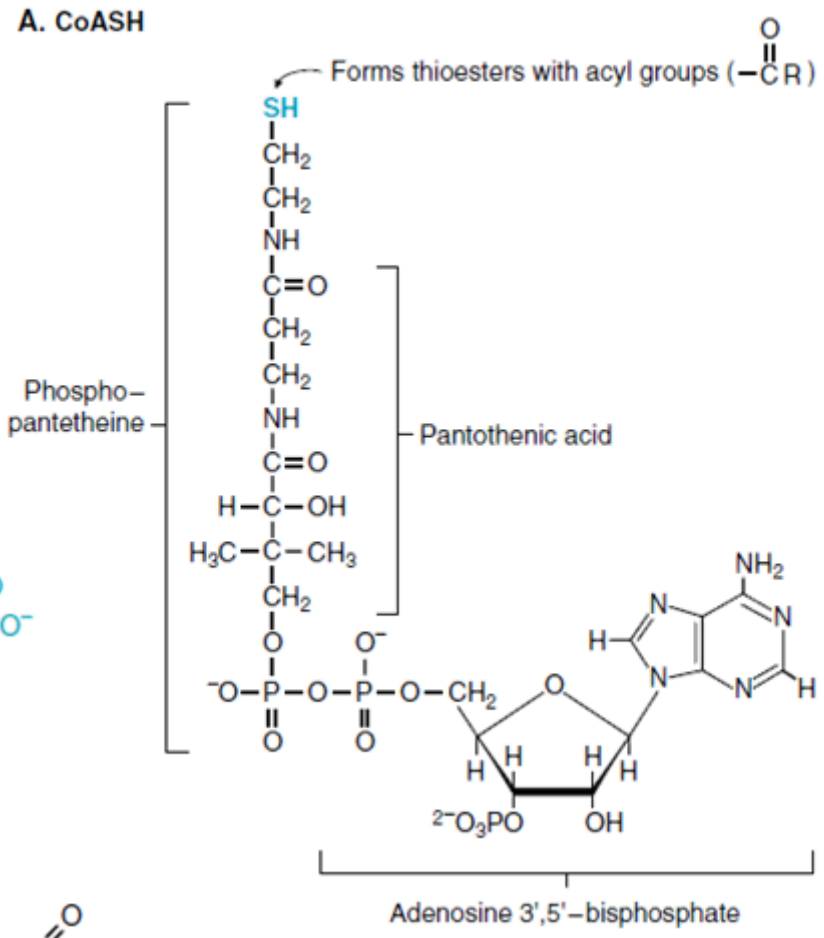
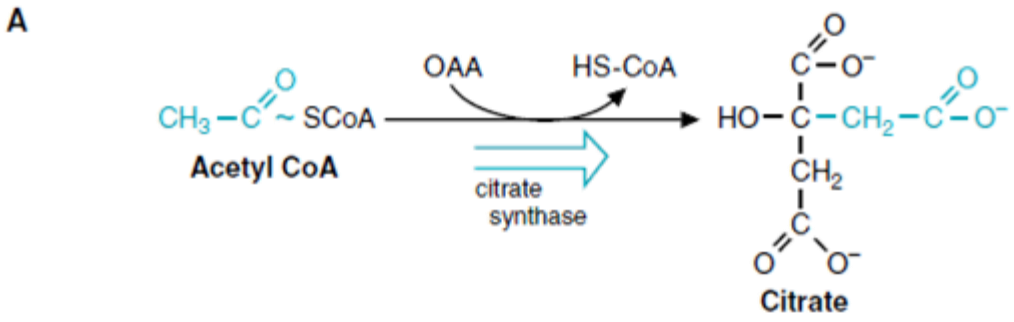
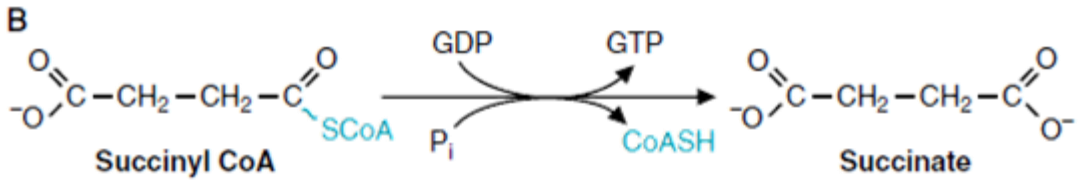
CoA

- 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)

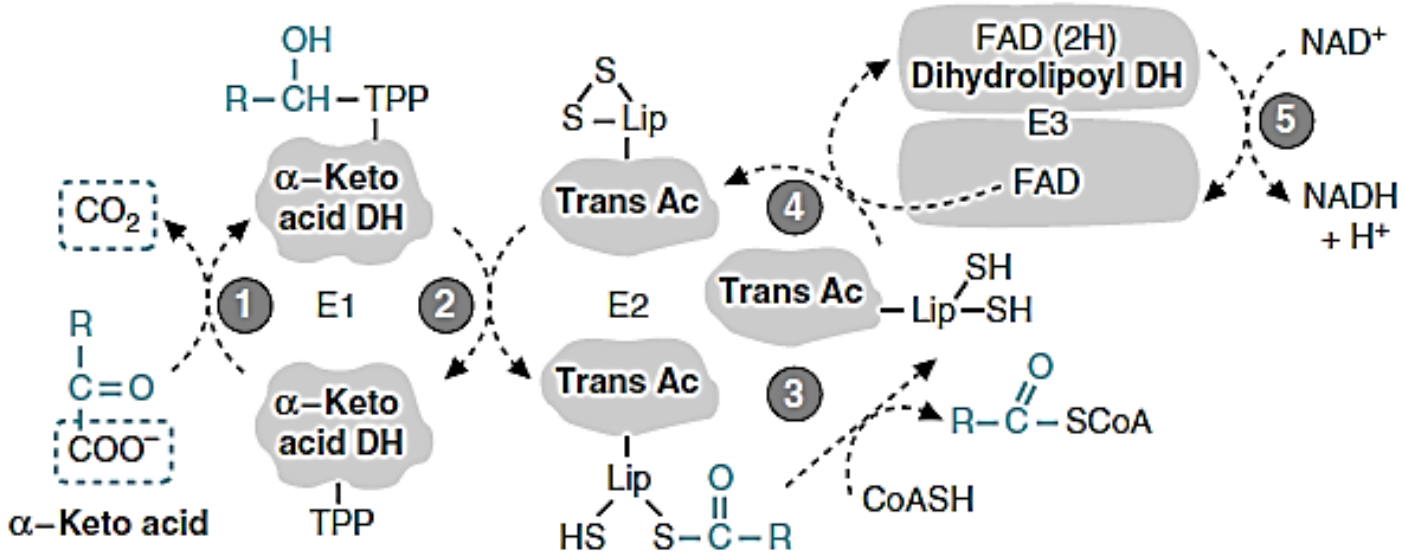


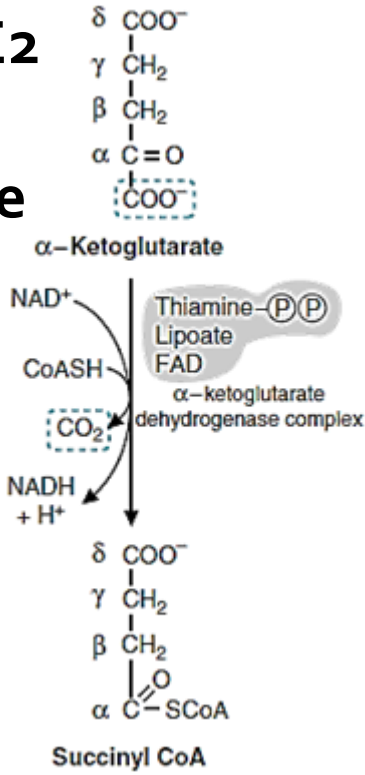




α-Ketoacid Dehydrogenase Complexes (TLCFN)

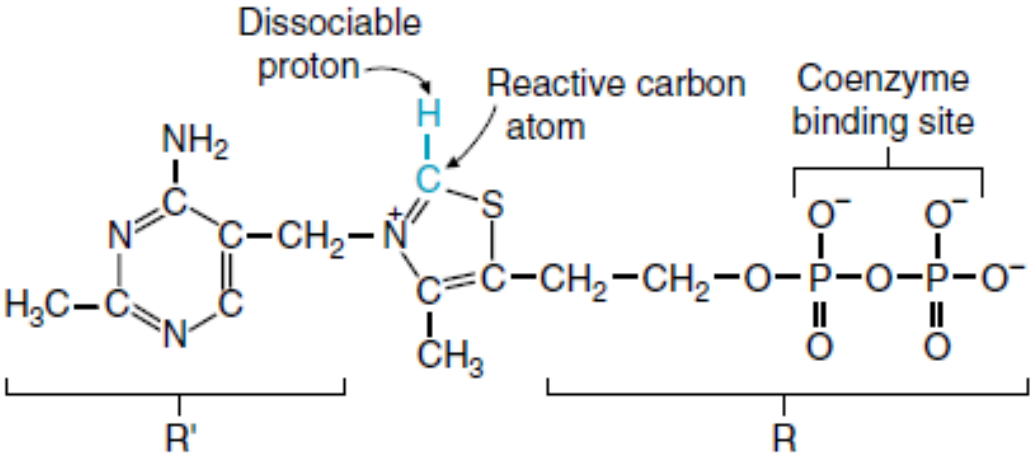
- (α-ketoglutarate, pyruvate, and branched chain α-keto acid) dehydrogenase complexes
- Huge enzyme complexes, multiple subunits of 3 different enzymes (no loss of energy, substrates for E2 and E3 remain bound → higher rate)
- E1, E2, & E3 are a decarboxylase (TPP), a transacylase (lipoate), & a dehydrogenase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



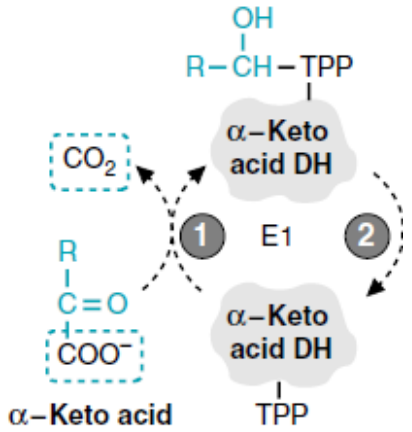


Thiamine Pyrophosphate

- Thiamine deficiency, α-ketoglutarate, pyruvate, & branched chain α-keto acids accumulate in the blood
- Wernicke-Korsakoff, an encephalopathy-psychosis syndrome due to thiamine deficiency, may be seen with alcohol abuse

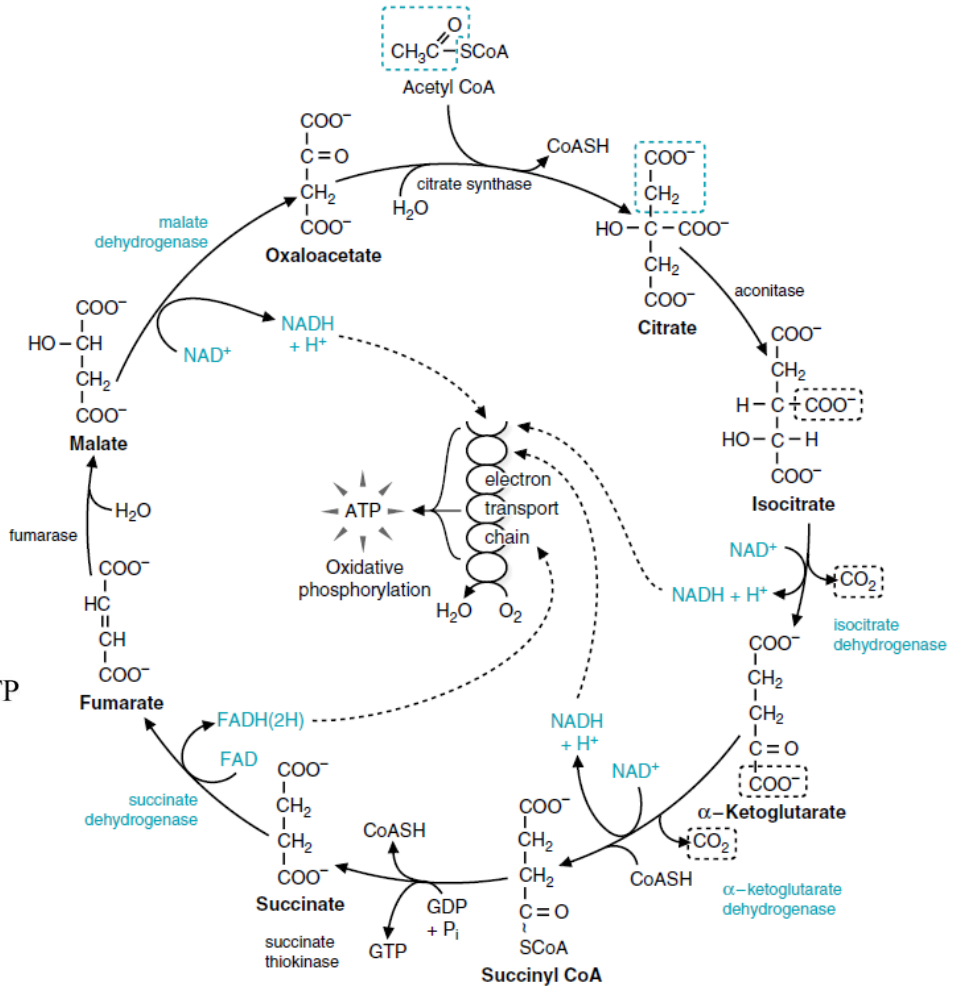


Thiamine pyrophosphate (TPP)



Generation of GTP

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



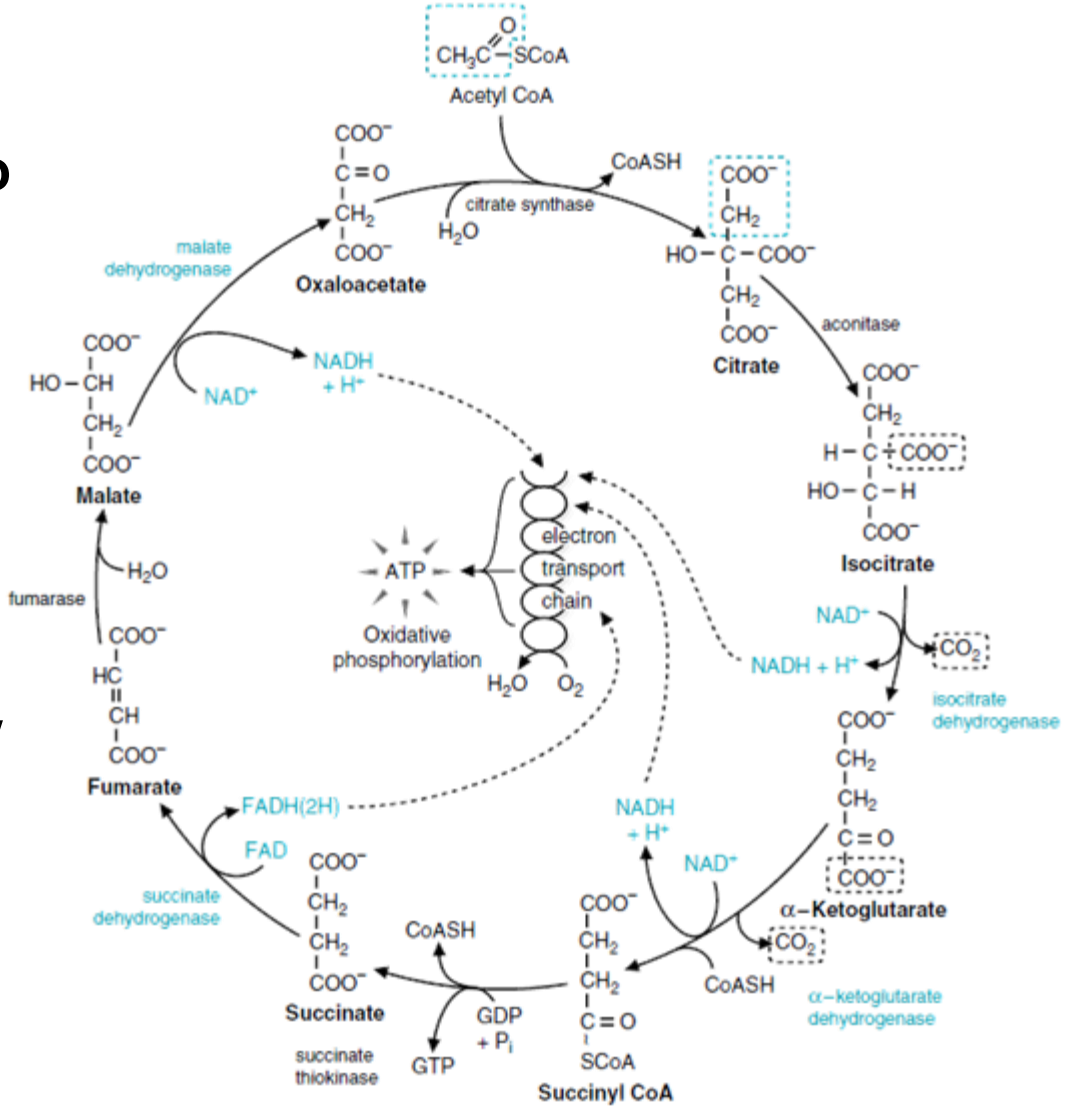
1,3-Diphophoglycerate + ADP $\xrightleftharpoons{\text{Phosphoglycerate kinase}}$ 3-Phophoglycerate + ATP

Phosphoenolpyruvate + ADP $\xrightleftharpoons{\text{Pyruvatekinase}}$ Pyruvate + ATP

SuccinylCoA +GDP $\xrightleftharpoons{\text{SuccinylCoA Synthase}}$ Succinate +GTP

Oxidation of Succinate to Oxaloacetate

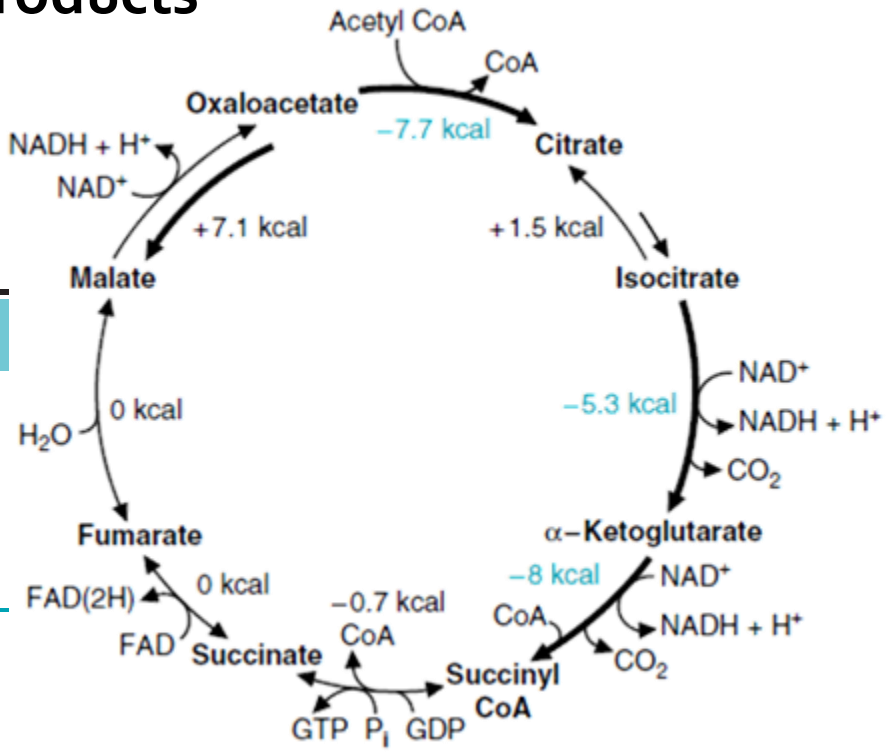
- Oxidation of succinate to fumarate, succinate dehydrogenase, FAD
- Fumarase, OH + H^+ from water, fumarate to malate
- Alcohol group of malate oxidized to a keto group, NADH



Bioenergitics of the TCA Cycle

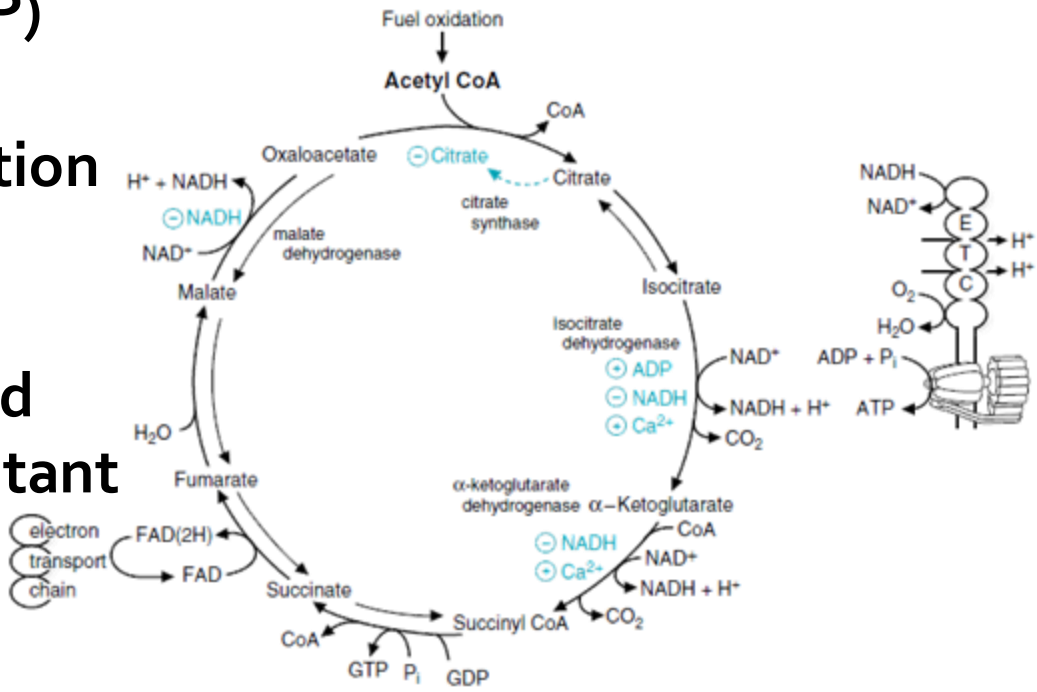
- Like all pathways, overall net -ΔG (-228 kcal/mole), not 100%
- NADH, FAD(H2), and GTP (10ATP), 207 Kcal, 90%
- Three reactions have large (-ve) values - Regulation
- Physiologically irreversible, low products

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

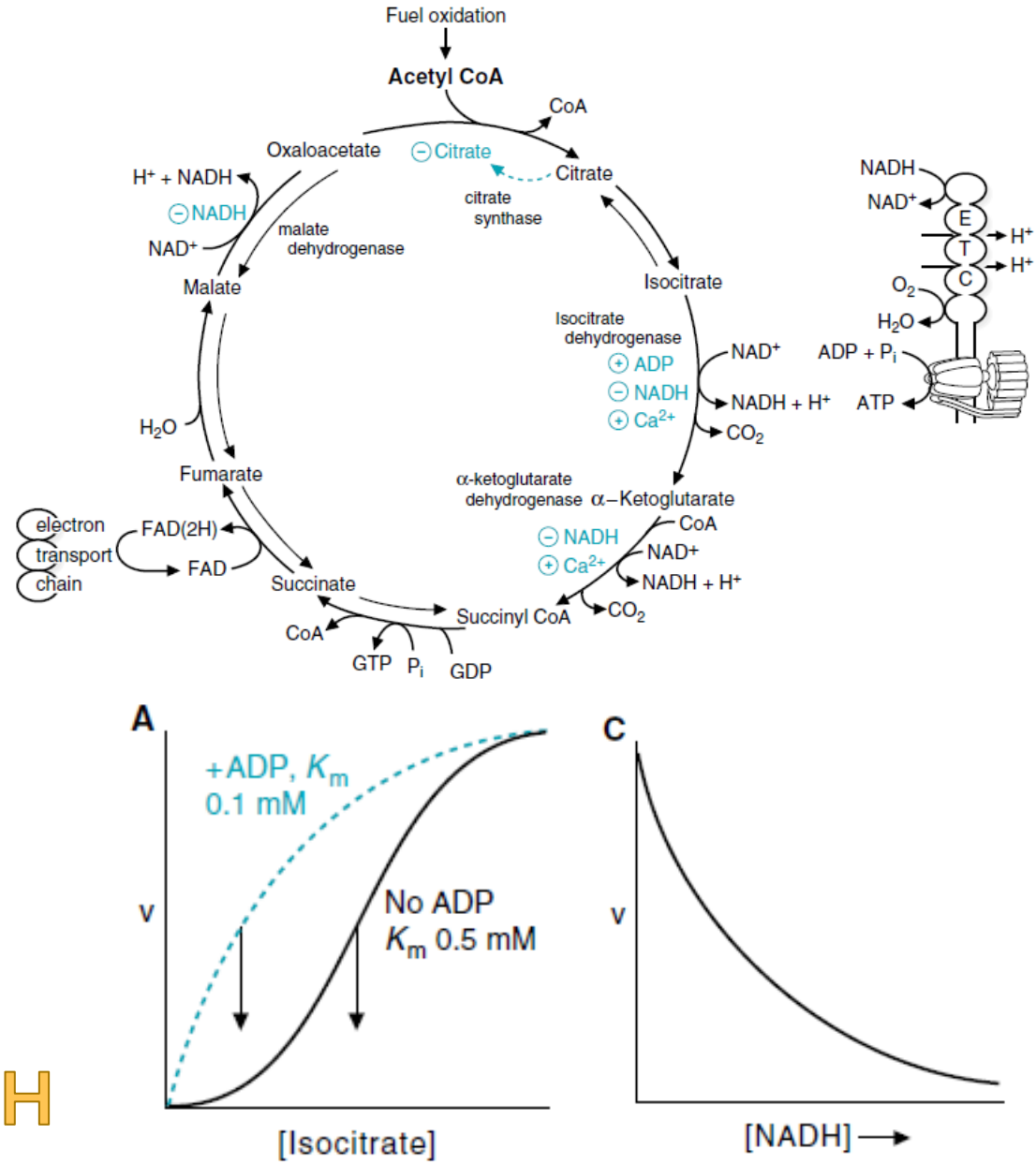


Citrate Synthase

- 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



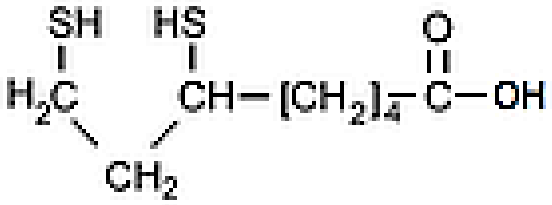
α-Ketoglutarate DH

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

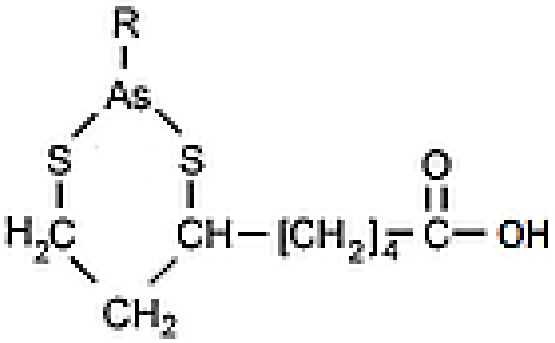
Oxidative decarboxylation of pyruvate (pyruvate to acetyl-CoA)

- Components & Coenzymes
- Regulation of PDH complex
- Deficiency of PDH: A deficiency in E1 component is the most common biochemical cause of congenital lactic acidosis (X-linked, no treatment)

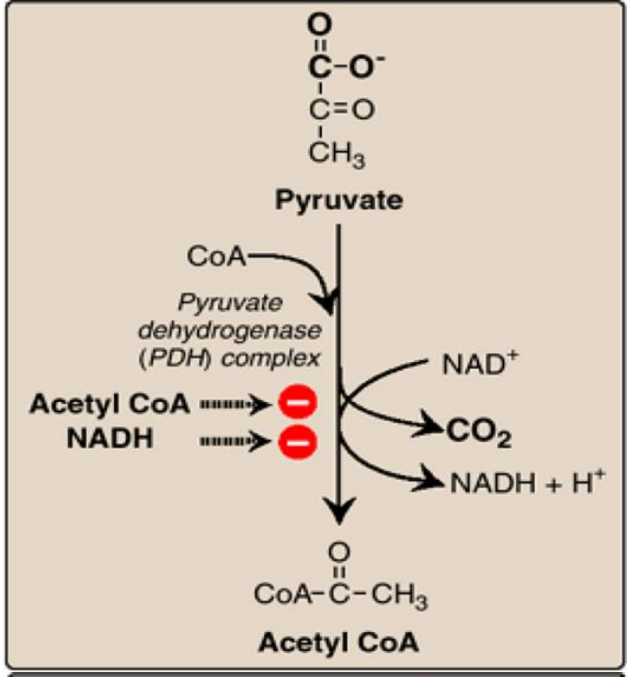
- Mechanism of arsenic poisoning

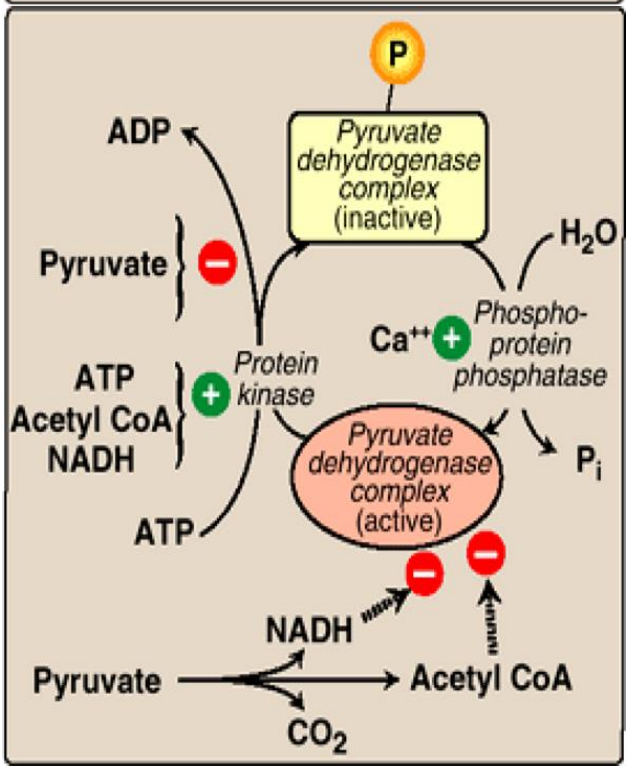


Dihydro lipoic acid



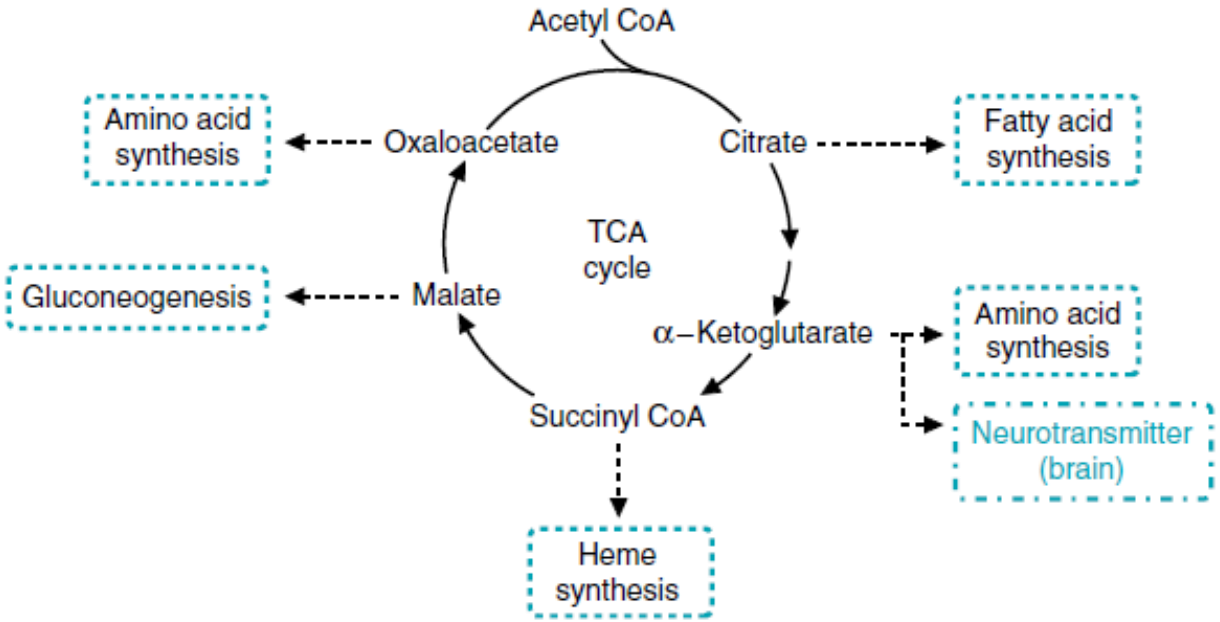
Arsenic-ringed lipoic acid





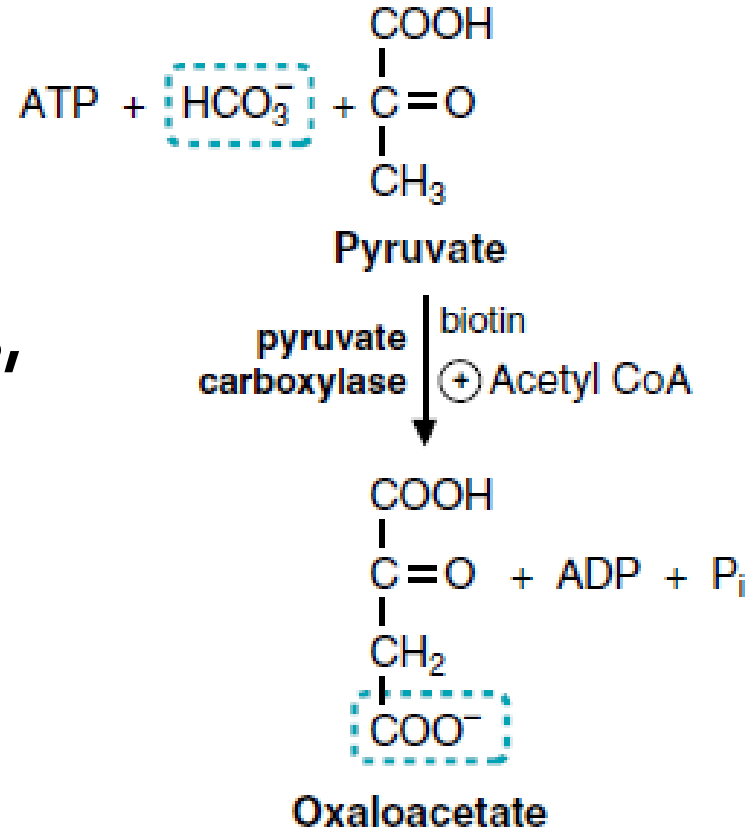
TCA Cycle Intermediates

- **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)