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Fatty acids
Long-chain fatty acids and inflammation

Philip C. Calder

Institute of Human Nutrition and Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Tremona Road, Southampton SO16 6YD, UK

Inflammation plays a key role in many common conditions and diseases. Fatty acids can influence inflammation through a variety of mechanisms acting from the membrane to the nucleus. They act through cell surface and intracellular receptors that control inflammatory cell signalling and gene expression patterns. Modifications of inflammatory cell membrane fatty acid composition can modify membrane fluidity, lipid raft formation and cell signalling leading to altered gene expression and can alter the pattern of lipid and peptide mediator production. Cells involved in the inflammatory response usually contain a relatively high proportion of the *n*-6 fatty acid arachidonic acid in their membrane phospholipids. Eicosanoids produced from arachidonic acid have well-recognised roles in inflammation. Oral administration of the marine *n*-3 fatty acids EPA and DHA increases the contents of EPA and DHA in the membranes of cells involved in inflammation. This is accompanied by a decrease in the amount of arachidonic acid present. EPA is a substrate for eicosanoid synthesis and these are often less potent than those produced from arachidonic acid. EPA gives rise to E-series resolvins and DHA gives rise to D-series resolvins and protectins. Resolvins and protectins are anti-inflammatory and inflammation resolving. Thus, the exposure of inflammatory cells to different types of fatty acids can influence their function and so has the potential to modify inflammatory processes.

Inflammation: Monocyte: Macrophage: Cytokine: Arachidonic acid

The aim of this article is to provide an update on some of the mechanisms by which long-chain fatty acids can influence inflammatory processes. Inflammation is a key component of normal host defence, which acts to protect the host from infection and other insults. Inflammation initiates the processes of pathogen killing and tissue repair. The five cardinal signs of inflammation are redness, swelling, heat, pain and loss of function. It involves interactions among many cell types and the production of, and responses to, a number of chemical mediators, including cytokines, chemokines, eicosanoids and reactive oxygen species. Self-regulation of the inflammatory response involves the activation of negative feedback mechanisms such as the secretion of anti-inflammatory cytokines, inhibition of pro-inflammatory signalling cascades, shedding of receptors for inflammatory mediators and activation of regulatory cells. Pathological inflammation involves a loss of these regulatory processes, and may cause excessive, irrepairable damage to host tissues[1]. The resulting diseases are characterised by markedly increased concentrations of inflammatory markers and of activated inflammatory cells at the site of tissue damage and in the systemic circulation[1]. Examples of such inflammatory diseases include rheumatoid arthritis, inflammatory bowel diseases and asthma.

Fatty acid functions of relevance to inflammation

Fatty acids are naturally occurring constituents of the diet. They have metabolic, structural and functional roles within the body, where they act as important sources of energy, major components of all cell membranes, precursors to signalling molecules and regulators of cellular responses[2]. Although all fatty acids can be used as energy sources, different fatty acids have different, often unique, structural

Abbreviations: COX, cyclooxygenase; IκB, inhibitory subunit of NF-κB; LPS, lipopolysaccharide; TLR, Toll-like receptor.

Corresponding author: Professor Philip C. Calder, fax +44 2380 795255, email pcc@soton.ac.uk

and functional roles and biological activities. Indeed, several fatty acids have roles and activities that oppose one another, indicating that the overall biological outcome will be the result of interactions among several fatty acids. With regard to inflammation it is often considered that it is the PUFA of the *n*-6 and *n*-3 families that are most important, these often acting to oppose one another's actions[3]. However, it is now recognised that other fatty acids and fatty acid families are likely also involved in inflammation, with fairly recent work focusing on SFA[4–6]. There are a number of general mechanisms by which fatty acid exposures could affect inflammatory cell function, and so inflammatory processes. This article will deal with three of these mechanisms:

(i) Action directly via surface or intracellular 'fatty acid receptors'.
(ii) Incorporation into the phospholipids of inflammatory cell membranes, where the fatty acids play important roles assuring the correct environment for membrane protein function, maintaining membrane order ('fluidity'), influencing lipid raft formation and modifying membrane-generated intracellular signalling cascades.
(iii) Acting as precursors of extracellular signalling molecules such as PG.

Fatty acids and NF-κB-induced inflammatory gene expression

NF-κB is a key transcription factor involved in up-regulation of inflammatory cytokine, adhesion molecule and cyclooxygenase (COX)-2 genes[7,8]. Inactive NF-κB is a trimer localised within the cytosol; it is activated via a signalling cascade triggered by extracellular inflammatory stimuli, and which involves phosphorylation of an inhibitory subunit (inhibitory subunit of NF-κB (IκB)), which then dissociates allowing translocation of the remaining NF-κB dimer to the nucleus[9]. Bacterial lipopolysaccharide (LPS), which is also known as endotoxin, induces inflammation by activating NF-κB, as do some inflammatory cytokines and UV irradiation. Cell culture studies with the *n*-3 PUFA EPA and DHA show inhibition of LPS-induced production of COX-2, inducible NO synthase, TNFα, IL-1, IL-6, IL-8 and IL-12 in endothelial cells[10,11], monocytes[12,13], macrophages[4] and dendritic dells[5,14]. Animal feeding studies with fish oil, a source of EPA and DHA, support the observations made *in vitro* with respect to the effects of *n*-3 PUFA on inflammatory cytokine production. For example, dietary fish oil decreased the production of TNFα, IL-1β and IL-6 by LPS-stimulated macrophages[15–17]. Some studies in healthy human subjects have demonstrated that oral fish oil supplements can decrease production of TNFα, IL-1β, IL-6 and various growth factors by LPS-stimulated monocytes or mononuclear cells[18–23], although not all studies confirm this effect. The effects of *n*-3 PUFA have been shown to involve inhibition of LPS-induced activation of NF-κB associated with decreased IκB phosphorylation[4,24]. In contrast, SFA, especially lauric acid, enhanced NF-κB activation in macrophages[4] and dendritic cells[5] and so promoted inflammatory gene expression. Lee *et al.*[4] found that EPA and DHA, as well as other unsaturated fatty acids (arachidonic, linoleic and oleic acids), were able to prevent the pro-inflammatory effect of lauric acid in macrophages.

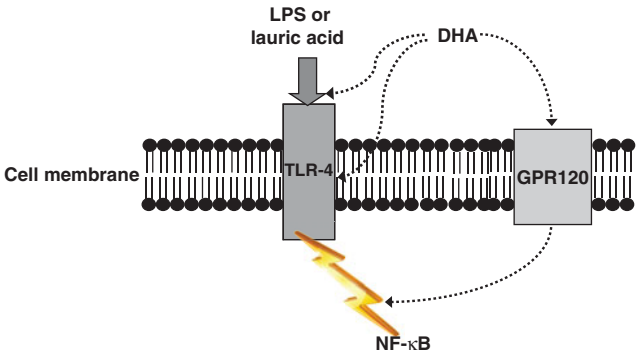

Fig. 1. Interaction between pro-inflammatory stimuli and DHA in regulating signalling to NF-κB. Lipopolysaccharide (LPS) and lauric acid both initiate NF-κB signalling through Toll-like receptor (TLR)-4. DHA inhibits responsiveness to both LPS and lauric acid acting to reduce activation of NF-κB. GPR120 is a cell membrane receptor that is linked to inhibition of NF-κB activation. GPR120 mediates some of the anti-inflammatory actions of DHA. A link between GPR120 and TLR-4 is not yet clear.

It has not been clear how fatty acids can influence activation of NF-κB although their effects might be as far upstream as the plasma membrane. Consistent with this, Lee *et al.*[4] showed that the activation of NF-κB and induction of COX-2 expression by lauric acid did not occur in macrophages expressing a dominant-negative mutant of the cell surface LPS receptor, Toll-like receptor (TLR)-4, suggesting that lauric acid somehow interacts with TLR-4 (Fig. 1). Myeloid differentiation primary response gene 88 is a cell membrane-associated adapter protein used by TLR-4 to activate NF-κB. DHA inhibited COX-2 expression in macrophages bearing constitutively active TLR-4 but not in those bearing constitutively active myeloid differentiation primary response gene 88 suggesting that the effects of DHA are at the level of TLR-4[4]. More recently, Wong *et al.*[6] demonstrated that exposure of macrophages to lauric acid induced association of TLR-4, myeloid differentiation primary response gene 88 and other signalling proteins into organised signalling platforms within the plasma membrane termed membrane rafts in much the same way as LPS acts. Furthermore they showed that DHA inhibited the ability of both LPS and lauric acid to promote recruitment of these signalling proteins into rafts. Thus, the differential effects of fatty acids on inflammatory signalling initiated through TLR-4 and impacting on NF-κB appear to relate to their ability to promote or disrupt membrane raft formation.

Actions of fatty acids on inflammation via fatty acid receptors

Fatty acids, PPARγ and inflammation

PPARγ is a transcription factor that acts in an anti-inflammatory manner[25]. It is able to directly regulate

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inflammatory gene expression, but it also interferes with the activation of the prototypical pro-inflammatory transcription NF-κB[26]. PUFA and their derivatives are endogenous ligands for PPARγ. The *n*-3 PUFA DHA induced PPARγ in dendritic cells and this was associated with reduced production of the pro-inflammatory cytokines TNFα and IL-6 following endotoxin stimulation[14]. In addition, DHA induced a number of known PPARγ target genes in dendritic cells, suggesting this as an important anti-inflammatory mechanism of action[27].

Fatty acids, GPR120 and inflammation

The cell surface G-protein coupled receptor termed GPR120 is highly expressed on inflammatory macrophages, and a GPR120 agonist GW9508 inhibited responsiveness of macrophages to LPS[28]. This involved reduced phosphorylation of the IκB and its maintenance in the cytosol (phosphorylated IκB is degraded) and reduced TNFα and IL-6 production. These observations suggest that GPR120 is anti-inflammatory. DHA and another *n*-3 PUFA, EPA, but not arachidonic, palmitic or myristic acids, promoted GPR120-mediated gene activation, although they were much less potent than GW9508. The effects of DHA were further explored[28]. Its inhibitory effects on LPS-induced IκB phosphorylation, IκB degradation and TNFα, IL-6 and also on monocyte chemotactic protein-1 production did not occur in GPR120 knockdown cells. These observations suggest that the inhibitory effect of DHA (and probably also those of EPA) on responsiveness to LPS occur via GPR120 (Fig. 1).

Modification of inflammatory cell membrane fatty acid composition and consequent alteration of lipid mediator profiles

Modification of inflammatory cell membrane fatty acid composition

PUFA are important constituents of the phospholipids of the membranes of inflammatory cells. Typically these contain a relatively high proportion of the *n*-6 PUFA, arachidonic acid; this is seen in both laboratory animals[29–38] and human subjects[18,21,39–48]. Increased oral supply of the *n*-3 PUFA EPA and DHA results in an increase in the amount of those fatty acids in inflammatory cells, seen in both laboratory animals[29,30,32–38] and human subjects[18,21,39–44,46–48]. The increase in content of EPA and DHA happens over the course of days[49] to weeks[42], occurs in a dose–response manner[48] and is accompanied by a decrease in content of arachidonic acid.

Fatty acid modification of eicosanoid profiles

Eicosanoids, which include PG, thromboxanes and leukotrienes, are long-recognised mediators and regulators of inflammation. They are formed from C_{20} PUFA, typically arachidonic acid, by the COX and lipoxygenase enzymes. In general, arachidonic acid-derived eicosanoids act in a pro-inflammatory way, although this is an oversimplification since it is now recognised that PGE_2, for example, has both pro- and anti-inflammatory effects[3], and that another eicosanoid derived from arachidonic acid, lipoxin A_4, is anti-inflammatory[50–53].

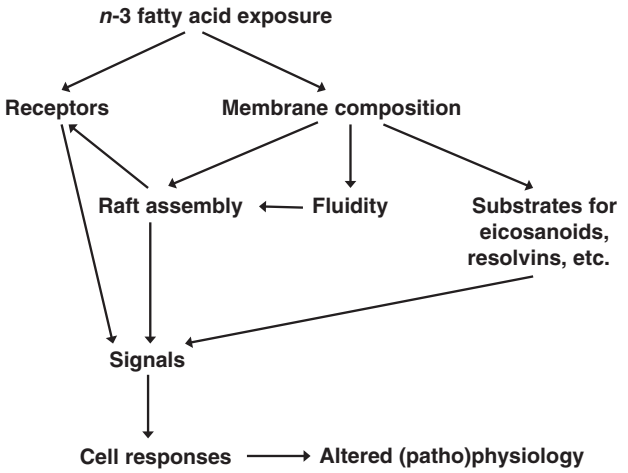

Fig. 2. Overview of the mechanisms by which fatty acids can influence inflammatory cell function. Modified from Calder[64] with permission from Elsevier.

The decrease in arachidonic acid content of inflammatory cell membranes that occurs with incorporation of the *n*-3 PUFA reduces the availability of the usual eicosanoid substrate and so the production of the major 2-series PG and 4-series leukotrienes is decreased[17–19,21,39,40,54–56]. EPA is also a substrate for the COX and lipoxygenase, but the mediators produced have a different structure from the arachidonic acid-derived mediators, and this often influences their potency[57]. For example EPA-derived leukotriene B_5 is ten- to 100-fold less potent as a neutrophil chemoattractant compared with leukotriene B_4[58,59]. Furthermore, EPA-derived eicosanoids may antagonise the action of those produced from arachidonic acid, as was recently demonstrated for PGD_3 *v.* PGD_2[60].

Novel anti-inflammatory and inflammation resolving mediators produced from EPA and DHA: resolvins and protectins

EPA and DHA are substrates for synthesis of fairly recently discovered lipid mediators that are potent anti-inflammatory and inflammation resolving agents. These include resolvins and protectins, which are produced through pathways involving COX and lipoxygenase enzymes[61–63]. Examples of the activities are these compounds include the inhibition of transendothelial migration of neutrophils by resolvin E1, resolvin D1 and protectin D1, and inhibition of TNFα and IL-1β production by protectin D1[63].

Therapeutic benefits of the anti-inflammatory actions of *n*-3 fatty acids

A number of human conditions and diseases have an inflammatory component, and it seems that, irrespective of the body compartment(s) involved, these conditions and

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diseases all involve excessive or inappropriate production of inflammatory mediators including eicosanoids and cytokines[1]. It is evident that the *n*-3 PUFA EPA and DHA act through multiple interconnected mechanisms (Fig. 2)[64] to reduce production of inflammatory eicosanoids and cytokines and to enhance production of anti-inflammatory and inflammation resolving resolvins and protectins. In these ways, *n*-3 PUFA act to oppose the pro-inflammatory actions of SFA and of *n*-6 PUFA. The roles of *n*-3 PUFA in shaping and regulating inflammatory processes and responses suggest that the level of exposure to these fatty acids might be important in determining the development and severity of inflammatory diseases. The recognition that *n*-3 PUFA have anti-inflammatory actions has led to numerous studies supplementing the diet of patients with inflammatory diseases to evaluate clinical benefit. Studies in patients with rheumatoid arthritis have been the most successful among those in patients with an overt inflammatory disease, with a number of trials reporting clinical benefits[65], these benefits being supported by meta-analyses[66,67]. Studies in patients with inflammatory bowel diseases (Crohn's disease and ulcerative colitis) provide equivocal findings with some showing some benefits and others not[68]. Similarly studies conducted in patients with asthma do not provide a clear picture with most studies conducted in adults not showing a clinical benefit, although there are indications of benefits of *n*-3 PUFA in children and adolescents[69]. In most other inflammatory diseases and conditions there are too few studies to draw a clear conclusion of the possible efficacy of *n*-3 PUFA. One reason for these discrepancies may be that the dose of *n*-3 PUFA required to treat different inflammatory conditions is not known, although it is evident that the anti-inflammatory effects of these fatty acids are dose-dependent[48].

Summary and conclusions

Fatty acids can influence inflammation through a variety of mechanisms, including acting via cell surface and intracellular receptors/sensors that control inflammatory cell signalling and gene expression patterns. Some effects of fatty acids on inflammatory processes involve lipid mediators generated from the fatty acids themselves. Often these fatty acids will be released from cell membrane phospholipids prior to their conversion to the bioactive mediators. Cells involved in the inflammatory response are typically rich in the *n*-6 fatty acid arachidonic acid which is a precursor to inflammatory eicosanoids. The membrane contents of arachidonic acid and of the *n*-3 fatty acids EPA and DHA can be altered through oral administration of EPA and DHA. EPA also gives rise to eicosanoids and these often have differing properties from those of the arachidonic acid-derived analogues, typically being less potent. EPA and DHA give rise to resolvins, and DHA to protectins which are anti-inflammatory and inflammation resolving. These relatively recently discovered mediators provide a novel mechanism by which *n*-3 PUFA can influence inflammatory processes. As a result of their anti-inflammatory actions *n*-3 PUFA may have therapeutic efficacy in inflammatory diseases. This is well described in rheumatoid arthritis, but less so in other inflammatory conditions. Currently the multiple mechanisms of action of fatty acids on inflammation are not fully integrated, but it seems likely that alterations in membrane composition are a key event since such alterations can influence lipid mediator profiles, membrane receptor function and cell signalling processes. Future work will focus on defining the membrane structure–function interaction that is associated with different fatty acid compositions and on describing the biosynthesis and actions of novel lipid mediators like resolvins and protectins and mechanisms that underlie their effects.

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