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Long-chain polyunsaturated fatty acids and inflammation

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Abstract

Although part of the normal host response to infection or injury, inflammation is involved in many pathological conditions and disease states. Most interest in the influence of fatty acids on inflammatory processes has centred on the opposing actions of n-6 and n-3 polyunsaturated fatty acids (PUFAs). The n-6 PUFA arachidonic acid gives rise to the eicosanoid family of inflammatory mediators (prostaglandins, leukotrienes and related metabolites) and through these regulates the activities of inflammatory cells, the production of inflammatory cytokines, etc. Consumption of long-chain n-3 PUFAs [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] decreases the amount of arachidonic acid in inflammatory cell membranes and so available for eicosanoid production. Thus, consumption of long-chain n-3 PUFAs results in decreased production of eicosanoids from arachidonic acid. EPA acts as an alternative substrate for eicosanoid synthesis giving rise to mediators that are less potent than the analogues produced from arachidonic acid. EPA and DHA give rise to newly discovered families of mediators termed E- and D-resolvins, respectively, which have anti-inflammatory and inflammation-resolving actions. In addition to this range of effects, long-chain n-3 PUFAs affect cell-signalling processes and gene expression in inflammatory cells, resulting in decreased expression of inflammatory cytokines and adhesion molecules. Such long-chain n-3 PUFA-induced effects may be of importance in protecting against the development of and lowering the severity of acute and chronic inflammatory conditions. There is good evidence for the efficacy of long-chain n-3 PUFAs in rheumatoid arthritis, with less strong evidence in other inflammatory conditions. The precursor n-3 PUFA, α-linolenic acid, exerts some anti-inflammatory effects at very high intakes, perhaps reflecting the need for its conversion to EPA to be effective.

Keywords: *arachidonic acid*; *cytokine*; *eicosanoid*; *fish oil*; *inflammation*; *macrophage*

Abbreviations: *COX: cyclooxygenase; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; HETE: hydroxyeicosatetraenoic acid; HPETE: hydroperoxyeicosatetraenoic acid; ICAM-1: intercellular adhesion molecule-1; IκB: inhibitory subunit of NF-κB; IL: interleukin; LOX: lipoxygenase; LT: leukotriene; NF-κB: nuclear factor-κB; PG: prostaglandin; PUFA: polyunsaturated fatty acid; TNF: tumour necrosis factor; TX: thromboxane; VCAM-1: vascular cell adhesion molecule-1.*

Inflammation in health and disease

Inflammation is part of the body's immediate response to infection or injury. It is typified by redness, swelling, heat and pain. These occur as a result of increased blood flow, increased permeability across blood capillaries, which allows large molecules (e.g. complement, antibodies, cytokines) to leave the bloodstream and cross the endothelial wall, and increased movement of leukocytes from the bloodstream into the surrounding tissue. Inflammation functions to begin the immunological process of elimination of invading pathogens and toxins and to repair damaged tissue. These responses must be ordered and controlled. The movement of cells into the inflammatory/infected site is

induced by the up-regulation of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin on the surface of endothelial cells allowing leukocyte binding and subsequent diapedesis. The earliest cells appearing at inflamed sites are granulocytes, with monocyte/macrophages and lymphocytes appearing later. Granulocytes and monocyte/macrophages are involved in pathogen killing, in clearing up cellular and tissue debris, and in tissue repair. The activity of these cells is induced by certain triggers, including components of bacterial cell walls. One such component is bacterial endotoxin (also known as lipopolysaccharide), part of the cell wall of Gram-negative bacteria. Endotoxin

can directly activate monocyte/macrophages, inducing them to form cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 and IL-8, eicosanoids, such as prostaglandin (PG) E_2, nitric oxide, matrix metalloproteinases and other mediators. Endotoxin also induces adhesion molecule expression on the surface of endothelial cells and leukocytes. The cytokines produced by monocyte/macrophages also serve to regulate the whole-body response to infection and injury. Thus, inflammation and the inflammatory response are part of the normal, innate immune response. Inflammatory mediators also provide a link between the innate and acquired immune responses.

Although inflammation is a normal response, when it occurs in an uncontrolled or inappropriate manner excessive damage to host tissues and disease can ensue. Such uncontrolled or inappropriate inflammatory responses are characterized by hyperexpression of endothelial and leukocyte adhesion molecules, appearance of soluble forms of adhesion molecules in the circulation, sequestration of leukocytes to sites where they are not usually found, production of inflammatory mediators and damage to host tissues. High levels of TNF-α, IL-1β and IL-6 are particularly destructive and are implicated in causing some of the pathological responses that occur in endotoxic shock, in adult respiratory distress syndrome and in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases. Chronic overproduction of TNF-α and IL-1 can cause muscle wasting and loss of bone mass and may account for alterations in body composition and tissue loss seen in inflamma-

Table 1. Examples of diseases or conditions that involve an inflammatory component

Rheumatoid arthritis	Multiple sclerosis
Crohn's disease	Neurodegenerative disease of ageing
Ulcerative colitis	Atherosclerosis
Lupus	Acute cardiovascular events
Type I diabetes	Obesity
Cystic fibrosis	Metabolic syndrome
Childhood asthma	Major surgery
Adult asthma	Trauma and critical illness
Chronic obstructive pulmonary disease	Acute respiratory distress syndrome
	Cancer cachexia
Allergic disease	Some cancers
Atopic dermatitis	
Psoriasis	

tory diseases. As well as its clear and obvious association with classic inflammatory diseases, inflammation is now recognized to play an important role in the pathology of other diseases such as cardiovascular disease. Table 1 lists some diseases and conditions that are recognized to have an inflammatory component.

The link between fatty acids and inflammation: arachidonic acid and eicosanoids

The eicosanoid family of inflammatory mediators is generated from 20-carbon polyunsaturated fatty acids (PUFAs) liberated from cell-membrane phospholipids. The membrane phospholipids of inflammatory cells taken from humans consuming Western-type diets typically contain approximately 20% of fatty acids as the n-6 PUFA arachidonic acid (1–7). In contrast, the proportions of other 20-carbon PUFAs such as the n-6 PUFA di-homo-γ-linolenic acid and the n-3 PUFA eicosapentaenoic acid (EPA) are typically about 2 and <1% of fatty acids, respectively (4, 6). Thus, arachidonic acid is usually the dominant substrate for eicosanoid synthesis. Eicosanoids include PGs, thromboxanes (TXs), leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs). Arachidonic acid in cell-membrane phospholipids can be mobilized by various phospholipase enzymes, most notably phospholipase A_2, and the free acid can subsequently act as a substrate for the enzymes that synthesize eicosanoids (Fig. 1). Metabolism by cyclooxygenase (COX) enzymes gives rise to the 2-series PGs and TXs. COX-2 is induced in inflammatory cells as a result of stimulation and is responsible for the markedly elevated production of PGs that occurs upon cellular activation. Monocytes and macrophages produce large amounts of PGE_2 and PGF_2, neutrophils produce moderate amounts of PGE_2 and mast cells produce PGD_2. Metabolism of arachidonic acid by the 5-lipoxygenase (5-LOX) pathway gives rise to hydroxy and hydroperoxy derivatives (5-HETE and 5-HPETE, respectively), and the 4-series LTs, LTA_4, B_4, C_4, D_4 and E_4. Neutrophils, monocytes and macrophages produce LTB_4, while LTC_4, D_4 and E_4 tend to be produced by mast cells, basophils and eosinophils.

PGE_2 has a number of proinflammatory effects including inducing fever, increasing vascular permeability and vasodilatation, and enhancing pain and oedema caused by other agents. PGE_2 has been

**Arachidonic acid in
cell membrane phospholipids**

Phospholipase A$_2$

Free arachidonic acid

| COX-2 | 15-LOX | 12-LOX | 5-LOX |

2-series PGs and TXs | **15-HPETE, 15-HETE and Lipoxin A$_4$** | **12-HPETE and 12-HETE** | **5-HPETE, 5-HETE, 4-series LTs**
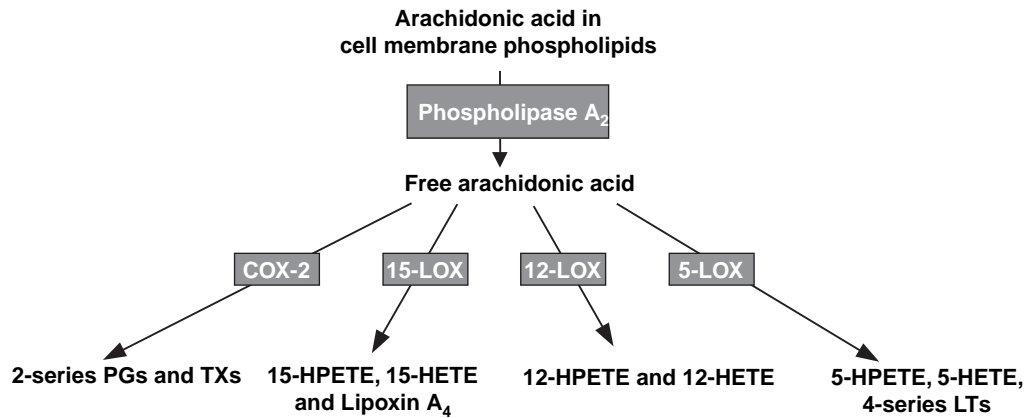
Fig. 1. General scheme of eicosanoid synthesis from arachidonic acid. Arachidonic acid is released from inflammatory cell membrane phospholipids by the action of phospholipases, especially phospholipase A$_2$, and the free arachidonic acid acts as a substrate for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, giving rise to prostaglandins (PGs), thromboxanes (TXs), hydroperoxyeicosatetraenoic acids (HPETEs), hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs). These mediators have various roles in the inflammatory process.

shown to induce COX-2 mRNA expression in cultured fibroblasts, and so to up-regulate its own production, and to induce production of the inflammatory cytokine IL-6 by macrophages (8). LTB$_4$ increases vascular permeability, is a potent chemotactic agent for leukocytes, induces release of lysosomal enzymes, and enhances generation of reactive oxygen species and production of inflammatory cytokines such as TNF-α, IL-1 and IL-6. The cysteinyl-LTs (LTC$_4$, D$_4$ and E$_4$) are broncho-constrictors, increase vascular permeability and promote hypersensitivity. In inflammatory conditions increased rates of production of arachidonic acid-derived eicosanoids occur and elevated levels of these eicosanoids are observed in blood and tissues from patients with acute and chronic inflammatory conditions. Despite the ongoing emphasis on the proinflammatory effects of arachidonic acid-derived eicosanoids, some of these mediators, for example lipoxin A$_4$, are actually anti-inflammatory (9). Indeed, recent studies have highlighted an anti-inflammatory action of PGE$_2$ which was shown to inhibit 5-LOX and so decrease production of 4-series LTs and to induce 15-LOX, so promoting the formation of anti-inflammatory lipoxins (9). Thus, PGE$_2$ exhibits both proinflammatory and anti-inflammatory actions.

Arachidonic acid and inflammatory mediator production

Animal feeding studies have shown a strong positive relationship between the amount of arachidonic acid in inflammatory cells and the ability of those cells to produce eicosanoids such as PGE$_2$ (10). In turn, the amount of arachidonic acid in inflammatory cells can be increased by including it in the diet (10, 11). The amount of arachidonic acid in inflammatory cells may also be influenced by the dietary intake of its precursor, linoleic acid, although the range of linoleic acid intake over which this relationship occurs has not been defined for humans. Increasing linoleic acid intake by 6.5 g per day in humans habitually consuming 10–15 g per day did not alter the arachidonic acid content of blood mononuclear cells (6). Nevertheless, the role of arachidonic acid as a precursor for the synthesis of eicosanoids indicates the potential for dietary n-6 PUFAs (linoleic or arachidonic acids) to influence inflammatory processes. Supplementation of the diet of healthy young male subjects with 1.5 g arachidonic acid per day for 7 weeks resulted in a marked increase in production of PGE$_2$ and LTB$_4$ by endotoxin-stimulated mononuclear cells, although production of TNF-α, IL-1β and IL-6 was not significantly altered (12). Thus, increased arachidonic acid intake may result in changes indicative of selectively increased inflammation or inflammatory responses in humans. Supplementation of the diet of healthy elderly subjects with arachidonic acid (0.7 g per day in addition to a habitual intake of about 0.15 g per day) (11) for 12 weeks did not affect endotoxin-stimulated production of TNF-α, IL-1β or IL-6 by mononuclear cells and did not alter plasma soluble VCAM-1, ICAM-1 or E-selectin concentrations

(13). This lack of effect occurred despite incorporation of arachidonic acid into target cells (11). Taken together, these studies suggest that modestly increased intake of arachidonic acid results in incorporation of arachidonic acid into cells involved in inflammatory responses, but that this does not affect production of inflammatory cytokines or shedding of adhesion molecules, although production of inflammatory eicosanoids is increased.

Long-chain n-3 polyunsaturated fatty acids and eicosanoid production

Increased consumption of the long-chain n-3 PUFAs, EPA and docosahexaenoic acid (DHA), typically found in oily fish and in fish oil liquids and capsules, results in increased proportions of those fatty acids in inflammatory cell-membrane phospholipids, partly at the expense of arachidonic acid (1–7). Thus, there is less substrate available for synthesis of eicosanoids from arachidonic acid. In accordance with this, fish oil supplementation of the human diet has been shown to result in decreased production of PGE_2 (2, 5, 14), TXB_2 (5), LTB_4 and 5-HETE (1, 3) and LTE_4 (15) by inflammatory cells. EPA also acts as a substrate for COX and LOX enzymes, so giving rise to a different family of eicosanoids: the 3-series PGs and TXs, and the 5-series LTs and hydroxyeicosapentaenoic acids. Thus, fish oil supplementation of the human diet has been shown to result in increased production of LTB_5, LTE_5 and 5-hydroxyeicosapentaenoic acid by inflammatory cells (1, 3, 15). The functional significance of this is that the mediators formed from EPA are frequently less potent than those formed from arachidonic acid. For example, LTB_5 is 10–100-fold less potent as a neutrophil chemotactic agent than LTB_4 (16, 17), while PGE_3 is a less potent inducer than PGE_2 of COX-2 gene expression in fibroblasts and of IL-6 production by macrophages (8).

In addition to long-chain n-3 PUFAs modulating the generation of eicosanoids from arachidonic acid and to EPA acting as substrate for the generation of alternative eicosanoids, recent studies have identified a novel group of mediators, termed E-series resolvins, formed from EPA by COX-2 and 5-LOX, that appear to exert anti-inflammatory actions (18). In addition, DHA-derived mediators termed D-series resolvins, docosatrienes and neuroprotectins, also produced by COX-2 and 5-LOX under some conditions, have been identified and these too appear to be anti-inflammatory and inflammation resolving (18).

Anti-inflammatory effects of n-3 polyunsaturated fatty acids other than altered eicosanoid production

Although their action in antagonizing arachidonic acid metabolism is a key anti-inflammatory effect of n-3 PUFAs, these fatty acids have a number of other anti-inflammatory effects that may occur downstream of altered eicosanoid production or may be independent of this.

Long-chain n-3 PUFAs affect the cell-surface expression of adhesion molecules that are involved in interactions between leukocytes and endothelial cells and that lead to leukocyte infiltration into sites of inflammatory activity. This was first demonstrated by de Caterina et al. (19), who showed that culture of human venous endothelial cells with DHA significantly decreased cytokine-induced surface expression of E-selectin, ICAM-1 and VCAM-1, and impaired the ability of ligand-bearing monocytes to adhere (20). Dietary fish oil decreased expression of ICAM-1 on the surface of murine macrophages (21) and decreased circulating levels of soluble VCAM-1 in elderly subjects (22), although it is not clear whether this represents decreased surface expression of VCAM-1.

Long-chain n-3 PUFAs also affect synthesis of inflammatory cytokines, a process that is regulated in part by PGE_2 and 4-series LTs. Cell-culture studies demonstrate that both EPA and DHA can inhibit the production of TNF-α and IL-1β by monocytes, and the production of IL-6 and IL-8 by venous endothelial cells (23, 24). Fish oil feeding decreased *ex vivo* production of TNF-α, IL-1β and IL-6 by rodent macrophages (23, 24) and decreased circulating concentrations of these cytokines in experimental endotoxaemia in mice (25). Supplementation of the diet of healthy human volunteers with fish oil has been reported to result in decreased *ex vivo* production of TNF, IL-1 and IL-6 by mononuclear cells (2, 5, 26–28), although not all studies agree on this point (29).

n-3 Polyunsaturated fatty acids and inflammatory gene expression

De Caterina et al. (19) demonstrated that the down-regulation of VCAM-1 expression on endothelial cells caused by DHA was exerted at the level of

VCAM-1 gene expression, and that this effect was independent of effects on eicosanoid production and on antioxidant status. Culturing bovine chondrocytes with EPA or DHA markedly decreased cytokine-mediated induction of expression of the COX-2, TNF-α and IL-1α genes (30). Including EPA or DHA in the culture medium of human osteoarthritic cartilage explants markedly decreased the cytokine-induced up-regulation of expression of the COX-2, IL-1α, IL-1β, TNF-α, and 5-LOX activating protein and matrix metalloproteinase genes in these cells (31). Inclusion of fish oil in the diet completely abolished mRNA for TNF-α, IL-1β and IL-6 in the kidneys of autoimmune disease-prone mice (32). Feeding mice a fish oil-rich diet significantly decreased the level of IL-1β mRNA in endotoxin- or phorbol ester-stimulated spleen lymphocytes (33); the lower IL-1β mRNA level was due

not to accelerated degradation but to impaired synthesis. Fish oil feeding to mice lowered basal and endotoxin-stimulated TNF-α mRNA levels in peritoneal macrophages (34). ICAM-1 mRNA levels were lower in fresh peritoneal macrophages from mice fed fish oil (21).

It is now emerging that n-3 PUFAs may exert their effects on inflammatory gene expression through direct actions on the intracellular signalling pathways that lead to activation of one or more transcription factors such as nuclear factor-κB (NF-κB). Studies have shown that n-3 PUFAs can decrease the extent of activation of NF-κB in cultured monocytes, an effect associated with decreased IκB (the inhibitory subunit of NF-κB) phosphorylation, perhaps due to decreased activation of mitogen-activated protein kinases (35). These observations suggest direct effects of long-
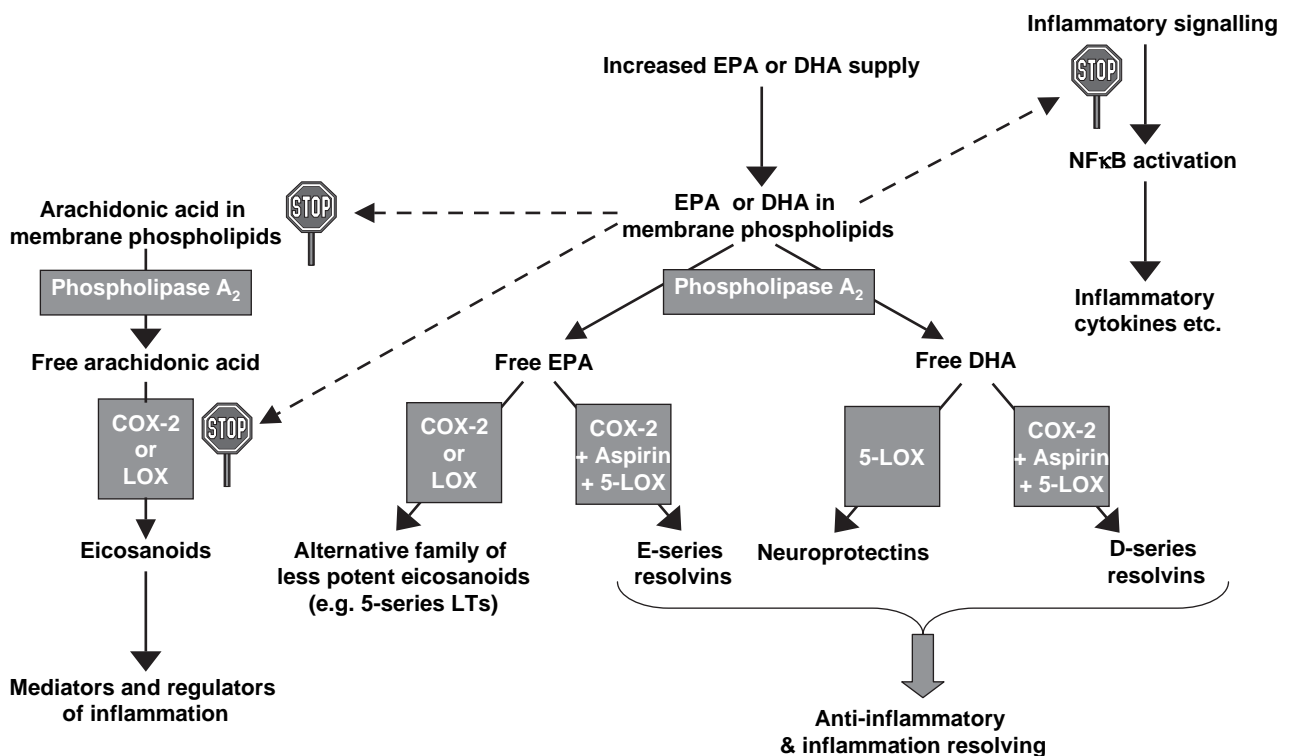

Fig. 2. Mechanisms by which long-chain n-3 polyunsaturated fatty acids exert anti-inflammatory effects. Increased dietary supply of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) results in their incorporation into inflammatory cell membranes partly at the expense of arachidonic acid. EPA and DHA also inhibit arachidonic acid metabolism by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Thus, EPA and DHA decrease the production of arachidonic acid-derived eicosanoids. EPA metabolism by COX-2 and 5-LOX enzymes gives rise to eicosanoids that are typically less potent than those formed from arachidonic acid. DHA metabolism by 5-LOX gives rise to anti-inflammatory neuroprotectins. Metabolism of EPA or DHA by COX-2 and 5-LOX in the presence of aspirin gives rise to anti-inflammatory resolvins. EPA and DHA also inhibit the signalling pathway, leading to activation of nuclear factor-κB (NF-κB), a transcription factor that induces expression of a number of inflammatory genes, including those encoding inflammatory cytokines, adhesion molecules and COX-2.

chain n-3 fatty acids on inflammatory gene expression via inhibition of activation of the transcription factor NF-κB.

Clinical applications of the anti-inflammatory actions of long-chain n-3 polyunsaturated fatty acids

Inflammation is an overt or a covert component of numerous human diseases and conditions (Table 1). Although the inflammation may afflict different body compartments, one common characteristic of these conditions and diseases is excessive or inappropriate production of inflammatory mediators including eicosanoids and cytokines. The recognition that the long-chain n-3 PUFAs have anti-inflammatory actions has led to the ideas that an absolute or relative lack of these fatty acids may contribute causally to inflammatory conditions and that supplementation of the diet of patients with inflammatory diseases may bring about clinical benefit. Supplementation trials with long-chain n-3 PUFAs have been conducted in many of the states listed in Table 1. In many cases these demonstrate anti-inflammatory effects, such as changes in circulating concentrations or *ex vivo* production of inflammatory mediators. There is evidence of clinical benefit from trials conducted in rheumatoid arthritis, but evidence of clinical efficacy is still lacking in most of the other conditions mentioned (see refs 23, 24, 35 and 36 for further discussion).

α-Linolenic acid and inflammation

Relatively few studies have examined the effect of the precursor n-3 PUFA α-linolenic acid on inflammatory outcomes in humans. Caughey et al. (5) reported that 13.7 g α-linolenic acid per day for 4 weeks resulted in a decrease in production of TNF-α and IL-1β by endotoxin-stimulated mononuclear cells by 27 and 30%, respectively. By comparison, fish oil providing 2.7 g EPA+DHA per day decreased production of these cytokines by 70 and 78%, respectively (5). Thus, on a grams per day basis long-chain n-3 PUFAs are about nine times more potent than α-linolenic acid with respect to this outcome in healthy subjects. Several studies using lower intakes of α-linolenic acid than used by Caughey et al. (2–9.5 g per day) did not find anti-inflammatory effects (37). Taken together, these data suggest that increasing α-linolenic acid intake to >10 g per day is required for anti-inflammatory effects to be seen. Even then, the effects will be much more modest than those exerted by long-chain n-3 PUFAs (5).

Conclusions

Long-chain n-3 PUFAs from oily fish and fish oils decrease the production of inflammatory eicosanoids, cytokines and adhesion molecules. They act both directly, by replacing arachidonic acid as an eicosanoid substrate, by inhibiting arachidonic acid metabolism and by giving rise to anti-inflammatory resolvins, and indirectly, by altering the expression of inflammatory genes through effects on transcription factor activation (Fig. 2). Thus, long-chain n-3 PUFAs are potentially useful anti-inflammatory agents and may be of benefit in patients at risk of a variety of acute and chronic inflammatory in settings. The precursor n-3 PUFA, α-linolenic acid, is much less potent.

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