Peroxisome Proliferator-Activated Receptors at the Crossroads of Obesity, Diabetes, and Cardiovascular Disease
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Since their discovery in the early 1990s, the members of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors have been recognized as therapeutic targets against dyslipidemia and diabetes. Recent studies also identified anti-inflammatory actions of PPARs in cells constituting the atherosclerotic lesion. Delineation of this activity extended the therapeutic potential of PPAR activators beyond their original design as metabolic controllers. The PPAR family consists of 3 PPAR isoforms: α, β/δ, and γ, which exert different and sometimes overlapping effects on whole-body physiology in particular on lipid and glucose metabolism. This review summarizes the current knowledge on the role of PPARs in cardiovascular disease, the metabolic syndrome, atherosclerosis, and cardiac function. (J Am Coll Cardiol 2006;48:A24–32) © 2006 by the American College of Cardiology Foundation

In 1990, Issemann and Green (1) discovered the mechanism by which peroxisome proliferation in the liver was induced by hypolipidemic drugs and plasticizers (2). This pioneering research paved the way to the current understanding of the physiological function of the peroxisome proliferator-activated receptors (PPARs). The PPARs belong to the nuclear receptor superfamily of transcription factors. Since their discovery, they have received increasing attention as potential pharmacologic targets for combating obesity and diabetes (3). The PPAR family consists of 3 PPAR isoforms (i.e., PPARα, PPARβ [also known as δ], and PPARγ), each with their own tissue distribution pattern (4–6). Whereas PPARα is predominantly expressed in tissues with a high oxidative capacity such as the heart and liver, PPARγ is highest expressed in adipose tissue, and the expression of PPARβ/δ is more ubiquitous, being highest in skeletal muscle and intestine. The PPARs can be activated by an array of natural (endogenous) ligands, ranging from long-chain fatty acids to eicosanoids, that all bind with different affinity (7–9). In addition, synthetic ligands have been designed for the 3 PPAR isoforms with the purpose of therapeutic application. On ligand-binding, PPARs trans-activate gene expression by heterodimerization with another member of the nuclear receptor superfamily, the retinoic X receptor, and this complex binds to a direct repeat sequence designated PPAR-responsive element (Fig. 1). Alternatively, PPARs are able to down-regulate or transrepress gene expression via a signal-transduction disrupting mechanism independent of DNA binding (10).

**ACTIONS OF PPAR AGONISTS**

**PPARα.** For a long time, the PPARα-activating fibrates have been used in the treatment of dyslipidemia. In dyslipidemic patients, these drugs improve the plasma lipid profile by lowering triglyceride, and to a lesser extent, low-density lipoprotein (LDL) cholesterol levels and by increasing high-density lipoprotein (HDL) cholesterol levels. For unknown reasons, the HDL-increasing effect of fibrates seems less pronounced in type 2 diabetic patients (11,12). These effects are achieved by a variety of mechanisms, such as an increase in lipoprotein lipase expression, reduction of apolipoprotein (apo)CIII expression, inhibition of triglyceride synthesis, and very-low-density lipoprotein production. Furthermore, fibrates increase the expression of fatty acid metabolizing genes in oxidative tissues, resulting in an increased oxidation of fatty acids (reviewed by Chinetti-Gbaguidi et al. [13]). Treatment of hyperlipidemia to reduce the risk of cardiovascular disease (CVD) has focused predominantly on LDL cholesterol-lowering strategies, mainly by use of statins (14). However, several large studies have shown that the use of PPARα-activating drugs is favorable in the reduction of CVD risk factors, as summarized by the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) investigators (15). Furthermore, it was shown that PPARα agonists prevented the progression of arterial lumen occlusion, reduced the incidence of myocardial infarction, and reduced cardiovascular events (11,12,16–23) (Table 1). Apart from the abovementioned effects, PPARα activators favorably affect CVD by influencing atherosclerotic plaque composition (24). Recently it was shown that PPARα is expressed in cell types involved in the process of atherosclerosis. This enables this isoform to affect this process at the cellular level independent of or in addition to acting via blood lipid changes. PPARα activation reduces the infiltration of macrophages into the atherosclerotic plaque, reduces intraplaque lipid accumulation in an animal model of mixed dyslipidemia, and reduces cholesterol esterification in human macrophages caused by an increased adenosine triphosphate-binding cassette A1–mediated cholesterol efflux (24,25). Furthermore, fibrates were shown to reduce the production of proinflammatory...
cytokines such as interleukin (IL)-6, interferon γ, tumor necrosis factor α, IL-1β, and high-sensitivity C-reactive protein that may contribute to reducing the risk of cardiovascular events (10,25–27). Recently it was discovered that PPARα is regulating cell-cycle genes and cell proliferation of vascular smooth muscle cells, implying that this nuclear receptor is a therapeutic target in restenosis after coronary angioplasty (10,28).

One of the few potentially undesirable effects reported on fibrate use is the increase of plasma homocysteine that occurs via a PPARα-dependent mechanism (29). However, the clinical consequences of these findings are debatable because the increase of homocysteine levels caused by fenofibrate had no effect on the reduction of vessel lumen diameter or clinical events in DAIS (Diabetes Atherosclerosis Intervention Study) (30). A recent study suggested that homocysteine could reduce hepatic apoAI production, at least in part, by decreasing PPAR

**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>PPAR</td>
<td>Peroxisome proliferator-activated receptors</td>
</tr>
<tr>
<td>SPPARM</td>
<td>Selective peroxisome proliferator-activated receptors modulator</td>
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<tr>
<td>TZD</td>
<td>Thiazolidinedione</td>
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The thiazolidinediones (TZDs) are PPARγ ligands in clinical use as insulin sensitizing drugs for the treatment of type 2 diabetes (47). Preclinical as well as clinical data accumulate on the beneficial effects of TZDs on CVD (Table 1) (48–52). The principal mechanism by which TZDs exert their insulin sensitization effect is via the activation of PPARγ in adipose tissue, resulting in improved insulin sensitivity in skeletal muscle and liver. By the induction of subcutaneous adipocyte differentiation and decreasing the visceral-to-subcutaneous adipose tissue ratio, TZDs help to store free fatty acids in less harmful depots. The TZDs on the market today are rosiglitazone and pioglitazone. These compounds have very similar activities, except on plasma lipids, which seem to be more favorably affected by pioglitazone (2,53). Although pioglitazone decreases triglyceride levels, rosiglitazone is neutral. Both drugs increase HDL cholesterol, but rosiglitazone treatment also increases LDL and total cholesterol levels. The mechanism explaining this difference is not yet clear. Although some claim pioglitazone to have, albeit limited, PPARα-activating properties, selective peroxisome proliferator-activated receptor-α (PPARα) agonists (32,33). Close review of the literature showed an increased risk only on gemfibrozil use, but not with fenofibrate (34). Gemfibrozil is believed to alter statin metabolism, resulting in increased statin plasma levels (35). The risk of rhabdomyolysis was greatly reduced by using lower concentrations of statins or combining other fibrates than gemfibrozil with other statins than cerivastatin, which was removed from the market (36,37). The recent FIELD study showed no adverse effects of the combined use of statins with fenofibrate (12).

**PPARβ/δ.** Exciting new developments were reported in the field of PPARβ/δ research. This isoform has long been the neglected PPAR isoform because it is ubiquitously expressed, making it difficult to pinpoint ligand-mediated effects to specific tissues. With the development and use of compounds such as L165041, GW501516, and GW610742 data concerning PPARβ/δ function in (patho)physiology is accumulating (38). In several animal models of obesity and diabetes, it was shown that these compounds increase HDL cholesterol and decrease white adipose tissue fat deposits, triglycerides, fasting insulin, and small-density LDL, suggesting PPARβ/δ to be a suitable target in hyperlipidemia (39,40). Additionally, it was discovered that PPARβ/δ activates fatty acid oxidation in heart and skeletal muscle by increasing the expression of genes involved in fatty acid handling and changing skeletal muscle fiber type from glycolytic to oxidative (41). Altogether these studies suggest that PPARβ/δ is a promising new target in the battle against obesity and diabetes and subsequent CVD. Extensive research into the function of this isoform in body physiology is warranted, together with safety studies of the available agonists of PPARβ/δ. The latter is important because PPARβ/δ was found to play a role in cancer in rodents (42–46).

**PPARγ.** The thiazolidinediones (TZDs) are PPARγ ligands in clinical use as insulin sensitizing drugs for the treatment of type 2 diabetes (47). Preclinical as well as clinical data accumulate on the beneficial effects of TZDs on CVD (Table 1) (48–52). The principal mechanism by which TZDs exert their insulin sensitization effect is via the activation of PPARγ in adipose tissue, resulting in improved insulin sensitivity in skeletal muscle and liver. By the induction of subcutaneous adipocyte differentiation and decreasing the visceral-to-subcutaneous adipose tissue ratio, TZDs help to store free fatty acids in less harmful depots. The TZDs on the market today are rosiglitazone and pioglitazone. These compounds have very similar activities, except on plasma lipids, which seem to be more favorably affected by pioglitazone (2,53). Although pioglitazone decreases triglyceride levels, rosiglitazone is neutral. Both drugs increase HDL cholesterol, but rosiglitazone treatment also increases LDL and total cholesterol levels. The mechanism explaining this difference is not yet clear. Although some claim pioglitazone to have, albeit limited, PPARα-activating properties, selective peroxisome proliferator-activated receptor-γ (PPARγ) is a promising new target in the battle against obesity and diabetes and subsequent CVD. Extensive research into the function of this isoform in body physiology is warranted, together with safety studies of the available agonists of PPARβ/δ. The latter is important because PPARβ/δ was found to play a role in cancer in rodents (42–46).

**Figure 1.** Schematic representation of the transcriptional action of peroxisome proliferator-activated receptors (PPARs) with their heterodimer partner retinoic X receptor (RXR) and their major physiological functions. *Major function for this isoform but not exclusive. L = ligand; PPRE = peroxisome proliferator-activated receptor-responsive element.
activated receptors modulator (SPPARM) effects could also be involved.

In addition to the insulin-sensitizing effect, TZDs possess anti-inflammatory properties. This, together with the discovery that PPARγ is expressed in endothelial cells, macrophages, vascular smooth muscle cells, lymphocytes, and platelets, raised the hypothesis that using TZDs could be a suitable therapeutic approach to combating the development and progression of the atherosclerotic plaque (54).

PPARγ activation results in a decrease of matrix metalloproteinase 9 and soluble cluster of differentiation 40–ligand expression as well as reduction of plasma IL-6, IL-8, fibrinogen, and C-reactive protein levels in both type 2 diabetic and nondiabetic patients (55–58). In addition, when added to statin therapy, further atherosclerotic plaque regression was observed in vivo in rabbits using high-resolution magnetic resonance imaging (59). The recently reported PROactive Study (Prospective Pioglitazone Clinical Trial in Macrovascular Events) showed that, although the primary end point composed of hard CVD, and more subjective, procedural end points, was not reached, pioglitazone significantly decreased the hard end points of CVD (all-cause mortality, nonfatal myocardial infarction, and stroke) (51). A first post-hoc analysis of patients with myocardial infarction furthermore showed that pioglitazone significantly reduced recurrent cardiovascular events (60).

A notorious effect of TZD use is the gain of weight as a result of increased body fat and edema. Although this gain of weight is paradoxically associated with an improved clinical status of the patient, it may be undesirable from a psychological point of view. Contributing to this weight gain is the TZD-induced fluid retention partly caused by PPARγ-mediated H2O and salt retention in the collecting duct of the kidney (61). This fluid retention together with increased vascular permeability may result in edema and could thus potentially, especially in type 2 diabetic patients with diminished cardiac function, precipitate congestive heart failure (62,63). The recent PROactive Study (51), investigating the use of pioglitazone in diabetic patients with macrovascular disease, showed that pioglitazone does not increase mortality caused by heart failure.

**POLYMORPHISMS AND GENETIC ALTERATIONS OF PPARs AND RISK OF CVD**

Variations in the PPAR genes may also modulate the risk and susceptibility of disease. The use of animal models together with pharmacologic intervention provided evidence underlining the importance of the PPAR family as major players in whole-body lipid and glucose homeostasis. These observations have been extended by genetic studies in humans showing that PPARs may influence risk factors of CVD (Table 2).

**PPARA.** Polymorphisms within the human PPARα gene have been reported to influence risk markers for CVD (Table 2) (64–68). The L162V polymorphism of PPARα was identified as a gain of function mutation associated with favorable differences in plasma lipid concentrations (69).

**Table 1.** PPAR Agonists in Clinical Trials

<table>
<thead>
<tr>
<th>PPAR Isoform</th>
<th>Ligand</th>
<th>Clinical Trial</th>
<th>Risk of CVD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARα</td>
<td>Fenofibrate</td>
<td>DAIS, FIELD*</td>
<td>Lumenø ↑, microalb ↓, MI ↓, CVD ↓, revasc ↓</td>
<td>(12,16,17)</td>
</tr>
<tr>
<td></td>
<td>Gemfibrozil</td>
<td>HHS, VA-HIT, LOCAT</td>
<td>CVD ↓, death ↓, stroke ↓, lumeno ↑, CABG lesions ↓</td>
<td>(11,18–21)</td>
</tr>
<tr>
<td>PPARγ</td>
<td>Rosiglitazone</td>
<td>IMT ↓, retenosition ↓</td>
<td>(48,50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>PROactive</td>
<td>Mortality ↓, MI ↓, stroke ↓</td>
<td>(51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restenosis ↓</td>
<td>(52)</td>
<td></td>
</tr>
<tr>
<td>Panagonist (αβγ)</td>
<td>Bezafibrate</td>
<td>BECAIT, BIP*</td>
<td>Lumenø ↑, MI ↓</td>
<td>(22,23)</td>
</tr>
</tbody>
</table>

*No difference in primary end point.

BECAIT = Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP = Bezafibrate Infarct Prevention; CARG = coronary artery bypass graft; CVD = cardiovascular disease; DAIS = Diabetes Atherosclerosis Intervention Study; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HHS = Helsinki Heart Study; IMT = intima-media thickness; LOCAT = Lopid Coronary Angiography Trial; lumeno = no progression of arterial lumen occlusion; MI = myocardial infarction; microalb = microalbuminuria; PPAR = peroxisome proliferator-activated receptor; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; Revasc = revascularization; VA-HIT = Veterans Affairs Low-HDL Cholesterol Intervention Trial.

**Table 2.** PPAR Polymorphisms and Risk Markers of Cardiovascular Disease (CVD)

<table>
<thead>
<tr>
<th>PPAR Isoform</th>
<th>Polymorphism</th>
<th>Risk Markers for CVD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARA</td>
<td>L162V</td>
<td>LDL ↑, apoB ↑, BMI ↓, diffuse atherosclerosis ↓, incidence DM ↓</td>
<td>(64,65–67)</td>
</tr>
<tr>
<td></td>
<td>Intron7 G/C</td>
<td>Cardiac hypertrophy ↑</td>
<td>(68)</td>
</tr>
<tr>
<td></td>
<td>[ +294T/C]</td>
<td>LDL ↑</td>
<td>(74)</td>
</tr>
<tr>
<td></td>
<td>h1</td>
<td>BMI ↑, fasting glucose ↓</td>
<td>(75)</td>
</tr>
<tr>
<td>PPARD</td>
<td>Pro12Ala</td>
<td>BMI ↑, IR ↓, sBP ↑</td>
<td>(80–83)</td>
</tr>
<tr>
<td></td>
<td>C161T</td>
<td>CAD ↓, apoB ↓, TotChol/HDL ↓, TG ↓</td>
<td>(84,85)</td>
</tr>
<tr>
<td></td>
<td>Pro115Gln</td>
<td>BMI ↑</td>
<td>(86)</td>
</tr>
<tr>
<td></td>
<td>Pro467Leu</td>
<td>IR ↑, BP ↑, TG ↑</td>
<td>(87,88)</td>
</tr>
<tr>
<td></td>
<td>Val290Meth</td>
<td>IR ↑, BP ↑, TG ↑</td>
<td>(88)</td>
</tr>
<tr>
<td></td>
<td>Arg425Leu</td>
<td>DM ↑, dyslipidemia ↑</td>
<td>(89)</td>
</tr>
<tr>
<td></td>
<td>hTGTGC</td>
<td>Metabolic syndrome ↑</td>
<td>(90)</td>
</tr>
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apoB = apolipoprotein B; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; DM = diabetes mellitus; IR = insulin resistance; LDL = low-density lipoprotein; sBP = systolic blood pressure; TG = triglycerides; TotChol/HDL = ratio of total cholesterol to high-density lipoprotein; other abbreviations as in Table 1.
Furthermore, haplotype analysis showed that the PPARα gene variation influences the onset of age-related diabetes in men (64).

In mice, genetic ablation of PPARα not only affects energy substrate metabolism by decreasing the ability to utilize fatty acids, but also impairs the immune system (70). Because both mechanisms are involved in the etiology of CVD, these observations strengthen the importance of PPARα in the process of CVD. The recently reported skeletal muscle–specific PPARα transgenic mouse model beautifully shows the complexity of physiological PPARα signaling and the necessary organ crosstalk in this process (71). This study shows an insulin-resistant phenotype in these mice. However, (pre)clinical use of fibrates has either no effect or induces a slight improvement of glucose metabolism (12,72,73).

PPARβ/δ. Only recently are data becoming available on mutations or polymorphisms of PPARβ/δ (Table 2) and their influence on body homeostasis or risk of CVD. Skogsb erg et al. (74) showed that of the 4 polymorphisms detected in PPARβ/δ, only +294T/C is associated with increased LDL cholesterol levels in healthy subjects. The rare C allele showed higher transcriptional activity at the promoter level that was partially mediated by an increased binding of Sp-1. Interestingly, in a Korean population, a haplotype containing 5 single nucleotide polymorphisms of PPARβ/δ was associated with a reduction of fasting glucose levels as well as increased body mass index in healthy volunteers (75). The clinical consequences of this polymorphism are uncertain because both parameters have opposite effects on risk for CVD (76). Further studies on PPARβ/δ polymorphisms are eagerly awaited.

In this respect, the data obtained from genetically altered mice are of interest. In PPARβ/δ null mice it was observed that gonadal adipose tissue was decreased compared with wild-type mice, and body weight tended to be decreased (significant in female mice) (77). Interestingly, adipose tissue–specific overexpression of an activated form of PPARβ/δ also resulted in a reduction of adipose tissue, an alteration that was shown to be protective against high-fat feeding (78). Although a function for PPARβ/δ in energy expenditure is established, its influence on atherosclerotic plaque formation or regression is not clear. Whereas an agonist for PPARβ/δ did not influence plaque progression, PPARβ/δ deficiency in macrophages resulted in altered atherosclerosis susceptibility (79).

PPARγ. Several polymorphisms in the PPARγ gene have been detected (Table 2) (80–90). They have been reported to influence body mass index, insulin resistance, blood pressure, and the development of type 2 diabetes. Of special interest are the Pro467Leu, Val929Met, and Arg425Leu mutations because these act in a dominant-negative manner, resulting in partial lipodystrophy with severe insulin resistance (87–89). Although these PPARγ mutations result in the increase of risk factors of CVD, they are very rare, limiting their epidemiologic significance in large population studies (81,91–93). Overall we can state that PPARγ mutations influence the risk and development of type 2 diabetes.

Comparing the data obtained in human studies with that from animal models copying PPARγ mutations allows us to propose whether polymorphisms in humans either a gain or a loss of function properties. Mice homozygous for PPARγ deficiency or in which the wild-type gene is replaced by a dominant negative PPARγ mutation L466A die in utero at embryonic day 10.5 to 11.5 (94). Interestingly heterozygous PPARγ knockout mice are more sensitive to insulin during an oral glucose tolerance test, whereas TZD treatment normalized insulin action and high-fat feeding–induced adipose tissue hypertrophy and insulin resistance in peripheral tissues and liver in both wild-type and PPARγ +/- animals (95). In addition to these whole-genome transgenic models, the tissue–specific knockout models for PPARγ have proven valuable in delineating the role of this receptor in specific tissues. Skeletal muscle–specific deletion of PPARγ resulted in glucose intolerance and insulin resistance (96,97). Interestingly, only 1 of these models had a response to TZD treatment, further feeding the controversy around the involvement of muscle in the insulin-sensitizing effect of TZDs. Adipose tissue–specific ablation of PPARγ using the aP2-Cre system was protective against insulin resistance and body weight gain on high-fat feeding in 1 case, whereas in a comparable model high-fat feeding induced insulin resistance in fat and liver (98,99). Selective knockout in adipose tissue of the PPARγ2 isoform also resulted in insulin resistance associated with reduced weight of white but not brown adipose tissue (100). Interestingly, introduction of the Prot12Ala mutation in exon B of the PPARγ gene resulted in a reduced expression of both PPARγ1 and PPARγ2 in white and PPARγ2 in brown adipose tissue (101). These hypomorphic PPARγ mice were indistinguishable from wild-type littermates at birth, but became growth retarded within the first week after birth, after which 24% of the mice died. Furthermore, PPARγhyp/hyp mice had less white adipose tissue and normal fasting glucose and insulin levels, which were elevated in the postprandial state compared with those of wild-type littermates. Rosiglitazone treatment only normalized glucose levels, and insulin levels remained increased. Free fatty acid levels of PPARγhypo/hypo mice were increased and did not change on fasting. The lack of adipose tissue in this model was accompanied by an increased expression in skeletal muscle of PPARα and PPARβ/δ, together with genes involved in β-oxidation.

Altogether the data gathered using tissue-selective PPARγ knockout models clearly confirm the role of this isoform in adipose tissue generation and function, but the metabolic consequences at the whole-body level remain unclear.

PPARs and cardiac function. With the clinical application of PPAR activators in type 2 diabetic patients at high risk of developing CVD, the effects on cardiac function
must be considered. Because the heart heavily relies on fatty acids as a source of energy, it is no surprise that PPARα and PPARβ/δ play an important role in cardiac physiology. Interestingly, the absence of PPARα was shown to be beneficial for cardiac performance after ischemia/reperfusion injury, whereas cardiac-specific overexpression of PPARα seemed to be detrimental to cardiac function (102,103). In contrast, several studies showed improved cardiac function and recovery after ischemia/reperfusion on PPARα activator treatment (104,105). Furthermore, fenofibrate was shown to protect the heart against inflammation and fibrosis in an animal hypertension model (106,107). In an in vitro cardiac-hypertrophy model, the PPARα agonists fenofibrate and Wy-14,643 and the PPARβ/δ agonist L165041 reduced hypertrophy, although the expression of both PPARα and PPARβ/δ were found to be decreased during hypertrophy (108). In contrast, in humans it was observed that protein expression of both PPARα and PPARγ were increased in failing left ventricle (109).

Cardiomyocyte-specific knockout of PPARβ/δ resulted in lipotoxic dilated cardiomyopathy caused by a decreased expression of fatty acid handling genes (110). Recently, the development of a cardiomyocyte-specific PPARγ knockout has shed some light on the role of this PPAR isoform in the heart and the cardiomyocyte in particular (111). This study shows PPARγ to be a suppressor of nuclear factor (NF)κB-signaling during growth and development, as can be concluded from the development of cardiac hypertrophy in knockout mice with a concomitant increase of atrial natriuretic factor expression and increased NFκB activity. These results substantiate the studies of others who showed cardioprotective effects of rosiglitazone via the NFκB-pathway after cardiac infarction (112,113). Overall, both vascular and cardiomyocyte-specific activation of all 3 PPAR isoforms may prove to be protective in humans. The results of the recent PROactive Study are in support of a cardioprotective activity of TZDs in type 2 diabetic patients (51).

NEW CONCEPTS AND THERAPEUTIC APPLICATIONS

Within PPAR research, basic and translational clinical approaches resulted in new concepts that can be translated and tested into clinical practice in the near future. The following section of this review discusses some new applications and new concepts of PPAR biology.

Dual PPAR activators. A new class of PPAR activators are the dual α/γ agonists or glitazars. Combining the properties of different PPAR isoforms in 1 drug should yield more global effects as compared with isoform-specific agonists. In line with this presumption are the results obtained from tesaglitazar-treated rats on a high-fat diet that show improved insulin sensitivity, increased non-esterified fatty acid (NEFA) clearance in white adipose tissue, and increased NEFA use by the liver and skeletal muscle (114). Recently, clinical data on a dual PPARα/γ agonist appeared. In a dose-finding study, the effects of ragaglitazar on type 2 diabetic patients was assessed for 12 weeks (115). Ragaglitazar reduced fasting plasma glucose levels and decreased triglycerides. Furthermore, a decrease was observed in total and LDL cholesterol, free fatty acids, and apoB, whereas HDL cholesterol was increased. Unfortunately, some adverse effects were reported, such as edema, anemia, and weight gain. In a multicenter double-blind placebo-controlled trial, the effect of the dual PPARα/γ agonist muraglitazar (BMS-298558) was tested as monotherapy in drug-naïve individuals for 24 weeks (116). The results showed a reduction in glycosylated hemoglobin, triglycerides, total and LDL cholesterol, and apoB. Furthermore, HDL cholesterol was increased and fasting glucose, insulin, and C-peptide levels were decreased, altogether results most favorable in reducing the risk of CVD. However, like PPARγ agonists, muraglitazar increases body weight as well as edema, limiting its clinical dose to 5 mg/day, a dose at which the drug likely activates PPARγ predominantly. Furthermore, a recent study suggested that at the dose of 5 mg/day, muraglitazar increased the incidence of the composite end point consisting of death or major adverse cardiovascular events (myocardial infarction, stroke, transient ischemic attack, and congestive heart failure) as compared with placebo or pioglitazone (117). These studies debate the suitability of this PPARα/γ agonist for clinical purposes. Compound 23 is a dual PPARγ/δ activator with triglyceride- and glucose-lowering as well as HDL-raising properties in zucker diabetic fatty rats (118). Recently, compound T913659 was reported to activate all 3 PPAR isoforms (panagonist) with PPARα and PPARβ/δ as the main targets (119). The T913659 increased HDL cholesterol levels in high-fat-fed St. Kitts Vervet monkeys, a model of nonhuman primate atherosclerosis. In perspective, bezafibrate, a relatively old fibrate, is a partial agonist for PPARα, PPARβ/δ, and PPARγ, acting thus also as a panagonist (120). Clinical studies with bezafibrate do not report edema or weight gain, promising a new future for compounds previously discarded by the industry because of their pan-PPAR action.

SPPARM. Recently, the concept of the SPPARM was introduced. This concept encompasses the principle of chemical alteration of PPAR-specific ligands to create compounds that possess differential gene-regulating properties (121). Thus far several compounds have been identified as SPPARMs, some of which are already in clinical testing (Table 3) (122–125). The focus of SPPARM research is PPARγ, because the control of adverse effects of PPARγ

| Table 3. Selective PPAR Modulators (SPPARMs) and Their Reported Effects |
|-----------------|------------------|------------------|------------------|
| SPPARM          | Effects          | Reference        |
| PAT5A           | Glucose ↓, TG ↓, IR ↓ | (122) |
| sTZDpa          | VSMC proliferation ↓ | (123) |
| FK614           | IR ↓             | (124) |

VSMC = vascular smooth muscle cell; other abbreviations as in Table 2.
could contribute greatly to improve the treatment of diabetes.

Conclusions. This review highlights the different levels at which the members of the PPAR family affect obesity, diabetes, and cardiovascular disease. The current publication rate on this topic is illustrative of the interest in this field. The combined efforts of basic and clinical science together with pharmaceutical developments resulted in the discovery of many new pathways, treatment strategies, and drugs of potential interest for the treatment of obesity, diabetes, and cardiovascular disease.

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