Introduction

Diabetes mellitus is a disease defined by elevated blood glucose levels. The causes of type 2 diabetes are not well understood. It is thought that both resistance of target tissues to the action of insulin and decreased insulin secretion (“β-cell failure”) occur. Major insulin-responsive tissues for glucose homeostasis are liver, in which insulin stimulates glycogen synthesis and inhibits gluconeogenesis; muscle, in which insulin stimulates glucose uptake and glycogen synthesis; and white adipose tissue (WAT), in which insulin stimulates glucose uptake and inhibits lipolysis. The relative importance of each tissue is not known; nor are the details of how they interact.

To understand the physiological roles of adipose tissue, we have generated a transgenic line of mice, named A-ZIP/F-1, which has virtually no white adipose tissue (I). These mice express a dominant negative protein in adipose tissue that heterodimerizes with and inactivates members of the C/EBP and JUN families of B-ZIP transcription factors. The A-ZIP/F-1 phenotype strikingly resembles that of humans with severe lipoatrophic diabetes, including the lack of fat, marked insulin resistance and hyperglycemia, hyperlipidemia, fatty liver, and organomegaly. The detailed mechanisms by which the lack of WAT causes insulin resistance are not established. Contributing components probably include deficiency of leptin (and other hormones) and the lack of a place to store triglycerides (2–5). It has been postulated that increased intracellular triglycerides (or metabolites such as fatty acyl-CoA or malonyl-CoA) inside nonadipose tissues could cause insulin resistance (6, 7).

The TZDs are a class of antidiabetic agents that act by increasing insulin sensitivity (8, 9). Currently, two drugs in this class are approved for use in the United States, rosiglitazone (formerly BRL49653; ref. 10) and pioglitazone. TZDs are agonist ligands for the transcription factor peroxisome proliferator-activated receptor γ (PPARγ), and their antidiabetic effects are thought to be mediated through PPARγ (11). PPARγ is expressed at high levels in adipose tissue, colon, and activated macrophages, and at lower levels in other tissues (12–17). The tissues at which TZDs act to increase insulin sensitivity are debated (8, 9, 18). TZDs increase glucose utilization (largely a muscle function) and, at higher doses, inhibit endogenous glucose production (largely a liver function) (19). However, liver and muscle have low PPARγ levels. Thus, WAT has been a leading candidate for the target of TZD actions, as it is the only insulin-responsive tissue with a high level of PPARγ. Additionally, PPARγ and its agonist ligands stimulate...
adipose differentiation (20), leading to increased numbers of small adipocytes, which are thought to be more insulin sensitive than are large, lipid-laden adipocytes (21). However, Burant et al., studying a partially lipoatrophic mouse, concluded that troglitazone effectively treated diabetes, independent of adipose tissue (22). Here, we have reexamined this question using the more severely lipoatrophic A-ZIP/F-1 mice and do not see an effect of TZDs on insulin and glucose levels. However, rosiglitazone greatly increases the hepatic steatosis of these mice, which may be due to their increased hepatic expression of PPARγ.

Methods
Mice. Generation and characterization of the “fatless” A-ZIP/F-1 mice have been reported (1, 3–5, 23). Studies were approved by the NIDDK animal care and use committee. All A-ZIP/F-1 mice used in this study were hemizygous females on the FVB/N background, produced by breeding hemizygous males with wild-type (WT) females. Controls were age- and sex-matched FVB/N mice. C57BL/6J-lepob/ob female mice were purchased from Jackson Laboratory (Bar Harbor, Maine, USA). Mice were typically reared three to a cage on a 12-hour light/dark cycle (lights on at 0600–1800 hours), fed water and pellet (NIH-07) or powder (AIN 93G; Dyets, Bethlehem, Pennsylvania, USA) diet ad libitum. Food was blended daily with rosiglitazone (0.012 mg/g diet, for a dose of ~3 mg/kg/d; Smith Kline Beecham, West Sussex, United Kingdom) in a coffee grinder. Troglitazone (Parke-Davis, Ann Arbor, Michigan, USA) treatment was given by oral gavage at dose of 10 mg/100 μl H2O daily for 2 weeks. All mice were sacrificed at between 0900 and 1200 hours. Tissues were fixed for histological analysis. Upon sacrifice, the grafts were examined visually, weighed, and fixed for histological analysis. Statistical analysis. Values are reported as means ± SEM. Statistical significance was determined using two-tailed t test or ANOVA, as appropriate.

Results
Rosciglitazone does not improve the diabetes of A-ZIP mice. Treatment of A-ZIP/F-1 mice for 5 weeks with rosiglitazone had no effect on their threefold elevated glucose levels or the 200-fold elevated insulin levels (Figure 1). Similarly, treatment for 2 weeks with troglitazone failed to reduce the glucose and insulin levels (Table 1). As a positive control for TZD effectiveness, we treated leptin-deficient ob/ob mice with rosiglitazone (Figure 1). As expected (27), the ob/ob mice showed vastly improved insulin levels and normalization of serum glucose.

A glucose tolerance test was performed to characterize the insulin resistance further. In the A-ZIP/F-1 mice, the baseline 6-hour–fasted blood glucose values were elevated, and the glucose levels rose higher and remained elevated for longer than in WT controls (Figure 2). Rosiglitazone treatment of the A-ZIP/F-1 mice did not alter the abnormal glucose tolerance test. Thus,
Female WT or A-ZIP/F-1 mice, 6–8 weeks old, were treated with troglitazone for 2 weeks. Animals were sacrificed in the fed state. Data are mean ± SEM.

Table 1: Treatment of A-ZIP/F-1 mice with troglitazone

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WT, Control</th>
<th>WT, Troglitazone</th>
<th>A-ZIP/F-1, Control</th>
<th>A-ZIP/F-1, Troglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>22.8 ± 0.8</td>
<td>22.3 ± 0.8</td>
<td>23.9 ± 1.3</td>
<td>23.7 ± 0.9</td>
</tr>
<tr>
<td>Food intake (g/d)</td>
<td>3.92 ± 0.18</td>
<td>3.83 ± 0.16</td>
<td>5.33 ± 0.18</td>
<td>4.91 ± 0.28</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>1.07 ± 0.02</td>
<td>1.06 ± 0.03</td>
<td>2.60 ± 0.26</td>
<td>2.68 ± 0.16</td>
</tr>
<tr>
<td>BAT weight (mg)</td>
<td>120 ± 13</td>
<td>144 ± 3</td>
<td>67 ± 5</td>
<td>53 ± 6</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>294 ± 18</td>
<td>271 ± 23</td>
<td>929 ± 90</td>
<td>859 ± 58</td>
</tr>
<tr>
<td>Insulin (ng/ml)</td>
<td>0.93 ± 0.20</td>
<td>0.82 ± 0.08</td>
<td>113 ± 24</td>
<td>99 ± 31</td>
</tr>
<tr>
<td>FFA (μM)</td>
<td>312 ± 43</td>
<td>264 ± 54</td>
<td>928 ± 150</td>
<td>617 ± 92</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>300 ± 43</td>
<td>259 ± 34</td>
<td>919 ± 83</td>
<td>595 ± 58</td>
</tr>
<tr>
<td>Liver triglyceride (μmol/g)</td>
<td>50 ± 6</td>
<td>24 ± 5*</td>
<td>279 ± 34</td>
<td>281 ± 21</td>
</tr>
<tr>
<td>Liver triglyceride (μmol/liver)</td>
<td>53 ± 7</td>
<td>25 ± 5*</td>
<td>732 ± 116</td>
<td>751 ± 63</td>
</tr>
</tbody>
</table>

Female WT or A-ZIP/F-1 mice, 6–8 weeks old, were treated with troglitazone for 2 weeks. Animals were sacrificed in the fed state. Data are mean ± SEM (n = 6). *P < 0.05 for difference within genotype between control and troglitazone-treated mice.
Rosiglitazone increases respiratory exchange ratio. The respiratory exchange ratio (RER; the ratio of CO₂ produced to O₂ consumed) is a measure of metabolic fuel source. Pure carbohydrate oxidation gives an RER of 1.00, whereas pure fat oxidation gives a ratio of approximately 0.71 (31). Fasting lipoatrophic humans (32) and A-ZIP/F-1 mice (33) have an elevated RER, indicating increased net fractional oxidation of carbohydrate. In WT mice, 4–7 hours of fasting was sufficient to reduce the RER maximally, irrespective of treatment with rosiglitazone. Under identical conditions, the A-ZIP/F-1 mice did not show a maximally reduced RER unless treated with rosiglitazone (Table 2). Thus rosiglitazone increases net fractional lipid oxidation, suggesting that increased fat oxidation (or decreased lipogenesis) contributes to rosiglitazone’s ability to reduce serum FFA and triglyceride levels.

Diabetes of fat-transplanted mice does not respond to rosiglitazone. We next studied whether the antidiabetic effect of rosiglitazone could be restored in A-ZIP/F-1 mice by transplantation of WT adipose tissue. A submaximal transplant amount (400 mg) (4) was chosen, enabling the potential for detection of a rosiglitazone effect. Similar to previous observations (4, 5), fat transplantation improved the glucose and insulin levels beginning 2 weeks after surgery, whereas sham-operated mice had persistent hyperglycemia and hyperinsulinemia (Figure 4, a and b). However, we did not detect any effect of rosiglitazone treatment on the final glycated hemoglobin (sham control, 11.6 ± 1.1%; sham rosiglitazone, 12.3 ± 0.8%; transplanted control, 7.2 ± 0.6%; transplanted rosiglitazone, 7.8 ± 1.2%; WT 6.6 ± 0.5%), glucose, or insulin levels in the fat-transplanted mice (data not shown). The rosiglitazone treatment was effective, as the weight of the brown adipose tissue in both the sham- and fat-transplanted groups was increased by rosiglitazone treatment (sham, from 60 ± 10 to 177 ± 21 mg; transplanted, from 27 ± 3 to 66 ± 6 mg).

We next examined the effect of fat transplantation on the increased hepatic size and steatosis caused by rosiglitazone treatment (Figure 4, c and d). As expected (4, 5), fat transplantation greatly decreased liver weight (by 42%) and triglyceride content (by 82%), but did not reduce either to WT levels. However, rosiglitazone treatment did not increase hepatic triglyceride content; the steatotic effect of rosiglitazone was abolished by WAT transplantation.

Hepatic PPARγ expression correlates with rosiglitazone-induced increase in liver triglyceride content. Given that hepatic levels of PPARγ are a possible determinant of

Table 2
Characteristics of rosiglitazone-treated mice

<table>
<thead>
<tr>
<th></th>
<th>WT, Control</th>
<th>WT, Rosiglitazone</th>
<th>A-ZIP/F-1, Control</th>
<th>A-ZIP/F-1, Rosiglitazone</th>
<th>ob/ob, Control</th>
<th>ob/ob, Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>21.9 ± 0.5</td>
<td>22.1 ± 0.4</td>
<td>22.4 ± 0.4</td>
<td>24.2 ± 0.4a</td>
<td>39.3 ± 0.6</td>
<td>41.3 ± 0.6a</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>0.95 ± 0.02</td>
<td>0.83 ± 0.03a</td>
<td>2.28 ± 0.13</td>
<td>4.27 ± 0.31b</td>
<td>3.69 ± 0.11</td>
<td>4.51 ± 0.19b</td>
</tr>
<tr>
<td>BAT weight (mg)</td>
<td>125 ± 6</td>
<td>271 ± 14a</td>
<td>65 ± 12</td>
<td>150 ± 17b</td>
<td>340 ± 12</td>
<td>531 ± 28a</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/l)</td>
<td>158 ± 18</td>
<td>126 ± 18a</td>
<td>211 ± 57</td>
<td>323 ± 71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/l)</td>
<td>51 ± 9</td>
<td>44 ± 7</td>
<td>101 ± 25</td>
<td>189 ± 47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase (U/l)</td>
<td>46 ± 3</td>
<td>47 ± 8</td>
<td>53 ± 7</td>
<td>35 ± 4a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>118 ± 5</td>
<td>119 ± 4</td>
<td>171 ± 11</td>
<td>134 ± 12a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.3 ± 0.1</td>
<td>3.2 ± 0.1</td>
<td>3.7 ± 0.1</td>
<td>3.9 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>3.31 ± 0.05</td>
<td>0.25 ± 0.03</td>
<td>0.55 ± 0.10</td>
<td>0.24 ± 0.03a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/l)</td>
<td>103 ± 108</td>
<td>564 ± 97</td>
<td>1,220 ± 390</td>
<td>1,830 ± 320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen consumption (ml/h/g0.75)</td>
<td>10.33 ± 0.36</td>
<td>10.86 ± 0.24</td>
<td>8.23 ± 0.20</td>
<td>8.23 ± 0.20</td>
<td></td>
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</tr>
<tr>
<td>RER</td>
<td>0.69 ± 0.006</td>
<td>0.692 ± 0.005</td>
<td>0.730 ± 0.007</td>
<td>0.698 ± 0.007a</td>
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</tr>
</tbody>
</table>

Female WT or A-ZIP/F-1 mice, 4–5 weeks old, were treated with rosiglitazone for 5 weeks. Female ob/ob mice, 6 weeks old, were treated for 2 weeks. Animals were sacrificed in the fed state. Data are mean ± SEM (n = 6). aP < 0.05 for differences within each genotype between control and rosiglitazone-treated mice. bP < 0.005 for differences within each genotype between control and rosiglitazone-treated mice.
the response to rosiglitazone treatment, we measured hepatic PPARγ mRNA levels. WT mice had levels of PPARγ mRNA near the limit of detection by Northern analysis. In contrast, in A-ZIP/F-1 mice, the PPARγ mRNA levels were increased (3- to 17-fold; quantitation of the increase is difficult owing to the low levels in the WT mice; Figure 4, e and f, and Figure 5). Rosiglitazone treatment had little effect on PPARγ mRNA levels in WT mice, but increased them 1.4-fold in A-ZIP/F-1 mice. Fat transplantation reversed the increase in the A-ZIP/F-1 mice. In skeletal muscle, Northern blots demonstrated barely detectable levels of PPARγ mRNA in A-ZIP/F-1 mice, FVB/N controls, and ob/ob mice, which did not change upon rosiglitazone treatment (data not shown).

Thus, there is a striking correlation between the hepatic PPARγ mRNA levels, the hepatic triglyceride content, and the response to rosiglitazone treatment. These data suggest that PPARγ levels are an important determinant of hepatic triglyceride content, presumably increasing lipogenesis and possibly fatty acid uptake.

The aP2 gene is transcribed predominantly in adipose and other PPARγ-responsive tissues (34, 35). Hepatic aP2 mRNA levels were similar in A-ZIP/F-1 and control mice but were induced by rosiglitazone treatment only in the A-ZIP/F-1 mice (FVB/N controls, 100 and 59, vs. A-ZIP/F-1, 101 and 565; first value is untreated, second is rosiglitazone-treated; data are given in arbitrary units and are averages of two different pooled samples). These data indicate that hepatic PPARγ drives liver expression of aP2, a gene usually thought of as an adipose marker.

We also quantitated the liver mRNAs encoding transcription factors and metabolic enzymes involved in lipogenesis, β-oxidation, and glucose homeostasis. In A-ZIP/F-1 mice, the lipogenic genes, fatty acid synthase (FAS) and stearoyl-CoA desaturase-1 (SCD1), were both higher than in control mice (Figure 5). After 5 weeks of rosiglitazone treatment, SCD1 levels increased approximately 1.7-fold in both WT and A-ZIP/F-1 mice, whereas FAS levels did not change. Liver mRNA levels for SREBP1 were slightly elevated in A-ZIP/F-1 mice, but were not affected by rosiglitazone treatment.

To study the effect of rosiglitazone on β-oxidation genes, we measured PPARα, carnitine palmitoyltransferase-1 (CPT1), and acyl-CoA oxidase (AOX) mRNA levels (Figure 5). These mRNAs were all expressed at similar levels in control WT and A-ZIP/F-1 mice. Rosiglitazone treatment significantly increased mRNA levels only for AOX, which catalyzes the first step of β-oxidation. The AOX increase was less than that seen with treatment with PPARα agonist treatment (24).

Phosphoenolpyruvate carboxykinase (PEPCK) mRNA levels indicate the level of gluconeogenesis. In A-ZIP/F-1 mouse, the PEPCK mRNA levels were comparable to those of control mice. IRS-2 mRNA levels, which correlate with insulin signaling (36), were reduced by 80% in A-ZIP/F-1 mice and were slightly less reduced after rosiglitazone treatment.

In summary, the mRNA levels in untreated A-ZIP/F-1 mice demonstrate increased expression of lipogenic enzymes, with no change in enzymes involved in β-oxidation. Rosiglitazone treatment caused a modest increase in AOX mRNA levels in A-ZIP/F-1, but not WT mice, consistent with an increase in β-oxidation.
Discussion

White adipose tissue is required for the insulin-sensitizing actions of TZDs. We show that rosiglitazone (or troglitazone) treatment of lipoatrophic A-ZIP/F-1 mice does not improve their hyperglycemia or hyperinsulinemia. This result is most consistent with the hypothesis that WAT is required for the antidiabetic effects of TZDs. The adipose site for TZD action is concordant with the observation that PPARγ is normally expressed at high levels in adipose tissue and not the other major insulin target tissues, muscle and liver. The effect of the TZDs in diabetics without lipoatrophy may be through the stimulation of adipocyte differentiation, generating more small adipocytes, which are more insulin sensitive. The TZDs may also increase insulin sensitivity by stimulating adipocyte glucose, fatty acid, and triglyceride uptake; reducing systemic levels; or altering release of adipose signaling molecules that affect insulin sensitivity in other tissues.

Fat transplantation did not confer rosiglitazone-responsiveness to the A-ZIP/F-1 mice. There are a number of possible explanations for this failure. First, the transplanted fat may have lowered the serum glucose and insulin too efficiently, such that a rosiglitazone effect was masked. Second, although fat implants vascularize and contain nerves, their function and regulation are not entirely normal (4), so the transplanted fat may not have been able to respond to TZDs. Third, the transplanted adipocytes may have enlarged to the point at which they were poorly responsive to TZDs. Finally, the transplanted WAT may have exhausted its proliferative potential. Thus the lack of restoration of the antidiabetic effects of rosiglitazone by fat transplantation does not detract from our belief in the importance of adipose tissue in mediating the antidiabetic effects of TZDs.

Mice lacking PPARγ have been produced (37–39). Homozygous PPARγ disruption is embryonic lethal, but PPARγ+/− mice are viable. Surprisingly, when challenged with a high fat diet, PPARγ−/− mice show increased insulin sensitivity relative to PPARγ+/− controls (38, 40). A proposed explanation is that the PPARγ−/− adipose tissue is not as lipid laden and is thus more insulin-sensitive, possibly with a contribution from the paradoxically higher leptin levels (41).

The conclusion that WAT is required for the antidiabetic effects of TZDs contrasts with that reached by Burant et al. (22). Using the aP2/DTA mouse model of lipoatrophy, they concluded that troglitazone action is independent of adipose tissue. The aP2/DTA mouse has a normal amount of WAT at weaning, which begins to diminish by approximately 5 months of age, and by the time of troglitazone treatment (8–9 months), these mice showed an approximately 90% reduction in gonadal fat. The effectiveness of thiazolidinediones in aP2-nSREBP-1c lipoatrophic mice with intermediate levels of adipose tissue (42) has not been reported.

There are multiple reasons for the difference between our conclusions and those of Burant et al. The mice express different transgenes and have different genetic backgrounds. Also, the greater residual adipose tissue of the aP2/DTA mouse may enable improvement in the diabetes via direct adipose effects, just as troglitazone effectively treats the diabetes of patients with partial lipodystrophy (32).
Rosiglitazone improves hypertriglyceridemia in A-ZIP/F-1 mice, independently of white adipose tissue. In contrast to its lack of antidiabetic effects, rosiglitazone lowered serum triglycerides and FFAs in A-ZIP/F-1 mice. Possible mechanisms are decreased dietary intake, decreased fatty acid production, increased β-oxidation, and redistribution away from the circulating compartment. Food intake was not decreased, indicating that triglyceride availability did not change. Although we have not measured fatty acid production directly, neither FAS nor SCD1 mRNA was decreased (and in fact these mRNAs were increased), indicating that decreased hepatic fatty acid synthesis is unlikely. In contrast, increased fat oxidation probably does contribute to the improvement in lipid levels, as hepatic AOX mRNA levels are increased and the elevated respiratory quotient was reversed by rosiglitazone treatment. We do not know which tissues contribute to the increased lipid oxidation in the A-ZIP/F-1 treatment. We do not know which tissues contribute to the increased lipid oxidation in the A-ZIP/F-1 mice; muscle and liver are candidates. It is also possible that redistribution of circulating triglycerides into tissue occurs. For example, uptake of circulating lipids may contribute to the fatty liver.

TZD actions and PPARγ physiology in mice with normal compared with steatotic livers. PPARγ is normally expressed prominently in white adipose tissue, with much lower levels in liver and skeletal muscle (12–14, 17). The A-ZIP/F-1 mice have increased hepatic PPARγ mRNA levels. This increase in PPARγ may be a general property of steatotic livers, as it is present in ob/ob mice (43), UCP-DTA mice fed a high-fat diet (14), PPARγ knockout mice (44), and slightly in aP2/DTA mice (22). The mechanistic relationship between the steatosis and increased PPARγ mRNA levels is unclear. Do increased PPARγ levels cause increased lipogenesis and/or lipid uptake, leading to steatosis? Does hepatic steatosis per se lead to increased PPARγ levels? Or are both true? One possibility is that during increased energy availability (such as obesity or a high-fat diet), a circulating factor stimulates hepatic PPARγ transcription, turning on the lipogenic program and producing a fatty liver.

The very different responses to rosiglitazone treatment of A-ZIP/F-1 and ob/ob mice (with PPARγ-rich, fatty livers) compared with WT and fat-transplanted A-ZIP/F-1 mice (with low PPARγ and normal or near-normal liver lipid) highlight a fundamental difference between normal and lipoatrophic mice. In normal mice, there is little hepatic PPARγ and thus little direct hepatic effect of rosiglitazone treatment. The major rosiglitazone action on adipocytes provides more storage capacity for triglyceride, resulting in slightly lower hepatic (and other tissue) triglyceride levels. In contrast, in lipoatrophic mice, the steatotic liver is a major direct target for rosiglitazone action and becomes more lipogenic upon rosiglitazone treatment, further increasing liver lipid content.

Although both rosiglitazone and troglitazone failed to lower glucose and insulin, and both did reduce triglycerides, there were significant differences between these two TZDs. Notably, only rosiglitazone increased hepatic triglyceride content. It is possible that one or both of these drugs have differential effects via PPARγ-independent mechanisms (45). Another likely explanation is that troglitazone is a partial PPARγ agonist in certain assays, whereas rosiglitazone is a full agonist, giving the drugs overlapping but distinct effects on gene expression (46). Recent reports of PPARγ antagonist (47) and weak agonist (48) ligands hint at the future pharmacological diversity. In theory, an ideal PPARγ ligand would target adipose tissue, but not liver, and increase insulin sensitivity, but not lipogenesis. Generation of A-ZIP/F-1 mice with liver-specific disruption of PPARγ will test the contribution of hepatic PPARγ to generation of the fatty liver.

Obesity is a major risk factor for both diabetes and hepatic steatosis, so it is likely that both conditions will be present in a significant number of people. Given that the physiology of PPAR action (particularly PPARγ) can be different between mice and humans, our results raise clinical questions that can only be answered with data from humans. Do people with steatotic livers have increased hepatic PPARγ levels? What about patients with type 2 diabetes? Do humans with hepatic steatosis respond differently to (certain) TZDs than do people with lean livers? We are not aware of studies measuring PPARγ levels in steatotic human livers. Nor do we know of reports specifically comparing the effects of TZDs in patients with fatty livers compared with controls. However, when a group of lipoatrophy patients was treated with rosiglitazone, both improved diabetes and a reduced liver volume (presumably due to reduced triglyceride content) were observed (32). The diabetes and liver volume improved even in the four patients with the most severe generalized lipoatrophy (E. Arioglu and S.I. Taylor, personal communication). One interpretation is that there are
differences in physiology between humans and mice. Our results suggest that the antidiabetic actions of TZDs require adipose tissue. However, the absence of adipose tissue causes severe hepatic steatosis with high PPAR γ levels. In this situation, rosiglitazone treatment worsened the steatosis, while lowering circulating triglycerides and increasing net fractional fatty acid oxidation. We postulate that the state of the liver determines the mouse’s response to rosiglitazone treatment, with PPAR γ-rich fatty livers becoming even more lipid-laden, whereas normal livers actually lose triglycerides.

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