بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Lecture #

Bioenergetics Pt.3

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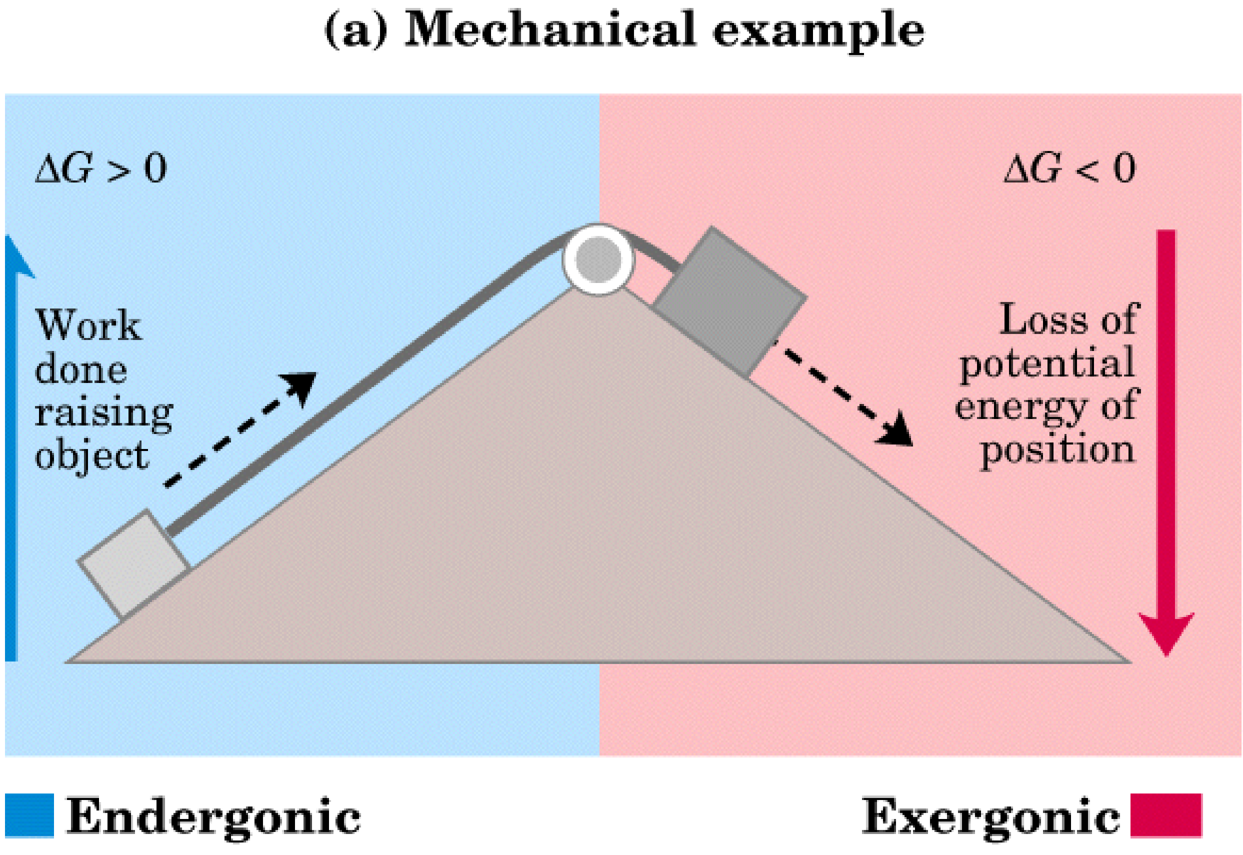


HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK? MAKING THE IMPOSSIBLE POSSIBLE

The coupling concept - **phosphoryl transfer reactions**

How our cells get energy for the unfavourable biochemical work? Making the impossible possible.

- **Endergonic reactions** occur in the body even though they are **unfavorable.**

- There are different ways in the body by which these reactions **occur**, such as :

1) **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).

2) **Breaking down of a highly energetic molecule** to release an energy that can drive an endergonic reaction.

3) **Energy Coupling :** Using a molecule of high energy (by breaking it down) to release an energy that is enough to drive an endergonic reaction and it also (the high energy molecule) give the reaction a reactant.

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).

How our cells get energy for the unfavourable biochemical work? Making the **impossible possible.**

- Notes Regarding energy coupling :

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

- Energy coupling doesn't include only the using of energy released from the breaking down of a highly energetic molecule, it also include the giving of a reactant for the reaction by the highly energetic molecule.

- Examples on Energy coupling :

Glucose + Phosphate Group ⟶ Glucose 6-Phosphate (Endergonic reaction).

ATP ⟶ ADP + Pi (Exergonic Reaction).

Glucose + ATP ⟶ Glucose 6 – Phosphate (Energy coupling)

Giving a reactant

Deriving the endergonic reaction

ATP -> ADP + Pi (releases energy)

- Glucose + Phosphate Group → Glucose 6-Phosphate **(Endergonic reaction).**

ATP → ADP + Pi **(Exergonic Reaction).**

Glucose + ATP → Glucose 6 - Phosphate **(Energy coupling)**

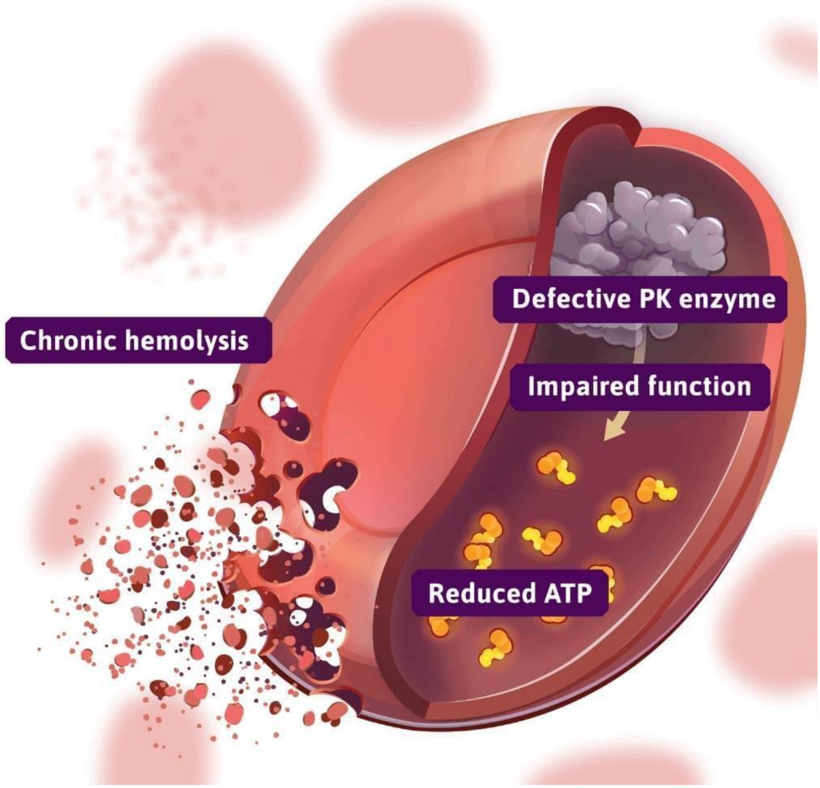
Hydrolysis of Acetyl CoA gives 7.5 kcal/mol which is similar to ATP hydrolysis in terms of energy; however, I can't use Acetyl CoA because I need the phosphate from ATP

Acetylcholine is synthesized by merging Acetate with choline which needs 3 kcal/mol. In this case, we use Acetyl CoA because it gives us Acetate.

CLINICAL CASE: PYRUVATE KINASE DEFICIENCY

Enzyme that catalyzes the last step of glycolysis.

- **Role of Pyruvate Kinase**
  - Pyruvate kinase catalyzes a crucial step (last step) in glycolysis, glycolysis is important for ATP generation in red blood cells and all other cells. RBCs are the most affected by pyruvate kinase deficiency, because RBCs only use glycolysis for energy production since it doesn't have mitochondria.
- **Impact of Deficiency**
  - Deficiency in pyruvate kinase reduces ATP production, causing red blood cell **rigidity and hemolytic anemia.** might demolish the cell.
- **Energy Coupling in Cells**
  - This case highlights how energy coupling via ATP is vital for maintaining cellular health and function.



Determinants of the 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 becomes GDP**. That's because the nitrogen 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 the same energy **as GDP to GMP** (about 7.3 kcal/mol) for the same reason – **the base is too distant to matter.**

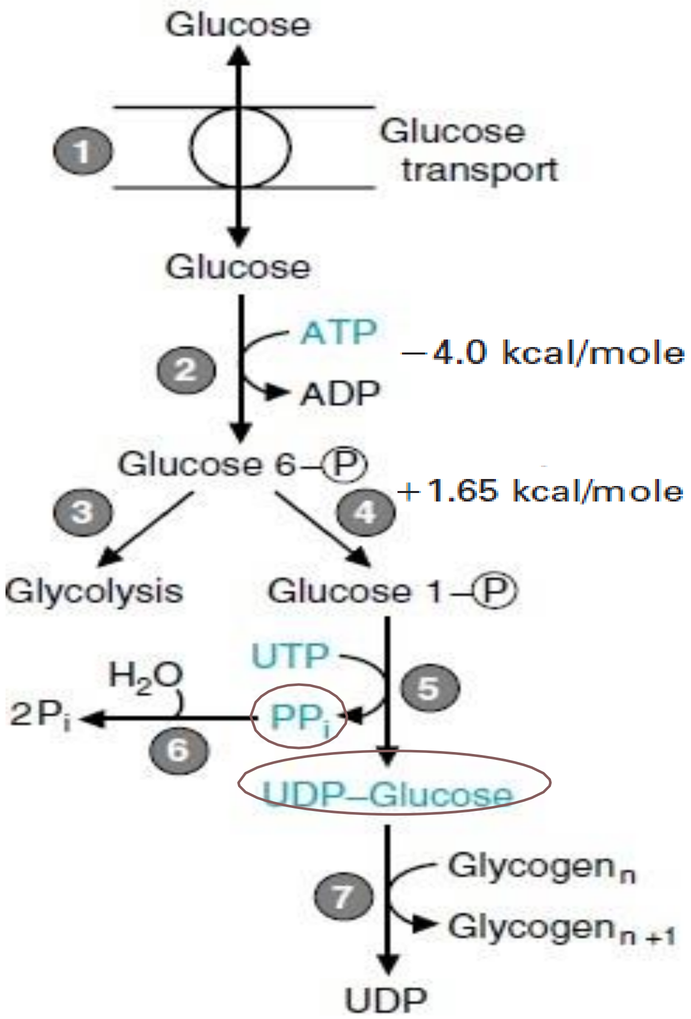
- However, **breaking the last phosphate bond in AMP versus GMP** gives **different energies**, since **this time the phosphate is close enough to the nitrogen base (A or G) to be affected by it.**

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
      - <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)

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)



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

Glycogenesis

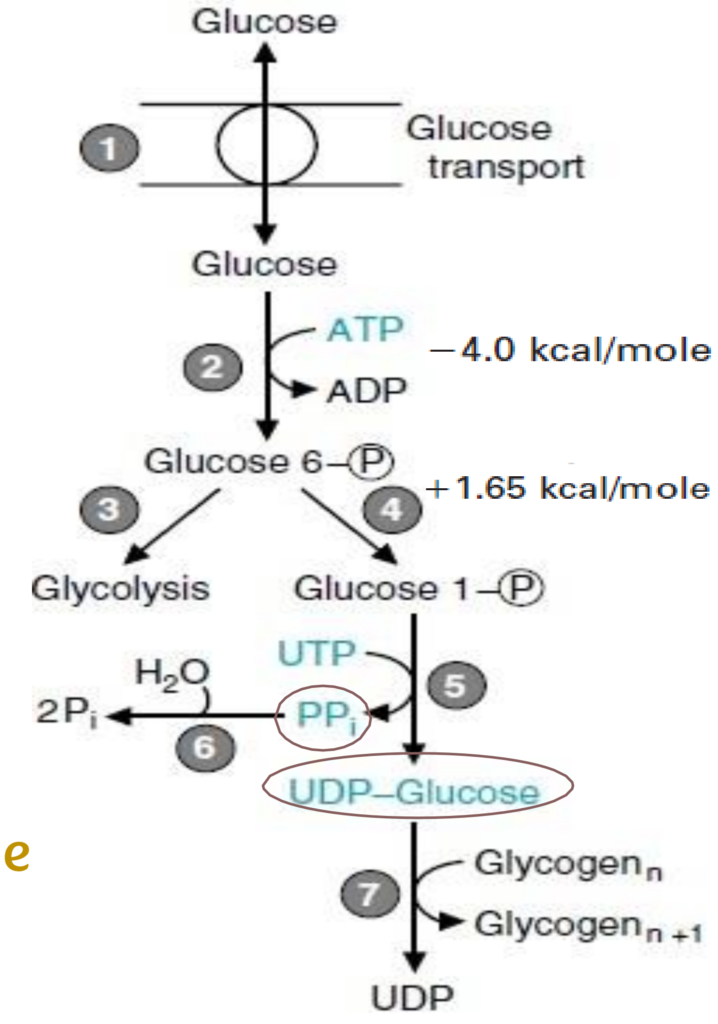
1) Glucose enters the cell.

2) Once glucose enter the **cell it should be phosphorylated.**

Glucose + ATP → ADP + Glucose 6-Phosphate (-4 Kcal/mol, happens by energy coupling).
ATP → ADP + Pi (releases 7.3 Kcal/mol).
glucose + Pi → Glucose 6 – Phosphate (absorbs 3.3 Kcal/mol).

4) **Glucose 6-Phosphate → Glucose 1 – Phosphate (needs energy , +1.65 Kcal/mol).**

In this step **the ratio between products to reactants in standard conditions (G1P/G6P) is 6/94** ,By **increasing** reactants so ratio will be **3/94** the ΔG will go from **+1.65 Kcal/mol to -0.4 Kcal/mol** (from endergonic to exergonic, or **from impossible to possible).**

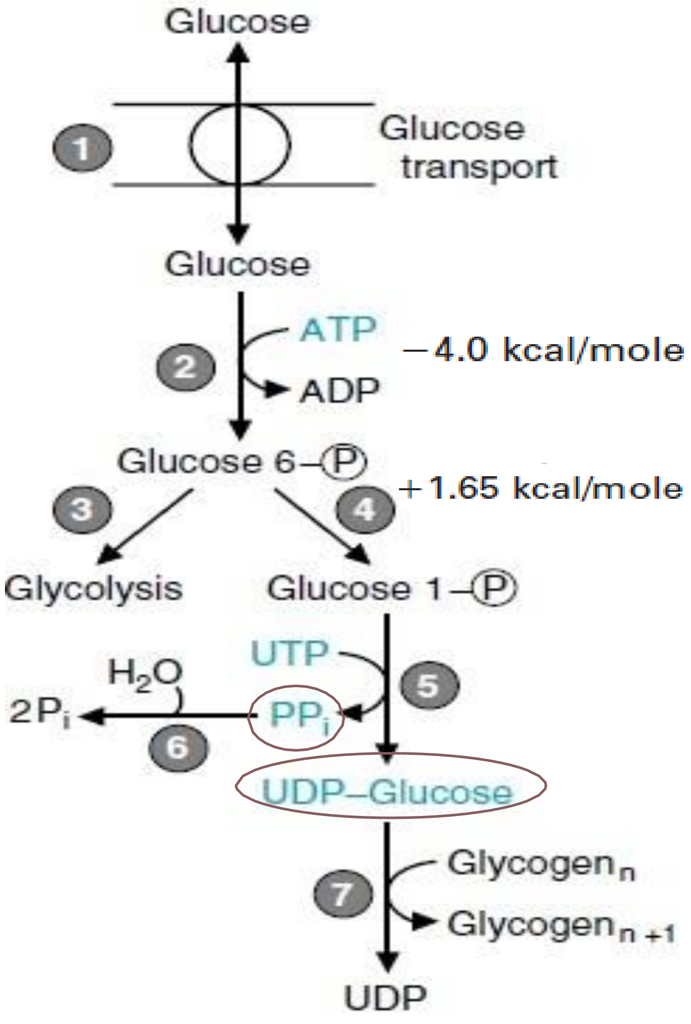


HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

Glycogenesis

5) Glucose 1-Phosphate + UTP → UDP-Glucose + PPi(Pyrophosphate) (by energy coupling).

UTP → UDP + Pi
Glucose 1-Phosphate → Glucose + Pi
UDP + Glucose → UDP-Glucose



7) UDP-Glucose + Glycogen(n) → Glycogen(n+1) + UDP (By energy coupling).

n: number of Glucose in glycogen

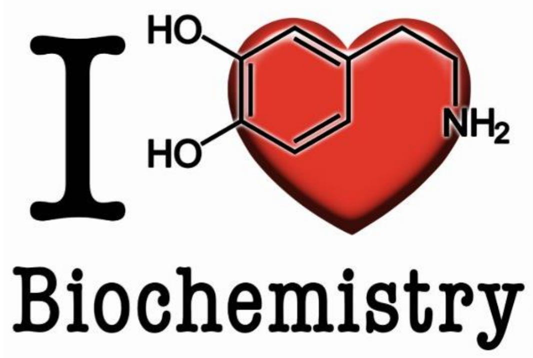
UDP-Glucose is a high energy intermediate, which is synthesized by our body during pathway to use it to run endergonic reaction

The difference in ATP, GTP, CTP in localization in deferent pathways

- There is a **specific localization of ATP, ADP, AMP within the cell in different pathways :**

- **Carbohydrate** Metabolism **: UTP** is used more than others.
- **Lipid** Metabolism **: CTP** is used more than other.
- **Protein** Metabolism **: GTP** is used more than others.

- Note : **ATP, CTP, GTP** is completely **the same except for the nitrogenous base** which **doesn't affect the amount of energy released upon hydrolysis**, but the **difference in nitrogenous base is important for regulation purposes.**

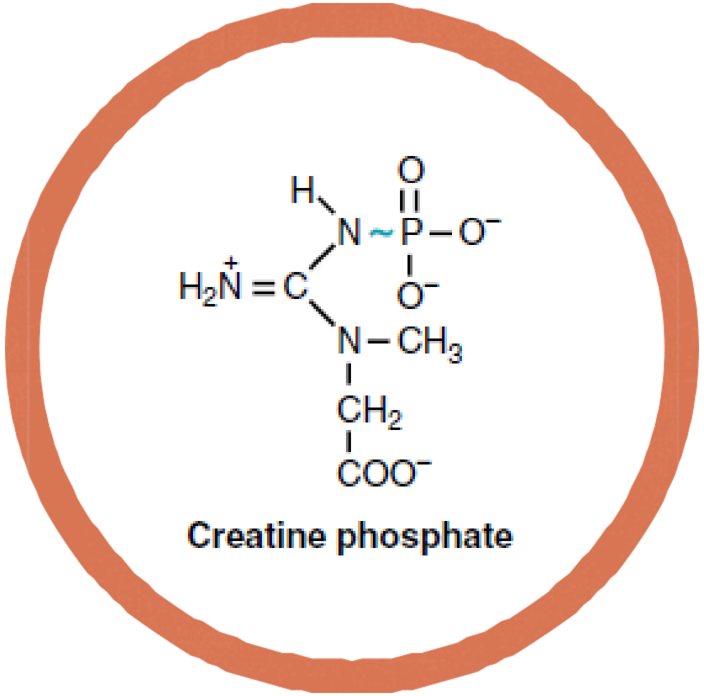


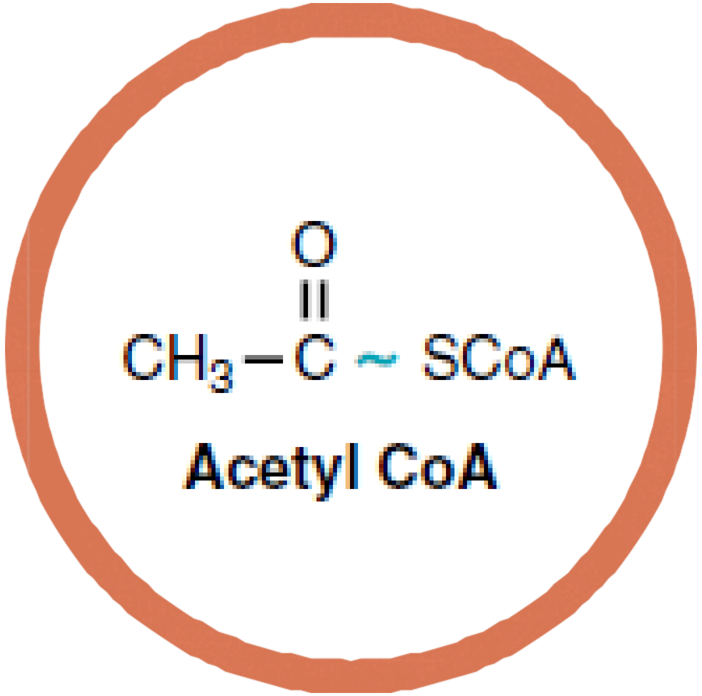
Question : which one is best for the cell?
Ans : make calculations and answer the highest energy.

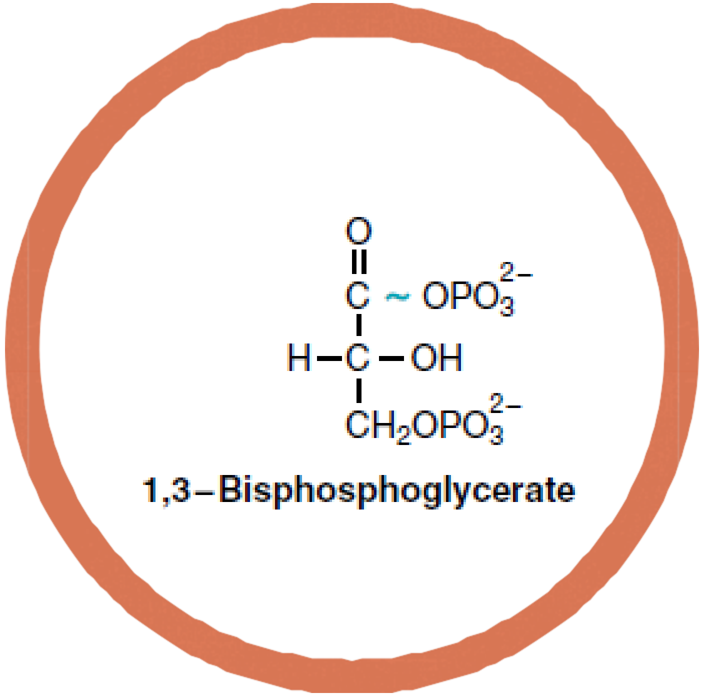
	Concentration (mM)*			
	ATP	ADP†	AMP	P_i
Rat hepatocyte	3.38	1.32	0.29	4.8
Rat myocyte	8.05	0.93	0.04	8.05
Rat neuron	2.59	0.73	0.06	2.72
Human erythrocyte	2.25	0.25	0.02	1.65
E coli cell	7.90	1.04	0.82	7.9

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

Not fixed and depends on concentrations





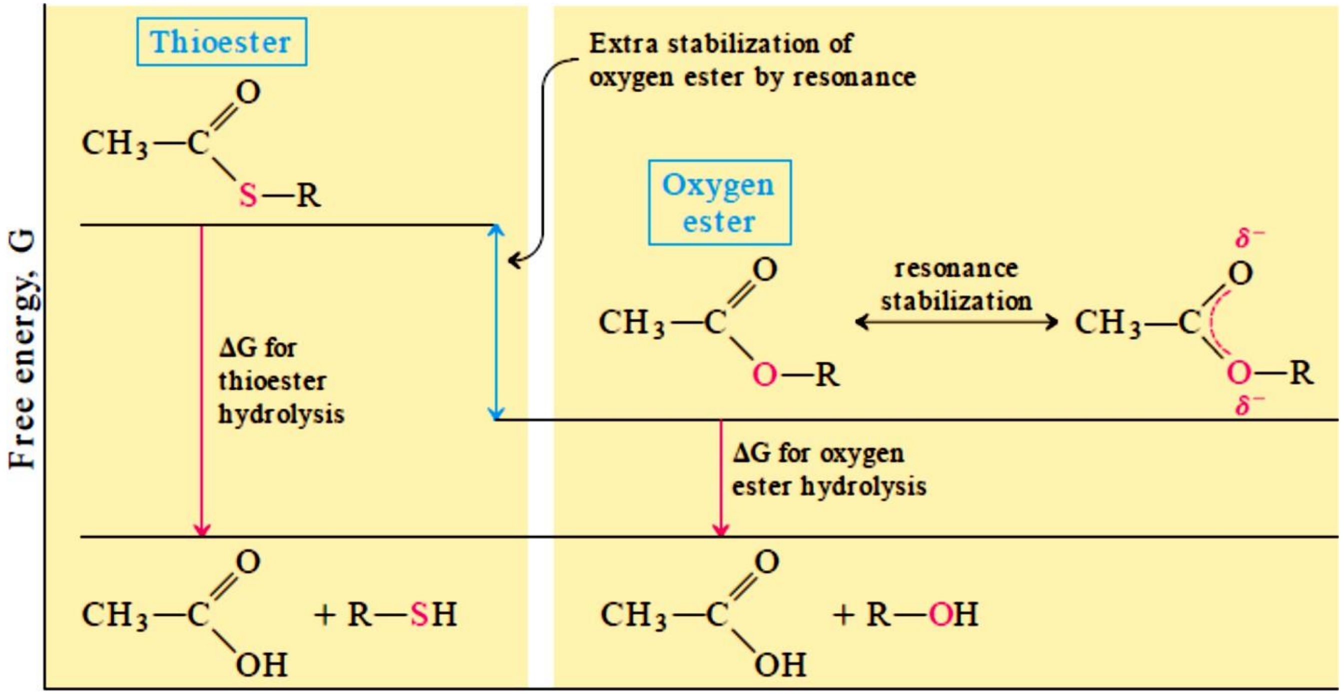


HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

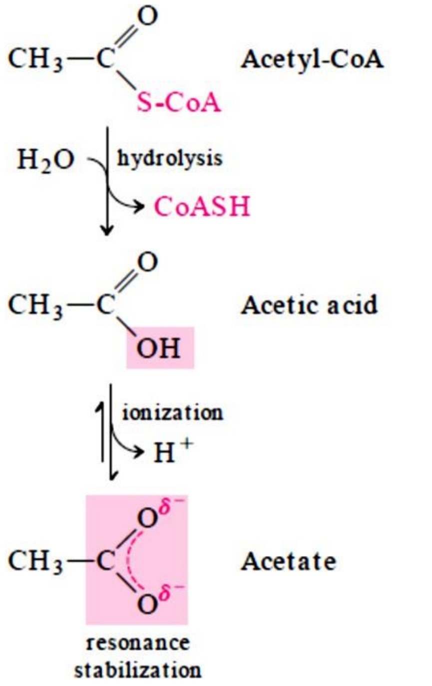
III. Activated Intermediates other than ATP; UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis

THE ACETYL COA AS AN EXAMPLE OF COUPLING

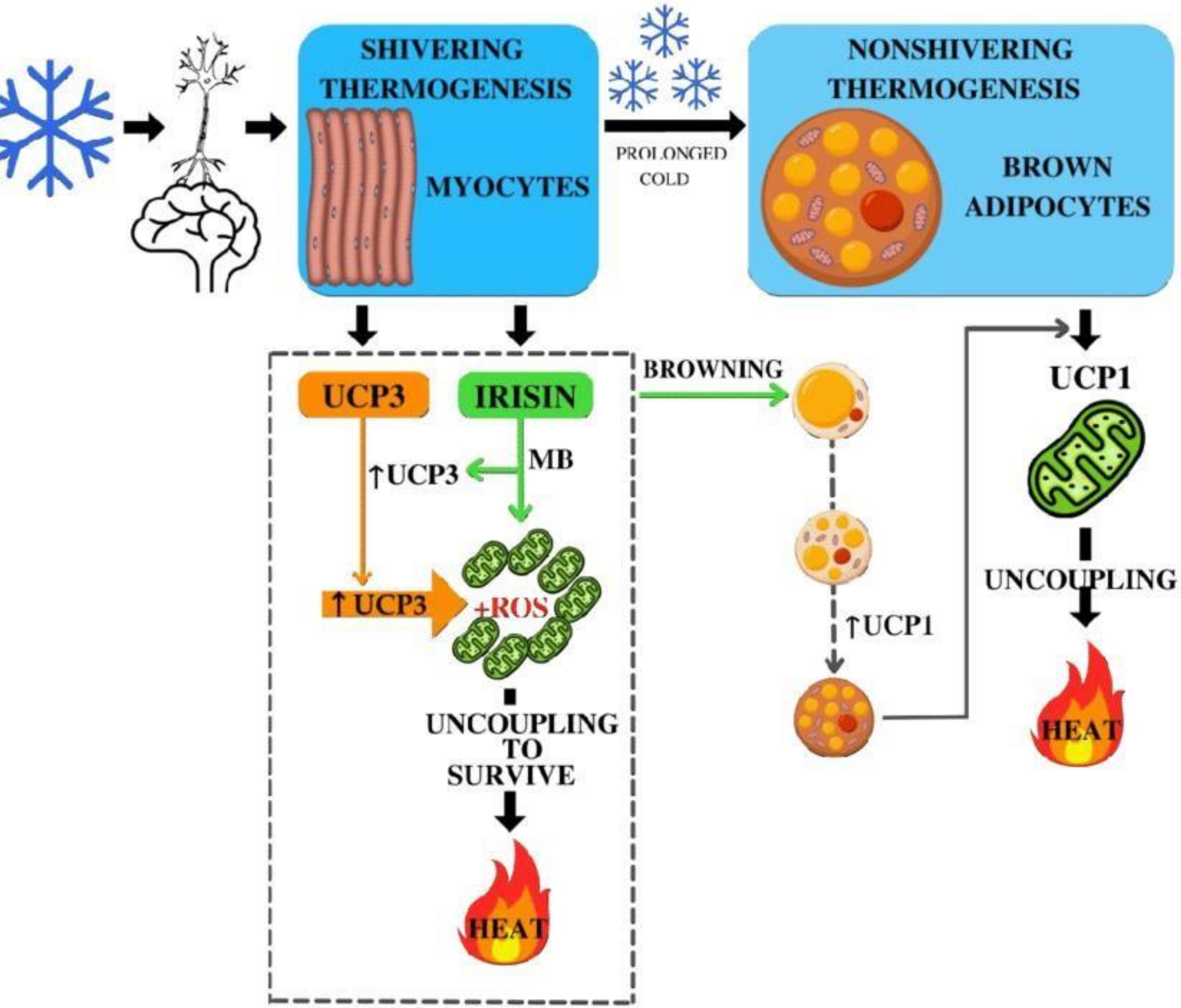
- CoA is a universal carrier (donor) of Acyl groups
- Forms a thio-ester bond with carboxyl group



- Acetyl CoA + H_2O → Acetate + CoA ΔG^o = -7.5kcal
- Acetylcholine + H_2O → Acetate + Choline ΔG^o = -3 kcal



Acetyl-CoA + H_2O ⟶ acetate$^-$ + CoA + H^+
$\Delta G'^{o} = -31.4$ kJ/mol



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

THERMOGENESIS

- What is Thermogenesis?

- Thermo : Heat.

- Genesis : Very well and Highly regulated process.

- Thermogenesis : Very well and Highly regulated mechanism of heat production.

- Question : Is the heat production in our body is random or highly regulated process?

- All humans body temperature (regardless of their weight, tall, gender or geographical localization) is between 36.5 – 37.5 ºC (At homeostasis) which means it is a process that is highly and precisely regulated and not random.

- Why we don't feel that our body is cold neither hot at 37 ºC but we feel it cold at 39 ºC (when we have flu for example)?
- Hypothalamus sets our body's **normal temperature** at which we feel neither cold nor hot.

- When we have the flu, our body temperature increases (for example, to 38 °C). We feel cold because the hypothalamus raises the **normal temperature** at which we feel neither hot nor cold (from 37 °C to 39 °C). So even though our body temperature is higher than normal, the body "thinks" it is lower and makes us feel cold. When we are having flu, our temperature is 38 C ° for example, while the normal temperature is 39 C °, so I am colder (38 C°) than the newly modified normal temperature. (39 C °).

THERMOGENESIS

Hypothalamus increases the temperature to kill microorganisms which is a protective mechanism

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- The mechanisms in which the heat production is maintained are classified into :

- Short-term Mechanism (Shivering thermogenesis) :

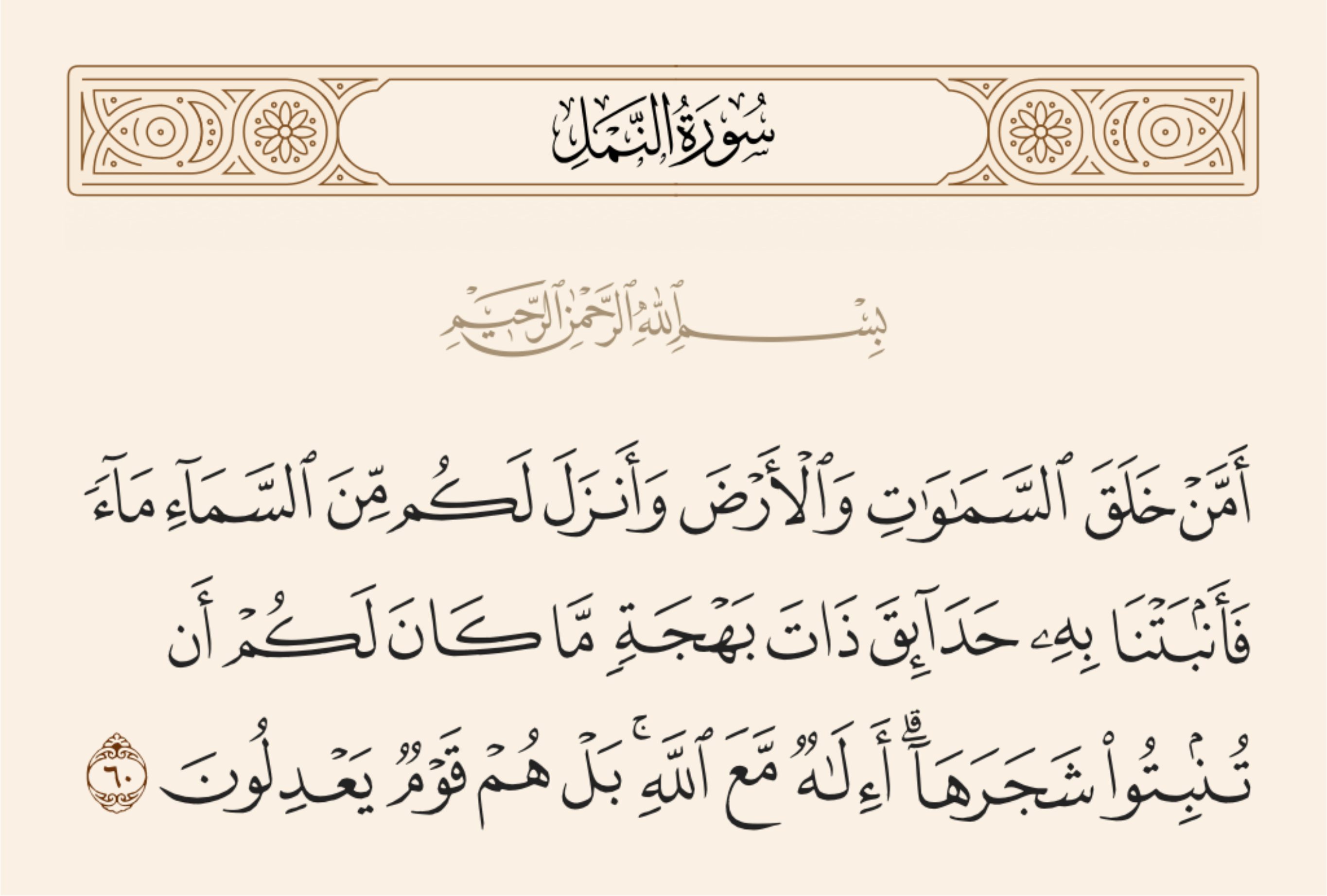
Shivering (ارتعاش) occurs due to sudden change in temperature in order to produce more heat.
In shivering, muscles contract and relax rapidly which uses ATP, but hydrolysis processes is not completely efficient, so there will be an energy loss as heat which rises our body temperature.

- Long-term Mechanism (Non-Shivering thermogenesis, also called Adaptive thermogenesis) :

Send a message to the cell for increasing ATP hydrolysis and since the ATP Hydrolysis is not that efficient, there will be a part of energy lost as heat which rises our body temperature.

In the mitochondria, the main driving force of ATP production is protons concentration in the intermembrane space.
Some of protons will be used for ATP production, others will be used for heat production
The usage of ATP for Heat production is different between individuals.

رسالة من الفريق العلمي:


سُورَةُ النَّمْلِ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

أَمَّنْ خَلَقَ السَّمَاوَاتِ وَالْأَرْضَ وَأَنزَلَ لَكُم مِّنَ السَّمَاءِ مَاءً
فَأَنبَتْنَا بِهِ حَدَائِقَ ذَاتَ بَهْجَةٍ مَّا كَانَ لَكُمْ أَن
تُنبِتُوا شَجَرَهَا ۗ أَإِلَٰهٌ مَّعَ اللَّهِ ۚ بَلْ هُمْ قَوْمٌ يَعْدِلُونَ ٦٠

واسألهم مَن خلق السموات والأرض، وأنزل لكم من السماء ماءً، فأنبت به حدائقَ ذات منظرٍ حسن؟ ما كان لكم أن تُنبتوا شجرَها، لولا أن الله أنزل عليكم الماء من السماء. إنّ عبادته سبحانه هي الحق، وعبادةُ ما سواه هي الباطل. أمعبودٌ مع الله فعل هذه الأفعال حتى يُعبَد معه ويُشرَك به؟ بل هؤلاء المشركون قومٌ ينحرفون عن طريق الحق والإيمان، فيُسوّونَ باللهِ غيرَه في العبادةِ والتعظيم.

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

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	9 17	reactants to products Intramembrane space	products to reactants Intermembrane space
V1 → V2			