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LIPOPROTEIN LIPASE AS AN ATTRACTIVE TARGET FOR CORRECTING DYSLIPIDEMIA AND REDUCTION OF CVD RESIDUAL RISK

Lipoprotein lipase has long been known to hydrolyse triglycerides from triglycerides-rich lipoproteins. It also the ability to promote the binding of lipoproteins to the wide variation of lipoprotein receptors. There are some studies that suggest the possible atherogenic role of lipoprotein lipase. In theory, lipoprotein lipase deficiency should help to clarify this question. However, the rarity of this condition means that it has not been possible to conduct epidemiological studies. During the last decade it became obvious that elevated plasma TG and low HDL-cholesterol are part of CVD residual risk. Thus LPL is an attractive target for correcting dyslipidemia and reduction of CVD residual risk.

Key words: Lipoprotein lipase; atherosclerosis; lipoproteins

INTRODUCTION

Lipoprotein lipase (LPL) is synthesized and secreted in several tissues, such as skeletal muscle, adipose tissue, cardiac muscle and macrophages (M), binding to the vascular endothelial cell surface of the capillary through heparan sulphate.

Lipoprotein lipase (LPL) plays a central role in lipoprotein metabolism by catalyzing hydrolysis of triglycerides (TG) in very low-density lipoprotein (VLDL) particles and chylomicrons [10, 24, 32]. It has been noted that besides its function of catalytic enzyme, LPL also acts as a mediator facilitating binding and/or incorporation of series of lipoproteins through either heparan sulfate proteoglycans or lipoprotein receptors [4, 5, 22, 25, 51] into several lines of cells. In clinical studies, post-heparin plasma (PHP) is usually used as a material for the measurement of LPL mass and activity. Several groups of researchers [2, 11, 15, 40, 41, 45, 46, 47] have shown the clinical significance of LPL protein mass measuring in plasma or serum by an enzyme-linked immunosorbent assay (ELISA) without the heparin injection (simply put as serum or plasma LPL mass). In recent years, the measurement of serum or plasma LPL mass has been conducted to clarify the pathophysiology of more common metabolic disorders. [40, 41]. The study by Watanabe et al. [11] has shown that serum LPL mass is lower in conditions where TG catabolism is disturbed, such as hypertriglyceridemia and individuals with increased remnant lipoproteins.

Studies which indicate that LPL is proatherogenic

LPL is expressed in atherosclerotic lesions

It was first reported in the 1990s that LPL in atherosclerotic lesions was derived from macrophages (M); differences in M expression of LPL contributed to differences in the development of atherosclerotic plaque formation. Concentrations of LPL protein, activity and mRNA in atherosclerosis-prone mice were found to be several-fold higher than in atherosclerosis-resistant counterparts. Ichikawa et al. compared atherosclerotic lesions in wild-type strains with lesions in rabbits with over-expressed M-specific human lipoprotein lipase, after giving both groups food containing 0.3 % cholesterol. Serum lipids were comparable but atherosclerotic lesions were more prominent in the former than in the latter. In a similar vein, peritoneal M from M-specific LPL / mice crossed with apo E / mice showed less susceptibility to foam cell formation compared to those from apo E / mice, suggesting that M LPL may contribute to the atherosclerosis development.

LPL mass and activity in post-heparin plasma in subjects with advanced atherosclerosis

Biochemical Properties of Pre-Heparin LPL

It has been shown that LPL activity in plasma increased about as high as 170-fold, whereas LPL mass increased only about 9-fold after heparin injection [41]. Most of the LPL protein in plasma elutes as an early peak from heparin-Sepharose, corresponding to the position for inactive monomeric lipoprotein lipase and is demonstrated to be full-length LPL, which is bound to plasma lipoproteins [45]. Therefore, it is unlikely that the measured plasma LPL mass directly catalyze the hydrolysis of triglycerides in TG-rich lipoproteins in the plasma. Several researchers have shown that this inactive protein may act as a ligand promoting lipoprotein binding to cell surfaces and receptors [47].

Correlation of Serum LPL to Post-Heparin Plasma (PHP) LPL Mass

It has been reported that serum LPL mass had a positive correlation with PHP- 4 LPL mass [11, 29, 46].

It should be noted that Hirano et al. [16] have shown that the delta LPL concentration was strongly related to the to post-heparin plasma LPL concentration. This study suggests that the optimal cut off point of serum LPL mass for predicting visceral fat accumulation could be around 40 ng/ml.

LPL is involved in the formation of atherogenic lipoproteins

LPL hydrolyses TG from VLDL and chylomicrons forming VLDL remnants and chylomicron remnants. These are rich in cholesterol esters that become incorporated into M in vitro. The free fatty acids formed by this LPL action are beeing reesterified, promoting cholesterol ester accumulation in M, wich leads to the transformation of M into M. foam cells. Lipoprotein lipase also converts VLDL into intermediate density lipoproteins (IDL), wich then being converted into the low density lipoproteins (LDL) by the action of hepatic lipase. LDL is oxidized in vascular subendothelium, incorporated into M through the scavenger receptor, again resulting the formation of foam cells [37].

LPL is produced by monocytes, macrophages, and smooth muscle cells in the atherosclerotic lesions

Foam cells in atherosclerotic lesions are mainly derived from M, and LPL secretion by this cells may therefore have a direct effect on the atherosclerotic lesions formation. LPL may induce the retention and/or uptake of atherogenic lipoproteins by cells in the arterial wall, promoting the atherosclerotic process. Furthermore, LPL has been demonstrated to increase the retention of VLDL and LDL by proteoglycans of the subendothelial matrix in the arterial wall, facilitate proteoglycan-mediated monocyte adhesion to the endothelium, and increase the permeability of the endothelium by formation of lipolysis products.

Studies which indicate that LPL is antiatherogenic

LPL deficiency and atherosclerosis

In LPL deficiency, plasma LDL cholesterol concentrations are reduced, and the elevated lipoproteins such as chylomicrons are too large to penetrate into the vascular endothelium; as a result, development of atherosclerosis is attenuated. Furthermore, in heterozygous LPL deficiency, reduced LPL activity is associated with premature atherosclerosis [28, 48] or the onset of familial combined hyperlipidemia [3]. Finally, Hu et al. [14] reported in a meta-analysis that lipoprotein lipase Asn291Ser mutations were associated with the low HDL levels, high TG and high rates of coronary artery disease. Conversely, LPL mutations leading to the increased LPL activity were protective against the development of coronary artery disease in another meta-analysis [30]. Zhang et al. [24] studied LPL-deficient mice, where human LPL gene was introduced at birth with adenoviral vectors. The mice exhibited the low HDL-C and marked hypertriglyceridaemia on a normal chow diet. Although at four months of age there were no atherosclerotic lesions of the aorta in the LPL-deficient mice but at 15 months of age more advanced atherosclerotic lesions were observed compared with those in wild-type or with heterozygous LPL deficiency. These results suggest that as individuals with LPL deficiency age, atherosclerotic lesions may progress.

Atherosclerosis in animal models over-expressing LPL

In animal models, over-expressing human LPL is associated with improved serum lipid profile [7, 33, 34]. Tsutsumi et al. [44] found that NO-1886, a compound that increases LPL activity, was associated with reduced TG and elevated HDL-C. He also found that its long-term (90-day) administration inhibits atherogenesis in the coronary arteries of rats with the experimental atherosclerosis. Shimada et al. [34] found that over-expression of human LPL in LDL receptor / mice was associated with the decreases in TG and remnants in plasma, as well as, significant reduction of aortic atherosclerotic lesions compared with LDL receptor/ mice without human LPL overexpression. Fan et al. [7] found that when transgenic rabbits expressing human LPL were fed a cholesterol-rich diet, the development of hypercholesterolaemia and aortic atherosclerosis was dramatically suppressed. Therefore, systemically increased LPL activity plays a crucial role in plasma lipoprotein conversion and plasma TG hydrolysis and affects the metabolism of all classes of lipoproteins. Overexpression of lipoprotein lipase appears to protect against diet-induced atherosclerosis and hypercholesterolaemia.

Studies suggesting serum LPL protein concentration is a useful biomarker predicting cardiovascular disease

In clinical practice, LPL used to be quantified by measuring its activity in post-heparin plasma (PHP) using isotope-labelled substrate. In 1993, it has been established a sandwich enzyme-linked immunoassay (EIA) system for quantifying LPL protein concentration in PHP, using antibovine milk LPL polyclonal antibody and antibovine milk LPL monoclonal antibody [16]. Subsequently, the clinical significance of measuring lipoprotein lipase concentrations in serum rather than PHP was clarified [17, 18]. Hitsumoto et al. [12, 13] found that men with coronary atherosclerosis had significantly lower pre-heparin lipoprotein lipase mass than healthy men. LPL mass appears to be an independent determinant of coronary artery disease [12, 13] even after adjusting for the metabolic parameters, including serum HDL-C and TG. The correlation of intima-media thickness (IMT) of the carotid artery was examined by the ultrasonography and serum LPL concentration in the patients with dyslipidemia. There was an inverse correlation between IMT and serum LPL concentration, independent of body mass index, age, gender, HDL-C, LDL-C, and TG. Shirakawa et al. [36] developed a new LPL measurement system using two different antihuman LPL monoclonal antibodies. They found that remnant-like particles associated with triglycerides (RLP-TG) or cholesterol (RLP-C) and RLP-TG/RLP-C ratio correlated inversely with the serum LPL protein concentrations.

Given that RLP-TG/ RLP-C ratio reflects the particle size of the RLP, this raises the possibility that LPL may play an important role in remnant metabolism [27].

Effect of LPL Activator NO-1886 on LPL, Lipid Metabolism and Atherosclerosis

The synthetic compound NO-1886 (ibrolipim, [4-(4-bromo-2-cyano-phenylcarbamoyl)-benzyl]-phosphonic acid diethyl ester, CAS 133208-93-2) is a LPL-promoting agent that increases high-density lipoprotein cholesterol levels, decreases plasma triglyceride levels, and prevents fat accumulation in high fat-fed rats.

Single doses of NO-1886 dose-dependently and significantly increased post-heparin plasma lipoprotein lipase activity in normal rats [43]. NO-1886 administration for 7 days also significantly increased HDL-C and decreased plasma TG concentrations in hamsters and rabbits [42]. NO-1886 resulted in increased increased plasma total cholesterol concentrations and plasma HDL-C in rats, but this phenomenon was not observed in hamsters, monkeys or rabbits. NO-1886 caused a marked elevation of plasma HDL-C, especially HDL2-C. Previous reports have clearly demonstrated that enhanced lipolysis of TG-rich lipoproteins resulted an increase in HDL2 particles, and therefore, could be a precursor-product relationship exists between the two [39]. The transfer of cholesterol from newly formed HDL2 particles to VLDL is mediated by cholesterol ester transfer protein (CETP) [38]. However, rats, dogs and mice lack CETP [15]. Because of this, the number of HDL particles following enhanced VLDL degradation by lipoprotein lipase was increased and accumulated in the circulation, resulting in a marked elevation of HDL-C. The increases in plasma total cholesterol are obviously a result of the increases in HDL2, as there was no change in cholesterol in the LDL fraction after NO-1886 administration. Rabbits, monkeys and hamsters have CETP, and therefore plasma total cholesterol did not increase. These results indicate that NO-1886 may not increase plasma total cholesterol levels in humans because of the presence of CETP [8].

Endothelial function is impaired before the development of initial lesions in hypercholesterolemic animals and closely related to the development of atherosclerosis [35]. Aging is associated with the progressive development of insulin resistance, dyslipidemia and obesity, all of which are the risk factors for cardiovascular diseases and atherosclerosis [20]. It is known that endothelium-dependent relaxation decreases with age [23]. Hara et al. reported that NO-1886 ameliorated the agingrelated deterioration of the endothelium-dependent relaxation in 10-month-old male rats thoracic aorta [9]. Kusunoki et al. reported that NO-1886 prevented the development of impaired endothelium-dependent relaxation of thoracic aorta in 2-year-old male rats [19]. These research groups speculated that NO-1886 might have improved the endothelium-dependent relaxation by elevating plasma HDL-C, which possesses antioxidant effects and is very important for such old rats due to the elevated plasma lipid peroxide levels caused by exercises [26]. Tsutsumi et al. reported that there was a significant reduction in the incidence of coronary arteriosclerosis following administration of NO-1886 for 90 days in rats on the atherosclerogenic rodent diet, describeing that the multivariate analysis identified elevation of serum HDL-C as a main factor inhibiting the development of arteriosclerosis.

In a study reported by Chiba and his colleagues, an elevation of the plasma HDL-C level, decrease of the plasma TG level, and inhibition of the aortic atheromatous plaque deposition were evident following 20-week treatment with NO-1886 in rabbits on a highcholesterol diet [6]. These reports indicate that it is possible to suppress the development of atherosclerosis by raising the activity of LPL, increasing the plasma HDL-C level and lowering the plasma TG level, even if the plasma cholesterol level is not lower than normal.

A novel Lipoprotein lipase (LPL) agonist rescues the enzyme from inhibition by angiopoietin-like 4 (ANGPTL4)

Recently, ANGPTL4 and other members of ANGPTL family have emerged as the physiological regulators of lipoprotein lipase activity *in vivo*. ANGPTL4 has been shown to potently inhibit LPL activity. Inhibition of LPL activity by ANGPTL4 and 3, results in the poor lipid profile and an elevated TG levels in the bloodstream [21, 31, 49]. ANGPTL4 deficiency has been shown to improve total triglyceride, cholesterol and reduce foam cell formation wich had a protective effect against atherosclerosis [1]. Thus antagonism of ANGPTL4 inhibition of LPL is a promising new strategy in management of cardiovascular deseases. A novel agonist of LPL was identified, using an established in vitro assay, as well as its structural analog that are both more potent than NO-1886 in LPL agonism. They also afford a unique advantage over this agonist with respect to their effect on ANGPTL4 inhibition of LPL. An in-house library of 24 compounds was screened in an in vitro lipoprotein lipase activity assay using a 384 well plate. Compound C10 was considered the most active, which showed the greatest increase in the lipoprotein lipase activity. The next steps of the study clearefied a dose response on the compound C10. A dose-dependent increase in lipoprotein lipase activity was observed in the presence of compound C10, with a maximum effect determined at 324 % of control LPL activity. A pilot structure activity relationship (SAR) study was initiated for the lead compound C10. In the same experiment the maximum induction of lipoprotein lipase activity (E-max) was compared between C10, its structural analogs and NO-1886. C10 showed greater activation of lipoprotein lipase compared to NO-1886. Further, analogs C10a, C10b and C10c exhibited a decrease in LPL agonism activity compared to C10. However, compound C10d showed a dramatic increase in activity compared to NO-1886 and C10. ANGPTL4 when added at the concentration of 0.2 lg/well inhibited the LPL activity by

greater than 50 %. We observed that both compounds C10d and C10 were able to stop lipoprotein lipase inhibition by ANGPTL4 in a dose dependent manner with C10d showing the greater efficacy than C10. NO-1886 failed to stop the LPL inhibition. According to the research, compounds C10 and C10d are the first small molecules that shown this activity of reversing ANGPTL4 inhibition of lipoprotein lipase. This activity is a unique advantage of these compounds over the known agonist – NO-1886.

CONCLUSIONS

This review has summarized various strands of evidence examining the relationship between LPL and atherosclerosis. Large-scale prospective cohort studies of the relationship between serum lipoprotein lipase concentration and cardiovascular disease in various populations may help to clarify this question. Among drug targets for hypolipidemic therapy, LPL holds a significant promise. NO-1886 has been shown to possess potent lipoprotein lipase agonist activity. Random screening identified a compound designated C10, showing greater LPL agonist activity than NO-1886, a known LPL agonist. These compounds have promise as lead structures for the development of treatments of elevated triglycerides in of metabolic syndrome.

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ЛІПОПРОТЕЇНЛІПАЗА ЯК МІШЕНЬ ДЛЯ КОРЕГУВАННЯ ДИСЛІПІДЕМІЇ І СКОРОЧЕННЯ ЗАЛИШКОВОГО РИЗИКУ СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАНЬ

Ліпопротеїнліпаза – фермент, що гідролізує тригліцериди тригліцеридзбагачених ліпопротеїнів. Вона також відповідає за приєднання ліпопротеїнів до широкого ряду ліпопротеїнових рецепторів. Існують дані про можливу атерогенну роль ліпопротеїнліпази. У теорії дефіцит ліпопротеїнліпази має допомогти роз'яснити це питання. Однак рідкість цього стану означає неможливість проведення епідеміологічних досліджень. Протягом минулого десятиліття стало очевидним, що підвищений рівень тригліцеридів у плазмі крові і низький рівень холестеролзбагачених ліпопротеїнів високої щільності є факторами ризику для розвитку кардіоваскулярних захворювань. Таким чином, ліпопротеїнліпаза – важлива мішень для вирішення проблем дисліпідемії і кардіоваскулярних захворювань.

Ключові слова: ліпопротеїнліпаза; атеросклероз; ліпопротеїни

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ЛИПОПРОТЕИНЛИПАЗА КАК МИШЕНЬ ДЛЯ КОРРЕКТИРОВКИ ДИСЛИПИДЕМИИ И СОКРАЩЕНИЯ ОСТАТОЧНОГО РИСКА СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

Липопротеинлипаза – фермент, который гидролизует триглицериды триглицеридобогащенных липопротеинов. Она также отвечает за присоединение липопротеинов к широкому ряду липопротеиновых рецепторов. Существуют данные о возможной атерогенной роли липопротеинлипазы. В теории дефицит липопротеинлипазы должен помочь разъяснить этот вопрос. Однако нераспространенность этого состояния означает невозможность проведения эпидемиологических исследований. На протяжении прошлого десятилетия стало очевидным, что повышенный уровень триглицеридов в плазме крови и низкий уровень холестеролобогащенных липопротеинов высокой плотности являются факторами риска для развития кардиоваскулярных заболеваний. Таким образом, липопротеинлипаза – важная мишень для решения проблем дислипидемии и кардиоваскулярных заболеваний.

Ключевые слова: липопротеинлипаза; атеросклероз; липопротеины

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