PPARs of the Heart
Three Is a Crowd

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The peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors within the broad nuclear receptor superfamily. The PPAR family includes three members encoded by distinct genes: \( \alpha \), \( \beta/\delta \), and \( \gamma \) (see reviews\(^1\)\(^2\)). PPAR\( \alpha \) was originally identified as the intracellular receptor for a class of nongenotoxic rodent hepatocarcinogens, which includes the hypolipidemic drug clofibrate, a potent inducer of hepatic peroxisomal proliferation and hypolipidemic agent. The three PPARs are now distinguished by tissue- and developmentally specific patterns of expression and by the distinct, albeit overlapping, nature of ligands capable of activating each receptor. PPAR\( \alpha \), which is abundant in tissues with high rates of mitochondrial fatty acid oxidation, such as heart, liver, and kidney, regulates a wide variety of target genes involved in cellular lipid catabolism. In contrast, PPAR\( \gamma \), an adipose-enriched nuclear receptor, directs the expression of genes involved in adipocyte differentiation and fat storage. The function of the ubiquitously expressed PPAR\( \beta/\delta \), is not well understood although some evidence suggests that it exerts actions on the epidermis and activates antiinflammatory programs. Ligand activation of PPARs leads to obligate heterodimerization with the 9-cis retinoic acid–activated receptor, RXR, promoting binding of the complex to cognate DNA response elements within PPAR target gene promoter regions (Figure). A variety of natural and synthetic compounds including fatty acids, eicosanoids, and arachidonic acid derivatives can serve as activators of the PPARs, some in a receptor-specific manner. However, the true endogenous ligands have not been identified.

PPAR\( \alpha \) has been shown to fulfill a critical role in the regulation of myocardial lipid and energy metabolism.\(^2\) PPAR\( \alpha \) activates the transcription of genes involved in every step of the cardiac myocyte fatty acid utilization pathway from uptake to mitochondrial fatty acid oxidation leading to ATP production. Accordingly, the activity of PPAR\( \alpha \) is an important determinant of myocardial energy production. As a fatty acid–activated transcription factor, PPAR\( \alpha \) also serves to match cardiac lipid delivery to oxidative capacity, a “lipostat” function. The activity of the PPAR\( \alpha \) gene regulatory pathway is altered in a variety of common myocardial diseases. In the pathologically hypertrophied heart, PPAR\( \alpha \) expression and activity are diminished, leading to a reduction in the capacity for fatty acid oxidation and increased rates of glucose utilization.\(^3\) The functional consequences of this metabolic switch are unknown, but some evidence indicates that it serves to preserve ventricular function in the context of chronic pressure overload.\(^4\) Similarly, the expression and activity of both RXR and PPARs are reduced in the hypoxic cardiac myocyte.\(^5\)\(^6\) Conversely, the activity of PPAR\( \alpha \) and its downstream targets are abnormally activated in the diabetic heart, leading to a marked increase in the uptake and oxidation of fatty acids. Recent evidence indicates that chronic activation of the cardiac PPAR\( \alpha \) pathway, such as occurs in the diabetic heart, may lead to myocardial lipid accumulation and features of diabetic cardiomyopathy.\(^7\)

In contrast to the explosion of new information about the cardiac PPAR\( \alpha \) gene regulatory pathway, little is known about the relative expression and functions of PPAR\( \gamma \) or PPAR\( \beta/\delta \) in heart. The role of PPAR\( \gamma \) as a critical regulator of adipose development and metabolism has been extensively characterized.\(^1\) PPAR\( \gamma \) agonists, several of which have been developed as therapeutic agents, improve insulin sensitivity in the diabetic patient.\(^1\) Recent studies have suggested that PPAR\( \gamma \) agonists are cardioprotective against ischemic insult\(^6\)\(^9\) and may modulate the cardiac hypertrophic growth response.\(^10\)\(^11\) However, the exact mechanisms whereby PPAR\( \gamma \) exerts its effects on cardiac metabolism and function are unclear. Given that the main target for PPAR\( \gamma \) is adipose tissue, it is possible that cardiac effects are due to indirect mechanisms. Essentially nothing is known about the activity and function of PPAR\( \beta/\delta \) in heart. However, previous studies have shown that the expression of PPAR\( \beta/\delta \) is expressed at levels similar to PPAR\( \alpha \), suggesting that it likely controls the expression of cardiac genes.\(^1\)\(^2\) Notably, most studies describing the cardiac expression of PPAR\( \gamma \) and PPAR\( \beta/\delta \) were performed with whole tissue extracts so that the relative expression in the myocyte versus nonmyocyte fraction, including pericardial adipocytes, has not been delineated.

The study by Gilde et al in this issue of Circulation Research\(^1\)\(^2\) provides important new information about the expression and function of PPAR\( \gamma \) and PPAR\( \beta/\delta \) in heart. The authors performed a careful analysis of the relative expression levels and activities of PPAR\( \alpha \), \( \beta/\delta \), and \( \gamma \) in isolated neonatal and adult rat cardiac myocytes. They found that both PPAR\( \alpha \) and PPAR\( \beta/\delta \) were expressed in comparably abundant levels. In contrast, PPAR\( \gamma \) was barely detectable. Exposure of cardiac myocytes to PPAR-specific ligands resulted in the activation of known endogenous PPAR target
genes in a pattern that paralleled PPAR isotype-specific expression levels. Specifically, exposure of myocytes to PPARα- or β/δ-specific agonists or long-chain fatty acids led to a significant induction of known PPAR target genes involved in fatty acid uptake and oxidation whereas a PPARγ agonist had no effect. These results contribute two new and significant findings to our understanding of cardiac PPAR biology. First, PPARγ levels and activity are low to absent in isolated rat cardiac myocytes. Second, PPARβ/δ is relatively abundant, fatty acid inducible, and activates the expression of known PPAR target genes involved in fatty acid utilization in cardiac myocytes.

The results of the study by Gilde et al. suggest that most of the cardiac effects of PPARγ may be mediated by indirect mechanisms. Previous studies have generally shown low levels of PPARα in heart and myocytes. However, several recent studies have indicated that PPARγ exerts cardiac effects. For example, studies using PPARγ-specific agonists have shown that activation of PPARγ inhibits the cardiac hypertrophic response to pressure overload. Others have reported that PPARγ agonists promote cardiac hypertrophy. The use of PPARγ agonists has been shown to reduce myocardial injury and dysfunction caused by ischemia/reperfusion. The mechanisms responsible for the cardiac effects of PPARα are unknown but effects on lipid and glucose metabolism or antiinflammatory responses have been suggested. The results of the study by Gilde et al. indicate that some or all of the cardiac effects following activation of the PPARγ pathway occur via indirect mechanisms. Potential indirect mechanisms could include changes in the delivery of glucose and fatty acids to the heart via actions on adipose metabolism. Alternatively, the cardiac response to PPARγ could be secondary to the effects of an extracardiac-derived circulating factor. It is important to note that the present results of Gilde et al. do not exclude the possibility that expression and activity of PPARγ may be induced in the heart under certain physiological or pathophysiological conditions.

In contrast to the wealth of information regarding the biologic functions of PPARα and γ, relatively little is known about PPARβ/δ. Recent evidence has implicated PPARβ/δ in the modulation of cellular differentiation and inflammatory responses of the epidermis. PPARβ/δ-specific agonists have been shown to increase the expression of noncardiac cellular lipid metabolic pathways including fatty acid thioesterification and cholesterol efflux. The study by Gilde et al. provides important new information about the role of PPARβ/δ in cardiac myocytes. The authors show that PPARβ/δ is expressed at levels similar to PPARα in myocytes, stimulates the expression of known PPAR targets involved in cellular fatty acid utilization, and is activated by fatty acids in this cellular context. This latter finding is particularly interesting in view of the results of a recent study demonstrating that PPARβ/δ is activated in macrophages by the triglyceride-rich, very-low-density particle. Future studies aimed at further characterizing PPARβ/δ targets and delineating relevant upstream regulatory pathways will be necessary to fully assign cell-specific biologic roles to the cardiac PPARβ/δ pathway.

The Gilde study underscores an important enigma relevant to the field of nuclear receptor biology. Why is it necessary to have two functional PPARs in a single cell type such as the cardiac myocyte? The answer to this question is unknown, but the following possibilities should be considered. First, PPARα and PPARβ/δ may activate overlapping but distinct downstream target metabolic pathways. Although the results of the present study by Gilde et al indicate that PPARβ/δ is capable of activating PPARα gene targets, a more complete analysis is necessary to define the full repertoire of genes downstream of these nuclear receptors. Second, although fatty acids activate both receptors, the bona fide endogenous ligands may be distinct for PPARα and PPARβ/δ. Ligand specificity could provide a mechanism whereby a distinct cellular metabolic response may be elicited by specific upstream lipid signaling pathways. Third, the expression of each PPAR could be regulated independently at the transcriptional or posttranscriptional levels by unique physiological stimuli. Finally, it is possible that PPARα and PPARβ/δ interact with a customized set of coactivators (Figure), providing an additional level of regulatory diversity.

As ligand-activated transcription factors, the PPARs represent an attractive target for the development of therapeutic agents. The results of the study by Gilde et al. add PPARβ/δ to the list of candidate nuclear receptor targets for pharmacologic modulation of cardiac metabolism. However, it will first be necessary to precisely define the biologic and physiological roles and regulatory features of PPARβ/δ in heart and other tissues. The current identification of specific PPARs that reside in heart is an important first step.
References


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