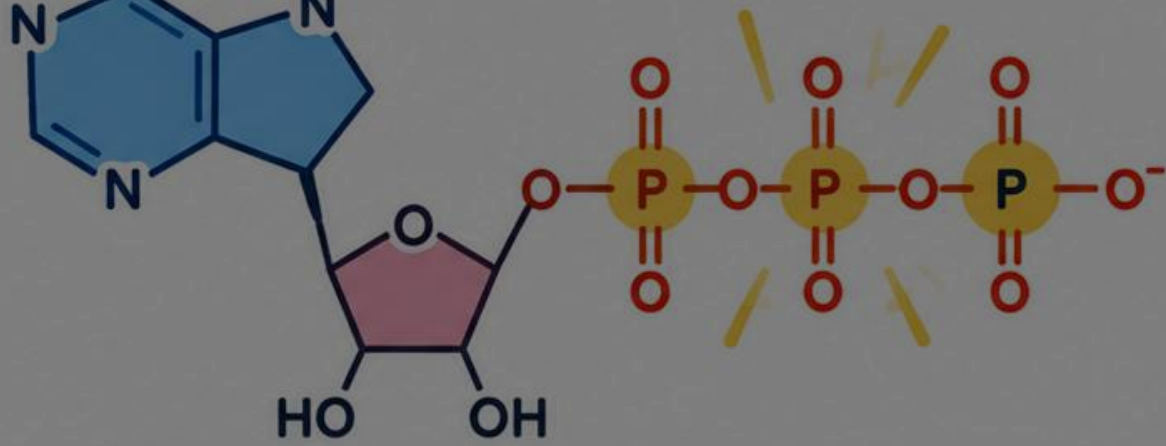
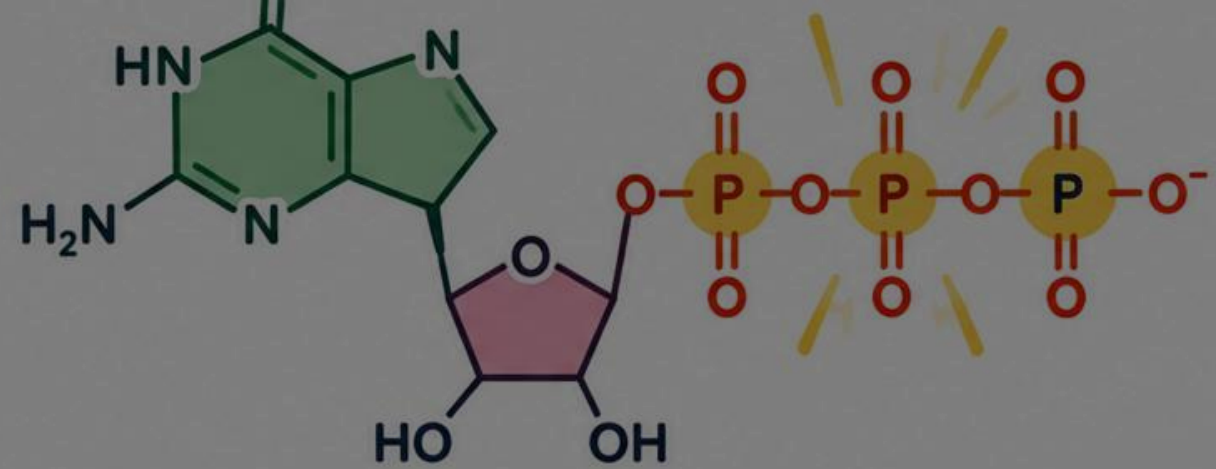


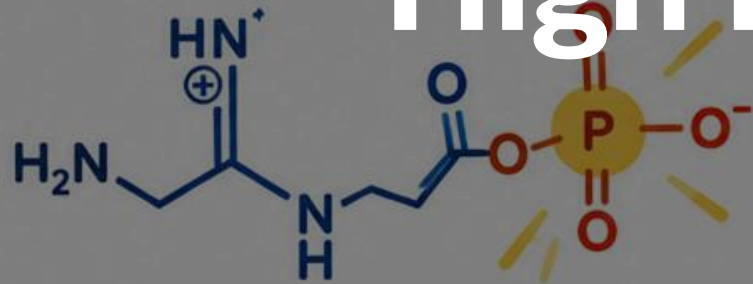


ATP



GTP

High Energy Compounds

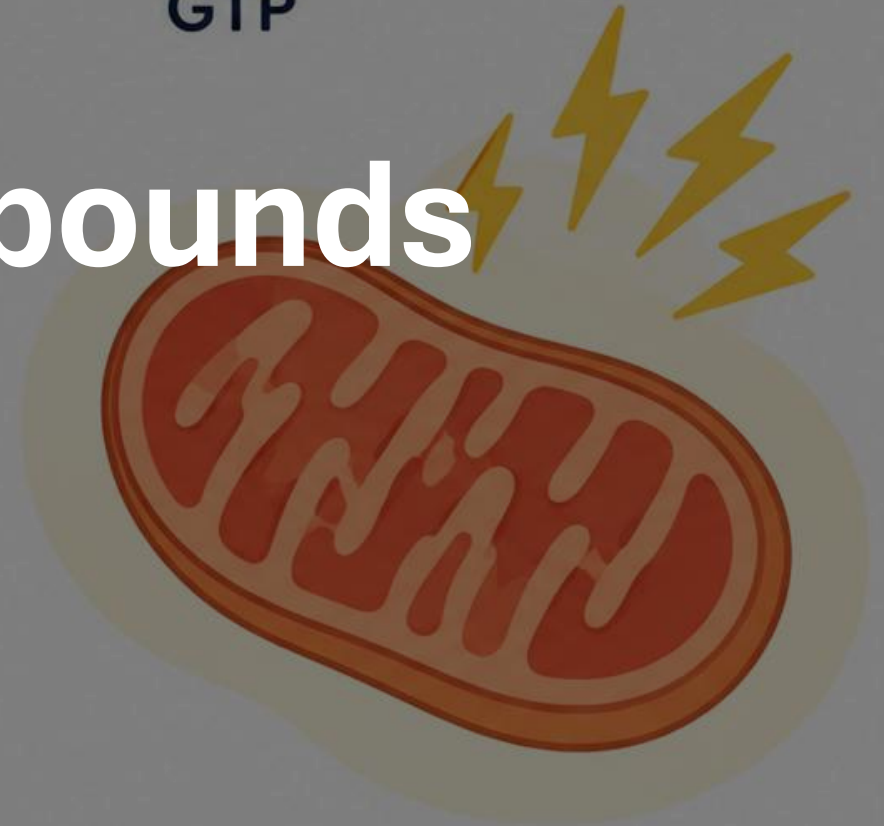


Creatine phosphate

Alkmini Anastasiadi, PhD

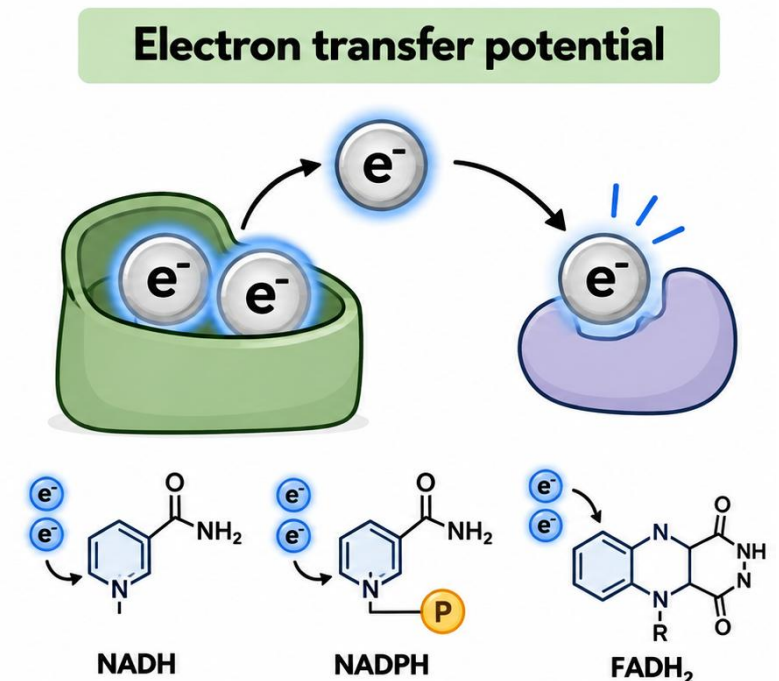
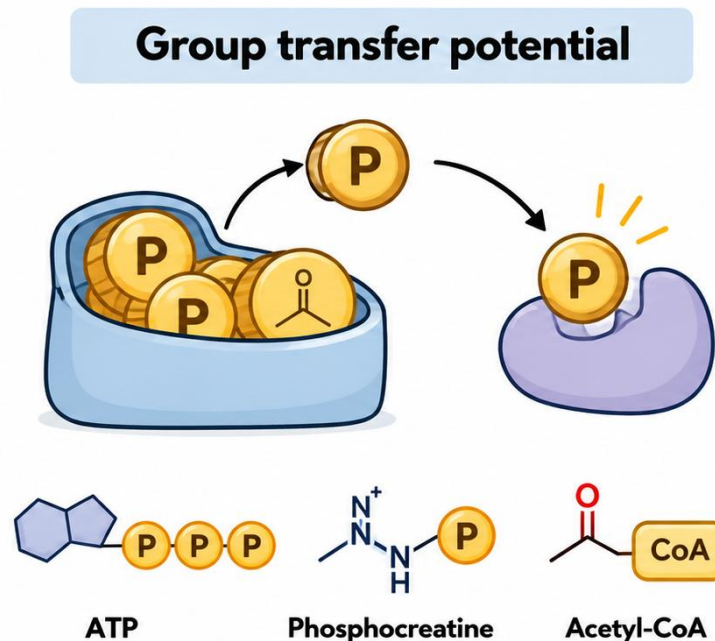


Pyrophosphate



High-Energy Compounds

- Cells use two different types of “energy coins”
 - **Group transfer potential:** these molecules save energy in their chemical structure and transfer it by transferring a chemical group (mainly phosphate or acyl group) to a substrate
e.g., ATP, phosphocreatine, acetyl-CoA
 - **Electron transfer potential:** these molecules save energy in the form of high energy electrons (or H^-)
e.g., NADH, NADPH, $FADH_2$

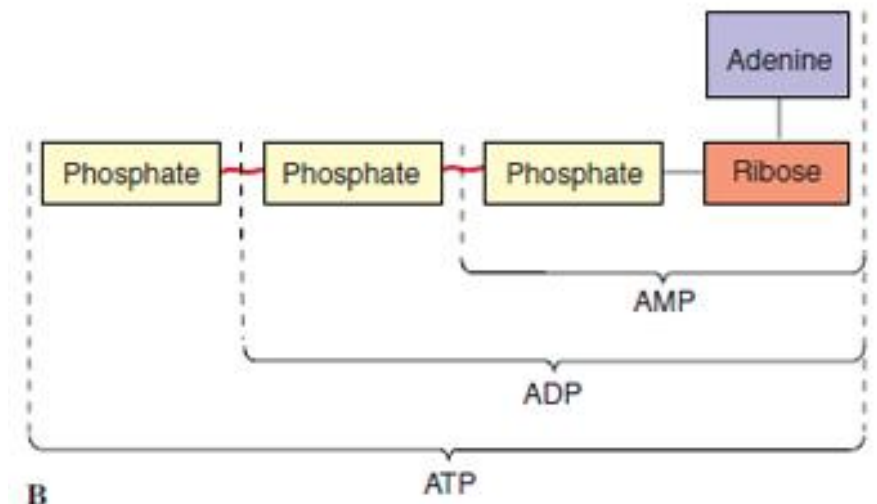
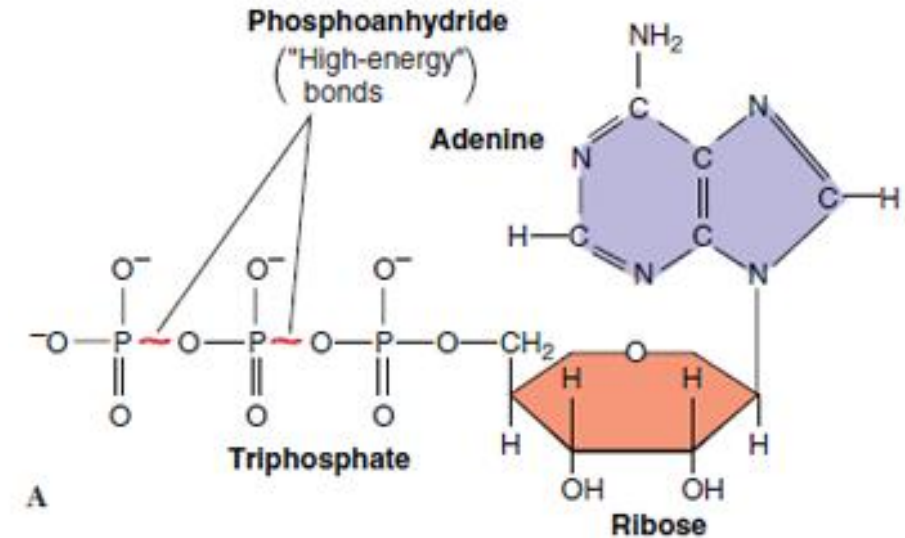


Group Transfer Potential

High Energy Bonds

- Definition: their **hydrolysis releases** a large amount of **free energy**, therefore, it is accompanied by a large negative standard free energy change (ΔG°)
- Symbol: squiggle (~) → denotes a **high group transfer potential**, indicating that the molecule is thermodynamically inclined to transfer its functional group, resulting in a favorable, large negative ΔG . It represents **immense intramolecular tension** that disappears when the bond is cleaved.

Exergonic (The Profit)		Endergonic (The Cost)	
$\Delta G < 0$	The ball rolls downhill. Energy is released spontaneously.	$\Delta G > 0$	The ball must be pushed uphill. Energy is consumed.



Group Transfer Potential

High Energy Bonds

○ Energy is liberated because the products of hydrolysis are significantly more stable than the reactants, because:

- **Relief of Electrostatic Repulsion**

Cleaving bonds between adjacent phosphate (phosphoryl) groups (phosphoanhydride linkages) separates closely packed negative charges

- **Resonance Stabilization**

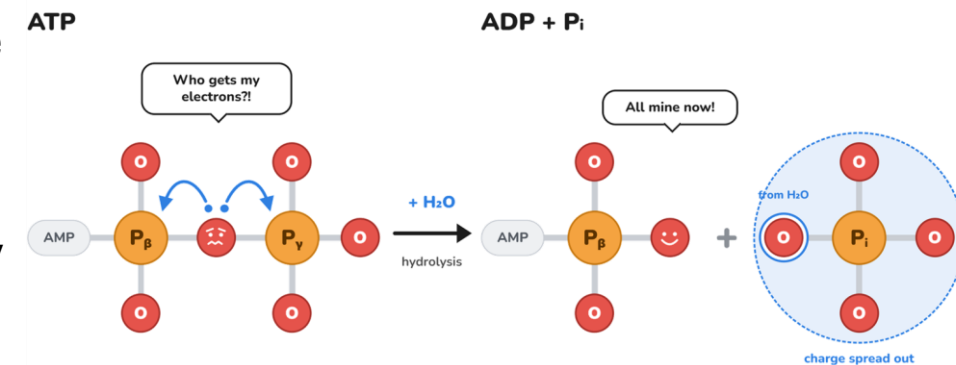
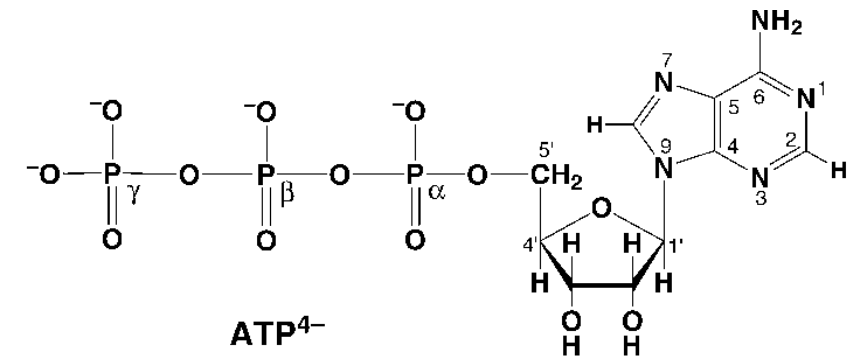
Hydrolysis products possess far more resonance forms than the intact parent molecule → they are more stable

- **Solvation & Hydration**

The resulting products are better hydrated and stabilized by surrounding water molecules

- **Entropy Increase**

Hydrolysis converts one single reactant molecule into two separate product molecules



One oxygen, two phosphates. Both pull on its electrons, so few resonance forms.

Each phosphate keeps its own oxygens. Electrons spread out, so many resonance forms.

Group Transfer Potential

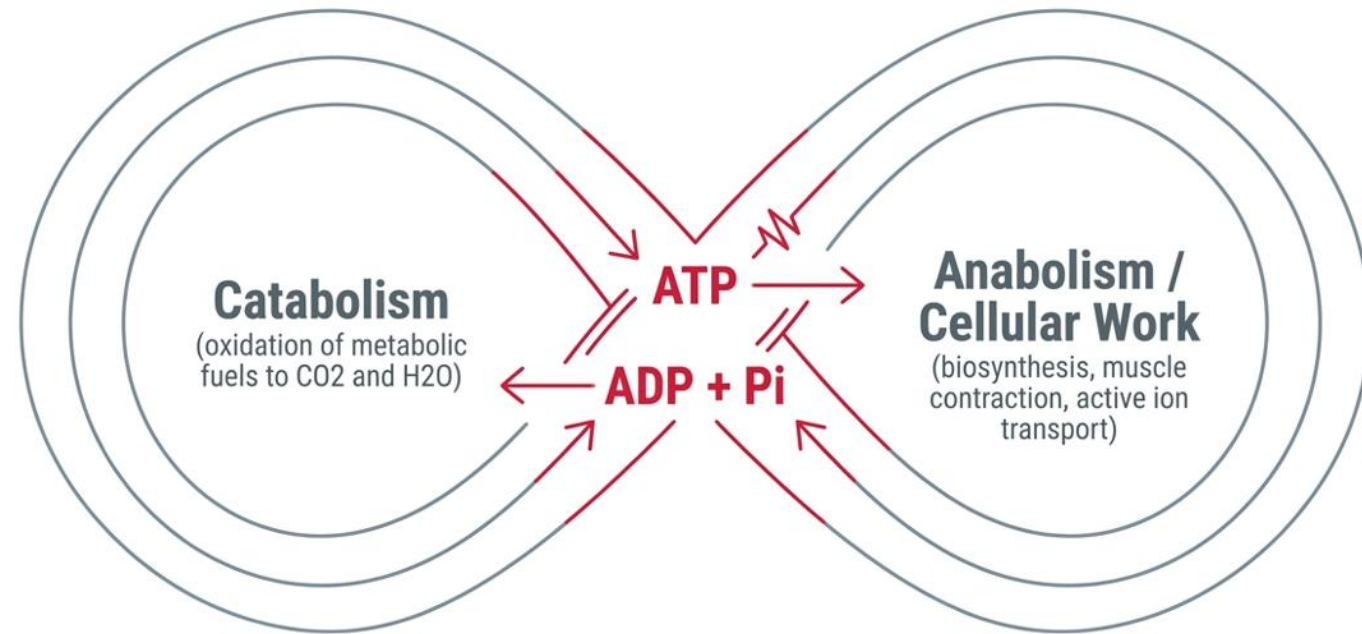
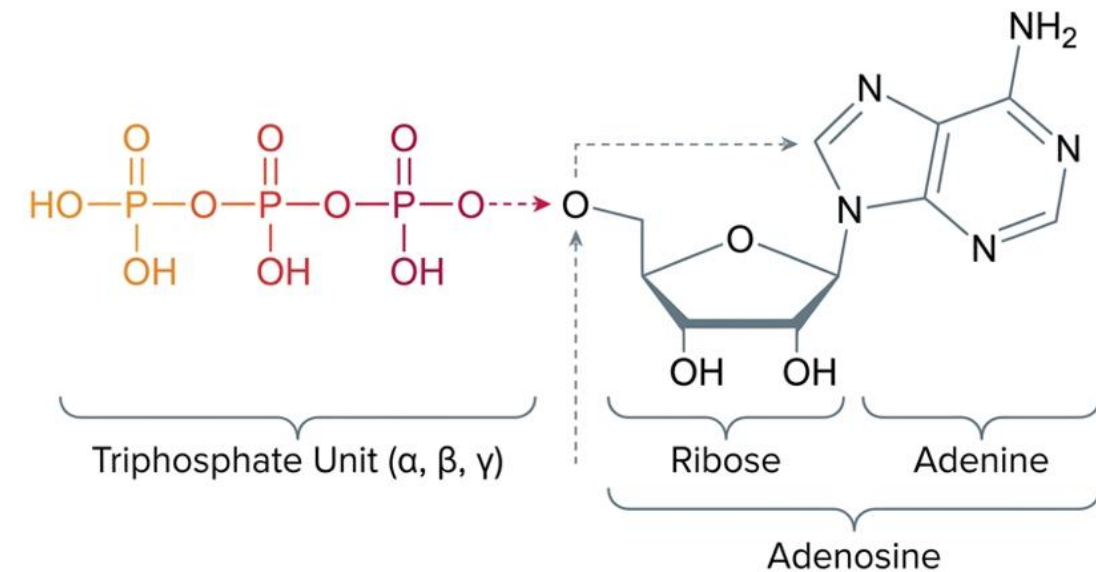
High Energy Bonds

	Relief of Electrostatic Repulsion	Resonance Stabilization	Solvation & Hydration	Entropy Increase
ATP/PPi	✓	✓	✓	✓
Phosphocreatine	X	✓	✓	✓
Acetyl-CoA	X	✓	~	✓

Group Transfer Potential

ATP

- ATP is the universal energy transducer: it captures energy from fuel oxidation and channels it to power the nonspontaneous processes of life



Group Transfer Potential

ATP

○ ATP synthesis:

- **Substrate-level phosphorylation:** direct, enzymatic transfer of a high-energy phosphate group ($\sim P$) from a phosphorylated metabolic intermediate ($X \sim P$) directly to ADP, producing ATP
- **Phosphagen System:** In tissues with rapid, intense energy demands (such as skeletal muscle, myocardium, and brain), stored Phosphocreatine serves as an immediate, high-energy phosphate buffer to rapidly regenerate ATP



- **Adenylate Kinase Emergency Reaction:** When ATP utilization is severe and ADP accumulates, adenylate kinase scavenges energy from two ADP molecules to regenerate one ATP



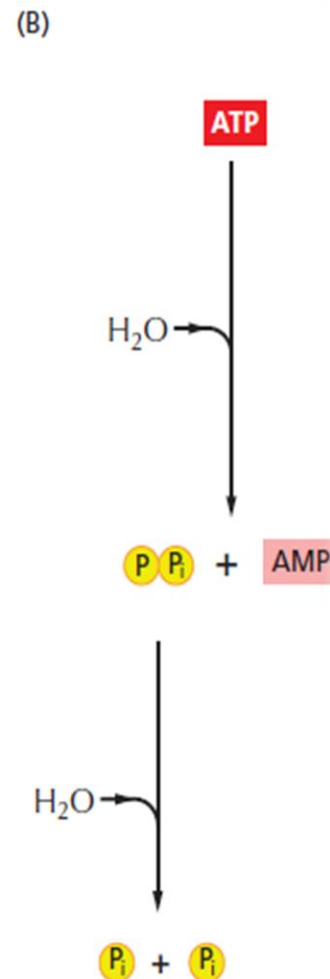
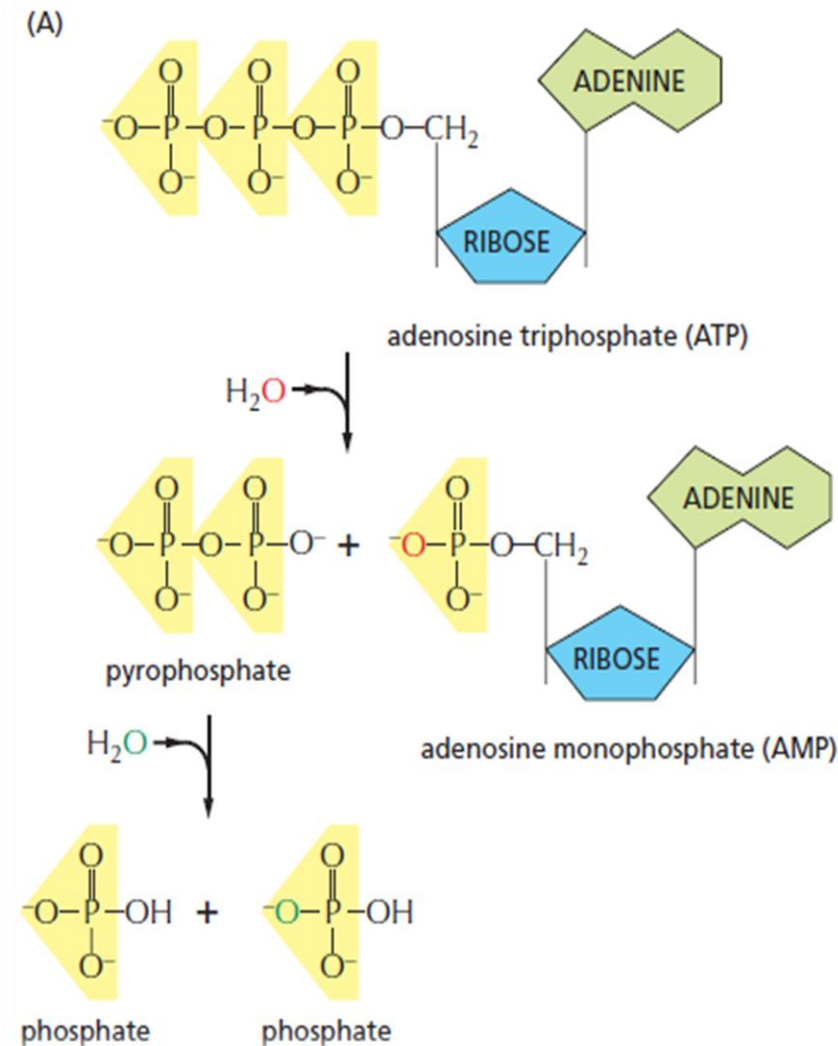
- **Oxidative phosphorylation** in mitochondria

Group Transfer Potential

ATP

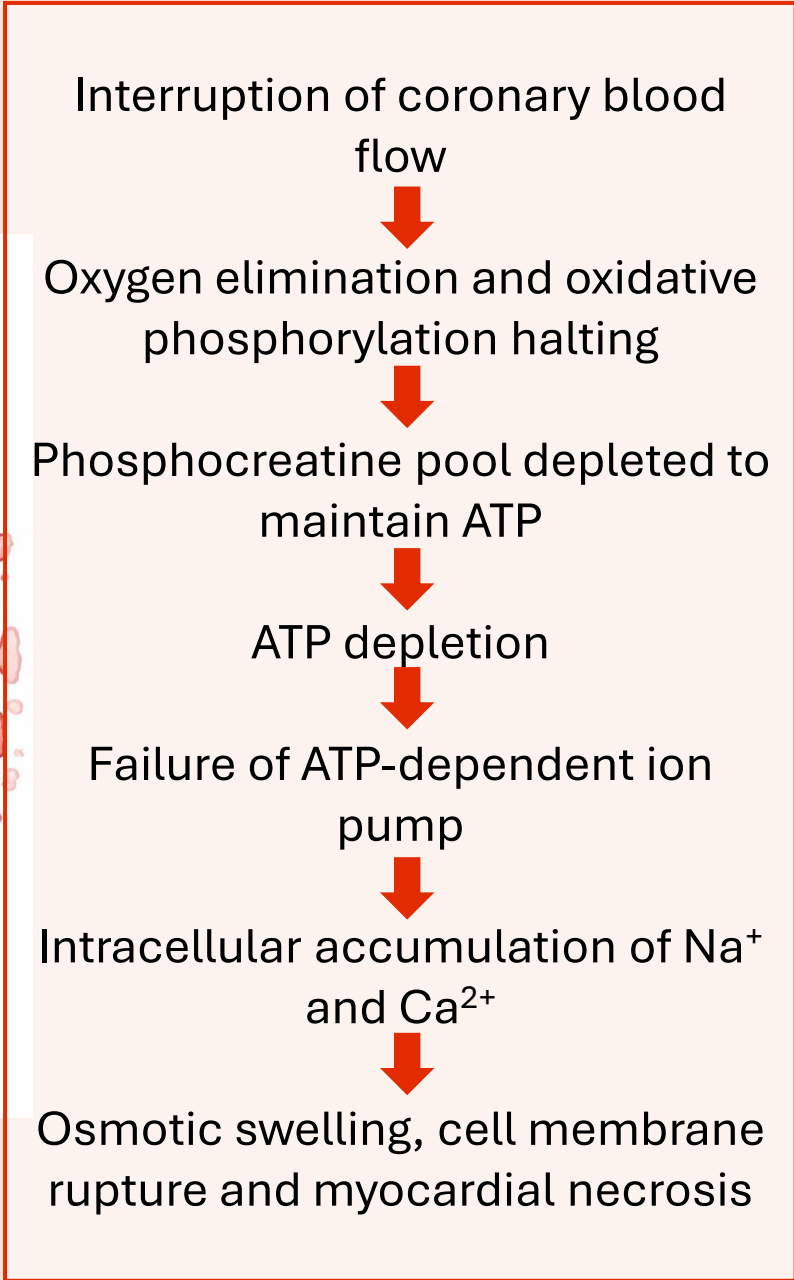
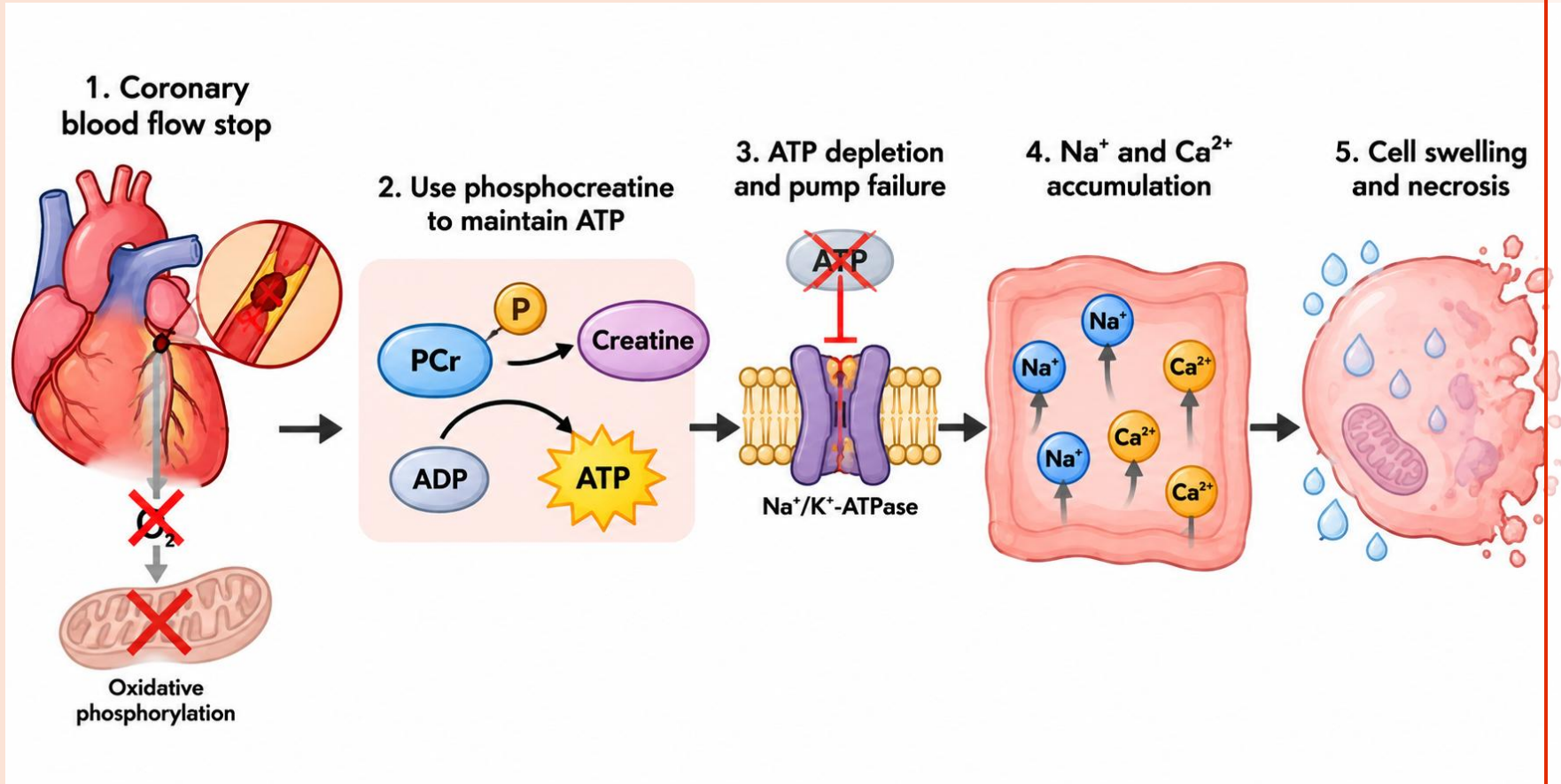
○ ATP hydrolysis:

- **Exergonic** reaction → **coupling an unfavorable reaction** to the hydrolysis of ATP → the massive negative free energy of ATP ensures the overall **coupled reaction is entirely exergonic**
- Hydrolysis of ATP to ADP results in a specific change in energy, which is not enough for all reactions → hydrolysis of **ATP to AMP + pyrophosphate (PPi)**, which is then **also hydrolyzed** results in a larger energy change → it can **promote more “difficult” reactions**



Myocardial Ischemia and Infraction

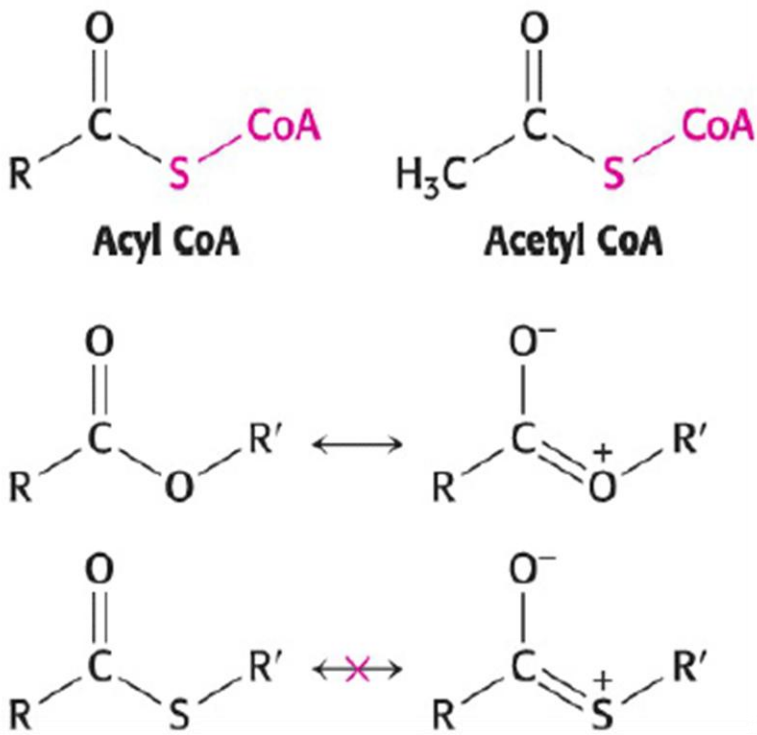
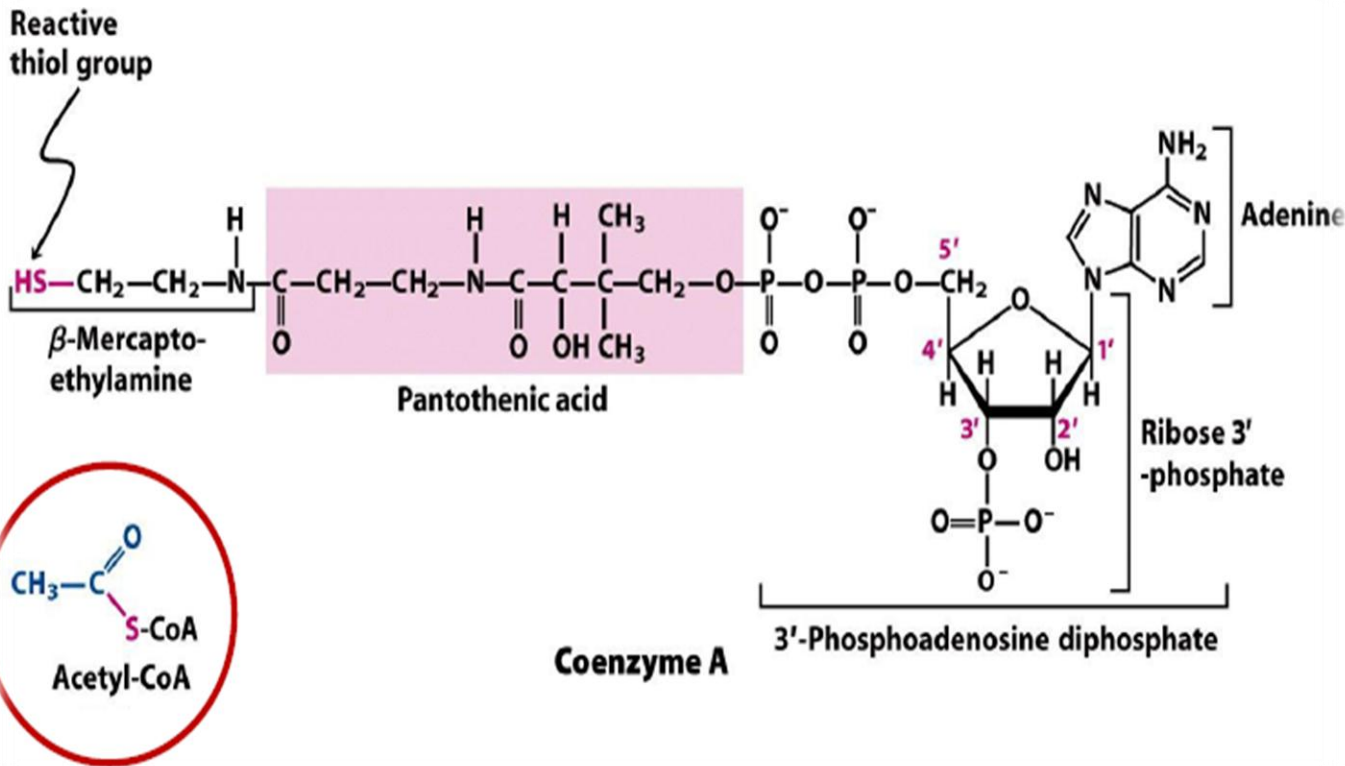
○ Target Molecules: ATP and phosphocreatine



Group Transfer Potential

Acetyl-CoA

- Coenzyme A (CoA-SH): the terminal sulfhydryl group can form a **high-energy thioester bond** with acyl groups



The sulfur atom in a thioester does not allow effective resonance stabilization with the carbonyl group

→ acetyl-CoA = thermodynamically unstable

→ high acetyl group transfer potential.

Group Transfer Potential

Acetyl-CoA

- Serves as a biochemical junction where catabolic pathways converge and key anabolic pathways originate

Sources:

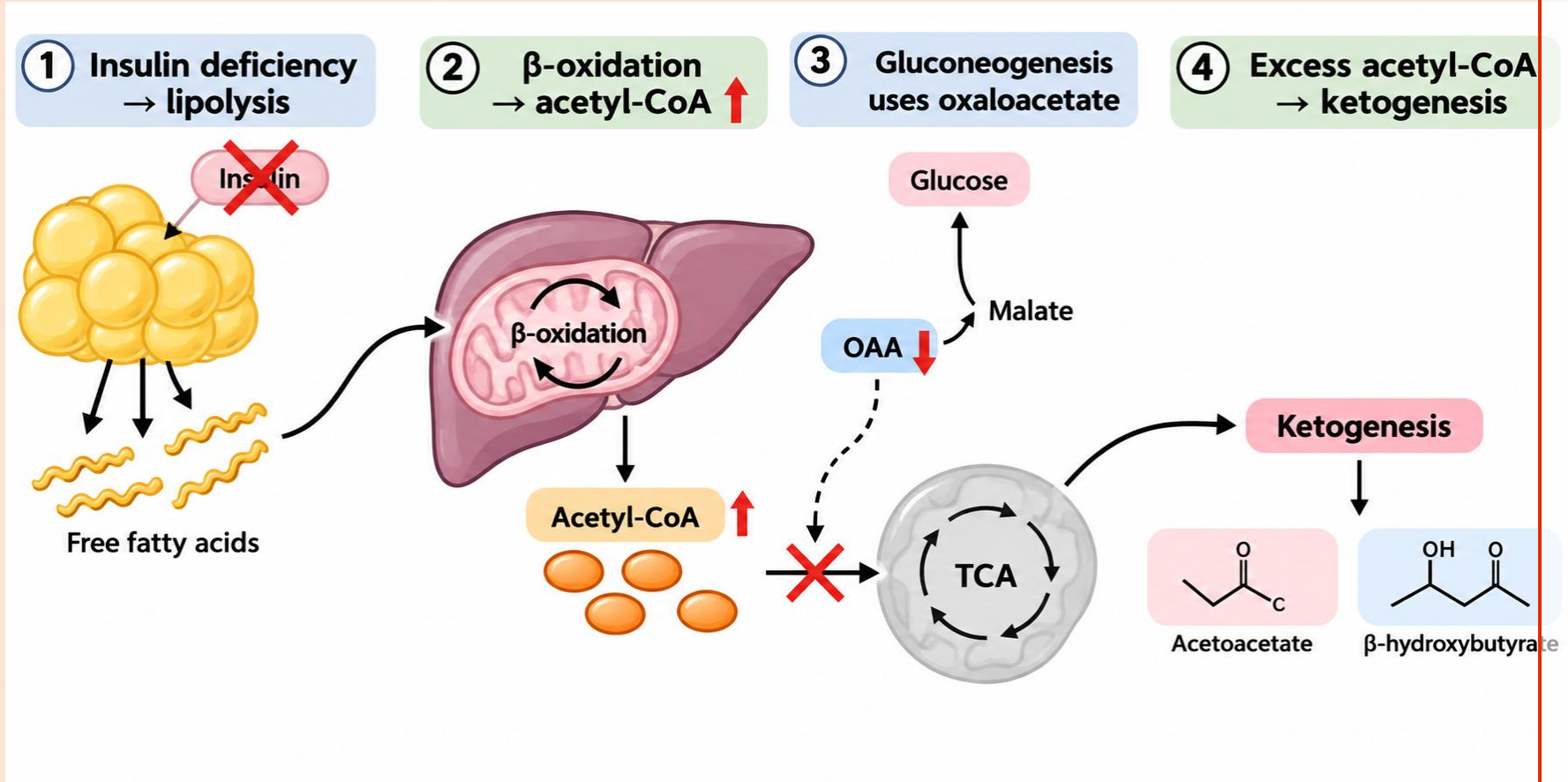
- Oxidative decarboxylation of pyruvate
- β -oxidation (sequential cleavage) of fatty acyl-CoA chains
- Ketogenic amino acid breakdown
- Ketone body utilization

Fates:

- Krebs cycle
- Fatty acid biosynthesis
- Ketogenesis
- Cholesterol and steroid hormone synthesis
- Protein and histone acetylation

Diabetic Ketoacidosis

○ Target Molecule: acetyl-CoA



Insulin deficiency triggers uncontrolled lipolysis

↓

Liver is flooded with free fatty acids

↓

β-oxidation breaks down fatty acids generating acetyl-CoA

↓

Acetyl-CoA cannot enter Krebs cycle because oxaloacetate is depleted (used to make glucose)

↓

Acetyl-CoA forced into ketogenesis

↓

ketoacidosis

Electron Transfer Potential

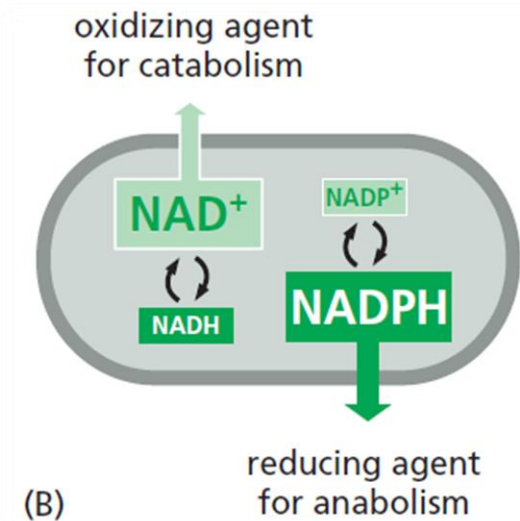
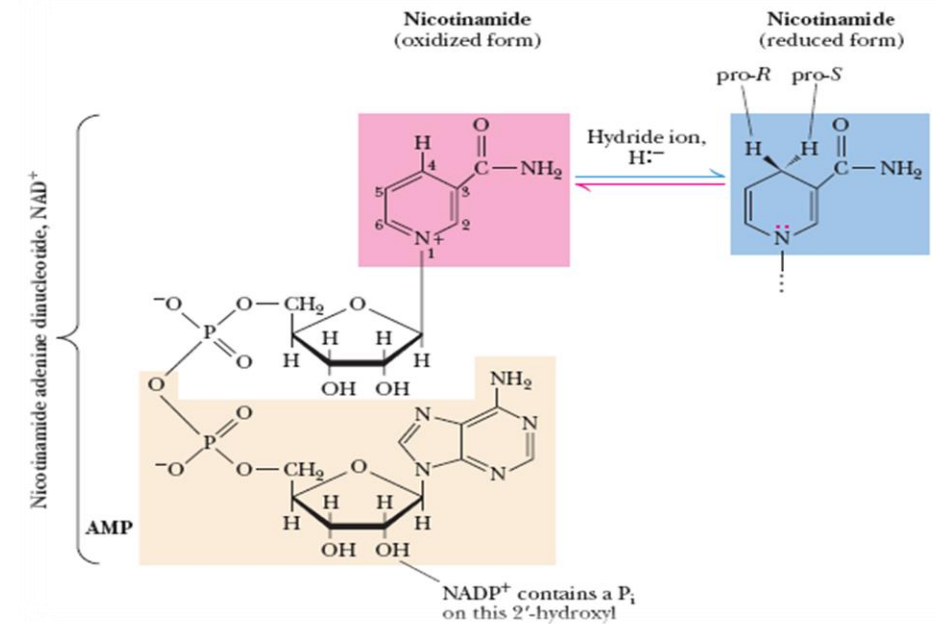
- **Electrons** released during chemical reactions **cannot freely circulate** in the cytosol → specialized **electron transporters** (NAD^+ , FAD) accept these electrons (NADH , FADH_2) to transfer them
- **Standard reduction potential** ($E^{\circ'}$): The quantitative measure of a redox couple's intrinsic **tendency to lose or gain electrons**.
 - $E^{\circ'} < 0$: strong reducing agent (low electron affinity, eager electron donor)
 - $E^{\circ'} > 0$: strong oxidizing agent (high electron affinity, eager electron acceptor)
 - Electrons flow spontaneously from couples with a more negative $E^{\circ'}$ toward couples with a more positive $E^{\circ'}$
 - Mathematic link with free energy: $\Delta G^{\circ'} = -nF\Delta E^{\circ'}$, n = number of transferred electrons, F = Faraday's constant ($96.48 \text{ kJ} \cdot \text{V}^{-1} \cdot \text{mol}^{-1}$)

Electron Transfer Potential

NADH vs NADPH

- They both transfer high energy electrons and hydrogen atoms
- They are used in different parts of metabolism
 - **NADH** is mainly used in **catabolic** reactions
 - **NADPH** is mainly used in **anabolic** reactions

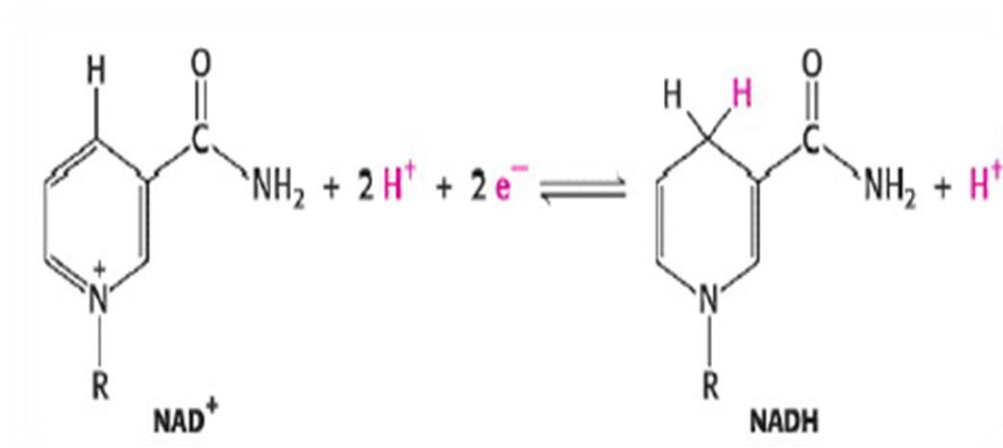
The phosphate group in NADPH acts like a “tag” that allows enzyme to distinguish between electrons destined for catabolism (NADH) and those destined for anabolism (NADPH)



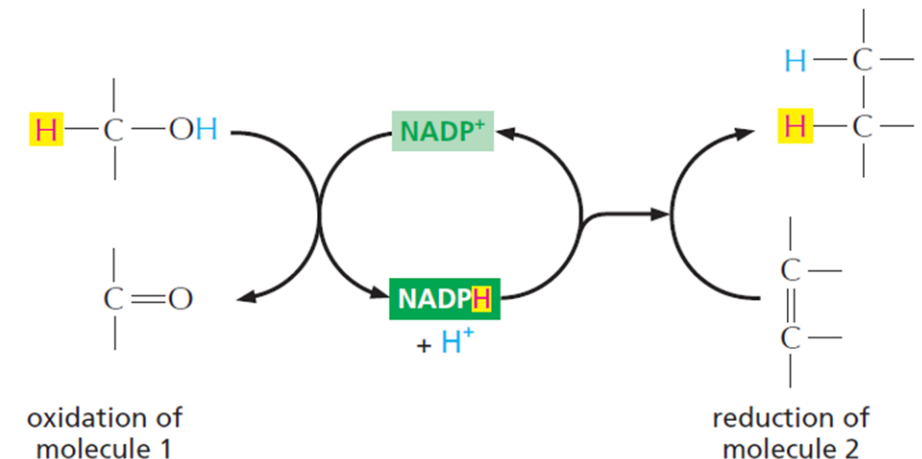
Electron Transfer Potential

NADH vs NADPH

- Both NAD^+ and NADP^+ can accept an “energy package” consisting of **2 electrons and a proton (H^+)** and get converted to NADH and NADPH
- NAD^+/NADH ratio: high in the cell $\rightarrow$ **large supply of NAD^+** as an oxidizing agent
- $\text{NADP}^+/\text{NADPH}$ ratio: low in the cell $\rightarrow$ **large supply of NADPH** as a reducing agent

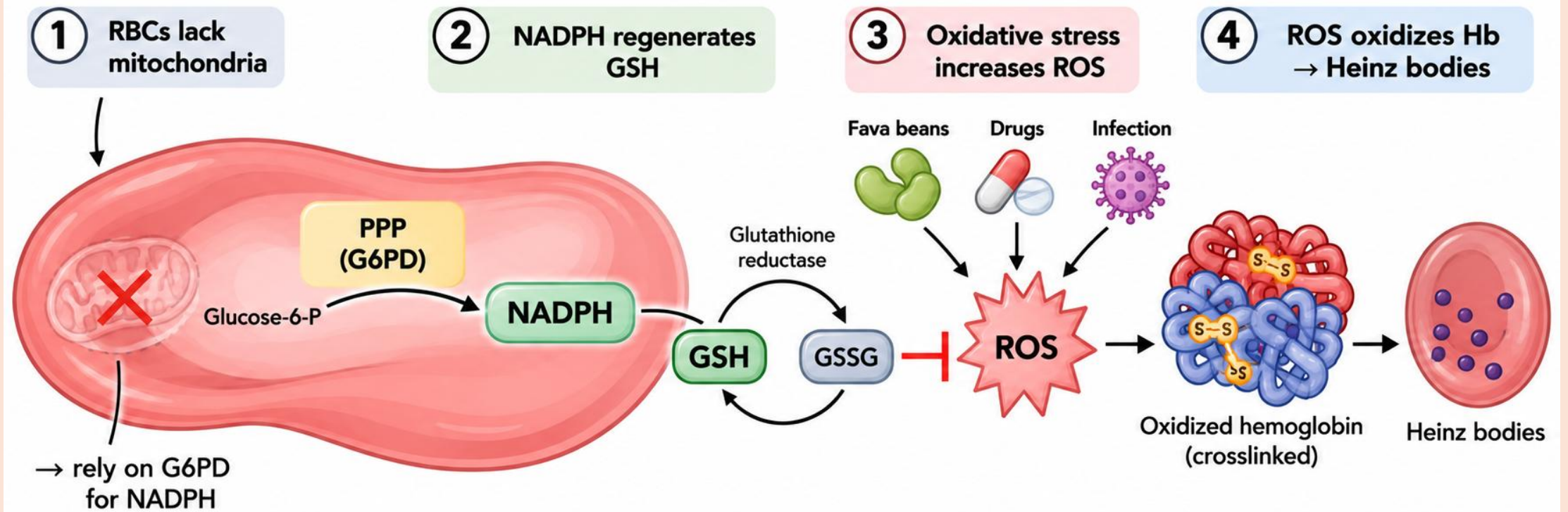


(A)



G6PD Deficiency

- Target Molecule: NADPH



Electron Transfer Potential

FADH₂

- FAD is another transporter used in fuel oxidation reactions
- FAD accepts an “energy packet” comprised by **2 electrons and 2 hydrogen atoms** and becomes FADH₂
- Both **NADH** and **FADH₂** are used **for ATP generation** via oxidative phosphorylation

