BCMB 3100 – Lipids
(Text Chapters 11, 12, 13)

- Definition
- Major classes
- Fatty acids
- Triacylglycerol
- Glycerophospholipids
- Sphingolipids
- Cholesterol

Lipids are hydrophobic or amphipathic

In BCMB3100 we will emphasize
* phospholipids
* glycolipids
* cholesterol (steroid)

_________: main lipids in most biological membranes
_________: 2nd most abundant lipid in membranes (abundant in CNS) from animals and plants

_________: water insoluble organic compounds in living organisms

Structural relationships of major lipid classes

Structure and nomenclature of fatty acids
### Table 11.1: Some common fatty acids (anionic forms)

<table>
<thead>
<tr>
<th>Number of carbons</th>
<th>Number of double bonds</th>
<th>Common name</th>
<th>IUPAC name</th>
<th>Melting point, °C</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0</td>
<td>Lauric</td>
<td>Methyl palmitate (CH₃CH₂CH₂COO⁻)</td>
<td>87</td>
<td>CH₃(CH₂)₁₀COO⁻</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>Myristic</td>
<td>Myristoleic acid (CH₃(CH₂)₁₃COO⁻)</td>
<td>53</td>
<td>CH₃(CH₂)₁₃COO⁻</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>Palmitic</td>
<td>Palmitoleic acid (CH₃(CH₂)₁₅COO⁻)</td>
<td>47</td>
<td>CH₃(CH₂)₁₅COO⁻</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>Stearic</td>
<td>Stearoleic acid (CH₃(CH₂)₁₇COO⁻)</td>
<td>64</td>
<td>CH₃(CH₂)₁₇COO⁻</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>Oleic</td>
<td>Oleoleic acid (CH₃(CH₂)₁₈COO⁻)</td>
<td>81</td>
<td>CH₃(CH₂)₁₈COO⁻</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>Linoleic</td>
<td>Linoleoleic acid (CH₃(CH₂)₂₀COO⁻)</td>
<td>47</td>
<td>CH₃(CH₂)₂₀COO⁻</td>
</tr>
</tbody>
</table>

* Common name: 18:0 stearate Octadecanoate
  18:1 oleate cis-Δ⁹-Octadecenoate
  18:2 linoleate cis,cis-Δ⁹,12-Octadecadienoate

You must be able to draw the structure of those marked *

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### Diagrams

- **Saturated FA**: no C-C double bonds
- **Unsaturated FA**: at least one C-C double bond

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**Fig. 11.1, Page 191**

- Palmitate (ionized form of palmitic acid)
- Oleate (ionized form of oleic acid)

**Pg. 210**

- Stearate
- Trans-Oleate
- cis-Oleate
Structural relationships of major lipid classes

Structure of a triacylglycerol
(a) Glycerol backbone
(b) Triacylglycerol

are a neutral storage form of fatty acids

See Pg. 211

An EXAMPLE

A triglyceride molecule. Left: glycerol; right (top to bottom): palmitic acid, oleic acid, alpha-linolenic acid

Note: the types of fatty acyl groups present in any given triacylglycerol may vary.

Figure 1  Adipose tissue fatty acid composition in 4258 and 3096 healthy men and women from 19 studies. Data are shown for individual studies (panels A–L) and collated values are shown in the histogram (panel M). Data are expressed as mean (mol%) and error bars represent SD.  

Leanne Hodson, C. Murray Skeaff, Barbara A. Fielding  
Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake  
Progress in Lipid Research Volume 47, Issue 5 2008 348 - 380 
http://dx.doi.org/10.1016/j.plipres.2008.03.003
**MEMBRANE LIPIDS:** 3 major types = phospholipids, glycolipids, & cholesterol

- Most abundant class of lipids in membranes (note: triacylglycerols most abundant on mass basis in mammals); derived from glycerol or sphingosine

* Lipids from glycerol = phosphoglycerides (also called glycerophospholipids)
* Phosphoglycerides consist of glycerol backbone, two fatty acids & a phosphorylated alcohol

See Fig. 11.5

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**Fatty acids in biological organisms**

Fatty acid chains (long aliphatic tails) in phospholipids & glycolipids contain even # of carbons (12-20) with 16 and 18 being most common

Fatty acids can be ____________ or ______________

Under physiological conditions fatty acids are ionized (pKa 4.5-5.0)

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**Structural relationships of major lipid classes**

(a) Glycerol 3-P and (b) phosphatidate

See Fig. 11.6
Three Common Glycerophospholipids in Biological Membranes

Three Common Glycerophospholipids in Biological Membranes

Phospholipases hydrolyze phospholipids

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Structural relationships of major lipid classes

(a) ___________: structural backbone of sphingolipids

(b) ___________: sphingosine + fatty acid at C2

See Fig. 11.8
(c) Sphingomyelin: present in plasma membrane & myelin sheath around neurons

Example of a Cerebroside: abundant in nerves
Sugar-Sphingosine
Fatty acid

Cerebrosides are found in the nervous system, including in the myelin sheath.

Structural relationships of major lipid classes
Structure of the steroid **cholesterol**.

Steroids are polyprenyl compounds

In eukaryotes but NOT in most prokaryotes

Other steroids: steroid hormones (estradiol, testosterone, corticosteroids), bile salts, sterols in plants, yeast, fungi

- Cholesterol modulates the fluidity of mammalian cell membranes
- It is also a precursor of the steroid hormones and bile salts

**Waxes**: esters of long-chain monohydroxylic alcohols and long-chain fatty acids (nonpolar)

Waxes are very water **insoluble** and **high melting point**

They are widely distributed in nature as protective waterproof coatings on leaves, fruits, animal skin, fur, feathers and exoskeletons

**Myricyl palmitate**, a wax

\[
\text{H}_3\text{C} - (\text{CH}_2)_{14} - \text{C} - \text{O} - (\text{CH}_2)_{29} - \text{CH}_3
\]
**Eicosanoids**: oxygenated derivatives of C20 polyunsaturated fatty acids (e.g. arachidonic acid)

- **Arachidonic acid**
- **Prostaglandin E₂**
- **Thromboxane A₂**
- **Leukotriene B₄**

- Can cause constriction of blood vessels (aspirin inhibits prostaglandin synthesis)
- Involved in blood clot formation
- Mediator of smooth-muscle contraction and bronchial constriction seen in asthmatics

Some vitamins are **Lipid Vitamins**

- Four lipid vitamins: A, D, E, K
- (All contain rings and long, aliphatic side chains
- All are highly hydrophobic
- The lipid vitamins differ widely in their functions

**Examples of isoprenoids**

See Fig. 15.19 for structures

**Fig. 15.19**

- **Vitamin C (Ascorbate)**
  - Roles in vision, growth, reproduction

- **Vitamin D₂ (Ergocalciferol)**
  - Antioxidant, regulation of calcium and phosphate metabolism

- **Vitamin D₃ (Cholecalciferol)**

**BCMB 3100 - Lipids**

- Biological Membranes
- Micelles
- Lipid Bilayer
- Peripheral membrane proteins
- Integral membrane proteins
- Lipid-anchored
- Transport across membranes
- Signal Transduction
Structure of a typical eukaryotic plasma membrane

- Highly selective permeability barriers that surround cells & cellular compartments
- Sheetlike structures of ~60-100 Å
- Consists mostly of lipids & proteins in ratio of 1:4 to 4:1 (typical 40% lipid; 60% protein). Lipids & proteins may be glycosylated.
- Lipids in biological membranes are 
  - hydrophilic (polar) head group & hydrophobic tail.
  - Spontaneously form bilayers in aqueous solution.

Lipids in biological membranes include phospholipids, sphingolipids, cholesterol (in some eukaryotes)
Amphipathic nature of cerebrosides:

Amphipathic lipids can take two different forms in aqueous media: _________ or ______________

__________ : a globular structure in which polar head groups are on the surface and hydrocarbon tails are on the inside

Salts of fatty acids tend to form micelles. Micelles usually are < 200 µm in diameter.

See Fig. 14.9 for an example
**Structure and nomenclature of fatty acids**

- Favored structure for phospholipids & sphingolipids since lipids with two fatty acyl chains are too large to fit into the center of a micelle. Bilayers can have large dimensions ($10^7\ \text{Å}$, 1 mm) (recall diameter = ~60-100Å).

Lipid bilayers self-assemble due to hydrophobic interactions between hydrocarbon tails (main force), van der Waals attractive forces between hydrocarbon tails, & electrostatic & H-bonding forces between polar head groups and water. Biolayers are extensive, closed, and self-sealing.

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**A liposome** Fig. 12.2

**Preparation of liposomes** Fig. 12.3
Lipid bilayers are permeability barriers to ions & polar molecules

Lipid vesicles (liposomes): aqueous compartments enclosed by lipid bilayers. Small vesicles (~ 500 Å), large vesicles (~10^4 Å, 1 µm)

Use lipid vesicles to measure membrane permeability
1. Form vesicles in solution containing A
2. Separate vesicles from free A
3. Measure flux of A out of vesicles

Fig. 12.2

Results
Permeability coefficient (cm/s)
Na⁺ 10⁻¹²; Trp 10⁻⁷; indole ~5x10⁻⁴; water ~5x10⁻³

Water & hydrophobic molecules readily traverse membranes while ions & most polar molecules do not

Fig. 12.4

Lipid Bilayers and Membranes
Are Dynamic Structures
(a) Lateral diffusion is very rapid
(b) Transverse diffusion (flip-flop) is very slow

Very, Very slow if at all

See Fig. 12.15

Experiment showing that lateral diffusion occurs in biological membranes via use of heterokaryons
(Frye & Edidin)
- Diffusion of membrane proteins
Fluorescence recovery after photobleaching (FRAP)
evidence for fluid membrane. Fig. 12.14

From such data rate is determined as diffusion coefficient

Biological Membranes (cont.)
• Contain ______ both embedded in the bilayer & on its surface. ______ may function as pumps, gates, receptors, energy transducers & enzymes.
• Held together by noncovalent interactions
• Asymmetric: the two surfaces (faces) differ in properties
• Two dimensional fluids - lipids & proteins rapidly diffuse in plane of membrane but NOT across membrane
  • ______ - membrane proteins and lipids can rapidly diffuse laterally or rotate within the bilayer (Singer & Nicolson, 1972)
• Compositions of biological membranes vary considerably among species and cell types

Freeze-fracture electron microscopy, shows the distribution of membrane proteins

1. Quick freeze liquid N
2. Fracture
3. Remove ice by vacuum
4. Layer thin layer C
5. Shadow with platinum vapor
6. Digest away organic matter
7. TEM of carbon-metal replica

TEM: Transmission electron microscopy

http://www.udel.edu/biology/Wags/histopage/empage/ecu/ecu14.gif
Transition from rigid to partly fluid state occurs at $T_M$, the____________________.
$T_M$ depends on_______ of fatty acyl chains & on degree of___________.
Rigid state favored by saturated fatty acyl chains
Disordered state favored by cis double bound(s) (i.e. $T_M$ is lowered)
Prokaryotes regulate membrane fluidity by varying # of double bonds & length of fatty acyl chains. As temperature changes from 42°C to 27°C ratio of saturated:unsaturated changes from 1.6 to 1.

*Packing of fatty acid chains in membrane is disrupted by double bounds and lowers Tm.
*Increasing the percentage of fatty acids with double bounds lowers Tm.
Effect of cholesterol on phase transition ($T_{m}$) of membranes

In eukaryotes, membrane fluidity is largely regulated by _______. Cholesterol moderates the fluidity of membranes (prevents tight packing of fatty acyl chains & blocks large motions)

Addition of 20 mol% cholesterol broadens phase transition

![Graph showing phase transition of membranes](image1)

Cholesterol modulates fluidity of the membranes. Also, association with sphingolipids leads to cholesterol-rich regions called lipid rafts that may effect specific membrane-protein function.

![Diagram of lipid raft](image2)

Structure of a typical eukaryotic plasma membrane

![Diagram of plasma membrane](image3)
Three types membrane associated proteins

- **Loosely bound to membrane**: loosely bound to membrane by H-bonds or electrostatic forces, generally water soluble once released from membrane using high salt or pH. Often bound to integral membrane proteins.

- **Firmly bound to membrane**: proteins firmly bound to membrane by hydrophobic interactions. Solubilized with detergents. Most have one or more membrane spanning domains (e.g., α-helix with ~20 amino acids).

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**Fig. 12.8**

**Stereo view of bacteriorhodopsin: an integral membrane protein**

- **Light-driven proton pump**
- [member of 7TM receptor family of proteins]

See Fig. 12.9

**Fig. 12.10**

**Bacterial porin**

- **Molecular filters for hydrophilic compounds**
- [family of proteins from the outer membrane of Gram-negative bacteria]
Lipid-anchored membrane proteins: proteins covalently linked to lipid membrane

Types of links:

* **direct amide or ester bond** between amino acid and fatty acyl group such as myristate or palmitate

* **prenylation**: link to an isoprenoid chain (e.g. farnesyl or geranylgeranyl) via the S of a Cys near the C terminus of the protein

* **glycosylphosphatidylinositol anchor**: C-terminal ω-carboxyl of protein-phosphoethanolamine-glycan-phosphatidylinositol

(continued)

**Characteristics of membrane transport**

Small uncharged and hydrophobic molecules can diffuse across membranes. Other molecules require protein assisted movement.

<table>
<thead>
<tr>
<th>Protein carrier</th>
<th>Saturable with substrate</th>
<th>Movement relative to concentration gradient</th>
<th>Energy input required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple diffusion</td>
<td>No</td>
<td>Down</td>
<td>No</td>
</tr>
<tr>
<td>Channels and pores</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Passive transport</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Active transport</td>
<td><strong>pumps</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (direct)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (ion gradients)</td>
</tr>
</tbody>
</table>

**TABLE 9.3 Characteristics of different types of membrane transport**
Membrane transport through a pore or channel

Central passage through water-filled pore allows specific molecules to transverse the membrane (e.g. porin in mitochondria outer membrane)

There are many types of channels; ion channels can transport ions much faster than pumps

[e.g. Transient receptor potential channels]

Examples: voltage-gated channels, ligand-gated channels, transient receptor potential channels

Active & passive transporters undergo a conformational change to drive transport

Active transporters move molecules against a concentration gradient:

1° transporters use 1° energy source (e.g. light, ATP, electron transport)

2° transporters driven by ion gradient
Active transporters move molecules against a concentration gradient: 1º transporters use 1º energy source (e.g. light, ATP, electron transport); 2º transporters driven by ion gradient.

Primary active transporter: Na⁺–K⁺ ATPase
Secondary active transporter: glucose transporter

Active transport in *E. coli*

- Oxidation of $S_{\text{red}}$ generates a transmembrane proton gradient
- Movement of $H^+$ down its gradient drives lactose transport (lactose permease)

Potassium ion channel (1) Fig. 12.22
Potassium ion channel (2) Fig. 12.23

Selectivity filter of $K^+$ ion channel
**Potassium ion channel (3) Fig. 12.24**
Energetic basis of ion selectivity in K+ ion channel.

**Potassium ion channel (4) Fig. 12.24**
Energetic basis of ion selectivity in K+ ion channel.

**Potassium ion channel (5) Fig. 12.25**
Rapid rate of K+ movement due to structure of channel and electrostatic repulsion of incoming K+

Molecules and complexes that are too large to be transported via transport proteins are transported in lipid vesicles out of the cell via exocytosis, and into the cell via endocytosis. We will not cover these processes in this course.
Signal transduction through a membrane

Three general classes of membrane receptor proteins:
• Seven-transmembrane-helix receptors
• Dimeric receptors that recruit protein kinases
• Dimeric receptors that are protein kinases

General mechanism of signal transduction across a membrane

Common secondary messengers Fig. 13.2

- detect
- amplify

To generate response
e.g. changes in gene expression, enzyme activity, ion channel, etc.
• G proteins are activated by binding to a receptor-ligand complex
• G-proteins are inactivated slowly by their own GTPase activity (kcat about 3/min)

Three general classes of membrane receptor proteins:

Seven-transmembrane-helix receptors (7TM)

Dimeric receptors that recruit protein kinases
Dimeric receptors that are protein kinases

All 7TM appear to be G-protein-coupled receptors (GPCRs)
• Summary of the adenyl cyclase signaling pathway

Example of seven-transmembrane-helix (7TM) receptor

See Fig. 13.6, 13.7; 13.8

Production, inactivation of cAMP

• Activation of protein kinase A by cAMP

See Fig. 13.7
Caffeine & theophylline inhibit cAMP phosphodiesterase

- Inhibition of cAMP phosphodiesterases prolongs the effects of cAMP
- This increases the intensity and duration of stimulatory hormones

![Caffeine and Theophylline Structures](image)

Inositol-phospholipid signaling pathway

See Fig. 13.11, 13.12

Phospholipases hydrolyze phospholipids

Lipases: enzymes that catalyze hydrolysis of triacylglycerols

Phospholipases: catalyze hydrolysis of glycerophospholipids

Phosphatidylinositol 4,5-bisphosphate (PIP$_2$) produces IP$_3$ and diacylglycerol

See Fig. 13.11
Activation of receptor tyrosine kinases by ligand-induced dimerization

Three general classes of membrane receptor proteins:
- Seven-transmembrane-helix receptors
- Dimeric receptors that recruit protein kinases
- *Dimeric receptors that are protein kinases

See Fig. 13.15

• Phosphorylated dimer phosphorylates cellular target proteins

• Each domain catalyzes phosphorylation of its partner
Insulin receptor and tyrosine kinase activity

• Insulin binds to 2 extracellular α-chains
• Transmembrane β-chains then autophosphorylate
• Tyrosine kinase domains then phosphorylate insulin-receptor substrates (IRSs) (which are proteins)

Insulin-stimulated formation of PIP₃

Insulin receptor (protein tyrosine kinase)

+ PIP₃ → Protein kinases

See Figs. 13.17 - 13.20

Phosphatidyl-inositol 3,4,5-trisphosphate

A different type of tyrosine kinase signal transduction:
Growth hormone receptor for which binding brings together associated proteins with tyrosine kinase domains

Three general classes of membrane receptor proteins:
- Seven-transmembrane-helix receptors
- *Dimeric receptors that recruit protein kinases
- Dimeric receptors that are protein kinases

Cross-phosphorylation of two JAK2 induced by hormone receptor dimerization

JAK2: Janus kinase 2

Fig. 13.13

Fig. 13.14
**Small G proteins (small GTPases)**

are a large superfamily of signalling proteins

They include: Ras, Rho, Aft, Rab, and Ran

**Small GTPases** cycle between an active GTP-bound form and an inactive GDP-bound form

**Small GTPases** are smaller (20-25kd) and monomer compared to the larger (30-35 kd) and trimeric G proteins

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### 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

<table>
<thead>
<tr>
<th>common name</th>
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<tbody>
<tr>
<td>18:0 stearate</td>
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</tr>
<tr>
<td>18:1 oleate</td>
<td>cis-Δ9-Octadecenoate</td>
</tr>
<tr>
<td>18:2 linoleate</td>
<td>cis,cis-Δ9,12-Octadecadienoate</td>
</tr>
</tbody>
</table>

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Another method to measure membrane permeability

Mueller & Rudin: dip paint brush into lipid membrane solution & paint across 1 mm diameter hole partitioned between two aqueous media. → macroscopic bilayer membrane

Measure electrical conductance from one media to the other

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Extra material