بسم الله الرحمن الرحيم

Electron transport chain(ETC)

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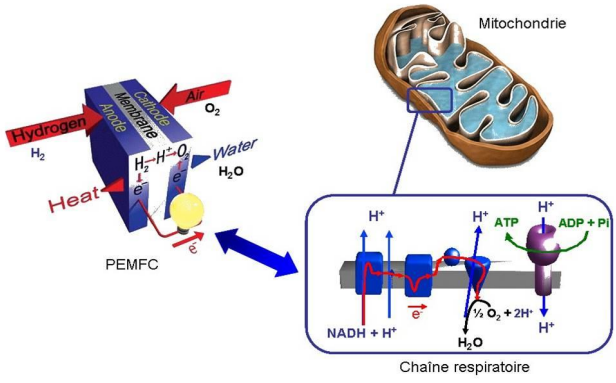
References:Kaplan
Lippincot Biochemistry

Bioenergetics
Electron transport chain(ETC)
Respiratory Chain (RC)

Objectives :

- Redox potential
- Electron transport chain
- ATP production
- Uncouplers and inhibitors
- of the oxidative phosphorylation & ETC



Oxidation-Reduction

Oxidation

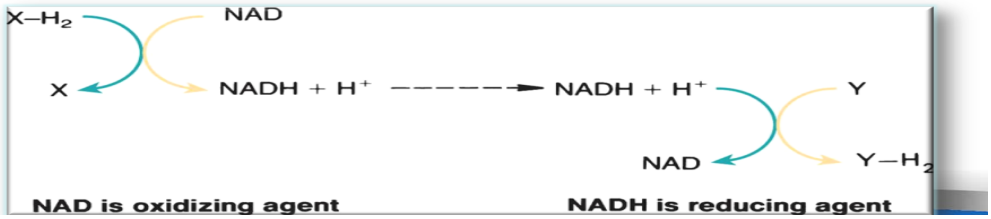
Addition of oxygen
or removal of **hydrogen or an electron**

Reduction

Addition of an electron or hydrogen
or removal of oxygen

REDOX reactions

Oxidation and reduction reactions are always coupled



Electron Transport Chain (ETC) or (RC)

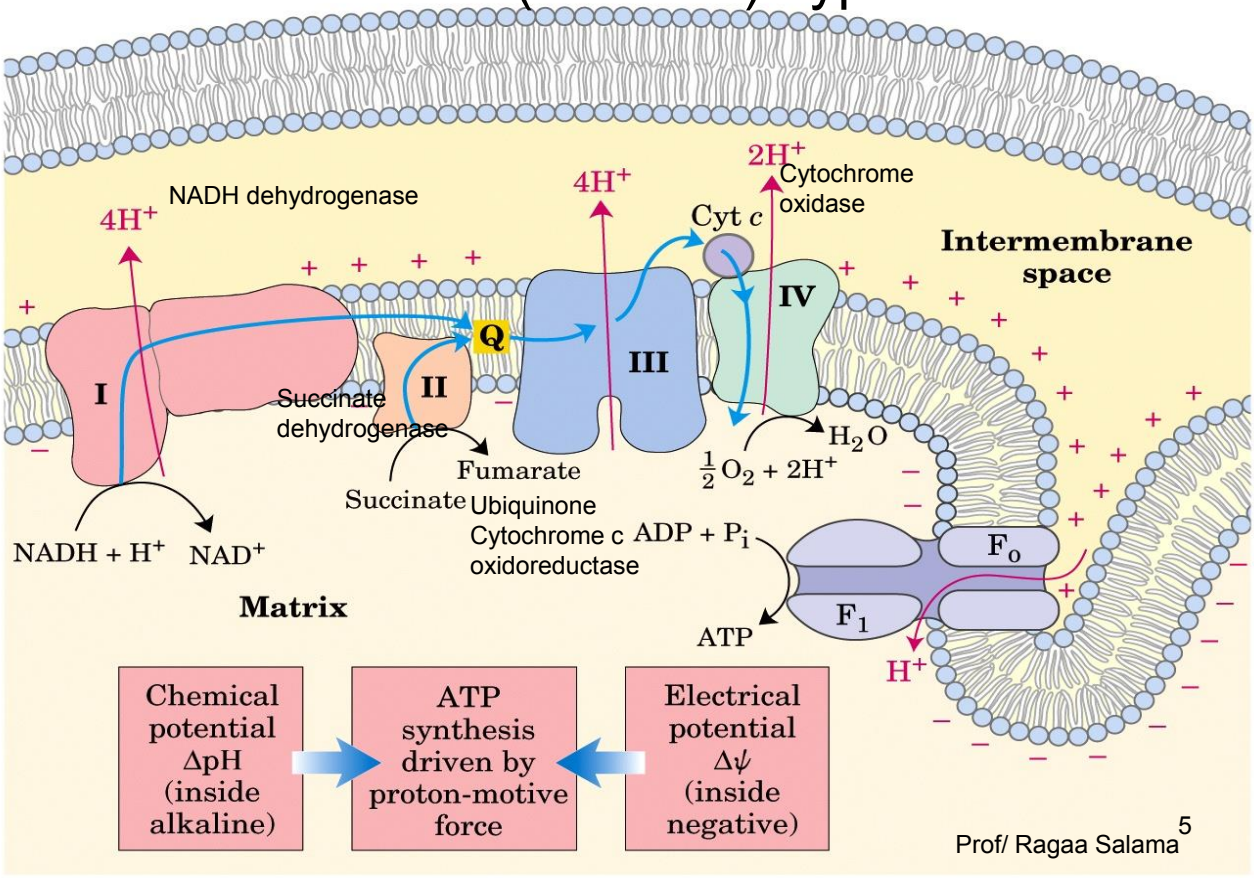
- The electrons are passed along a series(groups) of protein and lipid carriers that serve as the wire. NADH is oxidized to NAD by NADH dehydrogenase (complex I), delivering its electrons into the chain and returning NAD to enzymes that require it.

These include, in order:

- NADH dehydrogenase (complex I) accepts electrons from NADH
- Coenzyme Q (a lipid)
- Cytochrome b/c 1 (an Fe/heme protein; complex III)
- Cytochrome c (an Fe/heme protein)
- Cytochrome a/a3 (a Cu/heme protein; cytochrome oxidase, complex IV) transfers electrons to oxygen
- All these components are in the inner membrane of the mitochondria.
- Succinate dehydrogenase and the α-glycerol phosphate shuttle enzymes reoxidize their FADH2 to FAD and pass electrons directly to CoQ

(complex II)

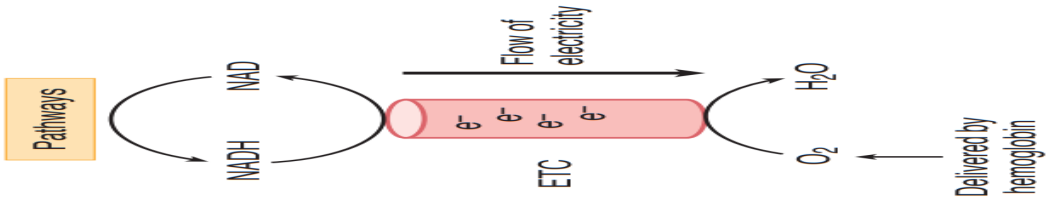
Chemiosmotic (Mitchell) hypothesis

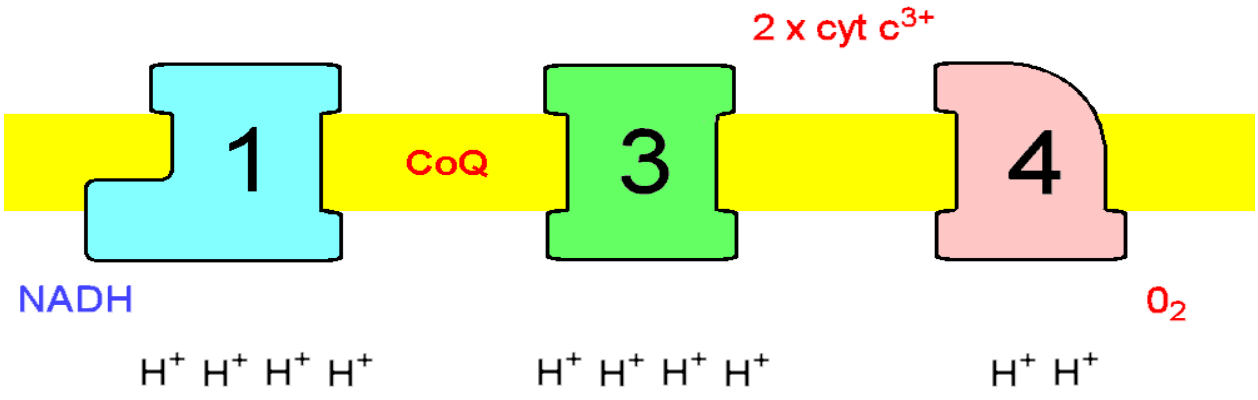


Proton Gradient

- The electricity generated by the ETC is used to run proton pumps (translocators),
- which drive protons from the matrix space across the inner membrane into the intermembrane space, creating a small proton (or pH) gradient.
- The 3 major complexes I, III, and IV
- NADH dehydrogenase, cytochrome b/c 1 , and cytochrome a/a3 all translocate protons in this way as the electricity passes through them.
- The end result is that a proton gradient is normally maintained across the mitochondrial inner membrane.
- If proton channels open, the protons run back into the matrix. Such proton channels are part of the oxidative phosphorylation complex (complex V).

Electron Transport Chain (ETC) or (RC)

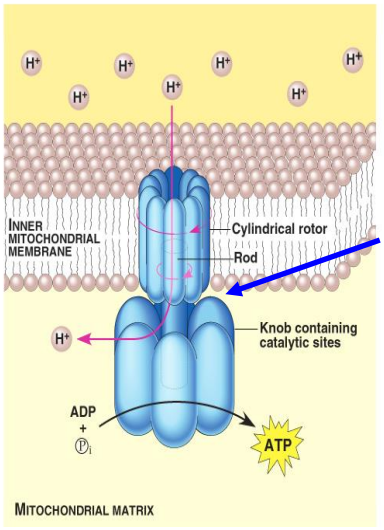




Oxidative Phosphorylation

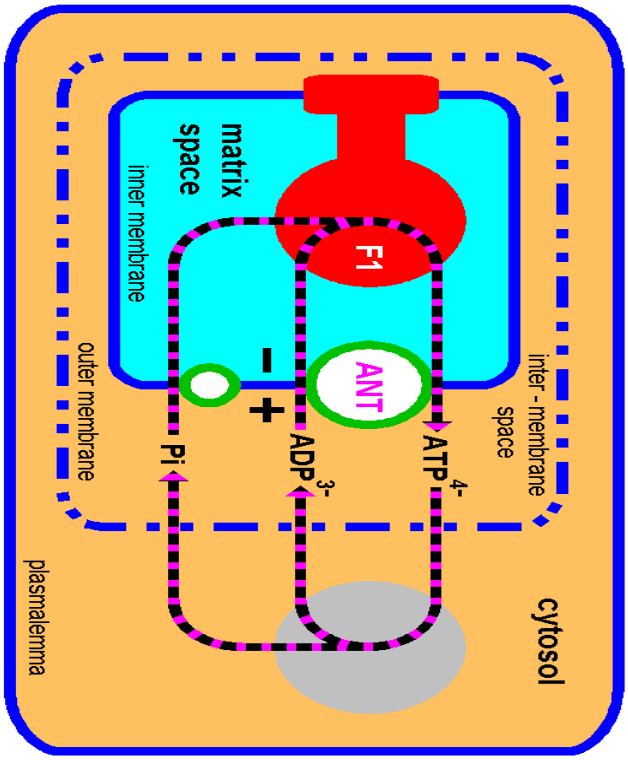
- ATP synthesis by oxidative phosphorylation
- uses the energy of the proton gradient and is carried out by the F0 F1 ATP synthase complex,
- spans the inner membrane.
- As protons flow into the mitochondria through the F0 component, their energy is used by the F1 component (ATP synthase) to phosphorylate ADP using Pi .
- A **proton gradient** is established. The energy of the proton gradient is known as the chemiosmotic potential = proton motive force PMF.
- Chemical potential and electrical potential are the 2 factors responsible for ATP synthesis

Complex V (ATP synthase)



inner mitochondrial membrane

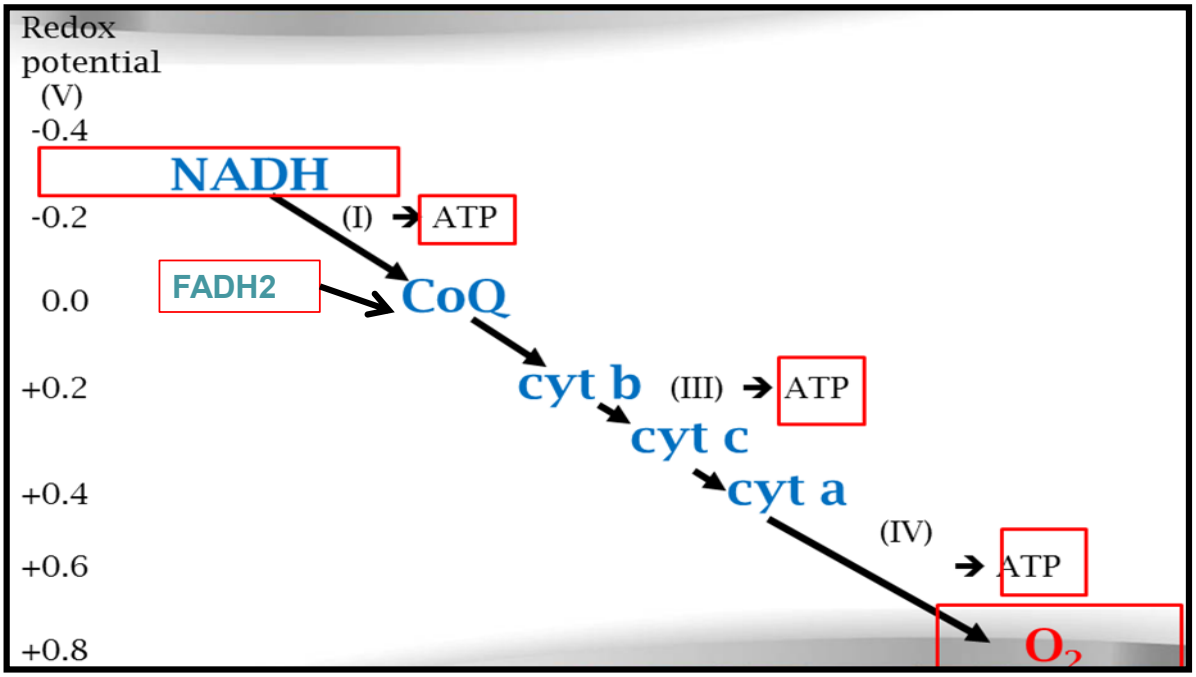
ATP synthase

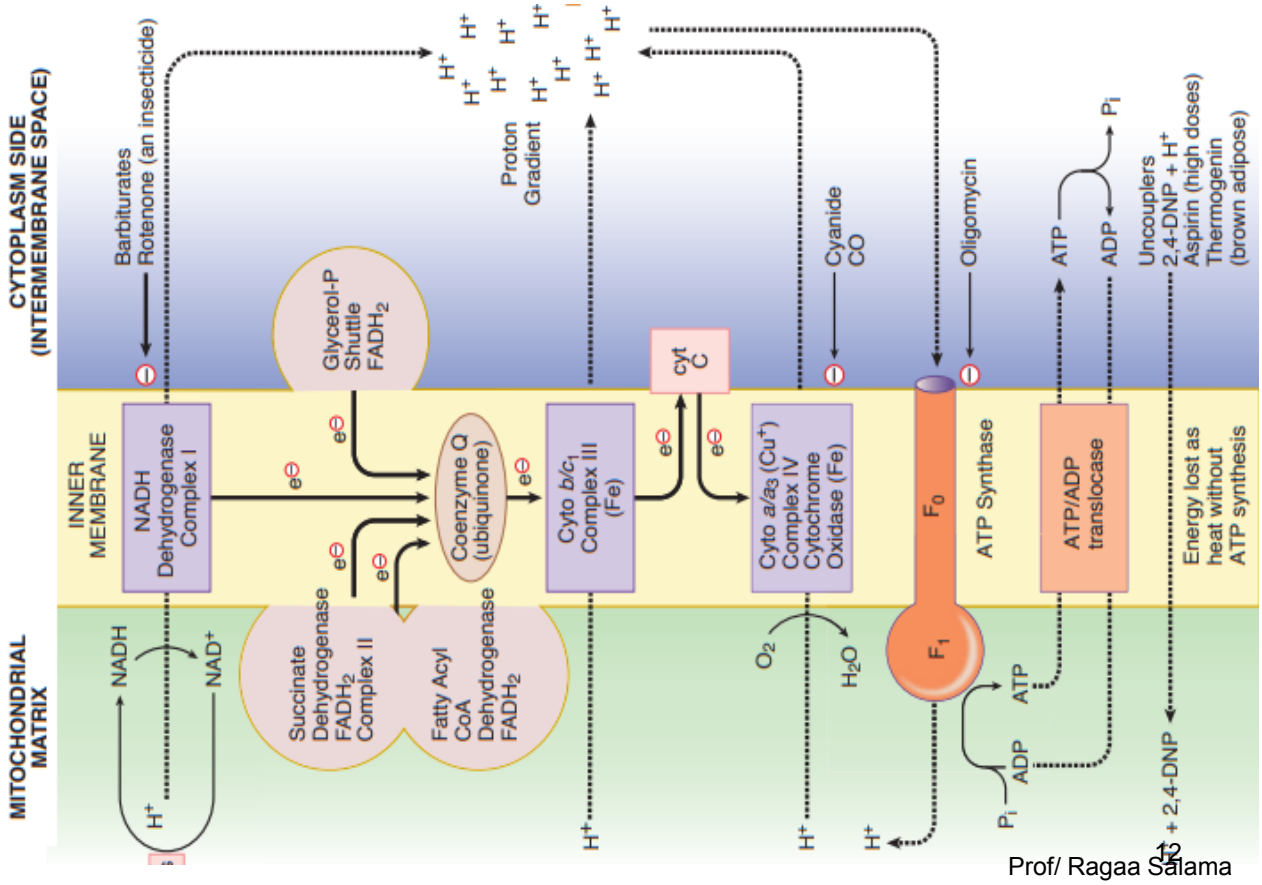


P/O ratios

- when an NADH is oxidized in the ETC, sufficient energy is contributed to the proton gradient for the phosphorylation of 3 ATP by F0 F1 ATP synthase.
- FADH2 oxidation provides enough energy for approximately 2 ATP.

ATP production (Oxidative phosphorylation) in ETC





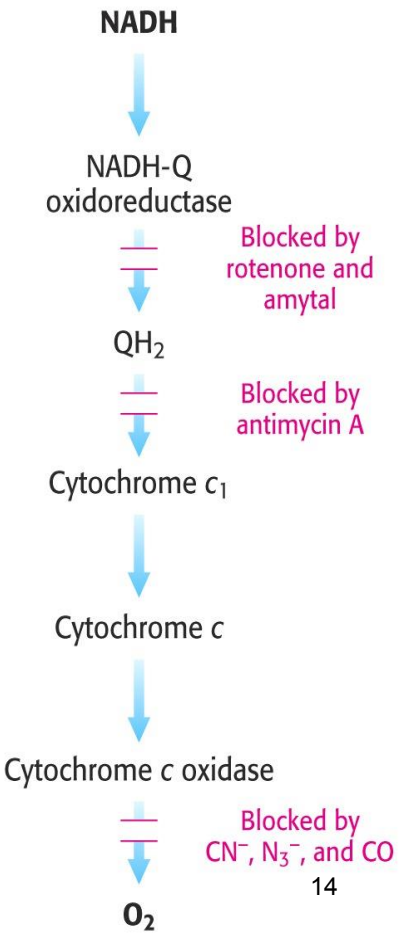
Component of ETC (5 complexes)

Complex	Name	Coenzyme	Cofactor	Proton pump	Reaction	Inhibitors
Complex I	**NADH-CoQ reductase**	FMN	iron-sulfur proteins	Yes ($4H^+$)	Reversible	barbiturates rotenone
Complex II	**succinate-CoQ reductase**	FAD	iron-sulfur	NO	Reversible	Malonate doxorubicin (CoQ)
Complex III	**CoQ - cytochrome c reductase**	Cyto b, c1,c	iron-sulfur	($4H^+$)	Reversible	antimycin A
Complex IV	**cytochrome oxidase**	Cyto aa3	**iron-cupper**	($2H^+$)	irreversible	cyanides, azide, carbon monoxide , hydrogen sulfide
Complex V	**ATP synthase**	ADP	Pi	NO	irreversible	Oligomycin (Fo)

Specific inhibitors of electron transport chain and ATP-synthase

Definition : compounds block hydrogen or electron transfer along the chain → no ATP→ no phosphorylation.

Complex I : prevent utilization of NADH as a substrate. barbiturates (sedatives and hypnotics), rotenone (a fish poison and insecticide), → block electron transfer in **Complex I.**
Complex II: inhibit succinate dehydrogenase, e.g., malonate, doxorubicin (CoQ)
Complex III: e.g., dimercaprol (used as anti-arsenic) and antimycin A (an antibiotic). They → H_2O_2.
Complex IV: e.g., cyanides, azide, carbon monoxide , hydrogen sulfide.
Complex V:. .oligomycin , prevent the influx of protons through ATP synthase. prevent ATP synthesis from ADP + Pi, by inhibition of ***ATP synthase***



Uncouplers

- Definition: They inhibit oxidative phosphorylation by disconnecting phosphorylation (ADP + Pi ⇒ ATP) from oxidation in the ETC
- Uncouplers are lipid-soluble aromatic weak acids
- Uncouplers deplete proton gradient by transporting protons across the membrane
- Result:→no ATP production although oxidation steps in ETC are running.
- Mechanism: by dissipating the proton gradient

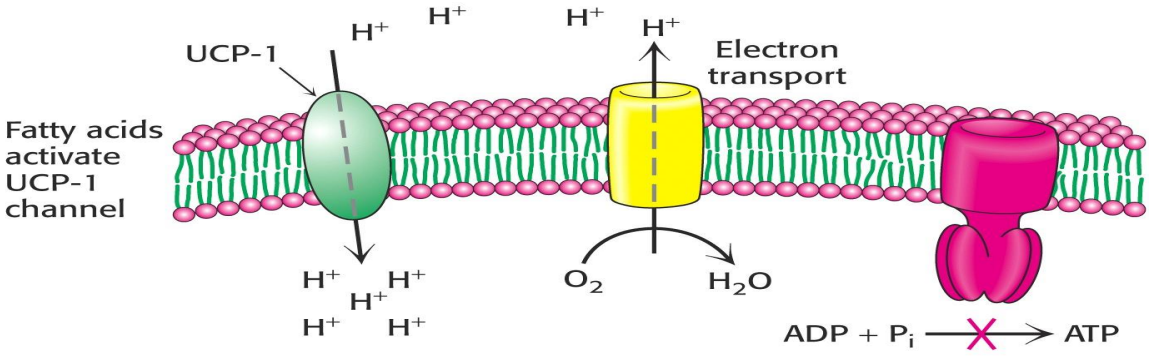
(H^+) & electrochemical gradient without activation of complex V.

Uncoupling of Electron Transport with ATP Synthesis

Uncoupling of oxidative phosphorylation generates heat to maintain body temperature in the **Brown adipose tissues of newborn** animals including **human** is specialized for thermogenesis.

Inner mitochondrial membrane contains ***uncoupling protein (UCP),*** or ***thermogenin***.

UCP forms a pathway for the flow of protons from the cytosol to the matrix.



Clinical importance of uncouplers

1- uncoupling protein UPC1(**Thermogenins)** in the inner mitochondrial membrane of **the brown adipose tissue** in newborn animals & human

Thermogenins are activated by free fatty acids by lipolytic hormones.

Thermogenins dissipate the H^+ gradient into free heat to warm newborns allows energy loss as heat to maintain a basal temperature around the kidneys, neck, breast plate, and scapulae in newborns.

2-Calcium Injection: dissipates H^+ gradient used for transport of Ca^{2+} into mitochondria and liberating free heat and leads to the sensation of increased body temperature.

3-Thyroxine: High concentration of thyroxine dissipates H^+ gradient and increasing oxygen consumption.

4-Progesterone: The release of progesterone at the mid-menstrual cycle during ovulation interferes with the oxidative phosphorylation. This increases the female's body temperature by about 0.5 ^oC that is used as an indicator for time of ovulation.

5-Chlorpromazine: It is an antiemetic drug used to prevent vomiting.

6- 2,4 Dinitrophenol (DNP), aspirin (and other salicylates) **:** They work as H^+ channel in mitochondrial membrane dissipating the electrochemical gradient as free heat and no ATP is produced.

7-Arsenic : used instead of Pi generating no ATP in glycolysis. Arsenic is a cumulative toxin, i.e., when it is taken in diet in small amounts it accumulates in the body until it reaches its lethal level leading to death.

Clinical importance of uncouplers

- Aspirin in high doses used to treat rheumatoid arthritis
- can result in uncoupling of oxidative phosphorylation,
- increased oxygen consumption, depletion of hepatic glycogen, and the pyretic effect of toxic doses of salicylate.
- Depending on the degree of salicylate intoxication, symptoms can vary from tinnitus to pronounced CNS and acid-base disturbance

	Inhibitors	Uncouplers
Definition	compounds block hydrogen or electron transfer along the chain → no ATP→ no phosphorylation.	They inhibit oxidative phosphorylation by disconnecting phosphorylation from oxidation in the ETC No ATP
Effect	inhibit the whole coupled process,	decrease the proton gradient,
ATP	Decreased ATP	Decreased ATP synthesis
O2	Decreased oxygen consumption	Increased oxygen consumption
NADH	Increased intracellular NADH/NAD and FADH2 /FAD ratios	Increased oxidation of NADH
examples	cyanides,, carbon monoxide	**uncoupling protein ,** Aspirin in high doses

Tissue Hypoxia

Hypoxia deprives the ETC of sufficient oxygen

decreasing the rate of ETC and ATP production.

- When ATP levels fall, glycolysis increases
- In the absence of oxygen, will produce lactate (lactic acidosis).
- Anaerobic glycolysis is not able to meet the demand of most tissues for ATP, especially in highly aerobic tissues like nerves and cardiac muscle.
- In a myocardial infarction (MI), myocytes swell ,membrane potential collapses and the cell gets leaky. Enzymes are released from the damaged tissue, and lactic acidosis contributes to protein precipitation and coagulation necrosis.
- Lactate dehydrogenase (LDH) isozyme analysis may be helpful if a patient reports chest pain that occurred several days previously because this change (LDH1 > LDH2) peaks 2–3 days following an AMI.

Clinical importance of inhibitors

- **Cyanide** is a deadly poison because it binds irreversibly to cytochrome a/a3 , preventing electron transfer to oxygen, and producing many of the same changes seen in tissue hypoxia.
- Sources of cyanide include:
- Burning polyurethane (foam stuffing in furniture and mattresses)
- Byproduct of nitroprusside (released slowly; thiosulfate can be used to destroy the cyanide) Nitrites may be used as an antidote for cyanide poisoning if given rapidly. "ey convert hemoglobin to methemoglobin, which binds cyanide in the blood before reaching the tissues. Oxygen is also given, if possible.
- **Carbon monoxide** binds to cytochrome a/a3 but less tightly than cyanide. It also binds to hemoglobin, displacing oxygen.
- Symptoms include headache, nausea, tachycardia, and tachypnea. Lips and cheeks turn a cherry-red color.
- Respiratory depression and coma result in death if not treated by giving oxygen. Sources of carbon monoxide include:
- Propane heaters and gas grills • Vehicle exhaust
- Tobacco smoke • House fires • Methylene chloride–based paint stripper

Coordinate Regulation of the Citric Acid Cycle and Oxidative Phosphorylation

"The rates of oxidative phosphorylation and the citric acid cycle are closely coordinated, and are dependent mainly on the availability of O2 and ADP.

If O2 is limited, the rate of oxidative phosphorylation decreases, and the concentrations of NADH and FADH2 increase.

The accumulation of NADH, in turn, inhibits the citric acid cycle.

The coordinated regulation of these pathways is known as "respiratory control."

• If O2 is adequate, the rate of oxidative phosphorylation depends on the availability of ADP. The concentrations of ADP and ATP are reciprocally related; an accumulation of ADP is accompanied by a decrease in ATP and the amount of energy available to the cell.

– Therefore, ADP accumulation signals the need for ATP synthesis. – ADP allosterically activates isocitrate dehydrogenase, thereby increasing the rate of the citric acid cycle and the production of NADH and FADH2. Elevated levels of these reduced coenzymes, in turn, increase the rate of electron transport and ATP synthesis.