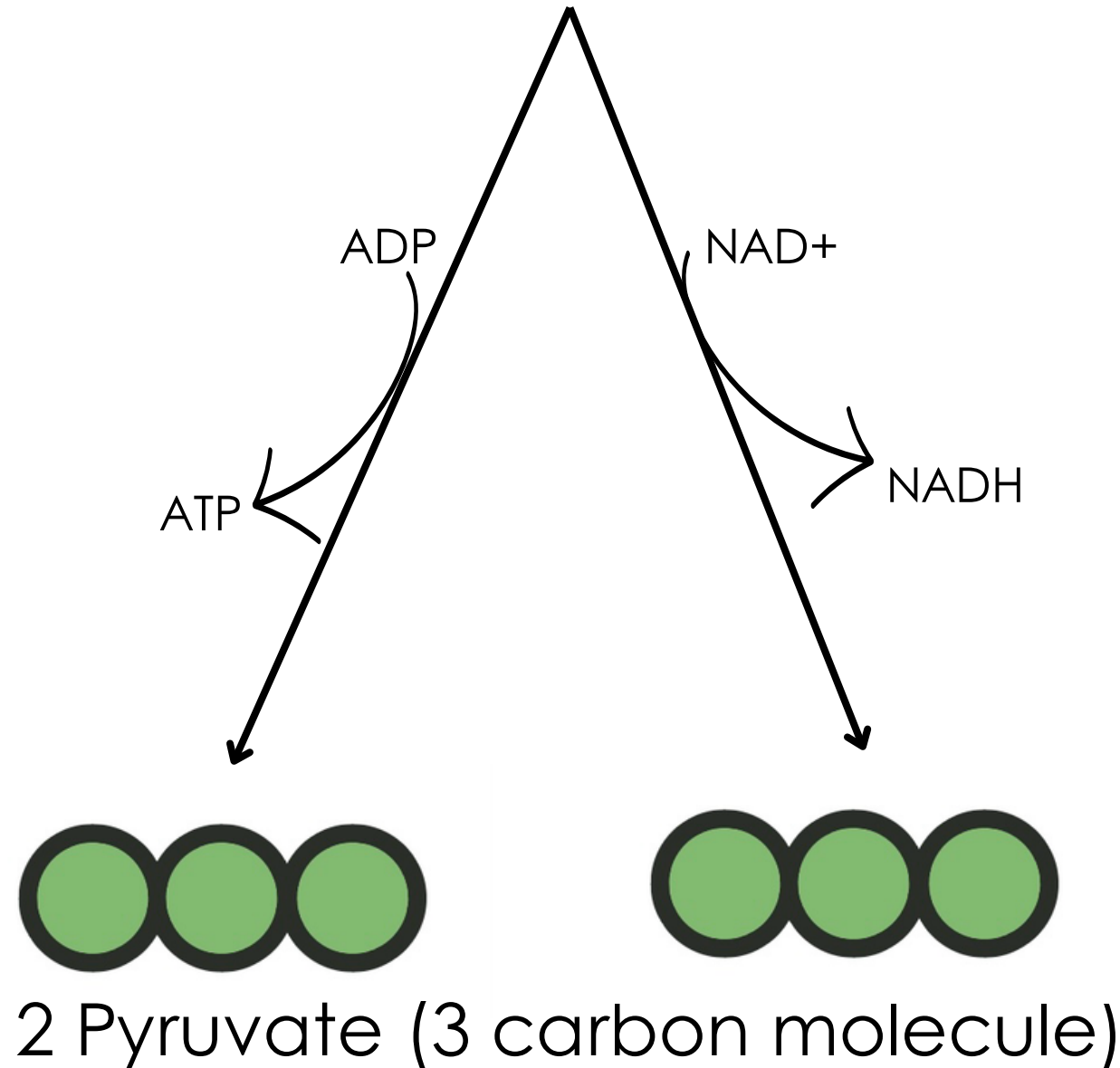
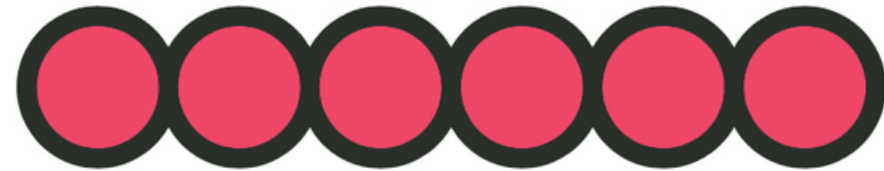


Krebs Cycle & Oxidative Phosphorylation

By Sarah Cullen

Glucose is converted into Pyruvate

Glucose (6 carbon molecule)



Glucose is converted from a 6 carbon fragment to a 3 carbon fragment named **pyruvate**

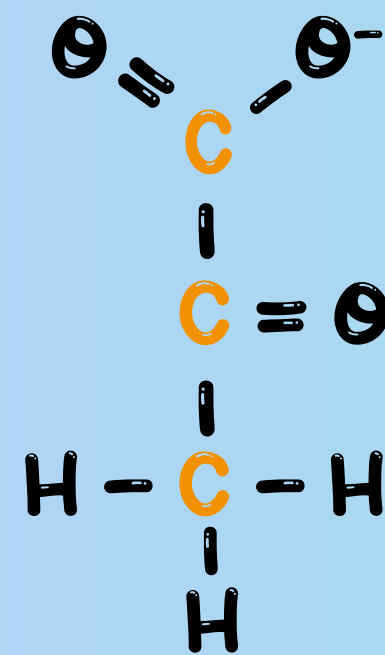
1 glucose = 2 pyruvate

2 NADH and 2 ATP are generated as a result

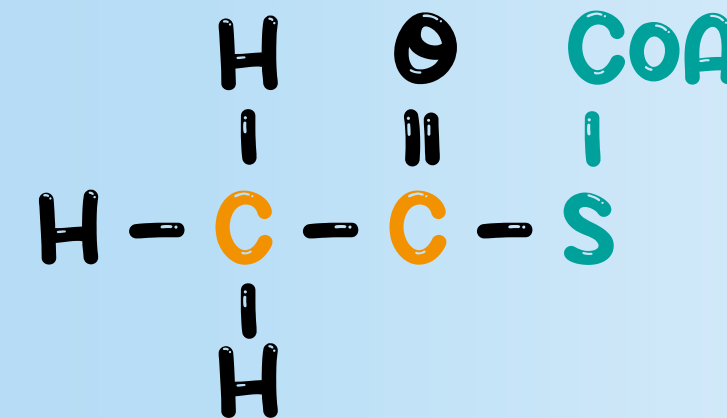
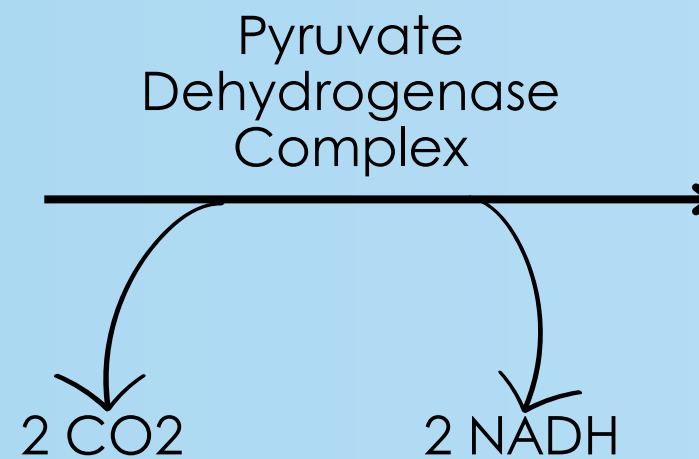
Pyruvate is then carried into the mitochondria if oxygen is present, where it enters a transition stage

Acetyl-CoA

CoA is added to pyruvate, forming a 2 carbon molecule, Acetyl CoA through a process called decarboxylation



Pyruvate

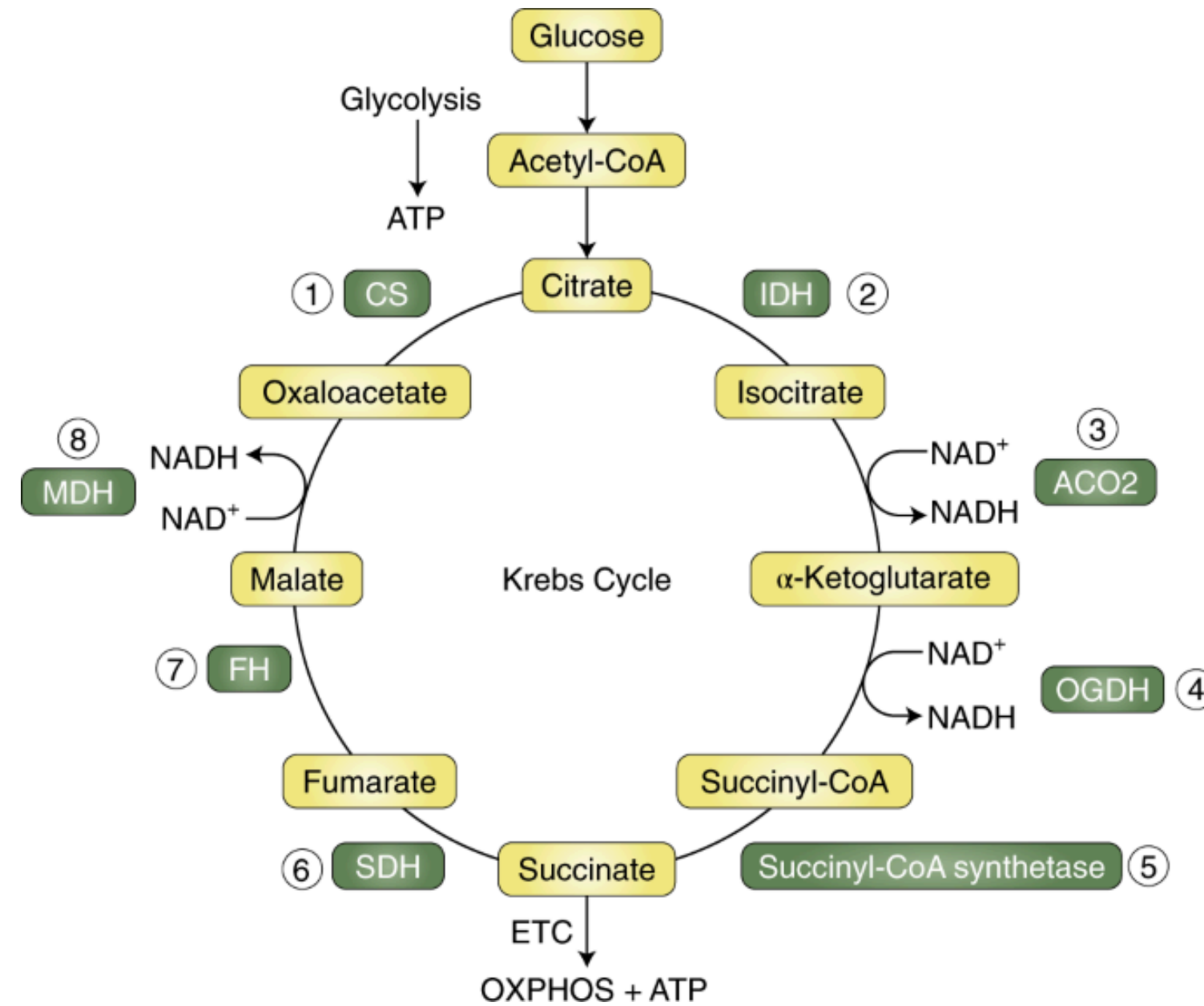


Acetyl-CoA

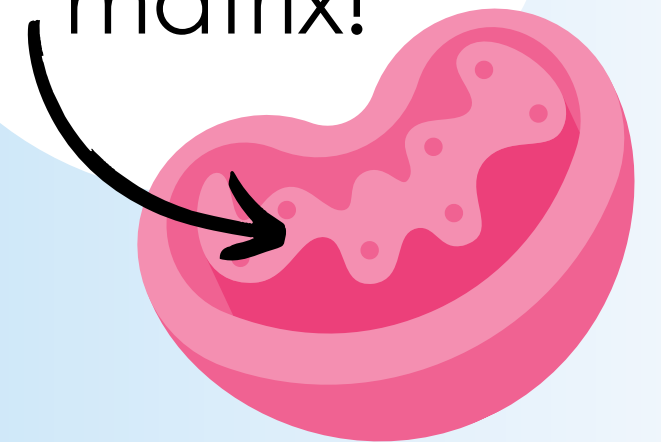
Generates:

2 CO₂
2 NADH

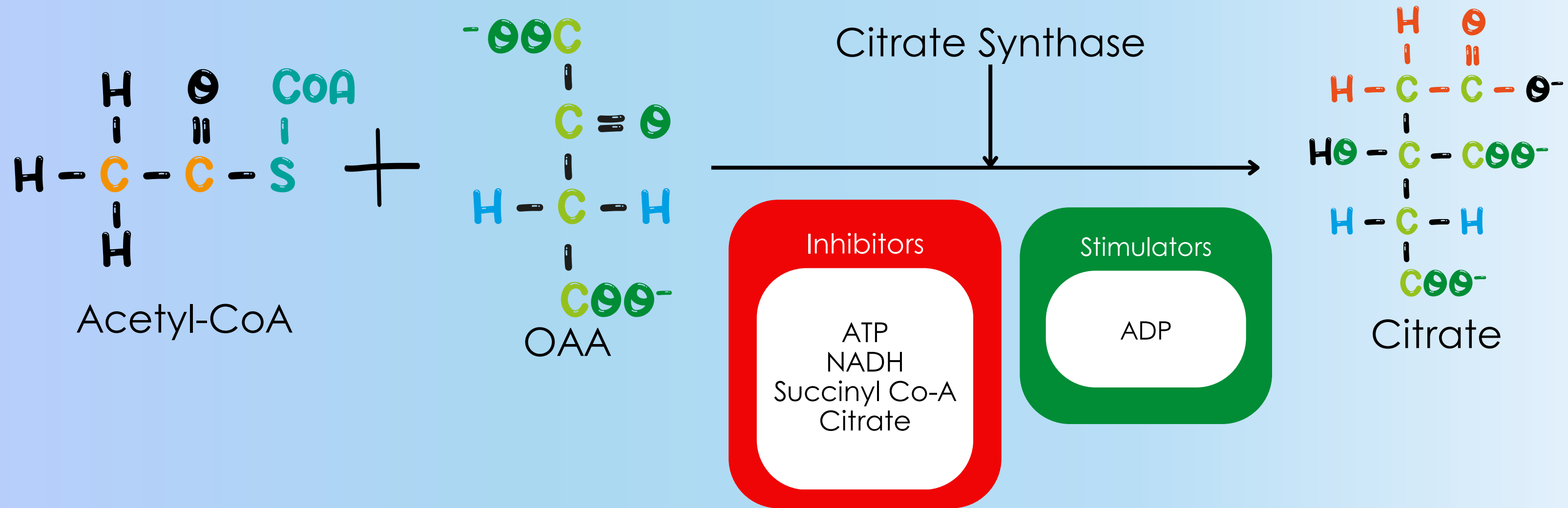
TCA (Krebs cycle)



Takes place within mitochondrial matrix!



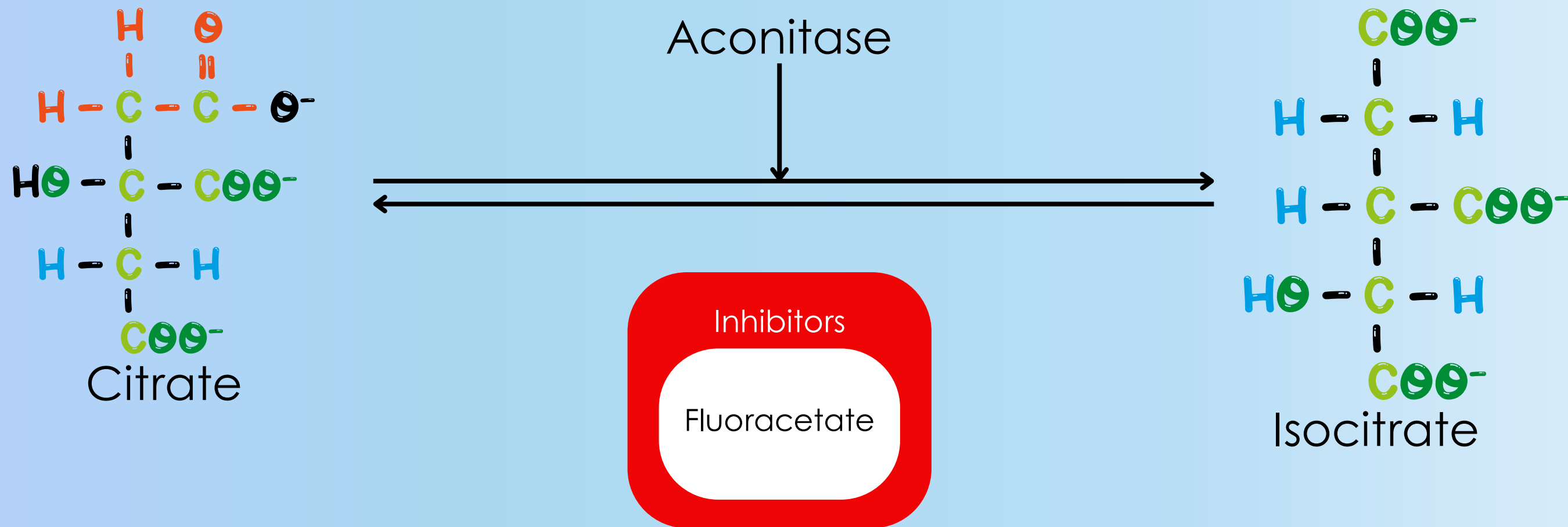
Citrate



Citrate synthase acts on Acetyl CoA and OAA to make Citrate

One way reaction - highly regulated and irreversible

Isocitrate



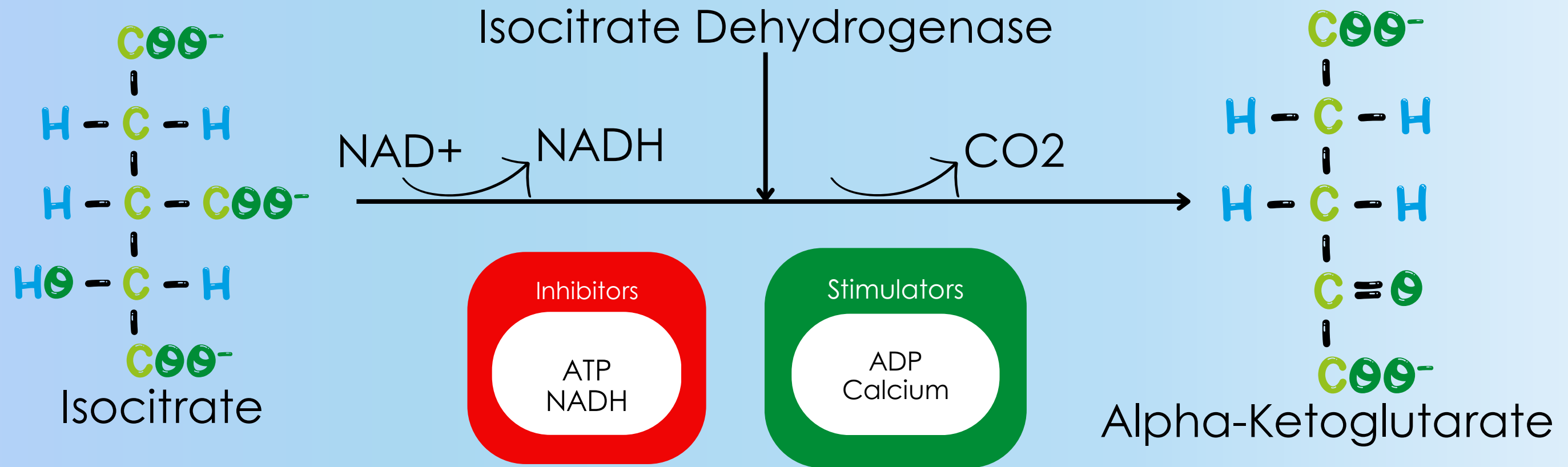
Isomerisation - Citrate is converted into Isocitrate

Enzyme: Aconitase

Reversible reaction

Fluoroacetate inhibits aconitase

Alpha-Ketoglutarate



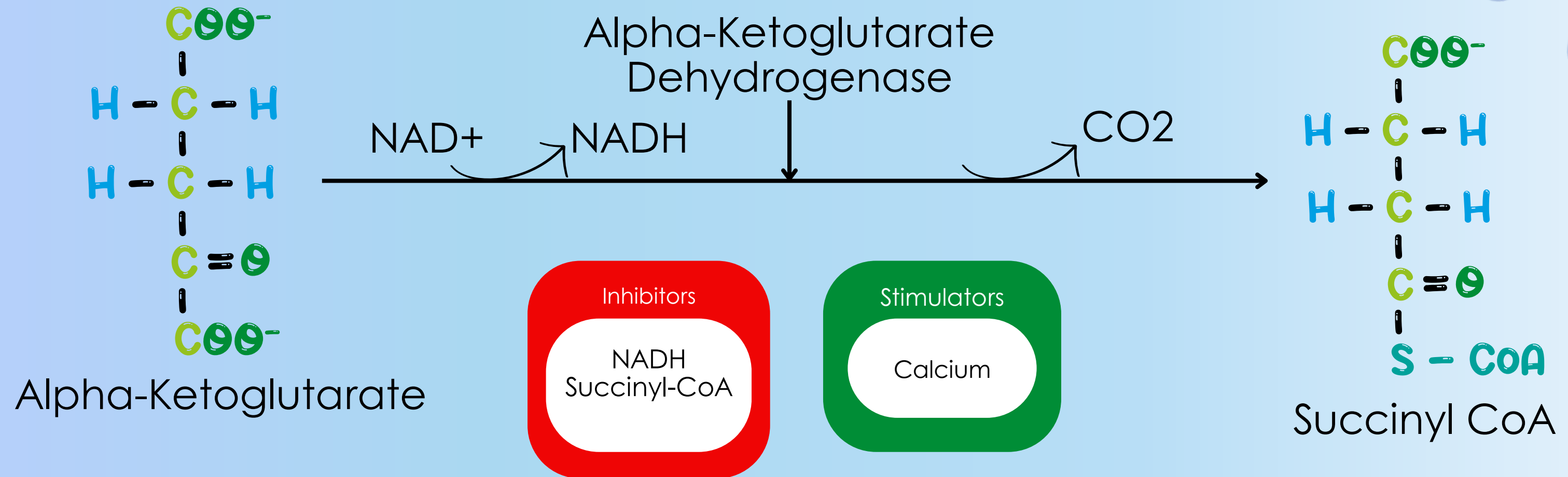
Decarboxylation - isocitrate is converted into alpha-ketoglutarate

Generates NADH and CO₂

Enzyme: Isocitrate Dehydrogenase

Moves in one direction and is irreversible

Succinyl-CoA

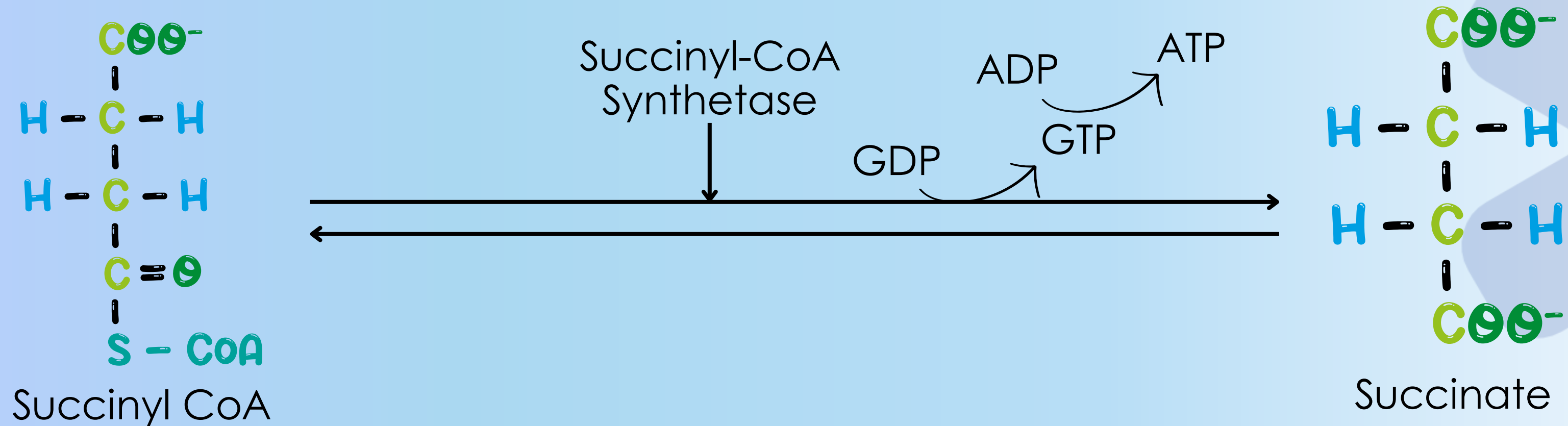


Decarboxylation - Alpha-ketoglutarate is converted into Succinyl CoA

Enzyme: alpha-ketoglutarate dehydrogenase

Generates NADH and CO₂

Succinate



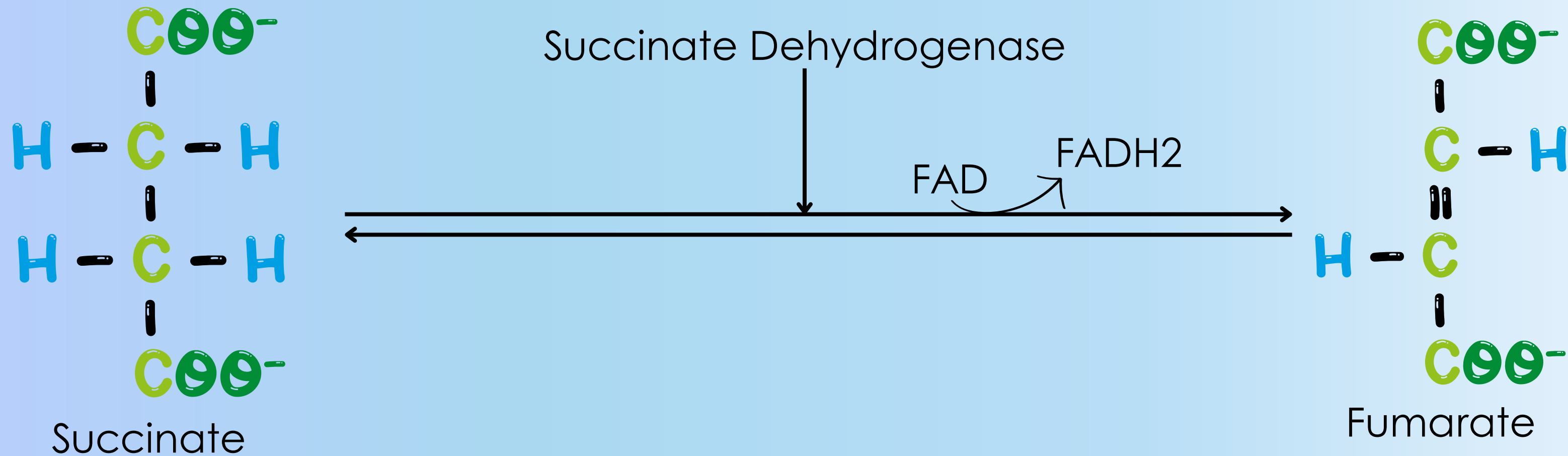
Succinyl-CoA is converted into succinate

GTP is generated from the energy of the reaction, ADP steals phosphate group to make ATP - substrate level phosphorylation (different from oxidative phosphorylation!)

Enzyme: Succinyl-CoA Synthetase

Reversible Reaction

Fumarate



Dehydrogenation - Succinate is converted into Fumarate

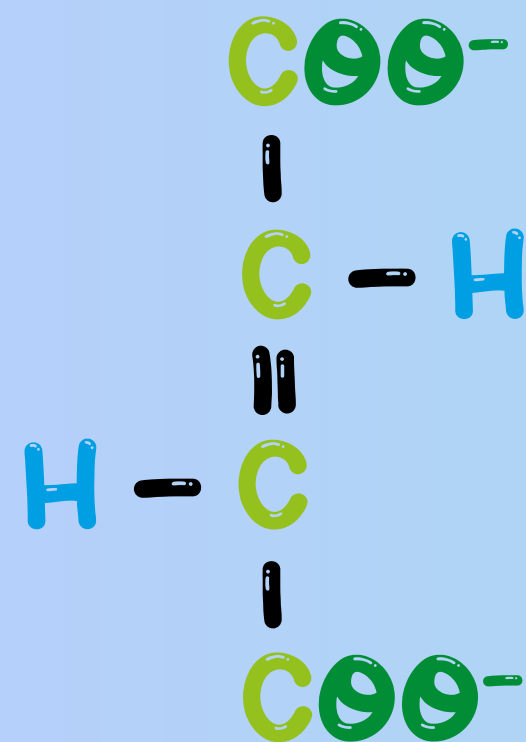
Enzyme: Succinate Dehydrogenase (located on cristae)

Products: FADH₂

Reversible reaction

Clinical Correlation - Pheochromocytoma

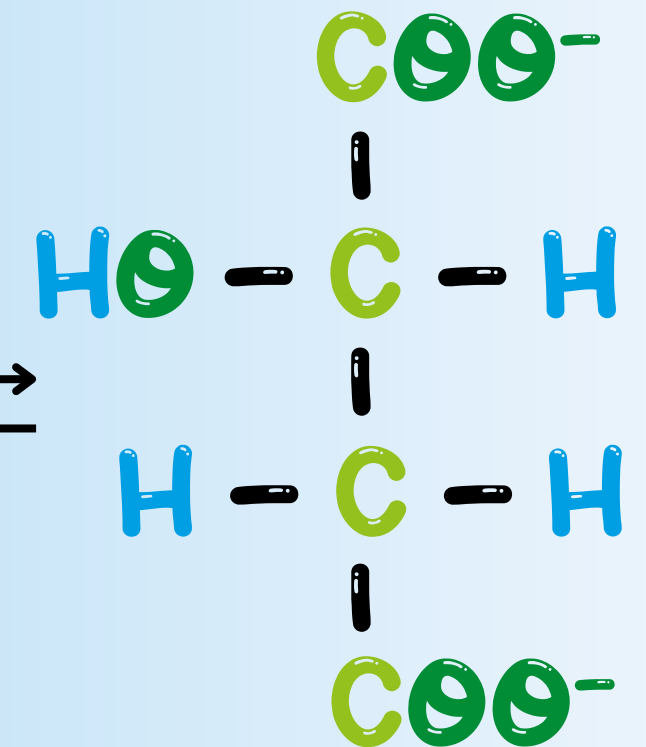
Malate



Fumarate

Fumarase

H₂O



Malate

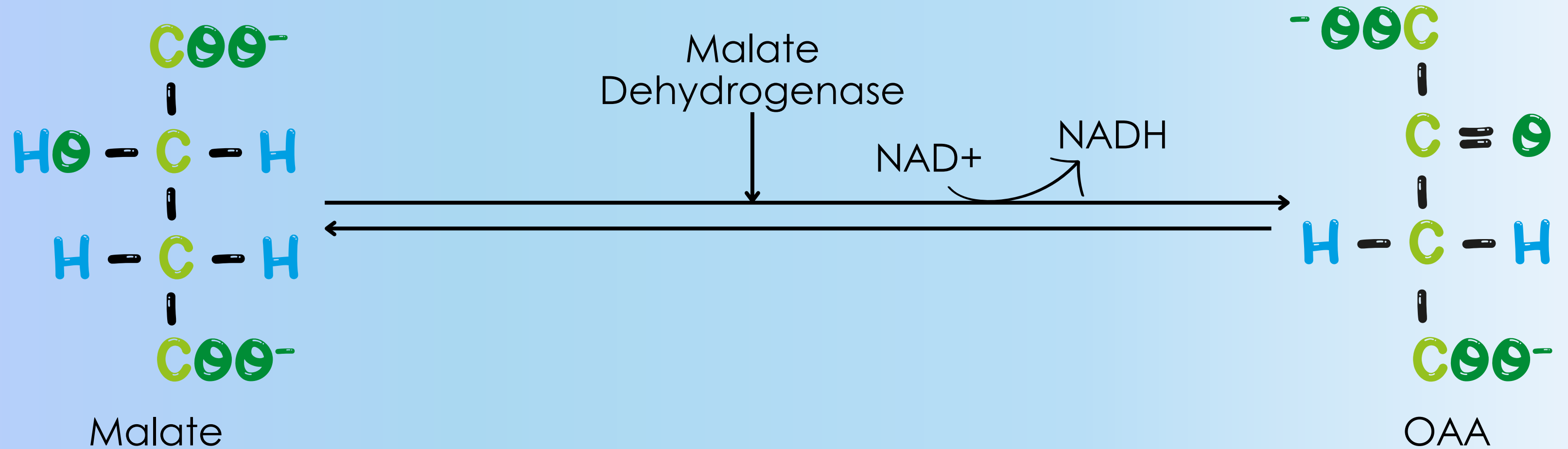
Fumarate is converted into Malate using H₂O

Enzyme: Fumarase

Reversible reaction

Clinical Correlation: Leiomyomas

OAA

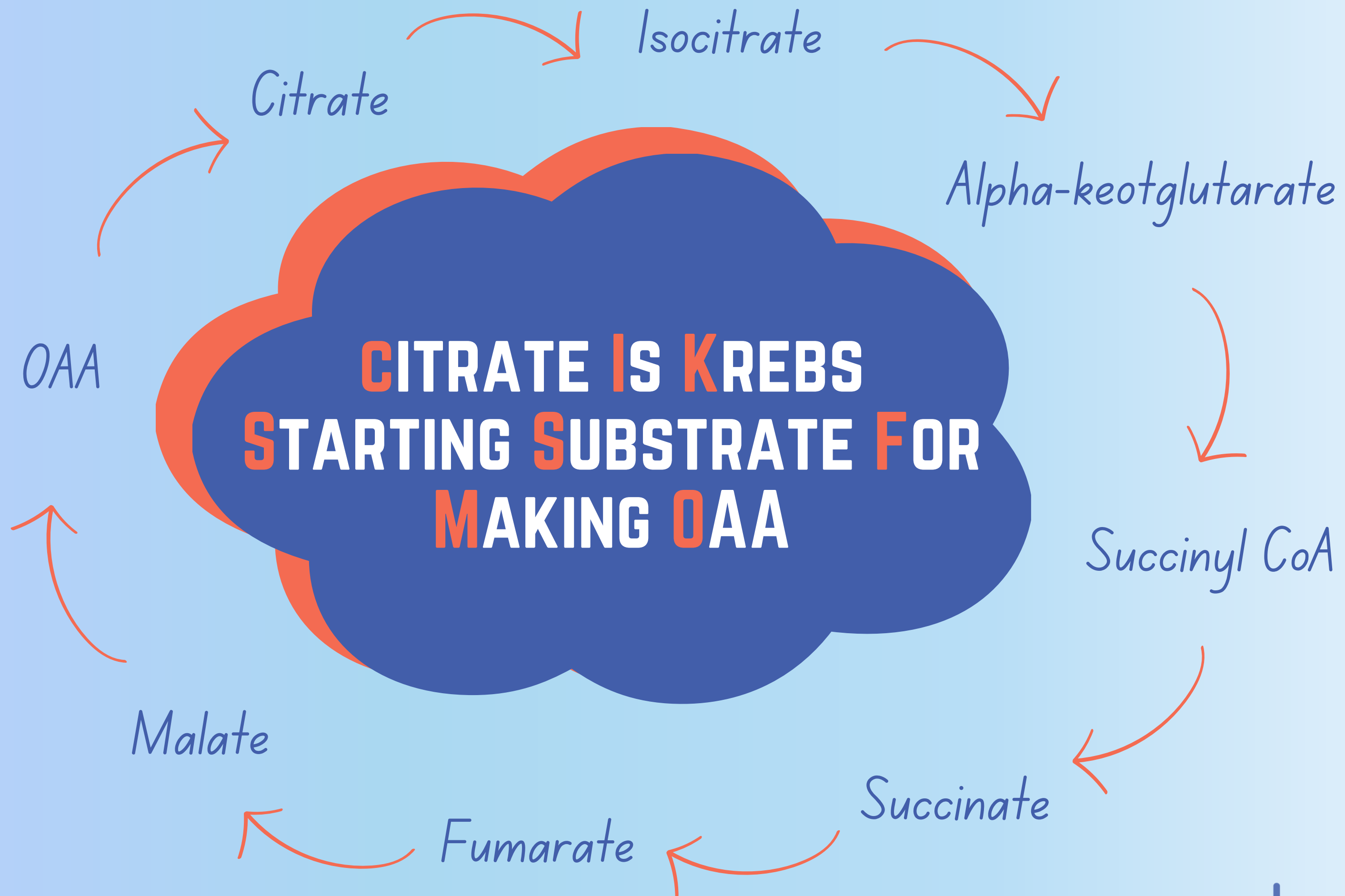


Dehydrogenation - Malate is converted into OAA

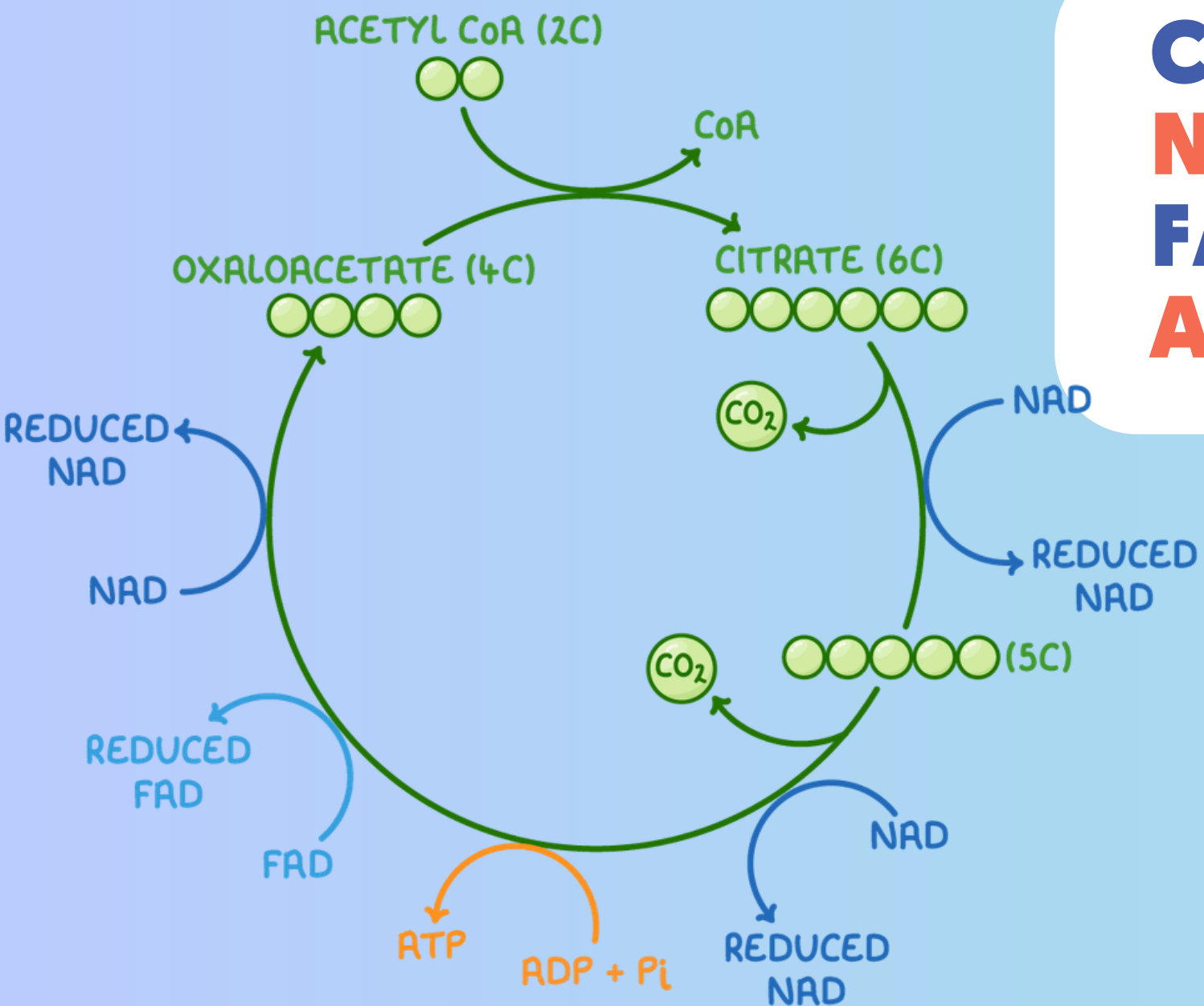
Enzyme: Malate Dehydrogenase

Products: NADH

Reversible reaction



Total Products of the TCA Cycle

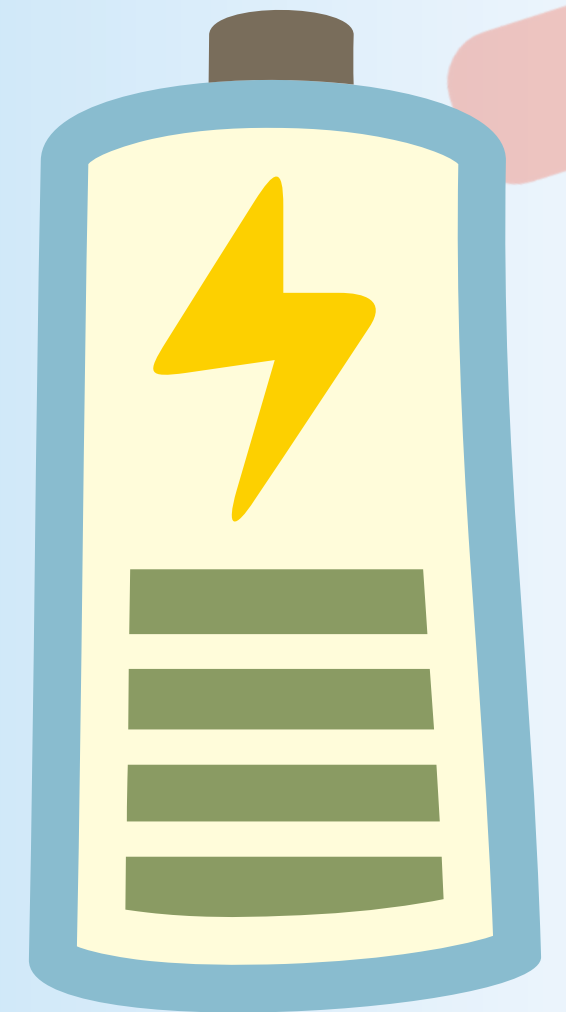


CO₂: $2 \times 2 = 4$
NADH: $3 \times 2 = 6$
FADH: $1 \times 2 = 2$
ATP: $1 \times 2 = 2$

1 NADH = 2.5 ATP

1 FADH - 1.5 ATP

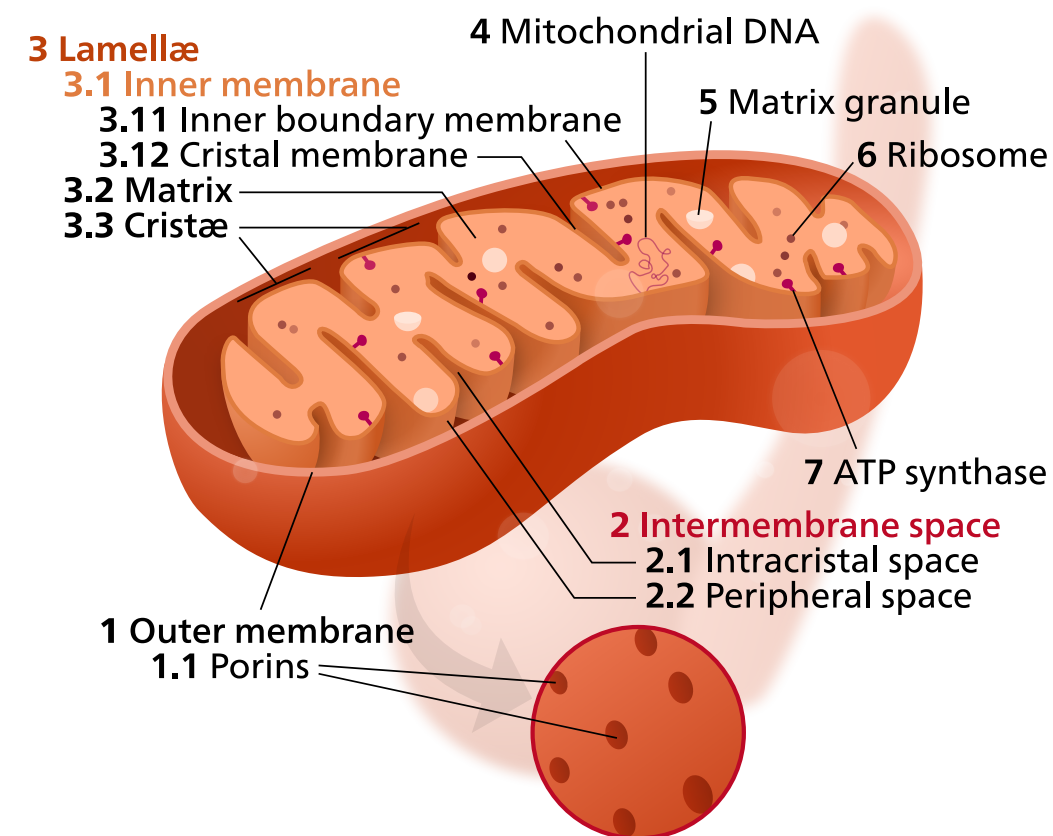
Total ATP per Cycle = 20



Oxidative Phosphorylation

Electron Transport Chain & Chemiosmosis

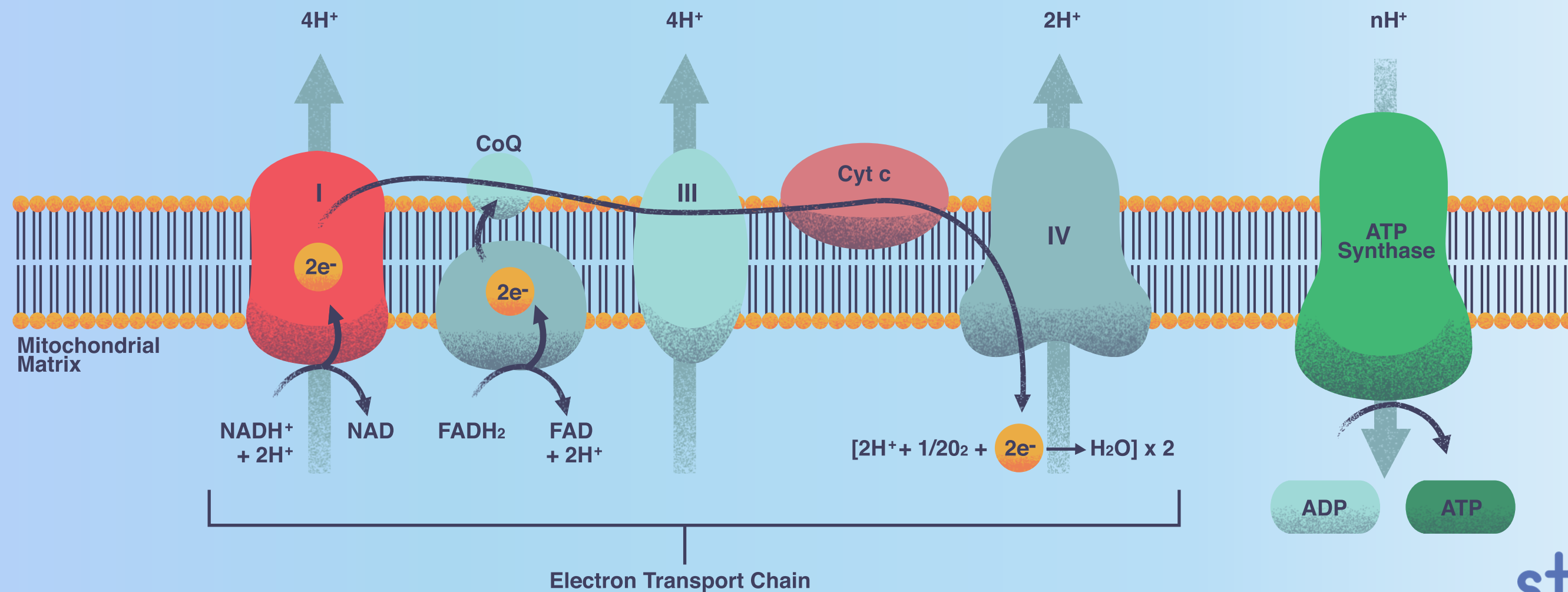
Location - cristae of the mitochondria + intermembrane space



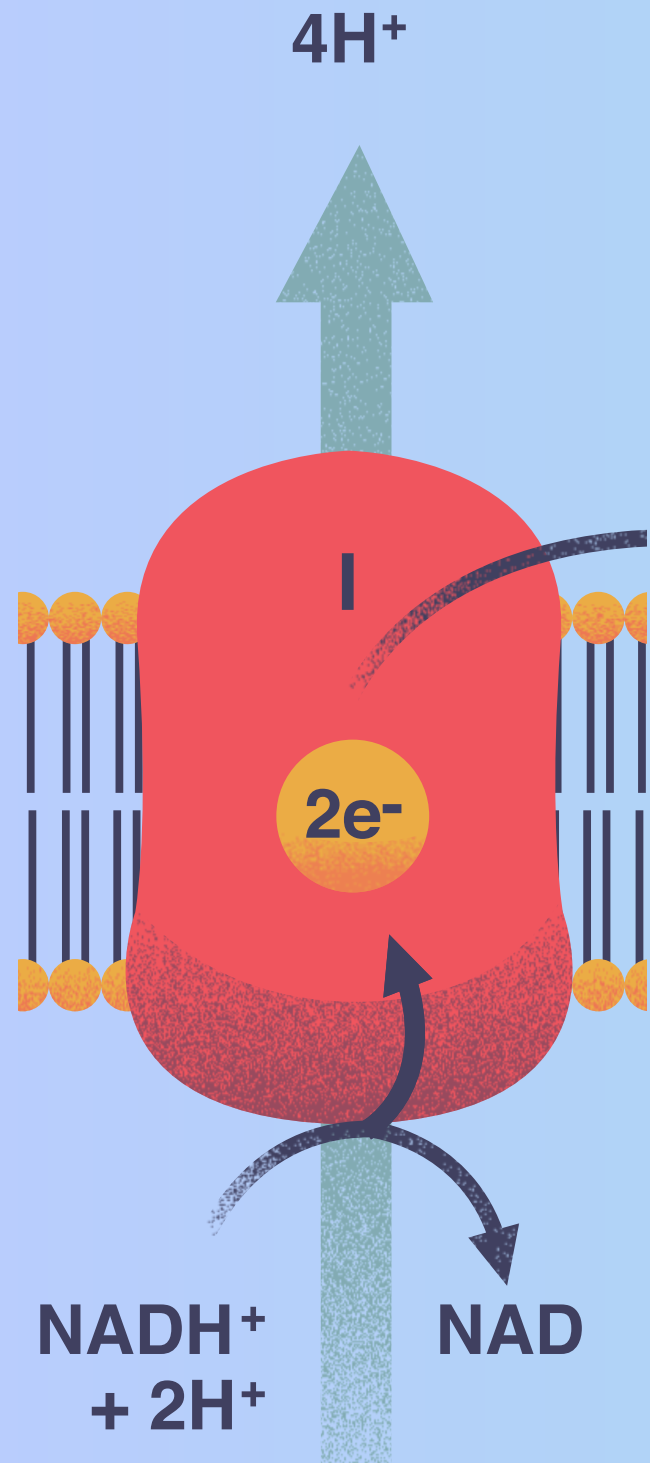
Electron Transport Chain

Occurs on the inner mitochondrial membrane initially

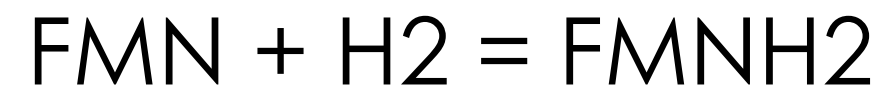
NADH (8), FADH₂ (2) and H⁺ act as shuttles to transport electrons through ETC



Complex I - NADH Dehydrogenase



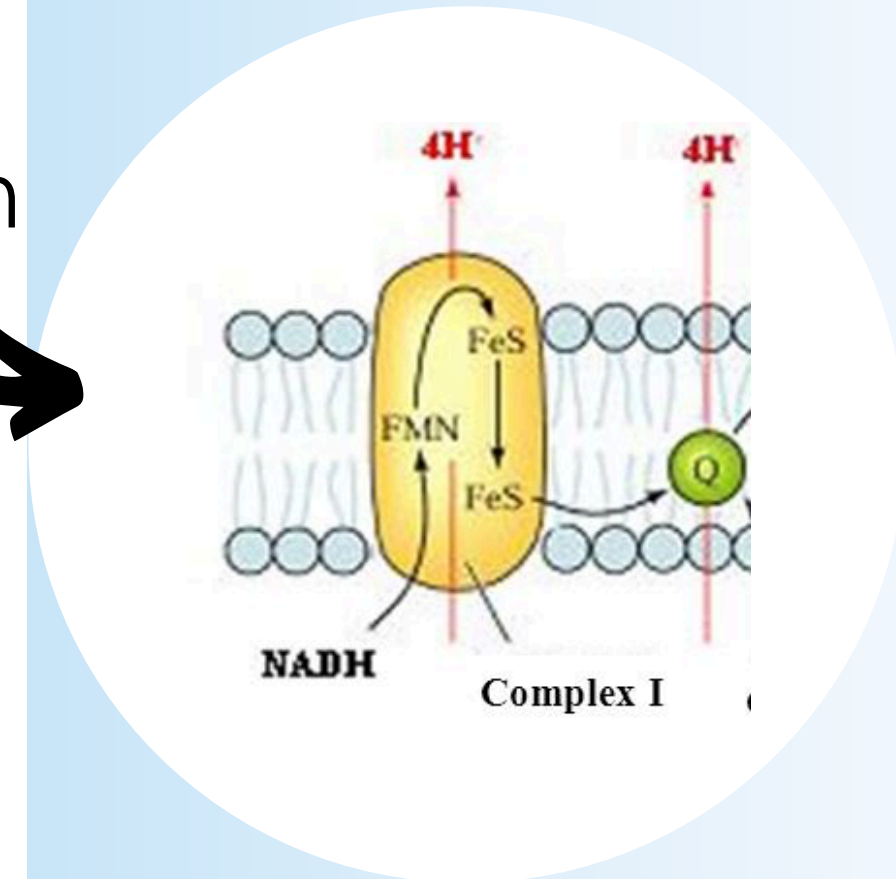
NADH is converted into NAD^+ , through the picking off of electrons by Flavin Mononucleotide (FMN)



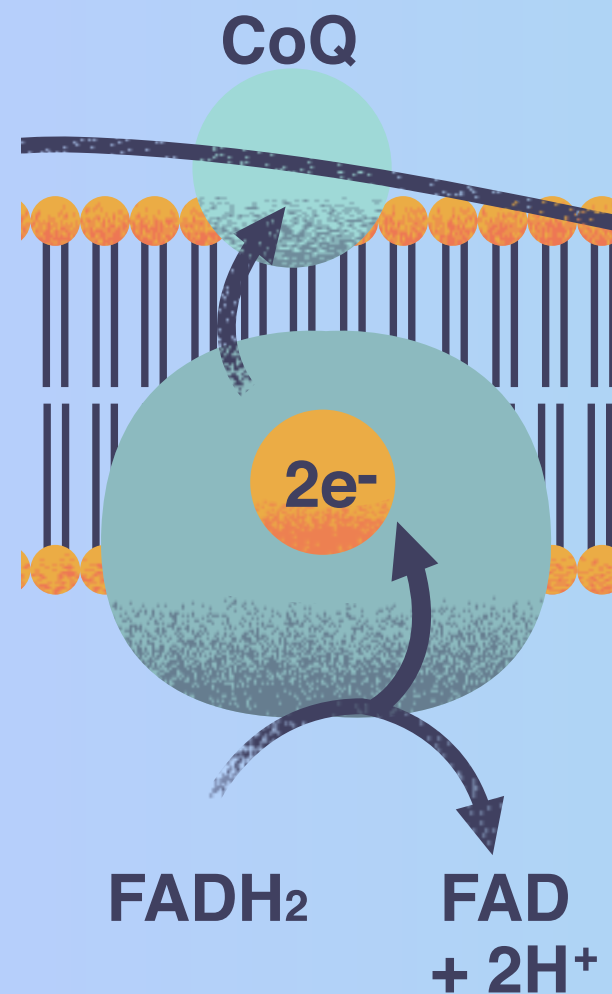
$FMNH_2$ passes its electrons to Fe-S and then to CoQ

This reduced form is unstable and so the electrons are passed onto CoQ

Protons pumped into intermembrane space through a pore



Complex II - Succinate Dehydrogenase (Quinone)



FADH is converted into FAD
FMN picks up these electrons and is converted into its reduced form FMNH₂

Coenzyme Q takes electrons from FMNH₂ and becomes reduced form QH₂

Unstable state, passes these electron on to CoQ (Ubiquinone), this passes the electrons from complex I and II to complex III

Complex does not have a pump and therefore cannot pump out its electrons

Complex III - Cytochrome bc1 Complex



Also known as CoQ-Cytochrome-b-Oxidoreductase

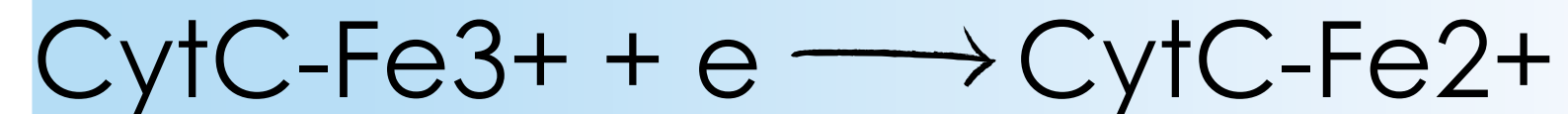
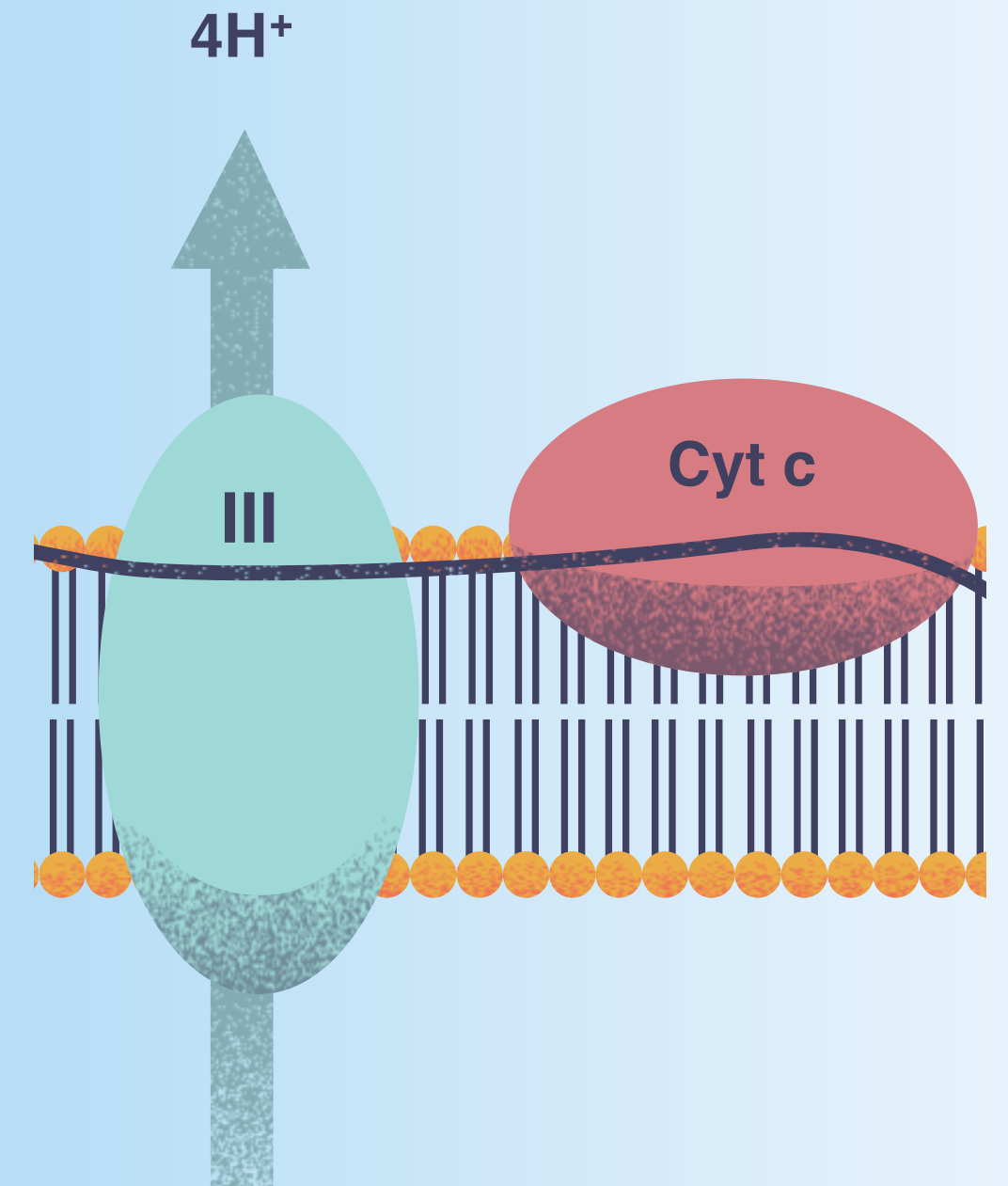
Contains Fe³⁺-CytB

Ubiquinone passes its electrons on to complex III

Electrons accepted and cytochrome becomes Fe²⁺-CytB

Unstable state and passes electrons on to Cytochrome C (CytC-Fe³⁺)

Pumps protons into intermembrane space via a pore



Complex IV - Cytochrome Oxidase

CytA-Fe³⁺ accepts electrons from CytC-Fe²⁺

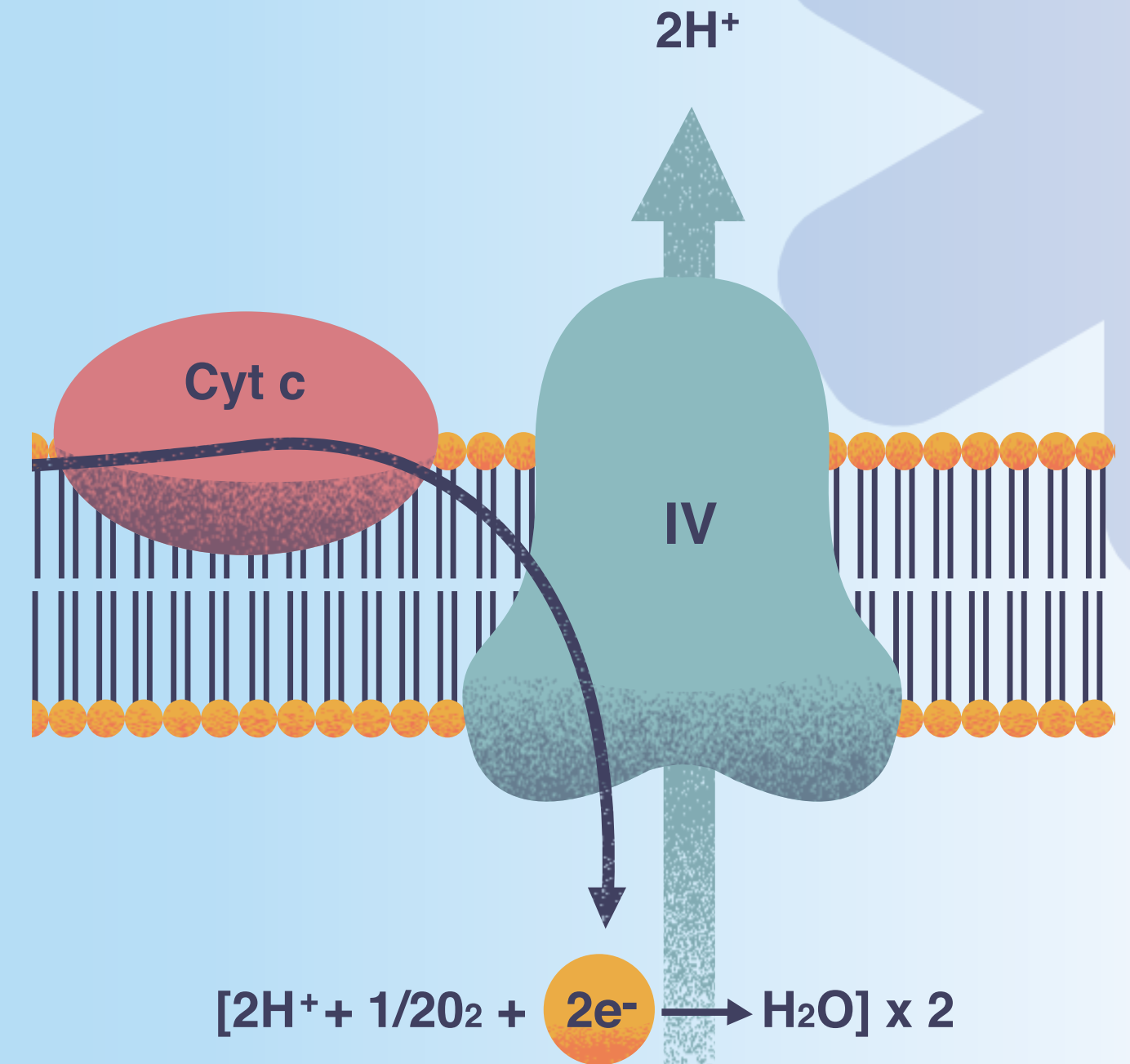
Unstable state and so passes its electrons away.

Energy is harvested into intermembrane space via a pump

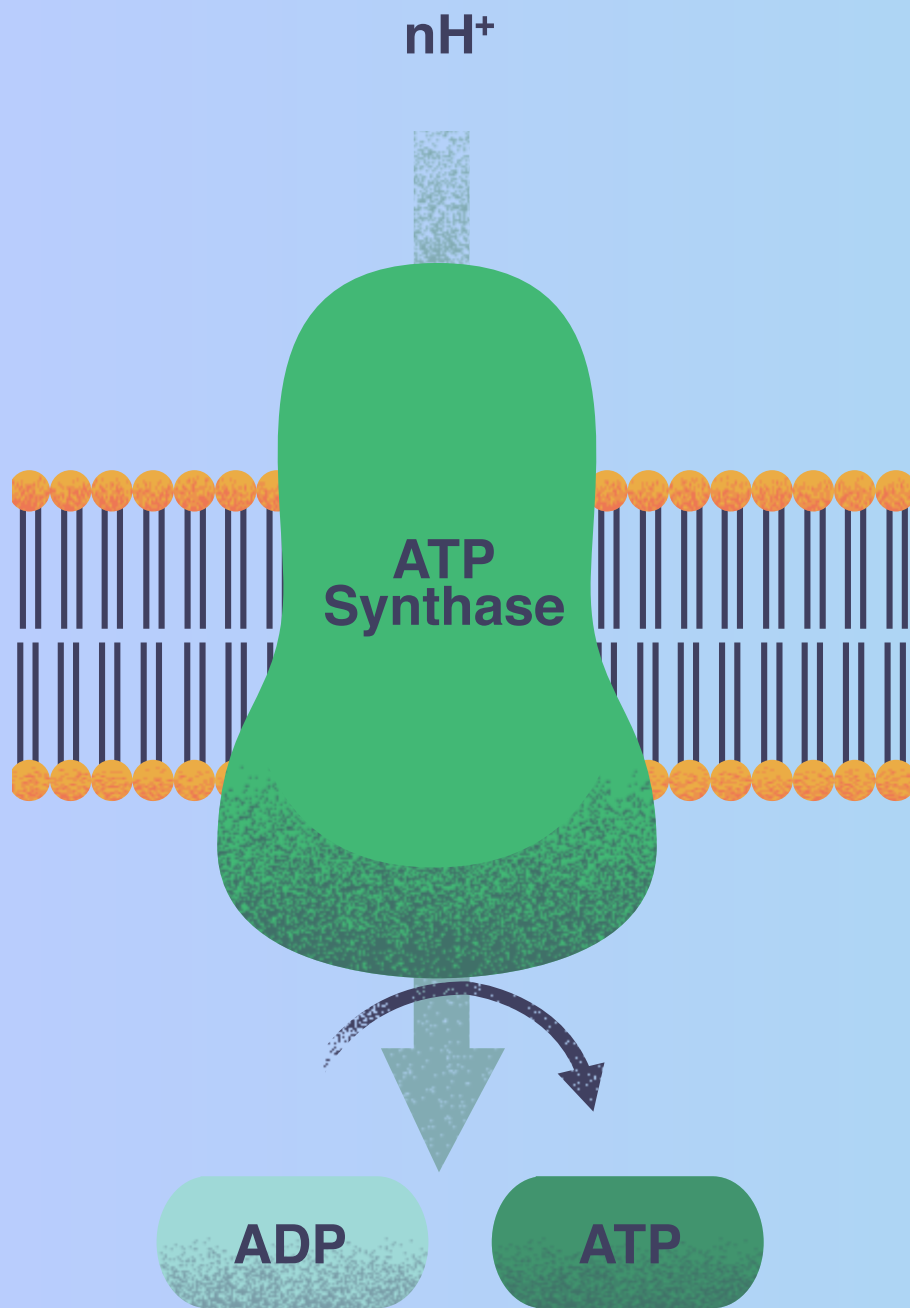
Fe²⁺ donates its electrons to 1/2O₂ located in the intermembrane space, also combining with 2 H⁺, forming water

$$\frac{1}{2}\text{O}_2 + 2\text{H}^+ + 2\text{e}^- = \text{H}_2\text{O}$$

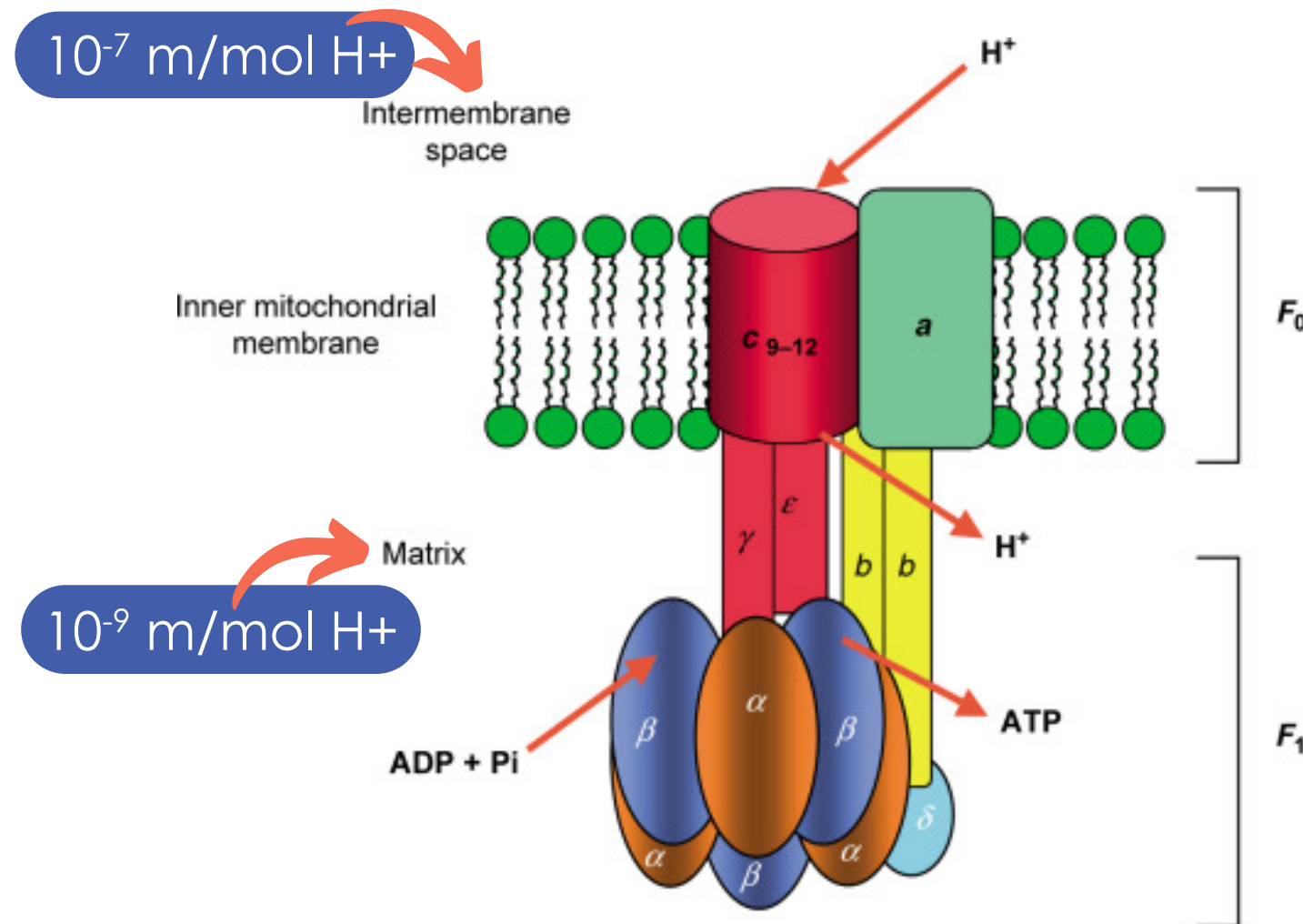
Clinical Correlation: Cyanide Poisoning



Chemiosmosis



Concentration Gradient - Proton concentration is much higher in intermembrane space compared to mitochondrial matrix after ETC



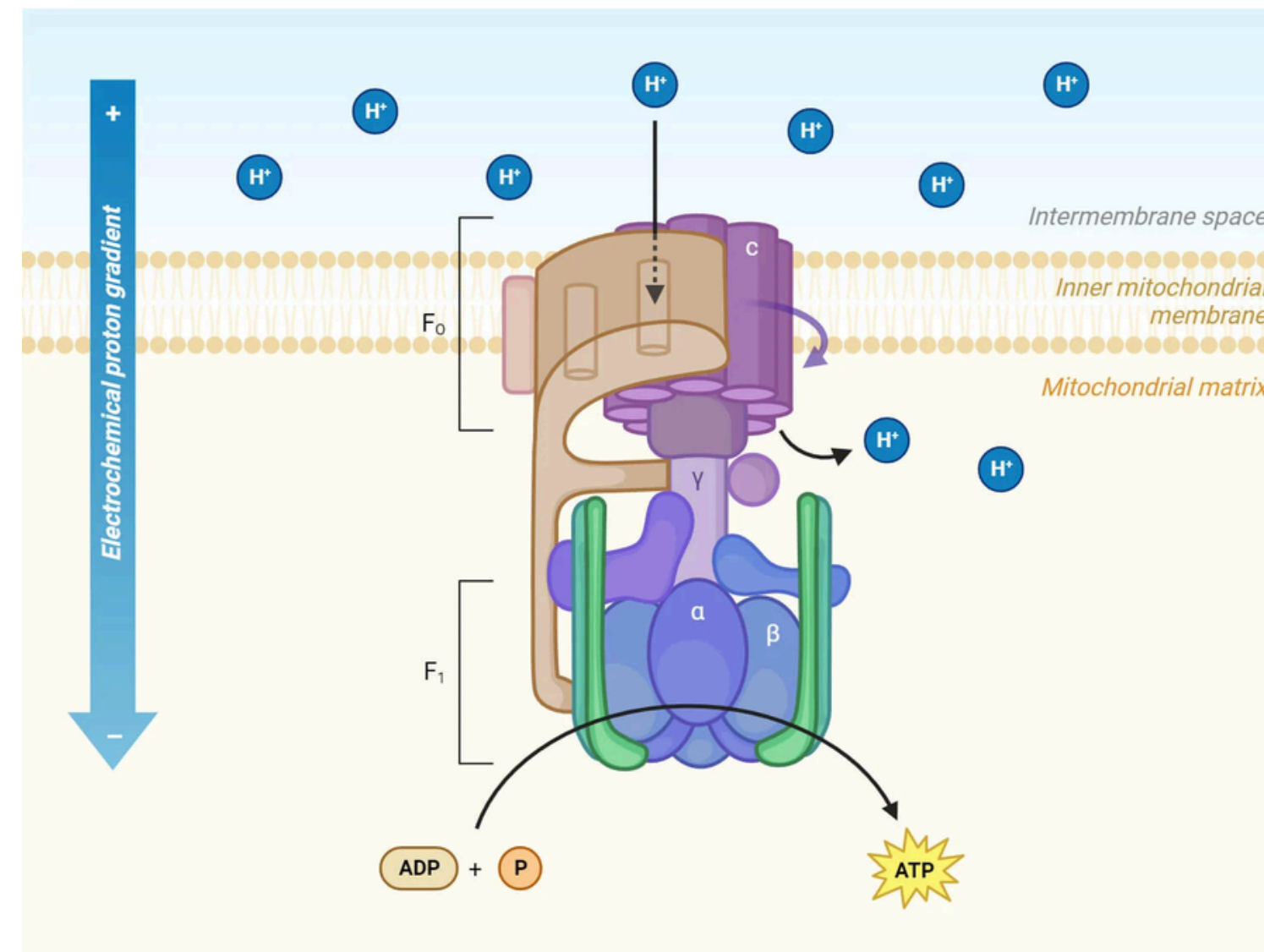
ATP Synthase

Component A - passive influx of protons

Arginine 2,10 - enzyme that facilitates transport from entry to exit

Component C + gamma protein - rotate generating proto-motor force

Beta-catalytic Subunit - uses protomotor force to make ATP



Generates much **larger** amounts of energy compared to substrate phosphorylation

Clinical Correlation - Weight loss drugs and oligomycin that can inhibit F₀ subunit

Electron Transport Chain Inhibitors

Complex I

Rotenone - inhibits transfer from Fe-S center to CoQ

Amytal - protects the heart generated during ischemia and reperfusion injury

Complex III

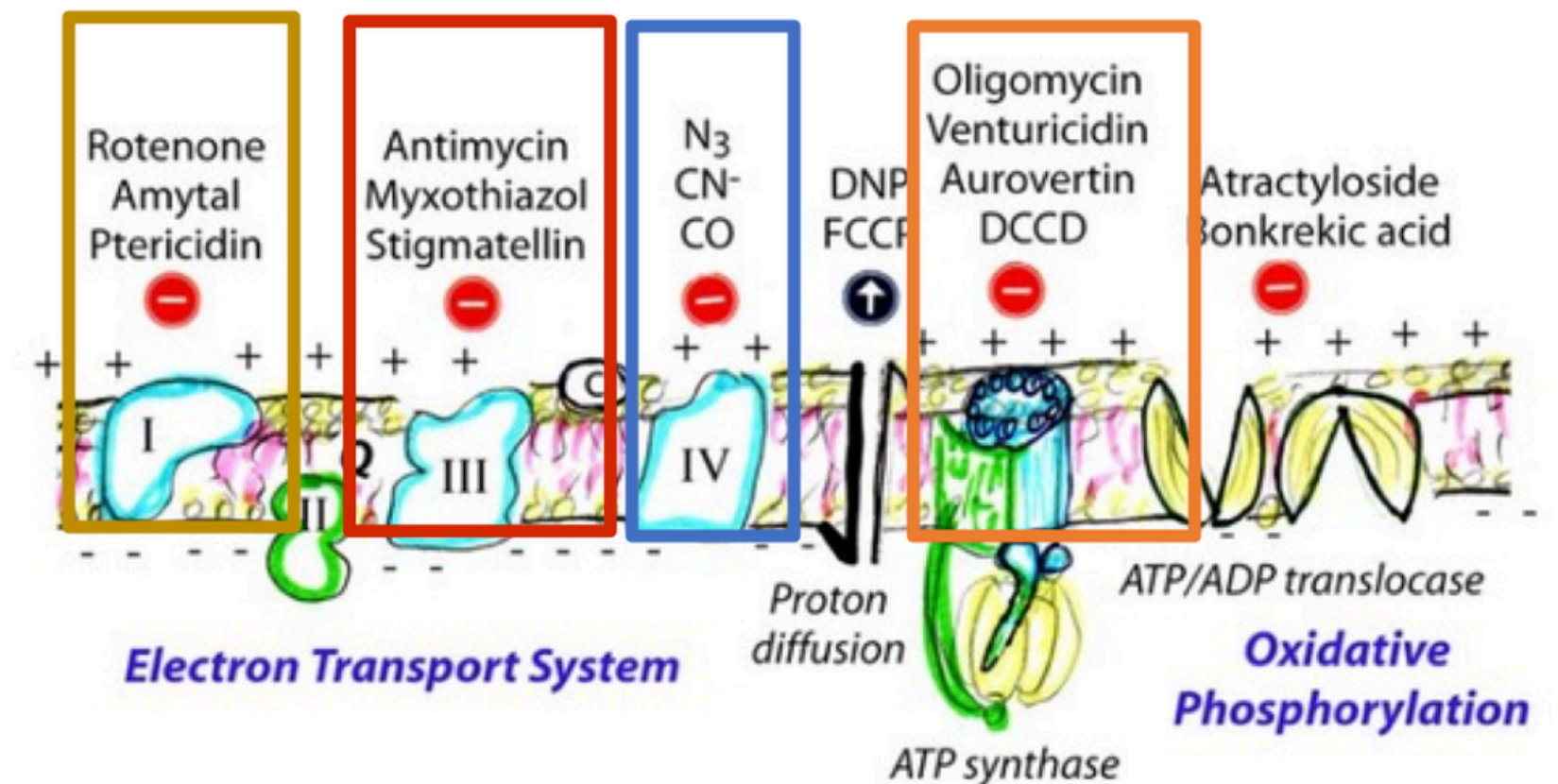
Antimycin A and C - binds to quinone reduction site

Complex IV

Cyanide - binds to ferric ion which blocks the ETC causing cell death, hypoxia and lactic acidosis

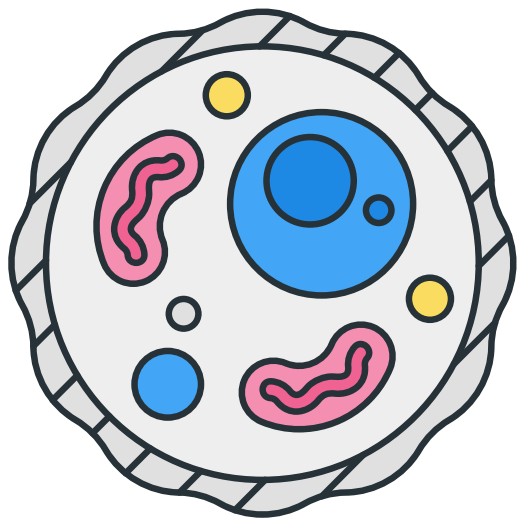
Carbon Monoxide - blocks electron flow between complex and O₂, and also inhibits Fe²⁺

Summary of known ETS and Ox Phos inhibitors



Total Energy Produced

Glycolysis → 2 ATP (Anaerobic) + 2 NADH (5 ATP)
Transition Step → 2 NADH (5 ATP)
Krebs Cycle → 6 NADH (15 ATP), 2 FADH (3 ATP), 2 ATP



32 ATP

