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Mini Review

Simplified Overview of Lipoprotein Metabolism

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Abstract

Because they are insoluble in an aqueous medium, fats are transported in the bloodstream in the form of water-soluble complexes of high molecular weight, called lipoproteins. Lipoproteins can be characterized by their physicochemical properties, such as electrophoresis and density range, which can be identified by ultracentrifugation. This lipoprotein is responsible for transporting lipids from the diet. The average lifespan of chylomicrons is small, 5 to 30 minutes, indicating rapid metabolism. This explains the large fluctuation in plasma triglyceride concentration after meals. Low-density lipoprotein (LDL) is the major source of cholesterol for extrahepatic cells and, unlike very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL), has a relatively long average life (approximately 3 days). The receptor is synthesized by the rough endoplasmic reticulum and transported to the cell surface, from there migrating to specific regions where it aggregates and awaits the arrival of LDL particles. The structure and composition of high-density lipoprotein (HDL), elucidated during the 1970s, have recently been expanded. This lipoprotein is the classic model of a lipoprotein complex, and its components derive from five main sources: liver and intestine which, by exocytosis, secrete nascent HDL; chylomicron and VLDL lipolysis; and uptake of lipids from peripheral cells that, in the bloodstream, contribute to the formation of mature HDL. Esterified cholesterol accumulates in the core of HDL particles, changing their shape from discoid to spheroid. This esterified cholesterol is exchanged for triglycerides derived from VLDL and HDL-mediated lipoproteins.

Keywords: Metabolism; Lipoproteins; Chylomicron; Apolipoproteins; LDL receptor

Abbreviations: Apo: Apoprotein; HDL: High Density Lipoprotein; HMG-CoA Reductase: 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase; IDL: Intermediate-Density Lipoprotein; LCAT: Lecithin Cholesterol Acyltransferase; LDL: Low Density Lipoprotein; LPL: Lipoprotein Lipase; QM: Chylomicron; VLDL: Very Low Density Lipoprotein

Introduction

Because they are insoluble in an aqueous medium, fats are transported in the bloodstream in the form of water-soluble complexes of high molecular weight, called lipoproteins. Both dietary lipids (exogenous) and those manufactured by the body itself (endogenous) are organized in the form of lipoprotein macroaggregates, in which triglycerides and esterified cholesterol are surrounded by phospholipids and free cholesterol, binding to specific proteins called apoproteins [1-8] (Figure 1). Lipoproteins can be characterized by their physicochemical properties, such as electrophoresis and density range, which can be identified by ultracentrifugation.

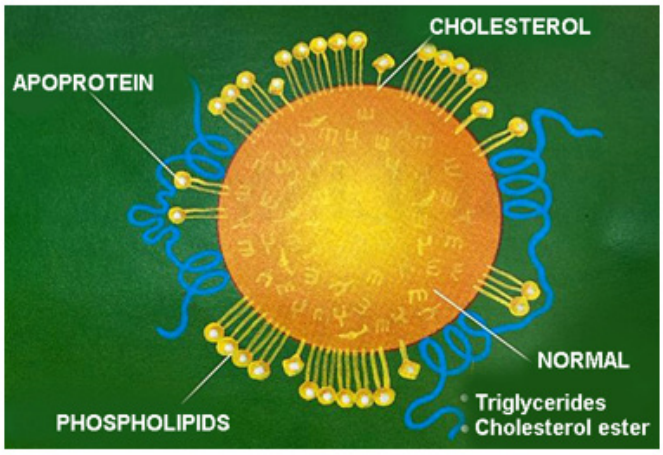

Figure 1: Structure of lipoproteins.

Exogenous cycle - Chylomicron (CM)

In the rough endoplasmic reticulum of intestinal mucosal cells, the synthesis of apoproteins, phospholipids, cholesterol and triglyceride resynthesis from free fatty acids, monoacylglycerol and diacylglycerol occurs.

CM is the result of the composition of these elements, which takes place in the passage of the reticulum to the Golgi complex, where it is stored, in the form of a secretory vesicles, which, after being released into the lymph, by exocytosis, reaches the bloodstream through the thoracic duct[9]. This lipoprotein is responsible for transporting lipids from the diet.

The particle released by the cells of the intestinal mucosa is called nascent CM, has a size ranging from 80 to 1000 nm and is composed of triglycerides (84%), esterified cholesterol (5%), free cholesterol (2%), phospholipids (7%) and apolipoproteins (2%) of the A series (Al, All and AlV) and also B-48, which is so called because it presents in the N-terminal portion 48% of the protein encoded by the apoprotein-B gene.

The average life of CMs is small, 5 to 30 minutes, indicating rapid metabolism. This explains the large fluctuation in plasma triglyceride concentration after meals.

As it reaches the plasma compartment, the CM interacts with the high-density lipoprotein (HDL), which serves as a reservoir of apoproteins C and E (apo-C and apo-E) and transfers them to the former, receiving in return the apoproteins Al and All (apo-Al and apo-All). Apo-E and apo B-48 together are important for the recognition of hepatic receptors, and apo-CIl is required for activation of lipoprotein lipase (LPL), which degrades the triglycerides contained in CM. Apo-CIll, the largest peptide found on the surface of CM, does not have a well-defined function. It is supposed to be the regulator of the lipolysis of this particle or to delay its hepatic catabolism. LPL activated by apo-CIl is negatively charged and resides in the capillary walls of most tissues, especially adipose, cardiac and skeletal muscle tissue, with the function of hydrolysis of triglycerides into monoacylglycerol, free fatty acids and glycerol. The monoacylglycerol will reach the target tissues, where it will be used as a source of energy, and the glycerol will be used, for the most part, by the liver, to produce glycerol-3-phosphate, which will be oxidized for the formation of energy (via glycolytic - Krebs cycle), or will be used in gluconeogenesis or will be reused in lipogenesis. As CM progresses in the lipolytic cascade, apoproteins from the C series return to HDL. The remaining CM, rich in esterified cholesterol, binds to hepatic receptors through apo B-48 and apo-E and, by endocytosis, enters the livers, where it is hydrolyzed, releasing amino acids, fatty acids and free cholesterol. The latter will regulate the "new" synthesis of cholesterol through the inhibition of 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase (HMG-CoA Reductase).

Endogenous cycle

Very Low-Density Lipoprotein (VLDL)

VLDL is produced by the liver, with the function of carrying triglycerides of endogenous origin to peripheral tissues, for energy supply, during periods of reduced exogenous availability. This lipoprotein is a particle with a diameter of 30 to 80 nm, with a density of around 1006 g/ml, rich in triglycerides (50 to 65%). It also includes free cholesterol (4 to 7%), cholesterol ester (8 to 14%) and phospholipids (12 to 16%). It is released from the liver, by exocytosis, as a nascent VLDL (similar to CM), and contains apo B-100 and apo-A1. It also obtains apo-CI (activates lecithin cholesterol acyltransferase - LCAT), apo-CIl (activates LPL), apo-CIII (possibly inhibits LPL) and apo-E from circulating HDL. The final compound is mature VLDL. Hepatic synthesis of triglycerides is substantially affected by diet. This, when rich in carbohydrates, can provide the production of more than 100 g/day of VLDL. When the diet is rich in fats, this exchange can be reduced to about 25 g/day, due to the high formation of CM.

An important substrate in the formation of endogenous triglycerides are free fatty acids, which, when increased, stimulate

the production of VLDL. While circulating, VLDL's structure is altered by interaction with LPL on the surface of the capillary endothelium. In addition, it is enriched with esterified cholesterol molecules from HDL, through the "lipid transfer reaction". Concomitantly, VLDL cedes triglycerides, phospholipids, apo-C and apo-E to HDL. The remaining VLDL, also called intermediate-density lipoprotein (IDL), with a diameter of 25 to 30 nm and a density of 1006 to 1019 g/ml, follows two pathways: it is apprehended by the liver or it is transformed into low-density lipoprotein (LDL) [7,8,10,11]. Normally, 60 to 70% of the remaining VLDL (IDL) is removed from the circulation by liver cells, apparently through specific receptors: B-E receptors and receptor-related protein (LRP). VLDL has a relatively short average life (approximately 12 hours), but considerably longer than CMs and their remnant. IDL not removed by the liver interacts with hepatic triglyceride lipase (HTGL), an enzyme located on the surface of the hepatocyte that hydrolyzes the remaining triglycerides of IDL, thus producing cholesterol-rich LDL.

LDL

LDL is the major source of cholesterol for extrahepatic cells and, unlike VLDL and IDL, has a relatively long average life (approximately 3 days). It carries approximately 1500 cholesterol-ester molecules, whereas VLDL carries 7000 molecules.

This lipoprotein has a density of 1019 to 1063 g/ml and a diameter of 20 to 23 nm. Its constituents are apoproteins (22 to 26%), with 95% of apo B-100 and only traces of apo-C and apo-E; cholesterol-ester (35 to 45%); free cholesterol (6 to 15%); triglycerides (5 to 6%) and phospholipids (22 to 26%) [12] (Figure 2).

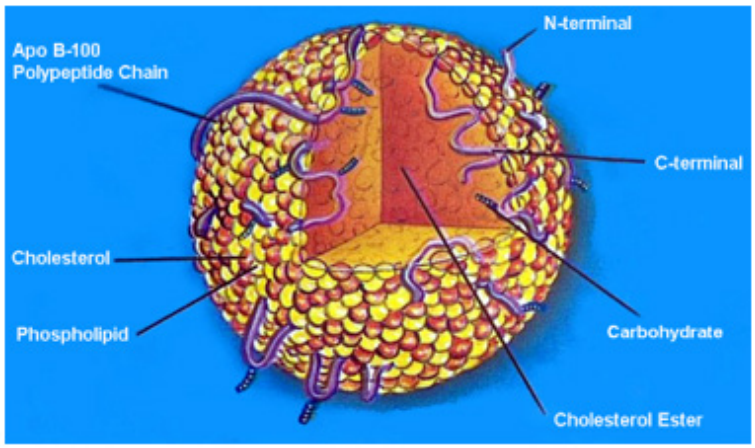

Figure 2: Structure of low-density lipoprotein (LDL).

Figure 3: Human low-density lipoprotein (LDL) receptor.

After fulfilling its role as a cholesterol carrier, 70 to 75% of LDL is taken up by the liver through binding to specific receptors. The receiver recognizes and binds to the surface apo B-100 and also to the apo-E, being called the apo B-100: apo-E receptor. The remainder uses a second pathway, not dependent on a receptor, and is slower acting. According to Goldstein & Brown, 1984[13], the LDL receptor is a protein composed of 839 amino acids. The binding region is the terminal portion, which is made up of eight repeating sequences of negatively charged amino acids. This part of the receptor contains 322 amino acids and interacts with positively charged amino acid residues of apo B-100. The C-terminal portion serves to locate the receptor on the surface of the cell, next to the hydrophobic region of the cell membrane. This receptor activity is important in determining LDL catabolism (Figure 3).

The self-regulation of free cholesterol within cells is given by mechanisms that control its concentration, production and expression of these receptors. The receptor is synthesized by the rough endoplasmic reticulum and transported to the cell surface, from there migrating to specific regions where it aggregates and awaits the arrival of LDL particles. The LDL-receptor binding forms a complex that is dissociated in the lysosomes, at which point the receptor is returned to the cell surface to be reused. Esterified LDL cholesterol is hydrolyzed into free cholesterol, and apo B-100 is degraded into amino acids. Non-esterified cholesterol can follow a few paths: serve as a constituent of the cell membrane; be re-esterified and stocked; leave the cell, being excreted through the bile and regulate the action of two enzymes that, in turn, modulate the intracellular free cholesterol balance.

The first of these enzymes is acyl-cholesterol-acyltransferase (ACAT), which works by transforming free cholesterol into esterified cholesterol. The second is HMG-CoA reductase, which regulates the rate of cholesterol synthesis by acting on the conversion of HMG-CoA into mevalonic acid. The inhibition of the action of HMG-CoA reductase is reversed in importance, since the blocking of the cholesterol formation cascade at this point has the advantage of reversing the previous steps, redirecting to acetyl-coenzyme A, which is an innocuous and metabolically important molecule. In this way, there is no accumulation of toxic intermediates. High concentrations of cholesterol acquired from HDL inhibit this enzyme by cholesterol-ester-transfer protein (CETP). The lipoproteins VLDL, IDL, LDL, now rich in esterified cholesterol, transport it to the liver, through binding with its specific receptors. This whole process is known as reverse cholesterol transport. High levels of LDL-cholesterol are related to an increased risk of cardiovascular disease.

HDL

The structure and composition of HDL, elucidated during the 1970s, have recently been expanded. This lipoprotein is the classic model of a lipoprotein complex, and its components derive from five main sources: liver and intestine which, by exocytosis, secrete nascent HDL; CM and VLDL lipolysis; and uptake of lipids from peripheral cells that, in the bloodstream, contribute to the formation of mature HDL. This diverse origin reflects HDL's large participation in the reverse transport of lipids. It is the smallest of the lipoproteins, with a diameter of about 8 to 13 nm and a density of around 1063 g/ml. It is composed of phospholipids (25%), free cholesterol (5%), triglycerides (7%) and cholesterol ester (10 to 20%). The remainder are apoproteins (65% apo-Al, 10 to 20% apo-All, apo-AIV traces, 5 to 15% apo-C, and 1 to 3% apo-E).

HDLs have important functions, such as acting as a circulating reservoir of apo-CII (LPL activator) and, possibly, of apo-E and apo-Al. These apoproteins are likely recycled to HDL; remove free cholesterol from extrahepatic tissues; they esterify free cholesterol by the action of LCAT synthesized in the liver and activated by apo-Al; They transfer free cholesterol to IDL, LDL and VLDL, by the action of the enzyme CETP (Cholesterol Ester Transfer Protein), which will carry out the reverse transport to the liver (reverse transport of cholesterol).

The nascent HDL, which is a bilaminar disc composed of phospholipids and apoproteins (apo-Al, apo-All, and apo-E), rapidly binds to free cholesterol coming from the cell membrane of various tissues or from the surface layer of other lipoproteins, transforming it into esterified cholesterol, under the action of the enzyme LCAT). This prompt removal prevents the enzyme from catalyzing the reverse reaction, maintaining the continued formation of esterified cholesterol. LCAT is an enzyme produced by the liver, in an inactive form, and for the reactions mediated by it to occur, it must be oriented under the lipid layer of the nascent HDL. In addition, the presence of apo-Al is essential for its activation. Esterified cholesterol accumulates in the core of HDL particles, changing their shape from discoid to spheroid. As these particles receive esterified cholesterol, they become denser. This esterified cholesterol is exchanged for triglycerides derived from VLDL and HDL-mediated lipoproteins. In spite of not going into more detailed information the article's proposal was to make the most remarkable aspects of the lipoproteins and their multiple metabolic interactions.

Acknowledgment

None.

Conflict of Interest

No Conflict of Interest.

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