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LIPOPROTEIN LIPASE AS A THERAPEUTIC TARGET FOR DYSLIPIDEMIA

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TABLE OF CONTENTS

1. ABSTRACT

The importance of lipoprotein lipase (LPL) in the regulation of overall lipid metabolism in humans and other animals is well documented. The major goal of this review is to identify and justify features that make LPL an important drug target for lipid management in particular for triglyceride lowering and HDL elevation, and propose strategies to modulate LPL activity.

2. BACKGROUND

The major function of LPL is the enzymatic cleavage of triglycerides (TG) of very low density lipoproteins (VLDL) and chylomicrons to generate free fatty acids (FFA) (1-3). Thus, a direct effect of increasing LPL activity would be lower triglycerides. LPL is expressed by the parenchymal cells of several extrahepatic tissues. Following its synthesis in parenchymal cells such as adipocytes and muscle cells, the enzyme is translocated across endothelium and bound to the luminal side of the capillary endothelium by its interaction with heparan sulfate proteoglycans (HSPG) and other proteins (4). FFA, the products of plasma TG hydrolysis, are absorbed by the underlying tissue for storage (adipose tissue) or energy production (muscle). In addition to its important enzymatic function, LPL has also been shown to act as a ligand or bridging factor for the receptor-mediated cellular uptake of various lipoproteins, lipids and lipophilic vitamins (5,6). LPL appears to play a critical role in the uptake and transcytosis of LDL and LDL-associated alpha-tocopherol across the blood-brain barrier (7). Thus, both enzymatic and non-enzymatic activities of LPL greatly affect the metabolism of plasma lipoproteins. Although adipose tissue and muscle parenchymal cells are the major source of LPL synthesis, LPL is also expressed and secreted by other cells such as adrenal cells, astrocytes and macrophages. The functional significance of LPL in these locations is not entirely clear.

By virtue of its TG hydrolyzing activity, LPL also plays an important role in HDL metabolism (Figure 1). Lipid-poor HDL precursors acquire phospholipid and cholesterol from lipolyzed TG particles as well as from cell membranes. HDL precursors (pre-βHDL, apoAI with very little lipid) are normally produced and secreted by hepatocytes or enterocytes. HDL precursor particles accept phospholipids and cholesterol from cells through an efflux mechanism that involves the ATP binding cassette transporter 1, ABC1 (8). These particles are then converted into mature, large, and spherical HDL-3 and HDL-2 by a sequence of events involving the esterification of cholesterol by lecithin:cholesterol acyltransferase (LCAT), the acceptance of surface remnants from TG-rich lipoproteins mediated by phospholipid transfer protein PLTP, and the fusion of HDL particles (9). Thus, the lack of TG lipolysis by LPL would impair the HDL precursor maturation thus leading to degradation of lipid-poor AI particles. Consistent with this notion, human LPL deficiency (type I hyperlipoproteinemia, a rare autosomal, recessively inherited disease) is characterized by elevated plasma TG levels, and drastically decreased HDL. In type 2 diabetics, a decrease in the LPL to hepatic lipase ratio was shown to induce HDL catabolism (10). Lack of TG hydrolysis can also facilitate exchange of cholesteryl esters from HDL to VLDL, which further contributes to low HDL levels. The notion that lipolysis of TG by LPL is an essential step in HDL metabolism was further confirmed in recent elegant studies done by Strauss et al (11). Homozygous LPL knock-out mice do not survive suckling and die between 18 and 24 h after birth. In this study, using an adenovirus-based protocol these investigators rescued LPL-deficient mice during suckling and generated adult mice that lack LPL. Adult LPL-deficient mice exhibited very high triglyceride levels in the fed and fasted state. Most strikingly, these mice lacked apoA-I-containing pre β-HDL particles as well as mature HDL resulting in undetectable HDL cholesterol and HDL-apoA-I levels. The absence of HDL in these LPL-deficient mice strongly supports the concept that the lipolysis of triglyceride-rich lipoproteins is an essential step for HDL maturation.

3. REGULATION OF LPL ACTIVITY

Transcriptional, translational, post-translational and extracellular mechanisms have been proposed for LPL activity regulation (1-3). Transient changes in LPL activity during fasting and feeding appears to be due to post-translational regulation. After processing and maturation into its active form, LPL is released from the cells and transported to the endothelium, where it is bound through interaction with heparan sulfate chains of proteoglycans. LPL can be released from the endothelium by heparin. On fasting, heparin-releasable LPL activity decreases in the adipose tissue and increases in muscle (1-3, 12). Feeding is thought to promote post-translational modifications to LPL, thus facilitating LPL maturation to the active form.

Several extracellular mechanisms might regulate LPL activity on endothelium. The well-known case is the regulation of LPL activity by apolipoproteins (13). Apo CII is required for LPL activity whereas apoCI has been shown to inhibit it. Recently a new LPL regulator, angiopoietin-like protein 3, has been identified

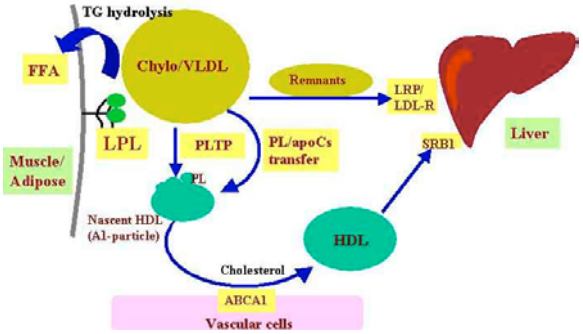

Figure 1. Role of LPL in TG and HDL metabolism. LPL contributes to triglyceride and HDL metabolism leading to decreased TG and increased HDL. TG are primarily carried in chylomicrons and VLDL. The triglycerides are hydrolyzed by LPL present in vascular endothelium of peripheral tissues – muscle and adipose. While this LPL-mediated lipolysis facilitates TG hydrolysis, it also, by generating TG-deficient remnant particles, facilitates rapid removal of these particles by liver receptors such as LDL-receptor and LDL-receptor related protein (LRP). TG hydrolysis by LPL also plays an essential role in HDL maturation. Nascent HDL (apoAI containing very little phospholipid) derives majority of its phospholipid from remnant particles, a process mediated by phospholipid transfer protein (PLTP). These HDL particles can in turn remove phospholipid/cholesterol from peripheral tissues (mediated by ABCA1) and facilitate their clearance by liver (by SRB-1), a process termed reverse cholesterol transport.

(14). This protein is a new class of lipid metabolism modulator, which regulates VLDL triglyceride levels through the inhibition of LPL activity. Further work is needed to elucidate the role of this interesting protein in LPL regulation. LPL activity can also be modulated by regulation of its binding sites on endothelium. For example, the number of LPL binding sites (HSPG) increase in heart during fasting (15). This can result in increased heparin-releasable LPL in heart tissue. Lipolysis can itself contribute to regulation of LPL activity. LPL forms complexes with fatty acids. This complexation can result in detachment of lipase from the endothelial site (16). This provides a molecular coupling device between the cellular metabolic state and the rate of lipoprotein catabolism. Lipolysis products may also regulate expression of enzymes involved in HSPG metabolism, and thus regulate LPL transport from adipocyte to endothelium (17).

Insulin stimulates LPL activity in adipose tissue. This may in part be due to increased glucose uptake since glucose has also been shown to induce LPL activity. Glucose-induced increase in LPL activity may be due to increased processing of LPL (18). Insulin, however, can also increase LPL mRNA and LPL protein synthetic rate in adipocytes independent of glucose (19). Insulin does not appear to increase LPL transcription rather it increases steady state mRNA levels, and the 3' untranslated region appears to play a key role in regulation of LPL translation (20). Similar to the mechanism behind insulin-induced glucose uptake, the effects of insulin on adipose LPL require PI-3 kinase and downstream signaling pathways (21). In contrast to the effect on adipose tissue, physiological concentrations of insulin decrease LPL mRNA in muscle. In a series of elegant studies, Kahn and colleagues showed that stimulation of LPL activity by feeding is blunted in transgenic mice overexpressing GLUT-4 selectively in adipose tissue (22). Thus, altering the partitioning of glucose between adipose tissue and muscle alters a critical step for the partitioning of lipoprotein fatty acids between these tissues.

Although much attention on LPL regulation was given to post-transcriptional and translational mechanisms, LPL expression can also be regulated at the transcriptional level. Various promoter elements have been identified by functional analysis of the human LPL promoter (23,24). Two hepatic nuclear factor (NF) 3- binding elements (between -702 and -666 and between -468 and -430), were suggested to contribute to differentiation-dependent promoter activity during adipogenesis. An NF-1-like binding site (between -517 and -491) was implicated in post-natal extinction of LPL expression in rat liver. A silencer element (from -169 to -152) was shown to suppress basal promoter activity in HeLa and CHO cells. Tumor necrosis factor alpha, which reduces adipose tissue LPL activity, eliminates binding of NF-Y and Oct-1 to the LPL promoter. Fatty acids, fibrates as well as anti-diabetic agents, thiazolidinediones, have been shown to induce rat LPL gene expression in liver and adipose tissue through their action on the peroxisome proliferator response element (from -169 to -157) of the LPL promoter (25). The peroxisome proliferator activated receptor gamma (PPAR gamma) is a critical transcriptional regulator of adipogenesis. LPL is one of the earliest genes induced following exposure of pre-adipocytes to PPAR gamma ligands such as the thiazolidinediones. A unique PPAR gamma DNA recognition element was mapped to the region between -171 to -149 bp of the murine LPL promoter. Other studies showed that PPARalpha or gamma and the 9-cis retinoic acid receptor (RXR) heterodimers bind to this sequence -169 TGCCCTTTCCCCC -157. These data provide evidence that transcriptional activation of the LPL gene by fibrates and thiazolidinediones is mediated by PPAR-RXR heterodimers and contributes significantly to their hypotriglyceridemic effects in vivo. Whereas thiazolidinediones predominantly affect adipocyte LPL production through activation of PPARgamma, fibrates exert their effects mainly in the liver via activation of PPARalpha. Recently, oxysterol liver X receptor, LXRα was shown to induce LPL expression in vivo (26). Analysis of the LPL gene revealed the presence of a functional DR4 LXR response element in the intronic region between exons 1 and 2. This response element directly binds rexinoid receptor (RXR)/LXR heterodimers and is sufficient for rexinoid- and LXR agonist-induced transcription of the LPL gene.

4. DRUGS AFFECTING LPL ACTIVITY

Increased activity of lipoprotein lipase (LPL) may explain the hypotriglyceridemic effects of fibrates, thiazolidinediones and fatty acids, which are known activators (and/or ligands) of the various PPARs (25,27-28). Treatment with compounds, which activate preferentially PPARα, such as fenofibrate, induced LPL expression exclusively in rat liver. In contrast, the thiazolidinediones, high affinity ligands for PPARgamma, had no effect on liver, but induced LPL expression in rat adipose tissue. In both the in vivo and in vitro studies, inducibility by either PPARalpha or gamma activators correlated with the tissue distribution of the respective PPARs i.e., PPARγ predominantly in adipocyte, whereas PPARα was expressed predominantly in liver. Like PPARα agonists, LXRα agonists appear to induce LPL activity in liver (26). Mice fed diets containing an LXR-selective agonist T0901317 exhibited a significant increase in LPL expression in the liver and macrophages, but not in other tissues (e.g. adipose and muscle). Studies in LXR-deficient mice confirmed that this response was dependent more on the presence of LXRα than LXRβ (26).

NO-1886 belongs to a new class of drugs, whose lipid modifying effects appear to be due exclusively to enhancement of LPL activity (28,29). Administration of NO-1886 increased LPL

mRNA and LPL activity in the post-heparin plasma, adipose tissue, and myocardium of rats, and produced a reduction in plasma triglyceride levels with concomitant elevation of HDL cholesterol levels. Administration of NO-1886 for as long as 90 d also significantly decreased the degree of atherosclerotic changes in the coronary arteries of cholesterol-fed rats. These studies were further confirmed in cholesterol-fed New Zealand White rabbits. The mechanism by which NO-1886 increases LPL mRNA is not clear. It does not appear to be due to a PPAR-related mechanism, since this compound increases LPL in both adipocyte and muscle cell lines (30). Unlike PPARγ activators, NO-1886 did not induce weight gain and in fact reduced both weight gain and fat-induced insulin resistance in rats.

5. IS LPL A TARGET FOR DRUG DISCOVERY?

Hypertriglyceredemia and low HDL are independent risk factors for coronary artery disease. Increasing LPL activity should address both of these aspects. Support for this comes from the fact that human mutations associated with enhanced LPL activity have low TG and high HDL and are protected from myocardial infarction. So a simple answer for the above question would be yes. A paradox, however, exists regarding LPL expression and atherosclerosis. Several in vitro studies and some recent animal studies suggest that LPL mediates atherogenic events in the vessel wall (5, 32,33). Supporting this proposition, LPL deficiency in humans, a common genetic cause of chylomicronaemia syndrome, results in very low plasma levels of low density lipoprotein (LDL) cholesterol and is believed to cause resistance to premature atherosclerosis. However, more recent studies show that several LPL-deficient patients develop relatively advanced atherosclerosis (34,35). Individuals who are heterozygous for LPL mutations that reduce enzymatic activity have been reported to be predisposed to premature atherosclerosis (36,37). In contrast, mutations associated with enhanced LPL activity have been shown to confer protection against coronary heart disease (38,39).

Efficient lipolysis of triglyceride-rich lipoproteins in adipose tissue, heart and skeletal muscle generally drives the profile of circulating lipoproteins in a non-atherogenic direction. Overexpression of LPL is highly effective in normalizing the atherosclerotic lipoprotein profiles of both apoE-deficient and LDL receptor-deficient mice and protects wild-type mice against diet-induced hyperlipidemia (40,41). Additionally, administration of the compound NO-1886, which increases tissue LPL activity, protects against atherosclerosis due to elevation of HDL. It is therefore likely that the role of LPL in atherogenesis may depend on the tissue in which it is expressed. In the arterial wall, LPL may be proatherogenic whereas in muscle and adipose tissue it may function protectively.

6. FUTURE DIRECTIONS IN LPL DRUG DISCOVERY

We have discussed above the various roles of LPL in normal physiology and the proposed role in atherogenesis. While there is no question that LPL plays a fundamental role in triglyceride metabolism, its role in atherogenesis is still evolving. It appears that in atherogenesis, not its triglyceride hydrolytic activity but LPL's non-enzymatic functions may play a role. With this background, how then would we approach LPL as a target for drug discovery? One approach would be to enhance the enzymatic activity of LPL, which would have beneficial affects in treatment of hypertriglyceridaemia and HDL elevation.

There are at least two ways to increase LPL activity, one by increasing gene expression and thereby its mass and the other would be to simply enhance the activity of an existing pool of LPL. The first approach while doable and rational may have the drawback that different tissues under various physiological conditions may use unique regulatory mechanisms. Therefore this approach would require a thorough understanding of tissue specific LPL gene regulation if any.

The other approach would be simpler in that there is prior knowledge of how to stabilize the enzyme activity of LPL, by binding to molecules such as heparin as well as enhancing the activation of LPL by apo CII. LPL-binding oligosaccharides have been defined (42). While these oligosaccharides bind and stabilize LPL activity, unlike heparin they do not release LPL from endothelium (17). Recent developments have facilitated oral delivery of otherwise injectable drugs, including polysaccharides (43). Similarly, one could attempt to develop the LPL-binding oligosaccharides into oral drugs. One could also envisage designing "apo CII" mimetics that would activate LPL activity without affecting the tissue distribution or gene expression of LPL. The precise domains on apo CII and LPL for the interaction that leads to activation are known and therefore rational drug design approaches using computer modeling are highly feasible (44,45). Several animal models to test such "CII mimetics" are available and would form the first step in assessing the value and utility of increasing LPL activity as a clinical therapeutic.

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