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REGULATION OF GENE EXPRESSION BY DIETARY FAT

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ABSTRACT

Dietary fat is an important macronutrient for the growth and development of all organisms. In addition to its role as an energy source and its effects on membrane lipid composition, dietary fat has profound effects on gene expression, leading to changes in metabolism, growth, and cell differentiation. The effects of dietary fat on gene expression reflect an adaptive response to changes in the quantity and type of fat ingested. Specific fatty acid–regulated transcription factors have been identified in bacteria, amphibians, and mammals. In mammals, these factors include peroxisome proliferator–activated receptors (PPARα, -β, and -γ), HNF4α, NFκB, and SREBP1c. These factors are regulated by (*a*) direct binding of fatty acids, fatty acyl–coenzyme A, or oxidized fatty acids; (*b*) oxidized fatty acid (eicosanoid) regulation of G-protein–linked cell surface receptors and activation of signaling cascades targeting the nucleus; or (*c*) oxidized fatty acid regulation of intracellular calcium levels, which affect cell signaling cascades targeting the nucleus. At the cellular level, the physiological response to fatty acids will depend on (*a*) the quantity, chemistry, and duration of the fat ingested; (*b*) cell-specific fatty acid metabolism (oxidative pathways, kinetics, and competing reactions); (*c*) cellular abundance of specific nuclear and membrane receptors; and (*d*) involvement of specific transcription factors in gene expression. These mechanisms are involved in the control of carbohydrate and lipid metabolism, cell differentiation and growth, and cytokine, adhesion molecule, and eicosanoid production. The effects of fatty acids on the

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genome provide new insight into how dietary fat might play a role in health and disease.

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INTRODUCTION

Dietary fat is an important macronutrient in the diet of all animals. It provides a source of energy and hydrophobic components that are utilized for the synthesis of complex lipids. Certain fatty acids are covalently linked to proteins whereas others are precursors for signaling molecules such as prostanoids and steroids. In addition to these well-established roles, dietary fat affects gene expression, leading to pronounced changes in metabolism, cell differentiation, and growth (21, 65). In light of the evidence implicating dietary fat in the onset or progression of chronic diseases (22, 44, 47, 53, 57, 76, 77, 80, 111, 126, 136–138), understanding the molecular basis for dietary fat action on the genome is critical to understanding its role in human health.

Genomic effects of dietary fat reflect an adaptive response to too much or too little fat or to a change in dietary fatty acid composition (21, 65). Prior to 1992, fatty acid effects on gene expression were thought to be secondary to changes in membrane phospholipid or eicosanoid production. However, in that year, two laboratories reported the discovery of nuclear receptors that were regulated by fatty acids, i.e. peroxisome proliferator–activated receptors (PPARs) (43, 59). Consequently, some fatty acids or their metabolites act like hormones to control the activity or abundance of specific transcription factors. These transcription factors interact with specific genes through *cis*-regulatory elements and interface with common components of the transcriptional apparatus.

Considerable effort has focused on PPARs as mediators of fatty acid and peroxisome proliferator effects on cell metabolism and differentiation. However, PPARs do not account for all fatty acid effects on the genome. In this review, we examine the evidence for fatty acid regulation of specific transcription factors and how these factors participate in cell-specific gene expression. Our previous reviews (21, 65) dealt with fatty acid structure and its relation to effects on gene expression. This review focuses on the most recent issues related to fatty acid regulation of transcription factor function. This area of research is progressing rapidly, and as such, we apologize for any recent findings that we may have not covered.

FATTY ACID REGULATION OF GENE EXPRESSION IN BACTERIA AND YEAST

The regulation of gene expression in bacteria and yeast often provides important clues to the existence of regulatory pathways and molecules in higher organisms. *Escherichia coli* has an inducible system for the uptake and oxidation of fatty acids. The FadR gene product regulates several unlinked genes and operons involved in fatty acid synthesis and degradation. FadR is a transcriptional repressor of genes required for fatty acid transport and β-oxidation, including fadL, fadD, fadE, fadBA, and fadH, as well as fabA, a transcriptional activator required for unsaturated fatty acid biosynthesis (5). FadR binds oleoyl-coenzyme (Co)A with high affinity (12 nM), and this binding regulates FadR binding to DNA (consensus: 5′-AGCTGGTCCGAYNTGTT-3′). Free fatty acids do not affect FadR binding (29, 30, 109).

Bm3R1 is a transcriptional repressor in *Bacillus magaterium*, and its binding to DNA is inhibited by fatty acids. Inhibition of Bm3R1 DNA binding activity results in the activation of transcription of the operon encoding a fatty acid hydroxylase, CYP102 (105). This system is thought to be the mediator of an adaptive response to fatty acid toxicity.

In *Saccharomyces cerevisiae*, unsaturated fatty acids are formed from saturated acyl-CoA precursors by Ole 1p, a Δ9-fatty acid desaturase. OLE1 mRNA levels are differentially regulated by saturated and unsaturated fatty acids. Saturated fatty acids induce OLE1 gene transcription (60%) whereas unsaturated fatty acids repress OLE1 gene transcription (60-fold) (19). Unsaturated fatty acids also enhance $mRNA_{OLE1}$ turnover (40).

Fatty acids affect bacterial and yeast gene expression, enabling these organisms to adapt to changes in the external milieu. Similar mechanisms exist in higher organisms. Unlike unicellular organisms, however, macronutrient control of gene expression in higher organisms interfaces with components of endocrine, paracrine, and autocrine regulatory pathways. These interactions can

augment or abrogate gene expression, leading to changes in cell metabolism, growth, and differentiation.

FATTY ACID REGULATION OF GENE EXPRESSION IN MAMMALS

Fatty Acid Transport and Metabolism

Dietary fat enters the circulation from the gut via the lymph in the form of chylomicrons. Hepatic very low–density lipoproteins (VLDL) production from dietary fatty acids and fatty acids synthesized de novo contribute to the serum lipid level in the postprandial state. Although the average concentration of free fatty acids and triglycerides in the postabsorptive state is <0.7 and <1.8 mM, respectively (4), these levels are much higher during the absorptive phase following ingestion of a fatty meal. Age, gender, diet, endocrine status, and genetic background affect these values. More important, the composition of plasma fatty acid (chain length and degree of unsaturation) is determined by the type of fat ingested.

Cellular uptake of lipid from chylomicrons and VLDL is similar. The majority of complex lipid is hydrolyzed by two related lipases, hepatic lipase and lipoprotein lipase. This hydrolysis enables free fatty acids to enter cells through membrane-associated fatty acid transporters (56) (Figure 1). At least five plasma membrane proteins have been identified as potential fatty acid transporters, including (*a*) fatty acid binding protein (FABP), (*b*) fatty acid translocase, (*c*) caveolin, (*d*) 56-kDa kidney fatty acid binding protein, and (*e*) fatty acid transport protein. A likely candidate for fatty acid transport in adipose and liver cells is fatty acid transport protein ($K_t \sim 0.2\ \mu$M) (94; Figure 1).

Once in the cell, most fatty acids are noncovalently bound to proteins, like FABP. Several FABP subtypes have been described, including liver, adipocyte, and intestinal (42). A requisite step for fatty acid entry into several metabolic pathways is the formation of fatty acyl–CoA–thioesters (FA-CoA), catalyzed by FA-CoA synthetases. Several FA-CoA synthetase subtypes display fatty acid chain-length specificity. The FA-CoA products of these enzymes also are bound to FABP. The FABP exists within both the cytosol and nucleus (7, 56), which suggests that fatty acids or FA-CoA may be in the nucleus and serve as ligands that regulate the activity of specific transcription factors. The total intracellular FA-CoA level is highly variable and depends on the cell examined. In liver, FA-CoA ranges from 110 to 152 μM, whereas in heart they range from 10 to 70 nmol/g wet weight of tissue (13, 42). Although the intracellular concentration of fatty acid and FA-CoA that is not bound to protein is low, $<10\ \mu$M (42), it is fatty acid or FA-CoA in this faction that is likely to serve as regulatory ligands for specific transcription factors.

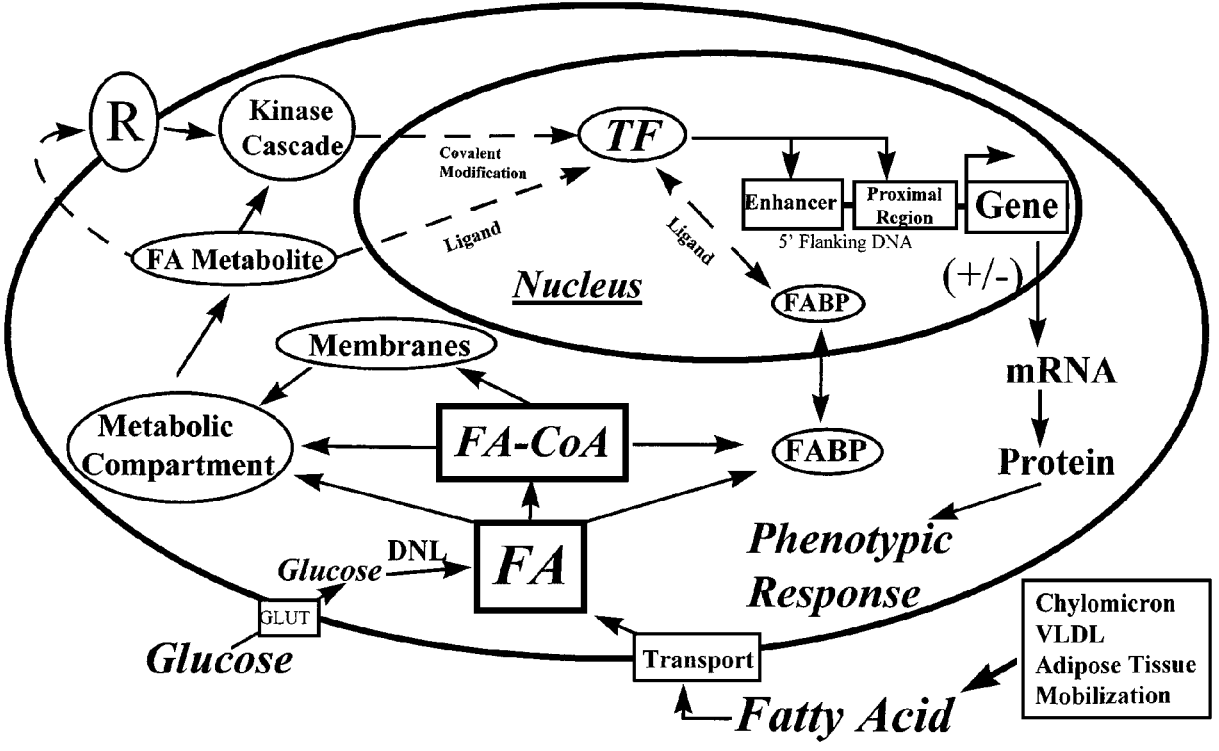


Figure 1 Fatty acid regulation of gene transcription. Fatty acids enter cells through membrane-associated transporters, undergo metabolic conversions, and affect many cellular processes. Some of these processes involve changes in gene transcription, leading to changes in cell growth and differentiation, metabolism, and production of various molecules such as triglycerides, apolipoproteins, cytokines, eicosanoids, and adhesion molecules. R, receptor; TF, transcription factor; FABP, fatty acid binding protein; GLUT, glucose transporter; FA, fatty acid; Fa-CoA, fatty acyl coenzyme A thioester; VLDL, very-low-density lipoprotein; DNL, de novo lipogenesis. The 5′-flanking DNA contains *cis*-regulatory elements involved in basal promotor activity (proximal region) and stimulated activity (enhancer). Both regions can be targeted by fatty acid–regulated transcription factors.

An alternate route for fatty acid regulation of transcription factor function involves intracellular metabolism (Figure 1). Fatty acids enter a number of metabolic pathways, including formation of complex lipids (triglycerides, phospholipids) as well as elongation, desaturation, and oxidization (13, 32, 34, 35, 39, 42, 65, 69, 82, 92, 93, 97, 102–104). Some metabolic routes are common to most cells, like β-oxidation, whereas others are tissue specific, e.g. prostanoid synthesis. FA-CoAs serve as substrates for phospholipids and triglyceride synthesis as well as subsequent fatty acid elongation and desaturation. Free fatty acids serve as substrates for fatty acid oxidation through the cyclooxygenase, lipoxygenase, or monooxygenase pathways.

A major route for fatty acid metabolism is through oxidation in mitochondria and peroxisomes (97, 112). In microsomes, unsaturated fatty acids are oxidized to form eicosanoids and epoxy- and hydroxy-fatty acids. Some of these oxidative steps generate regulatory molecules involved in cell signaling. For example, arachidonic acid released from the sn-2 position of the membrane phospholipids by the action of phospholipase A2 provides a substrate for cyclooxygenases (COX1, a constitutive enzyme, or COX2, an inducible enzyme), lipoxygenase, or monooxygenase. Cyclooxygenase and lipoxygenase products of arachidonic acid (20:4,n-6) give rise to prostanoids, thromboxanes, and leukotrienes (32, 39). These bioactive lipid mediators exit cells and act locally at nanomolar levels through autocrine or paracrine processes on cell surface receptors linked to G-proteins. Activation of G-proteins leads to changes in intracellular cAMP or calcium, and these changes serve as second messengers that can activate signaling mechanisms that have pronounced effects on transcription factor function (18, 26).

Monooxygenases are microsomal cytochrome P450 (CYP)-linked enzymes that are members of a large enzyme superfamily that catalyzes the oxidation of a diverse array of lipophilic compounds, including hormones, fatty acids, drugs, and xenobiotics (34, 104, 134). Tissue, gender, age, hormones, and diet affect the abundance of these enzymes. Two families that bear mentioning are the CYP2C and 4A families. The monooxygenase CYP2C23 generates epoxides from arachidonic acid, i.e. 5,6-, 8,9-, 11,12-, or 14,15-epoxyeicosatrienoic acids in liver and kidney. Although the effects of epoxyeicosatrienoic acids on cell function are tissue dependent, they involve changes in intracellular calcium (34, 69, 93, 104). CYP4A are ω- and ω-1 hydroxylases that are highly regulated by dietary fat at the pretranslational level (67, 101–103, 112, 129).

In summary, fatty acids enter cells, interact with specific binding proteins, and undergo metabolic conversions. The FABPs and metabolic conversions are tissue specific, and fatty acid structure dictates the route for metabolic conversion. Some routes generate ligands (prostanoids) for membrane or nuclear receptors, whereas others may affect intracellular second messenger levels. Because fatty acids are actively metabolized, the operative intracellular concentration for a

fatty acid or its metabolites on gene expression is likely to be far lower than the plasma level of the fatty acid. Thus, the capacity of the cell to respond to specific fatty acids will depend on its tissue-specific metabolism, the generation of ligands or second messengers, and the type of nuclear or membrane receptor. These are not static phenomena but can be induced or suppressed according to the type and quantity of dietary fat ingested.

Fatty acid–regulated transcription factors interact with specific regions within promoters, either by direct DNA binding or through protein-protein interaction. The *cis*-regulatory targets for control may be within an enhancer or the proximal promoter (Figure 1). It is important to keep in mind that many fatty acid–regulated genes are controlled by other regulatory networks, thus representing a complex integration of nutrient, endocrine, paracrine, and autocrine control of cell function. Specific examples are used to illustrate these points.

Fatty Acid Regulation of Gene Transcription

The type, quantity, and duration of fat ingested contribute to specific biological effects. For example, ingestion of diets high in saturated fat (>45% as calories) for several weeks increases serum triglycerides and promotes insulin resistance, hypertension, and obesity in rodents (77). However, changing the diet to one containing very long–chain n-3 polyunsaturated fatty acids (PUFA) ameliorates the insulin resistance and abnormal lipid profile (126). In contrast to these long-term effects, ingestion of a PUFA (either n-3 or n-6) diet for 1 day is sufficient to suppress hepatic de novo lipogenesis in rodents (63, 64).

Diets containing n-3 and n-6 PUFA rapidly suppress the transcription of the hepatic genes encoding fatty acid synthase (FAS), the S14 protein (S14), stearoyl CoA desaturase 1 (SCD1), and L-pyruvate kinase (L-PK) (6, 63, 81, 90, 98). Highly unsaturated n-3 PUFA, such as fibrates, also induce the expression of genes involved in fatty acid oxidation, e.g. acyl-CoA oxidase (AOX) and CYP4A2 (35, 102, 103, 114). However, PUFA suppression of glucose 6-phosphate dehydrogenase involves a posttranscriptional regulatory mechanism (52). These effects are due to the direct action of fatty acids on hepatic parenchymal cells and does not involve extrahepatic fatty acid metabolites or hormones (21, 65).

Analyses of the molecular bases for fatty acid regulation of gene transcription have focused on several candidate mechanisms, including PPAR- and prostanoid-regulated processes. Here we present evidence for these mechanisms as well as for other mechanisms that may account for the diverse actions of fatty acids on gene transcription.

Peroxisome Proliferator–Activated Receptors

PPARs were first discovered by Issemann & Green (59). These factors have a structure similar to other members of the steroid-thyroid supergene family of

nuclear receptors and are activated by the peroxisome proliferators, clofibric acid, nafenopin, and WY14,643. Accordingly, these factors were called peroxisome proliferator–activated receptors (PPARs). Fatty acid regulation of PPARs was first reported by Gottlicher et al (43) using a chimeric receptor containing the putative PPAR ligand binding domain fused to the glucocorticoid receptor DNA binding domain in transactivation assays. At 100 μM, the relative potency for PPAR activation was WY14,643 > linoleic acid > arachidonic acid > oleic acid = stearic acid > lauric = caproic acid. Dehydroepiandrosterone (DHEA) DHEA-SO_4, cholesterol, and 25-OH-cholesterol did not activate the chimeric receptor. This discovery was the first indication that fatty acid effects on the genome might be mediated through specific nuclear receptors.

Since these initial reports, several PPAR subtypes have been cloned from humans, rodents, and *Xenopus*. Three subtypes (α, δ, and γ) have been identified and are encoded by three separate genes (10, 31, 88, 132, 144). PPARα is expressed in hepatocytes, cardiomyocytes, renal proximal tubule cells, and enterocytes. PPARδ [PPARβ/δ, Nuc1 (human); FAAR (rodent)] is more widely expressed than is PPARα. PPARγ1 and -γ2 are encoded from the same gene, but PPARγ2 has an N-terminal extension. The PPARγ gene contains two promoters and through differential splicing gives rise to either PPARγ1 or -γ2 as a result of an upstream translation start site (145). PPARγ is expressed in adipose tissue, spleen, retina, hematopoietic cells (88, 132), and epithelial cells of the colon, prostate, and mammary gland (60, 79, 83, 100, 119).

PPARs are single polypeptide nuclear receptors that are structurally related to other members of the steroid/thyroid receptor superfamily. Two Zn-finger motifs in the DNA binding domain are important for receptor binding to peroxisome proliferator response elements (PPREs) located in the regulatory DNA of responsive genes (58, 101, 116). Sequence comparisons and mutation analysis indicate that PPREs are direct repeat-1 (DR1)-like motifs with 5′ extensions (consensus: AACTAGGNCAAAGGTCA) (58). PPAR binds DNA as a heterodimer with the retinoid X receptor (RXR). However, their orientation on the DR1 is opposite of that found for other heterodimer pairs, like thyroid hormone receptors (TR) and RXR. PPAR binds the 5′ half of the DR1, whereas RXR binds the 3′ half (58). PPARs interact with steroid receptor activator 1 (SRC-1) and PPAR-binding protein (PBP), factors that may play roles as coactivators (141).

Fatty acids are only one class of compounds known to activate PPARs. A wide variety of structurally diverse compounds activate PPARs, including hypolipidemic drugs (WY14,643, gemfibrozil, and clofibrate), plasticizers [di-(2-ethylhexyl)phthalate], steroids (DHEA and DHEA-SO_4), and thiazolidinediones (TZD) (troglitazone and pioglitazone). Because of this diversity and the fact that fibrates and TZD have major effects on lipid metabolism, an

intense effort has been directed at identifying native and pharmacological ligands for PPARs.

The TZD BRL49653 ($K_d \sim 43$ nM) was the first compound reported to bind PPARγ specifically (87). TZDs promote adipocyte differentiation (73) and have antidiabetic effects on animal models of non–insulin-dependent diabetes mellitus (16). The TZD troglitazone (Rezulin®, Parke-Davis) is used clinically to help control blood glucose levels in patients with non–insulin-dependent diabetes mellitus. Subsequent studies have shown that certain eicosanoids, like 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-J_2) also bind to PPARγ (K_d of 2.5 μM) (33, 36, 37, 74, 75, 78). PPAR activators like WY14,643, 8S-HETE, and cPGI bind to PPARα with a K_d of 1, 0.2, and 1 μM, respectively (36, 142). However, PPARα activators like PGA_1, PGA_2, PGB_2, PGD_2, and 15d-PGJ_2 failed to bind, which suggests that these compounds might require in vivo activation to become PPARα ligands or undergo metabolism, leading to the regulation of PPAR activity through some other mechanism. Kliewer et al (75) reported that the ligand binding domain of Xenopus PPARα (xPPARα) and xPPARγ bound both mono- (oleic) and polyunsaturated fatty acids (arachidonic, linoleic, linolenic) at concentrations comparable to values found in human serum (68). Although the leukotriene LTB4 was reported to bind ($K_d \sim 90$ nM) and activate xPPARα (28), others have not confirmed this binding activity using mouse PPARα (36).

Taken together, these reports indicate that structurally diverse compounds bind to and/or activate PPAR. The pharmacological ligands like the fibrates (WY14,643 and clofibrate) preferentially bind PPARα, whereas the TZDs BRL46653 and troglitazone and eicosanoids preferentially bind PPARγ. PPARδ binds some prostanoid agonists (iloprost and cPGI) and PUFAs (linoleic and arachidonic acid) but not fibrates (WY14,643) or TZDs (36). The finding that eicosanoids bind PPARγ indicates that these lipid mediators have two targets of action on gene expression, either through plasma membrane G-proteins or through nuclear receptors.

Peroxisome proliferators and PPARs have diverse effects on gene expression, leading to changes in metabolism and cell differentiation. Unsaturated n-3 and n-6 PUFA that have undergone significant desaturation and elongation along with other peroxisome proliferators induce peroxisomal β-oxidation and many of the mRNAs encoding peroxisomal enzymes (112). The recently developed PPARα null mouse (85) has allowed investigators to assess the role this receptor plays in lipid metabolism. Collaborative studies between the Gonzalez lab and others have shown that PPARα is required for WY14,643 and clofibrate induction of mRNAs encoding hepatic peroxisomal enzymes (acyl-CoA oxidase, bifunctional enzyme, thiolase), microsomal enzymes (CYP4A and 4A3), and liver FABP (85).

PPARα is also required for the peroxisome proliferator regulation of certain apolipoproteins (108), fatty acid translocases, and fatty acid transport proteins, (99) as well as for induction of the mitochondrial enzymes: carnitine palmitoyl transferase I (10, 46), very long–chain acyl-CoA dehydrogenase, long-chain acyl-CoA dehydrogenase, short-chain acyl-CoA dehydrogenase, short-chain–specific 3-ketoacyl–CoA thiolase, long-chain acyl-CoA synthetase, and malic enzyme through PPARα (3, 121).

PPARα is required for the fish oil–mediated induction of $mRNA_{AOX}$ and $mRNA_{CYP4A2}$, but not the fish oil–mediated suppression of mRNAs encoding FAS, S14, or L-PK (114). Diets supplemented with olive, corn, soybean, or walnut oil at $\leq$20% of total calories suppress lipogenic gene expression but do not induce hepatic mRNAs encoding AOX or CYP4A2 (114; S Langdon, A Thelen & DB Jump, unpublished observation). These studies provided the first indication that fatty acid regulation of hepatic de novo lipogenesis and fatty acid oxidation was not mediated through a common factor, i.e. PPARα.

In vitro transactivation studies using CV1 or HeLa cells indicated that a broad spectrum of fatty acids bind to and activate PPARα (36, 75, 78). However, when compared with WY14,643, fatty acids are weak activators of PPARα (36, 114). In contrast to CV-1 cells, fatty acid activation of PPARα in primary hepatocytes is selective: eicosapentaenoic acid (20:5,n-3) but not arachidonic acid (20:4,n-6) activates PPARα and induces $mRNA_{AOX}$ and $mRNA_{4A2}$ (114). The discrepancy between these results can be explained by the high capacity of hepatocytes for fatty acid oxidation, triglyceride synthesis, and VLDL secretion (118). These pathways may prevent intracellular fatty acid levels from accumulating and activating PPARα. Because eicosapentaenoic acid (20:5, n-3) is poorly oxidized in mitochondria or incorporated into complex lipids like triglycerides (118), eicosapentaenoic acid (20:5,n-3) or a metabolite might accumulate to a level sufficient to activate PPARα.

Although the role PPARα plays in rodent hepatic lipid metabolism is well established, its role in human liver is less clear. When compared with rodent liver, there is no evidence for peroxisomal proliferation by the fibrates used clinically. Moreover, PPARα is expressed at low levels, and splice variants have been identified in human liver (17, 41, 106). Despite the fact that hypolipemic drugs like gemfibrozil have similar effects on whole body lipid metabolism in both rodents and humans, the contribution of human hepatic PPARα to these processes is unresolved. As is discussed below, extrahepatic actions of PPARα might play a major role in the lipid-lowering effects of fibrates.

PPARδ, also known as PPARβ, FAAR (rodent), or Nuc1 (human), shows a wide tissue distribution. The ligand binding profile of PPARδ suggests that fatty acids or their metabolites rather than fibrates or TZD are more likely to regulate this factor (36). Although efforts to generate PPARδ null mice are

in progress, no specific proteins, metabolic pathways, or cell differentiation processes have been linked exclusively to PPARδ.

Two PPARγ have been identified, PPARγ1 and PPARγ2 (132, 144). Efforts to generate PPARγ null mice have not, as yet, been successful. PPARγ2 has been the focus of intense investigation because of its role in adipocyte differentiation (132). PPARγ2 is involved in the induction of enzymes involved in lipid storage in adipocytes. Fatty acids and some prostanoids induce adipocyte differentiation, a process marked by the augmentation of mRNAs encoding proteins involved in fatty acid transport, fatty acid binding, lipogenic enzymes, and enzymes involved in triglyceride synthesis as well as various lipogenic and lipolytic hormone receptors (23).

Because preadipocytes express FAAR (PPARβ/δ) and not PPARγ2, Amri et al (2) suggested that FAAR may be an early target of fatty acid action that is involved in initiating adipogenesis. PPARγ2 appears during the early phases of adipogenesis and may be involved in the progression of adipogenesis. Overexpression of either FAAR or PPARγ2 in myogenic cell lines followed by fatty acid treatment is sufficient to induce their differentiation to adipocytes (132). However, in a direct comparison of the adipogenic potential of PPAR in 3T3 cells, PPARα also was reported to induce some adipogenesis when stimulated by strong activators. Unlike PPARγ, PPARδ (FAAR) could not stimulate adipogenesis (12). Because many fibroblastic cell lines express low levels of PPARγ, previous suggestions that PPARδ was responsible for adipogenesis may have been due to the activation of endogenous PPAR (α or γ) with high concentrations of activating ligands (122).

Negative Regulation of Gene Transcription by PPARs

Although PPARs clearly induce the expression of many genes, they also suppress the expression of others, such as ApoCIII, transferrin, S14, and L-PK (49, 51, 66, 113). Hertz et al have reported that PPAR/RXR compete with hepatic nuclear factor-4 (HNF-4) for binding DR1 elements within the ApoCIII (49) and transferrin (51) promoters. Such competitive binding may explain the inhibitory effect of fibrates on these genes. Hepatic L-PK is suppressed by PUFA and peroxisome proliferators (66). Although the L-PK PUFA-response region (PUFA-RR) also contains a DR1 (LFA1) that binds HNF4, PPARs bind poorly to the L-PK promoter (D Pan & DB Jump, unpublished observation).

PPARs are one of several nuclear receptors (TR, retinoic acid receptors, and vitamin D receptors) that require RXR as a heterodimer partner for DNA binding. This raises the possibility that activation of PPAR might affect other nuclear signaling networks. Surprisingly, only thyroid hormone action has been reported to be affected by PPARs (20, 61, 113). Both in vivo and in primary hepatocytes, WY14,643 suppresses S14 gene transcription by interference

with T_3 activation of this gene (66, 113). This negative effect of PPARα on T_3-regulated genes can be overcome by overexpression of RXR (20, 61, 113). It is interesting that RXRα mRNA, and to a lesser extent RXR protein, was induced in rat hepatoma cells by glucocorticoids and fatty acids. Linolenic acid (18:3,n-3) at <1 mM did not induce $mRNA_{RXR\alpha}$ (125). Taken together, these studies indicate that fatty acid effects on RXR abundance or its activity may impact other signaling systems utilizing RXR as a heterodimer partner.

Other Nuclear Receptors as Targets for Fatty Acid Regulation

Although PPARs have emerged as important factors in fatty acid regulation of gene transcription, recent evidence indicates that the activity or abundance of other nuclear receptors may be affected by fatty acids or their metabolites, including HNF4, TR, and estrogen receptors.

HNF4α binds to DR1 motifs as a homodimer and is involved in the transcription of many proteins, such as the hepatic genes ApoCIII and L-PK (49, 90). Recently, Hertz et al (50) reported that palmitoyl-CoA ($K_d \sim 2.6\,\mu$M) bound the putative HNF4α ligand binding domain at levels near the free Fa-CoA in vivo concentration (42). HNF4α did not bind fatty acids, and PPAR and RXR did not bind FA-CoA. It is interesting that palmitoyl-CoA stimulated and stearoyl-CoA inhibited HNF4α binding to the ApoCIII DR1 and transcription ApoCIII-reporter gene in an in vitro assay. These results correlate with the known effect of dietary palmitate and stearate on plasma apolipoprotein profiles (45).

Are other genes that utilize HNF4 in their promoters also targets for fatty acid regulation? We have examined the fatty acid regulation of three genes that bind HNF4 within their promoters; they include tyrosine aminotransferase, phosphoenol-pyruvate carboxykinase, and L-PK. Of these, only L-PK is sensitive to fatty acid regulation in rodent liver (64, 90). HNF4 binds to the L-PK PUFA-RR located -145 and -125 bp upstream from the transcription start site. Our preliminary studies show that certain Fa-CoAs specifically affect HNF4 binding to the L-PK PUFA response region. However, more studies are needed to define further the acyl-CoA regulation of transcription factor function and to determine how diet influences cellular levels of these prospective regulatory ligands.

TRs play an important role in metabolism, growth, and differentiation. Several laboratories have reported that fatty acids or CoA-thioesters regulate TR activity through competitive binding (89, 135) or inhibit TR action independent of T_3 binding (131). Using partially purified TR from rat liver, Li et al (89) reported that T_3 binding to TR was competitively inhibited by fatty acyl–CoA thioesters ($K_d \sim 0.12\,\mu$M). Van der Klis et al (135) reported that saturated fatty

acids and PUFA inhibited binding of T_3 to bacterially expressed TRα and TRβ (K_i = 120–200 and 2–8 μM, respectively). Although several T_3-regulated hepatic genes are suppressed by PUFA, transfection studies using primary hepatocytes have failed to show that TR or thyroid hormone response elements are major targets for PUFA regulation of these genes (63, 65). An exception to this is seen when n-3 PUFA activate PPARα, leading to a sequestration of RXR and inhibition of gene transcription through the interference with T_3 action at the thyroid hormone response elements (20, 61, 113). Thus, in the absence of functional studies, the significance of these in vitro binding studies is unclear.

In contrast to these studies, Thurmond et al (131) used chick hepatocytes to show that medium-chain fatty acids (MCFA) inhibit thyroid and estrogen receptors action. MCFA did not block hormone binding to either receptor and did not interfere with TR silencing activity. MCFA did interfere with T_3- and estrogen-mediated transactivation but not glucocorticoid- or cAMP-mediated transactivation. MCFA or their metabolites may interfere with factors (coactivators like thyroid hormone receptor interacting protein) that interact with these receptors to inhibit ligand-stimulated transcription.

These studies indicate that fatty acids, fatty acid metabolites (HETE, 15-deoxy-$\Delta^{12,14}$-proslaglandin J_2), and specific FA-CoAs bind to and either activate or inhibit specific transcription factors. The dissociation constants for binding are in the range of the in vivo levels for these ligands. PPAR represents the most extensively characterized fatty acid–regulated transcription factors. Moreover, these receptors have specific pharmacological ligands, i.e. fibrates for hyperlipidemia and TZD for insulin resistance. Although other nuclear receptors, i.e. HNF4α, TR, RXR, and estrogen receptors, might be potential targets for fatty acid control, additional studies are required to evaluate the role fatty acids play in the physiological processes regulated by these nuclear receptors.

Prostanoid Effects on Gene Transcription

Prostanoids arise from the oxidative conversion of PUFA released from the plasma membrane (32, 39). PUFA (n-6 and n-3) released from phospholipids by phospholipase A2 are further metabolized via cyclooxygenase (COX1 and COX2) and lipoxygenase pathways to form bioactive lipid mediators. Arachidonic acid (20:4,n-6) metabolites, i.e. $PGF_{2\alpha}$, PGD_2, PGE_2, PGI_2, and TXA_2, act in an autocrine or paracrine fashion at nanomolar levels through G-proteins. These metabolites play important roles in organ function and disease (33, 39).

Some effects of eicosanoids are acute and represent rapid changes in the activity of preexisting proteins, whereas other effects are attributed to changes in gene expression. For example, the cyclooxygenase product of linoleic acid, hydroperoxy-octadecadienoic acids, induces c-Fos, c-Jun and c-myc mRNA levels in aortic smooth muscle cells (110). In Swiss 3T3 cells, arachidonate

(20:4,n-6) conversion to PGE_2 stimulates DNA synthesis and mitosis by activating expression of c-Fos and Egr-1 through a protein kinase C-regulatory pathway (25). Arachidonate suppresses FAS and S14 mRNAs in 3T3-adipocytes through a cyclooxygenase-dependent pathway coupled to a pertussis-sensitive G_1-linked receptor (95).

Other studies suggest that arachidonate and its metabolites regulate gene expression independently from G-proteins. Many genes involved in proinflammatory responses, such as COX2, cytokines, and adhesion molecules, require NFκB binding to specific response elements in their promoters (14, 15, 27, 71, 127). IκB/NFκB exist in the cytoplasm as a heterodimer. Following cell activation, IκB is phosphorylated and degraded, allowing NFκB to translocate to the nucleus to interact with specific response elements and induce the transcription of specific genes. Although arachidonate stimulates NFκB translocation in human U937, eicosapentaenoic acid (20:5,n-3) does not (15). Moreover, the n-3 PUFA inhibition of cytokine-induced VCAM-1 (27) and interleukin (IL)-6 (71) in cultured endothelial cells may also involve inhibition of NFκB translocation.

Eicosapentaenoic acid enrichment of membrane phospholipids arises from ingestion of n-3 PUFA, such as those in fish oils. Because eicosapentaenoic acid is a poor substrate for COX1 and COX2 (72, 82), its effect on NFκB signaling may be due to inhibition of arachidonate metabolism. Stuhlmeier et al (127) provided support for the notion that arachidonate metabolism was required for NFκB translocation. Their studies showed that ETYA (5,8,11,14-eicosatetraynoic acid), an inhibitor of arachidonate metabolism, blocked the tumor necrosis factor α–mediated up-regulation of E-selectin, intercellular adhesion molecule-1, and IL-8 through inhibition of IκB/NFκB dissociation and IκB phosphorylation and degradation. Unfortunately, some effects of ETYA on cells may not require arachidonate metabolism. ETYA and some nonsteroidal antiinflammatory drugs activate PPARα as well as inhibit arachidonate metabolism (70, 86). Treatment of human aortic smooth muscle cells with the PPARα agonist, WY14,643, inhibits IL-1 induced production of IL-6 and COX2 by repressing NFκB-mediated signaling (123). Human studies with fenofibrate (Tricor, Abbott Labs), another PPARα agonist, resulted in lower plasma levels of fibrinogen and C-reactive peptide (123), known risk factors for coronary artery disease that are controlled by cytokines (91, 130). Thus, the antiinflammatory effects of eicosapentaenoic acid, previously attributed to its interference with prostanoid synthesis (14, 15, 48), may also involve regulation of PPARα and interference with NFκB signaling.

These studies indicate that in vascular cells (smooth muscle and endothelial cells), fatty acids can potentially affect the production of inflammatory cytokines and cell surface adhesion molecules through effects on two signaling pathways, PPAR and cyclooxygenase dependent. These regulatory pathways

converge to interfere with NFκB-mediated signaling. Thus, the effects of highly unsaturated n-3 fatty acids on atherosclerosis and coronary artery disease may be attributed to their regulation of cyclooxygenase activity, PPARα activation, and the regulation of NFκB-mediated transactivation.

Fatty Acid Regulation of Hepatic Lipogenic Gene Expression

That hepatic de novo lipogenesis is suppressed by dietary PUFA has been known for over 30 years (1, 8). Ingestion of either n-3 or n-6 PUFA leads to a rapid (within hours) inhibition of the activation of many proteins/enzymes involved in both carbohydrate metabolism and lipogenesis. In neonates, medium- and long-chain fatty acids suppress hepatic de novo lipogenesis to redirect fatty acids from esterification to oxidation (97, 139). The resultant ketone bodies are then used as an energy source. In adults, the suppression of de novo lipogenesis occurs during the postabsorptive state, a time when the insulin/glucagon ratio is high. As in neonates, dietary fatty acids in postabsorbtive adults are partitioned toward oxidation and away from esterification. This is most obvious when animals are fed very long–chain n-3 PUFA (fish oils) that lead to enhanced hepatic fatty acid oxidation (a PPARα-stimulated process), diminished triglyceride synthesis, and decreased VLDL-triglycerides (47).

Both n-3 and n-6 PUFA inhibit rodent (and probably human) hepatic de novo lipogenesis by suppressing the mRNAs encoding several proteins involved in both lipogenesis and glucose metabolism, including acetyl-CoA carboxylase, FAS, L-PK, SCD-1, G6PD, malic enzyme, and the S14 protein (21, 52, 63–66). The PUFA-mediated inhibition of acetyl-CoA carboxylase, FAS, L-PK, SCD-1, and the S14 protein is at the transcriptional level of control, whereas PUFA suppression of G6PD is through posttranscriptional mechanisms (52, 63–66).

Although the expression rates of many proteins involved in de novo lipogenesis proteins are induced by insulin, carbohydrate, and T_3, PUFA overrides these stimulatory effects to exert a dominant negative effect. PUFA acts directly on the liver and does not require extrahepatic factors. Although fibrates and prostanoids have modest inhibitory effects on S14, FAS, and L-PK gene expression, the PUFA-mediated suppression of these genes does not require either PPARα activation or cyclooxygenase conversion of PUFA to eicosanoids (66, 98, 113, 114; MK Mater, A Thelen & DB Jump, submitted for publication). The PUFA-regulated *cis*-acting elements in the S14 and L-PK promoters bind nuclear factor Y (NFY) and HNF4, respectively. These factors play key ancillary roles in hormone-induced transactivation of these genes. Fatty acid control of these genes is promoter specific and does not involve generalized effects on hormone action (63, 90; MK Mater, A Thelen & DB Jump, submitted for publication).

The molecular basis of PUFA regulation of hepatic de novo lipogenesis has been examined using the S14 gene as a model. The S14 gene encodes a nuclear protein involved in the T_3 and carbohydrate regulation of other lipogenic genes in rodents and probably humans (11). Analysis of the S14 promoter (Figure 2) reveals several potential targets for control by PPARα, SREBP1, and prostanoids. Although WY14,643-activated PPARα and PGE_2 activation of prostanoid receptors inhibit S14 gene transcription, studies with the PPARα-null mouse (114), cyclooxygenase inhibitors (MK Mater, A Thelen & DB Jump, submitted for publication), or promoter analysis (65; MK Mater, A Thelen & DB Jump, submitted for publication) suggest these are not the principal mechanisms involved in PUFA suppression of this gene.

Instead, the proximal part of the 5′-flanking DNA of the S14 gene, extending to −290 bp upstream from the 5′ end of the gene, contains *cis*-regulatory elements that are targets for PUFA-mediated suppression of this gene. The PUFA-regulatory region (PUFA-RR, −220/−80 bp) also contains elements required for hormone-mediated transactivation (62). A Y-box (−104/−99 bp) within the PUFA-RR binds several CCAAT-box binding proteins, i.e. NFY, c/EBP, and NF1 (62). Of these, NFY, a heterotrimeric transcription factor known to bind histone acetyl transferases (24) plays an obligatory role in hormone-mediated transactivation through the two upstream enhancers, thyroid regulatory region, and CHORR. Any mutation within the Y-box abrogates S14 gene transcription.

It is interesting that when NFY is in the context of thymidine kinase promoter elements, i.e. Sp1, and the S14 thyroid regulatory region, the gene is not sensitive to PUFA (MK Mater, A Thelen & DB Jump, submitted for publication). Thus, the sensitivity of NFY to PUFA regulation is promoter-context dependent. In addition to recruiting histone acetyl transferases, NFY typically interacts with other transcription factors binding near Y-boxes (24). We speculate that PUFA regulates factors binding near the Y-box, thereby altering the capacity of NFY to participate in the enhancer-mediated transactivation.

DIETARY FAT AND HUMAN HEALTH

Dietary fat has been implicated in the onset and/or progression of several chronic diseases, including coronary artery disease, insulin resistance, hypertension, and various cancers, such as breast, prostate, and colon (22, 44, 47, 53, 57, 76, 77, 80, 111, 126, 136–138). These are complex diseases that are affected by both genetic and environmental factors. Figure 3 illustrates how several fatty acid–regulated transcription factors might be linked to specific cellular processes. Below is presented new evidence that suggests that these factors might be important for the progression of certain chronic diseases.

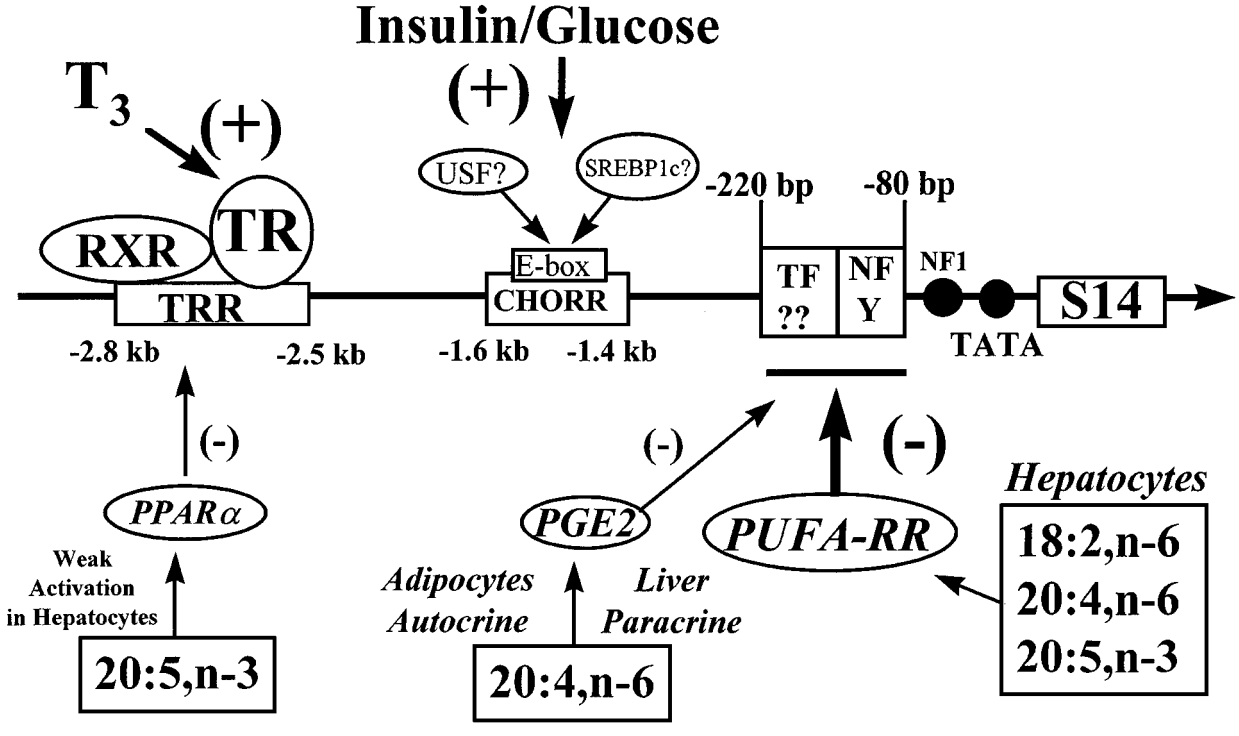
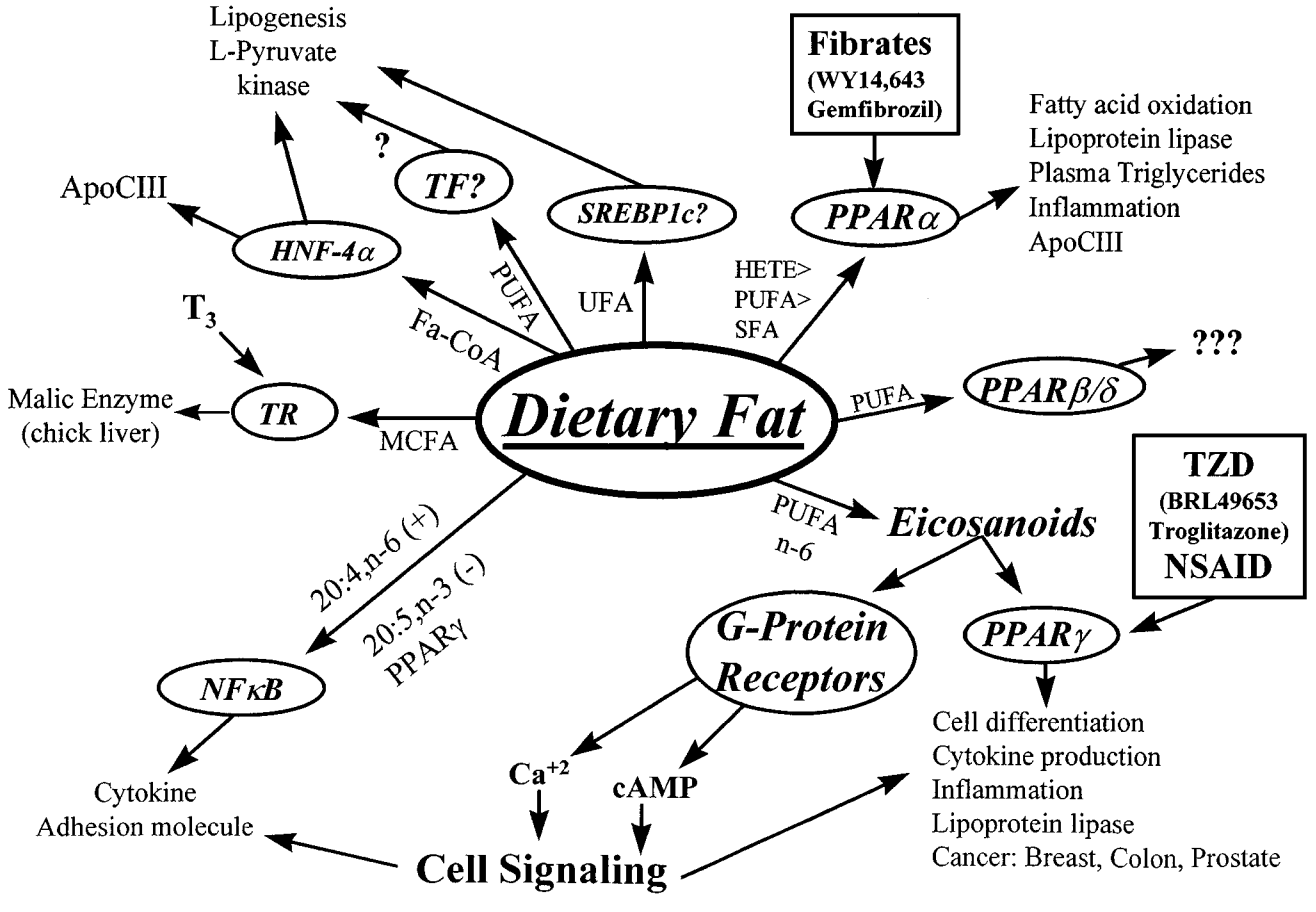


Figure 2 PUFA regulation of the rat liver S14 gene. A schematic of the S14 gene and its upstream flanking DNA is diagrammed. Three *cis*-regulatory regions are illustrated: a proximal region extending to −290 bp upstream from the 5′ end of the gene; a carbohydrate response region (CHORR) that is regulated by glucose and insulin. This region contains an E-box that can potentially bind USF (upstream stimulatory factors) and SREBP/ADD1; a thyroid regulatory region (TRR) that contains three thyroid hormone response elements that bind thyroid hormone receptor-retinoid X receptor heterodimers (TR/RXR). The PUFA-response region (PUFA-RR) (−220/−80 bp) is the predominant target for PUFA suppression of S14 gene transcription. PPARα interferes with T_3 regulation of this gene by sequestering RXR. Prostanoids activate G-protein–linked receptors that inhibit S14 gene transcription through the PUFA-RR. See text for additional details.



Hyperlipidemia

Plasma levels of VLDL-triglycerides are determined by rates of hepatic production and rates of clearance from the plasma. Hyperlipidemia is often associated with insulin resistance, coronary artery disease, hypertension, and obesity (44, 45, 47, 53, 77, 80, 107, 126, 136, 143). Clinical strategies designed to lower serum triglycerides have focused on reducing the dietary fat intake as well as the use of drugs such as fibrates [gemfibrozil (Lopid®, Parke-Davis), fenofibrate (Tricor®, Abbott), TZD (BRL49653, Glaxol) and troglitazone (Rezulin®, Parke-Davis)].

Hepatic VLDL assembly and secretion is regulated by ApoB and ApoCIII levels as well as by rates of triglyceride synthesis. Secretion of apoB is regulated posttransciptionally by processes that direct newly synthesized apoB to VLDL assembly/secretion or degradation in the endoplasmic reticulum (135a). With a surplus of lipid, apoB assembly into VLDL is favored, whereas lipid deficiency promotes apoB degradation. High-carbohydrate diets promote de novo lipogenesis and VLDL secretion (135a, 140). Recent studies suggest a link between lipoprotein secretion and lipid synthesis through a common transcription factor, i.e. sterol response element binding protein 1c, SREBP1C [rodent homolog, ADD1] (135a). SREBP1C binds E-boxes in the promoters of many genes, including two lipogenic genes, i.e. acetyl-CoA carboxylase and fatty acid synthase genes (128). SREBP1c may be involved in the hormonal and dietary regulation of these genes (54, 55, 128, 140).

Recently, Worgall et al (140) reported that both mono- and polyunsaturated fatty acid treatment of CHO, CV-1, and HepG2 cells lowered the mature (nuclear) form of SREBP1c, leading to a decline in expression of genes containing sterol response elements. It is interesting that in vivo feeding studies and studies with primary hepatocytes indicate that lipogenic gene expression is unaffected by monounsaturated fatty acids but is suppressed by PUFA (n-3 and n-6) (21). Moreover n-3, but not n-6, PUFA suppress triglyceride synthesis, VLDL secretion, and serum triglycerides (35, 47, 118). Although in vitro cell culture (135a, 140) and transgenic (54, 55) studies implicate SREBP1c as

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Figure 3 Fatty acids or their metabolites can potentially activate multiple pathways affecting gene expression. The diagram illustrates the fatty acids or their metabolites that regulate specific transcription factors. These transcription factors are linked to specific cellular processes involving metabolism, eicosanoid/growth factor production, cell growth, and differentiation. Fibrates and TZD/nonsteroidal antiinflammatory drugs (NSAID) are also indicated as pharmacological agonists that activate peroxisome proliferator–activated receptor (PPAR)α and PPARγ, respectively. G-proteins, G-protein–linked receptors; TF?, unknown transcription factors; TR, thyroid hormone receptors; SFA, saturated fatty acids; UFA, unsaturated fatty acids; MCFA, medium-chain fatty acids; HETE, hydroxyeicosatetraenoic acid; TZD, thiazolidinedione; Fa-CoA, fatty acyl coenzyme A thioester. See text for additional details.

a prospective target for nutritional regulation of lipogenic gene expression and VLDL secretion, additional factors appear to be involved in n-3 PUFA–specific control of VLDL synthesis/secretion.

A second target for the control of VLDL levels is ApoCIII synthesis. Fatty acids potentially affect ApoCIII gene transcription through two mechanisms. First, HNF4 binding and activity on the ApoCIII promoter is stimulated by palmitoyl-CoA and inhibited by eicosapentaenoyl-CoA (50). Second, PPARα (activated by fibrates and fatty acids) competes with HNF4 for binding the ApoCIII promoter. Either case can lead to suppression of ApoCIII transcription (49, 50). A third mechanism for fatty acid control of serum triglycerides involves its effects on lipoprotein lipase expression. Fibrates, TZD, and n-3 PUFA induce lipoprotein lipase, leading to enhanced triglyceride clearance from the plasma (47, 85, 120, 124). In rodents, n-3 PUFA affects both PPAR-dependent and PPAR-independent mechanisms to control serum triglycerides. However, human liver contains little PPARα (41, 106), therefore the contribution of hepatic PPARα to this process is not clear. Better definition of these mechanisms might provide an alternate therapeutic route for the control of serum triglycerides.

Atherosclerosis

Atherosclerosis is a complex disorder involving vascular wall damage and leads to the infiltration of macrophages, formation of a fatty streak, and smooth muscle hypertrophy. The generation of proinflammatory cytokines, eicosanoids, and growth factor agonists and antagonists at the site of injury contributes to this process (117). Recent evidence suggests that PPARγ, NFκB, and the generation of oxidized fatty acid metabolites may be important for the progression and arrest of atherosclerosis (60, 115, 133).

Atherosclerotic lesions and human monocytes exposed to oxidized LDL (oxLDL) express PPARγ (133). Ligand activation of PPARγ/RXRα heterodimers induces monocytic differentiation and promotes uptake of oxLDL through the induction of scavenger receptors such as CD36. TZD or 15d-PGJ2 activation of PPARγ suppresses induction of inducible nitric oxide synthase and cytokines by interfering with the action of AP1, STAT, and NFκB, transcription factors required for the cytokine induction (60, 115). The production of adhesion molecules (VCAM-1) from cultured endothelial cells is suppressed by n-3 PUFA (27). Moreover, n-3 PUFAs inhibit COX1 and COX2 activity (82). Taken together, these studies indicate that the levels of n-6 and n-3 PUFA in the phospholipid pool might influence the generation of locally generated fatty acid mediators of PPARγ and NFκB. Differential control of these transcription factors, as well as others, appear to significantly affect cellular differentiation, as well as eicosanoid, cytokine, and adhesion molecule production.

Cancer

A large body of epidemiological data and studies in rodents implicate dietary fat in cancer, particularly breast, colon, and prostate cancer. Several hypotheses have been advanced to explain this relationship; these include caloric intake and fatty acid composition, effects on membrane fluidity, cell signaling, hormone imbalance, and prostanoid synthesis (22, 44, 76, 136–138). Although studies with rodents provide support for these hypotheses, extrapolation to humans may be premature. Fatty acid effects on cell growth, differentiation, metabolism, and the production of eicosanoids, cytokines, and adhesion molecules are all likely to contribute to cancer cell growth.

PPARγ is expressed in human primary and metastatic breast adenocarcinoma (100) and in prostate (79) and colonic cancers and CaCo-2 colonic tumor cells (33, 80, 119). PPARγ is activated by TZD and eicosanoids. PUFA (n-3) inhibit COX1 and COX2, enzymatic steps required for the generation of eicosanoids (82). PGJ and higher doses of TZD induce some cancer cells to be less malignant (100). However, other studies indicate that TZD might enhance tumor growth in the colon (33, 80, 119). The question of how oxidized fatty acid contributes to PPARγ regulation of cancer cell growth and differentiation merits further investigation.

CONCLUSIONS

We have highlighted recent advances in dietary fat regulation of gene expression. In addition to its role as an energy source and its effects on membrane lipid composition, dietary fat has profound effects on gene expression. This nutrient-genome interaction interfaces with other signaling networks to allow integration of cellular control between the dietary and internal regulatory mechanisms. It reflects an adaptive response allowing cells to adjust to changes in the type, quantity, and duration of fat ingested for efficient cell growth and differentiation.

Although several transcription factors (PPARs, HNF4, TR, RXR, SREBP, and NFκB) have been identified as either direct or indirect targets of fatty acids, other transcription factors are likely to be discovered. The fatty acid control of these transcription factors involves either (*a*) direct binding of fatty acids, fatty acyl–CoA, or oxidized fatty acids; (*b*) oxidized fatty acid (eicosanoid) regulation of G-protein–linked cell surface receptors and activation of signaling cascades targeting the nucleus; or (*c*) fatty acid/oxidized fatty acid regulation of intracellular calcium levels that, in turn, affect cell signaling cascades targeting the nucleus. At the cellular level, the physiological response to fatty acids will depend on (*a*) the quantity, chemistry, and duration of the fat ingested; (*b*) cell-specific fatty acid metabolism (oxidative pathways, kinetics, and competing

reactions); (*c*) cellular abundance of specific nuclear and membrane receptors; and (*d*) cellular abundance of specific transcription factors involved in gene expression. As pointed out in the preceding sections, saturated and unsaturated fatty acids (n-3 or n-6) have different effects on cell function. These effects can be linked to the regulation of either eicosanoid synthesis or specific transcription factors such as PPARα, PPARγ, HNF4α, and SREPB1c. Although the contributions these factors make to various aspects of metabolism, cell growth, and differentiation are established, the role fatty acids play in the control of these factors is at an early stage of understanding. Clearly, additional research is needed to define further how changes in dietary fat intake contribute to the regulation of these transcription factors in health and disease.

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