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PPARγ AND GLUCOSE HOMEOSTASIS

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■ **Abstract** Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor involved in the control of metabolism. Research on PPARγ is oriented towards understanding its role in insulin sensitization, which was inspired by the discovery that antidiabetic agents, the thiazolidinediones, were agonists for PPARγ. PPARγ stimulation improves glucose tolerance and insulin sensitivity in type 2 diabetic patients and in animal models of insulin resistance through mechanisms that are incompletely understood. Upon activation, PPARγ heterodimerizes with retinoid X receptor, recruits specific cofactors, and binds to responsive DNA elements, thereby stimulating the transcription of target genes. Because PPARγ is highly enriched in adipose tissue and because of its major role in adipocyte differentiation, it is thought that the effects of PPARγ in adipose tissue are crucial to explain its role in insulin sensitization, but recent studies have highlighted the contribution of other tissues as well. Although relatively potent for their insulin-sensitizing action, currently marketed PPARγ activators have some important undesirable side effects. These concerns led to the discovery of new ligands with potent antidiabetic properties but devoid of certain of these side effects. Data from human genetic studies and from *PPARγ* heterozygous knockout mice indicate that a reduction in PPARγ activity could paradoxically improve insulin sensitivity. These findings suggest that modulation of PPARγ activity by partial agonists or compounds that affect cofactor recruitment might hold promise for the treatment of insulin resistance.

CONTENTS

INTRODUCTION

Noninsulin-dependent diabetes mellitus, or type II diabetes, affects between 5 to 10% of the Western population. The major underlying pathophysiologic defect of this disorder is a progressive resistance of glucose metabolism to the action of insulin in multiple tissues, termed insulin resistance, followed by a gradual decrease in insulin secretion caused by reduced pancreatic β-cell function (57). As long as pancreatic β-cells are able to secrete more insulin to compensate for insulin resistance, diabetes does not occur. Therefore, type II diabetes only develops in the context of both insulin resistance and β-cell failure. The frequency of insulin resistance in diabetic patients has been estimated around 60 (10) to 85% (75). Thus, decreasing insulin resistance will reduce the frequency of type II diabetes and improve the quality of life of over 100 million people who are diagnosed with diabetes worldwide (211). It will furthermore save part of the resources currently allocated to diabetes care (6, 48). This explains the excitement that followed the introduction of new insulin sensitizing drugs, the thiazolidinediones, which were subsequently shown to be ligands for the peroxisome proliferator-activated receptor gamma (PPARγ). Since then, a lot of effort has been made to better characterize the role of PPARγ in glucose homeostasis and other metabolic disorders. Several recent reviews discuss in great detail general issues related to PPARγ (8, 122, 190, 215). Here, only a succinct summary of this information is presented. Rather, this review focuses on the effects of PPARγ modulation on insulin sensitivity.

PPARγ AND INSULIN SENSITIVITY

General Issues

PPARγ belongs to the nuclear receptor superfamily, which also comprises PPARα and PPARβ/δ (43). Like other members of this family, PPARγ contains a ligand-dependent AF-2 transactivation domain in its C-terminal region, a highly conserved DNA binding domain composed of two zinc fingers, and a ligand-independent AF-1 activation domain in the NH_2-terminal region (215). Three different PPARγ mRNAs have been characterized in humans (54, 56). PPARγ1 and PPARγ3 transcription gives rise to the PPARγ1 protein. PPARγ2 mRNA encodes for a slightly different protein that contains 28 additional amino acids at its NH_2-terminal region, the function of which has not yet been elucidated (213, 231).

Several natural and synthetic ligands for PPARγ have been described so far. These molecules of lipophilic nature include fatty acids and fatty acid derivatives (105) such as 15-deoxy-delta12,14-prostaglandin J2 (62), eicosapentaenoic acid

(227), 9- and 13-hydroxyoctadecadienoic acids (146), and synthetic compounds such as the thiazolidinediones (62, 118), the L-tyrosine-based ligands (83), FMOC-L-leucine (173), and certain nonsteroidal antiinflammatory molecules (117). Upon ligand binding, PPARγ changes its structural conformation, which stimulates its heterodimerization with retinoid X receptor (RXR), and facilitates the recruitment of cofactors required for the activation of transcription. This heterodimer-cofactor complex controls the expression of genes that contain direct repeats of the consensus AGGTCA sequence interspaced with one nucleotide, called PPAR response elements.

Cofactor recruitment is crucial for the PPARγ-mediated stimulation of gene transcription (148). Cofactor activities range from chromatin remodeling and modification of core histones (acetylation and methylation status) to recruitment of the basic transcriptional machinery (72). Cofactors that have been experimentally shown to interact with PPARγ are those of the p160 family (SRC-1/TIF2/GRIP-1/ACTR) (81, 155, 207), p300/CBP (70, 230), PGC-1 (161), PRIP (229), PGC-2 (24), ARA70 (82), and RIP140 (200). NcoR (46) and SMRT (113, 156) have been described as corepressors of PPARγ activity. It should be noted that none of these cofactors seems to be specific for PPARγ, which suggests that cofactor squelching might be a more important feature for transcriptional activation than primarily thought (88). It has furthermore been established that different ligands induce docking of specific cofactors (106, 173), which likely translates in a distinct biological response. Studies in animals with mutations in the cofactors of PPARγ will undoubtedly help us understand how they modulate the PPARγ signaling pathway.

PPARγ is expressed at low levels in several tissues in adult mammals (20). PPARγ1 is expressed to a high extent in adipose tissue, large intestine, and hematopoietic cells. Kidney, liver, skeletal and smooth muscles, pancreas, and small intestine express lower amounts of PPARγ1 (7, 47, 94, 121). The PPARγ2 isoform is almost exclusively confined to white adipose tissue, where it represents approximately 30% of the PPARγ population, but was also detected in brown adipose tissue and skeletal muscle (51). PPARγ3 has only been reported to be expressed in large intestine and macrophages (56).

In rodents, adipose tissue PPARγ mRNA and protein levels are reduced after an overnight fast (51, 204) and in streptozotocin-induced diabetes (204), which is consistent with the stimulatory effect of insulin on PPARγ expression (169). In addition, chronic feeding with high fat diets was shown to increase PPARγ expression in adipose tissue (204). Whereas no enhancement of PPARγ expression was observed in several genetic rodent models of obesity (204), the situation differs in human obesity. Compared with lean subjects, PPARγ2, but not PPARγ1, is expressed at higher levels in obese patients (205). Most interestingly, compared with that of the subcutaneous fat depot, the relative expression of PPARγ is increased in visceral fat of obese subjects (115). Finally, the expression of PPARγ has been shown to be decreased during endotoxemia in vivo (85), which might in part contribute to the insulin resistant state that is associated with this condition.

Genetic Studies on PPARγ in Humans and Mice

PPARγ+/− MICE Unfortunately, PPARγ−/− mice die during intra-uterine development owing to defects in the placenta (111). Therefore, physiological characterization of PPARγ deficiency in mice has been limited to the study of heterozygous (+/−) PPARγ mice (111, 133). These studies have led to a complete re-interpretation of PPARγ's role in metabolic control. On a normal commercial diet, it was found that deletion of one *PPARγ* allele, theoretically reducing PPARγ activity in vivo by 50%, results in normal body weight and fat stores (133). Most surprisingly, PPARγ +/− mice displayed higher insulin-stimulated glucose disposal (133). Reduced levels of plasma insulin during glucose tolerance tests and enhanced insulin-mediated suppression of hepatic glucose production were also observed in PPARγ +/− mice (133). All these effects indicate that PPARγ +/− animals have increased insulin sensitivity. When exposed to conditions that favor weight gain, such as chronic feeding with a high fat diet, PPARγ +/− mice exhibit lower body weight gain and fat mass accretion. These animals also have an increased insulin sensitivity compared with their wild-type counterparts (111), which supports the hypothesis that reduced PPARγ activation can improve glycemic control.

HUMAN POINT MUTATIONS A point mutation in the B exon of the NH_2-terminal part of PPARγ2, changing proline to alanine in position 12, has been shown to decrease receptor activity (40, 225). Human subjects carrying this partial loss-of-function mutation (40, 225) have greater insulin sensitivity, a lower body mass index, and an improved lipid profile (3, 40, 79, 138, 159), which is consistent with the findings observed in PPARγ +/− mice. The association between the alanine substitution and insulin sensitivity disappears when the data are corrected for body mass index, suggesting a primary effect on body fat mass accretion (40). The strength of the relationship seems also to be dependent upon the population and ethnic group studied (49), as other studies have found no (139, 171, 176, 194) or even inverse (15, 45, 131) relationships between Pro12Ala mutations and insulin sensitivity. These conflicting results point to the existence of gene-gene and gene-environment interactions that might explain some of the discrepancies (92, 123). In addition to the effects on body fat mass and insulin sensitivity, it has been shown that the Pro12Ala mutation could affect insulin secretion in response to free fatty acids in healthy (191) and diabetic (138) subjects.

The substitution of proline with glutamine at position 115 renders PPARγ constitutively active through the modulation of the phosphorylation status of PPARγ by MAPK at serine 114 (1, 93, 172). In contrast with the Pro12Ala mutation, the Pro115Gln mutation is very rare (32, 172, 176). The four subjects carrying this mutation (out of 358 individuals screened) were all extremely obese and insulin resistant and three were diabetic (172). Other large studies failed to identify any additional subjects with this mutation (32, 176). The report of the Pro115Gln mutation is consistent with the role of PPARγ in adipogenesis and fat mass accretion

but again questions the paradox that increased PPARγ activity by synthetic drugs leads to insulin sensitization.

Two mutations affecting the ligand-binding domain of PPARγ in a dominant negative manner (Pro467Leu and Val290Met) have been described (12). Both mutations rendered the receptor less active in transfection assays. Human carriers for these loss-of-function mutations (3 out of 85 insulin resistant subjects) were characterized by severe insulin resistance, type II diabetes, and hypertension but had normal body mass index. These findings are a priori opposite to the metabolic consequences of the Pro12Ala and Pro115Gln mutations but are consistent with pharmacological studies characterizing the effects of synthetic PPARγ ligands. Hence, these discrepancies underscore the fact that the physiological consequences of Pro12Ala, Pro115Gln, Pro467Leu, and Val290Met mutations have to be confirmed in a controlled genetic and environmental background. A large heterogeneity in the response of metabolism was observed for these mutations, which is likely to influence the impact of these polymorphisms on insulin sensitivity.

How PPARγ Activation Results in Insulin Sensitivity

It is still a matter of debate which tissue is responsible for the glucose-lowering activity of PPARγ ligands. Although skeletal muscle is the principal tissue involved in glucose disposal, it is well established that adipose tissue is also required for proper glucose homeostasis, because lipoatrophic mice and humans are extremely insulin resistant (69, 137, 186). Although PPARγ is expressed in liver and muscle (121, 204, 205), its physiological relevance remains unclear because it represents only a fraction of the level of PPARγ found in fat (190). The central role of adipose tissue in the effects of PPARγ-activating drugs on glucose homeostasis has been highlighted by a recent study showing the absence of effects of thiazolidinediones on glycemia, but not on lipid metabolism, in mice that lack fat tissues (27). However, this issue remains controversial, as others have found that thiazolidinediones are still active under similar conditions (22). Because type II diabetes is a multi-organ disease, it is likely that the role of PPARγ in the control of glucose homeostasis extends beyond its primary effects in adipose tissue. Some of the potential mechanisms that could contribute to insulin sensitization are discussed below and are summarized in Figure 1.

INDUCTION OF GENES INVOLVED IN ADIPOGENESIS AND REMODELING OF WHITE ADIPOSE TISSUE The central role of PPARγ in adipogenesis and fat tissue formation has been unequivocally demonstrated (11, 174, 199). A number of excellent reviews have summarized this topic (55, 141, 175), and hence it is not discussed extensively here. The stimulatory effects of PPARγ activation on adipogenesis are based, on one hand, on an increased expression of genes that promote fatty acid trapping and storage in adipocytes, such as the genes coding for fatty acid binding protein (198), lipoprotein lipase (178), acyl-CoA synthase (179), and phosphoenol pyruvate carboxykinase (197), and, on the other hand, on repression of genes that

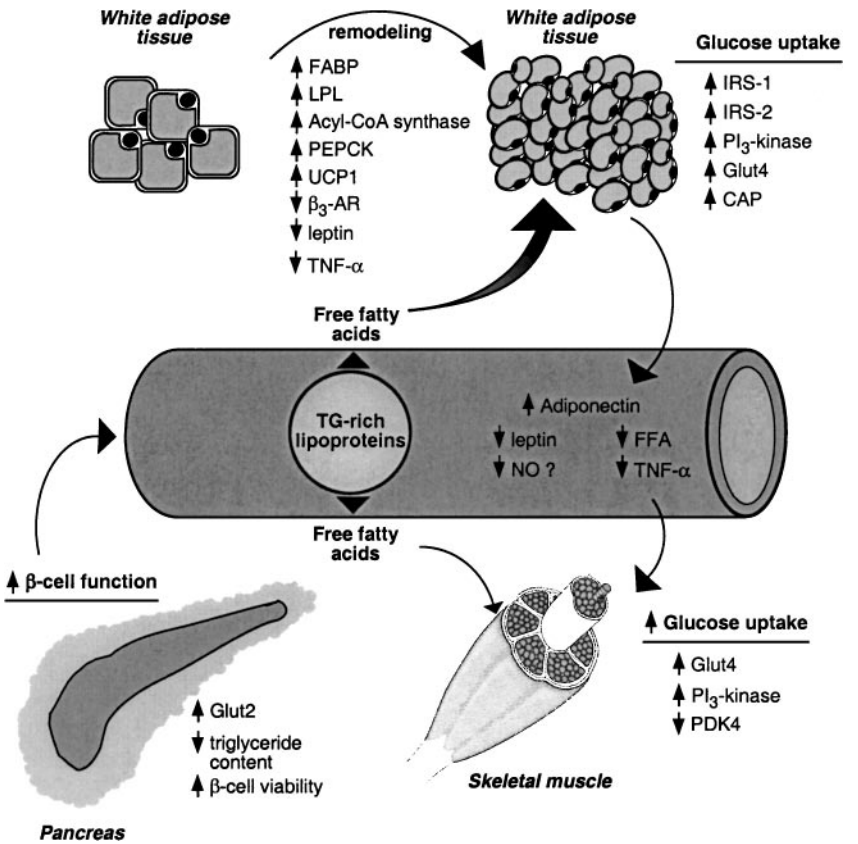

Figure 1 Schematic representation of the mechanisms by which PPARγ activation improves the sensitivity of glucose metabolism to the action of insulin. PPARγ increases adipose tissue remodeling and fat mass accretion brought about by an enhanced adipocyte differentiation through induction of target genes mainly involved in lipid metabolism. Fatty acids derived from hydrolysis of triglyceride-rich lipoproteins are redirected towards adipose tissue rather than skeletal muscle, which increases glucose metabolism in the muscle. This is concomitant with an increase in expression of genes involved in glucose uptake and insulin signaling in both adipose tissue and muscle, as well as a modulation of fat-derived signaling molecules that could affect glucose processing in the periphery. Finally, PPARγ seems to protect β-cells against the intracellular triglyceride accumulation that is often associated with type II diabetes, and hence PPARγ activation improves β-cell function. The size of the arrows reflects the importance of the effects.

induce lipolysis and release of fatty acids, such as the β_3-adrenergic receptor (9) and the cytokines leptin (39, 97) and TNF-α (87, 195).

Consistent with PPARγ's role in fatty acid storage in adipocytes, activation of PPARγ by thiazolidinediones has been shown to increase fat mass in both humans (101, 136) and rodents (23, 208). The PPARγ-mediated repression of leptin expression is likely to contribute in some parts to fat mass accretion through reduction of leptin's actions on food intake and energy expenditure (220, 222). Indeed, increases in energy intake and efficiency have been reported upon thiazolidinedione administration (38, 50, 185). Interestingly, treatment with thiazolidinediones seems to favor redistribution of white adipose tissue, with decreased visceral depots relative to those of the subcutaneous area (100, 101, 136, 140). However, white adipose tissue does not only expand upon treatment with PPARγ agonists, but it also undergoes significant morphological changes. There is a shift in the cell population that ultimately results in more small, newly differentiated adipocytes and fewer enlarged, mature adipocytes (38, 77, 153). Similar adipose tissue histology was observed in PPARγ heterozygous mice (111). The reduction in the number of mature adipocytes is thought to be caused by PPARγ-mediated induction of apoptosis (38, 153).

Interestingly, in white adipocytes, a strong induction of the expression of uncoupling protein-1, a mitochondrial protein usually found exclusively in brown adipose tissue, has been observed upon administration of PPARγ ligands (44, 66). This is likely associated with enhanced mitochondrial mass within the adipose cells as a result of PPARγ activation (120). Increased uncoupling protein-1 activity could affect lipid oxidation as it does in brown fat (168), and limit intracellular accumulation of triglycerides. Such an adipose tissue remodeling activity would increase insulin-mediated glucose disposal, because small adipocytes are more responsive to insulin than adipocytes with a large triglyceride content (130). Indeed, the blunting of adipocyte hypertrophy appears to be an important feature of PPARγ-mediated treatment of insulin resistance (220). In addition, upon PPARγ activation, the net number of adipocytes is increased for a given amount of fat tissue, which would likely enhance the total surface of cell membrane available for glucose uptake and subsequent metabolism.

ADIPOSE TISSUE-DERIVED MOLECULES White adipose tissue is able to produce and secrete a large number of hormones, cytokines, and proteins that affect energy homeostasis. Adipocyte-derived signaling molecules whose expression or circulating levels are modulated by PPARγ could have an impact on insulin action directly in fat and in other tissues such as muscle and/or liver. Likely mediators are free fatty acids. The reduction in circulating free fatty acids is an early consequence of PPARγ activation and happens before glucose lowering and the decrease in triglyceridemia (211). The PPARγ-mediated gene expression in fat tissues would promote fatty acid repartitioning (termed "fatty acid steal") towards adipose tissue rather than skeletal muscle (8, 129). This would indirectly improve insulin sensitivity (128, 149, 150, 218), because fatty acid accumulation in skeletal

muscle rapidly leads to insulin resistance (41, 58). In fact, under certain conditions, the same genes involved in lipid metabolism that are upregulated in adipose tissue by PPARγ activation were found to be either not modulated (37, 178, 187) or decreased in skeletal muscle (211), underscoring the physiological relevance of this hypothesis (129, 177). Indeed, the level of improvement of insulin sensitivity upon PPARγ activation seems to be tightly associated with a diminution in lipid accumulation in skeletal muscle (224).

Tumor-necrosis factor-α (TNF-α) is considered as another adipocyte-derived signaling molecule that could mediate the effects of PPARγ ligands on insulin sensitivity. TNF-α reduces insulin-stimulated glucose uptake (90) and it is found in high concentrations in obese and insulin-resistant individuals (73, 233). Because TNF-α expression is inhibited by PPARγ activation in adipocytes (87, 187), activation of PPARγ would blunt TNF-α expression and this could contribute to the improvement of glycemic control (195). The role of TNF-α in glucose homeostasis has been supported by the studies on mice mutated either for TNF-α or both isoforms of its receptor (p55 and p75). Compared with their wild-type counterparts, mice null for TNF-α develop slightly less pronounced obesity and insulin resistance when treated with high fat diets (203) or goldthioglucose (202). Similarly, double (p55 and p75) knockout mice for TNF-α receptor seem to be protected from insulin resistance and hyperglycemia when put on a *ob/ob* background (180). On the other hand, conflicting results have been reported in which the same TNF-α receptor knockout mice, exposed to high-fat diets, were as or even more insulin resistant than wild-type animals (202). Thus, the effects of the TNF-α signaling pathway on glucose metabolism remain somewhat controversial, and additional experimental evidence is needed to establish further conclusions about its role as a mediator of PPARγ's actions.

Leptin (34) and the recently discovered resistin (192) also belong to the class of signaling molecules whose expression is repressed by PPARγ and that could link the adipocyte to skeletal muscle. Both proteins are produced in proportion with adipose tissue mass and could mediate the effects of PPARγ on insulin sensitivity. On the other hand, the relevance of leptin and resistin as mediators of PPARγ activity also remains to be clarified, as other reports found that PPARγ activators stimulate rather than decrease resistin expression (210) and that most in vivo studies have demonstrated that leptin increases insulin sensitivity (76, 98).

Adiponectin is a fat-derived hormone produced in an inverse relationship with the amount of fat stores (5, 223). Reduced circulating adiponectin concentrations were found to be strongly associated with the progression of insulin resistance in humans (214) and rhesus monkeys (91), whereas adiponectin treatment was shown to enhance insulin sensitivity in mouse models of obesity (221). This effect might not be restricted to an amelioration of lipid metabolism (221), but also to an improvement in hepatic insulin action (16). Interestingly, the gene encoding adiponectin has been mapped in a locus of human chromosome *3q27* that is associated to susceptibility to diabetes (206) and the metabolic syndrome (103). It was recently demonstrated that PPARγ activation increases adiponectin expression

and production in humans (124) and insulin resistant mice (221), which could contribute to the mechanisms by which synthetic ligands for PPARγ improve the sensitivity of glucose metabolism to insulin's action.

Nitric oxide (NO) is overproduced in adipose tissues and muscles by inducible nitric oxide synthase (iNOS) in conditions such as chronic inflammation and diet-induced obesity and insulin resistance (160). NO strongly impairs insulin-stimulated glucose uptake in L6 myotubes and isolated skeletal muscles (157) and it is also involved in triglyceride metabolism through an action on skeletal muscle lipoprotein lipase activity (158). Recently, it was shown that activation of PPARγ results in a decrease in iNOS expression in mesangial cells (166), Kupffer cells (201), chondrocytes (53), and macrophages (125) via its effects on the NFκB, AP1, and STAT1 pathways. Although such PPARγ-induced repression of iNOS expression has to be confirmed experimentally in adipose tissue and skeletal muscle, NO might play an important role in the improvement of glucose homeostasis resulting from PPARγ activation. This hypothesis is supported by the fact that PPARγ activation by 15-deoxy-delta12,14-prostaglandin J2 blunts TNF-α-mediated insulin resistance in β-cells through inhibition of iNOS expression (112).

INDUCTION OF GENES INVOLVED IN GLUCOSE METABOLISM AND EFFECTS IN MUSCLE

The role of PPARγ in the transcriptional control of genes involved in glucose uptake and insulin signaling has not been investigated as much as its role in lipid metabolism. However, there is growing support for the hypothesis that PPARγ can directly modulate the expression of genes that are involved in glucose homeostasis.

It has been reported that exposure of differentiated adipocytes to thiazolidinediones triggers the expression of the genes for the insulin receptor subtrate-2 (189), the p85 subunit of phosphatidylinositol (PI) 3-kinase (170), and the insulin-dependent glucose transporter GLUT4 (36, 219). On a protein level PPARγ activation has been shown to result in an increase in insulin receptor and IRS-1 levels, as well as in the association of IRS-1 with the p85 subunit of PI_3-kinase in 3T3-L1 differentiated adipocytes rendered insulin resistant by TNF-α treatment (96). Insulin binding to its receptor triggers receptor modifications that result in phosphorylation of intracellular molecules mediating independent signaling pathways, such as the IRS proteins and the proto-oncogene c-Cbl. The Cbl-associated protein CAP is an adapter protein that serves to recruit Clb to the insulin receptor (14). Thus, it has been argued that CAP is an important feature of the early events modulating the insulin signaling pathway. Interestingly, in mature adipocytes it was shown that PPARγ activation increases CAP expression (167), which is likely due to the presence of a PPAR response element in the CAP promotor (13). Although the physiological relevance of such a PPARγ effect has to be clarified in muscle tissues and in animal models of insulin resistance, it suggests that PPARγ might be more tightly coupled to insulin signaling than originally speculated. All these observations hence suggest that PPARγ can also directly modulate glucose uptake and insulin signaling pathways in adipocytes. This direct action is in addition to its effects on lipid metabolism, which results in insulin sensitization.

Although PPARγ is expressed at low levels in skeletal muscle, the mass of muscle on a whole body basis could be sufficient to counterbalance low PPARγ activity (110, 205). Therefore, physiologically relevant effects of PPARγ ligands in muscle cannot be excluded (121). Because observed effects might be secondary to the increase in insulin sensitivity during administration, it is difficult to make conclusions based on data generated in isolated muscle of PPARγ ligand-treated animals or men (78, 212, 224, 232). However, direct effects of thiazolidinediones on insulin-stimulated glucose uptake have been reported in L6 myotubes (30, 228) and in cultured human skeletal muscle cells (26, 99). Pyruvate dehydrogenase kinase 4 (PDK4) inhibits glucose oxidation and was proposed to make an important contribution to the altered glucose-fatty acid cycle that characterizes insulin resistant states (162). Interestingly, expression levels of PDK4 were found to be negatively correlated with insulin-stimulated glucose uptake during hyperinsulinemic euglycemic clamps and positively associated with insulin levels after an overnight fast or two hours post glucose absorption (127). Using an elegant mRNA profiling technique, it was recently shown that PPARγ activation by a selective tyrosine-based agonist repressed the expression of PDK4 in skeletal muscle (211), which indicates a new possible mechanism by which PPARγ activation improves insulin sensitivity. In addition, increased translocation and activity of GLUT4 has also been reported after thiazolidinedione treatment of muscle cells in vitro (4, 226). Whereas the activity of the insulin receptor does not increase after thiazolidinedione administration in L6 myotubes (228), insulin-stimulated PI_3-kinase activity seems to be enhanced in similar conditions (99, 228). Thus, enhancement of insulin-stimulated PI_3-kinase activity through an increase of its expression appears to be a generalized mechanism in both fat and muscle tissues by which PPARγ might directly affect glucose metabolism.

ACTIONS IN PANCREATIC β-CELLS Both PPARγ mRNA and protein are found in pancreatic β-cells (47). Whereas activation of PPARγ does not acutely improve insulin secretion in isolated human pancreatic islets (47), evidence is accumulating that PPARγ activation can restore or protect β-cell function from failure and apoptosis during the development of type II diabetes. When circulating glucose and free fatty acids are elevated, energy homeostasis in β-cells is altered, resulting in intracellular accumulation of triglycerides. Treatment with thiazolidinediones has been shown to inhibit intracellular triglyceride accumulation in pancreatic β-cells through increases in fatty acid oxidation, thereby delaying β-cell failure (84, 184). Improvement of cell viability after troglitazone administration has also been found in streptozotocin-induced type I diabetes (152), which further suggests that activation of PPARγ prevents β-cell death. This hypothesis was recently demonstrated in a rodent model of type II diabetes (60). In addition, a functional response element for PPARγ has been found in the promoter region of GLUT2 (102), the protein responsible for glucose transport in β-cells. PPARγ-mediated stimulation of GLUT2 expression would increase glucose uptake and trigger the initial steps leading to insulin release. All these observations hence support the hypothesis that PPARγ-mediated restoration or protection of β-cell function is

likely to contribute, at least in part, to the mechanisms by which thiazolidinedione improves and controls glucose homeostasis in diabetic patients (18, 25).

ACTIONS IN LIVER Published reports have shown that chronic thiazolidinedione administration either strongly (95, 193) or weakly (126) reduces hepatic glucose production, whereas other studies have reported no effect at all (188). These conflicting data suggest that liver is not a primary site of action of PPARγ ligands. Furthermore, in the case of a significant effect of PPARγ activation on hepatic glucose production, it is still unclear whether it is a direct action on the liver or a consequence of a general increase in insulin action. Finally, it was found that thiazolidinedione treatment in diabetic *db/db* mice induces expression in the liver of adipose tissue PPARγ target genes, such as adipocyte FABP (132), which warns that hepatic lipid accumulation (steatosis) could occur during long-term administration (22, 27, 204).

THIAZOLIDINEDIONES

Current pharmacological treatment of type II diabetes includes insulin injection or inhalation and administration of drugs that either increase insulin secretion (sulfonylureas and meglitinides), decrease hepatic glucose output (biguanides), or reduce postprandial glucose absorption (α-glucosidase inhibitors). These drugs are being prescribed either as monotherapy or in combination when diet and physical exercise inadequately control fasting plasma glucose to concentrations below 7 mmol/liter. It is worth noting that they do not directly tackle peripheral insulin resistance per se, which could explain why PPARγ-activating compounds such as the thiazolidinediones have attracted so much interest from the clinical side (67).

In 1997 troglitazone (*Rezulin*, Parke-Davis) was the first of the thiazolidinedione class of compounds to be launched, initially in the United States and later in Europe. Within a few months 135 cases of severe hepatic toxicity and 6 deaths were reported, which caused the UK Medicines Control Agency to rapidly withdraw troglitazone from the market. In March 2000 the U.S. Food and Drug Administration (FDA) did the same, but by then 90 cases of liver failure (of which 60 resulted in death) were associated with the drug. Since 1999 two other thiazolidinediones, rosiglitazone (*Avandia*, GlaxoSmithKline) and pioglitazone (*Actos*, Takeda/Eli Lilly) have been approved by the FDA as first-line therapeutic agents (42, 95), which are now used by over a million patients (142). In Europe, however, these compounds have only been approved for limited use as second-line therapy in combination with other oral antidiabetic drugs. The efficacy and side-effects of marketed thiazolidinediones are briefly reviewed below.

Clinical Efficacy

It remains unclear whether the effects of thiazolidinediones in humans are due to compound efficacy or worsening of the control group, because in most of the studies they were tested against a control group composed of type II diabetic subjects

without medication (136). The outcome of these studies is therefore often biased, which is why this review does not discuss them. The situation is now being reviewed by the FDA (196), because diabetic people on placebo treatment are exposed to deterioration of their already poor glycemic control and general health condition during the period of the study. Furthermore, whereas a lot of information relies on abstracts presented during scientific meetings (19), no head-to-head comparison studies between thiazolidinediones and antidiabetic pharmacophores of other chemical class have been published in peer-reviewed journals, which adds to the difficulty of comparing them with existing drugs that have been proven to be safe and effective.

In a study using obese, nondiabetic subjects, 200 mg of troglitazone given twice daily effectively reduced plasma glucose and insulin concentrations during an oral glucose tolerance test, as well as during a meal tolerance test (147). This effect was reflected by an increase in glucose disposal rate during an euglycemic-hyperinsulinemic clamp (147). Troglitazone (64), pioglitazone (136), and rosiglitazone (163) were all reported to lower fasting plasma glucose (by −1.5 to −2.0 mmol/liter) and hemoglobin A_{1c} (HbA_{1c}) levels (by 1.0 to 1.5%) in type II diabetic subjects. At present, however, no single trial directly comparing troglitazone, pioglitazone, and rosiglitazone in a head-to-head protocol has been published. From a mechanistic point of view, reductions in circulating levels of nonesterified fatty acids were observed in studies that measured this endpoint. Decreased hepatic glucose output (64, 193) and increased hepatic insulin sensitivity were also noticed in some studies (136), but it is still unclear whether this is a direct effect of the thiazolidinediones on the liver or a consequence of a general increase in insulin action.

It must be noted that glucose-lowering efficacy in humans is lower than in animal models of insulin resistance (65, 109, 114, 134, 135). Furthermore, the thiazolidinedione-induced reductions in fasting glycemia and HbA_{1c} are rather modest and they do not outperform the effects of metformin or sulfonylurea treatment. Moreover, higher frequency of dropouts (caused by inefficacy) during trials has been reported for both troglitazone and rosiglitazone compared with metformin or sulfonylureas, indicating a lower rate of success. Therefore, it has been proposed that thiazolidinediones should be prescribed in combination with antidiabetic drugs of other classes that also have distinct mechanisms of action. In this view troglitazone administration plus insulin injection resulted, in 350 poorly controlled diabetic patients, in a net, dose-dependent decrease in fasting plasma glucose (−1.5 to −2.2 mmol/liter) and HbA_{1c} (−1.4%) over the 26-week study compared with the group receiving insulin only (181). Similarly, in a double-blind, multi-center study, type II diabetic patients were randomized into a three arm protocol with two doses of rosiglitazone plus insulin and compared with a placebo group receiving insulin only (164). In this trial, mean HbA_{1c} decreased by 1% in rosiglitazone-treated patients, whereas fasting glycemia was reduced by 2 mmol/liter. These observations on combination therapy were supported by a study in which adding troglitazone to metformin therapy further reduced glycemia and HbA_{1c} levels (95). Recently, this issue has been confirmed in a trial in which rosiglitazone administration was

combined with metformin therapy for 26 weeks in type II diabetic patients already on metformin (61). In this study HbA_{1c} and fasting glycemia were further decreased in rosiglitazone-treated patients by 1.1% and 2.5 mmol/liter, respectively, compared with metformin alone. Moreover, in patients inadequately controlled on sulfonylureas, the addition of troglitazone treatment improved glycemic control by 4.4 mmol/liter as well as elevated HbA_{1c} by 2.8% (89). These findings have been confirmed in well-controlled study of diabetic patients who were randomized to receive either placebo or rosiglitazone, 1 mg or 2 mg daily in addition to the sulfonylureas they were already taking (216). Rosiglitazone treatment resulted in a significant dose-dependent decrease in fasting plasma glucose (-1.4 and 2.4 mmol/liter, respectively) and HbA_{1c} (-0.6 and -1.0%, respectively) compared with sulfonylureas alone, which likely can be accounted for by a synergetic effect of the drugs. These observations underscore the fact that thiazolidinediones are more effective in combination therapy and hence support the incorporation of thiazolidinediones in antidiabetic regimens.

Side Effects

Perhaps because of the involvement of PPARγ in several metabolic processes, thiazolidinediones have significant and numerous side effects. The most severe is liver failure. High levels of alanine aminotransferase (more than 2.5 times the normal level) were among the most cited side effects, which indicates the toxicity of the drugs (209). Alterations in mitochondrial function in hepatocytes seem to contribute to the hepatotoxicity (80). Ninety cases of liver failure were reported with troglitazone treatment (183, 209), and two cases of idiosyncratic hepatotoxicity associated with rosiglitazone were also observed since 1999 (2, 63). No case of liver failure has yet been shown for pioglitazone.

Cardiac side effects have occurred frequently in studies of mice, rats, and dogs. These effects included fluid retention and reduced hematocrit, which in some cases were associated with pulmonary edema (86, 108). However, similar consequences of fluid retention have been reported with insulin therapy, and it remains questionable whether these effects of the thiazolidinediones are mainly a reflection of improved insulin action (52, 107, 165). Consistent with these side effects, increases in heart size and weight have also been observed upon thiazolidinedione administration, sometimes leading to cardiac hypertrophy. In some more susceptible patients this side effect had major serious consequences; 56 cases of heart failure were reported within the first 19 months of troglitazone use (71). These findings indicate that careful monitoring of both liver and cardiac function should be performed in diabetic patients who might be already at risk for these complications.

High blood cholesterol levels, especially that of the LDL fraction, are damaging to cardiovascular health. Increases in plasma LDL concentrations were seen to some extent with all the thiazolidinediones but are most prominent with rosiglitazone (61). The increase in LDL from thiazolidinedione treatment is likely to be the consequence of a PPARγ-mediated enhanced hydrolysis of circulating

triglyceride-rich lipoproteins into smaller particles. In some cases increases in LDL ranged from 18 to 33% in rosiglitazone-treated patients. Long-term follow up will determine whether this increase translates into damaged arterial walls and atherosclerosis. However, recent studies suggest that this might not be the case, as PPARγ seems also to favor the reverse transport of cholesterol (29, 31).

Activating PPARγ has been shown to favor weight gain in humans (74, 101, 136). Although part of this weight gain can be attributed to fluid retention, most studies also indicate an increase in adipose tissue mass. Usually, fat mass accretion (which can be from 1 to 4 kg per year of treatment with a particular compound) is proportional to the affinity of the ligand to PPARγ. This side effect could likely be deleterious, because increased fat mass is also associated with deterioration of insulin sensitivity. Therefore, it remains unclear whether, in the long-term, the glucose-lowering effects of PPARγ activating drugs will be able to overcome the consequences of weight gain on insulin sensitivity.

NONTHIAZOLIDINEDIONES PPARγ LIGANDS

To increase the PPARγ-mediated glucose lowering actions and bypass the side effects associated with the thiazolidinedione class of compounds, intensive research efforts were made to find new and better agonists for PPARγ. The scope of this section is not to list every nonthiazolidinedione-based PPARγ ligand that has been described, but rather to discuss some of the characteristics that distinguish each class of compound of potential clinical interest.

L-Tyrosine-Based PPARγ Ligands

It has been shown that the degree of PPARγ activation is correlated with antidiabetic activities of the thiazolidinediones (17). This hypothesis recently led to the design of compounds with high affinity to PPARγ, such as the L-tyrosine-based PPARγ ligands. These drugs were designed by replacing the thiazolidinedione ring with a carboxylic acid and introducing an amine function on the adjacent carbon while keeping the parahydroxybenzyl sequence. An optimal PPARγ activity was obtained when the amine on the alpha carbon of the L-tyrosine ligands was substituted with a benzoylphenyl function, leading to the development of *N*-(2-benzoylphenyl)-L-tyrosine derivatives (33, 35, 83). Rigidifying the benzoyl and phenyl moieties of this alpha-amino substituent through an additional phenyl-phenyl bond leads to compounds with good potencies. The prototypical compound of this group of ligands is represented by the compound GI 262570. The crystal structure of the PPARγ ligand binding domain with this ligand has been reported (68). These novel compounds bind PPARγ with higher affinity (30–100 times greater than thiazolidinediones) and are effective in the treatment of diabetes and insulin resistance in both humans and animal models of diabetes (21, 59). The higher potency of these ligands to bind and activate PPARγ does not, however, translate into an improved antidiabetic efficacy compared with the

thiazolidinediones. Furthermore, the L-tyrosine-based PPARγ ligands also seem to be very adipogenic (211) and appear to share the same side effects of the thiazolidinediones.

PPARγ Modulators and Antagonists

As for other nuclear receptors, more and more evidence accumulates that suggests that selective receptor modulators might in fact be more promising drug candidates than classical receptor agonists and antagonists. Such selective receptor modulators, in homology to the selective estrogen receptor modulators, could have some beneficial effects in some tissue, yet lack effects in other tissues in which activation is less desirable.

In studies using the PPARγ antagonists GW0072 (151) and BADGE (217), it has been demonstrated that these synthetic compounds inhibit adipocyte differentiation and adipogenesis in 3T3-L1 cells. Interestingly, the recently described PPARγ antagonist LG100641 was shown to blunt thiazolidinedione-induced target gene expression in differentiated 3T3-L1 adipocytes, yet it stimulated glucose uptake (144). Additionally, NC-2100, a new thiazolidinedione, acts as a weak agonist in transfection assays and adipocyte differentiation studies but has potent antidiabetic activities in obese KKAy mice (66). The weak PPARγ agonist MCC-555 shares these features, but its activity depends on cell type and the sequence recognition site (145). Interestingly, MCC-555 does not induce the recruitment of the same cofactors as other ligands, which could indicate a new way to affect PPARγ activity.

These observations suggest that decreasing PPARγ activity, rather than activating it, results in an altered adipogenesis as well as an enhanced glucose uptake, which to some extent supports the effects of the partial loss of PPARγ function caused by mutations in both humans (Pro12Ala) and mice (+/−). A recent study has addressed this hypothesis by directly injecting a PPARγ antagonist or an RXR antagonist to high fat–fed mice (222). It was found that inhibition of either PPARγ or RXR improved insulin sensitivity and was associated with a decreased triglyceride content in white adipose tissue and skeletal muscle. These observations of RXR antagonists furthermore suggest that alterations in PPARγ activity can be indirectly caused by targeting RXR. Although further evidence is clearly required, modulating RXR activity might be an additional approach to diabetes treatment (143) and atherosclerosis prevention (31). Overall, these observations suggest that the effects of PPARγ on adipogenesis and insulin sensitization can be dissociated by selectively modulating PPARγ activity.

FMOC-L-leucine (F-L-Leu), whose structure is lacking the parahydroybenzyl sequence present in both the thiazolidinediones and the L-tyrosine-based PPARγ ligands, was described in our laboratory as a new potent insulin-sensitizing compound with unique PPARγ-activating and -binding properties (173). F-L-Leu binds and activates PPARγ with weaker affinity compared with that of rosiglitazone. Upon activation by F-L-Leu, PPARγ changes its structural conformation, which

triggers specific cofactor recruitment. F-L-Leu induces the docking of SRC-1 and p300 to PPARγ; whereas rosiglitazone favors the recruitment of p300 and TIF2 but not SRC-1. This differential cofactor recruitment most likely contributes to the distinct biological effect of F-L-Leu relative to classical PPARγ ligands. In fact, F-L-Leu induces PPARγ target gene expression in vitro and in vivo, yet to a lower extent than rosiglitazone. F-L-Leu is less adipogenic than rosiglitazone in differentiation assays and does not induce weight gain in mice. On the other hand, it has very potent glucose-lowering activities in both diet-induced and genetic rodent models of insulin resistance. These findings indicate that it is possible to design new molecules that serve as selective PPARγ modulators and that partial agonists such as F-L-Leu might be better suited for the treatment of insulin resistance compared with full agonists because they do not stimulate fat mass accretion. Therefore, the development of new pharmacophores around this chemical class should be encouraged.

Dual Agonists

In an attempt to broaden the activity and the beneficial effects of PPARγ agonists, PPARγ-PPARα and PPARγ-PPARδ dual agonists have been designed. These drugs target multiple tissues at the same time, and it seems that activating one PPAR can complement the action of the other. For instance, PPARα activation triggers a reduction in circulating triglyceride levels and enhances fatty acid oxidation, which could counteract some of the effects of PPARγ activation that result in fatty acid trapping in the adipocytes. Proof of the beneficial effects of adding PPARα activity to that of PPARγ was provided by the combined administration of a PPARγ agonist (rosiglitazone) and a PPARα agonist (fenofibrate) (28). In animals such a combination results in an improved triglyceride lowering (28, 116) and potentially in glucose lowering efficacy. Novel thiazolidinedione derivatives such as KRP-297, AZ 242, and JTT-501 were developed as PPARα-PPARγ dual agonists and combine this beneficial effect in one compound (104, 145, 182). As type II diabetes is a multi-faceted disease associated with dyslipidemia and other complications, targeting the liver and the adipose tissue with one compound would clearly widen the therapeutic window. Such is also the case in theory for PPARγ-PPARδ coagonists, which could combine the antidiabetic effects of PPARγ activation with the beneficial effects that PPARδ has on HDL-cholesterol levels (119, 154). The clinical efficacy of dual agonists is still to be determined, as well as their side effects, which could also be increased along with their enhanced tissue targeting.

PERSPECTIVES

Whereas the mechanisms by which PPARγ activation leads to insulin sensitization are becoming much better characterized, it is less clear whether full agonist activity should remain the preferred goal in the design of future compounds. Indeed, new evidence suggests that antagonizing PPARγ activity in a pharmacological way improves insulin sensitivity as well. These findings are consistent with the genetic

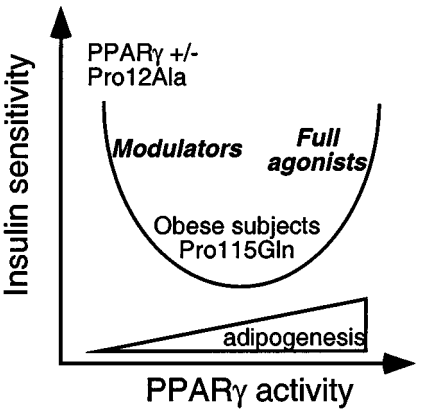

Figure 2 Hypothesis summarizing the role of PPARγ activation in glucose homeostasis. PPARγ heterozygous mice (PPARγ+/−) and human carriers of the Pro12Ala point mutation have increased insulin sensitivity, whereas obese patients and human carriers of the Pro115Gln mutation are insulin resistant. Activation of PPARγ by full agonists was shown to improve insulin sensitivity, but fat mass accretion and increase in body weight are also observed upon treatment. On the other hand, modulators of PPARγ such as FMOC-L-Leu have potent insulin sensitizing effects, yet they do not induce adipogenesis and fat mass accretion to the same extent as classical PPARγ agonists such as the thiazolidinediones.

studies on PPARγ that show that reduction in PPARγ, either by ablation of one allele or by partial loss-of-function mutation, results in higher sensitivity of glucose metabolism to the action of insulin. Such observations suggest that the effect of PPARγ on glucose homeostasis is U-shaped (Figure 2). Adipogenesis and fat mass accretion increase with enhanced PPARγ activity. The ideal situation would be to improve insulin sensitivity without promoting weight gain. Further analysis of this hypothesis is required to better understand the current paradox that both reducing and increasing PPARγ activity triggers insulin sensitization.

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LITERATURE CITED

1. Adams M, Reginato MJ, Shao D, Lazar MA, Chatterjee VK. 1997. Transcriptional activation by peroxisome proliferator-activated receptor gamma is inhibited by phosphorylation at a consensus mitogen-activated protein kinase site. *J. Biol. Chem.* 272:5128–32
2. Al-Salman J, Arjomand H, Kemp DG, Mittal M. 2000. Hepatocellular injury in a patient receiving rosiglitazone. A case report. *Ann. Intern. Med.* 132:121–24
3. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, et al. 2000. The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat. Genet.* 26:76–80
4. Arakawa K, Ishihara T, Aoto M, Inamasu M, Saito A, Ikezawa K. 1998. Actions of novel antidiabetic thiazolidinedione, T-174, in animal models of non-insulin-dependent diabetes mellitus (NIDDM) and in cultured muscle cells. *Br. J. Pharmacol.* 125:429–36
5. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, et al. 1999. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem. Biophys. Res. Commun.* 257:79–83
6. American Diabetes Association. 1998. Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care* 21: 296–309
7. Auboeuf D, Rieusset J, Fajas L, Vallier P, Frering V, et al. 1997. Tissue distribution and quantification of the expression of PPARs and LXRα in humans: no alterations in adipose tissue of obese and NIDDM patients. *Diabetes* 48:1319–27
8. Auwerx J. 1999. PPARγ, the ultimate thrifty gene. *Diabetologia* 42:1033–49
9. Bakopanos E, Silva JE. 2000. Thiazolidinediones inhibit the expression of beta3-adrenergic receptors at a transcriptional level. *Diabetes* 49:2108–15
10. Banerji MA, Chaiken RL, Gordon D, Kral JG, Lebovitz HE. 1995. Does intra-abdominal adipose tissue in black men determine whether NIDDM is insulin-resistant or insulin-sensitive? *Diabetes* 44:141–46
11. Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, et al. 1999. PPARgamma is recruited for placental, cardiac, and adipose tissue development. *Mol. Cell.* 4: 585–95
12. Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, et al. 1999. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 402:880–83
13. Baumann CA, Chokshi N, Saltiel AR, Ribon V. 2000. Cloning and characterization of a functional peroxisome proliferator activator receptor-gamma-responsive element in the promoter of the CAP gene. *J. Biol. Chem.* 275:9131–35
14. Baumann CA, Ribon V, Kanzaki M, Thurmond DC, Mora S, et al. 2000. CAP defines a second signalling pathway required for insulin-stimulated glucose transport. *Nature* 407:202–7
15. Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, et al. 1998. Association of the Pro12Ala variant in peroxisome proliferator-activated receptor gamma2 gene with obesity in two Caucasian populations. *Diabetes* 47:1806–8
16. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. 2001. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat. Med.* 7:947–53
17. Berger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, et al. 1998. Novel PPARγ and PPARδ ligands produce

distinct physiological effects: PPARγ activation correlates with antidiabetic activity. *J. Biol. Chem.* 274:6718–25

18. Berkowitz K, Peters R, Kjos SL, Goico J, Marroquin A, et al. 1996. Effect of troglitazone on insulin sensitivity and pancreatic beta-cell function in women at high risk for NIDDM. *Diabetes* 45:1572–79
19. Bloomgarden ZT. 1999. American Diabetes Association Annual Meeting, 1998. Treatment of type 2 diabetes. *Diabetes Care* 22:170–74
20. Braissant O, Foufelle F, Scotto C, Dauca M, Wahli W. 1995. Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-α, -β, and γ in the adult rat. *Endocrinology* 137:354–66
21. Brown KK, Henke BR, Blanchard SG, Cobb JE, Mook R, et al. 1999. A novel N-aryl tyrosine activator of peroxisome proliferator-activated receptor-gamma reverses the diabetic phenotype of the Zucker diabetic fatty rat. *Diabetes* 48: 1415–24
22. Burant CF, Sreenan S, Hirano K-I, Tai T-AC, Lohmiller J, et al. 1997. Troglitazone action is independent of adipose tissue. *J. Clin. Invest.* 100:2900–8
23. Burkey BF, Dong M, Gagen K, Eckhardt M, Dragonas N, et al. 2000. Effects of pioglitazone on promoting energy storage, not expenditure, in brown adipose tissue of obese fa/fa Zucker rats: comparison to CL 316,243. *Metabolism* 49:1301–8
24. Castillo G, Brun RP, Rosenfield JK, Hauser S, Park CW, et al. 1999. An adipogenic cofactor bound by the differentiation domain of PPARgamma. *EMBO J.* 18:3676–87
25. Cavaghan MK, Ehrmann DA, Byrne MM, Polonsky KS. 1997. Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. *J. Clin. Invest.* 100:530–37
26. Cha BS, Ciaraldi TP, Carter L, Nikoulina SE, Mudaliar S, et al. 2001. Peroxisome proliferator-activated receptor (PPAR) gamma and retinoid X receptor (RXR) agonists have complementary effects on glucose and lipid metabolism in human skeletal muscle. *Diabetologia* 44:444–52
27. Chao L, Marcus-Samuels B, Mason MM, Moitra J, Vinson C, et al. 2000. Adipose tissue is required for the antidiabetic, but not for the hypolipidemic, effect of thiazolidinediones. *J. Clin. Invest.* 106:1221–28
28. Chaput E, Saladin R, Silvestre M, Edgar AD. 2000. Fenofibrate and rosiglitazone lower serum triglycerides with opposing effects on body weight. *Biochem. Biophys. Res. Commun.* 271:445–50
29. Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, et al. 2001. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. *Mol. Cell.* 7:161–71
30. Ciaraldi TP, Gilmore A, Olefsky JM, Goldberg M, Heidenreich KA. 1990. In vitro studies on the action of CS-045, a new antidiabetic agent. *Metabolism* 39: 1056–62
31. Claudel T, Leibowitz MD, Fievet C, Tailleux A, Wagner B, et al. 2001. Reduction of atherosclerosis in apolipoprotein E knockout mice by activation of the retinoid X receptor. *Proc. Natl. Acad. Sci. USA* 98:2610–15
32. Clement K, Hercberg S, Passinge B, Galan P, Varroud-Vial M, et al. 2000. The Pro115Gln and Pro12Ala PPAR gamma gene mutations in obesity and type 2 diabetes. *Int. J. Obes. Relat. Metab. Disord.* 24:391–93
33. Cobb JE, Blanchard SG, Boswell EG, Brown KK, Charifson PS, et al. 1998. N-(2-benzoylphenyl)-L-tyrosine PPAR-gamma agonists. 3. Structure-activity relationship and optimization of the N-aryl substituent. *J. Med. Chem.* 41:5055–69
34. Cohen B, Novick D, Rubinstein M. 1996. Modulation of insulin activities by leptin. *Science* 274:1185–88
35. Collins JL, Blanchard SG, Boswell GE,

Charifson PS, Cobb JE, et al. 1998. N-(2-benzoylphenyl)-L-tyrosine PPARgamma agonists. 2. Structure-activity relationship and optimization of the phenyl alkyl ether moiety. *J. Med. Chem.* 41:5037–54

36. Dana SL, Hoener PA, Bilakovics JM, Crombie DL, Ogilvie KM, et al. 2001. Peroxisome proliferator-activated receptor subtype-specific regulation of hepatic and peripheral gene expression in the Zucker diabetic fatty rats. *Metabolism* 50:963–71
37. Davies PJ, Berry SA, Shipley GL, Eckel RH, Hennuyer N, et al. 2001. Metabolic effects of rexinoids: tissue-specific regulation of lipoprotein lipase activity. *Mol. Pharmacol.* 59:170–76
38. de Souza CJ, Eckhardt M, Gagen K, Dong M, Chen W, et al. 2001. Effects of pioglitazone on adipose tissue remodeling within the setting of obesity and insulin resistance. *Diabetes* 50:1863–71
39. De Vos P, Lefebvre AM, Miller SG, Guerre-Millo M, Wong K, et al. 1996. Thiazolidinediones repress *ob* gene expression via activation of PPARγ. *J. Clin. Invest.* 98:1004–9
40. Deeb S, Fajas L, Nemoto M, Laakso M, Fujimoto W, Auwerx J. 1998. A Pro 12 Ala substitution in the human peroxisome proliferator-activated receptor gamma2 is associated with decreased receptor activity, improved insulin sensitivity, and lowered body mass index. *Nat. Genet.* 20: 284–87
41. DeFronzo RA. 1988. The Triumvirate: beta-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–87
42. DeFronzo RA. 2000. Pharmacologic therapy for type 2 diabetes mellitus. *Ann. Intern. Med.* 133:73–74
43. Desvergne B, Wahli W. 1999. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr. Rev.* 20:649–88
44. Digby JE, Montague CT, Sewter CP, Sanders L, Wilkison WO, et al. 1997. Thiazolidinedione exposure increases the expression of uncoupling protein 1 in cultured human preadipocytes. *Diabetes* 47:138–41
45. Douglas JA, Erdos MR, Wanatabe RM, Braun A, Johnston CI, et al. 2001. The peroxisome proliferator-activated receptor-gamma Pro12Ala variant: association with type 2 diabetes and trait differences. *Diabetes* 50:886–90
46. Dowell P, Ishmael JE, Avram D, Peterson VJ, Nevrivy DJ, Leid M. 1999. Identification of nuclear receptor corepressor as a peroxisome proliferator-activated receptor alpha interacting protein. *J. Biol. Chem.* 274:15901–7
47. Dubois M, Pattou F, Kerr-Conte J, Gmyr V, Vandewalle B, et al. 2000. Expression of peroxisome proliferator-activated receptor gamma (PPARgamma) in normal human pancreatic islet cells. *Diabetologia* 43:1165–69
48. Eckersley RM. 2001. Losing the battle of the bulge: causes and consequences of increasing obesity. *Med. J. Aust.* 174:590–92
49. Ek J, Urhammer SA, Sorensen TIA, Andersen T, Auwerx J, Pedersen O. 1999. Homozygosity of the Pro12Ala variant of the peroxisome proliferator activated receptor γ2 (PPARγ2): divergent modulating effects on body mass index in obese and lean men of Caucasian origin. *Diabetologia* 42:892–95
50. Emilsson V, O'Dowd J, Wang S, Liu YL, Sennitt M, et al. 2000. The effects of rexinoids and rosiglitazone on body weight and uncoupling protein isoform expression in the Zucker fa/fa rat. *Metabolism* 49:1610–15
51. Escher P, Braissant O, Basu-Modak S, Michalik L, Wahli W, Desvergne B. 2001. Rat PPARs: quantitative analysis in adult rat tissues and regulation in fasting and refeeding. *Endocrinology* 142:4195–202
52. Evans DJ, Pritchard-Jones K, Trotman-Dickenson B. 1986. Insulin oedema. *Postgrad. Med. J.* 62:665–68

53. Fahmi H, Di Battista JA, Pelletier JP, Mineau F, Ranger P, Martel-Pelletier J. 2001. Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-1beta-induced nitric oxide and matrix metalloproteinase 13 production in human chondrocytes. *Arthritis Rheum.* 44:595–607
54. Fajas L, Auboeuf D, Raspe E, Schoonjans K, Lefebvre AM, et al. 1997. Organization, promoter analysis and expression of the human PPARγ gene. *J. Biol. Chem.* 272:18779–89
55. Fajas L, Debril MB, Auwerx J. 2001. Peroxisome proliferator-activated receptor-gamma: from adipogenesis to carcinogenesis. *J. Mol. Endocrinol.* 27:1–9
56. Fajas L, Fruchart JC, Auwerx J. 1998. PPARγ3 mRNA: a distinct PPARγ mRNA subtype transcribed from an independent promoter. *FEBS Lett.* 438:55–60
57. Ferrannini E. 1998. Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. *Endocr. Rev.* 19:477–90
58. Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA. 1983. Effect of fatty acids on glucose production and utilization in man. *J. Clin. Invest.* 72:1737–47
59. Fiedorek FT, Wilson GG, Frith L, Patel J, Abou-Donia M. 2000. Monotherapy with GI262570, a tyrosine-based non-thiazolidinedione PPARγ agonist, improves metabolic control in type 2 diabetes mellitus patients. *Diabetes* 49:157 (abstract)
60. Finegood DT, McArthur MD, Kojwang D, Thomas MJ, Topp BG, et al. 2001. β-cell mass dynamics in Zucker diabetic fatty rats: rosiglitazone prevents the rise in net cell death. *Diabetes* 50:1021–29
61. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. 2000. Effects of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA* 283:1695–702
62. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 1995. 15-deoxy-Δ12,14 prostaglandin J2 is a ligand for the adipocyte determination factor PPARγ. *Cell* 83:803–12
63. Forman LM, Simmons DA, Diamond RH. 2000. Hepatic failure in a patient taking rosiglitazone. *Ann. Intern. Med.* 132:118–21
64. Frias JP, Yu JG, Kruszynska YT, Olefsky JM. 2000. Metabolic effects of troglitazone therapy in type 2 diabetic, obese, and lean normal subjects. *Diabetes Care* 23: 64–69
65. Fujiwara T, Yoshioka S, Yoshioka T, Ushiyama I, Horikoshi H. 1988. Characterization of new oral antidiabetic agent CS-045. Studies in *KK* and *ob*/*ob* mice and Zucker fatty rats. *Diabetes* 37:1549–58
66. Fukui Y, Masui S, Osada S, Umesono K, Motojima K. 2000. A new thiazolidinedione, NC-2100, which is a weak PPAR-gamma activator, exhibits potent antidiabetic effects and induces uncoupling protein 1 in white adipose tissue of KKAy obese mice. *Diabetes* 49:759–67
67. Gale EA. 2001. Lessons from the glitazones: a story of drug development. *Lancet* 357:1870–75
68. Gampe RTJ, Montana VG, Lambert MH, Miller AB, Bledsoe RK, et al. 2000. Asymmetry in the PPAR gamma-RXR alpha crystal structure reveals the molecular basis of heterodimerization among nuclear receptors. *Mol. Cell.* 5:545–55
69. Garg A, Peshock RM, Fleckenstein JL. 1999. Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). *J. Clin. Endocrinol. Metab.* 84:170–74
70. Gelman L, Zhou G, Fajas L, Raspe E, Fruchart JC, Auwerx J. 1999. p300 interacts with the N- and C- terminal part of PPARγ2 in a ligand-independent and -dependent manner respectively. *J. Biol. Chem.* 274:7681–88
71. Ghazzi MN, Perez JE, Antonucci TK, Driscoll JH, Huang SM, et al. 1997. Cardiac and glycemic benefits of troglitazone

treatment in NIDDM. *Diabetes* 46:433–39
72. Glass CK, Rosenfeld MG. 2000. The coregulator exchange in transcriptional functions of nuclear receptors. *Genes Dev.* 14:121–41
73. Gonzalez F, Thusu K, Abdel-Rahman E, Prabhala A, Tomani M, Dandona P. 1999. Elevated serum levels of tumor necrosis factor alpha in normal-weight women with polycystic ovary syndrome. *Metabolism* 48:437–41
74. Gorson DM. 1999. Significant weight gain with Rezulin therapy. *Arch. Intern. Med.* 159:99
75. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, et al. 1997. Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. *Diabetes* 46:63–69
76. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, et al. 1995. Weight-reducing effects of the plasma protein encoded by the *obese* gene. *Science* 269: 543–46
77. Hallakou S, Doare L, Foufelle F, Kergoat M, Guerre-Millo M, et al. 1997. Pioglitazone induces in vivo adipocyte differentiation in the obese Zucker fa/fa rat. *Diabetes* 46:1393–99
78. Hallakou S, Foufelle F, Doare L, Kergoat M, Ferre P. 1998. Pioglitazone-induced increase of insulin sensitivity in the muscles of the obese Zucker fa/fa rat cannot be explained by local adipocyte differentiation. *Diabetologia* 41:963–68
79. Hara K, Okada T, Tobe K, Yasuda K, Mori Y, et al. 2000. The Pro12Ala polymorphism in PPAR gamma2 may confer resistance to type 2 diabetes. *Biochem. Biophys. Res. Commun.* 271:212–16
80. Haskins JR, Rowse P, Rahbari R, de la Iglesia FA. 2001. Thiazolidinedione toxicity to isolated hepatocytes revealed by coherent multiprobe fluorescence microscopy and correlated with multiparameter flow cytometry of peripheral leukocytes. *Arch. Toxicol.* 75:425–38
81. Heery DM, Kalkhoven E, Hoare S, Parker MG. 1997. A signature motif in transcriptional coactivators mediates binding to nuclear receptors. *Nature* 387:733–36
82. Heinlein CA, Ting HJ, Yeh S, Chang C. 1999. Identification of ARA70 as a ligand-enhanced coactivator for the peroxisome proliferator-activated receptor gamma. *J. Biol. Chem.* 274:16147–52
83. Henke BR, Blanchard SG, Brackeen MF, Brown KK, Cobb JE, et al. 1998. N-(2-benzoylphenyl)-L-tyrosine PPARgamma agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents. *J. Med. Chem.* 41:5020–36
84. Higa M, Zhou YT, Ravazzola M, Baetens D, Orci L, Unger RH. 1999. Troglitazone prevents mitochondrial alterations, beta cell destruction, and diabetes in obese prediabetic rats. *Proc. Natl. Acad. Sci. USA* 96:11513–18
85. Hill M, Young M, McCurdy C, Gimble J. 1997. Decreased expression of murine PPARγ in adipose tissue during endotoxinemia. *Endocrinology* 138:3073–76
86. Hirsch IB, Kelly J, Cooper S. 1999. Pulmonary edema associated with troglitazone therapy. *Arch. Intern. Med.* 159:1811
87. Hofmann C, Lorenz K, Braithwaite SS, Colca JR, Palazuk BJ, et al. 1994. Altered gene expression for tumor necrosis factor-α and its receptor during drug and dietary modulation of insulin resistance. *Endocrinology* 134:264–70
88. Hong H, Kohli K, Trivedi A, Johnson DL, Stallcup MR. 1996. GRIP1, a novel mouse protein that serves as a transcriptional coactivator in yeast for the hormone binding domains of steroid receptors. *Proc. Natl. Acad. Sci. USA* 93:4948–52
89. Horton ES, Whitehouse F, Ghazzi MN, Venable TC, Whitcomb RW. 1998. Troglitazone in combination with sulfonylurea restores glycemic control in patients with

type 2 diabetes. The Troglitazone Study Group. *Diabetes Care* 21:1462–69

90. Hotamisligil GS, Shargill NS, Spiegelman BM. 1993. Adipose tissue expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. *Science* 259:87–91
91. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, et al. 2001. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 50:1126–33
92. Hsueh WC, Cole SA, Shuldiner AR, Beamer BA, Blangero J, et al. 2001. Interactions between variants in the beta3-adrenergic receptor and peroxisome proliferator-activated receptor-gamma2 genes and obesity. *Diabetes Care* 24:672–77
93. Hu E, Kim JB, Sarraf P, Spiegelman BM. 1996. Inhibition of adipogenesis through MAP-kinase mediated phosphorylation of PPARγ. *Science* 274:2100–3
94. IJima K, Yoshizumi M, Ako J, Eto M, Kim S, Hashimoto M. 1998. Expression of peroxisome proliferator activated receptor γ (PPARγ) in rat smooth muscle cells. *Biochem. Biophys. Res. Commun.* 247:353–56
95. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, et al. 1998. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes. *N. Engl. J. Med.* 338:867–72
96. Iwata M, Haruta T, Usui I, Takata Y, Takano A, et al. 2001. Pioglitazone ameliorates tumor necrosis factor-alpha-induced insulin resistance by a mechanism independent of adipogenic activity of peroxisome proliferator-activated receptor-gamma. *Diabetes* 50:1083–92
97. Kallen CB, Lazar MA. 1996. Antidiabetic thiazolidinediones inhibit leptin (ob) gene expression in 3T3-L1 adipocytes. *Proc. Natl. Acad. Sci. USA* 93:5793–96
98. Kamohara S, Burcelin R, Halaas JL, Friedman JM, Charron MJ. 1997. Acute stimulation of glucose metabolism in mice by leptin treatment. *Nature* 389:374–77
99. Kausch C, Krutzfeldt J, Witke A, Rettig A, Bachmann O, et al. 2001. Effects of troglitazone on cellular differentiation, insulin signaling, and glucose metabolism in cultured human skeletal muscle cells. *Biochem. Biophys. Res. Commun.* 280: 664–74
100. Kawai T, Takei I, Oguma Y, Ohashi N, Tokui M, et al. 1999. Effects of troglitazone on fat distribution in the treatment of male type 2 diabetes. *Metabolism* 48:1102–7
101. Kelly IE, Han TS, Walsh K, Lean ME. 1999. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. *Diabetes Care* 22:288–93
102. Kim HI, Kim JW, Kim SH, Cha JY, Kim KS, Ahn YH. 2000. Identification and functional characterization of the peroxisomal proliferator response element in rat GLUT2 promoter. *Diabetes* 49:1517–24
103. Kissebah AH, Sonnenberg GE, Myklebust J, Goldstein M, Broman K, et al. 2000. Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. *Proc. Natl. Acad. Sci. USA* 97:14478–83
104. Kjellstedt A, Oakes N, Svensson L, Carlsson A-C, Ljung B. 2001. AZ 242, a novel PPARα/γ agonist, has potent and efficient insulin-sensitizing and antidyslipidemic properties in ob/ob mice and fa/fa Zucker rats. *Diabetes* 50(suppl 2):A121 (abstract)
105. Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, et al. 1997. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ. *Proc. Natl. Acad. Sci. USA* 94:4318–23
106. Kodera Y, Takeyama K, Murayama A, Suzawa M, Masuhiro Y, Kato S. 2000. Ligand type-specific interactions of peroxisome proliferator-activated receptor

gamma with transcriptional coactivators. *J. Biol. Chem.* 275:33201–4
107. Koivisto VA. 1993. Insulin therapy in type II diabetes. *Diabetes Care* 16(Suppl 3):29–39
108. Koshida H, Shibata K, Kemetani T. 1998. Pleuropulmonary disease in a man with diabetes who was treated with troglitazone. *N. Engl. J. Med.* 339:1400–1
109. Kraegen EW, James DE, Jenkins AB, Chisholm DJ, Storlien LH. 1989. A potent in vivo effect of ciglitazone on muscle insulin resistance induced by high fat feeding of rats. *Metabolism* 38:1089–93
110. Kruszynska YT, Mukherjee R, Jow L, Dana S, Paterniti JR, Olefsky JM. 1998. Skeletal muscle peroxisome proliferator-activated receptor-γ expression in obesity and non-insulin-dependent diabetes mellitus. *J. Clin. Invest.* 101:543–48
111. Kubota N, Terauchi Y, Miki H, Tamemoto H, Yamauchi T, et al. 1999. PPARγ mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. *Mol. Cell.* 4:597–609
112. Kwon G, Xu G, Marshall CA, McDaniel ML. 1999. Tumor necrosis factor alpha-induced pancreatic beta-cell insulin resistance is mediated by nitric oxide and prevented by 15-deoxy-Delta12,14-prostaglandin J2 and aminoguanidine. A role for peroxisome proliferator-activated receptor gamma activation and inos expression. *J. Biol. Chem.* 274:18702–8
113. Lavinsky RM, Jepsen K, Heinzel T, Torchia J, Mullen TM, et al. 1998. Diverse signalling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes. *Proc. Natl. Acad. Sci. USA* 95:2920–25
114. Lee MK, Miles PD, Khoursheed M, Gao KM, Moossa AR, Olefsky JM. 1994. Metabolic effects of troglitazone on fructose-induced insulin resistance in the rat. *Diabetes* 43:1435–39
115. Lefebvre AM, Laville M, Vega N, Riou JP, Van Gaal L, et al. 1998. Depot-specific differences in adipose tissue gene expression in lean and obese subjects. *Diabetes* 47:98–103
116. Lefebvre A-M, Peinado-Onsurbe J, Leitersdorf I, Briggs MR, Paterniti JR, et al. 1997. Regulation of lipoprotein metabolism by thiazolidinediones occurs through a distinct, but complementary mechanism relative to fibrates. *Arterioscler. Thromb. Vasc. Biol.* 17:1756–64
117. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. 1997. Peroxisome proliferator-activated receptors α and γ are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J. Biol. Chem.* 272:3406–10
118. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. 1995. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). *J. Biol. Chem.* 270:12953–56
119. Leibowitz MD, Fievet C, Hennuyer N, Peinado-Onsurbe J, Duez H, et al. 2000. Activation of PPARdelta alters lipid metabolism in db/db mice. *FEBS Lett.* 473: 333–36
120. Lenhard JM, Kliewer SA, Paulik MA, Plunket KD, Lehmann JM, Weiel JE. 1997. Effects of troglitazone and metformin on glucose and lipid metabolism: alterations of two distinct molecular pathways. *Biochem. Pharmacol.* 54:801–8
121. Loviscach M, Rehman N, Carter L, Mudaliar S, Mohadeen P, et al. 2000. Distribution of peroxisome proliferator-activated receptors (PPARs) in human skeletal muscle and adipose tissue: relation to insulin action. *Diabetologia* 43: 304–11
122. Lowell BB. 1999. PPARgamma: an essential regulator of adipogenesis and modulator of fat cell function. *Cell* 99:239–42
123. Luan J, Browne PO, Harding AH, Halsall DJ, O'Rahilly S, et al. 2001. Evidence for gene-nutrient interaction at the PPARgamma locus. *Diabetes* 50:686–89
124. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, et al. 2001.

PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094–99

125. Maggi LB Jr, Sadeghi H, Weigand C, Scarim AL, Heitmeier MR, Corbett JA. 2000. Anti-inflammatory actions of 15-deoxy-delta 12,14-prostaglandin J2 and troglitazone: evidence for heat shock-dependent and -independent inhibition of cytokine-induced inducible nitric oxide synthase expression. *Diabetes* 49:346–55
126. Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, et al. 1998. Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* 128:176–85
127. Majer M, Popov KM, Harris RA, Bogardus C, Prochazka M. 1998. Insulin downregulates pyruvate dehydrogenase kinase (PDK) mRNA: potential mechanism contributing to increased lipid oxidation in insulin-resistant subjects. *Mol. Genet. Metab.* 65:181–86
128. Martin G, Schoonjans K, Lefebvre A, Staels B, Auwerx J. 1997. Coordinate regulation of the expression of the fatty acid transport protein (FATP) and acyl CoA synthetase genes by PPARα and PPARγ activators. *J. Biol. Chem.* 272:28210–17
129. Martin G, Schoonjans K, Staels B, Auwerx J. 1998. PPARγ activators improve glucose homeostasis by stimulating fatty acid uptake in the adipocytes. *Atherosclerosis* 137:75–80
130. Mauriege P, Imbeault P, Langin D, Lacaille M, Almeras N, et al. 1999. Regional and gender variations in adipose tissue lipolysis in response to weight loss. *J. Lipid Res.* 40:1559–71
131. Meirhaeghe A, Fajas L, Helbecque N, Cottel D, Auwerx J, et al. 2000. Impact of the peroxisome proliferator activated receptor gamma2 Pro12Ala polymorphism on adiposity, lipids and non-insulin-dependent diabetes mellitus. *Int. J. Obes. Relat. Metab. Disord.* 24:195–99
132. Memon RA, Tecott LH, Nonogaki K, Beigneux A, Moser AH, et al. 2000. Up-regulation of peroxisome proliferator-activated receptors (PPAR-alpha) and PPAR-gamma messenger ribonucleic acid expression in the liver in murine obesity: troglitazone induces expression of PPAR-gamma-responsive adipose tissue-specific genes in the liver of obese diabetic mice. *Endocrinology* 141:4021–31
133. Miles PD, Barak Y, He W, Evans RM, Olefsky JM. 2000. Improved insulin-sensitivity in mice heterozygous for PPAR-gamma deficiency. *J. Clin. Invest.* 105: 287–92
134. Miles PD, Higo K, Romeo OM, Lee MK, Rafaat K, Olefsky JM. 1998. Troglitazone prevents hyperglycemia-induced but not glucosamine-induced insulin resistance. *Diabetes* 47:395–400
135. Miles PD, Romeo OM, Higo K, Cohen A, Rafaat K, Olefsky JM. 1997. TNF-alpha-induced insulin resistance in vivo and its prevention by troglitazone. *Diabetes* 46:1678–83
136. Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, et al. 2001. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 24:710–19
137. Moitra J, Mason MM, Olive M, Krylov D, Gavrilova O, et al. 1998. Life without fat: a transgenic mouse. *Genes Dev.* 12:3168–81
138. Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, et al. 2001. The Pro12Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. *Diabetes* 50:891–94
139. Mori Y, Kim-Motoyama H, Katakura T, Yasuda K, Kadowaki H, et al. 1998. Effect of the Pro12Ala variant of the

human peroxisome proliferator activated receptor $\gamma 2$ gene on adiposity, fat distribution, and insulin sensitivity in Japanese men. *Biochem. Biophys. Res. Commun.* 251:195–98

140. Mori Y, Murakawa Y, Okada K, Horikoshi H, Yokoyama J, et al. 1999. Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care* 22: 908–12
141. Morrison RF, Farmer SR. 2000. Hormonal signaling and transcriptional control of adipocyte differentiation. *J. Nutr.* 130:3116S–21S
142. Mudaliar S, Henry RR. 2001. New oral therapies for type 2 diabetes mellitus: the glitazones or insulin sensitizers. *Annu. Rev. Med.* 52:239–57
143. Mukherjee R, Davies PAJ, Crombie DL, Bischoff ED, Cesario RM, et al. 1997. Sensitization of diabetic and obese mice to insulin by retinoid X receptor agonists. *Nature* 386:407–10
144. Mukherjee R, Hoener PA, Jow L, Bilakovics J, Klausing K, et al. 2000. A selective peroxisome proliferator-activated receptor-gamma (PPARgamma) modulator blocks adipocyte differentiation but stimulates glucose uptake in 3T3-L1 adipocytes. *Mol. Endocrinol.* 14:1425–33
145. Murakami K, Tobe K, Ide T, Mochizuki T, Ohashi M, et al. 1998. A novel insulin sensitizer acts as a coligand for peroxisome proliferator-activated receptor α and γ. Effect of PPARα activation on normal lipid metabolism in liver of Zucker fatty rats. *Diabetes* 47:1841–47
146. Nagy L, Tontonez P, Alvarez JG, Chen H, Evans RM. 1998. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARγ. *Cell* 93:229–40
147. Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J. 1994. Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. *N. Engl. J. Med.* 331:1188–93
148. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, et al. 1998. Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor γ. *Nature* 395:137–43
149. Oakes ND, Camilleri S, Furler SM, Chisholm DJ, Kraegen EW. 1997. The insulin sensitizer, BRL 49653, reduces systemic fatty acid supply and utilization and tissue availability in the rat. *Metabolism* 46:935–42
150. Oakes ND, Kennedy CJ, Jenkins AB, Laybutt DR, Chisholm DJ, Kraegen EW. 1994. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. *Diabetes* 43:1203–10
151. Oberfield JL, Collins JL, Holmes CP, Goreham DM, Cooper JP, et al. 1999. A peroxisome proliferator-activated receptor gamma ligand inhibits adipocyte differentiation. *Proc. Natl. Acad. Sci. USA* 96:6102–6
152. Ogawa J, Takahashi S, Fujiwara T, Fukushige J, Hosokawa T, et al. 1999. Troglitazone can prevent development of type 1 diabetes induced by multiple low-dose streptozotocin in mice. *Life Sci.* 65:1287–96
153. Okuno A, Tamemoto H, Tobe K, Ueki K, Mori Y, et al. 1998. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J. Clin. Invest.* 101:1354–61
154. Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, et al. 2001. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc. Natl. Acad. Sci. USA* 98:5306–11
155. Onate SA, Tsai SY, Tsai MJ, O'Malley BW. 1995. Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* 270:1354–57
156. Perissi V, Staszewski LM, McInerney EM, Kurokawa R, Krones A, et al. 1999. Molecular determinants of nuclear

receptor-corepressor interaction. *Genes Dev.* 13:3198–208
157. Perreault M, Marette A. 2001. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. *Nat. Med.* 7: 1138–43
158. Picard F, Kapur S, Perreault M, Marette A, Deshaies Y. 2001. Nitric oxide mediates endotoxin-induced hypertriglyceridemia through its action on skeletal muscle lipoprotein lipase. *FASEB J.* 15:1828–30
159. Pihlajamaki J, Miettinen R, Valve R, Karjalainen L, Mykkanen L, et al. 2000. The Pro12A1a substitution in the peroxisome proliferator activated receptor gamma 2 is associated with an insulin-sensitive phenotype in families with familial combined hyperlipidemia and in nondiabetic elderly subjects with dyslipidemia. *Atherosclerosis* 151:567–74
160. Pilon G, Penfornis P, Marette A. 2000. Nitric oxide production by adipocytes: a role in the pathogenesis of insulin resistance? *Horm. Metab. Res.* 32:480–84
161. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. 1998. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 92:829–39
162. Randle PJ. 1998. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metab. Rev.* 14:263–83
163. Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI. 2000. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia* 43:278–84
164. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J. 2001. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* 24:1226–32
165. Ravi TS, Nelli P, Rai P, Kundaje GN. 1991. Insulin oedema: an uncommon complication of insulin therapy. *J. Assoc. Physicians India* 39:411–12
166. Reilly CM, Oates JC, Sudian J, Crosby MB, Halushka PV, Gilkeson GS. 2001. Prostaglandin J(2) inhibition of mesangial cell iNOS expression. *Clin. Immunol.* 98:337–45
167. Ribon V, Johnson JH, Camp HS, Saltiel AR. 1998. Thiazolidinediones and insulin resistance: peroxisome proliferator-activated receptor γ activation stimulates expression of the CAP gene. *Proc. Natl. Acad. Sci. USA* 95:14751–56
168. Ricquier D, Bouillaud F. 2000. Mitochondrial uncoupling proteins: from mitochondria to the regulation of energy balance. *J. Physiol.* 529 Pt 1:3–10
169. Rieusset J, Andreelli D, Auboeuf D, Roques P, Valier P, et al. 1999. Insulin acutely regulates the expression of the peroxisome proliferator-activated receptor γ in human adipocytes. *Diabetes* 48:699–705
170. Rieusset J, Auwerx J, Vidal H. 1999. Regulation of gene expression by activation of the peroxisome proliferator-activated receptor gamma with rosiglitazone (BRL 49653) in human adipocytes. *Biochem. Biophys. Res. Commun.* 265:265–71
171. Ringel J, Engeli S, Distler A, Sharma AM. 1999. Pro12Ala missense mutation of the peroxisome proliferator activated receptor gamma and diabetes mellitus. *Biochem. Biophys. Res. Commun.* 254:450–53
172. Ristow M, Muller-Wieland D, Pfeiffer A, Krone W, Kahn CR. 1998. Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. *N. Engl. J. Med.* 339:953–59
173. Rocchi S, Picard F, Vamecq J, Gelman L, Potier N, et al. 2001. A unique PPARgamma ligand with potent insulin-sensitizing yet weak adipogenic activity. *Mol. Cell.* 8:737–47
174. Rosen ED, Sarraf P, Troy AE, Bradwin G, Moore K, et al. 1999. PPARgamma is required for the differentiation of

adipose tissue in vivo and in vitro. *Mol. Cell* 4:611–17
175. Rosen ED, Walkey CJ, Puigserver P, Spiegelman BM. 2000. Transcriptional regulation of adipogenesis. *Genes Dev.* 14: 1293–307
176. Schaffler A, Barth N, Schimtz G, Zietz B, Pallizsch KD, Scholmerich J. 2001. Frequency and significance of Pro12Ala and Pro115Gln polymorphism in gene for peroxisome proliferator-activated receptor-gamma regarding metabolic parameters in a Caucasian cohort. *Endocrine* 14:369–73
177. Schoonjans K, Martin G, Staels B, Auwerx J. 1997. Peroxisome proliferator-activated receptors, orphans with ligands and functions. *Curr. Opin. Lipidol.* 8:159–66
178. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman R, Briggs M, et al. 1996. PPARα and PPARγ activators direct a tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J.* 15:5336–48
179. Schoonjans K, Watanabe M, Suzuki H, Mahfoudi A, Krey G, et al. 1995. Induction of the acyl-coenzyme A synthetase gene by fibrates and fatty acids is mediated by a peroxisome proliferator response element in the C promoter. *J. Biol. Chem.* 270:19269–76
180. Schreyer SA, Chua SC Jr, LeBoeuf RC. 1998. Obesity and diabetes in TNF-alpha receptor-deficient mice. *J. Clin. Invest.* 102:402–11
181. Schwartz S, Raskin P, Fonseca V, Graveline JF. 1998. Effect of troglitazone in insulin-treated patients with type II diabetes. *N. Engl. J. Med.* 338:861–66
182. Shibata T, Matsui K, Nagao K, Shinkai H, Yonemori F, Wakitani K. 1999. Pharmacological profiles of a novel oral antidiabetic agent, JTT-501, an isoxazolidininedione derivative. *Eur. J. Pharmacol.* 364:211–19
183. Shibuya A, Watanabe M, Fujita Y, Saigenji K, Kuwao S, et al. 1998. An autopsy case of troglitazone-induced fulminant hepatitis. *Diabetes Care* 21:2140–43
184. Shimabukuro M, Zhou YT, Lee Y, Unger RH. 1998. Troglitazone lowers islet fat and restores beta cell function of Zucker diabetic fatty rats. *J. Biol. Chem.* 273: 3547–50
185. Shimizu H, Tsuchiya T, Sato N, Shimomura Y, Kobayashi I, Mori N. 1998. Troglitazone reduces plasma leptin concentration but increases hunger in NIDDM patients. *Diabetes Care* 21:1470–74
186. Shimomura I, Hammer RE, Richardson JA, Ikemoto S, Bashmakov Y, et al. 1998. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: a model for congenital generalized lipodystrophy. *Genes Dev.* 12:3182–94
187. Singh Ahuja H, Liu S, Crombie DL, Boehm M, Leibowitz MD, et al. 2001. Differential effects of rexinoids and thiazolidinediones on metabolic gene expression in diabetic rodents. *Mol. Pharmacol.* 59:765–73
188. Sironi AM, Vichi S, Gastaldelli A, Pecori N, Anichini R, et al. 1997. Effects of troglitazone on insulin action and cardiovascular risk factors in patients with non-insulin-dependent diabetes. *Clin. Pharmacol. Ther.* 62:194–202
189. Smith U, Gogg S, Johansson A, Olausson T, Rotter V, Svalstedt B. 2001. Thiazolidinediones (PPARgamma agonists) but not PPARalpha agonists increase IRS-2 gene expression in 3T3-L1 and human adipocytes. *FASEB J.* 15:215–20
190. Spiegelman BM. 1998. PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 47:507–14
191. Stefan N, Fritsche A, Haring HU, Stumvoli M. 2001. Effects of experimental elevation of free fatty acids on insulin secretion and insulin sensitivity in healthy carriers of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene. *Diabetes* 50: 1143–48
192. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, et al. 2001. The hormone

resistin links obesity to diabetes. *Nature* 409:307–12

193. Suter SL, Nolan JJ, Wallace P, Gumbiner B, Olefsky JM. 1992. Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects. *Diabetes Care* 15:193–203
194. Swarbrick MM, Chapman CM, McQuillan BM, Hung J, Thompson PL, Beilby JP. 2001. A Pro12Ala polymorphism in the human peroxisome proliferator-activated receptor-gamma2 is associated with combined hyperlipidemia in obesity. *Eur. J. Endocrinol.* 144:277–82
195. Szalkowski D, White-Carrington S, Berger J, Zhang B. 1995. Antidiabetic thiazolidinediones block the inhibitory effects of TNFα on differentiation, insulin stimulated glucose uptake, and gene expression in 3T3-L1 cells. *Endocrinology* 136: 1474–81
196. Temple R, Ellenberg SS. 2000. Placebo-controlled trials and active-control trials in the evaluation of new treatment. I. Ethical and scientific issues. *Ann. Intern. Med.* 133:455–63
197. Tontonoz P, Hu E, Devine J, Beale EG, Spiegelman BM. 1995. PPARγ2 regulates adipose expression of the phosphoenolpyruvate carboxykinase gene. *Mol. Cell. Biol.* 15:351–57
198. Tontonoz P, Hu E, Graves RA, Budavari AI, Spiegelman BM. 1994. mPPARγ2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev.* 8:1224–34
199. Tontonoz P, Hu E, Spiegelman BM. 1994. Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor. *Cell* 79:1147–56
200. Treuter E, Albrektsen T, Johansson L, Leers J, Gustafsson JA. 1998. A regulatory role for RIP140 in nuclear receptor activation. *Mol. Endocrinol.* 12:864–81
201. Uchimura K, Nakamuta M, Enjoji M, Irie T, Sugimoto R, et al. 2001. Activation of retinoic X receptor and peroxisome proliferator-activated receptor-gamma inhibits nitric oxide and tumor necrosis factor-alpha production in rat Kupffer cells. *Hepatology* 33:91–99
202. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. 1997. Protection from obesity-induced insulin resistance in mice lacking TNF- alpha function. *Nature* 389: 610–14
203. Ventre J, Doebber T, Wu M, MacNaul K, Stevens K, et al. 1997. Targeted disruption of the tumor necrosis factor-α gene: metabolic consequences in obese and nonobese mice. *Diabetes* 46:1526–31
204. Vidal-Puig A, Jimenez-Linan M, Lowell BB, Hamann A, Hu E, et al. 1996. Regulation of PPARγ gene expression by nutrition and obesity in rodents. *J. Clin. Invest.* 97:2553–61
205. Vidal-Puig AJ, Considine RV, Jimenez-Linan M, Werman A, Pories WJ, et al. 1997. Peroxisome proliferator-activated receptor gene expression in human tissues: effects of obesity, weight loss, and regulation by insulin and glucocorticoids. *J. Clin. Invest.* 99:2416–22
206. Vionnet N, El Hani H, Dupont S, Gallina S, Francke S, et al. 2000. Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2-diabetes locus on chromosome 1q21-q24. *Am. J. Hum. Genet.* 67:1470–80
207. Voegel JJ, Heine MJS, Zechel C, Chambon P, Gronemeyer H. 1996. TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *EMBO J.* 15: 3667–75
208. Wang Q, Bing C, Al-Barzanji K, Mossakowaska DE, Wang XM, et al. 1997. Interactions between leptin and hypothalamic neuropeptide Y neurons in the control of food intake and energy homeostasis in the rat. *Diabetes* 46:335–41
209. Watkins PB, Whitcomb RW. 1998. Hepatic dysfunction associated with troglitazone. *N. Engl. J. Med.* 338:916–17

210. Way JM, Gorgun CZ, Tong Q, Uysal KT, Brown KK, et al. 2001. Adipose tissue resistin expression is severely suppressed in obesity and stimulated by peroxisome proliferator-activated receptor gamma agonists. *J. Biol. Chem.* 276:25651–53
211. Way JM, Harrington WW, Brown KK, Gottschalk WK, Sundseth SS, et al. 2001. Comprehensive messenger ribonucleic acid profiling reveals that peroxisome proliferator-activated receptor gamma activation has coordinate effects on gene expression in multiple insulin-sensitive tissues. *Endocrinology* 142:1269–77
212. Weinstein SP, Holand A, O'Boyle E, Haber RS. 1993. Effects of thiazolidinediones on glucocorticoid-induced insulin resistance and GLUT4 glucose transporter expression in rat skeletal muscle. *Metabolism* 42:1365–69
213. Werman A, Hollenberg A, Solanes G, Bjorbaek C, Vidal-Puig A, Flier JS. 1997. Ligand-independent activation domain in the N terminus of peroxisome proliferator-activated receptor γ (PPARγ). *J. Biol. Chem.* 272:20230–35
214. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, et al. 2001. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J. Clin. Endocrinol. Metab.* 86:1930–35
215. Willson TM, Lambert MH, Kliewer SA. 2001. Peroxisome proliferator-activated receptor γ and metabolic disease. *Annu. Rev. Biochem.* 70:341–67
216. Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan RN. 2000. Addition of low-dose rosiglitazone to sulfonylureas therapy improves glycaemic control in type 2 diabetes patients. *Diabet. Med.* 17:40–47
217. Wright HM, Clish CB, Mikami T, Hauser S, Yanagi K, et al. 2000. A synthetic antagonist for the peroxisome proliferator-activated receptor gamma inhibits adipocyte differentiation. *J. Biol. Chem.* 275: 1873–77
218. Wu M, Ventre J, Moller DE, Doebber T. 1997. Correction of elevated glucose and triglycerides in Zucker diabetic fatty rats by thiazolidinediones parallels increased I-glycogen synthase and lipoprotein lipase activity in muscle and fat. *Diabetes* 46(Suppl. 1):237A
219. Wu Z, Xie Y, Morrison RF, Bucher NLR, Farmer SR. 1998. PPARγ induces the insulin-dependent glucose transporter GLUT4 in absence of C/EBPα during the conversion of 3T3 fibroblast into adipocytes. *J. Clin. Invest.* 101:22–32
220. Yamauchi T, Kamon J, Waki H, Murakami K, Motojima K, et al. 2001. The mechanisms by which both heterozygous PPARgamma deficiency and PPARgamma agonist improve insulin resistance. *J. Biol. Chem.* 31:31
221. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, et al. 2001. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat. Med.* 7:941–46
222. Yamauchi T, Waki H, Kamon J, Murakami K, Motojima K, et al. 2001. Inhibition of RXR and PPARgamma ameliorates diet-induced obesity and type 2 diabetes. *J. Clin. Invest.* 108:1001–13
223. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, et al. 2001. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J. Clin. Endocrinol. Metab.* 86:3815–19
224. Ye JM, Doyle PJ, Iglesias MA, Watson DG, Cooney GJ, Kraegen EW. 2001. Peroxisome proliferator-activated receptor (PPAR)-alpha activation lowers muscle lipids and improves insulin sensitivity in high fat-fed rats: comparison with PPAR-gamma activation. *Diabetes* 50:411–17
225. Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, et al. 1997. Molecular scanning of the human peroxisome proliferator activated receptor gamma gene in

diabetic Caucasians: identification of a Pro12Ala PPARgamma 2 missense mutation. *Biochem. Biophys. Res. Commun.* 241:270–74

226. Yonemitsu S, Nishimura H, Shintani M, Inoue R, Yamamoto Y, et al. 2001. Troglitazone induces GLUT4 translocation in L6 myotubes. *Diabetes* 50:1093–101
227. Yu K, Bayona W, Kallen CB, Harding HP, Ravera CP, et al. 1995. Differential activation of peroxisome proliferator-activated receptors by eicosanoids. *J. Biol. Chem.* 270:23975–83
228. Zhang B, Szalkowski D, Diaz E, Hayes N, Smith R, Berger J. 1994. Potentiation of insulin stimulation of phosphatidylinositol 3-kinase by thiazolidinedione-derived antidiabetic agents in Chinese hamster ovary cells expressing human insulin receptor and L6 myotubes. *J. Biol. Chem.* 269:25735–41
229. Zhu Y, Kan L, Qi C, Kanwar YS, Yeldandi AV, et al. 2000. Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR. *J. Biol. Chem.* 275:13510–16
230. Zhu Y, Qi C, Calandra C, Rao MS, Reddy J. 1996. Cloning and identification of mouse steroid receptor coactivator-1 (mSRC-1), as a coactivator of peroxisome proliferator-activated receptor γ. *Gene Expression* 6:185–95
231. Zhu Y, Qi C, Korenberg JR, Chen X-N, Noya D, et al. 1995. Structural organization of mouse peroxisome proliferator activated receptor γ (mPPARγ) gene: alternative promoter use and different splicing yield two mPPARγ isoforms. *Proc. Natl. Acad. Sci. USA* 92:7921–25
232. Zierath JR, Ryder JW, Doebber T, Woods J, Wu M, et al. 1998. Role of skeletal muscle in thiazolidinedione insulin sensitizer (PPARgamma agonist) action. *Endocrinology* 139:5034–41
233. Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG. 1999. Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* 84:272–78