PASSION ACADEMIC TEAM

YU - MEDICINE

Cardiovascular System

Sheet# 2 - BIOCHEMISTRY

Lec. Date :

Lec. Title : Lipid Transport & Storage

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If you come by any mistake , please kindly report it to shaghafbatch@gmail.com

CVS – Biochemistry 2

Lipid transport & Storage

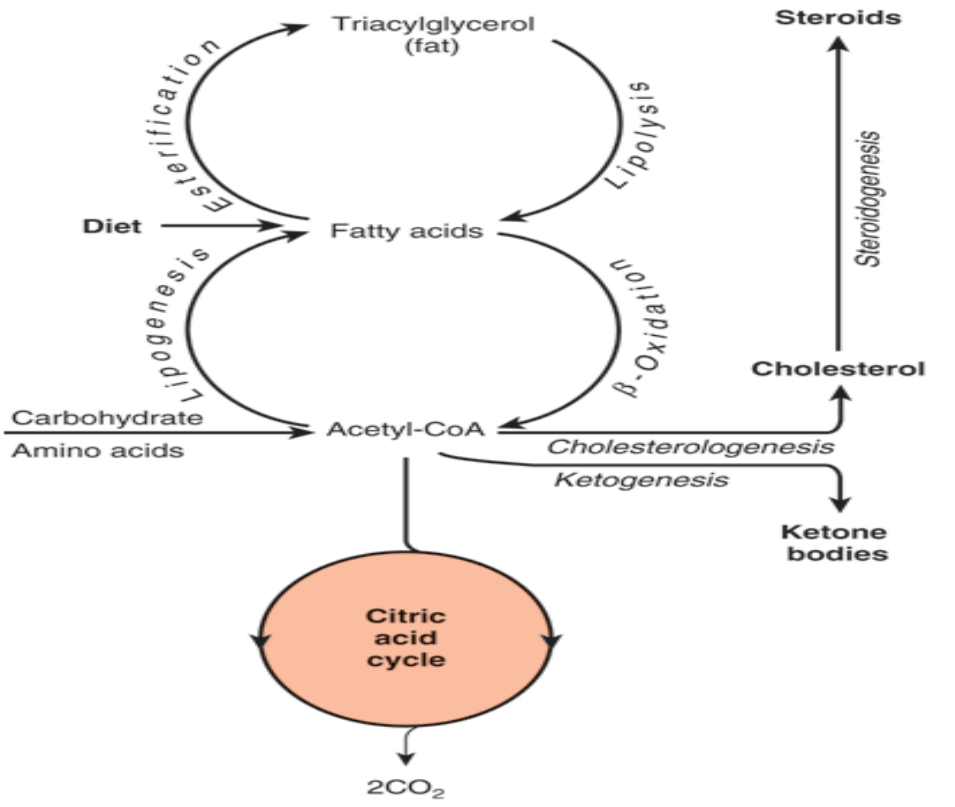
Done by: Bayan maqableh

Lipid transport & Storage

- When a human eat a meal, excess calories are ingested in the anabolic phase of the feeding cycle, followed by a period of negative caloric balance when the organism draws upon its carbohydrate and fat stores.
- Lipoproteins mediate this cycle by transporting lipids from the intestines as **chylomicrons**—and from the liver as very low density lipoproteins (**VLDL**)—***to most tissues for oxidation and to adipose tissue for storage***.
- Abnormalities of lipoprotein metabolism cause various hypo- or hyperlipoproteinemias.

- Fatty Acids can be Transported in the Blood as Free Fatty Acids (FFA)
  - Long chain unesterified FA are combined with other proteins like **Albumin**.
  - Short chain FA can be transported freely as anion.
- Most of fatty acids transported as esterified form in lipoproteins.
  - TAG
  - CE

Overview of Fatty Acid Synthesis



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil *Illustrated Biochemistry, 28th Edition:* http://www.accessmedicine.com

Overview of fatty acid metabolism showing the major pathways and end p hydroxybutyrate, and acetone.

Note:

fatty acids synthesize from acetyl CoA by lipogenesis process

And we talk in previous lecture about fates of FA as they are explained in figure.

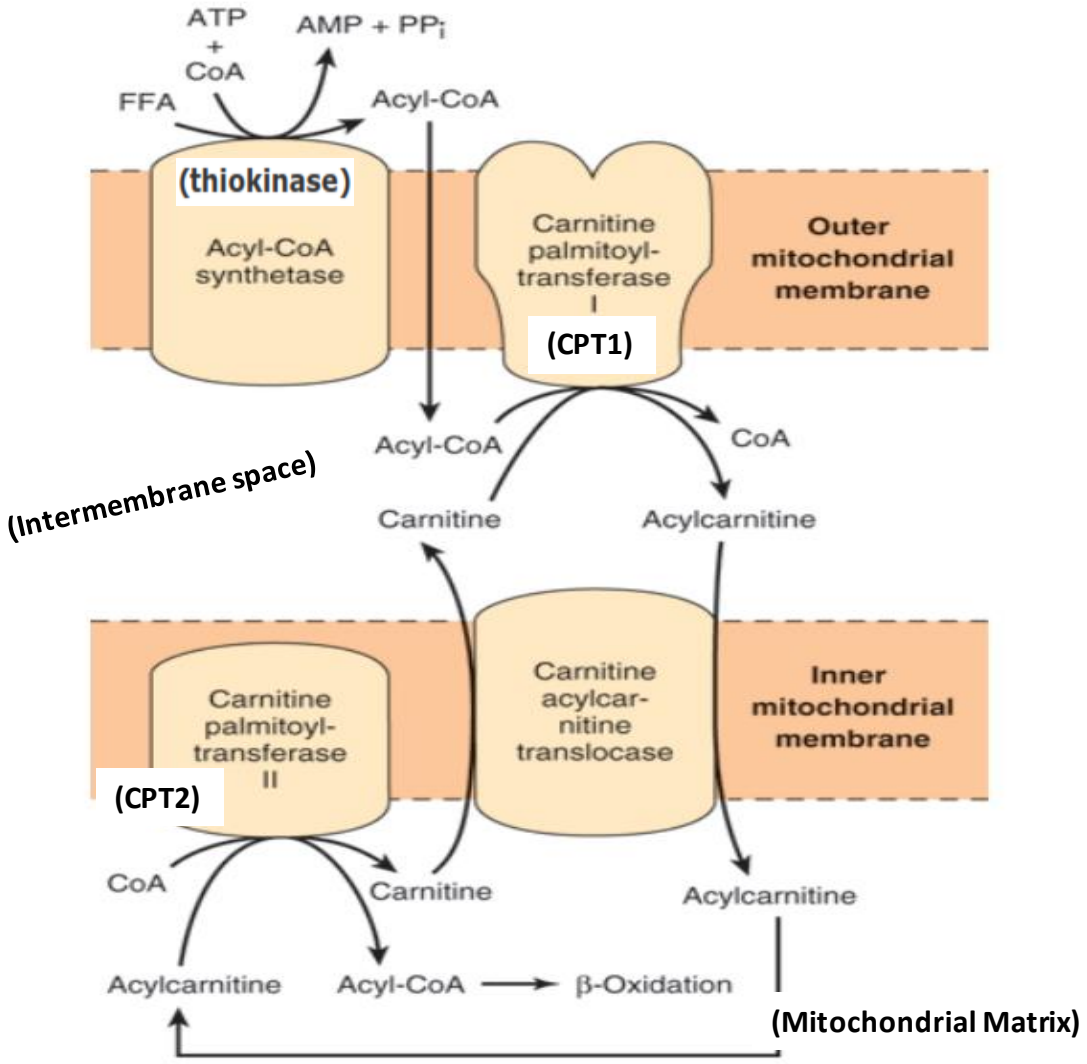
Fatty Acid Activation and Transportation to the Mitochondria

- For oxidation, fatty acids with carbon chains **more than 14 carbons** need activation before passing through the mitochondrial membrane.
- Free fatty acids obtained from diet or which are stored in the adipocytes are mainly 14 carbons or more in length.
- Fatty acids having ≤12 carbons can surpass activation and can easily pass through the mitochondrial membrane.
- The carnitine shuttle is responsible for transferring long-chain fatty acids across the barrier of the inner mitochondrial membrane to gain access to the enzymes of β-oxidation.
- **Impaired Oxidation of Fatty Acids Gives Rise to Diseases Often Associated with Hypoglycemia**

- (record)

- Fatty acids have to undergo to beta oxidation process to produce energy , but FA with more than (12-14) carbon can’t pass by mitochondrial membrane ,so they need activation process.
- Fatty acids having ≤12 carbons can surpass activation and can easily pass through the mitochondrial membrane.
- We will talk in next figure about movement of FA “ to produce Acetyl CoA” from outer membrane to matrix of mitochondria for beta oxidation which occurs in mitochondria to produce energy.

الصورة مهمه وحنشرحها بالتفصيل



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 28th Edition:* http://www.accessmedicine.com

Carnitine

is widely distributed and is particularly abundant in muscle.

Deficiencies in Carnitine: Deficiencies in carnitine lead to an inability to transport fatty acids into the mitochondria for oxidation. This can occur in newborns and particularly in pre-term infants. Carnitine deficiencies also are found in patients undergoing hemodialysis or exhibiting organic aciduria. Carnitine deficiencies may general symptoms or may be limited to only muscles. Symptoms can range from mild occasional muscle cramping to severe weakness or even death.

Treatment is by oral carnitine administration.

- (record) : Fatty acid metabolism :

-in beginning , thiokinase enzyme converts FA to Acyl CoA which is intermediate of FA and **this process need ATP.**

Then, Acyl CoA will enter to intermembrane space through shuttling system called CPT1 , after that Acyl CoA will bind with carnitine "which is transported to the intermembrane space by translocase enzyme" and they will form Acylcarnitine, then acylcarnitine translocase enzyme will transfer acylcarnitine from intermembrane space to the mitochondrial matrix .

-in the matrix we have another enzyme which called **(CPT2**) which converts Acylcarnitine to carnitine + Acyl CoA.

- Acyl CoA will enter different steps of beta oxidation to produce energy and carnitine will go again to intermembrane space to combine with another acyl CoA …. Cont (cycle)
- So ,acyl CoA can't enter alone from intermembrane space to the mitochondrial matrix.

- **Inherited CPT-I deficiency affects only the liver:**
  - **Reduced fatty acid oxidation and ketogenesis**
- **CPT-II deficiency affects primarily skeletal muscle and, when severe, the liver.**
- **The sulfonylurea** drugs **(glyburide [glibenclamide] and tolbutamide), used in the treatment of type 2 diabetes mellitus, reduce** fatty acid oxidation and, therefore, hyperglycemia by inhibiting CPT-I.

16 carbon

Energy Yield in β-oxidation

(C2) acetyl CoA 8 * 12 = 96
# of oxidation rounds = 7, last acetyl coA will be degraded.
NaDH 7 * 3 = 21
FaDH2 7*2 =14

Total: 131

In first step by the action of thiokinase require 2 ATP, so
131 – 2 = 129 total ATP result from FFA oxidation.

ATP per Carbon
FFA: 129/16= 8 ATP
Glucose: 38/ 6= 6.3 ATP

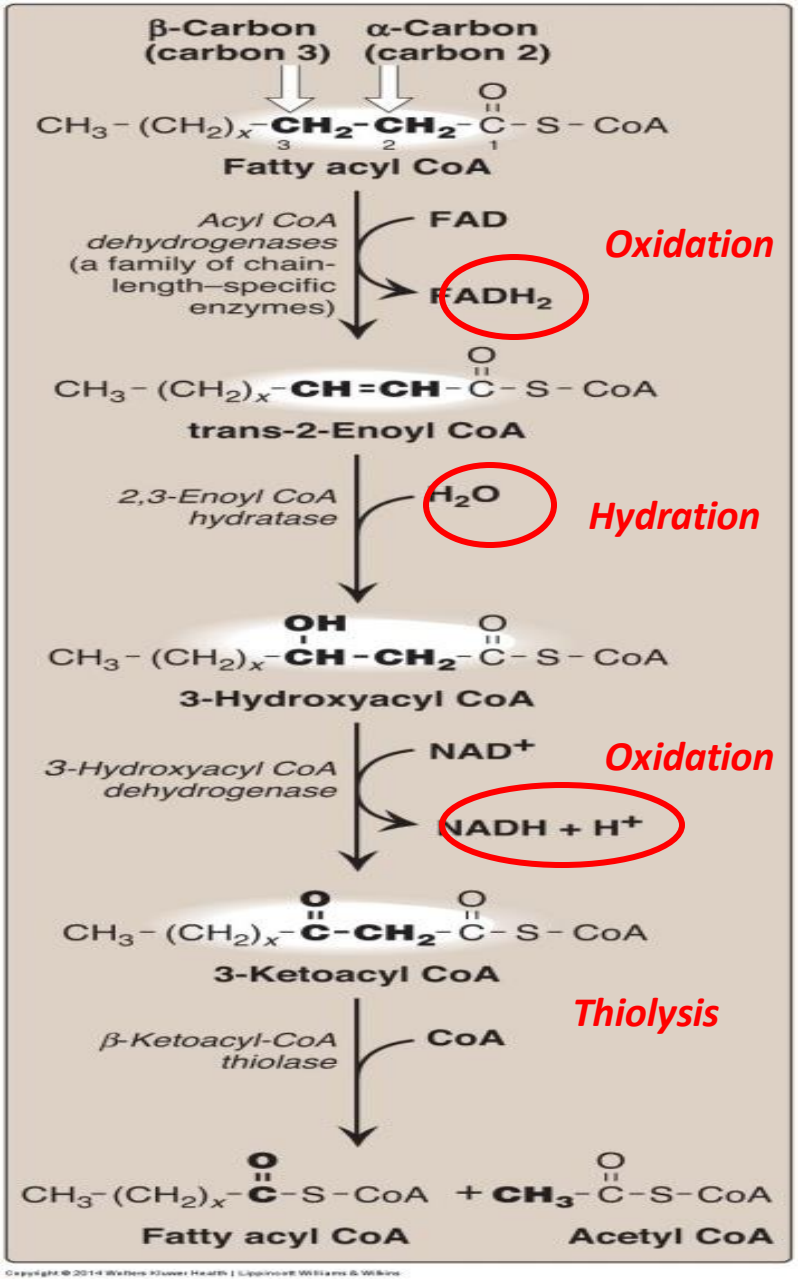


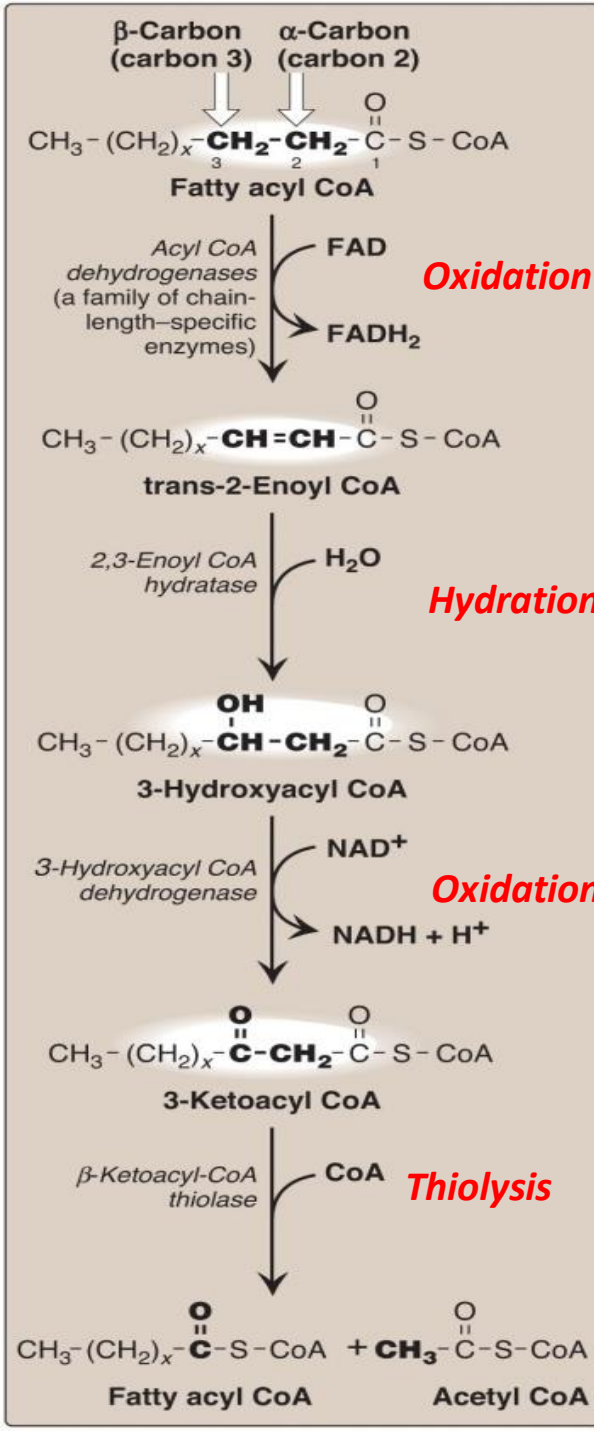
Figure 16.17
Enzymes involved in the β-oxidation of fatty acyl CoA. [Note: *Enoyl CoA hydratase* requires a trans double bond between carbon 2 and carbon 3.]

Note :

we will explain figure then number

- (RECORD)
- B-oxidation : multi steps process it has different reaction (oxidation , hydration , oxidation and thiolysis) for produce many hydrogen carriers that will use to provide ATP sources.

- In beginning, there is fatty acid CoA contains alpha carbon (carbon 2) and beta carbon (carbon 3), the first reaction will occur is oxidation ,there will be add of Hydrogen to FAD and form FADH2 and convert fatty acyl CoA to trans-2-Enoyl CoA
- then will occur hydration (addition of H2o) to carbon 3 this will form 3-hydroxycl CoA , then will occur oxidation , addition of H to NAD and form NADH and synthesize 3-ketoacyl CoA.



- (RECORD “cont.. “)
- Finally , Thiolysis “ adding CoA” then cleavage from middle carbon atom and synthesize of Acetyl CoA + fatty acyl CoA .
- Note :

This process involve produce FADH ,NADH which will get ATP.

NADH= 3ATP

FADH = 2ATP

(record) “ about energy yield”

- If we want compare between energy yield from glycolysis and energy from B-oxidation of FA:
- If we have fatty acid with 16 carbon , acyl CoA contain 2C so we will have 8Acyl CoA , so energy= 8*12= 96
- How we can determine number of cycles?

Cycles = Acyl CoA – 1

= 8-1 =7 “ because the last one will be degradated so we minus it ”

Each cycle involve produce NADH, FADH

Energy from NADH= 7*3=21

From FADH = 7*2= 14

Total = 96+ 14+ 21 = 131 ATP

In first step “ action of ATP “ consume 2ATP so , total be 129

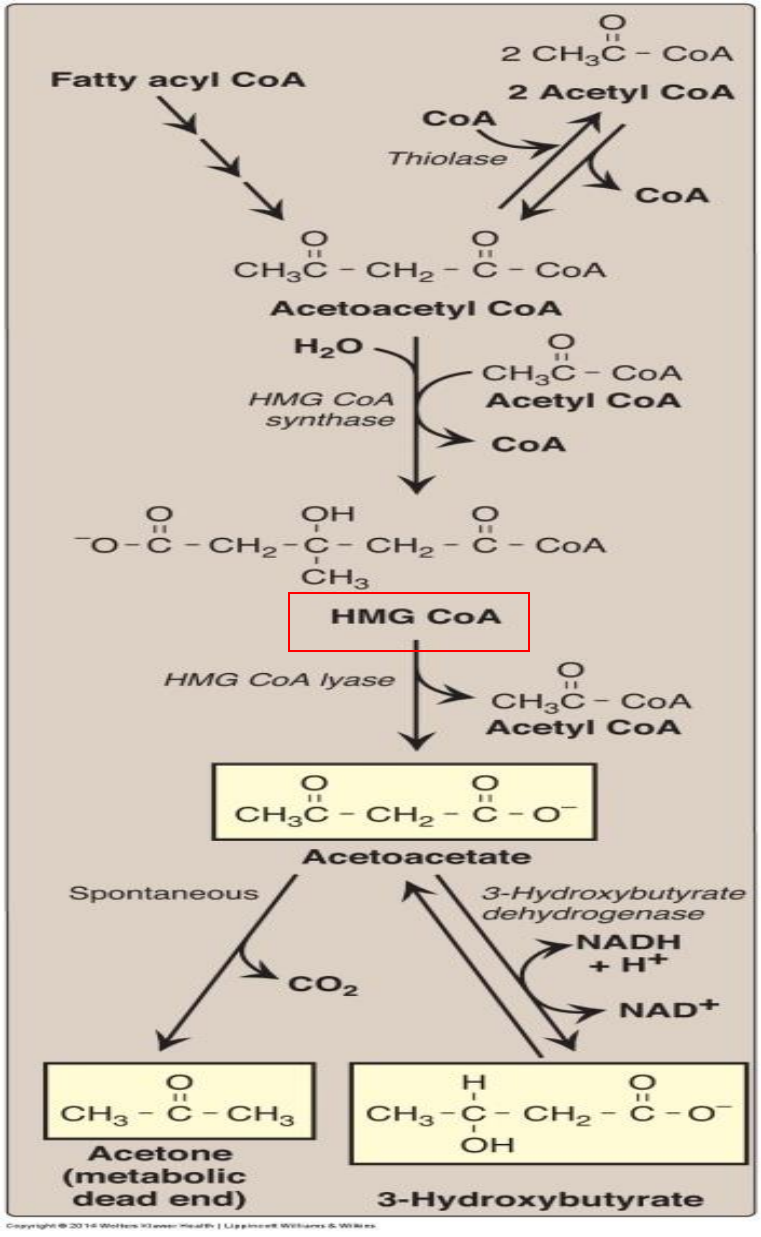
(record)

- ATP per Carbon
- FFA: 129/16= 8 ATP
- Glucose: 38/ 6= 6.3 ATP

* If we compare between ATP per carbon FFA and glucose , FFA give more ATP per carbon than glucose.

KETOGENESIS OCCURS WHEN THERE IS A HIGH RATE OF FATTY ACID OXIDATION IN THE LIVER

- ***Ketosis is mild in starvation but severe in diabetes mellitus***



(record)

* Now we will talk about ketogenesis process.

*KETOGENESIS OCCURS WHEN THERE IS A HIGH RATE OF FATTY ACID OXIDATION IN THE LIVER, like in starvation , diabetic mellitus patients produce energy from ketogenesis.

- **Explain of figure:**

-fatty acyl CoA will undergo thiolase and form acetoacetyl CoA, then HMG synthase enzyme will convert acetoacetyl CoA to HMG CoA, then HMG CoA lyase will convert HMG CoA to Acetoacetate which can give acetone or 3-hydroxybutyrate by dehydrogenase .

- Note :

- Keto compound cause acidosis .
- Acetone has fruity odor

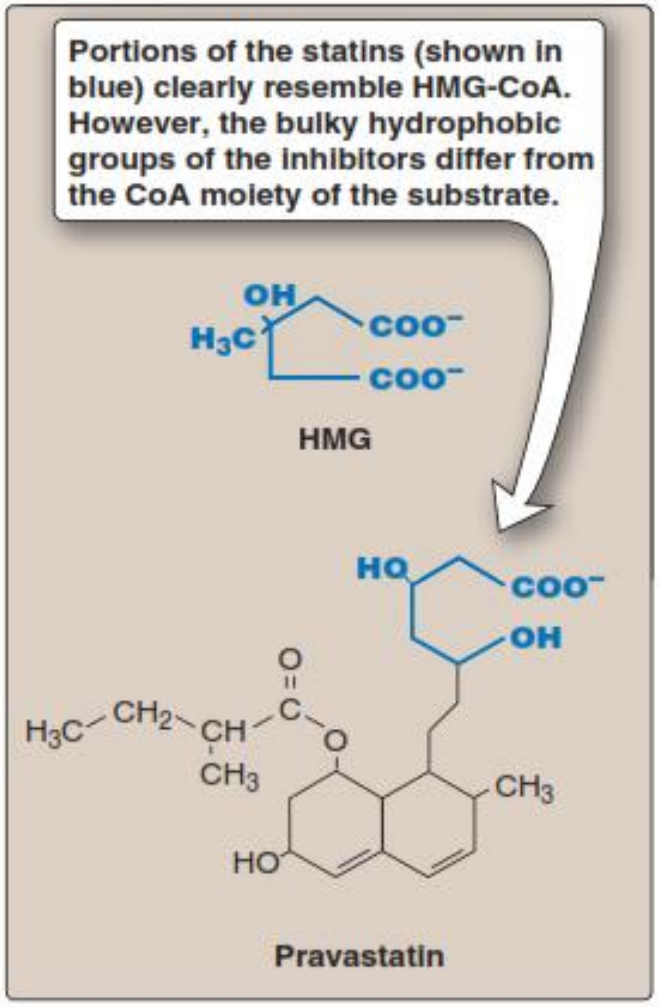


Figure 18.7
Structural similarity of HMG and pravastatin, a clinically useful cholesterol-lowering drug of the "statin" family.

- (record) :
- There is similarity between structure of HMG CoA and statin (pravastatin) , so statin used as cholesterol lowering drug by act as competitive inhibitor .
- Statin inhibit HMG CoA reductase enzyme by prevent binding it with HMG CoA and this will prevent synthesize of cholesterol.

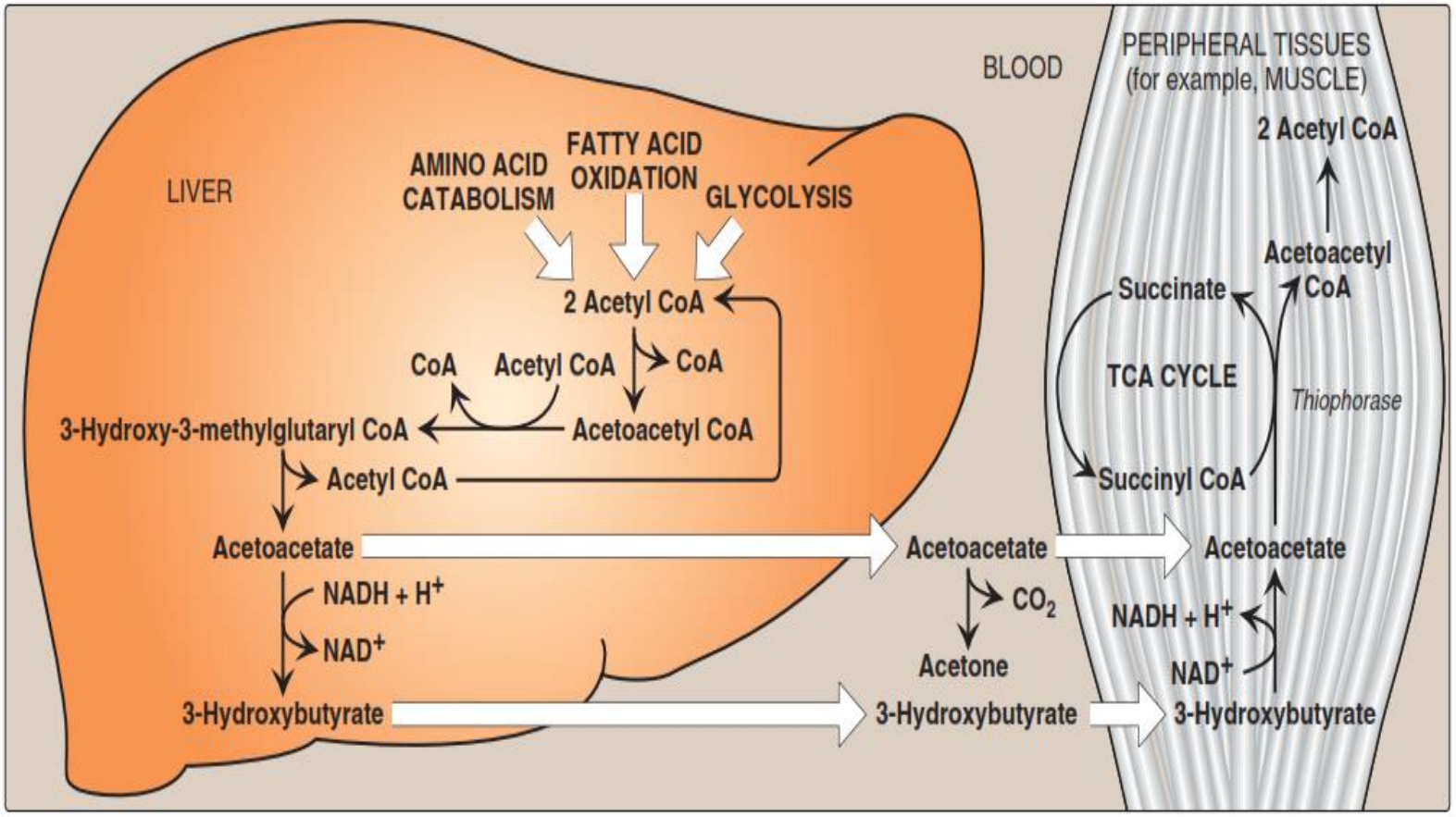


Figure 16.23
Ketone body synthesis in the liver and use in peripheral tissues. [Note: *Thiophorase* is also known as *succinyl CoA: acetoacetate CoA transferase*.]

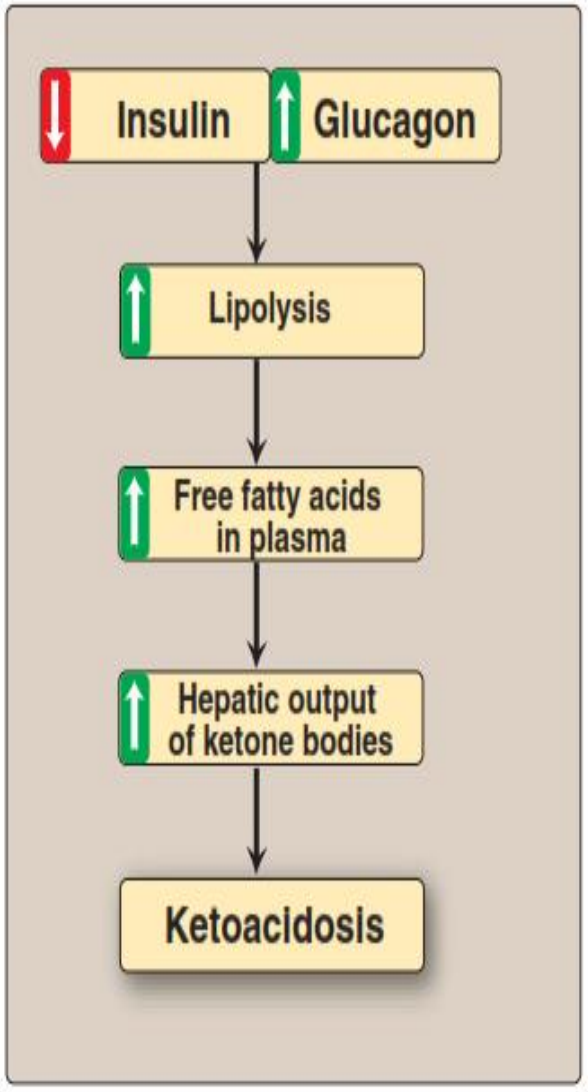


Figure 16.24
Mechanism of diabetic ketoacidosis seen in type 1 diabetes.

(RECORD)

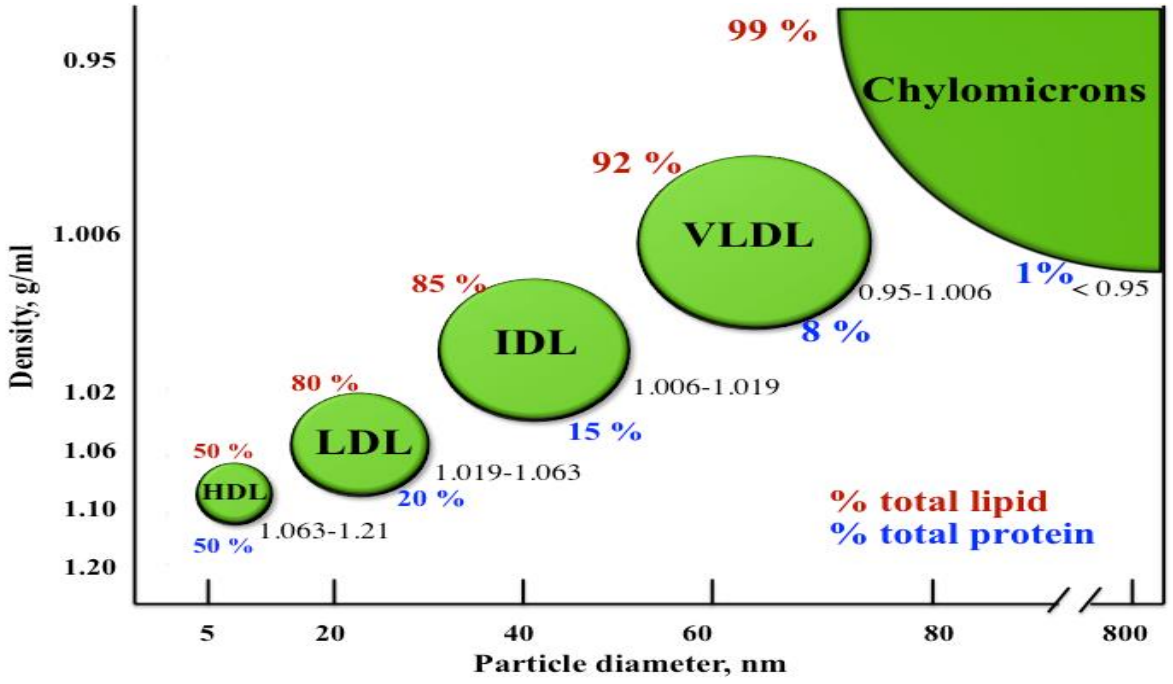
- In diabetic ketosis there is low insulin , high glucagon level , high lipolysis machinery , high FFA in plasma , high hepatic output of ketobodies all of these will lead to ketoacidosis.

Lipid Transport & Storage

The major function of lipoprotein is to transport dietary lipids from intestine to adipose, skeletal muscles and cardiac muscle tissue.

Recognition sites for cell surface receptor and serving as activator or coenzymes for enzymes involve in lipoprotein activation.

- Since fat is less dense than water, the density of a lipoprotein decreases as the proportion of lipid to protein increases. (important)



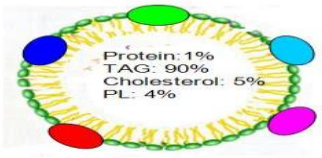
(record) :

-Lipid transport / storage

- The major function of lipoprotein is to transport dietary lipids from intestine to adipose, skeletal muscles and cardiac muscle tissue.
- There are different lipoproteins :

- Chylomicrons (bigger in size, lower in density) , 99% lipid and 1% proteins.
- VLDL (very low density lipoprotein) : 92% lipid , 8% protein.
- LDL : 80% lipid , 20% protein
- HDL : 50% lipid , 50% protein .

-Since fat is less dense than water, the density of a lipoprotein decreases as the proportion of lipid to protein increases. (important)

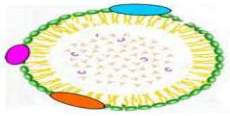


Lipoprotein type: Chylomicron
Density: <0.950 g/mL
Diameter: 80-1000 nm
Major lipids: dietary triacylglycerols
Apolipoproteins: B48, A1, A2, C, E

Protein: ~1%
Triglyceride: ~90%
Cholesterol: ~5%
Phospholipids: ~4%

Lipoprotein type: VLDL
Density: 0.950-1.006 g/mL
Diameter: 30-80 nm
Major lipids: endogenous triacylglycerols
Apolipoproteins: B100, C, E

Protein: ~10%
Triglyceride: ~65%
Cholesterol: ~13%
Phospholipids: ~13%



Lipoprotein type: IDL
Density: 1.006-1.019 g/mL
Diameter: 25-30 nm
Major lipids: endogenous triacylglycerols and cholesterol
Apolipoproteins: B100, C, E

Protein: ~18%
Triglyceride: ~34%
Cholesterol: ~22%
Phospholipids: ~22%

Lipoprotein type: LDL
Density: 1.019-1.063 g/mL
Diameter: 20-22 nm
Major lipids: cholesterol and cholesteryl ester
Apolipoproteins: B100

Protein: ~20%
Triglyceride: ~10%
Cholesterol: ~45%
Phospholipids: ~23%

Lipoprotein type: HDL
Density: 1.063-1.090 g/mL
Diameter: 9-15 nm
Major lipids: cholesteryl ester and phospholipid
Apolipoproteins: A1, A2, C, E

Protein: ~50%
Triglyceride: ~20%
Cholesterol: ~18%
Phospholipids: ~30%

Four Major Lipid Classes Are Present in Lipoproteins

1. Triacylglycerols (16%).
2. Phospholipids (30%).
3. Cholesterol (14%).
4. Cholesterylesters (36%) .
5. Smaller fraction of unesterified long-chain fatty acids (4%).

the free fatty acids (FFA), are metabolically the most active of the plasma lipids.

Major component of these lipoproteins , all of them contain protein and lipid "lipid can be TG or cholesterol or phospholipid."

Since fat is less dense than water, the density of a lipoprotein decreases as the proportion of lipid to protein increases.

TABLE 25–1 Composition of the Lipoproteins in Plasma of Humans

Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition		Main Lipid Components	Apolipoproteins
				Protein (%)	Lipid (%)		
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV,[1] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30–90	0.95–1.006	7–10	90–93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25–35	1.006–1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20–25	1.019–1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylomicrons					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[2] E
HDL_1		20–25	1.019–1.063	32	68		
HDL_2		10–20	1.063–1.125	33	67		
HDL_3		5–10	1.125–1.210	57	43		
Preβ-HDL[3]		< 5	> 1.210				A-I
Albumin/free fatty acids	Adipose tissue		> 1.281	99	1	Free fatty acids	

B

A

[1]Secreted with chylomicrons but transfers to HDL.
[2]Associated with HDL_2 and HDL_3 subfractions.
[3]Part of a minor fraction known as very high density lipoproteins (VHDL).
Abbreviations: HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low density lipoproteins.

- **(record “ about table”) :**

- These lipoproteins are different in percentage of lipid and protein , the density of lipoprotein decreases as the proportion of lipid to protein increases.
- Each lipoprotein has specialized surface receptor

(chylomicron : c-III E , chylomicron remnants : B-48,E ……)

Lipoproteins Consist of a Nonpolar Core & a Single Surface Layer of Amphipathic Lipids

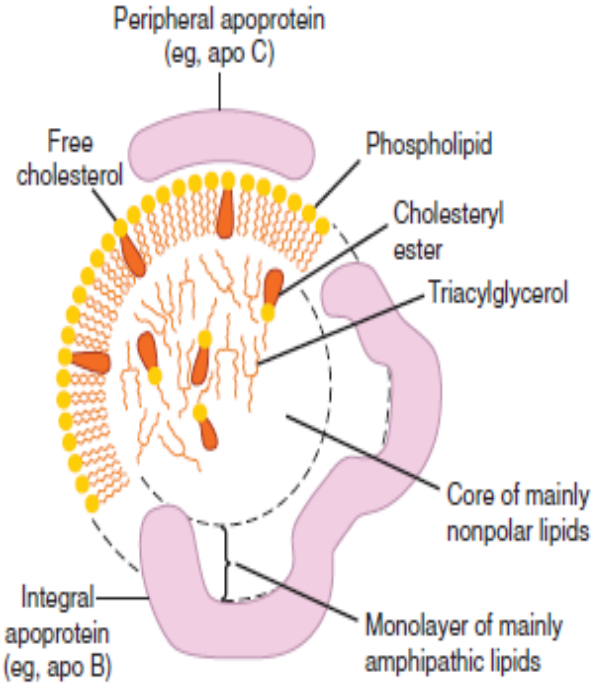


FIGURE 25–1 **Generalized structure of a plasma lipoprotein.** The similarities with the structure of the plasma membrane are to be noted. Small amounts of cholesteryl ester and triacylglycerol are found in the surface layer and a little free cholesterol in the core.

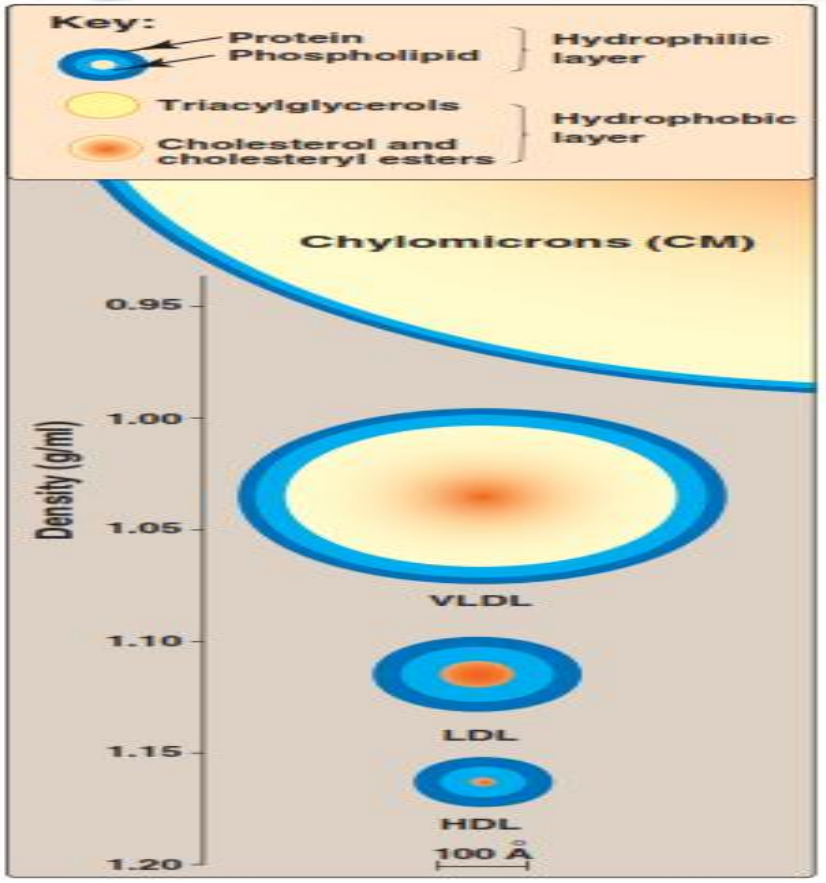


Figure 18.13
Approximate size and density of serum lipoproteins. Each family of lipoproteins exhibits a range of sizes and densities; this figure shows typical values. The width of the rings approximates the amount of each component. [Note: Although cholesterol and its esters are shown as one component in the center of

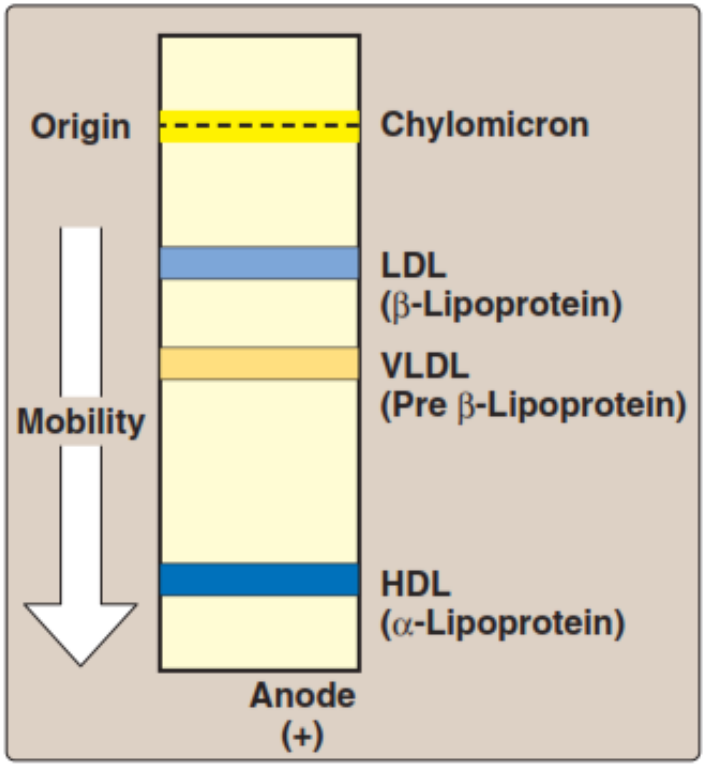
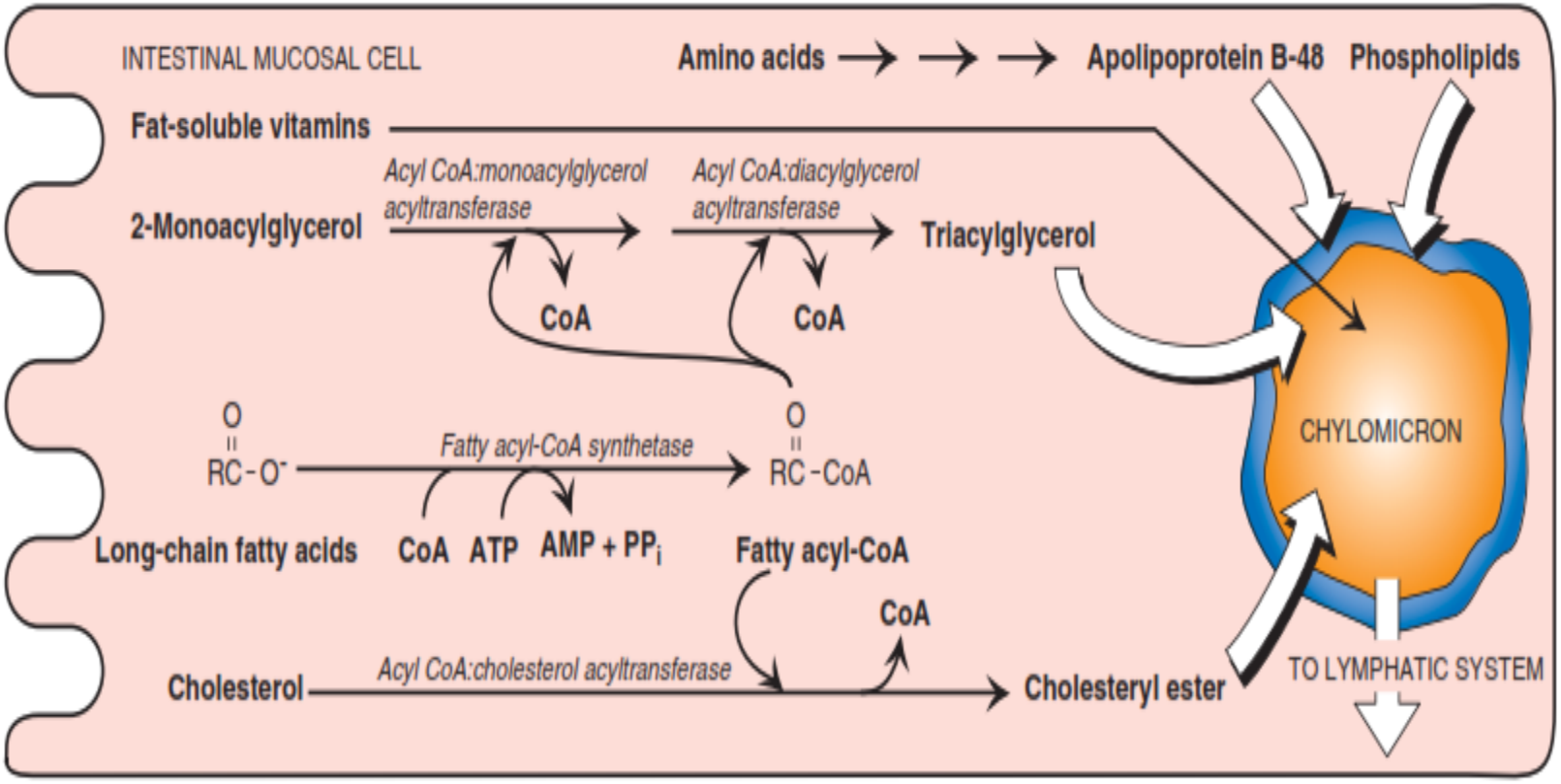


Figure 18.15
Electrophoretic mobility of plasma lipoproteins. The order of LDL and VLDL is reversed if ultra-centrifugation is used as the separation technique.

- The protein moiety of a lipoprotein is known as an **apolipoprotein** or **apoprotein**, constituting nearly 70% of some HDL and as little as 1% of chylomicrons.
- Some apolipoproteins are integral and cannot be removed, whereas others are free to transfer to other lipoproteins.
- The lipid components of lipoproteins are insoluble in water. However, because of their detergentlike (amphipathic) properties, apolipoproteins and other amphipathic molecules (such as phospholipids) can surround the lipids, creating the lipoprotein particle that is itself water-soluble, and can thus be carried through water-based circulation (i.e. blood, lymph).
- Apolipoproteins also serve as enzyme cofactors, receptor ligands, and lipid transfer carriers that regulate the metabolism of lipoproteins and their uptake in tissues

Apolipoprotein	Major Lipoproteins	Major Functions
Apo A-I	HDL	Structural protein for HDL Activator of LCAT
Apo A-II	HDL	Structural protein for HDL Activator of hepatic lipase
Apo A-IV	HDL, chylomicrons	Activator of LPL and LCAT
Apo B-100	VLDL, IDL, LDL	Structural protein for VLDL and LDL Ligand for binding to LDL receptor
Apo B-48	Chylomicrons, remnants	Structural protein for chylomicrons
Apo C-II	Chylomicrons, VLDL	Essential cofactor for LPL
Apo C-III	Chylomicrons, VLDL, HDL	Inhibitor of lipoprotein binding to receptors
Apo E	Remnants, VLDL, LDL, HDL	Ligand for binding to LDL receptor Ligand for binding to remnant (apo E) receptor
Apo(a)	Lp(a)	Structural protein for Lp(a) Inhibitor of plasminogen activation

* Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); LPL = lipoprotein lipase; VLDL = very low-density lipoprotein.



gure 15.6

Assembly and secretion of chylomicrons by intestinal mucosal cells. [Note: Short- and medium-chain length fatty acids do not require incorporation into micelles and directly enter into the blood.]

TRIACYLGLYCEROL (TAG) is transported from the intestine in **chylomicrons** (C), and transported from the liver in VLDL

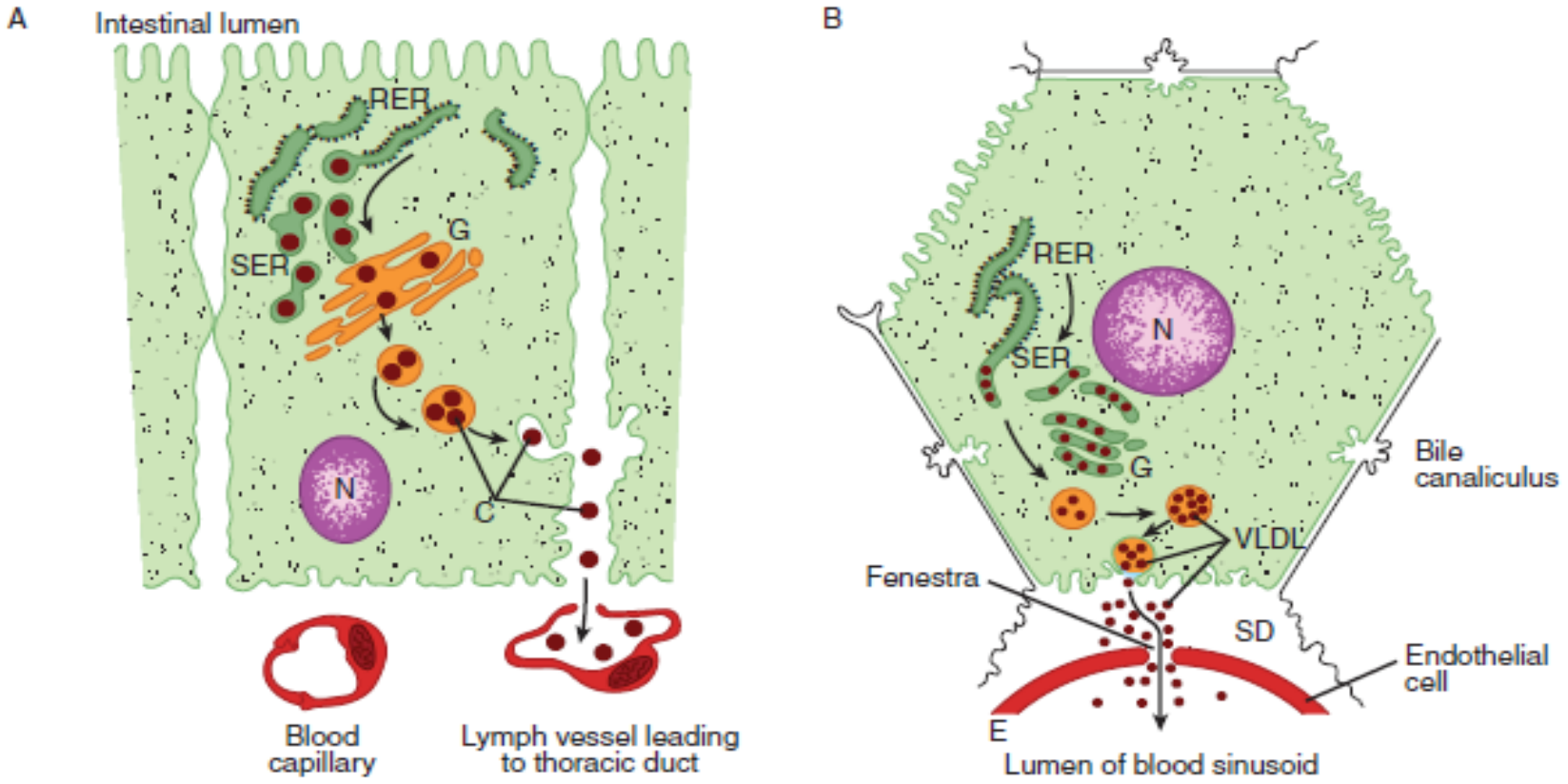


FIGURE 25–2 The formation and secretion of (A) chylomicrons by an intestinal cell and (B) very low density lipoproteins by a hepatic cell. (C, chylomicrons; E, endothelium; G, Golgi apparatus; N, nucleus; RER, rough endoplasmic reticulum; SD, space of Disse, containing blood plasma; SER, smooth endoplasmic reticulum; VLDL, very low density lipoproteins.) Apolipoprotein B, synthesized in the RER, is incorporated into particles with triacylglycerol, cholesterol, and phospholipids in the SER. After the addition of carbohydrate residues in G, they are released from the cell by reverse pinocytosis. Chylomicrons pass into the lymphatic system. VLDL are secreted into the space of Disse and then into the hepatic sinusoids through fenestrae in the endothelial lining.

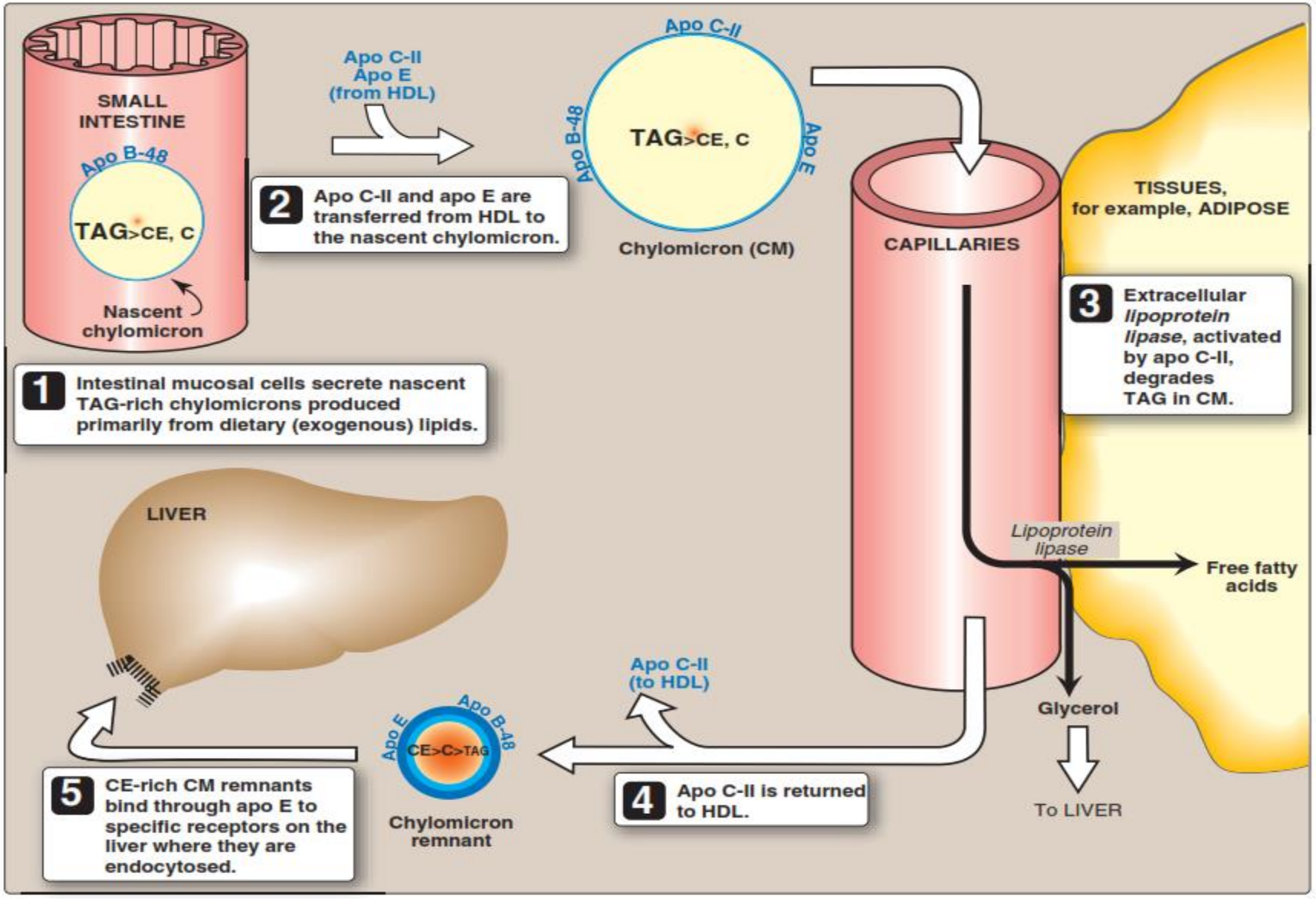


Figure 18.16
Metabolism of chylomicrons. CM = chylomicron; TAG = triacylglycerol; C = cholesterol; CE = cholesteryl esters. Apo B-48, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins. The lipoproteins are not drawn to scale (see Figure 18.13 for details of the size and density of lipoproteins).

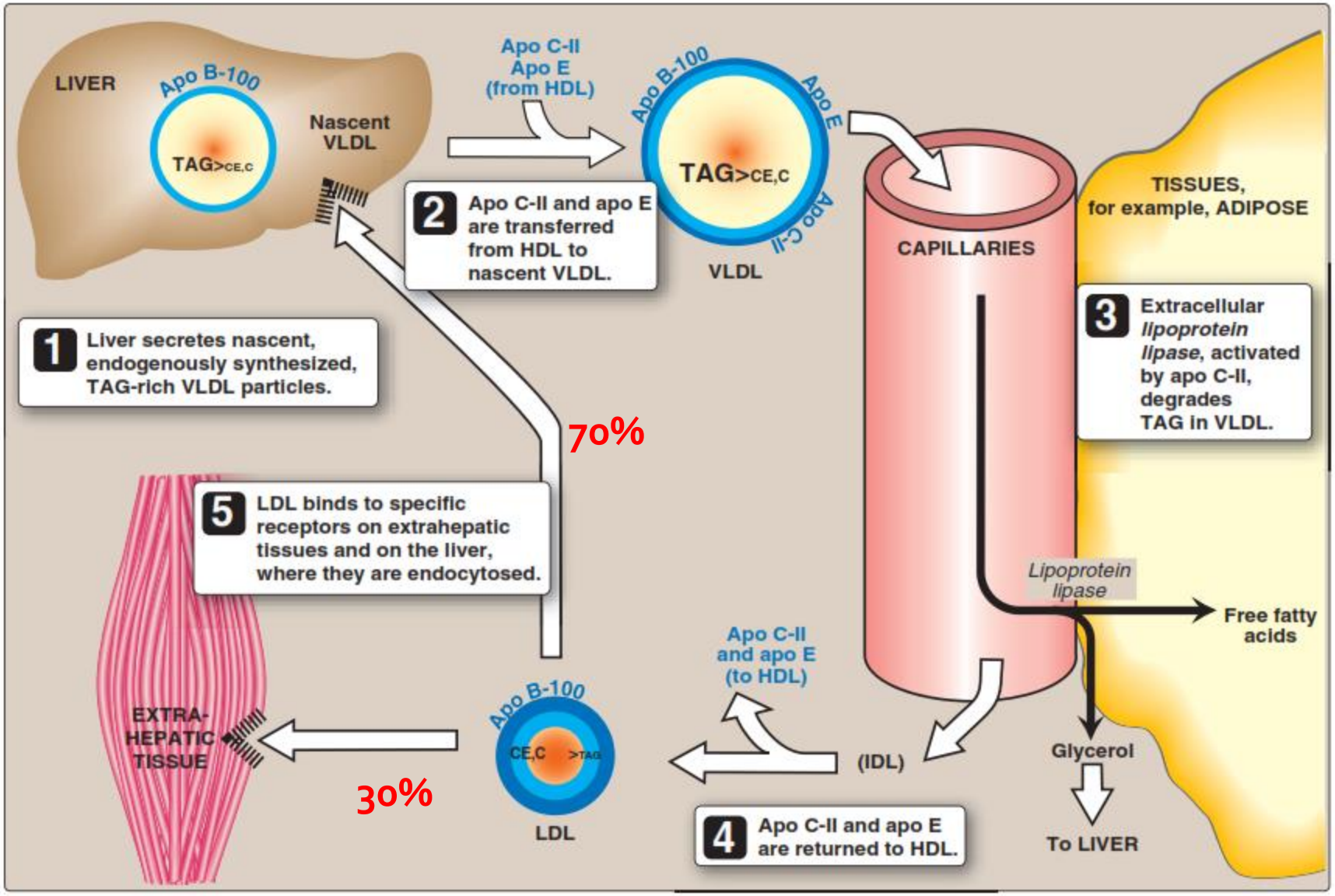


Figure 18.17

Metabolism of VLDL and LDL. TAG = triacylglycerol; VLDL = very-low-density lipoprotein; LDL = low-density-lipoprotein; IDL = intermediate-density lipoprotein; C = cholesterol; CE = cholesteryl esters. Apo B-100, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins. Lipoproteins are not drawn to scale (see Figure 18.13 for details of the size and density of lipoproteins).

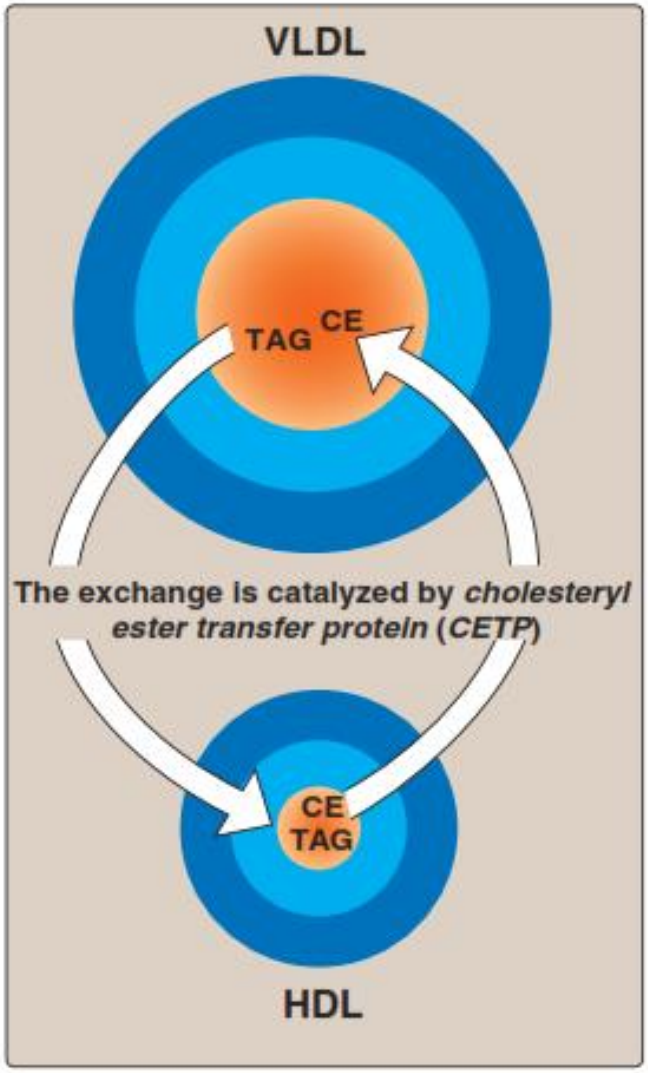


Figure 18.18
Transfer of cholesteryl esters (CE) from HDL to VLDL in exchange for triacylglycerol (TAG).

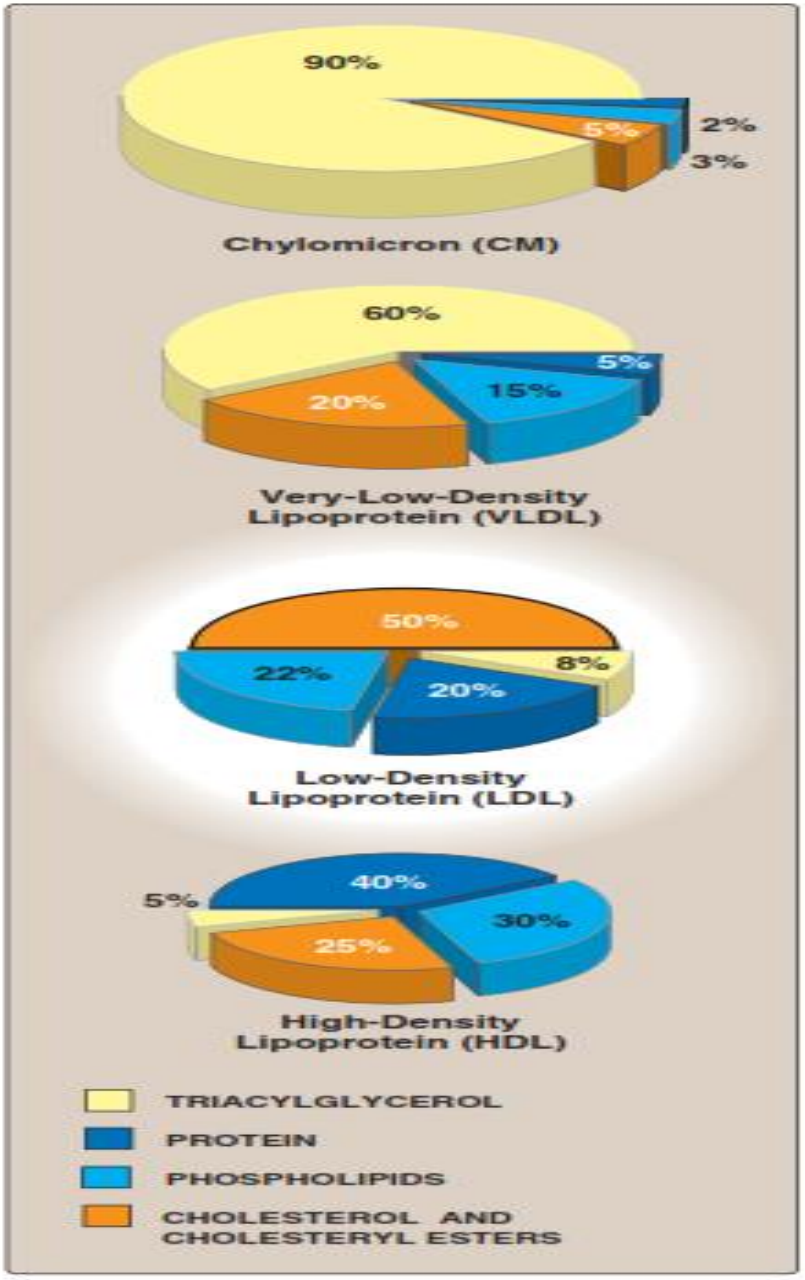


Figure 18.19
Composition of the plasma

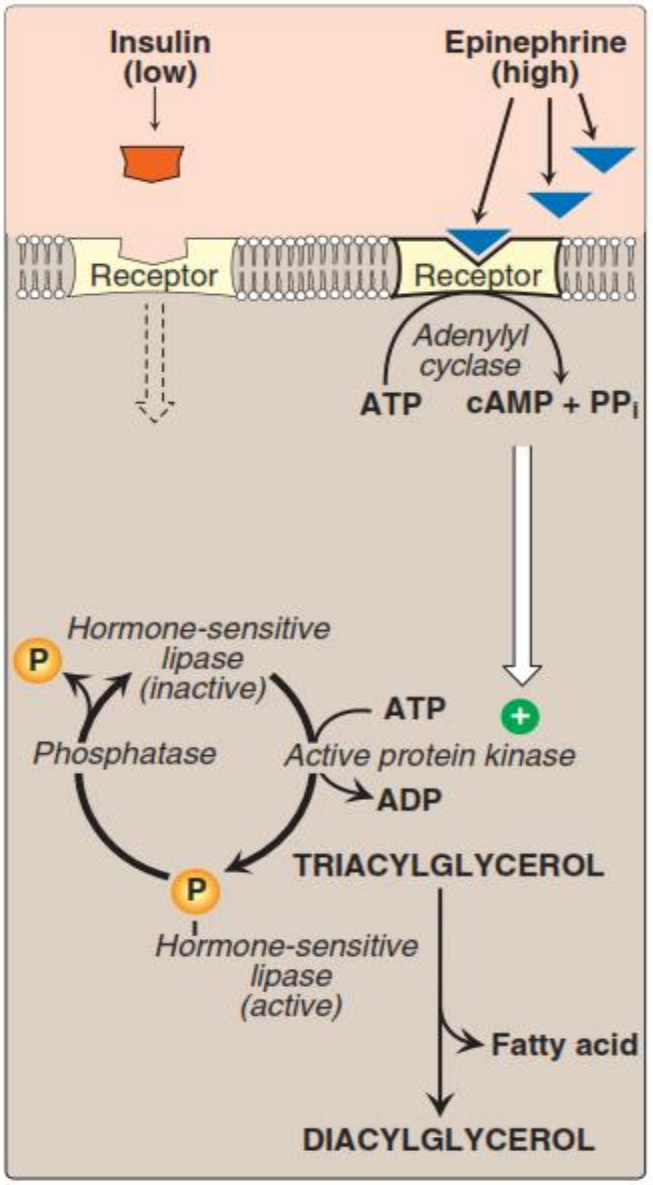
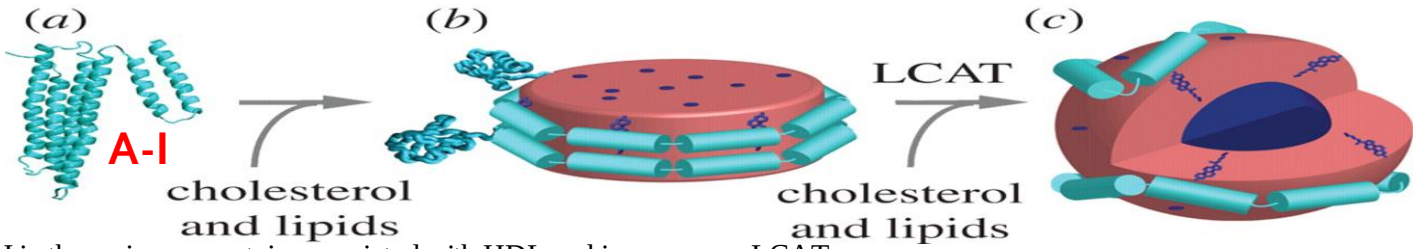


Figure 16.15
Hormonal regulation of triacylglycerol degradation in the adipocyte.

HDL2 is inversely related to the incidence of atherosclerosis.



Apoprotein A-I is the major apoprotein associated with HDL and is necessary LCAT

Disk shape to spherical shape in the circulation

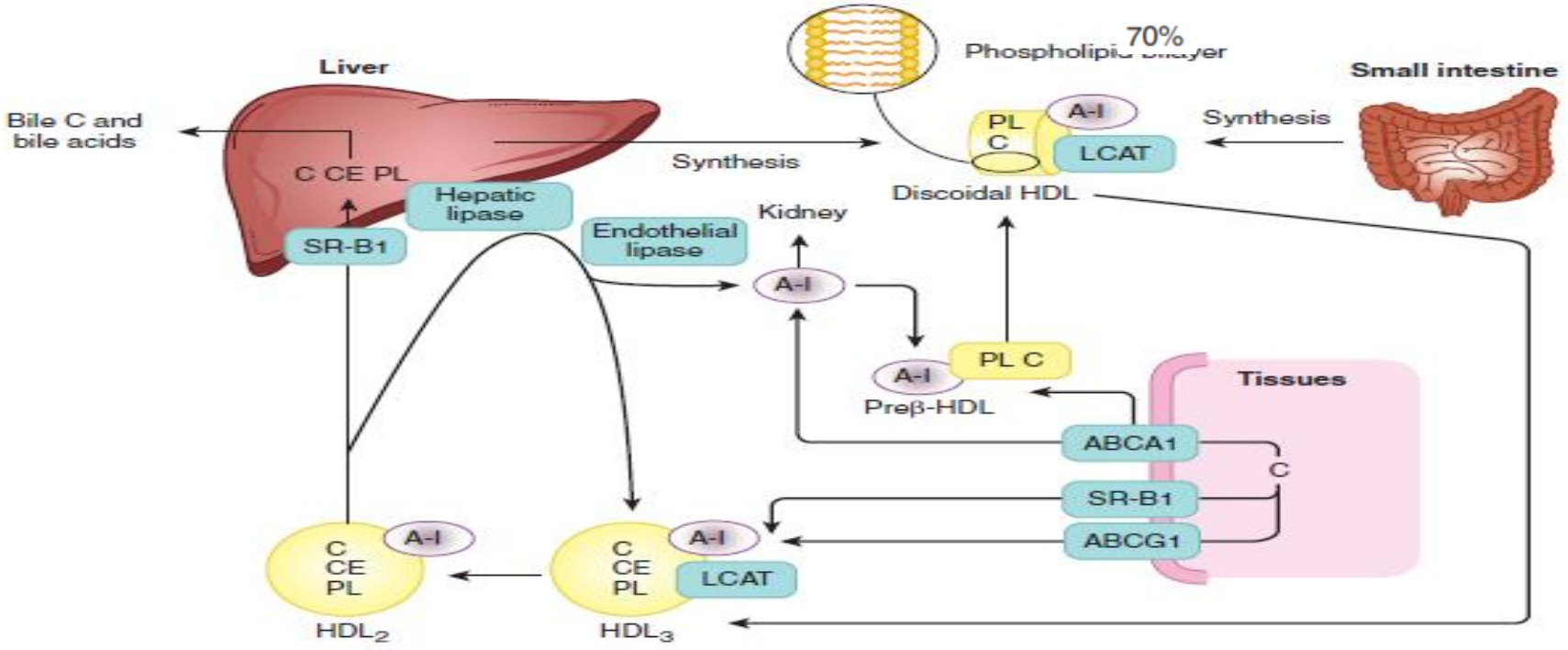


FIGURE 25–5 **Metabolism of high-density lipoprotein (HDL) in reverse cholesterol transport.** (A-I, apolipoprotein A-I; ABCA 1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; C, cholesterol; CE, cholesteryl ester; LCAT, lecithin:cholesterol acyltransferase; PL, phospholipid; SR-B1, scavenger receptor B1.) Preβ-HDL, HDL_2, HDL_3—see Table 25–1. Surplus surface constituents from the action of lipoprotein lipase on chylomicrons and VLDL are another source of preβ-HDL. Hepatic lipase activity is increased by androgens and decreased by estrogens, which may account for higher concentrations of plasma HDL_2 in women.