Lipid Transport & Storage

By

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Biological functions of lipids

- Storage of energy
- Cell membrane formation
- Prostaglandin precursors
- Bile acids , steroidal hormones, vit.D presursors (cholesterol)
- Chemical messengers
- Maintenance of body temperature

LIPIDS ARE TRANSPORTED IN THE PLASMA AS 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 (free fatty acids) (4%). This latter fraction, the **free fatty acids (FFA), is metabolically**

the most active of the plasma lipids.

Four Major Groups of Plasma Lipoproteins Have Been Identified

(1) **chylomicrons** derived from intestinal absorption of triacylglycerol and other lipids

(2) **Very low density lipoproteins (VLDL, or pre-β-lipoproteins),** derived from the liver for the export of triacylglycerol

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

(4) **high-density lipoproteins (HDL, or α-lipoproteins)** (reverse cholesterol transport system)

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	

Abbreviations: HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low density lipoproteins.

[1]Secreted with chylomicrons but transfers to HDL.

[2]Associated with HDL and HDL subfractions.

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

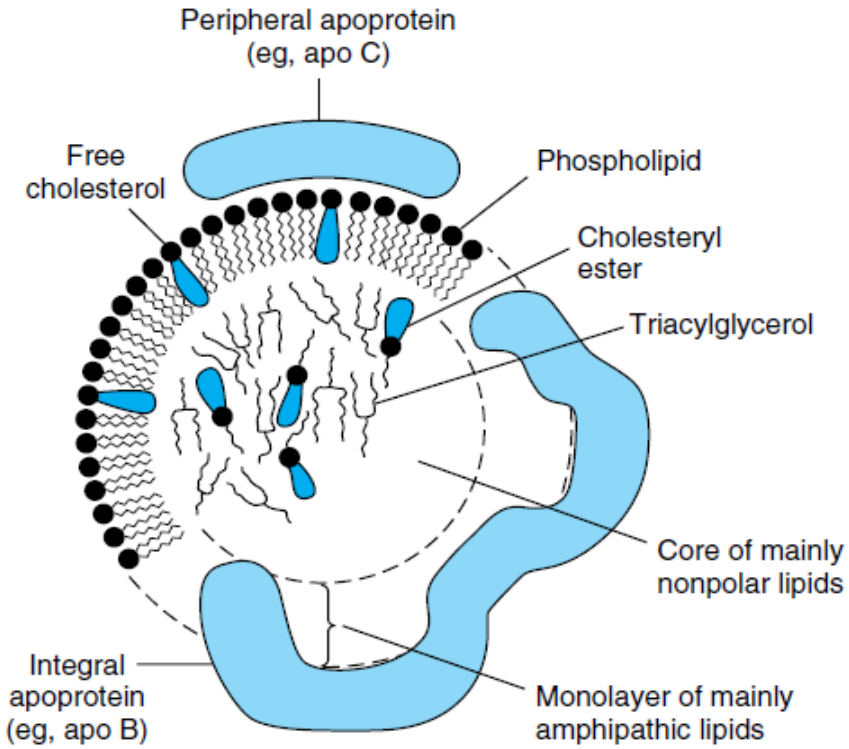


Figure 25–1. Generalized structure of a plasma lipoprotein. The similarities with the structure of the plasma membrane are to be noted. Small amounts of cholesteryl ester and triacylglycerol are to be found in the surface layer and a little free cholesterol in the core.

are also to be found in chyle; howeve plasma **VLDL** are of hepatic origin. **The cles of transport of triacylglycerol fro the extrahepatic tissues.**

There are striking similarities in the formation of chylomicrons by intestin VLDL by hepatic parenchymal cells (Fig haps because—apart from the mamma intestine and liver are the only tissues fr ticulate lipid is secreted. Newly secrete chylomicrons and VLDL contain only a of apolipoproteins C and E, and the full acquired from HDL in the circulation and 25–4). Apo B is essential for ch VLDL formation. In **abetalipoproteine** ease), lipoproteins containing apo B are r lipid droplets accumulate in the intestine

A more detailed account of the fact hepatic VLDL secretion is given below.

CHYLOMICRONS & VERY LOW DENSITY LIPOPROTEINS ARE RAPIDLY CATABOLIZED

Biological functions of apoproteins

(1) they can form part of the structure of the lipoprotein, eg, apo B .

(2) they are enzyme inducers , eg, C-II for lipoprotein lipase, A-I for lecithin:cholesterol acyltransferase, or enzyme inhibitors, eg, apo A-II and apo C-III for lipoprotein lipase, apo C-I for cholesteryl ester transfer protein;

(3) they act as ligands for interaction with lipoprotein receptors in tissues, eg, apo B-100 and apo E for the LDL receptor

FREE FATTY ACIDS ARE RAPIDLY METABOLIZED

The free fatty acids (FFA, nonesterified fatty acids, unesterified fatty acids) arise in the plasma from lipolysis of triacylglycerol in adipose tissue or as a result of the action of lipoprotein lipase during uptake of plasma triacylglycerols into tissues. They are found **in combination with albumin, a very effective solubilizer.**

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, free fatty acids are bound by intracellular **fatty acid-binding proteins.**

CHYLOMICRONS & VLDL ARE RAPIDLY CATABOLIZED

-The clearance of chylomicrons from the blood is rapid, the half-time of disappearance being under 1 hour .

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

TG of Chylomicrons & VLDL Are Hydrolyzed by Lipoprotein Lipase

-Lipoprotein lipase is located on the walls of blood capillaries, anchored to the endothelium. It is not normally found in blood; however, following injection of **heparin, lipoprotein lipase is released .**

-Both **phospholipids and apo C-II are required as** cofactors for lipoprotein lipase activity, while apo A-IIand apo C-III act as inhibitors. TG is hydrolyzed progressively through a diacylglycerol to a monoacylglycerol that is finally hydrolyzed to free fatty acid plus glycerol .

TG of Chylomicrons & VLDL Are Hydrolyzed by Lipoprotein Lipase

-Heart lipoprotein lipase has a **low *Km*** *for TG , about one tenth* of that for the enzyme in adipose tissue. This enables the delivery of fatty acids from TG to be **redirected from adipose tissue to the heart in the starved state when the plasma TG decreases.**

-A similar redirection to the mammary gland occurs during lactation, allowing uptake of lipoprotein triacylglycerol fatty acid for milk fat synthesis. The **VLDL receptor** plays an important part in the delivery of fatty acids from VLDL TG to adipocytes by binding VLDL and bringing it into close contact with lipoprotein lipase.

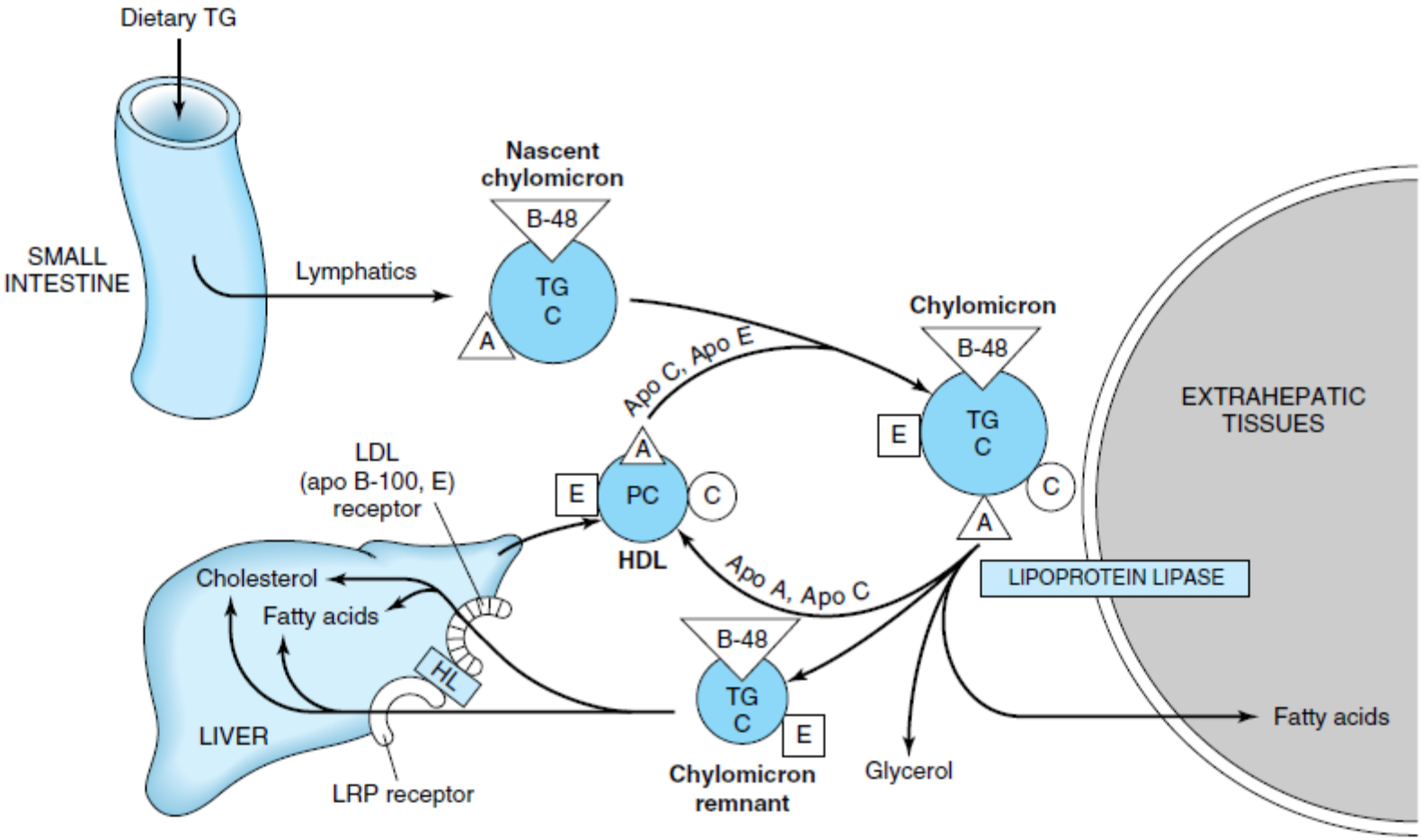


Figure 25–3. Metabolic fate of chylomicrons. (A, apolipoprotein A; B-48, apolipoprotein B-48; ©, apolipoprotein C; E, apolipoprotein E; HDL, high-density lipoprotein; TG, triacylglycerol; C, cholesterol and cholesteryl ester; P, phospholipid; HL, hepatic lipase; LRP, LDL receptor-related protein.) Only the predominant lipids are shown.

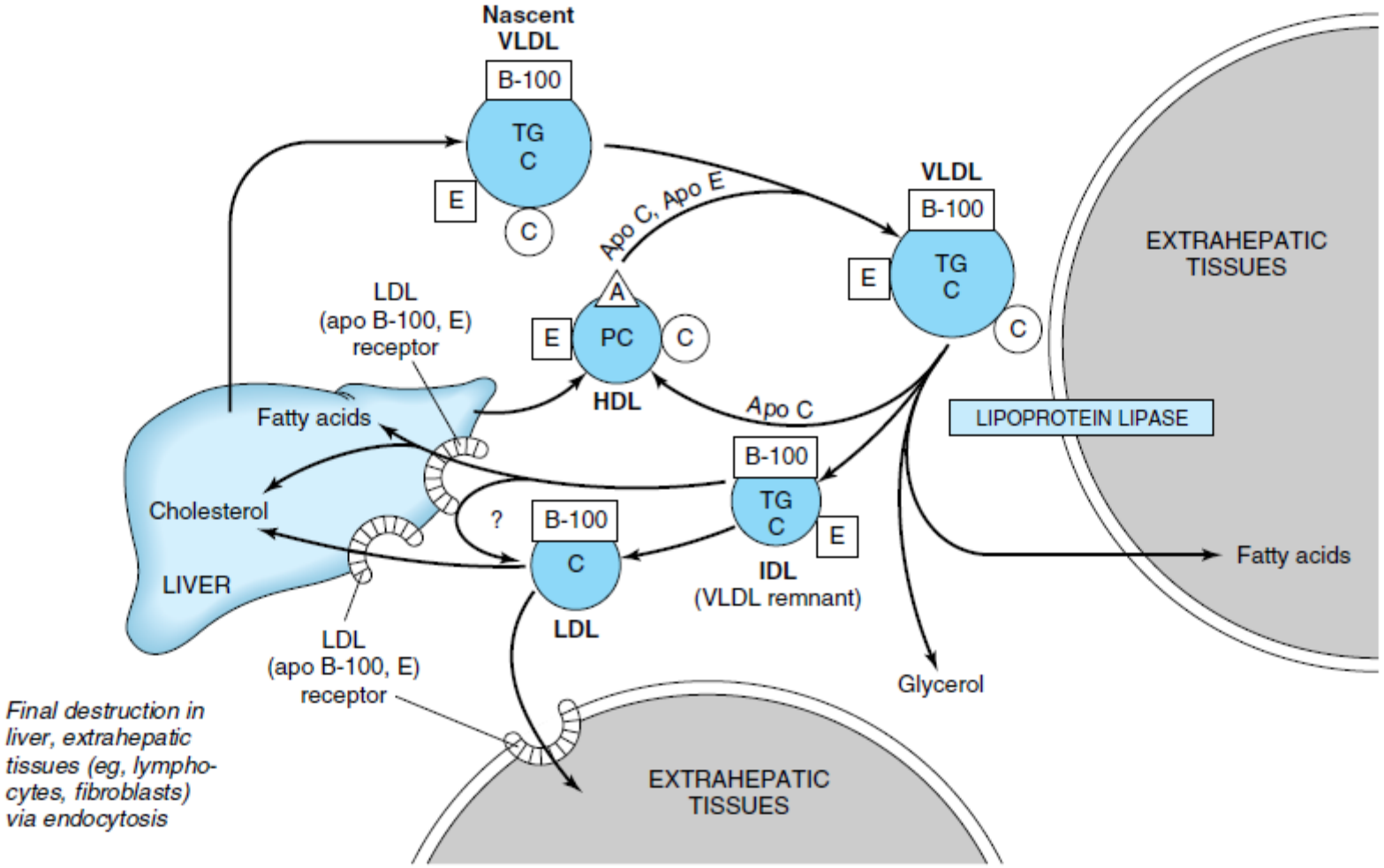


Figure 25–4. Metabolic fate of very low density lipoproteins (VLDL) and production of low-density lipoproteins (LDL). (A, apolipoprotein A; B-100, apolipoprotein B-100; ©, apolipoprotein C; E, apolipoprotein E; HDL, high-density lipoprotein; TG, triacylglycerol; IDL, intermediate-density lipoprotein; C, cholesterol and cholesteryl ester; P, phospholipid.) Only the predominant lipids are shown. It is possible that some IDL is also

HDL TAKES PART IN BOTH LIPOPROTEIN TG & CHOLESTEROL METABOLISM

-HDL is synthesized and secreted from both liver and intestine (Figure 25–5).apo C and apo E are synthesized in the liver and transferred from liver HDL to intestinal HDL when the latter enters the plasma.

-A major function of HDL is to act as a repository for the apo C and apo E required in the metabolism of chylomicrons and VLDL.

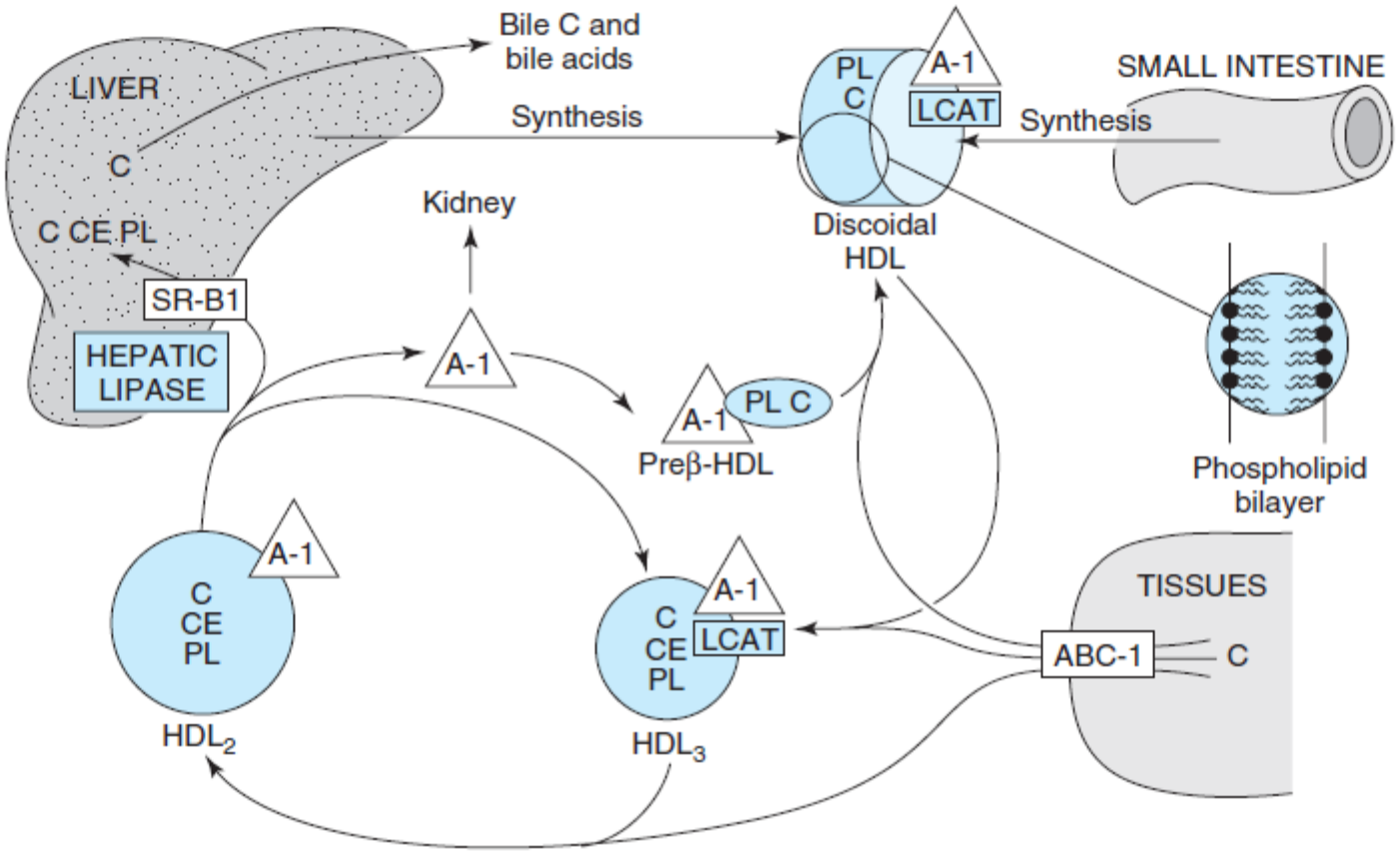


Figure 25–5. Metabolism of high-density lipoprotein (HDL) in reverse cholesterol transport. (LCAT, lecithin:cholesterol acyltransferase; C, cholesterol; CE, cholesteryl ester; PL, phospholipid; A-I, apolipoprotein A-I; SR-B1, scavenger receptor B1; ABC-1, ATP binding cassette transporter 1.) Preβ-HDL, 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 concentra-

THE LIVER PLAYS A CENTRAL ROLE IN LIPID TRANSPORT & METABOLISM

(1) It facilitates the digestion and absorption of lipids

(2) The liver has active enzyme systems for synthesizing and oxidizing fatty acids and for synthesizing TG and phospholipids

(3) It converts fatty acids to ketone bodies (ketogenesis)

(4) It plays an integral part in the synthesis and metabolism of plasma lipoproteins

Hepatic VLDL Secretion Is Related to Dietary & Hormonal Status

The fatty acids used are derived from two possible sources: (1) synthesis within the liver from acetyl-CoA derived mainly from carbohydrate and (2) uptake of free fatty acids from the circulation.

Factors that enhance both the synthesis of triacylglycerol and the secretion of VLDL by the liver include :

Hepatic VLDL Secretion Is Related to Dietary & Hormonal Status

(1)the fed state rather than the starved state;

(2) the feeding of diets high in carbohydrate (particularly if they contain sucrose or fructose), leading to high rates of lipogenesis and esterification of fatty acids;

(3) high levels of circulating free fatty acids;

(4) ingestion of ethanol.

(5) the presence of high concentrations of insulin and low concentrations of glucagon, which enhance

fatty acid synthesis and esterification and inhibit

their oxidation

The Provision of Glycerol 3-Phosphate Regulates Esterification: Lipolysis Is Controlled by Hormone-Sensitive Lipase (Figure 25–7)

-TG is synthesized from acyl-CoA and glycerol 3-phosphate .

-Because the enzyme **glycerol kinase is not expressed in adipose tissue, glycerol** cannot be utilized for the provision of glycerol 3-phosphate, which must be supplied by glucose via glycolysis.

Triacylglycerol undergoes hydrolysis by a **hormonesensitive lipase to form free fatty acids and glycerol.**

and may account for the increased metabolic clearance in this condition. Ethanol will also inhibit the metabolism of some drugs, eg, barbiturates, by competing for cytochrome P450-dependent enzymes.

$$CH_3—CH_2—OH + NADPH + H^+ + O_2 \xrightarrow{\text{MEOS}} CH_3—CHO + NADP^+ + 2H_2O$$

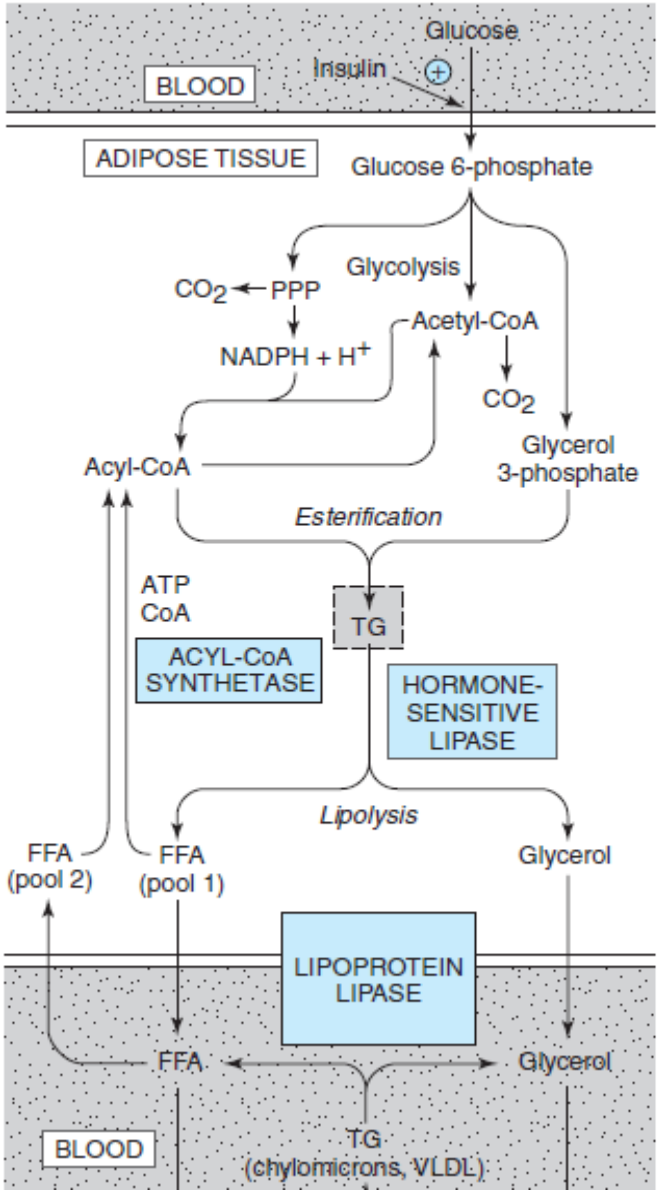
Ethanol → **Acetaldehyde**

In some Asian populations and Native Americans, alcohol consumption results in increased adverse reactions to acetaldehyde owing to a genetic defect of mitochondrial aldehyde dehydrogenase.

ADIPOSE TISSUE IS THE MAIN STORE OF TRIACYLGLYCEROL IN THE BODY

The triacylglycerol stores in adipose tissue are continually undergoing lipolysis (hydrolysis) and reesterification (Figure 25–7). These two processes are entirely different pathways involving different reactants and enzymes. This allows the processes of esterification or lipolysis to be regulated separately by many nutritional, metabolic, and hormonal factors. The resultant of these two processes determines the magnitude of the free fatty acid pool in adipose tissue, which in turn determines the level of free fatty acids circulating in the plasma. Since the latter has most profound effects upon the metabolism of other tissues, particularly liver and muscle, the factors operating in adipose tissue that regulate the outflow of free fatty acids exert an influence far beyond the tissue itself.

The Provision of Glycerol 3-Phosphate



HORMONES REGULATE FAT MOBILIZATION

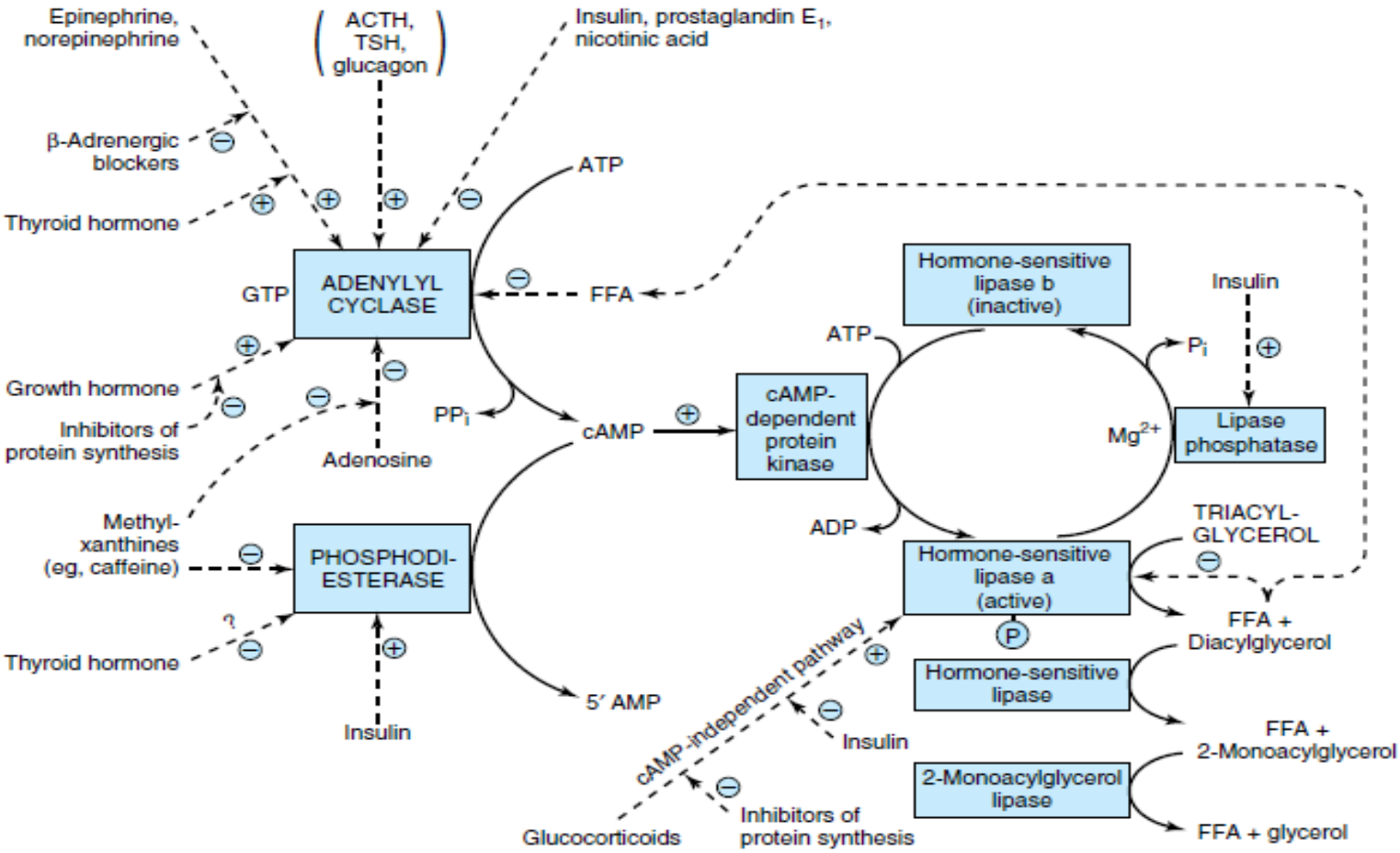


Figure 25–8. Control of adipose tissue lipolysis. (TSH, thyroid-stimulating hormone; FFA, free fatty acids.) Note the cascade sequence of reactions affording amplification at each step. The lipolytic stimulus is "switched off" by removal of the stimulating hormone; the action of lipase phosphatase; the inhibition of the lipase and adenylyl cyclase by high concentrations of FFA; the inhibition of adenylyl cyclase by adenosine; and the removal of cAMP by the action of phosphodiesterase. ACTH, TSH, and glucagon may not activate adenylyl cyclase in vivo, since the concentration of each hormone required in vitro is much higher than is found in the circulation. Positive (⊕) and negative (⊖) regulatory effects are represented by broken lines and substrate flow by solid lines.