Oxidation of Fatty Acid

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Surat
Mobilization of Stored Fats

- Insulin (low) → Hormone-sensitive lipase (inactive) → ATP
- Epinephrine (high) → Adenylyl cyclase → cAMP + PP_i → Hormone-sensitive lipase (active) → Fatty acid → DIACYLGLYCLEROL
Fatty Acid Oxidation

- Initial Step: Requires an ATP to synthesize acetyl CoA with the fatty acid.

![Diagram showing the initial step of fatty acid oxidation](image)
Carnitine Shuttle

Net effect: Long-chain fatty acyl CoA is transported from the outside to the inside of mitochondria.
• **Malonyl CoA inhibits**

• CPT-I, thus preventing the entry of long-chain acyl groups into the mitochondrial matrix.
• Therefore, when fatty acid synthesis is occurring in the cytosol (as indicated by the presence of malonyl CoA), the newly made palmitate cannot be transferred into the mitochondria and degraded.
• Fatty acid oxidation is also regulated by the acetyl CoA to CoA ratio: As the ratio increases, the thiolase reaction decreases.

• **Sources of carnitine**:
• Carnitine can be obtained from the diet, primarily in meat products.
• Carnitine can synthesized from lysine and methionine in the liver and kidney.
**Carnitine deficiencies result**

- Decreased use of LCFA as a metabolic fuel.
- Lead to severe hypoglycemia, coma, and death.

Secondary carnitine deficiency

1) liver disease - decreased synthesis of carnitine
2) Malnutrition
3) Strict vegetarian
4) pregnancy, severe infections, burns, or trauma - increased requirement
5) Hemodialysis - Removes carnitine from the blood.

**Treatment includes**

- avoidance of prolonged fasts,
- adopting a diet high in carbohydrate and low in LCFA,
- but supplemented with medium-chain fatty acid and,
- in cases of carnitine deficiency, carnitine.
Beta-Oxidation of Fatty Acids

In reaction 1, oxidation:

- Removes H atoms from the $\alpha$ and $\beta$ carbons.
- Forms a trans C=C bond.
- Reduces FAD to FADH$_2$.

Fatty Acyl CoA Dehydrogerase
Beta-Oxidation of Fatty Acids

In reaction 2, hydration:
- Adds water across the trans C=C bond.
- Forms a hydroxyl group (—OH) on the β carbon.

Enoyl CoA Hydratase
Beta (β)-Oxidation of Fatty Acids

In reaction 3, a second oxidation:

- Oxidizes the hydroxyl group.
- Forms a keto group on the β carbon.

Beta Hydroxyacyl CoA Dehydrogenase
Beta (\(\beta\))-Oxidation of Fatty Acids

In Reaction 4, acetyl CoA is cleaved:

- By splitting the bond between the \(\alpha\) and \(\beta\) carbons.
- To form a shortened fatty acyl CoA that repeats steps 1 - 4 of \(\beta\)-oxidation.

Thiolase
Beta (β)-Oxidation of Myristic (C₁₄) Acid

Matrix

React 1 Oxidation (dehydrogenation)

FAD
FADH₂

React 2 Hydration

H₂O

React 3 Oxidation (dehydrogenation)

NAD⁺
NADH + H⁺

React 4 Cleavage
Beta (β)-Oxidation of Myristic (C14) Acid (continued)

Reaction 4 Cleavage

6 cycles

C₁₂

C₁₀

C₈

C₆

C₄

2C₂

7 Acetyl CoA

CH₃-(CH₂)₆-CH₂-CH₂-C-CoA + CH₃-C-CoA

CH₃-(CH₂)₆-CH₂-CH₂-C-CoA + CH₃-C-CoA

CH₃-(CH₂)₄-CH₂-CH₂-C-CoA + CH₃-C-CoA

CH₃-(CH₂)₂-CH₂-CH₂-C-CoA + CH₃-C-CoA

CH₃-C-CoA + CH₃-C-CoA

Cycles of $\beta$-Oxidation

The length of a fatty acid:
- Determines the number of oxidations and
- The total number of acetyl CoA groups.

<table>
<thead>
<tr>
<th>Carbons in Fatty Acid</th>
<th>Acetyl CoA (C/2)</th>
<th>$\beta$-Oxidation Cycles (C/2 - 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>
Palmitic Acid - ATP Synthesis

- Palmitic Acid is C-16
- Initiating Step - requires 1 ATP (text says 2)
- Step 1 - FAD into e.t.c. = 2 ATP
- Step 3 - NAD+ into e.t.c. = 3 ATP
- **Total ATP per turn of spiral = 5 ATP**

Example with Palmitic Acid = 16 carbons = 8 acetyl groups

- Number of turns of fatty acid spiral = 8 - 1 = 7 turns
- ATP from fatty acid spiral = 7 turns and 5 per turn = 35 ATP.
- **NET ATP from Fatty Acid Spiral = 35 - 1 = 34 ATP**
Palmitic Acid (C-16) - ATP Synthesis

ATP Synthesis form Acetyl Coa Through Citric Acid Cycle

In Citric Acid Cycle

1 GTP = 1 ATP
3 NADH = 3 × 3 = 9 ATP
1 FADH = 2 × 1 = 2 ATP

Total ATP per Acetyl Coa in TCA cycle = 12

- 8 Acetyl CoA = 8 turns C.A.C.
- 8 turns × 12 ATP/C.A.C. = 96 ATP
- **GRAND TOTAL** = 35 – 1 + 96 = 130 ATP
Defects in beta oxidation

- Abnormalities in transport of fatty acids into mitochondria and defect in oxidation can lead to deficient energy production by oxidation of long chain fatty acids.

- Common features are:
  1. Hypoketotic hypoglycemia
  2. Hyperammonemia
  3. Skeletal muscle weakness
  4. Liver disease

- Acyl carnitine accumulates when the transferases or translocase is deficient.

- Dietary supplementation of carnitine has been found to improve the symptoms in some cases.
Organic aciduria

• They are disorders metabolism of fatty acids, branched chain and aromatic amino acids and citric acid cycle.

• The incidence of medium chain acyl coA dehydrogenase deficiency is about 1 in 2500 live birth, and is the second most common inborn error of metabolism.

• They are all characterised by the accumulation of organic acids in body tissues and their excretion in urine.
• The patient present with **acidosis**, vomiting, convulsions and coma.

• The children often die in infancy, in case they survive, there is severe mental and physical retardation.

• Diagnosis is confirmed by showing presence of organic acid in urine by chromatography.

• Dietary restriction, cofactor therapy and substrate removal are the general lines of management.
Odd chain Fatty acid Oxidation
Oxidation of odd chain fatty acids

- The odd chain fatty acids are oxidised exactly in the same manner as even chain fatty acids.
- However, after successive removal of 2 carbon units, at the end, one 3 carbon unit, propionyl coA is produced.
Propionyl CoA

\[
\text{CO}_2 \quad \text{ATP} \quad \text{Biotin}
\]

\[
\text{ADP + P}_i
\]

D- Methylmalonyl CoA

Methylmalonyl CoA racemase

\[
\text{COO}^- \\
H_3C-\overset{\text{CH}}{\text{C}}-\overset{\text{H}}{\text{C}}-\overset{\text{CoA}}{\text{C}}-\overset{\text{CoA}}{\text{O}}
\]

L-Methylmalonyl CoA

Methylmalonyl CoA mutase

Coenzyme form of vitamin B\text{\textsubscript{12}} (Deoxyadenosyl cobalamin)

\[
\text{COO}^- \\
H_2C-\overset{\text{CH}_2}{\text{C}}-\overset{\text{CoA}}{\text{C}}-\overset{\text{CoA}}{\text{O}}
\]

Succinyl CoA
Propionyl-CoA

\[ \text{propionyl-CoA carboxylase} \]

\[ \text{ATP} \rightarrow \text{ADP} + \text{P}_i \]

\[ \text{biotin} \]

\[ \text{d-Methylmalonyl-CoA} \]

\[ \text{methylmalonyl-CoA epimerase} \]

\[ \text{coenzyme B}_{12} \]

\[ \text{methylmalonyl-CoA mutase} \]

\[ \text{L-Methylmalonyl-CoA} \]

\[ \text{Succinyl-CoA} \]
Propionate is Glucogenic

- Ordinary fatty acid are cleaved to acetyl co-A units which on entering the krebs cycle are completely oxidised to CO2 and hence as a general rule. Fatty acid can not be used for gluconeogenesis.
- However, propionate is entering into the citric acid cycle at a point after CO2 elimination steps, so propionate can be channeled to gluconeogenesis.
- Thus 3-carbon units from odd chain fatty acids are glucogenic.
- Cows milk contain significant amount of odd chain fatty acid.
Inborn errors of propionate metabolism

1. Propionyl coA carboxylase deficiency
   - characterised by propionic acidemia, ketoacidosis & developmental abnormality.

2. Methyl malonic aciduria.
   - Some time patients responds to treatment with pharmacological doses of vitamin B12.
   - Deficiency of adenosyl B12 with deficient mutase activity.
   - The second type do not respond to cynocobalamin and had deficiency of the enzyme racemase and mutase.
   - The methyl malonate affects the metabolism of brain leading to mental retardation in these cases.
Alpha oxidation
• Removing carbon atoms **one at a time**
• From the carboxyl end.
• Important in **brain**.
• Does not need activation.
• Occurs in the **endoplasmic reticulum**
• Does not require CoA,
• Does **not** generate energy.
• Alpha-oxidation is mainly used for **Branch chain fatty acids** E.g. **Phytanic acid**.
• It is derived from milk and animal fat.
Refsum’s disease

• Due to lack of alpha-hydroxylase (phytanic acid oxidase)
• Alpha oxidation dose not occur
• Phytanic acid accumulates.
• Severe neurological symptoms,
  – polyneuropathy,
  – nerve deafness
  – cerebellar ataxia.
• Symptoms is observed with restricted dietary intake of phytanic acid.
• Milk is a good source of phytanic acid, which may be avoided.
Infantile Refsum’s disease

- It is a peroxisomal disorder, similar to Zellweger syndrome and adrenoleukodystrophy.
- Hence, phytanic acid accumulates along with VLCFA.
- Children do not survive long.
Omega oxidation

- Minor pathway taking place in Microsomes.
- Need NADH and Cytochrome P-450.
- Omega oxidation is defective and dicarboxylic acids (6C and 8C acids) are excreted in urine causing dicarboxylic aciduria.
- Omega oxidation occurs from omega end.
Ketogenesis and Ketone Bodies

In ketogenesis:
- Body fat breaks down to meet energy needs.
- Keto compounds called ketone bodies form.
Ketosis occurs:

- In diabetes, diets high in fat, and starvation.
- As ketone bodies accumulate.
- When acidic ketone bodies lowers blood pH below 7.4 (acidosis).