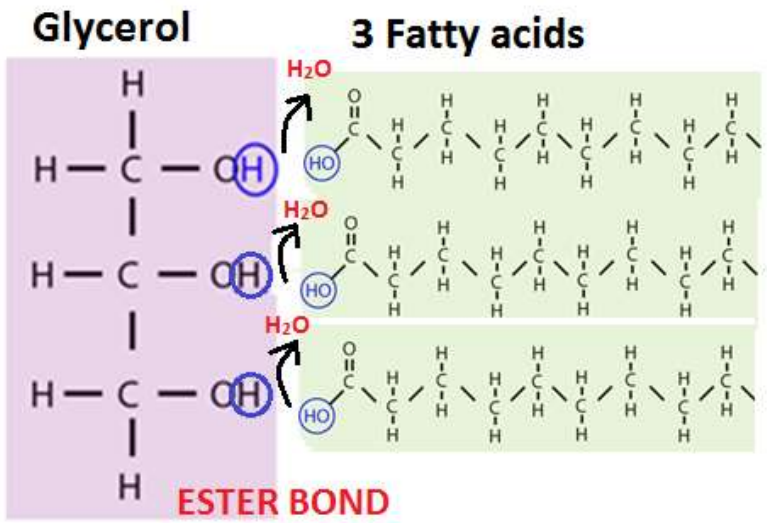
Lipids Metabolism

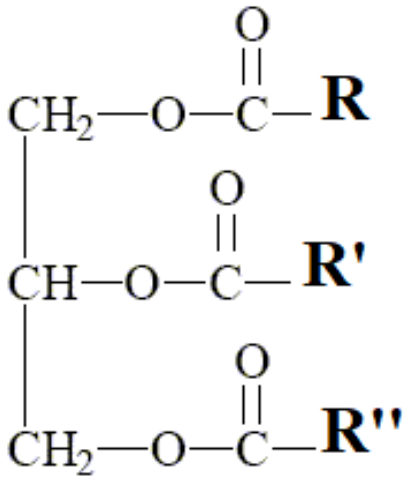
In this lecture:

- Triglyceride (Fat) Synthesis and degradation
- Glycerophospholipids synthesis
- Sphingolipids synthesis and degradation
- Cholesterol synthesis
- Transport of lipids in blood “Lipoproteins”

ال Structures للفهم
ليست للحفظ

Triglyceride (Fat) synthesis





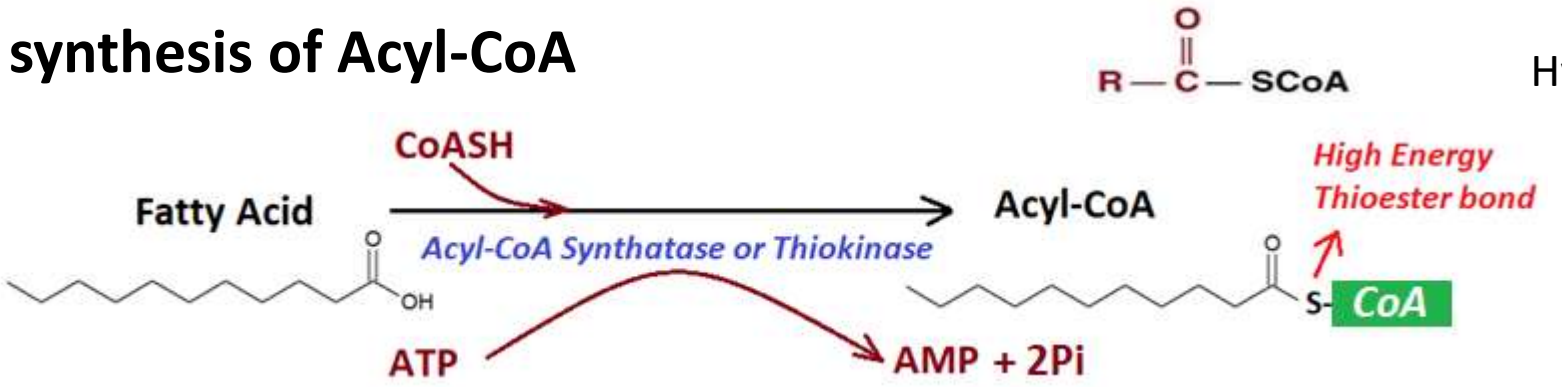
TAG synthesis occurs in ***Liver and Adipose cells or can be obtained from diet***, but stored only in ***adipose cells.***

To synthesize TAG you need 2 things:

1. Glycerol-3-phosphate
2. 3 Activated Fatty acid = 3 Fatty acyl-CoA

Note: if you want to add fatty acid to any molecule the fatty acid must be activated "bound to CoA by thioester bond" hydrolysis of the thioester bond will provide the energy required for the condensation

synthesis of Acyl-CoA



Hydrolysis of ATP to AMP + 2Pi is equivalent to consuming 2ATP to 2ADP + 2Pi

Acyl-CoA is a general name

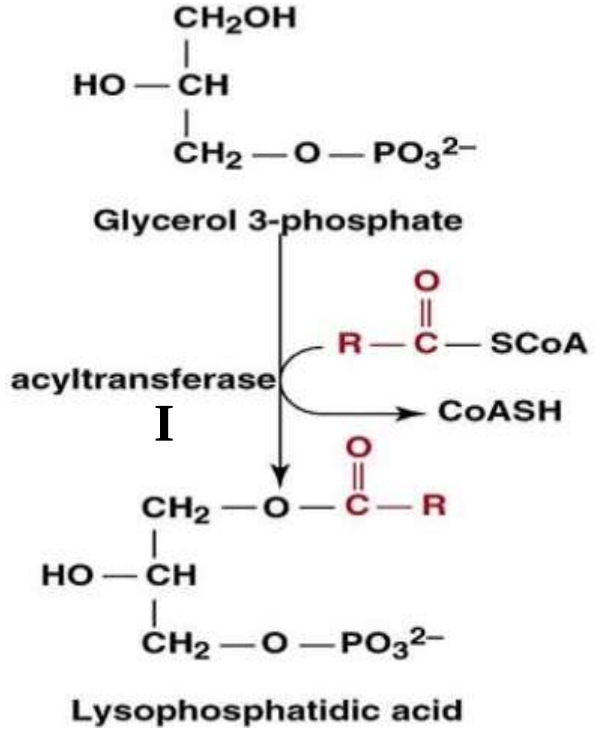
Palmitate (16:0) → Palmitoyl-CoA
Stearate (18:0) → Stearyl-CoA
Acetate (2:0) → Acetyl-CoA

} Acyl-CoA

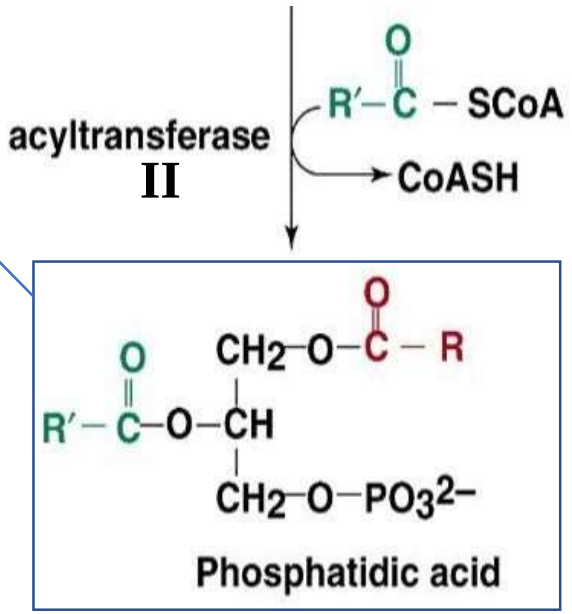
1. Addition of first fatty acid on C1 by acyl-transferase I producing ***Lysophosphatidic acid***
2. Addition of the second fatty acid at C2 by acyl-transferase II forming ***Phosphatidic acid*** (Phosphatidate)

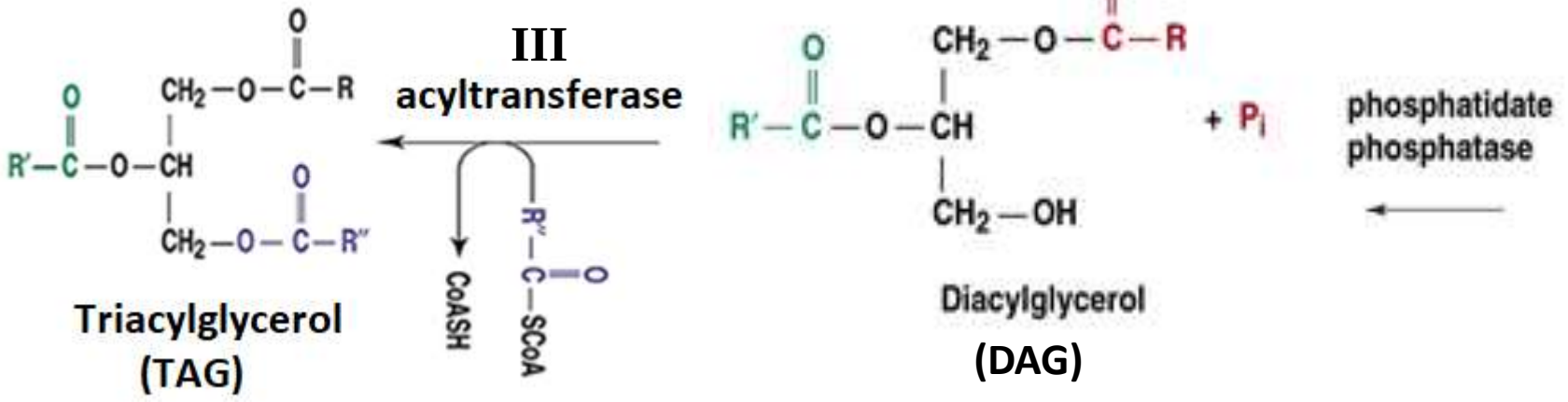
- Phosphatidic acid is a common intermediate (parent, Branch point) in TAG and Glycerophospholipids synthesis

3. Removing the Phosphate group by phosphatase forming Di-acyl-glycerol (***DAG***)
4. Addition of the third fatty acid by acyl-transferase III forming ***TAG***



Glycerophospholipids

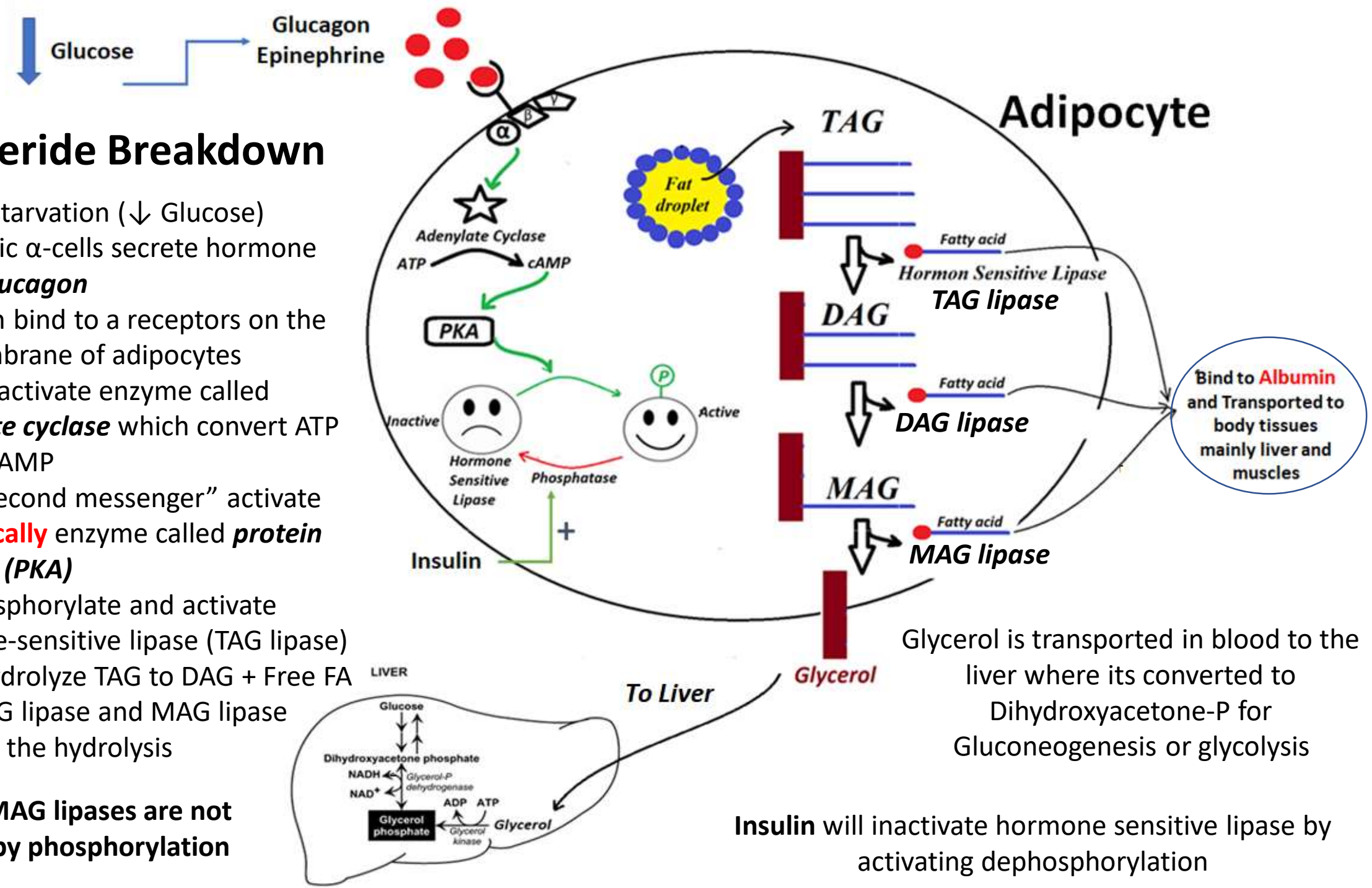




Triglyceride Breakdown

1. Fasting/starvation (↓ Glucose)
2. Pancreatic α-cells secrete hormone called ***Glucagon***
3. Glucagon bind to a receptors on the cell membrane of adipocytes
4. This will activate enzyme called ***adenylate cyclase*** which convert ATP to cyclic AMP
5. cAMP "second messenger" activate **allosterically** enzyme called ***protein kinase A (PKA)***
6. PKA phosphorylate and activate Hormone-sensitive lipase (TAG lipase) which hydrolyze TAG to DAG + Free FA
7. Then DAG lipase and MAG lipase continue the hydrolysis

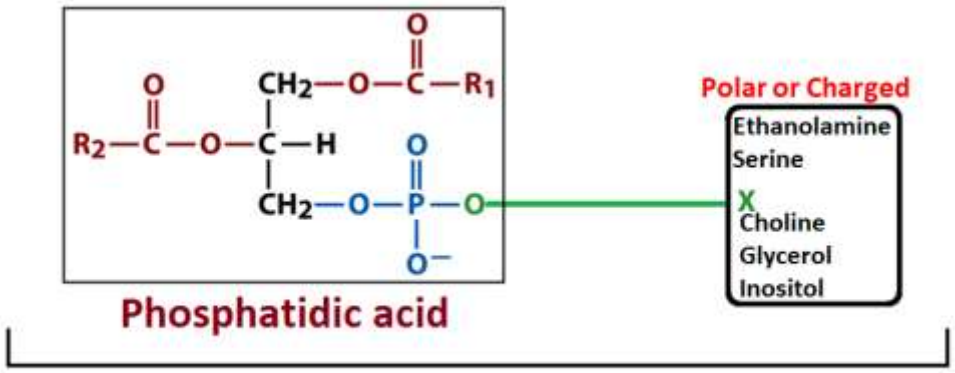
DAG and MAG lipases are not activated by phosphorylation

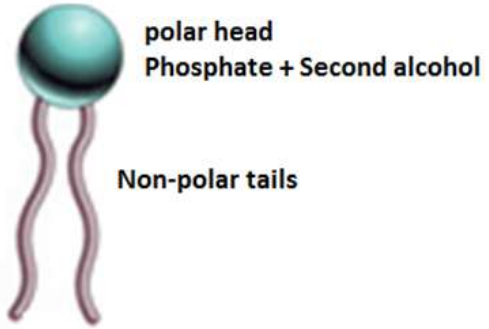


Glycerol is transported in blood to the liver where its converted to Dihydroxyacetone-P for Gluconeogenesis or glycolysis

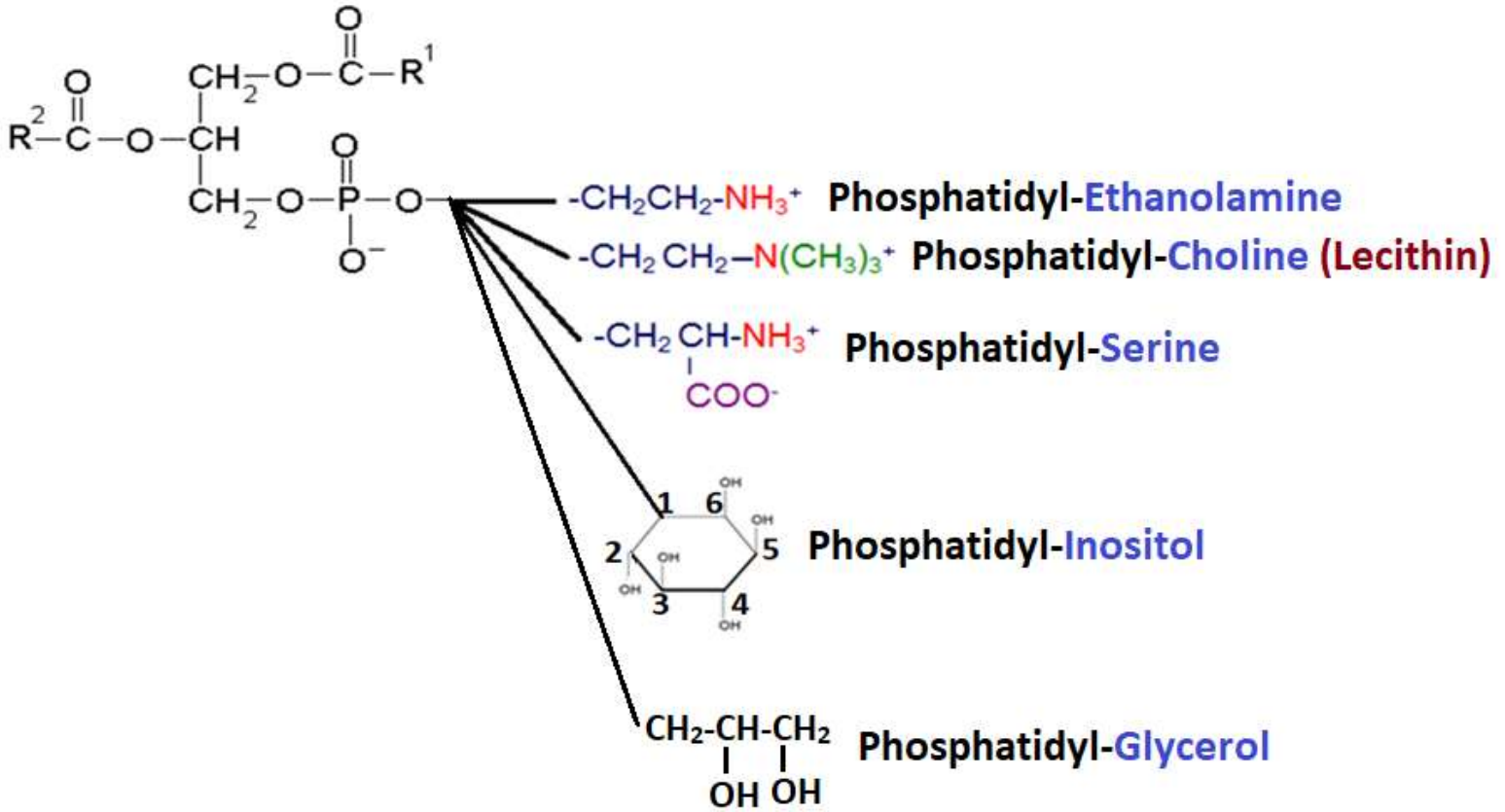
Insulin will inactivate hormone sensitive lipase by activating dephosphorylation

Synthesis of Glycerophospholipids/ phosphoglyceride/ Phosphatides





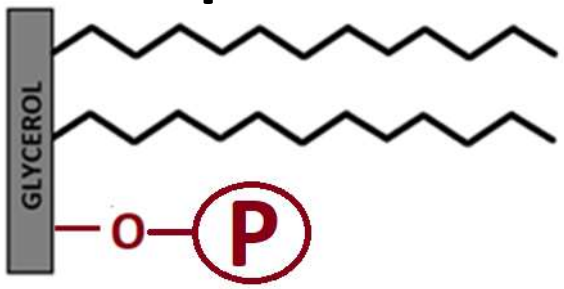
Phosphate group form another Ester with other Alcohol (Base)
متغير X



To synthesize Glycerophospholipids

You need:

Phosphatidic acid



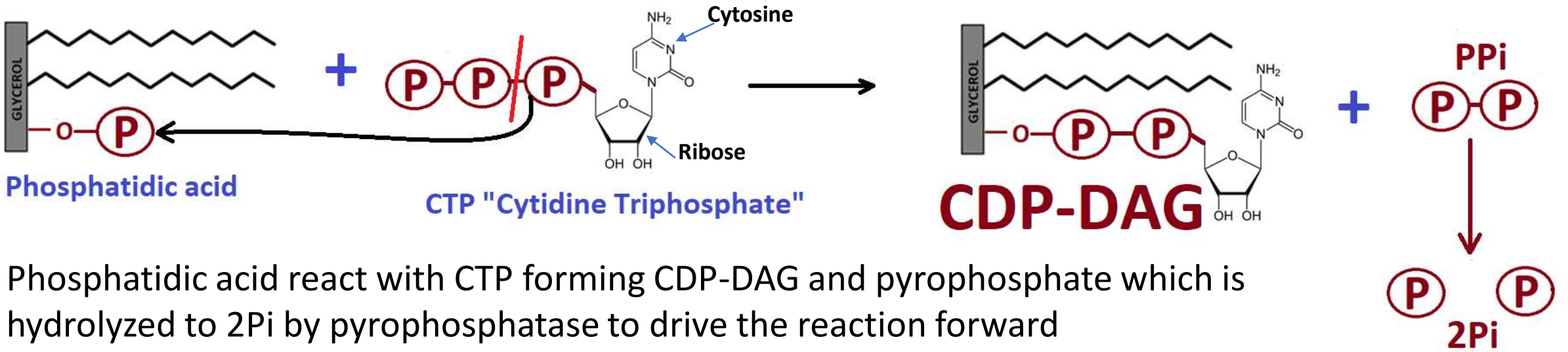
Second Acohol (Base)

Ehanolamine, Choline, Serine, Inositol, Glycerol

Cytidine Diphosphate - Diacylglycerol

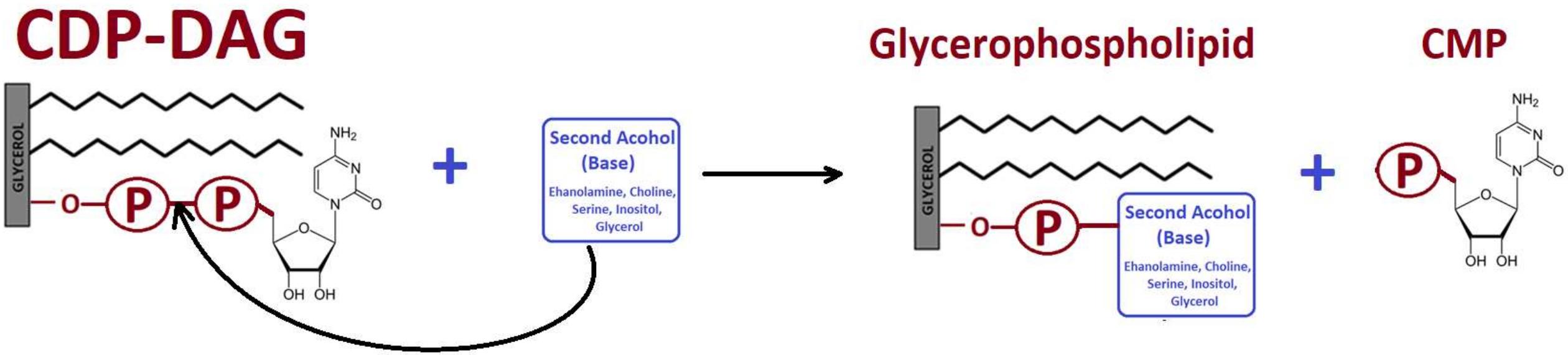
To join them together Phosphatidic acid must be activated → **CDP-DAG**

How to activate phosphatidic acid?



Phosphatidic acid react with CTP forming CDP-DAG and pyrophosphate which is hydrolyzed to 2Pi by pyrophosphatase to drive the reaction forward

Cytosine + Ribose = Nucleoside called Cytidine



CMP is Removed from CDP-DAG and the second alcohol (Base) is added instead forming Glycerophospholipid

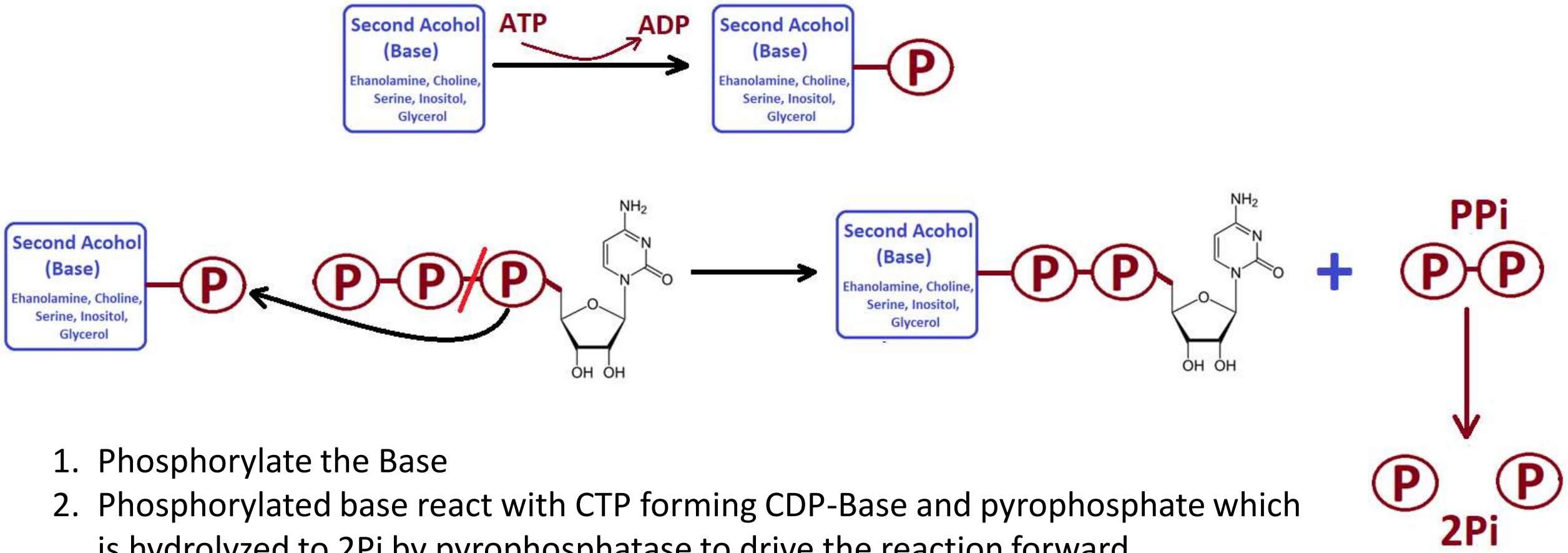
For Example:

CDP-DAG + Inositol → Phosphatidyl-Inositol + CMP

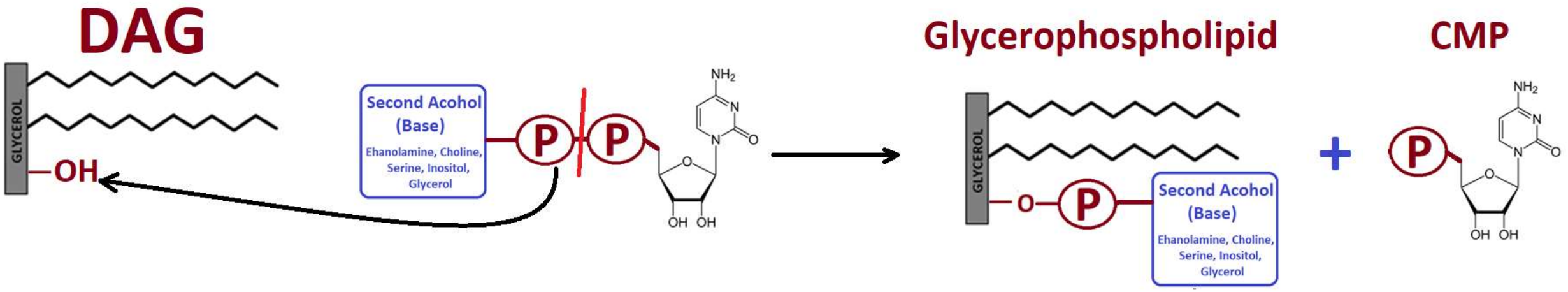
CDP-DAG + Glycerol → Phosphatidyl-Glycerol + CMP

Alternative way:

Activate the second alcohol (Base)→ CDP-Base



1. Phosphorylate the Base
2. Phosphorylated base react with CTP forming CDP-Base and pyrophosphate which is hydrolyzed to 2Pi by pyrophosphatase to drive the reaction forward



CMP is Removed from CDP-Base and DAG is added instead forming Glycerophospholipid

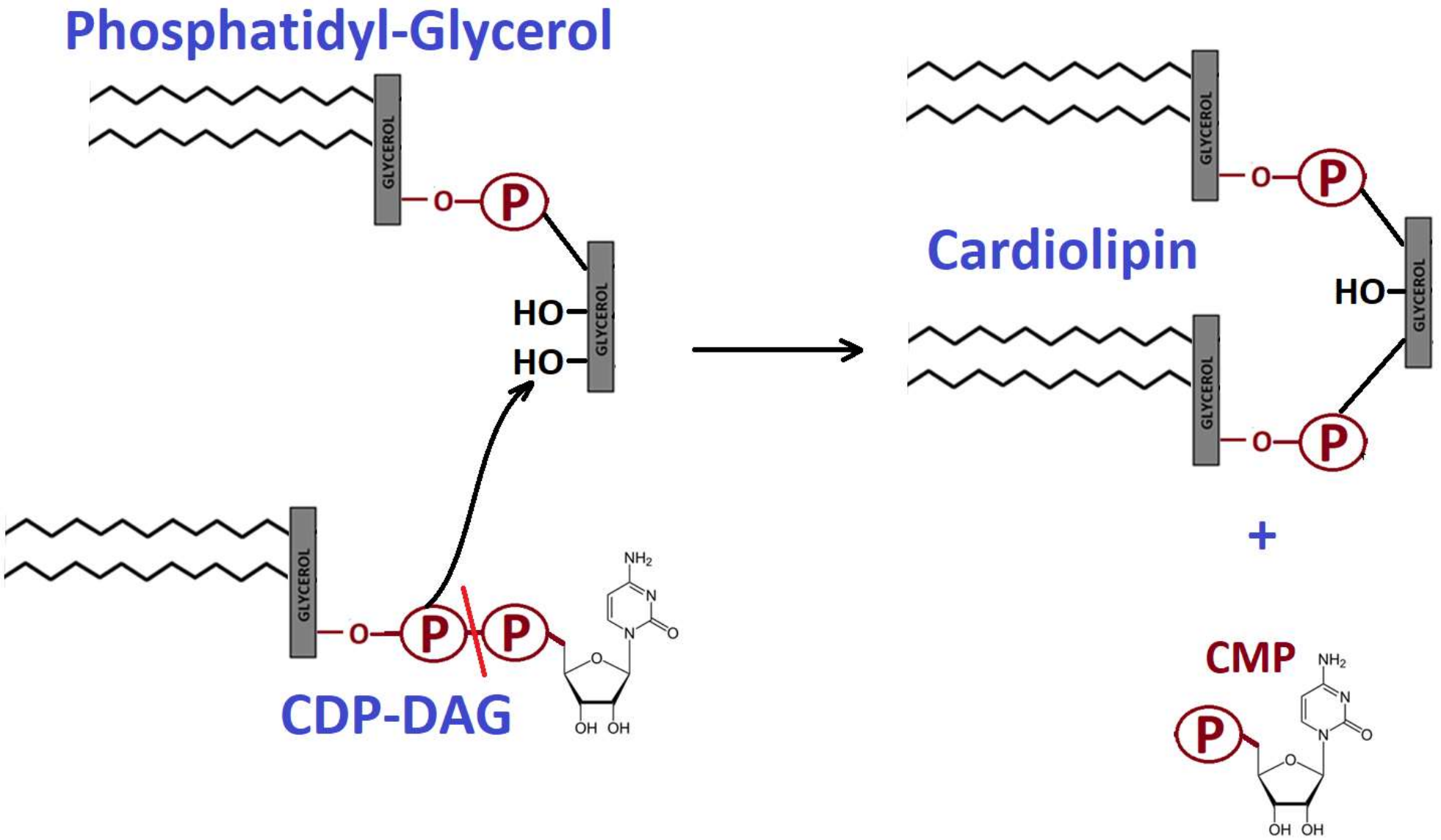
For Example:

CDP-Ethanolamine + DAG → Phosphatidyl-Ethanolamine + CMP

CDP-Serine + DAG → Phosphatidyl-Serine + CMP

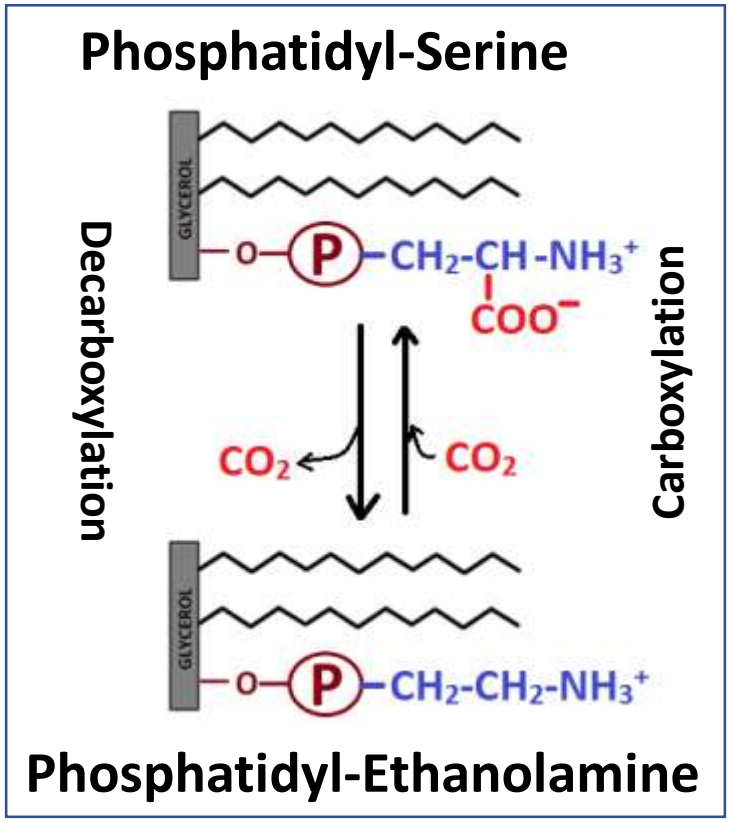
CDP-Choline + DAG → Phosphatidyl-Choline + CMP

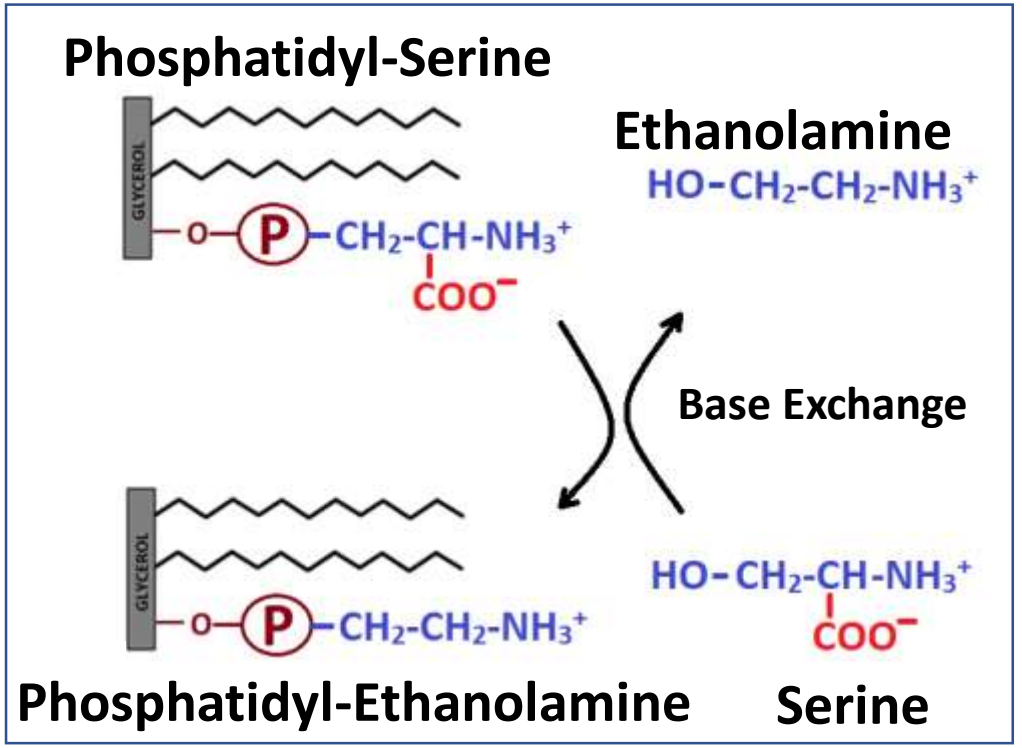
Synthesis of Cardiolipin (Diphosphatidyl-Glycerol)

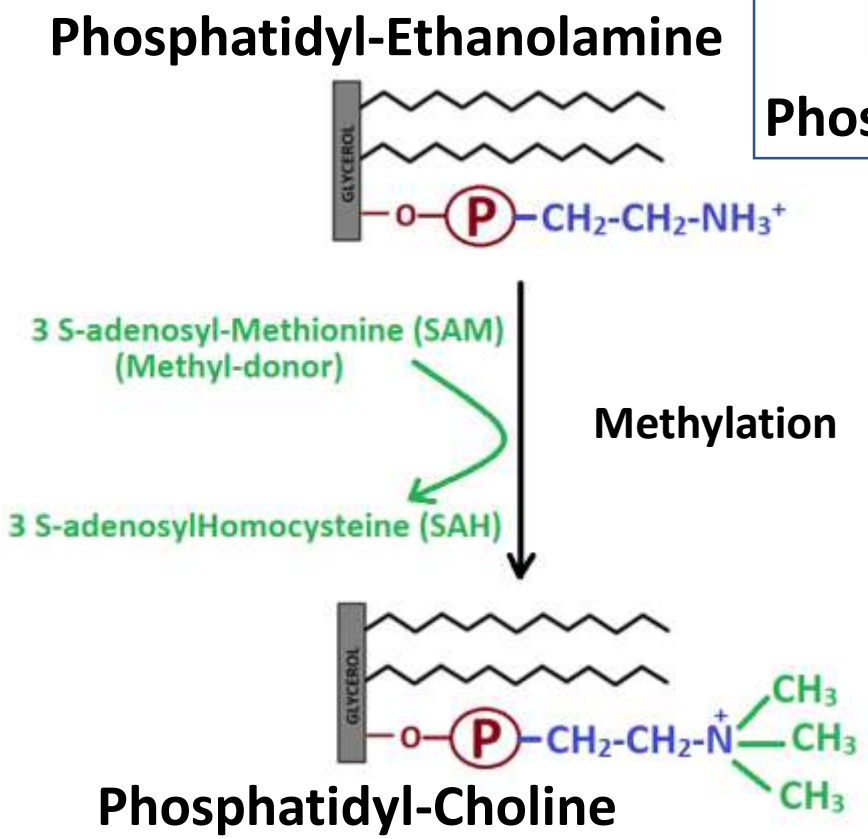


Phosphatidyl-Glycerol + CDP-DAG → Cardiolipin + CMP

modification of Glycerophospholipid head



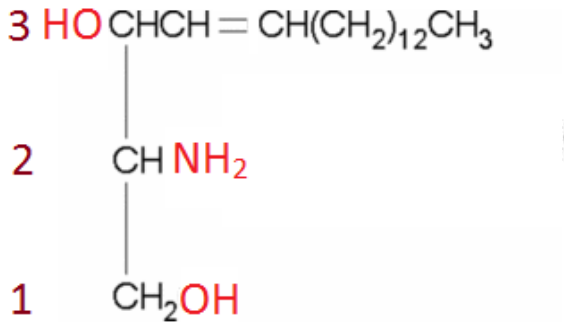




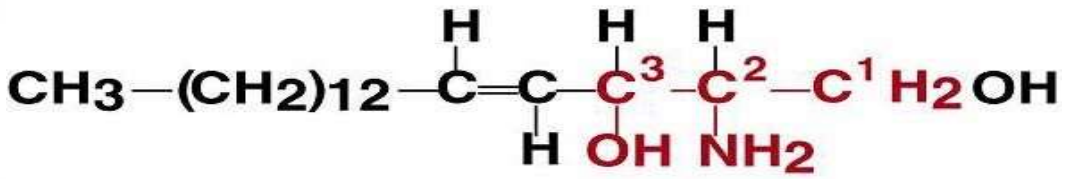
Sphingolipids

Amphipathic lipids, component (من مكونات) of cell membrane mainly in the Nervous system cell membrane

The backbone of sphingolipid is a large molecule called ***Sphingosine (18 C)***



Spingosine (Amino-Alcohol)

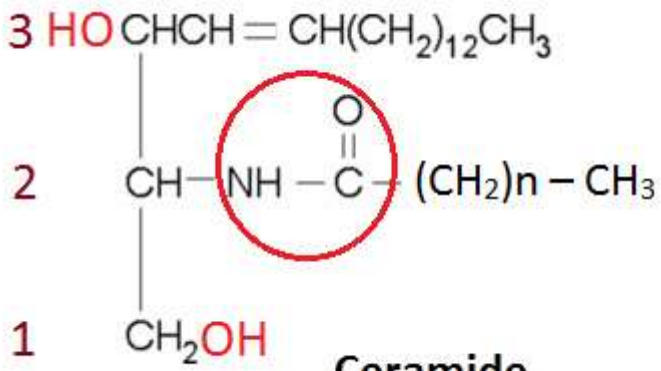


Sphingosine

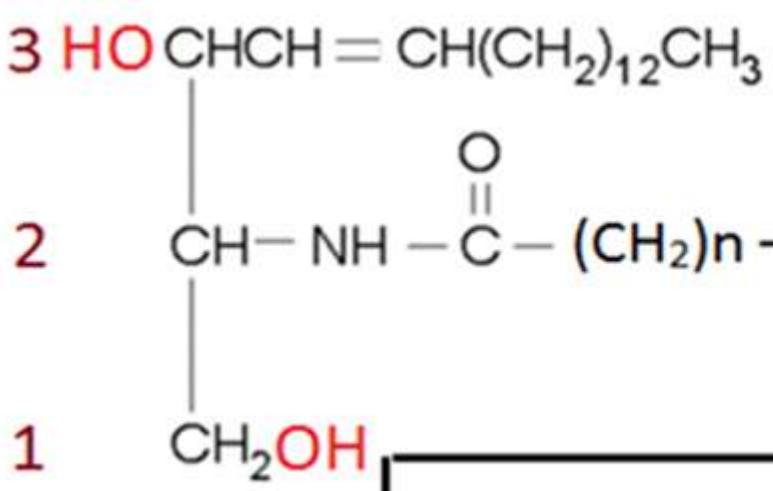
Without the C4 = C5 double bond we call it ***Dihydrosphingosine*** or ***Sphinganine***

The simplest sphingolipid called Ceramide

Sphingosine + fatty acid bind to C2 by amide bond



Ceramide



The primary alcohol of Ceramide can be bound to many molecules forming different members of Sphingolipids

Phosphocholine $\left(P-CH_2\,CH_2\,N(CH_3)_3^+\right)$ → **Sphingomyelin**

Major lipid in the Myelin Sheath

They are sphingophospholipids

Or

PhosphoEthanolamine $\left(P-CH_2\,CH_2\,NH_3^+\right)$

Monosaccharide Glc or Gal → **Cerebroside**

Oligosaccharide → **Ganglioside**

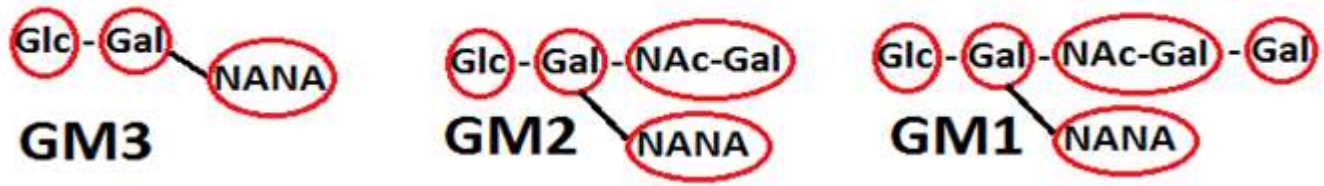
Glycolipids

توجد فقط على الطبقة الخارجية لغشاء الخلية

Markers and for Cell-Cell Recognition

That contain sugar called **NANA** (N-Acetyl Neuraminic acid)

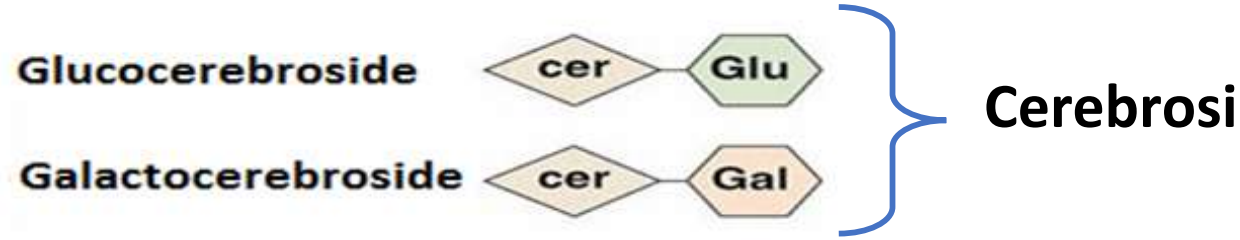
1 NANA = GM, 2NANA = GD, 3NANA = GT

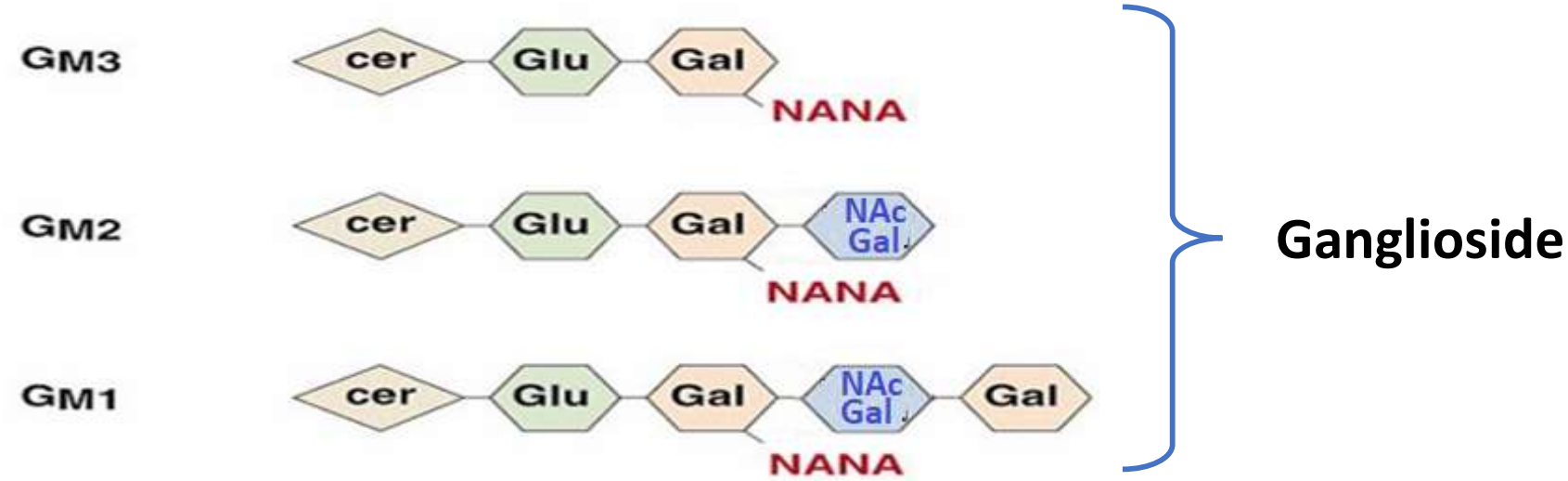


GM: Ganglioside Mono-NANA

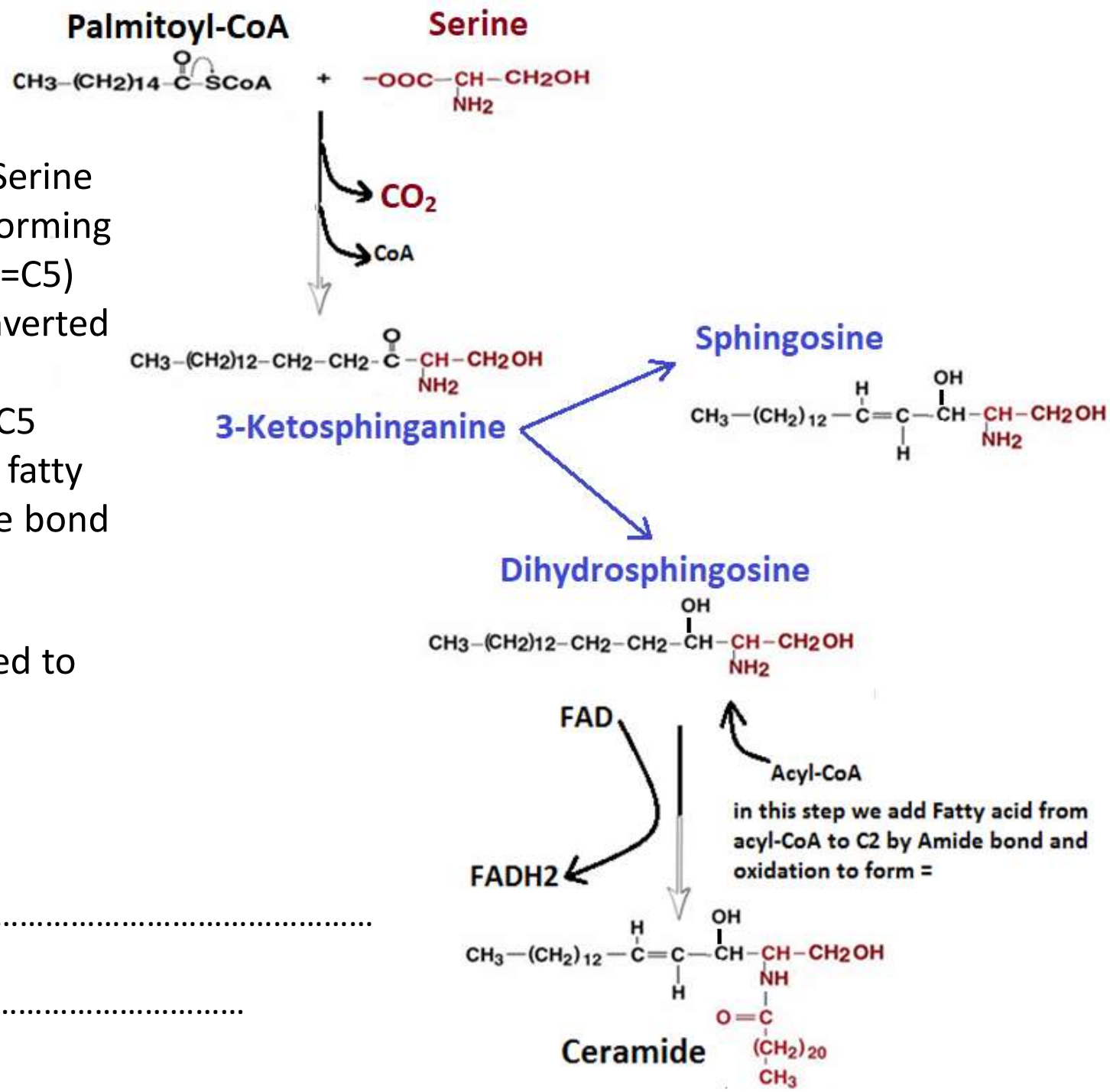
Nac-Gal: N-Acetyl galactosamine

Sphingolipids





Synthesis of Sphingosine, Ceramide



1. Starting material : Palmitoyl-CoA (16C) and Serine
- Remove CoA, Remove CO_2, then condense; forming ***3-Ketosphinganine*** (C3 is keto group, lack C4=C5)
- 3-Ketosphinganine (Branch point) can be converted to sphingosine or Dihydrosphingosine

2. Dihydrosphingosine is oxidized to form C4=C5 (FAD is reduced to $FADH_2$) and in the same step fatty acyl is transferred from Acyl-CoA to C2 by amide bond forming ***Ceramide***

Then the primary alcohol of Ceramide is attached to phosphocholine, phosphoethanolamine, monosaccharide or oligosaccharide

Q: the starting material of sphingolipid synthesis are……

Q: the amino group of sphingosine is derived from……

Sphingolipidoses

Also called ***Lipid Storage Diseases***

Genetic Defect in one of the Enzyme of ***sphingolipid degradation*** leads to accumulation of Specific Lipid and cell death

Inherited as Autosomal Recessive Disease

Brain and Nervous tissue is Mostly Affected

Examples:

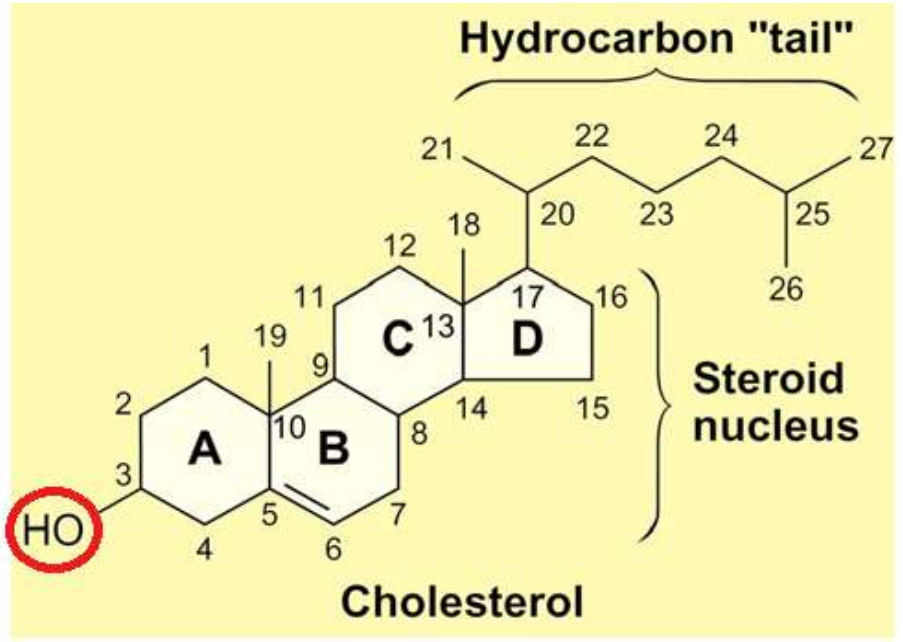
- GM1 Gangliosidosis
- Tay-Sach's disease
- Gaucher disease
- Farber disease
- Niemann-Pick disease
- Sandhoff-Jatzkwitz disease
- Fabry disease
- Krabbe disease
- Metachromatic Leukodystrophy

Cholesterol Synthesis

Features:

- 27 C atoms
- OH on carbon 3 (the only polar Part)
- Double bond between C5=C6
- Methyl groups at C10 and C13
- 8 carbon chain at C17
- Its amphipathic due to OH at ring A

So it can be found in cell membrane particularly Brain



De novo synthesis of Cholesterol requires:

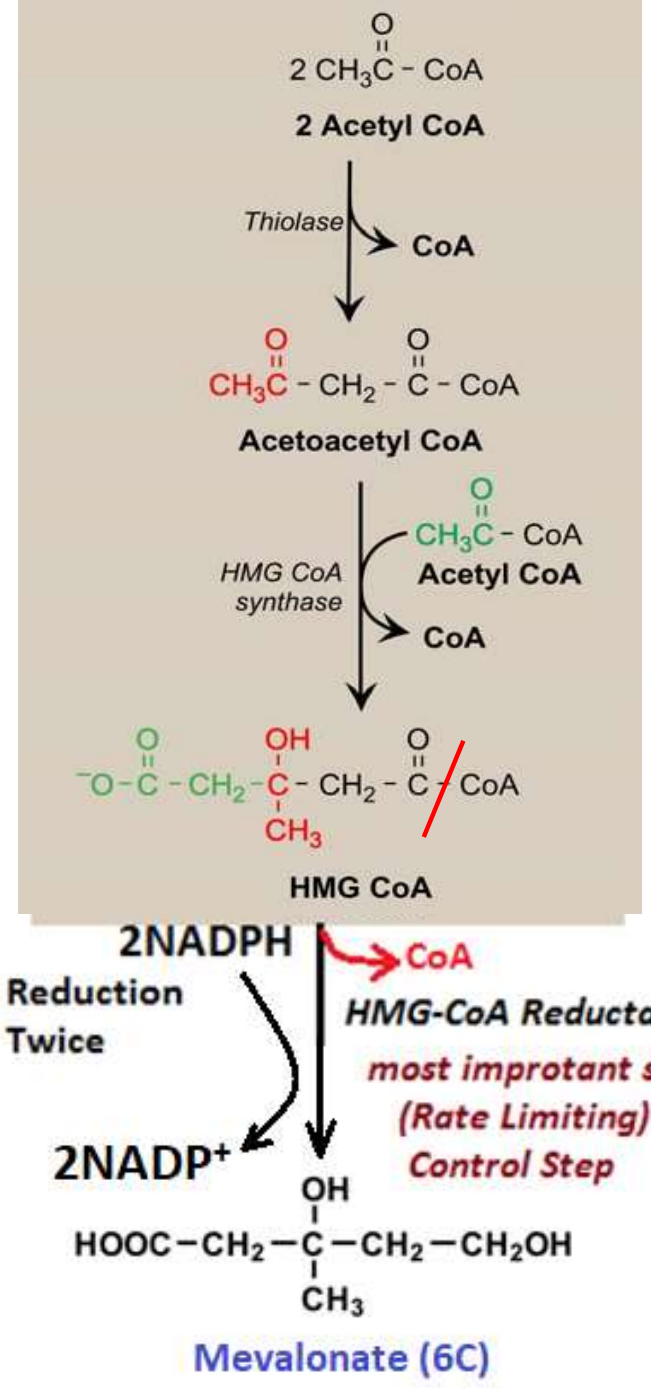
1. Acetyl-CoA (carbon Source “all the 27C atoms”)
2. Energy (ATP)
3. Reducing agent (NADPH)
4. O_2 :source of Oxygen of C3

De novo: من الصفر (مواد اولية)

Acetyl-CoA may come from Carbohydrates, Fatty acids, or Ketogenic amino acids

Cholesterol Synthesis occurs in Cytoplasm of all cells mainly Liver

Irreversible Pathway



1. **2** Acetyl-CoA bound together by ***Thiolase*** forming **Acetoacetyl-CoA (4C)**
2. Then another Acetyl-CoA is bound forming **HMG-CoA** (3-Hydroxy-3-Methyl-Glutaryl-CoA) by ***HMG-CoA synthase***

The first 2 steps exactly as Ketone bodies Synthesis , but cholesterol synthesis in Cytosol, while Ketone bodies in Liver Mitochondria, So HMG-CoA represent a branch point where it can be converted to

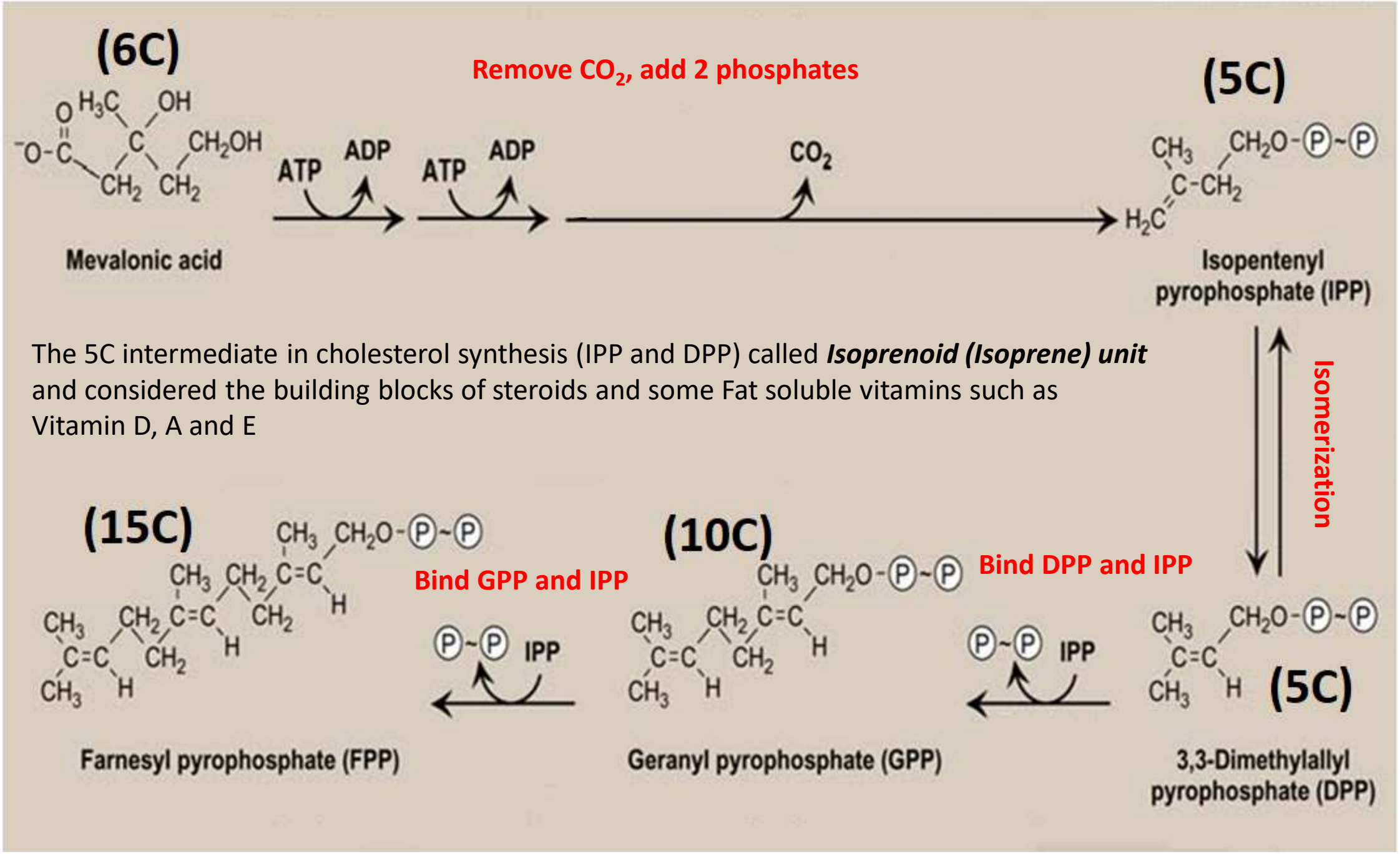
- Cholesterol
- Ketone bodies

3. CoA is removed from HMG-CoA and C=O is reduced twice to C-OH (2NADPH used) forming **Mevalonate**

This step in the rate limiting step of cholesterol synthesis, Control step

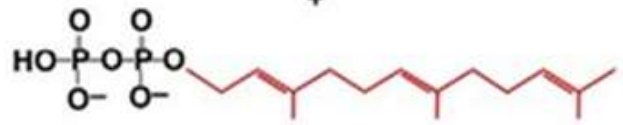
This enzyme is inhibited allosterically by high cholesterol level (Feed-back inhibition)

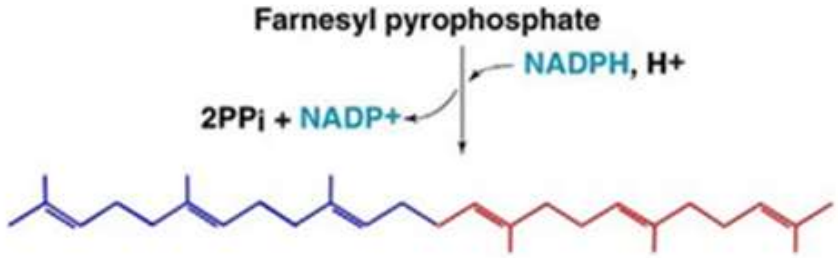
HMG-CoA reductase is targeted by many drugs such as **Statins** to inhibit de novo cholesterol synthesis


(6C)
Mevalonic acid
Remove CO_2, add 2 phosphates
ATP
ADP
ATP
ADP
CO_2
(5C)
Isopentenyl pyrophosphate (IPP)
Isomerization
The 5C intermediate in cholesterol synthesis (IPP and DPP) called ***Isoprenoid (Isoprene) unit*** and considered the building blocks of steroids and some Fat soluble vitamins such as Vitamin D, A and E
(15C)
Farnesyl pyrophosphate (FPP)
Bind GPP and IPP
IPP
(10C)
Geranyl pyrophosphate (GPP)
Bind DPP and IPP
IPP
(5C)
3,3-Dimethylallyl pyrophosphate (DPP)

(15 C) 

2 Farnesyl condensed together forming Squalene (30 C)

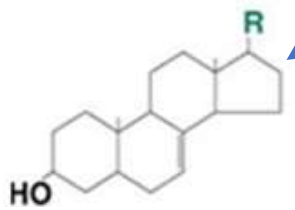
(15 C) 



Squalene
(30 C)

O_2

Cyclization

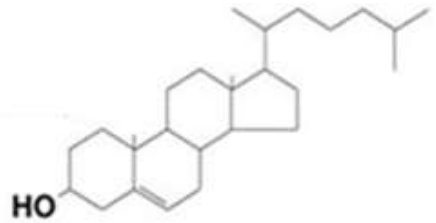


First Steroid intermediate

Lanosterol (30 C)

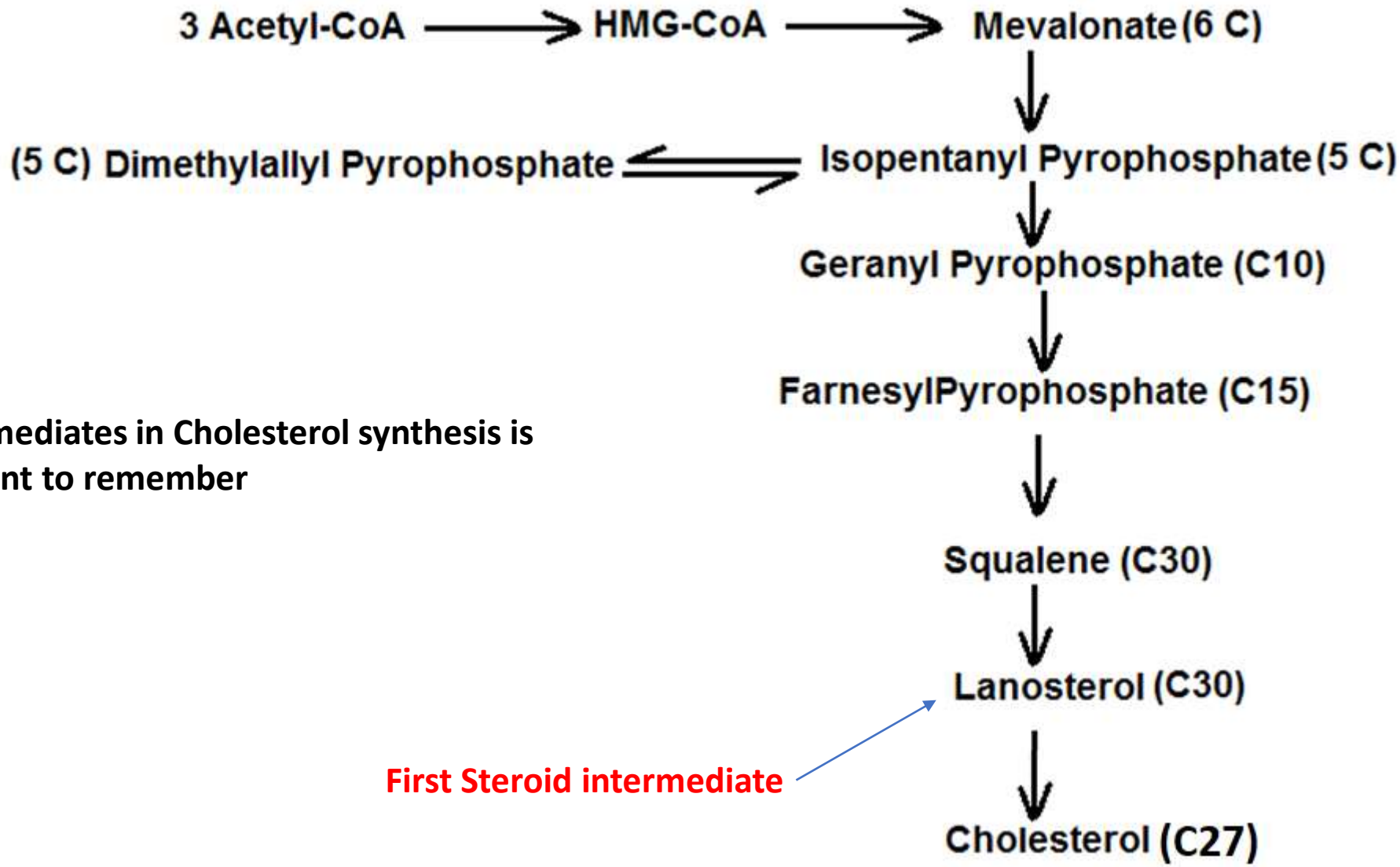
NADPH

19 Steps



Cholesterol (27 C)

Summary

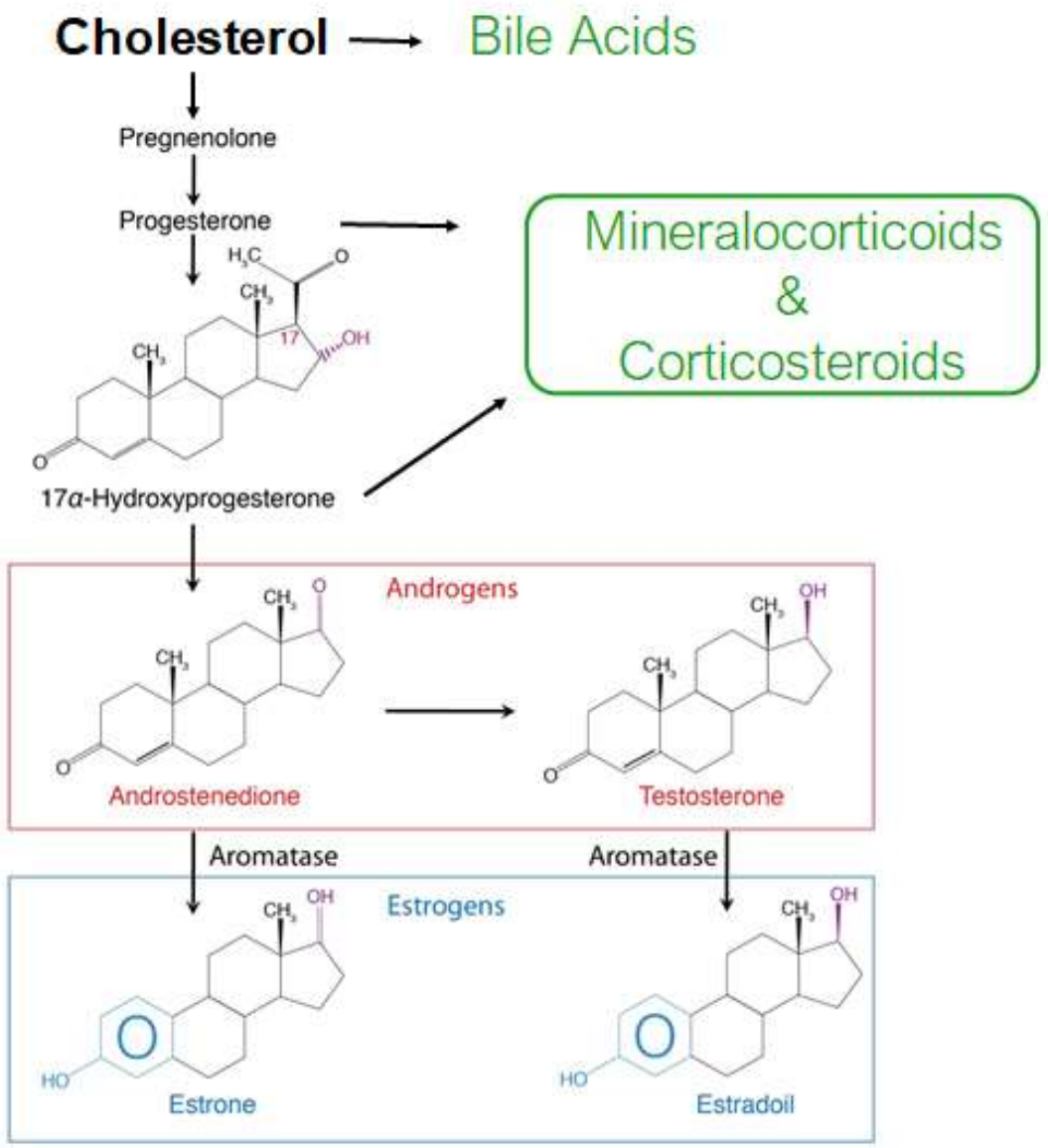


The correct order of intermediates in Cholesterol synthesis is important to remember

- **Cholesterol is the precursor of other steroids**

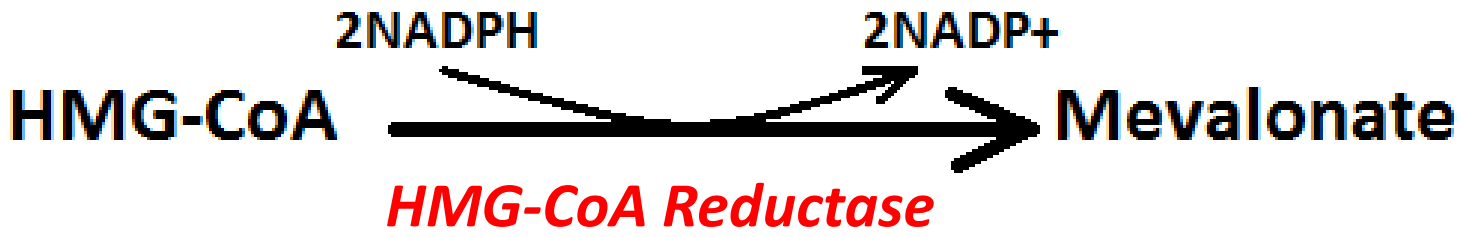
- ***Sex hormones*** ((Androgens “Male” and Estrogens “Female”)
- ***Adrenal Gland Hormone*** (Glucocorticoids such as Cortisol and Mineralocorticoids such as Aldosterone)
- ***Bile acids and salts*** which are synthesized in liver from cholesterol, stored in the gallbladder and important in lipids digestion and absorption

Also Cholesterol is the precursor of Vitamin D



Regulation of cholesterol synthesis

To control cholesterol synthesis, we control the activity of ***HMG-CoA reductase*** Enzyme



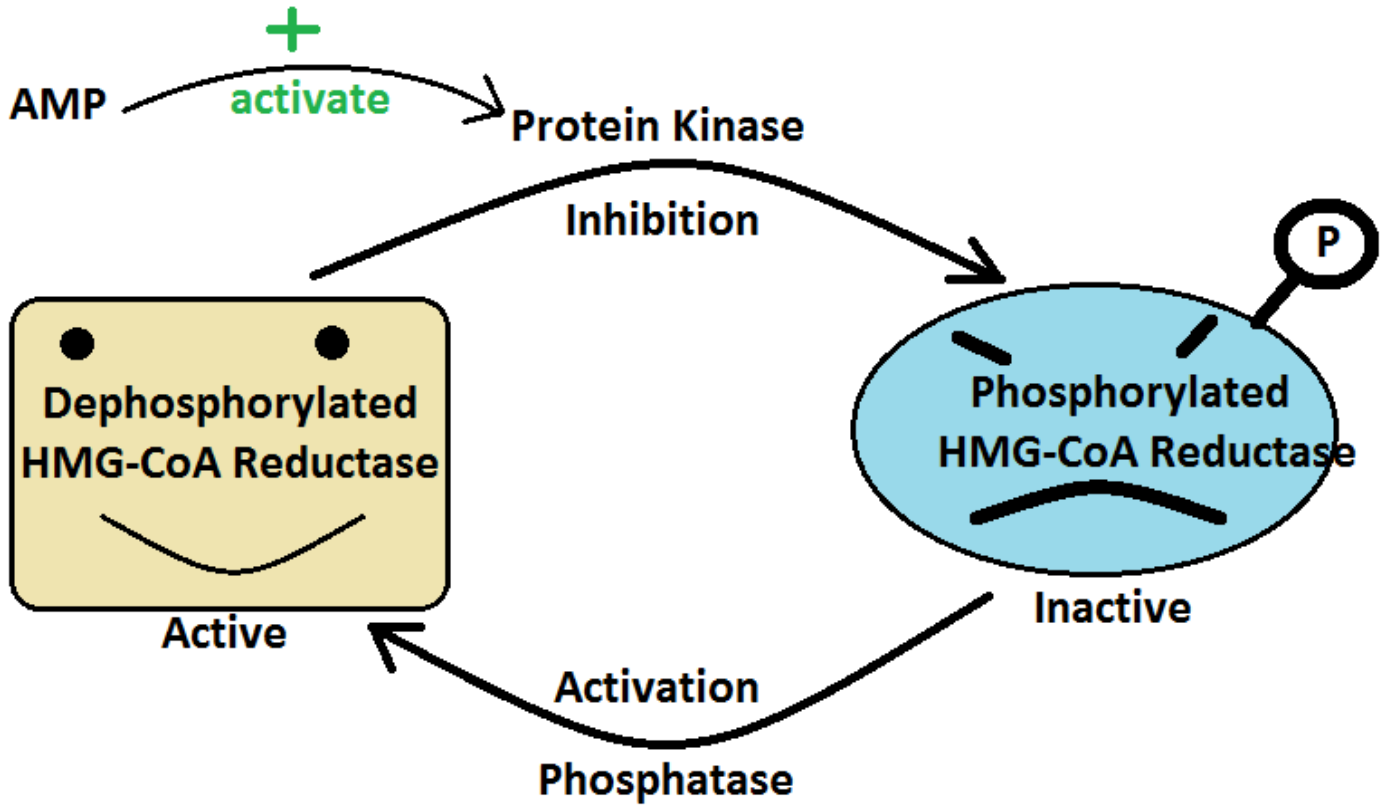
This Enzyme can be regulated by:

1. ***Allosteric control***
2. **Covalent Control** (Phosphorylation)
3. **Hormonal control** (Insulin, Glucagon)
4. **Genetic control**

1. Allosteric control: HMG-CoA reductase is allosterically inhibited by high cholesterol level (Feed-back inhibition)

2. Covalent Control (phosphorylation)

High AMP means low energy, this will inhibit cholesterol synthesis because it requires high amount of energy



3. Hormonal Control:

Glucagon → activate protein Kinase A Leads to phosphorylation and Inhibition

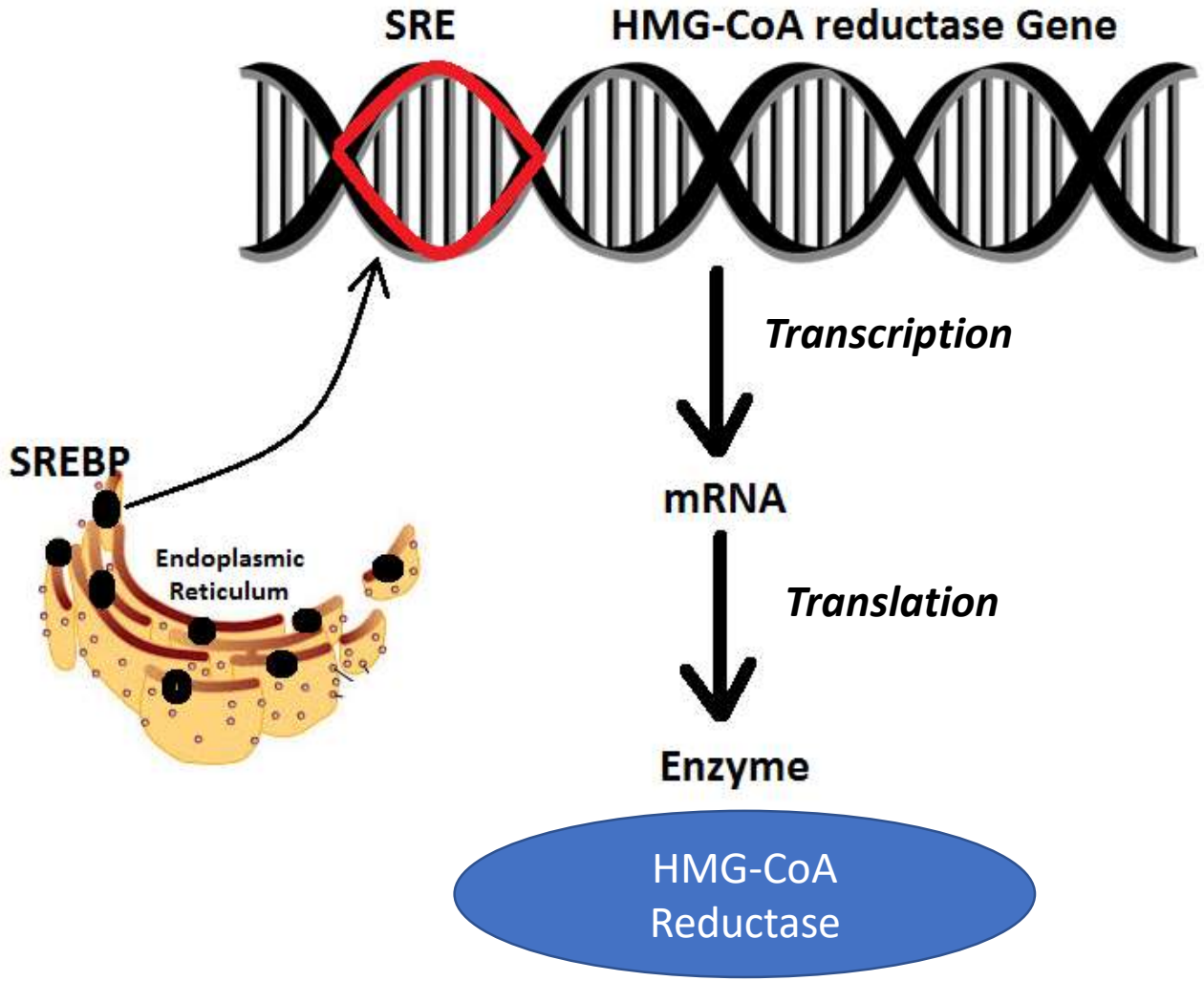
Insulin → activate Phosphatase Leads to dephosphorylation and activation

4. Genetic control

SRE: Sterol Regulatory Element, must bind to transcription factor (protein) called **SREBP** (SRE binding Protein) which found in the **ER** in order for the gene to be transcribed

↓cholesterol: this stimulate SREBP to move from ER to the nucleus and bind to SRE stimulate gene transcription, this will increase the enzyme concentration

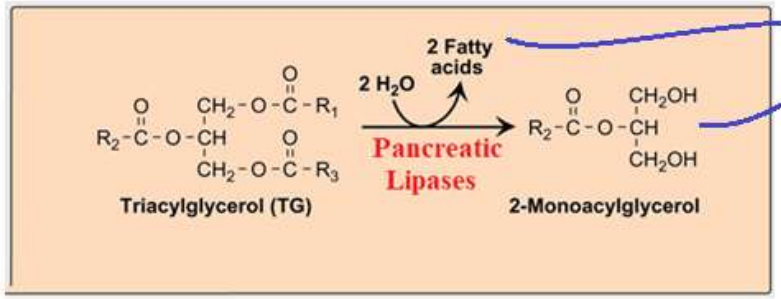
↑ cholesterol: SREBP remain in the ER.

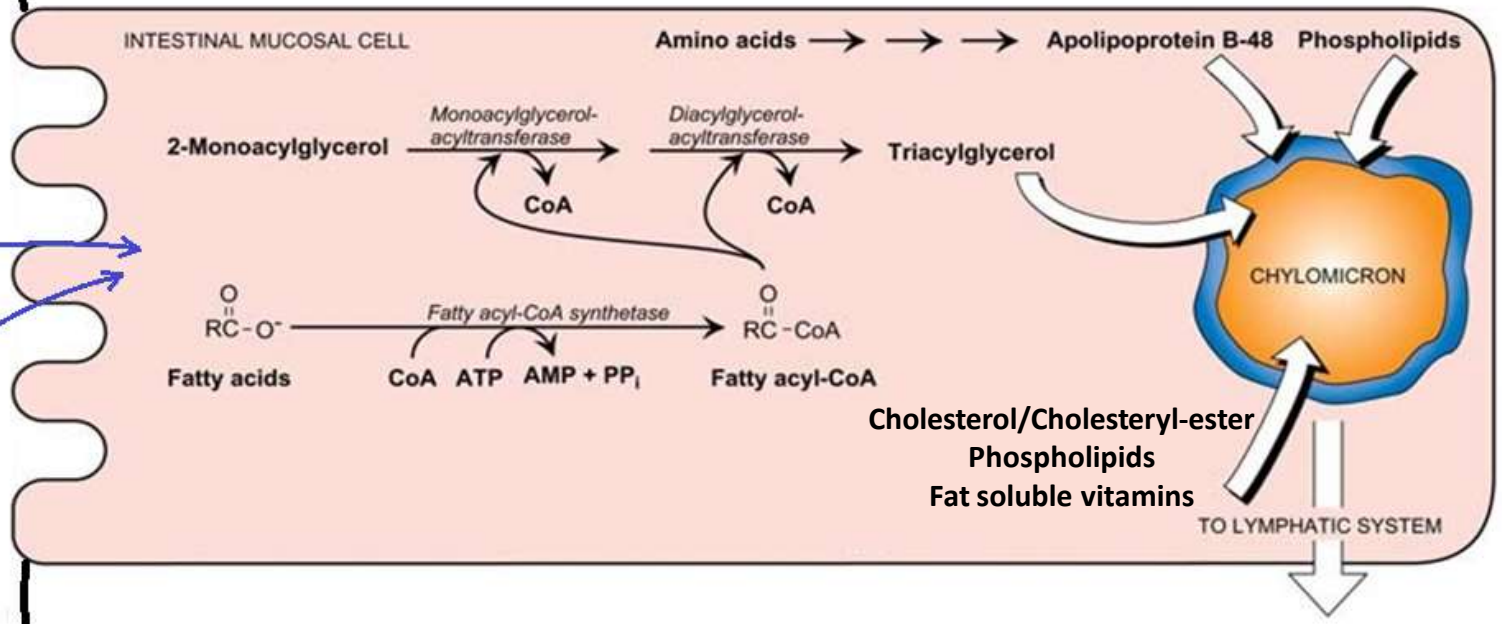


Fat Digestion and Absorption

Intestinal Lumen

Dietary Fat



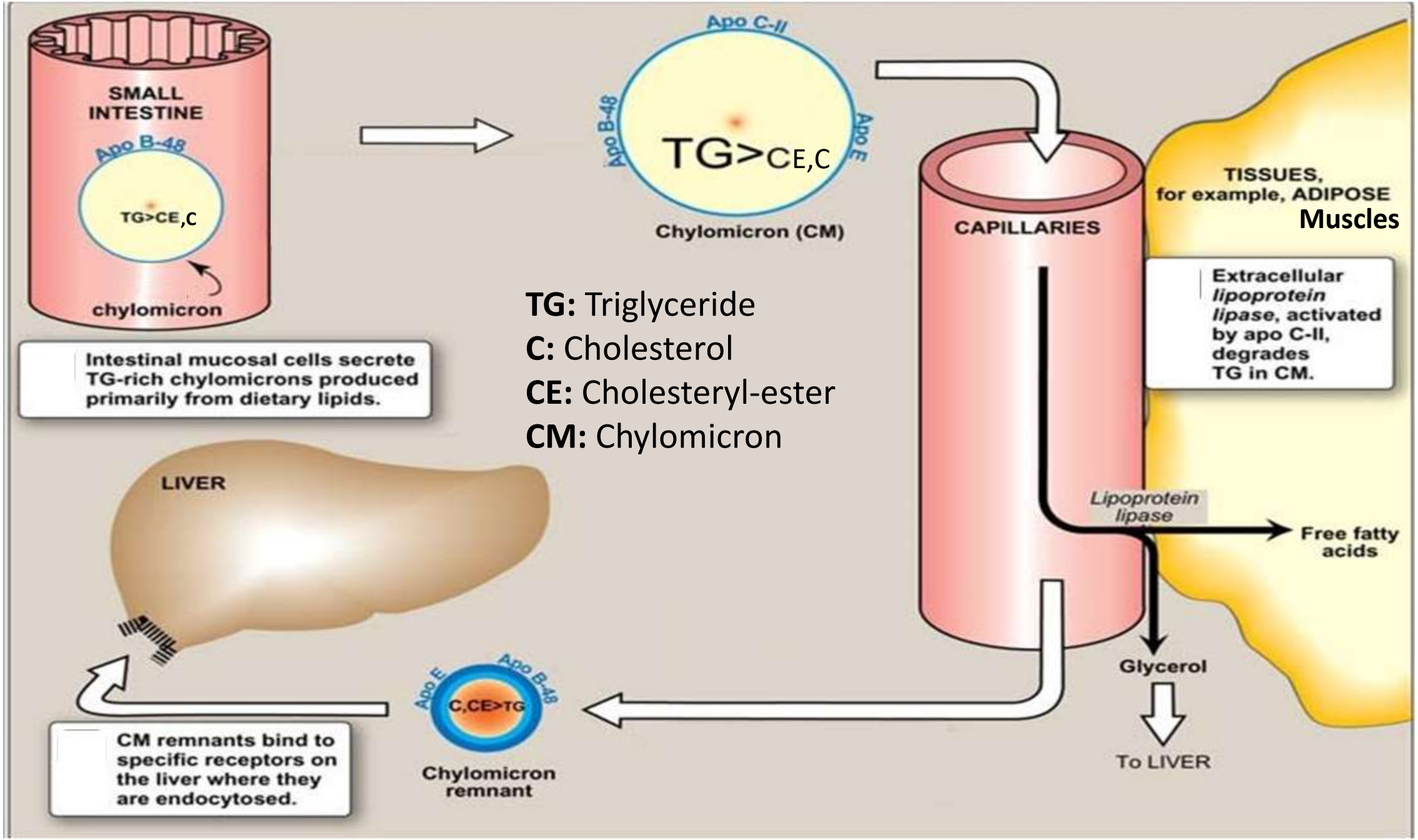


Dietary Triglycerides are digested by ***pancreatic lipase*** to 2 Free fatty acids + MAG

Fatty acids and MAG are absorbed into the intestinal mucosal cell where they are recombined to regenerate TAG

TAG + Cholesterol + Cholesteryl-ester + phospholipids + fat soluble vitamins **+ protein called Apo B48** aggregate together forming lipoproteins called ***Chylomicron*** which is then transported to Lymph vessels because its large and may block small capillaries after that it transported to large veins

Chylomicron (CM) Metabolism

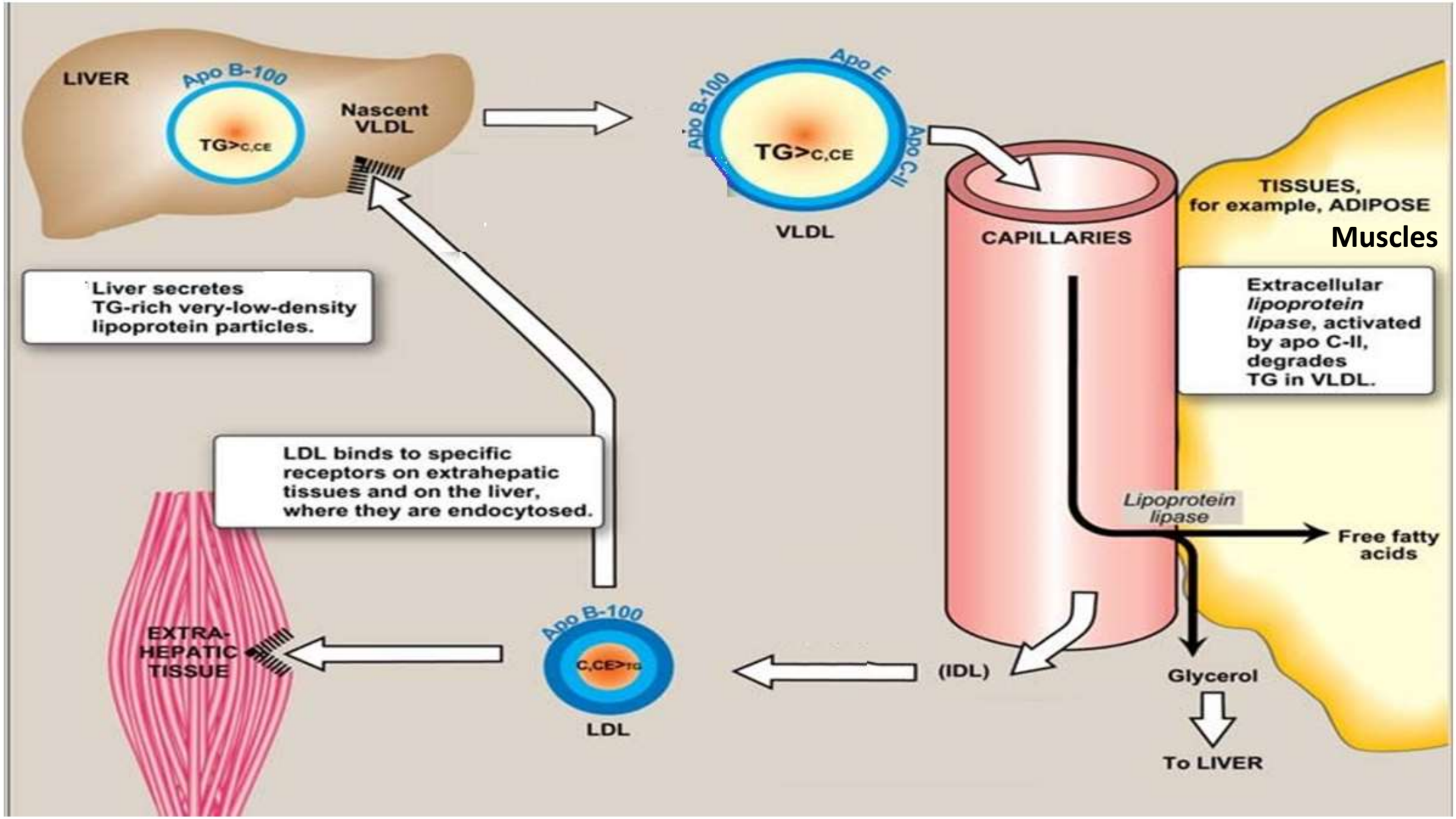


Chylomicron metabolism in words

- Inside intestinal mucosal cells Dietary TG, PL, C, CE aggregate with **Apo B48** forming ***CM*** (%TG>%C,CE)
- Then CM is transported to blood via Lymphatic system
- In tissues ccapillaries - mainly **Muscles** and adipose tissues - enzyme called ***Lipoprotein Lipase*** which found outside the cell (Extracellular Enzyme secreted by endothelial cells); this enzyme hydrolyze TG in the CM (Fatty acid go inside the cells and Glycerol transported to liver)
- Now %TG become less than %CE,C .what remains now called ***Chylomicron Remnant*** (% CE,C > % TG)
- CM Remnant bind to receptors in **liver** cells and phagocytosed
- **You can conclude the functions of CM**

- Transport Dietary TG to tissues (mainly muscle and adipose tissues)
- Transport of Dietary Cholesterol and CE to Liver

VLDL Metabolism



VLDL: Very Low Density Lipoprotein
IDL: Intermediate Density Lipoprotein
LDL: Low Density Lipoprotein (Bad Cholesterol)
HDL: High Density Lipoprotein (Good Cholesterol)

VLDL metabolism in words

- TG, Cholesterol, CE synthesized in **Liver** aggregate with phospholipids and **Apo B100** forming ***VLDL*** (%TG>%CE,C)
- Then VLDL is released to blood
- In tissues - mainly Muscles and adipose tissues - enzyme called ***Lipoprotein Lipase*** which found outside the cell (Extracellular Enzyme); this enzyme hydrolyze TG in the VLDL (Fatty acid go inside the cells and Glycerol transported to liver)
- Now %TG become less than %CE,C (VLDL becomes **IDL**)
- Then IDL become ***LDL (bad cholesterol)*** (% CE,C > % TG)
- LDL bind to receptors in **Extrahepatic tissues (e.g. Muscles) or to the liver** phagocytosed
- **You can conclude the functions of VLDL**

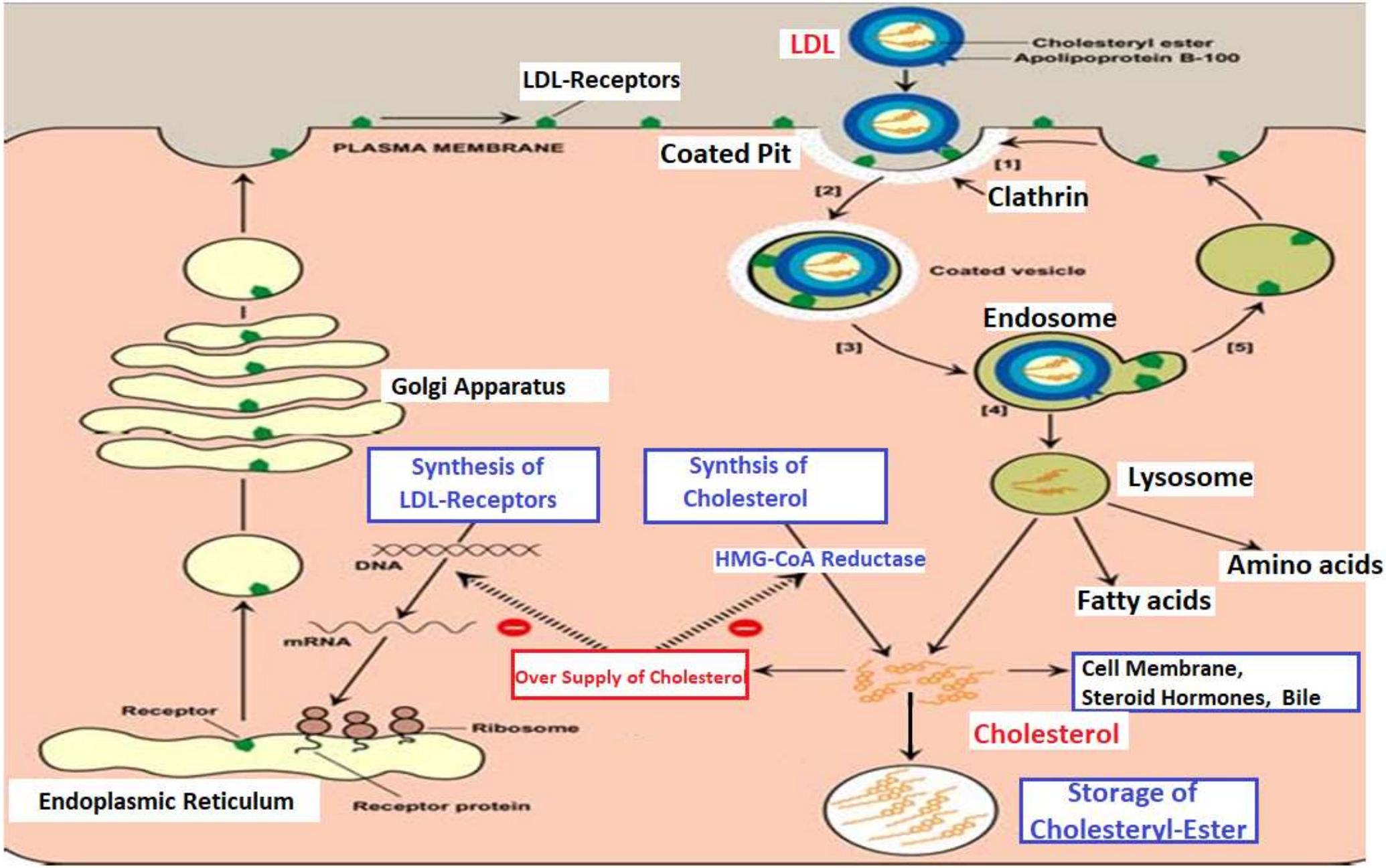
- Transport Liver TG to tissues (mainly muscle and adipose tissues)

- **You can conclude the functions of LDL**

- Transport Liver cholesterol to peripheral tissues

- **Function of HDL** (Good Cholesterol) is a **cholesterol Scavenger**; it collect excess cholesterol from blood and peripheral tissue and transport it to liver for elimination so it reduces the risk of cardiovascular diseases

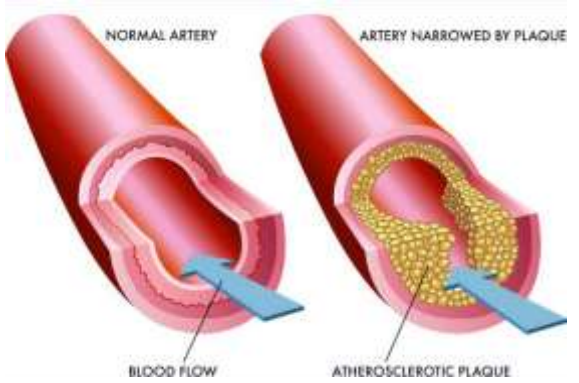
How Can cells Endocytose LDL??



- ***Apo B100*** of LDL bind to ***LDL-Receptors*** on the surface of the cell, these receptors are synthesized in the ER and then transported to the cell membrane
- The region of the membrane where the receptors found called ***Coated Pit***, this region is covered interiorly by protein called ***Clathrin***
- After binding, the cell Endocytose LDL along with LDL-receptors
- LDL is degraded by Lysosomal Enzymes, and the LDL-Receptors return back to the cell membrane

If cholesterol accumulate inside the cell

- Inhibit the synthesis of LDL-receptors **(Down regulation)**
- Inhibit HMG-CoA reductase → NO endogenous synthesis
- Stored as cholesteryl-ester



Macrophage Scavenger cells

- If LDL is accumulated in blood the unsaturated fatty acids within the LDL is oxidized
- The oxidized (damaged LDL) cannot bind to LDL receptors and stay in blood
- Macrophage scavenger cells are type of WBCs that endocytose ***Damaged (oxidized) LDL***
- When these cells phagocytose large amount of LDL it becomes **Foam Cell**
- Accumulation of Foam cells is an early evidence for **Atherosclerosis (formation of plaque within arteries)**

Familial Hypercholesterolemia ارتفاع الكوليستيرول الوراثي

Mutation in the LDL-receptor gene

you have 2 alleles for LDL-Receptors