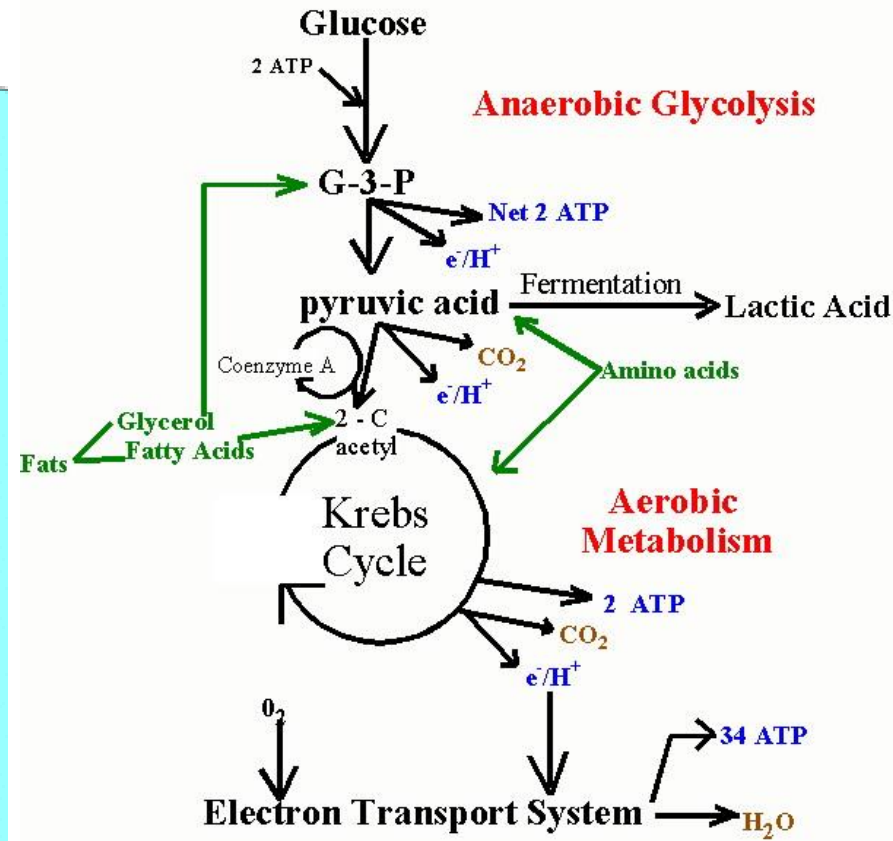
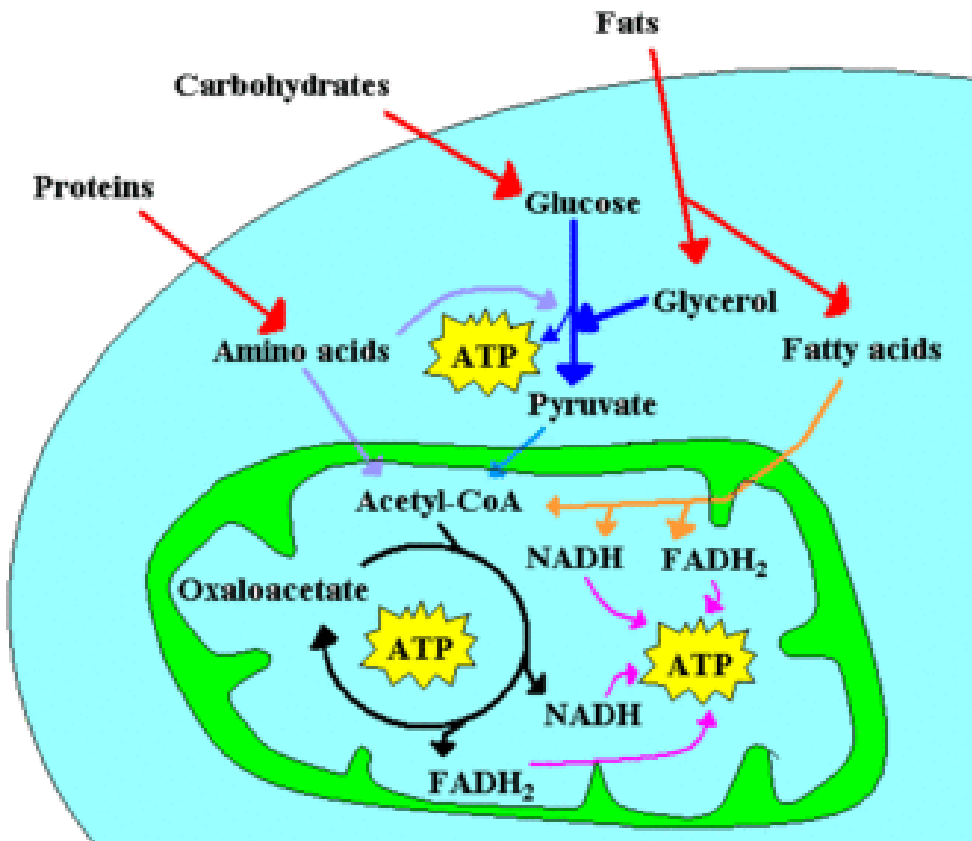


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(Kreb's, Citric Acid, TCA) Cycle

How does it fit?



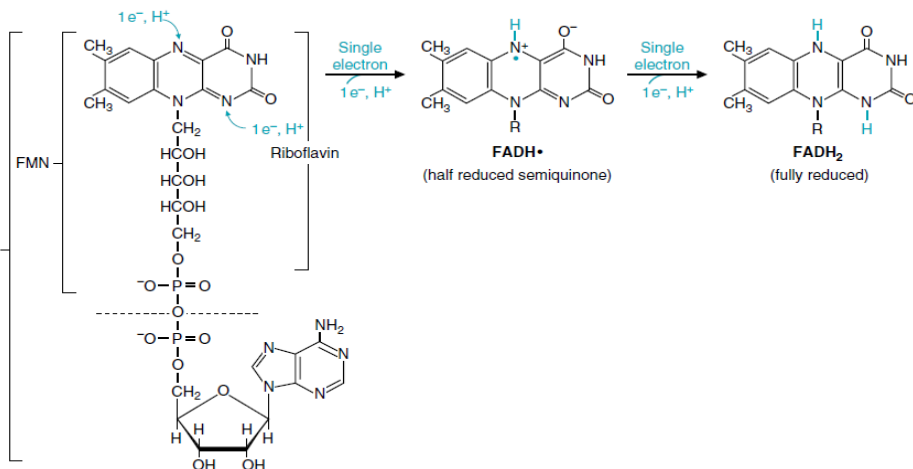
Electron (energy) Carrying Molecules (NAD+, FAD)

➤ FAD

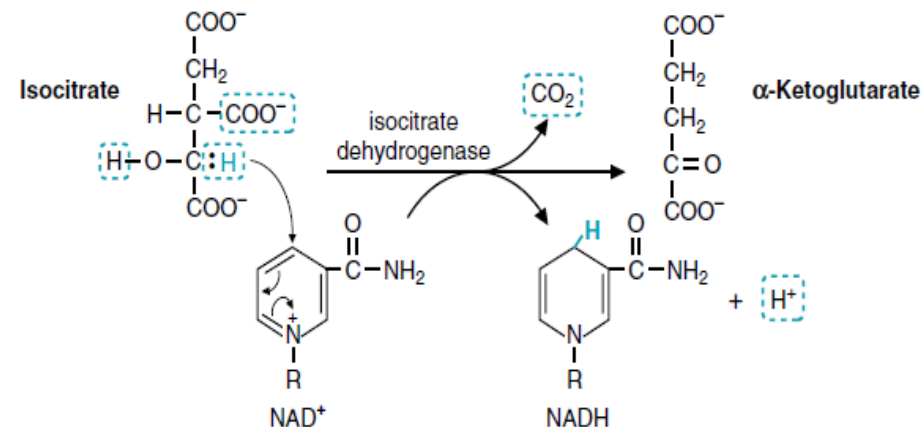
- Single electrons ($H\bullet$), different sources
- Succinate to fumarate, lipoate to lipoate disulfide in α -KG
- FAD must remain tightly, sometimes covalently, attached to its enzyme
- E° for enzyme-bound FAD varies

➤ NAD

- Pair of electrons (H^-), same source
- Alcohols to ketones by malate dehydrogenase & isocitrate dehydrogenase
- NADH plays a regulatory role in balancing energy metabolism



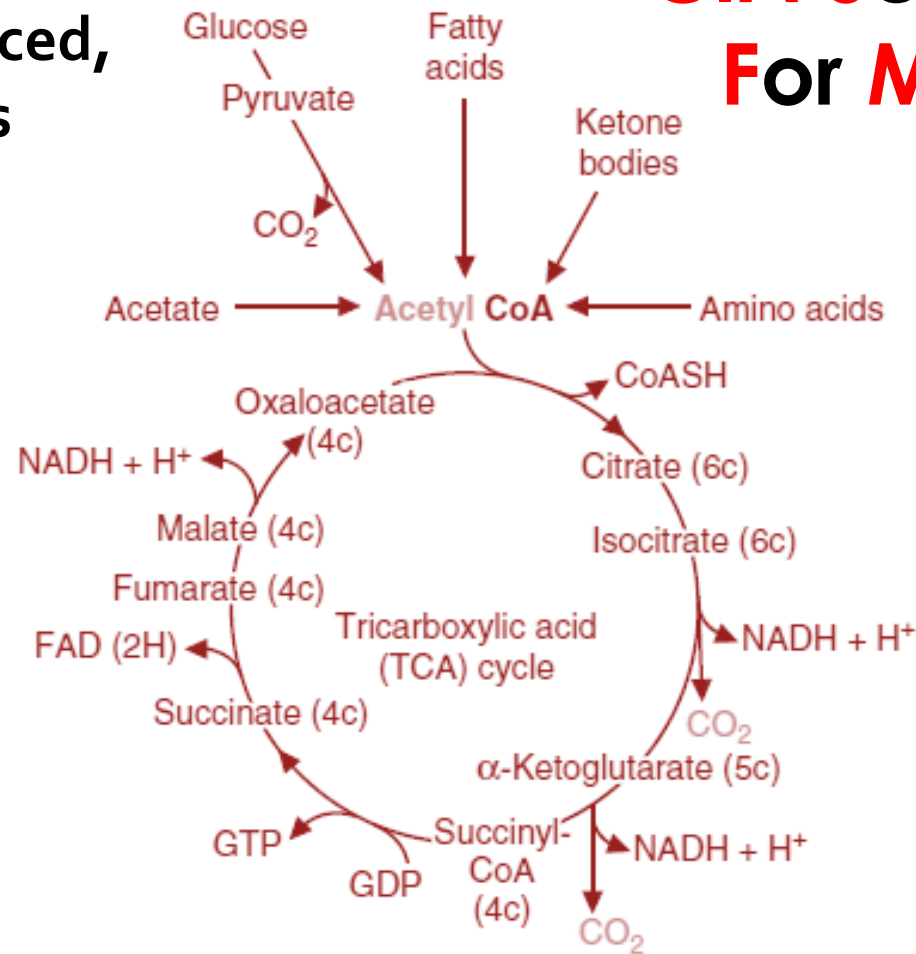
Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN)



Components & stepwise reactions

➤ No O₂ introduced,
two CO₂ exits

**CIA Sent Soldiers
For My Office**



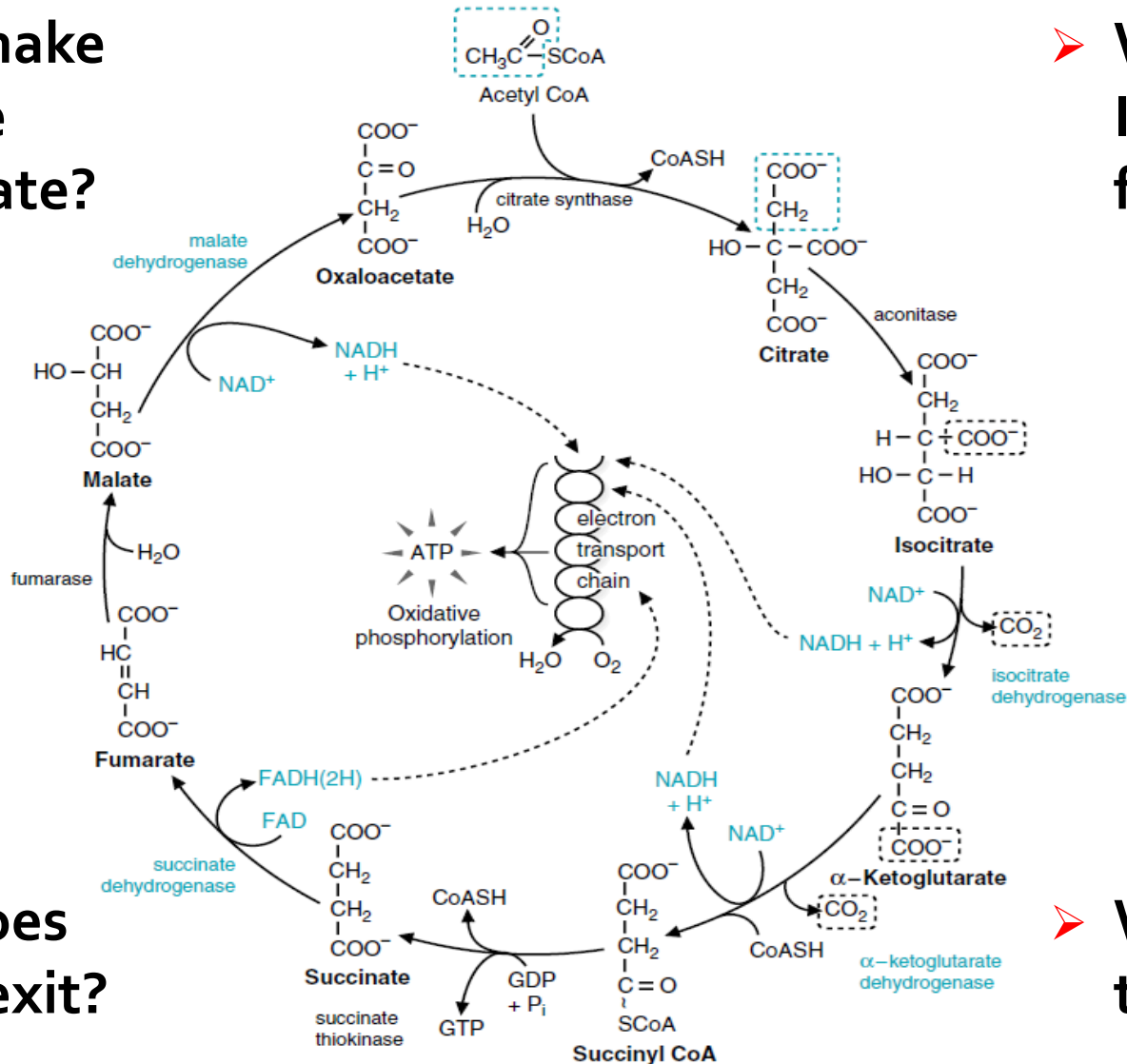
Net reaction



Does Acetyl-CoA exit as 2 CO₂?

➤ Why to make Isocitrate from citrate?

➤ Why to make Isocitrate from citrate?

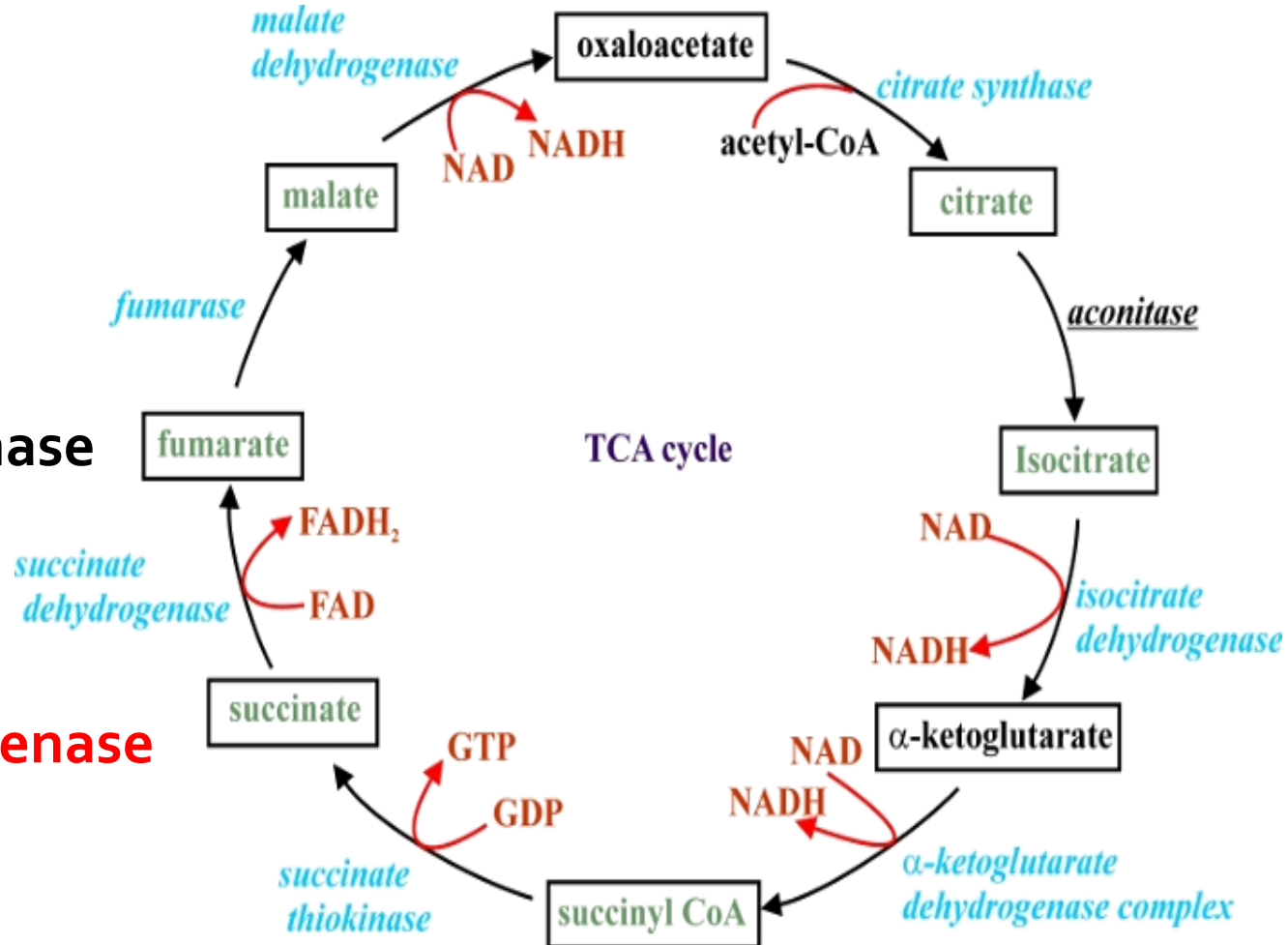


➤ Where does the CO₂ exit?

➤ Where does the CO₂ exit?

Enzymes of the TCA Cycle

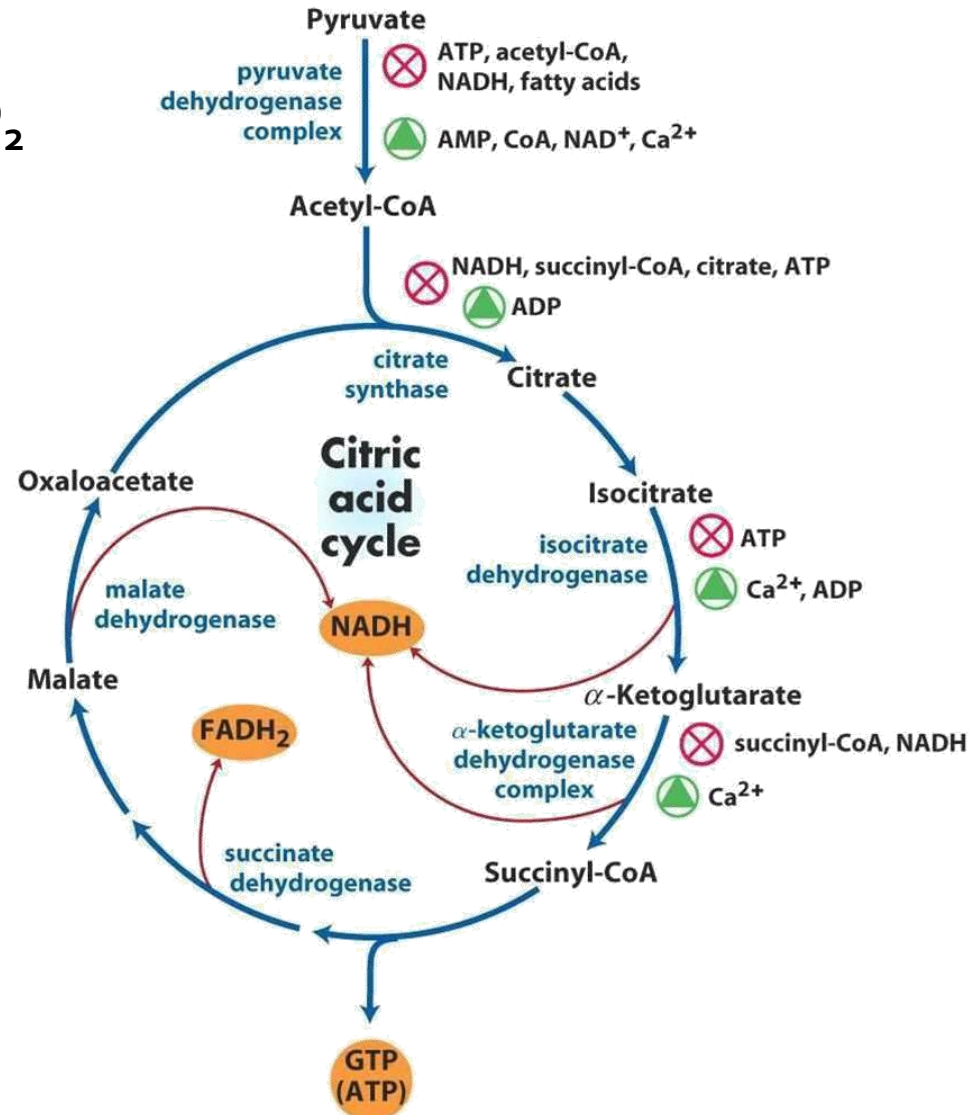
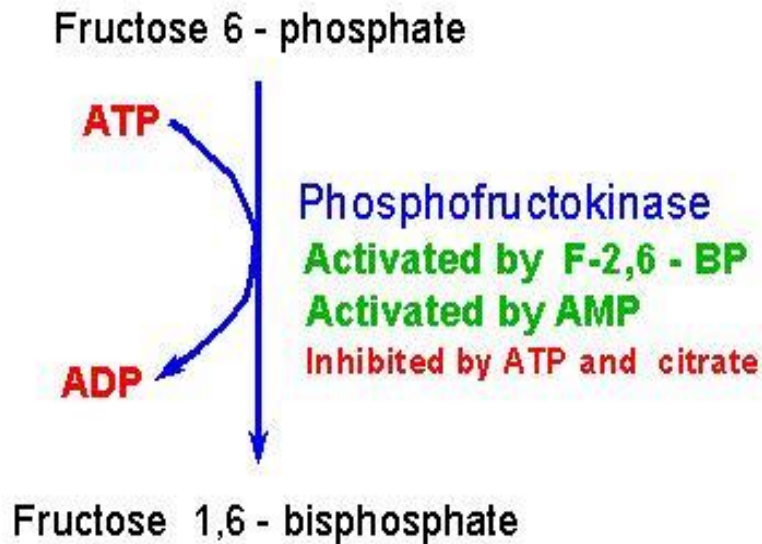
- Citrate synthase
- Aconitase
- Isocitrate dehydrogenase
- α -ketoglutarate dehydrogenase
- Succinate thiokinase
- Succinate dehydrogenase
- Fumarase
- Malate dehydrogenase



Formation and Oxidation of Isocitrate

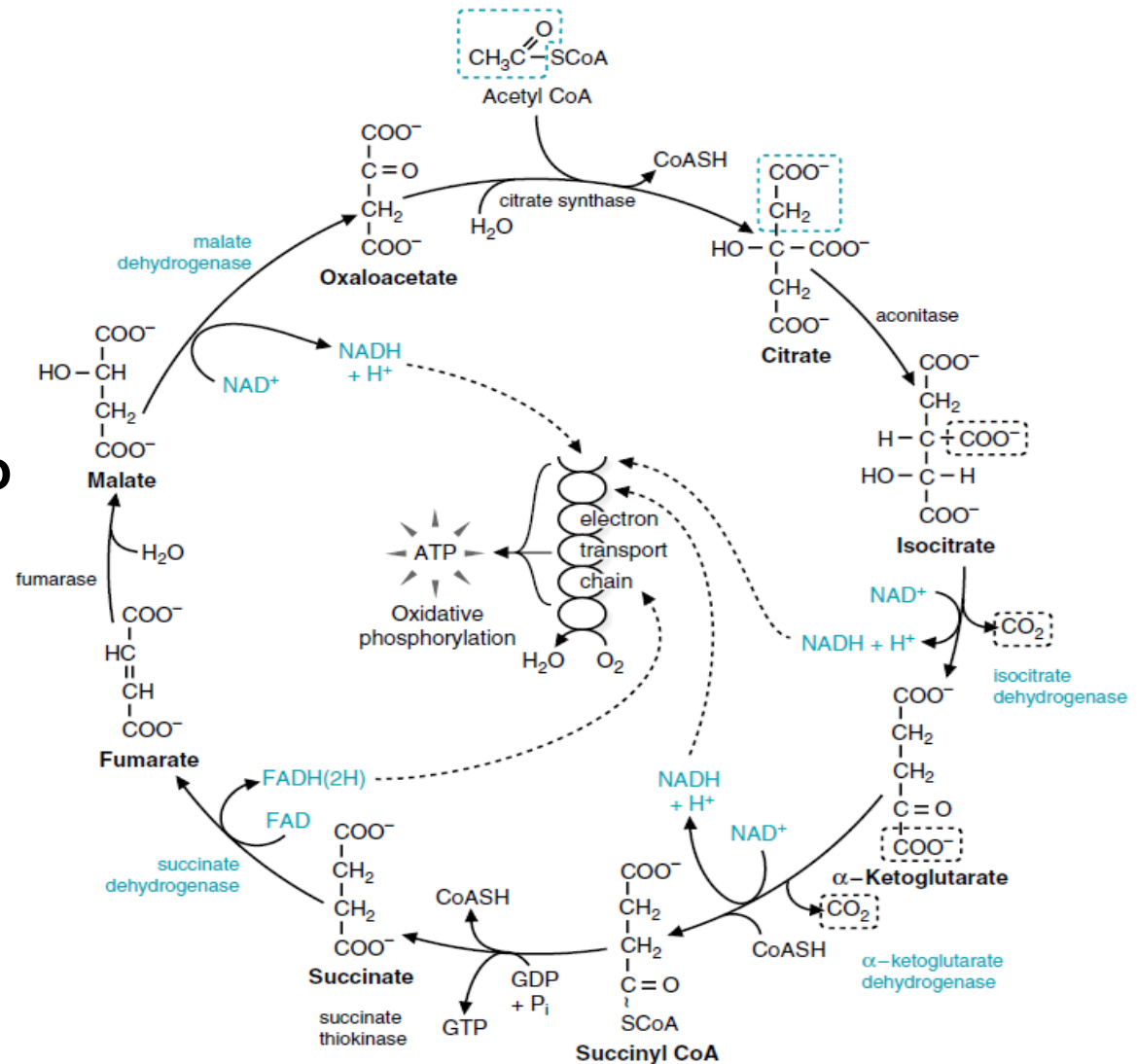
- Oxidative decarboxylation, CO_2
- 3° to 2° alcohol

Control at the committed step of glycolysis



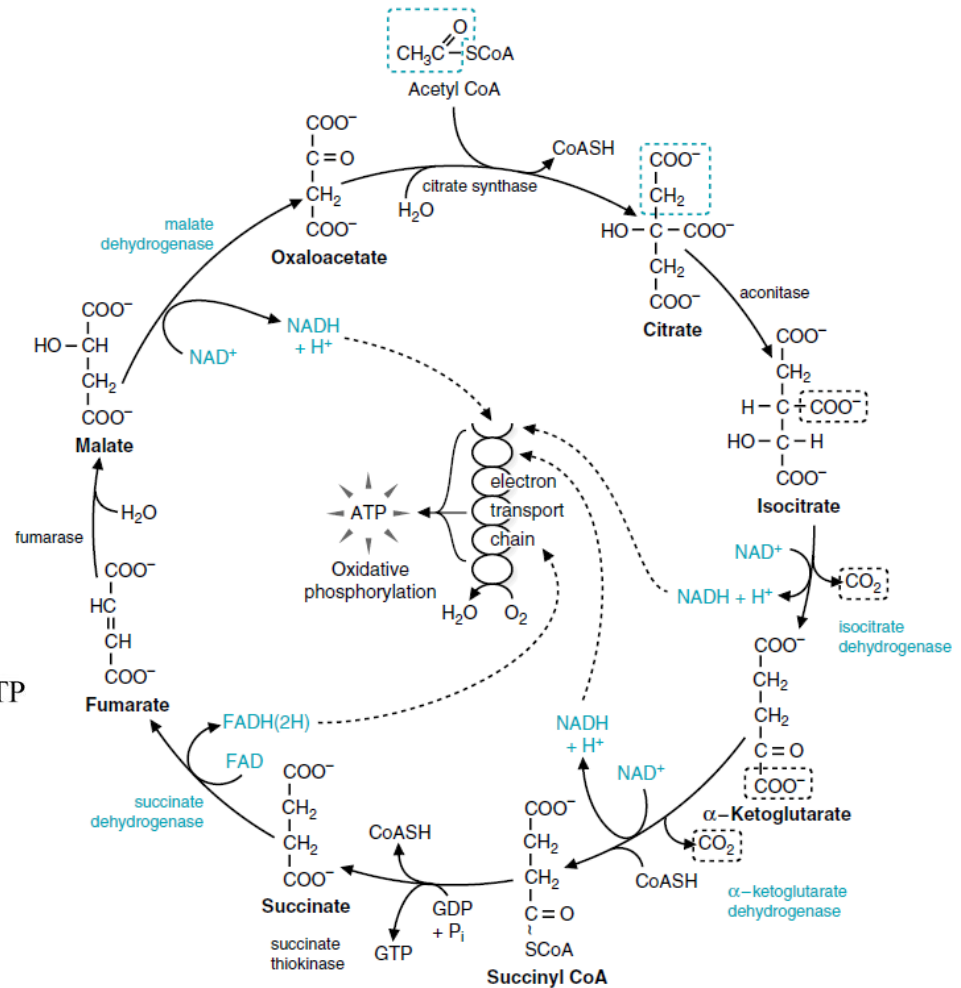
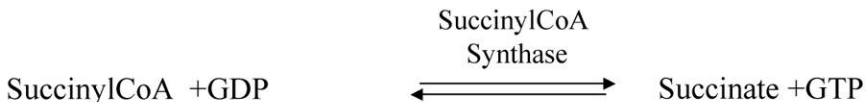
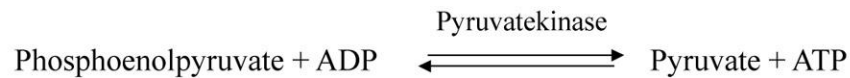
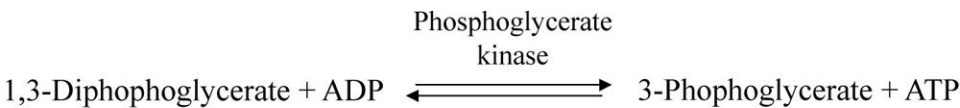
α -Ketoglutarate to Succinyl CoA

- Oxidative decarboxylation
- Thiamine pyrophosphate, lipoic acid, and FAD
- Keto group oxidized to acid, CoA-SH, succinyl CoA
- Energy conserved as NADH, thioester bond



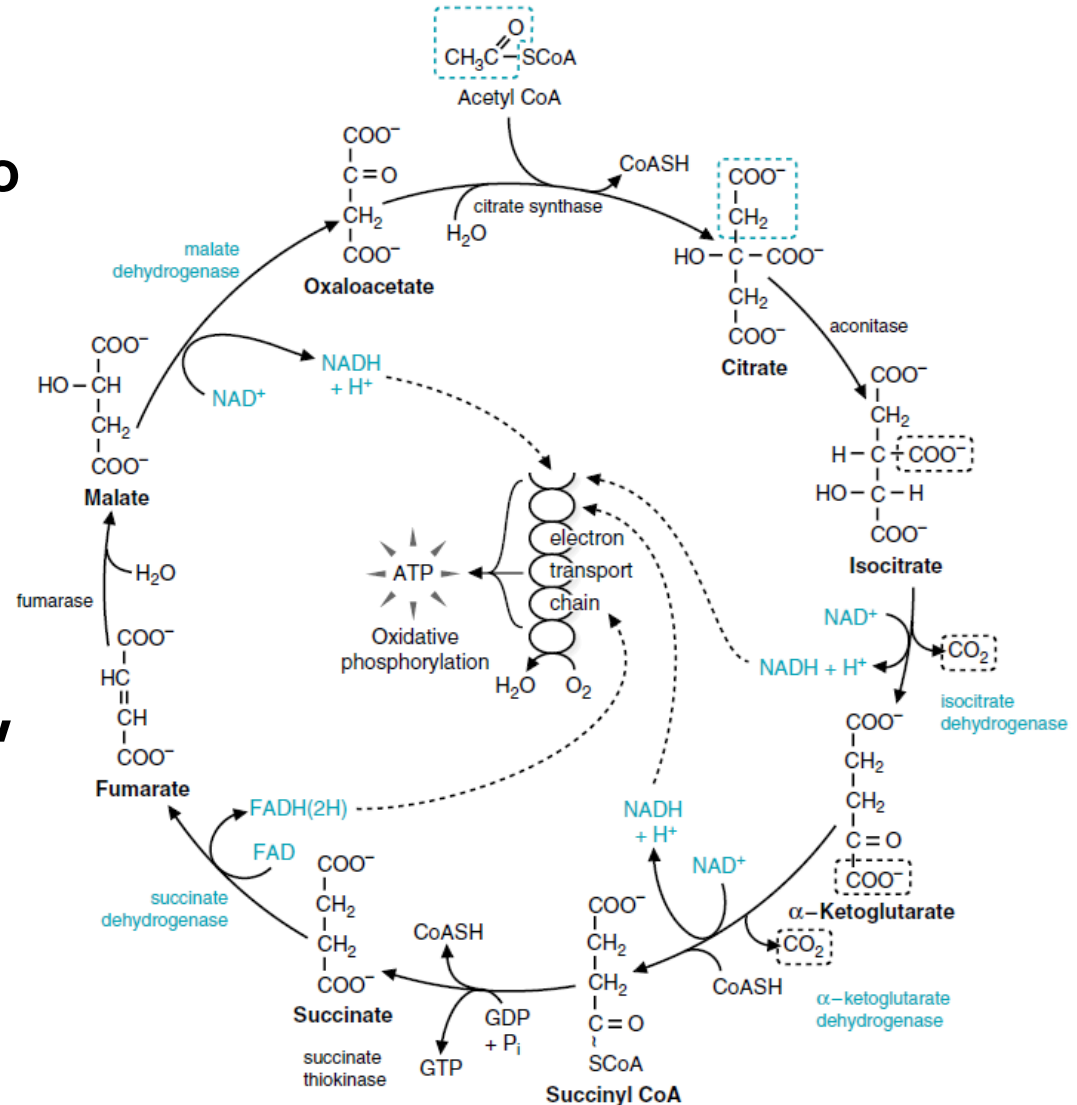
Generation of GTP

➤ **Succinyl CoA thioester bond, succinate thiokinase, substrate level phosphorylation**



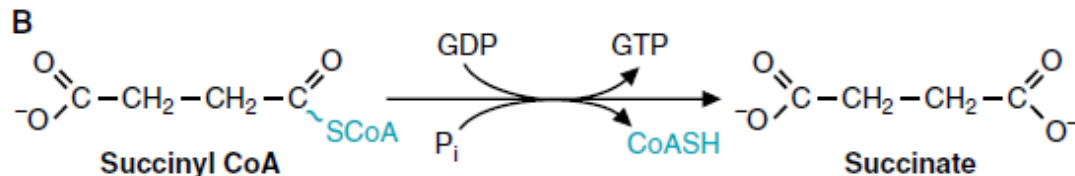
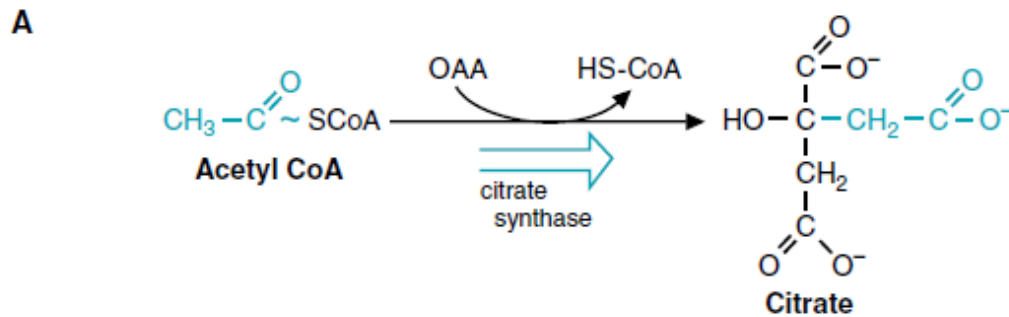
Oxidation of Succinate to Oxaloacetate

- Oxidation of succinate to fumarate, succinate dehydrogenase, FAD
- Fumarase, OH + H⁺ from water, fumarate to malate
- Alcohol group of malate oxidized to a keto group, NADH

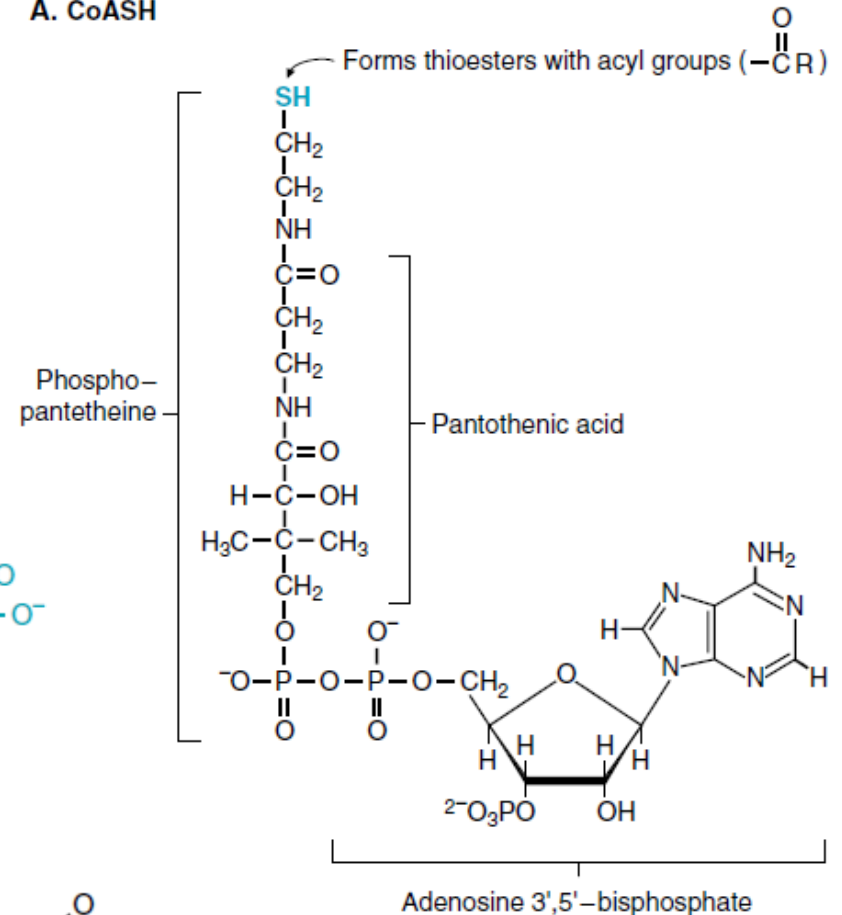


CoA

- Forms a thioester bond, CoASH & an acyl group (e.g., acetyl CoA, succinyl CoA)
- Sulfur vs. oxygen (carbon can be activated, -13kcal, GTP, keeps the reaction going)

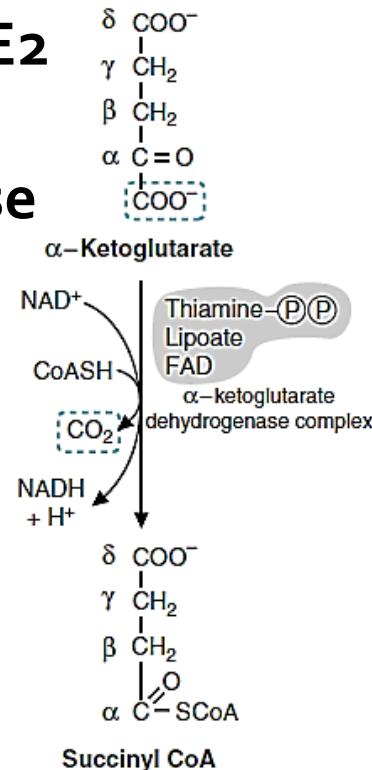
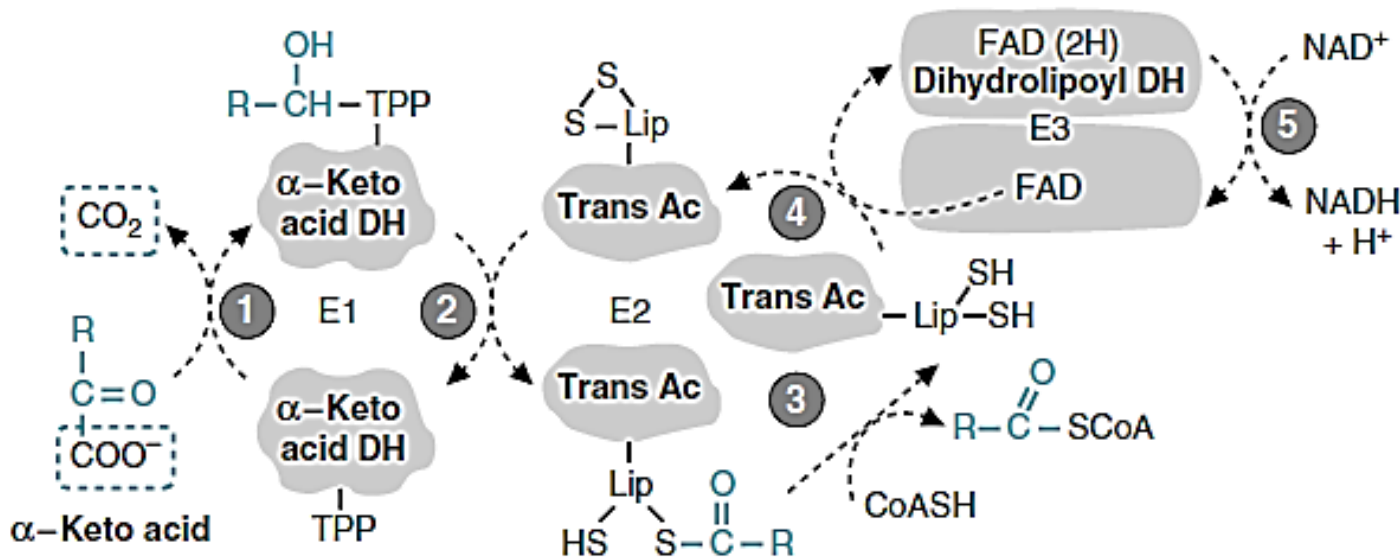


A. CoASH



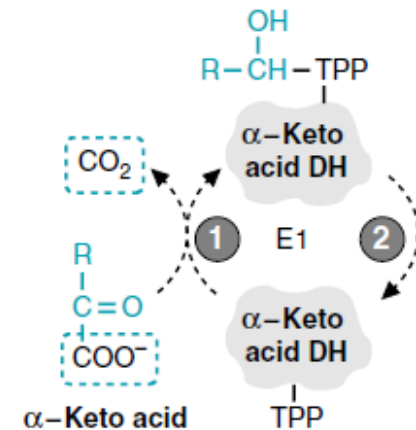
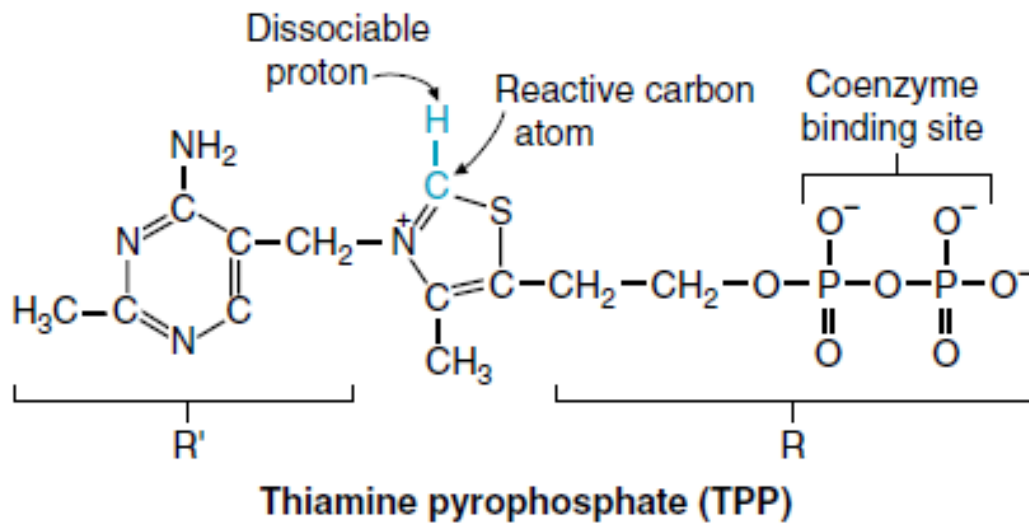
α -Ketoacid Dehydrogenase Complexes (TLCFN)

- (α -ketoglutarate, pyruvate, and branched chain α -keto acid) dehydrogenase complexes
- Huge enzyme complexes, multiple subunits of 3 different enzymes (no loss of energy, substrates for E2 and E3 remain bound \rightarrow higher rate)
- E1, E2, & E3 are a decarboxylase (TPP), a transacylase (lipoate), & a dehydrogenase (FAD)



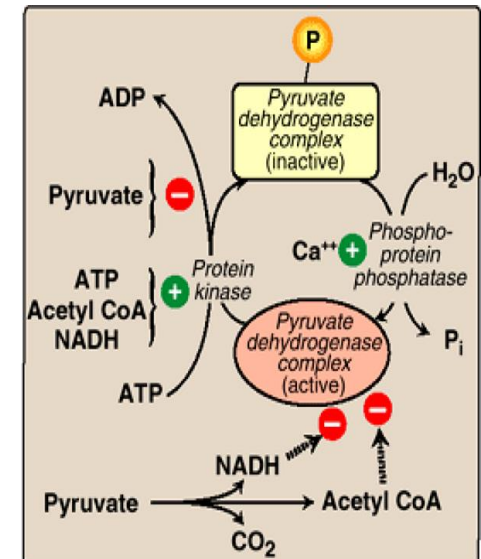
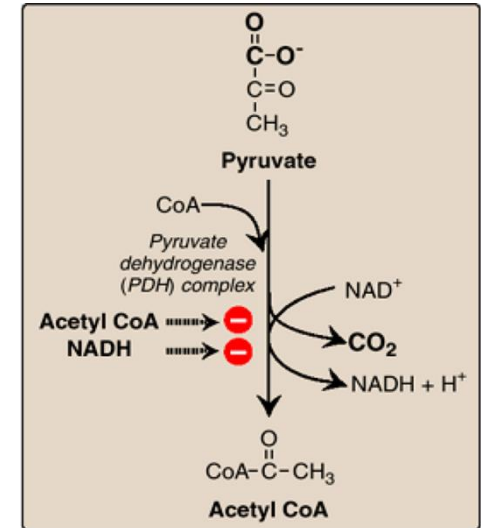
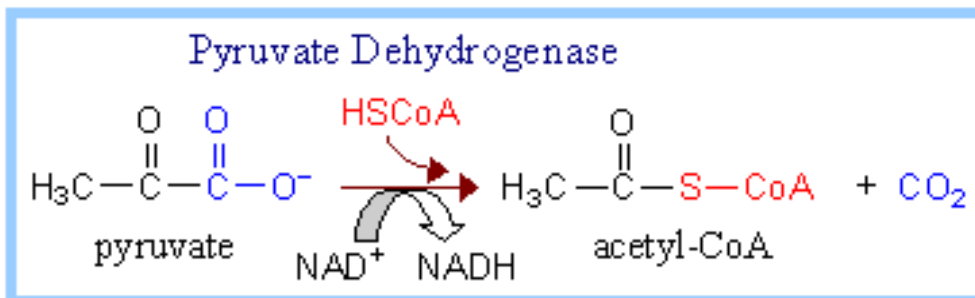
Thiamine Pyrophosphate

- Thiamine deficiency, α -ketoglutarate, pyruvate, & branched chain α -keto acids accumulate in the blood



Oxidative decarboxylation of pyruvate

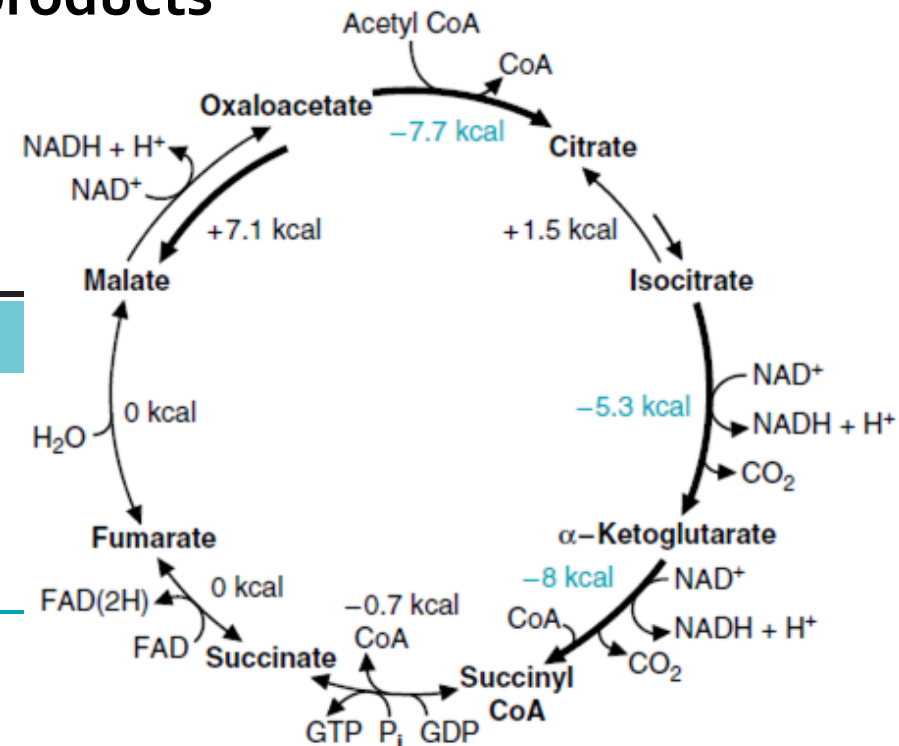
- Component enzymes
- Coenzymes
- Regulation of the pyruvate dehydrogenase complex
 - Pyruvate dehydrogenase deficiency: A deficiency in E₁ component is the most common biochemical cause of congenital lactic acidosis (X-linked, no treatment)
- Mechanism of arsenic poisoning



Bioenergetics of the TCA Cycle

- Like all pathways, overall net $-\Delta G$ (-228 kcal/mole), not 100%
- NADH, FAD(H₂), and GTP (10ATP), 207 Kcal, 90%
- Three reactions have large (-ve) values
- Physiologically irreversible, low products

kcal/mole	
3 NADH: 3×53	= 159
1 FAD(2H)	= 41
1 GTP	= 7
Sum	= 207

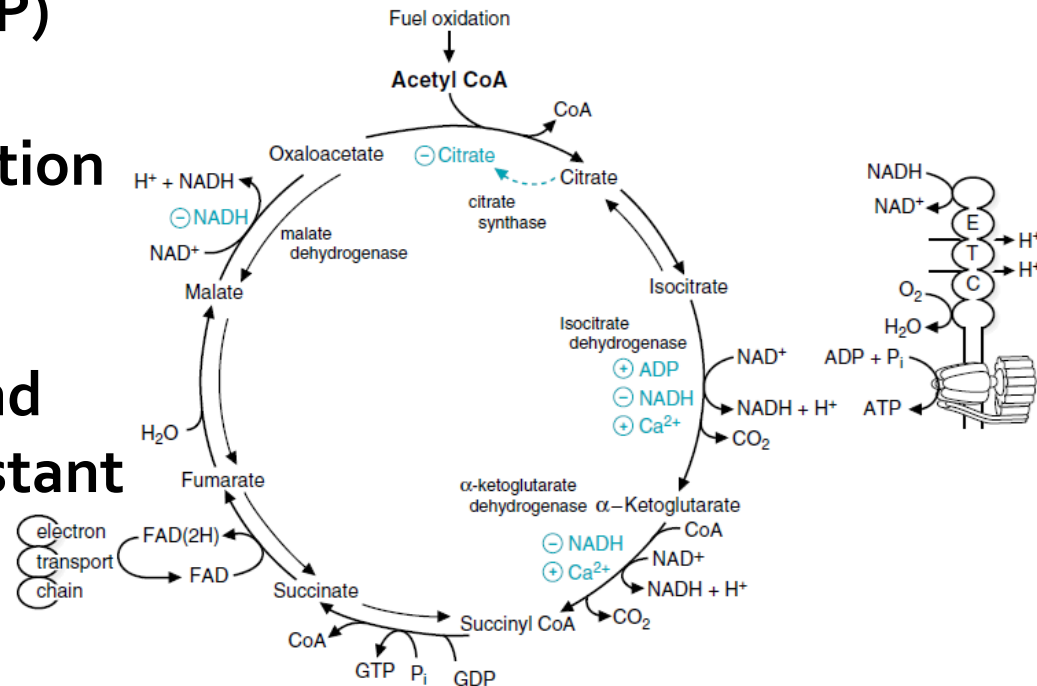


Regulation of the TCA Cycle

- Correspond to ETC (ATP/ADP)
- Two major messengers (feedback): (a) phosphorylation state of adenines, (b) the reduction state of NAD
- Adenine nucleotides pool and NAD pool are relatively constant

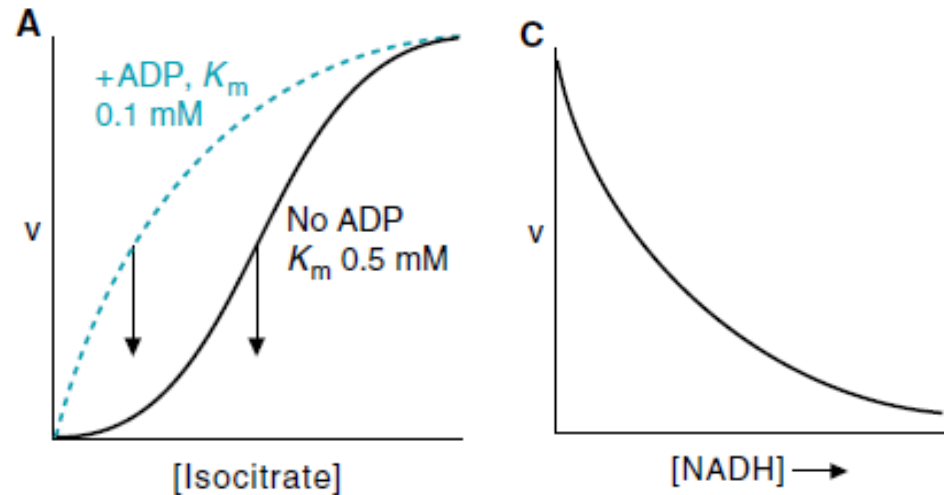
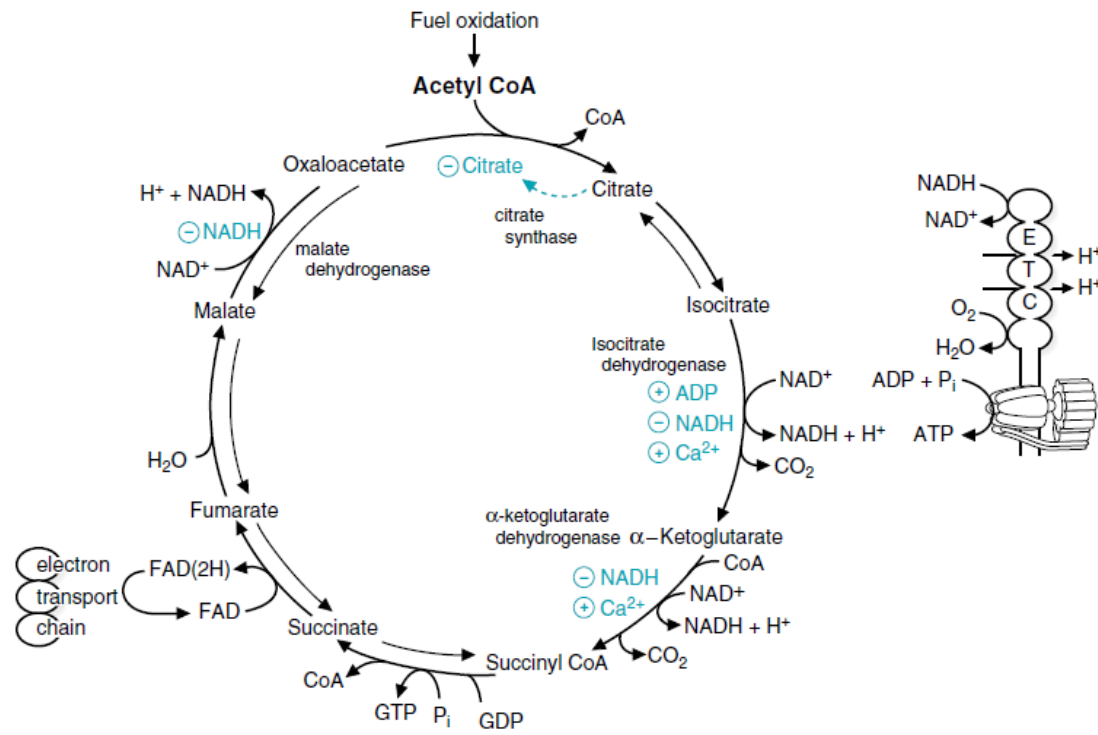
Citrate Synthase

- The first step, no allosteric regulation
- Rate regulated by oxaloacetate & citrate (inhibitor)



Isocitrate DH

- Best regulation at rate-limiting step (Isocitrate DH)
- Allosterically: activated (ADP, Ca^{+2})
- Inhibition (NADH)
- No ADP vs. ADP (K_m less), a small change in ADP, great effect

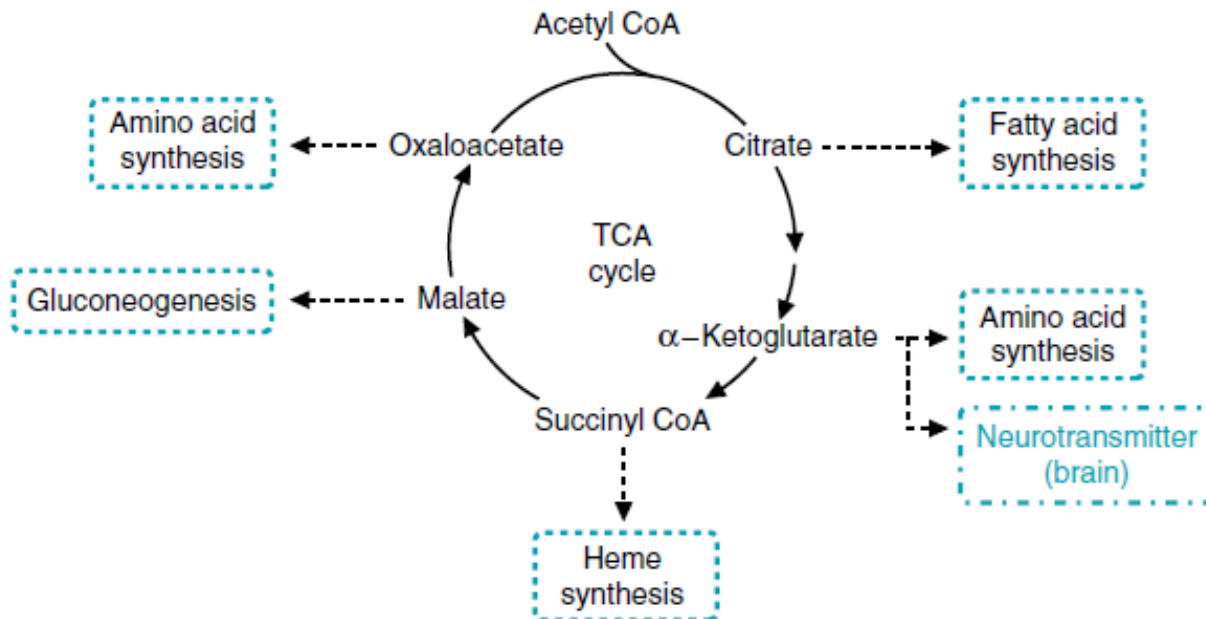


α-Ketoglutarate DH

- Inhibited by NADH and succinyl CoA, GTP
- Activated by Ca^{+2} , muscle contraction

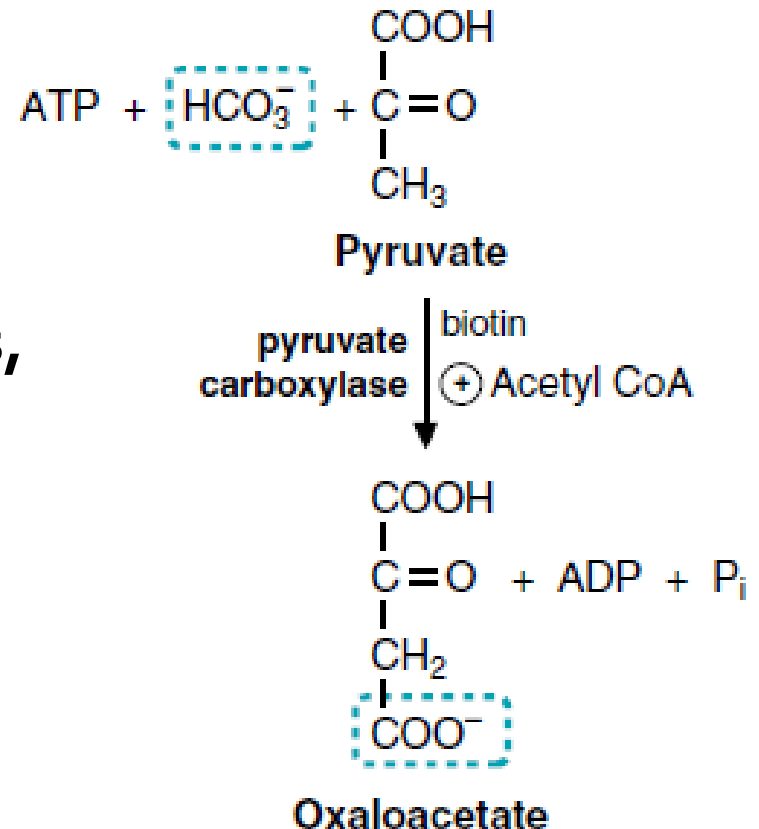
TCA Cycle Intermediates

- Intermediates are Precursors for Biosynthetic Pathways (citrate, acetyl CoA, fatty acid synthesis, liver) (fasting, malate, gluconeogenesis, liver) (Succinyl CoA, heme biosynthesis, bone marrow) (α -ketoglutarate, glutamate, GABA, a neurotransmitter, brain) (α -ketoglutarate, glutamine, skeletal muscle to other tissues for protein synthesis)



Anaplerotic Reactions

- Pathways or reactions that replenish the intermediates of the TCA cycle
- Pyruvate Carboxylase is a major anaplerotic enzyme (requires biotin)
- Found in many tissues, liver, kidneys, brain, adipocytes, and fibroblasts
- Very high conc. In liver and kidney (gluconeogenic pathway)
- Activated (acetyl CoA)



Other Anaplerotic Routes (Amino Acid Degradation)

