Fatty acid oxidation

by

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The purpose of oxidation of Fatty acid is to generate energy
Types of Fatty acid oxidation:

1. $\beta$- oxidation
2. Peroxisomal oxidation
3. $\omega$- oxidation
4. $\alpha$- oxidation
Fatty acid oxidation

- **Site**: all tissues, prominent in liver and skeletal muscle.
- **Intracellular location**: mitochondria.
- **Substrate**: fatty acids.
- **Product**: acetyl CoA, NADH, FADH2
Release of FA from adipose tissue
Steps in fatty acid oxidation

• Activation of fatty acids

• Transport of fatty acids across mitochondrial membranes into mitochondrial matrix

• Beta oxidation of fatty acids.
Activation of fatty acids

• FA are activated to fatty acyl CoA by acyl CoA synthase (thiokinase) present in the cytoplasm, outer mitochondrial membrane or ER.

• By activation the relative stability of -C-C- bond in a FA is overcome, which allows stepwise oxidation.

• There are different isoforms of Fatty acyl CoA synthase specific for different kind of FAs.

\[
\text{Fatty acid} + \text{ATP} + \text{CoA} \quad \longrightarrow \quad \text{Acyl-CoA} + \text{PPi} + \text{AMP}
\]
Fatty acid activation

fatty acid

$\text{R-COO}^{-}$

$\text{O-PO_3(OH)_2}$

ATP

acetyl-adenylate

$\text{CoA-SH}$

AMP

$\text{R-CO-S-CoA}$ acyl-CoA
Carnitine as a Carrier

*Carnitine carries fatty acyl groups across the inner mitochondrial membrane*

- Mitochondrial inner membrane is impermeable to bulky polar molecules like CoA.
- Hence acyl group from cytosol is carried into mitochondrial matrix by carnitine- carnitine shuttle.
- Short chain fatty acids are carried directly into the mitochondrial matrix
- Long-chain and medium chain FAs are converted to acyl carnitines and are then transported in to the mitochondria.
- Acyl-CoA are reformed inside the mitochondria
Carnitine

• Synthesized from lysine & methionine in liver and kidney

\[
\text{CH}_3\text{N}^+\text{CH}_2\text{CHCH}_2\text{COO}^- \\
\text{CH}_3\text{OH}
\]

Carnitine
Carnitine Palmitoyl Transferase

carnitine + CoA → fatty acyl carnitine + HSCoA

Carnitine shuttle

ATP + CoA - SH → AMP + PPI

FFA

ACYL - CoA

Carnitine palmitoyl transferase I

ACYL - Carnitine

Carnitine

ACYL - CoA

Carnitine palmitoyl transferase II

ACYL - Carnitine

Carnitine acylcarnitine translocase

CoA - SH

ACYL - Carnitine
Carnitine deficiency

- **Causes:**
  - **primary** - decreased production as in neonates.
  - **Secondary:**
    - Renal leakage
    - Hemodialysis
    - Valproic acid - inhibits renal reabsorption
    - Organic acidurias

- **Organs involved:**
  - Heart-cardiomyopathy, arrhythmias, sudden death.
  - Liver - hepatomegaly
  - Muscle – myopathy - mild cramps to severe muscle weakness.
  - CNS: encephalopathy, hypoketotic hypoglycemia

- Effects are due to decreased FA oxidation leading to FA accumulation. Utilization of glucose and decreased gluconeogenesis leads to hypoglycemia.

- **Treatment:** carnitine
Beta Oxidation

- Oxidation of fatty acids to acetyl CoA

In this process the $\beta$ carbon is oxidised via a ketone intermediate to a thioester
β-Oxidation of Fatty Acids

A Repeated Sequence of 4 Reactions

• Strategy: create a carbonyl group on the β-C

• First 3 reactions do that; fourth cleaves the "β-keto ester"

• Products: an acetyl-CoA and a fatty acid two carbons shorter
Beta-oxidation

Four enzymatic reactions:

1. **Dehydrogenation** between alpha and beta carbons (C2 and C3) in a FAD-linked reaction.

2. **Hydration** of the double by enoyl CoA hydratase.

3. **A second dehydrogenation** in a NAD-linked reaction.

4. **Thiolytic cleavage** of the thioester by beta-ketoacyl CoA thiolase.

This sequence of reactions repeated until the fatty acyl chain is completely degraded to acetyl CoA.
Acyl-CoA Dehydrogenase

Oxidation of the $C_{\alpha}-C_{\beta}$ bond

- There are three fatty acyl CoA dehydrogenases specific for a different acyl chain length. Different enzymes are involved in different stages of beta oxidation.
- Long chain acyl CoA dehydrogenase (LCAD) acts on chains greater than C12.
- MCAD acts on C6 to C12.
- SCAD acts on C4 to C6.
- MCAD deficiency is one of the most common errors of metabolism resulting in sudden infant death syndrome.
- Enzyme is inhibited by a metabolite of hypoglycin (from akee fruit)
Beta – oxidation of fatty acids
Beta – oxidation of fatty acids

H₃C-(CH₂)ₙ-C-CH₂-C-SCoA

3-L-hydroxyacyl-CoA

NAD⁺

H⁺ + NADH

Hydroxyacyl-CoA

Dehydrogenase

H₃C-(CH₂)ₙ-C-CH₂-C-SCoA

β-ketoacyl-CoA

β-Ketothiolase

HSCoA

H₃C-(CH₂)ₙ-C-SCoA + CH₃-C-SCoA

fatty acyl-CoA

(2 C shorter)

acetyl-CoA
Beta – oxidation of fatty acids

\[
\text{R-CH}_2\text{-CH}_2\text{-CH}_2\text{-C-SCoA} \quad \rightarrow \quad \text{Dehydrogenation}
\]

\[
\text{R-CH}_2\text{-CH}=\text{CH-C-SCoA} \quad \rightarrow \quad \text{Hydration}
\]

\[
\text{R-CH}_2\text{-C-C-CH}_2\text{-C-SCoA} \quad \rightarrow \quad \text{Oxidation}
\]

\[
\text{R-CH}_2\text{-C-C-SCoA} \quad \rightarrow \quad \text{Thiolysis}
\]

\[
\text{R-CH}_2\text{-C-SCoA} \quad \rightarrow \quad \text{CH}_2\text{-C-SCoA}
\]
Complete Beta Oxidation of Palmitoyl CoA

\[
\begin{align*}
\text{CH}_3\text{CH}_2&-\text{CH}_2\text{CH}_2-\text{CH}_2\text{CH}_2-\text{CH}_2\text{CH}_2-\text{CH}_2\text{CH}_2-\text{CH}_2\text{CH}_2-\text{CH}_2\text{CH}_2-\text{CH}_2\text{COSCoA} \\
\downarrow & 7 \text{ Cycles} \\
8 \text{ CH}_3\text{COSCoA} & + 7 \text{ FADH}_2 + 7 \text{ NADH} + 7 \text{ H}^+ 
\end{align*}
\]
For example for a 16 carbon fatty acid, Palmityl-CoA, it will take 7 cycle of $\beta$-oxidation to generate 8 acetyl-CoA.

Thus there will be production of 7 FADH$_2$, 7 NADH molecules during the $\beta$-oxidation cycles.

Oxidation of 8 acetyl-CoA in TCA cycle will produce 8 ATPs, 8 FADH$_2$, 24 NADH
Energy yield from palmitic acid

- **From palmitoyl CoA to acetyl CoA**: ATP
  - Acyl CoA dehydrogenase 7 FADH2 14
  - Beta-OH dehydrogenase 7 NADH 21

- **From 8 acetyl CoA**: 96

- Total energy yield 131
  - ATP are used for activation of FA -2
  - Hence net gain of ATP 129
Though it produces more energy, it does not directly produce ATP during the oxidation steps (no substrate level phosphorylation).

$\beta$-Oxidation yields Acetyl CoA, NADH & FADH, requiring TCA cycle and Respiratory chain for further metabolism.

TCA cycle and Respiratory chain requires $O_2$.

So Fatty acid cannot be used as an energy source in the absence of $O_2$. 
Regulation of fatty acid oxidation

1. **Factors regulating mobilization of FFA from adipose tissue**: liver has a large capacity to take as much as 30 - 50% of FFA from plasma both in fed and fasted state. But the release of FFA from adipose tissue is more in starvation (hypoglycemia inhibits Insulin release).

2. **Inhibitory effect of malonyl CoA on CAT-1**.
   Fed state: insulin activates Acetyl CoA carboxylase to form malonyl CoA. Malonyl CoA inhibits CAT-1 resulting in decreased beta oxidation.
   Starvation state: increase in FFA, inhibition of ACC activity, decreased malonyl CoA Concentration leading to increased fatty acid oxidation. Reinforced by insulin:glucagon ratio.
• CPT-1 (carnitine palmitoyl transferase-1) or CAT-1 (carnitine acyl transferase-1) is associated with the inner leaflet of the outer mitochondrial membrane.

• CPT-1 reaction is the rate limiting enzyme. It is allosterically inhibited by malonyl CoA. Malonyl CoA concentration is high during the fed state.
Hormonal Regulation of Fatty Acid Synthesis and Breakdown

Stimulates Glucagon

ATP → Adenylyl cyclase → cAMP → Activates Protein Kinase → Inactivates Acetyl CoA carboxylase by phosphorylation → Activates lipase → Inhibition of fatty acid synthesis and increase of lipolysis and release of FFA

Stimulates Insulin

AMP → Phosphodiesterase → Inactivates lipase

AMP → Phosphodiesterase → Activate acetyl CoA carboxylase