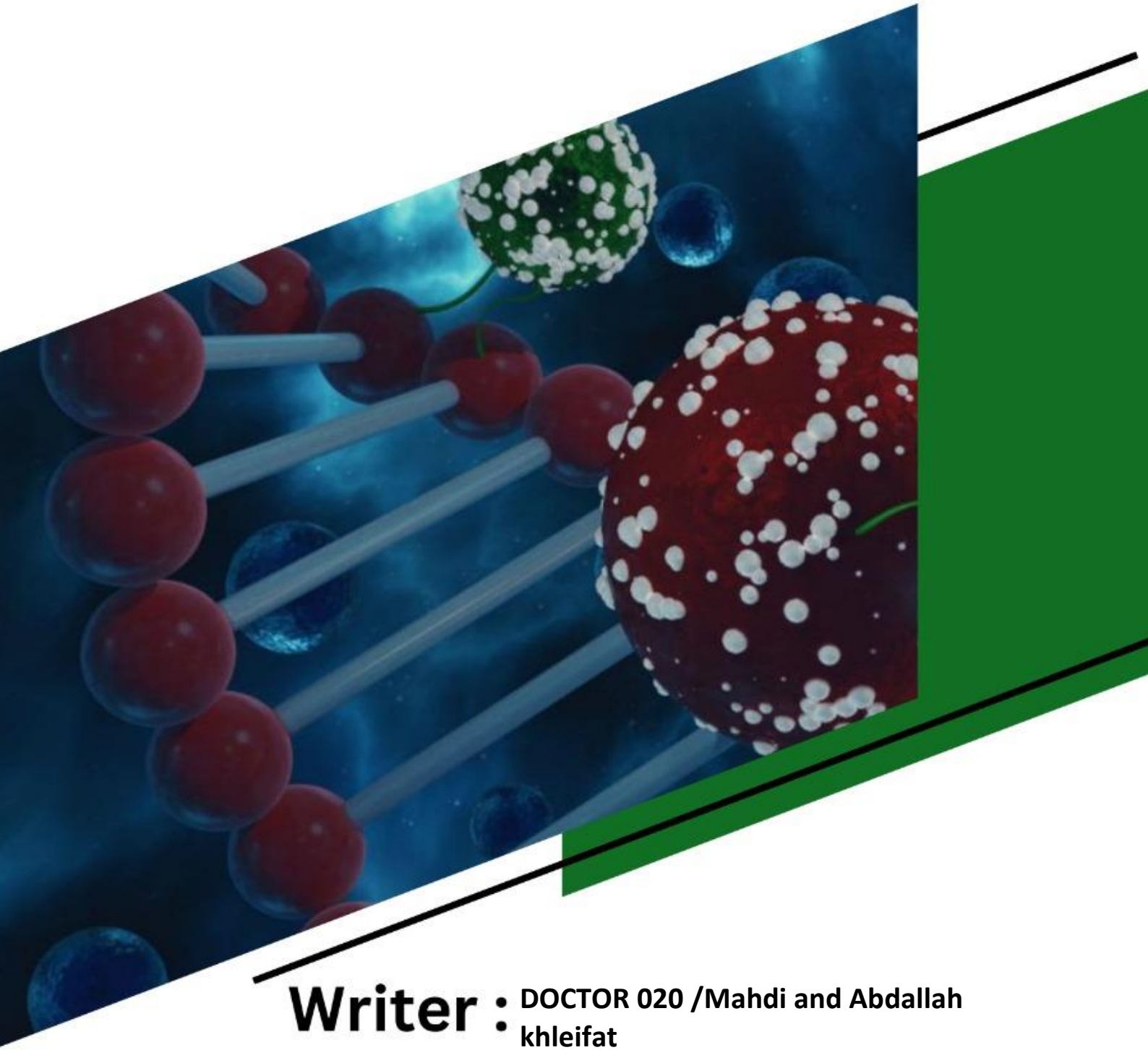
Doctor 021

METABOLISM

Sheet no. 3



Writer : DOCTOR 020 /Mahdi and Abdallah khleifat

Corrector : FIRAS AND DARAWSHEH

Doctor : nafeth

➢ **Addition to the previous sheet: -**

- similar molecules to ATP like CTP, GTP, TTP, UTP serve as energy molecules and release the same amount of energy when the 1st and 2nd phosphates are released but energy value would differ when it comes to third phosphate because atoms orientation differ between these molecules due to differences in the nitrogenous base in each molecule.

❖ metabolic pathways inside in the **mitochondria** like Krebs cycle and electron transport chain use **ATP** ONLY.

❖ other energy molecules are distributed in different pathways for organization purposes:

Example: in biosynthetic reactions like **protein** biosynthesis **GTP** is mainly used, **lipids**

biosynthesis **CTP** is used, **UTP** is used in **carbohydrates** metabolism.

IS ATP A GOOD LONG-TERM ENERGY STORAGE MOLECULE?

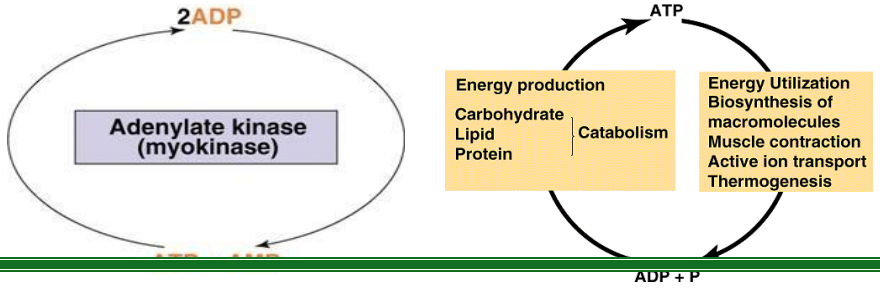
➢ **As food in the cells is gradually oxidized, the released energy is used to re-form the ATP so that the cell always maintains a supply of this essential molecule**

Tissue	ATP turnover (mole/day)
Brain	20.4
Heart	11.4
Kidney	17.4
Liver	21.6
Muscle	19.8
Total	90.6

- moles of ATP per day is used by the main tissues at resting state.
- ATP's molecular weight is 551 g/mole, considering the number of consumed ATP moles daily: 551*90 = 49,920 g = 50 kgs of ATP is consumed daily because of its high molecular weight, ATP isn't stored on the long term in the body, it is rather in constant replenishment being used and resynthesized all the time, meaning ATP would be hydrolyzed in a certain pathway and then resynthesized by other pathways.

❖ Main pathway for ATP production is the oxidative phosphorylation.

❖ Excess energy in the body is stored in other molecules on the long term like glycogen.

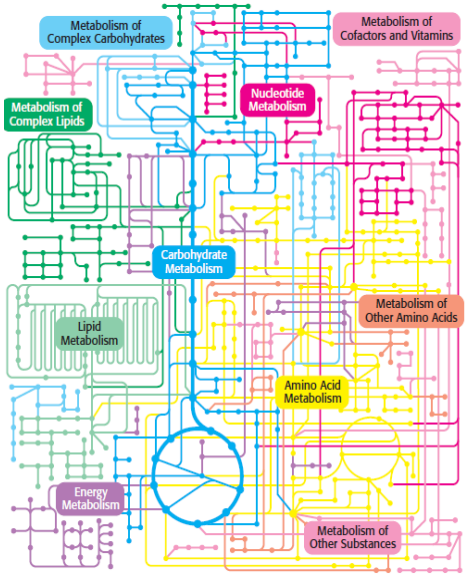


BIOCHEMICAL (METABOLIC) PATHWAYS

- **Are interdependent**
- **Are subjected to thermodynamics laws**
- **Their activity is coordinated by sensitive means of communication**
- **Allosteric enzymes are the predominant regulators**
- **Biosynthetic & degradative pathways are almost always distinct (regulation)**
- **Metabolic pathways are linear, cyclic or spiral**

• Biochemical reactions within the body are called pathways.

• Pathways: are a series of biochemical reactions of multiple steps where one step would lead to another until the final product is formed.



• described as interdependent; meaning that they don't occur as single reactions. examples: Glucose → pyruvate is a 10 steps process.

- The picture is actual representation of what goes inside the body, biochemical pathways are interconnected to each other, to conserve energy as much as possible.

• Pathways communicate with each other through allosteric enzymes which have 2 subunits: catalytic subunits where the reaction occurs and regulatory subunits where another materials bind.

Example on pathway communication:

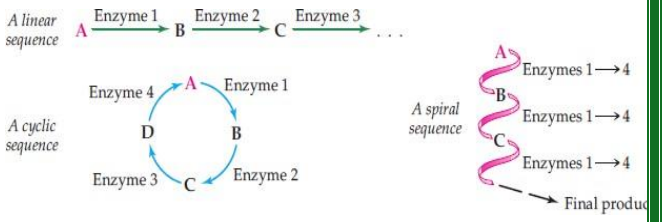
materials from the carbohydrate metabolic pathways would bind on a specific allosteric enzymes of lipids metabolic pathway.

the resulting regulatory effect would: activate/inhibit pathways, rates and molecule concentration regulations.

• Types of pathways:

1)linear pathways e.g., glycolysis

2)cyclic pathways series of reactions that lead to the first reactant regeneration e.g., urea cycle, Krebs cycle.



*Each step in metabolic linear and cyclic pathways is catalyzed by different enzymes

3)spiral pathways: each step is interconnected with the next, but all of them are catalyzed by the same set of enzymes

EXERGONIC REACTIONS IN BIOCHEMISTRY

- **Complex structures → simple structures**

Proteins →amino acids

Starch→ n glucose

glucose + O_2 →CO_2 + H_2O

- **More specifically: -**

✓ **Hydrolysis reactions** (molecules breakdown by H2O)

✓ **Decarboxylation reactions** (removal of carboxylic group → **CO_2 release)**

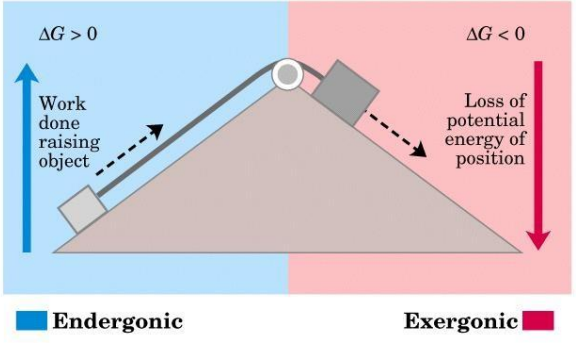
e.g., Pyruvate (C3) → acetyl-CoA(C2) +CO_2

✓ **Oxidation with O_2** e.g., glucose using molecular oxygen

❖ -in metabolic pathways:
Complex structures→ Simple structures proteins → amino acids starch → n(glucose) glucose + O2 → CO2 + H2O

HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

- **The concept of coupling**



I. **ΔG^0 Values are additive**

A. **Through phosphoryl transfer reactions:**

✓ **Step 2 (+3.3 vs. -4 kcal/mole)**

- ✓ **Step 2 + 4 = -2.35 kcal/mole**
- ✓ **<u>The net value for synthesis is irrelevant to the presence or absence of enzymes</u>**

B. Activated intermediates (step 4 is facilitated by steps 5&6)

II. ΔG Depends on Substrate and Product Concentration (step 4 has a ratio of 6/94; +1.65 kcal/mol, if 3/94; -0.4kcal/mol)

- ❖ On seesaw, the person with a higher weight will fall and pushes the lower weight person up, this is what happens in biochemical reactions inside the body, to run endergonic reactions, the body uses the energy produced from exergonic reactions and couple it with endergonic reactions. Both reactions run at the same time!
  meaning that both reactions are merging with each other and not running separately; the products of exergonic reactions are reactants in the endergonic reaction it coupled with.

- ❖ Example: Conversion of Glucose→Glucose-6-phosphate It's an endergonic rxn that needs two things: a 1phosphate group and 2energy to form the glucose-phosphate bond.

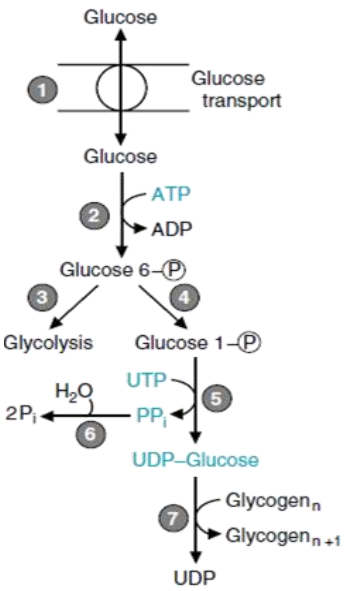
So, it will be coupled with an exergonic rxn that serves both energy and a phosphate group.

ATP is the perfect candidate for this specific reaction; releases energy by hydrolysis of the phosphoanhydride bonds between phosphates in ATP which releases energy and donates a phosphate group:

ATP→ADP + P (exergonic rxn: ATP hydrolysis) This chemical process is known as phosphoryl-transfer reactions.

An example to illustrate this is glycogen synthesis, which is an endergonic pathway that needs energy.

Glucose→glucose-6-phosphate → glucose-1-phosphate→ UDP-glucose → Glycogen



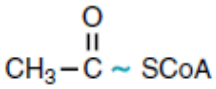
in Step 2: Glucose is always converted to glucose6-phosphate that need energy = 3.3 kcal/mol So, the ATP can supply that reaction with (material (phosphate) + energy needed. Notice that ATP hydrolysis provided 4 kcal/mole as an excess energy (this excess energy can be used during the pathway or in other reactions or heat)

Step 4 gets its energy by playing with the concentrations. As ΔG Depends on Substrate and Product Concentration. The original (products/reactants) ratio is 6/94 so ΔG= +1.65 kcal/mol but if we can withdraw some of the products out then the ratio will become 3/94 and ΔG= -0.4kcal/mol so the reaction will become exergonic.

Some pathways generate high energy intermediate like in step 5 where UDP-Glucose is produced which means that its separation will supply the energy needed for the pathway. So here in step 7, separation of UDP from glucose gives the energy to attach the glucose to glycogen.

In conclusion, playing with concentrations, high energy intermediate, Phosphorylation transfer reaction (coupling) are all strategies used by the body to provide energy for endergonic reactions.

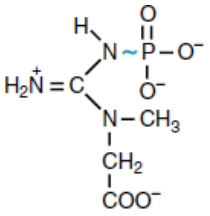
III. Activated Intermediates other than ATP; UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis.



Acetyl CoA

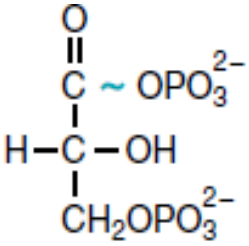
Activated Intermediates other than ATP:

UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis (as mentioned in page 8)



Creatine phosphate

- 1,3-bisphosphoglycerate and Creatine phosphate have a high energy phosphate bond in their structure.



1,3–Bisphosphoglycerate

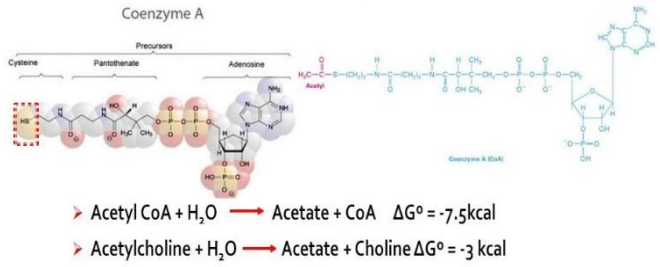
THE ACETYL COA AS AN EXAMPLE

- **Coenzyme A is a universal carrier (donor) of Acyl groups**
- **Forms a thio-ester bond with carboxyl group**

Acetyl choline is made of choline + acetate

Hydrolysis of acetyl coA will result in energy and acetate to be used as reactants in acetyl choline synthesis

- acetyl choline a neurotransmitter that binds to *receptors on nerves endings to contract the muscles, it gets broken down by the enzyme acetyl choline esterase causing muscle relaxation.



THERMOGENISES

- **The first law of thermodynamics**
- **Heat production is a natural consequence of "burning fuels"**
- **Thermogenesis refers to energy expended for generating heat (37°C) in addition to that expended for ATP production**
- **Shivering thermogenesis (ATP utilization): responding to sudden cold with asynchronous muscle contractions** (More ATP and generate heat)
- **Non-shivering thermogenesis (ATP production efficiency)**

(adaptive) the percentage of energy that you are ingesting inside your body to make heat.

OXIDATION-REDUCTION REACTIONS (REDOX)

Oxidation reduction reactions: (we are studying them now because they exist in most of the metabolism of energy reactions.)

✓ Oxidation reduction reactions include moving of electrons without changing the chemical structures.

ΔG: the difference in bond energies between materials when electrons move between molecules, we can't identify the change in energy content therefore we can't calculate ΔG using the original equation.

redox potential (E) (THE POTENTIAL ENERGY): the driving force of moving the electrons from one atom to another, these electrons are hold on chemical structures which can donate its electrons or accept its electrons.

✓ redox Potential measures the tendency of oxidant/reductant to gain/loss electrons, to become reduced/oxidized

✓ Electrons move from compounds with lower reduction potential (more negative) to compounds with higher reduction potential (more positive)
#Or there is a difference in the ability of accepting donating-electrons between any 2 chemical materials

✓ The electrons move from the material that has a higher ability to donate electrons to the one which has a lower ability to donate electrons.

✓ Oxidation and reduction must occur simultaneously

- **Oxidation:**
- ✓ **Gain of Oxygen**
- ✓ **Loss of Hydrogen**
- ✓ **Loss of electrons**

- **Reduction:**
- ✓ **Gain of Hydrogen**
- ✓ **Gain of electron**
- ✓ **Loss of Oxygen**
- ***E*= redox Potential: it is a POTENTIAL ENERGY that measures the tendency of oxidant/reductant to gain/loss electrons, to become reduced/oxidized**
- **Electrons move from compounds with lower reduction potential (more negative) to compounds with higher reduction potential (more positive)**
- **Oxidation and reduction must occur simultaneously**

❖ What makes an enzyme to function as redox enzyme is that it has a specific structure that can accept or donate electrons such as heme group, NAD, FAD…

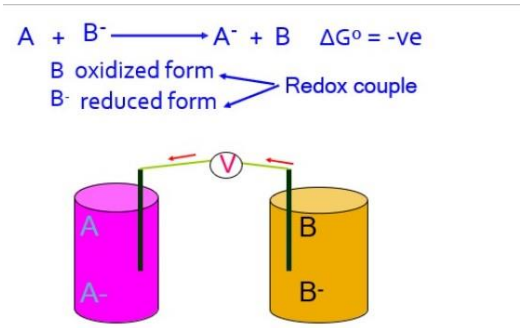
REDUCTION POTENTIAL AND DIRECTION OF THE REACTION

A-P + B —> A + B- P

- **Type of reaction: transfer of phosphate**
- **What determine the direction of the reaction? Delta G**

A++ + B++—> A+ + B+++

- **Type of reaction: redox**
- **What determine the direction of the reaction? Delta E**



Now look at this redox couple: (A) accepts electrons and is converted to the reduced from A- so we have redox couple (A, A-)

Another redox couple is shown in the illustration.

Now, can we measure redox potential experimentally?

The answer is yes. scientists were able to measure reduction potential for a wide variety of materials with respect to hydrogen electrode (as a standard electrode Eo = 0) and they arranged these values from the more negative to the more positive value in a large scale. **The more negative value has high capacity to lose electrons while the more positive value has high tendency to gain electrons.**

For example, of we have 2 reduction potentials: the first equals -600mv while the second equals -500mv then electrons move from the first to the second material.

The importance of this standard electrode is to obtain the exact value of reduction potential because if we used 2 materials of unknown reduction potential, then we will not be able to find the exact value for both, since they are Different, **another advantage of using hydrogen is that most materials can gain/lose hydrogen.**

REDUCTION POTENTIAL ABILITY TO ACCEPT ELECTRONS

- From the table, we notice 2 important points. Firstly, oxygen is the final electron acceptor for electrons (electrons from different nutrition materials are trapped by oxygen) thus it has the most positive reduction potential. secondly, NADH has a reduction

Oxidized + e^-	→ Reduced	*ΔE° (V)*
Succinate	α ketoglutarate	- 0.67
Acetate	Acetaldehyde	- 0.60
NAD^+	**NADH**	**- 0.32**
Acetaldehyde	Ethanol	- 0.20
Pyruvate	Lactate	- 0.19
Fumarate	Succinate	+ 0.03
Cytochrome^{+3}	Cytochrome^{+2}	+ 0.22
oxygen	**water**	**+ 0.82**

potential (Eo) of -320mv thus it gives electrons to oxygen with Eo=+820mv.

This direction of electron movements fits the science since we already know that **electron carriers like NADH after produced from Krebs cycle donate their electrons for materials with higher E.**

❖ As we talked before about delta G and its relation to bond energy, we can say the difference in energy caused by reduction potential is another diameter of what delta G measures. So, delta G is not only concerned with bond energy. The reduction potential, not bond energy, is the driving force for electrons movement.

➢ Therefore, **if we inverted the sign of reduction potential value then electrons will move in the backward direction**. There must be a mathematic relation that governs the direction of electron movement. Moreover, it should not contain any variable other than delta G and delta E.

- **$\Delta G^{\circ} = - nf\Delta E^{\circ}$**

F* = Farady constant = 23.06 kcal/ *Volt

➢ **Calculate ΔGº of the following reaction**

NADH + $1/2O_2$ → NAD^+ + H_2O

NADH → NAD+ + 2e delta Eo = + ,32v

O + 2e → O-2 delta Eo = + ,82v

Delta Go = -52.6 kcal/mol

Oxidation-Reduction reactions (Redox)

- $\Delta E = E_A - E_D$
- ΔE = Redox difference of a system in any condition
- ΔE^{o} = Redox difference of a system in standard condition (25C° and 1 atmosphere pressure, pH = 7)
- <u>Does ΔE determine the feasibility of a reaction?</u>
- $\Delta G^{o} = -nf\Delta E^{o}$
- In other words; energy (work) can be derived from the transfer of electrons Or
- Oxidation of food can be used to synthesize ATP

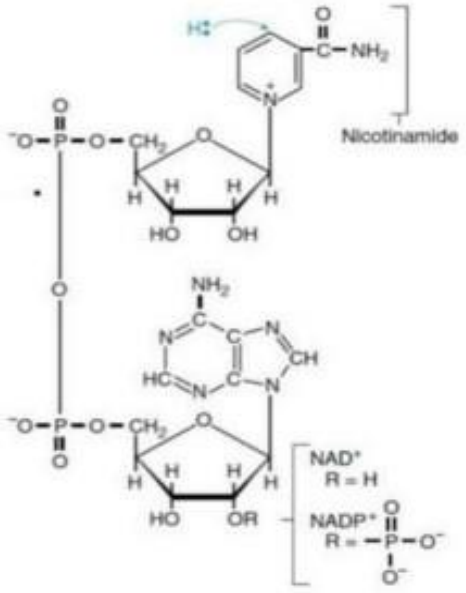
Now, let us talk about **electron carriers** (that transports electrons to ETC).

There are 2 main electron carriers:

- ✓ NAD+ (niacin, B3) & FAD (riboflavin, B2).

NAD+ accepts a single hydride ion H - (2 electrons) on nicotinic ring with one step, so it does not form a radical (will not be harmful) and thus can be found free as both NAD+/NADH in mitochondria/cytosol, as a result, it has a fixed reduction potential.

-NADP+ is different from NAD+ only by **a ssphosphate group** instead of **a hydrogen atom** as shown in the previous figure. Both of them carries 2 electrons but NAD+ participates in **catabolism** while NADP+ participates in **anabolism**. So, different structures that do the same function for better organization and regulation.



- ✓ FAD accepts 2 protons (2 electrons) sequentially since there are 2 Hatoms thus it forms a radical intermediate and passes through (one electron/free radical state) that is harmful. Therefore, **it cannot be found free in the cytosol** and is always bound to proteins. Also, its reduction potential depends on the protein it is bound to. FMN also carries 2 electrons sequentially, but for better organization: one works in anabolic reactions while the other in catabolic reactions.