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PPARs: regulators of metabolism and as therapeutic targets in cardiovascular disease. Part I: PPAR- α

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This article provides a comprehensive review about the molecular and metabolic actions of PPAR- α . It describes its structural features, ligand specificity, gene transcription mechanisms, functional characteristics and target genes. In addition, recent progress with the use of loss of function and gain of function mouse models in the discovery of diverse biological functions of PPAR- α , particularly in the vascular system and the status of the development of new single, dual, pan and partial PPAR agonists (PPAR modulators) in the clinical management of metabolic diseases are presented. This review also summarizes the clinical outcomes from a large number of clinical trials aimed at evaluating the atheroprotective actions of current clinically used PPAR- α agonists, fibrates and statin-fibrate combination therapy.

First draft submitted: 31 August 2016; Accepted for publication: 21 March 2017; Published online: 5 June 2017

In spite of the recent advances in the prevention and treatment of cardiovascular disease (CVD), it still remains the leading cause of death globally, accounting for 17.3 million deaths per year [1,2]. Both obesity [3–6] and diabetes [7–10] have been implicated as major risk factors for CVD and given the recent escalation of obesity and surge in the prevalence of diabetes, both reaching epidemic levels in the USA [11–13] and the world [14–16], have the potential to further fuel the epidemic of CVD and raise the death rate from disease in the future. Accompanying obesity is also a constellation of metabolic derangements, including central obesity, dyslipidemia and hypertension, insulin resistance with compensatory hyperinsulinemia and glucose intolerance, and prothrombotic and proinflammatory states that together are commonly referred to as metabolic syndrome (MetS) [17–19]. MetS increases the risk of CVD by approximately twofold [20,21] and raises the risk for Type 2 diabetes mellitus (T2DM) by approximately fivefold [20,22], and currently affects 5–39% of the global adult population [23,24]. Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the USA, other Western countries as well as in other parts of the developing world [25–35]. The disease encompasses a wide spectrum of pathological conditions ranging from simple steatosis (excessive accumulation of lipid mainly triglyceride [TG], a benign condition) to nonalcoholic steatohepatitis (NASH) with variable degrees of fibrosis, the more aggressive form of fatty liver disease, which can progress to cirrhosis and associated secondary complications including hepatic failure and hepatocellular carcinoma [26–28,30–32]. NAFLD is strongly associated with several core components of MetS including obesity, insulin resistance or T2DM and dyslipidemia [33–35]. Like MetS, NAFLD is also a risk factor for T2DM [36–39] and CVD [37,40–42]. Also, the risk of NAFLD

KEYWORDS

- cardiovascular disease
- dyslipidemia • fibrates
- insulin resistance • lipid and glucose homeostasis
- metabolic diseases
- NAFLD • obesity

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and NASH is escalating in parallel with the epidemic of obesity and MetS.

The peroxisome proliferator-activated receptors (PPARs) are a subfamily of ligand-activated nuclear receptors/transcription factors that belong to the superfamily of nuclear receptors [43]. This superfamily is represented by 48 members in humans and 49 members in mice [44]. The PPAR subfamily consists of three isotypes: PPAR- α (NR1C1), PPAR β/δ (NR1C2) and PPAR γ (NR1C3), which are encoded by separate genes [43] and show overlapping but unique tissue distribution [45–47] and regulate specific metabolic processes [48–58]. PPARs modulate genes that regulate energy balance, glucose homeostasis, TG and lipoprotein metabolism, fatty acid synthesis, oxidation, storage and export, cell proliferation, inflammation and vascular tissue function [48–70]; dysregulation of these metabolic processes contributes to the pathogenesis of metabolic diseases such as obesity, MetS, diabetes, NAFLD and atherosclerosis. Indeed, there is evidence that PPARs contribute to the pathophysiology of these metabolic diseases. Thus, PPARs represent important molecular targets for the development of new drugs to treat obesity, MetS, T2DM, NAFLD and CVD. Indeed, two classes of drugs, fibrates and thiazolidinediones (TZDs) that selectively activate PPAR- α and PPAR γ , respectively, are already in clinical use. Fibrates (PPAR- α agonists), gemfibrozil, clofibrate, fenofibrate and fenofibric acid are used in clinical practice primarily due to their ability to substantially decrease plasma TG levels and increase HDL levels [71–74]. TZDs (PPAR γ agonists), also called glitazones, are insulin sensitizers and used as oral hypoglycemic agents to treat patients with T2DM [75–78]. Two TZDs, rosiglitazone and pioglitazone, are currently available in the USA. Currently, there are no marketed drugs targeting PPAR β/δ . Although, currently no designated therapies are available to treat MetS and NAFLD, extensive efforts are being devoted to develop new dual or pan agonists with combined properties of any of the two or all three PPARs, respectively. The logic behind these strategies is that by combining the properties of two or all three PPARs will lead to a super agonist(s) that will target multiple components of MetS and NAFLD and thus, will be highly efficacious in the clinical management of these metabolic diseases. These highly effective agonists bear the hope to exert beneficial actions

against T2DM and CVD. Finally, new modulators that preferentially modulate the functional efficacy of the transcriptional complex assembly itself are under development.

This review article (part I) and companion review article (part II) is an update of a previous article, which was written by one of the authors and published in this journal in September 2010 [79]. In this article (part I), we focus on molecular and cellular events connected with the expression and metabolic functions of PPAR- α . We discuss its involvement in the pathophysiology of vasculature, and the current developmental status of new single, dual, pan (multiple) and partial PPAR agonists and specific PPAR modulators with a therapeutic potential to treat individual components of MetS, T2DM, CVD and NAFLD including NASH.

Molecular characteristics of PPAR- α

The PPAR- α isotype is transcribed from the human *PPARA* gene, which consists of eight exons and is located at chromosomal region 22q12-q13.1 [80]. Similar to other members of the nuclear receptor family, PPAR- α contains five main domains [79] shown in **Figure 1**. The five domains are: the NH₂-terminal end, ligand-independent transactivation domain (or A/B domain); the 70-amino-acid long PPAR DNA-binding domain (DBD) or C domain, which contains two highly conserved zinc finger motifs and promotes the binding of the receptor to a DNA sequence in the promoter region of target genes known as the peroxisome proliferator response element (PPRE); the hinge region or D domain acts as a docking site for cofactors and also connects the DBD to the ligand-binding domain (LBD); the C-terminal, E/F domain or LBD, which is responsible for ligand specificity, and activation of PPAR binding to the PPRE that leads to increased expression of target genes, contributes to the dimerization of the receptor with retinoid X receptors (RXRs) and is a site for binding of co-activators and co-repressors; and two activation domains: one in the amino terminus (AF-1) and one in the carboxyl terminus (AF-2). AF-1 activation alone is in general weak, but synergizes with AF-2 upon ligand binding, leading to an increased gene transcription and expression. PPAR- α , like other two PPARs, forms heterodimers with RXRs (α , β , γ) and binds to a consensus cis-element, PPRE, in target DNAs, which consists of a two-hexanucleotide, AGGTCA (or a related sequence), separated

Figure 1. Schematic representation of the principal domains of PPARs. PPAR- α , PPAR β/δ and PPAR γ possess a modular structure and composed of five principal domains: AF-1, a ligand-independent activation domain in the A/B region; DBD, D domain; the hinge region; LBD and AF-2 activation domain.

AF: Activation factor; DBD: DNA-binding domain; LBD: Ligand-binding domain.

by one base pair (AGGTCANAGGTCA), called direct repeat 1. Under the unliganded state, PPAR/RXR heterodimers are bound to multicomponent repressors containing histone deacetylase activity, such as nuclear receptor corepressor and the silencing mediator for retinoid and thyroid hormone receptor, thereby inhibiting gene transcription (Figure 2A) [81,82]. Following stimulation by PPAR- α activators, PPAR- α /RXR heterodimers dissociate from co-repressors, and recruit co-activators such as steroid receptor co-activator-1 and the PPAR-binding protein with histone acetylase activity, and subsequently bind to PPRE target genes to modulate gene transcription (Figure 2B) [81].

Natural & synthetic ligands of PPAR- α

PPAR- α is activated by natural ligands, including saturated, monounsaturated and polyunsaturated fatty acids and their metabolites such as 8S-HETE and 8-HEPE, leukotriene B₄ (LTB₄), oxidized phospholipids and

lipoprotein lipolytic products (Table 1) [51,79]. In addition, Chakravarthy *et al.* [83] reported the identification of 1-pamitoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (16:0/18:1 GPC) as a physiologically relevant PPAR- α ligand in liver. Synthetic PPAR agonists, cPGI, Iloprost, WY-14643 and hypolipidemic fibrate drugs (e.g., bezafibrate, ciprofibrate, clofibrate, fenofibrate, gemfibrozil and fenofibric acid) are also potent activators of PPAR- α [51,79]. Among the fibrates, bezafibrate functions as a pan-activator of all three PPAR isotypes.

Metabolic functions of PPAR- α

PPAR- α was the first member of PPAR isotypes to be cloned and was named based on its ability to be activated by peroxisome proliferator chemicals [48]. PPAR- α is expressed predominantly in high-energy requiring tissues such as skeletal muscle, heart, liver and brown adipose tissue [45–47,84]. Significant expression of PPAR- α also occurs in the proximal tubules of the kidney,

intestinal mucosa, the adrenal gland and brown adipose tissue and most cell types present in the vasculature including endothelial cells (ECs), smooth muscle cells and monocytes/macrophages [49,52,85]. In humans, fibrate activation of PPAR- α has been shown to increase the circulating levels of atheroprotective HDL-cholesterol,

lower plasma levels of TG, free fatty acids and apolipoprotein CIII (apo-CIII) and improve the overall atherogenic plasma lipid profile [86–90] and exert beneficial effects on inflammation, insulin resistance and MetS [89,91–93]. Fibrates also improve plasma HDL and TG levels via induction of apo-AI and apo-AII [61,94] and apo-AV [95],

Figure 2. PPAR-mediated gene regulation. Under unliganded state, PPAR/RXR heterodimers are bound to multicomponent repressors containing histone deacetylase activity, such as NcoR and SMART, thereby inhibiting gene transcription (A). Ligand binding to either PPAR or RXR causes displacement of bound repressors, recruitment of co-activators such as SRC-1 and the PBP and transcriptional modulation (primarily activation) of gene transcription (B).

DBD: DNA-binding domain; NcoR: Nuclear receptor corepressor; PBP: PPAR-binding protein; PPRE: Peroxisome proliferator response element; RXR: Retinoid X receptor; SMART: Silencing mediator for retinoid and thyroid hormone receptor; SRC: Steroid receptor co-activator.

Table 1. Partial list of endogenous and synthetic peroxisome proliferator-activated receptor α agonists.

Endogenous ligands	Synthetic PPAR- α agonists	Dual PPAR- α/γ agonists	pan-PPAR- $\alpha/\beta/\delta/\gamma$ agonists
Fatty acids:			
– Palmitic acid	GW7647	Muraglitazar	Chiglitazar
– Stearic acid	WY14643	Tesaglitazar	Netoglitazar
– Oleic acid	Clofibrate	Farglitazar	Sodelglitazar
– Petroselinic acid	Fenofibrate	Ragaglitazar	Indeglitazar
– Linoleic acid	Bezafibrate	Naveglitazar	Sipoglitazar
– α -Linolenic acid	Ciprofibrate	Imiglitazar	–
– γ -Linoleic acid	Gemfibrozil	Saroglitazar	–
– Dithomo- γ -linolenic acid	Carbaprostacyclin (cPGI)	Aleglitazar	–
– Arachidonic acid	–	GFT505 [†]	–
– Docosahexaenoic acid	–	–	–
– Eicosapentaenoic acid	–	–	–
– C6–C18	–	–	–
– ETYA	–	–	–
Eicosanoids:	–	–	–
– LTB4	–	–	–
– 8-HEPE	–	–	–
– 8-(R)HETE	–	–	–
– 8-(S)HETE	–	–	–
– 12-HETE	–	–	–
– 9-(R/S)HODE	–	–	–
– 13-(R/S)HODE	–	–	–
– 20,8,9-HEET	–	–	–
– 20,11,12-HEET	–	–	–
– 20,14,15-HEET	–	–	–
– 15d-PGI ₂	–	–	–
– PGJ ₂	–	–	–
– PGI ₂ (Prostacyclin)	–	–	–
– PGA _{1/2}	–	–	–
– PGB ₂	–	–	–
Oxidized phospholipids	–	–	–
Lipoprotein lipolytic products	–	–	–
1-Palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (16:0/18:1 GPC)	–	–	–

[†]Dual PPAR- $\alpha/\delta(\beta)$ agonist.

15d-PGI₂: 15-deoxy- $\Delta^{12,14}$ -PGJ₂; ETYA: Eicosatetraenoic acid; GFT505: 2-(2,6-dimethyl-4-(3-(4-(methylthio)phenyl)-3-oxo-1-propenyl)phenoxy)-2-methylpropanoic acid; GW7647: 2-((4-(Cyclohexylamino)carbonyl)[4-cyclohexylbutyl]amino)ethyl]-phenylthio)-2-methylpropanoic acid; HEET: Hydroxyepoxyeicosatrienoic acid; HEPE: Hydroxyeicosapentaenoic acid; HETE: Hydroxyeicosatetraenoic acid; HODE: Hydroxyoctadecadienoic acid; LTB4: Leukotriene B4; PGA: Prostaglandin A; PGB: Prostaglandin B; WY14643: 4-Chloro-6-(2,3-xylyldino)-2-pyrimidinylthio]acetic acid.

respectively. Increasing evidence also suggests that the fibrate class of drugs also decreases the rate of CVD events, especially in patients with dyslipidemia and T2DM [87–89]. As summarized below, PPAR- α also plays a critical regulatory role in the metabolic functions of liver, skeletal and cardiac muscle and the vascular system.

• Liver

PPAR- α controls the expression of a wide range of hepatic genes encoding enzymes/proteins involved in fatty acid uptake and intracellular transport,

fatty acid activation (acyl-CoA formation), fatty acid oxidation, lipogenesis, ketogenesis and lipoprotein/cholesterol metabolism (**Supplementary Box 1**). Definitive evidence about the pivotal role of PPAR- α in hepatic fatty acid and lipoprotein metabolism has been provided by studies involving the use of fibrates [61,65,69,86,96], and PPAR- α -knockout (KO; PPAR- $\alpha^{-/-}$) and PPAR- α transgenic mice (PPAR- α^{Tg} ; **Supplementary Box 2**). Ligand (fibrate) activation of PPAR- α is shown to enhance fatty acid catabolism as a result of upregulated transcriptional expression of genes involved

in lipid transport, fatty acid β - (mitochondrial and peroxisomal) and Ω - (peroxisomal) oxidation and ketogenesis [55,65,69,86,96–98]. PPAR- α activation also modulates the expression of key genes involved in VLDL-TG turnover (e.g., *APOC2*, *APOC3*, *LPL*, *ANGPTL4*) as well as apolipoproteins associated with HDL, such as APOA1 and APOA2 [55,65,69,86,96–98].

• Natural mutations & polymorphisms within the PPAR- α receptor

Additional evidence that PPAR- α plays a central role in the regulation of lipid metabolism is obtained from studies involving human subjects carrying genetic variants of the *PPAR- α* gene (i.e., single nucleotide polymorphisms) [99]. Over a dozen genetic variants in both the DBD and LBD that influence the transcriptional activity of human PPAR- α have been described. These include L162V (a leucine-to-valine change in codon 162 rs1800206) and V227A (a valine-to-alanine change in codon 227 rs1800234), which are the most common PPAR- α polymorphisms reported to date and associated with variations in lipid metabolism ([99] and references therein). The L162V polymorphisms in the LBD of the *PPAR- α* gene occur more commonly in European and North American Caucasian populations, whereas the V227A variant located in the hinge region between the DBD and LBD of the receptor occurs with relatively high allelic frequency in oriental populations including Chinese and Japanese ([99] and references therein). The L162V polymorphism is associated with increased levels of TG, total cholesterol, LDL cholesterol, and apo-AI and apo-B and reduced obesity [99]. While one report concludes that the L162V polymorphism is not associated with T2DM, BMI or body fat composition, several other studies suggest that single nucleotide polymorphisms within the *PPAR- α* gene are associated with cardiovascular risk factors including dyslipidemia and also impact fasting and postprandial lipid levels and the progression to T2DM ([99] and references therein). By contrast, the carriers of the V227A allele appear to have lower levels of total cholesterol and TG and the effect of V227A seems to be more noticeable in women than men [99]. In addition, significant interactions were also reported between the V227A polymorphism and alcohol-drinking habits, total cholesterol and TG [99].

• Skeletal muscle & heart

Skeletal and cardiac muscles are also major sites of fatty acid oxidation. In differentiated cultured human myotubes, agonist (GW7647)-mediated activation of PPAR- α results in increased fatty acid oxidation [100,101], diminished accumulation of TG [100] and upregulation of PDK4 [102]. Among the four isoforms, PDK4 is the most studied isoform, which phosphorylates and inhibits the pyruvate dehydrogenase complex activity [103], thereby restricting the pyruvate dehydrogenase complex-catalyzed formation of acetyl-CoA from pyruvate and its subsequent oxidation in the mitochondria [104]. Evidence was presented showing that feeding rats a selective PPAR- α agonist, WY-14643, leads to large increases in PDK4 activity, and protein and mRNA levels in gastrocnemius muscle [105]. It was further shown in humans that mRNA levels of PPAR- α strongly correlate with mRNA levels of several genes involved in lipid metabolism in skeletal muscle including *CD36*, *UCP-2*, *UCP-3*, *LPL* and *CPT-1* [106]. Oral gavaging of female rats with WY-14643 and fenofibrate with minimal PPAR γ and negligible PPAR δ activities and subsequent comparison of the transcriptional responses identified a PPAR- α activation signature that is visible in soleus (type I), but not in quadriceps femoris (type II), skeletal muscle fibers [107]. The PPAR- α -sensitive signature consists of most genes involved in fatty acid uptake and β -oxidation. Likewise, *in vivo* treatment of hamsters with a potent PPAR- α agonist, ureido-fibrate-5, approximately 200-fold more potent than fenofibric acid, significantly enhanced the expression of CPT-1 mRNA levels in soleus muscle [108]. Limited studies have also employed both gain-of-function and loss-of-function strategies to further examine the role of skeletal muscle fuel metabolism and function (Supplementary Box 2). The skeletal muscles from both wild-type (WT) and whole-body PPAR- α -null mice exhibit similar fatty acid oxidative capacity in the fed state but it is reduced by 28% in KO muscle in response to starvation. Two well-characterized PPAR- α target genes, *PDK4* and *UCP-3*, show no changes in their expression between WT and PPAR- α ^{-/-} muscles when mice are subjected to an exercising (running) regimen or starvation. These studies further suggest that high levels of muscle PPAR β/δ can compensate for loss of PPAR- α activity. Another study reported that skeletal muscle content of Krebs (TCA) cycle intermediates, amino acids and

short-chain acylcarnitine species are diminished in PPAR- α KO mice as compared with WT mice, suggesting that blunted TCA cycle flux and enhanced protein degradation are also significant pathophysiological effects of PPAR- α deficiency. In transgenic mice overexpressing skeletal muscle-specific PPAR- α (MCK-PPAR- α), the expression of a number of skeletal muscle genes involved in cellular fatty acid import, fatty acid binding, TG synthesis and mitochondrial and peroxisomal β -oxidation is increased. The expression of genes encoding UPC-2 and UPC-3 is also induced. Likewise, increased expression of genes encoding components of Krebs cycle and steps in mitochondrial electron transport chain (oxidative phosphorylation pathway) has been reported. In contrast, genes involved in cellular glucose utilization pathways including uptake (GLUT1 and GLUT4) and utilization (glycolytic enzymes such as phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase) are downregulated.

Similar to liver, PPAR- α is expressed at a relatively high level in the parenchymal cells of the heart. PPAR- α agonist treatment of myocytes *in vitro* or adenovirus-mediated PPAR- α overexpression results in the induction of multiple genes involved in fatty acid metabolism including fatty acid transport, esterification and β -oxidation (**Supplementary Box 2**). To further explore the cardiac-specific effects of PPAR- α , transgenic mice with cardiac-specific overexpression of PPAR- α under the control of the MHC promoter (MHC-PPAR- α) and PPAR- α KO mice have been evaluated (**Supplementary Box 2**). MHC-PPAR- α mice exhibit increased expression of genes involved in cardiac fatty acid transport and oxidative metabolism and reduced expression of genes involved in glucose uptake and use. Likewise, hearts from MHC-PPAR- α mice show increased rates of fatty acid uptake, and decreased rates of glucose uptake and cellular oxidation, respectively, and enhanced myocyte TG accumulation, a phenotype very similar to diabetic heart. These mice develop spontaneous cardiac hypertrophy, contractile dysfunction, 'fetal' gene induction and insulin resistance; the cardiac phenotype is exacerbated in MHC-PPAR- α mice when fed a high-fat diet enriched in long-chain fatty acids or made insulin-deficient. Besides ventricular hypertrophy, MHC-PPAR- α mice also exhibit impaired recovery of cardiac function when subjected to ischemic-reperfusion injury

and signs of dysregulated mitochondrial biogenesis. Compare to WT mice, PPAR- α -null mice exhibit decreased myocardial mitochondrial β -oxidation of medium (octanoic acid) and long-chain (palmitic acid) fatty acids. Likewise, expression of several PPAR- α target genes, including genes involved in mitochondrial fatty acid β -oxidation and fatty acid uptake in heart, is associated with reduced response to PPAR- α deficiency; these genes also do not respond to fasting or diabetes in PPAR- α -null mice. In contrast, peroxisomal β -oxidation of the very long-chain fatty acid (lignoceric acid) is unaffected by PPAR- α deficiency. Another study demonstrated that fatty acid oxidation rates were reduced significantly in beating hearts from PPAR- α ^{-/-} mice compared with WT mice. Interestingly, rates of glucose oxidation and glycolysis were increased along with elevated levels of malonyl CoA, which inhibits fatty acid oxidation by inhibiting CPT-1 in PPAR- α -null mice. The protein and mRNA levels of malonyl-CoA decarboxylase, which catabolizes malonyl CoA, were significantly decreased in the hearts from PPAR- α ^{-/-} mice. However, no changes in the expression levels of glucose transporters, GLUT1 and GLUT4, were noted in hearts of PPAR- α -deficient mice compared with WT control mice, suggesting that the observed increases in glucose oxidation and glycolysis were not simply as a result of enhanced glucose uptake. Experimental evidence also suggests that the PPAR- α plays an important regulatory role in the functional expression of myocardial uncoupling proteins. Although, treatment of WT mice with streptozotocin to induce diabetes, feeding them a high-fat diet or subjecting them to extended fasting, all lead to decreased cardiac expression of GLUT-4 protein and decreased glucose uptake during ischemia, no such effects were noted using PPAR- α ^{-/-} mice.

• Vasculature, inflammation & atherosclerosis

PPAR- α is expressed in the vasculature and its expression is detected in ECs, vascular smooth muscle cells (VSMCs) and monocytes/macrophages [49,51,52,54,59,109–113] (**Table 2**). In ECs, PPAR- α agonists interfere with the metabolic processes involved in recruitment and adhesion of inflammatory cells, and safeguard against vascular inflammation and injury. Synthetic PPAR- α activators, such as fibrates, attenuate cytokine-induced expression of vascular cell adhesion molecule-1 and thereby restrict the recruitment of inflammatory leukocytes to the activated

Table 2. Metabolic and vascular actions of peroxisome proliferator-activated receptor α .

Tissues/cells	Positive regulation	Negative regulation
Metabolic actions		
Liver	<ul style="list-style-type: none"> ↑ ApoAI; ↑ ApoAII; ↑ ApoAV ↑ Cholesterol catabolism ↑ FA oxidation and activation ↑ Fatty acid oxidation genes ↑ FATP; ↑ FAT/CD36 ↑ Gluconeogenesis and glycolysis ↑ Insig1 ↑ Ketogenesis ↑ Lipogenesis ↑ LPL and TG clearance 	<ul style="list-style-type: none"> ↓ Apoptosis ↓ HL ↓ Inflammation ↓ Oxidative stress ↓ Proteolysis of SREBF1 ↓ SREBF2 – – – –
Skeletal muscle	<ul style="list-style-type: none"> ↑ FA oxidation gene ↑ FA oxidation ↑ Insulin sensitivity 	<ul style="list-style-type: none"> ↓ Glucose intolerance – –
Cardiac muscle	<ul style="list-style-type: none"> ↑ AT₂ receptor ↑ FA uptake ↑ FA oxidation – – – – 	<ul style="list-style-type: none"> ↓ AT₁ receptor ↓ Cardiac hypertrophy and inflammation ↓ Genes for glucose uptake and oxidation ↓ ED-1 (CD68) expression ↓ NF-κB activity ↓ VCAM-1, ICAM-1 ↓ Platelet and endothelial cell adhesion
Plasma	<ul style="list-style-type: none"> ↑ HDL ↑ RCT – – – – – 	<ul style="list-style-type: none"> ↓ ApoC3 ↓ Dyslipidemia ↓ Inflammation ↓ IFN-γ ↓ TNFα ↓ sdLDL ↓ VLDL-TG
Vascular actions		
Blood vessels	<ul style="list-style-type: none"> ↑ RCT – – 	<ul style="list-style-type: none"> ↓ Ang II-elevated blood pressure ↓ Atherosclerosis ↓ Inflammation
VSMC	<ul style="list-style-type: none"> ↑ Apoptosis ↑ HO-1 ↑ p16^{INK4a} – – – – – – 	<ul style="list-style-type: none"> ↓ AP-1 ↓ β5 integrin ↓ Pro-inflammatory COX-2 ↓ IL-1, IL-6 and prostaglandin ↓ Inflammatory response ↓ Proliferation and migration ↓ NF-κB ↓ p38 MAPK ↓ sPLA₂-IIA
ECs	<ul style="list-style-type: none"> ↑ eNOS expression and NO release ↑ p38 MAPK ↑ SOD1 (Cu,Zn-SOD) ↓ MCP-1 – – – – 	<ul style="list-style-type: none"> ↓ AP-1 ↓ ET-1 expression and production ↓ Cytokine-mediated expression of VCAM-1 ↓ F3 ↓ IL-8 ↓ Leukocyte recruitment ↓ NF-κB ↓ VEGFR2

ABCA1: ATP-binding cassette transporter; Ang II: Angiotensin II; AT₁: Endothelin-1 receptor; AT₂: Endothelin-2 receptor; COX: Cyclooxygenase; EC: Endothelial cell; ET-1: Endothelin 1; FA: Fatty acid; LPL: Lipoprotein lipase; MMP: Matrix metalloproteinase; NPC: Nieman–Pick disease; PPAR: Peroxisome proliferator-activated receptor; RCT: Reverse cholesterol transport; sdLDL: Small-dense LDL; TF: Tissue factor; TG: Triglyceride; VSMC: Vascular smooth muscle cell.

Table 2. Metabolic and vascular actions of peroxisome proliferator-activated receptor α (cont.).

Tissues/cells	Positive regulation	Negative regulation
Monocytes/macrophages	↑ ABCA1	↓ F3
	↑ CLA-1	↓ Glycated LDL uptake
	↑ CPT-1	↓ iNOS
	↑ HO-1	↓ Inflammatory signal
	↑ NPC1, ↑NPC2	↓ IL-2; ↓IFN- γ
	↑ RCT	↓ Lipid accumulation
	–	↓ LPL
	–	↓ MMP-9
	–	↓ Proinflammatory cytokine osteopontin
	–	↓ TNF- α
	–	↓ TF and activity

ABCA1: ATP-binding cassette transporter; Ang II: Angiotensin II; AT₁: Endothelin-1 receptor; AT₂: Endothelin-2 receptor; COX: Cyclooxygenase; EC: Endothelial cell; ET-1: Endothelin 1; FA: Fatty acid; LPL: Lipoprotein lipase; MMP: Matrix metalloproteinase; NPC: Nieman–Pick disease; PPAR: Peroxisome proliferator-activated receptor; RCT: Reverse cholesterol transport; sdLDL: Small-dense LDL; TF: Tissue factor; TG: Triglyceride; VSMC: Vascular smooth muscle cell.

ECs [49,51,52,54,59,109–113]. In contrast, other studies suggest that such reduction in vascular cell adhesion molecule-1 expression is achieved in part through inhibition of the proinflammatory mediator, NF- κ B transcription factor. PPAR- α ligands have been shown to both inhibit and induce expression of MCP-1, implying both anti-inflammatory and proinflammatory and proatherogenic effects. In addition, PPAR- α agonists induce NOS expression and NOS catalyzed increased NO production in vascular ECs, suggesting a vasculoprotective effect [49,51,52,54,59,109–113]. Furthermore, treatment of ECs with PPAR- α activators leads to downregulation of agonist-stimulated endothelin-1 expression and production. PPAR- α has also been implicated in the regulation of redox responses in the endothelium, and increasing evidence suggests that excessive oxidative stress is a major contributor to endothelial dysfunction. PPAR- α induces the expression of the cytosolic Cu,Zn-SOD (SOD1), and also attenuates the induction of p22 and p47phox subunits of the superoxide-producing nicotinamide adenine dinucleotide phosphate oxidase (NOX) in primary ECs. PPAR- α exerts additional metabolic effects in ECs as summarized in **Table 2** (also see [49,51,52,54,59,109–113] and the references therein).

Similar to other vascular cells, PPAR- α is expressed in appreciable amounts in vascular smooth muscle cells (VSMCs) and plays an anti-inflammatory role (**Table 2**). PPAR- α agonists inhibit the synthesis of proinflammatory mediators such as IL-1-mediated activation of IL-6 production (a marker for SMC activation) and prostaglandin along with cyclooxygenase-2 through suppression of NF- κ B signaling

in VSMCs [49,51,52,54,59,109–112]. Treatment of VSMCs with PPAR- α (WY-14643, fenofibrate) and PPAR γ (rosiglitazone, troglitazone) ligands leads to enhanced expression of HO-1, a mediator of anti-inflammatory and antiproliferative actions of PPAR- α/γ . Synthetic PPAR- α ligands, fibrates, inhibit VSMC proliferation and migration by targeting the NF- κ B, TGF- β /Smad and MAPK pathways, and cyclin-dependent kinase inhibitor and tumor-suppressor CDKN2A/p16INK4a, leading to inhibition of retinoblastoma protein phosphorylation, decreased G₁- to S-phase transition and less intimal hyperplasia *in vivo* [49,51,52,54,59,109–113]. A PPAR- α -specific ligand, docosahexaenoic acid, was shown to exert proapoptotic effects on VSMCs *in vitro* mediated by the p38 MAPK signaling cascade. PPAR- α agonists have also been shown to abolish the IL-1 β -induced expression of group IIA secretory phospholipase A2, a proinflammatory mediator of atherosclerosis. PPAR- α agonists impact a number of other metabolites and metabolic processes as summarized in **Table 2**.

PPAR- α is expressed at variable levels in various inflammatory cells including human monocytes, lymphocytes, macrophages and macrophage-rich regions of human atherosclerotic regions. There are three main types of lymphocytes: B cells, T cells and natural killer cells. Among these, T (CD4⁺ T and CD8⁺ T cells) and B lymphocytes constitutively express PPAR- α and PPAR γ . PPAR- α is the predominant isoform expressed in lymphocytes but its expression is suppressed following activation of lymphocytes [49,51,52,54,59,109–113]. Furthermore, pro/pre-B-cells are significantly decreased in the bone marrow of mice treated with PPAR- α ligand WY-14643, indicating that PPAR- α is involved in

B-cell development. Ligand activation of PPAR- α in macrophages inhibits the activation of inducible NOS, the synthesis of tissue factor, matrix metallo-peptidase-9 (also called gelatinase B) and TNF- α secretion [49,51,52,54,59,109–113]. Agonist activation of PPAR- α also has been shown to attenuate the expression of platelet-activating receptor in monocytes and macrophages, IFN γ and IL-2 proinflammatory cytokine expression in human T cells and inhibits the expression of osteopontin in human macrophages via suppression of AP-1 activity. Similarly, PPAR- α activators cause accelerated degradation of the neutrophil chemoattractant potent proinflammatory LTB $_4$ expression in granulocytes and macrophages and promote apoptosis and clearance of old monocyte/macrophages. Interestingly, it should be noted that LTB $_4$ is a natural ligand of PPAR- α (Table 1) and, thus, LTB $_4$ most likely plays a dual role; it may initially boost the inflammatory response and subsequently it induces a genetic program that eventually attenuates inflammation. PPAR- α also regulates the process of reverse cholesterol transport by promoting cholesterol efflux from cholesterol-laden macrophages to ApoA-I/HDL acceptors. In addition, treatment of human macrophages with PPAR- α agonists increases the expression of cholesterol efflux proteins, ATP-binding cassette transporter-1 (ATP-binding cassette-1, subfamily A, member 1), CLA-1/SR-B1 (an HDL receptor which, in addition to ATP-binding cassette transporter-1, mediates cellular cholesterol efflux) and NPC1 and NPC2 proteins, which facilitate the transport of free cholesterol out of the lysosome after receptor-mediated endocytosis of LDL and participate in cellular cholesterol trafficking including cholesterol transport to plasma membranes for efflux. Likewise, PPAR- α agonist treatment of macrophages downregulates the expression of the apoB-48 remnant-type receptor and reduces the uptake of glycated LDL and TG-rich remnant lipoprotein particles. Moreover, PPAR- α activation results in attenuation of macrophage TG accumulation and increased translocation of intracellular cholesterol to the plasma membrane for its efflux. PPAR- α activators have also been shown to upregulate the mRNA and protein expression, but decrease secretion of the TG-hydrolyzing enzyme lipoprotein lipase and diminish ACAT-1 activity, an enzyme involved in cholesterol esterification and intracellular storage.

The role of PPAR- α in the pathogenesis of atherosclerosis has also been studied extensively. However, despite the overwhelming evidence

in support of a beneficial role of PPAR- α in atherosclerosis (as noted above) including existing clinical evidence, the use of genetic mouse models of atherosclerosis have yielded conflicting results. For example, it has been shown that PPAR- α deficiency improves insulin resistance and causes a reduction in atherosclerotic lesion areas in apoE-null mice [114]. In contrast, the PPAR- α ligand fenofibrate was shown to cause a significant reduction in the lesion surface area of the aortic sinus of human apoA-I transgenic-apoE-deficient (hapoA-I Tg $\times$ apoE-deficient) mice [115]. Likewise, PPAR- α agonist treatment of LDL receptor null mice (LDLR $^{-/-}$) was shown to inhibit both atherosclerosis and the formation of macrophage foam cells in the peritoneal cavity [116]. In another study, PPAR- α agonist fenofibrate treatment decreased atherosclerotic lesions in a nondiabetic dyslipidemic apoE KO mouse model overexpressing human ApoE2 (E2 knock-in mice) [117]. Moreover, macrophage overexpression of PPAR- α leads to attenuation of atherosclerosis in LDLR-deficient mice [118]. Two reports provide evidence that tesaglitazar, a dual PPAR- α/γ agonist, reduces atherosclerosis following treatment of normal [119] or diabetic [120] LDLR-deficient mice. Tesaglitazar also attenuated atherosclerosis in apoE*3Leiden CETP transgenic mice [121] and in insulin-resistant and hypercholesterolemic apoE*3Leiden mice [122], whereas another PPAR- α/γ dual agonist enhanced atherosclerosis in apoE KO mice [123].

• Post-translational modifications of PPAR- α receptor

Limited studies have demonstrated that PPAR- α is regulated by post-translational modification via phosphorylation [124,125]. Several consensus phosphorylation sites for PPAR- α have been identified, including sites for PKA, PKC, MAPK, CK2 and GSK3. It was reported that cholera toxin and other PKA activators can enhance mouse PPAR- α transcriptional activity both in the absence and presence of exogenous ligands in transient transfection assays [126]. The major site of phosphorylation was localized in the C-domain, although the enhancement of full activity also required the AF-2 domain [126]. In addition, an effect of PKA activators was also observed on PPAR- α –DNA interaction. Treatment of primary rat adipocytes with insulin increased the phosphorylation of PPAR- α , an effect that was associated with increased PPAR- α

transcriptional activity [127]. Moreover, it was shown that insulin promotes PPAR- α activation in HepG2 human hepatoma cells through extracellular regulated kinase 1/2 (ERK1/2)-catalyzed S12 and S21 phosphorylation of serine residues in the A/B domain of human PPAR- α [128]. Another study demonstrated that exposure of rat hepatic Fao cells to PPAR- α receptor agonist led to increased phosphorylation of PPAR- α [129]. In contrast, growth hormone was reported to inhibit PPAR- α transcriptional activity via the Janus kinase-signal transducer and activator of transcription 5B (JAK2/STAT5B) signaling pathway [124]. In addition, inhibition of ERK1/2 with MEK inhibitor PD98059 resulted in decreased PPAR- α activity, whereas pharmacological (LY2944004 or wortmannin) inhibition of PI3K activity led to a robust induction of PPAR- α activity [124]. Using *in vitro* assays, Barger *et al.* provided evidence that p38 MAPK phosphorylates the A/B domain of PPAR- α in cardiac monocytes at S6, S12 or S21 serine residues [130]. This phosphorylation in cardiac myocytes led to an enhancement of ligand-dependent transcriptional activity as a result of increased functional interaction with the transcriptional co-activator PPAR- γ -co-activator-1 α (PGC-1 α) [130]. In contrast, anisomycin, a p38 MAPK inhibitor, treatment caused a dose-dependent increased phosphorylation of PPAR- α and suppression of its transcriptional activity in COS-7 and H4IIE hepatoma cells [131]. Interestingly, in a rat cardiac myocyte cell line, activation of ERK1/2 was accompanied by a reduction in PPAR- α transcriptional activity [132]. Studies have also shown that synthetic PKC activators and the DAG analog phorbol myristol acetate can increase the cellular levels of the phosphorylated form of PPAR- α [125], while inhibitors of PKC decreased agonist-induced PPAR- α transactivation [133,134]. Furthermore, overexpression of PKC isoforms α , β , δ and ζ impacted both basal and agonist (WY-14643)-induced PPAR- α activity [135]. *In vitro* kinase assays revealed that PPAR- α is a substrate of GSK3 with preferential phosphorylation at its S73 serine residue in the A/B domain and that overexpression of GSK3 leads to accelerated degradation of PPAR- α protein [124]. There are some additional kinases that also catalyze the phosphorylation of PPAR- α as noted in previous reviews [124,125].

• Clinical trials to test the effectiveness of fibrates for primary & secondary prevention of CVD

As noted above, fibrates are a novel class of drugs that function as agonists for PPAR- α . They are effective for improving atherogenic dyslipidemia, including lowering high-circulating TG, raising HDL-cholesterol and lowering the small dense fraction of LDL-cholesterol. A number of clinical trials for the past three decades or so have been conducted to assess the efficacy of fibrates for primary and secondary prevention of cardiovascular events (Supplementary Box 3). The outcome of these primary prevention trials and as summarized by Jacob *et al.* [136] is that moderate-quality evidence suggests that fibrates lower the risk for cardiovascular and coronary events in primary prevention, although the absolute treatment effects in the primary prevention of cardiovascular events appear to be modest. The authors also reported that there is low-quality evidence that fibrates have no effect on overall or non-CVD mortality. Additionally, the authors point out that very low-quality evidence that exists suggests that fibrates are not associated with increased risk for adverse effects [136]. Likewise, critical evaluation of secondary prevention trials has led Wang *et al.* [137] to conclude that there is moderate evidence to suggest that fibrate drugs can be effective in the secondary prevention of the composite outcome of nonfatal stroke, nonfatal myocardial infarction and vascular deaths. However, it should be pointed out that these beneficial actions of fibrates were observed by mainly using clofibrate, a fibrate drug whose clinical use was discontinued in 2002 due to its adverse effects. Further trials with the use of currently clinically used fibrates in populations with previous stroke and also against a background treatment with standard care (statin treatment) are required.

• Statin-fibrate combination for mixed dyslipidemia

It is becoming increasingly clear that statin and fibrate combination therapy results in a more effective improvement in lipid parameters, especially in the case of severe or refractory mixed hyperlipidemia than either monotherapy [138–140]. Several large randomized clinical trials have shown that the combined administration of fenofibrate/simvastatin to patients with mixed dyslipidemia is not associated with significantly

increased incidence of severe undesirable effects compared with simvastatin monotherapy [140]. The incidence of rhabdomyolysis is slightly increased with fibrate/statin-combined therapy, but actual risk of developing rhabdomyolysis is a rare occurrence [140]. Although fenofibrate treatment is known to cause increases in creatinine and homocysteine serum levels, the incidence of diabetic nephropathy and thrombotic events was not significantly increased by the fenofibrate/simvastatin combination compared with simvastatin monotherapy in the Action to Control Cardiovascular Risk in Diabetes Lipid trial (Supplementary Box 3) [140]. Furthermore, a reduction in albuminuria was observed with fenofibrate in the Fenofibrate Intervention and Event Lowering in Diabetes and Action to Control Cardiovascular Risk in Diabetes Lipid trials (Supplementary Box 3) [140]. Overall, the fenofibrate/simvastatin combination therapy is safe and effective in normalizing the lipid profile in mixed dyslipidemia [140]; however, consistent evidence documenting that these lipid changes translate into improved clinical outcomes is generally lacking.

• Next-generation dual & pan PPAR- α agonists & selective PPAR- α modulators

The PPAR- α and PPAR γ agonists, fibrates and TZDs, respectively, are in clinical use for several decades as medications to treat dyslipidemia and hyperglycemia in patients with T2DM. No PPAR β / δ -specific drugs, however, are currently marketed or in routine clinical use (Table 3). Although various fibrates and TZDs are very effective in reversing or improving dyslipidemia and hyperglycemia/insulin resistance, respectively, many of these agonists also exhibit other biological responses and off-target side effects. This has been attributed primarily to drug-target complexes that involve many corepressor and co-activator proteins in relation to specific target gene promoters [141]. In addition, recent data provide evidence that some PPAR- α and PPAR γ agonists interact with other non-PPAR-sensitive targets. Currently, considerable efforts are underway to develop new highly PPAR-specific drugs that more selectively modulate PPAR-RXR transcriptional complex assembly, target more than one PPAR receptor simultaneously (dual or pan PPAR agonists), act as partial agonists or selective PPAR modulators (SPPARMs)/agonists with tissue-selective and targeted gene-selective activities.

Until now efforts to develop highly efficacious dual and pan PPAR agonists have not been very successful. Indeed development of a number of potent dual PPAR agonists, such as muraglitazar (Bristol-Myers Squibb Co.), naveglitazar (Eli Lilly and Company and Ligand Pharmaceuticals), ragaglitazar (Dr Reddy's Laboratories Ltd. and Novo Nordisk), tesaglitazar (AstraZeneca), imiglitazar (Takeda Pharmaceuticals) and aleglitazar (Hoffmann-La Roche), has been discontinued due to various safety concerns. Only two PPAR- α / γ agonists, saroglitazar and lobeglitazone, have been marketed and are now in clinical use in the countries in which they were developed. Saroglitazar was approved by the Indian regulatory authority Drug Controller General of India as a novel glucose- and lipid-lowering drug for the treatment of diabetic dyslipidemia, hyperglycemia and lipodystrophy [142–146]. Lobeglitazone sulfate was approved by the Ministry of Food and Drug Safety (Korea) on 4 July 2013. It was developed and marketed as Duvie by Chong Kun Dang Corporation. Lobeglatazone is an agonist for both PPAR- α and PPAR γ , and it works as an insulin sensitizer. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [147,148]. Recent studies indicate that lobeglitazone may also possess considerable therapeutic potential for the treatment of NAFLD [149] and atherosclerotic CVD [150]. In addition, a compound, chiglitazar [151,152] (PPAR- α / γ dual agonist), has completed Phase II, IIA and IIB clinical trials. Currently, Phase III is in progress in China in patients with T2DM and insufficient glycemic control despite diet and exercise. These are: Phase III Study of Chiglitazar in Patients With T2DM and Insufficient Glycemic Control Despite Diet and Exercise – A Multicenter, Randomized, Double-Blind and Placebo-Controlled Trial; and Phase III Study of Chiglitazar in Patients With T2DM and Insufficient Glycemic Control Despite Diet and Exercise – A Multicenter, Randomized, Double-Blind and Sitagliptin-Controlled Trial. GFT505, a dual PPAR- α / δ (β) agonist, is in development for the treatment of impaired glucose metabolism and insulin resistance, T2DM, atherogenic dyslipidemia, NASH/NAFLD [153–156]. Previously, development of several PPAR pan agonists, such as sipoglitazar, sodelglitazar (GW-677954), indeglitazar (DPM-204 and PLX-204) and GW-625019, have been terminated due to serious safety concerns.

Table 3. Dual and pan-peroxisome proliferator-activated receptor α agonists in development or marketed.

Compound	Class	Developer	Current status
Chiglitazar	PPAR- α/δ (β)/ γ pan agonist	Shenzhen Chipscreen Biosciences, Ltd.	Chiglitazar is in Phase III trials for Type 2 diabetes in China
Saroglitazar	Dual PPAR- α/γ agonist	Zydus Cadila, India	Saroglitazar is only marketed in India under the trade name Lipaglyn for the treatment of diabetic dyslipidemia or hypertriglyceridemia in Type 2 diabetes
GFT505	Dual PPAR- α/δ (β) agonist	GENFIT Corp.	GFT505 is in Phase III trials for the treatment of NASH
Fenofibric acid (ABT-335, Triplix)	PPAR- α agonist	–	On the market, fenofibric acid is a new formulation of fenofibrate that has been approved for the concomitant use with statins
Pemafibrate, also known as K-877 and (R)-K 13675	Selective PPAR- α agonist	Kowa Pharmaceutical Company Ltd	Pemafibrate had been filed as a new drug application by Kowa for the treatment of dyslipidemia (high TG and low HDL-cholesterol) in Japan in 2015. Pemafibrate is in Phase II clinical trials for the treatment of dyslipidemia in the USA and EU
Lobeglitazone	Dual PPAR- α/γ agonist	Chong Kun Dang; EQUIS & ZAROO	Lobeglitazone sulfate was approved by the Ministry of Food and Drug Safety (Korea) on 4 July 2013. It was developed and marketed as Duvie [®] by Chong Kun Dang Corporation. Lobeglatazone is an agonist for both PPAR- α and PPAR γ , and it works as an insulin sensitizer. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes

NASH: Nonalcoholic steatohepatitis; TG: Triglyceride.

Given that until now, the discovery of highly efficacious dual and pan PPAR agonists has been mainly disappointing; it underscores need for the development of other PPAR modulators modeled after estrogen receptor-type modulators that would retain their antihyperlipidemic or antidiabetic properties as the case may be, while minimizing the undesirable side or toxic effects. K-877 is a new SPPAR- α M, which exhibits greater PPAR- α activation (transcriptional activity) potency than existing PPAR- α agonists (such as fibrates) [157–159]. Currently, K-877 is undergoing a Phase III trial in Japan for the treatment of dyslipidemia. Phase II/III studies showed that K-877 significantly reduced plasma TG levels and increased HDL-cholesterol. It is further demonstrated that dietary administration of K-877 to high-fat diet-fed mice activates PPAR- α signaling pathway and attenuates dysregulated lipid metabolism [159].

Conclusion

PPARs are ligand-activated transcription factors that form a subfamily of the nuclear receptor superfamily. This PPAR subfamily consists of

three isotypes: PPAR- α (NR1C1), PPAR β/δ (NR1C2) and PPAR γ (NR1C3). PPARs heterodimerize with members of the RXRs and as such regulate gene expression. PPAR- α , the first identified member of the PPAR family, is predominantly expressed in tissues with a high level of fatty acid catabolism, such as liver, skeletal muscle and heart. Significant expression of PPAR- α also occurs in the proximal tubules of the kidney, intestinal mucosa, the adrenal gland and brown adipose tissue and vascular cells, including ECs, smooth muscle cells and macrophages/foam cells. Activators of PPAR- α include a variety of endogenously present fatty acids, eicosanoids, oxidized phospholipids, lipoprotein lipolytic products and synthetic agonists, including clinically used drugs such as fenofibrate and gemfibrozil and various synthetic single, dual and pan agonists. PPAR- α is also regulated by post-translational modification via phosphorylation and a number of protein kinases including PKA, PKC, ERK1/2, p38 MAPK, GSK3 and CK2 have been identified that catalyze the phosphorylation of this PPAR isotype.

PPAR- α controls the expression of genes involved in lipoprotein and TG metabolism, fatty acid oxidation, in particular β -oxidation, cellular uptake and export of fatty acids as well as indirectly lipogenesis. These characteristics, coupled with its involvement in metabolic diseases, make PPAR- α an ideal target for the development of new therapeutics to treat dyslipidemia, MetS, T2DM, NAFLD and associated cardiovascular complications. This notion is further strengthened by ongoing clinical use of fibrates, which activate PPAR- α . However, despite therapeutic importance of fibrates, this class of drugs affect only a single component of MetS (i.e., fibrates only ameliorate hyperlipidemia), which limits their utility as a monotherapy and, more importantly, their use is often associated with adverse side effects. A number of recently concluded clinical trials using fibrate drugs, including gemfibrozil, fenofibrate and bezafibrate, provided data showing that these drugs only modestly protect against CVD; however, these findings have not been uniformly observed.

Because of these various reasons and to improve treatment strategies in the management of MetS, T2DM, NAFLD and associated CVD, extensive efforts are underway to develop safer and more effective dual and pan PPAR- α agonists and SPPAR- α M compounds for treating these clinical conditions. Unfortunately, so far the efforts to develop new dual/pan agonists have met with little success. While a large number of structurally diverse dual/pan PPAR- α agonists have been synthesized and evaluated for their therapeutic potential, further clinical development of these PPAR- α / γ agonists such as muraglitazar, navelgilitazar, ragaglitazar, tesaglitazar, imiglitazar and aleglitazar has been discontinued due to various safety concerns. Only two PPAR- α / γ agonists, saroglitazar and lobeglitazone, have been marketed in India and Korea, respectively, and are now in clinical use. Saroglitazar was approved by the Indian regulatory authority, Drug Controller General of India, as a glucose- and lipid-lowering drug for the treatment of diabetic dyslipidemia, NAFLD and lipodystrophy. Lobeglitazone sulfate was approved by the Ministry of Food and Drug Safety (Korea) in 2013 and currently marketed as Duvie by Chong Kun Dang Corporation as an insulin sensitizer. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In addition, a compound, chiglitazar (PPAR- α / γ dual agonist), has completed Phase II, IIA and IIB clinical trials.

Currently, Phase III is in progress in China in patients with T2DM and insufficient glycemic control despite diet and exercise. GFT505, a dual PPAR- α / δ (β) agonist, is in development for the treatment of NASH/NAFLD. Development of several other pan (PPAR- α / β [δ]/ γ) agonists has been terminated due to various safety reasons. Currently, one PPAR- α modulator (SPPAR- α M) K-877 (pemafibrate) compound is undergoing clinical trials. It was designed to exhibit a higher PPAR- α agonistic activity and selectivity than existing PPAR- α agonists (such as fibrates). It is undergoing Phase II clinical trials as a potential drug for the treatment of dyslipidemic patients with high TG and low HDL-cholesterol.

Future perspective

Since PPAR α is a master regulator of genes involved in lipoprotein and triglyceride metabolism, in particular β -oxidation, cellular uptake and export of fatty acids, future directions should be directed at identifying PPAR α single, double or pan agonists with high selectivity and sensitivity towards these pathways while also minimizing off-target activity. In addition, experimental studies have shown that PPAR α is subject to post-translational regulation via phosphorylation and clearly a focus of future investigations should be to design, synthesize and characterize new PPAR α agonists with high specificity towards modulating the PPAR α phosphorylation status.

Acknowledgements

The authors also thank K Morrow for his assistance in creating illustrations.

Financial & competing interests disclosure

This work was supported by the Office of Research and Development, Medical Service, Department of Veterans Affairs, and grants from the National Institutes of Health (HL033881 and HL092473). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fca-2016-0059

EXECUTIVE SUMMARY

- Obesity has reached epidemic proportion worldwide both in adults and children and it is strongly associated with several metabolic diseases including metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), hypertension, major cardiovascular diseases (CVDs) and certain cancers.
- PPARs, which consist of three family members, PPAR- α , PPAR β/δ and PPAR γ form heterodimers with retinoid X receptors and play a central role in the regulation of various metabolic processes including lipid and glucose metabolism, inflammatory responses, cell proliferation and differentiation and vascular functions.
- PPARs have been implicated in the pathogenesis of metabolic syndrome, NAFLD, hypertension and CVDs.
- Weak PPAR- α agonists, fibrates and PPAR γ agonists thiazolidinediones (pioglitazone and rosiglitazone) are used clinically to treat dyslipidemia and Type 2 diabetes mellitus (T2DM).

Molecular characteristics of PPAR- α

- The PPAR- α isotype is transcribed from the human *PPARA* gene, which consists of eight exons and is located at chromosomal region 22q12-q13.1.
- Ligand-activated PPAR- α /retinoid X receptor heterodimers recruit co-activators and subsequently bind to peroxisome proliferator response element target genes to modulate gene transcription.

Natural & synthetic ligands of PPAR- α

- PPAR- α is activated by several natural ligands, including saturated, monounsaturated and polyunsaturated fatty acids, their metabolites, a physiologically relevant endogenous ligand, 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (16:0/18:1 GPC), and various synthetic ligands.

Metabolic functions of PPAR- α

- PPAR- α is expressed predominantly in high-energy requiring tissues such as skeletal muscle, heart, liver and brown adipose tissue.
- Significant expression of PPAR- α also occurs in the proximal tubules of the kidney, intestinal mucosa, the adrenal gland and brown adipose tissue and the majority of cell types that exist in the vasculature including endothelial cells, smooth muscle cells and monocytes/macrophages.
- PPAR- α controls the expression of a wide range of hepatic genes encoding enzymes/proteins involved in fatty acid uptake and intracellular transport, fatty acid activation (i.e., acyl-CoA formation), fatty acid oxidation, lipogenesis, ketogenesis and lipoprotein/cholesterol metabolism.
- PPAR- α is also critically involved in the metabolic functions in skeletal muscle, heart and vasculature.

Natural mutations & polymorphisms within the PPAR- α receptor

- Over a dozen genetic variants in both the DNA-binding domain and ligand-binding domain that influence the transcriptional activity of human PPAR- α have been described including L162V and V227A, which are the most common PPAR- α polymorphisms reported to date and associated with alterations in lipid metabolism.

Post-translational modifications of PPAR- α receptor

- PPAR- α is subjected to post-translational modification via phosphorylation. Several kinases were identified to catalyze the phosphorylation of PPAR- α .

Clinical trials to test the effectiveness of fibrates for primary & secondary prevention of CVD

- Some evidence suggests that fibrates lower the risk for cardiovascular and coronary events in primary prevention.
- Some evidence also indicates that fibrate drugs can be effective in the secondary prevention of the nonfatal stroke, nonfatal myocardial infarction and vascular deaths.

Statin-fibrate combination for mixed dyslipidemia

- Various clinical trials conducted in the past suggest that fenofibrate/simvastatin combination therapy in general is safe and effective in normalizing the lipid profile in mixed dyslipidemia.

EXECUTIVE SUMMARY (CONT.)

Next-generation dual & pan PPAR- α agonists & SPPAR- α M

- Two PPAR- α/γ agonists, saroglitazar and lobeglitazon, have been marketed and are now in clinical use in India and Korea, respectively.
- Chiglitazar, a PPAR- α/γ dual agonist, has completed Phase II, IIA and IIB clinical trials. Currently, Phase III is in progress in China in patients with T2DM and insufficient glycemic control despite diet and exercise.
- GFT505, a dual PPAR- $\alpha/\delta(\beta)$ agonist, is in development for the treatment of impaired glucose metabolism and insulin resistance, T2DM, atherogenic dyslipidemia and nonalcoholic steatohepatitis/NAFLD.
- K-877, a SPPAR- α M is currently undergoing a Phase III trial in Japan for the treatment of dyslipidemia. Phase II/III studies showed that K-877 significantly reduced plasma triglyceride levels and increased HDL-cholesterol levels.

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