Induction of the Peroxisomal Glycerolipid-synthesizing Enzymes during Differentiation of 3T3-L1 Adipocytes

ROLE IN TRIACYLGLYCEROL SYNTHESIS*

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The glycerophosphate backbone for triglyceride synthesis is commonly believed to be created through the conversion of dihydroxyacetone phosphate (DHAP) by glycerophosphate dehydrogenase (GPD) to sn-glycerol 3-phosphate (GP), which is then converted by glycero-phosphate acyltransferase (GPAT) to 1-acyl-GP. Consistent with this, GPD and GPAT are highly induced during differentiation of mouse 3T3-L1 preadipocytes. While the acyl dihydroxyacetone phosphate (acyl-DHAP) pathway for glycerolipid synthesis is commonly believed to be involved only in glycerol ether lipid synthesis, we report here that during conversion of 3T3-L1 preadipocytes to adipocytes, the specific activity of peroxisomal DHAP acyltransferase (DHAPAT) is increased by 9-fold in 6 days, while acyl-DHAP:NADPH reductase is induced by 5-fold. A parallel increase in the catalase (the peroxisomal marker enzyme) activity is also seen. In contrast, the specific activity of alkyl-DHAP synthase, the enzyme catalyzing the synthesis of the ether bond, is decreased by 60% during the same period. Unlike microsomal GPAT, the induced DHAPAT is found to have high activity at pH 5.5 and is resistant to inhibition by sulfhydryl agents, heat, and proteolysis. On subcellular fractionation, DHAPAT is found to be associated with microperoxisomes whereas GPAT activity is mainly present in microsomes. Northern blot analyses reveal that induction of DHAPAT can be largely explained through increases in DHAPAT mRNA. A comparison of microsomal and peroxisomal glycerolipid synthetic pathways, using [3-3H]-U-14Cglucose as the precursor of the lipid glycerol backbone shows that about 40–50% of triglyceride is synthesized via the acyl-DHAP pathway. These results indicate that the acyl-DHAP pathway is important not only for the synthesis of ether lipids, but also for the synthesis of triacylglycerol and other non-ether glycerolipids.

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Triacylglycerol Synthesis via Peroxisomal Pathway

MATERIALS AND METHODS

3T3-L1 cells were cultured and induced to differentiate as described (18). Cells were harvested from plates by removing the media and washing once with ice-cold homogenizing medium (0.25 M sucrose, 10 mM TES, pH 7.5, 1 mM EDTA), and then suspending them in 1 ml of ice-cold homogenizing medium. Suspended cells were homogenized in a ball homogenizer (19) and then centrifuged at 600 × g for 10 min to remove the unbroken cells and debris. The supernatant was centrifuged at 100,000 g for 1 h and the sediment containing the subcellular organelles was suspended in 0.25 M sucrose in 10 mM TES (pH 7.5) and stored frozen in small aliquots at −70 °C. Activities of the enzymes were measured in particulate fractions that had been thawed once only. For subcellular fractionation the freshly isolated total particulate suspension was layered onto a 20–50% Accudenz (from Accurate Chemical Co., previously called Nycodenz) density gradient and centrifuged for 70 min as described (20). After fractionation enzymes and protein were assayed (20).

DHA-3P and G3P were prepared by the enzymatic (glycerokinase, Roche Molecular Biochemicals) phosphorylation of dihydroxyacetone and glyceraldehyde-3-phosphate, respectively, by γ-[32P]ATP (ICN Biochemicals) (21). DHAPAT and GPAT were assayed as described for the assay of DHAPAT (15). Acylalkyl-DHAP reductase and alkyl-DHAP synthase were assayed as described (22, 23). For inhibition studies, the particulate fraction (0.5−1.0 mg of protein) in 1 ml of 25 mM Tris-HCl (pH 7.5) buffer was incubated on ice with different concentrations of NEM or MMTS for 15 min, and then aliquots were taken from this mixture to assay for DHAPAT and GPAT at 37 °C. After the heat denaturation studies the suspended organelles in 25 mM Tris buffer (pH 7.5) were heated at 50 °C and aliquots were removed at different time periods and chilled immediately in ice water. Samples were assayed for DHAPAT and GPAT activity at 37 °C. The trypsin treatment was as described (20). Catalase, NADPH-cytochrome c reductase, and succinate-cytochrome c reductase were assayed as described (20). Protein was assayed by the Bio-Rad method (24) using reagent from Pierce Biochemicals.

For the radioactive glucose incorporation experiments, adipocytes in 100-mm culture dishes were maintained overnight in glucose-free Dulbecco's modified Eagle's M13 medium. On the day of the experiment, the medium was replaced with 5 ml of the same medium containing 100 μCi of [3-3H]glucose (10.8 Ci/mmol, NEN Life Science Products Inc.) and 25 μCi of [3-14C]glucose (13.9 mCi/mmol, NEN Life Science Products Inc.). The cells were incubated with the radioactive substrate for 1 h at 37 °C in air with gentle shaking and the medium was removed. Cells were washed twice with ice-cold phosphate-buffered saline (pH 7.4) and were then removed from the plate in 2 ml of phosphate-buffered saline. After sonication disruption of the cells at 4 °C with a Branson sonic probe (model LS-75), the homogenate was subjected to isopropylmethanol extraction procedure as described (25). After solvent partition, GP was isolated from the aqueous layer using a combination of ion-exchange and enzymatic methods (25). Triglycerides (TG) and individual phospholipids were isolated from the organic layer by thin-layer chromatography (26). TG was subjected to alkaline methanolysis and the glycerol moiety released was isolated (27). The 3H and 14C present in each carbon of glycerol were determined by peridode oxidation as described (25). Briefly, one-half of the glycerol was oxidized directly with IO3− and the formaldehyde formed from C-1 + C-3 was quantitatively converted to water-insoluble Dimedone (5,5-dimethyl-1,3-cyclohexanedione from Sigma) adduct, which was separated from the water-soluble formaldehyde form (obtained from C-2) by toluene extraction (25). The other half of the glycerol was enzymatically converted to GP (25), which was oxidized with periodate when only C-1 is converted to HCHO, which was separated as Dimedone adduct from the water-soluble glycoldehyde phosphate (C-2 + C-3) as above. The major phopholipids PE and PC were hydrolyzed by phospholipase D to diacylglycerol (26), and the glycerol moiety of diacylglycerol was isolated and degraded as described for TG. The glycerol backbone of the ethanolamine plasmalogens was isolated as described (25). Since the radioactivity in the glycerol backbone of the ethanolamine plasmalogens was too low, the liberated glycerol was not directly degraded and the distribution of radioactivity in C-2 and combined C-1 + C-3 was determined. The completeness of degradation was verified by calculating the distribution of 14C which was uniform in all three carbons of glycerol.

Total RNA from cells was isolated and subjected to formaldehyde gel electrophoretic separation and transfer to polyvinylidene difluoride membrane as described (18). The template DNA used for making the creation of the GP backbone required for biosynthesis of triacylglycerol and other glycerolipids.

RESULTS

Differentiation-induced Increased Activity of Lipogenic Enzymes and Catalase—The activity of acyl-DHAP pathway enzymes (Fig. 1) and GPAT in the total particulate fraction of 3T3-L1 cells was assayed during a time course of adipogenesis (Fig. 2). As reported before (7−9), the specific activity of GPAT increases during differentiation by about 6.5-fold in 6 days. During adipogenesis, the activities of DHAPAT measured at both pH 7.5 and 5.5 increase by 9- and 6.5-fold, respectively (Fig. 2). The activity of acylalkyl-DHAP reductase increases, after an initial lag of 2 days, to about 5-fold in 6 days. In this period, the activity of catalase, the marker enzyme for microperoxisomes in these cells (4) also increases by about 7-fold. However, during the same period the specific activity of alkyl-DHAP synthase, the enzyme which catalyzes the synthesis of the ether bond, decreases by about 60%.

Comparison of the Properties of Induced DHAPAT and GPAT—These results indicate that, as in other mammalian cells (11), DHAPAT is active both at pH 7.5 and pH 5.5 (7.8 milliunits/mg of protein at pH 5.5 compared with 8.4 milliunits/mg at pH 7.5) in adipocytes 6 days after differentiation is induced. As expected (11, 28), GPAT has high activity at pH 7.5 (24.8 milliunits/mg of protein) and is inactive at pH 5.5. This indicates that peroxisomal DHAPAT is induced during differentiation of 3T3-L1 cells and DHAPAT activity in adipocytes is not due to the dual activity of GPAT. We further verified this by investigating the inhibition of these acyltransferases by sulf-hydryl group-reacting agents like NEM and MMTS (11, 28−31). In contrast to DHAPAT, GPAT is completely inhibited by both NEM and MMTS at low concentrations of the inhibitors (Fig. 3A). GPAT is also found to be more heat labile than DHAPAT (Fig. 3B).

Sensitivity of these acyltransferases to proteases has been widely used to distinguish between them. Microsomal GPAT is localized on the cytoplasmic surface of ER vesicles (32), and is highly susceptible to proteolysis. Peroxisomal DHAPAT, localized on the luminal side of peroxisomes, is comparatively resistant to proteolysis (20, 28). Results (Fig. 3C) show that the induced 3T3-L1 GPAT is very sensitive to trypsin treatment but most of DHAPAT is not, indicating that these two activities are not due to the dual activity of the same enzyme. The 30%
DHAPAT which is labile to trypsin is probably due to the presence of damaged peroxisomes and also partly due to the nonspecificity of GPAT (see later).

**Subcellular Distribution of DHAPAT in 3T3-L1 Cells**—We have found that the properties of the induced GPAT are as described for the ER membrane-bound enzyme and that the properties of the induced DHAPAT are the same as those of the peroxisomal enzyme. The parallel increase in the catalase activity (Fig. 2) shows that peroxisomes are also induced during differentiation, thus verifying previous morphological observations (4). To establish that DHAPAT in these cells is indeed peroxisomal, density gradient centrifugation was used to separate peroxisomes from other organelles (20, 33, 34). However, instead of using an enriched peroxisomal fraction (L fraction) the total particulate fraction was used so that the distribution of the enzymes in all extranuclear organelles can be analyzed in a single gradient. As seen in Fig. 4, the microperoxisomes (catalase-containing organelles) sediment to the bottom part of the tubes, while mitochondria (marker enzyme succinate-cytochrome c reductase) and ER vesicles (marker enzyme NADPH-cytochrome c reductase) remain higher in the gradient. The sedimentation pattern of DHAPAT, measured at both pH 7.5 and 5.5, follows that of catalase, indicating that DHAPAT is mainly localized in microperoxisomes. In contrast, GPAT follows the same profile as NADPH-cytochrome c reductase, indicating that GPAT is localized in ER. Acyl/alkyl-DHAP reductase is mainly localized in peroxisomes; however, as in other organs, this enzyme is also present in ER as well as in mitochondria (Fig. 4).

**Northern Blot Analysis of DHAPAT mRNA during Cell Differentiation**—The human DHAPAT cDNA has been cloned (16, 17) and a number of human and mouse EST clones are available. One EST clone (W54198) was used for Northern blot analysis of the DHAPAT mRNA in 3T3-L1 cells during differentiation. A number of such analyses reveal a 3–5-fold increase in the ~3.0 kilobases (16, 17) DHAPAT mRNA during adipogenesis (Fig. 5). Thus the induction of DHAPAT activity during

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**Fig. 2.** Time course showing changes in the specific activity of the GP and acyl-DHAP pathway enzymes during differentiation of 3T3-L1 cells. Two days after confluence, the differentiation in the 3T3-L1 cells was induced (day 0) by including insulin, dexamethasone, and methylisobutylxanthine in the culture media as described (18). Each day from day 0 to 6, the cells were harvested from two to three culture plates and the total particulate fraction of the cells was isolated as described in the text. The activities of the enzymes were determined in the total particulate fraction. The specific activities of the enzymes at day 0 were (nanomole/min/mg protein except for catalase): GPAT, 3.82; DHAPAT (pH 7.5), 0.91; DHAPAT (pH 5.5), 1.22; reductase, 10.1; synthase, 0.76, catalase, 108 units/mg.

**Fig. 3.** The data presented are the averages of at least triplicate determinations with low variations between the individual values (S.D. <1% of the average). A, the particulate fractions obtained from day 6 cultures were preincubated 15 min at 0 °C with different concentrations of inhibitors as shown. Aliquots of the reaction mixtures were assayed for enzymes as described in the text. The concentrations of the inhibitors in the final assay mixtures were 1/20th of that shown in the figure. Circles (○, ●) are for DHAPAT and triangles (△, ▲) are GPAT activity. The filled symbols are for MMTS inhibition and the open symbols for NEM. B, heat stability of DHAPAT (○) and GPAT (●) at 50 °C. See text for details. C, the particulate fraction was treated with trypsin for 10 min at room temperature, the proteolysis was stopped by adding trypsin inhibitor and assayed for enzyme activities (20). Trypsin inhibitor was added to the control (solid bar) before the addition of trypsin (20). Under permeabilizing conditions (presence of Triton X-100), both GPAT and DHAPAT activities were completely destroyed by trypsin (data not shown).
Differentiation of 3T3-L1 preadipocytes can be largely accounted for by an increase in DHAPAT mRNA.

Incorporation of D-[3-3H,U-14C]Glucose into the Glycerol Moiety of Lipids and GP—To investigate the proportion of non-ether lipids formed in these cells via the acyl-DHAP pathway, we measured the incorporation of radioactivity in each carbon of the glycerol moiety of GP and glycerolipids from D-[3-3H,U-14C]glucose. The methods used, the assumptions made, and the calculations involved have been described (25). The tritium and carbon flow pathways from labeled glucose to the glycerol moiety of lipids are summarized in Fig. 6. Briefly, a part of the 3H from the labeled glucose will be transferred via the pentose phosphate pathway to the 4-position of NADPH which is reductant for the acyl-DHAP pathway but not for the GP pathway (Fig. 1). Although NADPH is mainly believed to be formed via malic enzyme in 3T3-L1 cells (6), the pentose phosphate pathway is also present in these cells (35). We found a 3-fold increase in glucose-6-phosphate dehydrogenase activity during differentiation of these cells (data not shown). The major portion of the 3H, however, will be at the C-1 of DHAP (hence also in C-1 of GP) generated from the labeled glucose via glycolysis. This pro-R 3H at C-1 of DHAP is stereospecifically exchanged with the proton of water during the formation of the ether bond (11). From the labeling scheme in Fig. 6, it is evident that the relative amount of 3H present at the C-2 of the glycerol moiety of lipids compared with that of GP (0% formed via the acyl-DHAP pathway) and glycerol ether lipids (100% formed via the acyl-DHAP pathway) will be a measure of the fraction of the lipid formed via the acyl-DHAP pathway. Simultaneous use of [U-14C]glucose normalizes the variable 3H incorporation, so that a comparison of 3H/14C at C-2 will be a measure of the relative rate of incorporation of 3H via NADPH at this carbon.

Both 3H (2–3%) and 14C (4–5%) from the labeled glucose were incorporated into adipocyte lipids. In Table I the distribution of 3H in each carbon of the glycerol moiety of TG, PC, PE, and PE plasmalogens (pPE) is given. Two separate culture dishes were analyzed, and results are presented as the average of three (for GP and TG) or two (for PC, PE, and pPE) determinations. As seen in Table I, compared with GP, relatively more 3H is present in the C-2 of the glycerol moiety of all the lipids. A ratio calculation, assuming 0% of GP and 100% of plasmalogenic glycerol, are synthesized via the

FIG. 4. Fractionation of subcellular organelles of 3T3-L1 cells by Accudenz density gradient centrifugation. The total particulate fractions of day 6 cells were subjected to density gradient centrifugation in a vertical rotor, and 2-ml fractions collected as described in the text. The protein content and the activity of the enzymes in each fraction were determined. The equilibrium density of the microperoxisomes (catalase as the marker enzyme) in this gradient was found to be 1.17 g/ml.

FIG. 5. Northern blot analysis of DHAPAT mRNA during differentiation of preadipocytes and adipocytes. About 20 μg of cellular total RNA per lane was subjected to formaldehyde gel electrophoresis and the RNAs transferred to polyvinylidene difluoride membrane as described (18). Methylene blue staining of the blot indicated that comparatively much less RNA was loaded for the day 2 samples. Duplicate samples of RNA from two different cell cultures for the same day of growth were used to compare the relative amount of the mRNA present in the cells. The position of ribosomal RNAs on the blot are shown.

FIG. 6. Pathways of tritium (T) from D-[3-3H]glucose to the glycerol moiety of lipids.
glycerol are given along with the standard deviations for GP (the glycerol carbon of GP and of different glycerolipids are shown. The average values of the $^{14}$C ratio at the C-2 of the glycerol are given along with the standard deviations for GP ($n = 3$) and TG ($n = 3$). Duplicate values for PC and PE glycerol were within 7% and the values for plasmalogens (pPE) glycerol were within 10% of the average.

<table>
<thead>
<tr>
<th>Position</th>
<th>GP</th>
<th>TG</th>
<th>PC</th>
<th>PE</th>
<th>pPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>99.0%</td>
<td>95.2%</td>
<td>96.4%</td>
<td>97.2%</td>
<td>2.1%a</td>
</tr>
<tr>
<td>C-2</td>
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<td>4.5%</td>
<td>3.4%</td>
<td>2.5%</td>
<td>97.9%</td>
</tr>
<tr>
<td>C-3</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>$^{3}$H/$^{14}$C at C-2</td>
<td>0.05 ± 0.01</td>
<td>0.41 ± 0.06</td>
<td>0.35</td>
<td>0.21%</td>
<td>0.87</td>
</tr>
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a C-1 + C-3.

### DISCUSSION

Both peroxisomal DHAPAT and microsomal GPAT are induced during differentiation of 3T3-L1 cells. A small fraction of the DHAPAT activity might be due to the nonspecific action of GPAT as seen in the initial drop in DHAPAT at low NEM or MMTS concentrations (Fig. 3A). By extrapolating the values in this figure to zero inhibitor, it may be surmised that 10–20% of DHAPAT (4–7% of GPAT) activity is due to GPAT using hydrated DHAP as substrate (11). The increase in the peroxisomal DHAPAT activity is largely due to gene expression, since the amount of DHAPAT mRNA is also increased during differentiation (Fig. 5). This is the first report that along with the induction of lipogenic ER enzymes, peroxisomal lipogenic enzymes are also induced during the conversion of preadipocytes to adipocytes. These findings agree well with the morphological observation that microperoxisomes are induced during differentiation of 3T3-L1 cells (4, and with the reported high DHAPAT activity, highest among all other tissues, in rat adipose tissue (30).

The specific activity of another enzyme of the acyl-DHAP pathway, i.e. acyl/alkyl-DHAP reductase, was also found to increase by 5-fold during differentiation. This reductase is also high in adipose tissue (37). In contrast, the specific activity of the acyl-DHAP synthase, the peroxisomal enzyme catalyzing the ether bond synthesis was found to decrease by 60% in this time period. Considering that the protein content of the cells also increases by 2-fold during this time period (8), the total activity of the synthase per cell appears to remain constant. Coleman and Bell (10) reported about a 2-fold increase in the reductase activity, but could not detect any acyl-DHAP synthase activity in these cells. We found by using two-dimensional reaction thin-layer chromatography (38) that the cellular content of the ether lipid plasmalogens as a fraction of total phospholipids is fairly high which remains almost unchanged (9.3% at day 0 versus 8.1% at day 6) during differentiation.

Confirming reports by others (7–9), we also found a strong induction of GPAT during differentiation of 3T3-L1 cells. Although Jerkins et al. (39) and Ericsson et al. (40) reported a significant increase (up to 8-fold) in mitochondrial GPAT mRNA during differentiation of these cells, we found that most of the induced GPAT seems to be microsomal because very little of it is insensitive to NEM (Fig. 3). Yet et al. (41) found in differentiated cells that the specific activity of the NEM-insensitive mitochondrial GPAT was only 7% of that of microsomal GPAT. Considering that the cellular content of microsomal protein is much more than that of mitochondria (42), it may be concluded that the contribution of mitochondrial GPAT to total GPAT in these cells is negligible. This is also seen in the subcellular fractionation data presented in Fig. 4. The GPAT activity in these fractions followed the microsomal marker enzyme (NADPH-cytochrome c reductase) profile with no enrichment of the GPAT activity in the mitochondrial fractions (marker enzyme succinate-cytochrome c reductase).

It is not obvious why both the microsomal and the peroxisomal pathways are induced during differentiation of these cells. While ER contains the enzymes necessary for conversion of GP to TG or phospholipids, the end product of the peroxisomal pathway, i.e. lysophosphatidate, must be exported to ER for conversion to these lipids (11). It is possible that the lysophosphatidic acid is channeled toward making membrane lipids whereas TG is synthesized via the GP pathway. During differentiation there is an increase in the intracellular membranous organelles such as ER and microperoxisomes (43) and a 2–3-fold increase in activity of the phosphoglyceride biosynthetic enzymes (8). We have estimated the contribution of the acyl-DHAP pathway to the synthesis of non-ether lipids by determining the incorporation of $^{3}$H from $^{3}$[3-3H, U-14C]glucose into C-2 of the glycerolipids (25) and from the relative enrichment of $^{3}$H at this position it is estimated that almost half of the TG is synthesized via acyl-DHAP in these adipocytes (Table I). From these results and from the morphological observations of Novikoff and co-workers (4, 43) that after differentiation the fat droplets in these cells are surrounded by microperoxisomes and ER, it may be surmised that both pathways are utilized for the synthesis of TG. It should be pointed out that carbon flow through the pathways is controlled not only by the activity of the enzymes, but also availability of substrates and cofactors (11). A major difference between these pathways is the requirement of the reduced pyridine nucleotide coenzyme (Fig. 1). In general, the cellular concentration of NADPH is much higher than that of NADH (44), and NADPH synthesis via the malic enzyme in 3T3-L1 cells is highly increased during differentiation (6). Thus the cellular NADPH/NADH ratio probably controls the relative contribution of these two pathways for TG biosynthesis.

Although all three enzymes of the acyl-DHAP pathway are localized on peroxisomal membranes and the acyl-DHAP synthase may be associated with DHAPAT (45), they are regulated independently. The findings that peroxisomal DHAPAT and acyl/alkyl-DHAP reductase, but not the alkyl-DHAP synthase, are induced and that there is no increase in cellular ether lipid content support the conclusion that non-ether lipids are being synthesized in the adipocytes via the acyl-DHAP pathway (Fig. 1). These findings also agree with past results comparing lipid biosynthetic pathways (11) and also with a recent report that an acyl/alkyl reductase deficiency leads to impaired non-ether PC synthesis (46). However, the general consensus is that this peroxisomal pathway is solely for the biosynthesis of ether lipids (13). This assumption is based on the fact that there is a deficiency of ether lipids, but not other glycerolipids, in the tissues of patients suffering from congenital peroxisomal disorders (47), where there is also a deficiency of DHAPAT (48). On the other hand, a complete loss of GPD, in a mutant mouse...
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strain does not affect the animal's physiological functions (49). GPD is also absent in many fast growing tumor cells, but lipid synthesis proceeds in these cells at a high rate (50). It seems that because in mammals there are three routes, i.e. mitochondrial and microsomal GPAT and peroxisomal acyl-DHAP pathways, for the synthesis of cellular lysophosphatidate, the precursor of all non-ether glycerolipids, the impairment of one pathway is compensated for by increased activity of other pathways. Thus, 3T3-L1 adipocytes are a good system to study not only the mechanism of regulation of the peroxisomal pathway by hormones, but also to resolve the question of the physiological role of the peroxisomal lipid biosynthetic pathway.

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