Oxidative Decarboxylation and Krebs Cycle

Editing File

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Objectives: 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

Objectives: 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’sreactions

Fates of Pyruvate

Pyruvate

Ethanol

Occurs in yeast and some bacteria (including intestinal flora)
Thiamine pyrophosphate dependent pathway

Lactate

Enzyme:
Lactate dehydrogenase
Found:
Anaerobic glycolysis

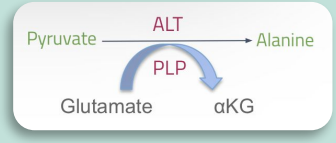
Acetyl CoA

Enzyme:
PDH Complex inhibited by acetyl COA
Found:
Krebs cycle

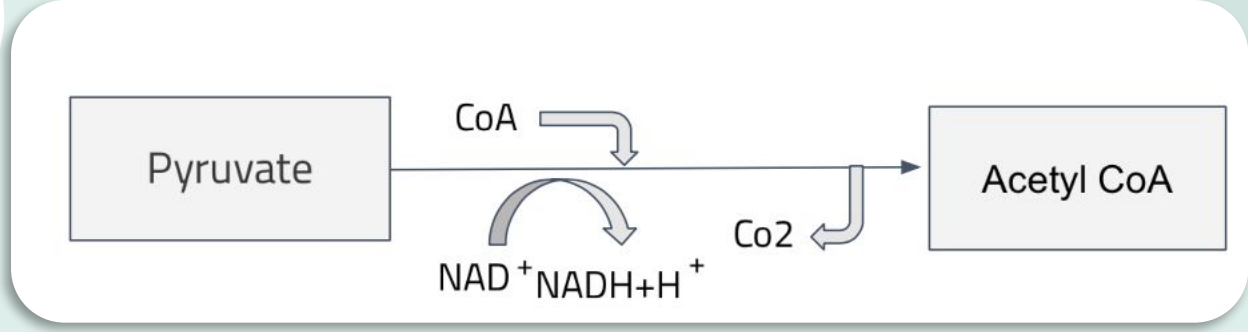
Oxaloacetate

Enzyme:
Pyruvate Carboxylase
Found:
Gluconeogenesis
Krebs cycle

Alanine



Oxidative Decarboxylation of Pyruvate



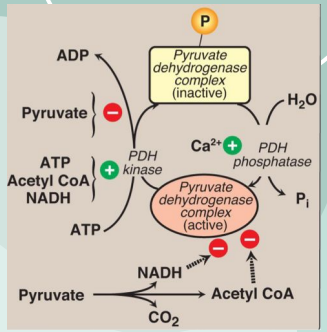
Enzyme: Pyruvate Dehydrogenase Complex (PDH)
Inhibitors: Allosteric Regulation: Acetyl CoA + NADH

- Irreversible
- energy producing
- 2 pyruvate produce 2 NADH = 6 ATP (1 NADH= 3 ATP)

PDH Complex: Covalent Regulation

Team 439
Kinase= enzyme that adds phosphate group "phosphorylates"
Phosphatase = enzyme that removes phosphate group

Enzyme: Pyruvate Dehydrogenase Complex (PDH)



Active

PDH
no P group

Produce Acetyl CoA

\- Pyruvate

\+ ATP
Acetyl CoA

PDH Kinase

ATP ADP

Inactive

PDH-P
P group

Inhibit producing Acetyl CaA

PDH phosphatase

\- NADH
Acetyl CoA

Pi H2O

\+ Ca 2+ (cofactor)

PDH Complex: Regulation

Girls' Slides

- Product Inhibition- Acetyl CoA and NADH
-Phosphorylation –PDH Kinase phosphorylates and makes PDH complex inactive
- Dephosphorylation- PDH Phosphatase dephosphorylates the phosphorylated enzyme(inactive) and makes it active.

	PDH Kinase	PDH Phosphatase
Activators	ATP Acetyl CoA NADH	Ca++
Inhibitors	Pyruvate	ATP Acetyl CoA NADH

PDH Reaction: Clinical application

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

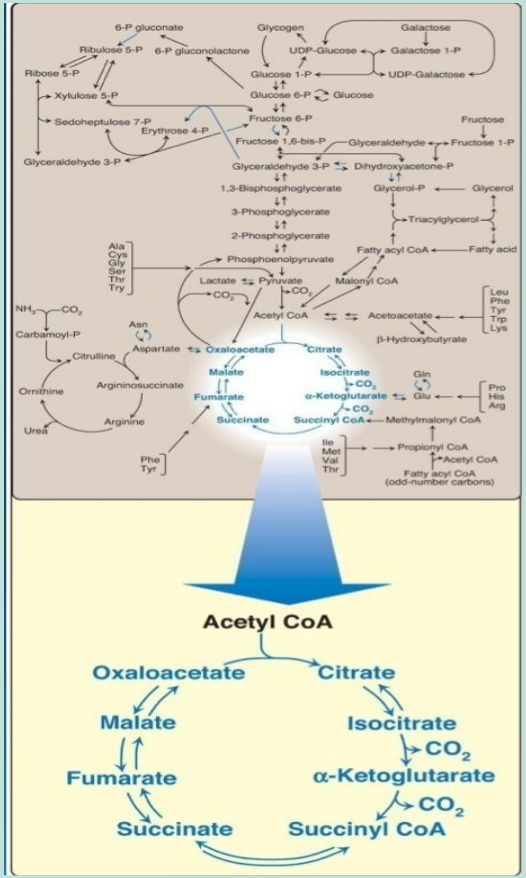
PDH complex requires 4 vitamins for its activity- Thiamine, pantothenic acid, riboflavin and niacin.

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.

Krebs Cycle

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



Tricarboxylic Acid Cycle: Krebs Cycle

Final common pathway for oxidation.

Major source for ATP.

Synthetic reactions (anabolic features):

- Glucose from amino acids
- Nonessential amino acids
- Fatty acids
- Heme an iron-containing compound which forms part of hemoglobin

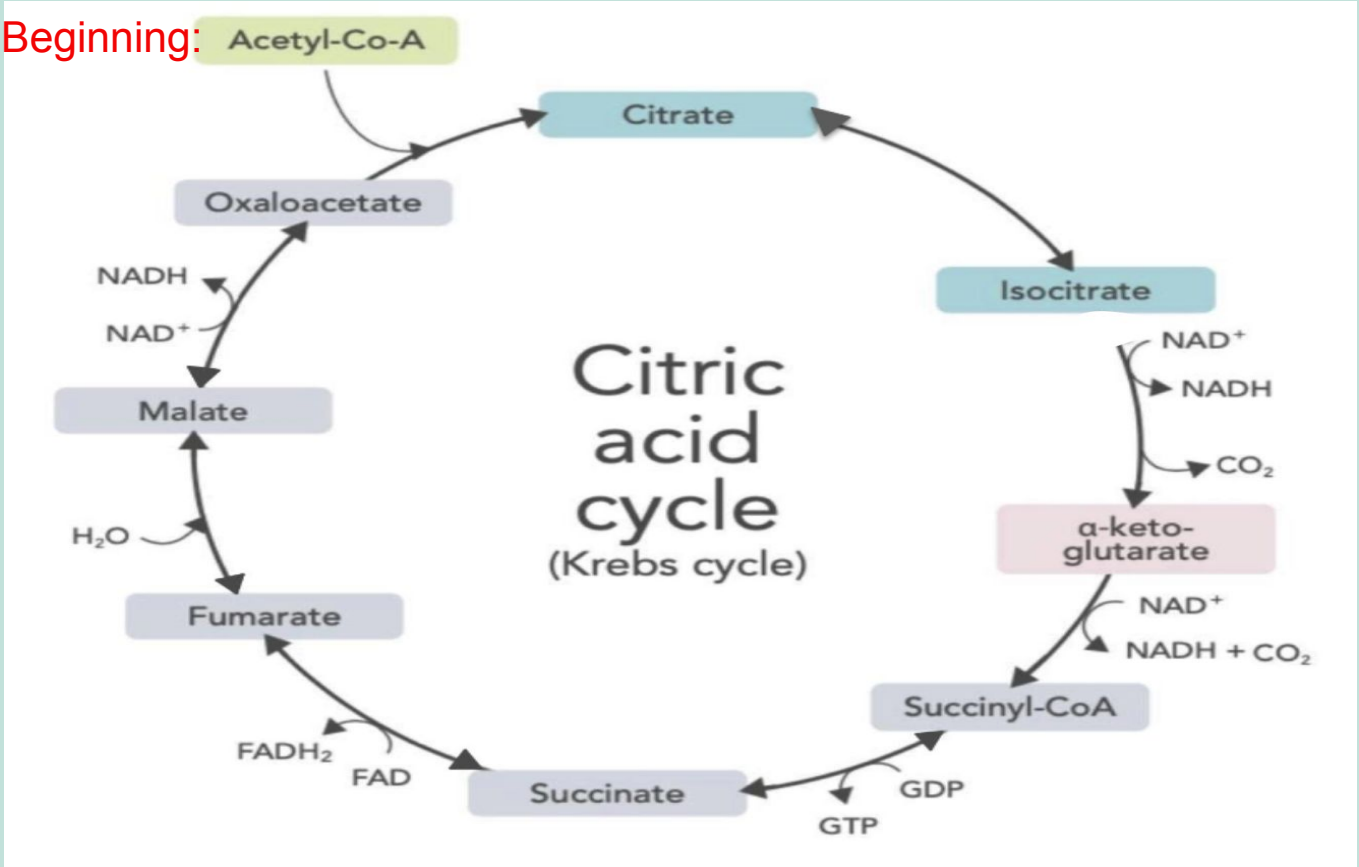
Exclusively in mitochondria.

Mainly catabolic with some anabolic features (amphibolic).

Krebs cycle: overview

Team 439:
Mnemonic to memorize the products of krebs cycle: Citrate Is Krebs Starting Substrate For Making Oxaloacetate

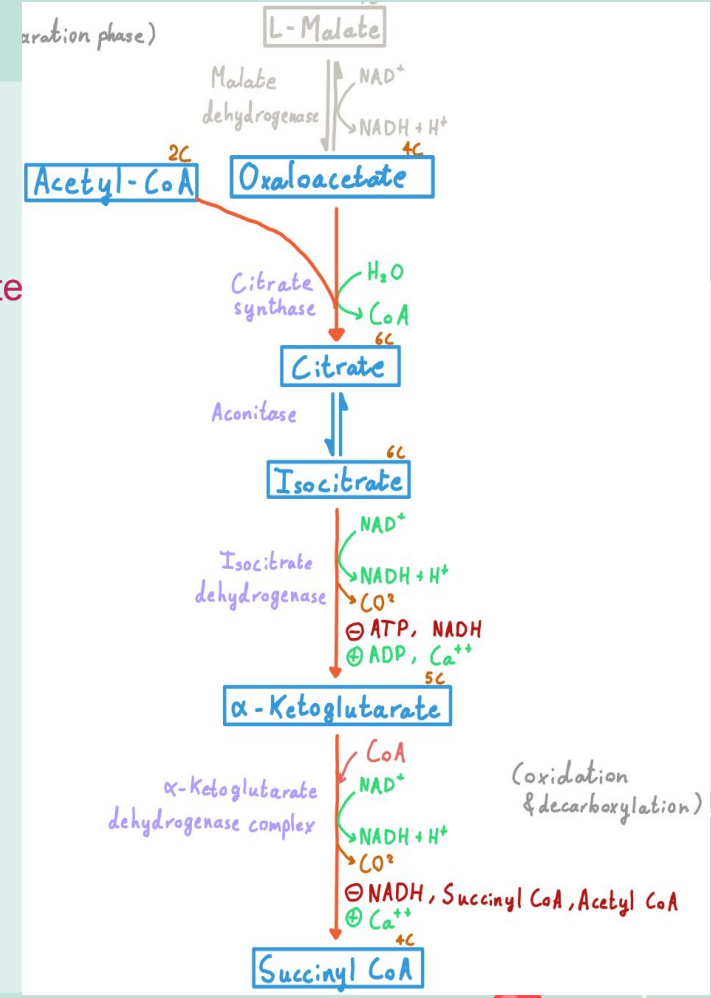
C = Citrate
I = Isocitrate
K = a-Ketoglutarate
S = Succinyl CoA
S = Succinate
F = Fumarate
M = Malate
O = Oxaloacetate



Krebs cycle (1)

1. Acetyl CoA (2C) (from pyruvate) + Oxaloacetate (4C) → Citrate (6C) (Oxaloacetate from cycle, pyruvate carboxylic or fatty acids oxidation)
   - **Enzyme**: Citrate synthase
   - **In**: H_2O
   - **Out**: CoA

2. Citrate ⇄ Isocitrate (isomerase reaction) (isomerization)
   - **Enzyme**: Aconitase

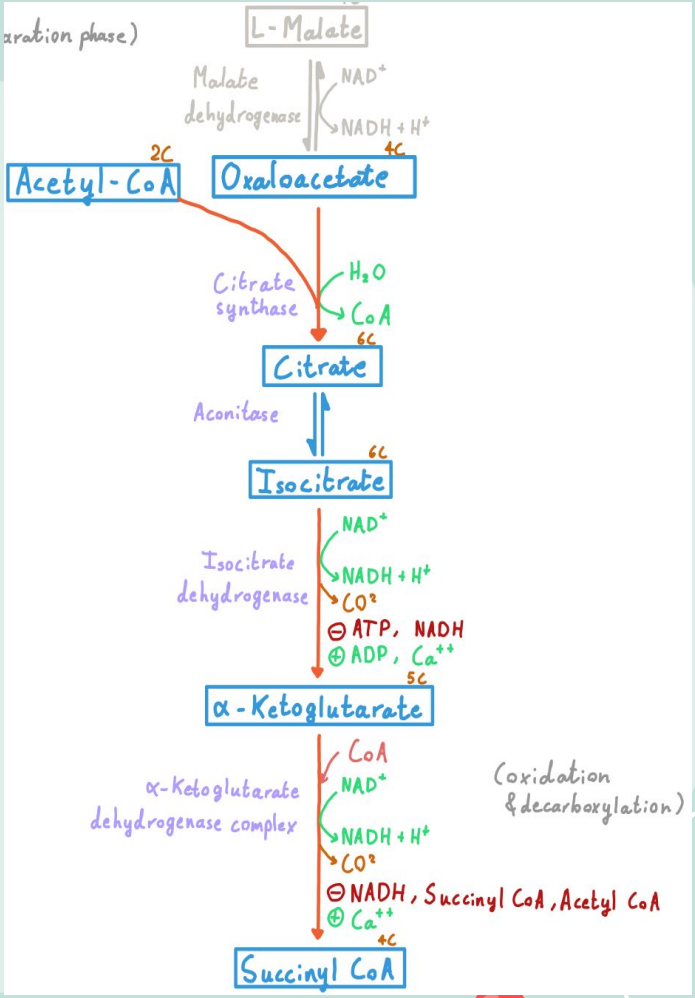


Krebs cycle (1) COUN..

3. Isocitrate (6C) → α-Ketoglutarate (5C)
- **Enzyme**: Isocitrate dehydrogenase
- **Regulation**:
  (-) ATP, NADH
  (+) ADP, Ca^{++} (cofactor)

4. α-Ketoglutarate (5C) → Succinyl CoA (4C)
- **Enzyme**: α-Ketoglutarate dehydrogenase complex
- **In**: CoA, NAD^+
- **Out**: CO_2, NADH + H^+
- **Regulation**:
  (-) NADH, Succinyl CoA
  (+) Ca^{++}

Reaction: 3&4 are important



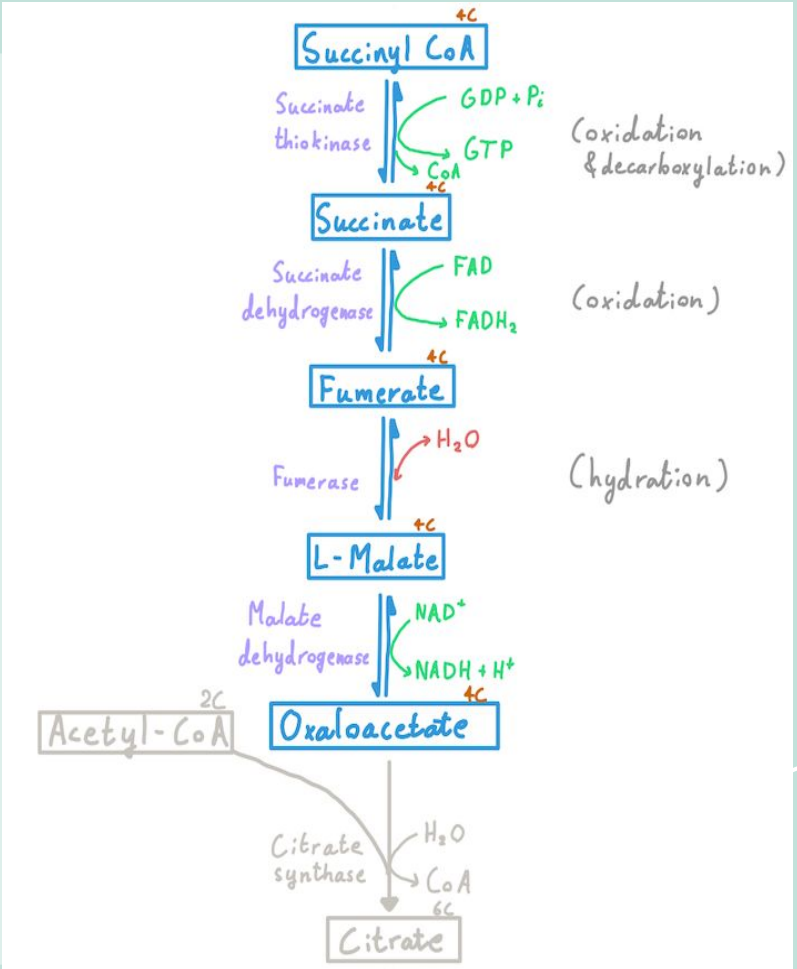
Krebs cycle (2) and (3)

Memorise energy producing R.A

5. Succinyl CoA ⇄ Succinate
   - **Enzyme**: Succinate thiokinase
   - **In**: GDP + P_i
   - **Out**: GTP, CoA

- Note: this is the only substrate level phosphorylation in krebs cycle

6. Succinate ⇄ Fumarate
   - **Enzyme**: Succinate dehydrogenase
   - **In**: FAD
   - **Out**: $FADH_2$



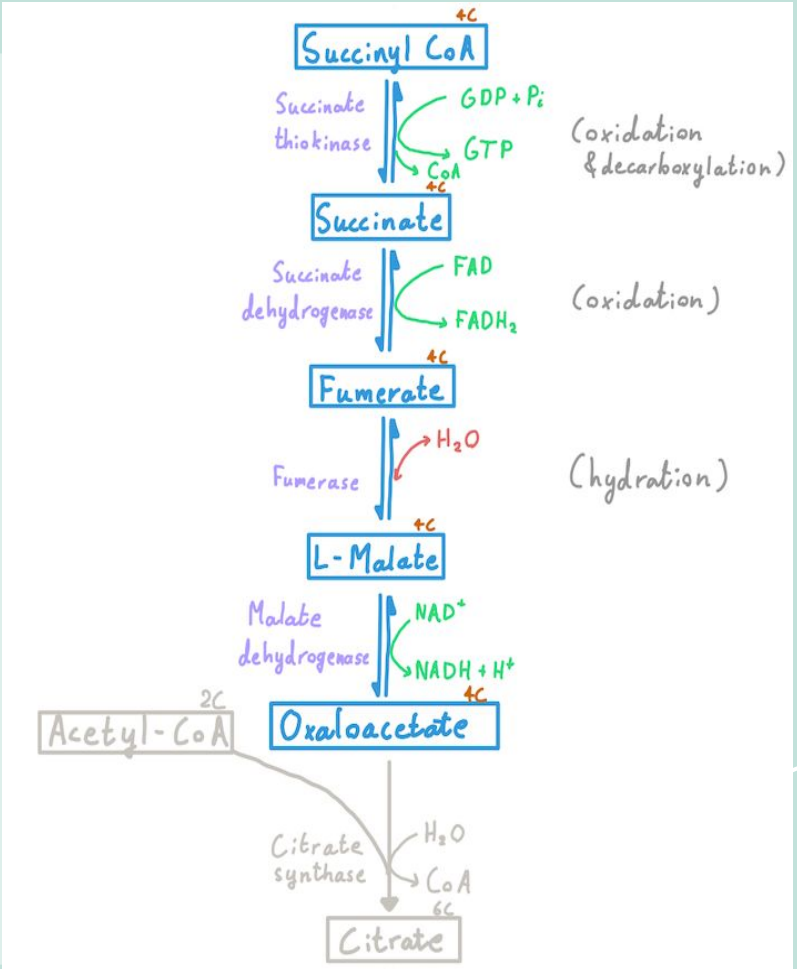
Krebs cycle (2) and (3)

Memorise energy producing R.A

7. Fumarate ⇄ Malate (L-Malate)
- **Enzyme**: Fumarase
- **In**: H_2O

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

Out: $NADH + H^+$



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 $FADH_2$ → 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 $FADH_2$ = 2 ATP

Might ask you:

-how many ATP we get per pyruvate in krebs cycle?
(12 ATP) 2 pyruvate 24 ATP

-how many ATP we get from one glucose from complete glucose oxidation ?
(38 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^+

To Inactivate the **krebs cycle:**
Increase in **ATP** and **NADH**
Decrease in **ADP** and **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.

MCQs

1. PDH kinase is inhibited by:			
A)ATP	B)NADH	C)Pyruvate	D)Acetyl CoA
2. TCA cycle activators are:			
A)ADP,Ca2+	B)ATP,NADH	C)FADH2,ADP	D)ADP,NADH
3. How many ATP produced per pyruvate in krebs cycle?			
A) 2	B) 12	C) 24	D) 38
4. How many ATPs produced per FADH2?			
A) 1	B) 2	C) 3	D) 4
5. Succinyl CoA			
A) activates isocitrate dehydrogenase	B) inhibits isocitrate dehydrogenase	C) activates a-Ketoglutarate dehydrogenase complex	D) inhibits a-Ketoglutarate dehydrogenase complex

Answer key: 1) C - 2) A - 3)B - 4) B - 5) D

SAQ Question 1

Enumerate the fates of pyruvate?

1- Ethanol, Lactate,Acetyl CoA, Oxaloacetate and Alanine

SAQ Question 2

What is the cofactor for PDH phosphatase?

Ca2+

SAQ Question 3

what is the only substrate level phosphorylation reaction in krebs cycle?

Succinyl CoA ⇄ Succinate by the enzyme: Succinate thiokinase

SAQ Question 4

mention two irreversible steps in TCA cycle?

1- Isocitrate → α-Ketoglutarate
2- α-Ketoglutarate → Succinyl CoA

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