



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ ۝

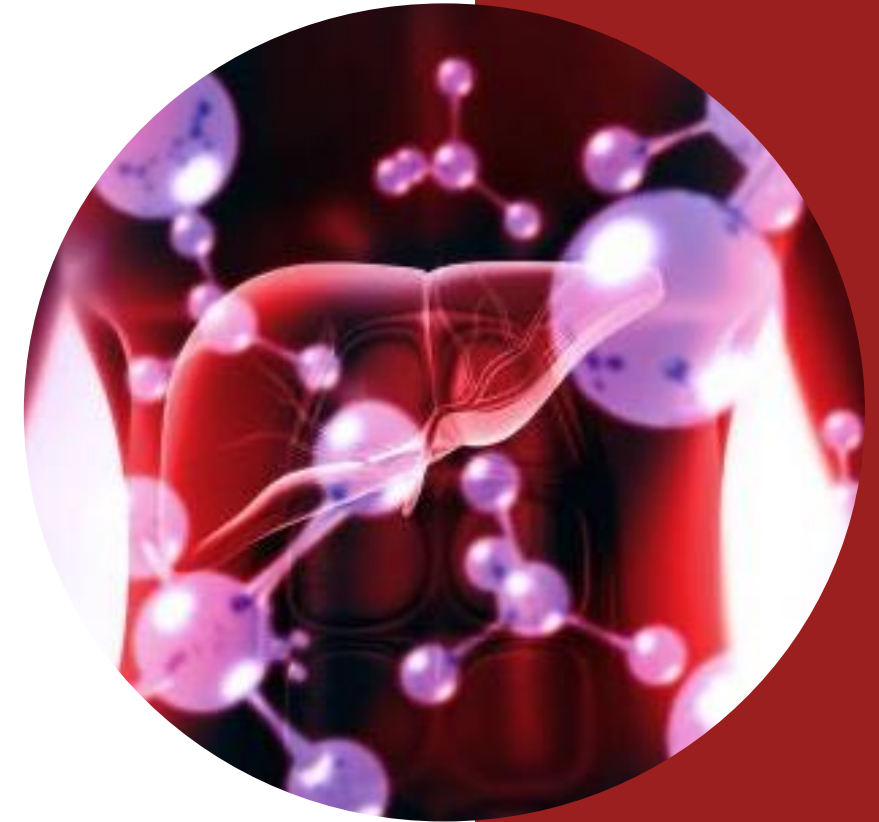
⚙ METABOLISM

MID | Lecture 3

Bioenergetics & Thermodynamics 3

Written & Reviewed by:

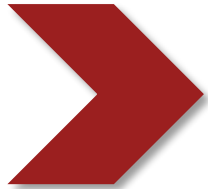
Raghad Farraj
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Color coding used in the modified:



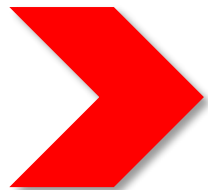
Black: the original slides



Maroon: the doctor's explanation/words



Gray: additional information and explanation



Red: important information

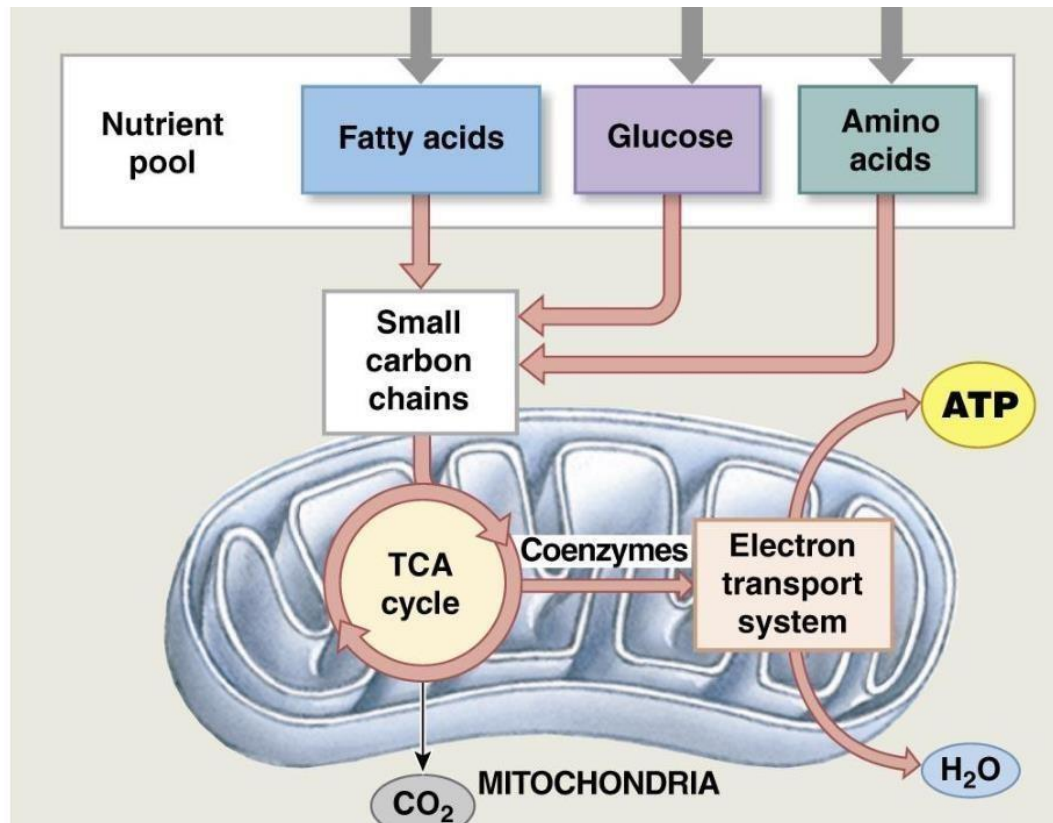
بسم الله الرحمن الرحيم

Principles of bioenergetics

2-Phosphoryl Group Transfers and ATP

THE ENERGY FLOW

This is a revision from last lecture!



- Ingestion, digestion, & absorption
- Metabolism (Acetyl CoA)
- TCA
- Oxidative phosphorylation

THE ENERGY MACHINERY OF THE CELL

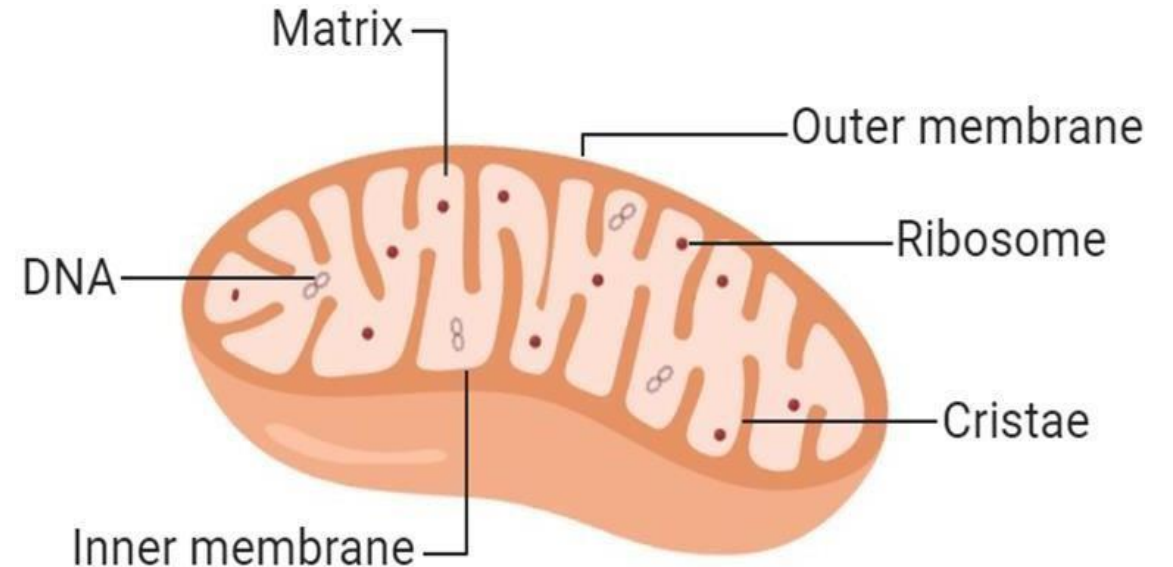
- Prokaryotic cells vs. eukaryotic cells

The mitochondria (singular: mitochondrion) **(90% body's energy ATP)**

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

- The ability of mitochondria to reproduce (athletes)
- Maternal inheritance

This is a revision from last lecture!



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
﴿إِنَّ اللَّهَ وَمَلَائِكَتَهُ يُصَلُّونَ عَلَى النَّبِيِّ يَا أَيُّهَا
الَّذِينَ آمَنُوا صَلُّوا عَلَيْهِ وَسَلِّمُوا تَسْلِيمًا﴾

اللَّهُمَّ صَلِّ وَسَلِّمْ وَبَارِكْ عَلَى نَبِيِّنَا مُحَمَّدٍ ﷺ

The mitochondria's Double Membrane

- **The outer membrane (mammalian)** permeable to charged molecules dependent on their size (if they are 5000 or 5K daltons or less they pass it)
- **The inner membrane (mitochondrial)** which is not permeable to any charged molecules even protons (the smallest charged molecule)
 - → Achieved by:
 - The high density of proteins throughout the whole membrane (ETC enzymes, ATP synthases, etc)
 - Cardiolipins (they are huge in size, 2-3% in the outer membrane and 22% in the inner mitochondrial)

Maternal Inheritance

When an egg and sperm unite during fertilization, the egg provides almost all the cytoplasm and organelles, including **mitochondria**.

The sperm's mitochondria are located in its tail, which usually does not enter the egg.

Therefore, the embryo's mitochondria –and its mitochondrial DNA– comes entirely from the mother's egg.

So, if a mutation exists in the mother's mitochondrial DNA, **all her children will inherit it**, but only her daughters will pass it to the next generation, because no paternal mutation will be passed to any of a man's children.

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**

ATP is made by the mitochondria through oxidative phosphorylation, two reactions coupled together (oxidation-reduction and phosphorylation)

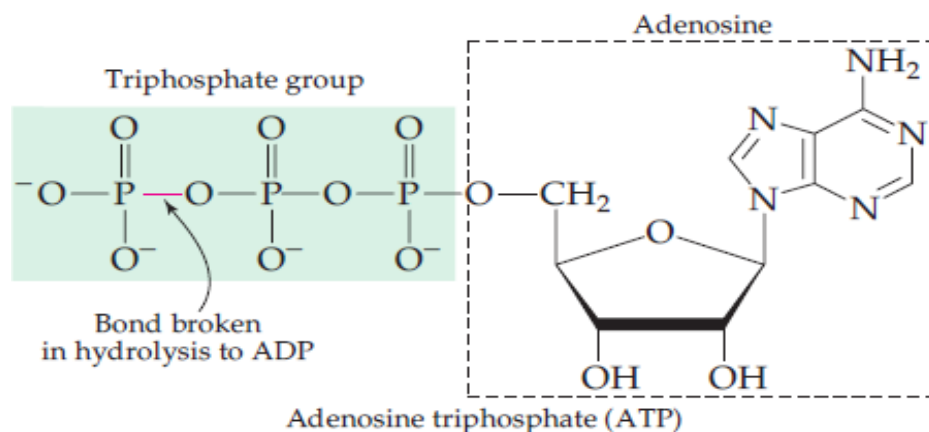


TABLE 13–6 Standard Free Energies of Hydrolysis of Some Phosphorylated Compounds and Acetyl-CoA (a Thioester)

	ΔG°	
	(kJ/ mol)	(kcal/ mol)
Phosphoenolpyruvate	−61.9	−14.8
1,3-bisphosphoglycerate ($\rightarrow$ 3-phosphoglycerate + P_i)	−49.3	−11.8
Phosphocreatine	−43.0	−10.3
ADP ($\rightarrow$ AMP + P_i)	−32.8	−7.8
ATP ($\rightarrow$ ADP + P_i)	−30.5	−7.3
ATP ($\rightarrow$ AMP + PP_i)	−45.6	−10.9
AMP ($\rightarrow$ adenosine + P_i)	−14.2	−3.4
PP_i ($\rightarrow$ 2 P_i)	−19.2	−4.0
Glucose 1-phosphate	−20.9	−5.0
Fructose 6-phosphate	−15.9	−3.8
Glucose 6-phosphate	−13.8	−3.3
Glycerol 1-phosphate	−9.2	−2.2
Acetyl-CoA	−31.4	−7.5

How did we obtain energy from ATP?

By breaking the bonds. Breaking any bond in ATP will result in energy. Building them together needs energy. And we all know that each bond has its own bond energy. There are bonds with normal energies—they are normal covalent bonds—but there are bonds with higher energy than others. Those bonds, we call them high-energy bonds, like:

- Phosphorus-oxygen bond
- Phosphorus-phosphorus bond
- Phosphorus-carbon bond
- Sulfur-carbon bond

So these molecules that have these bonds are called High -Energy Molecules

Why ATP?

1- Has an intermediate energy value, so it can be coupled:

Doctor's example for further understanding:

The High-Value Currency (50 JOD Note)

If a cell uses an excessively high-energy molecule to drive a small, low-energy endergonic reaction, the vast majority of the released energy cannot be captured and will be wasted as heat. It is as impractical as paying with a 50-dinars bill for a tiny purchase, forcing the seller to deal with unnecessary change or risk being unable to process the transaction.

Example: High-energy molecules like Phosphoenolpyruvate (~ 15 kcal/mol).

The Low-Value Currency (5-Piastre Coin)

If a reaction requires a substantial amount of energy, using low-energy molecules requires a massive quantity of them (e.g., paying a 2-dinar bill entirely in 40 individual coins). This creates metabolic inefficiency and places an unnecessarily heavy burden on the cell's synthetic machinery.

Example: Low-energy molecules like Glucose-1-phosphate (~3 Kcal/mol).

The Intermediate Value (The 5 or 10JOD Note)

Example: ATP (~ 7.3 kcal/mol).

Why it works: ATP sits right in the middle, between the highest energy molecule in the body (Phosphoenolpyruvate) and lower ones like Glucose-1-phosphate. This intermediate energy value makes it the most convenient “currency” for the cell to use—it provides enough energy to drive endergonic reactions without wasting excess energy or requiring an impractical number of molecules.

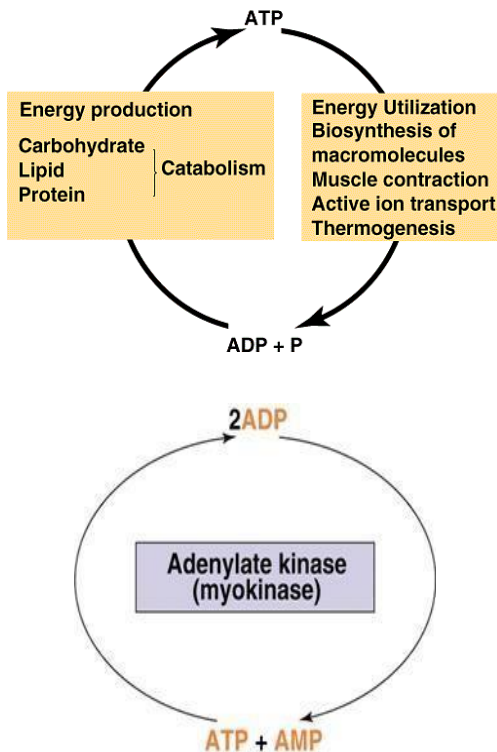
Why ATP?

If ATP had very low energy, the consequences would be:
Insufficient energy release.
More ATP needed over time.



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

$$90.6 * 551 \text{ (g/mole)} = 49,920 \text{ g ATP}$$

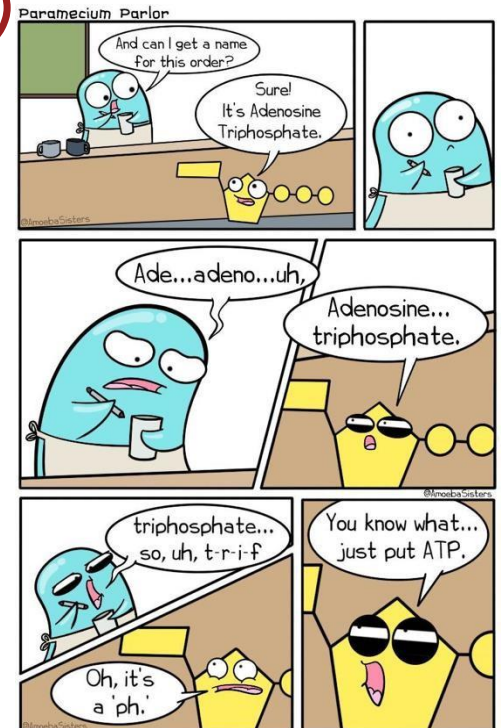
ATP has a high molecular weight, which is about 551 g/mol (one mole of it is nearly half a kilogram)

This is nearly 50kg of required ATP by our body. This tells us:

ATP isn't a long term energy molecule
ATP can't be stored
So we have high turn over of ATP at all times

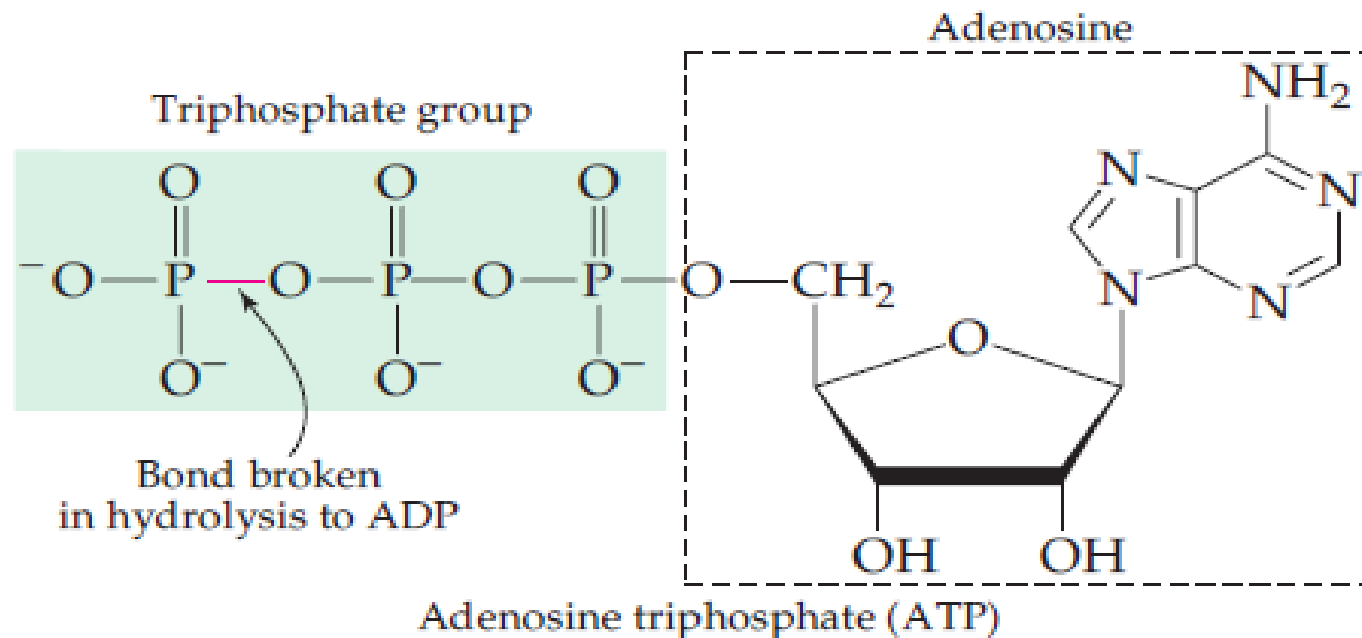
- ATP is not a long-term energy storage molecule.
- To understand why, first we need to know what molecular weight means – it is the total mass of one molecule based on the atoms it contains.
- ATP has a relatively high molecular weight, but the amount of energy released per molecule is quite low compared to its weight.
- That means its energy-to-mass ratio (energy density) is small.
- So, to store the amount of energy the cell needs, it would have to make and keep an enormous number of ATP molecules – which would be extremely heavy and inefficient.

- Therefore, ATP is not useful for long-term energy storage; instead, cells use fats and glycogen, which store much more energy in smaller, lighter amounts and are chemically more stable.
- The ATP turn over per day is 90.6 moles per day
Equals near 50 kg of ATP (multiply by molar mass)



The phosphate group on ATP is not a reason to choose ATP as a currency of the cell ; it's because ATP structure .

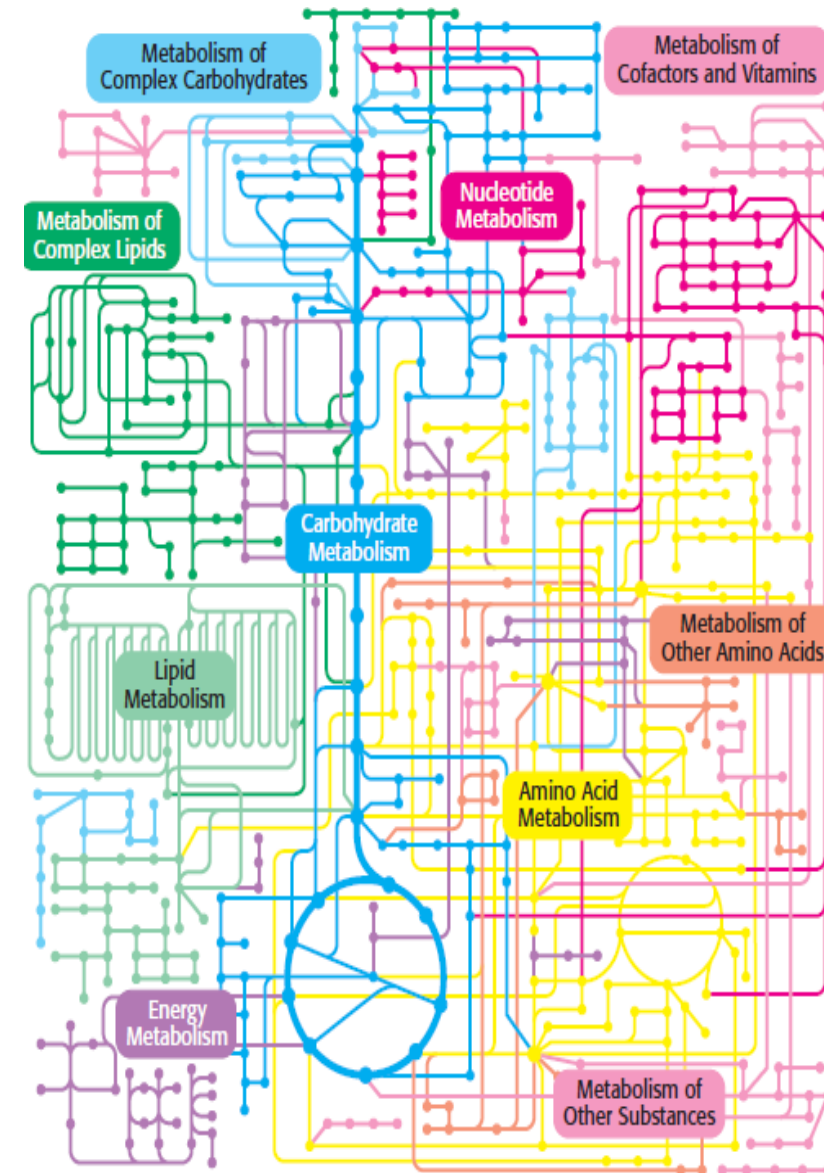
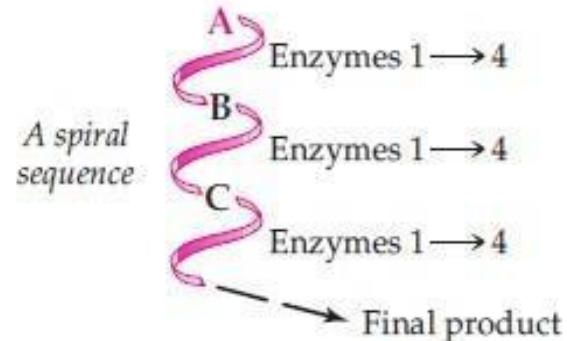
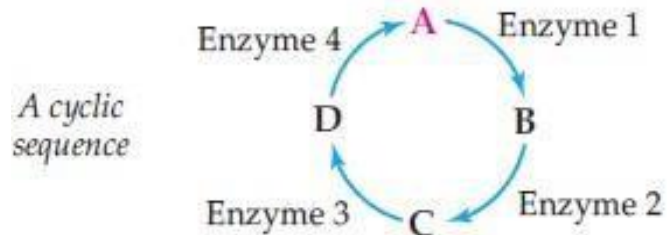
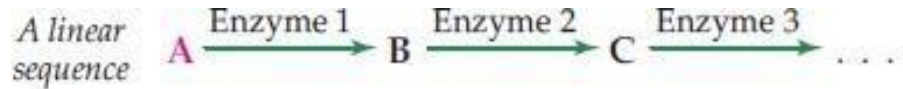
ATP unstable because of negative charges on phosphate groups in it accordingly breaking down ATP into ADP and P make it more stable because of the resonance .



BIOCHEMICAL REACTIONS OR PATHWAYS!

- Are interdependent
- Are subjected to thermodynamics laws
- Coordinated by sensitive means of communication
- Allosteric enzymes are the predominant regulators
- Pathways are linear, cyclic or spiral

Keep in mind that there is no reaction in your body occur in a single simple step .



- linear pathways is series of biochemical reactions where every reaction leads to the other one until we achieve the final product , and every reaction is catalyzed by different enzyme.
- cyclic pathways is the same definition of linear but with addition that the final product can regenerate the first molecule that we started with.
- Spiral pathways (in fatty acids synthesis) in each step there is the same set of enzymes that catalyzes subsequent steps.
- All these pathways are connected to each other in a way or another

Integration and Regulation of Interconnected Metabolic Pathways

Metabolic Coordination:

Intracellular metabolic processes do not operate in isolation; rather, multiple distinct pathways (e.g., Glycolysis, the Citric Acid Cycle, and Lipid Metabolism) function simultaneously and interdependently to maintain cellular homeostasis.

The Role of Rate-Limiting Enzymes:

Pathways are regulated via specific rate-limiting steps catalyzed by key enzymes. For instance, Phosphofructokinase-1 (PFK-1) serves as a major rate-limiting enzyme in Glycolysis, controlling overall glycolytic flux in response to cellular metabolic state.

Allosteric Regulation and Biological Fine-Tuning:

Inter-pathway communication is mediated predominantly by Allosteric Enzymes.

Structural Organization: Allosteric enzymes possess discrete catalytic subunits (where substrate binding and reaction catalysis occur) and regulatory subunits.

Regulatory Subunits: These subunits contain multiple binding sites for various metabolic effectors, substrates, and end-products.

Fine-Tuning Flux: Effector binding induces conformational changes that modulate enzymatic activity along a continuous spectrum—ranging from full catalytic capacity (100%), through partial activity, to complete allosteric inhibition (0%). This allows real-time modulation of metabolic flux based on the cellular supply of nutrients (such as amino acids, carbohydrates, or lipids).

- These pathways intersect and are regulated in a coordinated way.
- They “communicate” through allosteric enzymes and their regulatory subunits, which control the overall metabolic flow.
- The product of one pathway can bind to an allosteric site on an enzyme from another pathway, thereby regulating its activity and linking the two pathways together



EXERGONIC REACTIONS AND PATHWAYS IN BIOCHEMISTRY

- Complex structures → simple structures

Proteins → amino acids

Starch → glucose

glucose + O₂ → CO₂ + H₂O

- More specifically

- Hydrolysis reactions

- Decarboxylation reactions (release of CO₂)

pyruvate (C₃) → acetyl-CoA(C₂) + CO₂

- Oxidation with O₂

The terms catabolic (degradative) and anabolic (biosynthetic) can describe either individual enzymatic steps or entire metabolic pathways. Pathway-Level vs. Step-Level Thermodynamics: A pathway designated as overall catabolic (such as Glycolysis, which degrades glucose into two smaller molecules) may still incorporate individual endergonic, energy-consuming steps, such as the initial priming phosphorylation of glucose.

Exergonic Processes ($\Delta G < 0$):

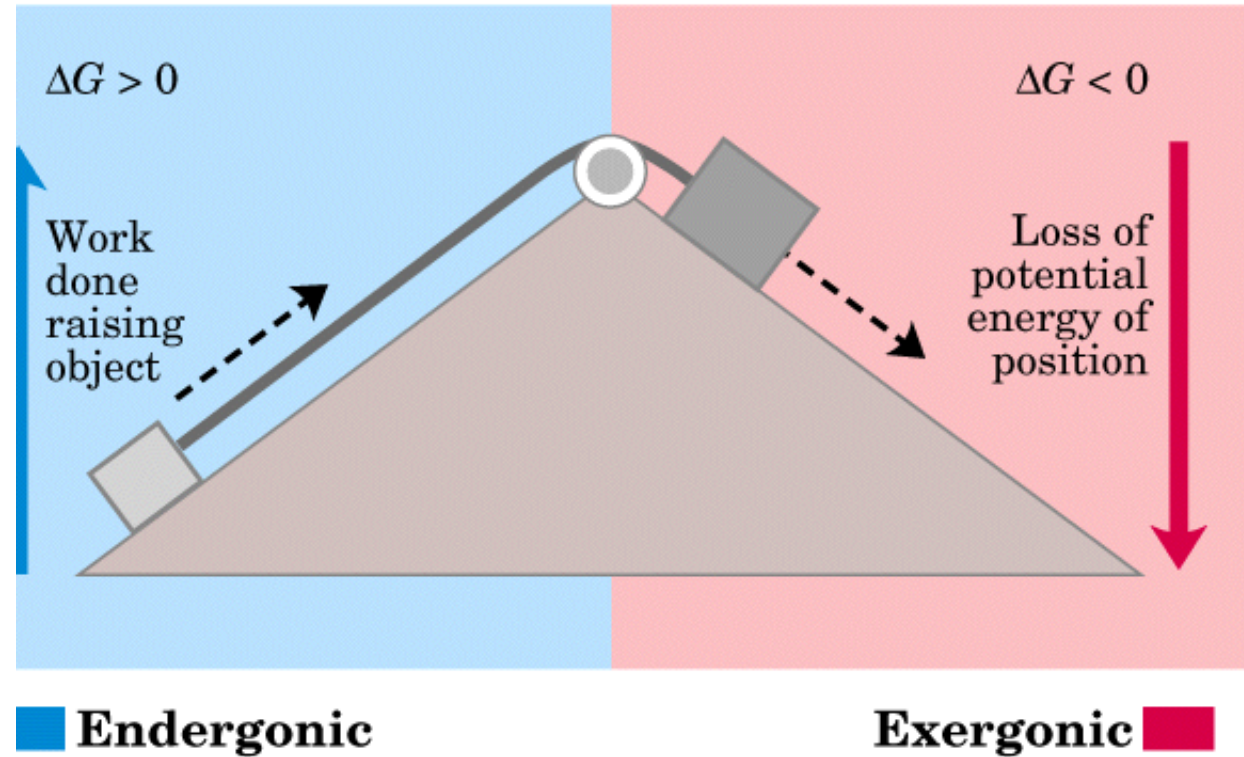
Thermodynamic Spontaneity: Exergonic reactions release free energy and proceed spontaneously under physiological conditions.

Examples:

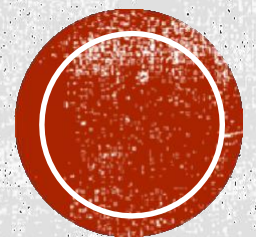
- **Macromolecular Degradation:** The breakdown of complex structures (proteins, carbohydrates, lipids) into simple molecules.
- **Decarboxylation Reactions:** The removal and release of carbon dioxide which is thermodynamically favored.
- **Oxidative Cleavage:** Reactions involving molecular oxygen as an electron acceptor.
- **Endergonic Processes ($\Delta G > 0$):**
- **Non-Spontaneity:** Endergonic reactions require net free-energy input to proceed and cannot occur spontaneously in isolation



(a) Mechanical example



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK? MAKING THE IMPOSSIBLE POSSIBLE



The coupling concept - phosphoryl transfer reactions

How endergonic reactions occur?

Endergonic reactions occur in the body even though they are unfavorable ,how?

- 1) Using high energy molecules by breaking them down** to release enough energy that can drive an endergonic reaction.
- 2) Energy Coupling : (like using a see-saw)** Using a high-energy molecule provides energy and also transfer a chemical group needed by the other reaction so the combined ΔG must be negative.
- 3) Changing the concentration of products and reactants** (by making concentration of reactants very high we could turn ΔG from being positive (Endergonic) at standard condition for being negative (Exergonic).
 - ATP production is important in the body, so a reduction in its production will cause an impairment in cells, (especially cells that require huge amounts of energy).

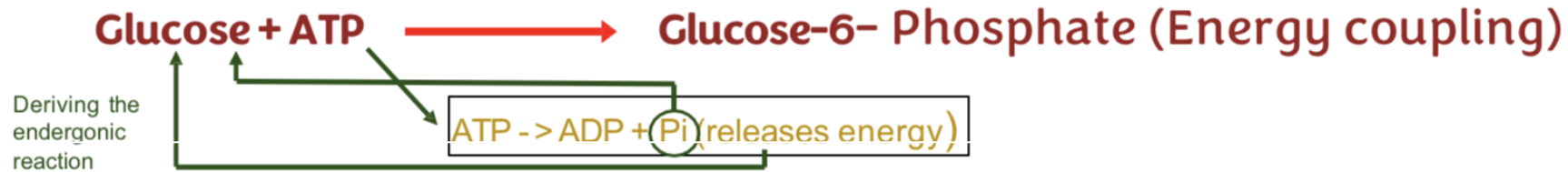
Notes regarding energy coupling:

1- The 2 Reactions happen at the same time and not subsequently.

2- Energy coupling doesn't include only the use of energy released from the breaking down of a highly energetic molecule, it should include the giving of a reactant for the reaction by the molecule with high energy .

Examples on Energy coupling :
(each reaction alone)

- Glucose + Phosphate Group $\rightarrow$ Glucose 6-Phosphate (Endergonic reaction).
- ATP $\rightarrow$ ADP + Pi (Exergonic Reaction).



Hydrolysis of acetyl-CoA releases about **7.5 kcal/mol**, similar to ATP hydrolysis under standard biochemical conditions. However, acetyl-CoA cannot directly replace ATP in a reaction that requires **phosphate transfer**, because it does not supply a phosphate group.

Determinants of Bond Energy

- **High-energy molecules** like ATP and GTP can power endergonic reactions through **energy coupling**.
- The amount of **energy stored in any bond depends** on which **atoms** are bonded to each other and **how they interact with nearby atoms in the same molecule**, including **bond angles**.
- When **ATP is hydrolyzed to ADP**, it releases the same amount of energy as **GTP does when it hydrolyzed GDP**. That's because the nitrogenous base (adenine or guanine) is **far from the phosphate bonds**, so the environment around the bond doesn't affect their energy. Similarly, hydrolyzing **ADP to AMP** releases **approximately the same energy as GDP to GMP** (about 7.3 kcal/mol) for the same reason **the base is too distant to matter**. However, **hydrolysis of the last phosphate bond in AMP versus GMP gives different energies**, since this time the phosphate is **close enough to the nitrogen base (A or G) to be affected by it**.

Determinants of Bond Energy

- **So, Why do cells use different nucleotides in energy-related processes?**
 - We got different types for organizational purposes although they give the same energy ,for example :
 - Energy metabolism we use usually ATP
 - Carbs metabolism we usually use UTP
 - Fats metabolism we usually use CTP
 - Protein metabolism we usually use GTP

CLINICAL CASE: PYRUVATE KINASE DEFICIENCY

- **Role of Pyruvate Kinase**

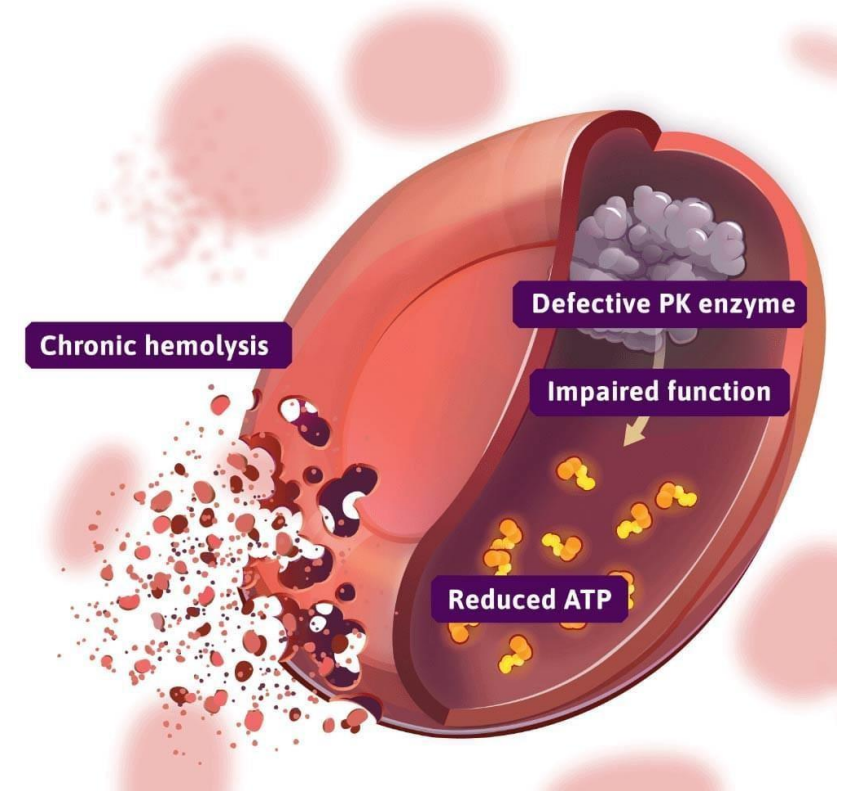
- Pyruvate kinase catalyzes a crucial step in glycolysis important for ATP generation in red blood cells.

- **Impact of Deficiency**

- Deficiency in pyruvate kinase reduces ATP production, causing red blood cell rigidity and hemolytic anemia.

- **Energy Coupling in Cells**

- This case highlights how energy coupling via ATP is vital for maintaining cellular health and function.



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

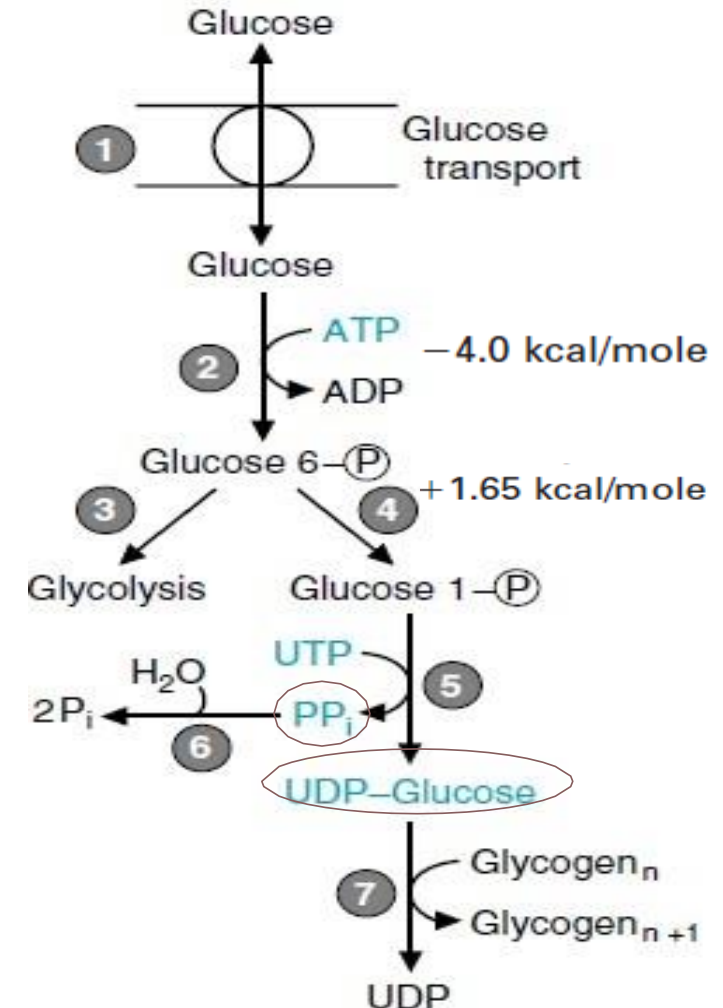
I. ΔG^0 Values are additive

i. Through phosphoryl transfer reactions:

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

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

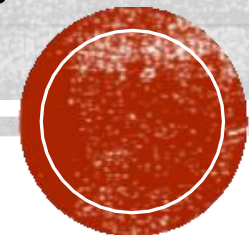
II. ΔG Depends on Substrate and Product Concentration (step 4 has a ratio of 6/94; +1.65 kcal/mol, if 3/94; -0.4kcal/mol)

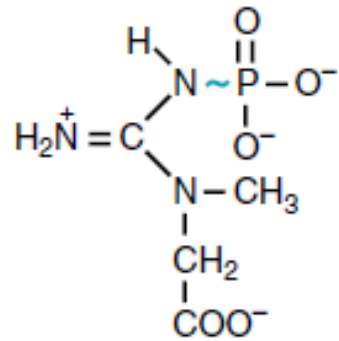


	Concentration (mM)*			
	ATP	ADP [†]	AMP	P _i
Rat hepatocyte	3.38	1.32	0.29	4.8
Rat myocyte	8.05	0.93	0.04	8.05
Rat neuron	2.59	0.73	0.06	2.72
Human erythrocyte	2.25	0.25	0.02	1.65
E. coli cell	7.90	1.04	0.82	7.9

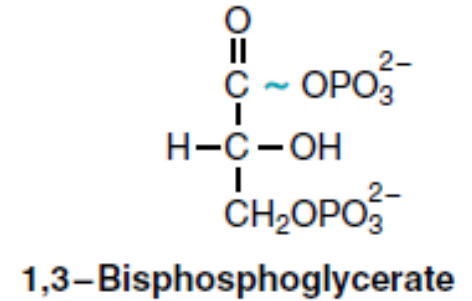
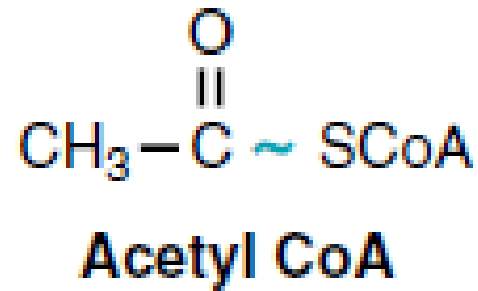
**THE FREE-
ENERGY CHANGE
FOR ATP
HYDROLYSIS IS
LARGE AND
NEGATIVE**

Not fixed and depends on
concentrations





Creatine phosphate



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

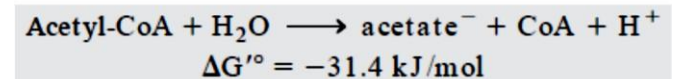
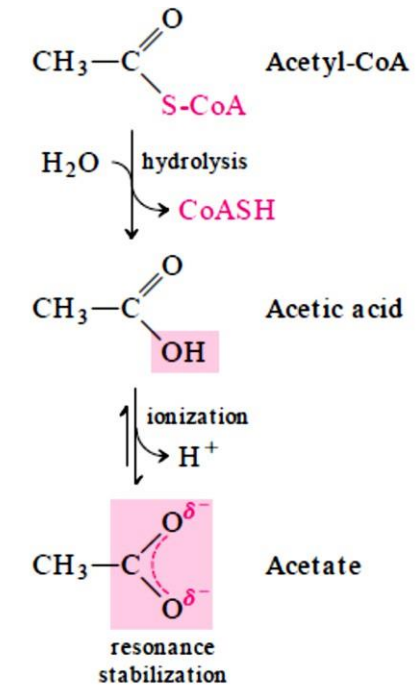
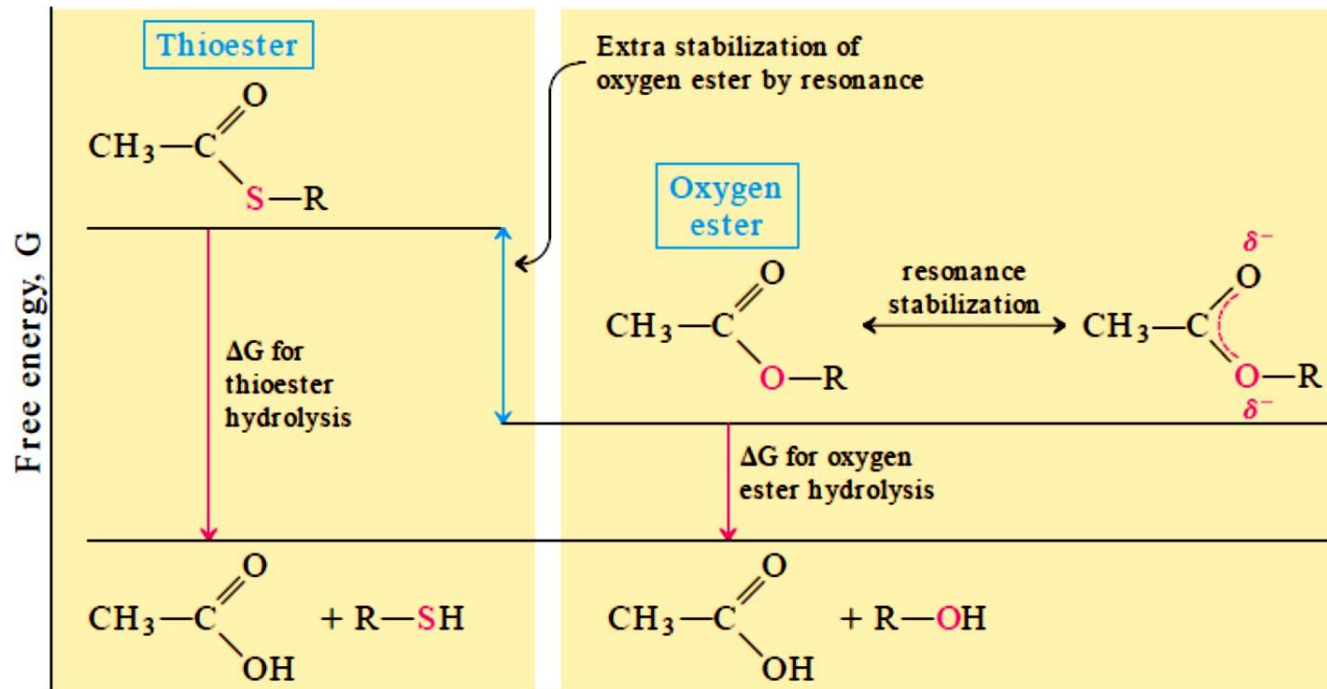
III. Activated Intermediates other than ATP; UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis

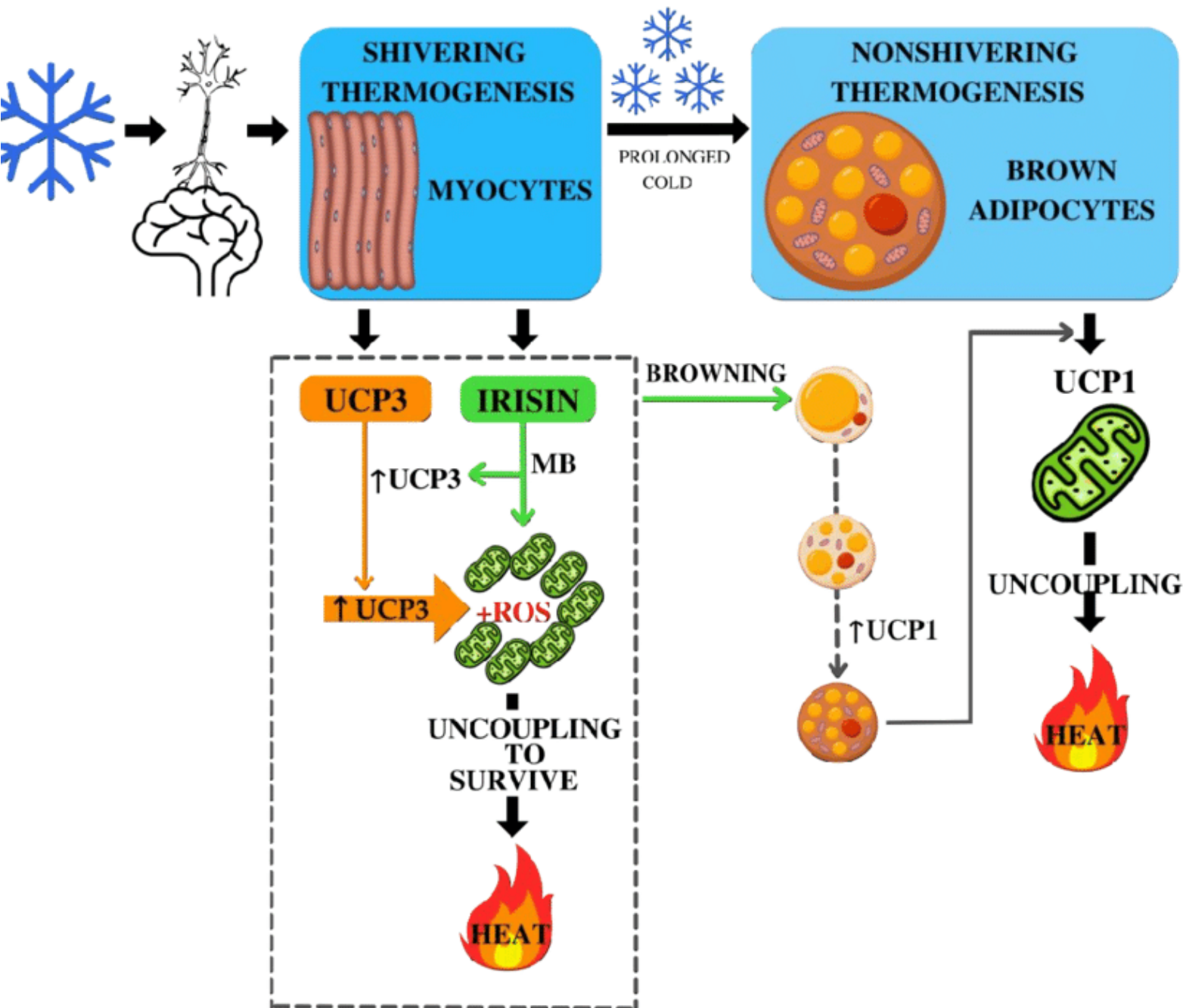


THE ACETYL COA AS AN EXAMPLE OF COUPLING

- CoA is a universal carrier (donor) of Acyl groups
- Forms a thio-ester bond with carboxyl group

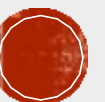
- Acetyl CoA + H₂O → Acetate + CoA $\Delta G^{\circ} = -7.5 \text{ kcal}$
- Acetylcholine + H₂O → Acetate + Choline $\Delta G^{\circ} = -3 \text{ kcal}$



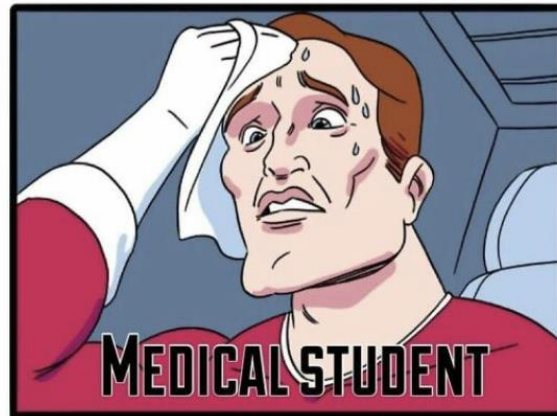


THERMOGENESIS

- The first law of thermodynamics
- Heat production is a natural consequence of “burning fuels”
- Thermogenesis refers to energy expended for generating heat
- Shivering thermogenesis
- Non-shivering thermogenesis



Quiz!



Additional resources

Reference Used:

Dr. Nafez Abutarboush's Lecture

سُبْحَانَ اللَّهِ
وَأَحْمَدُ لِلَّهِ
وَلَا إِلَهَ إِلَّا اللَّهُ
وَاللَّهُ أَكْبَرُ

رسالة من الفريق العملي

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



Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slides 3,4 and 5	-	Revision slides, you can understand them by referring to the previous modified
	Slides 27 through 32	Weren't even there	Now they are there!
V1 → V2			