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MINIREVIEW

PPAR-α and Insulin Sensitivity

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Summary

Peroxisome proliferator-activated receptors (PPAR) belong to the nuclear receptor superfamily of ligand-activated transcription factors. PPAR-α, first of its three subtypes (α, β, γ) has traditionally been considered an important regulator of lipid metabolism while its role in the regulation of insulin sensitivity has not been recognized until recently. Here we summarize the experimental and clinical studies focusing on the role of PPAR-α in the regulation of insulin sensitivity. In most of the experimental studies the activation of PPAR-α in rodents leads to improvement of insulin sensitivity by multiple mechanisms including improvement of insulin signaling due to a decrease of ectopic lipids in non-adipose tissues and decrease of circulating fatty acids and triglycerides. In contrast, the effect of PPAR-α agonist in humans is much less pronounced probably due to a lower expression of PPAR-α relative to rodents and possibly other mechanisms. Further clinical studies using more potent PPAR-α agonists on a larger population need to be performed to evaluate the possible role of PPAR-α in the regulation of insulin sensitivity in humans.

Key words

Peroxisome proliferator-activated receptor-alpha • Insulin sensitivity • Obesity• Adipose tissue

Introduction

Peroxisome proliferator-activated receptors (PPAR) belong to the nuclear receptor superfamily of ligand-activated transcription factors. These receptors have been implicated in diverse metabolic pathways such as lipid and glucose homeostasis, control of cellular proliferation and differentiation etc. PPARs, similarly to other nuclear receptors, interact with a number of nuclear proteins known as co-activators and co-repressors and subsequently heterodimerize with retinoid-receptors X (RXR) to form PPAR-RXR complex. This complex binds to cognate DNA elements called PPAR response elements and leads to activation and repression of numerous genes involved in the above mentioned metabolic pathways.

The name of PPAR has been derived from its ability to stimulate the proliferation of peroxisomes – organelles involved in the β-oxidation of long chain fatty acids – in rodents (Kersten *et al.* 2000). The proliferation of peroxisomes in rodents is accompanied by marked hepatomegaly and increases the transcription of genes

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involved in both peroxisomal and microsomal oxidation of fatty acids (Anderson *et al.* 2001). While this is true for rodents, peroxisome proliferation does not occur in humans.

To date, three different PPAR subtypes have been identified: PPAR-α, PPAR-β/δ and PPAR-γ. While PPAR-α has traditionally been recognized for its involvement in the regulation of lipid oxidation (Fruchart *et al.* 2001), PPAR-β/δ plays a role in the development, embryo implantation, myelinization of corpus callosum, epidermal cell proliferation and lipid metabolism (Peters *et al.* 2000). On the contrary, PPAR-γ is an essential regulator of adipocyte differentiation, regulating thus indirectly glucose and lipid homeostasis (Kubota *et al.* 1999). Moreover, activation of PPAR-γ in the liver and muscle tissues can according to some studies directly affect lipid handling and glucose metabolism (Matsusue *et al.* 2003). In addition to the above mentioned effects numerous other potential functions of PPARs have been described including those in the regulation of tumor growth, inflammation and others (Mueller *et al.* 1998, Su *et al.* 1999, Vamecq and Latruffe 1999).

Adipose tissue and insulin resistance: the potential of PPAR-α agonist to improve insulin sensitivity

The prevalence of obesity, insulin resistance, type 2 diabetes and related complication referred to as Reaven or Metabolic syndrome is increasing in virtually all developed countries of western world (O'Rahilly 1997). Over the last fifteen years considerable progress has been reached in understanding molecular mechanism of insulin resistance – a central defect in the etiopathogenesis of the metabolic syndrome. It has been found that adipose tissue plays a very important role in the onset and development of insulin resistance by several distinct mechanisms (Shulman 2000). The most important one is based upon the spillover of triglycerides and/or other lipid metabolites into non-adipose tissues such as muscles, liver and pancreas as a result of chronic energy overload of adipocytes in obese subjects (Saltiel 2001). This ectopic lipid deposition significantly interferes with intracellular insulin signaling cascade in the muscle and liver, thus directly inducing insulin resistance. Increased lipid content in the pancreatic islets of Langerhans impairs insulin secretion through the induction of β-cell apoptosis and numerous other mechanisms (Unger and Zhou 2001). A second mechanism connecting adipose tissue to insulin resistance is the increased release of free fatty acids into the circulation that in turn may induce insulin resistance in the muscle and possibly in the liver (Boden and Shulman 2002, Roden *et al.* 2000). Numerous studies have shown that increased free fatty acids can give rise to insulin resistance by several mechanisms that may or may not occur simultaneously. The original hypothesis of Randle *et al.* (1963) explaining decreased glucose metabolization by substrate competition with free fatty acids has been partially revised (Cline *et al.* 1999) because the defect already occurs at the levels of glucose transport inside cells rather than on the level of its intracellular metabolization as originally suggested. In some studies, direct effect of increased free fatty acids on the key enzymes involved in glucose metabolism such as glycogen synthase, glucokinase, hexokinase and others have been suggested (Perseghin *et al.* 2003).

Finally, adipose tissue produces several hormones that regulate energy homeostasis, lipid and glucose metabolism such as leptin, adiponectin, resistin, tumor necrosis factor-α and others (Hotamisligil *et al.* 1993, Havel 2002, Haluzík *et al.* 2004c). Disturbances in the production of these factors may contribute to the development of insulin resistance or impaired insulin secretion in patients with type 2 diabetes.

Numerous experimental and clinical studies have shown a close correlation between insulin sensitivity and ectopic lipid storage in the muscle and liver (Ravussin and Smith 2002). Therefore, the decreasing ectopic lipid content in non-adipose tissues by promoting its tissue oxidation would represent a logical approach to improve insulin sensitivity.

PPAR-α and insulin sensitivity: experimental studies

Although PPAR-α is a key regulator of lipid oxidation and as such could indirectly influence glucose metabolism, its effects on insulin sensitivity have not been extensively studied until recently. Exogenous PPAR-α agonists (fibrates) have been traditionally used as hypolipidemic agents with most prominent effects on circulating triglyceride levels (de Faire *et al.* 1996). Guerre-Millo *et al.* (2000) were the first investigators who demonstrated that the treatment of obese rodents (leptin-deficient ob/ob mice and Zucker diabetic rats) with PPAR-α agonist decreased body fat, blood glucose and insulin levels suggesting an improvement of insulin

sensitivity. The mechanism of the PPAR-α agonist effects has not been elucidated in this study, but these authors proposed that increased lipid oxidation with subsequent reduction of ectopic lipid storage may have been involved.

We have used the euglycemic-hyperinsulinemic clamp to differentiate the tissue specificity of insulin-sensitizing effects of PPAR-α agonists in two mouse models of insulin-resistance: lipoatrophic A-ZIP/F-1 mice and MKR mice overexpressing the dominant-negative IGF-1 receptor isoform in the skeletal muscle (Chou *et al.* 2002, Kim *et al.* 2003).

Transgenic lipoatrophic A-ZIP/F-1 mice have virtually a complete lack of white adipose tissue leading to markedly elevated circulating triglycerides and free fatty acids, severe insulin resistance and diabetes due to excessive ectopic lipid deposition in non-adipose tissues (Moitra *et al.* 1998). Two-weeks treatment of A-ZIP mice with PPAR-α agonist WY-14643 completely normalized their circulating free fatty acids and triglyceride levels and decreased blood glucose concentrations with no change in serum insulin levels (Chou *et al.* 2002). The activation of PPAR-α also markedly stimulated the muscle expression of two key enzymes involved in lipid oxidation, namely carnitin-palmitoyl transferase and acyl-CoA oxidase. Moreover, the liver and muscle tissue triglyceride content was significantly reduced after WY-14643 treatment suggesting that decreased ectopic lipid storage due to its increased oxidation may have been the leading mechanism of WY-14643 action. The euglycemic-hyperinsulinemic clamp demonstrated marked improvement in the liver insulin sensitivity and a borderline increase in the whole body insulin sensitivity.

The effect of PPAR-α activation in MKR transgenic mice was very similar to that in A-ZIP lipoatrophic mice (Kim *et al.* 2003). MKR mice overexpress the dominant negative form of IGF-1 receptor in skeletal muscles and their diabetes is due to severely impaired muscle insulin sensitivity at the younger age with subsequent deterioration of liver and adipose tissue insulin sensitivity at the older age (Fernandez *et al.* 2001). Treatment with PPAR-α agonist again stimulated the expression of the enzymes involved in lipid oxidation leading to a concomitant decrease of muscle and liver triglyceride levels (Kim *et al.* 2003). Consequently, blood glucose and insulin concentrations dropped remarkably indicating an improvement in the insulin sensitivity which was further demonstrated by the euglycemic-hyperinsulinemic clamp. Moreover, studies on isolated pancreatic islets showed an improvement in insulin secretion after PPAR-α agonist treatment.

In addition to PPAR-α agonists, the effect of combined PPAR-α/γ agonist ragaglitazar have been tested by Ye *et al.* (2003). Ragaglitazar completely eliminated high-fat feeding-induced liver triglyceride accumulation and visceral adiposity similarly to PPAR-α agonist WY-14643 but without causing hepatomegaly. It also lowered circulating triglyceride levels and muscle long-chain acyl-CoAs. The ability of ragaglitazar to suppress the hepatic glucose output was significantly greater relative to WY-14643 which may have been due to a threefold increase in plasma levels of insulin-sensitizing hormone adiponectin.

While most of the studies demonstrated reduced adiposity and improved insulin sensitivity after PPAR-α activation, this may not be true for all rodent models of the metabolic syndrome. Šedová *et al.* (2004) recently found that two-weeks fenofibrate administration in fact deteriorated insulin sensitivity in a genetic model of insulin resistance syndrome of polydactylous (PD/Cub) rat strain. Interesting data about PPAR-α and insulin sensitivity were obtained by studying glucose metabolism in transgenic PPAR-α knockout mice. Guerre-Millo *et al.* (2001) and Tordjman *et al.* (2001) demonstrated that the lack of PPAR-α protects against the development of insulin resistance induced by a high-fat diet feeding as measured by the glucose tolerance test and euglycemic-hyperinsulinemic clamp, respectively, in fasted mice. We measured insulin sensitivity of PPAR-α knockout mice fed high-fat diet using euglycemic-hyperinsulinemic clamp in the non-fasted state and found no protection against the development of insulin resistance relative to wild type mice (Haluzík *et al.* 2004b). The possible explanation of this contradiction could be in the defective response to fasting in PPAR-α knockout mice. The lack of PPAR-α leads to their inability to oxidize fatty acids with preferential use of glycogen stores as a fuel during fasting. As a result, the glycogen stores in PPAR-α knockout animals are depleted more quickly than in normal mice which can subsequently affect glucose uptake during an oral glucose tolerance test or glucose clamp.

Taken together, the above described data show that PPAR-α activation in most of the rodents models of obesity and insulin resistance/diabetes markedly improves insulin sensitivity mostly due to decreased ectopic lipid storage in non-adipose tissues. Moreover, improved insulin secretion after long term PPAR-α

agonist treatment may contribute to the overall improvement of the diabetic phenotype.

Adipose tissue hormones and PPAR-α effects on insulin sensitivity

Although PPAR-α activation in rodents induces marked changes in the adiposity, only few studies were focused on the influence of PPAR-α stimulation on the endocrine function of adipose tissue. Leptin levels normally positively correlate with body adiposity and decrease with body weight reduction in both humans and rodents (Maffei *et al.* 1995, Haluzík *et al.* 1999). The same was true for studies with PPAR-α agonists where reduction of body weight in mice or rats was accompanied by decreased leptin levels thus excluding the possible role of leptin in the mediation of PPAR-α effects (Lee *et al.* 2002).

Another adipose tissue-derived hormone, resistin was originally discovered as a potential mediator of obesity-induced insulin resistance increased in obese mice and rats and antagonizing insulin action (Steppan *et al.* 2001). Later studies did not fully support its causal role in the etiopathogenesis of insulin resistance but confirmed its role in the regulation of hepatic glucose production (Savage *et al.* 2001, Way *et al.* 2001, Banerjee *et al.* 2004, Haluzík *et al.* 2004a). Reports on the changes of resistin gene expression and/or serum levels after PPAR-α activation are limited. Fukui and Motojima (2002) found that PPAR-α knockout mice have significantly decreased constitutive resistin expression in the adipose tissue relative to control animals indicating a regulatory role of PPAR-α in the resistin expression (Fukui and Motojima 2002). In our study, circulating resistin levels were significantly increased after three weeks of fenofibrate treatment of C57BL/6J mice fed by either normal chow or a high-carbohydrate diet despite the improvement of insulin sensitivity (Haluzík MM and Haluzík M, unpublished results). In another study, resistin gene expression was increased in human subcutaneous adipose tissue after eight weeks of fenofibrate treatment relative to placebo group (Jove *et al.* 2003). Thus, similarly to leptin, the changes of resistin levels are not involved in PPAR-α insulin-sensitizing effects.

Adiponectin is a protein hormone produced exclusively by adipocytes with significant insulin-sensitizing and anti-atherosclerotic effects (Haluzík *et al.* 2004c). Its serum concentrations are inversely related to body adiposity and insulin sensitivity (Hotta *et al.* 2000). In contrast to resistin, adiponectin levels do not appear to be directly regulated by PPAR-α (Haluzík *et al.* 2004b). In our study, the treatment with PPAR-α agonist increased serum adiponectin levels in C57BL/6J mice on chow diet but not in mice on high-carbohydrate diet (Haluzík MM and Haluzík M, unpublished results). The changes in adiponectin levels therefore do not appear to mediate insulin sensitizing effects of PPAR-α activation.

PPAR-α and insulin sensitivity: clinical studies

PPAR-α agonists fibrates have been traditionally used in clinical practice in the treatment of combined hyperlipidemia and/or isolated hypertriglyceridemia. Numerous clinical studies showed that fibrates were very effective in decreasing triglyceride levels and increasing HDL cholesterol levels with subsequent reduction of both cardiovascular morbidity and mortality (de Faire *et al.* 1996). None of those studies, however, was directly focused on the changes of insulin sensitivity and in most of them neither the insulin levels nor other parameters of glucose tolerance/insulin sensitivity were measured. On the other hand, the major drawbacks of the studies testing the effect of PPAR-α agonists on the insulin sensitivity are very small number of patients and the fact that most of them were open-labeled and non-randomized. Here we briefly discuss the most important studies focusing on the effect of fibrates on the glucose tolerance/insulin sensitivity in humans (Table 1).

In the first study, Ferrari *et al.* (1977) tested the effect of one-week clofibrate treatment on the insulin sensitivity of 18 patients with hypertriglyceridemia without type 2 diabetes mellitus and 28 patients with hypertriglyceridemia with type 2 diabetes mellitus respectively. Even such short-term treatment improved glucose tolerance (measured by the glucose tolerance test) and decreased basal serum insulin levels.

Another clofibrate study on 15 patients with type 2 diabetes mellitus was performed by Murakami *et al.* (1984). Four weeks of clofibrate treatment significantly improved glucose tolerance and insulin sensitivity as measured by glucose and insulin tolerance tests, respectively. Kobayashi *et al.* (1988) published the results of double-blind randomized study of 70 patients with type 2 diabetes. The patients were treated with clofibrate for 12 weeks. This treatment significantly improved glucose tolerance and decreased basal glucose levels.

Table 1. Summary of selected clinical studies that tested the effect of PPAR-α agonist treatment on insulin sensitivity.

Study	Fibrate and treatment interval (in weeks)	Number of patients, disease	Change of insulin sensitivity/glucose tolerance
Ferrari *et al.* (1977)	clofibrate, 1 week	18, T2 DM	⇑ insulin sensitivity
Murakami *et al.* (1984)	clofibrate, 4 weeks	15, T2 DM	⇑ insulin sensitivity
Kobayashi *et al.* (1988)	clofibrate, 12 weeks	70, T2 DM	⇑ insulin sensitivity
Yong *et al.* (1999)	fenofibrate, 24 weeks	23, hypertriglyceridemia	⇑ insulin sensitivity
Škrha *et al.* (1994)	etofylinclofibrate, 12 weeks	8, T2 DM	⇓
	fenofibrate, 12 weeks	8, T2 DM	no change
Idzior-Walus 2001	fenofibrate, 12 weeks	37, metabolic syndrome	⇑ insulin sensitivity
Whitelaw *et al.* (2002)	gemfibrozil, 12 weeks	12, T2 DM	no change
Rizos *et al.* (2002)	ciprofibrate, 16 weeks	64, combined hyperlipidemia	no change*

T2 DM – type 2 diabetes mellitus. * Only blood glucose and insulin were measured, no glucose tolerance or insulin sensitivity tests were performed.

A more recent study by Yong *et al.* (1999) with 24-week fenofibrate treatment of 23 patients with hypertriglyceridemia showed no improvement in glucose tolerance. Interestingly, insulin concentrations during glucose tolerance test performed after treatment were significantly lower as compared to those before treatment. The authors suggested that this may indicate an improvement in insulin sensitivity. Another study by Idzior-Walus (2001) tested the effect of 12-week treatment with micronized form of fenofibrate on the glucose tolerance and other metabolic characteristics in 37 patients with combined hyperlipidemia and metabolic syndrome. Similarly to the previous study, fibrate treatment improved glucose tolerance as measured by the oral glucose tolerance test.

On the contrary, Whitelaw *et al.* (2002) found no effect of 12-week treatment with gemfibrozil on the insulin sensitivity as measured by euglycemic-hyperinsulinemic clamp in 12 subjects with type 2 diabetes mellitus. Similarly, Škrha *et al.* (1994) observed no difference in insulin sensitivity after 12 weeks of treatment with fenofibrate and described even deteriorating insulin sensitivity after administration of etylinclofibrate for 12 weeks. In another study, clofibrate treatment for 16 weeks did not affect serum glucose or insulin levels in 36 patients with combined hyperlipidemia or 28 patients with isolated hypercholesterolemia (Rizos *et al.* 2002).

Thus, in contrast to convincing results of experimental studies on rodents, the effect of PPAR-α agonists on insulin sensitivity in humans is less significant and there are several remarkable differences with respect to the fibrate effects in humans vs. rodents. Firstly, none of the human studies found any difference in body fat content in contrast to reduction of adiposity in most of rodents studies. Secondly, none of the fibrates has increased the liver size in humans in contrast to marked hepatomegaly in rodents. One of the reasons for such difference is that the human liver and muscle express much less PPAR-α than those of rodents (Loviscach *et al.* 2000). Moreover, as mentioned above the proliferation of peroxisomes stimulated by fibrates appears only in rodents but not in humans.

Conclusions and future directions of research

The activation of PPAR-α in rodents stimulates lipid oxidation with subsequent reduction of white adipose tissue depots, decrease in ectopic lipid storage in muscle and liver and the improvement of insulin sensitivity in these tissues. There is some evidence that the improvement in insulin secretion might be another contributing factor, while the involvement of adipose tissue endocrine production has not been consistently demonstrated. In contrast, the effect of PPAR-α agonist in humans appears to be less pronounced with relatively slight or no improvement of insulin sensitivity and with no effects on body weight and adipose tissue stores. This difference might be explained by the fact that the levels of expression of PPAR-α in human muscle and particularly the liver are much lower than in rodents. Further clinical studies using more potent PPAR-α agonists and measuring the changes in insulin sensitivity

by more sophisticated techniques such as glucose clamp are warranted to dissect whether and to what extent there is any role for PPAR-α agonists as insulin-sensitizing agents in humans.

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