Chapter 16 - Lipid Metabolism

Fatty acids have four major physiologic roles in the cell:

- Building blocks of phospholipids and glycolipids
- Added onto proteins to create lipoproteins, which targets them to membrane locations
- Fuel molecules - source of ATP
- Fatty acid derivatives serve as hormones and intracellular messengers

Absorption and Mobilization of Fatty Acids

- Most lipids are triacylglycerols, some are phospholipids and cholesterol.
- Digestion occurs primarily in the small intestine.
- Fat particles are coated with bile salts (amphipathic) from gall bladder.
- Degraded by pancreatic lipase (hydrolyzes C-1 and C-3 ---> 2 fatty acids and 2- monoacylglycerol).
- Can then be absorbed by intestinal epithelial cells; bile salts are recirculated after being absorbed by the intestinal epithelial cells.
- In the cells, fatty acids are converted by fatty acyl CoA molecules.
- Phospholipids are hydrolyzed by pancreatic phospholipases, primarily phospholipase A2.
- Cholesterol esters are hydrolyzed by esterases to form free cholesterol, which is solubilized by bile salts and absorbed by the cells.
- Lipids are transported throughout the body as lipoproteins.
- Lipoproteins consist of a lipid (tryacylglycerol, cholesterol, cholesterol ester) core with amphipathic molecules forming layer on outside.

Lipoproteins

- Both transported in form of lipoprotein particles, which solubilize hydrophobic lipids and contain cell-targeting signals.
- Lipoproteins classified according to their densities:
  - **chylomicrons** - contain dietary triacylglycerols
  - **chylomicron remnants** - contain dietary cholesterol esters
  - **very low density lipoproteins** (VLDLs) - transport endogenous triacylglycerols, which are hydrolyzed by lipoprotein lipase at capillary surface
  - **intermediate-density lipoproteins** (IDL) - contain endogenous cholesterol esters, which are taken up by liver cells via receptor-mediated endocytosis and converted to LDLs
  - **low-density lipoproteins** (LDL) - contain endogenous cholesterol esters, which are taken up by liver cells via receptor-mediated endocytosis; major carrier of cholesterol in blood; regulates de novo cholesterol synthesis at level of target cell
  - **high-density lipoproteins** (HDL) - contain endogenous cholesterol esters released from dying cells and membranes undergoing turnover
Storage of Fatty Acids

- Triacylglycerols are transported as chylomicrons and VLDLs to adipose tissue; there, they are hydrolyzed to fatty acids, which enter adipocytes and are esterified for storage.
- Mobilization is controlled by hormones, particularly epinephrine, which binds to β-adrenergic receptors on adipocyte membrane → protein kinase A activated → phosphorylates hormone-sensitive lipase → converts triacylglycerols to free fatty acids and monoacylglycerols.
-Insulin inhibits lipid mobilization (example of reciprocal regulation).
- Monoacylglycerols formed are phosphorylated and oxidized to DHAP (intermediate of glycolysis and gluconeogenesis).

\[
\begin{align*}
\text{ATP} & \quad \text{ADP} \\
\text{glycerol} & \quad \text{glycerol 3-phosphate} \\
\text{glycerol kinase} & \quad \text{dihydroxyacetone} \\
\text{glycerol phosphate dehydrogenase} & \\
\end{align*}
\]

Can be converted to glucose (gluconeogenesis) or pyruvate (glycolysis) in the liver.

Fatty Acid Oxidation (β-oxidation)

- Fatty acids are degraded by oxidation of the β carbon by β-oxidation.
- Pathway that removes 2-C units at a time → acetyl CoA → citric acid cycle → ATP
- There are three stages in β-oxidation:
  - Activation of fatty acids in cytosol catalyzed by acyl CoA synthetase; two high energy bonds are broken to produce AMP
  - 2) Transport of fatty acyl CoA into mitochondria via carnitine shuttle
  - 3) β-oxidation - cyclic pathway in which many of the same enzymes are used repeatedly (see pathway sheet)

β-oxidation of odd chain and unsaturated fatty acids

- Odd chain fatty acids undergo β-oxidation until propionyl CoA is formed.
- Propionyl CoA is then converted to succinyl CoA, which then enters the Krebs cycle.
- See pathway sheet for details

- Unsaturated fatty acids need two additional enzymes besides those of β-oxidation.
  - enoyl-CoA isomerase
  - 2,4-dienoyl-CoA reductase
- How the pathway looks depends upon the location of the double bond, but there are two possibilities.
- See pathway sheets for details.
ATP generation from Fatty Acid Oxidation:

- Can be estimated from the amount of acetyl CoA, QH$_2$, and NADH produced.
- See pathway sheet.

Regulation of Fatty Acid Oxidation

- Already talked about fatty acid mobilization via epinephrine.
- Net result is high concentrations of acetyl CoA and NADH via $\beta$-oxidation.
- Both molecules allosterically inhibit pyruvate dehydrogenase complex.
- Most of acetyl CoA produced goes to Krebs cycle; during periods of fasting, excess acetyl CoA is produced, too much for Krebs cycle.
- Also in diabetes, oxaloacetate is used to form glucose by gluconeogenesis --- concentration of oxaloacetate is lowered.
- Result is the diversion of acetyl CoA to form acetoacetate and 3-hydroxybutyrate; these two molecules plus acetone are known as ketone bodies.
- Acetoacetate is formed via the following reactions:

\[
\text{acetyl CoA} \xrightarrow{\text{HMG-CoA lyase}} \text{3-hydroxy-} \xrightarrow{\text{3-methylglutaryl CoA}} \text{acetoacetate}
\]

- Acetoacetate and 3-hydroxybutyrate are used in respiration and are important sources of energy.
- Cardiac muscle and the renal cortex perferentially use acetoacetate over glucose.
- Glucose is used by brain and RBCs; in brain, ketone bodies substitute for glucose as fuel because the brain cannot undergo gluconeogenesis.
- Acetoacetate can be converted to acetyl CoA and oxidized in citric acid cycle only in nonhepatic tissues.

Diabetes (insulin-dependent diabetes mellitus; IDDM)
- Decreased insulin secretion by beta cells of pancreas; could be caused by viruses (?)
- Juvenile onset
- Patients are thin, hyperglycemic, dehydrated, polyuric (pee a lot), hungry, thirsty
In these patients, glycogen mobilization, gluconeogenesis, fatty acid oxidation occurs ---> massive ketone body production; also, some of the glucose is in urine (tends to pull water out of body) ---> diabetic ketoacidosis

**FATTY ACID SYNTHESIS**

Important features of this pathway:

1) Synthesis takes place in cytosol; β-oxidation takes place in mitochondrial matrix.
2) Intermediates are bound to sulfhydryl groups of acyl carrier protein (ACP);
   intermediates of β-oxidation are bonded to CoA
3) Growing fatty acid chain is elongated by sequential addition of two-carbon units
   derived from acetyl CoA
4) Reducing power comes from NADPH; oxidants in β-oxidation are NAD⁺ and FAD
5) Elongation of fatty acid stops when palmitate (C₁₆) is formed; further elongation and
   insertion of double bonds carried out later by other enzymes

Fatty acid synthesis takes place in three stages:

1) Mitochondrial acetyl CoA is transported into cytosol via citrate transport system
   Acetyl CoA is condensed with oxaloacetate to form citrate ---> antiported out with
   inward movement of anion
   Citrate cleaved by cytosolic citrate lyase ---> oxaloacetate + acetyl CoA
2) Formation of malonyl CoA
   Acetyl CoA carboxylase is key regulatory enzyme
   Influenced by glucagon ---> inactivates enzyme in liver
   Epinephrine inactivates enzyme in adipocytes
   Citrate allosterically activates enzyme
   Fatty acyl CoA allosterically inhibits enzyme
3) Assembly of fatty acid chain via fatty acid synthase
   Consists of five separate stages:
   1) Loading - acetyl CoA and malonyl CoA are attached to acyl carrier protein
   2) Condensation - both are condensed by fatty acid synthase to from
      acetoacetyl-ACP
   3) Reduction - NADPH is oxidized to form hydroxybutyryl ACP
   4) Dehydration - formation of double bond
   5) Reduction - NADPH is source of e⁻ and H⁺ to form butyryl-ACP

Last four steps are repeated, each time with malonyl-ACP to elongate chain, until palmitate
is produced.
Overall reaction:

\[
\text{acetyl CoA} + 7 \text{ malonyl CoA} + 14 \text{ NADPH} + 20 \text{ H}^+ \rightarrow \text{palmitate} + 7\text{CO}_2 + 14 \text{NADP}^+ + 8 \text{HS-CoA} + 6 \text{H}_2\text{O}
\]

**Regulation of Fatty Acid Synthesis**

- Metabolism of fatty acids is under hormonal regulation by glucagons, epinephrine, and insulin.
- Fatty acid synthesis is maximal when carbohydrate and energy are plentiful.
- Important points of control are release of fatty acids from adipocytes and regulation of carnitine acyltransferase I in the liver.
- High insulin levels also stimulate formation of malonyl CoA, which allosterically inhibits carnitine acyltransferase I → fatty acids remain in cytosol and are not transported to mitochondria for oxidation.
- Key regulatory enzyme is **acetyl-CoA carboxylase** (catalyzes first committed step in fatty acid synthesis).
- Insulin stimulates fatty acid synthesis and inhibits hydrolysis of stored triacylglycerols.
- Glucagon and epinephrine inhibit fatty acid synthesis (enzyme is phosphorylated by protein kinase A; removal of phosphate group catalyzed by protein phosphatase 2A).
- Citrate is an allosteric activator, but its biological relevance has not been established.
- Fatty acyl CoA acts as an inhibitor.
- Palmitoyl CoA and AMP are allosteric inhibitors.

**Synthesis of Eicosanoids**

- Precursors for eicosanoids are 20-carbon polyunsaturated fatty acids such as arachidonate.
- Part of inner leaflet of cell membrane.
- There are two classes of eicosanoids:
  1) prostaglandins and thromboxanes
     Synthesized by enzyme cyclooxygenase
     Localized molecules such as thromboxane A₂, prostaglandins, prostacyclin are produced.
     Thromboxane A₂ leads to platelet aggregation and blood clots → reduced blood flow in tissues.
     Aspirin binds irreversibly to COX enzymes and prevents prostaglandin synthesis.
  2) leukotrienes
     Produced by lipoxygenases.
     Products were once called “slow-acting substances of anaphylaxis”, responsible for fatal effects of some immunizations.
Synthesis of Triacylglycerols and Glycerophospholipids

Most fatty acids are esterified as triacylglycerols or glycerophospholipids. Intermediate molecule in synthesis of these two molecules is phosphatidic acid or phosphatidate.

There are two pathways:
1) de novo - “from scratch”
2) salvage pathway - uses “old” pieces and parts to make new molecules

Synthesis of phosphatidate:
- Common intermediate in synthesis of phosphoglycerides and triacylglycerols
- Formed from glycerol 3-phosphate and 2 acetyl CoA molecules
- Enzyme is glycerol phosphate acyltransferase

Synthesis of triacylglycerols and neutral phospholipids:
- Uses phosphatidate, which is dephosphorylated to produce 1,2-diacylglycerol
  - If acetylated ---> triacylglycerol
  - If reacted with nucleotide derivative ---> phosphatidylcholine or phosphatidylethanolamine

Synthesis of acidic phospholipids:
- Uses phosphatidate and reacts it with CTP ---> CDP-diacylglycerol
  - Addition of serine ---> phosphatidylserine
  - Addition of inositol ---> phosphatidylinositol
- In mammals, phosphatidylserine and phosphatidylethanolamine can be interconverted - base-exchange occurs in ER.
- Decarboxylation occurs in mitochondria and procaryotes

Synthesis of Sphingolipids

- All have C_{18} unsaturated alcohol (sphingosine) as structural backbone, rather than glycerol
- Palmitoyl CoA and serine condense ---> dehydrosphinganine ---> sphingosine
- Acetylation of amino group of sphingosine ---> ceramide
- Substitution of terminal hydroxyl group gives:
  - sphingomyelin -- addition of phosphatidylcholine
  - cerebroside -- substitute UDP-glucose or UDP-galactose
  - gangliosides -- substitute oligosaccharide

Tay–Sachs disease = inherited disorder of ganglioside breakdown.
- Deficient or missing enzyme is β-N-acetylhexosaminidase, which removes the terminal N-acetylgalactosamine residue from its ganglioside.
- One in 30 Jewish Americans of eastern European descent are carriers of a defective allele.
- Can be diagnosed during fetal development by assaying amniotic fluid for enzyme activity.
- Causes weakness, retarded psychomotor development, blindness by age two, and death around age three.

**Synthesis of Cholesterol**

- Precursor of steroid hormones and bile salts.
- Most cholesterol is synthesized in liver cells, although most animal cells can synthesize it.
- Starts with 3 molecules of acetyl CoA to form 3-hydroxy-3-methyl-glutaryl CoA, which is reduced to mevalonate (C6) by **HMG-CoA reductase** (first committed step of cholesterol synthesis).
- Amount of cholesterol formation by liver and intestine is highly responsive to cellular levels of cholesterol.
- Enzyme HMG-CoA reductase is controlled in multiple ways:
  1) Rate of enzyme synthesis is controlled by sterol regulatory element (SRE); SRE inhibits mRNA production
  2) Translation of reductase mRNA is inhibited by nonsterol metabolites derived from mevalonate
  3) Degradation of the enzyme occurs at high enzyme levels
  4) Phosphorylation of enzyme
     If enzyme is phosphorylated via glucagon pathway --> decreased activity --> cholesterol synthesis ceases when ATP levels are low
     If enzyme is dephosphorylated via insulin pathway --> increased activity

- Cells outside liver and intestine obtain cholesterol from blood instead of synthesizing it **de novo**.
- Steps in the uptake of cholesterol by LDL pathway:
  1) apolipoprotein on surface of LDL particle binds to receptor on membrane of nonhepatic cells
  2) LDL-receptor complex internalized by endocytosis
  3) vesicles formed fuse with lysosomes, which breaks apart protein part of lipoprotein to amino acids and hydrolyzes cholesterol esters
  4) released unesterified cholesterol can be used for membrane biosynthesis or be reesterified for storage

- Defects in LDL receptor lead to **familial hypercholesterolemia** (FH), in which cholesterol and LDL levels are markedly elevated.
- Result is deposition of cholesterol in tissues because of high levels of LDL-cholesterol in blood
- Heterozygotes suffer from atherosclerosis and increased risk of stroke
- Homozygotes usually die in childhood from coronary artery disease
• Disease is the result of an absence (homozygotes) or reduction (heterozygotes) in number of LDL receptors.
• LDL entry into liver and other cells is impaired.
• Drug therapy can help heterozygotes
  1) can inhibit intestinal absorption of bile salts (which promote absorption of dietary cholesterol)
  2) lovastatin - competitive inhibitor of HMG-CoA reductase ---> blocks cholesterol synthesis

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