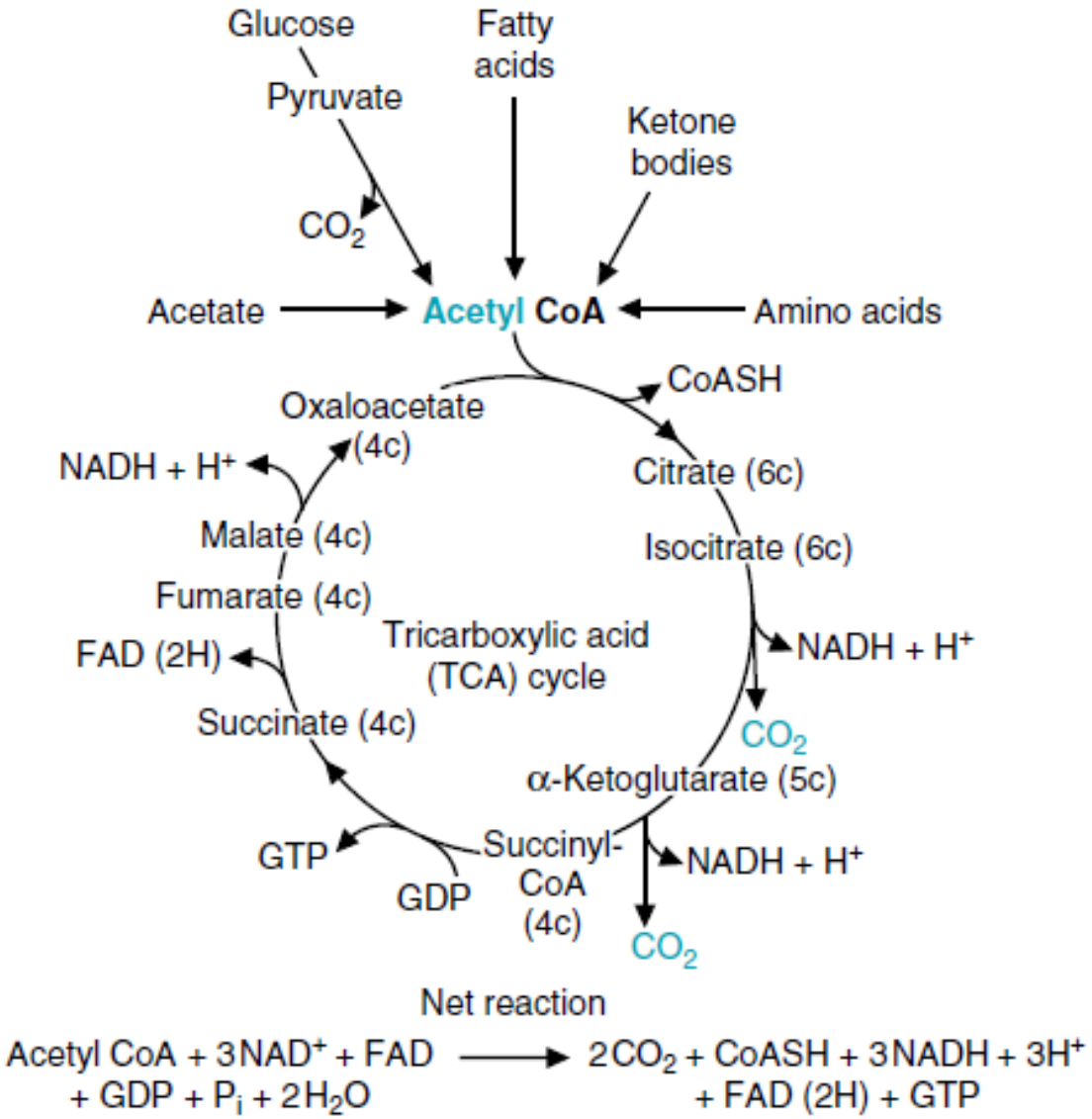
The Central Metabolic Hub

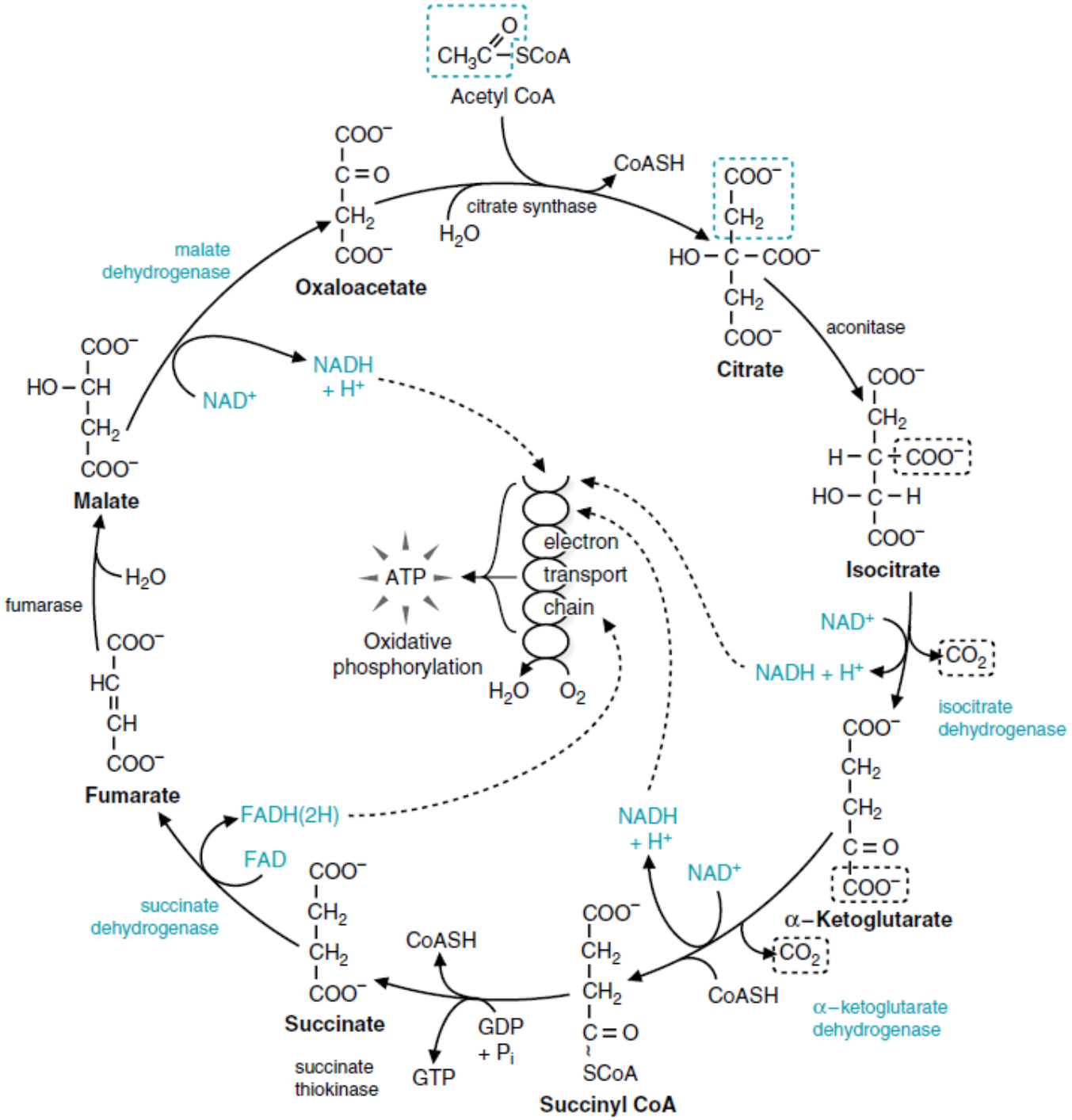
Prof. Nafez Abu Tarboush



COMPONENTS & STEPWISE REACTIONS

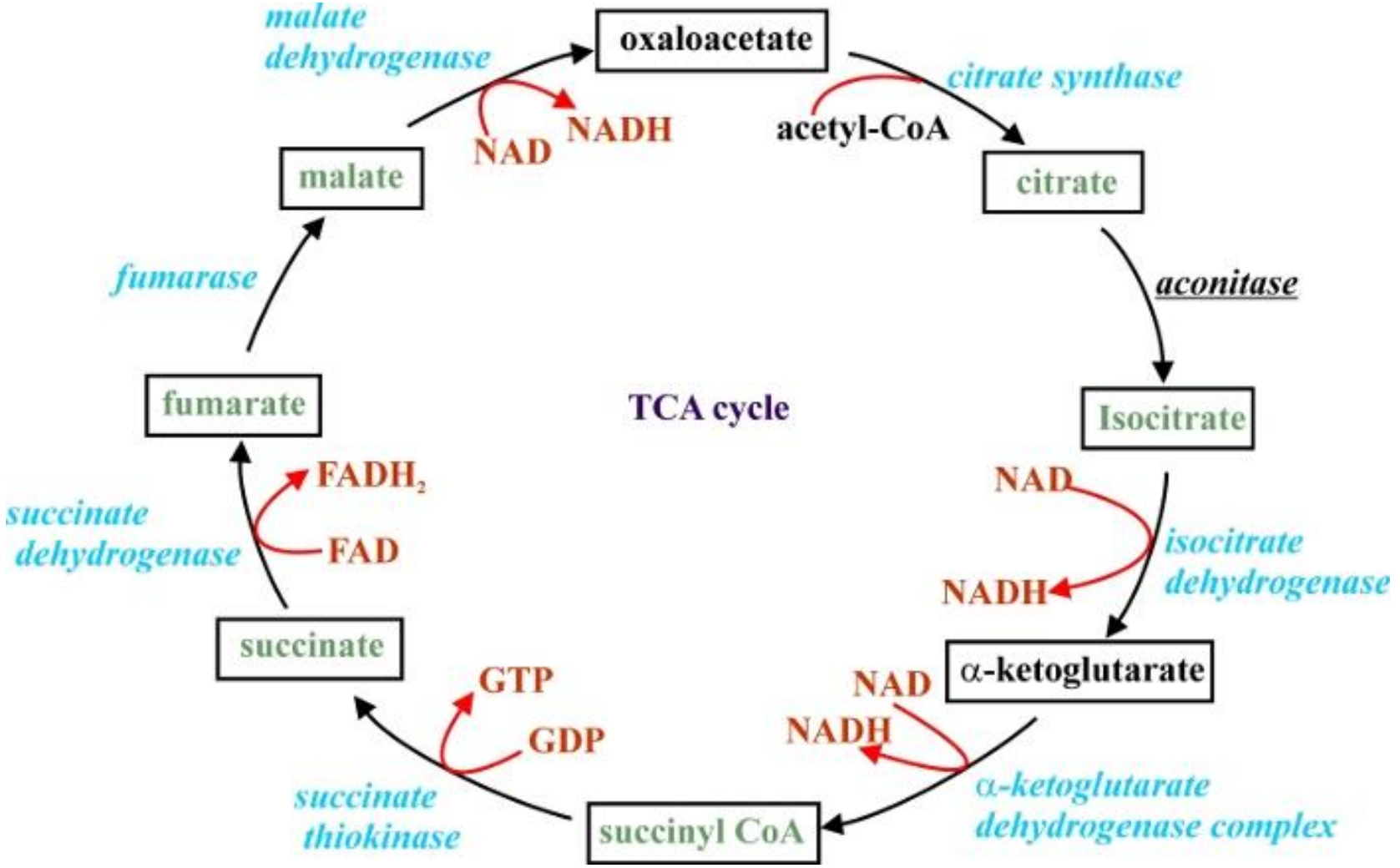
- **CIA Sent Soldiers For My Office**

COMPONENTS & STEPWISE REACTIONS



ENZYMES OF THE TCA CYCLE

- Citrate synthase
- Aconitase
- Isocitrate DH
- α-ketoglutarate DH
- Succinate thio-kinase
- Succinate DH
- Fumarase
- Malate DH



FORMATION OF CITRATE

What drives the reaction forward?

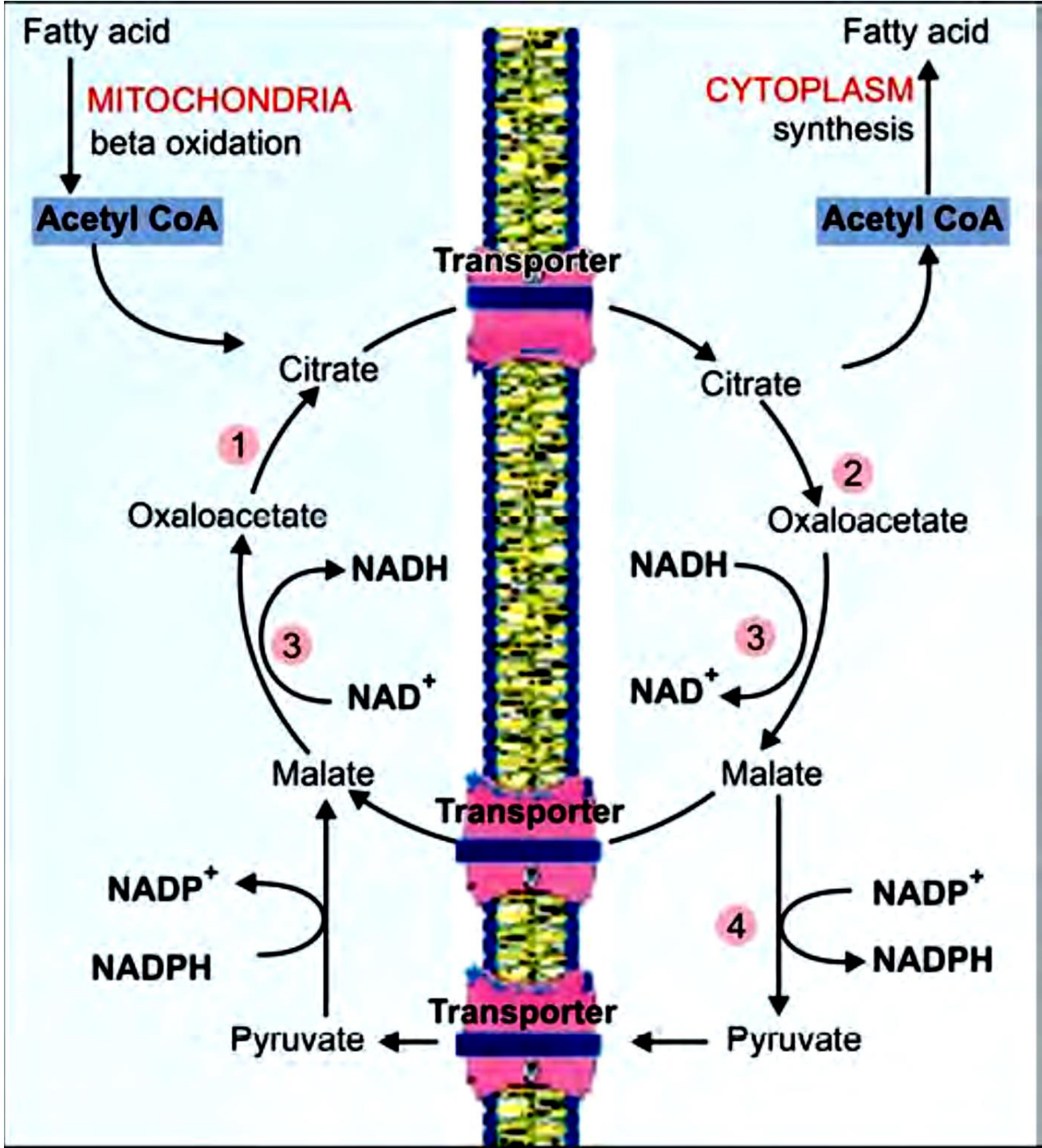
Is it reversible or irreversible?

Can it be reversed?

ATP-Citrate lyase or ATP-Citratase!

Activated by insulin and is highly expressed in lipogenic tissues like the liver and adipose tissue

Link to cancer metabolism



FORMATION AND OXIDATION OF ISOCITRATE

Control at the committed step of glycolysis

Fructose 6 - phosphate

ATP

ADP

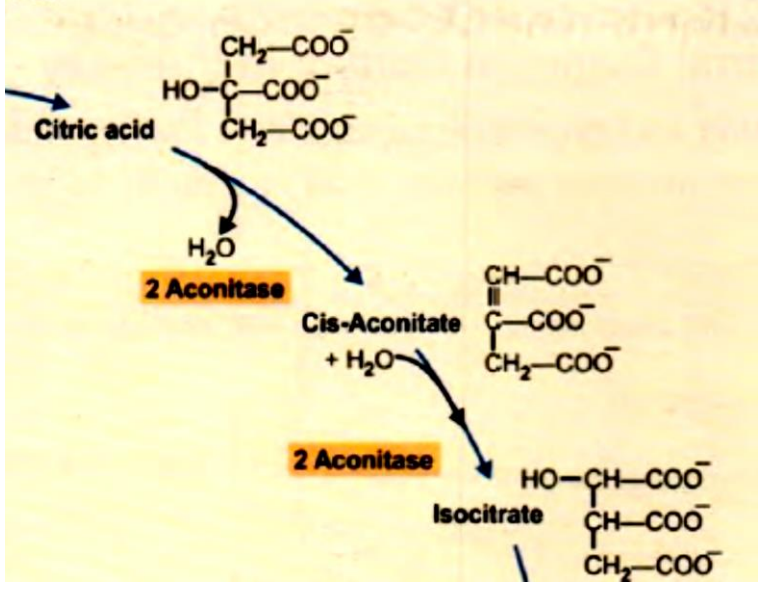
Phosphofructokinase

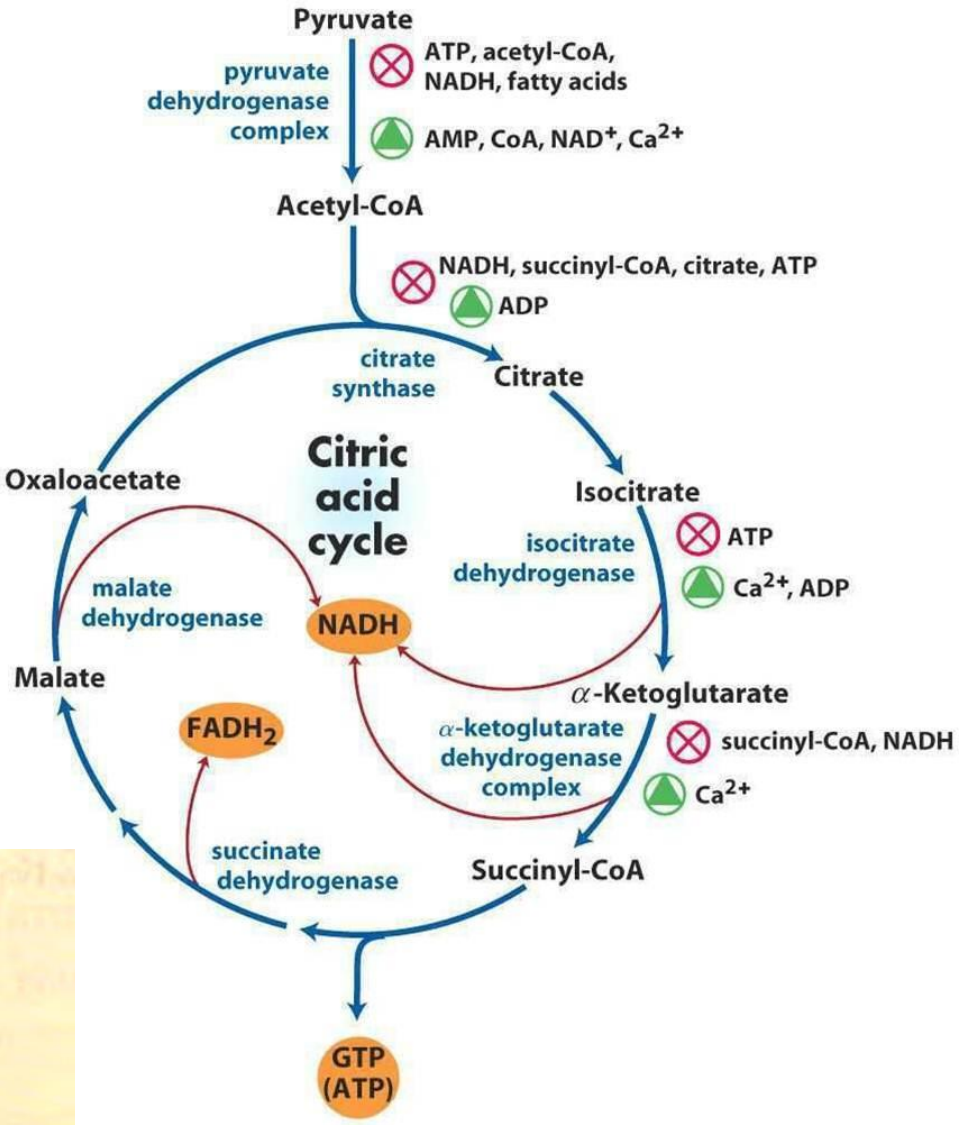
Activated by F-2,6 - BP

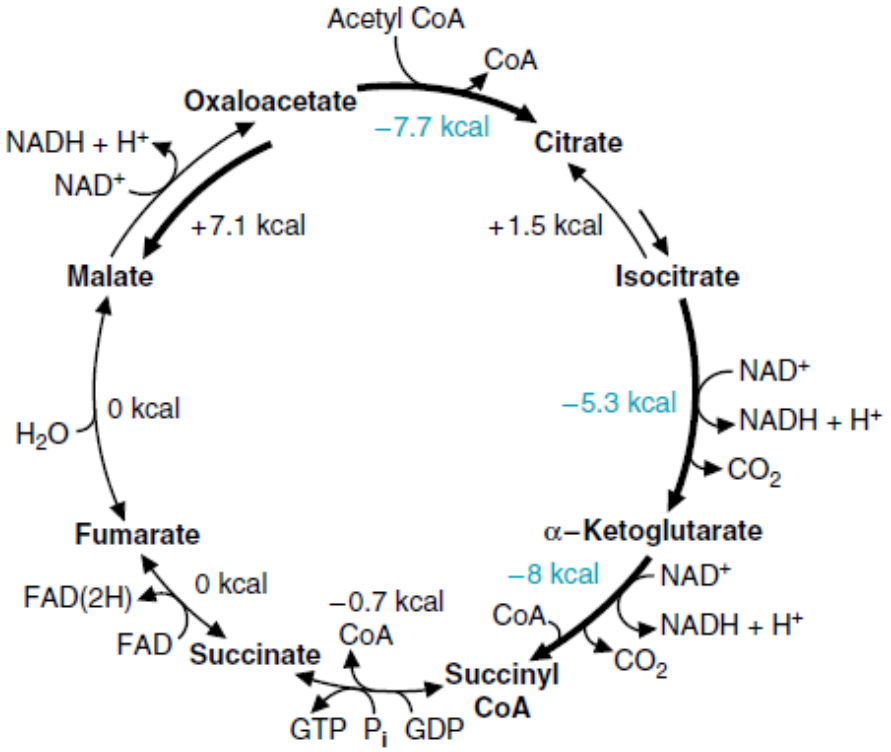
Activated by AMP

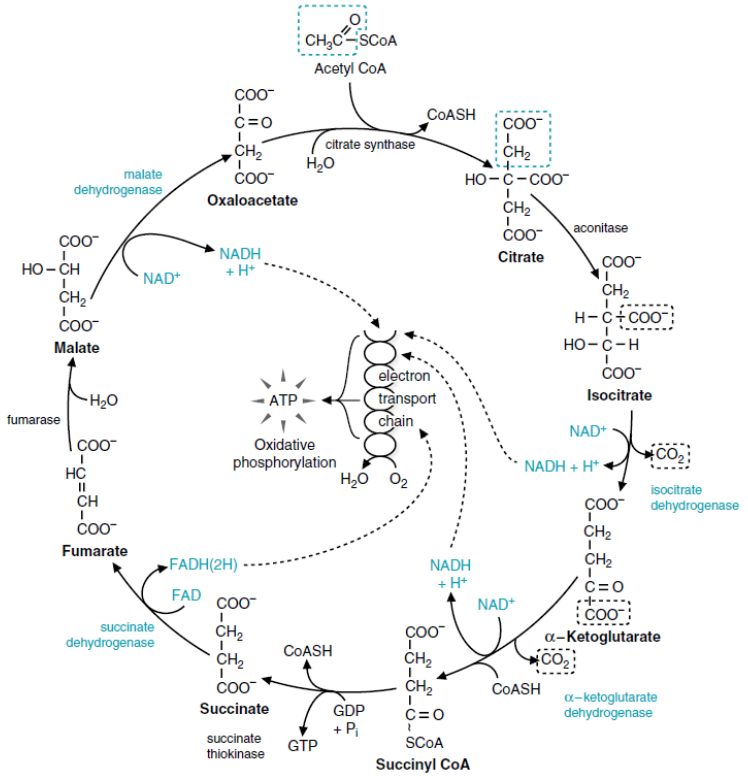
Inhibited by ATP and citrate

Fructose 1,6 - bisphosphate









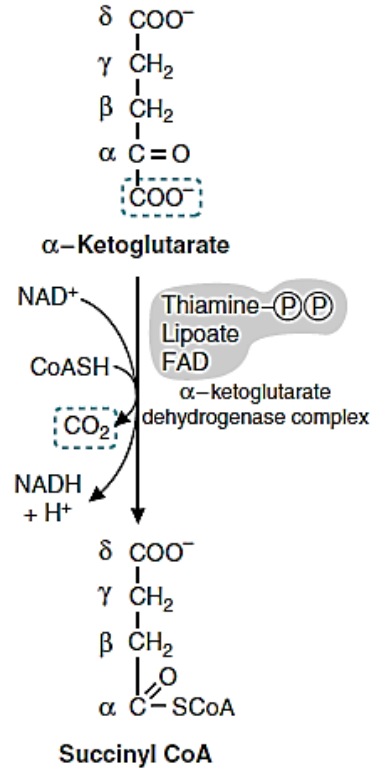
α-KETOGLUTARATE TO SUCCINYL COA

- **Oxidative decarboxylation**
- **Thiamine pyrophosphate, lipoic acid, and FAD**
- **Keto group oxidized to acid, CoA-SH, succinyl CoA**
- **Energy conserved as NADH, thioester bond**
- **The highest energy yield provided!**

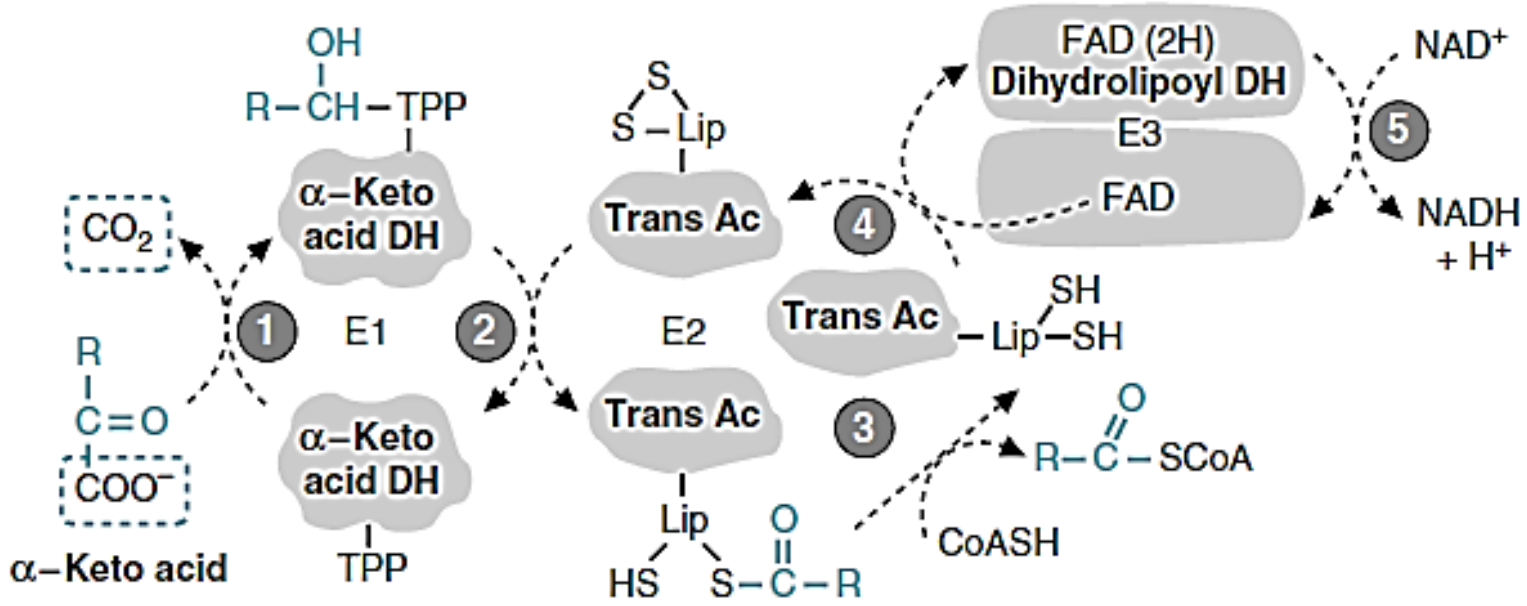
α-KETOACID DEHYDROGENASE COMPLEXES (TLCFN)

(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)

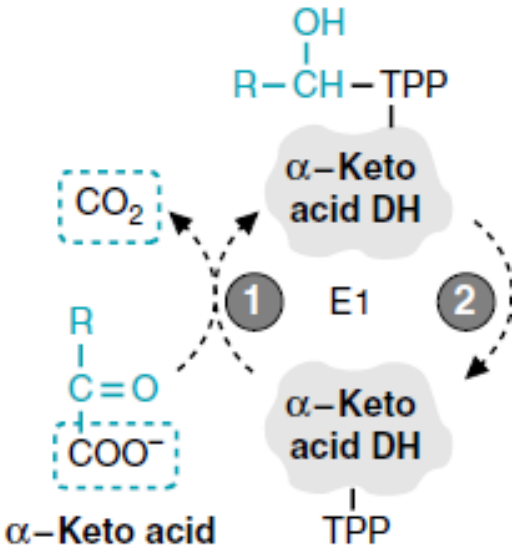


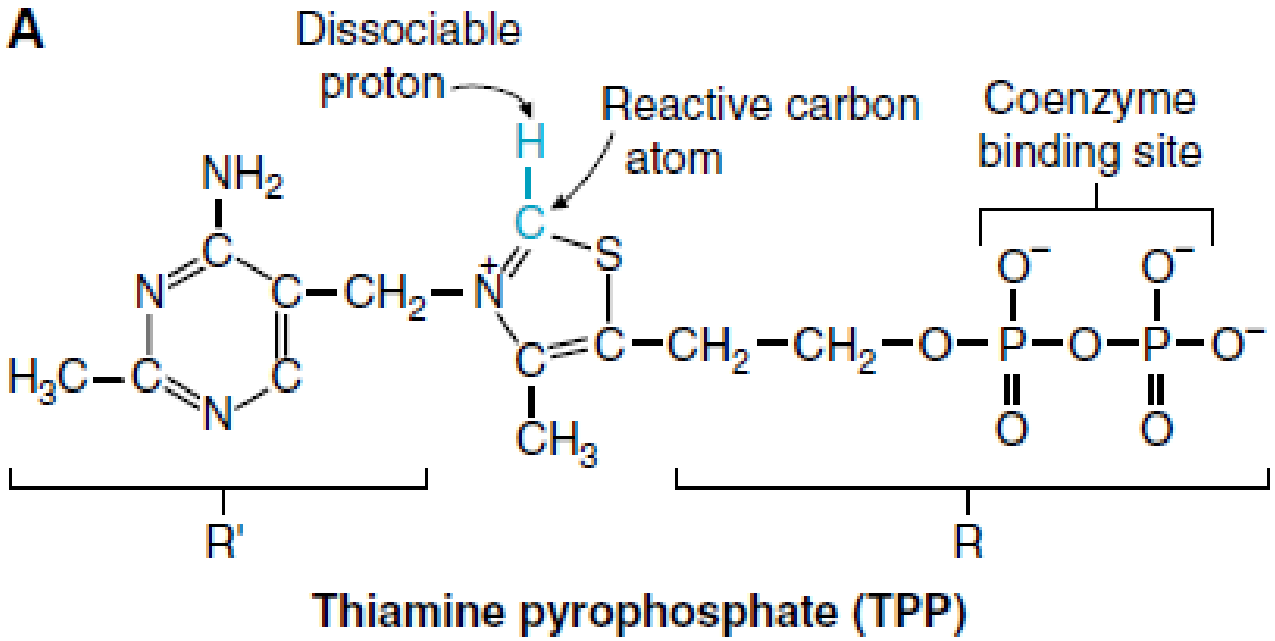
- E1, E2, & E3 are a decarboxylase (TPP), a transacylase (lipoate), & a dehydrogenase (FAD)



THIAMINE PYROPHOSPHATE

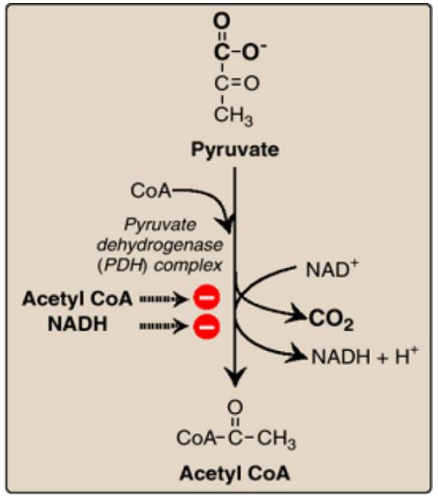
- Thiamine deficiency, α-ketoglutarate, pyruvate, & branched chain α-keto acids accumulate in the blood

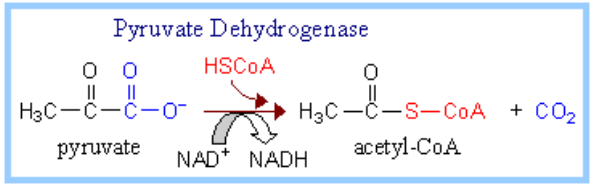


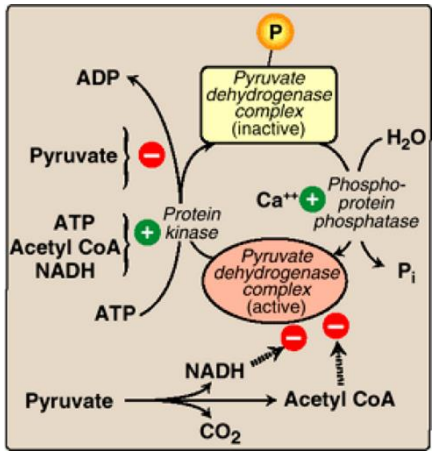


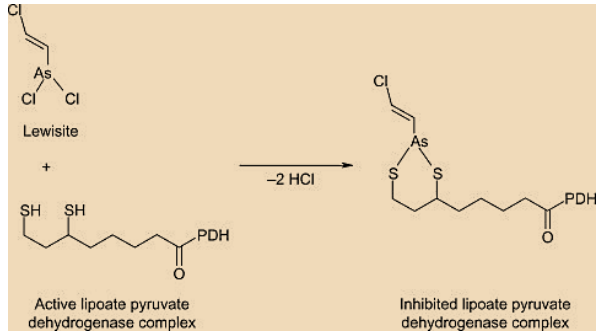
OXIDATIVE DECARBOXYLATION OF PYRUVATE

- Component enzymes
- Coenzymes
- Regulation of the pyruvate dehydrogenase complex
  - Pyruvate dehydrogenase deficiency: A deficiency in E_1 component is the most common biochemical cause of congenital lactic acidosis (X-linked, no treatment)
- Mechanism of arsenic poisoning









GENERATION OF GTP

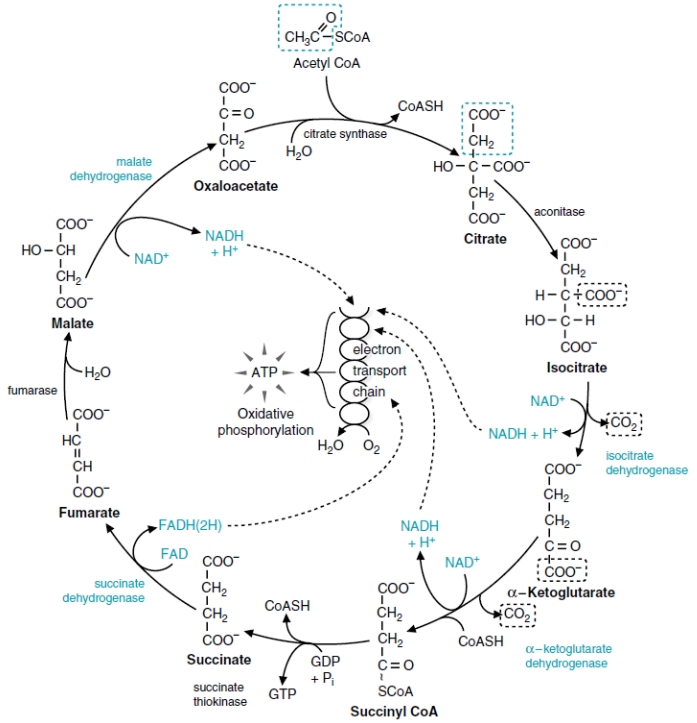
- Succinyl CoA thioester bond, succinate thiokinase, substrate level phosphorylation

GTP +ADP ↔ GDP + ATP

1,3-Diphophoglycerate + ADP ⟶ (Phosphoglycerate kinase) ⟵ 3-Phophoglycerate + ATP

Phosphoenolpyruvate + ADP ⟶ (Pyruvatekinase) ⟵ Pyruvate + ATP

SuccinylCoA +GDP ⟶ (SuccinylCoA Synthase) ⟵ Succinate +GTP



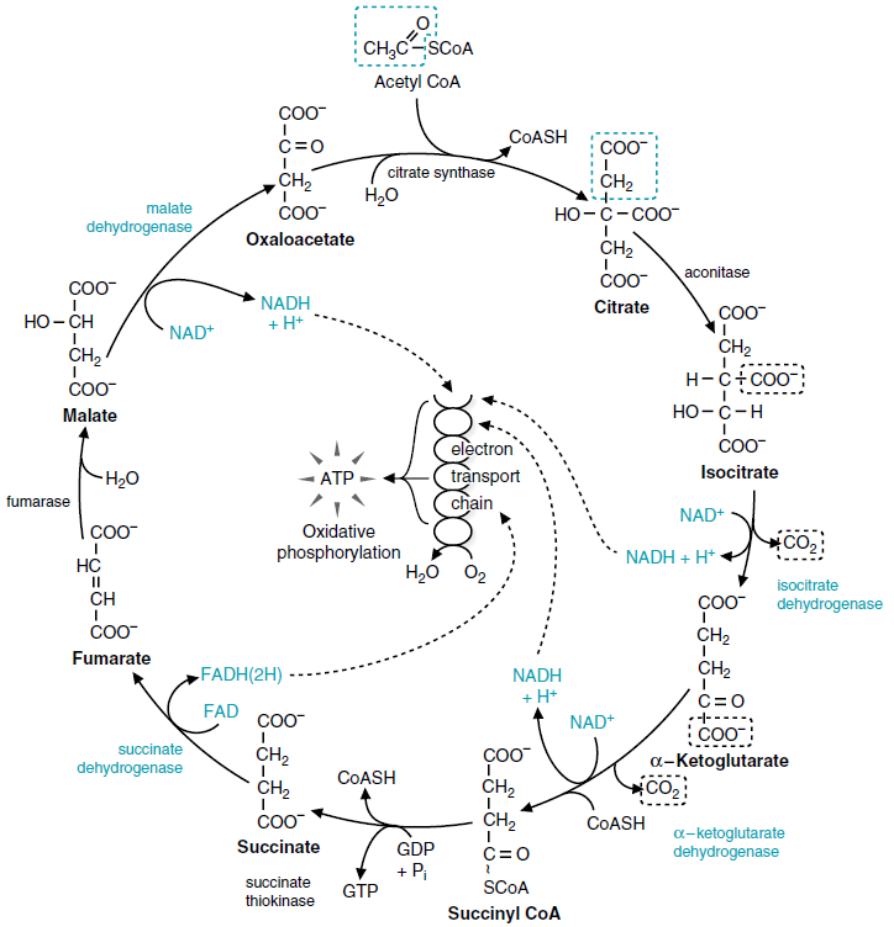
Critical Care

OXIDATION OF SUCCINATE TO OXALOACETATE

Oxidation of succinate to fumarate, succinate dehydrogenase, FAD

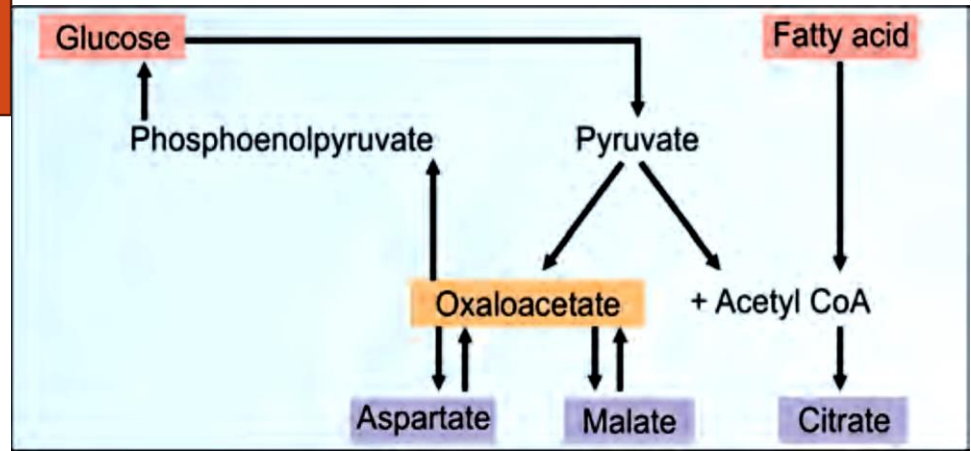
Fumarase, OH + H^+ from water, fumarate to malate

Alcohol group of malate oxidized to a keto group, NADH



Oxaloacetate as a Junction Point

- Viewed as a **catalyst**
- An important junction point in metabolism



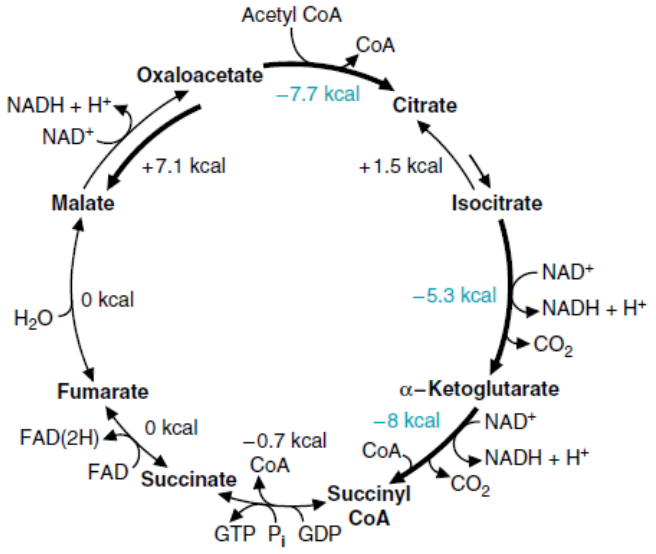
BIOENERGETICS OF TCA CYCLE

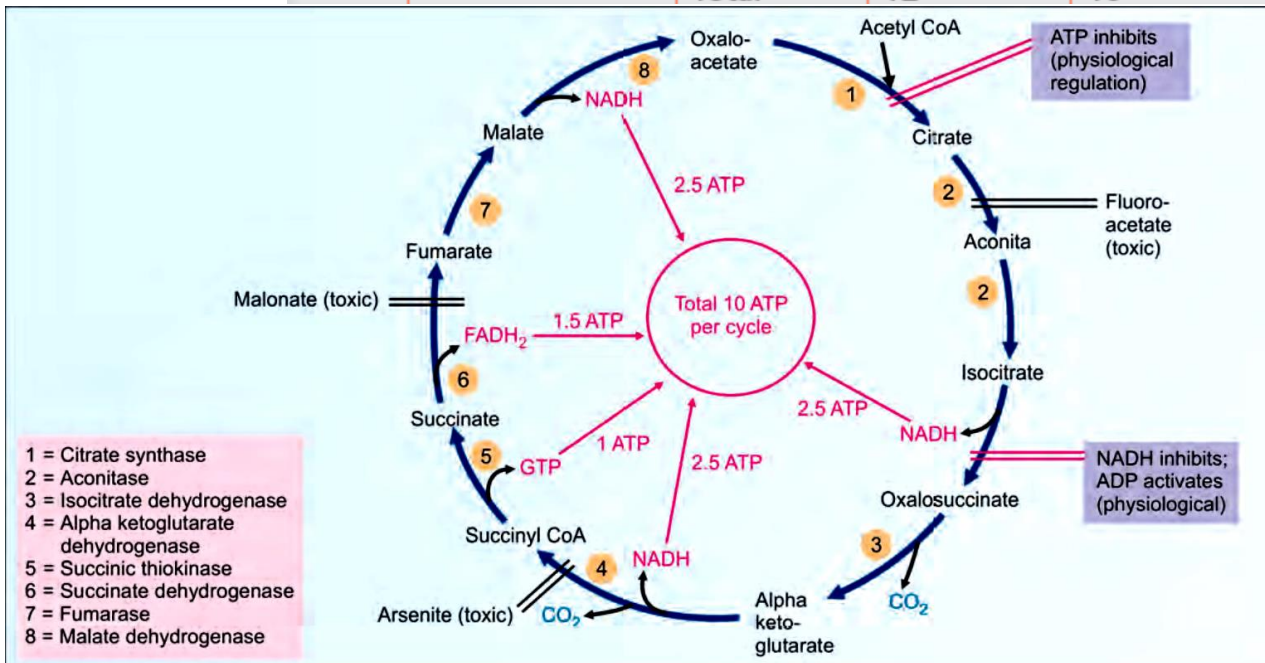
- **Like all pathways, overall net -ΔG (-228 kcal/mole), not 100%**
- **NADH, FAD(H2), and GTP (10ATP), 207 Kcal, 90%**
- **Three reactions have large (-ve) values**
- **Physiologically irreversible, low products**

TABLE 19.1: ATP generation steps

Step No	Reactions	Co-enzyme	ATPs (old-calculation)	ATPs (new calculation)
3	Isocitrate → alpha keto glutarate	NADH	3	2.5
4	Alpha keto glutarate → succinyl CoA	NADH	3	2.5
5	Succinyl CoA→Succinate	GTP	1	1
6	Succinate → Fumarate	$FADH_2$	2	1.5
8	Malate → Oxalo acetate	NADH	3	2.5
		Total	12	10

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





NET RESULT OF THE CYCLE & ITS SIGNIFICANCE

TABLE 19.2: Stoichiometry of the TCA cycle

Acetyl CoA Oxaloacetate FAD 3NAD+ GDP + PI GTP	→	2 CO_2 +CoA-SH Oxaloacetate $FADH_2$ 3 NADH

Why?

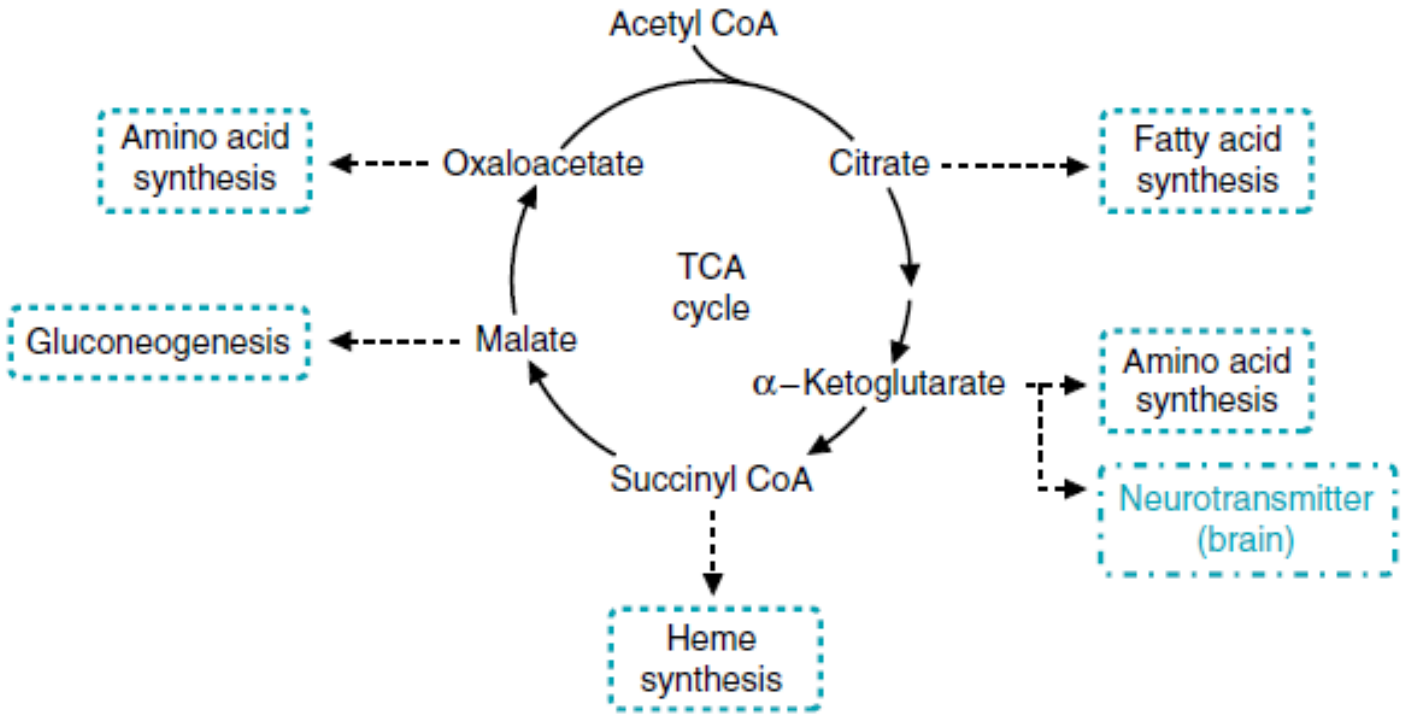
Box 19.1: Significance of citric acid cycle

1. Complete oxidation of acetyl CoA
2. ATP generation
3. Final common oxidative pathway
4. Integration of major metabolic pathways
5. Fat is burned on the wick of carbohydrates
6. Excess carbohydrates are converted as neutral fat
7. No net synthesis of carbohydrates from fat
8. Carbon skeletons of amino acids finally enter the citric acid cycle
9. Amphibolic pathway
10. Anaplerotic role.

- ✓ **Fats are burned in the fire of carbohydrates**
- ✓ **Fat cannot be converted to glucose because pyruvate dehydrogenase reaction is an irreversible step**

FAT IS BURNED ON THE WICK OF CARBOHYDRATES

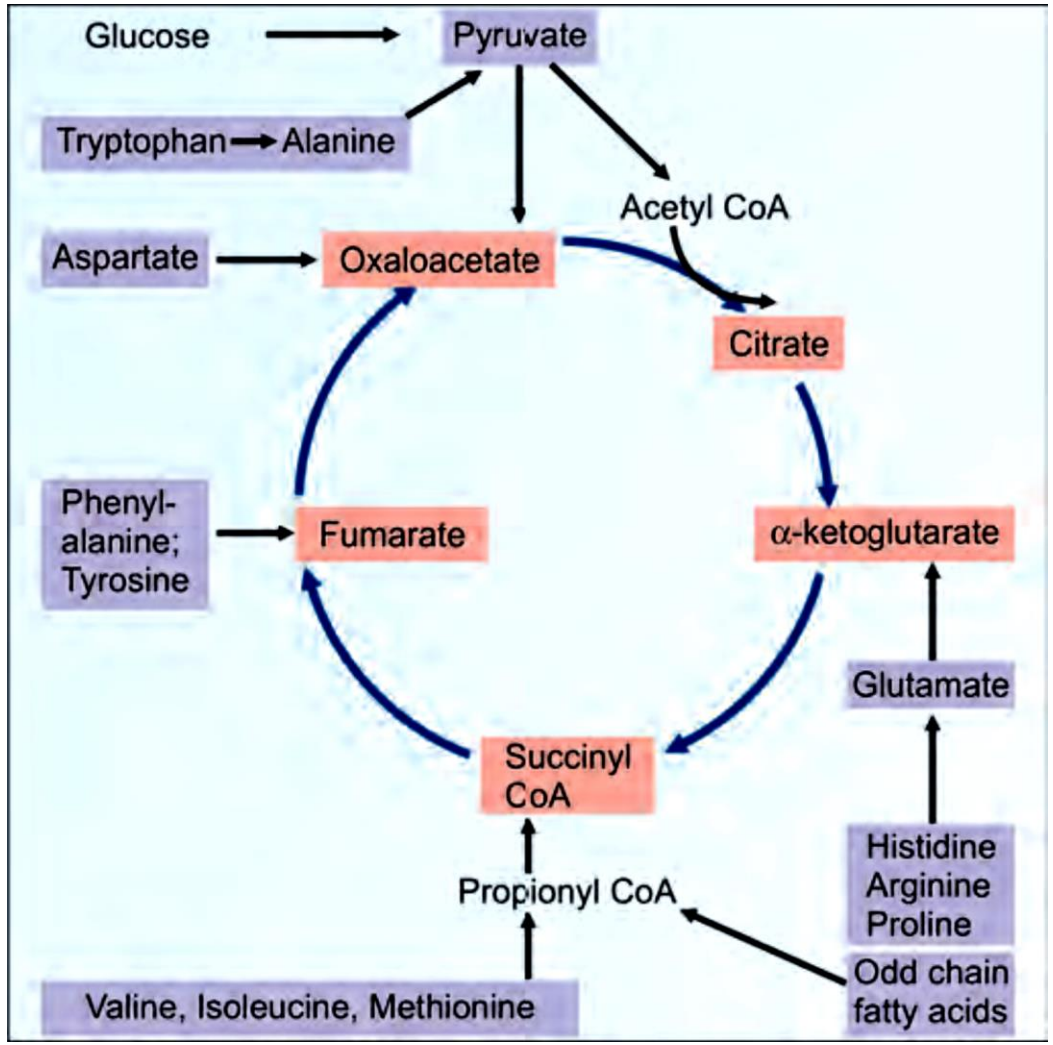
- What Happens in a Low-Carbohydrate State? (The "Fire Goes Out")
  - **OAA is Drained and Pyruvate is Diverted**
- **Krebs Cycle Stall!!!**
- **The Pathological Consequences: Ketogenesis**
- **Clinical Correlations**
  - **Diabetic Ketoacidosis (DKA), Starvation, Weight Loss Diets**

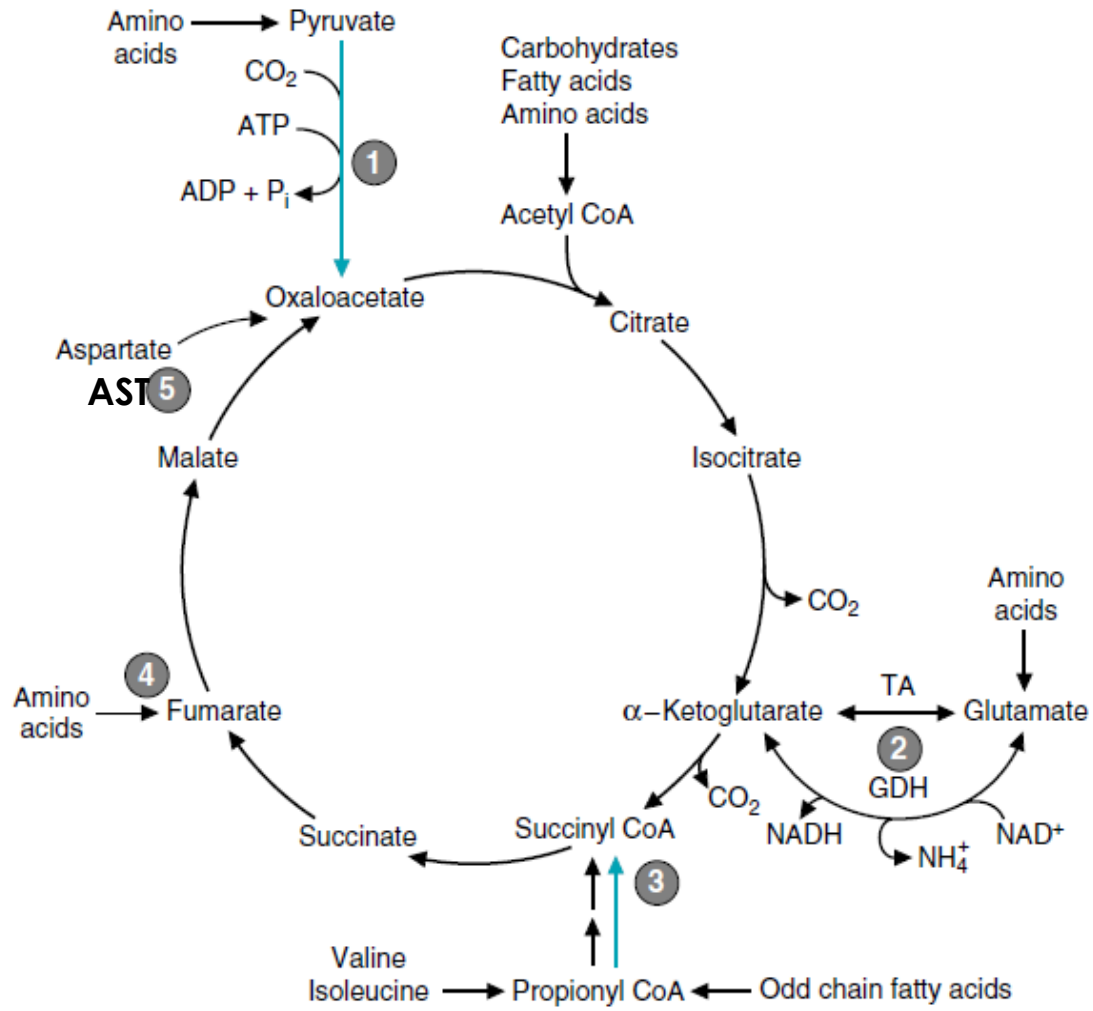


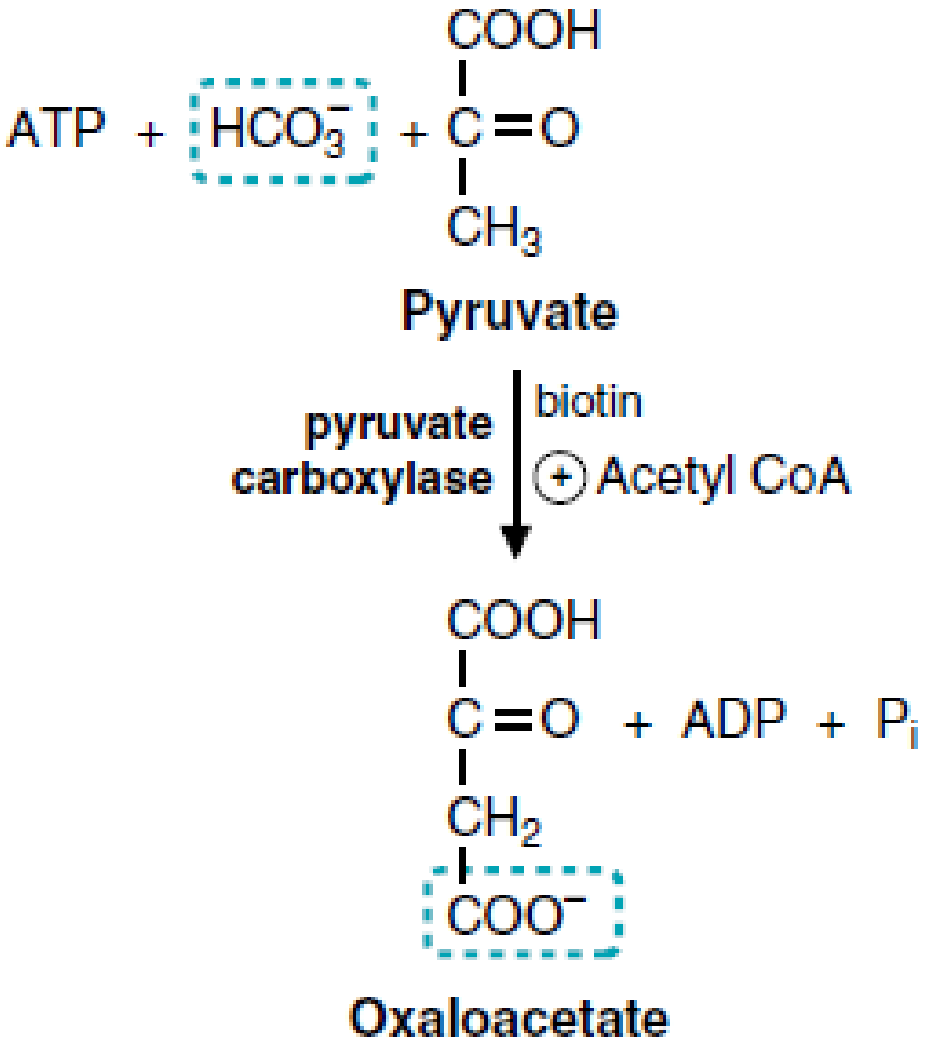
CATAPLEROSIS

- 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)
  - (OAA, Aspartate, Asparagine, Gluconeogenesis, liver)

ANAPLEROTIC ROUTES (AMINO ACID DEGRADATION)



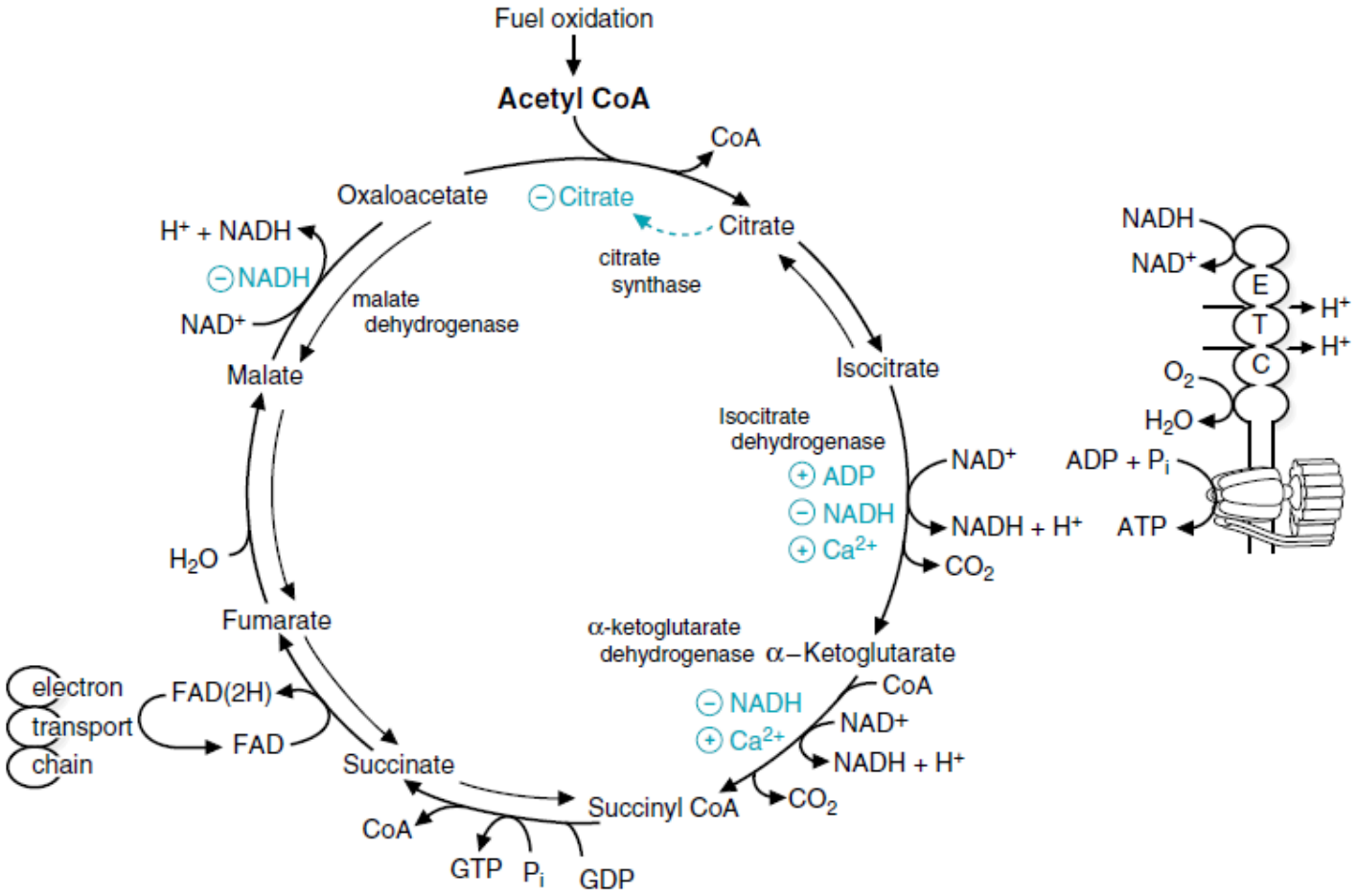




ANAPLEROTIC REACTIONS

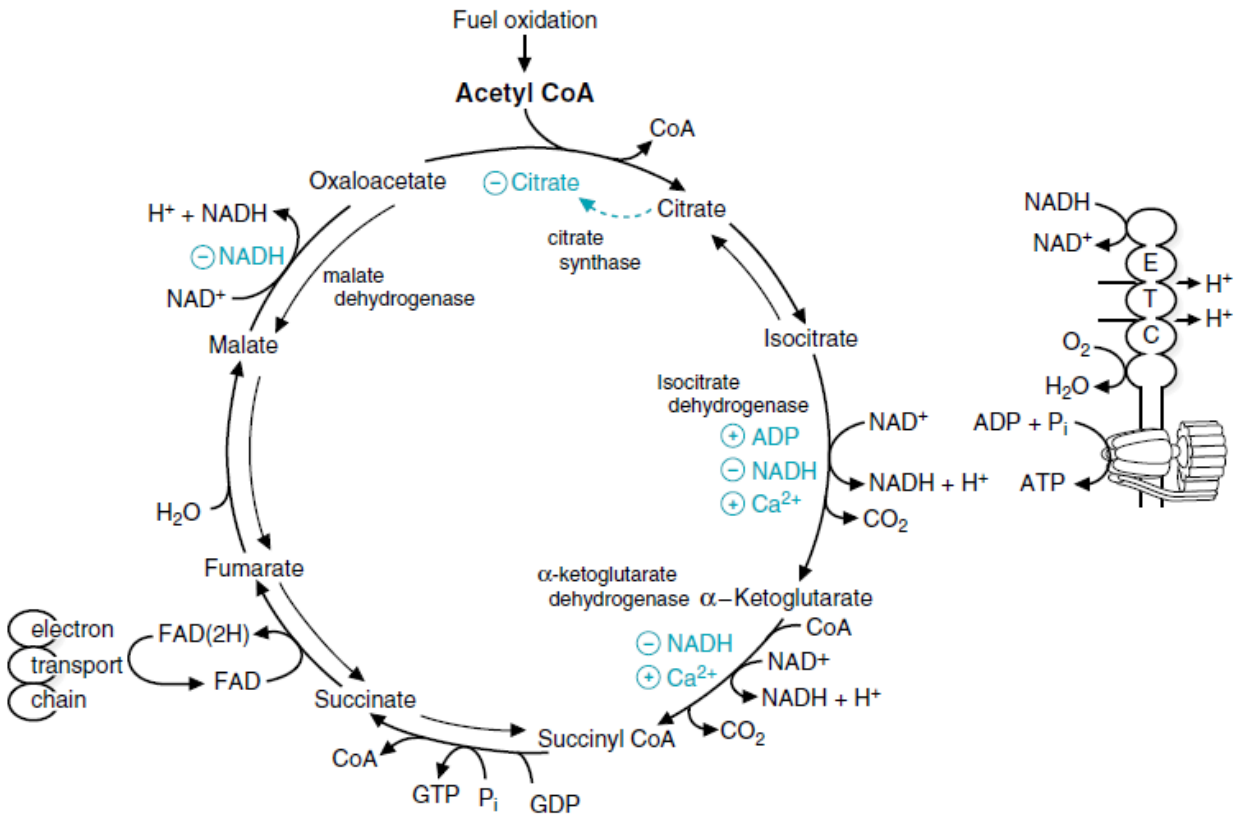
- Pathways or reactions that replenish the intermediates of the TCA cycle
- Pyruvate Carboxylase is a major anaplerotic enzyme (requires biotin)
- Found in many tissues, liver, kidneys, brain, adipocytes, and fibroblasts
- Very high conc. In liver and kidney (gluconeogenic pathway)
- Activated (acetyl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

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

REGULATION – CITRATE & CITRATE SYNTHASE



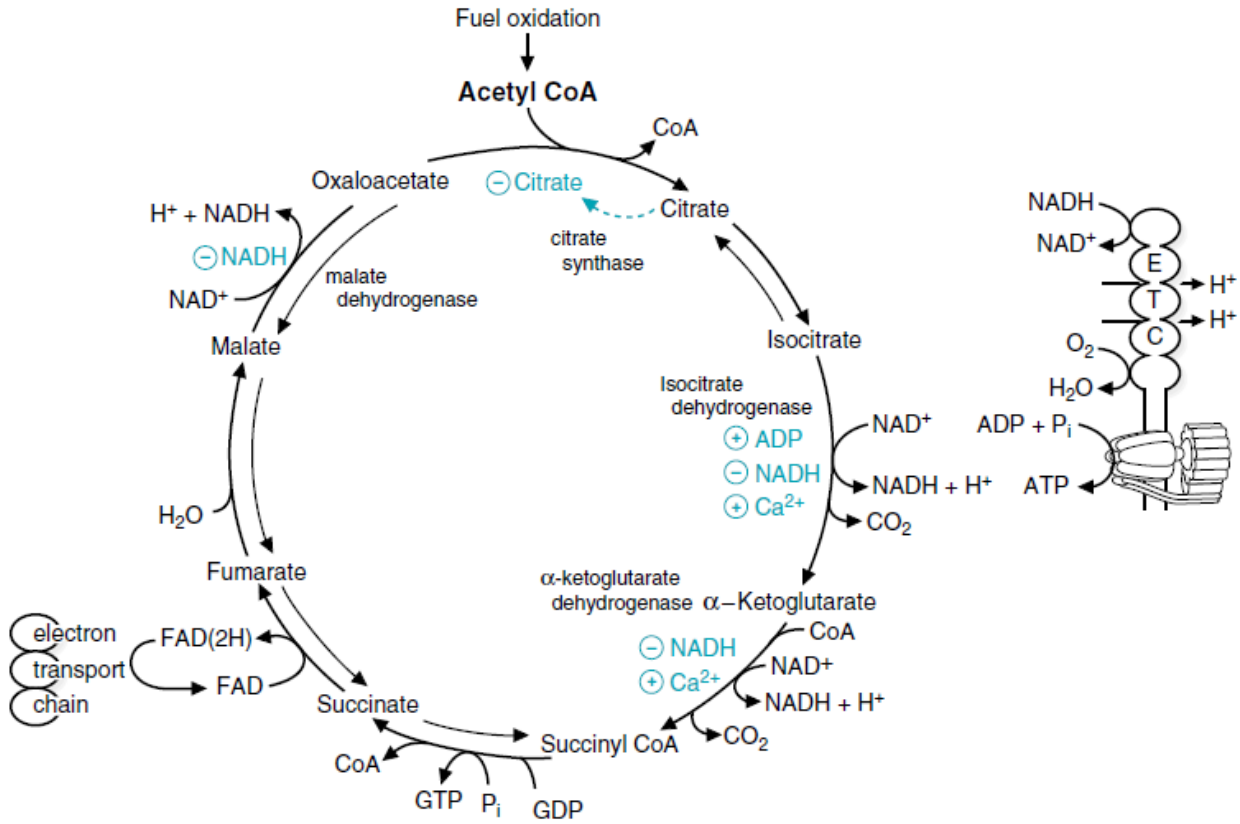
- Rate regulated by oxaloacetate & citrate (inhibitor)
- ATP: allosteric inhibitor
- Effect of citrate:
  - Allosterically inhibits PFK, the key enzyme of glycolysis
  - Stimulates fructose-1,6-bisphosphatase, a key enzyme of gluconeogenesis
  - Activates acetyl CoA carboxylase, a key enzyme of fatty acid synthesis

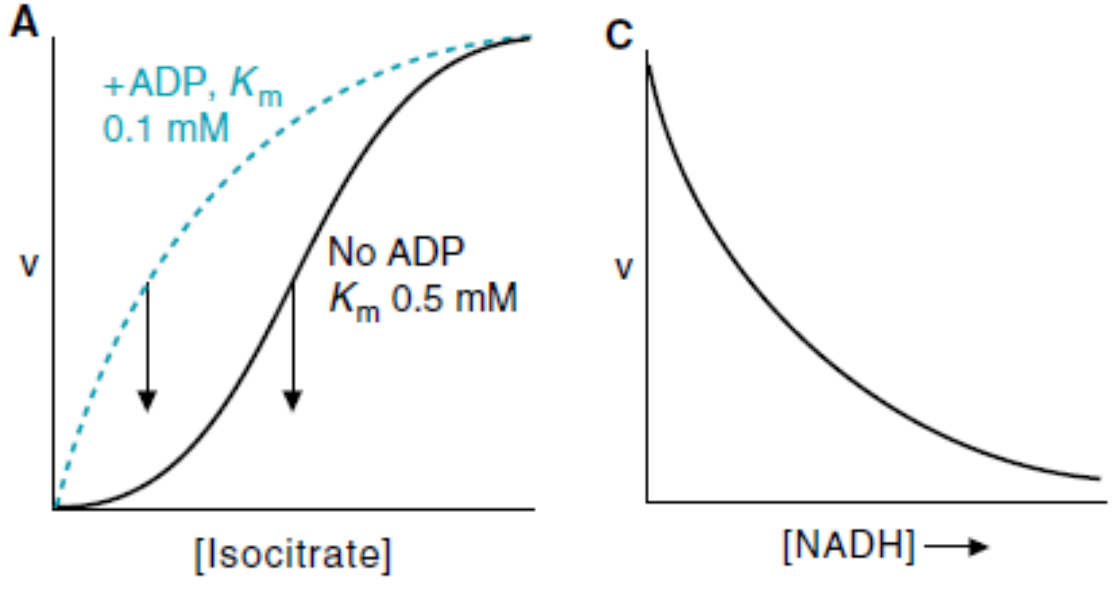
ISOCITRATE DH

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

α-Ketoglutarate DH

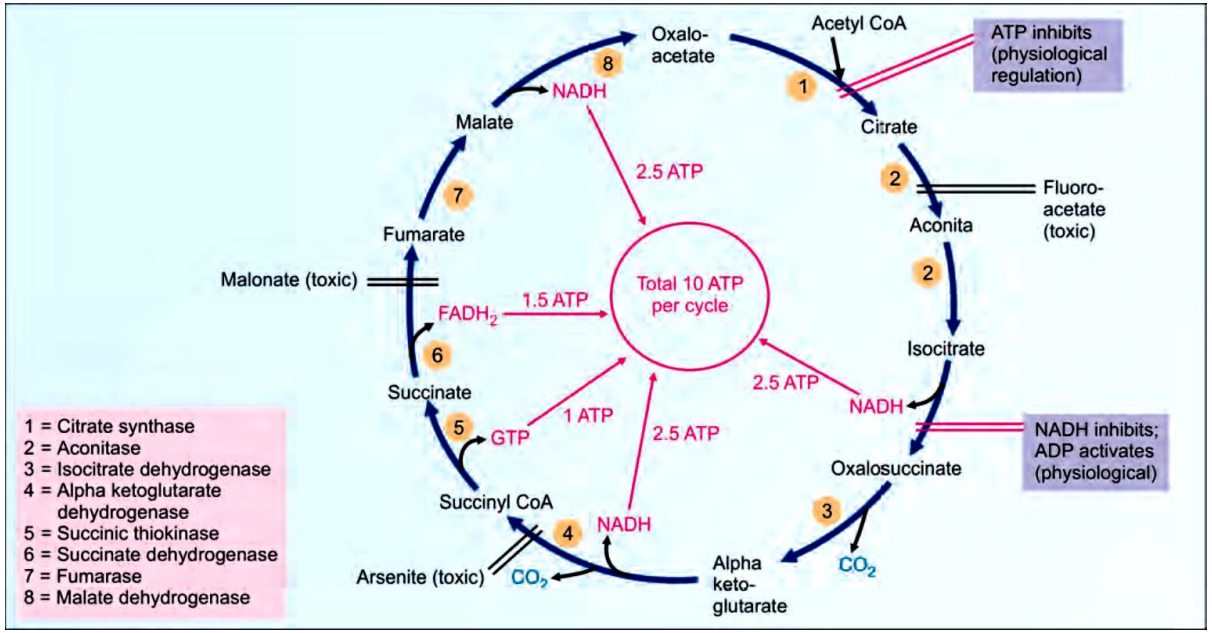
- Inhibited: NADH, succinyl CoA, GTP
- Activated: Ca^{+2}





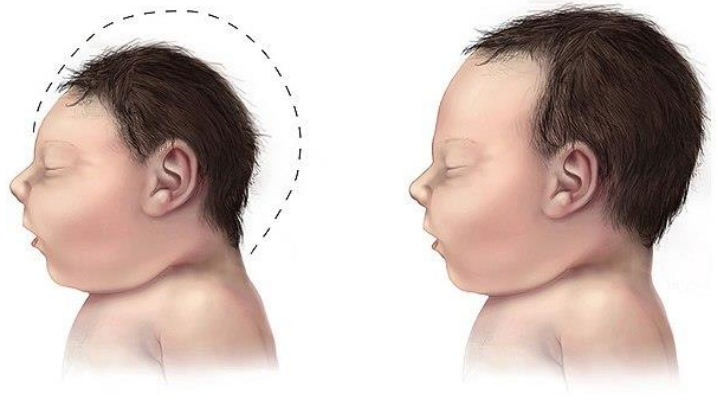
INHIBITORS OF TCA CYCLE (PHYSIOLOGICAL?)

- A. Aconitase (citrate to aconitate) is inhibited by fluoroacetate (non-competitive inhibition)
- B. Alpha ketoglutarate dehydrogenase (alpha keto-glutarate to succinyl CoA) is inhibited by Arsenite (non-competitive inhibition)
- C. Succinate dehydrogenase (succinate to fumarate) is inhibited by malonate (competitive inhibition)

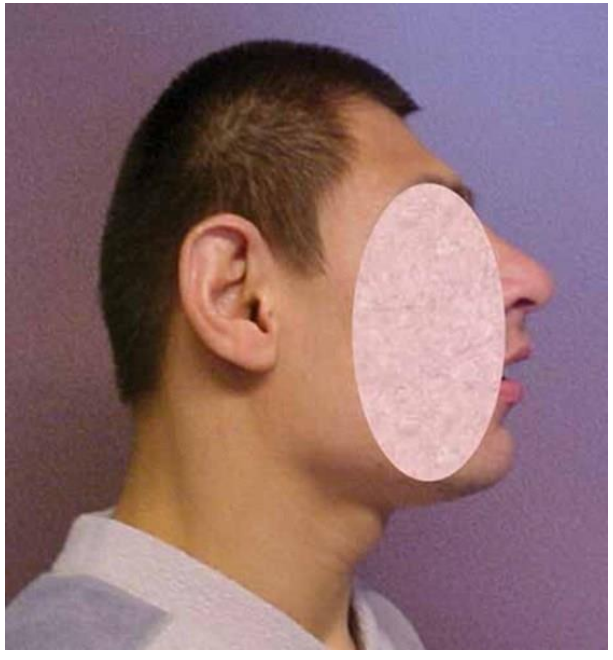


INBORN ERRORS OF METABOLISM

- **PDC Deficiency:**
  - Most common enzymatic cause of primary lactic acidosis
  - Often presenting in neonates with severe neurological impairment
  - Treatment involves a ketogenic diet to provide an alternative fuel source for the brain.



- **Fumarase Deficiency:** Causes severe encephalopathy, seizures, and developmental delay due to the accumulation of fumarate.



ONCOMETABOLITES AND CANCER:

- **IDH Mutations:**
  - Common in gliomas and acute myeloid leukemia (AML)
  - Confer a neomorphic activity that produces 2-hydroxyglutarate (2-HG): a competitive inhibitor of α-KG-dependent dioxygenases, leading to a hypermethylation of DNA and histones
  - This epigenetic dysregulation blocks cellular differentiation and promotes tumorigenesis.
- **SDH and FH Mutations:**
  - Cause hereditary paragangliomas and leiomyomatosis, respectively.
  - Accumulating succinate or fumarate inhibits prolyl hydroxylases (PHDs), leading to the stabilization of HIF-1α under normal oxygen conditions (pseudohypoxia).
  - This activates angiogenic and glycolytic programs, driving the Warburg effect and tumor growth.

NEURODEGENERATION

- Impaired mitochondrial function is the hallmark of neurodegenerative diseases like Parkinson's and Alzheimer's.
- The resulting energy deficit, oxidative stress, and disrupted calcium buffering contribute to excitotoxicity and neuronal death.