Effects of fenofibrate on lipid parameters in obese rhesus monkeys

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Abstract Fenofibrate is a member of the fibrate class of hypolipidemic agents used clinically to treat hypertriglyceridemia and mixed hyperlipidemia. The fibrates were developed primarily on the basis of their cholesterol and triglyceride lowering in rodents. Fibrates have historically been ineffective at lowering triglycerides in experimentally-induced dyslipidemia in nonhuman primate models. The spontaneously obese rhesus monkey is a well-recognized animal model for the study of human obesity and type 2 diabetes, and many of these monkeys exhibit naturally occurring lipid abnormalities, including elevated triglycerides and low HDL cholesterol (HDL-C), similar to patients with type 2 diabetes. To explore whether the obese rhesus model was predictive of the lipid lowering effects of fibrates, we evaluated fenofibrate in six hypertriglyceridemic, hyperinsulinemic, nondiabetic animals in a 20-week, dose-escalating study. The study consisted of a 4-week baseline period, two treatment periods of 10 mg/kg twice daily (b.i.d) for 4 weeks and 30 mg/ kg b.i.d. for 8 weeks, and a 4-week washout period. Fenofibrate (30 mg/kg b.i.d) decreased serum triglycerides 55% and LDL-C 27%, whereas HDL-C increased 35%. Apolipoproteins B-100 and C-III levels were also reduced 70% and 29%, respectively. Food intake, body weight, and plasma glucose were not affected throughout the study. Interestingly, plasma insulin levels decreased 40% during the 30 mg/kg treatment period, suggesting improvement in insulin sensitivity. III These results support the use of obese rhesus monkey as an excellent animal model for studying the effects of novel hypolipidemic agents, particularly agents that impact serum triglycerides and HDL-C.-Winegar, D. A., P. J. Brown, W. O. Wilkison, M. C. Lewis, R. J. Ott, W. Q. Tong, H. R. Brown, J. M. Lehmann, S. A. Kliewer, K. D. Plunket, J. M. Way, N. L. Bodkin, and B. C. Hansen. Effects of fenofibrate on lipid parameters in obese rhesus monkeys. J. Lipid Res. 2001. 42: 1543-1551.

Supplementary key words fibrate • PPAR α • triglyceride-lowering • HDL-C • apolipoprotein C-III

Fibrates are a class of hypolipidemic drugs used to treat hypertriglyceridemia and mixed hyperlipidemia. Fibrates effectively lower plasma TG and increase HDL cholesterol (HDL-C) levels. These drugs also reduce LDL cholesterol (LDL-C), particularly small dense LDL-C, which is associated with increased risk of atherosclerosis (1, 2). The TG-lowering activity of fibrates has been attributed to both inhibition of hepatic fatty acid synthesis and increased catabolism of TG-rich lipoproteins (3, 4). This increase in VLDL catabolism results from up-regulation of LPL expression (5) and increased LPL activity due to a reduction in serum apolipoprotein C-III (apoC-III) levels (6, 7). The elevation in HDL-C seen with fibrates correlates with increased expression of apoA-I and apoA-II (8, 9).

The fibrates were developed primarily on the basis of their cholesterol- and TG-lowering activity in rodents. In rodents, the fibrates induce a peroxisomal proliferation response in liver characterized by increased peroxisomal fatty acid β -oxidation and microsomal ω -hydroxylation, which lead to hepatomegaly and hepatocarcinogenesis upon prolonged exposure (10, 11). Both the peroxisome proliferation response and the lipid modulating effects of fibrates appear to be mediated through the peroxisome proliferator-activated receptor-a (PPARa), a member of the nuclear hormone receptor superfamily known to induce changes in the transcription of genes encoding enzymes involved in lipid and lipoprotein metabolism (reviewed in 12). PPARa regulates gene expression in response to naturally occurring fatty acids and other lipophilic ligands by binding as a heterodimer with the retinoid X receptor to peroxisome proliferator response elements located in the upstream regulatory regions of target genes. PPARα expression in rodents is greatest in tissues rich in mitochondrial and peroxisomal β -oxidation such as liver,

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Abbreviations: b.i.d., bis in die, twice daily; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; PPARα, peroxisome proliferator-activated receptor-α; VLDL-C, VLDL cholesterol.

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kidney, and intestine (13-15). In contrast, human PPAR α expression is greatest in skeletal muscle, followed by liver, kidney, and adrenal (15-17). Several studies have shown that fibrates do not elicit a rodent-type peroxisome proliferation response in primate liver or in primate-derived cultured hepatocytes (18-23).

We were interested in evaluating fibrate-type activators of PPAR α in a nonrodent animal model that does not exhibit hepatic peroxisome proliferation in response to fibrates. Nonhuman primates have typically been resistant to the lipid modulating effects of fibrates, except when these drugs are administered at doses well above the clinically effective dose (24–26). For example, gemfibrozil and clofibrate were required at 3 to 35 times the clinical dose to achieve significant changes in cynomolgus (26) and rhesus monkey serum lipids (24, 25). This may be due to low basal serum lipids among the subjects studied or to species differences in the pharmacokinetic profile of the drugs.

Diet-induced coronary artery atherosclerosis has been studied for many years in nonhuman primates. The progression of the disease in several nonhuman primate species resembles coronary atherosclerosis in humans in many respects (27–29). Complications associated with coronary atherosclerosis are the leading cause of death in patients with type 2 diabetes (30, 31). Because diabetic individuals frequently exhibit an abnormal serum lipid profile that may be altered by fibrate therapy (32), we searched for a suitable nonhuman primate model of type 2 diabetes to test the effectiveness of a fibrate on modulating serum lipoproteins.

The spontaneously obese rhesus monkey is a well-recognized animal model system for examining the sequence of metabolic changes that are associated with the onset and development of diabetes, including changes in serum lipoproteins (33-35). These animals frequently exhibit increases in serum triglycerides, VLDL-TG, and VLDL cholesterol (VLDL-C) and decreases in HDL-C, generally consistent with the lipoprotein abnormalities often seen in humans. To explore whether the obese rhesus model was predictive of the lipid-lowering effects of fibrates, we evaluated fenofibrate in six hypertriglyceridemic, hyperinsulinemic, nondiabetic animals in a 20-week dose-escalating study. We show here that fenofibrate produced the same lipid-lowering effects as have been observed in humans: reductions in serum TG, apoC-III, and small dense LDL-C along with increases in HDL-C.

MATERIALS AND METHODS

Test material

Fenofibrate was obtained from Sigma Chemical Co. (St. Louis, MO, catalog no. F6020, lot 11H0890) and micronized to a particle size $<10 \mu m$.

Cloning of rhesus PPARa

Full-length rhesus PPAR α sequence was identified using overlapping clones generated by PCR from a rhesus liver cDNA library. cDNA encoding the rhesus PPAR α ligand binding domain was amplified using the following oligonucleotides: forward, CACAAGTGCCTTTCTGTCGGGATG; reverse, TCAGTACATGTC CCTGTAGATCTC. An overlapping fragment encoding the NH_2 terminus of rhesus PPAR α was amplified using the following primer pair: forward, 5' untranslated human PPAR α -CCAGCAC CATCTGGTCGCGATG; reverse, rhesus PPAR α -TTCGCAGGTAA GAATTTCTGC). Thirty cycles of PCR amplification were performed using the following cycle conditions: 95°C for 30 s, 56°C for 30 s, and 72°C for 120 s. PCR products were subcloned into pUC18 (Amersham Pharmacia Biotech, Piscataway, NJ.), and 10 independent clones from each PCR reaction were sequenced to confirm the identity of rhesus PPAR α .

Cotransfection assay

Fibrates were assayed for their ability to activate rhesus and human PPAR-GAL4 chimeric receptors in transiently transfected CV-1 cells, as previously described (36). The rhesus PPAR α -GAL4 receptor construct was prepared by inserting the ligand binding domain of rhesus PPAR α (encompassing amino acids 167–468) COOH-terminal to GAL4 in the pSG5 expression vector (Stratagene), as previously described (37). EC₅₀s were calculated as the concentration of compound required to induce 50% of the maximal reporter activity.

Western blotting of rhesus tissues with PPARa antibody

Tissue lysates were prepared from young adult and adult normal rhesus monkeys and Western blotted with the PPAR α -specific monoclonal antibody P α B11.80A, as previously described (17).

Subjects

Six middle-aged male rhesus monkeys (Macaca mulatta) were studied (Table 1). All were obese (body fat >30%) and had elevated serum TG (100-325 mg/dl), low HDL-C (26-67 mg/dl), and elevated fasting insulin levels ($102-294 \mu U/ml$). LDL-C and fasting plasma glucose levels were normal. The monkeys were maintained in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and protocols were reviewed and approved by the Institutional Animal Care and Use Committee. The monkeys were housed in individual primate cages with a 12-hr light-dark cycle. They were fed Purina Monkey Chow 15 [protein 17.4 ppm, fat 12.6 ppm, carbohydrate 69.9 ppm, cholesterol 119 ppm (communication per Purina Mills)] ad libitum and had unlimited access to fresh water. Food intake was measured daily and recorded as number of biscuits consumed. Body weight was recorded weekly throughout the study.

Study design

The animals were studied during five consecutive 4-week treatment periods as follows: *1*) baseline (vehicle); *2*) 10 mg/kg

TABLE 1. Baseline characteristics of the study subjects

Parameter	Normal Rhesus	Obese Rhesus
Age (year)	9.8 ± 1.5	21.0 ± 1.0
Body weight (kg)	11.2 ± 1.1	20.3 ± 0.5
Triglycerides (mg/dl)	47.8 ± 8.0	189.8 ± 31.8
Total cholesterol (mg/dl)	152.5 ± 13.2	134.3 ± 11.3
LDL-C (mg/dl)	50.7 ± 8.1	73.8 ± 9.6
HDL-C (mg/dl)	90.2 ± 6.2	45.8 ± 6.2
Insulin $(\mu U/l)$	32.4 ± 5.8	162.0 ± 28.8
Glucose (mg/dl)	60.7 ± 1.1	65.9 ± 2.0

All parameters reflect study subjects at day 0 of study as compared to normal rhesus values described in reference 33. Lipid analyses (TG, total cholesterol, LDL-C, HDL-C) were performed on plasma lipoprotein fractions isolated by isopycnic centrifugation. Data are presented as the mean \pm SEM for six rhesus monkeys.

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b.i.d. fenofibrate; 3) 30 mg/kg b.i.d. fenofibrate (30A); 4) 30 mg/kg b.i.d. fenofibrate (30B); 5) washout (vehicle). Animals were dosed twice daily (~8 AM and 4 PM) with drug incorporated into a vehicle (food snack, banana) or vehicle alone. The doses of fenofibrate were selected based on reported steady state exposure levels in humans receiving a standard dose of 200 mg micronized fenofibrate per day (23 mg/l, $\sim 64 \mu$ M) (38), with consideration of historical data showing reduced efficacy of fibrates in nonhuman primates (24-26). A dose >30 mg/kg was originally planned for this study; however, it was found to require an unacceptably large amount of vehicle for delivery. Thus, it was decided to continue for an additional 4 weeks of dosing at 30 mg/kg b.i.d. Blood samples were collected biweekly under light ketamine sedation 4 h after the morning dose of either vehicle or drug. Before the morning dose on collection days, monkeys were fasted overnight for 16 h. Blood was collected in a vacutainer tube for whole blood and in an EDTA vacutainer tube for preparation of plasma. Serum was prepared by chilling whole blood on ice for up to 30 min followed by centrifugation.

Assays

All parameters were measured biweekly unless otherwise noted. Routine clinical chemistry analyses were performed on frozen serum samples with a Technicon AXON® instrument using standard reagents and protocols. Tests included total cholesterol; total TG; NEFA; liver, renal, muscle, and pancreatic function panels; electrolytes; and serum proteins. Glucose and insulin were measured on fresh plasma using a Beckman Glucose Analyzer II and a double antibody radioimmunoassay using anti-porcine insulin antiserum. Hematology and plasma lipoprotein analyses were performed five times throughout the study: at baseline, at the end of each of the three treatment periods, and at the end of the washout period. A standard hematology panel along with measurement of fibrinogen levels was performed on fresh whole blood by Antech Diagnostic Laboratories (Farmingdale, NY). Plasma lipoprotein analyses were conducted by Medlantic Research Laboratories (Washington, D.C.). Lipoprotein fractions isolated from fresh plasma by isopycnic centrifugation were analyzed for total cholesterol, total TG, HDL-C, LDL-C, VLDL-C, and VLDL-TG content. LDL size was determined by nondenaturing PAGE, and apoB and apoC-III were measured by automated immunoprecipitation analysis.

Serum concentrations of fenofibric acid were measured by a reverse phase HPLC assay. Fenofibric acid is the principal metabolite of fenofibrate and the active form in vivo. Monkey serum (50-500 µl) was extracted with 2 ml acetonitrile by vortexing and centrifugation for 5 min. The supernatant was transferred to a clean tube and evaporated with nitrogen. Samples were then reconstituted with 300 µl of 70% methanol/30% 5 mM ammonium acetate, pH 4.0, and centrifuged before HPLC injection. The HPLC system consisted of an HP1090 autoinjector and pumps, a Symmetry C18 column (3.9×150 mm) set at 40°C, and an HP1090 diode array detector set at 300 nm. The mobile phase consisted of 60% methanol/40% 5 mM ammonium acetate, with a flow rate of 1 ml/min and a run time of 15 min. Fenofibric acid eluted at 5.4 min. Calibration standards were prepared in normal rhesus serum. The limits of quantitation for the assay were 70 to 3,486 ng/ml ($0.19-9.7 \mu$ M). The concentrations of fenofibric acid in the serum samples were calculated from the least-squares linear regression analysis of the logarithmically transformed peak areas and calibration standard concentrations using Microsoft EXCEL.

All data are expressed as mean \pm SEM. Differences were evaluated by paired Student's *t*-test.

RESULTS

Cloning and activation of rhesus monkey PPARa

Our previous screening of fibrate analogs for activity against PPAR α revealed distinct species differences in the potency of these compounds between human and murine PPAR α (36), possibly due to differences in the nucleotide sequences coding for human and murine PPAR α (94% identity in the ligand binding domain). To determine whether rhesus monkeys are an appropriate model in which to study fibrate-type activators of PPAR α , we identified clones encoding the entire open reading frame of rhesus monkey PPAR α . and compared the sequence with human PPAR α . (**Fig. 1A** and **1B**). Rhesus PPAR α shares 97% and 99% identity with human PPAR α cDNA and putative protein sequence, respectively.

A transient cotransfection assay was used to screen fibrate analogs for their activity against rhesus and human PPAR α . Fenofibrate fully activated rhesus PPAR α with a potency similar to human PPAR α , confirming the functionality of the rhesus receptor (EC₅₀s = 42.5 μ M for rhesus, 30 μ M for human) (**Fig. 2**). Similar, though less potent, activation of rhesus and human PPAR α was obtained with bezafibrate and gemfibrozil (Fig. 2).

Tissue distribution of rhesus PPAR α

In rodents and humans, PPAR α is highly expressed in tissues that catabolize fatty acids such as liver, heart, kidney, and intestine (13–15). The relative expression of PPAR α in human skeletal muscle, however, is much higher than in rodent skeletal muscle (15–17). We explored the tissue distribution of PPAR α in normal rhesus monkeys by Western blotting using a PPAR α -specific monoclonal antibody raised to an NH₂-terminal fragment of human PPAR α . A representative Western blot in **Fig. 3** shows that rhesus PPAR α protein expression is similar to humans in that expression in rhesus is highest in skeletal muscle, followed by liver, heart, and brown adipose tissue. Very little PPAR α was expressed in white adipose tissue.

Effects of fenofibrate on lipid parameters in obese rhesus monkeys

The baseline serum TG levels of the six hypertriglyceridemic monkeys studied ranged from 101 to 325 mg/dl, with a mean of 190 mg/dl (Table 1). Treatment for 4 weeks with 10 mg/kg b.i.d. fenofibrate reduced serum TG \sim 32% (**Fig. 4A**). Increasing the dose to 30 mg/kg b.i.d. further reduced TG to \sim 50% of baseline levels. These effects were observed within the first 2 weeks of dosing at 30 mg/kg and were maintained through 8 weeks of dosing. After a 4-week washout period with vehicle, TG levels returned to baseline (Fig. 4A). In general, animals with the highest baseline TG levels showed the greatest reponse to fenofibrate.

There was a trend toward lower serum apoC-III concentrations upon fenofibrate treatment (**Table 2**). Serum apoC-III levels decreased 19% and 29% at the 10 and 30 mg/kg doses of fenofibrate, respectively; however, only at the higher dose was the effect significant (P < 0.01).

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1	GTAACAATCCACCT 810 GGCGGAGGTCCGCA 910 GACCTGAACGATCA GACCTGAACGATCA 1010 ATGGAAATGGGTTT ATGGAAATGGGTTT	ITTGTCATAC. 820 ICTTTCACTG TCTTTCACTG 920 AGTGACACTG AGTGACACTGTG 1020 ATAACTCGTG ATAACTCGTG	830 CTGCCAGTGC CTGCCAGTGC 930 CTAAAATACG CTAAAATACG 1030 SAATTCCTAAA	BACACTGTGT/ 840 ACATCGGTGG ACTOSGTGG 940 GAGTTTACGA GAGTTTA[]GA 1040 IAAGCCTAAGG IAAGCCTAAGG	ATGGCTGAGA 850 AGACCGTCACC 950 GGCCATATTT GGCCATATTT 1050 AAACCGTTTT AAACCGTTTT	AGACECTGGT 860 GGAGCTCACG GGAGCTCACG 960 GCCATGCTGT GCCATGCTGT 1060 GTGATATCAT GTGATATCAT	GGCCAAGCTG 870 GAATTCGCCA GGAATTCGCCA 970 ICTTCGGTGAT ICTTCfjGTGAT 1070 IGGAACCCAAG IGGAACCCAAG	STGGCCAATG 880 AGGCCATCCC AGGCCATCCC 980 GAACAAAGAC GAACAAAGAC GAACAAAGAC 1080 TTTGATTTTG	GCATCCAGAAG 890 AGGCTTCGCA AGGCTTCGCA 990 GGGATCCTGG GGGATCCTGG 1090 CCATGAAGTT CCATGAAGTT	AACTTG rhesus PP AACTTG rhesus PP AACTTG hPPARa.se 1000 TAGCAT rhesus PF TAGCTT hPPARa.se 1100 CAATGC rhesus PF CAATGC rhesus PF CAATGC rhesus PF	eq PARa.seq PARa.sec eq PARa.sec eq
1	GTAACAATCCACCT 810 GGCGGAGGTCCGCA 910 GACCTGAACGATCA GACCTGAACGATCA 1010 ATGGAAATGGGTTT ATGGAAATGGGTTT	ITTGTCATAC. 820 ICTTTCACTG 920 AGTGACACTG AGTGACACTG 1020 ATAACTCGTG ATAACTCGTG	830 CTGCCAGTGC CTGCCAGTGC 930 CTAAAATACG 1030 SAATTCCTAAA SAATTCCTAAA	BACACTGTGT/ 840 ACATCGGTGG ACTOSGTGG 940 GAGTTTACGA GAGTTTACGA GAGTTTA[GA 1040 JAAGCCTAAGG JAAGCCTAAGG	ATGGCTGAGA 850 AGACCGTCACC 950 GGCCATATTT GGCCATATTT 1050 AAACCGTT[TT AAACCGTT[T	AGACECTGGT 860 GGAGCTCACG GGAGCTCACG 960 GCCATGCTGT GCCATGCTGT 1060 GTGATATCAT GTGATATCAT	GGCCAAGCTG 870 GGAATTCGCCA GGAATTCGCCA 970 ICTTCGGTGAT ICTTCIIGTGAT 1070 IGGAACCCAAG	STGGCCAATG 880 AGGCCATCCC AGGCCATCCC 980 GAACAAAGAC GAACAAAGAC 1080 TTTGATTTTG	GCATCCAGAAG 890 AGGCTTCGCAJ AGGCTTCGCAJ 990 GGGATGCTGG GGGATGCTGG 1090 CCATGAAGTT CCATGAAGTT	AACTTG rhesus PP AACTTG rhesus PP AACTTG hPPARa.se 1000 TAGCAT rhesus PP TAGCAT rhesus PP TAGCAT rhesus PP TAGCAT rhesus PP CAATGC rhesus PF CAATGC rhesus PF	eq PARa.sec PARa.sec PARa.sec PARa.sec eq
1 1	GTAACAATCCACCT 810 GGCGGAGGTCCGCA GGCGGAGGTCCGCA 910 GACCTGAACGATCA GACCTGAACGATCA 1010 ATGGAAATGGGTTI ATGGAAATGGGTTI 1110	ITTGTCATAC. 820 TCTTTCACTG 720 AGTGACACTG AGTGACACTG AGTGACACTGTG 1020 ATAACTCGTG ATAACTCGTG 1120	830 CTGCCAGTGC CTGCCAGTGC 930 CTAAAATACG 1030 CAATTCCTAAA AATTCCTAAA 1130	BACACTGTGT/ 840 ACATCGGTGG ACTOSGTGG 940 GAGTTTACGA GAGTTTACGA GAGTTTA[GA 1040 AAGCCTAAGG AAGCCTAAGG 1140	ATGGCTGAGA 850 AGACCGTCACC 950 GGCCATATTT GGCCATATTT 1050 AAACCGTTTTT AAACCGTT[TT 1150	AGACECTGGT 860 GGAGCTCACG GGAGCTCACG 960 GCCATGCTGT 1060 GTGATATCAT GTGATATCAT 1160	GGCCAAGCTG 870 GAATTCGCCA GAATTCGCCA 970 TCTTCGGTGAT 1070 TGGAACCCAAG TGGAACCCAAG 1170	STGGCCAATG 880 AGGCCATCCC AGGCCATCCC 980 GAACAAAGAC GAACAAAGAC 1080 TTTGATTTTG TTTGATTTTC 1180	GCATCCAGAAG 890 AGGCTTCGCAJ AGGCTTCGCAJ 990 GGGATGCTGG 1090 CCATGAAGTT SCCATGAAGTT 1190	AACTTG rhesus PP AACTTG rhesus PP AACTTG hPPARa.se 1000 TAGCAT rhesus PP TAGCAT rhesus PP TAGCAT rhesus PP TAGCAT rhesus PP CAATGC rhesus PF CAATGC rhesus PF CAATGC rhesus PF CAATGC rhesus PF CAATGC rhesus PF CAATGC rhesus PF	۹ ARa.sec ۹ ARa.sec ۹ ۹ PARa.sec
11	GTAACAATCCACCT 810 GGCGGAGGTCCGCA 910 GACCTGAACGATCA GACCTGAACGATCA 1010 ATGGAAATGGGTTT 1110 ACTGGAACTGGATCTGATC	ITTGTCATAC. 820 TCTTTCACTG TCTTTCACTG 920 AGTGACACTG AGTGACACTG 1020 XTAACTCGTG XTAACTCGTG 1120 XACAGCGATAJ	830 CTGCCAGTGC. 930 CTAAAATACG 1030 SAATTICCTAAA 1130 ICTCCCTTTTCC	840 ACATCGGTGG ACTCGTGGTGG 940 GAGTTTACGA GAGTTTACGA GAGTTTACGA 1040 AAGCCTAAGG 1140 CCTGGCTGCTA	ATGGCTGAGA 850 AGACCGTCACC 950 GGCCATATTT GGCCATATTT 1050 AAACCGTTTTT AAACCGTTGT 1150 TCATTTGCTG	AGACECTGGT 860 GGAGCTCACG GGAGCTCACG 960 GCCATGCTGT 1060 GTGATATCAT GTGATATCAT 1160 TTGGAGATCG	GGCCAAGCTG 870 GGAATTCGCCA GGAATTCGCCA 970 TCTTCGGTGAT TCTTCGGTGAT 1070 TGGAACCCAAG TGGAACCCAAG 1170 CCCTGGCCTTC	STGGCCAATG 880 AGGCCATCCC AGGCCATCCC 980 GAACAAAGAC GAACAAAGAC 1080 TTTGATTTTG TTGATTTTC 1180 TTAAACGTAGC	GCATCCAGAAG 890 AGGCTTCGCAJ AGGCTTCGCAJ 990 GGGATGCTGG GGGATGCTGG 1090 CCATGAAGTT CCATGAAGTT 1190 GACACATTGAA	AACTTG rhesus PP AACTTG rhesus PP AACTTG rhesus PP AACTTG hPPARa.se 1000 TAGCAT rhesus PP TAGCAT rhesus PP TAGCAT rhesus PF CAATGC rhesus PF CAATGC rhesus PF 1200 AAAATG rhesus PF	PARa.sec PARa.sec PARa.sec PARa.sec PARa.sec PARa.sec
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111	GTAACAATCCACCT 810 GGCGGAGGTCCGCA 910 GACCTGAACGATCA GACCTGAACGATCA 1010 ATGGAAATGGTTT 1110 ACTGGAACTGGATC ACTGGAACTGGATC	ITTGTCATAC. 820 TCTTTCACTG TCTTTCACTG 920 AGTGACACTG AGTGACACTG 1020 ATAACTCGTG ATAACTCGTG 1120 SACAGCGATAT SACAGGGATAT	830 CTGCCAGTGC. 930 CTAAAATACG 1030 SAATTCCTAAA 1130 rCTCCCTTTTQ	BACACTGTGTA 840 ACATCGGTGG ACTO 940 GAGTTTACGA GAGTTTACGA GAGTTTACGA 1040 1040 1040 1140 CGTGGCTGCTA GAGCTGCTA GAGCTGCTGCTA GAGCTGCTGCTA	ATGGCTGAGAA 850 AGACCGTCACC 950 GGCCATATTT GGCCATATTTG 1050 AAACCGTTGT 1150 TCATTTGCTG TCATTTGCTG	AGACECTGGT 860 GGAGCTCACG GGAGCTCACG 960 GCCATGCTGT 1060 GTGATATCAT GTGATATCAT 1160 TTGGAGATCG TTGGAGATCG	BECCAAGCTG 870 GRAATTCGCCA GRAATTCGCCA 970 TCTTCGGTGAT 1070 TGGAACCCAAG TGGAACCCAAG 1170 CCCTGGCCTTCC CCTGGCCTTCC CCTGGCCTTCC	BRO AGOCCATCCC AGOCCATCCC 980 GAACAAAGAC GAACAAAGAC GAACAAAGAC 1080 TTTGATTTTC TTGATTTTC 1180 TTAAACGTAGC TAAACGTAGC	GCATCCAGAAG 890 AGGCTTCGCAJ 990 GGGATGCTGG GGGATGCTGG 1090 CCATGAAGTT CCATGAAGTT 1190 SACACATTGAA SACACATTGAA	AACTTG rhesus PP AACTTG rhesus PP AACTTG hPPARa.se 1000 TAGCAT rhesus PP TAGCGT hPPARa.se 1100 CAATGC rhesus PE CAATGC rhesus PE CAATGC hPPARa.se 1200 AAAATG rhesus PI AAAATG rhesus PI	¤q PARa.sec ¤q PARa.sec ¤q PARa.sec ¤q ₽ARa.sec ¤q
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Fig. 1. (Continued)

Fenofibrate had no significant effect on total serum cholesterol throughout the study (data not shown); however, the drug decreased LDL-C and increased HDL-C levels. LDL-C fell 22% during the first 10 mg/kg treatment period with fenofibrate and held steady through the subsequent two 30 mg/kg treatment periods (Fig. 3B). Changes in the composition of the LDL particles were apparent as serum apoB concentrations decreased and LDL particle size increased (Table 2). ApoB levels were reduced 47% at the 10 mg/kg dose and 70% at the 30 mg/ kg dose, whereas LDL particle size increased 8% at the 30 mg/kg dose.

As seen in hypertriglyceridemic, insulin-resistant humans, baseline HDL-C levels of the monkeys studied were low relative to normal adult rhesus, ranging from 26 to 67 mg/dl [HDL-C nonobese rhesus ~90 mg/dl (33, 39)] (Table 1). Treatment with fenofibrate increased HDL-C by 18% at the 10 mg/kg dose and 35% at the 30 mg/kg dose (Fig. 4B). HDL-C levels returned to baseline during the washout period. An increase was seen in all animals, regardless of the starting baseline HDL-C level. Unexpectedly, fenofibrate treatment did not increase serum apoA-I levels in parallel with the rise in HDL-C levels (data not shown).

In addition to their effects on serum lipids, fibrates are reported to affect other metabolic parameters including insulin and body weight (40–45). Fasting plasma insulin levels of the monkeys studied averaged 162 μ U/ml at baseline (range 102–294 μ U/ml) (Table 1). These levels



Fig. 2. Activity of fibrates on rhesus PPARα. Fenofibrate (solid circle), bezafibrate (solid triangle), and gemfibrozil (solid square) were assayed for their ability to activate rhesus PPARα-GAL4 chimeric receptors in transiently transfected CV-1 cells, as previously described (29). Data are expressed as a percentage of the maximal effect of a standard control. Each data point represents the mean ± SEM of assays performed in triplicate. EC_{50} values for fibrates on rhesus PPARα: fenofibrate = 42.5 μM; bezafibrate = 220 μM; gemfibrozil = 184 μM.

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are ~3-fold higher than normal rhesus (33). Fenofibrate reduced insulin by 12% within the first 10 mg/kg treatment period and up to 40% during the subsequent two 30 mg/kg treatment periods (**Fig. 5A**). Plasma glucose levels were within the normal range at the start of the study and remained unchanged with fenofibrate treatment (Fig. 5B). Similarly, body weight and food consumption were not affected by fenofibrate (data not shown). To assess potential liver toxicity, we monitored serum markers of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. All enzyme levels remained in the normal range throughout the study (data not shown).

In support of the efficacy parameters measured, serum levels of fenofibric acid, the principal metabolite of fenofibrate and the active form in vivo, were determined. (**Table 3**). Because fenofibric acid serum levels peak between 4 and 6 h after dosing in man, serum samples were taken 4 h after dosing. Fenofibric acid levels averaged 1.95 ± 0.43 µM after the first 10 mg/kg dose. After 2 weeks of 10 mg/



Fig. 3. Tissue distribution of PPAR α in normal rhesus monkey. Tissue lysates obtained from a representative normal rhesus monkey (100 µg/lane) were electrophoresed, transferred to PVDF membranes, and immunoblotted with the PPAR α -specific antisera P α b11.80A (0.5 µg/ml).



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Fig. 4. Effects of fenofibrate on serum lipid parameters. Data are presented as mean \pm SEM for n = 6. $^+P < 0.05$, $^*P < 0.01$, $^{**}P < 0.005$, compared to baseline levels. A: Triglycerides. B: LDL-C. C: HDL-C.

kg dosing b.i.d., fenofibric acid levels increased to 8.66 \pm 2.31 μ M. This 4-fold increase in fenofibric acid serum levels is suggestive of drug accumulation upon multiple dosing.

Fenofibric acid serum levels did not increase when the dose of fenofibrate was raised to 30 mg/kg (8.07 \pm 1.13 μ M). In addition, no significant increases were seen upon sustained dosing for a total of 8 weeks at 30 mg/kg b.i.d. This may have been due to differences in the dissolution rate of the compound in the gastrointestinal tract at the higher dose and/or to changes in the T_{max} during oral absorption. These drug levels are lower than the EC₅₀ for activation of rhesus PPAR α (42.5 μ M) (Fig. 2); however, because only a 4-h serum sample was taken, the drug level at

TABLE 2. Effects of fenofibrate on serumapolipoprotein concentrations

Treatment	apoB-100	apoC-III	LDL size
	mg/dl	mg/dl	nm
Baseline	49.0 ± 7.6	7.93 ± 1.06	26.2 ± 1.0
10 mg/kg	26.2 ± 4.0	6.42 ± 0.87	27.5 ± 1.3
30 mg/kg	14.5 ± 3.1^{a}	5.60 ± 0.77^{a}	28.2 ± 0.8
30 mg/kg	15.7 ± 3.1^{a}	5.80 ± 0.69	28.4 ± 0.9^a
Washout	38.8 ± 7.0	6.73 ± 0.87	26.4 ± 0.4

Serum apolipoprotein concentrations were determined by IP analysis and LDL size measured by ND-PAGE. Data are presented as mean \pm SEM for n = 6.

^{*a*} P < 0.01 compared to baseline levels.

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this time point may not accurately reflect expected increases in maximal serum concentrations.

DISCUSSION

It is now widely accepted that high plasma TG and low plasma HDL-C levels are associated with increased risk of developing coronary heart disease (46–48). Fibrates have been used effectively to treat hypertriglyceridemia for many years. Fibrates primarily lower plasma TG, although they also decrease LDL-C and increase HDL-C in some



Fig. 5. Effects of fenofibrate on serum insulin (A) and glucose (B) levels. Data are presented as mean \pm SEM for n = 6. * *P* < 0.01 compared with baseline levels.

Dose	Serum Concentratior of Fenofibric Acid		
	$\mu { m M}$		
10 mg/kg b.i.d.			
Single dose	1.95 ± 0.43		
2 weeks	8.66 ± 2.31		
30 mg/kg b.i.d.			
Single dose	8.07 ± 1.13		
2 weeks	12.59 ± 1.89		
4 weeks	12.05 ± 0.95		
6 weeks	10.80 ± 2.16		

Serum concentrations of fenofibric acid were measured following a single dose or continuous twice daily dosing of either 10 or 30 mg/kg fenofibrate. Samples were taken 4 h after dosing. Data are presented as mean \pm SEM for n = 6.

patients (1-4). Several primary and secondary prevention studies have proven the efficacy of certain fibrates in the prevention of coronary heart disease in dyslipidemic patients (1, 2, 32).

The principal molecular target of fibrates has been identified as the nuclear hormone receptor PPARa. An extensive body of data generated primarily in rodents suggests that fibrate activation of PPARα regulates the expression of genes involved in lipid and lipoprotein metabolism (3-9, 49). In rodent liver where PPAR α expression is the highest, fibrates induce the expression of the fatty acid transport protein (FATP), LPL, and several peroxisomal and mitochondrial fatty acid oxidation genes (5, 12, 49). In additon, fibrates decrease apoC-III gene expression (6, 7). These transcriptional events lead to increased hepatic uptake and metabolism of fatty acids and enhanced catabolism of TG-rich lipoproteins, which together may account for most of the TG-lowering effects of fibrates. There are few reports describing fibrate/PPARa regulation of gene expression in human tissues. Rodent responses to fibrates differ from humans in several respects, possibly related to differences in relative tissue distribution of PPARa. Although humans express significant amounts of PPARa protein in liver, expression of the receptor is highest in skeletal muscle (15-17). Fibrates induce a peroxisome proliferation response in the livers of rodents that leads to hepatomegaly and hepatocarcinogenesis upon repeated exposure (10, 11). Humans and nonhuman primates appear to be resistant to this peroxisome proliferative effect (18-23). Fibrates increase HDL-C levels in man by stimulating the production of its major protein constituents apoA-I and apoA-II (8, 9). Conversely, in rodents, fibrates tend to reduce plasma HDL-C levels and decrease the hepatic expression of apoA-I and apoA-II (8, 50). Our search for a nonrodent animal model more predictive of the human response to fibrate-type activators of PPAR α led us to explore the effects of fenofibrate in the spontaneously obese rhesus monkey.

Similar to its effects in man, chronic treatment of obese rhesus monkeys with fenofibrate markedly lowered serum TG and produced a favorable increase in HDL-C levels (Fig. 4). The decrease in serum TG is likely to be mediated through increased LPL-mediated lipoprotein lipolysis linked, at least in part, to a reduction in serum apoC-III levels (Table 2). In addition, fenofibrate may inhibit the production of TG-rich lipoproteins, as suggested by the decrease in serum apoB-100 levels (Table 2). Whereas LDL-C was modestly reduced upon fenofibrate treatment, LDL particle size increased significantly, indicating a trend toward the formation of less atherogenic LDL particles (1, 2). These changes in particle size are in response to the alterations in apolipoprotein composition and lipid content.

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Food intake, body weight, and plasma glucose were not affected by fenofibrate treatment in these normoglycemic subjects; however, plasma insulin levels were dosedependently decreased with fenofibrate. Gemfibrozil and bezafibrate have been shown to improve insulin action and glucose tolerance in hyperlipidemic patients without significant effects on body weight (42, 43). Fibrates have been shown to reduce body weight gain and improve insulin sensitivity in several rodent models of obesity, diabetes, and insulin resistance (40, 41, 44, 45). These effects are thought to be mediated through the coupling of increased flux of free fatty acids from peripheral tissues to the liver with enhanced hepatic lipid catabolism. By comparison, the insulin-sensitizing effects of PPARy agonists, manifested as a reduction in serum glucose, insulin, and TG and increased adipose tissue mass in rodents, reportedly result from free fatty acid flux from skeletal muscle to adipose tissue (reviewed in 12, 51). For several reasons, we believe that the apparent improvement in insulin resistance observed in these obese rhesus monkeys was not due to activation of PPARy. Fenofibrate exhibits at least a 10-fold selectivity for human PPAR α over human PPAR γ as determined in PPAR-GAL4 chimeric transfection assays (30 vs. 300 µM for human PPARa and PPARy, respectively) (36). Considering the high degree of homology between the human and rhesus PPARa sequences, it is expected that this subtype selectivity is preserved among the other two rhesus PPAR receptors. Furthermore, the exposure levels of fenofibrate measured at several time points during the study indicate that fenofibrate was not present at sufficient levels in the serum to fully activate PPARy (Table 3).

The results of this study support the obese rhesus monkey as an excellent animal model for evaluating the effects of novel lipoprotein-modulating agents, particularly agents that affect serum TG and HDL-C.

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