CVS module

Cholesterol metabolism; Hypercholesterolemia Hypocholesterolemia

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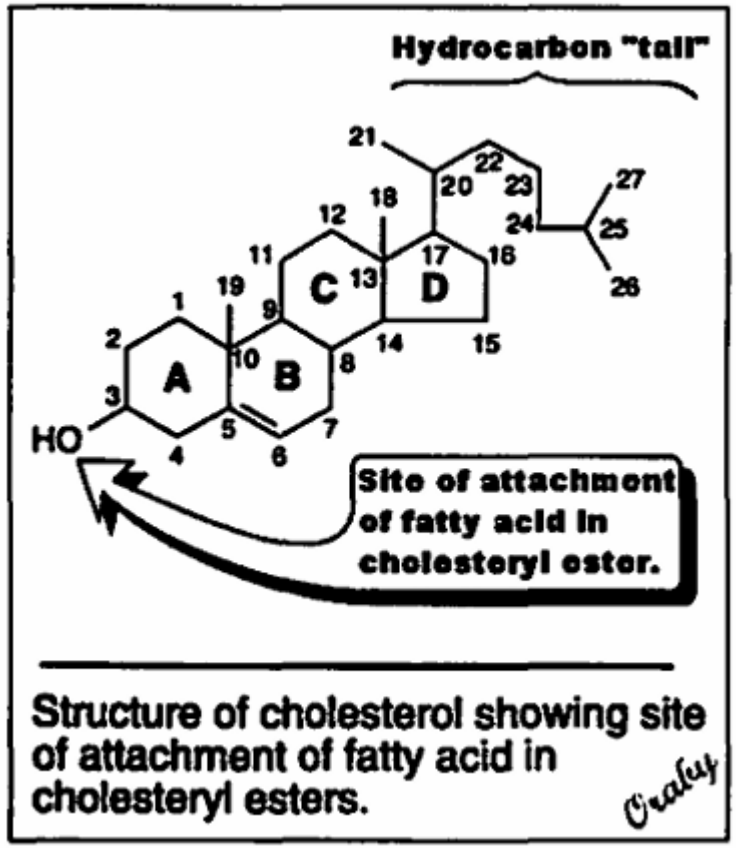
Structure and sources of cholesterol:

- Cholesterol is classified as an animal sterol (having -OH group at C3).
- Endogenous: Cholesterol is formed in the body almost in all nucleated cells from Acetyl-CoA (about 700 mg/day).
- Exogenous: Cholesterol occurs only in food of animal origin such as egg yolk, meat, liver and brain. Diet supplies about 400 mg/day.



Structure of cholesterol showing site of attachment of fatty acid in cholesteryl esters.

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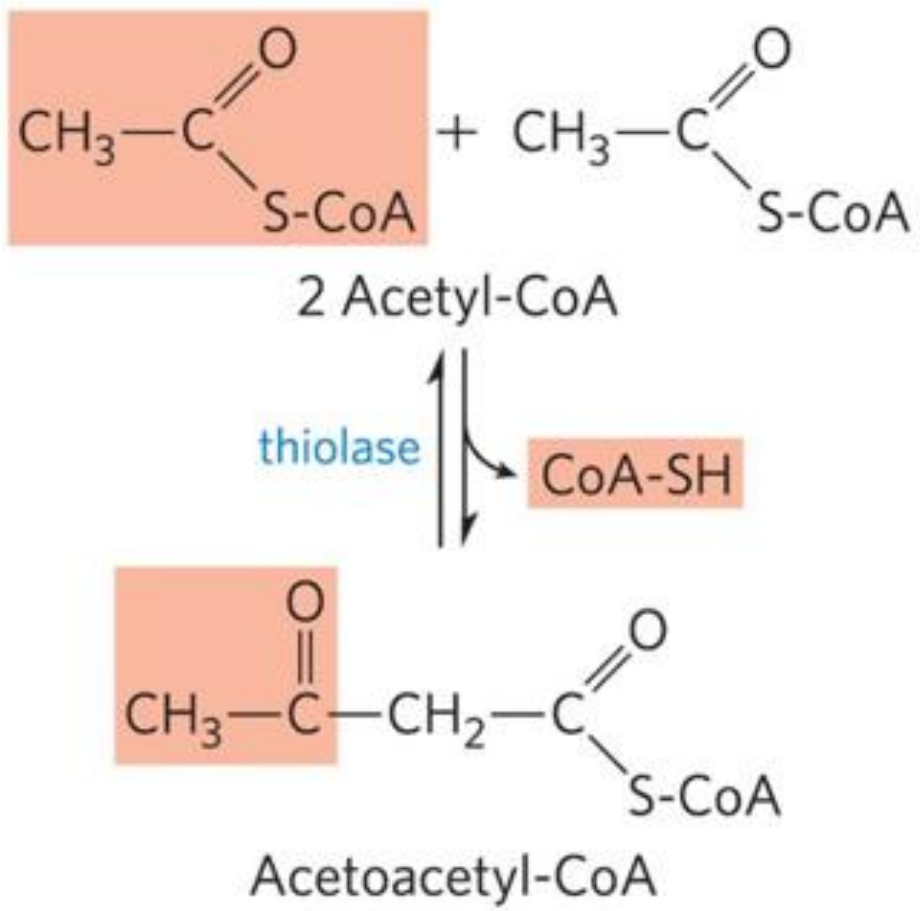
Synthesis of cholesterol:

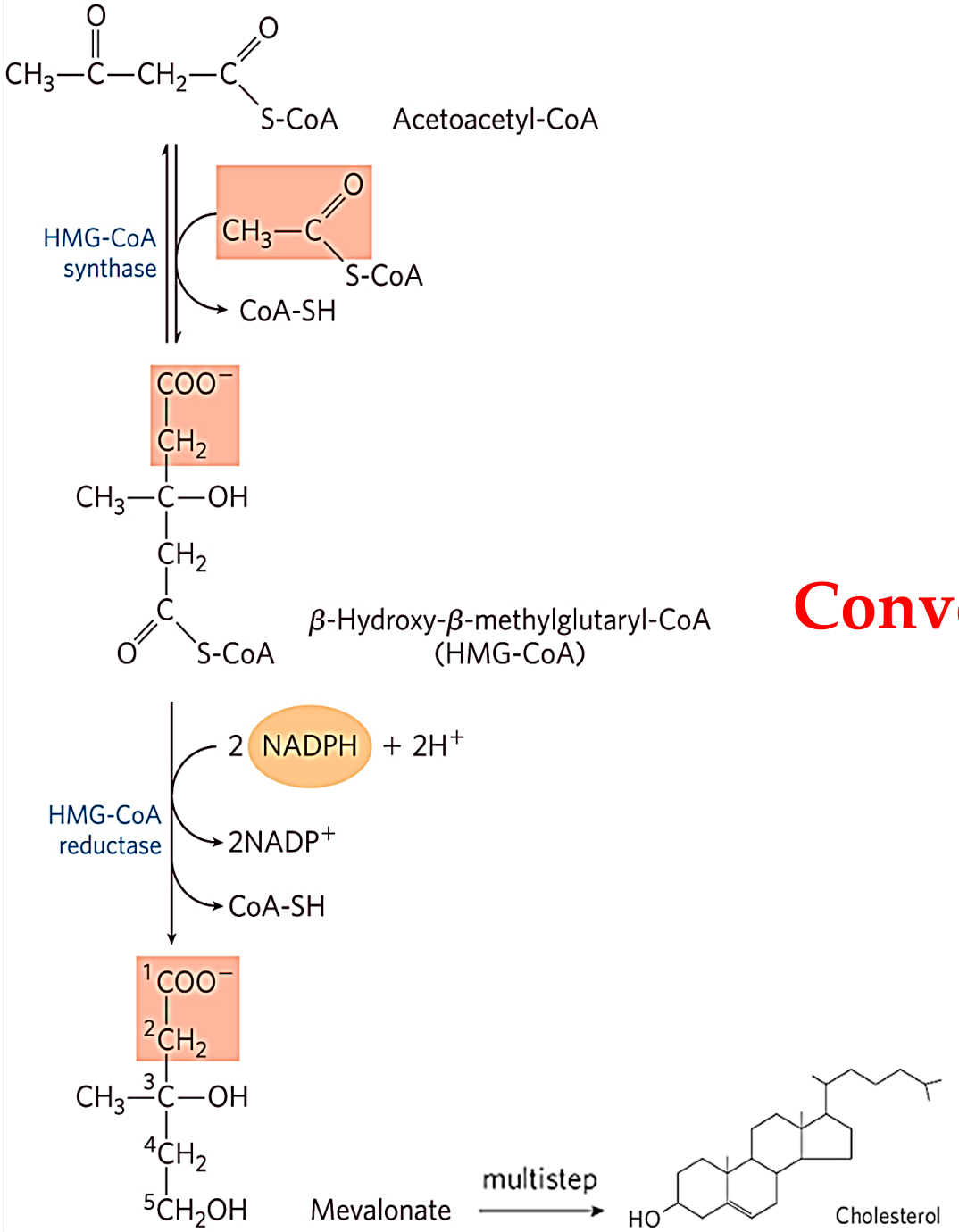
1. Location:
   - Intracellular location: Cytosol.
   - Organ location:
     - Liver is the major site of cholesterol synthesis.
     - Other tissues e.g. intestine, adrenal cortex, gonads and skin.
2. Precursor: Acetyl-CoA.

Steps of synthesis of cholesterol

- The first step of cholesterol synthesis is the condensation of two molecules of **acetyl-CoA** to form **acetoacetyl-CoA**.
- This reaction is catalyzed by the enzyme **thiolase.**



Conversion of acetoacetyl CoA to cholesterol



Regulation of Cholesterol Metabolism. HMG CoA reductase is the key enzyme for cholesterol synthesis

Major regulation is by gene expression

Minor regulatory mechanisms

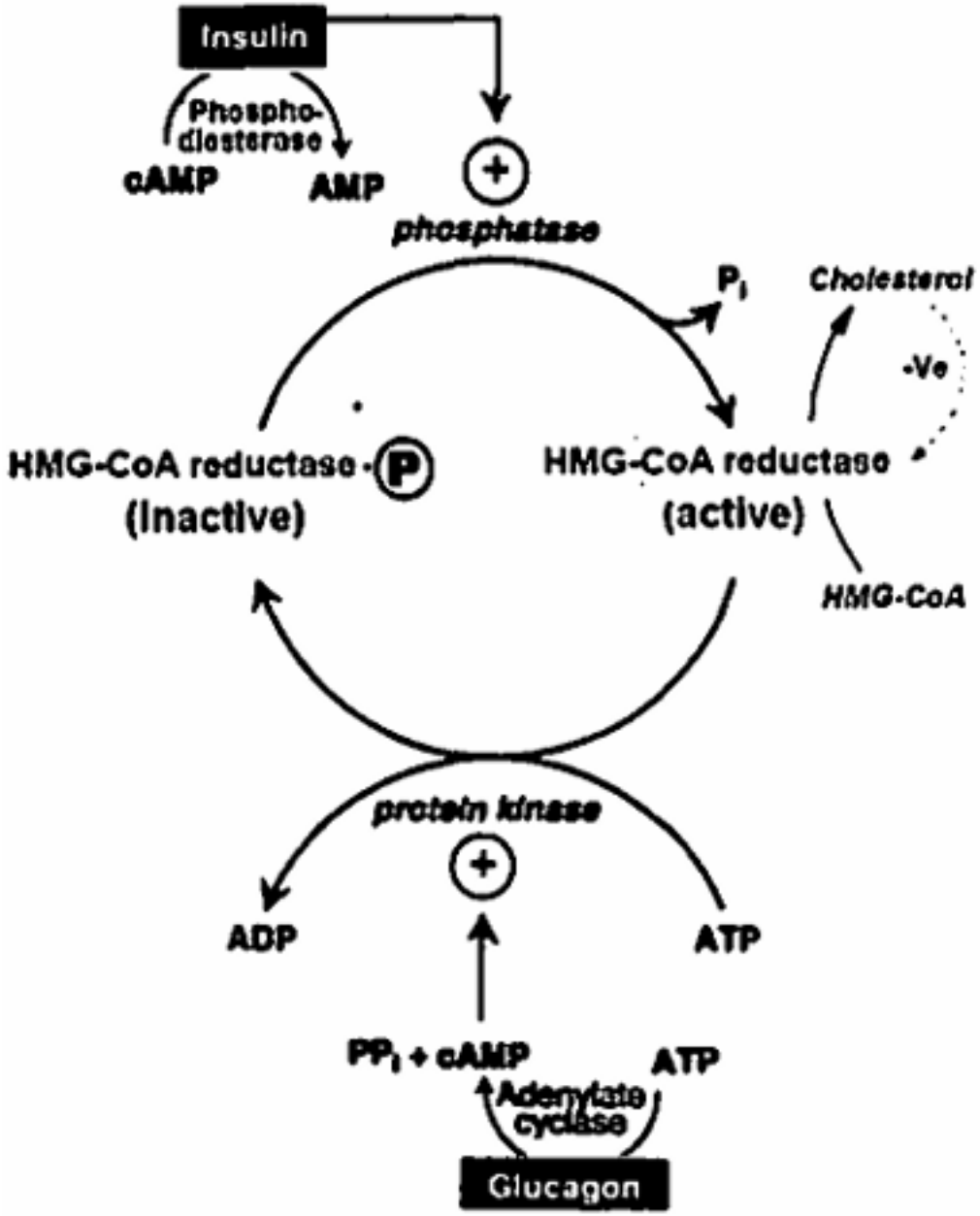
Major regulation is by gene expression: Three levels

1. Sterol regulatory element-binding proteins (SREBPs)
   - When sterol levels are high, SREBPs remain bound to the ER membrane
   - When sterol levels fall, the complex is cleaved and moves to the nucleus.
   - It activates transcription of HMG-CoA reductase
2. Translational control on mRNA stability
   - Increased mevalonate destabilize the HMG-CoA reductase mRNA
3. Post-translational control
   - High cholesterol produces oxysterol, which allosterically binds HMG-CoA reductase, inducing a conformational change that promotes its **ubiquitination**.
   - Proteolytic degradation of HMG-CoA reductase

Minor regulatory mechanisms:

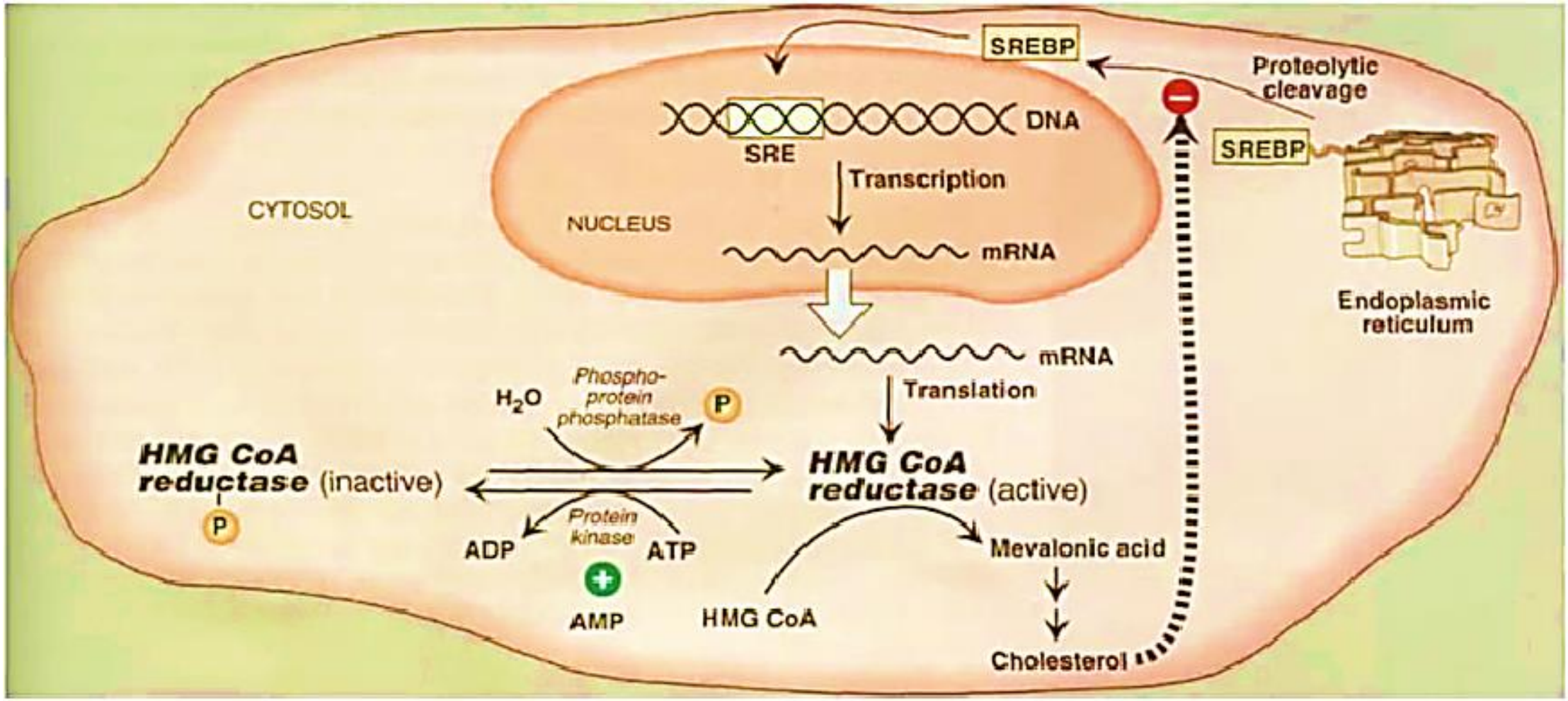
- Phosphorylation/de-phosphorylation
  - Covalent modification provides short-term regulation

1. Glucagon, epinephrine: cascades lead to phosphorylation, decrease the activity
2. Insulin: cascades lead to dephosphorylation, increase activity



Inhibition by drugs:

- Lovastatin and mevastatin are part of a class of drugs known as **statins** that specifically target **HMG-CoA reductase,** the enzyme responsible for the rate-limiting step in cholesterol biosynthesis. They're effective in treating hypercholesterolemia (high cholesterol levels).
- Competitive Inhibition of HMG-CoA Reductase: Lovastatin and mevastatin are structural analogs of HMG-CoA. Due to this structural similarity, they can bind to the active site of HMG-CoA reductase, effectively competing with HMG-CoA for binding.


SREBP
Proteolytic cleavage
DNA
SRE
Transcription
CYTOSOL
NUCLEUS
mRNA
SREBP
Endoplasmic reticulum
mRNA
Translation
H_2O
Phospho-protein phosphatase
P
HMG CoA reductase (inactive)
HMG CoA reductase (active)
P
Protein kinase
ADP
ATP
AMP
HMG CoA
Mevalonic acid
Cholesterol

Excretion of cholesterol

- About one gram of cholesterol is excreted dally. It is secreted as cholesterol, bile acids and coprostanol:
- A. ½ Gram cholesterol is excreted as such with bile, which transports it to the intestine for elimination.
- B. ½ Gram cholesterol is converted to bile acids, which is excreted in the feces.
- Some cholesterol is synthesized by intestinal cells and modified by bacteria before excretion. Bacterial enzymes reduce cholesterol into coprostanol, which is excreted into feces.

Plasma cholesterol and conditions associated

Hypercholesterolemia

Hypocholesterolemia

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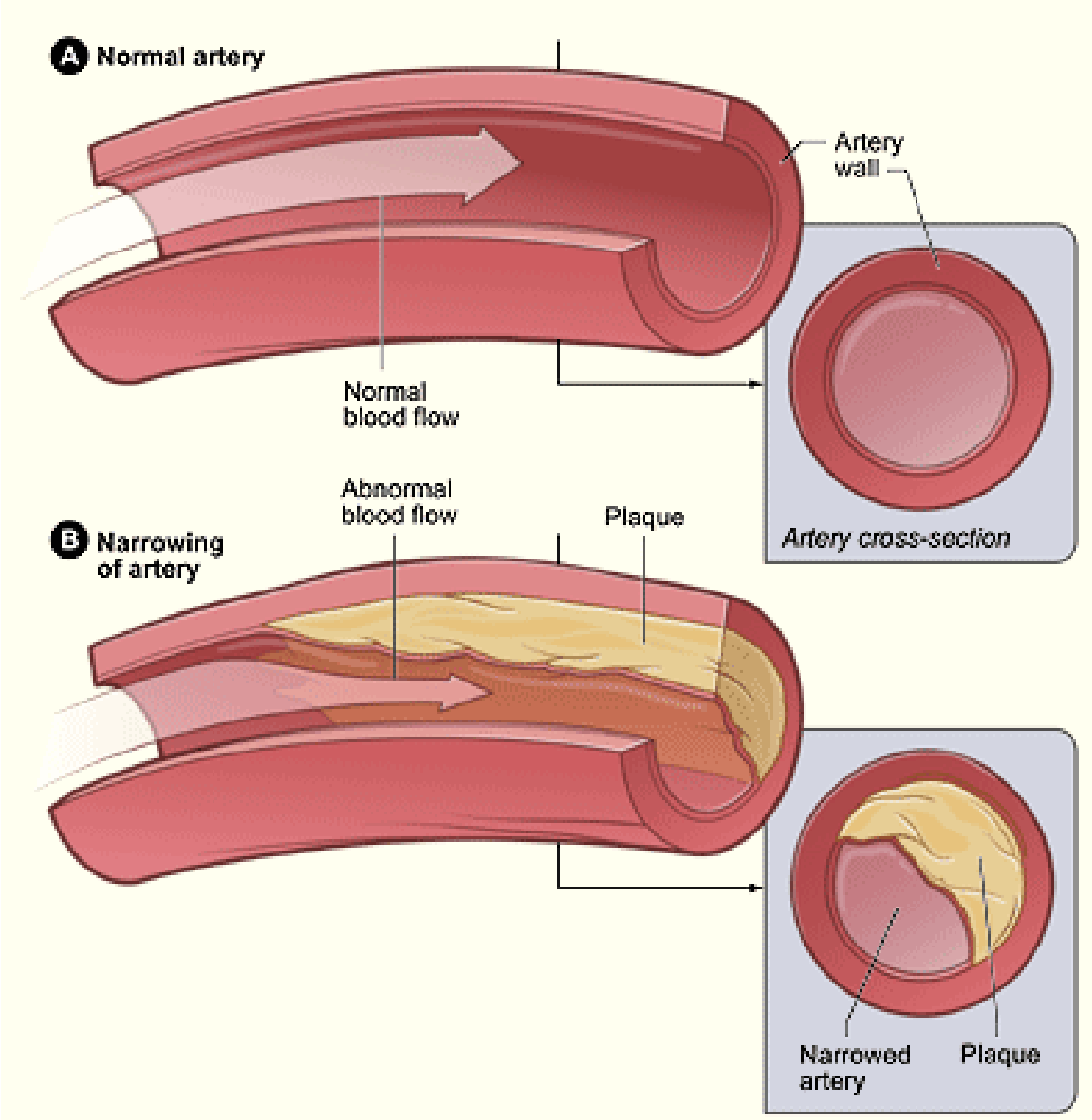
Plasma cholesterol

- In plasma, cholesterol exists in two primary forms: **free cholesterol** and **esterified cholesterol** (known as cholesteryl ester).
- **Normal Range**: Free cholesterol typically ranges from **26 to 126 mg/dL** in plasma
- **Normal Range**: The **optimal total plasma cholesterol level** typically falls between **140 and 220 mg/dL**.

Hypercholesterolemia

- Hypercholesterolemia is typically defined as a total plasma cholesterol concentration above **220 mg/dL**.
- This level is associated with an increased risk of atherosclerosis and cardiovascular diseases, as excess cholesterol in the blood can deposit on arterial walls, leading to plaque formation.



Causes of Hypercholesterolemia

1. Diet rich in carbohydrate, cholesterol and saturated fatty acids.
2. Hypothyroidism: Thyroxine (T4) regulates cholesterol metabolism by enhancing the conversion of cholesterol to bile acids and increasing the expression of LDL receptors on liver cells.
3. Diabetes is often associated with insulin resistance, which impairs lipid metabolism.
4. Kidney Disease (Nephrotic Syndrome)

Causes of Hypercholesterolemia

- Obstructive Jaundice blocks the excretion of bile acids and cholesterol from the liver into the intestine. This causes a build-up of cholesterol in the blood due to decreased biliary excretion.
- Familial hypercholesterolemia (FH) is a genetic disorder often caused by mutations in the LDL receptor gene, leading to reduced LDL receptor activity.
  - Because of deficient LDL receptors, individuals with FH cannot effectively clear LDL cholesterol from the blood, resulting in very high plasma cholesterol levels from birth.
  - This condition leads to early-onset atherosclerosis and significantly increases cardiovascular disease risk, even in young individuals.

Hypocholesterolemia:

- Plasma cholesterol levels below **140 mg/dL** are considered hypocholesterolemic. Causes:
- Prolonged fasting which causes decreased secretion of Insulin (decreased activation of HMG-CoA reductase).
- Diet Poor in Saturated Fatty Acids, Carbohydrates, and Cholesterol.
- **Liver Diseases** Liver diseases like **cirrhosis** or **hepatitis** impair this synthetic function
- **Hyperthyroidism:** excess thyroid hormones (T3 and T4) increase the metabolic rate and enhance **LDL receptor** activity in the liver. This accelerates LDL clearance from the bloodstream.

TRANSPORT OF CHOLESTEROL:

- Cholesterol is hydrophobic. It is transported in plasma in the more soluble lipoprotein forms: LDL, VLDL and HDL (next lecture).
- Free cholesterol is removed from tissues by HDL and transported to be excreted by the liver.

Storage of Cholesterol (Next lecture)

- Cholesterol ester is the storage form of cholesterol: It Is formed in both tissues and plasma.
- In tissues (liver), cholesterol is esterified by ACAT enzyme (acyl CoA cholesterol acyl transferase):

Cholesterol + Acyl CoA → Cholesteryl ester + CoASH

- In plasma, cholesterol is esterified by LCAT enzyme (lecithin cholesterol acyl transferase). LCAT is associated with HDL.

Cholesterol + lecithin → Cholesteryl ester + lysolecithin

Functions of cholesterol

Functions of cholesterol

1. Cholesterol enters in the structure of every body cell (e.g. cell membrane).

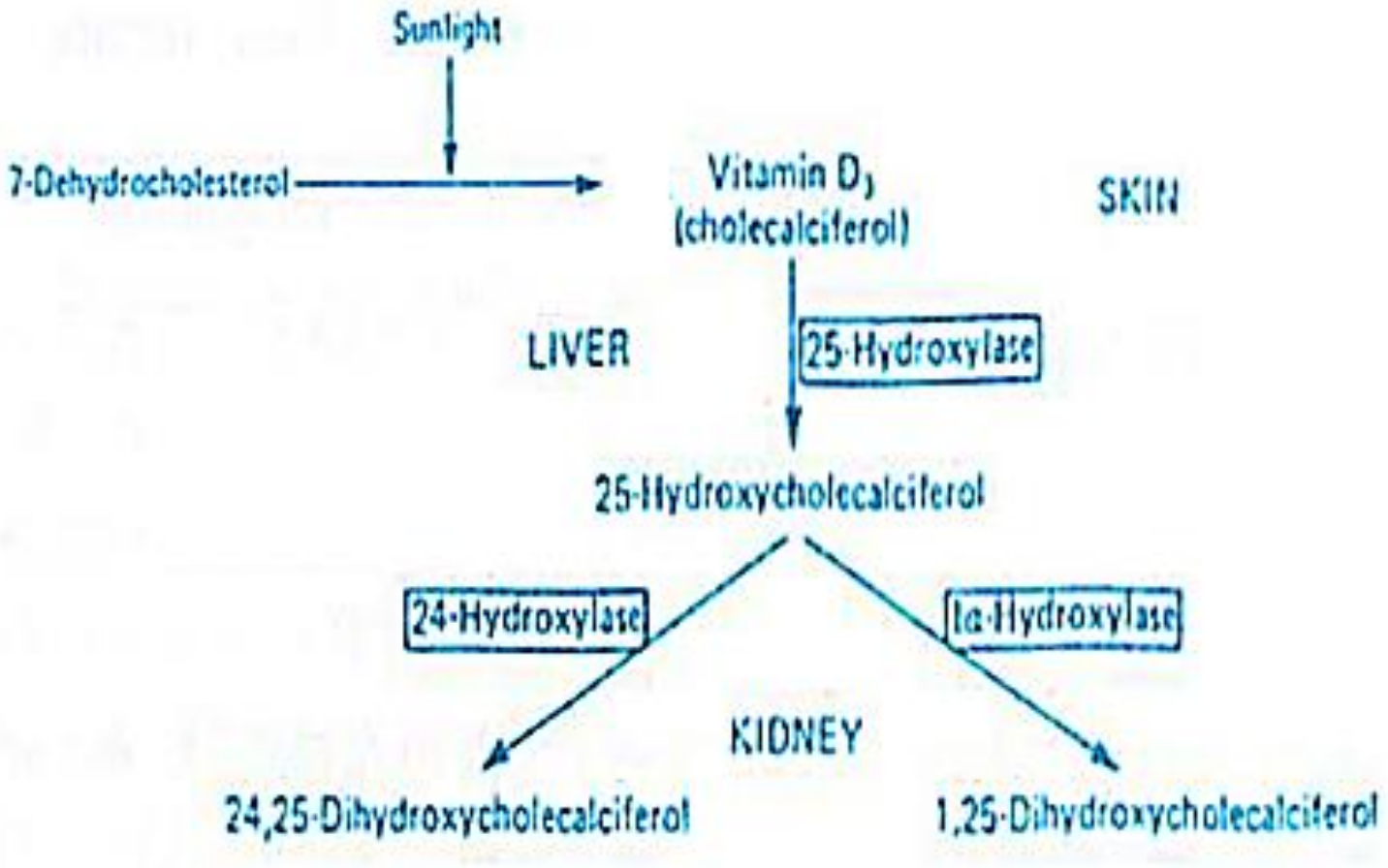
2. Cholesterol Is the precursor of:

1. **Vitamin D_3:** (subcutaneous fat) ➔ 7-dehydrocholesterol ➔ Vitamin D_3.
2. **Steroid hormones:**
   a) **Estrogens and progesterone** (ovaries).
   b) **Testosterone and androgens** (testes).
   c) **Glucocorticoids and mineralocorticoids** (Adrenal cortex).
3. **bile acids: (Liver)**

Generation the vitamin D_3 (1, 25 dihydroxycholecalciferol)

- Ultraviolet rays of sun generate the vitamin D_3 from the Provitamin 7-dehydrocholesterol (in human).
- 7-dehydrocholesterol is converted into cholecalciferol
- In the liver, cholecalciferol is converted into 25-hydroxyvitamin D3.
- Finally, the kidneys convert 25-hydroxyvitamin D into the active form of vitamin D, 1,25-dihydroxyvitamin D3.

Activation of vitamin D3 to 1,25 dihydroxycholccalcifcrol



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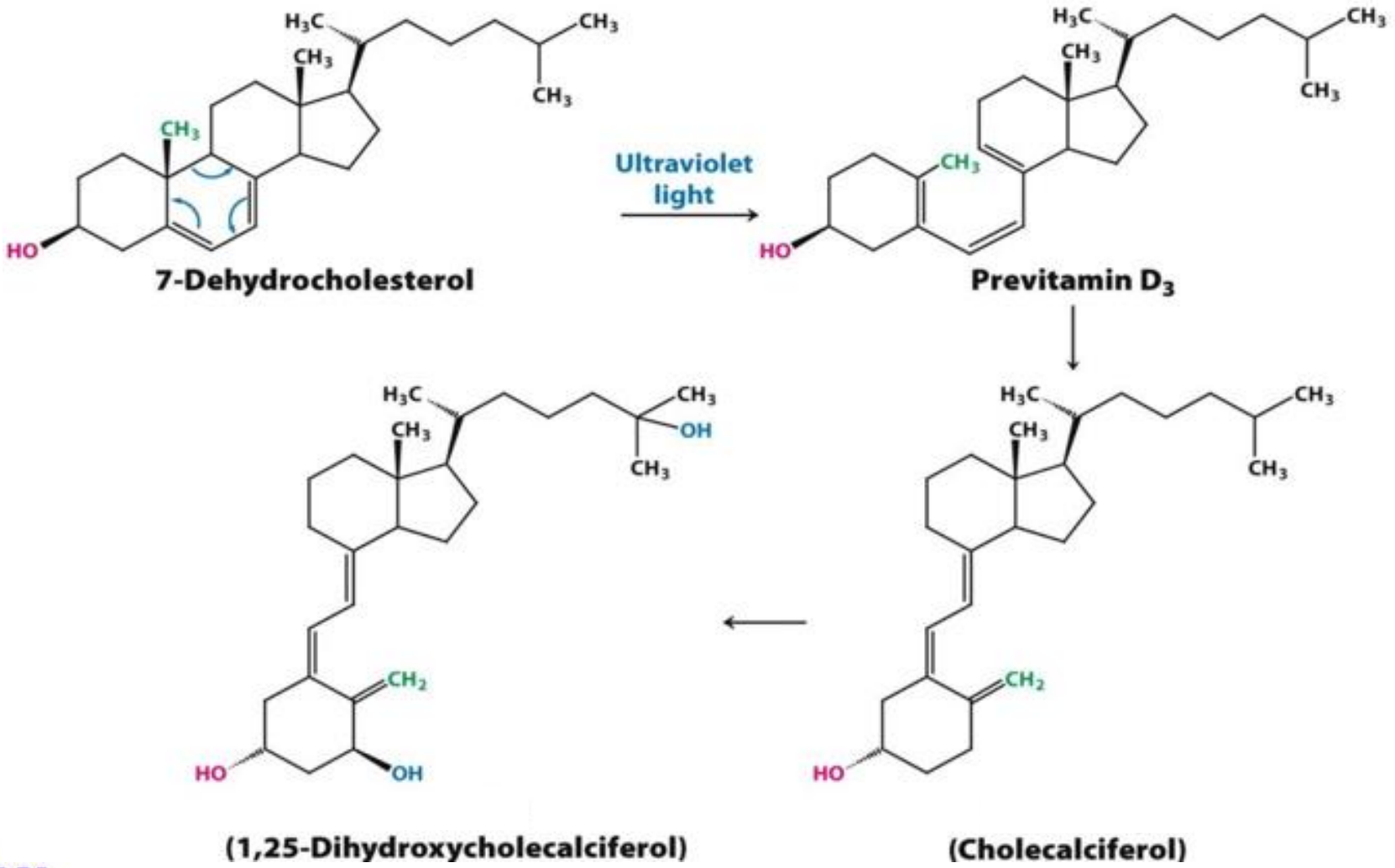
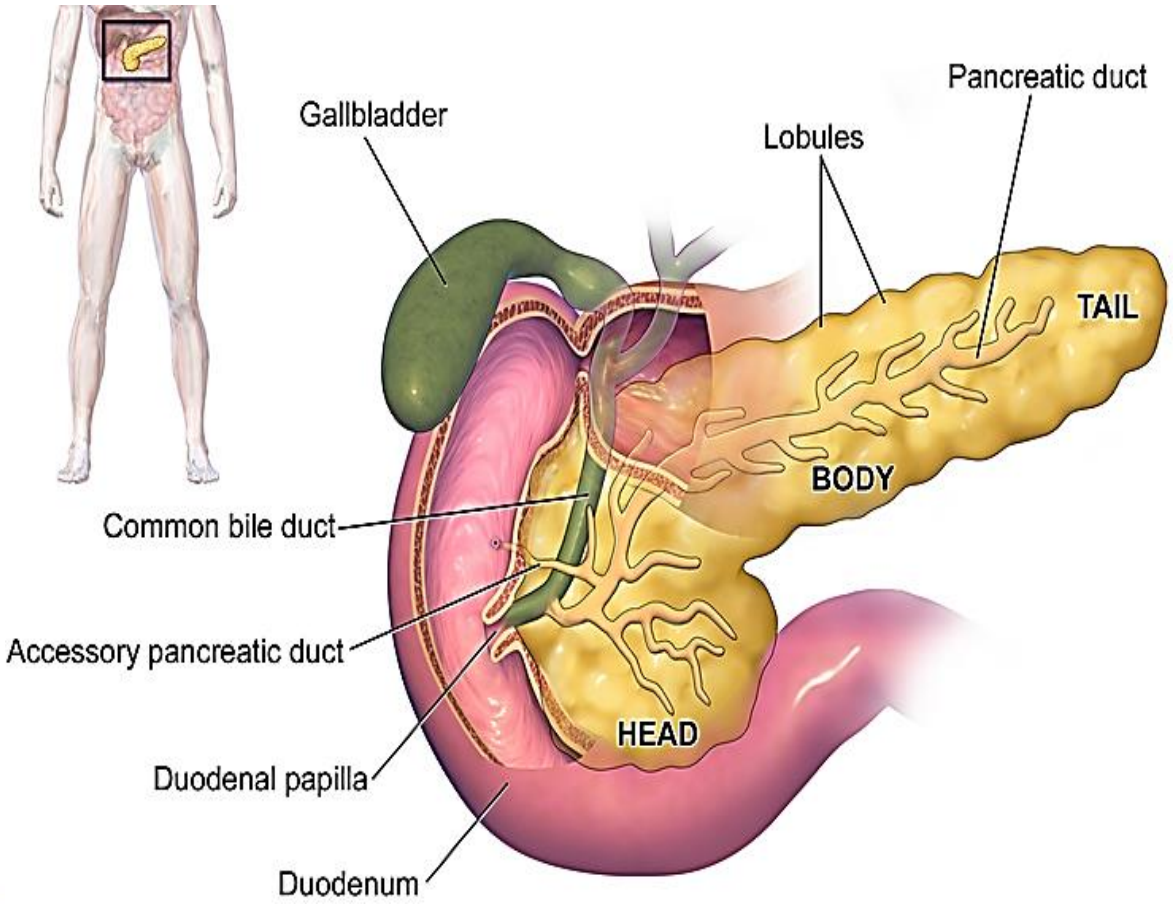
Activation of vitamin D3 to 1,25 dihydroxycholccalcifcrol



Bile, Bile acids and salts

Bile definition and content

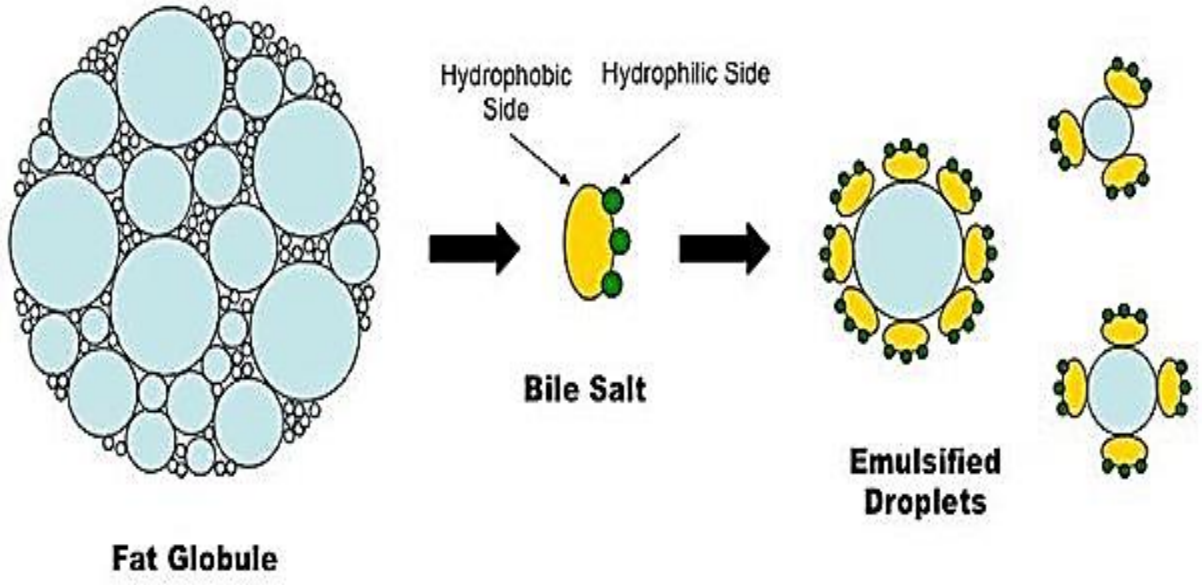
- Bile is a greenish-yellow fluid produced by the liver and stored in the gallbladder.
- It contains water, electrolytes, bile acids, bile salts, cholesterol, bilirubin, and phospholipid [phosphatidylcholine (lecithin)].



Importance of Bile

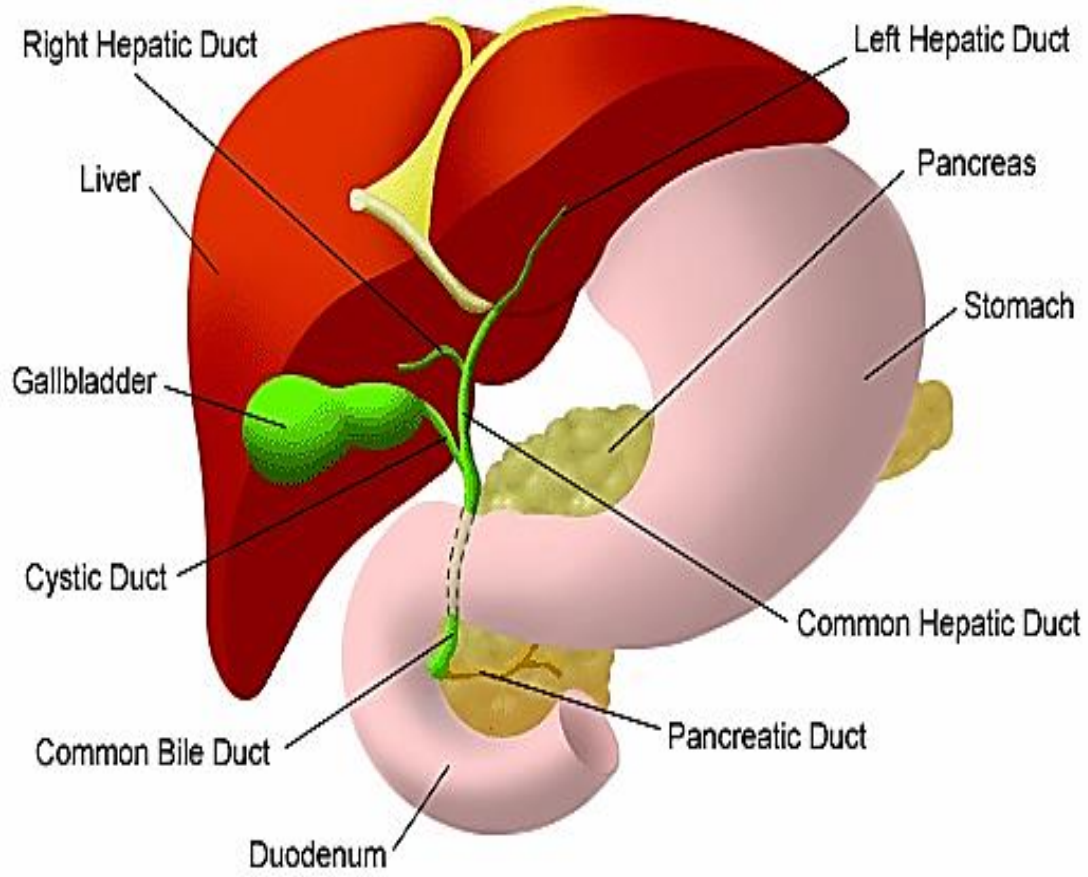
- Bile's role is to emulsify fats, which means it breaks down large fat drops into smaller droplets, making them more accessible to the action of enzymes.

- Bile is essential for the digestion and absorption of fats and fat-soluble vitamins (A, D, E, and K)



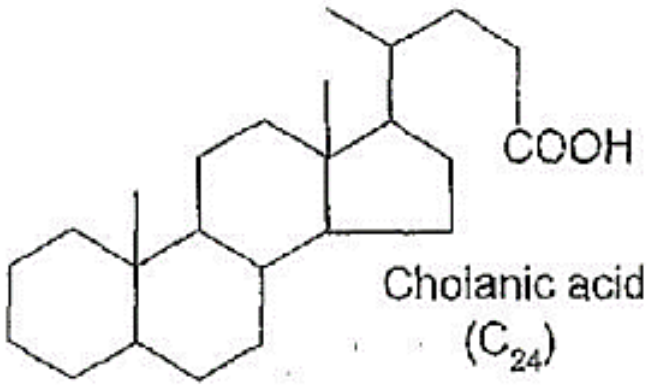
Bile has two potential pathways

- It can flow directly from the liver into the duodenum through the common bile duct, or it can be stored in the gallbladder for later use when immediate digestion is not required.



Bile acids

- Cholanic acid is a carboxylic steroidal compound (C24) that serves as the basis for the structure of various bile acids found in bile.
- Bile acids are hydroxyl derivatives of cholanic acid which is derived from cholesterol
- Types of bile acids: Primary & Secondary bile acids

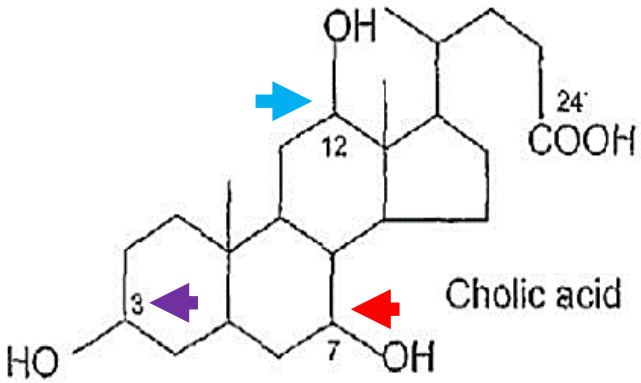


Cholanic acid
(C_{24})

Primary bile acids

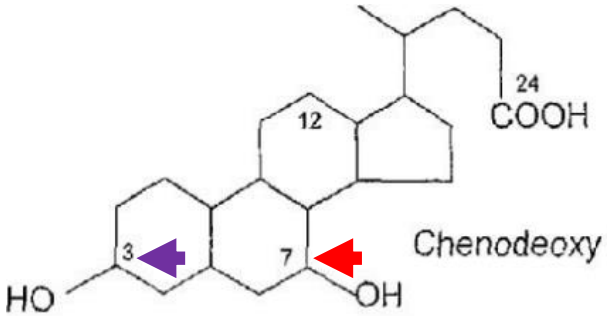
- Primary bile acids are synthesized in the liver:

1. Cholic acid (3, 7, 12 trihydroxy cholanic acid)
    - Cholic acid is one of the most abundant bile acids produced and is a major component of bile.



Cholic acid

2. Chenodeoxycholic Acid (3, 7 dihydroxycholanic acid)



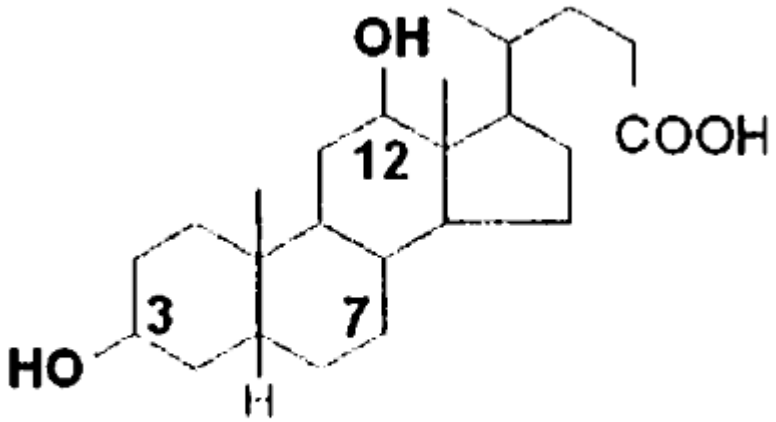
Chenodeoxy Cholic acid

Secondary bile acids

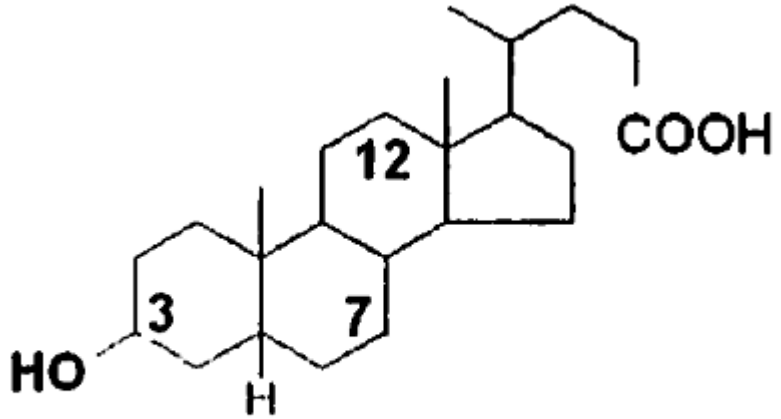
- **Secondary bile acids** are derived from primary bile acids in the intestine.
- This transformation occurs through the action of **intestinal bacteria**, which remove the hydroxyl group at the 7th carbon position (no OH on C7; contain 7α dehydroxylase).

Secondary bile acids

- Deoxycholic acid (3, 12 dihydroxy cholanic acid).
  - Formed from the primary bile acid **cholic acid** by bacterial dehydroxylation at the 7th carbon position.
- Lithocholic acid (3 monohydroxy cholanic acid).
  - It has a single hydroxyl group at the 3rd position.



Deoxycholic acid

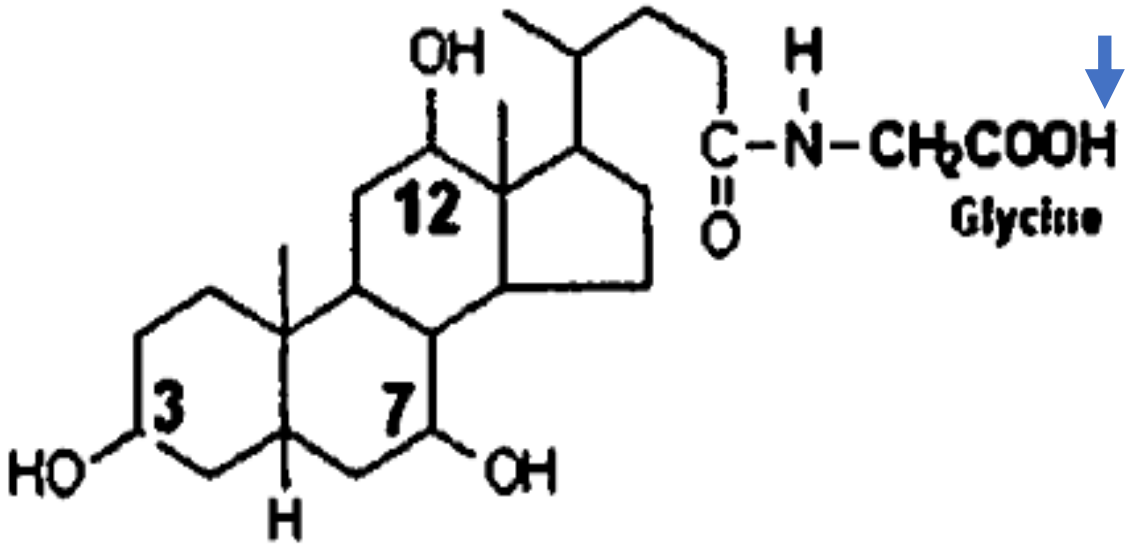


Lithocholic acid

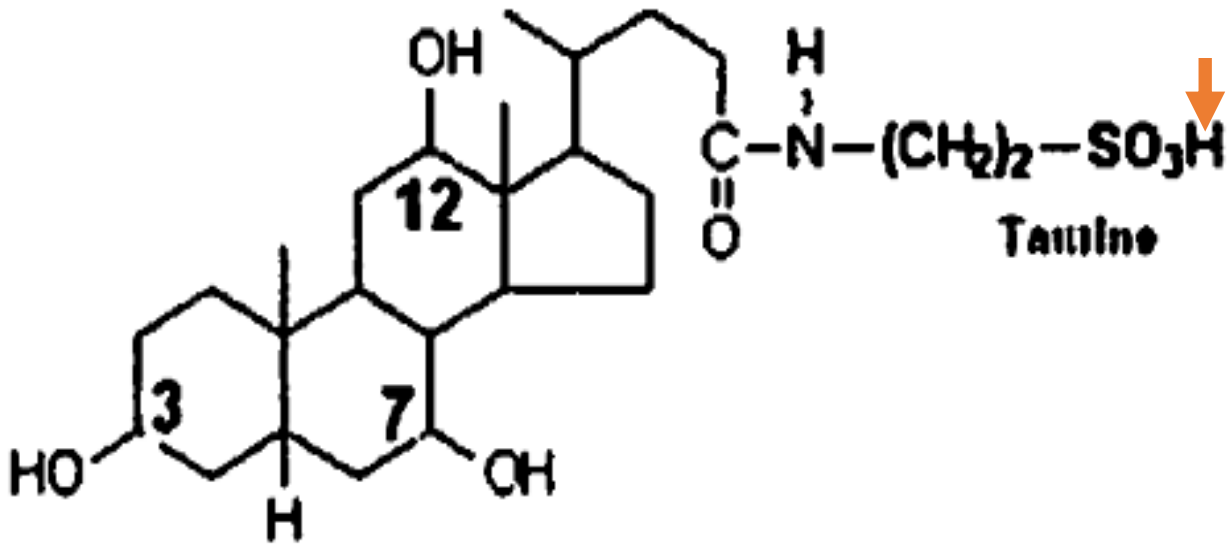
Bile salts

- Bile salts are bile acids conjugated with glycine (80%) and taurine (20%), they are excreted by liver in bile as sodium salts
  - Bile Acid + Glycine = Glycocholic OR Glycochenodeoxycholic acids
  - Bile Acid + Taurine = Taurocholic OR Taurochenodeoxycholic acids
    - sodium glycocholate and sodium taurocholate.

sodium glycocholate and sodium taurocholate.



Glycocholic acid



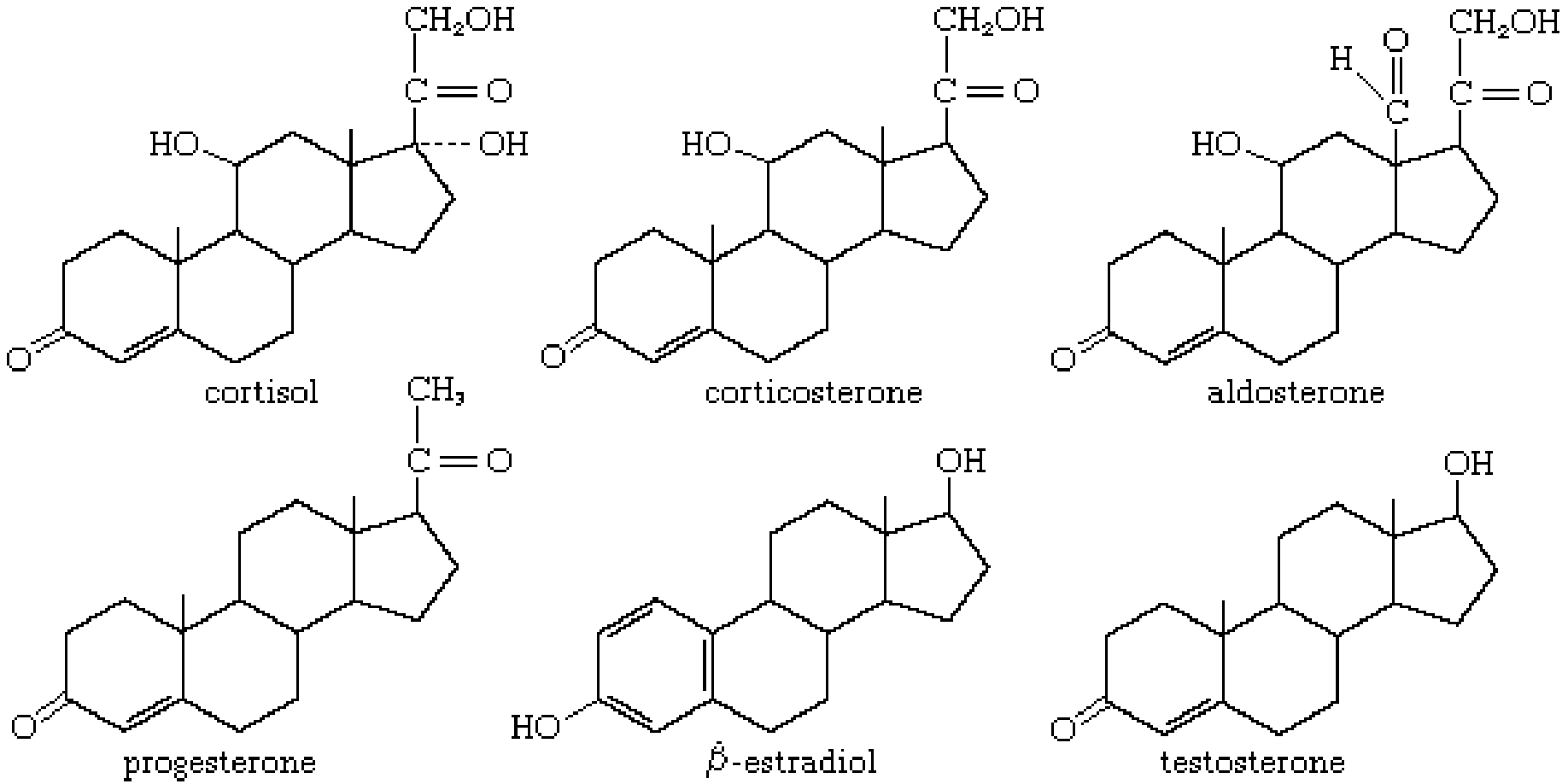
Taurocholic acid

Importance of bile salts

1. Main way for excretion of cholesterol.
   - Prevents precipitation of cholesterol & formation of cholesterol stones.
2. Digestion of fat due to emulsification.
3. Absorption of fat and fat soluble vitamins.

cyclopentano-perhydro-phenanthrene “CPPP

Steroid hormones



Thanks

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Lipoproteins and Their Metabolism: Understanding Hyperlipoproteinemia

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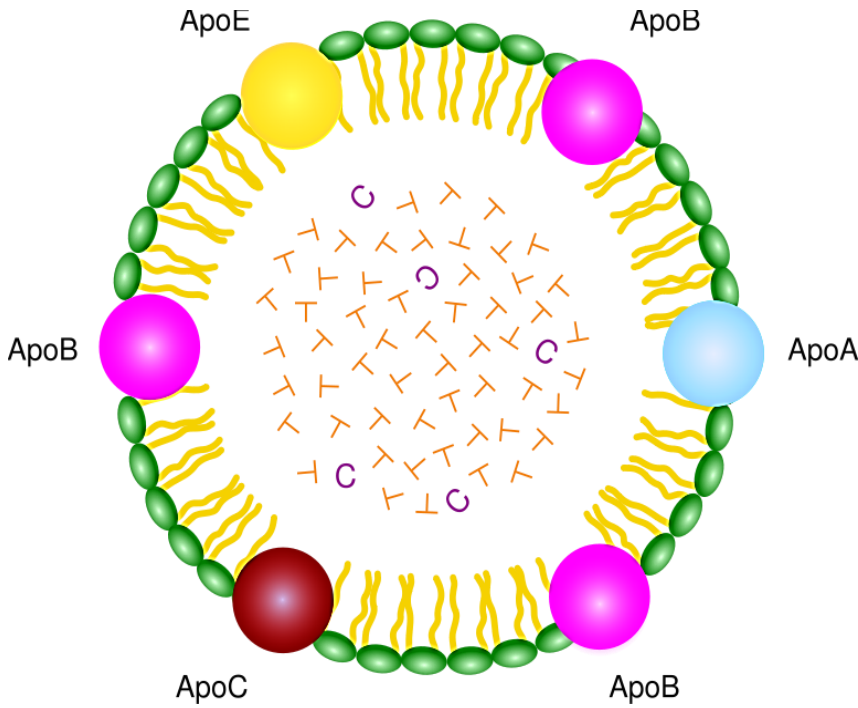
Lipoproteins

- These are complex lipids formed of lipids conjugated with protein.
- They are present in cell membrane, mitochondria and plasma (plasma lipoproteins).

Plasma Lipoproteins

- Plasma lipoproteins convert water insoluble lipids into water soluble complexes.

This facilitates transport of lipids between blood and different tissues.



Plasma Lipoproteins

The lipids present in plasma (total range: 360–820 mg/dL) include the following components:

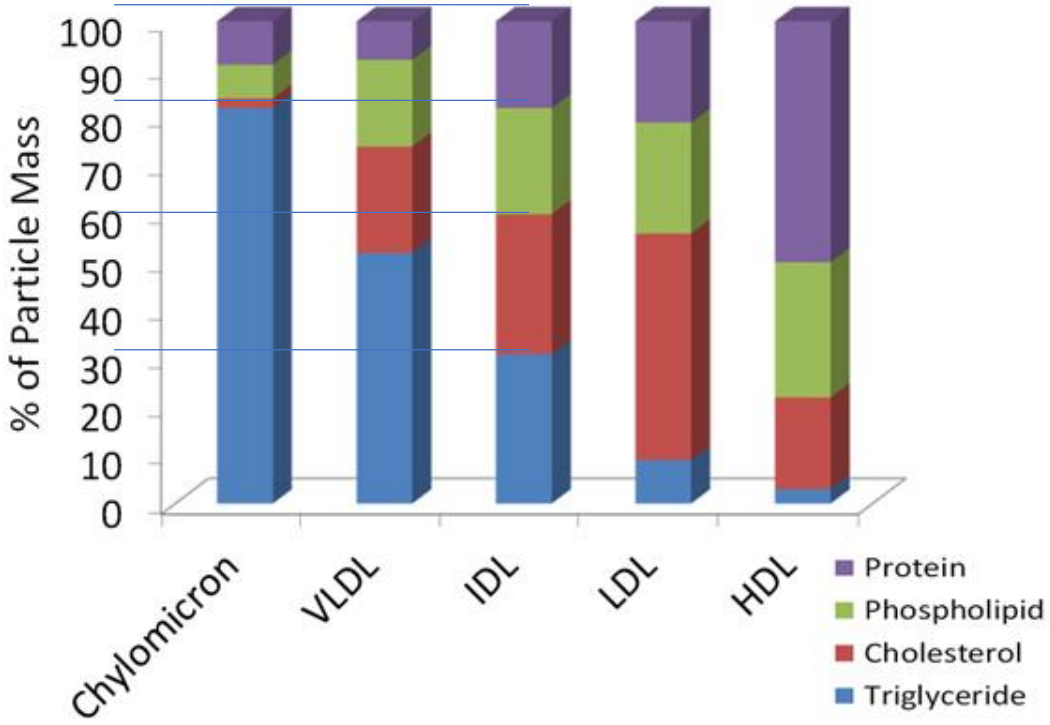
- The plasma lipids (360-820 mg/dl) are phospholipids, cholesterol (free and esterified) and lipids between triacylglycerols, free fatty acids.

1-Cholesterol :	140-220 mg/dl 70% Cholesteryl esters 30% Free cholesterol
2-Phospholipids :	150-200 mg/dl
3-Triacylglycerols :	40-160 mg/dl
4-Free fatty acids :	6-16 mg/dl

Plasma Lipoproteins

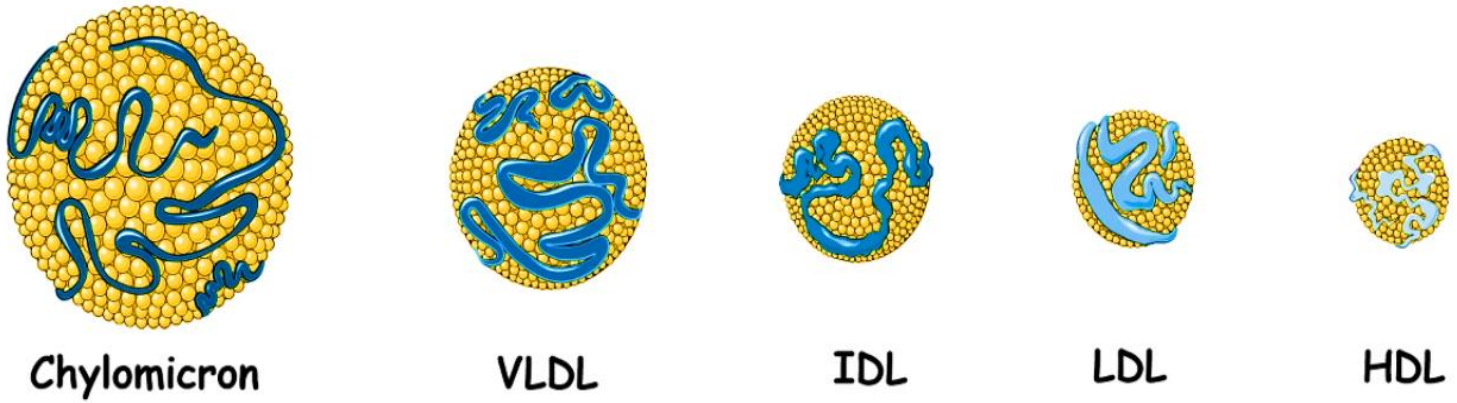
- The plasma lipoproteins are spherical macromolecular complexes of lipids and proteins (apolipoproteins).
- The lipoprotein particles include chylomicrons, very–low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs).
- They differ in lipid and protein composition, size, density, and site of origin.

Composition of lipoproteins



		Composition (wt %)				
Lipoprotein	**Density (g/mL)**	**Protein**	**Phospholipids**	**Free cholesterol**	**Cholesteryl esters**	**Triacylglycerols**
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

Data from D. Kritchevsky, *Nutr. Int.* 2:290, 1986.



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The density and diameter of different lipoproteins

Lipoprotein	Density (g/dL)	Diameter (nm)
Chylomicrons	0.95	75-1200
VLDL (very low-density lipoproteins)	0.95-1.006	30-80
IDL (intermediate-density lipoproteins)	1.006-1.019	25-35
LDL (low-density lipoproteins)	1.019-1.063	18-25
HDL (high-density lipoproteins)	1.063-1.21	5-12

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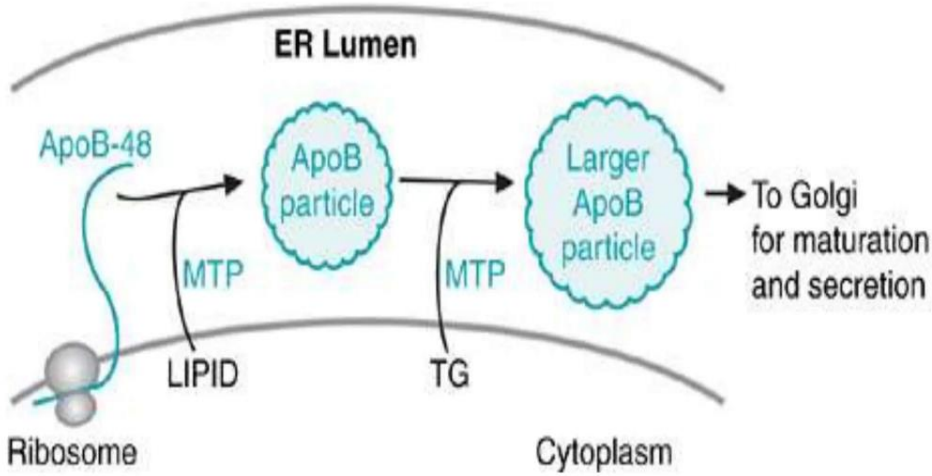
Chylomicrons

- **Chylomicrons** (TAG= 90%) are highly soluble in both lymphatic fluid and blood.
- **Function** in the transport of dietary triacylglycerol, cholesterol, and cholesteryl esters to other tissues.
- **Assembly of chylomicrons** occurs in the intestinal lining and results in a nascent chylomicron that contains lipids and apolipoproteins.

Chylomicron assembly in enterocytes

1. **Initial Assembly:**
   A. The synthesis begins with the translation of the apoB-48 protein.
   B. Lipid association occurs next, where small amounts of triglycerides and other lipids associate with the apoB-48 protein.
   C. This process is catalyzed by microsomal triglyceride transfer protein (MTP), leading to the formation of small apoB-containing particles.

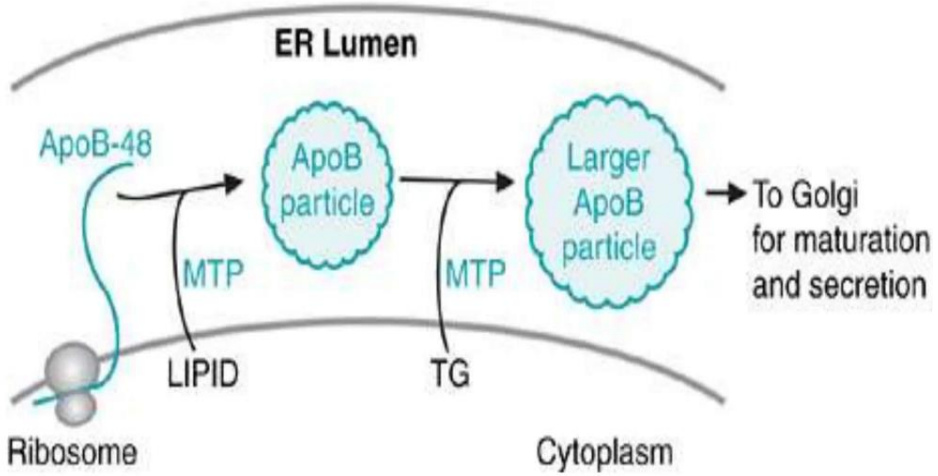
This process occurs within the endoplasmic reticulum (ER).



Chylomicron assembly in enterocytes

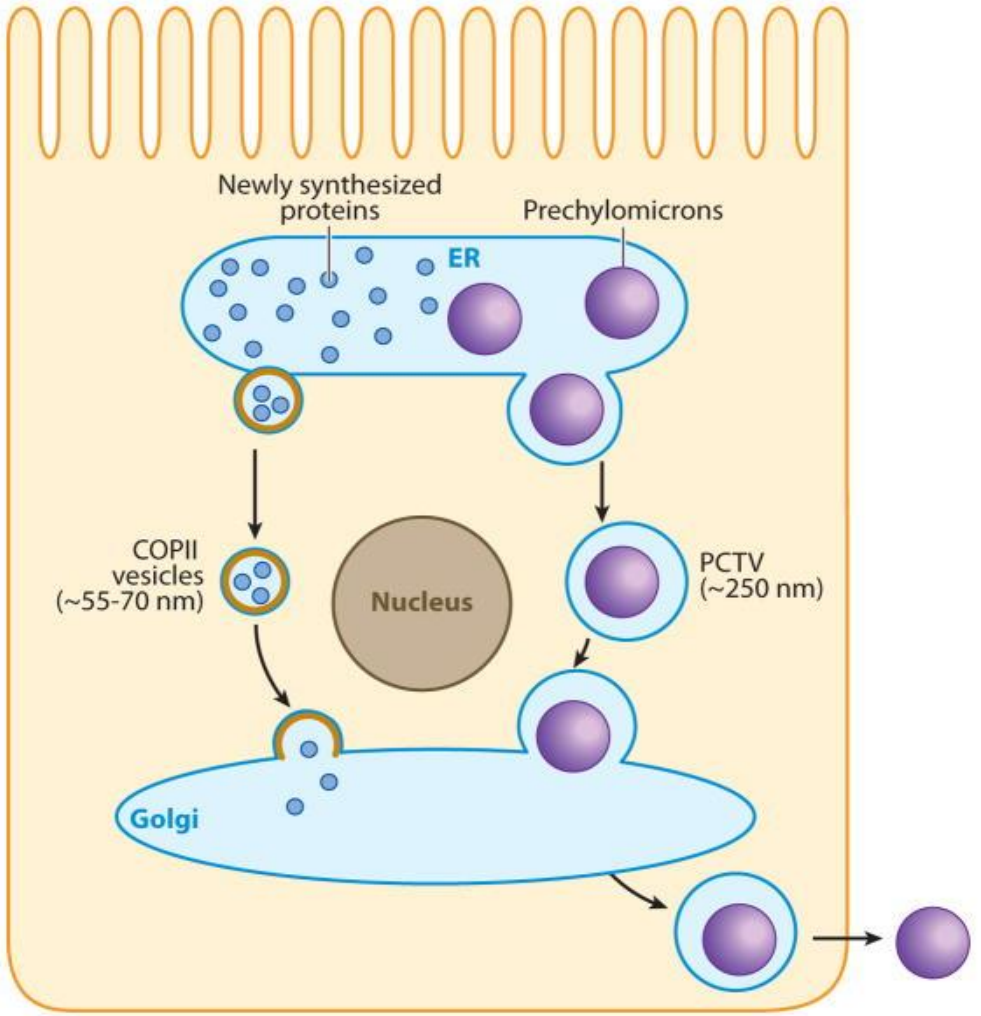
B. Particle Expansion:

- Large triacylglycerol droplets fuse with the initial apoB-containing particles.
- MTP also facilitates the transfer of additional triacylglycerol from the cytoplasm into the ER lumen, where it forms lipid droplets that are incorporated into the growing chylomicron.



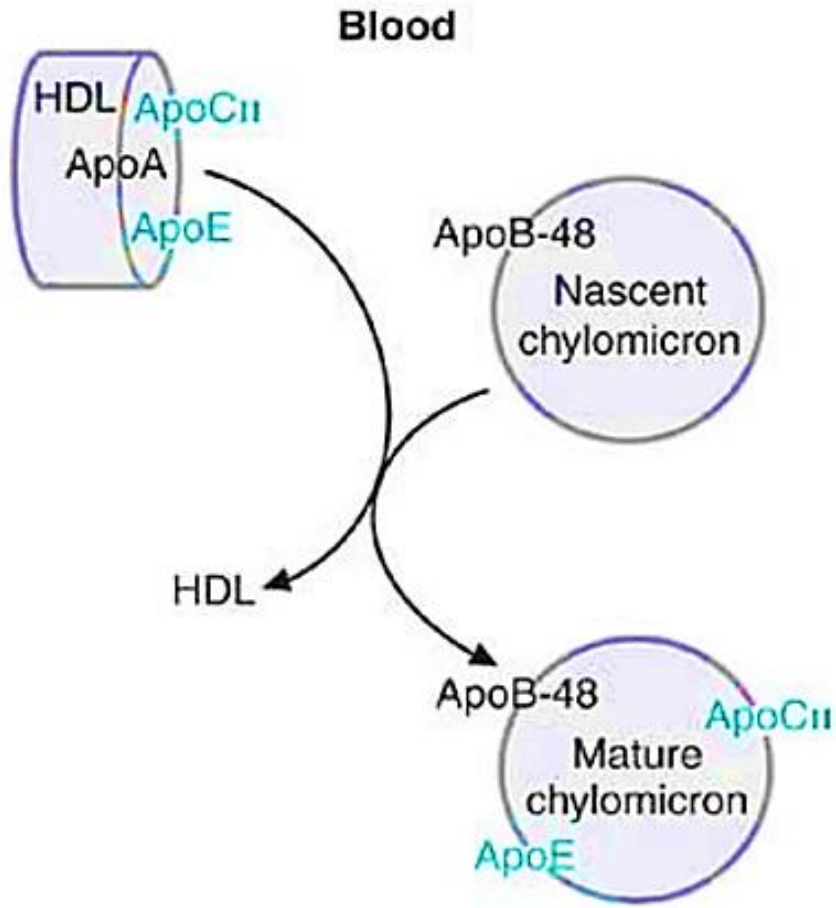
Chylomicron assembly in enterocytes

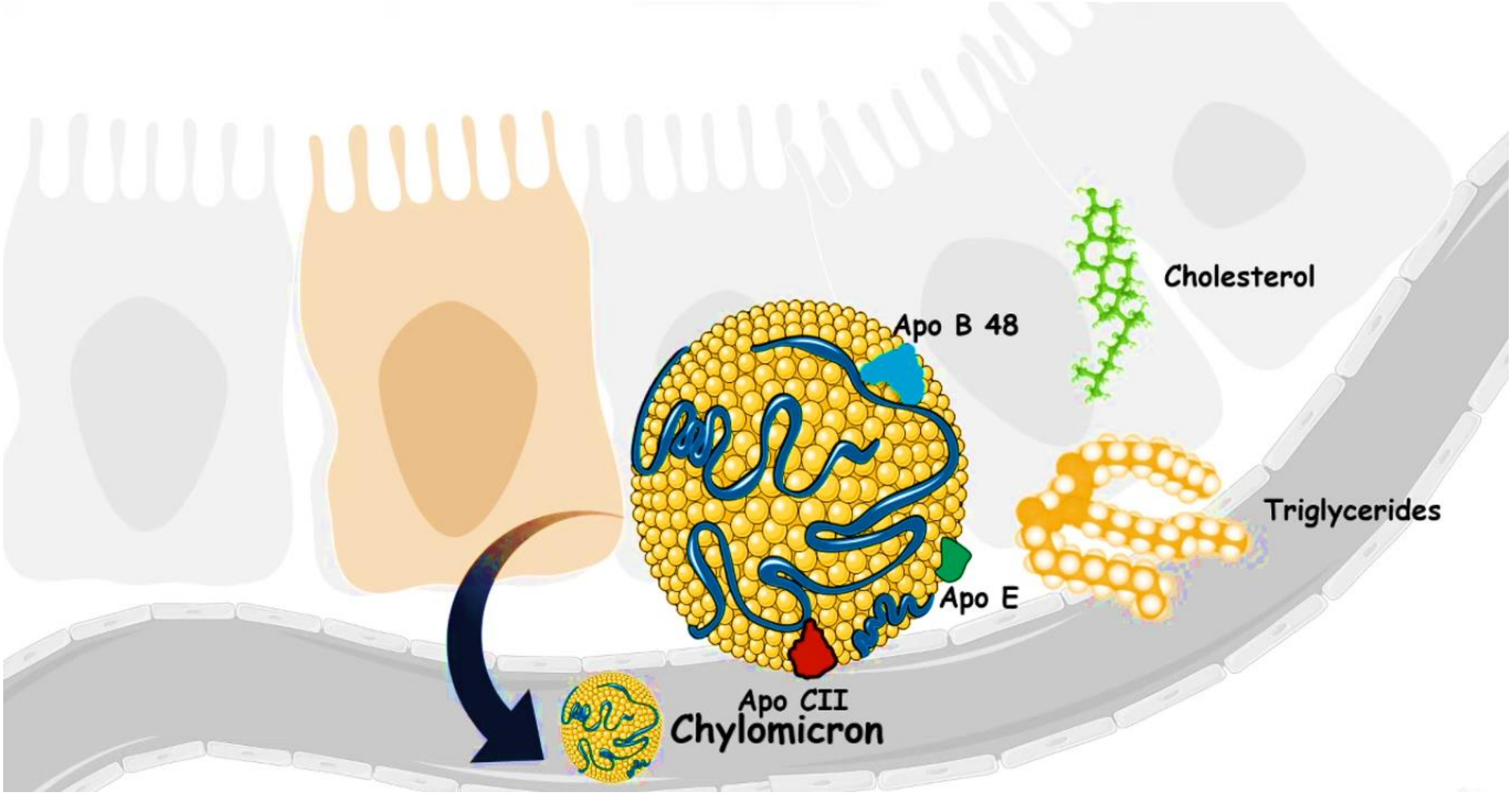
1. Transition of the chylomicrons to Golgi, where the particles are packaged in secretory vesicles.
2. These fuse with the plasma membrane releasing the lipoproteins to the blood.
3. When it reaches the plasma, the particle is rapidly modified, receiving apo E and apo C-II (The source of these apolipoproteins is circulating HDL).

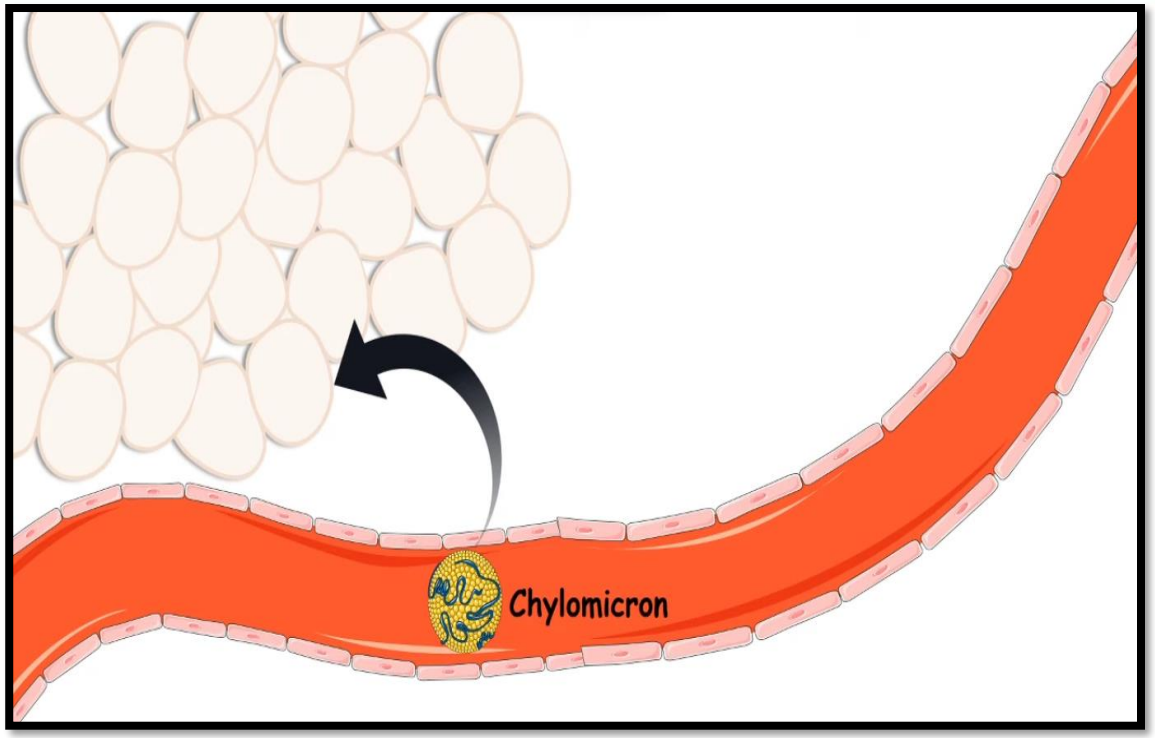


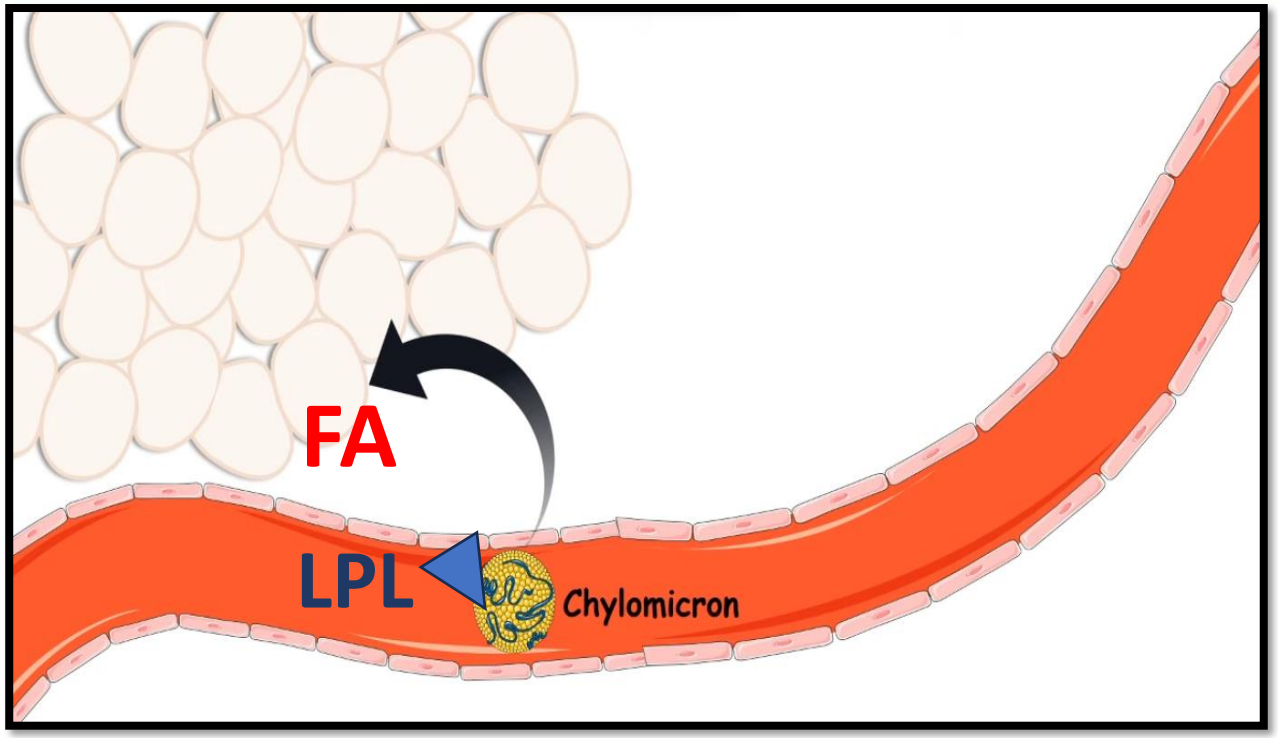
Transfer of proteins from HDL to chylomicrons

- Newly synthesized chylomicrons (nascent chylomicrons) mature as they receive apoC-ll and apoE from HDL.
- Roles of ApoC-II and ApoE:
  - ApoC-II: Essential for the activation of lipoprotein lipase (LPL), the enzyme responsible for hydrolyzing triglycerides in chylomicrons into free fatty acids and glycerol for uptake by tissues (e.g., muscle, adipose tissue).
  - ApoE: Serves as a ligand for receptors that mediate the uptake and clearance of chylomicron remnants by the liver.




Cholesterol
Apo B 48
Triglycerides
Apo E
Apo CII
Chylomicron





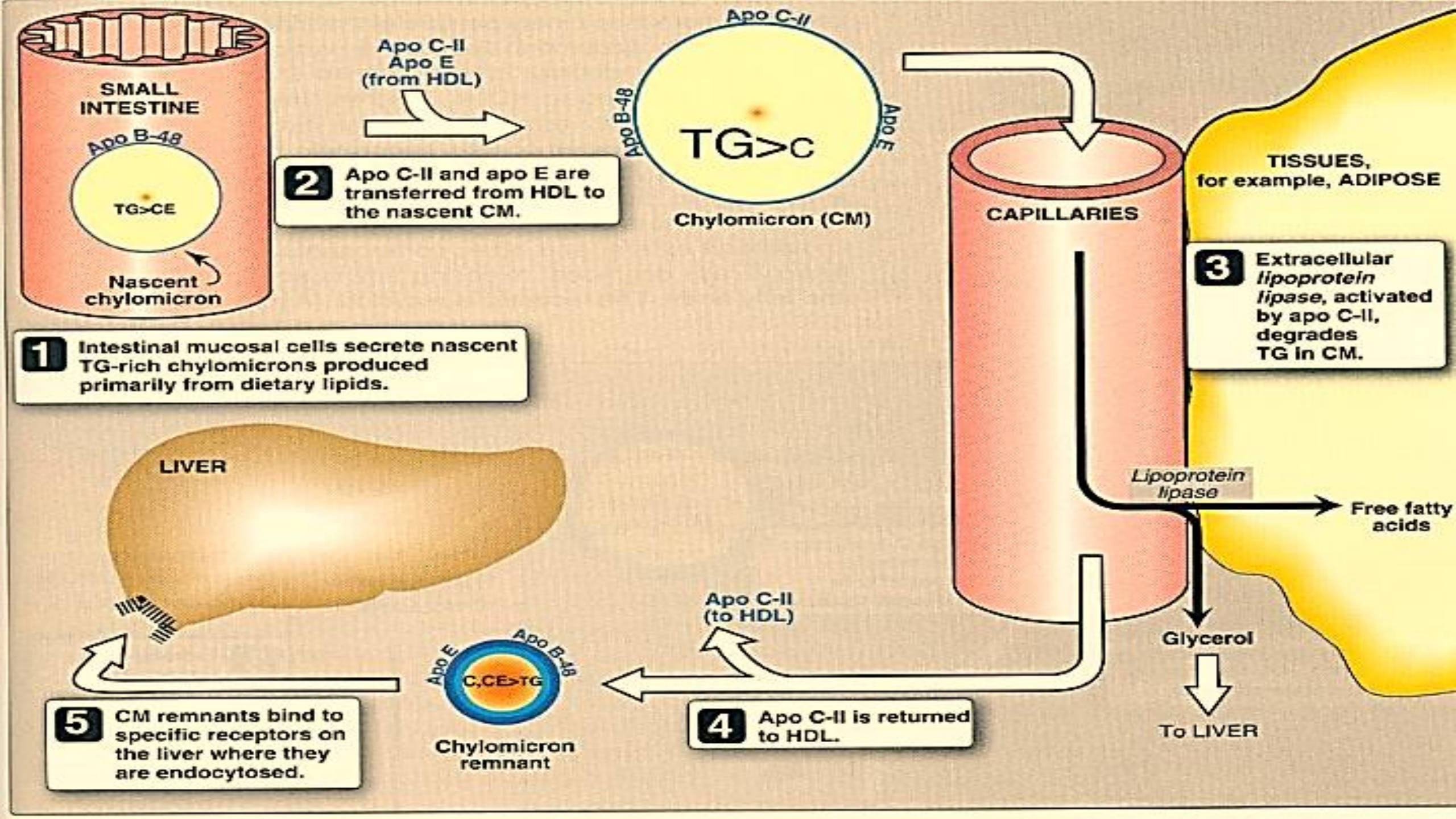
- **Lipoprotein lipase** (LPL) is an extracellular enzyme that is anchored to the capillary walls of most tissues but predominantly those of adipose tissue and cardiac and skeletal muscle.

Fate of Chylomicron

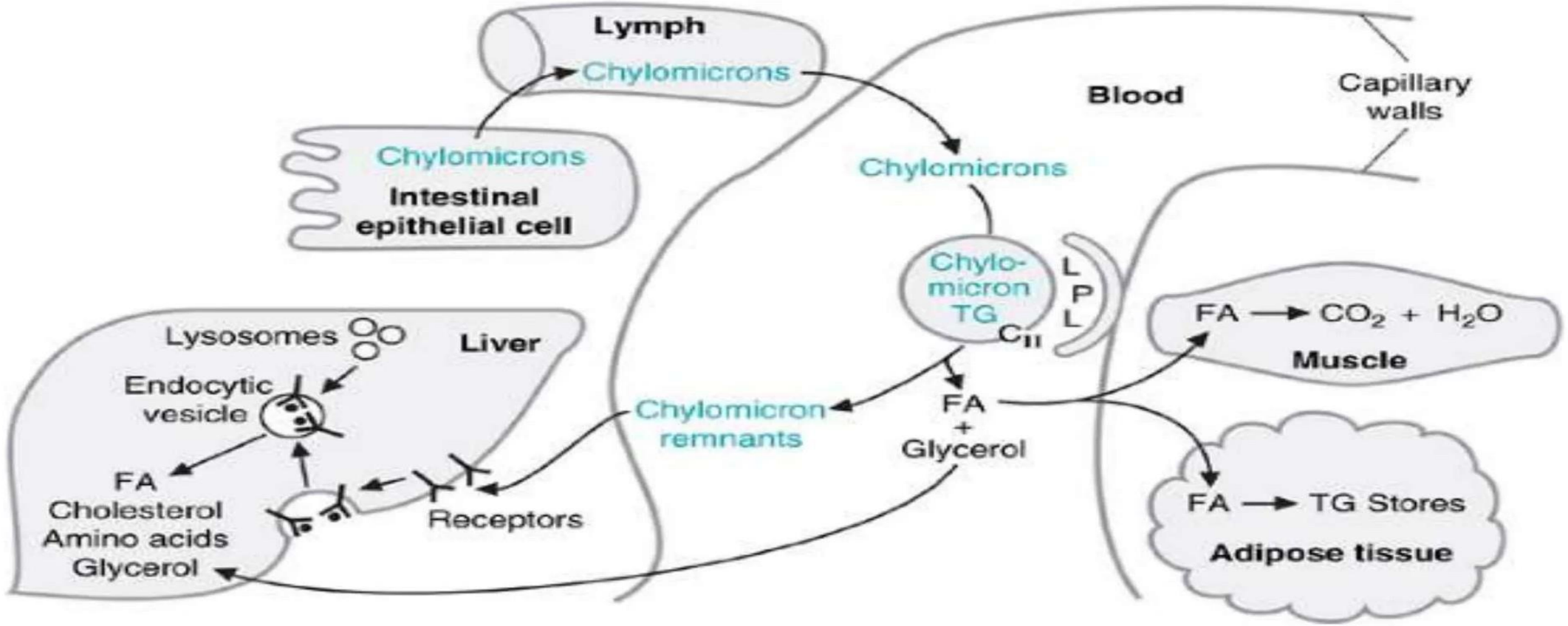
- LPL, activated by apo C-II on chylomicrons, hydrolyzes the TAG in these particles to FA and glycerol.
- The FA are stored (in adipose) or used for energy (in muscle).
- The glycerol is taken up by the liver, converted to dihydroxyacetone phosphate (an intermediate of glycolysis), and used in lipid synthesis or gluconeogenesis.

Fate of Chylomicron

- The remaining particle (remnant) is rapidly removed from the circulation by the liver, whose cell membranes contain lipoprotein receptors that recognize apo E and then taken into the hepatocytes by endocytosis.
- In the lysosome: the apolipoproteins, cholesteryl esters, and other components of the remnant are hydrolytically degraded, releasing amino acids, free cholesterol, and FA.


SMALL INTESTINE
Apo B-48
TG>CE
Nascent chylomicron
1 Intestinal mucosal cells secrete nascent TG-rich chylomicrons produced primarily from dietary lipids.
Apo C-II
Apo E
(from HDL)
2 Apo C-II and apo E are transferred from HDL to the nascent CM.
Apo C-II
Apo B-48
TG>C
Apo E
Chylomicron (CM)
CAPILLARIES
TISSUES, for example, ADIPOSE
3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TG in CM.
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
LIVER
Apo C-II
(to HDL)
4 Apo C-II is returned to HDL.
Apo E
Apo B-48
C,CE>TG
Chylomicron remnant
5 CM remnants bind to specific receptors on the liver where they are endocytosed.

Fate of chylomicrons. Chylomicrons are synthesized in intestinal epithelial cells, secreted into the lymph, pass into the blood, and become mature chylomicrons (see Fig.). On capillary walls in adipose tissue and muscle, lipoprotein lipase (LPL) activated by ApoC-II digests the triacylglycerols (TG) of chylomicrons to fatty acids and glycerol. Fatty acids (FA) are oxidized in muscle or stored in adipose cells as triacylglycerols. The remnants of the chylomicrons are taken up by the liver by receptor-mediated endocytosis. Lysosomal enzymes within the hepatocyte digest the remnants, releasing the products into the cytosol.

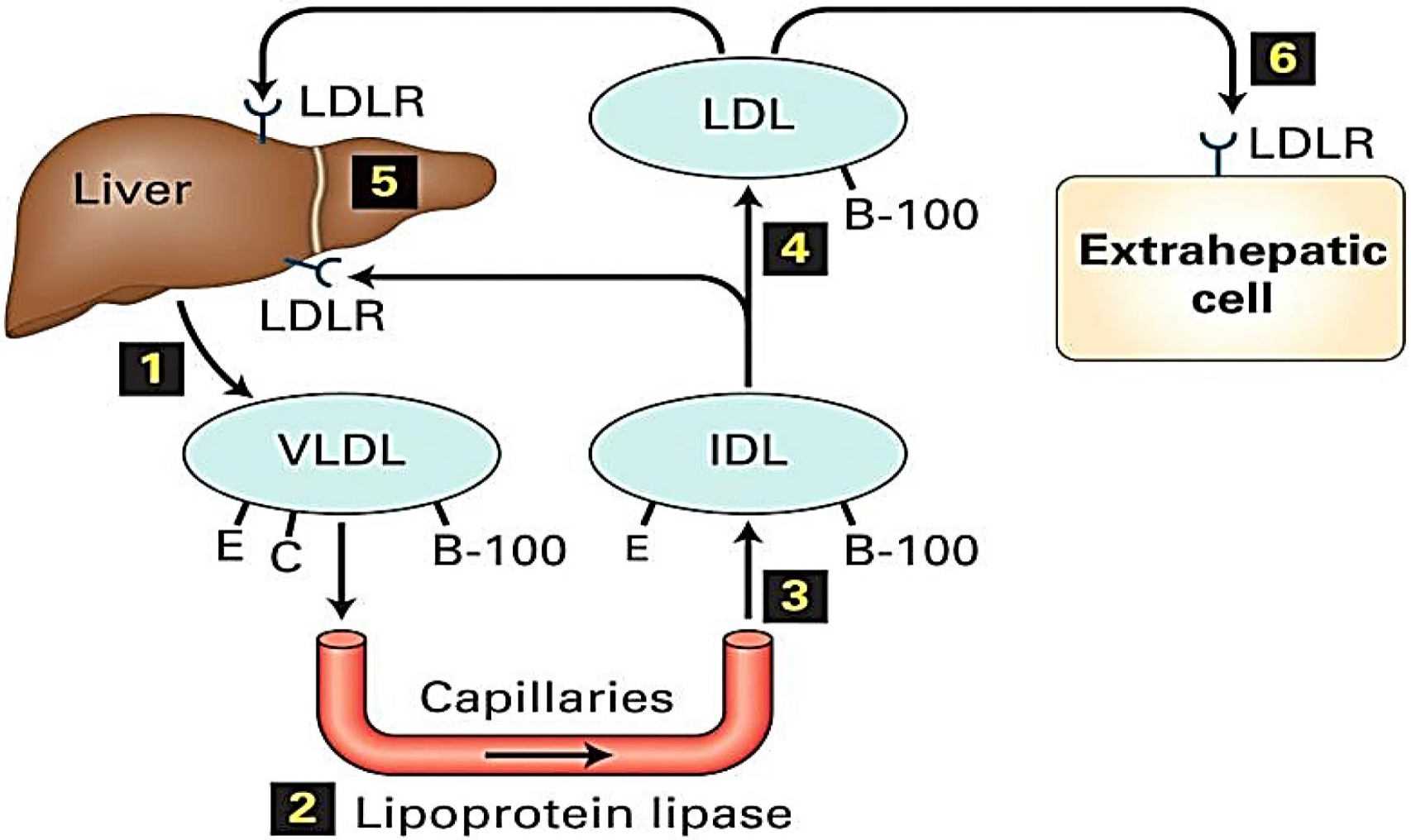


Type I Hyperlipoproteinemia (Familial Hyperchylomicronemia):

- Type I hyperlipoproteinemia is a rare autosomal recessive disorder characterized by the abnormal accumulation of chylomicrons in the plasma.
- Causes:

1. Deficiency of Lipoprotein Lipase (LPL), Deficiency or Mutation in ApoC-II:

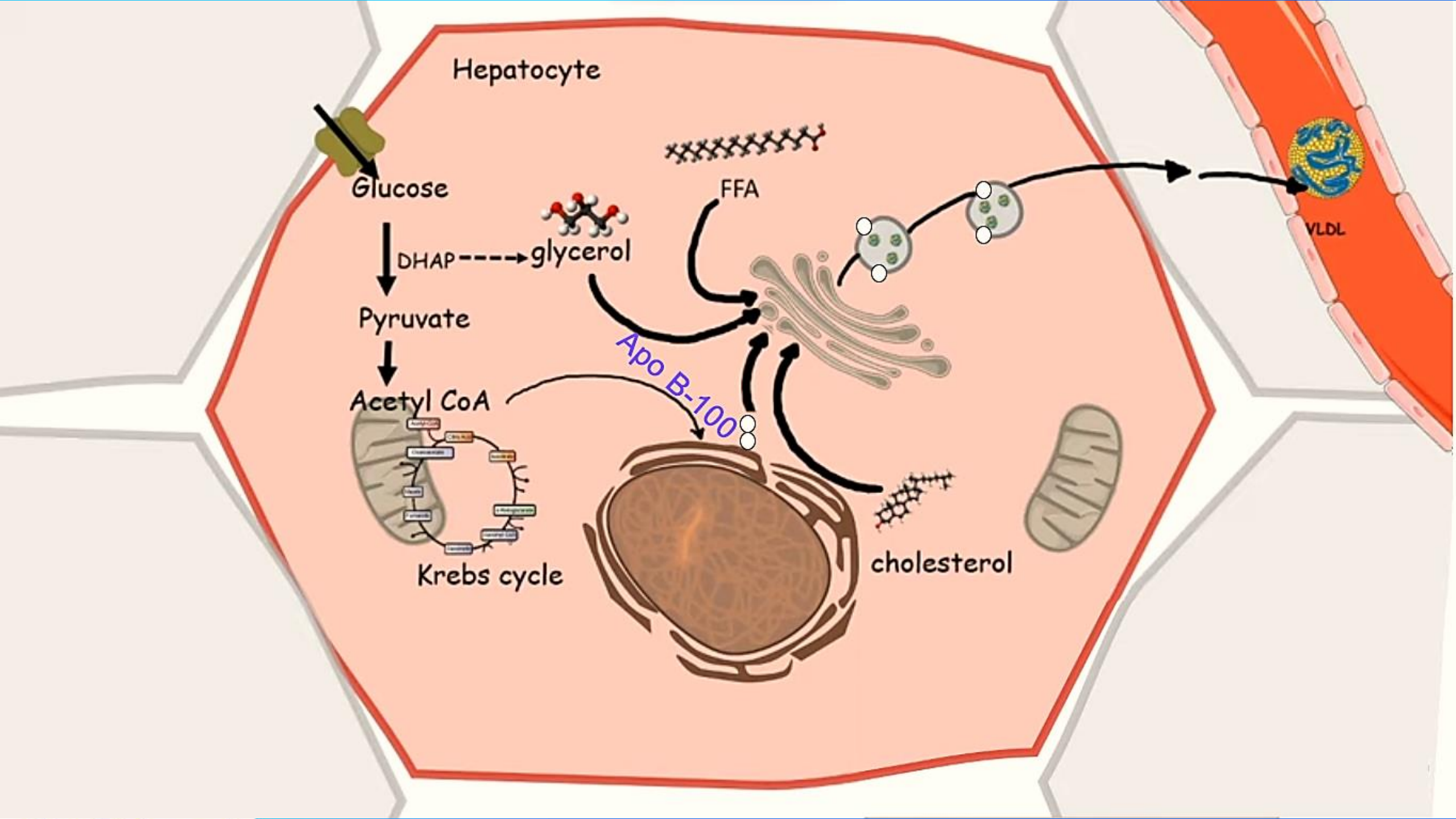
Endogenous Lipid Transport



Very–low-density lipoprotein metabolism (VLDLs)

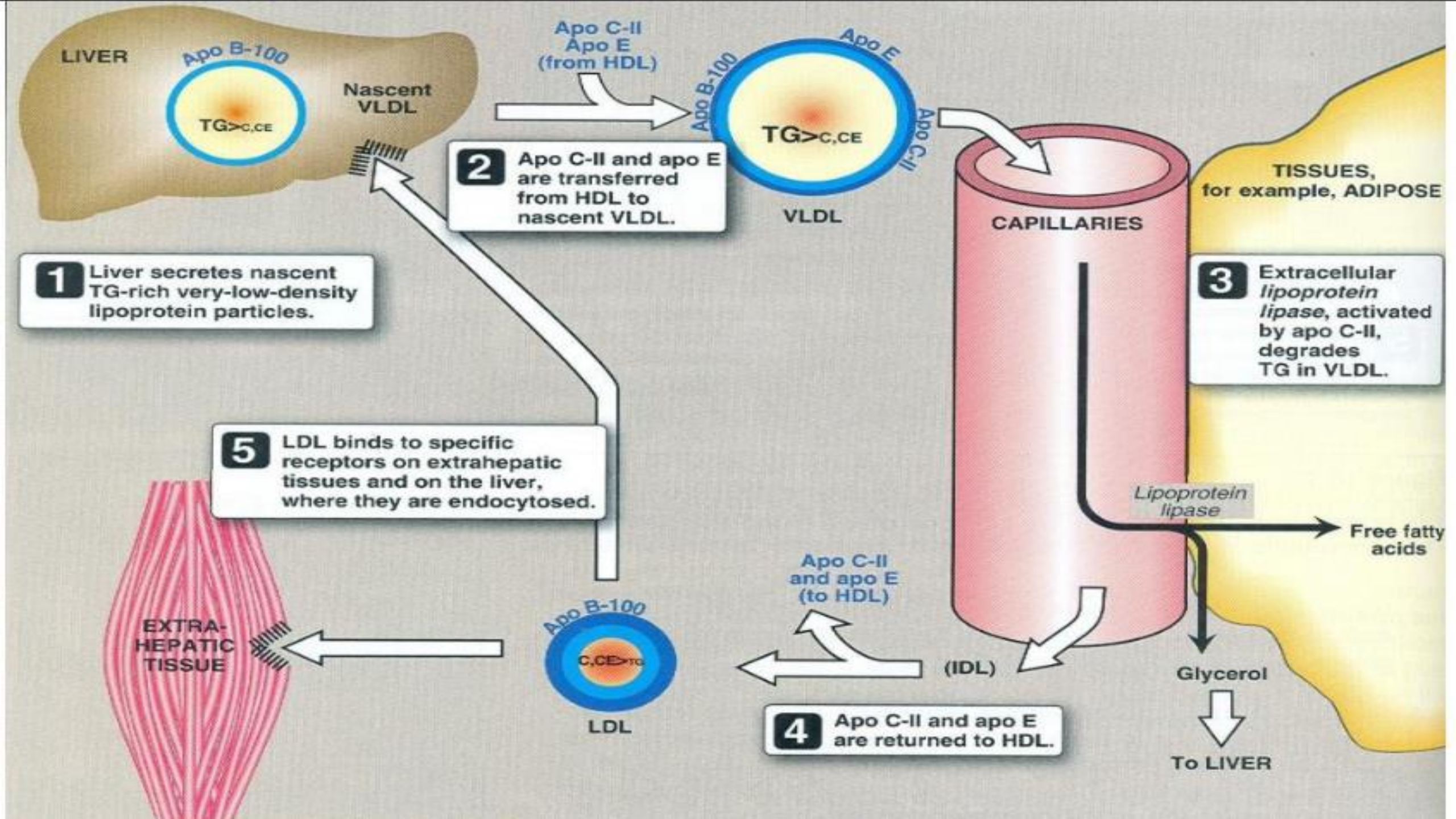
- VLDLs are produced in the liver.
- Their function is to carry this lipid from the liver (site of synthesis) to the peripheral tissues.
- There, the TAG is degraded by LPL, as discussed for chylomicrons.

Synthesis & Release of VLDLs from the liver


Hepatocyte
Glucose
DHAP
glycerol
FFA
Pyruvate
Acetyl CoA
Apo B-100
Krebs cycle
cholesterol
VLDL

Synthesis & Release of VLDLs from the liver

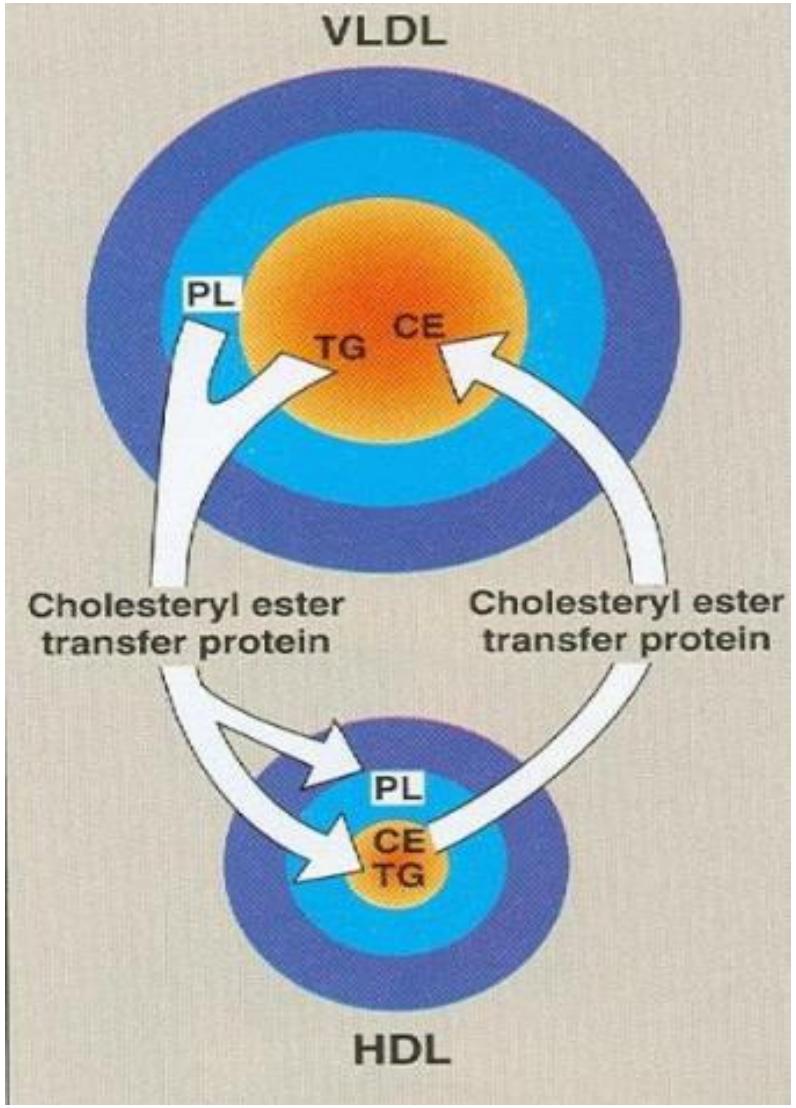
- They are composed predominantly of endogenous TAG (~60%).
- VLDLs are secreted directly into the blood by the liver containing apo B-100.
- They must obtain apo C-II and apo E from circulating HDL
- Apo C-II is required for activation of LPL.


LIVER
Apo B-100
TG>C,CE
Nascent VLDL
Apo C-II
Apo E
(from HDL)
Apo E
Apo B-100
Apo C-II
TG>C,CE
VLDL
2 Apo C-II and apo E are transferred from HDL to nascent VLDL.
1 Liver secretes nascent TG-rich very-low-density lipoprotein particles.
CAPILLARIES
TISSUES, for example, ADIPOSE
3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TG in VLDL.
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
5 LDL binds to specific receptors on extrahepatic tissues and on the liver, where they are endocytosed.
EXTRA-HEPATIC TISSUE
Apo B-100
C,CE>TG
LDL
Apo C-II and apo E (to HDL)
(IDL)
4 Apo C-II and apo E are returned to HDL.

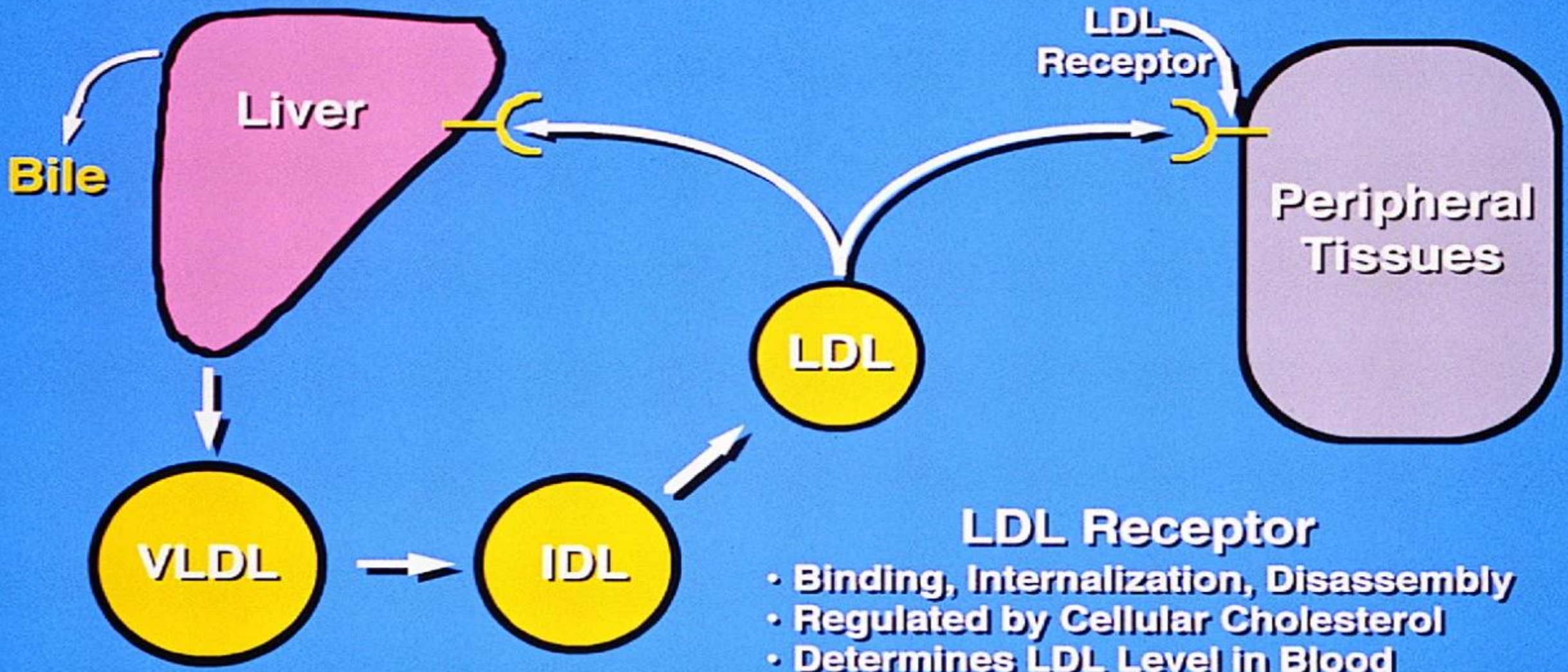
Modifications on VLDLs through their circulation

1. TAG is degraded by LPL.
2. The C and E apolipoproteins, are returned to HDL, but the particles retain apo B-100.
3. Additionally, some TAGs are transferred from VLDL to HDL in an exchange reaction that transfers cholesteryl esters from HDL to VLDL.
4. This exchange is accomplished by cholesteryl ester transfer protein (CETP)
5. With these modifications, the VLDL is converted in the plasma to LDL.

Transfer of cholesteryl ester (CE) from HDL to VLDL in exchange for triacylglycerol (TAG).



LDL and Cholesterol Transport

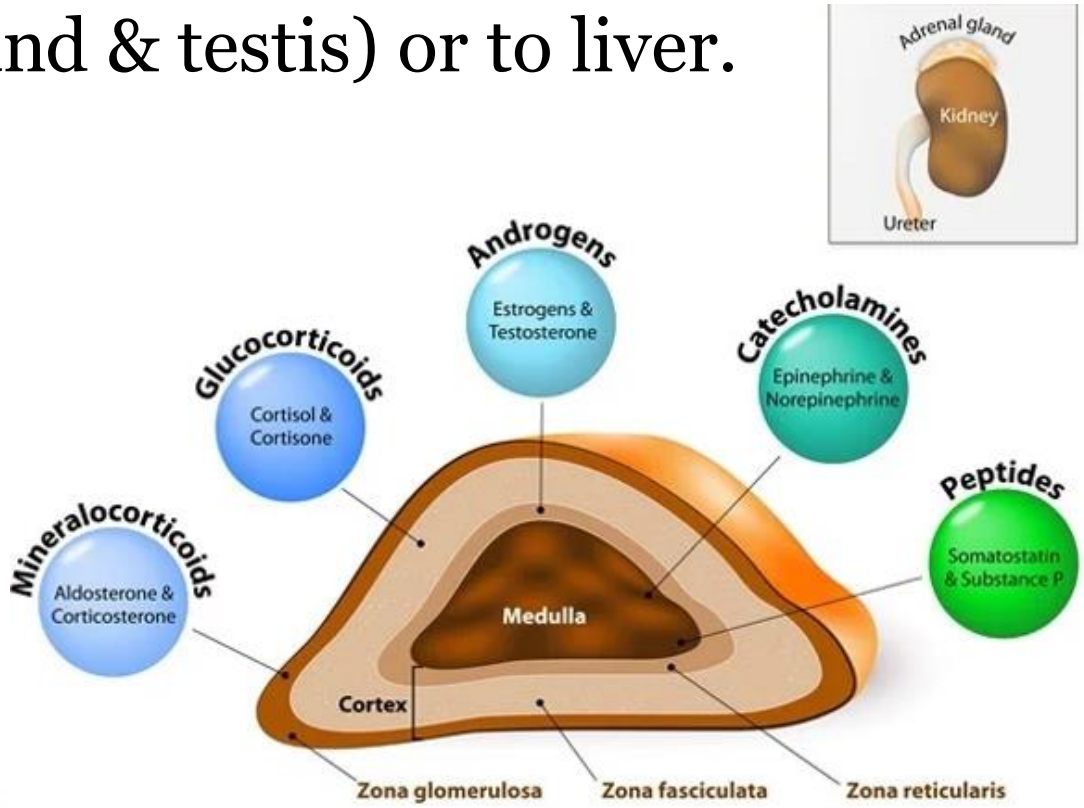


LDL Receptor

- Binding, Internalization, Disassembly
- Regulated by Cellular Cholesterol
- Determines LDL Level in Blood
- Defective in Familial Hypercholesterolemia
- Induced by 'Statin' Drugs

LDL and cholesterol transport

- The primary function of LDL particles is to provide cholesterol to the peripheral tissues (adrenal gland & testis) or to liver.
- They do so by binding to plasma membrane LDL receptors that recognize apo B-100 (but not apo B-48).



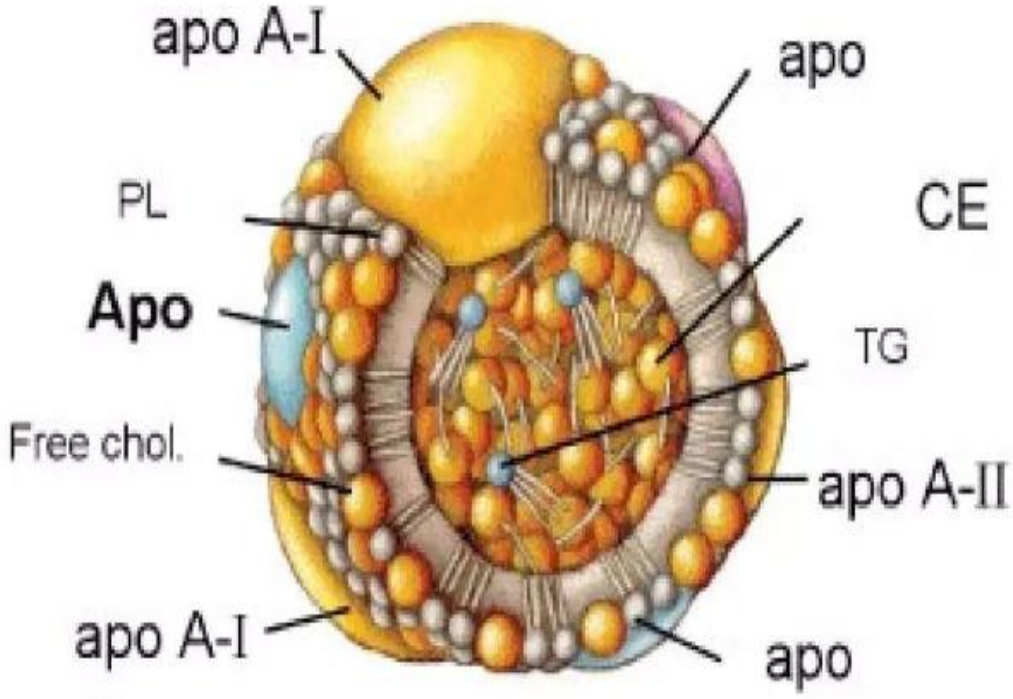
High-Density Lipoproteins (HDLs)

- HDLs are often referred to as "good cholesterol" because they play a critical role in reverse cholesterol transport—the process of transporting excess cholesterol from peripheral tissues back to the liver for excretion or recycling.

HDL

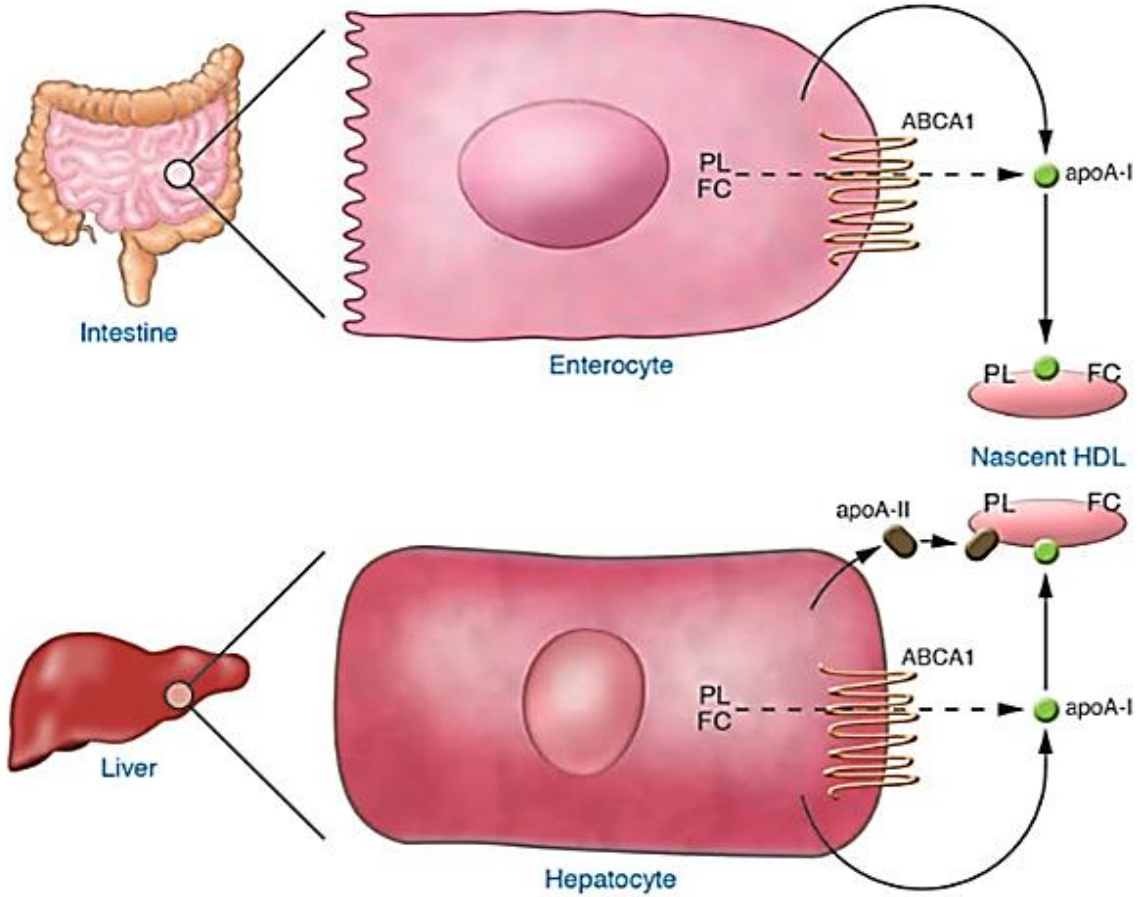
HDL contains several types of apolipoproteins

- apo-Al
- Apo-All
- apo-Cl
- apo-CII
- apo-D
- apo-E.
- Their most abundant apolipoproteins are apo A-I and apo A-II.



HDL Synthesis

- HDL particles are synthesized in two main locations:
- Liver: Produces nascent HDL particles containing phospholipids, cholesterol, and apolipoproteins (mainly apo A-I and apo A-II).
- Intestine: Produces nascent HDL with apo A-I.

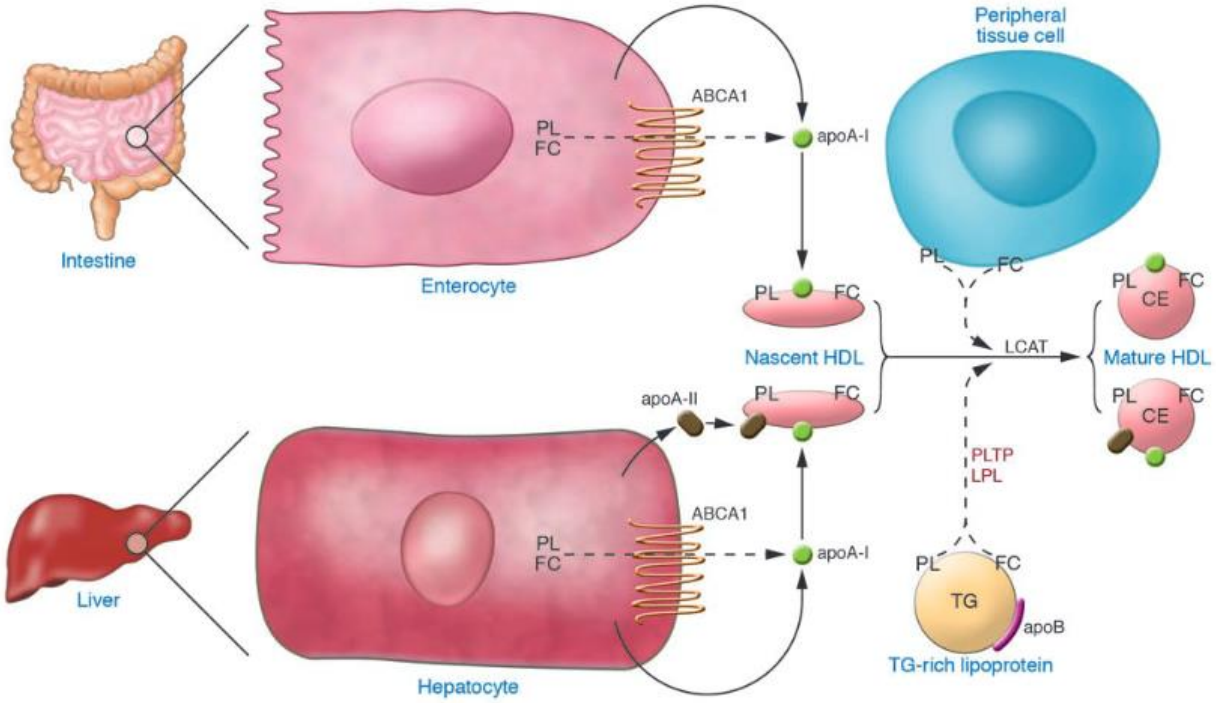


Maturation of HDL

- Nascent HDL collects additional lipids from:

1. Other peripheral tissues (via ABCA1 and ABCG1 transporters).
2. Other lipoproteins, such as VLDL and chylomicrons, during their metabolism.

1. Lecithin–cholesterol acyltransferase (LCAT)



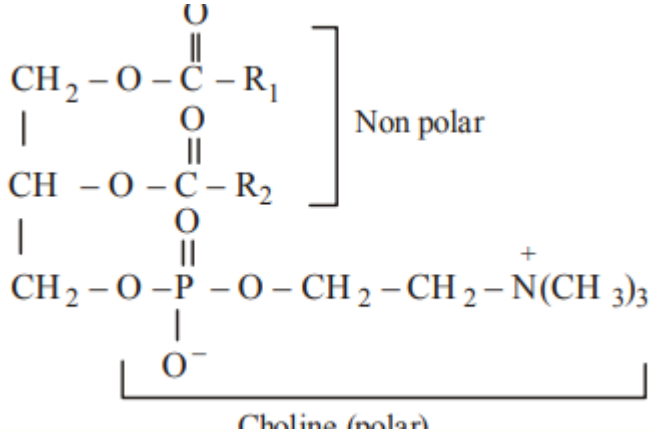
Storage of Cholesterol (Next lecture)

- Cholesterol ester is the storage form of cholesterol: It Is formed in both tissues and plasma.
- In tissues (liver), cholesterol is esterified by ACAT enzyme (acyl CoA cholesterol acyl transferase):

Cholesterol + Acyl CoA ➔ Cholesteryl ester + CoASH

- In plasma, cholesterol is esterified by LCAT enzyme (lecithin cholesterol acyl transferase). LCAT is associated with HDL.

Cholesterol + lecithin ➔ Cholesteryl ester + lysolecithin



Thanks

M.ELEYAN