Metabolism and Bioenergetics

Pratt and Cornely, Chapter 12

Fuel and Digestion

- Breakdown of food biomolecules to monomers
- Absorption of monomers
  - Storage
  - Metabolism
Carbohydrates

- Amylase in mouth, intestine
  - Amylose
  - Amylopectin
- Transported through intestine to portal vein
  - liver/bloodstream
- Storage
  - Muscle
  - Liver
  - Converted to fat

Proteins

- Breakdown of peptide bond
  - Gastric proteases
  - Pancreatic proteases
- Amino acids transported through intestine to blood/liver
  - Incorporated into proteins (if needed)
  - Broken down to carbs and fats (storage)
Lipids

- Digestion
  - Pancreatic lipases
  - Bile salts
- Transported through intestinal cell (diffusion or transport)
- Re-packaged
- Circulated as chylomicrons and lipoproteins
- Stored in adipose

Mobilization of Glycogen

- Required for brain
- Highly branched; release of energy
- Phosphorolysis
- Muscle: Energy conservation
- Liver: phosphate hydrolysis before entering blood
Mobilization of Lipids

- Primary energy for heart
- Compact energy form
- Lipases release from adipose
- Circulate as protein complexes
- Major basal energy source

Protein Processing

- Proteins not a storage form
- But do need constantly degraded (diet or outside source)
- Lysozome
  - Membrane and extracellular
  - pH 5 optimum
- Proteasome
  - Barrel shaped
  - Ubiquitin tag
Key intermediates

Problem 25

- Check the box of each pathway in which this intermediate is a reactant or product

<table>
<thead>
<tr>
<th></th>
<th>Glycolysis</th>
<th>Citric Acid Cycle</th>
<th>Fatty Acid metabolism</th>
<th>TAG synthesis</th>
<th>Transamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl-CoA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyceraldehyde-3-P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyruvate</td>
<td></td>
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</tr>
</tbody>
</table>
Redox Reactions

- Catabolism
  - Oxidation

- Anabolism
  - Reduction

\[ \text{Catabolism: } \text{Oxidation} \]
\[ \text{Anabolism: } \text{Reduction} \]

Redox Cofactors

- 2 electron transfer
  - NAD\(^+\)/NADH (catabolism)
  - NADP\(^+\)/NADPH (anabolism)
- 1 or 2 electron transfer
  - FAD/FADH\(_2\)
- 1 electron transfer
  - Ubiquinone, metals
  - membrane
Catalytic Cofactors

- Electron transport chain
- Purpose of breathing oxygen

Essential Nutrients

<table>
<thead>
<tr>
<th>TABLE 12-1</th>
<th>Some Essential Substances for Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino Acids</td>
<td>Fatty Acids</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Linoleate ( CH_2(CH_2)_2(CH=CHCH_3)(CH_2)_2COO^- )</td>
</tr>
<tr>
<td>Leucine</td>
<td>Linolenate ( CH_3CH(CH=CHCH_3)(CH_2)_2COO^- )</td>
</tr>
<tr>
<td>Lysine</td>
<td>Methionine</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Threonine</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Valine</td>
</tr>
</tbody>
</table>

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Vitamins

**Problem 33**

- Refer to table 12.2 to identify the vitamin necessary for these reactions:

![Chemical reactions](attachment:image.png)

*Image credit: Wiley, Inc.*
Vitamin Chemistry

- We will build throughout semester
- Introduction to fundamental chemistry of decarboxylation

![Thiamine (vitamin B₁)](image1)

![Pyridoxyl Phosphate (PLP) Vitamin B₆](image2)

Qualitative Energetics

- ATP: High energy bonds—inherent chemistry
  - Electrostatic repulsion
  - Solvation of products
  - Resonance
- Rxn goes to “completion”
Energy Currency

**Anaerobic systems**
- ATP
  - high jump
  - power lift
  - shot put
  - tennis serve
- Phospho-creatine
  - sprints
  - football line play

**Aerobic systems**
- Glycolysis
  - 200—400 m race
  - 100 m swim
- Oxidative phosphorylation
  - race beyond
  - 500 m

**Duration of activity**
- 4 s
- 10 s
- 1.5 min
- 3 min

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**Phosphoanhydride bonds**

![Diagram of ATP and its breakdown products](image)

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Formal Metabolism

Nutrient \[\rightarrow\] ADP + P_i \[\rightarrow\] Product

\[\text{catabolism}\] \[\text{anabolism}\]

Waste product \[\rightarrow\] ATP \[\rightarrow\] Precursor

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Uphill or Downhill?

Glucose \[\rightarrow\] Glucose-6-phosphate

Phosphocreatine \[\rightarrow\] Creatine

\[\text{thioester bond}\]

Acetyl-CoA \[\rightarrow\] HCO_2^- + CoA-SH

HPO_4^{2-} \[\rightarrow\] CH_2OPO_4^{2-}
Qualitative Predictions

• Inherently favorable, unfavorable, or near equilibrium?

\[ \text{GMP} + \text{ATP} \rightleftharpoons \text{GDP} + \text{ADP} \]
\[ \text{GDP} + \text{ATP} \rightleftharpoons \text{GTP} + \text{ADP} \]
\[ \text{AMP} + \text{ATP} \rightleftharpoons 2 \text{ADP} \]
\[ \text{AMP} + \text{ATP} + 2 \text{P}_i \rightleftharpoons 2 \text{ATP} + 2 \text{H}_2\text{O} \]

Thermodynamics vs Kinetics

• Gibbs Free Energy
  – Spontaneous
  – Favorable
  – exergonic
• \( \Delta G = G_{\text{pdt}} - G_{\text{rxt}} \)
  – Path independent
  – Doesn’t tell us about kinetics
Equilibrium

- You can’t understand thermodynamics until we clear up some common misconceptions about equilibrium...

- Is this reaction at equilibrium or not?
- If not, in which direction does the equilibrium lie?

Standard Free Energy

- Every reaction moves spontaneously toward equilibrium—but that could be either direction.
- There is a relationship between equilibrium constant and free energy of the reaction.
- If we start with 1M reactants and products, the free energy change of that reaction is called the “standard” free energy.
- \( \Delta G^0 \) is a reflection of the chemical potential (stability of bonds):
  - Negative \( \Delta G^0 \) means equilibrium favors products.
  - Larger \( \Delta G^0 \) means it is favored to a greater degree.

- \( \Delta G^0 = -RT \ln K_{eq} \)
- The 0 means “standard”
  - 1 M, 1 atm, 298 K
- The ‘ means “biological standard”
  - pH 7, 55M water
Standard Free Energy

Glutamate + NH₄⁺ ↔ glutamine + H₂O

\[ \Delta G^{\circ}_{\text{reaction}} = +14 \text{ kJ mol}^{-1} \]

What do these examples mean?

- Under standard conditions, glutamine will spontaneously turn into glutamate.
- Hydrolysis of ATP is more favorable than hydrolysis of glucose-6-phosphate

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \Delta G^{\circ} ) (kJ mol(^{-1}))</th>
</tr>
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<tbody>
<tr>
<td>Phosphoenolpyruvate</td>
<td>-61.9</td>
</tr>
<tr>
<td>1,3-Bisphosphoglycerate</td>
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<td>ATP → AMP + PP(_i)</td>
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Standard Free Energy vs. Free Energy

\[ \text{ATP} \leftrightarrow \text{ADP} + P_i \]

\( \Delta G^\circ = -32 \text{ kJ} \) and \( \Delta G = -32 \text{ kJ} \)

\[ \text{ADP} \leftrightarrow P_i \]

\( \Delta G^\circ = -32 \text{ kJ} \)

\( \Delta G = \text{zero} \)
Quantitative Problems

• What is \([\text{product}] / [\text{rxt}]\) ratio of ATP hydrolysis to ADP at equilibrium?
  \[\Delta G^{0'} = -RT \ln K_{eq}\]
  \[R = 8.314 \text{ J/mol K, } T \text{ in Kelvin}\]
  \[[\text{ADP}][\text{Pi}] / [\text{ATP}] = 4.1 \times 10^5 = K_{eq}\]

• What is the free energy of ATP hydrolysis when it reaches equilibrium?
  \[\text{Equilibrium} = \text{DEAD!}\]

A Second Misconception...

• I have mixed together some glutamate, ammonia, glutamine, and water. Will my reaction proceed spontaneously to the left or to the right?

\[\text{Glutamate} + \text{NH}_3 \overset{\text{reaction}}{\rightleftharpoons} \text{glutamine} + \text{H}_2\text{O}\]

\[\Delta G^{0'}_{\text{reaction}} = +14 \text{ kJ mol}^{-1}\]
A Second Misconception...

- We don’t know—it depends on HOW MUCH of each you have mixed together.
- Reactions always move spontaneously toward equilibrium, but we need to know ACTUAL CONCENTRATIONS to determine which direction that is... 

\[
\text{Glutamate} + \text{NH}_4^+ \rightleftharpoons \text{glutamine} + \text{H}_2\text{O} \\
\Delta G^\circ_{\text{reaction}} = +14 \text{ kJ mol}^{-1}
\]

Example

- Standard Free energy allows us to calculate equilibrium concentrations
- \(K_{\text{eq}} = 0.00352\), so for example
  - [glutamine] = 1 mM
  - [NH_4^+] = 0.53M
  - [glutamate] = 0.53M

- Fill in the table

<table>
<thead>
<tr>
<th>[glutamine]</th>
<th>[NH_4^+]</th>
<th>[glutamate]</th>
<th>Right or left?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td>1 M</td>
<td>1 M</td>
<td></td>
</tr>
<tr>
<td>0.1 mM</td>
<td>0.53M</td>
<td>0.53M</td>
<td></td>
</tr>
<tr>
<td>1 mM</td>
<td>0.53M</td>
<td>0.23M</td>
<td></td>
</tr>
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</table>
Free Energy

- The free energy of a PARTICULAR reaction depends on two factors
  - The nature of the bonds in the reaction
  - The concentration of the compounds
- A reaction with a $-\Delta G^0$ can be spontaneous or nonspontaneous under cellular conditions.

$$\Delta G = \Delta G^0 + RT \ln \frac{[p{dts}]}{[r{xts}]}$$

Free Energy of ATP hydrolysis

- Actual cellular concentrations don’t vary much from $[P_i]=[ATP] = 5$ mmol and $[ADP]= 1$ mmol
- **Problem 43**: What is the actual free energy of ATP hydrolysis in the cell? More or less than -32 kJ? What does this mean, physiologically?

$$\Delta G_{reaction} = \Delta G^0_{reaction} + RT \ln \frac{[products]}{[reactants]}$$
Two Types of Reactions

• Near-equilibrium reactions
  – Actual \([\text{pdt}] / [\text{rxt}]\) ratio near the equilibrium concentrations
  – \(\Delta G\) close to zero (regardless of \(\Delta G^\circ\))
  – Not regulated—part of overall flux of metabolism

• Metabolically irreversible reactions
  – \(\Delta G\) far from zero
  – Can only be overcome by energy input
  – regulated
ATP in Metabolism

• Overcoming a barrier...
  – Can’t change concentrations (ammonia is toxic!)
  – Couple the reaction to a spontaneous reaction!

\[
\text{Glutamate} + \text{NH}_4^+ \rightleftharpoons \text{glutamine} + \text{H}_2\text{O} \\
\Delta G'_{\text{reaction}} = +14 \text{ kJ mol}^{-1}
\]

– **Problem 59**: Write an equation to couple this reaction to ATP hydrolysis.

---

Mechanism of Coupling

\[
\text{Glutamate} \quad \xrightarrow{\text{ATP}} \quad \text{γ-Glutamyl phosphate} \quad \xrightarrow{\text{ADP}} \quad \text{Glutamine}
\]
Another Type of Coupling

• Problem 50: The standard free energy of formation of UDP-glucose from G-1-P and UTP is about zero. Yet the production of UDP-glucose is highly favorable. Explain.

Glucose-1-phosphate + UTP $\leftrightarrow$ UDP-glucose + PP$_i$

Phosphoryl Transfer in Energetic Intermediates

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Phosphoryl group transfer potential

PPI $\rightarrow$ 2 Pi = $-29$ kJ/mol
Problem 42

- Calculate the biological standard free energy for the isomerization of G-1-P to G-6-P. Is it spontaneous under standard conditions? Is it spontaneous when [G-6-P] is 5 mM and [G-1-P] = 0.1 mM?

### Table 12-4

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