Regulation of Stearoyl-CoA Desaturase 1 mRNA Stability by Polyunsaturated Fatty Acids in 3T3-L1 Adipocytes*

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The effects of arachidonic acid (20:4, n-6) and other fatty acids on the expression of stearoyl-CoA desaturase gene 1 were investigated in fully differentiated 3T3-L1 adipocytes. Treatment of 3T3-L1 adipocytes with arachidonic acid resulted in a decrease in stearoyl-CoA desaturase (Scd1) mRNA stability. Treatment of adipocytes with linoleic acid (18:2, n-6) and linolenic (18:3, n-3) acids also resulted in inhibition of Scd1 mRNA expression. Treatment of adipocytes with linoleic (18:2, n-6) and linolenic (18:3, n-3) acids also resulted in inhibition of Scd1 mRNA accumulation. By contrast, oleic acid (18:1, n-9) and stearic acid (18:0) had no effect on Scd1 mRNA levels. Taken together, these results suggest that polyunsaturated fatty acids repress the expression of the scd1 gene in mature adipocytes by reducing the stability of scd1 mRNA.

The mouse embryo 3T3-L1 preadipocytes (1–4) represent a useful model system for studying the mechanisms of cellular differentiation and development. Under appropriate stimuli, these cells differentiate in culture into cells possessing the morphological and biochemical characteristics of adipocytes (5–11). Accompanying acquisition of the adipocyte phenotype, the cells become responsive to both lipogenic (insulin) and lipolytic (ACTH) hormones (10, 12) and acquire increased levels of enzymes of the glycolytic, lipogenic, and lipolytic pathways (5, 7, 10, 12) as well as other adipocyte-specific proteins such as stearoyl-CoA desaturase (13, 14), the insulin receptor (8, 15), and myelin ap2 (16), which are expressed at high levels in adipocytes.

Over the years, several differentiation-induced genes have been isolated and characterized, and their promoters have been analyzed (14, 17, 18). Two of these genes, stearoyl-CoA desaturase 1 and 2 (scd1 and scd2) (14, 17), encode two isozymes of stearoyl-CoA desaturase, a key enzyme involved in the biosynthesis of unsaturated fatty acids as well as the regulation of this process. The enzyme activity increases 20–100-fold during the differentiation of 3T3-L1 preadipocytes (12). This increase is primarily due to increased transcription of the scd genes (14, 19). The enzyme catalyzes the Δ^4-ene desaturation of fatty acyl-CoAs (20); the predominant products are palmitoleoyl- and oleoyl-CoA. Palmitoleic and oleic acids are the major constituents of membrane phospholipids and triacylglycerol stores found in adipocytes (12). The ratio of stearic acid to oleic acid is one of the factors influencing cell membrane fluidity. Alteration of this ratio is implicated in aging, obesity, and various diseases such as cancer, diabetes, and heart disease (21–23).

Several studies using rat liver primary cultures and intact animals have established that genes encoding both glycolytic and lipogenic enzymes are regulated by dietary fatty acids (24–29). Polysaturated fatty acids (PUFAs), particularly the ω-6 and ω-3 series, repress the transcription of genes such as malic enzyme, acetyl-CoA carboxylase, fatty acid synthase (FAS), glucose transporter 4 (GLUT4), S14 protein, and scd1 (24–27, 30–32). Saturated and monounsaturated fatty acids have no effect on the transcription of these genes.

Liver and adipose tissue are the two major tissues involved in lipid biosynthesis. Although the regulation of lipogenic gene expression by PUFAs in liver is currently being studied, the effects of these molecules on gene expression in mature, fully differentiated adipocytes have not been extensively investigated. In view of the potential role of polyunsaturated fatty acids in regulating total fatty acid synthesis and the role stearoyl-CoA desaturase plays in this process, we examined the effect of polyunsaturated fatty acids on the expression of the scd1 gene in mature adipocytes. Our results suggest that PUFAs regulate the expression of the adipocyte scd1 gene by regulating stability of mRNA transcripts.

EXPERIMENTAL PROCEDURES

Materials—Dulbecco’s modified Eagle’s medium, fetal bovine serum, and actinomycin D were obtained from Life Technologies, Inc. Calf serum was purchased from Biowhittaker, and insulin was purchased from Lilly. β-3-Isobutyl-1-methylxanthine was obtained from Aldrich. Nytran membranes were supplied by Schleicher & Schuell, Inc. All radiolabeled compounds were obtained through DuPont NEN unless specified. Probe-labeling kits were purchased from Promega. Silica gel plates were obtained from Analtech. All other materials were obtained from Sigma.

Cell Culture—Murine 3T3-L1 preadipocytes were cultured and differentiated into adipocytes as described previously (14). Mature 3T3-L1 adipocytes, 6–9 days after induction of differentiation, were treated with albumin-bound fatty acids. Fatty acid–albumin stocks were prepared as 100 mM fatty acid with 2 mM fatty acid–free bovine serum albumin, 0.1% butylated hydroxytoluene, and 20 μM α-tocopherol (33) to minimize oxidation of the fatty acids.

Isolation and Analysis of RNA—Total cellular RNA was isolated

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Table I

Effect of arachidonic acid (AA) on Scd enzyme activity

Day 6 3T3-L1 adipocytes were treated with the indicated concentrations (μM) of arachidonic acid (AA) for 72 h and then harvested for measurement of enzyme activity. Values are expressed as percentage conversion of [1-14C]-palmitoyl-CoA to [1-14C]-palmitoleoyl-CoA. Similar results were seen in two independent experiments.

| AA (μM) | % Conversion |
|---------|--------------|
| 0       | 39.39 ± 0.27 |
| 100     | 30.64 ± 1.49 |
| 300     | 15.81 ± 0.16 |

FIG. 1. Regulation of Scd enzyme activity by arachidonic acid (AA). Graphical representation of enzyme activity in response to AA dose. Day 6 3T3-L1 adipocytes treated with 0, 100, or 300 μM AA for 72 h were harvested for measurement of enzyme activity. Values are expressed as percentage conversion of [1-14C]-palmitoyl-CoA to [1-14C]-palmitoleoyl-CoA.

Scd Regulation by Fatty Acids

from 3T3-L1 cells using guanidine isothiocyanate followed by ultracentrifugation through CsCl (34). Cytoplasmic RNA was isolated from cells by modification of the procedure previously described (35) using 10% Triton X-100 and 10% SDS for cell lysis. scd1 mRNA and pAL15 (36) mRNA expression were measured by RNAse protection or Northern blot analysis as described previously (37, 38) and quantified by laser densitometric scanning of autoradiograms.

Nuclei Isolation and Transcription Run-on Analysis—Nuclei from treated cells were isolated through a 2 m sucrose gradient after Deuece homogenization. Run-on transcription was performed as described previously (29) using a 2-kilobase cDNA probe for scd1 designated pC3 (14).

Measurement of Scd Enzyme Activity—Desaturation of [1-14C]palmitoyl-CoA was determined by modification of the procedure described previously (39, 40). Briefly, cells were washed with phosphate-buffered saline and scraped from the Petri dish. Pelleted cells were homogenized in 800 μl of 0.1 M PIPES (pH 6.0) extraction buffer containing 1% polyvinylpyrrolidone, 6000 units catalase, 0.1% bovine serum albumin, and 40 mM sodium ascorbate. The assay was conducted for 10 min at 25 °C in a total volume of 1 ml containing 1 mM dithiothreitol, 100 μM bovine serum albumin, 0.75 mM NADPH, 50 μg ferredoxin, 0.285 units Fd-NADP+ oxidoreductase, 4000 units catalase, and 6 μM [1-14C]palmitoyl-CoA (Amersham Corp.). The reaction was terminated with chloroform: methanol (v/v, 1:1).

Lipids from membrane samples were extracted by sequential addition of isopropl alcohol, methanol, chloroform, and butylated hydroxytoluene. After addition of 0.8% (v/v) aqueous KCl, the chloroform phase was dried under nitrogen and converted to methyl esters with boron trifluoride and then extracted into hexane. Separation of methyl esters was done by thin layer chromatography on silica gel plates containing 15% AgNO3 using a hexane-ether (9:1) solvent system. Spots were identified under UV light after spraying with 0.2% dichlorofluorescein ethanolic solution and compared with authentic standards. Plates were read on an automated thin layer chromatography analyzer (Berthold LB 2942). Desaturation activity was determined by integrating the area under the peaks corresponding to 16:1 and 16:0 methyl esters and expressed as the percentage conversion of 16:0 into 16:1.

RESULTS

Arachidonic Acid Decreases Scd Enzyme Activity—The effect of arachidonic acid on Scd enzyme levels was assessed by measuring Scd enzyme activity in adipocytes treated on day 6 of differentiation. Arachidonic acid treatment caused a decrease in Scd enzyme activity. The percentage conversion of 16:0 to 16:1 by Scd enzyme activity in untreated cells was greater than 50% with 100 and 300 μM arachidonic acid, respectively (Table I). Repression of enzyme activity by AA treatment was expressed as percentage repression over control levels and was calculated from the data in Table I. As shown in Fig. 1, 100 and 300 μM AA suppressed Scd enzyme activity by 22.5 and 60%, respectively. The dose-response curve in Fig. 1 showed a linear decrease in enzyme activity in response to AA.

Arachidonic Acid Decreases scd1 mRNA Levels—To determine whether the decrease in enzyme activity was due to changes in mRNA levels, RNAse protection analysis was performed on total RNA isolated from fully differentiated 3T3-L1 adipocytes treated with arachidonic acid for varying lengths of time (Fig. 2A). The hybridization pattern of scd1 mRNA to its specific RNA probe was quantitated by densitometric scanning. As shown in Fig. 2B, the greatest repression occurred between 6 and 12 h of AA treatment. Northern blot analysis using a cDNA probe corresponding to pAL15, which encodes a ribosomal protein (16, 36), indicated that pAL15 mRNA content was not significantly decreased after as much as a 48-h exposure of the cells to AA (Fig. 2C).

The repression of scd1 mRNA by arachidonic acid was also dose-dependent. Doses of AA as low as 10 μM decreased levels of scd1 message by approximately 20 - 12% from normal levels. As shown in Fig. 3, A and B, concentrations of AA greater than 50 μM exerted a significant effect on mRNA levels.
To determine whether changes in scd1 mRNA levels in response to AA treatment were due to alterations in gene transcription or mRNA stability, experiments were performed to examine both mechanisms. Nuclear run-on transcription assays showed no significant reduction in the transcription of the scd1 gene to account for the 80% reduction in scd1 mRNA accumulation (Fig. 4). As expected, transcription of pAL15 was also unaffected by AA treatment. Therefore, studies of the stability of scd1 mRNA upon exposure to AA were performed. Day 9 3T3-L1 adipocytes (control and 12 h after exposure to 300 μM AA) were exposed to the transcription inhibitor, actinomycin D (5 μg/ml), for increasing time periods. Levels of chased mRNA were determined by RNase protection analysis. As shown in Fig. 5A, treatment with arachidonic acid resulted in destabilization of scd1 mRNA. The hybridization patterns were analyzed by laser densitometry, and the values are plotted as a function of time (Fig. 5B). scd1 mRNA levels decreased more rapidly with time in cells treated with AA. The t\textsubscript{1/2} of scd1 declined from 25.1 ± 4.1 to 8.5 ± 0.6 h as calculated by linear regression analysis. In contrast, the t\textsubscript{1/2} of pAL15 mRNA did not decrease in response to AA treatment (Fig. 5C). The stability of actin mRNA was also not significantly affected by AA (data not shown). These results show that enhanced scd1 mRNA turnover is primarily responsible for AA-mediated repression of scd1 gene expression in 3T3-L1 adipocytes.

**Eicosanoid Synthesis Inhibitors Have no Effect on AA Suppression of scd1 mRNA Levels**—To determine whether the AA-induced regulation of scd1 mRNA was an arachidonic acid-specific effect or required oxidative metabolism, we investigated the effects of eicosanoid biosynthesis inhibitors on the levels of scd1 mRNA. Cyclooxygenase, lipoxygenase, and cytochrome P-450 epoxygenase inhibitors were employed to block metabolism of exogenously added AA to active eicosanoids. As shown in Fig. 6, cells pretreated for 30 min with ibuprofen (50 μM), nordihydroguaiaretic acid (10 μM), or caffeic acid (10 μM) followed by a 12-h treatment with AA still showed suppression of scd1 mRNA over control levels. However, when quantitated by densitometric scanning, the repression by AA in the presence of ibuprofen (78 ± 4.1%) is similar to that observed with AA alone. The repression in the presence of nordihydroguaiaretic acid and caffeic acid was 78.5 ± 3.5 and 77.4 ± 10%,
FIG. 6. Effects of eicosanoid biosynthesis inhibitors on AA suppression of scd1 mRNA levels. A, day 6 3T3-L1 adipocytes were pretreated with ibuprofen (50 μM), caffeic acid (10 μM), or nordihydroguaiaretic acid (NDGA) (10 μM) for 30 min. After pretreatment, cells were exposed to 300 μM AA for 12 h in the presence of inhibitor. RNA was then isolated and subjected to RNase protection analysis. B, Northern blot analysis of RNA in A using a pAL15 radiolabeled cDNA probe.

FIG. 7. Effect of fatty acids on scd1 mRNA levels. A, day 6 adipocytes were exposed to 300 μM oleic acid (OA), linoleic acid (LA), linolenic acid (LN), and arachidonic acid (AA) for a 12-h period. Total cellular RNA was subjected to RNase protection analysis using an scd1-specific probe. The results are representative of several independent experiments. B, the autoradiogram in A was quantitated by laser densitometry and the results reported as percentage repression relative to the maximum level of expression. C, RNA, as in A, was subjected to Northern blot analysis and probed with a radiolabeled pAL15 probe.

FIG. 8. Partial sequence of the 3′ untranslated region of mouse scd1 mRNA. Nucleotides from 1353–2079 are shown with AU-rich elements indicated by boxed sequences. Arrows show the location by base numbers. The / symbol represents a portion of the sequence not shown.

Scd Regulation by Fatty Acids

29857

respective. In addition, the acetylenic analog of AA (eicosatetraynoic acid) that cannot be metabolized to eicosanoids was able to repress scd1 mRNA accumulation (data not shown). Levels of pAL15 mRNA remained unaffected by either AA or AA + ibuprofen, nordihydroguaiaretic acid, or caffeic acid treatments (Fig. 6B). These results suggest that AA acts independently of eicosanoid metabolism to affect scd1-specific gene expression.

scd1 mRNA Levels in Mature Adipocytes Are Decreased by Other Polyunsaturated Fatty Acids—To determine if the observed repression was a general response to PUFAs or specific to AA only, additional fatty acids were tested for their effects on scd1 mRNA expression. As shown in Fig. 7A, 300 μM linoleic (LA, 18:2) and linolenic (LN, 18:3) acids, in addition to AA, repressed the level of scd1 mRNA within 12 h of treatment. In contrast, oleic acid and stearic acid (data not shown) did not decrease the amount of scd1 mRNA (Fig. 7). Eicosapentaenoic acid (20:5) reduced scd1 mRNA as did arachidonic acid (data not shown). The level of pAL15 mRNA, analyzed by Northern blot, did not change significantly in response to any fatty acid (Fig. 7C). These results demonstrate that PUFAs have an apparent, specific effect on the levels of scd1 mRNA in mature adipocytes.

DISCUSSION

In the present study, we have demonstrated that exposure of 3T3-L1 adipocytes to 300 μM arachidonic acid results in a decrease in Scd enzyme activity as well as scd1 mRNA levels (Figs. 1 and 2). As much as a 60% decrease in enzyme activity was observed, whereas mRNA levels were repressed by 80% of the original level. Treatment of 3T3-L1 adipocytes with AA also caused a 3-fold decrease in the half-life of scd1 mRNA (Fig. 5) and no apparent decrease in scd1 gene transcription. The pre-translational regulation of scd1 gene expression by PUFAs seems to result primarily from the decrease in mRNA stability. Furthermore, the repression was independent of AA metabolism to eicosanoids because cyclooxygenase, lipoxgenase, and epoxygenase inhibitors did not abolish the effect (Fig. 6). Other polyunsaturated fatty acids, such as linoleic, linolenic, and eicosapentaenoic acid, also decreased the scd1 mRNA levels when added exogenously to mature adipocytes. By contrast, oleic acid (Fig. 7) and stearic acid did not decrease scd1 mRNA levels; therefore, this response is unique to polyunsaturated fatty acids.

Stearoyl-CoA desaturase gene expression has previously been shown to be repressed by polyunsaturated fatty acids in liver tissue principally at the level of gene transcription (29–30). Until now, the effect of polyunsaturated fatty acids on scd1 gene expression in adipose tissue had not been studied. The rate of transcription from the scd1 gene was not dramatically affected in this adipocyte system. Although transcriptional regulation can not be completely ruled out by these experiments, changes in transcription that are below detectable levels suggest that transcriptional regulation does not play a significant role in PUFA suppression of adipocyte scd1 gene expression. Our results also suggest that posttranslational regulation is not a major factor in AA-mediated scd1 repression. The observed reduction in enzyme activity (60%) could be completely accounted for by decreases in scd1 mRNA levels (80%). Thus, there seems to be no additional down-regulation occurring posttranslationally. As opposed to hepatocytes, changes in mRNA stability are the major determinant of scd1 mRNA abundance in adipocytes.

Destabilization of mRNA encoding the predominantly expressed form of stearoyl-CoA desaturase in adipocytes may be regulated through mRNA sequences in the 3′ untranslated region. Both the mouse and rat scd1 cDNAs contain an unusually long 3′-noncoding stretch that is currently unknown, though it contains several structural motifs (AUUUA) characteristic of mRNA
destabilization sequences (42–43). Four of these sequences are clustered close to the 3’ end of the coding region (Fig. 8). Because these AU-rich elements play active roles in the selective degradation of several mRNAs in response to various factors, these sequences could be possible targets of PUFA effects on scd1 mRNA (44–47). For example, Pekala and Long (42) have suggested that such a motif in the GLUT4 gene expressed in 3T3-L1 adipocytes may confer destabilization of mRNA in response to tumor necrosis factor a treatment. With such generalized effects of AU-rich elements, it is possible to speculate that this motif plays a role in the adipocyte regulation of desaturase gene expression by regulating mRNA stability in response to PUFAs. Additional mapping studies would be necessary to identify whether the AU-rich elements in the scd1 3’ untranslated region are involved in this destabilization.

The nature of the PUFA metabolite that mediates the observed mRNA destabilization is currently unknown. As demonstrated in the present study, inhibiting eicosanoid synthesis by regulating mRNA stability in 3T3-L1 adipocytes may confer destabilization of several mRNAs in response to various factors, these sequences could be possible targets of PUFA effects on scd1 mRNA (44–47). For example, Pekala and Long (42) have suggested that such a motif in the GLUT4 gene expressed in 3T3-L1 adipocytes may confer destabilization of mRNA in response to tumor necrosis factor a treatment. With such generalized effects of AU-rich elements, it is possible to speculate that this motif plays a role in the adipocyte regulation of desaturase gene expression by regulating mRNA stability in response to PUFAs. Additional mapping studies would be necessary to identify whether the AU-rich elements in the scd1 3’ untranslated region are involved in this destabilization.

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