Oxidation of Fatty Acid

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Surat
Mobilization of Stored Fats
Fatty Acid Oxidation

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

\[
\begin{align*}
\text{Initial Step - Palmitic Acid} \\
\text{CH}_3(\text{CH}_2)_{14}\text{C-OH} + \text{HS-CoA} \\
\text{ATP} \rightarrow \text{ADP} \\
\text{CH}_3(\text{CH}_2)_{14}\text{C-S-CoA} + \text{H}_2\text{O}
\end{align*}
\]
Carnitine Shuttle

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

- Presence of Malonyl CoA indicate fatty acid synthesis in the cytosol.
- So at that time of fatty acid synthesis, the newly made palmitatic acid cannot be transferred into the mitochondria for oxidation of fatty acid, for degraded.
- “**Malonyl CoA inhibits Carnitine Palmitoyl Transferase-1 (CPT-I)**”
- Fatty acid oxidation is also regulated by the acetyl CoA to CoA ratio: As the ratio increases, the thiolase reaction decreases.
**Sources of carnitine:**
- Diet - mainly from meat.
- Synthesized from lysine and methionine – in Liver & Kidney.

**Carnitine deficiencies result**
- Decreased use of LCFA as a metabolic fuel.
- Lead to severe hypoglycemia and coma.

**Secondary carnitine deficiency**
- Liver disease - decreased synthesis of carnitine
- Pregnancy, severe infections, burns, or trauma - increased requirement
- Hemodialysis - Removes carnitine from the blood.
- Malnutrition
- Strict vegetarian

**Treatment includes**
- avoidance of prolonged fasting
- Take a diet high in carbohydrate and low in LCFA.
- More diet with medium-chain fatty acid.
- Carnitine supplement.
\[
\begin{align*}
\text{acyl-CoA} & \rightarrow \text{FAD} \rightarrow \text{FADH}_2 \\
\rightarrow \text{trans-enoyl-CoA} & \rightarrow \text{H}_2\text{O} \\
\rightarrow \text{enoyl-CoA hydratase} & \rightarrow \text{β-hydroxyacyl-CoA} \\
\rightarrow \text{β-hydroxyacyl-CoA dehydrogenase} & \rightarrow \text{NAD}^+ \rightarrow \text{NADH} \\
\rightarrow \text{β-ketoacyl-CoA} & \rightarrow \text{CoA-SH} \\
\rightarrow \text{acyl-CoAacyl-transferase} & \rightarrow \text{acyl-CoA 2 carbons-shortened + acetyl-CoA}
\end{align*}
\]
1. Oxidation
2. Hydration
3. Oxidation
4. Cleavage

Acetyl-CoA → Fatty acyl-CoA → β-Ketoacyl-CoA → trans-Δ^{2}-Enoyl-CoA → L-β-Hydroxyacyl-CoA → FADH₂ → Oxidation → Successive cycles
**Cycles of β-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>β-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 \times 3 = 9 ATP
1 FADH = 2 \times 1 = 2 ATP

Total ATP per Acetyl Coa in TCA cycle = 12

- 8 Acetyl CoA = 8 turns C.A.C.
- 8 turns \times 12 \text{ ATP/C.A.C.} = 96 \text{ 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. Hyperammononemia
  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 case.
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 presents 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 the 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 and , one 3 carbon unit, propionyl coA is produced.
Propionyl CoA

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

Propionyl CoA carboxylase

\[ \text{CO}_2 \]
\[ \text{ATP} \]
\[ \text{ADP} + \text{P}_i \]

Biotin

\[ \text{COO}^- \]
\[ \text{H} - \text{C} - \text{CH}_3 \]
\[ \text{C} - \text{CoA} \]

D- Methylmalonyl CoA

Methylmalonyl CoA racemase

\[ \text{COO}^- \]
\[ \text{H}_3\text{C} - \text{C} - \text{H} \]
\[ \text{C} - \text{CoA} \]

L-Methylmalonyl CoA

Methylmalonyl CoA mutase

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

\[ \text{COO}^- \]
\[ \text{H}_2\text{C} - \text{CH}_2 \]
\[ \text{C} - \text{CoA} \]

Succinyl CoA
Propionyl-CoA

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

\[ \text{ADP} + P_i \]

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

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

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

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

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

\[ \text{Succinyl-CoA} \]
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 cyanocobalamin 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

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).