PPAR Ligands: Potential Therapies for Metabolic Syndrome

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Metabolic syndrome (MS), a condition characterized by multiple related clinical disorders including insulin resistance, central obesity, hyperlipidemia, hypertension, and heart disease, is an increasingly prevalent disease in industrialized societies. The intense research interest in the peroxisome proliferator-activated receptors (PPARs), by both the pharmaceutical industry and academia, stems largely from the well-documented therapeutic actions of their synthetic agonists in alleviating several of the maladies associated with MS. This report focuses on the current understanding of the mechanisms of action of PPAR agents and their clinical use in the context of MS.

Introduction

Metabolic syndrome (MS) is an increasingly prevalent disease in western societies. Its clinical features include insulin resistance, central obesity, hyperlipidemia, hypertension, and heart disease (Fig. 1). Clinical diagnosis of MS requires that three out of the following five criteria be met: 1) a waist circumference greater than 40 inches in men and 35 inches in women; 2) fasting plasma glucose above 110 mg/dL; 3) triglycerides (TGs) in excess of 150 mg/dL; 4) a high-density lipoprotein (HDL) cholesterol under 40 mg/dL in men or under 50 mg/dL in women; and 5) blood pressure in excess of 130/85 mm Hg [1••]. It has been estimated that approximately 40 million individuals in the United States alone are afflicted with this condition [2]. The prevalence of MS increases dramatically with age but recently has also been occurring in dramatic numbers in the adolescent population [3]. In addition to exercise and dietary restriction, current therapies for MS are aimed at normalizing the individual symptoms associated with this disease.

Agonists of peroxisome proliferator-activated receptors (PPARs), which are often used in combination with other drugs, represent important putative lines of therapy for the treatment of MS. The three PPAR isoforms, γ, α, and δ, are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily [4]. Each of these isoforms forms an obligate heterodimer with another nuclear receptor, the retinoid X receptor α (RXRα). PPAR-RXRα heterodimers regulate the expression of target genes by binding to consensus DNA elements called peroxisome proliferator response elements (PPREs) [5]. PPREs mediate the response to PPARs and have been identified in the promoter regions of numerous genes involved in lipid metabolism [6–9]. Thus, PPARs are believed to modulate important metabolic events by coordinately regulating the expression of a large numbers of genes. In this report, the clinical use of PPAR agents in the context of treatment of the MS is discussed. In addition, emerging classes of novel PPAR agonists that have the potential for improved efficacy and tolerability are described.

Insulin Resistance

Thiazolidinedione (TZD) agonists of PPAR-γ comprise a class of insulin-sensitizing agents that have gained regulatory approval for the treatment of hyperglycemia in patients afflicted with type 2 diabetes mellitus (T2DM). The first such agent in this class, troglitazone, was approved in 1997 but has since been recalled from the market due to the induction of severe idiosyncratic hepatotoxicity in a small percent of patients taking this agent. Its successors, Avandia (GlaxoSmithKline, Research Triangle Park, NC; rosiglitazone) and Actos (Pharmaceuticals North America, Lincolnshire, IL; pioglitazone), have been marketed since 1999. Fortunately, these latter TZDs have not been linked with this particular adverse effect, indicating that troglitazone's hepatotoxicity was presumably a compound-specific phenomena.

Both Avandia and Actos are approved in numerous countries for the treatment of T2DM, both as monotherapy and in combination with sulfonylurea insulin secretagogues, insulin, or metformin (an insulin-sensitizing agent that appears to act via induction of hepatic AMP kinase activity). In 2001, more than 15 million prescriptions for these TZDs were filled in the United States [10]. Avandia and Actos both exert significant glucose-lowering effects in placebo-controlled studies, as evidenced by decreases in hemoglobin A_{1c} (HbA_{1c}) levels of approximately 1% to 1.5% in subjects with T2DM, which represents efficacy comparable to that of the other available oral antidiabetes drugs. However, because normalization of glycemic control

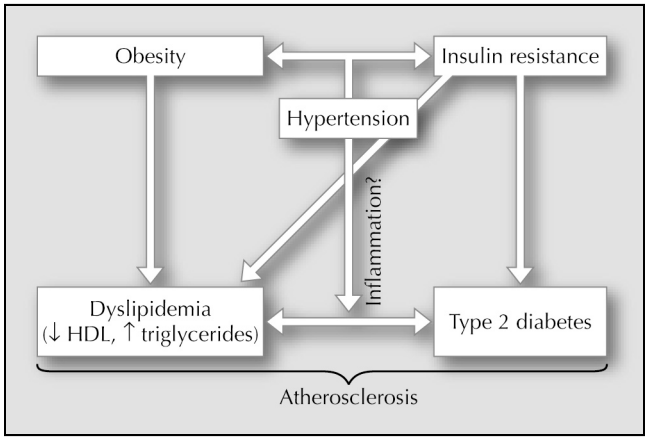

Figure 1. The metabolic syndrome is an array of individual clinical disorders that includes insulin resistance, central obesity, dyslipidemia, and hypertension. Although the interrelationships between these components are not well defined, they ultimately increase patient risk for developing atherosclerosis, the leading cause of mortality in western societies. HDL—high-density lipoprotein.

in a typical patient with T2DM is generally achieved by lowering HbA_{1c} levels by approximately 2.5% to 4.5%, the overall efficacy of TZDs and other antihyperglycemic agents used in monotherapy remains modest, thereby often necessitating their use in combination therapies [11–14]. As a consequence, an unmet medical need to develop novel antidiabetic agents that provide superior glycemic control still exists. As relatively recently introduced pharmaceutical agents, the long-term efficacy of TZDs has yet to be fully determined. Also, data that clearly identify specific patient populations as responsive to TZDs in terms of their efficacy or their adverse effects remain lacking.

The improvements in glycemic control conferred by PPAR-γ agonists, such as troglitazone, rosiglitazone, and pioglitazone, yield an additional benefit: the preservation of β-cell function in preclinical species [15]. These highly desirable effects were also noted in a randomized, placebo-controlled trial of troglitazone in women with prior gestational diabetes mellitus [16]. Similar beneficial effects on β-cell function have been noted clinically with other PPAR-γ agonists, suggestive of an important additional function of this class of insulin sensitizers.

Despite their glucose-lowering efficacy, more widespread use of TZDs in humans (particularly in Europe) has been limited by the adverse effects closely associated with their use [17]. Consistent with the well-established role of PPAR-γ in promoting adipogenesis in preclinical species [6], TZDs increase body weight gain in humans (2 to 3 kg for every percent decrease in HbA_{1c} values), effects mainly attributed to an increase in subcutaneous fat depot size [18••]. Thus, although TZDs ameliorate hyperglycemia, they worsen another clinical feature of MS, obesity. TZDs also promote fluid retention or edema, which in certain cases may be partially responsible for an increase in total body weight. A total of 4% to 6% of patients taking TZDs develop symptoms of edema, as compared with 1% to 2% in placebo-treated patients [18••]. In some cases, mild fluid retention can be treated by reducing the dose of TZD or adding a diuretic [19]. Importantly, an increase in body weight and edema is associated with an increased risk for congestive heart failure (2.5 times greater) in patients taking a combination therapy that includes TZDs and insulin [20]. Furthermore, in response to a growing concern over the potential risk of PPAR agonists in promoting carcinogenesis in preclinical species, under recently issued U.S. Food and Drug Adminstration guidelines, PPAR clinical trials of greater than 6 months in duration are precluded prior to the completion of 2-year rodent carcinogenicity studies. This regulatory change introduces significant delay and complexity into the development of new PPAR agents. At this juncture, the precise mechanisms by which certain PPAR agents induce tumorgenicity are unknown.

Potential Mechanisms of Efficacy of PPAR-γ Agonists

The original observation that TZDs were effective glucose-lowering agents preceded the elucidation of the precise mechanisms by which these drugs exert their effects. The discovery in 1995 that TZDs could bind to PPAR-γ with high affinity [21] was a seminal finding that first hinted at a potential role of PPAR-γ in diabetes and thereby led to intensive research efforts to better understand the biology surrounding this receptor. It was recognized that PPAR-γ is most abundantly expressed in adipose tissue, although it is also found in macrophages and intestine [6]. Paradoxically though, improvements in glycemic control by TZDs in animal models are primarily achieved by heightened insulin sensitization in skeletal muscle and liver tissues, tissues which have very low levels of PPAR-γ expression, but not adipose [22]. It has become increasingly evident, however, that adipose tissue is the primary target for the systemic insulin-sensitizing actions of PPAR-γ ligands, despite the prominent roles of both skeletal muscle and liver in whole-body glucose metabolism. In support of this, TZDs were shown to be effective in improving the insulin resistance of partially lipoatrophic but not A-ZIP fatless mice [23]. PPAR-γ activation is associated with the modulation of a wide array of genes in adipose, including those encoding proteins involved in lipid uptake, lipid metabolism, and insulin action [24••]. Recently, it was demonstrated that TZDs maintain their glucose-lowering efficacy in diabetic mice with skeletal muscle or liver-specific deficiency of PPAR-γ [25,26]. Thus, TZDs and other PPAR-γ agonists are believed to exert their pleiotropic effects directly in adipose, which ultimately leads to insulin sensitization in skeletal muscle and liver.

Numerous mechanisms by which PPAR-γ agonists exert their insulin-sensitizing actions have been proposed, and ultimately, the glucose-lowering efficacy of PPAR-γ agonists will likely rely on more than one such mechanism. For instance, one of the prominent physiologic

outcomes of TZD treatment is a diminution in the release of free fatty acids from adipose. Consequently, lipid levels in adipose tissue rise while circulating free fatty acids diminish [27•]. It has been proposed that by repartitioning lipids away from liver and muscle, the two primary tissues responsible for insulin-mediated glucose disposal and metabolism, PPAR-γ agonists ameliorate hyperglycemia by reversing lipotoxicity-induced insulin resistance. Data from subjects with T2DM and preclinical species also indicate that PPAR-γ agonists promote a redistribution of fat from visceral adipose tissue into small, newly differentiated, insulin-sensitive adipocytes within subcutaneous depots [28–31]. This may indirectly improve glucose homeostasis because subcutaneous depots are believed to be less able to deposit insulin resistance–promoting lipids into the bloodstream. This hypothesis is supported by the finding that humans with an inhibitory PPAR-γ polymorphism exhibit partial lipodystrophy characterized by decreased subcutaneous fat, increased visceral fat, hyperglycemia, and insulin resistance [32,33].

Adipocyte-specific secreted proteins that are mediators of insulin sensitivity may also provide an important functional link between adipose and distal sites associated with improved glucose homeostasis. PPAR-γ activation has been shown to modulate the expression levels of several such secreted proteins, referred to as "adipokines." For example, adiponectin, a potentiator of liver [34] and skeletal muscle insulin sensitivity [35], is upregulated in response to PPAR-γ activation [36,37]. Clinically, the circulating levels of adiponectin are low in diabetic patients and TZDs have been shown to induce them [37]. PPAR-γ ligands have also been shown to attenuate the expression of resistin and plasminogen activator inhibitor-1, proteins implicated in promoting insulin resistance [38,39]. Furthermore, activation of PPAR-γ reduces the expression of specific proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, as well as selected chemokines linked to insulin resistance [27•,40]. Alterations in endocrine signaling may also play a role in the efficacy of PPAR-γ agonists. For example, it was shown that the overexpression of adipocyte 11β-HSD1 (an enzyme that converts cortisone into its physiologically active form, cortisol) in adipose caused insulin resistance in mice [41]. Conversely, 11β-HSD1 knockout mice exhibit improved glucose and lipid homeostasis [42]. Thus, the downregulation of 11β-HSD1 in adipocytes that occurs with PPAR-γ agonist treatment in preclinical species [43] may help to improve insulin sensitivity by reducing the excessive glucocorticoid activity that has been associated with several features of MS.

Dyslipidemia

An elevation in circulating levels of TGs and low-density lipoprotein (LDL) cholesterol, along with decreased levels of HDL cholesterol, comprise a dyslipidemic profile common to many patients with MS. Treatment of this MS component is of particular importance because it is often a predecessor of cardiovascular disease, the major cause of mortality in western societies [44]. The fibrate class of PPAR-α agonists, including fenofibrate, clofibrate, and bezafibrate, has proven to be quite effective in reducing TGs (30% to 50%) and free fatty acids, as well as improving cholesterol profiles (increasing HDL cholesterol by 10% to 22% and decreasing LDL cholesterol by 10% to 25%) in both rodents and humans [45]. As is the case with TZDs, the molecular basis for such physiologic effects of fibrates is thought to originate at the level of gene expression. PPAR-α agonists modulate the expression of a number of genes encoding hepatic proteins that are critically involved in lipid catabolism. PPAR-α is highly expressed in liver, heart, and skeletal muscle, tissues that extract a high level of their energy requirements from lipids [46]. Fibrates promote the uptake, modification, and oxidation of fatty acids in liver and thus reduce free fatty acid levels in plasma. Fibrates also promote lipoprotein lipase (LPL)–mediated lipolysis of TGs by increasing the expression of LPL while reducing that of apoCIII, an inhibitor of LPL [47], thereby serving to lower TG levels. PPAR-α null mice were found to be refractory to the gene-modulating and lipid-lowering effects of fibrates, thereby confirming the critical role of PPAR-α in mediating their activation of lipid catabolism and resulting diminution in hypertriglyceridemia.

The beneficial effects of fibrates on cholesterol derive from their ability to promote reverse cholesterol transport. Fibrates have been shown to increase the expression of apoAI and apoAII, the major apolipoprotein components of HDL [47,48]. Fibrates also increase the expression of the cholesterol transporter, ABCA1, which helps to return cellular cholesterol to the liver. Furthermore, the HDL receptor, SRB1, is upregulated by fibrate treatment in animal models of dyslipidemia, again leading to improved removal of circulating cholesterol [45]. In the Helsinki heart study, treatment with gemfibrozil was shown to result in an 11% decrease in LDL cholesterol and an 11% increase in HDL cholesterol, as well as a 35% reduction in TGs [49]. In addition, to augment the beneficial lipid efficacy of fibrates, they are commonly used in combination with statins, which are particularly useful in lowering LDL cholesterol levels.

Although relatively rare, myopathy represents the major side effect associated with the clinical use of PPAR-α agonists. In most cases, it presents as muscle weakness corresponding to elevated levels of serum creatine phosphokinase (CPK). In rare instances, fibrates can trigger a potentially fatal condition known as rhabdomyolysis, characterized by rapid muscle degeneration that is accompanied by extremely elevated CPK levels (> 10,000 IU/L). Combination therapy of fibrates with cholesterol-lowering statins appears to potentiate the deleterious effects of PPAR-α agonists on muscle [50]. Besides myopathy, gastrointestinal side effects such as nausea and diarrhea have also been reported in humans treated with fibrates.

In contrast to fibrates, PPAR-γ agonists have only modest effects on lipid levels in humans. In several randomized, placebo-controlled clinical trials, rosiglitazone was shown to modestly elevate both HDL and LDL cholesterol levels (~ 10% and 8% to 16%, respectively), with no significant effect on TGs. Pioglitazone had similar beneficial effects on HDL cholesterol levels (~ 10%) without increasing that of LDL cholesterol [18••]. Pioglitazone also improved TG levels, an effect which may be attributable to off-target activities. As noted earlier, both marketed TZDs are effective in lowering serum free fatty acids levels by approximately 20% to 30%, which may be related to their ability to lower glucose levels as well.

A potent and selective agonist of PPAR-δ, GW501516, was also shown to beneficially affect serum lipid levels, increasing serum HDL cholesterol 79% and lowering TGs 56% in fasted obese rhesus monkeys [51]. Qualitatively, these effects are similar to what has been observed with fibrate treatment in humans and rodents. The increase in HDL cholesterol levels by PPAR-δ agonist treatment was attributed to an increase in cholesterol efflux through ABCA1 [51]. The fact that PPAR-δ agonists had beneficial effects on lipids in a small cohort (n = 6) of non-human primates provides some measure of optimism that such effects may extend to humans. However, the clinical effects of PPAR-δ selective agonists have yet to be reported.

Obesity

The development of safe and efficacious antiobesity agents represents a significant challenge for numerous pharmaceutical companies. Two of the primary mechanisms that have been exploited to support these endeavors include reducing food intake by modifying central nervous system signaling, as well as increasing metabolic rate via the central nervous system or periphery. Serving as an example of the latter approach, the PPAR-δ agonist, GW501516, was recently shown to mitigate diet-induced obesity and insulin resistance in rodents, concomitant with increased fatty acid oxidation in adipocytes and skeletal muscle [52]. Similarly, the results of studies using PPAR-δ genetic mouse models support a role for this receptor in fatty acid oxidation. Targeted activation of PPAR-δ expression in adipose was shown to result in reduced adiposity, concomitant with increased expression of genes required for fatty acid oxidation. Conversely, PPAR-δ null mice displayed significantly enhanced weight gain versus wild-type controls on a high-fat diet [53]. Recently, overexpression of constitutively active PPAR-δ in mouse skeletal muscle was found to induce differentiation of mitochondria-rich, oxidative type 1 muscle fibers [54]. Whether the effects of synthetic PPAR-δ agonists on insulin sensitivity are related to their beneficial effects on lipid catabolism remains to be further investigated.

Together, these preclinical data suggest that PPAR-δ agonists have the potential to ameliorate multiple clinical features of MS, simultaneously including obesity, insulin resistance, and dyslipidemia. GW501516, which has advanced into phase II, may provide confirmation as to whether these striking effects may be recapitulated in humans. One potential limitation surrounding the use of PPAR-δ agonists for the treatment of MS relates to their potential for broad-ranging physiologic effects in various tissues, because PPAR-δ is ubiquitously expressed. For example, early studies using PPAR-δ null mice demonstrated a role for this receptor in keratinocyte differentiation and epithelization [55]. Additionally, several groups have also reported a role for PPAR-δ in the modulation of tumor formation in intestine [56,57]. However, such studies have yielded conflicting results, perhaps due to differences between the genetic and pharmacologic approaches used. Therefore, the exact nature of PPAR-δ function in the modulation of tumorigenesis is still unclear.

Cardiovascular Disease

The clinical features of MS are associated with increased risk of cardiovascular disease [1••], the major cause of mortality in western societies. PPAR agonists are thus expected to have atheroprotective effects by virtue of their ability to ameliorate individual features of MS as described earlier. In the case of PPAR-α agonists, their abilities to lower TGs and activate reverse cholesterol transport contribute to a metabolic profile that is less likely to promote the development of atherosclerotic lesions. Apart from such hypolipidemic activities, PPAR-α agonists are thought to have additional vasoprotective effects at the atheroma site itself. This hypothesis is based on numerous studies demonstrating anti-inflammatory actions by PPAR-α agonists within smooth muscle, monocytic, and endothelial cells, major atheroma components that express significant levels of PPAR-α. Notably, fibrates reduce levels of C-reactive protein, a protein whose expression highly correlates with the appearance of atherosclerotic lesions. In addition, by decreasing expression of macrophage tissue factor, they may reduce thrombosis, resulting from atherosclerotic lesion rupture. The aforementioned effects of PPAR-α agonists on circulating lipid parameters and vascular cells yield important benefits, because these ligands have proven efficacious in reducing the progression of atherosclerosis and the incidence of coronary events in major clinical studies including the VA-HIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial) [58]. Interestingly, the atheroprotective benefit of PPAR-α agonists was particularly pronounced in diabetic patients as demonstrated in the VA-HIT [59] and the Diabetes Atherosclerosis Intervention Study [60]. Such results are noteworthy, because cardiovascular disease is the major cause of mortality in patients with T2DM, a cohort that displays a prevalence of dyslipidemia two to three times greater than the general population.

As noted earlier, TZDs have demonstrated anti-inflammatory properties in preclinical species and, likewise, have

been shown to reduce aortic lesion size in animal models of atherosclerosis. Interestingly, the antiatherogenic activity of TZDs could occur independently of improvements in dyslipidemia, insulin resistance, or hypertension, suggesting a direct vascular effect [61]. Such localized activity is plausible given that PPAR-γ is expressed within cells that form atherosclerotic lesions, including vascular endothelial and smooth muscle cells, macrophages, and macrophage-derived foam cells. Although final proof of the antiatherosclerotic efficacy of PPAR-γ agonists awaits the completion of ongoing human trials, early results provide reason for optimism. Troglitazone was shown to reduce intimal wall thickness of the common carotid artery in subjects with T2DM [62]. In addition, treatment of patients with T2DM with rosiglitazone diminished plasma levels of inflammatory biomarkers that are predictive of cardiovascular disease [63]. Because such decreases were observed prior to changes in metabolic parameters [64], they also support the supposition that PPAR-γ agonists have direct vascular actions.

Novel PPAR Agonists

PPAR-α/-γ dual agonists and PPAR-α/-γ/-δ pan agonists

The basis for the development of PPAR-α/-γ dual agonists derives from the concept that such ligands may induce the combined physiologic effects associated with the activation of both receptors and thus provide broader metabolic improvements than isoform selective agonists. Several challenges merit consideration, however, with respect to optimizing dual PPAR-α/-γ agonists for clinical applications. For instance, at this juncture it is unclear what ratio of PPAR-α and PPAR-γ activity will provide optimal efficacy in humans. Second, limited clinical data exist to determine whether synergistic or reductive effects on both efficacy and toxicity will ensue from the activation of both receptors. Additional challenges are posed by the difficulty in accurately extrapolating data from animal models to the treatment of humans because significant species differences (*ie,* rodent hypersensitivity to PPAR-α agonism) exist. Furthermore, preclinical species commonly used to assess lipid-lowering activities (PPAR-α effects) are often inadequate for examining glucose lowering (PPAR-γ effects), complicating assessment of optimal PPAR-α and PPAR-γ ratios in a single animal model.

Fortunately, however, researchers have successfully identified PPAR-α/-γ dual agonists that demonstrated both glucose- and lipid-lowering efficacy in animal models that are comparable to effects obtained with selective PPAR-α and PPAR-γ agonists. To date, several dual agonists with diverse PPAR-α/-γ ratios (including MK-0767, ragaglitazar, farglitazar, naveglitar, tesaglitazar, and muraglitazar among others) have advanced into clinical trials and recapitulated these preclinical observations in humans. For instance, in phase II clinical trials conducted with hypertriglyceridemic subjects with T2DM, ragaglitazar reduced fasting plasma glucose and HbA_{1c} (to a similar extent as pioglitazone), TG, free fatty acid and total cholesterol levels, while significantly elevating HDL cholesterol [65]. Muraglitazar was also reported to have beneficial effects on glucose and lipids in preclinical species and has advanced to phase III clinical trials. The future release of additional clinical data will likely provide clarity with respect to the optimal profile for a PPAR-α/-γ dual agonist.

Although progress with respect to the identification of potent PPAR-α/-γ/-δ pan agonists to date has been less dramatic, at least two pan agonists have advanced into clinical trials. And although in vivo characterization of these ligands to date has been less extensive, two early reports suggest that rodents treated with pan agonists do not gain weight or suffer from edema, unlike those treated with PPAR-γ selective agents or with PPAR-α/-γ dual agonists [66].

Selective PPAR-γ modulators

As noted previously, there are several undesirable side effects closely associated with the use of the TZD PPAR-γ full agonists rosiglitazone and pioglitazone in humans, including plasma volume expansion, hemodilution, edema, increased adiposity, and weight gain [18••]. Furthermore, PPAR-γ full agonists are known to induce cardiomegaly in certain preclinical species [67••,68]. These untoward effects, as well as concerns over potential cardiac risks in humans, limit the clinical application of these ligands. As a potential improvement upon TZDs, selective modulators of PPAR-γ (SPPARγMs) represent a "second generation" of PPAR-γ ligands that have been shown to provide comparable glucose-lowering efficacy with improved tolerability in preclinical species [67••]. Identification of such ligands is currently a significant focus for many pharmaceutical firms and several have advanced into clinical trials.

Recently disclosed compounds include SPPARγM 24 [69] and FK614 (currently in phase II) [70]. Both are potent SPPARγMs, exhibiting robust efficacy in rodent models of diabetes and improved therapeutic profiles relative to PPAR-γ full agonists. MBX-102 and telmisartan [71,72] have also have been characterized as SPPARγMs with improved therapeutic properties. More recently, T131, another potent SPPARγM currently in phase II, was reported to raise adiponectin levels (a potential biomarker for efficacy) in normal male volunteers in a dosage- and time-dependent manner [73]. However, unambiguous data demonstrating that SPPARγMs exhibit comparable or superior efficacy in the treatment of patients with T2DM, while providing an enhanced safety profile in comparison with currently available TZDs, remain pending.

Conclusions

The ability of PPARs to mediate a wide range of metabolic and therapeutic actions has made them a central focus of pharmacologic and genetic research for more than a decade. In the clinic, PPAR-γ agonists have demonstrated

efficacy in ameliorating insulin resistance and hyperglycemia, whereas PPAR-α agonists have provided significant antidyslipidemic and antiatherosclerotic outcomes. Recent preclinical data suggest that PPAR-δ ligands may beneficially impact on circulating lipids, insulin resistance, and obesity. Ongoing pharmaceutical research continues to seek out PPAR ligands with superior therapeutic windows and more extensive metabolic actions. SPPARγMs hold the potential to serve as more tolerable T2DM therapy than currently available TZDs, whereas PPAR-α/-γ agonists show promise in the simultaneous treatment of diabetic hyperglycemia and dyslipidemia. Continuing efforts to delineate PPAR physiology, pharmacology, and functional genomics will embellish our understanding of the beneficial and adverse effects of modulating their activity and should provide superior ligands with increased therapeutic impact. In addition, a broader goal exists to develop a better understanding of the interrelationships between the individual clinical features of MS and how they impact on patient morbidity and mortality. Such knowledge is expected to facilitate future research efforts aimed at developing novel therapies for the treatment of MS.

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