Routes of FA delivery to cardiac muscle: modulation of lipoprotein lipolysis alters uptake of TG-derived FA

AYANNA S. AUGUSTUS, YUKO KAKO, HIROAKI YAGYU, AND IRA J. GOLDBERG

Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York 10032

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Augustus, Ayanna S., Yuko Kako, Hiroaki Yagyu, and Ira J. Goldberg. Routes of fatty acid delivery to cardiac muscle: modulation of lipoprotein lipolysis alters uptake of TG-derived fatty acids. Am J Physiol Endocrinol Metab 284: E331–E339, 2003. First published October 15, 2002. 10.1152/ajpendo.00298.2002.—Long-chain fatty acids (FA) supply 70–80% of the energy needs for normal cardiac muscle. To determine the sources of FA that supply the heart, [14C]palmitate complexed to bovine serum albumin (BSA) was used to assess free FA delivery. In addition, [3H]triolein (TG) incorporated into Intralipid were simultaneously injected into fasted male C57BL/6 mice. The ratio of TG to FA uptake was much greater for hearts than livers. Using double-labeled Intralipid with [3H]cholesteryl oleoyl ether (CE) and [14C]TG, we observed that hearts also internalize intact core lipid. Inhibition of lipoprotein lipase (LPL) with tetrahydrolipstatin or dissociation of LPL from the heart with heparin reduced cardiac uptake of TG by 82 and 64%, respectively (P < 0.01). Palmitate uptake by the heart was not changed by either treatment. Uptake of TG was 88% less in hearts from LPL knockout mice that were rescued via LPL expression in the liver. Our data suggest that the heart is especially effective in removal of circulating TG and core lipids and that this is due to LPL hydrolysis and not its bridging function.

FATTY ACIDS (FA) are an important fuel source for heart and skeletal muscle, providing over 70% of the energy needs for cardiac function (2, 5, 33). FA are delivered to cardiac myocytes in three ways. 1) FA are derived from the hydrolysis of triglyceride (TG) stored in adipose tissue via hormone-sensitive lipase and circulated with albumin. 2) FA are produced from intracellular hydrolysis of TG in the core of internalized lipoproteins. 3) FA are also generated in the local capillary bed by lipoprotein lipase (LPL)-mediated hydrolysis of TG in circulating chylomicrons and very low-density lipoproteins (VLDL). Despite the fact that the molar concentration of FA in lipoprotein TG is an order of magnitude greater than that of albumin FA, it is widely believed that albumin-FA is the primary source of energy for the heart (21). However, cardiac muscle is the tissue with the greatest expression of LPL (9). Moreover, expression of LPL solely in the heart is adequate to maintain normal levels of plasma TG (19). Thus it is likely that hearts are continuously generating a large amount of FA from TG lipolysis.

A number of early studies that measured FA delivery to muscle (11, 14) were limited in their scope, measuring only the contribution of albumin-bound FA delivery to muscle without considering additional pathways. More recently, FA metabolism in isolated perfused working hearts has been studied and FA oxidation quantified (3, 11, 14, 24, 34). Comparison data on FA delivery to the heart under conditions that mimic those in vivo are limited. The contribution of lipoprotein-TG to heart energy production, especially in the postprandial period when the heart is bathed in dietary TG, is uncertain.

This study had two objectives. The first was to compare the heart uptake of FA bound to albumin and FA derived from the hydrolysis of TG-rich lipoproteins with that of other tissues. Kinetic studies were performed in mice to assess two or more pathways of FA delivery concurrently. This allowed us to assess, in vivo, FA delivery to the heart in the context of whole body metabolism. Intralipid emulsion particles, which are similar in size and TG content to chylomicrons (17), and VLDL were utilized to determine lipoprotein particle FA delivery. In addition, palmitate complexed to bovine serum albumin (BSA) was used to assess free FA delivery to tissues. The second objective was to assess the role of LPL in the delivery of TG-derived FA to the heart. LPL catalyzes the hydrolysis of TG in circulating chylomicrons and VLDL into FA and monoaoylglycerol (4). To assess its role in FA delivery to the heart, LPL activity was altered by heparin treatment, which increases LPL activity in the plasma (6) or abolished by an active site inhibitor, tetrahydrolipstatin (THL). In addition, we studied mice expressing LPL particle FA delivery. In addition, we studied mice expressing LPL exclusively in the liver to determine how their hearts compensate for loss of LPL expression.

METHODS

Animals. All experiments were conducted on 4-h-fasted, male C57BL/6 mice weighing 19–28 g. Animals were housed...
Labeled FFA was injected simultaneously with TG-labeled Intralipid particles into three fasting C57BL/6 male mice and into mice with a genetic deletion of murine LPL (A1L0; these mice express human LPL in the liver) to assess FA delivery to the heart via albumin-bound and TG-derived FA. A bolus of 400,000 cpm of [14C]palmitate with 1 × 10^6 cpm of labeled [3H]TG containing particles at a final concentration of 1 mg TG/mouse was injected. Eighty microliters of blood were

in a room undergoing a 12:12-h light-dark cycle and provided access to standard chow and water ad libitum.

Some experiments were performed in genetically modified mice. These mice express LPL only in the liver, because the LPL minigene is driven by the apoprotein (apo)AI promoter. These mice, termed A1L0, are described in detail in a previous publication (27).

Preparation of labeled FA-albumin complex. FA turnover utilized [9,10-3H]palmitate or [1-14C]palmitate in ethanol (NEC Life Sciences, Boston, MA; specific activity 60 and 56 mCi/mmol, respectively) complexed to 6% FA-free BSA (Sigma Aldrich) as described (7). To determine the appropriate end point for assessing FA uptake by the heart and other organs, 1 × 10^6 counts per minute (cpm) of [3H]palmitate were injected into three fasting male mice via jugular vein to assess free FA (FFA) turnover. In addition, a bolus of 1 × 10^6 cpm of [3H]palmitate and 300,000 cpm of [14C]oleate was injected into six fasting male mice to assess metabolism of both FAs by the heart.

Fig. 1. Metabolism of [3H]palmitate-BSA by fasting mice. A: plasma clearance of labeled fatty acids (FA) was measured at the indicated time points. Data represent the percentage of radioactivity at 30 s after injection. B: heart and liver uptake of labeled FA was measured 2 min (open bar), 4 min (filled bar), and 10 min (gray bar) after iv injection. Tissues were homogenized and counted as described in METHODS. Three mice per group were studied. *Significant differences between 2- and 4-min groups: P < 0.05; ##significant differences between 4- and 10-min groups: P < 0.01.

Fig. 2. Metabolism of [3H]VLDL- and [3H]Intralipid-triglyceride (TG). A: plasma decay curve for TG-labeled VLDL (n = 3) and TG-labeled Intralipid emulsion (n = 3) was determined over a 4-min period. Data represent the percentage of counts at 30 s after injection. B and C: tissue distribution of labeled Intralipid and VLDL in fasting mice 5 min after injection. Data are expressed as means ± SD. CPM, counts/min.
collected from the retroorbital plexus 30 s and 1, 2, and 4 min later. Ten microliters of plasma from each time point were used to determine plasma decay. At the completion of the study, mice were perfused with 10 ml of PBS through the left ventricle, tissues were collected and homogenized in 5 ml of PBS, 1-ml aliquots were added to 3.5 ml of scintillation fluid, and radioactivity was counted to determine tissue radioactivity.

**Preparation of Intralipid emulsions labeled with [3H]triolein or [3H]cholesteryl oleoyl ether and glycerol [14C]trioleate.** Twenty percent Intralipid (Kabi Pharmacia, Clayton, NC) was diluted in sterile PBS to a final 5% concentration and labeled with 60 μCi [3H]triolein or 40 μCi [3H]cholesteryl oleoyl ether (CE) and 8 μCi [14C]triolein (Amersham Pharmacia Biotech), as described by van Bennekum et al. (31). Briefly, labels were added to a small glass vial and slowly evaporated to dryness under N2. Five hundred microliters of a 5% solution of Intralipid were added to the small glass vial and sonicated three times for 20 s at a power level of 40 W to incorporate the triolein and CE into the emulsion. The resulting emulsion was stored at 4°C before use in experiments. Double-labeled emulsion was injected into four fasting male mice to assess whole particle uptake.

**Preparation of in vivo-labeled VLDL particles.** In vivo labeling of VLDL-TG was performed as described (1). Ten mice with a heterozygous deletion of LPL (LPL1) were injected intravenously with 400 μCi of [9,10-3H]palmitic acid complexed to BSA. Blood was collected 45 min after injection. [3H]VLDL was isolated from pooled plasma by ultracentrifugation at a density of 1.006 g/ml. Thin-layer chromatography (TLC) was performed on silica gel plates by use of a solvent system composed of hexane-diethyl ether-acetic acid (70:30:1), and 85% of total radioactive counts in the VLDL were in the TG fraction. Fasting C57BL/6 male mice were injected intravenously with 300,000 cpm of [3H]VLDL (0.04 mg TG/mouse) and 100,000 cpm of [14C]palmitate in BSA. Blood was collected, and tissues were excised as described.

**Acute heparin treatment.** Mice were injected intraperitoneally with 100 U of heparin in saline (18). Ten minutes after injection, 500,000 cpm of [14C]triolein and 1 × 10⁶ cpm of [3H]triolein-labeled Intralipid were injected intravenously into five fasting 12- to 14-wk-old male mice. A second group of mice (n = 3) was treated with heparin before receiving an intravenous injection of 1 × 10⁶ cpm of [3H]palmitate complexed to BSA. Blood was collected from the retroorbital plexus at 30 s and 1, 2, and 4 min. Five minutes after injection, mice were perfused with 10 ml of PBS, tissues were excised, and plasma decay and tissue counts were measured as previously described.

**Acute THL treatment.** To confirm THL inhibition of LPL activity, 100 μl of 2.5 mM THL (Roche, Nutley, NJ) solution in PBS were intravenously injected into five fasting male mice (THL was diluted from a 25 mM solution in DMSO). Three control mice received an injection of 100 μl of PBS. Ten minutes later, plasma was collected and assayed for LPL activity. LPL activity was measured by the method described by Hoquet et al. (15). A second set of experiments was performed to measure clearance and uptake of double-labeled Intralipid emulsion in five THL and five control fasting male. Ten minutes after PBS and THL injection, 500,000 cpm of [14C]triolein and 1 ×
10^6 cpm of [3H]CE-labeled Intralipid emulsion were injected via the jugular vein. Plasma clearance and tissue uptake were measured as described.

Plasma lipids. Blood was collected from the retroorbital plexus into tubes containing EDTA. TG concentrations in plasma or (lipoprotein fractions) were determined enzymatically by kits (Sigma) in duplicate.

Calculations. The Excel for Windows program was used to calculate the fractional catabolic rate (FCR). The values for radioactivity remaining in the plasma were fitted to the monoexponential decay function, i.e., N = N_0e^{-kt}.

Statistical analysis. Results are expressed as means ± SD. Student’s t-test was used to calculate statistical significance.

RESULTS

Delivery of FFA to the heart and liver. First, the decay and tissue uptake of FA were assessed over time. Figure 1A shows the plasma decay curve of [3H]palmitate in 4-h-fasted C57BL/6 male mice. The FCR was 0.654 pools/min; less than 10% of the injected dose remained in the circulation by 4 min. To determine the appropriate end point for assessing FA uptake by the heart and other organs, tissue incorporation of labeled FFA was measured at 2, 4, and 10 min after bolus injection of labeled FFA-BSA complex (Fig. 1B). We observed a decline in heart radioactivity at a 10-min end point. Therefore, a 4-min end point was used for further studies.

TG-derived FA delivery to the heart. Kinetic studies utilizing labeled TG were performed to determine TG-derived FA delivery to the heart. Plasma turnover and tissue uptake of [3H]FA-labeled TG on VLDL or Intralipid, injected with [14C]palmitate-BSA, were measured. The FCR of VLDL-TG was comparable to that of TG-labeled Intralipid particles (0.3527 ± 0.07 vs. 0.3734 ± 0.08 pools/min; Fig. 2A). However, more TG label from Intralipid than from VLDL was accumulated by the heart (Fig. 2, B and C). The ratio of labeled TG from Intralipid to FFA incorporated into the heart...
was up to $7.2 \pm 1.5$, whereas the ratio of VLDL-derived FA to palmitate was $1.9 \pm 0.2$ ($P = 0.001$; Fig. 3). Although the ratio of emulsion TG to FA uptake was always greater in the heart than in other organs, the sonication method to prepare the emulsion appeared to impact on this (the ratio varied from 3.3 to $>7$). This increased ratio of Intralipid TG to FFA delivery to the heart was also found using lower-emulsion TG concentrations, from 0.04 to 1 mg (data not shown). Thus differences in size or composition allow greater cardiac metabolism of Intralipid. We used Intralipid to further study the role of LPL in this process.

Because the labeled FA in the Intralipid TG was oleate whereas the FA-albumin studies used palmitate, we compared tissue uptake of albumin-associated oleate and palmitate. Despite a divergence between oleate and palmitate FCR ($0.595 \pm 0.04$ vs. $0.418 \pm 0.07$, $P < 0.001$) and heart uptake (Fig. 4, A and B), this difference was not large enough to account for greater uptake of Intralipid TG over FA by the heart. However, it does appear that hearts have a slightly greater uptake of oleate.

Although LPL hydrolyzes TG, CE is not a substrate for this enzyme. To determine whether Intralipid TG uptake was associated with uptake of nonhydrolyzed core lipids, double-labeled Intralipid with $[^3H]$CE and $[^14C]$TG was used. The ratio of heart uptake for the two labels was $1.6 \pm 0.26$ (Fig. 5); this suggests the uptakes of hydrolyzable (TG) and nonhydrolyzable (CE) core lipid were similar. In contrast, adipose tissue internalized relatively more TG than CE (ratio of $0.68 \pm 0.1$).

Fig. 7. Effects of acute heparin and tetrahydrolipstatin (THL) treatment on free fatty acid (FFA) clearance and tissue uptake. A: plasma clearance of $[^3H]$palmitate in control (□) and heparin (■)-treated mice. Data represent the percentage of radioactivity at 30 s after injection. B: heart and liver uptake of labeled FFA in control (open bar) and heparinized (filled bar) mice. C: plasma clearance of $[^3H]$palmitate in control (□) and THL-treated (■) mice. Data represent the percentage of radioactivity at 30 s after injection. D: heart and liver uptake of labeled FFA in control (open bar) and THL-treated mice (filled bar). Data represent percentage of control counts per gram tissue.

Fig. 8. Plasma TG following THL treatment. Plasma TG was measured at the indicated time points after injection of 2.5 mM THL (■) or PBS (□) in fasting male mice, 4 mice per group. Data are represented as means $\pm$ SD.
Intralipid turnover in heparin- and THL-treated mice. To assess the effects of altered LPL localization on FA delivery to the heart, we studied TG and FA uptake in heparinized C57BL/6 mice. Plasma LPL activity was measured, and levels were comparable to those found in mice given 10 U of heparin intravenously (data not shown). Plasma clearance of $^{14}$CFA-labeled TG in Intralipid was significantly faster in heparin-treated mice compared with controls (FCR $0.525 \pm 0.05$ vs. $0.2317 \pm 0.02$, $P < 0.0001$; Fig. 6A). $^3$HCE clearance was not significantly altered (Fig. 6B). Heart uptake of labeled TG and core lipid decreased by 67 and 72%, respectively ($P < 0.01$, $P < 0.001$; Fig. 6C). Uptake of labeled TG and CE by the liver was increased. Heparin treatment did not alter the plasma clearance or heart uptake of $^3$Hpalmitate-labeled FA (Fig. 7, A and B). These data suggest that LPL binding on the surface of coronary endothelial

Fig. 9. Metabolism of $^{14}$CTG- and $^3$HCE-labeled Intralipid emulsion in THL-treated mice. Fasting mice were injected (iv) with 100 $\mu$L of 2.5 mM THL-DMSO in PBS. Ten minutes after injection, 500,000 cpm of $^{14}$CTG-labeled TG and $1 \times 10^6$ cpm $^3$HCE-labeled Intralipid emulsion were injected (iv) in both THL-treated (□) and control (▲) groups ($n = 5$ for each group). A: plasma decay of labeled TG was measured in plasma at the indicated time points. Data represent the percentage of control counts at 30 s after injection and are expressed as means ± SD. B: CE plasma decay. C: labeled TG and CE emulsion in heart and liver. Data are presented as percentage of control counts per gram tissue. ***$P < 0.001$. Open bar, control mice; filled bar, THL-treated mice.

Fig. 10. Uptake of Intralipid-TG in mice expressing lipoprotein lipase (LPL) exclusively in the liver (A1L0); in these mice an apo-protein (apo)AI promoter drives an LPL minigene on the LPL-null background. A: uptake of $^3$HTG-labeled Intralipid emulsion and $^{14}$Cpalmitate into heart tissue after iv injection into 3 control (WT), filled bar, and 2 A1L0 mice (open bar). B: skeletal muscle uptake of $^3$HTG-labeled Intralipid and $^{14}$Cpalmitate. Data are percentage of control counts per gram tissue.
cells is required not only for uptake of TG but also for uptake of nonhydrolyzable core lipids such as CE.

To clarify the role of LPL activity on the delivery of Intralipid TG-derived FA to the heart, mice were acutely treated with THL (Fig. 8). An increase in plasma TG levels is an indicator of THL inhibition of LPL activity as seen in Fig. 8. Plasma clearance of TG (FCR 0.113 ± 0.02)-labeled and CE (FCR 0.088 ± 0.03)-labeled Intralipid was significantly decreased in THL-treated mice (Fig. 9, A and B) compared with controls (TG FCR, 0.352 ± 0.07; CE FCR, 0.20 ± 0.03, \( P < 0.01 \)). Cardiac uptake of TG and CE labels (Fig. 9C) was decreased by 81 and 87%, respectively, compared with controls (\( P < 0.001 \)). THL treatment did not alter uptake or plasma clearance of \(^{3}H\)palmitate by the heart (Fig. 7, C and D). This suggested that LPL activity, rather than its bridging function, is most important for delivery of TG-derived FA to the heart from Intralipid.

**TG uptake into LPL-deficient hearts.** TG uptake into hearts of mice with a genetic deletion of LPL, i.e., A1L0, was studied. As was found in wild-type mice with inhibition or dissociation of LPL, there was an 88% reduction in particle TG uptake by these hearts (Fig. 10A). In addition, skeletal muscle uptake was decreased by 70% (Fig. 10B), whereas liver and adipose tissue uptake was increased by 10 and 14%, respectively (data not shown).

**DISCUSSION**

There are several mechanisms for FA uptake by cardiac muscle. One option is that LPL is central to this process. LPL is the rate-limiting enzyme for the hydrolysis of TG-rich lipoproteins and also mediates binding of lipoproteins to cell surfaces and receptors (32). Another option is that the FA uptake is primarily via internalization of albumin-bound FA. Cardiac lipid metabolism has been studied in perfused hearts; the results of those experiments are in some ways conflicting (12, 24, 34). Although a large amount of lipolysis of TG-containing lipoproteins occurs while lipoproteins are recirculated through these hearts, it has been suggested that the major source of cardiac FA is via uptake of FFA (33). Our studies were designed to illustrate in vivo the mechanism of FA uptake by heart. Our data show the following. 1) Heart uptake of FA complexed to albumin is not dissimilar to that of other organs on a per gram basis. 2) In contrast, uptake of lipid emulsion-derived FA is greater in heart than in any other organ of the body. 3) VLDL-TG is not as avidly accumulated by cardiac muscle as Intralipid. 4) TG uptake is highly dependent on localized and active LPL. 5) To our surprise, nonhydrolyzable core lipid uptake (CE) also required active LPL.

Our studies showed FA uptake by the heart, measured as labeled palmitate complexed to albumin, was comparable to that of other tissues on a per gram basis. Although plasma clearance of labeled FA was rapid (Fig. 1A), 4 min after injection, uptake, as a percentage of injected dose (per gram tissue) by the heart and liver (Fig. 1B) and lung and kidney (data not shown), were similar. Thus tissue distribution of labeled FA did not reflect the notion that palmitate bound to albumin is more avidly accumulated by cardiac muscle. When olate-albumin complexes were studied in a similar manner, heart, but not liver, had a small preference for this label. Because the heart has extraordinary energy needs, another source of FA is likely utilized. Intralipid emulsion droplets are similar in size and lipid composition to chylomicrons (17, 22) and have been used by others as a model for postprandial lipoproteins (16, 22, 28, 29). Moreover, these emulsions are routinely used as therapeutic intravenous nutrition in patients who are unable to ingest and absorb nutrients through the gastrointestinal tract. When TG-labeled emulsion and \(^{14}C\)palmitate complexed to BSA were injected together, the ratio of lipid emulsion-derived FA to albumin-bound FA delivered to the heart was increased. Therefore, the heart clears a larger amount of FA derived from TG-rich lipoproteins than other organs. Other studies utilizing isolated working hearts to assess FFA metabolism have come to a dif-
different conclusion. These studies used a recirculating perfusate containing chylomicron-TG concentrations of ~35 mg/dl (17, 24) which are well below what the heart sees postprandially. In this in vitro system, the hearts utilized more FFA than TG-derived FA. Hydrolysis of lipoproteins generates three FA for each TG molecule delivered to the heart. Plasma TG concentrations are almost an order of magnitude greater than plasma FA (~1–2 vs. 0.2 mM for FA) (34). Therefore, if only a fraction (10%) of this TG is lipolyzed during a passage through the heart capillary beds, it would supply an equivalent amount of FA.

Surprisingly, heart uptake of VLTDerived FA was less than that of Intralipid-TG. VLTL are the major carriers of plasma TG in the fasting state. These particles are smaller than chylomicrons and are a less-optimal substrate for LPL-mediated TG lipolysis (35). Chylomicrons are reported to have a greater affinity for LPL (35), because they are larger and more likely to contact capillary walls where LPL resides (10) and because they enter the circulation via the thoracic duct, where they encounter the heart first before other major organs. LPL activity is regulated by nutritional status. Heart LPL activity is greater during the fasting state (8, 30); thus this increase in LPL activity may compensate for the less-efficient hydrolysis of VLTL by the fasting heart.

Double-labeled Intralipid was employed to compare uptake of nonhydrolyzable core lipid [3H]CE and [14C]TG. The uptake of CE was greater than that of TG by a ratio of 1.6 ± 0.26 (injected dose ratio = 1). This could have resulted from internalization of whole Intralipid particles. Alternatively, we postulate that lipolysis produces emulsion fragments containing both surface and core lipids that are internalized by the heart. This would be analogous to surface remnant containing apoproteins and lipids that transfer from TG-rich lipoproteins to HDL during intravascular lipolysis (13).

The importance of cardiac LPL for regulation of plasma lipoproteins is unclear, since lipolysis occurs in multiple sites including skeletal muscle and adipose tissue. Mice that were genetically engineered to express LPL solely in the heart have normal plasma TG and HDL levels (19); this suggests that heart LPL plays a significant role in TG catabolism. Our data suggest that much of this catabolism involves local LPL-mediated uptake of TG by the heart. In heparinized mice, LPL is released from its binding sites on capillary endothelium but is still able to hydrolyze TG within the circulation. After heparin treatment, plasma clearance of emulsion TG was faster. Approximately 80% of the injected dose was removed by 4 min. Conversely, heparin treatment significantly decreased heart uptake of emulsion TG. This confirmed that LPL localization on endothelial cell surfaces is necessary for heart-specific delivery of emulsion TG.

FA delivery was also assessed in mice treated with the lipase inhibitor THL. THL, a reversible inhibitor of LPL activity that does not interfere with LPL-heparin binding or bridging ability (20), allowed us to determine how important LPL hydrolysis is for FA delivery to the heart. THL treatment significantly inhibited plasma clearance of TG. Hultin et al. (16) reported that a large fraction of emulsion particles is removed from plasma with little lipolysis; thus it was possible that inhibition of lipolysis but retention of LPL “bridging function” would allow continued uptake of these particles (10, 17, 28). Moreover, nonenzymatically active LPL has been shown to increase TG hydrolysis and whole lipoprotein particle uptake (25, 26). However, our data show that localized LPL protein without activity was unable to effectively deliver emulsion TG and other core lipids to the heart. This suggests that some hydrolysis is necessary for the removal of core lipid from emulsion particles. A recent study also showed that lipid uptake by muscle expressing inactive LPL was greatest when some active LPL was also present (25).

In summary, FA derived from the hydrolysis of TG-rich lipoproteins may be the primary source of FA utilized by the heart, particularly in the fed state. The delivery of TG-derived FA from emulsion particles requires localized active LPL; active LPL is also required for uptake of nonhydrolyzable core lipid. Although in our study CE was used as a marker, it is likely that other core lipids such as retinyl esters are internalized in a similar manner (31). Even though further studies are necessary to elucidate the details of TG-rich particle uptake by the heart, we propose the following mechanism for uptake of emulsion core lipid by the heart (Fig. 11). Upon entry into the plasma, lipid particles bind to endothelial cell heparan sulfate proteoglycan-associated LPL. LPL then hydrolyzes the TG core, creating smaller particles. Some of these particles are similar to remnant lipoproteins that transverse the endothelial barrier (23) and are internalized via lipoprotein receptors. Other smaller lipid fragments are also likely to come in contact with myocytes. Their internalization might involve scavenger receptors or nonreceptor pathways. Regardless, a major source of cardiac FA is likely to be LPL-mediated uptake of TG-derived FA.

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