**Editorial Focus:** PPARγ differentially regulates energy substrate handling in brown vs. white adipose: focus on “The PPARγ agonist rosiglitazone enhances rat brown adipose tissue lipogenesis from glucose without altering glucose uptake”

Justin L. Grobe,1 Marcia Venegas-Pont,2 Curt D. Sigmund,1 and Michael J. Ryan2
1Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, Iowa; and 2Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi


Peroxisome proliferator-activated receptor γ (PPARγ) is a nuclear receptor and ligand-activated transcription factor that is highly expressed in brown adipose tissue (BAT) and is necessary for its development (1, 6, 7). BAT is well recognized for its functions in metabolic rate control in rodents (2), and recent work has also identified significant amounts of BAT in adult humans (9). BAT exhibits relatively high rates of lipid and glucose uptake, and generates significant heat in response to sympathetic activation and other stimuli through lipid oxidation and activation of uncoupling protein-1. In adipocytes, fatty acids are stored as triacylglycerol (TAG). Given the high metabolic activity of this tissue, the regulation of intracellular synthesis and storage of TAG is of great importance for normal BAT function.

Stimulation of PPARγ by synthetic thiazolidinedione (TZD) class agonists, such as rosiglitazone (Avandia) or pioglitazone (Actos) is a common treatment for type 2 diabetes. Activation of PPARγ results in increased whole body insulin sensitivity although the mechanisms involved are not completely understood (10). Rosiglitazone treatment results in a reduction in serum triglycerides, partially through increased sequestration into BAT (8). Unclear, though, are the molecular mechanisms by which PPARγ alters glucose and lipid handling within BAT.

Festuccia et al. (4) present an exciting series of studies into the role of PPARγ and its synthetic agonist, rosiglitazone, in the regulation of BAT glucose and lipid handling. The authors report that 1 wk of rosiglitazone treatment in rats results in decreased levels of plasma insulin and lipids but no effect on the level of plasma glucose. Focusing upon BAT, however, they determined that glucose uptake per adipocyte is depressed by rosiglitazone. This decrease correlated with a reduction in mRNA encoding the GLUT4 transporter leading the authors to speculate the decrease in glucose uptake was GLUT4-dependent. Furthermore, rosiglitazone treatment resulted in a reduction in BAT glycogen content, likely through a suppression of glucose uptake. Therefore, upon PPARγ activation there is a shift in intracellular metabolism favoring lipid storage over glycogen synthesis in BAT (Fig. 1). It remains to be examined whether decreased glucose uptake and storage by BAT results in a decreased thermogenic capacity in animals treated with sympathetic tone and plasma insulin with PPARγ treatment (5), although sympathetic tone was not directly measured in this study.

In contrast to the negative impact of rosiglitazone on BAT glycogen production, such treatment positively regulated several components of TAG synthesis. Specifically, rosiglitazone stimulated glycerokinase, phosphoenolpyruvate carboxykinase, glyceraldehyde 3-phosphate acyltransferase-3, and diacylglycerol acyltransferase-1 activities, possibly through increased transcription. Glycerokinase sequesters glycerol from the circulation and from TAG hydrolysis, phosphoenolpyruvate carboxykinase is involved in glyceroenogenesis, and glyceraldehyde 3-phosphate acyltransferase-3 directs the first fatty acid chain addition to the newly formed glycerol 3-phosphate, thus representing the first directed step in TAG synthesis. Addition of the third fatty acid chain by diacylglycerol acyltransferase-1 represents the final step in TAG synthesis. Thus, upregulation of these enzymes by rosiglitazone results in increased TAG synthesis within BAT. Therefore, upon PPARγ activation there is a shift in intracellular metabolism favoring lipid storage over glycogen synthesis in BAT (Fig. 1).

Fig. 1. Festuccia et al. (4) provide convincing evidence that within brown adipose tissue, the activation of peroxisome proliferator-activated receptor γ (PPARγ) by the thiazolidinedione (TZD) compound rosiglitazone results in a potent shift in cellular metabolism. Specifically, activation of PPARγ results in a reduction in GLUT4-mediated movement of glucose into the cell and reduced glycogen synthesis. In contrast, substantial increases in triacylglycerol (TAG) synthesis are induced through upregulation of multiple enzymes. Thus, the authors conclude that brown adipocytes are not directly involved in the insulin-sensitizing and glucose-clearing actions of TZD compounds, but likely play a key role in the lipid-clearing actions of these drugs.
PPARγ agonists. Alternatively, as the authors propose, it remains to be determined whether lipid substrates are spared for eventual thermogenic activation.

The discovery that BAT is not a contributor to the whole body glucose clearance observed with TZD treatment comes as a surprise, considering the high basal glucose uptake in BAT and the insulin-sensitizing effects of TZD compounds in general. In this regard, recent work from these investigators showed that treatment of rats with rosiglitazone for 1 wk increased glucose uptake in subcutaneous adipose tissue. Moreover, mRNA levels of proteins involved in glycogen synthesis, glycolysis, and the Krebs cycle were increased to a greater extent in subcutaneous adipose when compared to visceral adipose tissue (3). Therefore, the observations of Festuccia et al. (4), along with the previous work of Festuccia and colleagues (3), furthers our understanding of the mechanisms responsible for glucose and lipid homeostasis and highlights the differential effects of PPARγ activation in distinctive adipose tissues. Further investigations into the molecular actions of PPARγ within BAT (as compared to other cell types) may help identify even more efficacious targets for metabolic disorders.

REFERENCES