



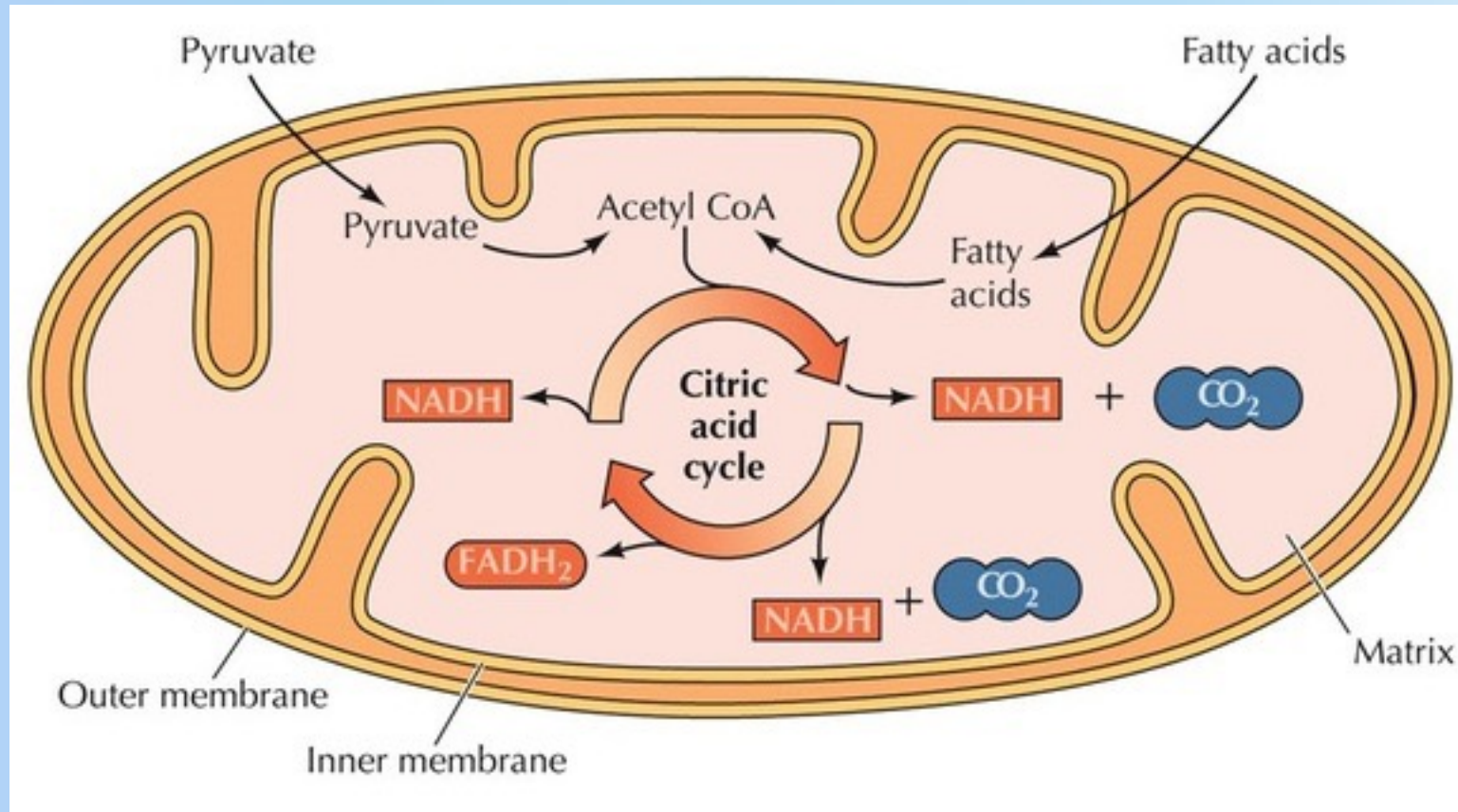
TCA cycle

Oxidative phosphorylation

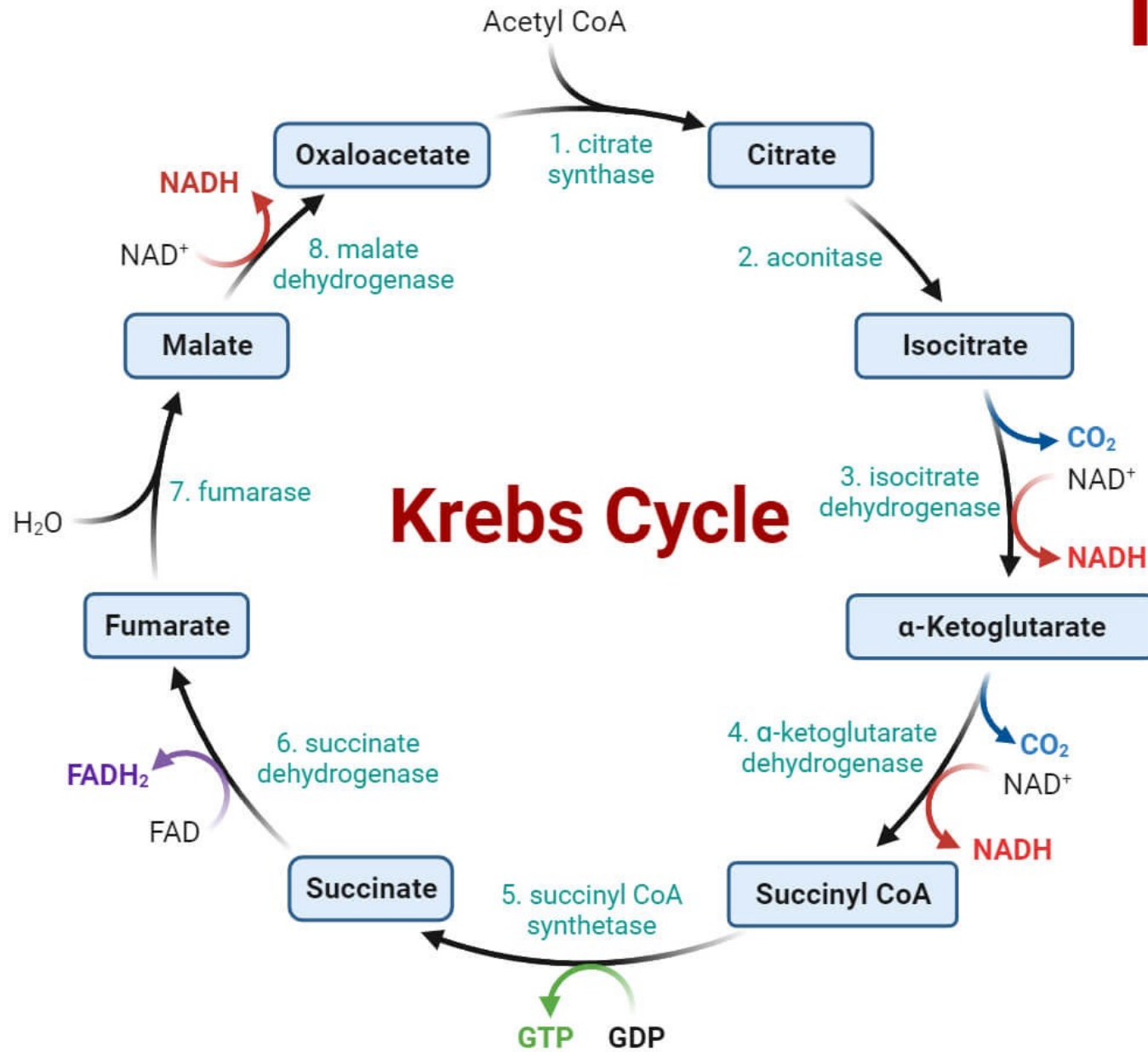
Ola Amland

TCA (Tricarboxylic acid cycle)

Krebs cycle, Citric acid cycle

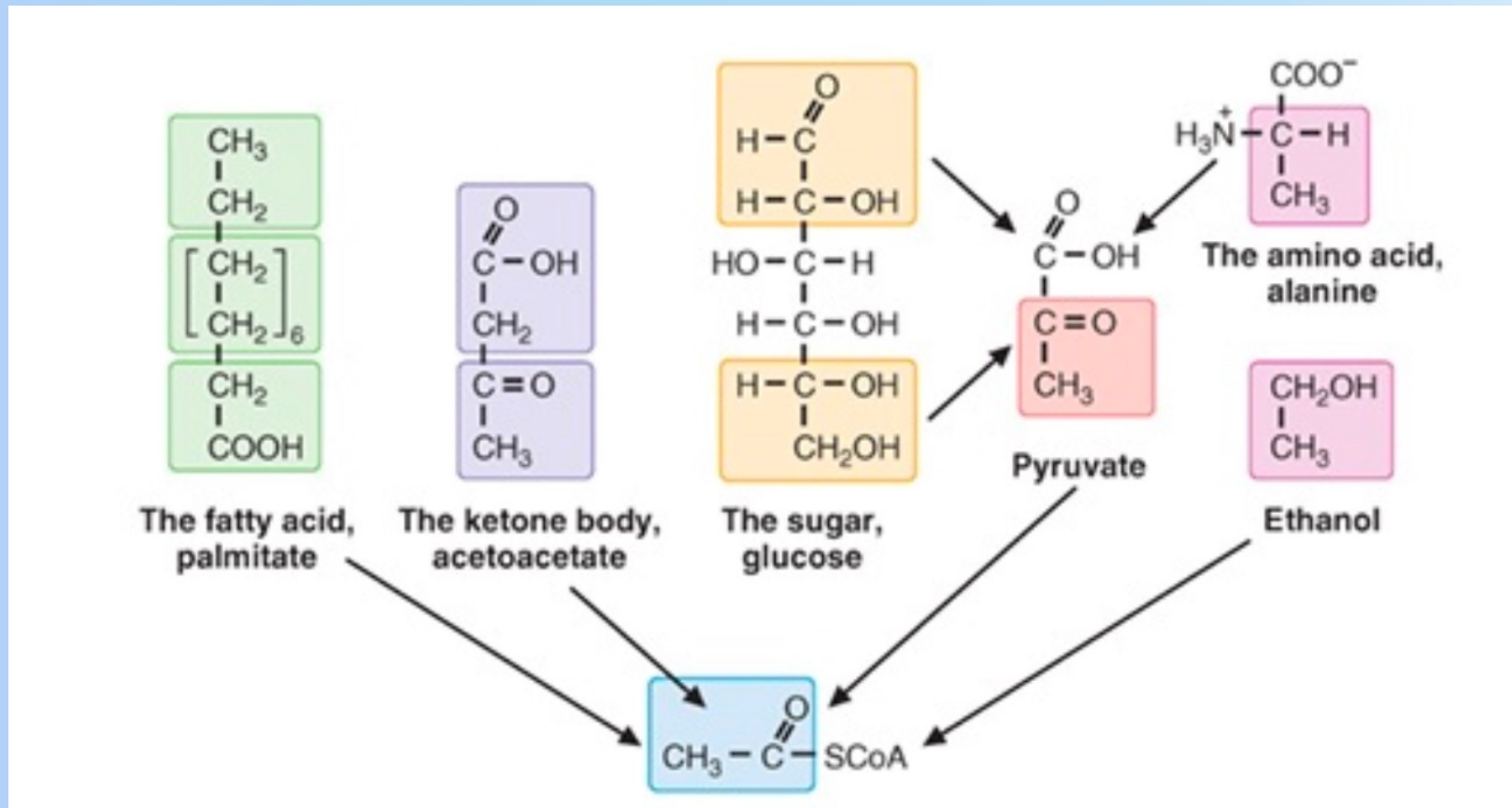


TCA Cycle

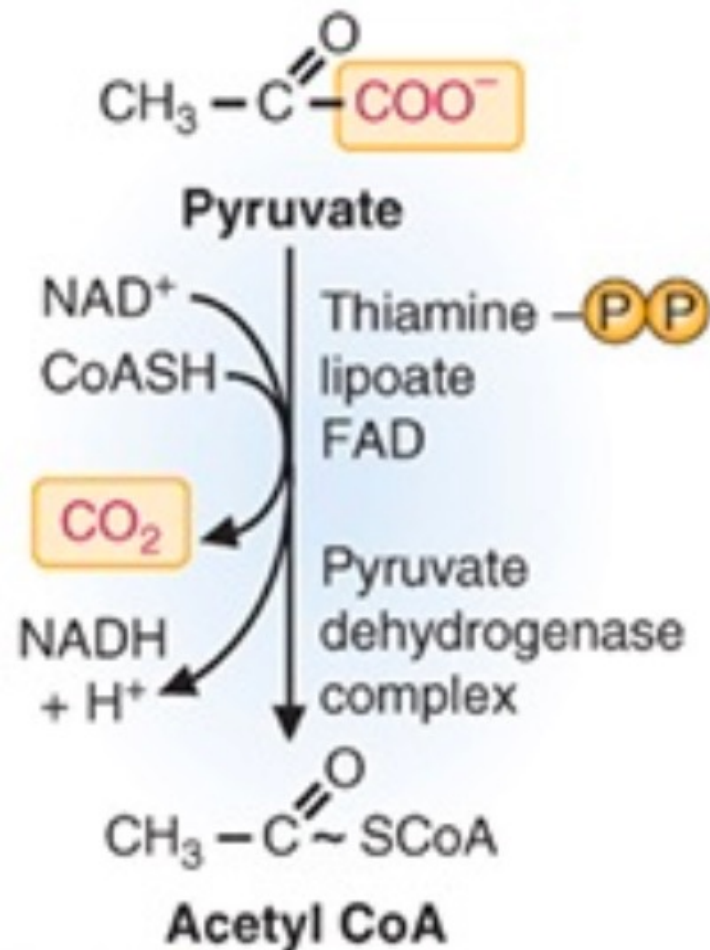


Products (Each Cycle)
1 ATP (GTP)
3 NADH
1 FADH ₂
2 CO ₂

Acetyl Coa production

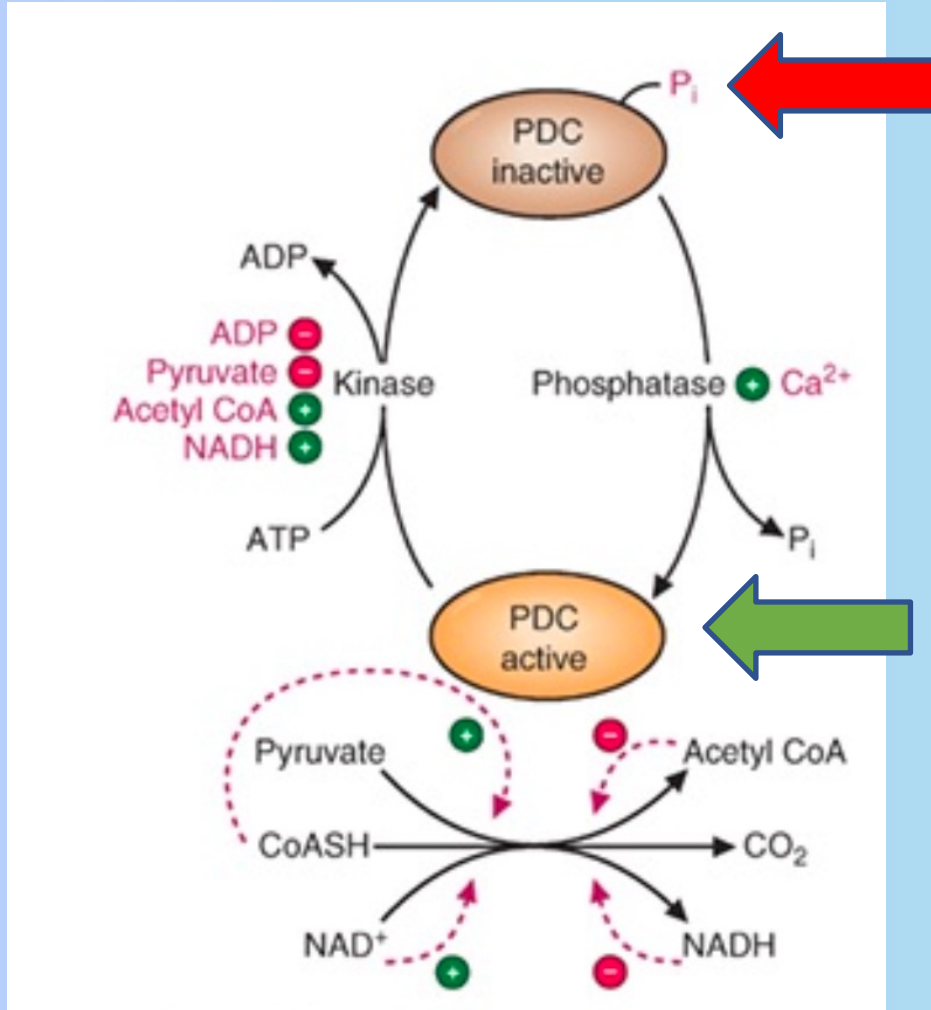


Acetyl CoA from pyruvate



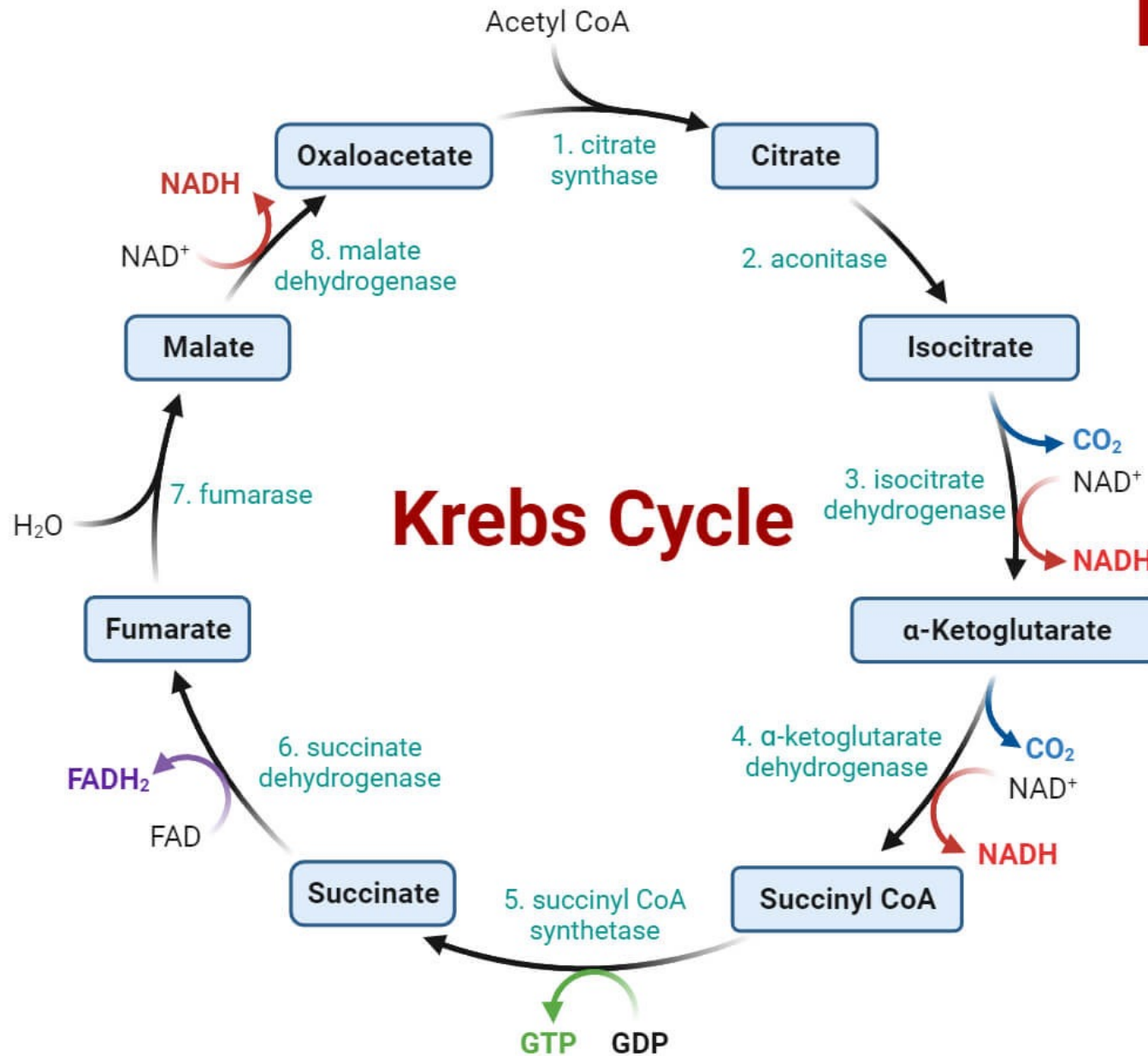
- Substrate: Pyruvate + NAD^+ + CoASH
- Products: Acetyl CoA + NADH + H^+ + CO_2
- Enzyme: Pyruvate dehydrogenase complex
- Coenzymes: TPP, lipoate, FAD, NAD^+
- **Activators: Pyruvate + NAD^+**
- **Inhibitors: Acetyl CoA + NADH**

Regulation of PDC



- If it is phosphorylated: **Inactive**
- Not phosphorylated: **Active**

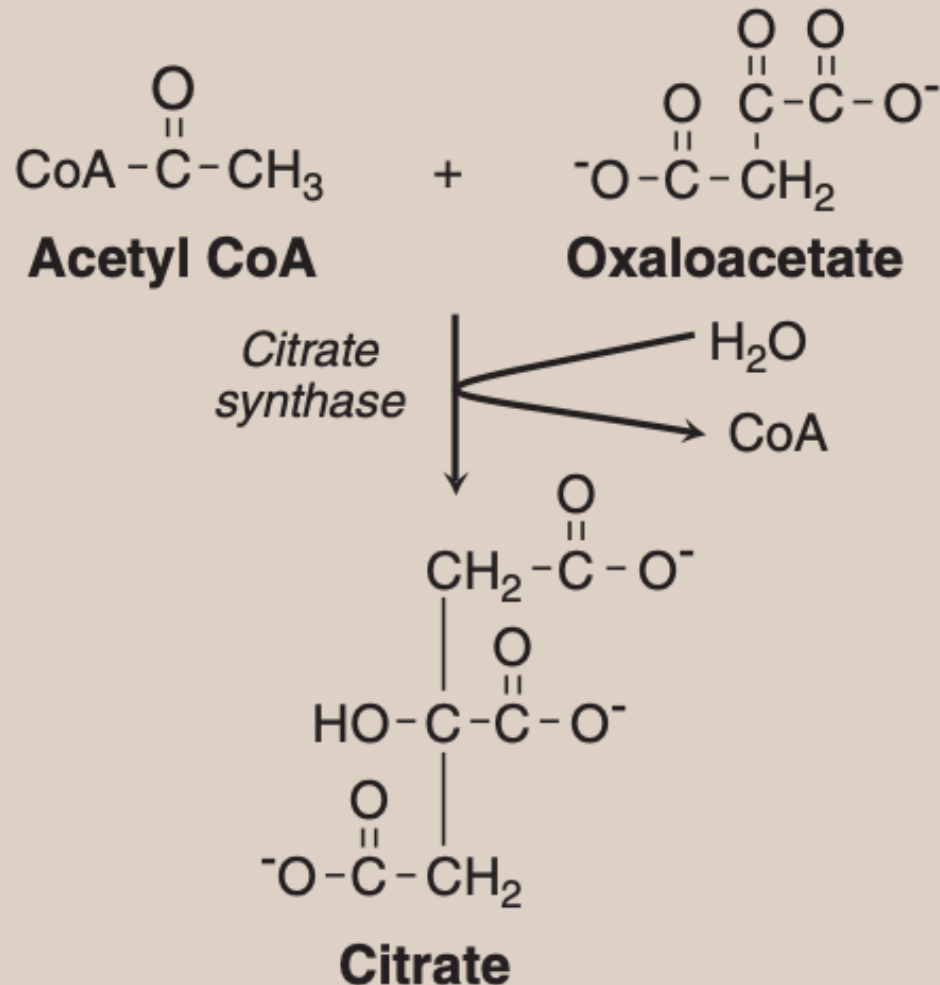
TCA Cycle



**Products
(Each Cycle)**

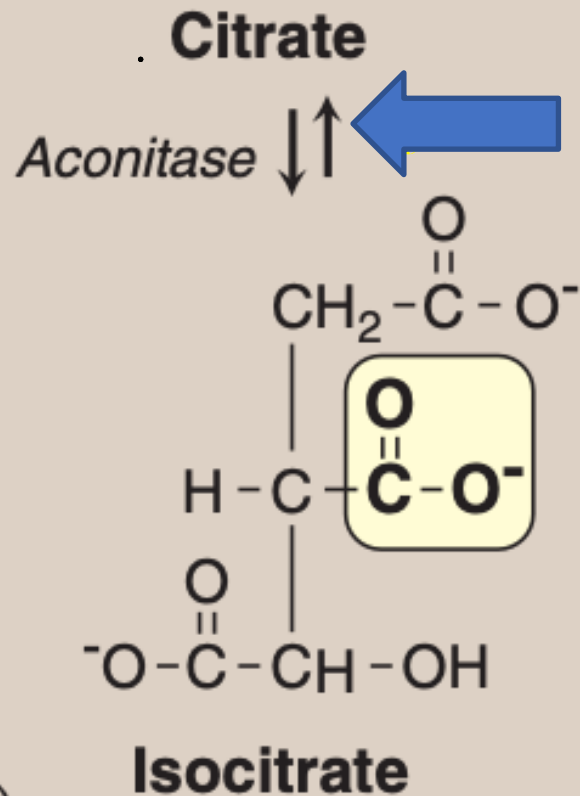
- 1 ATP (GTP)
- 3 NADH
- 1 FADH₂
- 2 CO₂

Citrate synthesis



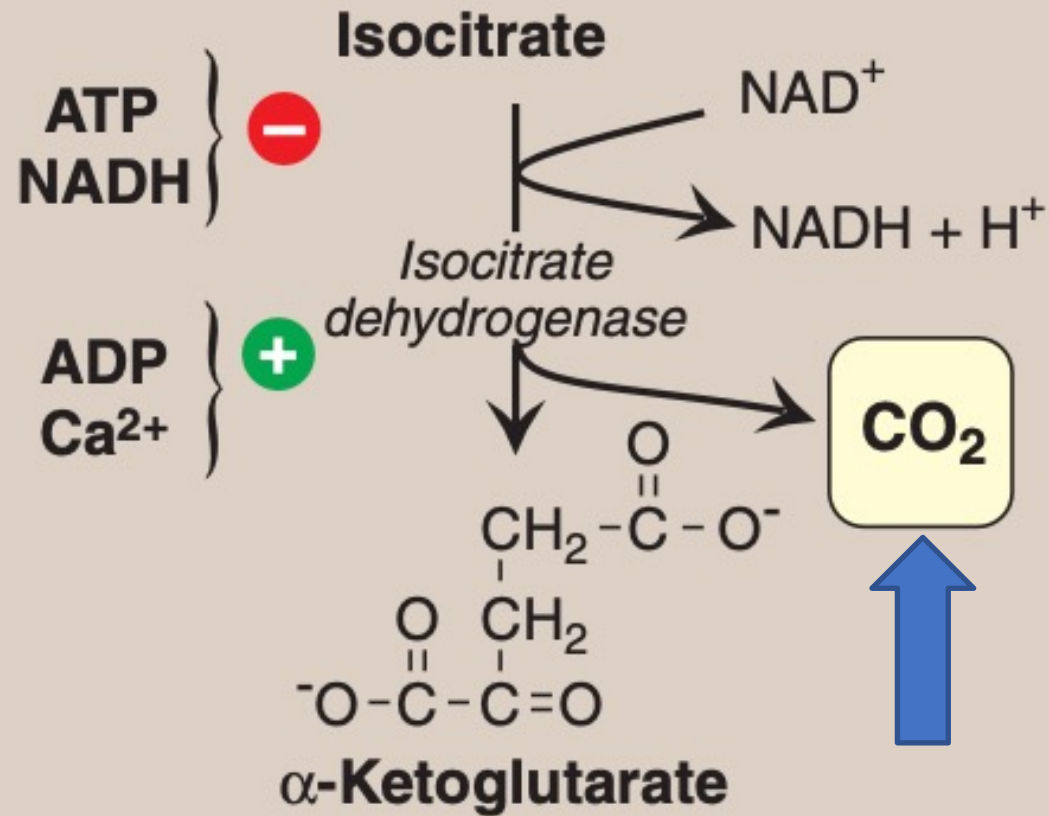
- Substrate: Acetyl-CoA + OAA + H₂O
- Product: Citrate + CoA
- Enzyme: Citrate Synthase
- **Inhibitor: Citrate**
- Condensation reaction

Isocitrate Synthesis



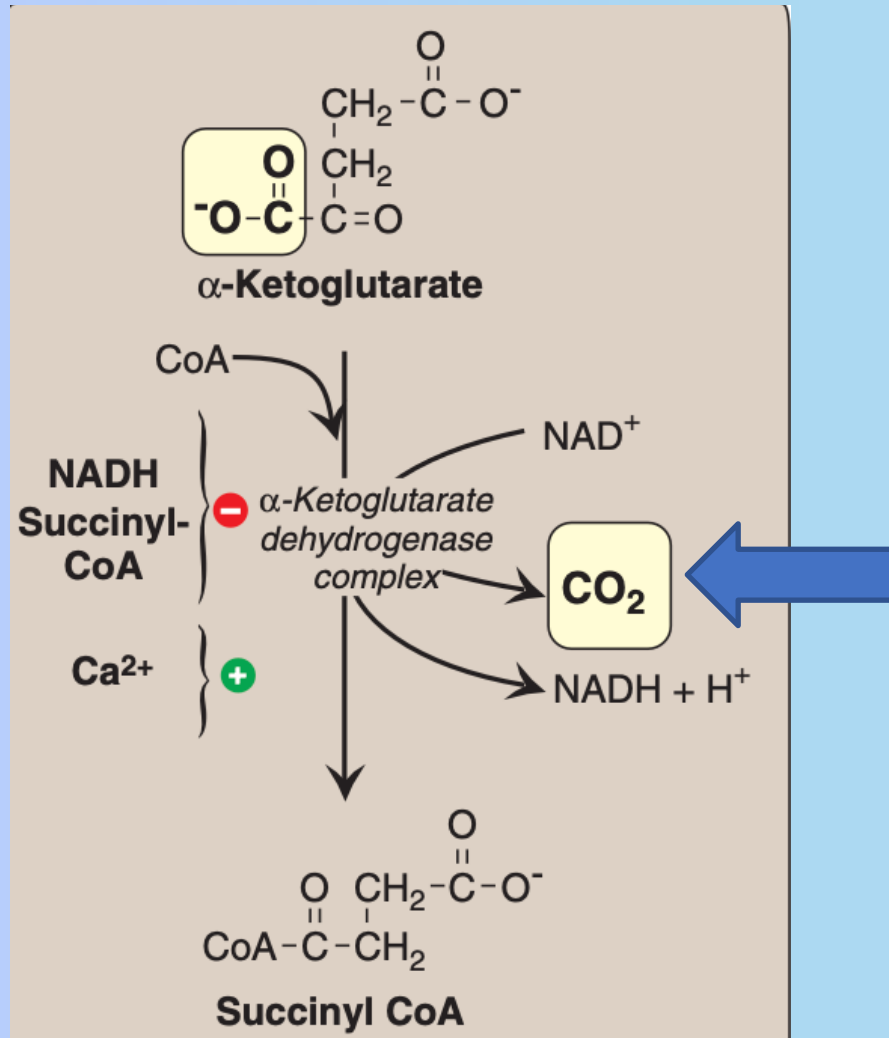
- Substrate: Citrate
- Product: Isocitrate
- Enzyme: Aconitase
- Reversible!
- Inhibitor: Fluoroacetate

α -ketoglutarate synthesis



- Substrate: Isocitrate + NAD^+
- Product: α -ketoglutarate + $\text{NADH} + \text{H}^+ + \text{CO}_2$
- Enzyme: Isocitrate dehydrogenase
- **Inhibitors: ATP, NADH**
- **Activators: ADP, Ca^{2+}**
- *Rate limiting step*

Succinyl CoA synthesis



- Substrate: α -ketoglutarate + CoA + NAD^+
- Product: Succinyl CoA + NADH + H^+ + CO_2
- Enzyme: α -kg dehydrogenase complex
- Coenzymes: TPP, lipoate, FAD, NAD^+
- **Inhibitor: NADH, succinyl CoA**
- **Activator: Ca^{2+}**

A-ketoacid dehydrogenase complexes

- A-kg dehydrogenase complex
- PDC (pyruvate dehydrogenase complex)
- Branched-chain amino acid α -keto acid dehydrogenase complex

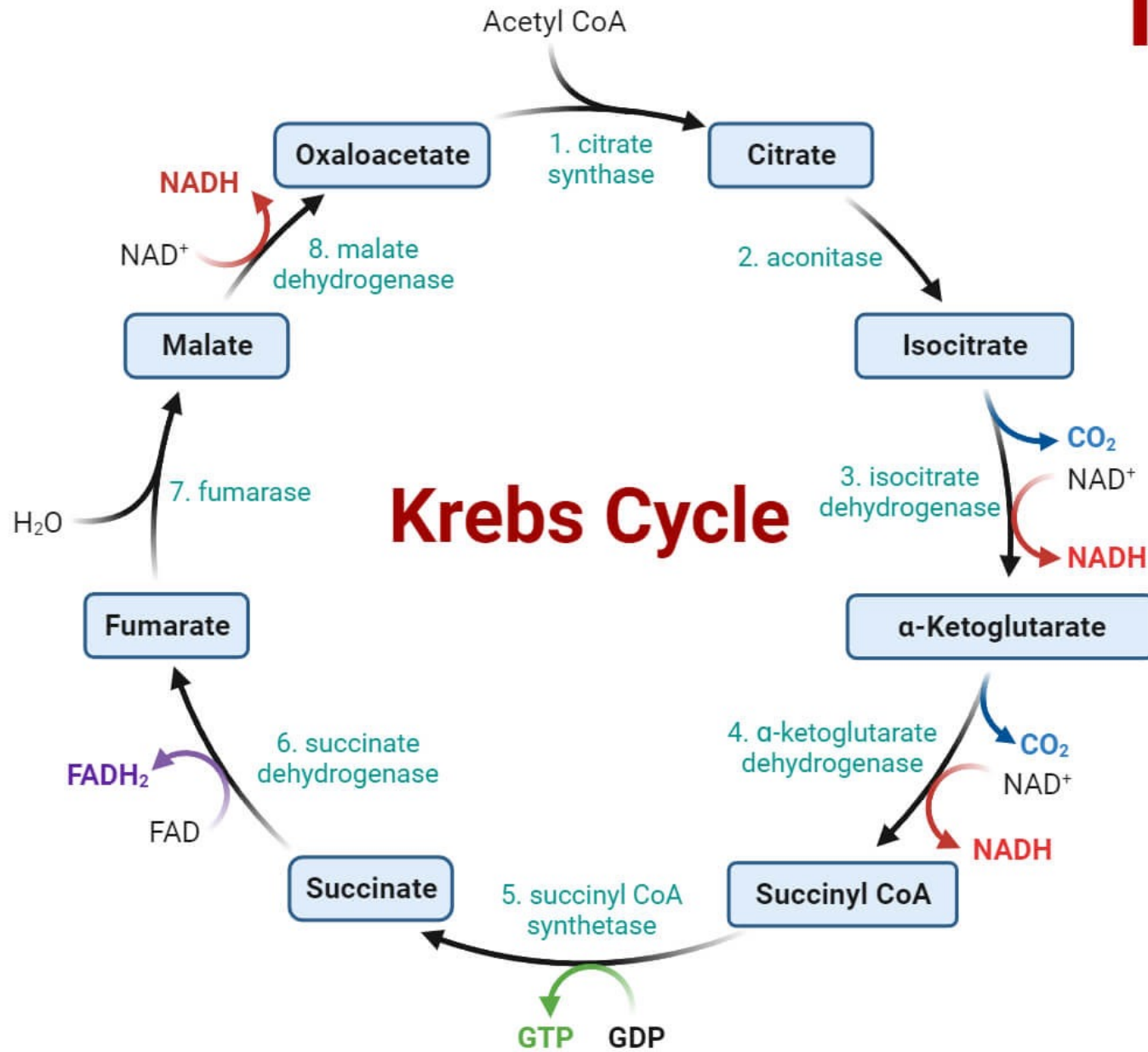
Complexes have 3 different enzymes:

- E₁: Contains thiamine pyrophosphate (TPP)
- E₂: Contains lipoate
- E₃: Contains FAD

Alcohol inhibits thiamine (Vit. B1) absorption, so thiamine deficiency is typical for chronic alcohol drinkers.



TCA Cycle

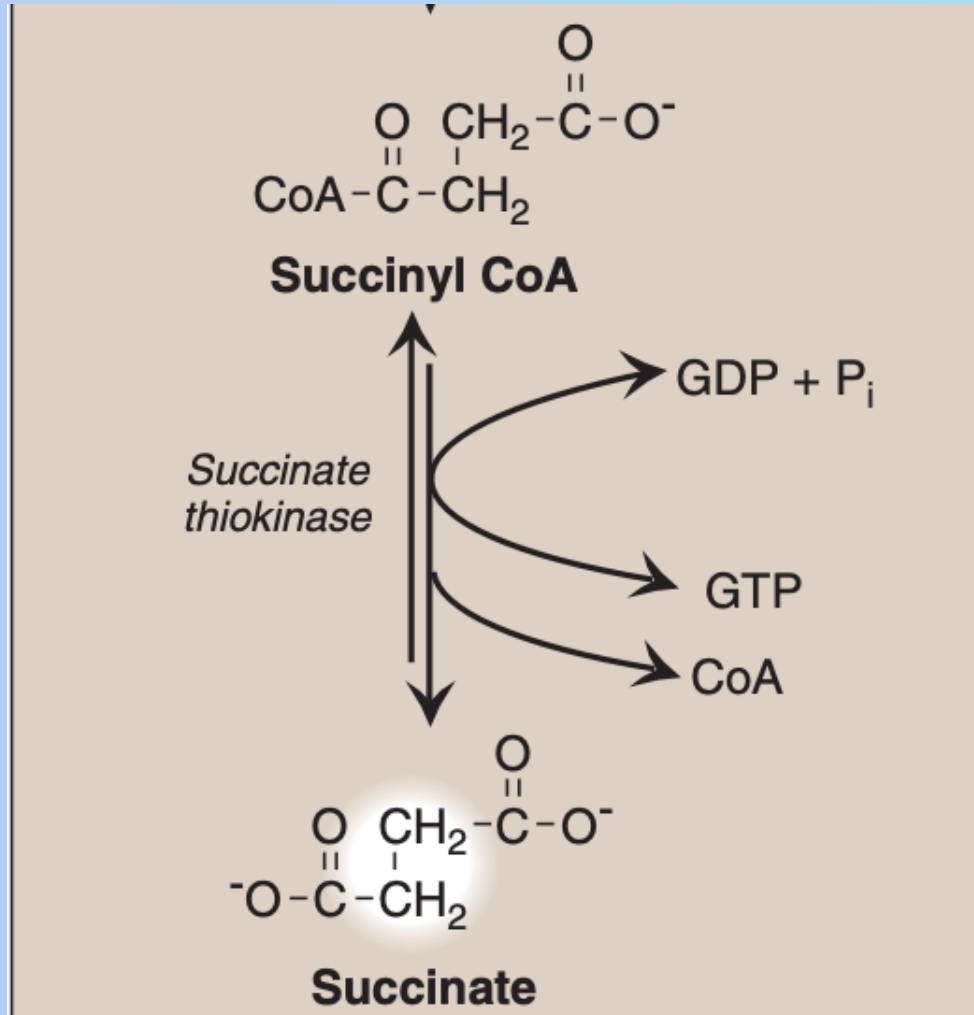


Krebs Cycle



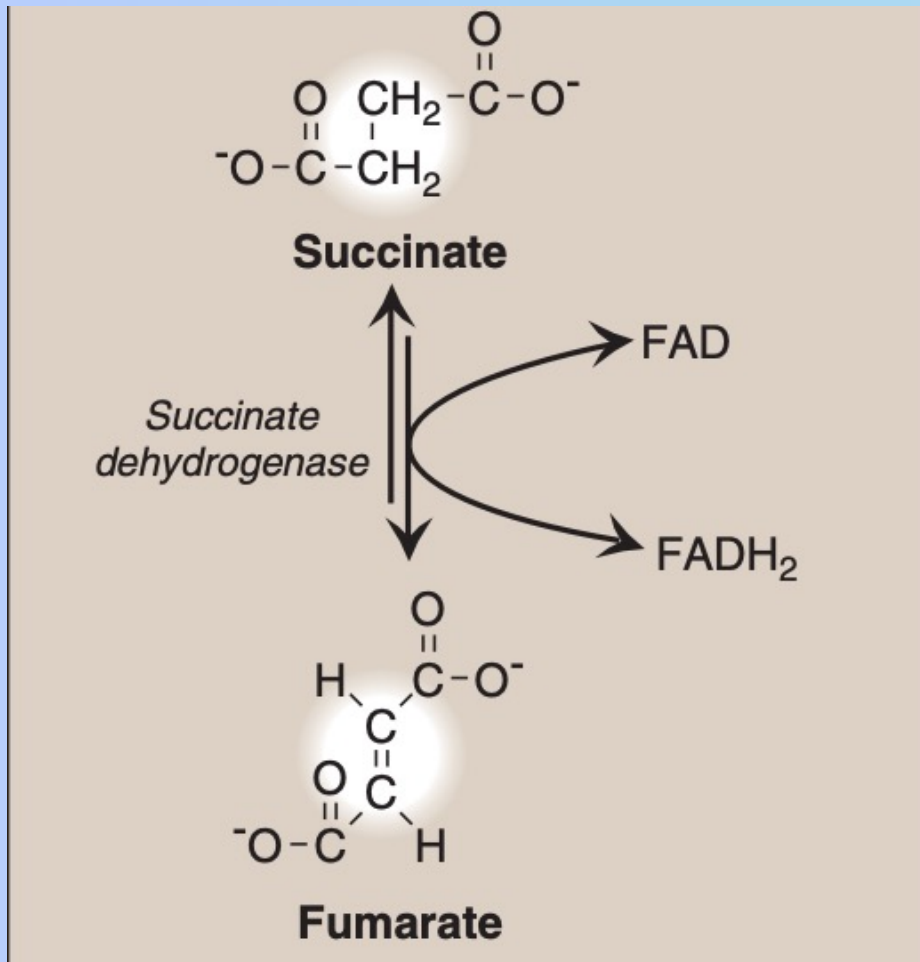
- Products
(Each Cycle)**
- 1 ATP (GTP)
 - 3 NADH
 - 1 FADH_2
 - 2 CO_2

Succinate synthesis



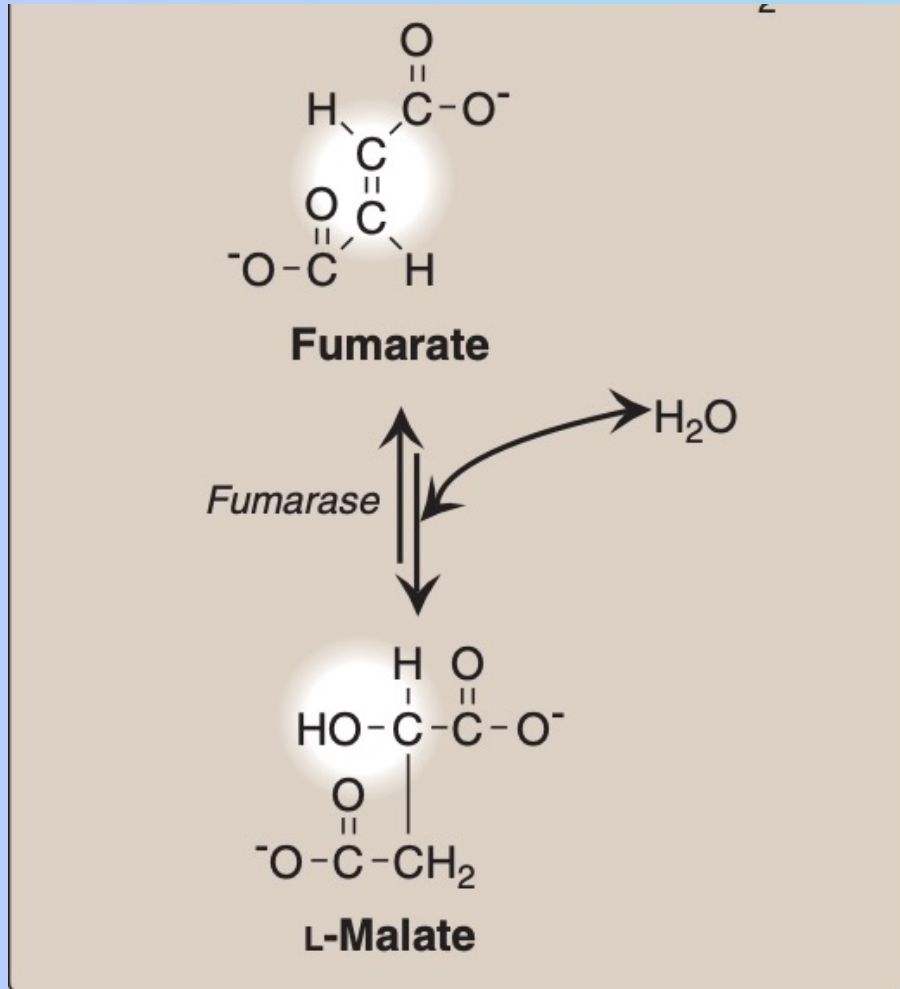
- Substrate: Succinyl CoA + GDP + P_i
- Product: Succinate + GTP + CoA
- Enzyme: Succinate Thiokinase (succinyl CoA synthetase)
- Reversible!
- Substrate level phosphorylation

Fumarate synthesis



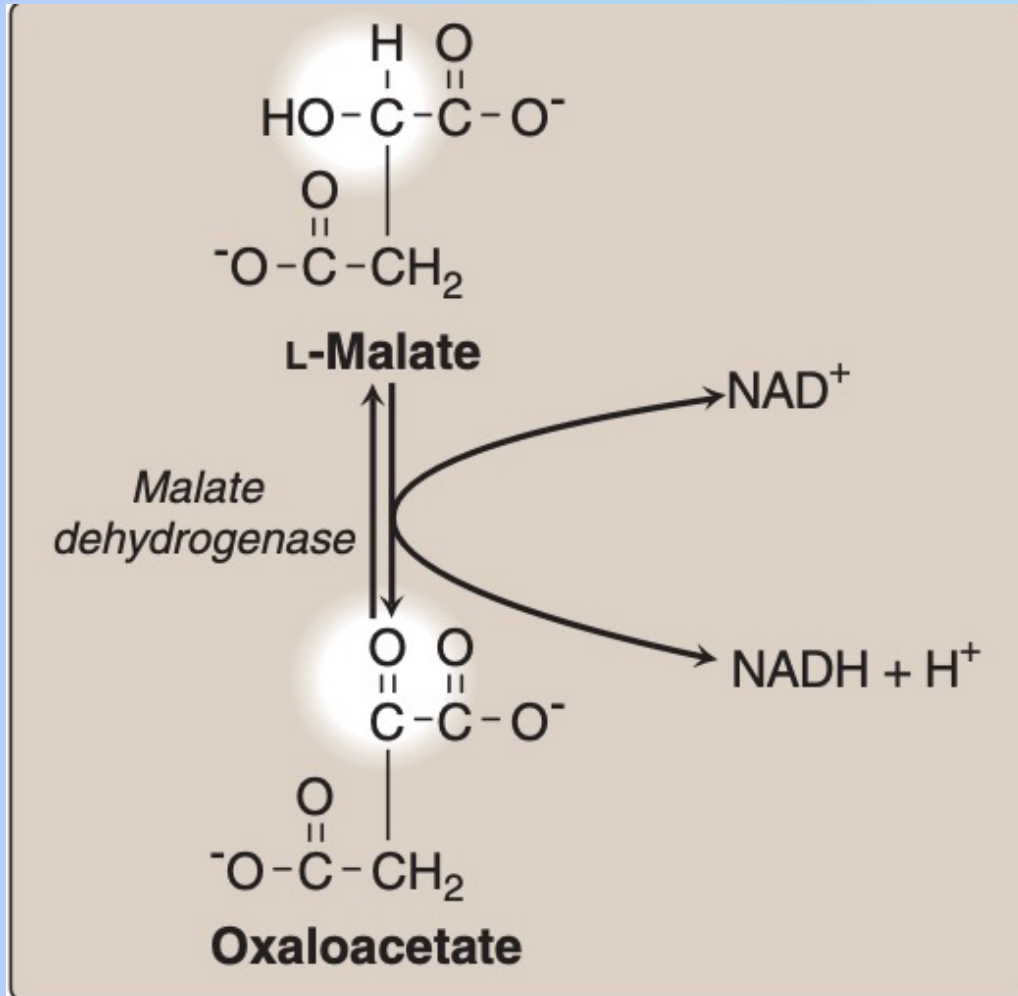
- Substrate: Succinate + FAD
- Product: Fumarate + FADH₂
- Enzyme: Succinate dehydrogenase
 - Complex II of ETC
 - Location: Inner mitochondrial membrane
- Reversible!

Malate synthesis

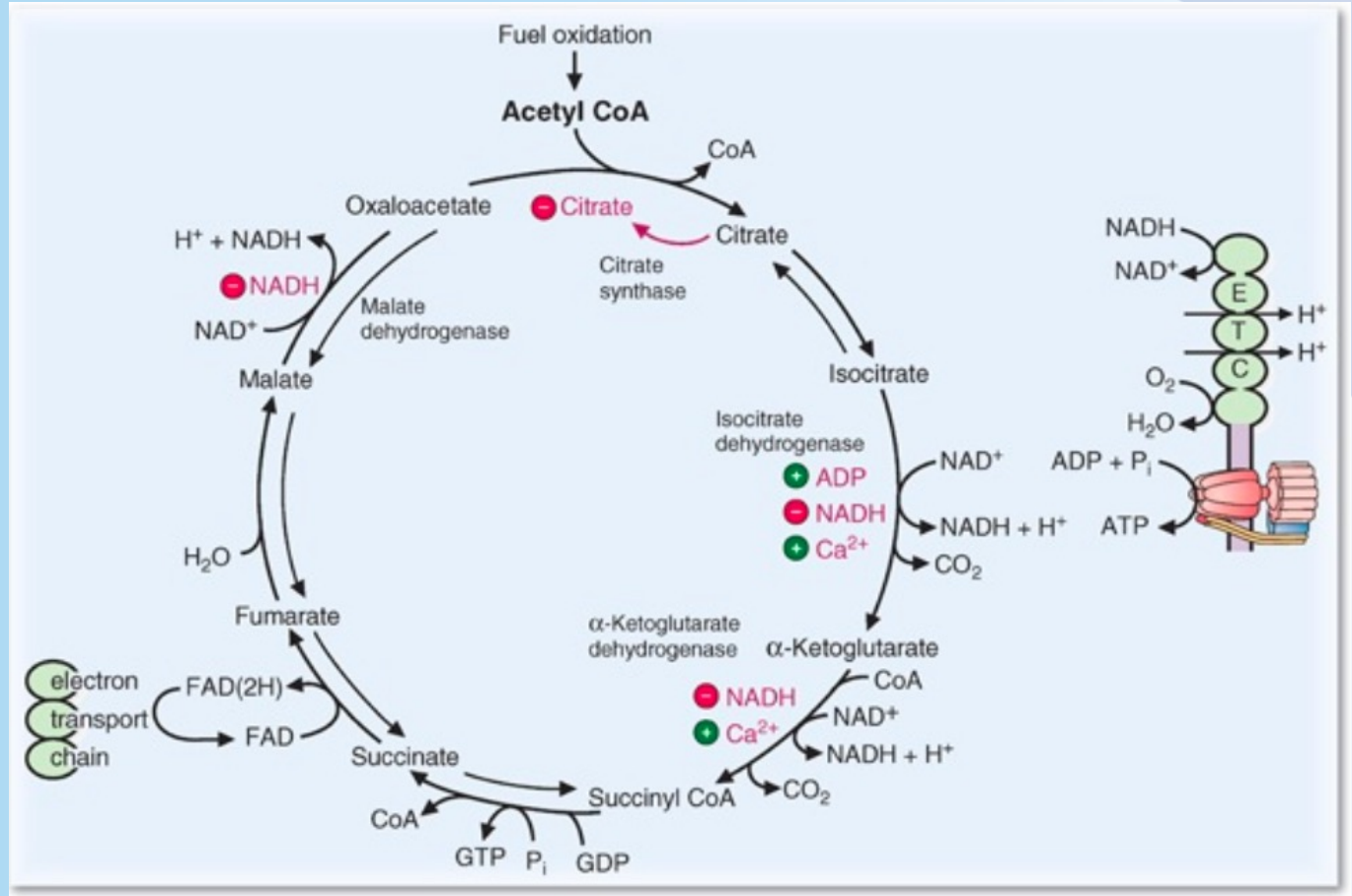
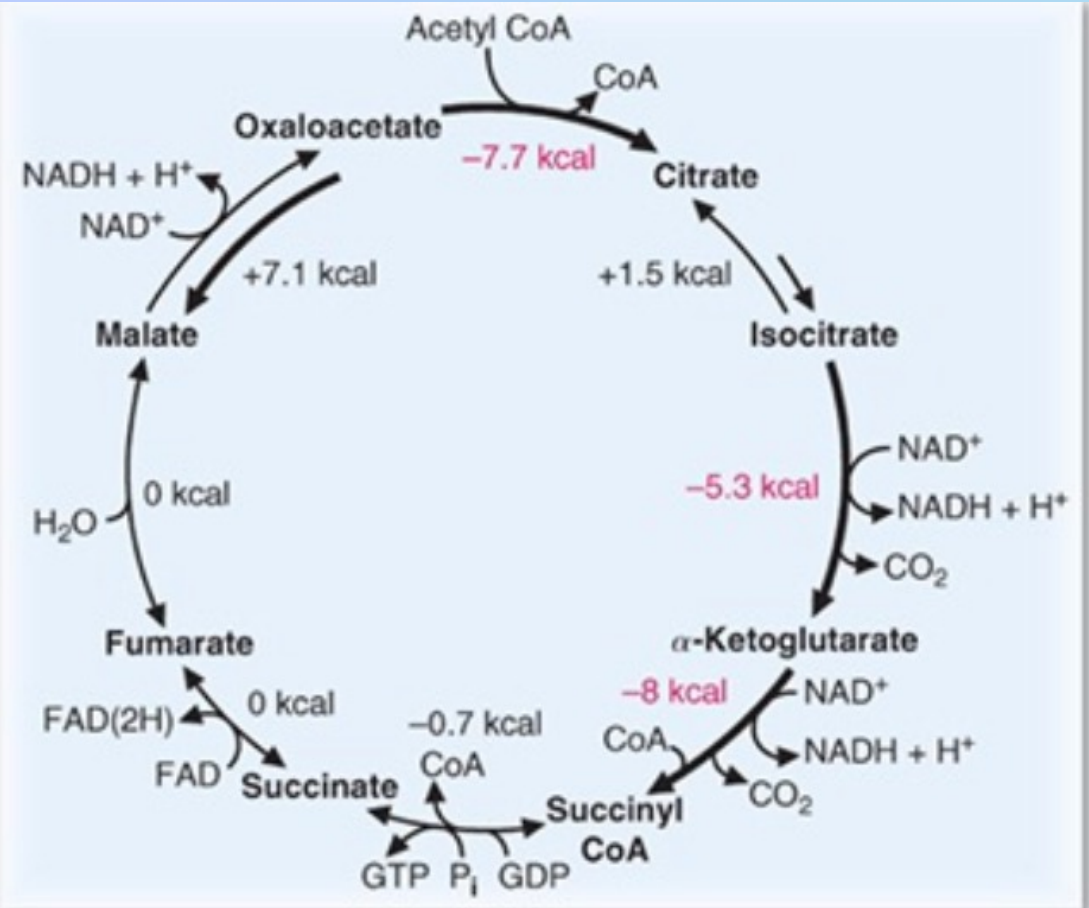


- Substrate: Fumarate + H₂O
- Product: Malate
- Enzyme: Fumarase
- Reversible!

Oxaloacetate synthesis



- Product: Malate + NAD⁺
- Product: OAA + NADH + H⁺
- Enzyme: Malate dehydrogenase
- **Inhibitor: NADH**
- Reversible!



Summarized

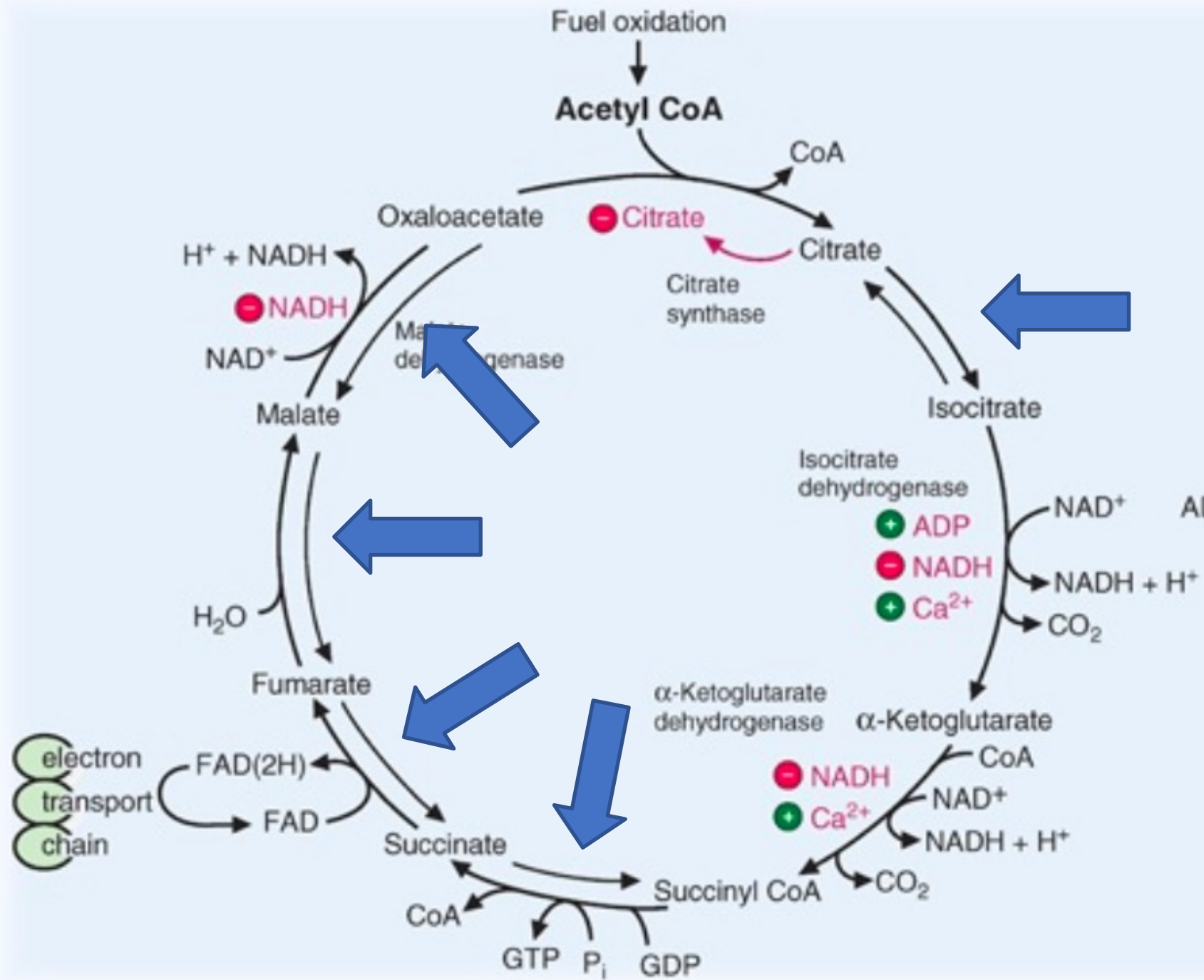
Total count:

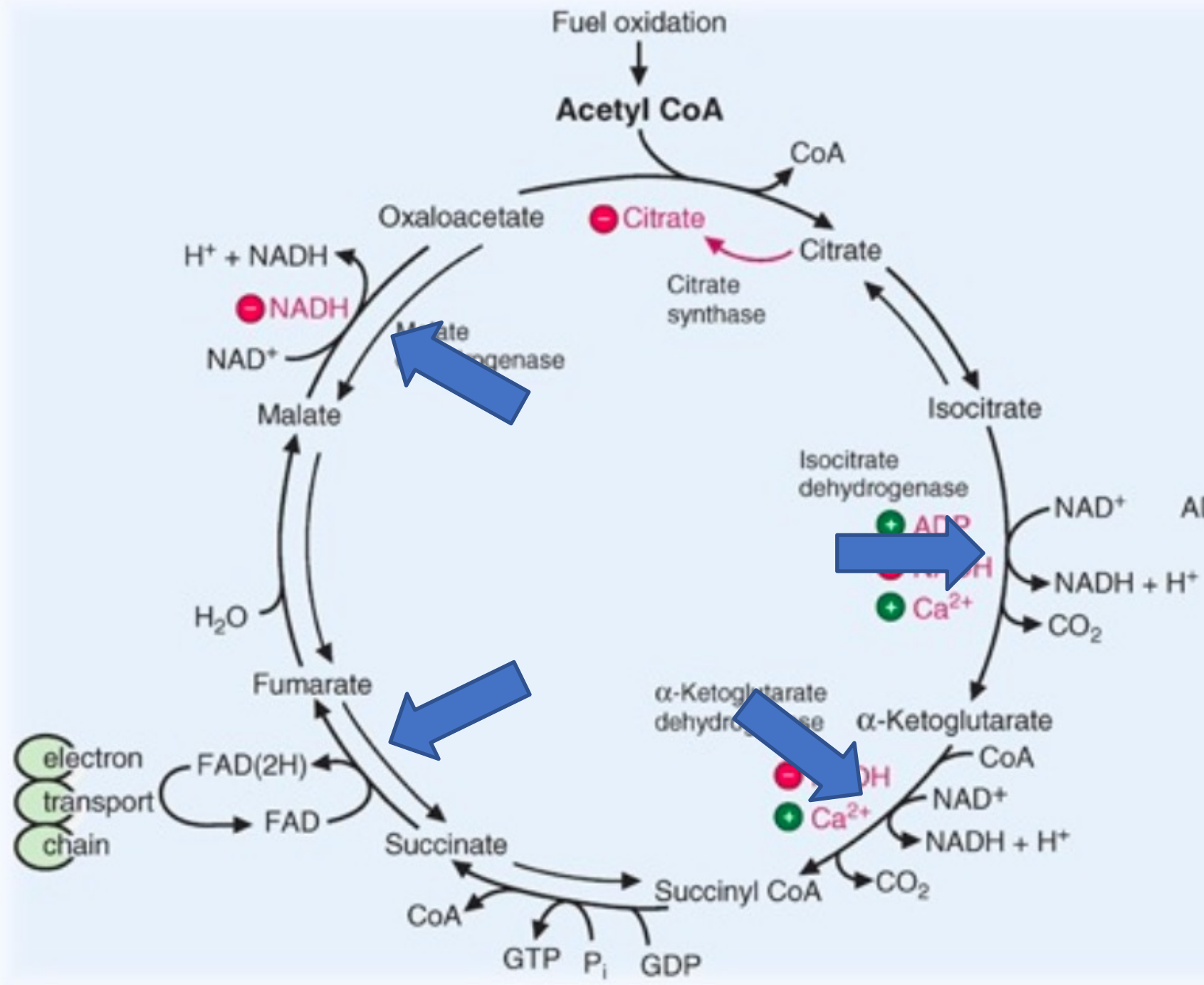
- 3NADH
- 1FADH
- 1GTP

- 1NADH=2,5 ATP
- 1FADH=1,5 ATP

Total ATP per Acetyl CoA = 10 ATP

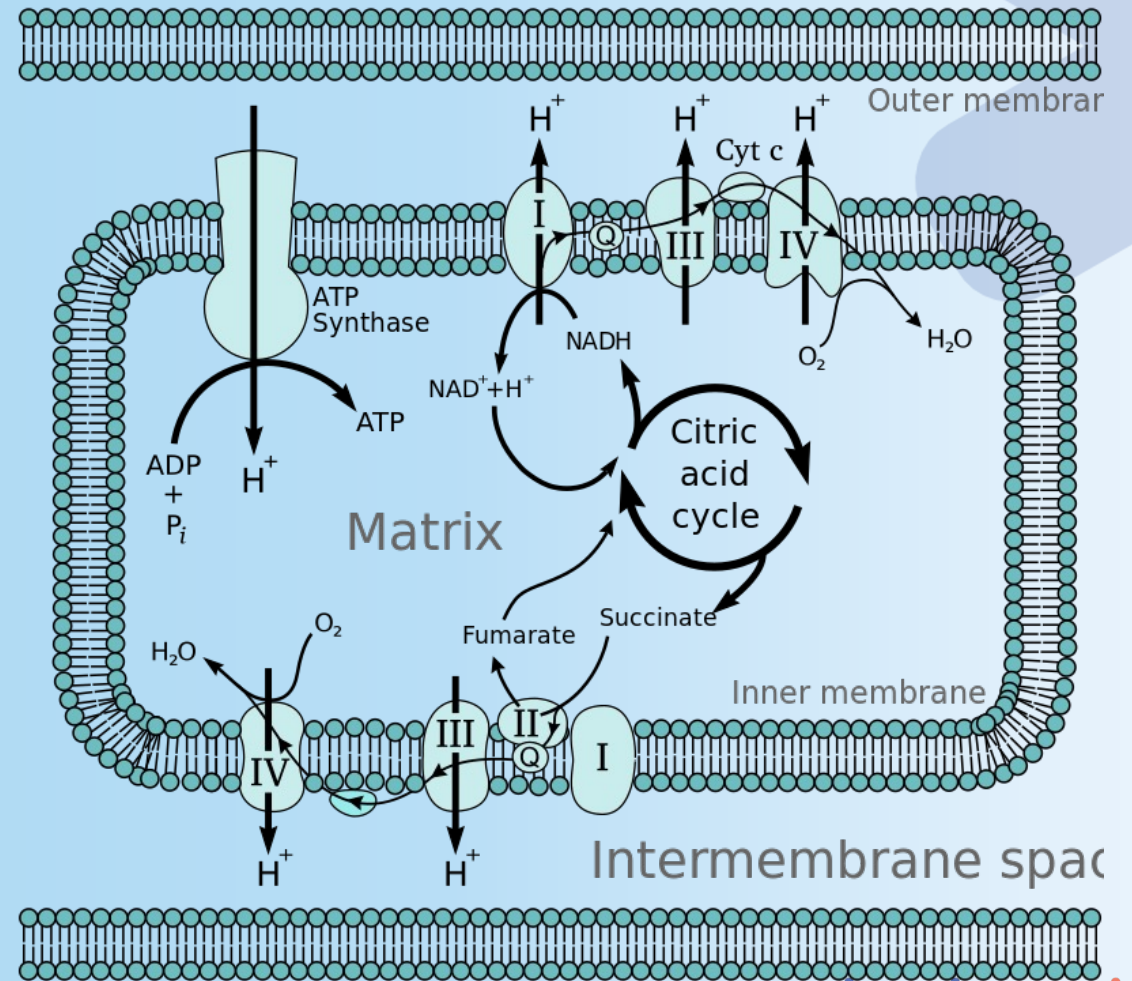
Total ATP per glucose molecule =
20 ATP (2*10=20)

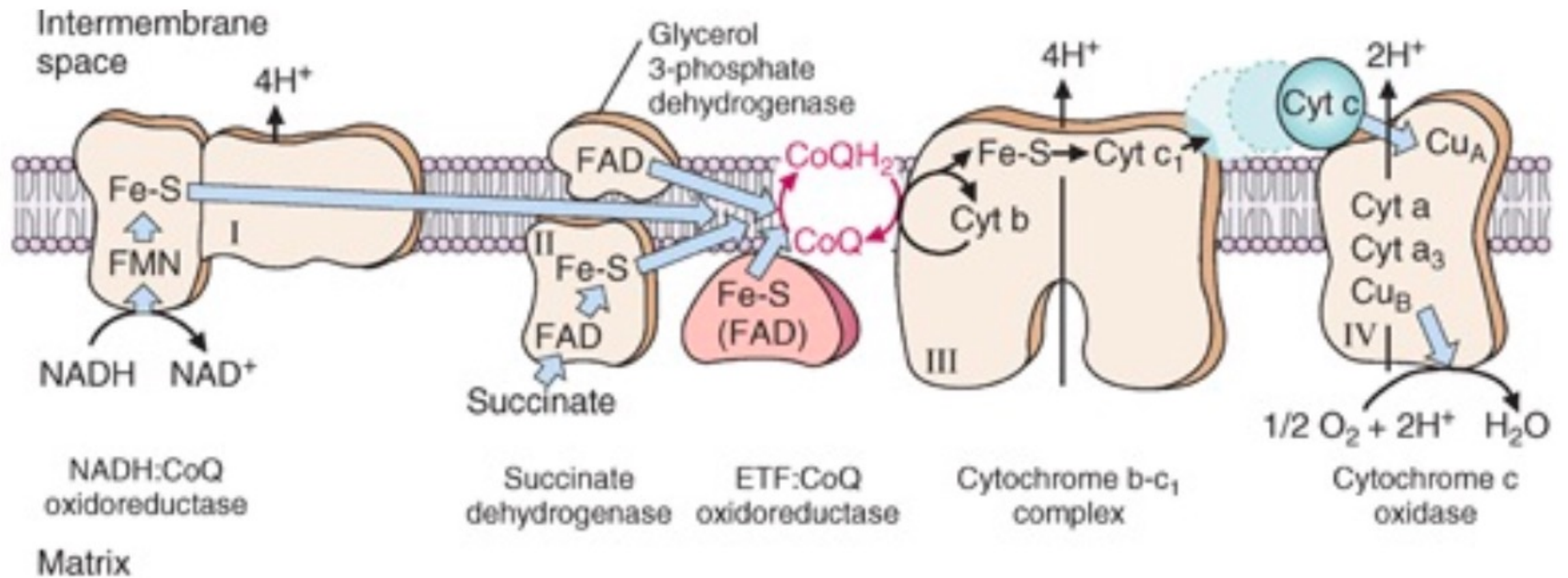




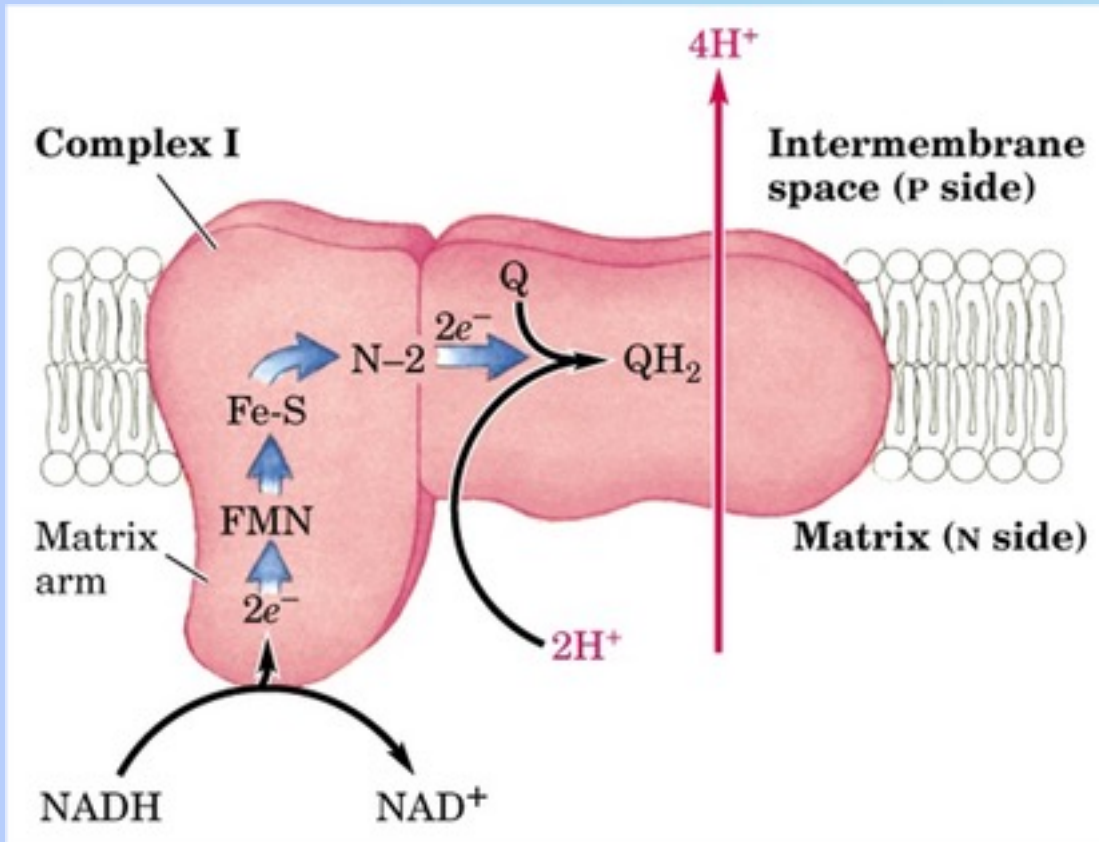
Oxidative phosphorylation!

- Donating electrons to oxygen to generate high energy bonds in the form of ATP
- Electrons comes in the form of H^+ from NADH and $FADH_2$
- Consists of electron transport chain and the ATP synthase
- Hydrogen ions are pumped out and create an electrochemical gradient -> Returns back to the matrix through ATP synthase and thus producing ATP





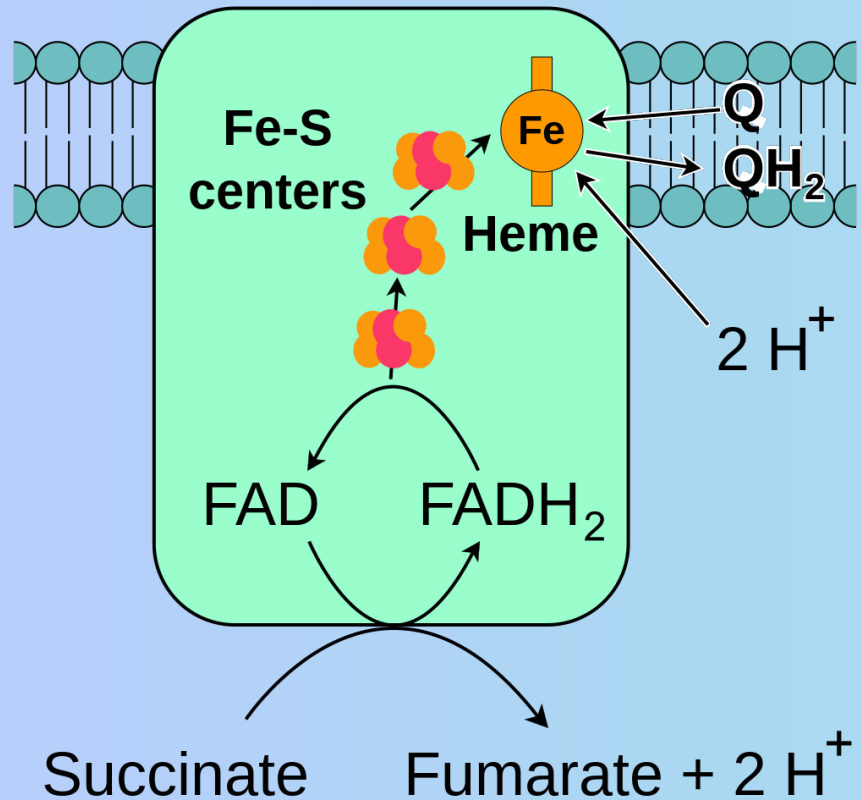
Complex I: NADH dehydrogenase



- NADH oxidoreductase
- NADH → FMNH₂ → Fe-S → CoQ
- 4H⁺ pumped to intermembrane space

Total pump count:
NADH: 4H⁺

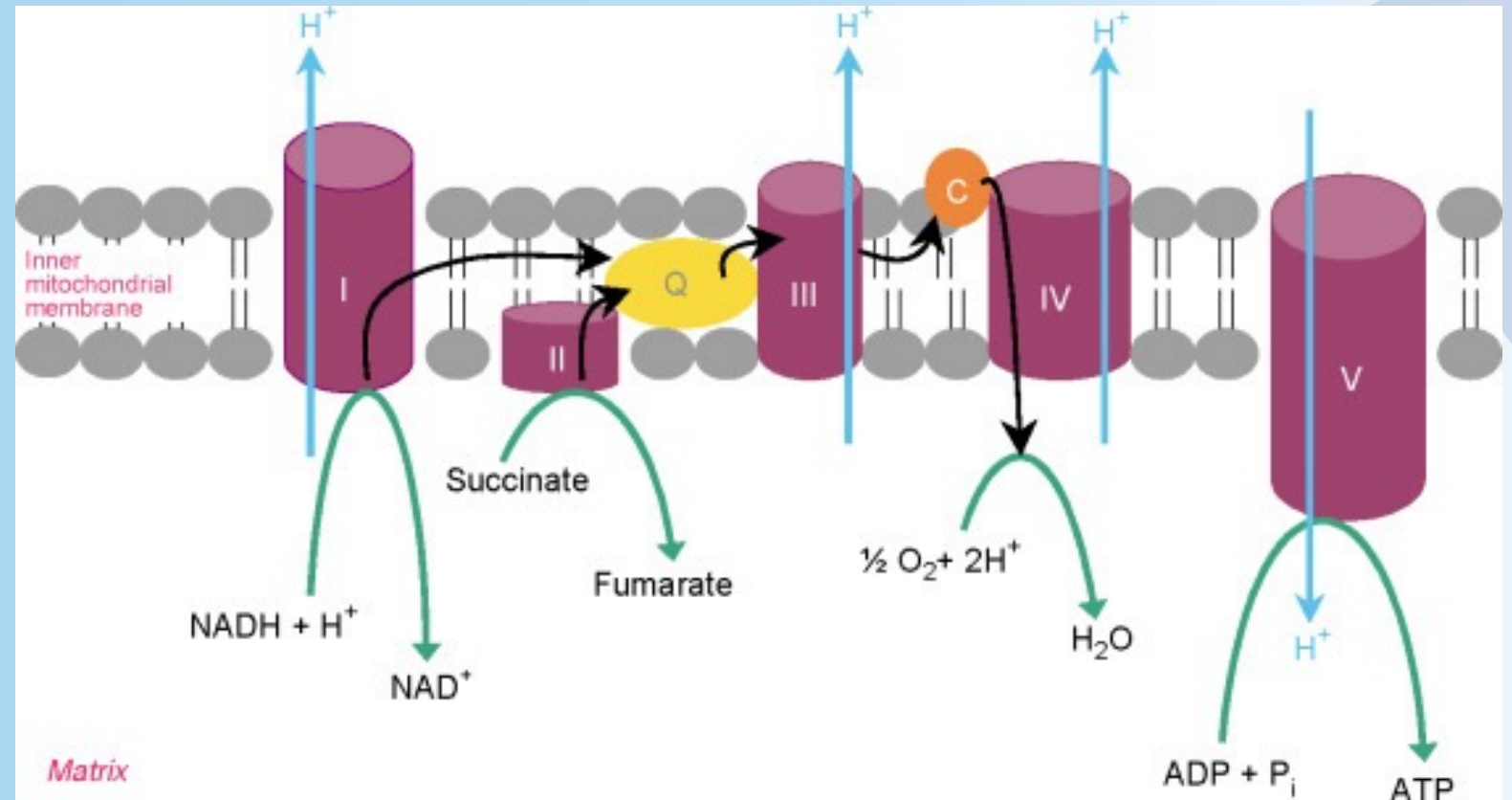
Complex II - Succinate dehydrogenase



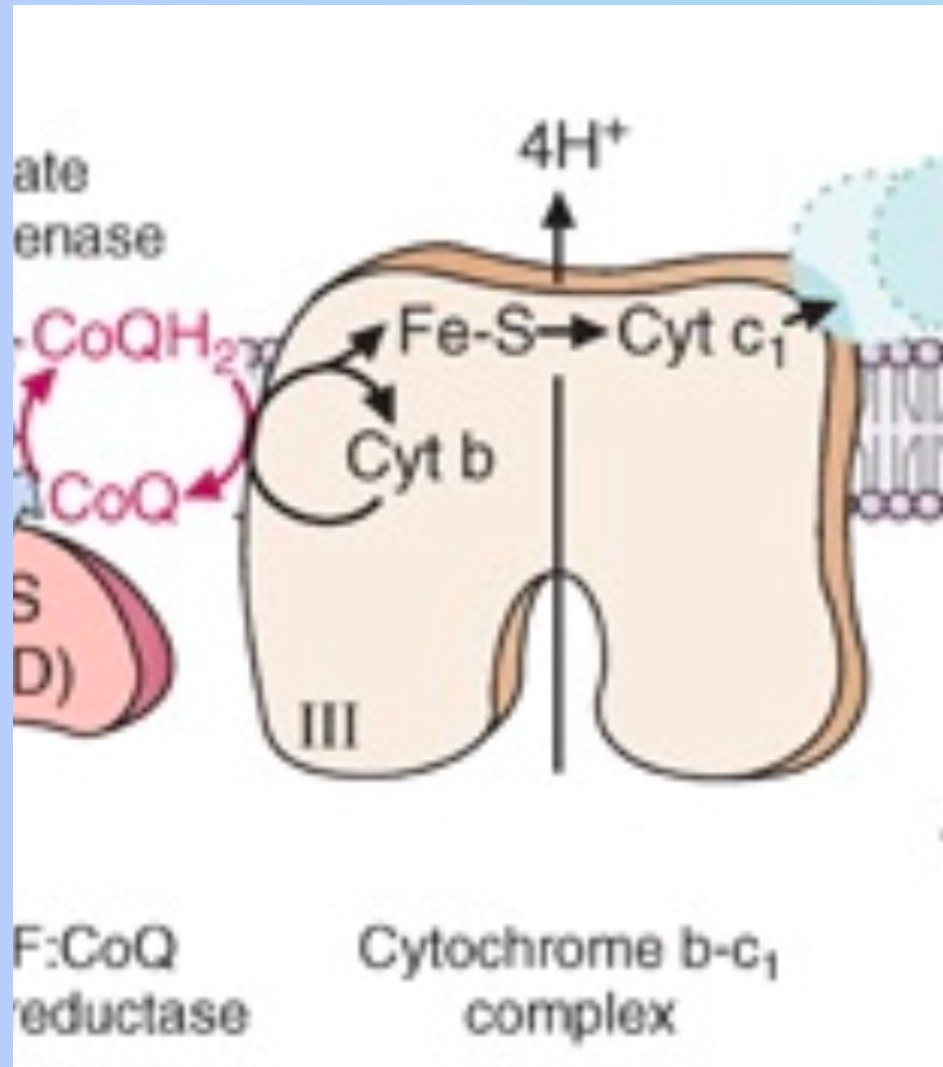
- Also called Quinone
- Succinate oxidized to fumarate
- FAD → FADH₂ → Fe-S → CoQ
- No H⁺ are pumped

CoQ (Ubiquinone)

- Mobile
- Transports electrons from complex I and II to complex III



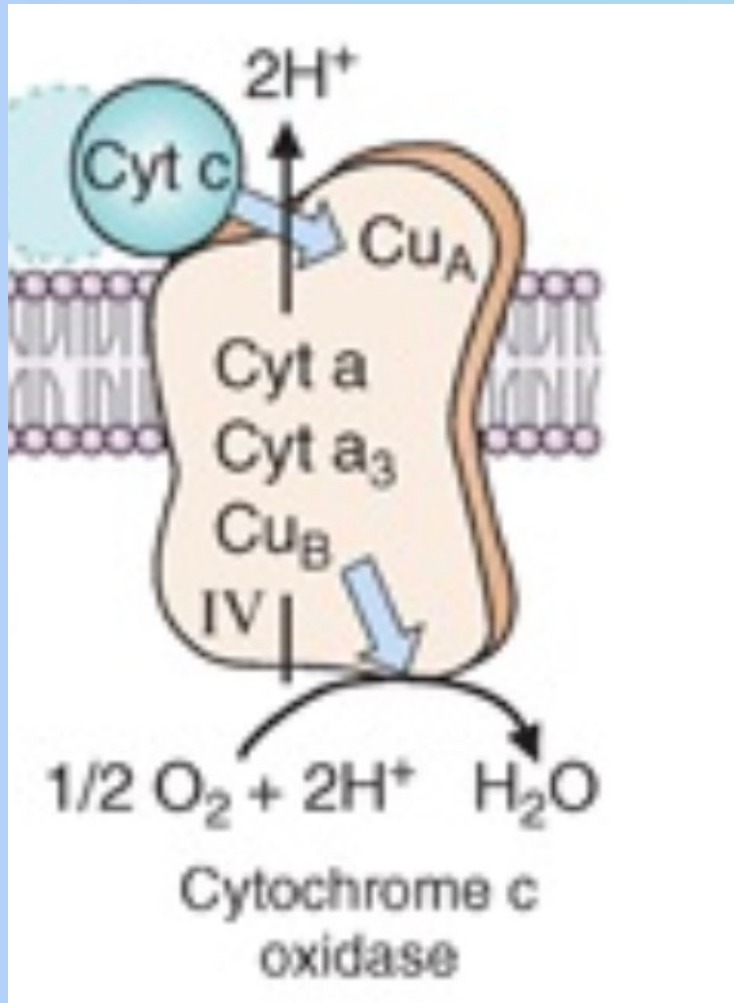
Complex III - cytochrome bc₁



- Q-cytochrome c oxidoreductase or Cytochrome reductase
- CoQH₂ → FeS → Cyt C₁
- 4H⁺ pumped to intermembrane space

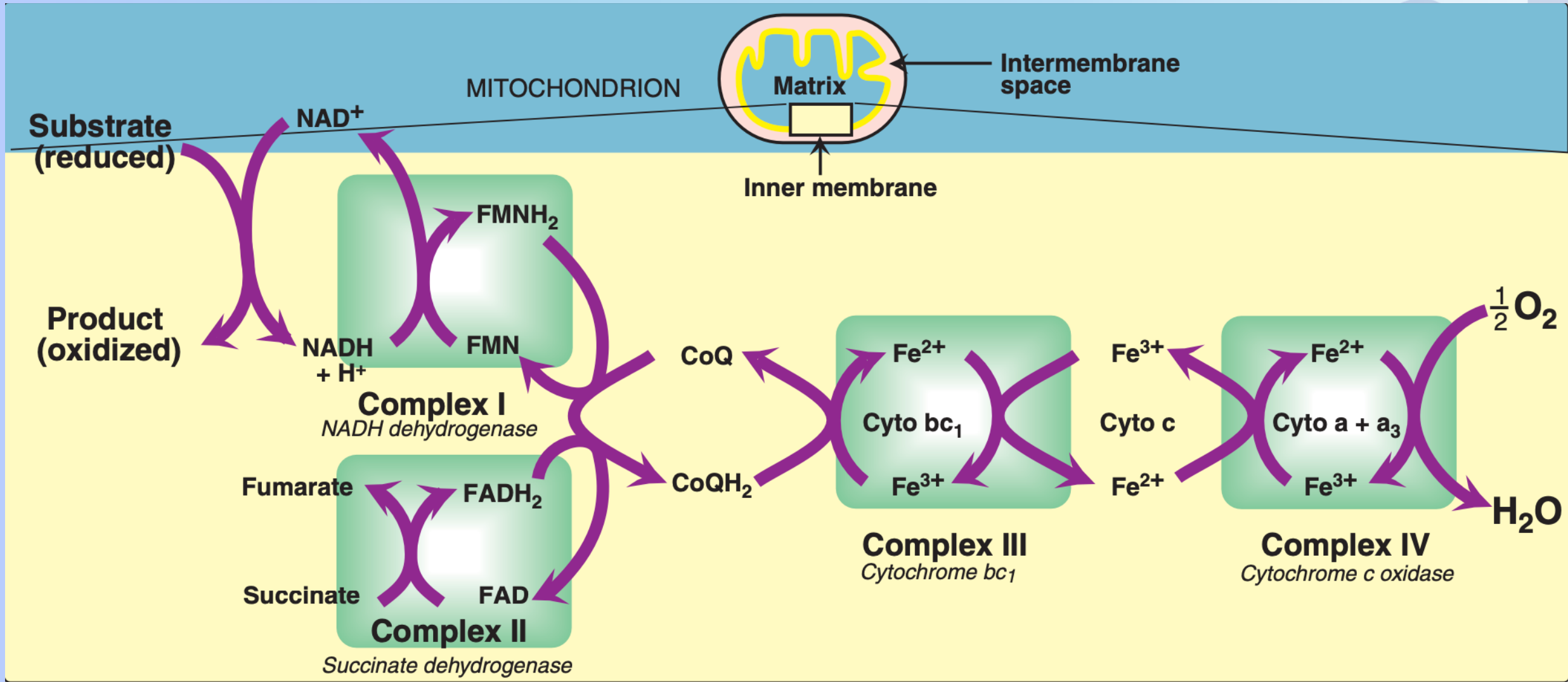
Total pump count
NADH: 8H⁺
FADH₂: 4H⁺

Complex IV - cytochrome c oxidase



- O₂ reduced to H₂O
- 2 H⁺ Pumped to intermembrane space

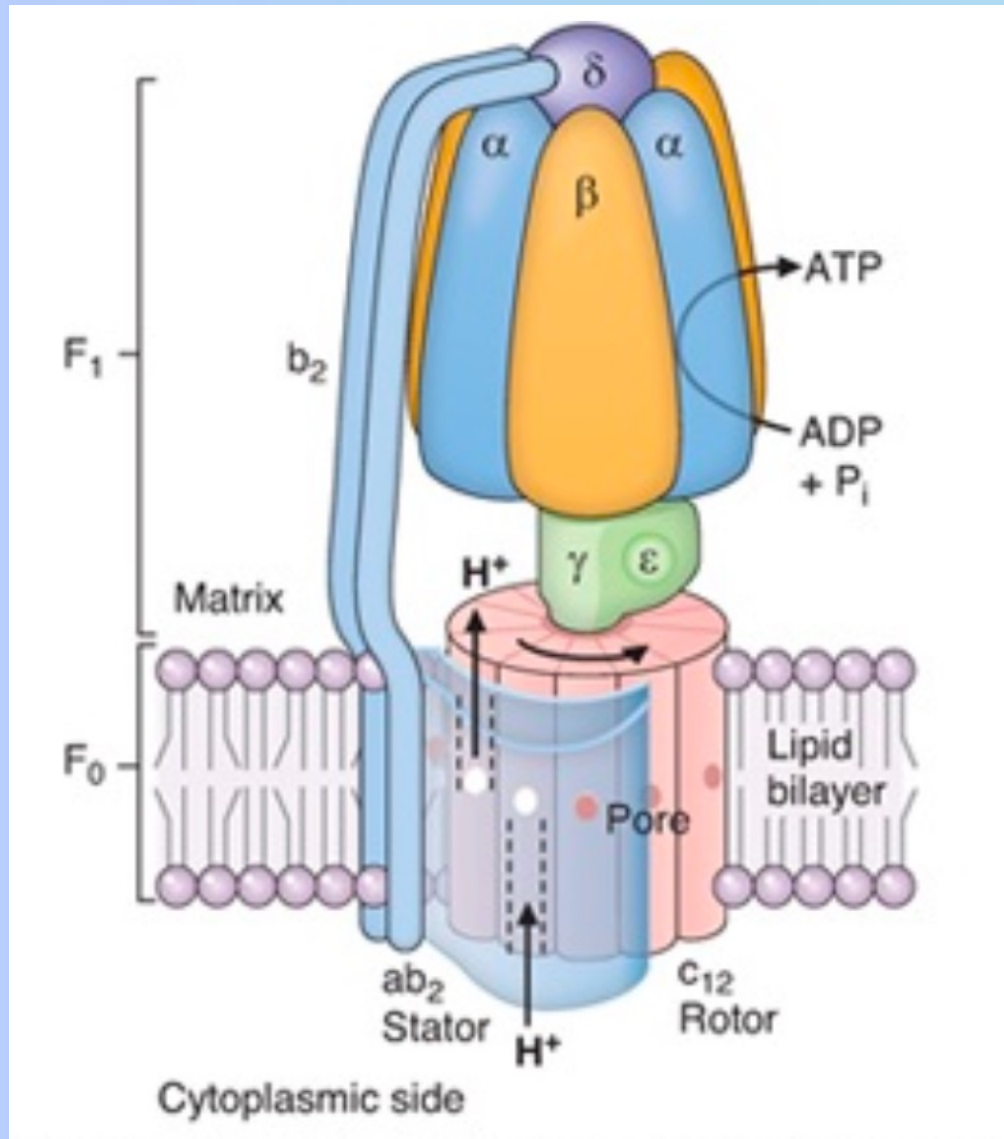
Total pump count
NADH: 10H⁺
FADH₂: 6H⁺



Chemiosmotic hypothesis

- Generation of ATP is based on the electrochemical gradient created by the H^+ ions pumped out of the inner mitochondrial membrane
- 2 gradients:
 - Membrane potential
 - Proton gradient
- 1 NADH pumps out 10 H^+
- 1 $FADH_2$ pumps out 6 H^+

Complex V: ATP synthase

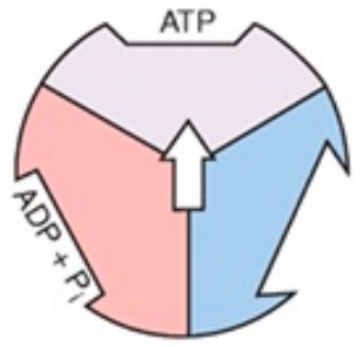


- F₀F₁-ATPase
- F₀: Membrane domain
- F₁: Stalk and headpiece
- H⁺ going through the channel rotates the ATP synthase

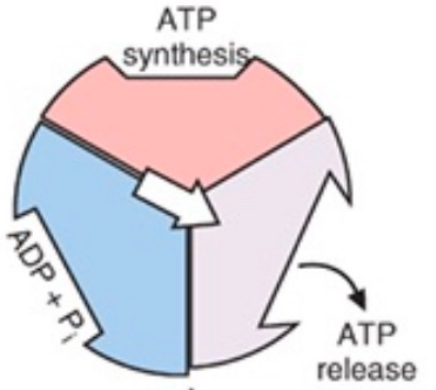
4 H⁺ ions = 1 ATP

1 NADH = 2,5 ATP (10 H⁺)

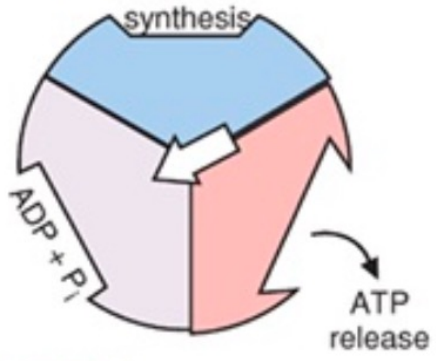
1 FADH = 1,5 ATP (6 H⁺)



1
ADP + P_i
Energy



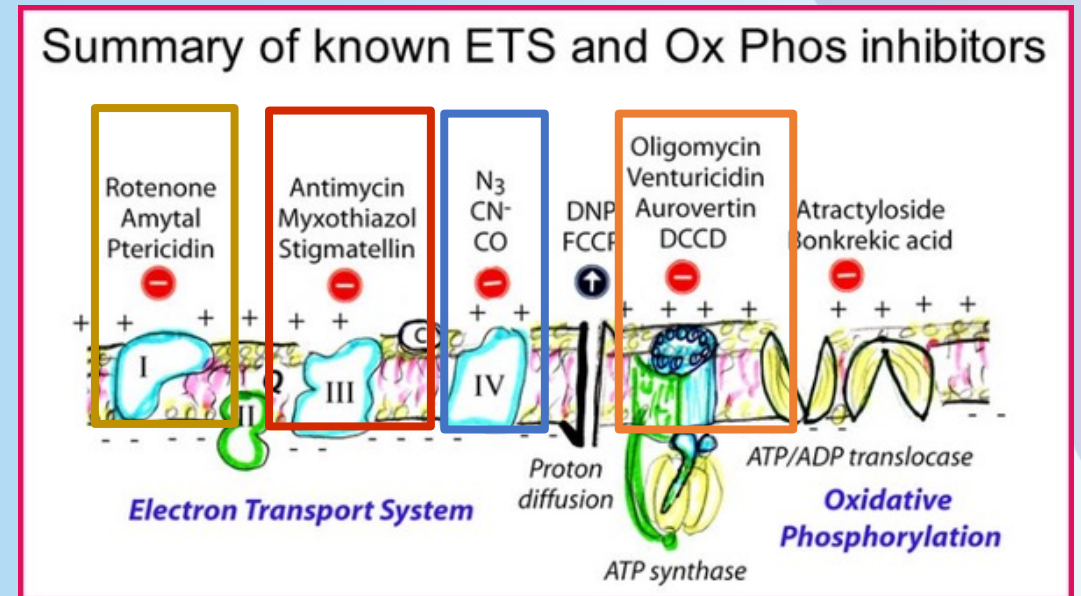
2
ADP + P_i





ETC inhibitors

- Complex I
 - **Amytal (Amobarbital)**
 - Shown to protect the heart during ischemia and reperfusion injury
 - **Rotenone**
 - Inhibits transfer from Fe-S center to CoQ
- Complex III
 - **Antimycin A and C**
 - Binds to quinone reduction site
- Complex IV
 - **Cyanide (CN⁻)**
 - Binds to ferric ion → blocking ETC → cell death, hypoxia, and lactic acidosis
 - **Carbon Monoxide (CO)**
 - Blocks electron flow between complex and O₂
 - Inhibits Fe²⁺



Iron deficiency anemia can cause fatigue due to decreased Fe for Fe-S centers and cytochromes



Uncoupling agents

- Decoupler: Facilitates proton transfer across inner mitochondrial membrane without generating ATP
 - Generate heat
- Salicylic acid
 - 2,4 Dinitrophenol (DNP)
 - Previously used in weight loss

Quiz time!



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