Peroxisome proliferator-activated receptors and cardiovascular remodeling

Ernesto L. Schiffrin

Canadian Institute of Health Research Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, Montreal, Quebec, Canada

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Schiffrin, Ernesto L. Peroxisome proliferator-activated receptors and cardiovascular remodeling. Am J Physiol Heart Circ Physiol 288. H1037–H1043, 2005; doi:10.1152/ajpheart.00677.2004.—Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that heterodimerize with the retinoid X receptor and then modulate the function of many target genes. Three PPARs are known: α, β/δ, and γ. The better known are PPAR-α and PPAR-γ, which may be activated by different synthetic agonists, although the endogenous ligands are unknown. PPAR-α is involved in fatty acid oxidation and expressed in the liver, kidney, and skeletal muscle, whereas PPAR-γ is involved in fat cell differentiation, lipid storage, and insulin sensitivity. However, both have been shown to be present in variable amounts in cardiovascular tissues, including endothelium, smooth muscle cells, macrophages, and the heart. The activators of PPAR-α (fibrates) and PPAR-γ (thiazolidinediones or glitazones) antagonized the actions of angiotensin II in vivo and in vitro and exerted cardiovascular antioxidant and anti-inflammatory effects. PPAR activators lowered blood pressure, induced favorable effects on the heart, and corrected vascular structure and endothelial dysfunction in several rodent models of hypertension. Activators of PPARs may become therapeutic agents useful in the prevention of cardiovascular disease beyond their effects on carbohydrate and lipid metabolism. Some side effects, such as weight gain, as well as documented aggravation of advanced heart failure through fluid retention by glitazones, may, however, limit their therapeutic application in prevention of cardiovascular disease.

arteries; endothelium; heart; inflammation

Peroxisome proliferator-activated receptors (PPARs) are nuclear factors initially shown to respond to xenobiotics with peroxisomal proliferation in the rodent liver (30). Later, they were demonstrated to modulate genes that regulate lipid and glucose metabolism (for review see Ref. 40). More recently, PPARs have been shown to participate in the regulation of cell growth and migration (36), oxidant stress (16, 59), and inflammation (13) in the cardiovascular system. PPAR-α is found in tissues where fatty acid catabolism is important (liver, kidney, heart, and muscle) and is stimulated by natural ligands such as fatty acids and eicosanoids (e.g., leukotriene B4) and by synthetic ligands, the lipid-lowering fibrates (14). PPAR-α affects target genes that participate in ω- and β-oxidation of fatty acids. PPAR-β/δ is expressed in many tissues (6, 34). Recent evidence suggests that PPAR-β/δ is involved in fatty acid and lipid metabolism, particularly in skeletal muscle (9, 40, 60). This may also occur in cardiovascular tissues (23). PPAR-γ controls adipocyte differentiation and lipid storage (60) and is accordingly highly expressed in adipose tissue. Through its effects on adipose tissue and skeletal muscle, PPAR-γ regulates the action of insulin. Selective activators of PPAR-γ are the insulin sensitizers thiazolidinediones or glitazones, such as troglitazone, pioglitazone, and rosiglitazone.

PPARs have an NH2-terminal domain that regulates PPAR activity, a DNA binding domain that binds to the PPAR response element (PPRE) in the promoter region of target genes, a domain for a cofactor, and a COOH-terminal ligand-binding domain that determines ligand specificity (62). PPARs are bound to coexpressor proteins when inactive. After stimulation by PPAR activators, PPARs disassociate from corepressors and recruit coactivators, which include a PPAR-binding protein and the steroid receptor coactivator-1 (37), and heterodimerize with retinoid X receptor-α. They then bind to PPRE in target genes to modulate gene transcription (27). Gene regulation by this mechanism results in the action of PPARs on carbohydrate and lipid metabolism (Fig. 1). PPAR-α and PPAR-γ also exert numerous effects by interaction with different transcription factors to repress proinflammatory genes (Fig. 1). Although the effects on carbohydrate and lipid metabolism affect the cardiovascular system mainly through their impact on atherogenesis, the anti-inflammatory and antioxidant actions of PPARs affect cardiovascular remodeling in many ways. Effects of PPARs on cardiovascular remodeling are the main subject of the present review, beyond their regulatory effects on glucose and lipid metabolism, which have been reviewed recently (40).

Vascular effects of PPAR-α

PPAR-α and PPAR-γ are expressed in the cardiovascular system (5). PPAR-α is found in endothelial cells (28), vascular smooth muscle cells (VSMCs) (56), and monocytes/macrophages (10). The role of these nuclear factors in the vasculature and the heart has been revealed over the past few years (40). The PPAR-α ligand docosahexaenoic acid (DHA) was shown to have proapoptotic effects on cultured VSMCs (19) that were
mediated by activation of p38 mitogen-activated protein kinase (21). Anti-inflammatory effects were demonstrated by the inhibition by PPAR-α ligands of interleukin (IL)-1β-induced production of IL-6 and prostaglandins and expression of cyclooxygenase-2. These effects occurred as a consequence of PPAR-α inhibition of signaling by the proinflammatory mediator nuclear factor-κB (NF-κB) and induction of apoptosis (10). Antagonism of signaling by NF-κB was also demonstrated by other investigators (12, 46). PPAR-α activators also downregulated cytokine-induced genes, such as vascular cell adhesion molecule (VCAM)-1 and tissue factor, in endothelial cells (42). PPAR-α-deficient mice demonstrated enhanced inflammatory responses to lipopolysaccharide (LPS) administration, and, in these mice, fibrates were unable to affect LPS-induced IL-6 (12). The PPAR-α activator fenofibrate also reduced plasma concentrations of the cytokines interferon-γ and tumor necrosis factor-α (TNF-α) in patients with hyperlipoproteinemia IIb (38).

Because PPARs might antagonize the effects of angiotensin II (ANG II), the action of the PPAR-α activator DHA was investigated in ANG II-infused rats (16). DHA reduced ANG II-induced oxidative stress (as demonstrated by NADPH oxidase activity measured by chemiluminescence) and expression of inflammatory mediators [the adhesion molecules intercellular adhesion molecule (ICAM-1) and VCAM-1] in blood vessels of ANG II-infused rats. Blood pressure (BP), elevated by ANG II, was reduced by DHA. The remodeling of small resistance arteries induced by ANG II was abrogated by the PPAR-α activator. Concomitantly, endothelial dysfunction typically found under ANG II infusion was prevented by DHA, together with reduction in NADPH oxidase-dependent superoxide anion formation. Although these effects cannot be conclusively and unambiguously shown to be unrelated to BP reduction, in some models such as the deoxycorticosterone acetate (DOCA)-salt hypertensive rat, they have occurred in response to PPAR-α activators in the absence of significant decline in BP (26). This suggests that they are probably not dependent on reduction of BP.

Recent studies have elucidated some of the mechanisms involved in the beneficial effects of PPAR-α activation on endothelial function. Goya et al. (24) demonstrated that fenofibrate increases endothelial nitric oxide (NO) synthase (eNOS) expression in bovine aortic endothelial cells. Interestingly, this does not occur through effects on eNOS gene promoter activity but, rather, through increases in mRNA stability (24).

**VASCULAR EFFECTS OF PPAR-γ**

Similar to PPAR-α, PPAR-γ has been reported to be present in the vasculature (40) and was demonstrated in endothelial cells (52), VSMCs (20, 35), and monocytes/macrophages (50). PPAR-γ activators inhibited proliferation and migration of VSMCs (35, 36). They enhanced expression of PPAR-γ in macrophages and inhibited expression of inducible NO synthase (iNOS), matrix metalloproteinase (MMP)-9, and scavenger receptor A. These effects of PPAR-γ were mediated in part by inhibition of transcription factors activator protein-1 (AP-1), signal transducer and activator of transcription, and NF-κB. PPAR-γ activators inhibited expression of TNF-α, IL-6, IL-1β (31), iNOS, MMP-9, and scavenger receptor A in monocytes (49). PPAR-γ activators attenuated TNF-α-induced VCAM-1 and ICAM-1 expression in endothelial cells and reduced monocyte/macrophage homing to atherosclerotic plaques in apolipoprotein E-deficient mice (45). PPAR-γ expression has indeed been demonstrated in human atherosclerotic plaques (48). However, 15-deoxy-D12,14-prostaglandin (15d-PG) J2 may stimulate the synthesis of IL-8 in endothelial cells in a PPAR-γ-independent manner (32). Mechanisms whereby PPAR-γ activation may induce anti-inflammatory effects include interactions with CCAAT/enhancer-binding protein-δ, present in tandem repeats in the PPAR-γ gene promoter. CCAAT/enhancer-binding protein induces expression of inflammatory cytokines but is inhibited by PPAR-γ in the vasculature by transactivation (58).

PPAR-γ activators (rosiglitazone and pioglitazone) prevented the BP rise and the structural, functional, and molecular changes induced by ANG II in blood vessels, inhibiting cell growth and inflammation (18). ANG II-induced small resistance artery remodeling and endothelial dysfunction were prevented. Vascular DNA synthesis, expression of cell cycle proteins, ANG AT1 receptors, VCAM-1, and platelet and endothelial cell adhesion molecule, and NF-κB activity, all of which were increased by ANG II infusion, were blunted by pioglitazone or rosiglitazone.
In DOCA-salt hypertensive rats, a hypertensive model associated with enhanced expression of preproendothelin (preproET)-1, BP increase was prevented in part by the PPAR-α activator rosiglitazone but not by the PPAR-α activator fenofibrate (26). Both PPAR activators, however, abrogated the increase of prepro-ET-1 mRNA in mesenteric blood vessels of these hypertensive rats and prevented the hypertrophic remodeling typically found in DOCA-salt rats. Rosiglitazone, but not fenofibrate, prevented endothelial dysfunction, but both abrogated the enhanced production of reactive oxygen species that occurs in blood vessels in DOCA-salt hypertensive rats.

Spontaneously hypertensive rats (SHR) exhibit insulin resistance, which has been associated with a mutation of cd36, which encodes for a fatty acid translocase. Insulin resistance thus results in decreased fatty acid translocation (1). cd36 is a target of PPAR-γ. It has been speculated that expression of PPARs could be decreased in blood vessels of SHR, which would exacerbate proliferation, migration, inflammation, and fibrosis, as found in this hypertensive model. Indeed, human mutations of PPAR-γ have been associated with diabetes, insulin resistance, and hypertension, all of which are accompanied by vascular disease (4). However, rather than decreased expression of PPAR-α and PPAR-γ in blood vessels and cultured VSMCs from SHR, their expression was increased (20). This may result from a feedback response to the decreased activity of the mutant cd36 of SHR.

Mechanisms whereby PPAR-γ activation improves endothelial function were investigated by Calnek et al. (8), who demonstrated that PPAR-γ ligands, 15d-PGJ2, or ciglitazone increased NO release by porcine and human aortic endothelial cells. PPAR-γ activation did not increase eNOS expression. Overexpression of PPAR-γ or treatment with 9-cis-retinoic acid also increased NO release. Neither 15d-PGJ2 nor ciglitazone altered eNOS mRNA. Thus PPAR-γ ligands stimulated NO release from endothelial cells through a transcriptional mechanism unrelated to eNOS expression (8).

Many studies have pointed toward an inhibitory role of PPARs in atherogenesis (40). The effect of rosiglitazone treatment on mechanisms involved in the initial stages of atherogenesis was evaluated in rabbits fed a high-cholesterol diet (59). Treatment with rosiglitazone enhanced the downregulated PPAR-γ expression, improved endothelium-dependent vasodilatation, suppressed gp91phox and iNOS expression, reduced superoxide and total NO production, and inhibited nitrotyrosine formation. The endothelial protective effects of PPAR-γ activators may reduce leukocyte accumulation in the vascular wall, contributing to antiatherosclerotic effects.

Ishibashi et al. (29) studied effects of pioglitazone in rats treated with Nω-nitro-l-arginine methyl ester to inhibit eNOS. The PPAR-γ activator pioglitazone did not affect BP, metabolic state, or serum NO levels but prevented Nω-nitro-l-arginine methyl ester-induced coronary inflammation and arteriosclerosis. Pioglitazone did not reduce local expression of monocyte chemoattractant protein-1 but attenuated the expression of the monocyte chemoattractant protein-1 receptor C-C chemokine receptor 2 in monocytes in the vascular wall and in the circulation. It prevented coronary arteriosclerosis, possibly by downregulation of C-C chemokine receptor 2, which could represent a novel anti-inflammatory mechanism of PPAR-γ activation independent of insulin sensitization.

A mechanism for improved endothelial function recently reported is the ability of PPAR-γ activators to modulate bone marrow-derived angiogenic progenitor cells (APCs) to promote endothelial lineage differentiation and early reendothelialization after vascular intervention. Rosiglitazone treatment attenuated neointima formation in mice after femoral angioplasty (65). Rosiglitazone caused a sixfold increase in colony formation by human endothelial progenitor cells, promoted the differentiation of APCs toward the endothelial lineage in mouse bone marrow in vivo and in human peripheral blood in vitro, and inhibited the differentiation toward the SMC lineage. Within the neointima, rosiglitazone stimulated APCs to differentiate into mature endothelial cells and caused early reendothelialization compared with controls. Rosiglitazone treatment is associated with enhanced expression of preproendothelin (preproET)-1. BP increase was prevented in part by the PPAR-γ activator rosiglitazone but not by the PPAR-α activator fenofibrate (26). Both PPAR activators, however, abrogated the increase of prepro-ET-1 mRNA in mesenteric blood vessels of these hypertensive rats and prevented the hypertrophic remodeling typically found in DOCA-salt rats. Rosiglitazone, but not fenofibrate, prevented endothelial dysfunction, but both abrogated the enhanced production of reactive oxygen species that occurs in blood vessels in DOCA-salt hypertensive rats.

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significantly reduced sCD40L serum levels. This further underscores the ability of PPAR-γ-activating thiazolidinediones to reduce sCD40L serum levels and exert anti-inflammatory and antiatherogenic effects.

Rosiglitazone has also been shown to reduce endothelial markers such as E-selectin and von Willebrand factor in nondiabetic CAD patients (54). Eighty-four patients with stable, angiographically documented CAD without diabetes mellitus were treated with rosiglitazone for 12 wk. Rosiglitazone significantly reduced E-selectin, von Willebrand factor, CRP, fibrinogen, and insulin resistance, as measured by HOMA index, compared with placebo. Thus PPAR-γ activation reduced markers of endothelial cell activation and levels of acute-phase reactants in CAD patients without diabetes. In addition, other studies showed that these agents improve endothelial function of patients with the metabolic syndrome. Wang et al. (67) studied 50 nondiabetic patients who met a definition for the metabolic syndrome and were treated with rosiglitazone for 8 wk. These patients experienced significant reductions in fasting plasma insulin levels, HOMA index, BP, and high-sensitivity CRP. Rosiglitazone treatment significantly improved endothelium-dependent flow-mediated and endothelium-independent nitroglycerin-induced vasodilatation of the brachial artery. Carotid intima-media thickness has been considered a surrogate of endothelial function. In 92 nondiabetic patients with angiographically documented CAD studied by Sidhu et al. (55), the reduction in intima-media thickness progression after 48 wk of rosiglitazone treatment compared with the placebo group was associated with reduced insulin resistance (estimated by HOMA index). Thus PPAR activation improves endothelial dysfunction, which is thought to be a mechanism for initiation and progression of atherosclerosis, a risk factor and a participant in the triggering of cardiovascular events.

In a study of 136 Japanese Type 2 diabetic patients, pioglitazone was administered for 3 mo, and changes in glycolipid metabolism, plasma high-sensitivity CRP, leptin, adiponectin, and pulse wave velocity (PWV, a parameter that increases with the stiffness of blood vessels and is indicative of the presence of vascular injury) were evaluated to investigate the relation between the antiatherogenic and anti-diabetic effects of pioglitazone (51). Pioglitazone treatment improved glucose metabolism, increased plasma adiponectin concentrations, and decreased CRP and PWV. Treatment with pioglitazone was associated with a low CRP and PWV independent of changes in carbohydrate metabolism. Thus the PPAR-γ agonist exerted antiatherogenic effects independent of its anti-diabetic action by lowering CRP, which contributes to vascular injury and the stiffness of blood vessels (a measure of vascular disease) and contributes to enhanced pulse pressure (another risk factor for vascular events).

**CARDIAC EFFECTS OF PPARS**

PPAR-α regulates cardiac energy and lipid metabolism and plays a role in mitochondrial fatty acid β-oxidation, which is critical for fuel generation in the heart (7). It serves as a molecular “lipostat” through the induction of target genes involved in fatty acid metabolism (22). PPAR-α controls myocardial lipid metabolism through activation of transcription of carnitine palmitoyltransferase I (7). In PPAR-α-null mice, the capacity for constitutive myocardial β-oxidation of medium- and long-chain fatty acids was markedly reduced (68). Constitutive β-oxidation of very-long-chain fatty acids such as lignoceric acid was unaffected in PPAR-α-deficient mice. This suggests that PPAR-α is not involved in the constitutive expression of enzymes that mediate β-oxidation.

During cardiac hypertrophy, PPAR-α is inhibited (3), which reduces the capacity of hypertrophied myocytes to metabolize myocardial lipids, resulting in intracellular fat accumulation. PPAR-α activators inhibited cardiac expression of TNF-α and NF-κB induced by LPS (57). Fenofibrate reduced prepro-ET-1 mRNA expression and collagen type I and type III mRNA, associated with decreased interstitial and perivascular cardiac fibrosis after pressure overload induced by abdominal aortic banding (44), probably through suppression of AP-1-mediated prepro-ET-1 gene activation. Additionally, fenofibrate reduced cardiac hypertrophy and inflammation, associated with an increase in the anti-inflammatory cytokine IL-10 (39). Fenofibrate had beneficial effects on inflammation and collagen deposition in the heart of ANG II-infused rats (17). NF-κB activity and VCAM-1, platelet and endothelial cell adhesion molecule, ICAM-1, and ED-1 (macrophage antigen) expression were decreased, AT1 receptors were downregulated, and AT2 receptors were upregulated, which may be considered a beneficial change, because AT1 receptors are prohypertrophic, proinflammatory, and profibrotic, whereas AT2 receptors are generally shown to exert opposite effects.

The role of PPAR-γ in the heart is less clear than that of PPAR-α. Expression of PPAR-γ in the heart is very low (33). PPAR-γ activators inhibited hypertrophy and brain natriuretic peptide expression in cultured cardiomyocytes (70). Aortic banding induced enhanced cardiac hypertrophy in heterozygous PPAR-γ-deficient mice (2), suggesting an inhibitory effect of PPAR-γ on cardiac growth. Pioglitazone, however, blunted myocardial hypertrophy in wild-type and PPAR-γ−/− mice, suggesting an effect independent of activation of PPAR-γ. ANG II-induced gene expression and cardiomyocyte hypertrophy were attenuated in vitro by thiazolidinediones. These data suggest that PPAR-γ inhibits cardiac hypertrophy. In diabetic rats, PPAR-γ improved left ventricular diastolic function and decreased collagen accumulation (61, 72) and also protected the myocardium from ischemic injury (53, 71). On the other hand, PPAR-γ activators may trigger an aggravation of congestive heart failure (66, 69), which is counterintuitive with respect to the cardiovascular preventive potential of these drugs. This appears to be mainly due to fluid retention as a consequence of their insulinomimetic action on the kidney rather than a negative inotropic effect. Thus caution has been urged in the use of thiazolidinediones in diabetic patients with advanced heart failure (43), even though these agents may have cardiovascular protective properties in patients with less advanced cardiovascular disease.

The hypertrophic heart typically experiences an increase in glucose utilization and decreased fatty acid oxidation. It is unclear whether PPAR-γ has effects on fatty acid metabolism comparable to those of PPAR-α. PPAR-α and PPAR-γ have partially overlapping ligand binding profiles. Thus PPAR-γ may mediate some intracellular signaling in cardiomyocytes similarly to PPAR-α, which could attenuate cardiac remodel-
ing via signaling pathways not involved in the control of lipid and energy metabolism. Inflammation plays a critical role in the progression of cardiac remodeling and dysfunction. In macrophages, PPAR-γ participates in the regulation of inflammatory responses by inhibition of transcription factors NF-κB and AP-1 (50). NF-κB is required for the hypertrophic response of neonatal rat cardiomyocytes in vitro (47). Recently, the PPAR-γ activator pioglitazone was shown to have beneficial long-term effects on cardiac hypertrophy and cardiac inflammation but no effect on cardiac function in stroke-prone SHR (15). However, whether PPAR-γ effects on the heart are exerted directly on cardiomyocytes or via infiltrating macrophages and other blood-borne cells or result from hormonal effects mediated from other organs has not been demonstrated (33).

CONCLUSION

PPAR-α and PPAR-γ modulate inflammatory, fibrotic, and hypertrophic responses in the cardiovascular system. The signaling pathways mediating the anti-inflammatory effect of PPARs, particularly in the heart, remain to be demonstrated. The contrast between the beneficial effect of PPAR-γ activators on the heart in experimental models and clinical reports of decompensated heart failure in some diabetic patients treated with PPAR-γ activators requires clarification. It is possible that salt and water retention induced by the insulin-sensitizing activators, may become interesting cardiovascular protective mechanisms of Health Research Grants 13570 and 37917 and a group grant to the CONCLUSION

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