BIOENERGETICS

- Dr. NABIL Bashir
- Metabolism ,Ist semester, 2023

Energy & why do we need it?

➢ **Definition: Capacity to perform work**

➢ **What for? Mechanical, Active transport, Biosynthesis, Heat**

➢ **Types of energy:**

 ✓ **1- Kinetic: Energy in the process of doing work or Energy of motion**

 ✓ **2- Potential: Energy content stored in a matter**

➢ **Whether a reaction occurs or not!**

➢ **metabolism vs. energy**

The major purpose of metabolism

➢ **Metabolism: Sum of all biochemical reactions in living organisms**

➢ **Mainly for energy generation**

➢ **Other purposes:**

- Synthesis of building blocks
- Synthesis of macromolecules
- Degradation of biomolecules

➢ **Bioenergetics: Energy transformations in the cell**

The different free energy terms

➢ ΔG = the free energy difference of a system at any condition

➢ ΔG^o = the free energy difference of a system at standard conditions ($25C^o$ & 1 atmospheric pressure, 1M concentration of reactants & products, pH = 7)

Gibbs free energy, ΔG

$$A \rightleftharpoons B$$
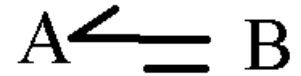
- this equilibrium is not determined by enzyme but determined by thermodynamics.
- more equilibrium to the A, you will not change the equilibrium by adding any amount of enzyme to the reaction.
- What determine the equilibrium between them? Gibbs free energy.
- ΔG which is related to equilibrium constant, can be used to determine if the reaction is favorable or not:
- if ΔG< 0, reaction is spontaneous,
- if ΔG> 0, reaction is not spontaneous
- if ΔG= 0, reaction is at equilibrium

Standard free energy change ΔG^o

- Concentrations of reactants and products = 1 mole/L

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

- $\Delta G = \Delta G^o + RT \; 2.3 \log \dfrac{[\text{Products}]}{[\text{Reactants}]}$

Standard free energy change (ΔG°) and equilibrium constant Keq

K_{eq} is obtained by dividing [products] by [reactants] when the reaction reaches equilibrium

$$K_{eq} = \frac{[Products]}{[Reactants]}$$

- At equilibrium

$$0 = \Delta G° + RT \ln K_{eq}$$

$$\Delta G° = - RT \ln K_{eq}$$

ΔG & Keq

K'_{eq}	$\Delta G^{o'}$ kJ/mol	Starting with 1 M reactants & products, the reaction:
10^4	- 23	proceeds forward (spontaneous)
10^2	- 11	proceeds forward (spontaneous)
$10^0 = 1$	0	is at **equilibrium**
10^{-2}	+ 11	reverses to form "reactants"
10^{-4}	+ 23	reverses to form "reactants"

For a reaction $A + B \longleftrightarrow C + D$

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

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

$$0 = \Delta G^{o'} + RT \ln \left(\frac{[C] [D]}{[A] [B]} \right)$$

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

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

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

ΔG° and K$_{eq}$

1	0

How much change in delta G
compared to changes in Keq

If K$_{eq}$ = 1,   then ΔG^0 = 0

If Keq > 1,   then ΔG^0 < 0

If Keq < 1,   then ΔG^0 > 0

Gibbs free energy conditions & ΔG`0

- ΔG depends on conditions: equilibrium & concentration
- A←→B at equilibrium, [A] and [B] are not changing. ΔG=0.
- If we add more A, leads to production of B,
- ΔG A-B <0, until you establish the equilibrium.
- If we add more B, leads to production of A, ΔG B-A <0, until you establish the equilibrium, or ΔG A-B >0.
- Does not matter how much A or B added, the equilibrium depends on the ratio of [B]/[A] not the absolute concentration of each species.

Direction of a reaction

- If ΔG $_{A-B}$ =0, ΔG`0 = -RT lin [B]/[A] , so you can calculate the equilibrium constant if you know the ratio or the concentrations of A and B.

- A➜ B

- If ΔG`0 < 0, then B is favored over A at equilibrium

- If ΔG`0 > 0, then A is favored over B at equilibrium

- So ΔG`0 is the convenient way to determine the direction of the reaction

- ΔG depends on conditions: ΔG`0 and the concentration of B &A

- If ΔG <0, then, the RX is spontaneous, energy is released,

- If ΔG >0, then, there is no RX without energy input

Stages of catabolism

- ➢ **1st stage:** Large molecules in food are broken down into smaller units. Preparation stage without capture of energy.
  - • **Proteins -> amino acids,**
  - • **Polysaccharides -> monosaccharides (glucose, ...)**
  - • **Fats -> glycerol, fatty acids.**

- ➢ **2nd stage:** Molecules are degraded to simple units that play a central role in metabolism. Most of them are converted into the acetyl unit of acetyl CoA. Some ATP is generated in this anaerobic stage, but amount is small compared with 3rd stage.

- ➢ **3rd stage:** ATP is produced from the complete oxidation of the acetyl unit of acetyl CoA. Acetyl CoA brings acetyl units into the citric acid cycle, where they are completely oxidized to CO_2. Four pairs of electrons are transferred (three to NAD^+ and one to FAD) for each acetyl group that is oxidized. Then, a proton gradient is generated as electrons flow from the reduced forms of these carriers to O_2, and this gradient is used to synthesize ATP.
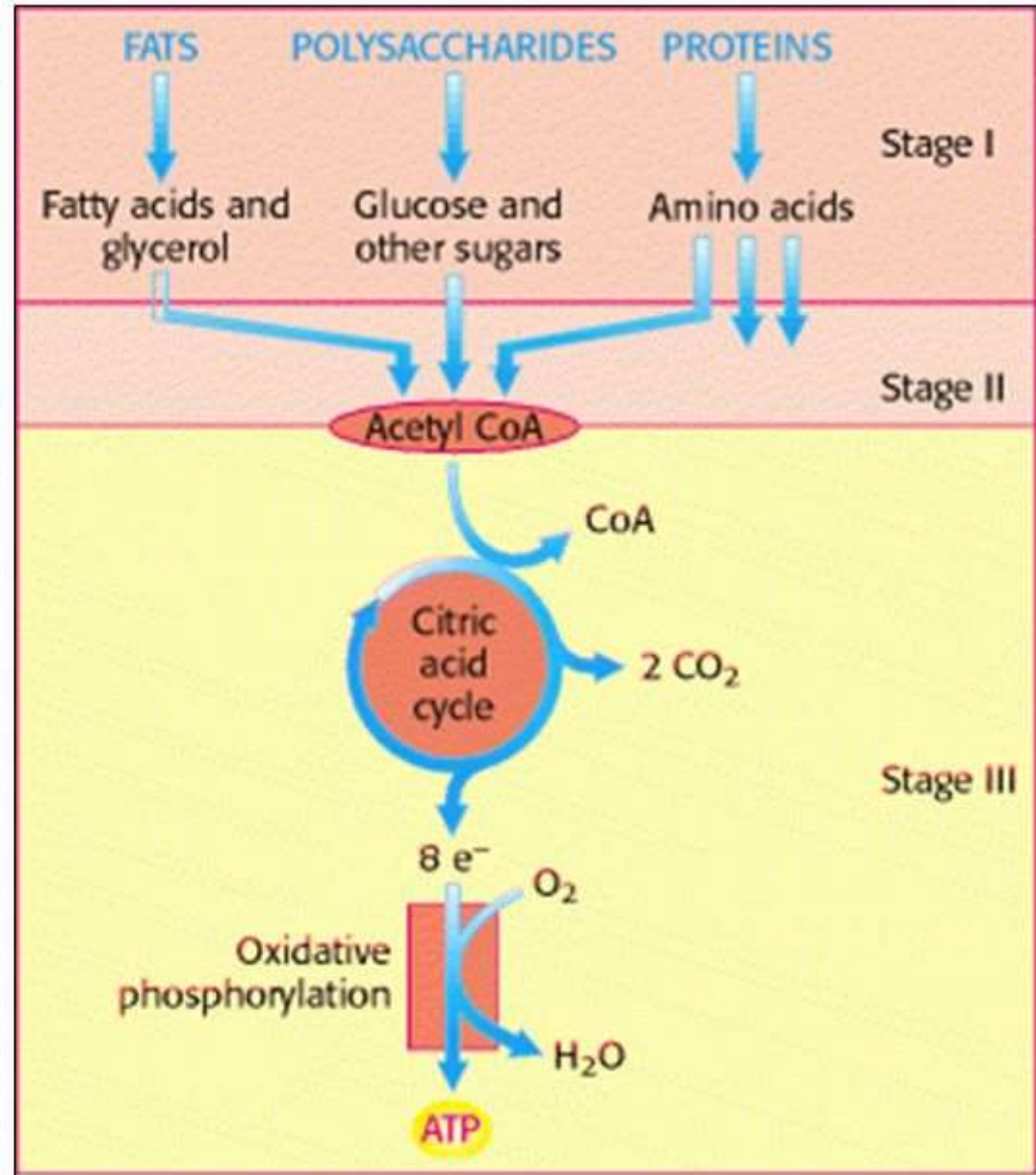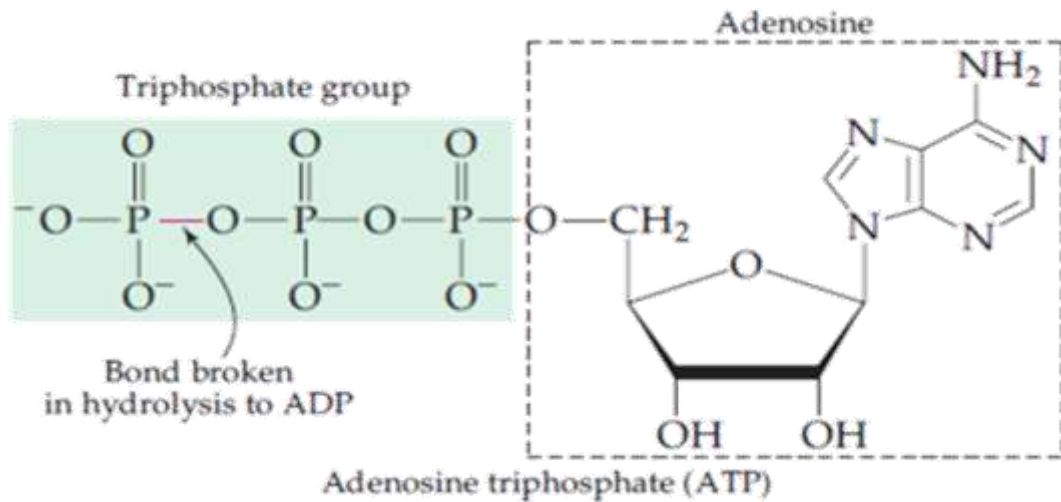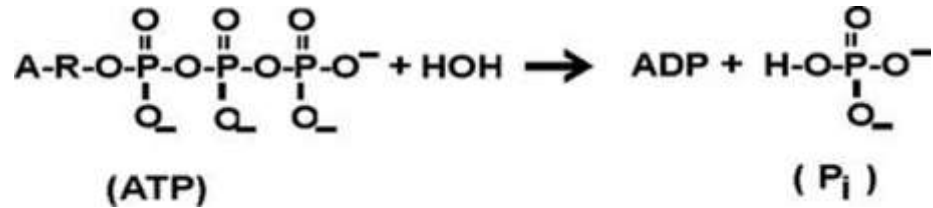
ATP is the energy currency of the cell
What is a high energy molecule?
Why ATP?
Has an intermediate energy value, so can be coupled

A-R-O-P-O-P-O-P-O⁻ + HOH → ADP + H-O-P-O⁻

(ATP)   (Pᵢ)

Adenosine

Triphosphate group

Bond broken
in hydrolysis to ADP

Adenosine triphosphate (ATP)

Compound +H_2O	Product + phosphate	$\Delta G°$
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

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**

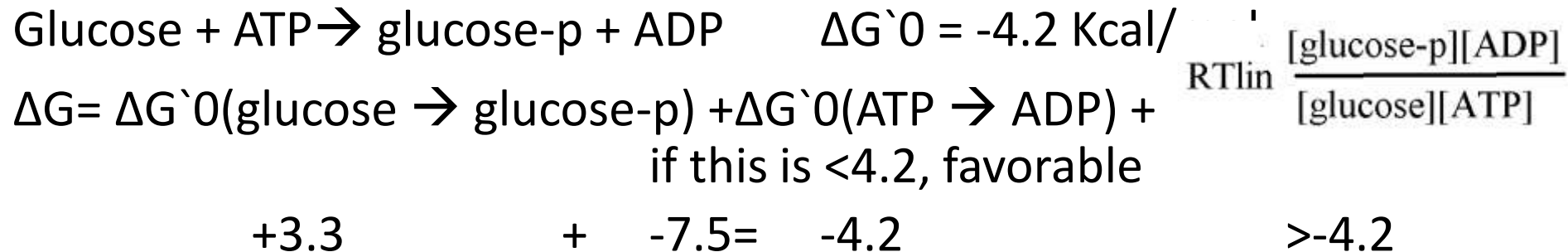PPi→2pi   ≈   ΔG`0 for both rxs <<0

Two tricks are done here:

- 2 favorable reaction to drive unfavorable polymer synthesis

- keeping ppi concentration very low

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/

ΔG= $\Delta G`0$(glucose → glucose-p) +$\Delta G`0$(ATP → ADP) + $RT \ln \dfrac{[glucose\text{-}p][ADP]}{[glucose][ATP]}$
                                       if this is <4.2, favorable

          +3.3   +   -7.5=   -4.2   >-4.2

How much energy needed to synthesize ATP?

- ADP +Pi → ATP $\quad\quad$ 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

2ADP

Adenylate kinase
(myokinase)

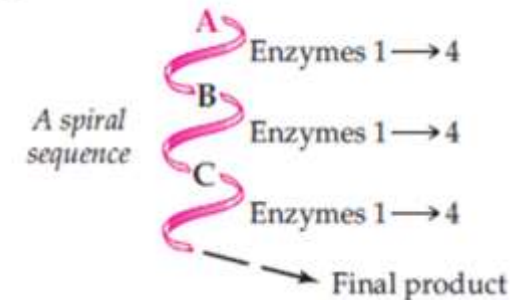ATP + AMP
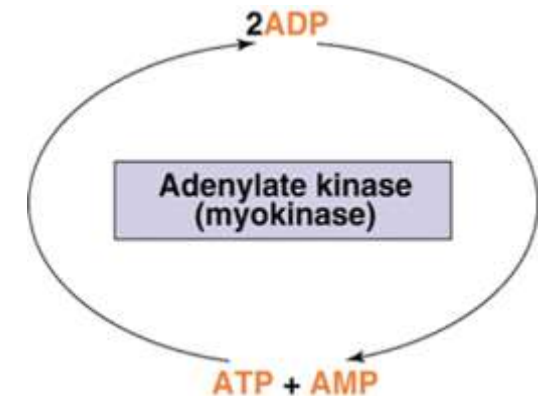
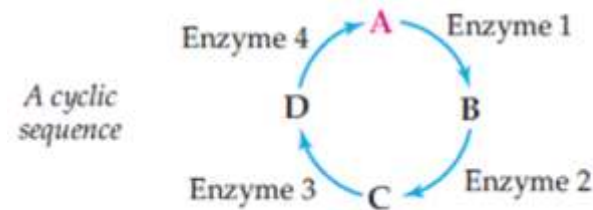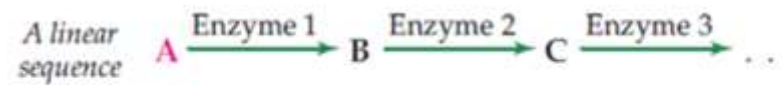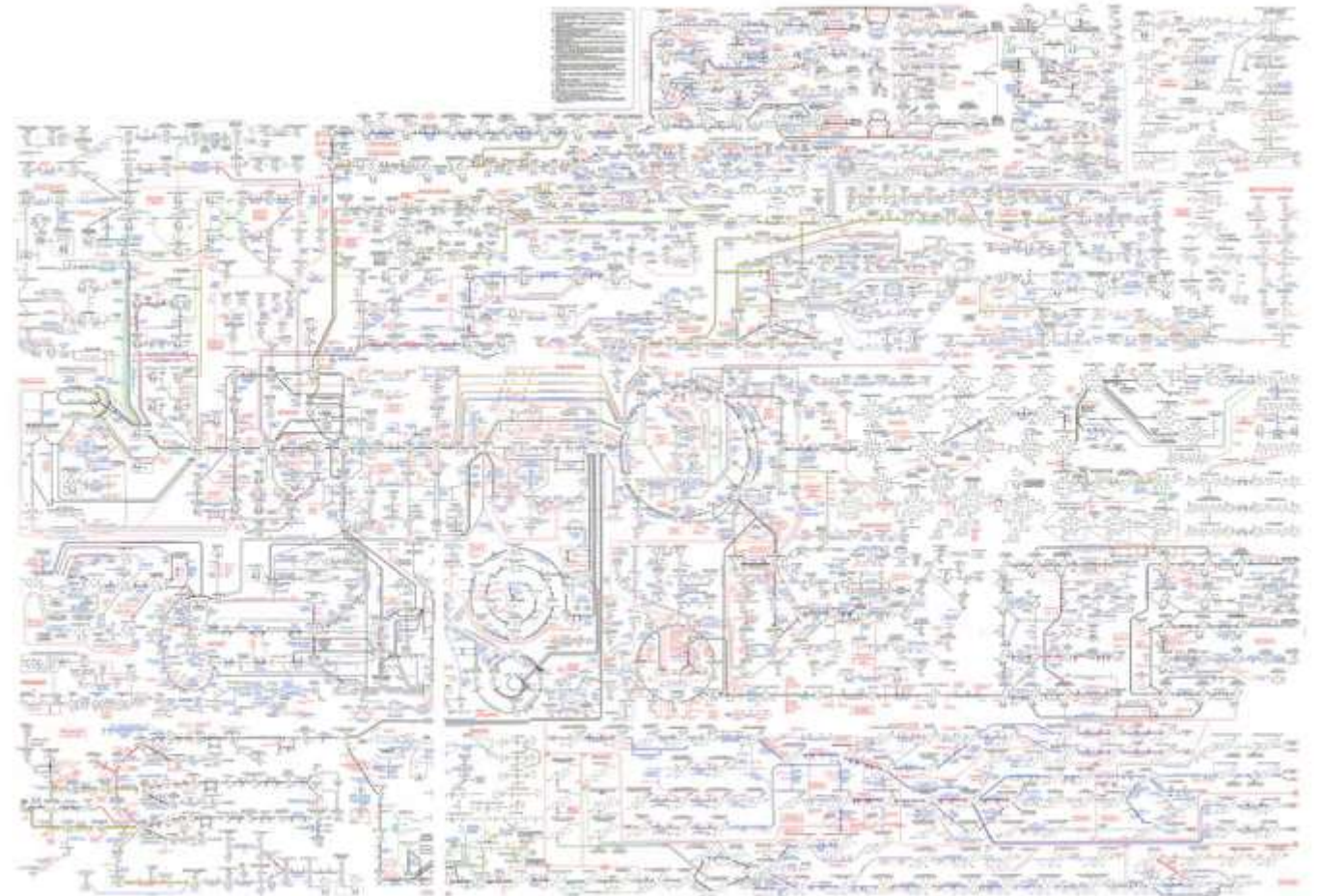# Is ATP a good long-term energy storage molecule?

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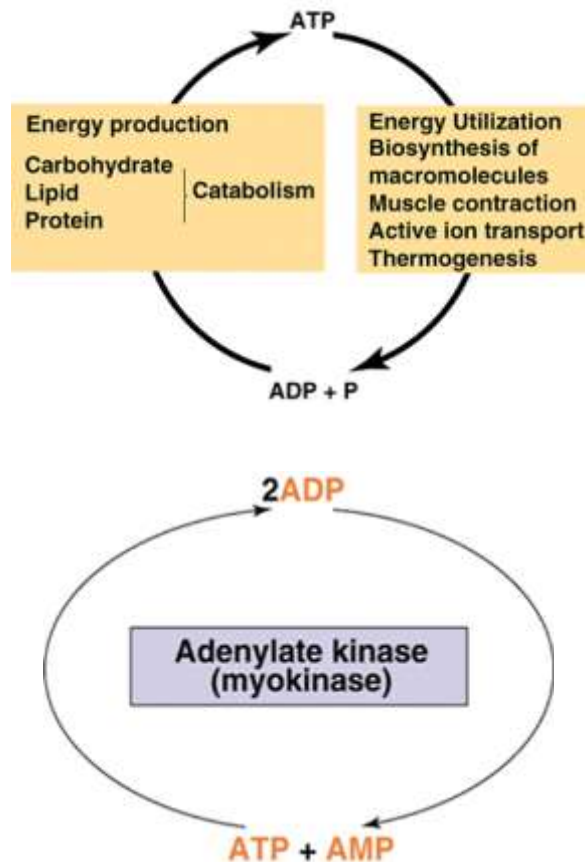
Tissue	ATP turnover (mole/day)
Brain	20.4
Heart	11.4
Kidney	17.4
Liver	21.6
Muscle	19.8
Total	90.6

Biochemical (metabolic) pathways

➢ **Are <u>interdependent</u>**

➢ **Are subjected to thermodynamics laws**

➢ **<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>**

A linear sequence: A —Enzyme 1→ B —Enzyme 2→ C —Enzyme 3→ . . .

A cyclic sequence: A —Enzyme 1→ B —Enzyme 2→ C —Enzyme 3→ D —Enzyme 4→ A

A spiral sequence: A —Enzymes 1→4→ B —Enzymes 1→4→ C —Enzymes 1→4→ Final product

How do our cells get energy for unfavorable biochemical work?

- **Coupling**
- **intermediate in metabolic pathways**

COUPLING: coupling unfavorable RX with favorable one

How do our cells get energy for unfavorable biochemical work?

A➔C (Unfavorable),
B➔D(Favorable)
coupled reactions, A +B ➔C +D

- $\Delta G = \Delta G`0_{(A\ to\ C)} + \Delta G`0_{(B\ to\ D)} + RT \lin \dfrac{[C]/[D]}{[A]/[B]}$

- Make: $\Delta G`0_{(A\ to\ C)} + \Delta G`0_{(B\ to\ D)}$ favorable, but still C/A and D/B concentrations are important.

Importance of finding an intermediate in metabolic pathways

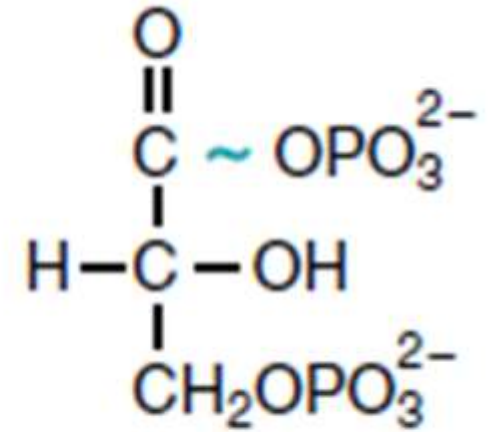- for the reaction A➜ B $\Delta G\`0 > 0$, the equilibrium is far to the A, so how could you convert A to B?
- ΔG _~ [B]/[A] .
- Cells can do that by lowring ΔG by keeping [B] very low
- $\Delta G = \Delta G\`0 + RT \, lin \, [B]/[A]$, then $\Delta G < 0$
  - ↑+ve   ↑-ve

•How to keep B very low? Build a pathway to consume B and keep it very low.

•A ➜ B ➜ C   for A ➜ B $\Delta G\`0 > 0$, for B ➜ C $\Delta G\`0 <<< 0$,

- 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 $\Delta G < 0$ for A ➜ C
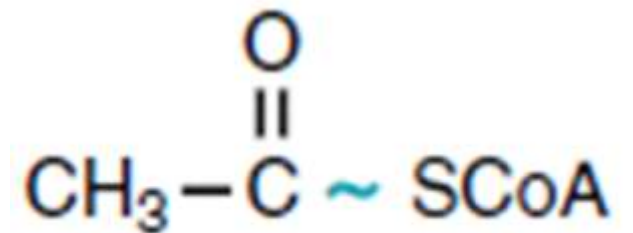
How do our cells get energy for unfavorable biochemical work?

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

$$H_2\overset{+}{N} = C \begin{array}{c} \overset{H}{\underset{}{N}} \sim P - O^- \\ \underset{O^-}{\overset{\parallel}{}} \\ N - CH_3 \\ | \\ CH_2 \\ | \\ COO^- \end{array}$$

Creatine phosphate

$$\begin{array}{c} O \\ \parallel \\ C \sim OPO_3^{2-} \\ | \\ H - C - OH \\ | \\ CH_2OPO_3^{2-} \end{array}$$

1,3–Bisphosphoglycerate

$$CH_3 - \overset{\overset{\textstyle O}{\parallel}}{C} \sim SCoA$$
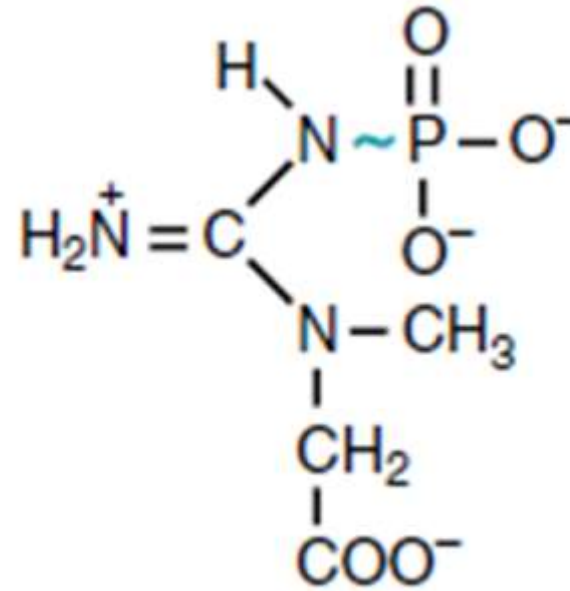
Acetyl CoA

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 $\Delta G`0$ =-10 Kcal/mol
- ATP→ADP+ Pi $\Delta G`0$ -7.5 Kcal/mol
- ATP +Creatin → Creatin-P + ADP $\Delta G`0$ =+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

THERMOGENESIS

➢ **Heat production is a natural consequence of "burning fuels"**

➢ **Thermogenesis refers to energy expended for generating heat (37^oC) 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)**

Oxidation-Reduction reactions (Redox)

➢**Oxidation:**

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

➢ *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)

- 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

- Sum:
- OAA+NADH+H+$\rightarrow$ 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$\rightarrow$OAA+NADH+H

- 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

- ΔGº = - n$f\Delta Eº$
  - 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$^-$ $Eº$ = +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
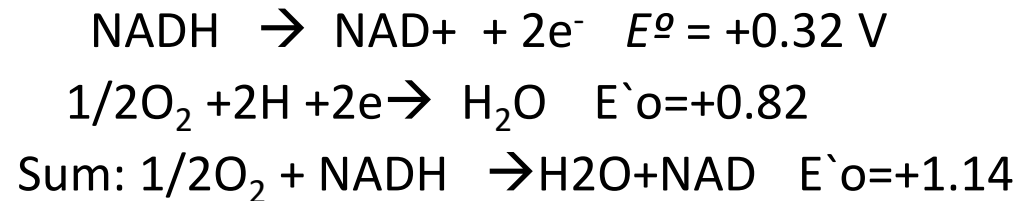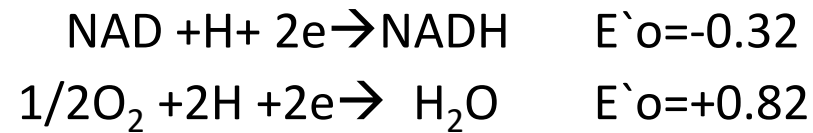
      ΔGº = - 52.6 kcal/mol

Reducing powers