Lipid Transport, Storage & Cholesterol synthesis

University of Anbar/College of Pharmacy

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References :

1- Harper’s Illustrated Biochemistry

2- Lehninger Principles of Biochemistry

By

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BIOMEDICAL IMPORTANCE

Fat absorbed from the diet and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage. Since lipids are insoluble in water, the problem of how to transport them in the aqueous blood plasma is solved by associating nonpolar lipids (triacylglycerol and cholesteryl esters) with amphipathic lipids (phospholipids and cholesterol) and proteins to make water-miscible lipoproteins.

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. Lipid is mobilized from adipose tissue as free fatty acids (FFAs) bound to serum albumin.

Abnormalities of lipoprotein metabolism cause various (hypo- or hyper) lipoproteinemias. The most common of these is in diabetes mellitus, where insulin deficiency causes excessive mobilization of FFA and underutilization of chylomicrons and VLDL, leading to hypertriacylglycerolemia. Most other pathologic conditions affecting lipid transport are due primarily to inherited defects, some of which cause hypercholesterolemia and premature atherosclerosis

LIPIDS ARE TRANSPORTED IN THE PLASMA AS LIPOPROTEINS

Four Major Lipid Classes Are Present in Lipoproteins

Plasma lipids consist of triacylglycerols (16%), phospholipids (30%), cholesterol (14%), and cholesteryl esters (36%) and a much smaller fraction of unesterified long-chain fatty acids (or FFAs) (4%).

Four Major Groups of Plasma Lipoproteins Have Been Identified

(1) Chylomicrons, derived from intestinal absorption of triacylglycerol and other lipids;

(2) VLDL, derived from the liver for the export of triacylglycerol;

(3) low-density lipoproteins (LDL), representing a final stage in the catabolism of VLDL.

(4) high-density lipoproteins, (HDL), involved in cholesterol transport and also in VLDL and chylomicron metabolism.

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,[a] 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,[b] 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[c]		<5	>1.210				A-I
Albumin/free fatty acids	Adipose tissue		>1.281	99	1	Free fatty acids	

TABLE 21-2 Apolipoproteins of the Human Plasma Lipoproteins

Apolipoprotein	Polypeptide molecular weight	Lipoprotein association	Function (if known)
ApoA-I	28,100	HDL	Activates LCAT; interacts with ABC transporter
ApoA-II	17,400	HDL	Inhibits LCAT
ApoA-IV	44,500	Chylomicrons, HDL	Activates LCAT; cholesterol transport/clearance
ApoB-48	242,000	Chylomicrons	Cholesterol transport/clearance
ApoB-100	512,000	VLDL, LDL	Binds to LDL receptor
ApoC-I	7,000	VLDL, HDL	
ApoC-II	9,000	Chylomicrons, VLDL, HDL	Activates lipoprotein lipase
ApoC-III	9,000	Chylomicrons, VLDL, HDL	Inhibits lipoprotein lipase
ApoD	32,500	HDL	
ApoE	34,200	Chylomicrons, VLDL, HDL	Triggers clearance of VLDL and chylomicron remnants
ApoH	50,000	Possibly VLDL, binds phospholipids such as cardiolipin	Roles in coagulation, lipid metabolism, apoptosis, inflammation

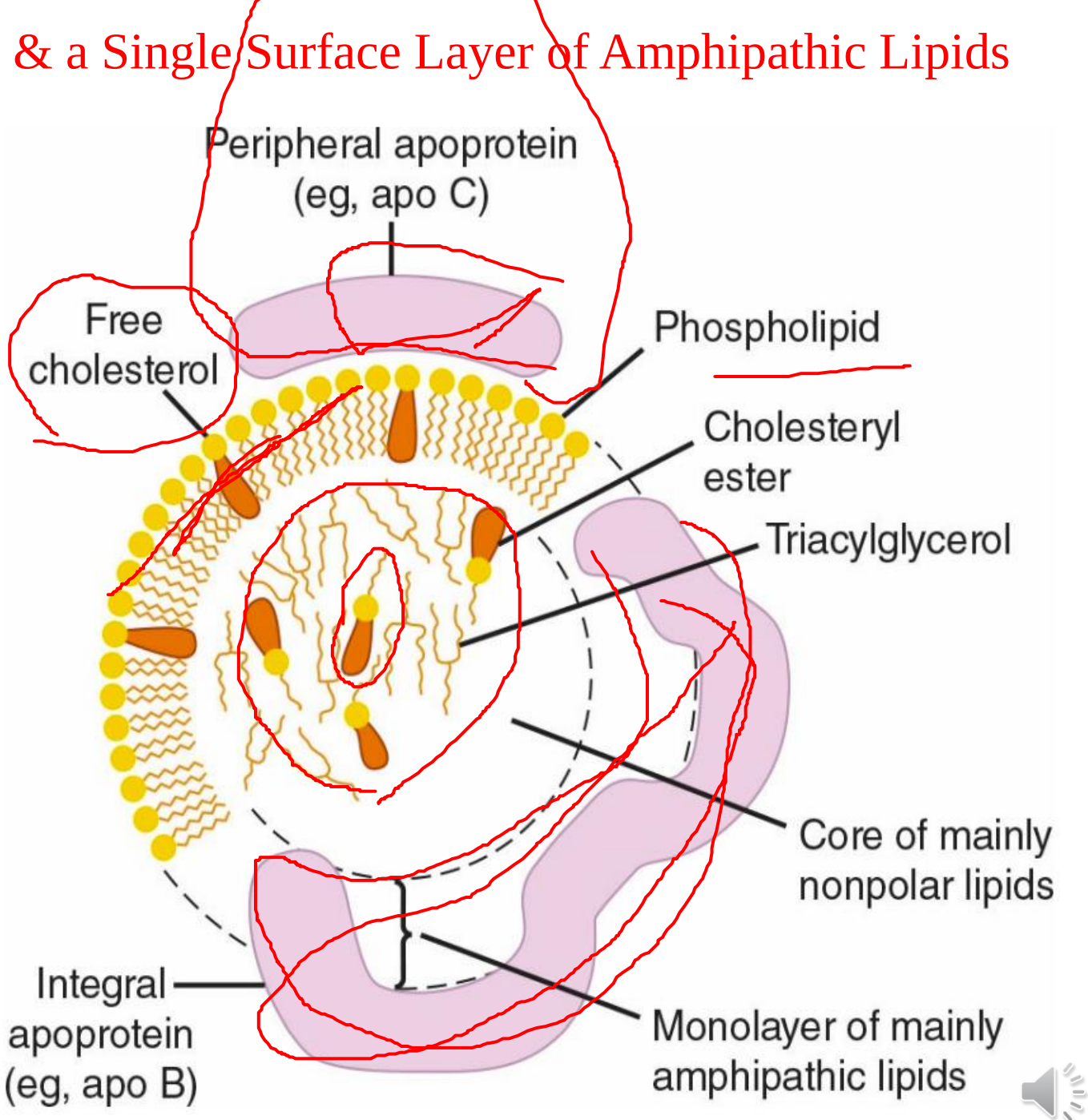
Source: Information from D. E. Vance and J. E. Vance (eds), *Biochemistry of Lipids and Membranes* , 5th edn,

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

The nonpolar lipid core consists of mainly triacylglycerol and cholesteryl ester and is surrounded by a single surface layer of amphipathic phospholipid and cholesterol molecules.

These are oriented so that their polar groups face outward to the aqueous medium, as in the cell membrane.

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.



FREE FATTY ACIDS (FFAs) ARE RAPIDLY METABOLIZED

The FFAs arise in the plasma from the breakdown of triacylglycerol in adipose tissue or as a result of the action of lipoprotein lipase on the plasma triacylglycerols.

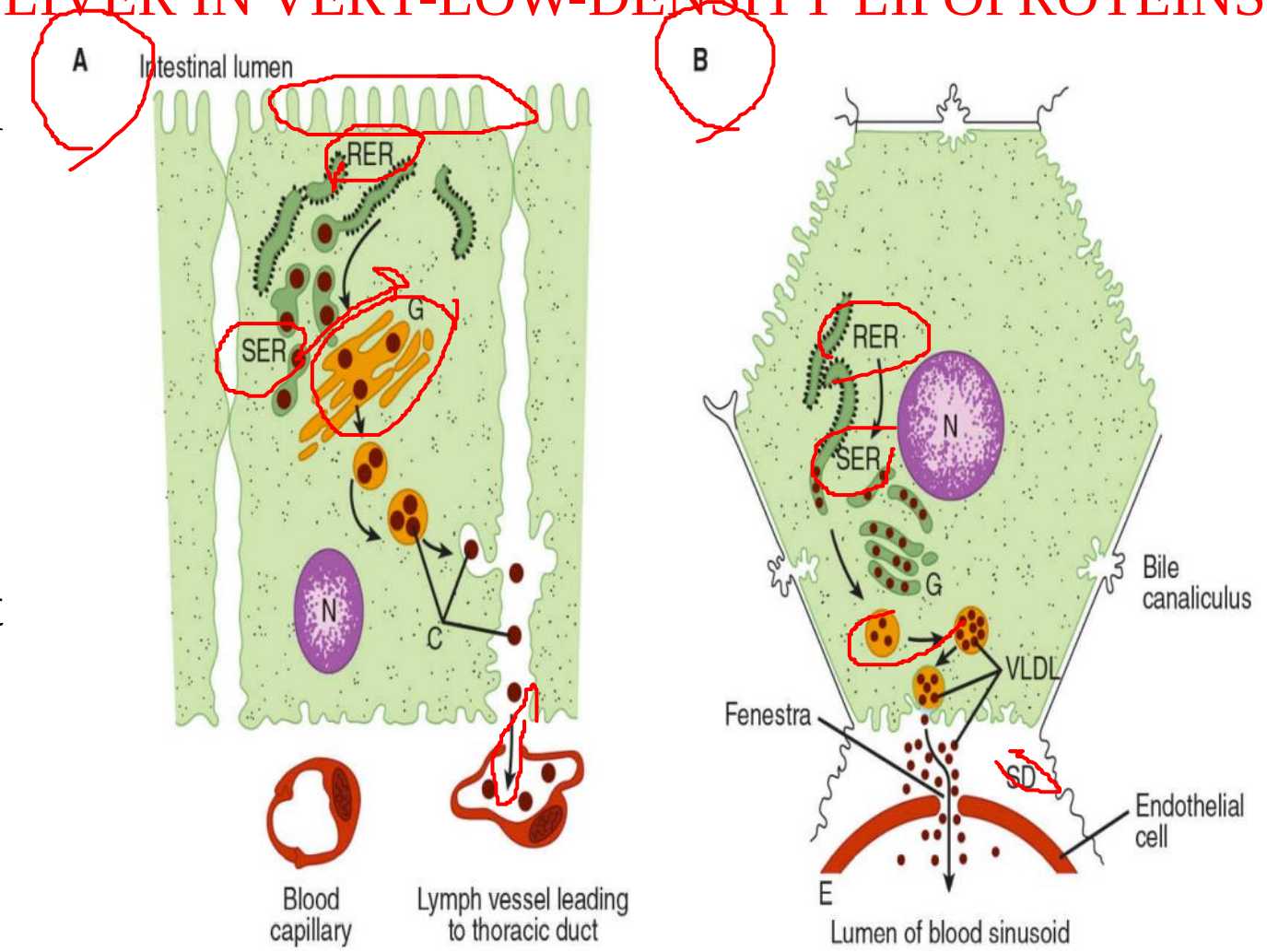
They are found in **combination with albumin**, a very effective solubilizer. FFAs are removed from the blood extremely rapidly by the tissues and oxidized (25-50% of energy requirements in starvation) or esterified to form triacylglycerol.

The FFA uptake by tissues is related directly to the plasma-FFA concentration, which in turn is determined by the rate of lipolysis in adipose tissue. After dissociation of the fatty acid–albumin complex at the plasma membrane, fatty acids bind to a membrane fatty acid transport protein that acts as a transmembrane cotransporter with Na+. On entering the cytosol, FFAs are bound by intracellular fatty acid–binding proteins.

TRIACYLGLYCEROL IS TRANSPORTED FROM THE INTESTINES IN CHYLOMICRONS & FROM THE LIVER IN VERY-LOW-DENSITY LIPOPROTEINS

Chylomicrons are found in chyle formed only by the lymphatic system draining the intestine. They are responsible for the transport of all dietary lipids into the circulation. Small quantities of VLDL are also to be found in chyle; however, most VLDL in the plasma are of hepatic origin. They are the vehicles of transport of triacylglycerol from the liver to the extrahepatic tissues.

abetalipoproteinemia (a rare disease), lipoproteins containing apo B are not formed and lipid droplets accumulate in the intestine and liver



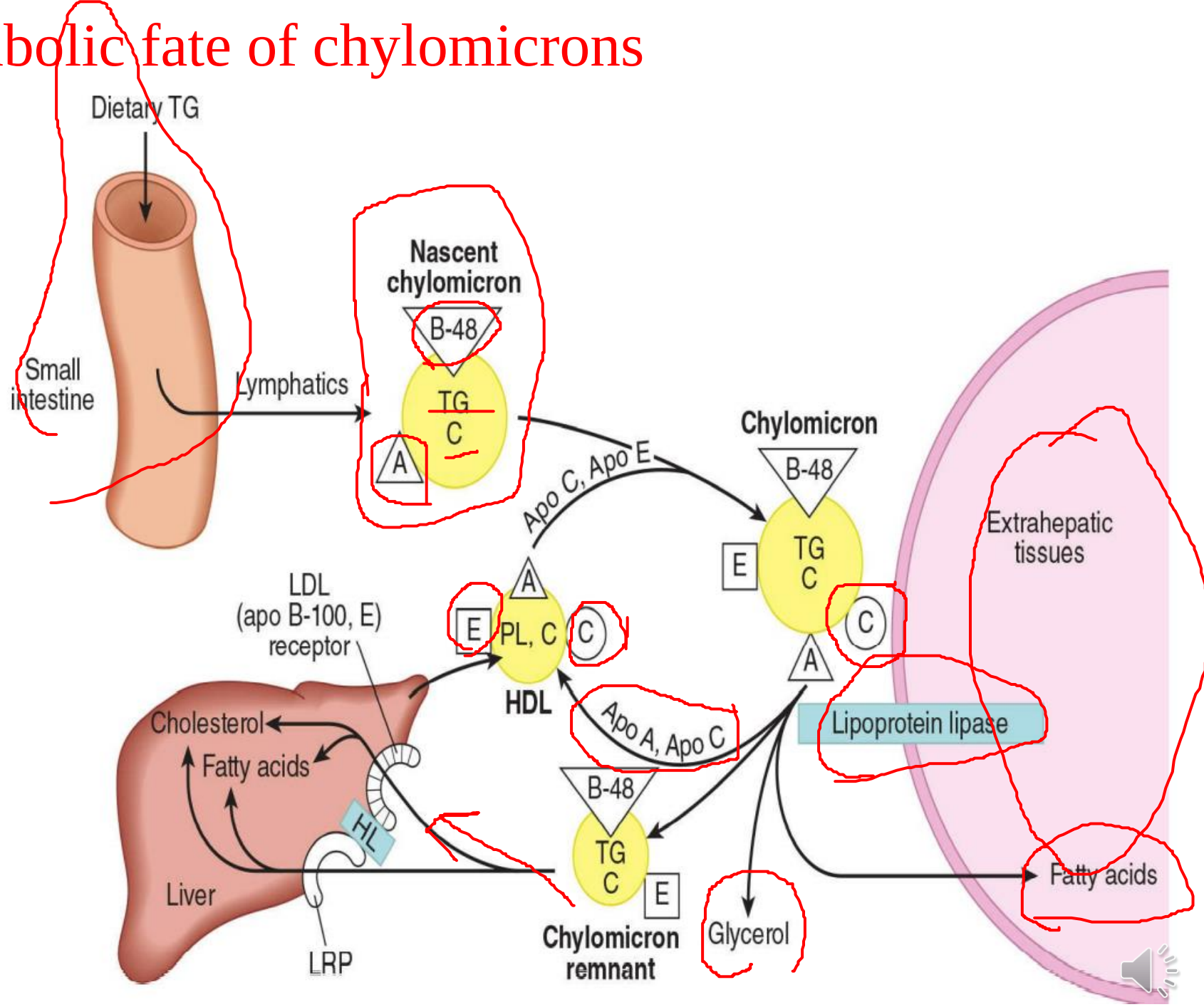
The formation and secretion of (A) chylomicrons by an intestinal cell and (B) very-low-density lipoproteins by a hepatic cell.

Metabolic fate of chylomicrons

The clearance of chylomicrons from the blood is rapid, the half-time of disappearance being under 1 hour in humans. Larger particles are catabolized more quickly than smaller ones.

Fatty acids originating from chylomicron triacylglycerol are delivered mainly to adipose tissue, heart, and muscle (80%), while ~20% goes to the liver.

the liver does not metabolize native chylomicrons or VLDL significantly; thus, the fatty acids in the liver must be secondary to their metabolism in extrahepatic tissues.



Metabolic fate of very-low-density lipoproteins (VLDL) and production of low-density lipoproteins (LDL)

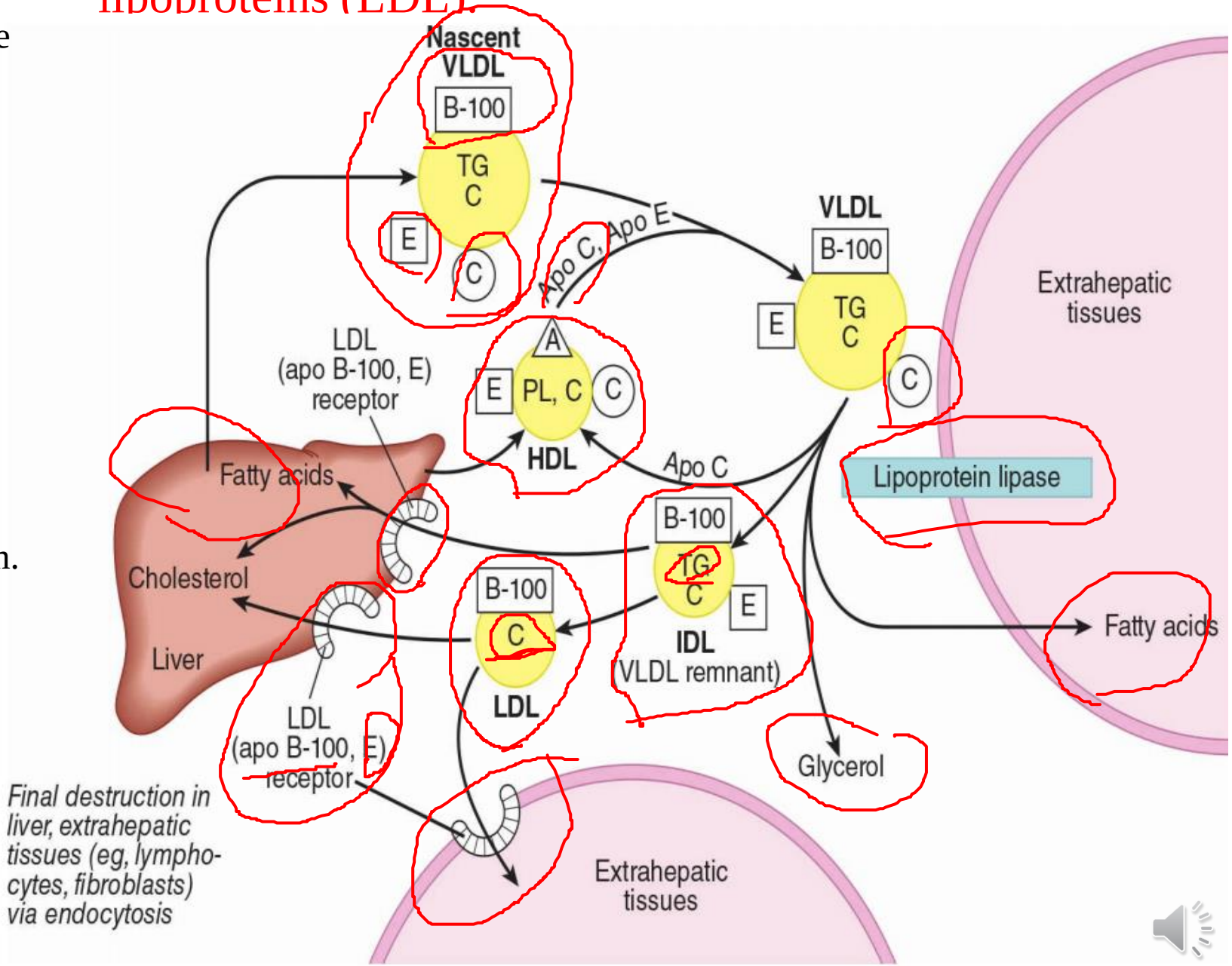
Lipoprotein lipase is an enzyme located on the walls of blood capillaries, anchored to the endothelium by negatively charged proteoglycan chains of heparan sulfate.

Hepatic lipase is bound to the sinusoidal surface of liver cells and is also released by heparin.

phospholipids and apo C-II are required as cofactors for lipoprotein lipase activity, while apo A-II and apo C-III act as inhibitors. Hydrolysis takes place while the lipoproteins are attached to the enzyme on the endothelium.

Heart lipoprotein lipase has a low Km for triacylglycerol, about one-tenth of that for the enzyme in adipose tissue.

In adipose tissue, insulin enhances lipoprotein lipase synthesis in adipocytes and its translocation to the luminal surface of the capillary endothelium.



The Liver Is Responsible for the Uptake of Remnant Lipoproteins

Chylomicron remnants are taken up by the liver by receptor-mediated endocytosis, and the cholesteryl esters and triacylglycerols are hydrolyzed and metabolized. Uptake is mediated by apo E, via two apo E-dependent receptors, the LDL (apo B-100, E) receptor and LDL receptor–related protein-1 (LRP-1).

Hepatic lipase has a dual role:

(1) It acts as a ligand to facilitate remnant uptake and (2) it hydrolyzes remnant triacylglycerol and phospholipid.

THE LIVER PLAYS A CENTRAL ROLE IN LIPID TRANSPORT & METABOLISM

The liver carries out the following major functions in lipid metabolism:

1. Facilitation of the digestion and absorption of lipids by the production of bile.
2. Active synthesis, oxidation of fatty acids, synthesis of triacylglycerols and phospholipids.
3. Conversion of fatty acids to ketone bodies (ketogenesis)
4. Synthesis and metabolism of plasma lipoproteins.

1- Chylomicrons are synthesized from dietary fats in the ER of enterocytes, epithelial cells that line the small intestine. The chylomicrons then move through the lymphatic system and enter the bloodstream via the left subclavian vein. The apolipoproteins of chylomicrons include apoB-48 , apoE, and apoC-II.

2- ApoC-II activates lipoprotein lipase in the capillaries of adipose, heart, skeletal muscle, and lactating mammary tissues, allowing the release of free fatty acids (FFA) to these tissues. Chylomicrons thus carry dietary fatty acids to tissues where they will be consumed or stored as fuel.

3- The remnants of chylomicrons, depleted of most of their triacylglycerols but still containing cholesterol, apoE, and apoB-48, move through the bloodstream to the liver. Receptors in the liver bind to the apoE in the chylomicron remnants and mediate uptake of these remnants by endocytosis.

4- In the liver, the remnants release their cholesterol and are degraded in lysosomes. This pathway from dietary cholesterol to the liver is the exogenous pathway.

5- They are converted to triacylglycerols or cholesteryl esters in the liver and packaged with specific apolipoproteins into very-low-density lipoprotein (VLDL). Excess carbohydrate in the diet can also be converted to triacylglycerols in the liver and exported as VLDL. In addition to triacylglycerols and cholesteryl esters, VLDL contains apoB-100, apoC-I, apoC-II, apoC-III, and apoE. VLDL is transported in the blood from the liver to muscle and adipose tissue.

6- In the capillaries of these tissues, apoC-II activates lipoprotein lipase, which catalyzes the release of free fatty acids from triacylglycerols in the VLDL. Adipocytes take up these fatty acids, reconvert them to triacylglycerols, and store the products in intracellular lipid droplets; myocytes, in contrast, primarily oxidize the fatty acids to supply energy. When the insulin level is high (after a meal), VLDL serves primarily to convey lipids from the diet to adipose tissue for storage. The loss of triacylglycerol converts some VLDL to VLDL remnants, also called intermediatedensity lipoprotein (IDL). Further removal of triacylglycerol from IDL (remnants) produces lowdensity lipoprotein (LDL). Rich in cholesterol and cholesteryl esters, and containing apoB-100 as
its major apolipoprotein,

7- LDL carries cholesterol to extrahepatic tissues such as muscle, adrenal glands, and adipose tissue. These tissues have plasma membrane LDL receptors that recognize apoB100 and mediate uptake of cholesterol and cholesteryl esters.

8- LDL also delivers cholesterol to macrophages, sometimes converting them into foam cells.

9- LDL not taken up by peripheral tissues and cells returns to the liver and is taken up via LDL receptors in the hepatocyte plasma membrane. Cholesterol that enters hepatocytes by this path may be incorporated into membranes, converted to bile acids, or reesterified by ACAT for storage within cytosolic lipid droplets.

HORMONES REGULATE FAT MOBILIZATION

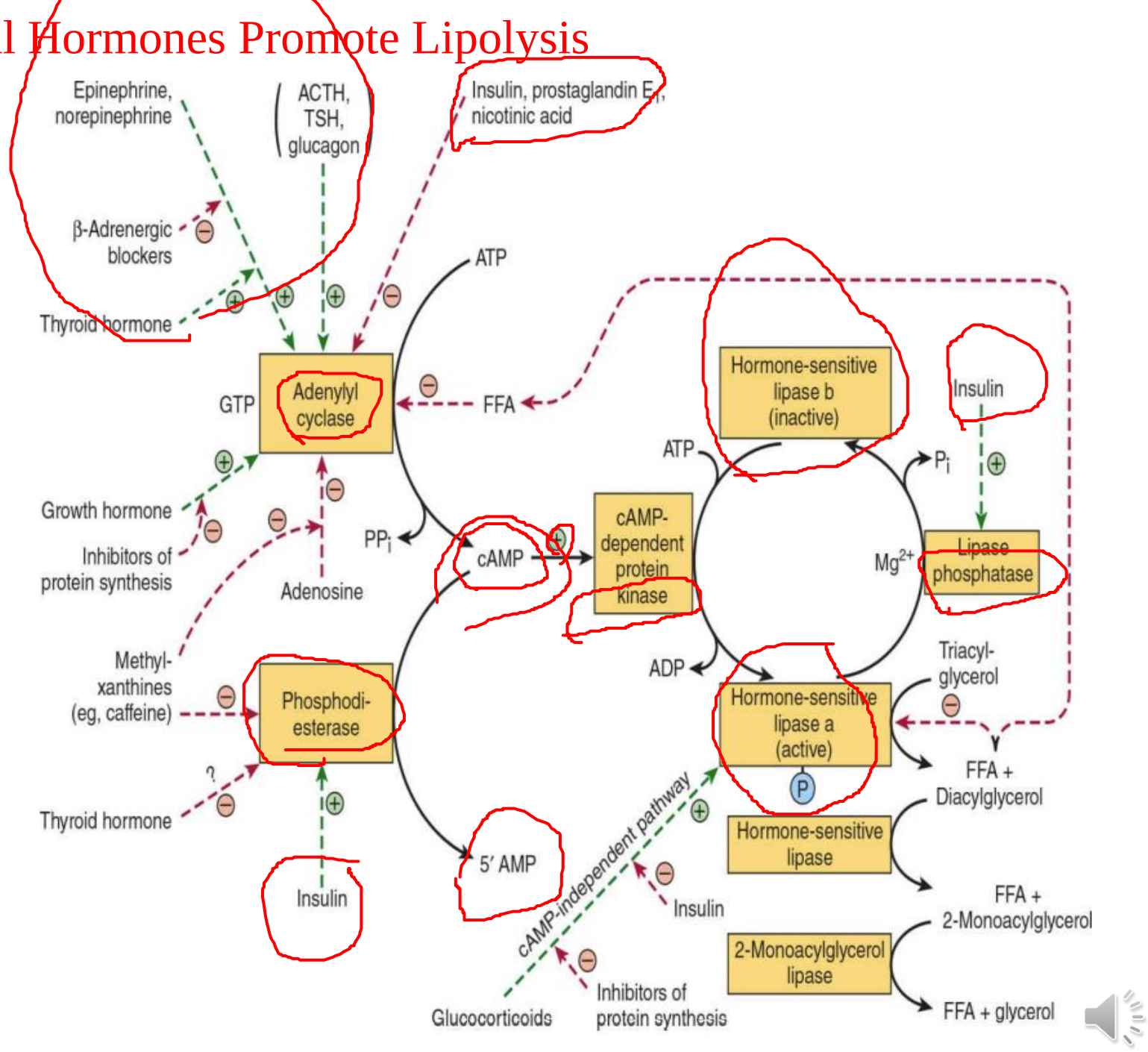
Adipose Tissue Lipolysis Is Inhibited by Insulin the rate of release FFA from adipose tissue is affected by many hormones that influence either the rate of esterification or the rate of lipolysis. Insulin inhibits the release of FFA from adipose tissue, which results in a fall in circulating plasma-free fatty acids. Insulin also enhances lipogenesis and the synthesis of acylglycerol and increases the oxidation of glucose to CO_2 via the pentose phosphate pathway.

Another principal action of insulin in adipose tissue is to inhibit the activity of hormone-sensitive lipase, reducing the release not only of FFA but also of glycerol.

Several Hormones Promote Lipolysis

Other hormones accelerate the release of FFA from adipose tissue and raise the plasma-free fatty acid concentration by increasing the rate of lipolysis of the triacylglycerol stores. These include epinephrine, norepinephrine, glucagon, adrenocorticotropic hormone (ACTH), α- and β-melanocyte-stimulating hormones (MSH), thyroid stimulating hormone (TSH), growth hormone (GH), and vasopressin.

Many of these activate hormone-sensitive lipase. For an optimal effect, most of these lipolytic processes require the presence of glucocorticoids and thyroid hormones.



Cholesterol Synthesis

Cholesterol is present in tissues and in plasma either as free cholesterol or combined with a long-chain fatty acid as cholesteryl ester, the storage form. In plasma, both forms are transported in lipoproteins. Cholesterol is an amphipathic lipid and as such is an essential structural component of membranes, where it is important for the maintenance of the correct permeability and fluidity, and of the outer layer of plasma lipoproteins. Plasma low-density lipoprotein (LDL) is the vehicle that supplies cholesterol and cholesteryl ester to many tissues. Free cholesterol is removed from tissues by plasma highdensity lipoprotein (HDL) and transported to the liver, where it is eliminated from the body either unchanged or after conversion to bile acids in the process known as reverse cholesterol transport . Cholesterol is a major constituent of gallstones. However, its chief role in pathologic processes is as a factor in the development of atherosclerosis .

CHOLESTEROL IS BIOSYNTHESIZED FROM ACETYL-COA

Acetyl-CoA is the source of all carbon atoms in cholesterol.

Cholesterol is a 27-carbon compound consisting of four rings and a side chain. It is synthesized from acetyl-CoA by a lengthy pathway that may be divided into five steps.

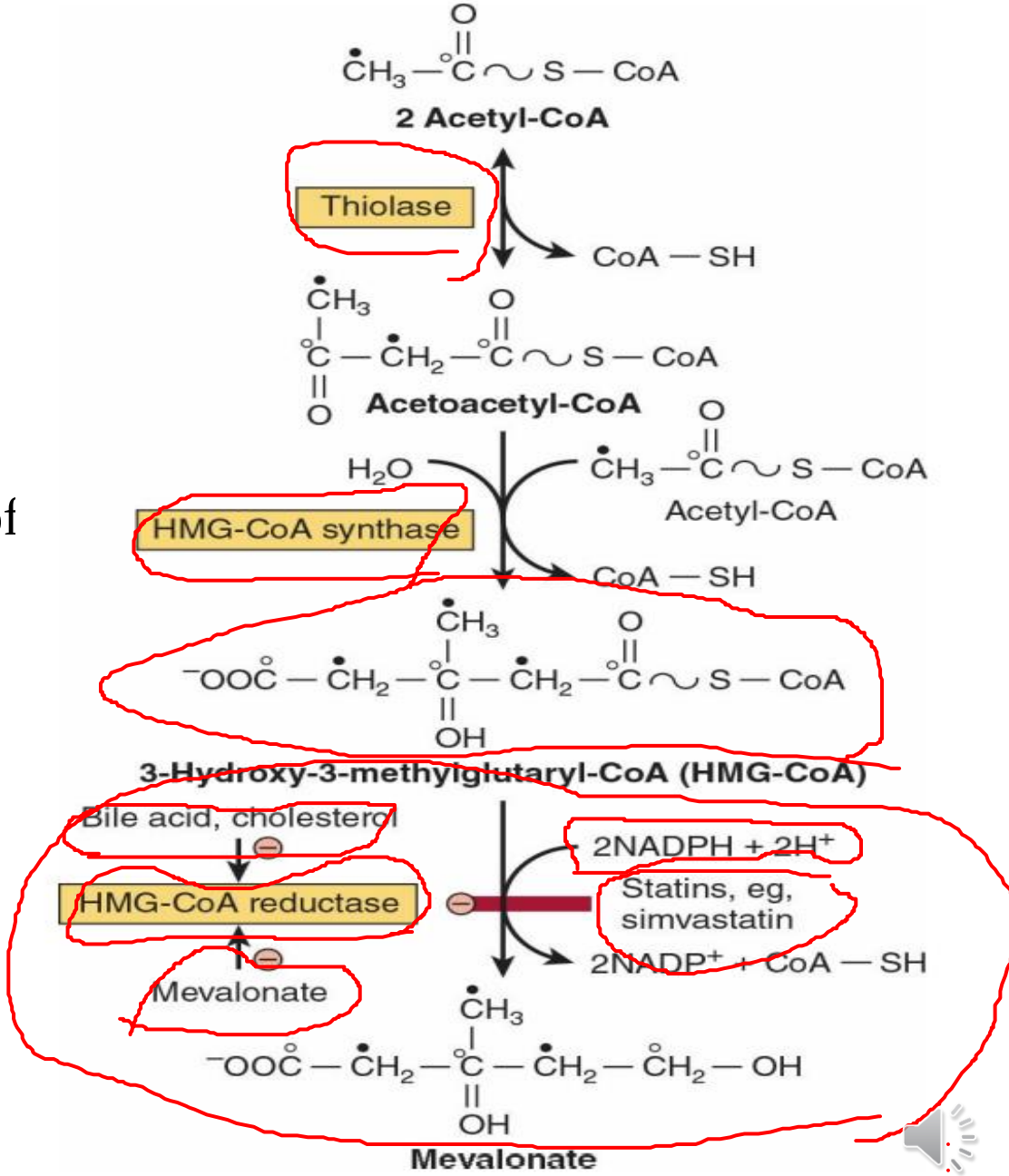
(1) synthesis of mevalonate from acetyl-CoA

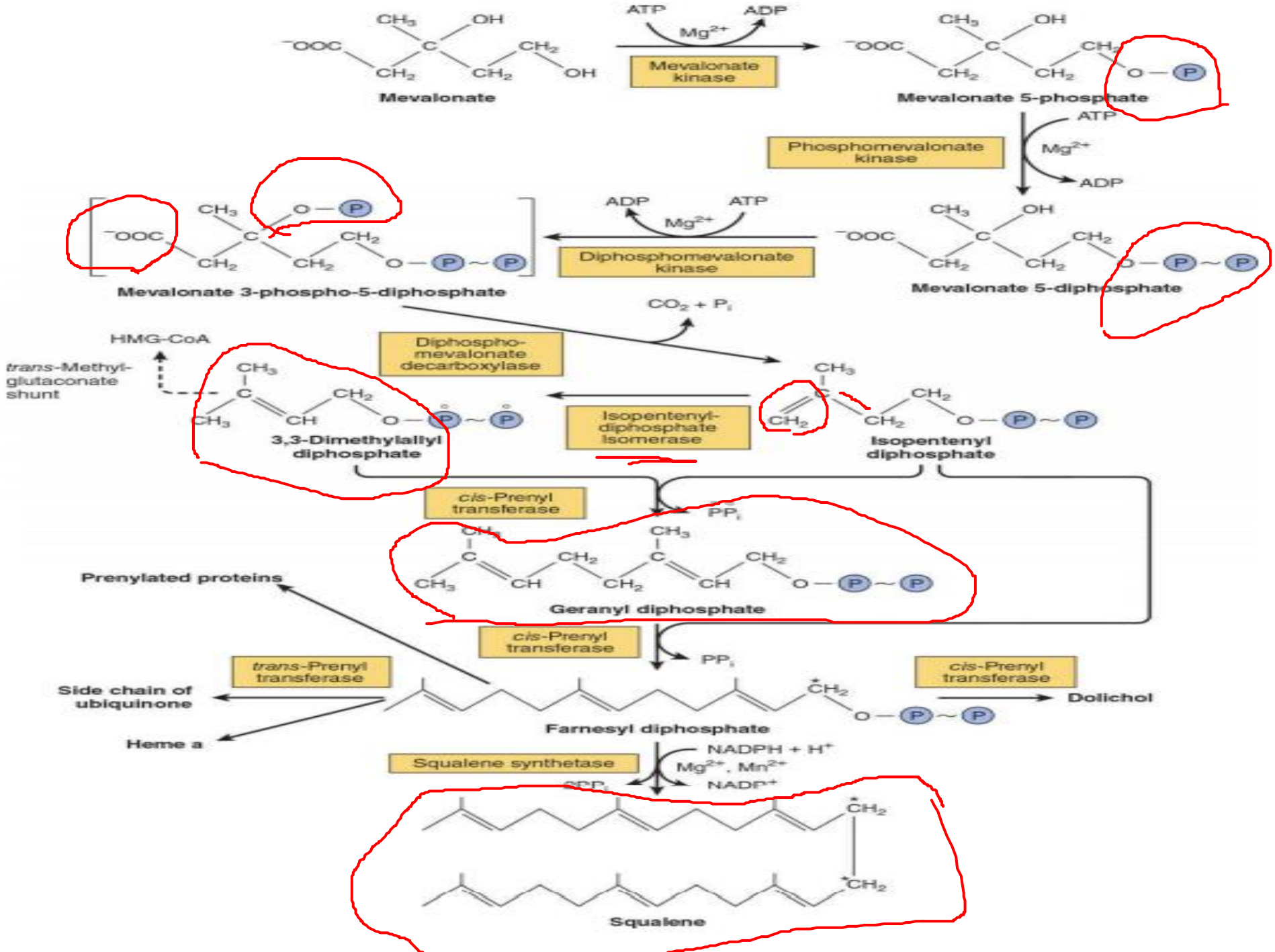
(2) formation of isoprenoid units from mevalonate by loss of CO_2

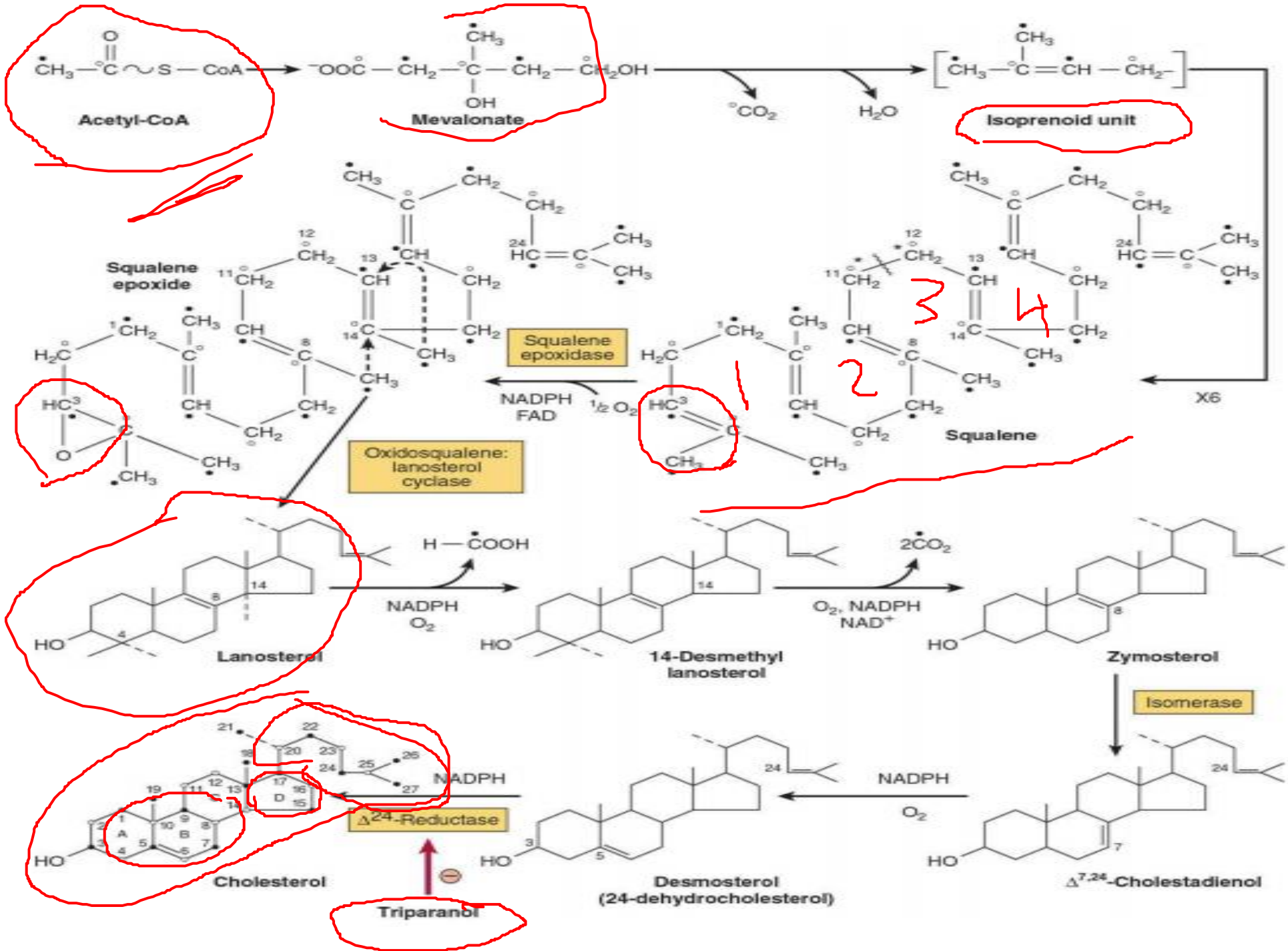
(3) condensation of six isoprenoid units form squalene

(4) cyclization of squalene gives increase to the parent steroid, lanosterol

(5) formation of cholesterol from lanosterol



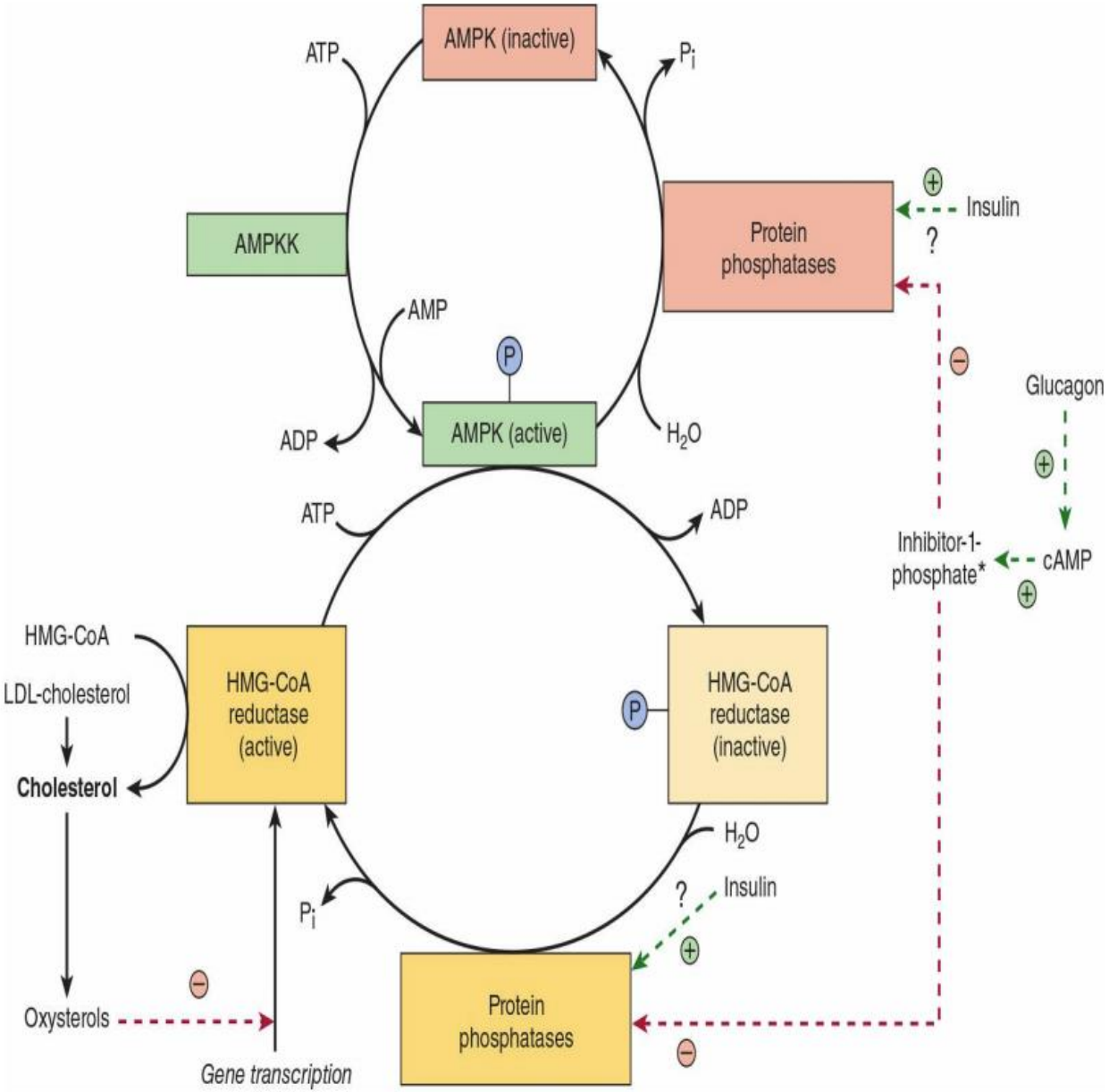

Mevalonate
ATP
ADP
Mg2+
Mevalonate kinase
Mevalonate 5-phosphate
Phosphomevalonate kinase
ATP
Mg2+
ADP
Mevalonate 3-phospho-5-diphosphate
ADP
ATP
Mg2+
Diphosphomevalonate kinase
Mevalonate 5-diphosphate
CO2 + Pi
Diphospho-mevalonate decarboxylase
HMG-CoA
trans-Methyl-glutaconate shunt
3,3-Dimethylallyl diphosphate
Isopentenyl-diphosphate isomerase
Isopentenyl diphosphate
cis-Prenyl transferase
PPi
Geranyl diphosphate
Prenylated proteins
cis-Prenyl transferase
PPi
trans-Prenyl transferase
cis-Prenyl transferase
Side chain of ubiquinone
Dolichol
Farnesyl diphosphate
Heme a
Squalene synthetase
NADPH + H+
Mg2+, Mn2+
NADP+
Squalene


Acetyl-CoA
Mevalonate
$^{\circ}CO_2$
H_2O
Isoprenoid unit
X6
Squalene
Squalene epoxide
Squalene epoxidase
NADPH
FAD
$^1/_2\ O_2$
Oxidosqualene: lanosterol cyclase
Lanosterol
NADPH
O_2
14-Desmethyl lanosterol
$2CO_2$
O_2, NADPH
NAD^+
Zymosterol
Isomerase
$\Delta^{7,24}$-Cholestadienol
NADPH
O_2
Desmosterol
(24-dehydrocholesterol)
NADPH
Δ^{24}-Reductase
Cholesterol
Triparanol

CHOLESTEROL SYNTHESIS IS CONTROLLED BY REGULATION OF HMG-COA REDUCTASE

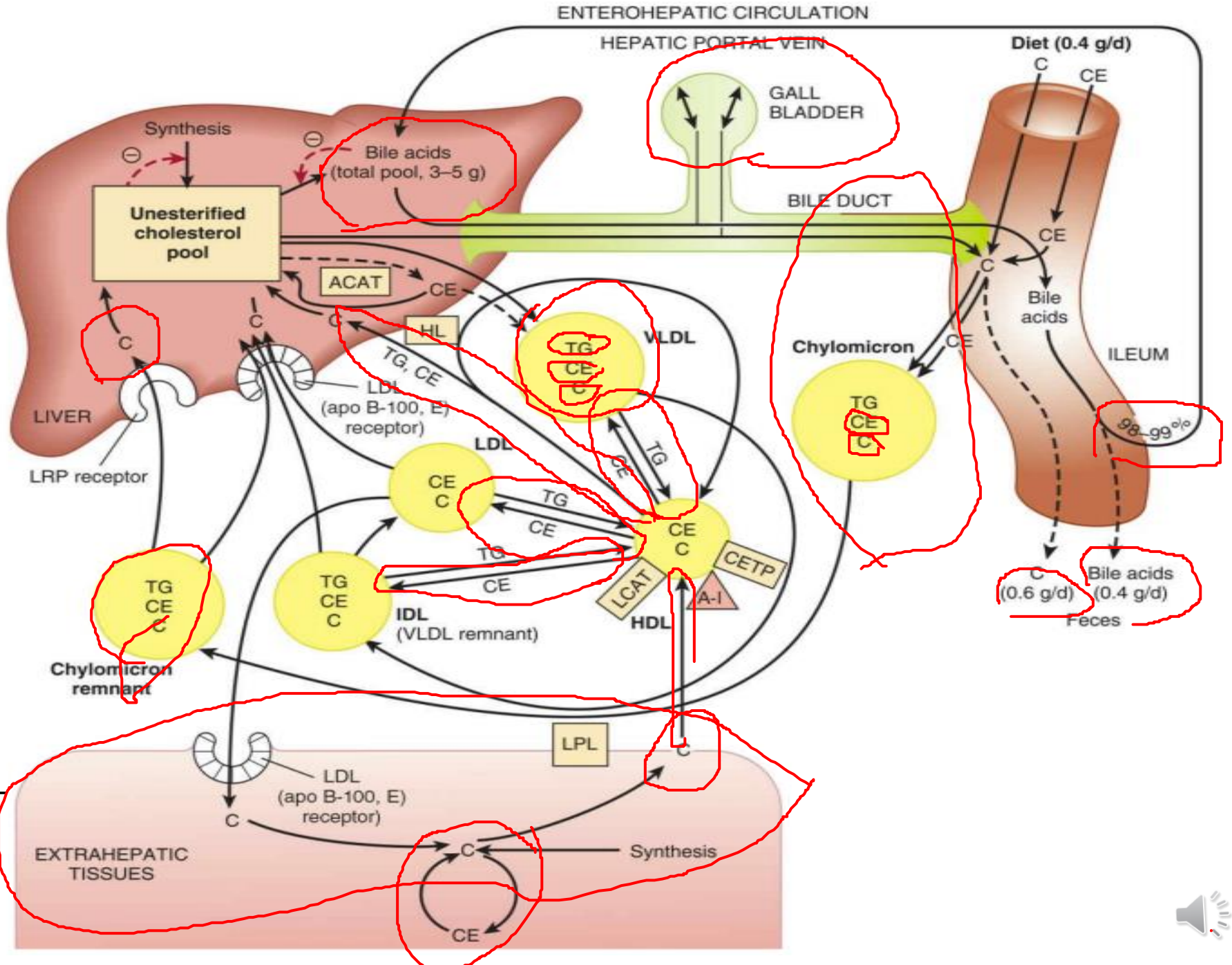
Cholesterol and metabolites repress transcription HMG-CoA reductase mRNA via inhibition of a sterol regulatory element-binding protein (SREBP) transcription factor.

Insulin has a dominant role compared with glucagon. (AMPK, AMP-activated protein kinase; AMPKK, AMP-activated protein kinase kinase.)

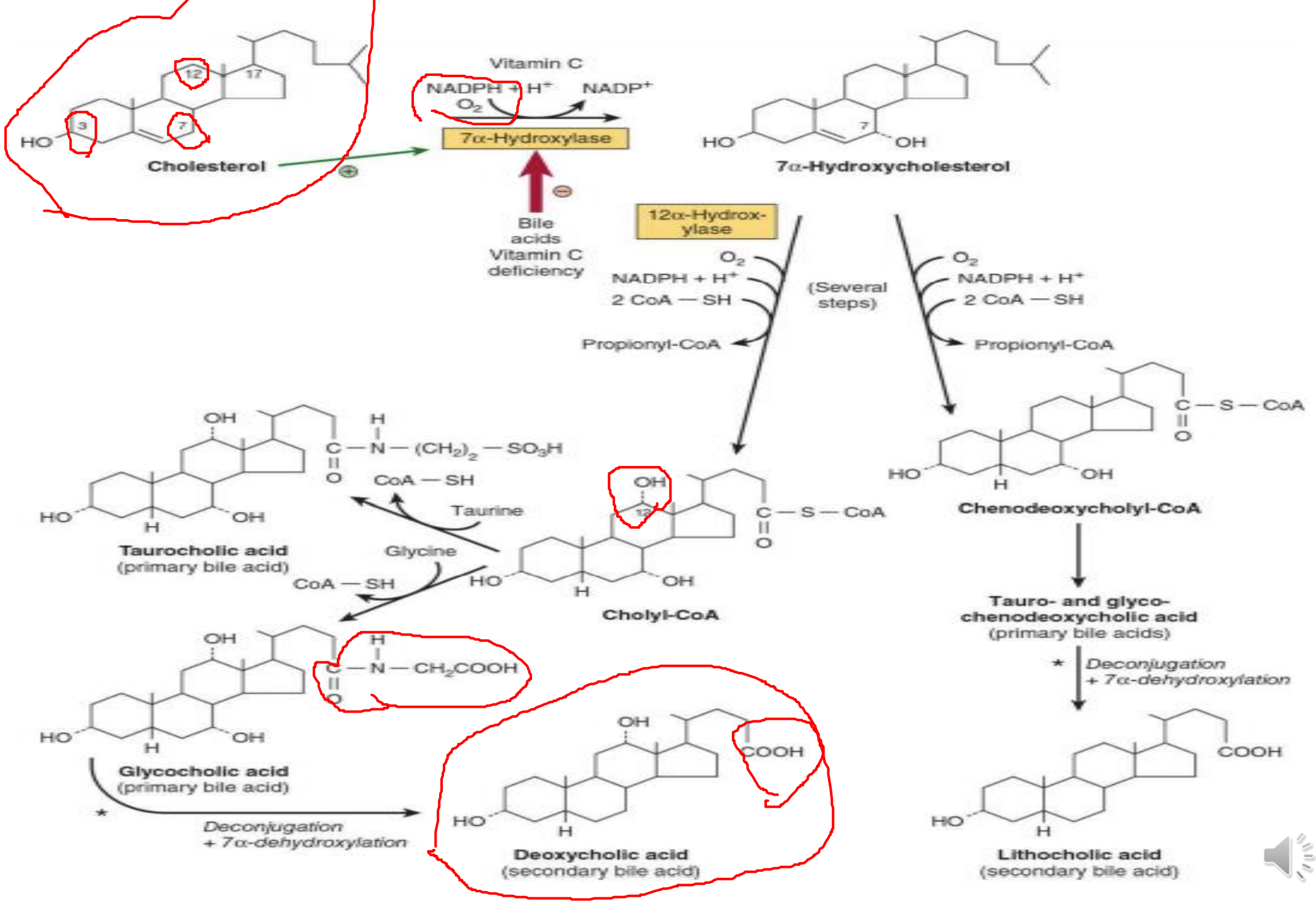


CHOLESTEROL IS TRANSPORTED BETWEEN TISSUES IN PLASMA LIPOPROTEINS

Transport of cholesterol between the tissues in humans. (ACAT, acyl-CoA:cholesterol acyltransferase; A-I, apolipoprotein A-I; C, unesterified cholesterol; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; LRP, LDL receptor–related protein-1; TG, triacylglycerol; VLDL, very-low-density lipoprotein.)



Bile Acids Are Formed From Cholesterol



THANK YOU