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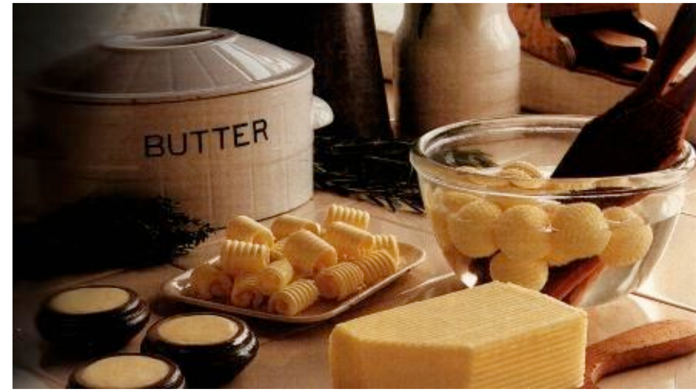
LEHNINGER
PRINCIPLES OF BIOCHEMISTRY

Fifth Edition

CHAPTER 10
Lipids

What are Lipids ?

Fats and oils are the principal stored forms of energy in many organisms.



Lipids are a chemically diverse group of compounds, the common and defining feature of which is their insolubility in water.

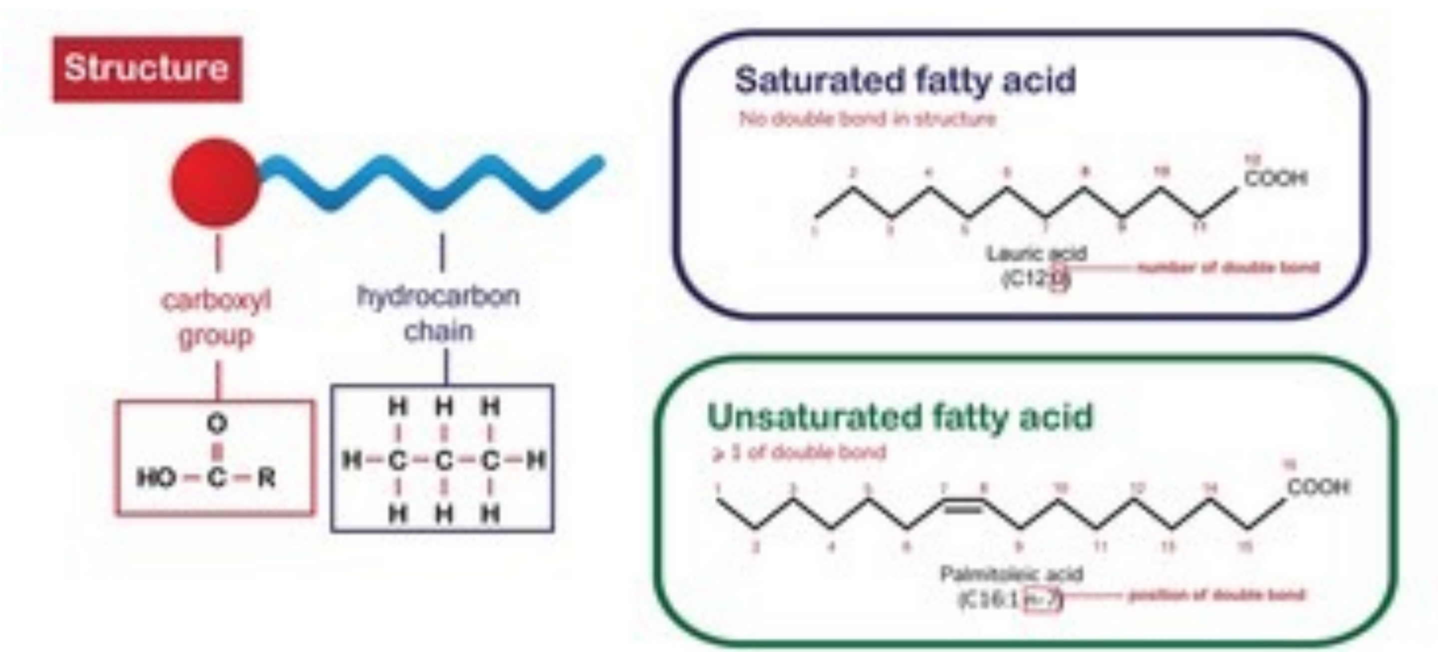
Phospholipids and sterols are major structural elements of biological membranes.

Other lipids, although present in relatively small quantities, play crucial roles as enzyme cofactors, electron carriers, light-absorbing pigments, hydrophobic anchors for proteins, “chaperones” to help membrane proteins fold, emulsifying agents in the digestive tract, hormones, and intracellular messengers.

Storage Lipids

The fats and oils used almost universally as stored forms of energy in living organisms are derivatives of **fatty acids.**

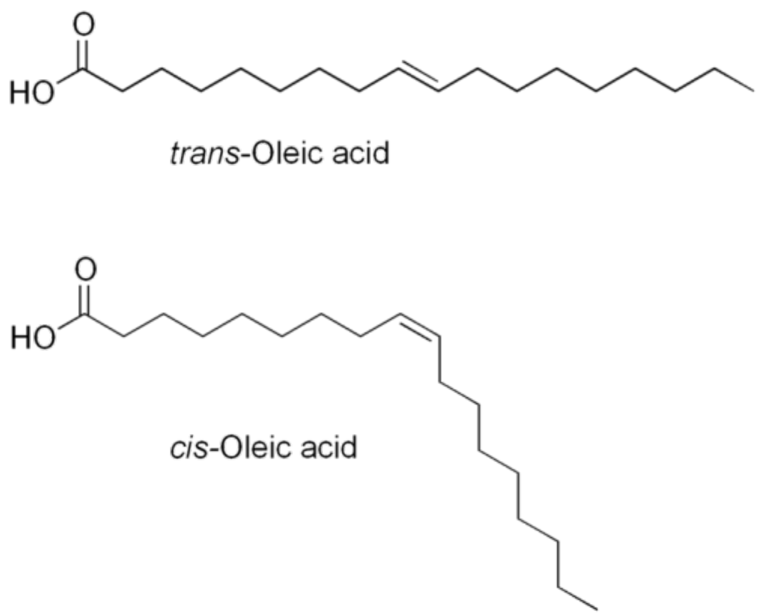
Fatty acids are carboxylic acids with hydrocarbon chains ranging from 4 to 36 carbons long (C4 to C36). In some fatty acids, this chain is unbranched and fully saturated (contains no double bonds); in others the chain contains one or more double bonds



Fatty acids

There is also a common pattern in the location of double bonds; in most monounsaturated fatty acids the double bond is between C-9 and C-10 (9), and the other double bonds of polyunsaturated fatty acids are generally 12 and 15.

In nearly all naturally occurring unsaturated fatty acids, the double bonds are in the *cis* configuration.
Trans fatty acids are produced by fermentation in the rumen of dairy animals and are obtained from dairy products and meat.



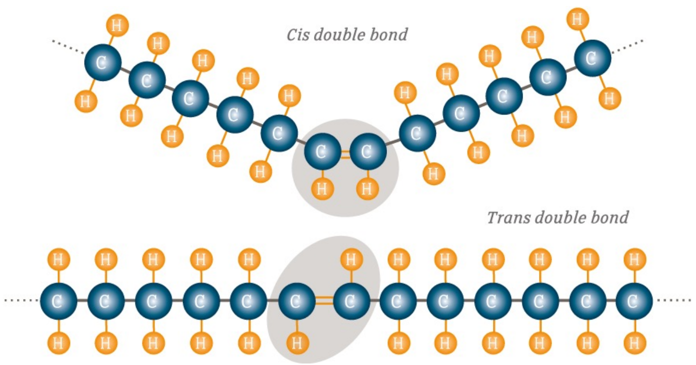


TABLE 10–1	**Some Naturally Occurring Fatty Acids: Structure, Properties, and Nomenclature**					
					Solubility at 30 °C (mg/g solvent)	
Carbon skeleton	Structure*	Systematic name†	Common name (derivation)	Melting point (°C)	Water	Benzene
12:0	$CH_3(CH_2)_{10}COOH$	*n*-Dodecanoic acid	Lauric acid (Latin *laurus*, "laurel plant")	44.2	0.063	2,600
14:0	$CH_3(CH_2)_{12}COOH$	*n*-Tetradecanoic acid	Myristic acid (Latin *Myristica*, nutmeg genus)	53.9	0.024	874
16:0	$CH_3(CH_2)_{14}COOH$	*n*-Hexadecanoic acid	Palmitic acid (Latin *palma*, "palm tree")	63.1	0.0083	348
18:0	$CH_3(CH_2)_{16}COOH$	*n*-Octadecanoic acid	Stearic acid (Greek *stear*, "hard fat")	69.6	0.0034	124
20:0	$CH_3(CH_2)_{18}COOH$	*n*-Eicosanoic acid	Arachidic acid (Latin *Arachis*, legume genus)	76.5		
24:0	$CH_3(CH_2)_{22}COOH$	*n*-Tetracosanoic acid	Lignoceric acid (Latin *lignum*, "wood" + *cera*, "wax")	86.0		
16:1(Δ^9)	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	*cis*-9-Hexadecenoic acid	Palmitoleic acid	1 to –0.5		
18:1(Δ^9)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	*cis*-9-Octadecenoic acid	Oleic acid (Latin *oleum*, "oil")	13.4		
18:2($\Delta^{9,12}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis-,cis*-9,12-Octadecadienoic acid	Linoleic acid (Greek *linon*, "flax")	1–5		
18:3($\Delta^{9,12,15}$)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis-,cis-,cis*-9,12,15-Octadecatrienoic acid	α-Linolenic acid	–11		
20:4($\Delta^{5,8,11,14}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	*cis-,cis-,cis-,cis*-5,8,11,14-Icosatetraenoic acid	Arachidonic acid	–49.5		

*All acids are shown in their nonionized form. At pH 7, all free fatty acids have an ionized carboxylate. Note that numbering of carbon atoms begins at the carboxyl carbon.

†The prefix *n*- indicates the "normal" unbranched structure. For instance, "dodecanoic" simply indicates 12 carbon atoms, which could be arranged in a variety of branched forms; "*n*-dodecanoic" specifies the linear, unbranched form. For unsaturated fatty acids, the configuration of each double bond is indicated; in biological fatty acids the configuration is almost always cis.

Table 10-1

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Melting points are also strongly influenced by the length and degree of unsaturation of the hydrocarbon chain. At room temperature (25 C), the saturated fatty acids from 12:0 to 24:0 have a waxy consistency, whereas unsaturated fatty acids of these lengths are oily liquids.

This difference in melting points is due to different degrees of packing of the fatty acid molecules

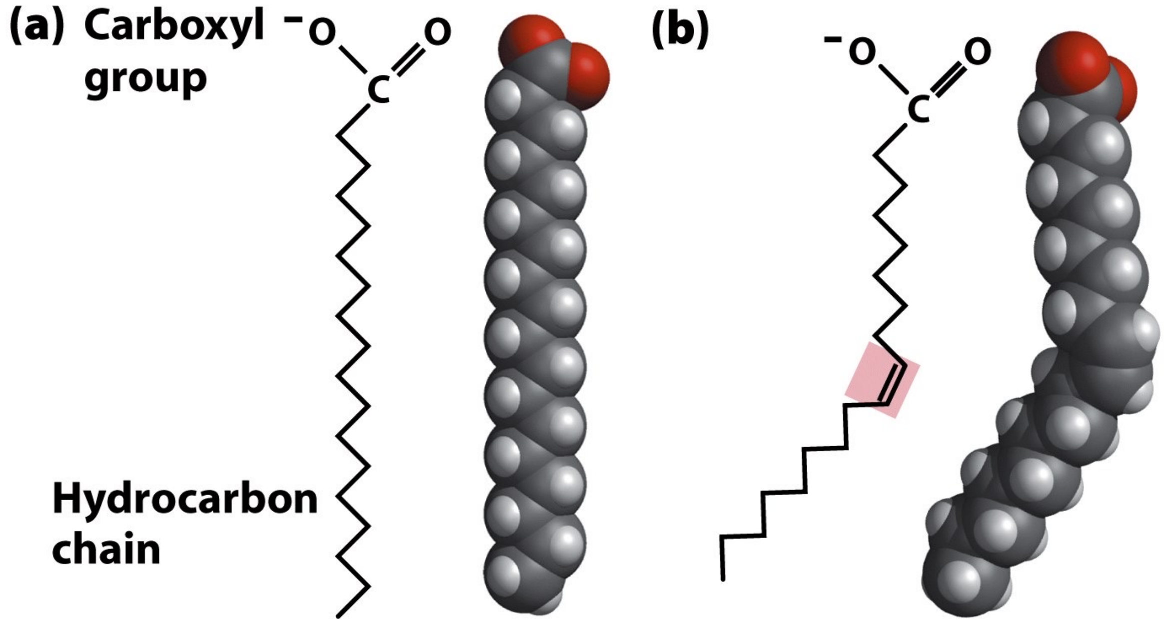

Figure 10-2ab
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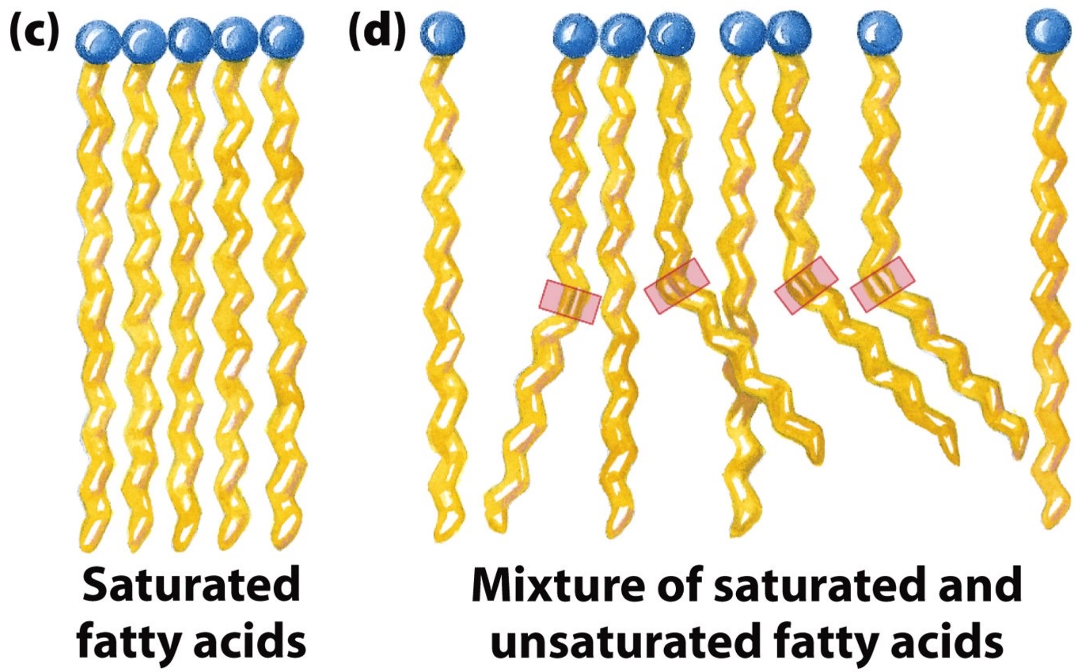
The cis double bond (shaded) in oleic acid (oleate) does not permit rotation and introduces a rigid bend in the hydrocarbon tail. All other bonds in the chain are free to rotate. **(c)** Fully saturated fatty acids in the extended form pack into nearly crystalline arrays, stabilized by many hydrophobic interactions. **(d)** The presence of one or more cis double bonds interferes with this tight packing and results in less stable aggregates.



Why are trans-fatty acids harmful ?

- Trans fats increase LDL (bad) cholesterol and decrease HDL (good) cholesterol. High LDL and low HDL levels can cause cholesterol to build up in your arteries, which can lead to heart disease and stroke.

- Cause inflammation in blood vessels: Trans fats can cause inflammation and constriction in blood vessels, which can lead to coronary artery disease.

- Increase the risk of heart attacks, stroke, and type 2 diabetes: Trans fats can increase the risk of heart attacks, stroke, and type 2 diabetes.

***Trans fats are found in margarine, vegetable shortening, Vanaspati ghee, fried foods, and baked goods.

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

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

Source: Adapted from Table 1 in Mozaffarian, D., Katan, M.B., Ascherio, P.H., Stampfer, M.J., & Willet, W.C. (2006) Trans fatty acids and cardiovascular disease. *N. Engl. J. Med.* 354, 1604–1605.

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

Table 10-2

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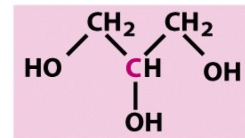
Triacylglycerols (TAGs)

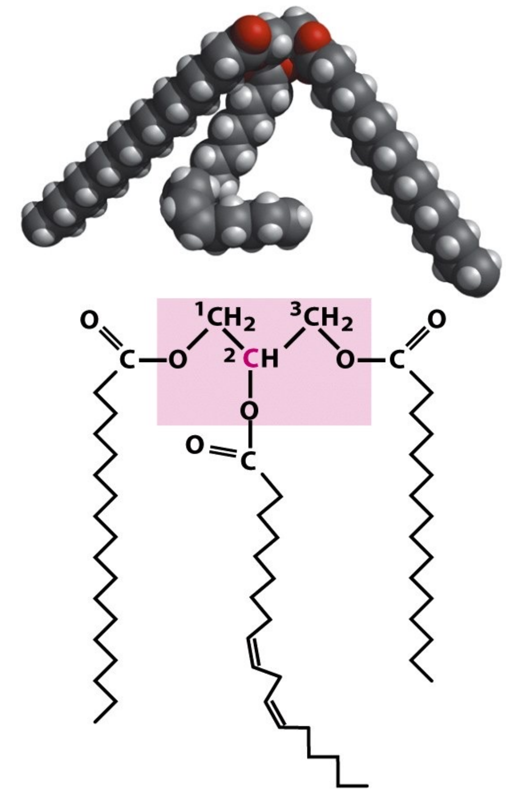
Triacylglycerols are Fatty Acid **esters** of Glycerol .

The simplest lipids constructed from fatty acids are the triacylglycerols, also referred to as triglycerides, fats, or neutral fats.

Triacylglycerols are composed of three fatty acids each in ester linkage with a single glycerol



Glycerol



1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol

Figure 10-3
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Because the polar hydroxyls of glycerol and the polar carboxylates of the fatty acids are bound in ester linkages, triacylglycerols are nonpolar, hydrophobic molecules, essentially insoluble in water.

Triacylglycerols Provide Stored Energy and Insulation

In most eukaryotic cells, triacylglycerols are stored as oily droplets in the aqueous cytosol, serving as depots of metabolic fuel.
These are **Lipid Droplets.**

In vertebrates, specialized cells called adipocytes, or fat cells, store large amounts of triacylglycerols as fat droplets that nearly fill the cell.
Triacylglycerols are also stored as oils in the seeds of many types of plants, providing energy and biosynthetic precursors during seed germination.

Adipocytes and germinating seeds contain **lipases,** enzymes that catalyze the hydrolysis of stored triacylglycerols, releasing fatty acids for export to sites where they are required as fuel.

Triacylglycerols Provide Stored Energy and Insulation

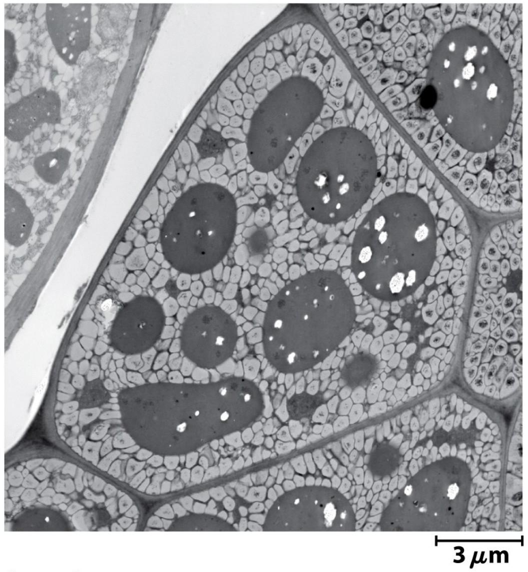

Figure 10-4b
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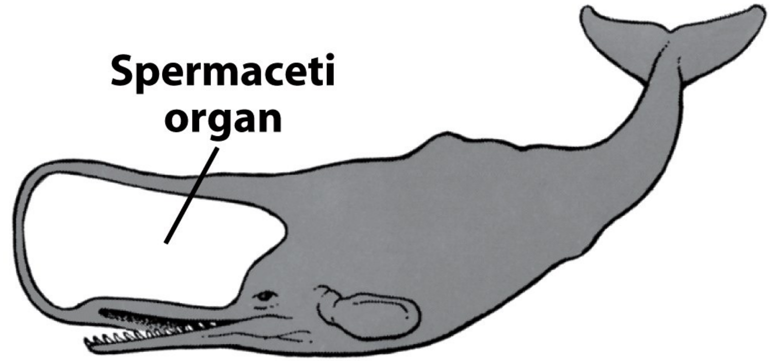

Box 10-1
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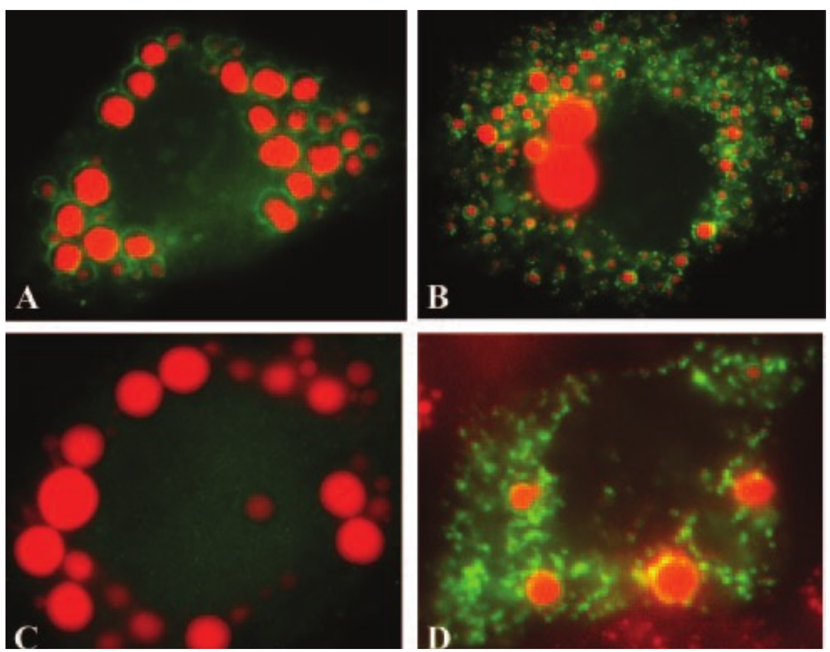
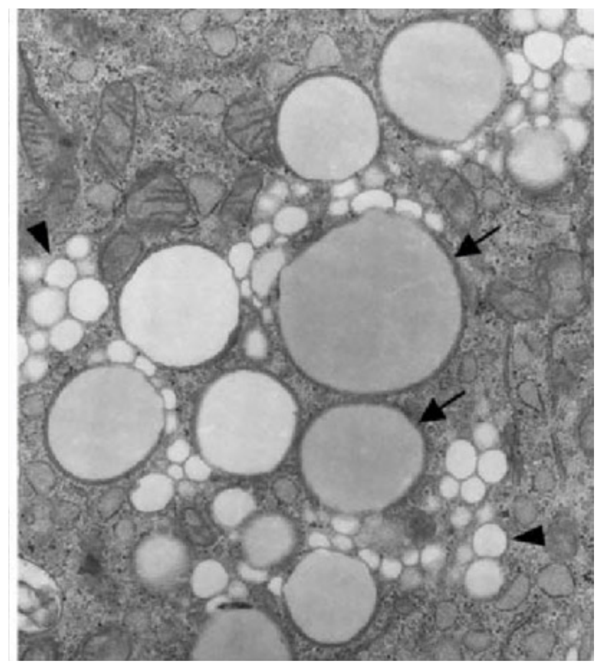




Triacylglycerols Provide Stored Energy and Insulation

There are two significant advantages to using triacylglycerols as stored fuels, rather than polysaccharides such as glycogen and starch.

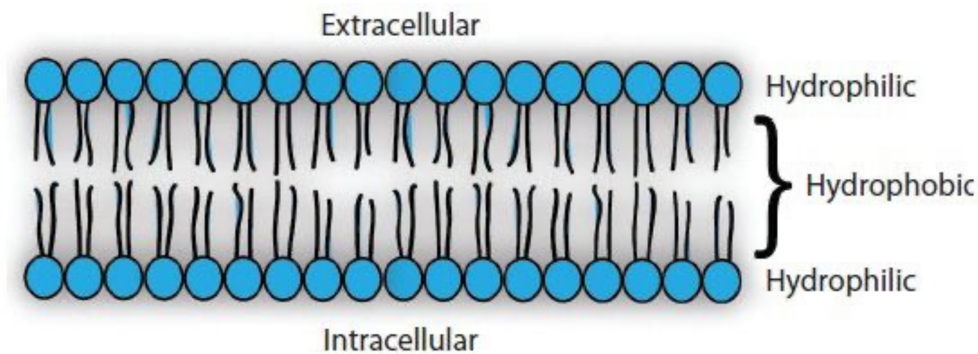
1. The carbon atoms of fatty acids are more reduced than those of sugars, oxidation of triacylglycerols yields more than twice as much energy, gram for gram, as the oxidation of carbohydrates.

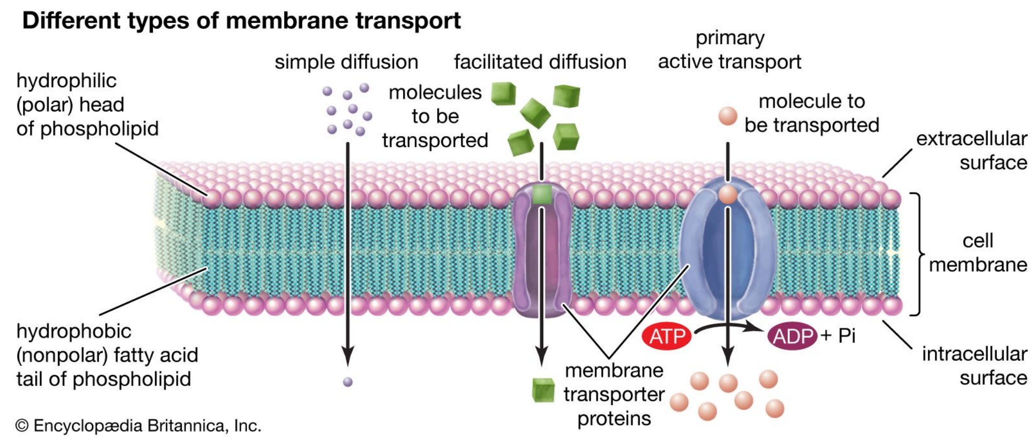
2. Triacylglycerols are hydrophobic and therefore unhydrated, the organism that carries fat as fuel does not have to carry the extra weight of water of hydration that is associated with stored poly-saccharides (2 g per gram of polysaccharide).

Structural Lipids in Membranes

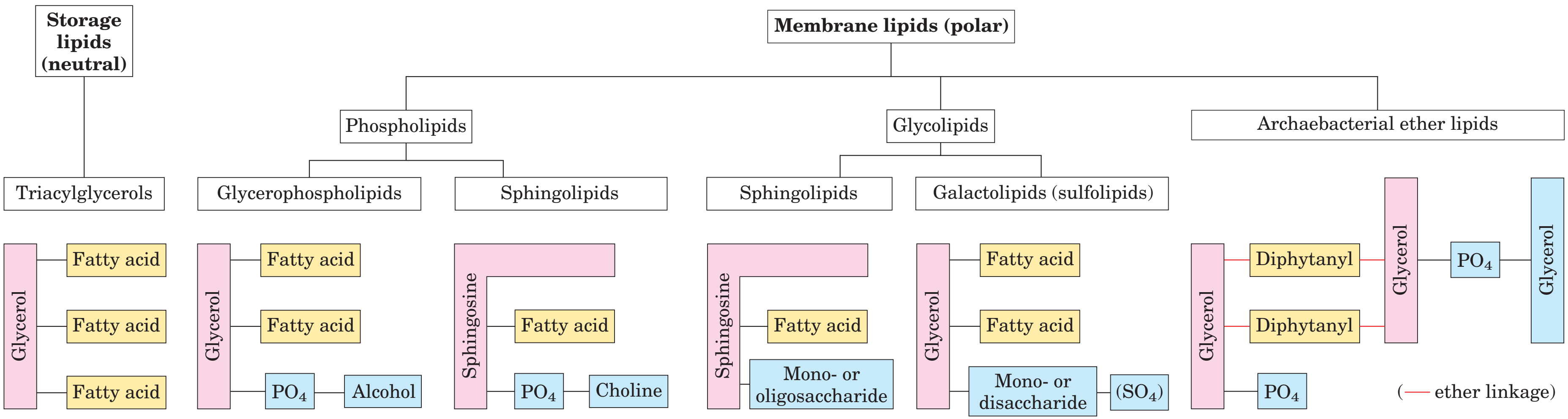
The central architectural feature of biological membranes is a double layer of lipids, which acts as a barrier to the passage of polar molecules and ions.

Membrane lipids are amphipathic: one end of the molecule is hydrophobic, the other hydrophilic. Their hydrophobic interactions with each other and their hydrophilic interactions with water direct their packing into sheets called membrane bilayers.





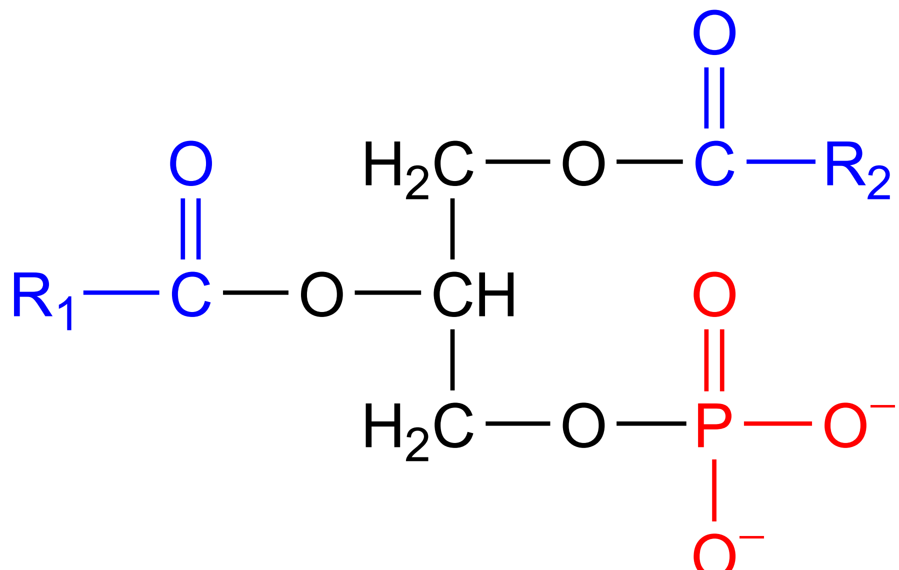
Structural Lipids in Membranes



Glycerophospholipids Are Derivatives of Phosphatidic Acid

In **phosphatidate**:

- **fatty acids** are esterified to hydroxyls on **C1** & **C2**
- the **C3** hydroxyl is esterified to $\mathbf{P_i}$.



phosphatidate

Glycerophospholipids, also called phosphoglycerides, are membrane lipids in which two fatty acids are attached in **ester** linkage to the first and second carbons of glycerol, and a highly polar or charged group is attached through a **phosphodiester linkage** to the third carbon.

Formation of an ester:

$$R'OH + HO\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R'' \longrightarrow R'\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R'' + H_2O$$

Glycerophospholipids are named as derivatives of the parent compound, phosphatidic acid, according to the polar alcohol in the head group. Phosphatidylcholine and phosphatidylethanolamine have choline and ethanolamine in their polar head groups, for example.

In all these compounds, the head group is joined to glycerol through a phosphodiester bond, in which the phosphate group bears a negative charge at neutral pH.

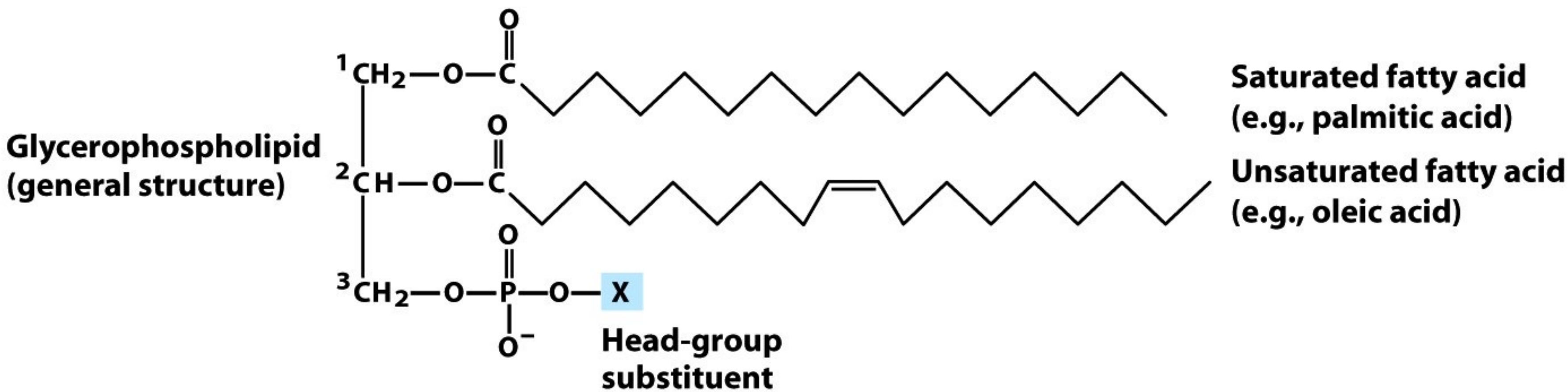


Figure 10-9 part 1
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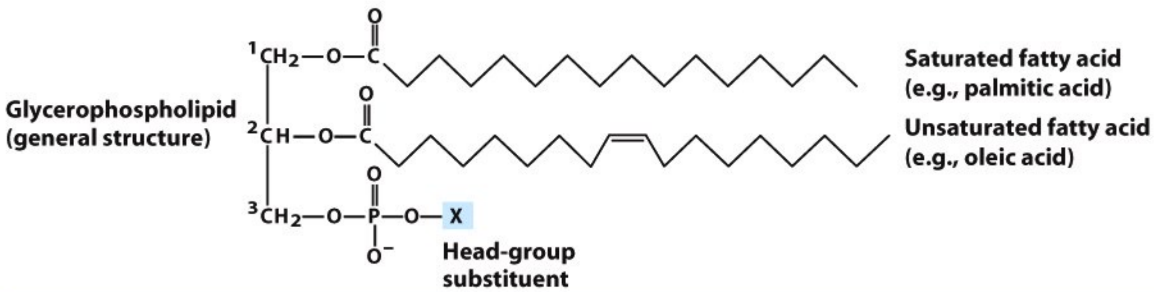


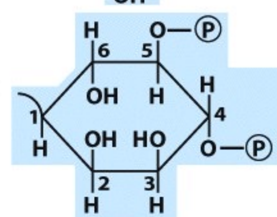
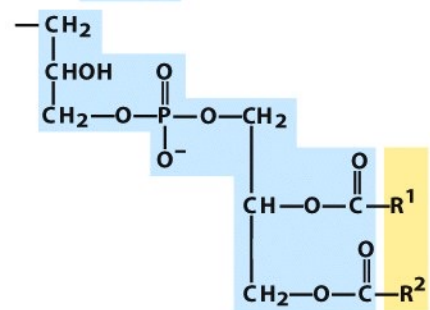
Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	$-\mathrm{H}$	– 1
Phosphatidylethanolamine	Ethanolamine	$-\mathrm{CH_2-CH_2-\overset{+}{N}H_3}$	0
Phosphatidylcholine	Choline	$-\mathrm{CH_2-CH_2-\overset{+}{N}(CH_3)_3}$	0
Phosphatidylserine	Serine	$-\mathrm{CH_2-CH(COO^-)-\overset{+}{N}H_3}$	– 1
Phosphatidylglycerol	Glycerol	$-\mathrm{CH_2-CH(OH)-CH_2-OH}$	– 1
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate		– 4
Cardiolipin	Phosphatidyl-glycerol		– 2

Figure 10-9

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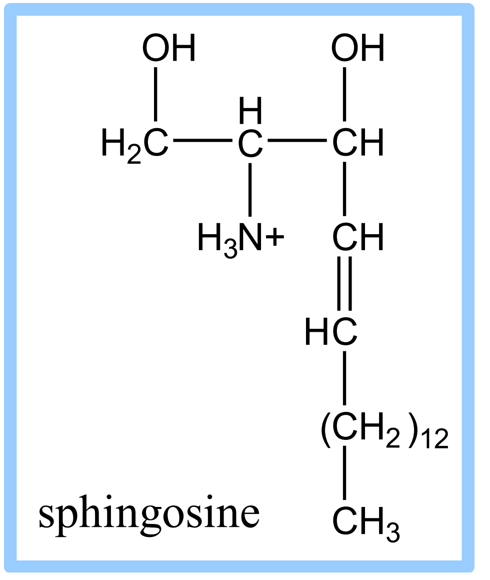
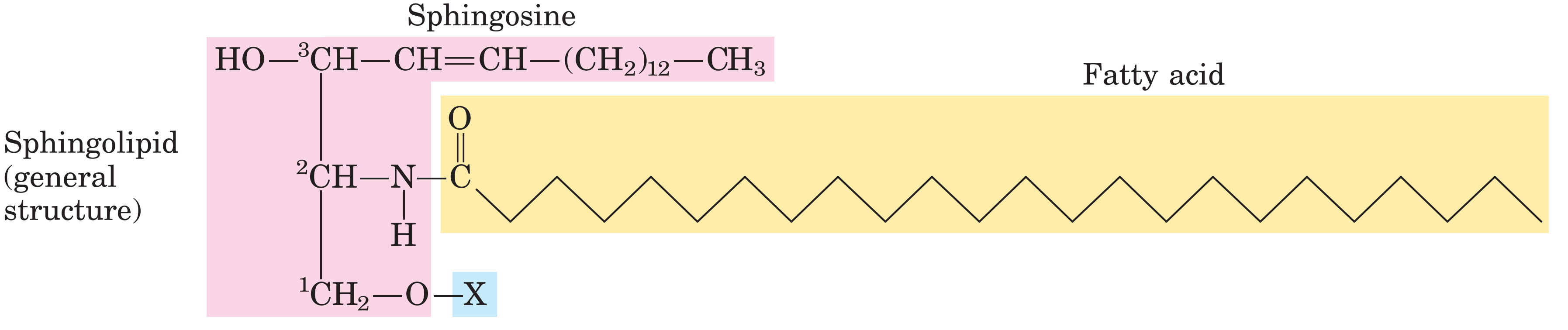
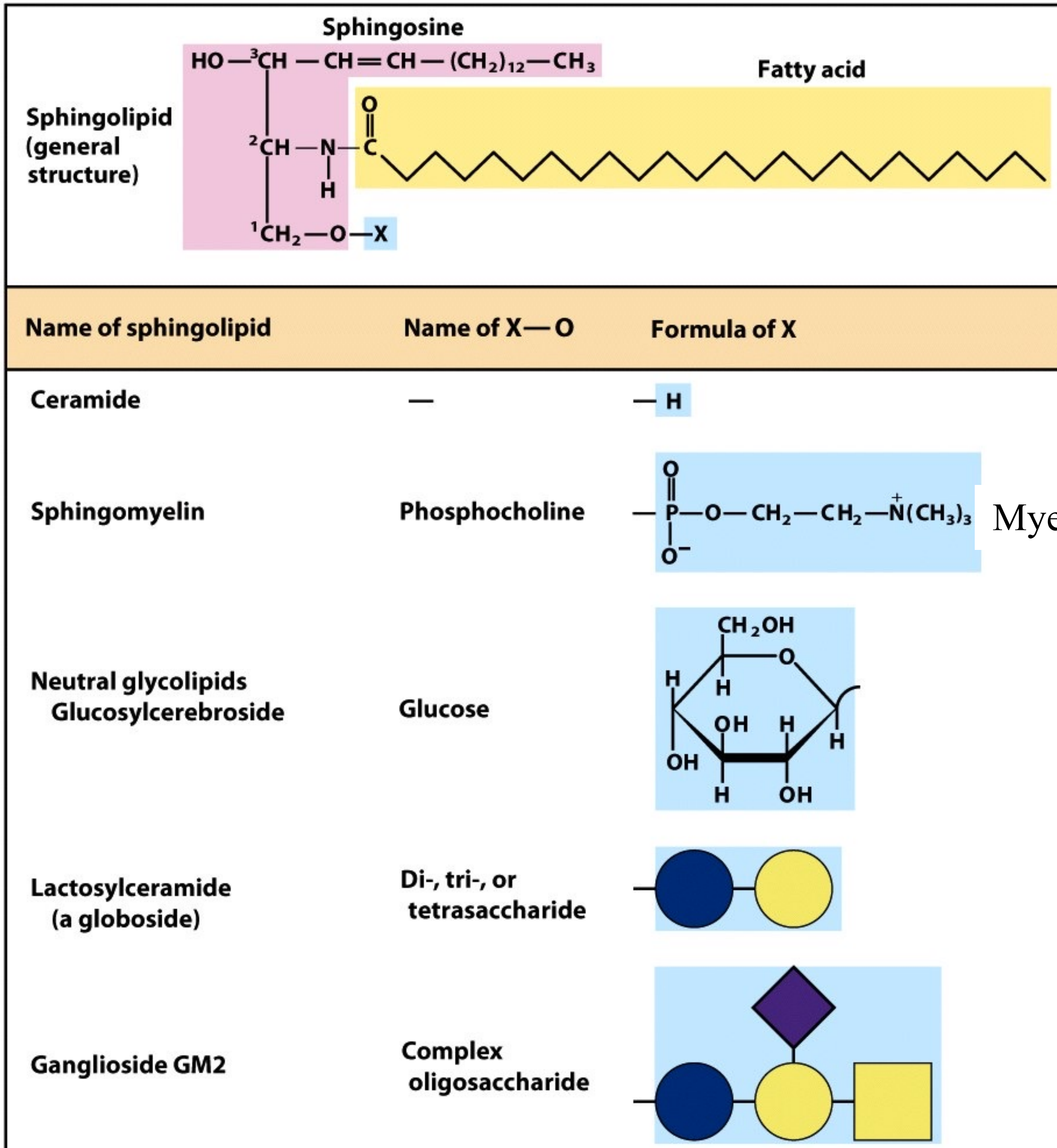
Sphingolipids Are Derivatives of Sphingosine

Sphingolipids are derivatives of the lipid sphingosine, a long-chain amino alcohol, which has a long hydrocarbon tail, and a polar domain that includes an amino group.





When a fatty acid is attached in amide linkage to the -NH2 on C-2, the resulting compound is a **ceramide**, which is structurally similar to a diacylglycerol. **Ceramide** is the structural parent of all sphingolipids.



Myelin sheath of neurons

Figure 10-13
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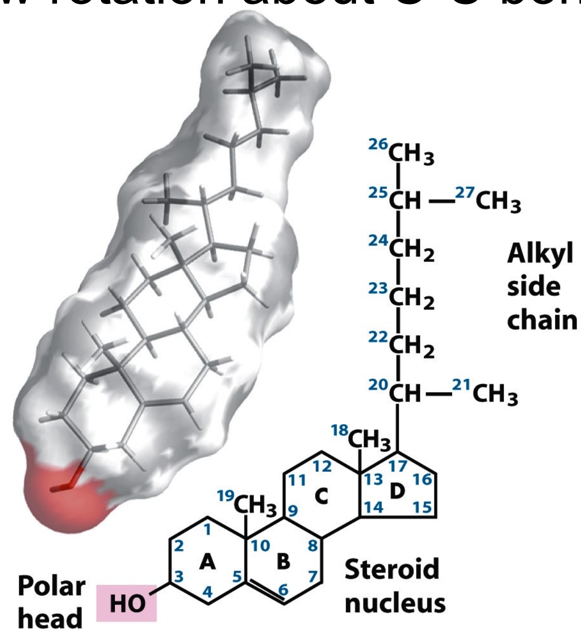
Sterols

Sterols are structural lipids present in the membranes of most eukaryotic cells.

The steroid nucleus consists of **four fused rings**, three with six carbons and one with five. The steroid nucleus is almost planar and is relatively rigid; the fused rings do not allow rotation about C-C bonds.



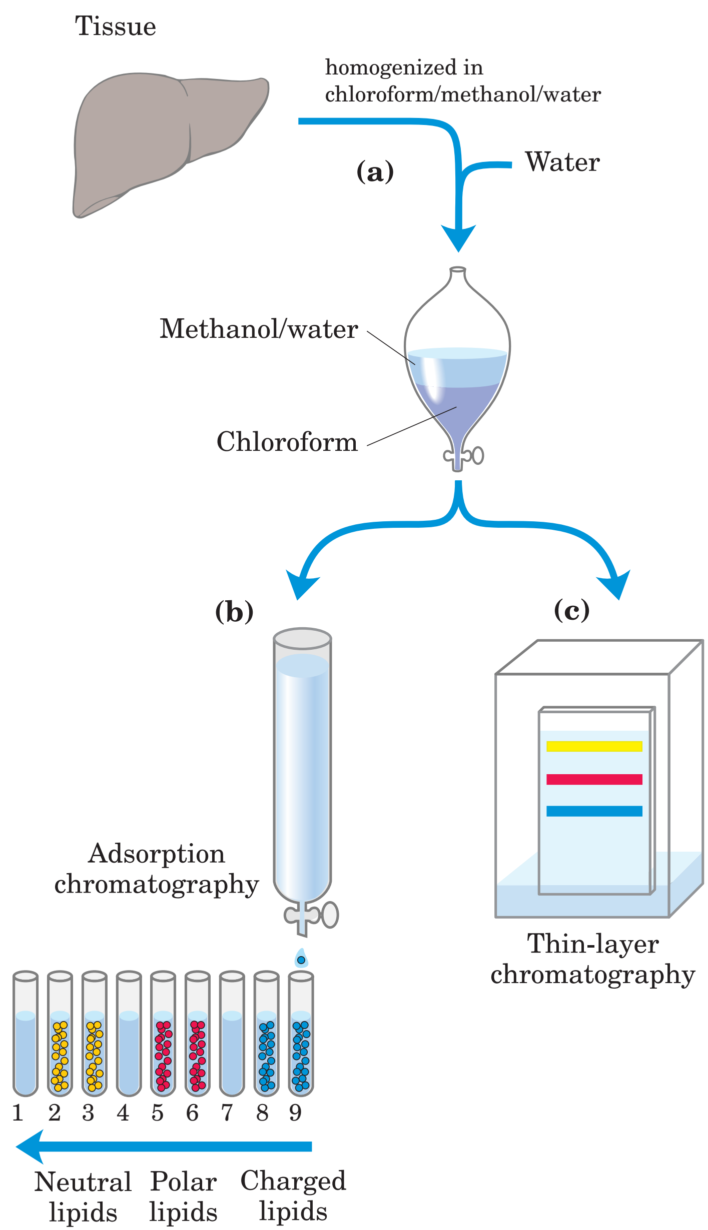
Cholesterol, the major sterol in animal tissues, is amphipathic, with a polar head group (the hydroxyl group at C-3) and a nonpolar hydrocarbon body (the steroid nucleus and the hydrocarbon side chain at C-17), about as long as a 16- carbon fatty acid in its extended form. Similar sterols are found in other eukaryotes: stigmasterol in plants and ergosterol in fungi, for example.

Lipid Extraction Requires Organic Solvents

Because lipids are insoluble in water, their extraction and subsequent fractionation require the use of organic solvents and some techniques not commonly used in the purification of water-soluble molecules such as proteins and carbohydrates. In general, complex mixtures of lipids are separated by differences in the polarity or solubility of the components in nonpolar solvents.

Neutral lipids (triacylglycerols, waxes, pigments, and so forth) are readily extracted from tissues with ethyl ether, chloroform, or benzene, solvents that do not permit lipid clustering driven by hydrophobic interactions.

Membrane lipids are more effectively extracted by more polar organic solvents, such as ethanol or methanol, which reduce the hydrophobic interactions among lipid molecules while also weakening the hydrogen bonds and electrostatic interactions that bind membrane lipids to membrane proteins.


Tissue
homogenized in
chloroform/methanol/water
(a)
Water
Methanol/water
Chloroform
(b)
(c)
Adsorption
chromatography
Thin-layer
chromatography
1 2 3 4 5 6 7 8 9
Neutral lipids
Polar lipids
Charged lipids

Digestion, Mobilization, and Transport of Fats

Because fats are insoluble in water, ingested triacylglycerols must be emulsified before they can be digested by water-soluble enzymes in the intestine, and triacylglycerols absorbed in the intestine or mobilized from storage tissues must be carried in the blood bound to proteins that counteract their insolubility.

To overcome the relative stability of the C-C bonds in a fatty acid, the carboxyl group at C-1 is activated by attachment to coenzyme A, which allows stepwise oxidation of the fatty acyl group at the C-3, or , position—hence the name **β-oxidation.**

The electrons removed from fatty acids during oxidation pass through the respiratory chain, driving ATP synthesis.

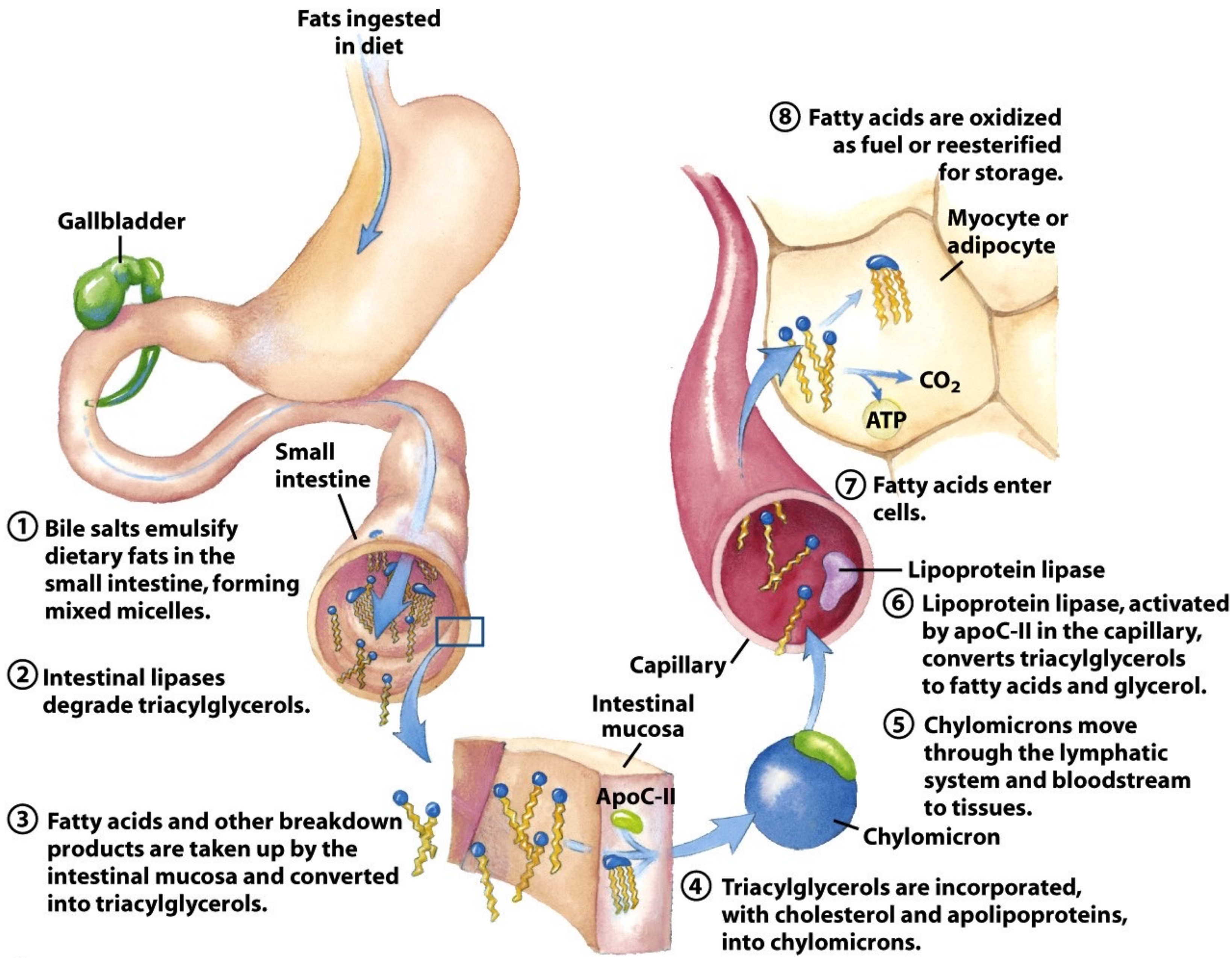


Figure 17-1
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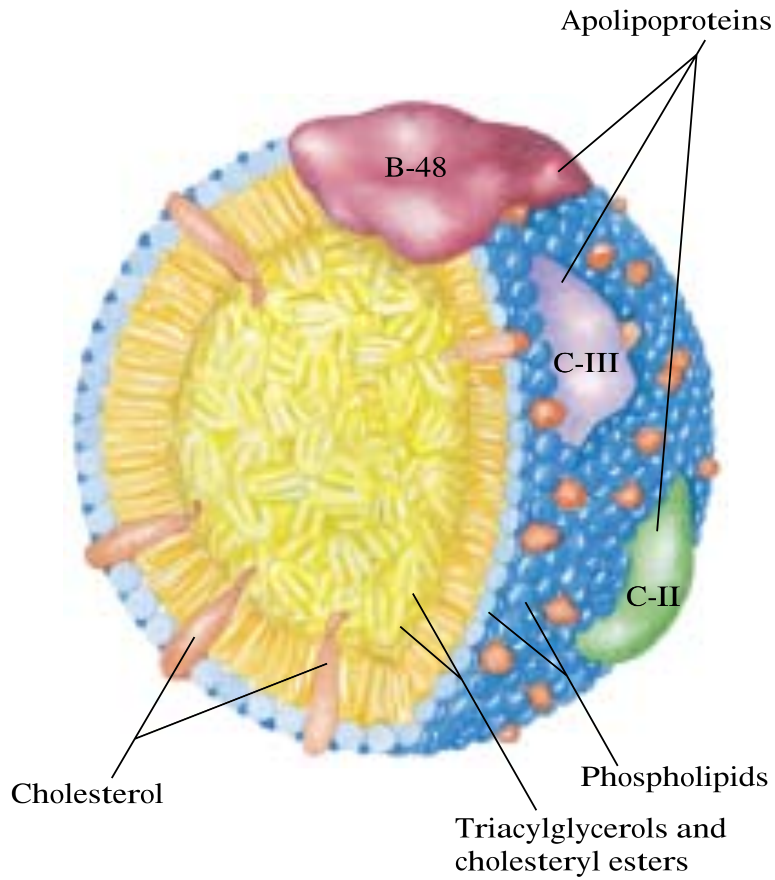

Molecular structure of a chylomicron. The surface is a layer of phospholipids, with head groups facing the aqueous phase. Triacylglycerols sequestered in the interior (yellow) make up more than 80% of the mass. Several apolipoproteins that protrude from the surface (B-48, C-III, C-II) act as signals in the uptake and metabolism of chylomicron contents. The diameter of chylomicrons ranges from about 100 to 500 nm.

Mobilization of triacylglycerols stored in adipose tissue

The surface of these droplets is coated with **perilipins,** a family of proteins that restrict access to lipid droplets, preventing untimely lipid mobilization. When hormones signal the need for metabolic energy, triacylglycerols stored in adipose tissue are mobilized (brought out of storage) and transported to tissues.

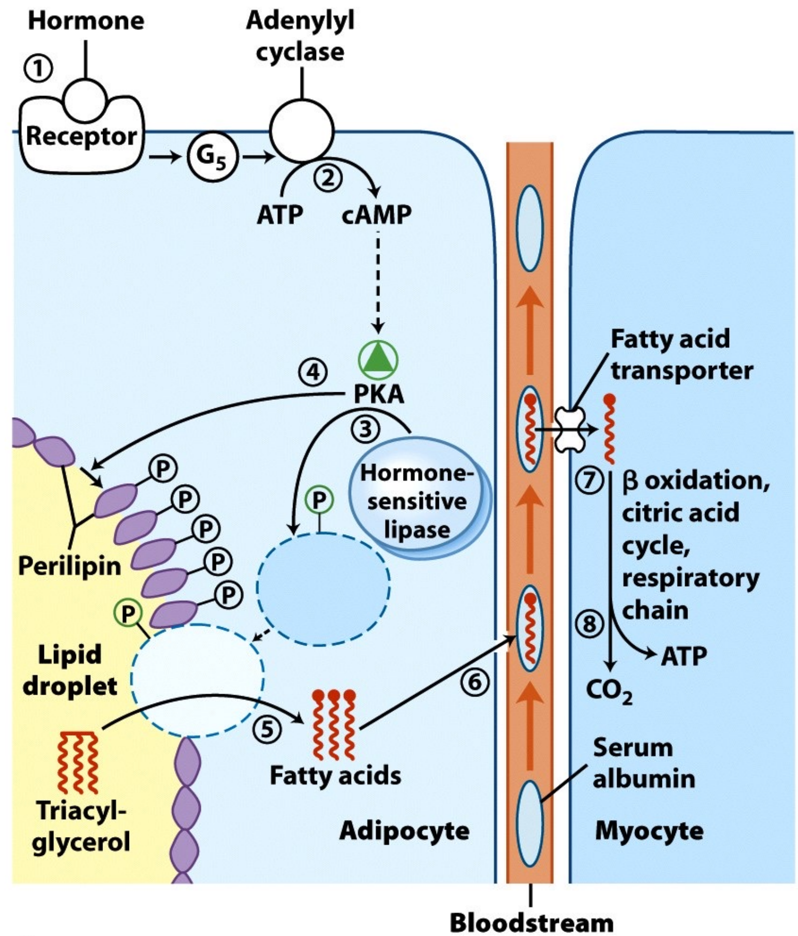

Figure 17-3
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As hormone-sensitive lipase hydrolyzes triacylglycerol in adipocytes, the fatty acids thus released **(free fatty acids, FFA)** pass from the adipocyte into the blood, where they bind to the blood protein **serum albumin.**

This protein which makes up about half of the total serum protein, noncovalently binds as many as 10 fatty acids per protein monomer.