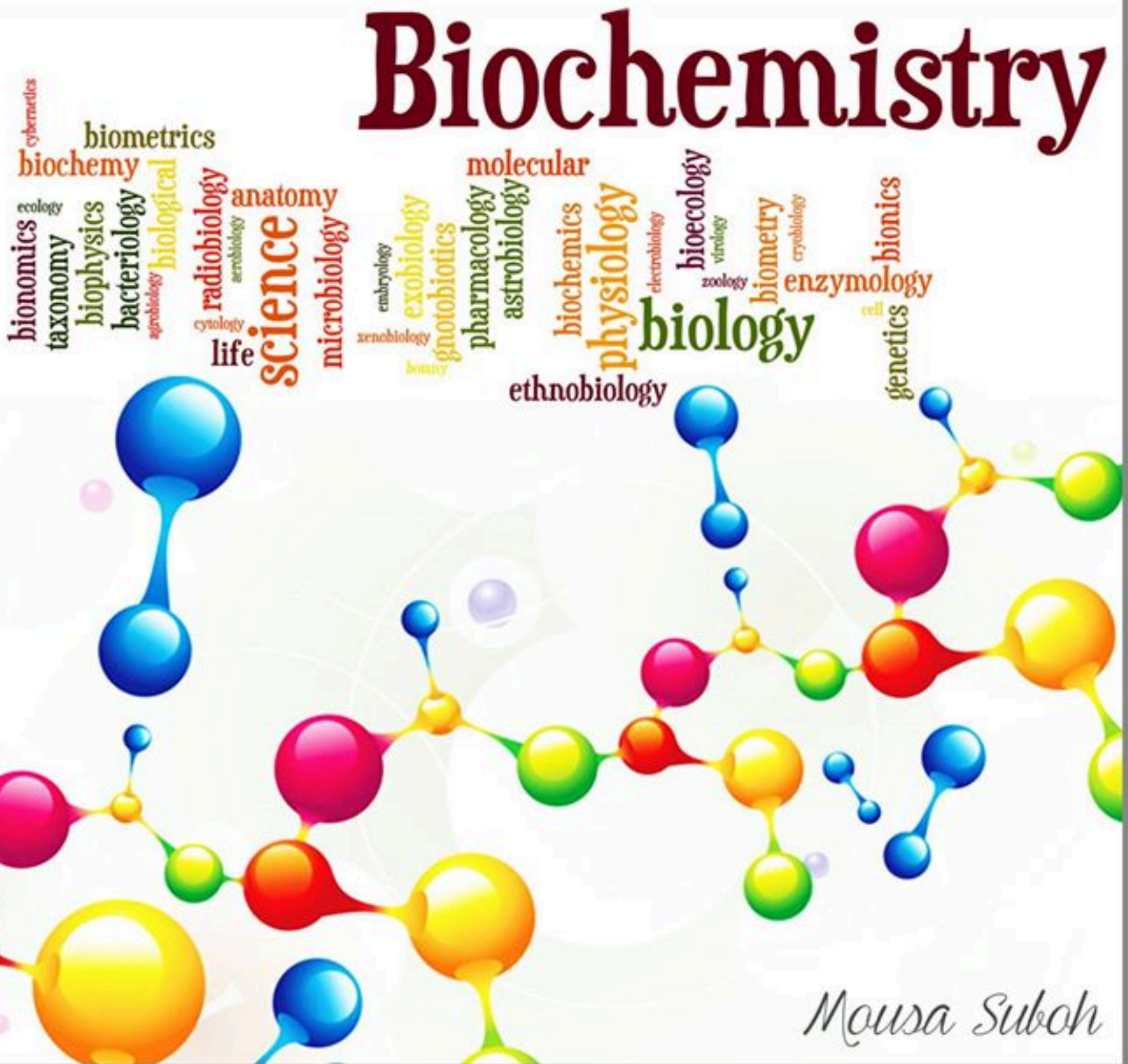
Slide : 2-Lipids Part (2)

Dr. Name : Dr.Nafez Abu-Tarboosh

Sections : 4-5-6

■ Slide ☐ Sheet

Medical Committee
The University of Jordan



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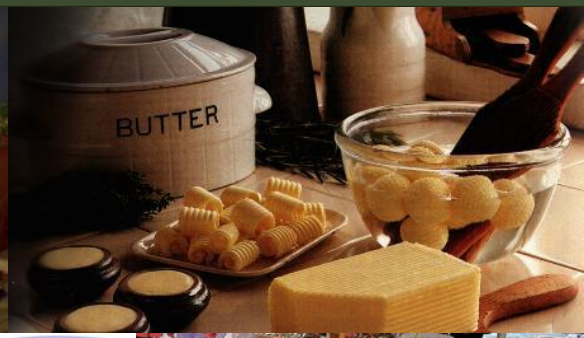
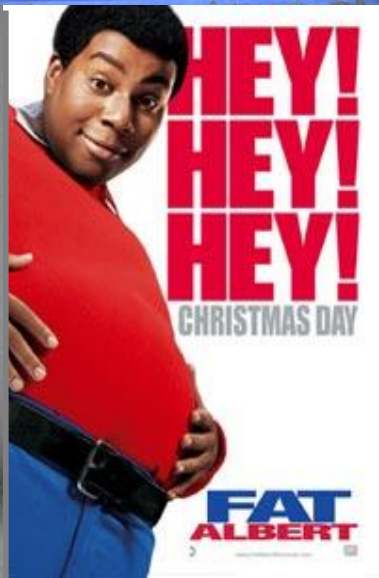
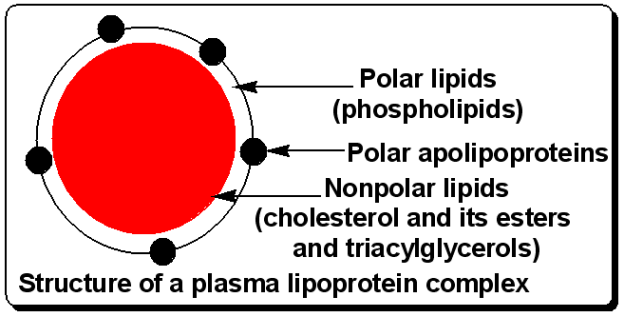
Lipids



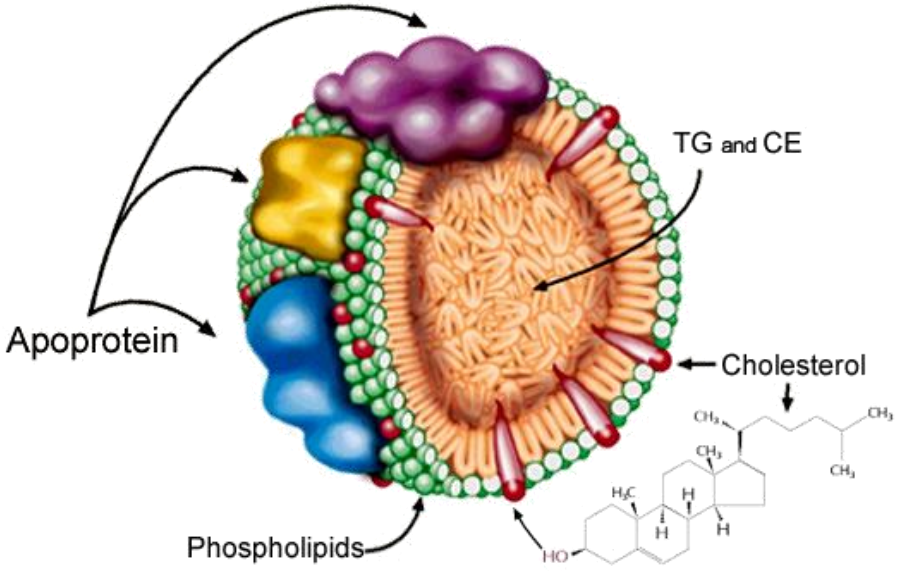


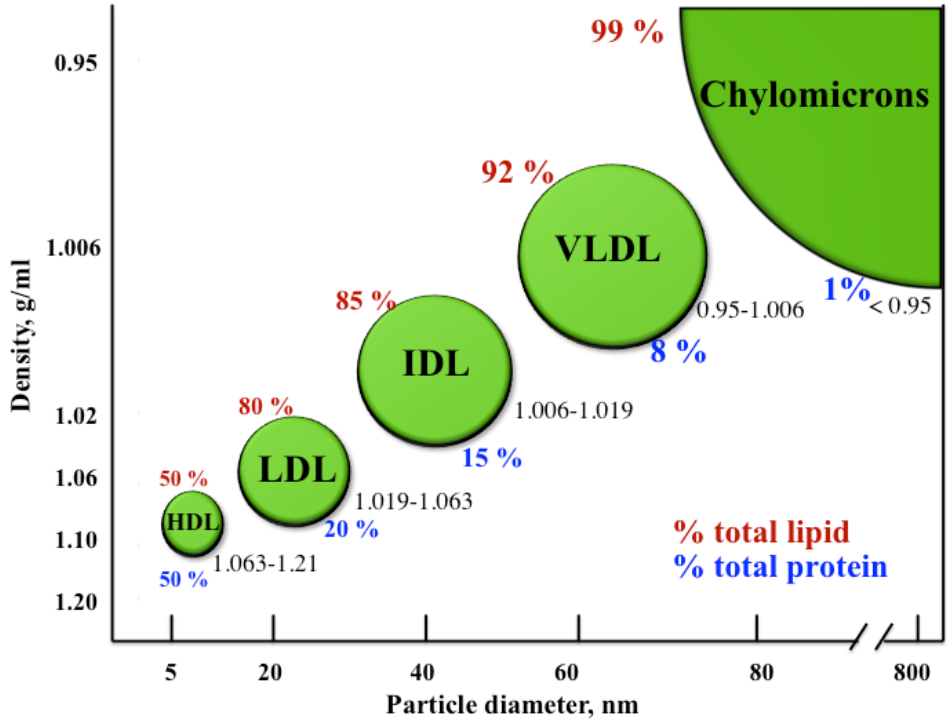
2. Lipoproteins



- Lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) combined with proteins (apolipoprotein) in tissues
- Function: transport of different types of lipids in blood plasma

✓ As lipid content increases, density decreases

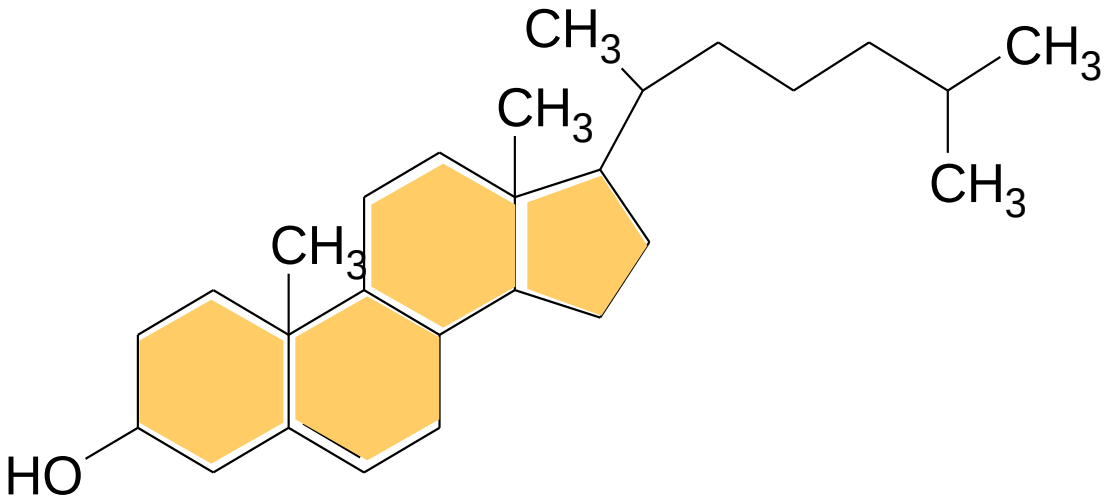




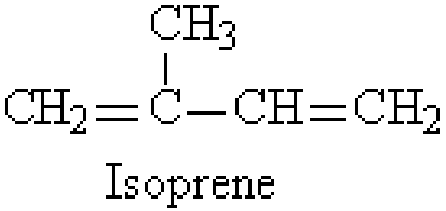
Features of lipoproteins

	Chylomicrons	VLDL	LDL	HDL
Density (g/ml)	< 0.94	0.94-1.006	1.006-1.063	1.063-1.210
Diameter (Å)	6000-2000	600	250	70-120
Total lipid (wt%) *	99	91	80	44
Triacylglycerols	85	55 Liver	10	6
Cholesterol esters	3	18	50 (bad)	40 (good)
Function	Transport of dietary TG	Transport of liver TG	Transport of cholesterol to peripheral tissues	Transport of cholesterol from peripheral tissues (cholesterol scavengers)

Cyclic lipids (Steroids): Cholesterol, Bile Salts, & Steroid Hormones

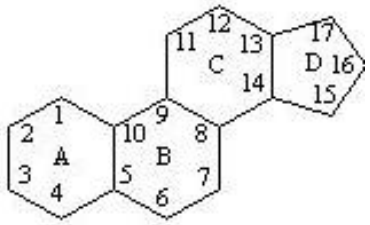


The precursor



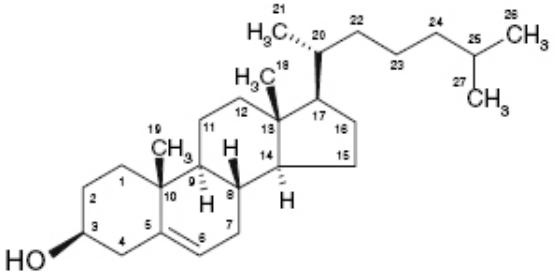
Isoprene

The nucleus

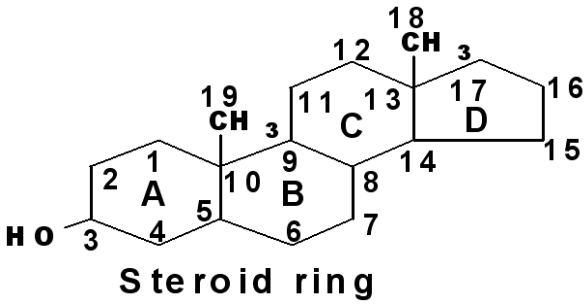


Steroid nucleus

The most common steroid

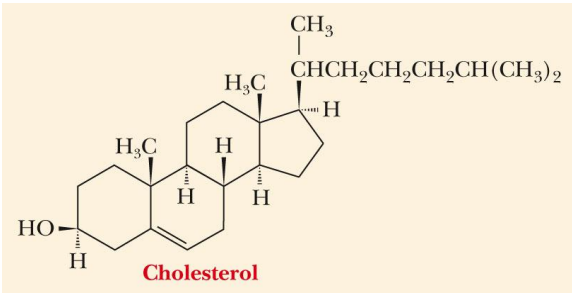


Steroids



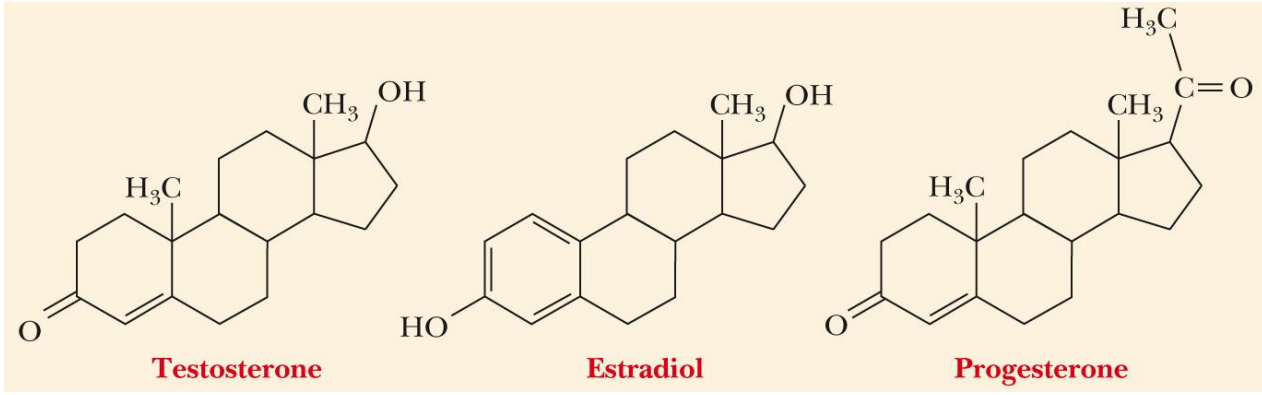
Steroid ring

- A group of lipids that have fused-ring structure of 3 six-membered rings, and 1 five-membered ring
- Usually found in association with fat
- Derivatives of cholesterol
- Biologically important groups of substances:



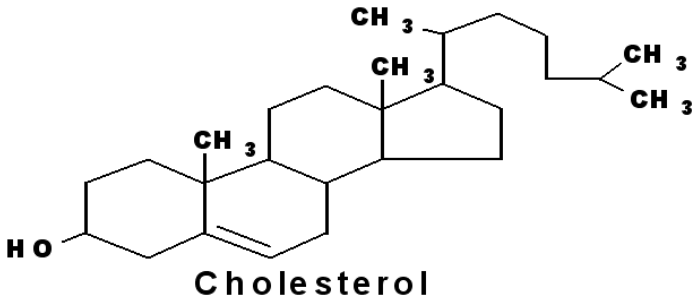
Cholesterol

1. Sterols
2. Adrenal cortical hormones
3. Male and female sex hormones
4. Vitamin D group
5. Bile acids

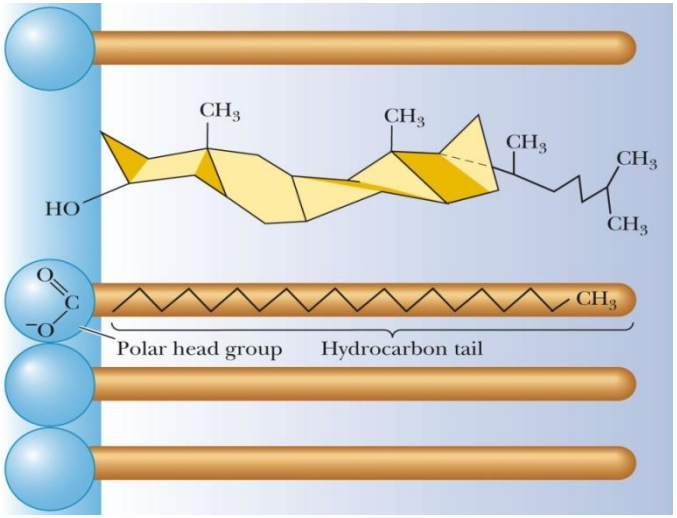


- Androgens: male 2° sex characteristics
- Estrogens: female 2° sex characteristics & control of menstrual cycle

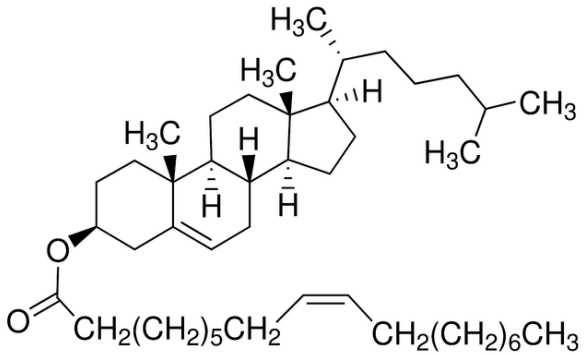
1. Cholesterol

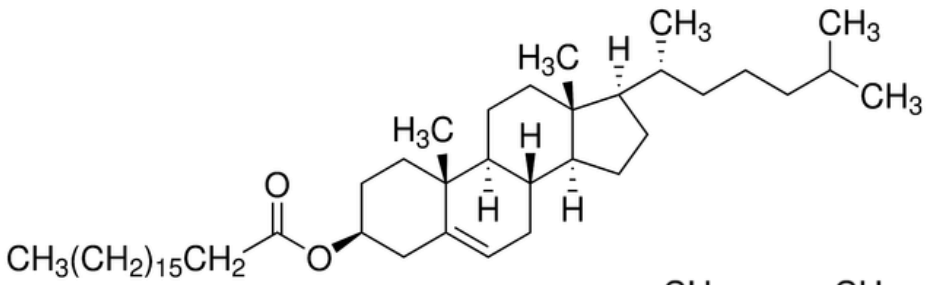


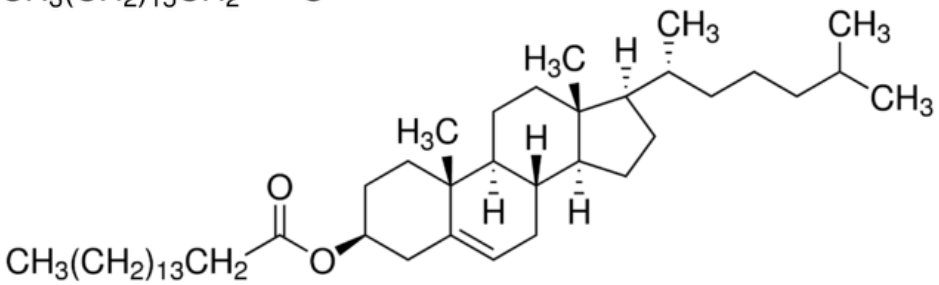
- The most important sterol in animal tissues
- Found as free alcohol or esterified to F.A (e.g. linoleic, oleic, palmitic)
  - Attached at (-OH) of C3
  - Naming
- Reduces membrane fluidity



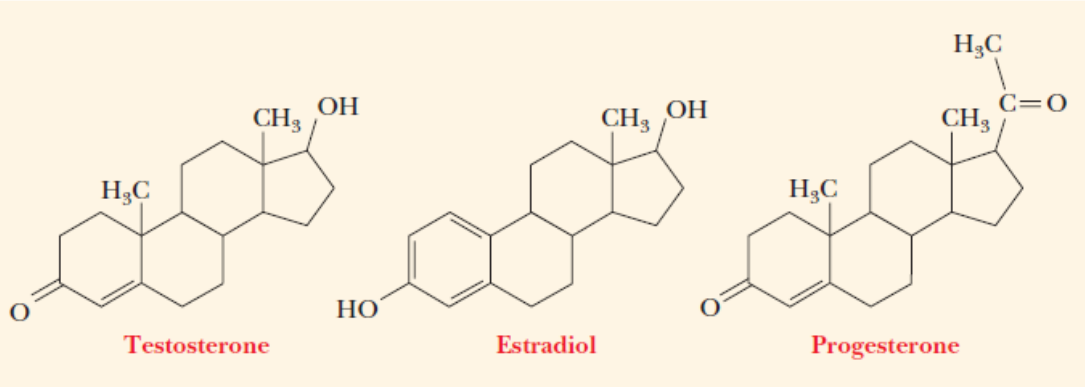
- Stabilizing extended chains of FA due to hydrophobic interactions



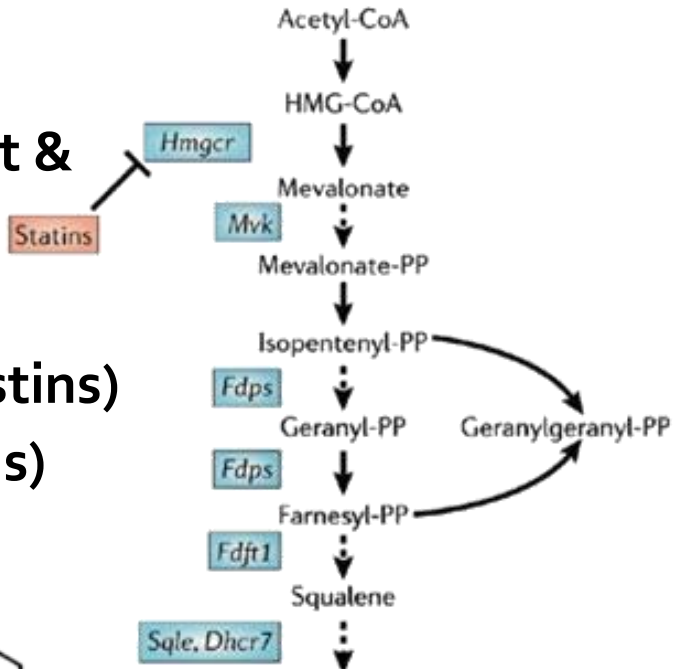




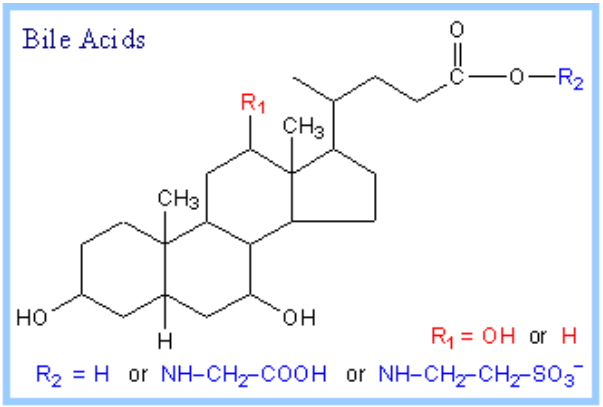
Cholesterol: sources & products

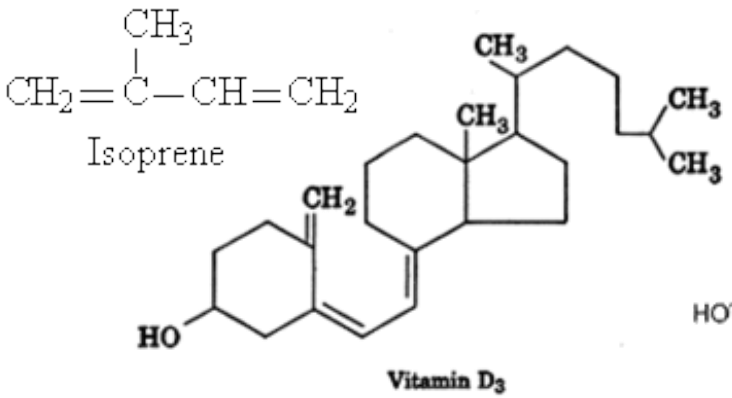


- Source:
  - ✓ Synthesized in the body from acetyl-CoA
  - ✓ Does not exist in plants
  - ✓ In the diet (butter, milk, egg yolk, brain, meat & animal fat)



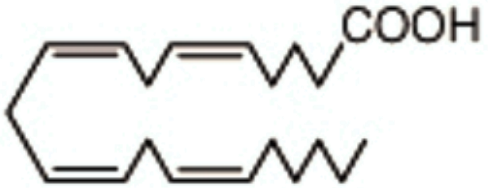
- Products:
  - ✓ Sex hormones (androgens, estrogens, progestins)
  - ✓ Some vitamins (ADEK: made from isoprenoids)
  - ✓ Bile acids (intestinal absorption of fat)



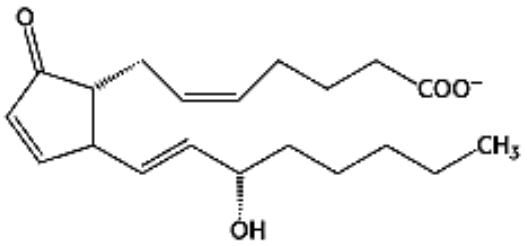


2. Eicosanoids (icosanoids)

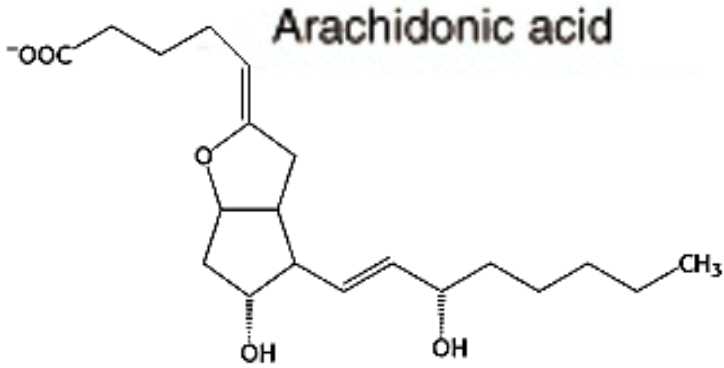
- Signaling molecules
- Made by oxidation of essential PUFA (20 C) : mainly Arachidonic acid (ω6)
- Source: either ω-3 or ω-6 fatty acids
- Paracrine or autocrine messengers molecules
- Half-lives (10 sec – 5 min)
- Most catabolism occurs in the lung
- Families of eicosanoids:
  - ✓ Prostaglandins
  - ✓ Prostacyclins
  - ✓ Thromboxanes
  - ✓ Lipoxins
  - ✓ Leukotrienes



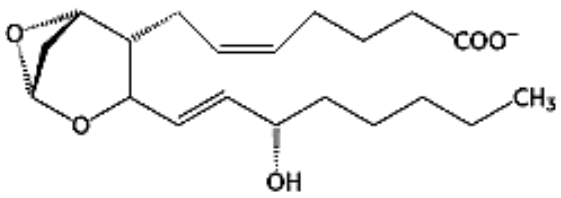
Arachidonic acid



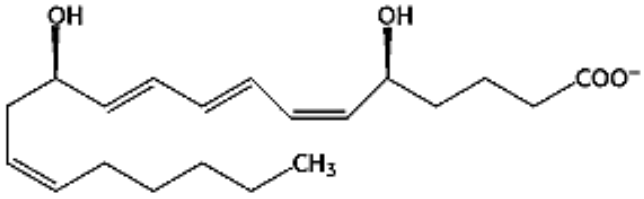
Prostaglandin A_2



Prostacylin (PGI_2)



Thromboxane A_2 (TXA_2)



Leukotriene B_4

Eicosanoids - Functions

- Induction of inflammation
- Mediation of pain signals
- Induction of fever
- Smooth muscle contraction (including uterus)
- Smooth muscle relaxation
- Protection of stomach lining
- Simulation of platelet aggregation
- Inhibition of platelet aggregation
- Sodium & water retention

Anti inflammatory Drugs inhibit Eicosanoid Synthesis

Membrane lipids

Steroids

Phospholipase A2

Arachidonic Acid

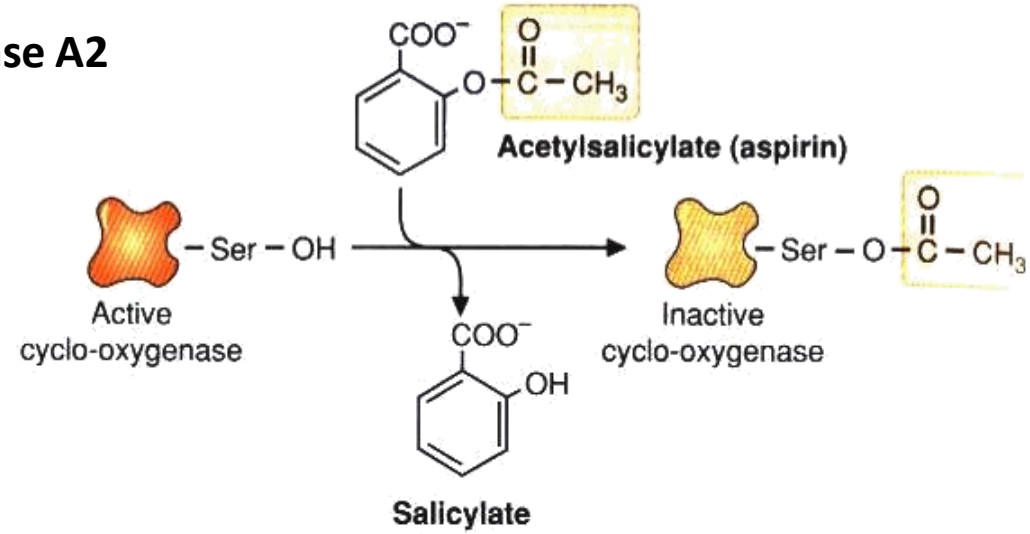
NSAIDs

Cyclo-oxygenase

Lipoxygenase

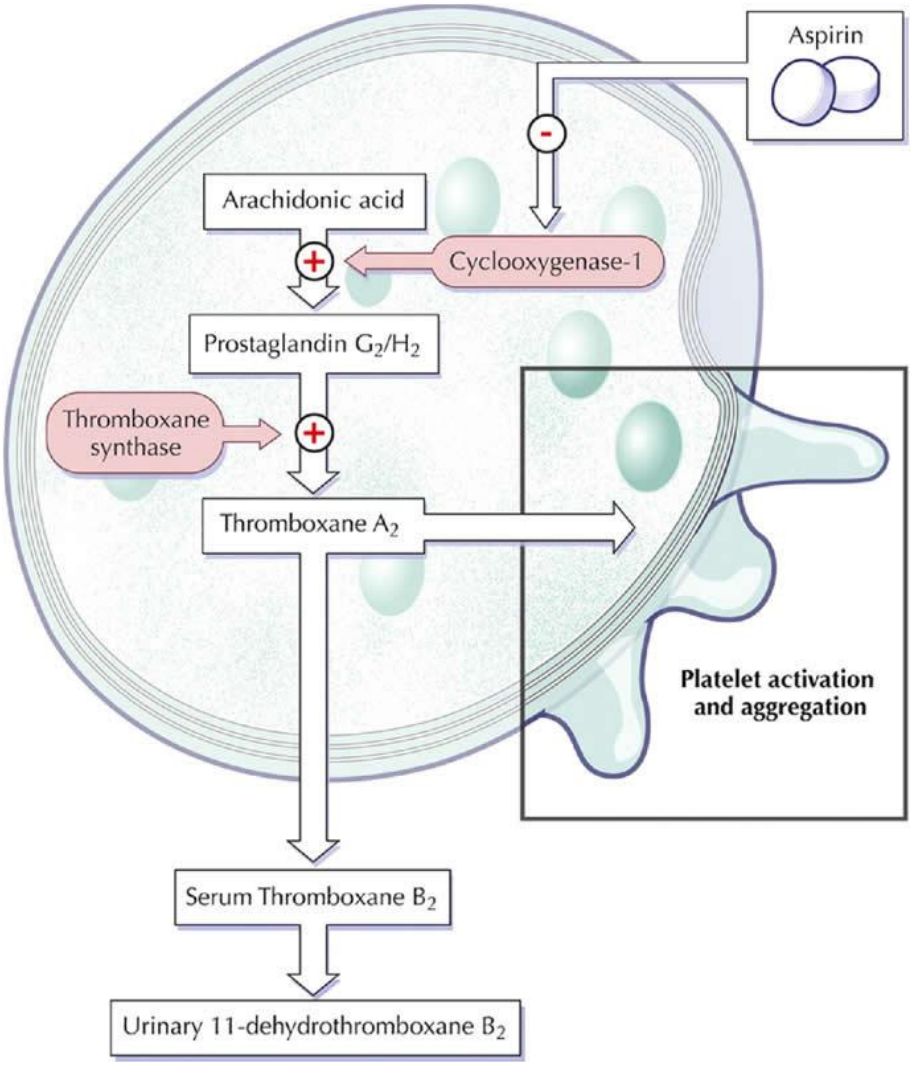
Prostaglandins, thromboxanes

Leukotrienes



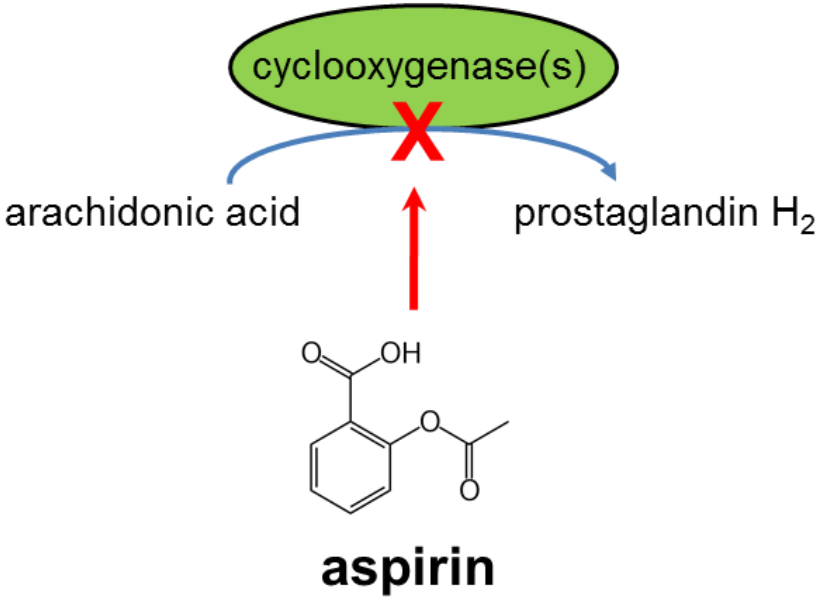
Aspirin & the heart

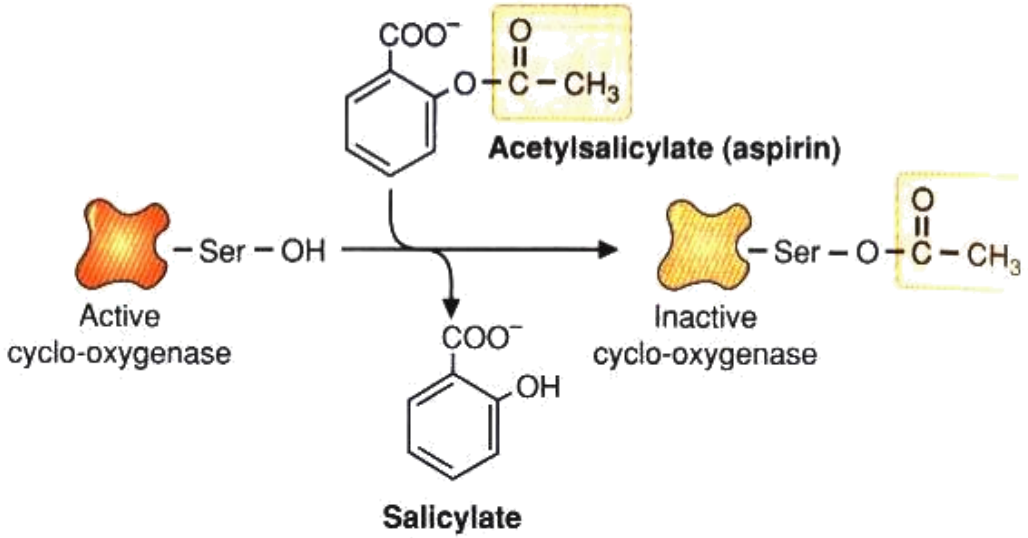
- Thromboxane A2 leads to platelet activation & aggregation
- Aspirin acts as a potent antiplatelet agent by inhibiting cyclooxygenase preventing thromboxane A2 (TXA2) generation



Aspirin

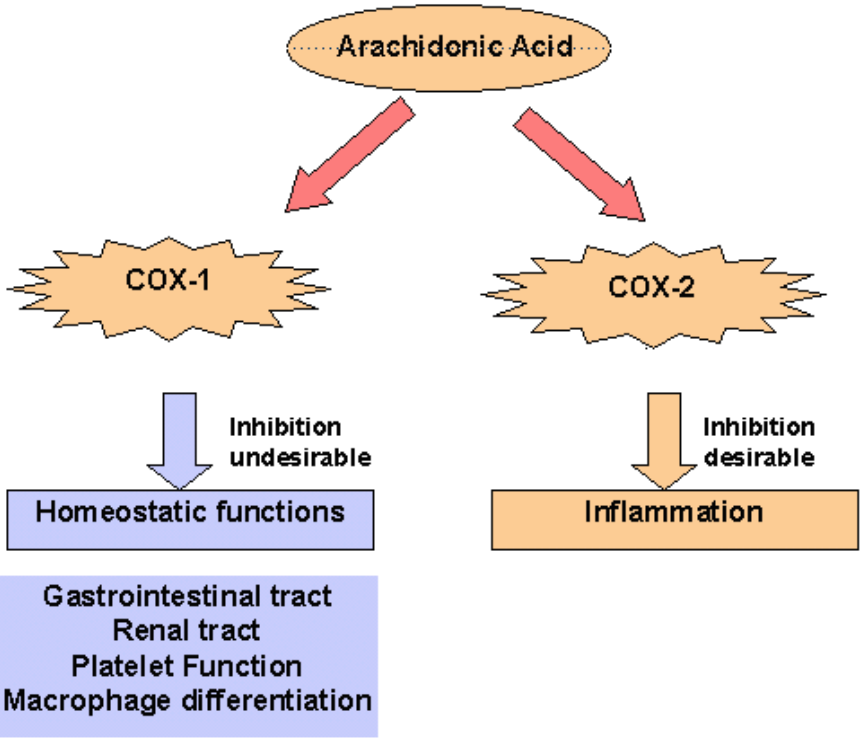
- Aspirin is anti-inflammatory and fever-reducing (antipyretic)
- It irreversibly inhibits cyclooxygenase (COX), the enzyme that catalyzes conversion of arachidonic acid to prostaglandins





Targets of Aspirin

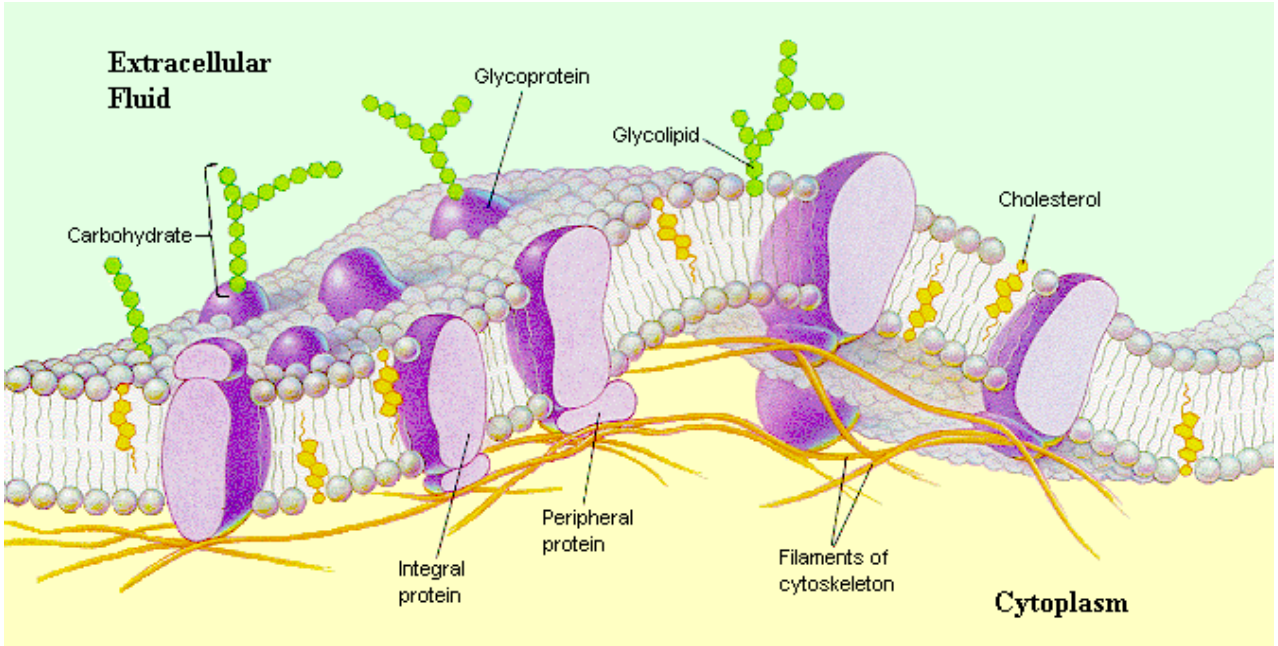
- Cyclooxygenase is present in two forms in cells, COX-1 & COX-2
- Aspirin targets both, but COX-2 should only be the target



Targets COX2

Cell membranes

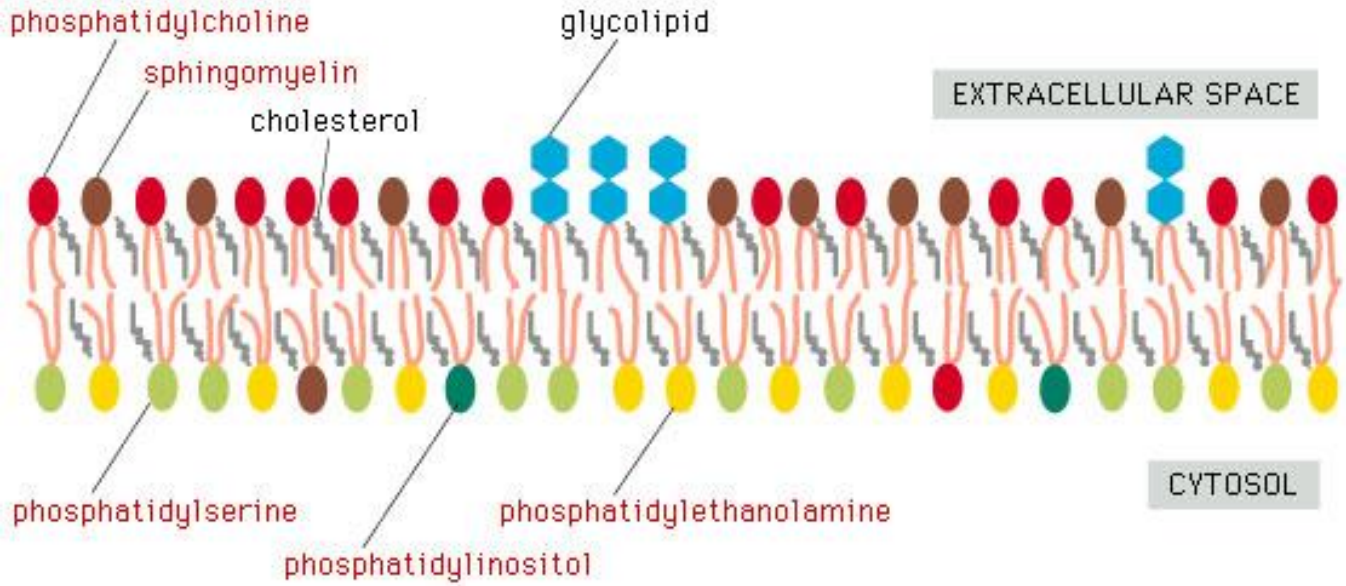
- The membrane is hypothesized in a model known as the fluid mosaic model
- Components: 45% lipid, 45% protein and 10% carbohydrate
- They exist side by side without forming some other substance of intermediate nature



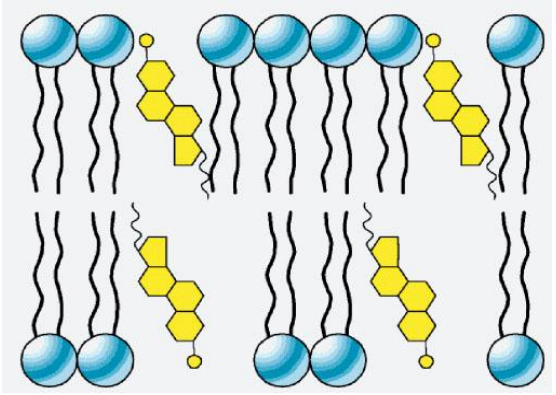
Phospholipids

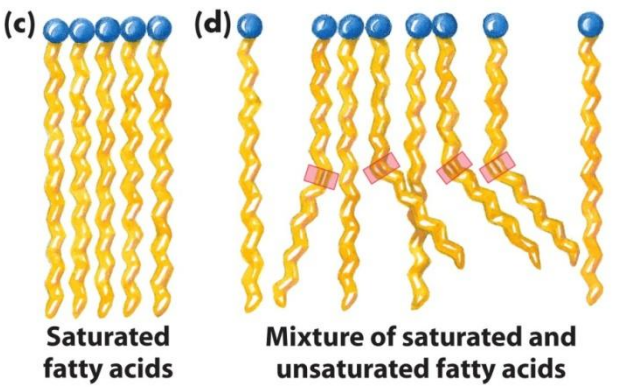
- Bulkier molecules (outer layer) vs. smaller molecules (inner layer)
- Outer: phosphatidylcholine, sphingomyelin, and glycolipids (recognition & interaction)
- Inner: phosphatidylethanolamine, phosphatidylserine, & phosphatidylinositol (signaling)

Cholesterol is distributed in both leaflets



Membrane fluidity



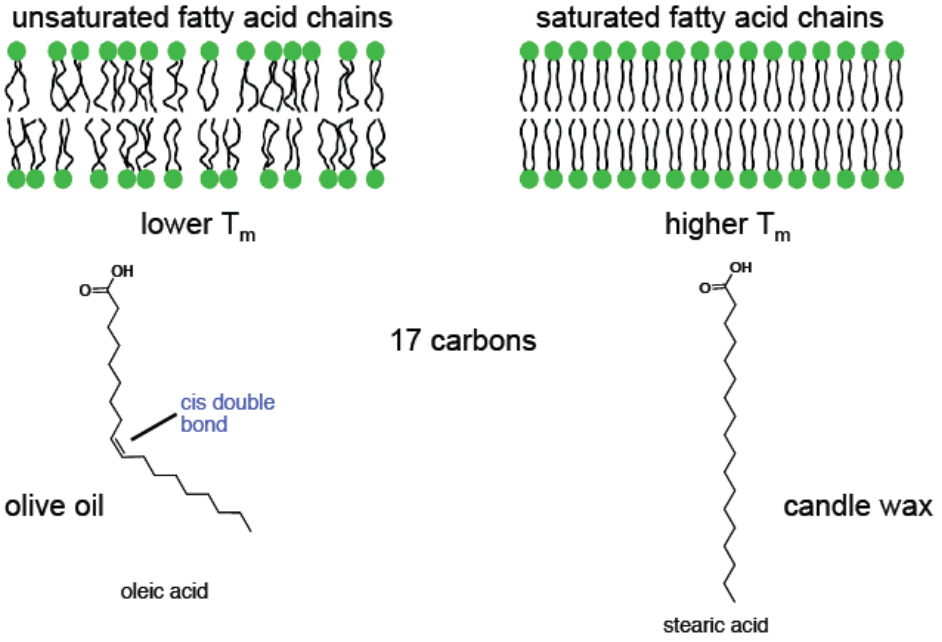


- Cholesterol content
- Fatty acid content

Cells
Prokaryotes; Plants; Animals

Fluidity

Rigidity

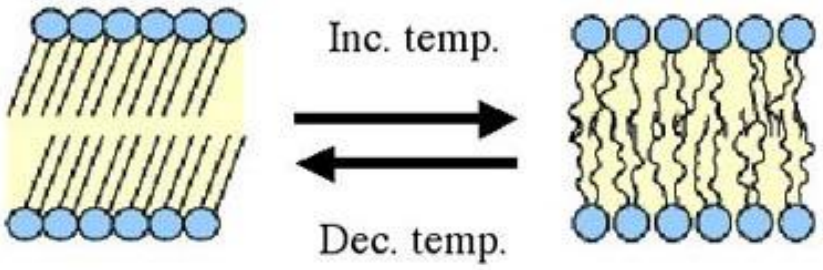


- Cholesterol Stabilizes the extended straight-chain saturated fatty acids by van der Waals interactions

- Cholesterol makes the membrane less solid at low temperatures & more solid at high temperatures

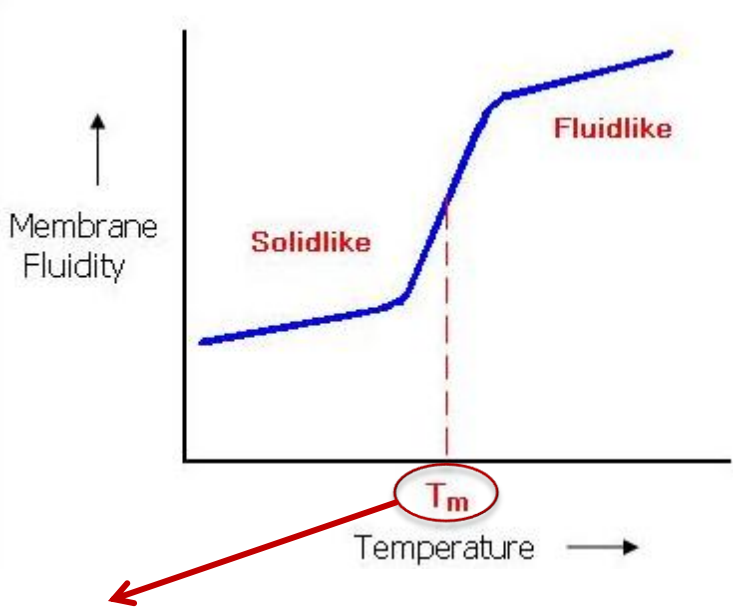
- Decreases the mobility of hydrocarbon tails of phospholipids
- Interferes with close packing of fatty acid tails in the crystal state

Membrane fluidity & temperature



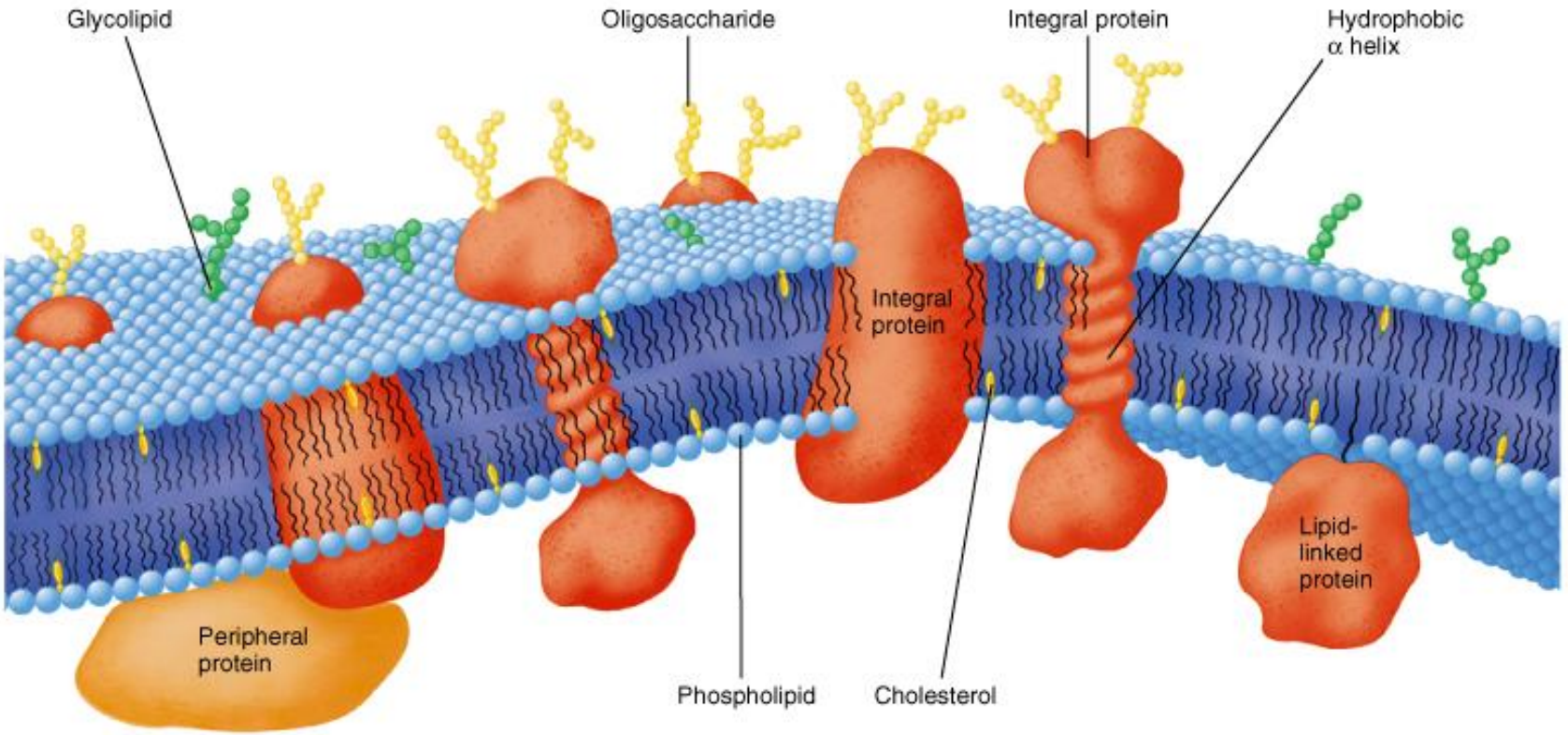
Very regular,
Ordered structure

Less tightly packed,
Hydrocarbon tails
Disordered.



Melting temperature (transition temperature)

Membrane proteins

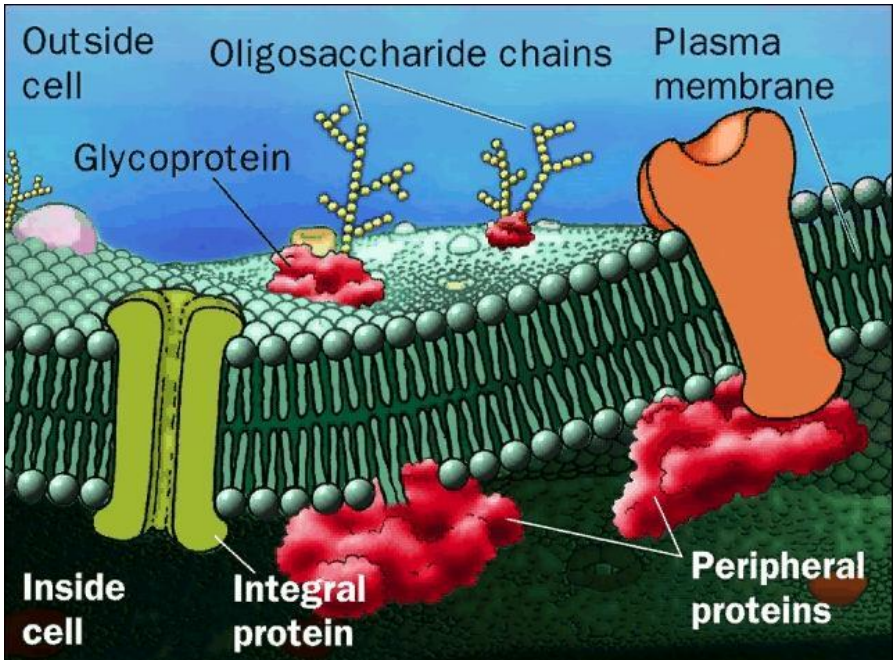


Types of membrane proteins

- Peripheral proteins:
  - Associated with the exterior of membranes via non-covalent interactions
- Integral membrane proteins:
  - Anchored into membrane via hydrophobic regions
- Lipid-anchored:
  - Associated via a lipid group

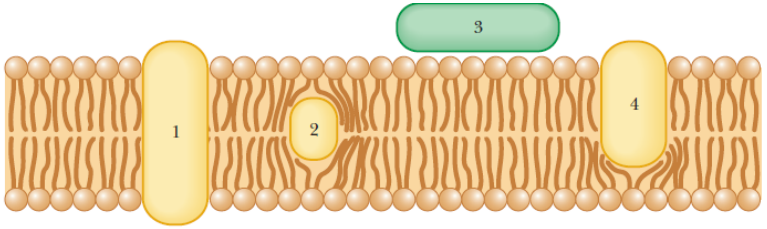
Peripheral membrane proteins

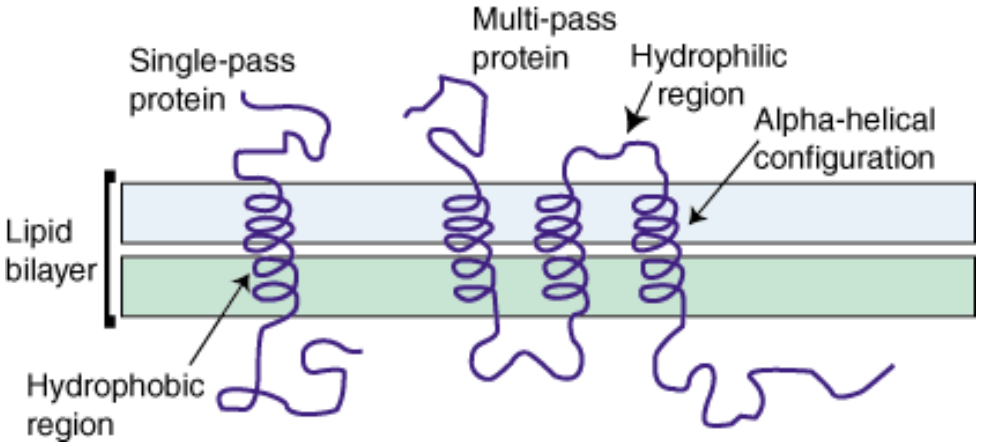
- Associated with membranes but do not penetrate the hydrophobic core of the membrane
  - Often associated with integral membrane proteins
- Not strongly bound to membranes & can be removed without disrupting the membrane structure
  - Treatment with mild detergent



Integral membrane proteins

The integral proteins can be associated with the lipid bilayer in several ways

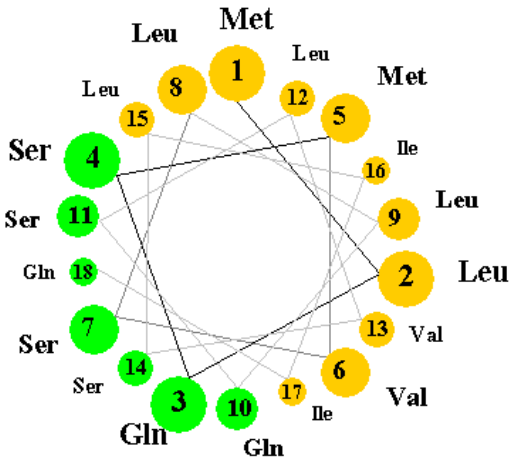


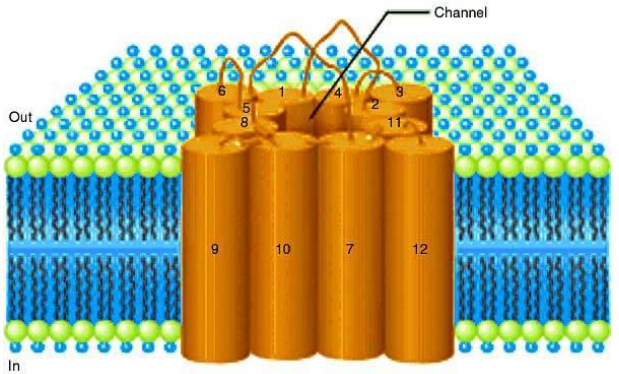


The membrane integral domains are:

1. Single or multiple
2. α-helix or β-sheet

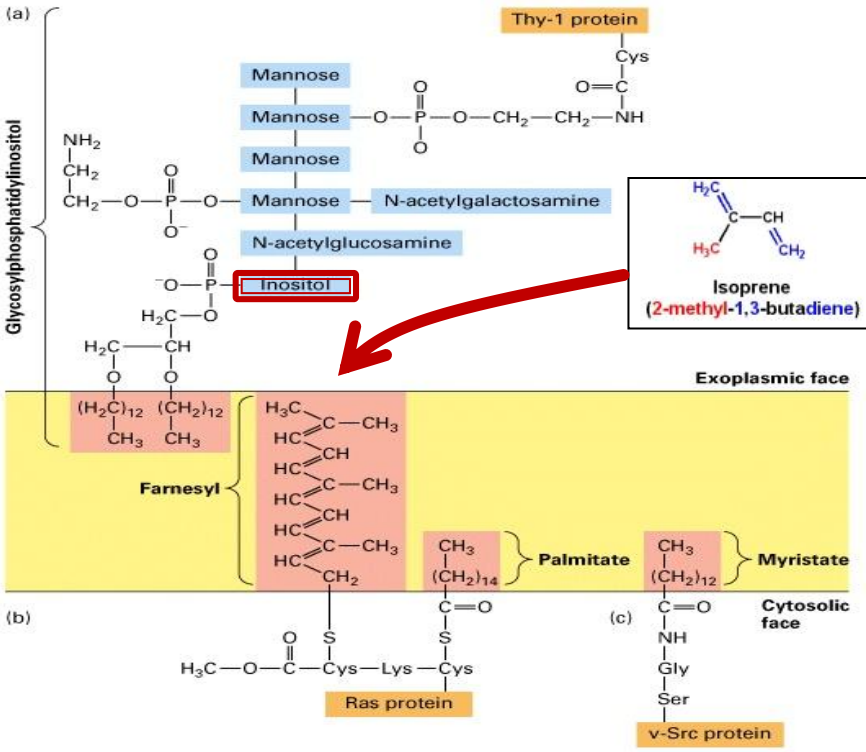
Amphipathic α helices

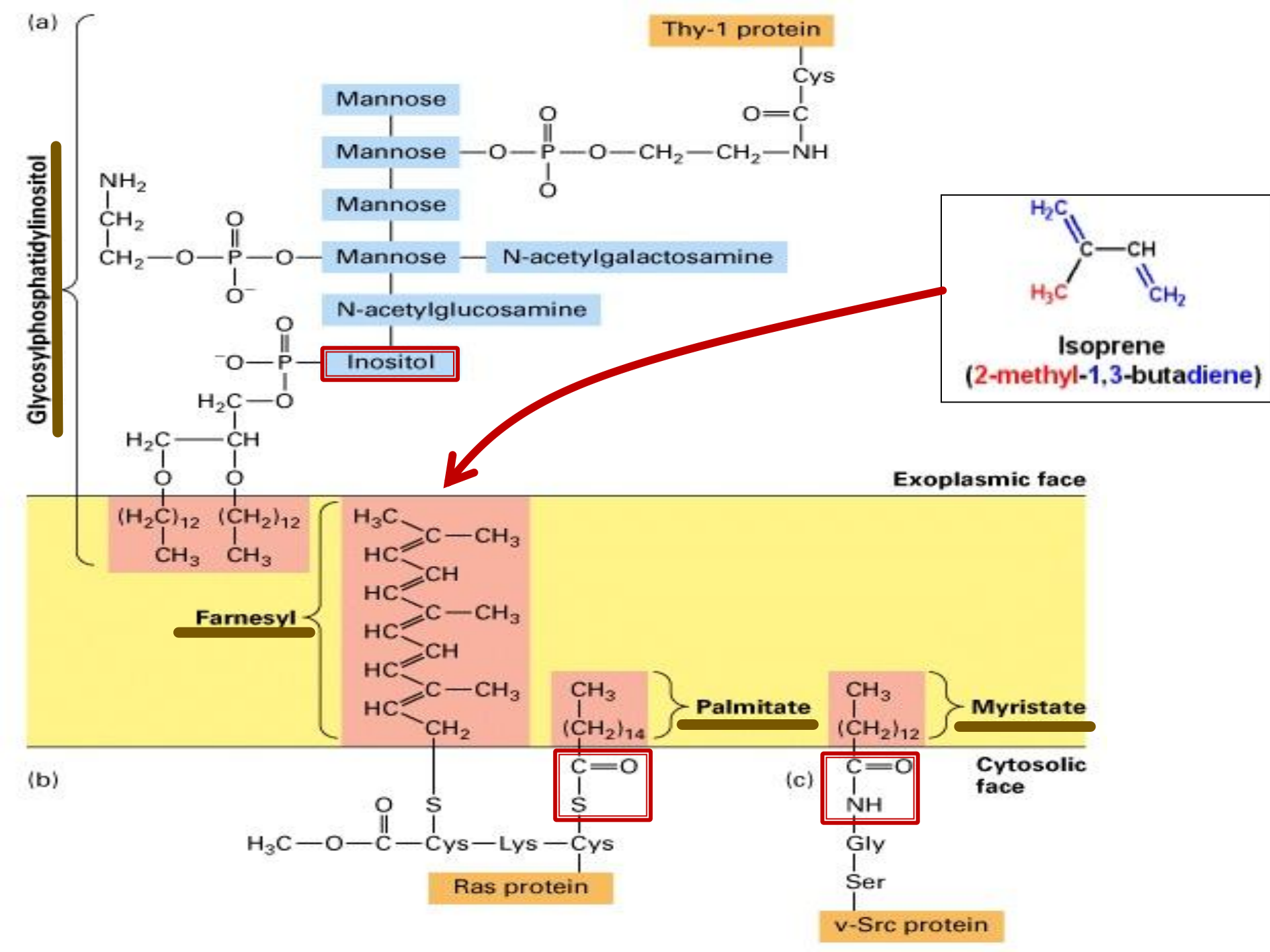




Lipid-anchored membrane proteins

- Four types:
  - Amide-linked myristoyl anchors
    - ✓Always myristic acid
  - Thioester-linked fatty acyl anchors
    - ✓Myristate, palmitate, stearate, oleate
  - Thioether-linked prenyl anchors
    - ✓Prenylation refers to linking of "isoprene"-based groups
  - Glycosyl phosphatidylinositol anchors
    - ✓Ethanolamine link to an oligosaccharide linked in turn to inositol of PI




(a)
Thy-1 protein
Cys
Mannose
Mannose
Mannose
Mannose
N-acetylgalactosamine
N-acetylglucosamine
Inositol
Glycosylphosphatidylinositol
Isoprene
(2-methyl-1,3-butadiene)
Exoplasmic face
Farnesyl
Palmitate
Myristate
Cytosolic face
(b)
(c)
Ras protein
Gly
Ser
v-Src protein

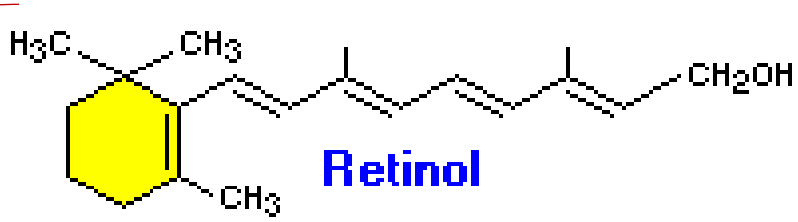
Structure-Function of Membranes

- Transport:
  - Membranes are impermeable barrier
  - Proteins can be carriers or channels
- Signaling
  - Protein receptors and small molecules (some can be lipids themselves)
- Catalysis
  - Enzyme-linked receptors

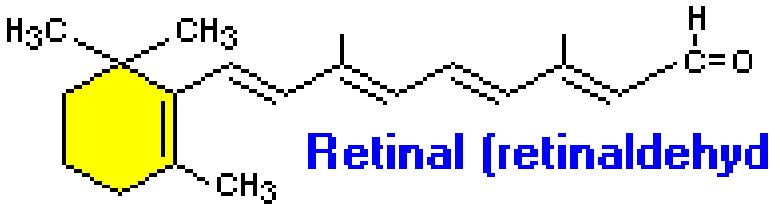
Vitamins

Vitamin A

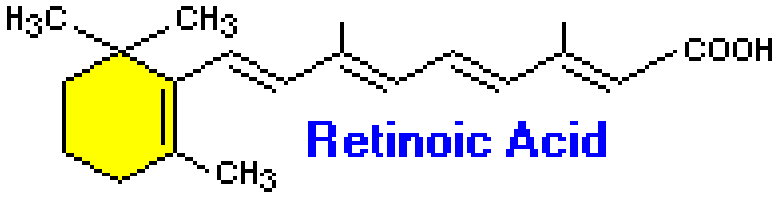
Forms of vitamin A



Retinol

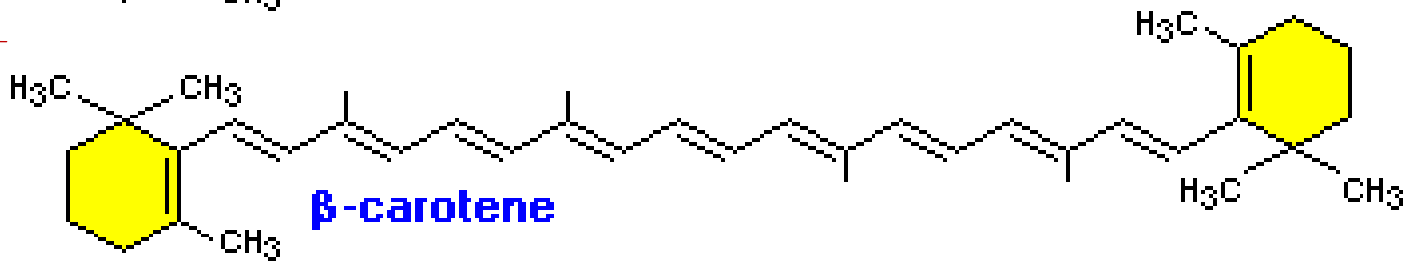


Retinal (retinaldehyde)



Retinoic Acid

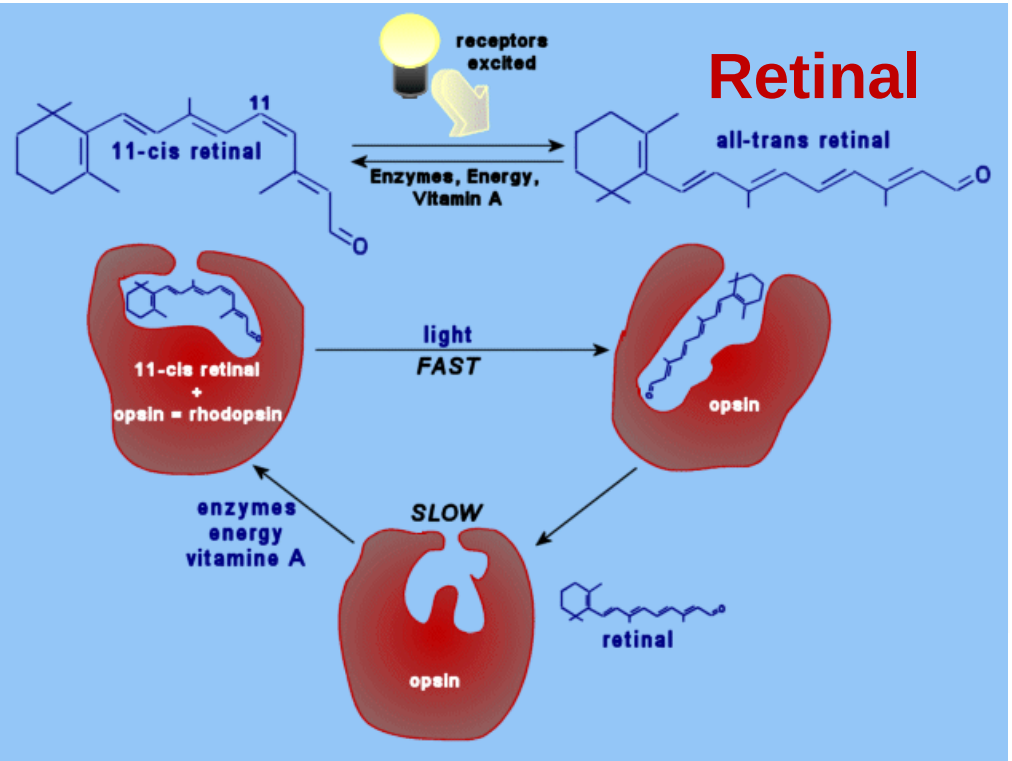
precursor

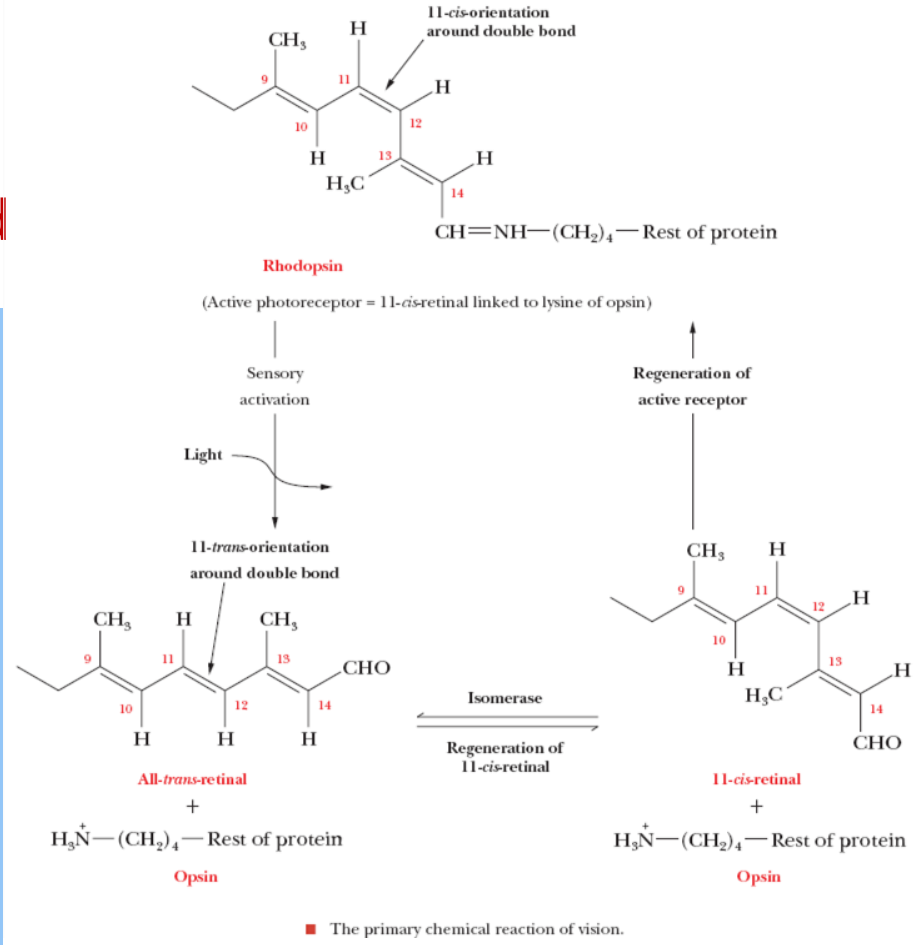


β-carotene

Vision

- The outer segment of rod cells contains flat membrane enclosed discs, the membrane consisting of about 60% rhodopsin and 40% lipid

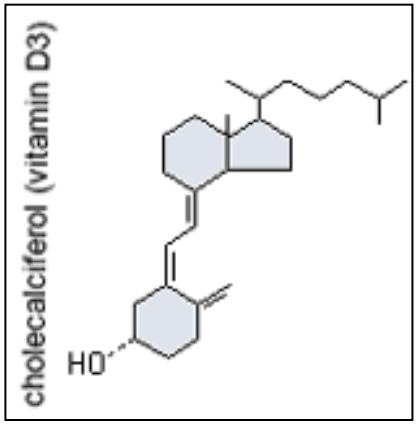


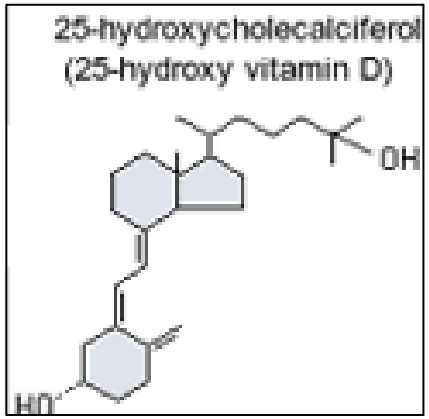


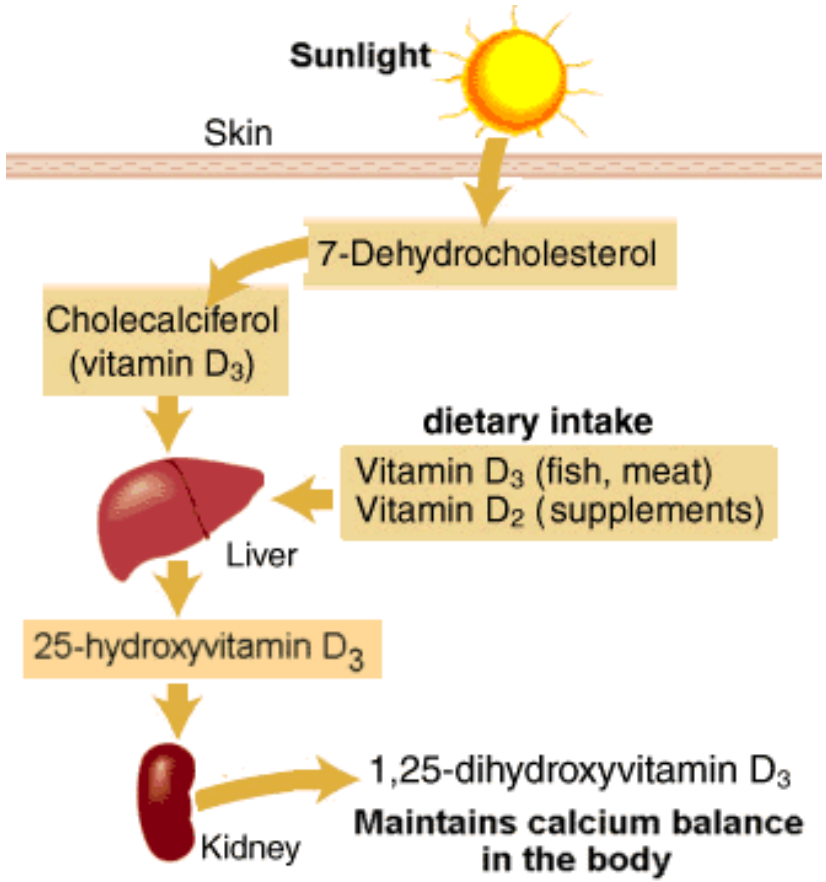
■ The primary chemical reaction of vision.

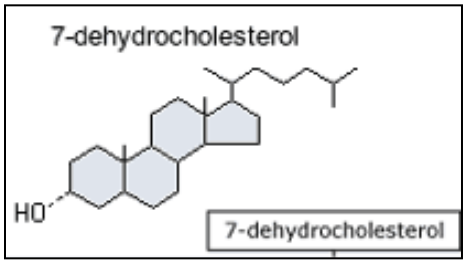
Vitamin D

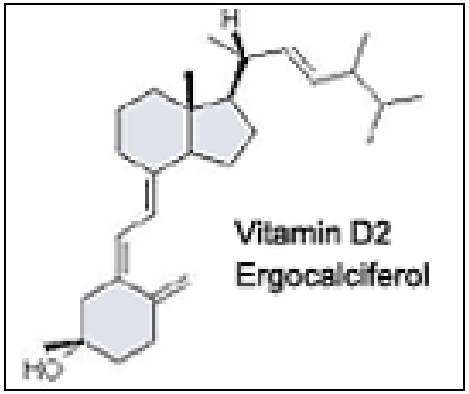
- Increases synthesis of a Ca^{2+} -binding protein, which increases absorption of dietary calcium in the intestines & calcium uptake by the bones

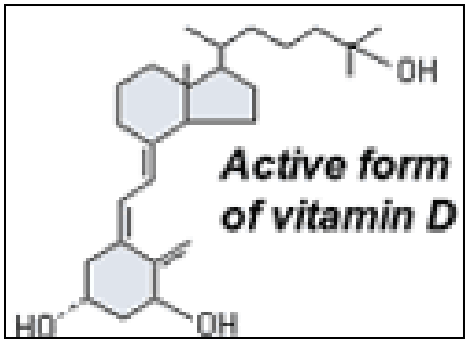






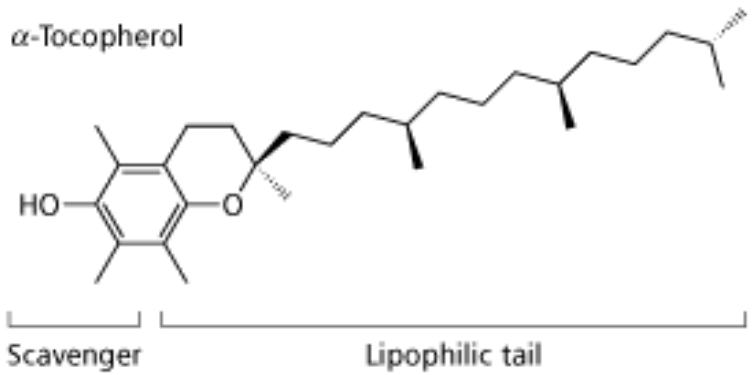




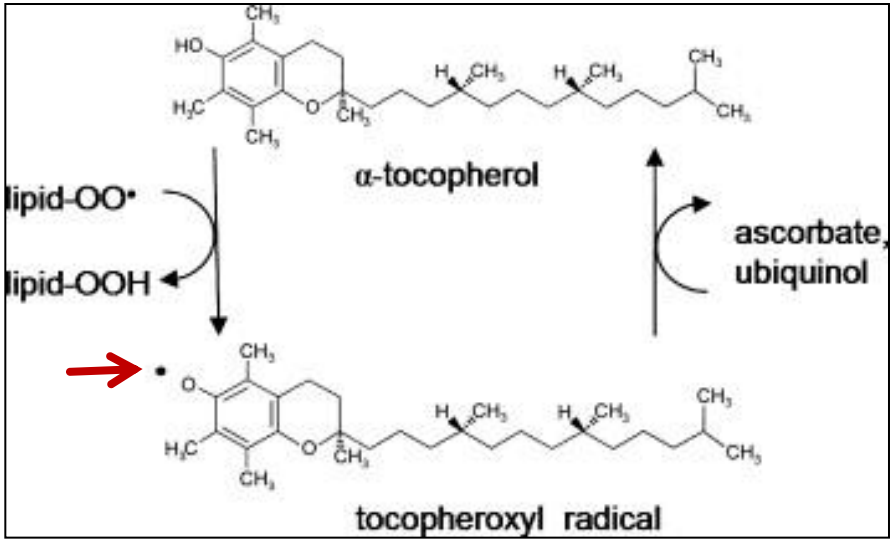


Vitamin E

- A group of molecules (tocopherols); α-tocopherol is the most active

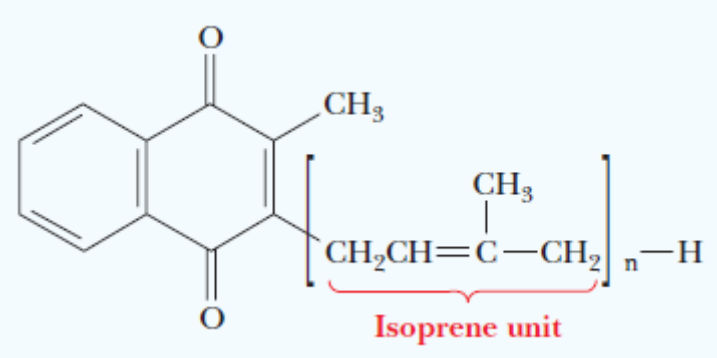


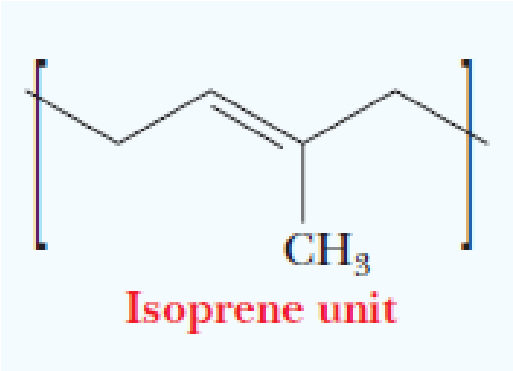
- A good reducing agent & an antioxidant (it reacts with oxidizing agents before they can attack other biomolecules)



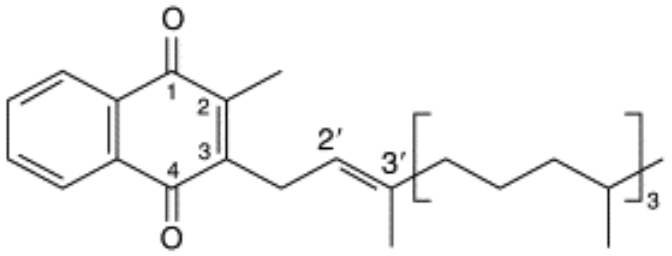
Vitamin K

- **The bicyclic ring system contains two carbonyl groups & a long unsaturated hydrocarbon side chain that consists of repeating *isoprene* Units**

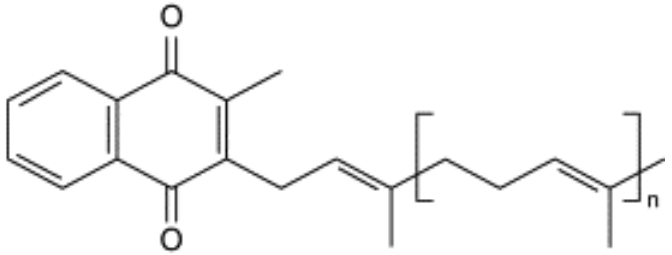




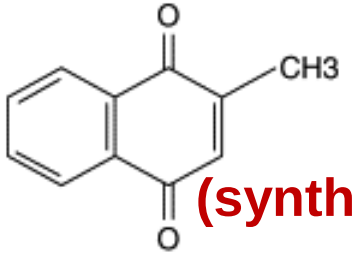
Vitamin K1



Vitamin K2



Vitamin K3



(synthetic vitamin K)

Biological function of vitamin K

- Carboxylation of glutamate producing γ-carboxyglutamate residues in the prothrombin protein
- The two carboxyl groups bind Ca^{2+} ion form a *bidentate ("two teeth") ligand*, which is required for blood clotting
- Two well-known anticoagulants, dicumarol & warfarin (a rat poison), are vitamin K antagonists