Chronic high-fat diet affects intestinal fat absorption and postprandial triglyceride levels in the mouse

Valerie Petit,† Laurent Arnould,§ Pascal Martin,§ Marie-Claude Monnot,*, Thierry Pineau,§ Philippe Besnard,*, and Isabelle Niot†,*

Physiologie de la Nutrition,† Ecole Nationale Supérieure de Biologie Appliquée à la Nutrition et à l’Alimentation, Unité Mixte de Recherche Centre Europeen des Sciences du Gout 5170-Centre National de la Recherche Scientifique/1214 Institut National de la Recherche Agronomique/Université de Bourgogne, Dijon; France; Department of Pathology,† Centre G-F Leclerc, Dijon, France; and Laboratoire de Pharmacologie et Toxicologie,§ Institut National de la Recherche Agronomique, Toulouse, France

Abstract The effects of chronic fat overconsumption on intestinal physiology and lipid metabolism remain elusive. It is unknown whether a fat-mediated adaptation to lipid absorption takes place. To address this issue, mice fed a high-fat diet (40%, w/w) were refed or not a control diet (3%, w/w) for 3 additive weeks. Despite daily lipid intake 7.7-fold higher than in controls, fecal lipid output remained unchanged in mice fed the triglyceride (TG)-rich diet. In situ isolated jejunal loops revealed greater [1-14C]linoleic acid uptake without TG accumulation in mucosa, suggesting an increase in lipid absorption capacity. Induction both in intestinal mitotic index and in the expression of genes involved in fatty acid uptake, trafficking, and lipoprotein synthesis was found in high-fat diet mice. These changes were lipid-mediated, in that they were fully abolished in mice refed the control diet. A lipid load test performed in the presence or absence of the LPL inhibitor tyloxapol showed a sustained blood TG clearance in fat-fed mice likely attributable to intestinal modulation of LPL regulators (apolipoproteins C-II and C-III). These data demonstrate that a chronic high-fat diet greatly affects intestinal physiology and body lipid use in the mouse.—Petit, V., L. Arnould, P. Martin, M-C. Monnot, T. Pineau, P. Besnard, and I. Niot. Chronic high-fat diet affects intestinal fat absorption and postprandial triglyceride levels in the mouse. J. Lipid Res. 2007. 48: 278–287.

Supplementary key words small intestine • intestinal proliferation • lipid binding proteins • triglyceridemia

It is well established that fat overconsumption leads to obesity in a number of animal models, including mice (1). Although the small intestine is responsible for body fat disposal, its role in this phenomenon has been neglected. The fact that the small intestine has long been considered a simple selective barrier able to efficiently absorb dietary fat explains this paradox. However, recent insights into intestinal physiology demonstrate that triglyceride (TG) absorption is more complex than initially believed. It is now well established that several membrane and soluble lipid binding proteins (LBPs) are involved in this process (2). By reason of their location throughout the enterocyte and their high binding affinity for long-chain fatty acids (LCFAs), LBPs are thought to play a direct or indirect role in each step of lipid absorption: uptake, trafficking, lipoprotein synthesis, and secretion. This physiological involvement has especially been highlighted by the generation of knockout mice. For instance, the invalidation of genes encoding the intestinal fatty acid binding protein (I-FABP) (3), the fatty acid transporter (FAT/CD36) (4), and the microsomal triglyceride transfer protein (MTP) (5) is associated with deep alterations of postprandial triglyceridemia. It is noteworthy that the gene expression of several intestinal LBPs is upregulated by LCFAs through the activation of nuclear receptors, the peroxisome proliferator-activated receptors (PPARs) (2).

Therefore, although the intestinal functions of most LBPs remain elusive, it can be hypothesized that a high fat supply triggers a coordinated change in LBP expression, increasing intestinal absorption capacity. Moreover, it is well known that the intestinal epithelium is characterized by a dramatic cellular turnover, the whole mucosa being renewed every 3 days in the mouse (6). This organ exhibits a remarkable capacity to adapt its morphology to nutritional status. Fasting decreases cell proliferation, leading to a progressive atrophy of rat intestinal epithelium (7). Conversely, refeeding restores the proliferative activity.


Supplementary key words: small intestine • intestinal proliferation • lipid binding proteins • triglyceridemia

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dietary lipids being the strongest stimulators of mucosal regeneration (8). Together, these observations strongly suggest that the high TG bioavailability of gut might not be attributable to inborn properties but to acquired properties. To determine whether such a lipid-mediated adaptation exists, a chronic high-fat diet effect on absorption capacity of the small intestine was studied in mice. Because the absorption efficiency could affect intestinal TG secretion and/or clearance (4), lipid load tests were also performed to explore the high-fat intestinal effect on postprandial triglyceridemia. The data reported here show that the small intestine can adapt its absorption capacity to the fat content of the diet in the mouse. They provide evidence that the small intestine plays an active role in the regulation of triglyceridemia, especially during the postprandial state.

MATERIALS AND METHODS

Animals and experimental treatment

French guidelines for the use and care of laboratory animals were followed. Protocols were approved by the ethics committee of the University of Burgundy. Five week old male B6D2F1 mice weighing 20–25 g were purchased from Janvier. Mice were housed in a controlled environment that provided constant temperature and humidity and a period of darkness from 6 PM to 6 AM. Mice were acclimated individually in metabolic cages and fed a semipurified control diet for 1 week (Table 1). Then, mice were fed for 3 weeks a semipurified control diet containing 3% lipids (w/w), a high-fat diet containing 40% lipids (w/w) (Table 1), or refed the control diet for 3 weeks after the high-fat diet. The diets were nutritionally adequate, providing for all known essential nutrient requirements.

[1-14C]linoleic acid uptake in the jejunum

To study the fatty acid uptake capacity of small intestine, an in situ isolated jejunal loop was realized in mice subjected to a control diet, a high-fat diet, or the high-fat diet followed by the control diet. After 16 h of starvation, mice were anesthetized with isoflurane and laparotomy. A 10 cm segment of jejunum was isolated between two ligatures. The in situ isolated segment was infused with 0.5 ml of linoleic acid in 2.19 mM solution containing 10% [1-14C]linoleic acid (51 mCi/mmol; Perkin-Elmer Life Science, Inc.) emulsified with 10 mM taurocholic acid. After an incubation period of 5 min, the intestinal loop was removed and the intestinal lumen was collected. The mucosa from the in situ isolated jejunal segment was then scraped off. Lipids contained in lumen and mucosa were extracted by Delsal’s method (9), and radioactivity was determined by liquid scintillation. The [1-14C]linoleic acid uptake by the jejunal segment corresponds to the difference between the quantity of [1-14C]linoleic acid infused and that remaining in the intestinal lumen at the end of the experiment.

Metabolic fate of [1-14C]linoleic acid in jejunal mucosa

A 100 µl aliquot of lipids contained in mucosa was evaporated to dryness under a nitrogen stream. Pellet was dissolved in 40 µl of chloroform, then separated by thin-monolayer chromatography in hexane-ethyl ether-glacial acetic acid (140:60:2, v/v/v). After migration, the different lipid species were identified according to standards, [3H]triolein, and [1-14C]linoleic acid. Then, the percentage of radioactivity found in TGs, fatty acids, diglycerides/monoglycerides, and phospholipids was quantified using a Berthold scanner.

Gene expression analysis using INRArray 01.4

To identify gene expression changes in jejunal mucosa, removed according to previous procedures (10) in mice subjected to a high-fat diet compared with a control diet, the low-density microarray INRArray 01.4 dedicated to lipid metabolism was used (11). The full list of 320 selected cDNA probes spotted onto the INRArray 01.4 is available at www.inra.fr/Internet/Centres/toulouse/pharmacologie/pt.htm). The two independent diet studies were analyzed (total of n = 11/group). Total RNA from jejunal mucosa extracted with Trizol reagent (Invitrogen Life Technologies) was controlled with a Bioanalyzer 2100 (Agilent Technologies, Massy, France). For each sample, 3 µg of total RNA along with a fixed amount of 12 spiked-in yeast RNAs (used for normalization) were labeled by reverse transcription with Superscript II reverse transcriptase (Invitrogen Life Technologies) in the presence of 40 µCi of [α-32P]dCTP (ICN, Orsay, France). Radiolabeled cDNA purification as well as hybridization, washing, scanning, and image analysis with the INRArray were performed according to previously described methods (11). Statistical analysis of microarray data was performed under R (www.r-project.org) using Bioconductor packages (www. bioconductor.org). Data were log-transformed and normalized by the mean log(signals) for the 12 spiked-in yeast RNAs. A total of 137 genes exhibiting log(signals) significantly above background intensities were further analyzed. An ANOVA with the experiment and diet factors was performed for each gene. Eighteen genes whose transcripts displayed a significant diet effect (P < 0.01) and exhibited at least a 1.5-fold change between the high-fat and control diets were declared differentially expressed. The expression data for these 18 genes were then transformed to Z-scores and clustered as a heat map using the Euclidean distance and the Ward criterion.

Northern blot analysis

Total RNA from jejunal mucosa of mice subjected to one of the three diets was extracted with Trizol Reagent (Invitrogen Life Technologies). Total RNA was denatured, subjected to electrophoresis on a 1% agarose gel, and transferred to a GeneScreen membrane (New England Nuclear) using 20-fold concentrated 3 mM NaCl and 0.3 mM trisodium citrate, pH 7 (NaCl-citrate). cDNAs of mouse fatty acid transport protein 4 (FATP-4) (12), mouse FAT/CD36 (a gift from Dr. P. Grimaldi, Nice, France), rat intestinal and liver fatty acid binding proteins (I-FABP and L-FABP; provided by Dr. J. I. Gordon, St. Louis, MO), and mouse apolipoprotein A-IV (apoA-IV; a gift from Dr. T. Pineau, Toulouse, France) were used as probes. MTP cDNA was obtained by Superscript II reverse transcriptase (Invitrogen Life Technologies). MTP primer sequences used were described by Sellers and Shelness (13). The reverse transcription reaction was carried out.
out at 48°C for 45 min followed by 95°C for 2 min. The conditions of PCR were 95°C for 30 s, 55°C for 1 min, 72°C for 1 min (35 cycles) and 72°C for 10 min. The expected size of PCR products was 699 bp for MTP. Probes were labeled with [α-32P]dCTP (3,000 Ci/mmol; Amersham) by a Megaprime kit (Amersham). A 24 residue oligonucleotide specific for 18S rRNA was used as a probe to ensure that equivalent quantities of RNA were loaded and transferred. This oligonucleotide was 5′ end-labeled with T4 polynucleotide kinase and [γ-32P]ATP (3,000 Ci/mmol; Amersham). Filters were prehybridized for 4 h and hybridized for 16 h at 42°C according to previously published procedures (14). Filters were washed successively twice in 2× NaCl-citrate at room temperature, twice in 2× NaCl-citrate with 1% sodium dodecyl sulfate at 60°C for 30 min, and finally once in 0.1× NaCl-citrate at room temperature. Autoradiograms were quantified with a calibrated densitometric scanner (Bio-Rad GS-800).

Real-time PCR analysis of jejunal and hepatic apoC-II and apoC-III mRNA levels

cDNA was reverse transcribed from 1 μg of total RNA pretreated with DNase (DNase I Amplification grade (Invitrogen Life Technologies) and Omniscript reverse transcriptase (Qiagen)). cDNA was diluted to 25 ng/μl using sterilized water, and real-time PCR was done in duplicate with 1 μl of cDNA, 12.5 μl of SYBR Green PCR Master Mix (qPCR™ Mastermix Plus for SYBR ® Green I Fluorescein; Eurogentec), 10.5 μl of distilled water, and 1 μl of forward and reverse primers (200 nM) for a final reaction volume of 25 μl. The primer sequences were as follows: apoC-II, 5′-ACTGGAGTGAGCCAGGATAG-3′ and 5′-ACATCAGGATGAGCAGGAT-3′; apoC-III, 5′-TCAGACTCCCTGAAAGGCTAC-3′ and 5′-ATAGCTGGAGTGTGGTGTC-3′. PCR was run on the iCycler iQ system (Bio-Rad Laboratories, Inc.) using the following conditions: 50°C for 2 min, 95°C for 10 min, and 45 cycles of 95°C for 15 s and 60°C for 30 s. The fluorescence measured used to calculate threshold cycle (Ct) was made at 60°C. Quantification of data was done by the comparative ΔΔCt method (15).

Determination of jejunal proliferative activity

After animals were euthanized, a 1 cm length of jejunum was taken from mice in each dietary group. Tissues were placed in ionized water, dehydrated, cleared, and mounted with permount (S3026; DAKO), which was then labeled with streptavidin conjugated to horseradish peroxidase (P0397; DAKO). Ki-67-positive cells were detected by counterstaining in hematoxylin.Slides were washed with deionized water, dehydrated, cleared, and mounted with permanent medium (S3026; DAKO).

All cells in the active phases of the cell cycle stained brown except for G0-phase cells, which remained blue. To determine mitotic activity, an average of 30 crypts were examined per animal. The labeling index (%) was defined as Ki-67-positive cells/total cryptic cells.

Biochemical analysis

Plasma samples were collected from the axilar vein on heparinized propylene tubes. Serum TG and free fatty acid concentrations were determined using a commercial kit (Biomerieux; Wako).

Stool lipids were extracted from an aliquot of feces (0.75 g) collected during the last 3 days of the control diet or the high-fat diet using the methanol/chloroform method (16). Resulting solvent was transferred to a balloon, evaporated under a nitrogen stream, placed in a vacuum desicator overnight, and weighed. The weight difference between the starting empty balloon and the balloon containing the dried lipid was the fecal lipid amount. [1-14C]oleic acid (51 mCi/mmol) was added during lipid extraction to evaluate the efficiency of the process.

Lipids were extracted from mucosa and dried. Extracts were dissolved into 1% Triton X-100/chloroform, dried under vacuum, and redisolved in water for the determination of TG using a commercial kit (Biomerieux). The cellular protein content was determined by bichinonic acid assay (Pierce). The mucosal content of TG is expressed as mg TG/g protein.

Lipid load test

Mice were maintained on a control diet or a high-fat diet for 21 days. After a 16 h fast, mice were weighed and received an intragastric bolus of lipids (0.5 ml of oil). Blood samples were collected from the tail vein before gavage and at 0.5, 1, 2, 3, and 4 h after gavage. Plasma TG concentration was assayed using a commercial kit (Biomerieux). The same experiment was performed in mice previously subjected to an intraperitoneal injection of tyloxapol (Sigma) in saline (500 mg/kg body weight) to block LPL activity.

Statistical methods

The results are expressed as means ± SEM. The significance of differences between groups was determined by Student’s t test.

RESULTS

High-fat feeding does not lead to steatorrhea

To determine whether the fat content of the diet can affect the TG absorption capacity of the small intestine, B6D2F1 mice, individually housed in metabolic cages, were fed for 3 weeks either a control diet or a high-fat diet. Lipids in feces collected during the 3 last days of treatment were extracted by the method Folch, Lees, and Sloane Stanley (16). Values shown are means ± SEM (n = 5).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control Diet (3% Fat, w/w)</th>
<th>High-Fat Diet (40% Fat, w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass (g)</td>
<td>19.97 ± 0.6</td>
<td>19.97 ± 0.7</td>
</tr>
<tr>
<td>After</td>
<td>22.96 ± 0.78</td>
<td>22.60 ± 0.92</td>
</tr>
<tr>
<td>Colanic intake (kcal/day)</td>
<td>12.39 ± 0.91</td>
<td>10.92 ± 0.91</td>
</tr>
<tr>
<td>Lipid intake (mg/day)</td>
<td>129.40 ± 8.59</td>
<td>996.14 ± 78.83</td>
</tr>
<tr>
<td>Total lipid content in feces (mg/day)</td>
<td>31.95 ± 1.14</td>
<td>30.88 ± 0.49</td>
</tr>
</tbody>
</table>

Mice, individually housed in metabolic cages, were fed for 3 weeks either a control diet or a high-fat diet. Lipids in feces collected during the 3 last days of treatment were extracted by the method Folch, Lees, and Sloane Stanley (16). Values shown are means ± SEM (n = 5). aP < 0.001.
subjected to the control or high-fat diet (Table 1) for 3 weeks followed or not by an additive period of 3 weeks on the control diet. In this strain, the high-fat diet did not affect the body mass, the daily caloric intake being similar regardless of the diet (Table 2). Despite a daily lipid intake 7.7-fold higher than in controls, the lipid elimination in feces remained unchanged in mice subjected to a chronic high fat supply. These data suggest either the existence in the mouse of an innate high absorption capacity for lipids or a fat-dependent adaptation of small intestine to the lipid content of the diet in the mouse.

A chronic high-fat diet affects jejunal fatty acid uptake and processing

To address this question, the impact of a chronic high-fat supply on intestinal LCFA uptake was studied using an
Intestinal cell proliferation is enhanced by a chronic high-fat diet

Intestinal epithelium undergoes rapid renewal. To explore whether a change in the cell proliferation rate of intestinal cells might contribute to the fat-mediated increase in TG absorption, the jejunal mitotic index was determined using the Ki-67 antigen method. Ki-67 protein is specifically expressed in the nucleus of cells in division. As shown in Fig. 2A, the mitotic index increased significantly in the jejunum of mice chronically subjected to the high-fat diet compared with the control diet. This change was reversible, because a return to the control value was found when mice were refeed the low-fat diet. Lipid-induced mitotic activity might lead to an increase in villi size and, thus, in absorptive area. The fact that the relative intestinal mass was increased by the fat content of the diet correlates quite well with this assumption (Fig. 2B).

A chronic high-fat diet affects the expression of key genes for fat absorption

To examine whether a chronic high-fat supply affects the intestinal gene profile and thereby influences intestinal TG absorption, the low-density microassay INRAarray 01.4, dedicated to genes mainly involved in lipid metabolism, was used (11). As shown in Fig. 3, two groups of genes were easily identified. Two genes implicated in the metabolic fate of intestinal TG-rich lipoproteins, apoA-I and apoC-III, were repressed by the high-fat diet. Conversely, this diet upregulated several genes known to play a crucial role in LCFA uptake/trafficking (FATP-4, L-FABP, L-FABP) and lipoprotein synthesis (apoA-IV). This global gene analysis highlights the strong effect of dietary fat on intestinal TG metabolism. To further analyze this regulation, a kinetic study was undertaken in a larger set of prototypical genes. As shown in Fig. 4, chronic high-fat diet led to a dramatic upregulation of FATP-4, FAT/CD36, I-FABP, L-FABP, MTP, and apoA-IV genes. This induction was rapid and maintained throughout the exposure to the high-fat diet. Except for FATP-4, a rapid return to basal values was observed as soon as mice were refeed the control diet.

Plasma TG clearance is improved in mice chronically fed a high-fat diet

ApoC-II and apoC-III are known to be a strong activator and a strong inhibitor, respectively, of LPL, an enzyme responsible for blood chylomicron clearance (17, 18). Because microarray analysis showed that the high-fat diet decreased intestinal apoC-III gene expression (Fig. 3),...
mRNA levels of apoC-II and apoC-III were assayed in jejunum by quantitative PCR. As shown in Fig. 5A, a huge increase in apoC-II mRNA levels was found in mice fed the TG-rich diet, whereas apoC-III mRNA levels decreased according to the microarray analysis. A return to control values was observed in mice refed standard laboratory chow, demonstrating that this gene regulation is adaptive. Because chylomicrons can also be enriched in apoC
by exchanges with hepatic lipoproteins, apoC-II and apoC-III gene expression was next determined in liver, but no change was found (Fig. 5B).

A high apoC-II/apoC-III ratio in chylomicrons is expected to increase their clearance from blood and, thereby, decrease postprandial triglyceridemia. To explore this assumption, plasma TG levels were assayed in overnight-fasted mice force-fed 0.5 ml of oil. Mice subjected to the high-fat diet displayed plasma TG levels lower than mice fed the control diet (Fig. 6A). This finding might be attributable to a decrease in intestinal TG release and/or an increase in blood TG hydrolysis by peripheral tissues. To address this question, the LPL inhibitor tyloxapol was injected intraperitoneally at 30 min before the intragastric lipid load was administered (0.5 ml). In contrast to the previous experiment, plasma TG levels from chronically fat-fed mice were similar to those of mice fed the control diet (Fig. 6B). Because no TG retention was observed in intestinal mucosa at 4 h after the fat load (Fig. 6C), the low plasma TG levels found in mice fed the high-fat diet were attributable to the more efficient TG clearance from blood. These intestinally mediated changes in the chylomicron composition might account for the lower postprandial TG levels found in mice chronically subjected to the high-fat diet. This phenomenon was rapid, because a significant decrease in blood TG levels was found as early as 3 days after high-fat feeding and was reversible (Fig. 6D).

**DISCUSSION**

This report demonstrates that the intestinal absorption capacity can be adapted to the fat content of the diet in the mouse. This fat-mediated adaptation takes place through
two complementary events. First, there is an enhancement of intestinal cell proliferation, which might lead to an increased absorptive area. Consistent with this assumption, rat studies show that fatty acid-enriched diets increase the height of villi and induce the rate of enterocyte migration along the crypt-to-villus axis (19, 20). Interestingly, the effect of dietary lipid on intestinal trophism appears to be more efficient than that of other nutrients. It is especially evident in situations in which the absorptive area has been deeply altered, as after long-term starvation or a drastic intestinal resection (8, 21). Second, our data show the existence of a fat-induced coordination of genes known to play a significant role in intestinal fatty acid uptake or intracellular processing (i.e., FATP4, FAT/CD36, L-FABP, L-FABP) and lipoprotein secretion (i.e., MTP, apoA-IV). FATP-4 upregulation might facilitate LCFA uptake by enterocytes through its acyl-CoA synthetase activity (12). Plasma membrane being impermeable to long-chain acyl-
CoA, a FATP-4-mediated esterification of LCFA must not only prevent their enterocyte efflux but also create a concentration gradient favoring LCFA influx (2). The fact that a positive relationship exists between FATP-4 protein and LCFA uptake by enterocytes in FATP4+/− mice is consistent with this assumption (22).

The efficiency of LCFA uptake is also modulated by I-FABP and L-FABP expression levels, which are known to facilitate cellular LCFA trapping and trafficking (23). Transfection studies suggest that I-FABP and L-FABP preferentially target LCFAs to the reesterification pathway, facilitating lipoprotein synthesis (23, 24). A tight correlation between I-FABP expression and TG synthesis was reported in human enterocyte-like Caco-2 cells (25). Similarly, the use of FAT/CD36-null mice revealed an involvement in intestinal lipoprotein metabolism (4). Moreover, the resident endoplasmic reticulum protein MTP, which controls the neutral lipid transfer to apoB-48 (26), was dramatically upregulated in high-fat-fed mice (Fig. 4). This protein plays a crucial role in chylomicron synthesis. Indeed, an intestine-specific MTP gene invalidation produces a dramatic decrease in chylomicron synthesis and secretion (5). Finally, the induction of apoA-IV expression found in lipid-fed mice might also facilitate intestinal lipoprotein production (27). Altogether, these lipid-mediated changes in gene expression must improve the intestinal lipid absorption and, thereby, deeply affect the postprandial triglyceridaemia. Interestingly, an increase in blood TG levels is systematically found after a targeted deletion of genes encoding FAT/CD36 (4), I-FABP (3), and MTP (5). In contrast, these last findings might explain why a low triglyceridaemia level was found in mice receiving the TG-enriched diet (Fig. 5D). Such a result has already been observed in rats, especially when, as in our conditions, a high monounsaturated fat diet was used (28). A higher efficiency of TG clearance by LPL is suggested by the concomitant increase in apoC-II and decrease in apoC-III gene expression. Indeed, these apolipoproteins are known to activate and inhibit LPL activity, respectively (17, 18).

Chylomicron size is also known to affect blood TG clearance, larger chylomicrons exhibiting a greater affinity for LPL than smaller lipoprotein particles (29). Chylomicron size is highly dependent on expression levels of a few LBPs and apolipoproteins. For instance, FAT/CD36 knockout mice secrete smaller chylomicrons than wild-type mice (30), and the induction of intestinal apoA-IV has been reported to lead to larger particles (27, 31). According to these data, the fat-mediated increase of genes encoding FAT/CD36 and apoA-IV might produce large chylomicrons rapidly hydrolyzed by LPL. This report provides evidence implicating the small intestine in postprandial triglyceridaemia.

The fact that in the rodent insulin resistance model of hypertriglyceridaemia has been demonstrated to result from the hypersecretion of intestinal lipoproteins indicates that the small intestine could participate in metabolic lipid disorders (32). Consistent with this assumption, Kondo and coworkers (33) reported, during the review of this work, that the fat-mediated adaptation of intestinal lipid metabolism is associated with susceptibility to obesity in the mouse. The molecular basis for this adaptation remains to be determined. The coordinated regulation of gene expression reported here suggests the involvement of a common regulatory factor. PPARβ/δ is a plausible candidate for such a function. Indeed, this nuclear receptor, which is especially highly expressed in the small intestine, is known to be involved in both the regulation of cell proliferation (34–36) and the gene expression of several intestinal LBPs (10, 37). The generation of mice in which the PPARβ/δ gene is invalidated or, conversely, overexpressed specifically in the small intestine might provide a useful tool to explore this hypothesis.

V.P. is supported by a fellowship from the Council of Burgundy and GlaxoSmithKline. The authors thank Alfediam, which also supported her work. The authors are grateful to Frederic Lassere and Sylvie Baumann for their technical assistance.

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