

Review article

Lipoprotein lipase and the disposition of dietary fatty acids

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(Received 23 March 1998 – Revised 8 July 1998 – Accepted 10 August 1998)

Lipoprotein lipase (*EC* 3.1.1.34; LPL) is a key enzyme regulating the disposal of lipid fuels in the body. It is expressed in a number of peripheral tissues including adipose tissue, skeletal and cardiac muscle and mammary gland. Its role is to hydrolyse triacylglycerol (TG) circulating in the TG-rich lipoprotein particles in order to deliver fatty acids to the tissue. It appears to act preferentially on chylomicron-TG, and therefore may play a particularly important role in regulating the disposition of dietary fatty acids. LPL activity is regulated according to nutritional state in a tissue-specific manner according to the needs of the tissue for fatty acids. For instance, it is highly active in lactating mammary gland; in white adipose tissue it is activated in the fed state and suppressed during fasting, whereas the reverse is true in muscle. Such observations have led to the view of LPL as a metabolic gatekeeper, especially for dietary fatty acids. However, closer inspection of its action in white adipose tissue reveals that this picture is only partially true. Normal fat deposition in adipose tissue can occur in the complete absence of LPL, and conversely, if LPL activity is increased by pharmacological means, increased fat storage does not necessarily follow. LPL appears to act as one member of a series of metabolic steps which are regulated in a highly coordinated manner. In white adipose tissue, it is clear that there is a major locus of control of fatty acid disposition downstream from LPL. This involves regulation of the pathway of fatty acid uptake and esterification, and appears to be regulated by a number of factors including insulin, acylation-stimulating protein and possibly leptin.

Dietary fatty acids: Adipose tissue: Lipoprotein lipase: Skeletal muscle

Lipoprotein lipase (*EC* 3.1.1.34; LPL) is a key enzyme regulating the disposal of lipid fuels in the body. The structure, function and regulation of LPL have been reviewed several times in recent years (Eckel, 1989; Bensadoun, 1991; Braun & Severson, 1992; Enerbäck & Gimble, 1993; Santamarina-Fojo & Dugi, 1994; Beisiegel, 1996; Goldberg, 1996). These reviews have covered mainly molecular aspects of LPL and its role in lipid metabolism. None has covered LPL primarily from a nutritional point of view. That aspect of LPL's function will be the subject of the present review.

LPL is expressed in a number of tissues and its regulation is tissue-specific in such a way that LPL expression correlates highly with both the need for, and the uptake of, lipid fuels by the tissue. Its preferential action on the larger chylomicron particles, carrying dietary lipid, potentially gives it a special role in regulating the disposition of dietary fatty acids. Such observations have led to the view that LPL

is the key factor determining the dietary lipid disposition between tissues, and to the description of this enzyme as the 'metabolic gatekeeper' (Greenwood, 1985).

However, current views of LPL action show that it is not the only factor determining lipid fuel disposition. In fact critical evaluation of present evidence suggests that LPL alone is neither necessary nor sufficient for normal partitioning of dietary lipid. This changing view of the role of LPL is the subject of the present review.

Lipoprotein lipase: background

Triacylglycerol (TG) is an extremely energy-dense fuel. However, unlike glucose, it is not soluble in the plasma. Therefore, it is transported in the circulation in the form of large multi-molecular aggregates, the lipoprotein particles. Dietary TG is packaged within the enterocytes into chylomicron particles which enter the circulation for distribution

Abbreviations: HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; NEFA, non-esterified fatty acids; TG, triacylglycerol; TRL, triacylglycerol-rich lipoproteins.

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of the TG-fatty acids to tissues, before the TG-depleted remnant particle is taken up by receptor-mediated processes. Endogenous TG is secreted by the liver packaged into VLDL particles, whose fate is similar to that of chylomicrons. However, removal of TG from VLDL particles is slower than from chylomicrons, and a proportion of the remnant particles will become TG-depleted to the extent that they are classified as LDL particles (Grundey & Mok, 1976; Havel, 1994).

A general feature of mammalian lipid metabolism is that TG molecules do not cross cell membranes (except when they are internalized as part of a remnant lipoprotein particle). Instead they are hydrolysed to liberate fatty acids and either free glycerol or a monoacylglycerol. In the small intestine dietary TG is hydrolysed by the enzyme pancreatic lipase (*EC* 3.1.1.3) and monoacylglycerol and fatty acids are taken up into enterocytes for re-esterification and packaging into chylomicron particles. In the circulation, TG in the chylomicron and VLDL particles (collectively known as the TG-rich lipoproteins, TRL) is hydrolysed by the LPL present in the capillary beds of several tissues. LPL is a member of the same family as pancreatic lipase and hepatic lipase, and the three enzymes have a number of structural features in common (Olivecrona *et al.* 1993; Murthy *et al.* 1996).

TRL particles are too large to cross the capillary endothelium in most tissues. Therefore, in order for LPL to gain access to the TG in these particles, it is necessary that LPL should operate within the vascular space. In fact, its site of action is the luminal side of the capillary endothelium, where the active enzyme, a homodimer, is bound by charge interactions to the proteoglycans forming the glycocalyx. In particular, the binding is to the highly-charged chains of heparan sulfate, as reviewed recently (Goldberg, 1996). (Heparan sulfate is a glycosaminoglycan, structurally related to heparin: Salmivirta *et al.* 1996.) However, LPL is synthesized not by the endothelial cells, but within the parenchymal cells of the tissue, e.g. adipocytes, muscle

fibres or cardiac myocytes. It is presumed that the existence of tissue-specific regulatory elements in the LPL gene promoter region then allows for its differential regulation in different tissues. In adipose tissue and muscle, the tissues in which LPL synthesis has been most closely studied, there is a large pool of enzyme within adipocytes, much of which is not active (Pradines-Figueroles *et al.* 1990). Within the parenchymal cell LPL is post-translationally modified, by glycosylation and further remodelling of the glycosyl chains (Carroll *et al.* 1992), before the active enzyme is exported to the endothelial cells. Within adipose tissue in particular it appears that a large proportion of the intracellular enzyme is destined for degradation without export, and activation of the enzyme (i.e. an increase in the amount of active enzyme at the endothelium) involves diversion of the intracellular enzyme from the degradative to the export pathway (Bergö *et al.* 1996).

The presence of LPL on the capillary endothelium allows the TG in the TRL particles passing through the capillary to be hydrolysed, so that fatty acids are generated and can be taken up by the parenchymal cells. Their further fate will depend on the tissue and the nutritional state. In adipose tissue most will be esterified for storage as TG; in skeletal muscle or myocardium, whilst they may enter a TG pool for temporary storage, their final fate will be oxidation. The movement of fatty acids from the site of LPL action into the parenchymal cells is not fully understood, but seems to follow concentration gradients across the endothelium to the interstitial space and into the cells (Frayn *et al.* 1994; van der Vusse & Reneman, 1996). The involvement of specific fatty acid transporters has been postulated (Goresky *et al.* 1994; Van Nieuwenhoven *et al.* 1995) but is still under investigation.

It has been shown that about forty LPL molecules may act on a TRL particle simultaneously to achieve the rates of TG hydrolysis observed (Scow & Olivecrona, 1977). The situation is envisaged to look like that in Fig. 1. During this process the particle is anchored by interaction with LPL

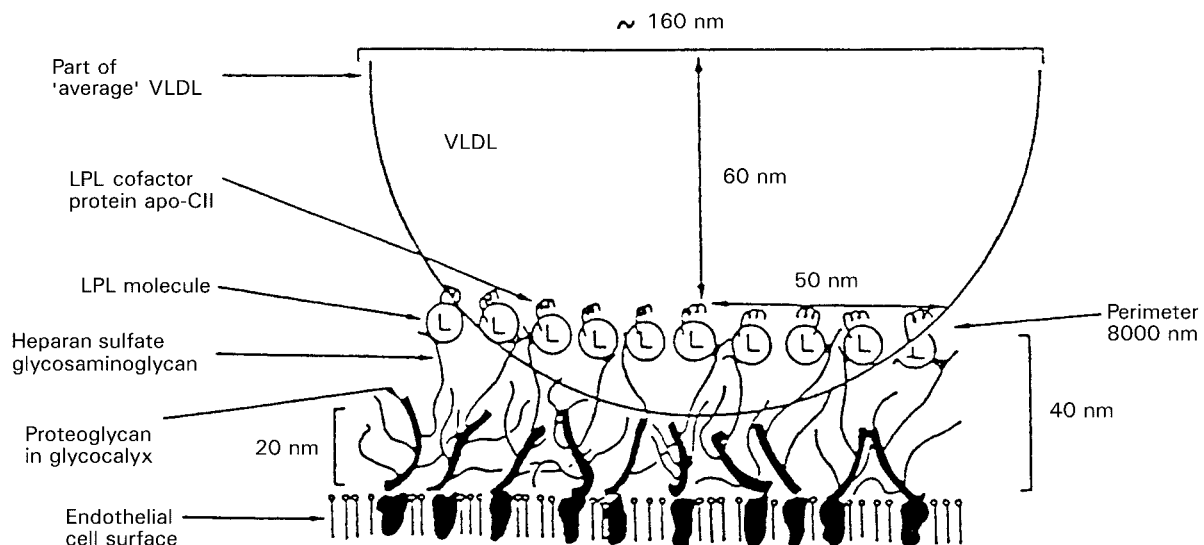


Fig. 1. Relationship of lipoprotein lipase (LPL; \odot) to endothelial cell surface and to a lipoprotein particle (a VLDL particle is shown). Apo-CII, apolipoprotein CII. Reproduced from Cryer (1981) with permission.

Table 1. Lipoprotein lipase activities in different tissues according to nutritional and physiological state: typical values*

Tissue	Units†
Mammary gland	
Pre-pregnancy	1
End pregnancy	7
Lactation	50
Adipose tissue	
Fed	3.6
Starved	0.6
Heart	
Fed	3.5
Starved	7.2
Skeletal muscle	
Untrained	0.9
Trained	1.4

* Values are taken from Nikkilä *et al.* (1978), Cryer (1981), Scow & Chernick (1987), Taskinen (1987), Kiens *et al.* (1989).

† Units are μmol fatty acid released/h per g wet weight.

itself and possibly by interaction of its apolipoproteins with the heparan sulfate proteoglycan chains (Goldberg, 1996). After hydrolysis of the TG, the TG-depleted particle detaches. During lipolysis LPL itself may dissociate from the endothelium and some LPL molecules may leave attached to the remnant particle (Saxena *et al.* 1989; Vilella *et al.* 1993). They will be replaced by newly secreted molecules from within the tissue. Thus, there is a continual turnover of LPL at the endothelial site of action (Braun & Severson, 1992). LPL circulating attached to lipoprotein particles may play an important role in their eventual

receptor-mediated uptake (Beisiegel, 1996; Beisiegel & Heeren, 1997).

Tissue-specific regulation of lipoprotein lipase

LPL is expressed to different extents in different tissues. Measurements of activity, usually made by homogenization of a sample of tissue, have shown characteristic patterns of activities in different tissues according to nutritional state (Table 1). These can readily be seen to correlate broadly with tissue requirement for fatty acids. For instance, in the fed state LPL is activated in white adipose tissue and down-regulated in skeletal muscle and heart; fatty acids will, therefore, be directed to adipose tissue for esterification and storage in a time of energy surplus (Cryer *et al.* 1976). On fasting, however, the situation is reversed, with up-regulation in muscle and suppression in adipose tissue, so that TRL-fatty acids are directed to the tissue in which they are needed as an oxidative fuel (Cryer *et al.* 1976; Kaciuba-Uscilko *et al.* 1980; Borensztajn, 1987). The highest levels of LPL activity are seen in the lactating mammary gland, with its enormous requirement for fatty acids to be incorporated into milk fat (Scow & Chernick, 1987). The idea of tissue-specific regulation of LPL according to the needs of the tissue has been developed by a number of workers, but the late Donald Robinson and his many colleagues have perhaps done more than any other group to build this into a consistent picture (Robinson *et al.* 1975).

This picture becomes very convincing when the end result of LPL action is studied, namely the uptake of fatty acids from TRL particles. In a series of experiments rats have been given chylomicrons containing radio-labelled

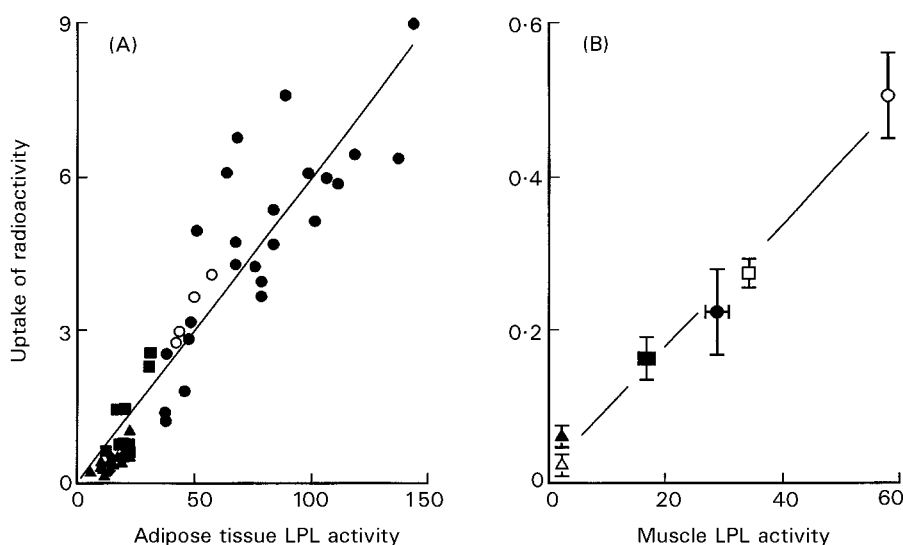


Fig. 2. Uptake of radioactively-labelled chylomicron-triacylglycerol fatty acids in relation to tissue lipoprotein lipase (LPL) activity. Tissues were removed from rats 30 min (A) or 10 min (B) after intravenous injection of a chylomicron preparation containing labelled fatty acids. Units for Y axis are arbitrary. LPL activity (X axis) was measured in a parallel sample of tissue: units are (A) units per fat pad, (B) μmol fatty acid/h per g. (A) White adipose tissue. Symbols show treatment of rats: (\blacktriangle), starved 24 h; (\blacklozenge), starved 24 h then refed with fructose; (\blacksquare), starved 24 h then refed with sucrose; (\circ), starved 24 h then refed with glucose; (\bullet), fed *ad libitum*. Redrawn from Cryer *et al.* (1976) with permission. (B) Skeletal muscle: (\triangle , \square , \circ), results from starved animals, (\blacktriangle , \blacksquare , \bullet), fed animals. (\triangle , \blacktriangle), White vastus muscle; (\square , \blacksquare), red vastus muscle; (\circ , \bullet), soleus muscle. Redrawn from Kaciuba-Uscilko *et al.* (1980) with permission.

fatty acids, and then after a suitable period of time samples of tissue taken for measurement of radioactivity. The uptake of labelled fatty acid is then compared with the tissue LPL activity. Typical results for skeletal muscle and white adipose tissue are shown in Fig. 2. There are strong correlations between tissue LPL activity and fatty acid uptake, apparently confirming the view of LPL as the major determinant of partitioning fatty acids of dietary origin, or the metabolic gatekeeper. However, before finally accepting this important role for LPL, it seems appropriate to ask whether it can be shown that LPL is both necessary and sufficient for partitioning of dietary fatty acids.

Is lipoprotein lipase necessary and sufficient for normal partitioning of dietary lipids?

What happens if lipoprotein lipase is absent?

If LPL is indeed necessary for normal partitioning of dietary lipids, then presumably absence of LPL will result in profound disruption of lipid metabolism. Complete absence of LPL is observed in individuals who are homozygous for mutations in the LPL gene that cause complete loss of activity. It leads to the phenotype known as Type 1 hyperlipoproteinaemia, or chylomicronaemia syndrome. This is a rare condition with a prevalence of about one per million in

the general population (Murthy *et al.* 1996). Over seventy mutations in the coding sequence of the LPL gene, leading to variable losses of LPL activity, are known (Murthy *et al.* 1996). Two of these mutations are found relatively commonly in people living in Québec province in Canada, reflecting a founder effect. One of these mutations (Pro207Leu) has been traced to a village in northern France, and it is believed that someone carrying this mutation travelled to, and settled in the Québec area in the seventeenth century. The other mutation (Gly188Glu) may have arisen in Scotland but travelled via northern France to Québec at about the same time (Murthy *et al.* 1996). There are now a number of people homozygous for complete LPL deficiency in Québec province, who have been studied in some detail by a group at Laval University (Brun *et al.* 1989; Julien *et al.* 1989; Peeva *et al.* 1992; Murthy *et al.* 1996).

As the term chylomicronaemia syndrome implies, the phenotype is characterized by massive accumulation of chylomicron-TG in the circulation when these people eat food containing fat. Thus, as expected, absence of LPL leads to inability to clear circulating TG normally. However, surprisingly, LPL-deficient subjects are of normal bodily habitus, and their fat cells are normally filled with lipid (Brun *et al.* 1989; Julien *et al.* 1989; Peeva *et al.* 1992) (Fig. 3). Nutrient partitioning to the tissues seems to occur quite normally in the complete absence of LPL. Therefore the necessary role of LPL seems to be in question. How such people manage to store TG in adipocytes is presently unclear and requires further study.

Further insight into the role of LPL comes from mouse models in which LPL has either been removed by targeted gene knockout or over-expressed in specific tissues in transgenic mouse lines. Within 18 h of birth, homozygous knockout animals showed an 80-fold increase in plasma TG (Weinstock *et al.* 1995). This was almost entirely due to fat ingested during sucking remaining uncleared in the plasma: the mice subsequently failed to survive longer than 16–18 h. The mice had depleted adipose tissue depots although heterozygous LPL knockout mice had normal body composition compared with normal littermates. Adult heterozygous LPL knockout mice showed delayed clearance of TRL. The lethal homozygous phenotype could be 'rescued' by muscle-specific expression of LPL; interestingly these animals had normal adipose tissue TG stores, but the composition of this TG suggested induction of *de novo* fatty acid synthesis in adipose tissue (Zechner, 1997). In contrast, transgenic mice which overexpress human LPL in skeletal muscle and heart have been developed (Levak-Frank *et al.* 1995; Jensen *et al.* 1997). In proportion to the level of LPL overexpression, the plasma TG concentration was decreased, fatty acid uptake into skeletal muscle was increased and the animals tended to be protected against obesity when fed on a high-fat diet.

These studies imply that complete absence of LPL in human subjects, although not in mice, is compatible with relatively normal tissue metabolism, although clearance of dietary TG from the blood is grossly disturbed. Site-specific regulation of LPL, however, clearly has some role in directing lipid fuels to different tissues, as seen in the tissue-specific over-expression models. We next ask to what extent LPL activity is sufficient for tissue lipid partitioning.

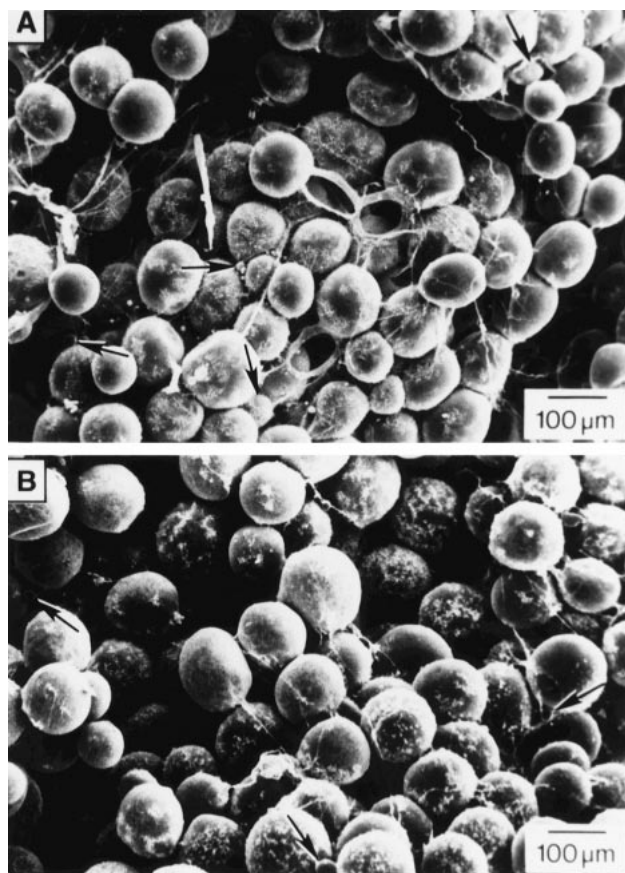


Fig. 3. Scanning electron photomicrographs of subcutaneous abdominal adipose tissue obtained from (A) a control subject and (B) a patient with complete lipoprotein lipase deficiency. Figure kindly supplied by Professor Pierre Julien, Laval University, and reproduced from Peeva *et al.* (1992) with permission.

Downstream regulation of dietary lipid partitioning

In adipose tissue, it is now clear that LPL is not the only regulatory step for fat deposition. The extraction of TG from blood by adipose tissue increases after a meal, reflecting an increased rate of action of LPL (Coppack *et al.* 1992; Frayn *et al.* 1994). However, not all the fatty acids released by LPL are directed into the tissue for esterification and storage; a proportion leave in the venous plasma as non-esterified fatty acids (NEFA), bound to albumin. This proportion appears to be highly regulated. In studies of normal subjects eating a typical mixed meal, the proportion of LPL-derived fatty acids which are entrapped in the tissue (rather than leaving as NEFA in the venous plasma) changes from close to zero after an overnight fast, to about 90% within about 60 min after the meal (Frayn *et al.* 1995). At 4–5 h after the meal, when TG extraction is maximal, approximately 50% of LPL-derived fatty acids are entrapped in the tissue (Fig. 4). The interplay between the increasing rate of LPL action and the proportion of fatty acids esterified produces a smooth increase in the flux of LPL-derived fatty acids into adipose tissue (Fig. 4). After a high-fat meal, both the inward flux of fatty acids from plasma to adipose tissue, and the release of LPL-derived NEFA into the venous plasma, are greater than after a lower-fat, mixed meal (Frayn *et al.* 1995). All these observations point very clearly to a major locus of control of fatty acid movement which is distal to the action of LPL.

This locus of action is probably the concentration gradient for fatty acids between adipocytes and plasma, generated both by regulation of the esterification of fatty acids in adipose tissue, and by regulation of the intracellular enzyme hormone-sensitive lipase (EC 3.1.1.3; HSL). The pathway of fatty acid esterification in adipocytes is

stimulated by insulin (Leboeuf, 1965; Campbell *et al.* 1992); its regulation is discussed further later. HSL is the enzyme responsible for mobilization of intracellular TG. It is activated by phosphorylation at a single serine residue in response to β -adrenergic agents such as adrenaline, and suppressed by dephosphorylation in response to insulin and other antilipolytic agents (Langin *et al.* 1996). In the fed state, therefore, HSL is suppressed and esterification is stimulated, and fatty acids generated by the increased rate of LPL action are drawn into the adipocytes down a concentration gradient. In the fasted state HSL is active, LPL less so, and the esterification pathway is not activated. Fatty acids then flow in a net sense from adipocytes out into the capillaries for distribution to other tissues via the circulation. There appears to be highly coordinated regulation of LPL, HSL and fatty acid esterification which governs fatty acid mobilization and deposition in adipose tissue (Frayn *et al.* 1995); regulation of LPL alone is not sufficient to explain the observations. This is illustrated in Fig. 5.

One factor now known to operate downstream from LPL is the acylation stimulating protein. This is the product of the interaction of three components of the alternative complement pathway secreted by adipocytes (Baldo *et al.* 1993), namely factors D (also known as adipsin), B and C3. The alternative complement pathway is a pathway known to have a role in host defence against bacterial invasion, but its role in adipose tissue may be concerned more with regulation of lipid metabolism (Sniderman & Cianflone, 1997). Acylation stimulating protein is the most potent known stimulator of fatty acid uptake and esterification in adipocytes (Sniderman & Cianflone, 1997). The production of acylation stimulating protein is stimulated by the arrival of chylomicrons (Maslowska *et al.* 1997) and correlates temporally with adipose tissue TG synthesis (Saleh *et al.*

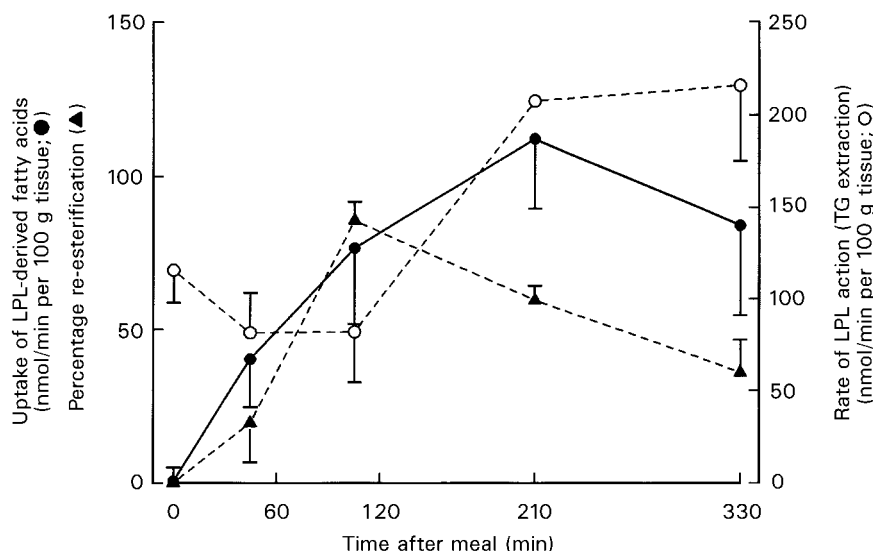


Fig. 4. Lipoprotein lipase (LPL) action and the regulation of fatty acid uptake in subcutaneous adipose tissue *in vivo* before and after a mixed meal. Results are from fourteen normal subjects fasted overnight (time 0) and then after eating a mixed meal (3.1 MJ, 41% energy from fat, described by Coppack *et al.* 1990). Studies were made by catheterization of the venous drainage from subcutaneous abdominal adipose tissue. (○), Rate of LPL action (measured as triacylglycerol (TG) extraction across the tissue); (▲), percentage of fatty acids (arising from both LPL and hormone-sensitive lipase, HSL) re-esterified in the tissue; (●), absolute uptake of LPL-derived fatty acids into the tissue calculated on the assumption of equal re-esterification of LPL- and HSL-derived fatty acids, as discussed by Frayn *et al.* (1994). Values are means with their standard errors represented by vertical bars. Based on data from the studies reported by Coppack *et al.* (1990) and Frayn *et al.* (1996a).

1998). Insulin is less potent but has similar effects (Frayn *et al.* 1994).

A further experiment illustrates the coordinated nature of this regulator. If adipose tissue blood flow is increased by infusion of adrenaline, the rate of TG extraction increases, presumably reflecting an increased rate of hydrolysis by LPL because of increased delivery of substrate (Samra *et al.* 1996). However, the fatty acids released by LPL action in that condition are released almost quantitatively into the venous plasma (Samra *et al.* 1996). Thus, up-regulation of LPL action in that situation does not lead to increased tissue retention of fatty acids. This illustrates the need for coordinated regulation of LPL with HSL and fatty acid esterification.

LPL may also be activated pharmacologically by various novel agents. In experiments in rats, these agents activate LPL in adipose tissue and skeletal muscle and lead to reduced plasma TG concentrations as expected. However, they do not lead to increased TG storage, but instead to elevated plasma NEFA concentrations and an increased rate of fat oxidation (Yokoyama *et al.* 1997; Hara *et al.* 1998). Again, therefore, the fact that LPL is but one link in the normal chain of events associated with dietary lipid partitioning is emphasized.

An interesting but unanswered question is whether downstream regulation of LPL-derived fatty acids is as important in other tissues such as skeletal muscle, as it is in adipose tissue. There is no net release of NEFA from skeletal muscle during high rates of LPL action during the postprandial period (Coppack *et al.* 1990, 1992), suggesting that in skeletal muscle LPL-derived fatty acids are effectively trapped in the tissue. Presumably the same would be true of myocardium. These observations remain to be confirmed,

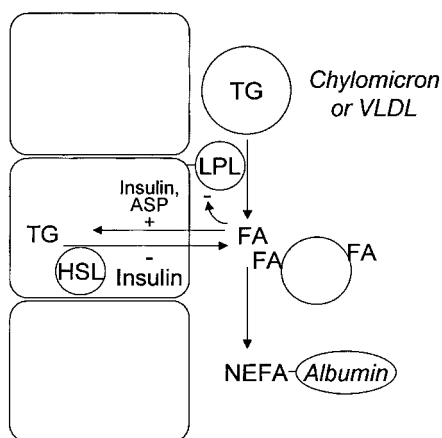


Fig. 5. Scheme for the regulation of fatty acid movement in white adipose tissue. Lipoprotein lipase (LPL) attached to the capillary endothelium acts on circulating triacylglycerol (TG)-rich lipoprotein particles (chylomicrons and VLDL) to release fatty acids (FA). These may be transiently attached to the surface of the remnant lipoprotein particle but the majority will either enter the adipocyte for esterification and storage as TG, or leave in the venous plasma as non-esterified fatty acids (NEFA) bound to albumin. The fate of LPL-derived fatty acids depends both on the activity of the intracellular hormone-sensitive lipase (HSL) and the activity of the pathway of fatty acid uptake and esterification. These are regulated by insulin and acylation stimulating protein (ASP), amongst other factors. Reproduced from Frayn *et al.* (1996b) with permission.

however, using appropriate techniques such as the use of labelled fatty acids. However, this view, if correct, would accord well with the effects of LPL over-expression in muscle discussed earlier.

Undoubtedly factors other than LPL also regulate tissue TG storage. For instance, the potential role of leptin has been recognized recently. Leptin-deficient animals accumulate TG in most tissues, and a marked effect of leptin administration is a widespread reduction in tissue TG content accompanied by an improvement in sensitivity to insulin (Chen *et al.* 1996; Shimabukuro *et al.* 1997). It is not yet clear, however, whether such effects of leptin might be mediated proximally by changes in the activity of LPL and other components of the pathway of fatty acid storage. As direct effects of leptin on peripheral tissues are increasingly being recognized (Frühbeck *et al.* 1997; Muoio *et al.* 1997; Siegrist-Kaiser *et al.* 1997), this becomes more likely.

Lipoprotein lipase in its physiological context

In adipose tissue it seems that LPL is but one component of a highly coordinated system for regulation of the deposition of dietary fatty acids. Normal fat storage can occur in the complete absence of LPL, and conversely up-regulation of LPL does not necessarily lead to fat deposition if not accompanied by coordinated regulation of other components of the pathway of fat deposition. In skeletal muscle and myocardium the situation may be somewhat less complex; since these tissues show consistent uptake of fatty acids, it may well be that LPL does indeed govern the delivery of fatty acids. However, it would equally be reasonable to assume that to some extent increased uptake of LPL-derived fatty acids might be balanced by a reduction in the uptake of plasma NEFA (this has not been tested, as far as we are aware).

Therefore, LPL is a major determinant of the delivery of dietary fatty acids to muscle and the mammary gland; in these tissues it may clearly be seen as a metabolic gatekeeper. The situation is different in other adipose tissue depots despite a close correlation in many circumstances between tissue LPL activity and storage of dietary fatty acids. The appearance of LPL as a gatekeeper for fat storage in white adipose tissue reflects the normal close coordination between different enzyme systems in that tissue. It is clear that in adipose tissue, at least, there is a major regulatory site downstream from LPL action. Compared with the amount of attention that has been directed to the action and regulation of LPL itself, little has been paid to regulation of the fate of its products. Elucidation of the regulation of this key metabolic branch point is an important goal for future research.

Acknowledgements

The review is based on a lecture given to the 8th European Congress on Obesity, Dublin, 1997 which has been published previously in abstract form (Frayn, 1997). K. N. F. would like to pay tribute to the late Donald Robinson who was responsible for introducing him to LPL and its many interesting facets.

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