

Dual Acting and Pan-PPAR Activators as Potential Anti-diabetic Therapies

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Abstract The thiazolidinedione PPAR- γ activator drugs rosiglitazone and pioglitazone suppress insulin resistance in type 2 diabetic patients. They lock lipids into adipose tissue triglyceride stores, thereby preventing lipid metabolites from causing insulin resistance in liver and skeletal muscle and β -cell failure. They also reduce the secretion of inflammatory cytokines such as TNF α and increase the plasma level of adiponectin, which increases insulin sensitivity in liver and skeletal muscle. However, they have only a modest effect on dyslipidaemia, and they increase fat mass and plasma volume. Fibrate PPAR- α activator drugs decrease plasma triglycerides and increase HDL-cholesterol levels. PPAR- δ activators increase the capacity for fat oxidation in skeletal muscle.

Clinical experience with bezafibrate, which activates PPAR- δ and - α , and studies on the PPAR- α/δ activator tetradecylthioacetic acid, the PPAR- δ activator GW501516, and combinations of the PPAR- α activator fenofibrate with rosiglitazone or pioglitazone

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have encouraged attempts to develop single molecules that activate two or all three PPARs. Most effort has focussed on dual PPAR- α/γ activators. These reduce both hyperglycaemia and dyslipidaemia, but their development has been terminated by issues such as increased weight gain, oedema, plasma creatinine and myocardial infarction or stroke. In addition, the FDA has stated that many PPAR ligands submitted to it have caused increased numbers of tumours in carcinogenicity studies.

Rather than aiming for full potent agonists, it may be best to identify subtype-selective partial agonists or compounds that selectively activate PPAR signalling pathways and use these in combination. Nutrients or modified lipids that are low-affinity agonists may also have potential.

Keywords Fibrate · Insulin sensitiser · Peroxisome proliferator-activated receptor · PPAR- α/γ activator · Thiazolidinedione

1 Introduction

The discovery of the three peroxisome proliferator-activated receptors (PPARs) as nuclear receptors functioning as lipid sensors hinged on the discovery of certain thiazolidinediones as insulin sensitiser agents. The original discovery stemmed from the finding by Takeda toxicologists that a potential triglyceride lowering agent of the fibrate type in which the carboxylate moiety was replaced by the acidic mimetic thiazolidinedione maintained normoglycaemic levels during long-term toxicology studies, whereas ageing control animals developed hyperglycaemia. Subsequent structure activity studies resulted in the compound ciglitazone. Further structure activity work at Sankyo, Beecham, and Takeda resulted in three compounds being progressed to market. These were troglitazone, which was subsequently withdrawn as a result of a liability for liver damage in some patients, rosiglitazone and pioglitazone.

It was the availability of these compounds, particularly the more potent agent rosiglitazone (then called BRL49653), that allowed the identification of the nuclear receptor PPAR- γ as the target for the thiazolidinedione insulin sensitiser drugs (Lehmann et al. 1995).

The three PPAR receptors [PPAR- α , PPAR- β (also called PPAR- δ , fatty acid-activated receptor) and PPAR- γ] form a subfamily of nuclear receptors. They function as lipid sensors and coordinate the regulation of expression of a large number of genes associated with metabolism. Each of the PPARs forms an obligate heterodimer with another nuclear receptor called the retinoid X receptor (RXR), which binds to peroxisome proliferator response elements (PPREs) that are located within the regulatory domains of target genes. Activation of the PPAR by an appropriate ligand results in recruitment of co-activators and loss of co-repressors that remodel the chromatin and activate transcription (Desvergne and Wahli 1999).

2 PPAR- γ

Although PPAR- γ is widely expressed in tissues, it is present in high concentrations in adipose tissue (Fajas et al. 1997). It is essential for adipocyte differentiation and promotes lipid accumulation in adipocytes (Tontonoz et al. 1994). Moreover, adipose-specific knock-out of PPAR- γ in mice results in adipocyte hypocellularity and the development of insulin resistance in liver but not in muscle (He et al. 2003).

The anti-diabetic thiazolidinediones suppress endogenous insulin resistance in adipose tissue but also have effects in liver and muscle despite low concentrations of PPAR- γ in these tissues. As noted above, the effect in liver is probably indirect and it is noteworthy that insulin-resistant, muscle-specific PPAR- γ null mice respond to the insulin sensitising effects of PPAR γ activators such as the thiazolidinediones (Hevener et al. 2003; Norris et al. 2003).

Gene expression studies have shown that the thiazolidinedione insulin sensitizers alter the expression of genes involved in lipid uptake, lipid metabolism and insulin action in adipocytes resulting in increased lipid accumulation in adipose tissue and decreased release of free fatty acids. This partitions lipid away from liver and muscle and reverses lipotoxicity-induced insulin resistance in these tissues (Mayerson et al. 2002; Spiegelman 1998).

A consequence of the adipocentric mechanism of action is a gain in fat mass. This is seen in animal models as well as in clinical studies. However, the PPAR- γ activators function as adipose site remodelling agents with a redistribution of fat from large insulin-resistant, lipolytic visceral fat adipocytes to small, newly differentiated insulin-responsive subcutaneous adipocytes (Kawai et al. 1999). This is consistent with human probands with inhibitory PPAR- γ mutations having decreased subcutaneous fat but increased visceral fat together with hyperglycaemia and insulin resistance (Hegele et al. 2002).

In addition to their effects on lipid metabolism, thiazolidinediones have a major effect on the secretion of adipokines. Thus, they reduce the secretion of inflammatory cytokines and chemokines that promote insulin resistance, such as TNF α . These actions occur in both the adipocyte and associated macrophages. Other adipokines are up-regulated, particularly adiponectin, which is known to potentiate insulin sensitivity in liver and skeletal muscle (Berg et al. 2001; Yamauchi et al. 2001). The effects of the thiazolidinedione insulin sensitizers in improving insulin sensitisation in liver and muscle are likely to be mediated in part through alterations in adipokine gene expression through PPAR- γ receptor activation.

Diabetes in animals and humans does not occur unless there is an islet cell malfunction. Thus, in the presence of a fully operational pancreatic islet, obesity-induced insulin resistance will result in impaired glucose tolerance but not frank diabetes. There is growing evidence that lipotoxicity plays an important role in pancreatic islet β -cell failure. By reversing the lipotoxicity, there is an inhibition of apoptosis in the islet cell and an increase in β -cell mass (Han et al. 2008; Ishida et al. 2004; Zeender et al. 2004). Indeed, analyses of diabetes prevention trials have

demonstrated that pioglitazone and rosiglitazone are able to reverse β -cell decline in pre-diabetic populations (DeFronzo 2009).

In addition to macrophages, PPAR- γ is expressed in endothelial cells, vascular smooth muscle cells and macrophage-derived foam cells that form the cells of atherosclerotic lesions. Consequently, it has been hoped that activating PPAR- γ might have important anti-atherosclerotic effects. Indeed, PPAR- γ ligands have been shown to decrease the size of atherosclerotic lesions in low-density lipoprotein receptor null mice (Li et al. 2000) and in apolipoprotein E null mice (Chen et al. 2001). The mechanism of this effect appears to relate to the anti-inflammatory properties of PPAR- γ activators together with reduced levels of chemotaxis and promotion of apoptosis. In humans, there has been a clear demonstration that treatment of type 2 diabetes mellitus (T2DM) patients with PPAR- γ activators reduces levels of inflammatory biomarkers of cardiovascular disease. However, a reduction in cardiovascular disease has not been categorically shown. Indeed, there have been claims that rosiglitazone increases macrovascular disease, based on a meta-analysis (Nissen and Wolski 2007) study. This analysis has been criticised on the statistical grounds and that it included a high proportion of trials, which had a very low number of cardiovascular incidents and excluded trials where there was no incidence of macrovascular disease or death. The Food and Drug Administration (FDA) analysis reported by Dr Mahoney at the American Diabetes Meeting in 2008 found no evidence of increased cardiovascular events in patients taking either rosiglitazone or pioglitazone.

3 PPAR- α

The first identified PPAR receptor was PPAR- α , activation of which was associated with increased liver weight in rodents but not in humans. PPAR- α is the molecular target for the fibrate hypolipidaemic agents such as fenofibrate and gemfibrozil.

PPAR- α is highly expressed in liver and activation of the receptor results in increased hepatic lipid uptake and oxidation. Thus, the phenotype of the PPAR- α knock-out mouse in the fasted state is hypoglycaemia, hypoketonaemia, hypertriglyceridaemia and hepatic steatosis (Kersten et al. 1999).

Activators of PPAR- α are used to treat dyslipidaemia. They decrease plasma triglyceride levels and increase high-density lipoprotein cholesterol (HDL-C) levels (Plutzky 2000). The latter effect is probably mediated by augmentation of hepatic production of major components of HDL-C, namely apolipoprotein AI and AII (Vu-Dac et al. 1994, 1995).

It is also possible that, like PPAR- γ activators, PPAR- α activators might have a direct vascular protective effect through action at the PPAR- α receptor in endothelial cells resulting in blockade of cytokine-induced cell adhesion. Moreover, by increasing the expression of the HDL receptor CLA-1/SR-BI (Chinetti et al. 2000) and the cholesterol transporter ABCA1 (Chinetti et al. 2001), they promote cholesterol efflux from the macrophages. Through all of these mechanisms, PPAR- α

activators have been shown to reduce the progression of atherosclerosis and decrease the incidence of coronary events in several major clinical studies.

4 PPAR- δ

Unlike PPAR- α and PPAR- γ , PPAR- δ is ubiquitously expressed but its pharmacology is less understood than that of the other subtypes. PPAR- δ knock-out mice show an obese phenotype when fed on a high fat diet. Over-expression of PPAR- δ or over-activation by the selective ligand GW501516 resulted in induction of oxidative, mitochondrial rich type 1 muscle fibres that allowed the mice to undertake greater levels of running activity – the so-called marathon mouse (Wang et al. 2004). These transgenic mice were also resistant to diet-induced obesity and insulin resistance. GW501516 also attenuates weight gain and insulin resistance in mice fed on high fat diets. This action appears to result from an increase in the expression of genes in skeletal muscle that promote lipid catabolism and mitochondrial uncoupling resulting in increased β -oxidation of fatty acids in skeletal muscle (Tanaka et al. 2003).

5 Logic for Dual and Triple PPAR Activators in the Treatment of Diabetes and Insulin Resistance

T2DM patients generally are overweight or obese and may additionally be dyslipidaemic. The major cause of mortality in diabetic patients is atherosclerotic macrovascular disease culminating in myocardial infarction. These events are linked to the diabetic dyslipidaemia. Unfortunately, the currently available PPAR- γ insulin sensitisers provide only negligible or modest effects on lipid parameters.

In addition to the weak effects on plasma lipids, the thiazolidinediones rosiglitazone and pioglitazone have been associated with adverse effects including plasma volume expansion, haemodilution, oedema, increased adiposity and weight gain and increased fat deposits in bone marrow (Yki-Jarvinen 2004). These undesirable side effects and the potential to cause congestive heart failure in a subset of diabetic patients with underlying cardiopathies and bone fractures have enhanced the search for PPAR- γ activators with an improved therapeutic window. One approach, based on selective oestrogen receptor modulators, which have equal efficacy, but less toxicity than full agonists at the oestrogen receptor (Miller 2002), has been to seek selective PPAR- γ activators, so-called SPPAR- γ modulator or SPPARMs. An alternative approach is to combine PPAR subtypes to enhance the metabolic effects (see Table 1). Thus, combining PPAR- α and PPAR- γ should lead to additional anti-hyperglycaemic effects by increasing hepatic fatty acid oxidation, alleviation of the dyslipidaemia and enhanced anti-atherosclerotic profile. By combining PPAR- γ

Table 1 Principal location of PPAR subtypes and metabolic effects

	PPAR- α	PPAR- γ	PPAR- δ
Location	Liver endothelial cells	Adipocytes vascular cells	Skeletal muscle
Main actions in target tissues	\uparrow FA uptake \uparrow FA oxidation \uparrow Apo AI, Apo AII	\uparrow FA uptake \downarrow FA release \downarrow Pro-inflammatory cytokines	\uparrow FA oxidation \uparrow Mitochondrial genesis
Consequential effects	\downarrow Circulating TG \uparrow HDL-C \downarrow Atherosclerosis \downarrow Liver fat	\uparrow Insulin action \downarrow Insulin resistance \uparrow Body weight gain \uparrow Vasoprotection	\downarrow Body fat \downarrow Circulating TG \uparrow HDL-C \uparrow Insulin action

FA fatty acid, TG triglyceride, HDL-C HDL-cholesterol

and PPAR- δ , one might expect a further improvement in insulin sensitivity with less or no weight gain and an improved ability to exercise and gain the beneficial effects of exercise. Clearly, there is also the potential to combine activation of all three PPAR receptors. Work to date has largely been to try to find dual or triple activator activity in a single molecule. This is an enormous challenge in obtaining acceptable therapeutic indices with regard to the potential receptor-mediated adverse effects. However, since there are currently both PPAR- γ activators (rosiglitazone and pioglitazone) and PPAR- α activators (fenofibrate) on the market, it is logical to examine the clinical effects of this combination.

6 The Bezafibrate Experience

Bezafibrate has been available for many years. It has been shown to be a good activator of PPAR- δ and - α but is only a weak activator of PPAR- γ (Krey et al. 1997). Elkeles et al. (1998) examined the effect of bezafibrate in diabetic patients given conventional diabetes treatment (diet and/or oral hypoglycaemic agents – presumably sulphonylureas and/or metformin but not glitazones, as the study was undertaken pre-marketing of these agents). The bezafibrate treatment was associated with significant reductions over 3 years in serum triglycerides, total cholesterol and total to HDL-cholesterol ratio and an increase in HDL-cholesterol. There was a trend to reduce fibrinogen. However, there was no effect on the progression of ultrasonically measured arterial disease. In general, the incidence of coronary heart disease in studies using bezafibrate has tended to be lower, but did not reach statistical significance (Tenenbaum et al. 2005a). However, in patients with metabolic syndrome and a history of recent myocardial infarction and/or stable angina, bezafibrate reduced the incidence of myocardial infarction and cardiac mortality (Tenenbaum et al. 2005b).

Beneficial effects of bezafibrate on glucose and insulin have been demonstrated by showing that there was a decreased incidence and delayed onset of T2DM in patients with impaired fasting glucose concentrations (Tenenbaum et al. 2004) and in obese patients (Tenenbaum et al. 2005c). However, studies on the treatment of patients with T2DM are lacking.

7 Use of Combined Therapy with Fenofibrate and Glitazones

Since fenofibrate is a potent PPAR- α activator, it is logical that the combination of this agent with the marketed glitazones should be examined in clinical studies. These clinical studies followed a mouse study (Carmona et al. 2005) in which C57Bl/6 *ob/ob* mice were given fenofibrate, rosiglitazone or the combination. Co-administration of fenofibrate prevented weight gain and increased fat mass induced by rosiglitazone. Although fenofibrate decreased blood glucose in *ob/ob* mice, it had no effect on plasma insulin, whereas, like rosiglitazone, both glucose and insulin concentrations were reduced by the combined treatment.

The published clinical studies were investigational rather than establishing therapeutic benefit. Thus, Boden et al. (2007) treated eight patients with rosiglitazone (8 mg/day) plus fenofibrate (160 mg/day) for 2 months and compared them with five rosiglitazone patients from an earlier study. The combination produced the benefits of the individual components on glycaemic and lipid parameters and surprisingly showed prevention of the fluid retention associated with rosiglitazone. A better controlled study examined the effect of fenofibrate or pioglitazone for 3 months followed by the addition of the other agent for 3 months in an open-label study (Bajaj et al. 2007). Pioglitazone alone decreased fasting blood glucose and HbA_{1C}, increased adiponectin and insulin-stimulated glucose disposal and reduced fasting plasma free fatty acids, triglycerides and hepatic fat content. Fenofibrate had no effect on any glycaemic parameter and the only lipid change was a fall in plasma triglycerides. Addition of pioglitazone to fenofibrate therapy resulted in all the benefits of pioglitazone being shown, whereas addition of fenofibrate to pioglitazone therapy only gave a further lowering of plasma triglycerides.

In a third trial involving 40 T2DM patients with poor metabolic control, the patients received rosiglitazone (4 mg/day) for 12 weeks on top of their existing therapy. Later, 200 mg/day fenofibrate was added for a further 12 weeks. The addition of fenofibrate did not significantly affect the HbA_{1C} level, but the change in LDL-cholesterol level became highly significant. Overall, the concomitant administration of rosiglitazone and fenofibrate did not produce significant improvement in glycaemic control relative to rosiglitazone alone. However, the combination did improve the atherogenic dyslipidaemic profile. Fenofibrate addition did not reverse the effect of rosiglitazone on body mass index (Seber et al. 2006).

Whilst these results are encouraging, large double-blind trials are needed to elucidate any advantage of combining fenofibrate with rosiglitazone or pioglitazone.

8 Dual PPAR- α / γ Activator Drugs

A number of pharmaceutical companies have attempted to develop compounds with dual PPAR- α and - γ activity. It is a difficult task, however, to predict the appropriate balance between these activities without undertaking whole animal, let alone clinical, studies.

Some of the compounds are listed in Table 2. As can be seen, many of the compounds have been discontinued, largely as a result of side effects rather than lack of therapeutic efficacy.

The compounds were all selected for entry into clinical studies following studies in rodents. These studies concentrated on showing efficacy at least similar to rosiglitazone and pioglitazone, although there were few direct comparisons. Some showed additional effects. Thus, Oakes et al. (2005) demonstrated that tesoglitazar gave improved lipid tolerance, reduced hepatic triglyceride secretion and enhanced plasma triglyceride clearance. The same compound was found to increase the clearance of non-esterified fatty acids (NEFA) under both basal and elevated NEFA availability (Hegarty et al. 2004). Their data produced the first direct evidence that a dual activator increased the ability of white fat, liver and skeletal muscle to use fatty acids whilst also improving insulin action in these tissues.

Guo et al. (2004) found that the experimental Merck compound TZD 18 [5-(3-[3-(4-phenoxy-2-propylphenoxy)propoxy]phenyl)-2,4 thiazolidinedione] lowered cholesterol and triglycerides in hamsters and dogs (which are better models for human lipid metabolism) and induced the genes for fatty acid degradation and triglyceride clearance. The authors also demonstrated complete normalisation of glycaemic control in diabetic *db/db* mice. Also, this compound appears generally well balanced between potency at PPAR- α and - γ receptors, but does have some activity at the PPAR- δ receptor, at least against the human receptor. The authors showed 100-fold higher potency for transactivation of both human PPAR- α and - γ versus human PPAR- δ but surprisingly did not test against the rodent receptor.

Table 2 Dual PPAR- α / γ activators that have been in clinical development

Muraglitazar	BMS	Approved then withdrawn from market
Tesoglitazar	AstraZeneca	Discontinued following phase III trials
Ragaglitazar	Dr Reddy	Discontinued 2003
Chiglitazar	Shenzhen Chipscreen, China	Development suspended
MK-767/KRP-297	Merck/Kyorin	Discontinued 2003
TZD 18	Merck	Unknown
PAR-5359	Dong-A, Korea	Pre-clinical
E3030	Eisai, Japan	Phase II?
Cevoglitazar	Novartis	Discontinued 2008
Aleglitazar	Hoffman-La-Roche	Phase III 2010
TAK-559	Takeda	Discontinued 2005
Naveglitazar	Lilly	Phase II?
AVE-0847	Aventis	Phase II?
Sipoglitazar	Takeda	Discontinued 2006

Chira et al. (2007) tested the ability of tesaglitazar to reduce atherosclerosis in a mouse model on the basis that activation of vascular cell PPAR- α and - γ would provide anti-inflammatory and anti-proliferative effects. LDL-receptor null mice fed on a “Western-type” diet for 12 weeks results in marked and predictable atherosclerotic lesions. Co-administration of tesaglitazar with the diet reduced atherosclerosis in female but not male mice without affecting cholesterol or triglyceride levels. Extension of these studies showed that tesaglitazar could reduce the effect of cholesterol on atherosclerosis and block the progression of pre-existing atherosclerosis in APOE*3 Leiden CETP transgenic mice (van der Hoorn et al. 2009; Zadelaar et al. 2006). The authors found that tesaglitazar reduced plasma cholesterol and triglycerides and the mass and activity of cholesterol ester transfer protein (CETP) and increased HDL-cholesterol. Moreover, it reduced vessel wall inflammation, modified lesions to a more stabilised phenotype and completely blocked progression of the pre-existing lesions.

Muraglitazar has a similar potency at human PPAR- α and PPAR- γ receptors in transactivation assays (EC_{50} 0.28 and 0.16 μ M, respectively). It has a similar potency to rosiglitazone at hPPAR- γ (EC_{50} 0.06 μ M). Rosiglitazone has negligible potency at PPAR- α (Mitra et al. 2007). Pre-clinical studies have largely focussed on animal models of diabetes such as *db/db* mice in which potent anti-diabetic effects, preservation of pancreatic islet insulin content, reduced hyperlipidaemia and hepatic steatosis were shown (Harrity et al. 2006). In follow-up studies, muraglitazar was found to prevent both the development of diabetes in *db/db* mice, including loss of normal β -cell morphology and function, and the deterioration of established diabetes (Tozzo et al. 2007). Treatment of mice with PPAR- γ activators increases weight gain in diabetic animals. This is particularly the case in *db/db* mice and arises from both oedema and adipogenesis. The question whether the addition of PPAR- α activity might reduce weight gain was raised. In fact, muraglitazar had a greater potential than rosiglitazone on weight gain and this involved both oedema and adipogenesis (Mitra et al. 2007). The oedema was coincident with increased expression of mRNA for Enac γ and Na⁺, K⁺-ATPase in kidneys, mediated by PPAR- γ .

Ragaglitazar also showed similar potency to rosiglitazone in the human PPAR- γ transactivation assay (Chakrabarti et al. 2003). Despite this, it appears more active than rosiglitazone and fenofibrate in head-to-head studies in Zucker *fa/fa* rats, high fat-fed hyperlipidaemic rats and high fat-fed hamsters. Moreover, in a late-stage intervention study in ZDF diabetic rats, ragaglitazar reduced HbA_{1c} by 2.3% compared with 1.1% by rosiglitazone (Brand et al. 2003).

A series of dual activators have been examined in other pre-clinical studies giving similar results. These include chiglitazar (Li et al. 2006), PAR 5359 (Kim et al. 2008), E3030 (Kasai et al. 2008), cevoglitazar (Laurent et al. 2009), and aleglitazar (Benardeau et al. 2009). Takeda attempted to take predictive pre-clinical work a step forward by undertaking rhesus monkey studies in a well-defined colony that is representative of humans and found improvements in glycaemic and lipid parameters without weight gain. Although suggestive that further human trials were warranted, the work was published 2 years after Takeda announced that

development was discontinued due to the lack of a sufficiently positive benefit/risk relationship in clinical studies (Ding et al. 2007).

Clinical studies on muraglitazar showed that the 5 mg dose reduced HbA_{1C} levels significantly more than pioglitazone (30 mg) in metformin-treated patients with T2DM in a phase III study (Kendall et al. 2006). Significant improvements over pioglitazone therapy were also seen in plasma triglycerides, apolipoprotein B, non-HDL-cholesterol and in increasing HDL-cholesterol. However, weight gain was greater with muraglitazar as was the oedema incidence.

Analysis of the phase II and phase III trial data in yet another meta-analysis by Nissen et al. (2005) indicated that death, myocardial infarction or stroke occurred in 35 out of 2,374 patients on muraglitazar as opposed to 9 out of 1,351 in the combined placebo- and pioglitazone-treated patients. The incidence of chronic heart failure was 13 out of 2,374 (0.55%) in muraglitazar-treated patients and 1 out of 1,351 in the controls. Both BMS and its marketing partner Merck abandoned the drug.

Measured by number of publications, clinical studies on tesaglitazar have been more extensive than on muraglitazar, although the total number of patients has been of a similar order. Tesaglitazar (0.5 or 1.0 mg/day) gave consistent improvements in glycaemic control and in lipid parameters, but studies reported consistent increases in serum creatinine levels, peripheral oedema and weight gain (Bays et al. 2007; Goke et al. 2007; Goldstein et al. 2006; Ratner et al. 2007; Schuster et al. 2008; Wilding et al. 2007).

As a result of the elevated creatinine levels found in its first four of eight phase III studies (Gallant 6-9) and the associated decrease in glomerula filtration rate, AstraZeneca decided to terminate its development programme on tesaglitazar on the basis that the overall benefit/risk profile was unlikely to offer patients significant advantage over marketed therapies.

9 Outlook for Dual PPAR- α / γ Activators

The data to date show that adding PPAR- α activation to the PPAR- γ profile results in improved lipid profile. However, it is clearly a very difficult task to obtain a balance of two separate properties in a single molecule. The logical approach would be to develop the safest and most appropriate PPAR- α activator and co-administer it with the safest and most efficacious PPAR- γ activator.

It is clear that the therapeutic window for PPAR- γ activation is quite narrow. It seems likely that muraglitazar and tesaglitazar failed largely because of their potency in PPAR- γ activation. The same probably applies to ragaglitazar. With hindsight the liabilities were probably apparent in pre-clinical studies.

Improving insulin sensitivity has added a powerful armamentarium to the treatment of diabetes and as yet the thiazolidinediones such as rosiglitazone and pioglitazone are the only drugs that are clinically proven to suppress pancreatic β -cell failure (DeFronzo 2009). Now that the claim of adverse cardiovascular

mortality has been discredited, the side effects of these drugs of weight gain and water retention can be managed and the drugs should not be given to potential congestive heart failure patients. However, there still remains the issue of potential fractures in women through a reduction in bone mineral density (Glintborg et al. 2008).

The therapeutic challenge for the pharmaceutical industry is to develop novel PPAR- γ activators with the therapeutic efficacy in improving insulin sensitivity, but with a lower risk of weight gain through adipogenesis and water retention. It seems unlikely that this will be achieved through a conventional full agonist and therefore researchers have focussed on partial agonists or so-called SPPARMs (selective PPAR- γ modulators) such as metaglidase (Chandalia et al. 2009). This agent is claimed to retain PPAR- γ -related anti-diabetic properties in the absence of weight gain and oedema and selectively modulates a subset of PPAR- γ target genes.

10 PPAR-Pan Activators and PPAR- δ Dual Activators

Earlier in this chapter, it was noted that bezafibrate was a pan-PPAR activator, although its PPAR- γ activation relative to PPAR- α and - δ was weak. This has prompted companies to seek single compounds with all three activities (Evans et al. 2005). Typically, these companies have used high throughput screening systems and adopted their usual approach of seeking compounds with high potency at each receptor. Seeking a compound with high potency at one receptor is a challenge, but seeking one compound with high potency and efficacy at three receptors is an “Everest of a task” and potentially likely to produce toxic liabilities. It may be better to seek low-affinity compounds. One such low-affinity ligand is tetracycloacetic acid (Bocos et al. 1995). In clinical studies in T2DM patients, it improved the lipid profile but had no effect on glucose metabolism possibly because it is predominantly PPAR- α /- δ with little PPAR- γ activity (Lovas et al. 2009; Rost et al. 2009).

The development of PPAR- α /- δ and PPAR- γ /- δ dual activators has not taken off in the same way as PPAR- α /- γ . This is possibly because the structure–activity around the PPAR- δ receptor has not been fully addressed. However, the studies to date on PPAR- δ suggest that it could be a good target to go alongside PPAR- γ in the treatment of T2DM, which is almost exclusively an obese population (Barish et al. 2006; Lee et al. 2006). Thus, Oliver et al. (2001) found that GW501516 increased the expression of the reverse cholesterol transporter ATP-binding cassette A1 and induced apolipoprotein A1-specific cholesterol efflux. In insulin-resistant, obese, middle-aged rhesus monkeys, GW501516 caused a dramatic and dose-dependent rise in serum HDL-C while lowering the levels of small-dense low-density lipoprotein, fasting triglycerides and insulin. In a recent clinical study (Riserus et al. 2008), GW501516 (10 mg/kg o.d.) given to overweight, but otherwise healthy, men for 2 weeks resulted in significant reductions in fasting plasma triglycerides (–30%), apolipoprotein B (–26%), LDL-cholesterol (–23%), and insulin (–11%).

There was a 20% reduction in liver fat and a 30% reduction in liver isoprostanes; HDL-cholesterol was unchanged. Biopsy samples of skeletal muscle and a 6 h meal tolerance test with stable fatty acid isotopes revealed more exhaled carbon dioxide coming from the meal and increased expression of carnitine palmitoyl transferase 1b. Together, these data support PPAR- δ activators increasing fat oxidation in skeletal muscle.

It is suggested that the identification of a safe and effective PPAR- δ activator would be a good partner for PPAR- γ activators in the treatment of T2DM and the metabolic syndrome.

11 Cancer Liability of PPAR Activators

A large number of PPAR ligands have been submitted to the US FDA over the past 15 years. Many of these, but not all, have been subsequently shown to cause an increased number of tumours in carcinogenicity studies. This involves multiple tumour types in mice and rats of both sexes and multiple strains. The site of tumour development is consistent with the distribution of the PPAR receptors, e.g. adipose, vascular endothelium, bladder, skin, and renal tubules. Consequently, the FDA has been requesting performance of 2-year carcinogenicity studies prior to the initiation of clinical studies longer than 6 months (Aoki [2007](#)).

12 Concluding Remarks

The development of dual and triple activators of PPAR receptors has proved to be difficult and to date no compound that is able to favourably influence the benefit/risk ratio relative to current treatments for T2DM including the thiazolidinediones, rosiglitazone, and pioglitazone has been identified. The widespread involvement of PPAR receptors as lipid sensors that regulate fatty acid and carbohydrate metabolism, together with knowledge that the natural ligands are almost certainly low-affinity activators, perhaps suggests that the standard pharmaceutical approach of seeking high-affinity ligands might be doomed to failure. This is likely to apply even more to a search for high-affinity dual or triple activators.

Despite these reservations, there appears to be potentially significant clinical benefits in adding either PPAR- α or PPAR- δ activation to the existing profile of the PPAR- γ -mediated insulin sensitisers.

Perhaps the best approach would be to identify subtype-selective partial agonists or SPPARMs for each receptor and use these clinically in appropriate combinations. Meanwhile, there may be scope for identifying nutrients or modified lipids that are low-affinity compounds that could be either used as pharmaceuticals or incorporated into foods such as spreads, ice cream, etc.

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Diabetes - Perspectives in Drug Therapy

Schwanstecher, M. (Ed.)

2011, XIII, 408 p. 69 illus., Hardcover

ISBN: 978-3-642-17213-7