25.1 Digestion of Triacylglycerols

• Triacylglycerols (TAGs) pass through the mouth unchanged and enter the stomach. The heat and churning action of the stomach break lipids into smaller droplets.

• The presence of lipids in consumed food slows down the rate at which the mixture of partially digested foods leaves the stomach because they take longer to digest.

• When partially digested food leaves the stomach, it enters the upper end of the small intestine (the duodenum), where its arrival triggers the release of pancreatic lipases, enzymes for the hydrolysis of lipids. The gallbladder simultaneously releases bile.
Bile contains **bile acids** and cholesterol, which are steroids, and phospholipids. Cholic acid is the major bile acid. These molecules use their hydrophilic and hydrophobic regions to emulsify the lipid droplets so they can be acted on by the pancreatic lipases.
Pancreatic lipase partially hydrolyzes the emulsified triacylglycerols, producing mainly mono- and diacylglycerols, plus fatty acids and a small amount of glycerol.
• Smaller fatty acids and glycerol are water-soluble and are absorbed directly through the surface of the **villi** that line the small intestine and enter the bloodstream through capillaries.

• The insoluble acylglycerols and larger fatty acids within the intestine packaged into the lipoproteins known as chylomicrons. Too large to enter through capillary walls, they are absorbed into the lymphatic system through lacteals within the villi.
Summary of pathways of lipids through the villi and into the transport systems of the bloodstream and the lymphatic system.
25.2 Lipoproteins for Lipid Transport

• Lipids enter metabolism from three different sources:
  – (1) the diet
  – (2) storage in adipose tissue
  – (3) synthesis in the liver

• Whatever their source these lipids must eventually be transported in blood.

• To become water-soluble, fatty acids released from adipose tissue associate with albumin, a very large protein that binds up to 10 fatty acid molecules. All other lipids are carried by lipoproteins of various types.
• **A lipoprotein:** A lipoprotein contains a core of neutral lipids, including triacylglycerols and cholesteryl esters.

• Surrounding the core is a layer of phospholipids in which varying proportions of proteins and cholesterol are embedded.
• Lipids are less dense than proteins, the density of lipoproteins depends on the ratio of lipids to proteins.

• Chylomicrons, which are the only lipoproteins devoted to transport of lipids from the diet, are the lowest-density lipoproteins (specific gravity < 0.95).

• Very-low-density lipoproteins (VLDLs) carry TAGs from the liver to peripheral tissues for storage or energy generation (0.96 < s. g. < 1.006).

• Intermediate-density lipoproteins (IDLs) carry remnants of the VLDLs from peripheral tissues back to the liver for use in synthesis (1.006 < s. g. < 1.019).
Lipids in diet

Fatty acids from storage in adipose tissue

Cholesterol synthesized in liver

Cholesterol from dead cells

Digestion—emulsification by bile acids

Transport by chylomicrons

Transport by serum albumin

Transport by VLDLs

Transport by LDLs

Transport by HDLs

Bloodstream

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• **Low-density lipoproteins (LDLs)** transport cholesterol from the liver to peripheral tissues, where it is used in cell membranes or for steroid synthesis. LDL cholesterol can also cause formation of arterial plaque (1.019 < s. g. < 1.063).

• **High-density lipoproteins (HDLs)** transport cholesterol from dead or dying cells back to the liver, where it is converted to bile acids. The bile acids are then available for use in digestion or are excreted when in excess (1.063 < s. g. < 1.210).
25.3 Triacylglycerol Metabolism: An Overview

• Triacylglycerols undergo hydrolysis to fatty acids and glycerol.
• Fatty acids undergo
  – Resynthesis of triacylglycerols for storage
  – Conversion to acetyl-SCoA

• Glycerol is converted to glyceraldehyde 3-phosphate and DHAP, which participate in
  – Glycolysis—energy generation
  – Gluconeogenesis—glucose formation
  – Triacylglycerol synthesis
Metabolism of triacylglycerols. Pathways that break down molecules (catabolism) are shown in light brown, and synthetic pathways (anabolism) are shown in blue. Connections to other pathways or intermediates of metabolism are shown in green.
• Acetyl-SCoA participates in
  – Triacylglycerol synthesis
  – Ketone body synthesis
  – Synthesis of steroids and other lipids
  – Citric acid cycle and oxidative phosphorylation
25.4 Storage and Mobilization of Triacylglycerols

- The passage of fatty acids in and out of storage in adipose tissue is a continuous process essential to maintaining homeostasis.
- After a meal, blood glucose levels are high and insulin activates the synthesis of TAGs for storage.
- The metabolism of glucose is needed to supply dihydroxyacetone phosphate that isomerizes to give the necessary glycerol 3-phosphate because adipocytes do not have the enzyme needed to convert glycerol to glycerol 3-phosphate.
• The reactants in TAG synthesis are glycerol 3-phosphate and fatty acid acyl groups carried by coenzyme A.
• TAG synthesis proceeds by transfer of first one and then another fatty acid acyl group from coenzyme A to glycerol 3-phosphate.
• Next, the phosphate group is removed and the third fatty acid group is added to give a triacylglycerol.
• When digestion of a meal is finished, blood glucose levels are low; consequently insulin levels drop and glucagon levels rise.
• The lower insulin level and higher glucagon level together activate triacylglycerol lipase, the enzyme within adipocytes that controls hydrolysis of stored TAGs.

• When glycerol 3-phosphate is in short supply, an indication that glycolysis is not producing sufficient energy, the fatty acids and glycerol produced by hydrolysis of the stored TAGs are released to the bloodstream for transport to energy-generating cells.

• **Mobilization (of triacylglycerols):** Hydrolysis of triacylglycerols in adipose tissue and release of fatty acids into the bloodstream.
25.5 Oxidation of Fatty Acids

• Once a fatty acid enters the cytosol of a cell that needs energy, three successive processes must occur.

• **1. Activation:** The fatty acid must be activated by conversion to fatty acyl-SCoA. Some energy from ATP must initially be invested in converting the fatty acid to fatty acyl-SCoA, a form that breaks down more easily.

\[
\text{Fatty acid} + \text{HSCoA} + \text{ATP} \rightarrow \text{Fatty acyl-SCoA} + \text{AMP} + \text{P}_2\text{O}_7^{4-}
\]
• **2. Transport:** The fatty acyl-SCoA must be transported into the mitochondrial matrix where energy generation will occur.

• **Carnitine,** a transmembrane protein found only in the mitochondrial membrane, specifically moves fatty acyl-SCoA across the membrane into the mitochondria.

• **3. Oxidation:** The fatty acyl-SCoA must be oxidized by enzymes in the mitochondrial matrix to produce acetyl-SCoA plus the reduced coenzymes to be used in ATP generation. The oxidation occurs by repeating the series of four reactions which make up the β-oxidation pathway.
• \(\beta\)-Oxidation refers to the oxidation of the carbon atom \(\beta\) to the thioester linkage in two steps of the pathway.

• **STEP 1: The first \(\beta\)--oxidation:** The oxidizing agent FAD removes hydrogen atoms from the carbon atoms \(\alpha\) and \(\beta\) to the C=O group in the fatty acyl-SCoA, forming a carbon–carbon double bond.

```
β carbon atom

R ─ CH₂CH₂ ─ CH ─ CH ─ C ─ SCoA
```

A fatty acyl-SCoA

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• **STEP 2: Hydration:** A water molecule adds across the newly created double bond to give an alcohol with the –OH group on the β-carbon.

• **STEP 3: The second β–oxidation:** NAD⁺ is the oxidizing agent for conversion of the β–OH group to a carbonyl group.

• **STEP 4: Cleavage to remove an acetyl group:** An acetyl group is split off and attached to a new coenzyme A molecule, leaving behind an acyl-SCoA that is two carbon atoms shorter.
The four steps of the $\beta$-oxidation pathway:

**Step 1.** A double bond is introduced by enzyme-catalyzed removal of two hydrogens from carbons 2 and 3. The coenzyme FAD is needed for this step.

**Step 4.** A carbon–carbon bond is broken to yield acetyl-SCoA and a chain-shortened fatty acid.

**Step 3.** The alcohol group is oxidized to a ketone. The coenzyme NAD$^+$ is used.

**Step 2.** Water adds to the double bond to yield an alcohol.
25.6 Energy from Fatty Acid Oxidation

- The total energy output from fatty acid catabolism is measured by the total number of ATPs produced. Current best estimates are that 2.5 ATPs result from each NADH and 1.5 ATPs from each FADH₂.
- The β-oxidation pathway produces 1 NADH and 1 FADH₂ or 4 ATPs per cycle.
- Each acetyl-SCoA produces 3 NADH, 1 FADH₂ and 1 ATP or 10 ATPs per acetyl-SCoA.
- Lauric acid, \( \text{CH}_3(\text{CH}_2)_{10}\text{COOH} \), has 12 carbons.
After initial activation (-2 ATP), five β-oxidations (5x4 ATP = +20 ATP) will change lauric acid into 6 acetyl-SCoA molecules (6x10 ATP = + 60 ATP). The total energy yield is 78 ATP per lauric acid.

- 1 mole (200g) lauric acid yields 78 moles ATP
- 1 mole (180g) glucose yields 30-32 moles ATP
- Fats and oils yield 9 Calories per gram
- Carbohydrates yield 4 Calories per gram
- Each gram of glycogen can hold as much as 2 grams of water so fats are almost 7 times more energy dense than carbohydrates in the body.