

# Peroxisome Proliferator-Activated Receptor $\alpha$ and Hypertensive Heart Disease

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## Abstract

Peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) is a ligand-activated transcription factor belonging to the nuclear hormone receptor superfamily. It is expressed by cardiomyocytes and regulates gene expression of key proteins involved in myocardial lipid and energy metabolism. Accordingly, the activity of PPAR $\alpha$  is an important determinant of cardiomyocyte lipid homeostasis and ATP production. Currently, animal and human data suggest that deactivation of PPAR $\alpha$  may contribute substantially to phenotypic changes that accompany cardiac growth in conditions of pressure overload, and the hypothesis emerges that a compromised PPAR $\alpha$  activity may participate in the transition from compensated left ventricular hypertrophy to heart failure in hypertensive heart disease. The availability of PPAR $\alpha$  activators (e.g. fibric acid derivatives and statins) must stimulate investigation into the potential cardioprotective actions of these compounds beyond their hypolipidaemic effects and via restoration of PPAR $\alpha$  activity in the hypertrophied and failing heart.

## 1. Introduction

The essential criterion in defining hypertensive heart disease is a greater than normal left ventricular mass in the absence of a cause other than arterial hypertension. However, it is now accepted that, besides left ventricular hypertrophy (LVH), alterations in diastolic or systolic cardiac function, or both, are frequently present in hypertensive patients and may evolve to overt heart failure. In fact, as demonstrated in the Framingham study, arterial hypertension is the most common risk factor for congestive heart failure.<sup>[1]</sup> In addition, hypertension has been shown to contribute to a large proportion of the cases of heart failure in population-based samples.<sup>[2]</sup>

From a pathophysiological point of view, hypertension affects the myocardium at two different stages.<sup>[3]</sup> In both humans and animal models,

pressure overload is characterised by a period of compensation in which concentric LVH normalises systolic wall stress and contractile function is preserved. The period of adaptation, which may last for weeks in rodents and for months to years in humans, is inexorably followed by a transition to heart failure. This transition is characterised by impaired survival, the onset of chamber dilatation with the failure of further concentric hypertrophic growth to normalise load, and progressive contractile dysfunction. A number of observations suggest that the transition to failure relates to remodelling of the myocardium secondary to several mechanisms including cardiomyocyte loss as a result of both apoptosis and necrosis,<sup>[4]</sup> changes in the composition of the motor unit and the cytoskeleton of cardiomyocytes,<sup>[5]</sup> alterations in the turnover of extra-

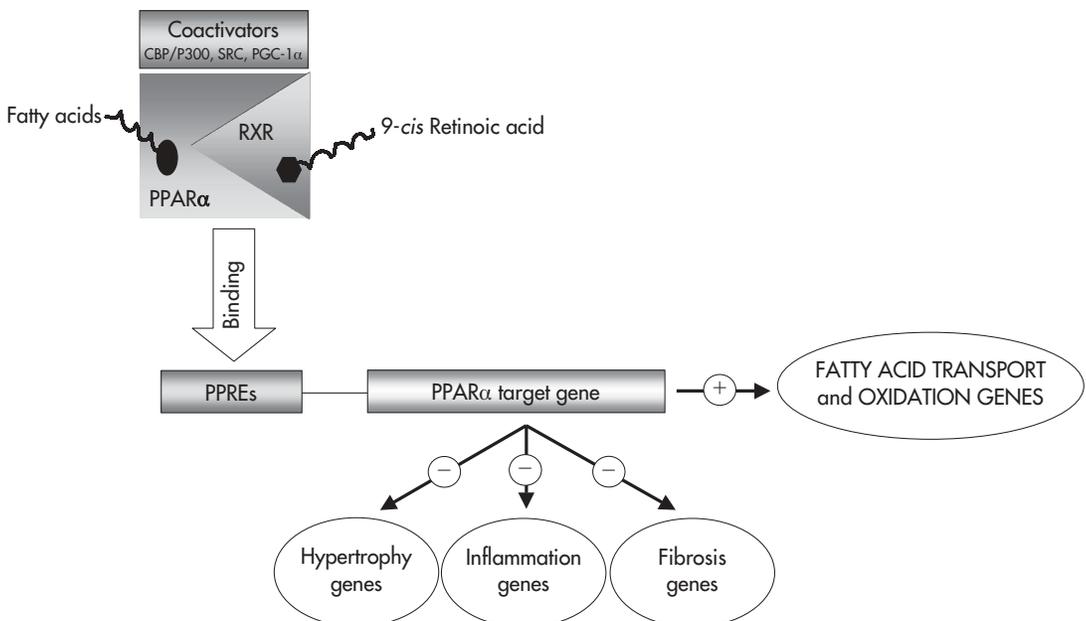
cellular matrix<sup>[6]</sup> and abnormalities in myocardial energy production.<sup>[7]</sup>

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. The PPAR family includes three members encoded by different genes:  $\alpha$ ,  $\beta/\delta$  and  $\gamma$ .<sup>[8]</sup> All three PPARs are expressed in cardiovascular tissue, where they have several metabolic and increasingly recognised cardiovascular effects.<sup>[9,10]</sup> This report focuses on the pathophysiological implications of PPAR $\alpha$  in hypertensive heart disease. Thus, in addition to some consideration of the mechanisms of altered cardiac expression and activity of PPAR $\alpha$  in hypertension, its potential detrimental impact on myocardial energetics and structure and on left ventricular function will be addressed. In addition, the available evidence and the perspectives of strategies aimed at modulating PPAR $\alpha$  activity in the failing heart will be considered.

## 2. General Aspects of PPAR $\alpha$

PPAR $\alpha$  was the first isoform to be identified in the PPAR family. Its expression is high in most tissues with an increased capacity for fatty acid oxidation, such as the heart.<sup>[11]</sup> PPAR $\alpha$  regulates the expression of target genes via binding to DNA response elements (called the peroxisome proliferator response elements, PPRE) with their obligate heterodimeric partner, the retinoid X receptor  $\alpha$  (RXR $\alpha$ )<sup>[12]</sup> (figure 1). The activity of the PPAR $\alpha$ /RXR $\alpha$  complex is modulated by the availability of ligands for PPAR $\alpha$  and RXR $\alpha$ . Whereas activating ligands for PPAR $\alpha$  include synthetic fibric acid derivatives (clofibrate and WY-14643) and fatty acids and their derivatives, RXR $\alpha$  is activated by 9-*cis* retinoic acid.<sup>[13]</sup>

In the inactivated state, PPAR $\alpha$  is bound to co-repressor proteins such as silencing mediator of retinoid and thyroid hormone receptor (SMRT) and



**Fig. 1.** Schematic representation of the cardiac peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) transcriptional regulatory complex. PPAR $\alpha$  binds to sequence-specific target elements (PPREs) as a liganded heterodimer with the retinoid X receptor (RXR). Major target genes are in capital letters and suspected target genes are in small letters. + = stimulation; - = inhibition.

nuclear receptor co-repressor (N-CoR)1. On ligand binding, PPAR $\alpha$  dissociates from co-repressors and recruits co-activators mediating an interaction with a transcriptional regulatory complex that includes pleiotropic binding proteins, such as CBP/p300, SRC1, PBP and PGC-1 $\alpha$ . In contrast to most known co-activators, PGC-1 $\alpha$  is tissue restricted, with high expression in brown adipose tissue and heart.<sup>[14]</sup> Recent findings show that PGC-1 $\alpha$  interacts directly with PPAR $\alpha$  to increase fatty acid oxidation rates, so this co-activator could be an important point in the regulation of PPAR $\alpha$  activity in the heart.<sup>[15]</sup>

Two variants of the human PPAR $\alpha$  transcription factor have been described. Palmer et al.<sup>[16]</sup> found a spliced isoform of PPAR $\alpha$  mRNA lacking the exon 6 in human liver. Later on, this isoform was also reported in other human tissues, including the heart.<sup>[17]</sup> Whereas the native PPAR $\alpha$  mRNA gives rise to an active PPAR $\alpha$  protein (53 kDa), the truncated PPAR $\alpha$  mRNA gives rise to a form of PPAR $\alpha$  protein (30 kDa) that lacks the ligand-binding domain.<sup>[18]</sup> In addition, recent findings suggest that, on nuclear translocation, the truncated isoform of PPAR $\alpha$  has a repressive activity on the native PPAR $\alpha$  function, probably through competition for essential co-activators.<sup>[18]</sup> So it is possible that the ratio between native and truncated PPAR $\alpha$  isoforms could be an index of the transactivation activity of PPAR $\alpha$  on its target genes.

Cardiac PPAR $\alpha$  is a critical regulator of myocardial fatty acid uptake and oxidation, through the activation of some genes encoding key-limiting steps in the fatty acid utilisation pathway:<sup>[13,19,20]</sup> (i) fatty acid transport and esterification; (ii) fatty acid mitochondrial import; and (iii) mitochondrial and peroxisomal fatty acid oxidation. Until now, two genes have been identified in the human heart that have one functional PPRE within the promoter sequence: carnitine palmitoyl-transferases-I and -II.<sup>[21]</sup> These proteins control mitochondrial fatty acid uptake. As a fatty-acid-activated transcription factor, PPAR $\alpha$  also serves to match cardiac lipid delivery to oxidative capacity, a 'lipostat' function.<sup>[13,19,20]</sup> It has been shown that PPAR $\alpha$  inhibits expression of the

glycolysis-activating pyruvate dehydrogenase kinase 4 gene in the heart.<sup>[22]</sup>

The activity of the cardiac PPAR $\alpha$  is developmentally regulated.<sup>[14]</sup> Its expression and activity are low in the foetal heart, in which glucose and lactate serve as the chief energy substrates. During the foetal period, the transcriptional repressor of PPAR $\alpha$  target genes, the orphan nuclear receptor chicken ovalbumin upstream promoter-transcription factor (COUP-TF), dominates the foetal metabolic programme. After birth, the PPAR $\alpha$  complex activates the expression of its targets to meet the high energy needs of the heart. Ageing is associated with reduced mRNA and protein expression of myocardial PPAR $\alpha$ , and a diminished binding to PPRE.<sup>[23]</sup>

Emerging evidence suggests that PPAR $\alpha$  may be involved in the regulation of other cardiac processes. For instance, it has been shown that PPAR $\alpha$  activators inhibit cardiac expression of the pro-inflammatory genes tumour necrosis factor  $\alpha$  and nuclear factor- $\kappa$ B<sup>[24]</sup> and increase the anti-inflammatory cytokine interleukin-10.<sup>[25]</sup> Moreover, cardiac PPAR $\alpha$  has been implicated in the regulation of extracellular matrix, as a result of its inhibitory effect on the expression of collagen types I and III.<sup>[26]</sup> Finally, the findings of *in vitro*<sup>[27,28]</sup> and *in vivo*<sup>[29]</sup> studies suggest that PPAR $\alpha$  may exert an inhibitory effect on cardiac growth responses to different stimuli.

Recent findings suggest that PPAR $\alpha$  may have functions similar to those of other PPARs also expressed in the heart. For instance, it has been demonstrated that, next to PPAR $\alpha$ , PPAR $\beta/\delta$  has a prominent role in the regulation of cardiac lipid metabolism.<sup>[30]</sup> In contrast, preliminary data would suggest that some of the non-metabolic cardiac actions of PPAR $\alpha$  are also shared by PPAR $\gamma$ .<sup>[31-33]</sup>

### 3. Alterations in Cardiac PPAR $\alpha$ in Pressure Overload and Heart Failure

During the development of ventricular hypertrophy induced by pressure overload, the PPAR $\alpha$  complex is deactivated at several levels, including by transcriptional and post-translational mechan-

isms. Sack et al.<sup>[34]</sup> found diminished expression of the 53 kDa PPAR $\alpha$  protein in hypertrophied right ventricles of mice with pulmonary artery banding. Coincident with the reduction in PPAR $\alpha$  expression, the expression of COUP-TF increased in the hypertrophied heart. In addition, expression of genes involved in transport and utilisation of fatty acids was coordinately downregulated after 7 days of right ventricular pressure overload. Barger et al.<sup>[35]</sup> reported that PPAR $\alpha$  mRNA levels were reduced within 7 days of LVH induced by pressure overload in mice submitted to aortic banding. Interestingly, PPAR $\alpha$  deactivation was associated with a reduction in the cardiac capacity for fatty acid oxidation and cellular lipid metabolism.<sup>[35]</sup> Finally, in rats, pressure overload induced by constriction of the ascending aorta for 7 days resulted in LVH and decreased expression of PPAR $\alpha$  and several PPAR $\alpha$ -regulated genes.<sup>[22]</sup>

Lower PPAR $\alpha$  concentrations have also been reported in the human hypertrophied left ventricle. Karbowska et al.<sup>[36]</sup> reported a 54% decrease in the expression of the 53 kDa PPAR $\alpha$  protein in the left ventricle of patients with heart failure who had normal coronary arteries compared with non-failing donor hearts. Another study reported a significant decrease in PPAR $\alpha$  mRNA levels in the hypertrophied left ventricle of non-ischaemic diabetic and non-diabetic patients with heart failure compared with donors.<sup>[37]</sup> The transcript levels of some PPAR $\alpha$ -regulated genes were decreased in both failing groups when compared with the non-failing group.

### 3.1 Potential Origin

Alterations in the expression and activity of PPAR $\alpha$  in the pressure-overloaded left ventricle may occur as a consequence of primary cell responses or paracrine signals induced by mechanical stress on the cardiac muscle. In support of the first possibility is the observation that a diminished expression of PPAR $\alpha$  and PGC-1 $\alpha$  genes occurred in a model of gross and cellular hypertrophy secondary to cardiac overexpression of a constitutively active mutant of serine-threo-

nine kinase (Akt).<sup>[38]</sup> In support of the second possibility are findings demonstrating that PPAR $\alpha$  activity was diminished by a post-transcriptional mechanism mediated by the extracellular signal-regulated kinase mitogen-activated protein kinase (ERK-MAPK) pathway, confirming that signal transduction cascades linked to G protein-coupled receptors can affect the activity of PPAR $\alpha$ .<sup>[35]</sup> In this conceptual framework, it is surprising that a recent study showed that phosphorylation of PPAR $\alpha$  by p38 MAPK resulted in activation of PPAR $\alpha$  function in cultured cardiomyocytes.<sup>[39]</sup> Collectively, these data would suggest that distinct limbs of the MAPK network, namely ERK and p38, have opposing effects with respect to the activity of PPAR $\alpha$  in the heart.

Whatever the molecular mechanism(s) underlying the differential response of PPAR $\alpha$  to MAPK signalling is/are, the possibility exists that some humoral factors that interact with cardiac cells through G protein-coupled receptors may modulate PPAR $\alpha$ . Interestingly, some of these factors have a role in the development of hypertensive LVH and the transition to heart failure.<sup>[40]</sup> For instance, it has been shown that  $\alpha_1$ -adrenergic agonist-induced cardiomyocyte hypertrophy is associated with a rapid reduction in PPAR $\alpha$  activity in a system in which recombinant PPAR $\alpha$  is overexpressed, implicating post-translational regulatory mechanisms.<sup>[35]</sup> Although angiotensin II has been shown to decrease PPAR $\alpha$  mRNA and protein in the aortic wall,<sup>[41]</sup> no changes in expression of PPAR $\alpha$  have been observed in the left ventricle of angiotensin II-infused rats.<sup>[42]</sup> Recently, activation of PPAR $\alpha$  has been shown to interfere with the signalling pathway of endothelin-1 in rat cardiomyocytes,<sup>[27]</sup> suggesting that endothelin-1 could also regulate PPAR $\alpha$  in these cells.

Myocardial expression of the PPAR $\alpha$  gene and PPAR $\alpha$ -regulated genes has been found to be diminished in two rat models of systemic hypoxia.<sup>[43]</sup> In addition, it has been shown that exposure to hypoxia reduces PPAR $\alpha$ /RXR $\alpha$  DNA binding activity in cultured rat cardiomyocytes.<sup>[44]</sup> Thus hypoxia may interfere with PPAR $\alpha$  activity at different levels. The potential pathophysiological

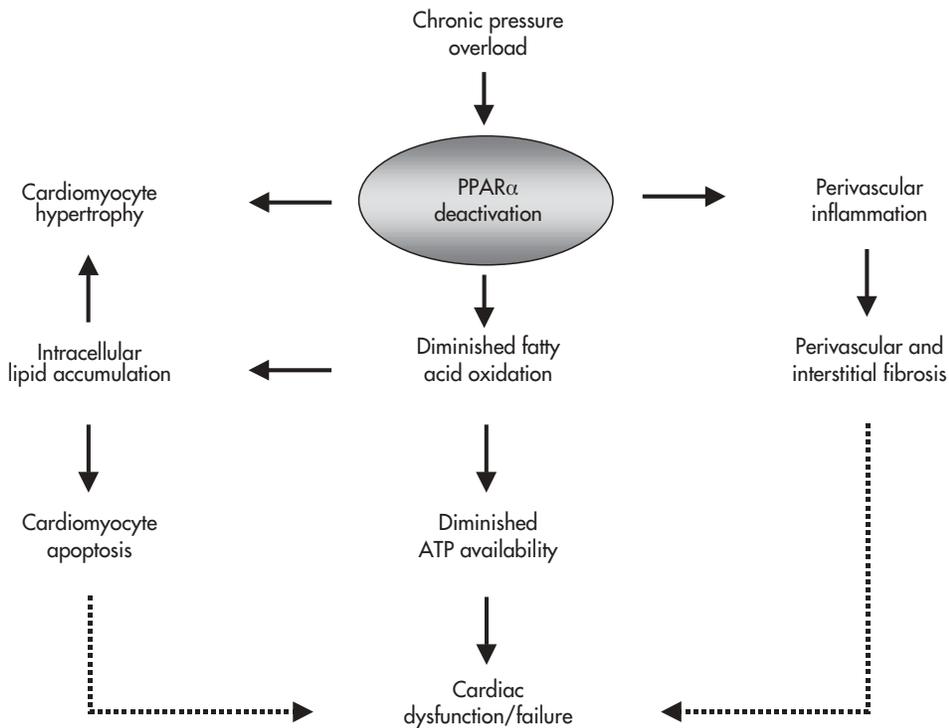
relevance of these findings is shown by the fact that structural and functional alterations in the intramyocardial vessels and the capillary network account for myocardial ischaemia in patients with hypertensive heart disease, even in the absence of coronary atherosclerosis.<sup>[45]</sup>

Finally, emerging evidence suggests that PPAR $\alpha$  activity can be genetically determined. The gene encoding PPAR $\alpha$  is located on the long arm of chromosome 22.<sup>[46]</sup> Several polymorphisms of the human PPAR $\alpha$  gene have been described. Of these, a cysteine (C) to glycine (G) transversion at position 484 in exon 5 leads to a substitution of valine (V) for leucine (L) at codon 162 (L162V).<sup>[47,48]</sup> The V<sup>162</sup> allele encodes a protein with altered ability to activate transcription *in vitro*. In fact, whereas the V<sup>162</sup> variant showed a diminished unstimulated baseline transcriptional activity compared with the L<sup>162</sup> variant in transfection

assays, in the presence of the PPAR $\alpha$  ligand WY-14643, V<sup>162</sup> showed greater transcriptional activity than L<sup>162</sup>.<sup>[48]</sup> This difference was not the result of enhanced protein production by the V<sup>162</sup> variant, because protein concentrations of both variants were similar after transfection. The potential clinical meaning of these data is shown by the fact that the V<sup>162</sup> allele is in allelic association with the C allele of a G/C polymorphism in intron 7 of the human PPAR $\alpha$  gene,<sup>[46]</sup> which appears to influence left ventricular growth in response to exercise and hypertension.<sup>[49]</sup>

### 3.2 Potential Consequences

Deactivation of cardiac PPAR $\alpha$  may be involved in some structural and functional changes that characterise the hypertensive myocardium (figure 2). Two lines of evidence link alterations in cardiac



**Fig. 2.** Potential pathways mediating the involvement of cardiac peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) deactivation in some structural and functional changes that develop in the hypertensive myocardium.

lipid metabolism with cardiac hypertrophy. First, genetic defects in several energy transduction/production pathways cause hypertrophic forms of cardiomyopathy.<sup>[50,51]</sup> Secondly, it has been shown in rats with spontaneous hypertension<sup>[52]</sup> and patients with essential hypertension<sup>[53]</sup> that depressed myocardial fatty acid metabolism is a primary determinant of left ventricular mass in hypertensive heart disease. Thus downregulation of PPAR $\alpha$  may be linked to cardiac hypertrophic growth via derangements in myocardial metabolism. Is this a cause–effect relationship, or an association related to secondary effects? The observation that pharmacological inhibition of the mitochondrial fatty acid oxidation pathway leads to ventricular hypertrophy<sup>[54]</sup> strongly suggests that a reduction in myocardial fatty acid utilisation is a primary trigger for cardiac growth. However, the mechanistic links remain unknown. It is possible that deactivation of PPAR $\alpha$  leads directly to cardiomyocyte growth through metabolic signals arising from metabolic cell derangements (see below).<sup>[55]</sup> Alternatively, deactivation of PPAR $\alpha$  may result in stimulation of transcription factors required for the hypertrophic response of cardiomyocytes (e.g. activator protein [AP]-1 and nuclear factor- $\kappa$ B).<sup>[56]</sup>

Given the pivotal role of PPAR $\alpha$  in the maintenance of cellular energy and lipid balance, reduced myocardial fatty acid oxidation rates, as demonstrated in the hypertensive left ventricle,<sup>[52,53]</sup> would be predicted to become detrimental for several reasons. First, despite the substrate switching to glucose that occurs in the hypertrophied heart, the energy reserve may become limited, given that the amount of ATP produced per mole of energy substrate is greater for fatty acids than for glucose. In addition, the failing heart does not develop a sufficiently high compensatory increase in glucose oxidation.<sup>[57,58]</sup> At a molecular level, the expression of glucose transporters-1 and -4 is severely downregulated in the failing human heart,<sup>[59]</sup> as is PPAR $\alpha$ . Therefore, ATP production has been found to be diminished in the failing human heart compared with the non-failing hypertrophied heart.<sup>[58]</sup> As

ATP availability and function of the heart are closely linked, it is reasonable to assume that deactivation of PPAR $\alpha$  leading to diminished fatty acid oxidation and reduced production of ATP might be involved in the compromise of cardiac function. However, the involvement of PPAR $\alpha$  in cardiac dysfunction is controversial. Whereas reactivation of PPAR $\alpha$  with its agonist WY-14643 results in contractile dysfunction in rats submitted to cardiac pressure overload,<sup>[22]</sup> left ventricular diastolic dysfunction may be prevented with the PPAR $\alpha$  agonist fenofibrate in diabetic rats.<sup>[60]</sup> Clearly, further studies are necessary to ascertain the role of PPAR $\alpha$  in the derangement of cardiac function involved in the transition from LVH to heart failure.

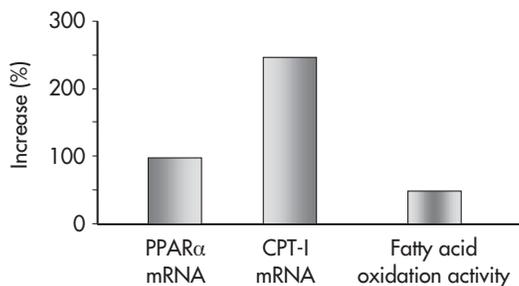
In contrast, the capacity for maintenance of cellular lipid homeostasis becomes limited. This prediction is supported by results demonstrating marked intracellular lipid accumulation in response to oleate loading in hypertrophied cardiomyocytes<sup>[35]</sup> and by the observation that PPAR $\alpha$ -null mice develop massive cardiomyocyte accumulation of long-chain fatty acid intermediates.<sup>[61]</sup> Some of these compounds, for example acylcarnitines, have been implicated in the genesis of ventricular rhythm disorders during myocardial ischaemia<sup>[62]</sup> and in patients with cardiomyopathy as a result of inborn errors of fatty acid oxidation.<sup>[63]</sup> Other compounds, for example ceramide, can induce the accumulation of reactive oxygen species, expression of inducible nitric oxide synthase and cardiomyocyte apoptosis.<sup>[64]</sup> Conversely, some lipid intermediates may be capable of activating cellular signalling pathways linked to cardiomyocyte growth pathways. In support of this notion, a recent study demonstrated that transgenic mice with increased myocardial uptake of fatty acids because of overexpression of fatty acyl-coenzyme A synthetase exhibit ventricular hypertrophy.<sup>[65]</sup>

Finally, some preliminary evidence suggests that deactivation of PPAR $\alpha$  might also play a part in the myocardial fibrosis that is present in the hypertensive heart. The heart from PPAR $\alpha$ -null mice shows progressive myocardial degeneration asso-

ciated with contraction band necrosis, inflammatory infiltrates and diffuse fibrosis in an age-dependent manner.<sup>[61]</sup> In contrast, PPAR $\alpha$  activation prevents myocardial fibrosis in mineralocorticoid- and angiotensin II-treated rats.<sup>[29,42]</sup> Moreover, in a model of cardiac pressure overload induced by abdominal aortic banding, PPAR $\alpha$  activation decreased interstitial and perivascular cardiac fibrosis.<sup>[26]</sup> Whether alteration in PPAR $\alpha$ -dependent regulation of inflammation mediates the connection between depressed PPAR $\alpha$  activity and fibrosis in these models of cardiac injury deserves further study.

#### 4. Pharmacological Modulation of Cardiac PPARs

It is unclear at present to what extent myocardial growth and reprogramming of cardiac gene expression are adaptive to haemodynamic overload and when they become detrimental as a result of the development of other structural and functional changes leading to the remodelling of the hypertensive myocardium. In this setting, modulation of cardiac PPAR $\alpha$  activity aimed at restoring the expression of its target genes might be of interest to protect the heart in hypertension. Fibric acid derivatives mimic the structure and biological functions of free fatty acids and, in this way, they bind to PPAR $\alpha$ . Besides ligand activation of PPAR $\alpha$ , fibric acid derivatives can induce PPAR $\alpha$  at the level of mRNA and protein also.<sup>[66]</sup> It is interesting to consider that myocardial fibrosis has been shown to be effectively inhibited by fenofibrate through suppression of AP-1-mediated augmentation of the endothelin 1 gene in the pressure-overloaded heart caused by aortic banding in rats.<sup>[26]</sup> HMG-CoA reductase inhibitors induce expression of PPAR $\alpha$  mRNA, as has been shown by *in vitro* and *in vivo* studies<sup>[67,68]</sup> (figure 3). In addition, it has been demonstrated that HMG-CoA reductase inhibitors can activate PPAR $\alpha$  by a reduction of the phosphorylative state via inhibition of the Rho signalling pathway.<sup>[69]</sup> Recent studies have reported antihypertrophic and antifibrotic properties of HMG-CoA reductase inhibi-



**Fig. 3.** Changes in liver peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) and carnitine palmitoyl-transferase-I (CPT-I) mRNAs, and hepatic fatty acid oxidation in rats fed fructose for 2 weeks and treated with atorvastatin (30 mg/kg), compared with untreated fructose-fed rats. (Adapted with permission from Roglans N, Sanguino E, Peris C, et al. Atorvastatin treatment induced peroxisome proliferator-activated receptor alpha expression and decreased plasma nonesterified fatty acids and liver triglyceride in fructose-fed rats. *J Pharmacol Exp Ther* 2002; 302: 232-9<sup>[68]</sup>)

tors in experimental models of LVH.<sup>[70-72]</sup> Finally, 9-*cis* retinoic acid, a ligand of RXR $\alpha$ , has also been shown to inhibit hypertrophy of primary cardiomyocytes.<sup>[73]</sup>

As mentioned previously, PPAR $\gamma$  may also be involved in myocardial remodelling. This is supported by *in vivo*<sup>[31,33]</sup> and *in vitro*<sup>[32]</sup> findings showing that thiazolidinediones inhibit LVH and fibrosis in conditions of pressure overload and ischaemia. Thus, besides activation of PPAR $\alpha$ , stimulation of PPAR $\gamma$  may represent a complementary approach to the prevention or correction of the cardiac remodelling that is associated with pressure overload.

#### 5. Conclusions and Perspectives

A growing body of evidence suggests that PPAR $\alpha$  downregulation and deactivation may participate in the pathophysiology of hypertensive heart disease. More specifically, decreased PPAR $\alpha$  activity may be critical in hypertensive patients with LVH at risk for developing heart failure. It is clear that future studies are required to test this possibility definitively. In contrast, PPAR $\alpha$  agonists with cardiac activity already exist as hypolipidaemic agents, although the potential

mechanisms involved in their cardioprotective effects are multifactorial and not completely understood. Thus more investigations, especially clinical studies, are required. This is of particular importance considering that 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.<sup>[74]</sup>

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