Krebs Cycle

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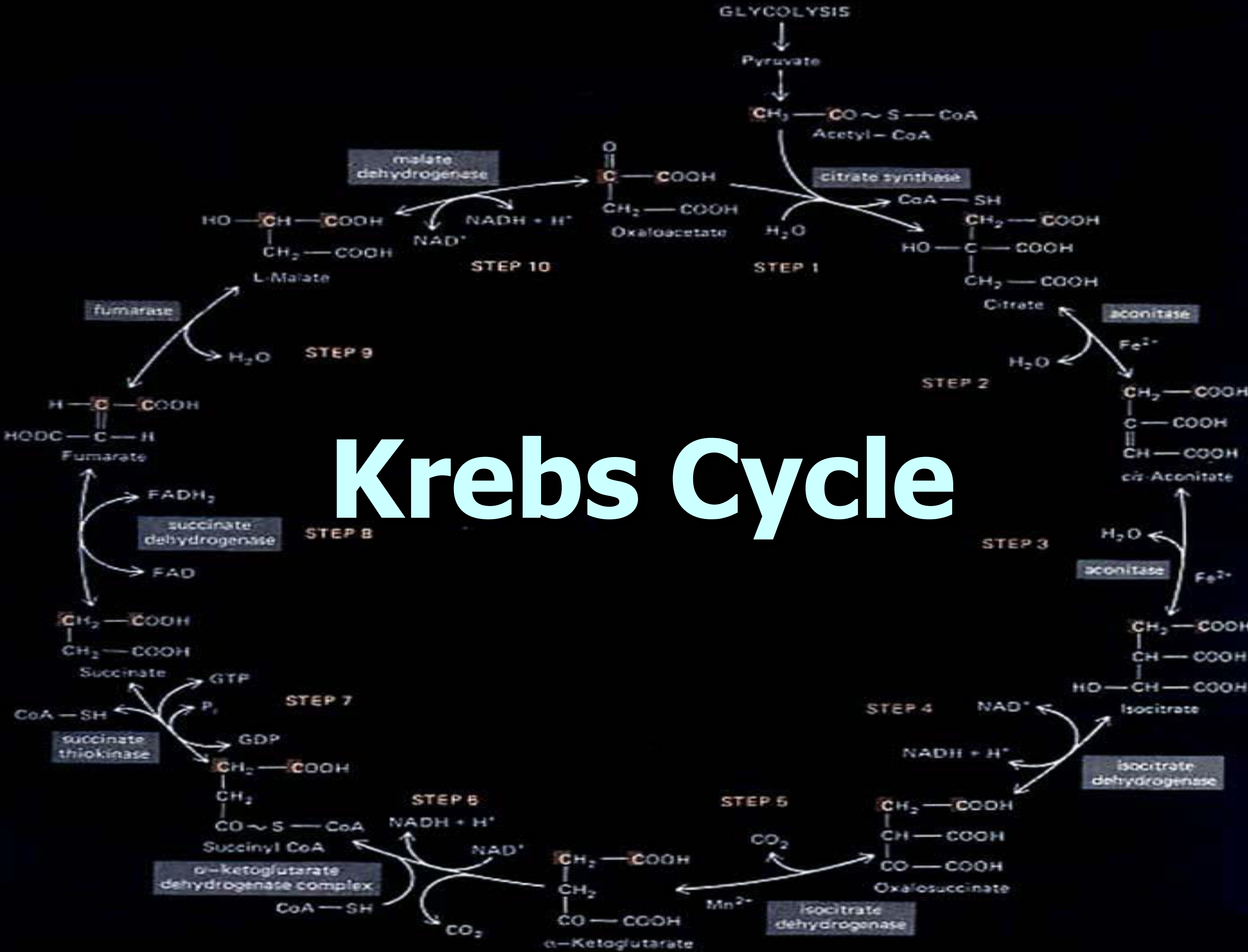
Krebs Cycle



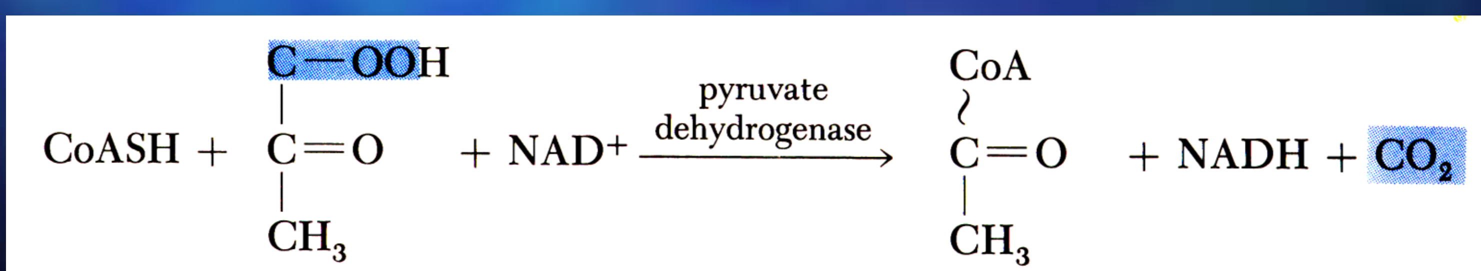
GLYCOLYSIS
Pyruvate
CH3 — CO ~ S — CoA
Acetyl — CoA
citrate synthase
CoA — SH
H2O
STEP 1
O
C — COOH
CH2 — COOH
Oxaloacetate
CH2 — COOH
HO — C — COOH
CH2 — COOH
Citrate
aconitase
Fe2+
H2O
STEP 2
CH2 — COOH
C — COOH
CH — COOH
cis-Aconitate
H2O
aconitase
Fe2+
STEP 3
CH2 — COOH
CH — COOH
HO — CH — COOH
Isocitrate
NAD+
NADH + H+
STEP 4
isocitrate dehydrogenase
CH2 — COOH
CH — COOH
CO — COOH
Oxalosuccinate
CO2
STEP 5
Mn2+
isocitrate dehydrogenase
CH2 — COOH
CH2
CO — COOH
α-Ketoglutarate
STEP 6
NADH + H+
NAD+
CoA — SH
CO2
α-ketoglutarate dehydrogenase complex
CH2 — COOH
CH2
CO ~ S — CoA
Succinyl CoA
succinate thiokinase
GTP
Pi
GDP
CoA — SH
STEP 7
CH2 — COOH
CH2 — COOH
Succinate
FADH2
FAD
succinate dehydrogenase
STEP 8
H — C — COOH
HOOC — C — H
Fumarate
fumarase
H2O
STEP 9
HO — CH — COOH
CH2 — COOH
L-Malate
malate dehydrogenase
NADH + H+
NAD+
STEP 10

Krebs Cycle (KC)

- Also known as TCA cycle, or citric acid cycle
- Reactions of KC occur in mitochondrial matrix
- Common final degradative pathway for breakdown of monomers of CHO, fat and protein to CO_2 and H_20
  - Electrons removed from acetyl groups and attached to NAD^+ and FAD
  - Small amount of ATP produced from substrate level phosphorylation
- KC also provides intermediates for anabolic functions (eg gluconeogenesis)

Pyruvate → Acetyl CoA

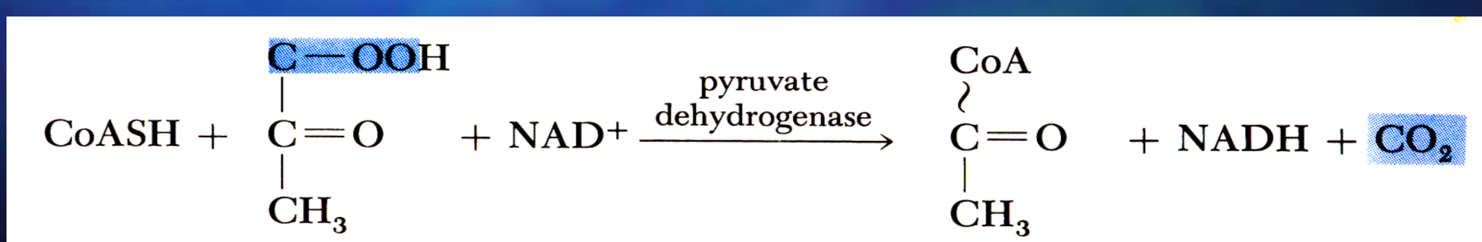
- Pyruvate produced in cytosol and transported into mitochondria
- Cannot directly enter KC
  - First converted to acetyl CoA by pyruvate dehydrogenase complex



From: Summerlin LR (1981) Chemistry for the Life Sciences. New York: Random House p 548.

Regulation of Pyruvate → Acetyl CoA

- PDH reaction regulated to spare pyruvate from being irreversibly lost
  - Glucose important for brain and once converted to Acetyl CoA cannot be used for glucose synthesis
- PDH regulated by phosphorylation and allosteric control
  - Dephosphorylation activates PDH
    - Phosphatase enzyme activated by high $Ca2^{+}$
  - Phosphorylation inactivates PDH
    - Kinase activated by acetyl CoA and NADH
  - PDH allosterically inhibited by:
    - ATP
    - Acetyl CoA
    - NADH



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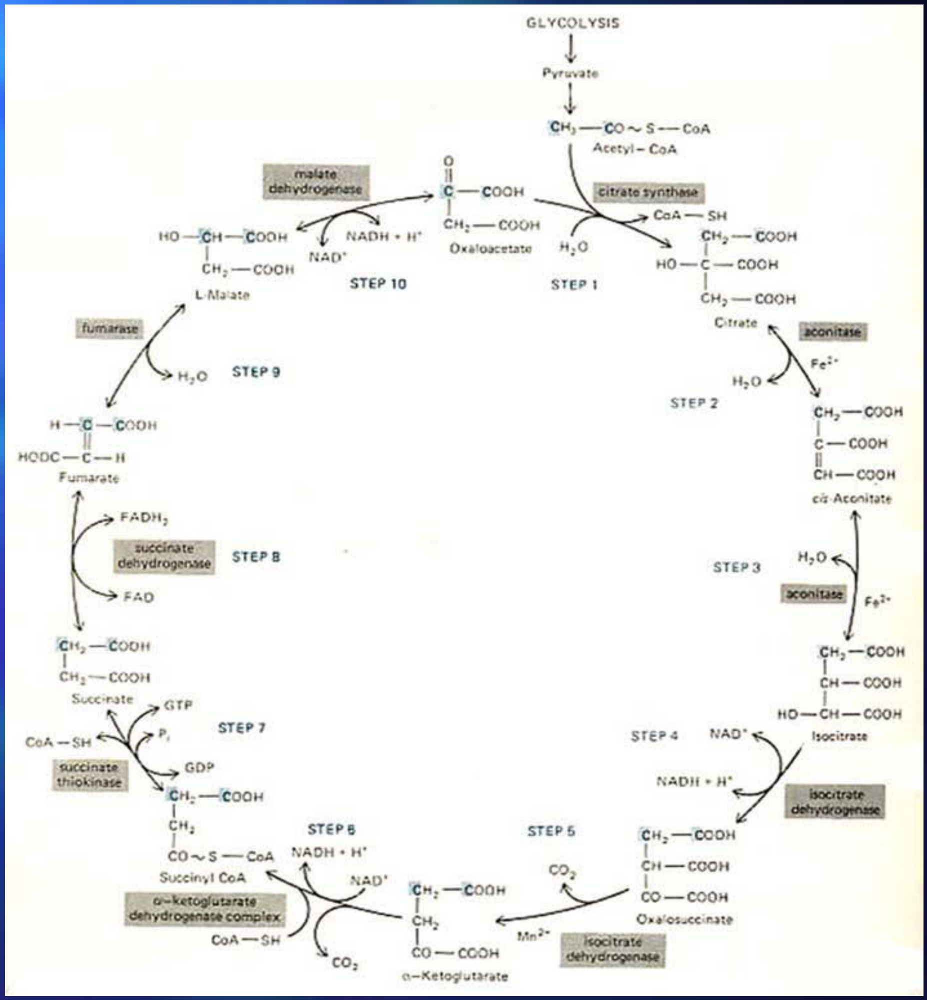
Formation of citrate

- Oxaloacetate condenses with acetyl CoA to form Citrate
- Non-equilibrium reaction catalysed by citrate synthase
  - Inhibited by:
    - ATP
    - NADH
    - Citrate - competitive inhibitor of oxaloacetate



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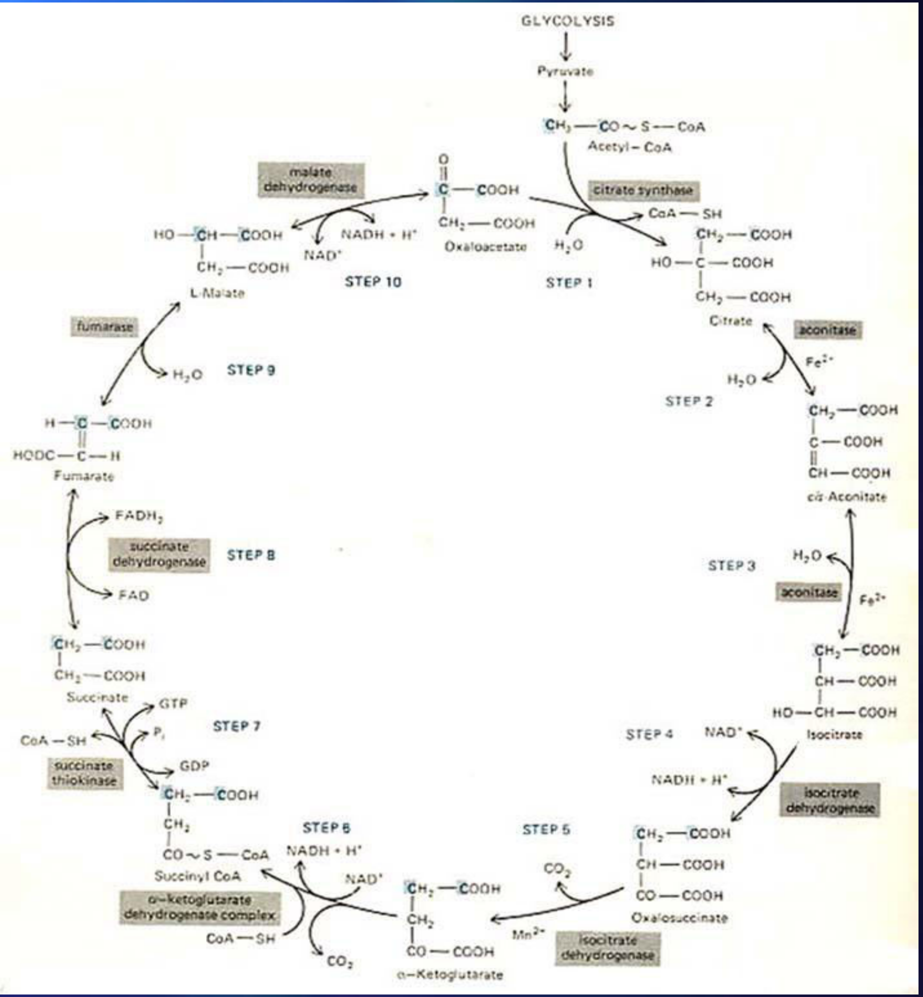
Citrate ↔ isocitrate

- Citrate isomerised to isocitrate in two reactions (dehydration and hydration)
- Equilibrium reactions catalysed by aconitase
- Results in interchange of H and OH
  - Changes structure and energy distribution within molecule
    - Makes easier for next enzyme to remove hydrogen



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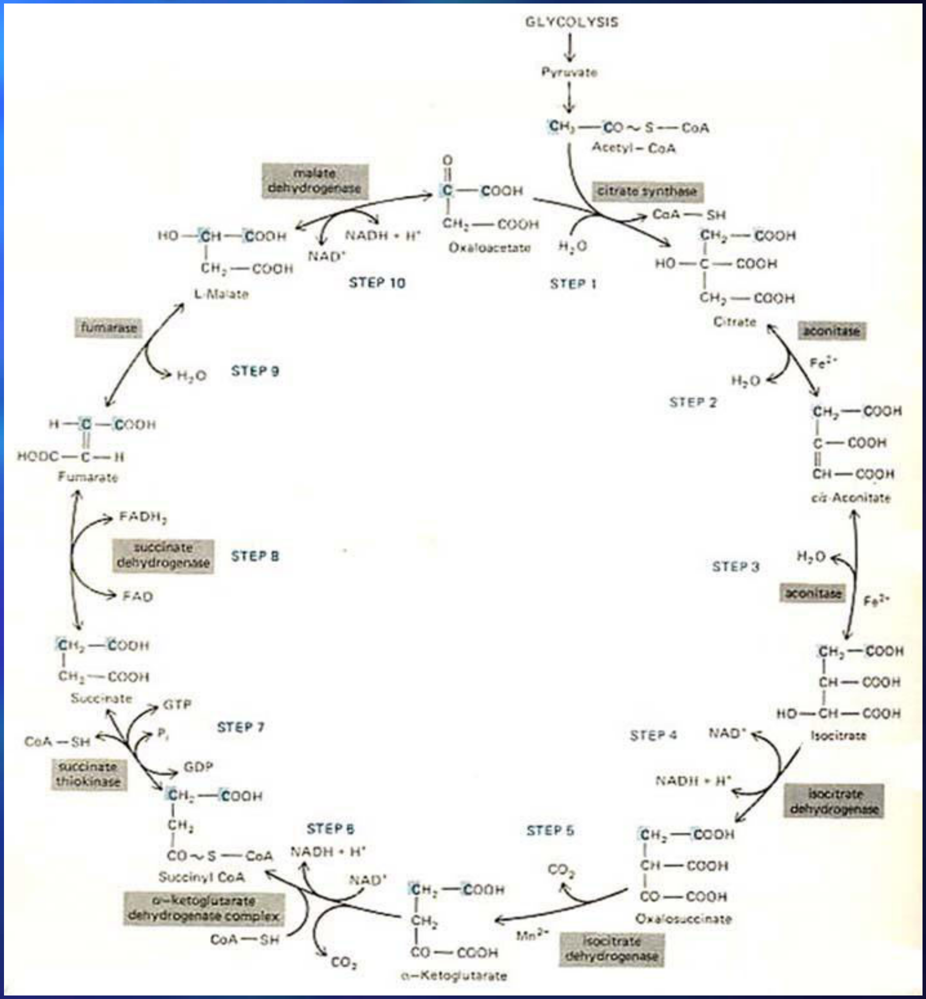
isocitrate → α-ketoglutarate

- Isocitrate dehydrogenated and decarboxylated to give α-ketoglutarate
- Non-equilibrium reactions catalysed by isocitrate dehydrogenase
- Results in formation of:
  - NADH + H^+
  - CO_2
- Stimulated (cooperative) by isocitrate, NAD^+, Mg^{2+}, ADP, Ca^{2+} (links with contraction)
- Inhibited by NADH and ATP



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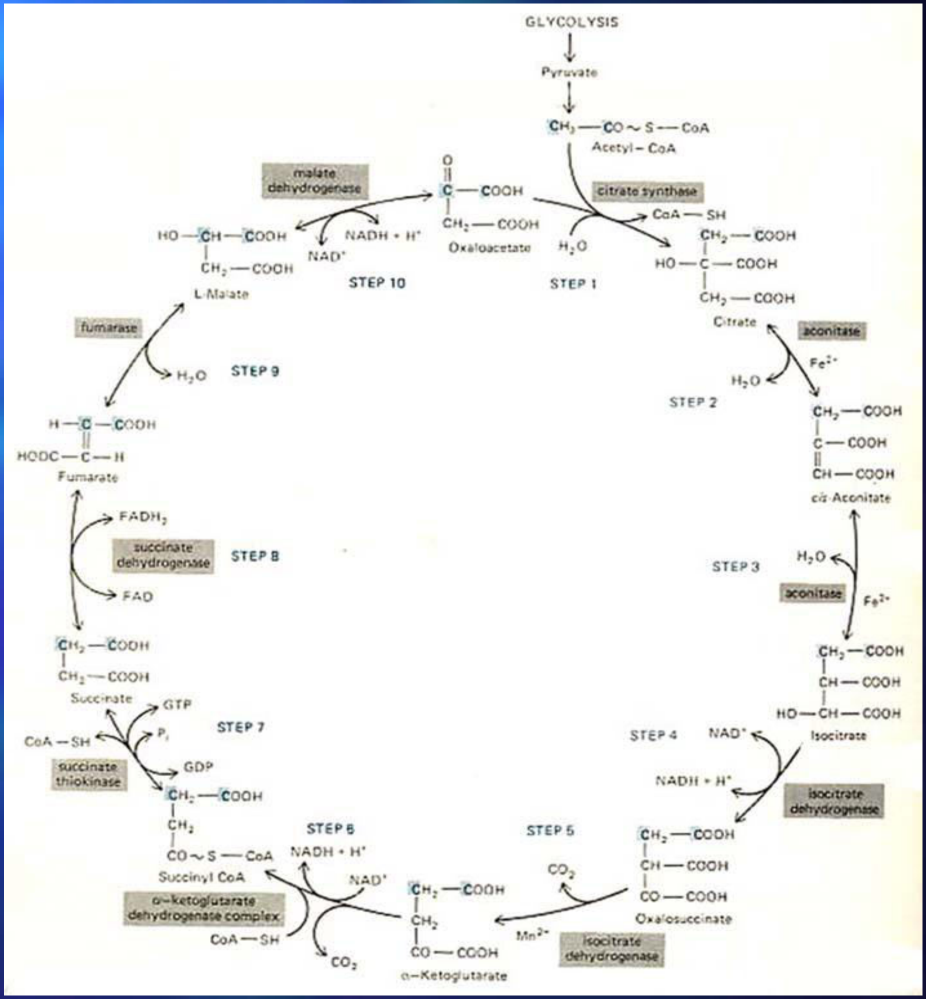
α-ketoglutarate $\rightarrow$ succinyl CoA

- Series of reactions result in decarboxylation, dehydrogenation and incorporation of CoASH
- Non-equilibrium reactions catalysed by α-ketoglutarate dehydrogenase complex
- Results in formation of:
  - CO_2
  - NADH + H^+
  - High energy bond
- Stimulated by Ca^{2+}
- Inhibited by NADH, ATP, Succinyl CoA (prevents CoA being tied up in matrix)



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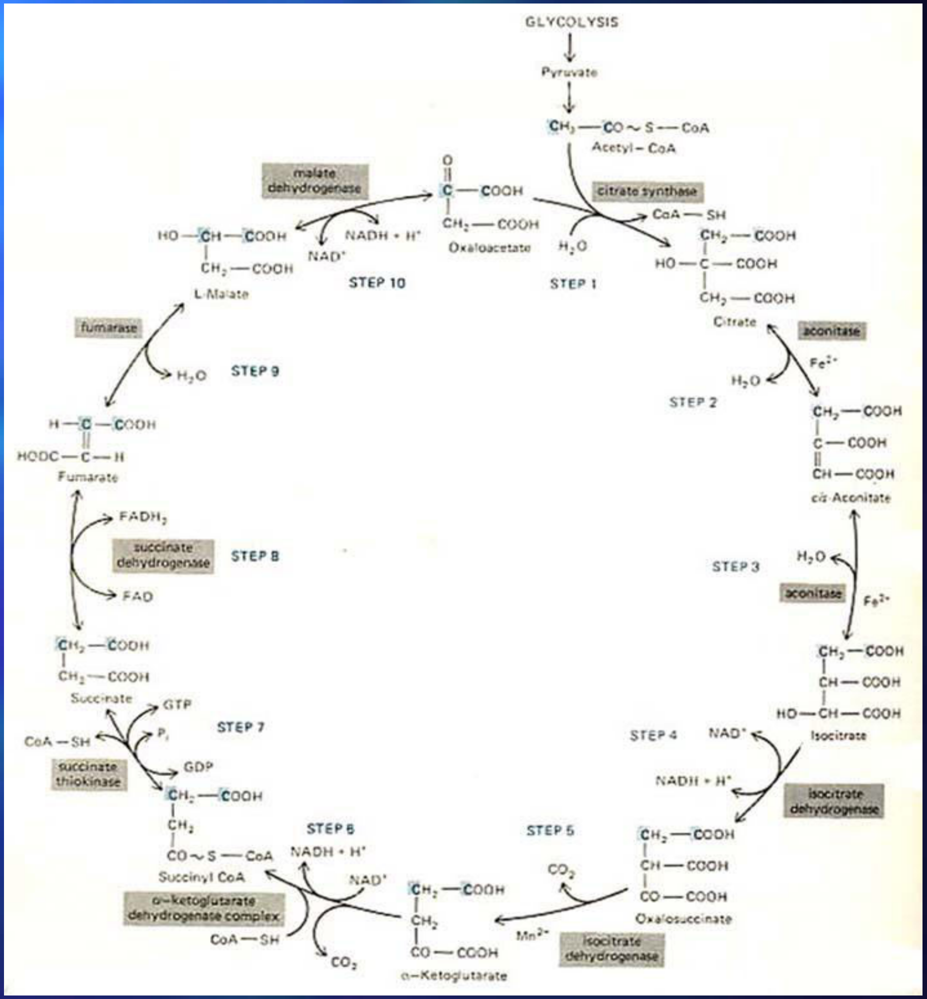
Succinyl CoA ↔ succinate

- Equilibrium reaction catalysed by succinate thiokinase
- Results in formation of:
  - GTP
  - CoA-SH



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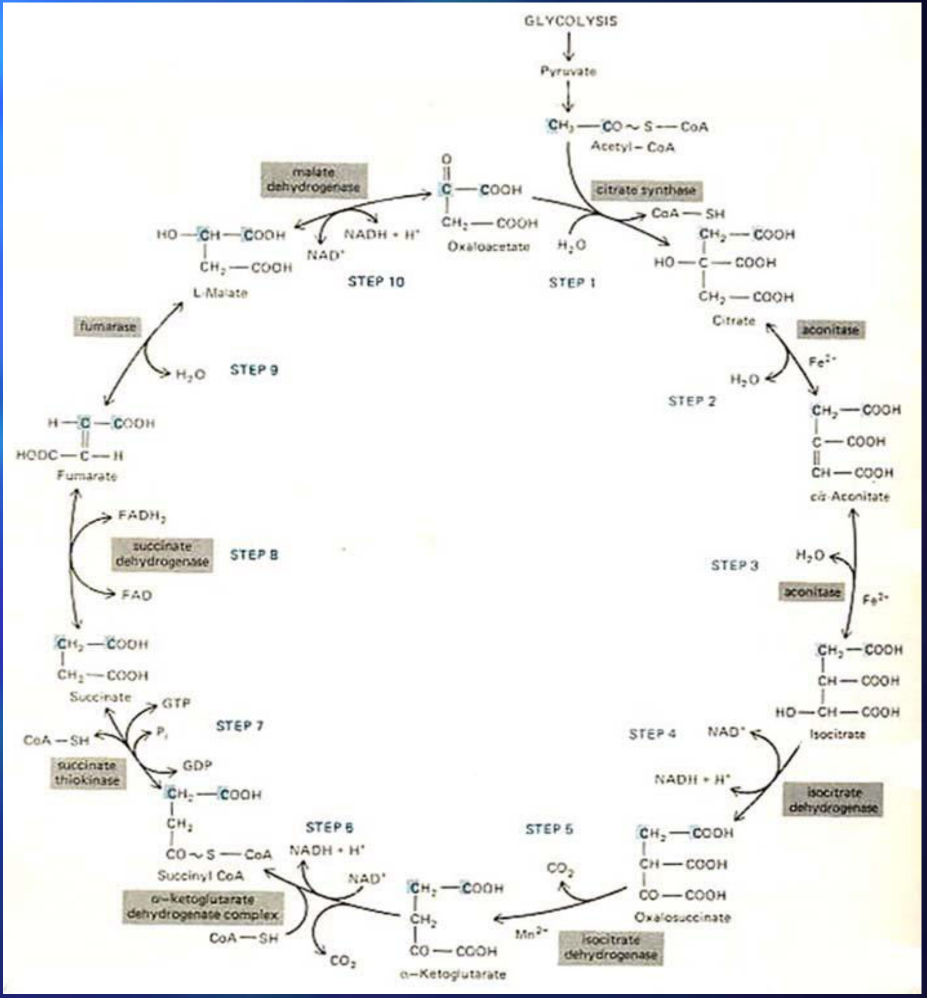
Succinate ↔ fumarate

- Succinate dehydrogenated to form fumarate
- Equilibrium reaction catalysed by succinate dehydrogenase
  - Only Krebs enzyme contained within inner mitochondrial membrane
- Results in formation of $FADH_2$



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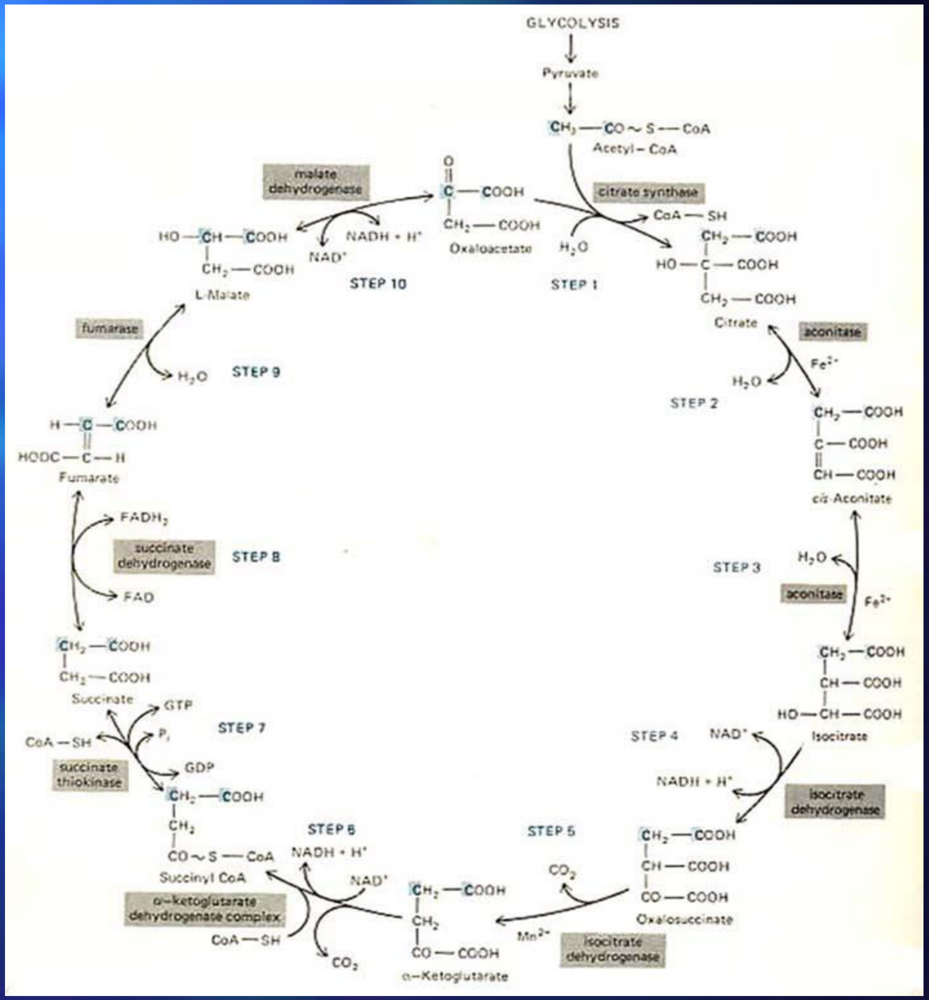
Fumarate ↔ malate

- Fumarate hydrated to form malate
- Equilibrium reaction catalysed by fumarase
- Results in redistribution of energy within molecule so next step can remove hydrogen



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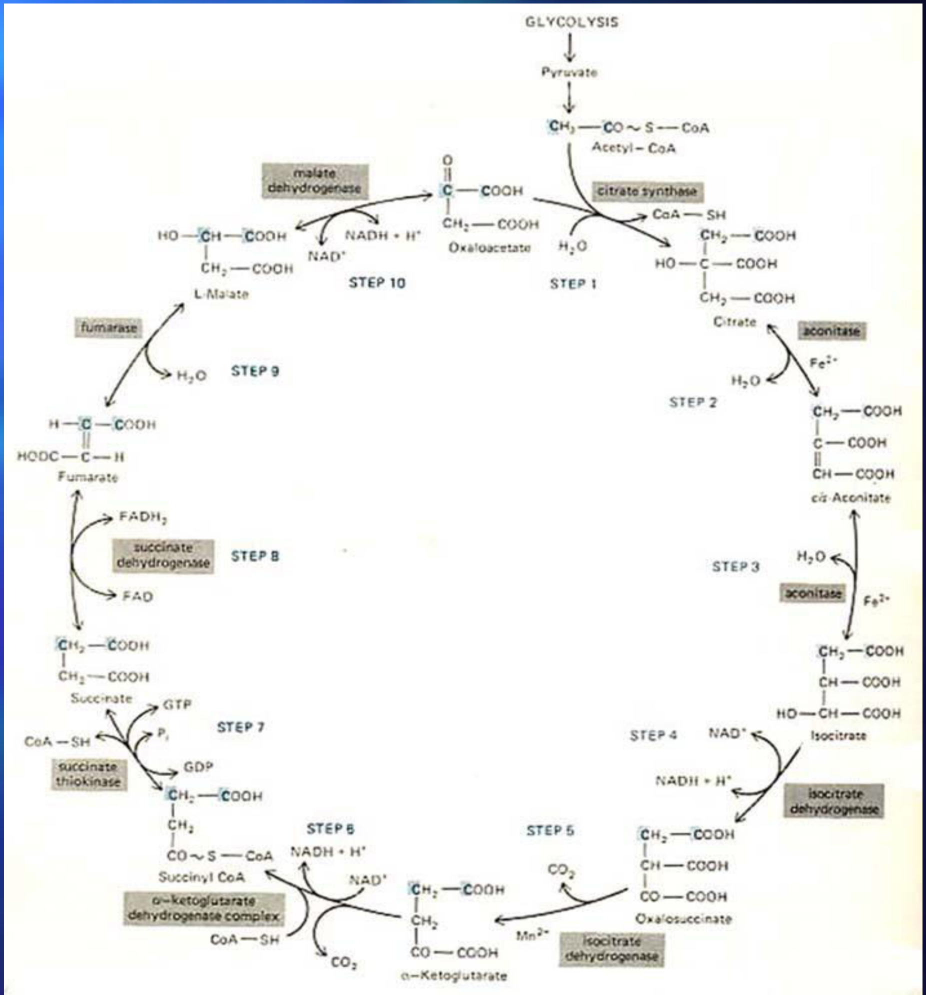
Malate ↔ oxaloacetate

- Malate dehydrogenated to form oxaloacetate
- Equilibrium reaction catalysed by malate dehydrogenase
- Results in formation of NADH + H^+



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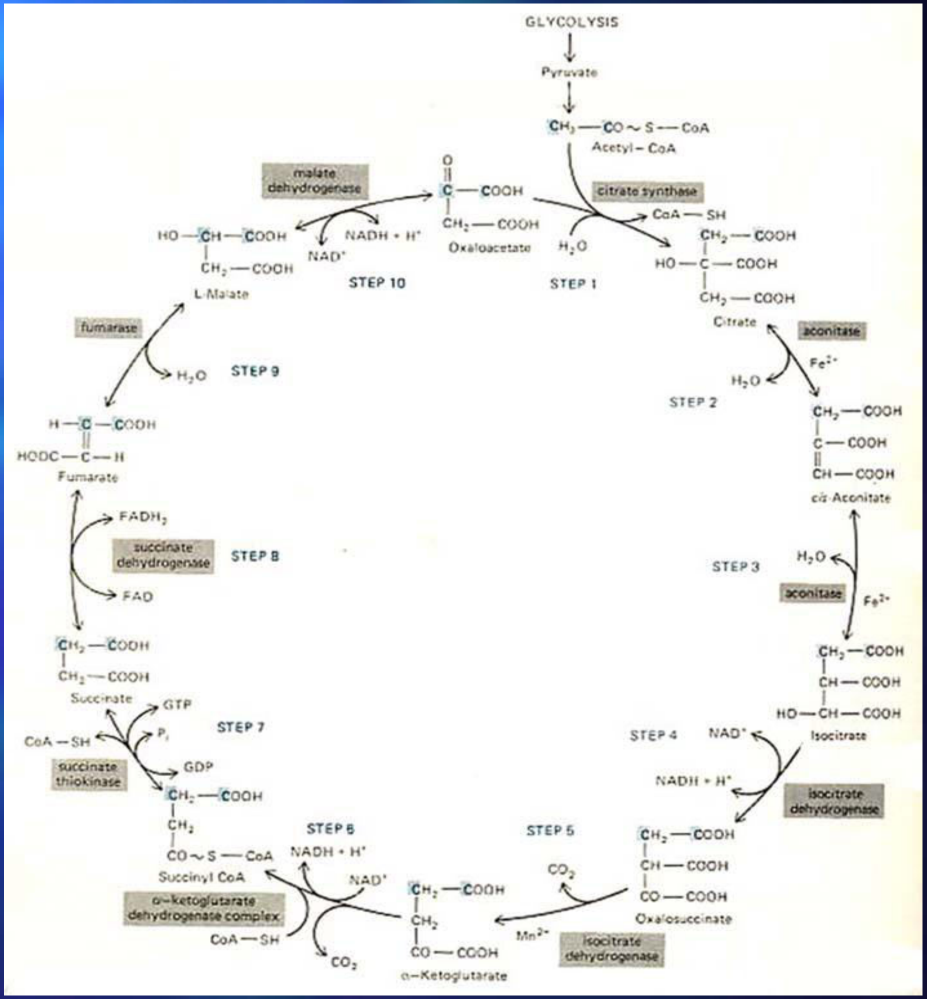
Regulation of Krebs Cycle

- Cycle always proceeds in same direction due to presence of 3 non-equilibrium reactions catalysed by
  - Citrate synthase
  - Isocitrate dehydrogenase
  - α-ketoglutarate dehydrogenase



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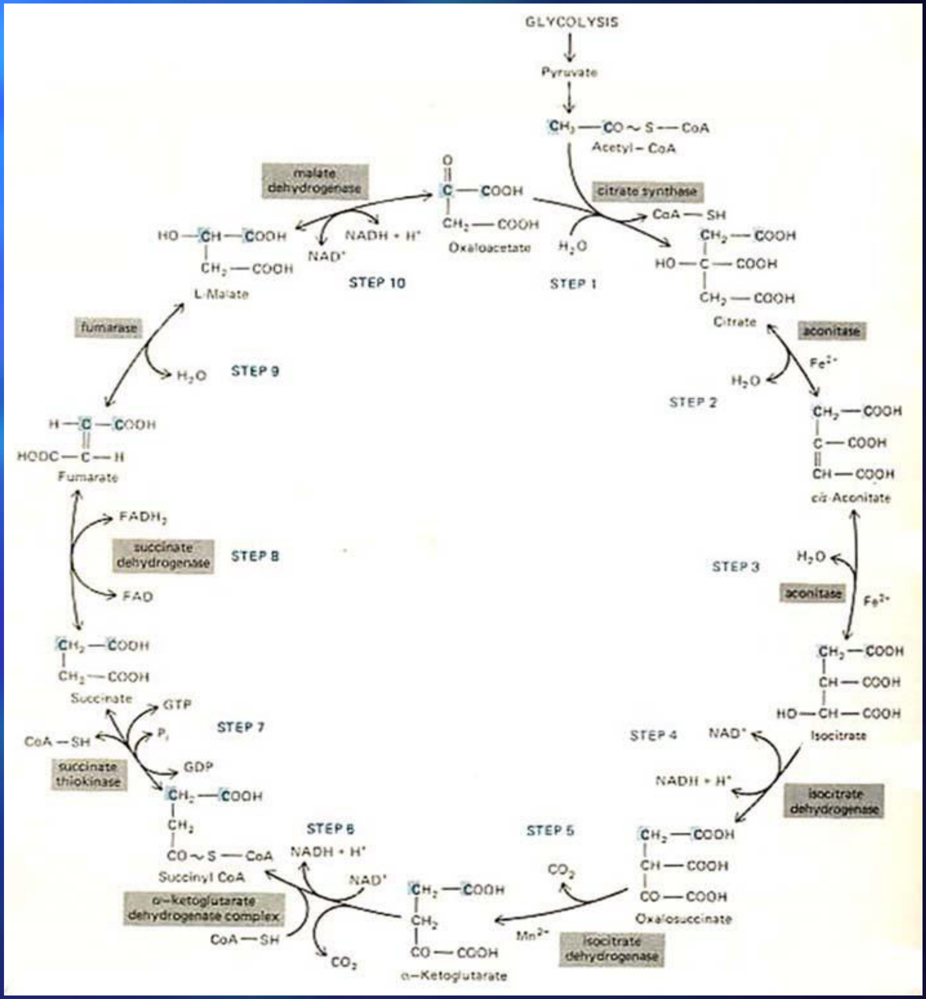
Regulation of Krebs Cycle

- Flux through KC increases during exercise
- 3 non-equilibrium enzymes inhibited by NADH
  - KC tightly coupled to ETC
    - If NADH decreases due to increased oxidation in ETC flux through KC increases
- Isocitrate dehydrogenase and α-ketoglutarate dehydrogenase also stimulated by Ca2$^+$
  - Flux increases as contractile activity increases



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