Peroxisome Proliferator Activated Receptor Agonists: Emerging Therapy for Cardiovascular Complications

Pitchai Balakumar, Madhankumar Rose and Manjeet Singh
Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India

Abstract: Peroxisome Proliferator Activated Receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily. The PPAR subfamily comprises of three members such as PPARα, PPARγ and PPARδ. Activation of PPARα induces gene expressions that promote fatty acid oxidation. Fibrates, which are currently used as hypolipidemic agents are PPARα ligands. PPARγ regulates gene expressions that promote insulin sensitization followed by glucose metabolism. Thiazolidinediones, which are presently employed as insulin-sensitizing anti-diabetic agents are PPARγ agonists. On the other hand, PPARδ also known as PPARβ is expressed ubiquitously and involved in fatty acid oxidation in tissues, which lack PPARα. But no selective PPARδ agonists are currently available for therapeutic use. Evidences from ongoing pre-clinical and clinical studies suggest that PPAR ligands exert broad spectrum of cardioprotective activities in addition to their above-mentioned properties. Agonists of PPARs are shown to inhibit the pathogenesis of atherosclerosis, endothelial dysfunction, heart failure and myocardial infarction. In this review, we discussed various recently developed PPAR ligands and their potential role in the prevention of pathogenesis of cardiovascular complications. Moreover, the novel class of currently developed PPAR dual agonists such as PPARα/γ and PPARα/δ agonists and pan agonists such as PPARα/γ/δ agonists have also been discussed, which may be novel emerging therapeutic agents for cardiovascular complications.

Key words: PPAR family, PPAR agonists, cardiovascular complications

INTRODUCTION

Peroxisome Proliferator Activated Receptors (PPARs) belong to the nuclear receptor superfamily (Huss and Kelly, 2004). Three isoforms of PPARs, encoded by different genes, have been identified such as PPARα, PPARγ and PPARδ (Busé, 2003). PPARα agonists regulate fatty acid uptake and oxidation and thus involved in maintaining energy homeostasis. Further, PPARα agonists are reported to have additional benefits of inhibiting the pathogenesis of atherogenesis (Verma and Szmitko, 2006), endothelial dysfunction (Sood et al., 2003), cardiac hypertrophy (Ichihara et al., 2006) and myocardial injury (Wayman et al., 2002). PPARγ agonists promote adipogenesis and insulin sensitization. Moreover, these agents have been found to possess pleiotrophic effects by inhibiting the pathogenesis of cardiovascular complications such as atherosclerosis (Blaschko et al., 2006), vascular remodeling (Wakino et al., 2000), endothelial dysfunction (Martens et al., 2006), hypertension (Wakino et al., 2004), cardiac hypertrophy (Dep et al., 2004) and myocardial infarction (Molavi et al., 2006). Hence, PPARα/γ dual agonists, which are under development as emerging therapeutic option for preventing diabetic cardiovascular complications. Recently, PPARα/γ dual agonism has been shown to improve insulin sensitivity and prevent left ventricular dysfunction, which suggests that dual agonists
may provide synergistic benefit of alleviating diabetes-associated cardiovascular complications (Verreth et al., 2006). PPARα is involved in fatty acid oxidation in tissues, which lacks PPARγ. PPARα agonists have been noted to attenuate atherosclerosis (Graham et al., 2005) and hypertrophy of heart (Planavila et al., 2005a). Therefore, current research programs are actively involving in development of agents that act collectively on PPARα, PPARγ and PPARδ. Few such compounds are under development, which may open a novel vista for the treatment of cardiovascular complications.

**Peroxisome Proliferator Activated Receptor α (PPARα)**

PPARα plays an important role in the oxidation of fatty acids. PPARα is highly expressed in tissues with high rates of fatty acid catabolism such as hepatocytes, cardiomyocytes, cortex of kidney, skeletal muscles, brown adipocytes and enterocytes (Braissant et al., 1996; Ricote et al., 1998). It is also present in Vascular Smooth Muscle Cells (VSMCs) (Staels et al., 1998), endothelial cells (Marx et al., 1999) and inflammatory cells (Marx et al., 2001). Fibrates, the well-known hypolipidemic agents, such as bezafibrate, fenofibrate, clofibrate and gemfibrozil are ligands for PPARα. Further newly developed compounds such as GW 7647, GW 9578, LY 318674 and WY 14643 (Yeh et al., 2006) are shown to have excellent selectivity for PPARα receptors (Singh et al., 2005; Javina and Patel, 2006). PPARα receptor regulates synthesis of enzymes that are necessary for peroxisomal and mitochondrial β-oxidation (Ferre, 2004). PPARα agonists are reported to have additional benefits such as inhibition of atherogenesis (Verna and Szmitko, 2006), cardiac hypertrophy ( Wakino et al., 2004), endothelial dysfunction (Sood et al., 2003) and myocardial injury (Yeh et al., 2006) (Fig. 1). These pleiotropic effects of PPARα agonists provide an effective therapeutic option in management of cardiovascular complications.

Atherosclerosis is a chronic inflammatory process within the arterial wall (Li and Glass, 2004) and it is associated with increased expressions of inflammatory markers such as C-reactive Protein (CRP), Tumor Necrosis Factor-alpha (TNF-α) and interleukin-6 (IL-6) (Zambon et al., 2006). PPARα ligands are beneficial in preventing atherosclerosis mainly through their anti-inflammatory property.

![Diagram](https://example.com/diagram.png)

**Fig. 1:** The complex molecular mechanisms involving in the cardioprotective effect of PPARα agonists. PPARα agonists inhibit various transcription factors, inflammatory mediators, adhesion molecules and oxidative stress to prevent vascular remodeling, endothelial dysfunction, atherosclerosis and cardiac hypertrophy.

206
PPARα agonists have been noted to possess potent anti-inflammatory activity by directly inhibiting nuclear factor kappa B (NF-κB), activator protein-1 (AP-1) and signal transducer and activators of transcription 1/3 (STAT1/3) signaling pathways (Stael and Fruchart, 2002). Further, the expression of pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS), CRP, monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), IL-1β, IL-6, IFN-inducible protein 10 (IP-10) and TNFα were suppressed by PPARα ligands (Stael et al., 1998; Cabrero et al., 2002; Kleemann et al., 2004; Stael and Fruchart, 2002; Blaschke et al., 2006). Moreover, PPARα ligands have been demonstrated to directly inhibit the expression of T-lymphocyte derived interferon gamma (IFN-γ), which plays an integral role in transplantation associated atherosclerosis (Marx et al., 2002; Schiffrin et al., 1993). In endothelial cells, PPARα agonists reduce cytokine-induced expression of vascular cell adhesion molecule-1 (VCAM-1), thus interfering with inflammatory cascade (Marx et al., 1999). Furthermore, it has been shown that the PPARα ligand reduced angiotensin II-induced oxidative stress and inflammation (Schiffrin et al., 2003). PPARα ligands also enhance cholesterol efflux by upregulating HDL receptor (Blaschke et al., 2006).

Endothelial dysfunction is a hallmark in the pathogenesis of hypertension and atherosclerosis and is characterized by local lesions and deficiency of Nitric Oxide (NO) production. Clofibrate, a PPARα agonist was shown to inhibit hyperhomocysteinemia-induced endothelial dysfunction by increasing the expression of endogenous anti-oxidant Superoxide Dismutase (SOD) and reducing the activity of NADPH oxidase. Further, clofibrate has been noted to inhibit the activation of MMP by reducing peroxynitrite formation (Sood et al., 2003). Recently fenofibrate, an another PPARα agonist has been noted to have protective effect towards age-associated endothelial dysfunction. The mechanism underlying this protective effect involves reduced release of thromboxane A2 (TXA2), decreased expressions of cyclooxygenase (COX) and increased expression of SOD (Alvarez de Sotomayor et al., 2006).

Cardiac hypertrophy is an adaptive response of the heart, during which terminally differentiated cardiomyocytes increase in size without undergoing cell division. Initially, the hypertrophic response may be adaptive, however, prolonged hypertrophy can become detrimental resulting in cardiac dysfunction and heart failure (Balakumar and Singh, 2006b). Various signaling proteins such as Rho-kinase (Balakumar and Singh, 2006c), poly (ADP-ribose) polymerase (PARP) (Balakumar and Singh, 2006b, d), caspase-3 (Balakumar and Singh, 2006e), endothelin (Miyachi and Masaki, 1999), P38-mitogen activated protein kinase (P38 MAPK), c-Jun N-terminal kinase (JNK) and redox regulated transcription factors such as NF-κB, AP-1, early growth response gene-1 (Egr-1), Surfactant Protein 1 (SP1), E26 transformation specificie-1 (Ets-1), c-Fos and c-Jun are implicated in the pathogenesis of cardiac hypertrophy (Purcell et al., 2001; Ritter and Neyes, 2003). Further, several inflammatory mediators such as TNFα, IL-1β, IL-6, IL-18, vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), CRP, MCP-1 and growth factors such as transforming growth factor-β (TGF-β), PDGF-B and osteopontin play crucial role in the progression of cardiac hypertrophy and heart failure (Balakumar and Singh, 2005, 2006a; Ichihara et al., 2006). Fenofibrate, has been shown to attenuate the development of cardiac hypertrophy by inhibiting the inflammatory response and activation of redox-regulated transcription factors (Liang et al., 2003; Irukayama-Tomobe et al., 2004; Ichihara et al., 2006). Ligand-induced activation of PPARα in the heart increases the expression of genes involved in the cellular fatty acid uptake, mitochondrial β-oxidation and peroxisomal β-oxidation. During cardiac hypertrophy, PPARα is downregulated, which reduce fatty acid oxidation and increase glycolysis (Firank and Kelly, 2002; Tian and Burge, 2005). This reduction in PPARα activity was considered as adaptive since the O2 utilization efficiency and cardiac performance are maintained. This hypothesis was further supported by the study in which short-term administration of PPARα ligands in pressure overload-induced cardiac hypertrophy resulted in severe depression of cardiac function (Young et al., 2001). However, it has been argued that chronic reduction in Fatty Acid Oxidation (FAO) due to downregulation of PPARα in prolonged cardiac hypertrophy.
may further reduce cardiac function due to insufficient production of ATP. Additionally, depression of cardiac FAO leads to the non-physiologic storage of lipids and is accompanied by cardiac myocyte apoptosis, a phenomenon termed as cardiac lipoxicicity. Therefore, long-term treatment with PPARα agonists may be beneficial. This contention is supported by the fact that long-term treatment with PPARα agonist ameliorated the extent of cardiac hypertrophy by reducing lipotoxicity and inhibiting various inflammatory cytokines (Ogata et al., 2002; 2004). Moreover, administration of PPARα ligand reduces myocardial lipid accumulation and improves insulin sensitivity in diabetic subjects (Aasum et al., 2002).

Reperfusion of the previously ischemic myocardium is often followed by detrimental changes in the coronary arteries and myocardial tissues, which ultimately results in tissue damage known as reperfusion injury. A brief myocardial ischemia leads to reversible contractile dysfunction associated with transient reduction in myocardial FAO due to reversible down regulation of PPARα (Kim et al., 2003). Studies have established that rate of FAO rapidly rise due to upregulation of PPARα during reperfusion that has been proposed to be involved in the further reduction in the myocardial contractility (Stanley et al., 1997; Belanger et al., 2002). Further, chronic cardiac overexpression of PPARα resulted in significant decrement in functional recovery of heart after ischemia (Sambandam et al., 2006). The possible mechanisms behind this detrimental effect may be high FAO-induced accumulation of lactate, proton (low pH) and reactive oxygen species. Based on the above evidence it may be suggested that downregulation of PPARα during ischemia may be an adaptive response (Dewald et al., 2005) and PPARα antagonism may be a potential therapeutic target to treat ischemia/reperfusion injury. Contravasally, it has been demonstrated that PPARα agonists caused a substantial reduction of infarct size of ischemic myocardium followed by reperfusion and this cardioprotection may be due to overexpression of heme-oxygenase-1 (HO-1) and subsequent inhibition of NF-κB activation (Wayman et al., 2002). This report is further strongly supported by the fact that WY 14643, a selective PPARα agonist has been shown to be involved in the attenuation of ischemia/reperfusion-induced myocardial injury that may be mediated via inhibition of caspase dependant and independent apoptotic cell death (Yeh et al., 2006). However, further studies are mandatory to elucidate the protective role of PPARα in the pathogenesis of ischemia/reperfusion-induced myocardial injury.

**Peroxisome Proliferator Activated Receptor γ (PPARγ)**

PPARγ is expressed mainly in white and brown adipose tissue, mucosa of colon, ecum and lesser extent in immune cells like monocytes and macrophages (Ferre, 2004). Recently, PPARγ has been found to be expressed in endothelial cells and VSMCs (Verma and Szmitko, 2006). PPARγ agonists promote adipocyte differentiation and fatty acid storage, thus reducing fatty acid-induced insulin resistance. Further, they increase glucose uptake by increasing the expression and translocation of glucose transporter-4 (GLUT-4) and decreasing the production of adipokines (Staels and Fruchart, 2005; Blaschke et al., 2006). PPARγ has received considerable attention since mid-1990s, when it was found to be the molecular target of insulin-sensitizing antidiabetic drugs known as thiazolidinediones. This class of drugs includes troglitazone, rosiglitazone and pioglitazone, which are currently employed. A series of newly synthesized PPARγ agonists such as G1262570 (farglitazar), GW 1929 and GW 7845, JTT-501 and KRP-297 show promising anti-diabetic activity (Javiya and Patel, 2006).

Several basic studies have shown that PPARγ ligands have pleiotropic effects of preventing cardiovascular complications (Fig. 2). PPARγ specific ligands inhibit the production of inflammatory mediators such as TNFα, IL-1, IL-6, iNOS, MMP, CRP, IP-10, endothelin-1 (ET-1) and osteopontin and thus reducing atherogenesis (Cabero et al., 2002; Wang et al., 2002; Staels and Fruchart, 2005; Blaschke et al., 2006). The anti-inflammatory property of PPARγ has been attributed to its inhibitory activity on NF-κB, Egr-1 and AP-1 (Staels and Fruchart, 2005; Blaschke et al., 2006). PPARγ agonists
Fig. 2: The complex molecular mechanisms involving in the cardioprotective effect of PPARγ agonists. PPARγ agonists reduce blood pressure by inhibiting the action of Rho-kinase, endothelin-1 and antagonizing calcium activity. They inhibit various inflammatory cytokines, adhesion molecules and growth factors to prevent remodeling, endothelial dysfunction, atherosclerosis and cardiac hypertrophy.

were found to downregulate angiotensin-II-AT1 receptor in VSMCs and block AT1 receptor mediated activation of extracellular signal-regulated kinase 1/2 (ERK1/2) of MAPK family and thus inhibit the proliferation and migration of VSMCs (Takoda et al., 2006; Toba et al., 2006). Further, treatment with rosiglitazone, a PPARγ ligand has lowered plasma levels of CD40 ligand (CD40L), a pro-inflammatory cytokine in type 2 diabetic patients (Marx et al., 2003). Recently, 15d-PGJ2, a PPARγ ligand was shown to downregulate CD40 receptor and reduce the expression of RANTES, an inflammatory cytokine that is involved in initiation and maintenance of inflammation, suggesting a novel anti-inflammatory mechanism of PPARγ agonists for limiting atherosclerotic complications in diabetes (Zhang et al., 2006).

Remodeling is a key contributory factor in cardiovascular disorders. Vascular cells undergo remodeling which is characterized by medial thickening due to smooth muscle cell hypertrophy and hyperplasia (Atkins et al., 2005). Glitazones were shown to inhibit VSMC growth and proliferation by inhibiting Platelet Derived Growth Factor (PDGF), increasing the level of cyclin-dependent kinase inhibitor p27 and decreasing the phosphorylation of retinoblastoma protein (Rb) and thus leading to cell-cycle arrest (Wakino et al., 2000; Takagi et al., 2003). Angiotensin-II involves in the pathogenesis of vascular and cardiac remodeling. Recently it has been shown that PPARγ activation reduced angiotensin-II-induced growth by inhibiting ERK1/2 and phosphorylation of 4E-binding protein 1 (4E-BP1) and Src homology (SH) 2-containing inositol phosphatase 2 (SHIP2). Modulation of these pathways by PPARγ activators may contribute to prevent of vascular remodeling in cardiovascular disorders (Benkirane et al., 2006).

Recent studies have elucidated the role of PPARγ agonists in endothelial dysfunction. Elevated levels of CRP and TNFα have been associated with endothelial dysfunction by decreasing the production of nitric oxide, increasing the endothelial cell apoptosis and stimulating the expression of NFκB, ICAM-1, VCAM-1 and E-selectin (Ridker et al., 2000; Sidhu et al., 2003; Szmitko et al., 2003). Further, endothelial dysfunction was found to be associated with increase in release of endothelin-1.
(ET-1), an endogenous vasoconstrictor and MCP-1, a chemokine, which facilitates leukocyte transmigration (Verna et al., 2002a, b; 2003; Verna and Sznitko, 2006). These consequences in endothelial dysfunction are attenuated by PPARγ stimulation (Natali et al., 2004; Siddha et al., 2004; Martens et al., 2006). The diacylglycerol-protein kinase C (DAG- PKC) signaling pathway has been implicated in insulin-resistance and pathogenesis of diabetic vascular diseases. Recently it has been demonstrated that PPARγ agonists have a novel molecular action of suppressing DAG-PKC signaling pathway by upregulating endogenous attenuator diacylglycerol kinase (DGK) (Verrier et al., 2004).

PPARγ agonists through their receptor mediated and receptor independent actions have been shown to attenuate the pathogenesis of hypertension. Rho-kinase, a target protein of GTPase Rho contributes to hypertension, cardiac dysfunction and various cellular functions such as actin cytoskeleton organization, cell adhesion and cytokinesis (Balakumar and Singh, 2006c). Rho-kinase mediates vascular smooth muscle cell contraction by phosphorylating myosin light chain kinase (Fukata et al., 2001). It has been noted that during sympathetic overactivation, the activity of Rho kinase is augmented and is involved in the pathogenesis of hypertension (Calnek et al., 2003; Seko et al., 2003). PPARγ agonists upregulate Src homology region 2-containing protein tyrosine phosphatase-2 (SHP-2), a negative regulator of Rho activity and dephosphorylates Vav protein, a guanine nucleotide exchange factor (GEF) leading to decrease in GTP bound Rho and Rho kinase activity and thus reducing systemic blood pressure (Wakino et al., 2004). Further, PPARγ ligands stimulate nitric oxide release from endothelial cells (Calnek et al., 2003), which upregulate SHP-2 protein (Chang et al., 2002) resulting in amelioration of hypertension apart from their direct vasodilatory action. Moreover, rosiglitazone was noted to have calcium antagonistic action, which may directly inhibit voltage-dependent calcium channels (Patel et al., 2003). Furthermore, PPARγ agonists attenuated the increase in blood pressure in DOCA-salt hypertensive rat through inhibition of ET-1 (Iglarz et al., 2003). These promising results have clearly demonstrated the protective role of PPARγ ligands in hypertension.

PPARγ ligands are also involved in inhibiting the pathogenic progression of cardiac hypertrophy and heart failure. Inflammation plays a critical role in the progression of cardiac remodeling and dysfunction (Purcell et al., 2001). In macrophages, PPARγ participates in the regulation of inflammatory responses by inhibiting NF-κB and AP-1 (Ricote et al., 1998). PPARγ activators such as troglitazone and 15d-PGJ2, were shown to prevent cardiac hypertrophy and inhibit the expression of brain natriuretic peptide (BNP) in cultured cardiomyocytes (Yamamoto et al., 2001). Recently, rosiglitazone was observed to have long-term beneficial effects on cardiac hypertrophy and cardiac inflammation (Diep et al., 2004). Further, aortic banding has enhanced the cardiac hypertrophy in heterozygous PPARγ-deficient mice suggesting the inhibitory effect of PPARγ on cardiac growth (Asakawa et al., 2002). Angiotensin-II-induced fetal gene expression and cardiomyocyte hypertrophy were markedly attenuated by thiazolidinediones (Frey and Olson, 2002). Moreover, rosiglitazone was noted to improve left ventricular function and decrease collagen accumulation in diabetic rats (Tsuji et al., 2001). These data suggest that PPARγ ligands have potential role in preventing the development of cardiac hypertrophy. Studies are underway to determine the beneficial effects of thiazolidinediones in long-term cardiovascular complications.

Diabetes is associated with increased risk of mortality as a consequence of acute myocardial infarction. The cardioprotective potential of PPARγ agonist is also being explored in ischemic myocardium. It has been demonstrated that chronic treatment with rosiglitazone, a PPARγ agonist has protected the heart against ischemia/reperfusion injury (Yue et al., 2001; 2005). Further PPARγ agonists are reported to inhibit c-Jun (Khandoudi et al., 2002), NFκB, MCP-1, ICAM-1, iNOS and the nitration of proteins by peroxynitrite resulting in reduced myocardial injury (Wayman et al., 2002). It has been shown that the zinc finger transcription factor Egr-1 acts as a master switch for the inflammatory response during ischemic injury. Activation of PPARγ was shown to suppress
Egr-1 and its inflammatory gene targets and thus protect the myocardium against ischemic injury (Okada et al., 2002). Recently the cardioprotective effects of rosiglitazone against myocardial ischemia-reperfusion injury has been shown to be associated with significant overexpression of AT1 receptors along with inhibition of p42/44 MAPK (Molavi et al., 2006). Further, pioglitazone has been noted to improve tolerance against ischemia reperfusion injury by enhancing cardiac insulin sensitivity through activation of PI3K-Akt signaling and expression of heat shock protein 72 (Tamiguchi et al., 2006). Furthermore, a recent study has shown that rosiglitazone provided beneficial effects in the ischemic reperfused myocardium by inhibiting lipid peroxidation and recovering normal level of SOD (Ha, 2006). These results suggest that PPARγ agonists may provide an effective therapeutic option for patients of diabetes who are at great risk for myocardial injury.

**Peroxisome Proliferator Activated Receptor δ (PPARδ)**

PPARδ remained an enigma for almost a decade after its cloning in 1992. It is expressed ubiquitously in all tissues. PPARδ activation has dual benefits of decreasing hypertriglyceridermia and insulin resistance, which highlight the broad potential of PPARδ in the treatment of metabolic diseases (Poutre et al., 2006). PPARδ enhances fatty acid catabolism and energy uncoupling in adipose tissue and muscle and it suppresses macrophage-derived inflammation. Its combined activities make it a multifaceted therapeutic target for the metabolic syndrome with the potential to control weight gain, enhance physical endurance, improve insulin sensitivity and ameliorate atherosclerosis. Newly synthesized compounds such as GW501516, GW610742, GW0742X and GW0742 are having selectivity to PPARδ (Graham et al., 2005; Barish et al., 2006).

Ongoing basic studies have demonstrated the role of PPARδ in amelioration of cardiovascular complications. PPARδ ligand has been noted to suppress the expressions of inflammatory genes such as TNFα, iNOS, IL-1β and COX (Rival et al., 2002; Lee et al., 2003; Welch et al., 2003; Barish et al., 2006). In addition, PPARδ ligands were noted to inhibit cytokine-induced MCP-1 and VCAM-1 expressions in endothelial cells (Rival et al., 2002). Recently GW0742X, a PPARδ agonist has been demonstrated to have potent anti-atherogenic effect with marked reduction of atherosclerotic lesion area, suggesting a therapeutic role of PPARδ agonists in the treatment of atherosclerosis (Graham et al., 2005).

PPARδ plays a critical role in regulation of myocardial fatty acid oxidation (Cheng et al., 2004). Like PPARα, the PPARδ is also downregulated in cardiac hypertrophy (Planavila et al., 2005b). Cardiac specific deletion of PPARδ has resulted in increased left ventricular end diastolic pressure, cardiac hypertrophy and impairment of cardiac contractility (Cheng et al., 2004). Further, PPARδ ligand has been demonstrated to attenuate phenylephrine-induced cardiac hypertrophy via inhibition of NFκB, MCP and atrial natriuretic factor (ANF) (Planavila et al., 2005b). Recently, GW0742, a PPARδ ligand has been reported to inhibit TNFα production by suppressing NFκB mediated pathway (Ding et al., 2006). Further studies with PPARδ ligands may explore their use therapeutically.

**PPAR Dual Agonists**

Given the favorable cardioprotective effects of PPARα and PPARγ ligands, the PPARα/γ dual agonists have been currently developed and they are glitazars class of drugs such as murahtiazar, ragaglitazaz, tegasoglitzaz, naveglitazaz, imiglitazaz, LY 929 and LSN862 (Poutre et al., 2006). By activating both PPARα and PPARγ receptors, they simultaneously reduce atherogenic triglycerides, raise cardioprotective HDL levels, improve insulin sensitivity and reduce cardiovascular risk (Etgen et al., 2002). Recently, the PPARα/γ dual agonist namely (S)-3-(4-(2-carbazol-9-yl-ethoxy)phenyl)-2-ethoxy-propionic acid has been shown to improve insulin sensitivity and prevent left ventricular dysfunction (Venneth et al., 2006). A study evaluating possible role of dual PPARα/γ in pressure overload-induced pathological cardiac hypertrophy is currently underway in our laboratory.
The synergies of such a combination may enable lower dosing. Moreover, PPARγ agonists increase adipogenesis and body weight. PPAR δ agonists counteract these effects by decreasing food intake and fat deposits (Egten et al., 2002; Carmona et al., 2005). Thus, increase in body weight that is seen with PPARγ treatment may not be seen with dual PPARα/γ agonists. With extended use, it is believed that these agents may reduce the risk of cardiovascular complications, but their long-term clinical effects are still unknown. Clinical studies evaluating the efficacy of PPAR dual agonists in reducing cardiovascular risks are currently underway.

Synthesis of PPARα/δ dual agonists is currently under development (Pourret et al., 2006). It may be expected that these agents may display interesting properties such as decreasing hyperlipidemia, insulin resistance and reducing risk of atherogenesis. Recently, T-639, a PPARα/δ dual agonist has been shown to increase HDL levels in primates (Wallace et al., 2005). Synthesis of such agents, which have affinity towards both PPARα and PPARδ, will open new panorama in the management of atherosclerosis and inflammation.

In addition, the multimodal drug concept can also be extended to combinations between PPARs and other receptors. Sulphonylureas and glinides are currently in clinical use for treatment of type II diabetes by virtue of their insulin secretagogue properties. Recently, it has been reported that these drugs also binds to PPARγ and enhance PPARγ mediated gene expression (Scarsi et al., 2006). Therefore synthesis of compounds which targets both sulphonylurea receptor and PPARγ may open a new pharmacological prospective in treatment of diabetes and diabetes associated cardiovascular complications by virtue of their insulin secretory and sensitizing properties.

PPAR Pan Agonists

Current research programs aim to combine the biological properties of PPARα, γ and δ agonists. The bezafibrate, an old and well-known lipid-lowering fibrin acid derivative, is first clinically tested pan PPAR (α, γ, δ) activator with more than a quarter of century of therapeutic experience with good safety profile (Javinya and Patel, 2006). It has produced beneficial effects in improving insulin sensitivity, inhibiting atherogenesis and preventing myocardial ischemic injury. Further, PPARγ induced weight gain may not be seen with PPAR pan agonists (Tenenbaum et al., 2005). Furthermore, bezafibrate was shown to decrease the rate of progression of coronary atherosclerosis and coronary risk factors (Ericsson et al., 1997; Elkeles et al., 1998). Novel agents such as LY-468608, DRF-11605, CS-204, GW-625019, GW 677954, PLX 204 and DRL-11605 are under investigation as PPAR pan agonists, which may be potent therapeutic agents in future for treatment of diabetes associated cardiovascular complications (Javinya and Patel, 2006; Pourret et al., 2006).

Clinical Prospective

Evidence from several clinical trials confirm the protective role of PPAR ligands in alleviating cardiovascular complications. The clinical trial named Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) demonstrated that fenofibrate, a PPARα agonist has reduced cardiovascular risk associated with diabetes (Zambon, 2006; Zambon et al., 2006). Further, the Veterans Affairs HDL Intervention Trial (VA-HIT) showed that gemfibrozil, which activates PPARα, significantly reduced the risk of cardiovascular disorders of patients with low HDL cholesterol and established coronary heart disease (Tai et al., 2006). Furthermore, Diabetes Atherosclerosis Intervention Study (DAIS) has demonstrated the beneficial effects of PPARα agonists, specifically fribic acid derivatives, on cardiovascular disease outcome (Israelian-Konaraki et al., 2005). Further, PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) study has shown that pioglitazone, a PPARγ agonist has reduced the incidence of non-fatal myocardial infarction and stroke in patients of type II diabetes who have a high risk of macrovascular events (Dornand et al., 2005). Moreover, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study is underway to evaluate the long-term impact of rosiglitazone on cardiovascular outcomes (Horne et al., 2005).
CONCLUSIONS

PPAR agonists have emerged as a promising group of agents for treating atherosclerosis, endothelial dysfunction, hypertension, heart failure and myocardial infarction. The dual and pan agonists provide reasonable promise in the prevention of pathogenesis of cardiovascular complications. Therefore, these novel PPAR agonists are indisputably an emerging therapeutic agents for diabetes associated and non-associated cardiovascular complications.

REFERENCES


