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Review

Regulation of adipocyte differentiation and function by polyunsaturated fatty acids

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Abstract

A diet enriched in PUFAs, in particular of the n-3 family, decreases adipose tissue mass and suppresses development of obesity in rodents. Although several nuclear hormone receptors are identified as PUFA targets, the precise molecular mechanisms underlying the effects of PUFAs still remain to be elucidated. Here we review research aimed at elucidating molecular mechanisms governing the effects of PUFAs on the differentiation and function of white fat cells. This review focuses on dietary PUFAs as signaling molecules, with special emphasis on agonistic and antagonistic effects on transcription factors currently implicated as key players in adipocyte differentiation and function, including peroxisome proliferator activated receptors (PPARs) (alpha, beta and gamma), sterol regulatory element binding proteins (SREBPs) and liver X receptors (LXRs). We review evidence that dietary n-3 PUFAs decrease adipose tissue mass and suppress the development of obesity in rodents by targeting a set of key regulatory transcription factors involved in both adipogensis and lipid homeostasis in mature adipocytes. The same set of factors are targeted by PUFAs of the n-6 family, but the cellular/physiological responses are dependent on the experimental setting as n-6 PUFAs may exert either an anti- or a proadipogenic effect. Feeding status and hormonal background may therefore be of particular importance in determining the physiological effects of PUFAs of the n-6 family.

Keywords: Polyunsaturated fatty acid; Adipocyte differentiation; Peroxisome proliferator-activated receptor; Sterol regulatory element-binding protein; Liver X receptor

1. Introduction

Obesity is the major factor predisposing individuals to different dyslipidemic conditions and is thus becoming an enormous challenge to health systems worldwide. Although the so-called obesity epidemic is now recognized by the World Health Organization as one of the top 10 global health problems, clinicians have had little success in the fight against obesity. During the last decade, several genetic defects have been associated with obesity in humans, among those a number of mutations in genes involved in appetite regulation [1]. However, such mutations have only been detected in a minor fraction of obese individuals and the dramatic increase in the number of obese individuals during the last decades is rather a result of changes in the environment and eating habits. Thus, habitual food intake in excess of energy expenditure is still the primary factor leading to obesity.

As dietary fat contains more calories than protein and carbohydrates, limiting the intake of fat has been recommended in order to prevent obesity. Moreover, ever since the

Abbreviations: AA, arachidonic acid; COX, cyclooxygenase; dex, dexamethasone; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ERK1/2, extracellular signal-regulated kinase 1/2; DMSO, dimethylsulfoxide; LA, linoleic acid; MAPK, mitogen-activated protein kinase; LOX, lipoxygenase; LXR, liver X receptor; mix, methylisobutylxanthine; MDI, methylisobutylxanthine, dexamethasone and insulin; Ole, oleic acid; Palm, palmitic acid; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; rosi, rosiglitazone; SCD, stearoyl-CoA desaturase; SREBP, sterol regulatory element-binding protein; TG, triacylglycerol

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relationship between elevated plasma cholesterol and coronary heart diseases was established, low-fat diets have been recommended by several official institutions, including the World Health Organization and the American Heart Association, as a prophylactic treatment for different lipid-related disorders. However, reducing the relative amount of fat in the diet alone apparently is not sufficient to prevent weight gain. In USA, energy intake from dietary fats dropped from 40% to 33% from the 1960s to 1995. In the same period, the number of obese adults (BMI>25) was steadily increasing, reaching 56% in the early 1990s and 65% at present [2–4]. Similarly, in Norway, the relative intake of dietary fats dropped from 40% to 34% from the middle of the 1970s to the middle of the 1990s [5]. In spite of this decrease in intake of dietary fats, the average male BMI increased from 24.8 to 26.6 (9.1 kg) and the average female BMI increased from 24.7 to 25.1 (3.7 kg) from 1960 to 1999 [6].

It is now clear that the effect of dietary fats on human health depends on the sources and nature of the fatty acids. Dietary fat associated with an increased risk of dyslipidemic disorders, including coronary heart disease, is primarily trans-fat, saturated fat and cholesterol. Generally, saturated fat of mammalian origin seems to be far more harmful to human health than unsaturated fat from plants and fish. A considerable number of studies have demonstrated the beneficial effects of PUFAs on lipid-related disorders in humans [7–11]. Thus, not only the quantity of ingested fats, but also the composition and nature of the fatty acids are of pivotal importance for human health.

The specific actions of different fatty acids are to a large extent determined by their metabolic properties. Chain-length, position and number of double bounds determine both physical and chemical properties of the fatty acids as well as their metabolic destinies. Most effects of fatty acids on cellular homeostasis are mediated by their metabolites. Inside the cell, fatty acids are elongated, desaturated, β-oxidized, peroxidized, incorporated into phospholipids and complex lipids such as ceramides and sphingolipids, or they participate in or interfere with eicosanoid synthesis. Enzymes in the eicosanoid pathway (cyclooxygenases, lipoxygenases, and P450 epoxygenases) normally use the major n-6 fatty acid, arachidonic acid, liberated from phospholipids by phospholipases, as substrates. Eicosanoids are not stored in the cells, but rather synthesized and immediately released (within 5–60 s) in response to a variety of hormones or cytokines. Arachidonic acid-derived eicosanoids have extremely short biological half-lives, and hence, the initial phases of the signaling cascades are stringently controlled. Of note, a number of pathologic states such as inflammation, asthma, hypertension and certain types of cancer are associated with the dysregulation of the eicosanoid pathway [12–14]. The structurally similar n-3 PUFAs may replace arachidonic acid in phospholipids. Some n-3 PUFAs are converted into products with properties distinct from those generated from arachidonic acid, while others, in particular DHA, are inhibitors of cyclo-oxygenases (and possibly lipoxygenases). The consumption of a diet enriched in n-3 PUFA (specifically EPA and DHA) may thereby affect eicosanoid biosynthesis [15–17].

Dietary fatty acids and their metabolites are able to modulate protein expression by several mechanisms. They may affect gene transcription, messenger RNA processing and modulate posttranslational modifications of proteins [18–21]. PUFAs are known to suppress lipogenic gene transcription by downregulating the expression of the sterol regulatory element-binding proteins (SREBPs) [22–25] and they may function as antagonists of liver X receptors (LXR) [26,27] and as activators/ligands for the peroxisome proliferator-activated receptors (PPARs) [28–32]. Knowledge regarding fatty acids as kinase cascade activators/inhibitors has also accumulated during the last decades [33–38].

Until now, far more attention has been focused on strategies for treating obesity-associated diseases rather than focusing on preventing or treating the major underlying risk factor, obesity. However, understanding the processes that lead to de novo differentiation of adipocytes and onset of obesity would be necessary for developing new rational modalities for the prevention and treatment of obesity. It has been demonstrated that diets enriched in n-3 PUFAs decrease adipose growth in rodents [39–48], but only few studies have addressed questions concerning the effects of different fatty acids on adipocyte differentiation. Here, we review research aimed at elucidating molecular mechanisms governing the effects of PUFAs on the differentiation and function of white fat cells, with special emphasis on dietary PUFAs as signaling molecules.

2. PUFAs and PPARγ

2.1. PUFAs as inducers of adipocyte differentiation and PPARγ activators

Feeding rodents a high-fat diet induces the replication and differentiation of preadipocytes as well as adipose tissue hypertrophy [49–55]. High-fat feeding leads to increased levels of expression of the transcription factors C/EBPα and PPARγ and a number of PPARγ-target genes involved in adipocyte differentiation and lipid storage [56]. The adipocyte differentiation process is strictly dependent on the activation of PPARγ [28,57–59], and the forced expression of PPARγ and/or administration of PPARγ-ligands induce adipocyte differentiation of fibroblasts as well as myoblasts in vitro [60,61]. PPARγ knock-out is embryonic lethal due to placental dysfunction [28,58,59]. By aggregation of PPARγ null embryos with tetraploid embryos, one PPARγ-deficient pup has been recovered, and this pup was completely devoid of adipose tissue [28]. Furthermore, adipose tissue-targeted knock-out of PPARγ results in severe lipodystrophic animals without adipose