فريق طوفان الأقصى

METABOLISM

Modifide N.

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- REMEMBER Many biochemical rxns in metabolism have a negative delta G which means the activity will be SPONTANUOUS (moves forward normally)
- Other biochemical rxns have a positive delta G which needs an input of energy

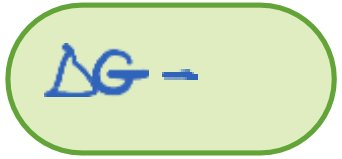
How ATP hydrolysis provide energy to make unfavorable reactions to occur

For any polymer synthesis: **unfavorable**

ATP is hydrolyzed as:

ATP→AMP +PPi **HIGHLY FAVORABLE**

PPi→2pi ≈



ΔG`0 for both rxs <<0

Two tricks are done here:

2 favorable reaction to drive unfavorable polymer synthesis

keeping ppi concentration very low

- It may use ATP/GTP/UTP for energy

The ppi is broken into 2 phostphate to keep its concentration low

- The complement in this slide: the 2 ATP hydrolysis steps are done **simultaneously** SINCE the standard delta G for these rxns is high on the negative (simultaneous) side leading to biosynthesis

Glucose Trapping by Phosphorylation:

ATP → ADP + Pi $\Delta G`0 = -7.5$ Kcal/mol

Glucose + Pi → glucose-p $\Delta G`0 = 3.3$ Kcal/mol , Equilibrium is toward glucose

+ Pi - no trapping.

If you couple these two reactions:

Glucose + ATP → glucose-p + ADP $\Delta G`0 = -4.2$ Kcal/mol

$\Delta G = \Delta G`0$(glucose → glucose-p) + $\Delta G`0$(ATP → ADP) + $RT\ln \frac{[\text{glucose-p}][\text{ADP}]}{[\text{glucose}][\text{ATP}]}$

if this is <4.2, favorable

+3.3 + -7.5= -4.2 >-4.2

- Glucose trapping is done by ATP and glucose coupling keeping the glucose inside the cell (if the cell is not phosphorylated the glucose will be stored inside the liver)
- Glucose phosphorylation needs energy in order to happen (the delta G is +) so it is coupled with ATP that releases energy

How much energy needed to synthesize ATP?

ADP +Pi → ATP ΔG`0 =+7.5 Kcal/mol

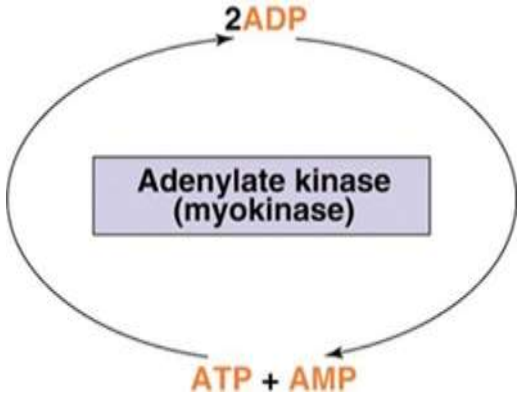
ΔG= 7.5 + RT lin [ATP]/[ADP] [Pi]

how much energy needed to synthesize ATP? Depends on this ratio and the ratio to support other reactions

ΔG for synthesis= RT lin [ATP]/[ADP] or ATP/AMP, because 2ADP→AMP +Pi

This reaction could occur if coupled with other **metabolic intermediates** to overcome this +7.5kcal/mol.

This is why we don't store energy as ATP to get energy from it

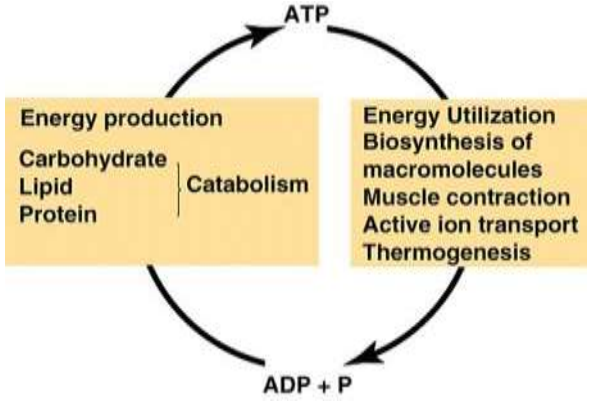


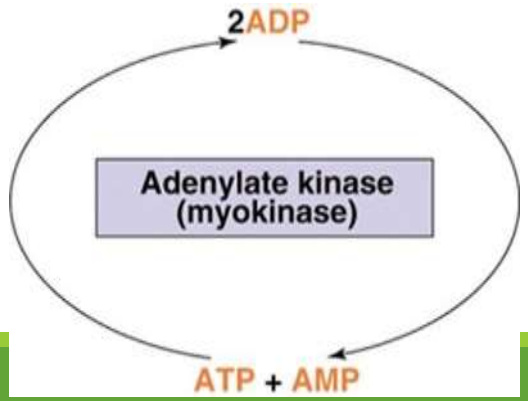
- The concept ENERGY CHARGE: **ATP/AMP** or ATP/ADP that controls the metabolic pathway that produces ATP
- If ATP/AMP or NADH/NAD is high the metabolic pathway that releases energy is switched off (inhibited)since its not needed
- If the ratio is high then the metabolic pathways that need ATP consumption (molecule synthesis) will be stimulated
- **ATP/AMP is more accurate since 2 molecules of ADP = ATP+ AMP**

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

ATP isnt a stable molecule in the physiological conditions of the body so it cannot be stored for energy later so the body has to depend on constantly oxidizing food for energy release which is a favorable rxn (negative delta g)





If a cell cant do glycoses for eg the concentrations of the other reactants will change as well

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

Biochemical (metabolic) pathways

- Are <u>interdependent</u>
- Are subjected to thermodynamics laws +ΔG (spontaneously)
- <u>Allosteric enzymes</u> are the predominant regulators
- Biosynthetic & degradative pathways are <u>almost always distinct</u> (regulation)
- Metabolic pathways are <u>linear, cyclic or spiral</u>

Some are done in cytoplasm others in the mitochondria

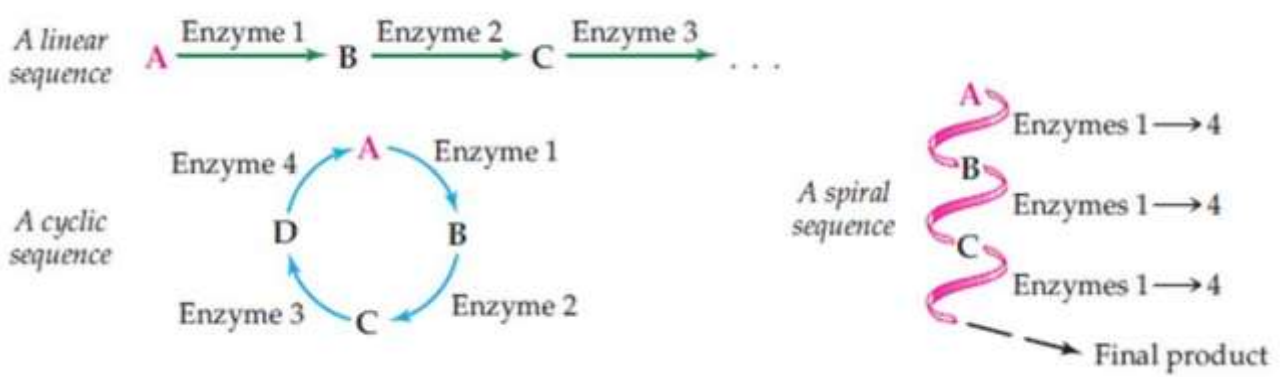
EG: glycolisis/ oxidative phosphorylation/ cac/ beta oxidation of fatty acids/ fermentation/ amino acid oxidation and biosynthesis / glucogenisis

Metabolites in a pathway can regulate for another
Products of one pathway can provide a substrate for another pathway

Eg : pyruvate becomes acetyl coa this product is a substrate for fatty acid synthesis

Positive/negative effect
Increase decrease cooperativity
Effect on shape

THIS IS VERY IMPORTANT since its not useful to synthesize and oxidize glucose at the same time in the same place(energy waste) so the synthetic and catabolism compartments are separated.



How do our cells get energy for unfavorable biochemical work?

Coupling intermediate in metabolic pathways

By coupling 2 reactions , one is favorable and the other is unfavorable

COUPLING: coupling unfavorable RX with favorable one

How do our cells get energy for unfavorable biochemical work?

Coupling favorable rxn with unfavorable makes the delta G lower, then making the whole rxn favorable

A→C (Unfavorable), **Delta G > 0**

B→D(Favorable) **Delta G < 0**

coupled reactions, A +B →C +D

→ Multiplication

$$\Delta G = \Delta G`0(\text{A to C}) + \Delta G`0(\text{B to D}) + RT \ln \frac{[C][D]}{[A][B]}$$

Make: ΔG`0(A to C) +ΔG`0(B to D) favorable, but still C/A and D/B concentrations are important.

Importance of finding an intermediate in metabolic pathways

for the reaction A→ B ΔG`0 > 0, the equilibrium is far to the A, so how could you convert A to B?

ΔG _~ [B]/[A] .

Cells can do that by lowring ΔG by keeping [B] very low

ΔG= ΔG`0 + RT lin [B]/[A] , then ΔG<0

- ↑+ve ↑-ve

By minimizing the concentration of b

- How to keep B very low? Build a pathway to consume B and keep it very low.
- A → B → C for A → B ΔG`0 > 0, for B → C ΔG`0 <<< 0,
- this means that the unfavorable equilibrium from A → B is overcome by the favorable equilibrium from B → C, B → C will pull A → B .
- This strategy of finding intermediates like B is useful in metabolism

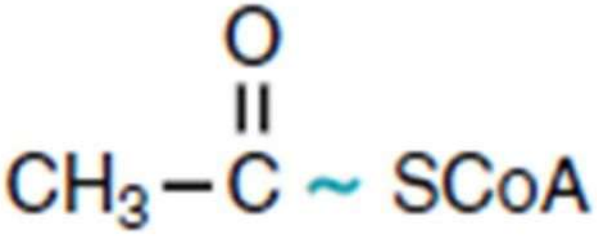
This will work if ΔG<0 for A → C

How do the cell minimize the b concentration? Follow me ..

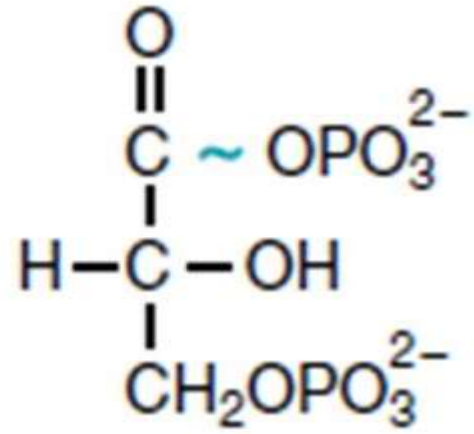
By building a reaction from a->b , then b->c , this will minimize the concentration of b..
And this rxn between b and c has highly negative charge of delta G
By this A will convert to B , and B will convert to C .. Thus B will be less

How do our cells get energy for unfavorable biochemical work?

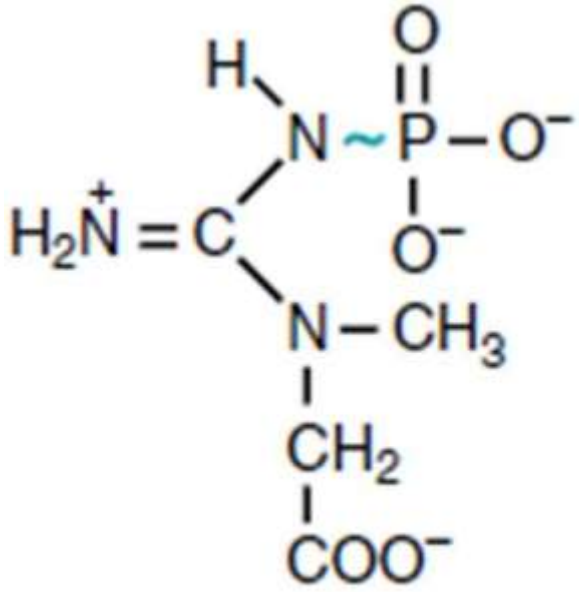
Activated .III Intermediates other than ATP; UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis



Acetyl CoA



1,3–Bisphosphoglycerate



Creatine phosphate

ACTIVE INTERMEDIATES

Our cells must always keep doing metabolism to provide ATP constantly and maintain the ATP/ADP ratio useful to drive other metabolic reactions

When ATP/ADP ratio suddenly drops down, the solution is to couple it with another x & y reactant product to keep the ATP/ADP ratio high

A buffer system is available to provide more ATP (Creatin/creatin-p system).

when ATP shut off in muscle

Creatin-p →Creatin +Pi ΔG`0 =-10 Kcal/mol

ATP→ADP+ Pi ΔG`0 -7.5 Kcal/mol

ATP +Creatin → Creatin-P + ADP ΔG`0 =+2.5 Kcal/mol , equilip←

ΔG= 2.5 + RT lin [Creatin-P] [ADP]/ [Creatin][ATP]

if the term <-2.5, Creatin-P will be formed, if the term >-2.5, ATP will be formed

If ATP/ADP ↑(high ATP) then Creatin-P will form-left to right direction

If ATP is low, then , ATP will be formed- right to left direction

When our tissues lack ATP, A buffer-like system occurs , which can convert a molecule (high energy molecule)(creatin) To ATP or the opposite, depending on who is more available.. But how ?

When creatin-p is hyrolyed, the rxn is done favorably and produces a P group

When coupling the rxn of hydrlosis the ATP whith rxn of hydrolysis of ATP , the delta G is +2.5 kcal which is unfavorable as shown below :

ATP +Creatin → Creatin-P + ADP ΔG`0 =+2.5 Kcal/mol , equilip←

So it will move in the opposite direction toward ATP and creatin .. Producing ATP

In the other hand, when there is a lot of ATP , the rxn will go towards the right producing more creatin-p and ADP

THERMOGENESIS

- **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**
- **Non-shivering thermogenesis (ATP production efficiency)**

As we know, the favorable reactions produce heat .. So when we exposed to sudden cold there is two types of thermogenesis to adapt this exposure:
Shivering and non shivering thermogenesis..
The heat produced from shivering is effective at counteracting the heat loss from cold exposure, but shivering is metabolically inefficient and uncomfortable. Ideally, nonshivering thermogenesis is the most effective way to adapt to a cold environment.

Oxidation-Reduction reactions (Redox)

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

Redox releases energy in the cell

- ***Reduction:***
  - ✓ **Gain of Hydrogen**
  - ✓ **Gain of electron**
  - ✓ **Loss of Oxygen**

Reduction potential and direction of the reaction

Redox potential- ΔEo(volts) : The energy of the transferred electrons under standard biological conditions .

A strong reducing agent has a negative redox potential,

A strong oxidizing agent has a positive redox potential

A positive redox potential means that a substance has a higher affinity for electrons than does a substance with a less positive redox potential

Standard oxidation-reduction potentials are by convention written as reductions:

OAA+2H+ + 2e→malate Eo`=-0.17 v……(1)

NAD + 2H+ +2e→NADH + H+ Eo`=-0.32 v……(2)

So Oxaloacetate is reduced to produce malate and NADH is reduced to produce NADH

Reaction 1 has a more positive redox potential and will go as written as reduction. Reaction 2 will be driven in reverse- as an oxidation

OAA+2H+ + 2e→malate Eo`=-0.17 v……1

NADH + H+ → NAD + 2H+ +2e Eo`=+0.32 v……2

These are two halves of the oxaloacetate oxidation reaction which is exist in Krebs cycle, in order to calculate delta G note then delta G we must convert the reaction to reduction reaction .

Sum:

OAA+NADH+H+→ Malate+ NAD $\Delta Eo`=+0.15$ v

A B C D

$\Delta Go`= nF\Delta E`o$ =-2 x 23060 x 0.15=-6918 cal/mol

$\Delta G = \Delta Go + 1360 \log [C][D]/[A][B]$

$\Delta G = -6918 + 1360 \log [1000][1000]/[1][1]$

=+1242 cal/mol

Thus, under these conditions the favorable rex would be:

Malate+NAD→OAA+NADH+H

From delta G we can know if the reaction is favorable or not(and the direction of the reaction), we can calculate delta G from delta G note and we can get delta g note from delta Eo'

$\Delta Go`= nF\Delta E`o$, n = number of electrons that are transferred, F = faraday's number

And if the delta G is positive, that means that the reaction is not favorable and happens in the opposite direction,

In the example the reaction occurs from right to left producing OAA and NADH

The reduction potential of a half reaction in which the substances are present at a concentrations other than 1M may be calculated from the Nerst equation:

$E=Eo` +2.303\ RT/nF\ \log [oxidized]/[reduced\ form]$.

Calculation of ΔGº from ΔEº

$\Delta G^\circ = - n f \Delta E^\circ$

- F = Farady constant = 23.06 kcal/*Volt*

Calculate ΔGº of the following reaction

NAD +H+ 2e→NADH E`o=-0.32

$1/2O_2$ +2H +2e→ H_2O E`o=+0.82

NADH → NAD+ + $2e^-$ E° = +0.32 V

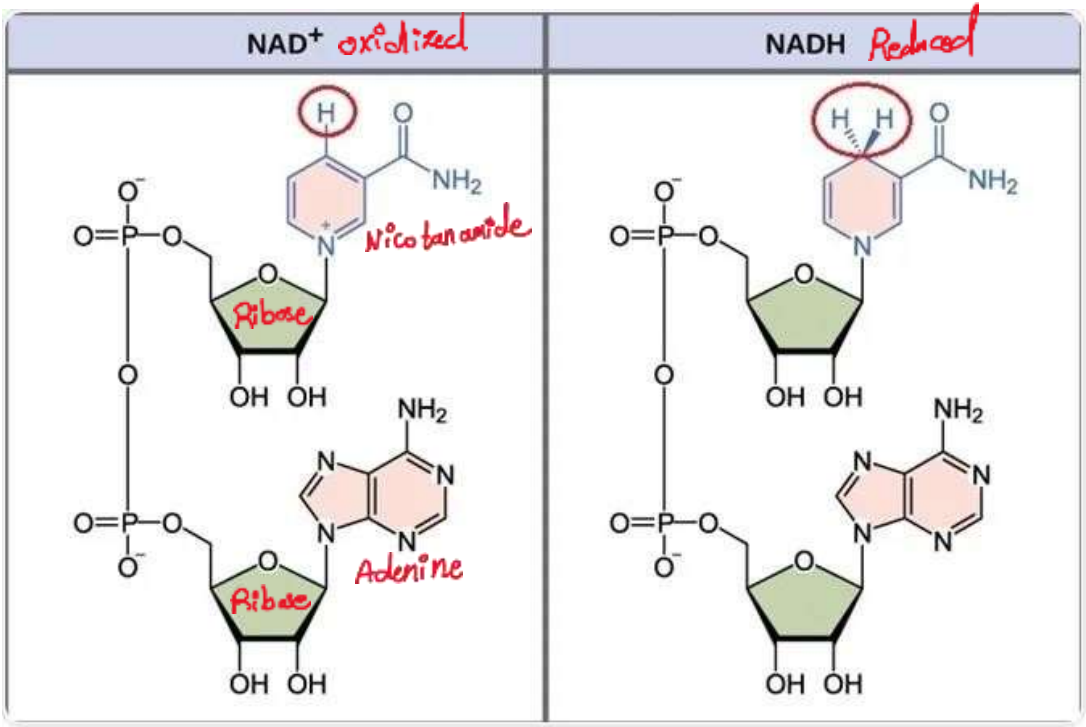
$1/2O_2$ +2H +2e→ H_2O E`o=+0.82

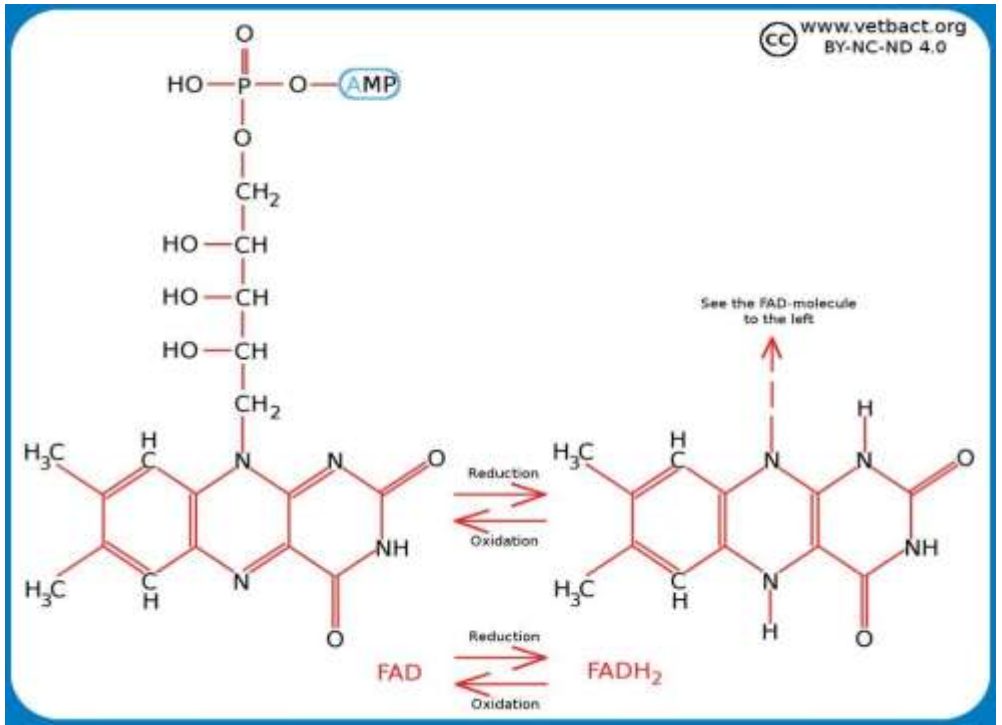
Sum: $1/2O_2$ + NADH →H2O+NAD E`o=+1.14

ΔGº = - 52.6 kcal/mol

Reducing powers

Those are co-enzymes that involve in redox reactions and act as a electron donor and acceptor
In oxidative phosphorylation.. ATP is synthesized by because of release of energy by the donating of electrons and protons.. This release phosphorylate ADP and becomes ATP





V2: slide no. 9

(ATP isnt a stable molecule in the physiological conditions of the body so it cannot be stored for energy later so the body has to depend on constantly oxidizing food for energy release which is a favorable rxn (negative delta g))

Instead of (The ratio needs to be negative to be out of the physiological concentrations so ATP isnt stable(its not a long term energy storage) so its better to oxidize food such as glycogen/ glucose/ fatty acid, and produce ATP that way instead)

(Rephrasing)

V3: slide 10 we delete glycogenosis

slide 20 NADH is reduced instead of produced