DGAT1 Is Not Essential for Intestinal Triacylglycerol Absorption or Chylomicron Synthesis*

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Dietary triacylglycerols are a major source of energy for animals. The absorption of dietary triacylglycerols involves their hydrolysis to free fatty acids and monoacylglycerols in the intestinal lumen, the uptake of these products into enterocytes, the resynthesis of triacylglycerols, and the incorporation of newly synthesized triacylglycerols into nascent chylomicrons for secretion. In enterocytes, the final step in triacylglycerol synthesis is believed to be catalyzed primarily through the actions of acyl-CoA:diacylglycerol acyltransferase (DGAT) enzymes. In this study, we analyzed intestinal triacylglycerol absorption and chylomicron synthesis and secretion in DGAT1-deficient (Dgat1−/−) mice. Surprisingly, DGAT1 was not essential for quantitative dietary triacylglycerol absorption, even in mice fed a high fat diet, or for the synthesis of chylomicrons. However, Dgat1−/− mice had reduced postabsorptive chylomicronemia (1 h after a high fat challenge) and accumulated neutral lipid droplets in the cytoplasm of enterocytes when chronically fed a high fat diet. These results suggest a reduced rate of triacylglycerol absorption in Dgat1−/− mice. Analysis of intestine from Dgat1−/− mice revealed activity for two other enzymes, DGAT2 and diacylglycerol transacylase, that catalyze triacylglycerol synthesis and apparently help to compensate for the absence of DGAT1. Our findings indicate that multiple mechanisms for triacylglycerol synthesis in the intestine facilitate triacylglycerol absorption.

The absorption of triacylglycerols by the intestine is highly efficient, and more than 95% of dietary triacylglycerols is absorbed, even if the diet is rich in fat. By comparison, only 30–70% of dietary cholesterol is absorbed in most animals (1). The high efficiency of triacylglycerol absorption is likely due to an evolutionary pressure that maximized the ability to absorb rich sources of energy (such as fat) when food sources were scarce.

Intestinal triacylglycerol absorption occurs by a series of steps in which dietary triacylglycerols are first hydrolyzed in the intestinal lumen and then resynthesized within enterocytes. In the lumen, dietary triacylglycerols are hydrolyzed by lipases to generate free fatty acids and monoacylglycerols. These molecules are taken up by enterocytes and then enter the triacylglycerol biosynthesis pathways. The triacylglycerol products are incorporated into nascent chylomicrons, which are subsequently secreted from enterocytes and enter the lymphatic system.

Triacylglycerol biosynthesis in the intestine is believed to occur mainly through the monoacylglycerol pathway. In this pathway, monoacylglycerol and fatty acyl-CoA are covalently joined to form diacylglycerol in a reaction catalyzed by monoacylglycerol acyltransferase (MGAT) (2). Diacylglycerol and fatty acyl-CoA are then used to synthesize triacylglycerol in a reaction catalyzed by acyl-CoA:diacylglycerol acyltransferase (DGAT) enzymes. High levels of DGAT activity are present in the small intestine (3–5), and both known DGAT genes, Dgat1 and Dgat2, are expressed in this tissue (6, 7). In addition, a fatty acyl moiety from one diacylglycerol can be transferred to a second diacylglycerol to synthesize triacylglycerol in a reaction catalyzed by diacylglycerol transacylase. This activity has been reported in rat small intestine (8). The relative contributions of DGAT1, DGAT2, and diacylglycerol transacylase in intestinal triacylglycerol synthesis and absorption are unknown.

To investigate the biological functions of DGAT1, we generated DGAT1-deficient (Dgat1−/−) mice (9). These mice are viable and healthy, in part because they can synthesize triacylglycerols through alternative mechanisms. However, they have reduced body triacylglycerol content and are resistant to obesity through a mechanism involving increased energy expenditure (9). Surprisingly, despite a marked reduction in DGAT activity in Dgat1−/− intestine (9), we found no evidence of overt fat malabsorption in the initial characterization of Dgat1−/− mice.

In this study, we used Dgat1−/− mice to further define the function of DGAT1 in the intestine. We sought to determine

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**The abbreviations used are: MGAT, monoacylglycerol acyltransferase; DGAT, acyl-CoA:diacylglycerol acyltransferase; BMIPP, 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid.
whether DGAT1 deficiency alters triacylglycerol metabolism in enterocytes and whether Dgat1−/− mice can synthesize chylomicron-sized lipoprotein particles. We also investigated the relative contributions of DGAT1, DGAT2, and diacylglycerol transacylase in intestinal triacylglycerol synthesis and absorption.

**EXPERIMENTAL PROCEDURES**

**Mice and Diets—**Dgat1−/− mice in a C57BL/6J background were generated and genotyped as described (9). Wild-type (Dgat1+/−) mice in a C57BL/6J background were from the Jackson Laboratory (Bar Harbor, ME). All mice were housed in a pathogen-free barrier facility (12-h light/12-h dark cycle) and fed either rodent chow containing 4.5% fat (Picolab 20, Ralston-Purina, St. Louis, MO), a synthetic, high milk fat diet containing 20% (w:w) anhydrous milk fat and 0.15% cholesterol (Harlan Teklad, Madison, WI) or a synthetic, high corn oil diet containing 20% (w:w) corn oil and 0.15% cholesterol (Harlan Teklad).

**Dietary Fat Absorption—** Dietary fat absorption was measured by a modification of a fecal isotope ratio method used to measure cholesterol absorption (10, 11). In brief, [14C]oleic acid (25 μCi) (Amersham Biosciences) and [5,6-3H]stearin (10 μCi) (American Radiolabeled Chemicals, St. Louis, MO), a nonabsorbed standard, in 15 ml of safflower oil were administered intragastrically to nonfasted mice by gavage. Feces were then collected for 5 days, and the ratio of 14C to 3H radioactivity in aliquots of fecal extracts was used to calculate the percent dietary fat absorption.

**Intestinal Gene Expression—** Intestines from nonfasted wild-type mice were divided into five sections of equal length (section 1 most proximal and section 5 most distal to the stomach). Total RNA was extracted from intestinal mucosa with RNA STAT60 (Tel-Test, Friendswood, TX), and equivalent amounts of RNA were pooled from four mice.

**Postabsorptive Plasma Analyses—** Plasma triacylglycerols were measured with a modification of a fecal isotope ratio method used to measure cholesterol absorption (10, 11). In brief, [14C]oleic acid (25 μCi) (Amersham Biosciences) and [5,6-3H]stearin (10 μCi) (American Radiolabeled Chemicals, St. Louis, MO), a nonabsorbed standard, in 15 ml of safflower oil were administered intragastrically to nonfasted mice by gavage. Blood samples were then collected for 5 days, and the ratio of 14C to 3H radioactivity in aliquots of blood samples was used to calculate the percent dietary fat absorption.

**In Situ Hybridization—** In situ hybridization was performed as described (12). Briefly, brief sections from wild-type mice were deparaffinized and fixed in 4% paraformaldehyde. After protease K digestion, the sections were hybridized at 55 °C for 12 h with 32P-labeled cDNA probes for Dgat1 and Dgat2. Membranes were reprobed for actin to normalize for sample loading differences, and signals were quantified with a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).

**Histology and Ultrastructure—** Tissues were fixed by cardiac perfusion with 1.5% glutaraldehyde, 4% polyvinylpyrrolidone, 0.05% calcium chloride, and 0.1 M sodium cacodylate, pH 7.4. Intestines were removed, divided into sections representing duodenum, jejunum, and ileum and put directly into fixative. For light microscopy, tissues were immersed in 2% osmium tetroxide in 0.1 M sodium phosphate, pH 7.4. Intestines were then dehydrated, dipped in photographic emulsion NTB2 (Eastman Kodak), and stored at 4 °C. After 8 weeks of exposure, the sections were developed and counterstained with hematoxylin and eosin.

**Dgat1 and Triacylglycerol Absorption**

**Postabsorptive Plasma Analyses—** A bolus of lipid (100 μl of corn oil) was administered intragastrically to fasted (4 h) mice by gavage. Blood samples were obtained from the tail before and 1 h after [125I]BMIPP administration. [125I]BMIPP radioactivity was measured with a γ counter.

**Histology and Ultrastructure—** Tissues were fixed by cardiac perfusion with 1.5% glutaraldehyde, 4% polyvinylpyrrolidone, 0.05% calcium chloride, and 0.1 M sodium cacodylate, pH 7.4. Intestines were removed, divided into sections representing duodenum, jejunum, and ileum and put directly into fixative. For light microscopy, tissues were immersed in 2% osmium tetroxide in 0.1 M sodium phosphate, pH 7.4, to stain neutral lipids. Tissues were then dehydrated in ethanol, transitioned into propylene oxide, and embedded in Epon 812 (DuPont, Wilmington, DE). Sections were counterstained in toluidine blue. For electron microscopy, the tissues were stained for lipid by the imidazole-buffered osmium tetroxide procedure (17), stained en bloc in 2% aqueous uranyl acetate at 1 h at 4 °C, and embedded in Epon 812. Ultrathin sections were stained for 5 min with 0.8% lead citrate and photographed with an electron microscope (Siemens Elmiskop 101, Siemens/CTI Corp., Knoxville, TN).

**Tissue Lipid Analyses—** Intestines were divided into five equal sections, and homogenates from section 2 as described above were prepared. Lipids were extracted from homogenates (250 μg of protein) with chloroform:methanol (2:1 v:v), dried under nitrogen, and separated by thin-layer chromatography (TLC) in hexane:ethyl ether:acetic acid (80:20:1 v:v:v). Lipids were visualized by immersing the TLC plate in a solution of cupric sulfate (10%) and phosphoric acid (8%) followed by heating at 180 °C for 15 min. The triacylglycerol and diacylglycerol bands were quantified by densitometry.

**Enzyme Activity Assays—** DGAT and diacylglycerol transacylase activities were measured in tissue homogenates (40–50 μg of protein) under apparent Vmax conditions as described (6, 8), except that diacylglycerol was added in an aceton solution (18). In brief, DGAT assays measured the incorporation of [14C]oleoyl-CoA (specific activity: ~20,000 dpm/μmol) into triacylglycerols in a 5-min assay. The reaction mixture contained 0.4 mM diacylglycerol and 25 μM oleoyl-CoA as substrates and 5 mM MgCl2. Diacylglycerol transacylase assays measured the incorporation of [14C]diacylglycerol (specific activity: 20 μCi/μmol) by intragastric tube with an intubation needle. Blood samples were obtained from the tail before and 1 h after [125I]BMIPP administration. [125I]BMIPP radioactivity was measured with a γ counter.

**FIG. 1. DGAT1 gene expression in mouse small intestine.** A, Dgat1 mRNA (2.0-kb transcript) is present in all regions of the small intestine. RNA samples from five equal-length sections of small intestine were analyzed by Northern blotting (section 1 most proximal and section 5 most distal to the stomach). B, in situ hybridization demonstrating expression of Dgat1 mRNA in the intestinal villi (top panel). Specific hybridization was not detected by a sense probe control (bottom panel).
These results all indicate that DGAT1 is not essential for the quantitative absorption of dietary fat.

**Diminished Chylomicronemia after an Acute Dietary Lipid Challenge**—Plasma triacylglycerol concentrations after a 4-h fast were similar in wild-type and Dgat1−/− mice (Fig. 2A), as reported previously (9). However, 1 h after the intragastric administration of a bolus of corn oil plasma triacylglycerol concentrations increased in wild-type mice but not in Dgat1−/− mice (Fig. 2A). This difference was attributable to differences in the amount of plasma chylomicrons, as demonstrated by analyzing plasma by ultracentrifugation (Fig. 2B) and agarose gel electrophoresis (Fig. 2C). Lipid staining in the chylomicron region of agarose gels was ~60% lower in Dgat1−/− mice than in wild-type mice (Fig. 2D). In addition, 1 h after intragastric administration, plasma levels of BMIPP, a 3-methyl-branched fatty acid analog that is only slowly catabolized by β-oxidation (16), were 75% lower in Dgat1−/− mice than in wild-type mice (Fig. 2E). Retinol palmitate absorption, an indicator of chylomicron synthesis and secretion (14), was also ~50% lower in Dgat1−/− mice than in wild-type mice 2 h after administration (Fig. 2F). These results indicate that Dgat1−/− mice have reduced postabsorptive chylomicronemia in response to an acute lipid challenge.

**Abnormal Accumulation of Neutral-lipid Droplets in the Cytosol of Enterocytes in Dgat1−/− Mice**—To better understand how DGAT1 deficiency affects lipid metabolism in enterocytes, we examined histological sections from the small intestines of wild-type and Dgat1−/− mice chronically fed a diet rich in milk fat or corn oil, the enterocytes in the duodenum and jejunum had large, neutral lipid-staining droplets in the cytoplasm of Enterocytes in Dgat1−/− mice.
The cyto- and Golgi apparatus (Figs. 5 and 6). In addition, some enterocytes from Dgat1−/− mice had a single, large, supranuclear lipid droplet in their cytoplasm (often several microns in diameter), whereas wild-type mice did not (Fig. 5).

**Alternative Mechanisms for Triacylglycerol Synthesis in the Small Intestine of Dgat1−/− Mice**

In mice fed a diet rich in milk fat and analyzed the intestinal DGAT activity levels (presumably reflecting DGAT2 activity) in all sections were ~10–15% of the levels in wild-type mice.

We were unable to examine DGAT1 and DGAT2 protein levels due to the lack of suitable antibodies. However, we measured DGAT activity in homogenates from intestinal segments of wild-type and Dgat1−/− mice using assay conditions (5 mM MgCl₂ in the assay mix) that detect both DGAT1 and DGAT2 activities (7). DGAT activity levels in wild-type intestines were highest in the proximal sections and were ~50% lower in the most distal section (Fig. 7B). In Dgat1−/− intestines, DGAT activity levels (presumably reflecting DGAT2 activity) in all sections were ~10–15% of the levels in wild-type mice.

An additional acyl-CoA-independent mechanism for synthesizing triacylglycerol from diacylglycerol may involve diacylglycerol transacylase (8). In wild-type mice, we found diacylglycerol transacylase activity in homogenates at high levels along the length of the intestine, with 2-fold higher activity levels in the most proximal section than in other sections (Fig. 7C). Dgat1−/− mice had similar levels of diacylglycerol transacylase activity.

**DISCUSSION**

DGAT1 is highly expressed in the small intestine, where it is believed to function in triacylglycerol synthesis and absorption. In this study, we analyzed intestinal triacylglycerol absorption and the ability to synthesize chylomicron-sized lipoprotein particles in Dgat1−/− mice. DGAT1 was not essential for quantitative dietary triacylglycerol absorption or for chylomicron synthesis. However, Dgat1−/− mice had reduced postabsorptive chylomicronemia and accumulated neutral-lipid droplets in the cytoplasm of enterocytes when chronically fed a high fat diet, suggesting a reduced rate of triacylglycerol absorption. At least two other enzymes, DGAT2 and diacylglycerol transacylase, appear to catalyze triacylglycerol synthesis in mouse intestine and help to compensate for the absence of DGAT1.

DGAT activity is present along the length of the small intestine, with the highest levels in the proximal region (3, 4). We found that the Dgat1 mRNA expression pattern in the small intestine was similar to that of DGAT activity and that DGAT1 appears to account for the majority of intestinal DGAT activity as measured by in vitro assays. Dgat1 mRNA was present at high levels in intestinal villus tips, consistent with reports of higher levels of DGAT activity in villus tips than in crypt cells (4). Dgat2 mRNA expression was also higher in proximal than in distal segments of the small intestine.

Although DGAT1 was not essential for quantitative dietary triacylglycerol absorption, DGAT1 deficiency had significant effects on intestinal triacylglycerol metabolism when the dietary load of fat was high. For example, Dgat1−/− mice had reduced postabsorptive chylomicronemia after the administra-
tion of a bolus of dietary triacylglycerol. In addition, lipid droplets accumulated in Dgat1−/− mice when the mice were chronically fed a high fat diet. These data suggest that the capacity for residual triacylglycerol synthesis in the absence of DGAT1 is adequate when dietary fat levels are low but is overwhelmed by high levels of dietary fat. As a result, movement of fat through the enterocyte is delayed, reducing the rate at which chylomicrons enter the plasma. The precise role of DGAT1 in this process remains unknown. Although enterocytes normally do not store large amounts of lipid in their cytoplasm, newly synthesized triacylglycerol may first have to enter a storage pool before subsequent hydrolysis and resynthesis for chylomicron assembly (19). DGAT1 may help synthesize triacylglycerol for a specific step in this sequence, and the absence of DGAT1 may therefore decrease throughput. A better understanding of the enzymes involved in triacylglycerol synthesis and their cellular location in enterocytes will be needed to determine the precise function of DGAT1. Nevertheless, our data indicate that DGAT1 is not directly required for the assembly of triacylglycerol-rich, chylomicron-sized particles.

**FIG. 4.** Accumulation of triacylglycerol and diacylglycerol in the small intestine of Dgat1−/− mice fed a high milk fat diet for 3 weeks. A, small intestines from wild-type and Dgat1−/− mice were divided into five equal-length sections, and homogenates were prepared from section 2. Lipids were extracted and separated by TLC. B, triacylglycerol and diacylglycerol bands were quantified by densitometry, and results were normalized for the protein content of the samples. *, p = 0.0495 versus wild-type, n = 3 mice of each genotype.

**FIG. 5.** Ultrastructural analysis of Dgat1−/− enterocytes. Low power electron micrographs (×6200) show a single, large neutral-lipid droplet (LD) in the cytoplasm typically above the Golgi apparatus (G) and nucleus (N) of some Dgat1−/− (B) but not wild-type enterocytes (A) from the duodenum of mice fed a diet rich in corn oil for 3 weeks. Chylomicron-sized particles are present in the Golgi apparatus of both wild-type and Dgat1−/− mice.

**FIG. 6.** Chylomicron-sized particles in Dgat1−/− enterocytes. Higher power electron micrographs (×19,000) show the presence of chylomicron-sized particles within the endoplasmic reticulum cisternae (open arrows), within membrane compartments of the Golgi apparatus (G) (arrowheads), and sometimes clustered in secretory vesicles (arrows) of both wild-type (A) and Dgat1−/− enterocytes (B) from the duodenum of mice fed a diet rich in corn oil for 3 weeks.
The histologic examination of Dgat1<−/−> intestines also revealed that feeding a diet rich in saturated fat to Dgat1<−/−> mice resulted in a greater accumulation of lipid droplets in the intestine than a diet rich in polyunsaturated fatty acids. This suggests that saturated fatty acids may be better substrates than polyunsaturated fatty acids for DGAT1. However, in vitro studies in insect cells demonstrated that fatty acids of different saturation and chain length are used equally well as substrates by DGAT1 and DGAT2 (7). Regardless, the data suggest that saturated fatty acids enter a chylomicron synthesis pathway in enterocytes that is relatively specific for DGAT1.

Our results indicate that at least two enzymes, DGAT2 and diacylglycerol transacylase, contribute to triacylglycerol synthesis in the absence of DGAT1. The relative importance of DGAT2 is currently unclear. Although Dgat2 was expressed throughout the small intestine, residual DGAT activity was low (~10–15%) in Dgat1<−/−> intestines. We suspect that the in vitro assay measurements of DGAT2 activity may underestimate the contribution of DGAT2 to intestinal triacylglycerol synthesis. This possibility is illustrated by studies of Dgat1<−/−> adipocytes, which accumulate triacylglycerols to levels ~50% of those in wild-type mice even though DGAT activity is virtually absent in Dgat1<−/−> adipose tissue membranes (7). The high levels of diacylglycerol transacylase activity indicate that this enzyme may also play a prominent role in triacylglycerol synthesis in mouse intestine. Defining the relative roles of DGAT2 and diacylglycerol transacylase in intestinal triacylglycerol synthesis and absorption is an important issue for future research.

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Our results illustrate the remarkable capacity of the small intestine to absorb dietary triacylglycerols, even in the absence of a key enzyme. Cytosolic lipid droplets were prominent in the duodenum and jejunum but not in the ileum of Dgat1<−/−> mice fed a high fat diet, suggesting that compensatory mechanisms were sufficient to prevent dietary fat from reaching the large intestine. The excess capacity for triacylglycerol absorption probably involves redundant mechanisms for synthesizing triacylglycerols and the great length and surface area of the small intestine. Indeed, the ileum can fully compensate to facilitate triacylglycerol absorption in the absence of the jejenum (20). The high efficiency and capacity for triacylglycerol absorption in the small intestine may reflect an evolutionary pressure to maximize the absorption of energy-rich fat during times of starvation.
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