Biological Oxidation

ZO 503 Physiological Chemistry

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Lecture Outlines

- Introduction.
- Bioenergetics
- Exergonic and Endergonic Reactions
- High Energy Compounds- ATP

- Electron Transport Chain (ETC).
- ETC components
- Organization of ETC.
- Oxidative Phosphorylation.
- Chemiosmotic Hypothesis.
- Electron Transport Chain Inhibitors.
- Oxidative Phosphorylation Inhibitors.

Introduction

- Energy is required to maintain the structure and function of the living cells. This energy is derived from oxidation of carbohydrates, lipids and protein in diets.

- The energy liberated is converted into ATP, which is known as the energy currency of the living cells.

- Each gram of carbohydrate and protein gives about 4 Kcal on oxidation, while each gram of fat gives about 9 Kcal.

BIOENERGETICS

- Bioenergetics or biochemical thermodynamics is the study of the energy changes (transfer and utilizations) accompanying biochemical reactions.

- Bioenergetics is concerned with the initial and final energy states of the reaction components and not the mechanism of chemical reactions.

Free Energy

- The energy actually available to do work (utilizable) is known as free energy.

- Change in free energy (ΔG): Also known as Gibb's free energy, are valuable in predicting the feasibility of chemical reactions.

- Reactions occur spontaneously if they are accompanied by decrease in free energy.

- All reactions in biological systems are considered to be reversible reactions, so that the free energy of the reverse reaction numerically equivalent, but opposite in sign to that of the forward reaction.

$$A \rightleftharpoons B$$

- The direction of reaction may be
  - $(A \longrightarrow B)$
  - $(B \longrightarrow A)$

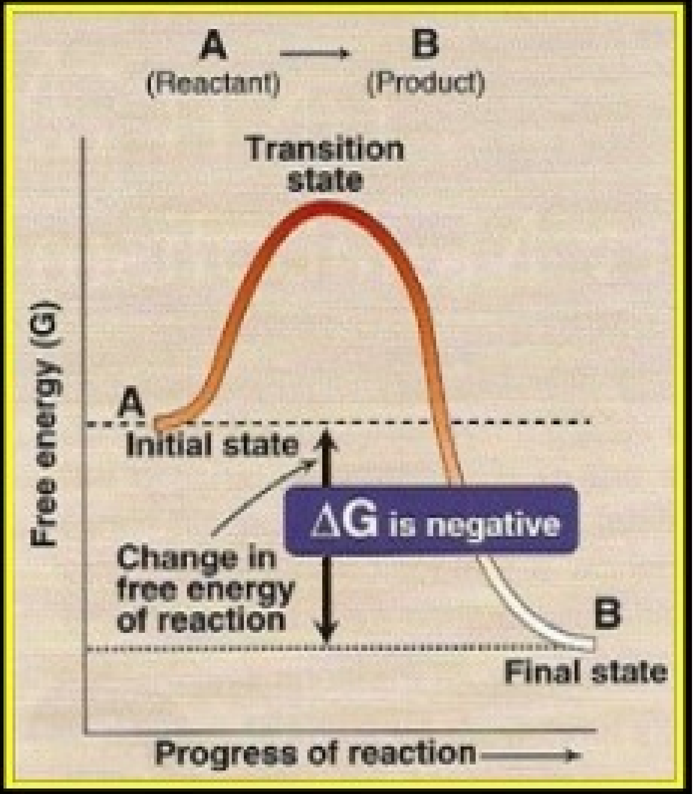
Exergonic Reaction

A ⟶ B

$\Delta G = G_B - G_A$

Where G_A & G_B are free energy of A & B

- Negative ΔG(A ⟶ B): If ΔG is negative , this means that the energy content of product (B) is less than that of reactant (A)



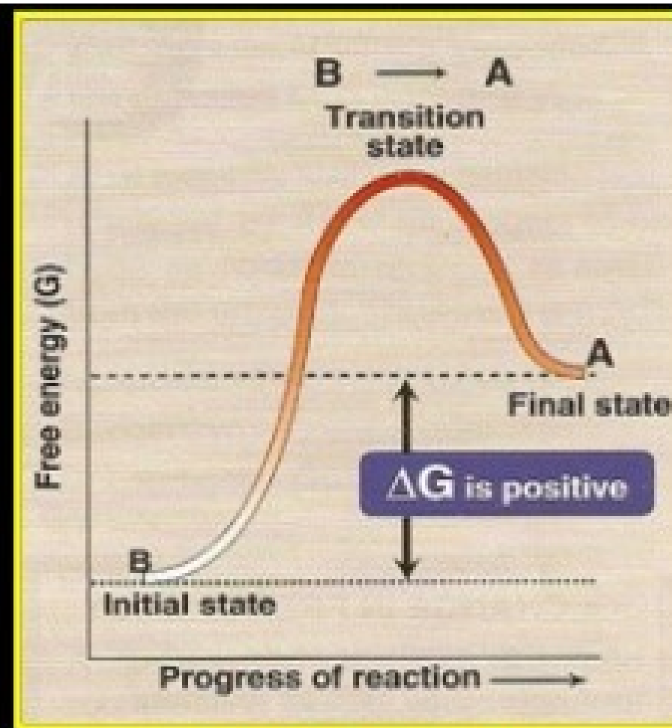
- There is a net loss of energy.
- The reaction proceeds spontaneously from A ⟶ B
- The reaction is said to be exergonic or energy releasing.
- Exergonic reactions result in products with less energy than the reactants.

Endergonic Reaction

$$B \longrightarrow A$$

$$\Delta G = G_A - G_B$$

Positive ΔG: If ΔG is positive, this means that the energy content of product (A) is more than that of reactant (B).



- There is a net gain of energy.
- The reaction does not proceed spontaneously from B → A
- The reaction is said to be endergonic or energy requiring.

$$B \xrightarrow[\text{Energy}]{} A$$

Energy ↑ from Carbohydrates, Lipids, Proteins

- Endergonic reactions result in products with more energy than the reactants.

- ΔG is zero: The reaction is in equilibrium.

- The exergonic reactions (energy producing reactions) are called catabolism e.g. glycogenolysis and fatty acid oxidation.

- The endergonic reactions (energy utilizing reactions) are called anabolism e.g. synthesis of glycogen and fatty acids.

- Catabolism and Anabolism constitute metabolism.

HIGH ENERGY COMPOUNDS

- High energy compounds or energy rich compounds is usually applied to substances in the biological system which on hydrolysis yield free energy equal to or greater than that of ATP i.e. $\Delta G = -7.3$ kcal/mol. The high energy compounds have anhydride bonds.

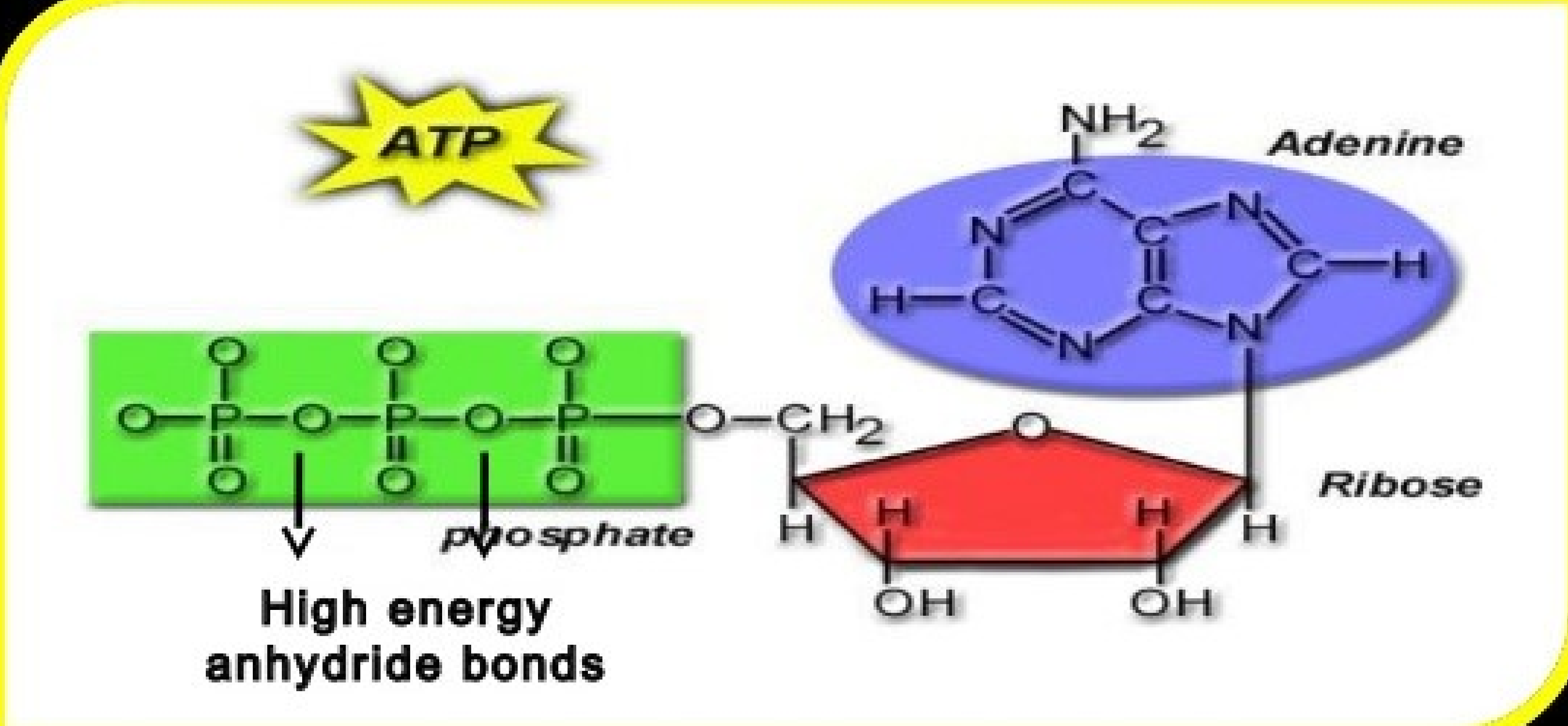
- Compounds which liberate less than 7.3 kcal/mol (lower than ATP hydrolysis to ADP + Pi) are referred to as low energy compounds.

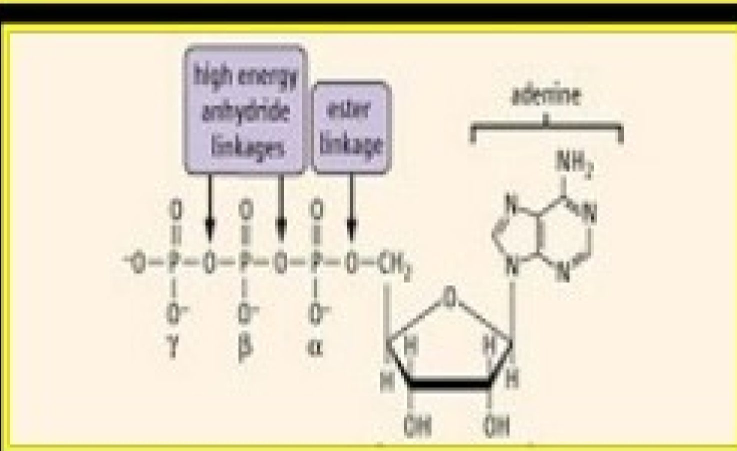
Metabolite	ΔG (kcal/mol)
phosphoenolpyruvate	-14.8
phosphocreatine	-12.0
1,3-bisphosphoglycerate	-11.8
Creatine Phosphate	- 10.3
ATP	-7.3
ADP	- 6.6
Glucose 1-Phosphate	-5.0
Fructose 6-Phosphate	-3.8
AMP	- 3.4
Glucose 6-Phosphate	-3.3

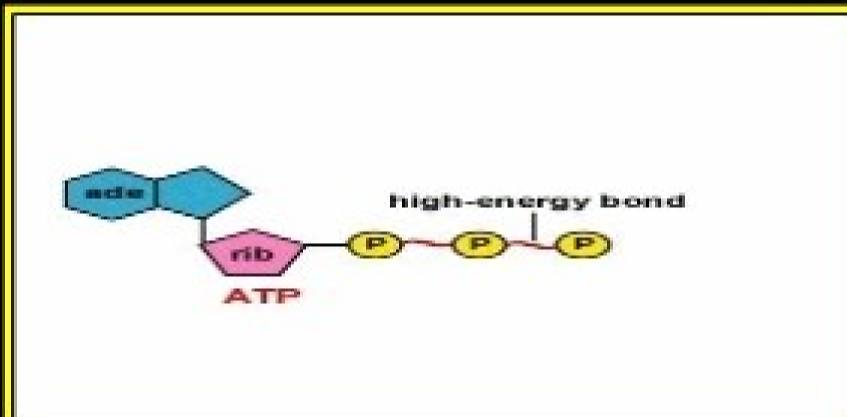
High Energy Compounds (phosphoenolpyruvate through ATP)

Low Energy Compounds (ADP through Glucose 6-Phosphate)

Adenosine Triphosphate (ATP)







Adenosine Triphosphate (ATP)

- ATP is the most important high energy compound in the living cell.
- It consists of an adenine, a ribose and a triphosphate.
- It is a high energy compound due to the presence two anhydride bond in the triphosphate unit.
- Hydrolysis of terminal phosphates yields a large negative change in free energy

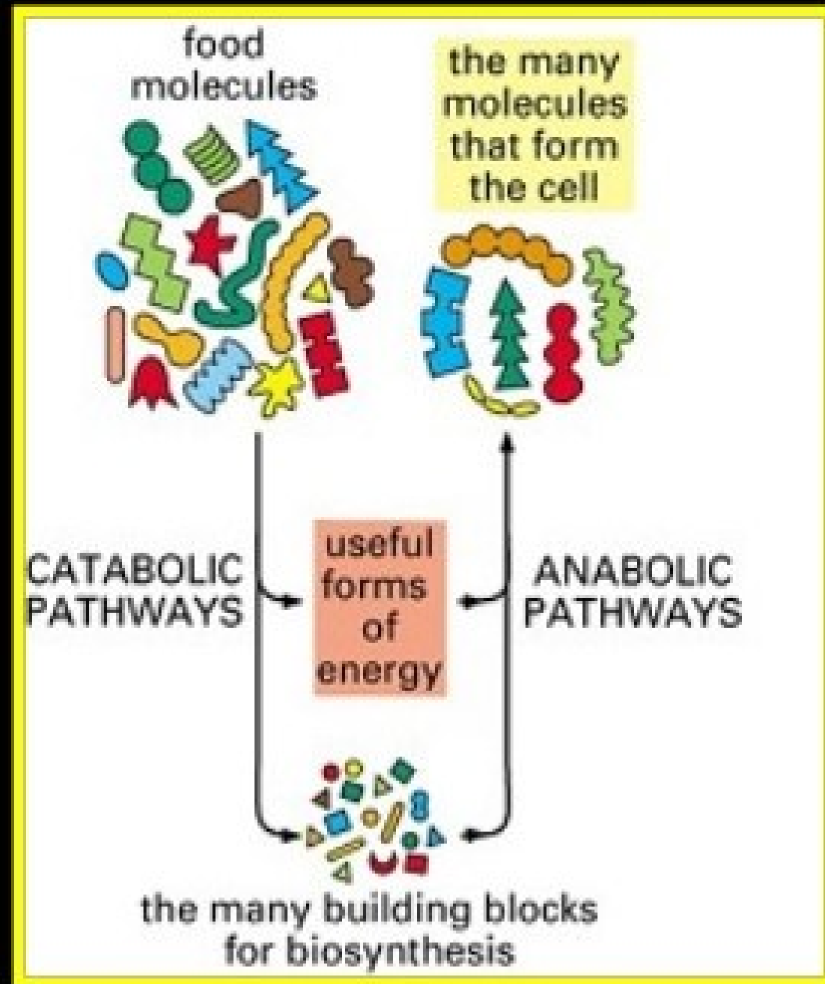
$$ATP + H_2O \longrightarrow ADP + Phosphate$$

Gives -7.3 kcal/mol

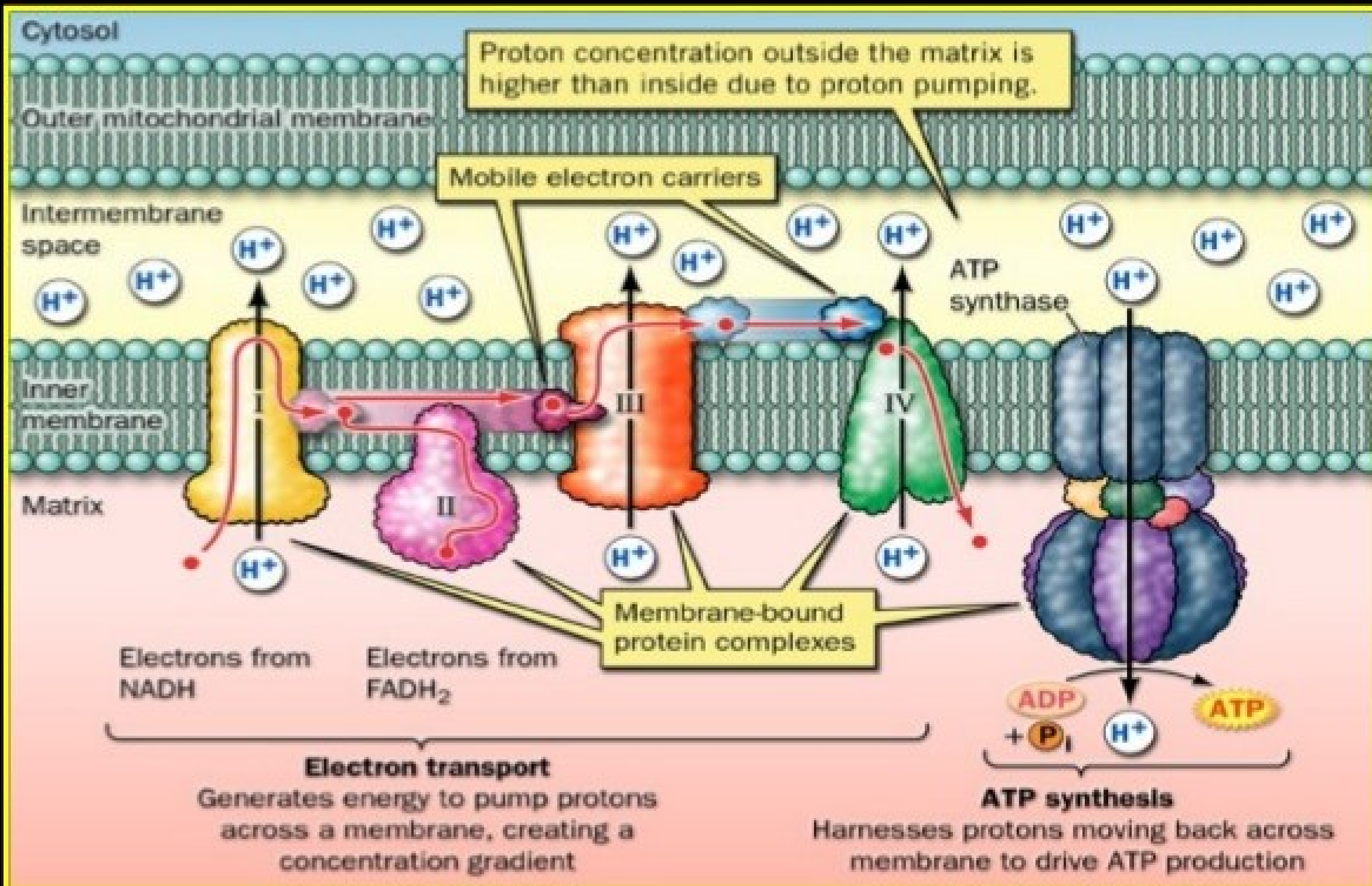
- ATP acts as an energy link between catabolism (exergonic reactions) and anabolism (endergonic reactions)

- Catabolic reactions give energy, in the form of ATP.

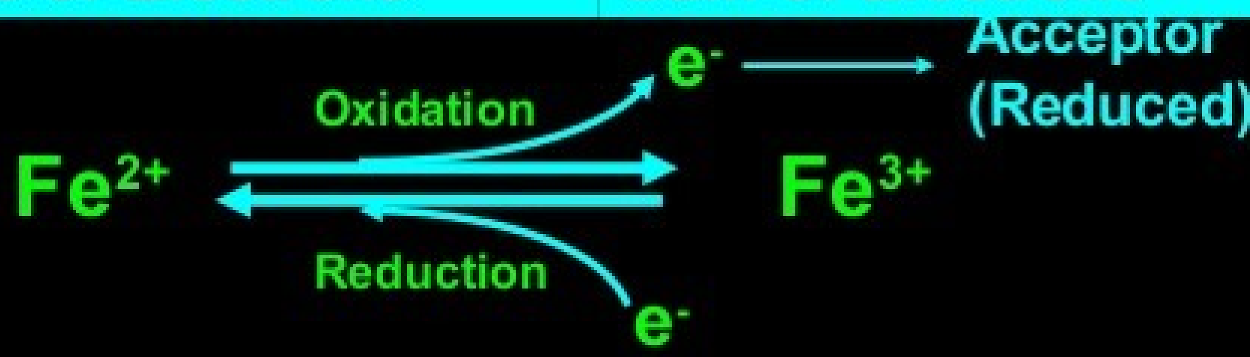
- Anabolic reactions can utilize energy through hydrolysis of ATP.



ELECTRON TRANSPORT CHAIN



Oxidation	Reduction
Addition of Oxygen	Removal of Oxygen
Removal of Hydrogen	Addition of Hydrogen
Loss of Electrons	Gain of Electrons



- The electron lost in the oxidation is accepted by an acceptor which is said to be reduced.
- Commonly oxidation reactions are accompanied by reduction reactions, and they are called as Redox Reactions.

Redox Potential (~ Electron Affinity): Redox potential of a system is the electron transfer potential (E_0')

- Low redox potential signifies Low Electron Affinity.

  - More negative (or low) redox potential

    ↓

    Greater Tendency to lose Electrons

- High redox potential signifies High Electron Affinity.

  - More positive (or high) redox potential

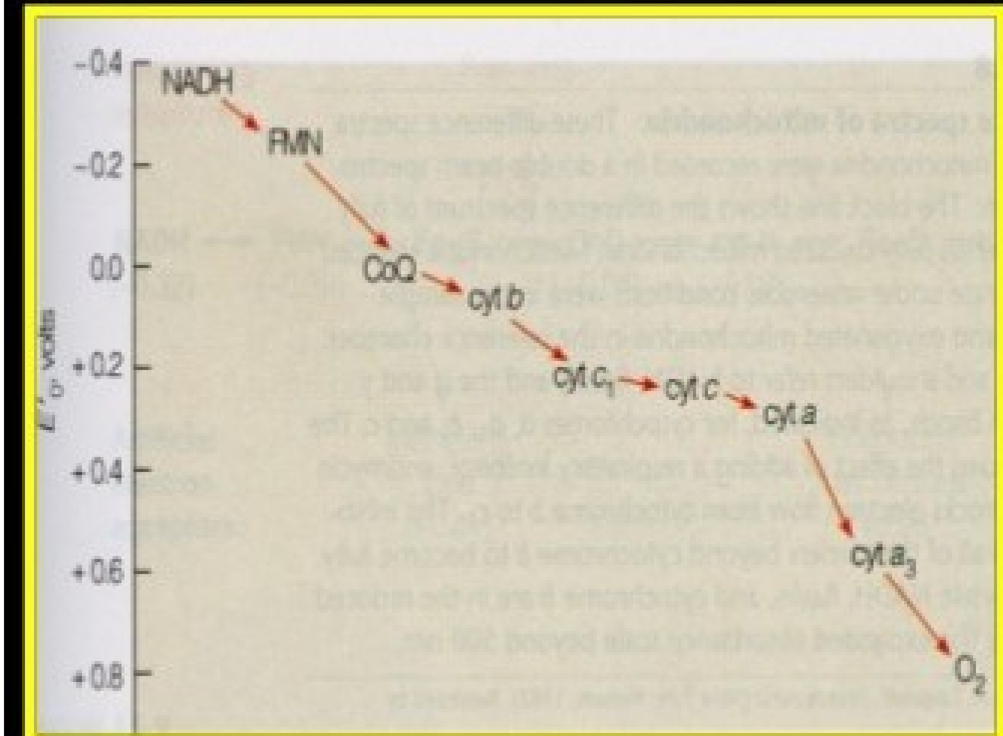
    ↓

    Greater Tendency to accept Electrons

Electron Transport Chain:

- It is a chain of protein complexes and coenzymes of increasing redox potentials.

‘Electrons flow through Electron Transport chain in steps from the more electronegative component (low redox potential) to the more electropositive component (high redox potential)’



NADH	−0.315
Complex I (NADH–CoQ oxidoreductase; ~900 kD, 46 subunits):	
FMN	−0.340
[2Fe–2S]N1a	−0.380
[2Fe–2S]N1b	−0.250
[4Fe–4S]N3, 4, 5, 6a, 6b, 7	−0.250
[4Fe–4S]N2	−0.100
Succinate	0.031
Complex II (succinate–CoQ oxidoreductase; ~120 kD, 4 subunits):	
FAD	−0.040
[2Fe–2S]	−0.030
[4Fe–4S]	−0.245
[3Fe–4S]	0.060
Heme b_{560}	−0.080
Coenzyme Q	0.045
Complex III (CoQ–cytochrome *c* oxidoreductase; ~450 kD, 9–11 subunits):	
Heme b_H (b_{562})	0.030
Heme b_L (b_{566})	−0.030
[2Fe–2S]	0.280
Heme c_1	0.215
Cytochrome *c*	0.235
Complex IV (cytochrome *c* oxidase; ~410 kD, 8–13 subunits):	
Heme *a*	0.210
Cu_A	0.245
Cu_B	0.340
Heme a_3	0.385
O_2	0.815

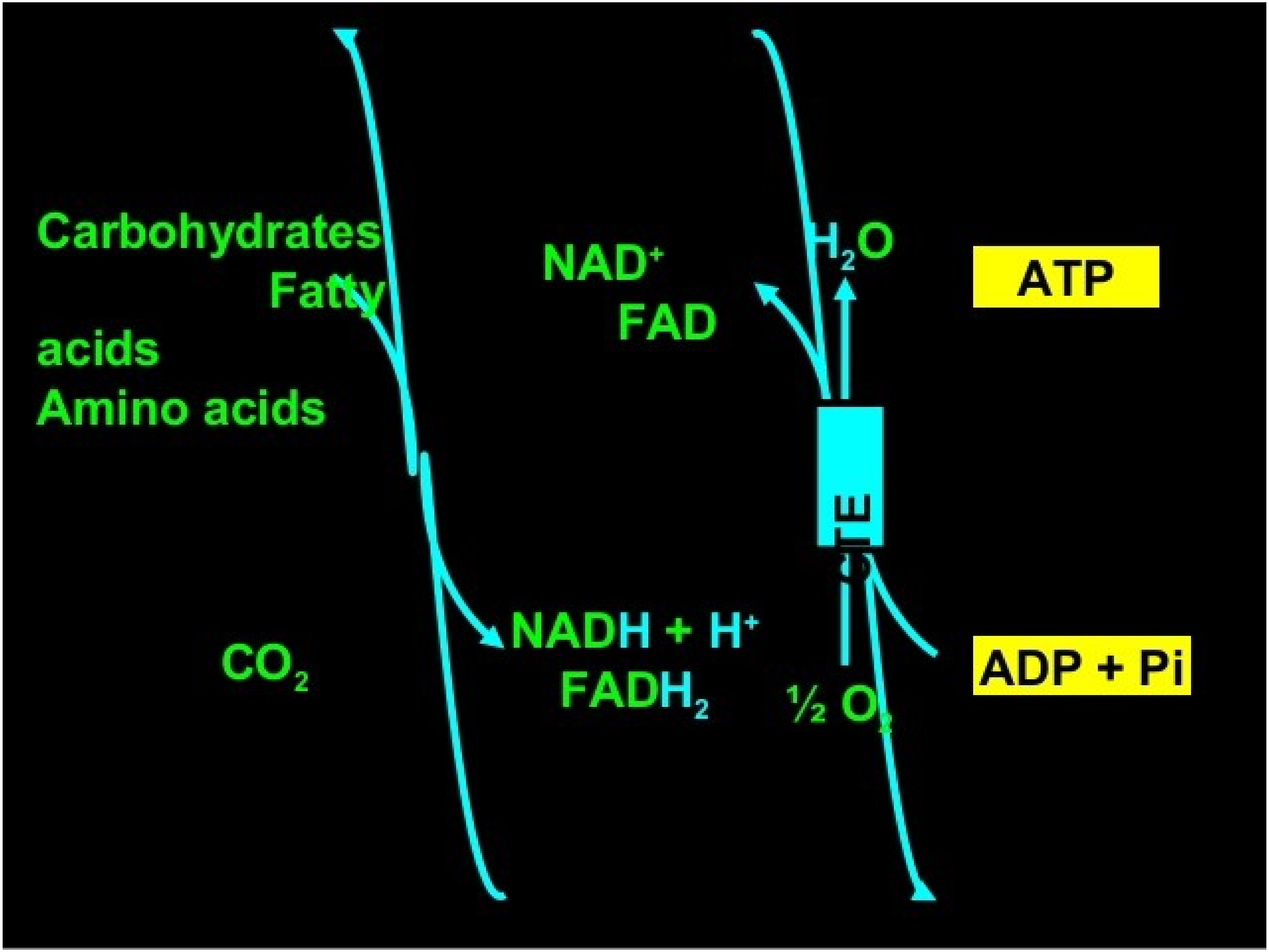
ELECTRON TRANSPORT CHAIN (ETC)

- Also known as respiratory chain, it is located in the inner mitochondrial membrane.

- Components of ETC are Complex I, II, III, IV & V which are membrane bound components.
    - Complex I to IV each contain part of the electron transport chain.
    - Complex V catalyzes ATP synthesis

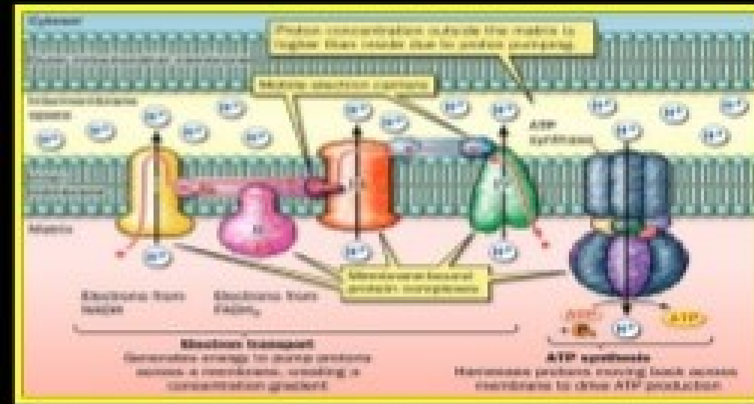
- Coenzyme Q & Cytochrome C are mobile components.

The reactions start by removal of Hydrogen (H^+ and one electron) from the substrate that is transferred through different components of Electron Transport Chain in accordance of “Increasing Redox Potential” to oxygen to form water.


Carbohydrates
Fatty
acids
Amino acids
NAD+
FAD
H2O
ATP
E
T
C
NADH + H+
FADH2
CO2
½ O2
ADP + Pi

- The energy rich carbohydrates, fatty acids and amino acids undergo a series of metabolic reactions and finally oxidized to CO_2 and H_2O.
- The reducing equivalents (Hydrogen and electrons) from various metabolic intermediates are transferred to coenzymes NAD^+ and FAD to produce NADH and $FADH_2$ respectively.
- Electrons from the two reduced coenzymes pass through the Electron Transport Chain or respiratory chain and, finally, reduce oxygen to water.
- The passage of electrons through the ETC is associated with loss of free energy.
- A part of this free energy is utilized to generate ATP from ADP and Pi.

ETC COMPONENTS



Membrane bound components

Complex I –NADH Dehydrogenase

Complex II –Succinate Dehydrogenase

Complex III – Cytochrome b–c_1 or Cytochrome Reductase.

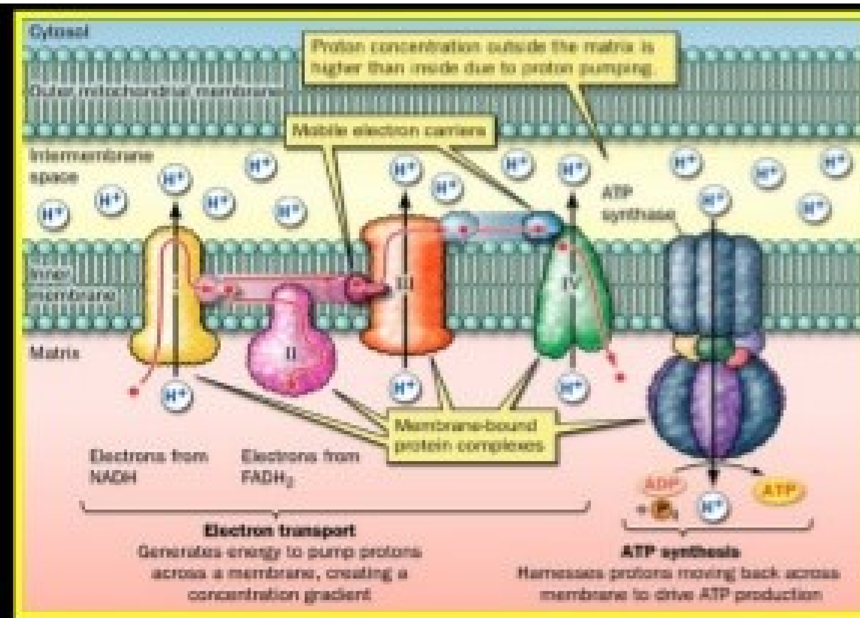
Complex IV – Cytochrome a + a_3 or Cytochrome Oxidase

Complex V – ATP Synthase

Mobile Components

- Coenzyme Q
- Cytochrome C

Organization of the ETC



- Complex I-IV accepts or donates electrons to a mobile electron carriers which are Coenzyme Q and cytochrome C.

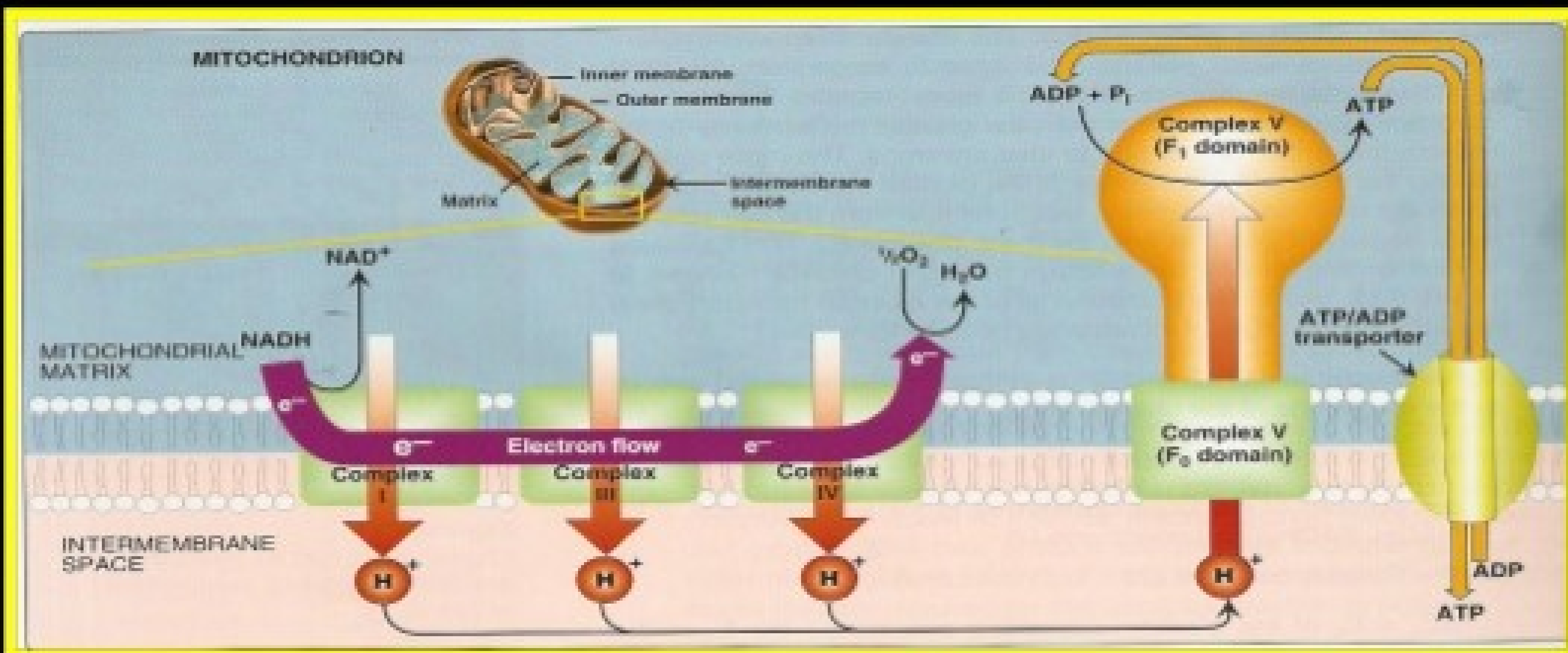
- Each carrier in the ETC can receive electrons from an electron donor, and can subsequently donate electrons to the next carrier in the chain.

- The electrons ultimately combine with oxygen and protons to form water (at complex IV).

- Complex V catalyzes ATP synthesis.

Oxidative Phosphorylation

- The flow of electrons from NADH+ to oxygen (oxidation) results in ATP synthesis by phosphorylation of ADP by inorganic phosphate Pi, (phosphorylation). Therefore, there is a "coupling" between oxidation and phosphorylation.



- The most accepted hypothesis is the chemiosmotic hypothesis.

Chemiosmotic Hypothesis

a. The transport of electrons down the respiratory chain releases energy.

b. This energy is used to transport H^+ from the mitochondrial matrix, across the inner mitochondrial membrane, to the intermembrane space.

c. This is done by complexes I, III and IV

d. This process creates across the inner mitochondrial membrane:

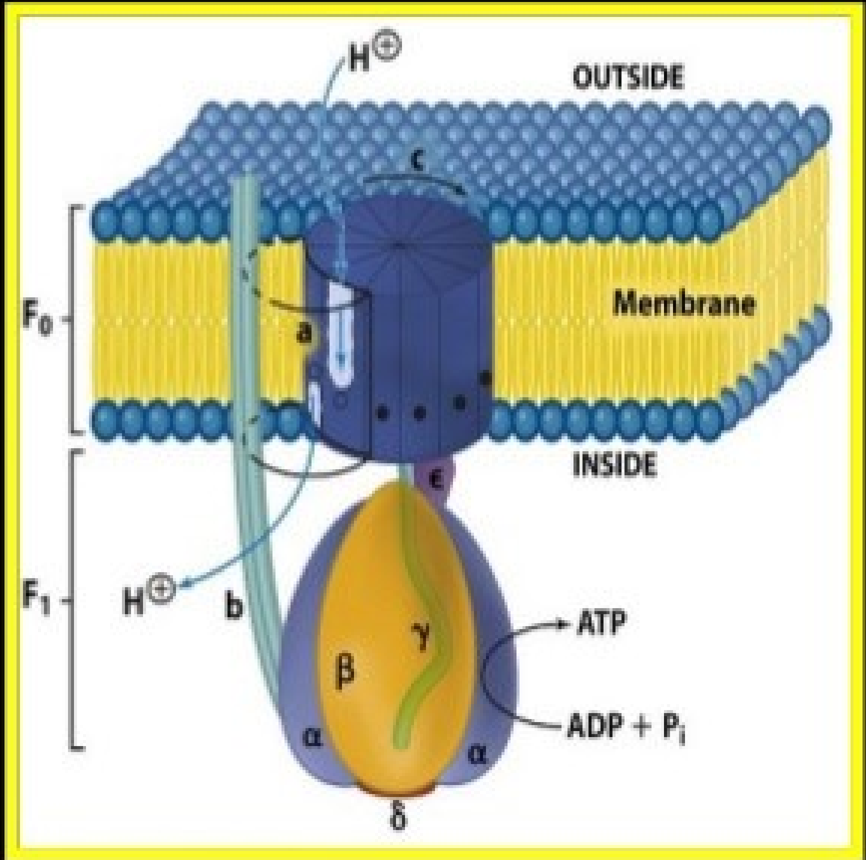
(i) An electrical gradient : More positive charges on the outside of the membrane than on the inside.

(ii) A pH gradient: Outside of the membrane is at a lower pH than the inside.

e. The energy generated by this proton gradient is utilized for ATP synthesis by ATP synthase (Complex V).

ATP Synthase

- The enzyme complex ATP synthase (complex V) synthesizes ATP, using the energy of the proton gradient (energy lost on proton entry) generated by the ETC

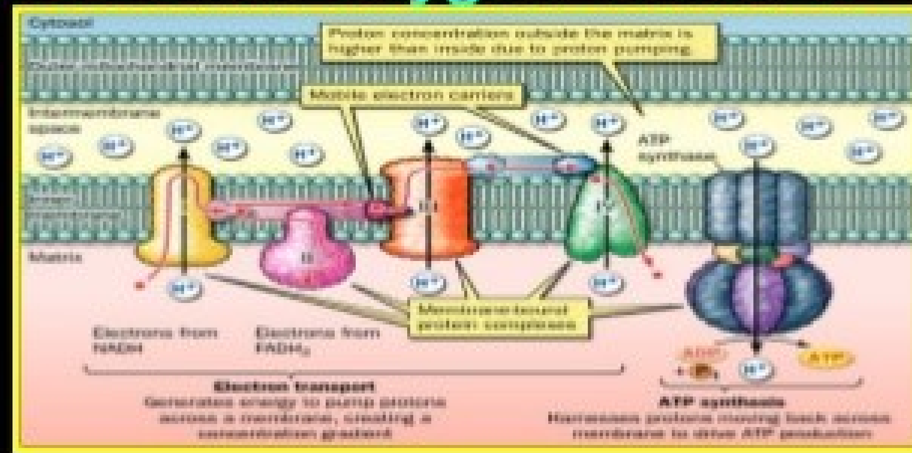


- It is composed of 2 subunits

    i) F_1 subunit: Protruding into the matrix.

    ii) F_o subunit:

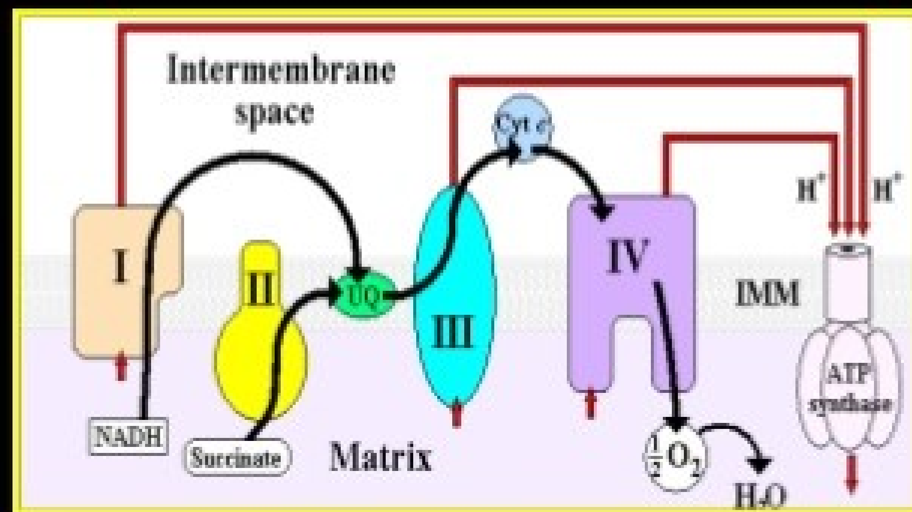
- Final electron acceptor is molecular oxygen which is reduced to water.



NADH

- Electrons from NADH enter through Complex I.

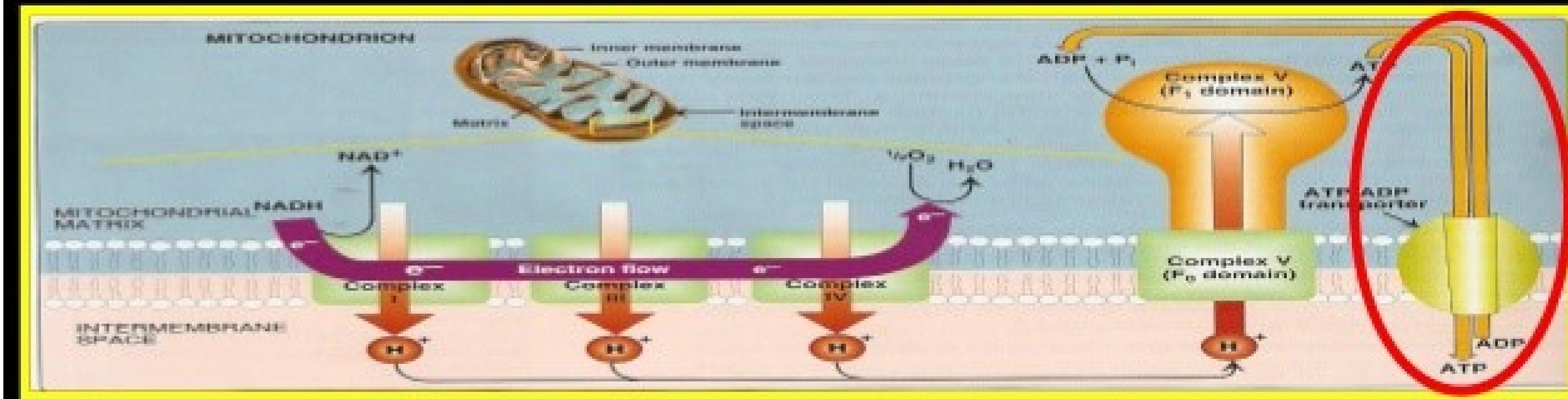
- For every pair of electrons transported through the three complexes, a sufficient number of protons is pumped for the synthesis of 'three moles' of ATP (from NADH).



$FADH_2$

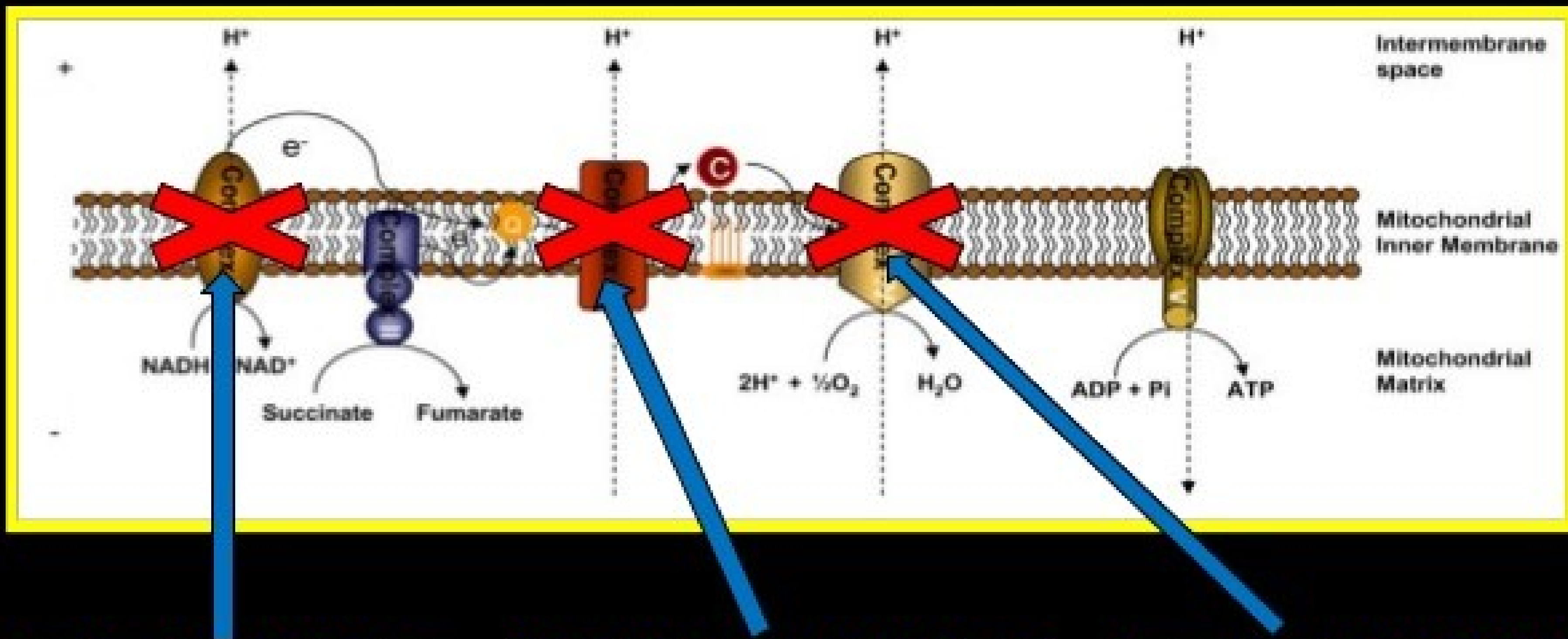
- Electrons from $FADH_2$ enter through Complex II.
- From $FADH_2$ only two moles of ATP are produced.

ADP/ATP Transporter



- ATP produced in the mitochondrial matrix must exit to the cytosol.
- ADP & P_i arising from ATP hydrolysis in the cytosol must reenter the matrix to be converted again to ATP.
- ATP/ADP Transporter is an antiporter that exchanges ADP for ATP across the inner mitochondrial membrane. It transport ATP outside the mitochondria while ADP inside the mitochondria.

Electron Transport Chain Inhibitors



Complex I Inhibitors

- Rotenone

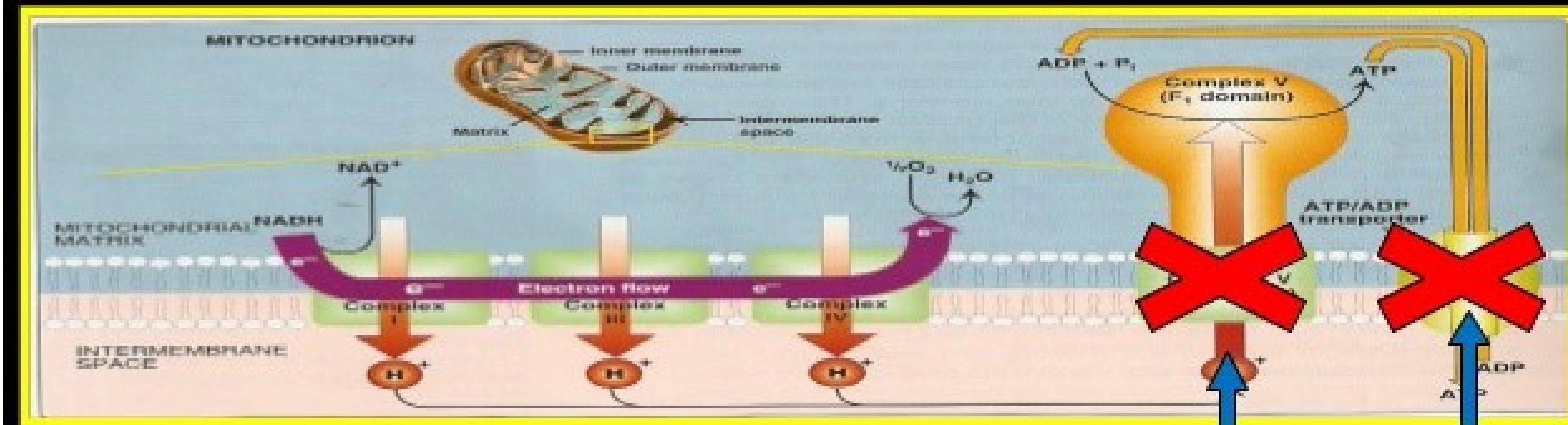
Complex III Inhibitors

- Antimycin A

Complex IV Inhibitors

- Cyanide
- Carbon Monoxide

Oxidative Phosphorylation Inhibitors



Oligomycin

Atractyloside

Oxidative Phosphorylation Inhibitors

- Oligomycin: Binds to ATP synthase and inhibiting it, closing the H^+ channel, preventing reentry of protons into the mitochondrial matrix, and thus preventing phosphorylation ADP to ATP.

- Atractyloside: Inhibits ATP/ADP Transporter (ATP Translocase), resulting in depletion of intramitochondrial ADP and cessation of ATP production.

Electron transport and ATP synthesis are tightly "coupled" processes; therefore, inhibition of the electron transport chain also results in inhibition of ATP synthesis.

THANK YOU