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

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

**Lipids:** water insoluble organic compounds in living organisms

Lipids are **hydrophobic or amphipathic**

In BCMB/BIOL/CHEM 3100 we will emphasize
* phospholipids
* glycolipids
* cholesterol (steroid)

**Glycerophospholipids:** main lipids in most biological membranes

**Sphingolipids:** 2nd most abundant lipid in membranes (abundant in CNS) from animals and plants
Structural relationships of major lipid classes

LIPIDS

- Fatty acids
  - Eicosanoids
  - Triacylglycerols
  - Waxes
  - Sphingolipids

Steroids
Lipid vitamins
Terpenes
Isoprenoids

Glycerophospholipids

- Ceramides
  - Plasmalogens
  - Phosphatidates
  - Sphingomyelins

Cerebrosides
Gangliosides

Phosphatidyl-cholines
Other phospholipids

Glycosphingolipids

Structure and nomenclature of fatty acids

Fatty acid
Fatty acyl group
Hydrocarbon tail
### Table 9.1: Some common fatty acids (anionic forms)

<table>
<thead>
<tr>
<th>Number of carbon</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>Laurine</td>
<td>Dodecanoate</td>
<td>44</td>
<td>CH₃(CH₂)₁₉COO⁻</td>
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<td>14</td>
<td>0</td>
<td>Myristate</td>
<td>Tetradecanoate</td>
<td>52</td>
<td>CH₃(CH₂)₁₂COO⁻</td>
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<tr>
<td>16</td>
<td>0</td>
<td>Palmitate</td>
<td>Hexadecanoate</td>
<td>63</td>
<td>CH₃(CH₂)₁₄COO⁻</td>
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<tr>
<td>18</td>
<td>0</td>
<td>Stearate</td>
<td>Octadecanoate</td>
<td>70</td>
<td>CH₃(CH₂)₁₆COO⁻</td>
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<tr>
<td>20</td>
<td>0</td>
<td>Arachidonate</td>
<td>Eicosanoate</td>
<td>75</td>
<td>CH₃(CH₂)₁₈COO⁻</td>
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<tr>
<td>22</td>
<td>0</td>
<td>Behenate</td>
<td>Docosanoate</td>
<td>81</td>
<td>CH₃(CH₂)₂₀COO⁻</td>
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<tr>
<td>24</td>
<td>0</td>
<td>Lignocerate</td>
<td>Tetraicosanoate</td>
<td>84</td>
<td>CH₃(CH₂)₂₂COO⁻</td>
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<td>16</td>
<td>1</td>
<td>Palmitoleate</td>
<td>cis-Δ⁹-Octadecenoate</td>
<td>−0.5</td>
<td>CH₃(CH₂)₁₅CH=CH(CH₂)COO⁻</td>
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<tr>
<td>18</td>
<td>1</td>
<td>Oleate</td>
<td>cis-Δ⁹-Octadecenoate</td>
<td>13</td>
<td>CH₃(CH₂)₁₅CH=CH(CH₂)COO⁻</td>
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<tr>
<td>18</td>
<td>2</td>
<td>Linoleate</td>
<td>cis,cis-Δ⁹,12-Octadecadienoate</td>
<td>−9</td>
<td>CH₃(CH₂)₁₆CH=CH(CH₂)CH=CH(CH₂)COO⁻</td>
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<tr>
<td>18</td>
<td>3</td>
<td>Linolenate</td>
<td>cis,cis,cis-Δ⁹,12,15-Octadecatrienoate</td>
<td>−17</td>
<td>CH₃(CH₂)₁₆CH=CH(CH₂)CH=CH(CH₂)CH=CH(CH₂)COO⁻</td>
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<tr>
<td>20</td>
<td>4</td>
<td>Arachidonate</td>
<td>cis-Δ⁵,8,11,14-Eicosatetraenoate</td>
<td>−49</td>
<td>CH₃(CH₂)₁₸CH=CH(CH₂)CH=CH(CH₂)CH=CH(CH₂)COO⁻</td>
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</tbody>
</table>

### Common names

- 18:0 stearate
- 18:1 olate
- 18:2 linoleate

### IUPAC names

- Octadecenoate
- cis-Δ⁹-Octadecenoate
- cis,cis-Δ⁹,12-Octadecadienoate
- cis,cis,cis-Δ⁹,12,15-Octadecatrienoate

### Diagrams

- **Saturated FA - no C-C double bonds**
- **Unsaturated FA - at least one C-C double bond**
**Fig. 11.1**

Palmitate
(ionized form of palmitic acid)

Oleate
(ionized form of oleic acid)

**Fig. 11.1**
Page 181

Stearate

trans-Oleate

cis-Oleate

Pg. 182
Structural relationships of major lipid classes

- **LIPIDS**
  - Fatty acids
  - Triacylglycerols
  - Waxes
  - Sphingolipids
  - Steroids
  - Lipid vitamins
  - Terpenes
  - Isoprenoids

Adipocytes

Fig. 11.3

Adipose cell: holds deposit of triacylglycerols
**Structure of a triacylglycerol**

(a) Glycerol backbone

(b) Triacylglycerol

*Triacylglycerols are a neutral storage form of fatty acids*

See Pg. 183

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**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

**Phospholipids:** most abundant class of lipids in membranes; derived from glycerol or sphingosine  
[Note: triacylglycerols are most abundant lipid on mass basis in mammals but they are not in membranes)]

*lipids from glycerol = phosphoglycerides (also called glycerophospholipids)*

* phosphoglycerides consist of glycerol backbone, two fatty acids & a phosphorylated alcohol

See Fig. 11.3
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 saturated or unsaturated

Under physiological conditions fatty acids are ionized (pKa 4.5-5.0)
(a) Glycerol 3-P and (b) phosphatidate

See Fig. 11.6

See Fig. 11.7
Phospholipases hydrolyze phospholipids

Lipases: enzymes that catalyze hydrolysis of triacylglycerols

Phospholipases: catalyze hydrolysis of glycerophospholipids

Structural relationships of major lipid classes
(a) **Sphingosine:** structural backbone of sphingolipids

(b) **Ceramide:** sphingosine + fatty acid at C2

See Fig. 11.8

(c) **Sphingomyelin:** present in plasma membrane & myelin sheath around neurons

See Fig. 11.8
Example of a **Cerebroside**: abundant in nerves

Sugar - Sphingosine  
Fatty acid

• **Structure of a galactocerebroside**

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Example of a **Ganglioside** Ganglioside G\(_{M2}\)
( NeuNAc in blue)

Cell surface, cell-cell interactions  
(e.g. blood group antigens)

Hexosaminidase A cleaves here  
Mutation → Tay-Sachs disease
Structural relationships of major lipid classes

- Fatty acids
- Eicosanoids
- Triacylglycerols
- Waxes
- Sphingolipids
- Steroids
- Lipid vitamins
- Terpenes
- Isoprenoids

- Glycerophospholipids
  - Phosphatidylethanolamines
  - Phosphatidylserines
  - Phosphatidylcholines
  - Phosphatidylinositols
  - Other phospholipids
- Ceramides
  - Ceramides
  - Gangliosides
  - Other glycosphingolipids
- Glycosphingolipids

Structure of the steroid cholesterol.

Steroids are **polyprenyl compounds**

See Pg. 187

In eukaryotes but NOT in most prokaryotes

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

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Cholesterol

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

Stereo view of cholesterol

- Polar OH (red), fused ring system nearly planar
**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**

\[
\begin{align*}
H_3C & \quad (CH_2)_{14} \quad C \quad O \quad (CH_2)_{29} \quad CH_3 \\
\text{Palmitate portion} & \quad \text{Myricyl alcohol portion}\n\end{align*}
\]

**Eicosanoids**: oxygenated derivatives of C20 polyunsaturated fatty acids (e.g. arachidonic acid)

(a) Arachidonic acid

(b) Prostaglandin E₂

(c) Thromboxane A₂

(d) Leukotriene D₄

**Arachidonic acid and three eicosanoids**
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. 15.18, Pg. 263 for structures

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Fig. 15.18

Vitamin C (Ascorbate): roles in vision, growth, reproduction

Vitamin K₁: blood coagulation

Vitamin A (Retinol)

Vitamin E (α-Tocopherol): antioxidant

Vitamin D₂ (Ergocalciferol): antioxidant, regulation of calcium and phosphate metabolism
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

See Fig. 12.1; 12.8
Biological Membranes

• **Highly selective permeability barriers** that surround cells & cellular compartments

• **Sheetlike structures** of ~60-100Å

• 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 **amphipathic**: hydrophilic (polar) head group & hydrophobic tail. Spontaneously form bilayers in aqueous solution.

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**Fig. 12.1**

(B) Polar head groups

Hydrophobic tails

Polar head groups
Lipids in biological membranes include phospholipids, sphingolipids, cholesterol (in some eukaryotes)

- Polar OH (red), fused ring system nearly planar
Amphipathic nature of cerebrosides
Amphipathic lipids can take two different forms in aqueous media: **micelles** or **lipid bilayers**

**Micelle**: 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 $< 200 \, \mu\text{m}$ in diameter.

**Structure and nomenclature of fatty acids**
Lipid bilayers: 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 \((10^7 \, \text{Å}, 1 \, \text{mm})\) (recall diameter = \(~60\text{-}100\,\text{Å}\))

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

Bilayers are extensive, closed, and self-sealing
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 of 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

<table>
<thead>
<tr>
<th>K⁺</th>
<th>Na⁺</th>
<th>Cl⁻</th>
<th>Tryptophan</th>
<th>Urea</th>
<th>Glycerol</th>
<th>Indole</th>
<th>H₂O</th>
</tr>
</thead>
</table>

Fig. 12.4

Lipid Bilayers and Membranes Are Dynamic Structures

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

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
Biological Membranes (cont.)

- Contain proteins both embedded in the bilayer & on its surface. Proteins may function as pumps, gates, receptors, energy transducers & enzymes.

- Membrane 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

- Fluid mosaic model - 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
Phase transition of a lipid bilayer

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

| Ordered state: a rigid state in which all C-C bonds have trans conformation (all trans) |
| Fluid state: a relatively disordered state in which some of the C-C bonds are in the gauche conformation |

Phase transition of a lipid bilayer

![Temperature vs. Fluidity graph](image)

**Fig 12.5**
Transition from rigid to partly fluid state occurs at $T_M$, the melting temperature

$T_M$ depends on length of fatty acyl chains & on degree of unsaturation

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.
Effect of cholesterol on phase transition ($T_M$) of membranes

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

Addition of 20 mol% cholesterol broadens phase transition

---

**Fig 12.7**

Pure phospholipid bilayer has a sharp phase transition
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.

http://en.wikipedia.org/wiki/Lipid_raft

Structure of a typical eukaryotic plasma membrane

http://en.wikipedia.org/wiki/Lipid_raft
Three types membrane associated proteins

*Peripheral membrane protein*: loosely bound to membrane by H-bonds or electrostatic forces, generally water soluble once released from membrane using high salt or pH. Bound to integral membrane proteins or polar head groups of lipids in membrane.

*Integral membrane proteins*: 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).
Stereo view of bacteriorhodopsin: an integral membrane protein
See Fig. 12.9

Bacterial porin
Fig. 12.10

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 \(\alpha\)-carboxyl of protein-phosphoethanolamine-glycan-phosphatidylinositol
Lipid-anchored membrane proteins

(c)

Protein

Glycosylphosphatidylinositol-anchored protein (GPI-anchored protein)

Phosphoethanolamine residue

Outer leaflet

(continued)

direct ester-linked protein

Prenylated protein

Inner leaflet

Protein (a)

Protein (b)
Characteristics of membrane transport. Small uncharged and hydrophobic molecules can diffuse across membranes. Other molecules require protein assisted movement.

<table>
<thead>
<tr>
<th>Characteristics of different types of membrane transport</th>
</tr>
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<tbody>
<tr>
<td>Protein carrier</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Simple diffusion</td>
</tr>
<tr>
<td>Channels and pores</td>
</tr>
<tr>
<td>Passive transport</td>
</tr>
<tr>
<td>Active transport</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
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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.

Examples: voltage-gated channels, ligand-gated channels, transient receptor potential channels
Types of passive and active transport

- Uniport
- Symport
- Antiport

See Fig. 12.19

Active & passive transporters undergo a conformational change to drive transport
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
(example of P-type ATPase)

**Secondary active transporter:**
glucose transporter

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**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. 12.23**

*Example of Passive Transport*

K⁺ K⁺

**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. 12.24
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.
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

(e.g. hormones)

External stimulus (First messenger) ↓

e.g. *G proteins*  
*Tyrosine kinase*  
*Adenylate cyclase*  
*Phospholipase C*

Membrane receptor ➔ Transducer ➔ Effector enzyme ➔ PLASMA MEMBRANE

↓

Second messenger

↓

Cytoplasmic and nuclear effectors

↓

Cellular response

---

Common secondary messengers **Fig. 13.2**

- **Cyclic AMP (cAMP)**, **Cyclic GMP (cGMP)**
- **Calcium ion**
- **Inositol 1,4,5-trisphosphate (IP_3)**
- **Diacylglycerol (DAG)**
G-protein cycle

- 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)

Understanding G Proteins:
Hydrolysis of GTP to GDP and $P_i$

![Chemical diagram of GTP hydrolysis]

Phosphate ($P_i$)
• **Summary of the adenylyl cyclase signaling pathway**

See Fig 13.6, 13.7; 13.8

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

**Production, inactivation of cAMP**

Continued next slide
• Activation of protein kinase A by cAMP

See Fig. 13.6
Caffeine & theophylline inhibit cAMP phosphodiesterase

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

[Chemical structures of Caffeine and Theophylline]

• Inositol-phospholipid signaling pathway

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

See Fig. 13.11, 13.12
Phosphatidylinositol 4,5-bisphosphate (PIP\textsubscript{2}) produces IP\textsubscript{3} and diacylglycerol

![Phosphatidylinositol 4,5-bisphosphate (PIP\textsubscript{2})](image)

Phosphatidylinositol 4,5-bisphosphate

Phospholipase C $\xrightarrow{H_2O}$

Diacylglycerol + Inositol 1,4,5-trisphosphate (IP\textsubscript{3})

See Fig. 13.11

(continued)

![Diacylglycerol](image) + ![Inositol 1,4,5-trisphosphate (IP\textsubscript{3})](image)
• 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. 13.16

(continued)

• Phosphorylated dimer phosphorylates cellular target proteins

nATP \xrightarrow{\text{autophosphorylation}} nADP
(continued)

- Each domain catalyzes phosphorylation of its partner

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**Insulin receptor and tyrosine kinase activity**

- Insulin binds to 2 extracellular $\alpha$-chains
- Transmembrane $\beta$-chains then autophosphorylate
- Tyrosine kinase domains then phosphorylate insulin-receptor substrates (IRSs) (which are proteins)
Insulin-stimulated formation of PIP₃

SEE Figs. 13.17-13.21

See also Figures 13.15 & 13.16 for EGF signaling pathway (another example of Tyr Receptor kinase)

A different type of tyrosine kinase signal transduction:
Growth hormone receptor for which binding brings together associated proteins with tyrosine kinase domains (i.e., ligand binding leads to changes in 4° structure)

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

Fig. 13.13
Cross-phosphorylation of two JAK2 induced by hormone receptor dimerization

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 (20-25 kd) and monomer compared to the larger (30-35 kd) and trimeric G proteins