Lipid Metabolism

Remember fats??
Triacylglycerols - major form of energy storage in animals

Your energy reserves:
~0.5% carbs (glycogen + glucose)
~15% protein (muscle, last resort)
~85% fat

Why use fat for energy?
1 gram fat = at least 2-fold more energy than 1 gram carb

Sources of fat:
1. Diet
2. Stored fat (adipose tissue)
3. Fat synthesized in one organ for export to another
   (excess carb converted to fat)
Lipid Metabolism

How can insoluble dietary fats be metabolized?

1. Bile salts emulsify dietary fats in the small intestine, forming mixed micelles.

2. Intestinal lipases degrade triacylglycerols.

3. Fatty acids and other breakdown products are taken up by the intestinal mucosa and converted into triacylglycerols.

4. Triacylglycerols are incorporated, with cholesterol and apolipoproteins, into chylomicrons.

5. Chylomicrons move through the lymphatic system and bloodstream to tissues.

6. Lipoprotein lipase, activated by apoC-II in the capillary, releases fatty acids and glycerol.

7. Fatty acids enter cells.

8. Fatty acids are oxidized as fuel or reesterified for storage.
Lipid Metabolism

Hormones trigger mobilization of stored triacylglycerols

Epinephrine, glucagon

Also heart, renal cortex
Lipid Metabolism

How are fatty acids burned for energy?

1. Transported to mitochondria
2. Oxidized to produce acetyl CoA, NADH, FADH₂
3. Acetyl CoA goes to citric acid cycle
NADH, FADH₂ donate e⁻ to oxidative phos
Lipid Metabolism

Oxidation of fatty acids - fatty acid breakdown
Transport of fatty acids into mitochondria
“Prime” fatty acid

\[ \Delta G^{\circ} = -19 \text{ kJ/mol} \]

\[ \Delta G^{\circ} = -15 \text{ kJ/mol} \] (for the two-step process)
Lipid Metabolism

Oxidation of fatty acids - fatty acid breakdown
Transport into mitochondria using carnitine intermediate

Carnitine recycled
Cytosolic and mitochondrial CoA pools stay balanced

\( \text{CoA}_{\text{matrix}} \) used for ox degrad of pyruvate, fatty acids, amino acids
\( \text{CoA}_{\text{cytosol}} \) used for fatty acid biosynthesis
Lipid Metabolism

**Oxidation of fatty acids - fatty acid breakdown**

**β-oxidation of fatty acids (even # carbons)**

\[
\text{(C}_{16}\text{)}\ R-\text{CH}_2-\text{CH}_2-\text{C}^\alpha-\text{C}^\beta-\text{S-CoA} \quad \text{Palmitoyl-CoA}
\]

- **Oxidation**
  - acyl-CoA dehydrogenase
  - FAD
  - FADH\(_2\) (Donates 2e\(^-\) to Q (ox phos))

- **Hydration**
  - enoyl-CoA hydratase
  - H\(_2\)O

- **Oxidation**
  - \(\beta\)-hydroxyacyl-CoA dehydrogenase
  - NAD\(^+\)
  - NADH + H\(^+\) (Donates 2e\(^-\) Ox Phos)

- **Thiolysis**
  - acyl-CoA acetyltransferase (thiolase)
  - CoA-SH

\[
\text{(C}_{14}\text{)}\ R-\text{CH}_2-\text{C}-\text{S-CoA} + \text{CH}_3-\text{C}-\text{S-CoA} \\
\quad \text{Citric acid cycle}
\]

Fatty acid shortened by 2 carbon atoms, cycle through \(\beta\)-oxidation again.
Lipid Metabolism

Oxidation of fatty acids - fatty acid breakdown
β-oxidation of fatty acids

C_{14} \rightarrow \text{Acetyl-CoA}
C_{12} \rightarrow \text{Acetyl-CoA}
C_{10} \rightarrow \text{Acetyl-CoA}
C_{8} \rightarrow \text{Acetyl-CoA}
C_{6} \rightarrow \text{Acetyl-CoA}
C_{4} \rightarrow \text{Acetyl-CoA

Acetyl-CoA

(b)
Lipid Metabolism

Oxidation of fatty acids - fatty acid breakdown

β-oxidation of fatty acids (odd # carbons)

β-oxidation gives a 3 carbon remnant

Need ATP to put CO$_2$ on biotin

(Citric acid cycle intermediate)
Lipid Metabolism

Oxidation of fatty acids - fatty acid breakdown
β-oxidation of fatty acids (unsat’d, double bonds)
Lipid Metabolism

Oxidation of fatty acids - regulation
Need to regulate so oxidation only occurs when the need for energy requires it

1. Rate-limiting rxn. - fatty acids entering mito. (acyltransferases)

2. Malonyl CoA (important molecule!!)
   1st intermediate in biosynthesis of fatty acids
   increases when lots carbohydrates
   presence of it inhibits carnitine acyltransferase I
   ensures that oxid of FA inhibited when liver has a lot of glc

3. \([\text{NADH}] / [\text{NAD}^+]\)

4. [acetyl CoA]

- High \([\text{NADH}] / [\text{NAD}^+]\)
- High [acetyl CoA]
Ketone Bodies
In the liver, some acetyl CoA is exported to blood as “ketone bodies” for use in other tissues, rather than burned in liver by the citric acid cycle.

During fasting, carbs not available to replenish cycle intermediates - so ketogenesis takes over
Lipid Metabolism

Ketone Bodies
Soluble, transportable
Reconverted back to acetyl CoA in other tissues
Fuel for heart muscle
Major fuel for brain (starvation)
Lipid Metabolism

Ketone Bodies

\[
\text{Acetone: } \text{CH}_3-\text{C}^\equiv-\text{CH}_3
\]

Transported to tissues other than liver, oxid in TCA cycle

\[
\text{Acetoacetate: } \text{CH}_3-\text{C}^\equiv-\text{CH}_2-\text{C}^\equiv-\text{O}^\text{-}
\]

Brain usually uses glc as fuel but in times of starvation, adapts to using acetoacetate or D-β-Hydroxybutyrate

\[
\text{D-β-Hydroxybutyrate: } \text{CH}_3-\text{C}^\equiv-\text{CH}_2-\text{C}^\equiv-\text{O}^\text{-}
\]

exhaled
Lipid Metabolism

**Ketone Bodies**
- Major fuel for heart muscle
- Major fuel for brain (starvation)

![Diagram of Ketone Body Metabolism](image)
Lipid Metabolism

Ketone Bodies overproduced in starvation and diabetes

*Starvation*

Gluconeogenesis (need to be making glc) depletes TCA intermediates, diverting acetyl CoA to ketone body production.

*Diabetes*

Not enough insulin, tissues cannot take up glc efficiently from blood to use as fuel or store as fat.

Malonyl CoA (fatty acid biosynthesis) not formed, so carnitine acyltransferase I not inhibited.

Fatty acids enter mitochondria to be degraded to acetyl CoA (which cannot go to TCA because cycle intermediates have been used in gluconeogenesis).

Accumulating acetyl CoA accelerates ketone body formation.

Increased acetone toxic, acetone volatile, characteristic odor to breath.

Increased acetoacetate or D-β-Hydroxybutyrate lowers blood pH causing acidosis (coma, death).

Lots of ketones in urine causes ketosis (ketoacidosis).

*Low carb/high protein diets*

End up using stored fats as energy source, levels of ketone bodies in blood and urine increase (ketoacidosis).
Lipid Metabolism

Lipid Biosynthesis
Most calories in diet = carbs, stored calories = fats
How do we convert sugar to fat?

Lots of lipid biosynthesis in liver, lipids exported through blood to other tissues as lipoproteins

<table>
<thead>
<tr>
<th>Class</th>
<th>Major lipid carried</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>dietary triacylglycerols</td>
<td>intestine</td>
</tr>
<tr>
<td>VLDL</td>
<td>endogenous triacylglycerols</td>
<td>liver</td>
</tr>
<tr>
<td>LDL</td>
<td>endogenous cholesterol</td>
<td>liver</td>
</tr>
<tr>
<td>HDL</td>
<td>cholesterol</td>
<td>liver, intestine</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>fatty acids</td>
<td>fat cells</td>
</tr>
</tbody>
</table>
Lipid Metabolism

Lipid Biosynthesis
Polymerize acetyl CoA into fatty acids, join them to glycerol to make triacylglycerol
Reverse of β-oxidation, but enzymes and control are different

β-oxidation - mitochondria, FA biosynthesis - cytosol

First committed step - acetyl CoA carboxylase
Lipid Metabolism

Lipid Biosynthesis
Fatty acid synthase
Growing FA chain-thioester
Lipid Metabolism

Lipid Biosynthesis
Repeating the process
Lipid Metabolism

Lipid Biosynthesis
Fatty acid synthase
Seven enzyme activities in one
Lipid Metabolism

Lipid Biosynthesis
NADP⁺ carries reducing power for FA biosynthesis
Sources of NADP⁺ = malic enzyme, pentose phosphate pathway

Separate pools of reducing power
NADPH for biosynthesis
NADH for energy production
Lipid Metabolism

Regulation
Highly Regulated steps
β-oxidation: rate limiting step = acyltransferases & lipases

Committed steps:

- β oxidation
- Triacylglycerol $\rightarrow$ glycerol + 3 fatty acids

fatty acid biosynthesis

- acetyl CoA
- carboxylase
- acetyl CoA + HCO$_3^-$ $\rightarrow$ malonyl CoA

Hormones:

- Insulin (peptide) signals fed state:
- Glucagon (peptide) & epinephrine (small molecule) signal fasted state.

- acetyl CoA
- carboxylase
- FA synth.
- Phosphorylates to inhibit

- glucagon
- epinephrine
- Phosphorylates to activate

- lipases
- β ox.

No futile cycles
Malonyl CoA - high [] signals FA synthesis and inhibits carnitine acyltransferase (blocks entry of FA into mito & blocks β-oxid.)
Lipid Metabolism

Synthesis of cholesterol

3 acetyl CoA → HMG CoA → Mevalonate

HMG CoA reductase

3 steps
3 ATP

CO₂

Squalene → C₃₀

Polymerize

4 steps
1 NADPH

Zipper up
2 steps
O₂

C₅

Lanosterol → Cholesterol

C₃₀

19 steps!
Lipid Metabolism

Synthesis of cholesterol - regulation

1. HMG CoA reductase is nonequilibrium rxn and committed step

2. Cholesterol inhibits HMG CoA reductase (feedback inhibition)

3. Metabolites in cholesterol biosyn. pathway inhibit HMG CoA reductase (feedback inhibition)

4. Cholesterol also activates a protease that degrades HMG CoA reductase
Lipid Metabolism

Synthesis of cholesterol

Cholesterol synthesized in liver

Delivered to tissues through blood as LDL/HDL particles
LDL receptor on cell surface binds protein component of LDL and allows cell to internalize LDL

Heart disease & cholesterol
Cholesterol in blood forms deposits inside arteries (narrowed)
Heart disease correlates with high serum cholesterol
<175 mg/100 mL is “good”

Familial hypercholesterolemia
Homozygous: 600 mg/100 mL - die in childhood
Heterozygous: 300 mg/100 mL - variable results

Primary defect: LDL receptors absent, [cholesterol] in cell low, so HMG CoA reductase always ON full blast!!
Lipid Metabolism

Heart disease & cholesterol
Rational prevention of heart disease

Lovastatin, inhibitor of HMG CoA reductase
Mimics natural substrate - competitive inhibitor
Blocks cholesterol biosynthesis & lowers serum cholesterol