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Knowing the basic mechanisms of lipid metabolism

Conociendo los mecanismos básicos del metabolismo de los lípidos

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INTRODUCTION

Lipids are biomolecules that are only found in living beings. The way and degree of interaction of these biomolecules with water determine important aspects in some biological processes. For example, the amphipathic character of phospholipids favors the efficient formation of micelles and bilayers. On the other hand, the nonpolar characteristic of fatty acids and triglycerides requires specific transport mechanisms in the blood, through plasma lipoproteins.

Lipoproteins are complex macromolecular structures which are formed by a shell and a core. The shell is composed by phospholipids and free cholesterol, whose polar portions (electrically charged) are oriented outwards, making them soluble in water and therefore transportable. On the other hand, the hydrophobic lipid core (insoluble in water) contains esterified CHOL and TG *(Figure 1)*. The outer shell contains proteins called apolipoproteins,[1] which are characterized by having both hydrophobic and hydrophilic regions, allowing them to maintain at the same time, physical relationships with both, the lipid components, and the aqueous environment.

Based on their density (amount of mass in relation to volume), lipoproteins can be classified and separated by ultracentrifugation in larger lipoproteins with lower density, with a high lipid content and other, smaller, and denser, with a higher content of proteins. Ranging from larger to smaller, there are chylomicrons (CHY), VLDL (very low-density lipoproteins), IDL (intermediate density lipoproteins), LDL (low density lipoproteins), and HDL (high density lipoproteins).[2] Different sizes and densities of several subspecies of VLDL, LDL, IDL, and HDL have been defined, and in turn subdivided in several classes, which have relevance from the clinical point of view.

Apolipoproteins are designated by letters and numbers: A-I, A-II, A-IV, A-V, B48, B100, C-I, C-II, C-III, D, E, among others, whose role is less known.[3] Apolipoproteins have four important functions, through which they regulate lipoprotein metabolism.

1. Production and secretion of lipoproteins (Apo A-I, B48, and B100).
2. Structural integrity and rigidity of the lipoprotein shell (Apo B, E, A-I, and A-II).
3. Activation or inhibition of enzymatic activity (A-I, A-V, C-I, C-II, and C-III).
4. Function as ligands for specific receptors (Apo A-I, B100, and E).

The functions of many lipoproteins are well established. In the first place, they yield to an efficient transport of TG from the intestine (exogenous triglycerides) and liver (endogenous triglycerides) to the tissues for their storage and obtention of energy, as occurs in adipose tissue or skeletal muscle. Secondly, the transport of CHOL to peripheral tissues, serves to the renewal of cell membranes and the synthesis of vitamin D, steroid hormones, or hepatic bile acids. Finally, the reverse CHOL transport from the peripheral tissues to the liver, through which it is eliminated by the bile to the intestine, is an important homeostatic mechanism.

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For a better understanding, lipid metabolism is divided into three stages: the exogenous pathway and endogenous pathways, and reverse CHOL transport.

EXOGENOUS PATHWAY

This pathway involves the transport of lipids from the intestine to the liver and other tissues. In the small intestine, bile salts, phospholipids, free CHOL, free fatty acids (FFA), and monoglycerides are assembled forming mixed micelles that permit their absorption in the intestinal mucosa.[4] The absorption of CHOL, plant sterols, and stanols is mediated by the Niemann-Pick C1-like 1 transporter (NPC1L1), located at the border of the jejunal enterocyte membrane and in the apical membrane of hepatocytes.[5] The enterocytes as all cells have a CHOL extrusion mechanism in which are involved several proteins of the superfamily called ABC (ATP bound cassettes), ABCA1, and G5 and G8. These ABCG5 and ABCG8 membrane transporters act as heterodimers, responsible for returning absorbed sterols to the intestinal lumen.[5]

Approximately half of the amount of cholesterol that has been taken up by the enterocytes and has not been returned to the intestinal lumen via the ABCG5/8 process is diffused to the endoplasmic reticulum, where it is resterified by the acetyl cholesterol acyltransferase-2 enzyme (ACAT2) present in the intestinal cells. The esterified CHOL, along with other molecules (TG, phospholipids, and FFA) are packaged by a protein called microsomal triglyceride transfer protein (MTP) to form the first lipoproteins named chylomicrons (CHY), whose function is to carry absorbed lipids inside the body. CHY have a diameter of 80 to 1000 nm, and are conformed of 90% triglycerides and 5% cholesterol, also containing several lipoproteins such as Apo B48, which is a truncated form of Apo B100, because the enterocyte has the Apo B editing enzyme.[6]

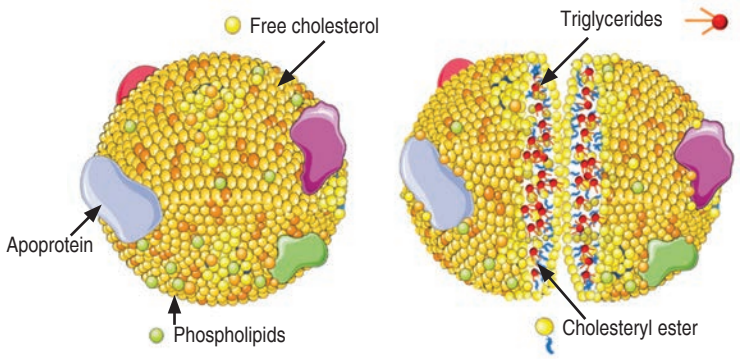

Figure 1: Characteristics and structure of lipoproteins. The cover is made up of free cholesterol, phospholipids and apoproteins, the central part or core contains esterified cholesterol and triglycerides.

CHY are transported to the lymphatic system and through the thoracic duct they reach the systemic circulation. Later, in the blood, they acquire Apo E and Apo C-II, transferred by HDL. They circulate in normal conditions and fasting no longer than 12 hours. Lipoprotein lipase enzyme (LPL) hydrolyzes most of its TG content (about 70%), turning the CHY into a smaller particle named chylomicron remnant, which is characterized by having Apo E. The FFA released are taken up by muscle cells and adipocytes. LPL activity, therefore, is the determining step in the rate of removal of dietary fat from the circulation and is highly regulated in the body.[7] Apo E and Apo C-II activate LPL, while Apo C-III and the angiopoietin 3 (ANGPTL3). and angiopoietin 4 (ANGPTL4) -like proteins inhibit its activity.[8] The presence of Apo E in the remnant is very important since through this apolipoprotein it can be recognized by the hepatic Apo E receptor, also called RRP (receptor-related protein), that traps the remnant, internalizes, and destroys it, using its lipid content for many purposes.

ENDOGENOUS PATHWAY

Endogenous lipid metabolism begins with the synthesis of VLDL, which is produced by the endoplasmic reticulum in the liver, assembling apolipoproteins and triglycerides. MTP is necessary for the secretion of VLDL. Genetic deficiency or chemical inhibition of MTP prevents the secretion of VLDL into the circulation.[9]

VLDLs have a variable diameter from 30 to 80 nm. They can be separated employing ultracentrifugation, in the range of densities

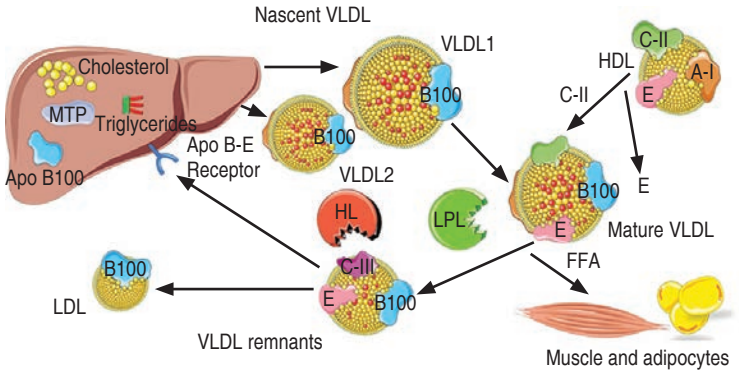

Figure 2: Endogenous pathway. VLDL is synthesized in the liver, which contains Apo B100, matures in the circulation upon receiving Apo E and Apo C-II from HDL. Lipoprotein lipase (LPL) hydrolyzes its triglycerides, releasing free fatty acids (FFA) that will be distributed to skeletal muscle and adipose tissue. As the remodeled VLDL particle lose triglycerides, it become IDL, which are eliminated by the liver or under the action of hepatic lipase (HL) giving rise to LDL.

from 0.95 to 1.006 g/mL. The lipid proportion of these lipoproteins is 60% TG 20% CHOL and the rest, phospholipids. VLDLs vary in size and composition but can be classified into two main classes: VLDL1, large and floating particles with a higher content of triglycerides, and VLDL2, which are smaller and denser.[10] The lipoprotein composition is similar to that of CHY except in two relevant aspects: they do not have Apo A-I and have the complete form of Apo B (Apo B100) since the liver does not express the Apo B-editing enzyme.

Apo B100 is the major structural protein of VLDL and derived catabolic lipoproteins. Other apolipoproteins that are minor components of VLDL are CI, C-II, C-III, and E. Immature VLDL are secreted into the circulation by the Golgi apparatus and once in plasma, VLDL mature acquiring more Apo C-II and Apo E from HDL. VLDLs serve as CHOL acceptors which are transferred from HDL, this transfer process is mediated by the enzyme cholesteryl ester transfer protein (CETP).

The content of TG in VLDL is a suitable substrate for the action of the enzyme LPL, which hydrolyzes the former in a similar process to that which occurs in CHY, releasing FFA, to be used as fuel in the muscle or to be stored in the adipocytes *(Figure 2)*. Because of the hydrolysis, the remnants of VLDL are smaller molecules named intermediate density lipoproteins (IDL). Likewise, to the catabolism of CHY, lipids and apolipoproteins are also released and incorporated into the HDL fraction.[11]

IDLs have a density of 1.006 to 1.019 g/mL with a dimension of 25 to 30 nm and constitute a reduced group of lipoproteins. Smaller in size have fewer TG and phospholipids with a greater amount of esterified CHOL. Their apolipoprotein content consists of Apo B100 and E. It is considered that approximately half of the IDL particles are captured in the liver by B/E receptors, through which they are internalized and degraded in the hepatocyte, while the other half is converted into LDL through a complex process in which hepatic lipase (HL) intervenes.

HL, originated in the liver and regulated mainly by insulin, modulates the lipolysis of TG in IDL and, unlike LPL, it does not require Apo C-II as an activator.[12] This enzyme is also involved in the metabolism of HDL, having a phospholipase activity.

Low-density lipoproteins or LDLs are the product of IDL catabolism. They have a density of 1.063 to 1.019 g/mL, with a diameter of 22 nm and a mass of ~3,000 kDa. Each particle has up to ~1,500 molecules of esters of cholesterol in the hydrophobic core that also contains TG, while the hydrophilic shell is composed by ~800 phospholipid molecules, ~600 free CHOL molecules, and a 500 kDa protein. Its apolipoprotein B-100 also acts as a ligand with cell membrane receptors, having a half-life of 2 to 3 days.[13] The role of LDL is the transport and delivery of CHOL to cells, including peripheral tissues and the liver.

The LDL receptor is a transmembrane glycoprotein that has an approximate molecular weight of 160 kDa and is made up of 839 amino acids with five well-defined regions.[14] The LDL receptor is synthesized by multiple cell lines (fibroblasts, hepatocytes, smooth muscle, adrenal cortex, ovary, and testes cells) and is translocated to the plasma membrane, where is fixed by a protein called clathrin in specific membrane areas called coated pits.[15] Approximately every 10 to 15 minutes, whether or not these coated pits have bounded LDL, they undergo endocytosis and are transported to the cytoplasm in the form of

endosomes. If they contain LDL bounded to the receptor, the latter dissociates and returns to the hepatocyte membrane, while lipoprotein content fuses with lysosomes, which through their enzymes (acid hydrolases), hydrolyze the lipoprotein components, forming amino acids and free CHOL. The pool of free CHOL created regulates different fundamental processes for cellular homeostasis:

1. Inhibition of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase), a key enzyme in the intracellular synthesis of CHOL.
2. Stimulation of acyl-coenzyme A cholesterol acyltransferase (ACAT-1) that promotes the esterification of free CHOL that will be deposited in the cytoplasm in its esterified form, which is partly eliminated in the bile canaliculus and partly used to synthesize bile acids.
3. Inhibition of the synthesis of more LDL receptors.

Unlike macrophages, the liver can regulate the concentration of CHOL, its synthesis, and receptors. The synthesis depends on the amounts of the sterol in the endoplasmic reticulum. Liver cell senses its concentration through a family of proteins called SREBPs (sterol regulatory element binding proteins 1 & 2) that regulate several genes involved in the biosynthesis and capture of CHOL.[16] If hepatic CHOL concentrations are low, the SREBPs, which are transcription factors, are activated and decode genes that increase the synthesis of LDL and CHOL receptors. On the contrary, if the concentration of CHOL is high in the hepatocyte, the SREBPs are not activated.

HDL AND REVERSE CHOLESTEROL TRANSPORT

High-density lipoproteins or HDL are characterized by having mainly Apo A-I, although it also contains Apo A-II, C-I, C-II, C-III, and E. HDLs have a density of 1.21 g/mL to 1.063 g/mL, with a diameter of 8 to 12 nm. Approximately 20% of its content is CHOL, 60% are phospholipids, and TG in a smaller proportion. Their origin come in a greater proportion from hepatic synthesis, and to a lesser degree from intestinal synthesis.[17]

The most important function of HDLs is to transport cholesterol from peripheral tissues to the liver, where it is recycled, used in the production of bile acids, or eliminated in the bile, to the gut. Here, CHOL and bile acids enter in the enterohepatic cycle through which around half of the intestinal sterol, and 95% of bile acids return to the liver to be reprocessed.[18] In addition, HDLs has other athero-protective properties, e. g.:

1. Inhibition of LDL oxidation, where the enzyme paraoxonase plays a relevant role.
2. Anti-inflammatory capacity through the inhibition of the synthesis and expression of endothelial adhesion molecules.
3. Cytoprotective action by inhibiting endothelial cell apoptosis.
4. Vasodilator action by stimulating the synthesis of cellular nitric oxide and prostacyclins.
5. Antithrombotic action by inhibiting platelet aggregation.

The role in the reverse transport of HDL depends largely on its content of Apo A-I, which captures phospholipids and free CHOL through the ABCA1 protein from the liver and extrahepatic cells, resulting in lipid poor-Apo A-I with a discoidal shape, called preβ-HDL or nascent HDL, which facilitates the release of intracellular cholesterol through specific mechanisms that require energy consumption. The release or efflux of free CHOL is determined by the interaction of nascent HDL with transporters of the ATP-binding cassette A1 and G1 (ABCA1 and ABCG1) but also with scavenger receptor class B type I (SR-BI receptors).[19] Once free CHOL reaches the nascent HDL, it is esterified by the enzyme lecithin cholesterol acyltransferase (LCAT) and is sent to the core, with which the HDL increases in size and change its form from a discoid shape to a spherical one.

The newly formed HDLs are known as HDL-3 (density 1.12-1.21 g/mL). In turn, they are classified as HDL-3a, 3b, and 3c. Mature HDL is known as HDL-2 (density 1.063-1.12 g/mL), which is classified in two sub-varieties

(HDL-2a and 2b), containing a greater amount of esterified CHOL than HDL-3. The conversion of HDL-3 to HDL-2 comprises an increase in the content of esterified CHOL and therefore an increase in size, requiring the transfer of phospholipids through the enzyme phospholipid transfer protein (PLTP), which contributes to the formation of HDL and VLDL remnants.

HDL catabolism occurs in the liver, kidney, and steroidogenic tissues (adrenal gland, ovaries, or testes). Elimination can be carried out by endocytosis and lysosomal degradation of the entire HDL particle or by its interaction with the SR-BI receptor, which can endocytose the entire particle or transfer CHOL to the interior of the cell, selectively releasing the lipoprotein back to circulation in the form of a nascent HDL. In the liver, the CHOL captured can be converted into bile acids, these being eliminated by the biliary and fecal routes if it is not absorbed beforehand at the intestinal level. Considering that CHOL cannot be degraded by the body, reverse cholesterol transport is the only straight way to eliminate cholesterol from our body.

Cholesteryl ester transfer protein (CETP) is expressed in various tissues, although its main source is the liver. It is an enzyme that participates in the metabolism of HDL and influences its concentration. CETP catalyzes the transfer of TG from VLDL and LDL to HDL, while passing on CHOL esters from HDL to VLDL and LDL.[20] Under normal conditions, CETP exchanges small amounts of HDL esterified CHOL for VLDL TG, resulting in a slight increase of TG content in HDL and minimal effects on VLDL. In contrast, in hypertriglyceridemia, CETP can significantly alter the lipoprotein profile and its catabolism. The accumulation of VLDL in the plasma provides a greater number of TG to exchange with HDL and LDL CHOL. HDLs with higher TG content are less efficient in generating CHOL efflux, while large LDL rich in TG, are more atherogenic. All these changes derived from the active participation of CETP, especially in hypertriglyceridemia, explain its proatherogenic nature.

CONCLUSION

Lipid metabolism is a rather complex process, but it is necessary and important to have basic knowledge of it since this allows to understand the pathophysiology of atherosclerosis and the mechanism of action of the several drugs used in the treatment of dyslipidemia, aimed to influence the different metabolic and enzymatic pathways intervening in the absorption, transport, and synthesis of lipids and lipoproteins, to reduce the serum concentrations of atherogenic CHOL and TG, and also increase those of HDL, and in this way reduce the risk of atherosclerotic cardiovascular diseases.

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