Thiazolidinediones Block Fatty Acid Release by Inducing Glyceroneogenesis in Fat Cells*

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Thiazolidinediones are used to treat type 2 diabetes mellitus because they decrease plasma glucose, insulin, triglyceride, and fatty acid levels. Thiazolidinediones are agonists for peroxisome proliferator-activated receptor γ, a nuclear receptor that is highly expressed in fat tissue. We identify glyceroneogenesis as a target of thiazolidinediones in cultured adipocytes and fat tissues of Wistar rats. The activation of glyceroneogenesis by thiazolidinediones occurs mainly in visceral fat, the same fat depot that is specifically implicated in the progression of obesity to type 2 diabetes. The increase in glyceroneogenesis is a result of the induction of its key enzyme, phosphoenolpyruvate carboxykinase, whose gene expression is peroxisome proliferator-activated receptor γ-dependent in adipocytes. The main role of this metabolic pathway is to allow the re-esterification of fatty acids via a futile cycle in adipocytes, thus lowering fatty acid release into the plasma. The importance of such a fatty acid re-esterification process in the control of lipid homeostasis is highlighted by the existence of a second thiazolidinedione-induced pathway involving glycerol kinase. We show that glyceroneogenesis accounts for at least 75% of the whole thiazolidinedione effect. Because elevated plasma fatty acids promote insulin resistance, these results suggest that the glyceroneogenesis-dependent fatty acid-lowering effect of thiazolidinediones could be an essential aspect of the antidiabetic action of these drugs.

Type 2 diabetes, a major complication of obesity, is a growing problem in many developed countries. Thus, it is important to determine the causes of this affliction and develop more effective treatments. An etiologic factor in type 2 diabetes is an elevated fatty acid level in the blood (1–6). Plasma fatty acids originate from the diet, or, during fasting, they derive from the lipolysis of triacylglycerol, the major form of stored energy in adipose tissue. High circulating levels of fatty acids are known to interfere with glucose utilization in muscle (3) and promote insulin resistance that develops into type 2 diabetes (4).

Obesity is a major risk factor for type 2 diabetes (5). The increased adipose tissue mass in obese people leads to a proportionally larger fatty acid release into the blood as compared with lean people. In one rodent model of obesity (Zucker rats), during development of insulin resistance, fasting plasma fatty acids increase before hyperglycemia arises, which is consistent with a cause and effect relationship (6). It is likely that one reason that a low-fat, low-calorie diet is often an effective treatment for type 2 diabetes is that it reduces circulating fatty acids.

Oral insulin-sensitizing drugs are an important adjunct to diet in the treatment of diabetes. Thiazolidinediones are a class of antidiabetic drugs that increase systemic insulin sensitivity in diabetic animal models and humans (1). Two such drugs, rosiglitazone and pioglitazone, are used in humans to treat type 2 diabetes. They are agonists for peroxisome proliferator-activated receptor γ (PPARγ),1 a member of the nuclear hormone receptor family of transcription factors, which is expressed in fat cells (7). Although much is known about the molecular mechanisms of thiazolidinedione action, many questions remain about the physiological targets mediating better insulin sensitivity. Several lines of evidence have led to the idea that the increased insulin sensitivity of liver and skeletal muscle is secondary to the direct effect of these drugs on adipocytes (1).

A potential thiazolidinedione target in adipocytes concerns fatty acid release. Indeed, thiazolidinedione treatment in vivo is associated with an increase of fatty acid uptake into fat depots, as observed by metabolic studies (8), and a decrease in circulating fatty acid levels (8, 9). Interestingly, in Zucker rats, this PPARγ agonist-induced decrease precedes the reduction in glucose levels. This suggests that decreases in fatty acid levels may be important for the insulin-sensitizing action of thiazolidinediones (10).

Plasma fatty acid levels represent a balance between their release from triacylglycerol stores in adipose tissue and their clearance into tissues that need energy. In humans, it is estimated that 30% or more of the fatty acids liberated by lipolysis are re-esterified into newly synthesized triacylglycerol. This apparent “futile cycle” of simultaneous lipolysis and re-esterification creates an important mechanism for energy homeostasis (11). Regulation of fatty acid re-esterification rate allows fat...
cells to adapt rapidly to changes in peripheral requirements for fatty acids. The re-esterification process requires the production of glycerol-3-phosphate as a substrate for fatty acid re-esterification into triacylglycerol (12). Because glucose supply to the tissue is limited during lipolysis and because adipocytes have no significant glycerol kinase activity, under physiological conditions (13), glycerol-3-phosphate must be synthesized from non-carbohydrate precursors such as lactate, pyruvate, and amino acids. This pathway, glyceroneogenesis, was discovered more than 30 years ago (14, 15).

We have shown that expression of the gene encoding the key glyceroneogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK-C, EC 4.1.1.32; Refs. 12, 14, and 15), is strongly induced by thiazolidinediones via a mechanism involving PPARγ binding and activation in adipose tissue (16). In the present work, we show that PEPCK-C is involved in the action of thiazolidinediones in lowering fatty acid release from adipose tissue. Glycerol kinase was recently demonstrated as another thiazolidinedione-induced enzyme involved in the same process (17). However, our analysis of the respective contributions of glycerol kinase and PEPCK-C suggests that in cultured adipocytes, glyceroneogenesis accounts for at least 75% of the thiazolidinedione effect.

**EXPERIMENTAL PROCEDURES**

**In Vivo and ex Vivo Experiments**—Animal studies were conducted according to the French Guidelines for the Care and Use of Experimental Animals. Female Wistar rats (13 weeks old) were obtained from Iffa Credo (Arbresle, France). The animals were maintained under a constant light/dark cycle (light from 7 a.m. to 7 p.m.) and given free access to food and water. The rats were treated by oral gavage with 5 mg/kg/day rosiglitazone or 5 mg/kg/day pioglitazone or 150 μM thiazolidinedione effect.

**Cell Culture**—The 3T3-F442A adipocyte cell line was differentiated as described previously (16) and then treated for 76 h with 1 μM rosiglitazone or 5 μM pioglitazone in Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum. The medium was changed daily. The day of the experiment, the last thiazolidinedione treatment was performed in Dulbecco’s modified Eagle’s medium without glucose and serum but supplemented with 0.3% fatty acid-free bovine serum albumin for 3 h.

In the experiments carried out under lipolytic conditions, 1 μM isoproterenol was added in the same medium described above, supplemented with 25 mM unlabeled pyruvate and [14C]pyruvate (0.5 μCi/60-mm plate) and 3-mercaptopicolinic acid where indicated. Fatty acid release and glyceroneogenesis (incorporation of pyruvate) were measured in the same procedure with fat extracted by hexane.

In the case of the experiments described in Fig. 5, radiolabeled substrates (1–2 μCi) were added in Krebs-Ringer phosphate buffer with 0.3% fatty acid-free bovine serum albumin for 1 h before lipid extraction. Various glycerol and pyruvate concentrations and 80 μM oleic acid were used as indicated in the figure.

**Biochemical Analyses and Statistics**—Glycerol and non-esterified fatty acids were measured in the incubation medium using colorimetric assays: the GPO Trinder, a glucose oxidase kit from Sigma-Aldrich, was used for glycerol, and the acyl-CoA oxidase kit from Roche Diagnostics was used for fatty acids.

PEPCK-C was measured in adipose tissue that was homogenized in 50 mM triethanolamine buffer, pH 7.2, containing 0.25 mM sucrose and submitted to a 100,000 × g centrifugation for 1 h to obtain the cytosol fraction. PEPCK-C enzymatic activity was determined spectrophoto-

**RESULTS**

**In Vivo Rosiglitazone Treatment Decreases Fatty Acid Release from Adipose Tissues in a Pyruvate-dependent Manner**—We have shown previously (16) that thiazolidinediones increase the amount of PEPCK-C mRNA in adipocytes through a PPARγ-mediated increase in gene transcription. Because PEPCK-C is rate-limiting for glyceroneogenesis, we asked whether the effect of thiazolidinediones on fatty acid release from adipose tissue might involve glyceroneogenesis.

We thus determined the effect of a 4-day treatment of rats with rosiglitazone on the subsequent in vitro release of glycerol and fatty acids from three sources of adipose tissue. Fatty acid release was measured with explants maintained in vitro for 2 h, with or without the glyceroneogenic precursor, pyruvate. Subcutaneous adipose tissue (SCAT) and two abdominal adipose tissues were chosen because of their known physiological differences (20). The two abdominal adipose tissue samples were from the fat pads adjacent to the kidneys (perirenal adipose tissue (PRAT)) and from the greater omentum (omentumal adipose tissue (OAT)).

Pyruvate had no effect on glycerol release (Fig. 1A), although it reduced fatty acid release about 2-fold in PRAT and 3-fold in OAT (Fig. 1B), a result consistent with an increased capacity for the adipocytes from abdominal adipose tissues to re-esterify fatty acids under these conditions. The complete lipolysis of 1 mol of triacylglycerol yields 1 mol of glycerol and 3 mol of fatty acids. Thus, if 100% of the fatty acids were released, then the fatty acid/glycerol ratio would be 3.0. However, fatty acid recycling causes this ratio to be less than 3.0 (Fig. 1C). The fatty acid/glycerol ratio in the absence of added pyruvate indicates that fatty acid re-esterification ranges from 25% in SCAT of control animals (because released fatty acids = 2.25/3.0, or 75%, and the remaining 25% are re-esterified) up to 40% in PRAT and OAT (Fig. 1C). Because pyruvate significantly decreased the fatty acid/glycerol ratio in PRAT, a stimulation of fatty acid recycling is probably occurring (Fig. 1C) in this tissue.

These data are easily explained by a pyruvate-dependent fatty acid recycling via glyceroneogenesis that contributes to a specific decrease in fatty acid release. Results also indicate that glyceroneogenesis is more active in adipose tissue samples taken from the abdomen than in those taken from the subcutaneous region.

Rosiglitazone caused a significant, 41–64% decrease in fatty acid release from all three depots, in both the absence and presence of pyruvate (Fig. 1B). However, rosiglitazone caused only moderate, 7–28% decreases in glycerol release (Fig. 1A). Thus, rosiglitazone treatment reduced fatty acid output to a much greater extent than glycerol release from abdominal adipose tissues. Indeed, the fatty acid/glycerol ratio was decreased by 2–3-fold by rosiglitazone treatment of the rats, depending on the presence of pyruvate in PRAT and OAT (Fig. 1C). Such an observation suggests that the stimulation of fatty acid re-esterification is quantitatively more important than the inhibition of glycerol release for rosiglitazone to decrease fatty
acid output from adipose tissue. This raises the possibility that thiazolidinediones block fatty acid release by stimulating glyceroneogenesis in a pyruvate-dependent manner.

Rosiglitazone Increases Fatty Acid Re-esterification via Glyceroneogenesis and PEPCK-C activity. To confirm that rosiglitazone actually increases glyceroneogenesis in adipose tissue, we carried out the same experiment as that shown in Fig. 1, but in the presence of [14C1]pyruvate. [14C1]Pyruvate was chosen because, in contrast to C2- or C3-labeled molecules, the C1 carbon of pyruvate is conserved in glycerol-3-phosphate synthesis and is thus a specific marker for glyceroneogenesis. Under this condition, the proportion of the released fatty acid molecules that are re-esterified in adipocytes can be detected because they are incorporated as [14C1]glycerol-3-phosphate in triacylglycerol. As shown in Fig. 2A, the incorporation of [14C1]pyruvate into triacylglycerol occurred in all three adipose tissue depots, although it was higher in visceral fat than in subcutaneous fat. Rosiglitazone increased [14C1]pyruvate incorporation 1.5–2-fold in visceral adipose tissues, whereas that in the subcutaneous depot was only slightly affected. Thus, rosiglitazone activates glyceroneogenesis in visceral adipose tissues with an inverse correlation to fatty acid release. The involvement of glyceroneogenesis in re-esterification implies that PEPCK-C specific activity is augmented. This was confirmed by direct measurement of PEPCK-C activity in Fig. 2B. Rosiglitazone treatment increased PEPCK-C specific activity 1.5–2-fold, and the magnitudes of the responses correlated with the depot-specific increase in [14C1]pyruvate incorporation (Fig. 2A) as well as with the decrease in fatty acid release (Fig. 1B). Hence, the rosiglitazone-induced increase in PEPCK-C mRNA that has been reported previously (16) results in the predicted increase of the enzyme itself.

Furthermore, we confirmed the functional involvement of PEPCK-C for fatty acid re-esterification by measuring the incorporation of [14C1]pyruvate into lipids in the presence of a specific inhibitor of PEPCK-C, 3-mercaptopicolinic acid (21). The addition of 150 µM 3-mercaptopicolinic acid in experiments carried out as described in Fig. 2A reduced the amount of
FIG. 3. Rosiglitazone decreases fatty acid release much more than glycerol release both in basal conditions and after a lipolytic stimulus. Experiments were performed as described in the Fig. 1 legend, in the absence of pyruvate (left panels) or in the presence of 25 mM pyruvate (right panels), and with or without 1 μM isoproterenol (IPR) for 2 h. Data are means ± S.E. from duplicate fat pads from three different rats. *, p < 0.05; **, p < 0.01; ***, p < 0.001 (Student’s t test, rosiglitazone versus corresponding control).

Rosiglitazone Specifically Decreases Fatty Acid Release in the Presence of a Lipolytic Stimulus—It was originally demonstrated that glyceroneogenesis was stimulated by fasting, a physiological condition during which CAM production and lipolysis are induced in adipose tissue (14). We thus asked whether rosiglitazone affected this pathway in the presence of a lipolytic stimulus. We used the β-adrenergic agonist, isoproterenol, to induce CAM in adipose tissue from rats that had been treated with rosiglitazone or vehicle, and we analyzed glycerol and fatty acid release. Results obtained with tissues cultured in the presence or absence of pyruvate are shown in Fig. 3 (compare A–C with D–F). As expected, isoproterenol stimulated glycerol and fatty acid release in all three adipose tissue depots whether cultured with pyruvate or not, although the magnitude of response was much higher in PRAT and OAT than in SCAT (Fig. 3, A, B, D, and E). Moreover, pyruvate did not modify glycerol release but strongly reduced fatty acid output with all treatment conditions. This is in agreement with a model whereby stimulation of fatty acid reesterification does not involve glycerol phosphorylation but requires glyceroneogenesis from pyruvate (Fig. 3, compare A and B with D and E). More importantly, rosiglitazone had either a weak effect or no effect on isoproterenol induction of glycerol release (Fig. 3, A and D), although it significantly reduced isoproterenol induction of fatty acid output in all three fat depots (Fig. 3, B and E). Hence, rosiglitazone action occurs whether or not cells are in a basal or lipolytic situation.

Pioglitazone and Rosiglitazone Activate PEPCK-C and Glyceroneogenesis and Decrease Fatty Acid Release from 3T3-F442A Adipocytes—We tested glyceroneogenesis-dependent fatty acid release in 3T3-F442A adipocytes because these cells have been established as a good model for adipose tissue metabolism. We analyzed the responses to rosiglitazone and a second thiazolidinedione, pioglitazone. We also used 3-mercaptopicolinic acid as the specific inhibitor of PEPCK-C (21) to determine the involvement of this enzyme in thiazolidinedione induction of glyceroneogenesis. Lipolysis was induced by isoproterenol for 30 min as described above, and then fatty acid release, glycerol release, and [14C1]pyruvate incorporation into lipids were measured in 3T3-F442A adipocytes that had been pretreated with 1 μM rosiglitazone or 5 μM pioglitazone for 3 days. Rosiglitazone and pioglitazone had similar effects (Fig. 4). Both glitazones significantly decreased fatty acid release (Fig. 4B) without affecting glycerol release (Fig. 4A). Moreover, both drugs increased glyceroneogenesis (Fig. 4D) and PEPCK specific activity 1.7-fold (Fig. 4C). In control cells, 3-mercaptopicolinate significantly enhanced fatty acid release (Fig. 4B) while inhibiting glyceroneogenesis as determined by the incorporation of [14C1]pyruvate into lipids (Fig. 4D). 3-Mercaptopicolinate not only abrogated the rosiglitazone and pioglitazone effects (Fig. 4D) but also increased fatty acid release, regardless of whether cells were thiazolidinedione-treated or not (Fig. 4B), without affecting glycerol release (Fig. 4A). These results indicate that PEPCK-C is involved in basal glyceroneogenesis and that an increase in its enzymatic activity is required for thiazolidinediones to stimulate glyceroneogenesis leading to an inhibition of fatty acid release.
Relative Contributions of PEPCK-C and GyK to Fatty Acid Re-esterification in Control and Rosiglitazone-treated Adipocytes—The results presented above suggest that thiazolidinediones increase fatty acid re-esterification by stimulating glyceroneogenesis. However, the thiazolidinedione induction of GyK, which was recently reported (17), suggested an alternative pathway that could provide glycerol-3-phosphate for fatty acid re-esterification. It was thus important to directly compare these two pathways in order to determine their relative contributions. The results shown in Fig. 5A confirm that rosiglitazone induces GyK ~2.5-fold after a 72-h treatment in adipocytes. As an assessment of the relative contributions of the GyK and PEPCK-C pathways, the extent of lipid labeling was measured by adding either [3H]glycerol or [14C]pyruvate to the culture media of 3T3-F442A adipocytes (Fig. 5, B and C). We reasoned that if rosiglitazone stimulated glyceroneogenesis and glycerol phosphorylation in proportion to the relative inductions of PEPCK-C and GyK, respectively, proportionate increases in triglyceride labeling should occur whether substrates are in limiting amounts or not. We thus used two different concentrations of glycerol (0.1 and 1 mM) and pyruvate (0.2 and 5 mM), the lowest of which was physiological, and the highest of which was saturating. We also reasoned that fatty acids originating from basal lipolysis could be rate-limiting at high glycerol-3-phosphate concentrations. We thus provided oleate (80 μM bound to 40 μM bovine serum albumin) when high substrate concentrations were used. Fig. 5, B and C, shows that rosiglitazone caused ~1.4-2-fold increases in lipid labeling with both substrates. These increases were in agreement with the increases in the enzymatic activities described above (Figs. 4C and 5A). However, a maximum of 5.4 nmol of [3H]glycerol was incorporated into lipids per hour per mg of protein, whereas ~3-fold more [14C]pyruvate was incorporated after rosiglitazone treatment. Taken together, these results suggest that rosiglitazone stimulates fatty acid re-esterification by inducing two pathways: direct glycerol phosphorylation by GyK, and glyceroneogenesis via PEPCK-C. However, glyceroneogenesis accounts for at least 75% of the whole thiazolidinedione effect.

DISCUSSION

The present results support the hypothesis that glyceroneogenesis (via its key enzyme, PEPCK-C) is a major target of the anti-diabetic drug thiazolidinediones by decreasing fatty acid release from adipocytes to control the systemic supply of fatty acids. We also conclude that thiazolidinediones exert a minimal effect on adipocyte lipolytic rate because (i) basal glycerol release is, at best, weakly affected by the drug and (ii) rosiglitazone has no effect on the induction of glycerol release by the β-agonist isoproterenol. In contrast, thiazolidinediones significantly restrained isoproterenol stimulation of fatty acid release because they increase their re-esterification at the same time they are produced from triacylglycerol breakdown. This futile cycle of fatty acid re-esterification during lipolysis is permitted because glycerol-3-phosphate is synthesized from non-carbohydrate sources, such as pyruvate, via glyceroneogenesis and PEPCK-C that are induced by thiazolidinediones.

The importance of glyceroneogenesis via adipocyte PEPCK in the regulation of lipid metabolism has very recently been documented in two transgenic mouse models (12). First, overexpression of PEPCK-C in adipose tissue resulted in obesity caused by activation of glyceroneogenesis and fatty acid re-esterification (22). Unlike other animal models of obesity, these obese transgenic mice never develop insulin resistance, perhaps because their circulating fatty acid levels remain lower than those in non-obese control mice. Second, mice with a tissue-specific ablation of PEPCK-C gene expression in their adipose tissues showed phenotypes consistent with the loss of glyceroneogenesis (23). These adipose specific null mice were mildly lipodystrophic and appeared to be slightly insulin resistant, although not diabetic. Their fat tissue mass was reduced, whereas the release of fatty acids was increased and was not affected by pyruvate. Beyond our own data, such models emphasize the important physiological role of glyceroneogenesis.

![Relative contribution of PEPCK-C and GyK in fatty acid re-esterification ability of control and rosiglitazone-treated adipocytes](http://www.jbc.org/content/18789/1/18789/F5)

**Fig. 5.** Relative contribution of PEPCK-C and GyK in fatty acid re-esterification ability of control and rosiglitazone-treated adipocytes. A, GyK specific activity after 72-h treatment with rosiglitazone (Rosi) in comparison with control (Cont) 3T3-F442A adipocytes. B and C, comparison of [3H]glycerol (B) and [14C]pyruvate (C) incorporation into lipids in response to rosiglitazone treatment. 3T3-F442A adipocytes (day 7 after confluence) were treated with rosiglitazone or vehicle for 72 h and then incubated with labeled metabolites ([3H]glycerol, 1 μCi or [14C]pyruvate, 1 μCi) in Krebs-Ringer phosphate buffer with 0.3% bovine serum albumin for 1 h before lipid extraction. Experiments were performed either in basal conditions (0.1 mM glycerol or 0.2 mM pyruvate) or in the presence of high substrate concentrations (1 mM glycerol or 5 mM pyruvate and 80 μM oleic acid). Data represent the mean ± S.E. of data from three experiments, each performed in triplicate. Statistical analyses are as described in the Fig. 1 legend.
in adipose tissue for controlling circulating fatty acid levels and perhaps preventing diabetes. Because elevated serum fatty acids can promote insulin resistance (4), taken together, these results suggest that glycerconeogenesis activation in adipose tissue, via its key enzyme (PEPCK-C), could help to abrogate diabetes by decreasing the systemic fatty acid supply.

Guan et al. (17) recently reported that thiazolidinediones induce GyK in adipocytes. They proposed this as the mechanism that activates the futile cycle in allowing fatty acid re-esterification. They were apparently unaware of glycerconeogenesis and its contribution to the futile cycle. Guan et al. (17) showed that overexpression of GyK was less than half as efficient as rosiglitazone treatment in decreasing fatty acid release in 3T3-L1 adipocytes. Such a result is in accordance with our data linking glycerconeogenesis to the effect of thiazolidinediones on fatty acid release.

Furthermore, glycerconeogenesis appears to be an important and immediate physiological pathway for regulation of fatty acid release, whereas GyK intervenes only as a response to thiazolidinediones because it has been detected in adipose tissue only at low levels in the absence of drug treatment. We recognize that glycerconeogenesis from pyruvate and direct phosphorylation of glycerol are not mutually exclusive pathways. Indeed, the present study suggests that their respective contributions to glycerol-3-phosphate synthesis for fatty acid re-esterification are in a ratio of 3:1 or more.

According to this revised model, thiazolidinediones would increase insulin sensitivity in tissues such as liver and skeletal muscle by decreasing the release of fatty acids from adipose tissue via the induction of glycerconeogenesis and GyK. In adipose tissue, the resulting increase of fatty acid re-esterification would be facilitated by the concomitant increase of proteins that allow their uptake and acyl-CoA activation, as expected from the reported increase in the corresponding mRNAs by PPARγ agonists (10, 24). Furthermore, it was observed that a 6-month rosiglitazone monotherapy in patients with type 2 diabetes enhances the body weight, although moderately (25).

A number of lines of investigation have implicated PEPCK-C as one etiological factor in type 2 diabetes (12). The present study reinforces that notion by implicating PEPCK-C in an anti-diabetic action of thiazolidinediones. This is perhaps the reason why “fattless” mice (A-Zip/F-1 mice, a lipodystrophic model) that develop type 2 diabetes are not responsive to thiazolidinedione treatment (26). In addition, PEPCK-C is known to lose its adaptive response to fasting with age in rats, whereas its expression is tightly regulated by insulin and counter-regulatory hormones in young animals (14). This could contribute to increased circulating fatty acid levels if such an age-related change occurs in humans. Finally, we found the regulation of glycerconeogenesis to occur mainly in visceral fat, the same fat depot that is specifically implicated in the progression of obesity to type 2 diabetes (27). This is important because the risk of insulin resistance can be predicted according to body fat distribution rather than generalized obesity in humans (27).

In summary, the major finding of this study is that stimulation of PEPCK-C by thiazolidinediones decreases fatty acid release from adipose tissues by increasing glycerconeogenesis. The recently developed adipose tissue PEPCK-C knockout model (23) should prove invaluable in testing the hypothesis that PEPCK-C is an important target for the anti-diabetic actions of thiazolidinediones. These mice will also be useful in testing whether PEPCK-C is involved in the etiology of type 2 diabetes.

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