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Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease

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ABSTRACT

Omega-3 (n−3) polyunsaturated fatty acids (n−3 PUFAs) have well documented anti-inflammatory properties, and consequently therapeutic potential in chronic inflammatory diseases. Here we discuss the effects of n−3 PUFAs on various inflammatory pathways and how this leads to alterations in the function of inflammatory cells, most importantly endothelial cells and leukocytes. Strong evidence indicates n−3 PUFAs are beneficial as a dietary supplement in certain diseases such as rheumatoid arthritis; however for other conditions such as asthma, the data are less robust. A clearer understanding of the pharmacology of n−3 PUFAs will help to establish targets to modulate chronic inflammatory diseases.

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Contents

1. Introduction

1.1. Omega-3 polyunsaturated fatty acids (n−3 PUFAs)

Fatty acids are carboxylic acids with a variable number of carbons atoms forming a hydrocarbon chain terminated by carboxyl and methyl groups (Fig. 1). The chains vary in length from two, to greater than thirty carbon atoms and exist in either saturated (no double bonds between adjacent carbon atoms), monounsaturated (one double bond) or polyunsaturated (more than one double bond) forms. Fatty acids have both systematic and common names. They are also described by a nomenclature which includes the number of carbon atoms in the chain (including the terminal carbons), the number of double bonds in the chain, and the location of the first double bond in the chain from the terminal methyl group, known as the 'n' or 'ω' carbon. For example, arachidonic acid (AA) is shown as 20:4n−6 using this nomenclature, thus describing a molecule with 20 carbon atoms in the chain, four double bonds, with the first double bond at the 6th carbon from the methyl terminus. This nomenclature enables discrimination of different families of polyunsaturated fatty acids (PUFAs) based on the position of the first double bond in the chain, i.e. n−3 and n−6 PUFAs (Ratnayake & Galli, 2009).

In this review we will focus on the biological effects of the so called marine n−3 PUFAs, eicosapentaenoic acid (EPA; 20:5n−3) (Fig. 1A) and docosahexaenoic acid (DHA; 22:6n−3) (Fig. 1B). In mammals, EPA and DHA can be synthesised from the dietary precursor and essential fatty acid, α-linolenic acid (ALA; 18:3n−3). Synthesis requires a

Abbreviations: AA, Arachidonic acid; ALA, alpha-linolenic acid; CD, Crohn's disease; COX, cyclooxygensae; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EC, endothelial cells; EPA, eicosapentaenoic acid; FFA, free fatty acids; IBD, inflammatory bowel diseases; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LA, linoleic acid; LOX, lipoxygenase; LT, leukotrienes; LX, lipoxin; n−3 PUFAs, omega-3 polyunsaturated fatty acids; NPD, neuroprotectin; PBMC, peripheral blood mononuclear cell; PD, protectin; PG, prostaglandin; PI, phosphatidylinositol; RA, rheumatoid arthritis; RCT, randomised controlled trial; Rv, resolvin; SPM, specialised pro-resolving mediators; TNF, tumour necrosis factor; UC, ulcerative colitis; VCAM-1, vascular cell adhesion molecule-1.

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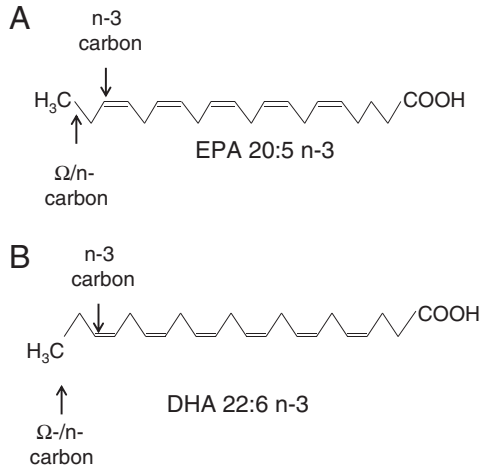

Fig. 1. *Schematic structure of the n−3 PUFAs EPA and DHA.* **A.** EPA has 20 carbons and 5 double bonds; **B.** DHA has 22 carbons and has 6 double bonds. In both fatty acids the first double bond occurs at the third carbon from the ω/n-end of the chain.

number of elongation and desaturation steps and is inefficient in humans. This makes dietary intake of pre-formed EPA and DHA a more effective route of assimilation. EPA and DHA in the human diet are derived indirectly from marine algae (higher plants lack the enzymes for their biosynthesis). Their availability is dramatically increased as they pass up the food chain, becoming concentrated in the flesh of marine fish. Both EPA and DHA are present in high amounts in the flesh of oily fish e.g. herring, mackerel and salmon, and they are the main PUFAs in fish oil supplements. Indications of the efficacy of these fatty acids as dietary interventions for chronic inflammatory disease originated from epidemiological studies conducted on populations of Greenland Inuits, native Alaskans and the residents of Okinawa, Japan. These studies uniformly showed a relationship between the burden of chronic disease and life style, with the consumption of high levels of n−3 PUFAs being common to all of the study populations (Dyerberg et al., 1978; Kromann & Green, 1980; Kagawa et al., 1982; Newman et al., 1993). Thus, the postulate that dietary marine n−3 PUFAs may be protective against chronic inflammatory diseases, in particular cardiovascular disease (CVD), was engendered. Since these initial studies, much research has been carried out to confirm this relationship and to investigate the efficacy of n−3 PUFAs, in other disease states with a chronic inflammatory component such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD) and asthma. Here we describe inflammation and the mechanisms by which EPA and DHA can modify inflammatory responses, and the relevance of this to chronic inflammatory diseases.

1.2. Inflammation

Inflammation is a physiological response to infection or injury characterised by five classical signs described by Celsus and Galen in antiquity, i.e. pain, heat, redness, swelling and loss of function. The overriding purpose of an acute, resolving inflammatory response is to protect the body from invasion and damage and to re-establish physiological homeostasis. Following infection, for example, inflammatory mediators with vasodilatory capacity increase blood flow, thereby causing redness and heat, and vessels also become more permeable leading to oedema (swelling). Sensitivity to pain is increased in response to agents such as bradykinin (Kenji, 2007). A major function of the inflammatory response is to deliver the molecular and cellular mediators of immunity to affected tissues. Thus, the concentration of plasma borne agents such as complement increases due to changes in vascular permeability. Leukocytes are recruited by appropriately activated vascular endothelial cells (EC) which support a tightly regulated series of events termed the leukocyte adhesion cascade (Ley et al., 2007) (Fig. 2). In response to stimulation by inflammatory cytokines, or agents such as histamine, leukocytes are captured from flowing blood by specialised receptors of the selectin and immunoglobulin super families (IgSF). These molecules also permit a form of dynamic adhesion termed 'rolling', during which the velocity of leukocytes is dramatically reduced in comparison to those being transported in the bulk flow of the blood. Rolling cells are able to assimilate EC borne signals from agents such as chemokines, which stabilise adhesion by activating leukocyte β1- and β2-integrins. Integrin-mediated adhesion to specific counter ligands on the EC surface, in the basement membrane and in stromal tissue support migration of leukocytes across the vascular barrier and towards the inflammatory locus. Once in tissue, leukocytes have powerful cytotoxic and tissue remodelling capabilities which must be tightly regulated, not least because uncontrolled or non-resolving leukocyte recruitment may be pathogenic. Indeed, it has been postulated that chronic inflammation represents a situation where normal programmes of resolution fail, resulting in continual influx of leukocytes into tissue, where their excessive activity results in inappropriate tissue remodelling and ultimately to loss of tissue function (reviewed in McGettrick et al., 2012).

A hallmark of chronic inflammatory disease is the continual infiltration of leukocytes from blood, across activated EC and into the affected tissue. Although the agents that activate EC may show variation in a disease specific manner, in general many of the receptors and mediators induced by these agents are common to the leukocyte recruitment cascade (Fig. 2). It is thus probable that n−3 PUFAs can regulate the magnitude, and possibly the identity, of the leukocytic infiltrate, in a range of inflammatory conditions by regulating aspects of EC activation generic to the inflammatory process. It is important to appreciate that studying the effects of n−3 PUFAs on EC function in the context of leukocyte recruitment is difficult in vivo. Indeed most of the data available to date have been generated in vitro using cultured cells with the addition of free fatty acids (FFA) to culture medium as a source of supplementary lipids. However, the significance of some of these studies must be questioned due the concentrations of FFA used. Physiologically, n−3 PUFAs are found in the blood plasma as FFA at concentrations less than 1 μM (Cawood et al., 2010) (but at higher concentrations in esterified forms such as triglycerides and phospholipids) and many supplementation regimens do not greatly increase the levels of the FFA. Most in vitro studies which investigate mechanisms of n−3 PUFA action utilise free n−3 PUFAs at concentrations 10–100 fold higher than this which may equate to total plasma concentrations of n−3 PUFAs achievable with supplementation. However, this does not account for the fact that the majority of circulating n−3 PUFAs are transported in esterified form within lipoprotein particles which do not have the same profile of bioavailability as FFA. This is an important point, as in our own experiments, n−3 PUFAs as FFA at concentrations of 10 μM or above induce non-specific calcium transients in cells such as neutrophils (unpublished observation; Yates & Rainger). Thus, we routinely utilise free fatty acid at sub-μM concentrations and do not normally exceed 5 μM, as we feel that this represents the maximal ceiling of free n−3 PUFA levels achievable in vivo with oral supplementation.

1.3. Polyunsaturated fatty acid-derived molecules as mediators of the inflammatory response

Dietary fatty acids are intimately linked with the inflammatory response, For example the n−6 PUFA, AA, is the main precursor of several important lipid mediators. AA can be derived directly from the diet (Jonnalagadda et al., 1995) but like the n−3 PUFAs, it can also be synthesised through a series of desaturation and elongation reactions from the essential fatty acid linoleic acid (LA; 18:2-n−6). AA from the diet or after synthesis is stored in membrane phospholipids, e.g. phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI), mainly at the sn2 position and is liberated under appropriate stimulatory conditions by the enzyme phospholipase A_2 (PLA_2). Phospholipase C (PLC) is also able to release AA specifically from PI via a series of reactions involving the formation of diacylglycerol (DAG) by the enzyme DAG

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