



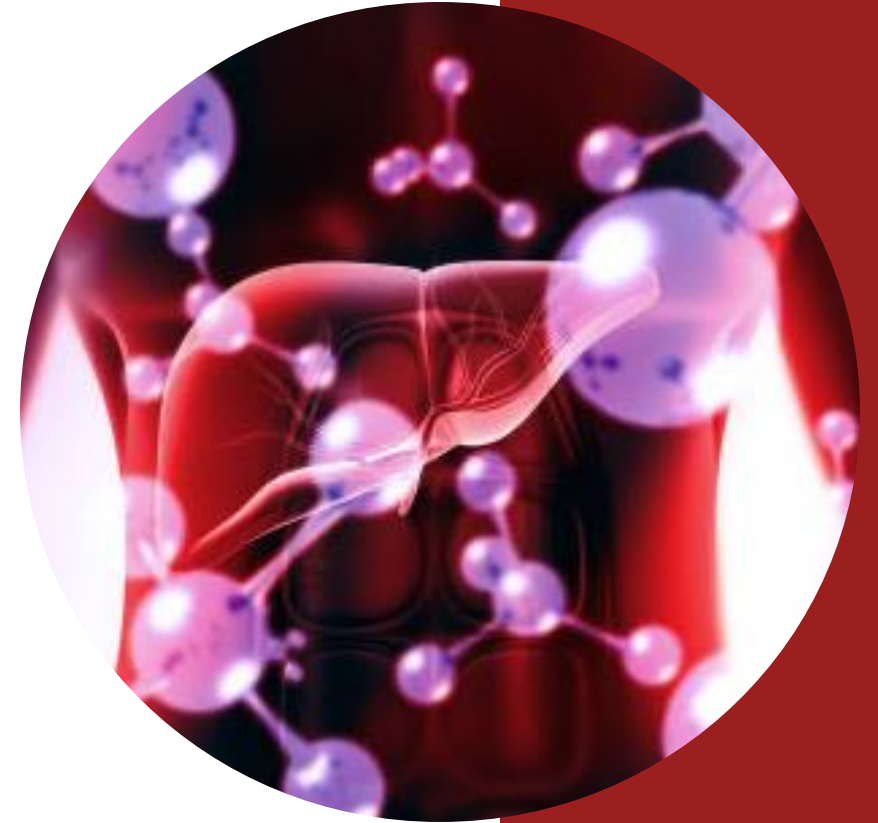
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ

⚙ METABOLISM

MID | Lecture 4

Bioenergetics & Thermodynamics pt.4

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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



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

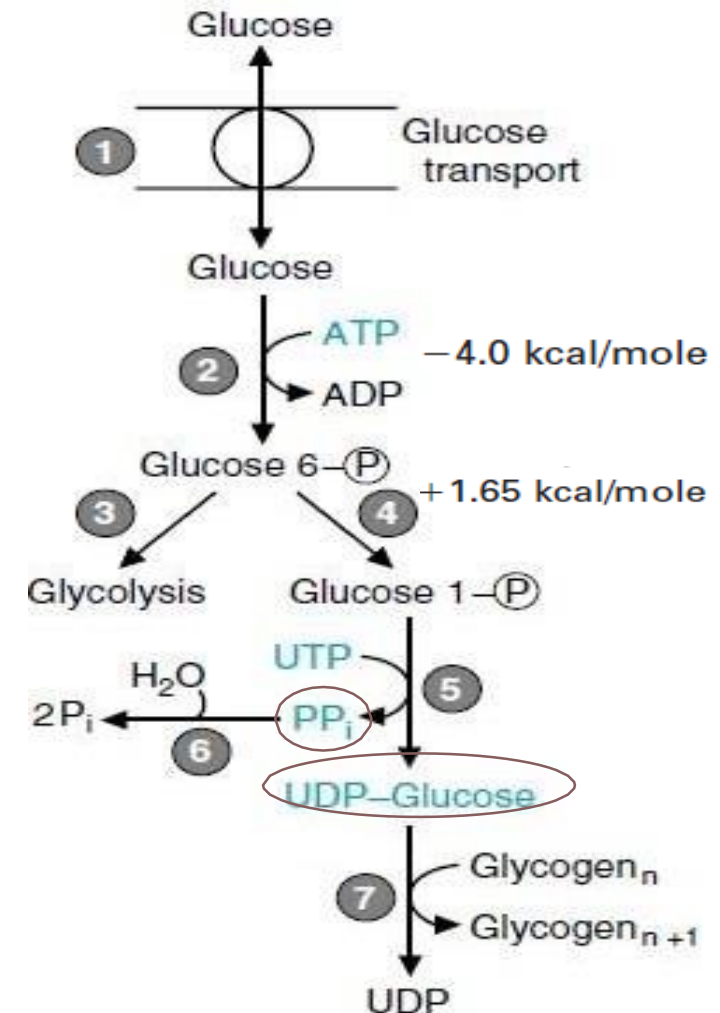
I. ΔG^0 Values are additive

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)



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

Glycogenesis

1) Glucose enters the cell.

Note: G6P has more Gibbs free energy than glucose, because it is the same molecule -has the same bonds- (bonds store energy) in addition to the bonds added when adding a phosphate group

2) Once glucose enter the cell it should be phosphorylated.
(To be trapped inside the cell, this occurs in all pathways not only this)

Glucose + ATP → ADP + Glucose 6-Phosphate (-4 Kcal/mol, happens **by energy coupling**).

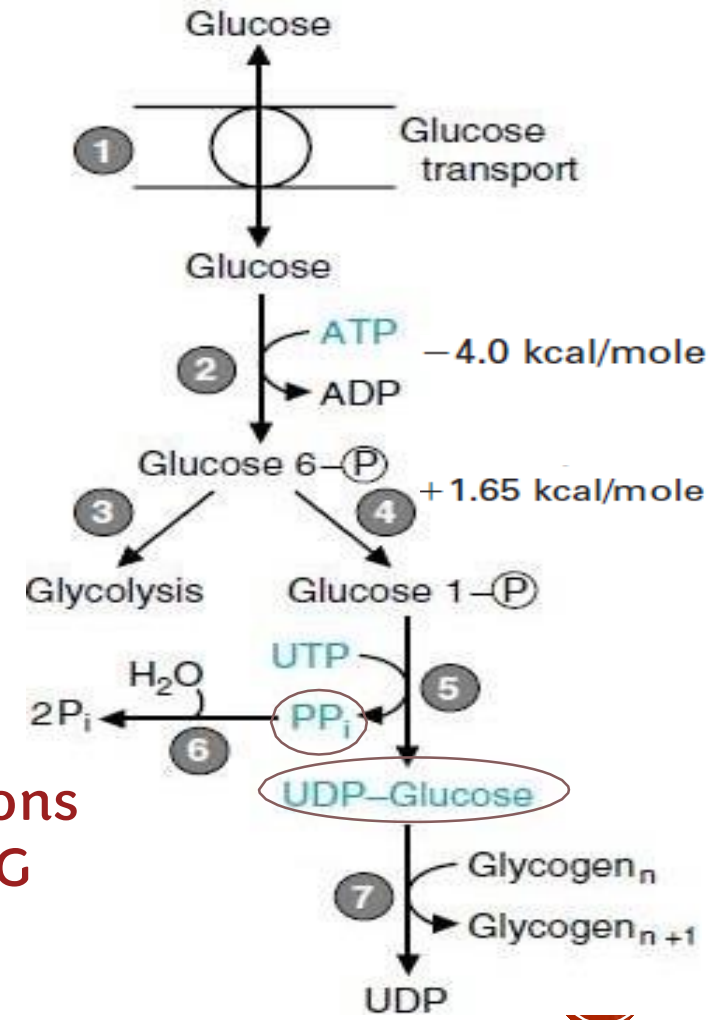
ATP → ADP + P_i (releases 7.3 Kcal/mol).

glucose + P_i → Glucose 6-Phosphate (absorbs 3.3 Kcal/mol).

The extra free energy (4Kcal/mol) is used to run next reactions

3) 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 (step 3)).



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

Glycogenesis

4) Glucose 1-Phosphate + UTP → UDP-Glucose + PP_i(Pyrophosphate)
(by energy coupling).
High energy intermediate

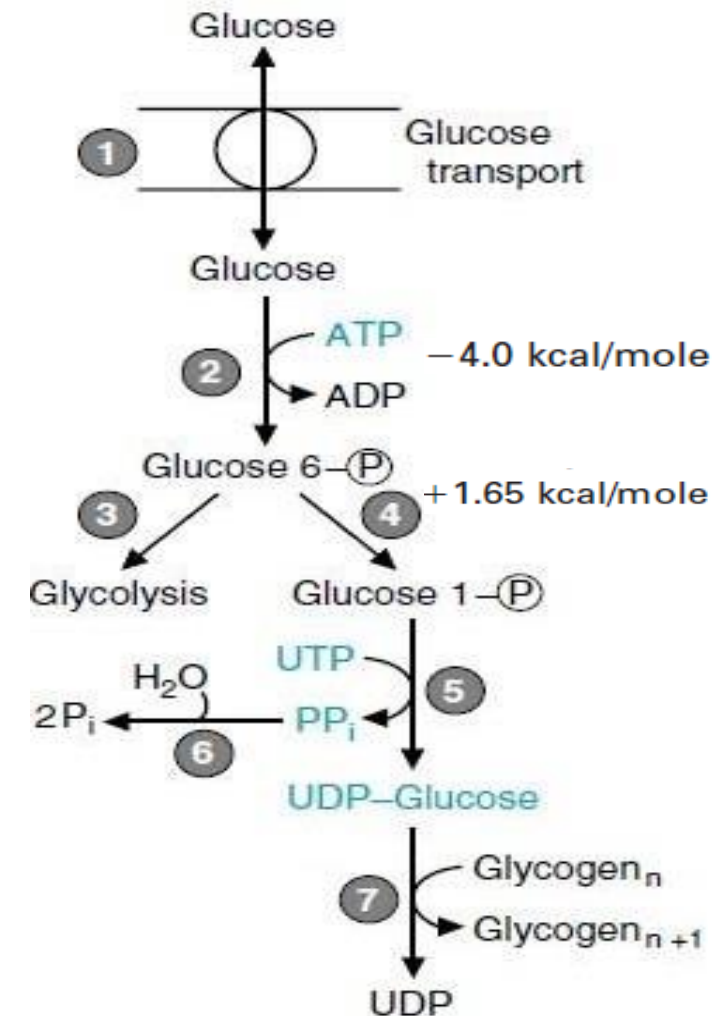
5) UDP-Glucose + Glycogen(n) → Glycogen(n+1) + UDP (By energy coupling).

n: number of Glucose in glycogen

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

6) PP_i → 2P_i

High energy intermediate



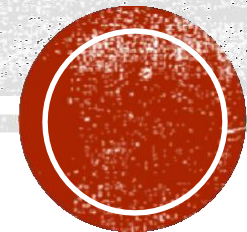
Question : which one is best for the cell?

Ans : make calculations and answer the highest energy.

	Concentration (mM)*			
	ATP	ADP ⁱ	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

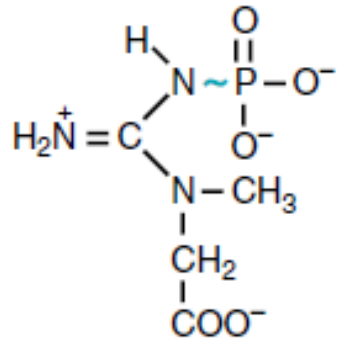


The difference in ATP, GTP, CTP in localization in different pathways

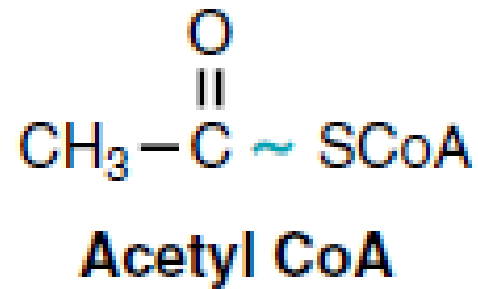
- There is a specific localization of ATP, ADP, AMP within the cell in different pathways :
 - **Carbohydrate Metabolism** : **UTP** is used more than others.
 - **Lipid Metabolism** : **CTP** is used more than other.
 - **Protein Metabolism** : **GTP** is used more than others.
- Note : **ATP, CTP, 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.



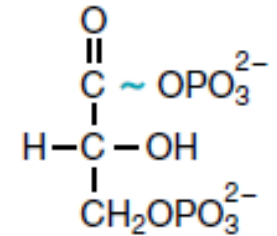
Another High energy molecules used in our bodies



Creatine phosphate



Acetyl CoA



1,3-Bisphosphoglycerate

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

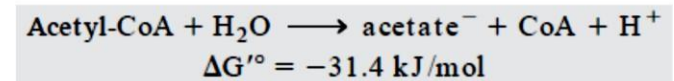
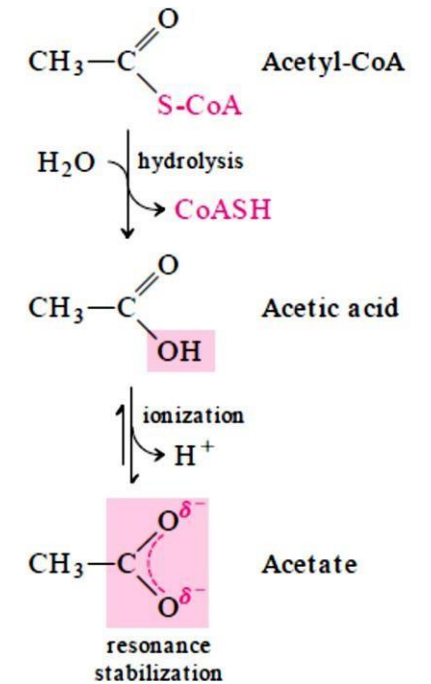
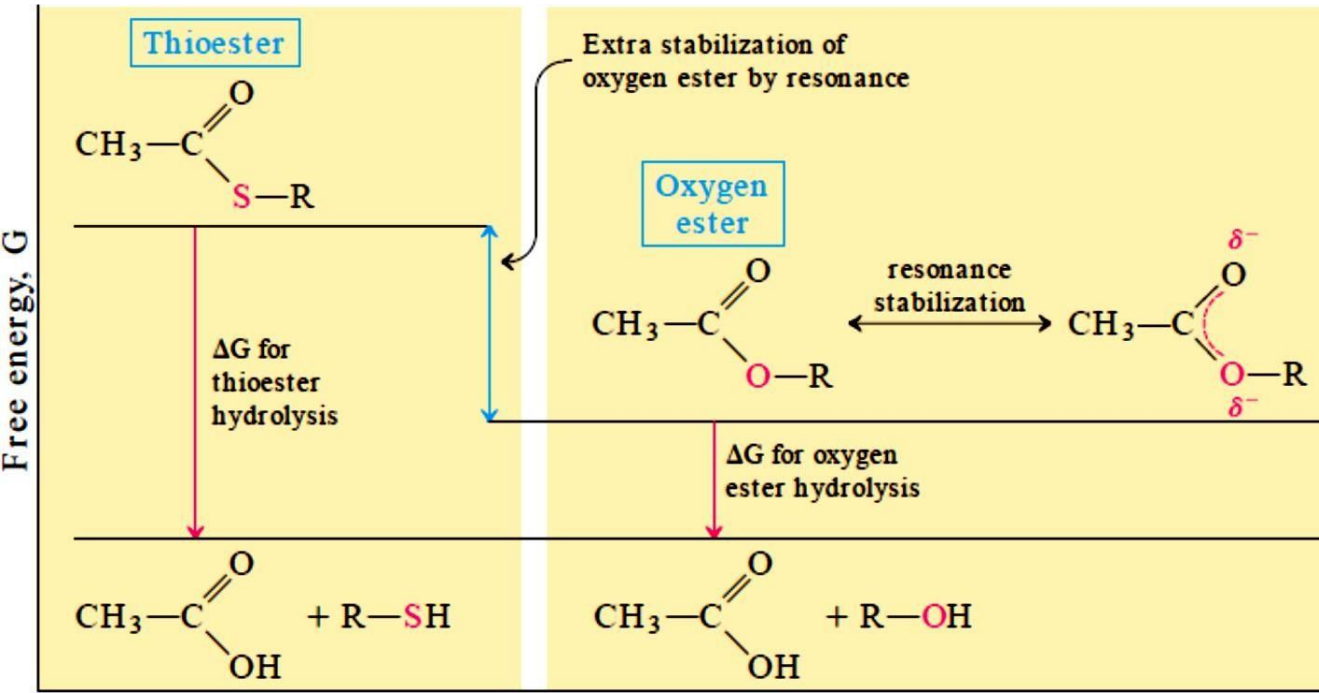


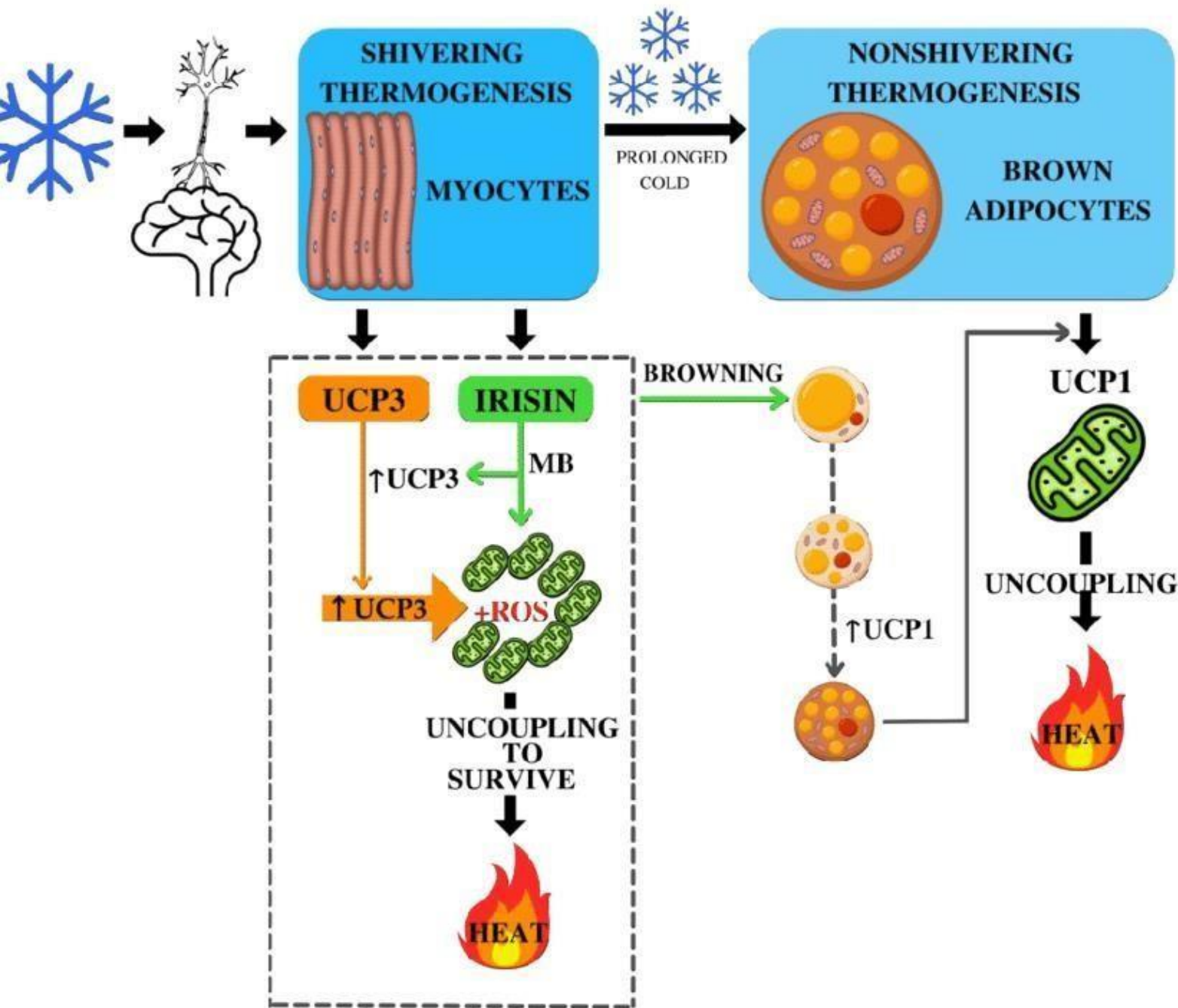
THE ACETYL COA AS AN EXAMPLE OF COUPLING

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

Synthesizing Acetylcholine is done by energy coupling using COA

choline + Acetyl-COA ----> Acetylcholine + COA





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 a highly regulated process?

- All humans body temperature (regardless of their weight, tall, gender or geographical localization) is between 36.5 – 37.5 °C (At homeostasis) which means it is a process that is highly and precisely regulated and not random.
- Why don't we feel that our body is cold neither hot at 37 °C (when we are healthy) but we feel it cold at 39 °C (when we have flu for example)?
- Hypothalamus sets our body's normal temperature at which we feel neither cold nor hot at 37 C.
- When we have the flu, the hypothalamus raises the set-point for temperature in order to kill the microorganisms in the body (for example, to 38 °C). So we feel cold because the normal temperature (set-point) at which we feel neither hot nor cold is raised (from 37 °C to 38 C) and the body's temperature is still lower than the set point (37 C). Until the body's temperature reaches 38 C , you will still feel cold.



THERMOGENESIS

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

➤ **Short-term Mechanism (Shivering thermogenesis) : (Uncontrolled)**

Shivering occurs due to sudden change in temperature. It occurs in order to produce more heat. In shivering, muscles contract and relax rapidly which uses ATP so the body compensates for the used ATP by synthesizing more ATP, and ATP synthesis produces heat as a byproduct so the body's temperature is raised.

➤ **Long-term Mechanism (Non-Shivering thermogenesis, also called Adaptive thermogenesis) :**
Send a message to the cell via proteins 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. It is called adaptive thermogenesis because it's different between individuals because of different factors (age, weight, gender, height, etc...). But it always aims to keep the body at a certain 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.



PRINCIPLES OF BIOENERGETICS

3- Biological Oxidation-Reduction Reactions
(Redox)

OXIDATION-REDUCTION REACTIONS (REDOX)

- They are highly associated and relevant to the topic of Bioenergetics because a lot of our metabolic pathways involve moving electrons and energy from different substances.
- Energy production is all about the transfer of electrons from one molecule to another (for example, Krebs cycles main goal is to produce an electron carrier molecules (NAD⁺ & FAD) which is an oxidation-Reduction reaction. Also, these electrons carrier molecules goes to the electron transport chain and give their electrons to complex I and complex III (this is also an oxidation reduction reaction). Also, these electrons will be transferred from one complex to another (which is also oxidation-reduction reaction).



OXIDATION-REDUCTION REACTIONS (REDOX)

Let's talk about electricity :

- When you are charging your phone, what is happening? The electricity (electron current) is moving from the energy source to your phone, why is this happening? This because there is a difference in potential energy between your phone battery and the energy source, and depending on that, the potential difference between the source and your phone battery is what drives the movement of electrons from the higher potential (source) to the lower potential (battery).
- Can we reverse the direction of electrons?
- ❑ Yes, if we reverse the potential, the direction of electron movement will be reversed since electrons are always moving from higher potential to lower potential.
- But, does this concept that apply to electricity apply to our body?
- ❑ Yes, the physical concepts that applies to electrons in the electricity applies to the electrons in our body molecules (eg. Electron transport chain).



Potential energy: is the energy stored in the electron

- **If there is a potential difference between 2 molecules there will be a transfer of electrons from the higher potential to the lower one.**
- **The electrons energy differs from a molecule to another**
To make it easier, think about electrons in an atom. The movement of an electron from its energy level to a one nearer to the nucleus decreases its energy and vice versa. That concept explains **that the location of an electron changes its energy**
- **In the electron transport chain, electrons moves from NADH (Highest potential of giving electrons) through complexes and reach finally to its final acceptor O₂ (lowest potential of giving and highest potential of accepting electrons)**
- **Some of these steps may be reversed according to conditions, because the potential energies of electrons in a place change when changing conditions (eg. In some cellular conditions, electrons may go from complex I to NAD⁺), but that is the case in standard conditions.**
- **When we breath, O₂ goes inside and diffuses into cells and then to the mitochondria. It binds to complex IV and accepts electrons finally, converting into H₂O (We have high constant (more or less) amounts of H₂O in our bodies (70%), due to the continuous production of it)**



OXIDATION-REDUCTION REACTIONS (REDOX)

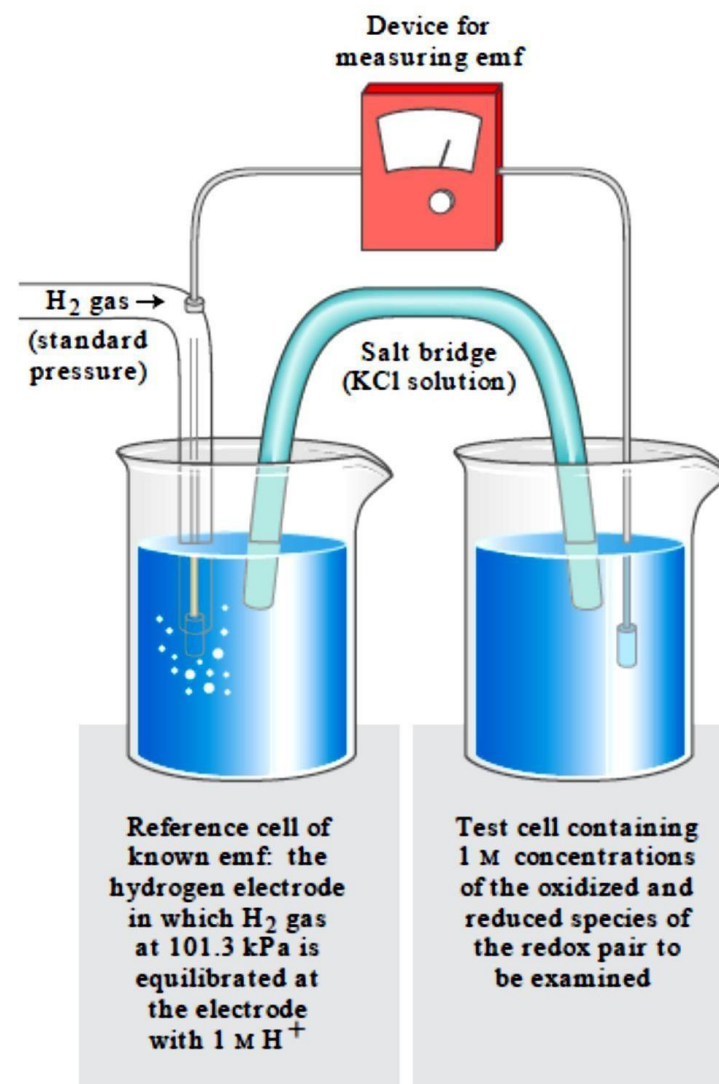
➤ How we can know the oxidation and reduction potential for all the molecules in the universe?

- 1) We standardize a molecule (or an element) as a standard electrode.



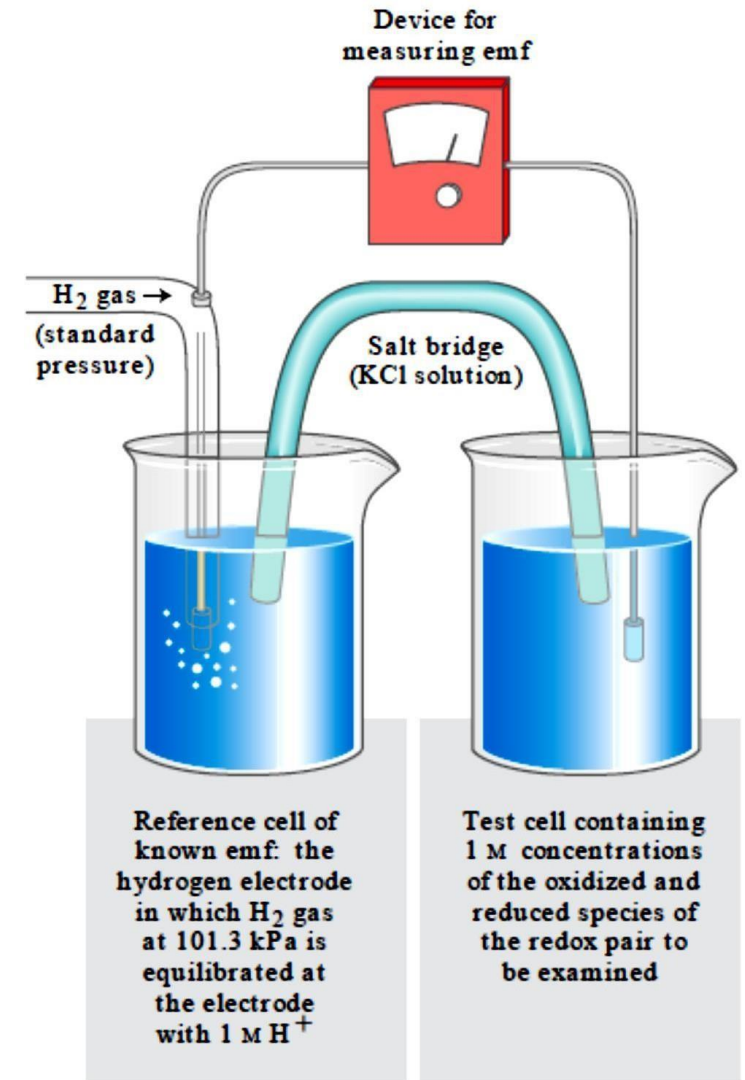
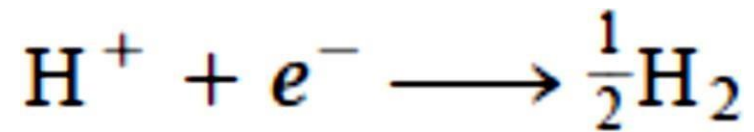
- 2) We put the molecule (or element) that we want to know its reduction (or oxidation) potential as the other electrode.
- 3) We write down the voltmeter readings and know the direction in which the electrons move, and we repeat that with every molecule (or element) in the universe.

By doing this over and over, we have got table shown in the next slide.



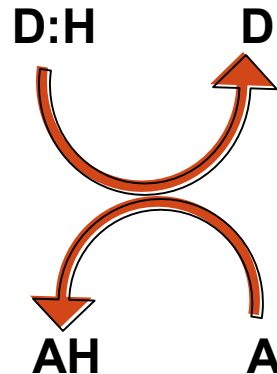
WHAT IS THE STANDARD?

- Hydrogen electrode
- H₂ Gas sensor



OXIDATION-REDUCTION REACTIONS (REDOX)

- **Oxidation:** Can happen through :
 - Gain of Oxygen
 - Loss of Hydrogen
 - Loss of electrons
- **Reduction:** Can happen through :
 - Gain of Hydrogen
 - Gain of electron
 - Loss of Oxygen
- **E (redox Potential):** it is a **POTENTIAL ENERGY** that measures the tendency of oxidant/reductant to gain/lose electrons, to become reduced/oxidized
- Electrons move from compounds with lower reduction potential (more negative) to compounds with higher reduction potential (more positive)
- Oxidation and reduction must occur **simultaneously**
- By knowing the reduction or oxidation potential of two molecules, we can know the potential difference and predict the direction of electrons transfer and the direction of the reaction.



REDUCTION POTENTIAL



Type of reaction? Group transfer reaction (if you calculate the oxidation number, you will find that it is an oxidation reduction reaction.)

What determine the direction of the reaction?

ΔG° and ΔE° ; and we are going to learn what is ΔE° as we are moving through the slides.



Type of reaction Oxidation & Reduction Reaction

What determine the direction of the reaction?

ΔG° and ΔE° ; and we are going to learn what is ΔE° as we are moving through the slides.



REDUCTION POTENTIAL AND DIRECTION OF THE REACTION

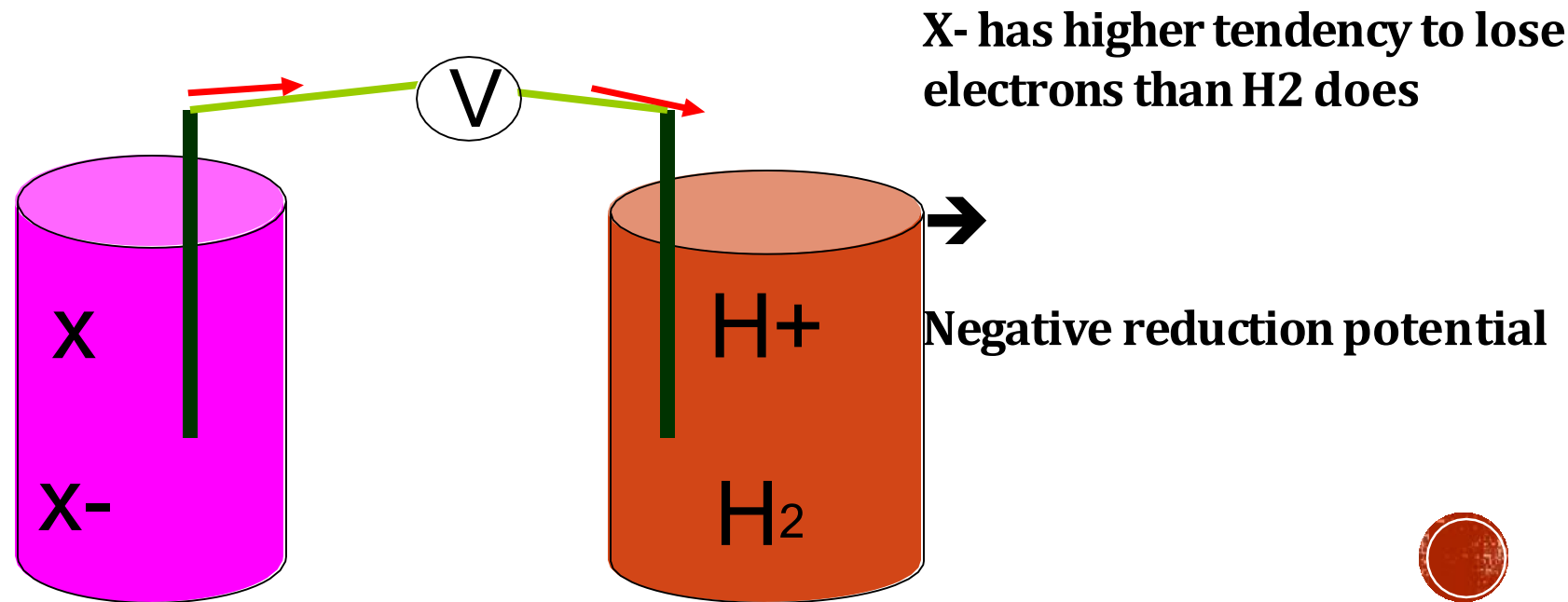


X oxidized form
 X^- reduced form

Redox couple

Any material that can switch between two states (**Oxidized & Reduced**) we call these two states (**A Redox Couple**), For Example :

☐ $\text{NAD}^+ + \text{H}^+ + 2\text{e}^- \rightarrow \text{NADH}$
 ($\text{NAD}^+ / \text{NADH}$) is a redox couple



STANDARD REDUCTION POTENTIAL (E°)

$$E = E^\circ + \frac{RT}{nF} \ln \frac{[\text{electron acceptor}]}{[\text{electron donor}]}$$

E : Reduction Potential

E° : Reduction Potential at standard condition

R : Gas constant, equals 8.314 J/(K.mol)

n : Number of transferred electrons

T : Temperature (in calvin)

Farady constant, equals
23.06 Kcal/mol

$$E = E^\circ + \frac{0.026 \text{ V}}{n} \ln \frac{[\text{electron acceptor}]}{[\text{electron donor}]}$$

$$\frac{RT}{F} = 0.026 \text{ Volt}$$



REDUCTION POTENTIAL

Oxidized + e-	→ Reduced	ΔE° (V)
Succinate	α -ketoglutarate	-0.67
Acetate	Acetaldehyde	-0.60
NAD+	NADH	-0.32
Acetaldehyde	Ethanol	-0.20
Pyruvate	Lactate	-0.19
Fumarate	Succinate	+0.03
Cytochrome+3	Cytochrome+2	+0.22
oxygen	water	+0.82

Electrons in
oxidative
phosphorylation

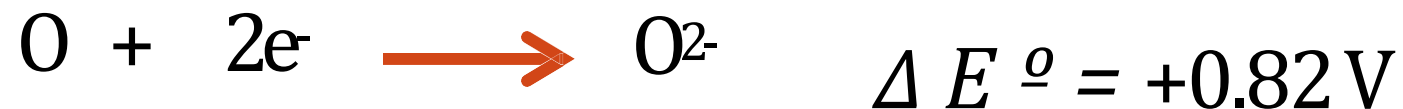


CALCULATION OF ΔG° FROM ΔE°

$$\Delta G^\circ = -nF\Delta E^\circ \quad \Delta G = -n\mathcal{F} \Delta E \quad \text{or} \quad \Delta G'^\circ = -n\mathcal{F} \Delta E'^\circ$$

F = Farady constant = 23.06 kcal/Volt

Calculate ΔG° of the following reaction



$$\Delta G^\circ = -52.6 \text{ kcal/mol}$$



CALCULATION OF ΔG° FROM ΔE°

- There is a direct relationship between the **standard Gibbs free energy change** (ΔG°) and the **standard difference in the reduction potential** (ΔE°) because both describe the thermodynamic favorability of a reaction, just in different units.
- The equation that connects them is:

$$\Delta G^\circ = -nF\Delta E^\circ$$

Where:

ΔG° = standard **Gibbs free energy change** (in Kcal/mol).

n = number of **electrons transferred** in the redox reaction.

F = **Faraday's constant** (23.06 Kcal/volt).

ΔE° = standard difference in **reduction potential** (in volts)

ΔE° = (E° of the electron acceptor - E° of the electron donor).

- ΔG° represent **the amount of energy difference** that is stored in the **same electron** but in different molecules (**the electron donor and acceptor**).

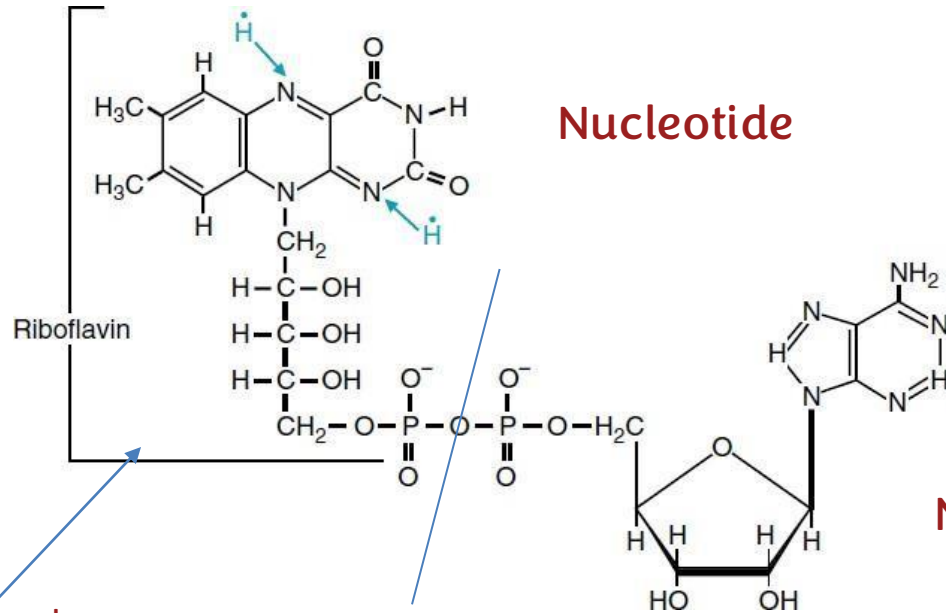


OXIDATION-REDUCTION REACTIONS (REDOX)

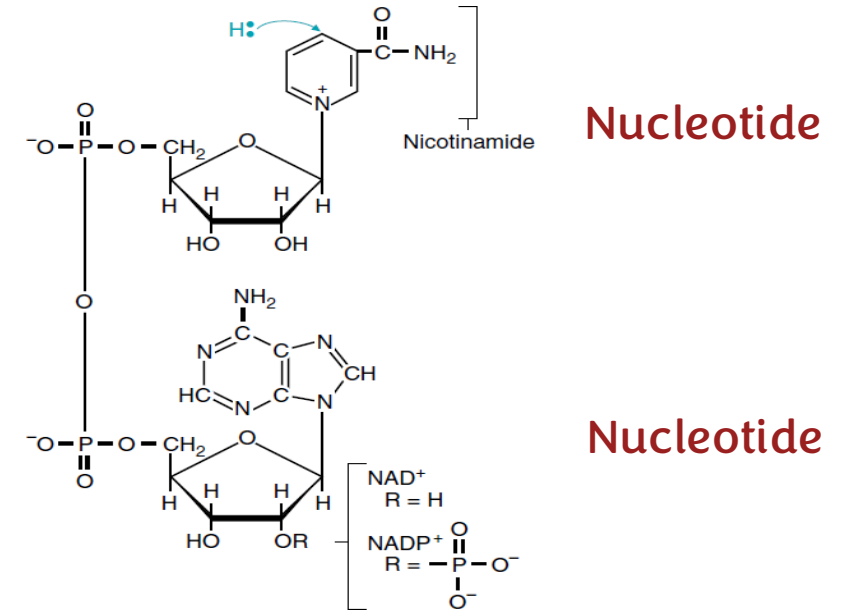
- $\Delta E = E_A - E_D$
- $\Delta E^o =$ at standard condition
- Does ΔE determine the feasibility of a reaction? Yes, Already explained
- $\Delta G^o = -nf\Delta E^o$
- In other words; energy (work) can be derived from the transfer of electrons.
- Or Oxidation of food can be used to synthesize ATP



FAD (Flavin Adenine Dinucleotide)



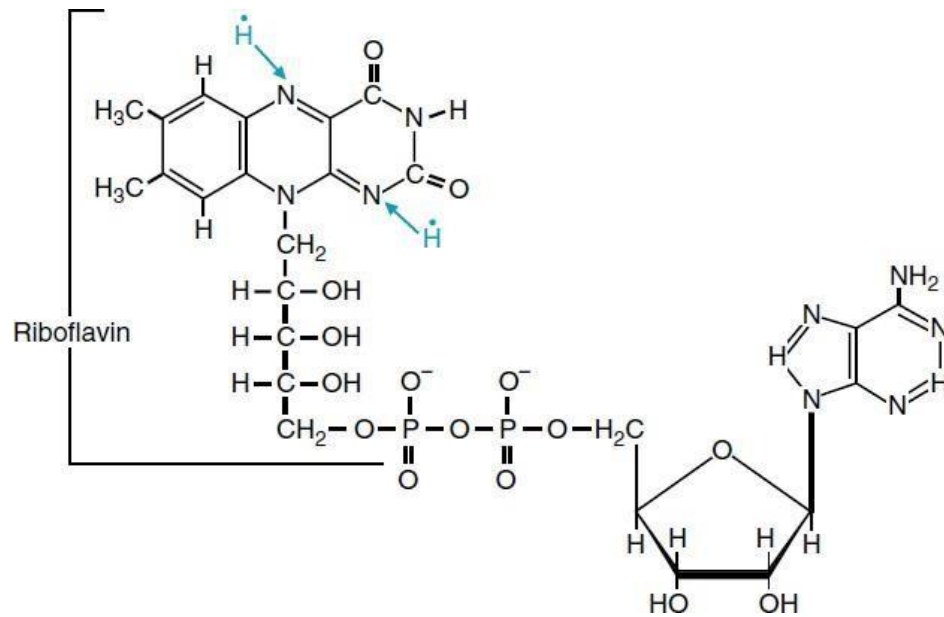
NAD+ (Nicotinamide Adenine Dinucleotide)



OXIDATION-REDUCTION REACTIONS (REDOX)

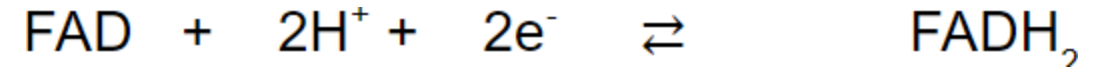
- Always involve a pair of chemicals: an electron donor and an electron acceptor (Food vs. NAD+)
- NAD+ vs. FAD
- NAD+ vs. NADP+ (fatty acid synthesis and detoxification reactions)





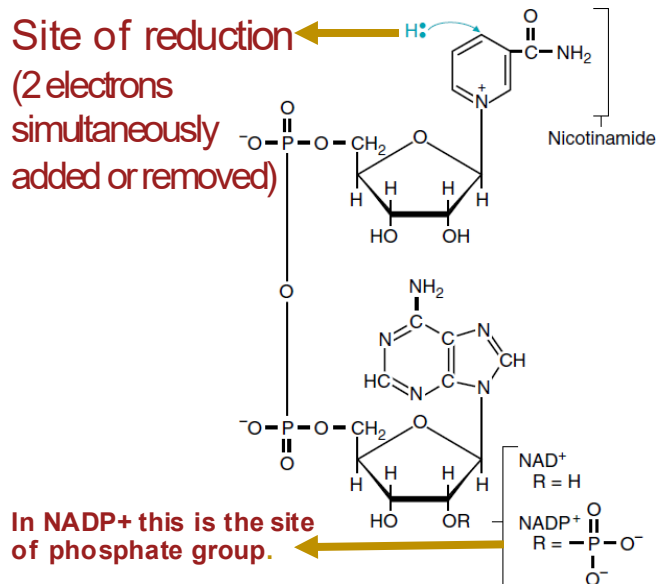
FAD

- Accept 2 electrons at 2 different places.

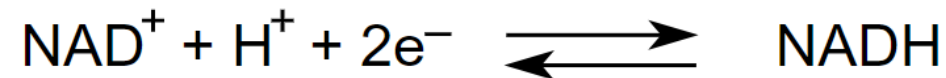


- You can't find it or (FMN) alone, it produces a free radical (which is harmful for the cell) after binding to the first H and then forms FADH₂ by binding to the other H subsequently.
- FMN (reduced to FMNH₂) and FAD (reduced to FADH₂) perform the same function, are present for organizational purposes.

NAD⁺



- Reduced by getting two electrons as a **hydride ion**.



- You can find it alone, it doesn't produce a free radical.
- There is another form of it that is phosphorylated called NADP⁺ and the phosphate is away from the site of action, they perform the same function, the benefit of having two molecules (NAD⁺/NADP⁺) performing the same function is for organizational purposes.

TABLE 13-7 Standard Reduction Potentials of Some Biologically Important Half-Reactions, at pH 7.0 and 25 °C (298 K)

<i>Half-reaction</i>	<i>E° (V)</i>
$\frac{1}{2}\text{O}_2 + 2\text{H}^+ + 2e^- \longrightarrow \text{H}_2\text{O}$	0.816
$\text{Fe}^{3+} + e^- \longrightarrow \text{Fe}^{2+}$	0.771
$\text{NO}_3^- + 2\text{H}^+ + 2e^- \longrightarrow \text{NO}_2^- + \text{H}_2\text{O}$	0.421
Cytochrome <i>f</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>f</i> (Fe^{2+})	0.365
$\text{Fe}(\text{CN})_6^{3-}$ (ferricyanide) + $e^- \longrightarrow \text{Fe}(\text{CN})_6^{4-}$	0.36
Cytochrome <i>a</i> ₃ (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>a</i> ₃ (Fe^{2+})	0.35
$\text{O}_2 + 2\text{H}^+ + 2e^- \longrightarrow \text{H}_2\text{O}_2$	0.295
Cytochrome <i>a</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>a</i> (Fe^{2+})	0.29
Cytochrome <i>c</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>c</i> (Fe^{2+})	0.254
Cytochrome <i>c</i> ₁ (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>c</i> ₁ (Fe^{2+})	0.22
Cytochrome <i>b</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>b</i> (Fe^{2+})	0.077
Ubiquinone + $2\text{H}^+ + 2e^- \longrightarrow$ ubiquinol + H_2	0.045
Fumarate ²⁻ + $2\text{H}^+ + 2e^- \longrightarrow$ succinate ²⁻	0.031
$2\text{H}^+ + 2e^- \longrightarrow \text{H}_2$ (at standard conditions, pH 0)	0.000
Gotoryl-CoA + $2\text{H}^+ + 2e^- \longrightarrow$ butyryl-CoA	-0.015
Oxaloacetate ²⁻ + $2\text{H}^+ + 2e^- \longrightarrow$ malate ²⁻	-0.166
Pyruvate ⁻ + $2\text{H}^+ + 2e^- \longrightarrow$ lactate ⁻	-0.185
Acetaldehyde + $2\text{H}^+ + 2e^- \longrightarrow$ ethanol	-0.197
FAD + $2\text{H}^+ + 2e^- \longrightarrow \text{FADH}_2$	-0.219*
Glutathione + $2\text{H}^+ + 2e^- \longrightarrow$ 2 reduced glutathione	-0.23
$\text{S} + 2\text{H}^+ + 2e^- \longrightarrow \text{H}_2\text{S}$	-0.243
Lipoic acid + $2\text{H}^+ + 2e^- \longrightarrow$ dihydrolipoic acid	-0.29
$\text{NAD}^+ + \text{H}^+ + 2e^- \longrightarrow \text{NADH}$	-0.320
$\text{NADP}^+ + \text{H}^+ + 2e^- \longrightarrow \text{NADPH}$	-0.324
Acetoacetate + $2\text{H}^+ + 2e^- \longrightarrow \beta$ -hydroxybutyrate	-0.346
α -Ketoglutarate + $\text{CO}_2 + 2\text{H}^+ + 2e^- \longrightarrow$ isocitrate	-0.38
$2\text{H}^+ + 2e^- \longrightarrow \text{H}_2$ (at pH 7)	-0.414
Ferredoxin (Fe^{3+}) + $e^- \longrightarrow$ ferredoxin (Fe^{2+})	-0.432

NAD⁺ reduction potential and all molecules (or elements) reduction potential is constant in all reactions.

FAD differ from NAD⁺, since it produces a free radical, so it is always accompanied with a protein, so its reduction potential differs depending on that protein, (reduction potential of FAD at Succinate dehydrogenase differ from reduction potential of FAD at other enzymes).

That's why FAD has a star.



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



Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			



Additional resources

Reference Used:

Prof Nafez Live lecture.

اللَّهُمَّ ارزقني صبراً جميلاً، وطمأنينةً في القلب لا يزول
معها هم، ولا يتسلل إليها جزع، اللَّهُمَّ قَوِّنِي عَلَى الْبَلَاءِ،
وَأَعِنِّي عَلَى نَوَائِبِ الدَّهْرِ، واملأ قلبي بالرضا بحكمك،
وحسن التفويض إليك، واجعل لي من كل ضيقٍ فرجاً، ومن
كل همٍّ مخرجاً، ومن كل عسرٍ يسراً، برحمتك يا أرحم
الراحمين.

