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Review

Targeting PPARα for the Treatment and Understanding of Cardiovascular Diseases

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Key Words
PPARα • Vascular injury • Cardiac injury • Blood pressure • Lipid disorder

Abstract
Three members of the peroxisome proliferator-activated receptor (PPAR) family, PPARα, PPARγ, and PPARβ/δ, have been investigated widely over the past few decades. Although the roles of these PPARs and their agonists/antagonists were defined in clinical and basic studies, the conflicting results from these studies indicate that more analysis is needed to understand the roles of PPARs. PPARα is a ligand-activated transcription factor that contributes to the regulation of a variety of processes, ranging from inflammation and immunity to nutrient metabolism and energy homeostasis. In this review, we focus on the function and mechanisms of PPARα in the cardiovascular system under various pathological conditions, including vascular and heart injury, blood pressure regulation, and lipid disorder-related cardiovascular injury, as well as its polymorphisms and pharmacogenetic associations with cardiovascular diseases. The anti-inflammatory effect of PPARα in cardiovascular injury is mainly through inhibition of pro-inflammatory signaling pathways and improvement of the lipid profile. Moreover, PPARα also modulates the activity of endothelial nitric oxide synthase and resets the renin-angiotensin system to regulate vascular tone. PPARα gene variants appear to be associated with some cardiovascular risk factors, such as higher plasma lipid levels, cardiac growth, and increased risk of coronary artery disease. Nowadays, novel PPARα drugs with broad safety margins and therapeutic potential for metabolic syndrome and cardiovascular diseases are being developed and applied in the clinical setting. The insights from the current review shed new light on areas of further study and provide a better understanding of the role of PPARα in cardiovascular diseases.

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Introduction

After a mouse gene linked to peroxisome proliferation was first described in 1990 [1], an orphan nuclear hormone receptor named peroxisome proliferator-activated receptor (PPAR) was subsequently discovered. The original receptor, known as PPARα (also termed NR1C), was classified as a PPAR forming group C in subfamily 1 of the nuclear hormone receptor superfamily. cDNAs encoding two other isotypes of this nuclear receptor subfamily, PPARβ/δ (NR1C2) and PPARγ (NR1C3), were then identified. All three PPARs are encoded by separate genes and expressed in amphibians [2], rodents [3, 4], and humans [5, 6]. PPARα and PPARγ appear to be highly conserved across species, whereas PPARβ/δ has diverged considerably [4].

PPARα is expressed in skeletal muscle, liver, intestine, kidney, and heart [7, 8], with different patterns of protein and mRNA expression in mice, rats, and humans [9]. In the cardiovascular system, the activation of PPARα by its ligands inhibits the development and progression of atherosclerosis, plaque rupture, and thrombus formation [10, 11]. In this review, we focus on the advances in our understanding of the roles of PPARα in cardiovascular disorders, namely, vascular injury, heart diseases, lipid disorders, and hypertension.

General characteristics and roles of PPARα, PPARγ, and PPARβ/δ

All members of this PPAR superfamily have a similar structure. The N-terminal region allows ligand-independent activation, confers constitutive activity on the receptor, and is negatively regulated by phosphorylation. This region is followed by a DNA-binding domain (two zinc finger motifs separated by a linker region) and a C-terminal ligand-binding domain [12, 13]. The three members of the PPAR family are encoded by separate genes with distinct but overlapping interspecies sequences and exert distinct functions [14]. PPARs form heterodimers with another nuclear receptor partner, retinoid X receptor, and bind to specific PPAR response elements in the promoter region of their target genes, thereby regulating gene function (Fig. 1). PPARs can also repress gene expression in a DNA binding-independent manner by interfering with other signaling pathways [15].

PPARα, the first identified PPAR, is expressed abundantly in skeletal muscle, liver, intestine, kidney, and heart [9, 16], and regulates fatty acid (FA) transport, esterification, and oxidation [17, 18]. Moreover, it also plays a critical role in inhibiting cell proliferation and tumorigenesis via unidentified mechanisms. PPARγ is the best studied PPAR subtype and is expressed predominantly in brown and white adipose tissues and to a lesser extent in immune cells and the intestinal mucosa [19]. PPARβ/δ is expressed at high levels in most tissues, but especially in skeletal muscle, liver, intestine, kidney, and abdominal adipose tissue. Its activation results in increased FA oxidation (FAO) in skeletal and cardiac muscle and improves insulin sensitivity in insulin-resistant animal models [20, 21].

PPARs are involved in multiple physiological functions [22] that are regulated by a large number of endogenous and exogenous compounds, including FAs and their metabolites. A variety of ligands, including n-3 and n-6 FAs, eicosanoids, and a few endocannabinoids and phospholipids, have been identified as endogenous ligands of PPARs, including 8-epoxyeicosatrienoic acids (8-EETs), the arachidonic acid lipoxygenase metabolite leukotriene B4 (LTB4), and the arachidonate monooxygenase metabolites epoxyeicosatrienoic acids, which have been shown to potently activate PPARα [23-25]. Besides these endogenous PPAR ligands, some exogenous PPAR ligands have been generated and applied in experimental studies and clinical practice. For example, fibrates, which are PPARα ligands, are used widely to ameliorate the microvascular risks associated with metabolic syndrome [26]. This class of exogenous PPARα ligands includes clofibrate, gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate [27-32]. Furthermore, the synthetic compounds GW501516, GW0742, L-165041, and GW2433 have been defined as selective PPARβ/δ ligands [33, 34]. Natural PPARγ ligands include 15-deoxy-(12, 14)-prostaglandin

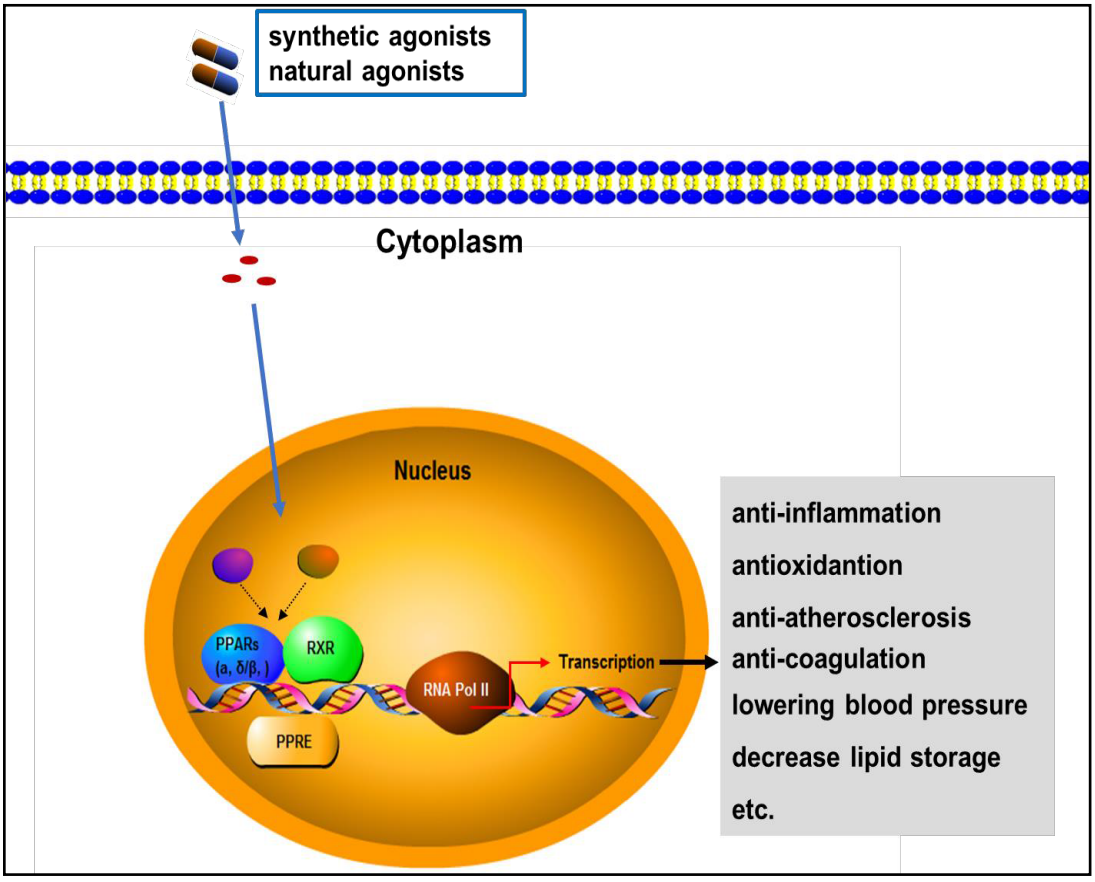

Fig. 1. Schematic of peroxisome proliferator-activated receptors-(PPARs) in cardiovascular diseases. PPARs have three forms: α, β/δ, and γ. PPAR heterodimerizes with retinoid X receptor- (RXR) and binds to the specific region of DNA sequence known as the peroxisome proliferator receptor response element (PPRE) located in the promoters of PPAR target genes, which leads to initiation of transcription by recruiting RNA polymerase II (RNA Pol II) and other transcription factors. In pathological conditions, PPARs protect against the vascular injury through multiple actions.

J2 [35] and the oxidized metabolites of linoleic acid 9-hydroxy- and 13-hydroxy-octadecadienoic acids [36, 37]. Synthetic thiazolidinedione (TZD) compounds, including rosiglitazone, pioglitazone, and lobeglitazone, are potent selective PPARγ agonists and are very effective at controlling hyperglycemia, angiogenesis, and cardiac fibrosis [36-39]. Agonists of PPARs have arisen with the ability to bind to multiple isoforms, which are known as dual agonists or pan agonists, such as saroglitazar (PPARα and γ dual agonist) [40, 41], elafibranor (also known as GFT505; PPARα and δ dual agonist) [42, 43], and IVA337 (agonist of PPARα, β/δ, and γ) [44]. However, most of these agonists were later abandoned because of serious adverse effects [45, 46]. To solve this problem, a new generation PPARα-specific agonist, pemafibrate, was developed to maximize receptor-mediated effects and diminish side effects [47]. Furthermore, a recent study found that arjunolic acid (assigned as a PPARα agonist) regresses cardiac fibrosis by inhibiting non-canonical transforming growth factor-β signaling [48].

PPARs are gaining interest for the treatment of metabolic and cardiovascular diseases. Accumulating evidence has shown that the three PPAR subtypes function in the cardiovascular system and influence disease development [28, 38, 48-54]. However, the detailed mechanisms of PPARs in cardiovascular remodeling and dysfunction are still elusive. Over the past few decades, PPARs have been investigated extensively as therapeutic targets in cardiovascular diseases [49, 55, 56]. In this field, diverse approaches, such as

transgenic animals with cardiac-restricted overexpression or deletion of PPAR genes or activation of PPARs with specific agonists in various models of cardiac diseases, have been used to define the roles of PPARs in the pathogenesis of cardiac disorders. Experimental studies in animal models of metabolic diseases also revealed that the activation of PPARs protects against vascular complications through anti-inflammatory, anti-atherogenic, and anti-oxidant actions. However, the molecular mechanisms mediating these protective effects are not understood fully.

PPARα in vascular injury

In the circulatory system, PPARα is expressed by endothelial cells, vascular smooth muscle cells (VSMCs) [57], and monocytes/macrophages [58, 59]. Evidence from animal models and clinical studies has demonstrated a link between inflammation and vascular injury, which is a complex cascade of events involving endothelial denudation, the release of growth factors and cytokines, platelet activation, and smooth muscle cell proliferation and migration to the subendothelial space to form neointimal hyperplasia, leading to vascular stenosis [57, 60, 61]. The inflammatory processes characterized by the adhesion of monocytes and the secretion of inflammatory cytokines alter vascular function [61]. PPARα activation limits the inflammatory response of endothelial cells and VSMCs by inhibiting pro-inflammatory signaling pathways and improving the lipid profile, thus contributing to the anti-atherogenic action of PPARα agonists [62]. The absence of PPARα in mice causes a prolonged response to inflammatory stimuli [63]. This anti-inflammatory effect of PPARα could result from its negative regulation of vascular inflammatory gene expression by interfering with nuclear factor (NF)-κB and activator protein-1 [64, 65]. Moreover, emerging evidence has also demonstrated that the ligand-activated transcription factor PPARα could act with the histone deacetylase sirtuin 1 (SIRT1) to regulate vascular pathophysiology. For example, Wang et al. reported that the activation of PPARα by fenofibrate inhibits cell apoptosis in vascular adventitial fibroblasts partly through the SIRT1-mediated deacetylation of FoxO1 [66]. In addition to modulating endothelial cell inflammatory processes, PPARα agonists enhance the expression of endothelial nitric oxide synthase (eNOS) and the release of nitric oxide (NO) [67, 68].

In the disease condition, some lipid metabolites such as eicosanoids and polyunsaturated FAs upregulate PPARα expression to modulate the expression of inflammatory cytokines and the proliferative response in smooth muscle cells [69]. Many contradictory effects have been ascribed to PPAR ligands in vascular and inflammatory cells. When the vasculature is damaged, VSMCs migrate into the intima of the arterial wall, where they subsequently proliferate and synthesize extracellular matrix, resulting in intimal hyperplasia. The activation of smooth muscle cell proliferation is a key event in the development of atherosclerotic complications. In such a case, the proliferative role of PPARα ligands might promote the entry of VSMCs into a proliferative state in spite of their anti-inflammatory action [70, 71]. On the contrary, studies from human and mouse primary VSMCs showed that PPARα can arrest the cell cycle in smooth muscle cells at the G1/S phase, thereby providing a molecular mechanism by which PPARα interferes directly with cell cycle progression [72, 73]. *In vivo* evidence demonstrated that p16 deficiency promotes smooth muscle cell proliferation and intimal hyperplasia, which were markedly enhanced in PPARα-deficient mice. Moreover, treatment with the PPARα agonist fenofibrate substantially reduces intimal hyperplasia [74]. These findings suggest a potential for PPARα agonism in preventing vascular restenosis. Further studies are necessary to clarify the discrepancies between these findings.

PPARα in heart injury

Besides the known role of PPARα in the regulation of energy homeostasis, its involvement in modulating the cellular redox response and inflammation in the heart undergoing ischemia/reperfusion (I/R) injury, hypertrophy, and cardiac fibrosis has been documented in recent reports [48, 75-77]. Bulhak et al. reported that the PPARα agonist WY-14643 protects the myocardium of type 2 diabetic Goto-Kakizaki rats from I/R injury via the activation of the PI3K/Akt and NO pathway [78]. In addition, dual PPARα and γ agonists might have additive effects on myocardial protection against I/R injury. Qian et al. found that the non-thiazolidinedione dual PPARα and γ agonist aleglitazar protects cardiomyocytes and the heart against I/R injury [79]. Evidence has also shown that PPARα activation reduces myocardial infarct size and improves postischemic contractile recovery in animal and *ex vivo* models of I/R [80-82]. Furthermore, this cardioprotective effect was abolished in PPARα$^{-/-}$ mice [83]. However, other studies have reported conflicting results. The cardiac-restricted overexpression of PPARα leads to impaired cardiac recovery after ischemia [84-86], and the use of the PPARα agonist WY-14643 during repetitive I/R results in the intramyocardial triglyceride (TG) accumulation, increased generation of reactive oxygen species (ROS), and subsequent enhancement of inflammation, apoptosis, and contractile dysfunction [87]. The detrimental effect of PPARα may be attributed to the increased production of ROS and lipotoxicity due to a switch of metabolism from glucose to FA utilization [88]. The contradictory results from cardiac-restricted PPARα overexpression and systemic PPARα activation in I/R heart models might be due to the effect of non-cardiac cells such as inflammatory cells. Moreover, the non-specific effects of these PPARα agonists on the heart need to be investigated further.

PPARα is a potent antagonist of inflammation. The synthetic PPARα activator fenofibrate prevents the development of hypertension and improves myocardial inflammation and fibrosis in angiotensin II-infused rats [89]. All three PPARs exert an anti-inflammatory action by interfering with pro-inflammatory signaling pathways such as NF-κB. PPARα activation inhibits the cardiac expression of transforming necrosis factor-α partly by antagonizing nuclear NF-κB activity in neonatal rat cardiac myocytes [90]. Moreover, the decreased activation of protein kinases, such as extracellular signal-regulated kinase 1/2, c-Jun N-terminal kinase, Akt, and glycogen synthase kinase 3 beta, may also contribute to the effect of PPARα on the heart [91-96].

Fibrates are used clinically for the treatment of dyslipidemia. They have been shown to enhance FAO, improve endothelial cell function, and decrease myocardial fibrosis and hypertrophy in animal models of heart failure [97]. Moreover, fenofibrate plus metformin exert a cardio-protective effect in a type 2 diabetes and acute myocardial infarction model [98]. Another PPARα agonist, AVE8134, has been shown to regress cardiac hypertrophy and fibrosis [99]. As the natural ligands for PPARα, FAs were reported to be defective in hypertrophic cardiomyopathy due to the reduced expression of the FA transporter cluster of differentiation-36 (CD36) [100, 101]. Overall, the cardiac response to various agonists of PPARα might be different because of ligand-dependent variation.

PPARα in blood pressure regulation

PPARα is expressed in both the endothelium and VSMCs [58, 59], suggesting that it may have an effect on vascular tone. The reactivity of the arterial wall is controlled in part by biomechanical inputs, including blood flow and blood pressure [10]. As mentioned above, the activation of PPARα by its ligands is important in the uptake, utilization, and catabolism of FAs through the upregulation of genes involved in FA transport and peroxisomal and mitochondrial FA β-oxidation. Moreover, PPARα ligands exert other actions on the vasculature [102, 103].

Blood vessel capacity and vasoconstriction are two important elements in the control of blood pressure. NO plays a significant role in the regulation of vascular tone, platelet aggregation, oxidative stress, leukocyte adherence, and smooth muscle cell mitogenesis [104]. Impairment of the NO/NOS system is one of the most important pathological events in the early phase of the development of hypertension. PPARs have been implicated as transcriptional regulators of the expression and activity of endogenous vasoconstrictors and their receptors. Therefore, it is possible that the induction of PPARα may attenuate the vasoconstriction response to major endogenous vasoconstrictors such as angiotensin II (Ang II), thromboxane A2 (TXA2), and endothelin 1 (ET-1) [102, 105]. The PPARα ligand clofibrate reduces high blood pressure and improves vascular reactivity in spontaneously hypertensive rats probably through the increased production of NO [106]. Some results have suggested that in the early stage of aortic coarctation-induced hypertension, stimulation of PPARα by clofibrate improves hypertension possibly by increasing antioxidant defenses, enhancing eNOS activity, and resetting the renin-angiotensin (RAS) system in the vasculature [105]. Overall, the blood pressure lowering effect of PPAR agonists are cardio-protective and could help to correct vascular structure and endothelial dysfunction in experimental models of hypertension [107].

PPARα in lipid disorder-related cardiovascular injury

PPARα regulates cardiac energy and lipid metabolism and plays a role in mitochondrial FA β-oxidation, which is critical for fuel generation in the heart through the transcriptional activation of carnitine palmitoyl transferase I [108]. The heart primarily relies on mitochondrial FAO to ensure ATP generation, but has metabolic flexibility to switch to other energy substrates, mainly glucose. This switch in substrate preference is observed in myocardial ischemia, cardiac hypertrophy, and heart failure [109]. The best evidence to support a causal role for metabolic disturbances in the development of cardiac dysfunction is the observation that children with genetic defects in FAO enzymes, which force the heart to rely on glucose, often develop cardiomyopathy [110]. However, PPARα expression can be downregulated by glucose, which can reduce FAO levels [107].

In addition to their direct anti-inflammatory and anti-atherosclerotic effects on the artery wall, PPARα and its agonists show a beneficial action on the metabolism of lipids and lipoproteins [111]. PPARα may alter lipid metabolism through multiple mechanisms that facilitate the transfer of FAs into mitochondria [108, 112]. Moreover, PPARα binds to synthetic and natural ligands to reduce the half-life of the PPARα receptor and finally alters lipid metabolism for the treatment of dyslipidemia, a major risk factor of cardiovascular diseases. Fibrates, which are PPARα agonists, are prescribed widely to reduce TG levels and raise high-density lipoprotein (HDL) levels with a modest effect on lowering low-density lipoprotein (LDL) levels. In the clinical setting, the recognized synthetic PPARα ligands for treating hyperlipidemia include clofibrate, ciprofibrate, fenofibrate, and gemfibrozil [113]. Fenofibrate therapy retards the development of atherosclerosis in $ApoE^{-/-}$ and $LDLR^{-/-}$ mice [114, 115]. Meanwhile, natural ligands, such as LTB4, and FAs, are enriched in tissues with a high capacity for FAO, including the heart, brown adipose tissue, and liver, and to a lesser extent in the kidney and skeletal muscle [8, 116]. During left ventricular hypertrophy, PPARα downregulation leads to a decrease of FAO and an increase of lipid accumulation in cardiac myocytes [17]. Moreover, the PPARα activator LTB4 regulates lipid metabolism and NO production in term placentas of diabetic rats, thereby regulating placental growth [117]. In addition, some novel dual PPAR agonists targeting both PPARα and PPARγ have beneficial effects on lowering glucose and maintaining lipid homeostasis.

The mechanisms mediating the hypolipidemic effects of PPARα may include: (1) the regulation of FAO metabolism and reduction of very low-density lipoprotein production; and (2) PPARα and their ligands reduce the expression of genes governing the intravascular hydrolysis of TG and LDLs, while they increase the expression of genes governing HDL

Table 1. PPARα polymorphisms associated with cardiovascular diseases

Studies	Polymorphisms	Associated diseases
Lin Y et al. 2012 [127]	PPARα Leu 162 Val (rs1800206)	Essential Hypertension
Arias et al. 2011 [131]	PPARα Leu 162 Val (rs1800206)	Stage C heart failure
Gouni-Berthold I et al. 2004 [132]	PPARα Leu 162 Val (rs1800206)	Atherosclerotic disease
Flavell et al. 2002 [128]	PPARα intron 7 G>C (rs4253778)	Coronary artery disease
Jamshidi et al. 2002 [133]	PPARα intron 7 G>C (rs4253778)	Left ventricular hypertrophy
Reinhard et al. 2008 [135]	PPARα rs135551/rs135543	Myocardial infarction
Enquobahrie et al. 2008 [125]	PPARα rs4253623	Myocardial infarction

production. In short, PPARα upregulates lipoprotein lipase and preserves HDLs [118, 119] by remodeling the size and composition of HDLs and facilitating TG metabolism through the increased transfer of unesterified cholesterol to HDLs [120-123].

Association of PPARα polymorphisms with cardiovascular diseases

Recently, reports have suggested a close relationship between PPARα polymorphisms and cardiovascular diseases (Table 1), including rs4253623, rs1800206 (L162V), rs4253778, rs135539, and rs135551 [124-127]. In the Lipid Coronary Angiography Trial, the V162 allele of L162V was associated with the reduced progression of angiographically assessed diffuse atherosclerosis, whereas the prospective Northwick Park Heart Survey found no impact of the L162V variant on the risk of ischemic heart disease [128]. In addition, subjects with the V162 allele are more likely to have high blood pressure [129]. Compared with L162 homozygotes, V162 allele carriers are more likely to develop diabetes mellitus or insulin resistance, but are associated with a reduced risk of cardiovascular events among the population of patients with diabetes mellitus/insulin resistance [130]. Another study found that the V162 allele of the human PPARα gene was a new risk factor for the development of stage C heart failure, likely via depressed cardiac PPARα activity [131]. Additionally, some data have suggested that the PPARα L162V polymorphism might protect against the development of atherosclerosis or coronary heart disease in patients with type 2 diabetes mellitus [132].

rs4253778 G>C is a polymorphism located in intron 7 of PPARα. Carriers of the C allele have significantly increased progression of coronary atherosclerosis compared with G allele homozygotes [128]. Studies revealed that 78% of V162 alleles are in combination with the intron 7 C allele, and the atheroprotective V162 allele strongly attenuates the proatherosclerotic effect of the intron 7 C allele [128]. PPARα intron 7 G/C was also associated with physiological and pathological left ventricular hypertrophy in 144 young male British Army recruits undergoing a 10-week physical training program and in 1148 men and women participating in the echocardiographic substudy of the Third Monitoring Trends and Determinants in Cardiovascular Disease Augsburg study [133]. In these studies, C allele homozygotes had a significantly greater left ventricular mass index compared with G allele homozygotes and C allele heterozygotes, which was greater in hypertensive subjects [133]. Moreover, Halder et al. found that the presence of the G allele of rs135542 was associated with higher cardiometabolic risk [134]. Another report found a significant association between rs135551 and myocardial infarction and an association trend between rs135543 and myocardial infarction [135]. The above evidence indicates that polymorphisms of the PPARα gene may influence the risk of developing cardiovascular diseases.

Table 2. Roles of PPARα ligands in cardiovascular diseases

Related diseases	Pathological roles	PPARα ligands
Vascular injury	Antiinflammation, improving lipid metabolism, acting with SIRT1, activation of NO pathway	LTB4, 8S-HETE, DHA, EPA, epoxyeicosatrienoic acids, and fenofibrate
Heart injury	Antiinflammation, activation of PI3K/Akt, activation of NO pathway	LTB4, 8S-HETE, DHA, EPA, epoxyeicosatrienoic acids, fenofibrate, WY-14643, GW7647, and AVE8134
BP regulation	Vasodilation, activation of NO pathway	LTB4, 8S-HETE, PEA, fenofibrate, and clofibrate
Lipid disorder-related cardiovascular injury	Enhancing cardiac FAO, antiinflammation, improving lipid metabolism	LTB4, 8S-HETE, FAs, and fibrates

Pharmacogenetic associations of PPARα with cardiovascular diseases

PPARs play important roles in many physiological and pathological processes including the modulation of cellular differentiation, metabolism of carbohydrates, lipids, and proteins, and tumorigenesis. All PPARs share the same structure comprising of a ligand-binding domain and a DNA-binding domain. In the clinical setting, PPAR agonists have been used to treat some diseases. PPARα is activated by fibrate hypolipidemic drugs and PPARγ is activated by insulin sensitizers of TZDs. No marketed drug is yet available for PPARβ/δ. The identification of fibrates and TZDs as respective ligands for PPARα and PPARγ was a groundbreaking finding that sparked notable pharmaceutical interest in PPARs as potential drug targets for the treatment of metabolic syndrome. One important study enrolled 5518 patients and analyzed the effects of combination therapy with fenofibrate and simvastatin; however, there was no beneficial effect of combined treatment with fenofibrate and simvastatin as compared with simvastatin alone in reducing cardiovascular risk in the majority of high-risk patients with type 2 diabetes [136]. Another study found that fibrates may decrease the incidence of combined cardiovascular outcomes according to meta-analysis of six clinical trials [137]. However, side effects associated with the clinical use of these ligands have emerged. In recent years, new and novel PPAR drugs with broad safety margins and therapeutic potential for metabolic syndrome are being developed, including partial, dual, and pan PPAR agonists, PPAR antagonists, and selective PPAR modulators.

Perspectives of PPARα in research and the clinical setting

The activation of PPARα by its agonists exerts a broad spectrum of biological actions in the vasculature and heart by regulating lipid metabolism and energy homeostasis, reducing inflammation, inhibiting oxidative stress and apoptosis, and improving contractile function. Such pleiotropic activity of PPARα makes it an interesting therapeutic target for the treatment of various pathologies, especially those linked to dyslipidemia and atherosclerosis that are frequently associated with cardiovascular diseases. Numerous studies using animal or specific cell models with genetic and/or pharmacological interventions have contributed to a better understanding of the pleiotropic effects of PPARα and have highlighted its protective role in the cardiovascular system under diverse pathological settings (Table 2). However, some aspects of the function of PPARα are still understood poorly and require further exploration via clinical and basic studies.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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