

**OVERVIEW
OF
LIPID
METABOLISM**

What are lipids

Digestion, absorption and transport

Lipolysis

Beta-oxidation of fatty acids

Ketone bodies

Biosynthesis of fatty acids

Biosynthesis of lipids

Biosynthesis of cholesterol

Plasma lipoproteins

What are lipids?

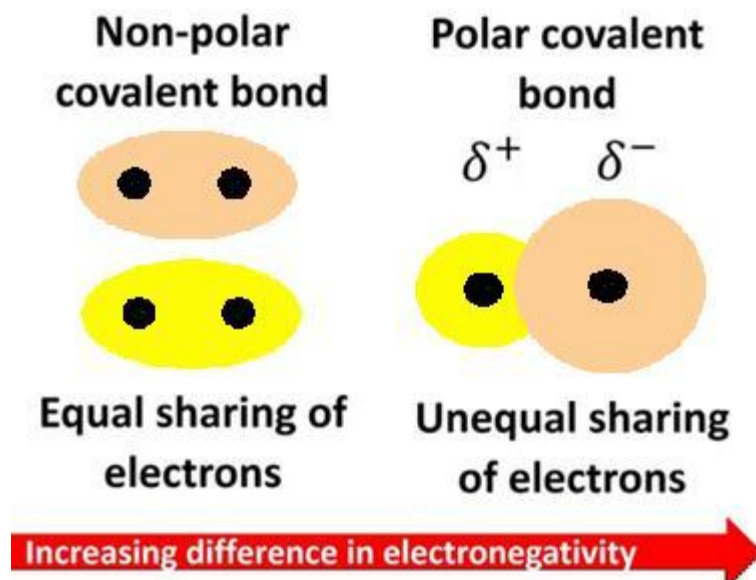
Broad definition:

molecules insoluble in water
(hydrophobic),
soluble in organic solvents.

Electronegativity is a measure of the tendency of an atom to attract a bonding pair of electrons

H	C	N	O
2.1	2.5	3.0	3.5

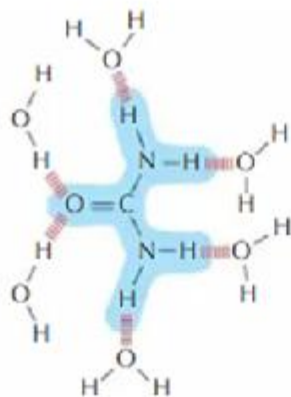
If the atoms are equally electronegative, both have the same tendency to attract the bonding pair of electrons, and so it will be found on average half way between the two atoms.



If one atom in the couple is slightly more electronegative than the other, it will attract the electron pair rather more than the other. One end of the bond will have more than its fair share of electron density and so will become slightly negative. At the same time, the other end (rather short of electrons) will become slightly positive.

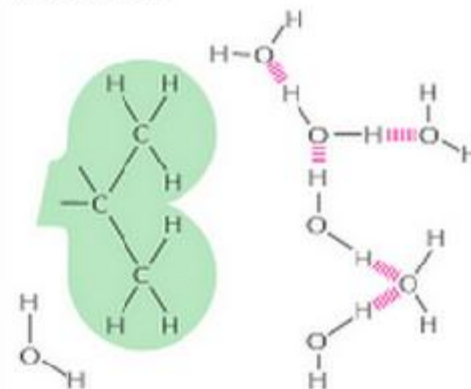
HYDROPHILIC MOLECULES

Substances that dissolve readily in water are termed **hydrophilic**. They are composed of ions or polar molecules that attract water molecules through electrical charge effects. Water molecules surround each ion or polar molecule on the surface of a solid substance and carry it into solution.



HYDROPHOBIC MOLECULES

Substances that contain a preponderance of nonpolar bonds are usually insoluble in water and are termed **hydrophobic**. Water molecules are not attracted to such hydrophobic molecules and so have little tendency to surround them and bring them into solution.



Hydrocarbons, which contain many C-H bonds, are especially hydrophobic.

What are lipids?

Broad definition:

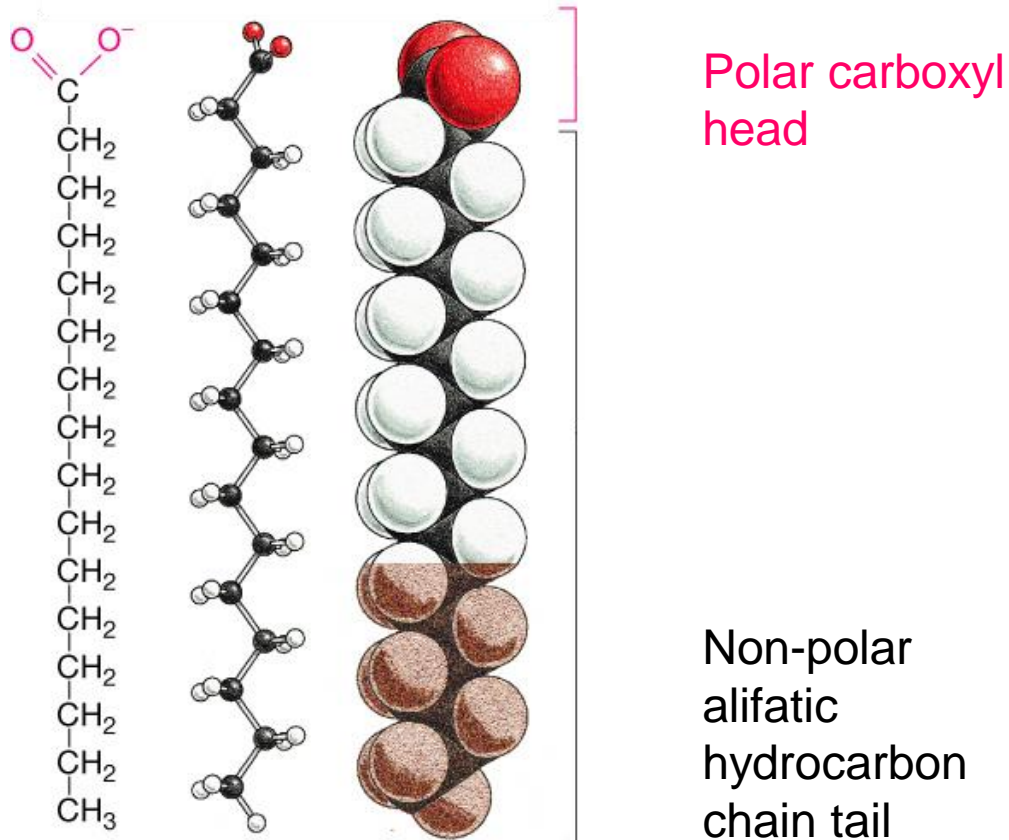
molecules insoluble in water, soluble
in organic solvents

Chemical definition:

molecules containing **fatty acids**

FATTY ACIDS

Carboxylic acids consisting of a hydrocarbon chain and a terminal carboxyl group, especially any of those occurring as esters in fats and oils



Some Naturally Occurring Fatty Acids

Carbon skeleton	Structure*	Systematic name [†]	Common name (derivation)	Melting point (°C)	Solubility at 30 °C (mg/g solvent)	
					Water	Benzene
12:0	CH ₃ (CH ₂) ₁₀ COOH	<i>n</i> -Dodecanoic acid	Lauric acid (Latin <i>laurus</i> , "laurel plant")	44.2	0.063	2,600
14:0	CH ₃ (CH ₂) ₁₂ COOH	<i>n</i> -Tetradecanoic acid	Myristic acid (Latin <i>Myristica</i> , nutmeg genus)	53.9	0.024	874
16:0	CH ₃ (CH ₂) ₁₄ COOH	<i>n</i> -Hexadecanoic acid	Palmitic acid (Latin <i>palma</i> , "palm tree")	63.1	0.0083	348
18:0	CH ₃ (CH ₂) ₁₆ COOH	<i>n</i> -Octadecanoic acid	Stearic acid (Greek <i>stear</i> , "hard fat")	69.6	0.0034	124
20:0	CH ₃ (CH ₂) ₁₈ COOH	<i>n</i> -Eicosanoic acid	Arachidic acid (Latin <i>Arachis</i> , legume genus)	76.5		
24:0	CH ₃ (CH ₂) ₂₂ COOH	<i>n</i> -Tetracosanoic acid	Lignoceric acid (Latin <i>lignum</i> , "wood" + <i>cera</i> , "wax")	86.0		
16:1(Δ ⁹)	CH ₃ (CH ₂) ₅ CH=CH(CH ₂) ₇ COOH	<i>cis</i> -9-Hexadecenoic acid	Palmitoleic acid	-0.5		
18:1(Δ ⁹)	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ COOH	<i>cis</i> -9-Octadecenoic acid	Oleic acid (Latin <i>oleum</i> , "oil")	13.4		
18:2(Δ ^{9,12})	CH ₃ (CH ₂) ₄ CH=CHCH ₂ CH=CH(CH ₂) ₇ COOH	<i>cis</i> -, <i>cis</i> -9,12-Octadecadienoic acid	Linoleic acid (Greek <i>linon</i> , "flax")	-5		
18:3(Δ ^{9,12,15})	CH ₃ CH ₂ CH=CHCH ₂ CH=CHCH ₂ CH=CH(CH ₂) ₇ COOH	<i>cis</i> -, <i>cis</i> -, <i>cis</i> -9,12,15-Octadecatrienoic acid	α-Linolenic acid	-11		
20:4(Δ ^{5,8,11,14})	CH ₃ (CH ₂) ₄ CH=CHCH ₂ CH=CHCH ₂ CH=CHCH ₂ CH=CH(CH ₂) ₃ COOH	<i>cis</i> -, <i>cis</i> -, <i>cis</i> -, <i>cis</i> -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.

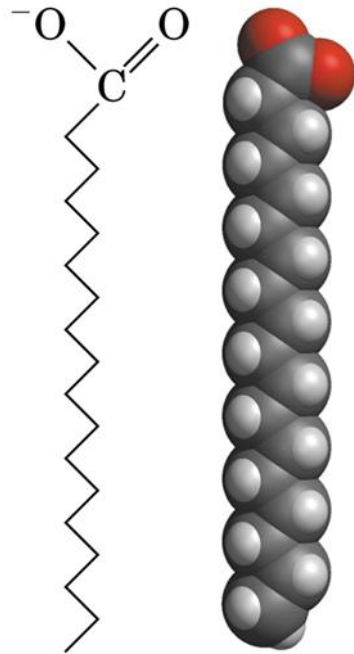
[†]The prefix *n*- indicates the "normal" unbranched structure. For instance, "dodecanoic" simply indicates 12 carbon atoms, which could be arranged in a variety of branched forms; "*n*-dodecanoic" specifies the linear, unbranched form. For unsaturated fatty acids, the configuration of each double bond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

Short-chain, medium-chain, long-chain fatty acids

Mostly with an even number of C atoms

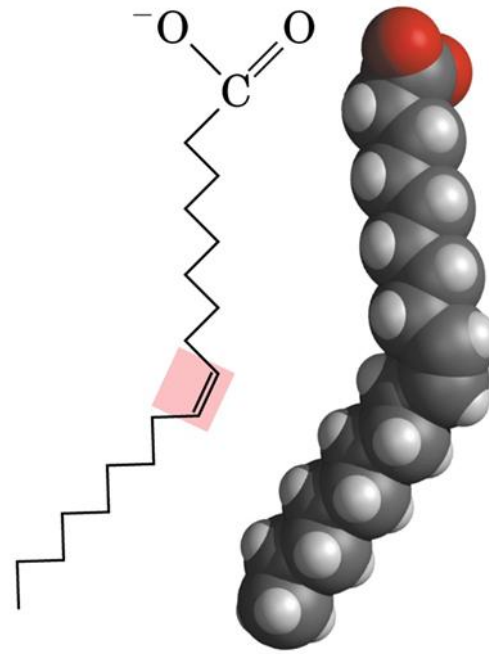
FATTY ACIDS

Carboxyl group



Hydrocarbon chain

Saturated (e.g. palmitate 16:0, stearate 18:0)



Unsaturated (*cis* double bonds):
mono-, di-, poly-unsaturated
(e.g. oleate 18:1, linoleate 18:2, arachidonate 20:4)

FATTY ACIDS

Position of double bond:

Δ (from carboxyl), ω (from distal methyl)

$\text{CH}_3\text{-CH}_2\text{-CH=CH-CH}_2\text{-CH}_2\text{-CH}_2\text{-COOH}$
is $\Delta 5$ octaenoic acid or $\omega 3$ octaenoic acid

Some examples

- Stearic acid 18:0 octadecanoic
- Oleic acid 18:1 Δ^9 -octadecenoic (ω 9)
- Linoleic acid 18:2 $\Delta^9,12$ -octadecadienoic (ω 6,9)
- Linolenic acid 18:3 $\Delta^9,12,15$ -octadecatrienoic (ω 3,6,9)

Carbon skeleton	Structure*	Systematic name [†]	Common name (derivation)	Melting point (°C)
18:0	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$	<i>n</i> -Octadecanoic acid	Stearic acid (Greek <i>stear</i> , "hard fat")	69.6
18:1(Δ^9)	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	<i>cis</i> -9-Octadecenoic acid	Oleic acid (Latin <i>oleum</i> , "oil")	13.4
18:2($\Delta^{9,12}$)	$\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	<i>cis</i> -, <i>cis</i> -9,12-Octadecadienoic acid	Linoleic acid (Greek <i>linon</i> , "flax")	-5
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Some examples

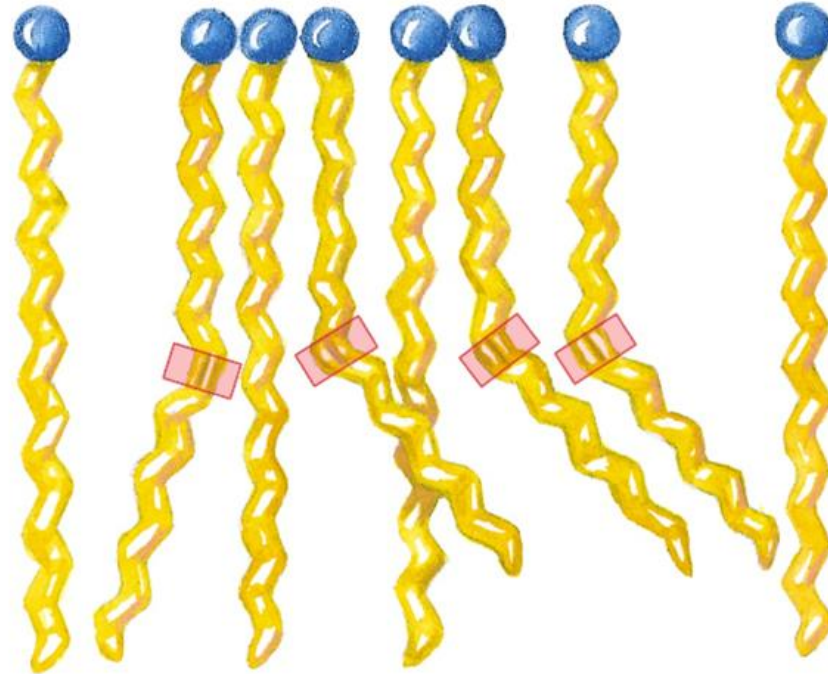
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Saturated
fatty acids

Lard

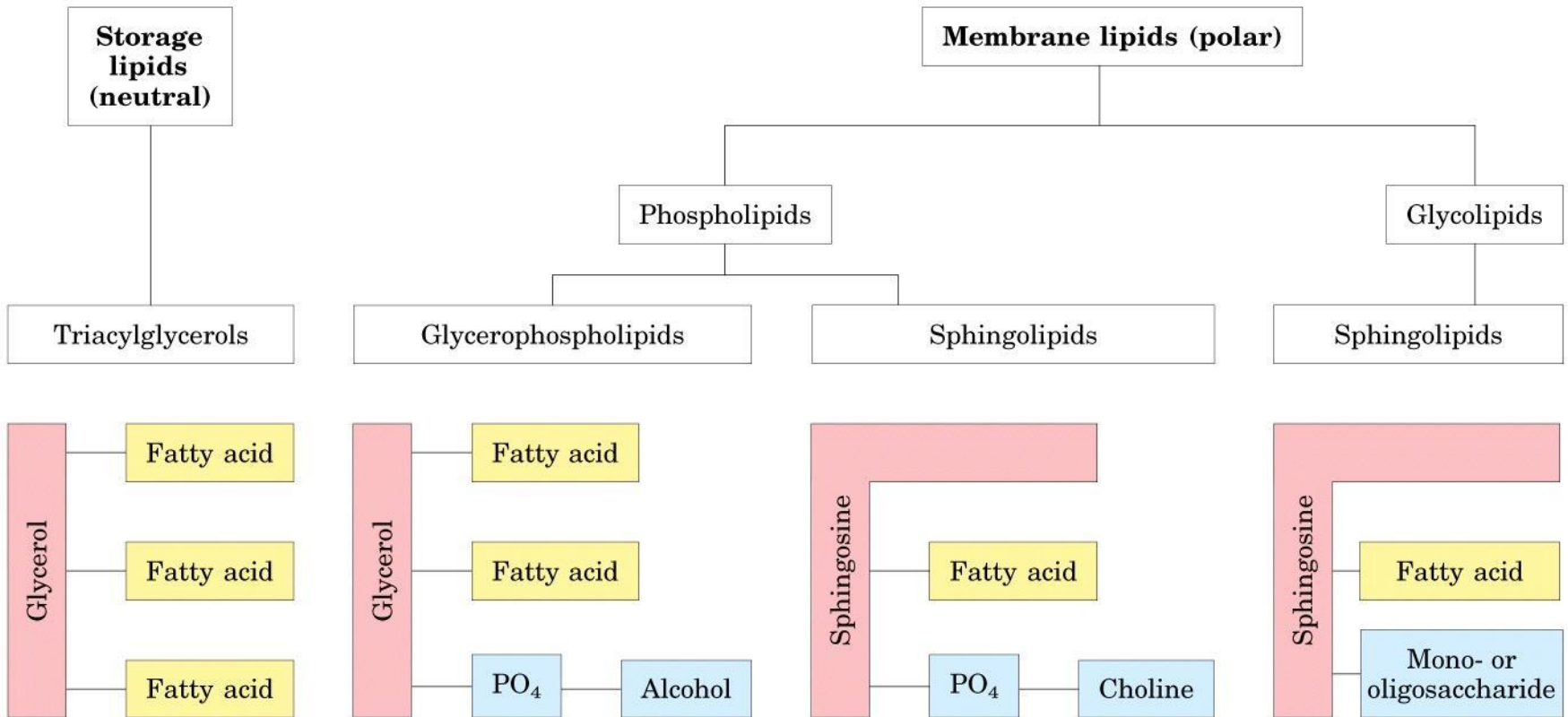


Mixture of saturated and
unsaturated fatty acids

Oil

FREE FATTY ACIDS vs LIPIDS

- Body concentration of free fatty acids is low
- The large majority of fatty acids are esterified in form of lipids (storage lipids and membrane lipids)
- Free fatty acids may be found in blood under fasting conditions; in cells they are immediately transformed into CoA derivatives and either oxidized or used for biosynthesis of lipids.



Storage lipids (neutral)

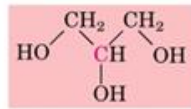
Triacylglycerols

Glycerol

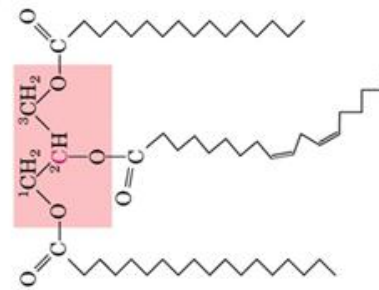
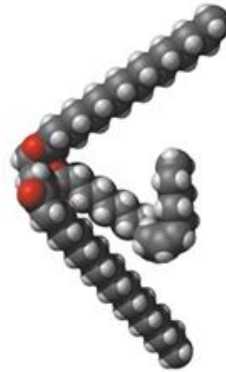
Fatty acid

Fatty acid

Fatty acid

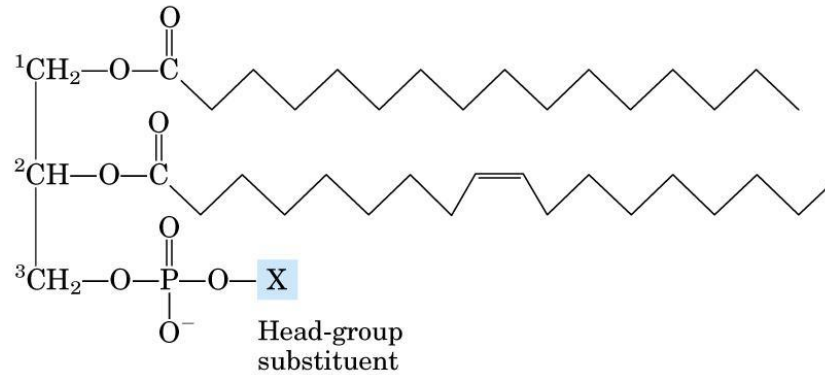


Glycerol



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

Glycerophospholipid
(general structure)

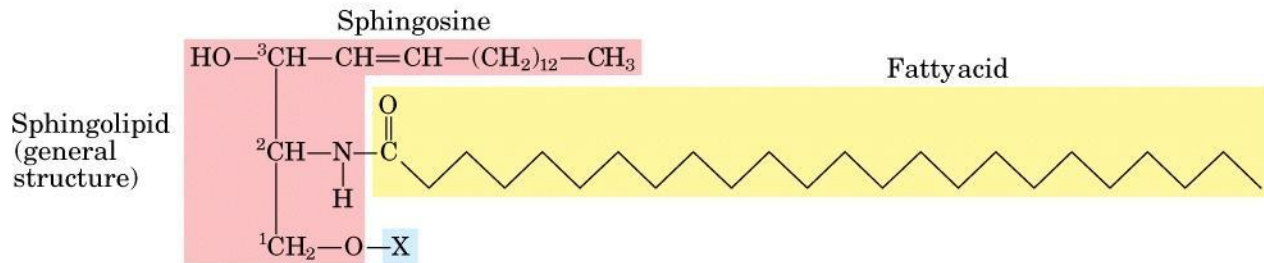


Saturated fatty acid
(e.g., palmitic acid)

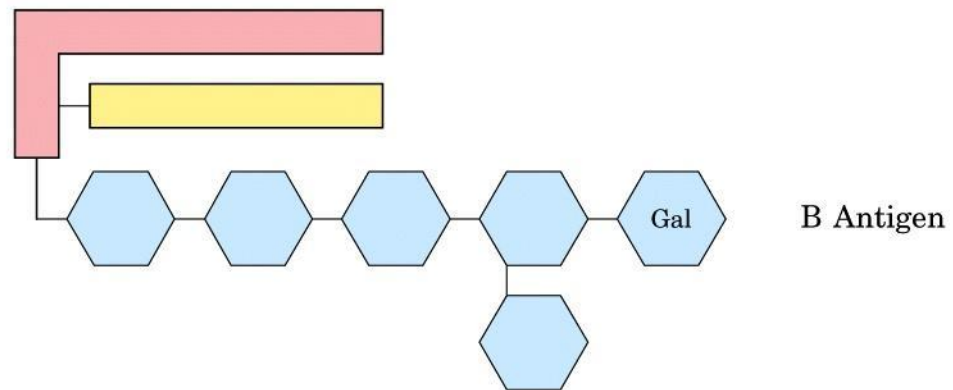
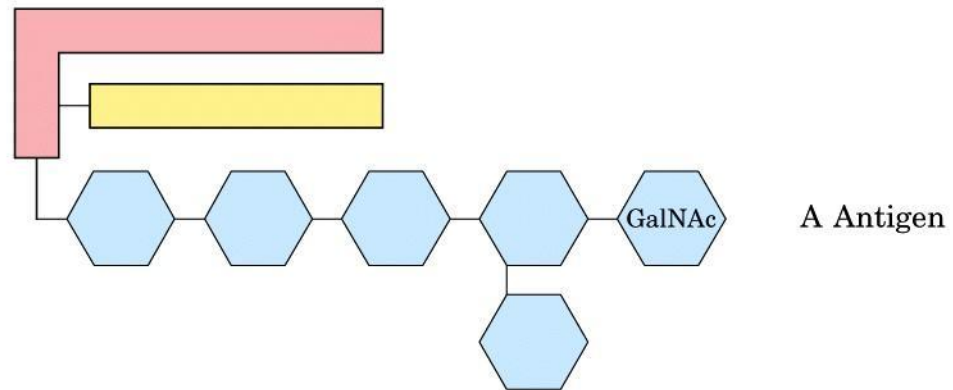
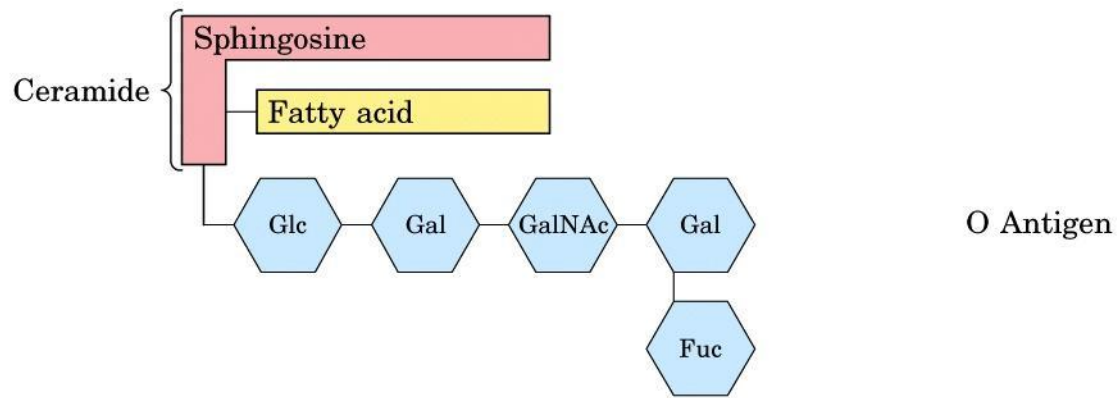
Unsaturated fatty acid
(e.g., oleic acid)

Head-group
substituent

Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	— H	-1
Phosphatidylethanolamine	Ethanolamine	— CH ₂ —CH ₂ —NH ₃ ⁺	0
Phosphatidylcholine	Choline	— CH ₂ —CH ₂ —N ⁺ (CH ₃) ₃	0
Phosphatidylserine	Serine	— CH ₂ —CH—NH ₃ ⁺ COO ⁻	-1
Phosphatidylglycerol	Glycerol	— CH ₂ —CH—CH ₂ —OH OH	-1
Phosphatidylinositol 4,5-bisphosphate	<i>myo</i> -Inositol 4,5-bisphosphate		-4
Cardiolipin	Phosphatidyl-glycerol		-2

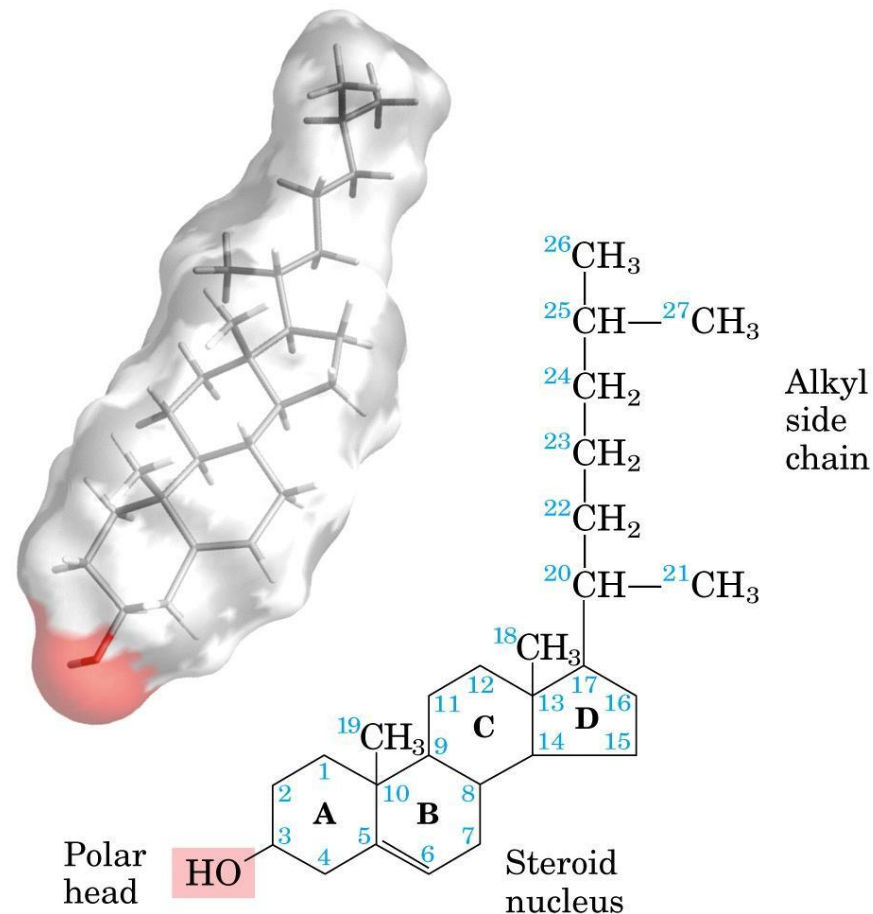


Name of sphingolipid	Name of X	Formula of X
Ceramide	—	— H
Sphingomyelin	Phosphocholine	$-\text{P}(=\text{O})(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}^+(\text{CH}_3)_3$
Neutral glycolipids Glucosylcerebroside	Glucose	
Lactosylceramide (a globoside)	Di-, tri-, or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	



Cholesterol is a steroid in the body.

It is a precursor to vitamins and many steroid hormones such as testosterone, estrogen, and cortisol.



Major Lipids in Food

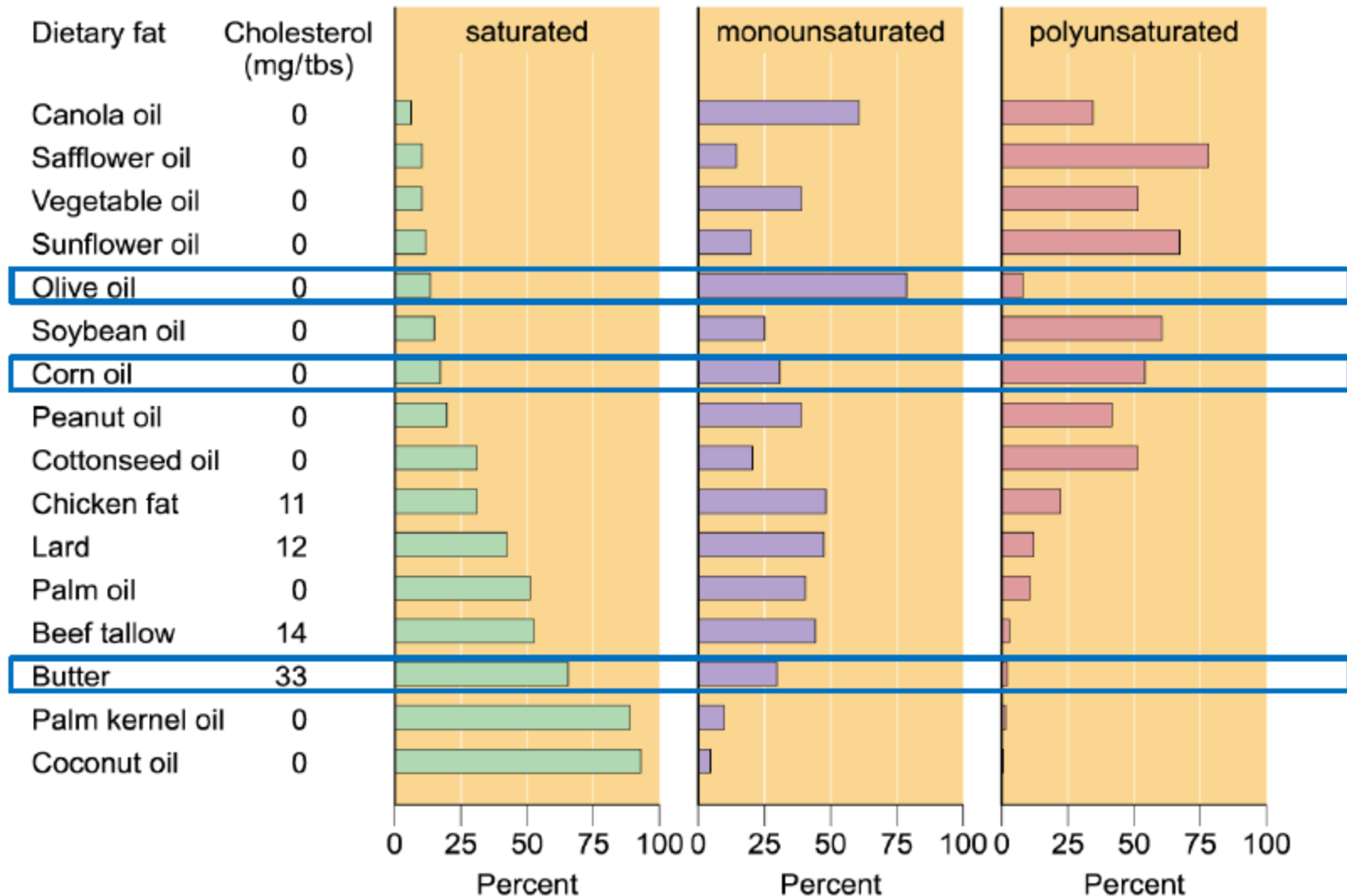
- Triglycerides

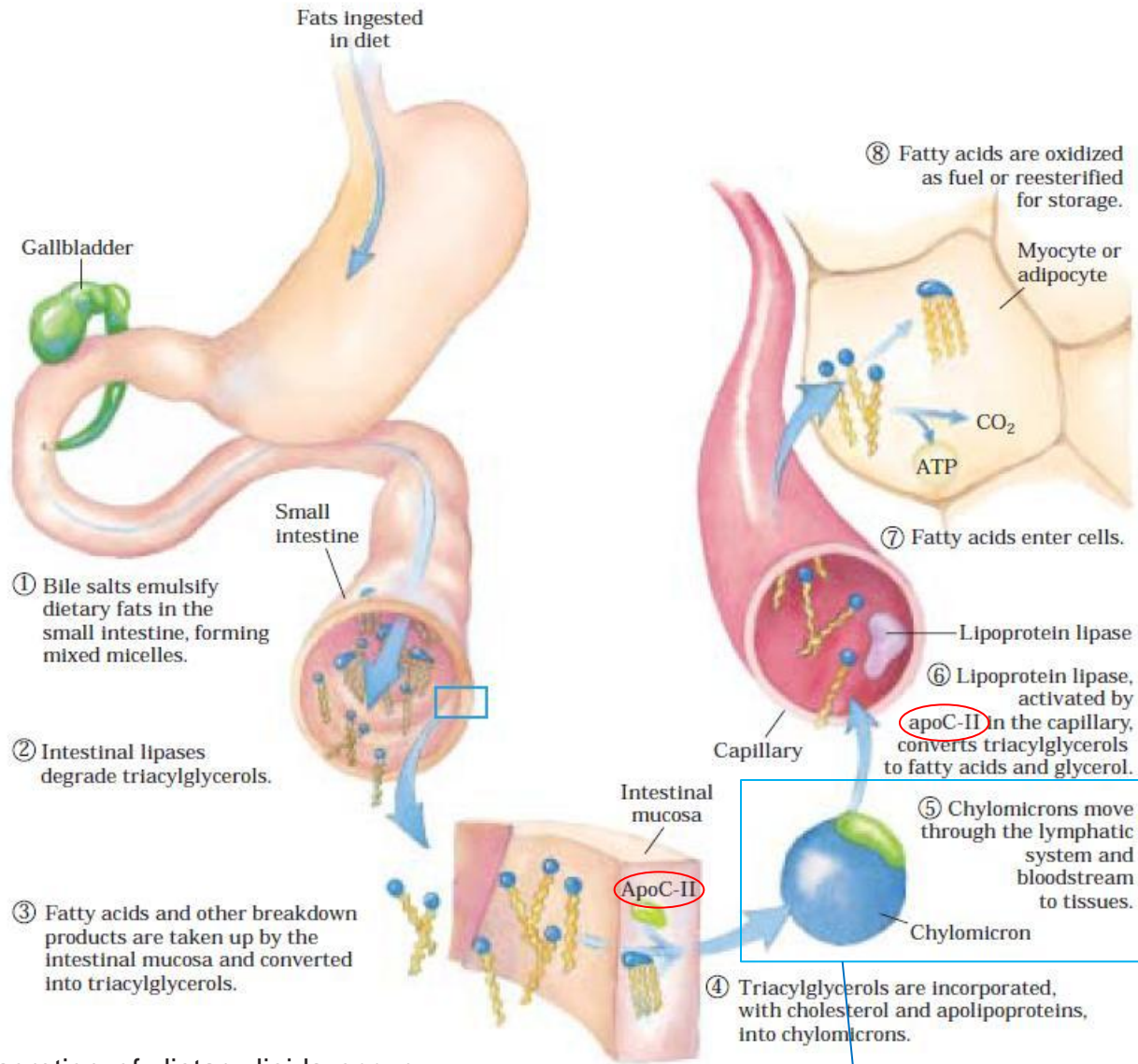
Fats

Oils

- Phospholipids
- Cholesterol

Fatty Acids in Common Food Fats

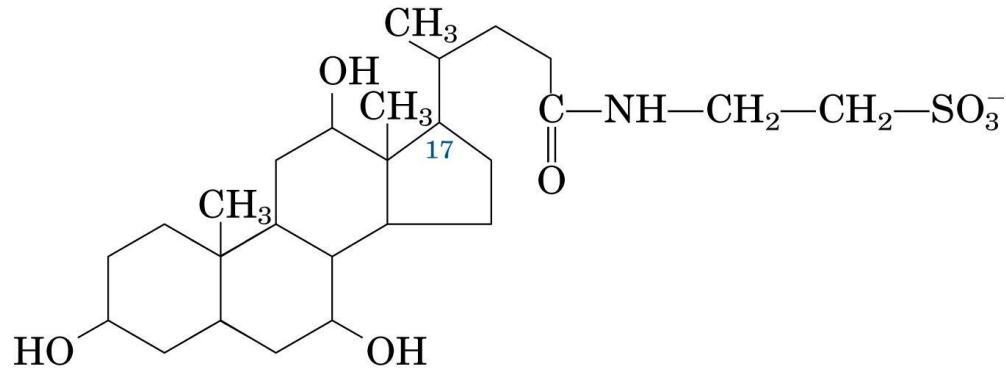




Digestion and absorption of dietary lipids occur in the small intestine, and the fatty acids released from triacylglycerols are packaged and delivered to muscle and adipose tissues.

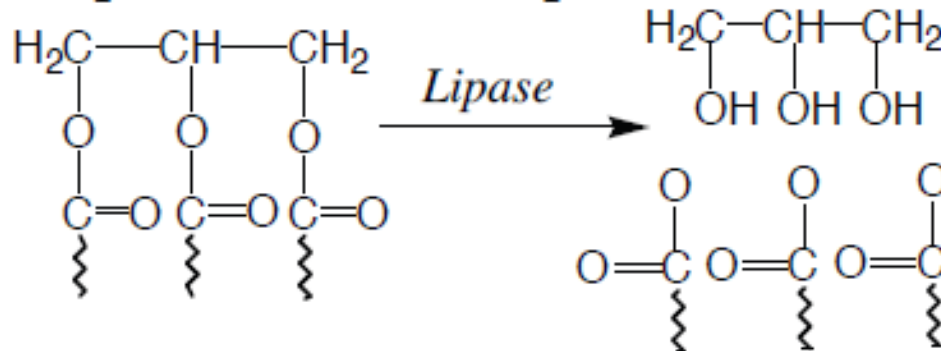
Digestion of Dietary Fats

- Bile salts are detergents: emulsification



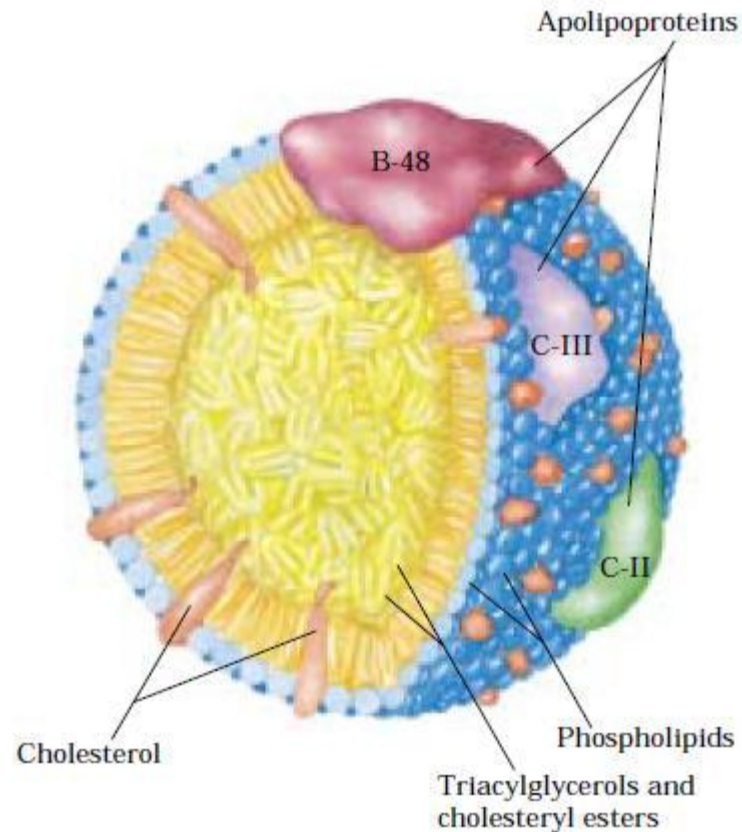
Taurocholic acid
(a bile acid)

- **Lipases:** hydrolysis to **fatty acids** which are the form transported across the plasma membrane.



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.



LIPOLYSIS

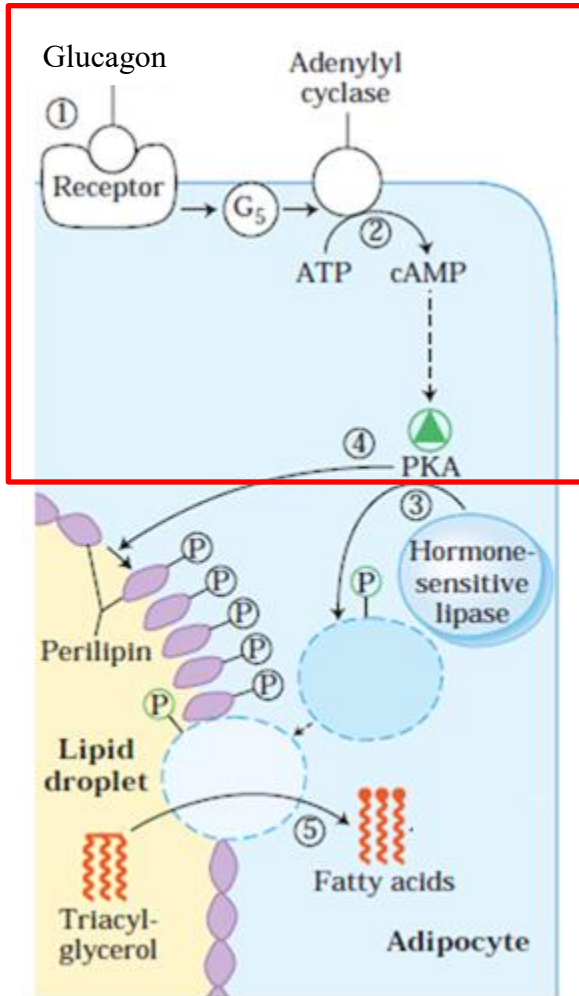
Under fasting conditions, triacylglycerols stored in adipocytes are hydrolyzed by hormone-sensitive lipase (lipolysis).

Lipolysis is activated by adrenaline and glucagon, inhibited by insulin.

Free fatty acids and glycerol are released in plasma

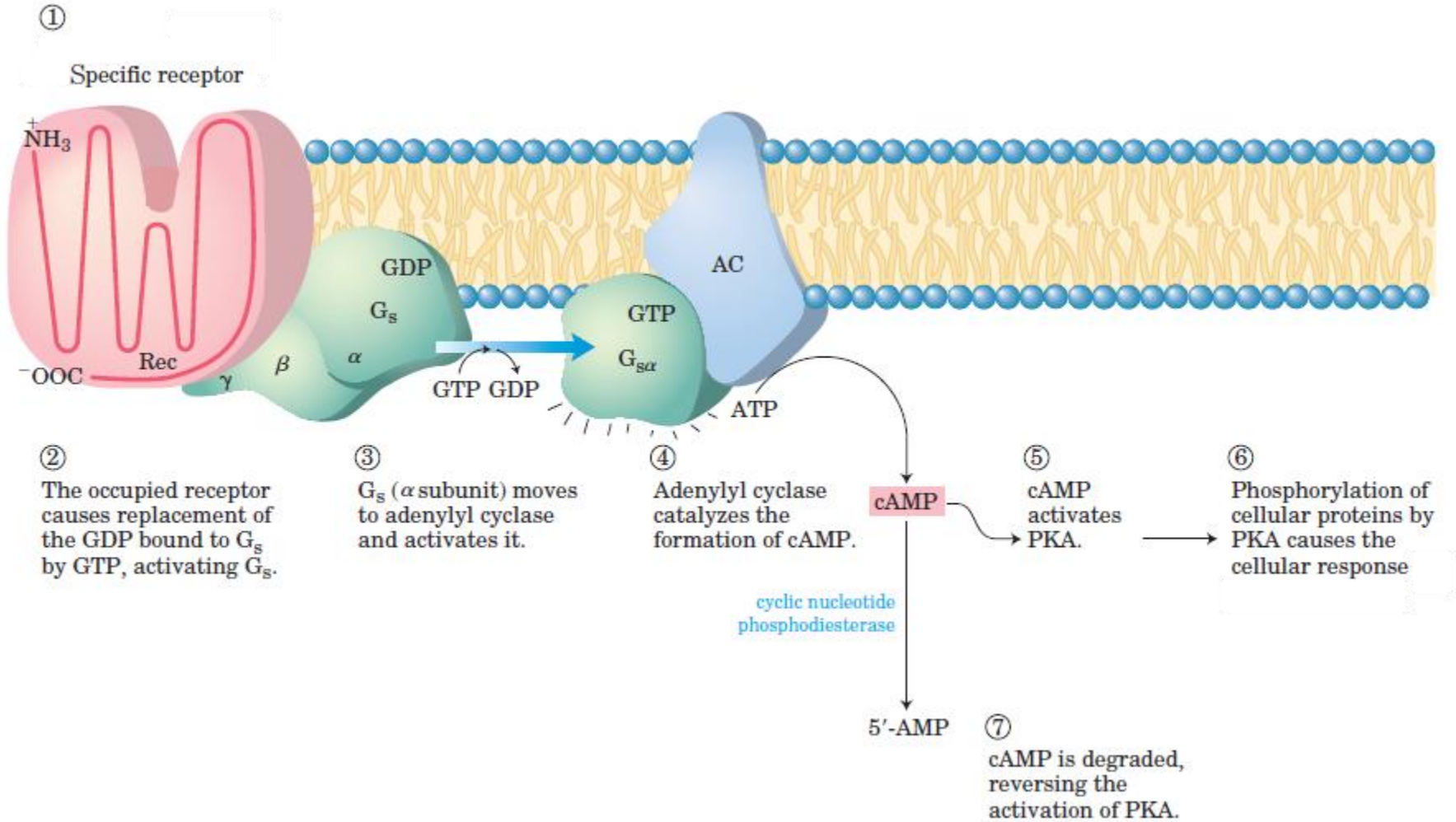
Free fatty acids are oxidized in tissues; in liver their oxidation produces ketone bodies

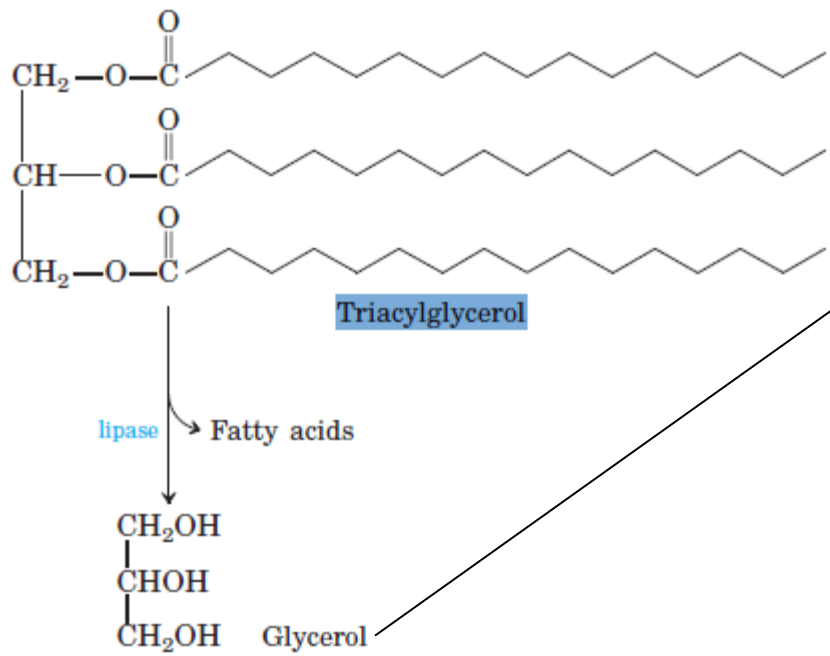
Glycerol is used in liver mainly for gluconeogenesis



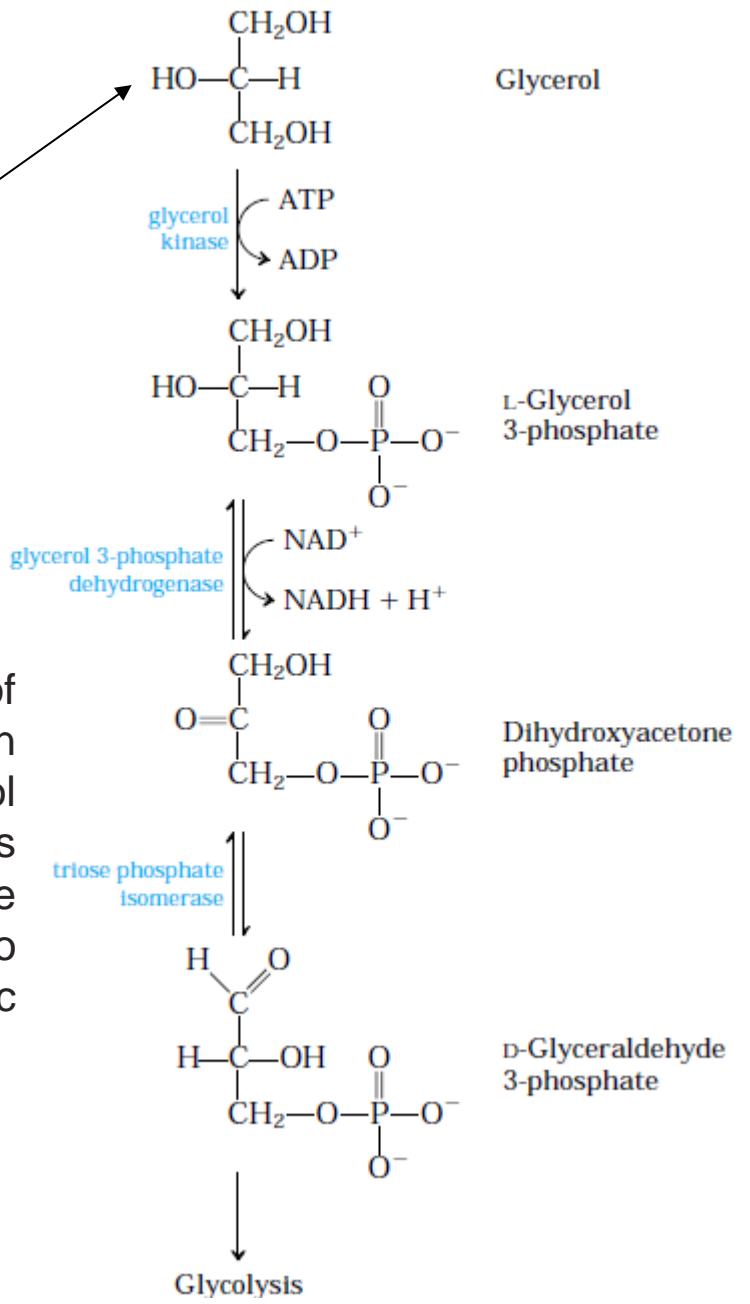
When low levels of glucose in the blood trigger the release of glucagon, 1 the hormone binds its receptor in the adipocyte membrane and thus 2 stimulates adenylyl cyclase, via a G protein, to produce cAMP. This activates PKA, which phosphorylates 3 the hormone-sensitive lipase and 4 perilipin molecules on the surface of the lipid droplet. Phosphorylation of perilipin permits hormone-sensitive lipase access to the surface of the lipid droplet, where 5 it hydrolyzes triacylglycerols to free fatty acids.

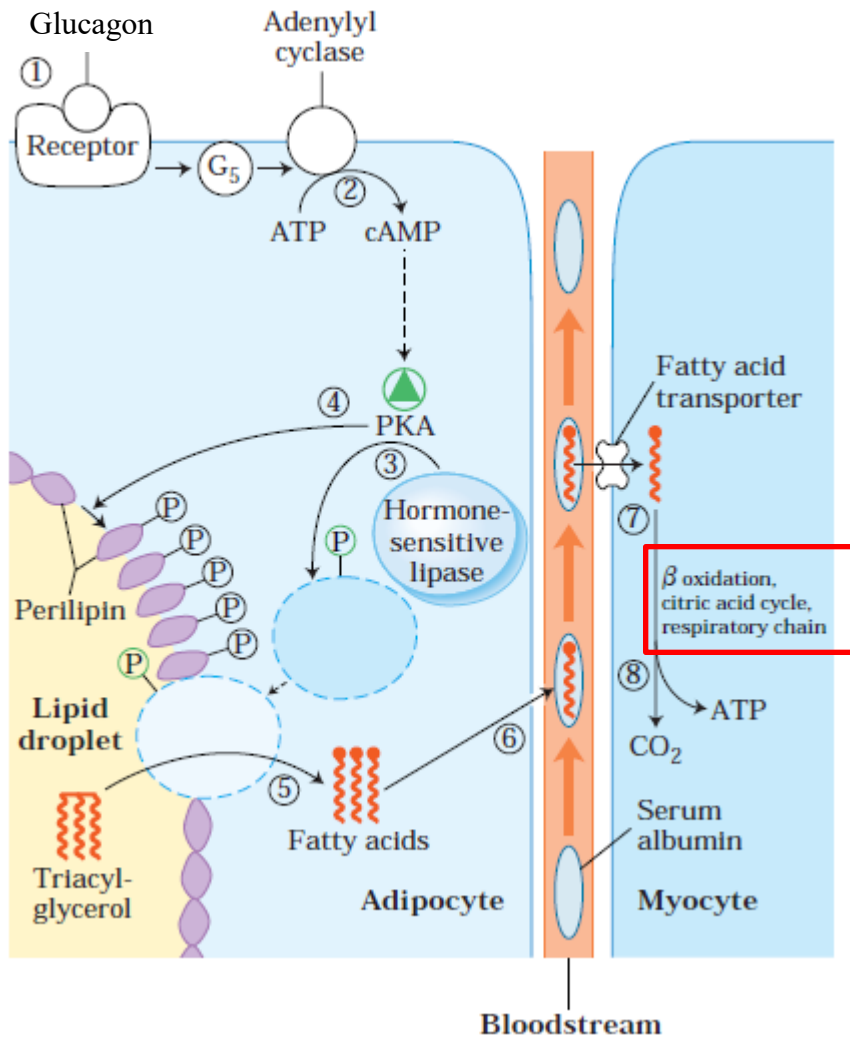
G Protein–Coupled Receptors and Second Messengers





About 95% of the biologically available energy of triacylglycerols resides in their three long-chain fatty acids; only 5% is contributed by the glycerol moiety. The glycerol released by lipase action is phosphorylated by glycerol kinase, and the resulting glycerol 3-phosphate is oxidized to dihydroxyacetone phosphate. The glycolytic enzyme triose phosphate isomerase converts this compound to glyceraldehyde 3-phosphate, which is oxidized via glycolysis.





6 Fatty acids leave the adipocyte, bind serum albumin in the blood, and are carried in the blood; they are released from the albumin and 7 enter a myocyte via a specific fatty acid transporter. 8 In the myocyte, fatty acids are oxidized to CO₂, and the energy of oxidation is conserved in ATP, which fuels muscle contraction and other energy requiring metabolism in the myocyte.

