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Regulation of Lipoprotein Lipase and Plasma Triglyceride in Acute Stress and Inflammation: Remaining Questions and Perspectives

Nishizawa K* and Seki R
School of Medical Technology, Teikyo University, Japan

Abstract

In addition to feeding and fasting, acute stress and inflammation can induce profound changes in lipid metabolism. Lipoprotein lipase (LPL) plays an important role in metabolic regulation and triglyceride partitioning. Recent studies have provided valuable insights into the molecular mechanisms of LPL-mediated regulation. Nonetheless, several questions on LPL and triglyceride regulation during acute stress and inflammation remain unanswered. In this short article, we consider the remaining questions and provide a focused perspective on LPL and triglycerides, especially relating to immobilization stress and endotoxemia, instead of comprehensively reviewing this area of research.

Introduction

Lipoprotein lipase (LPL) is a key enzyme that controls triglyceride (TG) plasma levels and partitioning. After synthesis, primarily in adipose and skeletal muscle, LPL is transported to the surface of the vascular endothelium. There, it is anchored to the heparan sulfate molecules of membrane proteoglycans and glycosyl-phosphatidyl-inositol-anchored HDL binding protein 1 (GPIHBP1) [1]. LPL hydrolyzes the TGs of chylomicrons and VLDL, thereby controlling the cellular uptake of fatty acids (FAs) in tissues. Moreover, the dimeric form of LPL functions as a tethering molecule that assists lipoproteins in binding to their receptors on the cell surface.

Recent studies have provided valuable insight into the regulation of LPL activity. For example, the long-held consensus that the active form of LPL is a dimer has recently been challenged [2]. The important roles of angiopoietin-like proteins (ANGPTLs) and GPIHBP1 in regulating LPL have also been well characterized [3]. Based on the results of oil-drop tensiometry experiments, an excellent model for explaining LPL regulation by apoC-II has been proposed; the model focuses on lipoprotein surface pressure [4].

Our interest is in the implications of these recent findings for research in lipid metabolism in stress and inflammation models. We recently observed an initial rapid decrease in serum TG level (~5 h) followed by a pronounced increase in serum TG level (~12 h) in our acute stress mouse model, in which repeated tail blood sampling using animal restrainer was the sole stressor (Seki et al. in manuscript preparation). This initial decrease was accompanied by a dramatic increase in the expression levels of *CD36* transcripts in the liver. CD36, also called fatty acid translocase (FAT), is the main transporter for cellular uptake of FAs, and it appears to assist the liver in delivering TGs to the plasma over a time-period measured in hours, as discussed in an earlier study [5]. However, several questions remain unanswered in this area. In this current article, these questions are listed as subheadings, followed by brief summaries of basic information and our commentary. To limit the number of references, we mainly cited excellent review articles instead of original articles, and encourage readers to consult the references cited therein.

How does LPL get released and enter the circulation in acute stress or endotoxemia?

After production, LPL is transported to the surface of vascular endothelial cells and remains there with support from GPIHBP1 and heparan sulfate [1]. In an immobilization stress rat model, LPL was rapidly released into the plasma from white adipose tissues (WAT) [6]. Catecholamines may mediate rapid changes in metabolism during acute stress [6]. Nitric oxide (NO) production by nitric oxide synthase (NOS) mediates the catecholamine-induced mobilization of LPL from WAT [7]. Although this can explain the rapidity of the process, how it mediates the process is largely unknown. It has been shown that NO causes nitration of LPL [8], but the significance of nitration in LPL regulation is largely unknown. Intriguingly, a link between NO production and LPL downregulation in WAT has been shown in studies using inflammation models in addition to stress models [9]. However, how these two different types of disruptions can trigger NO production and LPL release from adipose tissue remains unknown.

It is yet unknown whether stress-released LPL molecules have the same activity and stability as heparin-released or physiologically released LPL. Although heparin administration can release a large number of LPL molecules, which can subsequently bind to lipoproteins, these molecules have been shown to be unstable [10]. Acute stress and infection can be life-threatening. It is interesting to hypothesize that, under these conditions, specific mechanisms that stabilize and potentiate LPL activity may exist. The effects of apoCs, which modulate LPL localization and activity, complicate this issue.

In endotoxemia, LPL activity is downregulated in muscle and adipose tissue [9]. In contrast, in acute stress models, LPL activity increases in muscle tissue but decreases in adipose tissue [6]. Thus, tissue-specific control depends on how the system is stressed. However, the mechanism by which muscle LPL is regulated depending on the stressor remains elusive.

What happens to LPL released into plasma during stress and endotoxemia?

In human pre- and post-heparin plasma, LPL is associated with lipoproteins. Zambon et al. carefully inhibited the ex vivo activity of LPL and showed that plasma LPL mostly remains in dimeric form and is associated with TG-rich particles [11]. Recently, Sato et al. reported that most of the LPL in plasma was associated with remnant lipoproteins (RLPs) [12]. These RLPs were found to be identical to the ones that researchers, including Havel and Nakajima, have been studying as potential causal factors of atherosclerosis [10]. The monoclonal antibody-based isolation method developed by Nakajima and coworkers led to the characterization of RLPs as TG-rich lipoproteins rich in cholesterol esters, apoE, and apoC-III and containing either apoB48 or B100, although apoB100 (VLDL-remnant) particles predominate [10,13]. They showed that in pre-heparin plasma samples, most LPLs were bound to RLPs in a dimeric form and were inactive [12]. These findings suggest that when LPL is released from the endothelium, it is mostly complexed with RLPs and two of its inhibitors, apoC-I and C-III.

It is likely that LPL dimers that detach from the endothelium after heparin administration can hydrolyze RLPs in the blood but are unable to if they are attached to the endothelial surface. However, the rate and regulation of TG hydrolysis in pre-heparin plasma remain mostly unknown. In acute stress rodent models, several authors, including us, observed a remarkable decrease in plasma or serum TG levels within a few hours of the stressing procedure. It is possible that the number of LPL molecules per a RLP particle may become very high in the acute stress model but not in the control animals. If this is so, it would enable a rapid decrease in plasma TG level in the acute stress model as compared to the control; quantitative studies are needed to confirm this idea. Moreover, as discussed later, it is likely that a large increase in FA uptake occurs in hepatocytes. LPL hydrolysis products produced near the cell surface are potent PPAR-α activators, whereas albumin-bound FAs are not [14]. However, it is unknown whether hydrolysis in acute stress models occurs mainly in lipoproteins freed from the endothelium or those attached to the sinusoidal endothelium or hepatocytes. It is also unclear whether FAs generated in this way can enter cells without binding to albumin.

The behavior of apoCs in relation to LPL is also largely unknown. In our experiments in an acute stress model, a rapid decrease in plasma TG level was followed by an increase to a level higher than that of a normal control (Seki et al. in manuscript preparation). Such a decrease followed by an increase is likely to be associated with dramatic changes in the ratios of LPL, apoC-II, and apoC-III (apoC-II and apoC-III are both LPL inhibitors) on the chylomicron and VLDL surfaces, but the molecular details are poorly understood. In addition to regulating the number of molecules, regulating the stability of the LPL molecules is important. Although post-heparin plasma LPL is unstable, the stability of stress-released LPL remains unknown. Similar considerations also hold true for the LPL released in the endotoxemia model.

How does the liver react to LPL released into plasma during stress and endotoxemia?

Several studies, including those of Heeren et al., have demonstrated that LPL molecules bound to postprandial TG-rich lipoproteins (TRL) facilitate hepatic TRL clearance from the circulatory system, and that this effect is independent of the catalytic function of LPL [15]. LPL not only hydrolyzes TGs but also acts as a tethering molecule that binds lipoprotein particles to cell surfaces and receptors, including the LDL receptor-related protein (LRP) and the VLDL receptor. Thus, LPL stimulates the rapid endocytosis of TG-rich lipoproteins. It is likely that the LPL dimers associated with VLDLs play a role in tethering VLDL-derived remnants to the receptors and to LRP-1, which is an endocytotic receptor for remnants [11,12]. This would facilitate VLDL remnant catabolism.

In acute stress models, a large number of LPLs is likely to attach to the RLPs. Overall hydrolytic activity may also become very high after acute stress in the vicinity of hepatocytes. The fate of these LPL molecules is unknown. Specifically, it is unclear whether all LPL molecules that attach to RLPs have the ability to act as enzymes as well as tethering molecules, or whether LPL molecules are organized such that some molecules may only serve as tethers and others as only enzymes. Sato et al. showed that inactive LPL molecules stably reside on RLPs, whereas active LPL molecules are transferred to HDL [12]. However, the molecular mechanisms underlying this process remain largely unknown. Whether the transfer of apoCs occurs normally is also unknown.

Do ANGPTLs play significant roles in stress models and inflammation models?

Recent studies of ANGPTL members and their inhibitory effects on LPL have provided important insights into the post-translational regulation of LPL. ANGPTL8 is a feeding-induced hepatokine, and it can effectively inhibit LPL in postprandial muscle by forming complexes with ANGPTL3 [3]. It is likely that this process directs dietary FAs away from muscles and facilitates their storage in white adipose tissue instead [16]. Intriguingly, ANGPTL8 can suppress the inhibitory effects of ANGPTL4 [17-19]. Thus, during fasting, when the ANGPTL8 level in WAT becomes low, the inhibitory activity of ANGPTL4 against LPL and in WAT may be restored, thereby lowering the FA uptake of WAT [3,20]. Low ANGPTL8 expression level in the liver during fasting is likely to decrease ANGPTL3-8 complex levels and consequently activate muscle LPL activity [20]. Thus, the

ANGPTL3-4-8 system can explain the reciprocal features of LPL activity changes in muscle and adipose tissue in the feeding/fasting cycle. Such an ANGPTL system could also explain the difference between muscle and WAT LPL activity during physical exercise; physical exercise could induce ANGPTL4 in non-exercising muscles and shunt TG to exercising muscles [21].

However, it remains unclear whether the ANGPTL system plays an important role in acute stress models. What about ANGPTLs in inflammation and sepsis? Hypertriglyceridemia is known to occur in endotoxemia and sepsis models and is generally accompanied by decreased LPL activity in almost all tissues. This decrease is known to be mediated by a number of mechanisms including post-transcriptional and post-translational regulation [9,22,23]. It is notable that in inflammation models, such as endotoxemia models, it is unclear whether ANGPTLs play important roles, given that in such models and sepsis, β-oxidation is suppressed in all tissues. This means that a reciprocal regulation system such as the one described above would probably not work well in this case.

How do LPL mass and activity influence the expression level of CD36 in the liver?

CD36 is a multiligand scavenger receptor belonging to the SR family, and it accounts for a large proportion of FA uptake in many cells. However, the expression level of CD36 in the liver is low. In the adult liver, LPL expression level is also low. We recently found that in an acute stress mouse model, the levels of *CD36* transcripts dramatically increased in the liver (Seki et al. in manuscript preparation). Upregulation of *CD36* mRNA in an endotoxemia model has also been shown [5]. However, the reason for this dramatic increase is not yet fully understood. Under normal conditions, liver uptake of FAs from TG-rich lipoproteins is limited, but in acute stress and endotoxemia models, *CD36* transcript level dramatically increases, which likely enables rapid uptake of hydrolysis products into hepatocytes. As proposed by Feingold and coworkers, FAs transferred through CD36 tend to be used for re-esterification (i.e., the production of TGs and VLDLs) [5]. It is interesting to speculate that such rapid turnover of VLDLs facilitated by LPL may help clear lipophilic toxins within a few hours of acute stress. The subsequent re-esterification and increase in plasma TG levels may help guard against infection [24]. In animals, acute stress typically corresponds to a situation in which the animal is caught and bitten by other animals, and subsequent infections may often become a threat. Under these circumstances, the initial rapid clearance of VLDL could be beneficial for the clearance of toxic materials.

An important unanswered question is how CD36 is dramatically upregulated in hepatocytes in acute stress models. The same question holds true for endotoxemia models. Important signaling pathways upregulating *CD36* gene expression have been shown to include nuclear receptors, including the pregnane X receptor (PXR), PPAR-γ, and the liver X receptor (LXR) [25]. It seems possible that these receptors are activated by an initial increase in the amount of FAs entering hepatocytes. However, if this is the case, the low level of CD36 expression in the basal state might cause a time lag and become inconvenient when rapid induction is necessary. This leads us to speculate that some proteins, such as LPL, that bind to RLPs may have the ability to serve as adipokines that directly trigger a signaling pathway in hepatocytes that enables rapid upregulation of *CD36* transcription. This would further increase CD36 expression level in a feed-forward manner. Additional studies are warranted to analyze the mechanisms for the immediate upregulation of CD36 in the context of increased plasma LPL level.

Perspectives

Our observation of the rapid and pronounced upregulation of *CD36* transcripts in the liver that accompanies the remarkable decrease in plasma TG level in an acute stress mouse model suggests an unexpectedly high capacity of the liver to take up FAs derived from VLDLs and RLPs by hydrolysis. However, apart from the general technical challenges in studying lipid/water/protein systems, the fact that LPL expression and activity are controlled by several mechanisms indicate many challenges in this research area.

The structural details of LPLs bound to TG-rich lipoproteins and RLPs are not well understood. It is likely that the strength of binding (the binding free energy) varies depending on the conformation and the monomer/dimer configuration of LPL molecules, which in turn change depending on lipoprotein size [4]. Further investigation of the mechanisms for the coordination of the structures formed by LPLs and apoCs would help improve the understanding of mechanistic details, such as how LPL molecules released during acute stress stably attach to lipoproteins and how they behave near the surface of sinusoidal endothelial cells and hepatocytes.

Further studies are also necessary to determine how the regulation of LPL is mediated by apoCs in models other than feeding/fasting. Notably, Meyers et al. proposed a model explaining how apoC-II activates LPL on the surface of TG-rich lipoproteins and how the conformational changes of apoC-II and surface pressures are coupled to this activation efficacy [4]. This model can also explain several recent experimental findings.

Can molecular simulations be used to examine the validity of this hypothesis? While free-energy computations have been used for peptide/lipid/water systems under varied surface pressures, such computations have been mainly performed for short and rigidly folded peptides and with coarse-grained simulations, which cannot account for changes in protein secondary structures [e.g:26]. Atomistic simulations can account for structural changes well but require extensive computations for systems consisting of proteins, such as apoCs, as well as phospholipids, TGs, and water. Therefore, simulation-based studies of large systems containing, for example, both apoC-II and LPL are challenging. An in vitro experimental system using recombinant apoCs and LPLs with amino acid replacement may be more helpful.

Conflict of Interest

The authors declare that they have no conflict of interest.

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***Corresponding author:** Kazuhisa Nishizawa, Teikyo University School of Medical Technology, Kaga, Itabashi, Tokyo, 173-8605 Japan, Tel: +81-3-3964-1211, Fax: +81-3-5944-3354; Email: kazunet@med.teikyo-u.ac.jp

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