Biochemistry II third stage

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Lecture 3

Lipid Transport and Storage

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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.

In human, lipoproteins mediate the 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 hyperlipoproteinemias.

The most common of these is in diabetes mellitus, where insulin deficiency causes excessive mobilization of FFA leading to hypertriacylglycerolemia. Most other pathologic conditions affecting lipid transport are due primarily to inherited defects, some of which cause hypercholesterolemia and premature atherosclerosis. Obesity particularly abdominal obesity is a risk factor for increased mortality, hypertension, type 2 diabetes mellitus, hyperlipidemia and hyperglycemia.

Lipids are transported in the plasma as lipoproteins

Plasma lipoproteins are spherical macromolecular complexes of lipids and specific proteins (apolipoproteins or apoproteins). The lipoprotein particles include chylomicrons (CM), very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (**HDL**). They differ in lipid and protein composition, size, density, and site of origin (Table 1-1).

Lipoproteins are composed of a neutral lipid core [containing **triglycerides** (TGs) and **cholesteryl esters** (CE)] surrounded by a shell of **amphipathic apolipoproteins**, **phospholipid** (PL), and **nonesterified (free) cholesterol** (C). These amphipathic compounds are oriented so that their polar portions are exposed on the surface of the lipoprotein, thus making the particle soluble in aqueous solution. The TGs and cholesterol carried by the lipoproteins are obtained either from the diet (exogenous source) or from de novo synthesis (endogenous source).

Chylomicrons are the lipoprotein particles lowest in density and largest in size, and contain the highest percentage of lipid and the lowest percentage of protein. VLDLs and LDLs are successively denser, having higher ratios of protein to lipid. **HDL** particles are **the densest**. Plasma lipoproteins can be separated **on the basis** of their electrophoretic mobility.

Table (1-1) Characteristics of lipoproteins

Lipoprotein	Source	Composition (% mass)				Apolipoprotein	Electrophoretic mobility
		Pro	Cho	Tg	PL		
Chylomicrons	Gut	1	4	90	5	A, B, C, E	Origin
VLDL	Liver	8	25	55	12	B, C, E	Pre-β
LDL	VLDL via IDL	20	55	5	20	B	β
HDL	Gut/liver	50	20	5	25	A, C, E	α

Apolipoproteins: The apolipoproteins associated with lipoprotein particles have a number of diverse functions, such as providing **recognition sites** for cell surface receptors, and serving as **activators or coenzymes** for enzymes involved in lipoprotein metabolism. Some of the apolipoproteins are required as essential **structural components** of the particles and cannot be removed. Apolipo proteins are divided by structure and function into five major classes, A through E, with most classes having subclasses, for example, apolipoprotein or **apo A-I** and apo C-II.

Metabolism of chylomicrons (CM)

Chylomicrons are assembled in intestinal mucosal cells and carry **exogenous** dietary TGs, cholesterol, fat soluble vitamins, and cholesteryl esters to the peripheral tissues (Figure 1-1). Triacylglycerols (TAGs) account for close to 90% of the lipids in a CM.

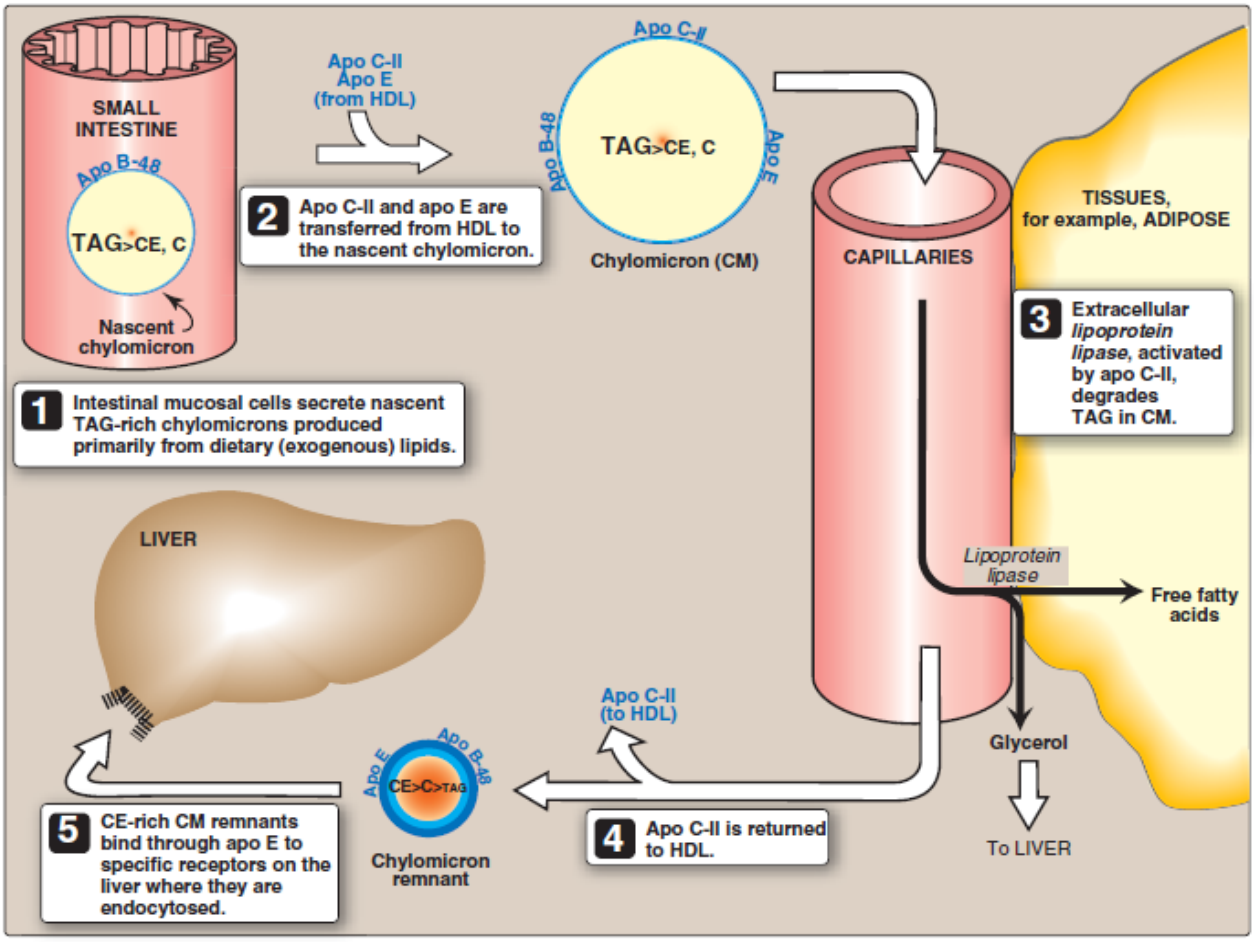

Figure (1-1) Metabolism of chylomicrons

Apolipoprotein B-48 is unique to CMs. Apo B-48 is so named because it constitutes 48% of the protein coded for by the gene for apo B. Apo B-100, which is synthesized by the liver and found in VLDL and LDL, represents the entire protein coded for by the apo B gene. The enzymes involved in triacylglycerol, cholesterol, and phospholipid synthesis are located in the smooth **endoplasmic reticulum** (**ER**).

Apolipoproteins and lipid into CMs requires microsomal TGs transfer protein, which loads apo B-48 with lipid. This occurs before transition from the ER to the

Golgi, where the particles are packaged in secretory vesicles. These fuse with the plasma membrane releasing the lipoproteins, which then enter the lymphatic system and, ultimately, the blood.

The particle released by the intestinal mucosal cell is called a "nascent" CM because it is functionally incomplete. When it reaches the plasma, the particle is rapidly modified, receiving **apolipoprotein E** (which is recognized by hepatic receptors) and apolipoprotein C. The latter includes **apo C-II**, which is necessary for the activation of lipoprotein lipase, the enzyme that degrades the TGs contained in the chylomicron. The **source** of **these apolipoproteins** is circulating **HDL**.

Lipoprotein lipase synthesis and transfer to the luminal surface of the capillary is stimulated by insulin. Also, lipoprotein lipase, activated by apo C-II on circulating lipoprotein particles, hydrolyzes the triacylglycerol contained in these particles to yield fatty acids and glycerol. The fatty acids are stored (by the adipose) or used for energy (by the muscle). Glycerol is used by the liver, for example, in lipid synthesis, glycolysis, or gluconeogenesis.

As the CM circulates and more than 90% of the TGs in its core is degraded by lipoprotein lipase, the particle decreases in size and increases in density. In addition, the **C apoproteins** (but not apo E) are returned to **HDL**. The remaining particle, called a "remnant," is rapidly removed from the circulation by the liver, whose cell membranes contain lipoprotein receptors that recognize apo E (Figure 1-1).

Chylomicron remnants bind to these receptors and are taken into the hepatocytes by endocytosis. The endocytosed vesicle then fuses with a lysosome, and the apolipoproteins, cholesteryl esters, and other components of the remnant are hydrolytically degraded, releasing amino acids, free cholesterol, and fatty acids. The receptor is recycled.

Metabolism of VLDL

VLDLs are produced in the liver (Figure 1-2). They are composed predominantly of endogenous TGs (approximately 60%) and their function is to carry this lipid from the liver (site of synthesis) to the peripheral tissues. There, the TGs is degraded by lipoprotein lipase, as discussed for chylomicrons. VLDL are secreted directly into the blood by the liver as nascent VLDL particles containing apo B-100. They must obtain **apo C-II** and **apo E** from circulating **HDL** (Figure 1-2). As with chylomicrons, **apo C-II** is required for activation of lipoprotein lipase.

As VLDL pass through the circulation, TG is degraded by lipoprotein lipase, causing the VLDL to decrease in size and become denser. Surface components, including the **C** and **E** apoproteins, are returned to **HDL**, but the particles retain apo B-100. With these modifications, the VLDL is converted in the plasma to LDL. Intermediatesized particles, the intermediate density lipoproteins (IDL) or VLDL remnants, are observed during this transition. IDLs can also be taken up by cells through receptor mediated endocytosis that uses **apo E** as the ligand.

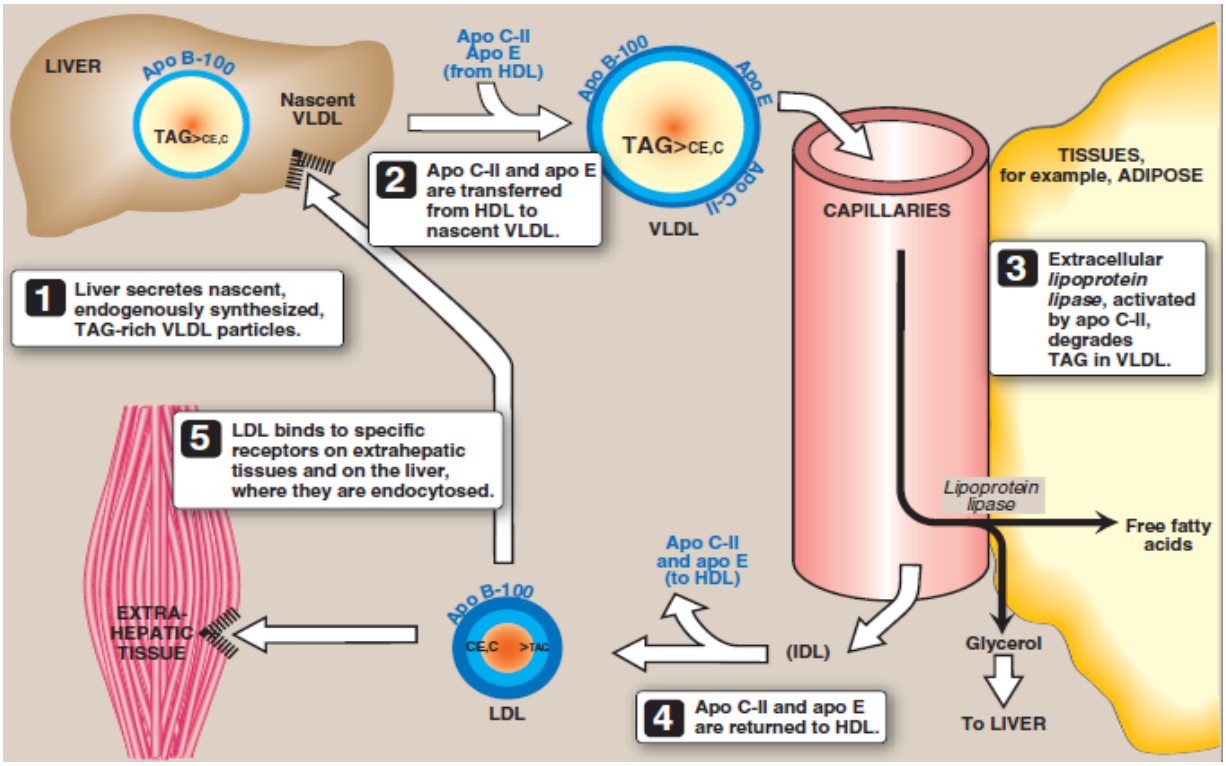

Figure (1-2) Metabolism of VLDL and LDL

Metabolism of LDL

LDL particles contain much less TG than their VLDL predecessors, and have a high concentration of cholesterol and cholesteryl esters. The primary function of LDL particles is to provide cholesterol to the peripheral tissues (or return it to the liver). [LDL particles named as bad cholesterol]. They do so by binding to cell surface membrane LDL receptors that recognize apo B-100 (but not apo B-48). Because these LDL receptors can also bind apo E, they are known as apo B-100/apo E receptors.

The chylomicron remnant-, IDL-, and LDL-derived cholesterol **affects** cellular cholesterol content in several ways:

First, HMG CoA reductase is inhibited by high cholesterol, as a result of which, de novo cholesterol synthesis decreases.

Second, synthesis of new LDL receptor protein is reduced by decreasing the expression of the LDL receptor gene, thus limiting further entry of LDL cholesterol into cells.

Third, if the cholesterol is not required immediately for some structural or synthetic purpose, it is esterified by **acyl CoA : cholesterol acyltransferase (ACAT)**. **ACAT** transfers a fatty acid from a fatty acyl CoA derivative to cholesterol, producing a cholesteryl ester that can be stored in the cell. The activity of **ACAT** is enhanced in the presence of increased intracellular cholesterol.

Metabolism of HDL

HDL particles are formed in blood by the addition of lipid to **apo A-1**, an apolipo protein made by the **liver** and **intestine** and secreted into blood. HDL perform a number of important functions, including the following:

1. HDL is a reservoir of apolipoproteins: HDL particles serve as a circulating reservoir of apo C-II (the apolipoprotein that is transferred to VLDL and CMs, and

is an activator of lipoprotein lipase), and **apo E** (the apolipoprotein required for the receptor mediated endocytosis of IDLs and CMs remnants).

2. HDL uptake of unesterified cholesterol: **Nascent HDL** are disk shaped particles containing primarily phospholipid [largely phosphatidylcholine (PC)] and apolipoproteins A, C, and E. They **take up** cholesterol from non-hepatic (**peripheral**) tissues and **return it to the liver** as cholesteryl esters (Figure 1-3). [HDL particles named as good cholesterol].

3. Esterification of cholesterol: When cholesterol is taken up by **HDL**, it is immediately esterified by the plasma enzyme lecithin:cholesterol acyltransferase (**LCAT**, also known as **PCAT**, in which "P" stands for phosphatidylcholine). This enzyme is synthesized by the liver. LCAT binds to **nascent HDL**, and is activated by **apo A-I**. LCAT transfers the fatty acid from carbon 2 of phosphatidylcholine to cholesterol. This produces a hydrophobic cholesteryl ester, which is sequestered in the core of the HDL, and lysophosphatidylcholine (lyso-PC), which binds to albumin.

As the discoidal nascent HDL accumulates cholesteryl esters, it first becomes a spherical, relatively cholesteryl ester **poor HDL3** and, eventually, a cholesteryl ester **rich HDL2** particle that carries these esters to the liver.

4. Reverse cholesterol transport: The selective transfer of cholesterol **from peripheral cells** to **HDL**, and **from HDL** to the **liver** for bile acid synthesis or disposal via the bile, and **to steroidogenic cells** for hormone synthesis, is a key component of cholesterol homeostasis. This is, in part, the basis for the inverse relationship seen between **plasma HDL** concentration and atherosclerosis, and for HDL's designation as the "**good**" cholesterol carrier.

The uptake of cholesteryl esters by the liver is mediated by a cell-surface receptor, SR-B1 (scavenger receptor class B type 1) that binds HDL. Hepatic lipase, with its

ability to degrade both TAG and phospholipids, also participates in the conversion of **HDL2** to **HDL3**.

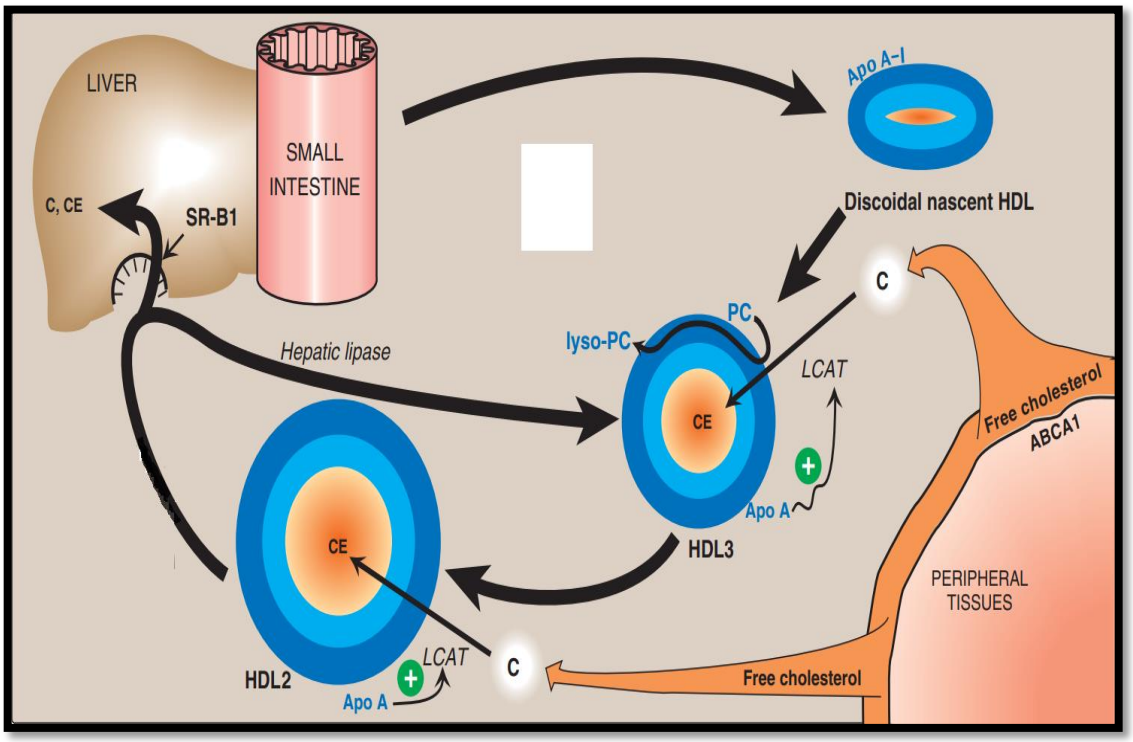

Figure (1-3) Metabolism of HDL

The liver plays a central role in lipid transport & metabolism

1. It facilitates the **digestion** and **absorption** of **lipids** by the **production of bile**, which contains cholesterol and bile salts synthesized within the liver de novo or after uptake of lipoprotein cholesterol.

2. It actively **synthesizes** and **oxidizes fatty acids** and also **synthesizes triacylglycerols** 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**.

Adipose tissue is the main store of triacylglycerol in the body

Triacylglycerols are stored in adipose tissue in large lipid droplets and are continually undergoing lipolysis (hydrolysis) and reesterification. 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 balance between these two processes determines the magnitude of the FFA pool in adipose tissue, which in turn determines the level of FFA circulating in the plasma.

Triacylglycerol undergoes hydrolysis by a hormone-sensitive lipase to form FFA and glycerol. This lipase is **distinct** from lipoprotein lipase, which catalyzes **lipoprotein triacylglycerol** hydrolysis before its uptake into extrahepatic tissues.