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THE DECISIVE ROLE OF THE HEPATIC LIPASE IN THE REVERSE CHOLESTEROL TRANSPORT

The review deals with modern data on the hepatic lipase (HL) role in the atherosclerosis development. HL enzyme facilitates the TG output from the pool of the very low density lipoproteins (VLDL), and this function is controlled by the high-density lipoprotein (HDL) particles composition and structure. The composition of HDL regulates the "liberation" of the HL from the liver, and the structure of HDL controls the HL transportation and activation of it in the bloodstream. Although the lipase activity is typically hard to detect in human plasma, heparin infusion increases the mass of HL and stimulates their activity in the circulation. In humans, the HL can be found primarily in association with the hepatocytes and endothelial cells of the liver cell surface. Human HL can be released from the HSPG cell surface via either heparin or HDL. Some results suggest that heparin interacts directly with lipases and/or competes for binding sites on the surface of HSPG cells. Increased levels of apolipoprotein B-containing lipoproteins (Apo-containing lipoproteins), LDL, and chylomicrons are connected with the development of atherosclerosis. Deposition of lipids in monocytes and macrophages leads to the further development of atherosclerosis. In general, these results indicate that dyslipidemia caused by deficiency HL in combination with a diet high in cholesterol causes inflammation of the liver steatosis.

Key words: hepatic lipase; atherosclerosis; high-density lipoprotein; very low density lipoprotein

INTRODUCTION

Hepatic lipase

Hepatic lipase (HL) – lipolytic enzyme, which is involved in the regulation of triglyceride (TG) level in plasma. High TG can increase the risk of coronary heart disease, and studies suggest that mutations in the HL gene may be associated with increased TG levels and, consequently, an increased risk of coronary heart disease. HL facilitates the TG output from the very low density lipoproteins (VLDL) pool, and this function is controlled by the composition and structure of high-density lipoprotein (HDL) particles. In humans HL is a liver enzyme adjusted by factors which ensure its output from the liver and its activation in the bloodstream. The composition of HDL regulates the HL "liberation" from the liver, and the HDL structure controls the HL transportation and activation of it in the bloodstream. Changes in the HDL apolipoprotein composition can disrupt the function of the HL by disturbance the output and the activation of the enzyme. The structure of HDL could therefore affect the plasma levels of TG and risk of coronary heart disease.

Excretion of TG-rich lipoproteins from the blood is performed by lipoprotein (LDL) and hepatic lipase (HL), as well as between lipoprotein exchange of TG under the effect of NO. Lipoprotein lipase (LPL) is a dominant TG lipase that is responsible for the TG hydrolysis in chylomicrons and VLDL, whereas HL is both phospholipase and TG-lipase, and has an important role in the metabolism of HDL cholesterol in VLDL and LDL transformation [61]. Single nucleotide polymorphisms (SNPs) in the HL gene (TGHL) are connected with high plasma lipid concentrations and an increased risk of acute coronary syndrome [1, 10]. HL deficiency is the result of a relatively rare mutations TGHL that give rise to a loss of activity of circulating HL (due to the decrease of secretion or inactivation of the enzyme) and cause triglyceride-rich VLDL level increase and HDL cholesterol decrease with rising risk of acute coronary syndrome [13, 37]. Common mutations of the SNPs have many different functional consequences. SNPs in the TGHL gene can be connected both with increased and reduced levels of HDL cholesterol content in plasma, as well as with different levels of acute coronary syndrome risk [24, 58]. Thus, the unique SNPs can combine pro- and antiatherogenic phenotypic consequences. This explains why association between TGHL mutations and the risk of acute coronary syndrome was not observed in a more detailed study [17]. Variable phenotypes may also be formed under the influence of secondary factors (environment, lifestyle and hormonal levels) [26], but they will depend primarily on the functional consequences of the SNPs on the activity of HL. SNPs in the TGHL gene may directly affect the ability of TG-hydrolytic activity of the HL, and can indirectly affect the HL, affecting the metabolism of HDL and its ability to regulate the function of the HL.

Hepatic lipase and liver

Hepatic lipase is synthesized and secreted by the liver and binds to heparan sulfate proteoglycans (HSPG) on the endothelial cells and hepatocytes cells surface [19, 34]. HSPG-bound lipase can be released into the bloodstream by heparin. In 1943, Heng showed that intravenous heparin stimulates TG-hydrolytic activity in lipemic serum [43]. Although the lipase activity is typically hard to detect in human plasma, heparin infusion increases the mass of HL and stimulates it's activity in the circulation [14]. Measurements of the HL postgeparin activity were carried out to display the functional levels of HL in the human body and are measured indirectly by subtracting NaCl-sensitive LPL activity from the total activity of the postgeparin lipase. Measurements of the postgeparin HL activity often give higher results in patients with hyperlipidemia, and they are often associated with the increased risk of acute coronary syndrome [47, 52]. This led to the theory that the HL can be proatherogenic enzyme [27, 48]. High postgeparin HL activity may also be connected with the higher risk of acute coronary syndrome as an indicator of reduced lipolytic activity. Increased postgeparin HL activity may represent the "pool" of storage of inactivated HL in the liver (due to a defective release and inactivation of the enzyme) [49, 50]. The surface of the cells HSPG-bound by the HL is the catalytically inactive enzyme, and HDL function is to mobilize and activate the "pool" of HL [49].

The impact of combined shortage of HL and endothelial lipase on the metabolism and content of HDL and apolipoprotein B-containing lipoproteins

Hepatic lipase (HL) and endothelial lipase (EL) are members of a family of extracellular lipases which comprises lipoprotein lipase (LPL) [12, 16, 20, 23, 28, 36]. These three heparin binding lipase are secured on the endothelial surface and engage in the hydrolysis of triglycerides (TG) and phospholipids (PL) within circulating lipoproteins. Although all three lipases have both TG and PL-hydrolytic activity, LPL predominantly is TG-lipase, while EL predominantly is phospholipase-P. HL separates TG and phospholipase activity [29, 38]. In addition to their catalytic functions these lipases are able to "combine" lipoprotein with cell surface proteoglycans independently from hydrolytic activity [5, 18, 30, 33]. To separate the overlapping roles of HL and EL mice with the deficit of HL and EL (HL/EL-knockout) are used to compare with mice with a single HL-knockout and with EL-knockout mice and wild-type mice. Plasma cholesterol levels, cholesterol-containing HDL, Non-HDL-C and phospholipids of mice with HL/EL-knockouts were evidently higher than of mice with a single knockout. First of all mice with HL/EL knockout showed an unexpected significant increase in small particles of low density lipoprotein. Kinetic studies with labeled [3H] with cholesterol ether showed that mice with HL/EL-knockouts accumulated small particles of low-density lipids, suggesting that this is the result of lipolysis of very low density lipoprotein. HDL from all three lipases knockout models have increased ability of cholesterol clearence, but a lower ability of "purification" of cholesterol esters versus control mice. Despite their higher levels of cholesterol containing HDL neither mice with HL-knockouts, EL-knockouts, nor mice with PL/EL-knockouts have not demonstrated raise of cholesterol transportation by the macrophages in vivo.

The release of the HSPG-bound HL

In humans, the HL can be found primarily in association with the cell surface of HSPG on hepatocytes and endothelial cells of the liver, that's why it is considered that the given enzyme is localized in the liver [21]. The specific residues in HL protein regulate HL association with HSPG [54, 61]. Studies using a plurality of peptides identified two HL-heparin-binding regions, one in the N-terminator (R310, K312, K314, R315) and the other in the C-terminator (R473, K474, R476) [54]. In rodents HL is also synthesized in the liver, but it can be found primarily in the circulation [7, 32]. Rat HL can probably more easily move from the surface of HSPG cells due to differences in the composition of amino acids C-terminator of the given enzyme [32]. Human HL can be released from the HSPG cell surface via either heparin or HDL. Some results suggest that heparin interacts directly with lipases and/or competes for binding sites on the surface of HSPG cells [57]. Results of other studies indicate that heparin may act through calcium and protein kinase on signal routes to stimulate the release of HL [39]. HDL-dependent release of HL is regulated by interactions between HL and HDL and affected by both lipid and composition of HDL apolipoprotein [50, 51, 59].

The composition of HDL directly affects the release of HP cells from the surface of HSPG [50, 59]. Rumseymie et al [20] showed that the various subclasses of HDL have a unique ability to move the HL. Larger, more active ApoA-II parts were more effective at moving the HSPG-bound HL than smaller, denser LPVP3 parts. Rohani et al. [59] showed that the various lipids in HDL have unique effects on the release of the HL. Increasing HDL-TGI and the phospholipid content directly blocked the release of the HL to the surface of cells, whereas changes in other lipid components of HDL have little effect on the HL issue. Later, HDL cholesterol, and serum isolated from meal's objects, showed an increased release of the HL relatively to the starving samples [51].

Research has shown that even though the LDL after the meal is TG-rich, APOE lipoproteins is scarce and more efficient than HDL in the binding and displacement of the HL to the surface of the cells [51]. The release of hepatic lipase, as it was mentioned, is controlled by apolipoproteins of HDL and is stimulated by ApoA-II LPVP content [51]. ApoA-II increases the release of SP from HSPG, increasing the HL connection with HDL cholesterol, and this contributes to the increased association of obstruction of HL activity [3, 4]. On the other hand, the release of HL is inhibited by HDL-Apo [51].Young et al [51] showed that HDL isolated from members of the experiment was

significantly more active in the movement of the HL from the surface of cells HSPG regarding HDL from participants of the experiment. HDL isolated from the plasma of women, also contained less ApoE, compared with the isolated HDL from men. The study identified an inverse relationship between HDL-ApoE and the amount of circulating of the HL in the bloodstream [51]. Increased content of ApoE in the HDL leads to a reduced production of HL. Treatment of HDL by the monoclonal antibodies ApoE directed against antigenic determinants in rich glutamic acid N-terminator ApoE succession led to the HL greater shift [51], which suggests that the HL connection to the HDL may be particularly sensitive to the ApoE-dependent electrostatic lipoprotein properties. Other work has shown that the HL activity was also dependent on electrostatic interactions that regulate HL connection with HDL [4, 6].

HDL regulates the release and activation of hepatic lipase (HL). Liver is the storage warehouse for catalytically inactive HL, which is attached to the surface heparan sulfate proteoglycans cells (HSPG). HDL is attached to the HL and produces given enzyme into the bloodstream.

Apolipoproteins exchange between HDL and TG-rich lipoproteins such as VLDL and intermediate density lipoproteins (IDL) postprandial [41, 42]. Especially ApoE moves from HDL to VLDL, where it acts as a lipolytic cofactor [41]. Therefore, the HDL is storage warehouse for ApoE in a state of starvation. A few hours after eating, when plasma levels of TG are high, ApoE moves from HDL to triglyceride-rich lipoproteins [40, 41]. This reduction in the content of HDL-ApoE starts the release of HL from the surface of the hepatocyte cells to the vascular compartment where the enzyme can hydrolyze circulating triglycerides [51]. At the end of the this act ApoE returnes to the pool of HDL and blocks the ability of HDL to produce HL from the liver.

Metabolism and modification of apolipoprotein B-containing lipoproteins involved in the development of dyslipidemia and atherosclerosis

Increased levels of apolipoprotein B-containing lipoproteins (Apo-containing lipoproteins), LDL, and chylomicrons are connected with the development of atherosclerosis. Chylomicrons, containing ApoB-48, are secreted from the intestine after meals, while VLDL, containing ApoB-100, is formed exclusively in the liver. Residues of chylomicrons and VLDL remnants are derived from lipoprotein lipase-mediated lipolysis of triglycerides, which is activated by apolipoprotein C-II connection. Implementation of these residues is stimulated by the action of ApoE, but inhibited by apolipoproteins C-I, C-II and C-III. In plasma, VLDL remnants are further converted to LDL triglyceride hydrolysis. ApoB-100 is responsible for the implementation of LDL to the liver. Podendotelial delay and modification of ApoB-containing lipoproteins are milestones in the initiation of atherosclerosis. In podendotelia implantation of modified lipoproteins by macrophages leads to the formation of fat cells that store excessive amounts of cholesterol ethers and subsequently to apoptosis. Thorough understanding of these mechanisms will help to develop new therapeutic strategies.

Regulation of lipolytic activity of HL

Humans have two pools of inactive HL, the first HL is connected with HSPG in the liver, and the second HL is connected with HDL in the bloodstream. HDL therefore regulates the activation of the HL in a two-stage process, where the first HDL binds and moves the HL on the surface of HSPG cells, and then separates HDL and activates the given enzyme. Under conditions of starvation HL in the bloodstream is catalytically inactive. The activity of hepatic lipase activity could be detected in plasma only after the enzyme will be released from liver under heparin injections [35]. Although ApoA-I and HDL are also able to free the HL to the surface of HSPG cells, the association of HDL with HL directly inhibits activity of the HL [4, 6, 49]. Hepatic lipase is inactivated by its connection with HDL particles containing ApoA-I and ApoA-II [3, 4, 22].

The activity of hepatic lipase stimulates the dissociation of SPs from HDL which is happening under the influence of electrostatic properties of lipoproteins [4, 6]. Enrichment of HDL, or serum with a free fatty acid or anionic phospholipids (such as phosphatidylserine, phosphatidylinositol) increases the clear negative charge on HDL cholesterol and stimulates the hydrolysis of VLDL-TG using HL [6]. ApoA-II, according to the research, increased the HL connection with HDL and directly inhibited the hydrolytic activity of the TG [3, 4, 22]. APOE has the opposite effect. ApoE blocks the HL association with HDL [51] but stimulates lipolytic activity HL [14]. Studies have shown that women have lower ApoE levels in plasma and the number of circulating SP is increased compared to men [51], also women have a decreased postgeparin HL activity, due to the inhibitory effect of estrogen effect on HL transcription [59]. Decreased postgeparin HL activity in women can be expected to cause lower levels of ApoE and reduced activation of the HL [51]. Apo, as demonstrated, directly interacted with Apo-II [25], and thus may block apoA-II-dependent association with of HL with HDL [4]. ApoA-II may therefore control the release and activation of the HL-P its action is modulated by the amount of ApoE, which can remain on the surface of HDL particles.

In the treatment HDL stays connected with HL to keep enzyme in an inactive state. Increased lipase movement between substrate molecules stimulated the majority of interphase lipolytic enzymes, including HL [11]. HDL plasma isolated by sequential ultracentrifugation from women normlipedemic lipids comprised a significant weight of HL [51]. In contrast, HDL isolated from normlipedemic men and giperlipedemic patients, contains far less protein HL. Thus, increased vascular pool HL in women may help to reduce the amount of postprandial lipemia relatively to men [46]. Increased cholesterol-containing HDL in blood can also affect the restructuring of HDL because APOA-2 formation, as shown by research, has been increased in the objects that can faster dispose food TG [9].

Deficiency of hepatic lipase causes glucose intolerance, inflammation of the liver steatosis

Metabolic syndrome and type 2 diabetes make up the main, the most global problems of health, and their level is increasing at an alarming rate. Nonalcoholic fatty liver disease, which affects up to 90 % of people who are obese and almost 70 % of overweight people, usually associated with such features as obesity, insulin resistance, hypertension and dyslipidemia. Deactivating the hepatic lipase in mice that are fed according to a diet high in cholesterol, caused dyslipidemia including hypercholesterolemia, hypertriglyceridemia and increased levels nonesterefecized fatty acids. These changes were accompanied by intolerance to glucose, and hepatic inflammation of the pancreas. Moreover, compared to DT mice, testee mice demonstrated an increased prevalence of MHP1, an agent that promotes deposition of monocytes and macrophages on the subendotel layer of the artery cells. Deposition of lipids in monocytes and macrophages leads to the further development of atherosclerosis. In general, these results indicate that dyslipidemia caused by deficiency HL in combination with a diet high in cholesterol causes inflammation of the liver steatosis [5].

Regulation of HL secretion from the liver

Since HDL can release HL from the surface of the HSPG cells, a hypothesis could arise that hepatic HDL secretion will affect the release of SP from the liver. This idea was confirmed in studies in human hepatocytes and HepG2 cells, which showed that factors that increase the secretion of apoA-I/HDL to the hepatocyte, also increase the secretion of HL [45]. Hattergy et al. [45] demonstrated that excessive secretion of apoA-I in HepG2 cells stimulated direct HL release from the cell surface. On the other side of the cessation of secretion of apoA-I using siRNA decreased the HL release into the environment. Therefore, recently secreted HDL can bind and displace the HL to the surface of cells. An alternative way is an intracellular communication with the HL complexes apoA-I/HDL and HDL together with secretion.

Processing of HepG2 and human normal hepatocyte cells with substances that block the apoA-I retroendocytosis also affects the release of the HL. Linoleic acid phospholipids such as dilinoleoilfosfatidilholin, increase hepatic secretion of apoA-I in a three times and promote double release of HL [41]. Phospholipid treatment does not affect the transcription of the HL because the phospholipids do not have any effect on the mRNA level [45]. Instead phospholipids stimulate the expression of [44] PPARα, and inhibit the function of membrane nucleotides at the cell surface to block retroendocytosal degradation routes [2]. It is believed that membrane phospholipids block dispose routes that leads to the recapture and degradation of cell surface proteins, such as HL. Degradation of hepatic lipase manifested by limited level of HL secretion and it has been connected with dimerization of the enzyme [45]. Doolittle et al. [15] showed that when the HL does not form active dimers, large amounts of monomer HL are accumulated in the cell and rapidly degrade. These studies later demonstrated that the maturation and homodimerization of HL and lipoprotein lipase can control chaperone protein in the endoplasmic reticulum, called lipase maturation factor 1 [8].

Hepatic lipase can be secreted from the hepatocytes as an inactive enzyme. HL secretion stimulators can increase the mass of the HL in hepatocyte environment twice, but have no effect on its activity [45]. This is a feature, which may be important to control phospholipase activity of HL. It is due to the inhibiting effect of certain species of HDL, which is connected to the HL environment. HL among hepatocyte is mostly associated with large HDL complex containing apoA-I and apoA-II. Phospholipid treatment increases the secretion of apoA-I and apoA-II [2, 45], and, as shown by Boucher et al [4], an association of SPs with HDL- rich apoA-II directly inhibits the hydrolytic activity of the HL.

Hepatic lipase as a reference point in the development of methodology of therapy of ischemic heart disease

The recent epidemiological data show that the decrease of cholesterol in the LDL composition is important for the reduction of risk of cardiovascular diseases, but it is true for the IHD part in complexwith lipid-lowering therapy. It became obvious in the last decade that the atherogenic properties of LDL particles are associated not only with their level in the blood plasma, but also with their size and density. Little dense LDL particles treble the risk of IHD progress. Hepatic lipase is the key enzyme in the formation of small dense LDL particles, it organizes their phospholipid and triglyceride structure. The higher HL activity is, the denser and more atherogenic a lipoprotein particle will be.

CONCLUSIONS

The interrelationship between TG plasma levels and HDL levels is implemented according to the feedback mechanism. Low levels of HDL are often associated with high TG, in turn, the HDL reduction and TG level augmentation are connected with the increased risk of the ACS progress [55]. The HDL is a storage for regulatory apolipoproteins, and changes in the HDL apolipoprotein composition may affect the TG metabolism, influencing both the HL and LPL functions. Mutations in the HL gene can have a direct effect on the HL function or indirectly affect lipolysis, causing the formation of reduced or dysfunctional HDL particles [24, 26, 58]. Therefore the stimulants of HDL hepatic production can functionby means of the co-factor to stimulate lipolytic enzymes and increase the excretion of TG [45]. This may partly explain why narcotic substanceswhich increase the HDL levels, such as niacin and fibrates, also reduce TG plasma levels.

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РЕШАЮЩАЯ РОЛЬ ПЕЧЕНОЧНОЙ ЛИПАЗЫ В ОБРАТНОМ ТРАНСПОРТЕ ХОЛЕСТЕРИНА

В данной статье рассматриваются современные данные о роли печеночной липазы (ПЛ) в развитии атеросклероза. ПЛ облегчает выход ТГ из пула липопротеинов очень низкой плотности (ЛПОНП), и эта функция контролируется липопротеинами высокой плотности (ЛВП), составом и структурой частиц. Состав ЛВП регулирует «освобождение» ПЛ из печени, а структура ЛВП контролирует транспортировку ПЛ и активацию ее в кровоток. Хотя активность липазы, как правило, трудно обнаружить в плазме крови человека, инфузия гепарина увеличивает массу ПЛ и стимулирует ее активность в кровотоке. В организме человека ПЛ можно найти, в первую очередь, в соединении с гепатоцитами и эндотелиальными клетками поверхности клеток печени. Человеческая ПЛ может быть освобождена от поверхности клеток с помощью гепарина или ЛВП. Некоторые результаты свидетельствуют о том, что гепарин взаимодействует непосредственно с липазой и/или конкурирует за места связывания на поверхности клеток. Повышенные уровни аполипопротеин В-содержащих липопротеинов (АРО-содержащих липопротеинов), ЛНП и хиломикронов связаны с развитием атеросклероза. Отложение липидов в моноцитах и макрофагах приводит к дальнейшему развитию атеросклероза. В целом, эти результаты указывают на то, что дислипидемия, вызванная дефицитом ПЛ в сочетании с высоким содержанием холестерина, вызывает воспаление и стеатоз печени.

Ключевые слова: печеночная липаза; атеросклероз; липопротеины высокой плотности; липопротеины очень низкой плотности

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ВИРІШАЛЬНА РОЛЬ ПЕЧІНКОВОЇ ЛІПАЗИ В ЗВОРОТНОМУ ТРАНСПОРТІ ХОЛЕСТЕРИНУ

У даній статті розглядаються сучасні дані щодо ролі печінкової ліпази (ПЛ) у розвитку атеросклерозу. ПЛ полегшує вихід ТГ з пулу ліпопротеїнів дуже низької щільності (ЛПДНЩ), і ця функція контролюється ліпопротеїнами високої щільності (ЛВП), складом і структурою частинок. Склад ЛГП регулює «звільнення» ПЛ з печінки, а структура ЛГП контролює транспортування ПЛ і активацію її в кровотік. Хоча активність ліпази, як правило, важко виявити в плазмі крові людини, інфузія гепарину збільшує масу ПЛ і стимулює її активність в кровотоці. В організмі людини ПЛ можна знайти в першу чергу, в з'єднанні з гепатоцитами і ендотеліальними клітинами поверхні клітин печінки. Людська ПЛ може бути звільнена від поверхні клітин за допомогою гепарину або ЛВП. Деякі результати свідчать про те, що гепарин взаємодіє безпосередньо з ліпазою і/або конкурує за місця зв'язування на поверхні клітин. Підвищені рівні аполіпопротеїн В-вмісних ліпопротеїнів (АРО-вмісних ліпопротеїнів), ЛНП і хіломікронів пов'язані з розвитком атеросклерозу. Відкладення ліпідів у моноцитах і макрофагах призводить до подальшого розвитку атеросклерозу. В цілому ці результати вказують на те, що дисліпідемія, викликана дефіцитом ПЛ в поєднанні з високим вмістом холестерину, викликає запалення і стеатоз печінки.

Ключові слова: печінкова ліпаза; атеросклероз; ліпопротеїни високої щільності; ліпопротеїни дуже низької щільності

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