Lipoprotein lipase: from gene to obesity

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Wang H, Eckel RH. Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab 297: E271–E288, 2009. First published March 24, 2009; doi:10.1152/ajpendo.90920.2008.—Lipoprotein lipase (LPL) is a multifunctional enzyme produced by many tissues, including adipose tissue, cardiac and skeletal muscle, islets, and macrophages. LPL is the rate-limiting enzyme for the hydrolysis of the triglyceride (TG) core of circulating TG-rich lipoproteins, chylomicrons, and very low-density lipoproteins (VLDLs). LPL-catalyzed reaction products, fatty acids, and monoacylglycerol are in part taken up by the tissues locally and processed differentially; e.g., they are stored as neutral lipids in adipose tissue, oxidized, or stored in skeletal and cardiac muscle or as cholesteryl ester and TG in macrophages. LPL is regulated at transcriptional, posttranscriptional, and posttranslational levels in a tissue-specific manner. Nutrient states and hormonal levels all have divergent effects on the regulation of LPL, and a variety of proteins that interact with LPL to regulate its tissue-specific activity have also been identified. To examine this divergent regulation further, transgenic and knockout murine models of tissue-specific LPL expression have been developed. Mice with overexpression of LPL in skeletal muscle accumulate TG in muscle, develop insulin resistance, are protected from excessive weight gain, and increase their metabolic rate in the cold. Mice with LPL deletion in skeletal muscle have reduced TG accumulation and increased insulin action on glucose transport in muscle. Ultimately, this leads to increased lipid partitioning to other tissues, insulin resistance, and obesity. Mice with LPL deletion in the heart develop hypertriglyceridemia and cardiac dysfunction. The fact that the heart depends increasingly on glucose implies that free fatty acids are not a sufficient fuel for optimal cardiac function. Overall, LPL is a fascinating enzyme that contributes in a pronounced way to normal lipoprotein metabolism, tissue-specific substrate delivery and utilization, and the many aspects of obesity and other metabolic disorders that relate to energy balance, insulin action, and body weight regulation.

LPL together regulate the supply of fatty acids to various tissues for either storage or oxidation. LPL has been intensively examined in vivo and in vitro and in humans and many animal models. In this review we are going to focus on the LPL gene and protein and how alterations in LPL gene expression, protein binding, enzyme activity, and tissue-specific regulation contribute to the metabolic disorders of hypertriglyceridemia and obesity.

LPL Gene and Protein

LPL is a member of the TG lipase gene family of proteins that includes hepatic lipase (HL), pancreatic lipase (PL), endothelial lipase (EL), and the Drosophila yolk proteins 1, 2, and 3 (YP1, YP2, and YP3, respectively) (36, 50, 99, 192). The Drosophila yolk proteins, although they exhibit sequence similarity, lack lipase activity and show no obvious functional similarity to LPL and other enzymes (99, 260). All of the enzymes in this family exhibit significant TG esterase activity. The LPL gene is mapped to human chromosome 8p22 (251).

The LPL gene is expressed in a variety of tissues, including adipose tissue, cardiac and skeletal muscle, islets, and macrophages. LPL is the rate-limiting enzyme for the hydrolysis of the TG core of circulating TG-rich lipoproteins, chylomicrons, and VLDLs. LPL-catalyzed reaction products, fatty acids, and monoacylglycerol are in part taken up by the tissues locally and processed differentially; e.g., they are stored as neutral lipids in adipose tissue, oxidized, or stored in skeletal and cardiac muscle or as cholesteryl ester and TG in macrophages. LPL is regulated at transcriptional, posttranscriptional, and posttranslational levels in a tissue-specific manner. Nutrient states and hormonal levels all have divergent effects on the regulation of LPL, and a variety of proteins that interact with LPL to regulate its tissue-specific activity have also been identified. To examine this divergent regulation further, transgenic and knockout murine models of tissue-specific LPL expression have been developed. Mice with overexpression of LPL in skeletal muscle accumulate TG in muscle, develop insulin resistance, are protected from excessive weight gain, and increase their metabolic rate in the cold. Mice with LPL deletion in skeletal muscle have reduced TG accumulation and increased insulin action on glucose transport in muscle. Ultimately, this leads to increased lipid partitioning to other tissues, insulin resistance, and obesity. Mice with LPL deletion in the heart develop hypertriglyceridemia and cardiac dysfunction. The fact that the heart depends increasingly on glucose implies that free fatty acids are not a sufficient fuel for optimal cardiac function. Overall, LPL is a fascinating enzyme that contributes in a pronounced way to normal lipoprotein metabolism, tissue-specific substrate delivery and utilization, and the many aspects of obesity and other metabolic disorders that relate to energy balance, insulin action, and body weight regulation.

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The LPL gene is mapped to human chromosome 8p22 (251). The complementary DNA for human LPL shows that the gene
encodes 448 amino acids (278). The gene is composed of 10 exons spanning ~30 kb (Fig. 1). The first exon encodes the 5′-untranslated region, the signal peptide plus the first two amino acids of the mature protein. The next eight exons encode the remaining 446 amino acids, and the 10th exon encodes the long 3′-untranslated region of 1,948 nucleotides (123). The organization of the LPL gene is very similar to the HL gene with all introns interrupting coding sequence in identical phases, resulting in exons of the same or nearly the same size. However, the organization of the EL gene is distinctly different from both LPL and HL, reflecting both functional and developmental divergence in the lipase gene family. In mice, the LPL gene is mapped to a region of mouse chromosome 8 that is homologous to the region of human chromosome 8, as judged by the conservation of linked genetic markers (107). Genomic clones for LPL have also been isolated in chicken, guinea pig, rat, and fish (42, 59, 62).

cDNA clones corresponding to the entire coding region of LPL have been isolated and sequenced from a number of species, including human, guinea pig, mouse, rat, chicken, baboon, ox, sheep, pig, and fish (5, 26, 206). The predicted amino acid sequence indicates that the mature mouse protein contains 447 amino acids with a molecular mass of 50,314 Da. Comparison of the nucleotide and amino acid sequence with those of HL and PL reveals extensive homology among the enzymes. Most striking is a conservation of five disulfide bridges in all three enzymes, strongly suggesting that the enzymes have similar overall folding patterns (280). The amino acid sequence of LPL is shown to be extraordinarily conserved among mouse, human, and bovine species (206).

LPL enzyme activity has been identified in a wide variety of extrahepatic tissues and cells, including adipose tissue, heart, skeletal muscle, lung, lactating mammary gland, brain, kidney, and macrophages (124). In rodents, LPL mRNA is most abundant in heart but is present in a wide variety of adult rat and mouse tissues at very different levels. There are two major species of mRNA in mouse and human tissues, 3.6 and 3.4 kb in size (278). Rat tissues contain only the 3.6-kb species, whereas bovine tissues contain an additional 1.7-kb species. These mRNAs are a consequence of different polyadenylation sites on the 3′-untranslated end of the mRNA.

LPL is synthesized in the parenchymal cells of heart, skeletal muscle, and white and brown adipose tissues and spread along the vascular mesh. In the lactating mammary gland, the enzyme is highly expressed but appears to be sourced from delipidated adipocytes and not the mammary epithelium (114). In the kidney, there is strong immunofluorescence at the vascular endothelium, particularly in the glomeruli, but little LPL mRNA is detected in surrounding cells. In the mammary gland, most of the enzyme appears to be secreted, partially in association with milk fat droplets (113). In tissues with low LPL activity (lung, spleen, and liver), the enzyme is made by scattered cells such as macrophages in the lung and spleen and Kupffer cells in the liver (33). LPL is expressed only transiently in the embryonic liver but not in adult liver. In the adult liver, strong immunoreactivity has been detected in the sinusoids, in contrast to the low levels of mRNA expression, suggesting that the liver takes up circulating LPL from blood (165, 268).

Following synthesis, LPL is secreted and then transported to the luminal surface of vascular endothelial cells, where it is anchored by ion interaction with heparin sulfate proteoglycans (HSPG) and/or by glycosyl phosphatidylinositol (61). The mechanism of this transport is still not completely understood, but it is well known that LPL can be released from the bound form into the circulation by the intravenous administration of heparin. This property has been widely used to assess LPL activity in vivo and to release LPL from cell membranes for purification by heparin-sepharose affinity chromatography. Although a purification scheme has existed for LPL for years, the crystal structure of the enzyme protein has not been solved yet. However, due to the high sequence similarity among the lipase gene family members, information from the crystal structure of PL has been used in combination with other biochemical studies to provide a good understanding of the structure-function relationship for LPL (280).

LPL protein is organized into two structurally distinct domains, an amino-terminal domain and a smaller carboxyl-terminal domain with a flexible peptide connecting the two domains (279). The amino-terminal domain contains the catalytic triad (Ser132, Asp156, and His241) responsible for lipolysis. The carboxyl-terminal domain contains the dominant heparin-binding domain and is thought to be important for binding lipoproteins. Native LPL monomers are arranged in a head-to-tail subunit orientation to form the noncovalent active homodimer (281). Dissociation to the monomeric form results in a loss of enzyme activity (94, 180), and the monomers tend to aggregate rather than reassociate (180). This dissociation occurs rapidly under the physiological conditions in the absence of stabilizing molecules such as heparan sulfate or HSPG (174, 196).

LPL requires a specific cofactor, apoC-II, to be fully active (38, 122). The binding site for this physiological activator has been located to 11 amino acid residues in two different regions of the NH2-terminal domain of LPL, and these two regions appear to act cooperatively to enable the activation of LPL by apoC-II (38, 148). Patients who have an inherited defect of the apoC-II gene are hypertiglyceridemic (28, 43, 71, 189, 217).
Moreover, a homozygous point mutation in the apoC-II gene leading to no detectable plasma apoC-II in infancy causes massive hyperchylomicronemia and a severe encephalopathy (277).

Interestingly, apoC-II transgenic mice that overexpress human apoC-II also develop hypertriglyceridemia attributable to delayed clearance of TG-rich lipoproteins (245). Furthermore, heart LPL activity in these mice is reduced by 30% (201), indicating alterations in the expression/activity of endogenous LPL in the heart. When mice transgenic for apoC-II are crossed with mice that are transgenic for the overexpression of LPL in skeletal muscle, a dose-dependent reduction of plasma TGs is observed, most likely due to the effect of lowering plasma TGs by overexpression of LPL in muscle (201). Together, these data suggest that the decrease of LPL activity in the heart, along with the inhibitory effects of excess apoC-II, contributes to the hypertriglyceridemia observed in apoC-II transgenic mice.

The enzymatic activity of LPL is regulated in a complex manner in response to energy requirements and hormonal changes. Increasing evidence suggests that LPL is regulated at transcriptional, posttranscriptional, translational, and postranslational levels in a tissue-specific manner. Tissue-specific regulation of LPL provides a mechanism for localized control of the uptake of lipoprotein lipids that results in a physiologically appropriate distribution of lipids among tissues. This tissue-specific expression and regulation of LPL has been shown to have major metabolic consequences on macronutrient fuel partitioning, energy homeostasis, insulin action, and lipoprotein metabolism. In the following sections of this review, we will dissect the complex mechanisms of LPL regulation by first reviewing the basic mechanisms of this regulation. Then we will discuss the different levels of LPL regulation by interacting proteins, nutrient state, and hormones. Finally, we will integrate all of the LPL regulatory mechanisms into a diagram (Fig. 2). The impact of altered regulation of LPL on metabolic diseases will be discussed last in this review.

Basic Mechanisms of LPL Regulation

Transcriptional regulation. The activity of the LPL promoter has been studied extensively using in vitro transcription assays. The 5′ regulatory region extends ≈4 kb from the transcription start site and contains a large number of specific cis-acting elements (reviewed in Ref. 199). Briefly, these regulatory elements include CT element (284), sterol regulatory element 2 (236), interferon-λ-responsive element (109), the peroxisome proliferator-activated receptor (PPAR)-responsive element (237, 262), the oxysterol liver X receptor-responsive element (294), the nuclear factor-1-like motif (239), anterior protein-1 (AP-1) element, and AP-1-like element (104, 235). Most of the cis-acting elements positively regulate the activity of the LPL promoter; however, silencing elements reducing promoter activity have been identified at regions −225 to −81 within the human LPL promoter (258) and from position −263 to position −241 in the chicken promoter (293). Interestingly, the DNA sequences between regions −169 and −151 account for both enhancer and silencer activity. This region has a functional peroxisome proliferator-activated receptor-responsive element site where both transcriptional activato

![Diagram of Tissue-Specific Regulation of LPL](http://ajpendo.physiology.org/)
177, 209–211, 213). Inhibition of protein kinase Cα in adipocytes results in decreases in LPL synthesis by translational inhibition (208, 212).

Mature functional LPL is a homodimer. The posttranslational steps (shown in Fig. 3) in forming the active enzyme involve the dimerization and asparagine-linked glycosylation in the endoplasmic reticulum (ER) and transportation to the Golgi apparatus (14, 146, 188). After sorting occurs in the trans-Golgi apparatus, LPL is first delivered to secretory vesicles and then either to lysosomes for intracellular degradation or to the parenchymal cell surface where the enzyme binds to HSPG. Finally, LPL is translocated to the functional HSPG-binding sites on the luminal surface of the capillary endothelium where hydrolysis of TG-rich lipoproteins takes place (27). Both HSPG and the VLDL receptor are important for the transcytosis of LPL across endothelial cells (170).

There is an inactive intracellular LPL pool, especially in adipose tissue and cardiac muscle (14, 19). LPL reaches a functional conformation in the ER. Active LPL, regardless of its cellular location, exhibits the expected dimer conformation. However, inactive LPL, found only in the ER, is highly aggregated. It appears that the inactive pool of LPL is not a precursor to the active form but rather contains misfolded LPL molecules that are trapped in an irreversible, inactive conformation destined for ER degradation (16). Calcium has been shown to trigger the folding of LPL into active dimers (292), a process that might also be involved in the posttranslational regulation of LPL activity.

Well-established transcriptional regulators of LPL such as PPARα and PPARA agonists have been proposed to act through posttranslational mechanisms to affect cellular LPL trafficking (37, 47, 80). Cellular trafficking also appears to be involved in the glucose-dependent, insulin secretion-independent translocation of LPL from intracellular to extracellular sites in pancreatic β-cells (44). In cardiomyocytes, it has been proposed that the involvement of a functional actin cytoskeleton is a prerequisite for glucocorticoid and insulin-dependent intracellular translocation of LPL to sites where the release by heparin is possible (65–67).

**LPL Regulation by Interactive Proteins**

**Lipase maturation factor 1.** Combined lipase deficiency (cld) is a recessive, lethal mutation specific to the tw73 haplotype on mouse chromosome 17. Mice carrying the cld mutation show severe hypertriglyceridemia secondary to decreases in LPL and HL activities. The mutation does not involve the structural genes of LPL or HL and does not affect the mRNAs or protein levels of either enzyme (219). The cld mutation results in LPL and HL proteins that are inactive, aggregated, and retained in the ER, indicating impairment in maturation of nascent LPL and HL polypeptides. The gene containing the cld mutation is identified as Tmem112, renamed as lipase maturation factor 1 (LMF1) (193, 194). LMF1 encodes a transmembrane protein that is localized to the ER with five transmembrane-spanning domains and a conserved domain of unknown function. This conserved domain is found in more than 50 proteins and comprises most of the COOH-terminal part of LMF1. One individual homozygous for a C/G mutation (nucleotide 1319 in NM_022773) in exon 9 of the LMF1 gene has been identified (193). This mutation causes a premature termination codon, resulting in a LMF1 truncation, Y439X, that removes 127 residues from the COOH terminus conserved domain. The Y439X subject is severely hypertriglyceridemic and has repeated episodes of pancreatitis. As expected, there is a 93% decrease in LPL activity and a 50% decrease in HL activity in the plasma of this affected individual.

**Angiopoietin-like proteins 3 and 4.** The angiopoietin-like (Angptl) family proteins share a structural motif with the angiopoietins, with an NH2-terminal coiled-coil domain and a COOH-terminal fibrinogen-like domain. Three of the Angptls impact metabolism (172, 225). Specifically, Angptl3 and Angptl4 inhibit LPL activity and are associated with hypertriglyceridemia (127, 136, 250). Knockout of the gene for either Angptl3 or Angptl 4 in mice leads to increased levels of heparin-releasable LPL activity and decreased levels of plasma TGs (78, 127). Alternatively, the overexpression of either Angptl leads to decreases in LPL activity and increases in plasma TGs (127). In addition, when Angptl4 is overexpressed only in the heart, LPL activity is reduced in cardiac muscle and lipoprotein TG utilization is reduced (290). Interestingly, Angptl3 and Angptl4 have also been shown to inhibit the functions of other members of the TG lipase gene family such as HL and EL (137, 249).

The mechanism of how Angptls inhibit LPL activity has been studied in adipose tissue. Current evidence suggests that a gene separate from the lipase gene prevents the LPL enzyme from becoming activated, although synthesis of the LPL protein continues (20). Angptl4 is expressed in adipose tissue, and its expression increases during fasting (287). The NH2-termi-
nal coiled-coil domain of Angptl4 can bind transiently to LPL and convert the enzyme from a catalytically active dimer to the inactive monomer, still folded but with decreased affinity for heparin. This unusual inactivation mechanism occurs with less-than-equal molar ratios of Angptl4 to LPL and is strongly temperature dependent. In addition, Angptl4 mRNA abundance is inversely correlated with LPL activity during both the fed-to-fasted and fasted-to-fed transitions. Of note, LPL activity is downregulated in adipose tissue during fasting and at the posttranslational level with no change in LPL mRNA or protein (53). It appears that Angptl4 is a fasting-induced regulator of LPL activity in adipose tissue and functions as an unfolding molecular chaperone (255). Angptl3 apparently inhibits LPL activity by a mechanism different from Angptl4. Enzyme kinetic analysis using purified recombinant proteins shows that Angptl3 reduces LPL catalytic activity but does not alter the self-inactivation rate of LPL. Furthermore, heparin is able to overcome the inhibitory effect of Angptl3 on LPL but not that of Angptl4 (246). Thus, Angptl3 and Angptl4 may play unique roles in modulation of lipid metabolism by inhibiting LPL activity through distinct mechanisms.

Receptor-associated protein. Receptor-associated protein (RAP) is a recognized chaperone/escort protein for members of the low-density lipoprotein receptor gene family (128, 150). Its function is confined largely to the ER, since RAP is an ER resident protein that is recycled by the KDEL receptor (31, 32). RAP overexpression in mice deficient in both the low-density lipoprotein receptor and low-density lipoprotein receptor-related protein (LRP) results in a defect in conversion of chylomicrons into smaller remnant particles and striking hypertriglyceridemia. This defect correlates with an increase in the concentration of inactive LPL in plasma, indicating a possible role of RAP in the maturation of LPL (265). RAP can also inhibit the LRP-mediated LPL degradation in adipocytes (171). Recent studies show that RAP binds to LPL with high affinity in both purified systems and cell extracts. RAP-deficient adipocytes secrete poorly assembled LPL that has defective binding to the plasma membrane (182). RAP may function as a chaperone/escort protein to prevent premature interaction of LPL with binding partners such as LRP and HSPG in the secretory pathway.

Apolipoprotein A5. Apolipoprotein A5 (APOA5) has emerged as a regulator of the lipolysis of TG-rich lipoproteins either by inhibiting hepatic VLDL production (9, 10, 274) or by activating intravascular TG hydrolysis by proteoglycan-bound LPL (155, 256). Common APOA5 single-nucleotide polymorphisms have been strongly associated with elevated plasma TG levels and familial combined hyperlipidemia (126), and a truncation mutation of APOA5 is associated with familial hyperchylomicronemia (144). In genetically engineered mice, APOA5 plasma levels are inversely correlated with plasma TGs. In APOA5 transgenic mice, catabolism of chylomicrons and VLDL is accelerated due to a faster plasma hydrolysis of TGs by LPL. By cross-breeding a human LPL transgenic line with APOA5-deficient mice and, conversely, the APOA5 transgene to an LPL-deficient background, it has been determined that increased LPL activity completely normalized the hypertriglyceridemia of APOA5-deficient mice. However, overexpression of human APOA5 modulates TG levels only slightly when LPL is reduced (155).

Despite the very low levels of APOA5 in plasma (~25 μg/dl) (45a) compared with other apolipoproteins, APOA5 appears to act as a potent regulator of plasma TG levels in humans. The interaction between APOA5 and LPL seems to be direct and proteoglycan dependent. Without proteoglycans, APOA5 derived from various sources does not alter the LPL hydrolytic rate (142, 155). In the presence of proteoglycans, APOA5 can lead to a dose-dependent increase of LPL-mediated hydrolysis (155). A proteoglycan-binding site exists in APOA5, and APOA5 can specifically increase the binding of chylomicrons and VLDL to proteoglycans. This effect is even increased in the presence of LPL and is abolished by heparin (142). APOA5 represents a protein that regulates LPL activity by facilitating its interaction with substrates.

Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1. Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) is a newly reidentified endothelial cell molecule that appears to play an important role in the LPL-mediated lipolytic processing of chylomicrons (289). First identified as a glycosylphosphatidylinositol-linked protein that facilitated the binding of high-density lipoproteins (HDL) to cultured cells (110), GPIHBP1-deficient mice exhibit a striking accumulation of large chylomicrons in the plasma, even on a low-fat diet, resulting in milky plasma and plasma TG levels as high as 5,000 mg/dl. Normally, GPIHBP1 is expressed highly in the heart and adipose tissue, the same tissues that express high levels of LPL. In these tissues, GPIHBP1 is located on the luminal face of the capillary endothelium. Expression of GPIHBP1 in cultured cells confers the ability to bind LPL, chylomicrons, and APOA5 (11).

A homozygous G56R mutation in GPIHBP1 has recently been identified in two siblings with type V hyperlipoproteinemia and relapsing pancreatitis resistant to standard therapy. The GPIHBP1 G56 residue is well conserved, and the G56R mutation is predicted to have compromised function (272). However, G56R substitution does not appear to affect the ability of GPIHBP1 to reach the cell surface, nor does the amino acid substitution have any discernible effect on the binding of LPL, chylomicrons, or APOA5 in vitro (84). G56R heterozygotes in the family have mild fasting hypertriglyceridemia, but the exact mechanism is yet to be determined.

Interestingly, mouse GPIHBP1 is N-glycosylated at Asn76 within the Lys6 domain. Human GPIHBP1 is also glycosylated. Mutating the N-glycosylation site in mouse GPIHBP1 results in an accumulation of GPIHBP1 in the ER and a markedly reduced amount of the protein on the cell surface. Consistent with this finding, cells expressing a nonglycosylated GPIHBP1 lack the ability to bind LPL or chylomicrons (12). It appears that glycosylation is a common posttranslational mechanism shared by both GPIHBP1 and LPL. GPIHBP1 harbors a strongly negatively charged acidic domain that can potentially bind to the positively charged domain of apolipoproteins contained in chylomicrons as well as the positively charged heparin-binding domain in LPL (179). Exactly how GPIHBP1 mediates LPL and chylomicron binding is still not clear. Whether GPIHBP1 can simultaneously bind chylomicrons and LPL also remains to be answered.
Nutritional and Hormonal Regulation of LPL

LPL is synthesized in a number of tissues and is regulated in a tissue-specific manner by nutrients and hormones (Table 1). Life stage is also important to LPL gene expression and regulation. For example, LPL is expressed in the liver during fetal and early postnatal life, but gene expression is then suppressed by a putative transcriptional regulatory mechanism (239). Thyroid hormone and glucocorticoids also play roles in the extinction of the hepatic expression of LPL (191). In the mammary gland, LPL activity is induced during late pregnancy and lactation (49, 90), and it appears that the partially differentiated and delipidated adipocytes rather than the epithelial cell are the source of the lipase (114). More recent evidence indicates that prolactin works through prolactin receptors to reduce LPL activity in cultured human abdominal adipose tissue (138). However, this effect has not been demonstrated in the mammary gland. In brown adipose tissue, cold exposure stimulates LPL activity by a combination of transcriptional and translational/posttranslational mechanisms that involve β-adrenergic stimulation (34, 35, 85). Both chronic and acute stress decrease LPL activity in white adipose tissue but increase the LPL activity through the effect of catecholamines in cardiac and skeletal muscle as well as in the adrenal glands (221).

Feeding and fasting regulate LPL activity in a tissue-specific manner as well. In both rodents and humans, nutritional regulation of LPL activity in white adipose tissue and muscle exists mostly at the posttranslational level. Adipose tissue LPL activity is high in fed animals and low when animals are fasted, but most studies have shown that the opposite is true in the heart and skeletal muscle. However, in a study with 25 human subjects consuming either a high-carbohydrate diet [50% carbohydrate (CHO), 30% fat] for 2 wk or a high-fat diet (50% fat, 30% CHO) for 2 wk, followed by the alternative diet for 2 wk, the high-carbohydrate exposure increases the LPL response to feeding in both adipose tissue and skeletal muscle (288). A significant difference between the two diets in the LPL meal response is observed only in adipose tissue (high carbohydrate > high fat). Of interest, there is no effect of diet composition on insulin sensitivity. In rats fasted for 1 day, the fall in adipose tissue LPL is not accompanied by changes in LPL mRNA or LPL mass (53, 64). Similar data are available in humans as well (175). Evidence also indicates that adipose tissue LPL is downregulated rapidly by fasting (173). It appears that during fasting there is activation of a gene whose product converts newly synthesized LPL into a catalytically inactive form (19, 20). On refeeding, the process is rapidly reversed and the activity reaches the fed level within 4 h (18). LPL activity in mice responds to the nutritional state in the same direction and by a similar mechanism as in rats, but the magnitude of the changes is less in mice (229).

The mechanism for LPL regulation in the heart appears to be more complex. The heparin-releasable LPL activity in the heart increases severalfold with fasting. The transition between active and inactive forms of LPL, similar to what happens in adipose tissue, is believed to be the major mechanism (282). However, alterations in the distribution of LPL between the vascular endothelium and other sites within the heart explain some of the differences in the enzyme activity with fasting and feeding (227).

Insulin has a major effect on LPL activity in adipose tissue during adipocyte differentiation by increasing LPL gene transcription (243). In mature adipocytes or adipose tissue, insulin not only increases the level of LPL mRNA but also regulates LPL activity through both posttranscriptional and posttranslational mechanisms (2, 3, 215, 243). Glucose also increases adipose tissue LPL activity. The glucose stimulatory effect appears to be mostly through the glycosylation of LPL, which is essential for LPL catalytic activity and secretion. Glucose also stimulates LPL synthetic rate and potentiates the stimulatory effect of insulin (117, 176). Unlike insulin, glucose does not affect the level of LPL mRNA.

Table 1. Differential responses of adipose tissue and skeletal muscle LPL to nutritional and hormonal signals and in metabolic disease states

<table>
<thead>
<tr>
<th>Condition</th>
<th>SC Adipose Tissue LPL</th>
<th>Skeletal Muscle LPL</th>
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<tbody>
<tr>
<td>Fasting</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High CHO</td>
<td>↑ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>High fat</td>
<td>↑ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Exercise</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>↑ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>↑ ↑</td>
<td>No change</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>↓ in rat, ↑ in human</td>
<td></td>
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<tr>
<td>Estrogen</td>
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<tr>
<td>Testosterone</td>
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<td>Obesity</td>
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LPL, lipoprotein lipase; SC, subcutaneous; CHO, carbohydrate; ↑ and ↓ represent directional effect and magnitude of the effect of the “condition” on LPL in 2 sites, SC adipose tissue and skeletal muscle.
testosterone and bioavailable testosterone levels are inversely correlated with femoral and abdominal wall adipose tissue LPL (207). Testosterone treatment of abdominally obese men also produces a decrease in visceral fat mass (216).

Estrogen reduces the fat mass gain following ovariectomy in rodents. The mechanism underlying this estrogen-dependent effect may in part relate to LPL. LPL mRNA as well as TG accumulation are decreased in 3T3-L1 adipocytes stably transfected with the estrogen receptor. Although there is no classical estrogen response element in the LPL promoter, it has been demonstrated that an AP-1-like TGAATTC sequence located at (−1,856/−1,850) is responsible for the reduction of LPL gene transcription by estrogen (104). In addition, a potential estrogen response element sequence has been located in the first intron of the mouse LPL gene (140). In mice, the addition of 17β-estradiol to hearts from ovariectomized females increases LPL mRNA. This estrogen effect on LPL is blocked by the estrogen receptor antagonist ICI-182,780 or by progesterone. In obese women, an inverse relationship between plasma estradiol levels and adipose tissue and postheparin plasma LPL is seen (111). However, in postmenopausal women, treatment with both estrogen and progestins increases the LPL activity in the adipose tissue and preferentially in the femoral depot (216).

There are marked variations in the activity of LPL in adipose tissue depots in humans. The steady-state mRNA levels for LPL as well as LPL mass are lower in omental (OM) than subcutaneous (SC) adipose tissue (73, 183). However, the specific LPL activity is greater in OM compared with SC adipose tissue (228). Insulin increases the levels of LPL mRNA and LPL activity in abdominal SC but not OM adipose tissue, whereas glucocorticoids increase the LPL mRNA and LPL activity more in OM adipose tissue, particularly in men (73). Insulin and glucocorticoids have synergistic effects on LPL activity in both depots, with the SC depot being more sensitive to the effects of glucocorticoids in the presence of insulin. The effects of insulin and glucocorticoids on human adipose tissue LPL activity are both transcriptional and post-translational. A positive correlation between LPL activity and glucocorticoid binding exists for both OM and SC depots in both men and women (190).

LPL activity has been reported to increase as a function of fat cell size (22, 57, 89, 230, 241), and sex differences seem to alter the relationship between LPL activity and fat cell size. Fat cell size is greater in females than males in the thigh and gluteal regions but not in the abdomen. Fasting LPL activity/fat cell correlates well with the fat cell size in females in all three areas, but only in the abdomen and thigh in men (270). This may relate to the fundamental differences in the regulation of TG uptake between males and females in different regions of adipose tissue.

The Tissue-Specific Regulation of LPL in Fuel Partitioning

Genetic modification using mouse models has been widely employed to characterize the tissue-specific role of LPL in lipid metabolism and energy balance. In this section we will review the tissue-specific mechanism of LPL regulation and its impact on fuel partitioning and energy metabolism revealed by these studies.

Mice with a generalized deletion of LPL (LPL−/−) have threefold higher plasma TGs and sevenfold higher VLDL cholesterol levels at birth. When permitted to suckle, LPL−/− pups become pale, then cyanotic, and die within 24 h either from ischemia or from hypoglycemia as a result of the inability to process the lipid nutrients in milk. Before death, LPL−/− pups are severely hypertriglyceridemic (~20,000 mg/dl) and have depleted tissue storage of TGs (275). Adenovirus-mediated expression of LPL can rescue LPL−/− pups, but the rescued mice are still hypertriglyceridemic with plasma TG levels of ~3,000 mg/dl on a chow diet (254). Mice with heterozygous LPL deficiency (LPL+/−) have somewhat lower levels of fasting plasma glucose with relative hyperinsulinemia, possibly due to increased insulin secretion as a result of reduced expression of LPL and TG content in islets (145). The fat mass/lean mass ratio difference in LPL+/− mice generally increases over time, indicating an age-dependent excessive accumulation of body fat (41). When LPL+/− mice are crossed with mice with cardiac muscle- or liver-specific overexpression of LPL, the hypertriglyceridemia is eliminated and adipose tissue development appears normal (134, 156).

Transgenic mice with generalized overexpression of human LPL have a fivefold higher LPL activity in adipose tissue and 1.7-fold higher postheparin plasma LPL activity with a 75% reduction in plasma TGs (248). Overexpression of LPL protects against diet-induced hypertriglyceridemia and hypercholesterolemia in these mice. It is interesting to note that over-expression of a catalytically inactive LPL (G188E-LPL) also seems to improve the high-fat diet-induced systemic insulin resistance and hypertriglyceridemia in these mice (247). In addition, studies carried out in LPL+/− mice indicate that inactive LPL can act in vivo to mediate VLDL removal from plasma and uptake into tissues in which it is expressed (154).

LPL in the liver. LPL is normally not made in the adult liver but is expressed in the liver of newborn animals. As the pups suckle, increases in LPL activity occur in the heart, skeletal muscle, and adipose tissue, whereas ultimate extinction of LPL activity is seen in the liver (40). However, LPL can be expressed in the liver under specific physiological and artificial conditions. For example, a single dose of TNFα can cause a marked increase in LPL mRNA levels in the liver (63). In mice with sarcoma 180, LPL activity in liver homogenates is increased significantly (147), and treatment with fibrates, a widely used class of lipid-modifying agents, can activate PPARs and stimulate LPL activity in the liver (75, 76, 238, 252). The detailed mechanism of how LPL is induced under these conditions is not well understood.

In liver-only LPL mice, the neonatal death of LPL knockout mice can be rescued, but mice develop severe cachexia during high-fat suckling and have elevated plasma TGs, increased plasma ketones and glucose, and excessive hepatic steatosis (156). When LPL is overexpressed in the liver in mice, a twofold increase in liver TG content and insulin resistance is observed (119). In these mice, increases in hepatic LPL activity impair the ability of insulin to suppress endogenous glucose production in the liver, and the defect in insulin action and signaling in the liver is associated with increases in intracellular fatty acid-derived metabolites.

LPL in the heart. The heart is a major site of LPL synthesis, and fatty acids provide >70% of the energy needs for cardiac muscle. Not surprisingly, cardiac muscle is the tissue with the greatest expression of LPL, and thus LPL is likely to be an important enzyme in cardiac lipid uptake and metabolism. The
role of LPL in the energy metabolism in the heart has been explored extensively in mouse models.

Mice without cardiac LPL survive (6, 156), although the loss of LPL in the heart leads to defective plasma TG-rich lipoprotein metabolism and compensatory increases in cardiac glucose metabolism (6). Of interest, the maintenance of normal fatty acid uptake in the setting of cardiac-specific LPL deletion indicates that fatty acids derived from lipoprotein TGs and not just albumin-associated fatty acids are important for cardiac lipid metabolism and gene regulation. Heart-specific LPL-knockout mice display elevated plasma TG levels and decreased clearance of postprandial lipids despite normal post-heparin plasma LPL activity (6). Loss of LPL-derived fatty acids in these mice also leads to increased cardiac glucose metabolism and cardiac dysfunction characterized by decreased fractional shortening and interstitial and perivascular fibrosis (7, 133). Moreover, mice with tamoxifen-inducible cardiomyocyte-specific LPL deletion show that acute loss of LPL leads to rapid increases in plasma TGs and decreases in expression of carnitine palmitoyl transferase I and pyruvate dehydrogenase kinase 4 in cardiac muscle (168). Acute LPL deletion in adult mice also leads to cardiac dysfunction, as shown by decreases in ejection fraction and increases in atrial natriuretic factor mRNA.

When LPL is expressed only in the heart, mice maintain normal levels of plasma TGs and HDL cholesterol despite the lack of skeletal muscle and adipose tissue LPL and a reduced amount of postheparin LPL activity (134). LPL apparently has additional roles in the heart, e.g., to promote nonhydrolyzable core lipid uptake. When mice express a GPI transgene to anchor LPL to cell membranes, the lipase protein localizes to the surface of cardiomyocytes and increases lipid uptake. The hearts of these transgenic mice experience cardiac lipotoxicity and a dilated cardiomyopathy (133, 283).

Cardiomyopathy also occurs in the hearts of patients with diabetes, and various mechanisms have been proposed. Of interest, heparin-releasable LPL activity is upregulated in the hearts of rats with diabetes in response to the increased need of fatty acids for energy, and this regulation is regulated by short-term changes in insulin rather than glucose (233). Several possible mechanisms have been suggested. One such process involves the effect of AMP-activated protein kinase on the uptake of postprandial lipids despite normal postprandial lipolysis. Moreover, when mice express a GPI transgene to anchor LPL to cell membranes, the lipase protein localizes to the surface of cardiomyocytes and increases lipid uptake. The hearts of these transgenic mice experience cardiac lipotoxicity and a dilated cardiomyopathy (133, 283).

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In summary, the results from rodent models of altered expression of LPL in heart emphasize the important role of cardiac LPL in TG-rich lipoprotein metabolism. Neither non-esterified fatty acids nor the compensatory increase in cardiac glucose metabolism can entirely replace the fatty acids not provided by LPL in the heart. Moreover, when LPL is over-expressed, excess lipoprotein-derived lipids appear to hinder cardiac bioenergetics and cardiac function. It appears that the heart needs an optimal balance of glucose and fatty acids to maintain normal biochemistry and physiology, and chronically altering this balance leads to cardiac dysfunction.

**LPL in skeletal muscle.** Arguably the most productive lines of research related to the tissue-specific effects of LPL on lipid fuel partitioning, body weight regulation, and insulin action have come from genetic modifications of the LPL gene in skeletal muscle.

Skeletal muscle is a major site for LPL synthesis, and skeletal muscle is also the major tissue responsible for whole body insulin-stimulated glucose uptake/disposal. There is an intense interest in what role lipid, and perhaps LPL-derived lipids, may play on substrate partitioning and insulin action. In addition, the important role of skeletal muscle LPL in the regulation of body weight and energy homeostasis has recently been established.

Mice that express human LPL exclusively in skeletal muscle have normal postheparin LPL activities, reduced plasma TG levels, and reduced HDL cholesterol levels, but the growth and body composition of these mice appear to be normal (135). However, mice transgenic for LPL overexpression in skeletal muscle are insulin resistant (70, 119), have increases in muscle TG (116, 119, 269), and have less carcass lipid. Male mice are also resistant to high-fat diet-induced obesity (116). Decreases in insulin-stimulated glucose uptake in skeletal muscle and insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol (PI) 3-kinase activity are also associated with increases in intracellular fatty acid-derived metabolites, i.e., diacylglycerol, fatty acyl-CoAs, and ceramides (119). Fasting decreases the free fatty acid turnover in these transgenic mice, indicating a lesser dependence on plasma free fatty acids during periods of nutrient deficiency (17). Very interestingly, transgenic overexpression of LPL in skeletal muscle increases cold tolerance of mice by enhancing metabolic rate and fat oxidation. These mice also display a remarkable switch to the more oxidative type IIA fibers over the more glycolytic type IIB fibers in the gastrocnemius and quadriceps muscles (115).

Mice with a skeletal muscle-specific deletion of LPL (SMLPL<sup>−/−</sup>) have recently been generated (271). At 9–11 wk, SMLPL<sup>−/−</sup> mice have normal glycemic responses to intraperitoneal glucose or insulin administration. During a steady-state insulin infusion, SMLPL<sup>−/−</sup> mice also have normal whole body glucose disposal. Yet, at the terminus of the euglycemic clamp, [³H]deoxyglucose disposal is increased in skeletal muscle but reduced in white adipose tissue, brown adipose tissue, and heart. Moreover, the suppression of hepatic glucose production is also reduced in SMLPL<sup>−/−</sup> mice. Skeletal muscle TG is reduced, and insulin-stimulated phosphorylated Akt (Ser<sup>473</sup>) is twofold greater in SMLPL<sup>−/−</sup> mice without changes in IRS-1 tyrosine phosphorylation and PI 3-kinase activity. Hepatic TG content and liver X receptor, carbohydrate response element-binding protein, and phosphoenolpyruvate carboxykinase mRNAs are unaffected in 9– to 11-wk-old SMLPL<sup>−/−</sup> mice, but PPAREγ coactivator-1α and IL-1β mRNAs are higher and stearyl-CoA desaturase-1 and PPAREγ mRNAs are reduced. Overall, LPL deletion in skeletal muscle seems to reduce lipid storage and increase insulin signaling in skeletal muscle without changes in body composition. Importantly, the lack of LPL in skeletal muscle results in insulin resistance in other key metabolic tissues, ultimately leading to age-dependent and diet-inducible obesity and systemic insulin resistance. SMLPL<sup>−/−</sup> mice provide another important model to study in detail the role of muscle LPL on lipid fuel partitioning and body weight regulation and energy balance.
LPL in adipose tissue. LPL is an important marker for adipocyte differentiation (24), and LPL expression increases in parallel with cellular TG accumulation as preadipocytes differentiate (243). Although adipose tissue can synthesize free fatty acids de novo, free fatty acids for lipid storage are preferentially provided by LPL-mediated hydrolysis of plasma TG-rich lipoproteins (101). LPL is thus considered a gatekeeper enzyme to play an important role in the initiation and/or development of obesity.

Transgenic mice expressing human LPL in adipose tissue have a twofold increase in LPL activity in white adipose tissue (98). However, these mice exhibit normal body weight, plasma lipids, glucose, and free fatty acid levels. In similar transgenic mice expressing human LPL without the proximal 3'-untranslated region, human LPL mRNA is low compared with the large amounts of human LPL protein and LPL activity. The 3’-untranslated region of the LPL gene has been shown to be critical for the inhibitory effect of constitutively expressed hormones such as catecholamines. Thus, the absence of 3’-untranslated region in transgenic mice results in a LPL protein that is readily expressed, leading to a moderate overexpression of adipose LPL activity (98).

Mice that have adipose tissue-specific deletion have not yet been reported. However, the role of adipocyte-derived LPL in the lipid storage function of adipose tissue has been studied indirectly in mice with muscle-specific expression of LPL on an LPL−/− background. In these cross-bred mice, LPL expression is absent in adipose tissue, and these mice appear to have normal body weight gain and body composition. However, closer examination of the adipose tissue composition indicates that LPL deficiency is compensated for by large increases in endogenous adipose tissue fatty acid synthesis to preserve normal lipid storage (276). In a much simpler, well-established, cultured model of adipocyte differentiation in 3T3-L1 preadipocytes, evidence supports that adipocyte-derived LPL is required for efficient fatty acid uptake and storage (87).

LPL in brain and central nervous system. LPL is present throughout all parts of the nervous system. In the brain, LPL mRNA is found in dentate granule cells, pyramidal cells in the cortex, Purkinje cells in the cerebellum, and CA1–CA4 cells in the hippocampus. In addition, LPL is distributed on the endothelial surfaces throughout the brain. LPL mRNA, protein, and enzyme activity are also found in the spinal cord and sciatic nerve (15, 21, 69, 108, 169). LPL activity is relatively high in the newborn brain and peaks between the 5th and the 10th day after birth, reaching activities five times higher than in the adult brain (169). The hippocampal area has the highest LPL activity among all brain regions (15, 169, 267), and the spinal cord of the rat, in particular the caudal spinal cord, appears to have even more LPL activity than each individual brain region (21).

LPL also appears to serve as a transport protein for cholesterol and vitamin E to neurons, a process that may help the survival, plasticity, and regeneration of neuronal processes (15, 108, 185, 186). LPL expression is essential for promoting VLDL-stimulated differentiation of Neuro-2A cells (186), and the active LPL is required for this process (187). In response to deafferentation, the murine hippocampus exhibits a marked induction of LPL mRNA and protein levels, indicating a potential role of LPL in the recycling and/or scavenging of lipids and cholesterol released from the degenerating nerve terminals (25). The hippocampus is well recognized as the learning center of the brain, where hippocampal neurons contribute to memory by rapidly assimilating information about the perceptual and behavioral structure of experience. The process by which this occurs is called long-term potentiation, whereby a series of conditioned impulses potentiate the size of synaptic potentials. The role of LPL in this process remains hypothetical but worthy of consideration as a protein that senses changes in macronutrient and/or energy balance.

LPL mRNA, protein, and enzyme activity are also found at a lower level in the hypothalamus. The hypothalamus plays a critical role in monitoring the nutritional status of the body and to initiate cogent behavioral and metabolic responses (130). Pharmacological and molecular manipulations of hypothalamic nutrient sensing affect appetite, disrupt energy balance, and contribute in a substantial manner to body weight regulation (96). It will be interesting to see whether LPL-derived lipids or other nonenzymatic functions of LPL contribute to nutrient sensing in the brain.

LPL in Metabolic Disorders: Hypertriglyceridemia and Obesity

Hypertriglyceridemia. There are three naturally occurring mutations related to LPL in mice that affect lipid transport and metabolism that result in hypertriglyceridemia (219).

Combined lipase deficiency (cld) is a recessively inherited disorder in mice associated with a deficiency of LPL and HL. LPL is synthesized in the tissues of cld mice but is retained in the ER (48). These mice have normal LPL synthesis, glycosylation, and dimerization but have impaired posttranslational processing of the lipase at the steps of activation and secretion. They develop severe hypertriglyceridemia and die within 3 days after birth (242). The cld mutation is believed to affect components in the ER that play roles in protein maturation (29). The gene that is affected by the cld mutation has recently been identified as LMF1, already described in an earlier section of this review.

Fatty liver dystrophy (fld) is an autosomal recessive mutation in mice characterized by hypertriglyceridemia and fatty liver during neonatal development. The fatty liver in fld/fld mice spontaneously resolves between the ages of 14 and 18 days, at which point the animals develop a neuropathy associated with abnormal myelin formation in the peripheral nerve. Serum and hepatic TG levels are elevated fivefold in suckling fld/fld mice, and white adipose tissue LPL activity is reduced by 15-fold. The fld mutation is mapped to a locus that is different from loci encoding LPL and HL and those in cld/cld mice. This indicates that the mutation is associated with developmentally programmed tissue-specific defects in the neonatal expression of LPL and HL activities (132). Adult fld/fld mice have adipose tissue deficiency, glucose intolerance, modest hyperinsulinemia, and insulin resistance. The lack of lipid accumulation in fld/fld adipose tissue can be attributed in part to a failure to induce LPL and enzymes involved in fatty acid synthesis (220).

Mice carrying fld mutations have features of human lipodystrophy, a genetically heterogeneous group of disorders characterized by loss of body fat, fatty liver, hypertriglyceridemia, and insulin resistance. The gene that is responsible for the fld mutation is lipin1, which encodes a novel nuclear protein that...
is expressed in high levels in adipose tissue and skeletal muscle (195). Lipin1 belongs to a family of related proteins that possess phosphatidate phosphatase type 1 activity (52). Of interest, lipin1 has been implicated as both a lipodystrophy and obesity gene (197) and potentially plays an important role in glucose metabolism and regulation of energy balance (143). The contribution of lipin1 to the tissue-specific, developmental regulation of LPL activity is worthy of further pursuit.

W/Wv mice have a genetic defect that leads to a deficiency of mast cells (125). Seventy percent of the W/Wv mice show hypertriglyceridemia combined with hypercholesterolemia with variable increases in chylomicrons, VLDLs, and IDLs. W/Wv mice have low postheparin plasma LPL activity, but the tissue LPL activity is not changed in heart and adipose tissue. The mast cell deficiency in W/Wv mice leads to a reduction in connective tissue heparin (253) that contributes to defects in LPL transport (95). The lack of transport of LPL to the endothelium substantially reduces LPL-dependent TG-rich lipoprotein catabolism.

In humans, type I hyperlipoproteinemia is a rare autosomal recessive disease (1/1,000,000) characterized by little or no LPL activity and severe hypertriglyceridemia, low levels of HDL cholesterol, and the variable presence of eruptive xanthomatata, lipemia retinalis, and pancreatitis when plasma TGs are not controlled by dietary fat restriction. Interestingly, LPL-deficient patients still have normal adiposity. Adipose tissue fatty acid composition analysis reveals an increase in 16:1 and a decrease in 18:0, 18:2, and 18:3 fatty acids (264). The reduction in essential fatty acids suggests that enhanced adipocyte lipogenesis is most likely responsible for maintaining normal lipid storage in these patients. Moreover, in mice deficient in adipose tissue LPL, fat mass is preserved by endogenous fatty acid biosynthesis (276). A similar adipose and plasma fatty acid composition has been found in normal and LPL-deficient cats wherein LPL deficiency also results in reductions in dietary fatty acid storage, preferential saturated vs. unsaturated fatty acid storage, and enhanced de novo fatty acid synthesis sufficient to maintain normal adiposity (266).

Most patients with LPL deficiency are compound heterozygotes. Several mutations occurring predominantly in exons 4, 5, and 6 of the LPL gene result in a LPL enzyme that is usually catalytically inactive and consequently being degraded within the cells, causing little or no postheparin LPL activity in the plasma of these patients (72, 100, 131, 286). Exemplary is a patient homozygous for two point mutations in the LPL gene (Asp <sup>3</sup> <sup>→</sup> Asn, Tyr<sup>262</sup> <sup>→</sup> His) with familial LPL deficiency (226), affecting the stability of the LPL dimer and subsequently reduced heparin affinity. In another very recent report, multiple family members of a familial LPL deficiency patient showed compound heterozygosity for the known Gly<sup>188</sup> <sup>→</sup> Glu missense mutation and a novel nonsense mutation Trp<sup>394</sup> <sup>→</sup> X (105). The latter nonsense mutation causes a truncated protein product that lacks the carboxy-terminal 12% of the mature LPL with residues that are important for binding lipid substrates. Patients with type I hyperlipoproteinemia can also have familial apo-C-II deficiency or an inhibitor to LPL (30, 166, 217). Most often, however, patients with severe hypertriglyceridemia do not have LPL deficiency but the combination of a genetic cause of overproduction of VLDL plus an additional acquired disorder(s) of VLDL production and/or reduction in LPL activity (39, 234).

About 20% of the patients with hypertriglyceridemia are carriers of common LPL gene mutations such as Asp<sup>3</sup> <sup>→</sup> Asn, Asn<sup>291</sup> <sup>→</sup> Ser, Trp<sup>250</sup> <sup>→</sup> Arg, Gly<sup>188</sup> <sup>→</sup> Glu, Pro<sup>207</sup> <sup>→</sup> Leu, and Asp<sup>250</sup> <sup>→</sup> Asn (81). The importance of the Asn<sup>291</sup> <sup>→</sup> Ser gene variant to hypertriglyceridemia has been reviewed using meta-analysis (106). This variant also predisposes to more severe dyslipidemia with increasing age and weight gain. Two common LPL polymorphisms (HindIII: T <sup>→</sup> G; Ser<sup>447</sup> <sup>→</sup> Ter: C <sup>→</sup> G) have also been shown to be associated with low HDL cholesterol levels and hypertriglyceridemia in Asian Indians (204). The Gly<sup>188</sup> <sup>→</sup> Glu mutation is the most frequent among French Canadians (72) and is by far the most frequent mutation in patients with LPL deficiency and chylomicronemia in the general population (82). Carriers for the Gly<sup>188</sup> <sup>→</sup> Glu mutation have increases in plasma TGs, decreases in HDL cholesterol, higher fasting insulin levels, and impaired insulin sensitivity (103).

In recent years, LPL mass in preheparin serum (preheparin LPL mass) has been suggested as a biomarker of the metabolic syndrome, a condition that is characterized by a combination of obesity, insulin resistance, and dyslipidemias (92, 159, 160, 232, 273). Preheparin LPL mass levels are not affected by aging and sex differences but are generally lower in the conditions in which TG catabolism is disturbed (273). Preheparin LPL mass reflects insulin sensitivity in the general population (92), and the level is significantly lower in patients with type 2 diabetes (160). Clinical studies have implicated that low preheparin LPL mass may reflect systemic oxidative stress (232), and preheparin LPL mass is inversely related to the extent of the metabolic syndrome (159, 232). Furthermore, preheparin LPL has been reported to be bound to postprandial TG-rich lipoproteins (such as remnants or IDLs) in humans when ex vivo lipolytic activity is inhibited (291, 295). This suggests that LPL may affect the receptor-mediated removal of these particles in vivo. A similar study conducted in transgenic mice that express inactive LPL exclusively in muscle reveals greater hepatic uptake (97), strongly suggesting that LPL is a structural component of postprandial TG-rich lipoproteins that facilitates hepatic TG-rich lipoprotein clearance from the circulation independent of its catalytic function. However, it is important to point out that the preheparin LPL activity does not accurately reflect LPL in postheparin plasma (56). Thus, postheparin plasma LPL activity remains the gold standard to address systemic LPL lipolytic capacity (102).

Obesity. Obesity is in epidemic proportions and demonstrates no signs of reduced incidence. Because weight loss is not only difficult to achieve but more difficult to sustain long term (46, 158, 263), mechanisms must exist to defend the expanded fat mass. Following weight reduction, increases in energy intake, decreases in energy expenditure, and modifications of energy partitioning, storage, and oxidation all contribute (1, 55). Therefore, it becomes increasingly important to understand how body weight and adipose tissue are regulated, including the role of macronutrient partitioning.

Lipid partitioning is important to insulin action, energy balance, and the regulation of body weight and composition. The normal physiology of lipid and lipoprotein fuel partitioning is controlled by the transport and uptake of adipose tissue-derived free fatty acids and lipoprotein-derived TG fatty acids. As previously stated in LPL Gene and Protein, lipoprotein lipid partitioning is largely dependent on the enzymatic action
of LPL. Mouse models of tissue-specific LPL deletion and overexpression (summarized previously) have implicated a direct role of LPL in the regulation of body weight and composition. Results from human studies also provide increasing evidence that LPL is an obesity gene.

Variants in the promoter of the LPL gene have been associated with changes in lipid metabolism leading to obesity and type 2 diabetes. The HindIII polymorphism is significantly associated with body mass index in obese people (112). The −T93G promoter variant single nucleotide polymorphism (SNP) of the LPL gene has been found to be associated with obesity but not type 2 diabetes among an urban Asian Indian population, whereas another promoter variant, −G53C SNP in the LPL gene, appears to be protective against both obesity and type 2 diabetes (205). The −T93G SNP is also found in high frequency in the black South African population, and the conservation of the −93G allele among different species suggests that it is the ancestral allele on which a transition to T and the Asp93→Asn mutation arises (60). The −T93G SNP has also been shown to be associated with lower plasma TG levels and increased LPL promoter activity in vitro (91).

In human and rodent obesity, LPL in adipose tissue is increased when expressed per cell (22, 57, 89, 230, 241). However, like other metabolic responses to insulin in obesity, the responsiveness of LPL to insulin and feeding is diminished (93, 230, 261). In skeletal muscle, LPL activity is either unchanged or modestly decreased after an overnight fast in obese subjects (22, 58, 198, 259). Of even greater importance is the impact of sustained weight reduction on the tissue-specific expression of LPL. In adipose tissue of reduced obese rodents or humans, LPL either fails to decrease or increases to a level above that present prior to weight reduction (22, 57, 118, 241, 259). Moreover, when weight-reduced subjects are given a meal or exposed to the hyperinsulinemia of a euglycemic clamp, increases in the responsiveness of the enzyme are seen (57), suggesting that there is a signal(s) during weight loss that promotes LPL gene expression and/or availability of the active enzyme.

In muscle, a divergent effect of sustained weight reduction on LPL is seen. In reduced-obese fa/fa (Zucker) rats, decreases in cardiac LPL are observed (22). In humans, a >70% decrease in skeletal muscle LPL occurs (58), an effect that can contribute to the increase in respiratory quotient (RQ) (74) and the decrease in fat utilization (214) that follow weight reduction. This is important in that the amount of LPL in skeletal muscle in humans is inversely correlated with RQ (68), and the amount of increase in RQ in reduced-obese subjects is predictive of resumption of the obese state (74). Together these tissue-specific changes in the regulation of LPL in reduced-obese subjects may play an important role in nutrient partitioning when energy intake exceeds energy expenditure, a precursor for weight regain that so often occurs. Ultimately, the ability to selectively modify LPL in skeletal muscle and/or adipose tissue may favorably influence body weight and composition.

Conclusions

LPL is an important multifunctional enzyme produced by many tissues. Although the predominant function of LPL is to hydrolyze the TG core of circulating TG-rich lipoproteins, the enzyme protein may also be important in the uptake of lipopro-tein lipids in the absence of TG hydrolytic activity. LPL is also important in HDL metabolism contributing to the transfer of surface lipid to small HDL after lipolysis. LPL functions at the endothelium but is synthesized in parenchymal cells. For the most part, LPL is regulated by posttranslational processing and not at the level of LPL gene transcription; however, the LPL gene has a number of cis-acting elements that may confer tissue-specific regulation. The mechanism of the tissue-specific regulation of LPL remains the most challenging topic in the field. In adipose tissue, LPL is increased by insulin and meals but decreased by fasting. In obesity, adipose tissue LPL is increased per cell but unresponsive to insulin and meals. However, following weight reduction and stabilization of the reduced-obese state, adipose tissue LPL is increased, as is the response of the enzyme to insulin and meals. In skeletal muscle, insulin does not stimulate LPL, and the enzyme activity is variably reduced in obesity; however, following weight reduction, LPL in skeletal muscle is markedly decreased. In heart, LPL is important to TG-rich lipoprotein metabolism, a process that is critical to cardiac physiology. LPL is also produced in the brain and spinal cord, but the function of LPL in the central nervous system has yet to be discerned. Limited mechanistic studies are available to facilitate the direct application of the knowledge we gain from mouse models to metabolic disorders in humans that relate to altered LPL expression. However, it is well established that the genetics of LPL deficiency in humans is autosomal recessive and typically a result of missence mutations, and heterozygous carriers have normal or minimal hypertriglyceridemia. It is thus important to consider that the nonhydrolytic functions of LPL, which are relatively understudied, prevail in the setting of LPL deficiency, including possible effects in the central nervous system. Overall, LPL is a fascinating enzyme that contributes in a pronounced way to normal lipoprotein metabolism, tissue-specific substrate delivery and utilization, and the many aspects of metabolism, including energy balance, insulin action, body weight regulation, and atherosclerosis.

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