ETC

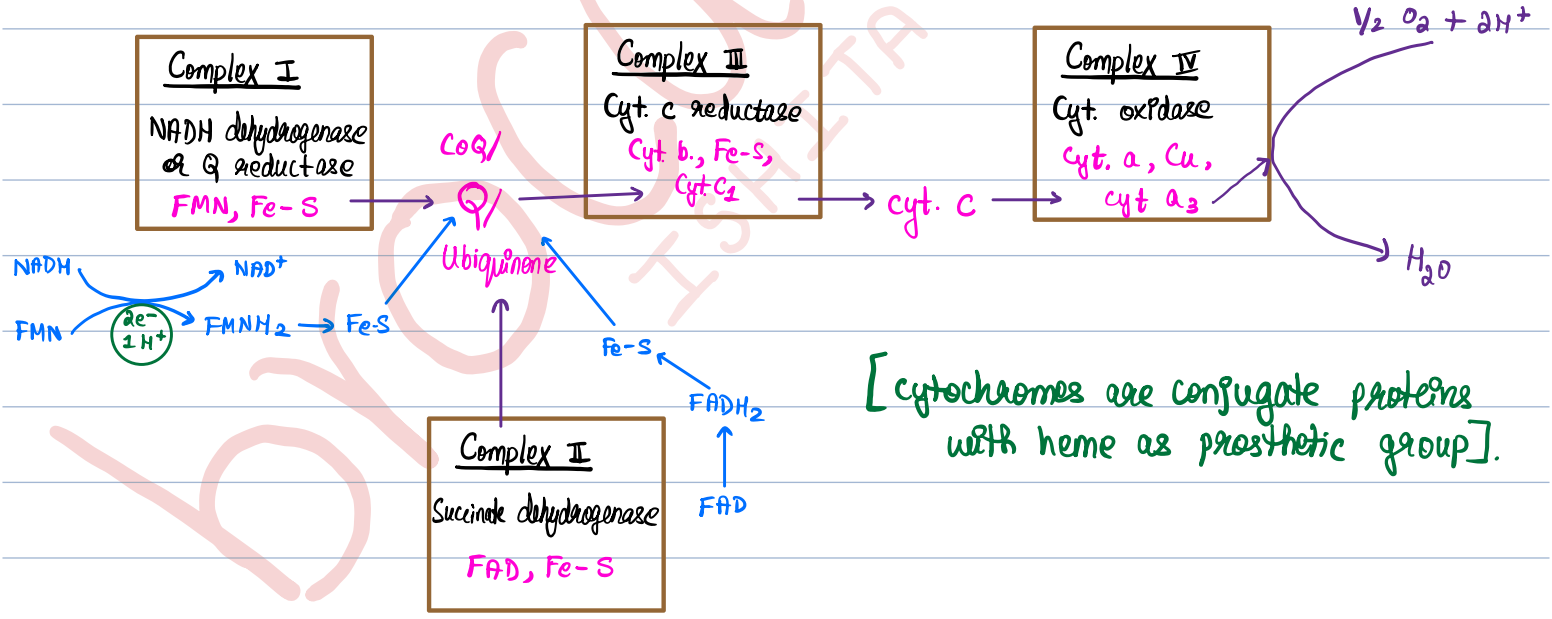
ETC: (Mitochondrial Respiration)

- energy exists as reducing equivalents in fuel molecules
- During oxidation, reducing equivalents are transferred to specialized coenzymes (NAD^+, FAD)
- Electrons from these reduced coenzymes ($NADH$, $FADH_2$) are transferred throug a set of electron carriers (ETC) present in inner mitochondrial membrane
- Molecular oxygen is the final e^- acceptor & is converted to H_2O
- As electrons pass down ETC, they lose most of their free energy
- Part of this free energy is utilized to produce ATP (from ADP & Pi) by ATP synthase complex; rest of the free energy is used to generate heat to maintain body temp.

∴ phosphorylation (of ADP to ATP) is coupled with energy released by oxidation ⇒ Oxidative phosphorylation.

[Lower E° (standard redox potential) indicates lower e^- affinity
∴ electrons are transferred from lower E° to higher E°] [$\Delta G^\circ = -nF\Delta E^\circ$]

ETC → 4 complexes, 2 mobile carriers } arranged in increasing order of redox potential (E°).



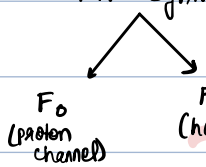
[cytochromes are conjugate proteins with heme as prosthetic group].

Inhibitors of ETC / Respiratory Poisons:

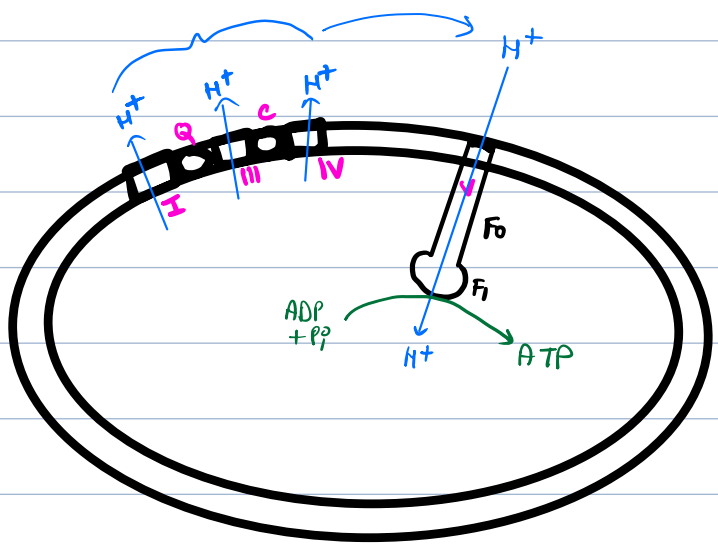
Complex	Inhibitors
complex I	• Barbiturates • Rotenone • Piericidin A
complex II	• Malonate
complex III	• Antimycin A (antibiotic) • BAL (British anti Lewisite – used as an antidote against war-gas) • Dimercaprol
Complex IV	• Cyanide • CO • H_2S, azides

Chemiosmotic / Peter-Mitchell Hypothesis:

- free energy that is released when electrons flow through ETC causes pumping of protons from mitochondrial matrix to intermembrane space
- complex I, III, IV act as proton pumps
- protons cannot diffuse back into mitochondrial matrix as inner mitochondrial membrane is impermeable to protons.
  ∴ accumulation of protons in intermembrane space generates a proton gradient ⇒ proton motive force
- these accumulate protons can flow back into matrix only through ATP-synthase complex (in inner mitochondrial membrane)
  ∴ ATP-synthase = Complex V



Protein	Inhibitor
ATP synthetase	oligomycin
ATP-ADP translocase	Atractyloside



Uncouplers: separate oxidation & phosphorylation

↳ act as proton channels & cause leakage of protons back into mitochondrial matrix ∴ prevent proton gradient

∴ oxidation - present ; phosphorylation - absent

Ionophores: lipophilic substances that promote transfer of ions across biological membranes.

→ All uncouplers are ionophores

Ex: 2,4-dinitrophenol (2,4-DNP) ; Dicumarol ; Gramicidin A ; thyroxine ; valinomycin ; 2,4-Dinitrocresol

Thermogenin: protein present in mitochondria of brown adipose tissue in newborns & hibernating animals.

↳ adipose tissue is brown due to presence of high content of mitochondria.

→ Thermogenin (uncoupler) allows ETC to proceed but not phosphorylation

∴ energy produced in ETC is released as heat to keep the body warm & play a protective role against obesity.

Current Energetics Concept:

NADH gives 2.5 ATP

$FADH_2$ gives 1.5 ATP

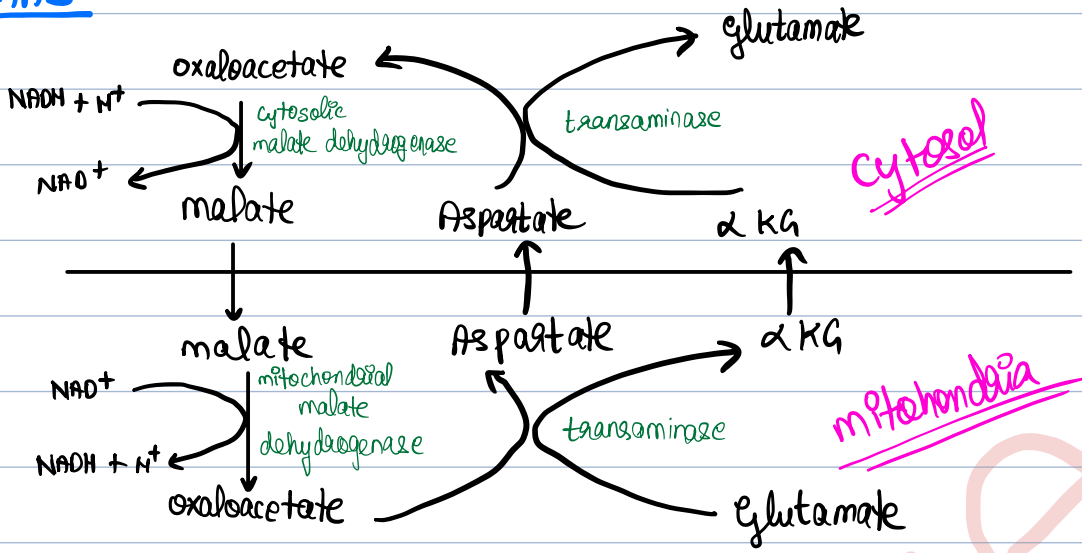
Transport of Reducing Equivalents from Cytosol to Mitochondria:

- NADH is produced in cytosol from glycolysis (glyceraldehyde-3-P dehydrogenase step) which has to be transported to mitochondria (but inner mitochondrial membrane is impermeable to NADH)

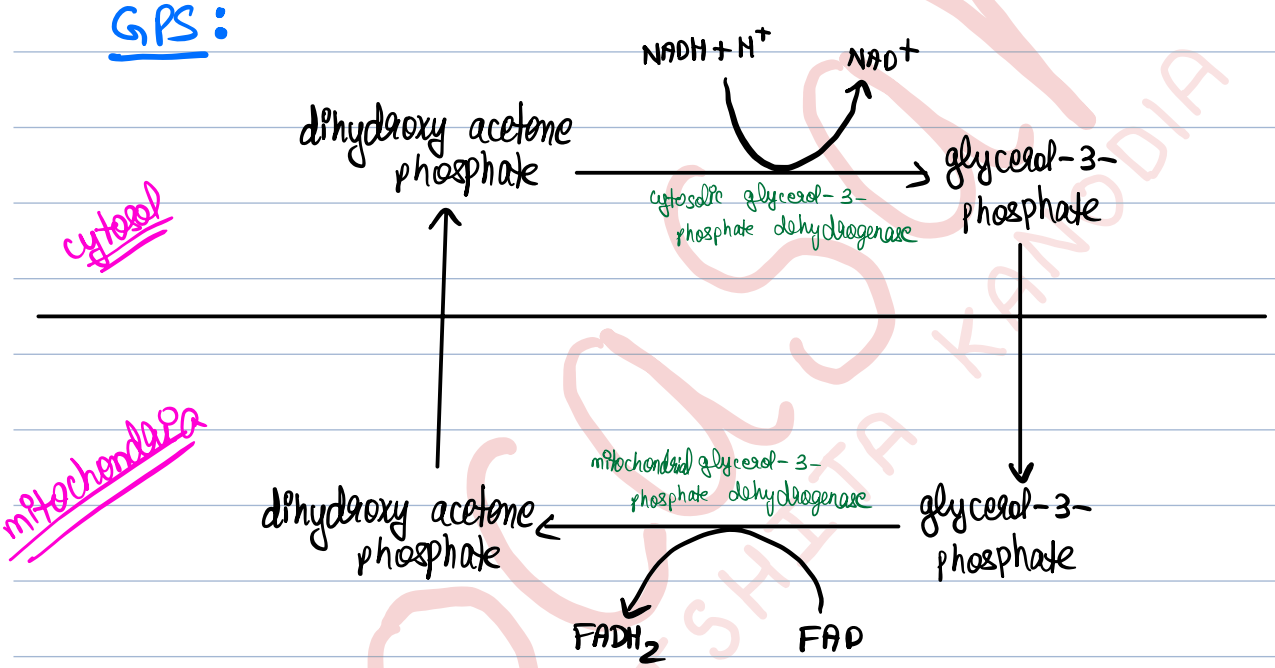
∴ 2 shuttle systems → Malate-aspartate shuttle (MAS)

→ Glycerol-phosphate shuttle (GPS)

MAS:



GPS:



ATP-ADP Transporter:

- ATP is produced in mitochondria; cytosolic reactions require ATP

∴ ATP needs to be transported from mitochondria to cytosol; but mitochondrial membrane is impermeable to ATP

→ ATP-ADP transporter (in inner mitochondrial membrane) transports ATP & ADP in opposite direction (ATP into cytosol; ADP into mitochondrial matrix)

High Energy Compounds: compounds which possess >7 kcal/mol of free energy (ΔG°)

Ex: → ATP, GTP, UTP, etc.

→ Acetyl coA, succinyl coA

→ S-Adenosyl Methionine (SAM)

→ 1,3- bisphosphoglycerate

→ cyclic AMP

→ Phosphoenol pyruvate, carbamoyl phosphate

Creatine Phosphate: storage form of high energy phosphate in muscle & brain

→ can rapidly provide high energy phosphate to regenerate ATP in contracting muscle by Lohmanns Reaction.