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BIOCHEMISTRY

UNIT 2

TOPIC :

- **Biological oxidation**

  Electron transport chain (ETC) and its mechanism.

  level Oxidative phosphorylation & its mechanism and substrate phosphorylation Inhibitors ETC and oxidative phosphorylation/Uncouplers

Biological Oxidation

→ Biological oxidation is the process by which cells release energy from nutrients (mainly carbohydrates, fats, and proteins) via redox reactions.
→ It involves oxidation of substrates to produce ATP, the energy currency of cells.
→ The final stage of this process is the Electron Transport Chain (ETC) in the mitochondria.
→ Oxidation = loss of electrons or hydrogen
→ Reduction = gain of electrons or hydrogen
→ Redox reactions drive the flow of electrons, releasing energy
→ Coenzymes like NAD^+ and FAD act as electron carriers

- $NAD^+ \rightarrow NADH$
- $FAD \rightarrow FADH_2$

Electron Transport Chain (ETC)

➢ The Electron Transport Chain (ETC) is the final step of aerobic respiration.
➢ It is also known as the Electron Transport System (ETS).
➢ Occurs in the inner mitochondrial membrane of eukaryotic cells.
➢ It is a series of protein complexes and mobile electron carriers.
➢ Electrons are transferred from molecules with low redox potential to those with high redox potential.
➢ This transfer of electrons releases energy, which is used to pump protons (H^+) across the membrane.
➢ The energy stored in the resulting proton gradient is used to generate ATP by a process called oxidative phosphorylation.

Main Complexes of ETC

Complex I – NADH: Ubiquinone Oxidoreductase

- Accepts electrons from **NADH**
- Transfers electrons to **Coenzyme Q (Ubiquinone)**
- **Pumps 4 H^+ ions** from the mitochondrial matrix to the intermembrane space
- Also called **NADH dehydrogenase**

Complex II – Succinate Dehydrogenase

- Accepts electrons from **$FADH_2$** (produced in the TCA cycle)
- Transfers electrons to **Coenzyme Q**
- **Does NOT pump protons**
- Also part of the **TCA cycle**

Complex III – Cytochrome bc_1 Complex

- Accepts electrons from **Coenzyme Q**
- Transfers electrons to **Cytochrome c**
- **Pumps 4 H^+ ions** into the intermembrane space

Complex IV – Cytochrome c Oxidase

- Accepts electrons from **Cytochrome c**
- Transfers electrons to **molecular oxygen (O_2) → Forms water (H_2O)**
- **Pumps 2 H^+ ions**
- Final complex in the chain

Mechanism of ETC

- ❖ NADH donates electrons to Complex I → electrons move to Coenzyme Q, 4 H^+ are pumped into intermembrane space.
- ❖ $FADH_2$ donates electrons to Complex II → passes them to Coenzyme Q (no H^+ pumping here).
- ❖ Coenzyme Q transfers electrons to Complex III → 4 H^+ are pumped into intermembrane space.
- ❖ Electrons are carried by Cytochrome c to Complex IV → 2 H^+ are pumped, and O_2 is reduced to water.
- ❖ Accumulated H^+ ions in intermembrane space generate proton motive force (PMF).

Significance of ETC and Biological Oxidation

- Major source of **ATP** production in aerobic organisms
- Essential for:
  - Muscle contraction
  - Nerve impulse conduction
  - Biosynthesis of macromolecules
- ETC is **aerobic** – requires **oxygen** as final electron acceptor
- Generates **heat** (thermogenesis) in brown fat (non-shivering)

Oxidative Phosphorylation

→ Oxidative phosphorylation is the process of ATP synthesis that occurs at the end of the Electron Transport Chain (ETC).
→ It uses the energy from electrons transferred through the ETC to pump protons (H^+) across the inner mitochondrial membrane.
→ The resulting proton gradient powers ATP synthase to form ATP from ADP + Pi.
→ It is called "oxidative" because it requires oxygen as the final electron acceptor.

Mechanism of Oxidative Phosphorylation

The process involves two major components:

A. Electron Transport Chain (ETC)

- NADH and $FADH_2$ donate electrons to the ETC.
- As electrons move through Complexes I, III, and IV:
  - **Protons (H^+)** are pumped from the mitochondrial matrix into the **intermembrane space**.
  - Creates a **proton gradient (proton motive force)**.

B. Chemiosmosis and ATP Synthesis

- The protons flow back into the matrix through **ATP synthase (Complex V).**
- This flow drives the formation of ATP:

$$ADP + Pi \xrightarrow{\text{ATP synthase}} ATP$$

C. Final Step

- At **Complex IV**, **electrons combine with O_2** and protons to form **H_2O**.

- **Oxygen is the final electron acceptor**.

Significance of Oxidative Phosphorylation

- Produces most of the ATP in aerobic respiration (≈ 26–28 ATP per glucose).
- Essential for energy-demanding processes: muscle contraction, nerve transmission, biosynthesis.
- Maintains cellular energy balance and life-sustaining functions.

Substrate-Level Phosphorylation (SLP)

Substrate-Level Phosphorylation (SLP) is the **direct synthesis of ATP (or GTP)** by the **transfer of a phosphate group** from a **high-energy phosphorylated intermediate** to **ADP (or GDP)**.

- Unlike oxidative phosphorylation, **SLP does not require oxygen** or an electron transport chain.
- The phosphate group is donated **directly by the substrate molecule** via enzyme-catalyzed reactions.

Examples of SLP Reactions

1. Glycolysis

Step: 1,3-Bisphosphoglycerate → 3-Phosphoglycerate

- **Enzyme**: Phosphoglycerate kinase
- **ATP Produced**: 1 per reaction
- **Reaction**:

$$1,3-BPG+ADP \rightarrow 3-PG+ATP$$

Step: Phosphoenolpyruvate (PEP) → Pyruvate

- **Enzyme**: Pyruvate kinase
- **ATP Produced**: 1 per reaction
- **Reaction:**

$$PEP+ADP \rightarrow Pyruvate+ATP$$

Significance of SLP

- Ensures ATP production during anaerobic conditions (e.g., intense exercise or low oxygen supply).
- Vital for red blood cells (which lack mitochondria and rely only on glycolysis).
- Important for quick energy bursts in muscle cells.
- Plays a key role in early evolution when oxidative phosphorylation was not yet developed.

Inhibitors of Electron Transport Chain (ETC)

➢ These inhibitors block the transfer of electrons at specific points in the ETC, thereby halting ATP synthesis and oxygen consumption.

1. Complex I Inhibitors (NADH → Coenzyme Q)

- **Rotenone** (a plant-derived insecticide)
- **Amytal** (a barbiturate drug)

Mechanism:

- Inhibit **NADH dehydrogenase**
- Prevent the transfer of electrons from NADH to Coenzyme Q (ubiquinone)
- **$FADH_2$ can still donate electrons via Complex II**

Effect:

- ATP production from NADH is blocked
- ETC partially functions using $FADH_2$

2. Complex II Inhibitors

- **Malonate** (competitive inhibitor of succinate dehydrogenase)

Mechanism:

- Inhibits **succinate dehydrogenase**, blocking electron entry from $FADH_2$
- **Less severe effect**, since NADH can still enter via Complex I

3. Complex III Inhibitor (CoQ → Cytochrome c)

- **Antimycin A** (an antibiotic)

Mechanism:

- Inhibits the **cytochrome bc_1 complex**
- Prevents electron flow from reduced CoQ (ubiquinol) to cytochrome c

Effect:

- Entire chain is blocked beyond Complex III
- Both NADH and $FADH_2$ electron entry is ineffective

4. Complex IV Inhibitors (Cytochrome c → O_2)

- **Cyanide (CN^-)**
- **Carbon monoxide (CO)**
- **Sodium azide (NaN_3)**

Mechanism:

- Inhibit **cytochrome c oxidase**
- Prevent the reduction of oxygen to water (final step of ETC)

Effect:

- Electron transport completely stops
- Rapid **ATP depletion**
- Highly **toxic and lethal**, especially cyanide

Uncouplers of Oxidative Phosphorylation

→ Uncouplers disrupt the link between electron transport and ATP synthesis by dissipating the proton gradient. They make the inner mitochondrial membrane permeable to protons (H^+), bypassing ATP synthase.

1. 2,4-Dinitrophenol (DNP)

- Synthetic chemical used historically for weight loss (now banned)

Mechanism:

- Acts as a **protonophore**: transports protons across the inner mitochondrial membrane
- Collapses the **proton gradient**, so **ATP synthase cannot function**

Effect:

- ETC continues to function and consumes oxygen
- **No ATP formed**
- Energy is **released as heat** → risk of **hyperthermia and death**

2. Thermogenin (UCP1 - Uncoupling Protein 1)

- Naturally found in **brown adipose tissue** of infants and hibernating animals

Mechanism:

- Forms a channel for protons to re-enter the mitochondrial matrix
- **Bypasses ATP synthase**

Effect:

- ATP not produced

- Heat is generated instead (used for **thermoregulation**)

3. Aspirin (in high doses)

- High concentrations of **salicylate** act as a mild uncoupler

  Mechanism:

  - Increases mitochondrial membrane permeability to protons

  Effect:

  - Leads to heat production and **fever**
  - Explains **fever in aspirin overdose**