

Biological oxidation

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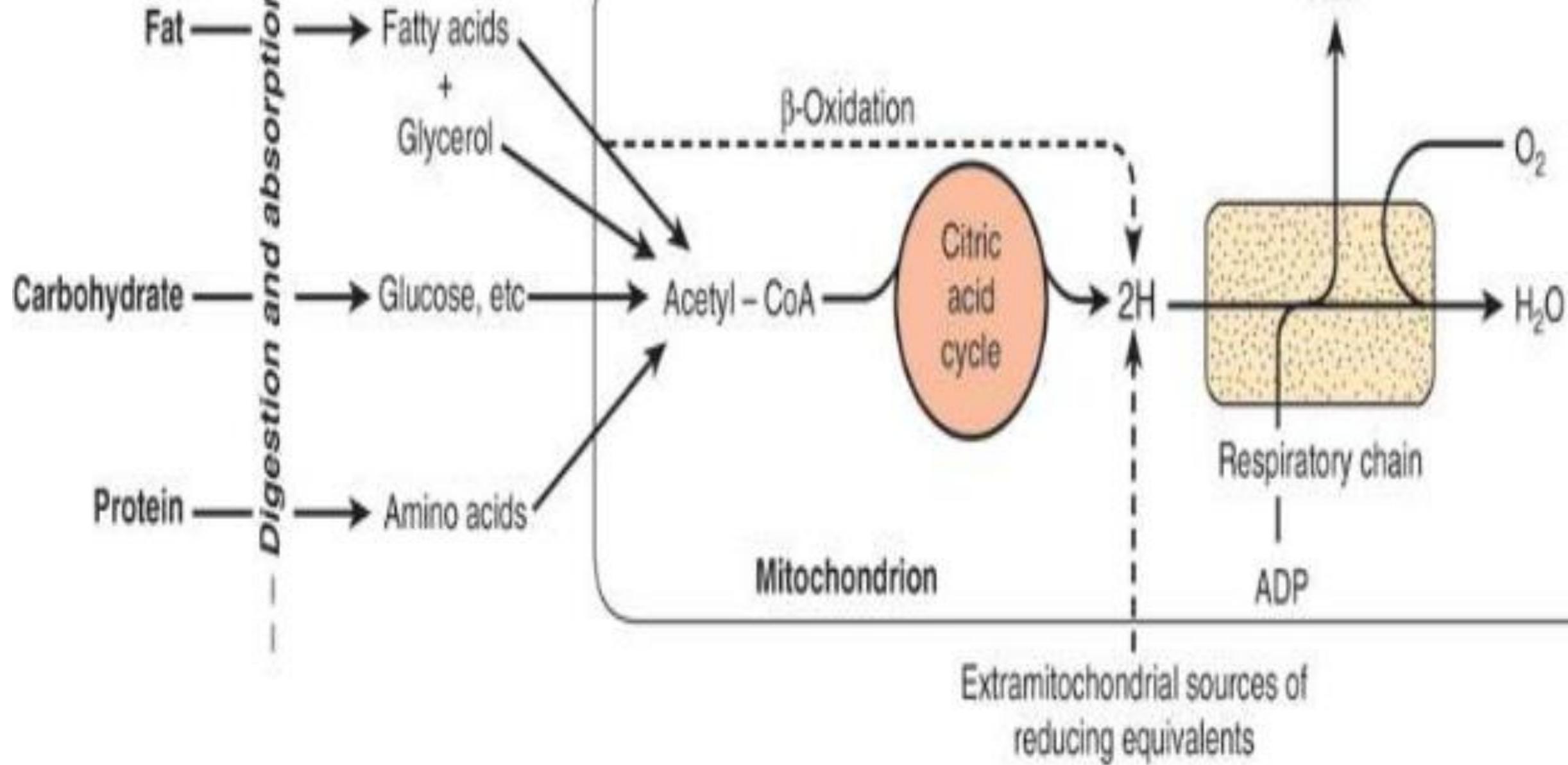
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Introduction

- 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.

Food



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.

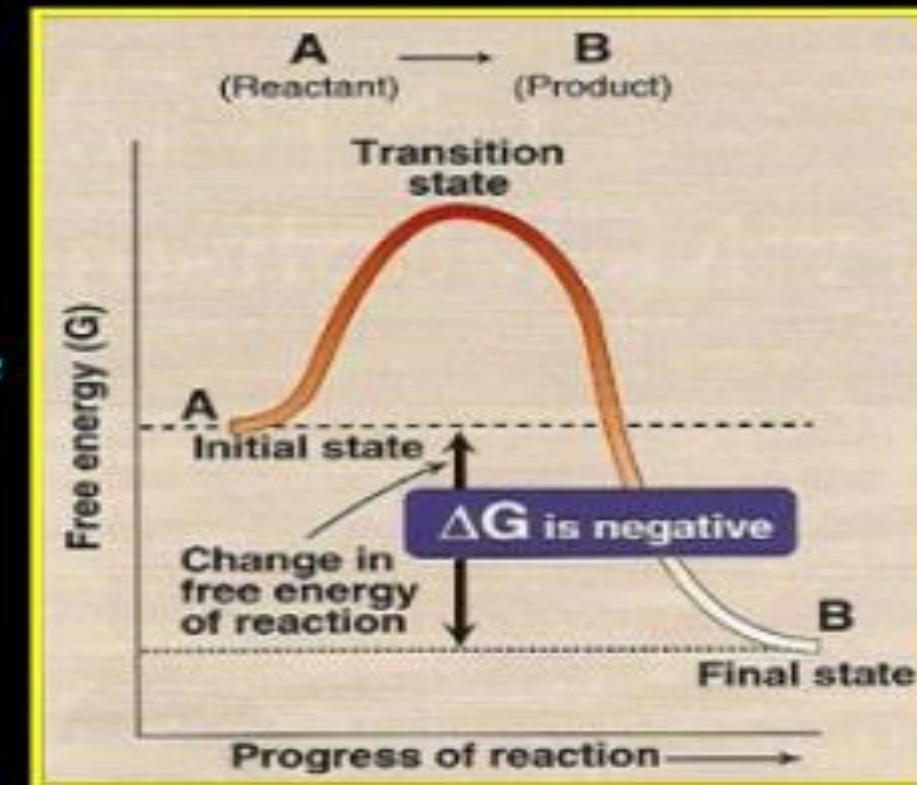
Exergonic Reaction



$$\Delta G = G_B - G_A$$

Where G_A & G_B are free energy of A & B

- Negative $\Delta G(A \longrightarrow B)$: 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 $A \longrightarrow B$
- The reaction is said to be exergonic or energy releasing.
- Exergonic reactions result in products with less energy than the reactants.



Endergonic Reaction



$$\Delta G = G_A - G_B$$

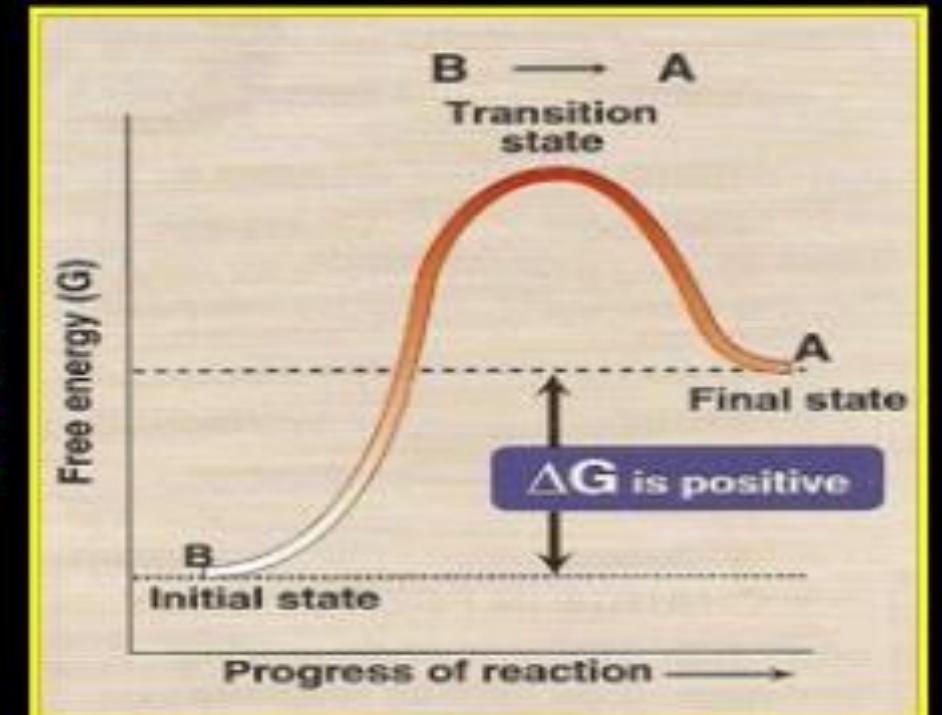
Positive ΔG : If ΔG is positive , this means that the energy content of product (A) is more than that of reactant (B).

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



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.

➤ Exergonic /catabolism

- $\text{ATP} + \text{H}_2\text{O} \rightarrow \text{ADP} + \text{Pi} - \Delta G = -7.3 \text{ cal/mol}$

➤ Endergonic/anabolism

- $\text{ADP} + \text{Pi} \rightarrow \text{ATP} + \Delta G = +7.3 \text{ cal/mol}$

1. Enthalpy is a measure of change in heat content of the reactant, when compared to product, which is denoted as ΔH .

2. ΔS is the change in **entropy**. It is the term used to express the degree of randomness or disorder created during a reaction. The randomness is increased when a biomolecule is broken down to smaller molecules. For example: $\text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O}$

- In this process there is an increase in randomness because 7 molecules produce 12 molecules. Whenever a chemical reaction proceeds, if there is an increase in the number of molecules, then, there is an increase in molecular disorder and thus an increase in entropy. This contributes to a **$-\Delta G$** .

- The relationship between change in **free energy**, **enthalpy** and **entropy** is expressed as

$$\Delta G = \Delta H - T \Delta S$$

T is the absolute temperature.

- The total of **anabolic** and **catabolic** processes is called as “**Metabolism**”.
- The overall net change in metabolism is **exergonic**.
- **Standard free energy change (ΔG°)**: It indicates the free energy change when the reactants or products are at concentration of **1mol/l** at pH 7.0

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.

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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	

Low Energy Compounds

High Energy Compounds

Classification of high energy compounds

- There are at least 5 groups of high energy compounds
 - Pyrophosphates, eg, ATP
 - Acyl phosphates, eg, 1,3-bisphosphoglycerate
 - Enol phosphates, eg, PEP
 - Thioesters, eg, Acetyl CoA
 - Phosphagens, eg, Phosphocreatine

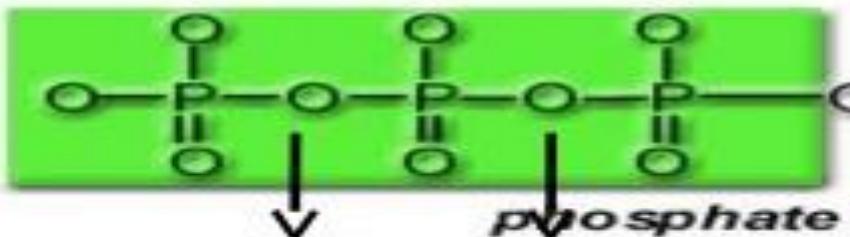
Table 11.2 High-energy compounds		
Class	Bond	Example(s)
Pyrophosphates	$-C-\overset{\circ}{P}-\overset{\circ}{P}-$	ATP, pyrophosphate
Acyl phosphates	$\begin{matrix} O \\ \\ -C-O\sim P \end{matrix}$	1,3-Bisphosphoglycerate, carbamoyl phosphate, acetyl phosphate
Enol phosphates	$\begin{matrix} CH \\ \\ -C-O\sim P \end{matrix}$	Phosphoenol pyruvate
Thiol esters (thioesters)	$\begin{matrix} C \\ \\ -C-O\sim S- \end{matrix}$	Acetyl CoA, acyl CoA
Guanidio phosphates (Phosphagens)	$\begin{matrix} \\ -N\sim P \end{matrix}$	Phosphocreatine, phosphoarginine

High-energy bonds

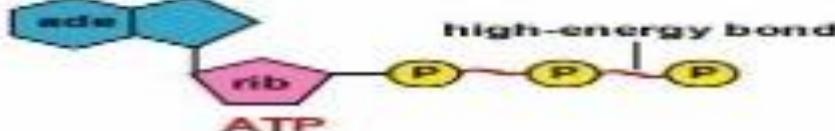
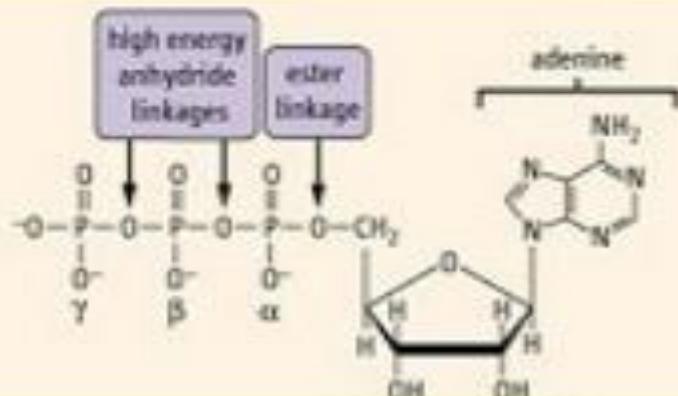
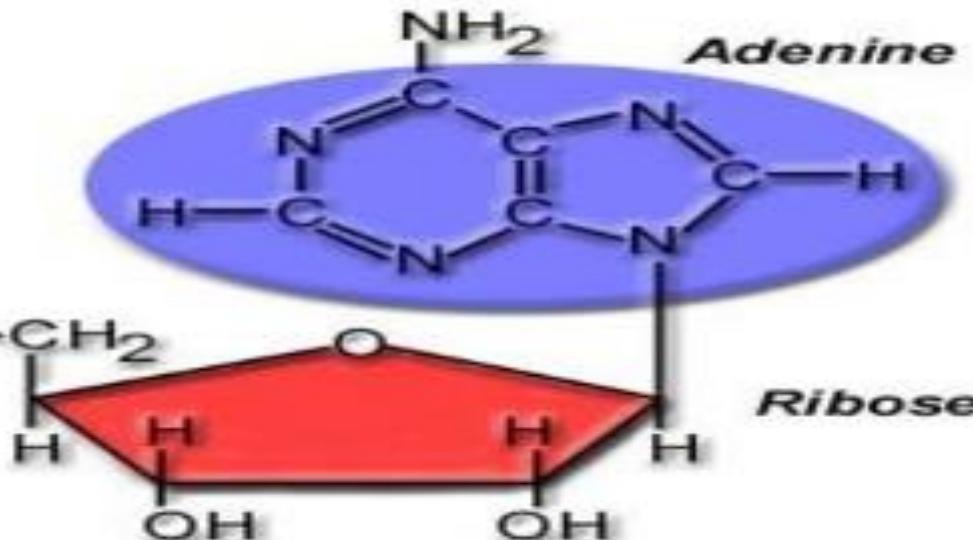
- The high-energy compounds possess acid anhydride bonds (mostly phosphoanhydride bonds) which are formed by the condensation of two acidic groups or related compounds.
- These bonds are referred as high-energy bonds.
- Free energy is liberated when these bonds are hydrolysed.
- ATP is most important high-energy compound

Adenosine Triphosphate (ATP)

ATP



High energy
anhydride bonds



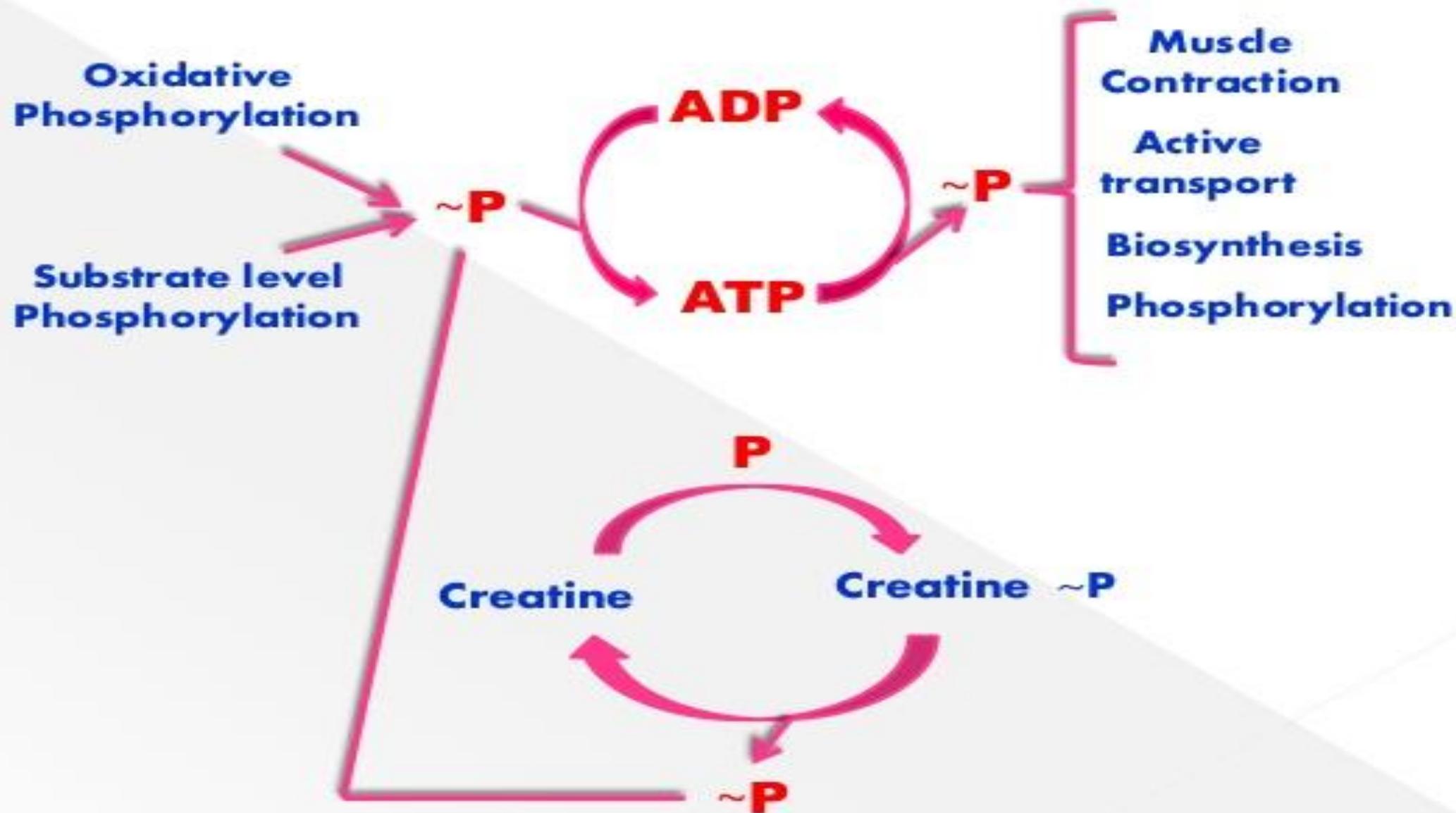
ATP-ADP Cycle

- **The hydrolysis of ATP is associated with the release of large amount of energy.**



- **The energy liberated is utilized for various process like muscle contraction, active transport etc.**
- **ATP can also acts as a donor of high-energy phosphate to low-energy compounds, to make them energy rich.**
- **ADP can accept phosphate to form ATP.**

ATP-ADP cycle along with sources & utilization of ATP



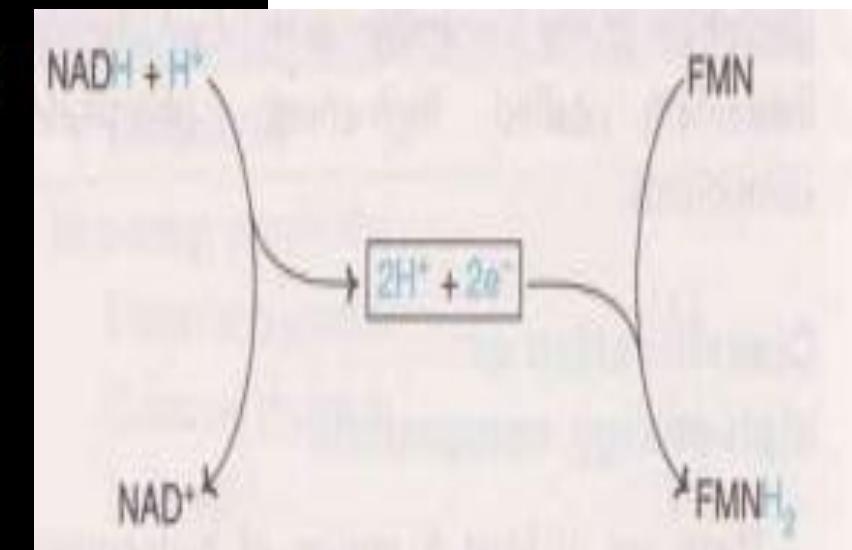
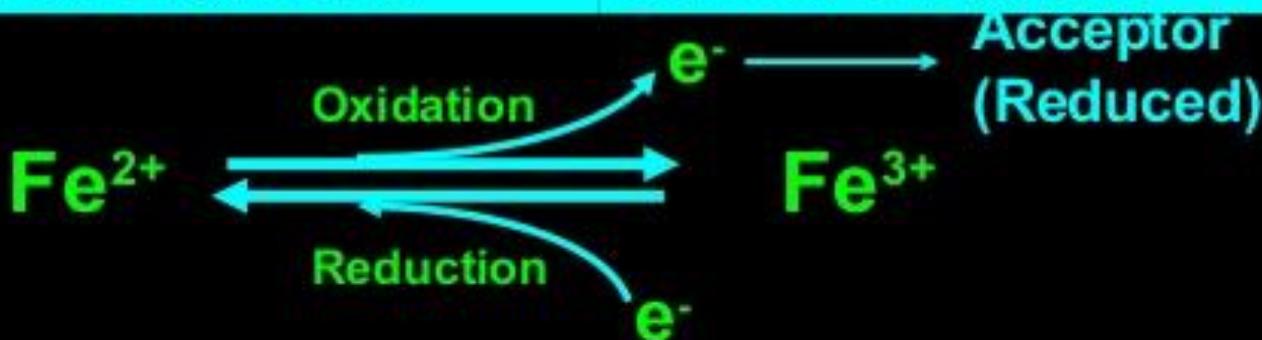
- ATP serves as an **immediately available energy currency of the cell** which is constantly being utilized & regenerated.
- ATP acts as an **energy link between the catabolism & anabolism** in the biological systems.
- Hydrolysis of ATP releases **7.3 kcal/mol.**

Synthesis of ATP

- **ATP can be synthesized in two ways**
- **Oxidative phosphorylation:**
- **Major source of ATP in aerobic organisms.**
- **It is linked with mitochondrial ETC.**
- **Substrate level phosphorylation:**
- **When the energy of high energy compound is directly transferred to nucleoside diphosphate to form a triphosphate without the help from ETC.**

- **Storage forms:**
- **Phosphocreatine (creatine phosphate)**
provides high energy reservoir of ATP to
regenerate ATP rapidly, catalyzed by
creatine kinase.
- **Stored mainly in muscle & brain.**
- **In invertebrates, phosphoarginine (arginine**
phosphate) is storage form.

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.

- 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.

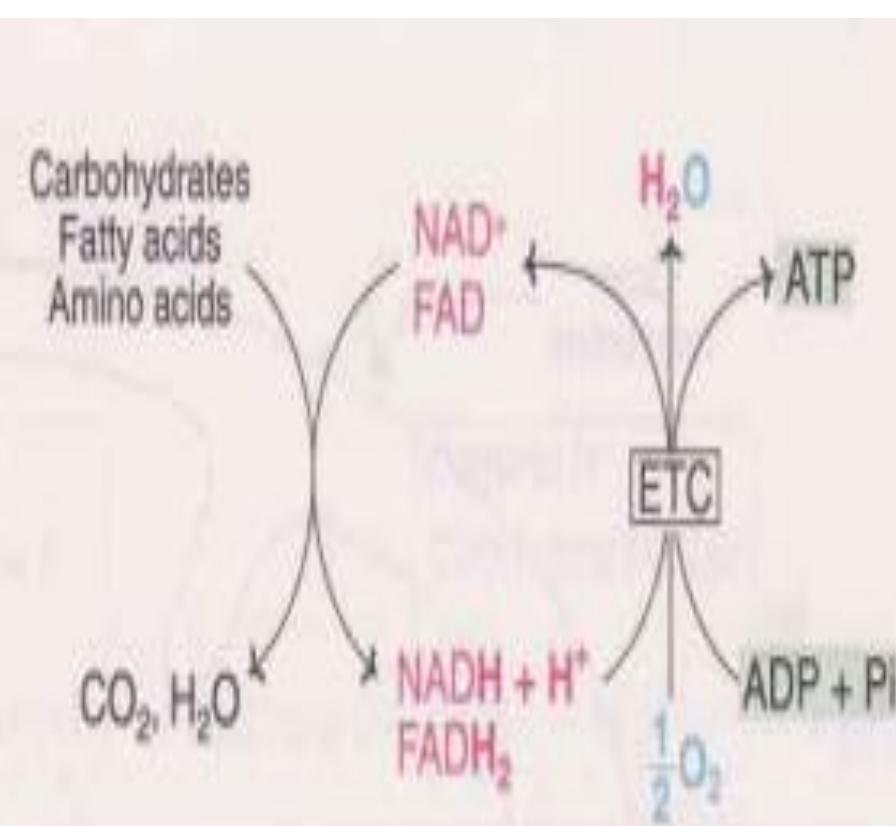


Fig. 11.3 : Overview of biological oxidation
(ETC-Electron transport chain).

Electron Transport chain/ Respiratory chain

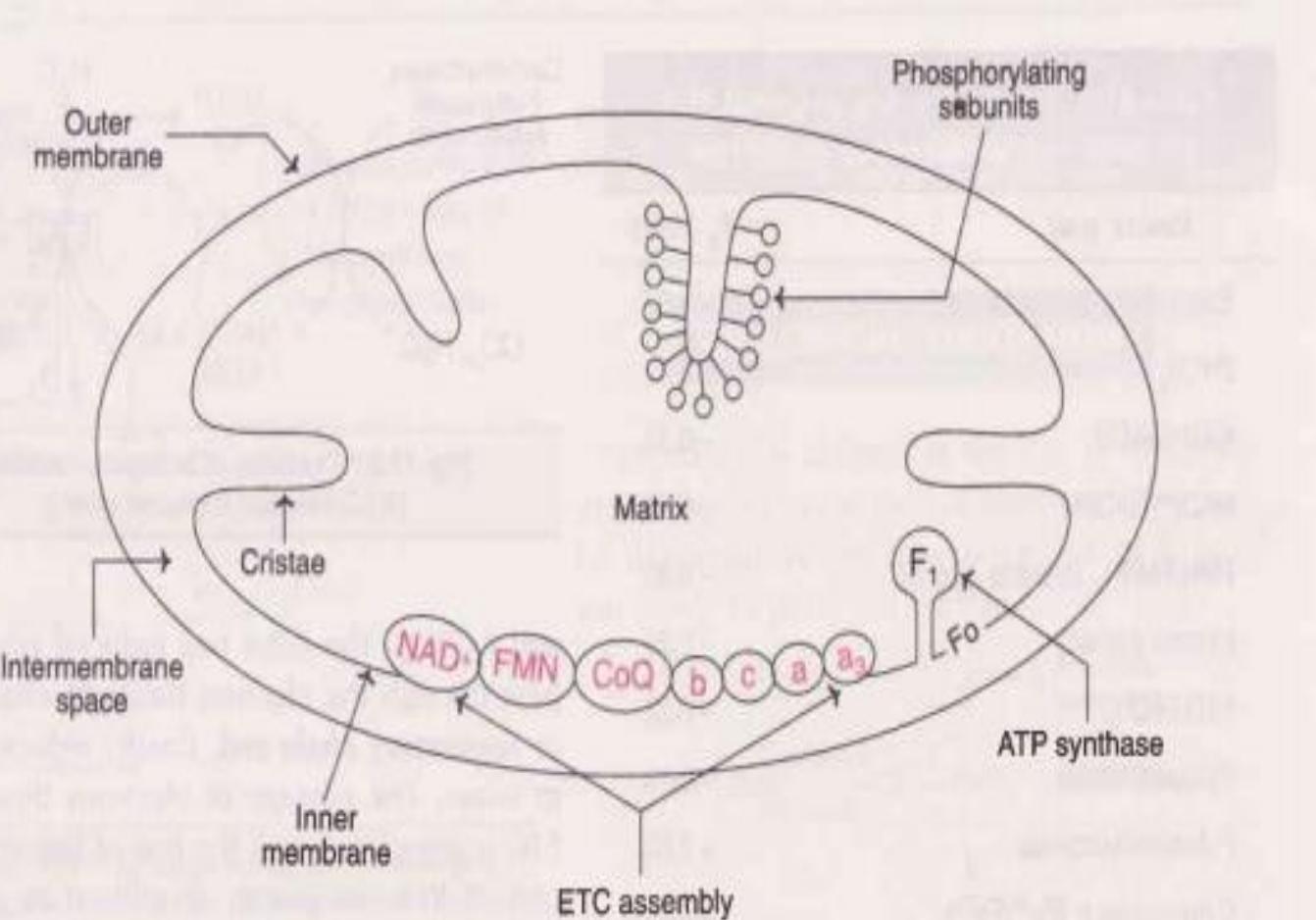
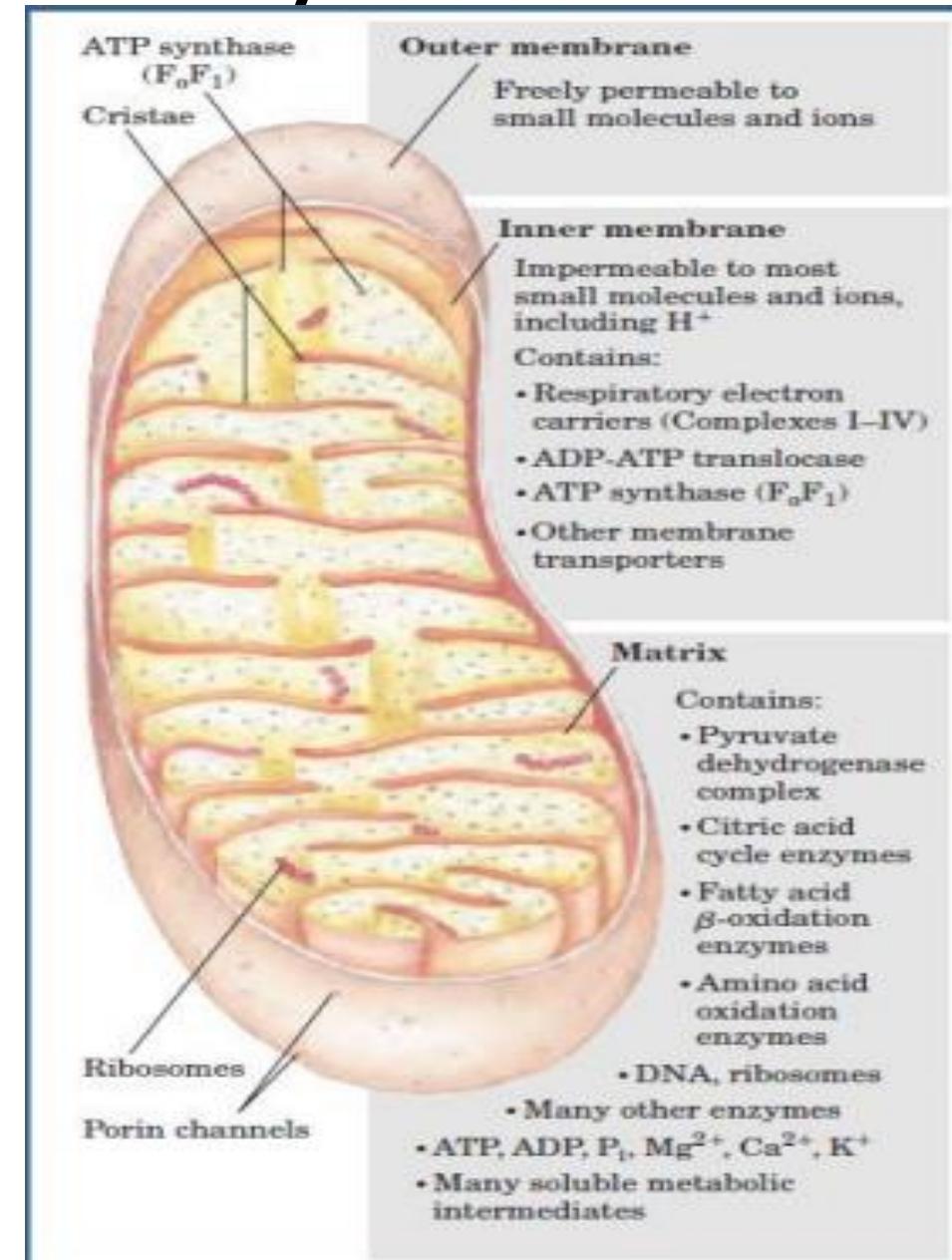


Fig. 11.5 : Structure of mitochondrion depicting electron transport chain (ETC) (F_0, F_1 —Protein subunits).



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.

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)’
- standard redox potential (E_0 volts) at pH 7.0 and 25°C

Table 11.3 Standard redox potential (E_0) of some oxidation-reduction systems

Redox pair	E_0 Volts
Succinate/ α -ketoglutarate	- 0.67
$2\text{H}^+/\text{H}_2$	- 0.42
NAD^+/NADH	- 0.32
$\text{NADP}^+/\text{NADPH}$	- 0.32
FMN/FMNH_2 (enzyme bound)	- 0.30
Lipoate (ox/red)	- 0.29
FAD/FADH_2	- 0.22
Pyruvate/lactate	- 0.19
Fumarate/succinate	+ 0.03
Cytochrome b ($\text{Fe}^{3+}/\text{Fe}^{2+}$)	+ 0.07
Coenzyme Q (ox/red)	+ 0.10
Cytochrome c, ($\text{Fe}^{3+}/\text{Fe}^{2+}$)	+ 0.23
Cytochrome c ($\text{Fe}^{3+}/\text{Fe}^{2+}$)	+ 0.25
Cytochrome a ($\text{Fe}^{3+}/\text{Fe}^{2+}$)	+ 0.29
$\frac{1}{2}\text{O}_2/\text{H}_2\text{O}$	+ 0.82

ETC COMPONENTS

Membrane bound components

Complex I –NADH Dehydrogenase

Complex II –Succinate Dehydrogenase

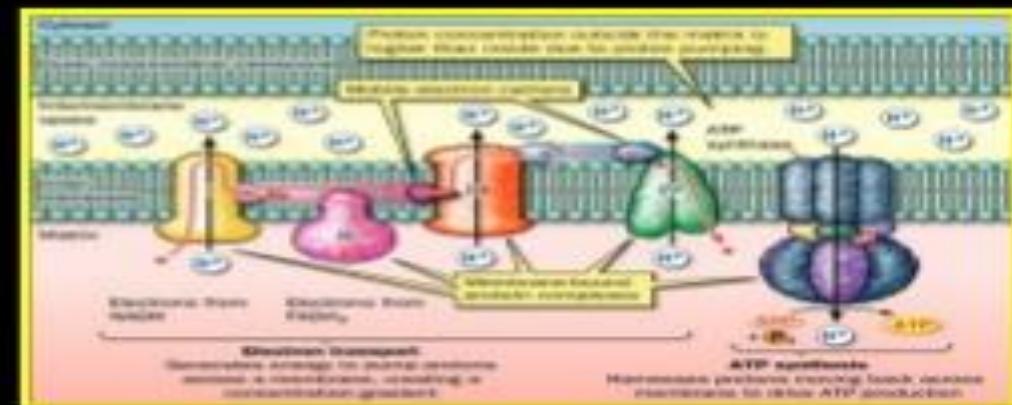
Complex III – Cytochrome b–c₁, or Cytochrome Reductase.

Complex IV – Cytochrome a + a₃ or Cytochrome Oxidase

Complex V – ATP Synthase

Mobile Components

- Coenzyme Q
- Cytochrome C



Cytochromes

Cytochrome is a class of **haemoprotein** (an iron(Fe)-containing haem group attached to protein).

- These “**cell pigments**” are present in all living tissues that require oxygen.
- They are involved in the transfer of electrons in association with a reversible change in oxidation state of the haem protein (**ferrous (Fe²⁺)** to **Ferric (Fe³⁺)**).

There are 4 major classes of cytochromes, viz., a, b, c and d.

The members of each subclass are distinguished from each other through numerical subscripts and by their characteristic wavelength of absorption maximum. E.g. Cytochrome C1, Cytochrome C555.

- They also differ from each other through their type of **haem group**.

Flavoproteins

The enzyme “dehydrogenase”, which removes electrons from NADH, or from substrates like succinate, contains flavins as prosthetic group. Flavins are referred to riboflavin (Vitamin -B2).

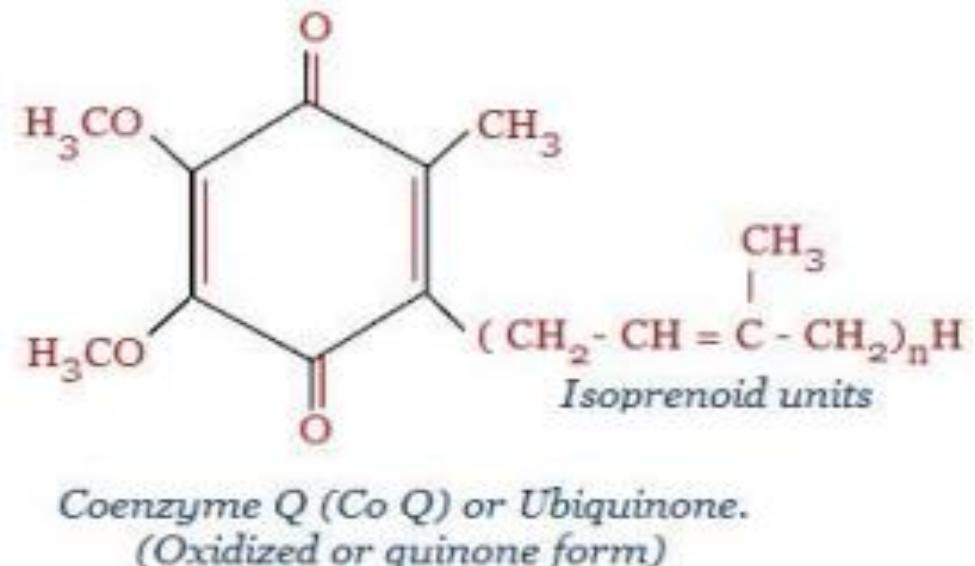
- There are 2 enzyme complexes,
- **NADH – dehydrogenase**, contain **FMN (Flavin mononucleotide)**,
- **Succinate dehydrogenase**, containing, **FAD (Flavin adenine dinucleotide)**

Fe –S protein

- These proteins contain **Fe atoms** that are bound to the **S-atom** of the **cysteine** residues of the protein.

Co-enzyme Q

- ✓ Co- enzyme Q is a **quinone derivative** with a long **10 isoprenoid side chain**.
- ✓ It is also called as “**Ubiquinone**”, because, it is present ubiquitously (ubiquitous = present everywhere) in all biological systems.
- ✓ It is a lipid soluble compound(**lipophilic electron carrier**) and therefore freely diffusible within the inner membrane. It is capable of undergoing reversible redox reactions.
- ✓ it is directly **synthesized in the body**.



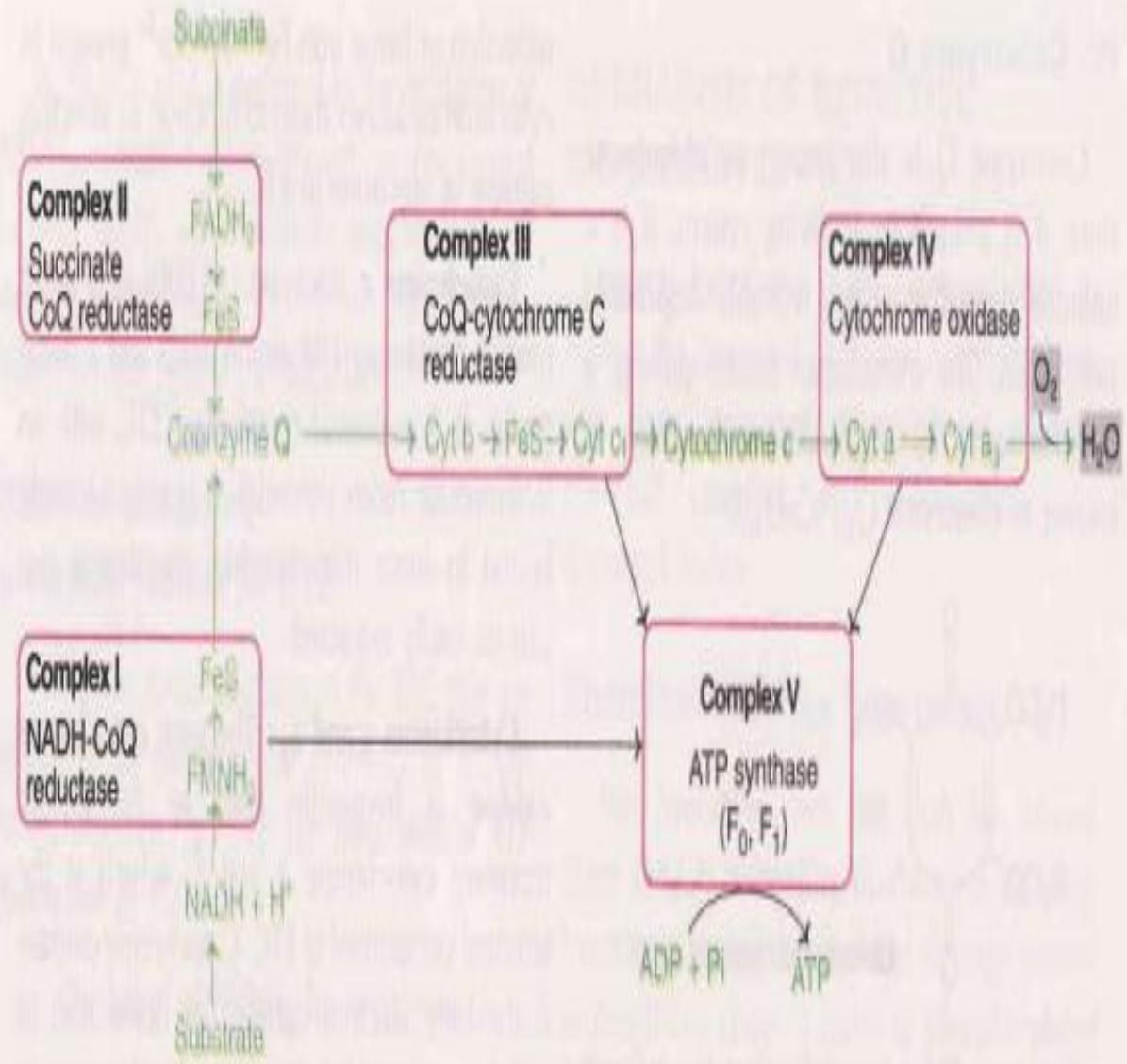
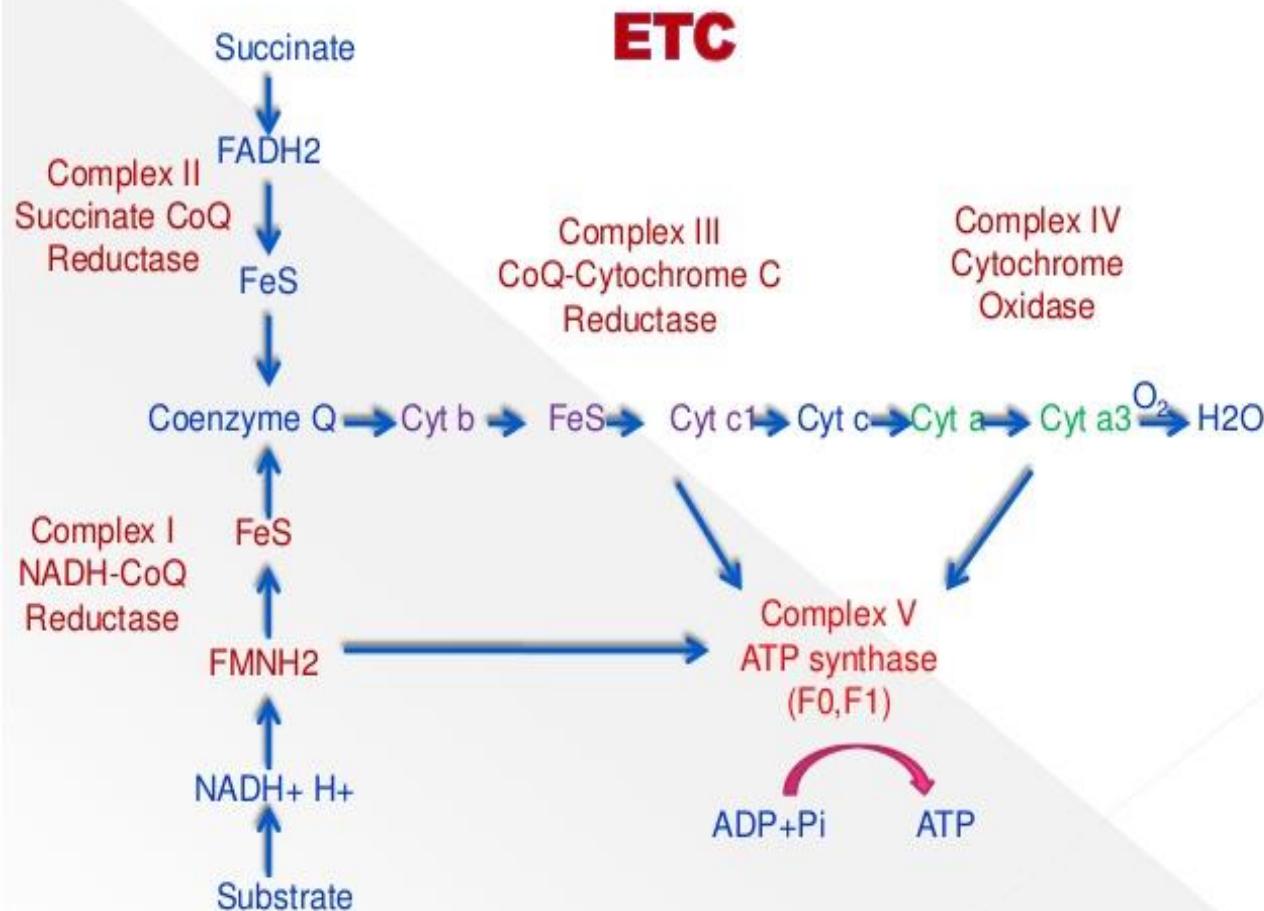
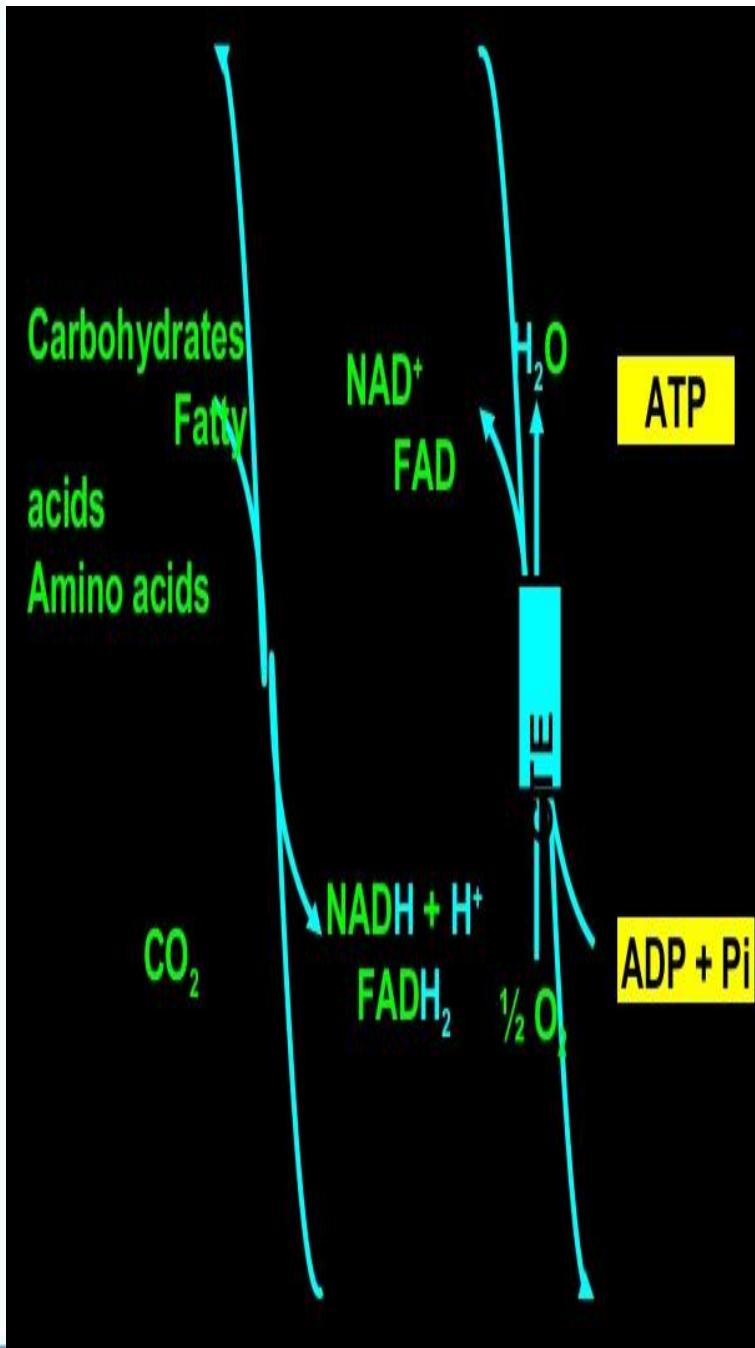
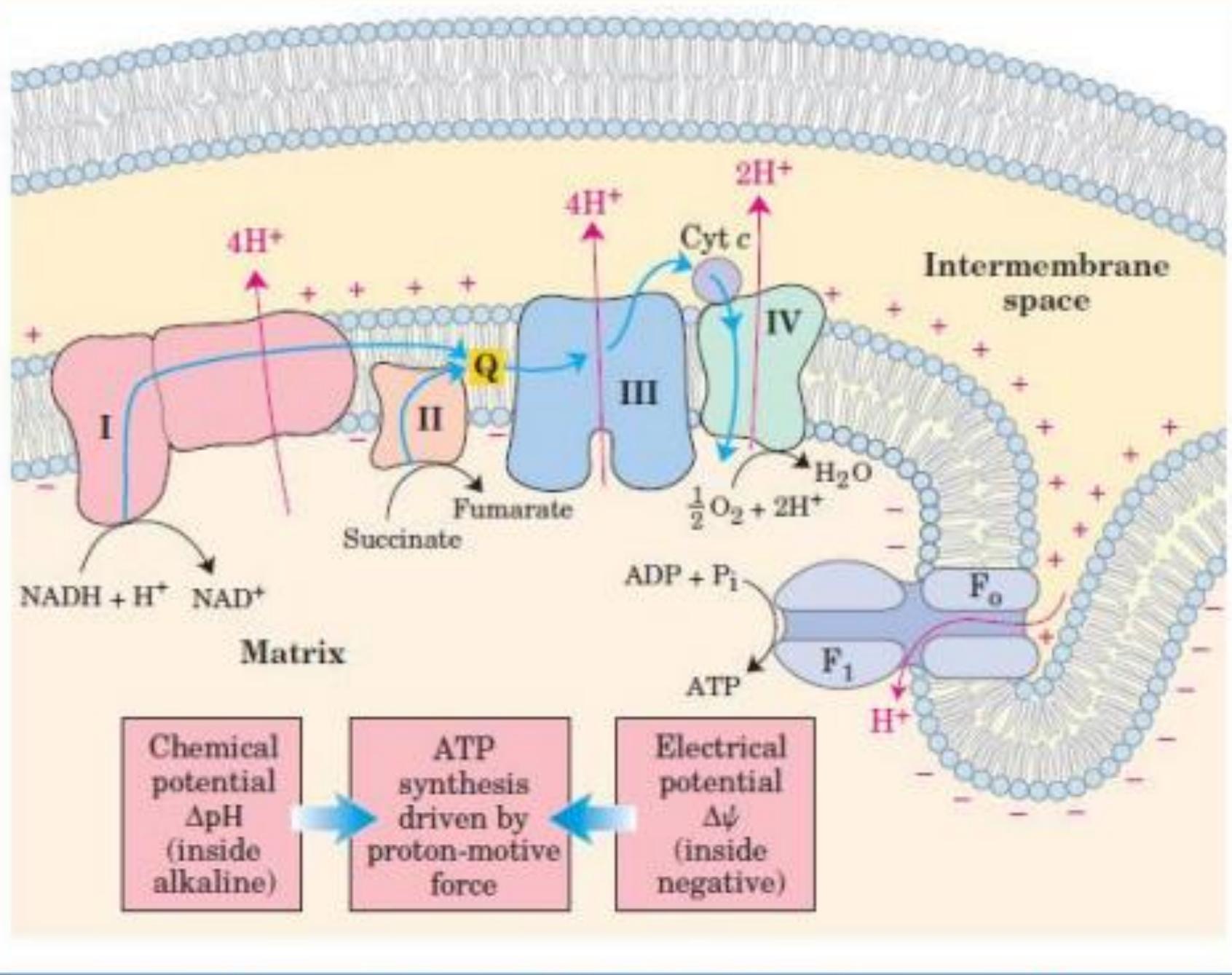


Fig. 11.6 : Multiprotein complexes in electron transport chain.





Source: "Lehninger's Principles of Biochemistry" by David Nelson and Cox, 4th edition.

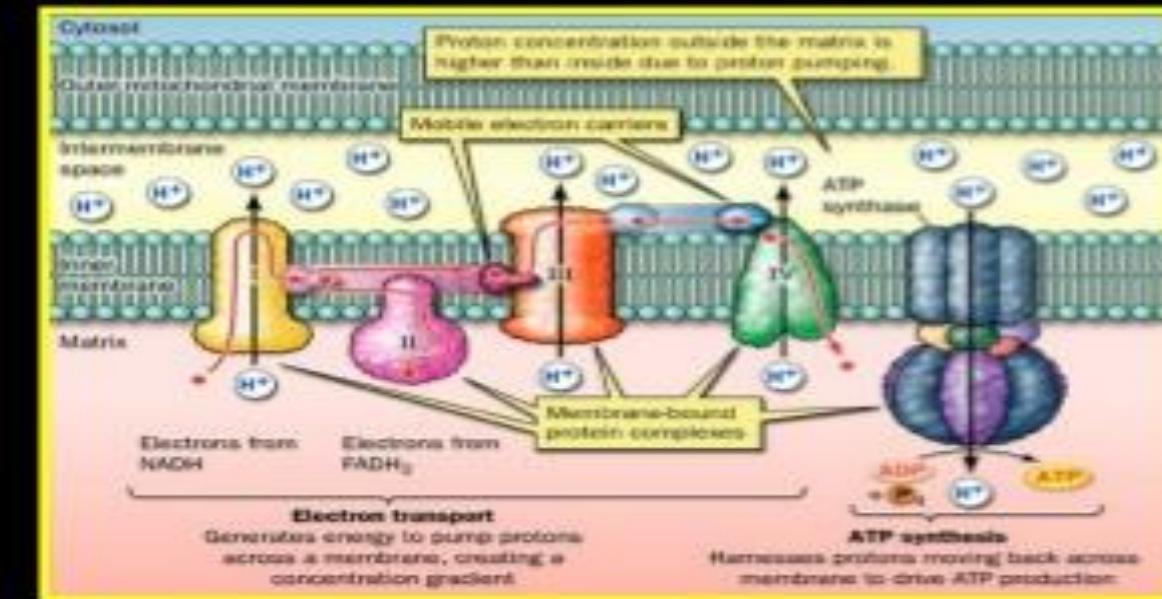
Complex	Name	Function
I	NADH dehydrogenase	Reduction of UQ by NADH
II	Succinate dehydrogenase	Reduction of UQ by succinate
III	Ubiquinol dehydrogenase	Transfer of electrons from UQH_2 to Cyt-C
IV	Cytochrome oxidase	Transfer of electrons from Cyt-C to O_2

- **Cytochrome oxidase** the only electron carrier, the **heme iron** of which can directly react with molecular oxygen. Besides heme (with iron), this oxidase also contains **copper** that undergoes oxidation reduction (Cu^{2+} to Cu^+) during the transport of electrons

Complex	No. of protons pumped out
Complex I	4
Complex III	--
Complex III	4
Complex IV	2
Complex V	--

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 (complex V)

- ✓ The process of synthesizing ATP from ADP and P_i coupled with the electron transport chain is known as oxidative phosphorylation

P/O ratio or P:O

- ✓ The number of molecules of ATP formed per pair of electrons transferred down the respiratory chain to atomic oxygen is termed P/O ratio.

- ❖ 1. When substrates are oxidized via NAD-linked dehydrogenase(complex I) in the respiratory chain,

P/O ratio is = 2.5

(10 proton)

4 proton = 1 ATP

10/4= 2.5 ATP=NADH

- ❖ 2. When a substrate like succinate is oxidized via a flavoprotein – linked dehydrogenase(complex II).

P/O =1.5

(6 proton)

4 proton = 1 ATP

6/4= 1.5 ATP = FADH₂

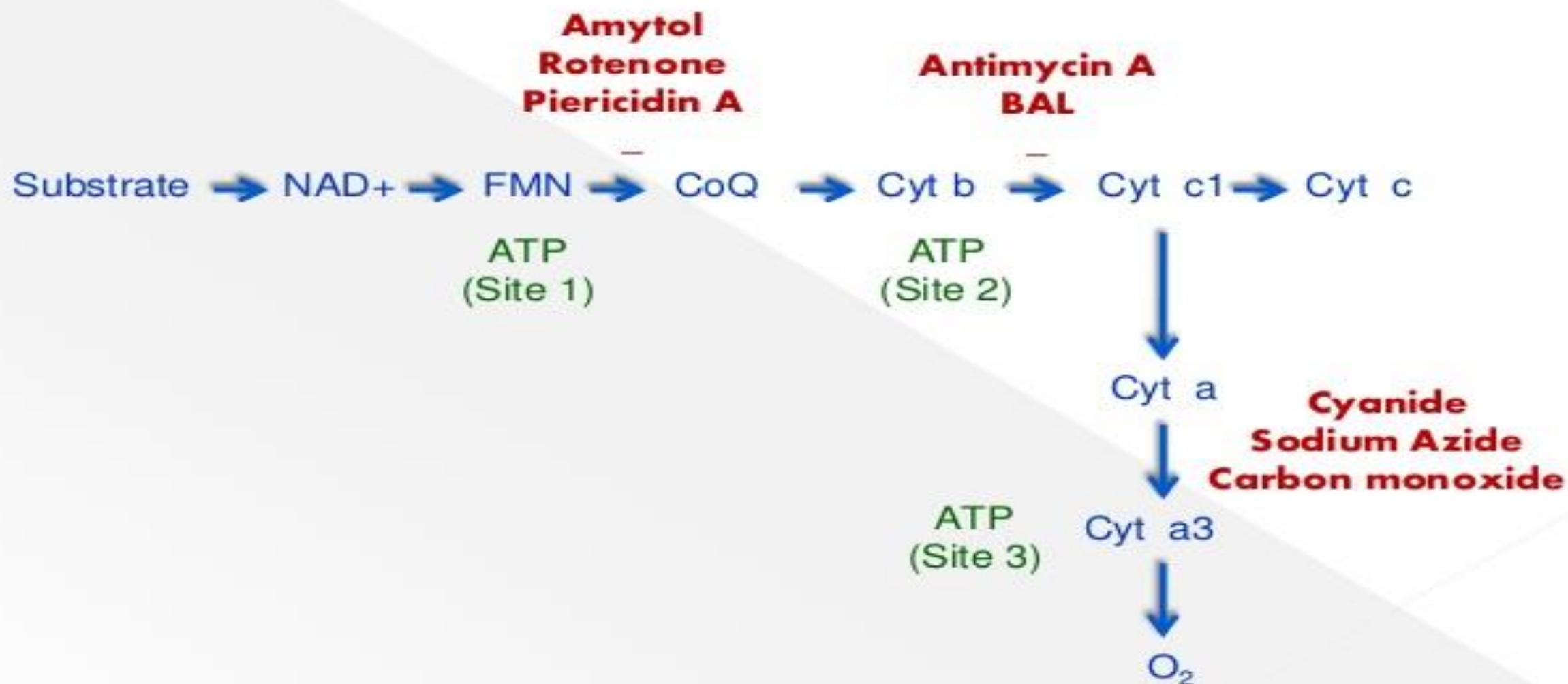
Sites of Oxidative Phosphorylation in ETC

- There are 3 reactions in the ETC that are exergonic.
- Where the energy change is sufficient to drive the synthesis of ATP from ADP and Pi.
- Site 1:
 - Oxidation of FMNH₂ by coenzyme Q.
- Site 2:
 - Oxidation of cytochrome b by cytochrome c₁.
- Site 3:
 - Cytochrome oxidase.

Energetics of oxidative phosphorylation

when NADH is oxidized, 35% of energy is trapped in the form of 2.5 ATP & remaining is lost as heat

Sites of ATP synthesis & Inhibitors



Mechanism of oxidative phosphorylation

Chemiosmotic Theory

- The transport of electrons through the respiratory chain is effectively utilized to produce ATP from ADP + Pi.

1. Proton gradient:

- The inner mitochondrial membrane, is impermeable to protons (H^+) & hydroxyl ions (OH^-).

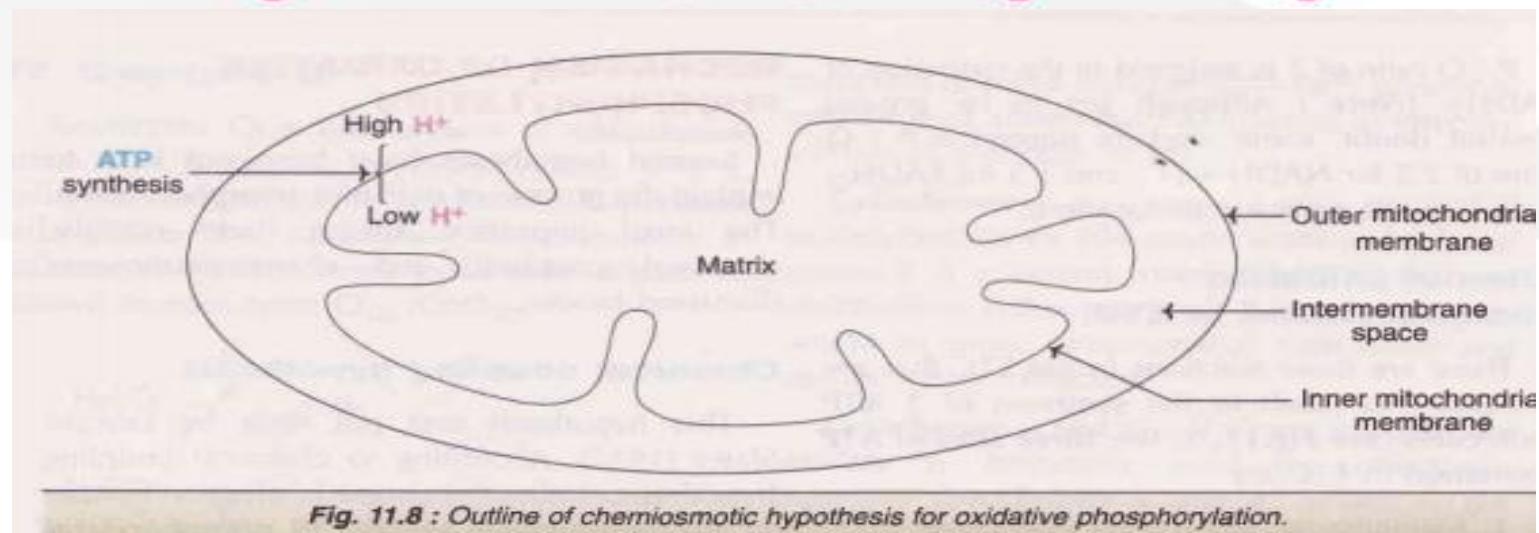


Fig. 11.8 : Outline of chemiosmotic hypothesis for oxidative phosphorylation.

- The transport of electrons through ETC is coupled with the translocation of protons (H^+) across the inner mitochondrial membrane from the matrix to the inter membrane space.
- The pumping of protons results in an electrochemical or proton gradient .

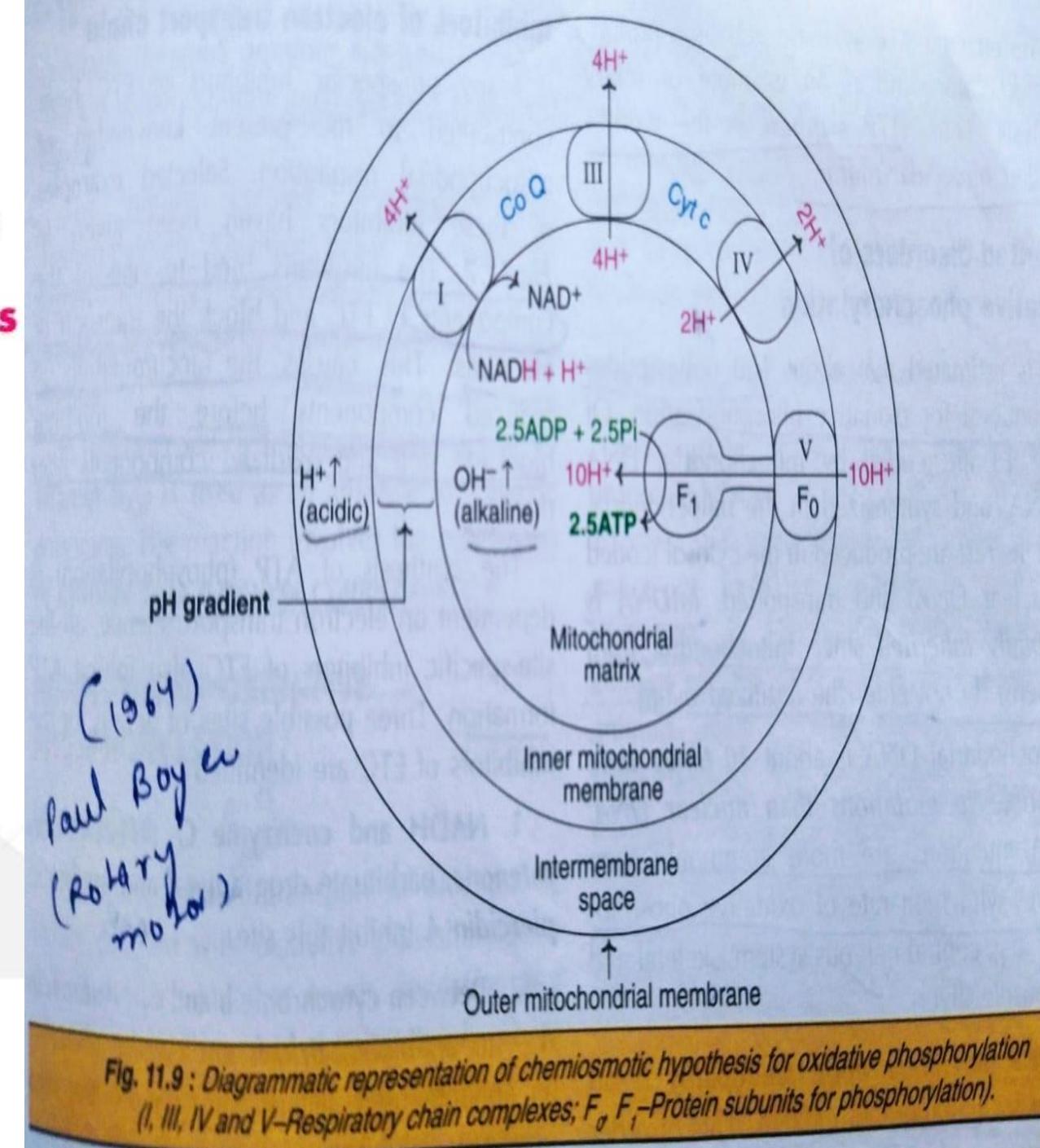


Fig. 11.9 : Diagrammatic representation of chemiosmotic hypothesis for oxidative phosphorylation (I, III, IV and V-Respiratory chain complexes; F_0 , F_1 -Protein subunits for phosphorylation).

- This is due to the accumulation of more H⁺ ions (low pH) on the outer side of the inner mitochondrial membrane than the inner side.
- The proton gradient developed due to the electron flow in the respiratory chain is sufficient to result in the synthesis of ATP from ADP +Pi.

2 Enzyme systems for ATP synthesis:

- **ATP synthase, present in the complex V, utilizes the proton gradient for the synthesis of ATP.**
- **This enzyme is also known as ATPase, since it can hydrolyze ATP to ADP + Pi.**
- **ATP synthase is a complex enzyme & consists of two functional subunits, namely F₁ & F₀.**

Rotor motor model for ATP generation

- **Paul Boyer in 1964 proposed that a conformational change in the mitochondrial membrane proteins leads to the synthesis of ATP**
- **This is now considered as rotary motor/engine driving model or binding change model, is widely accepted for the generation of ATP.**

- The enzyme ATP synthase is **F₀ & F₁ complex**
- The **F₀ sub complex** is composed of channel protein '**C**' subunits to which **F₁-ATP synthase** is attached.
- **F₁-ATP synthase** consists of a central gamma-subunit surrounded by alternating alpha & beta subunits (α_3 & β_3).
- In response to the proton flux, the gamma subunit physically rotates.

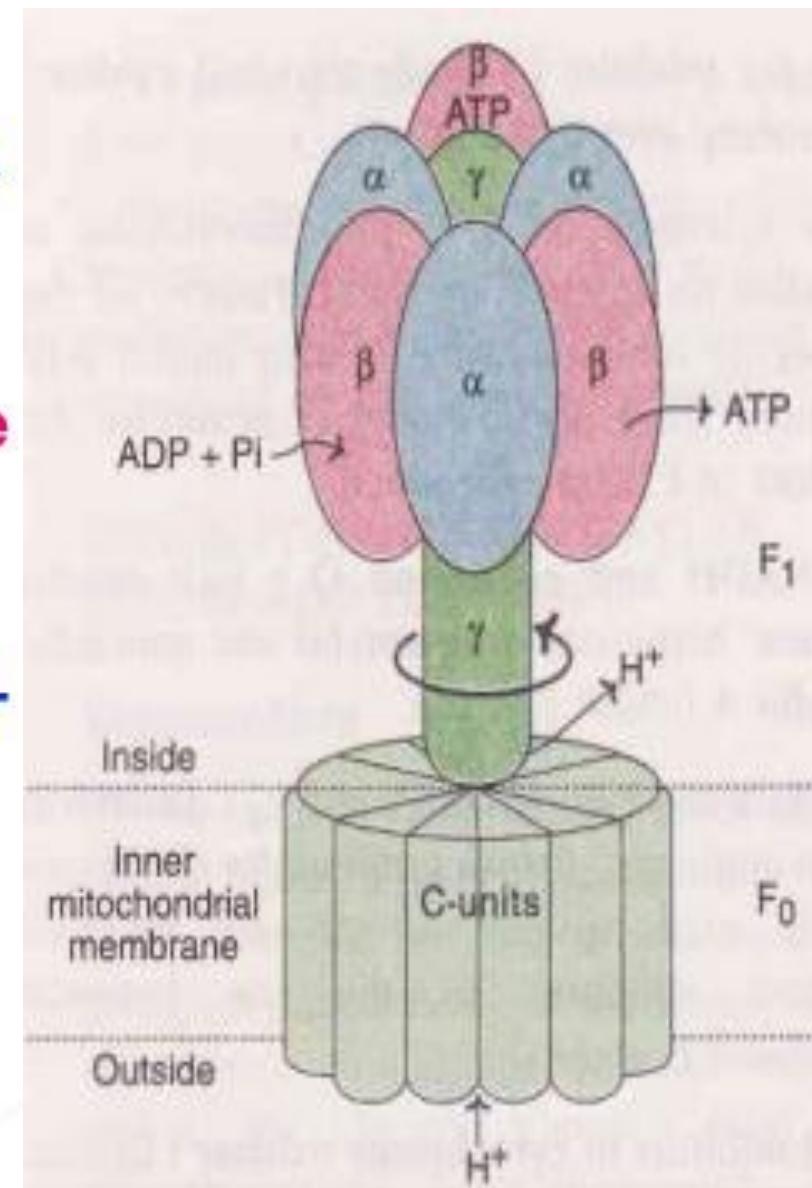


Fig. 11.10 : Structure of mitochondrial ATP synthase (F_0F_1) complex (C units-channel protein subunits; α , β , and γ are the subunits of F_1 -ATP synthase).

- This induces conformational changes in the β_3 subunits that finally lead to the release of ATP.
- According to the binding change mechanism, the three β subunits of F_1 -ATP synthase adopt different conformations.
- One subunit has Open (O) conformation, the second has loose (L) conformation while the third one has tight (T) conformation.
- By an known mechanism, protons induce the rotation of gamma subunit, which in turn induces conformation changes in β subunits..
- The substrates ADP & Pi bind to β subunit in L conformation.
- The L site changes to T conformation, & this leads to the synthesis of ATP.

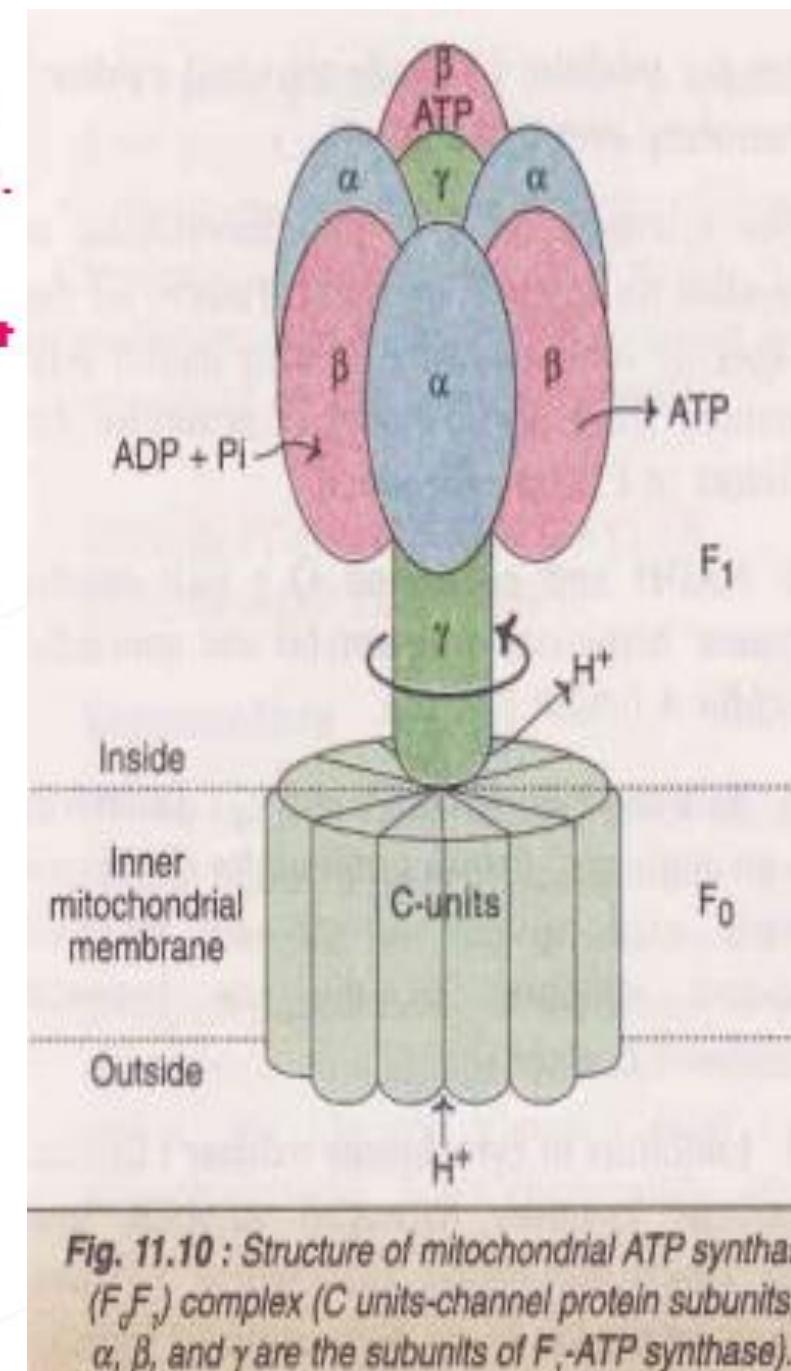


Fig. 11.10 : Structure of mitochondrial ATP synthase (F_1F_0) complex (C units-channel protein subunits; α , β , and γ are the subunits of F_1 -ATP synthase).

- The O site changes to L conformation which binds to ADP + Pi.
- The T site changes to O conformation & releases ATP.
- This cycle of conformation changes of β subunits is repeated.
- 2.5 ATP are generated for each revolution.

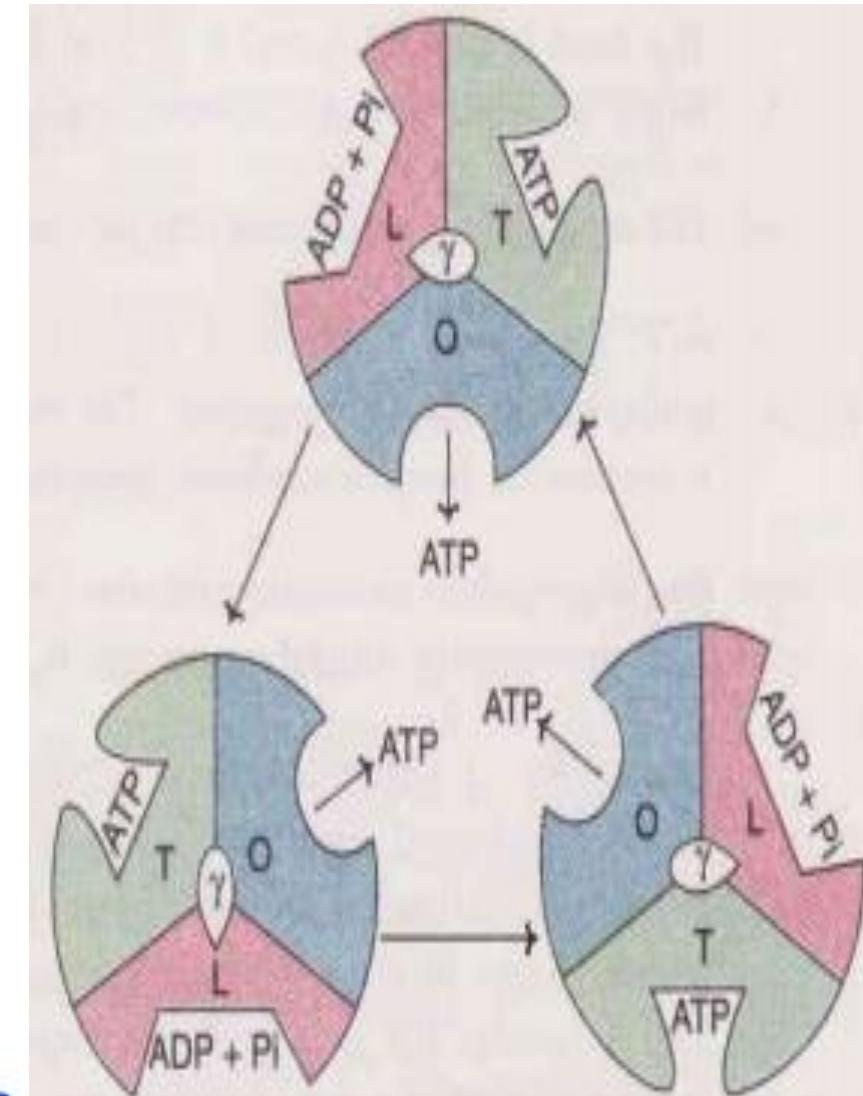


Fig. 11.11 : The binding change model (rotary motor/engine driving model) for ATP synthesis by F_1 -ATP synthase.

UNCOUPLERS OF OXIDATIVE PHOSPHORYLATION

- Uncouplers dissociate oxidation in the respiratory chain from phosphorylation.
- These compounds are toxic *in vivo*, causing respiration to become uncontrolled, since the rate is no longer limited by the concentration of ADP or P_i.
- 2,4-dinitrophenol
- 2, 4- dinitrocresol
- CCCP
- TCCP
- Valinomycin
- High dose of Aspirin
- The antibiotic **oligomycin** completely blocks oxidation and phosphorylation by blocking the flow of protons through ATP synthase

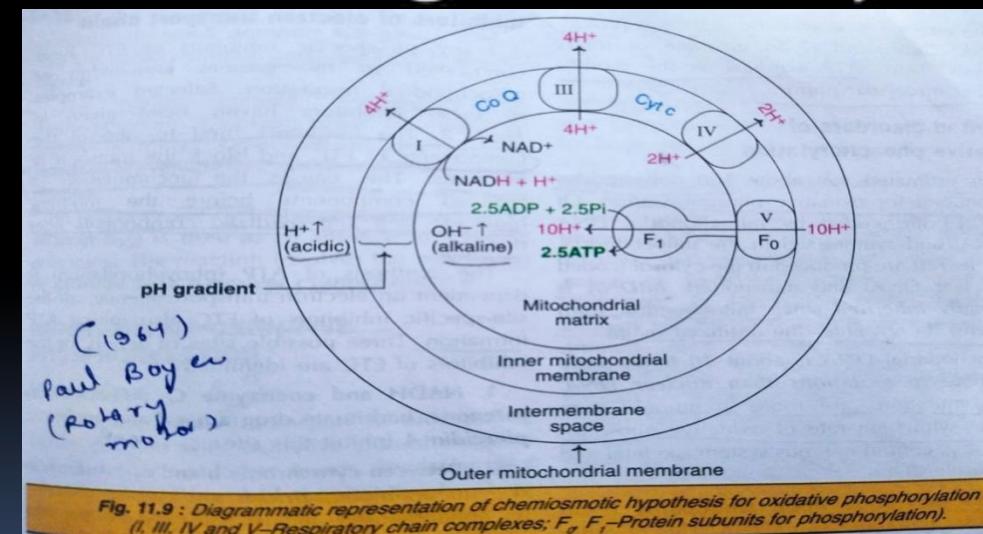


Fig. 11.9 : Diagrammatic representation of chemiosmotic hypothesis for oxidative phosphorylation (I, III, IV and V-Respiratory chain complexes; F₀, F₁-Protein subunits for phosphorylation).

UNCOUPLERS OF OXIDATIVE PHOSPHORYLATION

Physiological Uncouplers

- Long chain fatty acids
- Thyroxin
- Brown Adipose tissue-**Thermogenin (or the uncoupling protein)** is a physiological uncoupler found in brown adipose tissue that functions to generate body heat, particularly for the newborn and during hibernation in animals
- Calcium ions

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.

Shuttle pathways-transport of reducing equivalents

The inner mitochondrial membrane is **impermeable to NADH**. Therefore, the NADH produced in the cytosol cannot directly enter the mitochondria

Two main shuttle systems are of importance

- ❖ **Glycerol phosphate shuttle** – present in skeletal muscle and brain
- ❖ **Malate shuttle** – present in liver, kidney and heart mitochondria

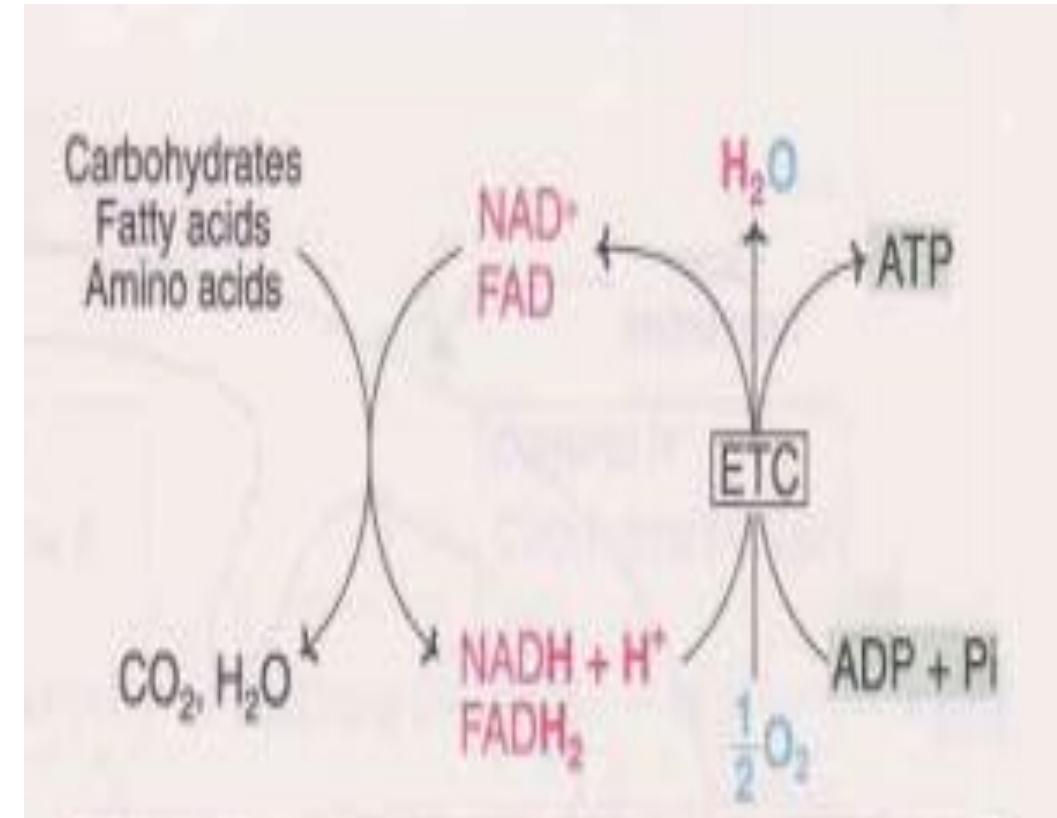


Fig. 11.3 : Overview of biological oxidation
(ETC-Electron transport chain).

Glycerol phosphate shuttle

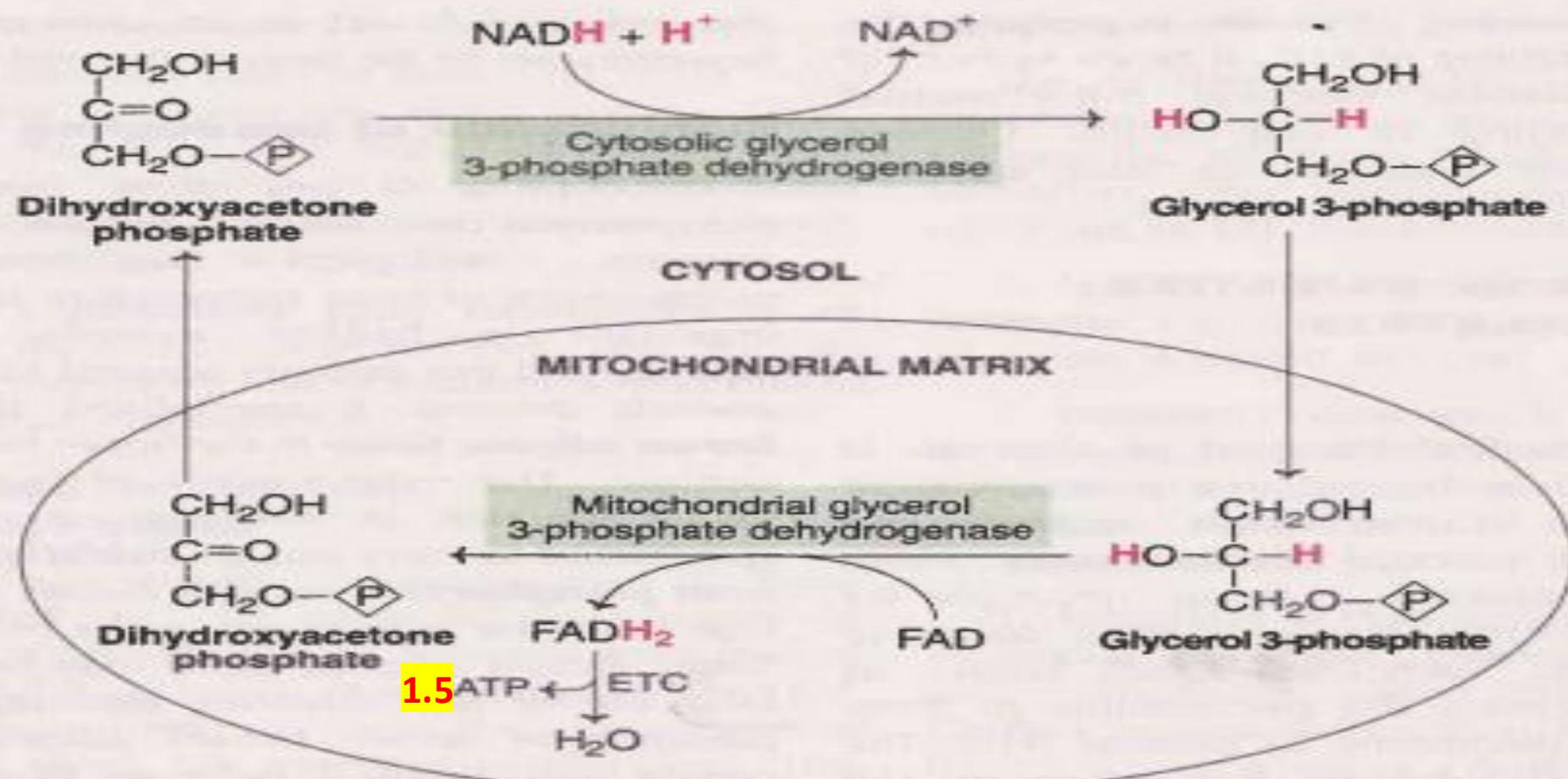


Fig. 11.12 : Glycerol-phosphate shuttle (reducing equivalents transported are shown in Blue).

- FADH_2 gets oxidized via ETC to generate **1.5 ATP**.

Malate aspartate shuttle

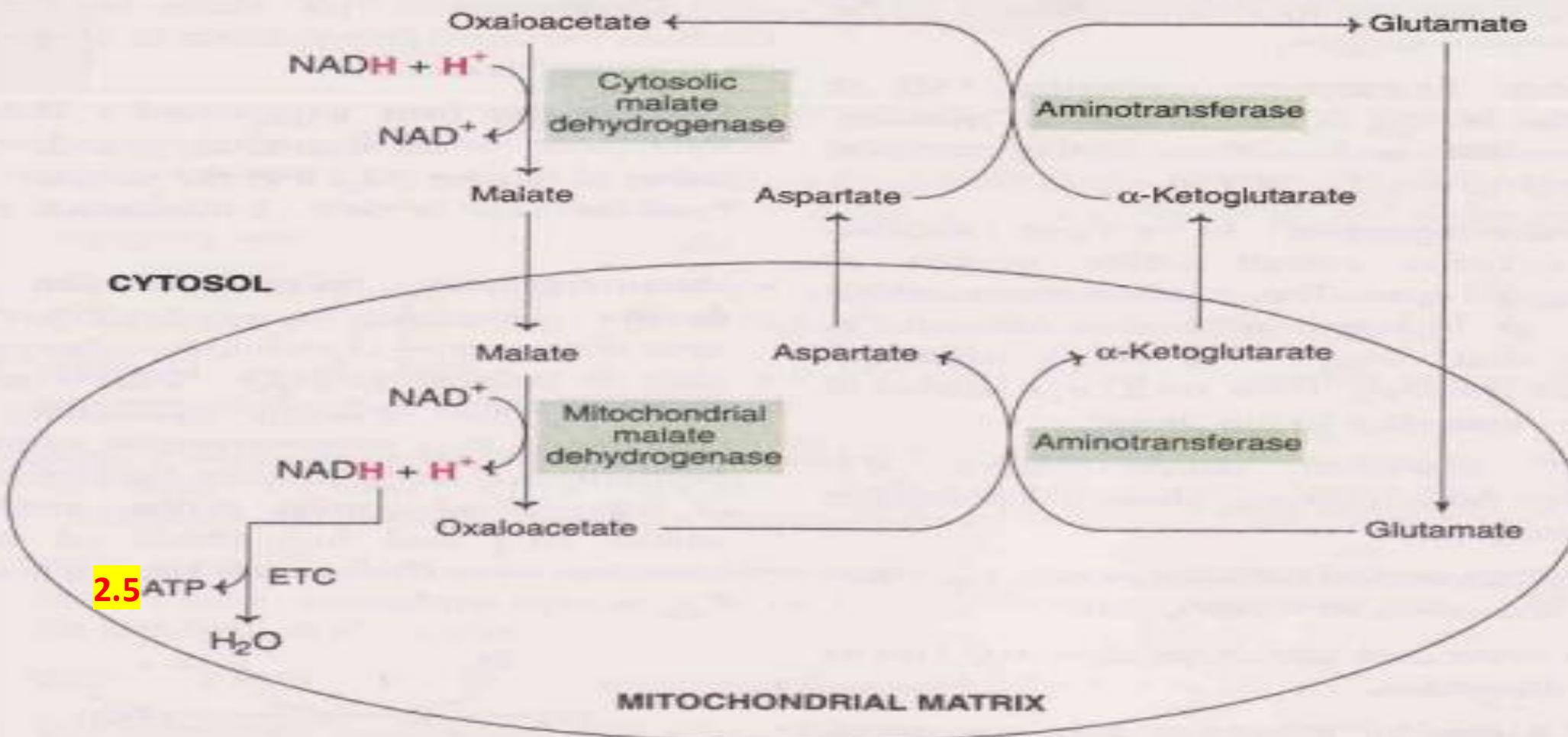


Fig. 11.13 : Malate-aspartate shuttle.

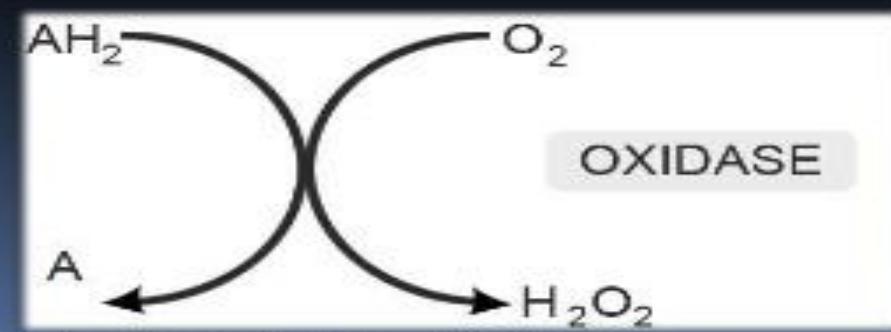
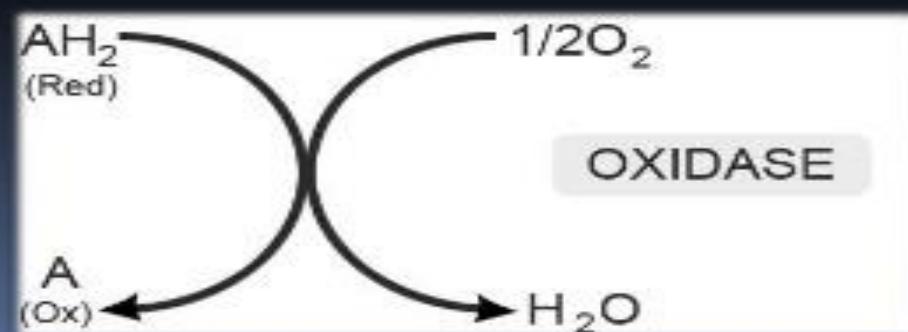
NADH gets oxidized via electron transport chain and **2.5 ATP** are produced

ENZYMES INVOLVED IN OXIDATION AND REDUCTION REACTIONS

- Are called as Oxidoreductases which include : oxidases, dehydrogenases, hydroperoxidases and oxygenases.
- Oxidases use oxygen as an electron acceptor
- Dehydrogenases can't use O_2 as an electron acceptor
- Hydroperoxidases use H_2O_2 as a substrate
- Oxygenases catalyze the direct transfer of O_2 into the substrate
- Oxidases & dehydrogenases are involved in respiration; hydroperoxidases neutralize free radicals & oxygenases are involved in biotransformation reactions.

OXIDASES

- Catalyze the removal of hydrogen from a substrate with the involvement of oxygen as a H – acceptor, forming water or hydrogen peroxide.
- Exist in two different forms :
 - ❖ some of them are copper containing such as, Cytochrome oxidase , the terminal component of ETC which transfer the e^- finally to O_2 .
 - ❖ Other are flavoproteins such as , L – amino acid oxidase (FMN linked) and Xanthine oxidase (FAD linked)



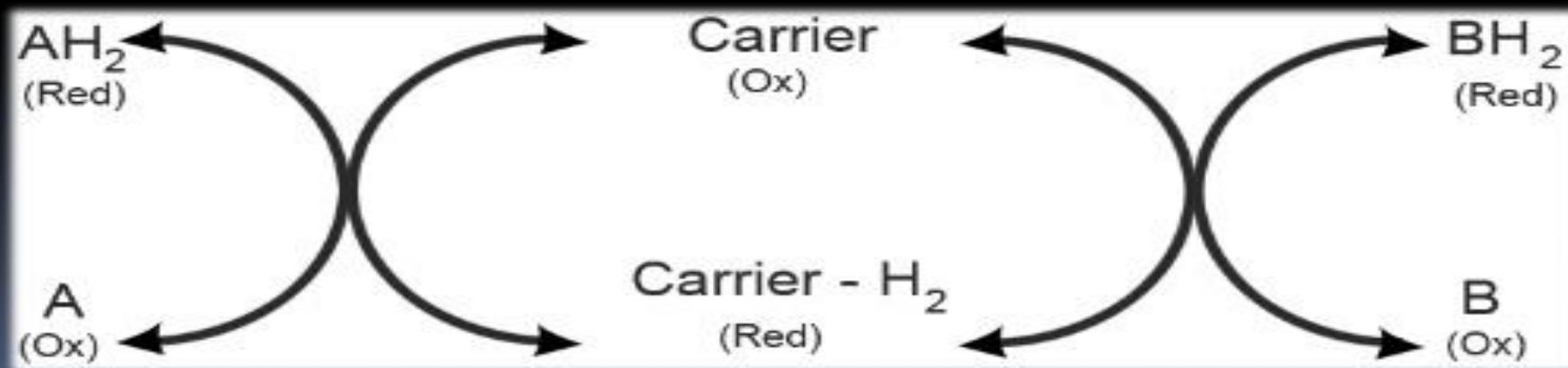
DEHYDROGENASES

Perform 2 main functions:

- Transfer hydrogen from one substrate to another in a coupled Oxidation / Reduction reaction
- As components of Electron transport chain such as cytochromes

Dehydrogenases use coenzymes – nicotinamides & riboflavin - as hydrogen carriers

- Nicotinamides can be in the form of NAD^+ or NADP^+
- Riboflavin can be – FMN or FAD same as oxidases

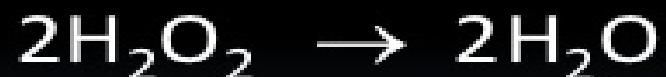


HYDROPEROXIDASES

- Includes 2 sets of enzymes : catalases and peroxidases
- Peroxidases reduce H_2O_2 at the expense of several other substances



- Catalases uses H_2O_2 as electron acceptor & electron donor



Peroxisomes are rich in oxidases and catalases

OXYGENASES

Catalyze the incorporation of O₂ into substrates in 2 steps

- Oxygen is bound to the active site of the enzyme
- Bound O₂ is reduced or transferred to the substrate

Consist of two sets of enzymes

1. Dioxygenases : incorporate both atoms of oxygen into the substrate ; A + O₂ → AO₂
2. Monooxygenases : incorporates one atom of oxygen into the substrate & the other is reduced to water



- **Monooxygenases** also known as hydroxylases, mixed function oxidases, mixed function oxygenases

Examples: **microsomal cytochrome P-450 monooxygenase**



thank you