Fatty Acid Synthesis

Chapter 28, Stryer Short Course

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>
<thead>
<tr>
<th>TABLE 17-1</th>
<th>Characteristics of Lipoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein</td>
<td>Diameter</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>1000-5000</td>
</tr>
<tr>
<td>VLDL</td>
<td>30-800</td>
</tr>
<tr>
<td>IDL</td>
<td>250-350</td>
</tr>
<tr>
<td>LDL</td>
<td>80-200</td>
</tr>
<tr>
<td>HDL</td>
<td>50-120</td>
</tr>
</tbody>
</table>

*Note: Values are approximate and may vary. Copyright 2008, W.H. Freeman and Company.
Role of LDL and HDL

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
Transport to Cytoplasm

- Acetyl CoA takes the oxaloacetate taxi out of the matrix
- Recycling transforms NADH into NADPH, which is reducing power needed for fatty acid synthesis

Integration of Pathways

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

- Acyl carrier protein is 77 residues
- Scaffold for building
- “macro CoA”

Four Step Elongation

- Enzyme complex coordinates synthesis
- Coordination of enzyme activity
- Makes palmitate (16 C)

Step 1: Condensation

- Opposite of thiolase
- Loss of CO₂ drives reaction to completion
Rough Mechanism

Steps 2-4: Opposite of beta Oxidation
- Input of 2 NADPH
- Major use of PPP
- Triclosan: broad spectrum antibiotic

Synthesis of Palmitate

\[
\text{Acetyl CoA} + 7 \text{ Malonyl CoA} + 14 \text{ NADPH} + 20 \text{ H}^+ \rightarrow \text{Palmitate} + 7 \text{ CO}_2 + 14 \text{ NADP}^+ + 8 \text{ HS-CoA} + 6 \text{ H}_2\text{O}
\]
- 16-carbon fatty acid produced in major synthesis complex
- **Problem 31**: What is the ATP cost of synthesizing palmitate from acetyl-CoA?
**Post-synthesis Modification**
- Elongations possible with other enzymes
- Many organisms can make odd-chain fatty acids
- Essential Fatty acids

**Prostaglandins and COX Inhibitors**

**Regulation**
- Carnitine Transporter
  - Matrix malonyl CoA
  - Error in this picture
  - Actually produced by acetyl CoA carboxylase isozyme in matrix
- Acetyl CoA carboxylase
  - Local
    - AMP level
    - Citrate and Fatty Acids
  - Hormones
AMP level

- AMP-activated protein kinase
  - Fuel sensor
  - Inactivates acetyl CoA carboxylase under low energy conditions in cell

Citrate and Fatty Acids

- [Citrate] high in well fed state
  - Lots of OAA and acetyl CoA
- Carboxylase forms active filaments
  - If [fatty acids] is high, no need to synthesize
  - Fatty acids break down filaments

Hormone-level control

- Glucagon and epinephrine
  - Suppress acetyl CoA carboxylase by keeping it phosphorylated
- Insulin—activates storage
  - Leads to dephosphorylation of carboxylase
Metabolism of Ethanol

- Liver damage
  - Too much NADH and acetyl CoA
  - Shuts down citric acid cycle
  - Fatty acid synthesis upregulated
    - "fatty liver"
  - Ketone bodies form
    - acidosis