Structure of Lipids
9.1 Structural Diversity of Lipids
9.2 Fatty Acids
9.3 Triglycerides
9.4 Glycerophospholipids
9.5 Sphingolipids
9.6 Steroids

Biological Membranes
9.8 Biological Membranes
9.9 Membranes are Dynamic Structures
9.10 Three Classes of Membrane Proteins
9.11 Membrane Transport
9.12 Transduction of Signals
Chapter 9 - Lipids and Membranes

Lipids are water insoluble organic compounds with diverse chemical structures and properties.

Classified by Composition (nonpolar: polar):

1. **Fatty acids** - R-COOH (R=hydrocarbon)
   - triacylglycerols
   - waxes
   - phospholipids
   - sphingolipids
   - eiconsanoids (C-20)

2. **Isoprenoids** - (C-5 isoprene)
   - steroids
   - lipid vitamins
   - terpenes

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**Structural relationships of major lipid classes**

![Diagram of lipid classes]

Figure 9-1: Principles of Biochemistry, 4/e © 2006 Pearson Prentice Hall, Inc. Prentice Hall c2002
9.2 Fatty Acids (Nomenclature)

Carboxyl carbon is C-1
(12 to 20 carbons)

Common nomenclature:
??????? etc. from C-1
and Carbon farthest
from carboxyl is ?

Double bonds are cis

Shorthand notation: 20:4? 5,8,11,14
(total # carbons : # double
bonds, ? double bond positions)

Names, Structures and Properties of Common Fatty Acids

<table>
<thead>
<tr>
<th>Number of</th>
<th>Number of</th>
<th>Common</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>Laurate</td>
<td>Dodecanoate</td>
<td>44</td>
<td>CH_{3}(CH_{2})_{11}COO^{-}</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>Myristate</td>
<td>Tetradecanoate</td>
<td>52</td>
<td>CH_{3}(CH_{2})_{13}COO^{-}</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>Palmitate</td>
<td>Hexadecanoate</td>
<td>63</td>
<td>CH_{3}(CH_{2})_{15}COO^{-}</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>Stearate</td>
<td>Octadecanoate</td>
<td>70</td>
<td>CH_{3}(CH_{2})_{17}COO^{-}</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>Arachidate</td>
<td>Eicosanoate</td>
<td>75</td>
<td>CH_{3}(CH_{2})_{19}COO^{-}</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>Behenate</td>
<td>Docosanoate</td>
<td>81</td>
<td>CH_{3}(CH_{2})_{21}COO^{-}</td>
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<tr>
<td>24</td>
<td>0</td>
<td>Lignocerone</td>
<td>Tetraicosanoate</td>
<td>84</td>
<td>CH_{3}(CH_{2})_{23}COO^{-}</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Palmitoleate</td>
<td>cis-Δ^5-Hexadecanoic acid</td>
<td>-0.5</td>
<td>CH_{3}CH(=CH=CHCH_{2})_{2}COO^{-}</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>Oleate</td>
<td>cis-Δ^9-Octadecenoic acid</td>
<td>13</td>
<td>CH_{3}CH(=CH=CHCH_{2})_{3}COO^{-}</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>Linoleic acid</td>
<td>cis,cis-Δ^9,12-Octadecenoic acid</td>
<td>-8</td>
<td>CH_{3}CH(=CH=CO(CH_{2})<em>{9}CH</em>{2})COO^{-}</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>Linolenic acid</td>
<td>all-trans-Δ^9,12,15-Octadecenoic acid</td>
<td>-17</td>
<td>CH_{3}CH(=CH=CO(CH_{2})<em>{11}CH</em>{2})COO^{-}</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>Arachidonate</td>
<td>all-trans-Δ^5,8,11,14-Octadecenoic acid</td>
<td>-49</td>
<td>CH_{3}CH(=CH=CO(CH_{2})<em>{13}CH</em>{2})COO^{-}</td>
</tr>
</tbody>
</table>

Common names are from common source
(e.g., Laurate = Laurel plant; Palmitate = Palm oil)
9.3 Triacylglycerols

Fatty acids are metabolic fuels (2-3 times the energy of proteins or sugars)

Triacylglycerols (TGs) store FAs in adipose cells in an anhydrous, neutral form (e.g., in fat droplets)

Lipases are enzymes that cleave TGs to FAs
9.4 Glycerophospholipids

Most abundant membrane lipid

Composition = Glycerol + 2 FAs + Phosphate

Polar alcohol

Phosphatidates are precursors to polar membrane lipids

Diacylglycerols

Amphipathic Lipids with Different Charges

Table 9.2 Some common types of glycerophospholipids

<table>
<thead>
<tr>
<th>Name of resulting phospholipid</th>
<th>Formula of $X$</th>
<th>Formula of $-(CH_2)_n$</th>
<th>Name of resulting glycerophospholipid</th>
</tr>
</thead>
</table>
| Phosphatidylethanolamine       | $X = \text{ethanol} \text{amine}$ | $-(CH_2)_n$ | Ethanolamine phosphatidyl-
| Phosphatidylcholine             | $X = \text{choline}$ | $-(CH_2)_n$ | Choline phosphatidyl-
| Phosphatidylglycerol            | $X = \text{glycerol}$ | $-(CH_2)_n$ | Glycerol phosphatidyl-
| Phosphatidylserine              | $X = \text{serine}$ | $-(CH_2)_n$ | Serine phosphatidyl-
| Phosphatidylcholine             | $X = \text{choline}$ | $-(CH_2)_n$ | Choline phosphatidyl-
| Phosphatidylethanolamine        | $X = \text{ethanol} \text{amine}$ | $-(CH_2)_n$ | Ethanolamine phosphatidyl-

Table 9.2 Principles of Biochemistry 4/e
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Phospholipases hydrolyze phospholipids

Products of Phospholipases

Phosphatidate (Phospholipase D)

Diacylglycerol (Phospholipase C)

Monoacylphospholipids (Phospholipases A1 or A2)

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9.5 Sphingolipids

Sphingolipids (abundant in central nervous system tissues) ↓ sphingosine

Ceramides - fatty acyl group amide linked to C-2 of sphingosine is the building block of this class of lipids
Three Types of Sphingolipids

**Sphingomyelins** - phosphocholine attached to C-1 of ceramide

**Cerebrosides** - monosaccharide attached to C-1 of ceramide

Ganglioside $G_{M2}$
(contain N-acetyl-neuraminic acid - NeuNAc)

**Gangliosides** - oligosaccharide attached to C-1 of ceramide
9.6 Steroids

**Isoprenoids**
- isoprene building block of Terpenes and Steroids

**Steroids** - four fused rings + isoprene tail
Rings are ~ planar down (?) or up (?)

**Cholesterol**
Modulates the fluidity of mammalian cell membranes
The fused ring system makes cholesterol less flexible than most other lipids
Steroid Hormones and Bile Salts

Cholesterol Esters

Cholesterol esters are very water insoluble and must be complexed with phospholipids or amphipathic proteins for transport.
9.7 Other Biologically Important Lipids

**Waxes** are nonpolar esters of long-chain fatty acids and long chain monohydroxylic alcohols (very water insoluble and high melting pt)

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

\[ \text{H}_3\text{C} - (\text{CH}_2)_{14} - \text{O} - (\text{CH}_2)_{29} - \text{CH}_3 \]

---

**Eicosanoids**

**Eicosanoids** ↓ synthesized from arachidonic acid

**Prostaglandins** - C<sub>20</sub> eicosanoids (O-containing cyclopentane ring) ↓ pain, fever, and inflammation

**Aspirin** inhibits the 1<sup>st</sup> step of prostaglandin synthesis (CycloOXgenase-Inhibitors)
Roles of Three Families of Eicosanoids

**Prostaglandin \( E_2 \)** - constriction of blood vessels

**Thromboxane \( A_2 \)** - involved in blood clot formation

**Leukotriene \( D_4 \)** - smooth-muscle contraction and bronchial constriction seen in asthmatics

9.8 Biological Membranes Are Composed of Lipid Bilayers and Proteins

**Biological membranes** define the external boundaries of cells and separate cellular compartments (Lipids; Proteins; Carbohydrates)
A. Lipid Bilayers: Phase transitions

Bilayers adopt ordered gel structures (anti conformations) and disordered structures (anti and gauche). Tm is the temperature of the phase transition (Red w/o; Blue w/ cholesterol).

9.9 Lipid Bilayers and Membranes Are Dynamic Structures
(a) Fast  (b) Slow (flip-flop)

Page 23
Rapid Lateral Diffusion in Cells

Diffusion of membrane proteins occurs within 40 minutes

Several important functions of membranes

Biological Membranes contain a wide variety of **proteins** embedded or associated with the lipid bilayer (~25-50% lipid and 50-75% proteins)

**Ion or Small Molecule Transport**

- **Active** (e.g., proton gradients for ATP synthesis)
- **Passive** (e.g., Glc movement INSIDE liver cell)

**Membrane receptors** respond to extracellular signals (**Hormones**) to communicate/control cell metabolism
B. 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)

Freeze-fracture electron microscopy reveal distribution of membrane proteins

Bumps show location of membrane proteins
9.10 Three Classes of Membrane Proteins

**Integral membrane proteins** – embedded in membrane; detergent needed to extract
(transmembrane – span membrane)

Bacteriorhodopsin
7 spanning α-helices
w/ hydrophobic exterior in contact w/
hydrophobic lipid bilayer ↓ Retinal ↓ PROTON PUMP

Transmembrane Protein Porin (E. Coli)

β-Barrel forms a Channel and allows protein-bound iron to pass thru the membrane
Peripheral membrane proteins

Associated with membrane through charge-charge or hydrogen bonding interactions to integral proteins or membrane lipids

Change in pH or ionic strength often releases these proteins (detergents not required)

Cytochrome C is a Peripheral Membrane Protein

Structure/Stability like other water soluble proteins (e.g., myoglobin)

Lipid-anchored membrane proteins

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

(a) Protein linked to fatty acyl group (e.g. myristate, palmitate)

(b) Protein linked to an isoprenoid chain (prenylated proteins)

(c) Protein linked to glycosyl-phosphatidylinositol
### 9.11 Membrane Transport

#### TABLE 9.3 Characteristics of different types of membrane transport

<table>
<thead>
<tr>
<th>Transport Type</th>
<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>No</td>
<td>Down</td>
<td>No</td>
</tr>
<tr>
<td>Channels and pores</td>
<td>Yes</td>
<td>No</td>
<td>Down</td>
<td>No</td>
</tr>
<tr>
<td>Passive transport</td>
<td>Yes</td>
<td>Yes</td>
<td>Down</td>
<td>No</td>
</tr>
<tr>
<td>Active transport</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Yes</td>
<td>Yes</td>
<td>Up</td>
<td>Yes (direct source)</td>
</tr>
<tr>
<td>Secondary</td>
<td>Yes</td>
<td>Yes</td>
<td>Up</td>
<td>Yes (ion gradient)</td>
</tr>
</tbody>
</table>

(A) Thermodynamics of Membrane Transport

\[ \downarrow G_{rx} = \downarrow G_{rx}^{\circ} + RT \ln Q; \quad Q = \text{Rx Quotient} \]

**Neutral Molecule Transport (e.g., Glc)**

\[ A_{\text{out}} \downarrow A_{\text{in}} \quad \text{Keq} = [A_{\text{in}}]/[A_{\text{out}}] \]

\[ \downarrow G_{rx}^{\circ} = 0 \quad \text{since Keq} = 1 \]

\[ \downarrow G_{\text{trans}} = RT \ln [A_{\text{in}}]/[A_{\text{out}}] \]

If \([A_{\text{out}}] > [A_{\text{in}}]\) \(\downarrow \downarrow G_{\text{trans}} < 0\) (spontaneous)

For \([A_{\text{in}}]/[A_{\text{out}}] = 1:100\) \(\downarrow \downarrow G_{\text{trans}} = -11.4 \text{ kJ/mol}\)

Energy released per mole of A transported into cell
Thermodynamics of Membrane Transport
Charged Molecule (Ion) Transport

Electric potential difference across membrane,
\[ A_{\text{out}} \downarrow A_{\text{in}} \quad \text{Keq} = [A_{\text{in}}]/[A_{\text{out}}] \]
\[ \downarrow \text{?} = \text{?}_{\text{in}} - \text{?}_{\text{out}} \ (V) \]
\[ \downarrow G_{\text{trans}} = zF \downarrow \ ? \quad F = 96.5 \text{ kJ-V}^{-1} \text{ and } z = \text{charge} \]

If \( \downarrow \text{?} < 0 \) (inside neg.) & \( z > 0 \) \( \downarrow \downarrow G < 0 \)
If \( \downarrow \text{?} = -0.1 \text{ V} \) & \( z = +1 \) \( \downarrow \downarrow G = -9.7 \text{ kJ/mol} \)

Transport: Concentration & Potential Gradients
\[ \downarrow G_{\text{trans}} = 2.3RT \log[A_{\text{in}}]/[A_{\text{out}}] + zF \downarrow ? \]

B. Pores and Channels
Pores and Channels are transmembrane proteins with a central passage for ions and small molecules (water-soluble); Switched on-off by small molecules or Voltages

Transport is Selective
(size, charge, structure)
Transport does not require energy (\( \downarrow G < 0 \))
Transport is Rapid
(~diffusion-controlled limit)
Transport is Slow w/o channel
C. Passive Transport

**Passive transport** does not require an energy source and is **saturable** (Protein binds solutes)

\[ S_{in} + T \rightarrow TS \rightarrow S_{out} \]

\[ V_0 = V_{max}\frac{[S]_{out}}{K_{tr} + [S]_{out}} \]

D. Active Transport

**Active transport** requires an **energy source** and is **saturable** (Protein binds solutes)

Free Energy of energy source (\( \uparrow G < 0 \)) needs to exceed free energy (\( \uparrow G > 0 \)) required to move solute across membrane

**Primary active transport** - energy source is ATP, light or electron transport  
**Secondary active transport** – energy source by secondary ion concentration gradient
Antiport and Symport Active Transport

Active transport with two solutes:
- **Antiport** (solutes move in opposite direction)
- **Symport** (solutes move in the same direction)

One transport process must release more energy than the second transport requires.

\[ \downarrow G \ll 0 \quad (\nabla) \]
\[ \downarrow G > 0 \quad (\nabla) \]
\[ |\downarrow G| > |\downarrow G| \]

Primary & Secondary Active Transport

**Primary** - Oxidation of $S_{\text{red}}$ generates a transmembrane proton gradient

**Secondary** - Movement of $H^+$ down its gradient drives lactose transport (lactose permease)

What are $|\downarrow G|$ for these transport processes?
Primary & Secondary Active Transport: Na\(^{+}\)-K\(^{+}\) ATPase

**Primary** – ATP hydrolysis generates a transmembrane sodium/potassium gradient

**Secondary** - Movement of Na\(^{+}\) down its gradient drives glucose transport inside cell

What are the | G |?

---

E. Endocytosis and Exocytosis

- Cells import/export molecules too large to be transported via pores, channels or proteins by:
  - **Endocytosis** - macromolecules are engulfed by plasma membrane and brought into the cell inside a lipid vesicle
  - **Exocytosis** - materials to be excreted from the cell are enclosed in vesicles by the Golgi (vesicles then fuse with plasma membrane)
9.12 Transduction of Extracellular Signals

Hormone Receptor – binds ligand outside (hormones, neurotransmitters, growth factors)

Protein Signal Transducer and Effector Enzyme generate a Second Messenger (inside cell)

A. G Proteins are Signal Transducers

G proteins – GTP-binding proteins that are bound to a membrane and act as Signal Transducers

Chemical Switch to Turn Hormone Signal Off

GTP \not\rightarrow GDP + Pi (GTPase activity)
G-protein Composition and Cycle

3 subunits - ?, ?, and ?

Inactive GDP-bound to resting state w/o Hormone Present

Active $G_\gamma$-GTP complex is formed when Hormone-Receptor Complex occurs $\uparrow$ interacts with the Effector Enzyme

B. The Adenylyl Cyclase Signaling Pathway

Adenylyl Cyclase – effector enzyme which is activated by G-Proteins signal transducers

Synthesize cAMP (cGMP) as a second messenger

[cAMP] Increases when Hormone-Receptor Complex is present and active
Protein Kinase A is Activated by cAMP

Two Forms of Protein Kinase A

- **Inactive**: 2R + 2C subunits
- **Active**: 2 (R-subunit-cAMP) and the 2 C subunits are free active monomers

Protein Kinase A catalytic units - phosphorylate specific sequence in key target enzymes to turn ENZYME ACTIVITY **ON (CATABOLIC)** or **OFF (ANABOLIC)**.

Adenylyl Cyclase Signaling Pathway

- **Hormone-Receptor (1)**
- **G-Protein Transducer (10)**
- **Adenylyl Cyclase Effector (100)**
- **cAMP 2nd messenger (1000)**

Signal Amplification
Ways to Turn Off Signaling Pathway

Remove Hormone
Inactive Hormone-Receptor Complex (phosphorylation of the receptor)
Release Inhibitory Hormone
Turn-off Transducer (GTP-hydrolysis)
Inhibit effector enzyme (inhibitory transducer)
Inhibit effector enzyme activity
Remove second messenger (activate cAMP phosphodiesterases)
Remove phosphorylation of Metabolic Enzymes (activate protein phosphatases)

C. Inositol-Phospholipid Signaling Pathway

**PIP**$_2$ produces two second messengers

**Diacylglycerol** – activates protein kinase C

**IP$_3$** – activates calcium channels

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Inositol-phosphate Signaling Pathway

Hormone-Receptor

G-Protein Transducer

Protein Lipase C Effector

IP$_3$ and DAG second messengers

**IP$_3$ and DAG Activate Signaling Processes which are coupled thru Ca$^{2+}$**

- **IP$_3$** binds to Ca-channels ↓ releases Ca$^{2+}$
  (oscillation of ion) ↓ Ca$^{2+}$ binds to calcium binding proteins (calmodulin) ↓ Ca-
  calmodulin complexes bind to calmodulin sensitive kinases ↓ turn metabolism on/off

- **DAG** binds to Protein Kinase C (PKC) and Ca-binds to PKC ↓ activates PKC to phosphorylates proteins (-R/K-X-Ser/Thr-) ↓ turn metabolism on/off
D. Receptor Tyrosine Kinases (TK)

Growth factors signaling involve tyrosine kinase

**TK** - multifunctional transmembrane protein hormone receptor, transducer & effector

Dimers of TK form with Ligand Binding

---

**Dimerization Leads to Autophosphorylation of Tyrosine Kinases**

Each kinase domain (intracellular) catalyzes the phosphorylation of **Tyr** in its dimer partner using ATP $\downarrow$

Phosphorylated Dimer catalyzes the phosphorylation of **Tyr** other target proteins/enzymes
**Insulin receptor and tyrosine kinase activity**

**Insulin** – a peptide hormone binds to 2 extracellular \( \alpha \)-chains \( \downarrow \) Transmembrane \( \beta \)-chains forms dimers and autophosphorylate **Tyr**

Tyrosine kinase domains then phosphorylate **Tyr** of proteins named insulin-receptor substrates (IRSs) \( \downarrow \) control metabolism (anabolic)

---

**Insulin-stimulated formation of PIP\(_3\)**

**Metabolism:**
- Active IRSs \( \downarrow \)
- Phosphatidylinositol Kinase (PI) \( \downarrow \)
- PIP\(_3\) (2nd messenger) \( \downarrow \)
- Protein Kinases \( \downarrow \)
- Glycogen synthesis & Glc uptake in liver

**Gene Expression:**
- Active IRSs \( \downarrow \) Ras (G-protein) \( \downarrow \)
- MAPKinase (signaling pathway) \( \downarrow \)
- Protein Expression (Glut receptors)
Steroid Hormone Signaling

- **Hormone** (Steroid Hormones; Retinoic Acids; Vitamin D; other lipophilic hormones w/polar groups)
- **Plasma Membrane**
- **Cytoplasm**
- **Nuclear Membrane**
- **Nucleus**
- **DNA**
- **Enhanced Gene Expression over Basal Level Gene Expression**

**Diagram Details:**
- Hormone enters the cell through the plasma membrane.
- The hormone binds to the NR dimer, which then enters the nucleus.
- The hormone-NR dimer complex binds to the HRE (Hormone Response Element) and the TATA box on the DNA.
- RNA Polymerase II is recruited to the DNA.
- Gene expression is enhanced over the basal level.