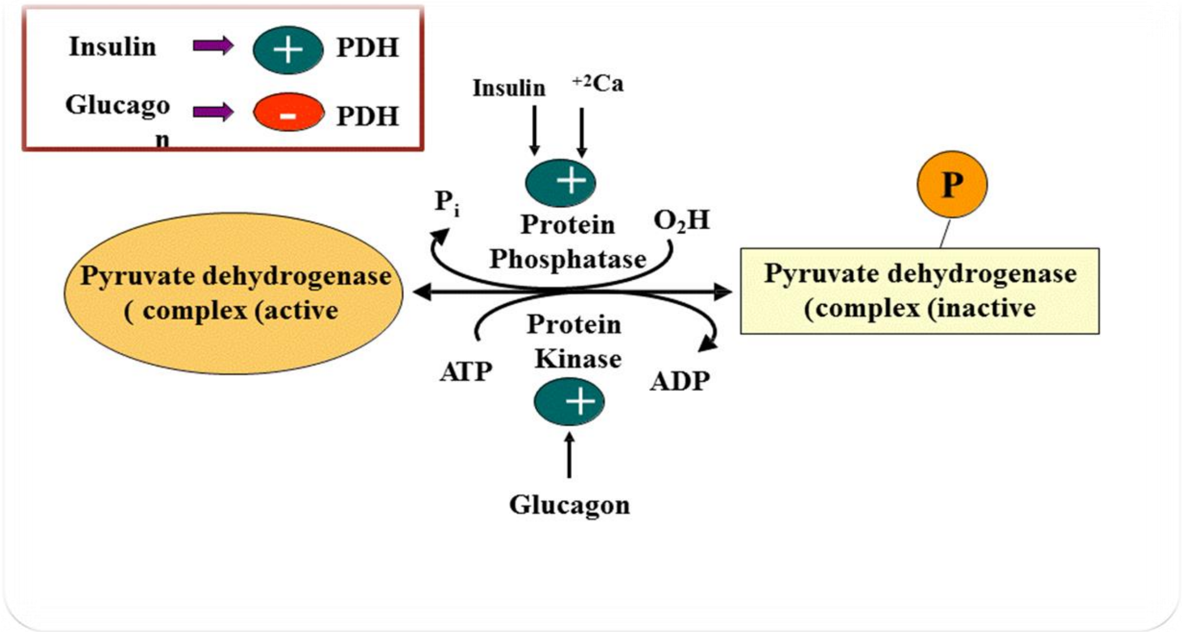
Regulation

(allosteric regulation)

(-) acetyl CoA
(-) NADH

(PDH covalent regulation)

(+) insulin , ca+2
(-) glucagon



PDH REACTION : CLINICAL APPLICATION

- ✓ **Deficiencies of thiamine or niacin serious CNS problems.** WHY?:

Brain cells are unable to produce sufficient ATP if the PDH complex is inactive.

- ✓**Wernicke-Korsakoff**

(encephalopathy-psychosis syndrome) due to thiamine deficiency, may be seen especially with alcohol abuse

- ✓**congenital lactic acidosis.**

PDH complex deficiency is the most common biochemical of it

OVERVIEW OF KREBS CYCLE

1-what is Krebs cycle?

- it is a part of the essential pathways of energy metabolism.
- It is the Final common pathway for oxidation

2- where does it occur ?

It occurs Exclusively in mitochondria (it occurs only in the mitochondria. 'aerobic')

3-Major source for ATP

4-Krebs cycle has different names:

Citric acid cycle.

Tricarboxylic acid cycle. (because the first product of the cycle "citrate" contains 3 carboxylic acid group)

5-Mainly catabolic with some anabolic features

Synthetic reactions (anabolic features):

Glucose from amino acids

Nonessential amino acids

Fatty acids

Heme

Recall:
Non essential amino acids are amino acids that are synthesized by our bodies

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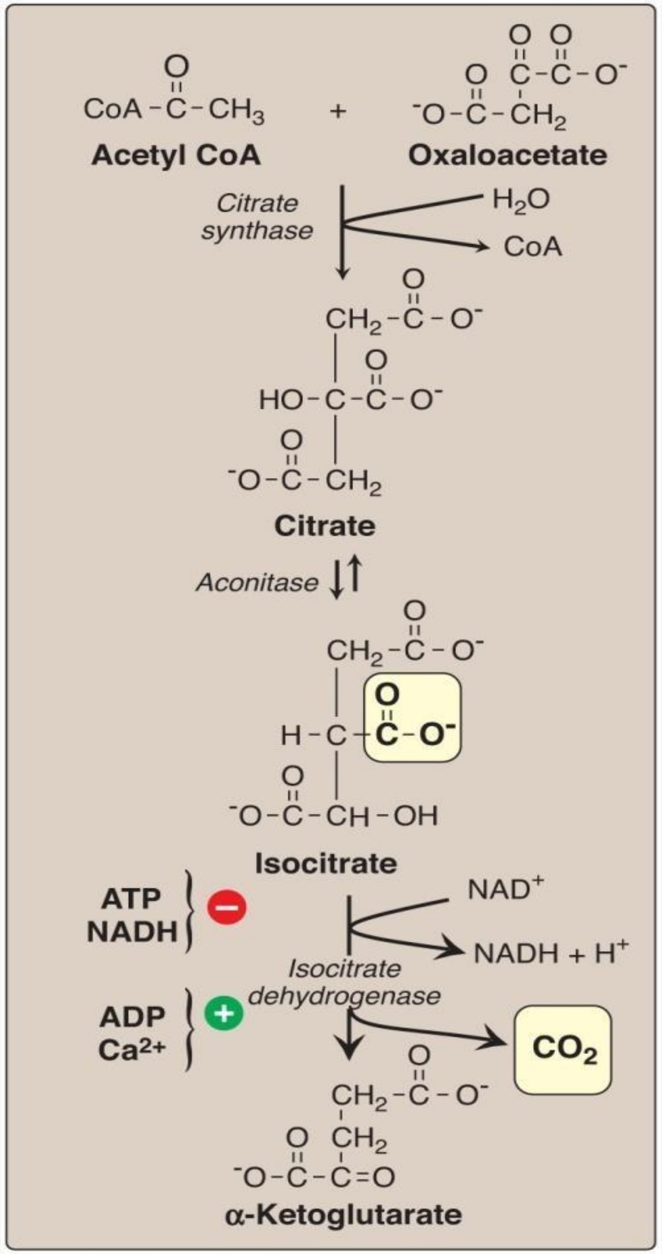


Step1 (joined by condensation reaction)

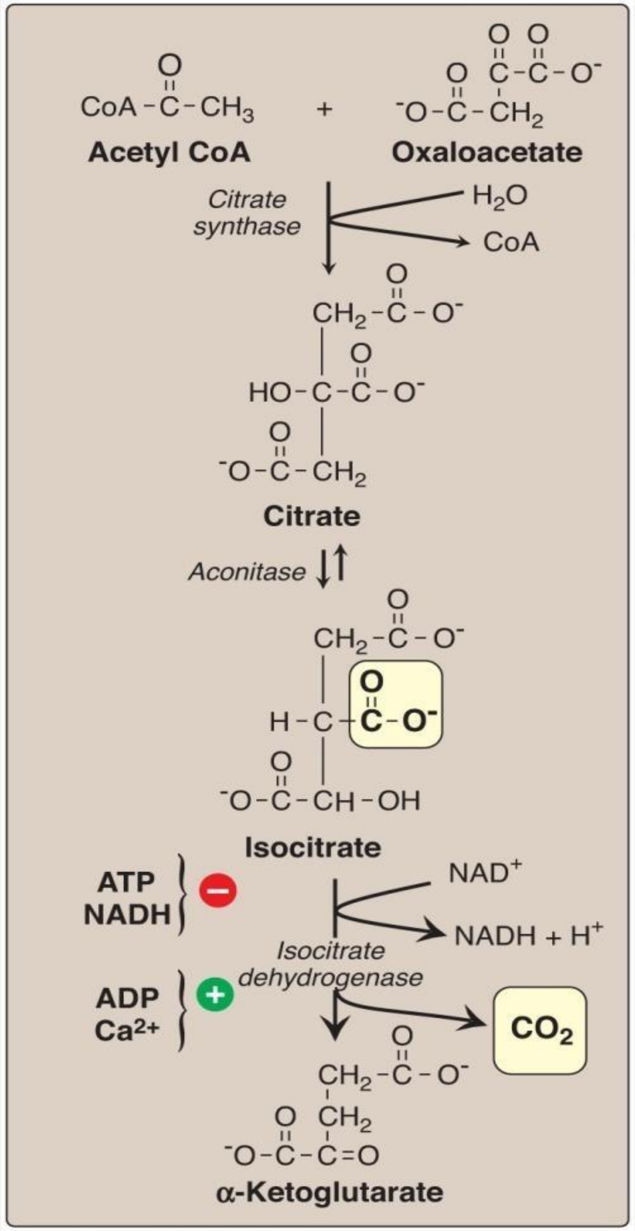
Acetyl CoA + Oxaloacetate → (Citrate synthase) Citrate (6 Carbons)

H_2O is in

CoA is out

Step 2 Isomerization of citrate to Isocitrate

Citrate → (Aconitase) Isocitrate (6 Carbons)



Isocitrate dehydrogenase is
Activated by: ADP and Ca2+
Inhibited by: ATP and NADH

Step 3 *Oxidation & decarboxylation of Isocitrate to α-Ketoglutrate*

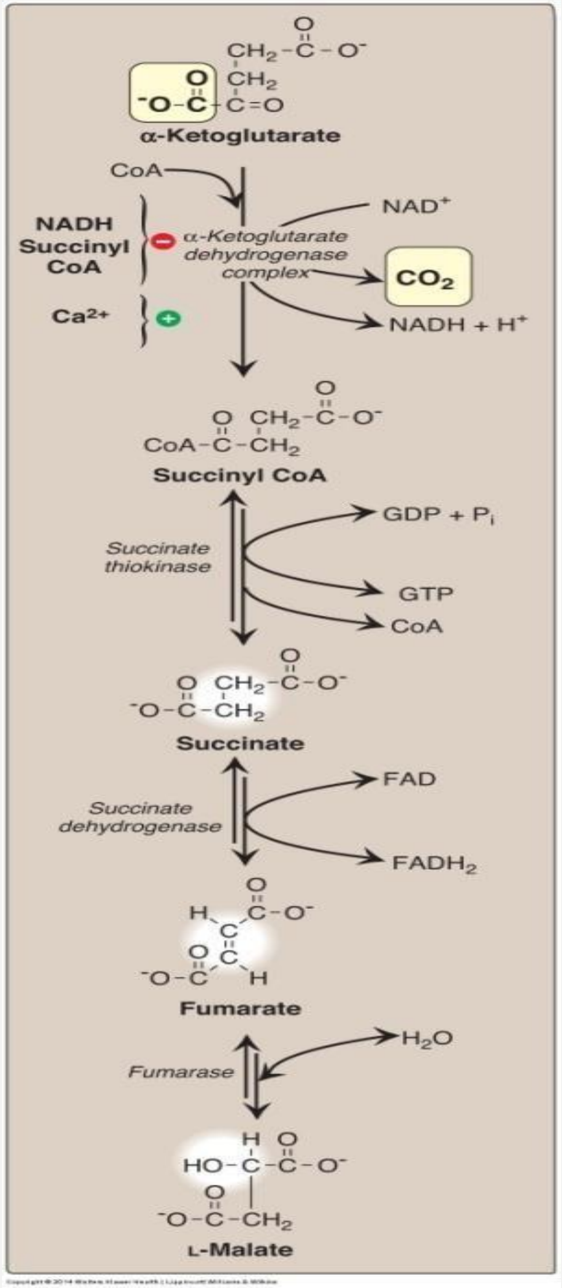
Isocitrate → Isocitrate dehydrogenase → a-ketoglutarate (5 Carbons)

Isocitrate: Oxidized by coenzyme NAD+

*NAD+ is reduced to NADH+H

*CO2 is out

Note: Isocitrate → a-ketoglutarate
Is very regulatory step. Why? Because we can activate it or inhibit it



Step 4 Oxidation & decarboxylation of α-Ketoglutarate to succinyl CoA

a-ketoglutarate → (a-ketoglutarate dehydrogenase complex) → Succinyl CoA (4 Carbons)

Oxidized by coenzyme NAD+

*NAD+ is reduced to NADH+H
*CO2 is out
*CoA is in

a-ketoglutarate dehydrogenase complex is
Activated by: Ca2+
Inhibited by: NADH and Succinyl CoA

Note:
- a-ketoglutarate → Succinyl CoA
Is very regulatory step. Why? Because we can activate it or inhibit it.
- a-ketoglutarate →glutamate
  a-keto acid → amino acid

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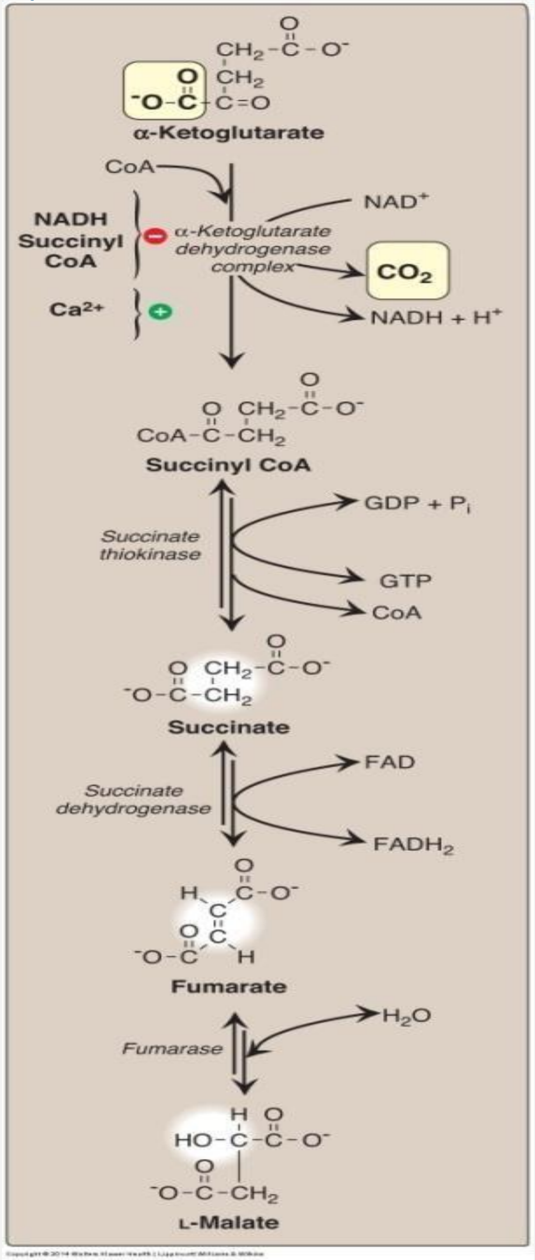


Step 5

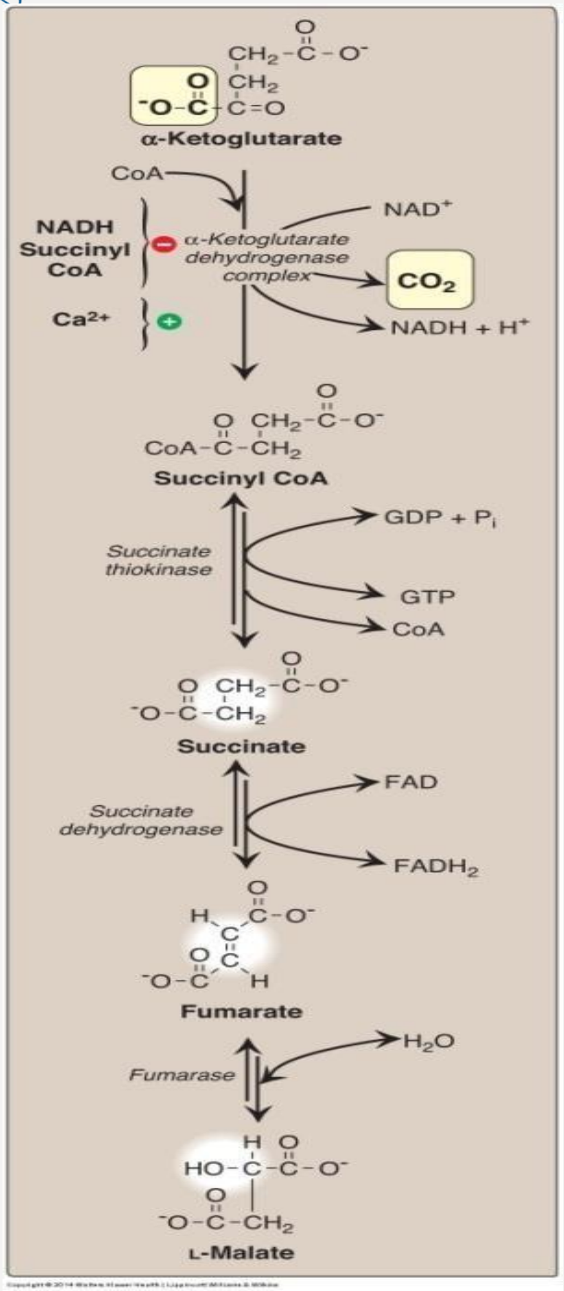
Succinyl CoA → (Succinate thiokinase) → Succinate (4 Carbons)

*CoA is out

*GDP + Pi turned into GTP

(because of the energy gained from the cleavage of CoA bond *high energy*)

*The only Substrate-Level Phosphorylation in krebs cycle



Step 6 *Oxidation of succinate to fumarate*

Succinate → (Succinate dehydrogenase; FAD is reduced to FADH2) → Fumarate (4 Carbons)

Succinate: Oxidized by coenzyme FAD

Step 7 *Hydration of fumarate to L-malate*

Fumarate → (Fumarase; *H2O is in) → L- Malate (4 Carbons)

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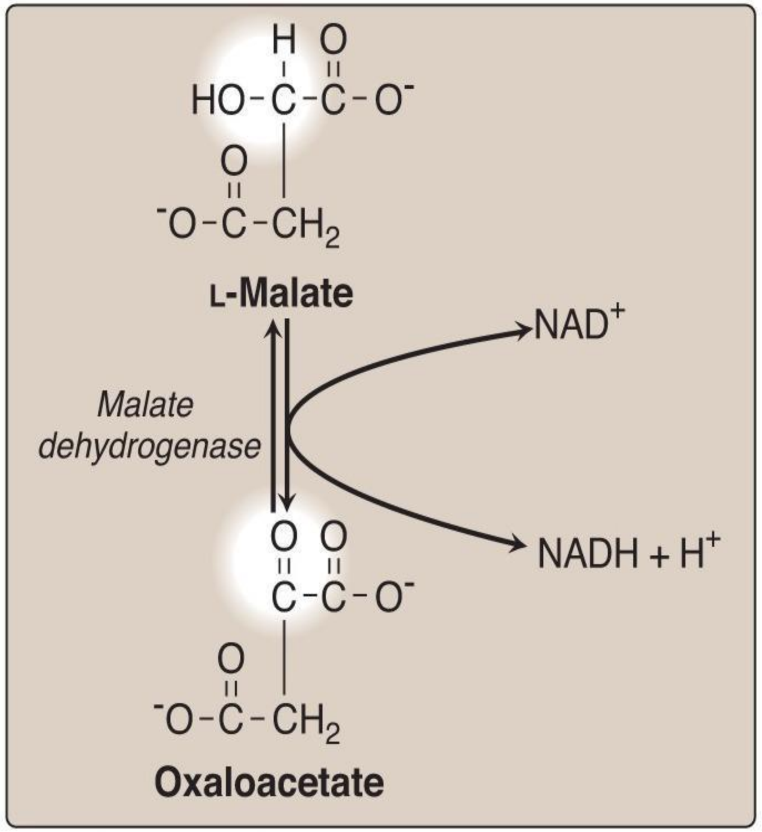


Step 8

L- Malate → (Malate dehydrogenase) → Oxaloacetate (4 Carbons)

Oxidized by coenzyme NAD+

*NAD+ is reduced to NADH+H

<u>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?</u>

Because we want to release more energy by :

1/Substrate level phosphorylation

2/ Oxidative phosphorylation

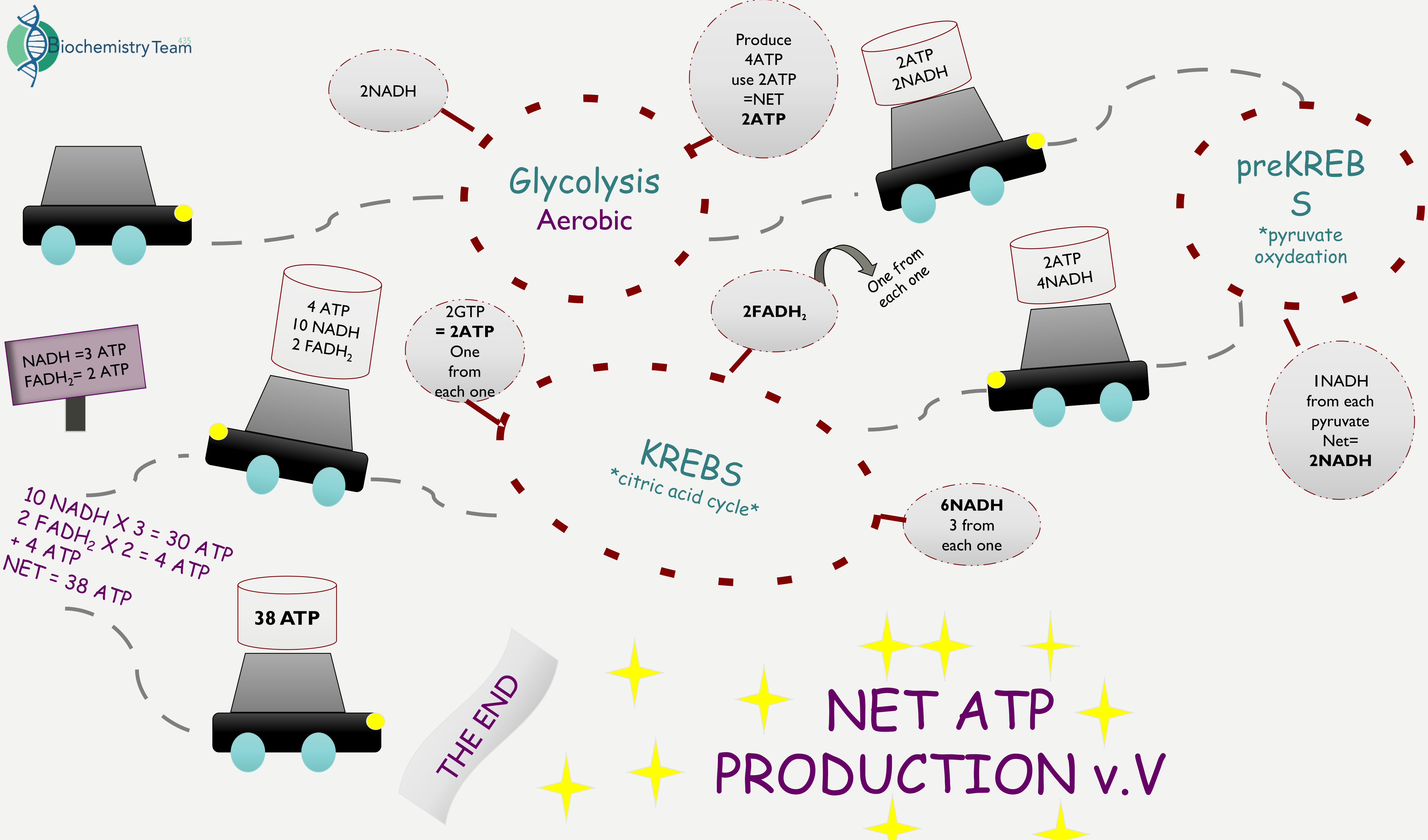
Irreversible steps:

Step1

Step 3

Step 4

Energy Yield



Energy yield

2 CO_2 are released :

1- isocistrate ➔ a-ketoyluterate.
2- a-ketokinase ➔ sccinyl CoA.

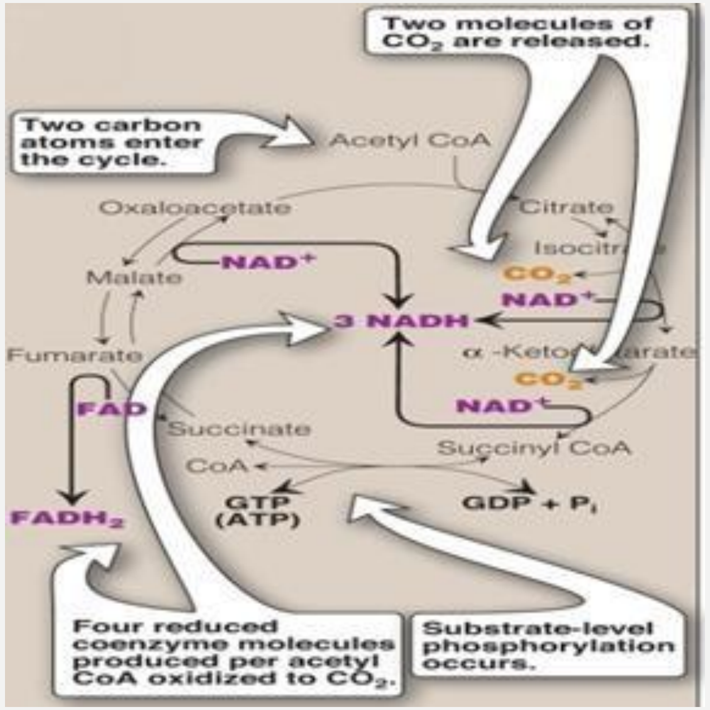
In Krebs cycle :

- 2 $FADH_2$ (one from each) : succinate ➔ fumarate .
- 2 GTP = 2 ATP (one from each) : succinyl coA ➔ succinate .
- 6 NADH (three from each) :

① Isocitrate ➔ a-ketogluterate .
② a-ketogluterate ➔ succinyl coA .
③ L- malate ➔ oxaloacetate .

Regulation of Oxidative Decarboxylation and Krebs Cycle

1. PDH complex and the TCA cycle are both up-regulated in response to a decrease in the ratio of **ATP : ADP** **NADH : NAD+**
2. TCA cycle activators are: **ADP , Ca2+**
3. TCA cycle inhibitors are: **ATP , NADH**



SUMMARY

step	reactant	product	enzyme	CO_2	ATP	NADH	$FADH_2$
Glycolysis (cytosol)	D-glucose	Glucose 6-phosphate	Hexokinase (all tissues) or Glucokinase (liver)	_	-1	_	_
	Glucose 6-phosphate	Fructose 6-phosphate	Phosphoglucos isomerase	_	_	_	_
	Fructose 6-phosphate	Fructose 1,6-bisphosphate	Phosphofructokinase-1 (PFK-1)	_	-1	_	_
	* Fructose 1,6-bisphosphate * Dihydroxyacetone phosphate	*(glyceraldehyde 3-phosphate+Dihydroxyacetone phosphate) *(glyceraldehyde 3-phosphate)	* Aldolase A * Triose phosphate isomerase	_	_	_	_
	2 (glyceraldehyde 3-phosphate)	2 (1,3-bisphosphoglycerate)	glyceraldehyde 3-phosphate dehydrogenase	_	_	2(1)= 2	_
	2 (1,3-bisphosphoglycerate)	2 (3-phosphoglycerate)	Phosphoglycerate kinase	_	2(1)= 2	_	_
	2 (3-phosphoglycerate)	2 (2-phosphoglycerate)	Phosphoglycerate mutase	_	_	_	_
	2 (2-phosphoglycerate)	2 (2-phosphoenolpyruvate)	Enolase	_	_	_	_
	2 (2-phosphoenolpyruvate)	2 (pyruvate)	Pyruvate kinase (PK)	_	2(1)= 2	_	_
Oxidative decarboxylation (mitochondria)	2 (pyruvate)	2 (acetyl CoA)	Pyruvate dehydrogenase complex (PDH)	2(1)= **2**	_	2(1)= 2	_
Krebs cycle [TCA cycle] (mitochondria)	2 (acetyl CoA) + 2 H_2O + 2 (Oxaloacetate)	2 (citrate)	Citrate synthase	_	_	_	_
	2 (citrate)	2 (isocitrate)	Aconitase	_	_	_	_
	2 (isocitrate)	2 (α- ketoglutarate)	Isocitrate dehydrogenase	2(1)= **2**	_	2(1)= 2	_
	2 (α- ketoglutarate)	2 (succinyl CoA)	αKG dehydrogenase	2(1)= **2**	_	2(1)= 2	_
	2 (succinyl CoA)	2 (Succinate)	Succinate thiokinase	_	2(1)= 2	_	_
	2 (Succinate)	2 (fumarate)	Succinatedehydrogenase	_	_	_	2(1)= 2
	2 (fumarate)	2 (malate)	fumerase	_	_	_	_
	2(malate)	2 (oxaloacetate)	Malate dehydrogenase	_	_	2(1)= 2	_

- NADH = 3 ATP *$FADH_2$ = 2 ATP *GTP = ATP
- net ATP production by complete glucose oxidation:

Aerobic glycolysis	* <u>ATP consumed:</u> Hexokinase (all tissues) or Glucokinase (liver).. ……….……..…-1 Phosphofructokinase-1 (PFK-1) …………..…….………….……-1 *<u>ATP produced:</u> • Substrate-level (ATP) Phosphoglycerate kinase……………………………….. …...2(1)= 2 Pyruvate kinase (PK)……………………………..………........2(1)= 2 • Oxidative-level (NADH=3ATP) glyceraldehyde 3-phosphate dehydrogenase.............................2(3)= 6	-2 +1o
Oxidative decarboxylation	Pyruvate dehydrogenase complex 2(NADH)..................…......2(3)= 6	+6
Krebs cycle	* <u>Substrate-level (GTP)</u> Succinate thiokinase…………………………..........………2(1)= 2 * <u>Oxidative-level</u> - NADH=3ATP Isocitrate dehydrogenase……………………………………2(3)= 6 αKG dehydrogenase………………………….....………….. .2(3)= 6 Malate dehydrogenase……….....………………………….. .2(3)= 6 - $FADH_2$=2ATP Succinatedehydrogenase…………………………….……. 2(2)= 4	+2 +22
		NET= 38

VIDEO:

[Krebs / citric acid cycle]

MCQS:

1-Krebs cycle occurs in:

a-Cytosol
b-Mitochondria
c-Both of them

2-The Irreversible steps from these:

a- L-Malate →Oxaloacetate
b- αKetoglutarate →Succinyl CoA
c-fumarate → L-malate

3-Isocitrate dehydrogenase is activated by:

a- Ca+2
b- ATP
c- NADH

4-The net ATP produced by glycolysis :

a. 10 ATP
b. 2 ATP
c. 8 ATP

1-b
2-b
3-a
4-c

MCQS:

5-Each FADH2 produce :

a. 3 ATP   b. 2 ATP   c. 4 ATP

6-The net ATP produced by CITRIC ACIDE CYCLE :

a. 38 ATP   b. 24 ATP   c. 18 ATP

7-The net ATP produced by pyruvate oxidation :

a. 0 ATP   b. 2 ATP   c. 6 ATP

8-……… CO_2 are released in oxidation of pyruvate :

a. Non   b. one   c. two

9-TCA cycle activators are:

a. ADP , Ca^{2+} b. ATP , NADH   c. FADH2 , ADP

10-Each Acetyl coA in the Citric Acid cycle produced :

a. 6 NADH   b. 3 NADH   c. 8 NADH

5- B
6- B
7- C
8- C
9- A
10- B

Boys Team:

- عبدالعزيز المالكي.
- مهند الزهراني.
- أحمد الرويلي .
- محمد الصهيل .
- خالد النعيم .
- إبراهيم الشايع.
- عبد الله الشنيفي.

Girls Team:

- شهد العنزي.
- نوره الرميح .
- جواهر الحربي.
- منيره الحسن.
- ساره العنزي.
- دلال الحزيمي.
- نوره القحطاني.
- بدور جليدان.
- علا النهير.
- أفنان المالكي.
- فاطمه الدين.
- جوهره المالكي.
- خوله العريني.
- لجين السواط.
- منيال باوزير.
- رزان السبتي .
- رهف العباد .
- وضحى العتيبي.
- ساره الحسين .

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