Metabolism: the fat big picture

Figure 14.9 extrapolated to:
- Hormone sensitive lipase
- Fatty acid transport
- Beta oxidation
- Generation of water
- Citric Acid Cycle
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 rely 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
Lipids are Transported in the Blood as Chylomicrons
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”
Glycerol

Figure 10-3
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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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Fatty Acids are Converted into Fatty Acyl-CoA
The carboxylate ion is adenylated by ATP, to form a fatty acyl-adenylate and PP$_i$. The PP$_i$ is immediately hydrolyzed to two molecules of P$_i$.

The thiol group of coenzyme A attacks the acyl-adenylate (a mixed anhydride), displacing AMP and forming the thioester fatty acyl-CoA.

$\Delta G^{\circ} = -19$ kJ/mol

$\Delta G^{\circ} = -15$ kJ/mol
(for the two-step process)
Fatty Acid Transport into Mitochondria

• Fats are degraded into fatty acids and glycerol 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

\[
\begin{align*}
\text{CH}_3 & - \text{N}^+ - \text{CH}_2 - \text{CH} - \text{CH}_2 - \text{COO}^- \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{OH}
\end{align*}
\]
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**
Figure 17-7
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Stage 3: Electron transfer and oxidative phosphorylation

NADH, FADH$_2$ (reduced e$^-$ carriers)

Respiratory (electron-transfer) chain

2H$^+$ + $\frac{1}{2}$O$_2$ → H$_2$O

ADP + P$_i$ → ATP
**Figure 19-1**

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Figure 17-8
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CHAPTER 16
The Citric Acid Cycle

Key topics:

– Cellular respiration
– Conversion of pyruvate to activated acetate
– Reactions of the citric acid cycle
– Regulation of the citric acid cycle
– Conversion of acetate to carbohydrate precursors in the glyoxylate cycle
Conversion of Pyruvate to Acetyl-CoA

- net reaction: oxidative decarboxylation of pyruvate
  - acetyl-CoA can enter the citric acid cycle and yield energy
  - acetyl-CoA can be used to synthesize storage lipids
- requires five coenzymes
- catalyzed by the pyruvate decarboxylase complex
Figure 16-2
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Pyruvate dehydrogenase complex ($E_1 + E_2 + E_3$)

$\Delta G^\circ = -33.4 \text{ kJ/mol}$
Pyruvate Dehydrogenase Complex (PDC)

- PDC is a large ($M_r = 7.8 \times 10^6$ Da) multienzyme complex
  - pyruvate dehydrogenase ($E_1$)
  - dihydrolipoyl transacetylase ($E_2$)
  - dihydrolipoyl dehydrogenase ($E_3$)
- short distance between catalytic sites allows channeling of substrates from one catalytic site to another
- channeling minimizes side reactions
- activity of the complex is subject to regulation (ATP)
Figure 16-6
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Sequence of Events in the Citric Acid Cycle

- Step 1: C-C bond formation to make citrate
- Step 2: Isomerization via dehydration, followed by hydration
- Steps 3-4: Oxidative decarboxylations to give 2 NADH
- Step 5: Substrate-level phosphorylation to give GTP
- Step 6: Dehydrogenation to give reduced FADH$_2$
- Step 7: Hydration
- Step 8: Dehydrogenation to give NADH
Net Effect of the Citric Acid Cycle

\[
\text{Acetyl-CoA} + 3\text{NAD}^+ + \text{FAD} + \text{GDP} + P_i + 2 \text{H}_2\text{O} \rightarrow \\
2\text{CO}_2 + 3\text{NADH} + \text{FADH}_2 + \text{GTP} + \text{CoA} + 3\text{H}^+
\]

- carbons of acetyl groups in acetyl-CoA are oxidized to CO}_2\n- electrons from this process reduce NAD\(^+\) and FAD
- one GTP is formed per cycle, this can be converted to ATP
- intermediates in the cycle are not depleted
Anaplerotic Reactions

- these reactions replenish metabolites for the cycle
- four carbon intermediates are formed by carboxylation of three-carbon precursors
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Tissue(s)/organism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate + ( \text{HCO}_3^- ) + ATP [\text{pyruvate carboxylase}] oxaloacetate + ADP + P(_i)</td>
<td>Liver, kidney</td>
</tr>
<tr>
<td>Phosphoenolpyruvate + CO(_2) + GDP [\text{PEP carboxykinase}] oxaloacetate + GTP</td>
<td>Heart, skeletal muscle</td>
</tr>
<tr>
<td>Phosphoenolpyruvate + ( \text{HCO}_3^- ) [\text{PEP carboxylase}] oxaloacetate + P(_i)</td>
<td>Higher plants, yeast, bacteria</td>
</tr>
<tr>
<td>Pyruvate + ( \text{HCO}_3^- ) + NAD(P)H [\text{malic enzyme}] malate + NAD(P)(^+)</td>
<td>Widely distributed in eukaryotes and bacteria</td>
</tr>
</tbody>
</table>

Table 16-2
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Figure 16-18
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