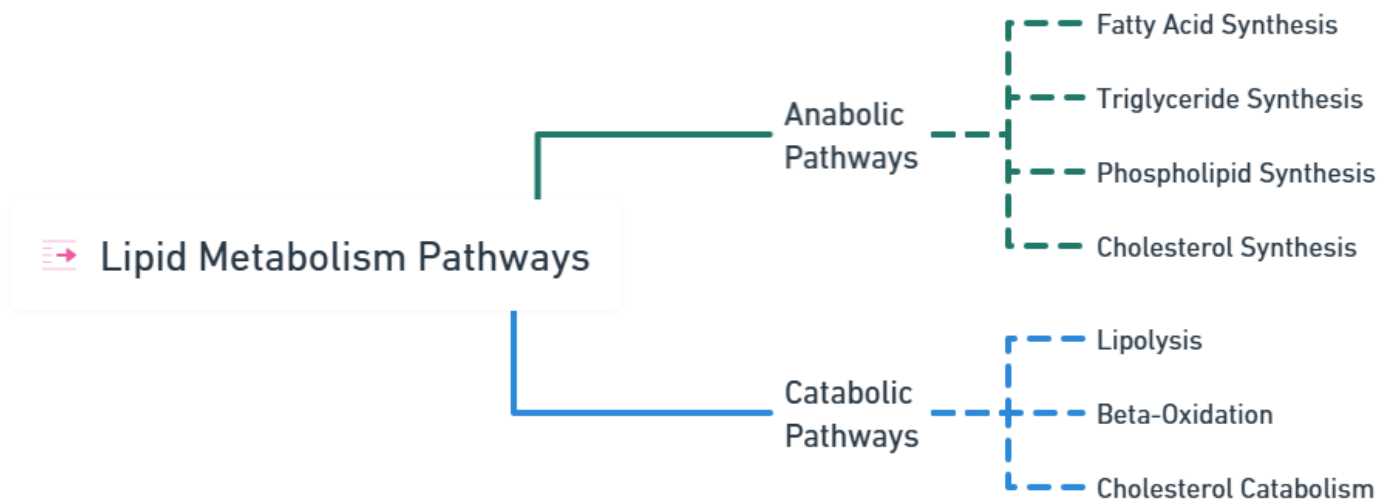


Lipid metabolism

Lipid Metabolism

- Lipid metabolism involves the synthesis, transport, and breakdown of lipids in the body.
- Lipids are diverse organic compounds, including:
 - Fatty acids
 - Triglycerides
 - Phospholipids
 - Cholesterol
- These molecules play critical roles in:
 - Cellular structure
 - Energy storage
 - Signaling
- Lipid metabolism is categorized into:
 - A. **Anabolic pathways** (lipid synthesis)
 - B. **Catabolic pathways** (lipid breakdown)



Anabolic Pathways

A. Fatty Acid Synthesis:

- **Process:** Fatty acids are synthesized from acetyl-CoA, which is mainly derived from glucose metabolism.
- **Location:** Occurs in the cytosol of cells, especially in the liver and adipose tissue.
- **Key Enzymes:** Acetyl-CoA carboxylase and fatty acid synthase.

B. Triglyceride Synthesis:

- **Function:** Triglycerides are the primary form of energy storage in adipose tissue.
- **Process:** Synthesized from glycerol-3-phosphate and fatty acids through esterification.
- **Location:** Takes place in the endoplasmic reticulum of cells.

C. Phospholipid Synthesis:

- **Function:** Phospholipids are essential components of cell membranes.
- **Process:** Synthesized from glycerol-3-phosphate, fatty acids, and a polar head group (e.g., choline, ethanolamine, serine).
- **Location:** Occurs in the endoplasmic reticulum.

D. Cholesterol Synthesis:

- **Function:** Cholesterol is vital for cell membranes and is a precursor for steroid hormones and bile acids.
- **Process:** Synthesized from acetyl-CoA in a complex, multi-step process.
- **Location:** Primarily occurs in the liver.
- **Key Enzymes:** HMG-CoA reductase and squalene synthase.

Catabolic Pathways

A. Lipolysis:

- **Process:** Triglycerides stored in adipose tissue are broken down into glycerol and fatty acids by lipases, particularly hormone-sensitive lipase.
- **Products:** Glycerol can be converted to glucose in the liver, and fatty acids can be used for energy through beta-oxidation.

B. Beta-Oxidation:

- **Process:** Fatty acids are transported into mitochondria and broken down into acetyl-CoA units through a series of enzymatic reactions.
- **Outcome:** Acetyl-CoA enters the citric acid cycle (TCA cycle) to generate ATP, carbon dioxide, and water.

C. Cholesterol Catabolism:

- **Process:** Excess cholesterol is converted to bile acids in the liver.
- **Excretion:** Bile acids are secreted into the small intestine and excreted in feces.

Regulation and Health Implications

1. **Regulation:** Lipid metabolism is regulated by hormones such as insulin, glucagon, and adrenaline, as well as dietary factors and cellular energy status.
2. **Health Issues:** Imbalances in lipid metabolism can lead to obesity, insulin resistance, and atherosclerosis.

β -Oxidation of saturated fatty acid (Palmitic acid)

Overview:

- β -oxidation is the catabolic process by which fatty acid molecules are broken down in the mitochondria in eukaryotes (or peroxisomes in some cases) to generate acetyl-CoA, NADH, and FADH_2 .
- Palmitic acid (C16:0)** is a **saturated fatty acid** with 16 carbon atoms and no double bonds.

Steps of β -Oxidation:

A. Activation of Fatty Acid (Cytosol)

- **Enzyme:** Acyl-CoA synthetase (thiokinase)
- **Reaction:** Palmitic acid + CoA + ATP $\rightarrow$ Palmitoyl-CoA + AMP + PPi
- This occurs in the **cytosol**, and the long-chain acyl-CoA is transported into the **mitochondria**.

B. Transport into Mitochondria (Carnitine Shuttle)

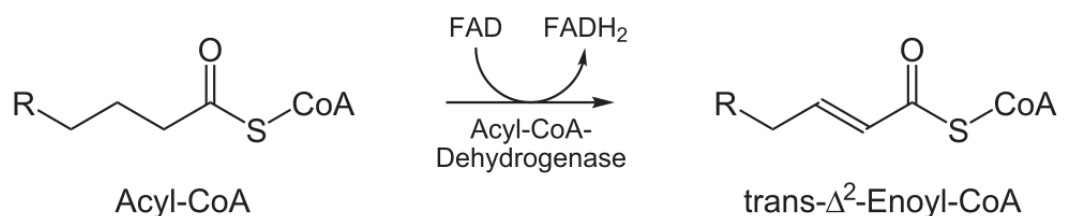
- Long-chain fatty acyl-CoA cannot directly cross the inner mitochondrial membrane.
- **Carnitine shuttle system** involves:
 - **CPT I (Carnitine Palmitoyltransferase I):** Converts Palmitoyl-CoA to Palmitoyl-Carnitine (on outer mitochondrial membrane).
 - **Translocase:** Transports Palmitoyl-Carnitine into the mitochondrial matrix.
 - **CPT II:** Converts Palmitoyl-Carnitine back to Palmitoyl-CoA in the matrix.

C. β -Oxidation Cycle (Mitochondrial Matrix)

- Each round of β -oxidation removes **2 carbon atoms** from the fatty acid chain, producing:
 - 1 molecule of **acetyl-CoA**
 - 1 molecule of **FADH_2**
 - 1 molecule of **NADH**
- A single round involves 4 steps:

Step 1: Oxidation

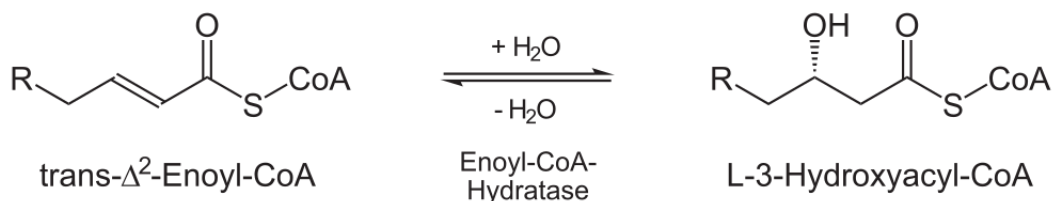
- **Enzyme:** Acyl-CoA dehydrogenase
- **Reaction:** Palmitoyl-CoA $\rightarrow$ trans- Δ^2 -Enoyl-CoA



- **Product:** FADH_2 (enters the electron transport chain)

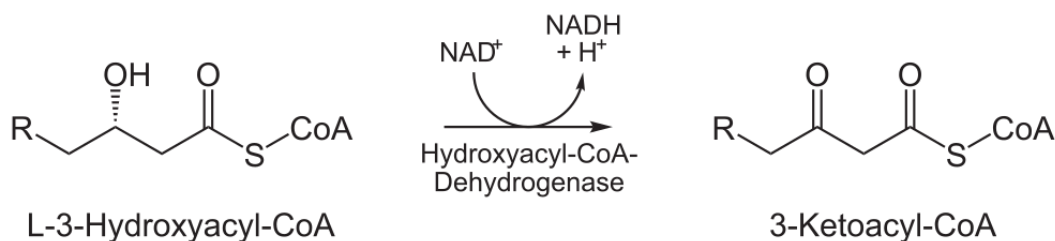
Step 2: Hydration

- **Enzyme:** Enoyl-CoA hydratase
- **Reaction:** $\text{trans-}\Delta^2\text{-Enoyl-CoA} + \text{H}_2\text{O} \rightarrow \text{L-3-Hydroxyacyl-CoA}$



Step 3: Oxidation

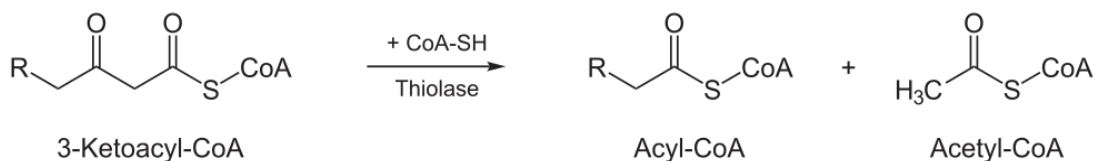
- **Enzyme:** Hydroxyacyl-CoA dehydrogenase
- **Reaction:** $\text{L-3-Hydroxyacyl-CoA} \rightarrow \text{3-Ketoacyl-CoA}$



- **Product:** NADH

Step 4: Thiolysis

- **Enzyme:** β -Ketothiolase
- **Reaction:** $\text{3-Ketoacyl-CoA} + \text{CoA} \rightarrow \text{Acetyl-CoA} + \text{shortened fatty acyl-CoA (by 2 carbons)}$



Total Energy Yield from Palmitic Acid

- Palmitic acid ($\text{C}_{16:0}$) undergoes **7 cycles** of β -oxidation:
 - Yields **8 acetyl-CoA**, **7 FADH_2** , and **7 NADH**
- These go into the **TCA cycle** and **ETC**:
 - $1 \text{ FADH}_2 \rightarrow 1.5 \text{ ATP}$
 - $1 \text{ NADH} \rightarrow 2.5 \text{ ATP}$
 - $1 \text{ Acetyl-CoA} \rightarrow 10 \text{ ATP (via TCA cycle)}$
- Total ATP:
 - $7 \text{ FADH}_2 = 10.5 \text{ ATP}$

- 7 NADH = 17.5 ATP
- 8 Acetyl-CoA = 80 ATP
- Total = 108 ATP
- Minus 2 ATP (used in activation) → **Net yield = 106 ATP**

Formation (Ketogenesis) and utilization (Ketolysis) of ketone bodies

What are Ketone Bodies?

- Water-soluble molecules produced in the **liver mitochondria** from **acetyl-CoA** derived mainly from **fatty acid β -oxidation**.
- Types:
 1. **Acetoacetate**
 2. **β -hydroxybutyrate (BHB)**
 3. **Acetone** (volatile, exhaled in breath)

Formation (Ketogenesis)

- Occurs when **acetyl-CoA accumulates**, especially during:
 - Fasting / starvation
 - Uncontrolled diabetes mellitus
 - Low-carbohydrate diet
 - Prolonged exercise

Steps of Ketogenesis (in Liver Mitochondria):

A. 2 Acetyl-CoA → Acetoacetyl-CoA

- Enzyme: **Thiolase**

B. Acetoacetyl-CoA + Acetyl-CoA → HMG-CoA (3-hydroxy-3-methylglutaryl-CoA)

- Enzyme: **HMG-CoA synthase** (rate-limiting enzyme of ketogenesis)

C. HMG-CoA → Acetoacetate + Acetyl-CoA

- Enzyme: **HMG-CoA lyase**

D. Acetoacetate can:

- Be reduced to **β -hydroxybutyrate** (enzyme: **β -hydroxybutyrate dehydrogenase**, uses NADH)



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