

Control of Gene Expression by Fatty Acids¹

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ABSTRACT The last decade provided evidence that major (glucose, fatty acids, amino acids) or minor (iron, vitamin, etc.) dietary constituents regulated gene expression in an hormonal-independent manner. This review focuses on molecular mechanisms by which fatty acids control the expression genes encoding regulatory protein involved in their own metabolism. Nonesterified fatty acids or their CoA derivatives seem to be the main signals involved in the transcriptional effect of long-chain fatty acids. The effects of fatty acids are mediated either directly owing to their specific binding to various nuclear receptors (PPAR, LXR, HNF-4 α) leading to changes in the *trans*-activating activity of these transcription factors, or indirectly as the result of changes in the abundance of regulatory transcription factors (SREBP-1c, ChREBP, etc.). The relative contribution of each transcription factor in fatty acid-induced positive or negative gene expression is discussed. J. Nutr. 134: 2444S–2449S, 2004.

KEY WORDS: • nonesterified fatty acids • acyl-CoA • nuclear receptors • transcription factors

All the cells regulate gene expression in response to changes in the external environment. In unicellular organisms, specific mechanisms evolved to allow the cells to metabolize fuels according to their availability in the external milieu. Most of the mechanisms involved conditional transcription of genes encoding enzymes specific to a metabolic pathway in response to appropriate nutrient. The best-characterized examples are the nutritional regulation of *lac* operon of *Escherichia Coli* and the *gal* regulon of *Saccharomyces cerevisiae*. In multicellular organisms, the needs of the individual cell and of the whole organism must be managed. Until recently, it was thought that in mammals most of the adaptations to environment were controlled by hormonal or neuronal signals. The last decade has provided evidence that major (glucose, fatty acids, amino acids) or minor (iron, vitamin, etc.) dietary constituents regulated gene expression in a hormonal-independent manner. This review focuses on molecular mechanisms by which fatty acids control in a positive or negative manner the expression of genes encoding regulatory protein involved in their own metabolism.

Regulation of gene expression by long-chain fatty acids

Long-chain fatty acids (LCFA)³ and/or their Coenzyme A derivatives (acyl-CoA, Fig. 1) have been reported to affect a large number of cellular systems and functions. This includes regulation of ion channels or pumps, membrane trafficking and composition, protein acylation and sorting, control of enzyme activities and immune process, and the regulation of gene expression and energy metabolism [reviewed in (1)]. Their high energetic value (9 kcal·g⁻¹ vs. 4 kcal·g⁻¹ for the glucose) coupled with their low storage bulk (as anhydrous shape in lipid droplets in white adipose tissue, liver and muscles) make fatty acids a major source of energy for the organism. Stored fatty acids arise either from the diet or from de novo synthesis from dietary glucose (lipogenesis, Fig. 1). Some pathologies such as atherosclerosis, noninsulin dependent diabetes, or certain form of cancer are associated with the amount and/or the type of dietary fatty acids secondarily to their effects on phospholipid composition of membranes or on the expression of specific genes.

Evidence that fatty acids regulate gene expression. When most of the studies emphasized the role of fatty acid chain length (>12 carbons) in the regulation of gene expression, a growing number of articles reported an effect of SCFAs (4–6 carbons) in the control of gene expression. For instance, in colorectal cancer

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³ Abbreviations used: ACBP, acyl-CoA binding protein; bHLH-Zip, basic helix-loop-helix-leucine zipper; ChREBP, carbohydrate responsive element binding protein; CPT I, carnitine palmitoyltransferase I; CYP7A, 7 α -hydroxylase; DR1, DR4, direct repeat 1, 4; FABP, fatty acid binding protein; Glc-6-Pase, glucose-6-phosphatase; HNF-4, hepatic nuclear factor 4; LBD, ligand binding domain; LCFA, long chain fatty acids; L-PK, liver-type pyruvate kinase; LXR, liver x receptor; NEFA, nonesterified fatty acids; PPAR, peroxisome proliferator-activated receptor; PPPE, peroxisome proliferator responsive element; RXR, retinoic x receptor; SREBP, sterol regulatory element binding protein.

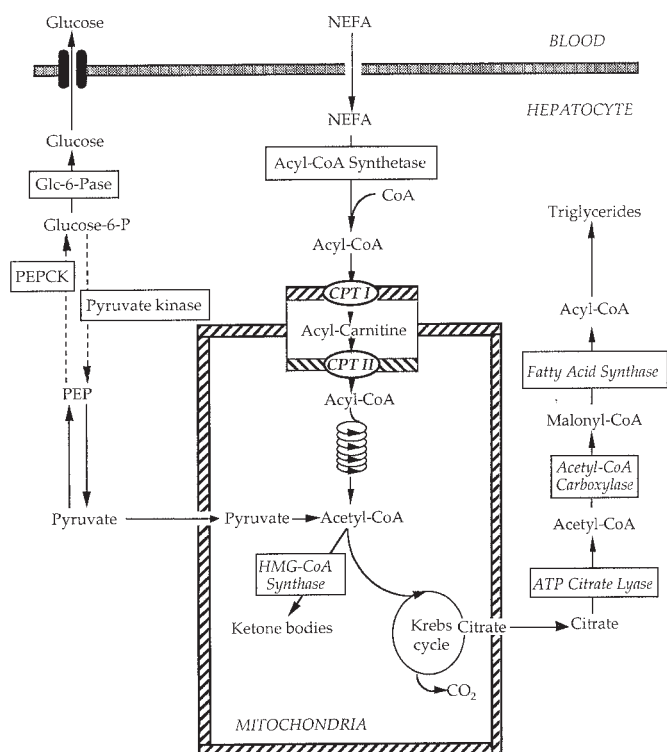


FIGURE 1 Schematic representation of fatty acid and glucose metabolism in the liver. Main regulatory enzymes of glycolysis (pyruvate kinase), gluconeogenesis (phosphoenolpyruvate carboxykinase [PEPCK], glucose-6-phosphatase [Glc-6-Pase]), fatty acid oxidation (acyl-CoA synthetase, carnitine palmitoyltransferase I [CPT I]) and lipogenesis (ATP citrate lyase, acetyl-CoA carboxylase, fatty acid synthase) are shown. PEP, phosphoenol pyruvate.

cell lines or in immortalized colon cells, butyrate affected the expression of a number of genes involved in the regulation of cell proliferation/differentiation/apoptosis (2,3). Similarly, butyrate induced the transcription of calcitonin gene in cultured human medullary thyroid carcinoma (4) and stimulated the expression of plasminogen activator inhibitor type 1 in HepG2 cells (5). Finally, it was suggested that the decreased expression of mitochondrial hydroxymethylglutaryl-CoA synthase in the colon of germ-free rats (6) could be due to the absence of butyrate, the most abundant SCFA produced by dietary fiber fermentation. Indeed, the transcriptional effect of butyrate has been recently demonstrated in human colon cancer cell line, on *WAF1/Cip1* gene promoter (7), a gene encoding a protein that inhibits the G₁-S phase transition. The transcriptional effect of butyrate seems mainly due to its inhibitory effect on histone deacetylase activity [reviewed in (8)] that alters chromatin structure and transcription rate (Fig. 2). The rest of this review will be focused only on the transcriptional effect of LCFAs.

Four classes of LCFAs are typically encountered in the diet: saturated fatty acids, (n-9) monounsaturated fatty acids, (n-6) and (n-9) PUFA. Dietary fish oil PUFA from (n-3) series, which decrease circulating concentration of VLDL and chylomicrons in hypertriglyceridemic patients, are actually considered to have protective effects on cardiovascular diseases [reviewed in (9)]. This effect of PUFA mainly results from a decrease in the activity of hepatic lipogenic enzymes [reviewed in (10)] due to an inhibition of gene transcription and/or to modifications in mRNA maturation and/or stability [reviewed in (10,11)]. Interestingly, it seems that downregulation of gene expression by fatty acids is restricted to fatty acid having >18 carbons and at least 2 double bonds [reviewed in (12)], whereas upregulation of gene is independent of the degree of saturation of the carbon chain of fatty acids. This has been reported for most of the genes depicted in Table 1.

Metabolite(s) responsible(s) for the effect of LCFAs. Fatty acids are delivered to cells either as complex lipoproteins

TABLE 1

Nonexhaustive list of fatty acid-regulated genes and role of the corresponding proteins

Upregulated	Downregulated
<p><i>Fatty acid transport</i></p> <p>Fatty acid binding protein (liver, adipose tissue, intestine)</p> <p>Adipocyte lipid-binding protein (aP2)</p> <p>Keratinocyte-lipid binding protein</p> <p><i>Activation of fatty acids</i></p> <p>Acyl-CoA synthetase</p> <p><i>Mitochondrial β-oxidation and ketogenesis</i></p> <p>Carnitine palmitoyltransferase I (liver, muscle)</p> <p>Medium chain acyl-CoA dehydrogenase</p> <p>Enoyl-CoA hydratase</p> <p>Ketoacyl-CoA thiolase</p> <p>Mitochondrial hydroxymethyl-glutaryl-CoA synthase</p> <p><i>Peroxisomal oxidation of fatty acids</i></p> <p>Acyl-CoA oxydase</p> <p><i>Others</i></p> <p>Glucose transporter glut-4</p> <p>Phosphoenolpyruvate carboxykinase (adipocyte)</p> <p>7α-hydroxylase (CYP7A)</p>	<p><i>Lipogenesis</i></p> <p>Fatty acid synthase</p> <p>Acetyl-CoA carboxylase</p> <p>ATP citrate lyase</p> <p>Spot 14</p> <p><i>Desaturation of fatty acids</i></p> <p>Stearoyl-CoA desaturase 1</p> <p><i>Glycolysis</i></p> <p>Pyruvate kinase (liver)</p> <p><i>Gluconeogenesis</i></p> <p>Glucose-6-phosphatase (liver)</p> <p><i>Others</i></p> <p>Transferrin</p> <p>Leptine</p>
<i>Lipoprotein metabolism</i>	
<p>Lipoproteine lipase</p> <p>Apolipoprotein AII</p>	<p>Apolipoprotein AI</p> <p>ApolipoproteinCIII</p>

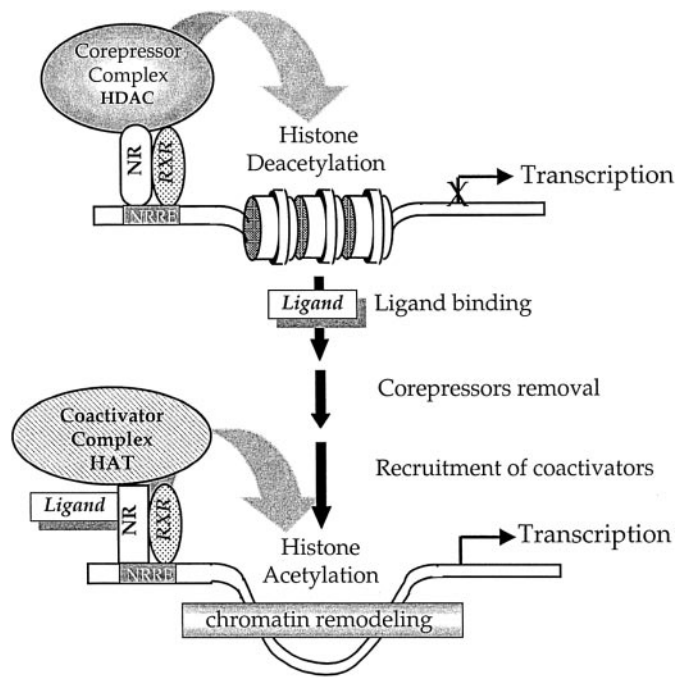


FIGURE 2 Schematic representation of the regulation of gene transcription by nuclear receptors. In the unliganded state, nuclear receptors (NR) are bound to their specific responsive element (NRRE) generally as heterodimer with *cis*-retinoic acid receptor (RXR). In this condition, heterodimers are associated with a multiprotein corepressor complex that contains histone deacetylase activity (HDAC). The deacetylated status of histones keeps the nucleosome in a conformation in which transcription is inhibited. Once a ligand binds to the receptor, the corepressor complex dissociates and a coactivator complex containing histone acetyltransferase activity (HAT) is recruited to the heterodimer. Acetylation of histone induces chromatin remodeling, a major event in activation of gene transcription.

(VLDL, chylomicrons) or as nonesterified fatty acids (NEFA). Triglycerides in chylomicrons and VLDL are hydrolyzed by the action of a lipoprotein lipase and NEFA enter cells via fatty acid transporters [reviewed in (13)]. Once in cells, NEFA are rapidly converted to fatty acyl-CoA thioesters by acyl-CoA synthetase (ACS, Fig. 1) specific for the carbon chain-length. At least 6 different ACS have been characterized. While each isoform can activate a wide range of fatty acids, they have tissue specific expression, subcellular distribution and specific spectrum of activity. For instance, ACS-1, 4, and 5 are expressed in the liver, ACS-1 activates C12 to C20 fatty acids, whereas the activity of ACS-4 is restrained to arachidonic and eicosapentenoic acids (14). The intracellular location of ACS-1 and 4 inside the endoplasmic reticulum is in agreement with their involvement in triglyceride synthesis. Conversely, ACS-5 is located in the outer mitochondrial membrane and thus play a crucial role in the regulation of β -oxidation (14). Once activated by ACS, fatty acyl-CoA are metabolized in many different metabolic pathways (β -oxidation, elongation, desaturation, triglyceride or cholesterol synthesis, prostanoid or leukotriene synthesis) where each intermediate metabolite or end product can be responsible for the transcriptional effect of LCFAs.

The nature of the signal responsible for the transcriptional effect of LCFAs is still controversial. For instance, some experiments have suggested that mitochondrial oxidation of LCFAs is required for their inhibitory effect on gene expression [reviewed in (15)]. On the other hand, several studies have shown that inhibitors of LCFA oxidation or nonmetabo-

lizable fatty acids did not prevent transcriptional effects of LCFAs [reviewed in (15,16)]. This suggested that the active molecule could be free fatty acid itself or their CoA derivatives. The role of LCFA-acyl-CoA in the regulation of gene transcription has been clearly demonstrated in bacteria [reviewed in (17)]. Similarly, several experiments have demonstrated that acyl-CoA esters are the active component on gene transcription in yeast (18). However, in mammals indirect evidence suggests that free fatty acids rather than acyl-CoA esters could be the active component on gene expression.

1) In COS-7 cells transfected with the peroxisomal acyl-CoA oxidase promoter linked to chloramphenicol acetyltransferase reporter gene, the transcription was increased more efficiently by free arachidonic acid than by arachidonyl-CoA (19);

2) In Ob 1771 adipocyte cell line, the LCFA-induced aP2 gene transcription precedes the expression of the gene encoding long-chain acyl-CoA synthetase (20);

3) In Fao hepatoma cells, the stimulation of carnitine palmitoyltransferase I (CPT I) gene expression by LCFA occurred even in the presence of long-chain acyl-CoA synthetase inhibitors (21).

Finally, it was shown that inhibitors of cyclo- or lipo-oxygenase pathways did not prevent the transcriptional effects of LCFAs (Chatelain, Girard, & Pégrier, unpublished results). Moreover, the activity of cyclo- or lipo-oxygenase pathways is very low in hepatic parenchymal cells (22). This suggests that compounds arising from cyclo- or lipo-oxygenase pathways (prostanoids, leukotrienes) are probably not involved in the regulation of gene expression by fatty acids. However, parenchymal cells possess prostaglandin receptors and thus can respond to prostaglandin generated by Kupffer or endothelial cells.

The presence of various putative metabolite signals (NEFA, Acyl-CoA, prostanoids) suggests that fatty acids can control gene transcription by different mechanisms according to the cell-specific context and the target gene. This aspect will be briefly discussed in the rest of this review.

Molecular mechanisms involved in fatty acid-induced regulation of gene expression

The regulation of gene transcription by fatty acids seems to be due to changes in the activity or abundance of at least 4 transcription factor families: PPAR (peroxisome proliferator-activated receptor), LXR (liver x receptor), HNF-4 α (hepatic nuclear factor 4) and SREBP (sterol regulatory element binding protein). Except for SREBP, all these transcription factors are members of the superfamily of steroid and thyroid hormone nuclear receptors [reviewed in (23,24)].

Peroxisome proliferator-activated receptors. Among the fatty acid-regulated nuclear receptors, PPARs are the most extensively characterized. Three isoforms of PPAR have been cloned: 1) PPAR- α is mainly expressed in liver, digestive tract, and kidney; 2) PPAR- β , δ or NUC-1 [respectively cloned in *Xenopus*, mouse and human] are ubiquitously expressed; and 3) PPAR- γ (γ 1, γ 2, γ 3 arising from an alternative splicing of a single gene) is mainly expressed in adipose tissues and in macrophages [reviewed in (25)]. Initially characterized for their capacity to be activated by peroxisome proliferators (fibrates, xenobiotics) it was shown recently that fatty acids (saturated and PUFA) and some eicosanoids (15 deoxy- Δ (12-14)-prostaglandin J2, leukotriene B4) are potent ligands of PPAR [reviewed in (25)]. The modulation of gene transcription is due to the binding of the heterodimer PPAR/RXR (retinoic x receptor) to a specific DNA sequence, the peroxisome proliferator responsive element [PPRE; Fig. 2, reviewed in (25)]. The consensus sequence consists of a

direct repeat of an hexamer AGGTCA with an interspacing of 1 base pair (DR1) with a 5' extension (AACT) which is essential for the polarity and specificity of DNA binding of the heterodimer PPAR/RXR [reviewed in (25)]. Structural analysis of PPAR reveals that ligands bind in a pocket of the LBD (ligand binding domain) (26) leading to an active conformation of the receptor through the stabilization of the AF-2 (activator function) region of the LBD (27). This conformational change leads to the removal of corepressor complex from the PPAR/RXR heterodimer and the recruitment of the coactivator complex [(28,29), Fig. 2] essential for the interaction with the transcriptional machinery. The recruitment of the transcriptional machinery can occur either directly (30) or in response to the chromatin remodeling (histone acetylation, Fig. 2) [reviewed in (31)].

The discovery of PPAR receptors and their involvement in the regulation of gene expression has led to the established dogma that regulated genes containing one or more PPRE sequences in their promoter respond to fatty acid via PPAR activation. However, a growing number of reports show that the regulation of gene expression by fatty acids is certainly more complex than the simple acceptance of this dogma. For instance, apo-AII and FAT-CD36 genes does not respond to fatty acids despite the presence of PPRE sequences in their promoter [(32), reviewed in (33)]. In the liver of PPAR α null mice (PPAR α -/-) the inhibitory effect of PUFA on the expression of genes encoding regulatory proteins of lipogenesis (acetyl-CoA carboxylase, fatty acid synthase, spot 14, Fig. 1) or glycolysis (L-pyruvate kinase, Fig. 1) is still present despite the absence of PPAR α receptor (34,35). PUFA inhibits the transcription of $\Delta 5$ and $\Delta 6$ desaturase genes whereas PPAR agonists stimulate the transcription of these genes (36,37). These results suggest that transcription factors different from PPAR are involved in the regulation of gene expression by fatty acids.

Liver x receptors. Oxysterols (22 R-hydroxycholesterol, 24,25 epoxycholesterol. . .) and LCFAs were recently identified as ligands for LXR α and LXR β receptors (38). These receptors regulate the expression of genes involved in hepatic bile acid synthesis (23) secondarily to their binding to DR4 regulatory element (LXRE) as heterodimer with RXR. The regulatory step of bile acid synthesis is catalyzed by 7 α -hydroxylase (CYP7A). The gene encoding this protein is upregulated by oxysterols [via the activation of LXR (23)] and by fatty acids (39) but downregulated by fibrates [PPAR α agonists (40,41)]. This gene represents another illustration of the dissociation between fatty acids and PPAR agonists in the regulation of gene transcription. Indeed, analysis of the promoter region of CYP7A gene reveals the presence of a DR1 sequence (see above) that binds specifically HNF-4 α receptor but not PPAR/RXR heterodimer (40,41). The relative contribution of these 2 receptors in the control of CYP7A gene transcription has been clearly demonstrated by phenotypic analysis of PPAR α (41) or HNF-4 α (42) knockout mice. The next section on HNF-4 α may provide some clues to explain the apparent contradictory effects of fatty acids and fibrates on CYP7A gene.

Hepatic nuclear factor-4 α . This nuclear receptor binds, with high affinity, long chain fatty acyl-CoA (43). While binding of saturated acyl-CoA (C14:0, C16:0) stimulates the transcriptional activity of HNF-4 α , binding of polyunsaturated fatty acyl-CoA (C18:3, C20:5, C22:6) inhibits the effects of HNF-4 α on gene transcription [reviewed in (11)]. The phenotypic analysis of CRE-Lox conditional HNF-4 α null mice has shown that this nuclear receptor controls either directly or indirectly the expression of several hepatic genes. This include genes encoding proteins of lipoprotein metabolism [apo CII, CIII, AII, AIV, reviewed in (10)], iron metabolism [transferrin

(44)], carbohydrate metabolism [L-pyruvate kinase, glucose-6-phosphatase, phosphoenolpyruvate carboxykinase (35,45)], and bile acid synthesis [CYP7A (42)]. Unlike PPAR or LXR, HNF-4 α binds DR1 sequences as homodimer making it a competitor of PPAR/RXR heterodimer for binding onto these DNA motifs (35,41,44). This has been recently demonstrated for the gene encoding glucose-6-phosphatase (Fig. 1) whose transcription is inhibited by PUFA as a loss of HNF-4 α binding to Glc-6-Pase gene promoter (45). Finally, it was shown recently that fibrates can be converted to CoA thioesters (as fatty acids) that bind to HNF-4 α and inhibit its transcriptional activity (46). This dual level of competition with PPAR receptors (binding to DR1 motifs, fibrate-CoA binding) could explain in part the complex regulation of CYP7A gene by fatty acids and fibrates.

Sterol regulatory element binding protein. SREBP belong to the basic helix-loop-helix-leucine zipper (bHLH-Zip) family of transcription factors, but differ from other bHLH-Zip protein in that they are synthesized as inactive precursors bound to the endoplasmic reticulum [reviewed in (47,48)]. In order to reach the nucleus and to act as a transcription factor, the NH₂-terminal domain of SREBP proteins must be cleaved proteolytically from the endoplasmic reticulum membrane [(4), reviewed in (47)]. Three SREBP isoforms have been cloned: SREBP-1a and 1c (derived from alternative transcription start site of a single gene) and SREBP-2 encoded by another gene [reviewed in (47,48)]. SREBP-1c preferentially enhances transcription of genes involved in fatty acid, triglyceride, and phospholipid synthesis whereas SREBP-1a and SREBP-2 activate genes involved in cholesterol synthesis [reviewed in (47,48)].

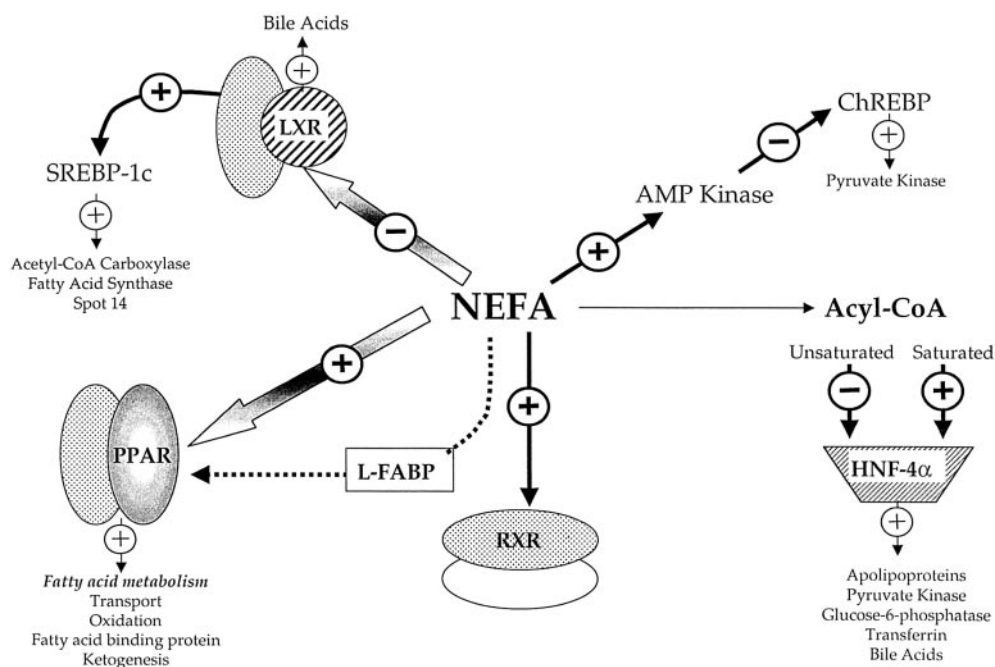
As previously mentioned, the regulation of gene transcription by fatty acids could be due to changes in the activity or abundance of transcription factors. Unlike nuclear receptors described above (PPAR, LXR, HNF-4 α), fatty acids or cholesterol do not bind to SREBP proteins but induce changes in the nuclear abundance of this transcription factor. At least 2 mechanisms have been described:

1) Treatment of CHO cells with PUFA activates a sphingomyelinase leading to the redistribution of cholesterol from the plasma membrane to the endoplasmic reticulum. The increase in cholesterol in endoplasmic reticulum membrane induces the inhibition of proteolytic process and thus a decrease in the abundance of SREBP in the nucleus (49);

2) PUFA decreases the transcription of SREBP-1a and 1c (not SREBP-2) secondarily to a competition with oxysterols binding to LXR receptor a positive regulator of SREBP-1 gene (50,51).

SREBP-1c upregulates the transcription of genes encoding regulatory enzymes of fatty acid synthesis [ATP citrate lyase, acetyl-CoA carboxylase, fatty acid synthase, spot 14, reviewed in (52)] and thus the reduction in nuclear SREBP-1c abundance probably represents the main mechanism by which PUFAs suppress the fatty acid synthesis gene expression. Indeed, overexpression of mature SREBP-1c in transgenic mice liver (53) or in cultured hepatocytes (54) overrides the PUFA suppression of lipogenic gene expression. A similar mechanism has recently been reported to explain the inhibitory effects of high fat diets on hepatic pyruvate kinase (L-PK) gene expression. Treatment of cultured hepatocytes with fatty acids induces an increase in intracellular AMP concentration that activates AMP Kinase leading to a phosphorylation of the transcription factor ChREBP (carbohydrate response element binding protein). Phosphorylation of ChREBP prevents its binding to DNA and inhibits its transcriptional activity (55). As ChREBP is responsible for glucose-induced L-PK gene transcription (56), these results explain the inhibitory effects of PUFA on

FIGURE 3 Schematic overview of fatty acid sensor proteins. Nonesterified fatty acids or their respective CoA thioesters regulate the transcription of target genes through direct activation of some nuclear receptors PPAR, LXR, and HNF-4 α . Furthermore, fatty acids inhibit in an indirect manner, the transcription of genes encoding lipogenic enzymes or liver-type pyruvate kinase secondarily to a reduction in nuclear abundance of stimulatory transcription factors such as SREBP-1c or ChREBP. Finally, fatty acid binding proteins (L-FABP) or another nuclear receptor (RXR) could be involved in the regulation of gene expression by fatty acids. Adapted from (59).



this gene, thus illustrating another example of the indirect effect of fatty acids in the regulation of gene expression.

All the experimental results presented in this chapter emphasize the great diversity of fatty acid-sensor proteins and the list of potential transcription factors involved in fatty acid-mediated gene expression is probably not closed. For instance, it was shown that the DNA motif responsible for the fatty acid-induced hepatic carnitine palmitoyltransferase I (L-CPT I) gene expression was located in the first intron of the gene whereas the PPRE sequence (PPAR/RXR heterodimer binding) was located at -2800 bp upstream the start site of transcription (15). Computer analysis of the intronic sequence of L-CPT I gene reveals no consensus sequences able to bind any known fatty acid sensor proteins either DR1 (PPAR, HNF-4 α) or DR4 (LXR), suggesting that other transcription factors could transduce the fatty acid signals to DNA. Potential candidates could be:

1) the *cis*-retinoic acid activated receptor (RXR). Indeed, PUFA bind to the 3 isoforms (α, β, γ) of RXR receptor and induce the *trans*-activation of retinoid-target genes (57);

2) the fatty acid or acyl-CoA binding proteins (FABP, fatty acid binding protein; ACBP, acyl-CoA binding protein). In keeping with this it was shown recently that liver FABP colocalize in the nucleus with PPAR α and that both proteins interact directly in a ligand-dependent manner (58). Furthermore, when the gene encoding for acyl-CoA binding protein (ACB1) is disrupted in yeast, the transport of acyl-CoA into nucleus is blocked and the inhibitory effect of fatty acid on OLE1 gene expression is raised (18).

A schematic overview of fatty acid sensor proteins is shown in Figure 3.

Conclusions

Until recently, it was generally thought that the regulation of gene expression in response to changes in nutritional environment was essentially mediated by hormones and/or the nervous system. However, during the last decade, the role of nutrients (glucose, fatty acids, amino acids, etc.) or their respective metabolites in the regulation of gene expression

became a major aspect of modern nutrition. The aim of this review was to describe the molecular mechanisms (metabolite signals, transcription factors, DNA motif, etc.) by which fatty acids control, in a hormonal-independent manner, the expression of target genes. From several recent experiments, it can now be inferred that the dogma stating that fatty acid regulation of gene transcription is a simple PPAR-mediated process should be revisited. Indeed, various sensors can relay the transcriptional effects of fatty acids either through direct binding to DNA (PPAR, LXR, HNF-4 α) or via modulations in the abundance of other transcription factors (SREBP, ChREBP) in an indirect manner. Knowledge of the mechanisms by which fatty acids control specific gene expression may provide insight into the development of new therapeutic strategies for a better management of whole body lipid metabolism and the control of blood levels of triglycerides and cholesterol, important risk factors for coronary heart diseases.

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