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Regulation of human stearoyl-CoA desaturase by omega-3 and omega-6 fatty acids: Implications for the dietary management of elevated serum triglycerides

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α-Linolenic acid (ALA);
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Stearoyl-CoA desaturase (SCD);
Sterol response element binding protein-1c (SREBP-1c);
Triglyceride (TG)

BACKGROUND: Polyunsaturated fatty acids lower serum triglycerides by a mechanism that may involve the inhibition of stearoyl-CoA desaturase (SCD).

OBJECTIVE: We sought to evaluate the effects of serum fatty acids on 1) the SCD index in a controlled clinical setting, and 2) SCD regulation in Hep G2 cells.

METHODS: The SCD index was determined in 23 subjects randomly sequenced through 3 diets for 6 weeks in a crossover study. Diets were variably enriched with n-3 and n-6 polyunsaturated fatty acids; notably, monounsaturated fatty acids were held constant. Effects of linoleic acid (LA), α-linolenic acid (ALA), and eicosapentaenoic acid (EPA) on mRNA levels of SCD, fatty acid elongases 5 and 6 (Elovl5 and Elovl6), fatty acid synthase, carnitine palmitoyltransferase-1, and sterol response element binding protein-1c were investigated in Hep G2 cells after 24-hour incubations.

RESULTS: The SCD indexes C18:1/18:0 and C16:1/C16:0 were significantly ($P < .0001$) correlated with serum TG with R^2 values of 0.71 and 0.58. The correlation was negatively associated with LA and positively associated with ALA. LA and EPA decreased SCD mRNA (EC_{50} of 0.50 and 1.67 μM), whereas ALA did not. Likewise, LA and EPA decreased sterol response element binding protein-1c mRNA (EC_{50} of 0.78 and 1.78 μM), but ALA did not. Similar results were observed for Elovl6. GW9662, a peroxisome proliferation activator receptor antagonist, did not obviate the effects of LA and EPA on SCD mRNA.

CONCLUSIONS: Diets enriched in LA, ALA, and by metabolic inference EPA, can regulate SCD activity at the level of transcription, a nutritional intervention that may be useful in the management of increased levels of serum triglycerides in cardiometabolic disorders.

Introduction

Serum triglycerides (TGs) are becoming recognized as an independent risk factor for cardiovascular disease.[1] In contrast to low-density lipoprotein cholesterol, which is directly atherogenic, elevated TG may be a marker for

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the presence of atherogenic remnant lipoproteins or associated with other cardiometabolic risk factors.[2] Regardless of the proximate biological mechanism, the management of elevated TG through lifestyle and drugs is now recommended.[3] To this end, understanding the hepatic regulation of very low-density lipoprotein (VLDL) metabolism is important to optimize the treatment of hypertriglyceridemia and its related metabolic disorders such as insulin resistance, metabolic syndrome, and type 2 diabetes.[4]

Hepatic stearoyl-CoA desaturase (SCD or Δ9 desaturase) is the rate-limiting enzyme in the endogenous biosynthesis of monounsaturated fatty acids, the most notable being oleate.[5,6] Although oleate is found ubiquitously throughout the body, endogenously derived oleate from SCD is special in terms of its preferential trafficking through acyl-coenzyme A:diacylglycerol acyltransferase 2 and driving TG synthesis.[7] The colocalization of SCD and acyl-coenzyme A:diacylglycerol acyltransferase 2 in the endoplasmic reticulum offers a topological explanation for the stringent de novo oleate requirement in TG biosynthesis[8] and the relative inability of exogenous oleate to bypass SCD deficiency.[9,10] SCD inhibitor studies in Hep G2 cells provide additional pharmacological support for the differential trafficking of fatty acids and subcellular compartmentalization of SCD pathways.[11]

Although the direct measurement of SCD activity is difficult to obtain in a clinical setting, the product-to-precursor ratio of serum oleate (C18:1) to stearate (C18:0) provides a convenient surrogate measure of hepatic SCD activity that correlates with TG levels in normal and hypertriglyceridemic subjects.[12,13] Recently, the SCD index of C18:1/C18:0 has been identified as a heritable trait in familial combined hyperlipidemia.[14] Although early research tended to focus on the ratio of C18:1 to C18:0, other fatty acid ratios can also be calculated as SCD exhibits similar K_m and comparable relative maximal velocity for acyl-CoAs ranging in chain length from C14 to C19.[15,16] It is important to note that the other product-to-precursor ratios track with different, albeit related, clinical conditions. For example, the C16:1/C16:0 index shows a correlation with systemic inflammation, insulin resistance, and metabolic syndrome.[17-21] Given the spectrum of clinical states correlating with SCD activity and the feasibility of monitoring changes in SCD activity through surrogate fatty acid ratios, it is not surprising that the pharmaceutical industry is interested in SCD as a novel drug target.[22,23]

Although the nutritional epidemiology in humans and diet studies in SCD1-deficient mice underscore the metabolic importance of SCD, controlled diet studies in humans are few in number. Of those reported, they tend to address the effects of dietary fatty acids at the general macronutrient level, ie, saturated, monounsaturated and polyunsaturated fatty acid.[18,24,25] Previously we reported on the effects of high linoleic acid (LA) and α-linolenic acid (ALA) diets on cardioinflammatory risk factors in a group of moderately obese, hypercholesterolemic men and women.[26] The design and data collected in this study afforded us a unique opportunity to go back and specifically examine the effects of individual serum fatty acids on the SCD index in a controlled clinical setting that used defined diets of known fatty acid composition. Our data confirm the general relationship between serum C18:1/C18:0 and TG and now describe its modification by ALA and LA under conditions of constant oleate intake. On the basis of the fatty acid regression models found in the clinical study and recognizing the metabolic conversion of ALA to eicosapentaenoic acid (EPA) that occurs in the body, we explored the molecular events that may underlie a causal relationship between the SCD index and TGs through studies of the effects of LA, ALA, and EPA on the transcriptional regulation of SCD in Hep G2 cells.

Methods

Subjects

Men (n = 20) and women (n = 3), 50 ± 2 years of age with baseline serum cholesterol and triglyceride levels of 226 ± 5 and 136 ± 14 mg/dL, respectively, with body mass index (BMI) of 28.1 ± 0.7 kg/m^2 and who were not taking lipid-lowering or anti-inflammatory medications and/or dietary supplements were studied according to a protocol approved by the Institutional Review Board of Pennsylvania State University. Subjects were nonsmokers and did not have any documented atherosclerotic disease, inflammatory disease, diabetes mellitus, uncontrolled hypertension, or other systemic diseases. The 3 women were postmenopausal and were not receiving hormone-replacement therapy. All subjects provided written informed consent before the initiation of the study.

Study design

The observations reported herein represent a secondary analysis of data collected from a randomized, 3-diet, 3-period, crossover study of the dietary effects of ALA on cardioinflammatory biomarkers; the study design, diets, baseline characteristics of study participants, and primary experimental outcomes have been described in detail elsewhere.[26,27] Each diet period was for 6 weeks; at the end of each period, fasting blood samples for the analysis of serum lipids were collected and stored at −70°C until the end of the study, at which time all samples were analyzed together. Subjects were required to maintain their usual activities and exercise levels; body weights were maintained by adjusting total energy intake on an as needed basis. The subjects daily interaction with the Diet Study Center ensured adherence to the research protocol, the success of which was confirmed by the changes observed in their serum fatty acids (see Figs. 1 and 2 in reference 26).

Study diets

In brief, the 3 experimental diets provided comparable amounts of total fat (35% of energy), carbohydrate (50% of

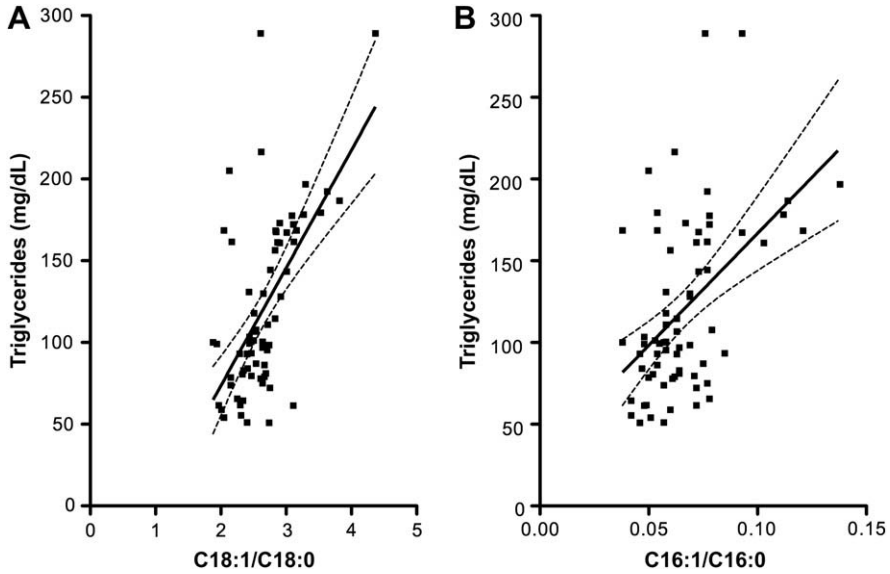

Figure 1 Correlations of the SCD index with serum triglyceride. The SCD index is a surrogate measure of hepatic SCD activity as reflected in the serum ratio of oleate (C18:1) to stearate (C18:0) or palmitoleate (C16:1) to palmitate (C16:0). (A) SCD (C18:1/C18:0) across all diets; $R^2 = 0.71$ for n = 69 at $P < .0001$. (B) SCD (C16:1/C16:0) across all diets; $R^2 = 0.58$ for n = 69 at $P < .0001$. SCD, stearoyl-CoA desaturase.

energy), protein (15% of energy), and cholesterol (300 mg/d) based on 2400 kcal/day. More specifically, the diets provided an intake of total polyunsaturated fatty acids of 9%, 16%, and 17% of energy, with n-3 (ALA % of energy)/n-6 (LA % of energy) ratios of 0.1 (0.8/7.7), 0.3 (3.6/12.6), and 0.6 (6.5/10.5), respectively; saturated fatty acids provided 13% of energy but decreased to 8% to accommodate increases in polyunsaturated fatty acids. Despite this decrease, total saturated fatty acid levels in the compartment of interest, the serum, remained relatively constant at 33.0 to 34.8%mol.

Most importantly, given our interest in SCD, the dietary intake of monounsaturated fatty acids was held constant at 12-13% of energy. In this and in previous publications, diets having n-3 to n-6 ratios of 0.1, 0.3, and 0.6 are referred to as the "average American diet," the "LA diet," and the "ALA diet," respectively. The high LA and ALA diets were achieved with inclusion of walnuts, walnut oil, and flaxseed oil. Because fish was not included in the diet and nutritional supplements were not allowed in the study, changes in serum EPA were secondary to metabolic conversion from ALA, and DHA remained constant as is commonly observed in such studies.[28]

Cellular and molecular protocols

Hep G2 cells were cultured in Eagle's minimal essential media at 37°C and 5% CO_2 with 10% fetal bovine serum albumin and 1% penicillin/streptomycin. When they reached confluence, cells were washed with phosphate-buffered saline and incubated with one of the fatty acids (ALA, EPA, or LA) complexed (4:1) with fatty acid-free albumin. Controls were conducted with albumin in the culture medium where appropriate. After 24-hour incubation, cell monolayers were washed with ice-cold phosphate-buffered saline and harvested. The Hep G2 cells were purchased from

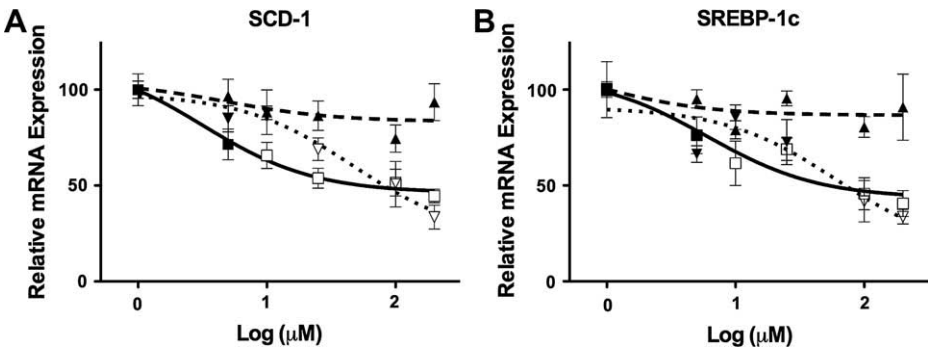

Figure 2 Dose-response effects of ALA, EPA, and LA on mRNA of SCD-1 (A) and SREBP-1c (B) after 24-hour Hep G2 cell incubations. SCD is an established gene target of the SREBP-1c. Values represent the mean ± SEM for n = 5. squares = LA, triangles = ALA, inverted triangles = EPA; open symbols are statistically significant from the vehicle control at $P < .05$. ALA, α-linolenic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; SCD, stearoyl-CoA desaturase; SREBP-1c, sterol response element binding protein-1c.

ATCC (Manassas, VA); cell culture reagents and GW9662 were purchased from Sigma (St. Louis, MO).

Total RNA was isolated by TriReagent (Sigma) according to the manufacturer's instructions. The total RNA was reverse transcribed using the ABI High Capacity cDNA archive kit (Applied Biosystems, Foster City, CA). Standard curves were made using serial dilutions from pooled cDNA samples. Real-time polymerase chain reaction (PCR) was performed with the use of the SYBR Green PCR Master Mix (Applied Biosystems) according to the manufacturer's protocol and amplified on the ABI Prism 7000 Sequence Detection System.

Statistical analyses

Data from men and women were pooled because the women were postmenopausal. Statistical analyses were performed with the use of SAS v9.1 (SAS Institute, Cary, NC). The analysis followed a stepwise procedure, the first step being an evaluation of potential carryover and sequence effects related to the 3 diets; notably, none were found. The second step was a regression analysis of associations between SCD fatty acid ratios and triglycerides and the major serum polyunsaturated fatty acids of interest, ie, ALA, EPA, docosapentaenoic acid, and LA. BMI also was included as a covariate in the regression analysis; docosahexaenoic acid was not included because it was unaffected by the dietary interventions. Transformation of responses to meet normality or variance homogeneity requirements for standard analyses was performed as needed, as was the identification and evaluation of outliers or influential observations. Probability values of $P < .05$ were considered significant.

Real-time PCR results are presented as means ± standard error of the mean. Comparisons between fatty acid doses were made using analysis of variance with repeated measures (REMANOVA) using Prism (GraphPad Software Inc., San Diego, CA) with post-hoc analyses by Newman-Keuls test. A significant effect of fatty acid dosage was defined as a significant contribution in the analysis of variance ($P < .05$ by F-test). All figures were generated using Prism (GraphPad Software Inc., San Diego, CA).

Results

Clinical observations

As previously described, 23 moderately obese, hypercholesterolemic men and women completed a randomized, controlled, 3-diet, 3-period, cross-over study that was designed to study the effects of dietary ALA on cardioinflammatory risk factors.[26] Notable among the effects were the statistically significant changes observed serum lipids and lipoproteins, specifically an 18% decrease in TG and 9% decrease in Apo B. The present study expands these observations to include a significant reduction (~14%) in the ratio of serum oleate to stearate by the LA (2.5 ± 0.1 mean ± SEM for $n = 23$, $P < .05$)- and ALA diet (2.5 ± 0.1, mean ± SEM for $n = 23$, $P < .05$)-enriched diets compared with the control average American diet (2.9 ± 0.1, mean ± SEM, $n = 23$). A similar trend was observed for the serum ratio of palmitoleate to palmitate (LA diet = 0.065 ± 0.004; ALA diet = 0.059 ± 0.003 vs. the average American diet = 0.074 ± 0.1).

The ratios of serum oleate/stearate (C18:1/C18:0) and palmitoleate/palmitate (C16:1/C16:0) were analyzed in detail by linear regression for the impact of specific serum fatty acids, notably ALA, EPA, and LA. EPA, but not DHA, was included in this analysis because serum EPA levels were increased by the LA- and ALA-enriched diets whereas DHA levels were unchanged.[27] As shown in Figure 1A, the serum C18:1/C18:0 ratio was positively correlated with serum triglycerides ($R^2 = 0.71$; $P < .0001$, repeated measures analysis of variance, $n = 69$). The slopes across diets were indistinguishable from each other. The regression models for each diet treatment were determined to be as follows: for the ALA diet: LnTG = 3.87 + 0.33(C18:1/C18:0) − 0.03(LA) + 0.06(ALA) + 0.03 (BMI); for the LA diet: LnTG = 3.87 + 0.33(C18:1/C18:0) − 0.03(LA) + 0.14(ALA) + 0.03(BMI), and for the average American diet: LnTG = 3.87 + 0.33(C18:1/C18:0) − 0.03(LA) + 0.40(ALA) + 0.03(BMI).

Linear regression revealed that serum ALA was a significant covariate in the relationship between C18:1/C18:0 and TG. After statistical adjustment for ALA, the slopes of the diets were significantly different for all 3 diets ($P < 0.004$). As shown in Figure 1B, the serum C16:1/C16:0 ratio was also positively correlated with serum triglycerides ($R^2 = 0.57$; $P < .0001$, repeated measures analysis of variance, $n = 69$). The regression models for each diet treatment were determined to be as follows: for the ALA diet: LnTG = 5.22 + 6.30(C16:1/C16:0) + 0.06(ALA) − 0.04(LA); for the LA diet: LnTG = 5.22 + 6.30(C16:1/C16:0) + 0.16(ALA) − 0.04(LA); and for the average American diet: LnTG = 5.22 + 6.30(C16:1/C16:0) + 0.44(ALA) − 0.04(LA). After statistical adjustment for serum ALA as a covariate, the slopes were different for each of the 3 diets ($P \leq .01$).

Hep G2 observations

Because SCD is subject to transcriptional regulation,[29] the dose-response effects of ALA, EPA, and LA on SCD mRNA levels were examined in Hep G2 cells. As shown in Figure 2A, EPA and LA, but not ALA, decreased SCD-1 mRNA in a dose-dependent manner with EC_{50} values of 1.7 and 0.5 μM, respectively. Given the role of the sterol regulatory element binding protein-1c (SREBP-1c) in the transcriptional regulation of SCD, parallel studies were performed to examine the effects of ALA, EPA, and LA on SREBP-1c mRNA. As shown in Figure 2B, EPA and LA, but not ALA, decreased SREBP-1c mRNA in a dose-dependent manner with EC_{50} values of 1.8 and 0.78 μM, respectively. Similar to that observed for

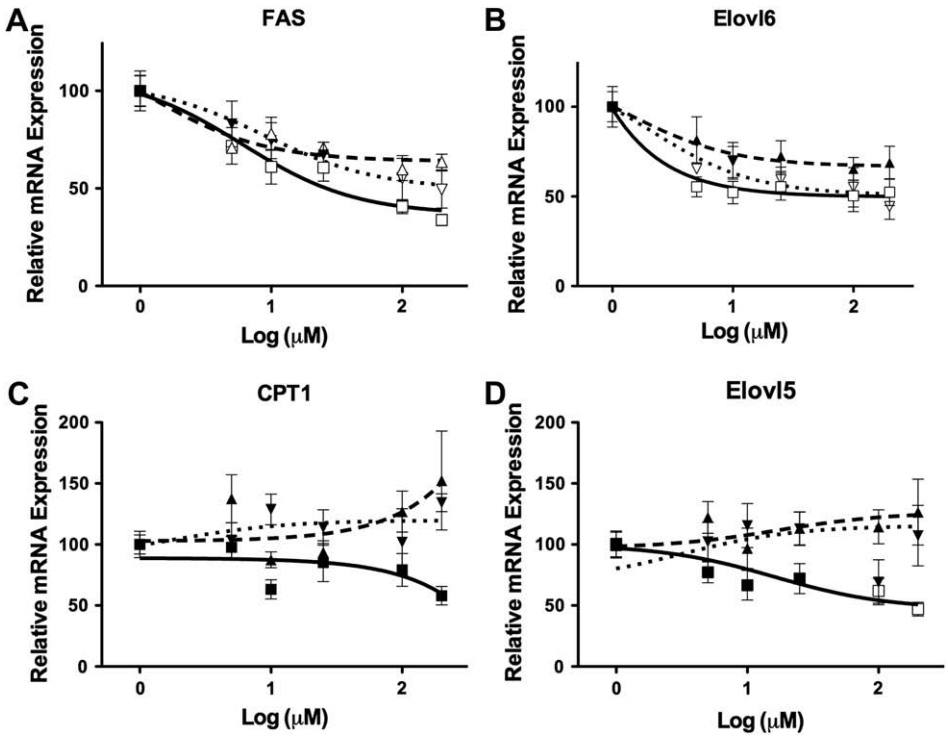

Figure 3 Dose-response effects of ALA, EPA, and LA on selected mRNAs of SREBP-1c and PPAR-α target genes after 24-hour Hep G2 cell incubations. Targets genes of SREBP-1c include fatty acid synthase (FAS) and fatty acid elongase-6 (Elovl6) as shown in (A) and (B), respectively. Target genes of PPAR-α include carnitine palmitoyltransferase-1 (CPT1) and fatty acid elongase-5 (Elovl5), as shown in (C) and (D), respectively Values represent the mean ± SEM for n = 5. Squares = LA, triangles = ALA, inverted triangles = EPA; open symbols are statistically significant from the vehicle control at $P < .05$. ALA, α-linolenic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; PPAR-α, peroxisome proliferator activator receptor-α; SREBP-1c, sterol response element binding protein-1c.

SCD-1, EPA and LA, but not ALA, decreased the mRNA levels of Elovl6 whereas all of the fatty acids decreased the mRNA levels of fatty acid synthase (Fig. 3A and 3B). Notably, carnitine palmitoyltransferase-1, and Elovl5, target genes of peroxisome proliferator activated receptor (PPAR-α), were relatively unaffected although high doses of LA did decrease Elovl5 expression (Fig. 3C and 3D). GW9662 at a pan-PPAR antagonistic dose did not obviate the effects of EPA and LA on SCD mRNA (Fig. 4).

Discussion

Elevated serum triglyceride is a common component of cardiometabolic disease and its management, whether by nutritional or pharmacological means, is an important step in reducing the risk of heart disease. As such, improving our understanding of the underlying biology of VLDL production is a key step in developing optimal strategies to manage elevated triglycerides. Recent advances in our understanding of the intracellular trafficking of de novo versus dietary oleate have revealed a special role for SCD in the regulation of TG synthesis and secretion. The role of SCD in VLDL production is supported by genetic mouse models and human nutritional epidemiology that highlight the correlation between serum TG and the SCD index. The TG-SCD index is a robust biological relationship that is log-linear over an extended range of TG values, ie, 27 − 1772 mg/dL.[12] In the current study the TG values ranged from 42 to 289 mg/dL. In our randomized cross-over design study, we confirm a strong statistically significant ($P < .0001$) correlation between serum TG and C18:1/C18:0 and C16:1/C16:0, and demonstrate its modulation by n-3 and n-6 polyunsaturated fatty acids. Notably, the coefficients of determination observed in our studies, R^2 of 0.71 and 0.58 for SCD (C18:1/C18:0) and SCD (C16:1/C16:0), respectively, are considerably greater than those initially reported in the literature.[12,13] We attribute this result to the use of controlled and defined diets in a clinical setting. In terms of study design features and clinical outcome measures, it is the noteworthy that MUFA intake was held constant across all diets at ∼12.6 % of energy and the LA and ALA diets were associated with significant decreases in both TG and apolipoprotein B.[26] Our clinical study expands the serum TG and SCD (C18:1/C18:0) correlation to include dietary modulation by PUFAs, specifically ALA and LA. Our Hep G2 studies underpin the correlation with a molecular mechanism based on the ability of EPA and LA, but not ALA, to directly regulate SCD via SREBP-1c. Although ALA may not regulate SCD directly, it can do so indirectly as a result of its bioconversion to EPA. This finding may explain the paradoxical observation of a positive ALA term in the fatty acid regression analysis and the absence of effect in the short-term Hep G2 studies.

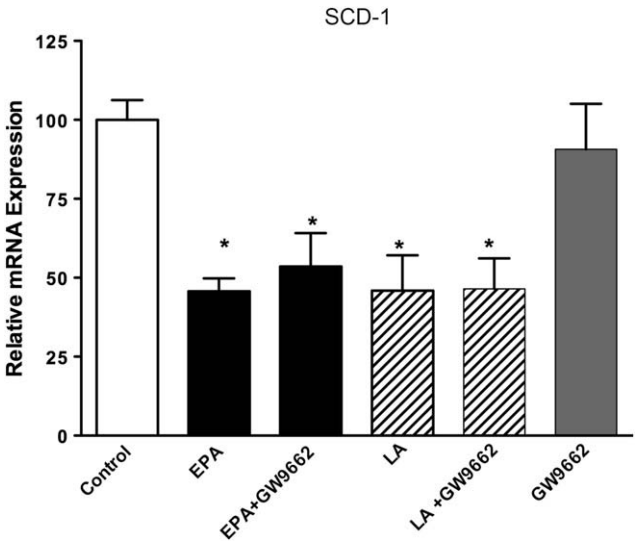

Figure 4 Absence of effect of GW9662 on EPA- and LA-induced decreases in mRNA for SCD-1 after 24-hour Hep G2 cell incubations. In these studies GW9662 was used at 10 μM and EPA and LA were used at 100 μM. Note: although GW9662 is a selective PPAR-γ antagonist at ηM concentrations, at the high concentration used in these experiments, it acts as a pan-PPAR antagonist. Values represent the mean ± SEM for n = 5. *Indicates values are statistically different from the vehicle control at $P < .05$. EPA, eicosapentaenoic acid; LA, linoleic acid; PPAR-γ, peroxisome proliferator activator receptor-γ.

Mechanistically, the results of the PPAR pan-antagonism study are important because they show the independence of the nutritional pharmacology of these fatty acids on SREBP-1c versus PPAR. In terms of the broader physiological reality, the 2 transcription factors are likely to be interdependent and subject to additional regulation by other ligand activated nuclear receptors. The concomitant regulation of Elovl6 with SCD was to be expected because both are target genes of SREBP-1c and it offers an example of coordinate regulation of intracellular fatty acid trafficking at the transcriptional level. The ability of LA and EPA to significantly down-regulate Elovl6 may be notable in lieu of the enzyme's proposed role in obesity-induced insulin resistance.[30]

Serum fatty acid profiling and fatty acid product-precursor indexing is becoming increasingly common because of its ease of measurement and emerging clinical utility. The Omega-3 index for coronary heart disease is particularly notable in this regard.[31] The SCD index, specifically SCD (C16:1/C16:0), has recently been shown in prospective population-based studies to be predictive of both total and cardiovascular mortality independent of smoking, physical activity, BMI, total cholesterol, and hypertension.[32] The simplicity of these indexes, however, can mask underlying complexities, which can limit their utility. For example, the Omega-3 index is the percent sum of the red blood cells of EPA + DHA where the level of each fatty acid is primarily driven by dietary intake; in contrast, the SCD Index is a product-precursor relationship in which the level of the determinant fatty acids is subject to dietary intake, endogenous biosynthesis and, as shown in the present study, nonindex fatty acid regulation. Another level of complexity can arise from the specific lipid fractions analyzed, e.g., total fatty acids, triglycerides, phospholipids, or cholesteryl esters, and the biological compartment from which the sample is taken, e.g., whole blood or lipoprotein particle. Until such time as harmonized protocols are developed for these indexes, it is important to collect as much information as possible to enable the broadest interpretation of changes therein.

The primary strengths of the current study were its randomized, cross-over design and the use of tightly controlled diets that kept monounsaturated fatty acid intake constant while varying the intake of polyunsaturated fatty acids. For the purposes of clarity, "randomization" in this study refers to the order in which subjects consumed the different diets, and "tightly controlled" refers to the fact that all meals were provided and calorically adjusted to maintain constant body weight. Because not all subjects rotated through the different diets in the same order, it was possible to statistically test and rule out an inherent risk of cross-over studies, ie, carry-over effects. A second strength of the study was the mechanistic follow-up in Hep G2 cells that builds the causal molecular basis for the correlation between TG and the SCD index. Notably, the cell culture work focused on key fatty acids, and in the case of ALA a metabolite thereof (EPA), identified in the regression analysis of the clinical data as been important.

In terms of study limitations, there are a number of caveats. First, the product to precursor ratio of serum fatty acids is a surrogate measure of hepatic SCD activity; second, the SCD index observations represent a secondary analysis of data from a study designed for other reasons; and third the targeted analysis of gene transcripts may be conceptually constraining in the context of other changes within the transcriptome. Finally, in future studies, it will be important to examine the effect of adding EPA directly to the diet rather than relying on its limited bioconversion from ALA. Nutritional interventions that focus on EPA may be particularly interesting in lieu of recent drug studies involving the ethyl ester of EPA showing positive outcomes in terms of decreasing the cumulative incidence of major coronary events in patients presenting with high TG with low HDL-C.[33]

In conclusion, the data presented herein indicate that diets enriched in LA, ALA, and by metabolic inference EPA, can regulate SCD activity at the level of transcription, a nutritional intervention that may be useful in the management of elevated triglycerides in cardiometabolic disorders. Figure 5 integrates the results of our study and places them in the broader context of SCD regulation via drugs and diet. In contrast to the formally approved clinical indications and dosing regimens of the prescription omega-3 fatty acid drugs, the dietary guidelines and health benefits of nutritional omega-3 fatty acids are still evolving[34] and a clear distinction needs to be maintained between omega-3 drugs and omega-3 enriched foods and dietary supplements.[35]

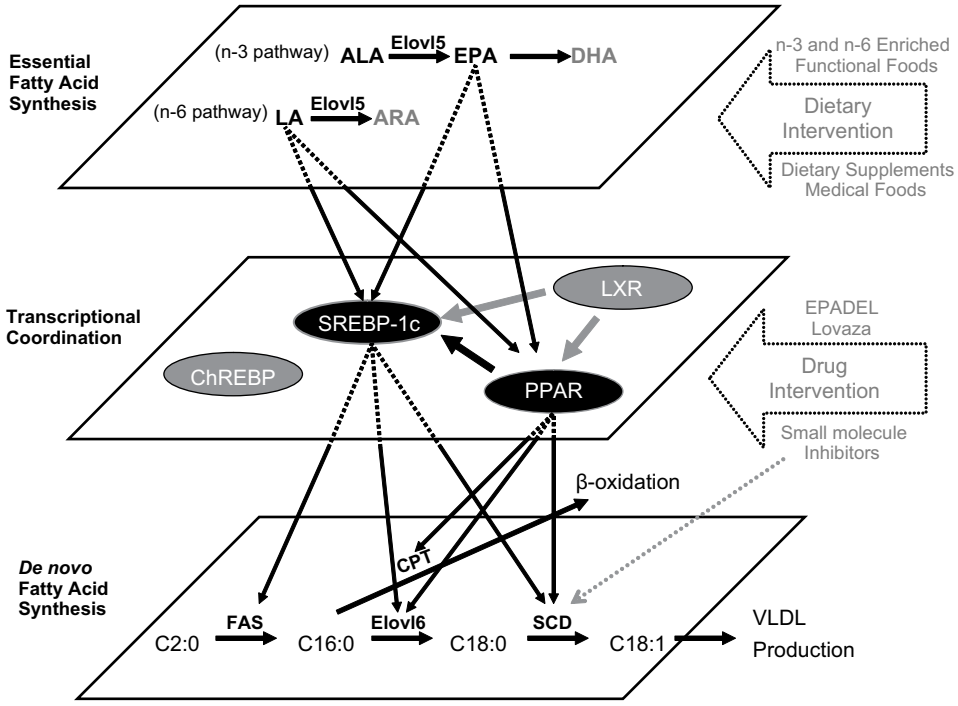

Figure 5 Interdependent regulation of stearoyl-CoA desaturase by diet and drugs. The upper plane identifies selected n-3 and n-6 fatty acids that interact with transcription factors shown in the middle plane, which in turn regulate de novo lipogenesis and fatty acid β-oxidation as shown in the bottom plane. Black and bolded fatty acid fatty acids and transcription factors were examined in the present study. In contrast to the natural triglyceride form of omega-3 fatty acids found in oil seeds, nuts, and fish, the prescription omega-3 fatty acids found in Lovaza (US) and EPADEL (Japan) are administered as ethyl ester pro-drugs. Lovaza contains 465 mg of EPA and 375 mg of DHA as ethyl esters in 1-g capsules with a recommended total dose of 4 g per day; EPADEL contains 300 mg of EPA as ethyl ester per capsule with two capsules being recommended 3 times a day for a total dose of 1800 mg. CPT, carnitine palmitoyltransferase-1; ChREBP, carbohydrate response element binding protein; Elovl5 and Elovl6, fatty acid elongases 5 and 6; FAS, fatty acid synthase; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor; SCD, stearoyl-CoA desaturase; SREBP-1c, sterol response element binding protein-1c.

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