BCH 4054 Chapter 24 Lecture Notes

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Chapter 24

Fatty Acid Catabolism

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Fatty Acids as Energy Source

- Triglycerides yield 37 kJ/g dry weight
  - Protein 17 kJ/g
  - Glycogen 16 kJ/g (even less wet weight)
- Total stored energy in body (Table 24.1)
  - Fat ~555,000 kJ
  - Protein ~ 102,000 kJ
  - Glycogen ~ 3,000 kJ
- More reduced than carbohydrate

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Fatty Acids as Energy Source, con't.

- Major Sources of Fatty Acids
  - Stored Fat (Adipose Tissue)
  - Dietary Fat
  - Biosynthetic Fat (from glucose in liver)
- Low solubility of Triglyceride and Fatty Acids require special transport mechanisms involving lipoproteins

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Adipose Tissue Triglycerides

- Triglycerides hydrolyzed by **hormone sensitive lipase**
  - Hormonal (epinephrine, glucagon, ACTH) stimulation activates the cyclic AMP pathway
  - Fatty acids and glycerol released to the blood
  - Fatty acids bound to **serum albumin** for transport in blood
  - See Fig 24.2

Binding to serum albumin helps to minimize the detergent properties of fatty acids, which otherwise might be strong enough to disrupt cellular membranes.

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Dietary Triglycerides

- Mixed with bile salts to form micelles
- Hydrolyzed in the duodenum by **pancreatic lipase** to fatty acids plus **monoglycerides**
- Micelles adsorbed into epithelial cells where triglycerides are resynthesized and packaged into **chylomicrons,** which are released into the lymphatic system, then the blood
  - Short chain fatty acids are transported directly to the portal vein.

(See Fig 24.3 and 24.4)

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Biosynthetic Triglycerides

- Made in the liver from carbohydrate
- Exported as part of a lipoprotein called **very low density lipoprotein** (VLDL)
  - (VLDL is discussed in Section 25.5, page 840)
- Triglycerides from both VLDL and chylomicrons are hydrolyzed in the blood by **lipoprotein lipase,** releasing free fatty acids (FFA) to tissues

Lipoprotein lipase is attached to the surface of blood vessels in tissues. The attachment can be released by administration of heparin.

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Fatty Acid Activation

- Once fatty acids get into the cell, they are immediately activated to thiol esters of coenzyme A.
  - This costs the equivalent of 2 ATP (Fig 24.7)
- Oxidation occurs in the mitochondria, but CoASH esters cannot cross the mitochondrial membrane

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Role of Carnitine in Fatty Acid Oxidation

- To cross the mitochondrial membrane, fatty acids are **transesterified** to form esters of the amino acid **carnitine**
  - The enzyme is **carnitine acyltransferase**
- A carnitine/acylcarnitine **antiport** transport protein transports the acyl carnitine across the inner mitochondrial membrane
- Carnitine acyl transferase in the mitochondria re-forms the fatty acyl-CoA (See Fig 24.9)

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Beta Oxidation

- Franz Knoop's early labeling experiments established that fatty acids are degraded two carbons at a time
  - Cleavage occurs at the beta-carbon, hence the term beta oxidation
- A series of phenyl derivatives of fatty acids with different chain lengths produced either phenyl acetate or benzoate as excreted products. (See Fig 24.5)

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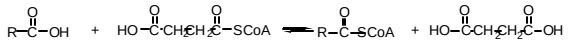
Activation of Short Chain Fatty Acids

- Short chain acids can bypass the cytoplasmic activation and enter the mitochondria directly.
- They are activated by a transfer of CoASH from succinyl CoA



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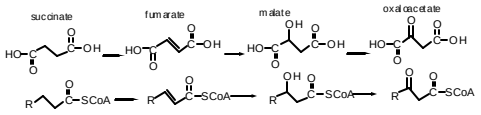
Beta Oxidation Spiral

- A series of four reactions that results in shortening the chain by two carbons
- First three reactions analogous to reactions of the TCA cycle:



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Acyl-CoA Dehydrogenase

- A family of three soluble matrix enzymes
- All are flavoproteins with differing chain length specificity (long, medium, short)
- Electrons passed to an electron transfer flavoprotein (ETF), then via an Fe/S protein to Coenzyme Q
  - See Fig 24.11
  - Enzyme inhibited by Hypoglycin from akee fruit. (Fig 24.14)

Note this pair of electrons would yield 1.5 ATP's when reduced coenzyme Q is reoxidized by the electron transport chain.

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Enoyl-CoA Hydratase

- Also called **crotonase**
- Converts **trans** enoyl CoA ester to the **L**-betahydroxy acyl-CoA ester
- Enzymes with other specificity also found
  - (See Fig 24.15)

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Hydroxyacyl-CoA Dehydrogenase

- Oxidizes L-hydroxy to keto
- NAD is the electron acceptor
  - Reoxidation of the NADH can produce 2.5 ATP
- See Fig 24.16

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Thiolase (or beta-ketothiolase)

- Thiolytic cleavage of C-C bond
  - Cysteine SH on enzyme first attacks the carbonyl, cleaving the alpha-beta bond
  - Acyl group then transferred to CoASH
  - See Fig 24.17
- Overall reaction is a "reverse Claisen condensation"
- Reaction is reversible
- Products are acetyl-CoA and fatty acyl-CoA two carbons shorter

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Beta Oxidation Summary

- Each turn of the "spiral" produces an acetyl-CoA, $CoQH_2$, and NADH
- Palmitic Acid (C_{16})
  - 8 Acetyl-CoA, 7 $CoQH_2$, 7 NADH
- Stearic Acid (C_{18})
  - 9 Acetyl-CoA, 8 $CoQH_2$, 8 NADH
- Acetyl-CoA can be oxidized by TCA cycle

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Odd Chain Fatty Acids

- Last unit is propionyl CoA
- Three reactions convert propionyl-CoA to succinyl-CoA (Fig 24.19)
  - Propionyl-CoA carboxylase
    - A biotin enzyme
  - Methylmalonyl-CoA epimerase
  - Methylmalonyl-CoA mutase
    - A B_{12} enzyme (See Fig 24.21 and Page 793)

Compare the biotin mechanism with pyruvate carboxylase (an anaplerotic reaction and a gluconeogenic enzyme) and acetyl-CoA carboxylase, which we will discuss in the next chapter.

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Unsaturated Fatty Acids

- As chain is degraded, double bond ends up in wrong place and must be isomerized.
- Extra double bonds in polyunsaturated fatty acids also require special enzymes.
- See Fig 24.23 and 24.24
- Don't worry about details

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Peroxisomal Oxidation

- Takes place in peroxisomes
- Initial double bond formation is by an acyl-CoA oxidase containing FAD
- $FADH_2$ of the oxidase is reoxidized by oxygen, producing hydrogen peroxide
  - Fig 24.25

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Branch Chain Fatty Acids

- Phytanic acid has CH_3 group on beta-carbon, so one could not produce a keto group there.
- Oxidation at the alpha carbon by a hydroxylase can cleave one carbon
- The process is called **alpha oxidation**
- **Also occurs in brain fatty acids producing some alpha hydroxy and odd chain fatty acids.**
- Defect in pathway found in **Refsum's Disease** in which phytanic acid accumulates.
  - Fig 24.26

Phytanic acid is produced from phytol in ruminant animals and thus appears in dairy products.

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Synthesis of Acetoacetate

- "Burning" acetyl-CoA requires oxaloacetate. (**OAA)**
- When **OAA** concentrations are low, acetyl-CoA can build up.
- Fatty acid oxidation would stop when all of the cell's CoASH is tied up as acetyl-CoA.
- How can the cell release the CoA?

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Synthesis of Acetoacetate, con't.

- **Thiolase** is reversible.
- As acetyl-CoA builds up, so does acetoacetyl-CoA.
- Cleavage of acetoacetyl-CoA can liberate CoASH, producing acetoacetate.
- While simple hydrolysis would accomplish that, it doesn't work that way.

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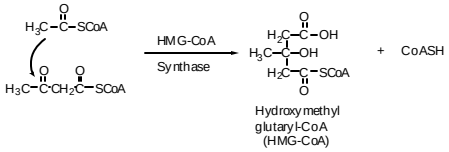
Synthesis of Acetoacetate, con't.

- Acetoacetyl-CoA condenses with acetyl-CoA in a reaction reaction similar to **citrate synthase** and **malate synthase**.



Note the addition of the methyl group of acetyl-CoA to a carbonyl carbon, coupled to the hydrolysis of the thiol ester bond.

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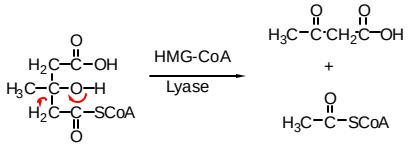
Synthesis of Acetoacetate, con't.

- After **HMG-CoA synthase** has formed a carbon-carbon bond, **HMG-CoA lyase** cleaves the other carbon-carbon bond.



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Synthesis of Acetoacetate, con't.

- The sum of these two reactions is the same as the hydrolysis of acetoacetyl-CoA.

acetoacetyl-CoA + acetyl-CoA ⟶ HMG-CoA + CoASH

HMG-CoA ⟶ acetoacetate + acetyl-CoA

sum:

acetoacetyl-CoA ⟶ acetoacetate + CoASH

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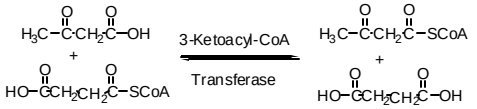
Metabolism of Acetoacetate

- The **liver** excretes acetoacetate from fatty acid breakdown as a fuel for other tissues.
- Acetoacetate is taken up in other tissues, enters the mitochondria, and is activated by **3-ketoacyl-CoA transferase**.



Note this reaction bypasses the synthesis of a GTP in the mitochondria, so the cost of activation of the acetoacetate is equivalent to one GTP (or one ATP).

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Metabolism of Acetoacetate, con't.

- Acetoacetyl-CoA is broken down by **thiolase** to acetyl-CoA, and the acetyl-CoA burned in the TCA cycle in peripheral tissues.
- Liver lacks the enzyme **3-ketoacyl-CoA transferase**, so it cannot re-activate acetoacetate once it is formed.

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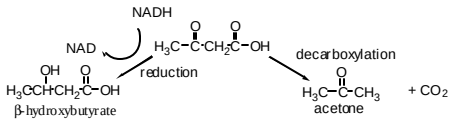
Ketone Body Formation

- When oxaloacetate is low, the acetyl-CoA cannot be metabolized, so acetoacetate builds up.
- Alternative reactions of acetoacetate include **reduction** and **decarboxylation**.



The three compounds **acetoacetate**, **beta-hydroxybutyrate**, and **acetone** constitute what are called **ketone bodies**.

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Ketone Body Formation

- Accumulation occurs when fatty acids are broken down for energy in absence of sufficient carbohydrate to make **OAA**.
  - Occurs in **starvation**.
  - Occurs in **high fat diets** (eating eskimo diet without adaptation to it).
  - Occurs in **diabetes**, where cells are "starved" for glucose because of lack of insulin.
- **Ketosis** can lead to drop in blood pH.

The state of ketosis can often be detected by the odor of acetone on the breath. The lowered pH can lead to **acidosis**, which can be a dangerous condition.