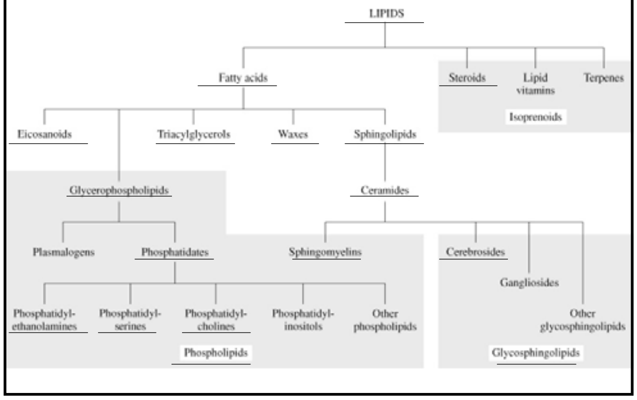
Chapter 9: Lipids

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)**

Structural relationships of major lipid classes



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 <u>even</u> <u>number</u> of carbons (synthesized from two-carbon units)
- IUPAC nomenclature: carboxyl carbon is C-1
- Common nomenclature: $\alpha,\beta,\gamma,\delta,\varepsilon$ 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

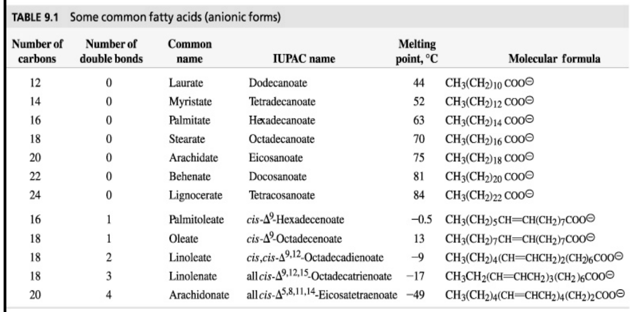
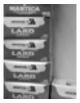


TABLE 9.1 Some common fatty acids (anionic forms)

Number of carbons	Number of double bonds	Common name	IUPAC name	Melting point, °C	Molecular formula
12	0	Laurate	Dodecanoate	44	$CH_3(CH_2)_{10}COO^{\ominus}$
14	0	Myristate	Tetradecanoate	52	$CH_3(CH_2)_{12}COO^{\ominus}$
16	0	Palmitate	Hexadecanoate	63	$CH_3(CH_2)_{14}COO^{\ominus}$
18	0	Stearate	Octadecanoate	70	$CH_3(CH_2)_{16}COO^{\ominus}$
20	0	Arachidate	Eicosanoate	75	$CH_3(CH_2)_{18}COO^{\ominus}$
22	0	Behenate	Docosanoate	81	$CH_3(CH_2)_{20}COO^{\ominus}$
24	0	Lignocerate	Tetracosanoate	84	$CH_3(CH_2)_{22}COO^{\ominus}$
16	1	Palmitoleate	*cis*-Δ^9-Hexadecenoate	−0.5	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COO^{\ominus}$
18	1	Oleate	*cis*-Δ^9-Octadecenoate	13	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COO^{\ominus}$
18	2	Linoleate	*cis*,*cis*-$\Delta^{9,12}$-Octadecadienoate	−9	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COO^{\ominus}$
18	3	Linolenate	all *cis*-$\Delta^{9,12,15}$-Octadecatrienoate	−17	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO^{\ominus}$
20	4	Arachidonate	all *cis*-$\Delta^{5,8,11,14}$-Eicosatetraenoate	−49	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COO^{\ominus}$



Can go rancid easily

Partially Hydrogenated

Trans Fatty Acids

Structure and nomenclature of fatty acids

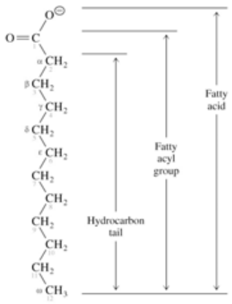
- **Saturated** FA - no C-C double bonds
- **Unsaturated** FA - at least one C-C double bond
- **Monounsaturated** FA - only one C-C double bond
- **Polyunsaturated** FA - two or more C-C double bonds

Double bonds in fatty acids

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

(total # carbons **:** # double bonds, $\Delta^{\text{double bond positions}}$)

Structure and nomenclature of fatty acids



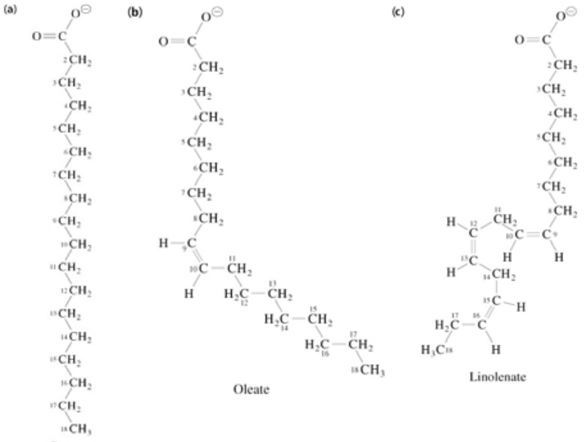
Structures of three C_{18} FA (next slide)

(a) Stearate (octadecanoate), saturated FA

(b) Oleate (*cis*-Δ^9-octadecenoate), a monounsaturated FA

(c) Linolenate (all-*cis*-$\Delta^{9,12,15}$-octadecatrienoate, a polyunsaturated FA

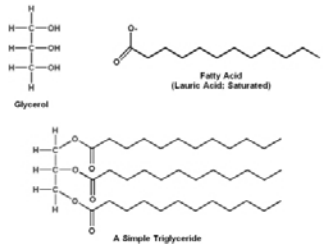
- The *cis* double bonds produce kinks in the tails of unsaturated FA



Triacylglycerols

- Fatty acids are important metabolic fuels (2-3 times the energy of proteins or carbohydrates)
- Fatty acids are stored as neutral lipids called **triaclyglycerols** (**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)



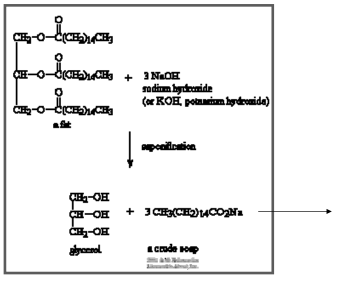
R1, R2 and R3
may be all the same
or they may be
all different

Physical properties depend on number of carbons and the number of double bonds

#C increases; melting point increases
#double bonds increase, melting point decreases

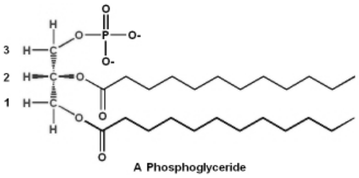
Triacylglycerols

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



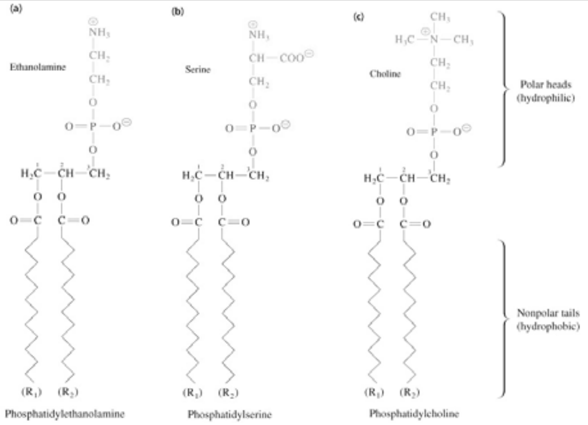
Form micelles in
aqueous solution

Phosphoglyceride (a type of phospholipid)



A Phosphoglyceride

- **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**



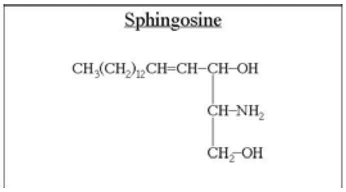
Notice: These are all amphiphilic

If the alcohol is choline, the phosphoglyceride is called <u>phosphatidylcholine or lecithins.</u>

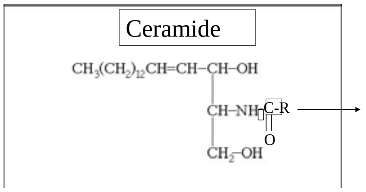
If the alcohol is not choline but some other alcohol such as ethanolamine and serine, the phosphoglyceride is called <u>cephalins.</u>

Sphingolipids

Structures based on an amino alcohol called sphingosine

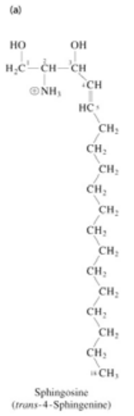


$$\begin{array}{rl} CH_3(CH_2)_{12}CH{=}CH{-} & CH{-}OH \\ & | \\ & CH{-}NH_2 \\ & | \\ & CH_2{-}OH \end{array}$$

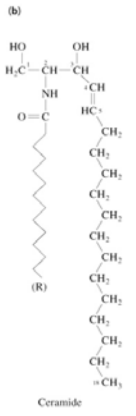


$$\begin{array}{rl} CH_3(CH_2)_{12}CH{=}CH{-} & CH{-}OH \\ & | \\ & CH{-}NH{-}\underset{\overset{\|}{O}}{\boxed{C}}{-}R \\ & | \\ & CH_2{-}OH \end{array}$$

Fatty acid attached to sphingosine by an amide bond



Sphingosine
(*trans*-4-Sphingenine)

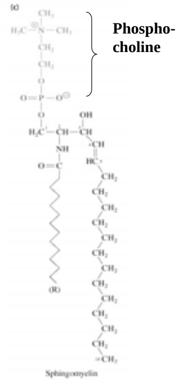


Ceramide

Ceramide
+ phosphocholine (or phosphoelthanolamine)

Sphingomyelin

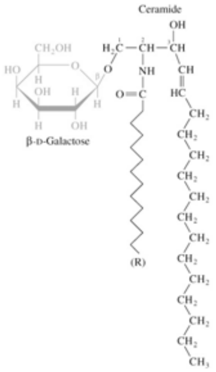
(phospholipid)



Ceramide
+ one or more monosaccharide

Cerebroside

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

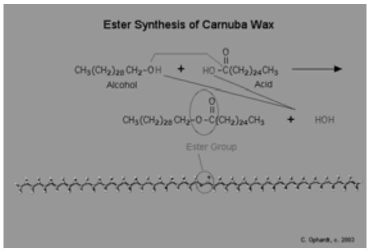


Waxes

- **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

Waxes

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

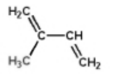


Should be able to build a wax if given an long chain alcohol and a fatty acid

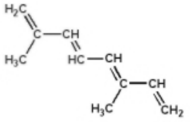
Steroids

- Classified as **isoprenoids** - related to 5-carbon isoprene (found in membranes of eukaryotes)
- Steroids contain <u>four</u> <u>fused</u> <u>ring</u> 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)

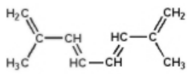
Polymers of Isoprene are the Building Blocks of Steroids



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

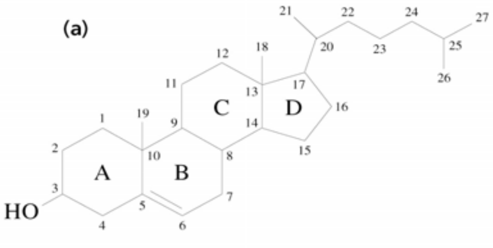


"Head to Tail" monoterpene



"Tail to Tail" monoterpene

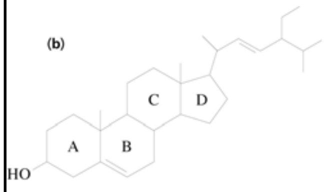
Structures of several steroids



Cholesterol

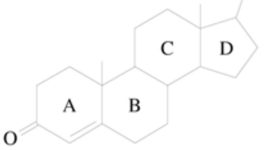
More Steriods

(b)



Stigmasterol
(a plant sterol)

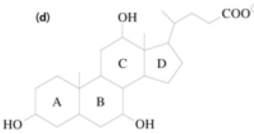
(c)



Testosterone
(a steroid hormone)

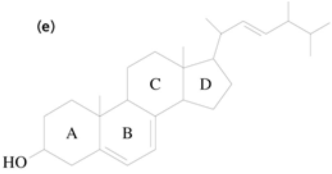
More Steriods

(d)



Sodium cholate
(a bile salt)

(e)



Ergosterol
(a sterol from fungi and yeast)

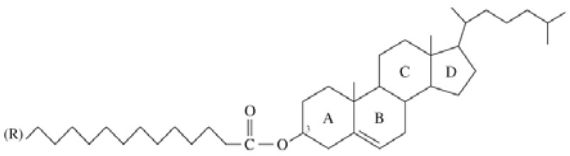
Cholesterol

- 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

Cholesteryl ester



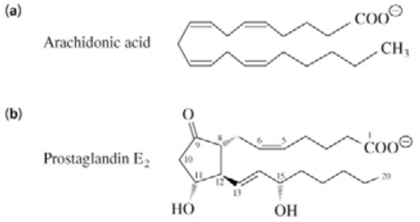
Eicosanoids

- **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

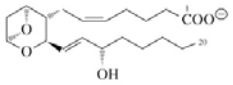
- Prostaglandin E_2 - can cause constriction of blood vessels
- Thromboxane A_2 - involved in blood clot formation
- Leukotriene D_4 - mediator of smooth-muscle contraction and bronchial constriction seen in asthmatics

Arachidonic acid and three eicosanoids derived from it



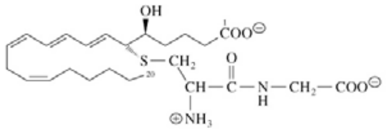
(c)

Thromboxane A_2



(d)

Leukotriene D_4



We study Lipids to Understand Biological Membranes

Biological Membranes are composed of:

43% lipid
49% protein
8% carbohydrate

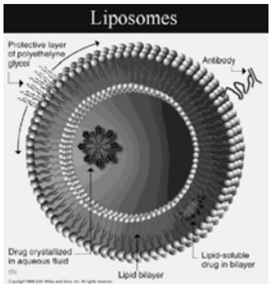
In a Rat Membrane the lipid fraction is:

24% cholesterol
31% phosphotidylcholine
8.5% sphingomyelin
15% phosphatidylethanolamine
2.2% phosphatidyl inositol
7% phosphatidyl serine
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

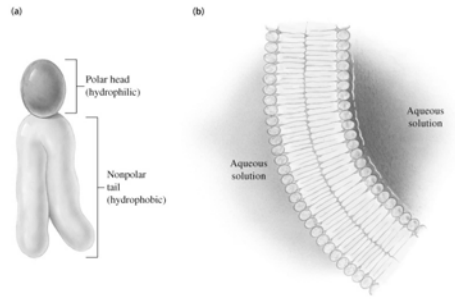
Several important functions of membranes

- 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

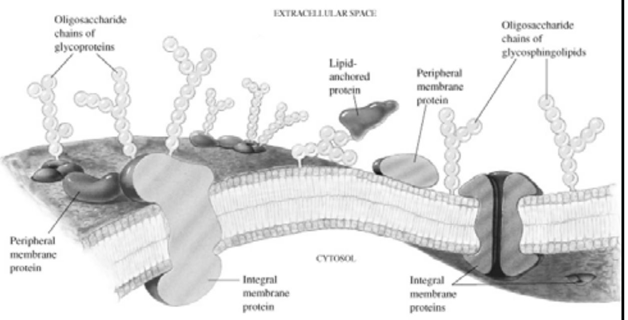
Membrane lipid and bilayer



Fluid Mosaic Model of Biological Membranes

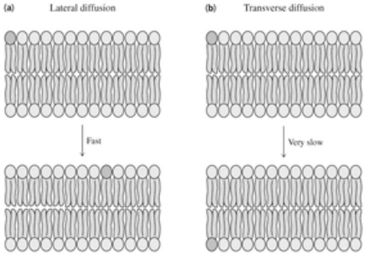
- **Fluid mosaic model** - membrane proteins and lipids can rapidly diffuse laterally or rotate within the bilayer (proteins “float” in a lipid-bilayer sea)
- Membranes: ~25-50% lipid and 50-75% proteins
- Lipids include phospholipids, glycosphingolipids, cholesterol (in some eukaryotes)
- Compositions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

Structure of a typical eukaryotic plasma membrane

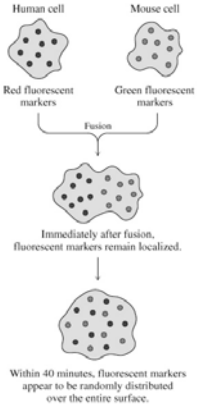


Lipid Bilayers and Membranes Are Dynamic Structures

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

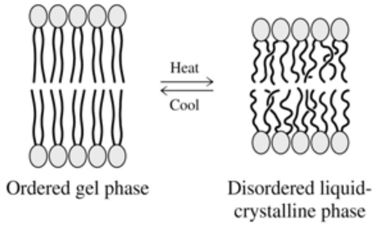


- Diffusion of membrane proteins



Phase transition of a lipid bilayer

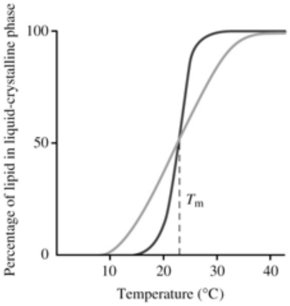
- Fluid properties of bilayers depend upon the flexibility of their fatty acid chains



Low Mobility **High Mobility**

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



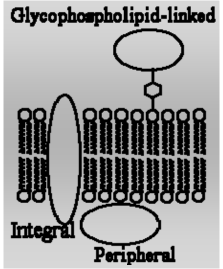
A pure phospholipid bilayer is essentially either gel or liquid crystal. However, the addition of cholesterol components makes possible a broader range of characteristics over a broader range of temperatures. The addition of proteins blurs the distinction further. Note that at 37 degrees, both bilayers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

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**

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

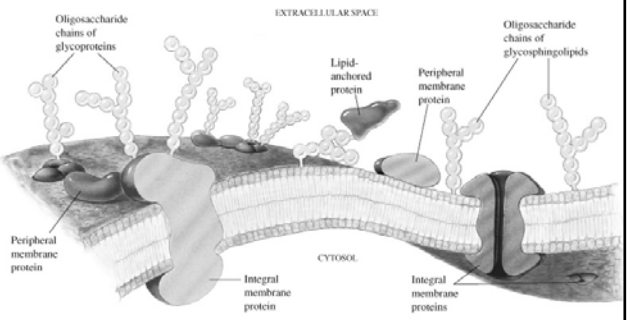
1. **Integral protein**
   extract with detergents
2. **Peripheral**
   extract with high salt, urea, EDTA
3. **Lipid anchored**
   covalently attached to lipids



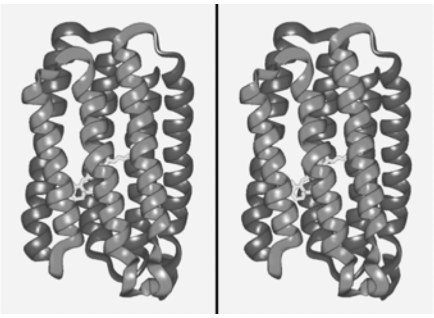
Integral Proteins

(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

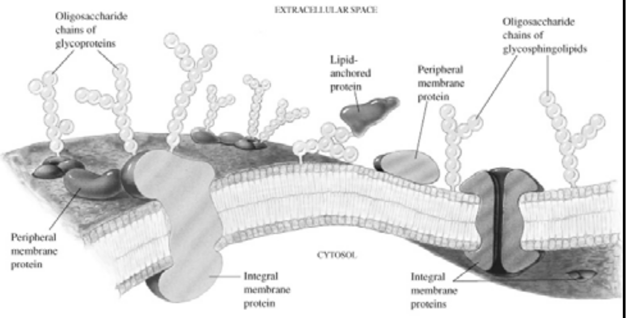


Stereo view of bacteriorhodopsin



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

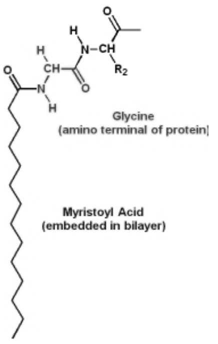
- Tethered to membrane through a <u>covalent</u> <u>bond</u> to a lipid anchor as:

(1) Protein amino acid side chain ester or amide link to fatty acyl group (e.g. myristate, palmitate)

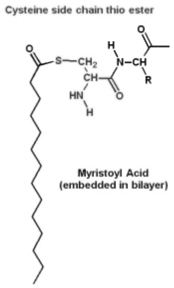
(2) Protein cysteine sulfur atom covalently linked to an isoprenoid chain (**prenylated proteins**)

(3) Protein anchored to glycosylphosphatidylinositol

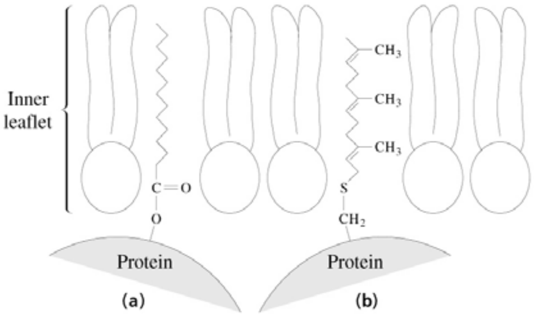
Amide-linked myristoyl anchors (N-myristolation)



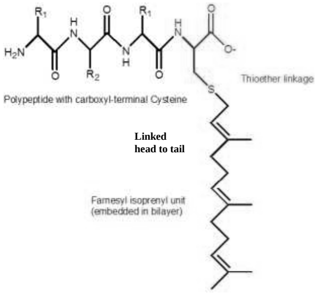
Thioester-linked Fatty Acid Acyl Anchors.



Myristate (14 carbons),
palmate (16 carbons),
stearate (18 carbons) and
oleate (18 carbons, unsaturated)
can be thioester linked to cysteine
residues in proteins.



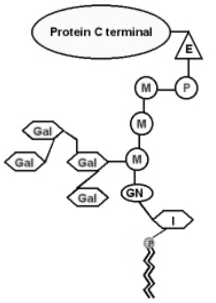
Thioether-linked Prenyl Anchors



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 polyprenyl ether linkage.

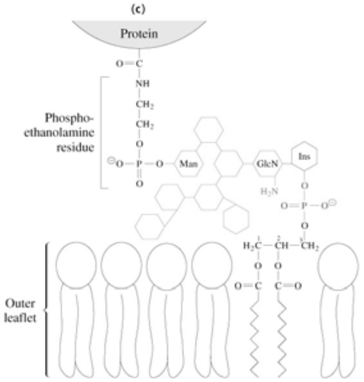
Anchoring may be switch on or off

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

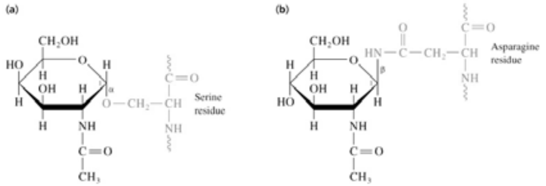


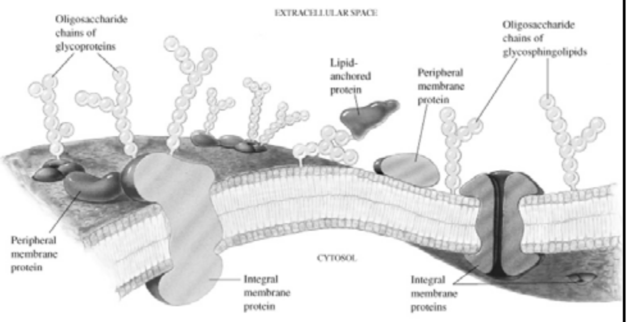
Carbohydrates are often attached to membrane proteins

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