ELSEVIER

Cardiovascular Research 73 (2007) 269–277

Cardiovascular Research

www.elsevier.com/locate/cardiores

Review

The PPAR regulatory system in cardiac physiology and disease

Brian N. Finck *

Center for Human Nutrition and Center for Cardiovascular Research, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8031, St. Louis, MO 63110, United States

Received 13 June 2006; received in revised form 24 August 2006; accepted 29 August 2006
Available online 1 September 2006
Time for primary review 28 days

Abstract

Myocardial energy metabolism is an important determinant of cardiac structure and function. Modulating metabolism is therefore an attractive therapeutic avenue for the treatment of cardiac disease. The peroxisome proliferator-activated receptor family (PPARα, β/δ, γ) of nuclear receptor transcription factors is an important regulator of cardiac metabolism and has been targeted for pharmacologic therapies designed to modulate metabolism. The PPARs control myocardial metabolism by transcriptionally regulating genes encoding enzymes involved in fatty acid and glucose utilization. The expression and activity of the PPARs and their coactivator protein PGC-1α is dynamically regulated in several cardiomyopathic and metabolic diseases. This review will summarize these findings and other recent studies regarding the effects of experimental PPAR activation and deactivation and its potential impact on cardiomyopathic remodeling.

Keywords: Lipid metabolism; Energy metabolism; Transgenic animal models; Mitochondria; Diabetes

1. Introduction

The myocardium requires an enormous and steady supply of ATP. This need is met by high-level mitochondrial catabolism of carbohydrates and fatty acids. Glucose, lactate, and fatty acids are oxidized in the mitochondrion and generate a common end product, acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle (Fig. 1). NADH and $FADH_2$, the reducing equivalents that transfer electrons to the electron transport chain, are produced by the TCA cycle and during fatty acid and glucose oxidation. The electron transport chain receives electrons from reducing equivalents and ultimately converts them to ATP. Finally, ATP is transported from the mitochondrial matrix to the cytoplasm through the adenine nucleotide transporter (ANT), making energy available for cellular work.

The mammalian heart demonstrates tremendous substrate selection plasticity depending upon the developmental stage, nutritional status or dietary composition, and cardiac performance demands. Due to limited oxygen and fatty acid availability, the fetal heart relies primarily on anaerobic glucose utilization pathways. However, the reliance on mitochondrial fatty acid oxidation (FAO) markedly increases in the immediate post-natal period [1,2] concomitant with the sudden increase in cardiac work and the abundance of fatty acids in the maternal milk supply. In addition, whereas the myocardium utilizes primarily fatty acids in the fasted state, cardiac glucose utilization significantly contributes to ATP synthesis post-prandially [3]. This flexibility allows the myocardium to maintain steady ATP production.

2. Perturbations in myocardial energy metabolism play a role in the development of cardiomyopathy

Several acquired forms of cardiomyopathy are associated with a decline in overall mitochondrial oxidative catabolism while reliance on anaerobic glycolytic pathways is increased [1,2,4–7]. Whereas altered metabolism was originally considered to be a byproduct of these pathologic states, evidence is emerging that metabolic abnormalities contribute to the pathogenesis of cardiac disease. This idea is supported by

* Tel.: +1 314 362 8963; fax: +1 314 362 8230.
E-mail address: bfinck@im.wustl.edu.

0008-6363/$ - see front matter © 2006 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.cardiores.2006.08.023

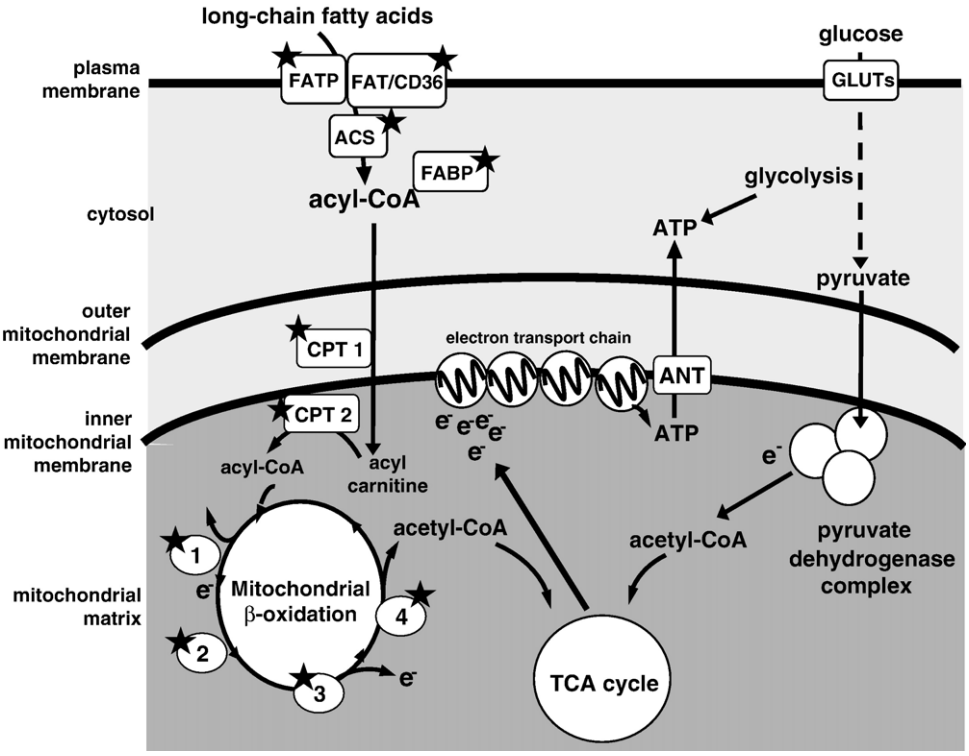

Fig. 1. Cellular energy metabolism pathways. The diagram depicts the major routes for ATP production from catabolism of fatty acids and glucose in the cardiac myocyte. Proteins and enzymes known to be regulated by PPARα are indicated by a star. Abbreviations: FATP, fatty acid binding protein; FAT/CD36, fatty acid translocase; FABP, fatty acid binding protein; ACS, acyl-CoA synthetase; GLUTs, glucose transporters; CPT, carnitine palmitoyltransferase; TCA, tricarboxylic acid; ANT, adenine nucleotide translocator; (1) four chain length-specific acyl-CoA dehydrogenases; (2) enoyl-CoA hydratase; (3) 3-hydroxyacyl-CoA dehydrogenase; (4) 3-ketoacyl-CoA thiolase.

several genetic studies demonstrating that mitochondrial DNA disorders resulting in a global impairment of mitochondrial respiratory function are associated with cardiac defects, including dilated cardiomyopathy, hypertrophic cardiomyopathy, and conduction defects [8–10]. Mutations in nuclear genes encoding FAO enzymes also often manifest as cardiomyopathy [11–14]. Cardiomyopathy in subjects with defects in mitochondrial metabolism usually appears during childhood and often presents as sudden onset heart failure, pulmonary edema, and ventricular arrhythmia, brought on by metabolic stress such as periods of fasting due to infectious illness. A chronic cardiomyopathic phenotype may also develop [12,14].

To model these mitochondrial defects, several genetically-engineered mouse models have been developed. Targeted deletion of ANT1, which transports mitochondrially-derived ATP to the cytosol, leads to mitochondrial dysfunction and cardiomyopathy [15]. In addition, mice with cardiac-specific deletion of mitochondrial transcription factor A (mtTFA or Tfam), which controls expression of the mitochondrial genome, also exhibit marked impairments in mitochondrial metabolism, ROS accumulation, severe cardiomyopathy, and premature mortality [16]. Cardiomyopathy and/or conduction defects are also observed in mouse models with targeted deletion of the fatty acid oxidation enzymes [17–19]. The mechanisms by which impaired mitochondrial metabolism lead to pathologic remodeling are still unclear. However, lipotoxicity, ROS overproduction, and ATP deficiency have been proposed to play a role. These examples of inherited metabolic cardiomyopathic disorders highlight the sensitivity of the heart to defects in mitochondrial metabolism.

3. The PPAR family transcriptionally regulates myocardial energy metabolism

Acute changes in flux through metabolic pathways are mediated by changes in substrate concentrations and allosteric modification of enzymes catalyzing these reactions. However, chronic changes in mitochondrial oxidative capacity and substrate selection are also mediated at the gene transcriptional level [20]. Cardiac metabolism is transcriptionally regulated by the PPAR family (PPARα, β/δ, and γ) of ligand-activated transcription factors. PPARα was initially identified for its role in mediating the hepatic peroxisome proliferative response to non-genotoxic rodent hepatocarcinogens [21], which are potent synthetic ligands for PPARα. The expression of PPARα is high in tissues with an elevated capacity for fatty acid oxidation (FAO), like liver, heart, brown fat, and kidneys [22]. PPARα regulates fatty acid homeostasis via transcriptional activation of genes encoding key enzymes in fatty acid metabolism. PPARβ/δ is almost ubiquitously expressed and transcriptionally regulates FAO

[23]. PPARγ is adipose tissue-enriched and thought to play a vital role in regulating fat storage. Synthetic ligands for PPARγ, the thiazolidinediones, are insulin-sensitizing drugs for insulin resistance and type 2 diabetes, ostensibly because they sequester fatty acid in adipose depots where it can be appropriately stored and by modulating the secretion of adipose-derived adipokines.

PPAR family members regulate the expression of target genes via binding to direct repeat response elements in the promoter region of target genes with their obligate heterodimeric partner, the retinoid X receptor (RXR) (Fig. 2). The activity of the PPAR/RXR complex is modulated by the availability of ligands for PPAR and RXR. Potentially the most relevant endogenous ligands for the PPARs are long-chain fatty acids and their metabolites. However, the specific species of fatty acid metabolite that serve as endogenous ligands for the PPARs have yet to be fully established.

When engaged by ligand, PPARs recruit transcriptional coactivators that are necessary to initiate target gene transcription [24]. These coactivators usually possess histone acetylase (HAT) activity or recruit other coactivators that have HAT activity. Acetylation of histones allows RNA polymerase to access target DNA and initiate transcription (Fig. 2). Several coactivators interact with PPARα including steroid receptor coactivators (SRC; [25]), PPAR-interacting protein (PRIP; [26]), p300 [27], and PPAR-binding protein (PBP; [28]). However, the best-characterized coactivator of PPARα in the heart is the cardiac-enriched PPARγ coactivator-1α (PGC-1α) (Fig. 2). PGC-1α is a coactivator without HAT activity that interacts with several members of the nuclear receptor superfamily [29–31]. PGC-1α acts through PPARα and other transcription factors in the heart to couple metabolic needs to the expression of genes involved in the control of energy metabolism. Given the strong influence of PGC-1α in regulating PPAR activity, its effects on cardiac metabolism and physiology are also described below.

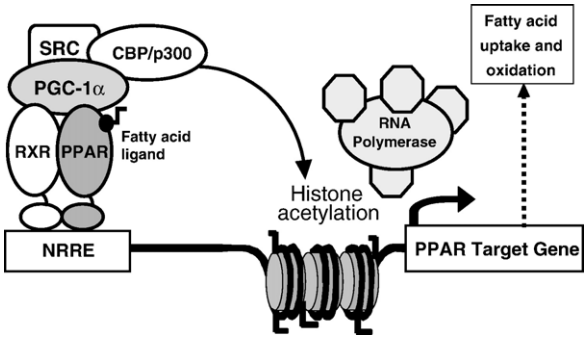

Fig. 2. The PPARα transcriptional regulatory complex controls the expression of fatty acid utilization genes. The schematic depicts key components of the PPARα transcriptional regulatory complex. PPARα binds to specific promoter DNA response elements (PPRE) with its heterodimeric partner, the retinoid X receptor (RXR). The cardiac-enriched coactivator, PGC-1, interacts with PPARα and recruits other cofactors with histone acetylase activity necessary to initiate gene transcription. Formation of the PPARα/RXR dimer, DNA binding, and recruitment of coactivator is influenced by the presence of ligands for PPARα (fatty acid metabolites).

4. PPARα

In the past few years, the role that the PPARα isoform plays in controlling cardiac energy metabolism and function has been evaluated using both gain-of-function and loss-of-function approaches. Treatment of cultured cardiac myocytes with PPARα agonists or adenoviral-mediated PPARα overexpression induces expression of many genes involved in fatty acid catabolic pathways [32–34], including fatty acid transport, esterification, binding, and β-oxidation. PPARα agonists also exhibit anti-inflammatory effects [35]. Interestingly, most studies have shown little effect of PPARα agonists on myocardial PPAR target genes when administered in vivo [36], suggesting that, at least in rodents, the peripheral (likely hepatic) actions of PPARα ligands explain many of the cardiac effects of the drugs. These compounds elicit strong effects on hepatic fatty acid metabolism including the inhibition of hepatic lipoprotein secretion to lower circulating lipid levels [37,38]. PPARα ligands administered in vivo actually decrease rates of cardiac FAO in diabetic mice [39,40] suggesting that these agonists influence cardiac metabolism indirectly by altering circulating endogenous substrate concentrations.

To distinguish the cardiac-specific effects of PPARα from the systemic effects of ligand administration, transgenic mice with cardiac-specific overexpression of PPARα driven by the myosin heavy chain (MHC) promoter (MHC-PPARα mice) were generated [41–45]. Heart-specific overexpression of PPARα induced several target genes involved in fatty acid utilization and increased cardiac fatty acid uptake and oxidation [41]. The expression of multiple genes involved in glucose metabolism was markedly diminished in hearts of MHC-PPARα mice leading to impaired glucose uptake and utilization [41,44]. These metabolic changes were also accompanied by ventricular hypertrophy and moderate systolic dysfunction. Interestingly, the functional abnormalities of MHC-PPARα mice were greatly exacerbated when MHC-PPARα mice were rendered insulin-deficient or placed on a high fat diet [42] — two stimuli that increase the supply of circulating lipids. The cardiomyopathic remodeling that occurred in diabetic or high-fat-fed MHC-PPARα mice was accompanied by striking steatosis and reactive oxygen species accumulation in the myocardium, suggesting a lipotoxic component to the cardiomyopathic changes. These findings indicate that PPARα-driven reliance on fatty acid utilization and coordinate inhibition of glucose metabolism can lead to pathologic remodeling and severe cardiomyopathy. The pathologic mechanisms whereby these metabolic abnormalities are still incompletely understood. However, metabolic inflexibility (uncontrolled FAO), toxic lipid intermediate accumulation, and reactive oxygen species accumulation have been observed in these hearts and are known to be linked to cardiomyopathic remodeling.

The cardiac phenotype of mice with targeted deletion of the PPARα gene has also been evaluated. PPARα null mice are viable and appear outwardly normal, but exhibit mild

aging-associated cardiac fibrosis [46]. The expression of several PPARα target genes and rates of FAO are diminished in hearts of PPARα null mice at baseline [46–48] and fail to be induced in response to fasting or diabetes [47]. PPARα null mice also exhibit increased glucose transporter (GLUT4) expression, glucose uptake, and reliance on glucose for cardiac ATP production [49,50]. The age-associated fibrosis notwithstanding, cardiac function is relatively normal in young PPARα null mice. However, the response to several physiologic stressors is perturbed in mice lacking PPARα. For example, isolated hearts from PPARα null mice are unable to compensate when challenged with an increased workload [49,51]. Although a definitive mechanism for these cardiac defects is lacking, it is likely that the inability to boost rates of FAO in response to increased work load leads to energy deprivation. In support of this, transgenic overexpression of the GLUT1 glucose transporter, which further enhanced glucose utilization in these mice, rescued the functional defect in response to increased workload [51]. In sum, PPARα overexpressing and null mouse models exhibit reciprocal metabolic phenotypes and demonstrate the important roles that PPARα plays in controlling cardiac energy substrate selection.

5. PPARβ/δ

Until recently, the PPARβ/δ (referred to as PPARβ from here on) isoform was little-studied. PPARβ is expressed fairly ubiquitously throughout the body and at relatively high levels in cardiac myocytes [32]. PPARβ ligand administration or adenoviral overexpression in cultured cardiac myocytes activates many PPAR target genes involved in FAO [32,52]. Also, the PPARβ/δ isoform has been shown to protect cardiac myocytes from oxidative stress-induced apoptosis by activating expression of catalase, which scavenges hydrogen peroxide [53]. Two strains of whole-animal constitutive PPARβ knockout mice have been developed [54,55], but the cardiac physiology and metabolic phenotype of these PPARβ null mice has not yet been reported. Recently, however, mice with conditional cardiac-specific deletion of PPARβ were generated and shown to exhibit severe impairments in myocardial FAO gene expression, diminished rates of FAO, increased cardiac lipid accumulation, and lipotoxicity [56]. Severe cardiomyopathy and congestive heart failure developed leading to premature death. Given that the cardiac PPARα system is intact in these mice, these findings suggest that PPARα is not sufficient to compensate for cardiac-specific PPARβ deficiency and indicate that PPARβ is a critical regulatory factor controlling myocardial energy metabolism.

6. PPARγ

PPARγ which is adipose-enriched, controls the expression of genes involved in fatty acid storage and adipogenesis. The exact mechanism by which PPARγ regulates myocardial metabolism is unclear. Whereas several manuscripts demonstrate significant expression of PPARγ in cardiac myocytes, other studies fail to detect this isoform in the myocardium [32,57–59]. This disparity could be explained by species-to-species variability, differing reagents used for detection, or contamination of myocardial samples with pericardial white adipose tissue, which is enriched in PPARγ. Agonists for PPARγ fail to increase FAO gene expression in cultured cardiac myocytes [32] and in vivo administration actually leads to diminished expression of known PPAR target genes in the myocardium [60]. Given that the main site of PPARγ agonist action in vivo seems to be white adipose tissue, the basis for this observation may be rooted in a systemic effect of PPARγ ligands, as was proposed above for PPARα. PPARγ agonists also possess potent anti-inflammatory effects [61,62]. In contrast to the lack of effect on metabolic gene expression, other studies suggest that PPARγ agonists retain their anti-inflammatory properties in cardiac myocytes in vitro [62,63].

The influence of the myocardial PPARγ system on cardiac structure and function has recently been tested using a loss-of-function approach. Unfortunately, constitutive, whole-body disruption of PPARγ results in embryonic lethality due to placental and cardiac defects [64], preventing the evaluation of the cardiac phenotype of these mice. However, cardiac-specific PPARγ (csPPARγ) null mice have recently been generated [65]. These studies revealed that csPPARγ deficiency caused modest ventricular hypertrophy, but did not impair systolic function [65]. Further work will be required to evaluate the effects of PPARγ deficiency on cardiac metabolism. Given the increased usage of PPARγ agonists as insulin-sensitizing drugs, this is an area of active investigation.

7. PGC-1α

The transcriptional coactivator of the PPARs, PGC-1α has recently emerged as a key player in the control of myocardial metabolism. In cardiac myocytes, activation of PGC-1α drives a strong induction of PPARα target genes encoding FAO enzymes [66]. PGC-1α also coactivates other transcription factors, including estrogen-related receptors (ERRα and γ) and the nuclear respiratory factor 1 (NRF-1), to stimulate mitochondrial biogenesis and enhance expression of components of the electron transport chain [66–68]. These findings suggest that PGC-1α acts to augment the capacity for ATP production in a “global” manner by inducing expression of enzymes involved in multiple components of these catabolic pathways.

Several interesting mouse models that explore the function of PGC-1α in cardiac myocytes have also been developed. The first model constitutively overexpressed PGC-1α under control of the myosin heavy chain (MHC) promoter. This approach resulted in profound mitochondrial proliferation, cardiomyopathy, and premature death due to heart failure [66]. The severity and rapid onset of cardiomyopathy

prevented a full investigation of the cardiac metabolic phenotype of these mice. To better assess this issue, a tetracycline-inducible transgenic system was employed to drive inducible cardiac-specific overexpression of PGC-1α [69]. This model revealed developmental stage-specific responses to acute PGC-1α overexpression. When PGC-1α was overexpressed in the neonatal stage, dramatic proliferation of mitochondria was observed without overt effects on cardiac function. In other studies, overexpression of PGC-1α after mice had reached adulthood revealed only modest mitochondrial proliferation. However, mitochondrial ultrastructural abnormalities and severe cardiac dysfunction was observed with PGC-1α overexpression in the adult. Further metabolic characterization of these mice is expected to unveil the mechanisms linking mitochondrial (dys)function to cardiomyopathic remodeling.

Two independently-derived PGC-1α-deficient mouse lines have been developed and characterized [70–72]. Studies characterizing both strains of PGC-1α-deficient mice demonstrate perturbations in mitochondrial OXPHOS pathway function and depressed expression of genes encoding enzymes involved in these pathways. Interestingly, the severity of the cardiac phenotype varies greatly between the two lines of null mice. One strain of PGC-1α null mice exhibit moderate age-related cardiac dysfunction and activation of several gene expression signatures of cardiomyopathic remodeling [72]. In contrast, the phenotype of the second PGC-1α null mouse line appears to be less severe [71]. In both models, the most obvious signs of cardiac dysfunction were unveiled under stress of dobutamine or following an exhaustive bout of treadmill exercise [71,72]. To summarize, these recent studies indicate that PGC-1α plays a critical role in controlling cardiac energy metabolism and suggest that perturbations in the PGC-1α system could predispose to cardiomyopathic remodeling.

8. The PPAR/PGC-1α system is deactivated in acquired cardiomyopathy and is a target for therapeutic intervention

Abnormalities in myocardial energy metabolism occur in several acquired forms of hypertrophy, ischemic heart disease, and in the failing heart. Specifically, overall mitochondrial oxidative catabolism decreases while reliance on anaerobic glycolytic pathways is increased [1,2,4–7,73]. These metabolic changes are mediated, at least in part, via decreased expression of genes encoding enzymes involved in mitochondrial FAO and OXPHOS pathways secondary to deactivation of the PPAR/PGC-1α axis [1,33,74–77]. The expression and/or DNA binding activity of the PPARα-RXR complex is markedly diminished by hypoxia [34,78], ischemic heart disease [79–81], and pressure overload-induced cardiac hypertrophy [33,82]. Similarly, PGC-1α expression is diminished in mouse models of experimentally-induced cardiomyopathy [74,83]. Deactivation of PPARα in human heart failure patients has also been observed [2,84], suggesting that this finding in rodent models translates to humans. It is likely that deactivation of the PPAR/PGC-1α complex in the failing heart plays a major role in the coincident metabolic remodeling.

Although much regarding the mechanisms whereby the PPAR/PGC-1 axis is deactivated in the failing heart remains to be discovered, several signaling pathways have been implicated. The activity of PPARα and PGC-1α is known to be increased by acute activation of the calcineurin [85] or p38 mitogen-activated protein kinase (MAPK) [86,87] pathways. PGC-1α is also under the control of the calcium/calmodulin-dependent protein kinase [85]. However, less is known regarding the pathways that deactivate PPARα and PGC-1. The extracellular signal-regulated kinase MAPK has been shown to directly phosphorylate PPARα, leading to diminished transcriptional activity [33]. In addition, chronic activation of cyclin-dependent kinase 9, a nuclear-localized kinase that is activated in cardiac hypertrophy, leads to diminished PGC-1α expression and activity [83]. Given the potential importance of metabolic remodeling in the progression of heart failure, the search for additional pathways that control PPAR/PGC-1 activity is ongoing.

The consequence of PPAR/PGC-1α complex deactivation in the hypertrophied and ischemic heart as an adaptive versus maladaptive response is also unclear. Increased myocardial reliance on anaerobic glycolytic pathways for the production of ATP is likely an adaptive response to reduce oxygen consumption. In support of this, partial inhibitors of mitochondrial FAO show promise as therapeutic treatment for cardiac disease [88–90]. Moreover, treatment with a PPARα agonist following pressure overload [82] or ischemic insult [79] to reactivate oxidative metabolism leads to contractile dysfunction. Conversely, there is also evidence that deactivation of mitochondrial metabolism can be maladaptive. Glycolysis yields far less ATP per mole substrate compared to FAO, possibly creating a relative energy-deficient state. Indeed, depletion of high energy phosphate intermediates, a key energy stockpile, has been detected in heart failure [91]. Alternatively or in addition, impairments in FAO are linked to lipid accumulation in the cardiac myocyte, which can have toxic effects (“lipotoxicity”) [92–94]. PGC-1α overexpression [83] and PPAR agonists [58,59,95] prevent cardiac hypertrophy or improve contractility in cultured cardiac myocytes. Thus, the end effects of PPAR/PGC-1α activity on pathologic remodeling are less than clear.

Despite this uncertainty, agonists for the PPARs have been targeted to improve the response to ischemic insult. While some studies fail to show an effect of PPAR agonism [57,96,97], many others demonstrate that ligands to PPARα or PPARγ improve the response to ischemic insult and may reduce infarct size in various experimental models [98–103]. The mechanisms involved are unclear, but may involve anti-inflammatory effects or increased myocardial glucose utilization [98,99,101,104,105]. Indeed, enhanced glucose oxidation during ischemia–reperfusion, especially in insulin resistant or diabetic heart, has been linked to improved

recovery [50]. Interestingly, the recent Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) clinical trial, a randomized, controlled study, failed to detect a significant benefit of daily PPARα ligand treatment on the incidence of ischemic heart disease, though there was a trend towards reduced risk of cardiovascular events [106]. In contrast, other smaller pre-clinical trials have demonstrated beneficial effects of fibrates on cardiovascular health, especially in the context of diabetes or insulin resistance [107,108]. The recent PROactive clinical study, a prospective randomized trial in patients diagnosed with pre-existing cardiovascular disease, also showed positive effects of pioglitazone, an insulin-sensitizing PPARγ agonist, on mortality and cardiovascular events [109].

The effects of PPARα on the response to ischemia–reperfusion have also been tested in genetically altered mice. PPARα null mice, which have diminished capacity for FAO and increased glucose use, exhibit resistance to ischemia–reperfusion injury [45,50]. In contrast, MHC-PPARα mice display an exacerbated response to ischemia–reperfusion [45]. It is postulated that the metabolic profile induced by PPARα deficiency or overexpression explains these findings. The PPARα null mouse heart prefers to utilize glucose, which may be protective during ischemia–reperfusion. In contrast, the MHC-PPARα heart cannot utilize glucose. However, further work is required to delineate the mechanisms involved and to determine whether PPAR agonists elicit protective effects during ischemia–reperfusion.

9. PPAR activity is altered in the diabetic heart

Cardiomyopathy is extremely prevalent in persons with diabetes mellitus even after corrections for risk factors (hypertension, hyperlipidemia, etc.) that abound in diabetic patients [110]. Idiopathic cardiac disease occurring in diabetic subjects is often referred to as “diabetic cardiomyopathy”, a term coined by Rubler et al. over 30 years ago [111]. However, the etiology of this condition is very poorly understood. Many have proposed that abnormalities in myocardial energy metabolism play a causative role in the development of diabetic cardiomyopathy. Whereas the healthy myocardium displays tremendous metabolic flexibility [3], due to the importance of insulin in the control of cardiac metabolism, FAO is the primary source of ATP production in insulin-resistant and diabetic heart [112–115]. Uncontrolled, high-level FAO and impaired glucose utilization may have detrimental effects on cardiac structure and function by a variety of mechanisms including glucotoxicity, lipotoxicity, reactive oxygen species accumulation, or higher oxygen consumption costs.

There is emerging evidence that the PPARα/PGC-1α complex is activated in the diabetic heart. The myocardial expression of several PPARα target genes involved in fatty acid utilization was induced by both insulin-deficient and obese type 2 diabetic mice [41,42,116]. When PPARα null mice were rendered insulin-deficient, the induction of PPAR target genes was markedly blunted [42]. The activation of PPARα by diabetes is consistent with increased availability of fatty acids, which serve as endogenous ligands for PPARα. However, it should be noted that other studies have shown that PPAR target gene expression is diminished in the diabetic heart [117,118]. These disparities could be due to the differences in the underlying causes of diabetes in the various models used. In addition, the duration of diabetic disease has also been shown to influence the expression of PPARα [116,117], suggesting a time-course effect.

10. Summary

The studies described herein describe the link between myocardial energy metabolism and cardiac structure and function. The deactivation of myocardial oxidative metabolism in acquired cardiomyopathies is not only a secondary effect, but may also play a significant role in the pathogenesis of cardiomyopathic remodeling. There is therefore rationale for metabolic therapy to remedy cardiac hypertrophy and dysfunction in cardiac disease. The importance of the PPARs and PGC-1α in the control of cardiac energy metabolism makes these regulatory pathways attractive targets for metabolic therapy. However, much needs to be learned concerning the intricacies of modulating their activity for optimal therapeutic benefit.

Acknowledgments

I wish to thank Daniel P. Kelly and all members of his laboratory, past and present, who have contributed to the work summarized herein. This work was supported by a KO1 award (KO1 DK062903) from the NIDDK and other NIH grants (RO1 DK45416, RO1 HL58493, PO1 HL57278, P30 DK56341, and P30 DK52574).

References

[1] Finck BN, Lehman JJ, Barger PM, Kelly DP. Regulatory networks controlling mitochondrial energy production in the developing, hypertrophied, and diabetic heart. Cold Spring Harb Symp Quant Biol 2002;67:371–82.
[2] Barger PM, Kelly DP. PPAR signaling in the control of cardiac energy metabolism. Trends Cardiovasc Med 2000;10:238–45.
[3] Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. Prog Cardiovasc Dis 1972;15:289–329.
[4] van Bilsen M, Smeets PJ, Gilde AJ, van der Vusse GJ. Metabolic remodelling of the failing heart: the cardiac burn-out syndrome? Cardiovasc Res 2004;61:218–26.
[5] Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. J Physiol 2004;555:1–13.
[6] Russell LK, Finck BN, Kelly DP. Mouse models of mitochondrial dysfunction and heart failure. J Mol Cell Cardiol 2005;38:81–91.
[7] Davila-Roman VG, Vedala G, Herrero P, de las Fuentes L, Rogers JG, Kelly DP, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2002;40:271–7.
[8] DiMauro S, Schon EA. Mitochondrial DNA mutations in human disease. Am J Med Genet 2001;106:18–26.

[9] Triepels RH, Van Den Heuvel LP, Trijbels JM, Smeitink JA. Respiratory chain complex I deficiency. Am J Med Genet 2001;106:37–45.
[10] Vallance HD, Jeven G, Wallace DC, Brown MD. A case of sporadic infantile histiocytoid cardiomyopathy caused by the A8344G (MERRF) mitochondrial DNA mutation. Pediatr Cardiol 2004;25:538–40.
[11] Strauss AW, Powell CK, Hale DE, Anderson MM, Ahuja A, Brackett JC, et al. Molecular basis of human mitochondrial very-long-chain acyl-CoA dehydrogenase deficiency causing cardiomyopathy and sudden death in childhood. Proc Natl Acad Sci U S A 1995;92:10496–500.
[12] Kelly DP, Strauss AW. Inherited cardiomyopathies. N Engl J Med 1994;330:913–9.
[13] Bennett MJ, Rinaldo P, Millington DS, Tanaka K, Yokota I, Coates PM. Medium-chain acyl-CoA dehydrogenase deficiency: postmortem diagnosis in a case of sudden infant death and neonatal diagnosis of an affected sibling. Pediatr Pathol 1991;11:889–95.
[14] Bennett MJ, Rinaldo P, Strauss AW. Inborn errors of mitochondrial fatty acid oxidation. Crit Rev Clin Lab Sci 2000;37:1–44.
[15] Graham BH, Waymire KG, Cottrell B, Trounce IA, MacGregor GR, Wallace DC. A mouse model for mitochondrial myopathy and cardiomyopathy resulting from a deficiency in the heart/muscle isoform of the adenine nucleotide translocator. Nat Genet 1997;16:226–34.
[16] Wang J, Wilhelmsson H, Graff C, Li H, Oldfors A, Rustin P, et al. Dilated cardiomyopathy and atrioventricular conduction blocks induced by heart-specific inactivation of mitochondrial DNA gene expression. Nat Genet 1999;21:133–7.
[17] Kurtz DM, Rinaldo P, Rhead WJ, Tian L, Millington DS, Vockley J, et al. Targeted disruption of mouse long-chain acyl-CoA dehydrogenase gene reveals crucial roles for fatty acid oxidation. PNAS 1998;95:15592–7.
[18] Ibdah JA, Paul H, Zhao Y, Binford S, Salleng K, Cline M, et al. Lack of mitochondrial trifunctional protein in mice causes neonatal hypoglycemia and sudden death. J Clin Invest 2001;107:1403–9.
[19] Exil VJ, Roberts RL, Sims H, McLaughlin JE, Malkin RA, Gardner CD, et al. Very-long-chain acyl-coenzyme a dehydrogenase deficiency in mice. Circ Res 2003;93:448–55.
[20] Desvergne B, Michalik L, Wahli W. Transcriptional regulation of metabolism. Physiol Rev 2006;86:465–514.
[21] Issemann I, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature 1990;347:645–50.
[22] Feige JN, Gelman L, Michalik L, Desvergne B, Wahli W. From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. Prog Lipid Res 2006;45:120–59.
[23] Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, Bayuga-Ocampo CR, et al. Regulation of muscle fiber type and running endurance by PPARdelta. PLoS Biol 2004;2:e294.
[24] Robyr D, Wolffe AP, Wahli W. Nuclear hormone receptor coregulators in action: diversity for shared tasks. Mol Endocrinol 2000;14:329–47.
[25] Zhu Y, Qi C, Calandra C, Rao MS, Reddy JK. Cloning and identification of mouse steroid receptor coactivator-1 (mSRC-1), as a coactivator of peroxisome proliferator-activated receptor gamma. Gene Expr 1996;6:185–95.
[26] Zhu Y, Kan L, Qi C, Kanwar YS, Yeldandi AV, Rao MS, et al. Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR. J Biol Chem 2000;275:13510–6.
[27] Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevrivy DJ, Leid M. p300 functions as a coactivator for the peroxisome proliferator-activated receptor alpha. J Biol Chem 1997;272:33435–43.
[28] Zhu Y, Qi C, Jain S, Rao MS, Reddy JK. Isolation and characterization of PBP, a protein that interacts with peroxisome proliferator-activated receptor. J Biol Chem 1997;272:25500–6.
[29] Puigserver P, Spiegelman BM. Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. Endocr Rev 2003;24:78–90.
[30] Lin J, Handschin C, Spiegelman BM. Metabolic control through the PGC-1 family of transcription coactivators. Cell Metab 2005;1:361–70.
[31] Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest 2006;116:615–22.
[32] Gilde AJ, van der Lee KA, Willemsen PH, Chinetti G, van der Leij FR, van der Vusse GJ, et al. Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. Circ Res 2003;92:518–24.
[33] Barger PM, Brandt JM, Leone TC, Weinheimer CJ, Kelly DP. Deactivation of peroxisome proliferator-activated receptor-alpha during cardiac hypertrophic growth. J Clin Invest 2000;105:1723–30.
[34] Huss JM, Levy FH, Kelly DP. Hypoxia inhibits the peroxisome proliferator-activated receptor alpha/retinoid X receptor gene regulatory pathway in cardiac myocytes: a mechanism for O_2-dependent modulation of mitochondrial fatty acid oxidation. J Biol Chem 2001;276:27605–12.
[35] Delerive P, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors in inflammation control. J Endocrinol 2001;169:453–9.
[36] Cook WS, Yeldandi AV, Rao MS, Hashimoto T, Reddy JK. Less extrahepatic induction of fatty acid beta-oxidation enzymes by PPAR alpha. Biochem Biophys Res Commun 2000;278:250–7.
[37] Dashti N, Ontko JA. Alterations in rat serum lipids and apolipoproteins following clofibrate treatment. Atherosclerosis 1983;49:255–66.
[38] Ide T, Oku H, Sugano M. Reciprocal responses to clofibrate in ketogenesis and triglyceride and cholesterol secretion in isolated rat liver. Metabolism 1982;31:1065–72.
[39] Aasum E, Belke DD, Severson DL, Riemersma RA, Cooper M, Andreassen M, et al. Cardiac function and metabolism in Type 2 diabetic mice after treatment with BM 17.0744, a novel PPAR-alpha activator. Am J Physiol Heart Circ Physiol 2002;283:H949–57.
[40] Aasum E, Cooper M, Severson DL, Larsen TS. Effect of BM 17.0744, a PPARalpha ligand, on the metabolism of perfused hearts from control and diabetic mice. Can J Physiol Pharmacol 2005;83:183–90.
[41] Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest 2002;109:121–30.
[42] Finck BN, Han X, Courtois M, Aimond F, Nerbonne JM, Kovacs A, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. Proc Natl Acad Sci U S A 2003;100:1226–31.
[43] Harris IS, Treskov I, Rowley MW, Heximer S, Kaltenbronn K, Finck BN, et al. G-protein signaling participates in the development of diabetic cardiomyopathy. Diabetes 2004;53:3082–90.
[44] Park SY, Cho YR, Finck BN, Kim HJ, Higashimori T, Hong EG, et al. Cardiac-specific overexpression of peroxisome proliferator-activated receptor-alpha causes insulin resistance in heart and liver. Diabetes 2005;54:2514–24.
[45] Sambandam N, Morabito D, Wagg C, Finck BN, Kelly DP, Lopaschuk GD. Chronic activation of PPARalpha is detrimental to cardiac recovery after ischemia. Am J Physiol Heart Circ Physiol 2006;290:H87–95.
[46] Watanabe K, Fujii H, Takahashi T, Kodama M, Aizawa Y, Ohta Y, et al. Constitutive regulation of cardiac fatty acid metabolism through peroxisome proliferator-activated receptor alpha associated with age-dependent cardiac toxicity. J Biol Chem 2000;275:22293–9.
[47] Leone TC, Weinheimer CJ, Kelly DP. A critical role for the peroxisome proliferator-activated receptor alpha (PPARalpha) in the cellular fasting response: the PPARalpha-null mouse as a model of fatty acid oxidation disorders. Proc Natl Acad Sci U S A 1999;96:7473–8.

[48] Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. J Clin Invest 1999;103:1489–98.
[49] Campbell FM, Kozak R, Wagner A, Altarejos JY, Dyck JR, Belke DD, et al. A role for peroxisome proliferator-activated receptor alpha (PPARalpha) in the control of cardiac malonyl-CoA levels: reduced fatty acid oxidation rates and increased glucose oxidation rates in the hearts of mice lacking PPARalpha are associated with higher concentrations of malonyl-CoA and reduced expression of malonyl-CoA decarboxylase. J Biol Chem 2002;277:4098–103.
[50] Panagia M, Gibbons GF, Radda GK, Clarke K. PPAR-alpha activation required for decreased glucose uptake and increased susceptibility to injury during ischemia. Am J Physiol Heart Circ Physiol 2005;288:H2677–83.
[51] Luptak I, Balschi JA, Xing Y, Leone TC, Kelly DP, Tian R. Decreased contractile and metabolic reserve in peroxisome proliferator-activated receptor-alpha-null hearts can be rescued by increasing glucose transport and utilization. Circulation 2005;112: 2339–46.
[52] Cheng L, Ding G, Qin Q, Xiao Y, Woods D, Chen YE, et al. Peroxisome proliferator-activated receptor delta activates fatty acid oxidation in cultured neonatal and adult cardiomyocytes. Biochem Biophys Res Commun 2004;313:277–86.
[53] Pesant M, Sueur S, Dutartre P, Tallandier M, Grimaldi PA, Rochette L, et al. Peroxisome proliferator-activated receptor delta (PPARdelta) activation protects H9c2 cardiomyoblasts from oxidative stress-induced apoptosis. Cardiovasc Res 2006;69:440–9.
[54] Peters JM, Lee SS, Li W, Ward JM, Gavrilova O, Everett C, et al. Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor beta(delta). Mol Cell Biol 2000;20:5119–28.
[55] Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, et al. Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. Proc Natl Acad Sci U S A 2002;99: 303–8.
[56] Cheng L, Ding G, Qin Q, Huang Y, Lewis W, He N, et al. Cardiomyocyte-restricted peroxisome proliferator-activated receptor-delta deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. Nat Med 2004;10:1245–50.
[57] Xu Y, Gen M, Lu L, Fox J, Weiss SO, Brown RD, et al. PPAR-gamma activation fails to provide myocardial protection in ischemia and reperfusion in pigs. Am J Physiol Heart Circ Physiol 2005;288: H1314–23.
[58] Asakawa M, Takano H, Nagai T, Uozumi H, Hasegawa H, Kubota N, et al. Peroxisome proliferator-activated receptor gamma plays a critical role in inhibition of cardiac hypertrophy in vitro and in vivo. Circulation 2002;105:1240–6.
[59] Yamamoto K, Ohki R, Lee RT, Ikeda U, Shimada K. Peroxisome proliferator-activated receptor gamma activators inhibit cardiac hypertrophy in cardiac myocytes. Circulation 2001;104:1670–5.
[60] Cabrero A, Jove M, Planavila A, Merlos M, Laguna JC, Vazquez-Carrera M. Down-regulation of acyl-CoA oxidase gene expression in heart of troglitazone-treated mice through a mechanism involving chicken ovalbumin upstream promoter transcription factor II. Mol Pharmacol 2003;64:764–72.
[61] Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. Inflamm Res 2000;49:497–505.
[62] Mendez M, LaPointe MC. PPARgamma inhibition of cyclooxygenase-2, PGE2 synthase, and inducible nitric oxide synthase in cardiac myocytes. Hypertension 2003;42:844–50.
[63] Takano H, Nagai T, Asakawa M, Toyozaki T, Oka T, Komuro I, et al. Peroxisome proliferator-activated receptor activators inhibit lipopolysaccharide-induced tumor necrosis factor-alpha expression in neonatal rat cardiac myocytes. Circ Res 2000;87:596–602.
[64] Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, et al. PPAR gamma is required for placental, cardiac, and adipose tissue development. Mol Cell 1999;4:585–95.
[65] Duan SZ, Ivashchenko CY, Russell MW, Milstone DS, Mortensen RM. Cardiomyocyte-specific knockout and agonist of peroxisome proliferator-activated receptor-gamma both induce cardiac hypertrophy in mice. Circ Res 2005;97:372–9.
[66] Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. J Clin Invest 2000;106: 847–56.
[67] Huss JM, Torra IP, Staels B, Giguere V, Kelly DP. Estrogen-related receptor alpha directs peroxisome proliferator-activated receptor alpha signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle. Mol Cell Biol 2004;24:9079–91.
[68] Huss JM, Kopp RP, Kelly DP. Peroxisome proliferator-activated receptor coactivator-1alpha (PGC-1alpha) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor-alpha and -gamma. Identification of novel leucine-rich interaction motif within PGC-1alpha. J Biol Chem 2002;277:40265–74.
[69] Russell LK, Mansfield CM, Lehman JJ, Kovacs A, Courtois M, Saffitz JE, et al. Cardiac-specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner. Circ Res 2004;94:525–33.
[70] Lin J, Wu PH, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, et al. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. Cell 2004;119:121–35.
[71] Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, et al. PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. PLoS Biol 2005;3:e101.
[72] Arany Z, He H, Lin J, Hoyer K, Handschin C, Toka O, et al. Transcriptional coactivator PGC-1 alpha controls the energy state and contractile function of cardiac muscle. Cell Metab 2005;1:259–71.
[73] van der Vusse GJ, van Bilsen M, Glatz JF. Cardiac fatty acid uptake and transport in health and disease. Cardiovasc Res 2000;45:279–93.
[74] Garnier A, Fortin D, Delomenie C, Momken I, Veksler V, Ventura-Clapier R. Depressed mitochondrial transcription factors and oxidative capacity in rat failing cardiac and skeletal muscles. J Physiol 2003;551: 491–501.
[75] Sack MN, Kelly DP. The energy substrate switch during development of heart failure: gene regulatory mechanisms (Review). Int J Mol Med 1998;1:17–24.
[76] Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation 1996;94:2837–42.
[77] Depre C, Shipley GL, Chen W, Han Q, Doenst T, Moore ML, et al. Unloaded heart in vivo replicates fetal gene expression of cardiac hypertrophy. Nat Med 1998;4:1269–75.
[78] Razeghi P, Essop MF, Huss JM, Abbasi S, Manga N, Taegtmeyer H. Hypoxia-induced switches of myosin heavy chain iso-gene expression in rat heart. Biochem Biophys Res Commun 2003;303: 1024–7.
[79] Dewald O, Sharma S, Adrogue J, Salazar R, Duerr GD, Crapo JD, et al. Downregulation of peroxisome proliferator-activated receptor-alpha gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity. Circulation 2005;112:407–15.
[80] Remondino A, Rosenblatt-Velin N, Montessuit C, Tardy I, Papageorgiou I, Dorsaz PA, et al. Altered expression of proteins of metabolic regulation during remodeling of the left ventricle after myocardial infarction. J Mol Cell Cardiol 2000;32:2025–34.
[81] Rosenblatt-Velin N, Montessuit C, Papageorgiou I, Terrand J, Lerch R. Postinfarction heart failure in rats is associated with upregulation of GLUT-1 and downregulation of genes of fatty acid metabolism. Cardiovasc Res 2001;52:407–16.
[82] Young ME, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with

contractile dysfunction in hypertrophied rat heart. J Biol Chem 2001;276:44390–5.
[83] Sano M, Wang SC, Shirai M, Scaglia F, Xie M, Sakai S, et al. Activation of cardiac Cdk9 represses PGC-1 and confers a predisposition to heart failure. EMBO J 2004;23:3559–69.
[84] Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation 1996;94:2837–42.
[85] Schaeffer PJ, Wende AR, Magee CJ, Neilson JR, Leone TC, Chen F, et al. Calcineurin and calcium/calmodulin-dependent protein kinase activate distinct metabolic gene regulatory programs in cardiac muscle. J Biol Chem 2004;279:39593–603.
[86] Barger PM, Browning AC, Garner AN, Kelly DP. p38 mitogen-activated protein kinase activates peroxisome proliferator-activated receptor alpha: a potential role in the cardiac metabolic stress response. J Biol Chem 2001;276:44495–501.
[87] Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY, et al. Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. Mol Cell 2001;8:971–82.
[88] Schofield RS, Hill JA. The use of ranolazine in cardiovascular disease. Expert Opin Investig Drugs 2002;11:117–1123.
[89] Rupp H, Zarain-Herzberg A, Maisch B. The use of partial fatty acid oxidation inhibitors for metabolic therapy of angina pectoris and heart failure. Herz 2002;27:621–36.
[90] Chandler MP, Stanley WC, Morita H, Suzuki G, Roth BA, Blackburn B, et al. Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. Circ Res 2002;91: 278–80.
[91] Tian R, Musi N, D'Agostino J, Hirshman MF, Goodyear LJ. Increased adenosine monophosphate-activated protein kinase activity in rat hearts with pressure-overload hypertrophy. Circulation 2001;104:1664–9.
[92] Chiu HC, Kovacs A, Blanton RM, Han X, Courtois M, Weinheimer CJ, et al. Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy. Circ Res 2005;96:225–33.
[93] Chiu HC, Kovacs A, Ford DA, Hsu FF, Garcia R, Herrero P, et al. A novel mouse model of lipotoxic cardiomyopathy. J Clin Invest 2001;107:813–22.
[94] Yagyu H, Chen G, Yokoyama M, Hirata K, Augustus A, Kako Y, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. J Clin Invest 2003;111: 419–26.
[95] Planavila A, Rodriguez-Calvo R, Jove M, Michalik L, Wahli W, Laguna JC, et al. Peroxisome proliferator-activated receptor beta/ delta activation inhibits hypertrophy in neonatal rat cardiomyocytes. Cardiovasc Res 2005;65:832–41.
[96] Morgan EE, Rennison JH, Young ME, McElfresh TA, Kung TA, Tserng KY, et al. Effects of chronic activation of peroxisome proliferator-activated receptor-alpha or high-fat feeding in a rat infarct model of heart failure. Am J Physiol Heart Circ Physiol 2006;290: H1899–904.
[97] Xu Y, Lu L, Greyson C, Rizeq M, Nunley K, Wyatt B, et al. The PPAR-{alpha} activator, fenofibrate, fails to provide myocardial protection in ischemia and reperfusion in pigs. Am J Physiol Heart Circ Physiol 2005.
[98] Ito H, Nakano A, Kinoshita M, Matsumori A. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates myocardial ischemia/reperfusion injury in a rat model. Lab Invest 2003;83:1715–21.
[99] Yue TL, Bao W, Jucker BM, Gu JL, Romanic AM, Brown PJ, et al. Activation of peroxisome proliferator-activated receptor-alpha protects the heart from ischemia/reperfusion injury. Circulation 2003;108:2393–9.
[100] Yue TlTL, Chen J, Bao W, Narayanan PK, Bril A, Jiang W, et al. In vivo myocardial protection from ischemia/reperfusion injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. Circulation 2001;104:2588–94.
[101] Wayman NS, Ellis BL, Thiemermann C. Ligands of the peroxisome proliferator-activated receptor-PPAR-a reduce myocardial infarct size. Med Sci Monit 2002;8:BR243–7.
[102] Shiomi T, Tsutsui H, Hayashidani S, Suematsu N, Ikeuchi M, Wen J, et al. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation 2002;106: 3126–32.
[103] Sidell RJ, Cole MA, Draper NJ, Desrois M, Buckingham RE, Clarke K. Thiazolidinedione treatment normalizes insulin resistance and ischemic injury in the zucker Fatty rat heart. Diabetes 2002;51: 1110–7.
[104] Hallsten K, Virtanen KA, Lonnqvist F, Janatuinen T, Turiceanu M, Ronnemaa T, et al. Enhancement of insulin-stimulated myocardial glucose uptake in patients with Type 2 diabetes treated with rosiglitazone. Diabet Med 2004;21:1280–7.
[105] Cuzzocrea S. Peroxisome proliferator-activated receptors gamma ligands and ischemia and reperfusion injury. Vascul Pharmacol 2004;41:187–95.
[106] Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–61.
[107] Israelian-Konaraki Z, Reaven PD. Peroxisome proliferator-activated receptor-alpha and atherosclerosis: from basic mechanisms to clinical implications. Cardiol Rev 2005;13:240–6.
[108] Han SH, Quon MJ, Koh KK. Beneficial vascular and metabolic effects of peroxisome proliferator-activated receptor-{alpha} activators. Hypertension 2005;46:1086–92.
[109] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.
[110] Keen H, Jarrett RJ. The WHO multinational study of vascular disease in diabetes: 2. Macrovascular disease prevalence. Diabetes Care 1979;2:187–95.
[111] Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972;30:595–602.
[112] Belke DD, Larsen TS, Gibbs EM, Severson DL. Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. Am J Physiol Endocrinol Metab 2000;279:E1104–13.
[113] Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. Biochim Biophys Acta 2005;1734:112–26.
[114] Paulson DJ, Crass III MF. Endogenous triacylglycerol metabolism in diabetic heart. Am J Physiol 1982;242:H1084–94.
[115] Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. Cardiovasc Res 1997;34:25–33.
[116] Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Jeong Yun U, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology 2005.
[117] Depre C, Young ME, Ying J, Ahuja HS, Han Q, Garza N, et al. Streptozotocin-induced changes in cardiac gene expression in the absence of severe contractile dysfunction. J Mol Cell Cardiol 2000;32:985–96.
[118] Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 2000;97:1784–9.