The vascular biology of peroxisome proliferator-activated receptors: Modulation of atherosclerosis

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Accumulating evidence suggests that peroxisome proliferator-activated receptor (PPAR) agonists possess powerful antiatherosclerotic properties, by both directly affecting the vascular wall and indirectly affecting systemic inflammation and insulin sensitivity. The PPARs are ligand-activated transcription factors, which play a number of important physiological roles in lipid and glucose homeostasis. Activation of PPAR γ appears to exert a vasculoprotective effect by limiting endothelial dysfunction, impairing atherogenesis and preventing restenosis, while simultaneously and favourably modulating adipokine expression and lipid metabolism. Several experimental and clinical studies have demonstrated the potential of the PPAR agonist drug class in terms of treating atherosclerotic disease. In the present review, the vascular biology of PPARs, and how the modulation of these molecular pathways may serve as a therapeutic strategy to prevent atherosclerosis, vascular inflammation and restenosis are discussed.

Key Words: Atherosclerosis; Endothelial dysfunction; Peroxisome proliferator-activated receptor agonists

Over the past few years, there has been an increasing amount of attention directed toward the role of peroxisome proliferator-activated receptors (PPARs) as potential targets for the treatment of atherosclerosis. In the present review, we will discuss the vascular biology of PPARs as they relate to the mechanisms behind atherosclerosis, and describe some of the clinical studies employing PPAR γ and PPAR α agonists for the prevention of atherosclerosis, inflammation and restenosis.

WHAT ARE PPARS?

The PPAR system is comprised of three different proteins: PPAR α , PPAR β/δ and PPAR γ (1). The PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily. Other members in this family include the receptors for estrogen, progesterone, thyroid hormone and the mineralocorticoids. Binding of a ligand to a nuclear receptor transforms it into a transcription factor, which then has the potential of modulating gene expression. The pharmacological ligands for the PPAR α system include the fibric acids gemfibrozil and fenofibrate (2,3). The pharmacological ligands for PPAR γ include the thiazolidinediones, such as troglitazone,

La biologie vasculaire des récepteurs activés par les proliférateurs de peroxysome et la modulation de l'athérosclérose

De plus en plus de données tendent à montrer que les agonistes des récepteurs activés par les proliférateurs de peroxysome (PPAR) possèdent de puissantes propriétés antiathéroscléreuses, d'une part en agissant directement sur la paroi vasculaire, d'autre part en agissant indirectement sur l'inflammation générale et la sensibilité à l'insuline. Les PPAR sont des facteurs de transcription activés par des ligands, qui jouent différents rôles physiologiques importants dans l'homéostasie du glucose et des lipides. L'activation des PPAR γ semble produire un effet vasculoprotecteur en limitant le dysfonctionnement endothélial, en entravant l'athérogenèse et en prévenant la resténose tout en modulant favorablement l'expression de l'adipokine et le métabolisme des lipides. Plusieurs études expérimentales et études cliniques ont montré le potentiel thérapeutique de la classe des agonistes des PPAR dans le traitement de l'athérosclérose. Il sera question, dans le présent article, de la biologie vasculaire des PPAR et de la façon dont la modulation des voies moléculaires étudiées peut servir de stratégie thérapeutique dans la prévention de l'athérosclérose, de l'inflammation vasculaire et de la resténose.

pioglitazone and rosiglitazone (4,5). The pharmacological ligands for PPAR β/δ have yet to be determined.

PPARs play a number of important physiological roles (1). It is well established that PPAR α participates in fatty acid oxidation and lipoprotein synthesis; however, it also appears to possess important anti-inflammatory effects. PPAR γ appears to play a role in adipocyte differentiation, lipid storage, fat metabolism and glucose homeostasis, with increasing evidence supporting its role as an important modulator of inflammation, atherosclerosis and macrophage differentiation. Evidence also implicates PPAR γ as a modulator of vascular cell growth and migration. PPAR β/δ has been linked to wound healing and may also be important in influencing cell growth, and in both lipoprotein and fat metabolism.

PPAR receptor signalling in vascular cells is dependent on interaction with their respective ligands. Upon ligand binding, PPARs form heterodimers with the nuclear retinoid X receptor. This PPAR-retinoid X receptor complex then binds to the specific PPAR response elements in the promoter region of target genes, several of which are involved in lipid and glucose homeostasis, controlling their expression.

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In addition to the important role PPARs play in facilitating the transactivation of genes involved in lipid and glucose homeostasis, they also have the ability to repress target gene expression in both DNA-binding-independent and -dependent pathways (1). The signalling pathways affected include p65/p50, Fos/Jun and STAT1/STAT3. This mechanism of transrepression may be partly responsible for the anti-inflammatory properties noted with PPAR agonist treatment. It is important to note that in addition to pharmacological ligands, a number of natural ligands have been identified for members of the PPAR family. For example, fatty acids and lipoprotein lipolytic products appear to serve as endogenous ligands for PPAR α (6). Furthermore, though PPAR α appears to be located primarily within the liver, it is also expressed in vascular smooth muscle (7), endothelial (8) and inflammatory cells (9). Natural ligands for PPAR γ include the prostaglandin D₂ derivative 15-deoxy-delta^{12,14}-prostaglandin J₂ (15d-PGJ₂) and forms of oxidized linoleic acid. PPAR γ , found predominantly within adipose tissue, is also expressed in liver, endothelial, vascular smooth muscle and inflammatory cells (10). Finally, the PPAR β/δ system may respond to some natural fatty acids and the receptor appears to be ubiquitously expressed.

PPARS AND ATHEROGENESIS

Over the past few years, it has become apparent that PPAR activation may have both direct and indirect effects on the modulation of atherosclerotic vascular disease. The potential of PPARs to modulate the atherosclerotic process may involve a coordinated interaction between the indirect effects of PPAR activation on glucose and fat metabolism, and their direct effects on improving insulin sensitivity and reducing inflammation (11). Also, since PPAR receptors are expressed in both vascular and inflammatory cells, their stimulation may lead to favourable vascular and anti-inflammatory effects, which may inhibit atherogenesis. Thus, when PPAR agonists are employed for the treatment of diabetes, the beneficial effects on atherosclerotic vascular risk may be ascribed to an indirect effect on insulin resistance, a direct inhibitory effect on limiting atherogenesis and endothelial dysfunction, and a very powerful anti-inflammatory effect on molecules such as monocyte chemoattractant protein-1 and C-reactive protein (CRP). Indeed, PPAR γ agonists have been demonstrated to exhibit pleiotropic vascular effects. These include a reduction in vascular inflammation (reductions in CRP, interleukin-6, interleukin-10, tumour necrosis factor [TNF], CD40 and angiotensin II), an improvement in endothelial function by enhancing nitric oxide bioavailability and reducing lectin-like oxidized low density lipoprotein receptor-1, a modulation of the bone marrow response to atherosclerosis by enhancing endothelial progenitor cell (EPC) survival and promoting the differentiation of stem cells toward the endothelial lineage, an improvement in the stability of vulnerable plaques by decreasing matrix metalloproteinase-9 (MMP-9) production, enhanced fibrinolysis by reducing plasminogen activator inhibitor-1 production, improved cardiac function in experimental animal models by decreasing left ventricular hypertrophy and fibrosis, and, finally, the modulation of adipokines, which appear to play a very important role in the molecular link between obesity and atherosclerosis.

Initial work done by Marx et al (12) established a critical role for PPAR γ in atherogenesis. Strong staining for PPAR γ was detected in macrophages from human atheromas.

Subsequently, PPAR γ expression was observed within both endothelial cells and vascular smooth muscle cells involved in atherosclerotic plaques in human coronary arteries (13,14). Thus, PPAR γ is expressed in all of the cell types involved in the development and propagation of adverse vascular remodeling and atherosclerosis.

The vasculoprotective effects of PPAR γ , in both acute and chronic vascular injuries, were first clearly demonstrated using a rat model (15). Wistar rats were treated with pioglitazone (3 mg/kg/day) for one week before, and two weeks after, undergoing carotid endothelial injury. The neointimal cross-sectional areas in pioglitazone-treated animals were significantly lower than in the untreated animals. Furthermore, pioglitazone treatment significantly inhibited the incorporation of bromodeoxyuridine, a marker of DNA synthesis, into the neointima. These findings suggested that PPAR γ ligands represented powerful inhibitors of vascular smooth muscle cell proliferation and that they may hold promise in the treatment of neointimal hyperplasia.

PPAR γ agonists may in part exert antiatherosclerotic effects by preventing the infiltration of macrophages into the vessel wall. Collins et al (16) demonstrated that troglitazone significantly reduced the number of macrophages within atherosclerotic lesions in both diabetic and nondiabetic mice. Rosiglitazone was also demonstrated to limit lesion formation in low density lipoprotein (LDL) receptor-deficient mice (17). Similar results were reported in an apolipoprotein E knockout mouse model (18,19). Thus, PPAR γ agonists appear to limit early atherosclerotic lesion formation by interfering with monocyte transendothelial migration, in both settings with or without insulin resistance, suggesting that PPAR γ ligands have separate proatherogenic activities in addition to their antidiabetic effects.

One of the first clinical studies to evaluate the effects of PPAR γ agonists on atherosclerosis progression was performed among Japanese type II diabetic patients who were treated with either pioglitazone (30 mg/day) or placebo for six months (20). These patients were also receiving treatment with sulfonylureas. Carotid intimal medial thickness (IMT) was measured at baseline, three months and six months after treatment using high-resolution, B-mode ultrasonography. In the placebo group, carotid IMT increased from baseline by an average of 0.019 mm and 0.022 mm after three and six months, respectively. In contrast, carotid IMT declined from baseline by an average of 0.050 mm and 0.084 mm after three and six months of pioglitazone therapy, respectively. These differences were statistically significant and suggested that short-term treatment with a PPAR γ agonist may result in an inhibition of early atherosclerotic processes. Recently, the effect of rosiglitazone on common carotid IMT progression in coronary artery disease (CAD) patients without diabetes was evaluated (21). In this study, 92 patients with CAD were randomly assigned to either placebo or rosiglitazone treatment (8 mg/day) for a 24-week period. Those patients who received rosiglitazone had a marked reduction in the progression rate of atherosclerosis compared with the placebo group, as assessed by changes in carotid IMT over both a 24- and a 48-week period. Thus, rosiglitazone appears to reduce the atherosclerotic burden in individuals without diabetes.

The Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial is an ongoing study to compare the effects

of pioglitazone with glimepiride on coronary atheroma volume over an 18-month period, as assessed by intravascular ultrasound and quantitative coronary angiography. The trial, which is currently underway, randomly assigned 600 patients in a prospective, double-blinded, multicentred fashion to provide critical evidence as to whether thiazolidinedione-driven versus sulfonylurea-driven treatment limits the progression of atherosclerosis.

In addition to the effects of PPAR γ described above, PPAR α is also widely expressed in vascular tissue and by the cells involved in atherogenesis (8). The clinical benefits of PPAR α stimulation on the cardiovascular system were examined in the Veterans Affairs High density lipoprotein Intervention Trial (VA-HIT), which assessed the effects of gemfibrozil on vascular events over a five-year period (22). For the combined end point of nonfatal myocardial infarction, CAD and stroke, there was a significant reduction in the gemfibrozil group versus the placebo group. More importantly, this effect was seen in people with or without diabetes.

DO PPAR AGONISTS PREVENT RESTENOSIS?

Recently, PPAR agonists have been investigated as potential agents to prevent restenosis. PPAR γ agonists have been demonstrated to inhibit hyperplasia and restenosis after balloon-mediated vascular injury in rats (15,23). Treatment with either troglitazone or pioglitazone resulted in a marked reduction in the neointimal to medial area ratio, suggesting a reduction in restenosis following vascular injury. PPAR γ appears to be markedly upregulated in the neointima after balloon injury (14). The ability of thiazolidinediones to prevent vascular smooth muscle cell proliferation appears to be dependent on their ability to limit retinoblastoma protein (Rb) phosphorylation (24). Rb protein phosphorylation allows cells to enter the S phase from G1. By virtue of decreasing Rb phosphorylation, thiazolidinediones inhibit mitogenic stimulation of cyclin-dependent kinases and, via this mechanism, are believed to inhibit vascular smooth muscle cell proliferation. PPAR γ ligands also inhibit platelet-derived growth factor-directed migration of vascular smooth muscle cells (14). Troglitazone, rosiglitazone and the PPAR γ -specific agonist 15d-PGJ2 all appear to produce this effect.

Clinical studies have examined the favourable effect of thiazolidinediones on neointimal hyperplasia after coronary stenting in patients with type II diabetes. Treatment with pioglitazone resulted in an almost 50% reduction in neointimal index at six months poststenting in diabetic patients (25). Similarly, rosiglitazone (4 mg/day) was found to favourably decrease in-stent restenosis.

PPARS, INFLAMMATION AND ENDOTHELIAL DYSFUNCTION

Inflammation, via mediators such as CRP, plays a critical role in promoting endothelial dysfunction, which sets the stage for atherogenesis (26). The PPAR γ ligand rosiglitazone has been demonstrated to reduce serum levels of CRP by 27% and 22%, respectively, in 258 patients with type II diabetes who took 4 mg or 8 mg of rosiglitazone for a period of 26 weeks (27). Rosiglitazone has similar effects on the level of CRP, on markers of endothelial cell activation and on fibrinogen levels in nondiabetic patients with CAD (28). Recently, Weissman et al (personal communications, American Diabetes Association

Meeting, 2004) demonstrated that the combination of rosiglitazone (8 mg/day) with metformin (1 g/day) was superior in terms of lowering CRP compared with monotherapy with metformin (2 g/day). The beneficial effects of PPAR γ stimulation with rosiglitazone on CRP appear to occur early, and appear to occur in patients with both obesity and diabetes (29).

Several recent studies, including those performed in Dr Verma's laboratory, have demonstrated that CRP, in addition to being a very powerful biomarker, is also a mediator of atherosclerosis (30). In this regard, CRP has been demonstrated to decrease nitric oxide production, destabilize nitric oxide synthase messenger (m)RNA, increase endothelial cell apoptosis and stimulate the expression of nuclear factor-kappa B (31-33). CRP upregulates the expression of endothelial adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin; promotes the release of MCP-1, a chemokine, which facilitates leukocyte transmigration; and stimulates vascular smooth muscle cell angiotensin type 1 receptor activation (34,35). These proatherogenic effects of CRP can be limited by PPAR γ stimulation. We demonstrated in vitro that CRP-mediated upregulation of adhesion molecules and MCP-1 release in endothelial cells could be attenuated by rosiglitazone treatment in the presence or absence of a hyperglycemic milieu (36).

Recent studies have compared rosiglitazone with metformin and netaglanide in terms of the effect on endothelial function, a crucial determinant of vascular health. In a study by Natali et al (37), rosiglitazone was demonstrated to be superior to metformin based on its effect on endothelial function, as assessed using forearm blood flow measurements in response to graded infusions of acetylcholine. This study demonstrated that despite similar glycemic control with either rosiglitazone or metformin, there was a differential effect on endothelial function favouring rosiglitazone. Similar results were seen when comparing rosiglitazone with netaglanide, despite similar levels of glycemic control (37). Recently, Sidhu et al (38) further demonstrated a beneficial effect of rosiglitazone on endothelial function as assessed by von Willebrand factor levels in nondiabetic patients with CAD.

In addition to the favourable effects of PPAR γ agonists on CRP, these agents have also been demonstrated to modulate the sCD40 ligand/CD40 system, which is also a major player in atherogenesis (26). Increasing evidence implicates CD40-mediated intracellular events, including the release of tissue factor and MMP-9, as key mediators of plaque vulnerability and eventual rupture. Rosiglitazone treatment (8 mg/day) reduces soluble CD40 ligand levels (39), and diabetic patients treated with rosiglitazone exhibit a dose-dependent reduction in MMP-9 production (27). Furthermore, PPAR α and PPAR γ ligands have been shown to reduce thrombin-stimulated endothelin-1 release (40). Endothelin-1 is one of the most powerful endogenous vasoconstrictors, and plays a significant role in the development of endothelial dysfunction.

PPARS AND EPCS

Bone marrow-derived EPCs play an important role in postnatal neovascularization (41). EPC number and migratory activity correlate inversely with risk factors for coronary atherosclerosis (42). Thus, EPC transplantation, or increasing EPC number, mobilization and function, may emerge as potential therapeutic interventions for ischemic disease. EPCs can be recruited to the myocardium by both endogenous and exogenous

stimuli. Some of the endogenous stimuli include angiopoietin-1, granulocyte macrophage colony-stimulating factor, vascular endothelial growth factor and MMP-9. Statins also appear to increase the survival and function of EPCs (43). Given the importance of EPCs towards postnatal neovascularization and vascular repair, we hypothesized that CRP, a powerful cardiovascular risk factor, would exert direct effects to inhibit EPC survival and differentiation. We tested the effects of CRP, at concentrations known to predict adverse cardiac events, on human EPC survival, differentiation, apoptosis and endothelial nitric oxide synthase (eNOS) mRNA expression (44). In addition, we evaluated the effects of rosiglitazone on these processes in the presence and absence of CRP. The following key observations were made: EPCs incubated with human recombinant CRP exhibited dose-dependent decreased survival; CRP-treated EPCs exhibited decreased expression of the endothelial cell specific markers, Tie-2 and EC-lectin, suggesting an inhibition of EPC differentiation; EPCs incubated with human recombinant CRP demonstrated increased apoptosis; CRP caused a significant decrease in EPC eNOS mRNA expression after 24 h of incubation; and rosiglitazone attenuated the effect of CRP on EPC survival, differentiation, apoptosis and eNOS mRNA levels. These data support a direct inhibitory effect by CRP on EPC survival and differentiation, an effect that could be reversed with rosiglitazone treatment.

We have also investigated the effects of rosiglitazone on angiogenic progenitor cell differentiation toward the endothelial lineage. EPCs have been shown to be beneficial in terms of early re-endothelialization after vascular injury and subsequent attenuation of neointimal formation (26). However, in response to a variety of factors, these putative EPCs can transform into cells with different phenotypes, including smooth muscle cells. We examined whether PPAR γ agonists would favourably modulate bone marrow-derived progenitor cells to differentiate into endothelial cells and promote early re-endothelialization following vascular intervention (45). C57/BL6 mice treated with or without rosiglitazone underwent femoral angioplasty. Rosiglitazone treatment attenuated neointimal formation. The contribution of bone marrow-derived cells to neointimal formation was investigated by bone marrow transplantation from eYFP mice to background mice. Almost 60% of the cells within the neointima at four weeks were derived from the bone marrow. Pure endothelial marker-positive, pure α -smooth muscle actin-positive or double-positive progenitor cells could be found between both mouse bone marrow stem cells and human circulating peripheral blood progenitor cells after culture in conditional media enriched with vascular endothelial growth factor. Rosiglitazone caused a significant sixfold increase in colony formation by human EPCs, promoted the differentiation of progenitor cells toward the endothelial lineage in mouse bone marrow *in vivo* and in human peripheral blood progenitor cells *in vitro*, and inhibited the differentiation of progenitor cells toward the smooth muscle cell lineage. Within the neointima, rosiglitazone also stimulated progenitor cells to differentiate into mature endothelial cells and caused earlier re-endothelialization compared with controls. Thus, rosiglitazone may serve as a critical factor to promote the differentiation of progenitor cells toward the endothelial lineage and, thus, to attenuate restenosis after angioplasty.

We have also recently demonstrated that PPAR γ agonists facilitate the transdifferentiation of progenitor cells into cardiomyocyte-like cells (Verma, unpublished observations,

2005). Thiazolidinediones have also been demonstrated to inhibit the expression of receptors for advanced glycation end products (46). This occurs both in the basal state and in the TNF α stimulated state, and is observed with both rosiglitazone and pioglitazone.

PPARS MODULATE ADIPOKINES

Adipokines appear to be at the interface of cardiometabolic disease, and PPARs have been demonstrated to have important effects on their expression. Adipokines, cytokines released from adipose tissue, participate in the development of insulin resistance, but may also modulate endothelial dysfunction and promote atherosclerosis (47). The majority of adipokines promote insulin resistance; however, adiponectin appears to be protective and may act to not only limit insulin resistance but also to limit atherosclerosis. We have recently evaluated the effects of resistin, an adipokine, on endothelial dysfunction, and demonstrated that it promotes endothelin-1 expression in endothelial cells in an activator protein-1-dependent fashion (48). Adipokines, in this fashion, appear to be key collaborators in linking insulin resistance to endothelial dysfunction and atherosclerosis. PPAR γ ligands have been shown to regulate adiponectin expression. Indeed, pioglitazone has been demonstrated to increase adiponectin levels in people with type II diabetes (49). Because adiponectin directly limits insulin resistance, endothelial dysfunction and inflammation, upregulation of adiponectin may play a dual role in modulating insulin sensitivity and, at the same time, limiting vascular injury. Adiponectin, in a concentration-dependent fashion, inhibits TNF α -mediated vascular cell adhesion molecule-1 induction and subsequent monocyte cell adhesion to the endothelium (50). The *in vivo* effects of adiponectin toward limiting atherosclerosis were confirmed in apolipoprotein E-deficient mice (51). Therefore, PPAR γ stimulation with resultant upregulation of the adiponectin gene appears to have important anti-inflammatory and antiatherogenic effects.

PPARS MODULATE LIPID METABOLISM

PPAR agonists appear to modulate lipid metabolism. Pioglitazone treatment (45 mg/day) has been demonstrated to reduce concentrations of small, dense LDL cholesterol in hypertensive nondiabetic patients (52). The effects of rosiglitazone on small, dense LDL cholesterol in patients with type II diabetes was described by Freed et al (53). In their studies, diabetic patients treated with rosiglitazone (8 mg/day for eight weeks) had a predominance of large, buoyant LDL cholesterol versus small, dense LDL cholesterol. The effect of pioglitazone on lipid metabolism was further studied in a 26-week, double-blind, placebo-controlled trial involving 408 patients with type II diabetes, who were randomly assigned to either 15 mg, 30 mg or 45 mg of pioglitazone per day (54). Pioglitazone treatment was associated with mean reductions in triglyceride concentrations ranging from 9% to 9.6% from baseline values. This was compared with a 4.8% increase in triglyceride concentrations in the placebo group. Also, the group taking pioglitazone 45 mg/day displayed a statistically significant increase in high density lipoprotein cholesterol concentrations compared with placebo, significantly improving 19.1% from baseline.

An important effect of PPAR α and PPAR γ includes the induction of ABCA1 expression, a member of the ATP-binding cassette transporter family, which is involved in the control of apolipoprotein AI-mediated cholesterol efflux from

macrophages (55-57). WY14643 (PPAR α agonist) and rosiglitazone were shown to increase, in a concentration-dependent fashion, the expression of *ABCA1* in human macrophages, supporting their role in the first steps of the reverse cholesterol transport pathway. In addition to these effects on cholesterol efflux, PPAR γ agonists may also have the ability to reduce the activity of scavenger receptor A-1 for oxidized LDL on macrophages (58). Small concentrations of the PPAR γ agonist 15d-PGJ2 caused a significant reduction in scavenger receptor A-1 gene activity, revealing another potential mechanism by which PPARs can modulate macrophage cholesterol metabolism and, thus, influence the progression of atherosclerosis.

The effects of PPAR α , β/δ and γ on the modulation of macrophage foam cell formation were described by Li et al (59). As described earlier, a number of in vitro studies have suggested that PPARs exert antiatherogenic effects by inhibiting the expression of inflammatory genes and enhancing cholesterol efflux by activation of the liver X receptor (LXR)-*ABCA1* pathway. Li et al (59) investigated the potential importance of these activities in vivo, with an emphasis on foam cell formation and atherosclerosis progression in male LDL receptor-deficient mice. Both PPAR γ - and PPAR α -specific agonists strongly inhibited atherosclerotic lesion progression and foam cell formation, whereas PPAR β -specific agonists failed to inhibit lesion or foam cell formation. However, the mechanism through which PPAR α and PPAR γ agonists inhibited foam cell formation in vivo appeared to occur through a distinct, *ABCA1*-independent pathway. Whereas the inhibition of foam cell formation by PPAR α required LXR, activation of PPAR γ reduced cholesterol esterification, induced expression of *ABCG1* and stimulated high density lipoprotein-dependent cholesterol efflux in an LXR-independent manner. Thus, both PPAR α and PPAR γ ligands protect against atherosclerosis and inhibit macrophage foam cell formation; however, PPAR γ influences cholesterol efflux through *ABCG1* in an LXR-independent fashion.

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CONCLUSION

There is accumulating evidence to suggest that PPAR agonists possess powerful antiatherosclerotic properties, by both directly affecting the vascular wall and indirectly affecting systemic inflammation and insulin sensitivity. As a result, PPARs are clearly at the metabolic interface and ongoing studies, such as the PROspective Pioglitazone Clinical Trial In MacroVascular Events (PROactive), the Action to Control of Cardiovascular Risk in Diabetes (ACCORD) and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D), as well as many others, will further elucidate the role of thiazolidinediones as antiatherosclerotic agents. It is our contention that the pleiotropic effects of PPARs, including their ability to decrease thrombosis, cell recruitment, cell activation, foam cell formation and inflammatory responses, and their concurrent ability to improve plaque stability, endothelial function, EPC biology and cholesterol efflux, showcase the potential of this drug class in terms of treating atherosclerotic disease in the future.

Recently, the results from the PROactive study have been published (60). In this prospective, randomized controlled trial, 5238 patients with type II diabetes who had evidence of macrovascular disease were assigned to oral pioglitazone titrated from 15 mg to 45 mg or matching placebo, in addition to their other glucose-lowering and cardiac medications. Three hundred one of 2605 patients in the pioglitazone group and 358 of 2633 patients in the placebo group reached the composite end point of all-cause mortality, nonfatal myocardial infarction and stroke (HR 0.84, 95% CI 0.72 to 0.98; P=0.027). Thus, pioglitazone treatment in patients with type II diabetes with preexisting cardiovascular disease reduces the risk of adverse cardiovascular events by approximately 16%. However, the incidence of heart failure was greater in the pioglitazone-treated group. Six per cent (149 of 2605) and 4% (108 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure although the mortality rates from heart failure did not differ between groups.

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