BIOC 384: M02.T01-Miesfeld

Assigned Reading: *Biochemistry* Chapter 2.2

THE UNIVERSITY OF ARIZONA

Coupled Reactions in Metabolism

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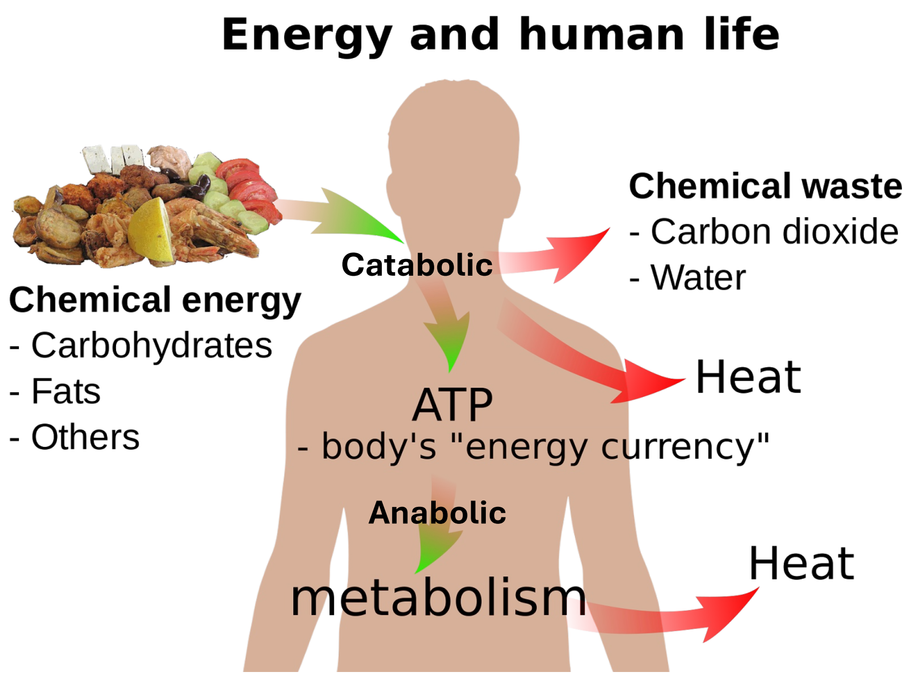
The Big Picture

- Nutrients contain high potential energy that is used in catabolic pathways to generate ATP, which then provides a source of potential energy to drive anabolic reactions.
- Metabolic pathways couple endergonic reactions (unfavorable) to exergonic reactions (favorable), which enables a set of reactions to be thermodynamically favorable.



Thermodynamics of Coupled Reactions

- Thermodynamically unfavorable reactions ($\Delta G > 0$) can proceed when coupled to favorable reactions ($\Delta G < 0$) that share intermediates.
- The total ΔG of coupled reactions is additive. Le Châtelier's principle explains how removal of an intermediate product shifts equilibrium to favor product formation; the product in the 1st reaction is a reactant in the 2nd reaction.

$$\text{Reaction 1: A + B} \xrightleftharpoons{\text{Enzyme 1}} \mathbf{C} \qquad \Delta G^{\circ}{}_1 = +3 \text{ kJ/mol (endergonic)}$$

$$\text{Reaction 2: } \mathbf{C} + \text{D} \xrightleftharpoons{\text{Enzyme 2}} \text{E} \qquad \Delta G^{\circ}{}_2 = -10 \text{ kJ/mol (exergonic)}$$

$$\text{Net reaction: A + B + D} \rightleftharpoons \text{E} \qquad \Delta G^{\circ}{}_1 + \Delta G^{\circ}{}_2 = \Delta G^{\circ}{}_3 = -7 \text{ kJ/mol (exergonic)}$$

Thermodynamics of Coupled Reactions

Question 1:

Using the $\Delta G^{\circ\prime}$ values for the reactions shown below, what is the $\Delta G^{\circ\prime}$ value for the conversion of phosphoenolpyruvate (PEP) <--> 3-phosphoglycerate (3PGA) by the enzymes enolase and phosphoglycerate mutase in the gluconeogenic pathway?

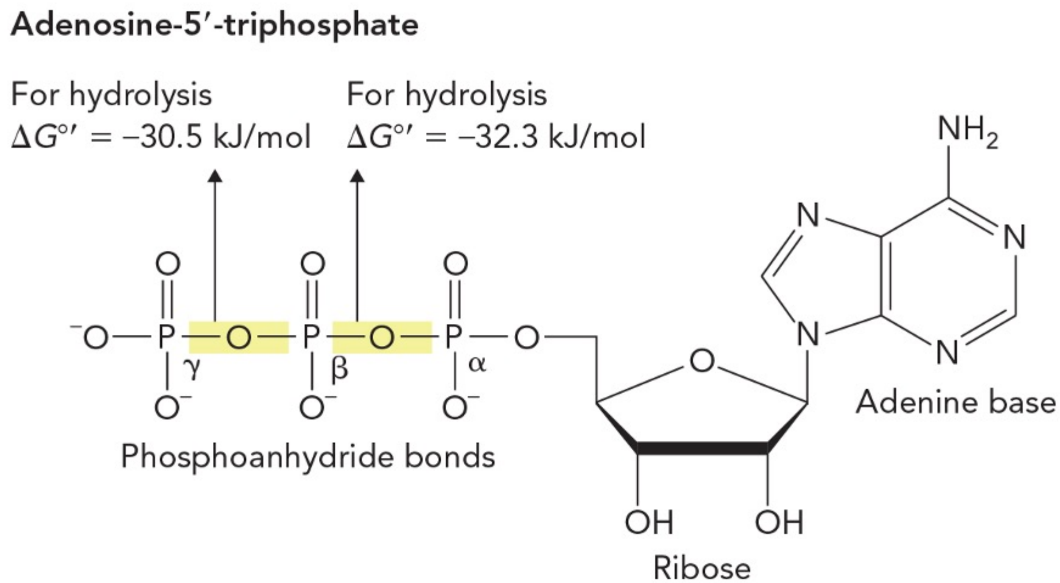
Phosphoenolpyruvate <--> 2-Phosphoglycerate	$\Delta G^{\circ\prime}$ = -1.7 kJ/mol
3-Phosphoglycerate <--> 2-Phosphoglycerate	$\Delta G^{\circ\prime}$ = +4.6 kJ/mol

Phosphoenolpyruvate <--> ~~2-Phosphoglycerate~~	$\Delta G^{\circ\prime}$ = -1.7 kJ/mol
~~2-Phosphoglycerate~~ <--> 3-Phosphoglycerate	$\Delta G^{\circ\prime}$ = -4.6 kJ/mol
Phosphoenolpyruvate <--> 3-Phosphoglycerate	**$\Delta G^{\circ\prime}$ = -6.3 kJ/mol**

In these coupled reactions, 2-phosphoglycerate is the shared intermediate

ATP Hydrolysis can Drive Coupled Reactions

- ATP contains two phosphoanhydride bonds, which can be hydrolyzed to yield adenosine diphosphate and inorganic phosphate (ADP + P_i) or adenosine monophosphate and pyrophosphate (AMP + PP_i).



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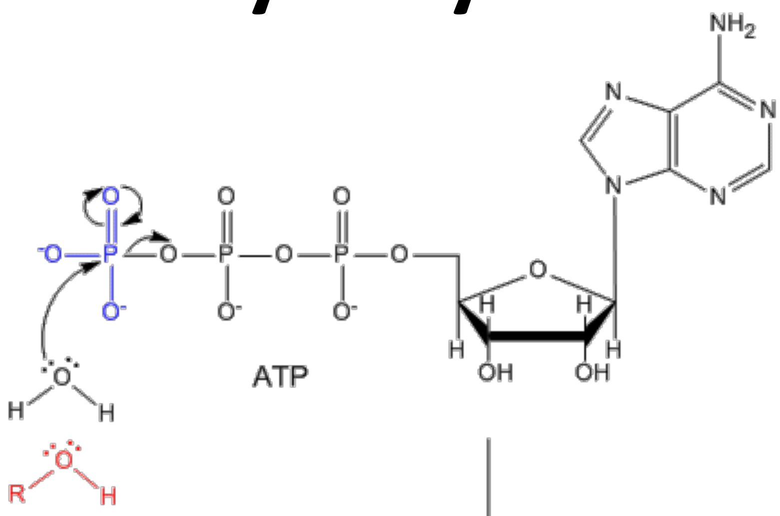
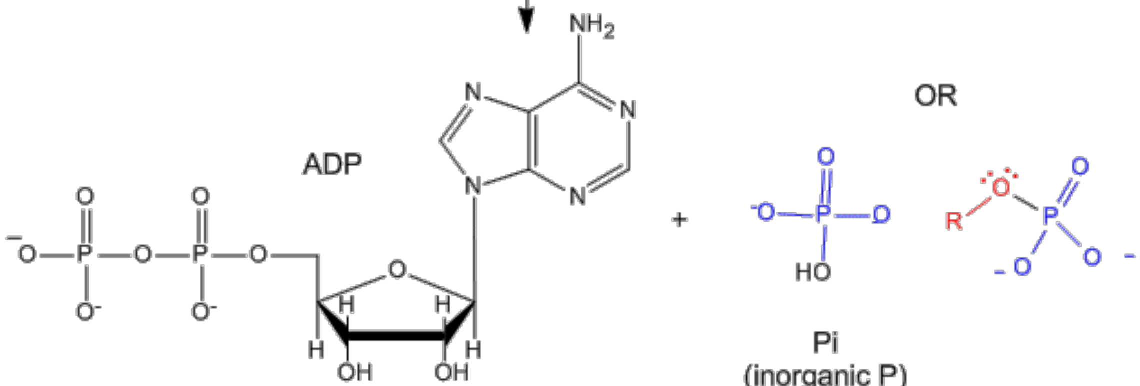
ATP Hydrolysis is an Exergonic Reaction



- Energy is absorbed to break the phosphate bond (**endergonic**), but the formation of new bonds (**exergonic**) between the phosphate and an acceptor molecule *releases more energy* than what was absorbed making ATP hydrolysis an *overall exergonic reaction*.



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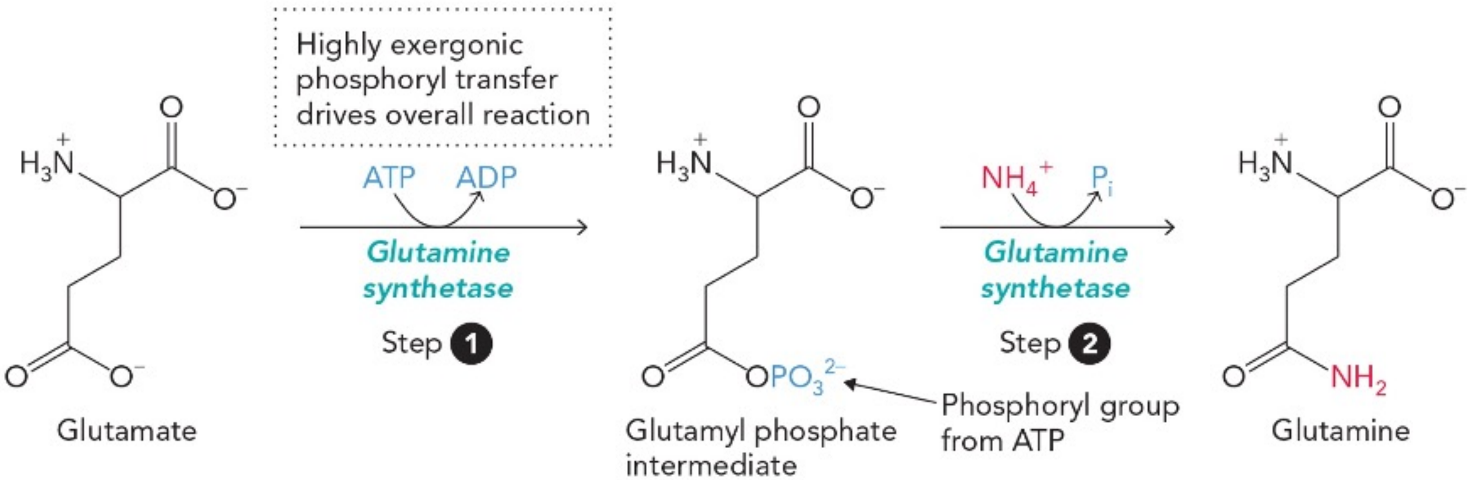
ATP-Coupled Phosphoryl Transfer Reactions

- The conversion of glutamate to glutamine by the enzyme glutamine synthetase is an ATP-coupled reaction; the γ-phosphoryl group of ATP is used in a phosphoryl transfer reaction to generate a highly reactive intermediate.

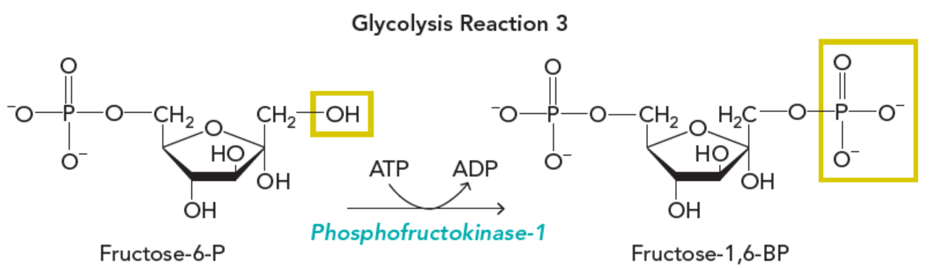


ATP-Coupled Phosphoryl Transfer Reactions

Question 2:

Calculate the ΔGº' for the conversion of glucose-6-phosphate to fructose-1,6-bisphosphate by the enzyme phosphofructokinase-1 (PFK-1) given the following standard Gibbs energy changes for each of the reaction components:

Glucose-6P <--> Fructose-6P	ΔGº'	+1.7 kJ/mol
Fructose-1,6-BP <--> Fructose-6P + Pi	ΔGº'	-16.3 kJ/mol
ATP <--> ADP + Pi	ΔGº'	-30.5 kJ/mol



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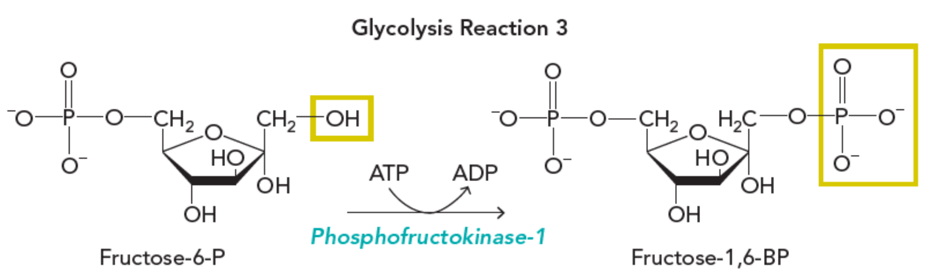
ATP <--> ADP + ~~Pi~~	ΔGº'	-30.5 kJ/mol
Glucose-6P + ATP <--> Fructose-1,6-BP + ADP	**ΔGº'**	**-12.5 kJ/mol**



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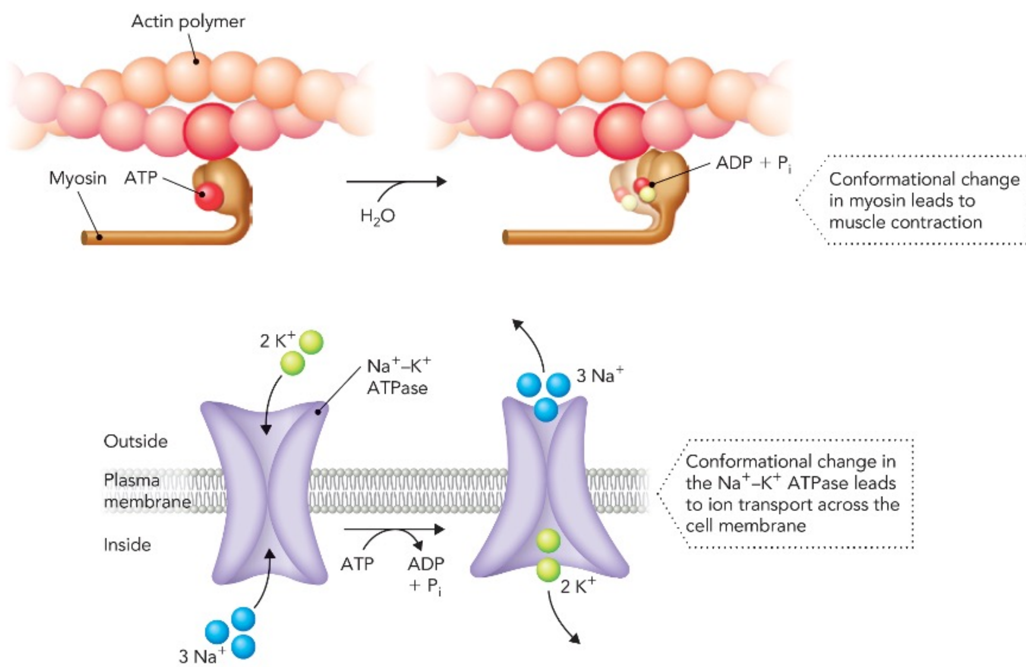
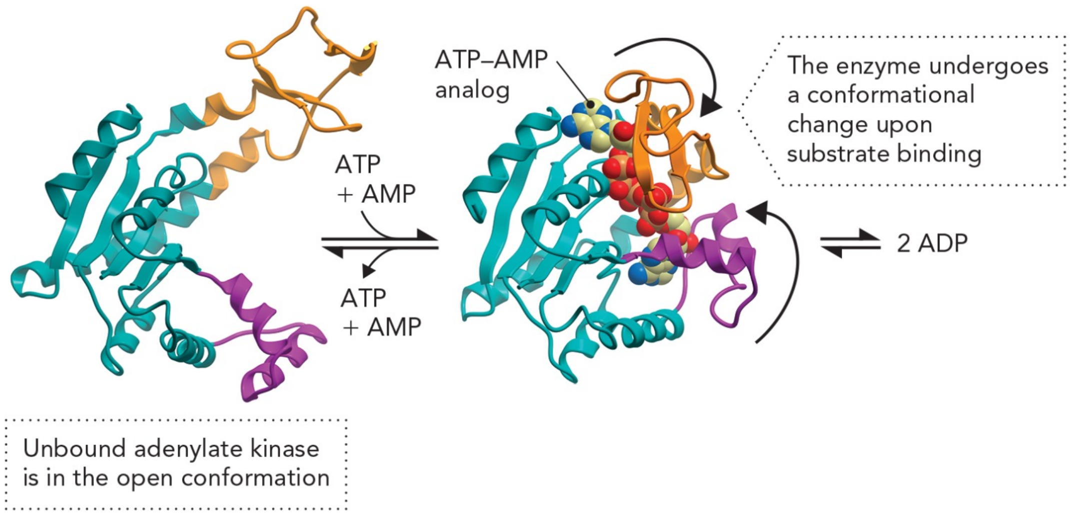
ATP-Coupled Phosphoryl Transfer Reactions

- Two examples of ATP hydrolysis being used for protein conformational changes:
  - Muscle contraction involving conformational changes in the myosin protein.
  - Conformational changes in the Na^+-K^+ ATPase protein that mediate ion transport.



Adenylate System: Energy Charge in the Cell

- The cell maintains ATP levels within a narrow range to avoid a metabolic catastrophe by interconverting ATP, ADP, and AMP using phosphoryl transfer reactions.



$$AMP + ATP \xrightleftharpoons{\text{Adenylate kinase}} 2\ ADP$$

$$2\ ADP + 2\ P_i \xrightleftharpoons{\text{ATP synthase}} ATP + ATP$$

$$\text{Net reaction: } AMP + 2\ P_i \xrightleftharpoons{\text{ATP synthase}} ATP$$

Adenylate System: Energy Charge in the Cell

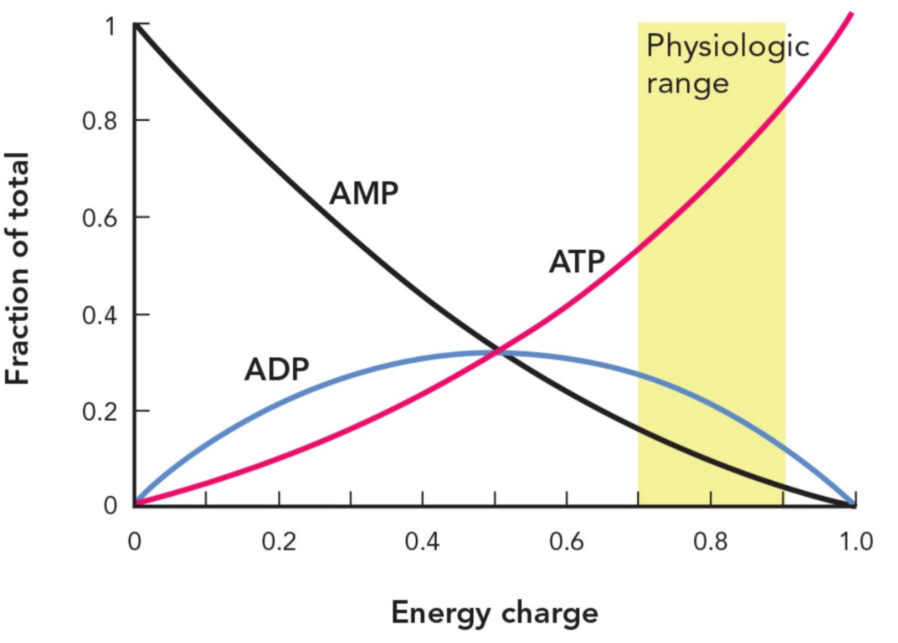
We can use the ratio of the concentration of ATP to the concentration of ADP and AMP in the cell at any given time as a measure of the energy state of the cell called the energy charge (EC). For example, the steady state concentrations of ATP, ADP and AMP in liver cells, which has a value energy charge of EC = 0.81:

$$EC = \frac{[ATP] + 0.5[ADP]}{[ATP] + [ADP] + [AMP]}$$

$$EC = \frac{3.4 \text{ mM} + 0.5(1.3 \text{ mM})}{3.4 \text{ mM} + 1.3 \text{ mM} + 0.3 \text{ mM}} = 0.81$$

Adenylate System: Energy Charge in the Cell

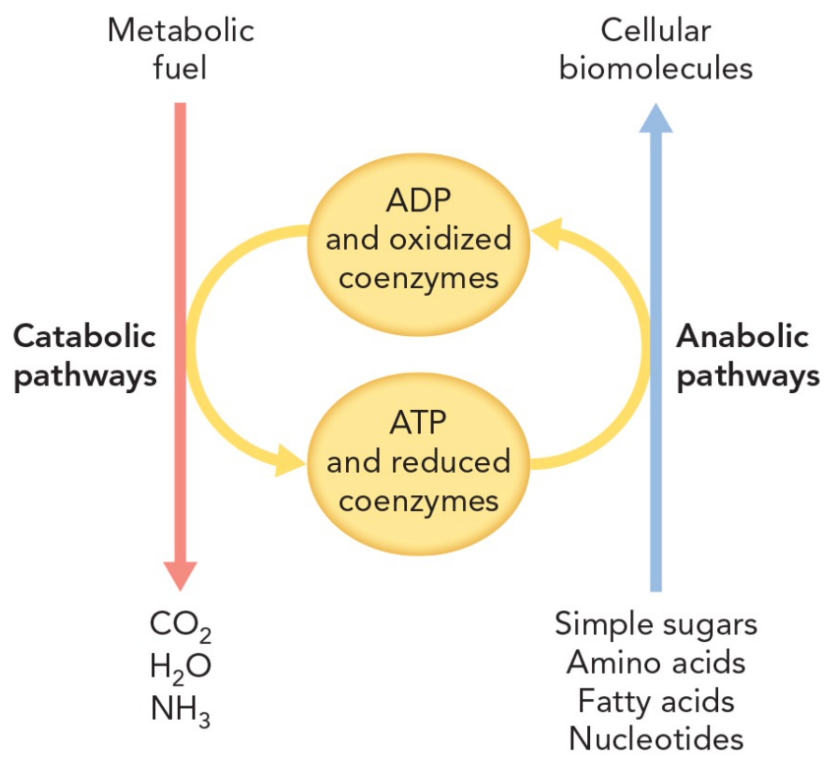
- Cells maintain the energy charge by regulating metabolic flux through anabolic and catabolic pathways.
- When EC is near 0.7, ATP levels are low, and ADP levels are near maximum. When EC is at 0.9, ATP levels are near maximum, and AMP levels are very low.



Regulating Anabolic and Catabolic Pathways

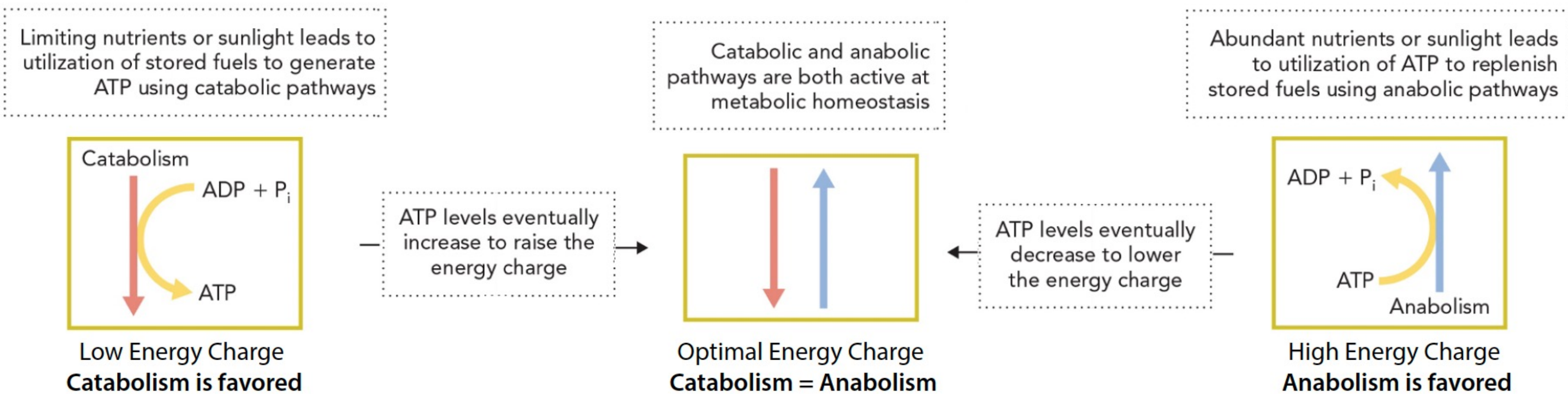
- Extracting energy from metabolic fuels is the function of **catabolic pathways**, which convert fuel into high-potential energy compounds ATP and NADH.

- These high-potential-energy compounds are then used for the biosynthesis of biomolecules through **anabolic pathways**.



Regulating Anabolic and Catabolic Pathways

- Under conditions of low nutrients (or sunlight), enzymes in catabolic pathways are activated to degrade stored metabolic fuels and generate ATP.
- When nutrients are abundant (or sunlight), then ATP is used to replenish supplies of stored metabolic fuel.



Key Concepts to Guide Your Learning

- The Δ*G* value of coupled reactions is equal to the sum of the Δ*G* values for each individual reaction through the use of a shared intermediate.
- ATP hydrolysis is thermodynamically favorable because the energy released by the formation of hydrogen bonds between P_i and an acceptor molecule (proteins, lipids, H_2O, etc.) is exergonic and is greater than the energy required to break the phosphoanhydride bond, which is endergonic.
- Phosphoanhydride bond energy in ATP can be used for protein conformational changes, e.g., in muscle myosin protein and Na^+–K^+ ATPase transporter protein.
- The energy charge (EC) of the cell reflects the relative concentrations of ATP, ADP, and AMP. When the EC is high, anabolic pathways (biosynthesis) are favored; when the EC is low, catabolic pathways (degradation) are favored.