We will continue talking about, how your cells overcome endergonic reactions? From where we can get energy to drive endergonic reactions?

Through coupling (الازدواج), we can couple an endergonic reaction to an exergonic one, and the energy produced from the exergonic reaction will be used to drive the endergonic reaction.

<u>Why chemical pathways/reactions in our bodies are additive?</u>

We can combine more than one reaction, energy pipes.

while it leads these pathways as one reaction {takes the starting material, define the material, and calculate the ΔG for the whole pathway} If It Is exergonic reaction the whole steps will proceed, one example is the formation of glycogen in the cells (glycogenesis) we will study this in carbohydrate metabolism enshallah, but what happens in brief is:-

1- Glucose enters the cell

2- After the glucose enters it will be phosphorylated

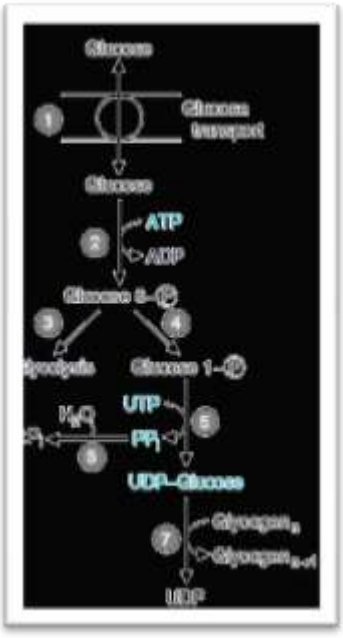
<u>Why glucose is phosphorylated when it enters the cell?</u>

To prevent its exit outside the cell.

3- Now we will have **Glucose 6-phosohate**, which will be converted to **glucose 1-phosphate** then to **UDP- glucose**.

4- Glucose will be separated from UDP, when glucose is separated this will give us **glycogen**.

→ Phosphorylation of glucose ofcourse needs energy (why?) because we are building up bonds between phosphate and glucose which needs 3 Kcal/mol of energy (from where I can get this energy?)



→In step no. 2 (check the slides for a better picture), this reaction is proceeding through coupling it to an ATP hydrolysis reaction which will provide me with 7 Kcal/mol so simply

we have 7 Kcal/mol provided to us by ATP hydrolysis but we only need 3 Kcal/mol to perform step 2 reaction soooo...the total sum will be -4kcal/mol (-7+3=-4 kcal/mol)

That means we have an excess energy of 4 Kcal/mol.

→ Isomerization process of Glucose 6-phosphate to Glucose 1-phosphate (step4) where the phosphate group shifts from carbon no. 6 to carbon no. 1,also this reaction is endergonic it needs 1.65 Kcal/mol.

→Steps in pathways are additive (total sum of step 2 + step 4 will be negative, -4+1.65=-2.35) SIGNS are used to express whether the energy absorbed from a reaction +, or released from a reaction -)

●This is how reactions are proceeded, we use the energy derived from the first reaction in step 2 to drive the second reaction in step 4.

●The presence of high energy intermediates, activating intermediates through any pathway will provide you with excess energy, as an example UDP-glucose.

How is UDP-glucose formed?

Glucose 1-phosphate already has a phosphate and UTP will provide the other phosphate (only one phosphate) and a pyrophosphate will exit out of the UTP

●Pyrophosphate will also provide you with energy by the hydrolysis of pyrophosphate into two phosphate molecules

●So hydrolysis of ATP, hydrolysis of UDP-Glucose ... all this will provide you with energy.

● The ratio between Glucose 6-p and Glucose 1-p

Glucose 1-p has 6 molecules (product) & Glucose 6-p has 94 molecules (reactant) [in reaction step 4]

This reaction is endergonic needs energy to proceed, $\Delta G=-RT \ln Keq$

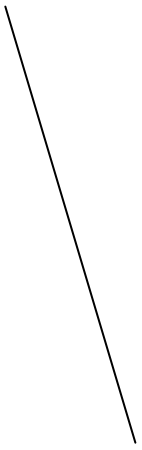
Ln(conc. of products/ conc. of reactants)

so ln 6/94 if we change the ratio to 3/94 by removing more products out of the reaction the ratio between products and reactants will decrease, so ln will be more negative so i will be able to switch the reaction to be exergonic, ΔG will equal -4 Kcal/mol.

That means that playing with the concentrations of products and reactions can also change the thermodynamics of a reaction.

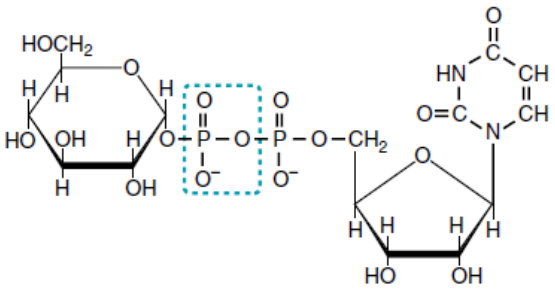
● We can use other active energy intermediates other than ATP such as:-

- UTP (as in the carbohydrate metabolism we talked about in glycogenesis)
- CTP (in lipid metabolism)
- GTP (in protein metabolism)
- Acetyl Co enzyme A
- Creatine phosphate
- BPG (1, 3- bisphosphoglycerate)

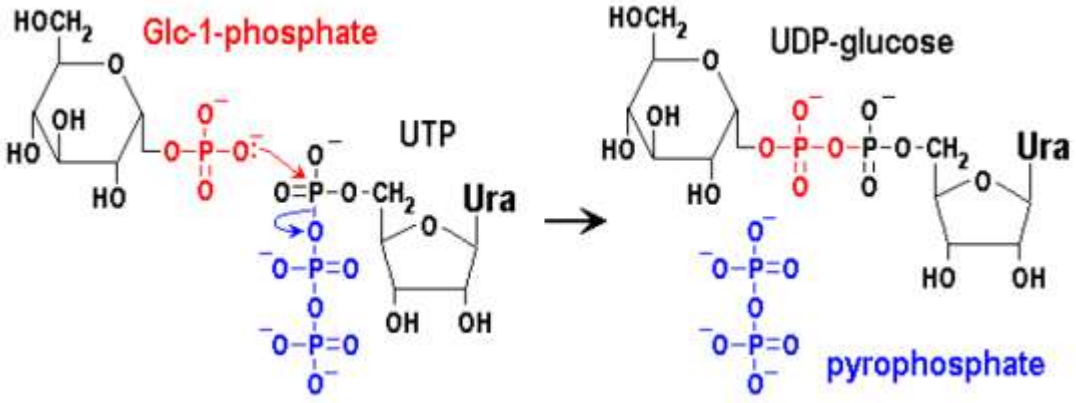


Separation of phosphate from any of these molecules will provide you with energy, so whenever they are found in pathways or reactions they will provide you with energy to drive endergonic reactions to be exergonic.

How does UDP attach to glucose-1 p in step 5 ?



Uridine diphosphate glucose
(UDP – glucose)



- Glucose 1 phosphate already has a phosphate group on it.

- The phosphate group from Glucose 1 phosphate will attack another phosphate group on UTP.

- Pyrophosphate will leave outside the reaction to be hydrolyzed again in a separate step.

Acetyl Co-A

● We talked about acetyl Co-A as a source of energy.

● Structure of Co enzyme A: it is composed of adenosine + pantothenic acid + cysteine

What is the pantothenic acid?

We took water soluble vitamins and they are either C- vitamins or B-vitamins, all B-vitamins are considered as part of co-enzymes. That's why we take water soluble vitamins after taking enzymes. One of these B-vitamins is B5 which is the pantothenic acid (pantothenate) which enters the structure of Co-A.

● Co-A has a cysteine molecule at the end which carries a free thiol group with sulfur which is reactive, this sulfur atom can attach to two carbon molecules forming acetyl Co-A.

● The acetate group will attach to the whole structure of Co-A .

● Breaking the bond between the sulfur (from Co-A) and the carbon (from acetyl) will provide you with energy comparable to the energy provided by the ATP hydrolysis of one phosphate molecule.

Acetyl Choline

● As we all know it's a neurotransmitter.

● Hydrolysis of acetylcholine will give us acetate + choline and provides you with energy of 3 Kcal/mol

●How does The process of formation of acetyl choline occur?

- Acetate + choline + (needs) 3 Kcal/mol..... But how will this reaction proceed?

-- Through the hydrolysis of acetyl Co- A, this gives a comparable energy amount as ATP around 7.5 Kcal/mol.

● The hydrolysis of Acetyl Co-A and formation of acetyl choline are coupled, and once they are coupled.... this is the final reaction with 4.5 Kcal/mol as excess energy.

- Acetate + Choline → Acetylcholine + H_2O $\Delta G^o = +3$ kcal
- Acetyl CoA + H_2O → Acetate + CoA $\Delta G^o = -7.5$ kcal

- Acetyl CoA + Choline → Acetylcholine + COA

Why ATP is not a good long term storage molecule for energy?

Energy is stored in the body in the form of bonds, but we can't store energy for long time usage as ATP, check the chart on slide no. 25 chart which shows the huge amount of energy the main tissues need daily in order to function... and the total is 90.6 mol of ATP/day

90.6 * 551 (g/mole) = 94,920 g ATP

→ This is how we calculate the mass

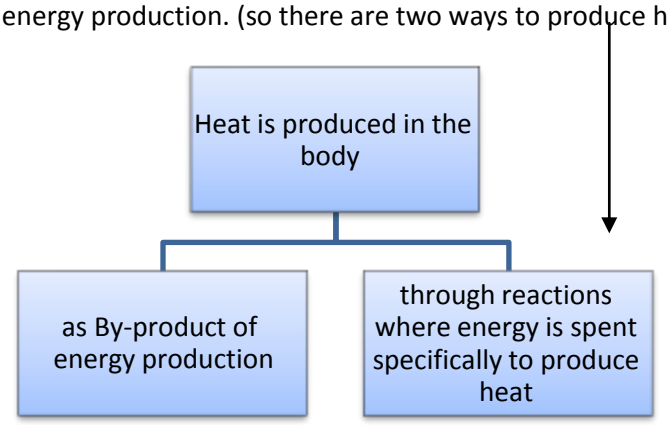
551= Molecular weight of ATP, so we need 94,920 g of ATP =94.920 kg each day, and this is why we don't store it. We need another human being to store ATP.

● One of the ways to regenerate the ATP all the time is through an enzyme called adenylate cyclase, it switches the ADP to ATP & ATP to ADP

THERMOGENESIS:-

What is thermogenesis as a concept?

It's the energy you spend to produce heat. It's not the by-product (lost) heat from other processes of energy production. (so there are two ways to produce heat: major/by product)



All of you know the first law of thermodynamics (Energy cannot be created nor destroyed but it can transfer from one form to another), the second law of thermodynamics shows where the lost energy goes (heat and entropy)

*extra note: (the entropy of an isolated system never decreases, because isolated systems spontaneously evolve toward thermodynamic equilibrium—the state of maximum entropy).

● We all know that our normal body temperature= 37, but how does our body preserves this temperature?

● How does our body produce this amount of heat and reach it to 37?

- For any process in any machine its role is inefficient, it's not 100% efficient, so there will be a loss in energy, this lost energy in the human is expressed as heat.

● Heat is not always expressed as a by-product, it needs a pathway to express it which occurs in the mitochondria, in the electron transport chain, heat forms.

● ***Thermogenesis has two parts:-***

1- Shivering (الارتعاش) **[Sudden]** 2-Non-shivering **[Adaptive]**

Why does someone shiver?

- Shivering causes contraction of muscles which in turn needs ATP, so you will introduce an imbalance to the system by consuming more ATP so you will need more and more ATP and the process of ATP production will start and heat will be generated because the process is inefficient.

What about Non-shivering Thermogenesis?

For those who live in cold places and cold environments, they will have adaptations to live there, by expelling more energy outside their body so as to make more heat to compensate for the decrease in temperature.

Oxidation reduction reactions:-

The last topic in biogenetics that has a relation to the energy metabolism.

What does oxidation mean?

Gain of Oxygen, loss of electrons or loss of hydrogen. And the reverse is true for reduction.

● For any protein or any enzyme that can undergo deep oxidation reduction reactions, there is certain potential.

الالكترونات بالنهاية عبارة عن كهرباء و هاي الكهرباء بنقدر نقيسها بالمختبرات

● Any complex that can undergo oxidation reduction reactions (proteins,enzymes,electrons) at the end we can measure its voltage in labs.

How this happens?

We make a reference control for that enzyme or protein (يعني بتصفرو) on a certain control, then we add a specific material that can add or extract electrons from that enzyme or protein, now electrons will start to move from one place to another on the enzyme so the electricity will change, you are measuring this voltage in the solution.

What does the redox potential/ oxidation potential mean as a term?

Potential>>> القابلية

It is a POTENTIAL ENERGY that measures the tendency of oxidant/reductant to gain/lose electrons, to become reduced/oxidized

>>>>> you are measuring a potential, you are not measuring an actual movement of electrons.
احنا بنقيس مدى قابلية المادة لاعطاء او فقد الاكترونات ما بنقيس حركة الاكترونات بالمادة

>>>Its a potential energy it mimics ΔG (which is also a potential energy).
P.S. All thermodynamics express potential energy (ΔG,ΔH,ΔS)

● ΔE as a redox potential expressing potential energy, it calculates the ability of a material to accept or donate electrons.
Redox reaction (حركة الكترونات)

● So if I'm calculating the ability of a material to accept or donate electrons, then I'm calculating the ability of the reaction to happen or not (the ability of this material to go on this reaction or not) after calculating we will get a number and the unit will be in millivolts or volts.
●When I calculate ΔE it's as if I'm calculating ΔG, because ΔG calculates whether this reaction will occur or not. (ΔG - >> SPONTANEOUS, ΔG + >> NON SPONTANEOUS)
●If ΔE expresses the tendency of a reaction to occur or not, then it should express ΔG in a way or another.
● Oxidation and reduction always occur simultaneously, if we have an oxidation reaction then we must have a reduction reaction. Oxidation doesn't occur without reduction.
● Electrons come out from oxidation (where will they go?)
They should go to another material to accept them, and this material will be reduced.

Material loses more electrons >>>> Reduction potential more negative >>>> has the ability to lose electrons more

Reduction potential more positive >>>> has the ability to accept electrons more
● The more negative the reduction potential, the more tendency to lose/donate these electrons..... and the more positive the reduction potential the more tendency to accept/gain these electrons.

● ΔE = expression of the reduction potential of the expected destination of electrons.
ΔE = destination - the start
P.S. any Δ= final-beginning

● ΔE = reduction potential of an acceptor molecule - donor molecule
ΔE= الفرق في القابلية للمنح أو الفرق في القابلية للكسب (لازم تكون في نفس الصفة)

●ΔE○ the same as ΔG○ ,,,,, under standard conditions, pH= 7

<u>Does ΔE determine the feasibility of a reaction ?</u>
Logic wise, it should, because it calculates the ability of the reaction to proceed or not

ΔE is directly proportional to ΔG (there is a linear relation between ΔG and ΔE, so if we know ΔE, for sure we will know ΔG)
$\Delta G^{o} = -nf\Delta E^{o}$
Where:
n = the number of transferred electron
F = the Faraday constant
E = the reduction potential (volts); G = the free energy (Kcal or KJ)

In brief we are measuring the ability to donate or accept electrons, electrons move and bonds are constantly breaking and forming between electrons, the energy in these bonds is voltage energy which we calculate, so ultimately it expresses reactions!!!

● Oxidation of food:-
All the nutrients we eat (lipids, proteins and carbohydrates) undergo oxidation, getting electrons out, decreasing the electron sharing, then bonds will break (because electrons have been removed), oxidation breaks down large molecules, it keeps breaking them down, then it goes to the Krebs cycle and breaks down the acetate molecule ..... All of this happens to extract the electrons out. (What to do with electrons when we extract them?)
So oxidation of food from the start to the end can be used to synthesize ATP, at the end you will result in energy production from oxidation/ from movement of electrons.

How do I carry these electrons to produce ATP?
Through electron carrier molecules, the main ones are NAD & FAD

What's the difference between NAD & FAD ?
Check their structures in slide no. 30
NAD= Nicotinamide Adenine Dinucleotide
FAD= Flavin Adenine Dinucleotide

Why dinucleotide?
Because we have two nucleotides in each.
In NAD we have Adenine & Nicotinamide, In FAD we have Flavin & Adenine.

● Structure of adenosine contains ribose; the two nucleotides in each molecule are connected via phosphate bonds

Nicotinamide is the nicotinic acid (COO-) when we add nitrogen to it instead of oxygen it will be an amide and that's why we call it nicotinamide. On the ring its self a hydrogen atom containing 2 electrons can be added. (What do we call this hydrogen? hydride ion)
-So NAD+ can accept 2 electrons from one hydrogen atom (hydride ion), so the source of electrons that come to NAD^+ is only from one hydrogen atom, and bind to the same place so I either gain two electrons at a time or lose two electrons at a time.
We have NAD and NADP..... Difference in groups (hydrogen or phosphate)
NAD+(carbohydrate and energy metabolism) vs. NADP+ (fatty acid synthesis and detoxification reactions)
- FAD has two nitrogen atoms on the flavin portion, it accepts two hydrogen atoms, each one on nitrogen, so the source of electrons is from two hydrogen atoms and they come sequentially so it can be FADH then FADH2 and this doesn't occur in NADH.
- FAD can go with one electron as a free radical in the ring FADH or two electrons for saturation as FADH2.
- So if only one electron comes to FAD then it will be dangerous to the cell because it will be a free radical. And that's why FAD is always found coupled to proteins inside the cell as a structure inside the protein, same as heme, to protect them they can donate electrons to decrease the effect of free radicals resulted from their gain of electrons (flavins in general are found always coupled to proteins).

● NAD will be present in solutions, cytoplasm and mitochondria because there is no free radical (this cannot happen in FAD)

Why oxygen is the best electron acceptor in the body?

Because it has the highest and the most positive reduction potential (the more positive the more tendency to gain electrons), that's why the final electron acceptor is the oxygen which will be reduced to water and that's how breath (electron carriers can for sure donate their electrons to oxygen).

Where is oxygen present?

In the mitochondria at the end of electron transport chain bound to complex 4.

The caloric value in each nutrient varies according to two things:-

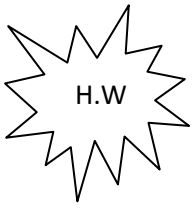
1- The value of energy inside bonds for this material and the nature of these bonds (that's why energy from lipids, carbohydrates....etc. differs)

Carbohydrates: 4kcal/gram, proteins: 3-4kcal/gram, lipids: 9kcal/gram.

2- If I have the ability to digest it, if I have the necessary enzymes to digest it.

Example:-

Cellulose found in wood, we cannot digest it, it is full of energy but we don't have the enzymes to digest it/ to break its bonds (not useful for humans).



ATP is present inside body/cells/solutions

For example you need 10 molecules of ATP so .of course we have ADP since we have ATP, and we can measure the ratio between them. You need all the time for example 10 molecules of ADP but if our body has 20 or 30 then there will be an excess , is there a logic of having an excess of ATP if we don't need it, this is what we will find.

The ratio of ATP/ADP is always kept high in our body; we always have higher amounts of ATP than we need ..... why the body behaves that way?

	Concentration (m.M)				
ATP	5.0	3.0	1.0	0.2	5.0
ADP	0.2	2.2	4.2	5.0	25.0
Pi	10	12.1	14.1	14.9	10.0

ATP/ADP ratio varies during metabolic process however it is usually kept high, for **ATP hydrolysis reaction (ATP>>ADP+Pi)**using the bioenergetics equation you have taken in the lecture, **please plot ΔG against lnx where x is the mass-reaction ratio concentration of products over reactants** at **25 degrees Celsius and pH 7** for the concentration of ATP,ADP and Pi are in the following table. ΔG^{o} **for the reaction is -30.5 Kj/mol** .According to the plot generated please provide a logical explanation for the high ratio of the ATP/ADP in metabolism.