Abstract—The heart has a tremendous capacity for ATP generation, allowing it to function as an efficient pump throughout the life of the organism. The adult myocardium uses either fatty acid or glucose oxidation as its main energy source. Under normal conditions, the adult heart derives most of its energy through oxidation of fatty acids in mitochondria. However, the myocardium has a remarkable ability to switch between carbohydrate and fat fuel sources so that ATP production is maintained at a constant rate in diverse physiological and dietary conditions. This fuel selection flexibility is important for normal cardiac function. Although cardiac energy conversion capacity and metabolic flux is modulated at many levels, an important mechanism of regulation occurs at the level of gene expression. The expression of genes involved in multiple energy transduction pathways is dynamically regulated in response to developmental, physiological, and pathophysiological cues. This review is focused on gene transcription pathways involved in short- and long-term regulation of myocardial energy metabolism. Much of our knowledge about cardiac metabolic regulation comes from studies focused on mitochondrial fatty acid oxidation. The genes involved in this key energy metabolic pathway are transcriptionally regulated by members of the nuclear receptor superfamily, specifically the fatty acid–activated peroxisome proliferator-activated receptors (PPARs) and the nuclear receptor coactivator, PPARγ coactivator-1α (PGC-1α). The dynamic regulation of the cardiac PPAR/PGC-1 complex in accordance with physiological and pathophysiological states will be described. (Circ Res. 2004;95:568-578.)

Key Words: mitochondria ■ fatty acids ■ peroxisome proliferator-activated receptor ■ gene regulation ■ PPARγ
uptake is coupled to esterification by fatty acyl-CoA synthetase (FACS).\textsuperscript{6} The resulting long-chain acyl-CoAs are converted by carnitine palmitoyltransferase I (CPT I) to their carnitine derivatives, which are transported into the mitochondria and enter the \( \beta \)-oxidation pathway (Figure 1).

Myocardial fuel selection is highly influenced by developmental stage and physiological/pathophysiological conditions (see review\textsuperscript{2}). Much of this regulation is achieved by coordinated changes in the expression of genes involved in cellular FA utilization. For example, a switch in cardiac fuel preference from glucose to FAs occurs during the fetal to newborn transition when \( O_2 \) availability and dietary fat content abruptly increase.\textsuperscript{8,9} The expression of genes encoding enzymes of FA uptake and \( \beta \)-oxidation is coordinately increased in parallel with this perinatal energy substrate switch. The critical importance of this metabolic switch in postnatal adaptation is evidenced in children with mutations in the FA-oxidation enzyme MCAD and VLCAD, who develop hepatic dysfunction when \( O_2 \) availability and dietary fat content abruptly increase.\textsuperscript{8,9} These proteins contain an NH\textsubscript{2}-terminal ligand-activated receptors. The remaining “orphan” NRs have no identified ligands, although it is likely that modulating ligands will be identified for some of these receptors. Because the heart must adapt to continuously changing energy demands but has limited capacity for storing FAs or glucose, myocardial energy substrate flux must be tightly matched with demand. Ligand-activated NRs are poised to rapidly respond to fluctuating substrate levels. As will be described later, the peroxisome proliferator-activated receptors (PPARs), as FA-activated NRs, are now recognized as key regulators of cardiac FA metabolism.

In addition, evidence is emerging that a select group of orphan NRs serve novel roles in regulating cardiac energy metabolism.\textsuperscript{7}

NRs have a conserved modular domain structure (Figure 2A). These proteins contain an NH\textsubscript{2}-terminal ligand-independent transcriptional activation (AF-1) domain, a conserved zinc-finger DNA binding domain (DBD), and a composite COOH-terminal region that includes the ligand binding domain (LBD) and a conserved ligand-dependent activation function (AF-2). NRs bind to regulatory DNA elements in target genes as homodimers, heterodimers, or in some cases as monomers. Unlike the classic steroid receptors that function as homodimers, many of the NRs involved in nutrient sensing and metabolic regulation heterodimerize with the retinoid X receptor (RXR).\textsuperscript{23} NR regulatory DNA elements are composed of variably spaced hexameric half-sites (AGGTCA) arranged as direct, indirect, or everted repeats. Once bound to their specific response element, receptors recruit coactivator proteins often coincident with displacement of corepressor proteins (Figure 2B). For ligand-activated receptors, it is through ligand binding that the LBD adopts a permissive conformation for coactivator interaction. More than 100 coactivator proteins have been identified for NRs, including ATP-dependent chromatin remodeling complexes, histone acetylases, histone methyltransfersases, and

**Nuclear Receptors: A Brief Primer**

Nuclear receptor (NR) transcription factors are particularly well-suited for regulating the cardiac metabolic gene program. NRs were originally described as ligand-dependent transcription factors, which is the case for roughly half the mammalian NRs.\textsuperscript{21} Ligand-activated receptors include the classical endocrine receptors that respond to steroid hormones or thyroid hormone. In recent years, a number of receptors identified without prior insight to their ligands have been shown to respond to dietary-derived lipid intermediates, including long-chain FAs, oxysterols, and bile acids.\textsuperscript{22–24} These receptors are generally involved in feed-forward regulation of pathways involved in the metabolism of these activating ligands. The critical importance of these activating ligands. The remaining “orphan” NRs have no identified ligands, although it is likely that modulating ligands will be identified for some of these receptors. Because the heart must adapt to continuously changing energy demands but has limited capacity for storing FAs or glucose, myocardial energy substrate flux must be tightly matched with demand. Ligand-activated NRs are poised to rapidly respond to fluctuating substrate levels. As will be described later, the peroxisome proliferator-activated receptors (PPARs), as FA-activated NRs, are now recognized as key regulators of cardiac FA metabolism. In addition, evidence is emerging that a select group of orphan NRs serve novel roles in regulating cardiac energy metabolism.

NRs have a conserved modular domain structure (Figure 2A). These proteins contain an NH\textsubscript{2}-terminal ligand-independent transcriptional activation (AF-1) domain, a conserved zinc-finger DNA binding domain (DBD), and a composite COOH-terminal region that includes the ligand binding domain (LBD) and a conserved ligand-dependent activation function (AF-2). NRs bind to regulatory DNA elements in target genes as homodimers, heterodimers, or in some cases as monomers. Unlike the classic steroid receptors that function as homodimers, many of the NRs involved in nutrient sensing and metabolic regulation heterodimerize with the retinoid X receptor (RXR).\textsuperscript{23} NR regulatory DNA elements are composed of variably spaced hexameric half-sites (AGGTCA) arranged as direct, indirect, or everted repeats. Once bound to their specific response element, receptors recruit coactivator proteins often coincident with displacement of corepressor proteins (Figure 2B). For ligand-activated receptors, it is through ligand binding that the LBD adopts a permissive conformation for coactivator interaction. More than 100 coactivator proteins have been identified for NRs, including ATP-dependent chromatin remodeling complexes, histone acetylases, histone methyltransfersases, and

---

**Figure 1.** Pathways involved in cardiac energy metabolism. FA and glucose oxidation are the main cardiac ATP producing pathways. Genes encoding enzymes involved in multiple stages of these metabolic pathways (ie, uptake, esterification, mitochondrial transport, oxidation) are regulated transcriptionally by NRs. The 4 mitochondrial \( \beta \)-oxidation reactions are (1) Acyl-CoA dehydrogenase, (2) Enoyl-CoA hydratase, (3) 3-hydroxyacyl-CoA dehydrogenase, (4) 3-Ketoacyl-CoA thiolase. Acetyl-CoA produced by FA and glucose oxidation pathways is further oxidized in the TCA cycle to generate NADH and FADH\textsubscript{2}, which enter the electron transport/oxydative phosphorylation pathway. FA indicates fatty acid; TCA, tricarboxylic acid; FAO, fatty acid oxidation; Cytc, cytochrome c.
RNA polymerase II recruiting complexes, that open up the chromatin structure and facilitate binding of basal transcription factors and RNA polymerase II. Histone-modifying proteins are often recruited into complexes by adapter proteins, which lack catalytic activity, bound to the NR LBD. One such adapter/coactivator, the PPAR coactivator-1 (PGC-1), serves as a key link between physiological cues and metabolic regulation in heart.

**PPARs: Regulators of Cardiac FA Metabolism**

The peroxisome proliferator-activated receptors (PPAR) are involved in various aspects of lipid metabolism. Three PPAR isoforms have been identified: PPARα, PPARβ/δ (hereafter PPARβ), and PPARγ. All three PPARs are activated by FAs and bind as obligate heterodimers with RXR to the consensus response element, AGGTCAAGGTCA (direct repeat with a single nucleotide spacing), within the regulatory regions of target genes. Functional specificity among the PPARs is achieved by isoform-specific tissue distribution, ligands, and cofactor interactions. PPARα has been characterized as the central regulator of mitochondrial FA catabolism, whereas PPARγ is thought to primarily regulate lipid storage. Until recently, the function of PPARβ was relatively unexplored. However, several lines of evidence suggest that all three isoforms modulate cardiac energy metabolism.

**PPARα**

PPARα is thought to be the primary transcriptional regulator of fat metabolism in tissues with high FA oxidation rates, such as heart, liver, kidney, and skeletal muscle. Although the endogenous ligand for PPARα has not been identified, PPARα is activated by a number of lipid-derived molecules, including long-chain FAs, eicosanoids, and leukotriene B4. The fibrate class of hyperlipidemic drugs, including fenofibrate and gemfibrozil, are synthetic PPARα ligands. In studies using gain- and loss-of-function strategies, genetically altered mice have shown that PPARα regulates genes involved in virtually every step of cardiac FA utilization including (1) FA uptake, (2) thioesterification to fatty acyl-CoA, (3) transport into the mitochondria, and (4) mitochondrial β-oxidation (Figure 1 and Table). The gene encoding medium-chain acyl-CoA dehydrogenase (MCAD), which catalyzes the first step in the β-oxidation pathway, was the first energy metabolic target identified for PPARα. The complex response element (NRRE-1) conferring PPARα responsiveness binds several NRs and dictates the developmental and FA responsiveness of the MCAD gene.

Definitive evidence for PPARα as a key regulator of cardiac energy metabolism has been provided by the PPARα “knockout” (PPARα−/−) mouse studies. Constitutive expression of genes involved in FA uptake (CD36/FAT, FATP, FACS-I), mitochondrial transport (CPT I, CPT II), and β-oxidation (MCAD, VLCAD, SCAD, SCHAD, trifunctional protein α) are decreased in hearts of PPARα−/− mice. Correspondingly, myocardial long chain FA uptake and oxidation rates are diminished in PPARα−/− hearts. Despite these metabolic derangements, cardiac function is maintained in unstressed adult animals. However, a fasting stress, which in wild-type mice induces cardiac β-oxidation enzyme gene expression, causes hypoglycemia and hepatic and cardiac triglyceride accumulation in PPARα−/− mice. With aging, PPARα−/− mice develop cardiac fibrosis and myofibrillar fragmentation associated with abnormal mitochondrial ultrastructure.
Murine PPARα gain-of-function strategies have also provided important evidence for the role of PPARα as a direct regulator of myocardial energy metabolic genes. Cardiac-specific PPARα overexpression (MHC-PPARα mice) activates expression of FA utilization genes.20 Metabolic studies showed that FA uptake and oxidation are increased in MHC-PPARα hearts, whereas glucose utilization is reciprocally decreased.20,42 Diminished glucose utilization is explained, in part, by well-described inhibitory effects of acetyl-CoA/CoASH, ATP/ADP, and NADH/NAD ratios, increased during high rates of FA oxidation, on the activity of the PDH complex.33,44 However, the reciprocal reduction in myocardial glucose oxidation in MHC-PPARα mice also involves gene regulatory effects. Expression of pyruvate dehydrogenase kinase 4 (PDK4), which decreases glucose oxidation through PDH inhibition, is markedly induced in MHC-PPARα hearts. In addition, the glucose transporter, GLUT4, and the glycolytic enzyme phosphofructokinase are downregulated in MHC-PPARα hearts.20 These results suggest that PPARα links circuits involved in reciprocal gene regulatory “crosstalk” between myocardial FA and glucose utilization. Collectively, the results of in vivo studies indicate that PPARα activates expression of genes involved in cardiac FA utilization and mediates dynamic metabolic regulation in response to diverse physiological stimuli allowing the heart to meet energy demands and maintain tight lipid balance.

PPARβ: An Emerging Player in the Regulation of Cardiac Energetics

Among the PPAR isoforms, PPARβ displays an expression pattern least suggestive of a distinct role in lipid metabolism. It is detectable in numerous cell types within all major organ systems, in contrast to PPARα and PPARγ, which are highly expressed in fat utilization or fat storage tissues, respectively.28,29,45 However, PPARβ is activated by FAs and the triglyceride component of VLDL particles implicating this NR in the regulation of lipid metabolism.64,67 Independent analyses of PPARβ−/− gene deletion have revealed varied phenotypic effects in skin, adipose, placenta formation and brain.48–50 Notably, one line of PPARβ−/− mice was deficient in brown and white adipose formation, supporting a role for PPARβ in lipid homeostasis.59

Gain-of-function studies involving PPARβ overexpression or treatment with selective PPARβ agonists have demonstrated a role for PPARβ in regulating expression of FA utilization enzymes and increasing FAO rates in skeletal muscle cells.51–53 Activation of the PPARβ regulatory pathway in vivo has been shown to increase lipid catabolism when ectopically expressed white adipose,54 to enrich slow-twitch oxidative fiber in skeletal muscle,55 and to increase skeletal muscle FAO and improve serum lipid profiles and insulin sensitivity in several obesity models in mice.56–58

Recent studies focusing on the role of PPARβ in cardiac metabolism have shown that PPARβ selective ligands induce expression of mitochondrial FAO enzymes and increase palmitate oxidation rates in neonatal and adult cardiac myocytes as effectively as PPARα-selective ligands.59,60 Furthermore, PPARβ activation rescues expression of FAO enzyme genes that are reduced at baseline in PPARα−/− cardiomyocytes.59,61

These results highlight the regulatory overlap between PPARα and PPARβ. It is unclear, however, whether PPARα and PPARβ regulate discrete, albeit overlapping, sets of genes or superimposed pathways. PPARα and PPARβ are not functionally redundant. PPARα−/− mice are phenotypically normal at baseline, but display myocardial lipid accumulation subacutely when subjected to a metabolic stress, and progressively with age, suggesting that PPARβ cannot compensate for PPARα under all physiological circumstances.37,40,62

PPARγ

PPARγ is primarily a regulator of lipid storage and is essential for adipose formation.22,63 Although its expression is adipose tissue–enriched, PPARγ is also expressed at low levels in extra-adipose tissues including the vascular wall, skeletal muscle, pancreatic β-cell, and heart. Thiazolidinediones (TZDs), such as pioglitazone, are PPARγ ligands used as insulin sensitizers to treat type II diabetes.64 TZDs are thought to mediate their effects largely through PPARγ activation in adipose tissue and skeletal muscle. In adipose tissue, PPARγ activation promotes glucose uptake and triglyceride synthesis/storage and inhibits lipolysis, which concurrently increase adipose mass and reduce serum glucose and free FAs. In skeletal muscle, the role of PPARγ remains controversial. Murine loss-of-function studies have provided conflicting results regarding the direct role of the muscle PPARγ pathway in the development of whole body insulin resistance and in insulin-sensitization by TZDs.65,66

It is generally thought that PPARγ modulates cardiac FA utilization through its effects on extra-cardiac tissues. Changes in circulating FAs resulting from PPARγ mediated effects on lipid storage will directly modulate PPARα and PPARβ activity and affect insulin sensitivity in the heart. Adipose tissue also secretes various signaling factors, such as tumor necrosis factor-α, leptin, and adiponectin that affect insulin sensitivity and metabolism in heart and other tissues.57,64 Direct regulation of cardiac metabolism by PPARγ is a subject of considerable debate. PPARγ is expressed in the heart at levels far below PPARα and β, and PPARγ ligands do not affect metabolic gene expression or FAO rates in cultured cardiac myocytes.59 However, PPARγ activation has been shown to inhibit the induction of hypertrophy markers in cardiac myocytes in response hypertrophic stimuli, suggesting that PPARγ is functional in these cells. Further studies using cardiac-specific PPARγ deletion will be required to determine PPARγ regulation of cardiac gene expression is mediated by direct or indirect mechanisms.

PGC-1 Family: Inducible NR Coactivators and Integrators of Cardiac Metabolic Gene Regulatory Pathways

PGC-1α was initially identified as a PPARγ coactivator, linked to adaptive thermogenesis in brown adipose.69 Two structurally related proteins, PGC-1β and PRC, have subsequently been cloned and shown to also regulate energy metabolic pathways.70–74 The tissue-specific and inducible nature of PGC-1α expression reflects its role in the dynamic regulation of cellular energy metabolic processes, including mitochondrial biogenesis and oxidation, hepatic gluconeogenesis, and skeletal
PGC-1α mediates its broad metabolic regulatory effects through coactivation of numerous transcription factor partners, including many NRs. Most relevant to the current focus are those linked to cardiac energy metabolism. PGC-1α coactivates PPARα and enhances FA-dependent regulation of PPARα responsive genes involved in the FAO pathway. PPARβ is also a transcriptional partner for PGC-1α. Consistent with its functional interaction with PPARs, PGC-1α activates expression of genes involved in FA uptake and oxidation when overexpressed in cardiac myocytes. Recent studies, discussed later, have implicated additional orphan NRs in mediating PGC-1α regulation of cardiac energy metabolism.

In addition to activating FA metabolic pathways via PPARs, PGC-1α has been shown to increase mitochondrial oxidative capacity in multiple cell and tissue models. PGC-1α overexpression increases mitochondrial number in brown adipocytes and skeletal and cardiac myocytes. In skeletal myocytes, PGC-1α primarily increases uncoupled respiration associated with induction of uncoupling proteins 2 (UCP2) and 3 (UCP3). In vivo PGC-1α effects on mitochondrial number and respiration causes a skeletal muscle fiber-type switch from fast glycolytic to slow oxidative. In cardiac myocytes, PGC-1α drives mitochondrial biogenesis, increases FAO and overall mitochondrial oxidative capacity in the form of ATP-generating, coupled respiration.

Estrogen-Related Receptors: Emerging Role for Orphan NRs in Regulating Cardiac Energy Metabolism

Evidence is emerging that the estrogen-related receptor (ERR) family of orphan NRs function as PGC-1α-activated regulators of cardiac and skeletal muscle energy metabolism. There are three members of the ERR family: ERRα, ERRβ, and ERRγ. ERRα and ERRγ expression is enriched in...
adult tissues that rely primarily on mitochondrial oxidative metabolism for ATP production, such as heart and slow-twitch skeletal muscle.\(^{99,101,102}\) ERR\(\alpha\) expression dramatically increases in heart after birth, in parallel with the global upregulation of enzymes involved in cellular FA uptake and mitochondrial oxidation.\(^{103}\) Recently, ERR\(\alpha\) and ERR\(\gamma\) were identified as novel partners for the PGC-1 family of coactivators.\(^{74,103-105}\) This functional relationship between ERR isoforms and PGC-1\(\alpha\) have stimulated interest in the role of ERRs in energy metabolism.

Deletion of the ERR\(\alpha\) gene reveals a tissue-specific role for ERR\(\alpha\) in constitutive regulation of lipid metabolism.\(^{106}\) White adipose mass is decreased in ERR\(\alpha\)^{−/−} mice coincident with decreased adipocyte size and lipid synthesis rates. In contrast, ERR\(\alpha\) likely plays a role in lipid catabolism in heart, consistent with its functional interaction with PGC-1\(\alpha\). ERR\(\alpha\)^{−/−} mice, which do not display an overt cardiac phenotype, exhibit a compensatory increase in cardiac PGC-1\(\alpha\) and ERR\(\gamma\) expression (J. Huss, unpublished data, 2004). These results suggest that ERR isoforms contribute to constitutive expression of FA metabolic genes in heart. However, the metabolic effects of the observed gene expression changes remain to be explored.

Gene expression profiling in cardiac myocytes overexpressing ERR\(\alpha\) have begun to identify cardiac ERR\(\alpha\) target genes. ERR\(\alpha\) activates genes involved in energy production pathways, including cellular FA uptake (LPL, CD36/FAT, H-FABP, FACS-1), \(\beta\)-oxidation (MCAD, VLCAD, LCHAD), and mitochondrial electron transport/oxidative phosphorylation (cytochrome c, COXIV, COXVIII, NADH ubiquinone dehydrogenase, flavoprotein-ubiquinone oxidoreductase, ATP synthase \(\beta\)). ERR\(\alpha\) also increases palmitate oxidation rates in cardiac myocytes. Activation of \(\beta\)-oxidation enzymes genes by ERR\(\alpha\) involves the PPAR\(\alpha\) signaling pathway. ERR\(\alpha\) directly activates PPAR\(\alpha\) gene expression, and ERR\(\alpha\)-mediated regulation of MCAD and M-CPT I is abolished in cells derived from PPAR\(\alpha\)^{−/−} mice (J. Huss, unpublished data, 2004). Recently, ERR\(\alpha\) has also been shown to be involved in the PGC-1\(\alpha\) regulation of mitochondrial biogenesis.\(^{107,108}\) ERR\(\alpha\) was found to mediate PGC-1\(\alpha\) activation of the NRF pathway through regulation of the \(\text{Gap}b\) gene, which encodes a subunit of the NRF-2 complex.\(^{108}\) ERR\(\alpha\) also directly activates genes involved in mitochondrial oxidative metabolism at the level of transcription. ERR\(\alpha\) with its coactivator PGC-1\(\alpha\) activates the MCAD,\(^{101-103}\) cytochrome c, and ATP synthase \(\beta\) gene promoters.\(^{107}\) Collectively, these results identify ERR\(\alpha\) as a regulator of cardiac oxidative energy metabolism through its involvement in the PGC-1 regulatory circuit. Studies using animal models of cardiac-specific ERR\(\alpha\) and ERR\(\gamma\) activation or inactivation will be essential to delineate the precise biologic roles of ERRs in heart.

**Altered NR Signaling in the Diseased Heart: Driver or Passenger?**

A central question regarding cardiac metabolism is the role that perturbations in cardiac energy transfer pathways play in the development of pathological cardiac remodeling and heart failure. Inherited and acquired forms of heart failure are associated with an overall decrease in mitochondrial oxidative capacity and a shift away from FA oxidation toward glucose utilization (Figure 4).\(^{19,109,110}\) It is unclear whether this metabolic shift is a protective response allowing the heart to maintain contractile function or an initial step in progressive decompensation. Conversely, diabetic cardiomyopathy develops in the context of chronically high FAO and inhibited glucose uptake and oxidation. Although this switch in fuel utilization may initially be adaptive, the drive on FA utilization and loss of substrate utilization flexibility may become an etiologic component of the disease.\(^{111,112}\)

**Altered PPAR\(\alpha\) Signaling in Pressure Overload Induced-Hypertrophy and Heart Failure**

During the progression of pathological cardiac hypertrophy in animal models and humans, the heart undergoes a shift from FAO toward increased glucose utilization (Figure 4).\(^{13,113}\) This metabolic switch is driven by the coordinated counter-regulation of FAO and glucose-metabolizing enzyme genes.\(^{14,19}\) Evidence implicates deactivation of the PPAR\(\alpha\) signaling pathway as the mechanism driving downregulation of FAO genes in the hypertrophied heart. Reduced expression and activity of PPAR\(\alpha\) closely correlates with decreased \(\beta\)-oxidation observed in car-
Diabetic Cardiomyopathy

Epidemiological studies have demonstrated that the incidence of cardiomyopathy in diabetics is significantly increased independent of additional risk factors, such as hypertension and vascular disease, present in diabetics. Therefore, attention has focused on the role diabetes-related metabolic dysregulation plays in the development of cardiomyopathy. In the diabetic state, cardiac energy demands are almost entirely fueled by FAO, a consequence of impaired glucose uptake and metabolism attributable to myocardial insulin resistance and increased circulating FAs. Leptin-deficient obese (ob/ob) mice and Zucker fatty rats exhibit myocardial triglyceride accumulation and increased expression of genes involved in lipid uptake and triglyceride synthesis. In both models, ventricular mass was increased. Functionally, decreased contractile function observed in Zucker fatty rats was attributed to lipotoxic effects of the accumulated lipid species. These studies implicate defective PPARα signaling in these models, causing a mismatch between FA uptake and metabolism. Indeed, the cardiac PPARα signaling pathway is activated in diabetic rodent models, including streptozotocin (STZ)-induced diabetes and the obese db/db mice, as evidenced by increased expression of PGC-1α, PPARα, and downstream metabolic target genes. Furthermore, PPARα−/− mice are resistant to cardiomyopathy that develops in STZ-induced diabetic wild-type mice. The observed induction of cardiac PGC-1α expression in diabetic mice contrasts with the downregulation of PGC-1α and mitochondrial oxidative phosphorylation enzymes reported in insulin resistant skeletal muscle.

The MHC-PPARα model has demonstrated a direct relationship between the chronic drive on myocardial FA metabolism and the development of cardiomyopathy. Cardiac PPARα overexpression replicates the diabetic metabolic profile: myocardial triglyceride accumulation, increased FAO rates, and decreased glucose uptake and metabolism. MHC-PPARα mice develop ventricular hypertrophy and dysfunction that is exacerbated with high fat feeding. These studies demonstrate the relationship between cardiac metabolic derangement and dysfunction and suggest that PPARα-driven increases in FA uptake and oxidation contribute to diabetic cardiomyopathy. Cardiac dysfunction in MHC-PPARα mice may be caused by toxic effects of myocardial lipid accumulation or free radical damage from chronically high oxidative flux. This model has important implications for human disease because it mimics the cardiac metabolic derangement that is chronic in obesity-related disorders, particularly type II diabetes.

Implications from studies of the MHC-PPARα mice are that activation of PPARα and downstream FA metabolism may contribute to heart failure progression in the diabetic. Thus, PPARα inhibition may be a means to delay or prevent heart failure in diabetic patients. Inhibiting mitochondrial β-oxidation with 3-ketoacyl-CoA thiolase inhibitors, such as trimetazidine, increased cardiac efficiency in patients with diabetes and ischemic cardiomyopathy by shifting metabolism toward glucose oxidation. However, chronic FAO inhibition may also predispose the heart to lipid accumulation and subsequent lipotoxicity. Furthermore, PPARα agonists are used to treat hyperlipidemia, a major risk factor for atherosclerosis. Bezlafibrate and gemfibrozil improve serum lipid profiles in type II diabetics, reducing serum triglycerides and increasing HDL levels. The VA-HIT study, which investigated the link between diabetes and cardiovascular outcomes, showed that gemfibrozil treatment reversed the increased incidence of major cardiovascular events associated with diabetes and low HDL cholesterol. The weight of clinical data suggests that systemic activation of the PPARα pathway in diabetics improves cardiovascular outcome likely via extracardiac effects. Clearly, additional studies are necessary to predict the effects of modulating lipid metabolism in the prevention and treatment of cardiomyopathy in the diabetic.

Future Directions

This review sought to provide a view of the current state of knowledge regarding the regulation of cardiac metabolism by NRs. As ligand-responsive transcription factors, NRs are well suited to respond to fluctuations in substrates and metabolic intermediates and to regulate pathways involved in their catabolism. Given the explosion of new information about PPARs and the development of isoform-specific PPAR agonists, this group comprises an important potential therapeutic target to modulate cardiac energy metabolism. Several chal-
challenges must be addressed to use NR modulators as therapeutic agents for myocardial disease. We must first determine whether NR-driven alterations in cardiac metabolism are adaptive or maladaptive in the hypertrophied or diabetic state. Another important consideration is the lack of tissue specificity of the compounds. Future studies combining tissue-selective genetic mouse models and pathophysiological models of hypertrophy and diabetes will test the utility of existing and novel NR ligands as potential therapies for heart failure.

Acknowledgments

This work was supported by NIH grants R01 DK45416, R01 HL58493, POI HL57278, and the Digestive Diseases Core Center Grant P30 DK52574 (D.P.K.). J.M.H. is supported by NIH grant K01 DK063051 and the Washington University School of Medicine Diabetes Research Training Center P60 DK20579 (J.M.H.). We thank Laurie K. Russell for allowing discussion of unpublished data. We also thank Mary Wingate for expert assistance in manuscript preparation.

References


Huss and Kelly

Nuclear Receptor and Cardiac Energetics 577


Nuclear Receptor Signaling and Cardiac Energetics
Janice M. Huss and Daniel P. Kelly

Circ Res. 2004;95:568-578
doi: 10.1161/01.RES.0000141774.29937.e3
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/95/6/568

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/