Peroxisome proliferator-activated receptors: a family of lipid-activated transcription factors[1-4]

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ABSTRACT Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear transcription factors that belong to the steroid receptor superfamily. This family of PPARs includes PPARα, PPARδ, PPARγ1, and PPARγ2. These PPARs are related to the T3 and vitamin D_3 receptors and bind to a hexameric direct repeat as a heterodimeric complex with retinoid receptor Xα. PPARs regulate the expression of a wide array of genes that encode proteins involved in lipid metabolism, energy balance, eicosanoid signaling, cell differentiation, and tumorigenesis. A unique feature of these steroid-like receptors is that the physiologic ligands for PPARs appear to be fatty acids from the n−6 and n−3 families of fatty acids and their respective eicosanoid products. This review describes the characteristics, regulation, and gene targets for PPARs and relates their effects on gene expression to physiologic outcomes that affect lipid and glucose metabolism, thermogenesis, atherosclerosis, and cell differentiation. *Am J Clin Nutr* 1999;70:566–71.

KEY WORDS Peroxisome proliferator-activated receptor, fat cells, differentiation, fatty acids, fatty acid synthase, transcription factor, retinoid receptor Xα, review

INTRODUCTION

Early in the evolution of life forms, cellular growth and evolutionary success required that developing organisms respond to myriad environmental factors. In particular, organisms had to possess an ability to fulfill their nutrient needs and to sense periods of nutrient deficiency and excess to turn on pathways of synthesis and storage. Because of this need to sense changes in the nutrient environment, the early cell life forms developed nutrient-regulated switches that governed the transcription of genes encoding proteins involved in metabolic functions such as sugar synthesis and amino acid transport. This regulation of gene expression was in essence a primitive hormonal signaling system that operated for the survival and growth of the organism. As single-cell organisms evolved into complex life forms, nutrients continued to be environmental factors that functioned as signals for the regulation of gene expression and metabolism. The signals derived from the dietary constituents we consume and the effects these signals exert on gene expression can play both beneficial and detrimental roles in the etiology of nutritionally related pathophysiologies such as diabetes, cancer, and heart disease.

One dietary constituent that clearly modifies the differentiation, growth, and metabolism of cells is dietary fat. Not only does the amount of fat in the diet influence the development of nutritionally related pathophysiologies such as cancer, but the type of dietary fat has particular effects on cellular functions. For example, the ingestion of a diet high in saturated fat leads to insulin resistance, whereas the consumption of fat rich in 20-carbon and 22-carbon n−3 polyunsaturated fatty acids (PUFAs) normalizes insulin sensitivity (1). The regulation of cell functions by dietary fats can occur on 2 general levels: modulation of signal transduction via manipulation of membrane fatty acid composition (2) and rapid and direct modification of gene transcription (3). The role that membrane phospholipid fatty acid composition plays in hormonal signaling and receptor activity has been extensively pursued over the past 50 y. However, the notion that lipids may govern gene expression by functioning as ligand activators for a wide array of nuclear transcription factors has emerged only in the past few years (3, 4). Thus, this review focuses on the concept that lipids, notably PUFAs and their eicosanoid products, modulate gene transcription by governing the DNA binding activity of specific transcription factors.

IDENTIFICATION AND CHARACTERIZATION OF PPARs

Dietary n−6 and n−3 PUFAs have long been recognized as being able to exert unique influences on metabolic pathways and cellular growth (3, 4). For example, the ingestion of very long-chain PUFAs (eg, eicosapentaenoate) enhances mitochondrial and peroxisomal fatty acid oxidation (5, 6); additionally, linoleate consumption suppresses the hyperproliferation of keratinocytes

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associated with essential fatty acid deficiency (7). On the other hand, arachidonate promotes cellular growth in chemically induced mammary cancer (8) and stimulates the conversion of preadipocytes to adipocytes (9). Many of these outcomes have traditionally been attributed to alterations in hormone receptor signaling resulting from changes in membrane fatty acid composition or to the fact that PUFAs provide the essential fatty acids for membrane formation. However, with the advent of molecular biology techniques came the ability to evaluate the effect of PUFAs on the expression of specific genes (10, 11) and to examine the minute-by-minute changes that occur in gene expression when dietary components are modified. Through the application of molecular biology techniques it was discovered that PUFAs elicit changes in gene expression that precede changes in membrane composition (10, 11) and that involve mechanisms often independent of eicosanoid synthesis (12). Such studies indicated that PUFAs may regulate gene expression by directly governing the activity of nuclear transcription factors. The idea of a lipid-regulated transcription factor gained significant support when the transcription factor responsible for the induction of hepatic peroxisomal acyl-CoA oxidase was cloned in 1990 (13). Because this transcription factor was activated by agents associated with peroxisomal proliferation, it was given the name peroxisome proliferator-activated receptor α (PPARα).

The predicted amino acid sequence for PPARα indicates that this receptor possesses structural features characteristic of steroid receptors, ie, a ligand binding domain and a zinc-finger DNA binding domain (13, 14). Moreover, characterization of the DNA recognition sequence in the 5′-flanking region of the peroxisomal acyl-CoA oxidase gene indicated that PPARα forms a heterodimer partnership with retinoid receptor Xα (RXRα) and that the DNA recognition sequence for the dimer involves 2 direct-repeat half-sites with the consensus hexameric sequence AGGTCA (14). The direct-repeat motif of AGGTCA is identical to the repeat sequence recognized by the T3 and vitamin D_3 receptors and by several orphan receptors such as apolipoprotein A-I regulatory protein 1, chicken ovalbumin protein transcription factor, and steroidogenic factor (14–17). In the PPAR response element, however, only 1 nucleotide separates the 5′-AGGTCA RXRα binding site from the 3′ PPAR binding site (18, 19), whereas there is a 4-nucleotide spacer between the RXRα binding site and the binding site for T3 and a 5-nucleotide spacer between the RXRα binding site and the binding site for vitamin D_3 (19). These early studies revealed that PPAR is a member of the steroid receptor family and that the binding of PPAR to its response element depends on ligand activation of PPAR and the nucleotide spacing between the repeat hexamer. Since the initial identification of PPARα, several PPAR family members have been cloned. These include PPARγ1, PPARγ2, PPARδ (NUC-1/FAAR), and 2 related lipid-activated transcription factors, liver X receptor and farnesoid X receptor (20–24). Numerous studies conducted in the past 5 y indicate that lipid activation of PPARs results in a wide array of cellular changes, including the up-regulation of lipid oxidation, the enhanced expression of certain cell surface receptors, the acceleration of leukotriene degradation, and the stimulation of cell differentiation events.

ROLE OF RXRα IN THE ACTIONS OF PPARs

PPAR binding to the direct hexameric repeat sequence requires that PPARs form a heterodimer complex with RXRα (14, 18–20). An example of the importance of RXRα to PPAR regulation of gene expression is particularly evident in differentiating 3T3-L1 preadipocytes (25). Although these preadipocytes contain ample amounts of PPARγ, PPARγ will not bind to the PPAR response element nor will it stimulate the transcription of genes encoding proteins involved in terminal fat cell differentiation (eg, adipose fatty acid binding protein) until RXRα synthesis is stimulated by adding dexamethasone to the media (25). PPAR response element binding by the PPAR-RXRα heterodimer requires the presence of both proteins, and the DNA interaction is greatly enhanced by the binding of ligands to RXRα (eg, 9-*cis* retinoic acid) and to PPAR partners (eg, thiazolidenediones) (25–27).

Because all PPAR family members form heterodimer complexes with RXRα, and because these heterodimer complexes bind to the same PPAR response element, it is not surprising to find that PPARs compete with each other for their RXRα partner and subsequent binding to the hexameric repeat recognition sequence (27). Given such competition, how then do PPARs target specific genes? The answer to this question is that selection of the appropriate gene target and PPAR partner is determined by the type and amount of PPAR within a cell, the type of ligand signal, the extent of phosphorylation of PPAR, and the type of competition that may exist among other steroid receptor family members (26–36). With respect to competition among steroid receptor family members, RXRα is not only the partner for PPARs but is also the heterodimer partner for T3 and vitamin D3 receptors (27). More importantly, recent evidence indicates that the partners for RXRα compete for dimerization (20, 27–31). As an example of such competition, Chu et al (30) found that T3 activation of the T3 receptor attenuated the PPARα signal by reducing the availability of RXRα for binding to PPARα. They also found that overexpressing PPARα impaired T3 signaling by depriving the T3 receptor of RXRα (30). Ren et al (20) also reported that ligand activation of PPARα in isolated hepatocytes inhibited S14 (a putative lipogenic gene) gene expression by interfering with the formation of the T3-RXRα heterodimer complex (20).

Because PUFAs are ligands for PPARα, these data suggest that PUFAs may modulate the expression of T3-responsive genes (eg, S14 and fatty acid synthase) by activating PPARα and interfering with T3-RXRα binding activity. Such an observation may explain the early observations that dietary PUFAs reduce the hepatic responsiveness of lipogenic genes to T3 (10). However, note that in addition to a possible interaction between PPAR and T3, PUFAs also regulate lipogenic genes by a mechanism that is independent of their role as a PPAR ligand (3, 12). Clearly, the regulation of gene transcription by PPAR ligands has several levels of complexity that go beyond the simple identification of *cis* elements and *trans* factors.

LIGAND ACTIVATORS OF PPARs AND THEIR PHYSIOLOGIC CONSEQUENCES

Fatty acid activators and lipid oxidation

The search for physiologic ligand activators of PPARs has relied extensively on a technique termed the ligand activation assay (32). The essence of this assay is that the ligand binding domain of PPAR is fused with the DNA binding domain of the glucocorticoid receptor. This chimeric construct is transfected into a cell line (eg, COS-1 cells) containing a reporter gene (eg, luciferase) under the control of the glucocorticoid response

element of the MMTV (a murine virus) promoter. The fold induction of the reporter gene is taken as an index of the biopotency of the putative PPAR activator. Results from the use of this technique indicate that numerous PUFAs, as well as monounsaturated and saturated fatty acids, induce the expression of reporter genes in a PPAR-dependent manner (32–36). In general, all isoforms of PPAR are more responsive to 18–22-carbon n−6 and n−3 PUFAs than to saturated and monounsaturated fatty acids (32–34).

The finding that polyenoic fatty acids are more potent activators of PPARs than are saturated and monounsaturated fatty acids parallels the metabolic findings that n−6 and n−3 PUFAs are more potent inducers of fatty acid oxidation and more potent suppressers of fatty acid and triacylglycerol synthesis (5, 6, 10, 11, 37–40). This correlation has led to the proposal that PPARs coordinately regulate the expression of genes involved in the oxidation and synthesis of lipids. Numerous reports over the past 5 y have in fact unequivocally established that the 5′ flanking regions of genes encoding carnitine *O*-palmitoyltransferase, acyl-CoA oxidase, mitochondrial hydroxymethylglutaryl-CoA synthase, fatty-acyl-CoA synthetase, and mitochondrial uncoupling proteins all contain DNA recognition sequences for PPAR (37–43). Moreover, dietary studies revealed that feeding a diet rich in 20-carbon and 22-carbon PUFAs (ie, PPAR ligand activators) significantly increases the expression of the aforementioned genes and that induction of these genes is associated with higher rates of fat oxidation and reduced body fat deposition (37–42). The pivotal role that PPARα plays in energy balance is convincingly supported by the recent report that transgenic mice deficient in PPARα display a maturity onset obesity and hypertriglyceridemia in the absence of hyperphagia (43). There appears to be little question that PPARs play a key role in lipid oxidation and energy balance, but numerous studies have failed to show that PPARs participate directly in the PUFA suppression of lipogenic and glycolytic genes. This indicates that fatty acids regulate gene transcription by 2 independent mechanisms, only one of which is dependent on PPAR.

Eicosanoid activators and cell differentiation

Transcription activation assays and gel shift studies indicate that in addition to fatty acids, eicosanoid products of cyclooxygenase and lipoxygenase are potent ligand activators of PPARs (44–48). As for fatty acid ligands, the activation potency of eicosanoids varies with type (36, 45, 46). This discovery that eicosanoids are ligand activators of nuclear transcription factors adds a new dimension to eicosanoid signaling.

Examples of eicosanoid ligands for PPARs are leukotriene B_4 and 8S-hydroxyeicosatetraenoic acid (44). Leukotriene B_4 is a strong chemotactic agent of inflammation that is synthesized by immune cells but degraded primarily by the liver (44). In ligand activation assays, leukotriene B_4 activates hepatocyte PPARα, PPARδ, and PPARγ (44), and the response of PPARα to leukotriene B_4 is 25–30-fold greater than that of the other PPARs (44). Because leukotriene B_4 is degraded by enzymes of the peroxisomes, activation of PPARα up-regulates the peroxisomal enzymes of leukotriene degradation and in this way governs the amplitude of the inflammatory signal (44). Eicosanoid activation of PPARs also appears to be a key mechanism by which prostaglandins govern the expression of genes involved in cellular differentiation (35, 45–48). For example, the binding and activation of PPARγ2 by 15-deoxy-12,14-prostaglandin J_2 (15-deoxy-12,14-PG-J_2) induces the expression of genes (eg, fatty acid binding protein and lipoprotein lipase) involved in the terminal differentiation of fat cells (46). Similarly, fatty acid activation of PPARδ (ie, NUC-1) reportedly stimulates human osteosarcoma cells to differentiate (35). PG-A_1, PG-D_2, and PG-J_2 reportedly exert antitumor effects on human cancer cells, including those derived from melanoma, leukemia, and ovarian carcinoma (47). Like fatty acid ligands, the potency for prostanoid activation of PPARs varies with the type of prostaglandin and the type of PPAR. For example, PPARγ, which is relatively insensitive to fatty acid activation, is activated 80–90-fold by PG-D_1 and PG-D_2 (46).

Clearly, n−6 and n−3 PUFAs and their respective eicosanoid products have marked effects on cellular metabolism and cellular differentiation. Elucidation of the mechanisms of these effects will contribute significantly to our understanding of how dietary fats are related to the development and prevention of nutritionally related pathophysiologies. It will be interesting to ascertain whether n−6 and n−3 PUFAs and their respective eicosanoid products exert different effects on gene expression and events of cell differentiation by functioning as competitive ligands for PPARs.

Thiazolidenedione activators of PPARγ and diabetes

In light of the observation that PPARs play a central role in cellular metabolism and differentiation, a significant effort has been underway to identify specific PPAR ligands with pharmacologic benefits (49–52). One of the most productive areas of research has been in the discovery and use of thiazolidenediones (49–52). Thiazolidenediones (eg, pioglitazone and troglitazone) are orally active insulin-sensitizing agents that appear to exert their effects by functioning as PPARγ activators (49–52). Adipose tissue and skeletal muscle appear to be the key targets for thiazolidenediones (52–55). Thiazolidenedione activation of PPARγ in adipose tissue accelerates the rate of fat cell differentiation, which is accompanied by an increase in cell number and an increase in the expression of glucose transporter 4, fatty acid binding protein, and lipoprotein lipase (49–53). Thiazolidenedione activation of PPARγ in skeletal muscle is associated with increased expression of lipoprotein lipase and glucose transporter 4 (52, 53). The collective outcome of these genomic responses is improved insulin sensitivity, enhanced glucose metabolism, and decreased blood triacylglycerol concentrations (49–53). Current efforts to identify potent ligand activators of PPARs may soon lead to the identification of factors that regulate tumor growth and inflammatory response.

PPAR involvement in atherosclerosis

Although PPAR activators have been found to exert several beneficial influences, not all outcomes of PPAR activation are beneficial (4, 56). For example, fibrates, which are ligands for PPARα and thereby function to enhance the expression of genes encoding proteins of lipid oxidation, also stimulate the production of apolipoprotein (apo) A-I and A-II (4). Unfortunately, apo A-II synthesis is stimulated to a greater extent than is apo A-I synthesis (4). The result is the formation of a less desirable HDL particle that contains a lower ratio of apo A-I to A-II (4). However, part of this detrimental outcome of fibrate activation of PPARα is offset by an apparent PPAR-dependent increase in the expression of lipoprotein lipase and a parallel decrease in apo C-III production (4).

In addition to the effect that fibrates may exert on apo profiles, recent evidence strongly indicates that the induction and activation of PPARγ by oxidized LDL is a key component in the formation of foam cells from monocytes (56). In the development of

an atherosclerotic plaque, monocytes migrate into the subendothelial space and rapidly accumulate lipid. These monocytes give rise to lipid-laden foam cells characteristic of an atherosclerotic plaque. Tontonoz et al (56) showed recently that treating monocytes with oxidized LDL causes a rapid and extensive increase in the expression of PPARγ. Moreover, ligand activation (presumably oxidized fatty acid) of the PPARγ enhanced the expression of the scavenger receptor CD36, which in turn was associated with enhanced uptake of LDL cholesterol (56). This exquisitely conducted study not only shows that PPAR activators play a role in the development of nutritionally related pathophysiologies (eg, atherosclerosis), but also suggests that PPAR antagonists may have pharmacologic benefits (much like PPARγ2 agonists, which have improved the treatment of insulin resistance).

ROLE OF PHOSPHORYLATION IN PPAR ACTION

PPAR ligands not only regulate the DNA binding activity of PPARs by binding to the ligand domain, but also may function to regulate phosphorylation cascades that in turn govern the phosphorylation status of PPARs (57–60). For example, incubation of quiescent ML457 murine hepatocytes with Wy-14643 not only activates PPARα and PPARδ, but also increases the tyrosine phosphorylation of extracellular-signal-regulated kinase (ERK)-1 and ERK-2, which in turn induce the transcription of several immediate-early genes (58). Activation of the ERK–mitogen-activated protein kinase (MAPK) cascade also appears to increase the phosphorylation state of certain PPARs, which in turn alters their DNA binding activity (57–60). As an example, insulin treatment of adipocytes and CV-1 cells increases the phosphorylation of PPARα by 3-fold within 30 min (59). Moreover, the increase in PPARα phosphorylation is associated with a 2-fold increase in the transcriptional activity of PPARα (59). Similarly, insulin activation of the MAPK cascade in adipocytes enhances the transcriptional activity of PPARγ1 and PPARγ2 (59). Mutation analysis revealed that the activation domain within PPARγ is located in the amino terminal, ligand-independent region of the protein (59). In contrast with these findings, Adams et al (61) reported that MAPK phosphorylation of PPARγ inhibits both ligand-independent and ligand-dependent *trans*-activation functions of PPARγ, which in turn is associated with a suppression of fat cell differentiation (61). Collectively, the available data indicate that PPARs undergo phosphorylation and dephosphorylation, but the effect of this on PPAR binding to its DNA recognition sequence and on gene transcription and cell differentiation remains to be determined.

IS THE PUFA REGULATION OF LIPOGENESIS A PPAR-REGULATED PROCESS?

PUFAs of the n−6 and n−3 families have a unique ability to function as intraorgan and interorgan fuel partitioners; ie, they suppress triacylglycerol storage and enhance lipid oxidation (3–6, 42, 62). With the discovery of PPAR came the attractive hypothesis that PPAR is a "master switch" transcription factor that can be activated by dietary fatty acids to induce the expression of genes encoding proteins involved in lipid oxidation, while suppressing the genes encoding enzymes involved in lipid synthesis. Certainly, the data supporting the idea that PUFAs induce the transcription of genes encoding enzymes of fatty acid oxidation by activating PPAR is unequivocal. However, the PUFA suppression of lipogenic and glycolytic genes appears to involve a unique, non-PPAR-dependent mechanism (12, 42, 63, 64). Note that this conclusion does not pertain to the acceleration in lipid synthesis that occurs during fat cell differentiation because this clearly involves PPARγ2-regulated genes. Rather, we are discussing the role that PUFAs play in suppressing the fatty acid biosynthetic pathway of liver and possibly skeletal muscle.

The first evidence suggesting that PPARs may not mediate the PUFA control of lipogenic gene expression was derived from ligand activation assays designed to identify PPAR ligand activators (32). In these assays, saturated fatty acids had nearly the same ligand activation capability as PUFAs. For example, 12:0 was nearly as potent as 18:2n−6 as an activator of PPARδ, and 18:1n−9 was nearly equivalent to 18:2n−6 as an activator of PPARα, but only 18:2n−6 was found to inhibit hepatic lipogenic gene expression (33). Second, a PUFA response region (PUFA response element) was located in the proximal promoter of the pyruvate kinase and S14 genes (65, 66). However, this DNA sequence does not correspond to a characteristic PPAR response sequence nor does it bind PPARα (64). A third piece of data arguing against a role for PPAR in the PUFA regulation of lipogenic gene transcription is derived from in vivo studies using the potent PPAR activator eicosatetraynoic acid (ETYA) (11, 12). When ETYA is fed to mice, it induces the expression of hepatic acyl-CoA oxidase as expected (12). However, ETYA has no inhibitory effect on hepatic fatty acid synthase expression (12). In fact, ETYA prevents 18:2n−6 from inhibiting fatty acid synthase gene transcription (12, 40). Similarly, treating cultured hepatocytes with 20:4n−6 suppresses fatty acid synthase promoter activity, but treating the hepatocytes with the potent PPARα activator Wy 14643, or with activators for PPARγ and PPARδ (eg, PG-J_2 and pioglitazone), has no effect on hepatocyte fatty acid synthase expression (MG Teran and SD Clarke, unpublished observations, 1998). Perhaps the most convincing data against the idea that PPARs coordinately regulate genes involved in lipid oxidation and synthesis come from the observation that PUFAs continue to suppress fatty acid synthase and S14 gene transcription in the PPARα knockout mouse, but PUFAs fail to induce the expression of peroxisomal acyl-CoA oxidase (63). Collectively, these data indicate that there appear to be 2 independent mechanisms by which fatty acids, particularly PUFAs, regulate gene expression and cell functions. The first of these involves the lipid activation of a steroid-type receptor termed PPAR; the second mechanism, which targets the pathways of glycolysis and fatty acid biosynthesis, remains to be elucidated.

SUMMARY

Because of a need to sense changes in the nutrient environment, early cell life forms developed nutrient-regulated switches that governed the transcription of genes encoding proteins involved in a variety of metabolic functions. Nutrient feedback can be viewed as an early form of hormonal signaling. Fatty acids, particularly those from the n−6 and n−3 families, appear to be among the most influential of the "nutrient hormones" because they actually function as ligand activators for a specific set of nuclear transcription factors termed PPARs. Through their action as PPAR activators, fatty acids govern metabolic pathways, cell differentiation, and membrane receptor expression (4, 9, 14, 20, 33, 37, 43–47). For example, fatty acid activation of PPARα in liver and skeletal muscle leads to the increased

expression of genes encoding enzymes of fatty acid oxidation, which appears to be associated with decreased body fat deposition and increased whole-body thermogenesis. Leukotriene activation of hepatic PPARα may be responsible for attenuating inflammatory signals. PPARγ binding of PUFAs and their eicosanoid products induces changes in cell differentiation that may result in both beneficial and detrimental outcomes. For example, oxidized LDL appears to enhance PPARγ activity in monocytes and this in turn leads to foam cell formation and possibly atherosclerosis. On the other hand, prostanoid activation of PPARγ in melanoma and leukemia cells reportedly exerts an antitumor effect. Such changes in cell metabolism and differentiation elicited by fatty acid activation of PPARs provide nuclear targets for elucidating the role that dietary fats play in the development of nutritionally related pathophysiologies. Moreover, although much attention has been paid to the identification of physiologic ligand agonists for PPARs, there is undoubtedly much to be gained from pursuing the identification of dietary antagonists for these influential *trans*-factors.

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