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Review

Physiological regulation of lipoprotein lipase

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ABSTRACT

The enzyme lipoprotein lipase (LPL), originally identified as the clearing factor lipase, hydrolyzes triglycerides present in the triglyceride-rich lipoproteins VLDL and chylomicrons. LPL is primarily expressed in tissues that oxidize or store fatty acids in large quantities such as the heart, skeletal muscle, brown adipose tissue and white adipose tissue. Upon production by the underlying parenchymal cells, LPL is transported and attached to the capillary endothelium by the protein GPIHBP1. Because LPL is rate limiting for plasma triglyceride clearance and tissue uptake of fatty acids, the activity of LPL is carefully controlled to adjust fatty acid uptake to the requirements of the underlying tissue via multiple mechanisms at the transcriptional and post-translational level. Although various stimuli influence LPL gene transcription, it is now evident that most of the physiological variation in LPL activity, such as during fasting and exercise, appears to be driven via post-translational mechanisms by extracellular proteins. These proteins can be divided into two main groups: the liver-derived apolipoproteins APOC1, APOC2, APOC3, APOA5, and APOE, and the angiopoietin-like proteins ANGPTL3, ANGPTL4 and ANGPTL8, which have a broader expression profile. This review will summarize the available literature on the regulation of LPL activity in various tissues, with an emphasis on the response to diverse physiological stimuli.

1. Introduction

Many tissues rely on plasma triglycerides (TG) as an important source of fatty acids for subsequent oxidation and/or storage. Plasma TG are packaged into the TG-rich lipoproteins chylomicrons and very low-density lipoproteins (VLDL), which carry TG coming from the diet or synthesized in the liver, respectively. Utilization of plasma TG is dependent on lipoprotein lipase (LPL), which is attached to the capillary endothelium and catalyzes the hydrolytic cleavage of TG into fatty acids. LPL, originally referred to as clearing factor lipase [1], is produced by a limited number of cells that include (cardio)myocytes and adipocytes, and upon release by these cells is transported to the lumenal side of the capillary endothelium by the protein GPIHBP1 [2,3]. The luminal or endothelial LPL is referred to as the functional LPL pool, as it represents the portion of tissue LPL that is actively involved in plasma TG hydrolysis. Additionally, LPL is produced by macrophages and mammary gland secretory cells, and by fetal hepatocytes. Maturation of nascent LPL occurs in the endoplasmic reticulum and is promoted by the lipase maturation factor 1 [4]. The LPL enzyme is catalytically active as a dimer composed of two glycosylated 55 kDa subunits connected in a head-to-tail fashion by non-covalent interactions [5,6].

The human LPL gene consists of 9 exons and encodes a protein of 475 amino acids that can be divided into distinct structural and functional domains, including an N-terminal signal sequence, a catalytic domain, a 'lid' domain that covers the active site, and a C-terminal domain [7,8]. The catalytic triad for the active site is formed by the amino acids Ser159, Asp183, and His266. Recent evidence indicates that the C-terminal portion of LPL, which mediates binding to heparin, is sufficient for binding to GPIHBP1 [9,10]. Accordingly, formation of the full length LPL homodimers is not required for interactions with GPIHBP1. Finally, LPL is subject to proteolytic cleavage by proprotein convertases at residue 297, which represents a potential regulatory mechanism [11].

The essential role of LPL in plasma TG clearance is illustrated by the severe hypertriglyceridemia in patients carrying mutations within the LPL gene [12]. Similarly, mice with a generalized deletion of LPL have markedly higher plasma TG levels at birth and die within 24 h due to an inability to process the milk lipids. At the time of death, LPL knockout (KO) pups are severely hypertriglyceridemic [13,14]. Tissue-specific deletions of LPL have further demonstrated the importance of LPL for local fatty acid uptake [15–17]. Deletion or disabling mutations in the GPIHBP1 gene also give rise to marked hypertriglyceridemia in mice and humans [3,18]. Conversely, transgenic mice overexpressing human LPL throughout the body show a 75% reduction in plasma TG [19].

Because LPL is a critical determinant of plasma TG clearance and resultant tissue uptake of fatty acids, the activity of LPL needs to be carefully regulated in order to match the rate of uptake of plasma TG-derived fatty acids to the needs of the underlying tissue and the ability of the tissue to dispose of the fatty acids, all while being confronted with huge fluctuations in the production of TG-rich lipoproteins. It will therefore come as no surprise that the activity of LPL is extensively regulated through multiple mechanisms, which primarily operate at the transcriptional and post-translational level. Regulation of DNA transcription is responsible for the upregulation of LPL gene expression and activity

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during (cardio)myogenesis and adipogenesis [20–22]. However, most of the physiological variation in LPL activity, such as during fasting and exercise, appears to be driven via post-translational mechanisms by extracellular proteins. This review will summarize the current literature on regulation of LPL activity in various tissues, focusing on LPL regulation in response to physiological stimuli.

2. LPL-modulating proteins

2.1. Two groups of LPL modulating proteins

As indicated above, physiological variation in LPL activity in various tissues is primarily achieved via post-translational mechanisms involving a number of extracellular proteins. These proteins can be divided into two main groups. The first group encompasses the apolipoproteins APOC1, APOC2, APOC3, APOA5, and APOE, which are mainly or exclusively produced in liver and are physically associated with a variety of lipoprotein particles including TG-rich lipoproteins. The second group includes several members of the family of angiopoietin-like proteins, specifically ANGPTL3, ANGPTL4 and ANGPTL8. A short description of the basic features of each of these LPL modulators is presented below.

2.2. Apolipoproteins C (APOC)

Three members of the APOC family have been associated with modulation of LPL activity: APOC1, APOC2 and APOC3 [23]. All three APOC proteins have a molecular weight of around 8 kDa, are mainly produced in liver, and are physically associated with the major lipoprotein classes. Human genetic and in vitro studies have provided overwhelming support for a plasma TG-lowering effect of APOC2 via stimulation of LPL activity (summarized in [23]). Paradoxically, overexpression of the human APOC2 gene in mice leads to marked hypertriglyceridemia via impaired plasma TG clearance [24], suggesting that at higher concentrations APOC2 may inhibit LPL [23]. Several factors were shown to impact plasma APOC2 levels, including obesity/diabetes and several hypolipidemic drugs (summarized in [25]). However, these factors are primarily pathological or pharmacological in nature, suggesting that based on current knowledge APOC2 does not appear to be a major mediator of regulation of LPL activity in response to physiological stimuli, such as feeding/fasting, exercise and cold exposure.

As opposed to APOC2, APOC1 and APOC3 inhibit LPL-dependent plasma TG clearance, as shown using transgenic mice overexpressing human and mouse APOC1 or C3 [26–28] or mice lacking APOC1 [29]. Recently, it was proposed that APOC1 and C3 inhibit LPL activity by displacement of the enzyme from TG-rich particles [30]. In addition, APOC1 and APOC3 may influence plasma lipoprotein metabolism via modulation of the activity of other enzymes involved in lipoprotein processing, as well as by altering the binding of APOC-containing lipoproteins to their receptors [23]. The plasma TG raising effect of APOC3 is supported by lower fasting and postprandial plasma TG levels in heterozygous carriers of a null mutation (R19X) in the APOC3 gene [31]. So far no APOC1 gene variants have been identified that give rise to reduced or elevated plasma TG levels in humans. Similar to APOC2, regulation of APOC3 production likely represents a key process in pharmacological modulation of plasma TG by fibrates [32], yet evidence is lacking for a major intermediary role of APOC3 in regulation of LPL activity by physiological events.

2.3. Apolipoprotein A5 (APOA5)

Gene targeting studies in mice and genetic studies in humans have unequivocally established the plasma TG-reducing effect of APOA5 [33]. Indeed, loss of function mutations in the APOA5 gene give rise to early- or late-onset hyperchylomicronemia in humans [34–36]. The primary mechanism for TG-lowering by APOA5 is stimulation of LPL-mediated plasma TG clearance, although other mechanisms have been suggested as well, including repression of VLDL synthesis via an intracellular mode of action and activation of receptor-mediated lipoprotein particle uptake in liver, either by serving as ligand for LDL-receptor family members or by facilitating binding of TG-rich lipoproteins to hepatic proteoglycan receptors [37]. How APOA5 stimulates LPL activity is not fully clear but it likely involves interactions between APOA5 and LPL, proteoglycans and GPIHBP1 [33]. So far there is little evidence that APOA5 production is altered as a key effector of physiological regulation of LPL activity. Whereas insulin downregulates APOA5 mRNA [38], glucose stimulates APOA5 gene expression [39]. The physiological relevance of these findings is probably limited, and they more likely contribute to dysregulation of plasma TG-clearance during insulin resistance and associated hyperinsulinemia. There is compelling data that stimulation of LPL-mediated plasma TG clearance by fibrates may be mediated by upregulation of APOA5, which has been shown to be a direct PPARα target gene in humans but not in mice [40–42]. APOA5 expression in human liver is correlated with CPT1A and PPARA mRNA, further indicating a role of PPARα in APOA5 regulation [43].

2.4. Apolipoprotein E (APOE)

Genetic variation at the APOE locus has been shown to impact cardiovascular disease risk in humans by altering plasma lipoprotein levels [44]. APOE is a 34.2 kDa component of TG-lipoproteins and is required for effective receptor-mediated hepatic uptake of their cholesterol-enriched remnants [45]. In contrast to APOA5 and the members of the APOC family, APOE is also produced in extra-hepatic cells and tissues, especially in macrophages. APOE elevates circulating levels of TG-rich lipoproteins, partly by reducing the LPL-mediated plasma TG clearance rate [46], and partly by stimulating hepatic VLDL-TG production [47,48]. The inhibitory action of APOE on LPL has been confirmed at the in vitro level [46,49]. Despite its importance as a major genetic determinant of plasma lipoprotein levels, there is little evidence that regulation of APOE production is responsible for physiological variations in LPL activity.

2.5. Angiopoietin-like protein 4 (ANGPTL4)

ANGPTL4 is a 50 kDa protein that shows homology with angiopoietins and angiopoietin-like proteins. It is secreted by numerous cells including hepatocytes, adipocytes, (cardio)myocytes, endothelial cells, intestinal epithelial cells, and macrophages. Expression of ANGPTL4 is under transcriptional control of peroxisome proliferator-activated receptors (PPARs). Indeed, ANGPTL4 was originally cloned as a target gene of PPARα and PPARγ [50,51]. Depending on the specific tissue, ANGPTL4 mRNA levels are governed primarily by PPARα (hepatocytes) [50,52], PPARδ ((cardio)myocytes and macrophages) [53–56], or PPARγ (adipocytes) [50,51]. Consequently, expression of ANGPTL4 is highly stimulated in vitro and in vivo by free fatty acids, which are agonists for PPARs [53, 56–58]. Overexpression of ANGPTL4 in mice reduces local and post-heparin plasma LPL activity, thereby impairing plasma TG clearance and elevating plasma TG levels [59–61], whereas ANGPTL4 deletion increases LPL activity and reduces plasma TG concentrations [62]. Biochemical studies indicate that ANGPTL4 disables LPL at least partly by dissociating the catalytically active LPL dimer into inactive LPL monomers [63,64]. However, according to another study, instead of acting as a catalyst, ANGPTL4 functions as a conventional, non-competitive inhibitor that binds to LPL to prevent the hydrolysis of substrate as part of a reversible mechanism [65].

Recent evidence indicates that ANGPTL4 is a major physiological regulator of LPL activity under conditions of fasting and exercise [50, 62,66,67]. In addition to functioning as paracrine factor in tissues that express LPL, ANGPTL4 may also have an endocrine function via its production in tissues that do not express LPL, such as liver and intestine (Fig. 1). Consistent with a role of ANGPTL4 in lipolytic processing of