Reduced intestinal fat absorptive capacity but enhanced susceptibility to diet-induced fatty liver in mice heterozygous for ApoB38.9 truncation

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Lin, Xiaobo, Pin Yue, Yan Xie, Nicholas O. Davidson, Nobuhiro Sakata, Richard E. Ostlund, Jr., Zhouji Chen, and Gustav Schonfeld. Reduced intestinal fat absorptive capacity but enhanced susceptibility to diet-induced fatty liver in mice heterozygous for ApoB38.9 truncation. Am J Physiol Gastrointest Liver Physiol 289: G146–G152, 2005. First published March 24, 2005; doi:10.1152/ajpgi.00309.2004.—Fatty liver is prevalent in apolipoprotein B (apoB)-defective familial hypobetalipoproteinemia (FHBH). Similar to humans, mouse models of FHBH produced by gene targeting (apoBapob27.6/H11001) manifest low plasma cholesterol and increased hepatic triglycerides (TG) even on a chow diet due to impaired hepatic VLDL-TG secretory capacity. Because apoB truncations shorter than apoB48 are expressed in the intestine, we examined whether FHBL mice may have limited capacity for intestinal dietary TG absorption. In addition, we investigated whether FHBL mice are more susceptible to diet-induced hepatic TG accumulation. Fat absorption capacity was impaired in apoB38.9 mice in a dose-dependent manner. Relative fractional fat absorption coefficients for apoBapob/H11001, apoBapobapob27.6/H11001, and apoBapobapob27.6/H11001 were 1.00, 0.96, and 0.71, respectively. To raise hepatic TG, we fed high-fat (HF) and low-fat (LF) pellets. Hepatic TG level was observed in rank order: HF > LF > chow. On both LF and HF, liver TG level was higher in the apoBapob27.6/H11001 than in apoBapob/H11001. Hepatic TG secretion remained impaired in the apoBapob/H11001 on the HF diet. Thus the FHBL mice are more susceptible to diet-induced fatty liver despite relatively reduced intestinal TG absorption capacity on a HF diet.

Familial hypobetalipoproteinemia; dietary fat; intestinal fat absorption; fatty liver; animal model

FATTY LIVER IS HIGHLY PREVALENT in the US and most other Western societies and may lead to steatohepatitis, cirrhosis, and end-stage liver disease (3, 23, 38). The majority of patients with nonalcoholic fatty liver are those with obesity, insulin resistance, and/or type 2 diabetes mellitus, i.e., various aspects of the metabolic syndrome or syndrome X (24, 33). Neither the initiating etiologies nor the factors causing the progression of fatty liver have been identified at the molecular level (12).

Familial hypobetalipoproteinemia (FHBH) is an autosomal codominant disorder characterized by low levels (<5th percentile) of plasma apolipoprotein B (apoB), LDL cholesterol (22, 30), and fatty liver. ApoB is required for exporting lipids from the liver in VLDL and from the intestine in chylomicrons (8, 42). The normal variants of apoB in humans are apoB100, which is secreted by the liver, and apoB48, which is secreted by the small intestine as a result of posttranscriptional RNA editing of the nuclear apoB mRNA (2, 28). ApoB mRNA editing also occurs in the mouse liver, which secretes both apoB100 and apoB48 (15, 16).

A subset of subjects with FHBL is characterized by a variety of premature stop codon-producing mutations of the apoB gene (apoB) that produce apoB truncations ranging in size from apoB2 to apoB89 (22, 30, 42). In humans heterozygous for apoB-defective FHBL, the hepatic secretion rate of apoB100 averages ~25% of normal, instead of the 50% expected from one normally functioning allele (1, 13, 39). The truncated variants of apoB, particularly those shorter than apoB48, have reduced capacities to assemble hepatic triglycerides (TG) into VLDL particles. As a result of these dual defects, VLDL export is impaired, rendering FHBL subjects susceptible to the accumulation of fat in the liver (7, 29, 31, 37).

In addition to being expressed in the liver, apoB truncations shorter than apoB48 also are expressed in the small intestine (19), and as noted, some apoB-defective humans may have diarrhea, especially following a high fat meal, implying defective fat absorption (37). Results from our own laboratory show normal fat absorption in FHBL subjects heterozygous for various apoB mutations shorter than apoB48 (4). However, potential differences in lipid transport capability among the various apoB truncations might have caused larger variability in the fat absorption indexes, which, in turn, might have masked the difference in fat absorption between the controls and the heterozygotes.

Recently, we have generated an FHBL mouse model carrying an apoB38.9-specifying mutation using gene-targeting in embryonic stem cells and the Cre-loxp system to remove any exogenous DNA (9). The heterozygous mice (apoBapobapob27.6/H11001) eating a mouse chow manifest the low plasma cholesterol and apoB phenotype. In addition, the livers of these mice, on average, contain 1.5- to 2-fold increased amounts of TG compared with the apoBapob/H11001. We also have reported on a second mouse model of FHBL heterozygous for the apoB27.6 mutation (apoBapobapob27.6/H11001) (11). The apoBapobapob27.6 mice on average have more severe fatty liver than the apoBapobapob27.6 mice and have lower levels of plasma total, LDL, and HDL cholesterol probably because the apoB27.6 protein has a lower capacity to assemble VLDL than the apoB38.9 (11). Hepatic fatty acid synthesis is downregulated (probably as a feedback mechanism) in the apoBapobapob27.6 (20) and in the apoBapobapob27.6 mice (unpublished observation), limiting the accumulation of TG in the liver. The downregulation is mediated by reduced mRNA levels of fatty acid synthase (FAS) and sterol-regulatory element binding protein 1c, the factor that activates the transcrip-

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tion of various lipogenic enzyme genes (18, 34). Because of these complexities, it is difficult in these FHBL mice to predict the quantitative magnitude of response of liver TG to diets that tend to raise liver TG content.

Diets high in fat, in particular saturated fat, may cause increases in hepatic TG, resulting from the delivery of excess fatty acids to the liver, even in livers with normal VLDL export (26). Diets high in carbohydrates, particularly simple sugars, enhance hepatic lipogenesis resulting in increased levels of hepatic TG and hypertriglyceridemia (32). The VLDL system adapts to increased needs for export 1) by producing more VLDL particles and 2) by packaging more TG molecules into each VLDL particle (17, 40), resulting in enhanced hepatic TG export. The liver may also increase the oxidation of fatty acids.

In the present study, we have examined two hypotheses: 1) that the capacities of the apoB38.9 mice to absorb dietary fat were impaired, 2) that the apoB<sup>+/38.9</sup> mice would accumulate more hepatic TG in response to liver TG-raising diets than the apoB<sup>+/+</sup>. The results support our hypotheses and provide a rationale for testing diet responsiveness in humans with apoB-defective FHBL, in an attempt to control hepatic fat accumulation.

MATERIALS AND METHODS

Mice. Apob<sup>+/38.9</sup> mice were generated using gene targeting in embryonic stem cells (9). All mice have a mixed genetic background of ~50% 129/SVJ and 50% C57BL/6J. Mice were housed in a pathogen-free barrier facility with a 12:12-h light-dark cycle (6:00 AM to 6:00 PM). Food was removed in the beginning of the light cycle, and mice were fasted for 4 h before death, except in the in vivo intestinal TG secretion and intestinal mucosal TG determination experiments, in which food was removed on the day before the experiment for an overnight fasting. All animal procedures were performed in accordance with guidelines of Washington University’s Animal Studies Committee.

Fat balance study. Mice were kept on the chow or high-fat (HF) diet. Three weeks after mice started receiving the experimental diets, food intake was recorded and feces were collected for 3 days. Lipids were extracted from ~1.0 g of dried chow, HF diet, or fecal powder by the Folch method (14). Fat absorption coefficients were determined gravimetrically and expressed relative to that of the apoB<sup>+/+</sup> control.

Determination of intestinal TG secretion rate in vivo and intestinal mucosal TG level after a bolus challenge. The proximal one-half of the small intestine was cut open, washed in cold PBS, weighed, cut into pieces that were then frozen in liquid nitrogen, and stored at -80°C until further analysis.

Hepatic TG production was measured after intravenous injection of Triton WR-1339 (500 mg/kg body wt) on mice fasted for 4 h (9). Tail vein blood samples were taken at the specified times after injection for TG measurement and measured as described above.

Hepatic TG assay. Lipid extraction, protein content, and TG determination were performed as described above. Hepatic TG content is expressed as milligrams of TG per gram of protein.

Quantitative real-time RT-PCR. Total RNA from livers of the apoB<sup>+/+</sup> or apoB<sup>+/38.9</sup> was isolated (20). Each individual RNA sample was treated with RNAse-free DNase (Promega) to avoid genomic DNA contamination. Levels of FAS and stearoyl-CoA desaturase 1 (SCD-1) mRNAs were quantified from the treated individual total RNA by fluorescence RT-PCR using SYBR Green dye (20). The proximal one-half of the small intestine was cut open, washed in cold PBS, weighed, cut into pieces that were then frozen in liquid nitrogen, and stored at -80°C until further analysis.

Primer sequences used for the amplification of FAS and SCD-1 mRNAs were: forward primer, 5'-AGGGTCCGGGACATC-3', backward primer, 5'-CTAACCCTAACGCCTTGTTC-3'. Statistical analyses. Statistical analyses were conducted using SAS (V8.2, SAS Institute, Cary, NC). Interactions among genotypes, genders, and diets were analyzed using PROC GLM. Comparisons among means of treatments were done using Duncan’s multiple tests or two-sample t-tests whenever it was appropriate. Diet-induced

### Table 1. Diet composition

<table>
<thead>
<tr>
<th>Nutrient composition</th>
<th>HF</th>
<th>LF</th>
<th>Chow</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFV, kcal/g</td>
<td>4.09</td>
<td>3.24</td>
<td>3.34</td>
</tr>
<tr>
<td>Protein</td>
<td>22.9</td>
<td>29.8</td>
<td>23.6</td>
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<tr>
<td>Fat</td>
<td>41.9</td>
<td>7.0</td>
<td>11.9</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>35.2</td>
<td>65.2</td>
<td>64.5</td>
</tr>
<tr>
<td>PFV, % by calories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>23.4</td>
<td>24.1</td>
<td>20.0</td>
</tr>
<tr>
<td>Fat</td>
<td>19.0</td>
<td>2.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>9.42</td>
<td>0.74</td>
<td>0.84</td>
</tr>
<tr>
<td>MUFA</td>
<td>7.92</td>
<td>0.79</td>
<td>1.04</td>
</tr>
<tr>
<td>PUFA</td>
<td>1.66</td>
<td>1.07</td>
<td>2.62</td>
</tr>
<tr>
<td>PFV, % by weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>36.0</td>
<td>51.1</td>
<td>54.8</td>
</tr>
<tr>
<td>Fat</td>
<td>26.72</td>
<td>35.60</td>
<td>32.10</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.10</td>
<td>0.24</td>
<td>0.20</td>
</tr>
<tr>
<td>Fruuctose</td>
<td>0.14</td>
<td>0.31</td>
<td>0.25</td>
</tr>
<tr>
<td>Sucrose</td>
<td>4.04</td>
<td>3.68</td>
<td>3.14</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.67</td>
<td>2.01</td>
<td>1.11</td>
</tr>
<tr>
<td>Fiber</td>
<td>4.70</td>
<td>5.30</td>
<td>4.70</td>
</tr>
</tbody>
</table>

Diets were pelleted. Diet composition was provided by the manufacturer. Feeding groups of mice are designated as chow, HF, and LF. The apoB<sup>+/38.9</sup> mice and apoB<sup>+/+</sup> controls were divided into three diet groups: 1) chow, 2) LF, and 3) HF. Body weight was recorded biweekly.

Mice were killed following 10 wk of feeding. Livers were excised, washed in cold PBS, weighed, cut into pieces that were then frozen in liquid nitrogen, and stored at -80°C until further analysis.

Hepatic TG production in apoB<sup>+/38.9</sup> mice on the HF diet. Control and the apoB<sup>+/38.9</sup> mice were maintained on the HF diet for 5 wk. Hepatic TG production was measured after intravenous injection of Triton WR-1339 (500 mg/kg body wt) on mice fasted for 4 h (9). Tail vein blood samples were taken at the specified times after injection for TG measurement and measured as described above.

Hepatic TG assay. Lipid extraction, protein content, and TG determination were performed as described above. Hepatic TG content is expressed as milligrams of TG per gram of protein.

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Statistical analyses. Statistical analyses were conducted using SAS (V8.2, SAS Institute, Cary, NC). Interactions among genotypes, genders, and diets were analyzed using PROC GLM. Comparisons among means of treatments were done using Duncan’s multiple tests or two-sample t-tests whenever it was appropriate. Diet-induced
differences in liver TG (ΔTG) by genotypes were compared using t-test assuming equal variances and adjusted numbers of degree of freedom (36). Data are expressed as means (SD). Differences between treatment means were designated as being significantly different if P < 0.05 (or otherwise as indicated).

RESULTS

Dietary intakes and body weights. In the chronic feeding study, mean starting ages and body weights of the comparison groups were similar (Table 2). Food intakes also were similar (means ~4 g/day). Rates of weight gain were alike among the six dietary genotypic groups (Table 2).

Fat balance. Relative fractional fat absorption was similar among the apob+/+, apob+38.9, and apob38.9/38.9 mice when fed the chow (Fig. 1A). However, relative fractional fat absorption was significantly lower in the apob+38.9 and apob38.9/38.9 mice compared with their wild-type controls when fed the HF diet (Fig. 1B). A further 25% reduction in relative fractional fat absorption was seen in apob38.9/38.9 compared with apob+38.9 on the HF diet.

Intestinal TG secretion rates and intestinal mucosal TG levels. The increase over the baseline value in serum TG after gavage of the lipid emulsion was in the following order at 2 and 3 h: apob+-/+ > apob+38.9 > apob38.9/38.9. At 1 h, the increase in serum TG was significantly higher in the apob+-/+ than those in the apob+38.9 or apob38.9/38.9 (Fig. 2A). In a separate experiment, apob+38.9 and apob+-/+ mice were fasted for 15 h and then injected with Triton WR-1339 but without gavage of lipid emulsion. Plasma TG levels, mainly reflecting hepatic origin, were similar at 2 h after Triton injection (450 ± 70 mg/dl for apob+-/+ and 465 ± 63.6 for apob+38.9). Similar plasma TG levels between these two genotypes also were observed for the rest of experimental time points (data not shown). When these TG levels were subtracted from analogous TG levels of animals given an oral fat load, the differences reflected the contributions of intestinal absorption. These differences remained statistically significant between the two genotypes at the respective time points. These results indicate that intestinal lipoprotein secretion, in response to an acute bolus challenge, is impaired in the setting of this apoB truncation.

The mucosal TG level measured after administration of the lipid emulsion (no Triton WR-01399 given) was significantly higher in the apob+38.9 than in the apob+-/+ (Fig. 2B). The increase in the mucosal TG level in the apob+38.9 mice suggests normal uptake and/or digestion of dietary TG in the heterozygotes, with a delay in the TG secretory step.

Effects of dietary perturbations on hepatic TG levels and production rates. Both HF and LF diets significantly increased liver TG in the apob+38.9 (Table 3). Compared with the chow, the LF diet had smaller effects. Only the HF diet increased hepatic TG in apob+-/+ (see “ΔTG by diets”). Of greatest interest, diet-induced rises in liver TG were greater in the apob+38.9 mice than in the controls (see “ΔTG by genotypes”). Hepatic TG production in the apob+38.9 mice on the HF diet was significantly lower than that of the apob+-/+ mice (Fig. 3). Two hours after Triton injection, the increase in serum TG level was 30% lower in the apob+38.9 than in the apob+-/+.
were significantly higher in the \( apob^{+/+} \) relative to \( apob^{+/38.9} \). The HF diet significantly reduced mRNA levels of both transcripts only in the \( apob^{+/+} \) but not in the \( apob^{+/38.9} \).

**DISCUSSION**

**Impaired intestinal lipid absorption.** ApoB variants shorter than apoB48 (i.e., apoB27.6 and apoB38.9) are produced and secreted from the liver (9, 11). In addition, truncations shorter than apoB48 also are produced in the intestine (19). The fat-balance study, reflecting intestinal fat digestion and enteroocyte uptake of dietary TG, demonstrated similar fat absorption coefficients among apoB38.9 heterozygotes, homozygotes, and wild-type controls, when all were fed the chow diet (Fig. 1A). This suggests that the capacity for intraluminal fat digestion and fat uptake into enterocytes may be sufficient even in the homozygotes, when low amounts of fat are ingested from the chow. However, when fed the HF diet, both the \( apob^{+/38.9} \) and \( apob^{38.9/38.9} \) mice showed reduced fractional fat absorption (Fig. 1B), albeit the reduction was minimal in the heterozygotes.

By contrast, intestinal TG secretion rates, measured in Triton WR-1339 pretreated mice gavaged with a lipid emulsion and reflecting the rates of chylomicron secretion by enterocytes and their entry into the circulation, were significantly decreased in the heterozygotes and even more so in the homozygotes (Fig. 2A). In addition, more intestinal mucosal TG was accumulated in the \( apob^{+/38.9} \) than in the controls in response to an oral fat overload (Fig. 2B). These findings suggest near-normal digestion of dietary TG and uptake into the enterocytes of the heterozygotes but impaired intestinal lipoprotein secretion in response to the acute bolus challenge. Both enterocyte uptake and secretion of dietary, intestinal TG appeared to be impaired in the homozygotes, resembling the physiological impairment seen in abetalipoproteinemia (5). One adaptation to the defective intestinal fat absorption may involve the recruitment of additional segments of the small intestine. To the extent that this occurred, it was clearly insufficient to compensate for the apoB defect in the apoB38.9-defective animals.

Vitamin A oral fat-loading test shows normal fat absorption in FHBL subjects heterozygous for apoB mutations smaller than apoB48 (4). However, the FHBL group consisted of subjects with various apoB truncations. Larger variability in fat absorption indexes in the heterozygotes, probably due to subtle differences among the various lengths of truncated apoB, weakened statistical power in that study. In fact, the apoB31 heterozygote vomited on two occasions 12–14 h after eating the test meal, suggesting possible reduced dietary fat tolerance (4). In light of results from the present study, further investigation on fat absorption in FHBL subjects with well-defined apoB truncations is warranted.

**Diet effects on hepatic TG accumulation.** In the most common variety of fatty liver, obesity and insulin resistance somehow stimulate the hepatic synthesis of fatty acids sufficiently to overcome the adaptive capacities of the liver, resulting in the accumulation of hepatic TG (35). By contrast, fatty liver in the apoB-defective FHBL results from the limited capacities for lipid transport of the truncated apoB (9, 11) and from the secretion of less-than-expected amounts of apoB100 (25–30% normal rates rather than the expected 50% based on 1 functioning apoB100 allele) (1, 10, 13, 39). We tested the hypoth...
esis that the apoB defects render the livers of FHBL mice more susceptible to dietary perturbation than the livers of controls. Direct testing was necessary because it would have been difficult to predict the results, because the liver seems to adapt to increased loads of TG. For example, the apoB mutation-induced accumulations of liver TG are accompanied by lower rates of endogenous hepatic fatty acid synthesis, mediated by the downregulation of hepatic FAS and SCD-1 (20). The $apoB^{+/38.9}$ mice accumulated additional hepatic TG on the LF diet when compared with the chow-fed group (Table 3). The $apoB^{+/38.9}$ mice accumulated even more hepatic TG on the HF diet compared with the chow-fed group (Table 3). In addition, the apoB-defective mice achieved higher hepatic TG levels than the $apoB^{-/-}$, and the diet-induced rises ($\Delta$TG) were greater in the apoB38.9 mice than in the controls (Table 3).

The mRNA levels of hepatic FAS and SCD-1 were increased on LF but reduced on HF diet in the $apoB^{-/-}$ (Fig. 4), demonstrating that the two diets raised hepatic TG by different mechanisms. The HF diet did not significantly reduce the

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**Table 3. Diet-induced differences in liver-triglycerides by genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Chow</th>
<th>LF</th>
<th>HF</th>
<th>$\Delta$TG by Genotypes</th>
<th>LF-chow $P$</th>
<th>HF-chow $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$apoB^{+/+}$</td>
<td>87.9</td>
<td>131</td>
<td>146</td>
<td>146.2</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$apoB^{+/38.9}$</td>
<td>66.6</td>
<td>81.2</td>
<td>89.8</td>
<td>89.8</td>
<td>14.6 NS</td>
<td>23.2 &lt;0.05</td>
</tr>
</tbody>
</table>

Values are means (SD) for the hepatic triglyceride (TG) concentrations (mg/g protein). Two-sample $t$-test was performed on between-diet-mean-difference from all mice on all diets [chow - $apoB^{+/+}$, $n = 13$ (6 males and 7 females); chow - $apoB^{+/38.9}$, $n = 10$ (6 and 4); LF - $apoB^{+/+}$, $n = 14$ (7 and 7); LF - $apoB^{+/38.9}$, $n = 11$ (6 and 5); HF - $apoB^{+/+}$, $n = 14$ (7 and 7); HF - $apoB^{+/38.9}$, $n = 11$ (6 and 5)]. Results were averaged from both males and females because there was no gender effect. NS, not significant.

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Fig. 3. Hepatic TG production in apoB38.9 mice and controls on the high-fat diet. Mice were fed the high-fat diet [apoB$^{+/+}$, $n = 6$ (3 males and 3 females); apoB$^{+/38.9}$, $n = 4$ (2 males and 2 females)] for 5 wk. Hepatic TG production was determined as described in MATERIALS AND METHODS. Values are means (SD). Significant differences in the TG levels between the genotypes are indicated by the letters a and b ($P < 0.05$).

Fig. 4. Effects of diets on hepatic mRNA levels of fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD-1). Levels of mRNAs for hepatic FAS and SCD-1 were determined by quantitative real-time PCR from individual mice fed the chow diet ($apoB^{+/+}$, 6 males and 7 females; $apoB^{+/38.9}$, 6 males and 4 females), low-fat (LF) ($apoB^{+/+}$, 7 males and 7 females; $apoB^{+/38.9}$, 6 males and 5 females), or high-fat (HF) diet ($apoB^{+/+}$, 7 males and 7 females; $apoB^{+/38.9}$, 6 males and 5 females). Each value (arbitrary, relative to apoB$^{+/+}$ fed the chow) represents means ± SD of individual determinations. The levels of statistical differences relative to the chow-fed group within each genotype or between LF-fed apoB$^{+/+}$ and apoB$^{+/38.9}$ are indicated by *$P < 0.05$ and **$P < 0.01$. 

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mRNA levels of either transcript in the apoB^{+/38.9}, probably due to their initial reduced expression levels on the chow diet. The LF diet was still able to increase hepatic FAS and SCD-1 mRNA levels in the apoB^{+/38.9} mice, albeit to a lesser extent than those in the apoB^{+/+}, indicating insufficient adaptation to the LF diet in the apoB^{+/38.9} mice. Recently, SCD-1 deficiency has been linked to increased fatty acid oxidation (27) and lower hepatic TG levels in mice (25). However, to the extent that hepatic fatty acid β-oxidation is reflected by plasma β-hydroxybutyrate concentrations, the greater susceptibility of the apoB^{+/38.9} mice to accumulate more hepatic TG (compared with the apoB^{+/+}) was not accounted for by differences in fatty acid oxidation, because plasma β-hydroxybutyrate did not differ across diets or genotypes (not shown).

Hepatic TG production in the apoB^{+/38.9} remained impaired under the HF diet compared with the wild-type controls (Fig. 3), similar to that reported on the chow diet (9). Mice heterozygous for apoB27.6, a protein with even lower TG-transport capacity, secreted more hepatic TG than those in the HF diet in the apoB^{+/38.9} mice. Recently, SCD-1 deficiency has been linked to increased fatty acid oxidation (27) and lower hepatic TG levels in mice (25). However, to the extent that hepatic fatty acid β-oxidation is reflected by plasma β-hydroxybutyrate concentrations, the greater susceptibility of the apoB^{+/38.9} mice to accumulate more hepatic TG (compared with the apoB^{+/+}) was not accounted for by differences in fatty acid oxidation, because plasma β-hydroxybutyrate did not differ across diets or genotypes (not shown).

In conclusion, mice heterozygous for apoB38.9 truncation with impaired hepatic TG secretion are more susceptible to diet-induced fatty liver despite reduced fat absorption capacity from the intestine. These feeding studies may have relevance for humans with apoB-defective FHBL in attempts to control the fat contents of their livers, but the clinical trials remain to be performed.

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