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REVIEWS: CURRENT TOPICS

N-3 polyunsaturated fatty acids regulate lipid metabolism through several inflammation mediators: mechanisms and implications for obesity prevention

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Abstract

Obesity is a growing problem that threatens the health and welfare of a large proportion of the human population. The n-3 polyunsaturated fatty acids (PUFA) are dietary factors that have potential to facilitate reduction in body fat deposition and improve obesity-induced metabolic syndromes. The n-3 PUFA up-regulate several inflammation molecules including serum amyloid A (SAA), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in hepatocytes and adipocytes. Actions of these inflammation mediators resemble those of n-3 PUFA in the modulation of many lipid metabolism-related genes. For instance, they both suppress expressions of perilipin, sterol regulatory element binding protein-1 (SREBP-1) and lipoprotein lipase (LPL) to induce lipolysis and reduce lipogenesis. This review will connect these direct or indirect regulating pathways between n-3 PUFA, inflammation mediators, lipid metabolism-related genes and body fat reduction. A thorough knowledge of these regulatory mechanisms will lead us to better utilization of n-3 PUFA to reduce lipid deposition in the liver and other tissues, therefore presenting an opportunity for developing new strategies to treat obesity.
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1. Introduction

Obesity is a worldwide problem. It is tightly associated with dyslipidemia, type 2 diabetes and cardiovascular diseases, all posing huge threats to human health. The n-3 polyunsaturated fatty acids (PUFA), such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are known as anti-obesity factors. Fish oil containing high concentrations of DHA and EPA is considered a good source of these n-3 PUFA. Weight loss and decreased fat deposition are observed in mice fed a diet containing a high concentration of DHA and EPA [1]. Dietary n-3 PUFA supplementation combined with very low calorie intake enhances weight loss in obese women [2]. The n-3 PUFA mainly exert their fat-lowering effect through extensive regulation of lipid metabolism by inhibiting lipogenesis, promoting lipolysis and fatty acid oxidation, and suppressing preadipocyte differentiation (Table 1). We will emphasize on discussing the roles of n-3 PUFA in modulating lipid metabolism and new findings that link n-3 PUFA with inflammatory factors that modulate lipolysis and other aspects of lipid metabolism to reduce fat deposition in the body.

2. Effect of n-3 PUFA on lipid metabolism

The major effects of n-3 PUFA on modulating lipid metabolism are to promote lipolysis and fatty acid oxidation and to inhibit lipogenesis. Treatments with DHA increase glycerol release, an indicator of lipolysis in murine and human adipocytes [10,12]. Treatments with EPA activate cAMP-dependent protein kinase A (PKA) to promote lipolysis [13,14]. The effects of n-3 PUFA on lipolysis may be mediated through perilipin and/or hormone-sensitive lipase (HSL). Perilipin coats the intracellular lipid droplets in adipocytes. Decreased perilipin increases the access of HSL to hydrolyze lipid droplets and thus leads to increased lipolysis [15]. Perilipin knockout mice exhibit increased basal lipolysis and resistance to diet-induced obesity [16,17]. Mutation of the PKA phosphorylation sites on perilipin terminates the PKA-induced lipolytic response [18]. The intracellular lipase, HSL, hydrolyzes diacylglycerols, triacylglycerols and acyl esters of cholesterol, steroids and retinoic acid [19]. The stimulation of several hormone receptors such as β-adrenergic receptors can increase intracellular cAMP levels to activate PKA signaling that in turn phosphorylates and activates HSL [20]. Phosphorylation of perilipin by PKA is also required for HSL in stimulating its translocation from the cytosol to the lipid droplets to induce its lipolytic activities [21,22]. At least part of the n-3 PUFA-induced increase in lipolysis appears to result from the n-3 PUFA activation of PKA that in turn phosphorylates perilipin and HSL [18,23]. The PUFA, especially DHA, can also enhance lipolysis through increasing the expression of HSL and decreasing the expression of perilipin [10,11].

Activity of the anabolic-associated lipase, lipoprotein lipase (LPL), is modulated by n-3 PUFA. The LPL enzyme is located on the endothelial layer of capillaries in the muscle and adipose tissues. It

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Table 1
Effect of n-3 PUFAs on lipid metabolism-related genes

Categories	Genes	Expression or activity	Reference
Lipogenesis	Stearoyl CoA desaturase 1	↓	[3]
	Fatty acid synthase	↓	[3,4]
	Acetyl CoA carboxylase	↓	[4,5]
Fatty acid oxidation	Carnitine palmitoyl transferase-1	↑	[6]
	Acyl CoA oxidase	↑	[6–8]
	Ketoacyl-CoA thiolase	↑	[7,8]
	Enoyl-CoA hydratase	↑	[7]
Fatty acid transport	Muscle lipoprotein lipase	↑	[9]
	Adipocyte lipoprotein lipase	↓	[9,10]
Lipolysis	Hormone-sensitive lipase	↑	[10,11]

hydrolyzes chylomicron- and VLDL-triacylglycerol to release fatty acids. Dietary fish oil supplementation enhances muscle LPL activity, but reduces adipocyte LPL activity [9]. The altered LPL activities are accompanied by decreased body fat and plasma triacylglycerol concentration in fish oil-fed rats, suggesting that triacyglycerol utilization is changed from storage in adipocytes to oxidation in muscles after the high n-3 PUFA treatment [9]. Mitochondrial and peroxisomal fatty acid oxidation rates in 3T3-L1 adipocytes and fish oil-fed rats are increased by n-3 PUFA [6,7]. These functions of n-3 PUFA are mediated by increasing the oxidation-related enzyme activities including carnitine palmitoyl transferase-1, acyl CoA oxidase, enoyl-CoA hydratase and ketoacyl-CoA thiolase [6,7]. Suppression of the expression of the transcription factor, sterol regulatory element binding protein-1 (SREBP-1), by n-3 PUFA leads to decreased expression of lipogenic genes such as fatty acid synthase, acetyl-CoA carboxylase (ACC) and stearoyl-CoA desaturase-1 in fish oil-fed mice and rats [3,4]. The n-3 PUFA regulate SREBP-1 expression via an ERK1/2-dependent pathway [24] and through PKA activation [25]. The n-3 PUFA transiently induce ERK phosphorylation, and the addition of ERK inhibitors negates the DHA-induced decrease in SREBP-1 expression in primary rat hepatocytes [24]. The DHA-mediated ERK activations are related to elevated reactive oxygen species (ROS) because DHA-induced ROS expressions facilitate ERK phosphorylation [26]. Activation of PKA suppresses SREBP-1 expression through phosphorylation of liver X receptor (LXR), thus inhibiting the LXR stimulation of transcription of SREBP-1 [25]. The PKA-mediated phosphorylation of SREBP-1 affects SREBP-1 binding to DNA to further inhibit lipogenesis [27].

In addition to the aforementioned metabolic effects, n-3 PUFA alter adipocyte differentiation. The reduced lipid accumulation and glycerol-3-phosphate dehydrogenase activities resulting from DHA treatments indicate that DHA reduces the differentiation of 3T3-L1 preadipocytes to adipocytes [12]. The SREBP-1 mRNA is also decreased by DHA in porcine adipocytes [28,29]. Higher concentrations of EPA and DHA induce apoptosis of adipocytes and subsequently reduce adipogenesis [12,30]. The suppression of cell survival signaling pathways such as the reduction in Akt phosphorylation and NF-κB DNA binding activity may contribute to n-3 PUFA-mediated apoptosis [31]. These apoptotic effects of n-3 PUFA could result in decreased adipose accumulation and therefore reduce obesity.

3. Inflammation mediators involved in n-3 PUFA-regulated lipid metabolism

Inflammation is a complex reaction of vascular tissues in response to harmful stimuli, such as infection, cell injury or toxin exposure. Inflammation involves extravascular accumulation of plasma proteins and recruitment of leukocytes from the circulation to the site of infection. Once macrophages, endothelial cells and mastocytes are activated by stimulating agents at the site of infection, they release inflammatory mediators responsible for the signs of inflammation. These inflammatory mediators include complements, chemokines, cytokines, leukotriens, prostaglandins and other lipid mediators [32]. Pro-inflammatory and anti-inflammatory effects of n-3 PUFA treatments can both be observed. Recently, inflammation mediators such as serum amyloid A (SAA), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) have been found to be associated with obesity development [33,34]. Their expressions are mildly elevated upon the onset of obesity. Numerous data also suggest that these inflammation mediators are involved in regulating lipid metabolism and therefore affect lipid accumulation. For example, they can mediate the effect of DHA to increase lipolysis and reduce lipid accumulation [35,36]. Here, we describe the involvement of these factors in lipid metabolism and obesity.

3.1. Serum amyloid A

SAA is an apolipoprotein mainly synthesized in mammalian liver. SAA can be divided into constitutive members and acute-phase members (A-SAA) in response to tissue damage and inflammation. The A-SAA are induced primarily by interleukin-1 (IL-1), TNF-α and IL-6 through the down-regulation of NF-κB and CCAAT/enhancer-binding proteins (C/EBP) whose binding elements have been located and characterized in A-SAA promoters [37]. There are about two- to sixfold higher increments of plasma A-SAA levels in obese than in lean children and adults [38,39]. SAA is known as a marker for obesity because its expression is well correlated with the degree of obesity [40]. The discoveries of the involvement of SAA in modifying lipid metabolism suggest that SAA functions in obesity through several aspects. Firstly, SAA reduces lipogenesis. Several lipogenic enzymes including ACC1, LPL and adipocyte fatty acid binding protein (aP2) are reduced in adipocytes by the SAA treatment [10,35]. Secondly, SAA increases lipolysis in porcine and human adipocytes [10,35,36]. SAA can activate NF-κB by increasing IκBα degradation [41–43], resulting in a proinflammatory cytokine-induced lipolysis [44,45]. SAA also enhances productions of lipolysis-promoting cytokines such as IL-6 through the induction of NF-κB [42]. Therefore, SAA may facilitate lipolysis via NF-κB and its target genes. In addition, SAA-induced increment of lipolysis can be attributed to the reduction of perilipin as well [10,35].

3.2. TNF-α and IL-6

TNF-α and IL-6 secreted from macrophages and monocytes during infection play important roles in immunity. In addition to immune cells, TNF-α and IL-6 are secreted by adipose tissues or adipocytes, suggesting potential regulatory roles in lipid metabolism [46,47]. Treatments of TNF-α decrease expression and activity of LPL and also increase lipolysis to reduce lipid accumulation in adipocytes [45,48]. Activation of PKA by TNF-α leads to increased phosphorylation of perilipin to increase lipolysis [49]. In adipocytes, lipolysis is enhanced by TNF-α through down-regulation of cAMP-phosphodiesterase 3B to increase cAMP concentration and, consequently, to intensify PKA signaling [48,49]. The lipolytic activities of TNF-α are partially attributed to the PKA-mediated phosphorylation of perilipin and HSL. Other mechanisms are also involved in TNF-α-mediated lipolysis. For instance, perilipin expression is decreased by stimulation of TNF-α via p44/42 and c-jun-NH2-terminal kinase [50]. Lipolysis promoted by TNF-α is reduced in the presence of NF-κB inhibitors, suggesting that NF-κB is essential in TNF-α-regulated lipolysis [45]. The enhancing effect of TNF-α in lipolysis can be blocked by overexpression of perilipin, suggesting that perilipin participates in TNF-α-induced lipolysis [51]. Similar to n-3 PUFA, TNF-α suppresses SREBP-1 expression through negative modulation of LXR and two LXL coactivators, peroxisome proliferator-activated

receptor γ coactivator 1α (PGC1α) and steroid receptor coactivator-2 [52,53].

The TNF-α treatment also decreases adipocyte cell numbers through the modulation of proliferation and differentiation. For example, TNF-α induces apoptosis in both preadipocytes and mature adipocytes [54] and blocks human preadipocyte differentiation [55]. The inhibitory effect of TNF-α on adipogenesis is through stabilizing antiadipogenic β-catenin and suppressing several adipogenic transcription factors such as PPARγ and C/EBPα [56].

In summary, SAA, TNF-α and IL-6 are involved in mediating n-3 PUFA effects on lipid metabolism (Fig. 1). For instance, the parallel effects of n-3 PUFA, SAA and TNF-α to decrease expression of LPL, SREBP-1 and perilipin indicate the tight connections of these factors. Accordingly, we speculate that SAA, TNF-α and IL-6 are potential candidates to mediate the n-3 PUFA-induced reduction in lipid accumulation.

4. Involvement of n-3 PUFA in inflammatory responses

4.1. Pro-inflammatory effects of n-3 PUFA

Because DHA and EPA enhance TNF-α and IL-6 secretion in macrophages [57–59], and dietary fish oil supplementation increases serum TNF-α concentration in response to endotoxin challenges [59], n-3 PUFA are regarded as pro-inflammatory factors. In addition to macrophages, DHA and EPA treatments also increase TNF-α, IL-1α, IL-6 and SAA expression in adipocytes, keratinocytes, splenocytes and hepatocytes [10,35,60–62]. The n-3 PUFA decrease production of prostaglandin E_2 (PGE_2) [63–65], a TNF-α suppressor [66–68]. The elevated TNF-α and IL-6 production induced by n-3 PUFA is inversely related to the PGE_2 concentration [57,69], suggesting that n-3 PUFA increase these pro-inflammatory mediators through regulation of PGE_2. Recent data show that DHA upregulates the expression of SAA through modulation of C/EBPβ by activating PKA [70]. suggesting another possibility of n-3 PUFA-induced pro-inflammatory response via increased SAA expressions. Although there are several potential n-3 PUFA-mediated pro-inflammatory effects, these effects need to be quantitatively and accurately evaluated.

4.2. Anti-inflammatory mechanism of n-3 PUFA

Numerous anti-inflammatory responses to n-3 PUFA have also been reported. In monocytes, EPA and DHA inhibit LPS-induced cytokine expression, including IL-1β, IL-6 and TNF-α [71,72]. Mononuclear cells from humans receiving supplemental EPA+DHA or fish oil express less TNF-α, IL-1β and IL-6 [73,74]. Adipocytes treated with DHA express more anti-inflammatory IL-10 compared to untreated cells [75]. The anti-inflammatory effect of n-3 PUFA mainly results from suppression of NF-κB [76]. In human THP-1

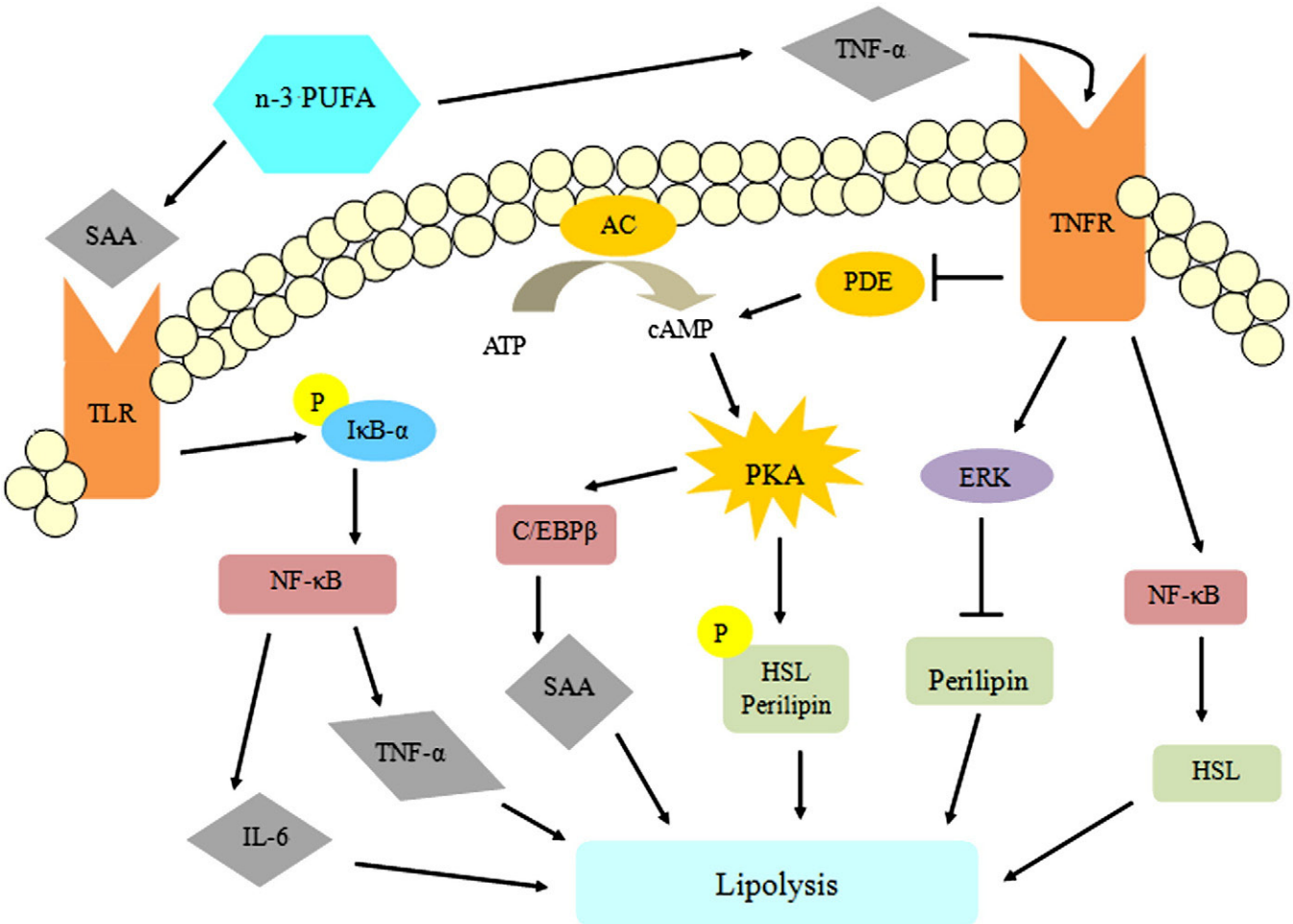

Fig. 1. Proposed mechanisms by which PUFA reduce lipid accumulation. AC, Adenylyl cyclase; PDE, phosphodiesterase; TNFR, TNF-α receptors; TLR, Toll-like receptors; PKA, cAMP-dependent protein kinase A; ERK, extracellular signal-regulated kinases; HSL, hormone-sensitive lipase; C/EBPβ, CCAAT/enhancer-binding protein β; SAA, serum amyloid A; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; NF-κB, nuclear factor-κB.

macrophages, DHA and EPA treatments cause less nuclear p65 and phosphorylated cytoplasmic IκB-α, leading to the reduction of LPS-induced NF-κB DNA-binding activities and TNF-α expression [71,72]. DHA and its metabolites inhibit NF-κB activation via the modulations on IκB kinase, leading to reduced phosphorylated IκB-α [77]. It was also reported that suppression of glutathione synthesis attenuates the n-3 PUFA-induced inhibition on NF-κB activation [78], suggesting that the anti-oxidative activity of n-3 PUFA may be involved in the process.

Peroxisome proliferator-activated receptors (PPAR) are also involved in n-3 PUFA-controlled negative regulation of NF-κB. PPAR are members of the nuclear receptor family of ligand-dependent transcription factors that regulate diverse gene expression, and EPA and DHA are putative natural ligands for PPAR [79]. Addition of PPARγ antagonists retards n-3 PUFA-mediated suppression of LPS-induced NF-κB activation, and overexpression of PPARγ reinforces the induced suppression, indicating that the anti-inflammatory effect of n-3 PUFA is PPARγ dependent [80]. The inhibitory effect of n-3 PUFA on NF-κB activation cannot be observed in PPARα-deficient cells [81], suggesting the importance of PPARα in mediating n-3 PUFA effects. The PPAR may interfere with the activating effect of NF-κB and activator protein-1 (AP-1) by direct protein–protein interaction to transrepress the expression of proinflammatory genes [82]. These observations lead us to conclude that n-3 PUFA could be an anti-inflammatory factor under many circumstances.

4.3. Anti- vs. pro-inflammatory responses

Saturated long-chain fatty acids activate Toll-like receptor signaling to increase expression of NF-κB and cytokine production in murine adipocytes [83,84] and macrophages [83,85,86], leading to inflammatory responses. However, the inflammatory property of n-3 PUFA is complicated and often oversimplified. The conflicting results of pro- or anti-inflammatory effects of n-3 PUFAs are related to different states (inflammatory vs. resident) of cells [87] or different cell types [71,88]. The immunomodulatory effect of n-3 PUFA is also influenced by polymorphisms in cytokine genes [89,90]. Sometimes the double-edged pro- and anti-inflammatory effects of n-3 PUFA appear at the same time. Fish oil increases both the pro-inflammatory cytokine, TNF-α, and the anti-inflammatory cytokine, interleukin-10, in splenocytes [91]. Despite the proinflammatory properties, the n-3 PUFA have either inhibitory or no impact on human systematic inflammation profiles. In humans, n-3 PUFA concentrations are negatively correlated with several pro-inflammatory biomarkers including C-reactive protein, IL-6 and TNF-α, and positively correlated with anti-inflammatory markers, such as TGF-β and IL-10 [92–94]. However, there are reports that supplementation with EPA and DHA has no effect on these cytokines [95–97]. It seems that the pro-inflammatory effect of n-3 PUFA is localized to some cell types or limited to selected cytokines. Regardless, the magnitude for the increase in inflammation molecules produced by n-3 PUFA is small compared to endotoxin-induced alteration in inflammation molecules (Table 2). The expression of SAA increases 30- to 500-fold in response to tissue damage and inflammation [102–104], whereas DHA treatments increase SAA expression only two- to fivefold in hepatocytes and adipocytes [10,35,60]. The IL-6 and TNF-α expressions increase two- to five-fold upon the treatment of macrophages with n-3 PUFA [57,105], whereas an acute inflammation response increases the expression of these cytokines to 50-fold [98,99].

The stimulatory effect of DHA on these pro-inflammatory proteins is relatively low compared with acute inflammation. However, the mildly and locally elevated TNF-α and SAA mRNA after n-3 PUFA treatment are similar to the low-grade inflammation state found in obesity [106]. The TNF-α mRNA expression is elevated five- or 10-fold, and protein expression is increased twofold in the adipose tissue from the obese compared to the lean mice [107]. These obese mice also have a 40% higher plasma TNF-α concentration [107]. Similar results are found in humans, wherein there is a twofold increase in TNF-α mRNA and protein in adipose tissue from obese compared to lean women [34]. In addition to TNF-α, plasma IL-6 concentration is three- to fivefold greater in obese compared to normal humans [108,109]. The plasma SAA concentration increases two- to sixfold in the obese, and SAA mRNA in adipose tissue from obese humans decreases about 50% after weight loss [38,110].

The chronic low-grade inflammation state in obesity is believed to participate in the pathogenesis of insulin resistance, leading to the metabolic syndrome [106]. Despite mildly increased TNF-α and SAA expression in obese animals, the n-3 PUFA do not cause insulin resistance; on the contrary, n-3 PUFA supplementation improves insulin resistance in rats, mice and humans [111–113]. The insulin-sensitizing effect of the n-3 PUFA may come from its positive regulation of glucose and lipid metabolism [114]. The high-fructose diet-induced elevation of blood glucose and insulin is reduced by fish oil supplementation, thus reducing insulin resistance [115]. The suppressive effect of n-3 PUFA on adiposity is assumed to be associated with the amelioration of insulin resistance. Hyperlipidemia in obesity often causes increased plasma free-fatty-acid level which results in insulin resistance via the activation of PKC θ and subsequently increased IRS-1 phosphorylation at Ser 307 [116,117]. The hypotriglyceridemic property of n-3 PUFA can therefore partially

Table 2
Relative response of inflammation mediators to different stimuli

Classification	Intervention	Biomarkers of inflammation	Subject	Tissue/cells	Detected product	Change	Ref.
Acute-phase inflammation	LPS	TNF-α	Healthy men	Plasma	Protein	50-fold	[98]
			Mice	Liver	mRNA	30-fold	[99]
		IL-6	Healthy human	Whole blood	Protein	9-fold	[100]
			Mice	Liver	mRNA	50-fold	[99]
		IL-1 β	Healthy human	Whole blood	Protein	10-fold	[100]
			Mice	Liver	mRNA	200-fold	[99]
		IFN-γ	Mice	Liver	mRNA	50-fold	[101]
		SAA	Mice	Serum	Protein	>100-fold	[102]
				Liver	mRNA	>500-fold	[103,104]
n-3 PUFA	Fish oil	TNF-α	Mice	Macrophage	mRNA or protein	2.3- or 2-fold	[58,105]
	DHA or EPA		Rat	Macrophages		21% or 15%	[57]
	DHA		Human	Adipocytes	mRNA	5-fold	[10]
	DHA or EPA	IL-6	Rat	Macrophages		69% or 40 %	[57]
	DHA		Human	Adipocytes	mRNA	12-fold	[10]
	DHA	SAA	Human	Adipocytes	mRNA	3-fold	[10]
			Porcine	Hepatocytes	mRNA	3-fold	[35]

explain its beneficial effect on insulin sensitivity. Moreover, the n-3 PUFA-induced improvement in insulin sensitivity is absent in PPARα knockout mice [113], indicating that n-3 PUFA modulate insulin sensitivity via a PPARα-dependent pathway. In addition, the up-regulation of adiponectin by n-3 PUFA changes insulin sensitivity. The crucial role of adiponectin in insulin actions is evidenced in adiponectin knockout mice with severe insulin resistance compared to wild-type mice [118,119]. Supplementation with n-3 PUFA increases adiponectin expression and simultaneously improves insulin resistance in rats fed a high-sucrose diet [120]. This result suggests that adiponectin may be responsible for the n-3 PUFA-mediated ameliorations of insulin resistance.

The mildly elevated proinflammmatory proteins induced by n-3 PUFA exert no obvious harmful effects. Therefore, we speculate that the slight increase in SAA, IL-6, TNF-α and adiponectin in response to n-3 PUFA may be beneficial because they increase the lipolytic activity and decrease lipogenic activity to enhance the utilization and to decrease the deposition of body fat.

5. Conclusion

The n-3 PUFA up-regulate the expression of inflammation mediators, SAA1, IL-6 and TNF-α, by modifying PKA activity, the functions of PPAR, or PGE_2 to mediate lipolytic effects. Even though these inflammation mediators are increased after treatment with n-3 PUFA, the increment of these factors is much less than that observed after an inflammatory response induced by LPS. Therefore, to characterize n-3 PUFA as a pro-inflammatory factor is not appropriate when the concentration in the diet is not extraordinarily high. Regardless, n-3 PUFA can induce lipolysis and reduce lipogenesis and such functions suggest new insights whereby PUFA may be used to reduce lipid deposition in the liver and other tissues, therefore presenting an opportunity for developing new strategies to treat obesity.

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