Organ-specific dietary fatty acid uptake in humans using positron emission tomography coupled to computed tomography

Sébastien M. Labbé,1 Thomas Grenier-Larouche,1 Etienne Croteau,2 François Normand-Lauzière,1 Frédérique Frisch,1 René Ouellet,2 Brigitte Guérin,2 Eric E. Turcotte,2 and André C. Carpentier1
1Department of Medicine, Division of Endocrinology, and 2Department of Nuclear Medicine and Radiobiology, Université de Sherbrooke, Sherbrooke, Quebec, Canada

Submitted 7 October 2010; accepted in final form 18 November 2010

Labbé SM, Grenier-Larouche T, Croteau E, Normand-Lauzière F, Frisch F, Ouellet R, Guérin B, Turcotte EE, Carpentier AC. Organ-specific dietary fatty acid uptake in humans using positron emission tomography coupled to computed tomography. Am J Physiol Endocrinol Metab 300: E445–E453, 2011. First published November 23, 2010; doi:10.1152/ajpendo.00579.2010.—A noninvasive method to determine postprandial fatty acid tissue partition may elucidate the link between excess dietary fat and type 2 diabetes. We hypothesized that the positron-emitting fatty acid analog 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid ([18FTHA]) administered orally during a meal would be incorporated into chylomicron triglycerides, allowing determination of interorgan dietary fatty acid uptake. We administered [18FTHA] orally at the beginning of a standard liquid meal ingested in nine healthy men. There was no significant [18FTHA] uptake in the portal vein and the liver during the 1st hour. Whole body PET/CT acquisition revealed early appearance of [18FTHA] in the distal thoracic duct, reaching a peak at time 240 min. [18FTHA] mean standard uptake value increased progressively in the liver, heart, quadriceps, and subcutaneous and visceral adipose tissues between time 60 and 240 min. Most circulating [18F] activity between time 0 and 360 min was recovered into chylomicron triglycerides. Using Triton WR-1339 treatment in rats that received [18FTHA] by gavage, we confirmed that >90% of this tracer reached the circulation as triglycerides. This novel noninvasive method to determine tissue dietary fatty acid distribution in humans should prove useful in the study of the mechanisms leading to lipotoxicity. Food metabolism

FATTY ACID OVEREXPOSURE IS TOXIC to lean tissues and is likely implicated in the development of several chronic pathophysiological states, including insulin resistance and type 2 diabetes (8). The current view is that accumulation of fatty acid metabolites such as long-chain acyl-CoA, phosphatidic acid, diacylglycerols, ceramides, and/or mitochondrial fatty acid overload from an imbalance between increased lean tissue fatty acid uptake and/or synthesis and reduced catabolism may lead to lipotoxicity and type 2 diabetes (9, 18, 24, 34). Thus, quantification of all sources of tissue fatty acid overexposure, including that coming directly from dietary intake, would be essential to understand the causes of lipotoxic tissue injury in pathological conditions. Methods using stable isotopic or radioactive fatty acid tracers have been used for noninvasive quantification of dietary fatty acid absorption and whole body oxidation (28, 30, 35) or even organ-specific nonoxidative disposal of dietary fatty acids in combination with magnetic resonance spectroscopy (29). To date, however, no method is available for noninvasive quantification of tissue partition and net uptake of dietary fatty acids in humans.

We have recently used the positron-emitting long-chain fatty acid analog 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid ([18FTHA]) administered by gavage to demonstrate increased myocardial dietary fatty acid uptake in diabetic rats using tissue extracts (23). Here we describe a novel method designed to quantify dietary fatty acid tissue uptake and partition in healthy humans using [18FTHA] administered orally with sequential positron emission tomography coupled to computed tomography (PET/CT) scanning. We hypothesized that [18FTHA] administered orally during a meal would be incorporated into chylomicron triglycerides (TG) and, from there, be delivered to the different organs, allowing determination of interorgan dietary fatty acid uptake and partition using PET/CT imaging. We opted for [18FTHA] because its total tissue uptake is quantitatively similar to that of palmitate, a long-chain fatty acid clearly involved in lipotoxic processes leading to insulin resistance and type 2 diabetes.

METHODS

Ethical approval. Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki, and the protocol received approval from the Human Ethics Committee of the Centre Hospitalier Universitaire de Sherbrooke. All animal protocols were approved by the Animal Ethics Committee of the Faculty of Medicine at the University of Sherbrooke in accordance with the guidelines of the Canadian Council on Animal Care.

Human subjects and animals. Nine healthy men between ages 18 and 60 without first-degree family history of type 2 diabetes and with normal glucose tolerance based on a 75-g oral glucose tolerance test participated in this metabolic study. None of the participants had a current medical condition or were taking drugs known to affect lipid levels or insulin sensitivity. Fourteen male Wistar rats (Charles River Laboratories) weighing 400–450 g and acclimatized to a 12:12-h day-light cycle at a constant temperature (22°C) for 7 days were used for the animal experiments.

Human experimental protocols. The subjects were instructed to follow an isocaloric diet (0% alcohol, 15% protein, 30% fat, and 55% carbohydrates) 48 h before the experimental protocol. On arrival, body weight, height, and waist circumference were measured, and lean body mass was determined by electrical bioimpedance (Hydra ECF/ICF; Xitron Technologies, San Diego, CA). An intravenous catheter was placed in one forearm for infusions, and another was placed in a retrograde fashion in the contralateral arm maintained in a heating pad (∼55°C) for blood sampling.

The metabolic protocol is depicted in Fig. 1A. Oral intake of a standard liquid meal consisted of a drink prepared by sonication of soybean oil (54 g/l), safflower oil (54 g/l), dried non-fat milk (263 g/l), egg phospholipids (0.18 g/l), and water with the addition of chocolate syrup (202 g/l) and sugar (15 g/l) to provide 2,465 kcal/l, 39% as fat, 16% as proteins, and 45% as carbohydrates (27). Its fatty acid composition is similar to that of a typical liquid dinner meal. All participants were seated in a retrograde fashion in the contralateral arm maintained in a heating pad to ensure that the temperature of the arm was close to that of the other arm. The metabolic protocol is depicted in Fig. 1A.
composition was similar to the composition of Intralipid, an intravenous fat emulsion that we have used in previous studies (4, 6). The oral intake of the drink corresponded to 80 ml every 5 min over 20 min for a total of 1,680 kcal.

Each participant underwent a PET/CT protocol that consisted of a 6-h postprandial procedure. Each subject was positioned supine in a 16-slice PET/CT scanner (Philips Gemini GXL; Philips, Eindhoven, The Netherlands) using a row action maximum likelihood tomography (PET) acquisitions, respectively, during the postprandial protocol. B: Post-oral gavage protocol in Wistar rats. 18FTHA, 14C(2S)-[18F]fluoro-6-thia-heptadecanoic acid.

Table 1. Characteristics of human subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (n = 9)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>29.0 ± 3.3</td>
<td>21.0–53.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8 ± 1.5</td>
<td>18.8–33.1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.2 ± 4.2</td>
<td>59.2–99.1</td>
</tr>
<tr>
<td>Lean weight, kg</td>
<td>61.9 ± 3.4</td>
<td>45.4–76.5</td>
</tr>
<tr>
<td>Nonlean weight, kg</td>
<td>16.4 ± 1.9</td>
<td>7.7–24.2</td>
</tr>
<tr>
<td>%Fat</td>
<td>20.8 ± 2.0</td>
<td>9.2–26.6</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.9 ± 0.3</td>
<td>4.0–6.8</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>76 ± 14</td>
<td>33–147</td>
</tr>
<tr>
<td>NEFA, µmol/l</td>
<td>331 ± 36</td>
<td>202–427</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1.0 ± 0.26</td>
<td>0.25–2.09</td>
</tr>
</tbody>
</table>

Data are means ± SE. BMI, body mass index; NEFA, nonesterified fatty acids; TG, triglycerides.
70% CAN-MeOH to remove the remaining TGs, which were collected in the same tube. The column was then eluted with 10 ml of 5%
formic acid-70% CAN-MeOH to collect nonesterified fatty acids
(NEFA) into another tube. TG and NEFA samples were transferred
into a counting/tube to measure 18F activity. Using this method, we
recovered 95% of [3H]triolein and [14C]palmitate internal standards
mixed into control plasma in the TG and NEFA phases, respectively.

For animal studies, plasma metabolite samples were precipitated
with methanol and centrifuged, and the supernatant fraction that
contained circulating lipids was separated onto thin-layer chromatog-
raphy C-18 reverse-phase plates (RP-18 F-254; Merck, Darmstadt,
Germany) to determine the fraction of 18FTHA in circulating NEFA,
TG, and phospholipids. The plates were eluted in a methanol-water-
acetic acid (85:15:0.4) solution and read using Instant Imager (Ver-
sion 1.27; Packard Instruments). Then, plates were stained with
dichlorofluorocein (1 mg/ml ethanol) and revealed with UV detection.

Table 2. Characteristics of animals

<table>
<thead>
<tr>
<th>Group</th>
<th>SAL (n = 7)</th>
<th>TRI (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, g</td>
<td>420 ± 10</td>
<td>417 ± 17</td>
<td>0.88</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>6.5 ± 0.7</td>
<td>7.4 ± 0.3</td>
<td>0.31</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>112 ± 15</td>
<td>181 ± 37</td>
<td>0.18</td>
</tr>
<tr>
<td>NEFA, μmol/l</td>
<td>564 ± 70</td>
<td>736 ± 130</td>
<td>0.06</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>0.42 ± 0.12</td>
<td>0.74 ± 0.13</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are means ± SE. SAL, saline group; TRI, Triton WR-1339 group. P values are from unpaired Student’s t-test.

RESULTS

Characteristics of human subjects and animals. The characteristics of the human participants and animals, including
fasting plasma metabolite and hormone concentrations, are shown in Tables 1 and 2, respectively. In animals, there was no
difference in these parameters between the SAL and TRI
groups. During the postprandial procedure in humans, we

Chylomicron separation. Chylomicrons were separated in Quick-
Seal centrifuge tubes (no. 344619; Beckman) from 1 ml of plasma
overlaid with 4.5 ml of distilled water centrifuged for 15 min at
33,000 rpm at 20°C (Optima L-100XP ultracentrifuge with a 100Ti
Beckman rotor). After centrifugation, the chylomicron fraction at the
top of the tube was removed (~800 μl) and transferred into the
counting γ-tube to measure 18F activity.

Other laboratory assays. Glucose, insulin, total NEFA, and TGs
were measured as described previously (6, 23).

Statistical analyses. Data are expressed as means ± SE. An
unpaired Student’s t-test was used to compare characteristics
between SAL and TRI groups. ANOVA for repeated measurements
with time as the independent variable was used to analyze differences
in plasma glucose, insulin, NEFA, and TGs throughout the
protocol. ANOVA for repeated measurements with tissue or organ
as the independent variable was used to analyze differences in
18FTHA tissue or organ biodistribution. A two-tailed P value
<0.05 was considered significant. All analyses were performed
with the SAS software for Windows version 9.1.3 (SAS Institute,
Cary, NC) or GraphPad Prism for Windows version 5.00 (Graph-
Pad, San Diego, CA).

Fig. 2. Postprandial plasma metabolites and insulin in humans. Plasma glucose (A), insulin (B), nonesterified fatty acids (NEFA; C), and triglycerides (TG; D) during the postprandial study in the nine participants. Data are means ± SE.
observed the expected increases in plasma glucose and insulin, with peaks at 60 (Fig. 2A) and 90 min (Fig. 2B), respectively. Plasma NEFA levels (Fig. 2C) decreased rapidly, reaching nadir at time 120 min, with a progressive increase thereafter up to the end of the postprandial protocol at 360 min. Total plasma TGs increased progressively, reaching a peak at time 330 min of the postprandial procedure (Fig. 2D).

Determination of absorption route of orally administered \(^{18}\text{FTHA}\) in humans. To ascertain that uptake into the circulation of orally administered \(^{18}\text{FTHA}\) does not occur through

Fig. 3. Determination of absorption route of orally administered \(^{18}\text{FTHA}\) in humans. A: Gemini GXL CT whole body acquisition. This image was performed for anatomic resolution of functional images and for determination of organ position. B: image integration of PET dynamic acquisition of the portal vein region. This scanning shows no early portal and significant liver \(^{18}\text{FTHA}\) uptake up to 60 min after meal consumption. C: PET dynamic acquisition of the thoracic duct. This scanning shows early and gradual apparition of \(^{18}\text{FTHA}\) in the thoracic duct reflecting tracer incorporation into chylomicrons for delivery into the circulation in the subclavicular vein.

Fig. 4. Distribution of orally administered \(^{18}\text{FTHA}\) into circulating lipids and chylomicrons in humans. A: \(^{18}\text{F}\) activity in plasma (●), chylomicron fraction (○), plasma TG (□), and plasma NEFA (■) after ingestion of \(^{18}\text{FTHA}\) during a meal in the 9 healthy participants. B: comparison between plasma \(^{18}\text{F}\) (● and solid line) and \(^{3}\text{H}\) activity (○ and dashed line) after ingestion of \(^{18}\text{FTHA}\) and \(^{3}\text{H}\)triolein with a meal in 5 healthy participants showing no significant difference between postprandial plasma excursion of the tracers. Data are means ± SE and are expressed as percent ingested dose (%ID)/100 ml plasma.
direct uptake into the portal circulation and is transported to the circulation through the thoracic duct, we performed dynamic acquisition of the liver and portal vein between time 30 and 60 min and of the thorax with the distal thoracic duct between time 90 and 120 min after meal ingestion. There was no detectable $^{18}$FTHA activity in the portal vein or significant liver accumulation of the tracer $\leq 60$ min after meal intake despite the presence of a significant amount of the tracer in the duodenum (Fig. 3B). However, we found early appearance of $^{18}$FTHA activity in the distal thoracic duct and joining the subclavicular vein (Fig. 3C) that demonstrates incorporation of this tracer into chylomicrons that reach the systemic circulation.

Plasma $^{18}$FTHA reaches the circulation at rate similar to other long-chain fatty acids. We simultaneously administered [$^{3}$H]triolein into the meal to compare its postprandial plasma excursion with that of $^{18}$FTHA. As shown in Fig. 4B, $^{18}$FTHA plasma activity was similar to that of [$^{3}$H]triolein. To confirm that $^{18}$FTHA were incorporated into chylomicron TG, we isolated chylomicrons hourly after the test meal and separated TGs and NEFAs from plasma. As shown in Fig. 4A, most of the plasma $^{18}$F was recuperated in chylomicrons, and $^{18}$F activity recuperated into circulating TG was almost superimposable to that of $^{18}$F activity in chylomicrons. In one subject, we separated chylomicron lipids by thin-layer chromatography and confirmed that $>95\%$ of $^{18}$F was incorporated into TG.

To further ascertain that $^{18}$FTHA indeed reached circulation as TG, we administered $^{18}$FTHA and [$^{3}$H]triolein by gastric gavage in Wistar rats. Prior to gastric gavage, we administered an intravenous injection of Triton WR-1339 (TRI group) to inhibit intravascular lipoprotein lipolysis (7) or saline (SAL group) as control. As shown in Fig. 5, A and B, TRI animals displayed significant and similar increases of $^{18}$F and $^{3}$H in plasma and significant increases in plasma TG levels (Fig. 5C). At time 120 min after gavage, 92% of plasma $^{18}$F was recuperated in TG in the TRI group compared with 17% in SAL animals, suggesting that almost all $^{18}$FTHA administered orally initially reached the circulation as TG in rats (Fig. 5D).

Uptake and partition of orally administered $^{18}$FTHA in tissues after meal ingestion. To demonstrate uptake and partition of $^{18}$FTHA in organs and tissues, we performed whole body PET/CT scanning every hour after meal ingestion. As shown in Fig. 6A, we observed progressive uptake of $^{18}$FTHA in the thoracic duct (shown by arrows). Figure 6, B and C, shows mean SUV of ROI over time. $^{18}$F mean SUV increased progressively in the distal thoracic duct, liver, heart, quadriceps femoris, and thigh subcutaneous adipose tissue up to time 240
and up to time 180 min in visceral adipose tissues (right perirenal fat). The mean slope of $^{18}$F SUV increase was 0.67 ± 0.07, 0.31 ± 0.04, 0.06 ± 0.01, 0.03 ± 0.01, and 0.17 ± 0.04 mean SUV/h in the liver, heart, quadriceps femoris, thigh subcutaneous, and perirenal adipose tissues, respectively ($P < 0.05$ for difference between all organs except between quadriceps femoris and thigh subcutaneous adipose tissue). Figure 7 shows relative orally administered $^{18}$FTHA uptake as assessed by area under the mean SUV curve over 6 h in the liver, heart, quadriceps femoris, thigh subcutaneous, and right perirenal adipose tissue (13.37 ± 0.37, 6.24 ± 0.36, 0.98 ± 0.19, 0.61 ± 0.05, and 3.73 ± 0.59, respectively; $P < 0.05$ between all organs and tissues).

DISCUSSION

Many investigators have used stable or long-life radioactive isotopic tracer methods to determine chylomicron metabolism in circulation and dietary fatty acid absorption, partition into circulating lipoproteins, uptake into subcutaneous adipose tissues and skeletal muscle, and whole body oxidation (1–3, 16, 28, 30, 35). $^{13}$C-labeled fatty acids administered orally have also been used to detect postprandial uptake of dietary fatty acids in skeletal muscle and liver in humans by magnetic resonance spectroscopy (29). However, the latter method can only determine tracer accumulation into nonoxidative metabolic pathways and does not have the sensitivity to determine
dietary fatty acid tracer uptake in most internal organs, such as, for example, the heart. To our knowledge, this is the first study to report a method that can quantify dietary fatty acid absorption and assembly into chylomicron, their delivery into the thoracic duct, and their simultaneous distribution and uptake into all tissues and organs in humans. Although it has been possible in some instances to use an arteriovenous gradient even across the heart or liver circulation or visceral adipose tissue biopsies during abdominal surgery to determine circulating TG and/or NEFA metabolism in these internal organs in humans (16, 21, 25, 26), these studies are very invasive and difficult to perform, making assessment of organ-specific metabolism of dietary fatty acids impossible in most situations. In addition, it has previously been impossible to simultaneously measure partition of dietary fatty acids in all internal organs in humans, a major advantage of the novel method described herein. Others have previously used 123I-heptadecanoic acid administered orally to perform imaging of the thoracic duct with planar scintigraphy, but without CT anatomic and spatial resolution of the cisternae their method was poor, and tissue uptake was confounded by a high rate of free 123I recirculation and uptake (14).

18FTHA administered intravenously was shown to be an excellent noninvasive method to quantify organ-specific NEFA uptake in the heart, skeletal muscles, liver, and adipose tissues (10–12, 15, 19, 23, 33). The thiol residue at position 6 leads to excellent noninvasive method to quantify organ-specific NEFA uptake in the heart, skeletal muscles, liver, and adipose tissues (10–12, 15, 19, 23, 33). The thiol residue at position 6 leads to trapping into mitochondria due to blockade of its β-oxidation after the first two iterations of 18F positioned downstream of the carbon chain. This property of the tracer allows quantification of tissue 18FTHA uptake by linearization methods, such as the Patlak method, for the determination of tissue uptake of plasma NEFA (19, 23, 33). In the context of oral administration, the very slow oxidative degradation of 18FTHA also allows detection of progressive tissue accumulation of the tracer delivered by chylomicrons, a process that is too slow to accurately detect with other PET fatty acid tracers such as [14C]palmitate. NEFA fractional tissue uptake determined with 18FTHA was shown to be similar to that reported for [14C]palmitate (17, 33). We found that total 18FTHA uptake in tissue lipids is similar to that of [3H]palmitate and that 18FTHA mitochondrial uptake is similar to that of [14C]bromopalmitate (10). These studies thus suggest that 18FTHA initial transport into cells and mitochondria is similar to that of endogenous long-chain fatty acids. We and others, however, have found relatively less 18FTHA esterification into tissue TG associated with reciprocal increase into tissue diacylglycerols and/or phospholipids (10, 32). Thus, 18FTHA tissue nonoxidative metabolism is qualitatively but not quantitatively different from endogenous fatty acids. One caveat, however, is that tissue 18FTHA accumulation may be less sensitive to differences in the final esterification step of diacylglycerol molecules into TG. However, it is interesting to note that almost all of the incorporation of 18FTHA into chylomicrons in humans as well as in rats in the present work occurred into TGs. Whether this may limit inference with regard to oral 18FTHA uptake in tissues such as adipose tissue that display relatively high fatty acid esterification into TG will need more investigation. All this evidence suggests that 18FTHA administered orally is a reasonably good tracer of net dietary fatty acid tissue uptake but cannot distinguish dietary fatty acid oxidation and nonoxidative metabolism.

The bulk of dietary long-chain fatty acids absorbed by the intestine undergo esterification and assembly into chylomicrons in enterocytes (20). Chylomicrons are then secreted and transported in the splanchnic lymphatic circulation to the thoracic duct and reach the circulation in the left subclavicular vein. Although short- and medium-chain fatty acids may be absorbed and transported directly into the portal circulation for efficient oxidative metabolism in the liver (31, 36, 37), this process is probably very limited for long-chain fatty acids, except perhaps in conditions associated with portal hypertension (5). The present study clearly demonstrates very poor direct absorption of 18FTHA into the portal circulation and preferential uptake and secretion into chylomicrons. Despite the relative inefficient 18FTHA esterification into tissue TG (10, 32), we found remarkably similar rates of incorporation of orally administered 18FTHA and [3H]triolein into plasma and chylomicron TG. Our findings in rats using Triton WR-1339 also strongly support preferential delivery of orally administered 18FTHA as TG in the circulation.

Whole body PET/CT determination of orally administered 18FTHA tissue uptake demonstrated that the highest uptake of dietary fatty acids per gram of tissue occurs in the liver in humans. This finding is consistent with the known preferential liver uptake of intravenously administered fatty acid tracers in animals (10). It is also consistent with the higher NEFA spillover rate from circulating TG in the splanchnic vs. systemic circulation in humans (25) and with hepatic uptake of chylomicron remnants (13). The relatively high cardiac dietary fatty acid uptake that we observed is also consistent with significant myocardial uptake of circulating TG in humans (26). The relatively high visceral adipose tissue (as assessed by uptake into right perirenal adipose tissue depot) vs. subcutaneous adipose tissue dietary fatty acid uptake that we observed...
was also expected on the basis of previous studies using radioactive tracers prior to adipose tissue biopsies during abdominal surgery in humans (16).

Our novel method has some limitations. First, as mentioned above, this method cannot make the distinction between oxidative vs. nonoxidative tissue dietary fatty acid metabolism. Second, it assumes that local tissue hydrolysis of \(^{18}\)FTHA esterified into chylomicron TG occurs at rate similar to long-chain dietary fatty acids. Third, although tissue \(^{18}\)FTHA clearance is very slow and probably negligible in most tissues over a few hours time frame (10), \(^{18}\)FTHA likely redistributes into VLDL-TG for secretion, thus leading to underestimation of liver uptake from tracer accumulation in that tissue over time. Likewise, it is possible that some of the \(^{18}\)FTHA uptake early in the postprandial period in adipose tissues may be released later into circulation, as suggested by the small reduction in \(^{18}\)F adipose tissue activity observed after 3–4 h (see Fig. 5).

Fourth, high gastrointestinal \(^{18}\)F activity prevents accurate measurement of dietary fatty acid uptake in most visceral adipose tissue depots because of spillover of radioactivity. Fifth, thoracic duct SUV was likely underestimated due to partial volume effect since its expected diameter is at the limit of resolution of the PET scanner. However, this actually supports our conclusion that \(^{18}\)FTHA incorporates first into chylomicrons and gets access to other organs through the thoracic duct because thoracic duct SUV was higher than in other organs despite this underestimation. Finally, to limit radioactivity exposure, we had to reduce whole body CT intensity that resulted in inadequate image qualities for accurate integration of the volume of most tissues. However, accurate measurement of organ volumes will be possible in future studies using magnetic resonance imaging or higher intensity CT scanning targeted at a specific organ of interest.

Because of the qualitative differences in \(^{18}\)FTHA esterification into TGs, it is possible that \(^{18}\)FTHA oral administration may underestimate tissue dietary lipid uptake from tracer recirculation into VLDL-TG late in the postprandial state. In the \(n = 1\) human study, we have isolated VLDLs and nevertheless found increased tracer uptake into the total VLDL fraction 5 and 6 h after \(^{18}\)FTHA oral administration. This investigation was very difficult to perform and limited because of the low radioactivity signal left after the time required for the VLDL isolation procedure (in addition to time delay in vivo). Furthermore, we have documented \(^{18}\)FTHA incorporation into VLDL-TG using plasma lipid separation by thin-layer chromatography after intravenous injection of \(^{18}\)FTHA in both humans and animals (see, for example, Ref. 10). We invariably find progressive increases of \(^{18}\)P signal into plasma TG 10–15 min after \(^{18}\)FTHA intravenous injection. Therefore, there is evidence that \(^{18}\)FTHA can recirculate into VLDL-TG, but whether tissue uptake of \(^{18}\)FTHA from VLDL is similar to that of endogenous fatty acids remains to be determined.

In conclusion, our findings suggest that orally administered \(^{18}\)FTHA with PET/CT scanning is a good tracer for noninvasive determination of dietary fatty acid absorption, secretion into chylomicrons, and organ-specific uptake in humans. This novel method will be invaluable for the investigation of conditions associated with disordered dietary fatty acid organ partition and metabolism.

**GRANTS**

This work was supported by a grant from the Canadian Institutes of Health Research (MOP 53094, A. C. Carpentier) and was performed at the Centre de Recherche Clinique Etienne-Le Bel, a research center funded by the Fonds de la Recherche en Santé du Québec (FRSQ). A. C. Carpentier is currently the recipient of a FRSQ Senior Scholarship Award. S. M. Labbé is the recipient of a Canadian Diabetes Association Doctoral Studentship Award.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**REFERENCES**


19. Maki MT, Haaparanta M, Nuuttila P, Oikonen V, Luotolahti M, 
Eskola O, Knutti JM. Free fatty acid uptake in the myocardium and 
skeletal muscle using fluorine-18-fluoro-6-thia-heptadecanoic acid. J Nucl 
21. Mårin P, Lönn L, Andersson B, Odén B, Olbe L, Bengtsson BA, 
Björntorp P. Assimilation of triglycerides in subcutaneous and intraab-
22. Menard SL, Ci X, Frisch F, Normand-Lauzière F, Cadorette J, 
Ouellet R, van Lier JE, Benard F, Bentourkia M, Lecomte R, Car-
pentier AC. Mechanism of reduced myocardial glucose utilization during 
van Lier JE, Des Rosiers C, Lecomte R, Carpentier AC. Abnormal in vivo myocardial energy substrate uptake in diet-induced 
24. Muoio DM. Intramuscular triacylglycerol and insulin resistance: guilty as 
spillover of extracellular lipase-generated fatty acids in overweight and 
circulating triglycerides in nondiabetic patients with heart disease. Diabe-
Cunnane SC, Carpentier AC. Increased postprandial nonesterified fatty acid appearance and oxidation in type 2 diabetes is not fully established in 
28. Park Y, Grellner WJ, Harris WS, Miles JM. A new method for the 