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REVIEW OF THE ROLE OF PPAR GAMMA AND AGONISTS IN THE DEVELOPMENT OF HEART

Maryam Peymani¹ --- Kamran Ghaedi^{2†} --- Mohammad Hossein Nasr-Esfahani³

¹Department of Biology, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran

²Isfahan, Iran; Department of Biology, School of Sciences, University of Isfahan, Isfahan, Iran

³Department of Cellular Biotechnology at Cell Science Research Center, Royan Institute for Biotechnology, ACECR, Isfahan, Iran

ABSTRACT

Peroxisome-proliferator activator receptor γ (PPAR γ) is a nuclear receptor of central importance in metabolic processes. Recent experimental pieces of evidence demonstrate that PPAR γ is implicated in cardiac function and development. Here we reviewed the role of PPAR γ and ligands that emerged as a potential new therapeutic target for several cardiac diseases.

Keywords: PPARs, PPAR γ .

1. INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors which consist of three major isoforms, termed α , β/δ and γ which are encoded by distinct single-copy genes (Sharifpanah *et al.*, 2008). PPARs influence enormous cellular events including proliferation, differentiation, and apoptosis (Gilde *et al.*, 2003). It is well documented that PPARs activation may play a role during cardiomyogenesis of embryonic stem cells (ESCs) as PPARs mRNA was observed during cardiac differentiation (Shamina *et al.*, 2004).

The involvement of PPAR γ in key metabolic processes has been uncovered by implication of its ligands. So far, a collection of agonist ligands for PPAR γ includes the natural eicosanoid 15-deoxy-D12, 14-prostaglandin J₂ as well as the synthetic thiazolidinedione (TZD) compounds have been attributed for activation of PPAR γ . TZDs including Rosiglitazone at nano-molar concentrations are also considered as drugs prescribed for type II diabetes and insulin resistance.

Recently, involvement of PPARs in cardiac function and development has been reported by numerous groups.

† Corresponding author

1.1. PPAR γ has not any Role

Whereas the energy request increases when cardiac progenitor cells are developing rhythmic contractile activity, PPAR activation may play a critical role during cardiomyogenesis of embryonic stem (ES) cells. Sharifpanah shown that ES cells express PPAR α , β , and γ mRNA during differentiation of ES cells towards cardiac cells. Treatment with PPAR agonists (WY14643, GW7647, and ciprofibrate) significantly increased cardiomyogenesis and expression of the cardiac genes MLC2a, ANP, MHC-, MLC2v, and cardiac α -actin. Furthermore, WY14643 increased PPAR α gene expression and the expression of the cardiogenic transcription factors GATA-4, Nkx2.5, DTEF-1, and MEF 2C. In contrast, the PPAR α antagonist MK886 decreased cardiomyogenesis, whereas the PPAR β agonist L-165,041 as well as the PPAR γ agonist GW1929 were without effects. Also in this study studied Expression of PPAR γ mRNA During the Differentiation of ES cells and was shown that PPAR γ expression showed 2 maxima of expression at days 8 and 18, respectively (Sharifpanah *et al.*, 2008).

Gilde showed the FA oxidation rate increased in cardiomyocytes in presence of PPAR α and PPAR β/δ ligands, but not to PPAR γ ligands. Similarly, the FA-mediated expression of FA-handling proteins was mimicked by PPAR α and PPAR β/δ , but not by PPAR γ ligands. As expected, in embryonic rat heart-derived H9c2 cells, which only express PPAR β/δ , the FA-induced expression of genes was mimicked by the PPAR β/δ ligand only, demonstrating that FA also act as ligands for the PPAR PPAR β/δ isoform. Together, the present findings reveal that, next to PPAR α , PPAR β/δ , but not PPAR γ , plays a noticeable role in the regulation of cardiac lipid metabolism, thereby warranting further research into the role of PPAR β/δ in cardiac disease (Gilde *et al.*, 2003).

The role of PPAR γ and thiazolidinediones in regulation of myocardial lipid metabolism is controversial. Barbieri assayed the role of PPAR γ on myocardial lipid metabolism and function and differentiate local/from systemic actions of PPARs agonists using cardiomyocyte-specific PPAR γ –knockout (CM-PGKO) mice. To this aim, the effect of PPAR γ , PPAR γ /PPAR α and PPAR α agonists on cardiac function, intra-myocyte lipid accumulation and myocardial expression profile of genes and proteins, affecting lipid oxidation, uptake, synthesis, and storage (CD36, CPT1MIIA, AOX, FAS, SREBP1-c and ADPR) was evaluated in cardiomyocyte-specific PPAR γ –knockout (CM-PGKO) and littermate control mice undergoing standard and high fat diet (HFD). At baseline, protein levels and mRNA expression of genes involved in lipid uptake, oxidation, synthesis, and accumulation of CM-PGKO mice were not significantly different from those of their littermate controls. In standard condition, pioglitazone and rosiglitazone do not affect myocardial metabolism while, fenofibrate treatment significantly increased CD36 and CPT1MIIA gene expression. In conclusion, at baseline, PPAR γ does not play a crucial role in regulating cardiac metabolism in mice, probably due to its low myocardial expression. PPARs agonists, indirectly protect myocardium from lipotoxic damage likely reducing fatty acids delivery to the heart through the actions on adipose tissue (Barbieri *et al.*, 2012).

1.2. Negative Roles of PPAR Gamma

To directly determine the role of cardiomyocyte PPAR γ , Duan developed a cardiomyocyte-specific PPAR γ knockout (CM-PGKO) mouse model. CM-PGKO mice developed cardiac hypertrophy with preserved systolic cardiac function. Treatment with a TZD, rosiglitazone, induced cardiac hypertrophy in both littermate control mice and CM-PGKO mice and activated distinctly different hypertrophic pathways from CM-PGKO. CM-PGKO mice were found to have increased expression of cardiac embryonic genes and elevated nuclear factor κ B activity in the heart, effects not found by rosiglitazone treatment. Rosiglitazone increased cardiac phosphorylation of p38 mitogen-activated protein kinase independent of PPAR γ , whereas rosiglitazone induced phosphorylation of extracellular signal-related kinase 1/2 in the heart dependent of PPAR γ . Phosphorylation of c-Jun N-terminal kinases was not affected by rosiglitazone or CM-PGKO. Surprisingly, despite hypertrophy, Akt phosphorylation was suppressed in CM-PGKO mouse heart. These data show that cardiomyocyte PPAR γ suppresses cardiac growth and embryonic gene expression and inhibits nuclear factor B activity in vivo. Further, rosiglitazone causes cardiac hypertrophy at least partially independent of PPAR γ in cardiomyocytes and through different mechanisms from Duan *et al.* (2005)

Nissen and Wolski demonstrated that Rosiglitazone increase the Risk of Myocardial Infarction and Death from Cardiovascular Causes (Nissen and Wolski, 2007).

1.3. Positive Roles of PPAR Gamma

SAKAI investigated the effects of the thiazolidinediones troglitazone and pioglitazone, activators of PPAR α , on cardiac hypertrophy due to pressure overload provoked by abdominal aortic banding (AB) in rats. Endothelin-1 (ET-1) causes cardiac hypertrophy, and ET receptor antagonists inhibit the development of cardiac hypertrophy in vitro and in vivo. Because the ET-1 gene has AP-1 response elements in its 5' flanking region, the thiazolidinediones troglitazone and pioglitazone may inhibit cardiac hypertrophy partly through suppression of AP-1-induced ET-1 gene up-regulation (Sakai *et al.*, 2002).

Ding studied study is to investigate in vivo role(s) of PPAR γ in the heart. Results showed PPAR γ null mice exhibited pathological changes around 3 months of age, featuring progressive cardiac hypertrophy with mitochondrial oxidative damage. Most mice died from dilated cardiomyopathy. Cardiac expression of Sod2 (encoding manganese superoxide dismutase; MnSOD), a mitochondrial antioxidant enzyme was downregulated both in transcript and protein levels in cardiac samples in PPAR γ knockout mice independent of pathological changes. Promoter analyses revealed that Sod2 is a target gene of PPAR γ . Consequently, myocardial superoxide content in PPAR γ knockout mice was increased, leading to extensive oxidative damage. They demonstrated that PPAR γ is critical to myocardial redox homeostasis (Ding *et al.*, 2007).

Ye investigated the effects of PPAR-g activation on myocardial miRNA levels and the role of miRNAs in IR injury. They evaluated the expression changes of miRNAs in the rat heart after

PIO administration using miRNA arrays and then confirmed the result by northern blot. miR-29a and c levels decreased remarkably after 7-day treatment with PIO. In H9c2 cells, the effects of PIO and rosiglitazone on miR-29 expression levels were blocked by a selective PPAR-g inhibitor GW9662. Downregulation of miR-29 by antisense inhibitor or by PIO protected H9c2 cells from simulated IR injury, indicated as increased cell survival and decreased caspase-3 activity. In contrast, overexpressing miR-29 promoted apoptosis and completely blocked the protective effect of PIO. Antagomirs against miR-29a or -29c significantly reduced myocardial infarct size and apoptosis in hearts subjected to IR injury. Western blot analyses demonstrated that Mcl-2, an anti-apoptotic Bcl-2 family member, was increased by miR-29 inhibition (Ye *et al.*, 2010).

Wayman investigate the effects of various chemically distinct activators of PPAR α and PPAR γ in a rat model of acute myocardial infarction. They documented the expression of the mRNA for PPAR γ (isoform 1 but not isoform 2) as well as PPAR α and PPAR β in freshly isolated cardiac myocytes and cardiac fibroblasts and in the left and right ventricles of the heart. They have discovered that various chemically distinct ligands of PPAR- (including the TZDs rosiglitazone, ciglitazone, and pioglitazone, as well as the cyclopentanone prostaglandins 15D-PGJ2 and PGA1) cause a substantial reduction of myocardial infarct size in the rat. The mechanisms of the cardioprotective effects of 15D-PGJ2 may include 1) activation of PPAR α , 2) activation of PPAR γ , 3) expression of HO-1, and 4) inhibition of the activation of NF κ B in the ischemic-reperfused heart. Inhibition by 15D-PGJ2 of the activation of NF κ B in turn results in a reduction of the 1) expression of inducible nitric oxide synthase and the nitration of proteins by peroxynitrite, 2) formation of the chemokine MCP-1, and 3) expression of the adhesion molecule ICAM-1 (Wayman *et al.*, 2002).

Shinmura showed to improve the efficacy of MSC transplantation in vivo by pretreatment of MSCs with pioglitazone. MSCs were cultured with or without medium containing 1 μ M of pioglitazone before cardiomyogenic induction. After cardiomyogenic induction in vitro, cardiomyogenic transdifferentiation efficiency (CTE) was calculated and demonstrated that Transplantation of pioglitazone-pretreated MSCs significantly improved cardiac function and can be a promising cardiac stem cell source to expect cardiomyogenesis (Shinmura *et al.*, 2011).

2. CONCLUSION

However, further research is required to investigate how PPAR γ activation affects cell commitment and function that may have a potential therapeutic application.

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