Journal of Pharmacology and Toxicology

ISSN 1816-496X

Academic Journals Inc.

www.academicjournals.com

Journal of Pharmacology and Toxicology 2 (3): 205-219, 2007
ISSN 1816-496X

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 (Buse, 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 (Blaschke *et al*., 2006), vascular remodeling (Wakino *et al*., 2000), endothelial dysfunction (Martens *et al*., 2006), hypertension (Wakino *et al*., 2004), cardiac hypertrophy (Diep *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

Corresponding Author: Dr. Pitchai Balakumar, Department of Pharmaceutical Sciences and Drug Research, Cardiovascular Pharmacology Division, Punjabi University, Patiala-147002 India
Tel: +91-9815557265 Fax: +91-175-2283073

may provide synergistic benefit of alleviating diabetes associated cardiovascular complications (Verreth *et al*., 2006). PPARδ is involved in fatty acid oxidation in tissues, which lacks PPARα. PPARδ 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 adiposites 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, LY518674 and WY 14643 (Yeh *et al*., 2006) are shown to have excellent selectivity for PPARα receptors (Singh *et al*., 2005; Javiya 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 (Verma 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.

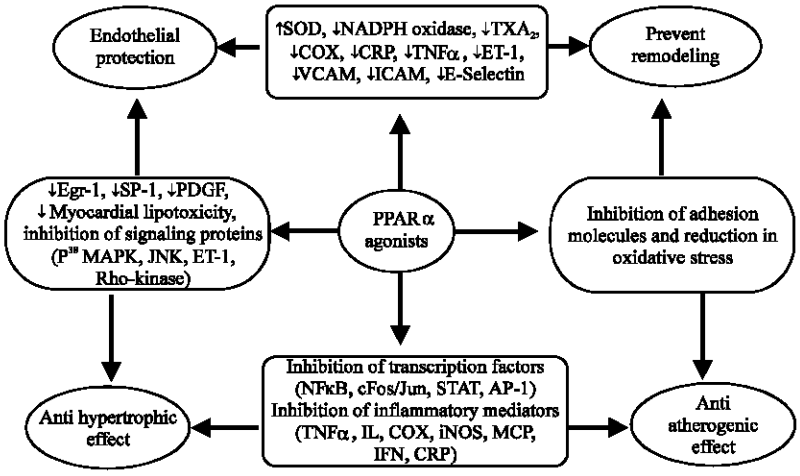

Fig. 1: The complex molecular mechanisms involving in the cardioprotective effect of PPARα agonists. PPARα agonists inhibit various transcription factors, inflammatory mediators, adhesion molecules and oxidative stress to prevent vascular remodeling, endothelial dysfunction, atherosclerosis and cardiac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

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 (Staels and Fruchart, 2005). Further, the expression of pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS), CRP, monocyte chemotactic 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 (Staels *et al*., 1998; Cabrero *et al*., 2002; Kleemann *et al*., 2004; Staels and Fruchart, 2005; Blaschke *et al*., 2006). Moreover, PPARα ligands have been demonstrated to directly inhibit the expression of T-lymphocyte derived interferon gamma (IFNγ), which plays an integral role in transplantation associated atherosclerosis (Marx *et al*., 2002; Schiffrin *et al*., 2003). 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 A_2 (TXA_2), decreased expressions of cycloxygenase (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 (Miyauchi and Masaki, 1999), P^{38}-mitogen activated protein kinase (P^{38} MAPK), cJun 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 specific-1 (Ets-1), c-Fos and c-Jun are implicated in the pathogenesis of cardiac hypertrophy (Purcell *et al*., 2001; Ritter and Neyses, 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 (Finck and Kelly, 2002; Tian and Barger, 2005). This reduction in PPARα activity was considered as adaptive since the O_2 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 lipotoxicity. 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 lipotoxcity 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 mechanism behind this detrimental effect may be high FAO-induced accumulation of lactate, proton (low pH) and reactive oxygen species. Based on the above evidences 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. Controversially, 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, cecum 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 pleiotrophic 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 (Cabrero *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

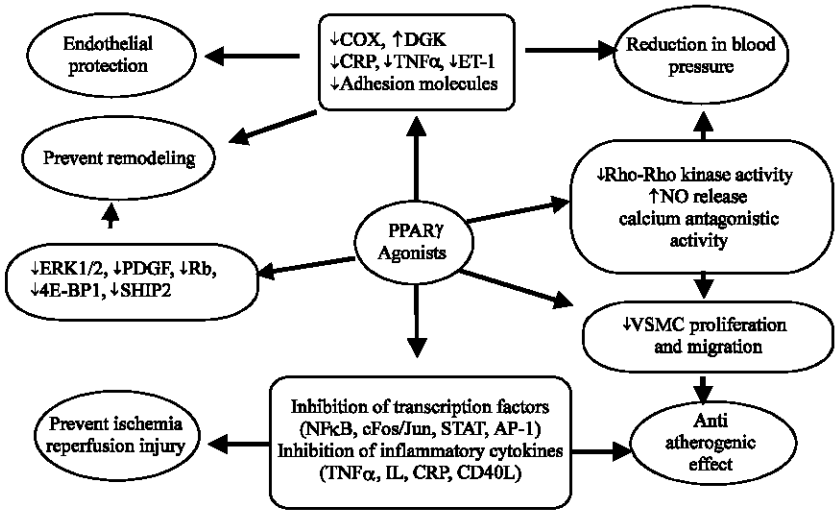

Fig. 2: The complex molecular mechanisms involving in the cardioprotective effect of PPARγ agonists. PPARγ agonists reduce blood pressure by inhibiting the action of Rho-kinase, endothelin-1 and antagonizing calcium activity. They inhibit various inflammatory cytokines, adhesion molecules and growth factors to prevent remodeling, endothelial dysfunction, atherosclerosis and cardiac hypertrophy

were found to downregulate angiotensin-II-AT_1 receptor in VSMCs and block AT_1 receptor mediated activation of extracellular signal-regulated kinase 1/2 (ERK1/2) of MAPK family and thus inhibit the proliferation and migration of VSMCs (Takeda *et al*., 2000; 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 ERK 1/2 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 (Verma *et al*., 2002a, b; 2003; Verma and Szmitko, 2006). These consequences in endothelial dysfunction are attenuated by PPARγ stimulation (Natali *et al*., 2004; Sidhu *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*., 2005). 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-PGJ_2 were shown to prevent cardiac hypertrophy and inhibit the expression of brain natriuretic peptide (BNP) in cultured cardiomyocytes (Yamamoto *et al*., 2001). Recently, pioglitazone 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, pioglitazone 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 AT_2 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 (Taniguchi *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 hypertriglyceridemia and insulin resistance, which highlight the broad potential of PPARδ in the treatment of metabolic diseases (Pourcet *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 IFNγ, 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, PPAR δ ligand has been demontrated 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 glitazar class of drugs such as muraglitazar, ragaglitazar, tesaglitazar, naveglitazar, imiglitazar, LY 929 and LSN862 (Pourcet *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 (Verreth *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. PPARα agonists counteract these effects by decreasing food intake and fat deposits (Etgen *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 (Pourcet *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-659, 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 secreting 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 fibric 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 (Javiya 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-465608, 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 (Javiya and Patel, 2006; Pourcet *et al*., 2006).

Clinical Prospective

Evidences 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 fibric 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 (Dormandy *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 (Home *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

Aasum, E., D.D. Belke, D.L. Severson, R.A. Riemersma, M. Cooper, M. Andreassen and T.S. Larsen, 2002. Cardiac function and metabolism in type 2 diabetic mice after treatment with BM 17.0744, a novel PPAR-alpha activator. Am. J. Physiol. Heart Circ. Physiol., 283: H949-957.

Alvarez de Sotomayor, M., C. Mingorance and R. Andriantsitohaina, 2006. Fenofibrate improves age-related endothelial dysfunction in rat resistance arteries. Atherosclerosis, (In Press).

Asakawa, M., H. Takano, T. Nagai, H. Uozumi, H. Hasegawa, N. Kubota, T. Saito, Y. Masuda, T. Kadowaki and I. Komuro, 2002. Peroxisome proliferator- activated receptor γ plays a critical role in inhibition of cardiac hypertrophy *in vitro* and *in vivo*. Circulation, 105: 1240-1246.

Atkins, K.B., C.A. Northcott, S.W. Watts and F.C. Brosius, 2005. Effects of PPAR-gamma ligands on vascular smooth muscle marker expression in hypertensive and normal arteries. Am. J. Physiol. Heart Circ. Physiol., 288: H235-243.

Balakumar, P. and M. Singh, 2005. The possible role of TNF-α in physiological and pathophysiological cardiac hypertrophy in rats. Ira. J. Pharmacol. Ther., 4: 138-142.

Balakumar, P. and M. Singh, 2006a. Anti-TNF-α therapy in heart failure: Future directions. Basic Clin. Pharmacol. Toxicol., 99: 391-398.

Balakumar, P. and M. Singh, 2006b. Possible role of poly (ADP-ribose) polymerase in pathological and physiological cardiac hypertrophy. Meth. Find. Exp. Clin. Pharmacol., 28: 1-7.

Balakumar, P. and M. Singh, 2006c. Differential role of rho-kinase in pathological and physiological cardiac hypertrophy in rats. Pharmacol., 78: 91-97.

Balakumar, P. and M. Singh, 2006d. Effect of 3-aminobenzamide, an inhibitor of poly (ADP-ribose) polymerase in experimental cardiac hypertrophy. Int. J. Pharmacol., 2: 543-548.

Balakumar, P. and M. Singh, 2006e. Possible role of caspase-3 in pathological and physiological cardiac hypertrophy in Rats. Basic Clin. Pharmacol. Toxicol., 99: 418-424.

Barish, G.D., V.A. Narkar and R.M. Evans, 2006. PPAR delta: A dagger in the heart of the metabolic syndrome. J. Clin. Invest., 116: 590-597.

Belanger, A.J., H. Lu, T. Date, L.X. Liu, K.A. Vincent, G.Y. Akita, S.H. Cheng, R.J. Gregory and C. Jiang, 2002. Hypoxia up-regualtes expression of peroxisome proliferator activated receptor gamma angiopoietin-related gene (PGAR) in cardiomyocytes; Role of hypoxia inducible factor1 alpha. J. Mol. Cell. Cardiol., 34: 765-774.

Benkirane, K., F. Amiri, Q.N. Diep, M. El Mabrouk and E.L. Schiffrin, 2006. PPAR-gamma inhibits ANG II-induced cell growth via SHIP2 and 4E-BP1. Am. J. Physiol. Heart Circ. Physiol., 290: H390-397.

Blaschke, F., Y. Takata, E. Caglayan, R.E. Law and W.A. Hsueh, 2006. Obesity, peroxisome proliferator-activated receptor and atherosclerosis in type 2 diabetes. Arterioscler. Thromb. Vasc. Biol., 26: 28-40.

Braissant, O., F. Foufelle, C. Scotto, M. Dauca and W. Wahli, 1996. Differential expression of peroxisome proliferator-activated receptors (PPARs): Tissue distribution of PPARalpha, -beta and -gamma in the adult rat. Endocrinology, 137: 354-366.

Buse, J.B., 2003. Glitazones and heart failure: Critical appraisal for the clinician. Circulation, 108: e57.

Cabrero, A., J.C. Laguna and M. Vazquez, 2002. Peroxisome proliferator-activated receptors and the control of inflammation. Curr. Drug Targets Inflamm. Allergy., 1: 243-248.

Calnek, D.S., L. Mazzella, S. Roser, J. Roman and C.M. Hart, 2003. Peroxisome proliferator activated receptor gamma ligands increase release of nitric oxide from endothelial cells. Arterioscler. Thromb. Vasc. Biol., 23: 52-57.

Carmona, M.C., K. Louche, M. Nibbelink, B. Prunet, A. Bross, M. Desbazeille, C. Dacquet, P. Renard, L. Casteilla and L. Penicaud, 2005. Fenofibrate prevents rosiglitazone-induced body weight gain in ob/ob mice. Int. J. Obes., 29: 864-871.

Chang, Y., B. Ceacareanu, M. Dixit, N. Sreejayan and A. Hassid, 2002. Nitric oxide-induced motility in aortic smooth muscle cells: Role of protein tyrosine phosphatase SHP-2 and GTP-binding protein Rho. Circ. Res., 91: 390-397.

Cheng, L., G. Ding, Q. Qin, Y. Huang, W. Lewis, N. He, R.M. Evans, M.D. Schneider, F.A. Brako, Y. Xiao, Y.E. Chen and Q. Yang, 2004. Cardiomyocyte-restricted peroxisome proliferator activated receptor-delta deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. Nat. Med., 10: 1245-1250.

Dewald, O., S. Sharma, J. Adrogue, R. Salazar, G.D. Duerr, J.D. Crapo, M.L. Entman and H. Taegtmeyer, 2005. Downregulation of peroxisome proliferator-activated receptor-alpha gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity. Circulation, 112: 407-415.

Diep, Q.N., F. Amiri, K. Benkirane, P. Paradis and E.L. Schiffrin, 2004. Long-term effects of the PPAR gamma activator pioglitazone on cardiac inflammation in stroke-prone spontaneously hypertensive rats. Can. J. Physiol. Pharmacol., 82: 976-985.

Ding, G., L. Cheng, Q. Qin, S. Frontin and Q. Yang, 2006. PPARdelta modulates lipopolysaccharide-induced TNF-alpha inflammation signaling in cultured cardiomyocytes. J. Mol. Cell. Cardiol., 40: 821-828.

Dormandy, J.A., B. Charbonnel, D. Eckland, E. Erdmann, M. Massi-Benedetti *et al*., 2005. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): A randomised controlled trial. Lancet, 366: 1279-1289.

Elkeles, R.S., J.R. Diamond, C. Poulter, S. Dhanjil, A.N. Nicolaides, S. Mahmood, W. Richmond, H. Mather, P. Sharp and M.D. Feher, 1998. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo controlled study of bezafibrate: The St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. Diabetes Care, 21: 641-648.

Ericsson, C.G., J. Nilsson, L. Grip, B. Svane and A. Hamsten, 1997. Effect of bezafibrate treatment over five years on coronary plaques causing 20% to 50% diameter narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT]). Am. J. Cardiol., 8: 1125-1129.

Etgen, G.J., B.A. Oldham, W.T. Johnson, C.L. Broderick, C.R. Montrose, J.T. Brozinick, E.A. Misener, J.S. Bean, W.R. Bensch and D.A. Brooks *et al*., 2002. The dual peroxisome proliferator-activated receptor-α/γ Agonist LY465608 ameliorates insulin resistance and diabetic hyperglycemia while improving cardiovascular risk factors in preclinical models. Diabetes, 51: 1083-1087.

Ferre, P., 2004. The biology of peroxisome proliferator-activated receptors: Relationship with lipid metabolism and insulin sensitivity. Diabetes, 53: S43-50.

Finck, B.N. and D.P. Kelly, 2002. Peroxisome proliferator-activated receptor alpha (PPARalpha) signaling in the gene regulatory control of energy metabolism in the normal and diseased heart. J. Mol. Cell. Cardiol., 34: 1249-1257.

Frey, N. and E.N. Olson, 2002. Modulating cardiac hypertrophy by manipulating myocardial lipid metabolism? Circulation, 105: 1152-1154.

Fukata, Y., M. Amano and K. Kaibuchi, 2001. Rho-Rho-kinase pathway in smooth muscle contraction and cytoskeletal reorganization of non-muscle cells. Trends Pharmacol. Sci., 22: 32-39.

Graham, T.L., C. Mookherjee, K.E. Suckling, C.N. Palmer and L. Patel, 2005. The PPAR delta agonist GW0742X reduces atherosclerosis in LDLR(-/-) mice. Atherosclerosis, 181: 29-37.

Ha, K.C., 2006. Effect of rosiglitazone on myocardial ischemia-reperfusion injury in rat heart. Korean J. Physiol. Pharmacol., 10: 181-186.

Home, P.D., S.J. Pocock, H. Beck-Nielsen, R. Gomis, M. Hanefeld, H. Dargie, M. Komajda, J. Gubb, N. Biswas and N.P. Jones, 2005. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): Study design and protocol. Diabetologia, 48: 1726-1735.

Huss, J.M. and D.P. Kelly, 2004. Nuclear receptor signaling and cardiac energetics. Circ. Res., 95: 568-578.

Ichihara, S., K. Obata, Y. Yamada, K. Nagata, A. Noda, G. Ichihara, A. Yamada, T. Kato, H. Izawa, T. Murohara and M. Yokota, 2006. Attenuation of cardiac dysfunction by a PPAR-alpha agonist is associated with down-regulation of redox-regulated transcription factors. J. Mol. Cell Cardiol., 41: 318-329.

Iglarz, M., R.M. Touyz, F. Amiri, M.F. Lavoie, Q.N. Diep and E.L. Schiffrin, 2003. Effect of peroxisome proliferator-activated receptor-alpha and -gamma activators on vascular remodeling in endothelin-dependent hypertension. Arterioscler. Thromb. Vasc. Biol., 23: 45-51.

Irukayama-Tomobe, Y., T. Miyauchi, S. Sakai, Y. Kasuya, T. Ogata, M. Takanashi, M. Iemitsu, T. Sudo, K. Goto and I. Yamaguchi, 2004. Endothelin-1-induced cardiac hypertrophy is inhibited by activation of peroxisome proliferator-activated receptor alpha partly via blockade of c-Jun NH2-terminal kinase pathway. Circulation, 109: 904-910.

Israelian-Konaraki, Z. and P.D. Reaven, 2005. Peroxisome proliferator-activated receptor-alpha and atherosclerosis: From basic mechanisms to clinical implications. Cardiol. Rev., 13: 240-246.

Javiya, V.A. and J.A. Patel, 2006. The role of peroxisome proliferator-activated receptors in human disease. Indian J. Pharmacol., 38: 243-253.

Khandoudi, N., P. Delerive, I. Berrebi-Bertrand, R.E. Buckingham, B. Staels and A. Bril, 2002. Rosiglitazone, a peroxisome proliferator-activated receptor-γ, inhibits the Jun NH2-terminal kinase/activating protein 1 pathway and protects the heart from ischemia/reperfusion injury. Diabetes, 51: 1507-1514.

Kim, S.J., A. Peppas, S.K. Hong, G. Yang, Y. Huang, G. Diaz, J. Sadoshima, D.E. Vatner and S.F. Vatner, 2003. Persistent stunning induces myocardial hibernation and protection: Flow/function and metabolic mechanisms. Circ. Res., 92: 1233-1239.

Kleemann, R., L. Verschuren, B.J. de Rooij, J. Lindeman, M.M. de Maat, A.J. Szalai, H.M. Princen and T. Kooistra, 2004. Evidence for anti-inflammatory activity of statins and PPARalpha activators in human C-reactive protein transgenic mice *in vivo* and in cultured human hepatocytes *in vitro*. Blood, 103: 4188-4194.

Lee, C.H., A. Chawla, N. Urbiztondo, D. Liao, W.A. Boisvert, R.M. Evans and L.K. Curtiss, 2003. Transcriptional repression of atherogenic inflammation: Modulation by PPARdelta. Science, 302: 453-457.

Li, A.C. and C.K. Glass, 2004. PPAR- and LXR-dependent pathways controlling lipid metabolism and the development of atherosclerosis. J. Lipid Res., 45: 2161-2173.

Liang, F., F. Wang, S. Zhang and D.G. Gardner, 2003. Peroxisome proliferator activated receptor (PPAR) alpha agonists inhibit hypertrophy of neonatal rat cardiac myocytes. Endocrinology, 144: 4187-4194.

Martens, F.M., T.J. Rabelink, J. op 't Roodt, E.J. de Koning and F.L. Visseren, 2006. TNF-alpha induces endothelial dysfunction in diabetic adults, an effect reversible by the PPARgamma agonist pioglitazone. Eur. Heart J., 27: 1605-1609.

Marx, N., G.K. Sukhova, T. Collins, P. Libby and J. Plutzky, 1999. PPARalpha activators inhibit cytokine-induced vascular cell adhesion molecule-1 expression in human endothelial cells. Circulation, 99: 3125-3131.

Marx, N., N. Mackman, U. Schonbeck, N. Yilmaz, V. Hombach, P. Libby and J. Plutzky, 2001. PPARalpha activators inhibit tissue factor expression and activity in human monocytes. Circulation, 103: 213-219.

Marx, N., B. Kehrle, K. Kohlhammer, M. Grub, W. Koenig, V. Hombach, P. Libby and J. Plutzky, 2002. PPAR activators as anti-inflammatory mediators in human T lymphocytes: Implications for atherosclerosis and transplantation-associated arteriosclerosis. Circ. Res., 90: 703-710.

Marx, N., A. Imhof, J. Froehlich, L. Siam, J. Ittner, G. Wierse, A. Schmidt, W. Maerz, V. Hombach and W. Koenig, 2003. Effect of rosiglitazone treatment on soluble CD40L in patients with type 2 diabetes and coronary artery disease. Circulation, 107: 1954-1957.

Miyauchi, T. and T. Masaki, 1999. Pathophysiology of endothelin in the cardiovascular system. Annu. Rev. Physiol., 61: 391-415.

Molavi, B., J. Chen and J.L. Mehta, 2006. Cardioprotective effects of rosiglitazone are associated with selective overexpression of type 2 angiotensin receptors and inhibition of p42/44 MAPK. Am. J. Physiol. Heart Circ. Physiol., 291: H687-693.

Natali, A., S. Baldeweg, E. Toschi, B. Capaldo, D. Barbaro, A. Gastaldelli, J.S. Yudkin and E. Ferrannini, 2004. Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. Diabetes Care, 27: 1349-1357.

Ogata, T., T. Miyauchi, S. Sakai, Y. Irukayama-Tomobe, K. Goto and I. Yamaguchi, 2002. Stimulation of peroxisome-proliferator-activated receptor alpha (PPAR alpha) attenuates cardiac fibrosis and endothelin-1 production in pressure-overloaded rat hearts. Clin. Sci., 103: 284S-288S.

Ogata, T., T. Miyauchi, S. Sakai, M. Takanashi, Y. Irukayama-Tomobe and I. Yamaguchi, 2004. Myocardial fibrosis and diastolic dysfunction in deoxycorticosterone acetate-salt hypertensive rats is ameliorated by the peroxisome proliferator-activated receptor alpha activator fenofibrate, partly by suppressing inflammatory responses associated with the nuclear factor-kappa-B pathway. J. Am. Coll. Cardiol., 43: 1481-1488.

Okada, M., S.F. Yan and D.J. Pinsky, 2002. Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) activation suppresses ischemic induction of Egr-1 and its inflammatory gene targets. FASEB. J., 16: 1861-1868.

Patel, C., K.L. Wyne and D.K. McGuire, 2005. Thiazolidinediones, peripheral oedema and congestive heart failure: What is the evidence? Diab. Vasc. Dis. Res., 2: 61-66.

Planavila, A., J.C. Laguna and M. Vazquez-Carrera, 2005a. Nuclear factor-kappaB activation leads to down-regulation of fatty acid oxidation during cardiac hypertrophy. J. Biol. Chem., 280: 17464-17471.

Planavila, A., R. Rodriguez-Calvo, M. Jove, L. Michalik, W. Wahli, J.C. Laguna and M. Vazquez-Carrera, 2005b. Peroxisome proliferator-activated receptor beta/delta activation inhibits hypertrophy in neonatal rat cardiomyocytes. Cardiovasc. Res., 65: 832-841.

Pourcet, B., J.C. Fruchart, B. Staels and C. Glineur, 2006. Selective PPAR modulators, dual and pan PPAR agonists: Multimodal drugs for the treatment of type 2 diabetes and atherosclerosis. Expert Opin. Emerg. Drugs, 11: 379-401.

Purcell, N.H., G. Tang, C. Yu, F. Mercurio, J.A. DiDonato and A. Lin, 2001. Activation of NFkappa B is required for hypertrophic growth of primary rat neonatal ventricular cardiomyocytes. Proc. Natl. Acad. Sci. USA., 98: 6668-6673.

Ricote, M., A.C. Li, T.M. Willson, C.J. Kelly and C.K. Glass, 1998. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature, 391: 79-82.

Ridker, P.M., N. Rifai, M. Pfeffer, F. Sacks, S. Lepage and E. Braunwald, 2000. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation, 101: 2149-2153.

Ritter, O. and L. Neyses, 2003. The molecular basis of myocardial hypertrophy and heart failure. Trends in Mol. Med., 9: 313-321.

Rival, Y., N. Beneteau and T. Taillandier *et al*., 2002. PPARalpha and PPARdelta activators inhibit cytokine-induced nuclear translocation of NF-kappaB and expression of VCAM-1 in EAhy926 endothelial cells. Eur. J. Pharmacol., 435: 143-151.

Sambandam, N., D. Morabito, C. Wagg, B.N. Finck, D.P. Kelly and G.D. Lopaschuk, 2006. Chronic activation of PPARalpha is detrimental to cardiac recovery after ischemia. Am. J. Physiol. Heart Circ. Physiol., 290: H87-95.

Scarsi, M., M. Podvinec, A. Roth, H. Hug, S. Kersten, H. Albrecht, T. Schwede, U.A. Meyer and C. Rücker, 2006. Sulfonylureas and glinides exhibit PPARγ activity: A combined virtual screening and biological assay approach. Mol. Pharmacol., (In Press).

Schiffrin, E.L., F. Amiri, K. Benkirane, M. Iglarz and Q.N. Diep, 2003. Peroxisome proliferator-activated receptors: Vascular and cardiac effects in hypertension. Hypertension, 42: 664-668.

Seko, T., M. Ito, Y. Kureishi, R. Okamoto, N. Moriki, K. Onishi, N. Isaka, D.J. Hartshorne and T. Nakano, 2003. Activation of RhoA and inhibition of myosin phosphatase as important components in hypertension in vascular smooth muscle. Circ. Res., 92: 411-418.

Sidhu, J.S., D. Cowan and J.C. Kaski, 2003. The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein and fibrinogen levels in non-diabetic coronary artery disease patients. J. Am. Coll. Cardiol., 42: 1757-1763.

Sidhu, J.S., D. Cowan and J.C. Kaski, 2004. Effects of rosiglitazone on endothelial function in men with coronary artery disease without diabetes mellitus. Am. J. Cardiol., 94: 151-156.

Singh, J.P., R. Kauffman, W. Bensch, G. Wang, P. McClelland, J. Bean *et al*., 2005. Identification of a novel selective PPARα agonist 2-methyl-2-(4-{3-[1 (4 methyl benzyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3yl] propyl}phenoxy) propanoic acid (LY518674) that produces marked changes in serum lipids and apolipoprotein A-1 expression. Mol. Pharmacol., 68: 763-768.

Sood, H.S., M.J. Hunt and S.C. Tyagi, 2003. Peroxisome proliferator ameliorates endothelial dysfunction in a murine model of hyperhomocysteinemia. Am. J. Physiol. Lung Cell Mol. Physiol., 284: L333-341.

Staels, B., W. Koenig, A. Habib, R. Merval, M. Lebret, I.P. Torra, P. Delerive, A. Fadel, G. Chinetti, J.C. Fruchart, J. Najib, J. Maclouf and A. Tedgui, 1998. Activation of human aortic smooth-muscle cells is inhibited by PPARα but not by PPARγ activators. Nature, 393: 790-793.

Staels, B. and J.C. Fruchart, 2005. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes, 54: 2460-2470.

Stanley, W.C., G.D. Lopaschuk, J.L. Hall and J.G. McCormack, 1997. Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions. Potential for pharmacological interventions. Cardiovasc. Res., 33: 243-257.

Szmitko, P.E., C.H. Wang, R.D. Weisel, J.R. De Almeida, T.J. Anderson and S. Verma, 2003. New markers of inflammation and endothelial cell activation. Circulation, 108: 1917-1923.

Tai, E.S., D. Collins, S.J. Robins, J.J. O'Connor Jr, H.E. Bloomfield, J.M. Ordovas, E.J. Schaefer, M.E. Brousseau, 2006. The L162V polymorphism at the peroxisome proliferator activated receptor alpha locus modulates the risk of cardiovascular events associated with insulin resistance and diabetes mellitus: The Veterans Affairs HDL Intervention Trial (VA-HIT). Atherosclerosis, 187: 153-160.

Takagi, T., A. Yamamuro, K. Tamita, K. Yamabe, M. Katayama, S. Mizoguchi, M. Ibuki, T. Tani, K. Tanabe, K. Nagai, K. Shiratori, S. Morioka and J. Yoshikawa, 2003. Pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus: An intravascular ultrasound scanning study. Am. Heart J., 146: E5.

Takeda, K., T. Ichiki, T. Tokunou, Y. Funakoshi, N. Iino, K. Hirano, H. Kanaide and A. Takeshita, 2000. Peroxisome proliferator-activated receptor gamma activators downregulate angiotensin II type 1 receptor in vascular smooth muscle cells. Circulation, 102: 1834-1839.

Taniguchi, Y., T. Ooie, N. Takahashi, T. Shinohara, M. Nakagawa, H. Yonemochi, M. Hara, H. Yoshimatsu and T. Saikawa, 2006. Pioglitazone but not glibenclamide improves cardiac expression of heat shock protein 72 and tolerance against ischemia/reperfusion injury in the heredity insulin-resistant rat. Diabetes, 55: 2371-2378.

Tenenbaum, A., M. Motro and E.Z. Fisman, 2005. Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: The bezafibrate lessons. Cardiovasc. Diabetol., 4: 1-5.

Tian, Q. and P.M. Barger, 2005. Do PPARs play a role in cardiac hypertrophy and heart failure? Drug Discovery Today: Dis. mechanisms, 2: 109-114.

Toba, H., S. Miki, T. Shimizu, Y. Funakoshi, N. Iino, K. Hirano, H. Kanaide and A. Takeshita, 2006. The direct antioxidative and anti-inflammatory effects of peroxisome proliferator-activated receptors ligands are associated with the inhibition of angiotensin converting enzyme expression in streptozotocin-induced diabetic rat aorta. Eur. J. Pharmacol., 549: 124-132.

Tsuji, T., K. Mizushige, T. Noma, K. Murakami, K. Ohmori, A. Miyatake and M. Kohno, 2001. Pioglitazone improves left ventricular diastolic function and decreases collagen accumulation in prediabetic stage of a type II diabetic rat. J. Cardiovasc. Pharmacol., 38: 868-874.

Verma, S., C.H. Wang, S.H. Li, A.S. Dumont, P.W. Fedak, M.V. Badiwala, B. Dhillon, R.D. Weisel, R.K. Li, D.A. Mickle and D.J. Stewart, 2002a. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation, 106: 913-919.

Verma, S., S.H. Li, M.V. Badiwala, R.D. Weisel, P.W. Fedak, R.K. Li, B. Dhillon and D.A. Mickle, 2002b. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation, 105: 1890-1896.

Verma, S., M.V. Badiwala, R.D. Weisel, S.H. Li, C.H. Wang, P.W. Fedak, R.K. Li and D.A. Mickle, 2003. C-reactive protein activates the nuclear factor-kappaB signal transduction pathway in saphenous vein endothelial cells: Implications for atherosclerosis and restenosis. J. Thorac. Cardiovasc. Surg., 126: 1886-1891.

Verma, S. and P.E. Szmitko, 2006. The vascular biology of peroxisome proliferator-activated receptors: Modulation of atherosclerosis. Can. J. Cardiol., 22: 12B-17B.

Verreth, W., J. Ganame, A. Mertens, H. Bernar, M.C. Herregods and P. Holvoet, 2006. Peroxisome proliferator-activated receptor-alpha, gamma-agonist improves insulin sensitivity and prevents loss of left ventricular function in obese dyslipidemic mice. Arterioscler. Thromb. Vasc. Biol., 26: 922-928.

Verrier, E., L. Wang, C. Wadham, N. Albanese, C. Hahn, J.R. Gamble, V.K. Chatterjee, M. A. Vadas and P. Xia, 2004. PPARgamma agonists ameliorate endothelial cell activation via inhibition of diacylglycerol-protein kinase C signaling pathway: Role of diacylglycerol kinase. Circ. Res., 94: 1515-1522.

Wakino, S., U. Kintscher, S. Kim, F. Yin, W.A. Hsueh and R.E. Law, 2000. Peroxisome proliferator-activated receptor gamma ligands inhibit retinoblastoma phosphorylation and $G_1 \rightarrow S$ transition in vascular smooth muscle cells. J. Biol. Chem., 275: 22435-22441.

Wakino, S., K. Hayashi, T. Kanda, S. Tatematsu, K. Homma, K. Yoshioka, I. Takamatsu and T. Saruta, 2004. Peroxisome proliferator-activated receptor gamma ligands inhibit Rho/Rho kinase pathway by inducing protein tyrosine phosphatase SHP-2. Circ. Res., 95: e45-55.

Wallace, J.M., M. Schwarz, P. Coward *et al*., 2005. Effects of peroxisome proliferator-activated receptor α/δ agonists on HDL-cholesterol in vervet monkeys. J. Lipid Res., 46: 1009-1016.

Wang, N., L. Verna, N.G. Chen, J. Chen, H. Li, B.M. Forman and M.B. Stemerman, 2002. Constitutive activation of peroxisome proliferator-activated receptor-gamma suppresses pro-inflammatory adhesion molecules in human vascular endothelial cells. J. Biol. Chem., 277: 34176-34181.

Wayman, N.S., Y. Hattori, M.C. McDonald, H. Mota-Filipe, S. Cuzzocrea, B. Pisano, P.K. Chatterjee and C. Thiemermann, 2002. Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size. FASEB. J., 16: 1027-1040.

Welch, J.S., M. Ricote, T.E. Akiyama, F.J. Gonzalez and C.K. Glass, 2003. PPARgamma and PPARdelta negatively regulate specific subsets of lipopolysaccharide and IFNgamma target genes in macrophages. Proc. Natl. Acad. Sci. USA., 100: 6712-6717.

Yamamoto, K., R. Ohki, R.T. Lee, U. Ikeda and K. Shimada, 2001. Peroxisome proliferator activated receptor gamma activators inhibit cardiac hypertrophy in cardiac myocytes. Circulation, 104: 1670-1675.

Yeh, C.H., T.P. Chen, C.H. Lee, Y.C. Wu, Y.M. Lin and P.J. Lin, 2006. Cardiomyocytic apoptosis following global cardiac ischemia and reperfusion can be attenuated by peroxisome proliferator-activated receptor α but not γ activators. Shock, 26: 262-270.

Young, M.E., F.A. Laws, G.W. Goodwin and H. Taegtmeyer, 2001. Reactivation of Peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. J. Biol. Chem., 276: 44390-44395.

Yue, T., J. Chen, W. Bao, P.K. Narayanan, A. Bril, W. Jiang, P.G. Lysko, J.L. Gu, R. Boyce, D.M. Zimmerman, T.K. Hart, R.E. Buckingham and E.H. Ohlstein, 2001. *In vivo* myocardial protection from ischemia/reperfusion injury by the peroxisome proliferator-activated receptor-γ agonist rosiglitazone. Circulation, 104: 2588-2594.

Yue, T.L., W. Bao, J.L. Gu, J. Cui, L. Tao, X.L. Ma, E.H. Ohlstein and B.M. Jucker, 2005. Rosiglitazone treatment in Zucker diabetic Fatty rats is associated with ameliorated cardiac insulin resistance and protection from ischemia/reperfusion-induced myocardial injury. Diabetes, 54: 554-562.

Zambon, A., 2006. Reducing vascular risk in the diabetic patient: Implications from the FIELD study. Diabetes and Vasc. Dis. Res., 3: S16-S20.

Zambon, A., P. Gervois, P. Pauletto, J.C. Fruchart and B. Staels, 2006. Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-alpha activators: Clinical and experimental evidence. Arterioscler. Thromb. Vasc. Biol., 26: 977-986.

Zhang, Y.J., X. Yang, Q.Y. Kong, Y.F. Zhang, W.Y. Chen, X.Q. Dong, X.Y. Li and X.Q. Yu, 2006. Effect of 15d-PGJ2 on the expression of CD40 and RANTES induced by IFN-gamma and TNF-alpha on renal tubular epithelial cells (HK-2). Am. J. Nephrol., 26: 356-362.