The effect of PPARγ ligands on the adipose tissue in insulin resistance

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Abstract

Insulin resistance is frequently accompanied by obesity and both obesity and type 2 diabetes are associated with a mild chronic inflammation. Elevated levels of various cytokines, such as TNF-α and IL-6, are typically found in the adipose tissue in these conditions. It has been suggested that many cytokines produced in the adipose tissue are derived from infiltrated inflammatory cells. However, the adipose tissue itself has proven to be an important endocrine organ, secreting several hormones and cytokines, usually referred to as adipokines. Peroxisome proliferator-activated receptor (PPAR)γ is essential for adipocyte proliferation and differentiation. In recent years, PPARγ and its ligands, the thiazolidinediones (TZD), have achieved great attention due to their insulin sensitizing and anti-inflammatory properties. Treatment with TZDs result in improved insulin signaling and adipocyte differentiation, increased adipose tissue influx of free fatty acids and inhibition of cytokine expression and action. As a result, PPARγ plays a central role in maintaining a functional and differentiated adipose tissue.

1. Introduction

During the last decades, the global prevalence of obesity and type 2 diabetes has increased epidemically which will impose an accelerating burden on society and health regulators. Insulin resistance, defined as an impaired ability of the insulin-responsive cells to elicit a normal response to a given insulin stimulation, precedes the development of type 2 diabetes. When the pancreatic β-cells fail to produce sufficient insulin to overcome the resistance, an impaired glucose tolerance proceeds to overt type 2 diabetes.

Most of the insulin-stimulated glucose disposal occurs in the skeletal muscle and only a minor part in the liver and adipose tissue. Until recently, skeletal muscle has been the main focus for studies on insulin resistance and diabetes while adipose tissue has been thought to be mainly a storage site for excess energy. The importance of the adipose tissue for insulin sensitivity became a major focus following the finding that the adipose tissue is an active endocrine organ secreting several factors that can affect whole-body insulin sensitivity. This enables a cross-talk between adipose tissue, skeletal muscle and liver in the regulation of glucose homeostasis. A good example of the ability of the adipose tissue to affect insulin sensitivity in other tissues is the adipose-specific ablation of glucose transporter 4 (GLUT4) in mice. These mice are insulin-resistant in both skeletal muscle and liver in vivo. However, the insulin-stimulated glucose uptake is normal in these tissues in vitro where endocrine signals from the adipose tissue are absent [1].

It is well-known that both excess adiposity and lipoatrophy cause insulin resistance in man as well as in animal models [2,3]. Thus, it is important to have a certain amount of fat, allowing lipids to be stored in the adipose tissue and not in skeletal muscle or liver since this may elicit or enhance insulin resistance in these tissues [4–6].

This review is focused on the importance of adipose tissue differentiation and function in regulating insulin sensitivity and the effect of the thiazolidinediones (TZD) (Peroxisome proliferator-activated receptor (PPARγ) ligands) in restoring these properties in a dysregulated and insulin-resistant adipose tissue.
2. Impaired adipose tissue differentiation and insulin signaling in insulin resistance and diabetes

Several studies have documented impairments in adipocyte insulin signaling in insulin resistance and type 2 diabetes, in particular a marked reduction of the insulin-stimulated tyrosine phosphorylation of the insulin receptor substrate-1 (IRS-1). This is mainly due to a reduction of the IRS-1 protein expression [7]. Increased serine kinase activity, which is associated with a reduced insulin-stimulated tyrosine phosphorylation, has also been observed in primary adipocytes of type 2 diabetic subjects [8]. The insulin-stimulated phosphatidyl-inositol (PI) 3-kinase activity is reduced in these individuals leading to a decreased downstream serine phosphorylation and translocation of protein kinase B (Akt/PKB) [9]. Furthermore, insulin-stimulated glucose uptake in vitro is decreased due to both the impaired insulin signaling as well as a marked reduction in GLUT4 mRNA and protein expression [10].

In addition to the reduced insulin signaling, we have recently provided evidence that adipocyte differentiation is also impaired. Fat cells from insulin-resistant individuals display decreased expression of several terminal adipocyte differentiation markers, such as adipocyte P2 (aP2) and adiponectin, and increased lipid partitioning with a subsequent enlargement of the existing adipose cells [11]. Furthermore, the activity of lipoprotein lipase (LPL) is decreased [12] in adipose tissue of both animal models and individuals with insulin resistance and type 2 diabetes probably due to the increased cytokine production in insulin resistance [13]. The overall reduction in LPL activity most likely contributes to the hypertriglyceridemia seen in diabetes. We have also found that genes and proteins involved in energy expenditure and characteristic for the brown adipocyte phenotype are reduced in adipose tissue of insulin-resistant individuals [14]. Furthermore, the mRNA and protein expression of the transcriptional co-activator of PPARγ, PGC-1α (PPARγ co-activator 1α), is reduced in these individuals [15].

In obese individuals with greater than expected insulin resistance, a mutation that increases PPARγ activity through impaired phosphorylation by mitogen-activated protein-kinases (MAP-kinases) has been found [16]. The importance of this posttranscriptional modification of PPARγ is significant since various growth factors and cytokines can regulate adipocyte differentiation and the expression of numerous genes involved in lipid metabolism through this pathway. To better understand the biological function of PPARγ phosphorylation, a mouse model with a modification of the PPARγ protein that prevents phosphorylation by MAP-kinases has been generated [17]. In contrast to the results from the obese individuals described above, these mice do not develop increased obesity when fed a normal chow but are, in fact, protected from insulin-resistance during high-fat diet-induced obesity through changes in gene expression, fat cell size and secreted factors.

3. The role of PPARγ in adipose tissue differentiation

3.1. PPAR nuclear receptors

PPARγ belongs to a sub-family of the nuclear receptor family that regulates gene expression in response to ligand binding. PPARs exist as an obligate heterodimer with the retinoic X receptor (RXR) [18] and are localized to the nucleus also in the unligated state [19]. Upon ligand binding, a conformational change leads to co-repressor release and co-activator binding. The ligand-binding properties of PPARs are not as restricted as those for other nuclear receptors. The binding pocket permits binding of ligands with quite diverse structures [20], probably resulting in different conformational changes which, in turn, affect the recruitment of co-factors, induce differences in the kinetics of the assembly of the transcription complex as well as the affinity for the specific PPAR response element (PPRE). The PPAR/RXR heterodimers can be activated by ligands of either receptor and simultaneous binding of both ligands has been shown to be more efficient in some cases [21]. After ligand binding and activation, the heterodimers are able to either enhance or repress gene expression through binding to PPRE in the promoter region of target genes.

Three PPARs have so far been identified, displaying differential expression patterns and physiological functions. PPARδ (also known as PPARβ) is ubiquitously expressed, with highest expression in skin, brain and adipose tissue. Deletion of PPARδ in animal models causes alterations in these tissues, such as impaired wound healing through effects on keratinocyte proliferation [22]. PPARα is predominantly expressed in liver, heart, skeletal muscle and also in the vascular wall. PPARγ is mainly involved in the regulation of genes related to fatty acid metabolism. Activation of hepatic PPARγ induces the expression of enzymes involved in fatty acid transport and oxidation [23,24] as well as the expression of key enzymes in the peroxisomal and mitochondrial β-oxidation [25,26]. PPARγ has also been ascribed anti-inflammatory properties in inflammatory cells through the modulation of nuclear factor-κB (NF-κB) activity [27]. PPARγ exists as two protein isoforms, PPARγ1 and γ2, that differ in their N-terminal end as a result of alternative promoter usage [28]. PPARγ1 has a similar expression pattern as PPARγ while PPARγ2 is predominantly expressed in adipose tissue where it regulates adipocyte differentiation. A number of naturally occurring ligands for PPARγ with
relatively low affinity have been identified, including various fatty acids and prostaglandins [29,30]. However, the importance of these ligands for PPARγ activation is still largely unknown.

3.2. PPARγ-regulated adipocyte differentiation

PPARγ is essential for adipocyte differentiation, and is a key transcription factor for the induction of markers of terminal differentiation. The adipogenic potential of PPARγ2 has been demonstrated in a number of studies. Tontonoz et al. [31] have demonstrated that retroviral PPARγ is a key transcription factor for the induction of markers of adipogenesis. They also showed that PPARγ agonists promote differentiation in a dose-dependent manner.

A recent report by Zhang et al. [32] showed that specific PPARγ2 knock-out mice, although having normal development of other tissues, display an overall reduction of the white adipose tissue, less lipid accumulation and reduced expression of adipogenic genes such as aP2, LPL, adipin, leptin and phosphohepoxynpyruvate carboxykinase (PEPCK). They also showed that cultured fibroblasts from the same mouse model had decreased adipogenic potential compared to fibroblasts from wild type mice. Furthermore, the expression of IRS-1 and GLUT4 in skeletal muscle of these mice was reduced, indicating disturbances in the expression and/or secretion of adipokines involved in the expression of insulin-responsive genes in skeletal muscle. PPARγ1 has also been shown to induce adipogenesis when overexpressed in fibroblasts. PPARγ2, however, has enhanced ability to interact with transcriptional co-activators and to induce adipocyte differentiation under conditions of limited availability of ligand [33].

PPARγ interacts with several other transcription factors. Together with C/EBPα (CAAT/enhancer binding protein), PPARγ initiates adipocyte differentiation following induction by another C/EBP family member, C/EBPβ, which is activated early after induction of differentiation through phosphorylation and dissociation from CHOP-10 (C/EBP homologous protein 10) [35]. C/EBPα can, when expressed at levels comparable to that in adipose tissue, cooperate with PPARγ and even in the absence of ligand produce an adipogenic response [31]. Another transcription factor that PPARγ interacts with is the sterol response-element binding protein 1 (SREBP1). Co-expression of this transcription factor with PPARγ increases the transcriptional activity of PPARγ. Since SREBP1 is able to increase the expression of several genes involved in fatty acid metabolism, it has been suggested that SREBP1 induces the production of an endogenous ligand that enhances the transcriptional activity of PPARγ [36].

Several genes specialized in lipid metabolism and storage are induced in the adipogenic differentiation process; many of which contain functional PPAR-response elements. aP2, which is a marker of terminal adipocyte differentiation and involved in free fatty acid (FFA) transportation and shunting within the cell, is one such gene [18]. Other genes include perilipin [37], covering the surface of mature lipid droplets; LPL [38], the hydrolyzing enzyme that releases fatty acids from chylomicrons and very low density lipoprotein in the circulation, and renders them available for uptake by the adipose cell; Acyl CoA synthase (ACS) [24], that unidirects the flux of fatty acids into the cells through an esterification process as well as adiponectin, an adipocyte differentiation marker, which improves insulin sensitivity [39]. All of these genes also display increased gene and protein expression after addition of PPARγ ligand.

PEPCK, which is the enzyme that catalyzes the rate-limiting step in both gluconeogenesis and glycogenesis, is an additional example of genes that are important for adipocyte differentiation and function and which contain PPRE in the upstream promoter [40].

The insulin signaling leading to glucose uptake is also an important pathway in the mature adipocyte. However, no PPRE has, so far, been found in the promoter region of any of the key molecules involved in insulin-stimulated glucose disposal, i.e., the insulin receptor, IRS-1, IRS-2, PI3-kinase, Akt/PKB and GLUT4.

3.3. PPARγ ligand-mediated improvement of adipocyte function

TZD are a group of agents used in the treatment of type 2 diabetes that enhance insulin sensitivity in the peripheral tissues without affecting insulin secretion from the β-cells [41]. Treatment of patients with TZDs consistently lowers fasting and postprandial glucose and fatty acid levels and increases high density lipoprotein cholesterol. These improvements are generally accompanied by a remodelling of the adipose tissue, where large adipocytes are replaced by small and more insulin-sensitive cells [42,43] and, paradoxically, some weight gain.

Several publications have reported on favorable effects of TZD treatment on insulin signaling and glucose uptake in adipocytes. We recently examined the effect of pioglitazone on the expression of different insulin signaling molecules in adipose tissue of non-obese, but insulin-resistant individuals with decreased expression of IRS-1 and GLUT4 in the adipose tissue [44]. We did not see any effect on the gene or protein expression of the insulin receptor. However, the tyrosine phosphorylation of both the insulin receptor and IRS was enhanced. Also, the downstream activation and serine phosphorylation of Akt/PKB were increased.
Since no increase in the expression level of either protein could be detected, the increased phosphorylation is likely due to a change in kinase and/or phosphatase activity. Furthermore, TZD treatment increased the expression of α2 and adiponectin, indicating enhanced differentiation of the adipose cells after treatment, as well as the expression of the insulin-responsive glucose transporter GLUT4. In another report of the effect of rosiglitazone on freshly isolated human adipocytes, no effect could be seen on the expression of GLUT4 [45]. However, this was short-term in vitro stimulation and the data might, therefore, not be comparable. In animal models of obesity and diabetes, where the expression of GLUT4 in adipose cells is reduced, treatment with troglitazone restored the expression to normal levels [46]. Although, no complete PPRE has been found in the GLUT4 promoter, PPARγ and its heterodimeric partner RXRα have been found to bind and repress the promoter activity of GLUT4. The repression is augmented in the presence of the natural ligand, 15A-prostaglandin J2, but completely alleviated by rosiglitazone [47]. This is a novel mechanism through which a PPARγ ligand can exert an antidiabetic effect; via detaching the PPARγ transcription complex from the promoter, thereby increasing the expression of the target gene.

In cultures of HEK293 cells and 3T3-L1 adipocytes, rosiglitazone reduces PMA-induced inhibitory serine-phosphorylation of IRS-1 and restores the downstream insulin signal [48]. Other data showed that the increased IRS-1 serine phosphorylation seen in adipose cells of obese Zucker rats was reduced after TZD treatment. One reason for this could be the lower circulating levels of FFA which, in turn, have been shown to induce serine phosphorylation of IRS-1 through activation of protein kinase C (PKC) [49]. In another study of obese Zucker rats, it was shown that short-term treatment with both rosiglitazone and a non-TZD PPARγ ligand could potentiate the insulin effect and increase the tyrosine phosphorylation of the insulin receptor and IRS-1, as well as the serine phosphorylation of Akt/PKB [50]. Effects of PPARγ activation have also been seen on the insulin receptor substrate-2 (IRS-2). Cultured human adipose tissue and 3T3-L1 adipocytes showed an increased IRS-2 gene and protein expression after pioglitazone treatment [51].

The effect of pioglitazone on genes related to lipid storage has also been studied in adipose tissue from type 2 diabetic patients. The expression of genes that regulate fatty acid availability in adipocytes, including LPL and ACS, was increased after treatment. Also the expression of genes involved in glycerol-3-phosphate synthesis, such as PEPCK, glycerol-3-phosphate dehydrogenase as well as the c-Cbl-associated protein was enhanced. However, not all genes previously shown to be PPARγ responsive were induced after treatment [52].

4. Adipokines in insulin resistance and the effect of PPARγ ligands

Secreted molecules from the adipose tissue are commonly referred to as adipokines and include several cytokines, hormones and growth factors. Obesity frequently changes adipokine secretion due to the increased mass of the adipose tissue. In addition to adipokines, the adipocytes express an array of different receptors responding to signals from hormones, cytokines and lipoproteins. Some adipokines, associated with the regulation of insulin sensitivity and modulated by the PPARγ ligands, are exemplified below.

Interestingly, a report recently claimed that approximately 90% of the cytokines secreted by the adipose tissue are derived from non-fat cells [53]. It has also been shown that macrophage infiltration of the adipose tissue (“inflamed adipose tissue”) could largely be responsible for the inflammatory response related to obesity. Furthermore, upon weight gain and as the adipocytes increase in size, expression of cytokines is induced and secreted. This stimulates the cells in the adipose tissue to secrete chemoattractants like monocyte chemoattractant protein-1, which recruit monocytes and macrophages. The recruited macrophages induce cytokines in the adipose tissue, which transduce inflammatory signals (e.g. activation of NF-κB pathway), further leading to insulin resistance and down-regulation of several genes related to adipocyte function [54–56]. Interestingly, preadipocytes and macrophages are genomically close, in fact they are even more closely related to each other than preadipocytes are to adipocytes [57]. Like adipocytes, macrophages express PPARγ and α2, and ligation of TZDs to these cells reduces macrophage activation and inhibits cytokine production [58,59]. Recently, it was shown that 3T3-L1 preadipocytes could be converted to macrophages in vivo, which reveals new possible links between obesity and inflammation [57].

4.1. Tumor necrosis factor-α (TNF-α)

TNF-α is a cytokine which was first described as an endotoxin-induced serum factor that causes necrosis of tumors [60]. Later it was shown to be identical to cachexin, a factor secreted by macrophages [61]. Nowadays, TNF-α is known as a multifunctional protein involved in proinflammation, cell apoptosis, lipid metabolism and insulin resistance.

mRNA and protein levels of TNF-α were shown to be highly induced in adipose tissue from obese and diabetic rodents [62]. The same observation was later made in human adipose tissue and it was concluded that mRNA expression of TNF-α was positively correlated with adipose tissue mass. Adipose tissue biopsies taken from obese patients after weight loss showed a significant decrease of TNF-α mRNA levels. Additionally, levels of
TNF-α correlated positively with degree of hyperinsulinemia [63,64].

One major molecular effect of TNF-α is the activation of NF-κB, which regulates many of the genes related to insulin resistance. In a study where the NF-κB activation was inhibited, the authors found a restoration of the levels of several genes normally modulated by TNF-α [65]. For example, high expression of TNF-α suppresses the transcription factor C/EBP-α which, in turn, activates the GLUT4 gene [66,67]. TNF-α also suppresses the expression of PPARγ [68]. Gene ablation of TNF-α or the TNF-α receptor leads to improved insulin sensitivity in rodents [69,70]. In addition, TNF-α activates the JNK pathway, mediating an increased serine phosphorylation of the IRS-1 and, thus, inhibiting its interaction with the insulin receptor and reducing insulin-stimulated tyrosine phosphorylation of IRS-1 [71,72].

Studies of the effects of TZD have shown suppressed activation of the TNF-α promoter and, subsequently, reduced TNF-α mRNA expression [58]. The inhibitory effect of TNF-α on insulin receptor and IRS-1 signaling is attenuated by TZDs, i.e. the insulin signal is improved [73]. TZDs also prevent the induction of NF-κB regulated genes activated by TNF-α. However, TZDs do not inhibit the NF-κB activation or nuclear translocation per se. It is more likely to be an antagonist of the transcriptional activity of NF-κB [74]. Furthermore, plasma levels of TNF-α significantly decrease in obese patients treated with TZDs [75]. Nevertheless, the ability of TZDs to improve insulin sensitivity is not likely to be dependent of TNF-α, since reduced TNF-α levels by immuno-absorption does not improve insulin resistance in man [76].

4.2. Interleukin-6 (IL-6)

The cytokine IL-6 is produced by various cell types, such as macrophages, B cells, hepatocytes, adipocytes and skeletal muscle cells [77]. IL-6 expression in adipose tissue and serum levels of IL-6 are positively correlated with obesity and insulin resistance [67,78,79]. The gene expression and protein secretion of the insulin-sensitizing adipokine adiponectin (discussed below), is reduced by IL-6 [80,81]. Unlike TNF-α, IL-6 does not increase the serine phosphorylation of IRS-1 but, similar to TNF-α, it suppresses gene transcription of IRS-1 and GLUT-4 as well as PPARγ [67]. IL-6 signaling results in a marked upregulation of, in particular, suppressor of cytokine signaling-3 (SOCS-3) which is a classical feedback regulator of cytokine action [82]. Recently, it was shown that induction of SOCS-3 reduced insulin signaling in 3T3-L1 adipocytes, resulting in decreased glucose transport activity [83].

Not much is known about the effect of TZDs on IL-6 secretion and cellular signaling. However, one study showed that the levels of IL-6 in serum from type 2 diabetic patients treated with TZDs were not significantly reduced [84]. In contrast, LPS-induced IL-6 expression in adipose tissue was reduced in mice treated with TZDs [85]. TZDs have also been shown to reduce the effects of IL-6 in vitro. A decreased IL-6 mRNA synthesis and secretion, together with a reduced mRNA expression of SOCS-3, was found in 3T3-L1 cells treated with TZDs [86]. However, more studies are required to clarify the effect of TZDs on IL-6 signaling and its cross-talk with insulin.

4.3. Leptin

Ever since leptin was cloned and characterized in 1994, it has been a subject of extensive studies [87]. It is now clear that adipocyte production and secretion of leptin is positively correlated to adipose tissue mass. Secreted leptin crosses the blood-brain barrier and interacts with neurons signaling to decrease food intake. Concordantly, during starvation, low levels of leptin are secreted which, in turn, trigger neural appetite signals [88]. Mutation of the leptin gene (ob) results in the genetic form of obesity seen in ob/ob mice [87]. However, as obesity is associated with high levels of leptin, a hypothesis about “leptin resistance” has been suggested but so far no clear evidence of such resistance has been shown. [89].

Leptin expression and secretion are induced upon insulin signaling, but increased plasma levels of leptin reduce insulin release and improve insulin signaling [90–92]. Like IL-6, leptin signals through the signal transducer and activator of transcription-3 signaling pathway and induces expression of the SOCS-3 gene. SOCS-3 has further been suggested to block leptin-induced signaling and in this way contributing to leptin resistance [93]. Even though most studies suggest that leptin enhances insulin sensitivity, there are several reports describing that leptin reduces insulin signaling in the adipose tissue [94–96].

Surprisingly, TZDs reduce leptin mRNA levels in adipocytes. As leptin increases insulin sensitivity, the down-regulation of leptin expression by TZDs is probably due to other factors than its effect on insulin signaling. [97,98]. The leptin gene is regulated by C/EBPz and it was found that PPARγ activation by TZDs antagonizes the C/EBPz-mediated transactivation of the leptin promoter [99].

4.4. Adiponectin

Four different research groups independently cloned and characterized adiponectin [100–103]. This 30-kDa adipocyte-derived hormone exists as trimers, hexamers and oligomers with higher molecular weights. The function of the different forms is not yet clear [104].
Overall, the molecular mechanism of adiponectin signaling is largely unknown. However, two adiponectin receptors (AdipoR1 and AdipoR2) were recently cloned and the intense on-going research on adiponectin function will hopefully soon reveal some answers [105]. Reduced levels of adiponectin are strongly associated with obesity and insulin resistance. Conversely, adiponectin levels increase in obese patients after weight loss. [100,106–108]. Adipose cell size is inversely correlated with adiponectin gene expression [11]. However, obesity is not required for hypoadiponectemia as circulating levels of plasma adiponectin are also reduced in non-obese but insulin-resistant individuals [109,110]. Non-obese patients with low levels of IRS-1 are markedly insulin-resistant, exhibiting hyperinsulinemia and reduced circulating levels of adiponectin [110]. Like leptin, it was recently reported that high levels of adiponectin in the brain lead to a decreased body weight but, in contrast to leptin, adiponectin does not influence the appetite. Instead, adiponectin is suggested to be involved in the stimulation of energy expenditure [111]. Furthermore, levels of adiponectin are inversely correlated to inflammation. For example, both TNF-α and IL-6 decrease the mRNA levels and protein secretion of adiponectin by adipose cells [65,80,81].

Recently, it was found that PPARγ2, but not C/EBPα, is required for gene transcription of adiponectin and that TZDs induce this transcription [112]. That TZDs increase adiponectin secretion has been shown in cell lines, animal models and in human subjects. The plasma levels of adiponectin in normal, obese and type 2 diabetic subjects were similarly increased in all groups following TZD treatment [44,108,113–115].

4.5. Resistin

Resistin (resistance to insulin) is a 12-kDa polypeptide which was first characterized in 2001. As the name indicates, resistin was first found to impair insulin action and to induce insulin resistance. Furthermore, the same study showed that a high-fat diet and obesity increased resistin expression and that TZDs could down-regulate the expression of the resistin gene [116]. These results are, to some extent, supported by other reports [117–119]. Mice deficient in resistin expression showed significantly lower fasting blood glucose levels due to a reduction in hepatic glucose production. This could be restored by administration of recombinant resistin, suggesting that resistin is involved in glucose metabolism [120].

However, there is an on-going debate about the role of resistin in insulin resistance associated with diabetes and obesity [121–123]. Instead of a consistent positive correlation between resistin levels and obesity, the opposite relation has been described in several animal models, i.e. obesity suppresses resistin expression [124–126]. Furthermore, administration of TZDs to ob/ob mice and obese, diabetic Zucker rats induced an
increased resistin expression [124]. Examination of the resistin expression in human, isolated adipocytes showed that no substantial mRNA levels could be detected [127,128]. Instead, resistin mRNA expression was elevated in preadipocytes and the levels declined during differentiation [129]. Additionally, resistin is highly expressed in human macrophages and its expression is regulated by PPARγ as it binds to PPRE elements in the resistin promoter [130]. Notably, it should be mentioned that the homology between mouse and human resistin is only 53%, indicating a possible variation of the gene function [121].

In conclusion, insulin signaling in the adipose tissue is impaired in insulin resistance and the signal can be restored upon activation of PPARγ by its ligands, the TZDs (summarized in Fig. 1). TZDs further improve the dysregulated insulin-resistant adipocyte cell, in part by counteracting the detrimental effects of cytokines on adipocyte differentiation and function. As a result, PPARγ plays a central role in maintaining an insulin-sensitive and functional adipose tissue.

Acknowledgements

This study was supported by grants from the Swedish Research Council (K2001-72X-03506-30B), the Swedish Diabetes Association, the Sonya Hedenbratt Memorial Fund, the IngaBritt and Arne Lundberg Foundation, the Novo-Nordisk Foundation, and the Torsten and Ragnar Söderberg Foundation.

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