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PPARα activation elevates blood pressure and does not correct glucocorticoid-induced insulin resistance in humans

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Subramanian, Savitha, Michael A. DeRosa, Carlos Bernal-Mizrachi, Nicholas Laffely, William T. Cade, Kevin E. Yarasheski, Philip E. Cryer, and Clay F. Semenkovich. PPARα activation elevates blood pressure and does not correct glucocorticoid-induced insulin resistance in humans. *Am J Physiol Endocrinol Metab* 291: E1365–E1371, 2006. First published July 25, 2006; doi:10.1152/ajpendo.00230.2006.—Fibrates, activators of the nuclear receptor PPARα, improve dyslipidemia, but their effects on insulin resistance and vascular disease are unresolved. To test the hypothesis that PPARα activation improves insulin resistance and vascular function, we determined the effects of fenofibrate in healthy adults with insulin resistance induced by short-term glucocorticoid administration. Eighteen normal-weight subjects were studied in four stages: at baseline, after 21 days of fenofibrate (160 mg/day) alone, after 3 days of dexamethasone (8 mg/day) added to fenofibrate, and after 3 days of dexamethasone added to placebo (dexamethasone alone). Dexamethasone alone caused hyperinsulinemia, increased glucose, decreased glucose disposal, and reduced insulin-induced suppression of hepatic glucose production as determined by hyperinsulinemic euglycemic clamp and increased systolic blood pressure as determined by ambulatory monitoring, features associated with an insulin-resistant state. Fenofibrate improved fasting LDL and total cholesterol in the setting of dexamethasone treatment but had no significant effect on levels of insulin or glucose, insulin-stimulated glucose disposal, or insulin suppression of glucose production during clamps, or ambulatory monitored blood pressure. In the absence of dexamethasone, fenofibrate lowered fasting triglycerides and cholesterol but unexpectedly increased systolic blood pressure by ambulatory monitoring. These data suggest that PPARα activation in humans does not correct insulin resistance induced by glucocorticoids and may adversely affect blood pressure.

peroxisome proliferator-activated receptor-α; dexamethasone; insulin sensitivity; metabolic syndrome

INSULIN RESISTANCE, frequently caused by obesity, is associated with vascular disease. The epidemic spread of obesity in industrialized countries has fueled an increase in metabolic abnormalities linked to insulin resistance and atherosclerosis. Glucose intolerance, dyslipidemia, and hypertension are associated with impaired insulin signaling, and each is implicated in vascular disease. These conditions, along with central obesity, comprise the metabolic syndrome, which is associated with atherosclerosis and may affect nearly one-quarter of adults in the United States (1). Although the syndrome (with its implied insulin resistance) may not impart vascular risk exceeding the presence of its individual components (11), it is clear that therapies to decrease atherosclerotic complications in people with insulin resistance are less than optimal.

Pharmacological activation of peroxisome proliferator-activated receptor-α (PPARα) has long been an attractive potential strategy for improving vascular disease in insulin resistance. Activation of the nuclear receptor PPARα by fibrates increases expression of several genes involved in lipid metabolism, including those that promote fatty acid oxidation and triglyceride metabolism (26). Because fibrate treatment in hyperlipidemic patients lowers triglycerides and increases HDL cholesterol, two of the parameters used to diagnose metabolic syndrome, it is reasonable to pursue the notion that fibrates may decrease insulin resistance. Animal studies have demonstrated a favorable effect of fibrates on insulin sensitivity. Treatment of Zucker diabetic rats and *ob/ob* mice with fenofibrate or other PPARα agonists reduced insulin resistance as well as adiposity (9). Insulin sensitivity is improved in lipoatrophic mice (7) and in mice with muscle-specific insulin resistance (13) after treatment with WY-14643, a potent PPARα agonist. These effects have been attributed to increased metabolism of intracellular lipids, leading to less lipotoxic interference with insulin signaling. However, this drug also activates PPARγ (16), raising the possibility that some of the effects of WY-14643 could be due to induction of PPARγ-dependent genes that enhance insulin sensitivity. Although accelerated fatty oxidation, a consequence of PPARα activation, could provide benefits by decreasing lipid stores, recent data also suggest that increasing fatty acid oxidation in the vasculature may be proatherogenic (8).

Results of human studies of the effects of fibrates on insulin sensitivity are less consistent than those in animals. Treatment with gemfibrozil in patients with phenotypes including type 2 diabetes, dyslipidemia with glucose intolerance, and hypertriglyceridemia with normal glucose tolerance has been reported to improve insulin sensitivity (4, 20), have no effect on insulin sensitivity (10, 33), or have beneficial effects in subsets of patients on the basis of glycemia (25). Treatment with fenofibrate enhances insulin sensitivity in dyslipidemic patients with normal glucose metabolism (36) but has no effect on insulin responses in subjects with metabolic syndrome (32). Bezafibrate prevents the progression of insulin resistance in patients with coronary artery disease (28).

One obvious contributor to the conflicting human data involving fibrates and insulin sensitivity is the heterogeneity of the study subjects. Insulin resistance can be manifested in

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Table 1. *Clinical and laboratory characteristics of subjects at baseline*

n	18
Age, yr	33.1±8
Sex (M/F)	7/11
BMI, kg/m^2	23.5±3
Fasting plasma glucose, mmol/l	5.1±0.37
Fasting serum insulin, pmol/l	35.8±3.4
SBP, mmHg	111±7
DBP, mmHg	70±6

Data represent means ± SD. SBP and DBP, systolic and diastolic blood pressure.

different ways in different individuals. Patients with dyslipidemia, adiposity, and normal fasting glucose, as well as those with glucose intolerance, adiposity, and hypertension, both fulfill the criteria for metabolic syndrome. To test the hypothesis that PPARα activation improves insulin resistance and vascular function, we studied the effects of fenofibrate in healthy, nonobese subjects in the setting of a uniform cause of insulin resistance, short-term glucocorticoid administration.

EXPERIMENTAL PROCEDURES

Study design. Potential participants underwent a screening with a 75-g oral glucose tolerance test, and only subjects with normal glucose tolerance were enrolled. Eighteen nonobese healthy volunteers, 7 men and 11 women, with normal blood pressure, normal serum lipids, and no personal or family history of diabetes were enrolled. Characteristics of the participants are presented in Table 1. All studies were approved by the Washington University Human Studies Committee and were performed at the General Clinical Research Center. Subjects were evaluated on four separate occasions as shown schematically in Fig. 1: *1*) at baseline (*limb 1*); *2*) after a 21-day course of 160 mg/day fenofibrate, a PPARα agonist (*limb 2*); *3*) after a 3-day course of 8 mg/day dexamethasone along with continued fenofibrate (*limb 3*); and *4*) after a 4-wk period of no interventions (washout), after taking a placebo for 21 days followed by a 3-day course of dexamethasone 8 mg/day (*limb 4*). Fenofibrate and the placebo were provided in identical capsules. For some subjects, *limb 4* was performed immediately after *limb 1*, which was then followed by a washout period and *limbs 2* and *3* to decrease the potential effect of limb order on the results. Subjects were unaware of medication assignment during each limb. Participants maintained their regular diet and did not change their usual activity levels during the study. Evaluations in women were conducted during the follicular phase of the menstrual cycle.

Hyperinsulinemic euglycemic clamps. For each of the four limbs, volunteers presented for studies after an overnight fast at 0700. Where applicable, participants took the allocated medication on the morning of the study. On the day of the study, a catheter was inserted into the antecubital vein for infusion of insulin, glucose, and tracer solutions. A second catheter was placed in a hand vein for blood sampling. The hand was placed in a temperature-regulated Plexiglas hotbox at ~55°C for arterialized venous sampling. Blood samples were obtained before the isotope infusions were begun to determine baseline glucose, insulin, C-peptide, glucagon, lipids and lipoproteins, creatinine, serum transaminases, renin, angiotensin II, and leptin.

An infusion of the stable isotope [6,6-$^2H_2$]glucose (22 μmol/kg prime and 0.25 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ constant infusion) was administered intravenously for 90 min (basal period) before the start of the clamp study to allow isotope equilibration and continued for the total duration of the study. Insulin sensitivity was determined by a two-step hyperinsulinemic euglycemic technique using methods described previously (23). Regular human insulin (Eli Lilly) was infused intravenously to achieve plasma insulin concentrations of ~40 μU/ml (287 pM) by using an infusion rate of 20 $mU \cdot m^{-2} \cdot min^{-1}$. During the second stage, insulin infusion was increased to 40 $mU \cdot m^{-2} \cdot min^{-1}$ to reach plasma insulin concentrations of ~100 μU/ml (720 pM). A simultaneously adjusted infusion of 20% dextrose solution (spiked with 1.5% [6,6-$^2H_2$]glucose) was used to maintain blood glucose at 5 mmol/l (90 mg/dl) for ~2 h with each step. Analysis of plasma for [6,6-$^2H_2$]glucose enrichment was performed by gas chromatography-electron impact quadruple mass spectrometry. Samples were obtained every 10 min during the last 30 min of the basal period and during each stage of the clamp to determine glucose concentrations and kinetics as well as plasma insulin, C-peptide, and glucagon. Plasma glucose was measured every 5–10 min from the end of the basal period throughout the entire clamp period.

A 75-g oral glucose tolerance test was performed on the day following the clamp study in all limbs. Glucose, insulin, C-peptide, and glucagon were measured at 0, 30, 60, 90, and 120 min.

Ambulatory blood pressure monitoring. Ambulatory blood pressure for 24 h during normal activities was recorded toward the end of each limb before each hyperinsulinemic euglycemic clamp study, using a portable oscillometric recorder (model 90207; SpaceLabs Medical, Issaquah, WA). Readings were recorded every 20 min from 0800 to midnight and every 1 h from midnight to 0800. Data were

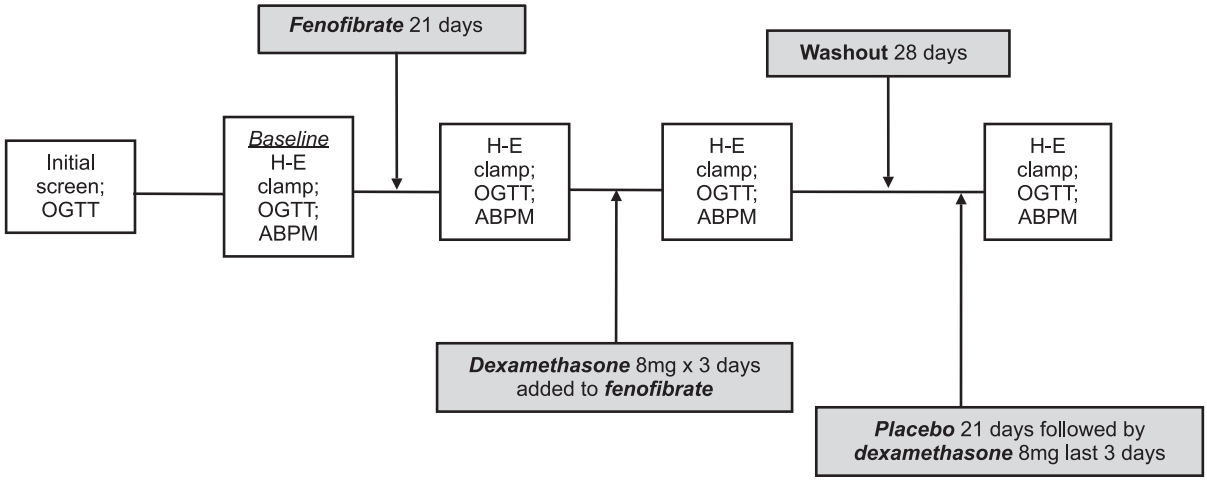

Fig. 1. Study design. OGTT, oral glucose tolerance test; H-E clamp, hyperinsulinemic euglycemic clamp; ABPM, ambulatory blood pressure monitoring. For some subjects, the placebo-followed-by-dexamethasone limb preceded the fenofibrate-followed-by-dexamethasone limbs.

analyzed as mean pressure over 24 h, daytime (0800 to 2200) pressure, and nighttime (2200 to 0800) pressure.

Forearm blood flow. Venous occlusion strain gauge plethysmography was performed as described (35). A strain gauge was placed on the upper half of the forearm so that the gauge was above the level of the right atrium. A venous occlusion cuff was placed over the upper arm to occlude venous outflow from the arm and was inflated to 50 mmHg using an automatic cuff inflator (ParksMedical, Aloha, OR); a smaller cuff was placed at the wrist and inflated to 270 mmHg to exclude blood flow to the hand. The signal was transmitted and recorded on a continuous recording device and flow measured as the percentage change of arm volume times cubic centimeters per 100 ml of tissue per minute.

Other assays. Plasma glucose was measured using a glucose oxidase method (Yellow Springs Analyzer 2; Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin, C-peptide, glucagon, and leptin were measured by radioimmunoassay. Lipids, lipoproteins, and other serum chemistries were assayed by the Core Laboratory for Clinical Studies at Washington University.

Statistical analysis. Results are expressed as means ± SE except where indicated. Statistical significance between baseline and each intervention was detected using repeated-measures ANOVA with post hoc testing using Tukey's analysis for intergroup differences.

RESULTS

Healthy subjects (Table 1) underwent the protocol shown in Fig. 1 involving ambulatory blood pressure monitoring on four separate occasions: baseline, after fenofibrate alone, after fenofibrate + dexamethasone, and after placebo + dexamethasone. There was no detectable effect of any of the interventions on body weight (not shown). Serum chemistries and other relevant metabolic parameters for each limb of the study are shown in Table 2. Liver enzymes were normal during all four limbs except for one female subject who developed a modest (~2-fold) asymptomatic elevation in transaminases after the fenofibrate-alone limb and was therefore excluded from the third and fourth limbs of the study. Dexamethasone treatment for 3 days following 21 days of placebo increased fasting glucose compared with baseline (5.1 ± 0.08 vs. 5.8 ± 0.12 mmol/l, $P < 0.001$) and fasting insulin compared with baseline (35.8 ± 3.38 vs. 62.9 ± 6.33 pmol/l, $P < 0.01$). Treatment with fenofibrate for 21 days prior to dexamethasone did not correct these increases, but total and LDL cholesterol were decreased by fenofibrate in the setting of dexamethasone treatment, consistent with the known effects of PPARα activation on lipid metabolism. Treatment with fenofibrate alone did not affect fasting glucose or insulin, but triglycerides and total cholesterol decreased, again consistent with the effects of PPARα activation on lipid metabolism.

The results of oral glucose tolerance tests were not significantly different between limbs (Fig. 2*A*). Insulin levels during these tests were higher in the dexamethasone limb compared with the baseline and fenofibrate-only limb, but there was there was no significant difference in insulin levels between the fenofibrate + dexamethasone and placebo + dexamethasone limbs (Fig. 2*B*). Significant individual comparisons are indicated in the figure. *P* values comparing the different curves by repeated-measures ANOVA were as follows: baseline vs. dexamethasone, $P = 0.119$ for glucose, $P = 0.003$ for insulin; fenofibrate-only vs. dexamethasone, $P = 0.853$ for glucose, $P = 0.007$ for insulin; fenofibrate + dexamethasone vs. dexamethasone, $P = 0.355$ for glucose, $P = 0.169$ for insulin; baseline vs. fenofibrate, $P = 0.159$ for glucose, $P = 0.704$ for insulin; baseline vs. fen+dex, $P = 0.594$ for glucose, $P = 0.073$ for insulin; fenofibrate vs. fenofibrate + dexamethasone, $P = 0.441$ for glucose, $P = 0.188$ for insulin. Nonparametric analysis of these data yielded the same results. These findings suggest that fenofibrate did not lower glucose and did not correct insulin resistance induced by glucocorticoid treatment.

The results of hyperinsulinemic euglycemic clamp studies for each limb are shown in Fig. 3. Dexamethasone treatment for 3 days following 21 days of placebo significantly decreased the glucose disposal rate with low-dose insulin infusion and high-dose insulin infusion compared with baseline (Fig. 3*A*). Treatment with fenofibrate for 21 days prior to dexamethasone did not correct this decrement in glucose disposal. Dexamethasone treatment alone resulted in resistance to the suppression of hepatic glucose production by low-dose insulin, an effect that was not corrected by prior fenofibrate treatment (Fig. 3*B*). Although the response of hepatic glucose production to insulin infusion was unaffected by treatment with fenofibrate, there was a small reduction in basal hepatic glucose production when

Table 2. *Effects of fenofibrate and dexamethasone on metabolic parameters*

	Baseline	Fenofibrate	Fen + Dex	Dexamethasone
Fasting plasma glucose, mmol/l	5.1±0.08	5.0±0.06	5.4±0.11[a]	5.8±0.12[b]
Fasting insulin, pmol/l	35.8±3.38	31.7±3.99	54.1±6.91[c]	62.9±6.33[d]
Fasting C-peptide, nmol/l	0.55±0.34	0.54±0.05	0.75±0.06[d]	0.89±0.06[b]
Fasting glucagon, ng/l	131.5±10.7	133.9±9.94	143±10.9	141.9±11.1
2-h OGTT glucose, mmol/l	6.1±0.53	6.1±0.27	6.3±0.30	6.4±0.54
2-h OGTT insulin, pmol/l	199.1±29.1	219.3±41.8	269.5±31.2	389.5±52.6[a]
Total cholesterol, mmol/l	4.1±0.19	3.5±0.18[e]	3.6±0.16[e]	4.1±0.22
HDL cholesterol, mmol/l	1.3±0.08	1.2±0.07	1.3±0.13	1.4±0.12[a]
LDL cholesterol, mmol/l	2.3±0.17	2.0±0.17[f]	1.9±0.14[g]	2.4±0.20
Triglycerides, mmol/l	1.2±0.14	0.71±0.07[h]	0.69±0.08[h]	0.69±0.08[h]
Leptin, ng/ml	7.9±1.52	7.7±1.2	15.4±2.20[b]	16.2±2.57[b]
AST, U/l	26.6±1.34	32.2±6.6	22.9±1.96	30±4.15
ALT, U/l	27.8±3.58	28.3±6.71	20.9±2.06	32.6±5.33
Creatinine, μmol/l	77.5±3.1	70.0±4.3	77.0±5.4	65.0±3.6[a]
Renin, ng · ml^{-1} · h^{-1}	0.8±0.16	0.7±0.12	0.7±0.19	0.7±0.14
Angiotensin, pmol/l	25.3±3.2	22.3±4.7	20.6±5.2	25.2±4.9

Data are expressed as means ± SE. AST, aspartate transaminase; ALT, alanine transaminase; Fen, fenofibrate; Dex, dexamethasone; OGTT, oral glucose tolerance test. [a]$P < 0.05$ vs. baseline, $P < 0.01$ vs. Fen; [b]$P < 0.001$ vs. baseline and Fen; [c]$P < 0.01$ vs. Fen; [d]$P < 0.01$ vs. baseline, $P < 0.001$ vs. Fen; [e]$P < 0.001$ vs. baseline and Dex; [f]$P < 0.05$ vs. baseline and Dex; [g]$P < 0.001$ vs. baseline and Dex; [h]$P < 0.001$ vs. baseline

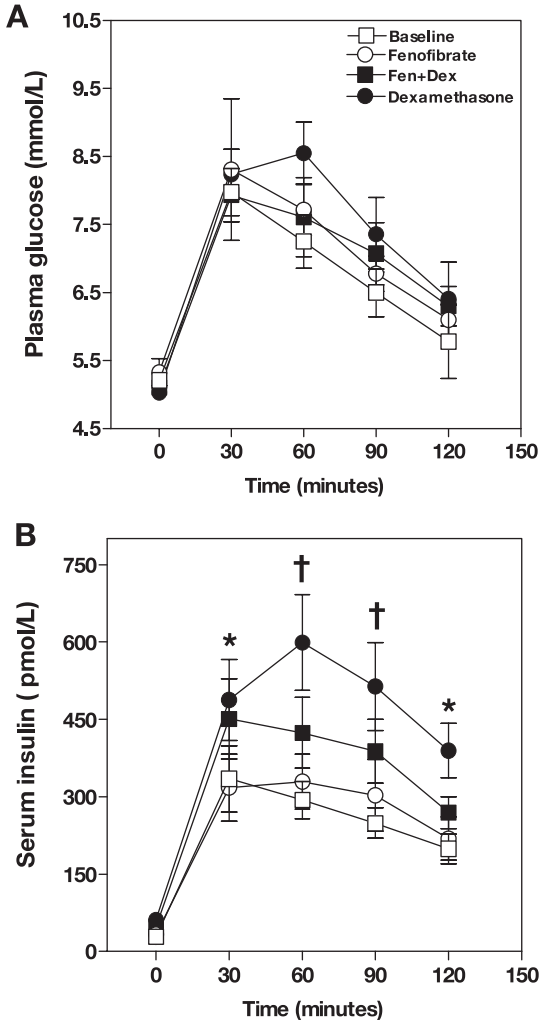

Fig. 2. Effects of fenofibrate (Fen) and dexamethasone (Dex) on oral glucose tolerance. Plasma glucose (*A*) and insulin (*B*) excursions are shown after a 75-g oral glucose challenge. Studies were performed at baseline (□), after 21 days of fenofibrate (○), after fenofibrate therapy was followed with 3 days of 8 mg/day dexamethasone (■), and after placebo followed by 3 days of 8 mg/day dexamethasone alone (●). *$P < 0.05$ vs. baseline; †$P < 0.01$ vs. baseline; $P < 0.05$ vs. fenofibrate. Data represent means ± SE.

fenofibrate was added to dexamethasone ($P < 0.05$ comparing basal production for dexamethasone and fenofibrate + dexamethasone).

Plasma free fatty acids assayed during the clamp procedure for each limb are shown in Fig. 4. At the beginning of the clamp, fatty acid levels were lower with fenofibrate + dexamethasone treatment compared with placebo + dexamethasone treatment ($P < 0.001$), suggesting that fenofibrate decreases the glucocorticoid-induced increase in circulating fatty acids, but there was no difference between these limbs in terms of insulin-induced suppression of free fatty acids (Fig. 4).

Mean blood pressure results for 24 h are shown in Table 3. There were no significant differences (*P* values ranged from 0.7 to 0.9) between the sexes for blood pressure values (24 h, day or night) in any limb. Therefore, data from males and females are presented together. Dexamethasone treatment for only 3 days following 21 days of placebo increased 24-h mean systolic blood pressure by 7 mmHg compared with baseline (111 ± 2 vs. 118 ± 2 mmHg, $P < 0.001$). Treatment with fenofibrate for 21 days prior to dexamethasone had no effect on the increase in blood pressure induced by dexamethasone, suggesting that PPARα activation does not reverse the blood pressure-elevating effect of glucocorticoid treatment. Surprisingly, treatment with fenofibrate alone for 21 days increased the 24-h mean systolic blood pressure by 3 mmHg compared with baseline (111 ± 2 vs. 114 ± 2 mmHg, $P < 0.05$). Daytime and nighttime measurements are also shown in Table 3. Blood pressure normally decreases during sleep (18), and values during each limb were lower between 2200 and 0800 compared with between 0800 and 2200. Both daytime and nighttime systolic pressures tended to be higher after fenofibrate treatment alone compared with baseline, but these differences were not significant. Daytime systolic blood pressures were identical in the placebo + dexamethasone and fenofibrate + dexamethasone groups and significantly greater than daytime systolic blood pressure at baseline. There were no significant effects on diastolic blood pressure for any limb.

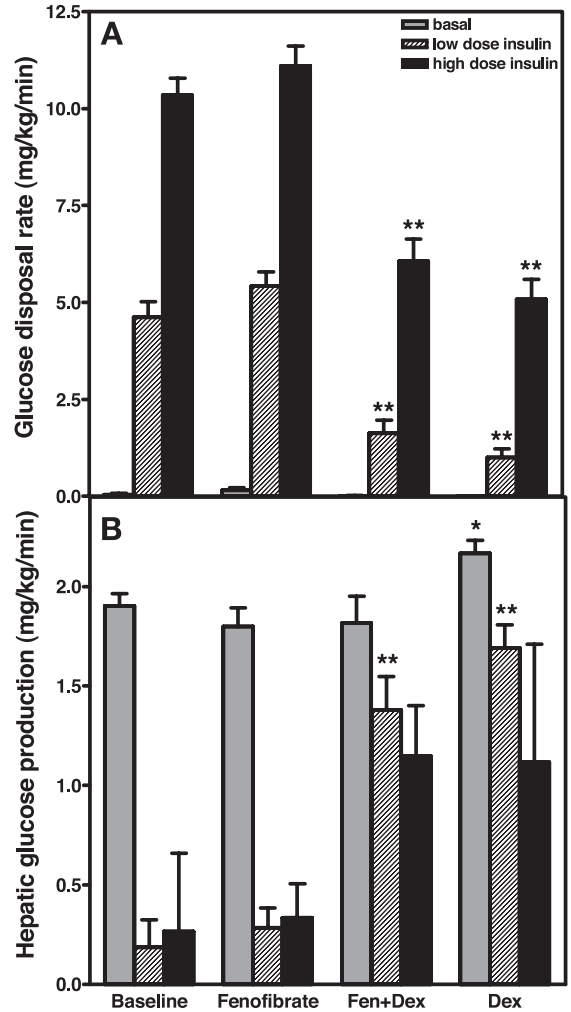

Fig. 3. Effects of fenofibrate and dexamethasone on 2-step clamp-determined glucose metabolism. *A*: effects of the drugs on glucose disposal under basal conditions (gray bars), low-dose insulin infusion (hatched bars), and high-dose insulin infusion (filled bars) during H-E clamp studies. *B*: effects of fenofibrate alone and in combination with dexamethasone on hepatic glucose production. **$P < 0.001$ vs. baseline and vs. fenofibrate. *$P < 0.05$ vs. fenofibrate and vs. Fen + Dex. Data represent means ± SE.

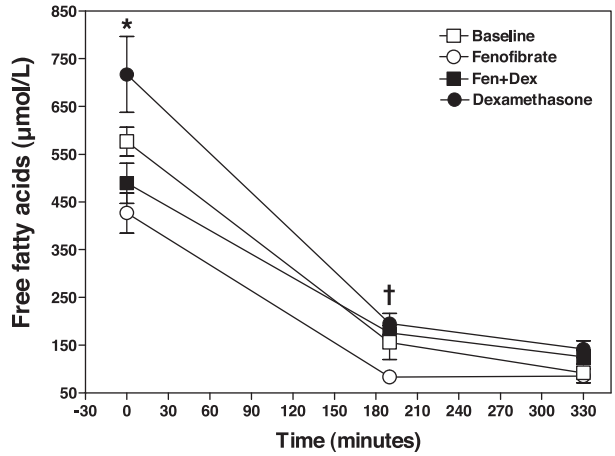

Fig. 4. Plasma free fatty acid levels under basal conditions and during low- and high-dose insulin infusions of the H-E clamps at each limb of the study. No significant changes in insulin-induced free fatty acid suppression were detected with fenofibrate therapy. *$P < 0.001$ vs. fenofibrate and vs. Fen + Dex; †$P < 0.05$ dexamethasone vs. fenofibrate.

As an additional measurement of vascular function, forearm blood flow was measured by plethysmography during hyperinsulinemic euglycemic clamp studies at each limb of the study. There were no detectable differences in blood flow between any of the limbs of the study (not shown).

DISCUSSION

Glucocorticoid induction of insulin resistance is relevant to the pathophysiology of obesity-associated insulin resistance. Patients with Cushing's syndrome caused by exogenous or endogenous glucocorticoid excess have a phenotype that is very similar to metabolic syndrome (2, 27, 34). Excessive tissue generation of active glucocorticoids by overexpression of 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) increases (19), and interference with this process decreases (14), insulin resistance. Inhibition of glucocorticoid activation has been proposed as a therapy for insulin resistance (31).

To address the possibility that conflicting data regarding the effects of PPARα activation on insulin sensitivity are due to variability in the characteristics of subjects with insulin resistance, we induced insulin resistance in healthy subjects by use of a uniform stimulus, short-term administration of glucocorticoids. Three days of dexamethasone treatment increased glucose, increased insulin levels, decreased glucose disposal and resistance to insulin suppression of endogenous glucose production during clamps, and increased blood pressure determined by ambulatory monitoring, thus establishing a human model of insulin resistance caused by a well-defined stimulus. Fenofibrate lowered lipids in the setting of dexamethasone treatment but did not reverse the effects of dexamethasone on glucose metabolism or blood pressure. Unexpectedly, treatment with fenofibrate alone in these healthy subjects resulted in a significant increase in systolic blood pressure, determined by ambulatory monitoring. Collectively, these results suggest that the activation of PPARα by fenofibrate in humans does not correct glucocorticoid-induced insulin resistance and may have adverse effects on blood pressure.

Activation of PPARα in mouse models of insulin resistance improves insulin sensitivity. There are clear potential explanations for the differences between these animal results and our results in humans. First, treatment with fibrates causes significant weight loss in these animal models. Weight loss enhances insulin sensitivity. Fenofibrate did not affect weight in humans in the current study. Second, the animal models (e.g., leptin deficiency, lipodystrophic mice) showing responses to PPARα activation have severe phenotypes associated with the considerable deposition of lipid in key tissues such as liver and muscle. Accelerated metabolism of these lipid stores induced by PPARα activation would have greater effects on insulin signaling than any changes in tissue lipids expected in humans treated with a relatively weak PPARα agonist. Third, fibrates have differential effects on peroxisome biology in rodents and humans (15), raising the possibility that effects of fibrates on insulin sensitivity in rodents could be species-specific.

Reports addressing the effects of PPARα activation on insulin sensitivity in humans are not consistent, although subjects with variable phenotypes have been studied because of the heterogeneous presentation of insulin resistance. We are unaware of studies demonstrating worsening of insulin resistance by PPARα activation, and some studies suggest improvement in this parameter with fibrates. There were reductions in basal hepatic glucose production and basal fatty acid levels with fenofibrate in dexamethasone-treated subjects in the present report, but fenofibrate did not alter the effects of insulin on these variables in the setting of dexamethasone treatment. At the beginning of our study, we estimated that 15 subjects (18 were recruited, and 17 completed every limb) would be

Table 3. *Ambulatory blood pressure changes with fenofibrate and dexamethasone alone or in combination*

	Baseline	Fenofibrate	Fen + Dex	Dexamethasone
24-h Mean ABPM, mmHg				
SBP	111±2	114±2[a]	118±2[b]	118±2[c]
DBP	70±2	68±1	70±2	70±2
Daytime ABPM (0800–2200)				
SBP	114±2	116±2	121±3[d]	121±2[e]
DBP	72±2	71±1	73±2	74±2
Nighttime ABPM (2200–0600)				
SBP	103±3	105±2	107±3	111±3[f]
DBP	60±2	60±2	62±3	62±2
Ratio of nighttime/daytime SBP*	0.89±0.02	0.91±0.01	0.88±0.02	0.92±0.01

Data are means ± SE. ABPM, ambulatory blood pressure monitoring. [a]$P < 0.05$ vs. baseline; [b]$P < 0.001$ vs. baseline; [c]$P < 0.001$ vs. baseline; [d]$P < 0.001$ vs. baseline and $P < 0.01$ vs. fenofibrate; [e]$P < 0.001$ vs. baseline and $P < 0.01$ vs. fenofibrate; [f]$P < 0.01$ vs. baseline. *A value of 0.9 or lower for the ratio of mean nighttime SBP to mean daytime SBP is defined as the normal drop in blood pressure during sleep.

required to detect a 20% improvement in insulin resistance (80% power and $\alpha = 0.05$). Fenofibrate had no effect on clamp-determined insulin resistance in terms of hepatic glucose production. There was a nonsignificant increase in glucose disposal with low-dose insulin, but this effect was small in relation to the defects in disposal induced by dexamethasone. It is possible that fibrates may improve insulin sensitivity in patients with specific, as yet undefined characteristics. However, the present data suggest that PPARα activation is unlikely to correct insulin resistance induced by glucocorticoids.

Dexamethasone administration for 3 days clearly resulted in insulin resistance but was also unexpectedly associated with triglyceride lowering in these healthy subjects with normal lipids (Table 2). Although insulin resistance is associated with hypertriglyceridemia, dyslipidemia is multifactorial, and short-term glucocorticoid exposure does not replicate the lipid milieu of the typical obese patient with insulin resistance. Another report of dexamethasone in healthy humans, employing a longer, 5-day course, showed no effect on triglycerides (6). Dexamethasone is known to induce lipoprotein lipase, rate-limiting for triglyceride removal, raising the possibility that short-term treatment could lower triglycerides by accelerating clearance, an effect that might be lost with longer glucocorticoid exposure.

Our results also indicate that fenofibrate treatment alone elevates systolic blood pressure in healthy subjects. Mean determinations over 24 h using ambulatory monitoring showed that fenofibrate increased systolic pressure by 3 mmHg. Although this effect may seem small, the Prospective Studies Collaboration demonstrated a 7% increase in ischemic heart disease mortality and a 10% increase in stroke mortality with a 2-mmHg elevation of systolic blood pressure (17). To the best of our knowledge, a comprehensive evaluation of the effects of PPARα activation on blood pressure by ambulatory monitoring has not been reported in humans. Previous studies focusing on atherosclerosis have reported sporadic blood pressures measured in the clinic setting. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (12), median systolic blood pressure decreased from 140 to 136 mmHg in the fenofibrate group and from 140 to 138 mmHg in the placebo group. In the Diabetes Atherosclerosis Intervention Study (DAIS) (3), fenofibrate was associated with a 2.5 mmHg increase in systolic pressure compared with a 0.5 mmHg increase for placebo (141.7 ± 18.9 at study end vs. 139.2 ± 19.4 at baseline for fenofibrate; 141.3 ± 17.5 at study end vs. 140.8 ± 17.6 at baseline for placebo). Experiments in mice suggest that PPARα may affect blood pressure. PPARα-deficient mice are protected from blood pressure elevations induced by feeding a high-fat diet or by chronic treatment with glucocorticoids through mechanisms that involve activation of the sympathetic nervous system (5, 30).

Despite impressive beneficial effects of fibrates on dyslipidemia, these agents have yielded mixed results in trials with cardiovascular endpoints. Outcomes have ranged from decreased vascular events with an unexplained increase in mortality (21, 22) to no effect on the primary cardiovascular endpoint, with trends suggesting increased mortality (12, 29), to overall favorable outcomes (24). On the basis of the results of the current study, it appears that fenofibrate does not reverse insulin resistance, a condition associated with several cardiovascular risk factors, and may elevate systolic blood pressure in healthy subjects. The use of PPARα activation to decrease cardiovascular events could be optimized by systematically assessing blood pressure responses using ambulatory monitoring in humans with well-defined phenotypes.

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