NEWS AND VIEWS

Current choices in omega 3 supplementation

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Summary

Our understanding of the significant role that long-chain fatty acids play in maintaining health and deterring the progression of disease is rapidly expanding. Much attention has been drawn to the benefits of increasing *n*-3 (omega-3) fatty acids in the diet, either through direct fortification of foodstuffs, or through supplementation. However, it is clear that there is some confusion among the general public as to the benefits of foods fortified with short-chain *n*-3 fatty acids compared with long-chain fatty acids and, indeed, over the role omega 3 fatty acids play in homeostasis. With the supplement market growing quickly and the general public seemingly increasingly 'health-conscious', emphasis should be focused upon educating the public more thoroughly about the biological roles that these fats play. Modern changes in our diet and the current general consensus that the UK is not an 'oily fish-loving' nation mean that many individuals run the risk of consuming insufficient amounts of the long-chain *n*-3 fatty acids for optimal function of the cardiovascular, immune and inflammatory systems. While supplementation is an easy way of modifying fatty acid intake, the quality of many cheaper products favoured by the public as the 'value for money' option are unlikely to offer the same health benefits as those that are molecularly distilled to exclude impurities and maximise concentrations of the active ingredients eicosapentaenoic acid and docosahexaenoic acid. This paper discusses the need for the public to be aware of the variation in the quality and dosage of *n*-3 supplements, delineates some of the vegetarian alternatives to fish-derived products and also discusses the potential role that General Practitioners may play in educating their patients about the possible long-term benefits of such products.

Introduction

Burr and Burr's (1929) discovery of the essential fatty acids *n*-6 (omega-6) linoleic acid and *n*-3 α-linolenic acid opened the doors to a greater understanding of the role fatty acids play in health and disease. Desaturation and elongation of these dietary precursor fatty acids are required for the synthesis of the long-chain polyunsaturated fatty acids (PUFAs) (Fig. 1) that comprise the framework for cell membranes, ensuring fluidity and therefore regulation of efficient cellular communication. The long-chain PUFAs are also precursors of eicosanoids, 'hormonal' molecules which exert opposing effects on the regulation of immunity, platelet aggregation and inflammation (Fig. 2). The *n*-3 fatty acids have strong anti-inflammatory effects, whereas *n*-6 fatty acids tend to be pro-inflammatory. Consumption of meat from land-based animals fed grains high in *n*-6 fatty acids and increased use of vegetable oils such as corn, sunflower and safflower has led to a rise in *n*-6 fatty acids intakes in the UK, whilst *n*-3 intake has declined. The subsequent rise in the ratio of dietary

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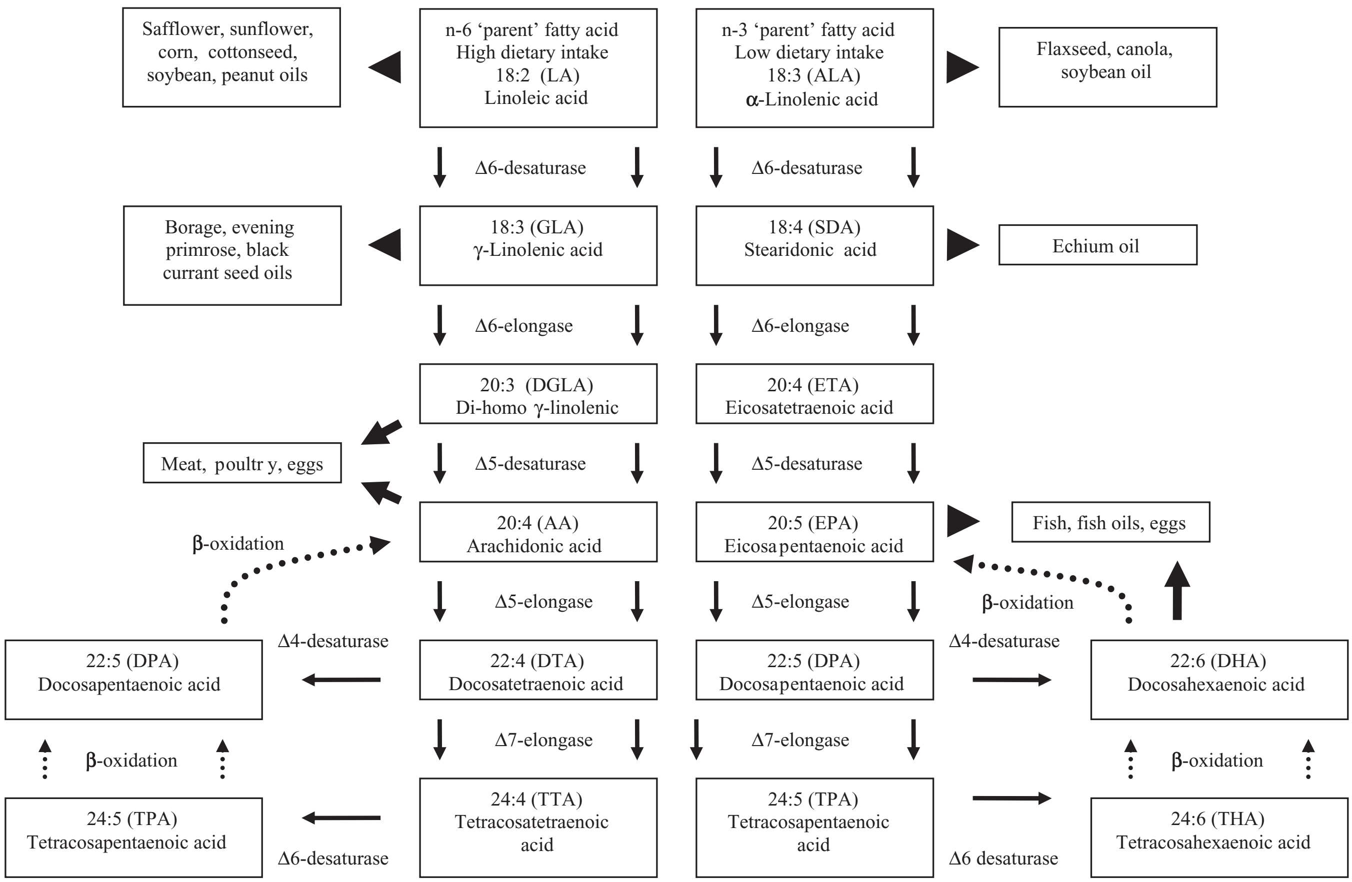

Figure 1 Metabolic pathway for *n*-6 and *n*-3 fatty acids with their corresponding dietary sources.

intake of *n*-6 and *n*-3 fatty acids has been suggested to have implications for a wide range of health conditions (Simopoulos 2006). However, the fact that our *n*-6 intake at a population level in the UK is not above the recommended daily intake from the Department of Health suggests that efforts should focus on boosting our omega 3 intake rather than reducing our *n*-6 intakes (Lunn & Theobald 2006).

Oily fish consumption as a direct source of long-chain *n*-3 fatty acids has many well-documented health benefits, stemming from epidemiological observations of the low incidence of cardiovascular, inflammatory and autoimmune disorders in Greenland Eskimos (Kromann & Green 1980). The significance of the benefits of long-chain *n*-3 fatty acids derived from fish and fish oils upon health and disease progression has since been well reviewed (Simopoulos 2003; Das 2008). In addition, reductions in cardiovascular risk, depression and rheumatoid arthritis symptoms have been correlated with long-chain *n*-3 fatty acid intake, and there is increased interest in the effect of *n*-3 fatty acid intake in relation to other psychiatric illnesses and prevention of Alzheimer's disease.

Restrictions for long-chain fatty acid synthesis

The *n*-6 and *n*-3 fatty acid families share and compete for the same enzymes involved in their biosynthesis. Delta-6 desaturase is the rate-limiting step in the synthesis of the long-chain fatty acids and decreased activity of this enzyme occurs in ageing, stress, diabetes, eczema and some infections (Horrobin 1993). In addition, various dietary and lifestyle factors can impair synthesis including a high intake of saturated, hydrogenated or 'trans' fatty acids, lack of vitamin and mineral co-factors (particularly zinc, magnesium and vitamins B3, B6 and C), smoking and heavy use of alcohol or caffeine. Genetic variations in the rate at which these enzymes convert the short-chain PUFAs into longer-chain PUFAs also mean that individuals require different amounts of dietary PUFAs. Direct dietary consumption

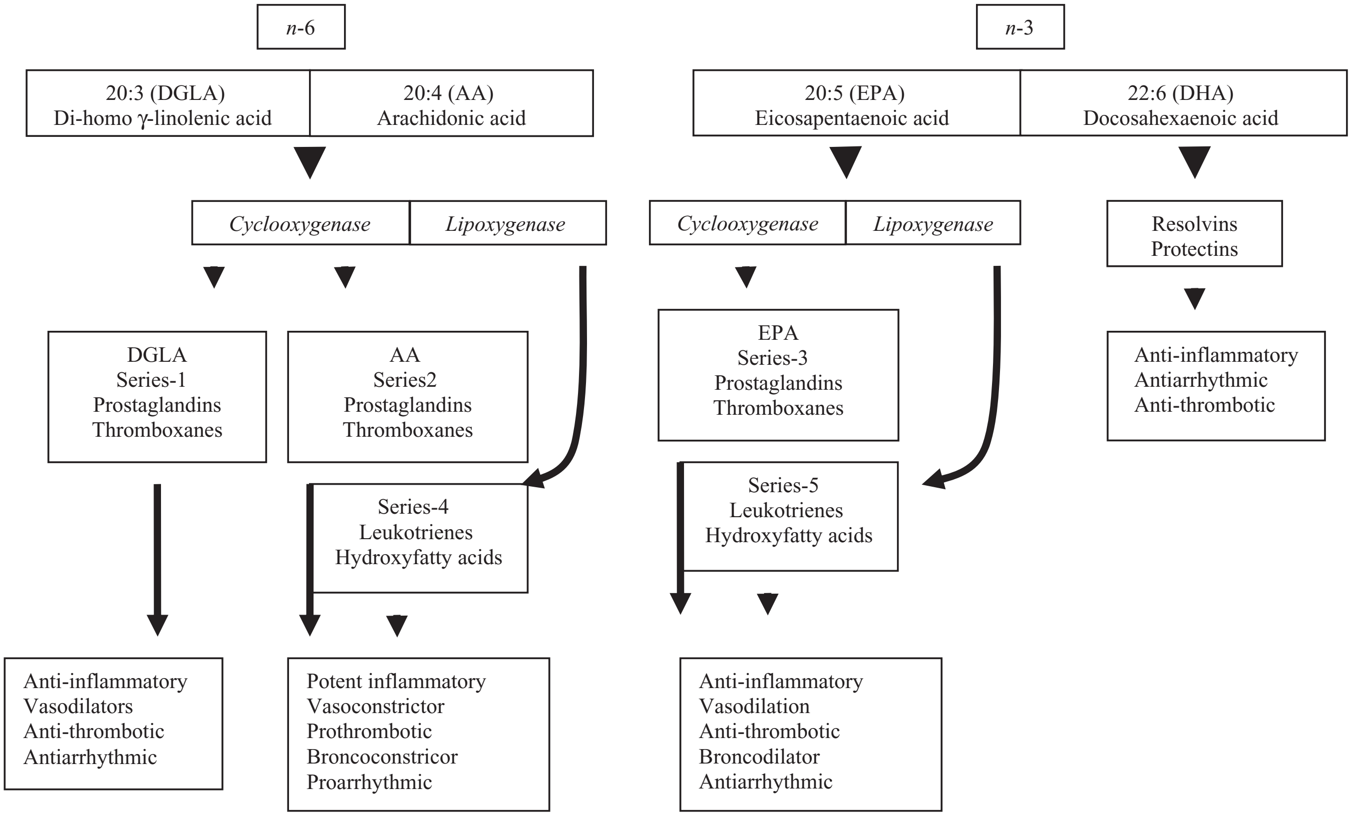

Figure 2 Pathways in the biosynthesis of eicosanoids from arachidonic acid (AA) di-homo γ-linolenic acid (DGLA) and eicosapentaenoic acid (EPA) with their related physiological functions.

of these long-chain PUFAs, through fish or fish oil supplements, may be necessary to achieve the biological effects required for homeostasis (Koletzko *et al.* 2008).

Oily fish consumption as a source of long-chain *n*-3 fatty acids

The flesh of oily fish such as salmon, sardines, anchovies, pilchards and mackerel is rich in the long-chain *n*-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). However, the majority of the UK population does not consume enough oily fish to ensure that dietary levels are met. The most recent government recommendation for consumption was set at two portions of fish per week (a portion is approximately 140 g), of which at least one portion should be oil-rich to provide a daily amount of 450 mg EPA and DHA (SACN/COT 2004).

However, there are concerns associated with fish consumption because of potential contaminants that fish may contain, such as methylmercury, dioxins, polychlorinated biphenyls (PCB) and organic pollutants from industrial processes. While dioxins and PCBs (which are actually found at low levels in all foods) have no immediate effect on health, the potential risks to health come from long-term exposure. The toxicity of dioxins and dioxin-like substances can be expressed as a toxic equivalent (TEQ) set by the World Health Organization (WHO), with the resulting overall concentrations referred to as WHO-TEQs. Current assessments for the tolerable daily intake of dioxins and dioxin-like PCBs are set at 2 pg WHO-TEQ/kg bw/day [with the most recent intake estimates for the UK population at 1.8 pg/kg bw/day for the average consumer and 3.1 pg/kg bw/day for the 97.5 percentile of consumers with a high-level fish intake (SACN/COT 2004)].

Those fish that sit higher in the food chain (*i.e.* those that live longer and grow to a greater size) will contain higher levels of contamination. For example, consumption of one portion of shark, swordfish or marlin a week could mean exceeding the guideline intake for methylmercury (0.23 μg/kg bw/day) (Maycock & Benford 2007). Salmon, a popular choice of fish in the UK and a principal source of *n*-3 fatty acids, is a reasonably low source of methylmercury in contrast with tuna which contains considerably higher levels of methylmercury

(Mahaffey *et al.* 2008). Contamination is not restricted to fish, but also includes commonly consumed shellfish species (Fernandes *et al.* 2008). Thus, the individual's choice of fish and shellfish for consumption should be an important consideration when estimating exposure to potential contaminants. Interestingly, while fresh tuna is an oil-rich fish, the oil is removed during the canning process so canned tuna has little impact on EPA and DHA status, although undesirable pollutants still remain. This fact is not generally well known among the general public. The Food Standards Agency (FSA) therefore advises pregnant and breastfeeding women, and women who intend to become pregnant, to limit their consumption of tuna to no more than two medium-sized cans or one fresh tuna steak per week. These women are also advised to avoid eating shark, swordfish and marlin (SACN/COT 2004).

Ideally, fish consumption should be the first choice for obtaining long-chain fatty acids, as the *n*-3 fatty acids from fish are more effectively incorporated into plasma lipids than when administered in capsule form (Visioli *et al.* 2003). Fish also provide a range of other important nutrients. However, as a result of the UK population's apparent dislike for oily fish and concerns over the potential accumulation within the body of detrimental toxins associated with eating fish, consumption of purified fish oils may well provide an alternative. Analysis of contamination levels of commercially available fish oil supplements sourced from retail outlets in the UK suggest a downward trend in the levels of dioxins in fish oil supplements over the last decade (Fernandes *et al.* 2006). Thus, purified fish oil supplements may provide a 'safer' alternative to oily fish consumption for the apprehensive individual or for those who simply do not have the palate for oily fish or shellfish.

Alternative options to fish oils

Increasing concerns regarding the sustainability of fish stocks and the subsequent effect on the fish oil industry is stimulating considerable research into other ways of incorporating the long-chain fatty acids associated with fish oils into the food chain. The European Union-funded project *Lipgene* is one such example. This project, completed in January 2009, looked at inserting genes from marine algae and encoding the synthesis of long-chain fatty acids into rapeseed, in a bid to produce an alternative, sustainable source of dietary omega-3. For more information about *Lipgene*, see Caswell (2009). The feasibility of using transgenic plants to synthesise fish oils as a sustainable alternative source of long-chain *n*-3 PUFA is currently under investigation. Fish, like humans, are not capable of synthesising long-chain PUFA and thus acquire their long-chain fatty acids from feeding on algae. Introducing the genes from marine algae into a plant host would enable the synthesis and accumulation of these fatty acids in the plants (Napier 2007). However, with current attitudes to genetically modified foods, it is difficult to judge how the public would accept such an alternative. Genetically modified foods have attracted a large amount of media attention with specific areas of concern targeted at risk to the environment and risk to human health. Before introducing fish oils derived from genetic modification of plants into the human food chain, the general public would have to be educated as to the advantages and disadvantages such technology has to offer.

In contrast, microalgae-derived *n*-3 fatty acids tend to have high levels of DHA and algal-oil DHA capsules represent a safe and convenient source of non-fish-derived DHA with accumulation in plasma phospholipids shown in humans (Arterburn *et al.* 2008). The recent application to the FSA's Advisory Committee on Novel Foods and Processes to extend the use of algal-oil DHA directly into the food chain may be a useful tool to indirectly boost long-chain fatty acid levels. However, concerns about how this will affect EPA levels need to be considered. High concentrations of pure DHA are needed to induce retroconversion and therefore the accumulation of EPA into plasma phospholipids (von Schacky & Weber 1985). While feeding pure EPA leads to the formation of other long-chain *n*-3 including DHA by elongation and desaturation, supplementing with pure DHA but at low levels can lead to exclusive accumulation of this *n*-3 fatty acid because retroconversion is a minor metabolic pathway (Sprecher *et al.* 1995). Feeding DHA only may therefore have detrimental consequences. For example, while DHA is important in the structure of neuronal membranes and EPA plays little or no structural role in the brain, it is essential for the regulation of brain function via its eicosanoid derivatives, such as prostaglandins, leukotrienes and thromboxanes.

Vegetarians and particularly vegans are typically found to have low levels of EPA and DHA in comparison with fish-eating populations (Rosell *et al.* 2005). In these cases, while α-linolenic acid (ALA) supplementation such as flaxseed oil increases plasma EPA, there is little effect on DHA and levels of both are still significantly lower than those of fish eaters. The recent approval of refined echium oil as a novel food ingredient is going to be of particular significance to those individuals who choose to avoid consuming fish or fish oil supplements. Unlike flaxseed oil, echium oil, derived from the seed of the plant *Echium plantagineum*, provides a rich source of *n*-3 stearidonic acid (SDA), the precursor of the long-chain fatty acid EPA normally found in fish oils (Fig. 1). SDA appears to inhibit many aspects of inflammation and exerts beneficial effects on coronary heart disease risk factors in a similar way to conventional fish oils (Guichardant *et al.* 1993; Ishihara *et al.* 2002; Surette *et al.* 2004; Horia & Watkins 2005). Dietary SDA, unlike ALA, can raise both EPA and DHA concentrations (Yamazaki *et al.* 1992; Miles *et al.* 2004a). Interestingly, SDA in combination with γ-linolenic acid, raises red blood cell EPA levels more efficiently than SDA alone (Miles *et al.* 2004b), making echium oil a useful source of anti-inflammatory precursors for those who do not consume oily fish or fish supplements.

If taking a supplement, what dosage is required?

The supplement market is saturated with a wide variety of products of which the average content appears to be 180 mg EPA and 120 mg DHA in 1000 mg fish oil. However, research uncovering the unique individual biological properties of DHA and EPA has given rise to high quality supplements containing pure EPA with no DHA and vice versa. These products tend to have much higher concentrations of pure EPA or DHA and hence the price of the product is often much higher than the average mainstream product. While there are health benefits attributed to supplementing the diet with fish oils, the dosages needed to exert biological changes within the body are much higher than levels typically consumed. For example, the dose of long-chain *n*-3 PUFA required for a beneficial effect on cardiovascular risk factors has shown to be around 1–1.5 g per day for reducing blood pressure (Geleijnse *et al.* 2002) and platelet aggregation (Hornstra 2001), with doses as high as 2–4 g per day needed to treat hypertriglyceridaemia (McKenney & Sica 2007). In relation to inflammatory bowel disease, one study of 5.36 g of fish oil decreased leukotriene B4 levels in ulcerative colitis (Stenson *et al.* 1992), whereas 2.7 g of fish oil preparation reduced the rate of relapse in patients with Crohn's disease in remission (Belluzzi *et al.* 1996, 1997; Endres *et al.* 1999). The use of fish oil as an alternative treatment to non-steroidal anti-inflammatory drugs (NSAIDs) in rheumatoid arthritis has been widely investigated and in a recent study a daily intake of 10 g (2.2 g of *n*-3) of cod liver oil was shown to reduce the daily NSAID requirement by more than a third in 39% of patients with rheumatoid arthritis (Galarraga *et al.* 2008). With regard to major depression and bipolar disorder, however, it appears that a relatively low dose of 1 g of ethyl-EPA per day may be more effective than higher doses (Peet & Horrobin 2002; Frangou *et al.* 2006; Keck *et al.* 2006; Jazayeri *et al.* 2008), although further research in this area is needed. With the current dispute over the benefits of anti-depressants (Kirsch *et al.* 2008; McAllister-Williams 2008), possible alternative approaches are being investigated. Further consideration of the role of *n*-3 fatty acids in neurological disorders is therefore warranted.

Are quality supplements only affordable to the rich?

If the benefits offered by natural supplements can equal those provided by pharmaceutical drugs, why is consumption of highly purified quality oils as a preventative measure, not recommended more by General Practitioners (GPs)? The answer, in part, is that while there is increasing scientific evidence that appears to support health benefits, very few products have Medicines and Healthcare Products Regulatory Agency approval for making health claims on product labels.

Individuals of lower socio-economic status (based on family income, parental education level, parental occupation and social status in the community) tend to be at greater risk of poor health (Steptoe *et al.* 2007; Cohen *et al.* 2008; Pollitt *et al.* 2008), partly because of differences in dietary intake compared with those on higher incomes. Owing to the possibly limited budget of those of low socio-economic status, they may be less willing to purchase better quality supplements – not only because of a possible lack of understanding of the differences between the types of *n*-3 supplements, but also because of the cost of purchasing what is considered to be a luxury – especially where cheaper, seemingly equivalent, alternatives are readily available. The endorsement of EPA/DHA by the National Institute for Health and Clinical Excellence and the availability of good quality *n*-3 for prescription on National Health Service are needed to help encourage GPs to consider *n*-3 fatty acids as a possible option when treating disease, and may also help in making available premium supplements for those whose financial situation cannot permit such investment. Further, the Parliamentary Food and Health Forum has recently called for the Scientific Advisory Committee on Nutrition to define further the optimum intake of *n*-3 PUFAs at different stages of life, especially for pregnant women and children (FHF 2007). Until the 1950s, fish oils were routinely given to children, which begs the question: is it prudent, therefore, to return to such a practice to ensure the long-term health of the next generation?

Conclusion

While environmental and genetic factors play a role in disease onset, progression can also be influenced by diet and lifestyle. Substantial research is needed to clarify the role that long-chain fatty acids play in health and disease to enable the public to modulate their diet accordingly. The use of supplements and the attempts to fortify foodstuffs could play an important role in improving our intake of *n*-3 fatty acids, at least in some groups. Making high-quality supplements more available to those subgroups of the population who may not normally be able to afford them, and may be likely to benefit most from them, could help individuals to achieve optimal health.

Conflict of Interest

Igennus Ltd provided financial support for the writing of this paper. However, the views expressed are those of the authors alone.

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