Lecture 12 - Epilogue
Metabolism: Basic Concepts and Design

Preview for Chem 454

Introduction

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- *How does a cell extract energy and reducing power from its environment (catabolism)?*

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Questions you will focus on in Chem 454:

- *How does a cell extract energy and reducing power from its environment (catabolism)?*
- *How does a cell synthesize the molecules it needs (anabolism)?*
- *How are these processes integrated and regulated?*

Introduction

Living organisms require an input of free energy to meet a variety of needs:

This free energy is required for

- Mechanical work (Lecture 11)
- Active transport of molecules and ions (Lecture 9)
- Synthesis of biomolecules (Chapters 24-26)

Introduction

The source of this free energy varies

- Phototrophs

  Use energy from the sun to convert energy-poor molecules into energy rich molecules (Chapters 19 & 20)

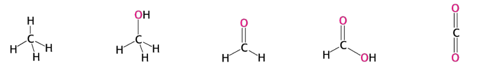
- Chemotrophs

  Obtain energy by oxidizing the energy-rich molecules made by the phototrophs (Chapters 15-18)

Introduction

- Reduced molecules are *energy-rich*
- Oxidized molecules are *energy-poor*

most energy ⟶ least energy



	Methane	Methanol	Formaldehyde	Formic acid	Carbon dioxide
$\Delta G^{\circ}_{oxidation}$ (kcal mol^{-1})	−196	−168	−125	−68	0
$\Delta G^{\circ}_{oxidation}$ (kJ mol^{-1})	−820	−703	−523	−285	0

Introduction

We have also seen how free energy can be stored as an unequal distribution of ions across a biological membrane.

The free energy that is stored in an ion gradient can be used to

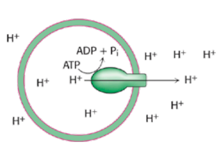
- Make ATP by a process called oxidative phosphorylation (Lecture 11 & Chapter 18)
- Transport ions and metabolites across membranes (Active transport (Lecture 9)
- Nerve transmission (The action potential) (Lecture 9)

Introductions

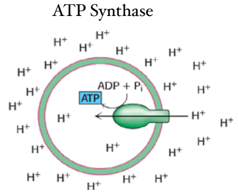
Ion gradients:

- Ion gradients an be produced by pumps that use ATP hydrolysis as a source of free energy (Lecture 9)
- Ion gradients can be use, in turn, to synthesize ATP from ADP and P_i.

Active Transport

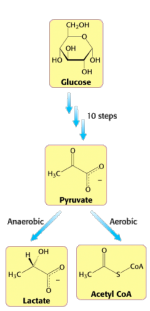


ATP Synthase

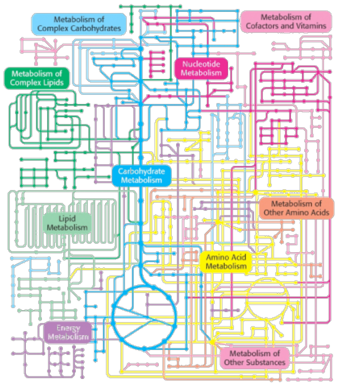


Metabolism

Metabolism is composed of many coupled, interconnected reactions



Metabolism



Metabolism

Classes of metabolic pathways:

- **Catabolic** pathways

  Those that convert energy into biologically useful forms

- **Anabolic** pathways

  Those that require an input of energy

Metabolism

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Fuels (carbohydrates, fats) ⟶ CO_2 + H_2O + useful energy

- **Anabolic** pathways

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Metabolism

Classes of metabolic pathways:

- **Catabolic** pathways

  Those that convert energy into biologically useful forms

Fuels (carbohydrates, fats) ⟶ CO_2 + H_2O + useful energy

- **Anabolic** pathways

  Those that require an input of energy

Useful energy + small molecules ⟶ complex molecules

Metabolism

Basic concepts of metabolism include:

- Thermodynamically unfavorable reactions can be driven by favorable reactions.
- ATP (NTP) is the universal currency of free energy.
- ATP hydrolysis drives metabolism by shifting the equilibrium constant of coupled reactions.
- There is a structural basis for the high phosphoryl transfer potential of ATP.
- The phosphoryl transfer potential is an important form of cellular energy transformation.

Thermodynamics

Thermodynamically unfavorable reactions can be driven by favorable reactions.
Free energy change for a reactions:

$$A + B \rightarrow C + D$$

$$\Delta G = \Delta G^{0'} + RT \ln\left(\frac{[C][D]}{[A][B]}\right)$$

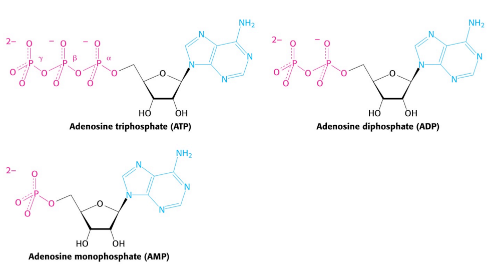
Thermodyamics

Coupling unfavorable reactions with favorable ones

$$\begin{array}{ll} A \leftarrow \boldsymbol{B} + C & \Delta G^{o'} = +5\ kcal\ mol^{-1} \\ \boldsymbol{B} \rightarrow D & \Delta G^{o'} = -8\ kcal\ mol^{-1} \\ \hline A \rightarrow C + D & \Delta G^{o'} = -3\ kcal\ mol^{-1} \end{array}$$

ATP

ATP is the universal currency of free energy



Adenosine triphosphate (ATP)
Adenosine diphosphate (ADP)
Adenosine monophosphate (AMP)

ATP

Hydrolysis of ATP:

$$ATP + H_2O \longrightarrow ADP + P_i \qquad \Delta G^{o\prime} = -7.3\ kcal\ mol^{-1}$$

$$ATP + H_2O \longrightarrow AMP + PP_i \qquad \Delta G^{o\prime} = -10.9\ kcal\ mol^{-1}$$

ATP Hydrolysis

- ATP hydrolysis drives metabolism by shifting the equilibrium of coupled reactions

ATP Hydrolysis

Phosphoryl transfer is a common means of energy coupling

- Molecular motors (Lecture 11)
- Muscle contraction (Lecture 5 & 11)
- Ion pumps (Lecture 9)

Phosphoryl Transfer

Structural basis for high transfer potential

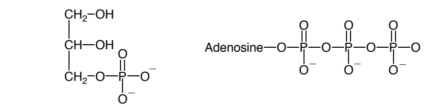
Compare:

$$ATP + H_2O \longrightarrow ADP + P_i \qquad \Delta G^{o\prime} = -7.3\ kcal\ mol^{-1}$$

$$\text{Glycerol 3-phosphate} + H_2O \longrightarrow \text{Glycerol} + P_i \qquad \Delta G^{o\prime} = -2.2\ kcal\ mol^{-1}$$

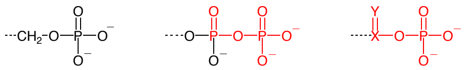
Phosphoryl Transfer

Phosphate ester *vs* Phosphate anhydride



Glycerol 3-phosphate

Adenosine triphosphate (ATP



Phosphate ester

Phosphate anhydryde

Phosphoryl Transfer

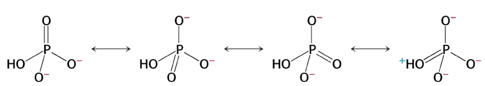
Stabilization of orthophosphate

- resonance stabilization
- electrostatic repulsion
- hydration

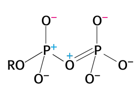
Stabilization of Orthophosphate

Resonance stabilization

Orthophosphate

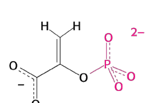


Pyrophosphate

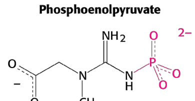


Phosphoryl Transfer and Energy Transfer

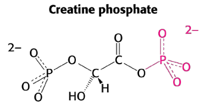
There are other molecules with favorable phosphoryl transferase energies



Phosphoenolpyruvate



Creatine phosphate



1,3-Bisphosphoglycerate

Phosphoryl Transfer

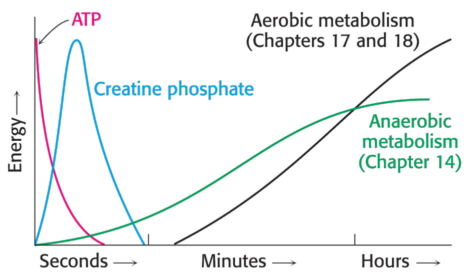
In terms of energy for phosphoryl transfer, ATP is intermediate:

TABLE 14.1 Standard free energies of hydrolysis of some phosphorylated compounds

Compound	kcal mol^{-1}	kJ mol^{-1}
Phosphoenolpyruvate	−14.8	−61.9
1,3-Bisphosphoglycerate	−11.8	−49.4
Creatine phosphate	−10.3	−43.1
ATP (to ADP)	− 7.3	−30.5
Glucose 1-phosphate	− 5.0	−20.9
Pyrophosphate	− 4.6	−19.3
Glucose 6-phosphate	− 3.3	−13.8
Glycerol 3-phosphate	− 2.2	− 9.2

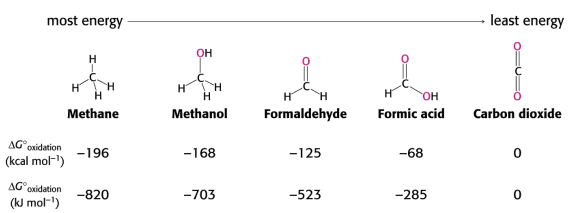
Phosphoryl Transfer

Creatine phosphate is used to generate ATP in the short term:



Cellular Energy

The oxidation of Carbon fuels is an important source of cellular energy



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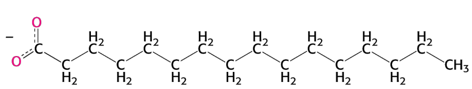
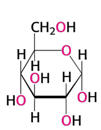


Fatty acid



Glucose

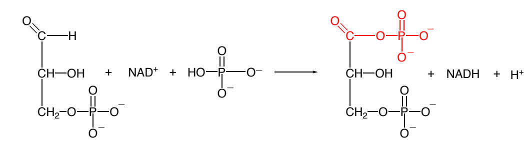
Cellular Energy

- The synthesis of high phosphoryl transfer potential compounds are used to couple carbon oxidation to ATP synthesis.
- Ion gradients across membranes also provide an important form of cellular energy that can be used to synthesize ATP.
- The extraction of energy from foodstuffs occurs in stages.

Coupling oxidation to ATP synthesis

The synthesis of high phosphoryl transfer potential compounds are used to couple carbon oxidation to ATP synthesis.

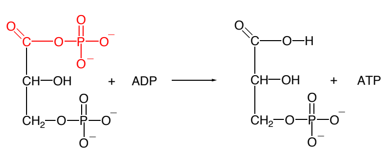
- Example from glycolysis:



Glyceraldehyde 3-phosphate → 1,3-Bisphosphoglycerate

Coupling oxidation to ATP synthesis

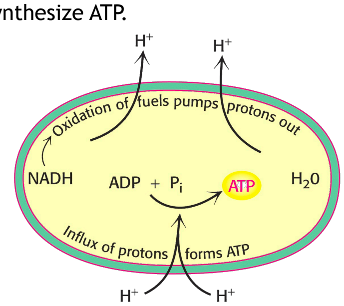
In the next step ATP is harvested from the high energy phosphate intermediate.



1,3-Bisphosphoglycerate → 3-Phosphoglycerate

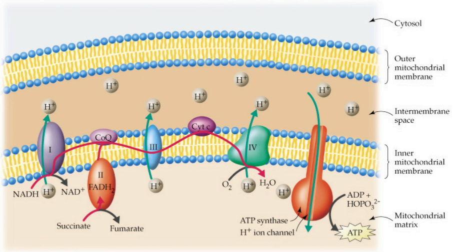
Ion Gradients

- Ion gradients across membranes also provide an important form of cellular energy that can be used to synthesize ATP.



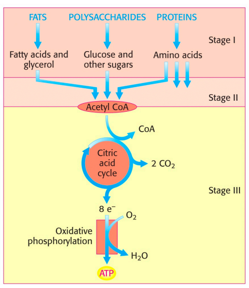
Cellular Energy

- Ion gradients across membranes also provide an important form of cellular energy that can be used to synthesize ATP. (Chapter 18)



Cellular Energy

Extraction of energy from foodstuffs is carried out in stages:



Recurring Motifs in Metabolism

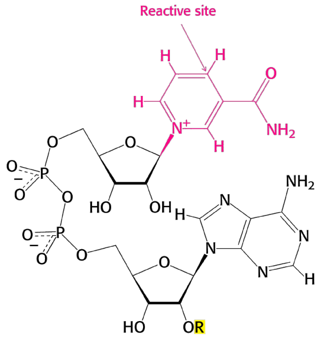
- Activated carriers exemplify the modular design and economy of metabolism.
- Key reactions are reiterated throughout metabolism.
- Metabolic processes are regulated in three principle way.

Activated Carriers

- ATP is an activated carrier of phosphate groups
- Other examples include:
  - Activated carriers of electrons in oxidation reactions (NADH, $FADH_2$, $FMNH_2$, et al.)
  - Activated carriers of electrons in reductive biosynthesis (NADPH, $FADH_2$, $FMNH_2$, et al.)
  - Activated carriers of two-carbon fragments (Acetyl-CoA)

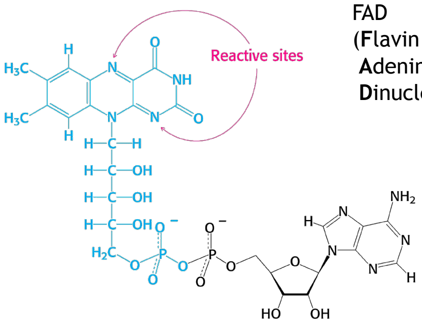
Activated carriers of electrons in catabolism

NAD[+]
(**N**icotinamide
Adenine
Dinucleotide)



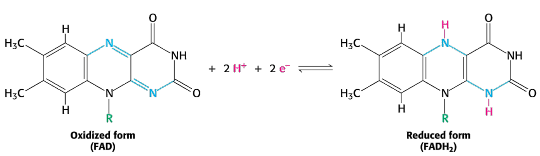
Activated carriers of electrons in catabolism

FAD
(**F**lavin
Adenine
Dinucleotide)



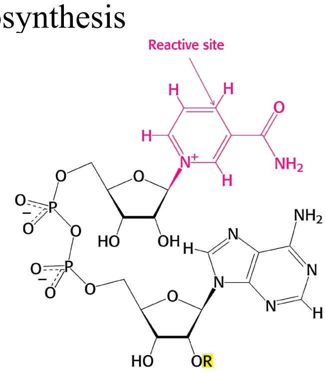
Activated carriers of electrons in catabolism

Reduction of isoalloxazine ring of FAD



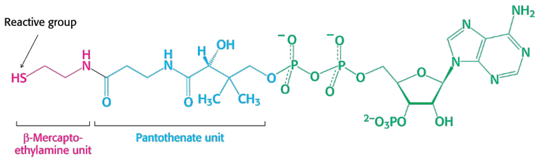
Activated carriers of electrons in biosynthesis

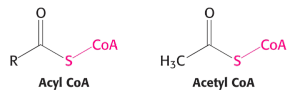
NADPH
(**N**icotinamide
Adenine
Dinucleotide
Phosphate)



Activated carriers of acyl groups

Coenzyme A is a carrier of Acyl groups





Activated Carriers

Other common activated carriers:

TABLE 14.2 Some activated carriers in metabolism

Carrier molecule in activated form	Group carried	Vitamin precursor
ATP	Phosphoryl	
NADH and NADPH	Electrons	Nicotinate (niacin)
$FADH_2$	Electrons	Riboflavin (vitamin B_2)
$FMNH_2$	Electrons	Riboflavin (vitamin B_2)
Coenzyme A	Acyl	Pantothenate
Lipoamide	Acyl	
Thiamine pyrophosphate	Aldehyde	Thiamine (vitamin B_1)
Biotin	CO_2	Biotin
Tetrahydrofolate	One-carbon units	Folate
S-Adenosylmethionine	Methyl	
Uridine diphosphate glucose	Glucose	
Cytidine diphosphate diacylglycerol	Phosphatidate	
Nucleoside triphosphates	Nucleotides	

Note: Many of the activated carriers are coenzymes that are derived from water-soluble vitamins (Section 8.6.1).

Key Reactions

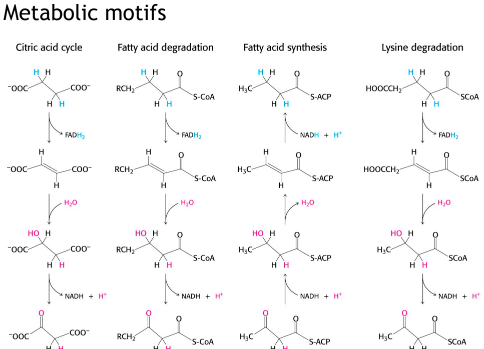
- There are six basic reactions in metabolism:

TABLE 14.3 Types of chemical reactions in metabolism

Type of reaction	Description
Oxidation–reduction	Electron transfer
Ligation requiring ATP cleavage	Formation of covalent bonds (i.e., carbon–carbon bonds)
Isomerization	Rearrangement of atoms to form isomers
Group transfer	Transfer of a functional group from one molecule to another
Hydrolytic	Cleavage of bonds by the addition of water
Addition or removal of functional groups	Addition of functional groups to double bonds or their removal to form double bonds

Key Reactions

Metabolic motifs



Metabolic Regulation

Metabolic processes are regulated in different ways:

- Enzyme levels
- Enzyme activity (Lecture 6)
- Accessibility of substrates to the enzyme (Compartmentalization)

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Metabolic Regulation

Degradative and biosynthesis pathways are usually distinct

- Compartmentalization
- Allosteric regulation

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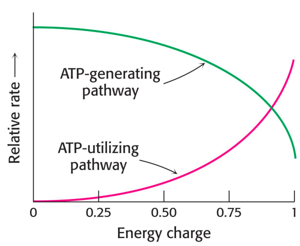
Metabolic Regulation

- The energy charge

$$\text{Energy Charge} = \frac{[\text{ATP}] + \frac{1}{2}[\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]}$$



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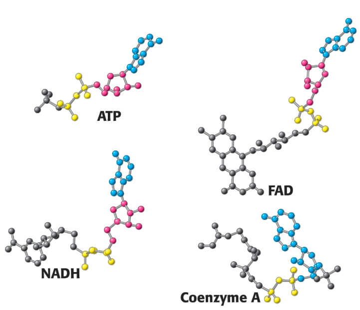
Evolution of Metabolic Pathways

The structures of ATP, CoEnzyme A NADH and $FADH_2$ belie their "RNA world" origin.



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