Kreb’s Cycle
(tricarboxylic acid (TCA)cycle, citric acid cycle)

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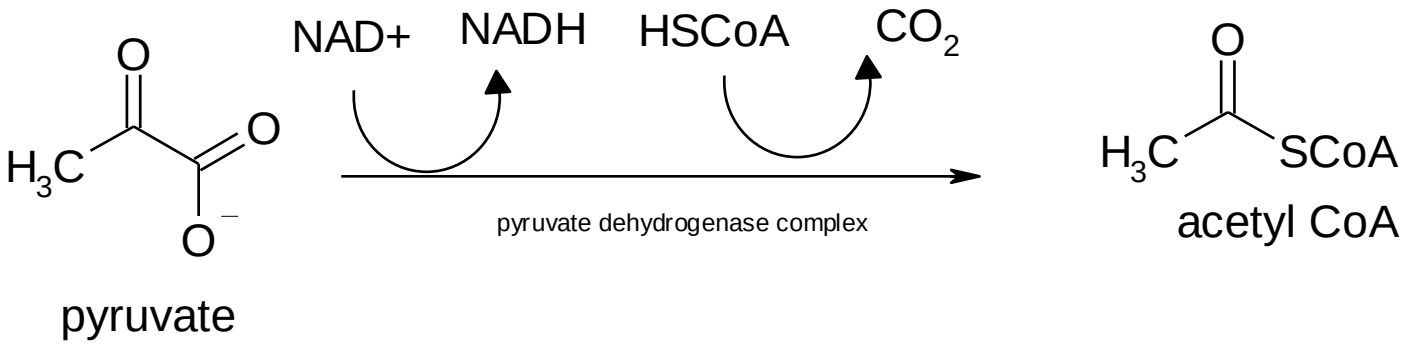
Overall goal

- Makes ATP
- Makes NADH
- Makes $FADH_2$
- Requires some carbohydrate to run .

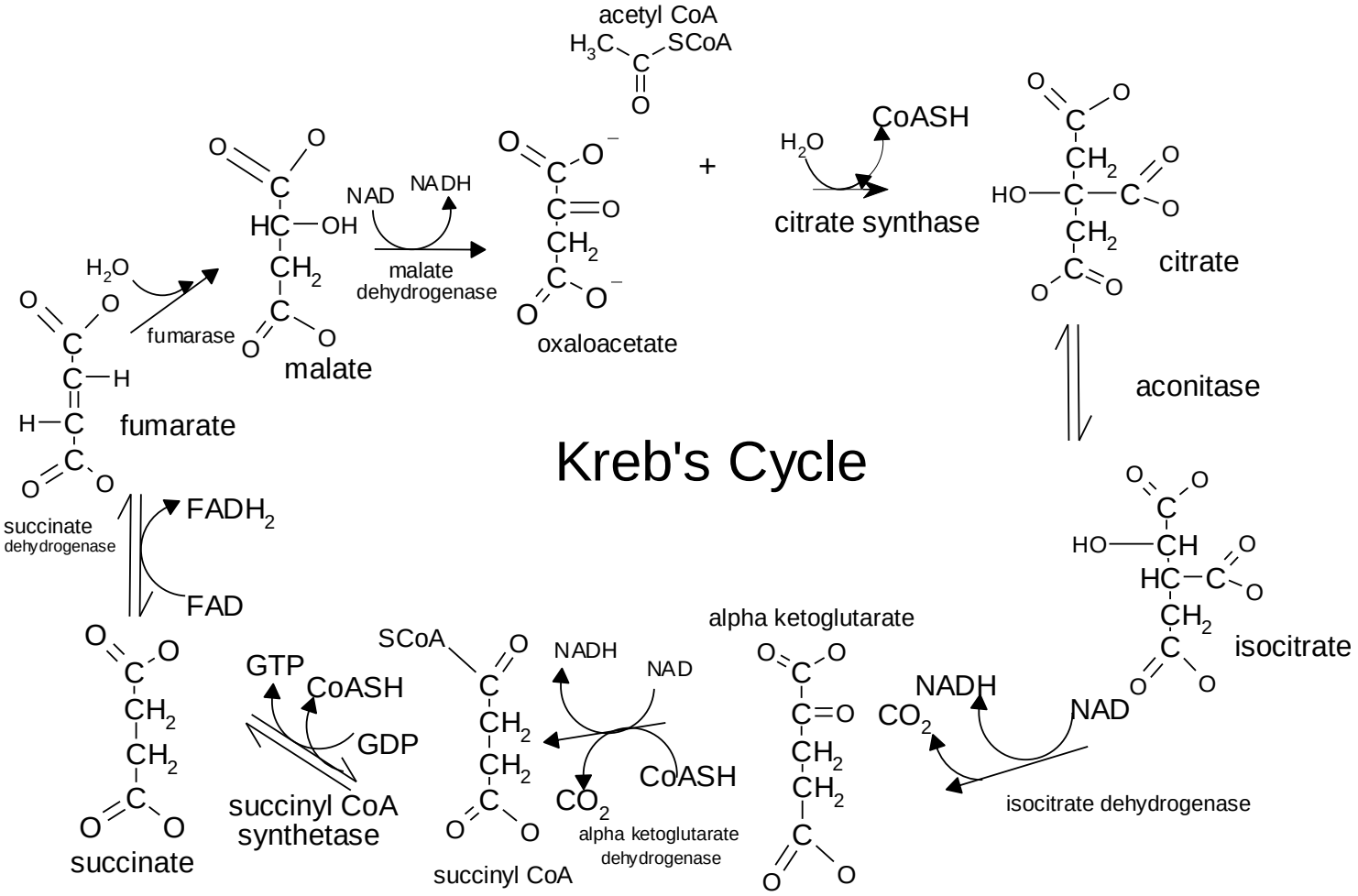
- Final common pathway of the carbohydrates , fats and proteins through formation of 2-carbon unit acetyl CoA .
- The whole process is aerobic , requiring O2 as the final oxidant of the reducing equivalents . Absence of O2 (anoxia) or partial deficiency of O2 (hypoxia) cause total or partial inhibition of the cycle .
- The cycle is occurs in the mitochondria of all body cells , except red blood cells .
- Acetyl coenzyme A (acetyl CoA) condenses with OAA to begin the cycle . Catabolism of carbohydrates , fats and proteins provides the acetyl CoA .

Conversion of pyruvate to Acetyl CoA



- PDH inhibited by dietary deficiency of thiamine (vitamin B1) , leading to accumulation of PA and LA , lactic acidosis is seen .
- The reaction is irreversible .

Kreb's Cycle


acetyl CoA
SCoA
oxaloacetate
citrate synthase
CoASH
citrate
aconitase
isocitrate
isocitrate dehydrogenase
NADH
NAD
CO2
alpha ketoglutarate
alpha ketoglutarate dehydrogenase
succinyl CoA
succinyl CoA synthetase
GTP
GDP
succinate
succinate dehydrogenase
FADH2
FAD
fumarate
fumarase
malate
malate dehydrogenase
H2O

- Intermediates of the TCA cycle are utilized in the fasting state in the liver for the production of glucose (this by the pathway of gluconeogenesis which involves intermediates of the TCA cycle , for example oxaloacetate) and in the fed state for the synthesis of fatty acids (from glucose , pyruvate is produced and converted to OAA by pyruvate carboxylase and to acetyl CoA by pyruvate dehydrogenase).

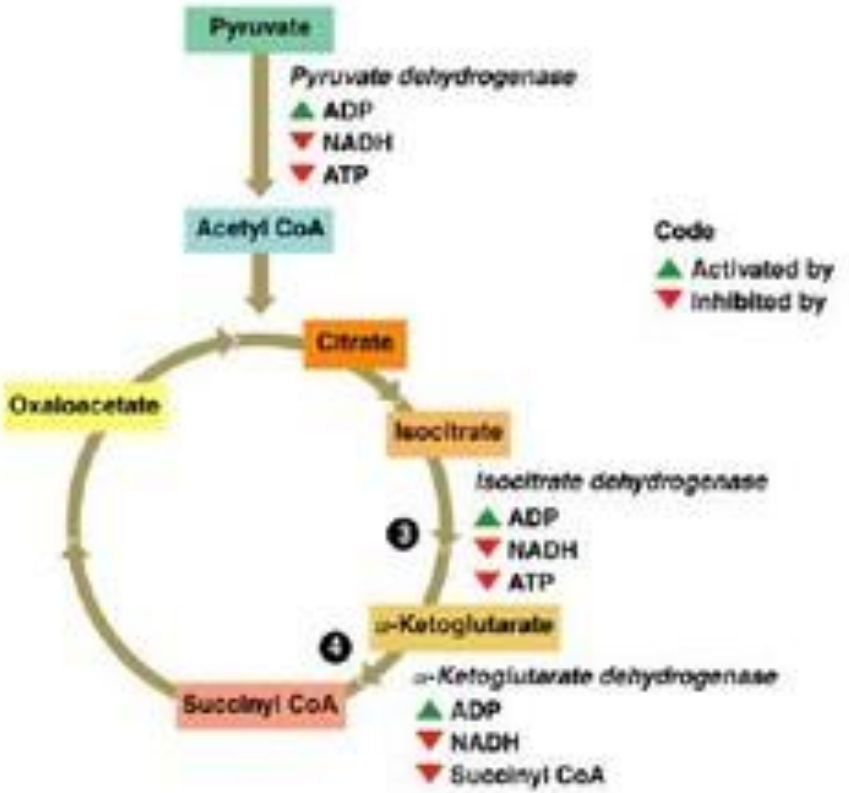
  OAA and acetyl CoA condense to form citrate which is used for fatty acid synthesis .

-Intermediates of the TCA cycle are also used to synthesis amino acids by transamination or by convert one amino acid to another (for example , α - keto glutarate via transamination → A.A. glutamate which is the most abundant excitatory neurotransmitter in the brain) .

Also tetrapyroles (Heme) biosynthesis utilize succinyl CoA as a starting material .

Regulation of Citric Acid Cycle

- Low levels of ATP stimulate the formation of acetyl CoA for the citric acid cycle.
- High ATP and NADH levels decrease the formation of acetyl CoA and slow down the citric acid cycle.



ATP from Two Pyruvate

Under aerobic conditions:

- **2 pyruvate are oxidized to 2 acetyl CoA and 2 NADH.**
- **2 NADH enter electron transport to provide 6 ATP.**

Summary:

2 Pyruvate ⟶ 2 Acetyl CoA + 6 ATP

ATP from Citric Acid Cycle

Reaction Pathway	ATP for One Glucose
ATP from Citric Acid Cycle	
Oxidation of 2 isocitrate (2NADH)	6 ATP
Oxidation of 2 α-ketoglutarate (2NADH)	6 ATP
2 Direct substrate phosphorylations (2GTP)	2 ATP
Oxidation of 2 succinate ($2FADH_2$)	4 ATP
Oxidation of 2 malate (2NADH)	6 ATP

Summary: $2\text{Acetyl CoA} \longrightarrow 4CO_2 + 2H_2O + 24\ \text{ATP}$

(Role of vitamins in the citric acid cycle)

Five B vitamins are associated with TCA cycle essential for yielding energy .

1 . Riboflavin (B2) : In the form of (FAD) flavin adenine dinucleotide .

2 . Niacin (B3) : In the form of (NAD) nicotinamide adenine dinucleotide.

3 . Thiamin (B1) :In the form of thiamine pyrophosphate .

4 .Pantothenic acid (B5)as part of Coenzyme- A .

5 . Lipoic acid : It is required as coenzyme for alpha - ketoglutarate dehydrogenase reaction .

Notes :

- Electrons that are generated from the action of this cycle are transferred to the electron transport chain (ETC) where they are used in the process of oxidative phosphorylation to generate ATP , this process is the main source of energy in aerobic cells where the free energy that is released when electrons are transferred along the ETC is coupled to the formation of ATP from ADP and Pi .

- Regulation of TCA cycle occurs by three enzymes (citrate synthase , isocitrate dehydrogenase and alpha ketoglutarate dehyrogenase) .