METABOLISM

بسم الله الرحمن الرحيم

MID – Lecture 2

Bioenergetics (Pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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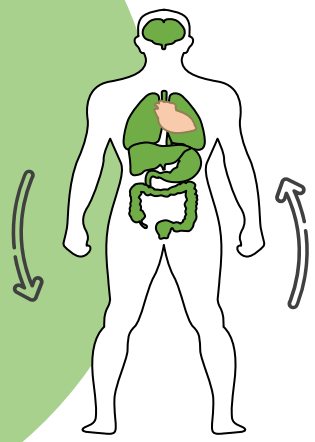


ΔG & K_{eq}

To use the relation at the right, the reaction equation must be balanced with simplest coefficients written.
The concentrations must be raised to the power of their respective coefficients in the balanced equation.
Ex: 2A+3B→C+4D
inside the ln: $([C][D]^4)/([A]^2[B]^3)$

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

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

- **At equilibrium, $\Delta G = o$**
- **Can a reaction have a + ΔG^o & still be favorable?**

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"

The standard conditions usually don't occur at the beginning of a reaction. They can occur at some point if the concentrations are equal to 1 M and if other conditions are met as well.

$$\Delta G = \Delta G^o + RT \ln \frac{[C]\,[D]}{[A]\,[B]}$$

$$0 = \Delta G^o + RT \ln \frac{[C]\,[D]}{[A]\,[B]}$$

$$\Delta G^o = - RT \ln \frac{[C]\,[D]}{[A]\,[B]}$$

defining K_{eq}

$$\frac{[C]\,[D]}{[A]\,[B]}$$

$$\Delta G^o = - RT \ln K_{eq}$$

ΔG^o and K_{eq}

K_{eq}	ΔG^o
10^3	- 4.08
10^2	- 2.72
10^1	- 1.36
1	0
10^{-1}	1.36
10^{-2}	2.72
10^{-3}	4.08

Reaction has no favored direction

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

Reaction favors forward direction

If $K_{eq} > 1$, then $\Delta G^o < 0$

Reaction favors reverse direction

If $K_{eq} < 1$, then $\Delta G^o > 0$

The phrases in green above only address the general case at standard conditions, where $\Delta G = \Delta G^o$.

If the reactants are present in large amounts, the reaction will favor the forward direction and vice versa.
(And this is no longer standard conditions)

ΔG & ΔG°

- The ΔG°s are additive in any sequence of consecutive reactions, as are the ΔGs

Glucose + ATP	→ glucose 6-phosphate + ADP	$\Delta G^0 = -4{,}000$ cal/mol	Spontaneous
Glucose 6-phosphate	→ fructose 6-phosphate	$\Delta G^0 = +400$ cal/mol	Nonspontaneous
Glucose + ATP	→ fructose 6-phosphate + ADP	$\Delta G^0 = -3{,}600$ cal/mol	Spontaneous (Overall)

- ΔGs of a pathway: A → B → C → D → …

Recall that enzymes change the activation energy but have no effect on ΔG nor $G_{reactants}$ nor $G_{products}$.

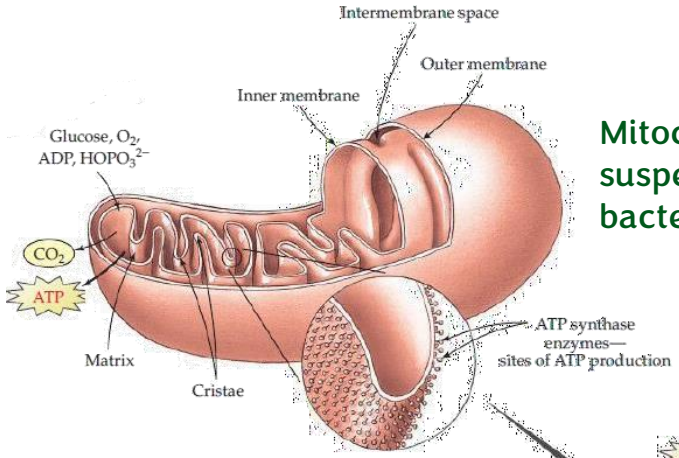
As long as the sum of the ΔGs of the individual reactions is negative, the pathway can proceed, even if some of the individual reactions of the pathway have a positive ΔG. However, the actual rates of the reactions depend on the lowering of activation energies (Ea) by the enzymes that catalyze the reactions

The energy machinery of the cell

Mitochondria are very active and dynamic organelles which are affected by the conditions surrounding them; they can undergo fission (divide); they can also fuse together.

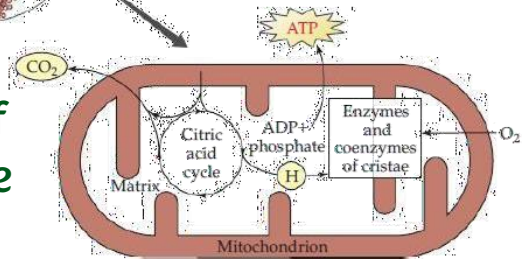
- **Prokaryotic cells vs. eukaryotic cells**
- **The mitochondria (singular, mitochondrion) (90% of the body's energy ATP)**
- **The number of mitochondria is greatest in <u>eye, brain, heart, & muscle</u>, where the need for energy is greatest**
- **The ability of mitochondria to reproduce (athletes)**

The # of mitochondria in a cell varies depending on the **<u>type</u>** and **<u>activity of that cell.</u>**



Mitochondria is suspected to have a bacterial origin.

Mitochondria have circular DNA (with a relatively small number of nucleotides) which include genes that encode some proteins in the mitochondria. The inner membrane is about 75% proteins.



→ Metabolically active organelles.

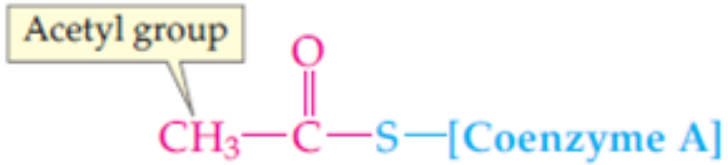
- **Maternal inheritance**

Nuclear DNA also encodes many mitochondrial proteins, while proteins which are synthesized in mitochondria don't exit it.

The zygote's cytoplasm comes from only the ovum, so the mitochondrial DNA is purely maternally inherited.
A disorder in the mother's mitochondrial DNA is thus directly passed to her **<u>children</u>** (not sex-linked).

Energy production stages

- **Stage 1 (Digestion):**
  - ✓ **Mouth, stomach, & small intestine**
  - ✓ **Carbohydrates to glucose & other sugars**
  - ✓ **Proteins to amino acids**
  - ✓ **Triacylglycerols to glycerol plus fatty acids**
  - ✓ **From there to blood**
- **Stage 2 (Acetyl-coenzymeA)**



- **Stage 3: citric acid cycle**
- **Stage 4: electron transport chain & oxidative phosphorylation**

Digestion of macromolecules in food may start early in the **mouth** or in the **stomach** or the **intestines**.
It may undergo stages, so it become absorbable monomers because we can't absorb disaccharides, polysaccharides, whole proteins nor Lipids. They must be digested first

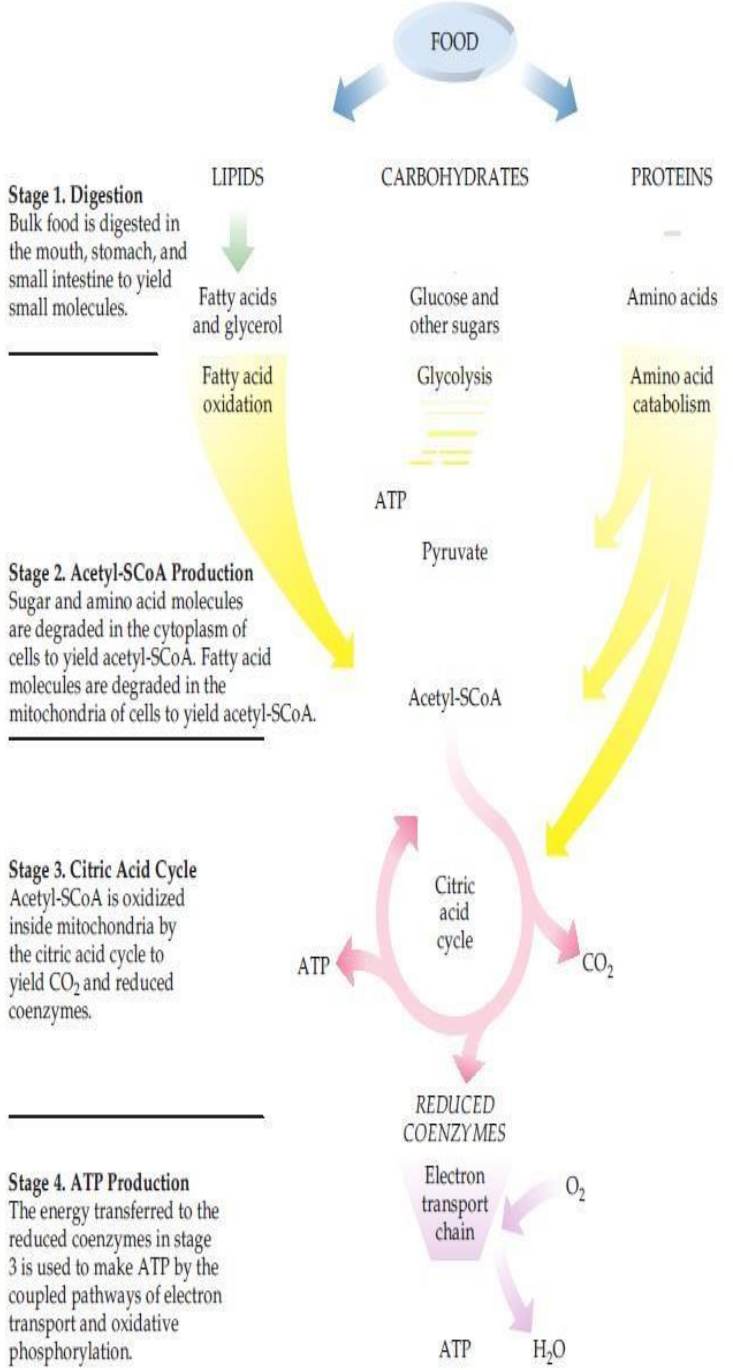
After digestion, they move to the **intestine** cells and then enter the **portal circulation** to the **liver** that checks and detoxifies them.
They then exit to the general circulation where cells could pick and degrade them. They are usually turned into Acetyl-CoA (which comes from multiple sources like amino acids, lipids and of course sugars), which then initiates the Krebs cycle.

Energy production is a stepwise process. First, we start with the food we eat, which is full of macromolecules. Digestion stage simplify food into absorbable form. Then the products are further metabolized (degraded) until they become nondegradable compounds (like H_2O, CO_2, or NH_3 which should be detoxified before excreting it with urine).

Why is Krebs cycle important?
It yields a relatively large amount of energy per molecule.

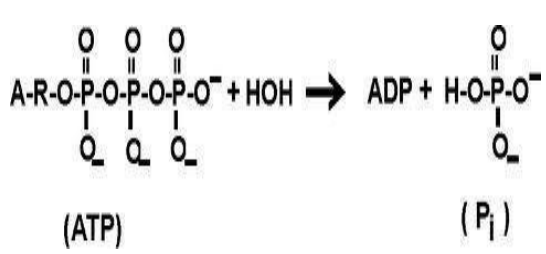
Direct energy is only 1 GTP per acetyl-CoA.

Indirect energy however is appreciable after the electron carriers NADH and FADH2 are harnessed in the electron transport chain generating ATP.



ATP

ATP is not the only energy molecule in the body, but it is the energy currency.

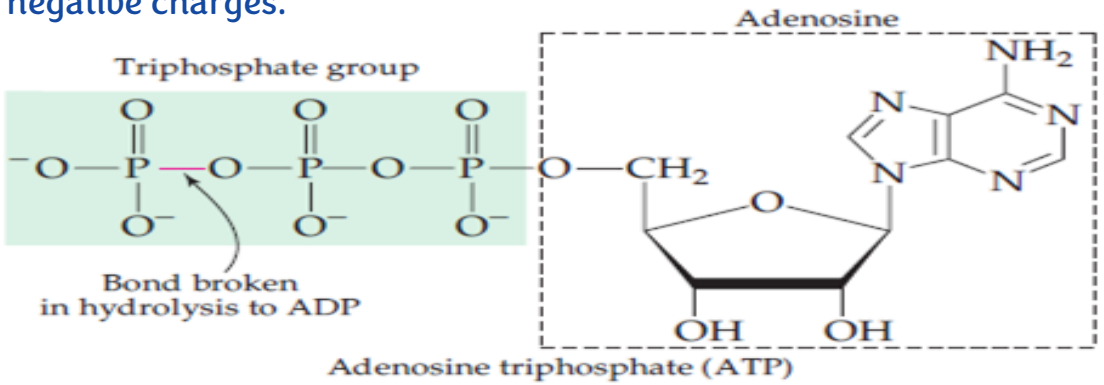


ATP to ADP and ADP to AMP
-7.3 kcal/mole
From AMP to adenosine and phosphate
-3.4 kcal/mole

- 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

ATP coupling occurs when we have an energetically infavorable reaction (ΔG > 0). ATP is hydrolysed to make the total ΔG less than 0.

These phosphate groups are rich in energy because of repulsion between negative charges.



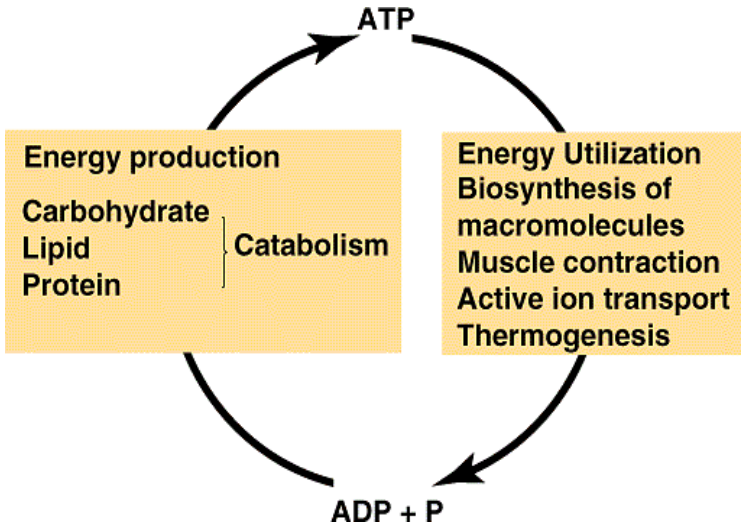
Among the other phosphate-bound compounds, ATP is

(1) **Intermediate in its energy output**, so it can couple with a wide range of reactions.
(2) ATP is also **present generally in all cases and all cells** unlike phosphoenol pyruvate or 1,3 BPG which are glycolytic intermediates, or creatine which is mainly in the muscles which limits its presence in other places.

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

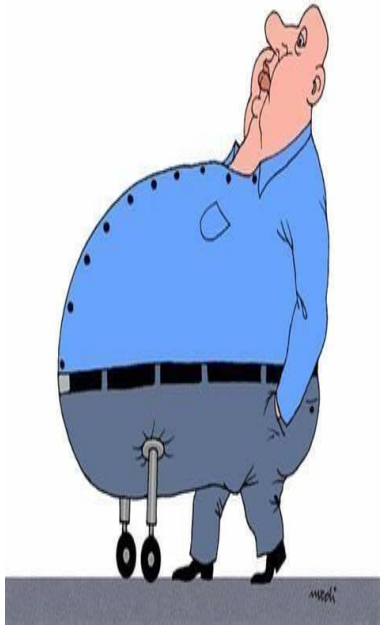
Is ATP a good long-term energy storage molecule?

- **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

ATP turnover depends on organs' activity, for ex: athletes who use their **muscles** more will have a higher turnover. note that these numbers have some variability, liver for ex has the highest turnover rate because of its protein synthesizing activity.



49 920 g ATP ≈ 50 kg ATP per day which is really high, so we must recycle ATP we use by some reactions.

90.6 * 551 (g/mole) = 49,920 g ATP

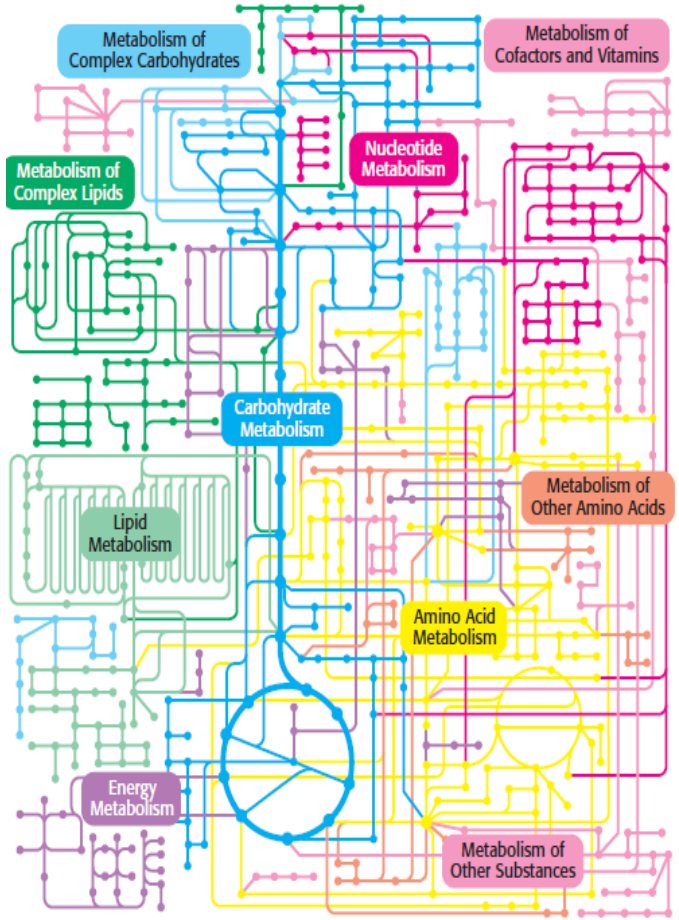
Biochemical metabolic pathways

They are interconnected.
Metabolism of carbohydrates have crosslinks with lipids metabolism, etc…
It does not mean that they are only linked head to tail as they could share a common molecule in the middle (cross talks between the pathways).

- Are <u>interdependent</u>
- Are subjected to thermodynamics laws
- Their activity is coordinated by sensitive means of communication
- <u>Allosteric enzymes</u> are the predominant Regulators

Enzymes have an excellent regulation ability, **<u>especially in irreversible steps.</u>**

Many of them are allosteric enzymes regulated by multiple regulators.

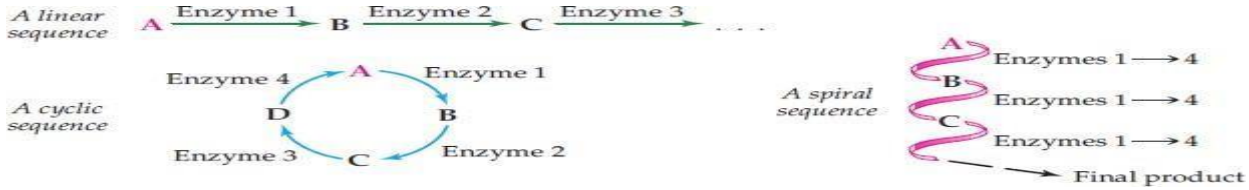


anabolic catabolic

- Biosynthetic & degradative pathways are <u>almost always distinct</u> (regulation)
- Metabolic pathways are <u>linear, cyclic or spiral</u>

Catabolic: provides energy and degrades macromolecules into smaller units.
Anabolic: requires energy and synthesizes macromolecules.

(1) **Linear**: from the initial until final product.
(2) **Cyclic:** like Krebs cycle; 1-its final and first products are the same, and it is initiated by interacting with an outside molecule .
2- the intermediates amounts don't change unless they are affected by other pathways externally.
(3) **Spiral**: <u>some</u> steps are repeated for a given number of times, like loops in coding (what we took in CS and grade-11 C++ class).



To optimize energy consumption, some regulators activate the pathway synthesizing a molecule and inhibits the pathway degrading it.

This prevents the simultaneous activation of opposite pathways which causes energy waste.

Exergonic reactions in Biochemistry

These are some ways to predict if the reaction is endergonic or exergonic without knowing ΔG:

- Complex structures ➔ simple structures

Catabolic reactions are mostly exergonic:

$$\text{Starch} \longrightarrow \text{n glucose}$$

$$\text{glucose} + O_2 \longrightarrow CO_2 + H_2O$$

$$\text{Proteins} \longrightarrow \text{Amino acids}$$

- More specifically

By some enzymes names that imply these reactions:

- ✓ Hydrolysis reactions
- ✓ Decarboxylation reactions (release of CO_2)

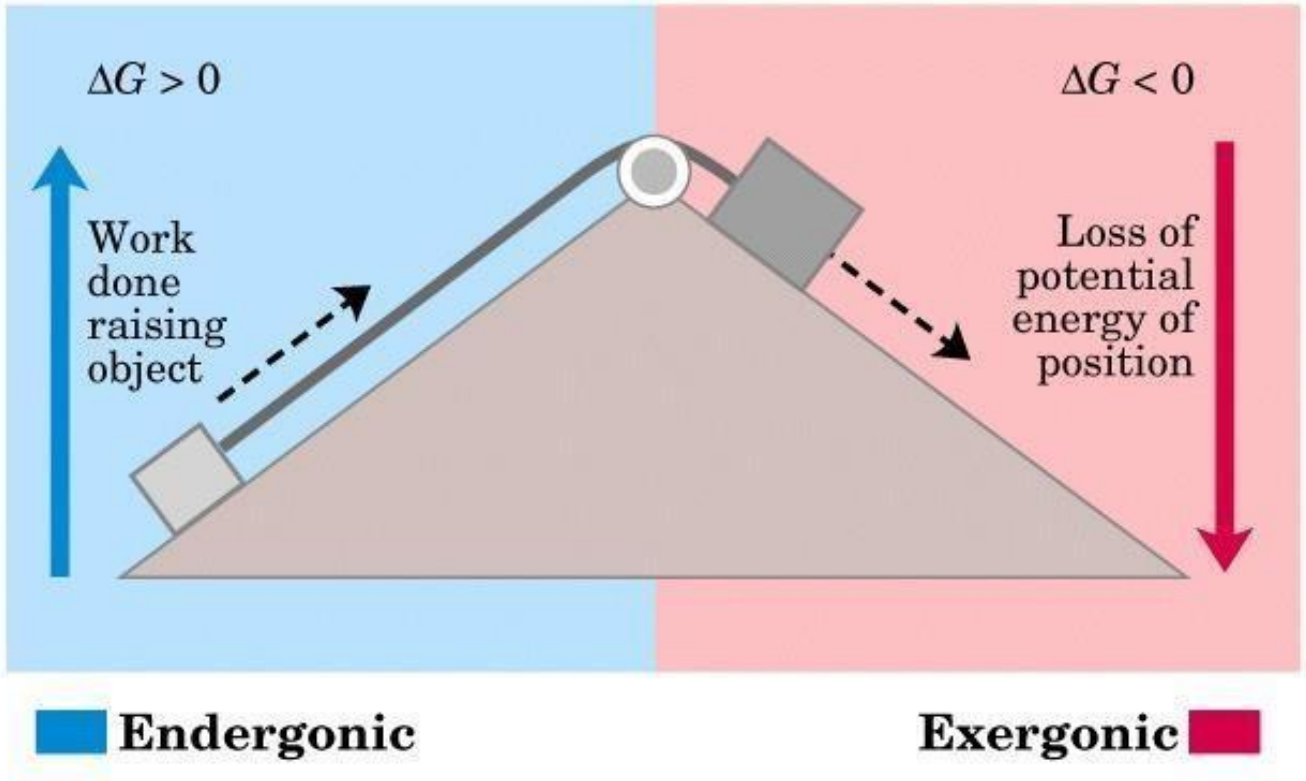
while **carboxylation** reactions are **endergonic**.

$$\text{pyruvate (C3)} \longrightarrow \text{acetyl-CoA (C2)} + CO_2$$

- ✓ Oxidation with O_2

Where do cells get energy for unfavorable biochemical reactions?

- **The concept of coupling**



How are endergonic reactions done in our bodies? We should remember that endergonic reactions are chemically possible as their products are stable (they are just less stable relative to reactants), but their ΔG is positive.
They are thus coupled with an exergonic reaction (usually ATP hydrolysis) to overcome this issue.

Where do cells get energy for unfavorable biochemical reactions?

I. ΔG^{o} Values are additive

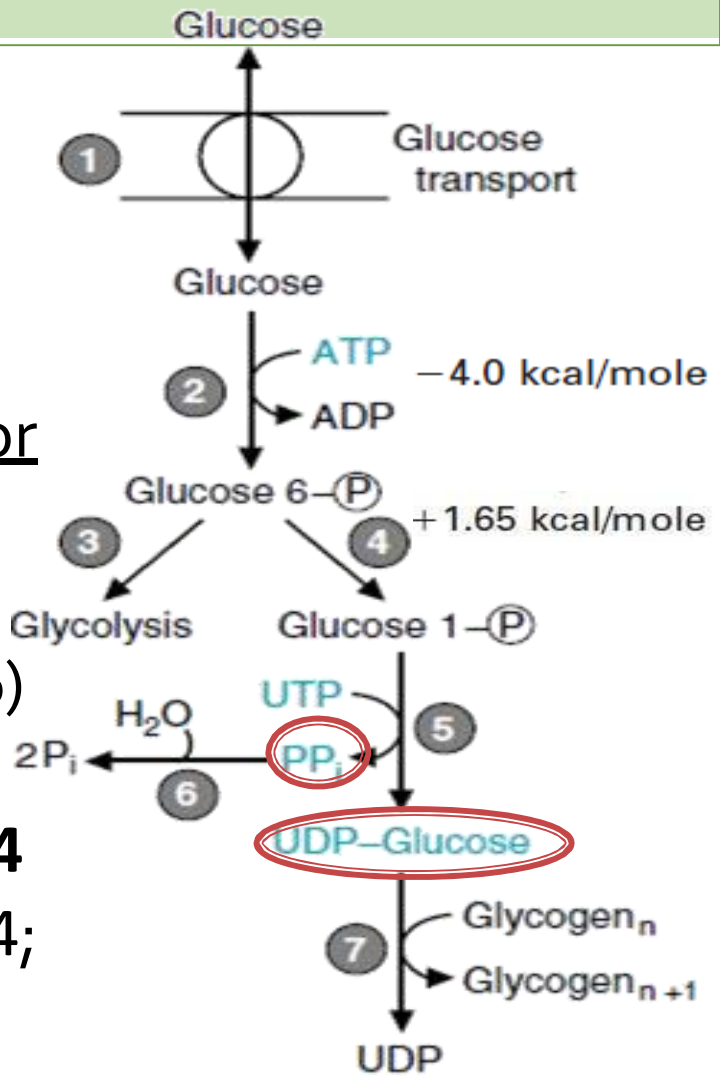
i. Through phosphoryl transfer reactions:

- ✓Step **2** (+3.3 vs. -4 kcal/mole)
- ✓Step **2** + **4** = -2.35 kcal/mole
- ✓<u>The net value for synthesis is irrelevant to the presence or absence of enzymes</u>

ii. Activated intermediates (step **4** is facilitated by steps **5 & 6**)

Adding phosphate from glucose 1 phosphate to UTP, would induce the making of pyrophosphate giving enough energy.

II. ΔG Depends on Substrate and Product Concentration (step **4** has a ratio of 6/94; ΔG = +1.65 kcal/mol → infavorable, if 3/94; ΔG = -0.4 kcal/mol → favorable)



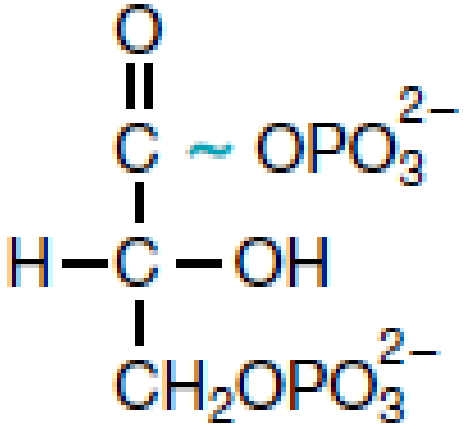
III. Activated intermediates other than ATP:

UTP is used for combining sugars;

CTP in lipid synthesis;

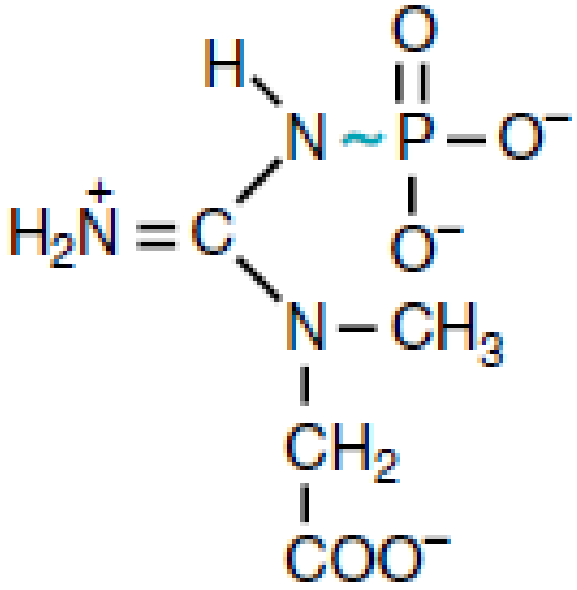
GTP in protein synthesis.

UTP carry sugars in reactions as **UDP**. It enters the reaction as **UTP** but then transforms into **UDP** to carry the sugar.

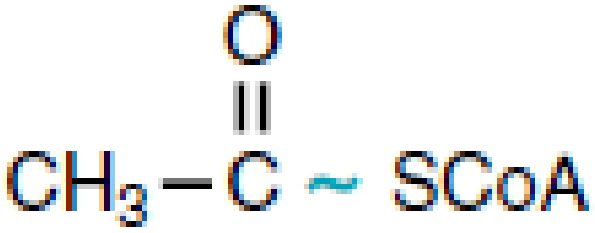


1,3–Bisphosphoglycerate

Glycolytic Intermediate



Creatine phosphate

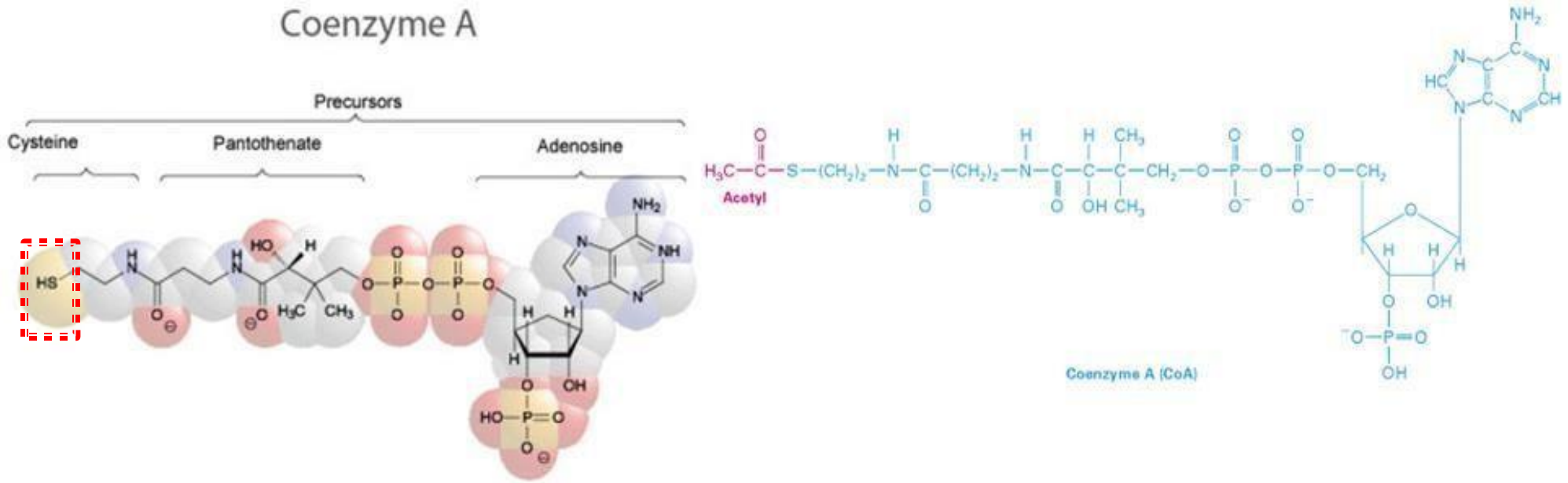


Acetyl CoA

Acetyl-CoA thioester bond is a high energy bond, and it participates in many reactions like Krebs cycle.

Acetyl-CoA

- **Coenzyme A is a universal carrier (donor) of Acyl groups** → Small as acetyl groups, Large as fatty acids
- **Forms a thio-ester bond with carboxyl group**



- $Acetyl\ CoA + H_2O \longrightarrow Acetate + CoA \quad \Delta G^\circ = -7.5kcal$

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide #	Before Correction	After Correction
V0 → V1	Slide 2: Slide 3: slide 6: slide 8 : slide 9: slide 11: slide 12 :	"The concentrations must be raised to the power…." "The phrases in green …." " digestion degrades food into a simpler…" "ATP turnover depends …" "(2) Cyclic: its final and first products are the same, …." "endergonic reactions are chemically possible .."	An example is added "where ΔG = ΔGº" is added "Digestion stage simplify food into absorbable form" "liver for ex has the highest….." is added some change in phrasing "(they are just less stable relative to reactants)" is added "Adding phosphate from glucose 1 phosphate to UTP…" is added

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Lippincott Illustrated Reviews:
   Unit II, chapter 6, concepts IV & V.

Extra References for the Reader to Use:

1. ATP and Biological coupling reactions

والدعاء من أنفع الأدوية، وهو عدو البلاء، يدافعه ويعالجه، ويمنع نزوله، ويرفعه، أو يخففه إذا نزل، وهو سلاح المؤمن.

- الداء والدواء لابن القيّم

لا تنسوا إخوانكم المستضعفين من صالح دعائكم
وفقنا الله وإياكم لما يحب ويرضى