Parallel activation of de novo lipogenesis and stearoyl-CoA desaturase activity after 3 d of high-carbohydrate feeding\(^1\)–\(^4\)

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**ABSTRACT**

**Background:** High-carbohydrate (HC) diets increase de novo lipogenesis (DNL), but effects on stearoyl-CoA desaturase (SCD) are not so well studied.

**Objective:** The objective was to investigate DNL and SCD in liver and adipose tissue by using fatty acid ratios after short-term dietary intervention.

**Design:** Eight subjects consumed isoenergetic 3-d HC (10% fat; 75% carbohydrates) or higher fat (HF; 40% fat; 45% carbohydrates) diets (sugar to starch ratio: 60:40 for both) in a crossover study. Blood was taken from an artery and a vein draining subcutaneous adipose tissue. DNL and SCD activity were investigated by using the ratios of 16:0 to 18:2\(^\text{n-6}\) and of 16:1\(^\text{n-7}\) to 16:0, respectively. A test meal, including \([\text{U-}^{13}\text{C}]\text{palmitate was given to trace dietary fatty acid incorporation into VLDL-triacylglycerol (TG). The conversion of intravenously infused \([^{2}\text{H}_2]\text{palmitic acid to } [^{2}\text{H}_2]\text{palmitoleic acid in VLDL-TG was quantified as a specific marker of hepatic SCD activity.**

**Results:** The VLDL-TG 16:0/18:2\(^\text{n-6}\) ratio, which reflects hepatic DNL, was greater after the HC diet than after the HF diet (\(P = 0.02\)). With the HC diet, increased plasma TG concentrations correlated with 16:0/18:2\(^\text{n-6}\) ratios (\(r = 0.76, P = 0.028\)). Plasma VLDL-TG and adipose venous nonesterified fatty acid (NEFA) 16:0/18:2\(^\text{n-6}\) ratios were higher after the HC diet (fasting: \(P = 0.01\) and \(P = 0.05\), respectively; postprandial: \(P = 0.03\) and \(P = 0.05\), respectively). Changes in fasting VLDL-TG 16:0/18:2\(^\text{n-6}\) and of 16:1\(^\text{n-7}\) to 16:0 ratios were associated (\(P = 0.06\)). The contribution of total fatty acids from splanchnic sources (including DNL) was higher after the HC diet (\(P = 0.02\)). Expression of lipogenic genes in subcutaneous adipose tissue was not significantly affected by diet.

**Conclusion:** Parallel activation of DNL and SCD was found after a short period of HC feeding. \(\textit{Am J Clin Nutr} \ 2008;87:817–23.\)

**INTRODUCTION**

De novo lipogenesis (DNL) reflects an adaptation of the body to handle high-carbohydrate loads \(1\). It plays a crucial role by converting excess carbohydrate to fatty acids and triacylglycerol (TG), which may contribute to increased fasting \(2\) and postprandial \(3\) plasma TG concentrations.

Many studies have quantified hepatic DNL after high-carbohydrate (HC) feeding \(2, 4, 5\). Positive correlations between hepatic DNL and high fasting plasma TG concentrations after HC feeding give further evidence that DNL contributes to carbohydrate-induced hypertriacylglycerolemia \(2\). Fasting hepatic DNL was previously estimated after \(\geq 5\) d of HC feeding (range: 5–25 diet intervention days), because 5 d is sufficient time for DNL to reach a new equilibrium \(6\).

DNL is reflected by plasma TG, becoming enriched in palmitate \(16:0\), the major fatty acid preferentially formed by mammalian fatty acid synthase, and depleted in linoleic acid \(18:2\) \(n-6\), an essential fatty acid. The desaturation of newly formed fatty acids is often regarded as the last stage of DNL. The enzyme stearoyl-CoA desaturase (SCD) is responsible for the biosynthesis of monounsaturated fatty acids (MUFA) from saturated fatty acids. MUFA are known to be necessary for normal rates of synthesis of TG and cholesterol esters \(7\). In rodent models, HC diets induce hepatic SCD gene expression \(8–10\). However, SCD and its relation to DNL have not been studied extensively in humans.

We aimed to investigate whether parallel regulation of hepatic DNL and SCD activity occurs early in the course of the development of carbohydrate-induced hypertriacylglycerolemia. We used a short-term intervention \(11\) to investigate the metabolic effects of a HC versus a higher-fat (HF) diet and calculated fatty acid ratios in the appropriate lipid fractions to estimate relative changes in DNL and SCD. Using stable-isotope techniques, we measured endogenous fatty acid desaturation during the metabolism of a mixed meal. We also estimated the contributions of different fatty acid sources (endogenous and dietary) to postprandial VLDL-TG separated by immunofinity techniques after the 2 dietary regimens.

In contrast with findings in the liver, clear evidence that adipose tissue is actively involved in carbohydrate-induced DNL and SCD activity is lacking. Aarsland et al \(12\) concluded that adipose tissue is likely to be a major site for DNL after 4 d of

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hyperenergetic carbohydrate feeding. There is also some evidence from gene expression studies (13) that DNL occurs in adipose tissue, but other studies have reported conflicting findings (14, 15). We sought to investigate this by measuring adipose tissue gene expression in abdominal subcutaneous adipose tissue biopsy samples and SCD activity (16:1n−7/16:0 ratio) in blood samples collected specifically from subcutaneous adipose tissue venous drainage.

SUBJECTS AND METHODS

Subjects

Eight healthy subjects (6 men) were recruited to take part in this randomized crossover dietary intervention study, in which subjects consumed either an HC or an HF isoenergetic diet for 3 d before a metabolic investigation (11), as described elsewhere (16). Briefly, the HC diet provided 10% of total energy (TE) as fat, 75% of TE as carbohydrates; the HF diet provided 40% of TE as fat and 45% of TE as carbohydrate. The ratio of sugar to starch was 60:40 for both diets.

A 6-wk washout period took place between diets, during which time the subjects resumed their usual dietary habits. The subjects ranged in age from 26 to 53 y (median: 42 y) and their weight (median: 24.6). The study was approved by the Oxfordshire Clinical Research Ethics Committee, and all subjects gave written informed consent.

The subjects first visited the metabolic unit for a screening visit to check their suitability for the study. A dietitian estimated their habitual energy requirements by taking diet histories and an account of their daily physical activities. A small adipose tissue biopsy sample was collected (17) so that the fatty acid composition of the 3-d diets could be matched with each subject’s adipose tissue fatty acid composition. This ensured that any changes in fatty acid ratios were not due to differential incorporation of fatty acids from the diet and adipose tissue according to the model of Hudgins et al (18). The subjects were then randomly assigned to either first receive the HC or HF diet as previously described.

Experimental procedures

On the day after the 3-d diet, the subjects arrived at the metabolic unit at 0700, having fasted from 2000 the previous evening. The femoral artery and a superficial epigastric vein draining subcutaneous abdominal adipose tissue were cannulated. A continuous intravenous infusion (0.04 μmol · kg⁻¹ · min⁻¹) of [13C₂]palmitic acid (isotope purity 97%; CK Gas Products Ltd, Hook, United Kingdom) complexed to human albumin (Blood Transfusion Service, John Radcliffe Hospital, Oxford, United Kingdom) was commenced. After 60 min of equilibration time, baseline blood samples were collected for 1 h, and then a high-fat, mixed test meal (40 g fat, 40 g carbohydrate) containing 100 mg [13C₂]palmitate was given. The [1,2-13C₂]palmitate represented 2% of the palmitate in the meal and was given in the form of a warm chocolate emulsion drink to ensure a homogeneous preparation. This form of administration of isotopically labeled palmitate was previously shown to result in 95% absorption (19). Serial blood samples were taken simultaneously from both sites for 6 h after the meal. A subcutaneous adipose tissue biopsy sample, for gene expression analysis and measurement of fatty acid composition, was collected at the end of the study.

Fatty acid indexes

We used the ratio of palmitic acid (16:0) to linoleic acid (18:2n−6) (16:0/18:2n−6) as an index of DNL (lipogenic index) (18). We used the desaturation index [the ratio of plasma palmitoleic acid (16:1n−7) to palmitic acid (16:1n−7/16:0)] as a marker of SCD activity. The desaturation index was used in previous human studies and has been shown to correlate with elevated plasma TG after HC diets (20). These ratios were calculated in VLDL-TG, and arterial and adipose venous nonesterified fatty acids (NEFAs). To obtain a more specific short-term measurement of SCD activity, we also assessed the conversion of [13C₂]palmitic acid to [13C₂]palmitoleic acid in the same lipid fractions. We call this the isotopic desaturation index. The use of the combination of specific blood sampling and VLDL separation together with stable isotope ratios allowed us to assess SCD activity in adipose tissue and liver. For the postprandial adipose venous plasma NEFA samples, only data from 5 subjects were available.

Analytic methods

Blood samples were collected into heparinized syringes, and plasma was rapidly separated by centrifugation at 4 °C. TG-rich lipoprotein fractions were isolated from 3-mL portions of plasma by density-gradient ultracentrifugation (21). Lipoprotein fractions with Svedberg flotation units (Sf) of 20–400 and >400 were collected after ultracentrifugation for 16 h and 32 min, respectively, at 202 048 × g. The Sf 20–400 lipoprotein fraction contains both VLDL [containing apolipoprotein (apo) B-100] and chylomicron remnants (containing apoB-48). The Sf 20–400 lipoprotein fraction was further separated by using immunoaffinity chromatography, as previously described (22, 23), to obtain the VLDL fraction.

Total lipids were extracted from the test drink, plasma, and VLDLs, and methyl esters of fatty acids (FAME) of the TG and plasma NEFA fractions were prepared after solid-phase extraction. Fatty acid compositions in these fractions were determined by gas chromatography (GC) as previously described (24). Plasma TG, lipoprotein-TG, and NEFA concentrations were measured enzymatically with kits (Randox Laboratories Ltd, Crumlin, United Kingdom; Alpha Laboratories Ltd, Eastleigh, Hampshire, United Kingdom). Plasma alanine aminotransferase (ALT) was measured with an I-Lab ALT/GPT kit (Instrumentation Laboratory, Warrington, United Kingdom).

[13C₂]- and [U-13C]Palmitate enrichment in plasma NEFAs and TG and [13C₂]palmitate in VLDL-TG were determined by GC–mass spectrometry (GC-MS) as previously described (25). The palmitate 13C/12C ratio in the FAME derivatives from the Sf >400 and VLDL-TG fractions was determined by using a Delta Plus XP GC-combustion-isotope ratio MS (Thermo Electron Corporation, Bremen, Germany). The results are expressed as tracer to tracee ratio (TTR) or tracer concentration (μmol/L).

Six of 8 of the subjects consented to having biopsy samples taken on the day of the metabolic investigations. Gene expression analysis of the adipose tissue samples was carried out as previously described (26). The genes analyzed were SCD (SCD 1), FASN (FAS), SREBF1 (SREBP1c), ACCA (ACC1), ACLY (ATP citrate lyase), and G6PD (G6PD). Four SCD genes have been cloned in mice, and SCD1 has been the most studied, whereas only 2 SCD genes have been characterized in humans to date.
Calculations and statistical analysis

The fold increase in fasting plasma TG after the HC diet was calculated by dividing the fasting plasma TG concentration after the HC diet by the fasting plasma TG concentration after the HF diet.

The contribution of different sources of fatty acids to VLDL-TG at 6 h after the test meal was calculated, as we recently described (27), according to Barrows and Parks (28) and Vedala et al (29). The calculations allow fatty acids from subcutaneous adipose tissue lipolysis and dietary spillover fatty acids (from the hydrolysis of chylomicron particles) in systemic plasma NEFAs to be distinguished. VLDL-TG fatty acids derived from the hepatic uptake of chylomicron remnants can also be estimated, and the remaining contribution of fatty acids from other sources includes splanchnic lipolysis (mainly visceral adipose tissue) and hepatic sources (such as DNL and stored TG). Contributions from other sources will be referred to as splanchnic sources.

Adherence to the diets

Both diets were well tolerated, and none of the subjects reported gastrointestinal side effects. Food records showed that the subjects generally adhered to the diets, except for 3 subjects who could not completely consume all of the high-sugar drinks during the HC diet.

Plasma TG and VLDL-TG concentrations

After the diets, all subjects had significantly higher fasting plasma TG (2023 ± 332 compared with 1072 ± 168 μmol/L, respectively; P = 0.02) and VLDL-TG (667 ± 140 compared with 355 ± 71 μmol/L, respectively; P = 0.005) concentrations.

Plasma ALT concentrations were measured as a marker of hepatic fat content (30). There was no significant difference between plasma ALT concentrations after the 2 diets (27.3 ± 6.3 compared with 18.7 ± 4.2 μL/L after the HF and HC diets, respectively).

Fatty acid composition of adipose tissue and diets

In accordance with the assumption that the fatty acid composition of adipose tissue will not change in the short term, there were no significant changes in the fatty acid composition of adipose tissue before and after either diet. Linoleic acid and palmitic acid in the diets were also closely matched to the composition of the adipose tissue (Table 1), although the palmitic acid content of the diet was higher with the HF diet. The adipose tissue contained 5.47 ± 0.32 g/100 g palmitoleic acid, and the HC and HF diets contained 0.76 ± 0.07 and 0.79 ± 0.1 g/100 g, respectively. The ratios of dietary palmitoleic acid to palmitic acid were 0.041 ± 0.002 and 0.036 ± 0.002 with the HC and HF diets, respectively.

Lipogenic index

A comparison of the fatty acid composition of VLDL-TG between diets showed a smaller proportion of linoleic acid after the HC diet than after the HF diet (Table 1; P < 0.01). Conversely, a larger proportion of palmitic acid was noted after the HC diet than after the HF diet (P < 0.01). The 16:0/18:2n–6 ratio reflected the above pattern, i.e., significantly higher VLDL-TG values were observed after the HC diet than after the HF diet (Figure 1). The fold increase in fasting plasma TG with the HC diet than with the HF diet was significantly correlated with the 16:0/18:2n–6 ratio (Figure 2). There were no significant differences in the lipogenic index, in either arterial or adipose venous NEFAs, between the diets.

Desaturation index

In the fasted state, the proportion of 16:1n–7 in VLDL-TG was significantly higher after the HC diet than after the HF diet (7.0 ± 0.6 compared with 4.2 ± 0.5; P = 0.017). The 16:1n–7/16:0 ratio in plasma VLDL-TG was higher than the ratio in the diets and was significantly higher after the HC diet than after the HF diet (Figure 3). The 16:1n–7/16:0 ratio of adipose venous NEFAs was also higher after the HC diet (Figure 3). No difference was seen between the 16:1n–7/16:0 ratio of arterial NEFAs after the HC and HF diets. The 16:1n–7/16:0 ratio in plasma VLDL-TG (representing the liver) was found to be correlated with the 16:1n–7/16:0 ratio in the adipose venous NEFA (representing subcutaneous adipose tissue) after the HC diet (r = 0.81, P = 0.01). There was a tendency for the change in the VLDL-TG 16:0/18:2n–6 ratio after the HC diet to be associated with the activation of SCD, as indicated by the difference in 16:1n–7/16:0 ratio (r = 0.68, P = 0.064).

### Table 1

| Fatty acid composition of adipose tissue (AT), diet, and fasting VLDL-triacylglycerol (TG)1 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | High-carbohydrate diet |                 | High-fat diet  |
|                                | 18:2n-6 | 16:0 | 18:2n-6 | 16:0 |
| AT before diet                 | 12.4 ± 0.9 | 21.9 ± 0.8 | 12.4 ± 0.9 | 21.9 ± 0.8 |
| Diet                          | 12.4 ± 0.5 | 19.1 ± 0.7 | 12.5 ± 0.7 | 22.0 ± 0.82 |
| Fasting VLDL-TG after diet     | 11.9 ± 1.3 | 28.1 ± 1.04 | 14.7 ± 1.13 | 25.7 ± 0.84 |
| (8–17)                         | (24–33) |                   | (12–22) |                   |
|                                |                 |                   |                 |                 |

1 All values are x ± SEM; range in parentheses.
2 Significantly different from 16:0 of high-carbohydrate diet, P < 0.0001.
3 Significantly different from diet values, P < 0.001.
The isotopic postprandial desaturation index

The isotopic postprandial desaturation index ($[^2\text{H}_2]$palmitoleic acid/$[^2\text{H}_2]$palmitic acid) of VLDL-TG was also significantly higher after the HC diet than after the HF diet (Figure 4). The mean conversion of $[^2\text{H}_2]$palmitic acid to $[^2\text{H}_2]$palmitoleic acid with the HC diet, between 240 and 360 min, was $5.03 \pm 1.65\%$ after the HC diet and $0 \pm 0.81\%$ after the HF diet. The negative values for the postprandial isotopic desaturation index occurred when isotopic enrichments were very low and less than, but not significantly different from, baseline values. The isotopic postprandial desaturation index of adipose venous NEFA was higher after the HC diet than after the HF diet (Figure 4), whereas no difference was seen between the isotopic postprandial desaturation indexes of arterial NEFA after the HC and HF diets ($P = 0.3$, ANOVA for effects of diet only).

After the HC diet, at 360 min, the isotopic postprandial desaturation index in VLDL-TG was positively correlated with the increase in fasting VLDL-TG during the HC diet ($r = 0.74, P = 0.04$).

Plasma isotopic enrichments and contribution of fatty acid sources to VLDL-TG

During the postprandial period, there were no significant differences in plasma $[^2\text{H}_2]$palmitic acid concentrations in the plasma VLDL-TG or NEFA fraction after the 2 diets (Figure 5).

The enrichments (TTRs) of $[^2\text{H}_2]$palmitic acid in arterial plasma TG and VLDL-TG were lower after the HC diet ($P = 0.04$ and $0.01$, ANOVA for diet × time interaction). The TTR of this tracer in plasma NEFA was not significantly different in response to the 2 diets.

The isotopic enrichment data were used to calculate the contributions of fatty acids from different sources to VLDL-TG at 6 h (Table 2). After both diets, the contribution of endogenous systemic plasma NEFAs was $>35\%$, whereas dietary fatty acids formed $<20\%$ of total VLDL-TG fatty acids. Fatty acids from splanchnic sources contributed $>45\%$. None of these proportions was significantly different in response to the 2 diets. When expressed as concentrations, the contribution of fatty acids from splanchnic sources, which would include hepatic DNL, was approximately 2-fold higher after the HC diet ($P = 0.02$, Table 2),
whereas there were no significant differences in contributions from endogenous or dietary sources.

Gene expression

Of all of the lipogenic genes analyzed from the 6 pairs of adipose tissue biopsy samples, only SCD 1 mRNA showed a trend of higher relative expression levels after the HC diet (5 of 6 subjects; data not shown). There were no significant differences in relative mRNA expression levels of the other lipogenic genes between the 2 diets.

DISCUSSION

We found that the VLDL-TG 16:0/18:2n−6 ratio was significantly higher after a 3-d HC diet than after a 3-d HF diet, which indicated greater hepatic DNL. This was significantly correlated with the fold increase in fasting plasma TG in response to the HC diet. In parallel, we reported an increase in hepatic SCD activity on the basis of the 16:1n−7/16:0 ratio in VLDL-TG. This short dietary intervention was sufficient to create the pattern of increased palmitic acid and decreased linoleic acid in VLDL-TG. This pattern is indicative of DNL and has consistently been seen in other studies with HC feeding for longer periods (4, 18, 31). Subjects with a greater increase in plasma TG in response to the HC diet had higher DNL, as previously found after a 5-d dietary intervention (2).

The 16:1n−7/16:0 ratio was used as a proxy marker of hepatic SCD activity in VLDL-TG, although it is not a specific marker of SCD activity because it may also reflect the selectivity of fatty acid pathways, such as preferential incorporation of palmitoleic acid rather than palmitic acid into TG. Nevertheless, the 16:1n−7/16:0 ratio was significantly higher after the HC diet, as previously found (20), and the change tended to be associated with the difference in 16:0/18:2n−6 ratio in the liver. This finding suggests that DNL and SCD are up-regulated in parallel. The increase in the 16:1n−7/16:0 ratio in response to the HC diet was considerably greater than that reported in response to rosiglitazone treatment in type 2 diabetic patients (26). The intravenous...
infusion of labeled fatty acids allowed us to measure endogenous fatty acid desaturation more specifically during the metabolism of a mixed meal. We believe it is a more robust marker of SCD uninfluenced by recent dietary fat intake. Desaturation of endogenous fatty acids in the postprandial period has not, to our knowledge, been shown before.

We found no evidence of DNL in adipose tissue on the basis of the 16:0/18:2n–6 ratio in adipose venous plasma or gene expression data. However, using both isotopic and nonisotopic methods, we found higher desaturation indexes in adipose venous NEFAs after the HC diet, but not in arterial NEFAs. After the test meal, the isotopic desaturation index rapidly decreased by 180 min in adipose venous NEFAs, but remained high in VLDL-TG. This may indicate more sustained desaturation in the liver than in the adipose tissue. Although spillover fatty acids from TG hydrolysis in the postabsorptive state are low in relation to total adipose venous NEFAs (32), we cannot rule out the possibility that lipoprotein lipase–mediated hydrolysis of VLDL-TG in adipose tissue contributed to the higher desaturation indexes observed in adipose venous NEFAs after the HC diet. However, the mRNA expression of SCD1 in adipose tissue tended to increase in subjects after the HC diet, in agreement with recent findings in overweight men (33).

Our finding of ≈5% and 0% desaturation of the 16:0 tracer with the HC and HF diets, respectively, compares with the previous findings of 3.9% desaturation in total plasma lipids from tracer that was given as part of a test drink, which represents the desaturation of exogenous fatty acids (34). DNL is known to increase in the postprandial period. For example, in response to a liquid mixed meal, lipogenesis rose significantly from 4.7 ± 3.3% at fasting and peaked at 18.2 ± 7.1% (3).

Our results suggest parallel activation of DNL and desaturation of 16:0 in liver after 3 d of high-carbohydrate feeding. This was likely to have been mediated through the transcription factor SREBP-1c, which is activated by many nutritional factors, including insulin and glucose, as recently reviewed (35). SREBP-1c is an activator of lipogenic genes and of SCD1. However, there is some evidence to suggest that DNL and SCD can be regulated independently. A diet high in the saturated fat stearate induces lipogenic genes in mice, with the induction of the SCD1 preceding that of other lipogenic genes (36). Our results suggest that, in adipose tissue, there may be up-regulation of SCD1 in response to an HC diet, without up-regulation of DNL. Because we found no evidence of up-regulation of SREBP-1c gene expression in adipose tissue, the mechanism responsible would have to be SREBP-1c independent (37).

The inclusion of stable-isotope tracers in the postprandial protocol also provided additional information to support the finding of up-regulation of DNL after the HC diet. We found that the only fatty acids supplying VLDL-TG to increase significantly after the HC diet were those from the splanchnic region, which must have occurred from any of 3 main sources. First, stored hepatic TG may have been higher after the HC diet, although the concentration of plasma ALT, representing hepatic TG, was not significantly different after the 2 diets. Second, lipolysis of visceral fat is a possible source of fatty acids for VLDL-TG production, although visceral fat is likely to provide <20% of the hepatic delivery of NEFAs in these nonobese subjects (38). However, the size of this adipose tissue depot is not likely to have changed during the period of the diets, especially because there was no change in the weight of the subjects. Third, in the postprandial period, dietary fat could contribute to VLDL-TG production. However, there were no significant differences in response to the diets in our estimate of the proportion or concentration of dietary fatty acids in VLDL-TG, which was perhaps surprising. Therefore, it is likely that de novo hepatic synthesis of palmitic acid significantly diluted the plasma and VLDL-TG after the test meal in response to the HC diet.

In conclusion, the present study indicates that hepatic DNL and fatty acid desaturation are highly sensitive, even to short-term dietary changes. Adipose tissue may be a less important site of DNL in response to diet, although we found evidence of up-regulation of SCD activity. Desaturation of fatty acids in parallel with DNL is required to prevent excessive accumulation of saturated fatty acids in response to increased DNL. However, the physiologic consequences of up-regulation of SCD, and of increased plasma TG, in the context of such dietary changes in humans are not known.

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REFERENCES


