The Biology of Peroxisome Proliferator–Activated Receptors

Relationship With Lipid Metabolism and Insulin Sensitivity

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Peroxisome proliferator–activated receptors (PPARs) are transcription factors belonging to the superfamily of nuclear receptors. Three isoforms (α, δ, and γ) have been described. They act on DNA response elements as heterodimers with the nuclear retinoic acid receptor. Their natural activating ligands are fatty acids and lipid-derived substrates. PPAR-α is present in liver, heart, and, to a lesser extent, skeletal muscle. When activated, it promotes fatty acid oxidation, ketone body synthesis, and glucose sparing. Fibrates, which are used as hypolipidemic drugs, are ligands of PPAR-α. PPAR-δ is ubiquitous and could also favor fatty acid oxidation in tissues in which PPAR-α is absent or less expressed. PPAR-γ is expressed in adipose tissue, lower intestine, and cells involved in immunity. Activation of PPAR-γ induces the differentiation of preadipocytes into adipocytes and stimulates triglyceride storage. Thiazolidinediones are compounds used as hypoglycemic, muscle insulin–sensitizing agents in type 2 diabetes. Unexpectedly, they are activators of PPAR-γ. Their action on muscle insulin sensitivity may be secondary to the lowering of circulating lipids on PPAR-γ activation and to the secretion by adipocytes of insulin-sensitizing hormones such as adiponectin, all promoting glucose utilization. The PPARs are thus major regulators of lipid and glucose metabolism, allowing adaptation to the prevailing nutritional environment. *Diabetes* 53 (Suppl. 1):S43–S50, 2004

Living organisms must continuously adapt their metabolism to the nutritional environment because the quality and quantity of available nutrients do not timely match their energetic needs. The main energy substrates, glucose and fatty acids, have specific characteristics that dictate adaptive strategies. All tissues are able to use glucose as a substrate. Some (erythrocytes, renal medulla, and retinal cells) depend on continuous glucose availability because they do not possess an oxidative capacity and have to rely solely on glycolysis. The brain is a glucose-dependent organ because fatty acids do not cross the blood-brain barrier. In the case of alimentary glucose shortage, mobilization of hepatic glycogen stores (around 80–90 g in humans) maintains the circulating glucose concentration for a few hours. Subsequently, the liver relies on gluconeogenesis, a process that requires energy and uses muscle protein as a precursor. Fatty acids can be used by organs with a high mitochondrial oxidative capacity, mainly the liver, the oxidative skeletal muscles, the heart, and the renal cortex. Fatty acids are stored as triacylglycerols in adipose tissue, which in a normal person amounts to 15–20% of body weight. They arise either from dietary lipid intake or from the lipogenic process (de novo synthesis of lipids from glucose in the liver and adipose tissue). In case of a glucose shortage, and because of a rapid decrease in insulin concentration, fatty acids are released (together with glycerol) into the bloodstream through the action of a hormone-sensitive lipase. In the liver, fatty acid oxidation provides the energy necessary to sustain the gluconeogenic process. In addition, fatty acids are transformed into ketone bodies, which can cross the blood-brain barrier and partly replace glucose as a substrate. In oxidative muscles, fatty acid and ketone body oxidation also spare glucose utilization. Replacing glucose as a fuel by fatty acids or ketone bodies limits the need for de novo glucose synthesis and hence muscle protein catabolism, allowing a much longer fasting period to be sustained.

Tight regulation of metabolic pathways involves the rapid modulation of the activity of specific proteins (enzymes, transporters) but also, on a longer-term basis, changes in their quantity. This can be achieved by modulating their transcription rate through the action of specific transcription factors. The discovery of the peroxisome proliferator-activated receptor (PPAR) family of transcription factors has revealed the mechanism of the strong link between lipid/glucose availability and long-term metabolic adaptation.

THE PPAR FAMILY

In rodents, different amphiphatic acids (such as fibrates) are able to induce a strong hepatic peroxisome proliferation (1). In humans, this effect is absent; fibrates are used as a pharmaceutical tool for reducing triglyceride levels and increasing the concentration of HDL cholesterol. The

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AMPK, AMP-activated protein kinase; IL-6, interleukin-6; L-FABP, liver type fatty acid–binding protein; PDK4, pyruvate dehydrogenase kinase 4; PGAR, PPAR-γ angiopoietin-related gene; PPAR, peroxisome proliferator–activated receptor; RXR, 9-*cis*-retinoic acid receptor; TNF, tumor necrosis factor; TZD, thiazolidinedione.

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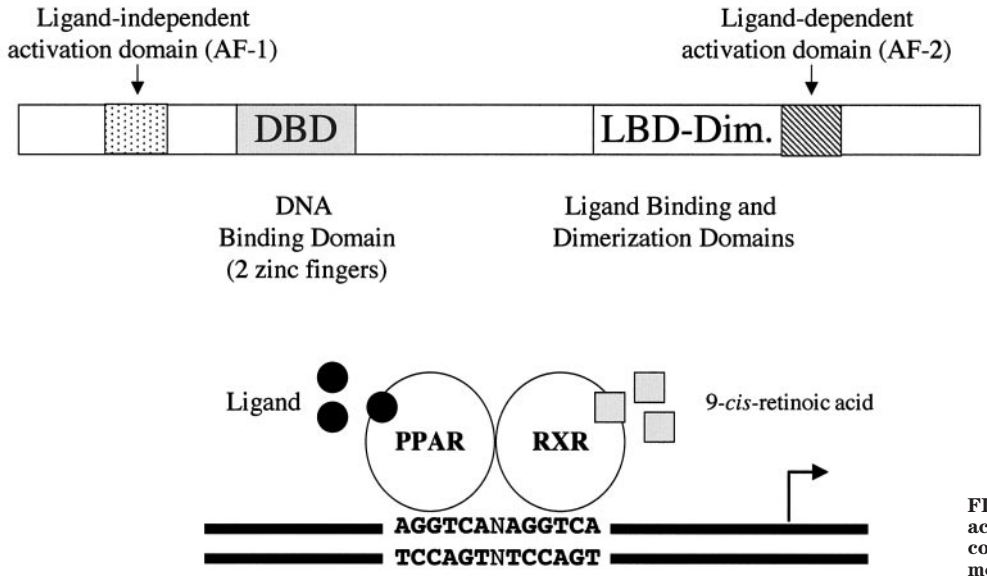

FIG. 1. General structure and mechanism of action of PPARs. PPAR isoforms share a common domain structure and molecular mechanism of action.

peroxisome proliferation in rodents occurs concomitantly with an increase in the transcription of genes involved in peroxisomal and microsomal fatty acid oxidation (1). The first member of the PPAR family (PPAR-α) was cloned as a novel murine nuclear receptor that mediates the transcriptional effects of peroxisome proliferators (2). Other closely related receptors encoded by different genes were subsequently cloned and named PPAR-δ (or -β) and PPAR-γ (3). It must be pointed out that, despite their name, neither PPAR-δ nor PPAR-γ responds to peroxisome proliferators.

PPARs possess the classic domain structure of other nuclear receptors (e.g., steroid or thyroid hormone receptors) (Fig. 1). They have an NH_2-terminal region with a ligand-independent transactivation domain (AF-1), followed by a DNA-binding domain (two zinc fingers) and, at the COOH-terminus, a ligand and dimerization domain and a ligand-dependent activation domain (AF-2).

The PPARs bind to the peroxisome proliferator response element on the DNA with the sequence AGGT CANAGGTCA (direct repeat with a single nucleotide spacer) as obligate heterodimers with the 9-*cis*-retinoic acid receptor (RXR) (Fig. 1). A thorough review of the mechanism of transcriptional activation can be found in the literature (4). In contrast with other nuclear receptors (e.g., the steroid receptors), the binding properties of the PPARs are rather promiscuous, and each PPAR can accommodate ligands with quite different structures. The PPAR/RXR complex can be activated by the ligand of either receptor, and the simultaneous binding of both ligands is more efficient. Some of the natural and synthetic ligands will be described below for each PPAR subtype.

TISSUE DISTRIBUTION OF PPARs

PPAR-α is highly expressed in hepatocytes, cardiomyocytes, the kidney cortex, skeletal muscles (i.e., tissues with a high capacity for fatty acid oxidation), and enterocytes (5,6). PPAR-γ is expressed mainly in white and brown adipose tissue (two tissues that store large amounts of fatty acids), and to a lesser extent in immune cells (monocytes, macrophages, and Peyer's patches in the digestive tract), in the mucosa of the colon and cecum and in the placenta. It is almost absent in skeletal muscle. PPAR-δ is ubiquitously expressed, often at higher levels than the two other PPARs. We will briefly review the characteristics of PPAR-α and -γ, which are the PPARs most implicated in lipid metabolism and insulin sensitivity.

PPAR-α LIGANDS

Ligands have been determined for each PPAR isoform in both functional (cell-based transactivation efficiency) and in vitro interaction assays (1,4). PPAR-α binds unsaturated fatty acids (with the highest affinity of the three isoforms); saturated fatty acids have lower affinity for PPAR-α. Among other potential endogenous ligands that have been tested, PPAR-α is able to bind 8-(*S*)-hydroxyeicosatetraenoic acid, a compound associated with inflammation induced by phorbol esters. However, it must be pointed out that the K_d of these natural ligands is in the 2–50 μmol/l range, an affinity much lower than that of other nuclear receptors for their ligands (this is true for all three isoforms). This could mean either that they do not represent true endogenous ligands or, more probably, that this low affinity is a feature of a "generous" (4) ligand pocket, allowing binding to many different types of lipid-derived substrates. Among synthetic ligands, compounds of the fibrate family (clofibrate, fenofibrate, and bezafibrate) and their derivatives have been widely used to characterize PPAR-α functions.

A ROLE FOR PPAR-α IN LIPID CATABOLISM

We will not address here the effects of PPAR-α on circulating lipoproteins and cholesterol metabolism (7), but rather the effects of PPAR-α on lipid oxidation. In the liver, activation of PPAR-α induces the expression of fatty acid transport proteins and long-chain acyl-CoA synthetase (activation of fatty acids into acyl-CoA is a prerequisite for their subsequent metabolism) (8,9). Several key enzymes involved in peroxisomal β-oxidation such as acyl-CoA oxidase are also direct targets of PPAR-α (3). Peroxisomal β-oxidation does not directly provide energy but is able to

shorten very long-chain fatty acids, thus allowing their subsequent mitochondrial β-oxidation. It also has a detoxifying action by oxidizing molecules such as eicosanoids and xenobiotics.

Although PPAR-α was initially cloned based on its properties to mediate fibrate effects in the liver, its actions extend far beyond the liver and the peroxisome organelle. Concerning mitochondrial β-oxidation, carnitine palmitoyl transferase I, the rate-limiting step of the pathway, has been described as a target of PPAR-α (10), although this remains a disputed issue (11). PPAR-α activation stimulates the expression of the medium-chain acyl-CoA dehydrogenase (12), a pivotal step in mitochondrial β-oxidation, and the expression of the mitochondrial form of hydroxymethylglutaryl-CoA synthase, involved in ketone body synthesis (13). In the intestine, fatty acids are able to induce the expression of a fatty acid binding protein (liver type fatty acid–binding protein [L-FABP]) (14), and this effect is mimicked by a clofibrate-enriched diet, thus suggesting that PPAR-α could control the cellular fatty acid flux in the intestinal cell. However, recent studies have suggested that PPAR-δ could be the true activator of intestinal L-FABP (15).

A stimulatory effect of PPAR-α on the pyruvate dehydrogenase kinase 4 (PDK4) gene expression and activity (16) has been described in rodent and human skeletal muscles. PDK4 is a kinase that phosphorylates and inactivates pyruvate dehydrogenase. An active pyruvate dehydrogenase complex (which transforms pyruvate into acetyl-CoA) favors the oxidation of glucose carbons. Its inactivation in skeletal muscle redirects glucose carbons from oxidation to lactate synthesis, thus ultimately sparing glucose carbons for hepatic glucose production. In skeletal muscles, starvation and diabetes, which are concomitant with a high fatty acid availability, could result in PPAR-α activation, inducing increased PDK4 expression, inactivation of pyruvate dehydrogenase, and glucose carbon sparing.

The use of PPAR-α–null mice has greatly contributed to our understanding of the physiological role of this PPAR isoform (17). It has confirmed that a number of enzymes involved in hepatic fatty acid activation, peroxisomal oxidation, and mitochondrial oxidation are indeed targets of PPAR-α. It has also allowed the extension of the role of PPAR-α to cardiac lipid catabolism. In the heart, fatty acid oxidative capacity is reduced in the PPAR-α–null mice, and at least seven mitochondrial fatty acid–metabolizing enzymes are expressed at much lower levels (18). In addition, this is concomitant with myocardial damage and fibrosis. In skeletal muscles, however, the defect in fatty acid oxidation is much less severe and PDK4 activity responds normally to starvation (19). It has been suggested that the PPAR-δ isoform, which is the predominant isoform in rodent skeletal muscles, is able to compensate for the PPAR-α deficiency. This could also indicate that in skeletal muscle, PPAR-δ is the isoform that is important for the response to increased availability of fatty acids. Recent data suggest that PPAR-δ indeed serves as a general regulator of fat oxidation (20).

PPAR-α–null mice reveal the striking importance of this nuclear receptor in the adaptation to starvation. Indeed, whereas the phenotype of normally fed PPAR-α–null mice is not fundamentally different from wild-type mice, starvation induces major differences (21,22). The liver and heart of PPAR-α–null mice during starvation are steatotic owing to a much lower fatty acid oxidation capacity. Circulating ketone bodies are extremely low because of the impairment of mitochondrial hydroxymethylglutaryl-CoA synthase expression. Interestingly, glucose metabolism is also severely affected because starvation in PPAR-α–null mice leads to marked hypoglycemia. This can be explained by the fact that *1*) hepatic glucose production is decreased because gluconeogenesis requires a high rate of fatty acid oxidation to provide energy and specific cofactors and *2*) glucose utilization is not reduced because the absence of ketone bodies does not allow the usual glucose-sparing mechanism in organs such as the brain. In addition, the heart cannot completely switch from glucose to fatty acids because of its reduced fatty acid oxidation capacity.

PPAR-α AND INSULIN SENSITIVITY

In PPAR-α–null mice, there is no gross alteration of insulin sensitivity (23). However, activation of PPAR-α in nutritional (high-fat diet), genetic (Zucker obese *fa/fa* rat), or lipoatrophic (A-ZIP/F-1) models of insulin resistance markedly improves insulin sensitivity (23–25) and reduces visceral fat in the two former models. Intracellular fatty acids and their derivatives are known to interfere with insulin-stimulated glucose metabolism, either through metabolic competition (the glucose/fatty acid cycle) or through an effect on the insulin-signaling pathway, possibly by activating an atypical protein kinase C. Activation of PPAR-α would increase the oxidation of fatty acids (an effect obvious in the liver), thus decreasing tissue content of lipids and minimizing lipotoxicity. In contrast with these observations suggesting a beneficial effect of PPAR-α activation in terms of insulin sensitivity, it has been reported that PPAR-α–null mice are protected from high-fat diet–induced insulin resistance (26). At present, there is no clear explanation for this discrepancy.

In summary, PPAR-α activation favors fatty acid oxidation, mainly in the liver and heart and to a lesser extent in muscles, and induces glucose sparing, either directly by inducing the expression of PDK4 or indirectly through the synthesis of ketone bodies and the increased fatty acid oxidation capacity. This increased fatty acid oxidation is one of the reasons why fibrates have lipid-lowering effects and why PPAR-α ligands could in some situations improve insulin sensitivity by reducing lipid accumulation in tissues.

PPAR-γ LIGANDS

Both synthetic and natural ligands have been identified. Among the natural ligands for PPAR-γ, several unsaturated fatty acids such as oleate, linoleate, eicosapentaenoic, and arachidonic acids can bind PPAR-γ as well as a prostanoid called 15-deoxy-δ-12,14-prostaglandin J2 (4). It is now clear that members of the thiazolidinedione (TZD) family of antidiabetic compounds (Fig. 2) are specific PPAR-γ ligands with a K_d in the 100 nmol/l range (1). Interestingly, these drugs were developed without knowing that they were ligands of PPAR-γ. The involvement of PPAR-γ in their antidiabetic effect will be addressed in the following paragraphs.

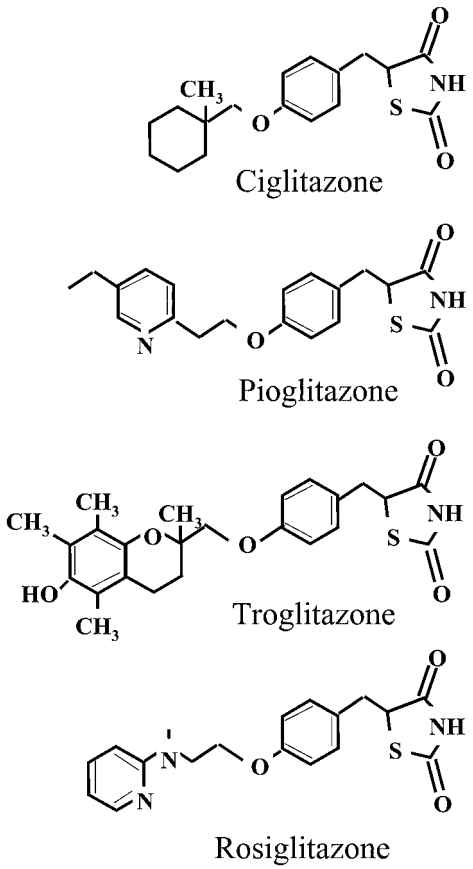

FIG. 2. PPAR-γ ligands of the thiazolidinedione family. Pioglitazone and rosiglitazone are presently used in type 2 diabetes as oral antidiabetic drugs.

A ROLE FOR PPAR-γ IN LIPID STORAGE

PPAR-γ exists in two protein isoforms (γ1 and γ2) because of the use of alternative promoter and alternative splicing. The γ2 form has 28 additional amino acids on the NH_2-terminal side in humans. In rodents, the γ2 isoform is the dominant form in adipose tissue, whereas the converse is true in humans (4,27).

PPAR-γ was initially identified as a factor binding to a fat-specific enhancer of the *ap2* gene (28), which encodes an adipose-specific fatty acid binding protein. Activation of PPAR-γ by a synthetic ligand was also able to induce the expression of another gene characteristic of mature adipocytes—PEPCK (see below) (29). The PEPCK promoter has a peroxisome proliferator response element that is functional only in adipocytes (and not in hepatocytes, in which PEPCK is also expressed). It was then shown that the ectopic expression of PPAR-γ is able to induce the differentiation of fibroblastic cells into adipocytes (30). In vivo in rodents, specific activation of PPAR-γ induces the differentiation of preadipocytes into small adipocytes within a few days (31). Activation of PPAR-γ also induces the differentiation of cultured human preadipocytes into mature adipocytes (32), an effect that is counteracted by a dominant-negative form of PPAR-γ. These differentiating effects are not seen with specific ligands of PPAR-α.

PPAR-γ homozygous inactivation results in embryonic death due to placental insufficiency (27). However, it has been shown in mice chimeric for wild-type and PPAR-γ–null cells that there was hardly any contribution of null cells to adipose tissue, confirming the essential role of PPAR-γ in adipose tissue differentiation (33).

PPAR-δ has also been implicated in adipocyte differentiation and more specifically in the differentiation induced by long-chain fatty acids (34), although contradictory evidence has also been presented.

PPAR-γ is also thought to exert an antimitotic action to stop cell proliferation during terminal adipocyte differentiation (27). Several lines of evidence have extended the antiproliferative ability of PPAR-γ to other cell types (27). Indeed, ectopic expression and activation of PPAR-γ in fibroblasts induces cell cycle withdrawal in exponentially growing cells. Antimitotic effects of specific PPAR-γ ligands have been described in human colorectal cancer cells and liposarcomas. Finally, it has been reported that loss-of-function mutations in PPAR-γ were associated with human colon cancer.

In addition to its effects on preadipocyte differentiation, thus augmenting adipocyte number, activation of PPAR-γ stimulates the storage of fatty acids in mature adipocytes by acting at several steps (27): release of fatty acids from the triglycerides contained in lipoprotein particles by stimulating lipoprotein lipase (35), intracellular fatty acid transport (ap2), activation of fatty acids (acyl-CoA synthase), and fatty acid esterification by stimulating the PEPCK gene, which provides α-glycerophosphate (29,36). A stimulating effect on the insulin-dependent glucose transporter GLUT4 has also been described (37), which could contribute to increased fatty acid synthesis from glucose. Activation of PPAR-γ modulates the expression of products secreted by the adipocyte (38): it reduces leptin expression and activates adiponectin expression, a protein potentially involved in insulin sensitivity (see below). PPAR-γ also induces the expression of a secreted protein (PPAR-γ angiopoietin-related gene [PGAR]) (39) from the angiopoietin family. These proteins usually serve as signaling molecules in vascular development. PGAR is also localized in placenta. This localization and the fact that PGAR expression is increased by hypoxia (40) could indicate that through this protein, PPAR-γ is able to modulate angiogenesis, a necessary component of adipose tissue development.

In summary, PPAR-γ is a potent stimulator of fatty acid storage in adipose tissue because it increases both the storage capacity and the fatty acid flux into adipocytes.

PPAR-γ AND INSULIN SENSITIVITY

Type 2 diabetes results from a decrease in glucose-induced insulin secretion and diminished efficiency in insulin action (insulin resistance). Insulin resistance is also characteristic of obesity and lipodystrophy. TZDs are potent antidiabetic compounds that lower the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia observed in type 2 diabetic subjects and in animal models of type 2 diabetes. TZDs act by enhancing the sensitivity of tissues to insulin, especially in skeletal muscle. Skeletal muscle is quantitatively the most important tissue when considering insulin-dependent glucose utilization. Involvement of PPAR-γ in insulin sensitivity stems from the discovery that TZDs are strong and specific activators of this PPAR isoform (1). It was then demonstrated that the antihyper-

glycemic effects of TZDs are indeed due to their capacity of activating PPAR-γ in adipose tissue. Hence, TZDs are unable to improve the diabetic state in a rodent model of lipoatrophy (41).

Because PPAR-γ is present in adipose tissue but nearly absent in muscle, the main insulin-sensitive tissue, it raises the question of the connection between adipose tissue and peripheral insulin sensitivity. A possible explanation is that activation of PPAR-γ leads to the channeling of fatty acids into adipose tissue and thus to a decrease in their plasma concentration. Reducing the fatty acid availability for muscles would alleviate insulin resistance.

Another interesting possibility is the action of PPAR-γ on adipocyte hormones. Indeed, a number of adipocyte hormones have been shown to modulate insulin sensitivity. Leptin is able to improve insulin sensitivity in lipoatrophic patients and in rodent models of lipoatrophy (42), probably by increasing muscle glucose uptake and fatty acid oxidation (43). However, because leptin expression is decreased rather than increased by PPAR-γ agonists, it is unlikely that it could play a significant role in TZD action. Resistin (also known as the adipocyte secreted factor and found in inflammatory zone 3) is a protein secreted specifically by adipose tissue. Resistin has been described as an inducer of muscle insulin resistance and as negatively regulated by TZDs (44). As such, it was a good candidate for linking adipose tissue and muscle. However, contradictory results have since been described for this protein, casting doubt on its involvement in TZD effects (45). Adipose tissue also secretes cytokines that are involved in insulin resistance (27). Tumor necrosis factor (TNF)-α impairs insulin receptor signaling, inhibits lipoprotein lipase, and stimulates lipolysis in adipocytes, which should result in an increased availability of fatty acids for muscles and may cause insulin resistance (38). TNF-α mRNA is overexpressed in the adipose tissue of most animal models of obesity. Interleukin-6 (IL-6) is also secreted by adipocytes, and its concentrations have been positively related to adiposity and negatively related to insulin action (46,47). TZDs decrease the expression of TNF-α in adipocytes and its plasma concentration in rodent models of obesity and antagonize TNF-α–mediated inhibition of insulin signaling in differentiated adipocytes (38). Concerning IL-6, it is not clear whether TZDs decrease its secretion by adipocytes, but TZDs are able to decrease IL-6 production by monocytes.

An interesting candidate for a link between adipose tissue and muscle is adiponectin (or AdipoQ or ACRP30) (38). Adiponectin is a protein secreted exclusively by mature adipocytes. A proteolytic cleavage product of adiponectin, which includes its globular head group, is present in human plasma. Adiponectin expression is decreased in situations concomitant with insulin resistance (obesity, type 2 diabetes) in both animal models and humans. Adiponectin is able to improve insulin sensitivity and glucose utilization in models of obesity or lipodystrophy (48). The adiponectin effect results probably from increased muscle fatty acid oxidation, thus reducing the intracellular concentrations of fatty acids or fatty acyl-CoA and their adverse effects on insulin-stimulated glucose utilization. Two reports have recently demonstrated that adiponectin activates a specific kinase called AMP-activated protein kinase (AMPK), which has important metabolic consequences because it activates glucose transport in muscles by a mechanism that is not entirely understood (49,50). In addition, AMPK phosphorylates and inactivates acetyl-CoA carboxylase, thus decreasing malonyl-CoA concentrations. Because malonyl-CoA is an inhibitor of carnitine palmitoyltransferase 1, the enzyme that regulates fatty acyl-CoA entry into β-oxidation, the ultimate effect of AMPK activation is increased oxidation of fatty acids in mitochondria. Interestingly, the oral antidiabetic agent metformin also activates AMPK (51). A number of articles have now shown that TZD treatment increases adiponectin expression and secretion in insulin-resistant humans and rodents (52,53).

PPAR-γ AND INSULIN SENSITIVITY: PROBLEMS AND UNRESOLVED QUESTIONS

Treating diabetic or obese animals with TZDs induces adipocyte proliferation and weight gain. The former can be explained by the strong adipogenic effect of PPAR-γ. However, increasing the number of adipocytes is not sufficient to explain weight gain: disequilibrium between energy intake and expense must be present. In fact, in most animal models, an increased food intake under TZD treatment was described. In humans, modest weight gains have also been shown, and this excess weight seems to be localized essentially in subcutaneous adipose tissue. The reason for this specific localization is presently unknown, as is the long-term consequences of this overweight condition on the metabolic control of type 2 diabetic subjects.

Intriguing results have been observed in heterozygous PPAR-γ (+/−) mice. When these mice are fed a high-fat diet, they are less insulin resistant and have smaller adipocytes than wild-type mice, and present lower plasma fatty acids and increased levels of leptin and adiponectin (54). TZD treatment paradoxically decreases the insulin sensitivity of PPAR-γ (+/−) mice. These counterintuitive results have presently no convincing explanation.

Mutations in PPAR-γ resulting in a functionally dominant negative form of the protein have been associated with severe insulin resistance in a limited number of patients (55). This fits with the general consensus that PPAR-γ is important for maintaining normal insulin sensitivity. However, a more common polymorphism (Pro12Ala, 13% in Caucasians), which is associated with a decreased transcriptional activity in in vitro experiments, is concomitant with improved insulin sensitivity (56). Nevertheless, it must be underlined that this polymorphism is also associated with a lower BMI.

It is possible that these various discrepancies stem from the fact that activation of PPAR-γ has different short- and long-term consequences. A short-term effect is to expand the adipose tissue mass by differentiating new adipocytes that secrete hormones improving insulin sensitivity. This phenomenon can be transiently beneficial because it reduces the circulating concentrations of lipid substrates and stimulates glucose utilization in insulin-sensitive tissues. However, in the long term, and when concomitant with a high caloric intake, it can lead to overweight, release of fatty acids, decreased beneficial hormone secretion, and insulin resistance. Thus, depending on the stage at which animal models (and human subjects) are studied, changes in PPAR-γ expression can yield seemingly contradictory results.

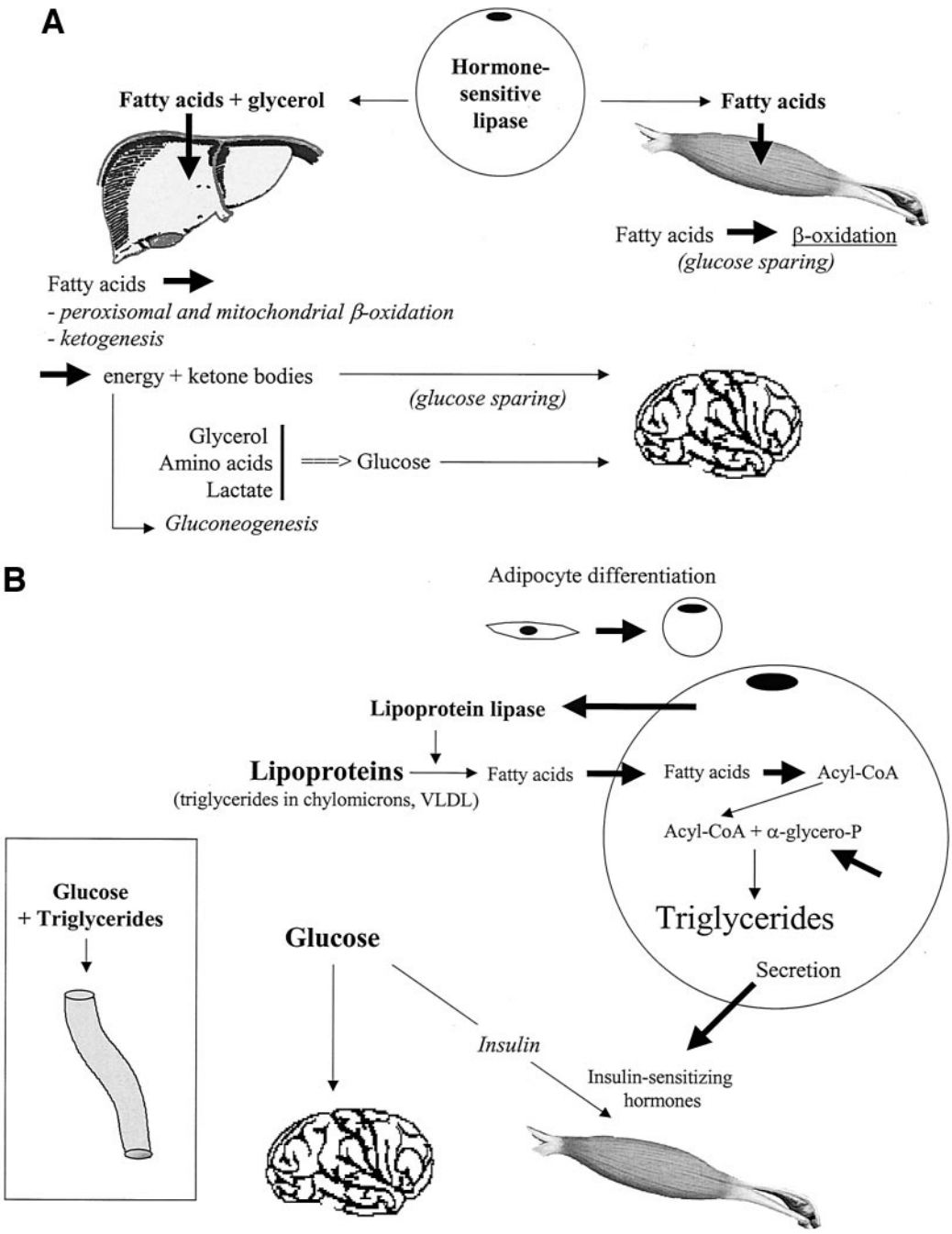

FIG. 3. Metabolic steps that are stimulated by PPARs in the fasted and fed state. *A*: Fasted state: fat mobilization and oxidation; glucose production and sparing. The steps that are stimulated by the activation of PPAR-α are indicated by bold arrows. *B*: Fed state: fat storage and glucose utilization. The steps that are stimulated by the activation of PPAR-γ are indicated by bold arrows.

CONCLUSIONS

PPARs are involved in the long-term regulation of lipid metabolism, and their activity is modulated by endogenous lipid-derived ligands. PPAR-α, by increasing fatty acid oxidation and ketone body production, is a "fasting–lipid oxidation–glucose sparing" regulator (Fig. 3*A*). PPAR-γ, by increasing triglyceride storage and improving insulin sensitivity, is rather a "well-fed–lipid storing–glucose utilizing" regulator (Fig. 3*B*). Clearly, their activation is a means of improving syndromes such as type 2 diabetes, which are characterized by high concentrations of plasma lipids and by insulin resistance. PPAR-α is active probably through its effect on lipid oxidation, whereas PPAR-γ acts by increasing lipid flux into storage and by inducing secretion of beneficial hormones. Some agonists with both PPAR-α and -γ selectivity are being presently tested and seem to combine positive effects on insulin sensitivity and on lipid parameters.

Finally, it must be pointed out that although the potential actions of PPARs are now known, thanks to synthetic ligands such as TZDs or fibrates, their activation in physiological and pathophysiological situations by endogenous ligands are still poorly understood. This may also explain some of the discrepancies described above.

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