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Therapeutic potential of omega-3 fatty acid-derived epoxyeicosanoids in cardiovascular and inflammatory diseases

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ABSTRACT

Numerous benefits have been attributed to dietary long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs), including protection against cardiac arrhythmia, triglyceride-lowering, amelioration of inflammatory, and neurodegenerative disorders. This review covers recent findings indicating that a variety of these beneficial effects are mediated by "omega-3 epoxyeicosanoids", a class of novel n-3 LC-PUFA-derived lipid mediators, which are generated via the cytochrome P450 (CYP) epoxygenase pathway. CYP enzymes, previously identified as arachidonic acid (20:4n-6; AA) epoxygenases, accept eicosapentaenoic acid (20:5n-3; EPA) and docosahexaenoic acid (22:6n-3; DHA), the major fish oil n-3 LC-PUFAs, as efficient alternative substrates. In humans and rodents, dietary EPA/DHA supplementation causes a profound shift of the endogenous CYP-eicosanoid profile from AA- to EPA- and DHA-derived metabolites, increasing, in particular, the plasma and tissue levels of 17,18-epoxyeicosatetraenoic acid (17,18-EEQ) and 19,20-epoxydocosapentaenoic acid (19,20-EDP). Based on preclinical studies, these omega-3 epoxyeicosanoids display cardioprotective, vasodilatory, anti-inflammatory, and anti-allergic properties that contribute to the beneficial effects of n-3 LC-PUFAs in diverse disease conditions ranging from cardiac disease, bronchial disorders, and intraocular neovascularization, to allergic intestinal inflammation and inflammatory pain. Increasing evidence also suggests that background nutrition as well as genetic and disease state-related factors could limit the response to EPA/DHA-supplementation by reducing the formation and/or enhancing the degradation of omega-3 epoxyeicosanoids. Recently, metabolically robust synthetic analogs mimicking the biological activities of 17,18-EEQ have been developed. These drug candidates may overcome limitations of dietary EPA/DHA supplementation and provide novel options for the treatment of cardiovascular and inflammatory diseases.

1. Introduction

The oxidative metabolism of polyunsaturated fatty acids (PUFAs) to bioactive lipid mediators is initiated by cyclooxygenases (COX), lipoxygenases (LOX), and, as discovered most recently, also by cytochrome P450 (CYP) enzymes (Gabbs, Leng, Devassy, Monirujjaman, & Aukema, 2015). Drugs targeting the formation and action of COX- and LOX-derived prostanoids and leukotrienes are

Abbreviations: 15-PGDH, 15-hydoxyprostaglandin dehydrogenase; AA, arachidonic acid; AF, atrial fibrillation; AKI, acute kidney injury; Akt, alpha serine/threonine-protein kinase; ALA, alpha-linolenic acid; AMD, age-related macular degeneration; Ang II, angiotensin II; BK, large-conductance calcium-activated potassium channel; BP, blood pressure; CF, cystic fibrosis; CHD, coronary heart disease; Cif, cystic fibrosis transmembrane conductance regulator inhibitory factor; CNV, choroidal neovascularization; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CVD, cardiovascular disease; CYP, cytochrome P450; DHA, docosahexaenoic acid; DHET, dihydroxyeicosatrienoic acid; DiHDPA, dihydroxydocosapentaenoic acid; DiHETE, dihydroxyeicosatetraenoic acid; DiHOME, dihydroxyoctadecenoic acid; EDP, epoxydocosapentaenoic acid; EEQ, epoxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acid; EPA, eicosapentaenoic acid; EPHX2, gene encoding sEH; EpOME, epoxyoctadecenoic acid; FADS, fatty acid desaturase; GPCR, G protein-coupled receptor; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HO-1, heme oxygenase 1; I/R, ischemia-reperfusion; K(ATP), ATP-sensitive potassium channel; LA, linoleic acid; LC-MS/MS, liquid chromatography tandem mass spectrometry; LOX, lipoxygenase; LPS, lipopolysaccharide; LTB4, leukotriene B4; LX, lipoxin; MAG, monoacylglycerol; MI, myocardial infarction; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; NO, nitric oxide; NRCM, neonatal rat cardiomyocytes; PGE2S, prostaglandin E2 synthase; PGI2, prostacyclin; PGIS, prostacyclin synthase; PI3K, phosphoinositide 3-kinase; PLA2, phospholipase A2; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RBC, red blood cells; RhoA, Ras homolog gene family, member A; ROCK, Rho-associated protein kinase; SAH, subarachnoid hemorrhage; SCD, sudden cardiac death; sEH, soluble epoxide hydrolase; SPM, specialized pro-resolving mediators; TNFα, tumor necrosis factor alpha; TXA2, thromboxane A2; TXA2S, TXA2 synthase; VSMCs, vascular smooth muscle cells

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already widely used for the treatment of inflammation, pain, asthma, and cardiovascular diseases (Funk, 2001). Prominent examples include non-steroidal anti-inflammatory drugs, prostacyclin analogs, and leukotriene antagonists. In comparison, we are only at the beginning to understand the novel opportunities for drug development based on the emerging role of the CYP-derived PUFA metabolites in the regulation of diverse physiological and pathophysiological processes (Konkel & Schunck, 2011; Spector & Kim, 2015).

This review is aimed at discussing novel insight into the therapeutic potential of the CYP-branch of eicosanoid formation as gained when searching for bioactive lipid mediators that contribute to the health benefits of dietary long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). Accordingly, we will consider first how these two research fields initially developed independently, to then discuss their common scientific questions and goals of clinical application. The following parts of this review will summarize our recent knowledge on omega-3 epoxyeicosanoids, including their CYP epoxygenase-catalyzed generation from n-3 LC-PUFAs, metabolic fate, and biological activities. We will particularly focus on recent preclinical studies that give an idea of the wide range of physiological and pathophysiological processes, in which omega-3 epoxyeicosanoids may directly function as essential and highly potent mediators of the beneficial effects originally attributed to their parental n-3 LC-PUFAs. Finally, we will discuss roads to clinical application based on the recent development of synthetic analogs of omega-3 epoxyeicosanoids.

2. Evidence for and limitations in the therapeutic use of n-3 LC-PUFAs

2.1. The discovery chain

This research field was initiated by the seminal observation in the 1970s of significantly lower myocardial infarction (MI) rates in Greenlandic Inuits, who traditionally live on sea food, compared to Danish control persons ingesting a “Western” diet (Dyerberg, Bang, Stoffersen, Moncada, & Vane, 1978). This observation provided an apparent paradox, considering that eating primarily meat and fat was otherwise claimed as unhealthy. Analysis of fat quality showed that the Inuit diet is characterized by an extraordinary high content of n-3 LC-PUFAs including, in particular, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3) (compare Fig. 1). Subsequent epidemiological studies revealed the general existence of striking cardiovascular mortality differences between populations living on n-3 PUFA- versus n-6 PUFA-rich diets (Lands, 2005; von Schacky & Harris, 2007). Corresponding extremes are populations in Western Europe and the US on the one hand and traditionally living populations in Greenland, Alaska, and Japan on the other hand.

Complementing the epidemiological evidence, first clinical studies demonstrated the utility of purified EPA/DHA supplements for the prevention of sudden cardiac death (SCD) in patients after recent myocardial infarction (Leaf, Kang, Xiao, & Billman, 2003; Marchioli et al., 2002). Also, animal studies clearly showed that n-3 LC-PUFA supplementation is associated with a significant protective effect against ischemia-reperfusion (I/R)-induced arrhythmias (Matthan et al., 2005). Key findings of this phase of research were (i) the identification of EPA and DHA as the major protective ingredients of marine fish oil and other sea food and (ii) the recognition of EPA/DHA-mediated anti-arrhythmic, anti-inflammatory, anti-thrombotic, and hypolipidemic effects, believed to confer in combination the observed cardiovascular protective effects (Lavie, Milani, Mehra, & Ventura, 2009; Mozaffarian, 2008) (Table 1). These and further studies provided strong concordant evidence that n-3 LC-PUFAs are bioactive compounds that reduce the risk of cardiac death and may have general health benefits (Mozaffarian & Wu, 2011).

In the early 2000s, several Cardiac Societies recommended the intake of 1 g/day of EPA and DHA for cardiovascular disease (CVD) prevention, treatment after MI, prevention of sudden cardiac death (SCD), and secondary CVD prevention (Kris-Etherton et al., 2002; von Schacky & Harris, 2007). Purified EPA/DHA-supplements have been approved as prescription products for reducing triglyceride concentrations in adults with severe hypertriglyceridemia as well as for secondary prevention after MI (Bays, 2006; Hoy & Keating, 2009; Ito, 2015). Moreover, studies are ongoing to test the potential of EPA/DHA-supplements in diverse indications (Table 1). Based on the important role of DHA in brain development and function, the utility of supplements has been investigated for improving cognitive function in children as well as preventing Alzheimer's disease and other neurological disorders in the elderly. Furthermore, the anti-inflammatory and immunomodulatory properties of EPA and DHA attracted attention in studies focusing on preventing and/or treating several chronic inflammatory conditions such as asthma, inflammatory bowel diseases, rheumatoid arthritis, nonalcoholic hepatosteatosis as well as ophthalmic indications including dry eye disease and adult macular degeneration (Table 1).

2.2. Recent clinical evidence

Several recent trials failed to yield conclusive results, in particular, regarding the confirmation of initial studies showing protection against fatal arrhythmia in MI patients (Rauch et al., 2010), the development of atrial fibrillation (AF) in patients undergoing cardiac surgery (Martino et al., 2016), or stroke (Rizos, Ntzani, Bika, Kostapanos, & Elisaf, 2012). These observations challenge the belief in the general clinical utility of n-3 LC-PUFAs. Very recently, the cumulative evidence for the use of EPA/DHA-supplements in the prevention of clinical cardiovascular diseases has been re-evaluated by reviewing the design and outcome of previous and recently conducted large randomized clinical trials (Siscovick, et al., 2017). This assessment resulted in a new Science Advisory from the American Heart Association, updating its previous recommendations of 2002 (Kris-Etherton et al., 2002). What remained after applying strict criteria of clinical evidence are positive recommendations for the use of EPA/DHA supplements in (i) secondary prevention of coronary heart disease (CHD) and SCD among patients with prevalent CHD and (ii) secondary prevention of outcomes in patients with heart failure (Siscovick, et al., 2017). In contrast, the level of evidence has been considered too low for a series of other indications, such as prevention of CVD mortality in diabetes or primary and secondary prevention of AF (Siscovick, et al., 2017).

2.3. Factors potentially limiting the therapeutic efficacy of n-3 LC-PUFA supplements

The problem of recently accumulating inconclusive data may be related in part to the fact that EPA/DHA-supplements have to be tested “on top” of other standard therapies. The latter state-of-affairs significantly advanced and reduced the number of events comparing similarly designed previous (Marchioli et al., 2002) and most recent studies (Rauch et al., 2010), which consequently need larger cohorts not to become statistically underpowered (Siscovick, et al., 2017). However, as discussed below, there are several other factors that merit specific attention to better understand the principles, opportunities, and limitations in the therapeutic use of n-3 LC-PUFAs and of their general impact on human health.

2.3.1. Background nutrition and kinetics

Unlike drugs that could be given, or not given, n-3 LC-PUFAs are essential constituents of the body (compare Fig. 1). Due to differences in nutritional behavior as well as the intake of over-the-counter supplements, the basal n-6/n-3 PUFA ratios are highly variable. Thus in a given clinical trial, the basal EPA and DHA levels as well as those in the control group may range from far below to already higher than the levels finally achieved after intentional EPA/DHA-supplementation.