Editing File

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Krebs Cycle

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Main text

IMPORTANT

Extra Info

Drs Notes

Foundation Block - Biochemistry Team

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MED439

Objectives:

- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoEnzyme A (CoA)
- Discuss the major regulatory mechanisms of PDH complex
- Recognize clinical consequences of abnormal oxidative decarboxylation reactions
- Recognize the importance of krebs cycle
- Identify various reactions of krebs cycle
- Define the regulatory mechanisms of krebs cycle
- Asses the energy yield of PDH reaction and krebs cycle's reactions

Fates of pyruvate

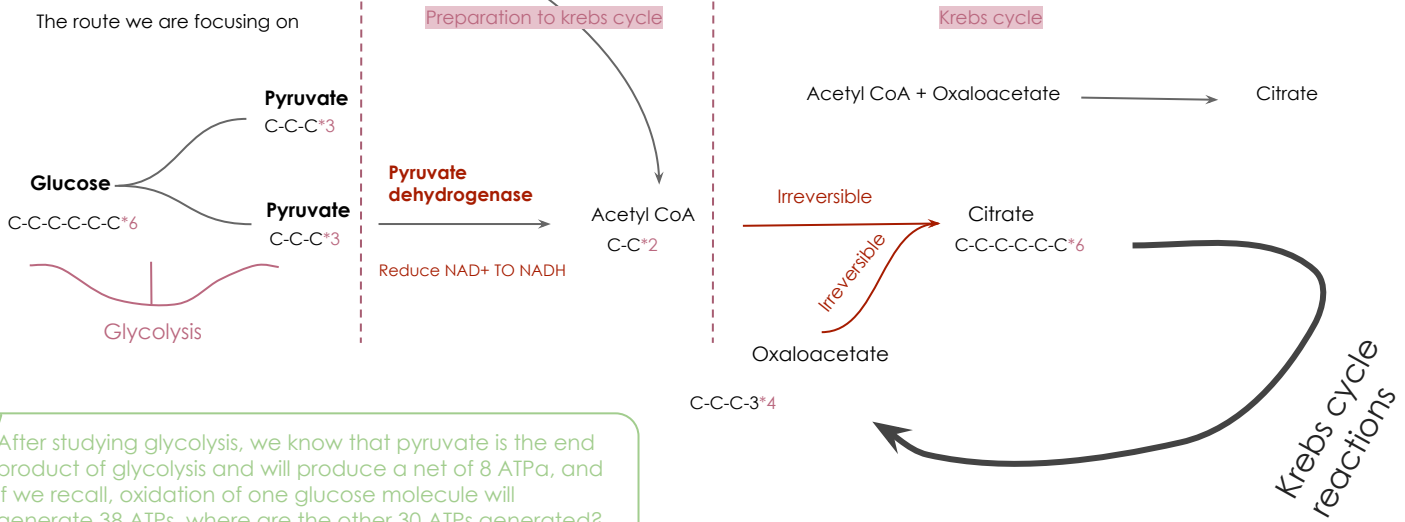
Pyruvate can eventually end up as ONE of the FIVE following substrates:

Lactate
in humans and some microorganisms in anaerobic conditions

Oxaloacetate (Pyruvate carboxylase)
In krebs cycle (it's an intermediate)
Activated by Acetyl CoA

Alanine
Synthesis of nonessential amino acid using pyruvate + glutamine "essential"
Done by Alanine transaminase (ALT) and Pyridoxal Phosphate (PLP)

Ethanol
It occurs in yeast and some Bacteria (including intestinal flora)"Anaerobic"



After studying glycolysis, we know that pyruvate is the end product of glycolysis and will produce a net of 8 ATPa, and if we recall, oxidation of one glucose molecule will generate 38 ATPs, where are the other 30 ATPs generated?

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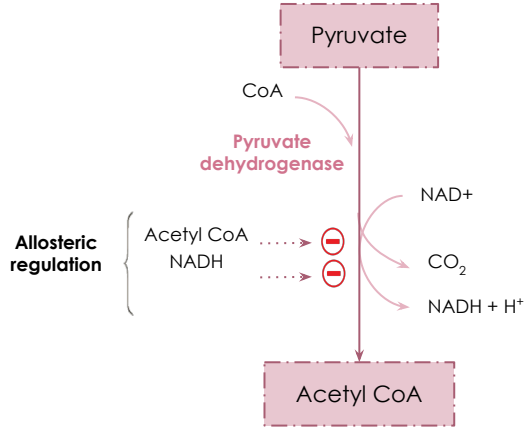
Oxidative decarboxylation of Pyruvate

- It's the process of making Acetyl CoA Oxaloacetate from Pyruvate by the enzyme Pyruvate Dehydrogenase.
- Outcomes of this Process: 2 x NADH (6 ATP) for two Pyruvate "Keep in mind that in every reaction we talk about, only one Pyruvate the other will have the same reactions and productions thus we explain one Pyruvate and multiply the outcomes by 2"
- Regulated by Allosteric regulation of Acetyl CoA and NADH.
- Inhibitors: Increased amount of Acetyl CoA and NADH act as "Negative Feedback" inhibitors of their respective reactions, the responsible enzyme for this is Pyruvate dehydrogenase kinase which phosphorylates and inactivates Pyruvate dehydrogenase.



- Kinase= enzyme that adds phosphate group "phosphorylates"
- Phosphatase = enzyme that removes phosphate group "dephosphorylates"
- Note: phosphorylation can either activate or inactivate, according to the enzyme.

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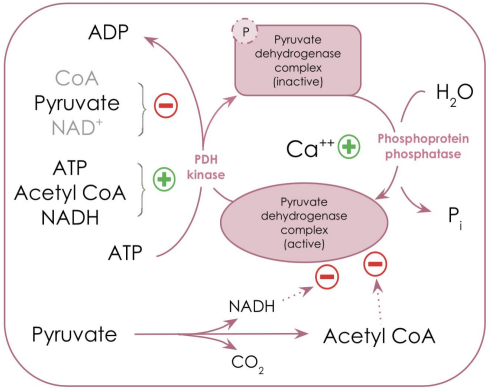
PDH Complex: Covalent Regulation

Inhibitors of pyruvate dehydrogenase complex (induces deactivation):
- ATP
- Acetyl CoA
- NADH

When there are high levels of ATP, Acetyl CoA and NADH it will inhibit Pyruvate dehydrogenase complex by activating PDH Kinase

Inducers of pyruvate dehydrogenase complex (induces activation):
- CoA
- Pyruvate
- NAD+

When there are high levels of CoA, Pyruvate and NAD+ it will induce Pyruvate dehydrogenase complex by inhibiting PDH Kinase



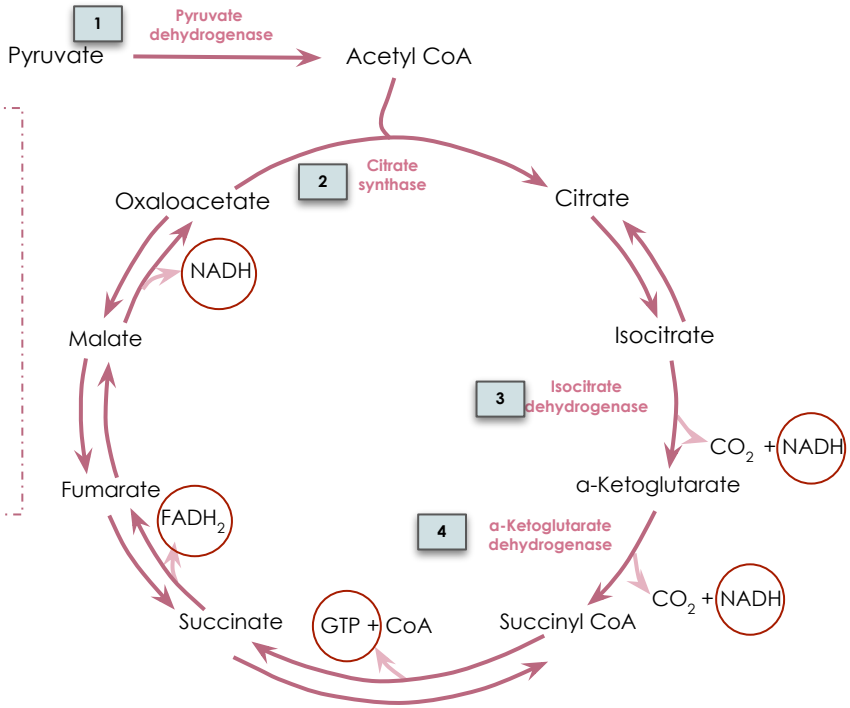
PDH Reaction: Clinical application

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"
- Deficiencies of thiamine or niacin can cause serious CNS problems
- Thiamine and niacin are co-factors that helps PDH complex

	Congenital lactic acidosis	Wernicke-Korsakoff (encephalopathy- psychosis syndrome)
Cause	PDH complex deficiency is the most common biochemical cause.in anaerobic conditions, pyruvate is converted to lactic acid and won't go any further in krebs cycle (accumulate).	Due to thiamine deficiency, may be seen especially with alcohol abuse. (Thiamine deficiency is Vitamin B1 deficiency)

A helpful video

Tricarboxylic Acid Cycle: Krebs Cycle (Overview)



Properties of the cycle

- Final common pathway for oxidation.
- Exclusively Major source for ATP (24 ATP)
- Mainly catabolic with some anabolic features
- Synthetic reactions (anabolic features):
  - ❑ Glucose from amino acids
  - ❑ Non-essential amino acids
  - ❑ Fatty acids
  - ❑ Heme (RBCs component, gives blood ability to carry oxygen)

Let's count together!
3 NADH (9 ATPs)
1 $FADH_2$ (2 ATPs)
1 GTP (1 ATP)
=
12 ATPs per Pyruvate x 2 = 24
+ 6 in the preparation phase + 8 in Glycolysis = 38 ATPs
(Hey look Ma, I made It!)

Citrate Is Krebs Starting Substrate For Making Oxaloacetate

- C = Citrate
- I = Isocitrate
- K = alpha-Ketoglutarate
- S = Succinyl CoA
- S = Succinate
- F = Fumarate
- M = L-Malate
- O = Oxaloacetate

Important note:
1 GTP = 1 = ATP
1 NADH = 3 ATP
1 $FADH_2$ = 2 ATP

Irreversible enzyme reactions

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Krebs Cycle Reactions (1)

Reversible ⇌ Irreversible →

1 Acetyl CoA (2C) + Oxaloacetate (4C) —(Citrate synthase)→ Citrate (6C)

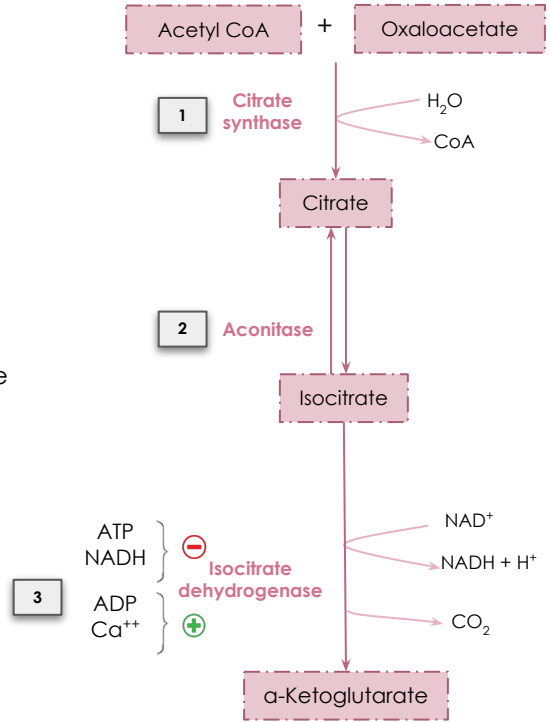
- H_2O In.
- CoA out.
- Acetyl CoA and Oxaloacetate joined by condensation with the help of **Citrate synthase** enzyme.

2 Citrate (6C) ⇌ (Aconitase) Isocitrate (6C)

- Citrate is isomerized into isocitrate. This is actually a two step process, involving first the removal and then the addition of a water molecule with the help of **Aconitase** enzyme.
- The conversion of citrate to isocitrate is important since it is needed to react with isocitrate dehydrogenase

3 Isocitrate (6C) —(Isocitrate dehydrogenase)→ a-Ketoglutarate (5C)

- NAD+ In.
- NADH + H^+ + CO_2 Out.
- Oxidation of Isocitrate, leaving behind a-Ketoglutarate with the help of **Isocitrate dehydrogenase** enzyme.
- Regulation of Isocitrate dehydrogenase enzyme:
  - ⊕ Presence of ADP and Ca^{++} activate "induce" Isocitrate dehydrogenase enzyme.
  - ⊖ Presence of ATP and NADH inhibit Isocitrate dehydrogenase enzyme.



Krebs Cycle Reactions (2)

4 a-Ketoglutarate (5C) —(a-Ketoglutarate dehydrogenase complex)→ Succinyl CoA (4C)

- $CoA + NAD^+$ In.
- $NADH + H^+ + CO_2$ Out.
- Oxidation and decarboxylation of a-Ketoglutarate with the help of **a-Ketoglutarate dehydrogenase complex**.
- Regulation of a-Ketoglutarate dehydrogenase complex:
- ⊕ Presence of Ca^{++} activates "induces" a-Ketoglutarate dehydrogenase complex.
- ⊖ Presence of NADH + Succinyl CoA inhibit a-Ketoglutarate dehydrogenase complex.

5 Succinyl CoA (4C) ⇌ (Succinate thiokinase) Succinate (4C)

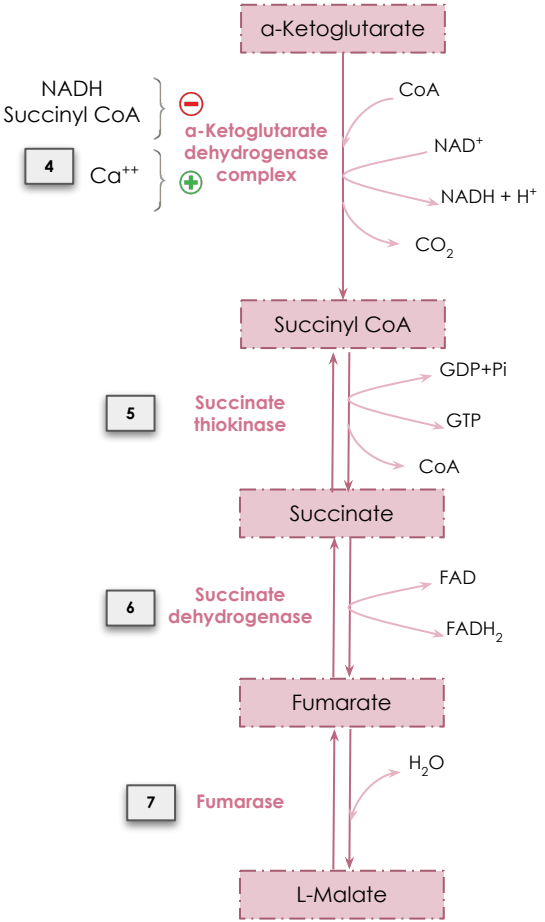
- GDP $+P_i$ In.
- GTP + CoA Out.
- Oxidation and decarboxylation of Succinyl CoA with the help of **Succinate thiokinase** enzyme.

6 Succinate (4C) ⇌ (Succinate dehydrogenase) Fumarate (4C)

- FAD In.
- $FADH_2$ Out.
- Oxidation of Succinate with the help of **Succinate dehydrogenase** enzyme.

7 Fumarate (4C) ⇌ (Fumarase) L-Malate (4C)

- H_2O In.
- Hydration "adding water" of Fumarate with the help of **Fumarase** enzyme.



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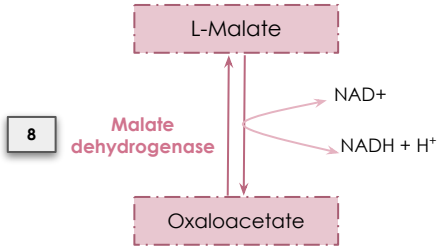
Krebs Cycle Reactions (3)

8 L-Malate (4) $\underset{\text{Malate dehydrogenase}}{\rightleftharpoons}$ Oxaloacetate (4C)



- NAD^+ In.
- $NADH + H^+$ out.
- Formation (regeneration) of oxaloacetate with the help of **Malate dehydrogenase** enzyme.

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

We do we convert succinyl CoA to Succinate to Fumarate to L-Malate to Oxaloacetate to even though they all have the same numbers of carbon?
Because we want to release more energy by:
1- Substrate level phosphorylation
2- Oxidative phosphorylation
Thanks to #435 team

★ extra explanation

Summary of the krebs cycle reactions In order for you to gain a better understanding (In tables)

Reaction 1	
Reactant	Acetyl CoA (2C) + Oxaloacetate (4C)
Product	Citrate
Enzyme	**Citrate synthase**
Action	joined by condensation
Produce	CoA

Reaction 2	
Reactant	Citrate
Product	Isocitrate
Enzyme	**Aconitase**
Action	Isomerization, involving first the removal and then the addition of a water molecule

Reaction 3	
Reactant	Isocitrate
Product	a-Ketoglutarate
Enzyme	**Isocitrate dehydrogenase**
Action	Oxidation of Isocitrate
Produce	$NADH + H^+ + CO_2$

Reaction 4	
Reactant	a-Ketoglutarate
Product	Succinyl CoA
Enzyme	**a-Ketoglutarate dehydrogenase complex**
Action	Oxidation and decarboxylation of a-Ketoglutarate
Produce	$NADH + H^+ + CO_2$

Reaction 5	
Reactant	Succinyl CoA
Product	Succinate
Enzyme	**Succinate thiokinase**
Action	Oxidation and decarboxylation of Succinyl CoA
Produce	GTP + CoA

Reaction 6	
Reactant	Succinate
Product	Fumarate
Enzyme	**Succinate dehydrogenase**
Action	Oxidation of Succinate
Produce	$FADH_2$

Reaction 7	
Reactant	Fumarate
Product	L-Malate
Enzyme	**Fumarase**
Action	Hydration "adding water"
Consume	H_2O

Reaction 8	
Reactant	L-Malate
Product	Oxaloacetate
Enzyme	**Malate dehydrogenase**
Action	(regeneration) of oxaloacetate
Produce	$NADH + H^+$

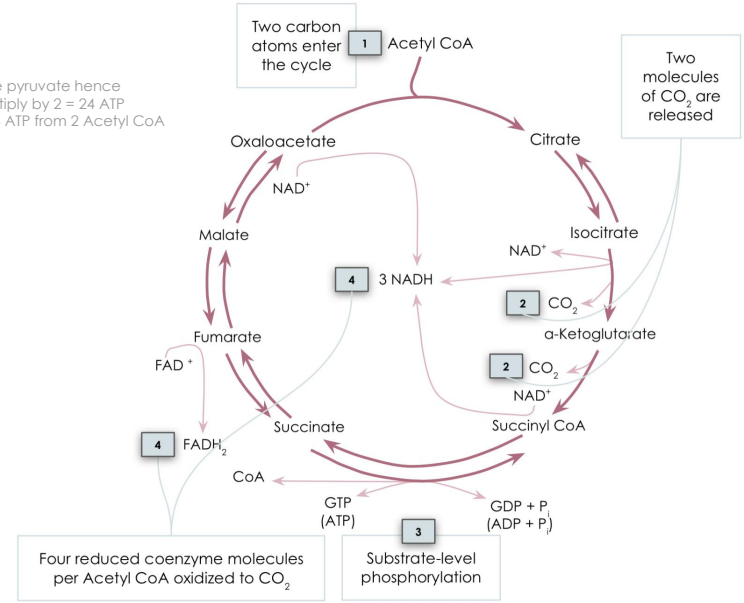
original pic

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.

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

For one pyruvate hence
We multiply by 2 = 24 ATP
So, we get 24 ATP from 2 Acetyl CoA



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

- We get $FADH_2$ from:
  - Succinate → Fumarate

- We get 2 CO_2 from:
  - Isocitrate → a-Ketoglutarate
  - a-Ketoglutarate → Succinyl CoA

Net ATP production by complete glucose oxidation

Aerobic Glycolysis	2 ATP 2 NADH	8 ATP
Oxidative decarboxylation (preparation phase)	1 NADH per Pyruvate = 2 NADH total	6 ATP
Krebs Cycle	3 NADH 1 FADH 1 GTP Per Pyruvate = 9,2,1 in total (respectively)	12 ATP Per Pyruvate = 24 ATP in total
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 (krebs) cycle activators are:
- ADP
- Ca^{++}

TCA (krebs) cycle inhibitors are:
- ATP
- NADH

PDH complex refers to Pyruvate Dehydrogenase complex, it converts the pyruvate (end product of glycolysis) into acetyl CoA (substrate of krebs cycle)
TCA is tricarboxylic acid cycle (aka as citric acid cycle, and Krebs cycle)

Take home messages

- 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.

Quiz

Q1 : Krebs cycle occurs in:			
A) Mitochondria	B) Nucleus	C) Nucleolus	D) Golgi apparatus
Q2 : The net yield energy of oxidative decarboxylation (preparation phase):			
A) 4 ATP	B) 2 ATP	C) 6 ATP	D) 8 ATP
Q3 : Which substrate involved in oxidative decarboxylation and also present in krebs cycle as a final product?			
A) Acetyl CoA	B) Oxaloacetate	C) Citrate	D) Malate
Q4 : Which enzyme responsible for conversion of citrate into isocitrate			
A) Citrate synthase	B) Aconitase	C) Isocitrate dehydrogenase	D) Fumarase
Q5 : PDH kinase is inhibited by:			
A) Acetyl CoA	B) Pyruvate	C) ATP	D) ADP
Q6 : Allosteric regulation in oxidative decarboxylation of pyruvate is done by:			
A) Acetyl CoA	B) NADH	C) ATP	D) A&B

SAQs :

Q1: The enzyme that converts a-ketoglutarate to succinyl CoA?

★ **MCQs Answer key:**

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

★ **SAQs Answer key:**

1) a-ketoglutarate dehydrogenase complex

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"You can't have a better tomorrow, if you're still thinking about yesterday ."

Shatha Aldhohair

Mishal Althunayan

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