LIPID CHEMISTRY

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Definition

- Lipids are organic compounds formed mainly from alcohol and fatty acids combined together by ester linkage.

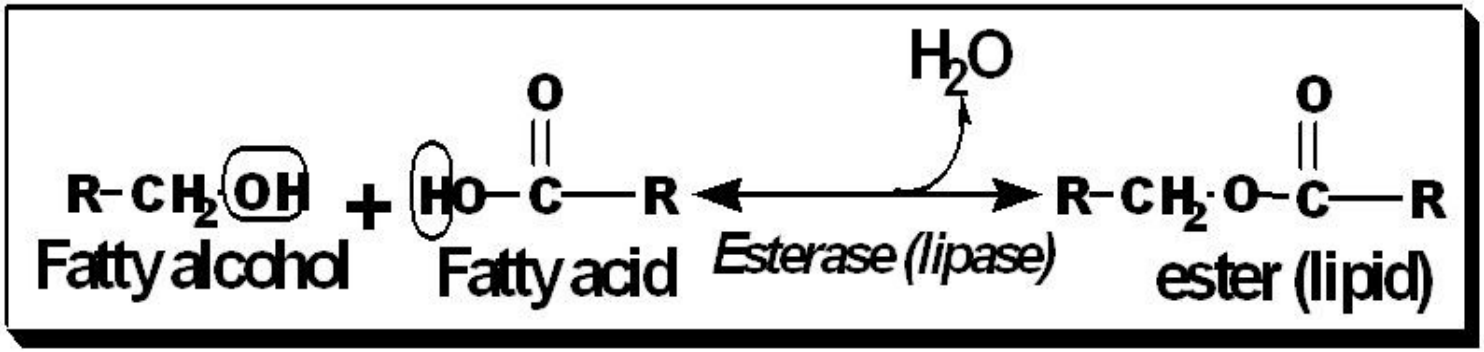
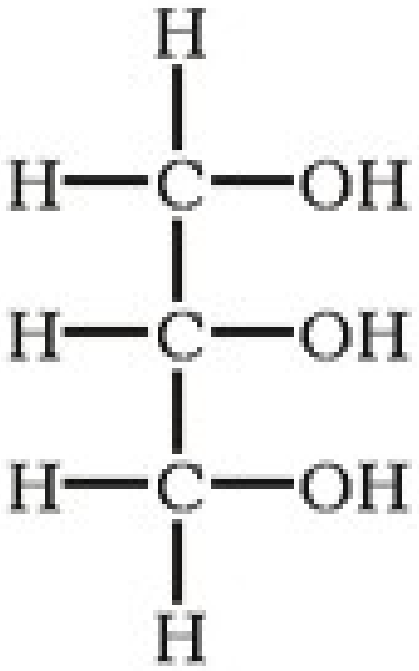
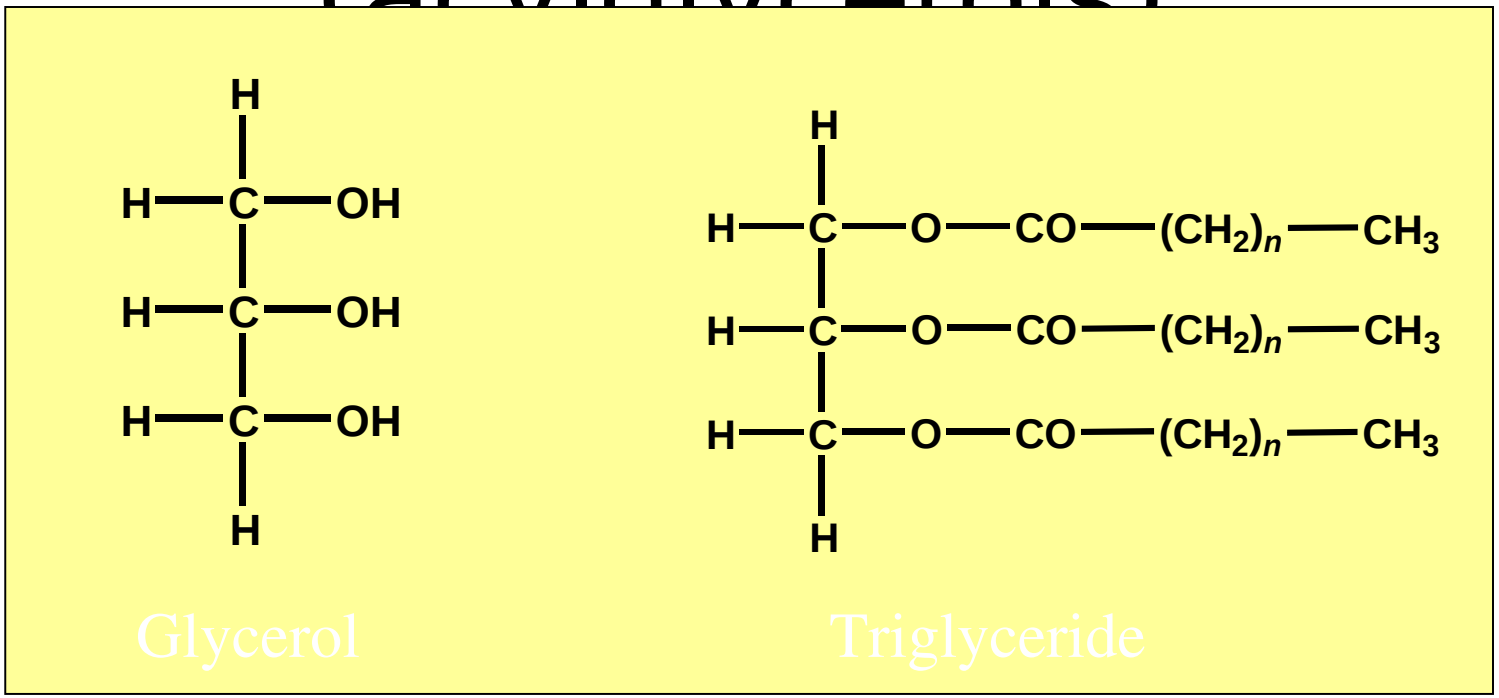


Figure 1. Structure of Glycerol

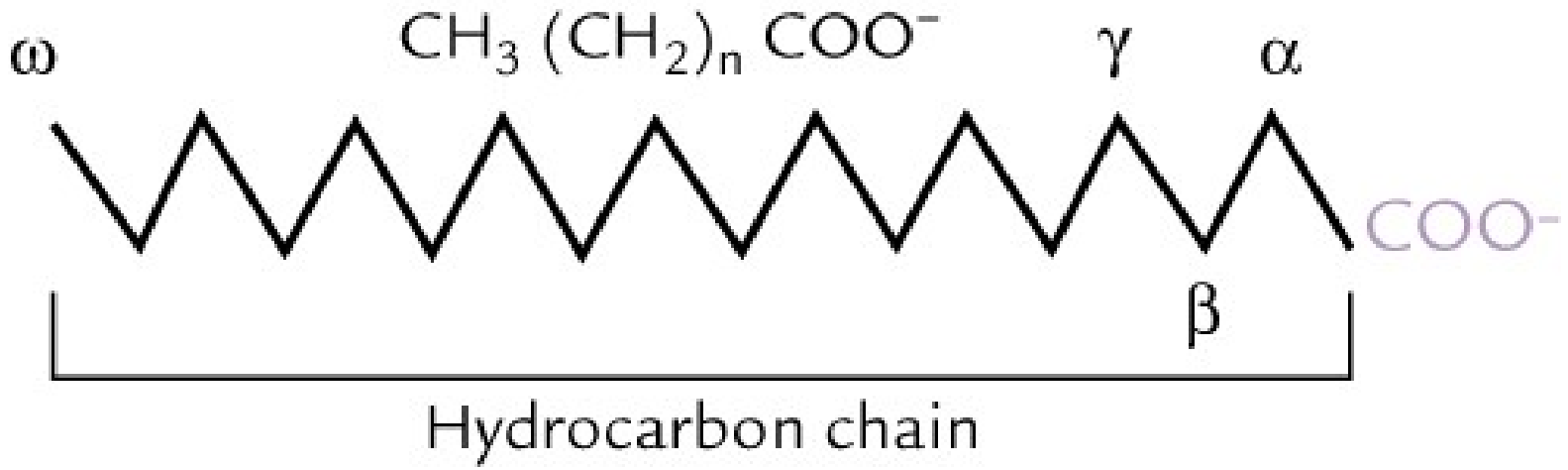


Glycerol esters (acylglycerols)

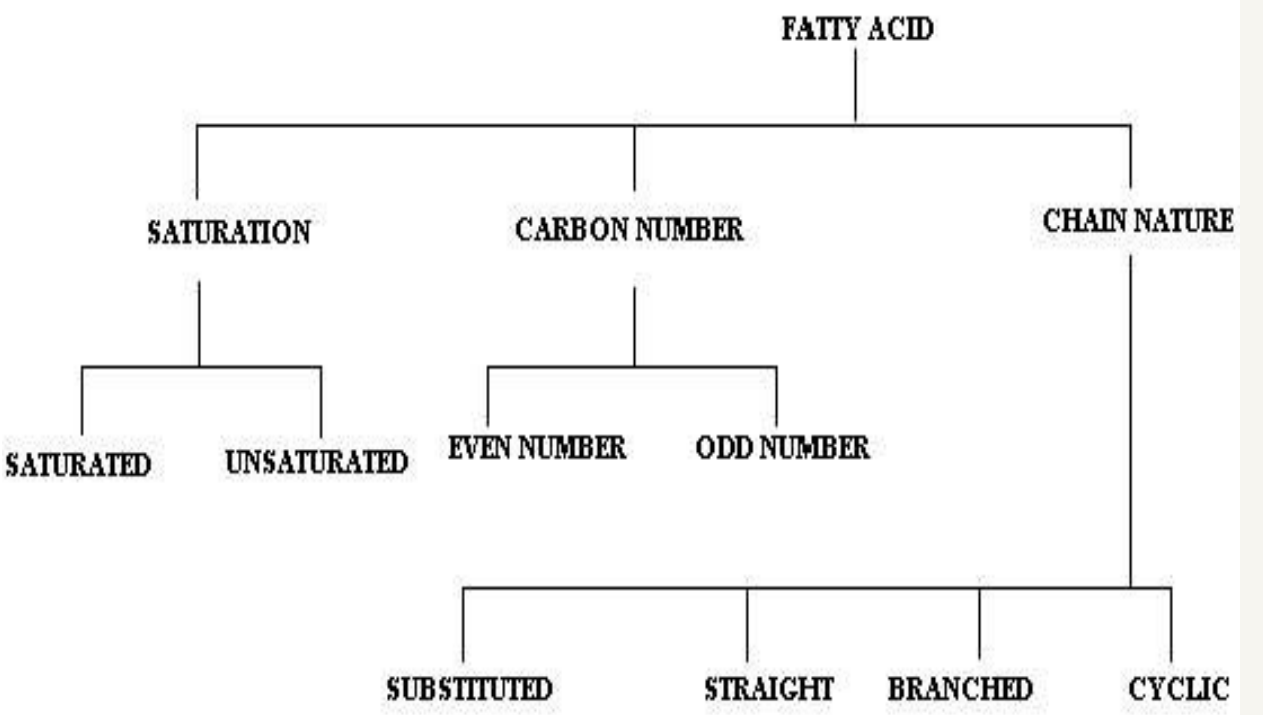


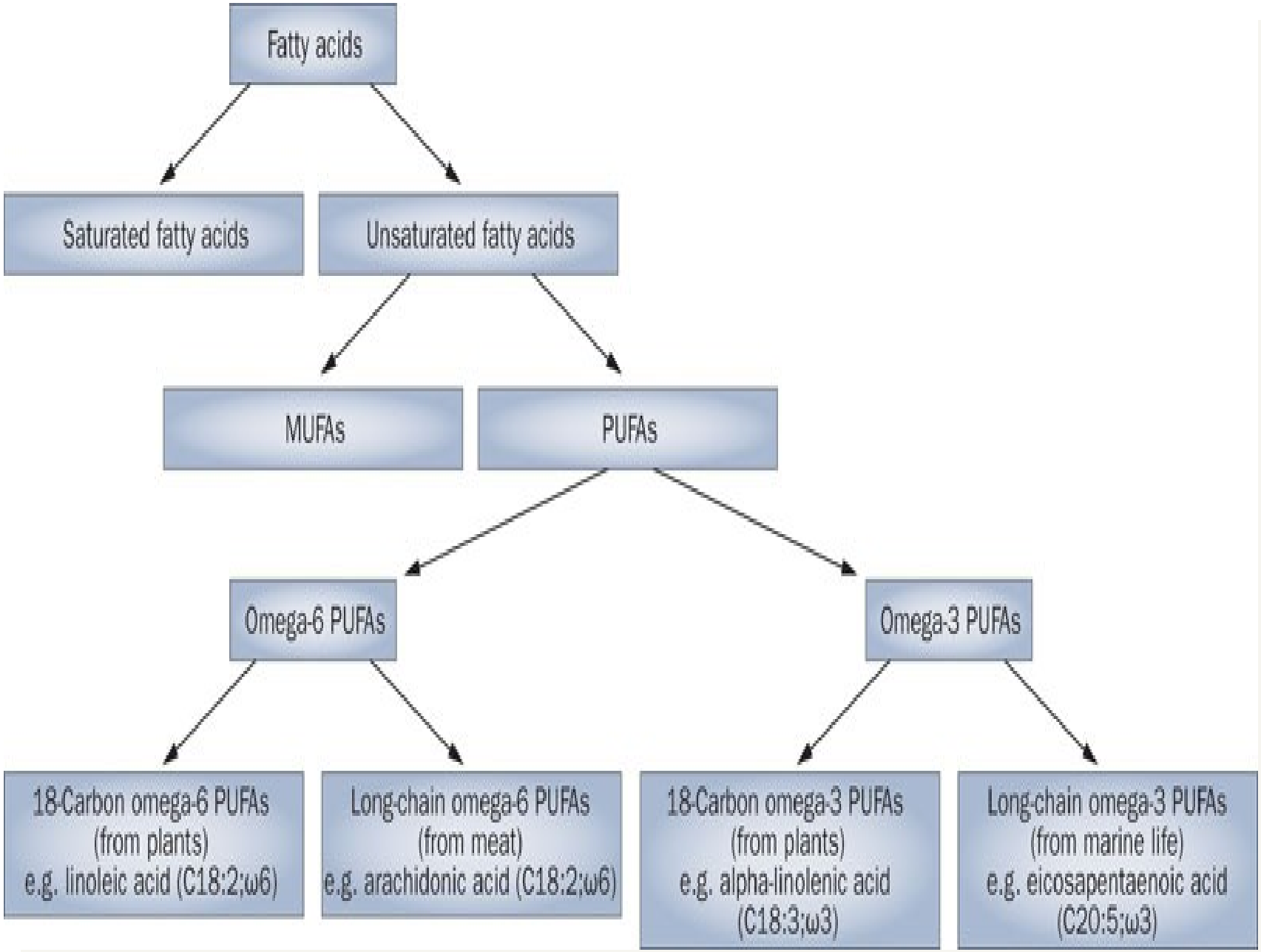
- Triglycerides : most abundant family of lipids in plant and animal cells.
- major components of the the human diet

Fatty acid

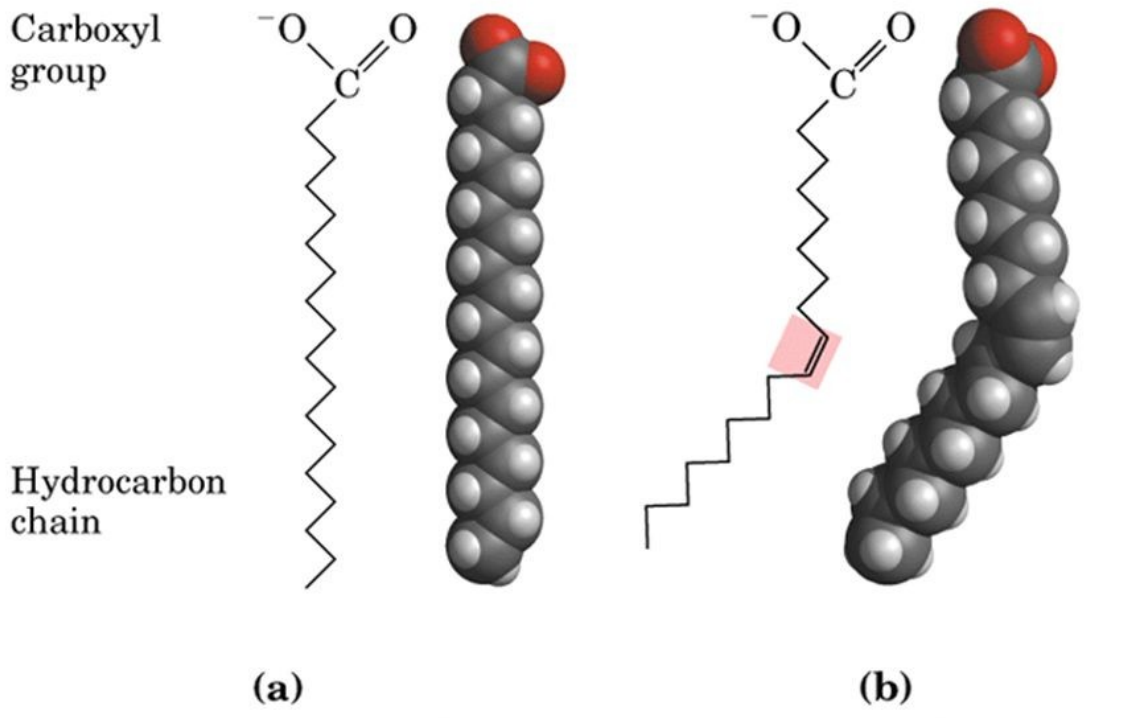


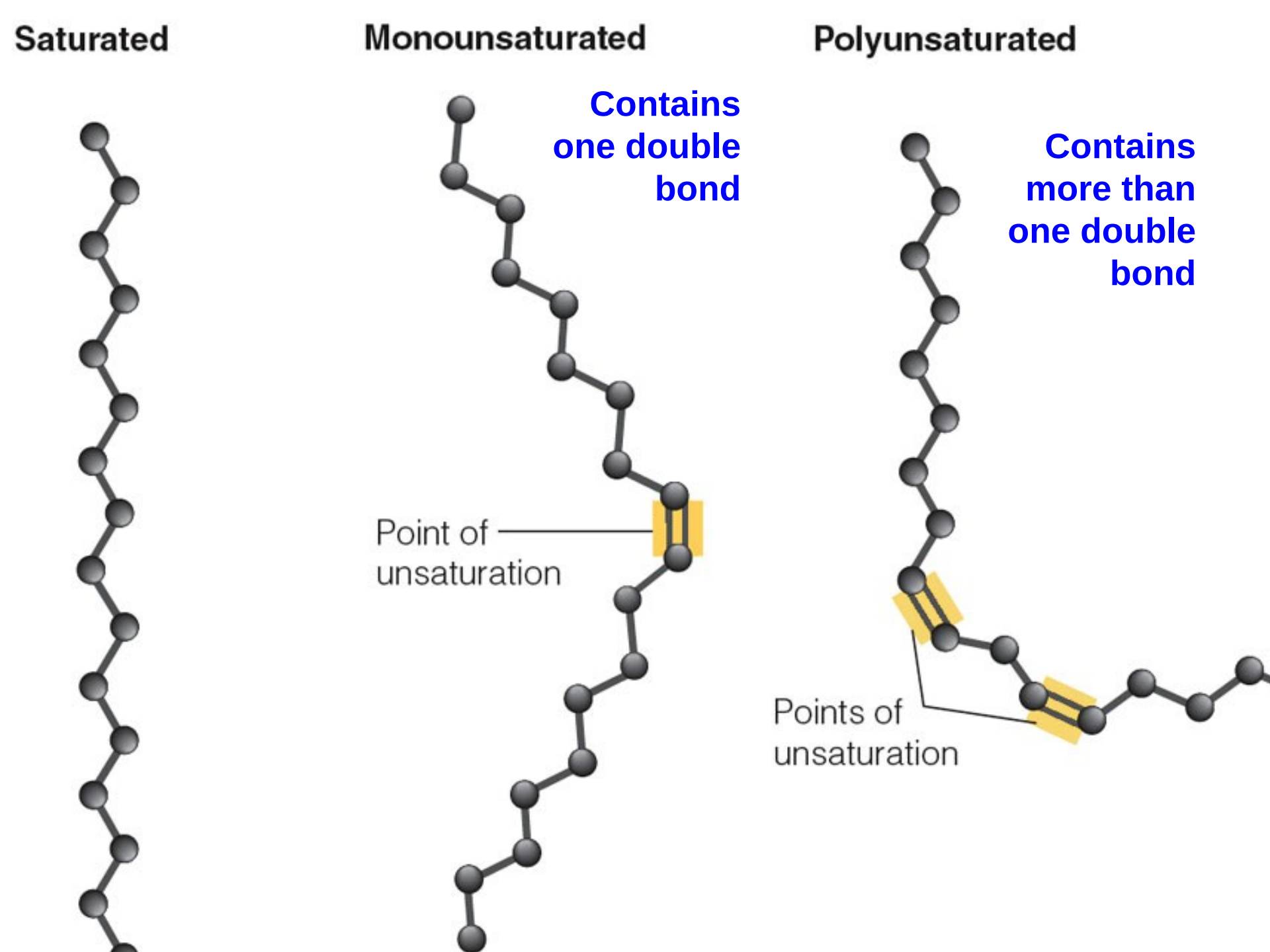
Classification



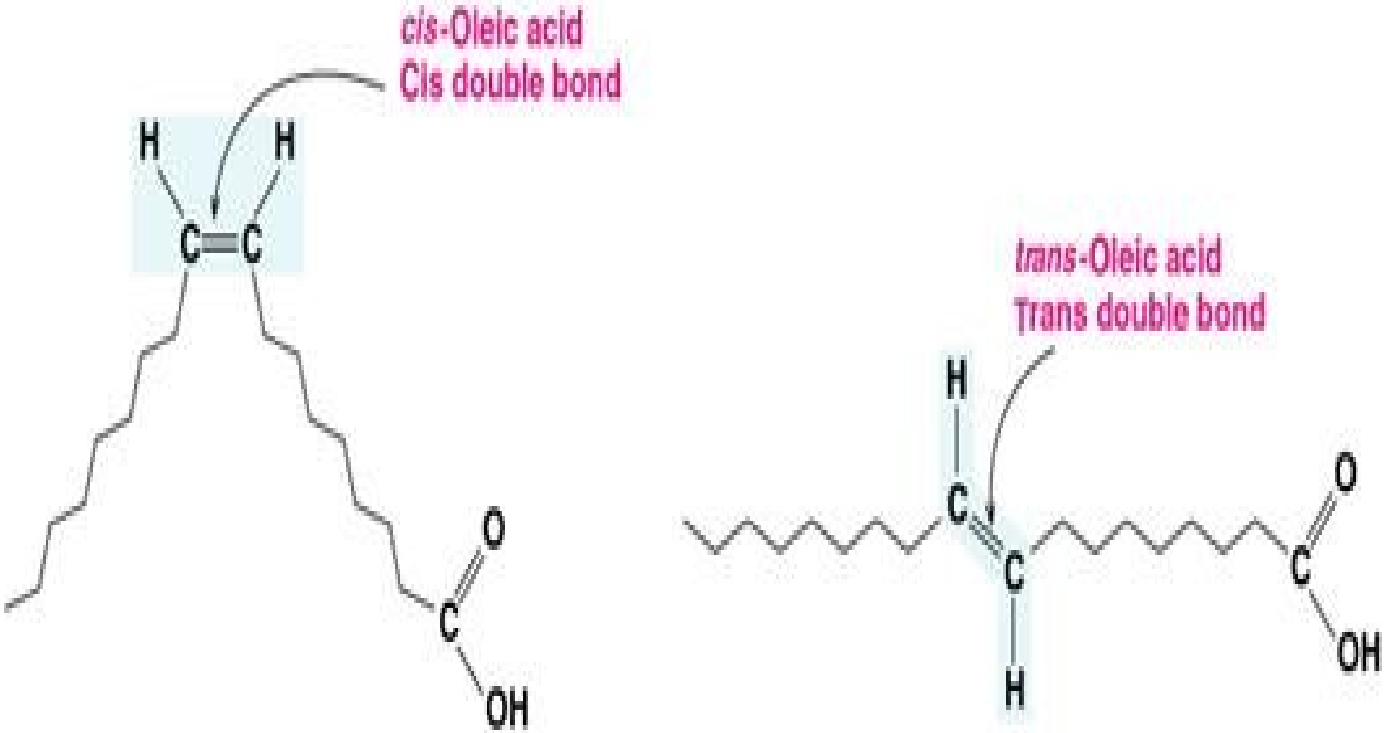

Fatty acids
Saturated fatty acids
Unsaturated fatty acids
MUFAs
PUFAs
Omega-6 PUFAs
Omega-3 PUFAs
18-Carbon omega-6 PUFAs (from plants) e.g. linoleic acid (C18:2;ω6)
Long-chain omega-6 PUFAs (from meat) e.g. arachidonic acid (C18:2;ω6)
18-Carbon omega-3 PUFAs (from plants) e.g. alpha-linolenic acid (C18:3;ω3)
Long-chain omega-3 PUFAs (from marine life) e.g. eicosapentaenoic acid (C20:5;ω3)

Saturated and Unsaturated Fatty Acids




Saturated
Monounsaturated
Contains one double bond
Point of unsaturation
Polyunsaturated
Contains more than one double bond
Points of unsaturation

Name	Type	Number of carbon atoms	Number of double bonds	Symbol
Palmitic acid	Saturated	16	0	16:0
Stearic acid	Saturated	18	0	18:0
Oleic acid	Monounsaturated	18	1	18:1n-9
α-linolenic acid (ALA)	ω-3 polyunsaturated	18	3	18:3n-3
Eicosapentaenoic acid (EPA)	ω-3 polyunsaturated	20	5	20:5n-3
Docosapentaenoic acid (DPA) n-3	ω-3 polyunsaturated	22	5	22:5n-3
Docosahexaenoic acid (DHA)	ω-3 polyunsaturated	22	6	22:6n-3
Linoleic acid (LNA)	ω-6 polyunsaturated	18	2	18:2n-6
DPA n-6	ω-6 polyunsaturated	22	5	22:5n-6
Arachidonic acid (ARA)	ω-6 polyunsaturated	20	4	20:4n-6


cis-Oleic acid
Cis double bond
H
H
C
C
O
C
OH
trans-Oleic acid
Trans double bond
H
C
C
H
O
C
OH

Functions OF PUFA :

1. Useful to prevent atherosclerosis.
2. Prostaglandin & eicosanoids are synthesized
3. They participate in structure of all cellular and subcellular membranes and the transporting plasma phospholipids.
4. Essential for skin integrity, normal growth and reproduction.
5. Important role in blood clotting.
6. Important in preventing and treating fatty liver.
7. Important role in health of the retina and vision.
8. They can be oxidized for energy production.

Deficiency: Their deficiency in the diet leads to nutritional deficiency disease. Its symptoms include:

1. Poor growth and health with susceptibility to infections, dermatitis,
2. Decreased capacity to reproduce,
3. Impaired transport of lipids, fatty liver,
4. Lowered resistance to stress.

Source: vegetable oils such as corn oil, peanut oil, olive oil, cottonseed oil, soybean oil and many other plant oils, cod liver oil and animal fats.

Property-Rancidity

Definition:

- It is a physico-chemical change in the natural properties of the fat leading to the development of unpleasant odour or taste or abnormal color particularly on aging after exposure to atmospheric oxygen, light, moisture, bacterial or fungal contamination and/or heat.

Types and causes of Rancidity:

1. Hydrolytic rancidity
2. Oxidative rancidity
3. Ketonic rancidity

1-Hydrolytic rancidity:
Due to hydrolysis of the fat
by lipase from bacterial contamination
at high temperature and moisture.
2-Oxidative Rancidity:
oxidation of fat or oil
Due to exposure to oxygen, light and/or heat
producing peroxide derivatives
that are toxic and have bad odor.
3-Ketonic Rancidity:
due to contamination with fungi
Moisture accelerates ketonic rancidity.

Prevention of rancidity is achieved by:

1. Avoidance of the causes (exposure to light, oxygen, moisture, high temperature and bacteria or fungal contamination).
2. By keeping fats or oils in well-closed containers in cold, dark and dry place.
3. Addition of anti-oxidants. The most common natural antioxidant is vitamin E.

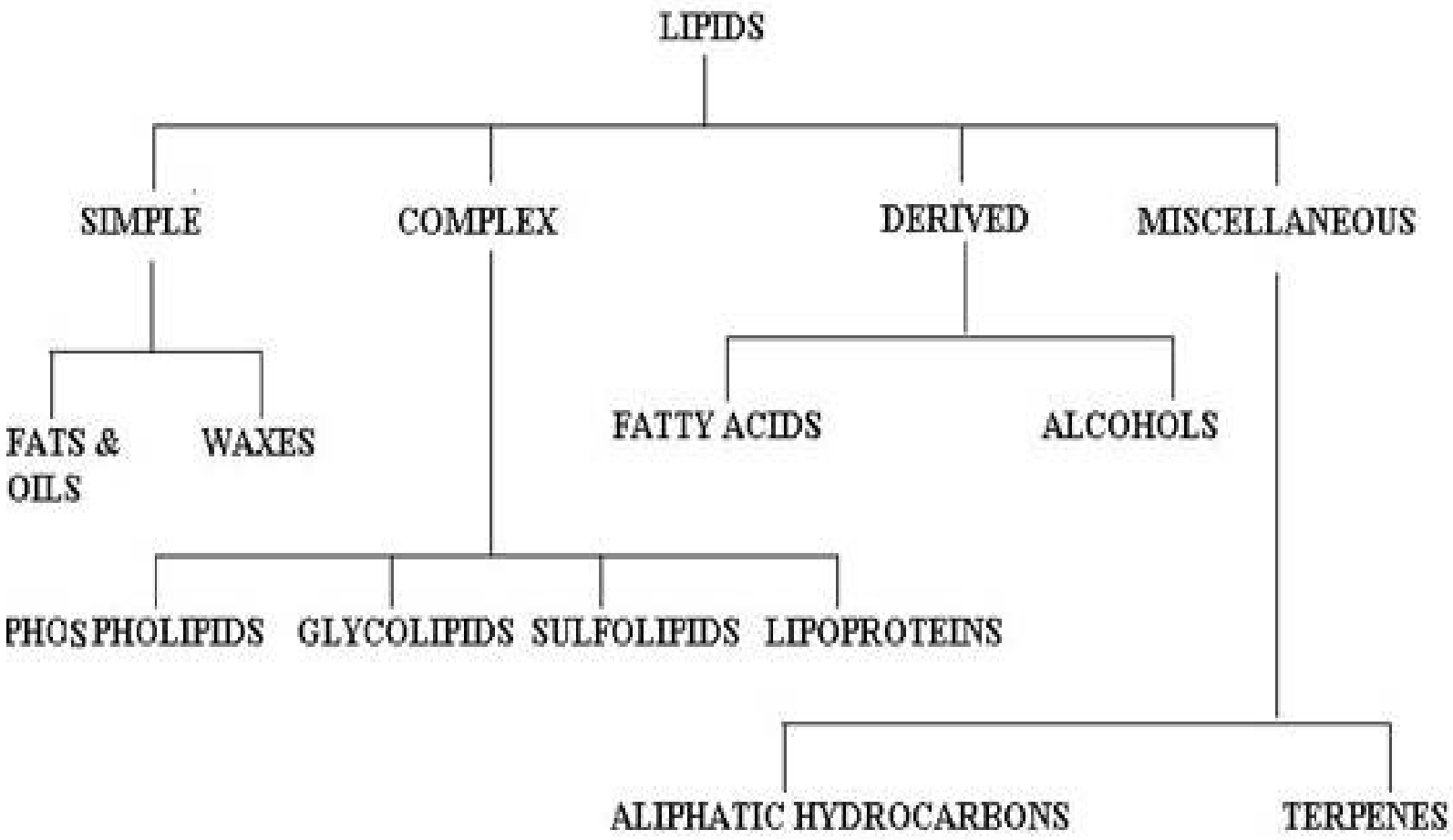
Hazards of Rancid Fats:

1. The products of rancidity are toxic, i.e., causes food poisoning and cancer.
2. Rancidity destroys the fat-soluble vitamins (vitamins A, D, K and E).
3. Rancidity destroys the polyunsaturated essential fatty acids.
4. Rancidity causes economical loss because rancid fat is inedible(Unfit to eat).

Lipids

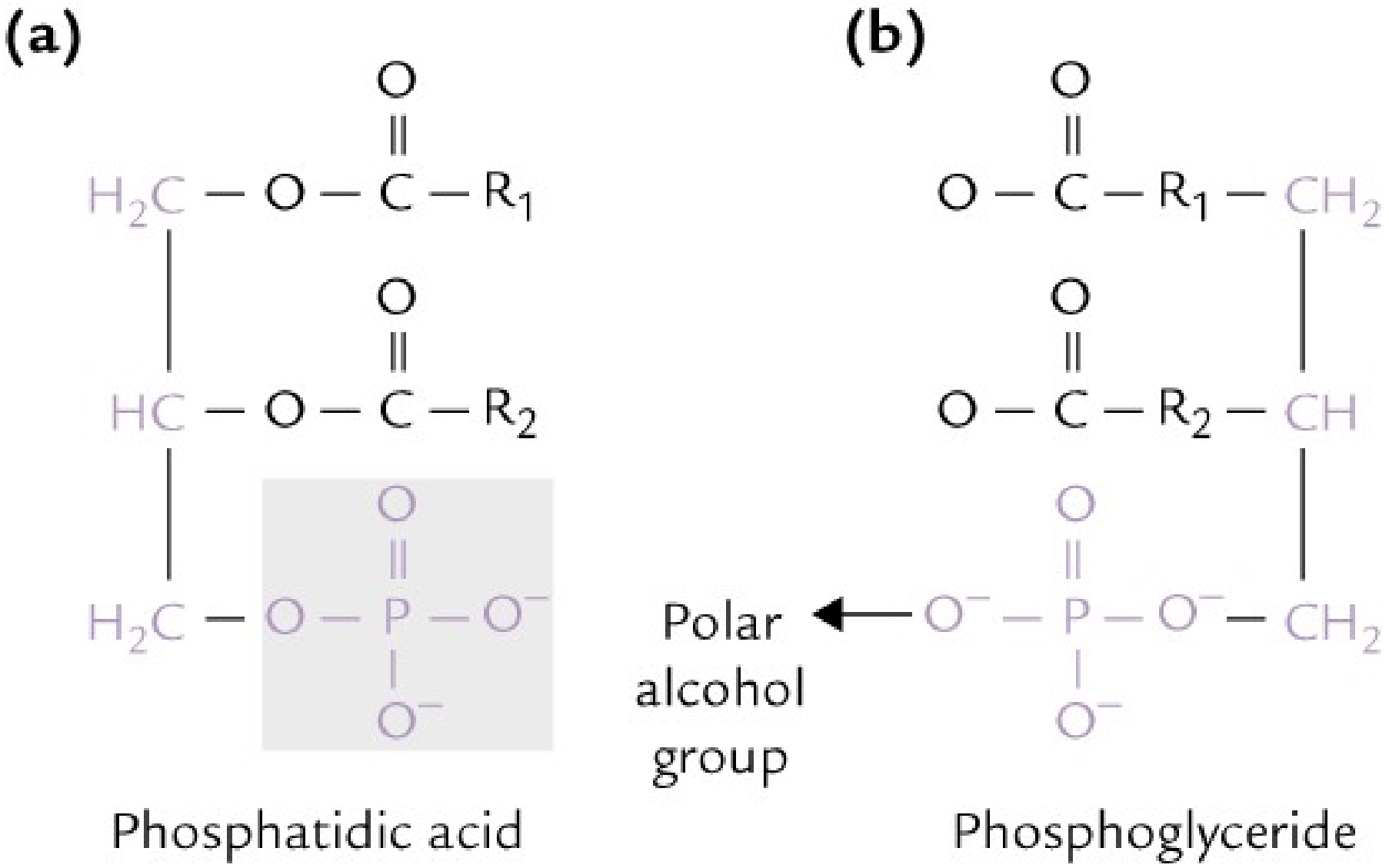
?ARE LIPIDS BAD? DO THEY HAVE ANY FUNCTION

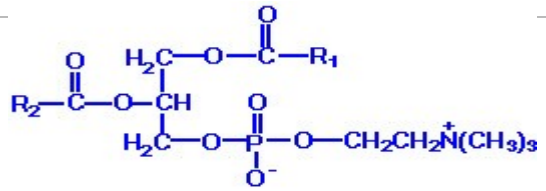
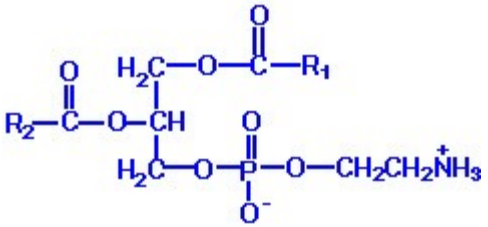
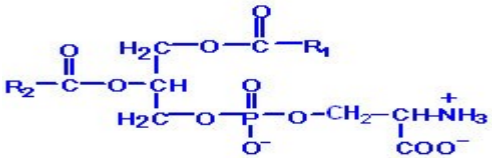
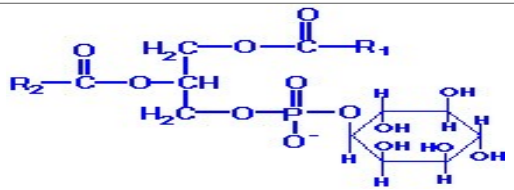
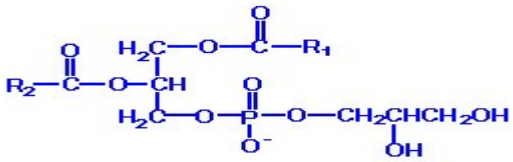
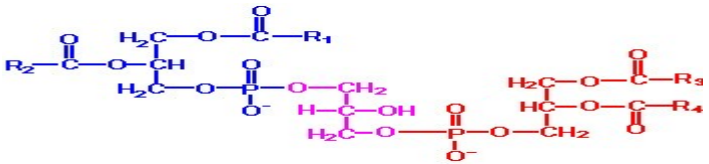
- **ENERGY SOURCE**
- **LIPID STORAGE**
- **INSULATION**
- **STRUCTURAL ROLE**
- **ENDOCRINE FUNCTION**
- **NERVOUS SYSTEM**
- **VITAMIN ABSORPTION**:


LIPIDS
SIMPLE
COMPLEX
DERIVED
MISCELLANEOUS
FATS & OILS
WAXES
FATTY ACIDS
ALCOHOLS
PHOSPHOLIPIDS
GLYCOLIPIDS
SULFOLIPIDS
LIPOPROTEINS
ALIPHATIC HYDROCARBONS
TERPENES

COMPOUND (COMPLEX) LIPIDS

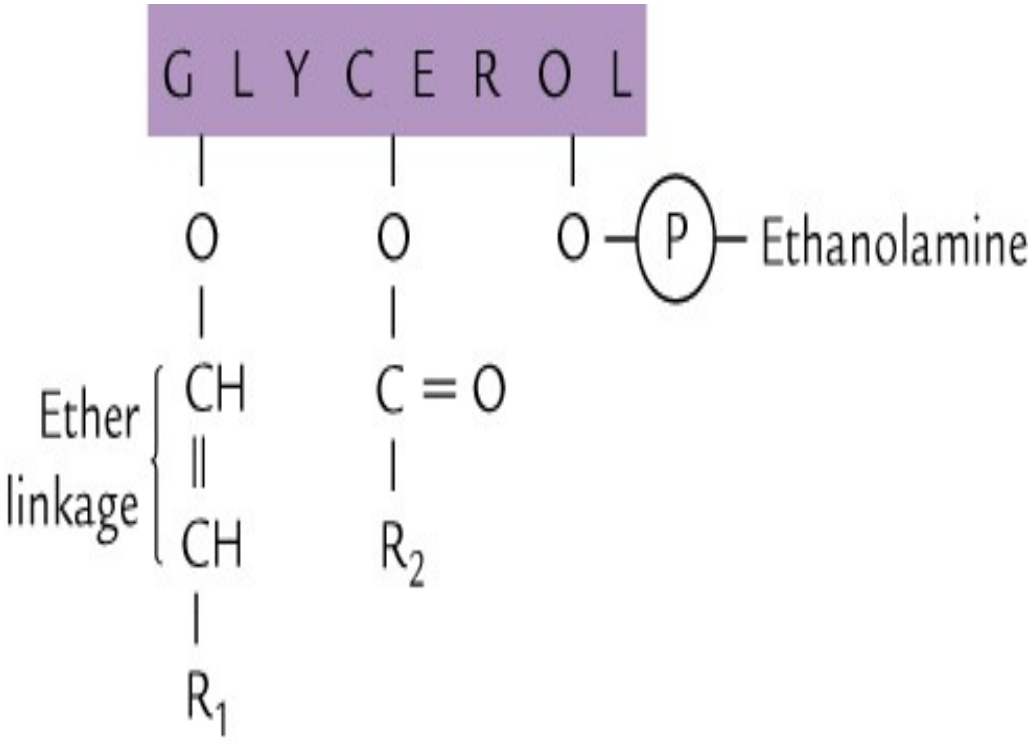
Esters of F.A with different alcohols but carry in addition other substances such as phosphate, nitrogenous carbohydrates & protein

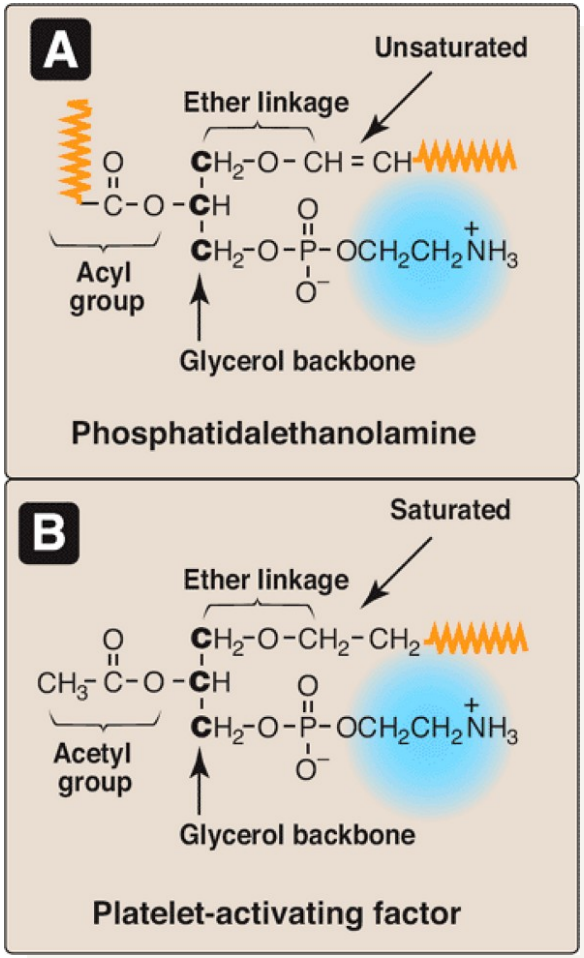

(a)
(b)
Polar alcohol group
Phosphatidic acid
Phosphoglyceride

	**Phosphatidylcholine (PC)**
	**Phosphatidylethanolamine (PE)**
	**Phosphatidylserine (PS)**
	**Phosphatidylinositol (PI)**
	**Phosphatidylglycerol (PG)**
	**Diphosphatidylglycerol (DPG)**

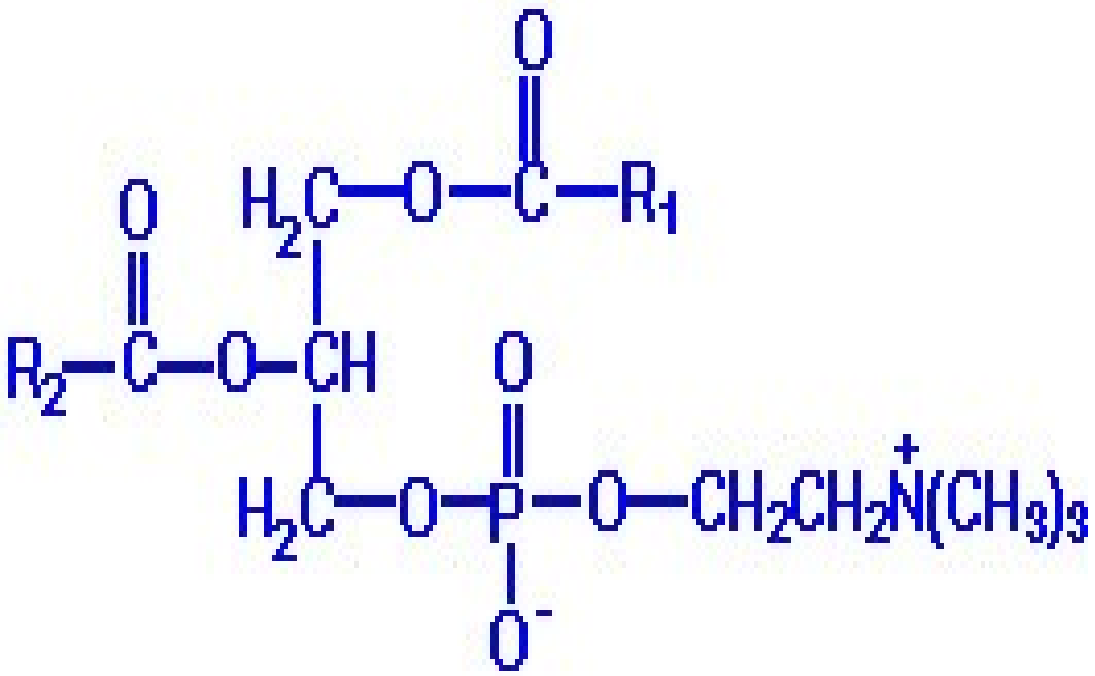
Serine	+ PA →	phosphatidylserine
Ethanolamine	+ PA →	phosphatidylethanolamine (cephalin)
Choline	+ PA →	phosphatidylcholine (lecithin)
Inositol	+ PA →	phosphatidylinositol
Glycerol	+ PA →	phosphatidylglycerol

Phosphotidylethanolamine

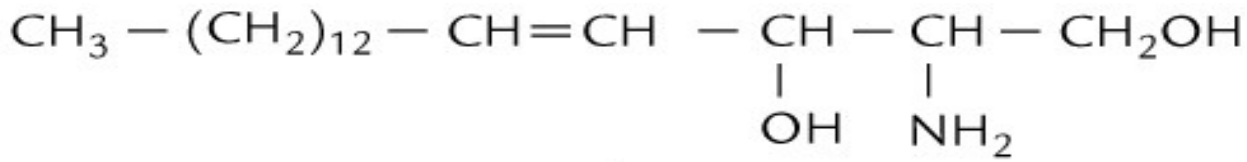



A
Unsaturated
Ether linkage
Acyl group
Glycerol backbone
Phosphatidalethanolamine
B
Saturated
Ether linkage
Acetyl group
Glycerol backbone
Platelet-activating factor

Phosphatidylcholine (PC)

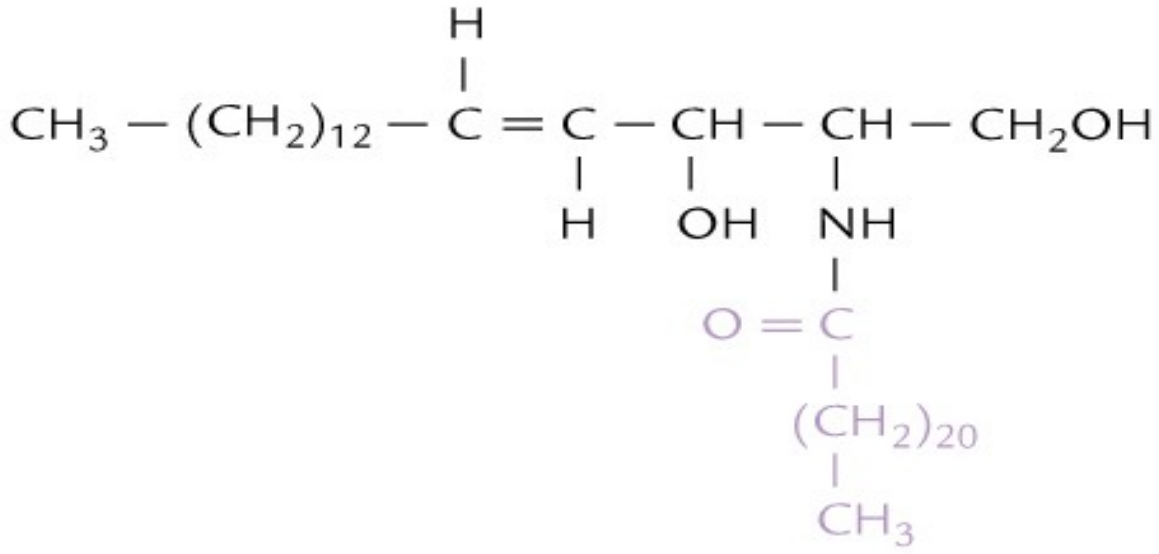


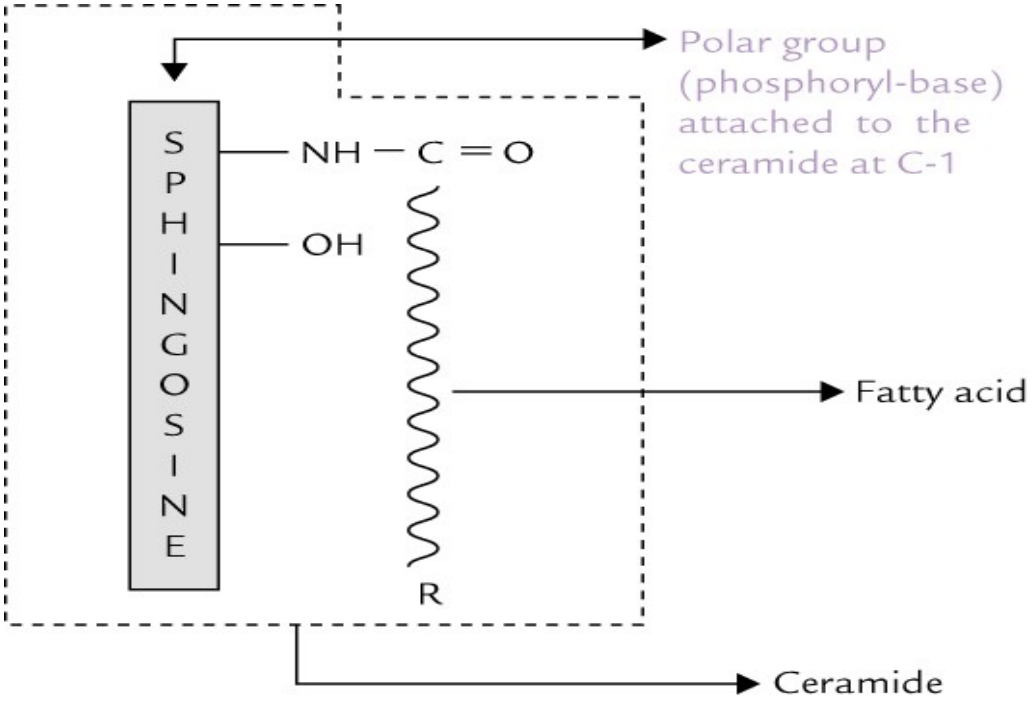
(a)



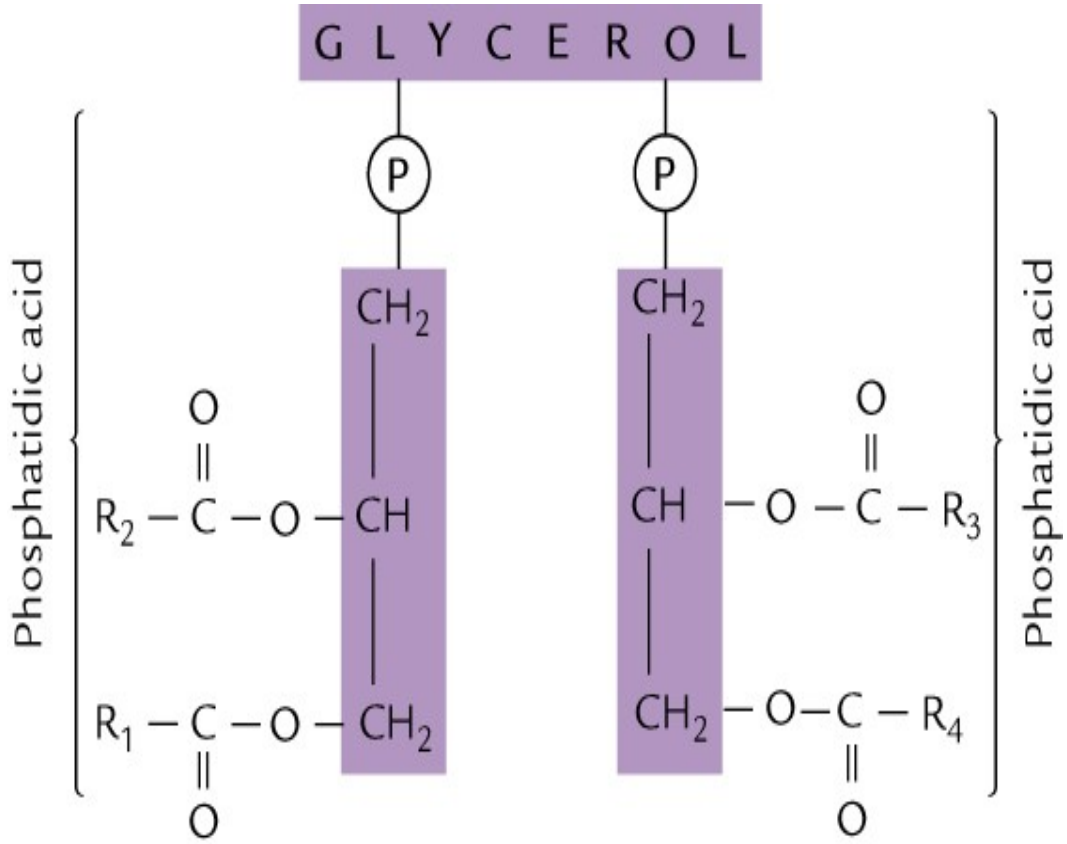
Sphingosine

(b)

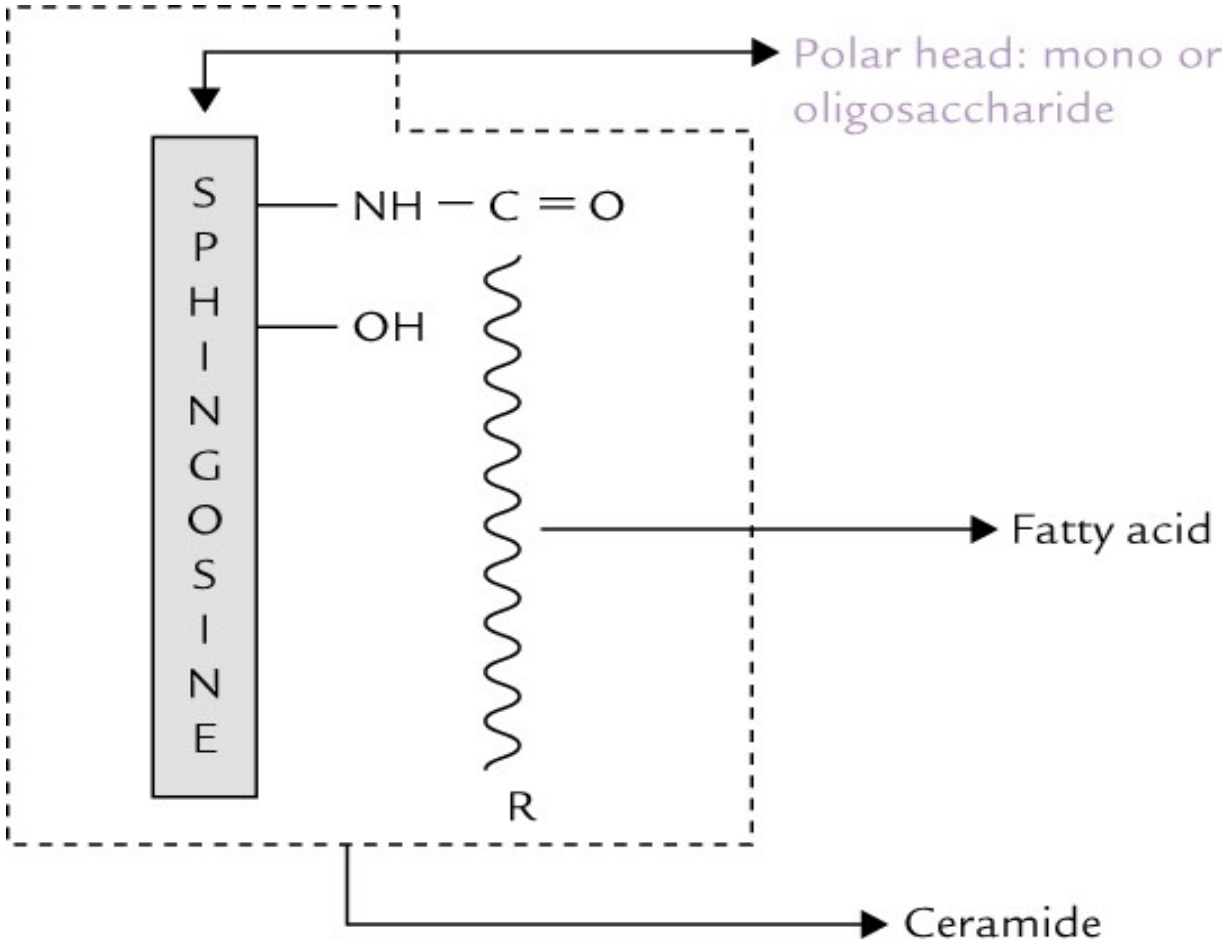



Polar group
(phosphoryl-base)
attached to the
ceramide at C-1
SPHINGOSINE
NH — C = O
OH
R
Fatty acid
Ceramide

Cardiolipin(Diphosphotidylglycerol)



Glycolipid

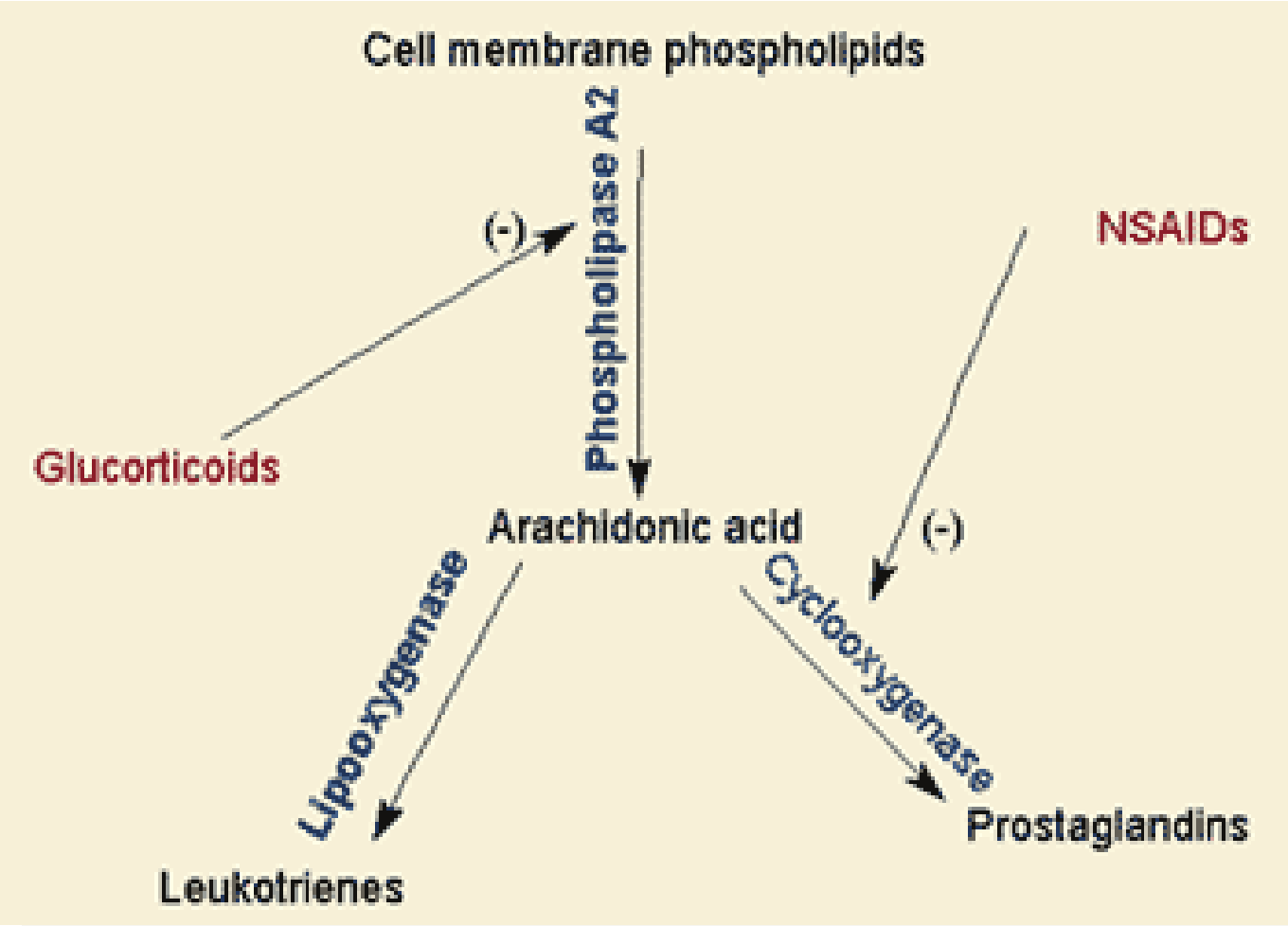

Polar head: mono or oligosaccharide
SPHINGOSINE
NH — C = O
OH
R
Fatty acid
Ceramide

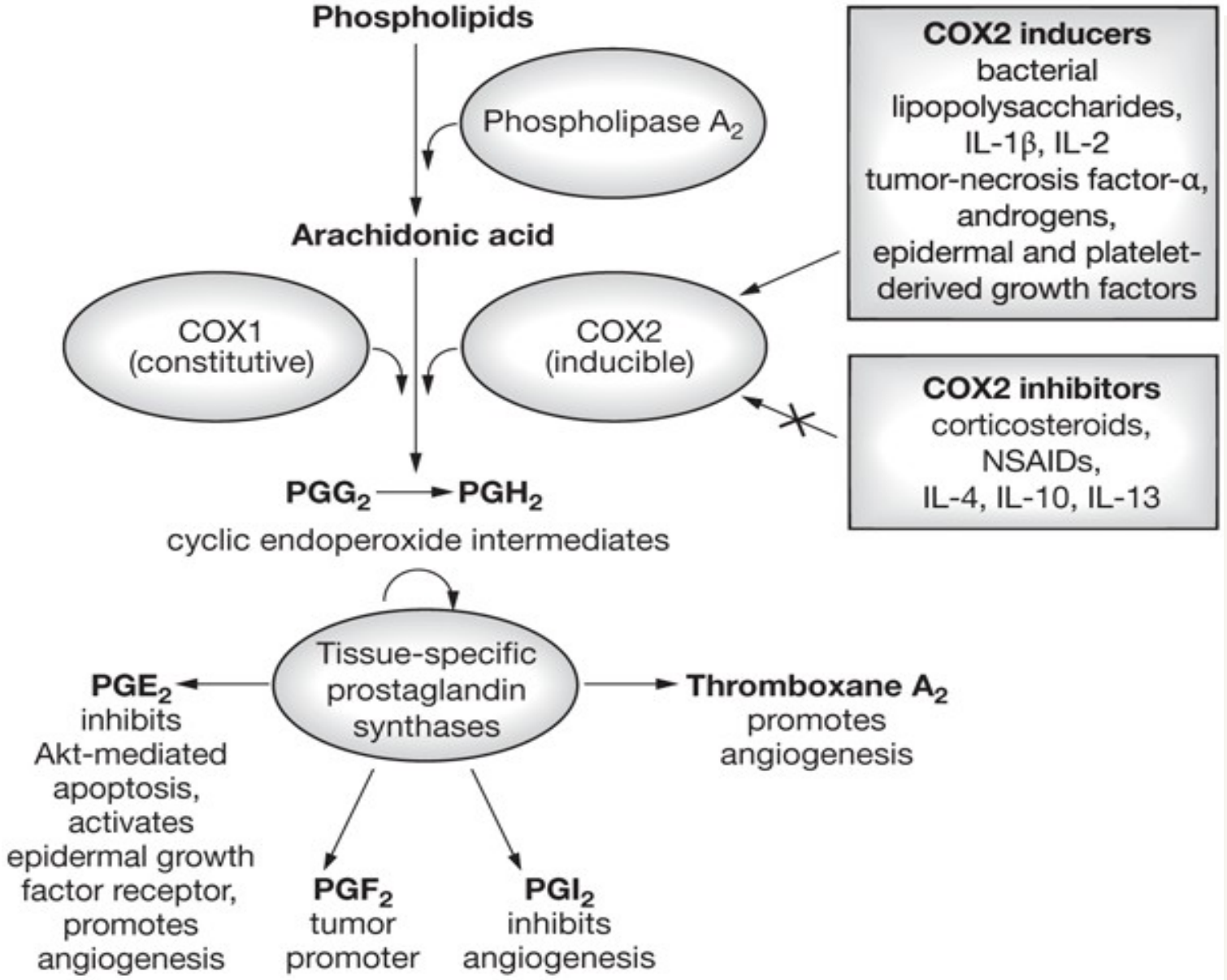
- **Structural Role:**
- **Role in blood coagulation:**
  - They are required at the stage of conversion of prothrombin by active factor X
  - activation of factor VIII by activated factor IX.
- **Role in lipid absorption in intestine:**
  - Lecithin lowers the surface tension of water and aids in emulsification of lipid water mixture,.

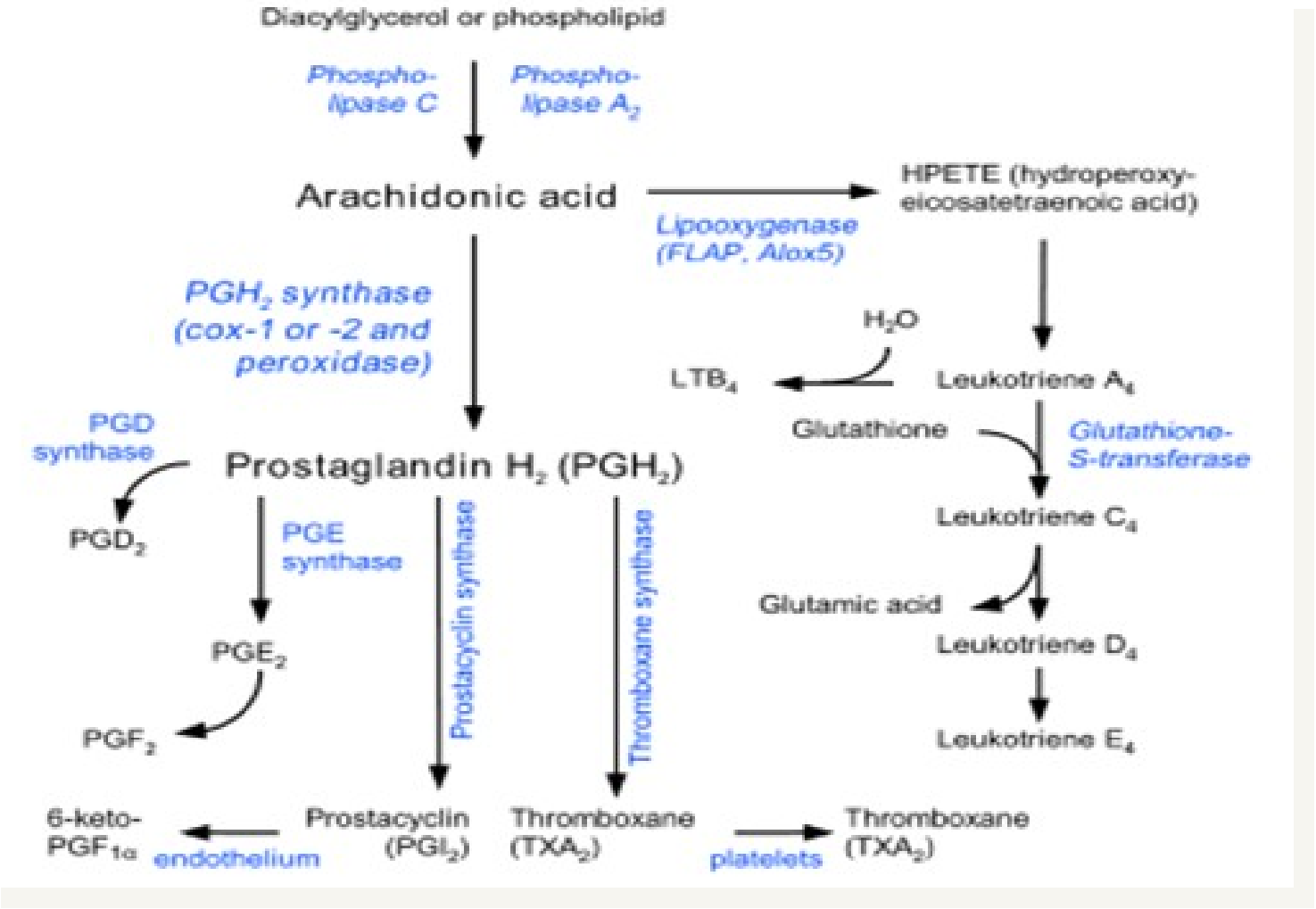
- **Role in transport of lipids from intestines:**
  - Exogenous triglycerides is carried as lipoprotein complex, chylomicrons, in which phospholipids takes an active part.
- **Role in transport of lipids from liver:**
- **Role in electron transport:**
- **Lipotrophic action of Lecithin:**
- **Membrane phospholipids:**

- **Insulation:**
  - Phospholipids of myelin sheaths provide the insulation around the nerve fibers.
- **Role in Hormone action:**
  - provide communication between the hormone receptor on the plasma membrane and intracellular Calcium reservoirs.

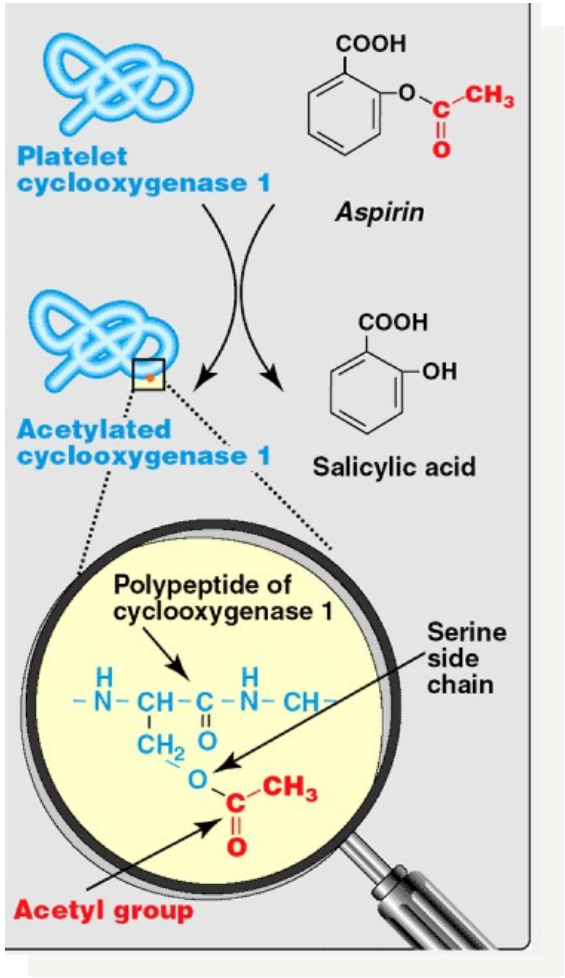
Role in PGs and leukotrienes




Phospholipids
Phospholipase A_2
Arachidonic acid
COX1
(constitutive)
COX2
(inducible)
COX2 inducers
bacterial
lipopolysaccharides,
IL-1β, IL-2
tumor-necrosis factor-α,
androgens,
epidermal and platelet-
derived growth factors
COX2 inhibitors
corticosteroids,
NSAIDs,
IL-4, IL-10, IL-13
PGG_2 → PGH_2
cyclic endoperoxide intermediates
Tissue-specific
prostaglandin
synthases
PGE_2
inhibits
Akt-mediated
apoptosis,
activates
epidermal growth
factor receptor,
promotes
angiogenesis
PGF_2
tumor
promoter
PGI_2
inhibits
angiogenesis
Thromboxane A_2
promotes
angiogenesis


Diacylglycerol or phospholipid
Phospho-lipase C
Phospho-lipase A2
Arachidonic acid
HPETE (hydroperoxy-eicosatetraenoic acid)
Lipooxygenase (FLAP, Alox5)
PGH2 synthase (cox-1 or -2 and peroxidase)
H2O
LTB4
Leukotriene A4
Glutathione
Glutathione-S-transferase
PGD synthase
Prostaglandin H2 (PGH2)
PGD2
PGE synthase
Leukotriene C4
Glutamic acid
PGE2
Leukotriene D4
PGF2
Prostacyclin synthase
Thromboxane synthase
Leukotriene E4
6-keto-PGF1α
endothelium
Prostacyclin (PGI2)
Thromboxane (TXA2)
platelets
Thromboxane (TXA2)

Aspirin


COOH
O
C
CH3
O
Platelet cyclooxygenase 1
Aspirin
COOH
OH
Acetylated cyclooxygenase 1
Salicylic acid
Polypeptide of cyclooxygenase 1
Serine side chain
H
N
CH
C
H
N
CH
CH2
O
O
C
CH3
O
Acetyl group

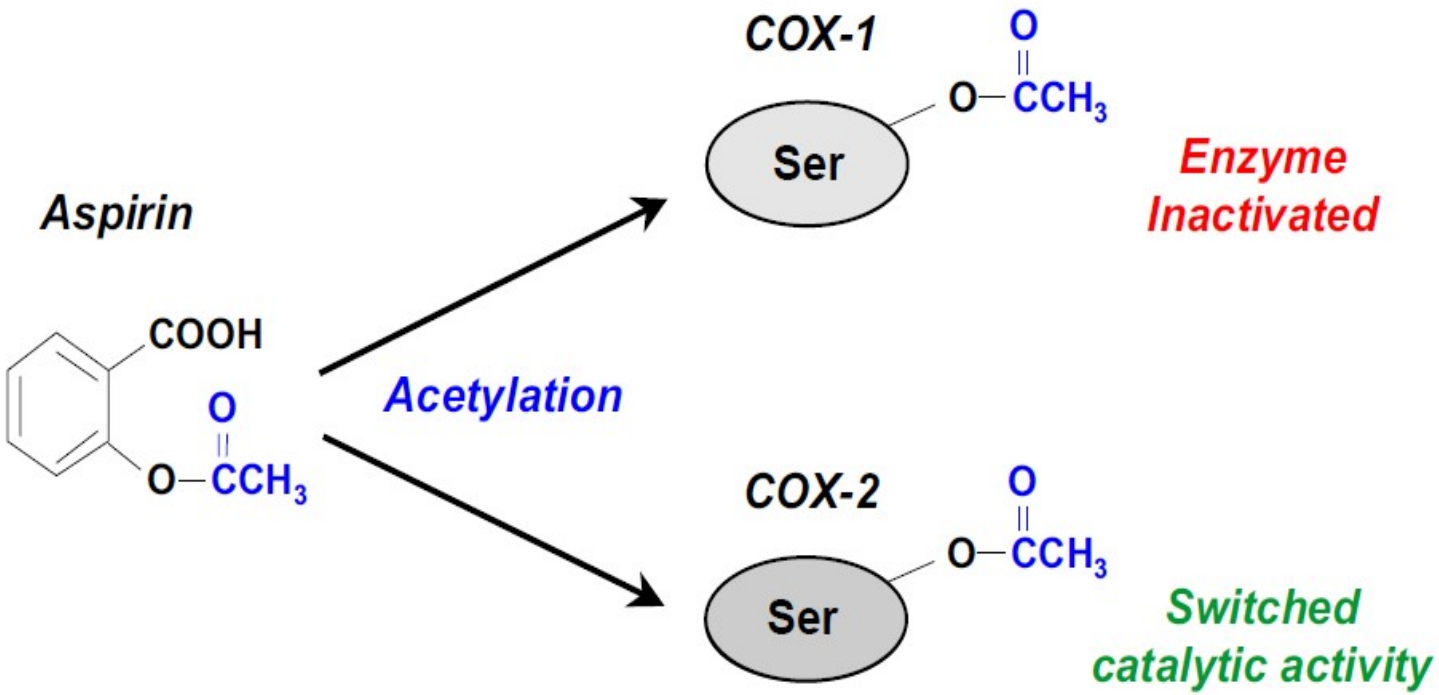


Figure 1. Aspirin mechanism of action -- acetylation of cyclooxygenase (COX). Aspirin acetylates a serine (Ser) residue of COX and irreversibly inactivates COX-1. In the case of COX-2, aspirin "turns off" its ability to generate prostaglandins, but "switches on" its capacity to produce novel protective lipid mediators.

Two main forms of Cyclooxygenases (COX)

- **Cyclooxygenase-1 (COX-1)**

- Produces prostaglandins that mediate homeostatic functions
- Constitutively expressed

- **Homeostatic**
  Protection of gastric mucosa

  Platelet activation

  Renal functions

  Macrophage differentiation

- **Cyclooxygenase-2 (COX-2)**

- Produces prostaglandins that mediate inflammation, pain, and fever.
- Induced mainly in sites of inflammation by cytokines

- Pathologic
  Inflammation

  Pain

  Fever

  Dysregulated proliferation

Selective inhibition by Aspirin

- Aspirin inhibits the production of PGI2 and TXA2
- PGI2-
  - vasodilatation
  - Decrease platelet aggregation
- TXA2-
  - vasoconstriction
  - increase platelet aggregation

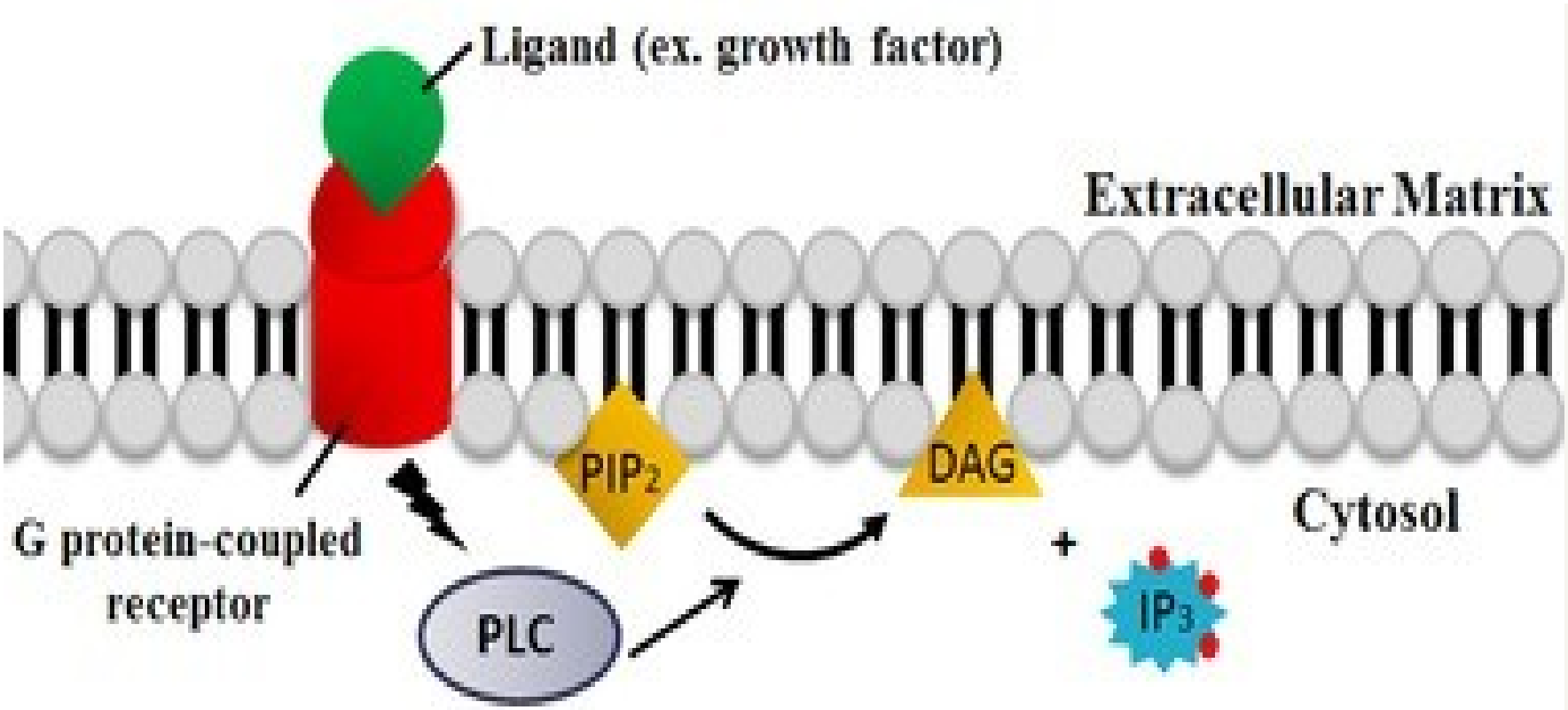
- PGI2- Endothelium
- TXA2-Platelets

Irreversible inhibition of COX- present in platelets

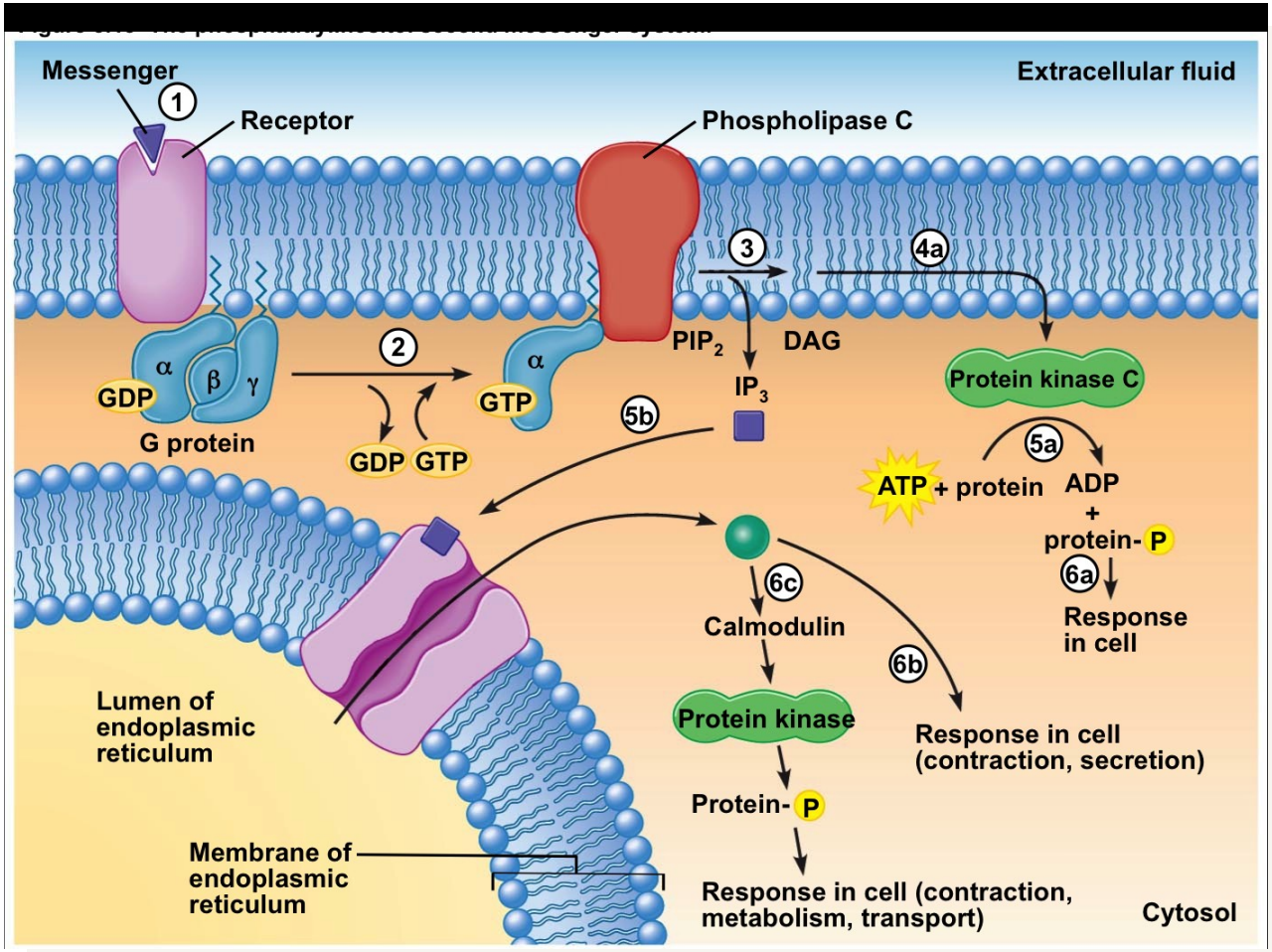
Endothelial COX will regenerated.

- In Low dose - less aspirin reach to peripheral tissue compare to platelets.
- In High dose – do effect on both platelets as well as endothelium

Role as second messenger

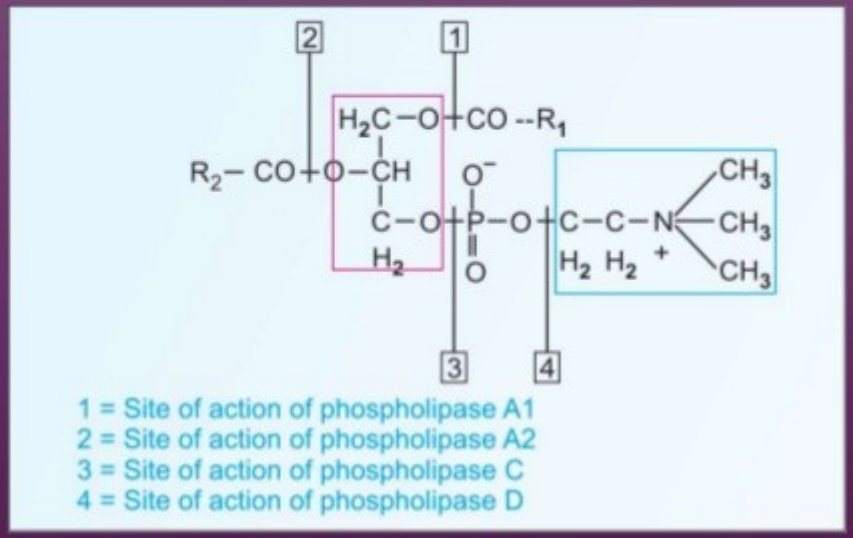


Role as second messenger

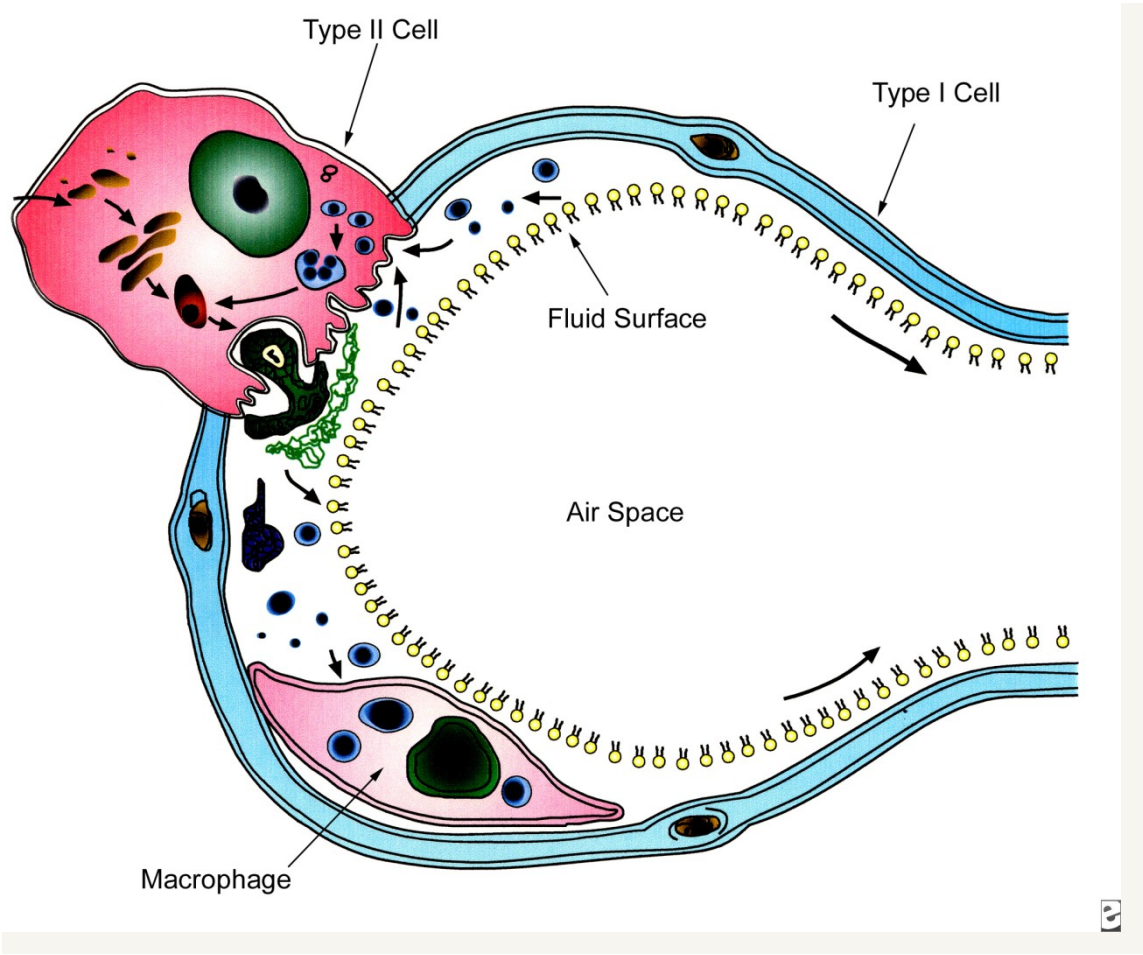


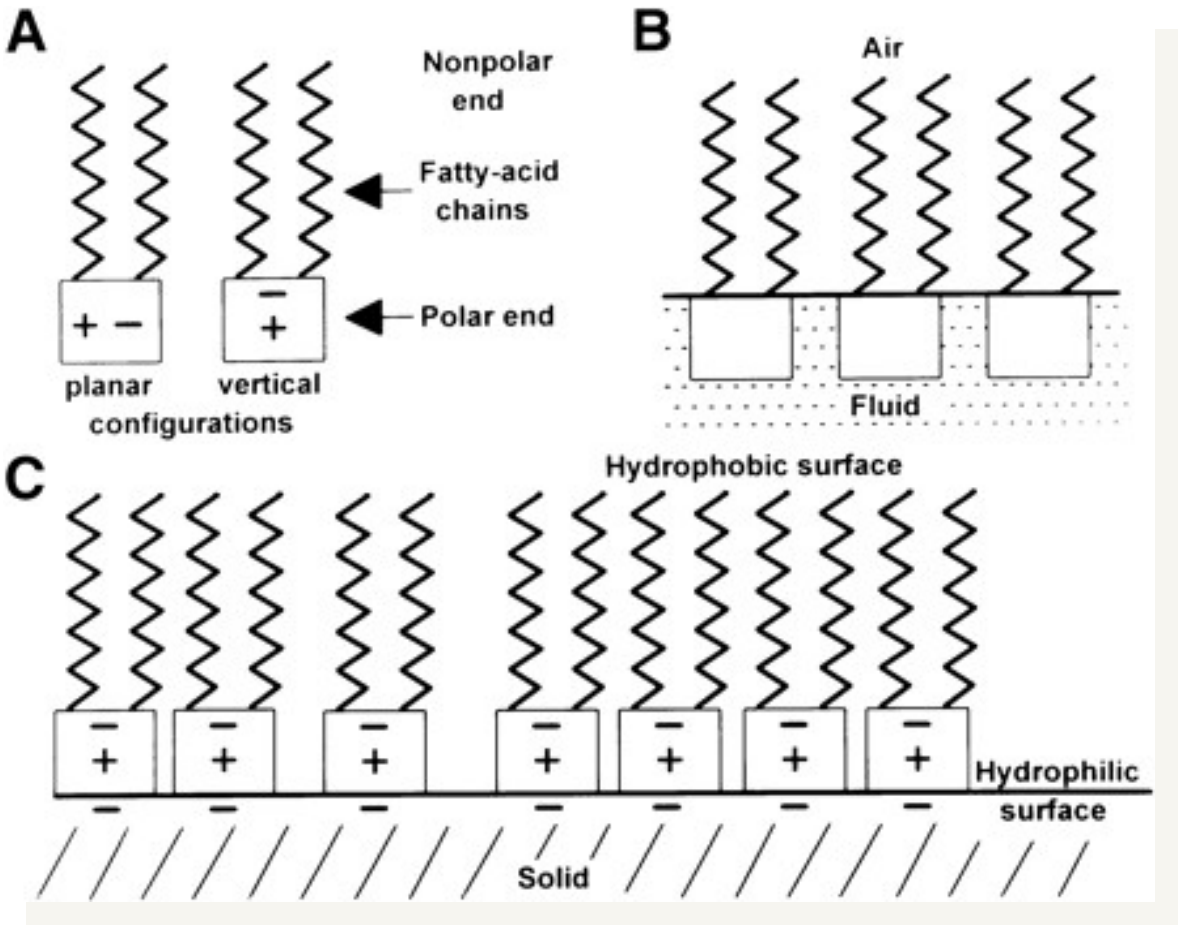
Phosphatidylcholine or Lecithin

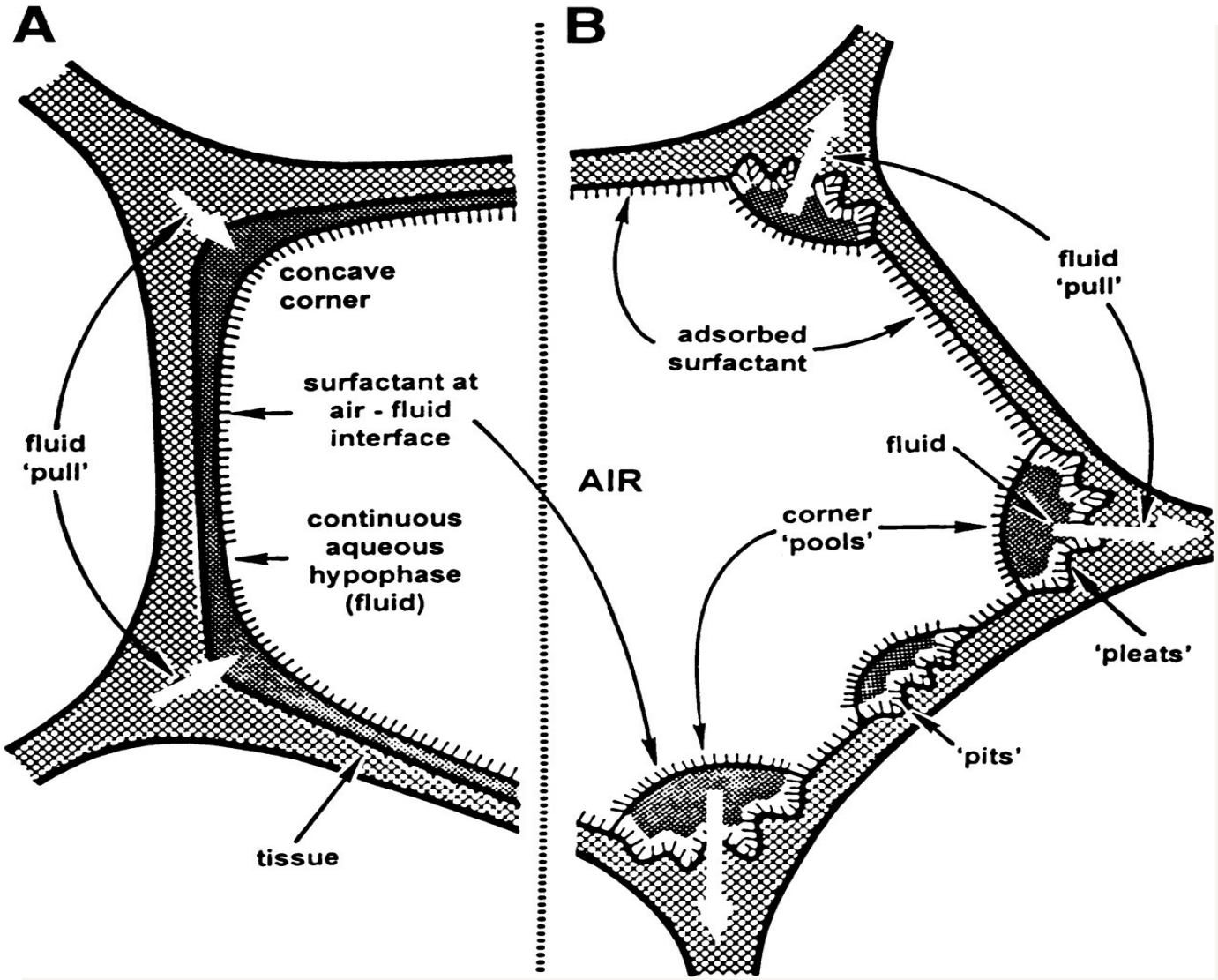
Lecithin R1 and R2 are fatty acids.
Red rectangle depicts glycerol group.
The blue rectangle is choline which shows polar or hydrophilic property



Role as surfactant



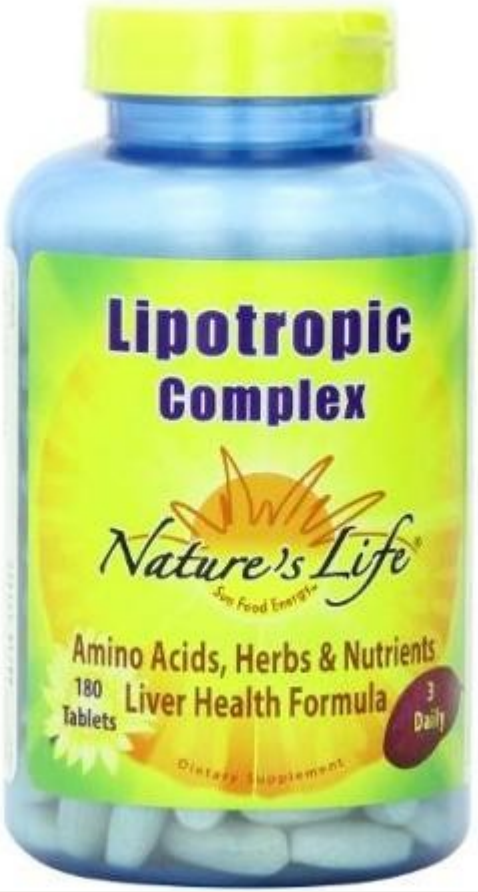

A
Nonpolar end
Fatty-acid chains
Polar end
planar
vertical
configurations
B
Air
Fluid
C
Hydrophobic surface
Hydrophilic surface
Solid


A
concave corner
surfactant at air - fluid interface
fluid 'pull'
continuous aqueous hypophase (fluid)
tissue
B
adsorbed surfactant
fluid 'pull'
fluid
AIR
corner 'pools'
'pleats'
'pits'

Lung surfactant

- **Premature baby can suffer from ARDS(Acute Respiratory Distress Syndrome)**
- **Following are Lung surfactant**
  - **Dipalmitoyl-lecithin**
  - **Sphingomyelin**
- **L to S ratio for lung maturity**

- **In premature babies, this surfactant is deficient and they suffer from <u>Respiratory Distress Syndrome</u>.**
- **Glucocorticoids increase the synthesis of the surfactant complex and promote differentiation of lung cells.**


Lipotropic
Complex
Nature's Life
Amino Acids, Herbs & Nutrients
180 Tablets
Liver Health Formula
3 Daily

Lipotropic factors

❖ Are substances that prevent deposition of excess FAT in liver by different mechanism.

✓ Deficiency of Lipotropic factors - FATTY LIVER

❖ **Choline , Inositol** - reqd. for syn. of lecithin (PL) in VLDL.

❖ **Betaine, Methionine** - labile CH_3 grs - used for choline synthesis .

➢ EFA /PUFA - syn. of PL

➢ Vitamin E, Selenium - Antioxidant - prevent lipid peroxides

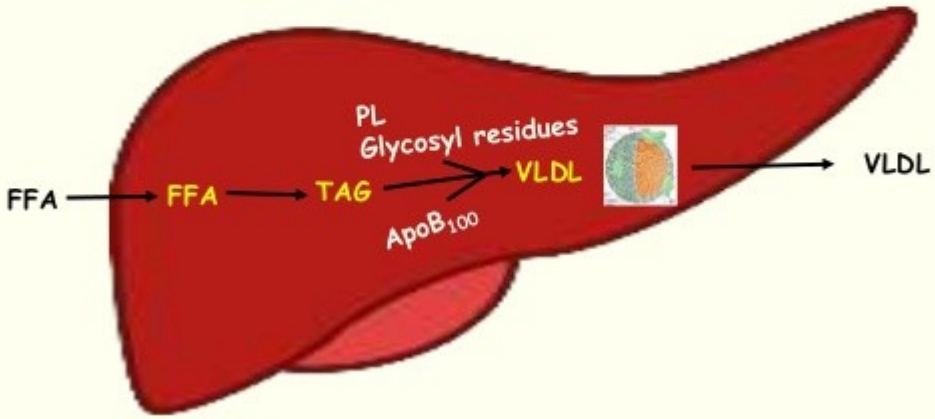
❖ B_5, B_6, B_9, B_{12}, Glycine, serine - serve as lipotropic factors to some extent

Clinical conditions / causes of Fatty Liver

1. Starvation
2. Diabetes mellitus
3. Obesity, Excess calories intake
4. Alcohol abuse
5. Hepato toxins– CCl_4, $CHCl_3$, Pb, Arsenic, Ethionine, Orotic acid
6. Drugs – Puromycin
7. PEM – deficiency of protein, Essential FA, Lipotropic factors
8. Hormones – Epinephrine, Ant. Pituitary hormone

Hepatocyte - Lipid content – 50 %
1/3 – TAG

Excessive amounts of TAG accumulated in the liver – FATTY LIVER



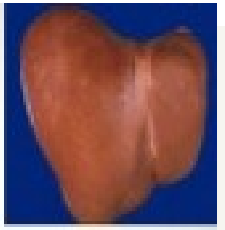
Normal liver

Synthesis of TAG = Export of TAG as VLDL

Fatty liver

Synthesis of TAG

Export of TAG as VLDL



Non Alcoholic Fatty Liver disease (NAFLD)

↓ *Chronic ,inflammatory & fibrotic changes leads to*

Non Alcoholic Steatohepatitis (NASH)

↓ *Progress to*

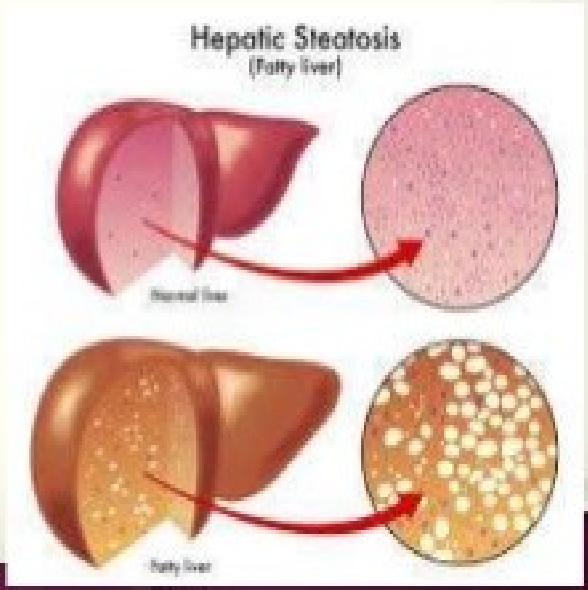
Cirrhosis

↓

Hepatocellular carcinoma

↓

LIVER failure



↑Plasma FFA

- ✓Mobilization of FAT from Adipose tissues
- ✓Hydrolysis of lipoprotein TAG by LPL in extra hepatic tissues

The capacity of the liver to take up FFA from the blood far exceeds its capacity for excretion as VLDL - TAG to accumulate in LIVER

- High FAT diet
- Starvation
- Diabetes Mellitus

Under utilization / unavailability of CHO - breakdown of stored FAT - inc. FFA

- Alcoholism - inc. NADH - inhibits FA oxidation- inc. FA syn.- Deposition

Block in production of VLDL – allowing TAG to accumulate

- Block in Apo-protein synthesis
  PEM , EAA deficiency - dec. a.a - dec. Apoproteins

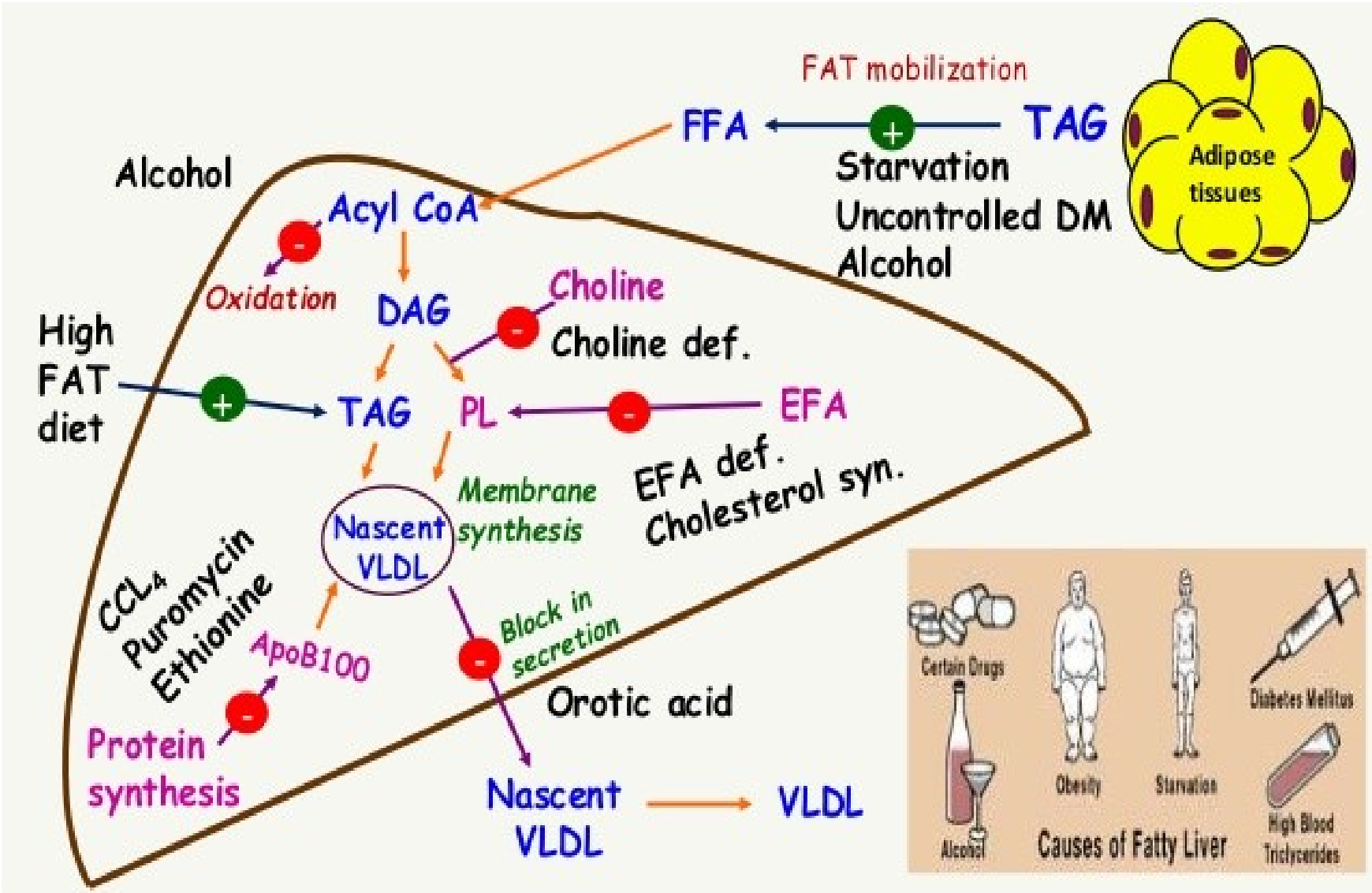
- Block in synthesis of LP from lipid & ApoLP – DEC. PROTEIN SYN.

CCL_4, chloroform, PO, Pb & Ar – generates FR – lipid peroxides – disrupts lipid membrane,

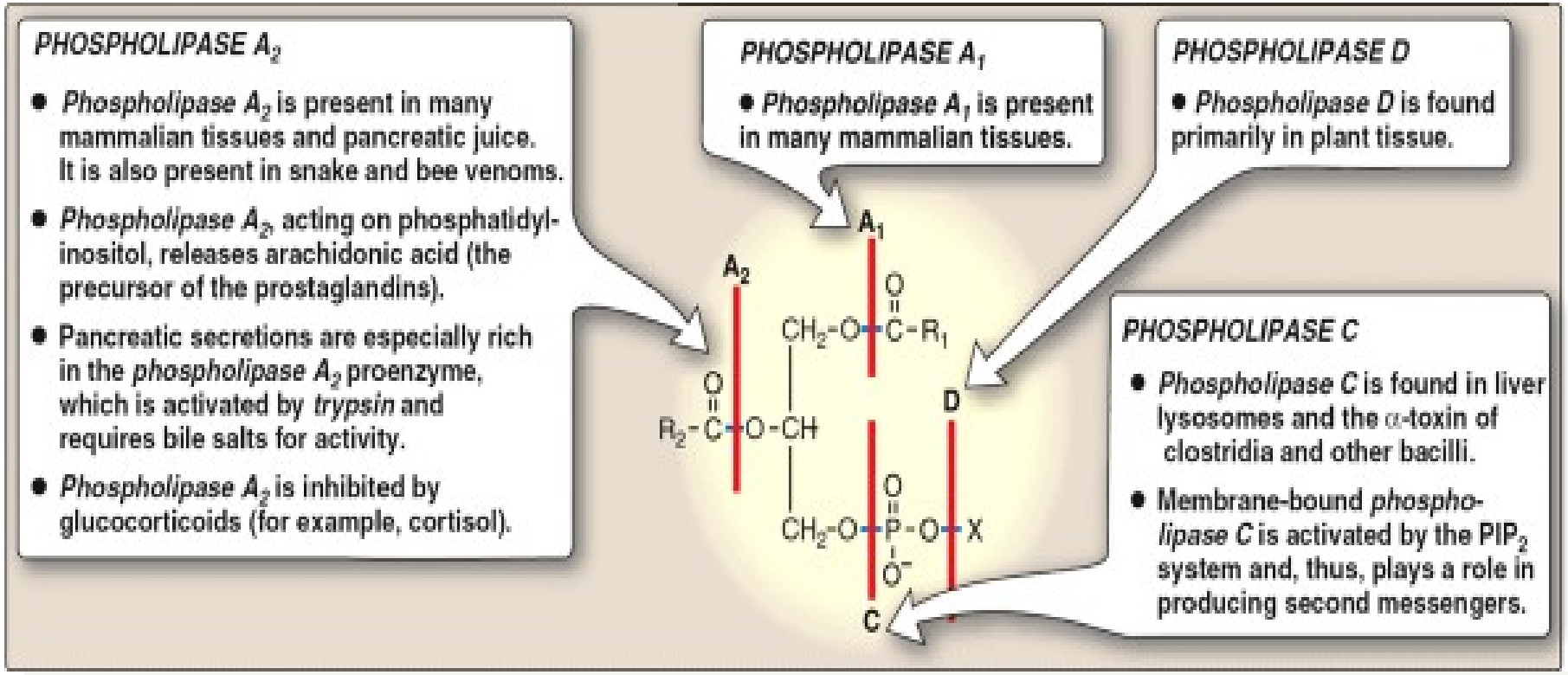
Puromycin – antibiotic,

Ethionine – replaces methionine - traps adenosine – dec. ATP syn

- Failure in delivery of PLs that are found in LP
  EFA & Choline def., inc. Cholesterol - competes with EFA for esterification - impairs PL syn
- Failure in the secretory mechanism
  Orotic acid - interfere with glycosylation of LP - inhibits its release.
- Deficiency of Lipotropic factors


FAT mobilization
FFA
TAG
Starvation
Uncontrolled DM
Alcohol
Adipose tissues
Alcohol
Acyl CoA
Oxidation
DAG
Choline
Choline def.
High FAT diet
TAG
PL
EFA
EFA def.
Cholesterol syn.
Membrane synthesis
Nascent VLDL
CCl4
Puromycin
Ethionine
ApoB100
Block in secretion
Orotic acid
Protein synthesis
Nascent VLDL
VLDL
Certain Drugs
Obesity
Starvation
Diabetes Mellitus
Alcohol
Causes of Fatty Liver
High Blood Triglycerides

Role of Phospholipase



Snake bite cause severe haemolysis

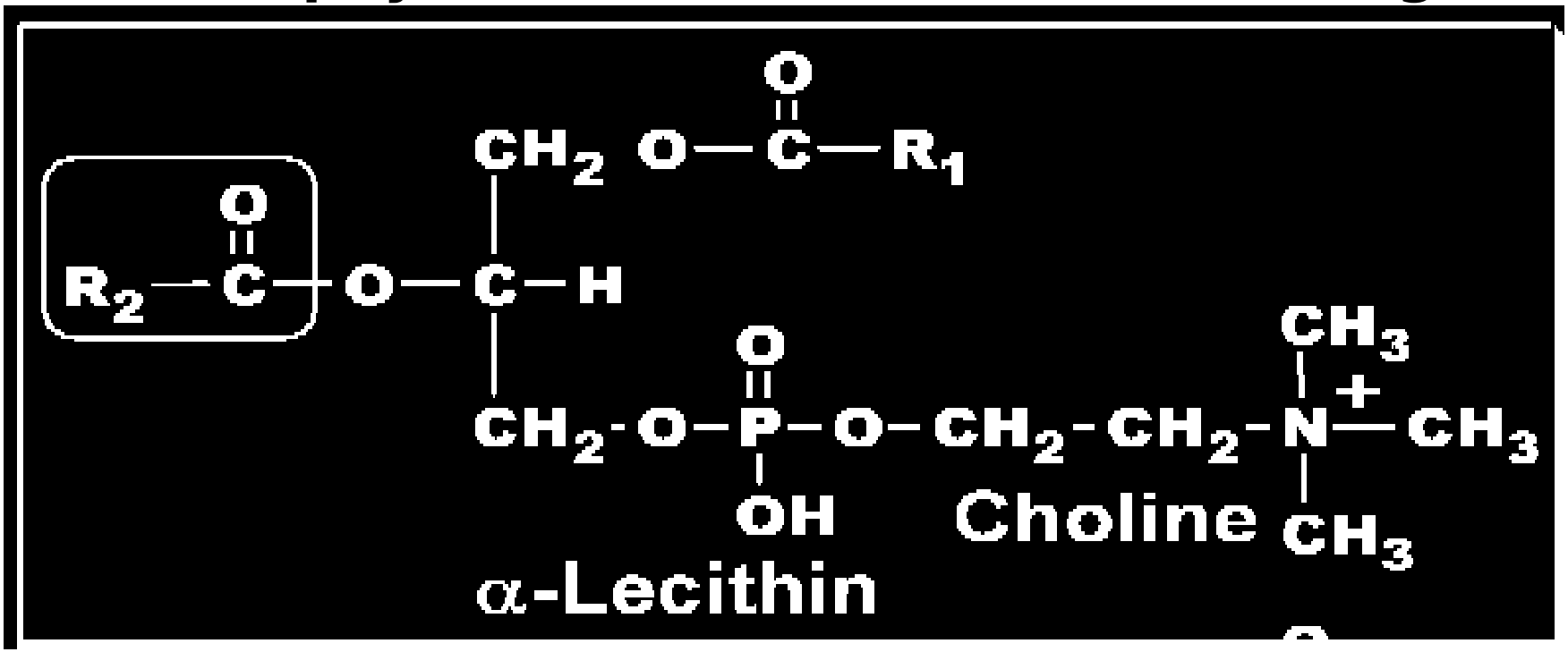
The venom contains lecithinase,

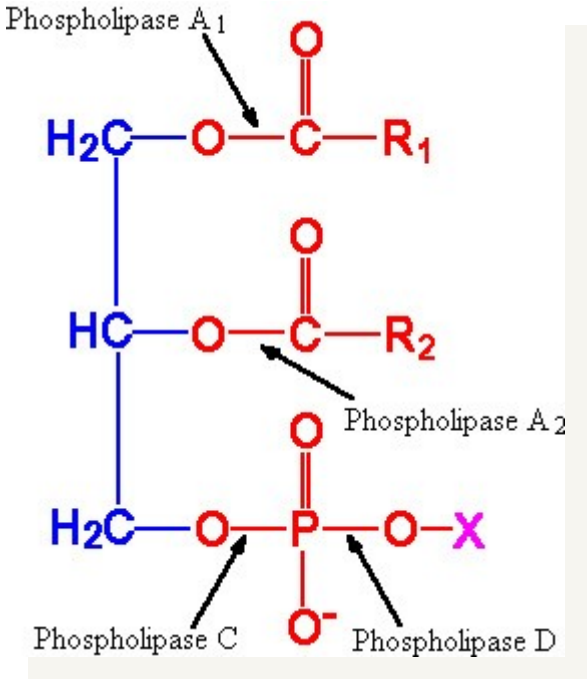
hydrolyzes the PUFA

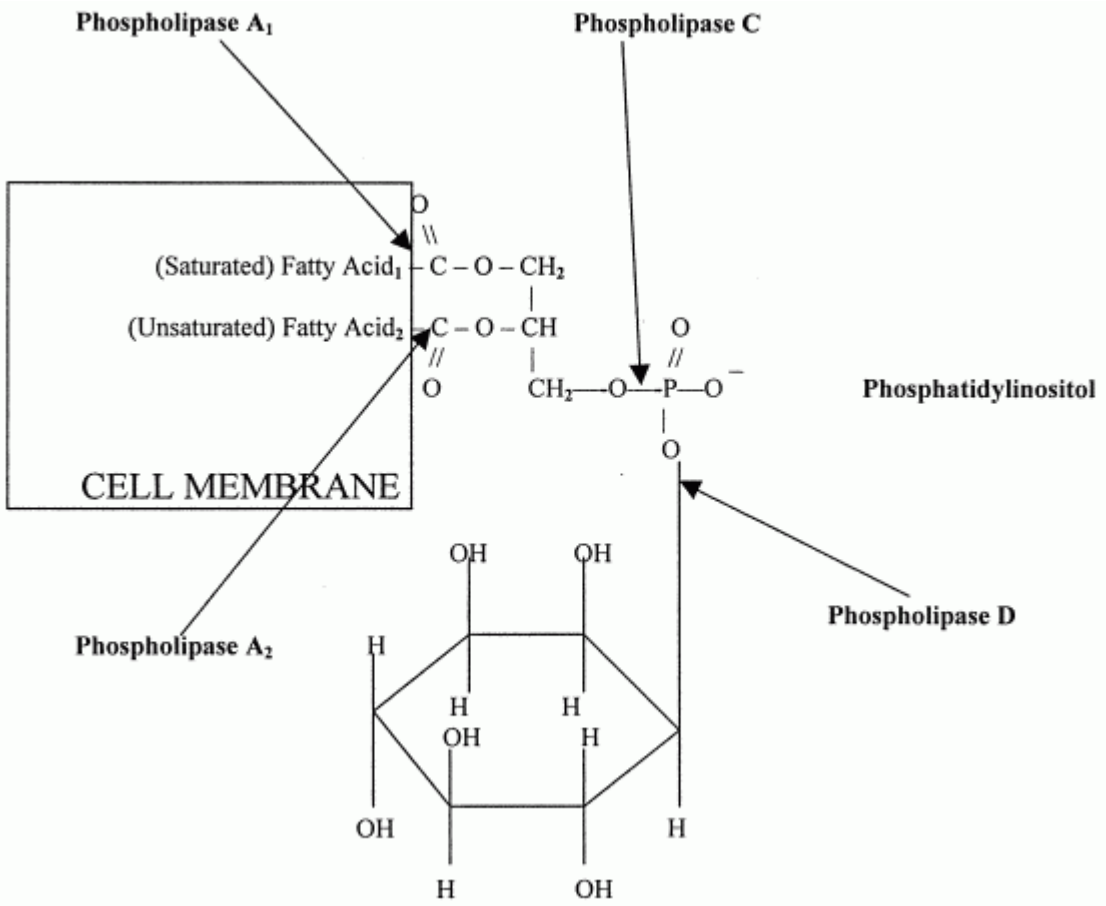
converting lecithin into lysolecithin (detergent like action).

Lysolecithin causes hemolysis of RBCs.

cause anaphylactic shock as well as bleeding




Phospholipase A 1
O
H2C
O
C
R1
O
HC
O
C
R2
Phospholipase A 2
O
H2C
O
P
O
X
O-
Phospholipase C
Phospholipase D


Phospholipase A1
Phospholipase C
(Saturated) Fatty Acid1
(Unsaturated) Fatty Acid2
Phosphatidylinositol
CELL MEMBRANE
Phospholipase A2
Phospholipase D