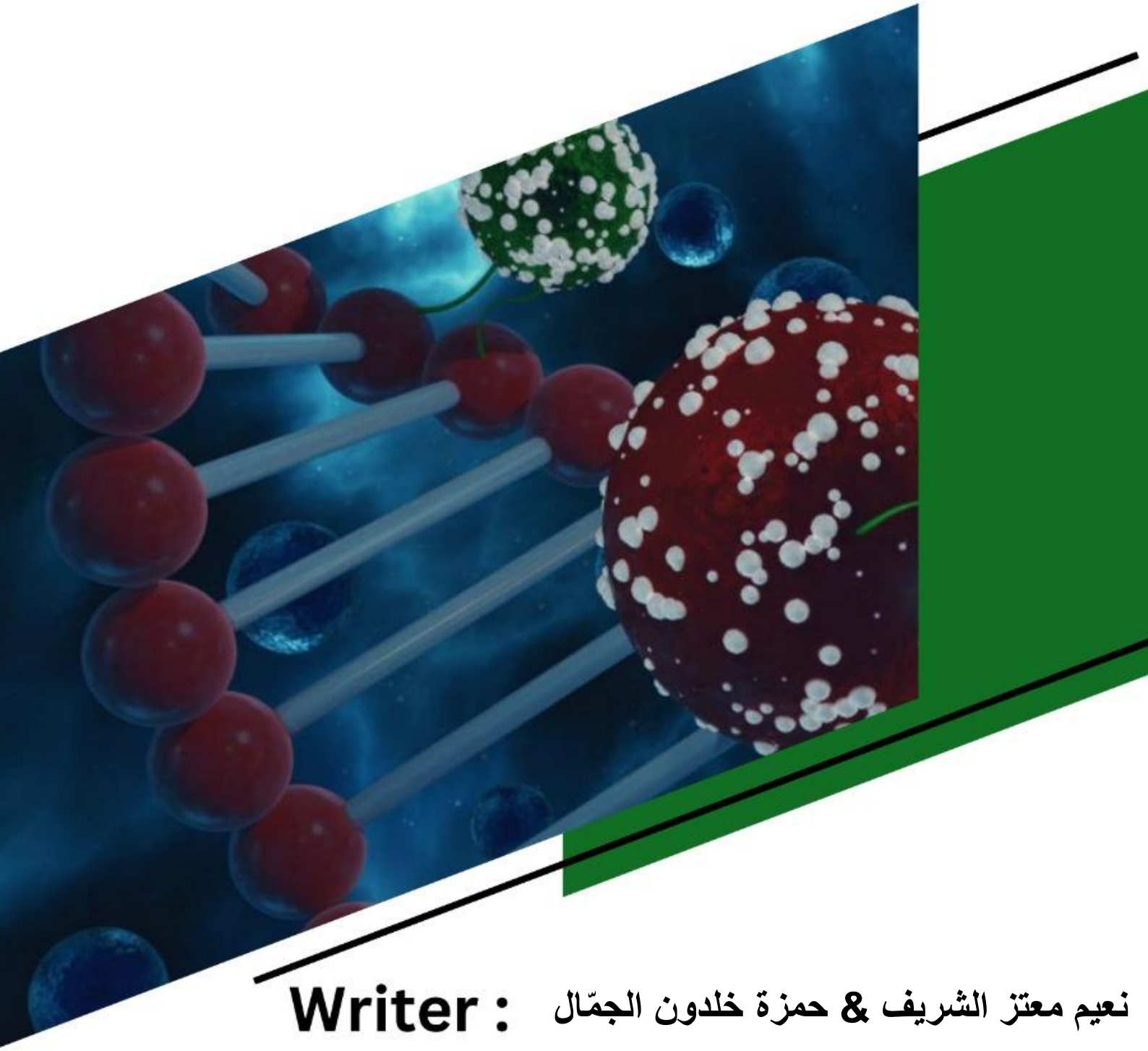
Doctor 021

METABOLISM

Sheet no. 6



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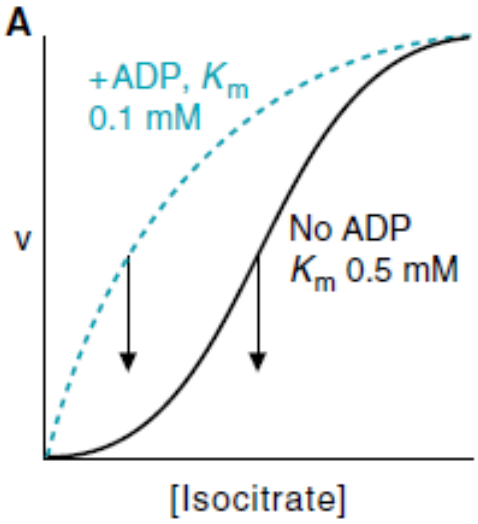
REGULATION OF THE TCA CYCLE:

ISOCITRATE DH:

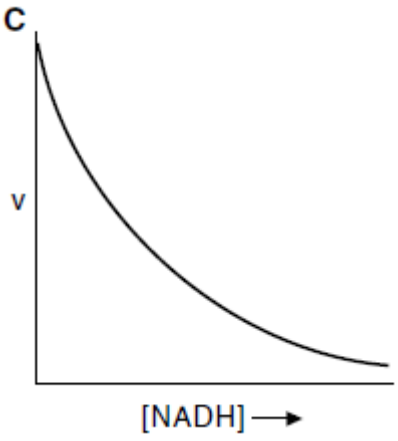
- BEST REGULATION (RATE-LIMITING)
- ALLOSTERICALLY: ACTIVATED (ADP, CA+2)
- INHIBITION (NADH)
- NO ADP VS. ADP (KM), A SMALL CHANGE IN ADP, GREAT EFFECT



As we know isocitrate dehydrogenase is an allosteric enzyme so its curve will be sigmoidal in shape but when activating it by ADP the curve will be shifted to the left making it more hyperbolic, but it will never be hyperbolic (stay sigmoidal) as in the figure.

. ALPHA - KETOGLUTARATE DH :

- Inhibited: NADH, succinyl CoA, GTP
- Activated: Ca+2



As u notice darling both enzymes are activated by Ca+2

ISN'T THIS MYSTERIOUS!!!

As we know Ca+2 activates muscle contraction, but the new information is that it works as a second messenger…here is the tale:

Neurons and hormones control the body (homeostasis and metabolism).

Hormones bind to the cell surface and affect the enzyme phospholipase C which releases Ca+2, releasing Ca+2 stimulates kinase C that drives the phosphorylation of many molecules such as (enzymes and hormones) which control metabolism and energy in the body .

Inhibitors Of TCA Cycle:

all of the regulators that we've mentioned before were physiological regulators, now we will talk about non-physiological regulators.

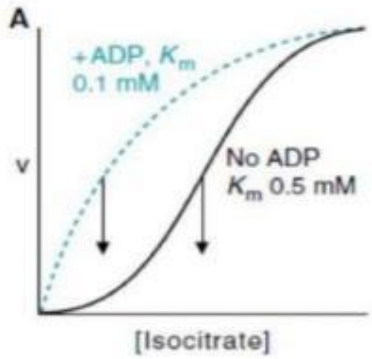
A. Aconitase (citrate to aconitate) is inhibited by fluoroacetate (noncompetitive inhibition).

B. Alpha ketoglutarate dehydrogenase (alpha keto glutarate to succinyl CoA) is inhibited by Arsenite (noncompetitive inhibition).

C. Succinate dehydrogenase (succinate to fumarate) is inhibited by malonate (competitive inhibition).

Malonate competes with Succinate on its receptors taking its place and inhibiting succinate function that's what we mean by saying competitive.

This schedule is just for recapping …..enjoy looking at it.

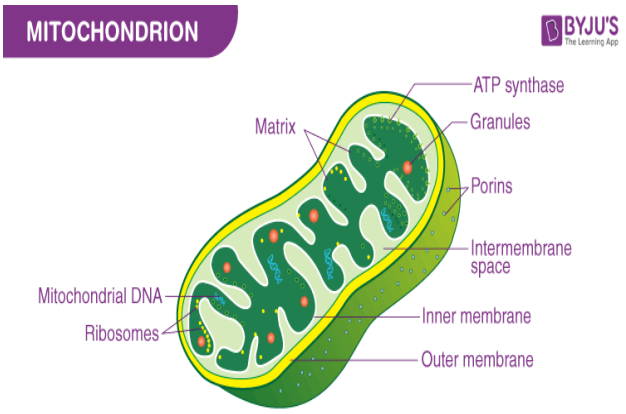
Citrate synthase	-It is the first enzyme in the cycle. It is a enzyme allosteric -Excess amounts of citrate will inhibit the activity of this enzyme.
Isocitrate dehydrogenase 	-It facilitates the rate limiting step (isocitrate → alpha ketoglutarate). This step is highly regulated. -It is inhibited by NADH and ATP. Activated by ADP and Ca ions. -It is the only enzyme in the cycle that is activated by ADP. **(ADP is an allosteric activator for isocitrate DH)** **-km** for this enzyme with the presence of ADP decreases. (affinity for substrates increases). -A small change in ADP concentration will affect the enzyme's activity greatly.
α-ketoglutarate dehydrogenase	-Inhibited by its products NADH and succinyl CoA (feedback inhibition). -Activated by Ca ions.

DEFENETION OF OXIDATIVE-PHOSPHORYLATION

Firstly, we are to talk about some general information needed for proceeding in this sheet:

Here is the structure of Mitochondria: our story takes place on the two membranes so look on their properties sweety.

Outer Mitochondrial Membrane (OMM): permeable to small molecules (MW<5000 dalton) & ions, porins (transmembrane channels).



This membrane is similar to other membranes in composition.

It contains a high percentage of cholesterol (45%) and a low content of Cardiolipin(3%).

Inner Mitochondrial Membrane (IMM): impermeable even to H+; specific transporters.

That's because of its special structure which is mainly composed of Cardiolipin and NO cholesterol 22% CARDIOLIPIN

IMM contains the enzymes of oxidative phosphorylation and electron transport chain.

IMM bears the components of the respiratory chain and the ATP synthase.

Matrix: contains pyruvate dehydrogenase complex & TCA cycle enzymes, fatty acid β-oxidation pathway, and the pathways of amino acid oxidation.

In other words: matrix contains all pathways of fuel oxidation except glycolysis (cytosol).

AND NOW LETS ROCK THE OXIDATIVE PHOSPHORYLATION

Oxidative phosphorylation is a complex process which involves two processes inside it: oxidation and phosphorylation.

They are separated from each other (each one happens alone) but they are coupled(one is causing another).

Oxidative phosphorylation (OxPhos)

- **Generation of ATP aided by the reduction of O2.**
- **Was discovered by Peter Mitchell (1961): the chemiosmotic theory.**
- **Oxidative phosphorylation has 3 major aspects:**

(1) It involves flow of electrons (reduction potential driving force) through a chain of membrane-bound carriers (prosthetic groups)

(2) The free energy available (exergonic) is coupled to transport protons across a proton-impermeable membrane (pumping the protons against their electrochemical gradient).

(3) The transmembrane flow of protons down their concentration gradient provides the free energy for synthesis of ATP (ATP synthase).

The electrons that produced by Krebs cycle will be used in the oxidative phosphorylation via the electron transport chain (ETC) to be delivered from complex to another reaching the final electron acceptor (oxygen).

These electrons are carried by NADH and FADH2 (electron carriers in Krebs cycle).

There is not any phosphorylation in ETC it is just repeated redox reactions

Side note...Reduction: The process of gaining electrons.

Oxidation: The process of losing electrons.

Electrons transfer from one complex to another in ETC due to the difference of potential energy between these complexes.

(The difference of potential energy = free energy $\Delta G = - \Delta E$).

Electrons are transferred from NADH (so NADH will be oxidized) to the first complex of ETC (so it will be reduced).

Electrons transfer from a higher energy state to a lower energy state in ETC so ETC is favorable and produces energy (this energy will be utilized in pumping protons (H+) against its concentration gradient from the mitochondrial matrix to the intermembranous space which increases the electrochemical gradient between the two sides of the inner membrane).

This electrochemical gradient combined with the impermeability of the IMM will make a pressure on the IMM(if the IMM is permeable the H+ protons will turn back into the mitochondrial matrix و هيك ما رح نستفيد اشي من سلسلة نقل الالكترونات معلم)

Side note: wherever we say pump we mean that substances are moving against their concentration gradient and need energy.

Side note: electrochemical gradient depends on both concentration of the molecule and net charge.

The only way for protons to come to the inner side of the IMM down their concentration gradient is through a carrier (in our case it is ATP Synthase) this passage of protons through ATP synthase will generate energy this energy is used to phosphorylate ADP synthesizing ATP .

Because you are genius it is a must that u have discovered the linker between oxidation and phosphorylation which is H+ gradient another name of it is proton motive force.

The H+ gradient that result is referred to as proton motive force which is the force that drives H+ back across the membrane through ATP Synthase.