Lecture 13

Oxidative Decarboxylation and Krebs Cycle

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- Girls' slides
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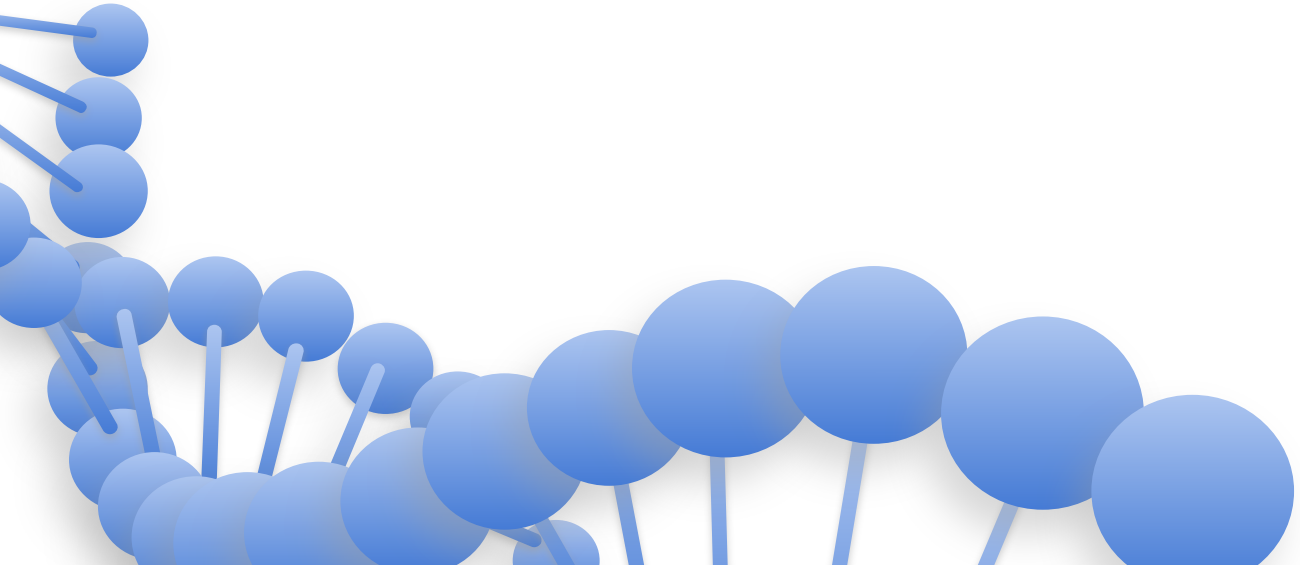
- Doctors' notes
- Important
- Extra info

Editing File



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Objectives

Nice video

Nice video

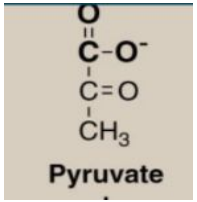
Oxidative Decarboxylation:

- 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

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

Fates of Pyruvate



Pyruvate

is the end product of glycolysis

Ethanol

Occurs in yeast and some bacteria (including intestinal flora)

Thiamine pyrophosphate-dependent pathway

Lactate

Enzyme: Lactate dehydrogenase

Found: Anaerobic glycolysis

Acetyl CoA

Enzyme: PDH Complex inhibited by acetyl CoA

Found: Krebs cycle

PDH: Pyruvate Dehydrogenase

Oxaloacetate

Enzyme: Pyruvate Carboxylase

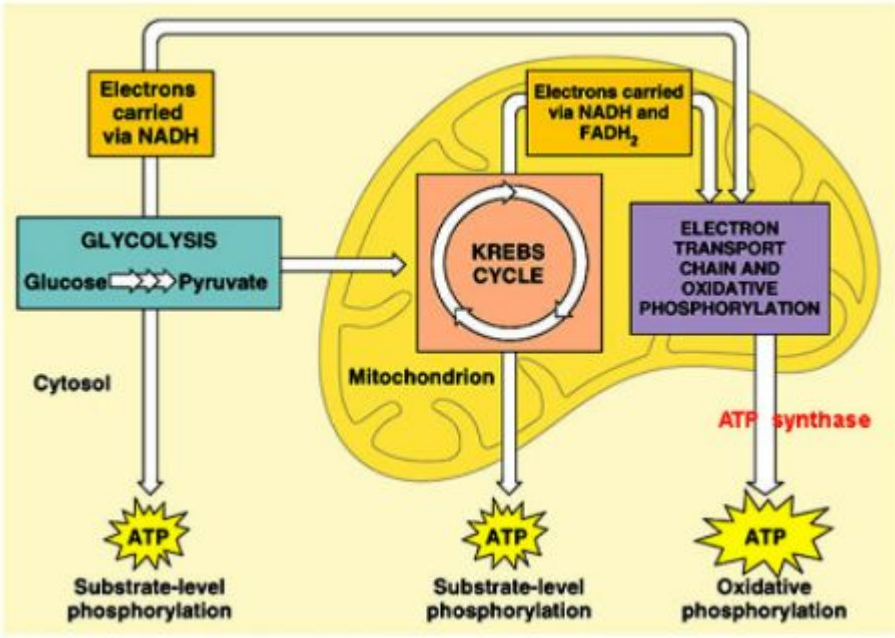
Found: -Gluconeogenesis -Krebs cycle

Alanine

PLP: Pyridoxal Phosphate (cofactor)

ALT: Alanine aminotransferase

* just to see how glycolysis is related to our lesson*



Oxidative Decarboxylation of Pyruvate

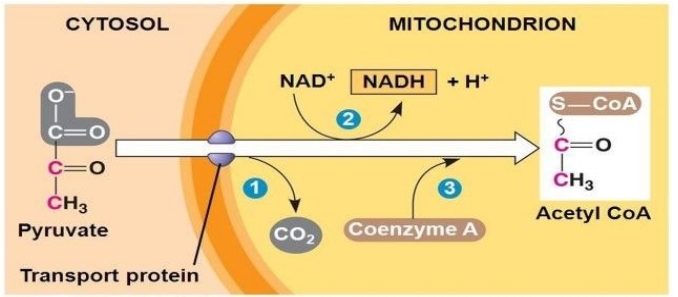
-It's the process of making Acetyl CoA Oxaloacetate from Pyruvate by the enzyme **Pyruvate Dehydrogenase**.

Irreversible

-Outcomes of this Process: 2 x NADH (6 ATP) for two Pyruvate

-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**.



Oxidative decarboxylation of Pyruvate

PDH Complex: Covalent Regulation

Inhibitors of PDH: ATP | Acetyl CoA | NADH

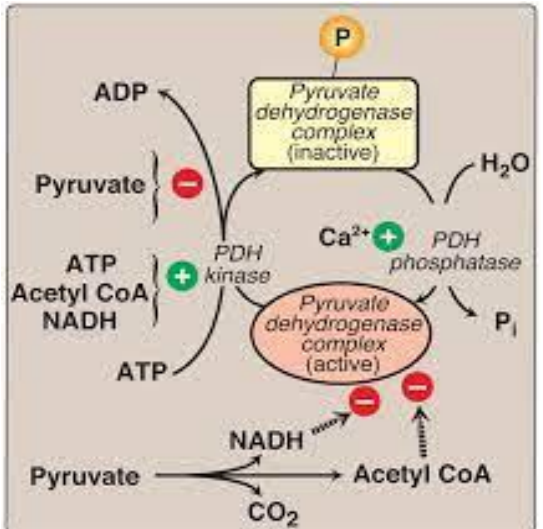
When there are high levels of ATP, Acetyl CoA and NADH it will inhibit Pyruvate dehydrogenase Complex by activating PDH Kinase

Inducers of PDH: CoA | Pyruvate | NAD+

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

important

Kinase=enzyme that add phosphate group
Phosphatase =enzyme that remove phosphate



PDH Reaction: Clinical application

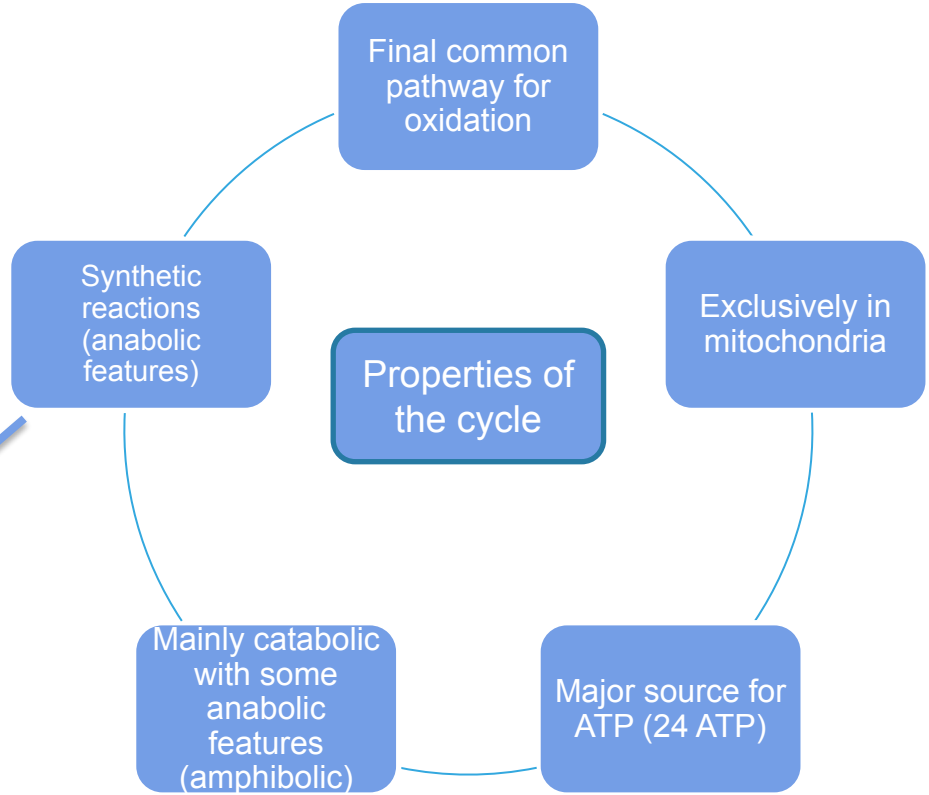
Deficiencies of thiamine (vitamin B1) or niacin (vitamin B3) can cause serious CNS problems. **WHY**? Because Brain cells are unable to produce sufficient ATP if the PDH complex is inactive

"no production of acetyl CoA thus, no Krebs cycle thus, no ATP"

PDH complex deficiency is the most common biochemical cause of congenital lactic acidosis

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

Tricarboxylic Acid Cycle: Krebs Cycle



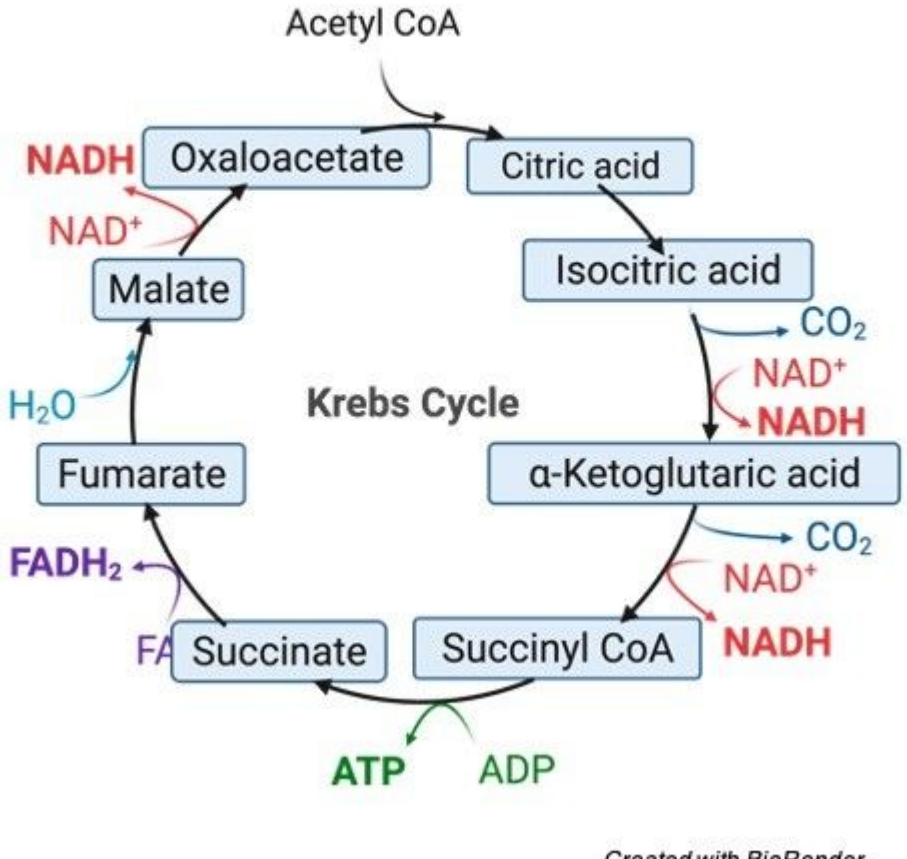
-Glucose from amino acids
-Nonessential amino acids
-Fatty acids
-Heme (hemoglobin remember?)

Krebs cycle:

Mnemonic to memorize the products of Krebs cycle:

Citrate
Is Krebs Starting
Substrate For
Making
Oxaloacetate

C
I
K
S
S
F
M
O



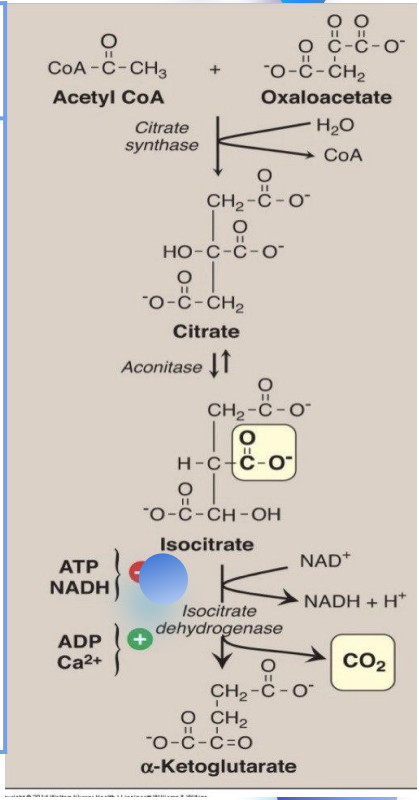
Important note:
1 GTP = 1 = ATP
1 NADH = 3 ATP
1 $FADH_2$ = 2 ATP

PRODUCTS
2 ATP
8 NADH
2 $FADH_2$
6 CO_2

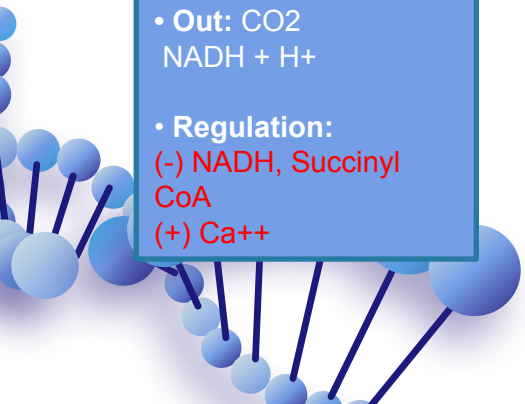
2GTP also

Krebs cycle reactions:1

1	2	3
1. Acetyl CoA (2C) (from pyruvate) + Oxaloacetate (4C) ⟶ Citrate (6C) ● Acetyl CoA and Oxaloacetate joined by condensation with the help of the Citrate synthase enzyme • Enzyme: Citrate synthase • In: H2O • Out: CoA	2. Citrate ⇄ Isocitrate (isomerase reaction) • Enzyme: Aconitase The conversion of citrate to isocitrate is important since it is needed to react with isocitrate dehydrogenase	3. Isocitrate (6C) ⟶ α-Ketoglutarate (5C) • Enzyme: Isocitrate dehydrogenase ● NAD+ In. ● NADH + H + CO2 Out. • Regulation: (-) ATP, NADH (+) ADP, Ca++



Krebs cycle reactions:2



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4. α-Ketoglutarate (5C) → Succinyl CoA (4C)

- **Enzyme**: α-Ketoglutarate dehydrogenase Complex
- **In:** CoA, NAD+
- **Out:** CO2 NADH + H+
- **Regulation:** (-) NADH, Succinyl CoA (+) Ca++

2

5. Succinyl CoA ⇄ Succinate

- **Enzyme**: Succinate thiokinase
- **In**: GDP + Pi
- **Out:** GTP, CoA
- Note: this is the only substrate level phosphorylation in krebs cycle

3

6. Succinate ⇄ Fumarate

- **Enzyme**: Succinate dehydrogenase
- **In**: FAD
- **Out**: FADH2

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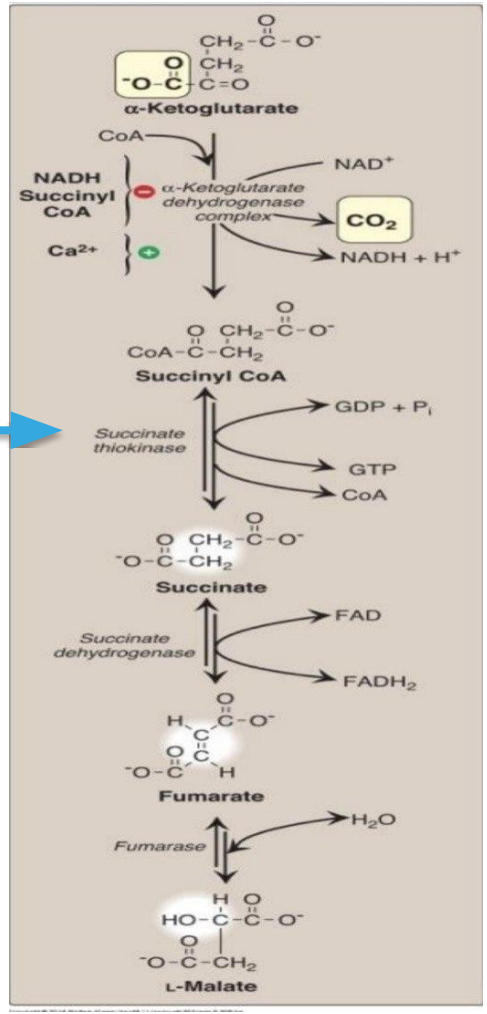
7. Fumarate ⇄ Malate (L-Malate)

- **Enzyme**: Fumarase
- **In**: H2O

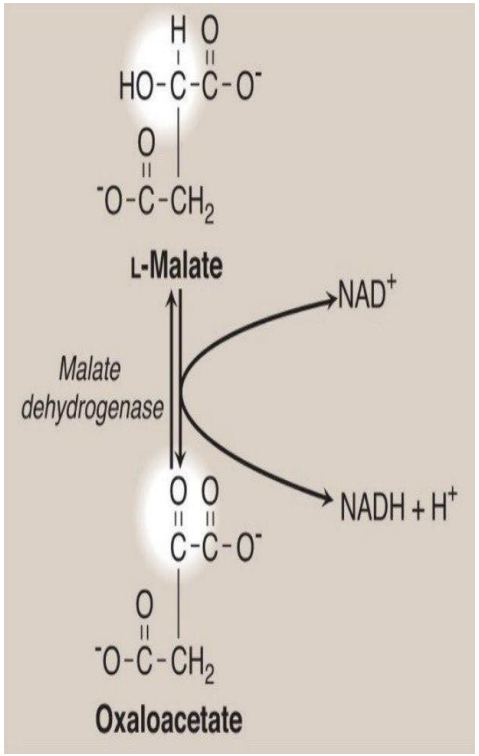
Succinate thiokinase
substrate level
phosphorylation



Note:
NAD(H) = nicotinamide adenine dinucleotide
GDP = guanosine diphosphate
P = phosphate
FAD(H2) = flavin adenine dinucleotide.

Krebs cycle reactions: 3

8. Malate (L-Malate) ⇄Oxaloacetate
- **Enzyme**: Malate dehydrogenase
- **In:** NAD+
- **Out:** NADH + H+



Net ATP production by complete glucose oxidation:

Aerobic glycolysis	**2 ATP** **2 NADH → 6 ATP** **2+6 = 8 ATP**
Oxidative decarboxylation (preparation)	**per pyruvate:** **1 NADH → 3 ATP** **3x2 = 6 ATP**
Krebs cycle	**per pyruvate:** **3 NADH → 9 ATP** **1 FADH2 → 2 ATP** **1 GTP → 1 ATP** **12x2 = 24 ATP**
Total	**8 + 6 + 24 = 38 ATP**

Note:
1 GTP = 1 ATP
1 NADH = 3 ATP
1 FADH2 = 2 ATP

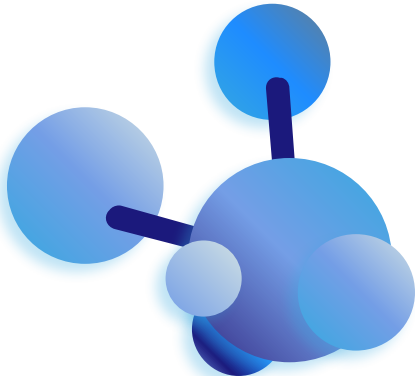
Regulation of oxidative decarboxylation & krebs cycle:

• PDH complex & krebs cycle are both up-regulated in response to decrease in the ratio of:
• ATP : ADP
• NADH : NAD+

• Krebs cycle activators:
• ADP
• Ca++

• Krebs cycle inhibitors:
• ATP
• NADH

Note:
Krebs cycle AKA TCA cycle (tricarboxylic acid cycle) AKA Citric
acid 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:which of the following is an activator of kreb's cycle?			
a) ADP	b) Ca2	c) ATP	d) a&b
PDH complex deficiency is the most common biochemical cause of ?			
a) congenital lactic acidosis	b) cancer	c) Brain damage	d) TB
Which of the following is the major source for ATP?			
a) Glycolysis	b) Krebs cycle	c) Anabolic pathway	d) A&c
Succinate thiokinase is an enzyme used to convert succinyl CoA to?			
a) malate	b) Isocitrate	c) Succinate	d) Fumarate

D1
A2
B3
C4

Our Team

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