Pleiotropic Actions of Peroxisome Proliferator–Activated Receptors in Lipid Metabolism and Atherosclerosis

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Abstract—Peroxisome proliferator–activated receptors (PPARs) are nuclear receptors activated by fatty acids and derivatives. Although PPARα mediates the hypolipidemic action of fibrates, PPARγ is the receptor for the antidiabetic glitazones. PPARα is highly expressed in tissues such as liver, muscle, kidney, and heart, where it stimulates the β-oxidative degradation of fatty acids. PPARγ is predominantly expressed in adipose tissues, where it promotes adipocyte differentiation and lipid storage. PPARβ/δ is expressed in a wide range of tissues, and recent findings indicate a role for this receptor in the control of adipogenesis. Pharmacological and gene-targeting studies have demonstrated a physiological role for PPARs in lipid and lipoprotein metabolism. PPARα controls plasma lipid transport by acting on triglyceride and fatty acid metabolism and by modulating bile acid synthesis and catabolism in the liver. All 3 PPARs regulate macrophage cholesterol homeostasis. By enhancing cholesterol efflux, they stimulate the critical steps of the reverse cholesterol transport pathway. As such, PPARs control plasma levels of cholesterol and triglycerides, which constitute major risk factors for coronary heart disease. Furthermore, PPARα and PPARγ regulate the expression of key proteins involved in all stages of atherogenesis, such as monocyte and lymphocyte recruitment to the arterial wall, foam cell formation, vascular inflammation, and thrombosis. Thus, by regulating gene transcription, PPARs modulate the onset and evolution of metabolic disorders predisposing to atherosclerosis and exert direct antiatherogenic actions at the level of the vascular wall. (Arterioscler Thromb Vasc Biol. 2002;22:1300–1306.)

Key Words: nuclear receptors • HDL • inflammation • cholesterol • atherosclerosis

The metabolic syndrome, which can be defined as the clustering of cardiovascular risk factors with insulin resistance, is characterized by the simultaneous presence of ≥1 of the following metabolic disorders: glucose intolerance, hyperinsulinemia, dyslipidemia, coagulation disturbances, and hypertension. Peroxisome proliferator–activated receptors (PPARs) modulate these metabolic risk factors for cardiovascular disease associated with the metabolic syndrome. Whereas previous articles have summarized our present understanding of the role of PPARs in the control of glucose homeostasis, insulin resistance, and hypertension (see reviews1–2), the present review will focus on the plasma lipid–controlling actions of PPARs and their effects on atherogenesis.

Levels of Control of PPAR Activity

Fatty acids (FAs) and FA-derived compounds are natural ligands for PPARα and PPARγ. Natural eicosanoids derived from arachidonic acid via the lipoxxygenase pathway, such as 8-S-hydroxyeicosatetraenoic acid and leukotriene B4, and oxidized phospholipids from oxidized lipoproteins activate PPARα.3 PPARγ is a receptor for eicosanoid metabolites formed via the cyclooxygenase pathway, eg, prostaglandins, such as PGJ2, PGH1, and PGH2,4 and via the lipoxxygenase pathway (15-hydroxyeicosatetraenoic acid).3 Similar to PPARα and PPARγ, PPARβ/δ is a receptor for unsaturated FAs.

Synthetic agonists of PPARs are used in the treatment of metabolic diseases, such as dyslipidemia and type 2 diabetes. The antidiabetic glitazones, which are insulin sensitizers, are synthetic high-affinity ligands for PPARγ.5 The hypolipidemic fibrate drugs are PPARα ligands.3 Recently, a series of subtype-specific high-affinity PPAR agonists have been synthesized. These include the human PPARα ligand GW7647,6 the PPARγ activators GW1929 and GW7845,7,8 and the PPARβ/δ-specific synthetic agonist GW501516.9

On ligand activation, PPARα, PPARγ, and PPARβ/δ regulate transcription by dimerizing with the retinoid X receptor and binding to PPAR response elements (PPREs), within the regulatory regions of target genes (see review7). These PPREs usually consist of a direct repeat (DR1 or DR2) of the hexanucleotide AGGTCA sequence separated by 1 or 2 nucleotides.2

PPARs can also repress gene transcription in a DNA-binding–independent manner by interfering with the nuclear factor-κB, signal transducer(s) and activator(s) of transcription, activator protein-1, nuclear factor of activated T cells, CAAT box/enhancer binding protein, and Smad3 signaling pathways via protein–protein interactions and cofactor com-
petition.\textsuperscript{10–13} Such a trans-repression mechanism is likely to explain the anti-inflammatory actions of PPARs (see review\textsuperscript{10}).

The PPAR transcriptional pathway is controlled by the following: the level of receptor expression and stability; its posttranslational modifications, ligand specificity, and availability; and cofactor recruitment (Figure 1).

Although PPAR\textsubscript{a} is expressed preferentially in tissues in which FAs are catabolized, PPAR\textsubscript{g} is present in adipose tissue, mammary glands, and numerous other tissues, and PPAR\textsubscript{b/d} is ubiquitously expressed (see review\textsuperscript{2}). The expression levels of PPARs are modulated by stimuli as varied as circadian rhythm,\textsuperscript{14} fasting,\textsuperscript{15,16} stress,\textsuperscript{14} and cold.\textsuperscript{17} Furthermore, various factors, such as corticosteroids,\textsuperscript{18,19} insulin,\textsuperscript{18,20} phorbol esters, and different cytokines,\textsuperscript{21} affect PPAR expression. Additionally, PPAR and retinoid X receptor ligands also modulate PPAR mRNA levels.\textsuperscript{22,23}

PPAR protein levels are also subject to regulation. Although thiazolidinediones (TZDs) were shown to induce PPAR\textsubscript{g} receptor ubiquitination and subsequent degradation by the proteasome,\textsuperscript{24} fibrates inhibit PPAR\textsubscript{a} ubiquitination and increase PPAR\textsubscript{a} protein half-life.\textsuperscript{25,26} PPAR\textsubscript{a} and PPAR\textsubscript{g} are phosphoproteins, and their phosphorylation status affects their transcriptional activity.\textsuperscript{27} For instance, Hansen et al\textsuperscript{28} reported that the cAMP signaling pathway, most likely via protein kinase A, increases PPAR\textsubscript{b/d}-mediated transactivation.

The ligand dependence of PPAR activity renders the availability of an activator an important regulator of receptor function. In that way, albumin, which sequesters PGJ\textsubscript{2}, controls the activity of PPAR\textsubscript{g}.\textsuperscript{29} Similarly, ligand binding to FA-binding proteins (FABPs) has been proposed as a mechanism of intracellular transport of PPAR agonists from the cytoplasm to the nucleus, thus modulating the activation of the receptor.\textsuperscript{30}

On binding, different ligands induce distinct conformations of the receptor, leading to differential coactivator recruitment (see review\textsuperscript{27}) and, consequently, differential biological responses.\textsuperscript{31,32} These observations are at the basis of the “selective PPAR modulator” concept.\textsuperscript{33}

**PPARs and Dyslipidemia**

The dyslipidemia associated with the metabolic syndrome is characterized by elevated plasma levels of triglycerides and small dense LDL particles and decreased HDL cholesterol. In vivo and in vitro data demonstrate that PPARs play a central role in the control of FA and lipoprotein metabolism.

**Role of PPARs in Triglyceride and LDL Metabolism**

In rodents, the central role of PPAR\textsubscript{a} in FA metabolism under feeding/fasting conditions has been clearly demonstrated.\textsuperscript{15,16} On severe fasting, PPAR\textsubscript{a} activity and expression are induced, allowing the catabolism of FAs to produce ketone bodies, which serve as an energy source for extrahepatic tissues. In humans, pharmacological PPAR\textsubscript{a} activation with fibrates decreases plasma triglyceride concentrations by acting on different metabolic pathways.\textsuperscript{34} Fibrates increase FA uptake and catabolism, resulting (as a consequence) in limited triglyceride and VLDL production by the liver\textsuperscript{34} (Figure 2). Simultaneously, these hypolipidemic drugs enhance intravascular triglyceride metabolism.

The intracellular concentration of FAs is partly controlled by the regulation of their cellular uptake, which is mediated through different transporters, such as FA transport protein 1 (FATP1) and FA translocase (FAT/CD36). Fibrate treatment induces FATP1 and FAT mRNA levels in rodent liver, whereas glitazones induce the expression of these genes in white adipose tissue.\textsuperscript{35,36} In addition, the expression of the intracellular FABP, L-FABP, is regulated by fibrates in the liver.\textsuperscript{37} Interestingly, PPAR\textsubscript{a} agonists failed to modulate L-FABP expression in the small intestine, whereas PPAR\textsubscript{a-null} mice treated with a novel PPAR\textsubscript{b/d}-PPAR\textsubscript{a}-specific
agonist (GW2433) display an increase in L-FABP expression in this tissue, indicating that PPARβ/δ also regulates the expression of genes involved in FA metabolism. However, the physiological consequences of this regulation are presently unclear.

Intracellular FA flux is regulated by key proteins, i.e., acyl coenzyme A synthetase (ACS), which catalyzes the esterification of FAs, favoring their cellular retention. By modulating the expression of ACS, PPARα and PPARγ polarize FA fluxes.

Furthermore, PPARα induces FA uptake and catabolism in mitochondria via stimulation of muscle and liver carnitine palmitoyltransferase I and II and several mitochondrial FA-catabolizing enzymes. When mitochondrial FA import is inhibited in male PPARα-null mice, massive cardiac and hepatic lipid accumulation and hypoglycemia are observed. This inhibition provokes a feedback upregulation of PPARα target genes in wild-type, but not in PPARα-null, mice.

PPARα controls mitochondrial hydroxymethylglutaryl coenzyme A synthase expression and, thus, promotes ketone body synthesis. In rodent, but not human, hepatocytes, PPARα induces the expression of various enzymes involved in peroxisomal β-oxidation.

Intravascular lipolysis activity is controlled by the activity of lipoprotein lipase (LPL). Fibrate-activated PPARα controls LPL activity by inducing its expression in the liver and by inhibiting the hepatic expression of apoC-III, an LPL activity and remnant catabolism inhibitor. These effects promote lipolysis and triglyceride-rich lipoprotein catabolism, thus decreasing the plasma levels of triglycerides. The role of PPARα on circulating VLDL levels is demonstrated in vivo in PPARα-null/apoE-null mice, which display higher VLDL production on high-fat diet feeding than do control mice.

Glitazones also affect the circulating levels of free FAs, cholesterol, and triglycerides. In obese animal models, TZDs and non-TZD glitazones decrease the circulating levels of triglycerides by inducing lipolysis (via activation of LPL expression in adipocytes) and clearance of triglyceride-rich lipoproteins. In rodents, simultaneous administration of PPARα and PPARγ activators results in a more efficient hypotriglyceridemic activity, which is likely due to combined actions on liver apoC-III and adipose tissue LPL expression. The induction of LPL by PPARγ promotes FA delivery, whereas induction of FATP and ACS results in enhanced FA uptake. These actions contribute to enhanced triglyceride storage in adipose tissue. PPARγ also modulates the expression of enzymes involved in the synthesis of FA and triglycerides, such as malic enzyme.

Although the triglyceride-lowering activity of PPARγ agonists in animal models is well documented, substantial controversy exists concerning their hypotriglyceridemic activity in humans.

**PPARs, HDL Metabolism, and the RCT Pathway**

The reverse cholesterol transport (RCT) pathway mediates the centripetal transport of cholesterol from peripheral cells back to the liver. Cholesterol from peripheral cells is captured by HDL particles, which transport it back to the liver, where cholesterol is eliminated either directly into the bile or after metabolism in bile acids. PPARs influence the RCT pathway by regulating macrophage cholesterol efflux, HDL cholesterol transport in plasma, and bile acid synthesis (Figure 3).

Cholesterol efflux, the first step of the RCT, occurs either via passive diffusion or via transmembrane transporters, such as the scavenger receptor (SR) class B type 1 (SR-B1/CLA-1) and the ATP-binding cassette A1 (ABCA1) proteins. In
human macrophages, PPARα and PPARγ activators induce protein levels of SR-BI/CLA-1, whereas ligands of all 3 PPAR isotypes induce the expression of ABCA1. PPARα and PPARγ induce ABCA1 by an indirect mechanism via induction of the nuclear liver X receptor (LXR)α. However, the molecular mechanism of ABCA1 induction by PPARβ/δ activators appears to be LXRα independent. Increased ABCA1 expression results in a higher cholesterol efflux from macrophages. The major contribution of ABCA1 in the control of plasma HDL cholesterol levels has been highlighted by the identification of mutations in the ABCA1 gene in patients with familial HDL deficiency and Tangier disease.

ApoA-I and apoA-II are the major HDL apolipoproteins. In humans, PPARs increases the transcription of these 2 genes via binding to PPREs in their promoters, an effect that contributes to the increase of HDL concentrations after fibrate treatment. Although the increase of plasma apoA-I is undoubtedly beneficial, substantial controversy exists concerning the role of apoA-II in atherosclerosis. Indeed, whereas transgenic mice overexpressing murine apoA-II are more prone to develop atherosclerosis, overexpression of human apoA-II protects against atherosclerosis. PPARβ/δ-specific agonists also increase plasma HDL cholesterol concentrations in insulin-resistant mice and obese rhesus monkeys. The molecular mechanisms behind this increase remain to be clarified.

Recently, Bouly et al have shown that PPARα agonists induce the expression and activity of the phospholipid transfer protein (PLTP), an enzyme catalyzing the transfer of phospholipids from VLDL/LDL to HDL, in mice. PLTP induction contributes to the marked enlargement of HDL in fenofibrate-treated mice. Such action may also be antiatherogenic, inasmuch as PLTP deficiency results in an enhanced susceptibility to atherosclerosis, which is due to decreased antioxidant transfer to endothelial cells. However, although fibrates influence the expression of HDL-remodeling enzymes, such as PLTP and lecithin-cholesterol acyltransferase, in rat liver, little is known about the regulation of these proteins in humans.

Cholesterol is excreted from the liver into the bile either directly or after conversion to bile salts. Genes regulated by PPARs, either directly or indirectly, are indicated by gray background arrows (human genes in plain white and rodent genes in hatched). CETP indicates cholesteryl ester transfer protein; FC, free cholesterol; and EC, esterified cholesterol.

Figure 3. PPARs stimulate the reverse cholesterol pathway. PPARs regulate the RCT pathway by modulating macrophage cholesterol efflux and cholesterol transport in plasma and bile acid synthesis. Cholesterol efflux via transmembrane transporters ABCA1 and, possibly, SR-BI is stimulated by PPAR activators in human macrophages. Nascent HDL particles accept cholesterol, which is subsequently esterified by lecithin-cholesterol acyltransferase (LCAT). Fibrates stimulate the expression and activity of the HDL-remodeling enzyme PLTP in rodents. Hepatic SR-BI mediates the uptake of cholesterol esters from HDL in the liver, where cholesterol is excreted into the bile either directly or after conversion to bile salts. Genes regulated by PPARs, either directly or indirectly, are indicated by gray background arrows (human genes in plain white and rodent genes in hatched). CETP indicates cholesteryl ester transfer protein; FC, free cholesterol; and EC, esterified cholesterol.

PPARs and Atherogenesis

Atherosclerosis is a complex process characterized by lipid accumulation in the arterial wall. Atherogenesis starts with the attraction, recruitment, and activation of different cell types, including monocytes/macrophages, T lymphocytes, endothelial cells, and intimal smooth muscle cells (SMCs). This cellular activation provokes a local inflammatory response. As regulators of lipid and lipoprotein metabolism, PPARs control plasma levels of cholesterol and triglycerides, which constitute major risk factors for coronary heart disease. Clinical studies have shown that fibrates prevent atherosclerotic lesion progression. Although less data are available in humans with respect to glitazones, in rodents, the PPARγ ligand troglitazone inhibits SMC proliferation and decreases...
the intima and media thickness of carotid arteries. PPARs are expressed in most cell types of the vascular wall as well as in atherosclerotic lesions (see review), where they affect atherogenic processes.

**PPARs Modulate Early Stages of Atherogenesis**

Figure 4 shows the modulation of atherogenesis and atherothrombosis by PPARs. PPARs regulate chemotraction and cellular adhesion to endothelial cells. PPARα and PPARγ activators repress thrombin-induced expression of endothelin-1, a potent vasoconstrictor peptide and inducer of SMC proliferation. Although the expression of monocyte chemoattractant protein (MCP)-1, a chemokine that promotes monocyte chemotaxis, is clearly inhibited by PPARγ ligands, the effect of PPARα activators is still unclear. In human aortic endothelial cells, natural and synthetic PPARα ligands stimulate the synthesis of MCP-1. In contrast, Pasceri et al have reported that fibrates reduce C-reactive protein (CRP)-induced expression of MCP-1 in human umbilical vein endothelial cells. PPARγ activation blocks endothelial expression of interferon (IFN)-γ-inducible 10-kDa protein, a monokine induced by IFN-γ, and IFN-inducible T-cell α-chemoattractant, which are chemokines that promote T-cell recruitment to sites of inflammation. Furthermore, PPARs modulate T-lymphocyte proliferation and immune activation.

In monocytes, glitazones decrease the expression of CCR2, the transmembrane receptor for MCP-1. PPARα and PPARγ activators reduce cytokine-induced expression of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1. These adhesion molecules play a critical role in the recruitment of leukocytes and monocytes to atherosclerotic lesions. In vivo studies have demonstrated that troglitazone significantly reduces monocyte/macrophage recruitment to atherosclerotic lesions in apoE-null mice.

**PPARs Control Lipid Accumulation Within the Plaque**

Although PPARs do not influence macrophage differentiation, they play an important role in regulating cholesterol homeostasis in macrophages. As described above, PPARα, PPARγ, and PPARβ/δ activators induce the expression of ABCA1 and SR-BI, thus promoting cholesterol efflux from macrophages. By acting through posttranscriptional mechanisms, PPARγ ligands decrease the protein level of SR-A, which is involved in the uptake of modified LDL. In addition, PPARγ agonists induce the expression of CD36, a scavenger receptor for oxidized LDL in macrophages. The net effect is that neither PPARα nor PPARγ promotes cholesterol accumulation in macrophages or foam cell formation. In contrast, activation of PPARβ/δ, whose expression is increased during the differentiation of THP-1–derived human macrophages, increases the expression of genes involved in lipid uptake and storage, such as SR-A and CD36. These results identify PPARβ/δ as a potential promoter of macrophage lipid accumulation and suggest a role for PPARβ/δ in the pathology of atherosclerosis.

The atheroprotective role of PPARγ has been further documented in animal models of atherosclerosis. In male LDL receptor–null mice, rosiglitazone and GW7845 treatment reduces the progression of atherosclerotic lesions and decreases macrophage accumulation in intimal xanthomas. Intriguingly, in these studies, female mice did not exhibit a reduction in atherosclerosis in response to PPARγ ligand treatment. This lack of response could be partly explained by the decrease of HDL levels in female mice treated with PPARγ ligands. Li et al related these differences to influences of estrogens and progestins, inasmuch as their preliminary studies indicate the metabolic response to rosiglitazone and GW7845 in ovariectomized female mice to be much more similar to that in male mice. In male and female apoE-null mice, troglitazone inhibits fatty streak formation while enhancing HDL cholesterol levels and increas-
PPARs and the Local Inflammatory Response

The activation of cells in atherosclerotic lesions leads to the release of proinflammatory molecules and the onset of a chronic inflammatory response. Various studies have demonstrated that PPARs inhibit the expression of inflammatory genes, such as cytokines, metalloproteases, and acute-phase reactants (see review98). PPARs exert anti-inflammatory activities in different immunological and vascular cell types, such as monocytes/macrophages, endothelial cells, SMCs, dendritic cells, and T lymphocytes.

Incubation of human monocytes with natural (PGJ2) and synthetic PPARγ ligands inhibits the production of inflammatory cytokines, such as tumor necrosis factor-α, IL-1β, IL-6, IL-8, and IL-10.99,100 However, most pronounced effects are observed with PGJ2, which is not very selective for PPARγ and also acts via PPAR-independent mechanisms.98 Furthermore, certain anti-inflammatory properties of PPARγ agonists were observed in PPARγ-null embryonic stem cell–derived macrophages, albeit at extremely high concentrations.92 Thus, glitazones and natural PPARγ ligands appear to exert anti-inflammatory activities via PPARγ-dependent and -independent mechanisms.

In human aortic SMCs, PPARα activators inhibit the expression of inducible cyclic oxysgenase-2 and IL-6.101 In human monocytes/macrophages, PPARα activators inhibit cytokine-induced expression of vascular cell adhesion molecule-1 and tissue factor.88,102,103 In rat aortic SMCs, PGJ1 and 9-HODE induce the expression of type II–secreted phospholipase A2 (type II-sPLA2), an enzyme involved in the hydrolysis of phospholipids. Induced expression of type II-sPLA2 generates lipid inflammatory mediators, such as lysophosphaticid and arachidonic acids.104 Type II-sPLA2 increases lipooxygenase-mediated PPAR agonist (HODE) production from LDL105 and may initially lead to a PPAR-independent proinflammatory activity, followed by a PPAR-dependent arrest of the inflammatory response. Results from studies using PPARα-null mice clearly demonstrate a role for PPARα in the control of the inflammatory response.80,106

The anti-inflammatory activities of PPARα and PPARγ activators have been evidenced in humans. In patients with mild hyperlipidemia, fenofibrate treatment has been shown to decreased the circulating levels of IL-6 and to lower the plasma levels of various risk factors for cardiovascular disease, such as fibrinogen and CRP, whose production is controlled by cytokines.83,101 Similarly, rosiglitazone treatment of patients with type 2 diabetes significantly reduces plasma levels of IL-6 and CRP.107

PPARs, Plaque Stability, and Atherothrombosis

Plaque rupture is the end stage of the atherogenic process, leading to thrombus formation, occlusion, and the clinical sequels of atherosclerosis. Plaque instability is partly due to the degradation of the extracellular matrix in the fibrous cap. PPARγ activators inhibit the expression of metalloproteinase-9, a secreted matrix-degrading protein.109 This PPARγ-dependent inhibition may prevent the rupture of the atherosclerotic plaque and subsequent thrombosis. On the other hand, troglitazone and PGI2 inhibit the migration of SMCs, which occurs during atherosclerotic plaque formation. This effect may be due to the inhibition of secretion of metalloproteinases, which contribute to this process.109 Furthermore, glitazones inhibit vascular SMC (VSMC) expression of Ets-1, a transcription factor regulating matrix metalloproteinase gene transcription.110 This inhibition results in a decreased VSMC migration within the plaque.

In addition, PPARs also modulate platelet aggregation. PPARγ activators inhibit the expression of thromboxane synthase by a mechanism involving protein–protein interaction between PPARγ and the nuclear factor-E2–related factor 2.114 This results in a decreased production of thromboxane A2, a potent platelet aggregation inducer. Moreover, the expression of the thromboxane receptor is inhibited by PPARγ activators in rat VSMCs.112 PPARα also inhibits the expression of the platelet-activating factor receptor and tissue factor in human monocytes and macrophages.102,103,113 These actions may result in a decreased thrombogenic response.

Glitazones and fibrates also modulate the secretion of the thrombosis inducer plasminogen activator inhibitor type 1.114,115 However, the molecular data are still confusing.116,117 and the role of PPARs in the regulation of plasminogen activator inhibitor type 1 and its consequences for atherosclerosis remain to be clarified.

Apoptosis is a major event in the pathophysiology of atherothrombosis. However, the significance of apoptosis in this process is unclear (see review118). PPARα and PPARγ control apoptosis via negative cross talk with the antiapoptotic nuclear factor-κB pathway in macrophages.119 Furthermore, PPARγ inhibits the mitogenic induction of the cyclin-dependent kinase inhibitor p21 by modulating the protein kinase C-δ pathway in VSMCs.120 In addition, PPARγ stimulates the expression of PTEN, a tumor suppressor that modulates the inflammatory response and several cellular functions, including cell migration, survival, and proliferation.121 However, it remains to be determined whether apoptosis induction by PPARs also occurs in vivo and is of clinical importance.
PPAR Activators in Clinical Practice

A wealth of clinical studies have affirmed that fibrates improve the cardiovascular risk profile. Several angiographic intervention trials, including the Lipid Coronary Angiographic Trial (LOCAT), the Diabetes Atherosclerosis Intervention Study (DAIS), and the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT), have demonstrated beneficial effects of fibrates on atherosclerotic lesion progression.75–77 Furthermore, secondary prevention trials, such as the Veterans Administration-HDL-Cholesterol Intervention Trial (VA-HIT)122 and the Helsinki Heart Study,123 have demonstrated a decreased incidence of cardiovascular events after fibrate treatment. In patients with type 2 diabetes, who are characterized by moderate hypertriglyceridemia and low HDL cholesterol concentrations, fibrates decrease the incidence of myocardial infarction, as observed in the St. Mary’s, Ealing, Northwick Park Diabetes (SENDCAP) study.124 Several studies have been performed testing the effects of glitazone treatment on glucose homeostasis in various diabetic and insulin-resistant patient populations.125,126 Glitazone therapy lowers fasting and postprandial glucose levels and improves insulin-stimulated glucose disposal. However, the effect of glitazone on the plasma lipid profile in humans is controversial, and intervention trials assessing the influence of these compounds on the incidence of cardiovascular disease are still lacking. Nevertheless, troglitazone treatment of patients with type 2 diabetes has clearly established this molecule to be a potent inhibitor of early atherosclerotic lesion progression.127 In patients with type 2 diabetes, pioglitazone and rosiglitazone appear to have distinct effects on the plasma levels of triglycerides and LDL. Although pioglitazone treatment lowers serum concentrations of LDL and triglycerides, rosiglitazone treatment does not appear to lower triglyceride or to increase the levels of LDL cholesterol.125,128 Although the mechanistic basis for these differences is unclear, one possible explanation may be that pioglitazone has, albeit limited, PPARα activity.129 Despite their atheroprotective properties, certain glitazones present a significant risk of hepatotoxicity and heart failure; thus, their clinical use should be carefully monitored.130 Troglitazone has been withdrawn worldwide because of its hepatotoxic effects. The risk of heart failure with glitazones, which is likely due to plasma volume expansion, is enhanced when they are used in combination therapy with insulin.130

Running trials, such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and PROACTIVE trials, will provide additional evidence for possible clinical cardiovascular benefits of PPARα and PPARγ agonists in the diabetic population.

Conclusions

The intimate and causative relationships between lipid metabolism and coronary heart disease have stimulated research involving the physiological functions of the lipid-activated transcription factors of the PPAR family. This research has resulted in the development and understanding of the action mechanism of drugs useful in the treatment of metabolic disorders predisposing to atherosclerosis. With the use of recently developed potent subtype-specific agonists, it has been demonstrated that all 3 PPARs control lipid metabolism; however, the precise role of PPARβ/δ remains to be clarified at the molecular and physiological levels. The next years will be exciting with the prospect of development of novel PPAR agonists, with, for instance, mixed PPARα and PPARγ activity. Moreover, it is conceivable that future development of drugs exerting their activity via PPARs will focus not so much on the search of more potent activators but on selective receptor modulators in an attempt to separate desirable from unwanted side effects. Finally, ongoing clinical studies with specific PPARα-PPARβ/δ-PPARγ (co)activators should prove (or disprove) their potent activity in reducing coronary events and total mortality.

References


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