thematic review

Lipoprotein lipase: genetics, lipid uptake, and regulation

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Abstract Lipoprotein lipase (LPL) regulates the plasma levels of triglyceride and HDL. Three aspects are reviewed. *1*) Clinical implications of human LPL gene variations: common mutations and their effects on plasma lipids and coronary heart disease are discussed. *2*) LPL actions in the nervous system, liver, and heart: the discussion focuses on LPL and tissue lipid uptake. *3*) LPL gene regulation: the LPL promoter and its regulatory elements are described.—Merkel, M., R. H. Eckel, and I. J. Goldberg. **Lipoprotein lipase: genetics, lipid uptake, and regulation. *J. Lipid Res.* 2002.** 43: **1997–2006.**

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Although the initial description of lipoprotein lipase (LPL) was the observation in dogs that heparin "cleared" postprandial lipemia (1), the description by Havel and Gordon that postheparin plasma from patients with severe forms of genetic hyperlipidemia was unable to clear chylomicrons (CMs) from the bloodstream (2) established LPL as the primary enzyme required for CM catabolism. The key to this observation was the use of CMs to assess lipolytic activity. Subsequent studies using artificial emulsions discovered that LPL-deficient patients had significant triglyceride (TG) lipolytic activity in their postheparin plasma. This led to the discovery of hepatic lipase. By following patients with elevated TG levels, Brunzell et al. (3) showed that elevations of VLDL resulted in chylomicronemia, an observation that they correctly attributed to saturation of LPL activity.

In the 1970s, two groups independently purified the factor in serum that activated LPL; apolipoprotein CII (apoCII) was found in both human (4) and rat sera (5). Families with defects in apoCII leading to hyperchylomicronemia were not found until the late 1970s (6). Inhibition of LPL by other serum apolipoproteins such as apoCIII and apoCI was also noted (7). Although apoCIII-deficient subjects were shown to have rapid plasma VLDL catabolism (8), only after genetic overexpression of these proteins in mice (9, 10) has their role and the possible role of apoE (11) as lipase inhibitors been fully appreciated.

The physiological actions of LPL in catabolism of CMs and VLDL and in the production of much of the lipids and apolipoproteins that form HDL have been appreciated for more than a decade (12, 13). The evolving role of LPL as a molecule that can anchor atherogenic lipoproteins to matrix molecules within the artery wall was first noted in vitro (14) and appears under some circumstances to modulate atherosclerosis in mice (15), reviewed in (13, 16). In this review, we will focus on three topics that have not recently been reviewed in detail: *1*) the LPL molecule in humans: how its genetic modifications illustrate its role(s) in both lipoprotein metabolism and atherosclerosis; *2*) tissue-specific actions of the molecule in three tissues: the neurological system, the liver, and the heart; and *3*) transcriptional control of LPL expression.

LPL GENETICS: HUMAN DIVERSITY

The LPL gene is located on chromosome 8p22, spans ~30 kb and is divided into 10 exons, and has substantial sequence homology among most of the species that have been examined (17). The cDNA codes for a 475-amino-acid protein including a 27-amino-acid signal peptide. The catalytic center is formed by three amino acids: Ser^{132}, Asp^{156}, and His^{241} (18). Almost 100 naturally occurring mutations in the LPL gene have been described in humans. There are 61 missense mutations, most of which are located on exons 5 and 6; 12 nonsense mutations, 10 frameshift mutations or small insertions/deletions, 3 gross mutations, 8 splicing mutations, and 4 promotor

Abbreviations: CAD, coronary artery disease; FA, fatty acid; LPL, lipoprotein lipase; TG, triglyceride.

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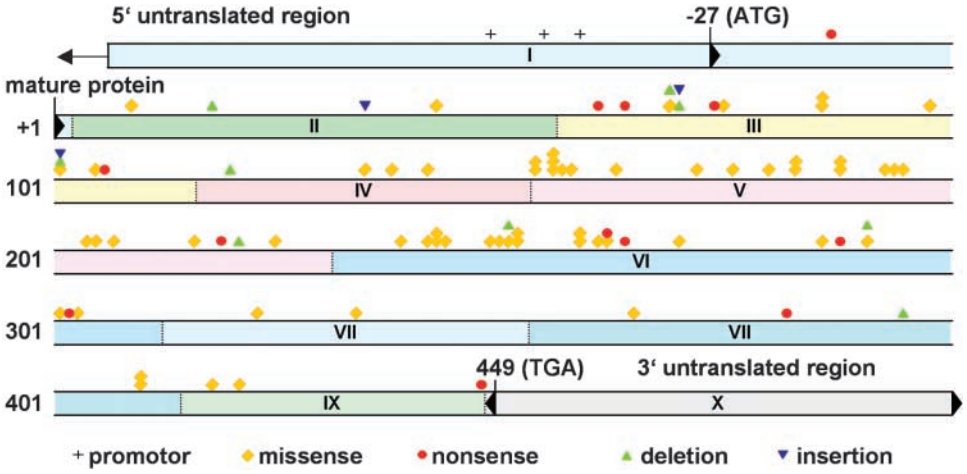

Fig. 1. Distribution of missense, nonsense, frameshift, and promoter mutations on the lipoprotein lipase (LPL) gene. Most mutations are in exons 5 and 6; some clusters are found. Gross mutations (a total of three) and splicing mutations (a total of eight) are not shown. Individual exons are numbered and color-coded. A list of known LPL mutations is provided as supplemental material.

variants (**Fig. 1**). The most common mutations in the LPL gene are summarized in **Table 1** and briefly characterized below. A list of known LPL mutations is provided as supplemental material (see supplemental data).

The frequency of individual LPL mutations differs widely between populations. Ser447stop is found in up to 20% of the general population (19) and is the only variant associated with increased LPL activity. Of mutations reducing LPL activity, Asn291Ser is the most common; the Caucasian population has 2–5% heterozygote carriers (20). Less common mutations are Asp9Asn (1.5%) (21) and Gly188Glu (0.06%) (22). The French Canadian population has an especially high rate of LPL mutation carriers, up to 17% (Pro207Leu, Gly188Glu, and Asp250Asn) (23). In the Japanese population, the frameshift mutation G916 deletion (first position of Ala221) is most common (24). The promoter variant T-93G was found in 76.4% of South African Blacks and in only 1.7% of Caucasians (25). This promoter variant is in near-complete linkage disequilibrium with the Asp9Asn mutation in Caucasians, but not in South African Blacks (25).

Heterozygous LPL mutations associated with a reduction or loss of LPL activity may increase the risk of familial combined hyperlipidemia (FCHL) and premature atherosclerosis. Although it seems obvious that a reduction of LPL activity should lead to increased TGs, decreased HDL, and therefore premature atherosclerosis, only some studies show this connection. Sometimes contradictory results were achieved. Other genes or factors, such as hyperinsulinemia, adiposity, or apoE2/E2, may modify the effects of LPL mutations. The type of LPL mutation may also affect its role in atherosclerosis.

Mutations in the LPL gene have been linked to other diseases: Alzheimer's disease risk was increased in Asn291Ser carriers (26) and decreased or not affected by Ser447stop (27). Hypertension was linked to the LPL gene locus, but only in some studies (28, 29). In heterozygote LPL deficiency, severe hypertriglyceridemia and pancreatitis can occur during pregnancy and with diabetes (30, 31). Carriers of Asn291Ser or the combined Asp9Asn/T-93G mutations may have an increased risk of preeclampsia (32).

TABLE 1. Most common LPL mutations and variants

Mutation	Location	Lipids	CAD	Comments
−93T→G	Promotor	?	?	Heterozygote in Caucasians linkage disequilibrium with Asp9Asn. Possibly FCHL and; G allele most common in South African Blacks, T allele in Caucasians.
Asp9Asn	Exon 2, GAC→AAC	⇑TG ⇓HDL	⇑	In Caucasians linkage disequilibrium with −93T→G.
Gly188Glu	Exon 5, GGG→GAG	⇑TG ⇓HDL	⇑⇑	Homozygote chylomicronemia. Strongest link to increased risk of CAD of all LPL mutations.
Ala221del	Exon 5, 916 gCT→CT	⇑TG ⇓HDL	?	Homozygote chylomicronemia. Most common LPL mutation in Japan, called LPL "Arita".
Asn291Ser	Exon 6, AAT→AGT	⇑TG ⇓HDL	?⇑	Most common mutation in Caucasians slightly decreasing LPL activity. No chylomicronemia in homozygotes. Increased risk of CAD in patients with FCHL.
Ser447stop	Exon 9, TCA→TGA	⇓TG ⇑HDL	⇓	Increases LPL activity.

LPL, lipoprotein lipase; FCHL, familial combined hyperlipidemia; TG, triglyceride; CAD, coronary artery disease. A list of known LPL mutations is provided as Supplemental Material. Amino acid numbers are based on the mature protein; numbering of nucleotides is as in (112).

Ser447Stop

The Ser447Stop mutation results in a truncation of the LPL protein by two amino acids. The *Hind*III polymorphism of intron 8 in the LPL gene is strongly associated with this mutation (19). Two meta studies found reduced TGs, increased HDL cholesterol, and 0.8-fold reduced risk of ischemic heart disease in Ser447stop carriers (33, 34). The beneficial effect of the mutation may be most apparent in patients using beta-blockers (35). Ser447Stop appears to increase LPL protein expression without changing specific activity (35, 36).

Asn291Ser

Asn291Ser is a common mutation that does not, alone, lead to hyperchylomicronemia, although it leads to slightly reduced enzymatic activity (36). A chylomicronemic patient who was heterozygous for this mutation was postulated to have a second unknown mutation (37). Asn291Ser has been estimated to increase TGs by 31% and reduce HDL-cholesterol by 0.12 mmol/l (4.8 mg/dl) (33). Although this mutation does not increase coronary artery disease (CAD) in the general population (33, 34), in patients with FCHL it increases CAD more than 3-fold (34). Women may be more affected than men (34, 38). Recently, this mutation was also associated with increased cerebrovascular disease in women (2-fold), but not in men (39). As mentioned above, associations with other genetic factors such as apoE-3 deficiency or familial hypercholesterolemia are likely to modulate the effect of this mutation on plasma lipids CAD and the FCHL phenotype. Some data suggest that the Asn291Ser mutation increases postprandial lipemia (40, 41).

Asp9Asn

Homozygous Asp9Asn does not cause chylomicronemia, probably because this mutation leads to only a 20% decrease in LPL-specific activity (42). However, a hyperchylomicronemic patient who was heterozygous for Tyr262His and Asp9Asn has been reported (43). Asp9Asn has been linked frequently to hypertriglyceridemia, low HDL, small dense LDL, FCHL and increased risk of CAD, especially if combined with other risk factors (21, 44–46). According to a meta-analysis by Wittrup, Tybjaerg-Hansen, and Nordestgaard (33), Asp9Asn leads to a 20% increase in TGs, 0.8 mmol/l (3.2 mg/dl) decrease in HDL, and 1.4-fold increased risk of ischemic heart disease, borderline significant. Another meta-analysis, by Hokanson (34), determined the relative risk of CAD in combined Asp9Asn/T-93G heterozygote carriers to be 2.0. In the Caucasian population, Asp9Asn is strongly linked to the promoter mutation T-93G, which also leads to decreased LPL activity (47, 48). The effect of the mutation Asp9Asn on CAD without the additional promoter mutation has not been determined.

T-93G

The high frequency in the South African Black population and the conservation of the -93G allele among different species suggest that the -93G allele is the ancestral allele on which a transition to T and the Asp9Asn mutations arose (25). Individuals homozygous for the G allele showed mildly decreased TGs compared with individuals homozygous for the T allele (25). However, others found in Caucasians that the -93T variant had a lower promoter activity than the -93G variant (49, 50). Therefore, the role of this variant is not yet clear.

Gly188Glu

The Gly188Glu mutation is most frequent among French Canadians in Quebec; however, it is wide-spread among populations (51). It is by far the most frequent cause of chylomicronemia in the general population. Because it is the major mutation resulting in an enzymatically nonfunctional LPL protein, its relationship to CAD can be studied. Gly188Glu increases TGs (~80%) and decreases HDL (0.25 mmol = 10 mg/dl) (33). Although two studies report that this mutation increases the relative risk of CAD 5-fold (22, 52), the number of mutation carriers is very low.

Chylomicronemia syndrome

A marked deficiency in LPL activity resulting from homozygous or compound heterozygous mutations leads to the Familial Chylomicronemia Syndrome. In this syndrome, lack of plasma TG hydrolysis leads to a dramatic increase of CMs; TG levels are over 1,000 mg/dl and HDL-cholesterol is extremely low. Patients can suffer from recurrent abdominal pain, pancreatitis, memory loss, xanthomas and/or dyspnea (18). The diagnosis is made by measuring LPL activity in postheparin plasma. LPL protein mass may be low, normal, or increased, depending on the effect of the mutation on the LPL structure. In has been proposed that the phenotype in patients with compound heterozygous mutations may be less severe than that in patients with homozygous mutations (53).

LPL is thought to function as a "gate keeper" for fatty acid (FA) uptake into organs (54); however, patients with LPL deficiency have no obvious defect in adipose tissue. In part, this may be the result of increased adipose TG synthesis, because adipose tissue in LPL-deficient humans contains less essential FA (e.g., linoleic acid) (18:2) than that of normal persons (55). This was confirmed in a mouse model with adipose LPL deficiency. These animals had normal body weight, but a markedly decreased amount of adipose tissue was found after crossing them onto the ob/ob (leptin-deficient) background. Because both humans and mice without adipose tissue LPL still have some essential FAs in the adipose tissue, there must be other pathways mediating organ FA uptake. These could be receptor-mediated lipoprotein uptake or actions of other lipases, such as hepatic lipase or endothelial lipase.

ORGAN-SPECIFIC LPL ACTIONS

Animal studies have illustrated metabolic functions of LPL exclusive of control of plasma lipoproteins (56). The major tissues thought to control the circulating levels of

plasma lipoproteins are the adipose tissues and muscles. However, LPL is expressed in other sites, including the nervous system, heart, liver, adrenals, macrophages, proximal tubules of the kidneys, pancreatic islet cells, and lungs. In these organs, LPL may have specialized functions. Islet cells of the pancreas express LPL, and this activity has been related to insulin secretion and lipotoxicity (57). In the lung, LPL-mediated lipolysis may be of importance for surfactant production (58). Most interesting is the expression of LPL within the neurological system. Humans with a genetic deficiency of LPL appear to be normal except for their hypertriglyceridemia and its complications. This might indicate that brain LPL is of limited importance, or that there are other compensating pathways for LPL actions. Studies in neurological tissues, liver, and heart have provided insights into LPL actions in tissue repair, whole-body energy homeostasis, and uptake of core nonlipolyzed lipids.

LPL in neurological tissues

LPL is present throughout the nervous system, including the brain, spinal cord, and peripheral nerve. In the brain, LPL mRNA is found in dentate granule cells, as well as in CA1, CA2, and CA4 cells in the hippocampus, pyramidal cells in the cortex, and Purkinje cells in the cerebellum. However, the lipase protein is distributed on endothelial surfaces throughout the brain. In the spinal cord, LPL mRNA and protein are localized predominately in tracts, but also in areas where populations of motor neurons and secondary sensory neurons are located (59). Because Schwann cells make LPL in vitro (60), it appears likely that at least some of the LPL in the spinal cord is derived from glial cells rather than from neurons. LPL mRNA, protein, and enzyme activity are also present in the sciatic nerve (61).

Peripheral nervous system. LPL is present in the peripheral nervous system; however, the role of the lipase in the physiology and pathophysiology of the peripheral nerve remains unknown. Physical injury to a peripheral nerve, such as a crush or a cut, induces a series of responses known collectively as Wallerian degeneration. Myelin lipid (phospholipids, cholesterol, glycolipids, sulfolipids) and protein synthesis in the nerve portion distal to the injury site ceases as the pre-existing myelin begins to degrade. The lipids released by myelin degradation, primarily cholesterol and FAs derived from phospholipids and glycolipids, are actively reutilized by the regenerating proximal end. HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis, is down-regulated as cholesterol released from the degrading myelin sheath is reutilized for new myelin synthesis (62). Axonal components also degenerate, leaving behind Schwann cells that proliferate in response to axonal and myelin debris. Infiltration of macrophages into the distal stump also occurs soon after injury, and both types of cells serve to scavenge myelin lipids from the degrading distal end. Although Schwann cells appear to be the cells of origin of LPL in the sciatic nerve, macrophages also appear to contribute to the production and secretion of LPL following nerve crush injury (61). The timing of the rise in LPL in the peripheral nerve after nerve crush injury (approximately day 4) coincides with the increase in neutral glycerolipid accumulation (63). The importance of LPL for FA supply after nerve injury is unclear.

LPL, apolipoproteins, and lipoprotein receptors may all help maintain normal neurological function. A major advance in the understanding of how myelin lipids are reutilized for new myelin synthesis in the regenerating nerve was the discovery that non-neuronal cells, primarily macrophages, secrete apoE. The identification of LDL receptors on the surface of neurites in vitro (64) and regenerating axons in vivo (65) suggested that regenerating nerves take up locally synthesized lipoprotein particles (composed of myelin lipids and apolipoproteins from the degenerating distal end) by LDL receptor-mediated binding to apoE. Indeed, an autoradiographic study directly demonstrated the recycling of myelin cholesterol into apoE-containing lipoproteins in the crush-injured nerve (66). Moreover, the identification of the LDL receptor-related protein, which mediates uptake of lipoproteins enriched in apoE, on the neuronal cell surface and a number of other ligands including LPL itself, further implicates apoE as a vital component of the regeneration process. However, the generation of apoE$^{-/-}$ mice proved that this model of myelin lipid reutilization is not absolutely dependent on apoE-containing lipoprotein production. In these mice, as well as in double "knockout" mice expressing neither apoE nor apoA-I, nerve regeneration proceeded normally after crush injury (67). Thus, mechanisms other than those dependent on apoE exist in the peripheral nerve to facilitate the provision of degraded myelin lipids to the regenerating nerve. Although other apolipoproteins also increase around the nerve following nerve crush injury (i.e., apoD, apoA-I, apoA-IV, and apoJ), only the role of apoA-1 has been examined (i.e., in the experiments just noted above).

LPL provides lipids for energy or cellular constituents. Huey et al. (60) showed LPL production in an immortalized rat sciatic nerve Schwann cell line. Moreover, when cells were incubated with emulsified [^{14}C]triolein, over 80% of the incorporated [^{14}C]oleic acid was in polar lipids. This process was almost entirely LPL dependent, with nearly total inhibition demonstrated in the presence of tetrahydrolipistatin. Additionally, LPL-mediated hydrolysis of exogenous triacylglycerol provides free FA to these cells (unpublished observation). Thus, LPL may be important for myelin synthesis in the peripheral nervous system.

Central nervous system. The expression of LPL mRNA is most impressive in the CA1, CA2, and CA4 layers of the hippocampus (68). This area is well recognized to be 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 potentiates the size of synaptic potentials. Perhaps LPL provides FA-derived energy or lipids required for this process.

The hypothalamus also has LPL mRNA, enzyme pro-

tein, and activity. Recent evidence indicates that oleic acid injected directly into the third ventricle can signal nutrient availability through ATP-sensitive K^+ channels (69). Presumably, FAs derived from lipoproteins could do the same.

LPL in the liver

More than two decades ago, a careful study in aging rats showed that the LPL activity in the liver and peripheral tissues is reciprocally related (70). LPL is normally not made in adult liver; however, it is expressed in the liver of newborn animals. Either because the pups ingest milk or because of a developmental genetic program, LPL activity increases in the heart, skeletal muscle, and adipose tissue. At the same time, LPL activity in the liver is extinguished. What is the reason for perinatal hepatic LPL expression and why is the enzyme expression extinguished soon after birth? One other time that LPL is expressed in the liver is as a response to tumor necrosis factor (TNF) (71) and after tumor implantation (72), i.e., during cachexia. When mice were produced that expressed LPL solely in the liver, the neonatal death of LPL knockout mice was averted (73), probably because the severe hypoglycemia found in completely LPL-deficient mice was prevented. Liver LPL targeted circulating TG to the liver and increased ketone body production. Ketone bodies can be used as energy as an alternative to glucose. However, many pups died several weeks later and had fatty livers.

Another intervention that induces LPL in the liver is the use of peroxisome proliferator-activated receptor (PPAR) agonist drugs (74). Although PPARα drugs increase liver oxidation of FAs, drugs with predominantly PPARγ activity are associated with fatty livers in some rodents (75). Presumably they cause an increase in TG synthesis and/or uptake similar to that which occurs in peripheral tissues like adipose. The oxysterol-responsive transcription factor, LXR, also increased LPL expression in the liver (76) and caused fatty liver.

LPL in the heart

Although the heart is a major site of LPL synthesis, the role of cardiac LPL in both the energy balance of this tissue and in the regulation of plasma lipoproteins is under renewed investigation. FAs are an important fuel source for heart and skeletal muscle, providing over 70% of the energy needs for cardiac function. LPL is likely to be the central enzyme in cardiac FA uptake. Although FAs can be delivered to the heart while circulating on albumin, their molar concentration is ~10-fold less than that of lipoprotein TG. Therefore, if only 10% of the TG is hydrolyzed during its passage through the heart vasculature, this would create an equivalent amount of FAs. Cardiac muscle is the tissue with the greatest expression of LPL (77) and it is likely, especially in the postprandial period, that a large amount of dietary TG is converted to FA within the heart.

The heart is not generally viewed as a "major player" in the regulation of plasma lipoprotein levels. Mice without cardiac LPL survive (73), although their heart function has not been examined in detail. In contrast, heart-only LPL-expressing mice maintained normal levels of plasma TG and HDL despite the lack of skeletal muscle and adipose LPL and a reduced amount of postheparin LPL (78). An additional role of LPL in the heart may be to provide it with nonhydrolyzable core lipids. Studies several decades ago by Goodman et al. (79) showed that peripheral tissues, including the heart, internalize core lipids from CMs; not all core lipids or remnants are destined to end their circulatory life in the liver. Uptake of retinyl esters correlates with LPL overexpression in heart and skeletal muscle (80). Using labeled chylomicrons and emulsions, Hultin et al. (81) found a large amount of uptake of core lipids into peripheral tissues. A similar observation was recently made by Qi et al. (82), who noted that uptake of cholesteryl esters was modified by the lipid composition of emulsions. How does this occur? One option is that capillaries become leaky and allow large TG-rich lipoproteins to enter the subendothelial space. FAs disrupt endothelial monolayers in vitro (83), and LPL-mediated hydrolysis of VLDL also makes arteries more permeable (84) (**Fig. 2**). Perhaps the pool of LPL that is present on the myocyte surface (85), as well as that on the endothelial lumen, participates in tissue lipid uptake. The in vitro observations that LPL will anchor lipoproteins to cell surfaces and then augment their uptake either via receptors or internalization of proteoglycans may be operative in vivo. This pathway can also be mediated by enzymatically inactive LPL, which, in the presence of active LPL, appears to capture lipoproteins and increase the efficiency of lipolysis; in tissues without active LPL, the inactive LPL can still increase tissue cholesterol uptake (86, 87).

LPL-mediated uptake of lipid in excess of that required for tissue energetics may be harmful. Adipose tissue has been developed as a site of storage of fat-derived calories; this occurs even in LPL deficiency (see above). Several models of dilated cardiomyopathy are associated with excess lipid accumulation in the heart. Thus, although FAs are the preferred fuel for cardiac muscle, too much fat, excess oxidation of Fas, or accumulation of other lipids may lead to dysfunction. The other potential complication of excess LPL-mediated fat uptake may be insulin resistance, as reported by two labs (88, 89), but not by one other (90).

LPL GENE TRANSCRIPTION

Important *cis*-acting elements in the human promoter have been identified that bind DNA binding proteins and appear to confer basal and/or ligand-mediated LPL gene transcription (**Fig. 3**). Particularly important to basal transcription are the proximal octamer site (ATTTGCAT) at −46, which appears to bind the transcription factor TFIIB and which functions as a TATA box (91), and the downstream CCAAT box at −65, which binds NF-Y (92). An additional CCAAT box sequence (−505 to −501) and two Oct-1 sites are further upstream (−186 to −179, −589 to −582) (93). The SRE at−90 is a nonconsensus 10 bp se-

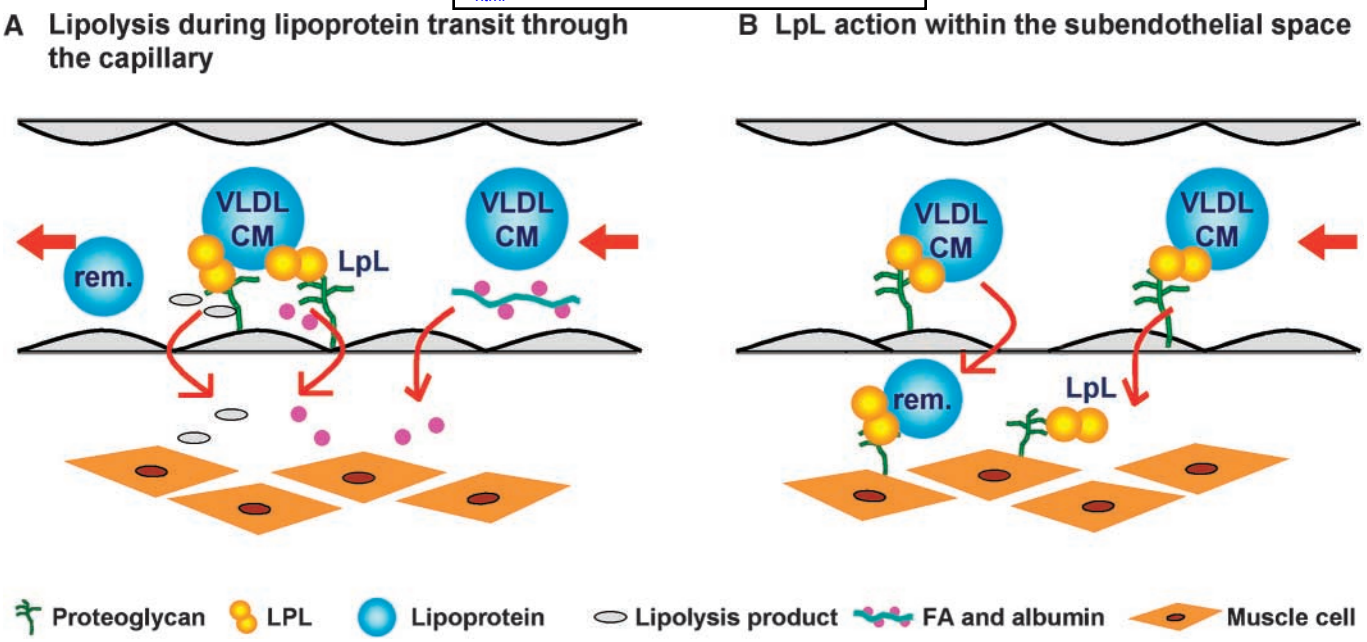

Fig. 2. LPL-mediated tissue-uptake of lipids. LPL appears to mediate uptake of both lipolyzed lipids (fatty acids [FAs]) and core lipids, such as triglycerides (TGs), cholesteryl ester, and retinyl esters. A: Several pathways allow organ uptake of lipids. FA associated with albumin can cross the endothelial barrier. Lipolysis of VLDL or chylomicrons (CMs) releases FA. In addition, as is known to occur for transfer of lipids and apolipoproteins from TG-rich lipoprotein to HDL, surface lipid, apolipoproteins, and some core lipids may dissociate from the particle as a complex (lipolysis product). B: Although lipolysis of nascent TG-rich lipoproteins probably requires initial hydrolysis within the circulation, lipolysis may continue within the subendothelial space either because the smaller lipoproteins are able to cross the capillary endothelial barrier or because the barrier is "leaky." Lipolysis itself will cause capillary leakage. LPL, present on the surface of parenchymal cells such as adipocytes and myocytes, could interact with these particles.

quence that is regulated by sterols (94). Sites entitled LP-α (−702 to −666) and LP-β (−468 to −430) are similar to sequences that bind the adipose tissue differentiation-dependent transcription factors HNF-3/fork head, a function implied following transfection into 3T3-442A preadipocytes (95). Other sites include a CRE-like sequence in reverse orientation (−372 to −367), a PPRE (−169 to −157), two FSE-2-like sites (−362 to −355, −206 to −200), a TRE in reverse orientation (+22 to +29), five GREs (four in reverse orientation) (−1,543 to −1,538, −1,272 to −1,267, −881 to −876, −777 to −772, −645 to −640), an AP-2 site (−790 to −783), two heptamer sites (−80 to −84, −57 to −51), a nonconsensus SRE (−90 to −81), a GATA site (−501 to −446), IRS (−75 to −68, −367 to −360), a Krox site (−430 to −422) and VDRE (−408 to −403) (94–98). Despite the identification of these numerous sites of potential LPL promoter regulation by a wide variety of ligands, experiments remain to be implemented to document their relevance.

The mouse has two LXREs (−274 to −279, +635 to +650) that may confer cholesterol-induced expression of LPL in macrophages (76). Alternatively, the inhibition of LPL gene transcription in murine macrophages appears to be a consequence of the binding of Sp1 and Sp3 to regions of the proximal promoter (−31 to +187) (99). In murine 3T3-L1 adipocytes, an AP-1-like sequence (−1,856 to −1,850) was responsible for the inhibition of LPL gene transcription by estrogen (100). Transcription of the LPL gene increases during adipocyte differentiation (101), and decreases in mature adipocytes after treatment with TNF-α (102, 103) and agents that increase cAMP (104, 105). In the mouse, the inhibition of LPL gene transcription by TNF-α is secondary to the binding of at least two DNA binding proteins, NF-Y to the CCAAT box, and an octamer binding protein other than Oct-1 (102). Sites responsible for adipose tissue differentiation-dependent increases in LPL gene transcription include but may not be limited to SREBP 1-c sites and PPRE sites (106, 107). FA, particularly α-linolenate, may also increase LPL gene transcription during adipocyte differentiation (108). Of interest, the re-

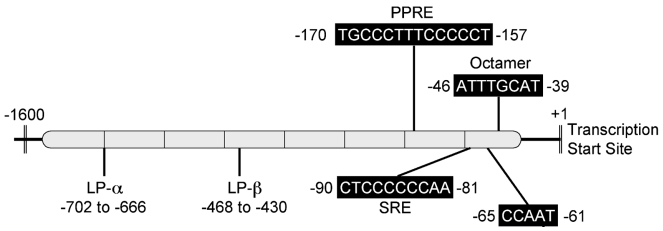

Fig. 3 The human LPL promotor. Sequences in the human LPL promoter that mediate basal or ligand-mediated LPL gene transcription are shown. Lp-α and Lp-β are similar to sequences that bind the adipose-dependent transcription factors HNF-3/fork head. PPRE is a sequence that binds peroxisome proliferator-activated receptors (PPARs), typically as PPAR:RXR (9-*cis*-retinoic acid receptor) heterodimers. SRE is a nonconsensus sequence sterol response element. The CCAAT binds NF-Y; the proximal octamer sequence binds Oct-1 and TFIIB.

duction in LPL gene expression in the liver following birth may be conferred by a silencer, identified in the −263 to −241 location of the chicken LPL promoter (109). PPAR-α agonists may be able to override this silencing in adult animals (94). Transcription of the LPL gene in the rat heart increases 10-fold in 10- to 20-day rat pups (110). Despite these examples of the potential regulation of LPL by gene transcription, much of the regulation of the enzyme protein occurs at the post-translational level (111).

In summary, the six decades of LPL research have led to an understanding of a human disease and highlighted the role of this enzyme in regulation of lipoprotein metabolism and atherosclerosis in man and in animals. Additional genetic information is showing that minor variations in the LPL gene also modulate lipoprotein profiles. Within the last two decades, as information has accrued on uptake of lipids by tissues and how this in turn regulates both lipid and glucose metabolism, additional roles of LPL protein have become apparent; some of these roles are exclusive of its enzymatic actions. The goal for the next decade may be, as in the past, to translate animal physiology and tissue culture information into information relevant to the functioning of human organs and tissues and to how LPL modulates their responses to disease.

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