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Effects of antihyperlipidemic agents on hepatic insulin sensitivity in perfused Goto-Kakizaki rat liver

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Background. We previously reported that the Goto-Kakizaki (GK) rat, an animal model of type 2 diabetes, has hepatic insulin resistance using a perfused rat liver model. Pioglitazone, eicosapentaenoic acid (EPA), and fenofibrate are antihyperlipidemic agents and improve glucose tolerance. There have been few studies showing that these agents directly improve hepatic insulin sensitivity in type 2 diabetes mellitus. The aim of this study was to explore the effects of these agents on hepatic insulin sensitivity directly using a perfused GK rat liver model. ***Methods.*** GK rats were treated with oral pioglitazone (6 or 10mg/kg body weight), EPA (1 or 2g/kg body weight), or fenofibrate (30mg/kg body weight) for 2 weeks. Livers were perfused in situ with glucagon or with glucagon and insulin, and hepatic glucose outputs were measured. ***Results.*** In the pioglitazone-treated GK rats, blood glucose levels were significantly decreased. In the pioglitazone- and EPA-treated GK rats, insulin infusion significantly attenuated hepatic glucose output stimulated by glucagon. In the fenofibrate-treated GK rats, fat deposits in the hepatocytes were decreased, and glucose output elicited by glucagon was significantly decreased compared with that in the untreated GK rats, whereas insulin infusion did not affect glucose output by glucagon. ***Conclusions.*** These findings suggest that pioglitazone and EPA may improve glucose tolerance by directly increasing hepatic insulin sensitivity, while fenofibrate may improve glucose tolerance by improving hepatic glycogen metabolism in the GK rats.

Key words: type 2 diabetes mellitus, insulin sensitivity, liver, pioglitazone, eicosapentaenoic acid, fenofibrate

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Introduction

Type 2 diabetes mellitus is characterized by a relative defect of insulin secretion or insulin sensitivity.[1] Insulin resistance in peripheral tissue, such as adipose tissue and skeletal muscle, decreases glucose utilization, and insulin resistance in liver increases glucose production.[2] The Goto-Kakizaki (GK) rat is a spontaneous model of type 2 diabetes.[3] We previously reported that in the liver of the GK rat an antagonistic effect of insulin on glucagon-induced hepatic glucose production was decreased using a perfused rat liver model.[4]

Pioglitazone, an antidiabetic agent belonging to the thiazolidinedione class of drugs, was reported to be a ligand for peroxisome proliferator-activated receptor (PPAR)-γ and to lower blood glucose in insulin-resistant obese or diabetic rodent models by improving insulin sensitivity and by correcting dyslipidemia.[5] A few studies have reported the mechanism by which thiazolidinedione improves insulin sensitivity on target tissues, i.e., fat,[6] muscle,[7,8] and liver.[9]

A possible role for dietary fatty acid composition in insulin resistance was reported. The fatty acid composition of muscle phospholipids is strongly related both to fasting insulin levels and to insulin sensitivity.[10] Some studies reported that eicosapentaenoic acid (EPA), polyunsaturated fatty acid, reduces plasma lipids and improves glucose intolerance in diabetic rats.[11] The mechanism of these compounds on improvement of insulin resistance in the liver remains unknown.

Fibrates have been used successfully to treat hyperlipidemia.[12] The action of fibrates on lipid metabolism is mediated by the activation of PPAR-α.[13] Because fibrate treatment stimulates hepatic fatty acid oxidation without stimulating skeletal muscle fatty acid oxidation,[14] the Randle hypothesis[15] would predict that an increase in hepatic fatty acid oxidation improves peripheral glucose tolerance. Recent findings suggested that PPAR-α activation improves insulin sensitivity in

two different animal models of insulin resistance, obese fa/fa Zucker rats and high-fat-fed C57BL/6 mice.[16]

The liver is a key regulatory organ of glucose homeostasis. Blood glucose levels are maintained within a narrow range because the liver is able to take up glucose in the fed state and to release it into the circulation during starvation and exercise. Impairments in both hepatic glucose production and uptake are characteristic of the diabetic state.[17] There has been little direct evidence that pioglitazone, EPA, and fenofibrate improve insulin sensitivity in the liver. The aim of this study was to explore the effects of these antihyperlipidemic and antidiabetic agents on hepatic insulin sensitivity directly using a perfused GK rat liver.

Materials and methods

Animals

Diabetic male GK rats were obtained from our local colony with progenitors issued from the original colony established by Goto et al.[3] Male GK rats were kept on a 12-h light : dark cycle (lights on 6 A.M. to 6 P.M.) with free access to water and laboratory chow (MF; Oriental Yeast, Tokyo, Japan). Male Wistar rats (Clea Japan, Osaka, Japan) were used as nondiabetic controls of the same genetic origin. The experimental protocol was approved by the Animal Studies Committee of Ehime University.

Reagents

Pioglitazone, 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy] benzyl]-2,4-thiazolidinedione, was provided by Takeda Chemical Industries, Osaka, Japan. EPA, C 20 : 5 ω-3 polyunsaturated fatty acid, was provided by Mochida Pharmaceutical (Tokyo, Japan). Fenofibrate was obtained from Kaken Pharmaceutical (Tokyo, Japan). Some GK rats weighing about 130 g were daily treated with oral pioglitazone (6 or 10 mg/kg body weight), EPA (1 or 2 g/kg body weight), or fenofibrate (30 mg/kg body weight) for 2 weeks.

Liver perfusion

Liver perfusion was started between 11 A.M. and noon. Livers were perfused in situ without recirculation in a 37°C cabinet via the portal vein using Krebs–Henseleit bicarbonate buffer as previously reported.[4] The medium was equilibrated with 95% O_2 and 5% CO_2. The perfusion pressure was constant at about 10 cm H_2O with a flow rate of 3.7–4.2 ml/min/g liver weight under basal conditions. The flow rate was measured by fractionating the effluent. Glucagon and insulin (Sigma, St. Louis, MO, USA) were first dissolved in 0.1 M HCl at 10 and 100 nM, respectively, and diluted into the perfusion medium to 0.06 and 0.3 nM, respectively, for infusion. Glucagon was infused from minute 10 to minute 15, and insulin was from minute 5 to minute 15, during the perfusion period.

Measurement of glucose output

Blood samples during the liver perfusion were taken from the inferior caval vein. Glucose concentration was assayed by a colorimetric method using glucose oxidase (Blood Sugar-GOD-PAP; Roche Diagnostics, Mannheim, Germany).

Statistical analysis

All observations were repeated at least three times in independent experiments and were expressed as means ± SEM. Data were analyzed using the Kruskal–Wallis test or two-tailed analyzed using two-way analysis of variance followed by Newman–Keul's test for multiple comparisons. A $P < 0.05$ was regarded as significant.

Results

Body and liver weights of the rats at liver perfusion

Body weight of the rats in each group was almost the same. Liver weight in the GK rats treated with more than 60 mg/kg fenofibrate was increased two times heavier than that in the untreated GK rats, whereas that in the 30 mg/kg fenofibrate-treated GK rats was slightly heavier (Table 1). We decided the dose of administration of fenofibrate was 30 mg/kg per day.

Blood glucose concentration levels in the rats

Blood glucose levels at the time of liver perfusion were significantly decreased in the pioglitazone-treated GK rats compared with the untreated GK rats, whereas those in the EPA- or fenofibrate-treated GK rats did not differ (Table 2).

Glucose output in the GK rats

In the GK rats, infusion of 0.3 nM insulin beginning at 5 min before the onset of 0.06 nM glucagon infusion did not decrease glucose output compared with that in the Wistar rats (Fig. 1).

Effect of pioglitazone on glucose output in the GK rats

In the 6 and 10 mg/kg pioglitazone-treated GK rats, insulin infusion significantly attenuated (~30%, $P < 0.05$) glucose output induced by glucagon (Fig. 2).

Table 1. Body and liver weights of the rats in each group at liver perfusion

	n	Body weight (g)	Liver weight (g)	Liver/body weight ratio (%)
Wistar				
G	7	210 ± 4[a]	8.6 ± 0.7	4.1 ± 0.2
G + I	5	215 ± 6	9.1 ± 0.8	4.2 ± 0.1
GK				
G	5	214 ± 5	8.7 ± 0.5	4.1 ± 0.1
G + I	7	213 ± 7	8.9 ± 0.6	4.2 ± 0.2
GK + pioglitazone 6 mg/kg body weight				
G	3	213 ± 7	8.4 ± 0.4	3.9 ± 0.1
G + I	3	216 ± 8	8.7 ± 0.5	4.0 ± 0.1
GK + pioglitazone 10 mg/kg body weight				
G	3	208 ± 5	8.7 ± 0.3	4.2 ± 0.1
G + I	3	211 ± 6	8.5 ± 0.3	4.0 ± 0.1
GK + eicosapentaenoic acid 1 g/kg body weight				
G	5	212 ± 5	8.6 ± 0.4	4.1 ± 0.1
G + I	3	207 ± 5	8.7 ± 0.5	4.2 ± 0.1
GK + eicosapentaenoic acid 2 g/kg body weight				
G	3	211 ± 6	8.6 ± 0.4	4.1 ± 0.1
G + I	3	209 ± 5	8.6 ± 0.5	4.1 ± 0.1
GK + fenofibrate 30 mg/kg body weight				
G	4	214 ± 7	11.1 ± 0.8[b]	5.2 ± 0.1[b]
G + I	3	211 ± 5	11.0 ± 0.8[b]	5.2 ± 0.2[b]

G, Stimulated by glucagon during liver perfusion; G + I, stimulated by glucagon and insulin during liver perfusion; GK, Goto-Kakizaki rats
[a] Mean ± SEM
[b] Significant difference from the group of untreated GK rats ($P < 0.05$)

Table 2. Blood glucose levels in the rats of each group before and after treatment with antihyperlipidemic agents

	n	Before (mg/dl)	After (mg/dl)
Wistar			
G	7	99 ± 5[a,b]	102 ± 5[c]
G + I	5	103 ± 4[b]	100 ± 5[c]
GK			
G	5	144 ± 6	141 ± 8
G + I	7	142 ± 7	138 ± 7
GK + pioglitazone 6 mg/kg body weight			
G	3	146 ± 7	117 ± 5[c]
G + I	3	143 ± 6	119 ± 7[c]
GK + pioglitazone 10 mg/kg body weight			
G	3	143 ± 5	121 ± 10[c]
G + I	3	148 ± 6	120 ± 11[c]
GK + eicosapentaenoic acid 1 g/kg body weight			
G	5	151 ± 6	132 ± 7
G + I	3	148 ± 5	133 ± 5
GK + eicosapentaenoic acid 2 g/kg body weight			
G	3	149 ± 6	133 ± 10
G + I	3	150 ± 6	135 ± 7
GK + fenofibrate 30 mg/kg body weight			
G	4	152 ± 6	135 ± 8
G + I	3	149 ± 5	133 ± 7

G, Stimulated by glucagon during liver perfusion; G + I, stimulated by glucagon and insulin during liver perfusion; GK, Goto-Kakizaki rats
[a] Mean ± SEM
[b,c] Significant difference from the group of untreated GK rats ($P < 0.05$)

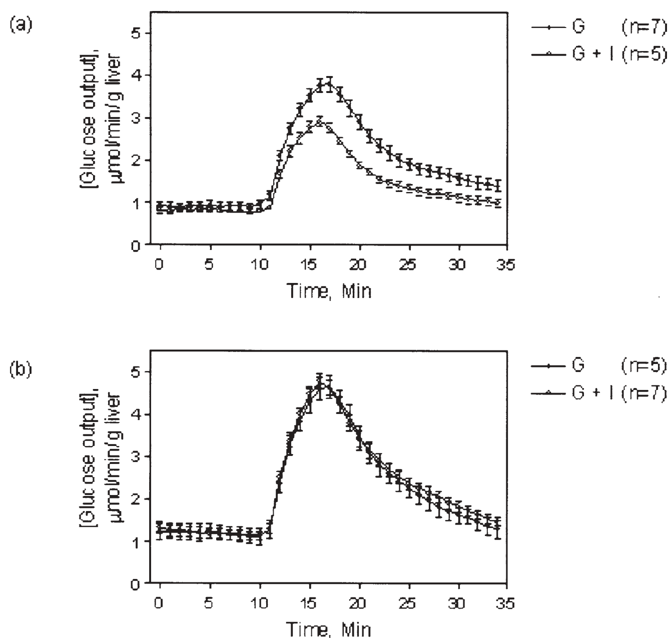

Fig. 1a,b. Hepatic glucose output from perfused liver. **a** Wistar rats. **b** Goto-Kakizaki (GK) rats. Insulin (*I*) did not decrease glucose output induced by glucagon (*G*) in GK rats compared with that in Wistar rats

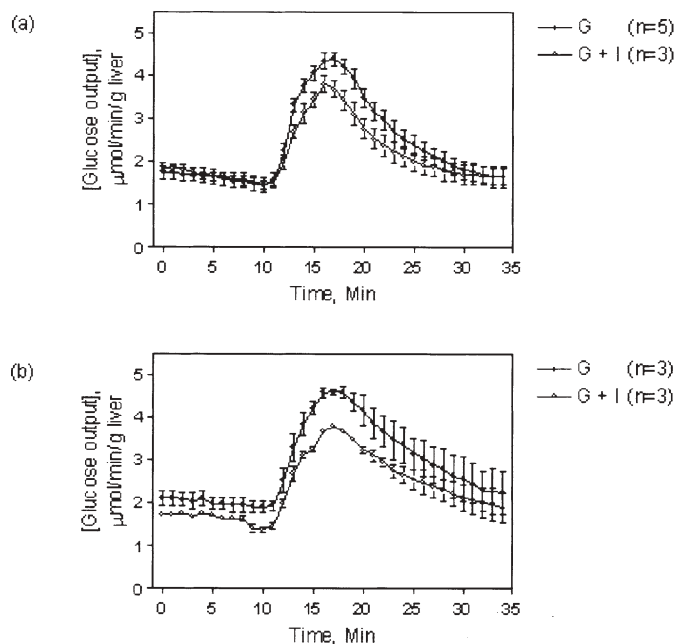

Fig. 3a,b. Effect of eicosapentaenoic acid (EPA) on glucose output in 1 g/kg (**a**) and 2 g/kg (**b**) EPA-treated GK rats. In both groups of EPA-treated GK rats, insulin (*I*) significantly attenuated glucose output by glucagon (*G*)

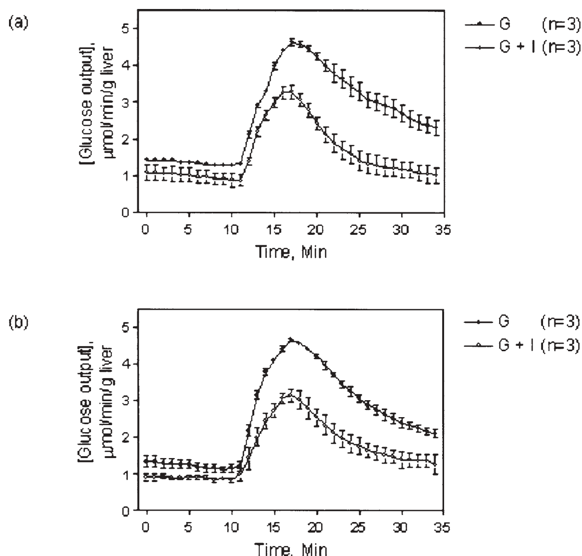

Fig. 2a,b. Effect of pioglitazone on hepatic glucose output in 6 mg/kg (**a**) and 10 mg/kg (**b**) pioglitazone-treated GK rats. In both groups of pioglitazone-treated GK rats, insulin (*I*) significantly attenuated glucose output by glucagon (*G*)

Effect of EPA on glucose output in the GK rats

In the 1 and 2 g/kg EPA-treated GK rats, insulin infusion significantly attenuated (~20%, $P < 0.05$) glucose output stimulated by glucagon (Fig. 3).

Effect of fenofibrate on glucose output in the GK rats

The liver in the fenofibrate-treated GK rats was heavier than that in the untreated GK rats. Histological examination revealed that in the fenofibrate-treated GK rats the fat deposition in the hepatocytes was decreased and the cell number of hepatocytes was increased (Fig. 4). In the fenofibrate-treated GK rats, glucose output elicited by glucagon was significantly decreased compared with the untreated GK rats. On the other hand, insulin infusion did not affect glucose output by glucagon in these rats (Fig. 5).

Discussion

The exact mechanism underlying the insulin-sensitizing actions of thiazolidinedione remains unclarified. Using a euglycemic glucose clamp technique, improvement in the glucose disposal rate and reduced hepatic glucose output were observed in obese or insulin-resistant animals[18] and human subjects[19] treated with thiazolidinedione. Enhanced glucose uptake and oxidation were also demonstrated in isolated muscles and adipocytes from Wistar fatty rats treated with pioglitazone.[7] Thiazolidinedione stimulated glucose transport in cultured muscle cells and glucose utilization in hepatocytes,[20] when these cells were incubated with the drugs for hours to days. It was reported that using a perfused

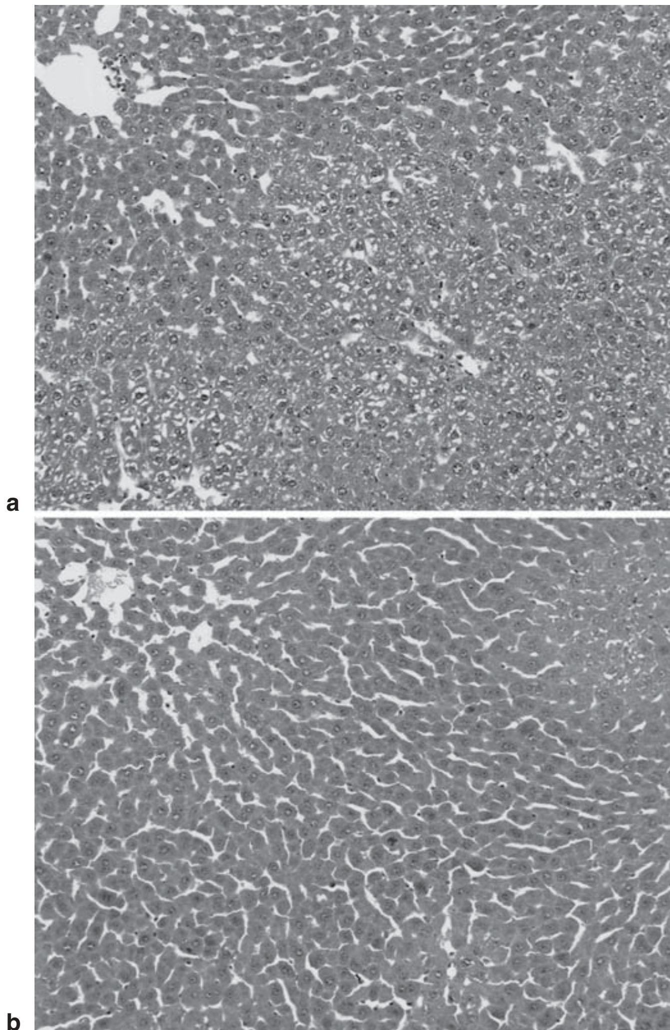

Fig. 4a,b. Histological changes of liver in GK rats. **a** Untreated GK rat. **b** 30 mg/kg fenofibrate-treated GK rats. Fat deposition in hepatocytes was decreased in fenofibrate-treated GK rats compared with that in untreated GK rats. H&E, ×40

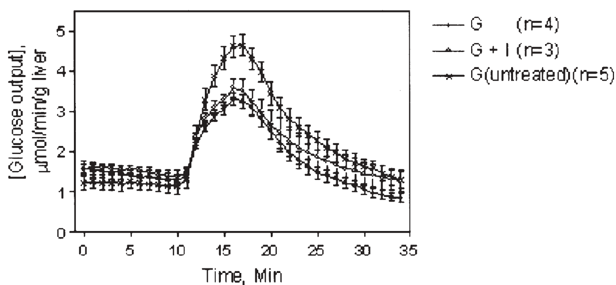

Fig. 5. Effect of fenofibrate on glucose output in 30 mg/kg fenofibrate-treated GK rats. Glucose output induced by glucagon (*G*) was markedly decreased compared with that in untreated GK rats, whereas insulin (*I*) no longer affected glucose output

rat liver system, oral pioglitazone treatment for 2 weeks decreased hepatic glucose output in high-fructose-fed insulin-resistant rats,[8] and pioglitazone in the perfusion medium decreased glucose output dose dependently in the nondiabetic rat.[9] In the present study of the GK rats, pioglitazone improved the decreased action of insulin in the liver, and improved blood glucose levels.

Concerning the mechanism of the decrease of hepatic glucose output by pioglitazone, pioglitazone may stimulate glycolysis or inhibit gluconeogenesis. Ikeda et al. reported that pioglitazone improved hepatic insulin resistance by enhancing glycogen synthesis and inhibiting glycogenolysis.[8] In the present study, glucose output induced by glucagon was not significantly different between the untreated GK rats and the pioglitazone-treated GK rats. These results suggest pioglitazone does not affect glycogen synthesis or glycogenolysis in the liver. Nishimura et al.[9] reported that pioglitazone inhibited the gluconeogenic pathway from lactate by increasing the fructose 2,6-bisphosphate, an activator of 6-phosphofructo-1-kinase, the rate-limiting enzyme in glycolysis,[21] and is an inhibitor of fructose 1,6-bisphosphate, an enzyme operating in gluconeogenesis.[22] It was reported that phosphoenolpyruvate carboxykinase (PEPCK), another important regulator in the gluconeogenesis in the liver, was increased in the diabetic state. Hofmann et al. showed that pioglitazone inhibited gluconeogenesis, because elevated PEPCK activity was normalized by the treatment with pioglitazone to diabetic rodent models.[23]

Dietary fish oil was reported to prevent insulin resistance induced by a high-fat diet in rats and patients with noninsulin-dependent diabetes mellitus (NIDDM).[24,25] Minami et al.[25] reported that in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats treated with EPA, oral glucose tolerance was improved and the glucose disposal rate in the hyperinsulinemic euglycemic glucose clamp was reduced. Mori et al.[24] reported that in the muscle of the OLETF rats treated with EPA GLUT4 expression was elevated and glucose incorporation was improved. In the present study, blood glucose levels were not decreased in the EPA-treated GK rats, while glucose output stimulated by glucagon was significantly decreased in the EPA-treated GK rats, compared with that in the untreated GK rats. It is suggested that EPA treatment for a long period improves blood glucose levels in the GK rats.

In the liver of the OLETF rats treated with EPA, triacylglycerols were reduced because of suppression of the expression of pyruvate kinase, fatty acid synthase, and S14 protein.[11,26] Murata et al.[27] reported exposure of hepatoma cells to EPA caused upregulation of several insulin-induced activities including tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), IRS-1-associated phosphatidylinositol 3-kinase, and its

downstream target Akt kinase activity, in addition to downregulation of gluconeogenesis. These findings suggest that polyunsaturated fatty acids, such as EPA, coordinately regulate the expression of several enzymes involved in carbohydrate and lipid metabolism, not only in muscle but also in liver. It was recently reported that EPA prevented chemically induced diabetes mellitus in rats by enhancing the antioxidant status, such as activities of superoxide dismutase, catalase, and glutation-*S*-transferase and the concentrations of vitamin E and ceruloplasmin, and by suppressing production of insulin-resistant cytokines, such as IL-1, IL-2, and tumor necrosis factor-alpha (TNF-α).[28]

Fibrate is one of the PPAR-α activators. Fibrate induces DNA synthesis and suppresses apoptosis in rodent hepatocytes, so the liver volume of the rats treated with fibrate is increased.[29] In the present study, the liver of the fenofibrate-treated GK rats was heavier than that of the untreated GK rats, whereas tumor formation was not found in the fenofibrate-treated GK rats. Recently, it was reported that PPAR-α activator improved insulin resistance in diabetic animals[16] and humans.[30] The mechanisms of the antiinsulin-resistant effect of PPAR-α activators were suggested to be as follows[31]: (1) PPAR-α activator increases the catabolism of fatty acid in liver, which results in decreasing systemic and local levels of free fatty acid. PPAR-α activator relieves the fatty acid-mediated inhibition of insulin-stimulated oxidative and nonoxidative glucose disposal in skeletal muscle.[14] (2) PPAR-α activator reduces the triglyceride content in skeletal muscle, which is significantly related to insulin resistance.[32] (3) PPAR-α activator decreases the production of cytokines, such as insulin-resistant TNF-α.[33]

In this study, in the fenofibrate-treated GK rats fat deposition in the hepatocytes was decreased, whereas blood glucose levels were not significantly changed compared with the untreated GK rats. Gustafson et al.[34] reported that fibrate did not improve glucose tolerance by improving hepatic glucose or glycogen metabolism. They reported that in the fibrate-treated high-fat-feeding rats, the activities of glycogen synthase (a + b), glycogen phosphorylase (a + b), pyruvate kinase, and glucokinase were reduced and the activity of glucose 6-phosphatase was unchanged. They also reported that the glycogen contents in the liver of fibrate-treated high-fat-feeding rats were decreased at the level of about 60% compared with control rats. The present findings have demonstrated the glycogen content in the liver of the fenofibrate-treated GK rats might be decreased according to glucose output by glucagon stimulation. A possible explanation for the effect of fibrates to improve glucose tolerance may be that an increase in hepatic mitochondrial fatty acid oxidation drains free fatty acids from the circulation and decreases the competition between glucose and fatty acids for oxidation in the peripheries.

References

1. DeFronzo RA. The triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37:667–87.
2. Tobey TA, Mondon CE, Zavaroni I, Reaven GM. Mechanism of insulin resistance in fructose-fed rats. Metabolism 1982;31:608–12.
3. Goto Y, Kakizaki M. The spontaneous-diabetes rat: a model for noninsulin dependent diabetes mellitus. Proc Jpn Acad 1981;57:381–4.
4. Doi Y, Iwai M, Matsuura B, Onji M. Glucagon attenuates the action of insulin on glucagon output in the liver of Goto-Kakizaki rat perfused in situ. Eur J Physiol 2001;442:537–41.
5. Ye J-M, Frangioudakis G, Iglesias MA, Furler SM, Ellis B, Dzamko N, et al. Prior thiazolidinedione treatment preserves insulin sensitivity in normal rats during acute fatty acid elevation: role of the liver. Endocrinology 2002;143:4527–35.
6. Ikeda H, Taketomi S, Sugiyama Y, Sohda T, Meguro K, Fujita T. Effect of pioglitazone on glucose and lipid metabolism in normal and insulin resistant animals. Arzneim-Forsch/Drug Res 1989;40:156–60.
7. Sugiyama Y, Taketomi S, Shimura Y, Ikeda H, Fujita T. Effects of pioglitazone on glucose and lipid metabolism in Wistar fatty rats. Arzneim-Forsch/Drug Res 1990;40:263–8.
8. Ikeda T, Fujiyama K. The effect of pioglitazone on glucose metabolism and insulin uptake in the perfused liver and hindquarter of high-fructose-fed rats. Metabolism 1998;47:1152–5.
9. Nishimura Y, Inoue Y, Takeuchi H, Oka Y. Acute effects of pioglitazone on glucose metabolism in perfused rat liver. Acta Diabetol 1997;34:206–10.
10. Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Campbell LV. The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. N Engl J Med 1993;328:238–44.
11. Sasagawa T, Ishii K, Hasuda K, Kubota M, Ota Y, Okita M. The effect of dietary polyunsaturated fatty acid on insulin sensitivity and lipid metabolism in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Prostaglandins Leukot Essent Fatty Acids 2001;64:181–7.
12. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237–45.
13. Everett L, Galli A, Crabb D. The role of hepatic peroxisome proliferator-activated receptors (PPARs) in health and disease. Liver 2000;20:191–9.
14. Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J. Coordinate regulation of the expression of the fatty acid transport protein and acyl-Co A synthetase genes by PPAR alpha and PPAR gamma activators. J Biol Chem 1997;272:28210–7.
15. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose-fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785–9.
16. Guerre-Millo M, Gervois P, Raspe E, Madsen L, Poulain P, Derudas B, et al. Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and adiposity. J Biol Chem 2000;275:16638–42.
17. Consoli A. Role of liver in pathophysiology of NIDDM. Diabetes Care 1992;15:430–41.
18. Lee M-K, Miles PDG, Khoursheed M, Gao K-M, Moossa AR, Olefsky JM. Metabolic effects of troglitazone on fructose-induced insulin resistance in the rats. Diabetes 1994;43:1435–9.

19. 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 1994;331:1188–93.
20. Ciaraldi TP, Gilmore A, Olefsky JM, Goldberg M, Heidenreich KA. In vitro studies on the action of CS-045, a new antidiabetic agent, Metabolism 1990;39:1056–62.
21. Pilkis SJ, El-Maghrabi MR, Pilkis J, Claus TH, Cumming DA. Fructose 2,6-bisphosphate. A new activator of phosphofructokinase. J Biol Chem 1990;256:3171–4.
22. Pilkis SJ, El-Maghrabi MR, Claus TH. Fructose 2,6-bisphosphate in control of hepatic gluconeogenesis. From metabolites to molecular genetics. Diabetes Care 1990;13:582–99.
23. Hofmann C, Lorenz K, Williams D, Palazuk BJ, Colca JR. Insulin sensitization in diabetic rat liver by an antihyperglycemic agent. Metabolism 1995;44:384–9.
24. Mori Y, Murakawa Y, Katoh S, Hata S, Yokoyama J, Tajima N, et al. Influence of highly purified eicosapentaenoic acid ethyl ester on insulin resistance in the Otsuka Long-Evans Tokushima Fatty rat, a model of spontaneous non-insulin-dependent diabetes mellitus. Metabolism 1997;46:1458–64.
25. Minami A, Ishimura N, Sakamoto S, Takishita E, Mawatari K, Okada K, et al. Effect of eicosapentaenoic acid ethyl ester v. oleic acid-rich safflower oil on insulin resistance in type 2 diabetic model rats with hypertriacylglycerolaemia. Br J Nutr 2002;87:157–62.
26. Jump DB, Clarke SD, Thelen A, Liimatta M. Coordinate regulation of glycolytic and lipogenic gene expression by polyunsaturated fatty acids. J Lipid Res 1994;35:1076–84.
27. Murata M, Kaji H, Iida K, Okimura Y, Chihara K. Dual action of eicosapentaenoic acid in hepatoma cells. Up-regulation of metabolic action of insulin and inhibition of cell proliferation. J Biol Chem 2001;276:31422–8.
28. Mohan IK, Das UN. Prevention of chemically induced diabetes mellitus in experimental animals by polyunsaturated fatty acids. Nutrition 2001;17:126–51.
29. Chevalier S, Roberts RA. Perturbation of rodent hepatocyte growth control by nongenotoxic hepatocarcinogens: mechanisms and lack of relevance for human health (review). Oncol Rep 1998;5:1319–27.
30. Jones IR, Swai A, Taylor R, Miller M, Laker MF, Alberti KGMM. Lowering of plasma glucose concentrations with bezafibrate in patients with moderately controlled NIDDM. Diabetes Care 1990;13:855–63.
31. Lee HJ, Choi SS, Park MK, An YJ, Seo SY, Kim MC, et al. Fenofibrate lowers abnormal and skeletal adiposity and improves insulin sensitivity in OLETF rats. Biochem Biophys Res Commun 2002;296:293–9.
32. Chalkley S, Hettiarachi M, Chisholm DJ, Kraegen EW. Five hour fatty acid elevation increases muscle lipids and impairs glycogen synthesis in the rat. Metabolism 1998;47:1121–6.
33. Hatamisligil GS, Arner JF, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409–15.
34. Gustafson LA, Kuipers F, Wiegman C, Sauerwein HP, Romijn JA, Meijer AJ. Clofibrate improves glusose tolerance in fat-fed rats but decreases hepatic glucose consumption capacity. J Hepatol 2002;37:425–31.