

Regulation of gene expression by polyunsaturated fatty acids

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Abstract

Consumption of polyunsaturated fatty acids (PUFAs) has been shown to be beneficial in the prevention of several human diseases, including obesity, diabetes, heart disease, and stroke. It has become clear that linolenic (n-3) and linoleic (n-6) PUFAs can act at the nuclear level to affect expression of genes involved in diverse metabolic pathways. PUFAs act via nuclear receptors such as peroxisome proliferator activated receptor α and liver X receptor α , and through the transcription factor, sterol regulatory element binding protein-1c, to elicit a favorable hypolipidemic phenotype. Further understanding of the molecular effects of PUFAs will be key to devising novel approaches to the treatment and prevention of disease.

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Introduction

Linoleic (n-6) and linolenic (n-3) acids are polyunsaturated fatty acids (PUFAs) that cannot be synthesized de novo by mammals and are hence considered to be essential to the diet. n-3 (or omega-3) PUFAs, including eicosapentaenoic acid and docosahexanoic acid, are concentrated in marine mammals and high-fat fish, whereas the main sources of dietary n-6 PUFAs are vegetable oils and organ meats. n-3 PUFAs have been shown to promote fatty acid oxidation while decreasing the rates of lipid synthesis [1]. They have also been shown to decrease plasma lipid concentrations [2] and enhance insulin sensitivity [3]. In addition, they are believed to be preventive in various chronic diseases, including rheumatoid arthritis [4], coronary heart disease [5], and stroke [6], and certain types of cancer, including breast, prostate, and colorectal cancers [7,8]. These beneficial effects of PUFAs

are of obvious therapeutic interest; however, there has also been some concern over excess consumption of n-6 PUFAs, because of their proinflammatory and proaggregatory effects [9]. Thus understanding the mechanisms by which these fatty acids exert their effects will be key to understanding whether and how PUFAs can help promote optimal health and in establishing a much-needed healthy dietary n-3 : n-6 ratio.

Regulation of genes by polyunsaturated fatty acids

Once fatty acids enter the cell, they are rapidly converted to fatty acyl coenzyme A (CoA) thioesters by an acyl CoA synthetase [10] (*Figure 1*). This reaction is essential to the further partitioning of fatty acids into various pathways, including complex lipid synthesis, β -oxidation, elongation/desaturation, and production of secondary signaling intermediates such as prostaglandins, thromboxanes, and leukotrienes

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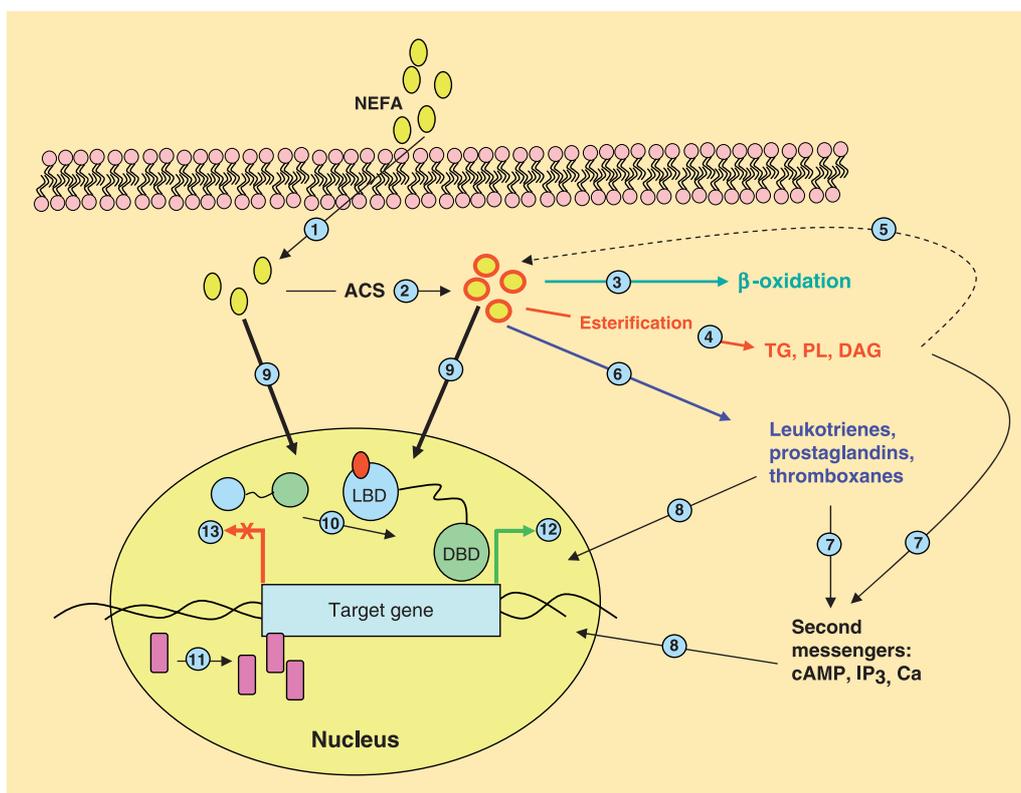


Figure 1. Regulation of gene expression by fatty acids and their metabolites. Non esterified fatty acids (NEFA) are transported into the cell (1) and are rapidly converted to acyl coenzyme A (CoA) by acyl CoA synthetase (ACS) (2). The acyl CoA can be oxidized (3) or can be esterified into complex lipids (4) such as triglycerides (TG), phospholipids (PL), or diacylglycerols (DAG). These complex lipids can also replenish the cellular fatty acid stores as necessary (5). Alternatively, fatty acyl CoAs can give rise to leukotrienes, prostaglandins, and thromboxanes (6). These secondary metabolites, in addition to complex lipids such as DAG, can increase cellular concentrations of second messengers such as cyclic AMP (cAMP), inositol triphosphate (IP₃), and calcium (Ca) (7). These second messengers or their lipid precursors can all have effects on gene expression (8). Alternatively, free fatty acids and fatty acyl CoAs can act directly at the nuclear level (9). In the nucleus, signaling through fatty acids or their metabolites can lead to changes in nuclear receptor activation (10), as in the case of peroxisome proliferator activated receptors and liver X receptors, or to changes in transcription factor abundance (11), as in the case of sterol regulatory element binding protein-1c, leading to upregulation (12) or downregulation (13) of target genes. DBD, DNA binding domain; LBD, ligand binding domain.

(Figure 1), which can in turn lead to changes in production of cellular second messengers such as inositol triphosphate, cyclic AMP (cAMP) and calcium (Figure 1). Because of the rapid nature of the acyl CoA synthetase reaction and the several fates of cellular fatty acids, the free fatty acid concentration within the cell is generally maintained at very low values. Thus the molecular effects of fatty acids within cells are likely to be mediated, not only by free fatty acids, but also by fatty acyl CoAs and second messengers (Figure 1).

It is now clear that PUFAs do not regulate gene expression exclusively through changes in membrane composition or through production of secondary signaling intermediates. The discovery by Gottlicher et al [11] of a nuclear receptor capable of binding fatty acids established a direct role for PUFAs in gene regulation. PUFAs have been shown to exert their effects on gene transcription very rapidly [12]. Within hours of animals being fed diets rich in

PUFAs, there is coordinated induction of expression of genes involved in hepatic and skeletal muscle fatty acid oxidation, and repression of genes that encode lipogenic, glycolytic, and cholesterolgenic enzymes [12]. This dual action results in a hypolipidemic phenotype [1,2].

Regulation through nuclear receptors and transcription factors

Among other mechanisms, PUFAs have been shown to exert their effects on gene transcription via nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs), and through the transcription factor, sterol regulatory element binding protein (SREBP).

Nuclear receptors are found only in metazoan organisms and consist of two domains: the ligand binding domain and the DNA binding domain.

Binding of a ligand causes the receptor to bind to a nuclear receptor response element on target genes (Figure 1) and regulate transcription of the target gene [13].

PPARs are a family of nuclear receptors consisting of three isoforms: PPAR α , PPAR β/δ , and PPAR γ . PPAR α is strongly activated by the fibrate class of drugs used in the management of high plasma cholesterol, whereas PPAR γ is a target of the thiazolidinediones used in the clinical management of diabetes and insulin resistance [14]. In general, both n-3 and n-6 PUFAs have been shown to function via PPAR α to upregulate transcription of genes involved in β -oxidation, such as carnitine palmitoyl transferase-1 (CPT-1), acyl CoA oxidase and CYP4A2 [1,15].

Another set of nuclear receptors shown to mediate the hypolipidemic effects of PUFAs are the liver X receptors. LXRs α and β bind oxysterols as endogenous ligands and function to regulate genes involved in fatty acid and cholesterol metabolism [16], including *SREBP-1c*, lipoprotein lipase, fatty acid synthase (*FAS*), acetyl CoA carboxylase (*ACC*), and stearoyl CoA desaturase-1 (*SCD1*). LXRs also regulate genes involved in bile acid synthesis, such as 7- α hydroxylase [17]. Studies in established cell lines have suggested that PUFAs may inhibit the hyperlipidemic effects of LXRs in a variety of ways [18,19]. However, there is also evidence that, although the administration of PUFA in vivo does decrease the expression of lipogenic genes, this is not accompanied by changes in classical LXR α target genes [20]. Thus further research is needed to clarify whether PUFAs have a role in modulating LXR α activity in vivo [21].

One of the best-characterized modes of regulation of gene expression by PUFAs is through the lipogenic transcription factor, SREBP. SREBP-1c is the predominant SREBP isoform in human and rodent liver, and regulates genes of fatty acid and triglyceride synthesis [22]. PUFAs have been shown to inhibit expression of the *SREBP-1c* gene [23] and proteolytic maturation [24], resulting in decreased transcription of SREBP-1c target genes such as *ACC*, *FAS*, glycerol phosphate acyl transferase, *SCD1*, and *SREBP-1* itself.

Conclusion

Research undertaken over the past few decades has certainly made it clear that fat is more than just an inert storage form of energy. Even in the face of the growing obesity epidemic that brings with it a host of secondary lipid-related conditions, there is growing understanding, not only that is fat an essential nutrient, but also that the type and amount of fat ingested can have dramatic effects on health. At the same time, there is some controversy regarding the use of n-3 PUFAs to improve health. The findings of a

recent meta-analysis suggested that n-3 fatty acids may offer no added protection against cardiovascular disease or cancer as previously believed [25]. Rather, the risk of exposure to toxic chemicals such as methylmercury dioxins and polychlorinated biphenyls, which are also concentrated in fatty fish high in n-3 fatty acids, may negate any beneficial effects of n-3 PUFAs [25]. The emergence of such conflicting reports on the possible effects of an essential nutrient makes further research on the topic all the more essential. Understanding the site-specific molecular effects of particular fatty acids will no doubt be key both to establishing valid dietary recommendations and to formulating new approaches to combat growing medical issues. ■

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