Fatty Acid and Triacylglycerol Metabolism 1

Mobilization of stored fats and oxidation of fatty acids

Lippincott’s Chapter 16
The $pK_a$ of carboxyl group in fatty acid $\approx 4.8$

So, at physiological pH fatty acid exists as anion

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COO}^-$$

Or

$$\text{CH}_3 (\text{CH}_2)_n \text{COO}^-$$

The hydrocarbon chain can be saturated or it may contain one or more double bonds

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2\text{CH}=\text{CH}-\text{(CH}_2)_7\text{COO}^-$$

Unsaturated Fatty Acid

18:2$\Delta^{9,12}$ or 18:(9,12)

Linoleic Acid

$\omega 6$
Some fatty acids of physiological importance

<table>
<thead>
<tr>
<th>COMMON NAME</th>
<th>STRUCTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formic acid</td>
<td>1</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>2:0</td>
</tr>
<tr>
<td>Propionic acid</td>
<td>3:0</td>
</tr>
<tr>
<td>Butyric acid</td>
<td>4:0</td>
</tr>
<tr>
<td>Capric acid</td>
<td>10.0</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>16:0</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
<td>16:1(9)</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>18:0</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>18:1(9)</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>18:2(9,12)</td>
</tr>
<tr>
<td>Linolenic acid</td>
<td>18:3(9,12,15)</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>20:4(5, 8,11,14)</td>
</tr>
<tr>
<td>Lignoceric acid</td>
<td>24:0</td>
</tr>
<tr>
<td>Nervonic acid</td>
<td>24:1(15)</td>
</tr>
</tbody>
</table>

**Triacylglycerol (TAG) or FAT is the major energy reserve in the body**

It is more efficient to store energy in the form of **TAG**
Why FAT not Carbohydrates?

* More reduced:
  9 kcal per gram compared with
  4 kcal per gram of carbohydrates

* Hydrophobic:
  can be stored without H$_2$O
  carbohydrates are hydrophilic
  1 gram carbohydrates: 2 grams H$_2$O

Why FAT not Carbohydrates? (Continued)

Average adult has 10 Kg of Fat
How many calories?
90,000 kcal

What is the mass of carbohydrates that produces 90,000 kcal?
90,000 / 4 = 22.5 Kg

How much water with it?
FATTY ACID as FUELS

- The major fuel used by tissues but Glucose is the major circulating Fuel

<table>
<thead>
<tr>
<th>Fuel type</th>
<th>Amount used/12 hours (kcal)</th>
<th>Amount in Fluids (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>540</td>
<td>3</td>
</tr>
<tr>
<td>Glucose</td>
<td>280</td>
<td>80</td>
</tr>
</tbody>
</table>

Mobilization of stored fats
The need for hormonal signal

- Fat is stored in Adipose tissue
- When needed a hormonal signal reaches the adipocyte.
- Hydrolysis of TAG

\[
\text{TAG} + 3 \text{H}_2\text{O} \rightarrow 3 \text{FA} + \text{glycerol}
\]
Hormones that activate the Hormone Sensitive Lipase

- Glucagon
- Epinephrine
- Norepinephrine
- ACTH
Fate of Glycerol

β Oxidation of Fatty Acids

- Fatty Acids are transported to tissues bound to albumin
- Degraded by oxidation at β carbon followed by cleavage of two carbon units

\[ -\text{CH}_2^- \longrightarrow -\text{C}^- \]
β Oxidation of Fatty Acids (overview)

\[
\begin{align*}
\text{CH}_3 (\text{CH}_2)_n \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COO}^- & \xrightarrow{\text{CH}_3 (\text{CH}_2)_n \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO} \sim \text{CoA}} \\
\text{CH}_3 (\text{CH}_2)_n \cdot \text{C} \cdot \text{CH}_2 \cdot \text{CO} \sim \text{CoA} & \xrightarrow{\text{CH}_3 (\text{CH}_2)_n \cdot \text{CO} \sim \text{CoA} + \text{CH}_3 \cdot \text{CO} \sim \text{CoA}}
\end{align*}
\]

Activation of Fatty Acids

- Joining F.A with Coenzyme A
- RCO\sim SCoA (Thioester bond)

\[
\begin{align*}
\text{FA} + \text{HSCoA} + \text{ATP} & \rightleftharpoons \text{FA} \sim \text{CoA} + \text{AMP} + \text{PP}_i \\
\text{PP}_i + \text{H}_2\text{O} & \rightarrow 2 \text{P}_i \\
\text{FA} + \text{HSCoA} + \text{ATP} & \rightarrow \text{FA} \sim \text{CoA} + \text{AMP} + 2 \text{P}_i \\
\text{AMP} + \text{ATP} & \rightleftharpoons \text{ADP} + \text{ADP}
\end{align*}
\]
Activation of Fatty Acids (cont.)

- ATP conversion to AMP + 2 P$_i$ is equivalent to hydrolysis of 2 ATP to 2ADP
- Enzyme: thiokinase (Acyl CoA Synthetase)
- Location: - outer mitochondrial membrane
  - mitochondrial matrix (for short and medium chain FA)

Transport of long chain Acyl CoA across inner mitochondrial membrane

- Inner mitochondrial membrane is impermeable to Acyl CoA
- Carrier system is required (Carnitine Shuttle)
- It consists of:
  - Carrier molecule
  - Two enzymes
  - Membrane transport protein
CARNITINE SHUTTLE

β Oxidation of Fatty Acids (overview)

\[
\text{CH}_3 (\text{CH}_2)_n \text{-CH}_2 \text{-CH}_2 \text{-COO}^- \\
\rightarrow \text{CH}_3 (\text{CH}_2)_n \text{-CH}_2 \text{-CH}_2 \text{-CO} \sim \text{CoA} \\
\rightarrow \text{CH}_3 (\text{CH}_2)_n \text{-C} \text{-CH}_2 \text{-CO} \sim \text{CoA} \\
\rightarrow \text{CH}_3 (\text{CH}_2)_n \text{-CO} \sim \text{CoA} + \text{CH}_3 \text{-CO} \sim \text{CoA}
\]
Energy Yield from FA Oxidation

\[ \text{CH}_3(\text{CH}_2)_{14}\text{-CO-CoA} \]

\[ \downarrow \]

\[ \text{6 FADH}_2 \]
\[ \text{6 NADH} \]
\[ \text{6 Acetyl CoA} \]

\[ \text{CH}_3\text{-CH}_2\text{CH}_2\text{-CO-CoA} \]

\[ \downarrow \]

\[ \text{CH}_3\text{-CO-CoA} + \text{CH}_3\text{-CO-CoA} + \text{FADH}_2 + \text{NADH} \]

Energy Yield from FA Oxidation (cont.)

- Oxidation of C 16 FATTY ACID
  - 7 FADH2 \(\Rightarrow\) 14 ATP
  - 7 NADH \(\Rightarrow\) 21 ATP
  - 8 Acetyl CoA \(\Rightarrow\) 96 ATP

- Activation of the Acid consumes 2 ATP
- Net 129 ATP mole per mole of C16 Fatty Acid
Carnitine

\[
\text{H}_3\text{C}-\text{N}^+\text{CH}_2\text{CH}_2\text{CH}_2\text{C}-\text{OH}
\]

* Other functions:
  - Export of branched chain acyl groups from mitochondria
  - Excretion of acyl groups that cannot be metabolized in the body

Carnitine Deficiencies

- Secondary deficiencies: Liver disease, malnutrition, ↑ requirements
- Congenital Deficiencies: ↓ Enzyme, ↓ uptake, ↓ tubular reabsorption
- ↓ Ability to use FA as a fuel
- Accumulation of F.A and branched Acyl groups in cells
**Oxidation of unsaturated F.A: Oleic Acid**

CH$_3$ – (CH$_2$)$_7$-CH = CH (CH$_2$)$_7$-CO~CoA

3 rounds
Of β oxidation

3 Acetyl CoA

CH$_3$ – (CH$_2$)$_7$-CH = CH CH$_2$-CO~CoA

12:cis Δ$^3$

isomerase

CH$_3$ (CH$_2$)$_7$ CH$_2$-CH=CH-CO~CoA

12:trans Δ$^2$

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**Oxidation of Unsaturated F.A: Linoleic Acid**

18:Δ$^{9,12}$

3 Cycles of β oxidation

↓ ↓ ↓

3 Acetyl CoA

Isomerase

12:Δ$^{3,6}$

↓

12:Δ$^{2,6}$

Acetyl CoA

CH$_3$-(CH$_2$)$_4$-CH=CH-CH$_2$-CH$_2$-CO-CoA

(10:Δ$^4$)

Dehydrogenase

↓

CH$_3$-(CH$_2$)$_4$-CH=CH-CH=CH-CO-CoA

Reductase

CH$_3$-(CH$_2$)$_4$-CH-CH=CH-CH=CH-CO-CoA
Oxidation of FA with odd number of carbons

\[ \text{CH}_3-(\text{CH}_2)_{13}-\text{CO} \sim \text{CoA} \]

Six Cycles of \( \beta \) oxidation ↓

↓

\[ \text{CH}_3-\text{CH}_2-\text{C} \sim \text{CoA} + 6 \text{Acetyl CoA} \]

Propionyl CoA