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High fat fed hamster, a unique animal model for treatment of diabetic dyslipidemia with peroxisome proliferator activated receptor alpha selective agonists

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Abstract

Dyslipidemia, a major risk factor for cardiovascular disease, may be directly linked to diabetic hyperglycemia and insulin resistance. An appropriate dyslipidemic animal model that has diabetes would provide an important tool for research on the treatment of diabetic dyslipidemia. Ten days of high fat feeding in golden Syrian hamsters resulted in a significant increase in insulin resistance and baseline serum lipid levels accompanied by a pronounced dyslipidemia. Thirteen days of treatment with fenofibrate, a peroxisome proliferator-activated receptor alpha (PPARα) selective agonist, produced a dose-dependent decrease in serum lipid levels. The pattern observed was characterized by lowered very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) and raised high-density lipoprotein (HDL) cholesterol in a fashion similar to that seen in man. Diabetic conditions were also significantly improved by fenofibrate with a normalization of impaired glucose tolerance and an improvement of insulin sensitivity during an oral glucose tolerance test. These data suggest that fenofibrate may correct not only the dyslipidemia but also the insulin resistance caused by a high fat diet, and the high fat fed hamster may be a good animal model for research on the treatment of diabetic dyslipidemia with PPARα selective agonists. © 2001 Published by Elsevier Science B.V.

Keywords: Fenofibrate; Diabetic dyslipidemia; Insulin sensitivity; Animal model

1. Introduction

Dyslipidemia (high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol and elevated triglyceride), a major risk factor for cardiovascular disease (Gotto, 1998; Brewer, 1999), may be directly linked to diabetic hyperglycemia and insulin resistance. Lowering triglyceride and free fatty acid (FFA) levels have been shown to decrease hyperglycemia in type 2 diabetes because of both a suppression of glucose production and an accompanying increase in glucose utilization (Foley, 1992).

Fenofibrate, a widely used drug in the treatment of dyslipidemia, produces a considerable decrease in serum triglyceride, a moderate reduction of LDL cholesterol and an increase in HDL cholesterol concentration (Packard, 1998; Watts and Dimmitt, 1999). Recent studies indicate that the action of fenofibrate on lipid metabolism is mediated principally by activation of peroxisome proliferator-activated receptor alpha (PPARα) leading to altered expression of genes involved in lipid and lipoprotein metabolism in liver (Kloer, 1987; Lefevbre et al., 1997; Schoonjans et al., 1996). There is increasing evidence that fibrates may significantly reduce the incidence of cardiovascular events in patients with type 2 diabetes (Elkeles et al., 1998; Watts and Dimmitt, 1999). Results on animal studies have also shown that PPARα selective activators can correct high serum triglyceride and consequently improve insulin sensitivity (Chaput et al., 2000; Guerre-Millo et al., 2000). However, the effects on lipoproteins were not reported.

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Table 1
Time course for alterations in serum biochemical parameters in high fat-fed hamsters [Mean (S.E.M.); $N = 14$]. Hamsters were fed high fat diet for three weeks. On 1st, 7th, 14th and 21st day, different groups of animals were weighed and euthanized and blood samples were taken through heart puncture. Serum was isolated and immediately analyzed for lipid profile. An aliquot of serum samples were frozen for analysis of insulin and glucose levels. Statistically significant difference between normal and high fat fed animals (Student's *t*-test) at $P < 0.05$ and $P < 0.001$ are indicated by "a" and "b", respectively

	Day 1	Day 7	Day 14	Day 21
Total cholesterol (mg/dl)	112 (4)	250 (8)[b]	496 (36)[b]	440 (57)[b]
Triglyceride (mg/dl)	243 (13)	785 (65)[b]	1791 (152)[b]	1731 (256)[b]
Free fatty acid (mEq)	1.32 (0.07)	2.20 (0.06)[a]	5.54 (0.56) [b]	4.53 (0.52)[b]
Glucose (mg/dl)	119 (5)	162 (38)	228 (24)[a]	279 (45)[a]
Insulin (ng/ml)	7.47 (0.95)	6.86 (0.97)	6.15 (1.08)	5.39 (1.34)
Body weight (gm)	143 (4)	148 (5)	160 (6)[b]	165 (10)[a]

Lack of appropriate animal models has always been a challenge for research on the link between the treatment of dyslipidemia and diabetes. Results from recent studies have suggested that the high fat fed hamster is a better animal model than other species for investigating cholesterol metabolism because the hamster reacts to dietary lipids in a fashion similar to that of humans (Ohtani, 1990; Sullivan et al., 1993). Despite the strong link between dyslipidemia and diabetes (Migdalis et al., 1997; Packard, 1998; Gavish et al., 2000), hamsters have yet to be used as an animal model to study diabetic dyslipidemia.

The purposes of the present study were to develop the high fat fed hamster model for evaluating the link between development of lipid disorders and diabetes and to test the hypothesis that fenofibrate, a PPARα selective agent, not only lowers serum lipids and modifies lipoprotein metabolism but also improves insulin resistance and hyperglycemia. Here, we show that dyslipidemia and insulin resistance are induced by a high fat diet in hamsters and that both conditions are corrected by fenofibrate.

2. Materials and methods

2.1. Animals and diets

Male Syrian Golden hamsters (Charles River, Wilmington, MA), weighing 120–150 g, were used in the present study. The animals were given either normal chow or commercially available high fat diet (Purina chow no. 5001 with 11.5% coconut oil, 11.5% corn oil, 0.5% cholesterol, and 0.25% deoxycholate; Dyets, Bethlehem, PA) with 10% fructose in drinking water. The ethical guidelines described in the National Institutes of Health Guide for Care and Use of Laboratory Animals were followed throughout the experiments described. All in vivo experiments were approved by the Merck Institutional Animal Care and Use Committee.

2.2. Development of the high fat fed hamster model

Hamsters were given either normal chow (20 per group) or high fat diet (20 per group) for 10 days. On the 11th

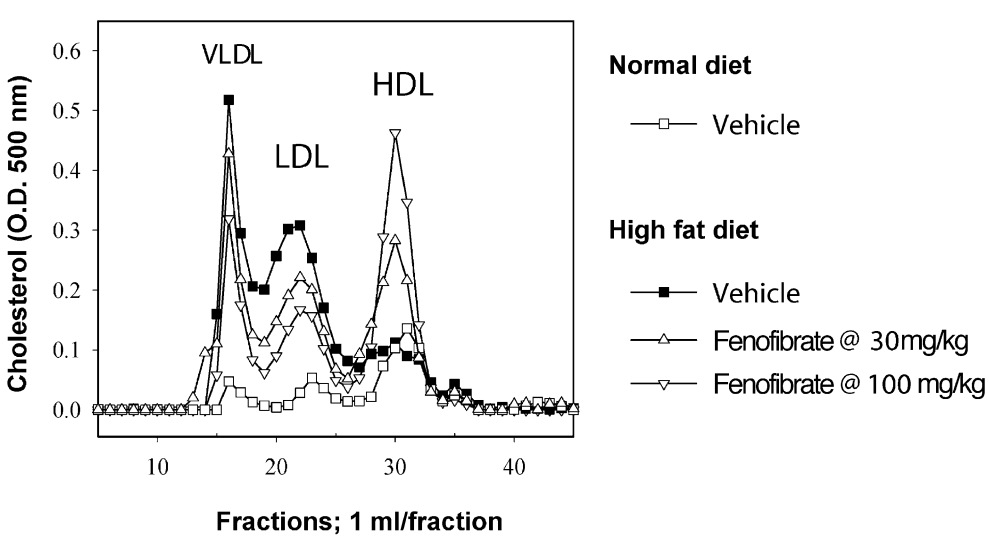

Fig. 1. Effects of fenofibrate on serum lipoprotein profiles in high fat fed hamsters. Hamsters (100 total) were given high fat diet for 10 days. After 10 days of high fat diet, hamsters were equally divided and orally dosed for 13 subsequent days with vehicle (0.5% methyl cellulose) or fenofibrate at various dosages: 30, 50, 100, 300 mg/kg (20 per group). On the 14th day, hamsters were euthanized and weighed. Blood samples were taken through heart puncture. Serum was isolated and centrifuged immediately. Lipoproteins were fractionated into VLDL, LDL, and HDL using standard FPLC method.

Table 2
Effects of high fat diet for 10 days on relative mRNA expression levels of genes related to lipid metabolism in the hamster liver ($N = 5$). Hamsters were fed either normal or high fat diet for ten days. On the 11th day, animals were euthanized and the livers were excised. Total RNA was isolated from the livers and the relative mRNA expression levels of the genes were measured by TaqMan PCR analysis. The data in the table are expressed as the fold change normalized to GAPDH expression, where the value for the normal hamsters was set at 1.00. Statistical analysis was performed to compare the high fat fed and normal animals. None of the changes were statistically significant

Hamster/gene	HMGR	ACO	LPL	FAS	LDLR
Normal diet	1.00	1.00	1.00	1.00	1.00
High fat diet	0.25	0.81	3.37	0.57	0.51

day, oral glucose tolerance tests were performed in both normal chow and high fat diet groups (Section 2.4). Hamsters were euthanized and weighed. Liver tissues were collected for the determination of gene expressions (Section 2.6). Blood samples were taken through heart puncture. Serum was isolated and immediately analyzed for lipid, glucose, and insulin profiles (Section 2.5).

2.3. Anti-dyslipidemic and anti-diabetic effects of fenofibrate in high fat fed hamsters

Hamsters (100 total) were given high fat diet for 10 days. After 10 days of high fat diet, hamsters were equally divided and orally dosed for 13 days with vehicle (0.5% methyl cellulose) or fenofibrate (Sigma, St. Louis, MO, USA) at various dosages: 30, 50, 100, 300 mg/kg (20 per group). On the 14th day, oral glucose tolerance tests were performed (Section 2.4). Hamsters were euthanized and weighed. Liver tissues were collected for the determination of gene expression (Section 2.6). Blood samples were taken, and serum was isolated for immediate analysis of lipid, glucose, and insulin profiles (Section 2.5).

2.4. Oral glucose tolerance test (OGTT)

Hamsters were orally dosed with glucose at 3 g/kg in the morning. Then, different groups of animals (five per group) were euthanized at 0, 0.5, 1, 2 h post glucose loading. Serum was isolated and immediately stored at −20 °C until further analysis.

2.5. Serum and tissue assay

Total cholesterol, triglyceride, FFA levels were measured by using Wako Kits # Cholesterol CII, Triglyceride E, and NEFA-C, respectively (Wako, Richmond, VA). Serum glucose levels were determined using the standard glucose oxidase assay kit, and β-hydroxybutyrate concentration in serum was assayed by measuring the reduction of NAD to NADH with standard assay kit (Sigma). Serum insulin concentrations were measured with the enzyme-immunoassay kit from ALPCO (Windham, NH). Rates of peroxisomal fatty acid oxidation in liver homogenates were measured by the method of Mannaerts et al. (1979). Carnitine palmitoyltransferase 1 (CPT 1) activity in liver homogenates was assayed by the method of McGarry et al. (1983).

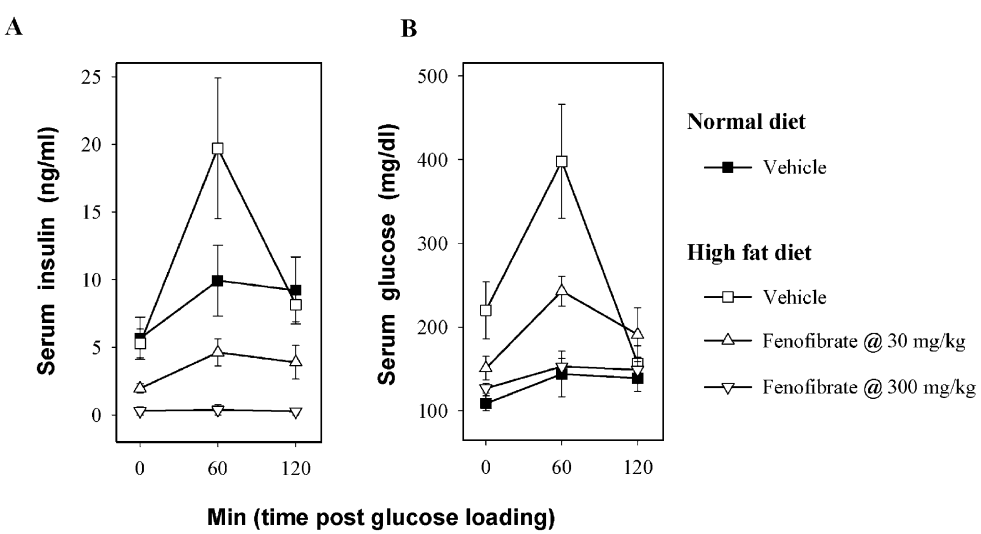

Fig. 2. Fenofibrate treatment decreases serum insulin response (A) to glucose (B) during the oral glucose tolerance test in high fat fed hamsters. Hamsters (100 total) were given high fat diet for 10 days. After 10 days of high fat diet, hamsters were equally divided and orally dosed for 13 subsequent days with vehicle (0.5% methyl cellulose) or fenofibrate at various dosages: 30, 50, 100, 300 mg/kg (20 per group). On the 14th day, oral glucose tolerance test (3 g/kg) was performed. Blood samples were taken at 0, 60, and 120 min post glucose load (five per time point). Serum was isolated and immediately stored at −20 °C. The insulin and glucose levels were determined as described under "Experimental Procedures". Values are mean ± S.E.M.

2.6. Serum fast protein liquid chromatography

Serum lipoproteins were separated by a fast protein liquid chromatography (FPLC) system using a Superose 6 HR column (Amersham Pharmacia Biotech). The column was equilibrated with PBS buffer and was run at a flow rate of 0.2 ml/min. The serum samples were pooled (three animals per pool) and filtered with 0.65 μm microcentrifuge filters to remove clotting agents. Two hundred microliter samples were then loaded into the column. Fractions (0.5 ml) were collected and analyzed for total cholesterol concentration as described above.

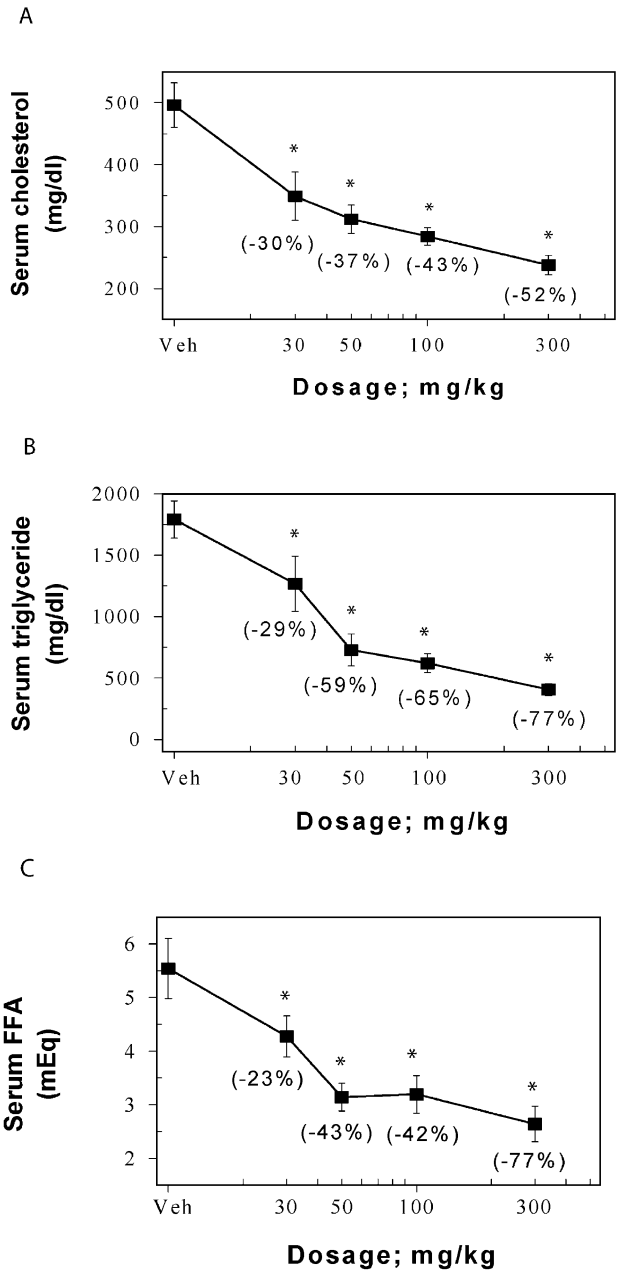

Fig. 3. Effects of fenofibrate on serum cholesterol (A), triglyceride (B), and FFA (C) levels in high fat fed hamsters. Animal protocol is the same as described in Fig. 1. Determination of serum cholesterol, triglyceride and FFA levels were described under "Experimental Procedures". Values are mean ± S.E.M. * Indicates a statistically significant difference ($P < 0.05$) in relation to high fat vehicle group by Student's *t*-test.

Table 3
Correlation between serum lipid lowering and hepatic LPL mRNA levels in high fat-fed hamsters. Hamsters ($N = 5$) were fed with high fat diet for 10 days and continued with fenofibrate treatment, at various dosages, for 13 subsequent days. On the 14th day, animals were euthanized, blood samples were taken and the livers were excised. Serum was immediately isolated for analysis of total cholesterol and triglyceride levels. Total RNA was isolated from the livers and the relative mRNA expression levels of the genes were measured by TaqMan PCR analysis. The data in the table are expressed as the fold change normalized to GAPDH expression, where the value for the vehicle controls was set at 1.00. The correlation coefficient (R) between hepatic LPL mRNA versus serum total cholesterol and triglyceride lowering in fenofibrate treated hamsters was analyzed. Statistically difference between vehicle control and fenofibrate treated animals at $P < 0.001$ is indicated by "a"

Fenofibrate (mg/kg)	Total cholesterol (% change)	Triglyceride (% change)	LPL (folds change)
Vehicle control	0	0	1.00
30	−30 (3.5)[a]	−29 (2.1)[a]	15.49[a]
100	−43 (4.1)[a]	−65 (5.4)[a]	65.59[a]
300	−52 (3.8)[a]	−77 (4.1)[a]	93.41[a]
R (vs. LPL)	0.95	0.99	

2.7. Real-time quantitative PCR analysis of gene expression

TaqMan primers and probes were designed using Primer Express 1.0 and following the general rules outlined by the manufacturer and were synthesized by PE Biosystems. Total RNA was isolated from livers (five animals per group) using Trizol™ (Gibco, Gaithersburg, MD) according to the manufacturer's instructions. The RNA was then treated with RQ1 RNase-Free DNase (Promega, Madison, WI) for 60 min at 37 °C twice following ethanol precipitation to eliminate the contaminating genomic DNA in the RNA samples. Reverse transcription-polymerase chain reaction (RT-PCR) reactions were carried out at 25 °C for 10 min, 48 °C for 30 min, 95 °C for 5 min in a 96-well plate using TaqMan Reverse Transcription Reagents (PE Biosystems). The TaqMan assay was performed in a 25-μl volume of TaqMan Universal PCR Master Mix (PE Biosystems) containing 25 ng cDNA, 300 nM primers, 200 nM FAM-labeled TaqMan probes for the target genes, and 80 nM for both glyceralaldehyde-3-phosphate dehydrogenase (GAPDH) primers and VIC-labeled TaqMan probe. PCR conditions were as follows: 2 min at 50 °C, 10 min at 95 °C for one cycle, and then 40 cycles at 95 °C for 15 s followed by 1 min at 60 °C on an ABI PRISM 7700 Sequence Detector System (PE Biosystems) based on the

Table 4
Effects of fenofibrate on serum glucose and insulin levels in high fat fed hamsters [Mean (S.E.M.); $N = 14$]. Hamsters were fed high fat diet for 10 days and continued with fenofibrate treatment, at various dosages, for 13 subsequent days. On the 14th day, animals were euthanized and blood samples were taken through heart puncture and centrifuged immediately. Serum glucose and insulin levels were determined as described under "Experimental Procedures". Statistically difference between vehicle control and fenofibrate treated animals at $P < 0.001$ is indicated by "a"

Fenofibrate (mg/kg)	Serum glucose		Serum insulin	
	mg/dl	% change	ng/ml	% change
Vehicle control	228 (24)	0	6.05 (0.18)	0
30	174 (15)[a]	−24[a]	1.82 (0.19)[a]	−70[a]
100	166 (14)[a]	−27[a]	1.23 (0.14)[a]	−80[a]
300	138 (7)[a]	−39[a]	0.69 (0.10)[a]	−89[a]

manufacturer's protocol. The analyses were performed in duplicates. Relative quantitation of mRNA expression levels (compounds treated animals/vehicle ratio) was calculated by comparing the target gene/GAPDH of the treated animals to those of the vehicles.

2.8. Calculation

Insulin resistance index ($I \times G$), a product of the area of insulin and glucose curves, was calculated in this study according to Mondon et al (1981). A large index reflects elevated insulin resistance with insulin being less effective in lowering plasma glucose levels.

2.9. Statistical analysis

Student's *t*-test was performed to analyze the data.

3. Results

3.1. Effects of dietary lipids on baseline levels of serum lipid, glucose, and insulin

As depicted in Table 1, high fat diet dramatically increased FFA, triglyceride, and glucose levels in hamsters. Serum total cholesterol was markedly increased as reflected in an increase in LDL- and very low density lipoprotein (VLDL)-cholesterol concentrations (Fig. 1). A decrease in hepatic LDL receptor mRNA level may have contributed to the increase in LDL cholesterol (Table 2). Hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) mRNA expression was reduced in dyslipidemic hamsters (Table 2) suggesting cholesterol synthesis was inhibited by dietary lipids. Serum triglyceride was increased by 7.3-fold (243–1791 mg/dl) and FFA levels increased by 4.2-fold (1.321–5.542 mEq). Serum glucose level increased 91% (119–228 mg/dl) despite unchanged insulin levels. The insulin response during the OGTT load was considerably increased (Fig. 2) indicating insulin resistance.

3.2. Lipid lowering by fenofibrate in dyslipidemic hamsters

In this high fat fed hamster model, 13 days of treatment with fenofibrate resulted in a dose-dependent decrease in total cholesterol (Fig. 3A). Fractionation of plasma by FPLC (Fig. 1) showed that the VLDL- and LDL-cholesterol were reduced while HDL-cholesterol rose. The decrease of serum triglyceride (Fig. 3B) and FFA (Fig. 3C) levels was dose-related with a maximum reduction of 77% for both parameters. The decrease in serum cholesterol and triglyceride were tightly correlated with increases in hepatic lipoprotein lipase (LPL) mRNA expression (Table 3).

3.3. Anti-diabetic effects of fenofibrate in dyslipidemic hamsters

Fenofibrate treatment resulted in a dose-dependent correction of hyperglycemia with a 24% reduction at 30 mg/kg and a maximum 39% reduction at 300 mg/kg (Table 4). Fenofibrate also caused a dramatic, dose-related decrease in insulin levels with a 70% decrease at 30 mg/kg and a maximum decrease of 89% with 300 mg/kg (Table 4). Fenofibrate also improved the response to the oral glucose tolerance test (Fig. 2), reflecting a significant improvement in insulin sensitivity (Table 5).

3.4. Effects of fenofibrate on parameters of liver fatty acid oxidation in dyslipidemic hamsters

All doses of fenofibrate led to a considerable increase in β-hydroxybutyrate levels as compared to that in vehicle

Table 5
Fenofibrate treatment improves insulin sensitivity in high fat fed hamsters. Hamsters (100 total) were given high fat diet for 10 days. After 10 days of high fat diet, hamsters were equally divided and orally dosed for 13 days with vehicle (0.5% methyl cellulose) or fenofibrate at various dosages: 30, 50, 100, 300 mg/kg (20 per group). On the 14th day, oral glucose tolerance test (3 g/kg) was performed. Blood samples were taken at 0, 30, 60, and 120 min post glucose load (five per time point). Serum was isolated and immediately stored at −20 °C. The insulin and glucose levels were determined as described under "Experimental Procedures". The insulin resistance index, a product of the area of insulin and glucose curves, was calculated according Mondon et al. (1981). Statistically difference between vehicle control and fenofibrate treated animals at $P < 0.001$ is indicated by "a"

Fenofibrate mg/kg	Insulin sensitivity index	
	(mg/dl) (ng/ml) (min)	% change
Vehicle control	572802 (17544)	0
30	191062 (39165)[a]	−67[a]
50	89568 (31624)[a]	−84[a]
100	68401 (14877)[a]	−88[a]
300	25542 (24087)[a]	−96[a]

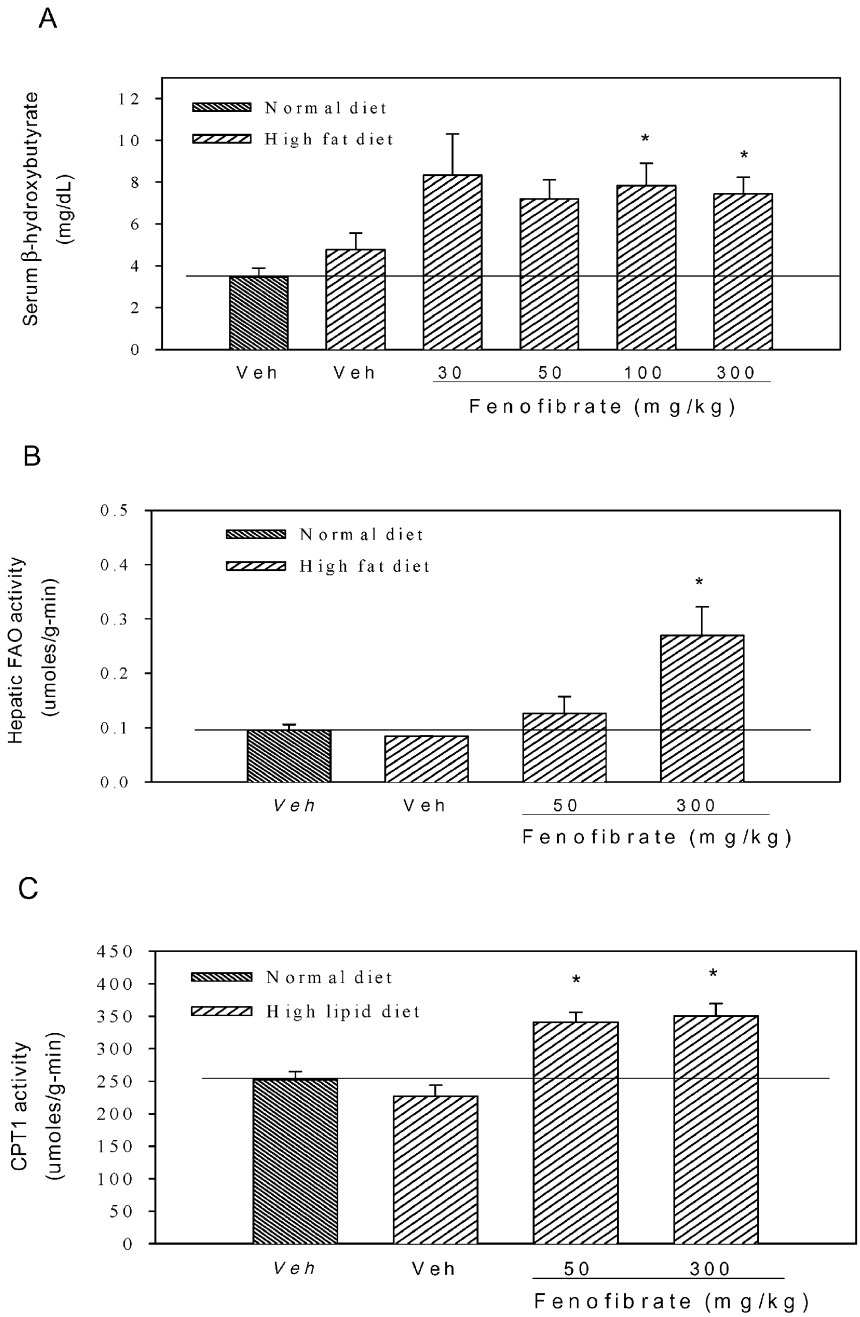

Fig. 4. Fenofibrate increases serum β-hydroxybutyrate concentration (A), hepatic peroxisomal fatty acid oxidation activity (B), and hepatic mitochondria CPT 1 activity (C) in high fat fed hamsters. Animal protocol is the same as described in Fig. 1. Determination of serum β-hydroxybutyrate concentration, hepatic peroxisomal fatty acid oxidation activity, and hepatic mitochondria CTP 1 activity was described under "Experimental Procedures". Values are mean ± S.E.M. * Indicates a statistically significant difference ($P < 0.05$) in relation to high fat vehicle group by Student's *t*-test.

controls (Fig. 4A). The rate of oleate oxidation by liver homogenates was measured under conditions that permit only peroxisomal fatty acid oxidation. These studies (Fig. 4B) demonstrate that peroxisomal oxidation under physiological conditions increased up to 250% with fenofibrate administration. CPT 1, a rate limiting step in mitochondria fatty acid oxidation, also increased with fenofibrate treatment (Fig. 4C).

4. Discussion

4.1. Effects of dietary fat on the development of dyslipidemia and diabetes

Hamsters are known to be a useful species for cholesterol research because their lipid metabolism is comparable to humans (Anderson and Cook, 1986; Spady and Di-

etschy, 1998). Despite the strong link between dyslipidemia and diabetes (Migdalis et al., 1997; Packard, 1998; Gavish et al., 2000), hamsters have yet to be used as an animal model for diabetic studies.

In the current work, we observed that hamsters became hypercholesterolemic when fed a high fat diet, with a dramatic down-regulation of hepatic HMGR mRNA expression suggesting inhibition of endogenous cholesterol synthesis by the high dietary fat intake. An increase in LDL cholesterol was observed, an effect potentially related to the down-regulation of hepatic LDL receptor mRNA expression. The lipoprotein changes observed here are consistent with published data (Sullivan et al., 1993; Packard, 1998; Gavish et al., 2000) and correspond well with the pattern observed in human diabetic dyslipidemia with elevated triglyceride and lowered HDL/LDL ratio. As compared to other rodent models (Sullivan et al., 1993; Sessions and Salter, 1994), both serum triglyceride and FFA levels were considerably higher in our high fat fed hamster which may be advantageous since it would provide a wider window for evaluating agents that lower serum lipid concentration. The model also showed insulin resistance, as judged by the elevated insulin excursion during OGTT. This is in agreement with recent findings that there exists a strong link between the development of dyslipidemia and diabetes (Rocchini et al., 1997; Laakso, 1998; Howard, 1999; Kaiyala et al., 1999). To our knowledge, we are the first group to successfully develop a hamster model in which a human-like dyslipidemia occurs in association with insulin resistance, even though other rodent models have been explored (Chaput et al., 2000; Kobayashi et al., 2000).

4.2. Anti-hyperlipidemic effects of fenofibrate

Our hamster model is potentially useful for evaluating PPARα agonists. Although fenofibrate, a well known PPARα selective agonist, has been consistently reported to decrease serum cholesterol and triglyceride levels in humans (Blane, 1989; Balfour et al., 1990; Gholami et al., 1998; Yong et al., 1999), the results from different animal studies have been less consistent. These variations may be explained by the gender differences in these animal models. Plancke et al. (1988) reported that fenofibrate in either normal chow-fed or high fat-fed female hamsters, unlike humans or other species (rat, dog, monkey), increased plasma triglyceride, even though it lowered cholesterol. Krause and Princen (1998) have also claimed that for fibrate-like compounds, only the male rat has provided data which seems to reliably predict the human response. Our data, however, demonstrate that fenofibrate not only decreased serum cholesterol but also lowered triglyceride levels in high fat-fed male hamsters similar to the response in humans. Therefore, the gender differences in rodent models may cause different response in their serum lipid levels when treated with fibrate-like compounds. Additionally, the effect of fenofibrate on lipoprotein profile in normal chow fed animals including rat, hamster, and dog was also different from that in humans: it decreased serum HDL cholesterol concentration in all these species (Wang, unpublished data). In the present study, however, fenofibrate treatment exerted a similar response to humans on lipoprotein metabolism in the high fat fed hamsters; it dramatically decreased serum LDL and VLDL but raised HDL cholesterol levels. The increase in HDL-cholesterol levels was correlated with increases in hepatic apoA-I, ABCA1, and SR-BI mRNA expressions (Wang, unpublished data). These observations suggested that dietary fat may have effects on lipoprotein metabolisms in animals treated with fibrate-like compounds.

4.3. Anti-diabetic effects of fenofibrate

Despite the close association of hypertriglyceridemia and insulin resistance, whether hypertriglyceridemia contributes to insulin resistance remains unclear. It had been reported that a decrease in triglyceride by gemfibrozil did not improve insulin sensitivity in either nondiabetic or diabetic subjects with hypertriglyceridemia (Vuorinen-Markkola et al., 1993; Sane et al., 1995). However, more recent studies have shown that fibrate-like compounds such as fenofibrate and gemfibrozil would improve insulin sensitivity in patients with dyslipidemia (Watts and Dimmitt, 1999; Yong et al., 1999; Gavish et al., 2000; Idzior-Walus, 2000; Mussoni et al., 2000). The discrepancy among studies may be from different effects of gemfibrozil on serum FFA concentration, another important factor for causing insulin resistance in humans (Fanelli et al., 1993). Lowering serum FFA level has been shown to potentiate insulin response in type 2 diabetes (Paolisso et al., 1998). In studies that showed the diabetic condition was not improved by gemfibrozil treatment, FFA concentration was not affected either (Vuorinen-Markkola et al., 1993). On the other hand, in studies that insulin sensitivity was improved by gemfibrozil, not only triglyceride but also FFA levels were considerably reduced (Watts and Dimmitt, 1999; Mussoni et al., 2000). Our suggested mechanisms for fibrates' antihyperlipidemic and the associated antidiabetic effects in the high fat fed hamsters are (i) increase in hepatic LPL expression and consequently increased hepatic triglyceride clearance, decreased plasma triglyceride levels, reduced delivery of triglyceride to skeletal muscle and finally decreased skeletal muscle triglyceride content, a direct link to peripheral insulin resistance (Goodpaster and Kelly, 1998); (ii) decrease in hepatic FFA levels by fenofibrate caused by the observed decrease in fatty acid synthesis, increase in peroxisomal fatty acid β-oxidation, and increase in mitochondria CPT 1 activity. As a consequence of reduction of FFA concentration in the liver, the substrate for hepatic gluconeogenesis would be decreased which may contribute to the observed improvement of glucose homeostasis. This hypothesis was

supported by recently published data showing that hepatic FFA level is positively correlated with hepatic glucose output, a major factor in determining the fasting serum glucose concentration (Rebrin et al., 1995; Sindelar et al., 1996, 1997); and (iii) a decrease in serum FFA levels by fenofibrate would improve hepatic and peripheral insulin sensitivity (Paolisso et al., 1998).

In summary, our results clearly indicate that (i) there was a strong link between the development of lipid disorders and diabetes in our high fat fed hamsters; (ii) fenofibrate, a PPARα selective agonist, not only lowered serum lipid levels but also significantly improved insulin sensitivity in high fat fed hamsters which suggested that PPARα selective agonists might be promising in the treatment of diabetic dyslipidemia; (iii) unlike other species, the high fat fed hamster responds to fenofibrate treatment in a similar way to humans in terms of its lipoprotein metabolism; (iv) the window for lipid and glucose lowering became much wider in high fat fed hamster which is good for evaluating lipid and glucose lowering agents; (v) dyslipidemic hamster, overall, is a very attractive model for research in the pathogenesis and treatment in diabetes and associated dyslipidemia.

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