# BIOCHEMISTRY- BP203T

UNIT : 1 METABOLISM OF CARBOHYDRATES

CLASS:10

## TOPIC: INHIBITORS

### INHIBITORS OF ELECTRON TRANSPORT CHAIN

Many site-specific inhibitors of ETC have contributed to the present knowledge of mitochondrial respiration. Selected examples of these inhibitors haven been given in Fig.11.7.

The inhibitors bind to one of the components of ETC and block the transport of electrons.

This causes the accumulation of reduced components before the inhibitor blockade step and oxidized components after that step.

The synthesis of ATP (phosphorylation) is dependent on electron transport. Hence, all the site-specific inhibitors of ETC also inhibit ATP formation.

Three possible sites of action for the inhibitors of ETC are identified

**1. NADH and coenzyme Q:**

Fish poison rotenone, barbituate drug amytal and antibiotic piercidin A inhibit this site.

**2. Between cytochrome b & c1:**

Antimycin A — an antibiotic, British antilewisite (BAL)— an antidote used against war-gas— are the two important inhibitors of the site between cytochrome b and c1.

**3. Inhibitors of cytochrome oxidase:**

Carbon monoxide, cyanide, hydrogen sulphide and azide effectively inhibit cytochrome oxidase. Carbon monoxide reacts with reduced form of the cytochrome while cyanide and azide react with oxidized form.

**Cyanide poisoning:**

Cyanide is probably the most potent inhibitor of ETC. It binds to Fe3+ of cytochrome oxidase blocking mitochondrial respiration leading to cell death.



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Cyanide poisoning causes death due to tissue asphyxia (mostly of central nervous system).

## INHIBITORS OF OXIDATIVE PHOSPHORYLATION

### UNCOUPLERS:

The mitochondiral transport of electrons is tightly coupled with oxidative phosporylation (ATP synthesis).

In other words, oxidation and phosphorylation proceed simultaneously.

There are certain compounds that can uncouple (or delink) the electron transport from oxidative phosphorylation.

Such compounds, known as uncouplers, increase the permeability of inner mitochondrial membrane to protons (H+).

The result is that ATP synthesis does not occur. The energy linked with the transport of electrons is dissipated as heat.

The uncouplers allow (often at accelerated rate) oxidation of substrates (via NADH or FADH2) without ATP formation.

**The uncoupler,**

- 2,4-dinitrophenol (DNP), has been extensively studied.
- It is a small lipophilic molecule.
- DNP is a proton-carrier and can easily diffuse through the inner mitochondrial membrane.
- In the people seeking to lose weight, DNP was used as a drug.
- However, this is now discontinued, as it produces hyperthermia and other side effects.
- In fact, Food and Drug Administration (USA) has banned the use of DNP.
- The other uncouplers include dinitrocresol, pentachlorophenol, trifluorocarbonylcyanide phenylhydrazone (FCCP).
- The last compound (FCCP) is said to be 100 times more effective as an uncoupler than dinitrophenol.
- When administered in high doses, the drug aspirin acts as an uncoupler.

### PHYSIOLOGICAL UNCOUPLERS:

Certain physiological substances which act as uncouplers at higher concentration have been identified. These include thermogenin, thyroxine and long chain free fatty acids.

The unconjugated bilirubin is also believed to act as an uncoupler. This is, however, yet to be proved beyond doubt.

**SIGNIFICANCE OF UNCOUPLING:**

Uncoupling of respiration from oxidative phosphorylation under natural conditions assumes biological significance.

The maintenance of body temperature is particularly important in hairless animals, hibernating animals and the animals adapted to cold.

These animals possess a specialized tissue called brown adipose tissue in the upper back and neck portions.

The mitochondria of brown adipose tissue are rich in electron carriers and are specialized to carry out an oxidation uncoupled from phosphorylation.

This causes liberation of heat when fat is oxidized in the brown adipose tissue. Brown adipose tissue may be considered as a site of non-shivering thermogenesis.

The presence of active brown adipose tissue in certain individuals is believed to protect them from becoming obese.

The excess calories consumed by these people are burnt and liberated as heat, instead of being stored as fat.

**THERMOGENIN** (or uncoupling protein, UCPI) is a physiological uncoupler, located in the inner mitochondrial membrane of brown adipose tissue.

It blocks the formation of ATP, and generates heat. This assumes significant in the newborn, and during hibernation in animals.

**IONOPHORES:**

The term ‘ionophores’ is used to collectively represent the lipophilic substances that promote the transport of ions across biological membranes.

All the uncouplers (described above) are, in fact, proton ionophores.

The antibiotics valinomycin, gramicidin A act as ionophores for K+ ions.

Both these compounds are also capable of dissipating proton gradient across the inner mitochondrial membrane and inhibit oxidative phosphorylation

**Other inhibitors of oxidative phosphorylation :**

**Oligomycin:**

This antibiotic prevents the mitochondrial oxidation as well as phosphorylation. It binds with the enzyme ATP synthase and blocks the proton (H+) channels.

It thus prevents the translocation (re-entry) of protons into the mitochondrial matrix.

Due to this, protons get accumulated at higher concentration in the intermembrane space.

Electron transport (respiration) ultimately stops, since protons cannot be pumped out against steep proton gradients.

**Atractyloside:**

This is a plant toxin and inhibits oxidative phosphorylation by an indirect mechanism.

Adenine nucleotide carrier system facilitates the transport of ATP and ADP.

Atractyloside inhibits adenine nucleotide carrier and, thus, blocks the adequate supply of ADP, thereby preventing phosphorylation