Role of Peroxisome Proliferator–Activated Receptor-γ in the Glucose-Sensing Apparatus of Liver and β-Cells

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Type 2 diabetes develops in the context of both insulin resistance and β-cell failure. Thiazolidinediones are a class of antidiabetic agents that are known to improve insulin sensitivity in various animal models of diabetes. The improved insulin sensitivity may be achieved either by systemic insulin sensitization or by direct action of peroxisome proliferator–activated receptor (PPAR)-γ on the transcription of genes involved in glucose disposal. Evidence supporting the direct action of PPAR-γ on glucose metabolism is observed in the genes involved in insulin-stimulated glucose disposal. We already showed that GLUT2 and β-glucokinase were directly activated by PPAR-γ. Recently, we have identified and characterized the functional PPAR response element in the GLUT2 and liver type glucokinase (LGK) promoter of the liver. It is well known that adipose tissue plays a crucial role in antidiabetic action of PPAR-γ. In addition, PPAR-γ can directly affect liver and pancreatic β-cells to improve glucose homeostasis. *Diabetes* 53 (Suppl. 1):S60–S65, 2004

Type 2 diabetes affects >5% of the population. The major underlying defect of type 2 diabetes is insulin resistance and progressive deterioration of β-cell functions (1). Diversity of causes including aging, genetic defects, environmental factors, and obesity can trigger the development of insulin resistance. Once insulin resistance develops in several tissues, insulin-stimulated glucose disposal is decreased and adipocytes release many free fatty acids. Furthermore, increased free fatty acids inhibit the insulin action on liver, resulting in increased gluconeogenesis in the hyperglycemic state. Hence, secretory demand of insulin from β-cells is increased. As long as pancreatic β-cells can sense blood glucose levels and secrete sufficient insulin to compensate for insulin resistance, diabetes does not occur. Therefore, type 2 diabetes only develops in the context of both insulin resistance and β-cell failure. The most prominent feature of β-cell failure is the loss of glucose-stimulated insulin secretion (GSIS) resulting from the loss of glucose-sensing ability.

Peroxisome proliferator–activated receptor (PPAR)-γ is a nuclear hormone receptor that comprises an agonist-dependent activation domain (AF-2), DNA binding domain, and agonist-independent activation domain (AF-1). It is expressed predominantly in adipose tissue but is expressed in other tissues as well (2). Upon the binding of the agonists, PPAR-γ heterodimerizes with retinoid X receptor-α and activates the transcription of target genes through the binding of the PPAR response element (PPRE). Synthetic agonists of PPAR-γ, thiazolidinediones (TZDs), have been developed to improve glucose tolerance by enhancing insulin sensitivity and restoring the function of β-cells in diabetic subjects (3–5). There is a strong correlation between the TZD–PPAR-γ interaction and antidiabetic action of TZDs; the relative potency of TZDs for binding to PPAR-γ and activation of PPAR-γ in vitro correlates well with their antidiabetic potency in vivo (6). Patients with a dominant-negative mutation in the PPAR-γ gene show severe hyperglycemia, which provides a genetic link between PPAR-γ and type 2 diabetes (7). TZDs stimulate adipocyte differentiation, preferentially generating smaller adipocytes that are more sensitive to insulin, producing less free fatty acids, tumor necrosis factor-α, and leptin (Fig. 1) (8,9). Although the antidiabetic action of PPAR-γ agonists is well established, there is an argument about the mechanism explaining how these agonists affect glucose metabolism. Improved glucose homeostasis may be achieved either by systemic insulin sensitization or by direct action of PPAR-γ on the transcription of genes involved in the glucose disposal. Evidence supporting the direct action of PPAR-γ on glucose metabolism has been reported. TZDs increase the expression of insulin receptor substrate (IRS)-1 (10), IRS-2 (11), the p85 subunit of phosphatidylinositol 3-kinase (12), and the Cbl-associated protein (13,14). These results are in line with the fact that TZDs increase insulin-stimulated glucose uptake in L6 myotubes (15) and in cultured human skeletal muscle cells (16,17). In addition to the insulin-sensitizing effects in peripheral tissues, PPAR-γ is known to increase the glucose-sensing ability of pancreatic β-cells. TZDs can reduce hepatic glucose production and increase glycogen synthesis in diabetic animal models, although controversial results have been reported.

In this perspective, we present evidence that PPAR-γ agonists directly activate genes of the glucose-sensing apparatus in liver and pancreatic β-cells. These data show a direct involvement of liver and pancreatic β-cells in the

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GK, glucokinase; GSIS, glucose-stimulated insulin secretion; LGK, liver type glucokinase; PPAR, peroxisome proliferator–activated receptor; PPRE, PPAR response element; TZD, thiazolidinedione.

TABLE 1
The effects of TZDs on insulin secretion and glucose-stimulated insulin secretion

Model	Plasma		Insulin secretion	Glucose-stimulated insulin secretion	Reference
	Glucose	Insulin			
HIT-T15 cells			Increased insulin secretion in 11 mmol/l glucose		38
Primary islets from humans			No change	No change	30
Primary islets from ZDF rats			Decrease	Increase	39
Type 2 diabetic humans	Decrease	Decrease	Decrease	Increase	4
db/db mice	Decrease	Increase*	Increased intracellular insulin content of β-cells		35
db/db mice	Decrease	No change	Increased intracellular insulin content of β-cells		37
ob/ob mice	Decrease	Decrease		Increase	34
KK mice	Decrease	Decrease		Increase	34
ZDF rats	Decrease	Decrease	Decrease, increased insulin transcription	Increase	5,33,34,36,40

*NS.

improvement of glucose homeostasis in type 2 diabetes subjects using PPAR-γ agonists.

GLUCOSE-SENSING APPARATUS IN β-CELLS AND LIVER

Blood glucose levels are tightly regulated in the range of ~5 mmol/l in concentration. Several tissues are involved in maintaining glucose homeostasis. Among them, liver and pancreatic β-cells are most important because they can sense and respond to changing blood glucose levels. The glucose-sensing apparatus consists of glucose transporter isotype 2 (GLUT2) and glucokinase (GK) (18). Whereas the GLUT2 gene is known to contain one promoter, the GK gene contains two widely separated and functionally distinct promoters that express tissue-specific GK isotypes in liver (liver type glucokinase [LGK]) and pancreatic β-cells (βGK) (19). Glucose is taken up into the cell through GLUT2, and GK traps glucose in the cytoplasm by phosphorylation. Both GLUT2 and GK, which have high K_m, high capacity, and low affinity in nature, can afford to sense the fluctuation of glucose concentration in the blood (20).

In pancreatic β-cells, glucose is the primary physiological stimulus for insulin secretion, the process that requires glucose sensing (18). βGK is the rate-limiting step in glycolytic flux for insulin secretion, and a small change in GK activity significantly affects the threshold for GSIS (20). GLUT2 is known to play more permissive roles, allowing rapid equilibration of glucose across the plasma membrane. However, it is also essential in GSIS because normal glucose uptake and subsequent metabolic signaling for GSIS cannot be achieved without GLUT2. In diabetic subjects, GLUT2 and GK expression is decreased before the loss of GSIS. β-Cell–specific knockout of GLUT2 or GK results in infant death because of severe hyperglycemia (21,22). In addition, the fact that adenovirus-mediated expression of GLUT2 and GK in IL cells results in gaining of glucose sensitivity supports the integral relationship between these two proteins (23).

Glucose is known to regulate the transcription of several genes involved in the major metabolic pathways in the liver (24). The hepatic glucose-sensing apparatus enables glucose to regulate the expression of glucose-responsive genes such as L-type pyruvate kinase, S14, fatty acid synthase, and GLUT2. Thus, the glucose-sensing apparatus exerts a strong influence on glucose utilization and glycogen synthesis. Increased intracellular glucose-6-phosphate triggers glycolysis and glycogen synthesis (25). Even small changes in the expression of LGK lead to a measurable impact on the blood glucose concentration (26–28). In addition, liver-specific GLUT2 knockout mice showed decreased GK expression in liver (29). Thus, these two proteins play key roles in hepatic glucose metabolism and lipogenesis.

ROLE OF PPAR-γ IN THE GLUCOSE-SENSING APPARATUS OF PANCREATIC β-CELLS

GLUT2 and βGK work as glucose sensors for GSIS under physiological conditions in pancreatic β-cells. In diabetic β-cells, gene expressions of GLUT2 and GK are decreased and high-affinity low-capacity hexokinase expression is increased instead, which results in a decrease in glucose threshold for insulin secretion. As a consequence, basal insulin secretion will be increased. Thus, β-cells lose their

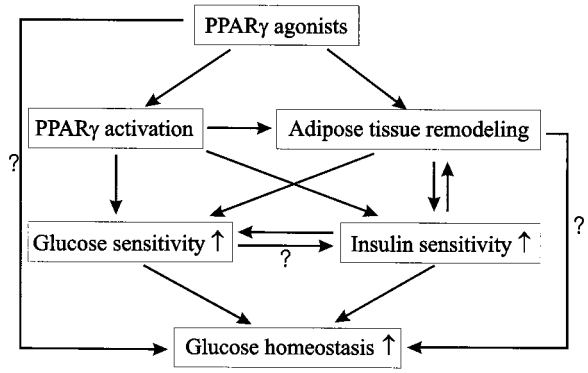

FIG. 1. Effect of PPAR-γ agonists on glucose homeostasis. It is generally accepted that PPAR-γ agonists induce adipose tissue remodeling. Improved glucose homeostasis is achieved by both increased glucose and insulin sensitivity of tissues. Direct action of PPAR-γ activation on the genes involved in glucose homeostasis is not well understood.

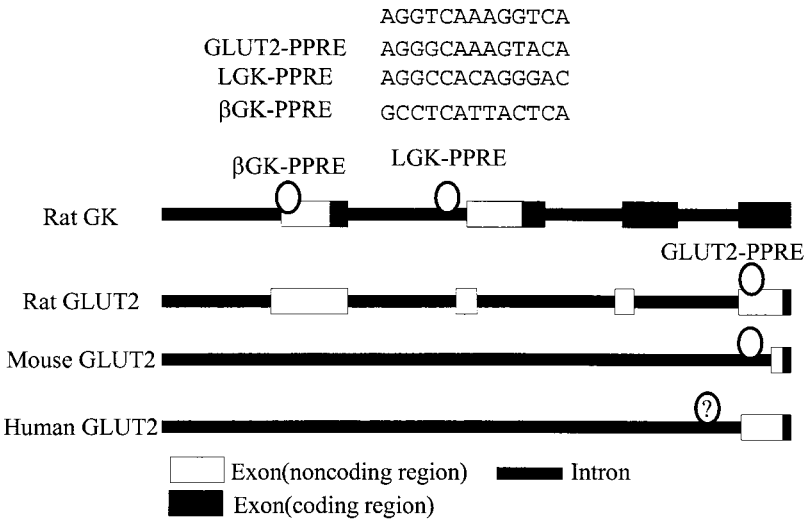

FIG. 2. Structure and localization of PPRE in the glucose sensor promoters of liver and β-cells.

ability to control the insulin secretion in response to blood glucose concentration, thereby gradually losing their predominant position in blood glucose regulation in insulin-resistant states.

Moderate amounts of PPAR-γ are expressed in pancreatic β-cells, and its expression is increased in the diabetic state (30,31). TZDs are known to enhance pancreatic growth (32). But the fundamental role of PPAR-γ in β-cells is not fully understood. Currently, the reports on the effects of PPAR-γ on insulin secretion are contradictory. PPAR-γ agonists can decrease insulin secretion in diabetic animal models, whereas activation of PPAR-γ does not acutely improve insulin secretion in isolated human islets (Table 1) (4,5,30,33–40). However, it is reported that PPAR-γ agonists can protect the β-cells from apoptosis and restore the function of β-cells, including GSIS (39,41,42). In ZDF rats, which have obese and diabetic phenotypes, blood glucose and free fatty acid levels are elevated, resulting in intracellular accumulation of triglyceride. Intracellular triglyceride accumulation induces apoptosis of β-cells by increasing ceramide formation and nitric oxide production; therefore, β-cell failure develops (so called, "lipoapoptosis hypothesis," as proposed by Unger [43]). TZDs are known to decrease intracellular fat accumulation by increasing fatty acid oxidation and inhibit the expression of iNOS, suggesting that PPAR-γ can prevent apoptosis of β-cells. In addition, TZDs can restore the GSIS, both in diabetic animal models and in primary isolated islets (39,41). Activation of PPAR-γ leads to restoration of the glucose-sensing ability of β-cells through the activation of GLUT2 and βGK gene expression in diabetic subjects. The functional response element for PPAR-γ was identified in the promoters of GLUT2 and βGK (44,45). The PPREs of GLUT2 and βGK genes are located in the 5′ untranslated region. In transient transfection assays, βGK and GLUT2 promoters are activated by PPAR-γ in insulin-producing β-cell lines (HIT-T15, Min6). In addition to the direct activation of GLUT2 and βGK,

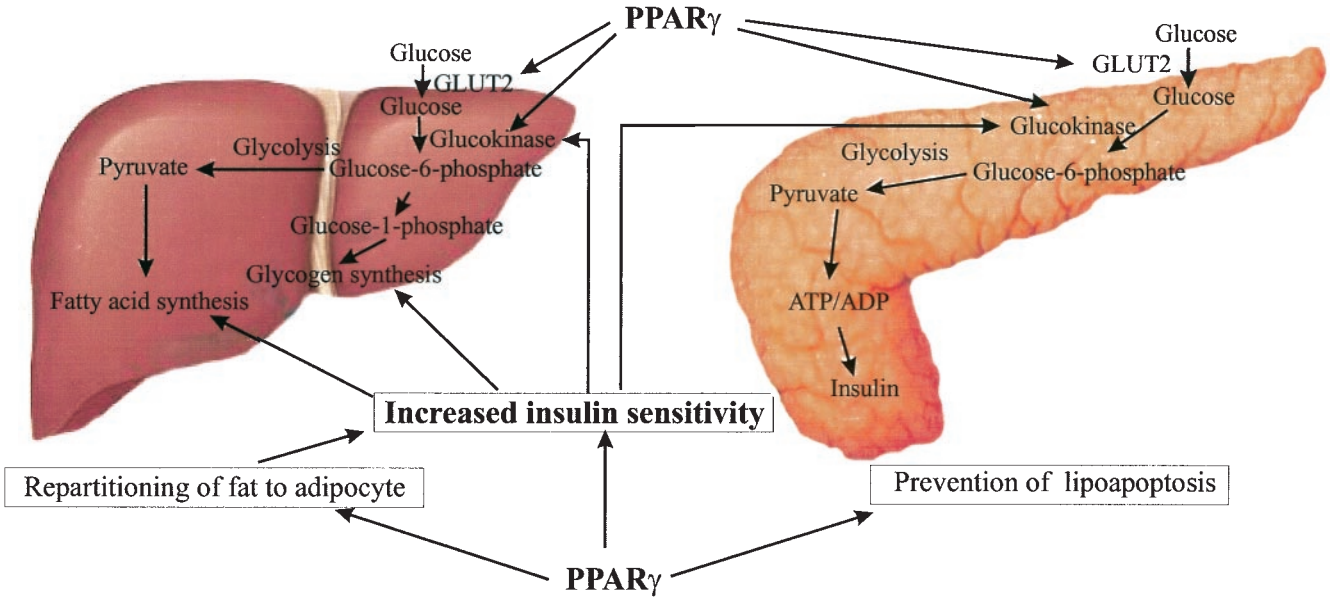

FIG. 3. Schematic diagram illustrating possible mode of action of activated PPAR-γ on the glucose sensors of the β-cell and liver. The increased transcription of GLUT2/GK genes by PPAR-γ ligands may contribute to improved glucose homeostasis.

TZDs can prevent glucotoxic effects on PDX-1 expression in diabetic β-cells, indirectly resulting in an increase in the expression of GLUT2 and βGK (40). Oral administration of TZDs increases the expression of GLUT2 and βGK in the β-cells of diabetic ZDF rats. Restoration of GSIS and a decrease in basal insulin secretion are achieved by TZD treatment in the primary isolated islets from diabetic ZDF rats (39). These TZD-induced changes of GSIS in isolated diabetic β-cells resemble the hyperinsulinemic pattern of compensated β-cells. In this context, it is assumed that TZDs play some role in restoring β-cells of type 2 diabetes to a normal state.

In the course of studying the PPRE present in the genes of the β-cell glucose-sensing apparatus, we observed some differences between the PPRE of GLUT2 and βGK. Firstly, the DNA sequence of βGK-PPRE is different from conventional PPRE, known as DR+1 (a hexameric consensus sequence [AGGTCA] in a direct repeat spaced by one nucleotide), whereas GLUT2-PPRE is similar to DR+1 (Fig. 2) (46). Secondly, GLUT2-PPRE is highly ligand dependent but βGK-PPRE is not. These differences suggest that transcriptional regulation of βGK by PPAR-γ is different from that of GLUT2 and the detailed mechanism for the differences needs to be clarified.

ROLE OF PPAR-γ IN THE GLUCOSE-SENSING APPARATUS OF THE LIVER

TZDs are known to decrease free fatty acid and hepatic glucose production. When diabetic ZDF rats are treated with PPAR-γ agonists, PEPCK and glucose-6-phosphatase expressions are decreased and GK and lipogenic gene expressions are increased, suggesting that PPAR-γ agonists decrease gluconeogenesis and increase adipogenesis and glycolysis (33). But it is still unclear whether these effects are due to a direct action of PPAR-γ on the liver or secondary effects of increased systemic insulin sensitivity. PPAR-γ agonists decrease circulating triglyceride and free fatty acid levels by repartitioning fatty acids in adipocytes. Increased free fatty acids are associated with hepatic insulin resistance, resulting in the increased gluconeogenesis (47). In diabetic ZDF rats treated with PPAR-γ agonists, a PPAR-γ–induced decrease of free fatty acid levels precedes the decrease of glucose and triglyceride levels, suggesting that a decrease in free fatty acid levels may be important for the insulin-sensitizing action of PPAR-γ agonists (33). Thus, PPAR-γ agonists may indirectly affect hepatic glucose metabolism by lowering free fatty acid levels.

However, mice lacking adipose tissue still showed increased insulin sensitivity by TZDs, suggesting that TZDs can enhance insulin sensitivity independent of adipose tissues (48), although controversial results were reported. The fact that liver expresses moderate amounts of PPAR-γ led us to explore the possibility that PPAR-γ can directly regulate the genes responsible for glucose homeostasis. Thus, we have searched for the presence of PPRE in the glucose-sensing apparatus of the liver. The mouse GLUT2 promoter is highly activated by PPAR-γ in liver cell lines, and we identify the functional PPRE in the mouse GLUT2 promoter. In primary isolated hepatocytes, TZDs can increase GLUT2 expression (Kim et al., unpublished data). In addition, we also identified a functional PPRE in the LGK promoter. In transient transfection assays, the LGK promoter is activated by PPAR-γ in Alexander cells, whereas the activation of the promoter is not remarkable in CV-1 and Min-6 cells. Like GLUT2, GK expression is also increased by TZDs in primary hepatocytes (S. Kim, H.I.K., S.-K. Park, S.-S. Im, T. Li, H.G. Cheon, Y.H.A., unpublished data). These results indicate that GLUT2 and GK can be direct targets of PPAR-γ in the liver, and PPAR-γ agonists can directly increase glucose uptake and glycolysis. Furthermore, accompanying glycolysis and glycogenesis can counteract the hepatic glucose production. However, the direct action of PPAR-γ agonists on the LGK gene cannot be the sole mechanism of LGK activation because insulin is known to induce LGK expression in the liver.

CONCLUSIONS

We have identified functional PPREs in the promoters of GLUT2 and GK in pancreatic β-cells and liver. This work suggests that the antidiabetic action of TZDs could be not only due to systemic improvement of insulin sensitivity but also due to direct action of PPAR-γ on the genes involved in the glucose transport and subsequent glycolysis. Thus, based on the direct action of PPAR-γ on the glucose-sensing apparatus in liver and β-cells of pancreas, the antidiabetic action of TZDs can be summarized as combinatorial effects involving several target tissues (Fig. 3). Enhanced insulin sensitivity improves peripheral glucose disposal, which reduces the demand for insulin secretion from β-cells and hepatic glucose production. Considering that liver and pancreatic β-cells are targets of insulin, enhanced insulin sensitivity contributes to the insulin-dependent activation of hepatic glucose metabolism and functional restoration of β-cells. In addition, glucose is known to play important roles in the maturation of β-cells (49); an enhanced glucose-sensing ability induced by PPAR-γ may help functional and morphological restoration of β-cells by TZDs (41). Increased expression of GK and GLUT2 in liver can increase glycolysis and glycogen synthesis. Therefore, TZDs may decrease blood glucose and insulin levels efficiently.

Taken together, PPAR-γ–mediated activation of GLUT2 and GK in liver and β-cells is likely to contribute to the beneficial effects by which TZDs improve glucose homeostasis in type 2 diabetic patients.

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REFERENCES

1. Saltiel AR: New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell* 104:517–529, 2001
2. Auboeuf D, Rieusset J, Fajas L, Vallier P, Frering V, Riou JP, Staels B, Auwerx J, Laville M, Vidal H: Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator–activated receptors and liver X receptor-alpha in humans: no alteration in adipose tissue of obese and NIDDM patients. *Diabetes* 46:1319–1327, 1997
3. Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J: Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. *N Engl J Med* 331:1188–1193, 1994
4. Cavaghan MK, Ehrmann DA, Byrne MM, Polonsky KS: Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. *J Clin Invest* 100: 530–537, 1997

5. Sreenan S, Sturis J, Pugh W, Burant CF, Polonsky KS: Prevention of hyperglycemia in the Zucker diabetic fatty rat by treatment with metformin or troglitazone. *Am J Physiol* 271:E742–E747, 1996
6. Berger J, Bailey P, Biswas C, Cullinan CA, Doebber TW, Hayes NS, Saperstein R, Smith RG, Leibowitz MD: Thiazolidinediones produce a conformational change in peroxisomal proliferator–activated receptor-gamma: binding and activation correlate with antidiabetic actions in db/db mice. *Endocrinology* 137:4189–4195, 1996
7. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA, Maslen GL, Williams TD, Lewis H, Schafer AJ, Chatterjee VK, O'Rahilly S: Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 402:880–883, 1999
8. Auwerx J: PPARgamma, the ultimate thrifty gene. *Diabetologia* 42:1033–1049, 1999
9. Spiegelman BM: PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 47:507–514, 1998
10. Iwata M, Haruta T, Usui I, Takata Y, Takano A, Uno T, Kawahara J, Ueno E, Sasaoka T, Ishibashi O, Kobayashi M: Pioglitazone ameliorates tumor necrosis factor-alpha-induced insulin resistance by a mechanism independent of adipogenic activity of peroxisome proliferator–activated receptor-gamma. *Diabetes* 50:1083–1092, 2001
11. Smith U, Gogg S, Johansson A, Olausson T, Rotter V, Svalstedt B: Thiazolidinediones (PPARgamma agonists) but not PPARalpha agonists increase IRS-2 gene expression in 3T3–L1 and human adipocytes. *FASEB J* 15:215–220, 2001
12. Rieusset J, Auwerx J, Vidal H: Regulation of gene expression by activation of the peroxisome proliferator–activated receptor gamma with rosiglitazone (BRL 49653) in human adipocytes. *Biochem Biophys Res Commun* 265:265–271, 1999
13. Ribon V, Johnson JH, Camp HS, Saltiel AR: Thiazolidinediones and insulin resistance: peroxisome proliferator activated receptor gamma activation stimulates expression of the CAP gene. *Proc Natl Acad Sci U S A* 95:14751–14756, 1998
14. Baumann CA, Chokshi N, Saltiel AR, Ribon V: Cloning and characterization of a functional peroxisome proliferator activator receptor-gamma-responsive element in the promoter of the CAP gene. *J Biol Chem* 275:9131–9135, 2000
15. Zhang B, Szalkowski D, Diaz E, Hayes N, Smith R, Berger J: Potentiation of insulin stimulation of phosphatidylinositol 3-kinase by thiazolidinedione-derived antidiabetic agents in Chinese hamster ovary cells expressing human insulin receptors and L6 myotubes. *J Biol Chem* 269:25735–25741, 1994
16. Kausch C, Krutzfeldt J, Witke A, Rettig A, Bachmann O, Rett K, Matthaei S, Machicao F, Haring HU, Stumvoll M: Effects of troglitazone on cellular differentiation, insulin signaling, and glucose metabolism in cultured human skeletal muscle cells. *Biochem Biophys Res Commun* 280:664–674, 2001
17. Cha BS, Ciaraldi TP, Carter L, Nikoulina SE, Mudaliar S, Mukherjee R, Paterniti JR Jr, Henry RR: Peroxisome proliferator–activated receptor (PPAR) gamma and retinoid X receptor (RXR) agonists have complementary effects on glucose and lipid metabolism in human skeletal muscle. *Diabetologia* 44:444–452, 2001
18. Schuit FC, Huypens P, Heimberg H, Pipeleers DG: Glucose sensing in pancreatic beta-cells: a model for the study of other glucose-regulated cells in gut, pancreas, and hypothalamus. *Diabetes* 50:1–11, 2001
19. Magnuson MA: Glucokinase gene structure: functional implications of molecular genetic studies. *Diabetes* 39:523–527, 1990
20. Matschinsky FM, Magnuson MA: Molecular pathogenesis of MODYs. In *Frontiers in Diabetes*. Vol. 15. Belfiore F, Ed. Basel, Karger, 2000
21. Thorens B, Guillam MT, Beermann F, Burcelin R, Jaquet M: Transgenic reexpression of GLUT1 or GLUT2 in pancreatic beta cells rescues GLUT2-null mice from early death and restores normal glucose-stimulated insulin secretion. *J Biol Chem* 275:23751–23758, 2000
22. Postic C, Shiota M, Niswender KD, Jetton TL, Chen Y, Moates JM, Shelton KD, Lindner J, Cherrington AD, Magnuson MA: Dual roles for glucokinase in glucose homeostasis as determined by liver and pancreatic beta cell-specific gene knock-outs using Cre recombinase. *J Biol Chem* 274: 305–315, 1999
23. Faradji RN, Havari E, Chen Q, Gray J, Tornheim K, Corkey BE, Mulligan RC, Lipes MA: Glucose-induced toxicity in insulin-producing pituitary cells that coexpress GLUT2 and glucokinase: implications for metabolic engineering. *J Biol Chem* 276:36695–36702, 2001
24. Girard J, Ferre P, Foufelle F: Mechanisms by which carbohydrates regulate expression of genes for glycolytic and lipogenic enzymes. *Annu Rev Nutr* 17:325–352, 1997
25. Aiston S, Trinh KY, Lange AJ, Newgard CB, Agius L: Glucose-6-phosphatase overexpression lowers glucose 6-phosphate and inhibits glycogen synthesis and glycolysis in hepatocytes without affecting glucokinase translocation: evidence against feedback inhibition of glucokinase. *J Biol Chem* 274:24559–24566, 1999
26. Ferre T, Riu E, Bosch F, Valera A: Evidence from transgenic mice that glucokinase is rate limiting for glucose utilization in the liver. *FASEB J* 10:1213–1218, 1996
27. Hariharan N, Farrelly D, Hagan D, Hillyer D, Arbeeny C, Sabrah T, Treloar A, Brown K, Kalinowski S, Mookhtiar K: Expression of human hepatic glucokinase in transgenic mice liver results in decreased glucose levels and reduced body weight. *Diabetes* 46:11–16, 1997
28. Niswender KD, Shiota M, Postic C, Cherrington AD, Magnuson MA: Effects of increased glucokinase gene copy number on glucose homeostasis and hepatic glucose metabolism. *J Biol Chem* 272:22570–22575, 1997
29. Burcelin R, del Carmen Munoz M, Guillam MT, Thorens B: Liver hyperplasia and paradoxical regulation of glycogen metabolism and glucose-sensitive gene expression in GLUT2-null hepatocytes: further evidence for the existence of a membrane-based glucose release pathway. *J Biol Chem* 275:10930–10936, 2000
30. Dubois M, Pattou F, Kerr-Conte J, Gmyr V, Vandewalle B, Desreumaux P, Auwerx J, Schoonjans K, Lefebvre J: Expression of peroxisome proliferator–activated receptor gamma (PPARgamma) in normal human pancreatic islet cells. *Diabetologia* 43:1165–1169, 2000
31. Laybutt R, Hasenkamp W, Groff A, Grey S, Jonas JC, Kaneto H, Sharma A, Bonner-Weir S, Weir G: Beta-cell adaptation to hyperglycemia. *Diabetes* 50 (Suppl. 1):S180–S181, 2001
32. Jia DM, Otsuki M: Troglitazone stimulates pancreatic growth in normal rats. *Pancreas* 24:303–312, 2002
33. Way JM, Harrington WW, Brown KK, Gottschalk WK, Sundseth SS, Mansfield TA, Ramachandran RK, Willson TM, Kliewer SA: Comprehensive messenger ribonucleic acid profiling reveals that peroxisome proliferator-activated receptor gamma activation has coordinate effects on gene expression in multiple insulin-sensitive tissues. *Endocrinology* 142:1269–1277, 2001
34. Fujiwara T, Yoshioka S, Yoshioka T, Ushiyama I, Horikoshi H: Characterization of new oral antidiabetic agent CS-045: studies in KK and ob/ob mice and Zucker fatty rats. *Diabetes* 37:1549–1558, 1988
35. Fujiwara T, Wada M, Fukuda K, Fukami M, Yoshioka S, Yoshioka T, Horikoshi H: Characterization of CS-045, a new oral antidiabetic agent. II. Effects on glycemic control and pancreatic islet structure at a late stage of the diabetic syndrome in C57BL/KsJ-db/db mice. *Metabolism* 40:1213–1218, 1991
36. Brown KK, Henke BR, Blanchard SG, Cobb JE, Mook R, Kaldor I, Kliewer SA, Lehmann JM, Lenhard JM, Harrington WW, Novak PJ, Faison W, Binz JG, Hashim MA, Oliver WO, Brown HR, Parks DJ, Plunket KD, Tong WQ, Menius JA, Adkison K, Noble SA, Willson TM: A novel N-aryl tyrosine activator of peroxisome proliferator–activated receptor-gamma reverses the diabetic phenotype of the Zucker diabetic fatty rat. *Diabetes* 48:1415–1424, 1999
37. Lenhard JM, Lancaster ME, Paulik MA, Weiel JE, Binz JG, Sundseth SS, Gaskill BA, Lightfoot RM, Brown HR: The RXR agonist LG100268 causes hepatomegaly, improves glycaemic control and decreases cardiovascular risk and cachexia in diabetic mice suffering from pancreatic beta-cell dysfunction. *Diabetologia* 42:545–554, 1999
38. Masuda K, Okamoto Y, Tsuura Y, Kato S, Miura T, Tsuda K, Horikoshi H, Ishida H, Seino Y: Effects of troglitazone (CS-045) on insulin secretion in isolated rat pancreatic islets and HIT cells: an insulinotropic mechanism distinct from glibenclamide. *Diabetologia* 38:24–30, 1995
39. Shimabukuro M, Zhou YT, Lee Y, Unger RH: Troglitazone lowers islet fat and restores beta cell function of Zucker diabetic fatty rats. *J Biol Chem* 273:3547–3550, 1998
40. Harmon JS, Gleason CE, Tanaka Y, Oseid EA, Hunter-Berger KK, Robertson RP: In vivo prevention of hyperglycemia also prevents glucotoxic effects on PDX-1 and insulin gene expression. *Diabetes* 48:1995–2000, 1999
41. Higa M, Zhou YT, Ravazzola M, Baetens D, Orci L, Unger RH: Troglitazone prevents mitochondrial alterations, beta cell destruction, and diabetes in obese prediabetic rats. *Proc Natl Acad Sci U S A* 96:11513–11518, 1999
42. Shimabukuro M, Wang MY, Zhou YT, Newgard CB, Unger RH: Protection against lipoapoptosis of beta cells through leptin-dependent maintenance of Bcl-2 expression. *Proc Natl Acad Sci U S A* 95:9558–9561, 1998
43. Unger RH: Lipotoxic diseases. *Annu Rev Med* 53:319–336, 2002
44. Kim HI, Kim JW, Kim SH, Cha JY, Kim KS, Ahn YH: Identification and

functional characterization of the peroxisomal proliferator response element in rat GLUT2 promoter. *Diabetes* 49:1517–1524, 2000
45. Kim HI, Cha JY, Kim SY, Kim JW, Roh KJ, Seong JK, Lee NT, Choi KY, Kim KS, Ahn YH: Peroxisomal proliferator–activated receptor-gamma upregulates glucokinase gene expression in beta-cells. *Diabetes* 51: 676–685, 2002
46. Palmer CN, Hsu MH, Griffin HJ, Johnson EF: Novel sequence determinants in peroxisome proliferator signaling. *J Biol Chem* 270:16114–16121, 1995
47. Randle PJ: Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metab Rev* 14:263–283, 1998
48. Burant CF, Sreenan S, Hirano K, Tai TA, Lohmiller J, Lukens J, Davidson NO, Ross S, Graves RA: Troglitazone action is independent of adipose tissue. *J Clin Invest* 100:2900–2908, 1997
49. Dudek RW, Kawabe T, Brinn JE, O'Brien K, Poole MC, Morgan CR: Glucose affects in vitro maturation of fetal rat islets. *Endocrinology* 114:582–587, 1984