Lipoprotein lipase transport in plasma: role of muscle and adipose tissues in regulation of plasma lipoprotein lipase concentrations

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Abstract Lipoprotein lipase (LPL) is synthesized in tissues involved in fatty acid metabolism such as muscle and adipose tissue. LPL is also found in the circulation, but is mostly lipolytically inactive. The proportion of active circulating LPL increases after a fatty meal. We investigated the release of active and inactive LPL from adipose tissue and muscle in the fasting and postprandial states. Arteriovenous concentration gradients of LPL across adipose tissue and forearm muscle were measured in male subjects before and after a fat-rich meal (n = 7) and before and during infusion of a triacylglycerol emulsion (Intralipid) (n = 6). Plasma LPL activity rose after the meal and more so during Intralipid infusion. Plasma LPL mass (>95% inactive LPL) increased after the meal but decreased after Intralipid infusion. In the fasting state (n = 13) muscle efflux of LPL activity was 0.263 ± 0.098 mU/min per 100 ml of muscle tissue whereas there was an influx of LPL activity to adipose tissue of 0.085 ± 0.100 mU/min per 100 g of adipose tissue ($P < 0.02$ muscle vs. adipose tissue). Similarly in the postprandial state only muscle released LPL activity. Both tissues released LPL mass. In the fasting state efflux was 17.8 ± 8.8 ng/min per 100 ml muscle and 55.2 ± 21.3 ng/min per 100 g of adipose tissue ($P < 0.05$ muscle vs. adipose tissue). Release of LPL, either active or inactive, was not correlated with levels of non-esterified fatty acids or plasma triacylglycerol. In conclusion, there is a substantial release of LPL from adipose tissue and muscle, most of which is inactive. A small proportion of active LPL seems to be redistributed from muscle to adipose tissue.—Karpe, F., T. Olivecrona, G. Olivecrona, J. S. Samra, L. K. M. Summers, S. M. Humphreys, and K. N. Frayn. **Lipoprotein lipase transport in plasma: role of muscle and adipose tissues in regulation of plasma lipoprotein lipase concentrations. *J. Lipid Res.* 1998.** 39: **2387–2393.**

Supplementary key words lipoprotein lipase • adipose tissue • skeletal muscle • triacylglycerol • non-esterified fatty acids

Lipoprotein lipase (LPL) is a key enzyme in lipoprotein metabolism (1, 2). It is synthesized in the parenchymal cells of extrahepatic tissues including adipose tissue, skeletal and cardiac muscle, and is translocated to its physiological site of action in the capillaries, where it is bound to heparan sulfate proteoglycan chains on endothelial cells. In that location it can act upon the triacylglycerol (TG) in the TG-rich lipoprotein (TRL) particles, chylomicrons and very low density lipoproteins (VLDL). The hydrolysis of TG by LPL results in the generation of fatty acids, which may be taken up into the tissue for esterification or oxidation or released into the plasma bound to albumin as non-esterified fatty acids (NEFA).

It is now recognized that some LPL leaves its endothelial binding site and appears in plasma. Binding of LPL to heparan sulfate proteoglycans is a rapidly reversible process although with high apparent affinity (3). The released LPL probably associates with lipoproteins in plasma. Of the total LPL present in plasma, most is in an inactive form and is associated with lipoprotein particles (4, 5). The circulating concentrations are kept low due to efficient uptake in the liver (6). Although the major effect of LPL on TRL metabolism seems to depend on the lipolytic conversion of TRL to remnant lipoproteins, a minor residual effect of non-lipolytic character of the LPL molecule in binding to cellular receptors has been proposed (7, 8) from studies of a rat liver perfusion system, but no effect has also been observed in cultured hepatocytes (9). The amount of active enzyme in plasma increases after an oral fat load (10). It has been suggested that dissociation of LPL from its binding sites is facilitated by local accumulation of fatty acids resulting from its hydrolytic action on plasma TG (11). If this occurs, it is likely to reflect the ac-

Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; LPL, lipoprotein lipase; NEFA, non-esterified fatty acids; TG, triacylglycerol; TRL, triacylglycerol-rich lipoproteins; U, units for lipase activity (1 μmol fatty acid released per minute); VLDL, very low density lipoprotein.

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tion of a specific localized pool of fatty acids, whose relationship to plasma NEFA is not clear.

The release of LPL from tissues in vivo has not been extensively studied. Coppack et al. (12) showed that forearm muscle released LPL activity into plasma in both postabsorptive and postprandial states, whereas there was no release of LPL activity from adipose tissue in the postabsorptive state and a small release of activity after feeding. These results are surprising because the activity of the enzyme is usually greater in adipose tissue than in skeletal muscle, and in the studies of Coppack et al. (12) TG extraction was greater in adipose tissue than in muscle. One possible explanation for this apparent discrepancy would be if adipose tissue tended to release LPL into the circulation in an inactive form.

The aim of the present study was therefore to characterize the release of both active and inactive enzyme from subcutaneous adipose tissue and skeletal muscle in vivo in relationship to net NEFA exchange in those tissues, before and after ingestion of a fat-rich mixed meal to introduce TG-rich particles into the system. In addition, further experiments were performed in which a TG emulsion, Intralipid, was infused, to determine whether responses would be observed similar to those produced by intestinally derived lipoprotein particles.

Some other aspects of the two sets of studies have been published separately (13, 14). The data for LPL in the mixed meal studies have been published in abstract form (15).

METHODS

Subjects and protocol

Both sets of studies were carried out on normal male subjects who had abstained from alcohol and smoking for 24 h, and had consumed a low-fat meal on the previous evening. The details are shown on **Table 1**. The subjects arrived at the laboratory after a 12–14-h fast. The studies were approved by the Central Oxford Research Ethics Committee, and all subjects gave informed consent.

A catheter (22 gauge × 10 cm, Secalon Hydrocath, Ohmeda, Swindon, UK) was introduced over a guide wire into a small vein on the abdominal wall and advanced until its tip lay near, but superior to, the inguinal ligament. As described previously (16, 17), blood obtained from such a vein has all the characteristics expected of the venous drainage from adipose tissue. A cannula was inserted retrogradely into a vein draining a hand which was warmed in a box with an air temperature of 65°C to provide arterialized blood (18). A further cannula was placed retrogradely into an antecubital vein draining deep forearm tissues on the contralateral arm. For the Intralipid studies, a further antecubital cannula was placed on the arm with the warmed hand for infusion. Cannulae were kept patent by slow infusion of saline; no heparin was used.

TABLE 1. Characteristics of male subjects studied

	Mixed Meal Study	Intralipid Study
Number	7	6
Age, years	30 (21–47)	21 (21–37)
BMI, kg/m^2	23.2 (19.3–27.9)	24.1 (23.0–25.9)
Plasma glucose, mmol/l	4.98 (4.83–5.24)	4.90 (4.63–5.09)
Plasma TG, mmol/l	1.07 (0.61–1.68)	0.75 (0.62–1.56)

Biochemical data are for arterialized samples after overnight fast. Median values are shown; range in parentheses.

Subcutaneous abdominal adipose tissue blood flow was measured by the ^{133}Xe washout technique (19, 20) after injecting 2 MBq ^{133}Xe into the region drained by the subcutaneous abdominal catheter. At least 30 min elapsed after injection of the ^{133}Xe before readings were taken, and blood flow was then measured before each set of blood samples. Forearm blood flow was measured by strain-gauge plethysmography (21) on the arm with the deep antecubital cannula, just after each set of blood samples.

After a 30-min rest period, basal blood samples were taken simultaneously from the arterialized vein, the subcutaneous abdominal catheter, and the deep antecubital cannula. A cuff was inflated to a pressure of 200 mm Hg around the wrist for 2 min before taking the deep venous samples, to occlude superficial flow from the hand.

Mixed meal study

The details of this study have been published elsewhere (13). After two sets of basal blood samples, the subjects consumed a mixed meal containing 85 g carbohydrate, 60 g fat, and 13 g protein in the form of a milk shake containing corn oil with cornflakes. Further blood samples were taken at 40-min intervals until 240 min after the meal.

Intralipid study

Details of this study have previously been published (14, 22). After withdrawal of two sets of basal blood samples, an intravenous infusion of Intralipid 10% (w/v) (Pharmacia Ltd., Milton Keynes, UK) was started at a rate of 1.85 ml·kg^{-1}·h^{-1}, equivalent to a TG infusion rate of 185 mg·kg^{-1}·h^{-1}. Blood samples were withdrawn at 30-min intervals for 2 h and then hourly. The infusion was continued for 4 h and then further blood samples were taken at 30-min intervals over the next 90 min.

Analytical methods

Blood samples were taken into heparinized syringes and a sample was immediately deproteinized with perchloric acid for enzymatic estimation of whole-blood glycerol concentration. The remaining plasma was separated rapidly at 4°C. A portion was kept for estimation of glucose concentration, and the remainder was stored in aliquots at −20°C. Plasma for LPL activity and mass determination was immediately frozen at −70°C.

Plasma concentrations of glucose and non-esterified fatty acids (NEFA) and whole-blood glycerol concentrations were estimated with enzymatic methods adapted to an IL Monarch centrifugal analyzer (Instrumentation Laboratory (UK) Ltd, Warrington, UK). Plasma insulin concentrations were measured with a radioimmunoassay kit (Pharmacia AB, Uppsala, Sweden).

Portions of frozen plasma were sent on dry ice to Umeå for measurement of LPL activity and immunoreactive mass. LPL activity in plasma was determined after immuno-inhibition of hepatic lipase activity in plasma, essentially as described previously (10). A synthetic Intralipid containing ^{3}H-labeled trioleoylglycerol, kindly incorporated by the manufacturer, was used instead of the sonicated emulsion described previously, to increase reproducibility between assays. Lipase activity is expressed in units (U) corresponding to release of 1 μmol fatty acid per min. Measurements were made in triplicate for LPL activity and on three dilutions of plasma for measurement of LPL mass. LPL mass was also determined as described previously (4, 5). In essence, an ELISA with a polyclonal chicken anti-human LPL antibody was used for capture and a peroxidase-conjugated monoclonal 5D2 antibody was used for detection.

Calculations and statistical methods

Adipose tissue and forearm plasma flow were calculated from blood flow and hematocrit. Uptake and release of LPL mass or activity were calculated by multiplying the arteriovenous difference by the rate of plasma flow. The terms efflux and influx will be used only for absolute measurements of net uptake or release calculated in this way.

Changes in concentrations with time, and arteriovenous differences across the tissues, were assessed by repeated-measures analysis of variance (ANOVA) using time and site (arterialized, forearm venous and adipose venous) as within-subjects factors. For LPL activity and immunoreactive mass, areas-under-curves (AUCs) were calculated for the three sampling sites (arterialized, forearm, and adipose venous) and compared by ANOVA with post-hoc tests between sites using Tukey's Honestly Significant Difference test (23). For efflux of LPL from tissues, mean basal and postprandial values were calculated and were compared with each other within subjects using Wilcoxon's Signed Rank test. Calculations were done with SPSS for Windows Release 7.1 (SPSS Inc., Chicago, IL). Results are shown as mean value ± SEM.

RESULTS

Mixed meal study

Plasma concentrations of energy substrates and insulin. Arterialized plasma glucose concentrations rose to a peak at 40 min after the meal (**Fig. 1**). Plasma insulin concentrations also rose to a peak at the same time (Fig. 1).

Plasma NEFA and glycerol concentrations are shown in **Fig. 2**. Arterialized concentrations of NEFA (Fig. 2A) and glycerol (Fig. 2B) fell after the meal and then rose over the next 4 h. There was consistent release of both NEFA and glycerol from adipose tissue. In contrast, there was no significant net exchange of NEFA across the forearm, but again consistent release of glycerol. Plasma TG concentrations have been published separately (13); they rose after the meal, and TG extraction across the tissues increased.

*LPL activity and mass (**Fig. 3**).* LPL activity in plasma rose steadily after the meal ($P = 0.035$ for time effect, repeated measures). The immunoreactive mass of LPL in plasma tended to increase in the postprandial period ($P = 0.065$).

There was consistent release of LPL activity from forearm muscle. In contrast, there was no release of LPL activity from adipose tissue in the postabsorptive or postprandial state. For LPL immunoreactive mass, however, there was consistent release from adipose tissue and less so from forearm muscle (Fig. 3).

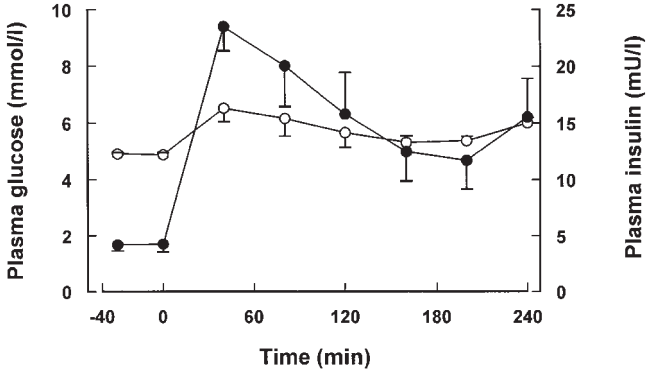

Fig. 1. Arterialized plasma glucose (○) and insulin (●) responses to the mixed meal.

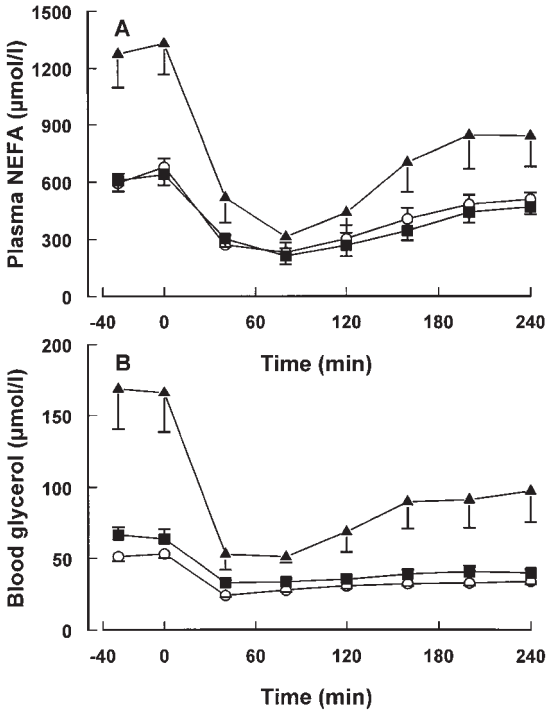

Fig. 2. Plasma NEFA (A) and blood glycerol (B) concentrations before and after the mixed meal; ○, arterialized; ■, forearm (muscle) venous; ▲, adipose tissue venous. Statistics: NEFA: repeated measures ANOVA shows significant time effect ($P < 0.001$) and differences between sampling sites ($P = 0.001$); adipose venous was significantly different from arterialized ($P = 0.014$) whereas forearm venous was not. Glycerol: repeated measures ANOVA shows time effect significant ($P < 0.001$), site effect significant ($P = 0.001$); both forearm venous ($P = 0.013$) and adipose venous ($P = 0.007$) were significantly different from arterialized.

The fluxes of LPL activity and immunoreactive mass, calculated by multiplication of veno-arterial differences by plasma flow, are summarized on **Fig. 4**. Efflux of activity from the forearm (per 100 ml of tissue) was greater than that from adipose (per 100 g tissue), and efflux of activity from the forearm increased in the postprandial period. For immunoreactive mass, however, the picture was reversed, with greater efflux from adipose tissue than from muscle. Further analyses of LPL efflux in the basal state are presented below.

The contribution of active LPL to the total LPL mass is minor compared with the release of inactive LPL. The specific activity of active dimeric LPL is approximately 0.35–0.5 U/μg (5) and with an arteriovenous difference in LPL activity of 0.2 U/l that corresponds to a mass of 0.4–0.5 μg/l, which is approximately 2–5% of the total release of LPL mass from muscle.

Intralipid study

Plasma NEFA and glycerol concentrations in this study have been reported elsewhere (14, 22). As in the mixed meal study, there was release of NEFA and glycerol from adipose tissue but not from forearm muscle.

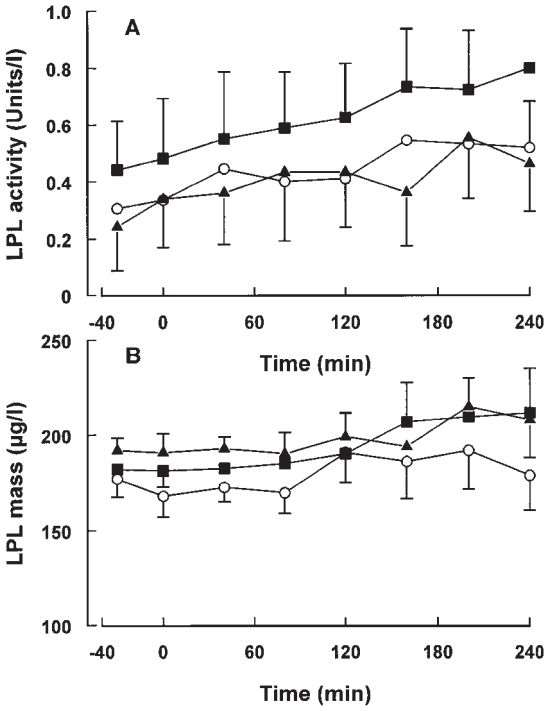

Fig. 3. LPL activity (A) and immunoreactive mass (B) in plasma before and after the mixed meal; ○, arterialized; ■, forearm (muscle) venous; ▲, adipose tissue venous. Statistics: LPL activity: repeated measures ANOVA shows significant time effect ($P = 0.035$) and differences between sampling sites ($P < 0.001$); ANOVA with post-hoc tests on AUCs shows overall differences by site ($P < 0.001$), significant between arterialized and forearm venous ($P < 0.001$) but not between arterialized and adipose venous. LPL mass: repeated measures ANOVA shows time effect not significant, site effect significant ($P = 0.004$); ANOVA with post-hoc tests on AUCs shows overall differences by site ($P = 0.009$), significant between arterialized and adipose venous ($P = 0.008$) and borderline between arterialized and forearm venous ($P = 0.054$).

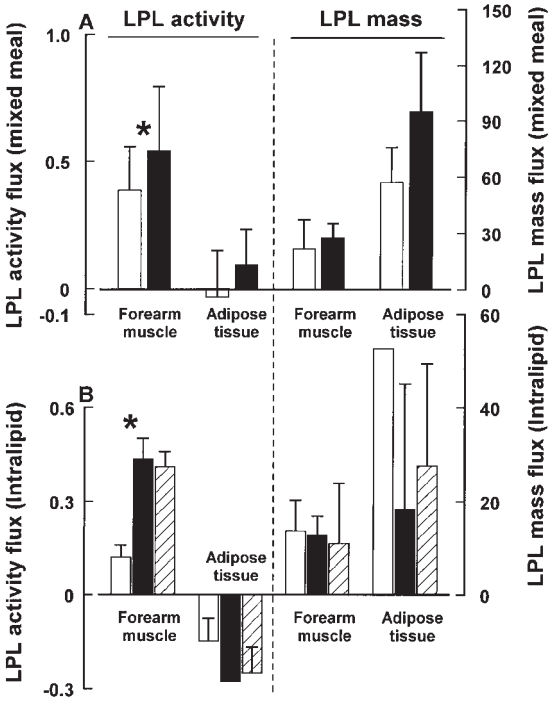

Fig. 4. LPL efflux from tissues, (A) in the mixed meal studies, (B) in the Intralipid infusion studies. (A) Open bars, mean basal efflux; solid bars, mean postprandial efflux (calculated as AUC for efflux averaged over postprandial period). (B) Open bars, mean basal efflux; solid bars, mean efflux during Intralipid infusion; hatched bars, mean efflux after Intralipid infusion. *Difference between basal and postprandial/infusion significant by Wilcoxon Signed Rank test ($P < 0.05$). Missing standard error bars were: LPL activity efflux from adipose tissue during Intralipid infusion, 0.11 (not shown for clarity) and LPL mass efflux from adipose tissue, basal, Intralipid infusion, 43. The large SEM reflects the fact that one subject in the basal state showed consistent uptake of LPL mass. Units: efflux of LPL activity, mU per min per unit tissue; LPL immunoreactive mass, ng per min per unit tissue. Units of tissue are 100 ml (forearm muscle) and 100 g (adipose tissue).

As in the mixed meal study, LPL activity (**Fig. 5**) in arterialized plasma increased during the Intralipid infusion and was released from forearm muscle. However, the activity in the adipose venous plasma was significantly lower than in arterialized plasma, i.e., there was uptake from plasma of LPL activity by adipose tissue.

LPL immunoreactive mass in plasma tended to fall during the study ($P < 0.05$ by repeated measures ANOVA for time effect), and as in the mixed meal studies there was release of LPL immunoreactive mass in adipose venous plasma, but no difference was found between arterialized and forearm muscle venous plasma.

The efflux of LPL from tissues was again calculated as veno-arterial difference multiplied by plasma flow. Results are shown on Fig. 4 (B) and are similar to the data for the mixed meal study, with more pronounced uptake of LPL activity by adipose tissue in the basal state.

Baseline data for LPL flux from both studies

Data for LPL efflux in the basal state from the two studies (13 subjects) were combined (**Table 2**). They show highly significant differences between the tissues for both LPL activity and LPL immunoreactive mass. For LPL activity, adipose tissue showed significant extraction from plasma in the basal state, whereas muscle showed release. For LPL mass, on the other hand, efflux from adipose tissue was significantly greater than that from muscle.

DISCUSSION

These studies show clearly that LPL is released from tissues into plasma in both postabsorptive and postprandial states. However, there are some interesting differences between the two tissues studied. Whilst forearm muscle consistently released active LPL into the plasma, adipose tissue did not; in fact, adipose tissue removed LPL activity from the plasma in the overnight fasted state and during Intralipid infusion. In contrast, there was consistent release of LPL immunoreactive mass (i.e., inactive enzyme) from adipose tissue and a less consistent pattern of release of LPL immunoreactive mass from forearm muscle.

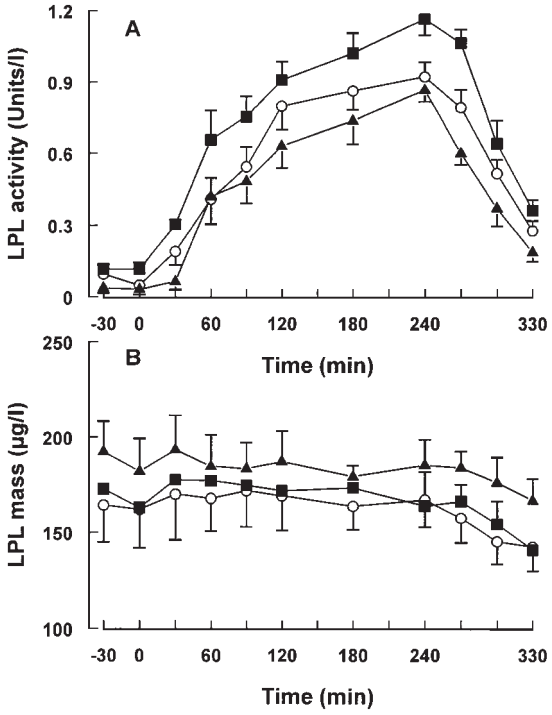

Fig. 5. LPL activity (A) and immunoreactive mass (B) in plasma before, during and after the Intralipid infusion from 0 to 240 min; ○, arterialized; ■, forearm (muscle) venous; ▲, adipose tissue venous. Statistics: LPL activity: repeated measures ANOVA shows significant time effect ($P < 0.001$); ANOVA with post-hoc tests on AUCs shows overall differences by site ($P < 0.001$), significant between arterialized and forearm venous ($P < 0.001$) and between arterialized and adipose venous (uptake of LPL activity, $P = 0.001$). LPL mass: repeated measures ANOVA shows significant time effect ($P = 0.047$); ANOVA with post-hoc tests on AUCs shows overall differences by site ($P = 0.04$), significant between arterialized and adipose venous ($P = 0.04$) but not between arterialized and forearm venous.

We previously described that LPL activity in plasma increases in response to oral fat intake (10). At that time the source of LPL was unknown. From the present work it is concluded that muscle is likely to be the major source of the increased plasma levels of active LPL in the postprandial state. On the basis of earlier studies (11, 24), we hypothesized previously that the release of active LPL was in response to NEFA accumulating close to endothelial surfaces . The present findings shed new light on LPL release from tissues. NEFA concentrations in adipose tissue venous drainage were very high in the fasting state, but this did not provoke release of active LPL into plasma. However, in the fasting state it can be argued that these NEFA arise from intracellular lipolysis and might not impinge directly upon LPL bound to the capillary endothelium. It is therefore more interesting that there was no release of LPL activity from adipose tissue in the late postprandial phase as it is well established that adipose tissue venous drainage contains a mixture of endogenous NEFA and NEFA derived directly from LPL action on chylomicron-TG (25, 26). The mechanism for release of the enzyme in its active form from muscle is not clear from the present results. It is not obvious that metabolic regulators such as elevated local NEFA concentrations are involved in this process as there was a significant release of LPL in both the fasting and postprandial states. The marked difference comparing adipose tissue and muscle in this respect rather argues for differences in tissue-specific mechanisms of LPL binding to vascular endothelium. The previously described coordinated increase of LPL activity and plasma NEFA (10) was not found in the present study. Rather, it seemed as if the LPL activity arose from one type of tissue (muscle) and the postprandial increase of NEFA level from another (adipose tissue).

It is also possible that the differences between adipose tissue and muscle LPL release reflect differences in the process that leads to LPL inactivation. For instance, if LPL were inactivated upon release from adipose tissue this would account for the greater release of inactive and smaller release of active LPL from adipose tissue compared with muscle. However, it is unlikely that differences in NEFA metabolism underlie such a difference between tissues. LPL is stabilized by contact with plasma lipoproteins and by interaction with fatty acids (27, 28). Therefore it seems likely that if LPL dissociates from the endothelium in its active form, for instance by interaction with lipoprotein particles or fatty acids, it will remain active. Another possibility is direct release of inactive LPL from intracellular pools within adipose tissue. A large proportion of LPL protein in adipose tissue is in an inactive form, especially in the fasted state (29). Perhaps this inactive LPL is turned over by release into plasma for eventual degradation in the liver.

Our observation of significant uptake of LPL activity by

TABLE 2. LPL efflux from tissues in the overnight fasted state

	Forearm Muscle	Adipose Tissue	Significance of Difference between Tissues
LPL activity efflux (mU/min per unit tissue)	0.263 ± 0.098	−0.085 ± 0.100	$P < 0.02$
Significance of difference from zero	$P = 0.001$	$P < 0.05$	
LPL mass efflux (ng/min per unit tissue)	17.8 ± 8.8	55.2 ± 21.3	$P < 0.05$
Significance of difference from zero	$P < 0.05$	$P < 0.02$	

Data from the basal samples in the mixed meal and Intralipid infusion studies were combined (n = 13). Calculation of efflux is described in the text. The data for the individual studies are shown in Fig. 4. Units of tissue are 100 ml (forearm muscle) and 100 g (adipose tissue). The negative value for adipose tissue LPL activity efflux implies significant removal of LPL activity from plasma. Significance of differences between tissues and significance of flux (compared to zero) was tested by Wilcoxon's Signed Rank test.

adipose tissue in the fasting state and also during Intralipid infusion is intriguing. It has been described that the LPL molecule may be transported through the circulation between tissues, before eventual clearance by the liver (30, 31). Our data may show this in action, but they imply that the process is tissue-specific, with release of LPL activity from muscle and uptake by adipose tissue, at least under particular conditions. There is a precedent for tissue uptake of lipase activity in the case of hepatic lipase, which is present in adrenals and ovaries and presumed to arise from uptake from plasma (32, 33).

The release of LPL mass from adipose tissue tended to respond in opposite directions in the mixed meal study (increase) compared with the Intralipid infusion study (decrease) (see Fig. 5). One of the principal differences in experimental condition between the two studies is the lack of a carbohydrate-mediated insulin response in the Intralipid study. One possible explanation for the difference in kinetics of release of LPL mass in the two studies is, therefore, that the rate of LPL mass release is partially insulin dependent.

With use of the arteriovenous difference in LPL concentration and the blood flow estimates, the present data could be used for extrapolating the 24-h release of LPL mass from adipose and muscle tissues. Obviously, a number of assumptions should be made for these calculations. First, the metabolic conditions over the day must be approximated to fasting and postprandial and we have not studied the influence of working muscle. The fasting situation was calculated from determinations made at −30 min and 0 min whereas the postprandial determinations were derived from the mean of +200 min and +240 min. Second, adipose tissue depots and striated muscle are approximated to behave similarly all over the body, and total weights of adipose tissue and muscle have been estimated for lean or obese or thin or muscular subjects, respectively, to give ranges of values. Based on the blood flow estimates, arterio-venous concentrations of LPL and the above mentioned assumptions, calculations of 24-h release of LPL mass were made (**Table 3**). In order to test the validity of the calculated 24-h estimation of LPL release, a calculation was made from completely different assumptions. First, we have previously described that heparin administration to normal healthy men gives rise to an immediate release of endothelial-bound LPL mounting to a final plasma concentration of approximately 750 ng/ml (5). Second, the time needed for complete restoration of endothelial LPL, which has been washed away by heparin, is between 2 and 4 h (34). With a plasma volume of 3000 ml and a calculated 50% loss of enzyme (very rapid uptake by the liver), the 24-h whole-body turnover of LPL is in the range of 24–48 mg. Interestingly, this figure is in the same order of magnitude as data in this work (Table 3).

TABLE 3. Approximate estimate of 24-h release of LPL mass from skeletal muscle and adipose tissue

	Skeletal muscle		Adipose tissue	
	Thin	Muscular	Lean	Obese
Organ weight assumed (kg)	20	40	5	25
LPL release: fasting (mg)	10	20	37	35
LPL release: postprandial (mg)	30	60	9	45

For discussion of assumptions, see text.

A general conclusion from this study is that tissues producing LPL handle the enzyme in different ways. Muscle seems to waste the enzyme by constantly releasing it, in contrast to adipose tissue, which maintains active LPL. The mechanistic background of this difference is unknown, but differences in metabolic regulation between the tissues as well as endothelial binding capacity of the enzyme must be taken into account. These findings are important for the understanding of the regulation of energy disposal between tissues.

This study was supported by grants from the Swedish Medical Research Council (727 and 8691), the Swedish Heart-Lung Foundation, and in the UK by the Wellcome Trust and the Ministry of Agriculture, Fisheries and Food.

Manuscript received 19 February 1998 and in revised form 29 July 1998.

REFERENCES

1. Olivecrona, G., and T. Olivecrona. 1995. Triglyceride lipases and atherosclerosis. *Curr. Opin. Lipidol.* **6:** 291–305.
2. Goldberg, I. J. 1996. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. *J. Lipid Res.* **37:** 693–707.
3. Lookene, A., R. Savonen, and G. Olivecrona. 1997. Interaction of lipoproteins with heparan sulfate proteoglycans and with lipoprotein lipase. Studies by surface plasmon resonance technique. *Biochemistry.* **36:** 5267–5275.
4. Vilella, E., J. Joven, M. Fernández, S. Vilaró, J. D. Brunzell, T. Olivecrona, and G. Bengtsson-Olivecrona. 1993. Lipoprotein lipase in human plasma is mainly inactive and associated with cholesterol-rich lipoproteins. *J. Lipid Res.* **34:** 1555–1564.
5. Tornvall, P., G. Olivecrona, F. Karpe, A. Hamsten, and T. Olivecrona. 1995. Lipoprotein lipase mass and activity in plasma and their increase after heparin are separate parameters with different relations to plasma lipoproteins. *Arterioscler. Thromb. Vasc. Biol.* **15:** 1086–1093.
6. Wallinder, L., J. Peterson, T. Olivecrona, and G. Bengtsson Olivecrona. 1984. Hepatic and extrahepatic uptake of intravenously injected lipoprotein lipase. *Biochim. Biophys. Acta.* **795:** 513–524.
7. Beisiegel, U., W. Weber, and G. Bengtsson-Olivecrona. 1991. Lipoprotein lipase enhances the binding of chylomicrons to low density lipoprotein receptor-related protein. *Proc. Natl. Acad. Sci. USA.* **88:** 8342–8346.
8. Skottova, N., R. Savonen, A. Lookene, M. Hultin, and G. Olivecrona. 1995. Lipoprotein lipase enhances removal of chylomicrons and chylomicron remnants by the perfused rat liver. *J. Lipid Res.* **36:** 1334–1344.
9. Huff, M. W., D. B. Miller, B. M. Wolfe, P. W. Connelly, and C. G. Sawyez. 1997. Uptake of hypertriglyceridemic very low density lipoproteins and their remnants by HepG2 cells: the role of lipoprotein lipase, hepatic triglyceride lipase, and cell surface proteoglycans. *J. Lipid Res.* **38:** 1318–1333.
10. Karpe, F., T. Olivecrona, G. Walldius, and A. Hamsten. 1992. Lipoprotein lipase in plasma after an oral fat load: relation to free fatty acids. *J. Lipid Res.* **33:** 975–984.
11. Peterson, J., B. E. Bihain, G. Bengtsson-Olivecrona, R. J. Deckelbaum, Y. Carpentier, and T. Olivecrona. 1990. Fatty acid control of lipoprotein lipase: a link between energy metabolism and lipid transport. *Proc. Natl. Acad. Sci.USA.* **87:** 909–913.
12. Coppack, S. W., T. J. Yost, R. M. Fisher, R. H. Eckel, and J. M. Miles. 1996. Periprandial systemic and regional lipase activity in normal humans. *Am. J. Physiol.* **270:** E718–E722.

13. Karpe, F., S. M. Humphreys, J. S. Samra, L. K. M. Summers, and K. N. Frayn. 1997. Clearance of lipoprotein remnant particles in adipose tissue and muscle in humans. *J. Lipid Res.* **38:** 2335–2343.
14. Samra, J. S., C. L. Ravell, S. L. Giles, P. Arner, and K. N. Frayn. 1996. Interstitial glycerol concentration in human skeletal muscle and adipose tissue is close to the concentration in blood. *Clin. Sci.* **90:** 453–456.
15. Karpe, F., K. N. Frayn, S. M. Humphreys, G. Olivecrona, and T. Olivecrona. 1997. Lipoprotein lipase transport in plasma: role of muscle and adipose tissues in regulating plasma levels of lipoprotein lipase. *Proc. Nutr. Soc.* **56:** 202A.
16. Frayn, K. N., S. W. Coppack, S. M. Humphreys, and P. L. Whyte. 1989. Metabolic characteristics of human adipose tissue in vivo. *Clin. Sci.* **76:** 509–516.
17. Frayn, K. N., S. W. Coppack, and S. M. Humphreys. 1993. Subcutaneous adipose tissue metabolism studied by local catheterization. *Int. J. Obesity.* **17 (Suppl. 3):** S18–S21.
18. McGuire, E. A. H., J. H. Helderman, J. D. Tobin, R. Andres, and M. Berman. 1976. Effects of arterial versus venous sampling on analysis of glucose kinetics in man. *J. Appl. Physiol.* **41:** 565–573.
19. Larsen, O. A., N. A. Lassen, and F. Quaade. 1966. Blood flow through human adipose tissue determined with radioactive xenon. *Acta Physiol. Scand.* **66:** 337–345.
20. Samra, J. S., K. N. Frayn, J. A. Giddings, M. L. Clark, and I. A. Macdonald. 1995. Modification and validation of a commercially available portable detector for measurement of adipose tissue blood flow. *Clin. Physiol.* **15:** 241–248.
21. Greenfield, A. D. M., R. J. Whitney, and J. F. Mowbray. 1963. Methods for the investigation of peripheral blood flow. *Br. Med. Bull.* **19:** 101–109.
22. Samra, J. S., S. L. Giles, C. L. Ravell, M. L. Clark, S. M. Humphreys, and K. N. Frayn. 1997. Suppression of endogenous lipolysis during exogenous triacylglycerol infusion. *Proc. Nutr. Soc.* **56:** 91A.
23. Bland, M. 1995. An Introduction to Medical Statistics. Oxford University Press, Oxford.
24. Saxena, U., L. D. Witte, and I. J. Goldberg. 1989. Release of endothelial cell lipoprotein lipase by plasma lipoproteins and free fatty acids. *J. Biol. Chem.* **264:** 4349–4355.
25. Frayn, K. N., S. W. Coppack, B. A. Fielding, and S. M. Humphreys. 1995. Coordinated regulation of hormone-sensitive lipase and lipoprotein lipase in human adipose tissue in vivo: implications for the control of fat storage and fat mobilization. *Adv. Enzyme Reg.* **35:** 163–178.
26. Fielding, B. A., J. Callow, R. M. Owen, J. S. Samra, D. R. Matthews, and K. N. Frayn. 1996. Postprandial lipemia: the origin of an early peak studied by specific dietary fatty acid intake during sequential meals. *Am. J. Clin. Nutr.* **63:** 36–41.
27. Fielding, C. J. 1968. Inactivation of lipoprotein lipase in buffered saline solutions. *Biochim. Biophys. Acta.* **159:** 94–102.
28. Bengtsson, G., and T. Olivecrona. 1980. Lipoprotein lipase. Mechanism of product inhibition. *Eur. J. Biochem.* **106:** 557–562.
29. Bergö, M., G. Olivecrona, and T. Olivecrona. 1996. Forms of lipoprotein lipase in rat tissues: in adipose tissue the proportion of inactive lipase increases on fasting. *Biochem. J.* **313:** 893–898.
30. Camps, L., M. Reina, M. Llobera, S. Vilar, and T. Olivecrona. 1990. Lipoprotein lipase: cellular origin and functional distribution. *Am. J. Physiol.* **258:** C673–C681.
31. Camps, L., M. Reina, M. Llobera, G. Bengtsson Olivecrona, T. Olivecrona, and S. Vilaro. 1991. Lipoprotein lipase in lungs, spleen, and liver: synthesis and distribution. *J. Lipid Res.* **32:** 1877–1888.
32. Doolittle, M. H., H. Wong, R. C. Davis, and M. C. Schotz. 1987. Synthesis of hepatic lipase in liver and extrahepatic tissues. *J. Lipid Res.* **28:** 1326–1334.
33. Hixenbaugh, E. A., T. R. Sullivan, Jr., J. F., Strauss, E. A. Laposata, M. Komaromy, and L. G. Paavola. 1989. Hepatic lipase in the rat ovary. Ovaries cannot synthesize hepatic lipase but accumulate it from the circulation. *J. Biol. Chem.* **264:** 4222–4230.
34. Chevreuil, O., M. Hultin, P. Ostergaard, and T. Olivecrona. 1993. Depletion of lipoprotein lipase after heparin administration. *Arterioscler. Thromb.* **13:** 1391–1396.