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Review

Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance☆

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ABSTRACT

Inflammation is a condition which contributes to a range of human diseases. It involves a multitude of cell types, chemical mediators, and interactions. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 (n−3) fatty acids found in oily fish and fish oil supplements. These fatty acids are able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and leukocyte–endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n−6 fatty acid arachidonic acid, production of inflammatory cytokines, and T-helper 1 lymphocyte reactivity. In addition, EPA gives rise to eicosanoids that often have lower biological potency than those produced from arachidonic acid and EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, protectins and maresins. Mechanisms underlying the anti-inflammatory actions of marine n−3 fatty acids include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B so reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor γ and binding to the G protein coupled receptor GPR120. These mechanisms are interlinked, although the full extent of this is not yet elucidated. Animal experiments demonstrate benefit from marine n−3 fatty acids in models of rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and asthma. Clinical trials of fish oil in RA demonstrate benefit, but clinical trials of fish oil in IBD and asthma are inconsistent with no overall clear evidence of efficacy. This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".

1. Introduction

1.1. Inflammation: an overview

Inflammation is a key part of the host's defence mechanism against pathogenic organisms. Inflammation creates an environment that is hostile to pathogens, it initiates pathogen killing, and it induces changes of metabolism in the host. The inflammatory response involves interactions amongst many cell types and the production of, and responses to, a vast number of chemical mediators. Key early steps in the inflammatory response are an increased supply of blood to the site of inflammation and an increase in vascular wall permeability that permits plasma and large molecules to cross the endothelium, so delivering soluble mediators to the site of inflammation. Leukocytes migrate from the blood stream into the surrounding tissue, a process promoted by release of chemoattractants from the site of inflammation and by the up-regulation of adhesion molecules on the endothelium. These newly arrived and activated leukocytes then release chemical mediators at the site of inflammation. These mediators may include lipid-derived mediators (e.g. prostaglandins (PGs), leukotrienes (LTs), endocannabinoids,

Abbreviations: AEA, arachidonoyl ethanolamide; 2-AG, 2-arachidonoylglycerol; ARA, arachidonic acid; CB, endocannabinoid receptor; COX, cyclooxygenase; DHA, docosahexaenoic acid; DP, prostaglandin D receptor; DPA, docosapentaenoic acid; EP, prostaglandin E receptor; EPA, eicosapentaenoic acid; GP130, glycoprotein 130; IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; IκB, inhibitory subunit of nuclear factor κB; IL, interleukin; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; MyD88, myeloid differentiation primary response gene 88; NFκB, nuclear factor κB; NSAIDs, non-steroidal anti-inflammatory drugs; PAF, platelet-activating factor; PG, prostaglandin; PPAR, peroxisome proliferator activated receptor; RA, rheumatoid arthritis; RXR, retinoid X receptor; Th1, T-helper 1; Th2, T-helper 2; Th-17, T helper 17; TLR, toll-like receptor; TNF, tumour necrosis factor; TX, thromboxane; VCAM, vascular cell adhesion molecule

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platelet activating factor (PAF)), peptide mediators (e.g. cytokines, chemokines), reactive oxygen species (e.g. superoxide anion, hydrogen peroxide), amino acid derivatives (e.g. histamine, nitric oxide) and enzymes (e.g. matrix proteases) depending upon the cell type involved, the nature of the inflammatory stimulus, the anatomical site involved, and the stage during the inflammatory response. This influx of cells into the site of inflammatory activity and the presence of the inflammatory mediators produced as a result generate the cardinal signs of inflammation: redness, swelling, heat, pain and loss of function.

The cellular activities involved in the inflammatory response and the chemical mediators produced, although designed to be damaging to pathogens, can cause damage to host tissues. However, inflammation is normally self-limiting and resolves, often rapidly, due to the activation of negative feedback mechanisms like secretion of anti-inflammatory cytokines or pro-resolving lipid mediators, inhibition of pro-inflammatory signalling cascades, shedding of receptors for inflammatory mediators, and activation of regulatory cells. Loss of these regulatory processes can result in excessive, inappropriate or on-going inflammation that can cause irreparable damage to host tissues. As a result, inflammation may become pathological and disease can occur (Table 1). In some cases, such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD) and asthma, the central role of inflammation to the pathology is well recognized: individuals with these conditions have heavy infiltration of inflammatory cells at the site of disease activity (e.g. the joints, the intestinal mucosa, the lungs), they have elevated concentrations of inflammatory mediators at those sites and in the systemic circulation, and they are treated with anti-inflammatory drugs. In other cases, such as atherosclerosis and obesity, the role of inflammation has emerged more recently and its contribution to the pathology alongside the many other factors involved is less clear. Certainly, individuals with these conditions show infiltration of inflammatory cells at the site of disease activity (e.g. the blood vessel wall, adipose tissue), and have moderately elevated concentrations of inflammatory mediators in the systemic circulation, but they are not treated, primarily, with anti-inflammatory drugs.

This article will describe the actions of marine omega-3 (n−3) fatty acids within the inflammatory system, the mechanisms involved, and the attempts to use these fatty acids to help treat diseases with an inflammatory component. This article is updated and extended from previous reviews on the topic [1,2].

Table 1
Some diseases and conditions with an inflammatory component.

Disease/condition
Rheumatoid arthritis
Crohn's disease
Ulcerative colitis
Lupus
Type-1 diabetes
Cystic fibrosis
Childhood asthma
Adult asthma
Allergic disease
Chronic obstructive pulmonary disease
Psoriasis
Multiple sclerosis
Atherosclerosis
Cancer
Obesity
Non-alcoholic fatty liver disease
Neurodegenerative diseases of ageing
Cachexia
Acute cardiovascular events
Response to surgery, injury, trauma and critical illness

1.2. Marine n−3 fatty acids — an overview

Omega-3 (ω−3 or n−3) fatty acids are a family of polyunsaturated fatty acids characterised by having the last double bond between carbon numbers 3 and 4 in the hydrocarbon (acyl) chain counting the terminal methyl carbon as number one. Longer chain n−3 fatty acids include eicosapentaenoic acid (EPA; 20:5n−3), docosapentaenoic acid (DPA; 22:5n−3) and docosahexaenoic acid (DHA; 22:6n−3). Although EPA, DPA and DHA can be synthesised from simpler plant-derived n−3 fatty acids (Fig. 1), this metabolic pathway does not appear to be very efficient in many humans [3]. It is not possible to fully consider the roles of marine n−3 fatty acids within inflammatory processes without considering also the roles of saturated and n−6 fatty acids. Saturated fatty acids are fatty acids without double bonds in their hydrocarbon chain, while n−6 fatty acids are a family of polyunsaturated fatty acids characterised by having the last double bond between carbon numbers 6 and 7 in the hydrocarbon chain counting the terminal methyl carbon as number one. Within inflammation the major n−6 fatty acid is arachidonic acid (ARA; 20:4n−6), which is synthesised from simpler plant-derived n−6 fatty acids in a pathway that competes with the synthesis of EPA (Fig. 1).

EPA, DPA and DHA are found in significant quantities in fish and other seafood, and so they may be collectively referred to as marine n−3 fatty acids. These fatty acids are found in the flesh of both lean and oily fish, with much greater amounts in the latter, and in the livers of some lean fish (e.g. cod). In people who eat little fish, intakes of marine n−3 fatty acids are low (typically <0.2 g/day [4] and probably much lower than this [5]). A single lean fish meal (e.g. one serving of cod) could provide about 0.2 to 0.3 g of marine n−3 fatty acids, while a single oily fish meal (e.g. one serving of salmon or mackerel) could provide 1.5 to 3.0 g of these fatty acids. Fish oil is prepared from the flesh of oily fish (e.g. tuna) or from the livers of lean fish (e.g. cod liver). In a typical fish oil supplement EPA and DHA together comprise about 30% of the fatty acids present, so that a 1 g fish oil capsule will provide about 0.3 g of EPA + DHA. More concentrated oils are also available. In fish and in traditional fish oil supplements most of the fatty acids are present as components of triacylglycerols. Marine n−3 fatty acids are also available in other forms such as in krill oil, which provides EPA and DHA partly in the form of phospholipids, and as ethyl esters in pharmaceutical grade, highly concentrated preparations.

2. Marine n−3 fatty acids and the fatty acid composition of the phospholipids in the membranes of cells involved in inflammation

It is generally considered that the influence of fatty acids on inflammatory cell responses, and so on inflammatory processes, involves their incorporation into cell membrane phospholipids [6]. Hence there has been much interest in the fatty acid composition of cells involved in inflammation and how that might change when the intake of marine n−3 fatty acids is increased. Cells like lymphocytes, macrophages or neutrophils taken from laboratory rodents fed standard low fat diets in which the bulk of the fat comes from vegetable oil have high amounts (often ~20% of total fatty acids) of ARA in their membrane phospholipids and very low amounts of EPA and DHA [7–9]. Inclusion of EPA or DHA or both in the diets fed to laboratory rats or mice results in increased amounts of those fatty acids in phospholipids of lymphocytes, macrophages and neutrophils [9,10]. Phospholipids of blood cells involved in inflammatory processes taken from humans consuming a typical Western diet typically contain 15 to 20% of fatty acids as ARA, 0.5 to 1% as EPA and 2 to 3% as DHA [11–22]. Increased intake of marine n−3 fatty acids results in increased amounts of EPA and DHA (and also DPA) in these phospholipids [11–22]. In both animal and human experiments incorporation of marine n−3 fatty acids into membrane phospholipids of cells involved in inflammation occurs in a time- [15–22] and dose-dependent fashion [16,20,22] and is largely at the expense of ARA

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