Digestion and Metabolism

Metabolism
The complete set of reactions living organisms carry out in order to:

- obtain energy
- synthesize the compounds they require

Three requirements on Energy
- Must be released from food **GRADUALLY**. (Why?)
  - Glucose → 687 kcal/mol
- Must be **stored in readily accessible** forms. (Why?)
- Must be **finely controlled**. (Why?)

Spontaneous reactions (Exergonic)
  - A reaction that will occur “on its own.”

E.g.
ATP + H₂O → ADP + Pi + 7.3 kcal/mol

Nonspontaneous reactions (Endergonic)
  - “Does not occur without the addition of energy”. It needs to be “pushed”.

E.g.
Glucose + Pi + 3.3 kcal/mol → Glucose-6-P + H₂O

Coupled Reactions
  - Endergonic reactions can be pushed by exergonic (spontaneous), through a shared intermediate.

\[
\begin{align*}
ATP + H₂O & \rightarrow ADP + Pi + 7.3 \text{ kcal/mol} \\
\text{Glucose} + Pi + 3.3 \text{ kcal/mol} & \rightarrow \text{Glucose-6-P} + H₂O \\
\hline
\text{ATP} + \text{Glucose} & \rightarrow \text{ADP} + \text{Glucose-6-P} + 4.0 \text{ kcal/mol}
\end{align*}
\]

ATP and Energy
  - Is the energy form stored in cells.
  - Is obtained from the oxidation of food.
  - Requires 7.3 (31 kJ) per mole to convert ADP + Pi to ATP.

Stages of Metabolism:
  - Stage 1. Digestion
  - Stage 2. Acetyl-SCoA Production
  - Stage 3. Citric Acid Cycle
  - Stage 4. ATP Production

Redox reactions
  - The net result of catabolism is the oxidation of food to release energy.
  - A steady supply of redox agents must be available.

<table>
<thead>
<tr>
<th>Reduced</th>
<th>Oxidized</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>NADH + H⁺</td>
<td>NAD⁺</td>
<td>Produces a carbon-oxygen double bond (C=O)</td>
</tr>
<tr>
<td>FADH₂</td>
<td>FAD</td>
<td>Produces a carbon-carbon double bond (C=C).</td>
</tr>
<tr>
<td>HSCoA</td>
<td>Acetyl-SCoA</td>
<td>Activates acyl groups for transfer.</td>
</tr>
</tbody>
</table>
Metabolic Pathways
- Sequences of reactions (catalyzed by enzymes) that produce intermediates (called metabolites).
- Major three traits of metabolic pathways:
  - Individual rxns may be reversible, but not the overall pathway.
  - The first rxn is often the rate-limiting step.
  - Can be turned on and off when needed.
- Not always linear.

Stage 2: Glycolysis
- A metabolic pathway that uses glucose.
- Degrades 6C glucose molecules to 3C molecules (pyruvate).
- Takes place in the cytoplasm
- Is an anaerobic (no oxygen) process.

Glycolysis: Energy-Investment
Rxns 1-5: Phosphate groups are added and Glucose is converted to two three-carbon molecules.

Glycolysis: Energy-Production
Rxns. 6-10: Sugar phosphates are cleaved and four ATP molecules are produced.

Overall Reaction
\[ \text{C}_6\text{H}_{12}\text{O}_6 + 2\text{ADP} + 2\text{Pi} + 2\text{NAD}^+ \rightarrow 2\text{C}_3\text{H}_3\text{O}_3^- + 2\text{ATP} + 2\text{NADH} + 2\text{H}^+ \]

Glucose Pyruvate

Regulation of Glycolysis
Three enzymes:
What do these three reactions have in common…???
- Reaction 1 is inhibited by high [glucose-6-phosphate].
- Reaction 3 is inhibited by high [ATP] and activated by high [ADP].
- Reaction 10 inhibited by high [ATP] or [acetyl CoA].

Fates of Pyruvate
1) Pyruvate: Aerobic Conditions (Yields the most energy)
Matrix of the mitochondria.
- Three-carbon pyruvate is decarboxylated.
- Two-carbon acetyl CoA and CO\(_2\) are produced.

\[ \text{pyruvate} + \text{HS—CoA} + \text{NAD}^+ \rightarrow \text{acetyl—S—CoA} + \text{CO}_2 + \text{NADH} + \text{H}^+ \]

2) Pyruvate: Anaerobic Conditions
Under anaerobic conditions (without oxygen),
- Pyruvate is reduced to lactate.
- NADH oxidizes to NAD\(^+\) allowing glycolysis to continue.

\[ \text{pyruvate} + \text{NADH} + \text{H}^+ \rightarrow \text{lactate} + \text{NAD}^+ \]

Lactate in Muscle
During strenuous exercise,
- Anaerobic conditions are produced and lactate accumulates (muscles tire and hurt).
- After exercise, a person breathes heavily.

Cori Cycle
- The flow of lactate and glucose between the muscles and the liver. In the liver lactate is oxidized back to pyruvate; then pyruvate is converted to glucose, which is carried back to the muscles.
3) Fermentation
- Occurs in anaerobic microorganisms such as yeast.
- Decarboxylates pyruvate to acetaldehyde, which is reduced to ethanol.
- Regenerates NAD\(^+\) to continue glycolysis.

\[
\text{Pyruvate} + \text{NADH} + H^+ \rightarrow \text{Ethanol} + \text{NAD}^+ + \text{CO}_2
\]

Citric Acid Cycle (Stage 3)
- Operates under aerobic conditions only.
- Oxidizes the two-carbon acetyl group in acetyl-CoA to 2CO\(_2\).

Overall Chemical Reaction for the Citric Acid Cycle
\[
\text{acetylS-CoA} + 3\text{NAD}^+ + \text{FAD} + \text{ADP} + P_i + 2\text{H}_2\text{O} \rightarrow 2\text{CO}_2 + 3\text{NADH} + 3\text{H}^+ + \text{FADH}_2 + \text{HS-CoA} + \text{ATP}
\]

Regulation of Citric Acid Cycle
- Increases when [ATP] or [NADH] are low.
- Decreases when [ATP] or [NADH] are high.

Regulation of Electron Transport (For a description of the process, look at your other handout on metabolism.)
- ADP/ATP ratio
- Low levels of ADP, P\(_i\), and oxygen decrease electron transport activity.
- High levels of ADP that activate electron transport.

Utilization of Glucose
Glucose
- Is the primary energy source for the brain, skeletal muscle, and red blood cells.
- Deficiency can impair the brain and nervous system.

Glycogenesis
- Stores glucose by converting glucose to glycogen when [glucose-6-phosphate] is high.
- Stops when energy stores (glycogen) are full. (i.e. additional glucose is converted to body fat.)

Glycogenolysis
- Glycogen is broken down to glucose.
- Molecules are removed one by one.

Gluconeogenesis: Glucose Synthesis
- The synthesis of glucose from carbon atoms of noncarbohydrate compounds.
- Required when glycogen stores are depleted.

Regulation of [Glucose]
When [glucose] is high (after eating)
- Insulin (produced in the pancreas) is released into the bloodstream.
  - Glycolysis (+)
  - Glycogenesis (+)
  - Gluconeogenesis (–)
  - Glycogenolysis (–)
- If we have enough glycogen, the extra glucose is converted to fat.
Regulation of Glucose
When [glucose] is low

- Glucagon (produced in the pancreas) is secreted into the bloodstream.

<table>
<thead>
<tr>
<th>Metabolic Pathway</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis</td>
<td>(−)</td>
</tr>
<tr>
<td>Glycogenesis</td>
<td>(−)</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>(+)</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>(+)</td>
</tr>
</tbody>
</table>

- Epinephrine (adrenaline) is released from the adrenal glands when we need a “burst of energy” (the “fight or flight” mode) to signal for glycogenolysis.

Fat Mobilization (Lipids)

- Breaks down TAG’s in adipose tissue.
- Forms fatty acids and glycerol.

Fatty Acids and Glycerol

- Glycerol is converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, which participate in:
  - **Glycolysis**—energy generation
  - **Gluconeogenesis**—glucose formation
  - Triacylglycerol synthesis

- Fatty acids undergo
  - Resynthesis of triacylglycerols for storage
  - **Conversion to acetyl-SCoA (The process is known as beta oxidation).**

Summary of Fatty Acid Activation

- Fatty acid activation is complex, but it regulates the degradation and synthesis of fatty acids.
- Two ATP’s are invested.

Beta-Oxidation of Fatty Acids

In reaction 1, oxidation

- Forms a trans C=C bond.
- Reduces FAD to FADH2.

In reaction 2 hydration

- Adds water across the trans C=C bond.
- Adds a hydroxyl group to the β carbon.

In reaction 3 is a second oxidation

- Forms a keto group on the β carbon.

In Reaction 4 acetyl CoA is cleaved

- By splitting the bond between the α and β carbons.
- Forms a shortened fatty acyl CoA that repeats β-oxidation.

Fatty Acid Length and β-Oxidation

The length of a fatty acid determines the number of oxidations and of acetyl-CoA groups.

<table>
<thead>
<tr>
<th>Carbons in Fatty Acid</th>
<th>Acetyl CoA (#C’s/2)</th>
<th>β-Oxidation Cycles (#C’s/2) − 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>
The β-Oxidation of Unsaturated Fatty Acid yields less ATP’s. Why?

Unsaturated fatty acids already have double bonds in their structures, so reaction number 1 (and formation of \( \text{FADH}_2 \)) is not needed. Since the double bonds in nature are cis, reaction one is just an isomerization to the trans structure for the double bond. Due to this factor, for every \( \text{C} = \text{C} \) that appears in the structure of an unsaturated fatty acid, we get 2 ATP’s less than we would with a saturated fatty acid with the same number of carbons.

Ketone Bodies

If carbohydrates are not available
- Body fat breaks down to meet energy needs.
- Keto compounds called ketone bodies form. \((\text{Ketogenesis})\)

Ketosis occurs
- In diabetes, diets high in fat, and starvation.
- [ketone bodies] is high!!
- Lowers blood pH below 7.4 (acidosis).

Ketosis Causes:
Dehydration (due to increased urine flow).
Labored breathing.
Coma and death (if untreated).

Lipogenesis: Fatty Acid Synthesis
- Is the synthesis of fatty acids from acetyl CoA. (Opposite of beta oxidation.)
- Allows the body to divert the energy of excess carbohydrates and amino acids into storage as \( \text{TAG} \)’s.

In fatty acid synthesis
- A high level of blood glucose and insulin stimulates glycolysis and pyruvate oxidation.
- More acetyl \( \text{CoA} \) is available to form fatty acids.

Proteins in the Body (Amino Acid Pool)
Proteins provide
- Amino acids for protein synthesis.
- Nitrogen atoms for nitrogen-containing compounds.
- Energy when carbohydrate and lipid resources are not available.

Metabolism of Amino Acids
- Each of the 20 amino acids is degraded via its own unique pathway (when not used for proteins).
- General scheme:
  - Removal of the amino group
  - Use of nitrogen in synthesis of new nitrogen compounds
  - Passage of nitrogen into the urea cycle
  - Incorporation of the carbon atoms into compounds that can enter the citric acid cycle

Urea Cycle
The urea cycle
- Detoxifies ammonium ion from amino acid degradation.
- Converts ammonium ion to urea in the liver.
- Provides 25-30 g urea daily for urine formation in the kidneys.

Sources of Amino Acids
- Essential amino acids must be obtained in the diet.
- Nonessential amino acids are synthesized in the body. \((\text{See your handout on amino acid side chains})\)