Fatty Acid Catabolism

Lehninger 5th ed. Chapter 17

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Prof. Shimon Schuldiner
Email: Shimon.Schuldiner@huji.ac.il
Phone: 6585992
CHAPTER 17
Fatty Acid Catabolism

Key topics:

- How fats are digested in animals
- How fats are mobilized and transported in tissues
- How fats are oxidized
- How “ketone bodies” are produced
Oxidation of Fatty Acids is a Major Energy-Yielding Pathway in Many Organisms

• About one third of our energy needs comes from dietary triacylglycerols
• About 80% of energy needs of mammalian heart and liver are met by oxidation of fatty acids
• Many hibernating animals, such as grizzly bears, relay almost exclusively on fats as their source of energy
Fats Provide Efficient Fuel Storage

• The advantage of fats over polysaccharides:
  – **Fatty acid carry more energy** per carbon because they are more reduced
  – **Fatty acids carry less water** along because they are nonpolar

• **Glucose and glycogen are for short-term energy needs**, quick delivery

• **Fats are for long term (months) energy needs**, good storage, slow delivery
Triacylglycerols: Stored energy

- Moderately obese people (15-20Kg of fat) could live off their Triglycerides for months as opposed to a day off their glycogen stores.
Triacylglycerols: storage location

• Eukaryotic cells: oily droplets form inclusion in the aqueous cytosol.
• Vertebrates: adipocytes are specialized cells that store fat, located mainly under the skin.
• Plants: located in seeds.
Adipocytes

Figure 10-4a
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Arabidopsis seed
Triglycerides in Foods

- $C_{16}$ and $C_{18}$ saturated
- $C_{16}$ and $C_{18}$ unsaturated
- $C_4$ to $C_{14}$ saturated

Natural fats at 25 °C

- Olive oil, liquid
- Butter, soft solid
- Beef fat, hard solid
Dietary Fatty Acids Are Absorbed in the Vertebrate Small Intestine

1. Bile salts emulsify dietary fats in the small intestine, forming mixed micelles.
2. Intestinal lipases degrade triacylglycerols.
3. Fatty acids and other breakdown products are taken up by the intestinal mucosa and converted into triacylglycerols.
4. Triacylglycerols are incorporated, with cholesterol and apolipoproteins, into chylomicrons.
5. Chylomicrons move through the lymphatic system and bloodstream to tissues.
6. Lipoprotein lipase, activated by apoC-II in the capillary, releases fatty acids and glycerol.
7. Fatty acids enter cells.
8. Fatty acids are oxidized as fuel or reesterified for storage.
Lipids are Transported in the Blood as Chylomicrons

Figure 17-2
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(b) Blood plasma after fast
(b) Blood plasma after meal
Hormones Trigger Mobilization of Stored Triacylglycerols
Figure 17-3

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Hydrolysis of Fats Yields Fatty Acids and Glycerol

• hydrolysis of triacylglycerols is catalyzed by lipases
• some lipases are regulated by hormones glucagon and epinephrine
  • epinephrine means: “we need energy now”
  • glucagon means: “we are out of glucose”
1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol
Glycerol from Fats Enters Glycolysis

- Glycerol kinase activates glycerol at the expense of ATP
- Subsequent reactions recover more than enough ATP to cover this cost
- Allows limited anaerobic catabolism of fats
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Figure 17-4 part 2
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**Figure 17-4 part 3**

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Fatty Acids are Converted into Fatty Acyl-CoA
Figure 17-5
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Fatty Acid Transport into Mitochondria

- Fats are degraded into fatty acids and glycerol in the cytoplasm
- Generation of fatty acyl-CoA occurs in the cytoplasm
- β-oxidation of fatty acids occurs in mitochondria
- Small (< 12 carbons) fatty acids diffuse freely across mitochondrial membranes
- Larger fatty acids are transported via acyl-carnitine / carnitine transporter
Carnitine

\[
\text{CH}_3\text{N}^+\text{CH}_2\text{CH}\text{CH}_2\text{COO}^-\text{CH}_3\text{OH}
\]
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Stages of Fatty Acid Oxidation

- **Stage 1** consists of oxidative conversion of two-carbon units into acetyl-CoA with concomitant generation of NADH
- **Stage 2** involves oxidation of acetyl-CoA into CO\(_2\) via citric acid cycle with concomitant generation of NADH and FADH\(_2\)
- **Stage 3** generates ATP from NADH and FADH\(_2\) via the respiratory chain
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The $\beta$-Oxidation Pathway

- Each pass removes one acetyl moiety in the form of acetyl-CoA
Figure 17-8
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Step: 1
Dehydrogenation of Alkane to Alkene

- Catalyzed by isoforms of acyl-CoA dehydrogenase (AD) on the inner mitochondrial membrane
  - Very-long-chain AD (12-18 carbons)
  - Medium-chain AD (4-14 carbons)
  - Short-chain AD (4-8 carbons)

Analogous to succinate dehydrogenase reaction in the citric acid cycle
FAD Cofactor

• FAD undergoes **2-electron reduction**
  – possibly by hydride transfer, followed by protonation

• Electrons from the bound FADH$_2$ are passed to **electron-transferring flavoprotein (ETF)**
Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN)

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Step: 2
Hydration of Alkene

- Catalyzed by two isoforms of enoyl-CoA hydratase:
  - Soluble short-chain hydratase (crotonase)
  - Membrane-bound long-chain hydratase, part of trifunctional complex
- Water adds across the double bond yielding alcohol
- Analogous to fumarase reaction in the citric acid cycle
Figure 17-8a part 1
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Step: 3
Dehydrogenation of Alcohol

- Catalyzed by \( \beta \)-hydroxyacyl-CoA dehydrogenase
- The enzyme uses NAD cofactor as the hydride acceptor
- Only L-isomers of hydroxyacyl CoA act as substrates
- Analogous to malate dehydrogenase reaction in the citric acid cycle
Figure 17-8a part 2
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Step: 4
Transfer of Fatty Acid Chain

- Catalyzed by acyl-CoA acetyltransferase (thiolase) via covalent mechanism
  - The carbonyl carbon in β-ketoacyl-CoA is electrophilic
  - Active site thiolate acts as nucleophile and releases acetyl-CoA
  - Terminal sulfur in CoA-SH acts as nucleophile and picks up the fatty acid chain from the enzyme
- The net reaction is thiolysis of carbon-carbon bond
Figure 17-8a part 2

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Trifunctional Protein

- **Hetero-octamer**
  - Four $\alpha$ subunits
    - enoyl-CoA hydratase activity
    - $\beta$-hydroxyacyl-CoA dehydrogenase activity
    - Responsible for binding to membrane
  - Four $\beta$ subunits
    - long-chain thiolase activity

- May allow substrate channeling
- Associated with inner mitochondrial membrane
- Processes fatty acid chains with 12 or more carbons; shorter ones by enzymes in the matrix
Fatty Acid Catabolism for Energy

• Repeating the above four-step process six more times results in the complete oxidation of palmitic acid into eight molecules of acetyl-CoA
  – FADH$_2$ is formed in each cycle
  – NADH is formed in each cycle

• Acetyl-CoA enters citric acid cycle and is further oxidizes into CO$_2$
  – This makes more GTP, NADH and FADH$_2$
NADH and FADH$_2$ Serve as Sources of ATP
**TABLE 17–1** Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO₂ and H₂O

<table>
<thead>
<tr>
<th>Enzyme catalyzing the oxidation step</th>
<th>Number of NADH or FADH₂ formed</th>
<th>Number of ATP ultimately formed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyl-CoA dehydrogenase</td>
<td>7 FADH₂</td>
<td>10.5</td>
</tr>
<tr>
<td>β-Hydroxyacyl-CoA dehydrogenase</td>
<td>7 NADH</td>
<td>17.5</td>
</tr>
<tr>
<td>Isocitrate dehydrogenase</td>
<td>8 NADH</td>
<td>20</td>
</tr>
<tr>
<td>α-Ketoglutarate dehydrogenase</td>
<td>8 NADH</td>
<td>20</td>
</tr>
<tr>
<td>Succinyl-CoA synthetase</td>
<td>8 FADH₂</td>
<td>12</td>
</tr>
<tr>
<td>Succinate dehydrogenase</td>
<td>8 FADH₂</td>
<td>12</td>
</tr>
<tr>
<td>Malate dehydrogenase</td>
<td>8 NADH</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>108</strong></td>
</tr>
</tbody>
</table>

*These calculations assume that mitochondrial oxidative phosphorylation produces 1.5 ATP per FADH₂ oxidized and 2.5 ATP per NADH oxidized.

†GTP produced directly in this step yields ATP in the reaction catalyzed by nucleoside diphosphate kinase (p. 510).

Table 17-1

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- Palmitoyl-CoA + 23O₂ + 108Pᵢ + 108ADP
  \[ \rightarrow \text{CoA} + 108\text{ATP} + 16\text{CO}_2 + 23\text{H}_2\text{O} \]
Oxidation of Monounsaturated Fatty Acids
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Oxidation of Polyunsaturated Fatty Acids
Figure 17-10 part 1
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β oxidation (three cycles) → 3 Acetyl-CoA

Linoleoyl-CoA cis-Δ^9 , cis-Δ^12

Δ^3 , Δ^2 -enoyl-CoA isomerase

cis-Δ^3 , cis-Δ^6

β oxidation (one cycle, and first oxidation of second cycle) → Acetyl-CoA

trans-Δ^2 , cis-Δ^6

trans-Δ^2 , cis-Δ^4
2,4-dienoyl-CoA reductase

NADPH + H^+

2,4-dienoyl-CoA

NADP^+

enoyl-CoA isomerase

trans-Δ^2, cis-Δ^4

trans-Δ^3

trans-Δ^2

β oxidation (four cycles)

5 Acetyl-CoA

Figure 17-10 part 2
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Oxidation of Propionyl-CoA

- Most dietary fatty acids are even-numbered.
- Many plants and some marine organisms also synthesize odd-numbered fatty acids.
- Propionyl-CoA forms from β-oxidation of odd-numbered fatty acids.
- Bacterial metabolism in the rumen of ruminants also produces propionyl-CoA.
Figure 17-11
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Propionyl-CoA

\[ \text{H} - \text{C} - \text{H} \]
\[ \text{H} - \text{C} - \text{H} \]
\[ \text{C} - \text{O} \]
\[ \text{CoA-S} \]

propionyl-CoA carboxylase

\[ \text{HCO}_3^- \]

ATP

biotin

\[ \text{ADP} + P_i \]

\[ \text{O} \]
\[ \text{H} - \text{C} - \text{H} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{C} - \text{O} \]
\[ \text{CoA-S} \]

\[ \text{d-Methylmalonyl-CoA} \]
Figure 17-11 part 2
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Intramolecular Rearrangement in Propionate Oxidation Requires Coenzyme B$_{12}$
Box 17-2 figure 1
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Complex Cobalt-Containing Compound: Coenzyme B$_{12}$
Regulation of Fatty Acid Synthesis and Breakdown
Figure 17-12
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**β-Oxidation in Plants Occurs in Mainly in Peroxisomes**

- **Mitochondrial** acyl-CoA dehydrogenase passes electrons **into respiratory chain** via electron-transferring flavoprotein
  - Energy captured as ATP
- **Peroxisomal** acyl-CoA dehydrogenase passes electrons directly **to molecular oxygen**
  - Energy released as heat
  - Hydrogen peroxide eliminated by catalase
Formation of Ketone Bodies

- Entry of acetyl-CoA into citric acid cycle requires oxidoxaloacetate
- When oxaloacetate is depleted, acetyl-CoA is converted into ketone bodies
- The first step is reverse of the last step in the β-oxidation: thiolase reaction joins two acetate units
2 Acetyl-CoA

thiolase

CoA-SH

Acetoacetyl-CoA

HMG-CoA synthase

Acetyl-CoA + H₂O

CoA-SH

β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)

Figure 17-18 part 1

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Figure 17-18 part 2
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Liver as the Source of Ketone Bodies

- Production of ketone bodies increases during starvation
- Ketone bodies are released by liver to bloodstream
- Organs other than liver can use ketone bodies as fuels
- Too high levels of acetoacetate and β-hydroxybutyrate lower blood pH dangerously
Figure 17-20
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Chapter 17: Summary

In this chapter, we learned that:

• Fats are an important energy source in animals
• Two-carbon units in fatty acids are oxidized in a four-step \( \beta \)-oxidation process into acetyl-CoA
• In the process, lots of NADH and FADH\(_2\) forms; these can yield lots of ATP in the electron-transport chain
• Acetyl-CoA formed in the liver can be either oxidized via the citric acid cycle or converted to ketone bodies that serve as fuels for other tissues