Chapt. 23 Oxidation of fatty acids, ketones

Student Learning Outcomes:

- Explain how fatty acids are a major fuel source, especially after fasting
- Explain how liver makes ketone bodies, fuel for other cells
- Describe the basic categories of fatty acids: VLC, LC, med
- Explain β-oxidation pathway of fatty acids
- Describe the role of the peroxisome for VLCFA

Overview fatty acid metabolism

Long-chain FA metabolism:
- Lipolysis -> blood has FA-albumin
- FABP transfer LCFA into cell and bind them cytoplasm
- Fatty acyl CoA forms
- Carnitine transports Fatty acyl group into mitochondria
- Transfers back to CoA
- β-oxidation spirals yield NADH, FAD(2H), Acetyl CoA
- Different fates for Acetyl CoA

Fatty acids are fuels

1. Fatty acids are fuels:
   - Released from adipose tissue during fasting or increased demand (exercise)
   - Dietary lipids or synthesized from liver
   - Long-chain Fatty Acids (LCFA) major ones degraded: common in diet, liver synthesizes
   - Fat ~ 38% of calories of average diet mostly triacylglycerols transported to adipose tissue by VLDL
   - LCFA transported in blood bound to albumins (binding in hydrophobic pocket)

Common dietary Long chain fatty acids include:
- Palmitate (C16)
- Oleate (C18)
- Stearate (C18:1)
- Linoleate (C18:2)
Fatty acid oxidation

Activation of fatty acid to FA-CoA requires ATP:
Fatty acyl CoA synthetase specific for C12-20
Different possible fates of Fatty acyl CoA

Figs. 2,3

Chain-length specificity of Fatty Acid Enzymes

<table>
<thead>
<tr>
<th>Acyl CoA synthetases</th>
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Carnitine

Carnitine carries Fatty acyl group across mitochondrial membrane:
- then transfers Fatty acyl group back to CoA
- Carnitine from diet or made from lysine (muscle then liver)
  - Lot in muscles

Fig. 4  Fatty acyl carnitine

Carnitine carries Fatty acyl group across membranes:
- CPTI transfers FA from FA-CoA to carnitine
- Translocase carries Across inner membrane
- CPTII transfers FA back to CoA -> FA-CoA
- Translocase returns carnitine Fig. 5

Table 1

Acyl CoA synthetases  length comments
Very-long-chain  14-26  only in peroxisomes
Long-chain  12-20  membranes of ER, mitochondria, peroxisomes
Medium-chain  6-12  mt matrix kidney, liver
Acetyl  2-4  cytoplasm, ?mt matrix
### C. Overview of β-oxidation of LCFA

**Overview of β-oxidation of LCFA:**
- **Spiral path:** series of 2-C pieces released as Acetyl CoA
- **Oxidize β-carbon**
- **Cleavage of α–β bond**
- Also FAD(2H) and NADH
- Acetyl CoA oxidized TCA
- Or ketone body (liver)

*Fig. 6*: 16-C palmitoyl CoA

### Details of β-oxidation pathway

**Details β-oxidation:**
- β-C oxidized to ketone:
  - Gain 1 NADH, 1 FAD(2H)
  - Cleavage (thiolyase) forms 1 Acetyl CoA, Fatty acyl CoA (n-2)
  - Acetyl CoA -> lots ATP through TCA cycle, ETC; or forms Ketone body
  - [Cost 2 PPI to form 1st Fatty acyl CoA (Fig. 3)]

*Fig. 7*

### β-oxidation

**Details of FAD transfer to Electron transfer chain:**
- FAD tightly bound to proteins
- Sequential transfers:
  - Acyl CoA dehydrogenase
  - ETF (electron-transferring flavoprotein):
  - ETF-QO (ETF coenzyme Q reductase):
- Co-Q in ETC

*Fig. 8*

### Energy yield in β-oxidation

**Energy yield of β-oxidation:**
1 mol of 16-C palmitate -> 8 Acetyl CoA:
- at 4-C Acyl CoA, just splits to 2 Acetyl CoA
- [2 high energy PPI to form palmitoyl CoA]
- 7 NADH x 3 ATP/NADH -> 21 ATP
- 7 FAD(2H) x 2 ATP/FAD(2H) -> 14 ATP
- If 8 Acetyl CoA oxidized through TCA,
  - get 8 GTP, 24 NADH, 8 FAD(2H) -> 96 ATP
- Total 129 ATP
**Unsaturated fatty acid β-oxidation**

**Unsaturated fatty acids:**
- About half diet:
- Oleate, linoleate most common
- Linoleate essential f.a.
- Only oxidize excess
- Must isomerize the *cis* double bonds to *trans*
- Later reduce double bond
- Then β-oxidation continue

**Oxidation of odd chain-length fatty acids:**
- Yields 1 propionyl CoA, rest Acetyl CoA
- Propionyl CoA→ Succinyl CoA
  - Goes to TCA cycle, or gluconeogenesis

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**Regulation of β-oxidation**

**Regulation of β-oxidation:**
- Hormones released from fasting, energy demand
  - Levels ATP, NADH, CoASH pool
  - Aerobic path since needs TCA, ETC
  - Tissues needs lots of mitochondria

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**D. Medium chain fatty acids**

**Oxidation of medium chain-length fatty acids:**
- More water-soluble, not stored in adipose tissue
- Enter blood, into liver; transported to mitochondrial matrix by transporters.
- Activated to acyl CoA derivatives; β-oxidation
- MCL acyl CoA synthetase has broad specificity, including carboxyl groups:
  - Forms acyl CoAs with salicylate (aspirin), valproate and benzoate
  - These are conjugated to glycine, excreted urine
II. Alternate routes of Fatty Acid oxidation

Alternative pathways of fatty acids include:

- Peroxisomal β- oxidation – very long-chain F.A.
- Peroxisomal α-oxidation – branched, CH₃- F.A.
  - From plants, degraded chlorophyll
- Microsomal ω-oxidation - distal to COOH, in ER

VLCFA in degraded to 4-6 C;
Yields Acetyl CoA, NADH
- 1st oz oxidation -> H₂O₂
  - not energy
  - Contrast β-oxidation (Fig. 7)

III. Metabolism of ketone bodies

Fatty acids are major fuel during fasting:
- Complete oxidation in some tissues
- Liver forms ketone bodies
- Skeletal muscles convert ketone bodies to Acetyl CoA
  complete oxidation TCA

Synthesis of Ketone bodies

Synthesis of ketone bodies:
- From Acetyl CoA
- Thiolase (last reaction of FA oxidation) is reversible (not favored)
- Another Ac-CoA added by HMG CoA synthase
- Different Ac-CoA released

- 3 different ketones:
  - NADH/NAD ratio affect ratio of products;
  - Acetone volatile
Oxidation of ketone bodies occurs in most tissues (not liver)

- Ketone bodies in blood to tissues, mitochondrial matrix
- Get NADH from 1st reaction
- Converted back to Acetyl CoA
- Requires activation by Succinyl CoA (TCA cycle intermediate)
- Energy yield ~ 2 Acetyl CoA
- Liver lacks thiotransferase

Fatty acids, ketone bodies in fuel homeostasis

- Fatty acids are fuels during fasting, high-fat diet, exercise, starvation
- Lipolysis stimulated by ↓ Insulin, ↑ glucagon, ↑ epinephrine
- Brain uses ketones
- saves glucose for red blood cells

Preferential use of fatty acids:

- FA in blood used by skeletal muscle over glucose
- FA oxidation gives NADH, FAD(2H) by β-oxidation; TCA cycle -> high ATP/ADP, NADH/NAD+ and Acetyl CoA concentrations
- AMP-dep PK adjusts [malonyl CoA] so CPT1 and β-oxidation operate as needed
- If lot ATP from FA (or ketone bodies), less from glycolysis (see Chapt. 22 regulators glycolysis)
  (see also effect of insulin, Chapt. 36)

Preferential use of ketone bodies by tissues:

- skeletal muscle, heart, liver use fatty acids in fasting or other conditions increasing F.A.

Ketone bodies are used by:

- Brain cells
- Intestinal mucosa – transport fatty acids to blood
- Adipocytes – store fatty acids in TAG
- fetus – ketone bodies cross placenta

Liver and red blood cell do not oxidize ketone bodies
Regulation ketone body synthesis:

Regulation of ketone body synthesis: in fasting
1. F.A. from adipocytes
2. Release inhibit malonyl CoA
3. β-oxidation gives ATP, NADH buildup
4. Oxaloacetate -> malate if NADH -> gluconeogenesis
5. Ac CoA -> ketone bodies

Key concepts:
- Fatty acids are major fuels, during fasting
- Liver converts F.A. to ketone bodies, used by brain during prolonged fasting

Review questions
3. The oxidation of fatty acids is best described by which of the following sets of reactions?
   a. Oxidation, hydration, oxidation, carbon-carbon bond breaking
   b. Oxidation, dehydration, oxidation, carbon-carbon bond breaking
   c. Oxidation, hydration, reduction, carbon-carbon bond breaking
   d. Oxidation, dehydration, reduction, oxidation, carbon-carbon bond breaking
   e. Reduction, hydration, oxidation, carbon-carbon bond breaking

Review question:
An individual with a deficiency of an enzyme in the pathway for carnitine synthesis is not eating adequate amounts of carnitine in the diet. Which of the following effects would you expect during fasting as compared with an individual with an adequate intake and synthesis of carnitine?
   a. Fatty acid oxidation is increased
   b. Ketone body synthesis is increased
   c. Blood glucose levels are increased
   d. Levels of dicarboxylic acids in the blood are increased
   e. Levels of VLCFA in the blood are increased