Journal of Cardiology 66 (2015) 271–278

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Review

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

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ARTICLE INFO

Article history:
Received 12 March 2015
Received in revised form 8 May 2015
Accepted 14 May 2015
Available online 10 June 2015

Keywords:
Peroxisome proliferation-activated receptor gamma
Cardiovascular disorders
Cardiovascular surgery
Cardiovascular surgical interventions

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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http://dx.doi.org/10.1016/j.jjcc.2015.05.004
0914-5087/

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