



Medical Committee  
The University of Jordan

 SLIDE  SHEET



LECTURE#: 8

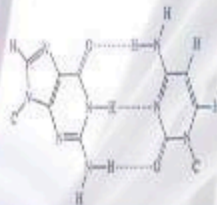


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Biochemistry



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# بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

## \*Quick revision!

-In the previous lecture, we talked about energy ,thermodynamics, the relationship between them, we defined the equilibrium constant, and the factors affecting equilibrium, and then we talked about metabolism, the anabolic and metabolic reactions and pathways and how they are interdependent and what connects them, and the last thing we talked about was energy production and ATP as the cell currency .

## \*New lecture :

The body uses many ways in order to make the unfavorable reactions occur :

- 1- Energy coupling
- 2- Considering the pathway as a one reaction ( reactions are additive to each other )
- 3- Producing high energy intermediates
- 4- Manipulating the conc. Of the reactants and the products to affect K at equilibrium , and changing  $\Delta G$  also.  
And each way will be discussed .

## Energy coupling concept

-We have 2 types of reactions in the body: **endergonic** & **exergonic**.

**Endergonic**: energy *requiring* reactions ( $\Delta G= +ve$  ) unfavorable

**Exergonic**: energy *releasing* reactions (  $\Delta G= -ve$ ) favorable

**Q: how does our body make unfavorable reactions(energy requiring reactions) occur?**

**How do our cells get energy to run unfavorable reactions ?**

**A:** there's more than one way as mentioned , and one of them is **energy coupling.**

**Coupling** : endergonic and exergonic reactions are coupled (joined) at the same time, and the energy from the exergonic reaction is used to run the endergonic one.

●**Note:** enzymes do not affect the favorability of the reaction , so enzymes are not the way used to make endergonic reactions occur .

**Illustration Example :**

**Mechanism of action of the see-saw:**

-At first, the lighter person will go up due to his small weight, and the one with heavier weight will stay down, and then, the heavy person will push against the ground and decreases his weight ( which is not constant like the mass ) and decreases the force of gravity on him too, so his weight will become less than the other one and thus he'll be lifted up and the other person will descend down.( we used force/energy on one side to make the other side moves)

And that's basically how coupling works on reactions.

-When endergonic is coupled with exergonic, the total sum of energy ( $\Delta G$ ) will be negative and the process will be exergonic, and by this way, unfavorable reactions can occur.

***Example .in Glycogenesis pathway:*** ( a reaction pathway that synthesizes glycogen from glucose)

\*Refer to the figure on the slides\*

-In the first step : glucose enter the cells via transporters , then in the next step it will be phosphorylated to be trapped in the cell ( so it can't get out )

- in step ②: glucose → glucose-6phosphate: the addition of phosphate to glucose is energetically expensive(needs energy: +3.3kcal/mole).

**Q: how to solve this problem?**

**A:** by coupling; you couple it at the same time with ATP hydrolysis. It needs +3.3kcal/mole, and we couple it with ATP hydrolysis( $\text{ATP} + \text{H}_2\text{O} \rightarrow \text{ADP} + \text{P}$ ) which results in -7.3kcal/mole. the total amount of energy will be:  $+3.3 - 7.3 \approx -4.0$  kcal/mole.

**The second way to run endergonic reaction is how the body looks to the pathways :**

The body considers the whole pathway as one reaction .(steps are additive to each other) .

if we have a pathway of 10 steps:

The 1<sup>st</sup> and 5<sup>th</sup> steps need energy (endergonic), And the other steps produce energy ( exergonic ) . However , the total sum of energy of the whole reaction is – ve (spontaneous, exergonic) because the body looked at the pathway as a single reaction and the steps were added , so the resultant was to be exergonic .

**Q. How does the body see this reaction?**

**A:** it sees the potential energy of the first material you started with ( first reactant ), and the potential energy in the final product, and if  $\Delta G = -ve$  then the whole pathway is spontaneous ,and energy was used from one step to run the other step.

-In other words: it sees the pathway as one unit.

And that what happens in fourth step of glycogenesis :

**Step ④: glucose-6phosphate → glucose-1phosphate:** this reaction requires +1.65kcal/mole, and because the body sees this pathway ( glycogenesis ) as one

unit, the addition of two reactions - step 2 and step 4 - (  $-4 + 1.65 = -2.35$  kcal/mol) will result in a -ve value of  $\Delta G$  .

-Which means we used the excess energy from the first reaction to run the subsequent one, and that's another way to run endergonic reactions.

So , let's revise ,What are the ways that are used in the body to run endergonic reactions ?

1)Energy coupling: again, it's to couple endergonic and exergonic reactions to have a sum of an exergonic reaction, usually occurs with ATP hydrolysis.( Step ② in glycogenesis)

2)the body looks at the pathway as one unit: we have two reactions, one exergonic and the next one is endergonic, the body uses the excess energy of the first reaction to run the subsequent one( the body saw step ② and ④ as one spontaneous reaction and added  $\Delta G$  , which make the result -ve ).

3)generation of high energy intermediates: **some** reactions have intermediates with high energy, and upon their degradation, they give energy to run subsequent reactions.

**Example : glycogenesis ...**

**Step ⑤: glucose-1phosphate+ UTP  $\rightarrow$  UDP-glucose (high energy intermediate )**

To add glucose to glycogen in step 7 , we need high energy,so we get this energy from degrading the high energy intermediate ( UDP-Glucose ) formed in step 5 ,and now we can add glucose to the glycogen polymer.

●Note: We used UTP here because it's related to carbohydrates' metabolism .

4)manipulation of the reactants and products' concentrations: How?

$$\Delta G = \Delta G^{o'} + RT \ln \left( \frac{[C][D]}{[A][B]} \right)$$

- we have the equilibrium constant ( K ) = conc. Of products(C,D)/ conc. of reactants(A,B) .

- ln ( natural logarithm ) here is a certain number.

**Consider**  $\Delta G^0 = +10$  for a certain reaction . so if the ratio = 1 , then ln = zero and  $\Delta G = \Delta G^0$

-If we *decrease* the products' concentrations(C,D)→ the ratio *decreases*→ ratio less than 1 → ln of anything < 1 = -ve → we'll end up with a more -ve value as we decrease the conc. Of the products until we overcome the positive  $\Delta G^0$  . and  $\Delta G$  for the whole reaction becomes negative .

-on the other hand ,If we *increase* the substrates' concentrations(A,B)→ ratio also *decreases*→ we'll result in a more -ve value for ratio's Ln

Let's go back and apply it on gylcogenesis:

**Step ④: glucose-6phosphate→ glucose-1phosphate**(endergonic : needs +1.65kcal/ mole) : if I decrease the amout of products by eliminating them once they're formed, their concentration will be less compared to reactants→ ratio will be less than 1 →ln of anything < 1 = -ve.

Assume that :

-Concentration of products(glucose-1Ⓢ) = 6kcal/mole

-Concentration of reactants(glucose-6Ⓢ) = 49kcal/mole

$$\Delta G = +1.65 \text{ kcal/mol}$$

If we *decrease* glucose-1Ⓢ from 6→3,  $\Delta G = - 0.4\text{kcal/mole}$

**Q:how is it done?**

**A:**In this step, at a certain time ,the value of  $\Delta G$  is +ve as the conc. of the product was high enough to make it positive . We can decrease  $\Delta G$  more and more by

decreasing the conc. of products  $\rightarrow$  more  $-ve$  value keeps adding to  $\Delta G^0$  ( as  $\ln$  will be more  $-ve$  )  $\rightarrow$  it overcomes the  $+ve$  value of  $\Delta G^0$   $\rightarrow$  reaction flips from endergonic to exergonic.

### Examples on High energy intermediates in pathways:

-ATP, UTP , CTP, and GTP:

All are the same energy wise , because all of them produce energy by breaking the phospho\_anhydride bond that links the three phosphates together , but their structure and the pathways that they are involved in are different , and that is important for regulation .

1)ATP: general energy molecule for most pathways.

2)UTP: more specific to the **carbohydrates** metabolism. (e.g. glycogenesis) , but to some extent ( i.e not all the carbohydrates metabolic pathways use UTP as a source of energy )

3)CTP: more specific to **lipid** metabolism.

3)GTP: more specific to **protein** metabolism.

-Other intermediates:

1)Acetyl-CoA: anything connected to Co-A will be a high energy intermediate.

*Q*:why?

*A*: due to Sulfur-Carbon bond, which is a high energy bond, and breaking off this bond will result in energy comparable to the energy produced from ATP ( it gives off  $-7.5$  kcal/mol .. and ATP gives  $-7.3$  kcal/ mol ).

●Note: many molecules in our body bind Co-A to form high energy intermediates, so as to produce energy similar to the one produced by ATP when we break the carbon – sulfur bond in the Acetyl coA complex ) .

2) **1,3-bisphosphoglycerate**: intermediate in glycolytic process , and the high energy bond is C-P bond

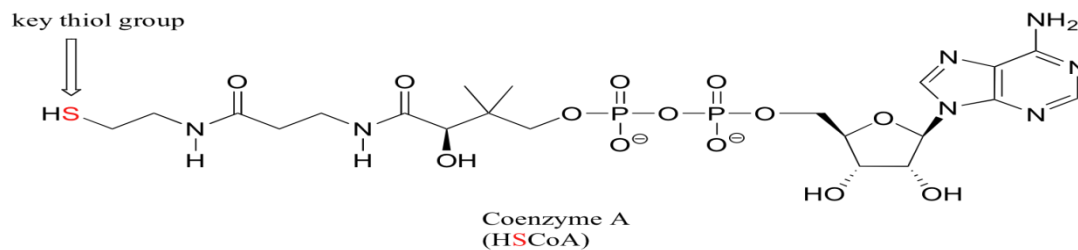
3) **creatine phosphate**. Which produce -10kcal/mol

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### Slide #21

\*mechanism of UDP intermediates formation is not required, all you have to know is that UTP provides UDP , which will form high energy intermediate with glucose in glycogenesis .

### Coenzyme A



-The structure of Coenzyme A :

it has **adenosine** ( adenine and ribose ), **pantothenic acid** : derivative of vitamin B5, and **cysteine**.

**Q: why does it have cysteine?**

**A:** because cysteine has a Sulfhydryl group that can attach to the Carbon of the acetyl group ,forming a high energy bond and a high energy intermediate .

**-Mechanism of Coenzyme A usage:**

like ATP, we can use CoenzymeA for *coupling*:

for example , in acetylcholine synthesis reaction , we have:

\*Acetate + Choline → acetylcholine ,  $\Delta G = +3$  kcal/mole (endergonic)



But the hydrolysis of acetylCo.A is exergonic

\*AcetylCoA +H<sub>2</sub>O→ ΔG= -7.5 kcal / mole (exergonic)

Thus, If the two reactions were coupled , the total amount of energy will be -4.5 kcal / mole(exergonic) ( +3-7.5= - 4.5 )

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**Q: is ATP a good long term energy-storage molecule?**

A: no , energy is stored in bonds of macromolecules ( like lipids , glycogen and proteins ), not in the form of ATP always , **why?**

-If we want to store energy as ATP, we have an **ATP turnover of ≈90mole/day** in the highly active tissues(brain, heart. Kidney, liver, and muscle ) which require 90moles of ATP per day)

**molecular weight x number of moles /day = the mass of ATP we need per day:**

551g/mole x 90.6moles/day = 49,920g ATP/day(the number in the slide #23 is wrong).

**≈50 kg/day of ATP is needed, and this is just for the active tissues , and we can't store such heavy weight in our bodies everyday then burn it! Thus , ATP is not a good long-term source of energy storage.**

**Q: can we store energy in ATP for a short term ( for minutes, hours)?**

A: yes.

### **Thermogenesis**

**Thermogenesis:** the process of producing heat within the body, in order to keep the temperature around 37 °

**Q: how to produce heat?**

A: the same way of making ATP. the energy that is not being used to make ATP will be used to make heat, in the same pathway of ATP generation .

**-Thermogenesis is sub-divided into two types:**

1) **Shivering thermogenesis**: the process of making heat through shivering of the muscles . It keeps your body at 37°when you feel cold suddenly .

-You're feeling cold → there will be a shivering process immediately in the muscles → producing ATP to move the muscles → as a byproduct , heat will be produced → body temperature will rise.

- A student asked : why we can't just hydrolyze ATP to produce heat ?

Because ATP hydrolysis produces energy that can be used to do work , not to be dissipated as heat .

2) **Non-shivering thermogenesis**: (adaptive thermogenesis):

-it is how to teach your body to adapt on the long term to the very cold environment.

*Example*: people who live in cold places spend more energy to keep their bodies' temperature around 37°, they *spend more energy on making heat on the expense of making ATP*, and in comparison with normal people, they'll need much more energy to make the same amount of ATP produced by people who live in normal conditions ,because most energy is spent on producing heat.

### **Oxidation-reduction reactions**

**Oxidation**: loss of e<sup>-</sup>/ loss of hydrogen/ gain of oxygen

**Reduction**: Gain of Hydrogen/ Gain of electrons/ Loss of Oxygen

**Q: why do we mention oxidation-reduction reactions in bioenergetics?**

A: because all reactions involve movement of electrons from one place to another ( reactions involve making and breaking bonds , and bonds are electrons ) , and all

what we've talked about ( $\Delta G$  of the reaction , favorability..etc) should apply to these reactions too.

**Q: the movement of  $e^-$  from a material to another is based on what?**

**A:** it is based on **reduction potential** , it's how much the material is willing to donate electrons and how much is capable to reduce other materials.

-When the electrons are moving ,they create a current that has a certain direction .  
( from negative to positive )

**Q:why do electrons move?**

**A:** due to the difference in potential between two points/molecules.

And that's how electricity is generated .. they move the electrons from point to another due to the potential difference between the two points (فرق الجهد الكهربائي)

**Direction of movement:** from a material that has a high ability to donate  $e^-$  → a material that has less ability to donate  $e^-$

❖ **Some terms :**

**reduction potential** : measures the ability of a material to *donate* electrons.

**Oxidation potential** : measures the ability of a material to *accept* electrons.

Oxidation -reduction reactions are catalyzed by **oxidoreductases**.

**Note :**

When we say " potential " or "E" , we mean the reduction potential unless it is specified .

Potential is measured in Volts or milivolts.

**Q: can we tell if the reaction is spontaneous or not depending on movement of  $e^-$ ?**

**A:** yes, based on potential. What applies on bioenergetics applies on redox reactions. **How?**

-You have two materials(**X,Y**), and depending on their willingness/ability to donate electrons you can predict whether the movement of electrons will be **X→Y** or **Y→X**, so you can predict the direction of the reaction .

**Do you remember what is ΔG ?**

**ΔG** = the potential difference between reactants and products.

However:

**ΔE** = the difference in the ability to donate e<sup>-</sup> between two materials.

$$\Delta E = E_A - E_D$$

**\*E** : it is the reduction potential of any material ( expresses willingness to donate e<sup>-</sup>

-Each material of the 2 materials in the redox RxN has an E value.

**\*ΔE** : final destination ( acceptor ) – starting point(donor E<sub>D</sub>)

: E of the electron Acceptor – E of the electron donor

-And when I can tell in which direction the reaction is going( according to the direction of movement of electrons), I can know whether it's favorable or not, and spontaneous or not. ( I can know ΔG from ΔE)

**Q:** what's the mathematical connection between ΔG and ΔE ?

**A:** **ΔG° = -nfΔE°**

Where *n*: number of electrons ( always +ve )

*F*: Faraday's constant ( always +ve )

ΔE: is the reduction potential difference between the acceptor and the donor .

-From the equation , ,  $\Delta E$  is the only determinant of  $\Delta G$  here , based on the difference in the ability to donate electrons between two materials. ( i.e. the sign of  $\Delta E$  determines the sign of  $\Delta G$  )

-if you were given two materials with their abilities to donate  $e^-$  ( reduction potentials of them ), you should know how to tell if the reaction is spontaneous or not , as well as its direction.

- ❖ The **more -ve** the value of  $E \rightarrow$  the **more** the ability to donate  $e^-$
- ❖ The **more +ve** or the **less -ve** the value of  $E \rightarrow$  the **lower** the ability to donate  $e^-$

**Example:**

we ingest food  $\rightarrow$  it will be degraded and finally produce AcetylCoA  $\rightarrow$  goes to Krebs cycle  $\rightarrow$  make  $FADH_2$  and  $NADH$  ( electron carries)  $\rightarrow$  they go to electron transport chain (complex1  $\rightarrow$  complex 2  $\rightarrow$  complex 3  $\rightarrow$  complex 4  $\rightarrow$  reach oxygen and reduce it into water.)

**Q: what is the final acceptor of all electrons?**

A: oxygen, it has the highest ability to accept  $e^-$ , the lowest ability to donate  $e^-$ , and the highest +ve E-value, and it will be then reduced to water ( $O_2 \rightarrow H_2O$ )

- the oxygen is the best acceptor of electrons .

-the reaction between  $NADH$  and oxygen is spontaneous( as  $\Delta G$  is negative )

-direction of electron movement :  $NADH \rightarrow$  oxygen because  $NADH$  has a higher -ve value of reduction potential  $E$  . And same story applies to  $FADH_2$

**Q: how to calculate  $\Delta G$  of the reaction between  $NADH$  or  $FADH_2$  and  $O_2$ ?**

A: through calculating  $\Delta E$  ,by measuring the difference of reduction potential between oxygen and NADH or oxygen and  $FADH_2$ , then calculate "n " ( which equals 2 electrons ), and faraday's constant and apply them to this equation.

$$\Delta G^\circ = -nf\Delta E^\circ$$

$$\Delta G = - 2 * f * \Delta E$$

NADH generates an energy difference ( $\Delta G$  )of -53kcal/mole

FADH<sub>2</sub> generates an energy difference ( $\Delta G$  ) of  $\approx$  -41kcal/mole

So energy from NADH while moving  $e^-$  is larger than energy from  $FADH_2$

Q. why there is a -ve sign in the equation ?

A: if we want to predict the spontaneous direction of the reaction , the RxN will proceed spontaneously in the direction in which the electrons move from the electron donor to the acceptor , and as we know that the acceptor has a less negative or more positive E , and the Donor have more negative E , and as

$\Delta E = E_A - E_D$  , so if the reaction is spontaneous  $\Delta E$  must be positive , that's why we put the -ve sing in the equation , as  $\Delta G$  is negative when the reaction is spontaneous .

Q: to have a -ve  $\Delta G$ , what should be the sign of  $\Delta E$ ? A: +ve

Quick revision on the differences between NADH and  $FADH_2$  : ( both are coenzymes)

	NAD <sup>+</sup>	FAD
Name	nicotinamide adenine dinuclotide	flavin adenine dinuclotide
No. of $e^-$ accepted	$2e^-$	$2e^-$
Form of $e^-$ accepted	hydride ion $H^-$	2 Hydrogen atoms sequentially
Generation of radicals	no	yes

<b>Found free in the cells</b>	yes	No, only bound to proteins ( because it can form free radicals )
<b><math>\Delta G</math> when transporting electrons to <math>O_2</math></b>	-53 kcal /mole	-41 kcal/ mole

●**Note:** 1-  $FADH_2$  : accepts  $e^-$  in a sequential manner

2-  $NAD^+$  accept a hydride ion with two electrons that will attach to the nicotinamide ring .

3-  $FAD$  accepts 2 hydrogen atoms that will attach to the nitrogens of the flavin rings.

### NAD and NADP :

They are not different energy wise , but differ in structure and the pathway they participate in .

### What is the difference between $NAD^+$ and $NADP^+$ structurally ?

\*They differ in the attachment to carbon 2 of the ribose sugar of the adenosine nucleotide

-If it is attached a  $H \rightarrow NAD^+$  ( for energy production)

-If it is attached to phosphate  $\rightarrow NADP^+$  ( for fatty acid degradation and synthesis)

### Q: What's the difference between $NAD^+$ and $NADP^+$ functionally ?

A:-function wise and energy wise : no difference, the function is to carry electrons.

- they differ in pathway they are used in : each one specializes in different pathways:

$NAD$  is used in energy producing pathways .

$NADP$  is used as an electron carrier in lipid synthesis and degradation .

This specialization offers you a better regulation.

### Caloric values of fuels :

≈ 9.0kcal/g of fat

≈ 4.0kcal/g from proteins or carbohydrates.

**Q: what determines if a substance is beneficial or not, and how much energy it will give upon degradation ?**

A: - 1- types of atoms it contains.

2- the types of bonds in this material( the more hydrocarbon content , the more useful the substance and more energy can be produced )

3- presence of enzymes that can degrade these materials( ex: cellulose in wood which contains high energy can't be used by your body as a source of energy , because we don't have the enzyme cellulase that can break it down )

How could we know that cellulose has high content of energy ?

When we burn wood , the energy produced is very high .

The end !

“may the odds ever be in your favor”

..

shout-outs to Lojain Rahahleh !





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