Activation of Receptors δ (PPARδ) by Agonist (GW0742) may Enhance Lipid Metabolism in Heart both In Vivo and In Vitro

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Key words
- cardiomyocytes
- digoxin
- fatty acid oxidation
- TCA cycle gene
- PPARδ

Abstract

It has been documented that cardiac agents may regulate the lipid metabolism through increased expression of PPARδ in cardiac cells. However, the effect on lipid metabolism by direct activation of PPARδ is still unknown. The present study applied specific PPARδ agonist (GW0742) to investigate this point in the heart of Wistar rats and in the primary cultured cardiomyocytes from neonatal rat. Expressions of PPARδ in the heart and cardiomyocytes after treatment with GW0742 were detected using Western blots. The fatty acid (FA) oxidation and the citric acid (TCA) cycle related genes in cardiomyocytes were also examined. In addition, PPARδ antagonist (GSK0660) and siRNA-PPARδ were employed to characterize the potential mechanisms. After a 7-day treatment with GW0742, expressions of PPARδ in the heart were markedly increased. Increased expressions of FA oxidation and TCA cycle related genes were also observed both in vivo and in vitro. This action of GW0742 was blocked by GSK0660 or by siRNA-PPARδ. The obtained results show that activation of PPARδ by GW0742 is responsible for the increase of FA oxidation and TCA cycle related genes in hearts. Role of PPARδ in the regulation of lipid metabolism in heart is then established.

received 16.04.2013
accepted 21.05.2013

Bibliography
DOI http://dx.doi.org/10.1055/s-0033-1348317
Published online: June 26, 2013
Horm Metab Res 2013; 45: 880–886

ISSN 0018-5043

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Introduction

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcriptional factors that regulate the expression of genes involved in lipid metabolism and inflammation [1]. Three subtypes of PPARs, including PPARα, PPARγ, and PPARδ, modulate the expressions of many genes to exert various bioactivities [1]. PPARα is relatively abundant in tissues with a high oxidative capacity, such as liver and heart. PPARγ expression is confined to a limited number of tissues, primarily adipose tissue [1,2]. The ubiquitously expressed PPARδ enhances fatty acid catabolism in adipose tissue and muscle [1]. PPARδ-dependent maintenance of inotropic function and metabolic effects is crucial for cardiomyocytes [3–5]. The activation of PPARδ increases basal fatty acid (FA) oxidation to maintain the energy balance and cardiac function [6,7]. Many FA oxidation-related enzymes and mitochondrial respiratory uncoupling genes are regulated by PPARδ in cardiomyocytes, such as pyruvate dehydrogenase kinase and acyl-CoA oxidase 1 [8,9]. Deletion of cardiac PPARδ, which is accompanied by decreased contraction, increased left ventricular end-diastolic pressure, and lowered cardiac output, leads to decreased contraction and increased incidence of cardiac failure [3]. Various cardiac pathologies have been shown to involve decreased lipid metabolism and impaired ATP generation in heart failure [10–12], but it remains unknown whether PPARδ is involved in the pathogenesis of cardiac disorders. Our previous study showed that cardiac agents improved cardiac contraction in STZ-diabetic rats is associated with a marked increase in cardiac PPARδ expression [13]. Also, an increase of PPARδ by digoxin is related to the regulation of FA oxidation genes [14].

GW0742 is a ligand of PPARs, which has 300–1000-fold selectivity for PPARδ vs. other PPARs [15], and shows full PPARδ agonist-like action in cell cultures and animal models [16–18]. It has been documented that activation of PPARδ by GW0742 increases cardiac contractility in rats [19]. However, the effects on cardiac lipid metabolism by GW0742 remain unclear. In the present study, we used Wistar rats and primary

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Table 1 Real-time PCR primers and universal library probes (UPL) of target genes.

Gene Name	Forward	Reverse	UPL Number
Acetyl-coenzyme A dehydrogenase, very long chain (VLCAD)	ggtggtttgggcctctcta	gggtaacgctaacaccaagg	53
Pyruvate dehydrogenase kinase, isoenzyme 4 (PDK4)	gagctgttctcccgctacag	ttctctcacaggcattttctga	120
Uncoupling protein 3 (UCP3)	cccctacactgtatgctgagg	agaaaggagggcatgaatcc	79
Malonyl-coenzyme A decarboxylase (MCD)	bbctgtgatggcgtatc	gagctggtgaggcctttg	158
Acetyl-coenzyme A dehydrogenase, long chain (LCAD)	gcagttacttgggaagagcaa	ggcatgacaatatctgaatgga	81
Acetyl-coenzyme A oxidase 1, palmitoyl (ACOX1)	caccttcgagggagagaaca	cgcacctggtcgtagatttt	112
Hydroxymethylbilane synthase (HBMS)	tccctgaaggatgtgcctac	aagggttttcccgtttgc	79

neonatal cardiomyocytes of rats to investigate the effects of GW0742 on cardiac FA oxidation and TCA cycle genes in relation to PPARδ.

Materials and Methods

Materials

GW0742 (a specific PPARδ agonist) and GSK0660 (a specific PPARδ antagonist) were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA). The TRIzol RNA extraction reagent, Opti-MEM® I Reduced Serum Medium, Stealth™ Select RNAi (siRNA-PPARδ), scramble siRNA (siRNA-control), and Lipofectamine 2000™ were from Invitrogen (Carlsbad, CA, USA). Antibodies to PPARδ and actin were purchased from Abcam (Cambridge, MA, USA). The LightCycler TaqMan Master kit, primers, and universal library probes for analyzing PPARδ, fatty acid oxidation and TCA cycle related genes (**Table 1**) were purchased from Roche Diagnostics Corp. (Mannheim, Germany).

Animals

The male Wistar rats, weighing from 200 to 250 g, were obtained from the Animal Center of National Cheng Kung University Medical College. All experiments on rats were conducted under anesthesia with 3% isoflurane. All animal procedures were performed according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Drug administration

Animals were randomly assigned into 3 groups: (I) the control group (n = 8) treated with the vehicle, saline (0.9% sodium chloride, intravenously); (II) the GW0742 (GW) group (n = 8) treated with GW0742 at 5 mg/kg, intravenously for 7 days as described previously [20], and (III) the GW0742 + GSK0660 (GW + GSK) group (n = 8) treated with GW0742 (5 mg/kg) and GSK0660 at effective dose (3 mg/kg) [21] intravenously for 7 days. At the end of experiment, hearts of each group were dissected for detections using Western blotting analysis and real-time reverse transcription-polymerase chain reaction.

Cell culture and treatment

Primary cultures of neonatal rat cardiomyocytes were prepared by modification of a previously described method [22]. Briefly, the heart tissue from a 1–2-day-old Wistar rat was cut into 1–2 mm pieces and predigested with trypsin to remove red blood cells. The heart tissue was then digested with 0.25% trypsin and 0.05% collagenase. The dissociated cells were placed in uncoated 10 cm dishes and incubated at 37 °C in a 5% CO_2 incubator for at least 1 h to remove the nonmyocytic cells. This procedure caused most of the fibroblasts to attach to the dishes, while most of the cardiomyocytes remained unattached. The population of cells enriched in cardiomyocytes was then collected and counted. The cells were cultured in DMEM (GIBCO BRL, Gaithersburg, MD, USA) with 1 mmol/l pyruvate, 10% fetal bovine serum (FBS), 100 units/ml penicillin, and 100 units/ml of streptomycin. On the second day after plating, the medium was replaced. 3 days after plating, the cells were exposed to hyperglycemic conditions as described in detail later. Animal handling and disposal were performed in accordance with NIH guidelines. The GW0742-treated cardiomyocytes were generated from the incubation of cells with GW0742 (10^{-6} mol/l; M) for 24 h [23], and the PPARδ silenced cardiomyocytes were also used for the same treatment with GW0742. After the treatment, cells were washed twice, and harvested by trypsinization. Then, cells were collected and subjected to real-time reverse transcription-polymerase chain reaction or Western blotting analysis.

Western blotting analysis

Similar to our previous report [13], protein was extracted from tissue homogenates or cell lysates using ice-cold RIPA buffer supplemented with phosphatase and protease inhibitors (50 mmol/l sodium orthovanadate, 0.5 mM phenylmethylsulfonyl fluoride, 2 mg/ml aprotinin, and 0.5 mg/ml leupeptin). Protein concentrations were determined with the Bio-Rad protein assay (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Total proteins (30 µg) were separated by SDS/polyacrylamide gel electrophoresis (10% acrylamide gel) using the Bio-Rad Mini-Protein II system. Protein was transferred to expanded polyvinylidene difluoride membranes (Pierce, Rockford, IL, USA) with a Bio-Rad Trans-Blot system. After transfer, the membranes were washed with PBS and blocked for 1 h at room temperature with 5% (w/v) skimmed milk powder in PBS. The manufacturer's instructions were followed for the primary antibody reactions. Blots were incubated overnight at 4 °C with an immunoglobulin-G polyclonal rabbit anti-mouse antibody (Affinity BioReagents, Inc., Golden, CO, USA) (1:500) in 5% (w/v) skimmed milk powder dissolved in PBS/Tween 20 (0.5% by volume) to bind the PPARδ in the heart specimens. The blot was incubated with goat polyclonal antibody (1:1 000) to bind the actin serving as internal control. After the removal of primary antibody, the blots were extensively washed with PBS/Tween 20. The blots were then incubated for 2 h at room temperature with the appropriate peroxidase-conjugated secondary antibody diluted in 5% (w/v) in skimmed milk powder and dissolved in PBS/Tween 20. The blots were developed by autoradiography using the ECL-Western blotting system (Amersham International, Buckinghamshire, UK). The immune blot of PPARδ (49 kDa) was quantified with a laser densitometer.

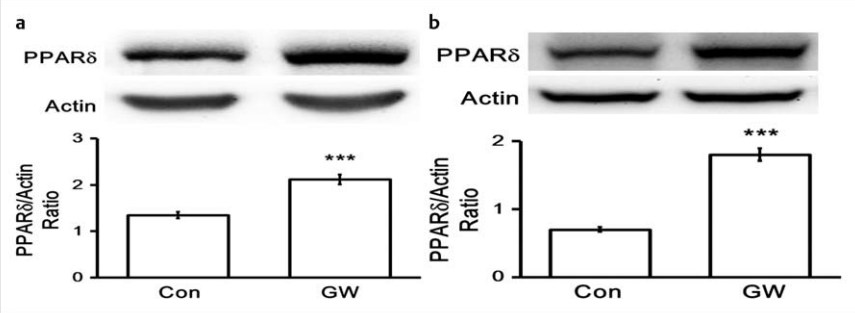

Fig. 1 Effects of GW0742 on PPARδ expression in the heart of rats and in the cardiomyocytes. Changes in cardiac PPARδ protein expression were investigated in the heart of rats **a** and neonatal rat cardiomyocytes **b**. The rats were intravenously injected with GW0742 (5 mg/kg/day) (GW) for 7 days and the cells were incubated with GW0742 (10^{-6} mol/l; M) for 24 h. The expressions were compared with vehicle-treated control group (Con). All values are expressed as mean ± SEM (n = 6 per group). ***p < 0.001 as compared with control.

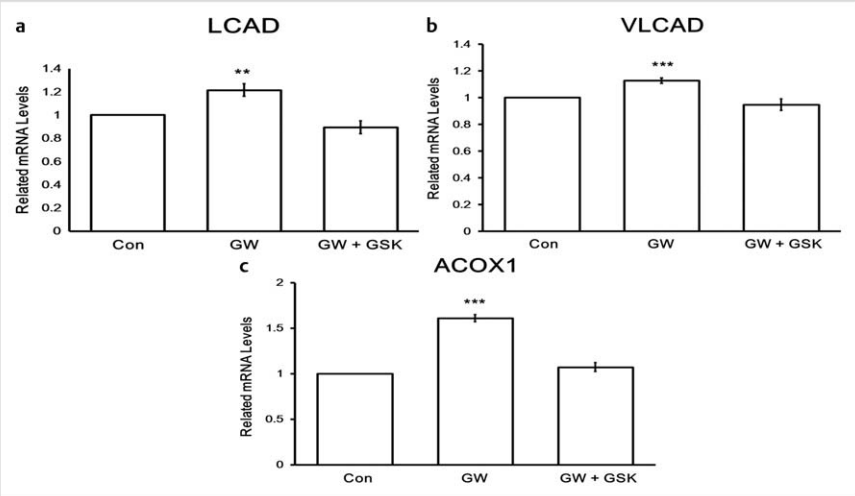

Fig. 2 Effects of GW0742 on the levels of fatty acid β-oxidation related genes in the heart of rats. The rats were intravenously injected with GW0742 (GW) (5 mg/kg/day) for 7 days, and then were co-treated with or without 3 mg/kg GSK0660 (GSK). Hearts were harvested for examining the gene expression using real-time PCR. The relative levels of gene were compared with internal control using LightCycler software 4.05 (Roche Diagnostics). Long-chain acyl-CoA dehydrogenase (LCAD) **a** very long-chain acyl-CoA dehydrogenase (VLCAD) **b** and acyl-CoA oxidase 1(ACOX1) **c** are shown. All values are presented as mean ± SEM (n = 6 per group). **p < 0.01 and ***p < 0.001 as compared with the vehicle control.

Real-time reverse transcription-polymerase chain reaction

Total RNA was extracted from heart ventricles and cell lysates with TRIzol reagent (Invitrogen Corp., Carlsbad, CA, USA). The web-based assay-design software from the Universal Probe Library Assay Design Center (http://www.roche-applied-science.com/sis/rtpcr/upl/adc.jsp) was used to design TaqMan primer pairs and to select appropriate hybridization probes. All the PCR experiments were performed using a LightCycler (Roche Diagnostics GmbH, Mannheim, Germany). Reactions were performed in 20 µl of a mixture consisting of 13.4 µl of PCR buffer, 0.2 µl of each of the Universal Probe Library probes (10 mmol/l) (**Table 1**), 0.2 µl of each primer (20 µmol/l), 4 µl of LightCycler TaqMan Master (Roche Diagnostics GmbH) and 2 µl of template cDNA. The thermal cycling conditions consisted of an initial denaturation step at 95 °C for 10 min, followed by 45 cycles at 94 °C for 10 s, 60 °C for 20 s, and 72 °C for 1 s. The crossing point for each amplification curve was determined by the second derivative maximum method. The concentration of each gene was calculated by reference to the respective standard curve with the aid of the LightCycler software. Relative gene expression was expressed as the ratio of the concentration of the target gene to that of a housekeeping gene hydroxymethylbilane synthase (HBMS).

Small interfering RNA (siRNA)

Duplexed RNA oligonucleotides for rat PPARδ (Stealth RNAi™) were synthesized from Invitrogen. According to our previous method [13], cardiomyocytes were transfected with 40 pmol of PPARδ-specific siRNAs (siRNA-PPARδ) or scramble siRNA using Lipofectamine 2000 (Invitrogen) and they were treated 48 h post-transfection. The sequences of the siRNA-PPARδ are UUGCAGAUCCGAUCGCACUUCUCGU (sense strand) and ACGAGAAGUGCGAUCGGAUCUGCAA (antisense strand).

Statistical analysis

Data are expressed as the mean ± SEM for the number (n) of animals in 1 group as indicated. Statistical analysis was carried out using repeated measures analysis of variance (ANOVA) and Newman-Keuls post-hoc analysis. Bonferroni's correction was applied to the data, which were obtained from relatively small groups. A p-value of 0.05 or less was considered significant.

Results

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Effects of GW0742 on PPARδ expression in the heart of rats and in the cardiomyocytes

The level of PPARδ protein was significantly increased in the heart of rats, which received GW0742-treatment as compared with the control rats (**Fig. 1a**). Also, a significant induction of the expression of PPARδ protein was observed in GW0742-treated neonatal rat cardiomyocytes (**Fig. 1b**).

Effects of GW0742 on the levels of fatty acid β-oxidation related genes in the heart of rats

We examined the transcription levels of fatty acid β-oxidation genes using real-time PCR [3]. The relative levels of gene expression were compared to the internal control with the LightCycler software 4.05. Long-chain acyl-CoA dehydrogenase (LCAD), very long-chain acyl-CoA dehydrogenase (VLCAD), and acyl-CoA oxidase 1 (ACOX1) were increased in the heart of GW0742-treated rats. As compared to the control rats treated with vehicle, the transcription levels were increased by 122 % for LCAD, 113 % for VLCAD, and 161 % for ACOX1, respectively (**Fig. 2**). In addition, effects of GW0742 on these genes were blocked by co-treatment with GSK0660 (**Fig. 2**).

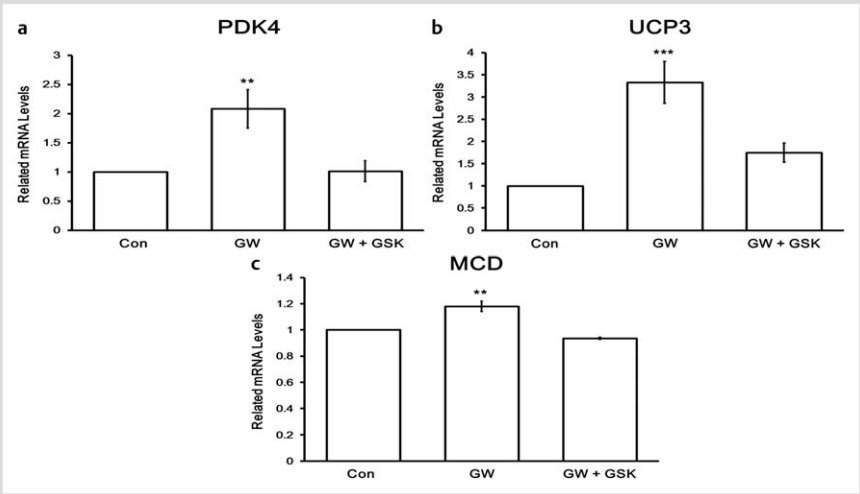

Fig. 3 Effects of GW0742 on the levels of TCA cycle related genes in the heart of rats. The rats were intravenously injected with GW0742 (GW) (5 mg/kg/day) for 7 days, and then were co-treated with or without 3 mg/kg GSK0660 (GSK). Hearts were harvested for examining the gene expression using real-time PCR. The relative levels of gene were compared with internal control using LightCycler software 4.05 (Roche Diagnostics). Pyruvate dehydrogenase kinase 4 (PDK4) **a** uncoupling protein 3 (UCP3) **b** and malonyl-CoA decarboxylase (MCD) **c** are shown. All values are presented as mean ± SEM (n = 6 per group). $^{**}p<0.01$ and $^{***}p<0.001$ as compared with the vehicle control.

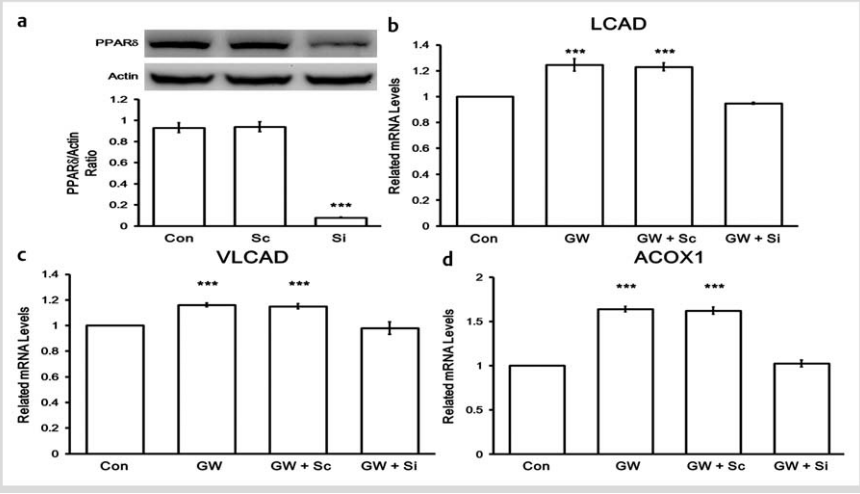

Fig. 4 Effects of GW0742 on the levels of fatty acid β-oxidation related genes in the neonatal rat cardiomyocytes. Cells were treated with siRNA-PPARδ (Si) or scramble siRNA (Sc) **a** Cells were incubated with GW0742 (10^{-6} mol/l; M) (GW) for 24 h and were harvested for examining the gene expression by real-time PCR. The relative levels of gene were compared with internal control using LightCycler software 4.05. Long-chain acyl-CoA dehydrogenase (LCAD) **b** very long-chain acyl-CoA dehydrogenase (VLCAD) **c** and acyl-CoA oxidase 1 (ACOX1) **d** are shown. All values are presented as mean ± SEM (n = 6 per group). $^{**}p<0.01$ and $^{***}p<0.001$ as compared with the vehicle control.

Effects of GW0742 on the levels of TCA cycle related genes in the heart of rats

We examined the transcription levels of TCA cycle genes using real-time PCR [3]. The relative levels of gene expression were compared to the internal control with the LightCycler software 4.05. Uncoupling protein 3 (UCP3), malonyl-CoA decarboxylase (MCD) and pyruvate dehydrogenase kinase 4 (PDK4) were raised in the heart of GW0742-treated rats. As compared to control rats treated with vehicle, the transcription levels were increased by 208% for PDK4, 333% for UCP3 and 118% for MCD, respectively (▶ **Fig. 3**). Also, effects of GW0742 on these genes were blocked by the co-treatment with GSK0660 (▶ **Fig. 3**).

Effects of GW0742 on the levels of fatty acid β-oxidation related genes in the neonatal rat cardiomyocytes

The transcription levels of fatty acid β-oxidation genes were further examined in neonatal rat cardiomyocytes using real-time PCR [3]. The mRNA levels of long-chain acyl-CoA dehydrogenase (LCAD), very long-chain acyl-CoA dehydrogenase (VLCAD), and acyl-CoA oxidase 1 (ACOX1) were also raised in neonatal rat cardiomyocytes by GW0742. As compared to control group, the transcription levels were increased by 125% for LCAD, 116% for VLCAD and 164% for ACOX1, respectively (▶ **Fig. 4**). In addition, effects of GW0742 on these genes were reversed in cells transfected with PPARδ-specific siRNA (▶ **Fig. 4**).

Effects of GW0742 on the levels of TCA cycle related genes in the neonatal rat cardiomyocytes

The transcription levels of TCA cycle genes were further examined in neonatal rat cardiomyocytes using real-time PCR [3]. The mRNA levels of uncoupling protein 3 (UCP3), malonyl-CoA decarboxylase (MCD), and pyruvate dehydrogenase kinase 4 (PDK4) were markedly raised in neonatal rat cardiomyocytes by GW0742. As compared to control rats treated with vehicle, the transcription levels were increased by 258% for PDK4, 298% for UCP3, and 121% for MCD, respectively (▶ **Fig. 5**). Also, effects of GW0742 on these genes were blocked in cells transfected with PPARδ-specific siRNA (▶ **Fig. 5**).

Discussion

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The present study showed that administration of GW0742 causes an increase of PPARδ expression in the heart of rats and neonatal rat cardiomyocytes. We also demonstrated the fatty acid β-oxidation and TCA cycle related genes could be upregulated by GW0742 both in the heart of rats and neonatal rat cardiomyocytes. Furthermore, the increased expressions of these genes by GW0742 were suppressed by GSK0660 or siRNA-PPARδ in the heart of rats or neonatal rat cardiomyocytes. Thus, it can be identified that an activation of PPARδ by GW0742 is related to

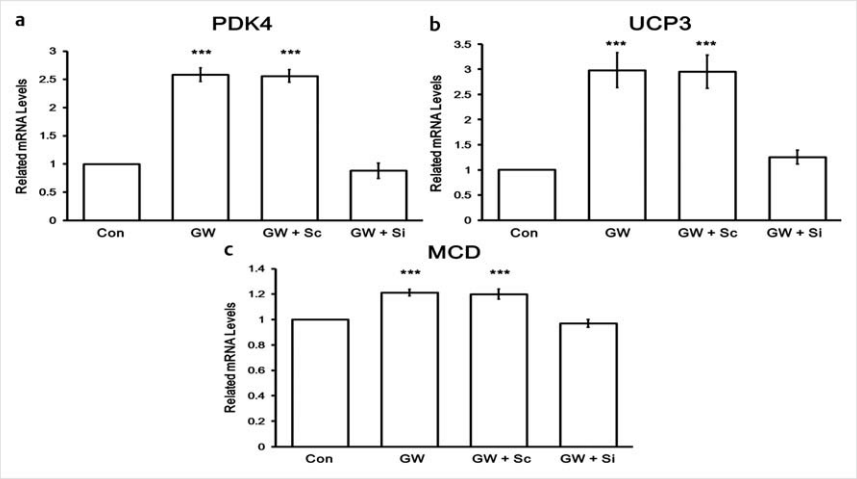

Fig. 5 Effects of GW0742 on the levels of TCA cycle related genes in the neonatal rat cardiomyocytes. Cells were incubated with GW0742 (10^{-6} mol/l; M) (GW) for 24 h and were harvested for examining the gene expression by real-time PCR. The relative levels of gene were compared with internal control using LightCycler software 4.05. Pyruvate dehydrogenase kinase 4 (PDK4) **a** uncoupling protein 3 (UCP3) **b** and malonyl-CoA decarboxylase (MCD) **c** are shown. All values are presented as mean ± SEM (n = 6 per group). $^{**}p<0.01$ and $^{***}p<0.001$ as compared with the vehicle control.

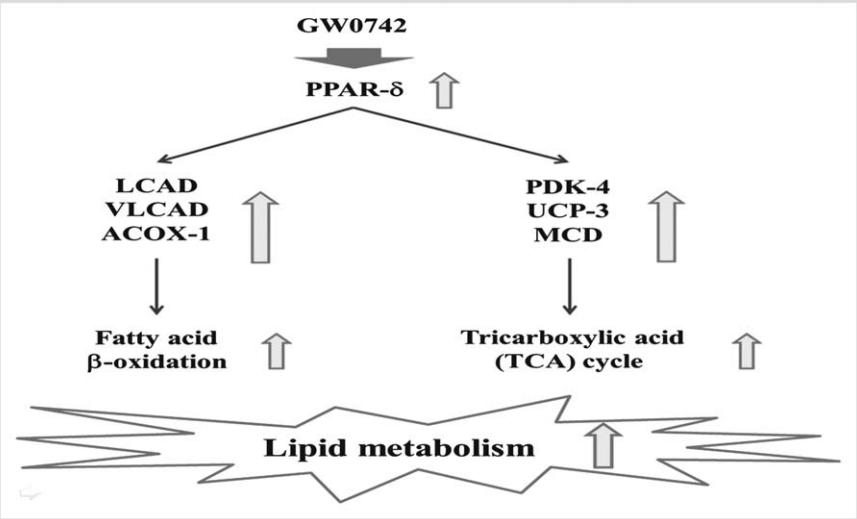

Fig. 6 Signal pathway of lipid metabolism enhanced by GW0742 in the heart of rats. Cardiac PPARδ is activated by GW0742. Then, GW0742 has the ability in regulation of fatty acid (FA) metabolism via increased LCAD, VLCAD, ACOX-1 and PDK-4, UCP-3, and MCD leading to the enhancement of β-oxidation and TCA cycle.

the increase of lipid metabolism in heart; this view has not been mentioned before.

It has been established that PPARδ plays an important role in the regulation of cardiac performance [24–26]. In our previous study, an activation of PPARδ using the selective agonist GW0742 enhanced the cardiac contractility in isolated hearts and the hemodynamic dP/dt_{max} in rats; both actions of GW0742 were blocked by GSK0660 at a concentration sufficient to block PPARδ [27, 28]. In the present study, we have found that a 7-day treatment of GW0742 not only increased the level of PPARδ expression but also upregulated the fatty acid β-oxidation and TCA cycle related genes in the hearts and cardiomyocytes. Moreover, PPARδ activation in muscle is responsible for the lowering of plasma triglycerides in obese monkeys [29] and diabetic mice [30]. This supports the view that PPARδ activation in muscle seems beneficial in the metabolism of lipids [31] by increasing the catabolism of lipids and decreasing lipid accumulation [31]. The enhancing effects of cardiac agent on lipid accumulation in heart appear to be related to the increased expression of PPARδ [25]. In this report, we have demonstrated that GSK0660 and siRNA-PPARδ suppressed the GW0742-induced actions regarding the increase in both expressions of PPARδ and lipid metabolism related genes. These results suggest the mediation of PPARδ in GW0742-induced actions for increased expressions of fatty acid β-oxidation and TCA cycle related genes in the heart.

The expression of PPARδ is more ubiquitous, with relatively high levels in metabolically active tissues, such as muscle, liver, and adipose tissue [32]. Selective activation of PPARδ by agonists has been shown to improve glucose metabolism and insulin sensitivity in mouse models of obesity and insulin resistance, and these results are mainly related to the agonists' capacity for activation of fatty acid transport and oxidation [33]. Activation of PPARδ in skeletal muscle increases the expression of regulatory genes involved in FA metabolism and mitochondrial oxidative phosphorylation, such as CPT-1 and the uncoupling proteins [34, 35]. In the present study, transfection with siRNA-PPARδ suppressed the GW0742-induced PPARδ expression and lipid metabolic genes in cardiomyocytes. Thus, it shows that expressions of FA oxidation and mitochondrial respiratory uncoupling genes are regulated by PPARδ activated by GW0742.

PPARδ activation reduced adiposity by decreasing intracellular triglyceride accumulation in mouse adipose tissue and liver. PPARδ also enhanced β-oxidation in mouse preadipocytes [36]. PPARδ mRNA is expressed at 10 and 50 times the concentrations of PPARα and PPARγ mRNA [32], respectively, in skeletal muscle, and administration of PPARδ agonists results in an increase in expression of genes involved in fatty acid oxidation, mitochondrial respiration, and oxidative metabolism, decreasing muscle fatigability. In addition, activation of PPARδ may increase the mitochondrial gene expression and function. It has been reported

that TCA cycle related genes could be upregulated in skeletal muscle of rats after administration of PPARδ agonist, such as acyl-CoA dehydrogenase long chain, acyl-CoA synthetase long-chain family member, carnitine palmitoyltransferase, inositol(myo)-1 (or 4)-monophosphatase, 2,4-dienoyl CoA reductase, hormone-sensitive lipase, high-density lipoprotein-binding protein, mitochondrial acyl-CoA thioesterase 1, pyruvate dehydrogenase kinase, peroxisomal D3,D2-enoyl-CoA isomerase, uncoupling protein, etc. [34]. Concordantly, PPARδ transgenic mice display the enhanced exercise endurance as compared with the wild-type mice and showing more fatigue resistant of skeletal muscle Type I fibers [37,38]. In the current study, GW0742 increases the expression of TCA cycle related genes. Moreover, GSK0660 and siRNA-PPARδ suppressed this action of GW0742. Relation of PPARδ with mitochondrial gene expression and function in heart can thus be considered. But it needs more investigations in the future.

In conclusion, expression of PPARδ is raised by GW0742 in the heart and primary cultured rat cardiaomyocytes. Also, GW0742 increases lipid metabolism via an increase in LCAD, VLCAD, ACOX-1 and PDK-4, UCP-3, and MCD leading the enhancement of β-oxidation and TCA cycle as shown in ▶ **Fig. 6** by the direct activation of PPARδ. These findings show that PPARδ may play a role in the regulation of cardiac lipid metabolism and this is the first work showing the effects of GW0742 on metabolism of heart. Our previous study demonstrated that treatment of PPARδ agonist could enhance cardiac contractility [27,28]. The metabolic activation in cardiac muscle may serve to supply the metabolic requirements for periods of increased physical load. Thus, PPARδ agonist could be used as a good cardiac tonic agent in clinical application in the future.

Conflicts of Interest

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The authors declare that they have no conflicts of interest in the authorship or publication of this contribution.

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