Peroxisome Proliferator-Activated Receptors and the Control of Fatty Acid Oxidation in Cardiac Hypertrophy

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Abstract: Cardiac hypertrophy is a response of the heart to a wide range of extrinsic stimuli, such as arterial hypertension, valvular heart disease, myocardial infarction, and cardiomyopathy. Although this process is initially compensatory for an increase workload, its prolongation frequently results in congestive heart failure, arrhythmia, and sudden death. Cardiac hypertrophy is associated with an increase in glucose utilization and a decrease in fatty acid oxidation. It is unclear at present, however, which consequences might result from impaired oxidation of fatty acids in the heart, but several studies have demonstrated that substrate utilization is important in the pathogenesis of cardiac hypertrophy. Here we will focus on the effects of cardiac hypertrophy on the activity of Peroxisome proliferator-activated receptors (PPARs), ligand-activated transcription factors that regulate the expression of genes involved in fatty acid uptake and oxidation, lipid metabolism and inflammation. Interestingly, activation of the Nuclear Factor (NF)-κB signaling pathway, which is one of the most important signal transduction pathways involved in the hypertrophic growth of the myocardium, may suppress the activity of the PPARs, affording a link between cardiac hypertrophy and the fall in fatty acid oxidation in the hypertrophied heart. As a result, inhibition of NF-κB activation during cardiac hypertrophy may also ameliorate cardiac fatty acid oxidation, achieving a better improvement in the prevention or inhibition of this pathological process.

Keywords: PPAR, cardiac hypertrophy, NF-κB, fatty acid metabolism.

INTRODUCTION

Cardiac hypertrophy is an adaptive response of the heart to many mechanical and hormonal stimuli such as hypertension, valve disorders, and ischemic events. At present it is believed that the hypertrophic response is a compensatory mechanism that reduces wall stress and oxygen consumption [1,2]. However, longstanding cardiac hypertrophy often precipitates the development of more serious complications. Several epidemiologic studies have demonstrated that chronic hypertrophy is associated with a significant increase in the risk of arrhythmia, dilated cardiomyopathy, ischemic heart disease, and sudden death, resulting in increased cardiovascular mortality [1-5].

Cardiac hypertrophy also precedes heart failure, a complex disorder in which cardiac contractility is insufficient to meet the metabolic demands of the body, which is the leading cause of death in the Western world. Nowadays, heart transplantation represents the most effective therapy for end-stage heart failure, but this treatment cannot reach all the patients and is not suitable for those patients with milder forms of the disease. Current pharmacological therapies for heart failure involve the use of multiple drugs to improve cardiac contractile function by modifying neurohormonal signaling (e.g. β-blockers and angiotensin-converting enzyme inhibitors) or normalizing calcium handling by the cardiomyocyte [6]. Although these strategies promote short-term improvement in cardiac function, the 5-year mortality rate for heart failure is still close to 50%. Therefore, there is a need for the development of new therapies, especially pharmacological treatments, which may improve the survival and the quality of life of heart failure patients. A better understanding of the mechanisms leading to cardiac hypertrophy may represent an essential step toward that goal.

The hypertrophic growth of cardiac myocytes is a complex, integrative process that involves several signaling networks [7-10] (Fig. **1**). In addition, all these signaling pathways do not operate in isolation, but participate in a more orchestrated response that generates interindependent and cross-talking networks. Cardiac hypertrophy is initiated by neuroendocrine factors and/or intrinsic stretch-sensitive sensors, which signal through G protein-coupled receptors, receptor tyrosine kinases, or directly to second messengers. Among the signal transduction pathways involved in the hypertrophic growth of the myocardium, the nuclear factor (NF)-κB signaling pathway plays a pivotal role, since it has been shown that NF-κB inhibition blocks or attenuates the hypertrophic response of cultured cardiac myocytes [11]. The activation of these upstream events during cardiac hypertrophy finally result in changes in transcription, translation and cytoskeletal organization.

At the cellular level the development of cardiac hypertrophy is detected by an increase in cell size, enhanced protein synthesis, heightened organization of the sarcomere and reactivation of the fetal gene program, such as enhanced expression of the atrial natriuretic factor [12,13]. In addition, cardiac hypertrophy is characterized by a dramatic reduction in fatty acid oxidation, since a shift in the source of energy is observed from fatty acids to glucose, which is characteristic of fetal heart [11]. The adjustments of cardiac metabolism to the substrate availability seem to involve

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changes in the transcriptional control of genes implicated in the transport and metabolism of fatty acids and glucose, which are mainly regulated by a class of transcription factors called peroxisome proliferator-activated receptors (PPARs). Interestingly, a negative cross-talk between PPARs and NF-κB has been described [14], suggesting that this cross-talk between these two signaling pathways may contribute to the change in the use of energy substrate during the development of cardiac hypertrophy. Here we will review the mechanisms responsible for the fall in fatty acid utilization during cardiac hypertrophy.

PPARS: TISSUE DISTRIBUTION, MECHANISMS OF ACTION AND LIGANDS

Constant pump function of the heart requires a high-energy demand, which is mainly satisfied by fatty acids and glucose. The oxidation of fatty acids and glucose covers, respectively, 65% and 30% of the energy demand of the adult heart [15]. The heart, in contrast to other tissues such as the brain, adapts its metabolism to substrate availability. For example, during cardiac hypertrophy an increase in glucose utilization and a decrease in fatty acid oxidation is observed [16-18]. Nonetheless, little is known about the molecular mechanisms linking cardiac hypertrophy and the fall in the expression of genes involved in cardiac fatty acid metabolism.

Recent reports have suggested that PPARs may play an important role in cardiac disease. Thus, it has been reported that the shift in the substrate utilization from fatty acids to glucose observed during the cardiac hypertrophic growth is associated with deactivation of PPARα [19]. These results suggest that reduced activity of this transcription factor may account for the down-regulation of enzymes involved in fatty acid oxidation.

PPARs are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid and thyroid hormone receptors. They act as lipid sensors and regulate transcription of lipid metabolizing enzymes (reviewed in [20]). The PPAR subfamily consists of three subtypes, PPARα (NR1C1 according to the unified nomenclature system for the nuclear receptor superfamily), PPARδ/β (NR1C2) and PPARγ (NR1C3) [21]. PPARα is expressed primarily in tissues that have a high level of fatty acid catabolism such as liver, brown fat, kidney, heart and skeletal muscle [20,22]. PPARδ/β is ubiquitously expressed, and PPARγ has a restricted pattern of expression, mainly in white and brown adipose tissues, whereas other tissues such as skeletal

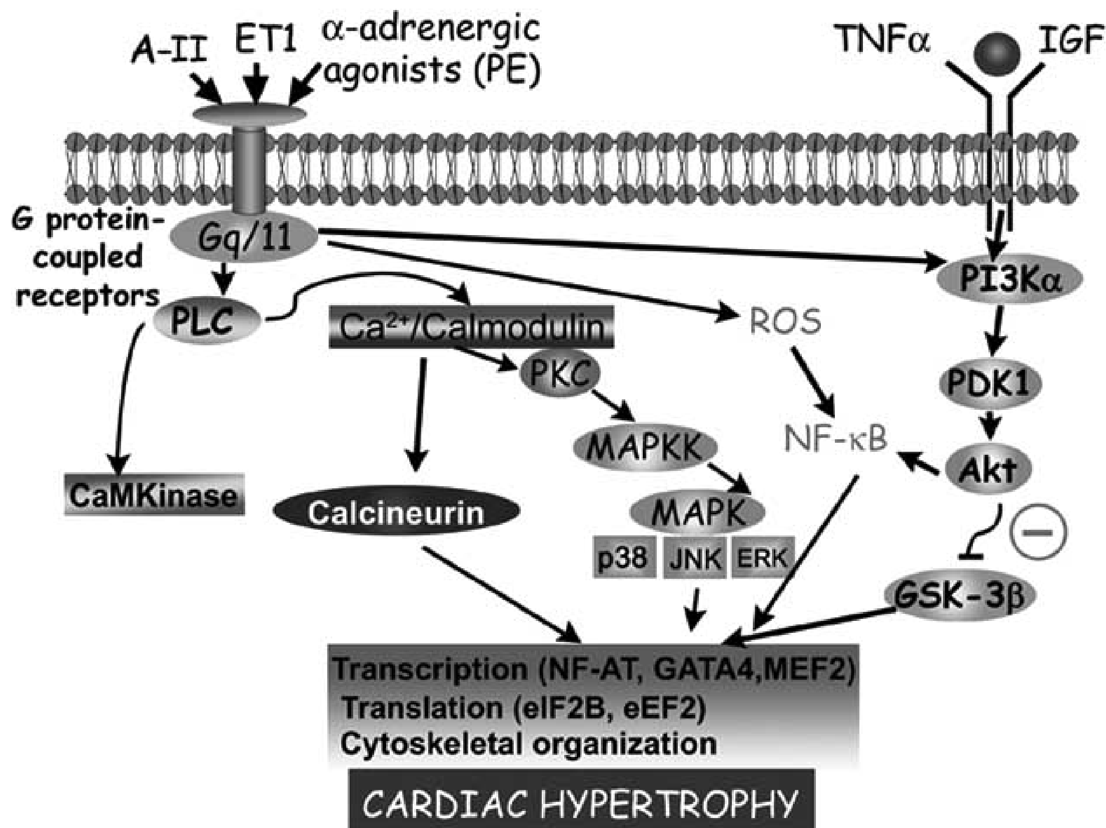

Fig. (1). Hypertrophic stimuli. This graph shows some of the biochemical pathways involved in the development of cardiac hypertrophy. Activation of these pathways in cardiac hypertrophy finally result in changes in transcription, translation and cytoskeletal organization. To reduce complexity, some of the biochemical pathways have been omitted. Akt, protein kinase B; A-II, angiotensin II; CaMkinase, calcium/calmodulin-dependent protein kinase; ET1, endothelin 1; ERK, extracellular signal-related kinase; GSK-3β, glycogen synthase kinase 3β; IGF, Insulin-like growth factor; JNK, Jun N-terminal kinases; MEF2, myocyte enhancer factor 2; NF-AT, nuclear factor of activated T cells; p38; p38-mitogen-activated protein kinases; PDK1, 3-phosphoinositide-dependent protein kinase 1; PE, phenylephrine; PI3K, Phosphoinositide 3-kinase; PKC, protein kinase C; PLC, phospholipase C; ROS, reactive oxygen species.

muscle and heart contain limited amounts. In order to be transcriptionally active, PPARs need to heterodimerize with the 9-*cis* retinoic acid receptor (RXR) (NR2B)[23-27] (Fig. **2**). PPAR-RXR heterodimers bind to DNA specific sequences called peroxisome proliferator-response elements (PPREs), consisting of an imperfect direct repeat of the consensus binding site for nuclear hormone receptors (AGGTCA) separated by one nucleotide (Direct repeat 1, DR-1). These sequences have been characterized within the promoter regions of PPAR target genes. The binding is produced in a way that PPAR is always oriented in the DNA's 5'-end, while RXR is in the 3'-end. In the absence of ligand, high-affinity complexes are formed between the PPAR-RXR heterodimers and nuclear receptor co-repressor proteins, which avoid transcriptional activation by sequestering the heterodimer from the promoter. Binding of the ligand to PPAR induces a conformational change resulting in dissociation of co-repressor proteins, and then the PPAR-RXR heterodimer can bind to PPREs. Moreover, once activated by the ligand the heterodimer recruit co-activator proteins that promote the initiation of transcription [28]. As a consequence of these changes in the transcriptional activity, binding of ligands to the receptor results in changes in the expression level of mRNAs encoded by PPAR target genes. In a determined cellular context the activity of PPARs regulating the transcription of their target genes depends on many factors (relative expression of the PPARs, the promoter context of the target gene, the presence of co-activator and co-repressor proteins, etc.).

However, the regulation of gene transcription by PPARs extends beyond their ability to transactivate specific target genes in an agonist-dependent manner. PPARs are also able of regulating gene expression independently of binding to PPREs. They can interact physically with other types of transcription factors and influence their function without binding to DNA, through a mechanism termed receptor-dependent *trans*-repression [29] (Fig. **2**). Most of the anti-inflammatory effects of PPARs are likely explained by this mechanism [30,31]. Thus, through this DNA-binding independent mechanism PPARs suppress the activities of several transcription factors, including nuclear factor κB (NF-κB), activator protein 1 (AP-1), signal transducers and activators of transcription (STATs) and nuclear factor of activated T cells (NFAT).

There are three main transrepression mechanisms by which ligand-activated PPAR-RXR complexes can

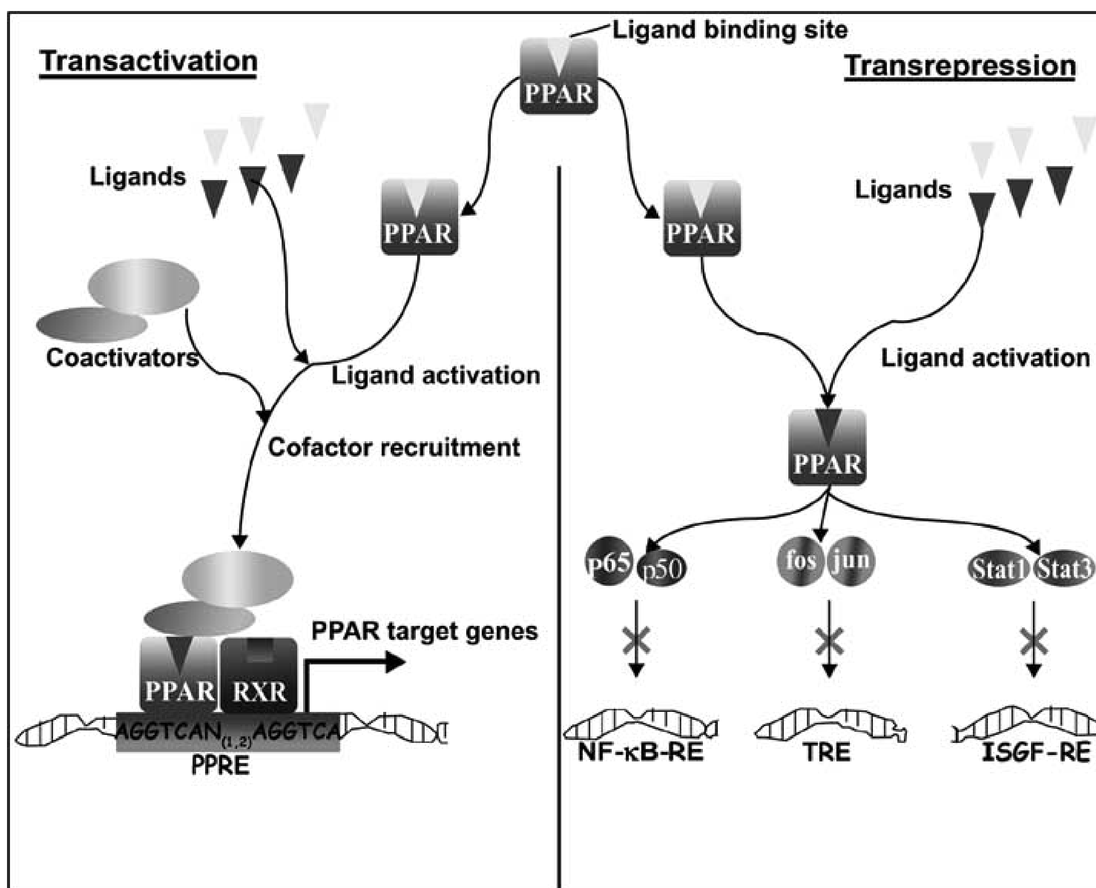

Fig. (2). Molecular mechanisms of Peroxisome Proliferator-Activated Receptors (PPARs). PPARs are ligand-activated transcripticon factors that regulate gene expression through two mechanisms: transactivation and transrepression. In transactivation PPAR-RXR heterodimers bind to DNA specific sequences called peroxisome proliferator-response elements (PPREs), which are located in the promoter regions of genes involved in glucose and fatty acid metabolism. PPARs may also regulate gene expression through a DNA-independent mechanism called transrepression. Through this mechanism, PPARs inhibit the activity of several transcription factors, such as Nuclear Factor-κB, leading to antinflammatory effects. STAT denotes signal transducers and activators of transcription, IS-GFRE interferon-stimulated gene factor responsive element, and TRE, TPA responsive element, where TPA is a phorbol ester.

negatively regulate the activities of other transcription factors. First, transrepression may result from competition for limiting amounts of shared co-activators. Under conditions in which the levels of specific co-activators are rate limiting, activation of PPAR may suppress the activity of other transcription factors that use the same co-activators [32,33]. In the second mechanism, activated PPAR-RXR heterodimers are believed to act through physical interaction with other transcription factors (for example AP-1, NF-κB, NFAT or STATs). This association prevents the transcription factor from binding to its response element and thereby inhibits its ability to induce gene transcription [34]. The last trans repression mechanism relies on the ability of activated PPAR-RXR heterodimers to inhibit the phosphorylation and activation of certain members of the mitogen-activated protein kinase (MAPK) cascade [35], avoiding activation of downstream transcription factors.

PPARs are very permissive regarding the structural requirements they impose to their ligands, probably as a result of the unusual size of its ligand-binding cavity. Mono- and polyunsaturated fatty acids at physiological concentrations behave as PPAR ligands, showing a slightly higher affinity for PPARα, except in the case of erucic acid that shows a higher selectivity for the human form of PPARβ [36]. Oxidation products of fatty acid are also ligands of PPARs; 15-deoxy-$\Delta^{12,14}$-PGJ_2 is a potent ligand for PPARγ [37], while leukotriene B_4 (LTB_4) and 8-S-hydroxyeicosatetraenoic acid (8-S-HETE) are PPARα selective [20,38,39]. Synthetic compounds such as hypolipidemic fibrates and antidiabetic thiazolidinediones are selective ligands for PPARα and PPARγ, respectively, whereas bromopalmitic acid and new structures derived from the basic fibrate backbone act as specific ligands for PPARβ [38].

CARDIAC HYPERTROPHY AND ENERGY METABOLISM

Development of cardiac hypertrophy is associated with changes in glucose and fatty acid utilization. It is still a matter of controversy whether changes in intracellular substrate and metabolite levels in cardiomyocytes are the consequence or the reason for the shift of cardiac metabolism from fatty acids to glucose observed in cardiac hypertrophy [11]. However, several facts demonstrate that substrate utilization is important in the pathogenesis of hypertrophy. Thus, defects in mitochondrial fatty acid oxidation enzymes cause childhood hypertrophic cardiomyopathy [40]. In addition, perturbation of fatty acid oxidation in animal models results in cardiac hypertrophy [41,42]. Moreover, it has been reported that an increase in the activities of several glycolytic enzymes has been reported prior to cardiac hypertrophy [43] and treatment with the antidiabetic thiazolidinediones have been associated with cardiac hypertrophy in animal studies at doses far exceeding those recommended for therapeutic use [44]. Further, etomoxir, an irreversible inhibitor of carnitine palmitoyltransferase I, and, therefore of fatty acid β-oxidation, was discontinued in the clinical development due to presence of cardiac hypertrophy [45,46]. Interestingly, we have reported that both thiazolidinediones (at high doses) and etomoxir increase NF-κB activation in heart [47,48], suggesting that treatments affecting glucose and fatty acid utilization, finally result in an increase in the activity of this proinflammatory transcription factor that it is involved in the development of cardiac hypertrophy [49-51]. It is worth noting that thiazolidinediones also inhibit cardiac hypertrophy [52,53], as it will be explained below, suggesting that depending on the different concentrations used these drugs can inhibit or promote cardiac hypertrophy.

Recent reports have suggested that PPARs may play an important role in cardiac disease. Thus, as explained before, the shift in the substrate utilization from fatty acids to glucose observed during the cardiac hypertrophic growth is associated with deactivation of PPARα [15,54,55]. Moreover, the fact that PPARα gene influences human left ventricular growth in response to exercise and hypertension, indicates that maladaptative cardiac substrate utilization can play a causative role in the pathogenesis of left ventricular hypertrophy [56]. These results suggest that reduced activity of this transcription factor may account for the down-regulation of enzymes involved in fatty acid oxidation. In fact, PPARα controls the oxidative metabolism of fatty acids in tissues with a high catabolism, such as the heart. Thus, PPARα activation facilitates the uptake and oxidation of fatty acids in the mitochondria by increasing the transcription of proteins involved in its transport into the mitochondria (for review see reference 14). However, the role of PPARβ/δ in the development of this process is largely unknown. Recently, Gilde and co-workers [57] clearly demonstrated that both PPARα and PPARβ/δ were expressed in comparable levels in heart, whereas PPARγ was barely detectable. Further, PPARβ/δ was fatty acid inducible and activated the expression of PPARα target genes involved in fatty acid utilization in cardiac myocytes. The authors of this study suggested that PPARα and PPARβ/δ shared similar functions in cardiac cells regarding cardiac fatty acid metabolism. In agreement with this idea, Muoio *et al.* [58] shown that fatty acid oxidation in skeletal muscle of $PPAR\alpha^{-/-}$ mice was not impaired, probably because of PPARβ/δ compensated for the lack of PPARα in these mice. On the other hand, we have recently reported that the levels of both PPARα and PPARβ/δ are reduced in pressure-overload cardiac hypertrophy [59].Therefore, it can be argued that the fall in the expression of both PPAR subtypes during the development of cardiac hypertrophy seems necessary to down-regulate the expression of genes involved in fatty acid metabolism. Interestingly, the changes caused by cardiac hypertrophy on the expression of genes involved in fatty acid metabolism were not observed when NF-κB activity was inhibited [59]. These data pointed to the involvement of NF-κB in these changes. In agreement with this hypothesis, a recent study demonstrated that inhibition of NF-κB increased the expression of the well-known PPARα-target gene apoA-I [60], confirming the negative cross-talk between NF-κB and PPARα. Therefore, we evaluated in an additional study whether, in addition to the reported reduction in the expression of PPARs during cardiac hypertrophy [61], other mechanisms, such as protein-protein interaction between NF-κB and PPAR, may contribute to the changes in the expression of genes involved in cardiac fatty acid metabolism (Fig. **3**). Using both *in vitro* and *in vivo* models of cardiac hypertrophy we studied the contribution of NF-κB activation during this process to

the down-regulation of fatty acid oxidation. Stimulation of rat neonatal cardiomyocytes with phenylephrine (PE), which leads to NF-κB activation [62], caused cardiac hypertrophy that was accompanied by a fall in the expression of pyruvate dehydrogenase kinase 4 (*Pdk4)*, a PPARβ/δ target gene involved in fatty acid metabolism [63], and palmitate oxidation. Further, the fall in the expression of *Pdk4* and fatty acid oxidation observed in PE-stimulated rat neonatal cardiomyocytes was restored by NF-κB inhibitors. These data pointed to the involvement of NF-κB in the downregulation of fatty acid oxidation during the development of cardiac hypertrophy. In agreement with this idea, a recent study demonstrated that cardiomyocyte-restricted PPARβ/δ deletion in heart of mice reduced myocardial fatty acid oxidation and the mRNA expression of genes involved in this process, such as *Pdk4*, and led to cardiomyopathy [64]. The mechanism by which activation of NF-κB results in reduced expression of PPARβ/δ target genes seems to involve reduced interaction of this PPAR subtype with its *cis*-regulatory element, since NF-κB activation caused a dramatic reduction in the binding of PPARβ/δ protein to the PPRE probe. This reduction was partially reversed by coincubation of the cells with NF-κB inhibitors, confirming the involvement of this transcription factor in the changes observed. Therefore, the reduced binding activity of PPARβ/δ seemed to be related to the activation of NF-κB in cardiac cells. However, it remained to establish through which mechanism NF-κB activation avoided the interaction of PPARβ/δ with its response element. NF-κB is present in the cytoplasm as an inactive heterodimer, consisting of the p50 and p65 subunits. However, after activation this heterodimer translocates to the nucleus and regulates the expression of genes involved in inflammatory and immune processes. Our results indicate that once the p65 subunit of NF-κB reaches the nucleus interacts with PPARβ/δ. This association prevents PPARβ/δ from binding to its response element and thereby inhibits its ability to induce gene transcription, leading to a reduction in the expression of *Pdk4*. These findings are in concordance with the results reported by Westergaard *et al*. [65], who showed that PPARβ/δ physically interacts with p65 in psoriatic lesions. Further, they showed a p65-dependent repression of PPARβ/δ, but not of PPARα or PPARγ.

All these data suggest that an incorrect cardiac substrate utilization in heart may be involved in the development of cardiac hypertrophy [66]. Confirmation of this fact may lead to the use of PPAR activators, which may increase fatty acid utilization in the hypertrophied heart, as drugs useful for the prevention or treatment of this pathology. In agreement with this idea, it has been recently published that fibrates, which are PPARα activators used for decades in the treatment of hyperlipemias, prevent endothelin-1-induced cardiac hypertrophy, through a mechanism that may involve inhibition of the p38 signaling pathway [67] and blockade of c-Jun NH_2-terminal kinase pathway [68-70].

In addition to PPARα activators, it has been shown that PPARγ agonists inhibit *in vitro* and *in vivo* cardiac

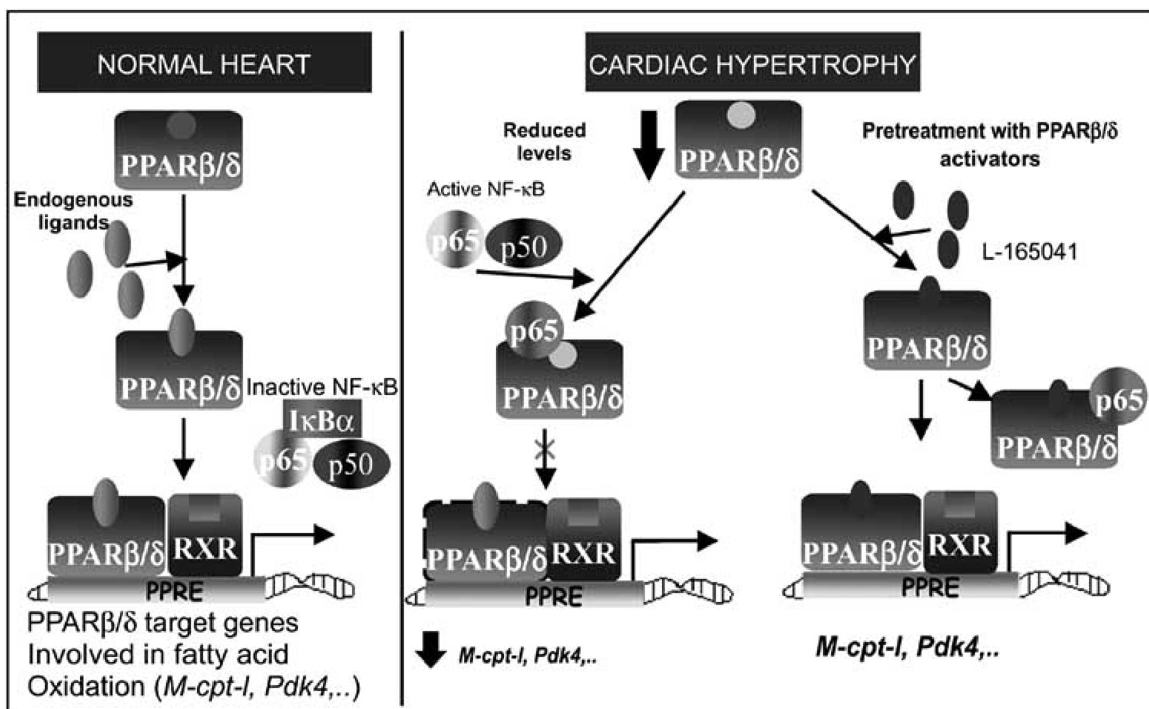

Fig. (3). Proposed role of PPARβ/δ in the development of cardiac hypertrophy. PPARs, mainly the α and β/δ isoforms, control the expression of genes involved in fatty acid oxidation (e.g., muscle type carnitine palmitoyltransferase, M-cpt-I; pyruvate dehydrogenasekinase, PDK-4). During the development of cardiac hypertrophy the expression of PPARs is reduced. As a result, fatty acid oxidation is diminished. In addition, cardiac hypertrophy increases NF-κB activity. Activation of this redox transcription factor may also reduce PPAR activity through a *trans*repression mechanism. Pre-activation of PPARβ/δ prevents the development of cardiac hypertrophy and the fall in the expression of genes involved in fatty acid oxidation. PPARβ/δ activation prevents NF-κB activation by hypertrophic stimuli through a *trans*activation mechanism that involves enhanced protein-protein interaction between the p65 subunit of NF-κB and PPARβ/δ.

hypertrophy [52]. This fact is surprising given that, in contrast to PPARα and β/δ, PPARγ is only expressed in heart in limited amounts [57]. In these studies it was shown that pressure-overload cardiac hypertrophy was more prominent in heterozygous PPAR γ-deficient mice than in wild-type mice, whereas treatment of wild-type mice with PPARγ ligands thiazolidinediones inhibited pressure overload-induced cardiac hypertrophy, but this effect was of less intensity in heterozygous PPAR γ-deficient mice [52]. Similar results were obtained by Yamamoto *et al*. [53], who showed that PPARγ ligands were able to block the hypertrophic response in cultured cardiomyocytes. Taken together these data support a role for PPARγ in the development of cardiac hypertrophy, although the mechanism involved is not yet well understood. However, it remains to study the PPAR-isoform specificity of the antihypertrophic effect of thiazolidinediones, since PPARα and PPARβ/δ are the predominant cardiac isoforms. In fact, the three PPAR isoforms have a partially overlapping ligand profile and some anti-inflammatory effects attained with high (50μM) concentrations of thiazolidinediones were partially explained by activation of PPARβ/δ [71,71]

In summary, activation of both cardiac PPARα and PPARγ receptors prevents the development of cardiac hypertrophy. However, the role of PPARβ/δ in the development of this process is unknown. The recent availability of specific synthetic ligands for PPARβ/δ, such as L-165041, now makes possible to study the role of this nuclear receptor in cardiac cells. We recently reported that activation of PPARβ/δ by the specific ligand L-165041 inhibited PE-induced cardiomyocyte hypertrophy in neonatal rat cardiomyocytes [72]. Treatment with the PPARβ/δ ligand also inhibited PE-induced expression of the NF-κB-target gene MCP-1, suggesting that the antihypertrophic effect of this compound involved down-regulation of NF-κB signaling pathway. Further, it was shown that L-165041 inhibited LPS-induced NF-κB activation through enhanced physical interaction of PPARβ/δ with the p65 subunit of NF-κB. Moreover, stimulation of rat neonatal cardiomyocytes with PE, which leads to NF-κB activation [62], caused cardiomyocyte hypertrophy that was accompanied by a fall in the expression of genes involved in fatty acid metabolism, such as carnitine palmitoyl transferase I (*m-cpt-I*) and *pdk4*. This effect was abolished by the addition of the PPARβ/δ activator, which strongly induced the expression of these genes. Further studies are necessary to clearly establish whether pharmacological modulation of cardiac fatty acid metabolism with either PPARα or PPARβ/δ activators is enough to alleviate or inhibit cardiac hypertrophy. However, it is worth noting that treatment of cells of cardiac origin with LPS for 24 hours caused a similar pattern of changes in the expression of M-CPT-I and PDK-4 to those observed in PE-induced cardiomyocyte hypertrophy. Interestingly, the PPARβ/δ activator reduced the induction of the NF-κB target gene MCP-1 in cardiac cells stimulated by either PE or LPS, suggesting that PPARβ/δ may antagonize NF-κB activation. Enhanced myocardial MCP-1 has been described in the hypertrophied and failing heart [73] and may lead to the infiltration and activation of inflammatory cells, such as monocytes/ macrophages and lymphocytes. In addition, it has been reported that activation of MCP-1 expression contributes to left ventricular remodeling and failure after myocardial infarction [74]. Therefore, PPARβ/δ activation may become a therapeutic option to reduce the expression of MCP-1 in heart.

PPARα activators may inhibit NF-κB signaling through different mechanisms [75-77]. One of these mechanisms involves physical interaction of PPARα and the p65 subunit of NF-κB. We demonstrated that PPARβ/δ activation enhanced the protein-protein association between PPARβ/δ and p65, indicating that this mechanism may interfere NF-κB transactivation capacity. Therefore, PPARα and PPARβ/δ may also share similar mechanisms of action inhibiting NF-κB signaling. It remains to study whether PPARβ/δ activation may inhibit the NF-κB signaling pathway through additional mechanisms or affects the activity of other transcription factors involved in cardiac hypertrophy, such as nuclear factor of activated T lymphocyte (NFAT).

In summary, further studies are needed to clarify the role of PPARs in cardiac hypertrophy and whether it proves to be a useful therapeutic target. Moreover, it is still unclear at present to what extent energy metabolism contributes to the development of cardiac hypertrophy. The answer to these questions will direct future efforts in the prevention and treatment of cardiac hypertrophy.

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Received: July 12, 2005 Revised: September 26, 2005 Accepted: September 27, 2005

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