Lipid Metabolism

Pratt & Cornely, Chapter 17

Catabolism Overview

- Lipids as a fuel source—diet
- Beta oxidation
  - Mechanism
  - ATP production
- Ketone bodies as fuel
TAG and FA

- High energy
  - More reduced
  - Little water content
  - 9 Cal/g vs 4 Cal/g for carbs
- Unsaturated FA
- Glycerol

Digestion

- Cross from intestine into bloodstream
Lipoprotein Metabolism

- Liver is the packaging center
- VLDL are sent out of liver
- Constant cycling of LDL in blood
- Genetic cholesterol problem: no LDL receptors in non-liver cells
- HDLs are “good cholesterol”

### TABLE 17-1 Characteristics of Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Diameter (Å)</th>
<th>Density (g·cm⁻³)</th>
<th>% Protein</th>
<th>% Triacylglycerol</th>
<th>% Cholesterol and Cholesteryl Ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>1000–5000</td>
<td>&lt;0.95</td>
<td>1–2</td>
<td>85–90</td>
<td>4–8</td>
</tr>
<tr>
<td>VLDL</td>
<td>300–800</td>
<td>0.95–1.006</td>
<td>5–10</td>
<td>50–65</td>
<td>15–25</td>
</tr>
<tr>
<td>IDL</td>
<td>250–350</td>
<td>1.006–1.019</td>
<td>10–20</td>
<td>20–30</td>
<td>40–45</td>
</tr>
</tbody>
</table>
Role of LDL and HDL

Utilization Stage 1: Mobilization

Hormone Sensitive Lipase
Utilization Stage 2: Activation and Transport into Matrix

- FA must be attached to CoA
- High energy bond
- Costs $\text{ATP} \rightarrow \text{AMP}$ (2 ATP equivalents)
Utilization Stage 2: Transport into Matrix

- Matrix is site of fatty acid breakdown
  - Goes into citric acid cycle
- Carnitine ester: another high energy bond
- Transporter: Major site of regulation of FA degradation

Problem 7

- A deficiency of carnitine results in muscle cramps, which are exacerbated by fasting or exercise. Give a biochemical explanation for the muscle cramping, and explain why cramping increases during fasting and exercise.
Utilization Stage 3: Beta Oxidation

- Four step process
- Production of
  - QH₂
  - NADH
  - Acetyl CoA

3. Oxidation of acyl-CoA at the 2,3 position is catalyzed by an acyl-CoA dehydrogenase to yield a 2,3-enediol-CoA. The two electrons removed from the acyl group are transferred to an FAD prosthetic group. A series of electron transfer reactions eventually transfers the electrons to ubiquinone (Q).

2. The second step is catalyzed by a hydratase, which adds the elements of water across the double bond produced in the first step.

3. The hydroxyacyl-CoA is oxidized by another dehydrogenase. In this case, NAD⁺ is the electron acceptor.

4. The final step, thiolysis, is catalyzed by a thioloxyenase and releases acetyl-CoA. The remaining acyl-CoA, one carbons shorter than the starting substrate, undergoes another round of the four reactions (electrof liver).
Step 1: Acyl CoA Dehydrogenase

- Similar to succinate DH from citric acid cycle
- Prosthetic FAD/FADH$_2$
- High energy electrons passed on to QH$_2$
- 1.5 ATP

Step 2: Enoyl CoA Hydratase

- Similar to fumarate hydratase from citric acid cycle
- Addition of water
- No energy cost/production
Step 3: 3-hydroxyacyl CoA DH

- Similar to malate DH from citric acid cycle
- Oxidation of secondary alcohol to ketone
- NADH production
- 2.5 ATP

\[
\begin{align*}
\text{R-} & \quad \text{OH} \\
\text{CoA} & \quad \text{O} \\
\downarrow & \quad \text{R-} \\
\text{CoA} & \quad \text{O} \quad \text{O}
\end{align*}
\]

Step 4: Thiolase

- CoA is used as a nucleophile in a “nucleophilic acyl substitution”
- FA shortened by 2 carbons
- Acetyl CoA produced

\[
\begin{align*}
\text{R-} & \quad \text{O} \\
\text{CoA} & \quad \text{O} \\
\downarrow & \quad \text{HS-CoA} \\
\text{R-} & \quad \text{O} \\
\text{CoA} & \quad \text{O} \\
\end{align*}
\]
Problem 13

- The β-Oxidation pathway was elucidated in part by Franz Knoop in 1904. He fed dogs fatty acid phenyl derivatives and then analyzed their urine for the resulting metabolites. What metabolite was produced when dogs were fed

\[
\text{Phenylpropionate}
\]

\[
\text{Phenylbutyrate}
\]

<table>
<thead>
<tr>
<th>One round of β oxidation</th>
<th>Citric acid cycle</th>
<th>Oxidative phosphorylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 QH₂</td>
<td></td>
<td>1.5 ATP</td>
</tr>
<tr>
<td>1 NADH</td>
<td></td>
<td>2.5 ATP</td>
</tr>
<tr>
<td>1 Acetyl-CoA</td>
<td>3 NADH → 7.5 ATP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 QH₂ → 1.5 ATP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 GTP → 1 ATP</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14 ATP</td>
<td></td>
</tr>
</tbody>
</table>

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ATP Accounting

• How much ATP is netted from palmitate (16 carbons)?
  – Cost 2 ATP to activate to palmitate CoA
  – Run through beta oxidation SEVEN times
    • 7 QH2 = 10.5 ATP
    • 7NADH = 17.5 ATP
  – 8 acetyl CoA produced = 80 ATP
• Total: 106 ATP, or 6.625 ATP per carbon
• Compare to glucose, which is 5.33 ATP per C

Processing Other FA

• Unsaturated and trans fatty acids
  – Trans is natural intermediate
  – Produce 1.5 ATP less for unsaturation, 4 ATP less for di-unsaturation
Processing Other FA

- Odd chain fatty acids
  - Rare, but do occur in diet
  - One of 2 requirements for Vitamin B₁₂ (cobalamine) in human diet

Production of Succinate

- Carboxylase (biotin)
- Rearrangement (vitamin B₁₂-radical)
- Net glucose can be produced
**Peroxisome**

- Handles long fatty acids
  - Chain shortening
- Branched fatty acids
- Chemistry of first oxidation is different

**Biosynthesis of Lipids**

- Triacylglycerides as fuels
- Glycerophospholipids in membrane
- Prostaglandins as signal molecules
- Cholesterol and derivatives
Fatty Acid Synthesis

• Opposite of beta oxidation in the sense that 2-carbon acetate units are linked to form even-chain, saturated fatty acids
• Differs from Fatty acid degradation
  – In cytoplasm, not matrix
  – Acyl carrier protein rather than CoA
  – Enzymes linked in a complex
  – Utilizes NADPH
  – Energetically linked to ATP hydrolysis
Activation of Acetyl Group

- Acetyl CoA carboxylase (analogous to pyruvate carboxylase of gluconeogenesis)
- Requires biotin, ATP
- A regulation step—shifts fuel away from CAC

Transfer to Acyl Carrier Protein
Four Step Elongation

• Step 1: Condensation
  – Loss of CO₂ drives reaction to completion
  – All happens on enzyme complex
  – Mechanism:

\[
\text{Malonyl-ACP} \quad \rightarrow \quad \text{Acetyl-Cys} \quad \rightarrow \quad \text{Acetoacetyl-ACP}
\]
Steps 2-4: Opposite of beta Oxidation

- Input of 2 NADPH
- Major use of PPP

\[
\begin{align*}
\text{CH}_2\text{O} \quad &\text{NADPH} \rightarrow \quad \text{CH}_2\text{O} \quad &\text{NADPH} \\
\text{CH}_2\text{O} \quad &\rightarrow \quad \text{CH}_2\text{O} \\
\text{CH}_2\text{O} \quad &\rightarrow \quad \text{CH}_2\text{O}
\end{align*}
\]

Synthesis of Palmitate

\[
\text{Acetyl CoA} + 7 \text{ Malonyl CoA} + 14 \text{ NADPH} + 20 \text{ H}^{\circ} \rightarrow \text{Palmitate} + 7 \text{ CO}_2 + 14 \text{ NADP}^{\circ} + 8 \text{ HS-CoA} + 6 \text{ H}_2\text{O}
\]

- 16-carbon fatty acid produced in major synthesis complex
- **Problem 31:** What is the ATP cost of synthesizing palmitate from acetyl-CoA?
Regulation

• Explain Regulation
  – Acetyl CoA carboxylase
    • Citrate is acetyl CoA equivalent
    • Fatty Acid
  – Carnitine Transporter
    • Malonyl CoA

Alternate Fate of Acetyl CoA

• Fasting, Diabetes
  – Glycolysis is down, gluconeogenesis is up
  – Oxaloacetate depleted
  – Citric acid cycle has diminished capacity
  – Acetyl CoA levels build up
• Ketone bodies are formed
Ketone Bodies

- Water soluble form of lipids
- Less potential energy than FA
- Main energy source of brain in starvation
- Also used in muscle and intestine
Post-synthesis Modification

- Elongations possible with other enzymes
- Many organisms can make odd-chain fatty acids
- Essential Fatty acids

Prostaglandins and COX Inhibitors
Cholesterol Biosynthesis

- Three Stages: Acetyl CoA $\rightarrow$ Isopentyl diphosphate $\rightarrow$ Squalene $\rightarrow$ Cholesterol

Stage 1

- Similar to ketogenesis, but in cytosol
- HMG-CoA reductase
- Isoprene building block for many lipids
Stages 2 and 3

Medical Applications

• Statins inhibit HMG-CoA Reductase
• Problem: inhibits all steroid biosynthesis
Medical Applications

• Another strategy for lowering cholesterol is to trap bile salts in intestine so that cholesterol is diverted.

Parasites like malaria make isopentenyl diphosphate through a different mechanism.

• A competitive inhibitor can selectively kill malaria.