SHEET NO. 3

METABOLISM

DOCTOR 2019 | MEDICINE | JU

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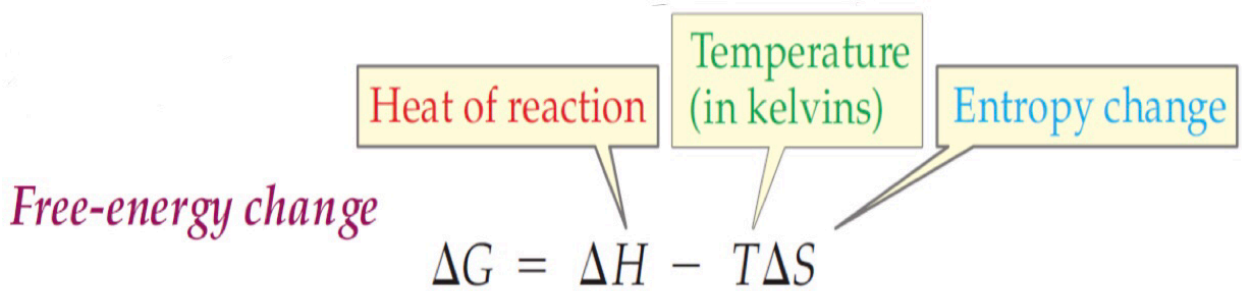
Metabolism: Sum of all biochemical reactions in living organisms (anabolism or catabolism) (building up or breaking down materials)
Bioenergetics :is the study of energy transformation in cells from the thermodynamic point of view (potential energy not kinetic energy within mater)
Energy is the life .
So, many processes in our body need energy : Mechanical, Active transport, Biosynthesis, Heat

types of energy are:
1-Kinetic energy : the energy during motion which deals with movement (that we studied in last semesters)
2-potential energy : energy stored within materials that can be converted to kinetic energy if needed . KEEP in mind that food is an example of potential energy (which is our course).
Can determine whether the reaction occurs or not (according to favorability we'll discuss in this sheet)

Relation between Energy and stability
(Energy has inverse relationship with stability)
High energy(either potential or kinetic energy) material indicates low stability
Main concept or causes for chemical reaction is to achieve more stable situation.

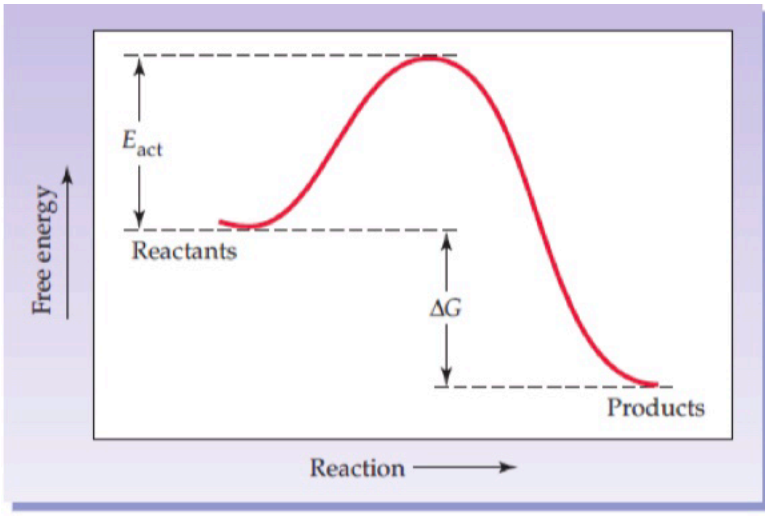
Gibbs Equation



For any delta =final -initial (Difference between the potential energy of product and reactant)
Dr said that we should know the difference between enthalpy change(ΔH) and entropy change(ΔS).

Enthalpy change(ΔH) : measure the bond energy in between different atoms and different molecules in materials

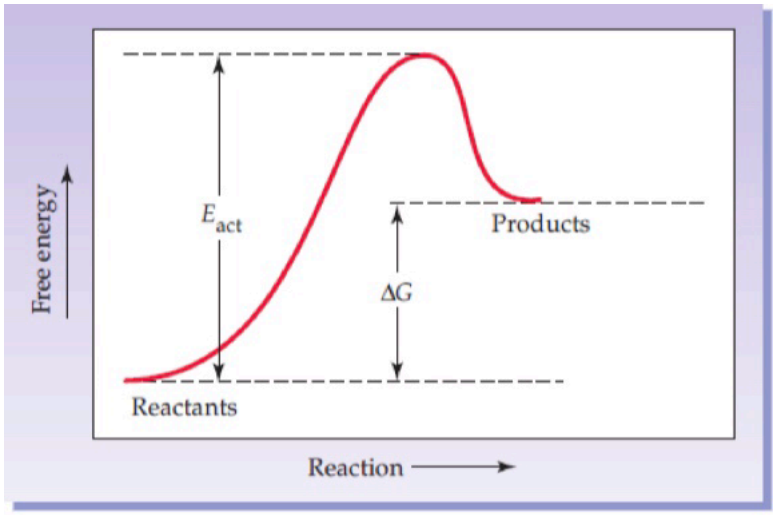
Entropy change (ΔS) : measure the disorder between the different molecules (close or farther to each other, they can go randomly , etc…) for nature system increase in time



(a) An exergonic reaction

- ΔG is negative, there is a loss of energy (product more stable than reactant)
- Reaction goes spontaneously(favorable)
- The reaction is exergonic.

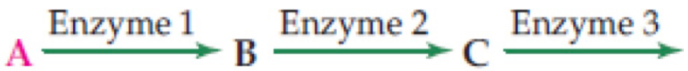
#it isn't spontaneously as it state , because it should go to a high energy state (transition state) and the energy that is needed is called activation energy .



(b) An endergonic reaction

- ΔG is positive, there is a gain of energy (reactant more stable than product)
- Reaction does not go spontaneously (unfavorable)
- The reaction is said to be endergonic.

*ΔG is not affected by the mechanism of the reaction (presence or absence of enzymes)
*ΔG is not affected by the pathway of the reactions only cares about initial and final states ,so that we called it state function . (ΔG from A to B to C = ΔG from A to C)



- $A \rightarrow B \rightarrow C$

$$\Delta G_{A\rightarrow B} = \cancel{GB} - GA$$
$$\Delta G_{B\rightarrow C} = GC - \cancel{GB}$$
$$GC - GA = \Delta G_{A\rightarrow C}$$

For example: combustion of glucose outside the body will release (— 680 kcal/mol)
Inside the body glucose undergo 10 steps to be oxidise but also it will release (—680kcal/mol)
So, we will repeat that ΔG cares ONLY about initial and final states .

Glucose + O 2 → CO 2 + H2 O ΔG = - 680 kcal/mol
In the cell

Glucose →→→→→→→ CO 2 + H2 O ΔG = - 680 kcal/mol

#Standard free energy change (ΔGo) VS Free energy change (ΔG)
ΔG = the free energy difference of a system at any condition (may be different because of changing concentration or temperature, etc…)
Determine the favorability of reaction

ΔGo= the free energy difference of a system at standard conditions (25C o & 1 atmospheric pressure, 1M concentration of reactants & products, pH = 7)
It is always constant

Our body have changing conditions such as temperatures , concentration and pressure so the same reaction in different region may have different ΔG value , but the same(ΔGo) value

$$\Delta G = \Delta G^{o} + RT \ln \frac{[Products]}{[Reactants]}$$

$$\Delta G = \Delta G^{o} + RT\ 2.3 \log \frac{[Products]}{[Reactants]}$$

***ΔG o= the free energy difference of a system at standard conditions**
***R is the gas constant**
***T is the absolute temperature (K)**
ln represents the natural logarithm
<u>#KEEP in mind that , if the value of</u>

$\frac{[Products]}{[Reactants]}$	= 1 the ln will be zero Greater than 1 ln will be +ve Less than 1 ln will be -ve

In other words , if [P] = [R] ln equals zero
[P] > [R] ln has positive value
[P]< [R] ln has negative value

اعتمادًا على المعادلة ، لنفترض قيمة دلتا في الظروف المعيارية = 4 ، كان تركيز المتفاعلات أعلى من النواتج و بالتالي قيمة اللوغاريتم سالبة و بتساوي -5 و حسب القانون ΔG= 4 – 5 = -1
و نستنتج انه
An endergonic reaction under standard conditions can be exergonic under physiological conditions.

<u>Equilibrium</u>
Equilibrium: is the state of balance when 2 rates(rate of products converting to reactants, and rate of reactants converting to products) are equal .
But , that doesn't mean that equilibrium is equally of concentration to both reactant and product .

معلومتين حبيت أوضحهم بالعربي ....

1)How does the concentration affect ΔG???

مادة تركيزها واحد مول لما اكسرها بتعطيني 5كالوري بس لو استخدمت بدل واحد مول 2مول رح تصير تعطيني 10كالوري و بالتالي زيادة التركيز بتأثر على قيمة ΔG

2)Delta G has nothing to do about reaction rate

تخيل انه فيه غرفتين الأولى فيها 100طالب و الثانية فيها 10 طلاب (يعني تركيز الأولى أعلى من الثانية) يعني ؟ حسب كلامنا الفوق الأولى دلتا جي فيها أعلى من الثانية
عملت حركة منتظمة للطلاب بحيث ينتقل 3طلاب كل دقيقة من الغرفة الأولى للغرفة الثانية و 3طلاب من الثانية للأولى (يعني rateتبعهم نفسه و يساوي 3طلاب بكل دقيقة على الرغم من الاختلاف الكبير بالدلتا)
و هيك بنفهم كيف انه **Delta G has nothing to do about reaction rate**

At equilibrium:
ΔG=0 (since the driving force of any reaction at equilibrium is zero) substitute ΔG=0 we get;

$$\cancel{\Delta G} = \Delta G^\circ + RT \ln \frac{[Products]}{[Reactants]}$$

$$K_{eq} = \frac{[products]}{[reactants]}$$

$$\Delta G^\circ = -RT \ln K$$

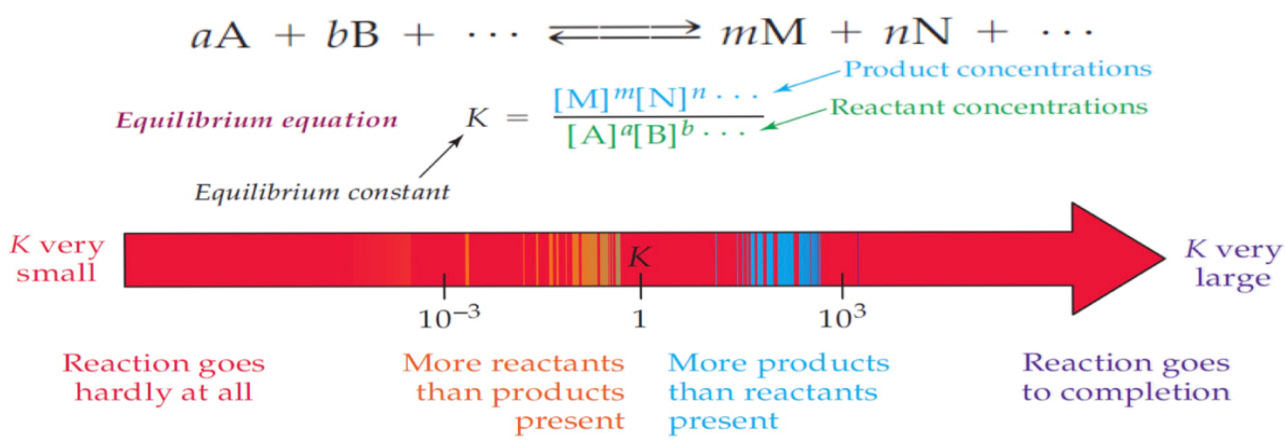
How much change in delta G compared to changes in Keq

If $K_{eq} = 1$, then $\Delta G^\circ = 0$

If $Keq > 1$, then $\Delta G^\circ < 0$

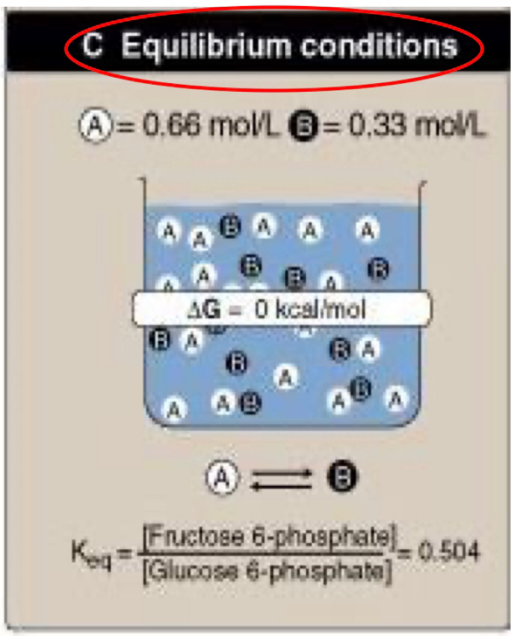
If $Keq < 1$, then $\Delta G^\circ > 0$

where Keq is the equilibrium constant. So, once we know the Keq for a reaction we can tell the ratio between products and reactants when the reaction reaches equilibrium.
e.g. if the Keq=100 that means at equilibrium [P]=100*[R]
If K eq is high (>1000) then we know that at equilibrium the reaction is mostly composed of products and a small proportion of reactants, thus we can say that the reaction is almost completed.
while when K eq is low (<0.001) we can say that the reaction is hardly going.



Glucose 6- phosphate $\rightleftharpoons$ Fructose 6- phosphate

0.66 mol/L 0.33 mol/L



less than 1
So, -ve

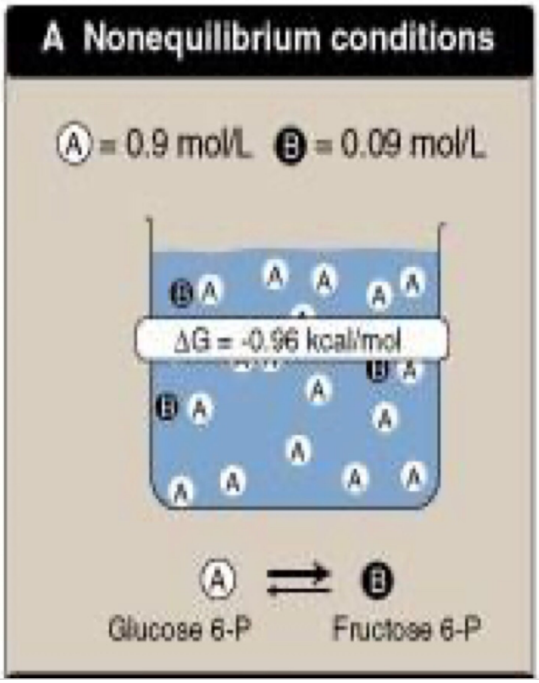
$\Delta G = \Delta G^o + RT\ 2.3 \log 0.33/0.66$

$\Delta G^o = -RT\ 2.3 \times (-ve)$

$\Delta G^o = +0.4$ kcal/mol

Glucose 6- phosphate ⇌ Fructose 6- phosphate

0.9 mol/L 0.09 mol/L



$\Delta G^o = +0.4$ kcal/mol

endergonic under standar conditions

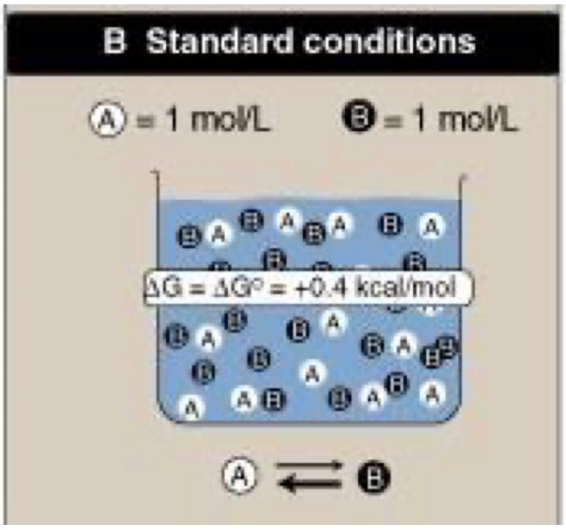
$\Delta G = \Delta G^o + RT\ 2.3 \log 0.09/0.9$

$\Delta G = -0.96$

exergonic under physiological conditions

Glucose 6- phosphate ⇌ Fructose 6- phosphate

1 mol/L 1 mol/L



$\Delta G = \Delta G^o + RT\ 2.3 \boxed{\log 1/1}$

equals zero

$\Delta G = \Delta G^o$

The Effect Of Changing Conditions On Equilibrium

$$\text{defining } K'_{eq} = \left(\frac{[C][D]}{[A][B]}\right)$$

$$\Delta G^{o\prime} = -RT \ln K'_{eq}$$

How the equilibrium is getting affected by different factors?
What are the factors that affects the equilibrium?

When a stress (any change that disturbs the original equilibrium) is applied to a system at equilibrium, the equilibrium shifts to relieve the stress.

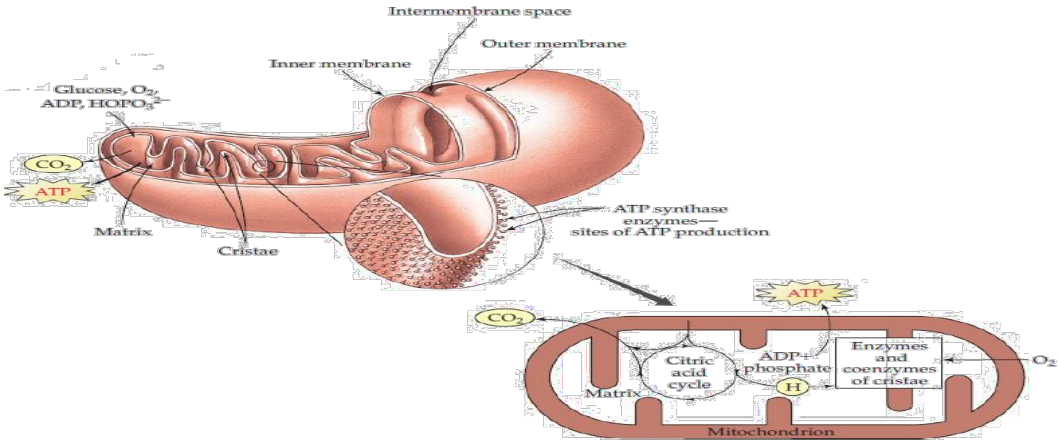
1)Effect Of Changes In Temperature

—> The goal behind that is to consider temperature as one of the reactants or one of the products depending on your knowledge of this reaction if it is exothermic or endothermic
—> If the reaction is exothermic then heat is being released during the reaction and thus heat content is considered to be a part of the products, so increasing T is the same as increasing products concentration therefore the reaction shifts toward making more reactants (⬆️T —> encouraging the backward direction)
—>If the reaction is endothermic then heat is being consumed during the reaction and thus heat content is considered to be a part of the reactants, so increasing T is the same as increasing reactants concentration therefor the reaction shifts toward making more products (⬆️T —> encouraging the forward direction) Until we reach the equilibrium state
So : endothermic/exothermic are favored by increase/decrease in temperature, respectively

2)Effect Of Changes In Concentration

What happens if a reactant/product is continuously supplied/removed?
—>If you have an equilibrium state, and you increase the reactants concentration, the reaction will go forward, until achieving a balance state
—>If you have an equilibrium state, and you increase the products concentration, the reaction will go backward, until achieving a balance state
—>Metabolic reactions sometimes take advantage of this effect
3)no effect of a catalyst (enzyme) on equilibrium :
it just helps the reaction to achieve equilibrium faster, because catalysts play on what is between the reactants and products,
while when discussing ▲G we are not concerned on what is in between the tow points,
as ▲G represents the difference in free energy between products and reactants

Energy Machinery In The Cell



—>90% of the body's energy (ATP) is made inside mitochondria (single:mitochondrion) the rest of it (10%) is made mainly through glycolysis in the cytosol

—> The number of mitochondria is greatest in eye, brain, heart, & muscle, where the need for energy is greatest

—>mitochondria is found only in eukaryotic cells

—>according to the evolution theory a mitochondrion is a prokaryote that invades an eukaryotic cell in reciprocal relationship to give it energy, while the cell gives the mitochondria the supply according to that,

—>The reason why they consider this ⬆️is that the mitochondria is different in every thing : it has an outer membrane, a convoluted inner membrane (cristae), a space between them, a matrix inside where all processes happen, reproduction happens by division (like the reproduction of bacteria) and not by mitosis, it has its own circular DNA which produces **some** of the proteins that are needed in the mitochondria (not all of them because it's a small DNA, while other needed proteins are produced by nuclear DNA)

Reproduction of mitochondria

—>Reproduction of mitochondria is governed (determined) by the need of energy

—>When needing more energy mitochondria will start replicating, this is why training and exercises are beneficial for the human body —>it creates more mitochondria so more energy sources **in the presence of oxygen** —>this is why athletes behave better in exercises than ordinary people, (they have more mitochondria, more oxygen supplies, more ATP)

—>Maternal inheritance, mitochondria are normally inherited exclusively from the mother; the mitochondria in sperm are usually destroyed by the egg cell after fertilization so the paternal genetic material only gets transmitted.

Nuclear DNA has two copies per cell (except for sperm and egg cells), one copy being inherited from the father and the other from the mother. Mitochondrial DNA, however, is strictly inherited from the mother.

During cell division the mitochondria segregate randomly between the two new cells

مش شرط عدد الميتوكوندريا يتوزع بالتساوي على الخلايا الناتجة من الانقسام خلال التكاثر

As DNA is copied when mitochondria proliferate, they can accumulate random mutations, a phenomenon called heteroplasmy.

—>If a mutation happens in the **nuclear** DNA 🧬 that produces a **protein that is needed inside the mitochondria** then that mutation will be all over the body because the way of replication of nuclear DNA is through mitosis which will renew the mutation in all daughter cells

—>While there is no regulated way distributes mitochondrial DNA between daughter cells mitochondria when mother cells replicate, so mutated mitochondria can exist in one daughter cell but other daughter cell might have normal mitochondria,

If this mutation happens in the first fetal stages and : (for example) the daughter cell that has a mutated mitochondrial DNA is designated to form the nervous system, and the second is designated to make the muscle tissue, mitochondrial disease will affect the nervous system while the muscular system is healthy

Stages Of Energy Production

Stage 1 (Digestion): it includes ingestion of food, degradation, absorption then all molecules will be moved to the blood so it can reach all cells.

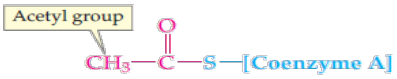
*Carbohydrates to glucose & other sugars

*Proteins to amino acids

*Triacylglycerols to glycerol plus fatty acids

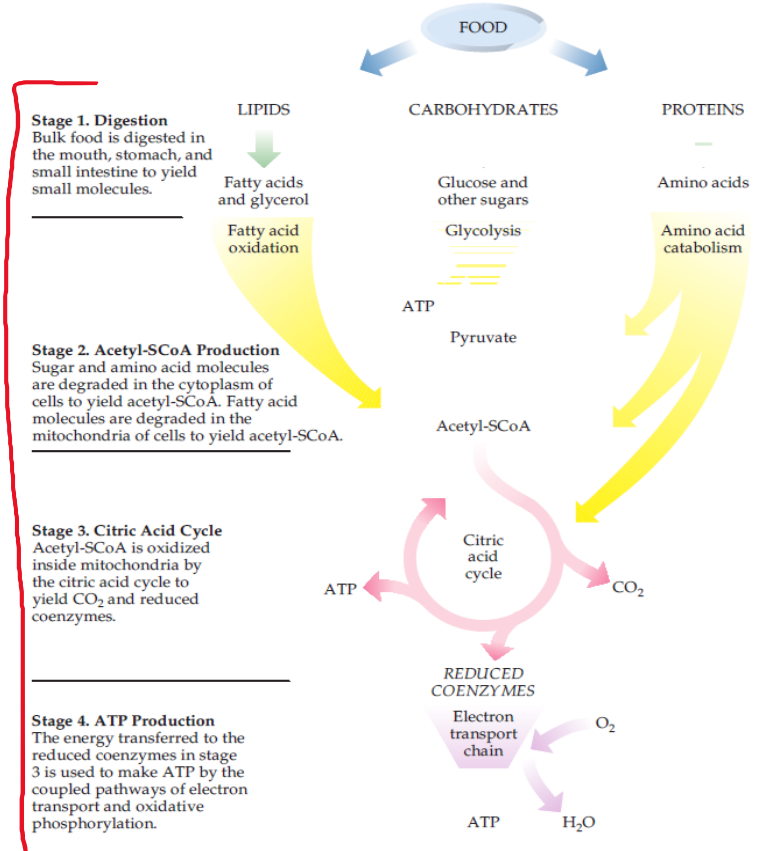
Stage 2 (Acetyl-coenzyme A)

Attachment of acetyl group to coenzyme A



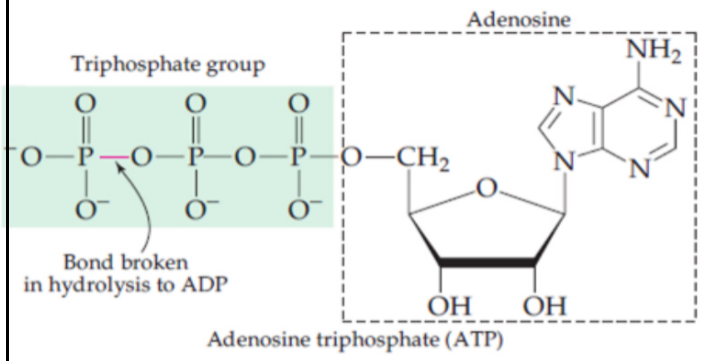
Stage 3: Acetyl CoA enters the Kreps cycle seeking for energy production
and it produces molecules that carry electrons(NADH and FADH2).

Stage 4: electron transfer chain & oxidative phosphorylation

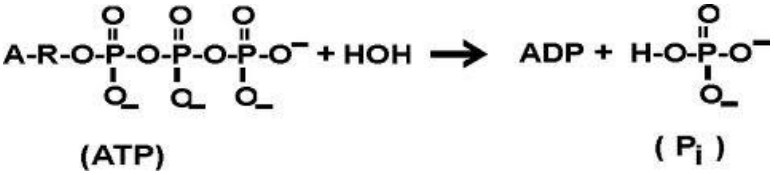


الكلام المكتوب جون مهم

ATP



What determines the amount of energy a bond stores —>is the atoms that are involved directly in the bond (phosphate and oxygen for example in ATP) and the distribution of atoms around this bond which makes strain on the bond so it changes the energy of the bond.



-7.3 kcal/mole
-3.4 kcal/mole

Compound +H_2O	Product + phosphate	ΔG°
Phosphoenol pyruvate	Pyruvate	-14.8
1,3 bisphosphoglycerate	3 phosphoglycerate	-11.8
Creatine phosphate	Creatine	- 10.3
ATP	**ADP**	**- 7.3**
Glucose 1- phosphate	Glucose	-5.0
Glucose 6- phosphate	Glucose	-3.3

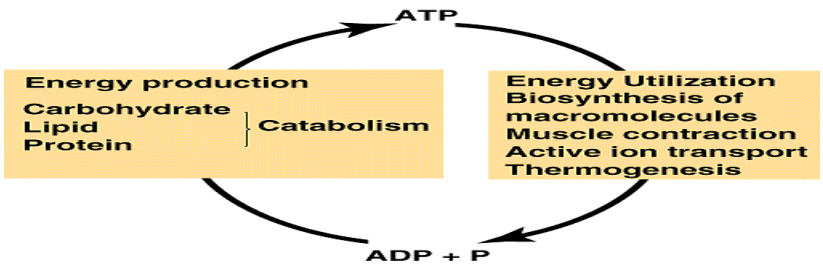
ATP is the energy currency of the cell, it has a triphosphate group and breaking down each P-O bond gives energy

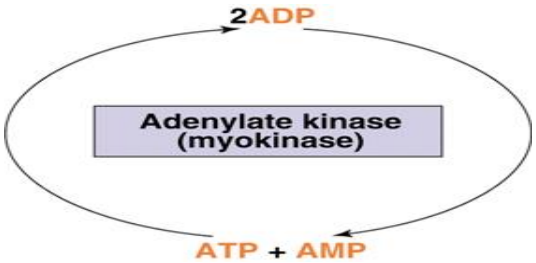
—>Why ATP is the energy currency of the cell?

NOT because it has 3 phosphate or it has high energy or the negative charges it carries. But because it has an intermediate energy value, so can be coupled we need a molecule with an intermediate amount of energy (ATP) so it can be broken down and resynthesized easily (the same amount of energy released from breakage of ATP to ADP must be supplied to ADP to synthesis ATP again).

This means that if we assume that breaking P—O bond in ATP gives 20 kcal/mole, it means that I need a reaction in the body that gives 20 kcal/mole when it breaks in order to use this energy to form ATP again and this is not actually found in the body. So we need a molecule with an intermediate energy value that suffices most reactions in the body by using 1molecule of ATP (when I need more I can use 2 or 3 ATPs).

There are also many reactions that give the same amount of energy that ATP produces so it can compensate ATP.





There is no place where ATP is stored in the body, energy is stored as bonds in (carbohydrates , lipids , …) …Why??
Because we consume a huge amount of ATP everyday that equals 90.6 moles / day

The amount of ATP needed per day :

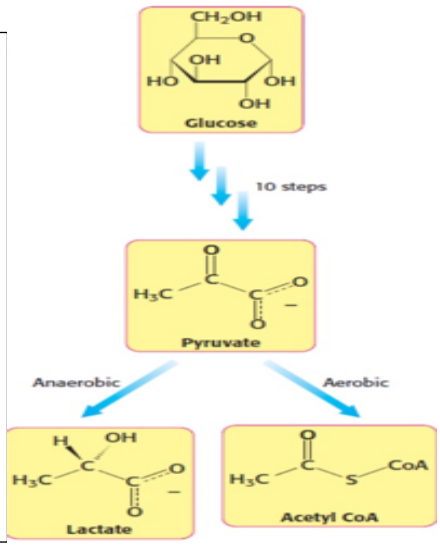
Tissue	ATP turnover (mole/day)
Brain	20.4
Heart	11.4
Kidney	17.4
Liver	21.6
Muscle	19.8
Total	90.6

If you know that M.W of ATP = 551 g/ mole
—>551(g/mole) * 90.6 (moles/ day) = 49,920 g
So , you need 49,920 g ATP (approximately 50,000 g ATP)!!!
That means if your body store energy as ATP molecules you'll add 50 Kg to your weight , also your size after eating will be increased and when you're hungry it'll decrease (unreality)

Pathways

Why do we need energy?
(1) the performance of mechanical work in muscle contraction and cellular movements. (2) the active transport of molecules and ions
(3) the synthesis of macromolecules and other biomolecules from simple precursors.

Sun is the main source of energy, it gives energy to plants (autotrophs) to produce their own food and then animals (heterotrophs)will feed on plants, then human can eat both of them to get his food.
*Cellular metabolism: the sum of the total biochemical activities of all cells (anabolism and catabolism).
Mainly for energy generation
*Metabolism consists of energy-yielding (exergonic) and energy-requiring (endergonic) reactions.



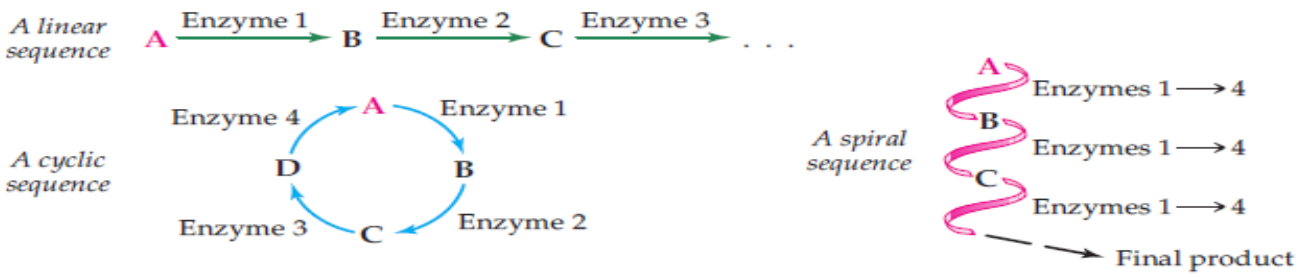
Pathways in our body

Pathways in the body are treated as single reactions with respect to thermodynamics and bioenergetics, So if I know the starting molecule and the end molecule, I can know if this pathway is exergonic or endergonic.

1.Linear pathway : every material converted to another material until achieve product , and each step is driven by different enzyme.

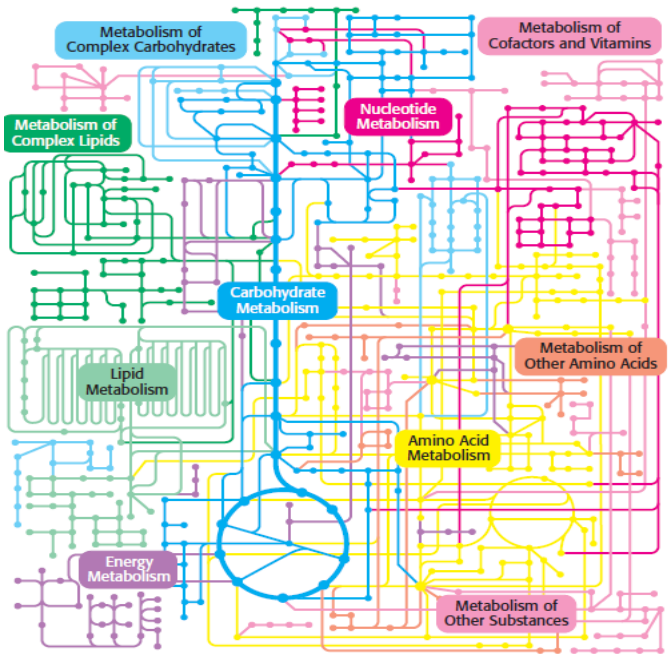
2.cyclic pathway : each step causes another one and by the end of pathway , first material is regenerated . Each step is catalysed by different enzymes .

3.spiral pathway : every material converted to another material until achieve product each step is catalysed by same set of enzymes(تشبه لينير بالنمط العام ، و لكن الاختلاف هو موضوع الانزيمات



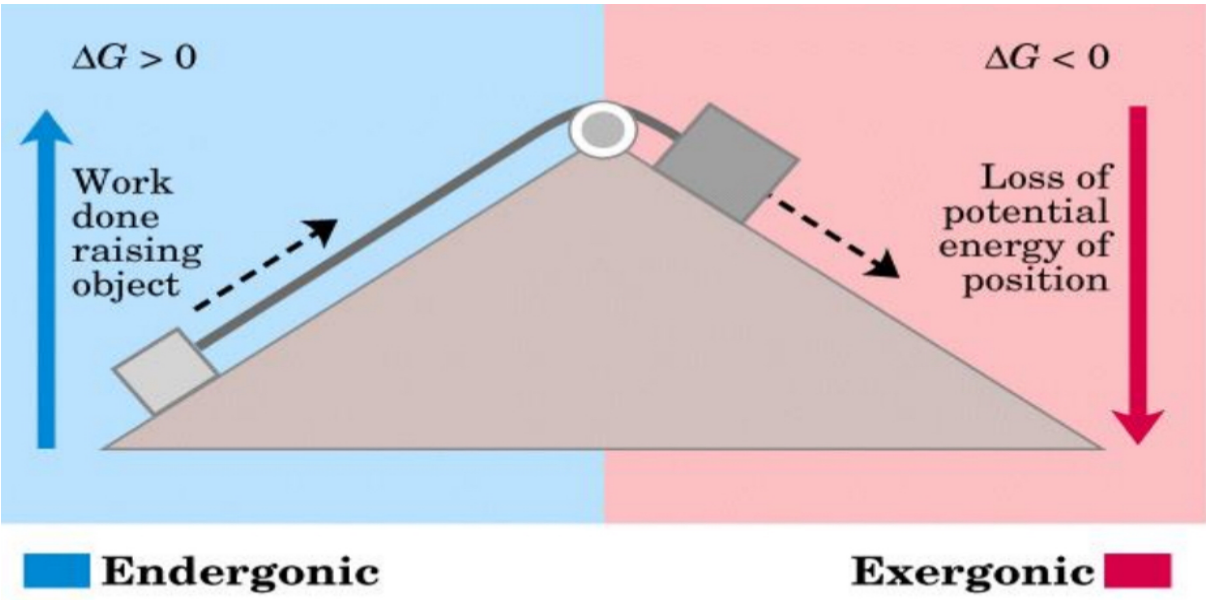
All pathways in our body need to understand each other to conserve energy from loosing , allosteric enzyme helps in this process… How?

Allosteric enzyme : enzyme that have multiple binding sites for different molecules from different pathways and areas ,that helps molecules to collaborate with each other and conserve energy .

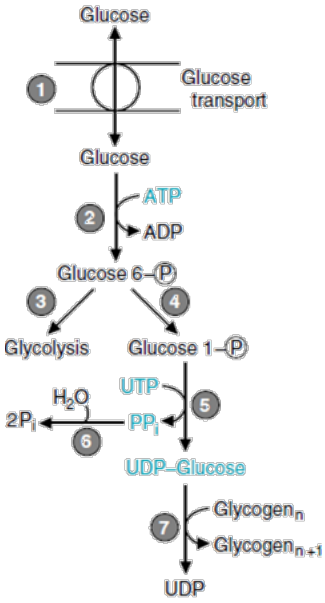


Exergonic pathways
Breaking down all molecules so, releasing energy
Complex structures —> simple structures
Proteins → amino acids
Starch → n glucose
glucose + O2→ CO2 + H2O
E.g
More specifically:
🌸Hydrolysis reactions
🌸Decarboxylation reactions (release of CO2)
pyruvate (C3) → acetyl-CoA(C2) +CO2
🌸Oxidation withO2

Endergonic pathways …. How do our cells get energy for it ?
By concept of Coupling : couple the reaction that consumed energy with the reaction that released energy (that not very smart) ,,,, complete reading to know the smartest concept on our body
Coupling a reaction consume energy to add certain material and other reaction release energy and that material, too.



Best example on that smartest concept is Phosphorylation transfer reaction



Step2: Glucose is always converted to glucose-6-phosphate that need energy = 3.3 kcal/mol
So , the ATP can supply that reaction with (material (phosphate) + energy needed), so here we will have some excess energy 4 kcal/mole (this excess energy can be used during the pathway or in other reactions).
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.

It's not just ATP that can be used, we can also use any other molecule that gives energy and part of this molecule is needed in the reaction. Activated Intermediates other than ATP; UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis

<u>Eg2 :</u>
Remmember always actyle coA provides energy because its connected with coenzyme A which has sulfhydril group, because it has modified cystine, breaking down of the bond between sulfur and carbon will release energy comparable to ATP or more
Now all of you know the acytle colin (by having the acetate and the colin —> the acetate from acytle coA), the energy needed for combining acetate+cholin is released from breaking the bond in acytle coA

وبس كده يمؤمن✋😉