CHAPTER 10
Lipids

'I'M SORRY... WE JUST CAN'T BE TOGETHER

IS IT BECAUSE I'M FAT!?!
Lipids: Structurally Diverse Class

Organic molecules that are characterized by low solubility in water, that is, are relatively hydrophobic.
FIGURE 10–2a The packing of fatty acids into stable aggregates. The extent of packing depends on the degree of saturation. (a) Two representations of the fully saturated acid stearic acid, 18:0 (stearate at pH 7), in its usual extended conformation.

FIGURE 10–3 Glycerol and a triacylglycerol. The mixed triacylglycerol shown here has three different fatty acids attached to the glycerol backbone. When glycerol has different fatty acids at C-1 and C-3, C-2 is a chiral center (p. 17).

FIGURE 10–9 (part 1) Glycerophospholipids. The common glycerophospholipids are diacylglycerols linked to head-group alcohols through a phosphodiester bond. Phosphatidic acid, a phosphomonoester, is the parent compound. Each derivative is named for the head-group alcohol (X), with the prefix “phosphatidyl-.” In cardiolipin, two phosphatidic acids share a single glycerol (R₁ and R₂ are fatty acyl groups). *Note that the phosphate esters in phosphatidylinositol 4,5-bisphosphate each have a charge of about -1.5; one of their —OH groups is only partially ionized at pH 7.

FIGURE 10–17 Cholesterol. In this chemical structure of cholesterol, the rings are labeled A through D to simplify reference to derivatives of the steroid nucleus; the carbon atoms are numbered in blue. The C-3 hydroxyl group (shaded blue) is the polar head group. For storage and transport of the sterol, this hydroxyl group condenses with a fatty acid to form a sterol ester.

FIGURE 10–22d Some other biologically active isoprenoid compounds or derivatives. Units derived from isoprene are set off by dashed red lines. In most mammalian tissues, ubiquinone (also called coenzyme Q) has 10 isoprene units. Dolichols of animals have 17 to 21 isoprene units (85 to 105 carbon atoms), bacterial dolichols have 11, and those of plants and fungi have 14 to 24.
Biological Functions of Lipids

• **Storage of energy**
  – Reduced compounds: lots of available energy
  – Hydrophobic nature: good packing

• **Insulation from environment**
  – Low thermal conductivity
  – High heat capacity (can “absorb” heat)
  – Mechanical protection (can absorb shocks)

• **Water repellant**
  – Hydrophobic nature: keeps surface of the organism dry
    • Prevents excessive wetting (birds)
    • Prevents loss of water via evaporation

• **Buoyancy control and acoustics in marine mammals**
  – Increased density while diving deep helps sinking (just a hypothesis)
  – Spermaceti organ may focus sound energy: sound stun gun?
More Functions

- Membrane structure
  - Main structure of cell membranes

- Cofactors for enzymes
  - Vitamin K: blood clot formation
  - Coenzyme Q: ATP synthesis in mitochondria

- Signaling molecules
  - Paracrine hormones (act locally)
  - Steroid hormones (act body-wide)
  - Growth factors
  - Vitamins A and D (hormone precursors)

- Pigments
  - Color of tomatoes, carrots, pumpkins, some birds

- Antioxidants
  - Vitamin E
Lipids can provide pigment; I had to leave this one in, it is too crazy not to!
Classification of Lipids

- Based on the structure and function
  - Lipids that do not contain fatty acids: cholesterol, terpenes, ...
  - Lipids that contain fatty acids (complex lipids)
    - can be further separated into:

![Classification of Lipids Diagram](image)

Some common types of storage and membrane lipids.

- All the lipid types shown here have either glycerol or sphingosine as the backbone (light red screen), to which are attached one or more longchain alkyl groups (yellow) and a polar head group (blue). In triacylglycerols, glycerophospholipids, galactolipids, and sulfolipids, the alkyl groups are fatty acids in ester linkage. Sphingolipids contain a single fatty acid, in amide linkage to the sphingosine backbone. The membrane lipids of archaea are variable; that shown here has two very long, branched alkyl chains, each end in ether linkage with a glycerol moiety. In phospholipids the polar head group is joined through a phosphodiester, whereas glycolipids have a direct glycosidic linkage between the head-group sugar and the backbone glycerol.
Fatty Acids

- Carboxylic acids with hydrocarbon chains containing between 4 to 36 carbons
- Almost all natural fatty acids have an even number of carbons
- Most natural fatty acids are unbranched
- Saturated: no double bonds between carbons in the chain
- Monounsaturated: one double bond between carbons in the alkyl chain
- Polyunsaturated: more than one double bond in the alkyl chain
Fatty Acid Nomenclature

• Omega-3 fatty acids are essential nutrients
  – Humans need them but cannot synthesize them
  – Including ALA, DHA, and EPA
    • Although DHA and EPA can be synthesized from ALA

(a) $18:1(\Delta^9)$ cis-9-Octadecenoic acid

(b) $20:5(\Delta^{5,8,11,14,17})$ Eicosapentaenoic acid (EPA), an omega-3 fatty acid
Two conventions for naming fatty acids. (a) Standard nomenclature assigns the number 1 to the carboxyl carbon (C-1), and α to the carbon next to it. Each line segment of the zigzag represents a single bond between adjacent carbons. The position of any double bond(s) is indicated by Δ followed by a superscript number indicating the lower-numbered carbon in the double bond. (b) For polyunsaturated fatty acids (PUFAs), an alternative convention numbers the carbons in the opposite direction, assigning the number 1 to the methyl carbon at the other end of the chain; this carbon is also designated ω (omega; the last letter in the Greek alphabet). The positions of the double bonds are indicated relative to the ω carbon.
Conformation of Fatty Acids

- The saturated chain tends to adopt extended conformations.
- The double bonds in natural unsaturated fatty acids are commonly in cis configuration, which kinks the chain.
- The packing of fatty acids into stable aggregates. The extent of packing depends on the degree of saturation. (a) Two representations of the fully saturated acid stearic acid, 18:0 (stearate at pH 7), in its usual extended conformation. (b) The cis double bond (red) in oleic acid, 18:1(Δ^9) (oleate), restricts rotation and introduces a rigid bend in the hydrocarbon tail. All other bonds in the chain are free to rotate.
Melting Point and Double Bonds

- Saturated fatty acids pack in a fairly orderly way
  - extensive favorable interactions
- Unsaturated cis fatty acid pack less orderly due to the kink
  - less-extensive favorable interactions
- It takes less thermal energy to disrupt disordered packing of unsaturated fatty acids:
  - unsaturated cis fatty acids have a lower melting point

- The packing of fatty acids into stable aggregates. The extent of packing depends on the degree of saturation. (c) Fully saturated fatty acids in the extended form pack into nearly crystalline arrays, stabilized by many hydrophobic interactions. (d) The presence of one or more fatty acids with cis double bonds (red) interferes with this tight packing and results in less stable aggregates.
These are important food groups!
Everything taste better with bacon!!!!

- Trans fatty acids form by partial dehydrogenation of unsaturated fatty acids
  - Done to increase shelf life or stability at high temperature of oils used in cooking (especially deep frying)
- A trans double bond allows a given fatty acid to adopt an extended conformation
- Trans fatty acids can pack more regularly and show higher melting points than cis forms
- Consuming trans fats increases risk of cardiovascular disease
  - Avoid deep-frying partially hydrogenated vegetable oils
  - Current trend: reduce trans fats in foods (Wendy’s, KFC).

**GREASE FOR PEACE!**

### TABLE 10–2: Trans Fatty Acids in Some Typical Fast Foods and Snacks

<table>
<thead>
<tr>
<th></th>
<th>Trans fatty acid content</th>
<th>Trans fatty acid content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In a typical serving (g)</td>
<td>As % of total fatty acids</td>
</tr>
<tr>
<td>French fries</td>
<td>4.7–6.1</td>
<td>28–36</td>
</tr>
<tr>
<td>Breaded fish burger</td>
<td>5.6</td>
<td>28</td>
</tr>
<tr>
<td>Breaded chicken nuggets</td>
<td>5.0</td>
<td>25</td>
</tr>
<tr>
<td>Pizza</td>
<td>1.1</td>
<td>9</td>
</tr>
<tr>
<td>Corn tortilla chips</td>
<td>1.6</td>
<td>22</td>
</tr>
<tr>
<td>Doughnut</td>
<td>2.7</td>
<td>25</td>
</tr>
<tr>
<td>Muffin</td>
<td>0.7</td>
<td>14</td>
</tr>
<tr>
<td>Chocolate bar</td>
<td>0.2</td>
<td>2</td>
</tr>
</tbody>
</table>


Note: All data for foods prepared with partially hydrogenated vegetable oil in the United States in 2002.

Table 10-2
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Triacylglycerols; Non-polar

- Majority of fatty acids in biological systems are found in the form of **triacylglycerols**
- Solid ones are called **fats**
- Liquid ones are called **oils**
- The primary storage form of lipids (body fat)
- Less soluble in water than fatty acids due to the lack of charged carboxylate group
- Less dense than water: **fats and oils float**
- The mixed triacylglycerol shown here has three different fatty acids attached to the glycerol backbone. When glycerol has different fatty acids at C-1 and C-3, C-2 is a chiral center

![Glycerol](image)
Fats Provide Efficient Fuel Storage

- The advantage of fats over polysaccharides:
  - Fatty acids carry more energy per carbon because they are more reduced
  - Fatty acids carry less water per gram because they are nonpolar
- Glucose and glycogen are for short-term energy needs, quick delivery
- Fats are for long-term (months) energy needs, good storage, slow delivery
- Cross section of human white adipose tissue. Each cell contains a fat droplet (white) so large that it squeezes the nucleus (stained red) against the plasma membrane.
Waxes

- Waxes are esters of long-chain saturated and unsaturated fatty acids with long-chain alcohols
- Insoluble and have high melting points
- Variety of functions:
  - Storage of metabolic fuel in plankton
  - Protection and pliability for hair and skin in vertebrates
  - Waterproofing of feathers in birds
  - Protection from evaporation in tropical plants and ivy
  - Used by people in lotions, ointments, and polishes

\[
\begin{align*}
CH_3(CH_2)_{14} & \quad -C-O-CH_2-(CH_2)_{28}-CH_3 \\
\end{align*}
\]

- Palmitic acid
- 1-Triacontanol
Structural Lipids in Membranes (Polar)

- Contain polar head groups and nonpolar tails (usually attached fatty acids)
- Diversification can come from:
  - modifying a different backbone
  - changing the fatty acids
  - modifying the head groups
- The properties of head groups determine the surface properties of membranes
- Different organisms have different membrane lipid head group compositions
- Different tissues have different membrane lipid head group compositions
Glycerophospholipids

- Primary constituents of cell membranes
- Two fatty acids form ester linkages with the first and second hydroxyl groups of L-glycerol-3-phosphate
- Head group is charged at physiological pH

**L-Glycerol 3-phosphate, the backbone of phospholipids.** Glycerol itself is not chiral, as it has a plane of symmetry through C-2. However, glycerol is prochiral—it can be converted to a chiral compound by adding a substituent such as phosphate to either of the —CH₂OH groups. One unambiguous nomenclature for glycerol phosphate is the D, L system, in which the isomers are named according to their stereochemical relationships to glyceraldehyde isomers. By this system, the stereoisomer of glycerol phosphate found in most lipids is correctly named either L-glycerol 3-phosphate or D-glycerol 1-phosphate. Another way to specify stereoisomers is the *sn* (stereospecific numbering) system, in which C-1 is, by definition, the group of the prochiral compound that occupies the pro-S position. The common form of glycerol phosphate in phospholipids is, by this system, *sn*-glycerol 3-phosphate (in which C-2 has the R configuration). In archaea, the glycerol in lipids has the other configuration; it is D-glycerol 3-phosphate.

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![Figure 10-8](Lester/Principles of Biochemistry, Sixth Edition © 2013 W.H. Freeman and Company)
General Structure of Glycerophospholipids

- Unsaturated fatty acids are commonly found connected to C2
- The highly polar phosphate group may be further esterified by an alcohol; such substituent groups are called the head groups

![Diagram of Glycerophospholipid Structure]

**Glycerophospholipids.** The common glycerophospholipids are diacylglycerols linked to head-group alcohols through a phosphodiester bond. Phosphatidic acid, a phosphomonoester, is the parent compound. Each derivative is named for the head-group alcohol (X), with the prefix “phosphatidyl-.” In cardiolipin, two phosphatidic acids share a single glycerol (R₁ and R₂ are fatty acyl groups). *Note that the phosphate esters in phosphatidylinositol 4,5-bisphosphate each have a charge of about -1.5; one of their —OH groups is only partially ionized at pH 7.*
### Examples of Glycerophospholipids

<table>
<thead>
<tr>
<th>Name of glycerophospholipid</th>
<th>Name of X — O</th>
<th>Formula of X</th>
<th>Net charge (at pH 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphatidic acid</td>
<td>—</td>
<td>$-\text{H}$</td>
<td>$-2$</td>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
<td>Ethanolamine</td>
<td><img src="image" alt="Ethanolamine" /></td>
<td>$0$</td>
</tr>
<tr>
<td>Phosphatidylcholine</td>
<td>Choline</td>
<td><img src="image" alt="Choline" /></td>
<td>$0$</td>
</tr>
<tr>
<td>Phosphatidylserine</td>
<td>Serine</td>
<td><img src="image" alt="Serine" /></td>
<td>$-1$</td>
</tr>
<tr>
<td>Phosphatidylglycerol</td>
<td>Glycerol</td>
<td><img src="image" alt="Glycerol" /></td>
<td>$-1$</td>
</tr>
<tr>
<td>Phosphatidylinositol 4,5-bisphosphate</td>
<td>myo-inositol 4,5-bisphosphate</td>
<td><img src="image" alt="myo-inositol 4,5-bisphosphate" /></td>
<td>$-4^*$</td>
</tr>
<tr>
<td>Cardiolipin</td>
<td>Phosphatidylglycerol</td>
<td><img src="image" alt="Cardiolipin" /></td>
<td>$-2$</td>
</tr>
</tbody>
</table>

*Figure 10-9*

*Lehninger Principles of Biochemistry, Sixth Edition*

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Phosphatidylcholine

- Phosphatidylcholine is the major component of most eukaryotic cell membranes.
- Many prokaryotes, including *E. coli*, cannot synthesize this lipid; their membranes do not contain phosphatidylcholine.

The molecular structures of two types of membrane lipid classes are similar. Phosphatidylcholine (a glycerophospholipid) and sphingomyelin (a sphingolipid) have similar dimensions and physical properties, but presumably play different roles in membranes.
Ether Lipids: Plasmalogen

- Vinyl ether analog of phosphatidylethanolamine
- Common in vertebrate heart tissue
- Also found in some protozoa and anaerobic bacteria
- Function is not well understood
  - Resistant to cleavage by common lipases but cleaved by few specific lipases
  - Increase membrane rigidity?
  - Sources of signaling lipids?
  - May be antioxidants?

**Ether lipids.** Plasmalogens have an ether-linked alkenyl chain where most glycerophospholipids have an esterlinked fatty acid. Platelet-activating factor has a long ether-linked alkyl chain at C-1 of glycerol, but C-2 is ester-linked to acetic acid, which makes the compound much more water-soluble than most glycerophospholipids and plasmalogens. The head-group alcohol is ethanolamine in plasmalogens and choline in platelet-activating factor.
**Ether Lipids: Platelets-Activating Factor**

- Aliphatic ether analog of phosphatidylcholine
- Acetic acid has esterified position C2
- First signaling lipid to be identified
- Stimulates aggregation of blood platelets
- Plays role in mediation of inflammation

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**Ether lipids** Platelet-activating factor has a long ether-linked alkyl chain at C-1 of glycerol, but C-2 is ester-linked to acetic acid, which makes the compound much more water-soluble than most glycerophospholipids and plasmalogenes. The head-group alcohol is ethanolamine in plasmalogenes and choline in platelet-activating factor.
Sphingolipids

- The backbone of sphingolipids is NOT glycerol.
- The backbone of sphingolipids is a long-chain amino alcohol sphingosine.
- A fatty acid is joined to sphingosine via an amide linkage rather than an ester linkage as usually seen in lipids.
- A polar head group is connected to sphingosine by a glycosidic or phosphodiester linkage.
- The sugar-containing glycosphingolipids are found largely in the outer face of plasma membranes.
**Sphingolipids**

- **Sphingolipids.** The first three carbons at the polar end of sphingosine are analogous to the three carbons of glycerol in glycerophospholipids. The amino group at C-2 bears a fatty acid in amide linkage. The fatty acid is usually saturated or monounsaturated, with 16, 18, 22, or 24 carbon atoms. Ceramide is the parent compound for this group. Other sphingolipids differ in the polar head group (X) attached at C-1. Gangliosides have very complex oligosaccharide head groups. Standard symbols for sugars are used in this figure, as shown in Table 7–1.
Sphingomyelin

- Ceramide (sphingosine + amide-linked fatty acid) + phosphocholine attached to the alcohol
- Sphingomyelin is abundant in myelin sheath that surrounds some nerve cells in animals

The molecular structures of two types of membrane lipid classes are similar. Phosphatidylcholine (a glycerophospholipid) and sphingomyelin (a sphingolipid) have similar dimensions and physical properties, but presumably play different roles in membranes.
Sphingomyelin is structurally similar to phosphatidylcholine

The molecular structures of two types of membrane lipid classes are similar. Phosphatidylcholine (a glycerophospholipid) and sphingomyelin (a sphingolipid) have similar dimensions and physical properties, but presumably play different roles in membranes.
Glycosphingolipids and Blood Groups

- The blood groups are determined in part by the type of sugars located on the head groups in glycosphingolipids.
- The structure of sugar is determined by an expression of specific glycosyltransferases
  - Individuals with no active glycosyltransferase will have the O antigen
  - Individuals with a glycosyltransferase that transfers an N-acetylgalactosamine group have A blood group
  - Individuals with a glycosyltransferase that transfers a galactose group have B blood group
Glycosphingolipids determine blood groups

- **Glycosphingolipids as determinants of blood groups.** The human blood groups (O, A, B) are determined in part by the oligosaccharide head groups of these glycosphingolipids. The same three oligosaccharides are also found attached to certain blood proteins of individuals of blood types O, A, and B, respectively. Standard symbols for sugars are used here (see Table 7–1).

![Diagram of Glycosphingolipids](image)
Defects in the turnover of membrane lipids lead to a number of diseases. A defect in the enzyme hydrolyzing a particular step is indicated by $\times$; the disease that results from accumulation of the partial breakdown product is noted.

Pathways for the breakdown of GM1, globoside, and sphingomyelin to ceramide. A defect in the $\beta$-galactosidase pathway leads to Generalized gangliosidosis. Pathways involving hexosaminidase A lead to Tay-Sachs disease and Sandhoff's disease. Pathways involving $\alpha$-galactosidase A lead to Fabry's disease and Niemann-Pick disease. Pathways involving glucocerebrosidase lead to Gaucher's disease and sphingomyelinase leads to Niemann-Pick disease.
Sterols and Cholesterol

- **Sterol**
  - Steroid nucleus: four fused rings
  - Hydroxyl group (polar head) in the A-ring
  - Various nonpolar side chains
- The steroid nucleus is almost planar

- **Cholesterol.** In this chemical structure of cholesterol, the rings are labeled A through D to simplify reference to derivatives of the steroid nucleus; the carbon atoms are numbered in blue. The C-3 hydroxyl group (shaded blue) is the polar head group. For storage and transport of the sterol, this hydroxyl group condenses with a fatty acid to form a sterol ester.
Physiological Role of Sterols

• **Cholesterol** and related sterols are present in the membranes of most eukaryotic cells
  – Modulate fluidity and permeability
  – Thicken the plasma membrane
  – Most bacteria lack sterols

• Mammals obtain cholesterol from **food** or **synthesize it** *de novo* in the liver

• Cholesterol, bound to proteins, is transported to tissues via blood vessels
  – Cholesterol in **low-density lipoproteins** tends to deposit and clog arteries

• Many **hormones** are derivatives of sterols
Steroid Hormones

• Steroids are **oxidized derivatives of sterols**
• Steroids have the sterol nucleus, but lack the alkyl chain found in cholesterol
• **More polar** than cholesterol
• Steroid hormones are synthesized from cholesterol in gonads and adrenal glands
• They are carried through the body in the bloodstream, usually attached to carrier proteins
• Many of the steroid hormones are **male and female sex hormones**
Steroid Hormones

- Steroids derived from cholesterol. Testosterone, the male sex hormone, is produced in the testes. Estradiol, one of the female sex hormones, is produced in the ovaries and placenta. Cortisol and aldosterone are hormones synthesized in the cortex of the adrenal gland; they regulate glucose metabolism and salt excretion, respectively. Prednisone and prednisolone are synthetic steroids used as antiinflammatory agents. Brassinolide is a growth regulator found in vascular plants.
Biologically Active Lipids

- Are present in much smaller amounts than storage or structural lipids
- Play vital roles as signaling molecules between nearby cells
- Lipid soluble vitamins (A, D, E, and K)
Arachidonic Acid Derivatives as Signaling Lipids

- Enzymatic oxidation of arachidonic acid yields
  - Prostaglandins (inflammation and fever)
  - Thromboxanes (formation of blood clots)
  - Leukotrienes (smooth muscle contraction in lungs)
Vitamin D regulates calcium uptake

(a) Cholecalciferol (vitamin D₃) is produced in the skin by UV irradiation of 7-dehydrocholesterol, which breaks the bond shaded light red. In the liver, a hydroxyl group is added at C-25; in the kidney, a second hydroxylation at C-1 produces the active hormone, 1α,25-dihydroxyvitamin D₃. This hormone regulates the metabolism of Ca²⁺ in kidney, intestine, and bone.
Vitamin A (Retinol)

Vitamin $A_1$ and its precursor and derivatives. (a) $\beta$-Carotene is the precursor of vitamin $A_1$. Isoprene structural units are set off by dashed red lines. Cleavage of $\beta$-carotene yields two molecules of vitamin $A_1$ (retinol) (b). Oxidation at C-15 converts retinol to the aldehyde, retinal (c), and further oxidation produces retinoic acid (d), a hormone that regulates gene expression. Retinal combines with the protein opsin to form rhodopsin (not shown), a visual pigment widespread in nature. In the dark, retinal of rhodopsin is in the 11-\textit{cis} form (c). When a rhodopsin molecule is excited by visible light, the 11-\textit{cis}-retinal undergoes a series of photochemical reactions that convert it to all \textit{trans}-retinal (e), forcing a change in the shape of the entire rhodopsin molecule. This transformation in the rod cell of the vertebrate retina sends an electrical signal to the brain that is the basis of visual transduction.

- Involved in visual pigment
- Precursor for other hormones involved in signaling
Vitamin E, K, and other lipid quinones are antioxidants

- Some other biologically active isoprenoid compounds or derivatives. Units derived from isoprene are set off by dashed red lines. In most mammalian tissues, ubiquinone (also called coenzyme Q) has 10 isoprene units. Dolichols of animals have 17 to 21 isoprene units (85 to 105 carbon atoms), bacterial dolichols have 11, and those of plants and fungi have 14 to 24.

Figure 10-22
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Polyketides are biologically active lipids with medicinal uses.

Figure 10-24
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