Chapter 9: Lipids

Definition: those molecules which can be extracted from biological tissue with a nonpolar solvent

- Lipids are essential components of all living organisms
- Lipids are water insoluble organic compounds
- They are hydrophobic (nonpolar) or amphipathic (containing both nonpolar and polar regions)

Fatty Acids

- Fatty acids are carboxylic acids with a long hydrocarbon chain
- Fatty acids (FA) differ from one another in:
  1. Length of the hydrocarbon tails
  2. Degree of unsaturation (double bond)
  3. Position of the double bonds in the chain

Nomenclature of fatty acids

- Most fatty acids have 12 to 20 carbons
- Most chains have an even number of carbons (synthesized from two-carbon units)
- IUPAC nomenclature: carboxyl carbon is C-1
- Common nomenclature: α, β, γ, δ, ε etc. from C-1
- Carbon farthest from carboxyl is ω
Saturated Fatty Acids contain NO double bonds

Unsaturated Fatty Acids contain at least one double bond

All double bonds in naturally occurring unsaturated fatty acids are in the cis conformation

Table 9.1

<table>
<thead>
<tr>
<th>Number of</th>
<th>Number of double bonds</th>
<th>Common name</th>
<th>IUPAC name</th>
<th>Melting point, °C</th>
<th>Molecular formula</th>
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<tbody>
<tr>
<td>12</td>
<td>0</td>
<td>Lactic acid</td>
<td>12 CH₃(CH₂)₁₀CO₂H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>Myristic acid</td>
<td>14 CH₃(CH₂)₁₂CO₂H</td>
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<td></td>
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<tr>
<td>16</td>
<td>0</td>
<td>Palmitic acid</td>
<td>16 CH₃(CH₂)₁₄CO₂H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>Stearic acid</td>
<td>18 CH₃(CH₂)₁₆CO₂H</td>
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<td></td>
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<tr>
<td>20</td>
<td>0</td>
<td>Arachidic acid</td>
<td>20 CH₃(CH₂)₁₈CO₂H</td>
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<td></td>
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<tr>
<td>22</td>
<td>0</td>
<td>Behenic acid</td>
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<td></td>
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<tr>
<td>24</td>
<td>0</td>
<td>Lignoceric acid</td>
<td>24 CH₃(CH₂)₂₂CO₂H</td>
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<td></td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>Palmitoleic acid</td>
<td>cis-Δ⁹(10)lauric</td>
<td>-0.5</td>
<td>C₁₆H₃₁O₂(C=O)</td>
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<tr>
<td>18</td>
<td>1</td>
<td>Oleic acid</td>
<td>cis-Δ⁹(10)palmitic</td>
<td>0</td>
<td>C₁₈H₃₃O₂(C=O)</td>
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<tr>
<td>18</td>
<td>2</td>
<td>Linoleic acid</td>
<td>cis,cis-Δ⁹,₁₂(13)linoleic</td>
<td>-9</td>
<td>C₁₈H₃₄O₂(C=O)</td>
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<td>18</td>
<td>3</td>
<td>Linolenic acid</td>
<td>cis,cis,trans-Δ⁹,₁₂,₁₅linolenic</td>
<td>-17</td>
<td>C₁₈H₃₅O₂(C=O)</td>
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<tr>
<td>20</td>
<td>4</td>
<td>Arachidonic acid</td>
<td>cis,cis,trans-Δ⁹,₁₂,₁₄,₁₇arachidonic</td>
<td>-49</td>
<td>C₂₀H₃₇O₂(C=O)</td>
</tr>
</tbody>
</table>

Structure and nomenclature of fatty acids

- **Saturated FA** - no C-C double bonds
- **Unsaturated FA** - at least one C-C double bond
- **Monounsaturated FA** - only one C-C double bond
- **Polyunsaturated FA** - two or more C-C double bonds
Double bonds in fatty acids

- Double bonds are generally cis
- Position of double bonds indicated by \( \Delta^n \), where \( n \) indicates lower numbered carbon of each pair
- Shorthand notation example: 20:4\( \Delta^5,8,11,14 \)

(total # carbons : # double bonds, \( \Delta \) double bond positions)

Structure and nomenclature of fatty acids

Structures of three C\(_{18}\) FA (next slide)

(a) Stearate (octadecanoate), saturated FA
(b) Oleate (cis-\( \Delta^9 \)-octadecenoate), a monounsaturated FA
(c) Linolenate (all-cis-\( \Delta^9,12,15 \)-octadecatrienoate, a polyunsaturated FA

- The cis double bonds produce kinks in the tails of unsaturated FA
Triacylglycerols

- Fatty acids are important metabolic fuels (2-3 times the energy of proteins or carbohydrates)
- Fatty acids are stored as neutral lipids called triacylglycerols (TGs)
- TGs are composed of 3 fatty acyl residues esterified to a glycerol (3-carbon sugar alcohol)
- TGs are very hydrophobic, and are stored in cells in an anhydrous form (e.g. in fat droplets)

Structure of a Triacylglycerol (Triglyceride)

- Physical properties depend on number of carbons and the number of double bonds
  - #C increases; melting point increases
  - #double bonds increase, melting point decreases

Phosphoglyceride (a type of phospholipid)

- The most abundant lipids in membranes
- Possess a glycerol backbone
- A phosphate is esterified to both glycerol and another compound bearing an -OH group
- Phosphatidates are glycerophospholipids with two fatty acid groups esterified to C-1 and C-2 of glycerol 3-phosphate

Primary energy storage for animals: Get 2 times metabolic energy per gram of fat as compared to per gram of carbohydrate

Form micelles in aqueous solution
Notice: These are all amphiphilic

If the alcohol is choline, the phosphoglyceride is called phosphatidylcholine or lecithins.

If the alcohol is not choline but some other alcohol such as ethanolamine and serine, the phosphoglyceride is called cephalins.

Sphingolipids
Structures based on an amino alcohol called sphingosine

Sphingosine
CH₃(CH₂)₄CH=CH–CH–OH
CH=NH₂
CH₂–OH

Ceramide
CH₃(CH₂)₄CH=CH–CH–OH
CH=NH₂
CH₂–OH
Fatty acid attached to sphingosine by an amide bond
Ceramide + phosphocholine (or phosphoethanolamine) → Sphingomyelin (phospholipid)

Waxes
- **Waxes** are nonpolar esters of long-chain fatty acids and long chain monohydroxylic alcohols
- Waxes are very water insoluble and high melting
- They are widely distributed in nature as protective waterproof coatings on leaves, fruits, animal skin, fur, feathers and exoskeletons

Ceramide + one or more monosaccharide → Cerebroside

(in this case the monosaccharide is B-D-galactose)
Waxes

Waxes are the ester of a fatty acid and a long chain alcohol

Steroids

- Classified as isoprenoids - related to 5-carbon isoprene (found in membranes of eukaryotes)
- Steroids contain four fused ring systems: 3-six carbon rings (A,B,C) and a 5-carbon D ring
- Ring system is nearly planar
- Substituents point either down (α) or up (β)

Polymers of Isoprene are the Building Blocks of Steroids

Isoprene (2-methyl-1,3-butadiene)

*Head to Tail* monoterpane

"Tail to Tail" monoterpane

Structures of several steroids
Cholesterol

- Cholesterol modulates the fluidity of mammalian cell membranes
- It is also a precursor of the steroid hormones and bile salts
- It is a sterol (has hydroxyl group at C-3)
- The fused ring system makes cholesterol less flexible than most other lipids

Cholesterol esters

- Cholesterol is converted to cholesteryl esters for cell storage or transport in blood
- Fatty acid is esterified to C-3 OH of cholesterol
- Cholesterol esters are very water insoluble and must be complexed with phospholipids or amphipathic proteins for transport
Eicosanoids

- **Eicosanoids** are oxygenated derivatives of C_{20} polyunsaturated fatty acids (e.g. arachidonic acid)
- **Prostaglandins** - eicosanoids having a cyclopentane ring
- **Aspirin** alleviates pain, fever, and inflammation by inhibiting the synthesis of prostaglandins

Roles of eicosanoids

- Prostaglandin E\textsubscript{2} - can cause constriction of blood vessels
- Thromboxane A\textsubscript{2} - involved in blood clot formation
- Leukotriene D\textsubscript{4} - mediator of smooth-muscle contraction and bronchial constriction seen in asthmatics

Arachidonic acid and three eicosanoids derived from it

- [a] Arachidonic acid
- [b] Prostaglandin E\textsubscript{2}
We study Lipids to Understand Biological Membranes

Biological Membranes are composed of:
- 43% lipid
- 49% protein
- 8% carbohydrate

In a Rat Membrane the lipid fraction is:
- 24% cholesterol
- 31% phosphatidylcholine
- 8.5% sphingomyelin
- 15% phosphatidylethanolamine
- 2.2% phosphatidylinositol
- 7% phosphatidylserine
- 0.1% phosphatidic acid
- 3% glycolipid

If you study these lipids you find that most of them are amphiphilic.

Amphiphilic molecules can form organized structures in aqueous solution

Example: liposome

Biological Membranes Are Composed of Lipid Bilayers and Proteins

- **Biological membranes** define the external boundaries of cells and separate cellular compartments
- A biological membrane consists of proteins embedded in or associated with a lipid bilayer
Several important functions of membranes

- Some membranes contain protein pumps for ions or small molecules
- Some membranes generate proton gradients for ATP production
- Membrane receptors respond to extracellular signals and communicate them to the cell interior

Lipid Bilayers

- Lipid bilayers are the structural basis for all biological membranes
- Noncovalent interactions among lipid molecules make them flexible and self-sealing
- Polar head groups contact aqueous medium
- Nonpolar tails point toward the interior

Membrane lipid and bilayer

Fluid Mosaic Model of Biological Membranes

- Fluid mosaic model - membrane proteins and lipids can rapidly diffuse laterally or rotate within the bilayer (proteins “float” in a lipid-bilayer sea)
- Membranes: ~25-50% lipid and 50-75% proteins
- Lipids include phospholipids, glycosphingolipids, cholesterol (in some eukaryotes)
- Compositions of biological membranes vary considerably among species and cell types
Structure of a typical eukaryotic plasma membrane

Lipid Bilayers and Membranes Are Dynamic Structures

(a) Lateral diffusion is very rapid (b) Transverse diffusion (flip-flop) is very slow

Phase transition of a lipid bilayer

• Fluid properties of bilayers depend upon the flexibility of their fatty acid chains

• Diffusion of membrane proteins
Effect of bilayer composition on phase transition

- Pure phospholipid bilayer (red) has a sharp phase transition
- Mixed lipid (blue) bilayer undergoes a broader phase transition

A pure phospholipid bilayer is essentially either gel or liquid crystal. However, the addition of cholesterol components makes possible a broader range of characteristics over a broader range of temperatures. The addition of proteins blurs the distinction further. Note that at 37 degrees, both bilayers shown would be 100% disordered liquid crystal at normal body temperature.

Three Classes of Membrane Proteins (classified by how they are extracted)

1. **Integral protein** extract with detergents
2. **Peripheral** extract with high salt, urea, EDTA
3. **Lipid anchored** covalently attached to lipids

Integral Proteins

(1) **Integral membrane proteins** (or intrinsic proteins or trans-membrane proteins)
- Contain hydrophobic regions embedded in the hydrophobic lipid bilayer
- Usually span the bilayer completely
- Bacteriorhodopsin has seven membrane-spanning α-helices

Factors that Affect $T_m$

1. Number of carbons and number of double bonds in hydrocarbon chain
2. Polar head groups
3. Calcium and magnesium ions
4. Cholesterol
Peripheral membrane proteins

- Associated with membrane through charge-charge or hydrogen bonding interactions to integral proteins or membrane lipids
- More readily dissociated from membranes than covalently bound proteins
- Change in pH or ionic strength often releases these proteins
Lipid-anchored membrane proteins

• Tethered to membrane through a covalent bond to a lipid anchor as:

1) Protein amino acid side chain ester or amide link to fatty acyl group (e.g. myristate, palmitate)
2) Protein cysteine sulfur atom covalently linked to an isoprenoid chain (prenylated proteins)
3) Protein anchored to glycosylphosphatidylinositol

Thioester-linked Fatty Acid Acyl Anchors.

Myristate (14 carbons), palmitate (16 carbons), stearate (18 carbons) and oleate (18 carbons, unsaturated) can be thioester linked to cysteine residues in proteins.
Thioether-linked Prenyl Anchors

The cysteine to be modified is part of a carboxyl terminal recognition sequence of Cys-Ala-Ala-X. After attachment, a specific protease removes the AAX sequence to leave the carboxyl terminal cysteine with the polypropenyl ether linkage.

Anchoring may be switch on or off.

Glycosyl phosphatidylinositol anchors (GPI anchors)

They modify the carboxyl terminal amino acid of a protein with an ethanolamine group linked to an oligosaccharide. The oligosaccharide is linked to the inositol group of a phosphatidylinositol. The oligosaccharide comprises a tetrasaccharide core (3 mannose, 1 glucosamine). Various derivatives of this basic organization are found. GPI anchors are unique to animals.

Lipid-anchored membrane proteins

Carbohydrates are often attached to membrane proteins

Two things to consider:
How is the sugar attached?
What are the carbohydrate structures?
O-Linked versus N-Linked

http://biology.kenyon.edu/HHMI/Biol113/passive_vs_active.htm