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Review

Peroxisome proliferator-activated receptor (PPAR) gamma in cardiovascular disorders and cardiovascular surgery

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ABSTRACT

Peroxisome proliferation-activated receptor gamma (PPARγ) is a nuclear receptor regulating transcription of several genes involved mainly in fatty acid and energy metabolism. PPARγ agonists are used as insulin sensitizers for treatment of diabetes. However, according to the results of recent studies, their clinical application can be broadened. Activation of PPARγ has a wide spectrum of biological functions, regulating metabolism, reducing inflammation, influencing the balance of immune cells, inhibiting apoptosis and oxidative stress, and improving endothelial function. These effects appear to be beneficial not only in diabetes and atherosclerosis, but also in a number of other conditions, including cardiovascular surgical interventions. In this review we discuss the role of PPARγ in various conditions associated with cardiovascular risk, including diabetes mellitus, atherosclerosis, and hypertension, and will focus on current applications of PPARγ activators and their therapeutic use. We will also give an overview of the potential use of PPARγ agonists in cardiovascular surgical intervention.

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Introduction

Peroxisome proliferation-activated receptors (PPARs) are a family of ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily [1]. Upon interaction with their ligands, PPARs translocate into the nucleus, where they dimerize with the retinoid X receptor (RXR). The heterodimers regulate the transcription of a series of genes that have a PPAR response element in the promoter region, to which they can directly bind [2]. Natural ligands of PPARs include unsaturated fatty acids (FA) and prostaglandins, and many of the PPAR-responsive genes are involved in lipid metabolism and homeostasis [3]. PPARs play an important role in regulating energy metabolism and, as recently discovered, linking it to the circadian rhythm [4]. Activation of PPARs was shown to improve the lipid profile and glucose homeostasis in animal models of dyslipidemia and diabetes, as well as in clinical trials, making them an interesting target for novel therapies. In humans, there are three isoforms of PPARs encoded by different genes: PPARα, PPARβ/δ, and PPARγ that have only partially overlapping activity profiles and are differently expressed in organs and tissues [5].

PPARα is expressed in tissues with high metabolic activity, such as liver, kidney proximal tubules, brown fat, heart, and skeletal muscle [6]. Its target genes include some key elements of the β-oxidation pathway, FA transporter protein (FATP) and FA translocase (FAT), lipoprotein lipase (LPL), and apolipoprotein A-I and -II. PPARα is activated by fibric acid derivatives (fibrates) and some recently developed specific agonists [7]. Activation of PPARα promotes lipolysis and FA oxidation, decreases plasma triglyceride levels, and increases high-density lipoprotein cholesterol (HDL-C) [8]. PPARβ/δ is ubiquitously expressed, with relatively high levels in skeletal muscle and macrophages. Its activation results in the increased FA oxidation in muscles and improved insulin sensitivity in insulin-resistant animal models. Activation of PPARβ/δ in macrophage foam cells reduced lipoprotein lipase activity, enhanced β-oxidation and FA uptake and also inhibited the very low-density lipoprotein (LDL)-induced expression of inflammatory cytokines [9]. PPARβ/δ agonists gained interest as potential drugs for treatment of obesity, diabetes, and atherosclerosis, as they appear to normalize the plasma lipid profile, prevent the formation of foam cells, and reduce the cardiovascular risk, although none of them have been approved for clinical use so far [10].

PPARγ is abundantly expressed in the adipose tissue and to a lesser extent in macrophages and other cell types, and regulates adipogenesis, lipid storage, and glucose homeostasis. The PPARγ gene has several promoters and 5′ exons resulting in three distinct mRNAs (PPARγ1, PPARγ2, and PPARγ3). Translation of PPARγ1 and 3 results in identical proteins, while the product of PPARγ2 contains an additional N-terminal region composed of 30 amino acids [11]. The three isoforms differ in their expression patterns; PPARγ1 is expressed in all cell types whereas PPARγ2 is limited to adipose tissue, being, however, a more potent transcription activator [12]. Adipose PPARγ protects non-adipose tissues from lipid overload by maintaining the adequate expression of adipocytokines adiponectin and leptin that mediate the insulin signaling in peripheral tissues [13]. PPARγ activators, thiazolidinediones (TZDs), were shown to reduce inflammation and improve insulin sensitivity. They are currently used in clinical practice for treatment of diabetes, but have a therapeutic potential for a wide spectrum of other conditions because of their pleiotropic activity. In this review we will discuss the current use of PPARγ agonists for therapy of the disorders associated with cardiovascular risk, as well as their potential application in cardiovascular surgery.

PPARγ in diseases associated with cardiovascular risk

Diabetes

Current treatment of diabetes with glucose-lowering medications allows controlling of microvascular complications, such as retinopathy, and improving the patient's quality of life. It has, however, little effect on macrovascular pathology that accounts for the increased risk of fatal cardiovascular events. Moreover, aggressive glycemic control appears to provide little benefit at the advanced disease stages, and may even be harmful [14]. Numerous clinical studies aimed to improve the anti-diabetic therapy with novel medications that have potential benefits for patients. PPARγ agonists normalize the glucose profile by indirectly increasing insulin-stimulated glucose uptake by peripheral tissues and decreasing hepatic gluconeogenesis [15,16]. They also have modest effects on lowering LDL cholesterol, although the mechanisms of this effect are currently poorly understood. Anti-inflammatory activity of PPARγ agonists can also contribute to their anti-atherosclerotic effect. Studies on mouse models demonstrated that PPARγ activation reduced inflammation and improved insulin sensitivity through the activation of T regulatory cells in visceral fat [17]. Another study demonstrated that anti-diabetic effects of PPARγ activation are also mediated by the inhibition of tumor necrosis factor-α-induced expression of progranulin, which has a pro-inflammatory effect in adipose tissue [18]. Further studies are necessary to reveal molecular mechanisms of anti-diabetic activity of PPARγ agonists in more detail.

The advantage of PPAR agonists is that their glucose-lowering activity is not complicated by hypoglycemia or gastrointestinal adverse effects, as in the case of sulphonylureas and metformin. Moreover, they have a potential to reduce cardiovascular risk in patients with type 2 diabetes by affecting such risk factors as altered blood lipid profile or elevated blood pressure [19]. However, TZDs are not free from side effects and can increase sodium retention and alter endothelial permeability leading to peripheral edema and heart failure and cause imbalance in osteoblast and osteoclast formation resulting in bone fractures [20,21]. Weight gain has also been reported as a TZD side effect, and they may cause adipocyte hyperplasia, decreased glucosuria, fluid retention, and redistribution of fat from central to peripheral sites [22].

Three TZDs have been approved for treatment of type 2 diabetes: rosiglitazone, pioglitazone, and troglitazone, the latter being withdrawn shortly after the approval because of toxicity issues [14]. The effects of pioglitazone on macrovascular outcomes in diabetes have been studied in a large, prospective, randomized, double-blind study conducted on patients with type 2 diabetes and cardiovascular disease (PROactive study) [23,24]. Pioglitazone was used as an addition to the established anti-diabetic therapy that included glucose- and lipid-lowering, anti-hypertensive, and anti-thrombotic drugs, and reduced the all-cause mortality, non-fatal myocardial infarction, and stroke in patients with high cardiovascular

risk in comparison with placebo. Other macrovascular outcomes, such as endovascular or surgical intervention on coronary or leg arteries, were also reduced, although the statistical significance for them has not been reached. The other PPARγ agonist, rosiglitazone, was, on the contrary, associated with a significantly increased rate of myocardial infarction and fatal cardiovascular events [25,26]. Further comparative studies confirmed the elevated risks associated with the drug. To explain this discrepancy, different authors pointed to the beneficial effects of pioglitazone on the lipoprotein profile that are not shared by rosiglitazone. Indeed, pioglitazone not only increased HDL, but also decreased fasting triglycerides and FA in blood plasma, whereas rosiglitazone had only effects on HDL [27,28]. Moreover, rosiglitazone increased the total and LDL cholesterol levels that were unaffected by pioglitazone [27,29]. Taken together, the results of several clinical trials demonstrate that pioglitazone has a strong advantage over rosiglitazone in normalization of plasma lipoprotein and cholesterol profile. Because of the safety issues, the approval for rosiglitazone has been withdrawn by the European Medicines Agency [21].

PPARγ ligands are involved in the development of cardiac hypertrophy, which is frequently associated with diabetes, demonstrating contradictory effects. Treatment with TZDs was shown to be associated with cardiac hypertrophy in diabetic patients and animal models. Some authors proposed that hypertrophy develops to compensate for chronic volume overload, a result of enhanced sodium reabsorption associated with TZD treatment [30]. Co-treatment with diuretics could reduce the TZD-induced volume expansion and cardiac events [31]. Studies on animals have also demonstrated the presence of direct effects of rosiglitazone on cardiac hypertrophy by inducing phosphorylation of p38 mitogen-activated protein kinase and extracellular signal-related kinase 1/2 [32] and by the mammalian target of rapamycin pathway [33]. On the other hand, the PPARγ ligands were demonstrated to play a protective role against cardiac hypertrophy in animal and human studies [34]. TZDs inhibited angiotensin II-induced hypertrophy of neonatal rat cardiac myocytes [35]. Cardioprotective effects of rosiglitazone had been confirmed in a study on diabetic rats [36]. It is likely that the observed discrepancies could be explained by differences in the experimental models and drug administration regimens.

Atherosclerosis

Accumulating evidence demonstrates that PPARγ agonists have potential for treatment of atherosclerosis to improve the endothelial function, slow down the progression of atherosclerotic plaques, and reduce chronic inflammation and thrombosis resulting in lowering the risk of cardiovascular events [37]. The development and progress of atherosclerosis is tightly associated with inflammation. One of the pathological changes of the immune system observed in atherosclerosis is altered macrophage polarization toward pro- or anti-inflammatory (M1 or M2) phenotypes [38,39]. PPARγ appears to be a potent regulator of this process [40]. Its agonists were shown to suppress M1 phenotype, inhibiting the expression of pro-inflammatory cytokines tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 [41]. On the other hand, M2 differentiation of macrophages resulted in the increased PPARγ expression [42]. Such regulation of macrophage polarization is one of the mechanisms underlying the anti-inflammatory and anti-atherosclerotic activity of PPARγ. Immunogenecity of dendritic cells which are crucially involved in inflammatory mechanisms in atherosclerosis [43,44] is also regulated by PPARγ [45,46]. Despite that, possible effects of dendritic cells, mediated by PPARγ, on lipid metabolism and the development of atherosclerosis have been studied in a number of studies [47–51], the contribution of PPARγ *via* dendritic cell function in atherogenesis warrants further investigation.

Further understanding of anti-atherosclerotic properties of TZDs came from the study of their influence on the thromboxane system [52]. Thromboxane is a metabolite of arachidonic acid that plays an important role in atherosclerosis progression by influencing the proliferation of vascular smooth muscle cells and platelet aggregation. It has been demonstrated that PPARγ agonists suppress the expression of thromboxane synthase in macrophages and thromboxane receptor in smooth muscle cells [53,54]. Activated PPARγ inhibited interactions of the transcription factor nuclear factor E2-related factor 2 (NRF2) to the promoter with the thromboxane synthase gene and Sp1 with thromboxane receptor gene by protein–protein interactions.

Preclinical studies suggested that PPARγ agonists have beneficial effects on endothelial function in diabetic animal models [55,56]. Studies on patients with type 2 diabetes and non-diabetic individuals with coronary artery disease treated with pioglitazone confirmed these observations [57,58]. The mechanisms of pioglitazone activity were studied on human umbilical vein endothelial cells (HUVEC) by means of DNA microarray. It was demonstrated that pioglitazone at a concentration, which corresponds to plasma concentration in humans after single-dose administration, altered the gene expression pattern in cultured endothelial cells, up-regulating the tissue inhibitors of metalloproteinases-3, prostacyclin and prostaglandin E2 receptors, kallikreins 6 and 11, and microsomal glutathione S-transferase 3 and inhibiting matrix metalloprotease-10 and plasminogen activator inhibitor-2 [52]. It is therefore likely that the beneficial effect of PPARγ agonists on endothelial cells is mediated by changes in gene translation.

Hypertension

PPARs have been actively studied as potent regulators of hypertension. The blood pressure-lowering effect of PPARγ agonists has been reported in several clinical studies, including a large double-blind prospective study performed on patients with type 2 diabetes [23,59]. Animal studies have demonstrated that TZDs decreased the expression of one of the components of renin-angiotensin-aldosterone system, angiotensin II type 1 receptor (AT1R), in vascular smooth muscle cells in a dose-dependent manner [60]. Moreover, *in vitro* studies demonstrated that PPARγ agonists had an inhibitory effect on angiotensin II-induced aldosterone synthase and aldosterone secretion [61]. Other authors have demonstrated that PPARγ agonists suppress the angiotensin II-induced phosphatidylinositol 3-kinase and MAP kinase *in vivo* [62]. Together these observations indicate that PPARγ activation plays an important role in controlling blood hypertension by interfering with angiotensin II-mediated pathways.

Studies on animal models demonstrated that dominant negative mutations of PPARγ were associated with hypertension without affecting the renin-angiotensin-aldosterone system components [63]. It is therefore likely that PPARγ exerts its hypotensive activity through several different mechanisms.

Angiogenesis

Angiogenesis plays an important role in cardiovascular diseases, including ischemic heart disease and limb ischemia, providing a means to save hypoperfused tissues. The process is also important in cancer, where it contributes to the tumor growth. Regulation of angiogenesis is performed by a number of growth factors and cytokines, which are produced in response to hypoxic and inflammatory signals. Vascular endothelial growth factor (VEGF) is one of such factors, which stimulates endothelial proliferation and differentiation [64]. PPARs are involved in angiogenesis in various conditions, although their role remains contradictory, since both pro- and anti-angiogenic effects have

been observed [65,66]. It has been also demonstrated that the effect of PPARγ agonists on endothelial cells was dependent on the dose, with angiogenic effect present only at low concentrations [67]. PPARγ was shown to positively regulate angiogenesis by enhancing the expression of VEGF receptor-2. The authors report that anti-angiogenic activity of aldosterone was mediated by inhibition of expression of PPARγ and subsequently VEGF receptor-2 in vascular endothelial cells [68]. Another study has demonstrated that suppression of PPARγ signaling in pulmonary artery endothelial cells by endothelin-1 reduced angiogenesis in persistent pulmonary hypertension [69]. In hepatic stellate cells, however, PPARγ activation inhibited angiogenic signal transduction through trans-repression of platelet-derived growth factor (PDGF) beta receptor, leading to reduced VEGF expression [70]. It is therefore likely that pro- and anti-angiogenic properties of PPARγ are dependent on local background and signaling processes. Nevertheless, further study of PPARγ might be interesting for understanding and possible regulation of angiogenesis in various pathological conditions.

Renal dysfunction

PPARγ activation has been demonstrated to have protective effects in renal dysfunction, including diabetic nephropathy, and non-diabetic conditions, both in animal models and in clinical studies [71,72]. TZDs appeared to be potent agents for reducing proteinuria in diabetic patients. They had also beneficial effects in patients with chronic renal failure and hemodialysis [73,74]. Numerous animal models demonstrated the potential of PPARγ agonists for renal protection in various conditions, including induced renal injury, polycystic kidney disease, and nephritic syndrome [75–77]. Lowering of blood pressure and improving the endothelial function contribute to the renoprotective activity of PPARγ agonists; however, the exact mechanisms of this activity remain to be elucidated.

Potential of PPARγ agonists for cardiovascular surgery

Recent studies indicate that PPARγ might play important roles in cardiovascular interventions, regulating cell survival, signaling processes and inflammation (Fig. 1). We summarize these findings in the following chapters.

Aortic aneurysm

Aortic aneurysm is a dilation of the artery that develops as a result of maladaptive remodeling of the vascular extracellular matrix [78,79]. This condition can be idiopathic or caused by specific genetic syndromes, such as Marfan syndrome, Loeys–Dyetz syndrome, or Ehlers–Danlos syndrome, all the three of them being associated with enhanced transforming growth factor-β (TGF-β) signaling [80]. The pathogenesis of aortic aneurysm involves enhanced proteolysis of extracellular matrix material by matrix metalloproteinases and loss of smooth muscle cells [81,82]. In Marfan syndrome, the aneurysm pathogenesis is linked to mutations in the gene encoding fibrillin-1, an essential component of the extracellular matrix. Abnormalities in fibrillin-1 lead to the enhanced proteolysis by serine proteases and matrix metalloproteases and degradation of the elastic fibers [83]. The pathology is also associated with sequestration of TGF-β complexes in the extracellular matrix that can enhance TGF-β signaling [84]. TGF-β is a potent inducer of inflammation, fibrosis, and activation of several matrix metalloproteases, and its abnormally high level of activity has been reported in Marfan syndrome. Loeys–Dyetz syndrome is caused by mutations encoding TGF-β receptors 1 and 2 and presents with symptoms similar to those of Marfan syndrome, including the increased TGF-β signaling [85]. Ehlers–Danlos syndrome is associated with the deletion in type III procollagen gene and also mutations in TGF-β receptor genes. As in the previous cases, patients with this syndrome have enhanced TGF-β signaling [86]. Current treatment of aortic aneurysm is restricted to controlling blood pressure, as arterial hypertension is the major risk factor of aneurysm rupture.

Several studies have demonstrated that activation of PPARγ can attenuate TGF-β signaling [87,88]. Moreover, pioglitazone is an inhibitor of angiotensin II signaling that plays an important role in the aneurysm pathogenesis, enhancing collagen secretion and oxidative stress [89,90]. It has also been demonstrated that abdominal aortic aneurysm was independently associated with elevated concentrations of circulating glycoprotein osteoprotegerin, which causes aneurysm phenotype *in vitro*, although its causative role in the pathology development remains contradictory. PPARγ agonist pioglitazone was demonstrated to suppress osteoprotegerin secretion by cultured human abdominal aortic aneurysm explant by

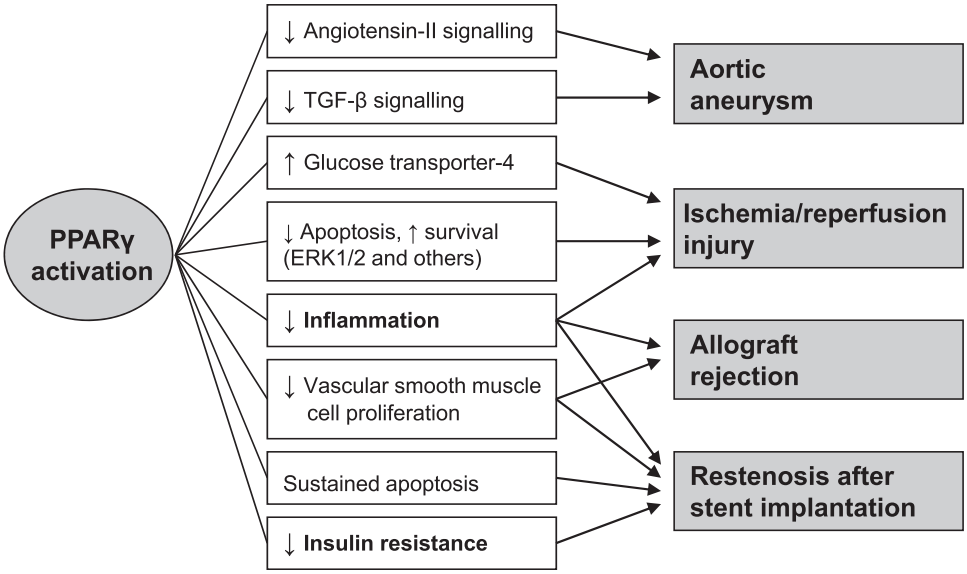

Fig. 1. Simplified scheme of pleiotropic effects of PPARγ activation for cardiovascular surgery. PPARγ, peroxisome proliferator-activated receptor-gamma; TGF-β, transforming growth factor-β; ERK, extracellular signal-regulated kinases.

2-fold and to reduce the tissue concentration of metalloproteinase-9 by 3-fold [91]. Moreover, a single nucleotide polymorphism in the gene encoding PPARγ was found to be associated with abdominal aortic aneurysm [92]. Taken together, these observations reveal an intriguing possibility that PPARγ may have beneficial effects not only on the blood pressure, but also on the pathological mechanisms that lead to the aneurysm development. It has been proposed that PPARγ agonists can be used as additional therapeutic agents for treatment of the aortic aneurysm syndromes [80].

Restenosis following cardiovascular interventions

Restenosis after cardiovascular interventions, such as balloon angioplasty or coronary stent implantation, is a common problem in patients with diabetes [93,94]. It has been found that one of the factors promoting this complication is insulin resistance [95]. Therefore insulin sensitizers gained attention as potential drugs to attenuate the development of restenosis. Animal studies demonstrated that PPARγ activity attenuated restenosis following angioplasty. Overexpression of PPARγ wild-type gene in rats with dominant negative PPARγ mutation reduced neointima formation after balloon injury, inhibited smooth muscle cell proliferation, and sustained apoptosis [96]. In atherosclerotic rabbits, pioglitazone significantly reduced in-stent restenosis following implantation of balloon-expandable stents in affected iliac arteries. The analysis of extracted arterial segments demonstrated a reduction in neointimal macrophages and decreased production of monocyte chemoattractant protein-1 (MCP-1) and TGF-β, suggesting that the protective effects of the PPARγ agonist were mediated by its anti-inflammatory activity [88].

The effect of pioglitazone therapy on restenosis after coronary stent implantation in humans has been evaluated in both diabetic and non-diabetic subjects. A randomized double-blind study on non-diabetic patients with coronary artery disease demonstrated that pioglitazone significantly reduced neointima volume after 6 months of treatment in comparison to placebo [97]. Similar results were obtained in a study conducted on type 2 diabetes patients, which demonstrated that pioglitazone treatment significantly reduced leptin levels, improved insulin resistance and endothelial function that can contribute to its protective activity [98]. Finally, the potential of TZD therapy to reduce restenosis in patients after coronary stent implantation has been demonstrated in a meta-analysis of five randomized clinical trials, three of them employing pioglitazone, and two rosiglitazone [99]. Patients who received TZDs in addition to standard therapy were less likely to undergo revascularization due to restenosis at 6-month follow-up. No adverse effects were recorded in patient groups receiving pioglitazone or rosiglitazone, although the total number of patients was insufficient to draw final conclusions on the drugs' safety.

Several mechanisms have been proposed to explain the beneficial effects of PPARγ agonists on restenosis. One of such mechanisms is the improved insulin resistance and endothelial function through leptin reduction [98]. Results from animal studies confirmed on human cells suggested that pioglitazone inhibited growth factor-stimulated vascular smooth muscle cell proliferation and migration and sustained apoptosis leading to the regression of neointimal tissue after stent implantation [100,101]. Treatment of non-diabetic patients with pioglitazone resulted in reduced neointimal volume and total plaque volume without affecting blood glucose, insulin, or hemoglobin α1c levels, suggesting that the protective effect of TZDs is independent of their hypoglycemic activity.

Valvular calcification

Cardiovascular calcification may occur in atherosclerotic lesions and can affect the aortic valve. The results of several studies suggest that calcification is an active process and can, therefore, be attenuated by adequate therapy [102,103]. It is likely that PPARγ agonists possess a protective activity against cardiovascular calcification. Apart from its anti-atherosclerotic effects, activated PPARγ inhibits differentiation of progenitor cells into osteoblasts and reduces oxidative stress and inflammation that play an important role in the pathological process [104–106]. The effect of pioglitazone on valvular calcification has been investigated in a recent study conducted on hypercholesterolemic mice [107]. It was demonstrated that pioglitazone prevented the diet-induced lipid deposition, attenuated apoptosis and reduced calcification in the aortic valve, although had no effect on fibrosis development. At the same time, the drug failed to prevent lipid deposition and calcification in the aorta. The protective activity of pioglitazone was ascribed to changes in the gene expression pattern [107].

Ischemia/reperfusion injury

Myocardial ischemia-reperfusion frequently accompanies coronary angioplasty, coronary artery bypass surgery, and thrombosis and greatly influences the outcome and prognosis in patients with myocardial infarction. Ischemia-caused changes in FA β-oxidation and glucose oxidation may disrupt the energy metabolism in the heart muscle, leading to massive cell death and affecting the cardiac function and survival during reperfusion, the condition known as ischemia/reperfusion injury [108]. Apoptosis was demonstrated to be one of the major causes of cell death, especially at early stages of ischemia/reperfusion [109]. PPARγ, as a potent regulator of FA metabolism and inhibitor of inflammation, plays an important protective role in the heart muscle during ischemia/reperfusion, and TZDs had beneficial effects in animal models. On the other hand, conditional deletion of PPARγ in cardiomyocytes significantly augmented the myocardial damage through inflammation [110].

A study on rats with induced acute myocardial ischemia/reperfusion injury demonstrated that pre-treatment with rosiglitazone reduced the myocardial infarct volume, protected cardiomyocyte mitochondrial function, and prevented the pathological structural changes in the heart muscle [111]. Anti-inflammatory effects of the PPARγ agonist were evaluated by the analysis of the expression of pro- and anti-inflammatory factors.

Since apoptosis plays a key role in myocardial cell death, anti-apoptotic effects of PPARγ activation might partially explain its cardioprotective function. Ischemia/reperfusion causes activation of pro-survival signaling cascades, including extracellular signal-regulated kinases (ERK1/2) that are implicated in regulating cell proliferation and differentiation and promote cell survival by recruiting anti-apoptotic pathways [112]. One of the downstream targets of ERK1/2 is cyclooxygenase (COX)-2 [113] that is involved in cardioprotection by increasing the production of cytoprotective prostanoids. Treatment with TZDs enhanced ERK1/2 phosphorylation in myocardium and increased COX-2 activity in ischemia/reperfusion animal models. Akt kinase is another key player in the intracellular signaling regulating cell proliferation and survival. Pioglitazone caused a substantial reduction of apoptosis and infarct size in rats after myocardial ischemia/reperfusion, and these effects were partially blocked by an ERK1/2 inhibitor [114]. Rosiglitazone anti-apoptotic activity was linked to facilitation of Akt kinase rephosphorylation during reoxygenation in cultured cardiomyocytes.

The beneficial effects of PPARγ agonist on glucose metabolism in ischemia/reperfusion injury were demonstrated in dogs that underwent cardiopulmonary bypass. During reperfusion following a prolonged ischemia, the expression of glucose transporter-4 was inhibited significantly, leading to decreased glucose uptake,

impaired energy metabolism, and cardiac function damage. The addition of rosiglitazone into cardioplegic solution increased expression of glucose transporter-4 at mRNA level and resulted in the attenuation of myocardium damage, alleviation of insulin resistance [115].

Taken together, these results suggest that PPARγ agonists have pleiotropic pro-survival activity, influencing several metabolic and signaling pathways to reduce cardiomyocyte apoptosis during ischemia/reperfusion. They can be considered as potential therapeutic agents to reduce myocardial damage caused by acute conditions such as myocardial infarction and surgical interventions. Further studies are needed, however, to evaluate the possible risks and benefits of their clinical use.

Allograft survival

Allograft rejection is a major concern for long-term patient survival after cardiac transplantation. Acute and chronic rejections remain common causes of graft failure despite the advances in immunosuppressive therapy. Inflammation is a key process in both acute and chronic graft rejections. In the acute process, macrophages and pro-inflammatory T cells infiltrate into the graft and produce a series of cytokines and chemokines [116]. Chronic rejection is associated with intimal hyperplasia caused by infiltrating inflammatory cells, proliferation of smooth muscle cells, and accumulation of extracellular matrix [117]. The effect of pioglitazone on cardiac graft survival has been studied in a mouse model of cardiac transplantation [118]. It exerted immunosuppressive activity as demonstrated by mixed lymphocyte reaction suppression.

Treatment with pioglitazone resulted in significantly lower expression of IL-10, interferon gamma (IFN-γ), and MCP-1 in allografts in comparison with controls. These allografts also had a reduced infiltration of CD4-, CD8-, and CD11b-positive cells. Another mouse study demonstrated that activation of PPARγ with eicosapentaenoic acid (EPA) was associated with increased proliferation of T regulatory (Treg) cells and suppressed IL-17-positive T cells [119]. Treg cells play a key role in regulating alloimmune responses and have anti-inflammatory properties and therefore protect the graft against acute rejection. Study on a rat model demonstrated that activation of PPARγ by dietary n-3 FA resulted in suppressed NF-kB activation and reduced secretion of MCP-1 and interferon-inducible protein-10, as well as in decreased expression of chemokine receptor-2 (CCR2) [120]. These effects are beneficial against cardiac allograft vasculopathy and hence chronic allograft rejection. PPARγ activation by rosiglitazone combined with treatment with anti-IL-5 antibody prevented the rejection of MHC class II-mismatched cardiac grafts in a mouse model [121].

Rosiglitazone reduced graft vasculopathy by favorably influencing the balance between the T cell types in the graft. In conclusion, activation of PPARγ may become a potent therapeutic instrument to suppress both acute and chronic graft rejections. However, the available studies of its allograft-protective activity are currently limited to animal models, and more results are needed to evaluate the efficacy and safety of TZDs for cardiac transplantation.

Conclusions

Activators of PPARγ exert a broad spectrum of biological functions, regulating FA metabolism, reducing inflammation, influencing the balance of immune cells, inhibiting apoptosis and oxidative stress, and improving endothelial function. Such pleiotropic activity makes them interesting therapeutic targets for treatment of various conditions, especially linked to dyslipidemia, atherosclerosis, and diabetes that are frequently associated with cardiovascular disorders. Numerous clinical studies have demonstrated the efficiency of PPARγ agonists as additional therapeutic agents for treatment of vascular complications of diabetes and atherosclerosis. At the same time, the accumulating evidence suggests that the scope of therapeutic use of these agents can be broadened, including implementation as protective agents in cardiovascular surgery. TZDs were demonstrated to be beneficial to prevent restenosis after stent implantation and were proposed as potential treatments of aortic aneurysm, and as protective agents against ischemia/reperfusion injury and allograft rejection. Clinical use of TZD has been limited because of safety concerns, with several drugs withdrawn from humans in recent years. To date, pioglitazone remains the most widely used PPARγ agonist allowed for clinical application that has not been reported to have deleterious adverse effects. Future studies should be directed at more accurate evaluation of safety issues and exploration of novel clinical applications of PPARγ-activating agents.

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