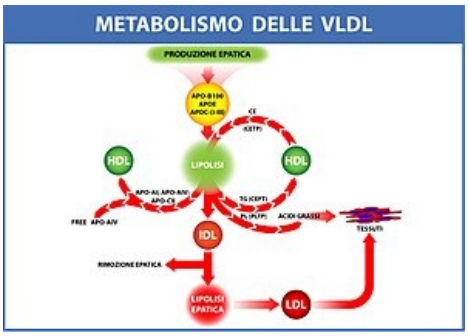
Metabolism of Lipids and Lipoproteins

Chylomicrons

Chylomicrons (particles which contains a lot of triacylglycerols) are made in the cells of the small bowel mucosa by absorption of lipids in food. The presence of apolipoprotein B48 (=ApoB48) is required so that the chylomicrons are secreted from the Golgi apparatus of enterocytes. This apolipoprotein contains only 48 % of the peptide chain of the liver apolipoprotein, which is called as ApoB100 (it means 100% of the peptide chain). Chylomicrons are not normally present in blood plasma after 12-14 hours of fasting. They are immediately hydrolysed at the entry to the blood circulatory system by endothelial lipoprotein lipase (LPL) giving rise to chylomicron remnants. During lipolytic activity of these enzymes, the fatty acids are released; some parts of chylomicrons (apoA-I, apoA-II, apoC and phospholipids) are transmitted to the HDL particles and other components (apoE and cholesterol esters) are transmitted from HDL to chylomicrons. Chylomicron remnants containing apoB48 and apoE bound by their receptors in the liver. The formation of these receptors in the liver cells is regulated by the amount of cholesterol and lipids in the diet. Their activity decreases with age. ApoE facilitates the uptake of the chylomicron remnants, whereas apo C-III inhibits this process. The physiological role of chylomicrons consists in the delivery of fatty accids from food to the adipocytes and muscle cells.

VLDL

VLDL synthesis is occurring in the liver and it is more intensive in obese population. It is partly regulated by diet and hormones and it is slowed down by the uptake of chylomicron remnants in the liver.

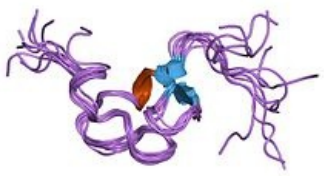


VLDL Metabolism

Lipoprotein lipase (=LPL) which is located on the membrane of capillary endothelial cells in the presence of apoC-II as a cofactor hydrolyses triacylglycerols which are carried by the VLDL particles, so they can be used in the cells as a energy source or stored in the form of reserve triacylglycerols. During this process some parts of VLDL (apoE, apoC) are transferred to HDL, whereas apoB10 remains on the VLDL-remnants (or intermediate-density lipoprotein= IDL). The finished product of the VLDL catabolism is LDL. In pathological situations (like in some patients with severe hypertriglyceridemia) VLDL particles are cleaved from blood plasma without the transformation into LDL particles. The liver produces huge variety of VLDL particles: in low-fat diet it makes particles Sf 60-400, which are bigger and do not have atherogenic properties; in high-fat diet, the liver predominantly makes small dense VLDL Sf 12-60, which are highly atherogenic and they give rise to small dense LDL-B. The receptor for "lipoprotein remnants" (VLDL remnants and chylomicron remnants) is so called LDL receptor related protein. The specific ligand is Apo E *Lipoprotein lipase (=LPL)* which has a catalytic function in fatty acid cleavage from the triacylglycerols in chylomicrons and VLDL particles and its is found on the surface of the capillary endothelium mainly in the fat tissue and muscles where is essential for the synthesis of triacylglycerols for storage and for mobilisation of fatty acids as a energy source. The activator is Apo CII. Insuline does not influence the activity of LPL directly but it is needed for its maintenance. On the other hand, the hormone-sensitive lipase (=HSL) that hydrolyses intracellular triacylglycerols (free fatty acids enter the systemic circulation, bound to albumin and goes to the liver), is directly influenced by insuline; insuline inhibits its action. Contrarily, glucagon its action stimulates. So after a meal the insuline facilitates the storage of fatty acids in adipocytes whereas during fasting, the fatty acids are released to the circulation and used in the liver and muscles.

LDL

LDL particles are the main vehicles of cholesterol in the blood plasma. Their biggest part is made from the VLDL transformation, but some of them are synthetized directly (especially in patients with familiar hypercholesterolemia). The major protein component of the LDL is apoB100. LDL particles can be catabolized by numerous kind of cells, by the *LDL-receptor dependent mechanism or by the LDL-receptor non-dependent mechanism* („scavenger“ mechanism).


LDL receptor

After the binding to the membrane receptor (its duration is about 5-7 minutes) the LDL particle is internalised and broken down by the cell. The newly-created free cholesterol inhibits the activity of the 3-hydroxy-3-methylglutaryl-CoA-reduktase which is crucial enzyme for the de novo synthesis of cholesterol in the cell. This is how the cholesterol synthesis is controlled based on the cell demand. The LDL which are not uptaken particles by the receptors of the peripheral tissues (approximately one third) are catabolised by the scavenger cells. However, this mechanism is not regulated by the cell demand. Some part of LDL particles are also metabolised in the liver. The free cholesterol is either catabolised into bile acids or excreted to the bile or re-used for the synthesis of lipoproteins.

Oxides LDL particles are "pathological", highly atherogenic. They are made by the oxidation of the conjugated double bonds in the fatty acids by activity of reactive oxygen species. The oxidation of the LDL particles positively correlates with the amount of polyunsaturated fatty acids (PUFA) and negatively with the amount of monounsaturated acids, ubiquinol (=coenzyme Q10) and non-esterified cholesterol in the lipoprotein particles. Ubiquinol inhibits the early phase of LDL oxidation and it is an important first antioxidant which destroys free radicals. Other agents inhibiting the LDL oxidation are flavan-3-ols, β-carotene (the last protection). Non-esterified cholesterol decreases the surface fluidity of particles, thus inhibiting the diffusion of free radical into the particle. Whereas acceleration of the oxidation is caused by copper, iron, nickel, cadmium and magnesium deficiency but also sunlight.

Small dense LDL-B are easily oxidized than bigger *LDL-A* which has higher amount of antioxidants. The LDL oxidation does not probably take action in blood plasma which contains a lot of antioxidants and also other substances that binds the metal ions necessary for Fenton reaction, but in the wall of arteries where the oxidation stress can easily take place. Oxidized LDL are highly atherogenic because they are not uptaken by the LDL-receptors but by the "scavenger cells" receptors thus facilitating the production of foamy cell of atheromatous plaques. The early state of persistent hyperglycemia leading to increased formation of glycated proteins (and also lipoproteins) stimulates the LDL oxidation. Advanced Glycosylation End products (=AGE) are created as well that make cross links between LDL particles which are than easily oxidized.

HDL

HDL particles are synthetized in hepatocytes and enterocytes. From their formation they undergo multiple steps of development; they entry the blood in the precursor form called *nascent HDL.* This particles are discoid shaped and are made up of only phospholipid double layer and Apo A I, Apo A II, Apo C a Apo E. Nascent HDL are acceptors of non-esterified cholesterol originated from the cell membranes of various tissues or surface structures of other blood lipoproteins. On the surface of HDL particle, the cholesterol is esterified by the catalysation of the enzyme lecithin cholesterol-acyltransferase (LCAT). The activator is Apo A I, Apo C I and maybe Apo A-IV too. The accumulation of cholesterol esters, the discoid particle is changed to spherical - *HDL3*. With the accumulation of other cholesterol ester, the HDL3 is changing to *HDL2*. In serum of healthy individuals the HDL3/ HDL2 ratio is 2: 1 up to 3: 1. The HDL particles undergo another transformation during the interaction with lipoproteins rich in triacylglycerols by cyclic transformation: HDL3 is transformed by the accumulation of cholesterol esters into *HDL2a*; than, replacing the cholesterol ester by triacylglycerols this particle is changed to HDL2b. This exchange is mainly done by the VLDL particles and chylomicrons which gradually turn into remnant particles (IDL or chylomicron remnants). The exchange is mediated by the specific protein: CETP (=Cholesterol-Ester-Transfer-Protein). The HDL2b particle enriched by triacylglycerols is again transformed into HDL3 by triacylglycerols and phospholipids lipolysis by the action of liver triacylglycerol lipase (=HTGL). Its activator is Apo A II.

The cholesterol esters in VLDL and in chylomicron remnants get into the liver by two pathways:

1. the uptake of remnant particles by the receptor for Apo B/E on hepatocytes
2. indirect pathway by the IDL, which undergo in liver another hydrolysis by the liver triacylglycerol lipase turning into LDL. The LDL particles are from 2/3 uptaken in the liver by the LDL-receptors; only 1/3 ends up in the peripheral cells where they are uptaken by their LDL-receptors.

Besides that, the whole HDL particles can be uptaken by hepatocytes and degraded, so even this alternative pathway brings cholesterol from peripheral tissue to liver. The HDL particles play a crucial role in so called reverse cholesterol transport which enables the cleavage of excess cholesterol from peripheral tissue and from other classes of lipoproteins back to the liver, that is the only organ that can metabolize cholesterol (into bile acids) and excrete them as a bile from the organism. So that it prevents the cholesterol accumulation in macrophages in the wall of arteries and slows down the atherosclerosis process.

Metabolic association between HDL and triacylglycerols

Particles rich in triacylglycerols (VLDL, or IDL, chylomicrons, chylomicron remnant, LDL-B) and high-density lipoproteins (HDL) change their components between each other: From HDL apolipoprotein E and C and cholesterol esters are transferred, contrarily a part of triacylglycerols from VLDL (or other lipoproteins rich in triacylglycerols) are transferred into HDL. This interaction in influenced by LCAT and CETP; the CETP activity is also influenced by the fatty acids concentration released during VDL lipolysis especially in states leading to hypertriglyceridemia. The increased activity of CETP leads to reduction of HDL-cholesterol. This increased activity was found for example in smokers or in obese patient where the low HDL-C level is typical finding. After smoking cessation or weight reduction the CETP activity normalizes. The determinative factor in esterification regulation and HDL transformation (HDL2a → HDL2b) thus regulation of HDL-C levels is the triacylglycerols concentration in plasma. The primary cause of HDL-C reduction in hypertriglyceridemia is probably the level of free fatty acids (FFA). The typical example is *metabolic syndrome X (Reaven)*: Insuline resistance leads not only to malfunction entry of the glycose into the cells but also the entry of FFA into the adipose tissue. The elevated plasma concentration of FFA than leads to its increased uptake in the liver, which makes from them new triacylglycerols, that are later incorporated into VLDL and than released into the circulation. As a consequence of insuline resistance (thus hyperinsulinemia) the LPL activity is inhibited which is another cause of persistent hypertriglyceridemia. It is not only quantitative change in the amount of synthetized VLDL, but also the quality of VLDL; instead of "normal" VLDL Sf 60 - 400, the atypical VDL are made, very rich in triacylglycerols that are moreover resistant to LPL activity. Atypical VLDL are converted into highly atherogenic dense particles (=„small dense LDL“) with concurrent decrease of HDL-C. The high

concentration of atypical VLDL very rich in triacylglycerols leads to increase change of triacylglycerols for cholesterol esters with HDL-particles by the CETP; this is causing the progressive depletion of cholesterol in HDL particles.

Some part of lipoprotein particles (especially when the levels in the plasma are raised or if its composition is abnormal, for example due to lipoperoxidation), they are uptaken by the so called „scavenger cells“ i.e. macrophages and histiocytes, by the special type of receptors which give rise to foamy cells. This process is not regulated by the amount of the cholesterol in the cells and it can be associated with the xanthoma formation, lymphadenopathy or hepatosplenomegaly.

Links

- ws: Metabolismus lipidů a lipoproteinů

Sources

- MASOPUST, Jaroslav a Richard PRŮŠA, et al. *Patobiochemie metabolických drah* [online] . 2. vydání. Praha : vlastním nákladem, 2004. 208 s. Dostupné také z <http://dotdiag.cz/page.php?cid=8

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