Polyunsaturated Fatty Acid Regulation of Gene Expression[1,2]

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ABSTRACT For the past three decades, polyunsaturated fatty acids (PUFA) have been recognized as important energy sources and membrane components. PUFA also play key roles in many cellular events, such as gene regulation. Most recently, research has focused on identifying the mechanisms by which PUFA modulate gene transcription, mRNA stability and cellular differentiation. It is the purpose of this review to examine the effects of PUFA on gene expression in lipogenic as well as other tissues. Because the (n-3) and (n-6) series of PUFA are intimately involved in gene regulation, they will be the focus of review. The effects of other fatty acid families on gene expression are reviewed elsewhere. J. Nutr. 128: 923–926, 1998.

KEY WORDS: • polyunsaturated fatty acids • peroxisome proliferator responsive element • adipocyte • gene regulation

The lipid requirement of all mammals is met by their dietary intake or by de novo synthesis of fatty acids. The (n-3) and (n-6) polyunsaturated fatty acids (linolenate and linoleate, respectively) are essential fatty acids that cannot be synthesized by mammals and therefore must be obtained from dietary sources. Apart from the role of polyunsaturated fatty acids (PUFA)[4] in membrane structure, metabolism and signal transduction, it has become increasingly clear that they also have a role in the control of adipogenesis as well as physiologic events that reduce the genetic expression of many enzymes involved in lipid and carbohydrate metabolism. These latter aspects have been extensively reviewed by Clarke and Jump (1993 and 1994) and Clarke et al. (1997a and 1997b). This review will focus on the most recent reports of the effects of dietary (n-3) and (n-6) PUFA on gene expression and adipogenesis.

PUFA as regulators of gene expression in lipogenic tissues. Flick et al. (1977) and Jeffcoat and James (1978) showed that a diet containing 60% linoleic acid fed to rats decreased the activity of liver enzymes involved in lipogenesis. Further studies by Clarke et al. (1990) showed that expression of lipogenic enzymes increased in rat pups during weaning from the high fat nursing diet to a low fat, nonpurified diet. In cultured preadipocyte cells, Amri (1991) and Distel et al. (1992) showed that fatty acids induced expression of adipocyte fatty acid binding protein (aP2) mRNA. With these observations, dietary fat was established as a significant nutrient involved in metabolic regulation. To date, many hepatic genes have been shown to be regulated by the fat component of the diet. The levels of expression of genes encoding rodent malic enzyme, acetyl-CoA carboxylase (Salati and Clarke 1986), L-type pyruvate kinase, fatty acid synthase (FAS) (Clarke et al. 1990), glucose transporter 4 (GLUT4) (Tebbey et al. 1994), S14 protein (Clarke et al. 1990) and stearoyl-CoA desaturase (SCD1) (Landschulz et al. 1994, Ntambi 1992) are all known to be decreased (60–90%) by dietary (n-3) and (n-6) PUFA (Clarke and Jump 1993 and 1994, Jump et al. 1994). In general, most studies investigated both (n-3) and (n-6) PUFA; however, those limited to one of the two PUFA series will be specified in this review.

Most of the original data derived from these and other studies using different tissues suggested that the PUFA response was liver specific. Thus, research in the past few years has focused on PUFA regulation of gene expression in liver tissue and cultured hepatocytes. However, the PUFA response has recently been identified in adipose tissue as well. Amri et al. (1991) showed that an adipocyte-specific gene was regulated by the (n-3) fatty acid linolenate (18:3). More recently, Jones et al. (1996) observed a 75% decrease in adipose tissue SCD1 mRNA when lean or obese Zucker rats were fed a diet high in (n-6) PUFA relative to a control diet. Interestingly, the adipose SCD1 mRNA of obese rats was much higher than that of normal rats (Jones et al. 1996). Similar results have been observed in tissue culture systems. In the 3T3-L1 adipocyte cell line, arachidonic acid [AA, (n-6)] decreased SCD1 mRNA stability in a dose-dependent manner (80% maximum repression), as did linoleic (n-6), linolenic (n-3) and eicosapentaenoic acid [EPA, (n-3)] (Sessler et al. 1996). This is also the case with GLUT4 (Long and Pekala 1996, Tebbey et al. 1994).

Recent studies suggest that the adipose tissue response is more complex than originally anticipated. There are many reports concerning adipose depot-specific differences in general cell metabolism (Cousin et al. 1993, Maslowska et al. 1993). Examination of rat white adipose tissue from two different anatomical locations showed that FAS and lipoprotein lipase gene expression of internal fat depots, retroperitoneal adipose tissue, was affected specifically by (n-3) PUFA. Subcutaneous, inguinal adipose showed no response (Raclot et al. 1997). This recent report suggests that the PUFA response of FAS and lipoprotein lipase gene expression in adipose tissue is site specific and that perhaps not all white adipose tissue depots in the body are controlled in the same manner. This variance should be kept in mind in future studies concerning adipose tissue gene regulation.

PUFA regulation of gene expression in non-lipogenic tissues. Although fatty acid regulation in hepatic and adipose lipogenic tissues is the most intensively studied, regulation of gene expression by PUFA in other tissue types has also been observed. Immune tissues are susceptible to changes in proliferation and differentiation in response to PUFA. Both AA and EPA significantly inhibit the proliferation rate of promyelocytic leukemic HL-60 cells (Finstad et al. 1994). These fatty acids also initiate differentiation of cultured cells into mono-

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[4] Abbreviations used: AA, arachidonic acid; aP2, adipocyte fatty acid binding protein; 15d-PGJ_2, 15-deoxy-$D^{12,14}$-prostaglandin J_2; EPA, eicosapentaenoic acid; ETYA, 5,8,11,14-eicosatetraynoic acid; FAS, fatty acid synthase; GLUT4, glucose transporter 4; NDGA, nordihydroguariatic acid; PG, prostaglandin; PPAR, peroxisome proliferator activated receptor; PRE, peroxisome proliferator responsive element; PUFA, polyunsaturated fatty acids; PUFA-BP, polyunsaturated fatty acid-binding protein; PUFA-RE, polyunsaturated fatty acid response element; RXR, retinoid X receptor; SCD1, stearoyl-CoA desaturase 1.

cytes and granulocytes, as well as induce cell necrosis and apoptosis. Furthermore, both (n-3) and (n-6) PUFA increase the expression of Thy-1 antigen on a T lymphocyte cell line (Deglon et al. 1995). However, in a different T lymphoma cell line, AA decreases SCD2 expression (Tebbey and Buttke 1993). PUFA have also been shown to regulate the expression of intestinal genes, L-FABP, apolipoprotein A-IV and apolipoprotein C-III (Niot et al. 1997); the cardiac myocyte's Na^+ channel gene; the pancreatic β-cell's acetyl-CoA carboxylase gene (Brun et al. 1997) and the brain SCD2 gene (DeWille and Farmer 1993). Such a diversity in sites of action suggests that PUFA regulation is much more widespread than originally envisioned.

Mechanisms of PUFA control of gene expression. The molecular mechanisms of PUFA regulation of gene expression are still poorly understood, although progress has been made in the last few years. PUFA suppression of several hepatic genes was shown to be due largely to a decrease in the rate of gene transcription (Clarke and Jump 1993 and 1994, Landschulz et al. 1994, Ntambi 1992). Recently, studies on Δ-9 desaturase (SCD1), GLUT4 in adipocytes and the Δ-9 desaturase 2 (SCD2) gene in lymphocytes have shown that the effect of PUFA on gene expression can be at the level of both gene transcription and mRNA stability (Sessler et al. 1996, Tebbey et al. 1994). In mature adipocytes, the half-life of SCD1 mRNA is 67% lower in cells treated with AA (Sessler et al. 1996), whereas GLUT4 mRNA stability is reduced by 43% (Tebbey et al. 1994). Preadipocyte fatty acid–induced expression of aP2 is also suspected to be regulated through message stability because transcription of the gene was not increased with fatty acid treatment (Distel et al. 1992). With these observations, it seems reasonable to suggest that PUFA regulation of gene expression in adipocytes is controlled through mRNA stability. However, the same studies indicate that although mRNA transcripts of SCD1 and GLUT4 are destabilized by PUFA, there are transcriptional components that contribute to the total decrease in protein expression caused by PUFA. Transcription of GLUT4 is 50% lower in AA–treated adipocytes (Tebbey et al. 1994).

The most recent studies have focused on the mechanism by which PUFA regulate gene transcription. These studies are based on the idea that a *cis*-acting PUFA responsive element (PUFA-RE) is located in the promoter region of the PUFA-regulated genes. To alter gene transcription, a transcription factor (putative PUFA-binding protein) could bind to a PUFA-RE and block or enhance transcription. The PUFA-RE of the rat S14 protein and pyruvate kinase genes have been mapped (Jump et al. 1993, Liimatta et al. 1994), but no regulated nuclear factor binding to these elements has yet been demonstrated. Recently, our laboratory localized the SCD1 and SCD2 PUFA-RE to a 60-bp region in the promoters of these genes and demonstrated nuclear factor binding to this element (Waters et al. 1997).

The identification of proteins that bind to the PUFA-RE has been the effort of many laboratories, and several potential candidates have been proposed. It was shown that peroxisome proliferators such as WY14643, fibrates and thiazolidinediones were involved in activating peroxisomal β-oxidation, the same events activated by fatty acids. PUFA activate peroxisome proliferator-activated receptors (PPAR), and have therefore been hypothesized to be the endogenous activator of this receptor (Gottlicher et al. 1992). Lipogenic genes, such as S14 and FAS, are repressed by both peroxisome proliferators and PUFA (Bing et al. 1996, Blake and Clarke 1990, Jump et al. 1995). On the basis of these reports, it was then speculated that PUFA work through a peroxisome proliferator responsive element (PPRE), and that once activated, PPAR, along with their heterodimer partner, retinoid X receptor (RXR), were the common mediators of positive and negative effects on lipogenic and β-oxidative genes, respectively. This theory was partially refuted by our in vivo studies on SCD1 gene expression, which showed that PUFA and peroxisome proliferators had opposing effects on the SCD1 gene in liver. In addition, transient transfection experiments localized the SCD1 PPRE to an area of the SCD1 promoter that is distinct from the PUFA-RE (Miller and Ntambi 1996).

There have been several other reports showing that the PPAR are not the sole mediators in PUFA-coordinated gene regulation. Bing et al. (1996) and Baillei et al. (1996) have provided support of PPAR-independent PUFA regulation of the rat S14 gene. This group mapped the PPAR-RE to a separate and distinct location from the PUFA-RE of the S14 gene. The most recent reports provide definitive evidence that PUFA do not repress gene expression by acting as the endogenous activators of PPAR. Bing and colleagues (1997) used a PPARα-deficient rat strain to show that negative PUFA effects are PPAR-independent. A diet containing fish oil high in (n-3) PUFA did not induce mRNAs of the aceyl-CoA oxidase or CYP4A2 genes. This suggests that PPARα is required for the normal PUFA induction of these genes. However, the same diet repressed S14 and FAS mRNAs expression by $\geq$70%, levels of repression equal to that observed in normal rats. Thus, PPARα is not required for (n-3) PUFA to repress gene expression (Bing et al. 1997). With these current reports, a new hypothesis emerges in which there are two mechanisms for PUFA control of gene expression: a PUFA-PPAR–dependent mechanism responsible for up-regulation and repression of gene expression and a PPAR-independent or PUFA-specific mechanism for repression of gene expression (**Fig. 1**). Crosstalk, although not firmly established, could exist between these two pathways.

Because the PPAR does not mediate PUFA repression of gene transcription, the search for a PUFA-specific transcription factor has now become an important focus in PUFA research. The SCD1 and SCD2 genes are the first to exhibit the binding of nuclear proteins to their PUFA-responsive regions. Whether these proteins are regulated by PUFA has not been demonstrated. The identity of the PUFA-RE binding proteins in the SCD1 and SCD2 genes is presently unknown.

The binding of a protein to the PUFA-RE of the SCD1 and SCD2 genes (Waters et al. 1997), implicates a polyunsaturated fatty acid binding protein (PUFA-BP)–dependent mechanism for repression of gene transcription (Fig. 1). It is hypothesized that the interaction of an effector molecule with the PUFA-BP results in repression of gene transcription (Fig. 1). The original hypothesis suggested that the effector molecule was a prostaglandin (PG) metabolite of fatty acids and not the fatty acid itself. However, since then, cells culture studies using ibuprofen and indomethacin, inhibitors of PG synthesis by cyclooxygenase, and nordihydroguariatic acid (NDGA), an inhibitor of lipoxygenase, showed that PUFA exert their effects in the absence of prostaglandin synthesis. AA was able to repress SCD1 and GLUT4 gene expression in adipocytes by 78% even though prostaglandin metabolism was completely blocked (Long and Pekala 1996, Sessler et al. 1996). Clarke et al. (1997b) showed that the AA analog 5,8,11,14-eicosatetraynoic acid (ETYA), a potent inhibitor of Δ-6 desaturase, blocked the repression of hepatic FAS by (n-6) PUFA. However, ETYA could still induce acetyl-CoA oxidase as expected. These results suggest that AA must undergo Δ-6 desaturation before becoming a potent negative regulator of hepatic gene transcription (Clarke et al. 1997a). It would therefore appear

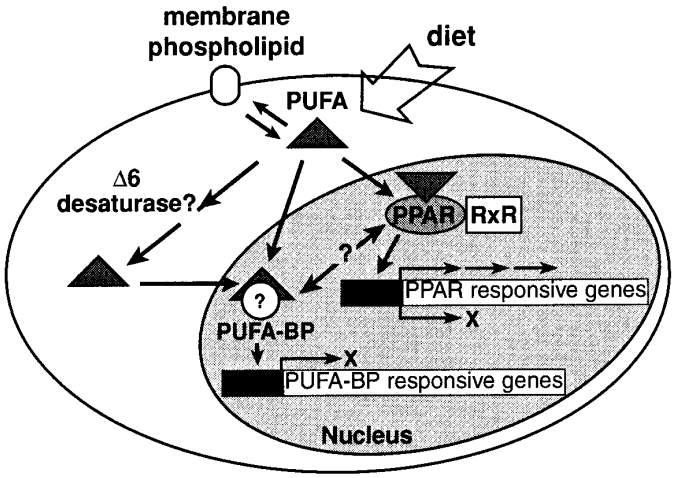

FIGURE 1 Coordinate transcriptional responses to polyunsaturated fatty acids via PPAR-dependent and -independent gene regulation. Dietary PUFA or those released from membrane phospholipids bind to the PPAR/RXR heterodimer and activate or repress transcription of genes by interacting with the PPRE. PUFA also independently bind the putative binding protein and repress transcription of lipogenic genes by binding the polyunsaturated fatty acid response elements. Crosstalk between the two pathways, as well as a possible conversion of the PUFA by a Δ-6 desaturase to an active metabolite, are suggested and designated by the arrows and question marks. Abbreviations: PPAR, peroxisome proliferator activated receptor; PUFA, polyunsaturated fatty acid; RXR, retinoid X receptor; PPRE, peroxisome proliferator responsive element; PUFA-RE, PUFA-response element.

that there are differences in repression among PUFA-regulated genes in different tissues.

PUFA in adipocyte differentiation. In addition to PUFA repression of lipogenic gene expression in adipocytes, there appears to be a secondary function. The most recent advances indicate that PUFA of the (n-6) series may control adipogenesis. Dietary linoleic acid is converted to AA which serves as a precursor for prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$ and PGI_2, **Fig. 2**). Prostaglandins play a critical role in the adipocyte differentiation program. Recently, 15-deoxy-$D^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a metabolite of PGD_2, was shown at micromolar concentrations to stimulate the differentiation of 3T3-L1 and 3T3-F422A preadipocytes into adipocytes through its interaction with the γ isoform of PPAR (Forman et al. 1995, Kliewer et al. 1995). This interaction, in turn, serves to transcriptionally activate numerous adipocyte genes.

On the other hand, $PGF_{2\alpha}$ and a metabolite of PGD_2, 9α,11β-$PGF_{2\alpha}$, (Fig. 2) block adipocyte differentiation through a cell surface prostanoid receptor (Casimir et al. 1996, Miller and Ntambi 1996, Serrero and Lepak 1997). Further investigation identified that the inhibition of differentiation by $PGF_{2\alpha}$ is mediated through a transient increase in intracellular calcium and activation of a calcium/calmodulin–dependent protein kinase leading to increased DNA synthesis (Miller and Ntambi 1996). In recent studies, Reginato et al. (1998) have shown that $PGF_{2\alpha}$ also blocks adipogenesis through activation of the mitogen-activated protein kinase, resulting in inhibitory phosphorylation of the nuclear hormone receptor and adipogenic transcription factor PPARγ2. The phosphorylated PPARγ2 does not effectively transactivate adipocyte genes to turn on the differentiation program. Thus, prostaglandins have opposing effects on adipogenesis through the use of different mechanisms, one through a nuclear receptor transcription factor and the other through a cell surface prostanoid receptor. Our laboratory has shown that $PGF_{2\alpha}$ is produced by preadipocytes and that its levels are decreased during differentiation (Casimir et al. 1996); however, it is not known whether 15d-PGJ_2 and 9α,11β-PGF_{2a} are produced or present in preadipose or adipose tissue. A mechanism to accumulate significant concentrations of 15d-PGJ_2 in the nucleus is currently unidentified. If these compounds are produced by the preadipocytes, then the balance between the two pathways would presumably determine the net effect on the differentiation program. Thus, regulating the levels of $PGF_{2\alpha}$ or 9α,11β-$PGF_{2\alpha}$ and 15d-PGJ_2 may be central to the development of obesity and diabetes.

Indeed, obese mice (*ob/ob*) fed a diet high in PUFA gain more weight than those fed a low PUFA-containing diet. Furthermore, enhanced expression of the *ob* gene was shown in normal rats weaned to a high fat diet, relative to those weaned to a low fat diet (Rousseau 1997). Whether these differences are mediated by PPARγ2 has not been established. Although the expression of PPARγ2 in rat white adipose tissue during weaning to a low fat diet did not change (Rousseau et al. 1997), the levels of activating ligands (i.e., fatty acids, PGJ2) remain undetermined.

Taken together, current data suggest two opposing roles for PUFA in adipocytes. Although fat synthesis and accumulation in mature adipocytes is down-regulated by PUFA of both the (n-6) and (n-3) series, the formation of new adipose cells is regulated

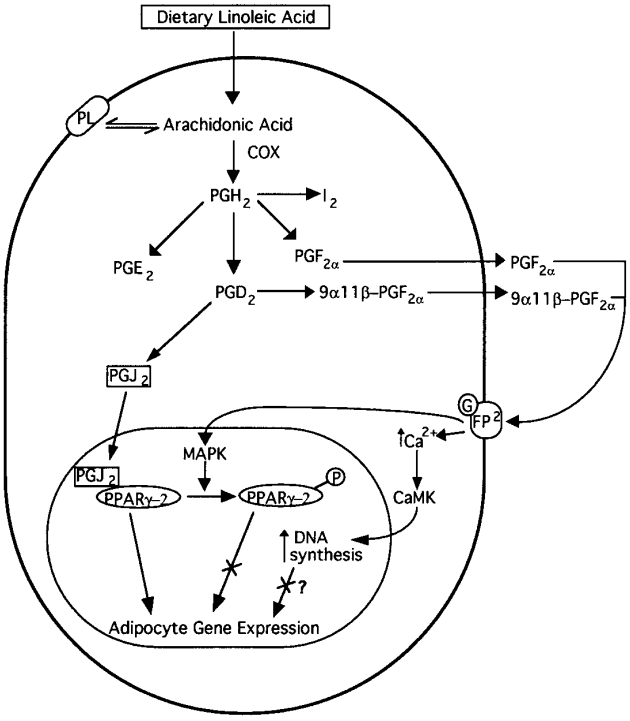

FIGURE 2 Opposing actions of arachidonic acid metabolites on adipocyte differentiation. $PGF_{2\alpha}$ and 9α,11β-$PGF_{2\alpha}$(a PGD2 metabolite) interact with the prostanoid FP2 G-protein coupled receptor, which activates a MAPK and CaMK resulting in phosphorylation of $PPAR_{2\alpha}$ and an increase in DNA synthesis, respectively. Both pathways could lead to inhibition of adipocyte gene expression. PGJ2, also a metabolite of PGD2, is shown as being endogenously produced by the preadipocyte and acts as a ligand to activate the PPAR receptor leading to activation of adipocyte genes. Arachidonic acid can also be derived from membrane in response to appropriate stimuli. Abbreviations: PG, prostaglandin; MAPK, mitogen-activated protein kinase; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; PPAR, peroxisome proliferator activated receptor; COXII, cyclooxygenase II; PL, membrane phospholipid.

by the (n-6) series through PPARγ2 and possibly other transcription factors. This seemingly paradoxical circumstance can be explained by the physiologic state of dietary fat excess. The adipocyte responds to increased dietary fat by shutting off its mechanisms that would lead to adipose hypertrophy. These are the lipogenic genes that are suppressed by PUFA. However, the same molecules that sense abundance of fat enable the organism to provide more space for storage by regulating the differentiation of the preadipocytes into adipocytes.

The data reported in the past few years have confirmed the importance of PUFA as universal cellular regulators. The discovery that fatty acids can affect gene transcription, and thus, modulate the cell's metabolic state, is essential to our understanding of responses to dietary changes. Furthermore, it has led to the careful dissection of the mechanisms by which PUFA modulate lipid metabolism. Because of the complexity of this response, the search for the molecules involved continues. Although it has now been shown that PUFA gene control involves both PPAR-dependent and -independent pathways, the links between the coordination of metabolic gene expression remain to be identified. Perhaps the recent progress on the effects of PUFA on cellular differentiation holds the most promise. These data suggest that PUFA may also function in development. Our understanding of new roles for PUFA is expanding, and continued research should provide insight into diseases such as obesity, diabetes and atherosclerosis.

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