Improvement of myocardial lipid accumulation and prevention of PGC-1α induction by fenofibrate

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Abstract. We recently demonstrated that fenofibrate induces the activities of citrate synthase and NADH oxidase in cardiac mitochondria. To further determine the molecular mechanisms underlying fenofibrate action, 8-week-old mice were administered fenofibrate (100 mg/kg/day) for 7 and 14 days, and the expression of genes involved in cardiac mitochondrial function, such as nuclear respiratory factor 1 transcript variant 2 (NRF-1-L) and 6 (NRF-1-S), mitochondrial outer membrane protein 40 (Tom40), lipoic acid synthetase (Lias), cytochrome b, medium-chain acyl-coenzyme A dehydrogenase (MCAD) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) was determined. Expression of PGC-1α, a key regulator of the entire fatty acid oxidation system, was significantly downregulated after 14 days of fenofibrate administration. Moreover, ventricular triglycerides were also accumulated following 14 days of fenofibrate administration. Thus, fenofibrate functions to improve myocardial lipid accumulation and to prevent PGC-1α induction, which is crucial for understanding the molecular mechanisms underlying fenofibrate action on the heart.

Introduction

Fatty acids are the preferred energy substrates for the postnatal and adult heart to generate ATP. To meet heightened energy demands, myocardial lipids undergo a lipolysis process to release free fatty acids (FFAs) into the fatty acid β-oxidation and the tricarboxylic acid (TCA) cycle, which is tightly coupled to the oxidative phosphorylation in mitochondria; therefore, cardiac mitochondria undoubtedly have a significant role in lipid metabolism (1,2).

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Cardiac mitochondria have important roles in lipid metabolism through coordinated changes in the expression of genes involved in mitochondrial function. These genes include nuclear respiratory factor 1 transcript variant 2 (NRF-1-L) and 6 (NRF-1-S), which are the key activators of nuclear genes that encode cytochrome c and all five respiratory complexes (3); mitochondrial outer membrane protein 40 (Tom40), which is an import channel of the mitochondrial outer membrane and is active in the sorting of imported proteins (4); lipoic acid synthetase (Lias), which is responsible for synthesis of lipoic acid, a potent mitochondrial antioxidant and enzyme cofactor in multi-enzyme complexes such as the pyruvate dehydrogenase complex (5); medium-chain acyl-coenzyme A dehydrogenase (MCAD), which is a key enzyme involved in mitochondrial fatty acid β-oxidation (6); and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), which is a key regulator of the entire fatty acid oxidation system (7). All these genes consist of a regulatory network to modulate cardiac lipid metabolism.

Peroxisome proliferator-activated receptor α (PPARα) also regulates cardiac lipid metabolism. Cardiac-specific overexpression of PPARα (MHC-PPARα) mice and PPARα null mice exhibit upregulation and downregulation of genes involved in fatty acid β-oxidation, respectively (8-10). PPARα also regulates myocardial cytosolic lipid droplet protein (MLDP), which functions to increase the rate of lipolysis (11). Thus, PPARα predominantly has a role in cardiac lipid metabolism (12).

Being a member of the nuclear hormone receptor superfamily, PPARα achieves its effects on gene regulation through a ligand-dependent mechanism. Upon binding to its ligands, PPARα can release transcriptional corepressors and recruit transcriptional coactivators to transactivate (13). Fenofibrate is one of the PPARα ligands and has been used to treat dyslipidemia since 1998 by reduction of serum triglycerides (TG) and low density lipoprotein cholesterol (LDLC) (14). Subsequent research revealed that fenofibrate attenuates cardiac dysfunction (15), prevents the development of microvascular complications in diabetes (16) and exerts antidiabetic effects (17), but its exact roles in cardiac mitochondria and lipid metabolism remain unclear.

In this study, we performed ventricular triglyceride analysis, and determined the mRNA level of genes involved in cardiac mitochondrial function. Our results indicate that feno-

Table I. Primer sequences.

Gene	Forward primer	Reverse primer
Ribosomal protein S16	ATCTCAAAGGCCCTGGTAGC	ACAAAGGTAAACCCCGATCC
Mitochondrial outer membrane protein (Tom40)	GTGCCTCCTTTGGGTATCAG	GTCTGCAGAGGAAGGACAGG
Lipoic acid synthetase (Lias)	ATACGGCAAGTGGTCCTTTG	GCCATCAGACCCTTCAGAAC
Cytochrome b	CTAATCCACTAAACACCCCAC	TGAGAAGTATGAGATGGAGGC
Medium-chain acyl-coenzyme A dehydrogenase (MCAD)	ACCCTCGTGTAACTAAGCTC	AATGCTGCTATGTCACAGTC
Nuclear respiratory factor 1 transcript variant 2 (NRF-1-L)	AACTCCATCTGGGCCATTAG	GACGACGCAAGCATCAGAG
Nuclear respiratory factor 1 transcript variant 6 (NRF-1-S)	TACTCTGCTGTGGCTGATGG	ATGCTCACAGGGATCTGGAC
Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)	AAGAGCGCCGTGTGATTTAC	AGCAGGGTCAAAATCGTCTG

fibrate functions to improve myocardial lipid accumulation and prevent the induction of PGC-1α, a key regulator of the entire fatty acid oxidation system. Our analyses identified the PPARα ligand fenofibrate as a potential regulator of cardiac mitochondrial function and lipid metabolism.

Materials and methods

Animals. Eight-week-old mice were randomly divided into three groups: Group 1, vehicle control; Group 2, fenofibrate treatment for 7 days; and Group 3, fenofibrate treatment for 14 days. Each group consisted of 6-8 mice. Fenofibrate was dissolved in a 0.5% (w/v) suspension of sodium carboxymethylcellulose and administered at a dose of 100 mg/kg/day. Group 1 only received the 0.5% sodium carboxymethylcellulose suspension via oral gavage. The mice were housed in the animal facility at the Zhengzhou University Health Center and fed standard chow. All animal procedures were approved by the Committee on the Ethics of Animal Experiments of the University of Zhengzhou (permit number: SYXK yu 2007-0009). All animals were allowed free access to food and water throughout the treatment period.

Chemicals and reagents. Fenofibrate was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). TRIzol reagent was purchased from Invitrogen (Carlsbad, CA, USA). The Omniscript RT kit and SYBR Green PCR kit were purchased from Qiagen (Hilden, Germany). Real-time polymerase chain reaction (PCR) primers were synthesized by Invitrogen Shanghai Incorporation (Shanghai, China). The triglyceride quantification kit was purchased from Sigma-Aldrich Chemical Co.

Quantitative real-time PCR. RNA was extracted from the ventricles of fenofibrate-treated (100 mg/kg/day, for 7 and 14 days) or control mice using TRIzol reagent (Invitrogen). The first-strand cDNAs were synthesized from 2 μg of total RNA in a 20-μl reaction using the Omniscript RT kit (Qiagen) and oligo-dT as the primer. The cDNAs were then used as the template for real-time PCR reactions containing the SYBR Green PCR kit (Qiagen) on an MX3000P real-time PCR machine (Stratagene). The primer sequences are shown in Table I. A comparative quantification was used, and the relative expression of mRNAs was normalized to the ribosomal protein S16 levels.

Myocardial triglyceride levels. Lipids were extracted from the ventricular tissue of mice treated or not treated with fenofibrate (100 mg/kg/day) for 7 and 14 days using a modified Bligh and Dyer technique. In brief, every ventricle was homogenized in 3.8 ml of an ice-cold chloroform/methanol/water (2:1:0.8) solution, and then was centrifuged at 12,000 x g. After centrifugation, the top layer was aspirated away and the lower layer (organic phase) was transferred to another tube followed by evaporation to dryness. The triglyceride was resuspended in 0.1 ml isopropanol and quantified using a triglyceride quantification kit (Sigma-Aldrich).

Statistics. The data are reported as the means ± SEM. A Student's unpaired t-test was used to compare the two groups. In all cases, differences were considered to be statistically significant when $P<0.05$.

Results

Effect of fenofibrate treatment on NRF-1-L and NRF-1-S gene expression. Nuclear receptor PPARα is a ligand-inducible transcription factor and is highly expressed in the heart (18). In the absence of the ligand, PPARα recruits corepressors to repress transcription with its obligate heterodimeric partner, the retinoid X receptor (RXR). Once engaged by the ligand, PPARα-RXR heterodimers clear corepressors and recruit transcriptional coactivators to initiate target gene transcription (19-21). Fenofibrate is one of the PPARα ligands and reduces serum triglycerides (TG) and low density lipoprotein cholesterol (LDLC) (14). Fenofibrate also attenuates cardiac dysfunction and exerts antidiabetic effects (15,17). Given the important roles of mitochondria on cardiac function and metabolism, we reasoned that the actions of fenofibrate on cardiac mitochondria would uncover these metabolic

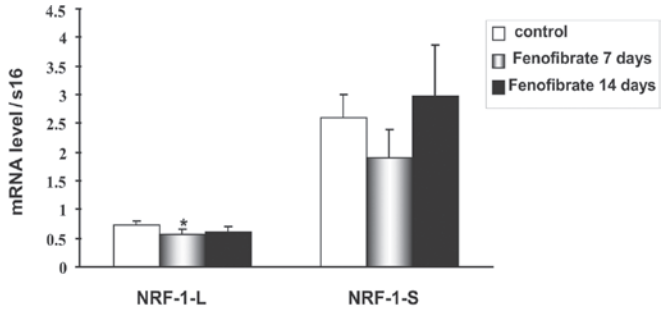

Figure 1. Fenofibrate treatment alters mRNA levels of NRF-1-L and NRF-1-S. Mice (8-week-old) were treated or not treated with fenofibrate (100 mg/kg/day) for one or two weeks. RNA was extracted from the ventricles of control or fenofibrate-treated mice and the transcript levels for NRF-1-L, NRF-1-S and S16 were determined. Data are the means ± SEM with 6-7 mice per group. *P<0.05 vs. control. NRF-1-L, nuclear respiratory factor 1 transcript variant 2; NRF-1-S, nuclear respiratory factor 1 transcript variant 6.

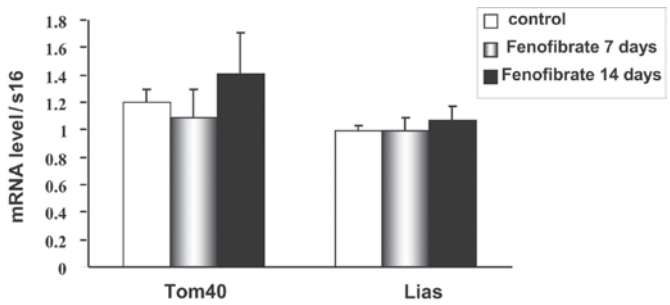

Figure 2. Effect of fenofibrate treatment on gene expression of Lias and Tom40. Mice (8-week-old) were treated or not treated with fenofibrate (100 mg/kg/day) for one or two weeks. RNA was extracted from the ventricles of control or fenofibrate-treated mice and the transcript levels for Lias, Tom40 and S16 were determined. Data are the means ± SEM with 6-7 mice per group. Lias, lipoic acid synthetase; Tom40, mitochondrial outer membrane protein 40.

properties. Therefore, we investigated the effect of fenofibrate on the expression of genes involved in mitochondrial function.

We performed quantitative real-time PCR (QPCR) analysis on the left ventricles of 8-week-old mice treated with fenofibrate (100 mg/kg/day) for 7 or 14 days or control mice. Transcript levels for NRF-1-L and NRF-1-S, the key activators of nuclear genes that encode cytochrome c and all five respiratory complexes (3), were downregulated at baseline (22 and 27%, respectively) in ventricles following treatment with fenofibrate for 7 days (Fig. 1). However, this downregulation was not continued upon administration of fenofibrate for 14 days, and expression levels of NRF-1-L and NRF-1-S were decreased by 16% and increased by 15%, respectively, compared with the controls (Fig. 1). The results suggest that the time course of changes in mRNA levels of NRF-1-L and NRF-1-S occur upon administration of fenofibrate.

Effect of fenofibrate treatment on changes in the Tom40 and Lias gene expression. QPCR analysis was performed on left ventricles of 8-week-old mice treated or not treated with fenofibrate (100 mg/kg/day) for 7 and 14 days. The mRNA level of Lias, which is responsible for synthesis of lipoic acid, a potent mitochondrial antioxidant and enzyme cofactor in the multi-enzyme complexes such as the pyruvate dehydrogenase complex (5), was determined. Our results showed that fenofibrate treatment caused no significant changes in Lias gene expression at baseline (Fig. 2). However, the transcript level for Tom40, an import channel of the mitochondrial outer membrane that is active in sorting imported proteins (4), also showed no significant changes following a 7-day treatment with fenofibrate. However, after 14 days of treatment, its expression level was increased by 15% compared with the control (Fig. 2), indicating that induction of Tom40 was modest at baseline.

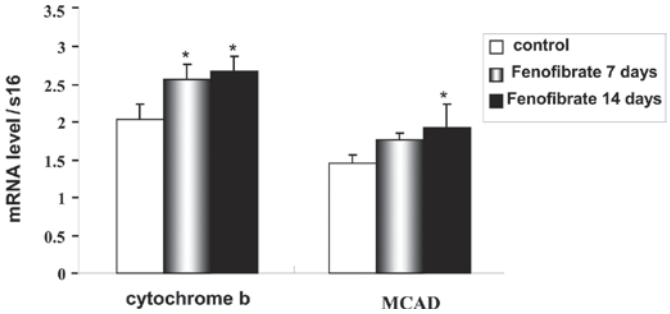

Figure 3. Fenofibrate upregulates the expression of cytochrome b and MCAD genes. Mice (8-week-old) were treated or not treated with fenofibrate (100 mg/kg/day) for one or two weeks. RNA was extracted from the ventricles of control or fenofibrate-treated mice and the transcript levels for cytochrome b, MCAD and S16 were determined. Data are the means ± SEM with 6-7 mice per group. *P<0.05 vs. control. MCAD, medium-chain acyl-coenzyme A dehydrogenase.

Fenofibrate upregulates the expression of the cytochrome b and MCAD genes. The expression of cytochrome b and medium-chain acyl-coenzyme A dehydrogenase (MCAD) involved in fatty acid oxidation were also analyzed by real-time PCR (6). Both cytochrome b and MCAD mRNA levels were steadily increased in response to fenofibrate from 7 to 14 days. Following 14 days of treatment, expression of the two genes was significantly upregulated at baseline (31 and 32%, respectively) (Fig. 3), suggesting there is a time course of induction in mRNA levels of cytochrome b and MCAD upon administration of fenofibrate.

Fenofibrate downregulates the expression of the PGC-1α gene. Real-time PCR analysis of PGC-1α, which is a key regulator of the entire fatty acid oxidation system (7), showed insignificant changes at baseline following the 7-day administration of fenofibrate (Fig. 4), but upon administration for 14 days, the PGC-1α mRNA level was significantly reduced by 31% compared with control (Fig. 4), indicating that fenofibrate exerts specific effects on mitochondrial function-related genes.

Fenofibrate causes myocardial lipid accumulation. PGC-1α is expressed at relatively high levels in the heart and serves as an important regulator of cardiac energy metabolism (22,23). In the heart, PGC-1α expression sharply increases at birth consistent with an energy shift from glucose metabolism to fat oxidation (24). Consistent with these, in the ventricle of mice treated with fenofibrate for 14 days, downregulation of PGC-1α was also accompanied by accumulation of myocardial lipid (Fig. 5), suggesting that fenofibrate administration results in myocardial lipid accumulation.

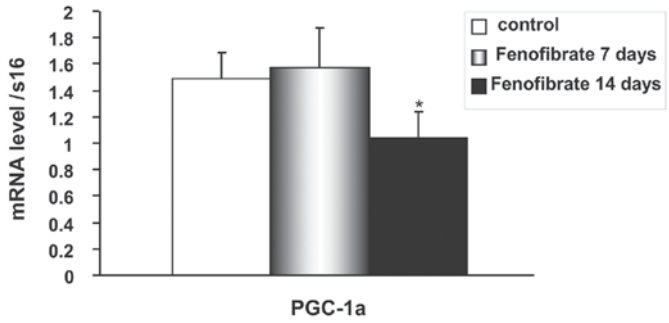

Figure 4. Fenofibrate downregulates the expression of the PGC-1α gene. Mice (8-week-old) were treated or not treated with fenofibrate (100 mg/kg/day) for one or two weeks. RNA was extracted from the ventricles of control or fenofibrate-treated mice and the transcript levels for PGC-1α and S16 were determined. Data are the means ± SEM with 6-7 mice per group. *P<0.05 vs. control. PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α.

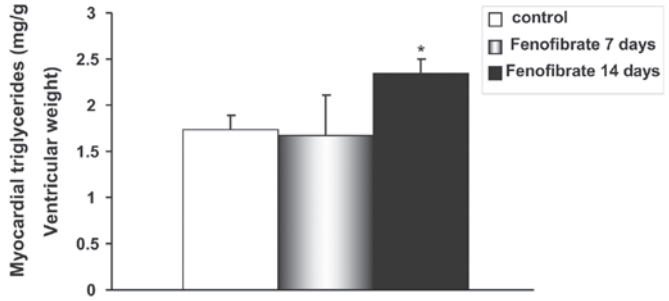

Figure 5. Increased triglycerides in fenofibrate-treated hearts. Triglycerides were extracted from the ventricles of control or fenofibrate-treated 8-week-old mice and quantified. Data are the means ± SEM with 5-6 mice per group. *P<0.05 vs. control.

Discussion

Fenofibrate is a ligand of PPARα and is used to lower serum triglycerides (25,26). In this study, the combined use of ventricular triglyceride and gene expression assays showed that 7 days of fenofibrate treatment modestly induced mRNA levels of cytochrome b and MCAD, and inhibited NRF-1-L and NRF-1-S gene expression, but had no significant effect on myocardial lipid and mRNA levels of Tom40, Lias and PGC-1α. However, 14 days of fenofibrate treatment not only significantly induced cytochrome b and MCAD expression, but also significantly inhibited the expression of PGC-1α. Moreover, downregulation of PGC-1α was also accompanied by accumulation of myocardial lipids, thus fenofibrate has a time-course effect on cardiac lipids and expression of genes involved in cardiac mitochondrial function. Undoubtedly, fenofibrate has a significant role in cardiac mitochondrial function and lipid metabolism.

Previous studies reported that fenofibrate also has cardioprotective effects on the heart. Fenofibrate not only prevents the development of hypertension and hypertensive heart disease (27), but also prevents the progression of cardiac hypertrophy either in the pressure-overloaded rat or in the spontaneously hypertensive rat (28,29). Moreover, fenofibrate was shown to protect the heart from isoproterenol-induced acute myocardial ischemic injury (30). All of these studies suggest the cardioprotective actions of fenofibrate, but the exact mechanisms remain unclear. Here, we demonstrated that fenofibrate prevents PGC-1α induction, thus decreases fatty acid utilization to meet myocardial hypoxia during pathological cardiac disease (31), which may partly explain the cardioprotective effects of fenofibrate.

Consistent with our findings, Palomer *et al* showed that PGC-1α downregulation results in an increase in the glucose oxidation rate (32). In the heart, PGC-1α expression increases sharply at birth consistent with the energy shift from glucose metabolism to fat oxidation (24), indicating that PGC-1α acts as an upstream regulator of cardiac lipid metabolism.

As with PGC-1α, nuclear respiratory factor 1 transcript variant 2 (NRF-1-L) and 6 (NRF-1-S), mitochondrial outer membrane protein 40 (Tom40), lipoic acid synthetase (Lias), cytochrome b and medium-chain acyl-coenzyme A dehydrogenase (MCAD) are all involved in cardiac mitochondrial function. However, 14 days of fenofibrate treatment had no significant effect on Tom40 and Lias transcript levels, and only modest changes were observed in NRF-1-L and NRF-1-S mRNA levels. Conversely, the expression levels of cytochrome b and MCAD were significantly increased in response to fenofibrate, suggesting that fenofibrate affects cardiac mitochondrial function through regulation of specific genes.

Other studies have directly implicated fenofibrate in the control of genes related to cardiac mitochondrial function. For example, fenofibrate increases cardiac mitochondrial thioesterase I (MTE-I) mRNA, and reduced acyl-CoA oxidase (ACO) activity in diet-induced obese (DIO) mice (33,34). All the altered expression of these genes involved in cardiac mitochondrial function is coupled to a change in glucose utilization and fatty acid oxidation (35). Indeed, reduced ACO activity is linked to increased glucose oxidation and decreased fatty acid oxidation (34), and our studies also showed that downregulation of PGC-1α by fenofibrate is coupled to myocardial lipid accumulation. Consistent with our results, another PPARα ligand, K-111, was found to result in reduced cardiac fatty acid utilization in hyperlipidaemic animals (36,37). As we know, decreased oxidation of fatty acids results in decreased free radical production, and the decreased free radical production in the electron transport pathway is a potential contributor to cardiac function, also by which fenofibrate affects the cardioprotective roles of the heart.

In conclusion, we demonstrated that 14 days of fenofibrate treatment not only significantly induces cytochrome b and MCAD expression, but also significantly inhibits the expression of PGC-1α. Moreover, downregulation of PGC-1α is also accompanied by accumulation of myocardial lipids, so fenofibrate has a significant role in cardiac mitochondrial function and lipid metabolism. However, future research is required to determine whether the exact mechanism of fenofibrate on the heart is mediated by a cardiac marker gene through PPARα, coactivators or corepressors.

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