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Non-enzymatic cyclic oxygenated metabolites of omega-3 polyunsaturated fatty acid: Bioactive drugs?

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ABSTRACT

Non-enzymatic oxygenated metabolites derived from polyunsaturated fatty acids (PUFA) are formed *in vivo* through free radical reaction under oxidative stress conditions. It has been over twenty-five years since the discovery of cyclic oxygenated metabolites derived from arachidonic acid (20:4 n-6), the isoprostanes, and since then they have become biomarkers of choice for assessing *in vivo* OS in humans and animals. Chemical synthesis of n-3 PUFA isoprostanoids such as F_3-Isoprostanes from eicosapentaenoic acid (20:5 n-3), and F_4-Neuroprostanes from docosahexaenoic acid (22:6 n-6) unravelled novel and unexpected biological properties of such omega-3 non-enzymatic cyclic metabolites as highlighted in this review.

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1. Introduction

Docosahexaenoic acid (22:6 n-3, DHA) and eicosapentaenoic acid (20:5 n-3, EPA) are the major n-3 polyunsaturated fatty acids (PUFAs) of marine fish oil. Evidences from epidemiological studies, clinical trials, animal and cellular experiments showed fish oil and specifically n-3 PUFA, to have beneficial effects in numerous diseases [1]. Paradoxically, due to the abundance of double bonds in the structure of EPA and DHA, they are prone to free radical attack and can undergo spontaneous non-enzymatic peroxidation to generate cyclic oxygenated metabolites [2] together with acyclic metabolites. The excessive release of these EPA and DHA metabolites [3] are related to neurological disorders such as Alzheimer's disease, Parkinson's disease and mild cognitive dysfunction since their elevations in plasma were reported to correlate with disease progression [4,5].

Under oxidative stress (OS) condition, PUFA precedes to peroxidation and numerous cyclic oxygenated products are released [4,6,7], the most famous being the isoprostanes and the isofurans. For example, arachidonic acid (20:4 n-6, AA) under OS generates 64 isomers of F_2-isoprostanes (F_2-IsoPs) [8] (Scheme 1) and 258 isomers of isofurans (IsoFs) [9], EPA generates 96 isomers

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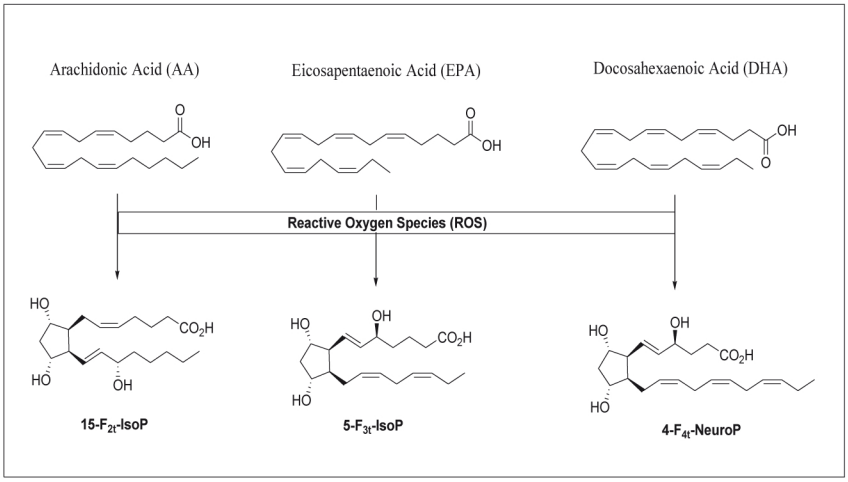


Scheme 1. Structures of bioactive isoprostanoids F_2-IsoPs, F_3-IsoPs and F_4-NeuroPs released from their respective PUFA precursors.

of F_3-isoprostanes (F_3-IsoPs) and DHA generates 128 isomers of F_4-neuroprostanes (F_4-NeuroPs) [10] and 512 isomers of neurofurans (NeuroFs) [11].

In the nineties, measurement of 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) were one of the few biomarkers to assess OS in biological systems. However, common contentious suggested F_2-IsoPs as more robust biomarker [12] in assessing endogenous OS in humans [7], animals models [12] and in biological fluids [13,14]. These molecules are oxidized *in situ* on the phospholipid membranes and hydrolyzed via phospholipase A_2 (PLA_2) and platelet activating factor acetylhydrolase into the free form, and released in tissues and systemic circulation. Among these metabolites, some have been commonly, and in some cases routinely measured as OS biomarkers related to vascular systems and neurodegeneration [6,11].

The discovery and study of notable isoprostanoids (Scheme 1) have provided a major step forward in the field of free radical research. The quantification of these molecules has opened up new areas of investigation regarding the role of free radicals in human physiology and pathology, and appears to be the most useful tool currently available to explore the role of endogenous lipid peroxidation in human diseases. However, as explained below such molecules are not simple biomarkers but also exert bioactive properties.

Evidences in favour of the bioactive role of isoprostanoids from n-6 PUFA were shown in various biological systems [14–16]. In particular, 15-F_{2t}-IsoP and 15-E_{2t}-IsoP are known to possess potent biological activities ranging from the effects on vascular and bronchial smooth muscle, endothelium function, platelet function and to cell proliferation [4] (Scheme 1).

This review will focus solely on the non-enzymatic cyclic oxygenated metabolites of n-3 PUFA and their potential biological actions in human health and diseases.

2. Biological activities of n-3 PUFA metabolites

The understanding of the role of n-3 PUFA peroxidation in the pathogenesis of various diseases continues to expand but the biological activity of their cyclic oxygenated metabolites remains unclear. The bioactive effects of non-enzymatic products from n-3 PUFA have been largely undermined by investigators and remain unexplored. The reasons for this paucity of investigation could be due to the false idea that the rate of non-enzymatic PUFA oxidation *in vivo* is negligible, and/or to the previously held idea that any form of lipid peroxidation is undesirable as it is unconditionally toxic. Moreover, not all of these metabolites are commercially available and needs to be custom synthesized.

The biological roles of oxygenated metabolites from the peroxidation of n-3 PUFA mainly emphasise on enzymatic pathways, especially on their anti-inflammatory activities and the reduction of pro-inflammatory eicosanoids stemming from AA [7,18]. For example, lipoxygenase regulate metabolites such as resolvins, protectins and maresins [19,20] and such compounds have shown a large range of potent anti-inflammatory activities. Nevertheless, recent studies showed that isoprostanoids *per se* derived from n-3 PUFA (mainly from EPA, DHA and α-linolenic acid (C18:3 n-3, ALA) are new actors to be considered [5,17,20,21] suggesting that bioactive role of oxygenated n-3 PUFA is not limited to those released through enzymatic pathway.

Sethi's group demonstrated for the first time that DHA in OS environment regulates anti-inflammatory activities [22]. In this study, the authors demonstrated that pre-incubation of endothelial cells with oxidized EPA and DHA (generated by the reaction of copper sulphate) reduced adhesion of monocyte cells to endothelial cells while the native EPA and DHA had no effect. The authors hypothesized that the reduced expression of adhesion molecules such as VCAM-1 by the endothelial cells decreased the interaction of phagocyte/endothelial cells through the action of anti-inflammatory property of the unknown forms of oxidized EPA and DHA metabolites. Follow up to this, the same group evidently showed the reduction of pro-inflammatory cytokines MCP-1 (a monocyte chemoattractant protein) in the endothelial cells when exposed to oxidized n-3 PUFA [23]. Following these seminal works, others studies clearly demonstrated biological properties of n-3 PUFA were dependent on their peroxidation [24–29] but the exact nature of the bioactive molecules was not elucidated.

In order to identify the oxidized compounds for the biological role of n-3 PUFA, it is necessary to design studies that use a single molecule of interest. Nonetheless, only a few research groups have successfully synthesized cyclic oxygenated metabolites from n-3 PUFA [30–32] such as F_3-IsoPs from EPA [33] and F_4-NeuroPs from DHA [34], and their availability allowed a better understanding of their biological roles.

2.1. Metabolites of EPA

Over a decade ago, one study highlighted that unlike the 15-F_{2t}-IsoP derived from AA, 15-F_{3t}-IsoP from EPA does not activate the

platelet aggregation [35]. This notable difference of activity between almost similar cyclic oxygenated products derived from n-6 PUFA and n-3 PUFA suggests a very subtle structure-activity relationship [7]. More recently, Jamil et al. [39] investigated the ability of another isomer of F_3-IsoPs, the 5-F_{3t}-IsoP (Scheme 1) which shown to regulate glutamatergic neurotransmission. Hence, 5-F_{3t}-IsoPs could have important pharmacological implications in neurology since EPA is rich in the brain and retina. Glutamate serves as the primary excitatory neurotransmitter in several vertebrate retinal cells, including ganglion cells. The group also investigated the modulatory role of 5-*epi*-5-F_{3t}-IsoP on K^+-induced glutamate release in isolated bovine retina. They found that 5-*epi*-5-F_{3t}-IsoP attenuates K^+-induced [^{3}H] D-aspartate release in a concentration-dependent manner and indicated that the mechanism involved is due to, in part pre-junctional prostanoid EP1-receptors activation. This result displays the beneficial role of 5-*epi*-5-F_{3t}-IsoP by reducing excitatory neurotransmitter release, thereby retarding the progression of ocular neuropathic disease.

A_3/J_3-IsoPs, the EPA-derived cyclopentenone isoprostanoids were also identified for their biological qualities *in vivo* under OS environment. Two studies observed the bioactivities of these EPA-cyclopentenones to have anti-inflammatory and antioxidant properties. Indeed, when pre-treated for 30 min with 15-A_{3t}-IsoP, the expression and the activity of iNOS and COX-2 in mouse macrophages were inhibited in a concentration-dependent manner. It is postulated that 15-A_{3t}-IsoP exerts an anti-inflammatory activity via the inhibition of the nuclear factor kappa B (NF-κB) by blocking the degradation of inhibitory subunit IκBα [36]. The second study was performed in hepatocarcinoma cells and the authors found that the compound J_3-IsoP isomer from EPA induced the nuclear related factor 2 (Nrf2)-based antioxidant response through the inhibition of Keap-1, a negative regulator of Nrf2 [37].

2.2. Metabolites of DHA

DHA also generates its own group of isoprostanoids *in vivo* and are commonly noted as neuroprostanes (NeuroPs) [18]. The group of Morrow and Roberts who pioneered the *in vivo* identification of NeuroPs also demonstrated the biological effects of A_4/J_4-NeuroPs, cyclopentenone derived from DHA to be mainly anti-inflammatory mediators in the murine macrophage cell line [38]. Notably, they reported that 14-A_4-NeuroP suppressed the effect of pro-inflammatory mediators such as lipopolysaccharide in macrophages, and confirmed the inhibition of the NFκB pathway as the major mechanism of action of DHA as well as peroxidized metabolites of EPA.

Recently, Saraswathi *et al.* [40] hypothesized that fish oil may mediate anti-atherosclerotic effect in part by reducing white adipose tissue specific inflammation and thereby modulate adipose tissue storage and/or secretory functions. In LDLR$^{-/-}$ mice, the authors observed reduced macrophage infiltration and inflammatory gene expression in white adipose tissue, which was associated with increased lipid storage. In particular, the cholesterol storage within the white adipose tissue was associated with reduced liver and plasma lipids, and ameliorated atherosclerotic lesion formation. Interestingly, the data also provided evidence for the increased formation of F_4-NeuroPs. However, the authors did not investigate the relationship between the production of F_4-NeuroPs and atherosclerosis regression. Regardless, the group speculated that the F_4-NeuroPs could play a role in the prevention of atherosclerosis.

This hypothesis was further investigated by another team using an integrated approach associating a dose–response intervention study with DHA in LDLR$^{-/-}$ mice [41]. Targeted lipidomic analyses revealed that both the profiles of EPA and DHA, and their corresponding cyclic oxygenated metabolites were substantially modulated in plasma and liver. Among 120 metabolites of the n-3 and n-6 PUFAs assessed, F_4-NeuroPs were the best predictor of atherosclerosis prevention and showed a negative correlation with atherosclerotic plaque size. Altogether, these results reinforced the hypothesis that F_4-NeuroPs could contribute to the anti-atherogenic effects of DHA. This study also suggested that although F_4-NeuroPs could be a predictor for atherosclerosis, it could have an active role in the prevention of atherosclerosis by anti-atherogenic effects.

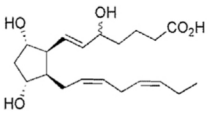
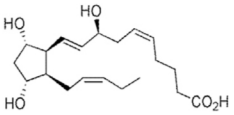
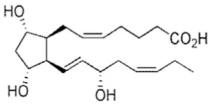
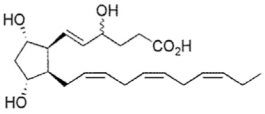
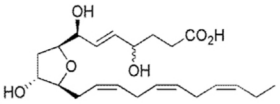
A few years ago, De Felice's group showed evidence of enhanced OS and specifically lipid peroxidation in blood samples from patient with Rett Syndrome (RTT) [42]. RTT is a neurodevelopment disorder due to genetic defect in young females and the disease could be reproduced in mice model by mutating the gene encoding the methyl-CpG binding protein 2 (MeCP2) [43]. F_4-NeuroPs and isoprostanoids from n-6 PUFAs were elevated in these MeCP2 knockout (or truncated) mice brain and the molecular pathways linking the MeCP2 gene mutation to the OS derangement are therefore open to discussion and debate. Currently it is unclear whether the nature of the relationship between MeCP2 gene mutation and abnormal redox homeostasis is causal or correlational [44]. As DHA is highly concentrated in neuronal membranes [34] and a primary target for reactive oxygen species (ROS) attack they hypothesized that the levels of peripheral F_4-NeuroPs and particularly so F_2-dihomoIsoPs (from adrenic acid, AdA, C22:4 n-6) could be associated with the neurological severity [45]. Indeed, when fish oil concentrated in n-3 PUFA was supplemented to RTT patients, plasma levels of free F_4-NeuroPs were reduced and cardiac function improved [46]. It is plausible in that case that F_4-NeuroPs are biomarkers of OS but that other metabolites of DHA are produced explaining that a decreased production of F_4-NeuroPs is associated with improved cardiac function.

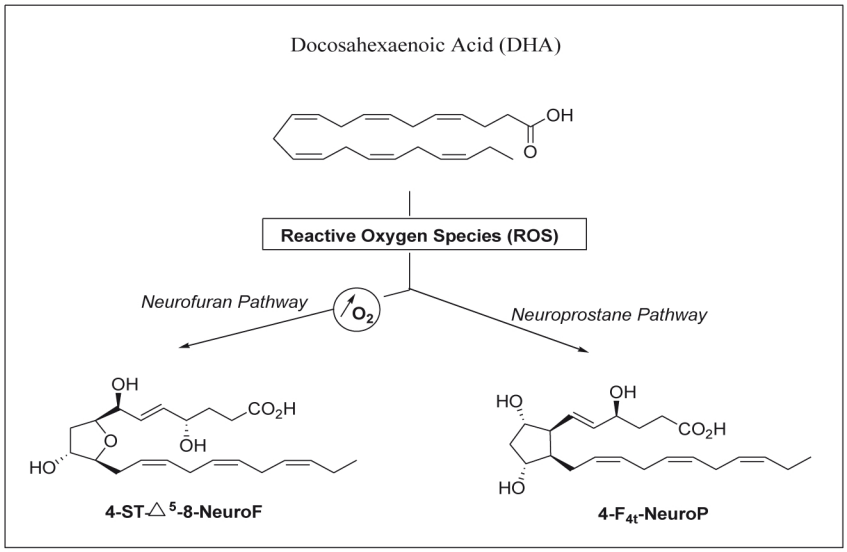
2.3. Future perspectives of cyclic oxygenated metabolites of EPA and DHA

The most recent study on the biological effects of a non-enzymatic DHA metabolite was performed in the cardiovascular system [47]. It is proposed that the oxidation of DHA and generation of 4(*RS*)-4-F_{4t} NeuroP (Scheme 1) is necessary to prevent ischemia-induced arrhythmias in mouse with myocardial infarction [48]. As previously observed in different oxidative conditions [25], we proposed that in ischemic diseases, non-enzymatic cyclic oxygenated metabolites of DHA formed by peroxidation of phopholipidic DHA in cardiac membrane lipids, namely 4(*RS*)-4-F_{4t} NeuroP are responsible for the anti-arrhythmic properties of DHA by countering the cellular stress by ROS. Importantly, it appears that non-enzymatically released cyclic oxygenated metabolites of n-3 PUFA regulate cell communication, exert a physiological role and potentially act as a therapeutic agent [48]. Besides 4(*RS*)-4-F_{4t}-NeuroP, Le Guennec's group evaluated the *in vitro* anti-arrhythmic properties of others oxygenated metabolites of EPA and DHA (Table 1) on single cardiac cells isolated from mice hearts. They observed that several cyclic oxygenated metabolites showed anti-arrhythmic properties (4(*RS*)-4-F_{4t} NeuroP and 15-F_{3t}-IsoP from EPA) or pro-arrhythmic (5(*RS*)-5-F_{3t}-IsoP and 8-F_{3t}-IsoP from EPA), therefore opening the way for likely biological roles.

Of recent interest, other cyclic oxygenated metabolites from PUFA termed isofuranes (IsoFs from AA) (Scheme 2) are know to be synthesized *in vivo* along with the isoprostanes. Both metabolites share a parallel biosynthetic pathway [9], which differ in the terminal steps implicating that isofuranoids are preferred over their isoprostanoids counterparts in hyperoxia condition. Such pathway was also confirmed *in vivo* for DHA with the formation of neurofurans (NeuroFs) [49]. Recently, specific NeuroFs were synthesized by chemists and were analysed in the rat brain and heart tissues [50]. Also NeuroFs

Table 1
Effects of different cyclic oxygenated metabolites of n-3 PUFAs on cardiac single cell arrhythmias. Single cardiac cells from mice heart were incubated for 20 min in the presence of 10, 100 or 1000 nM cyclic oxygenated metabolites of n-3 PUFAs. Arrhythmia (extrasystole) was induced by challenging the cells with 10 nM isoproterenol and electrical stimulation at 1 Hz for 30 s. During the following 30 s rest period, arrhythmic events were evaluated. Each concentration was tested on approximately 30 cells (n = 4–5 mice). Results are expressed as percentage of arrhythmic cells in the different treatments relative to control (no treatment).

Oxygenated metabolites	Structure	Percentage of arrhythmia		
		10 nM	100 nM	1000 nM
5(*RS*)-5-F_{3t}-IsoP		+20	+28	+31
8-F_{3t}-IsoP		+4	–27	+14
15-F_{3t}-IsoP *commercially available*		–9	–24	–26
4(*RS*)-4-F_{4t}-NeuroP		–22	–50	–86
4(*RS*)-ST-Δ^5-8-NeuroF		/	+3	–18



Scheme 2. Simplified depiction on the synthesis pathways of NeuroFs and NeuroPs from DHA.

were measured in the brain cortex and cerebellum of Alzheimer's disease transgenic mice and reported to be predominant in the cortex [11]. The recent discovery of these new products and their *in vivo* measurement in a high oxidative context open a new insight of investigations involving systemic biology. Also, among them, 4(*RS*)-ST-Δ^5-8-NeuroF seems to show biological properties (Table 1) revealing a new chapter in the study of non-enzymatic cyclic oxygenated metabolites.

3. Conclusion

The experimental evidences outlined here support the notion that several of the biological activities of n-3 PUFA in OS conditions could be explained by the action of some non-enzymatic peroxidized products. In general, it appears that non-enzymatically cyclic oxygenated metabolites of n-3 PUFA could exert a physiological role. This highlight that in diseases which involves ROS

production, some non-enzymatic oxygenated metabolites of n-3 PUFAs could be produced and prevent deleterious consequences of OS, such as arrhythmias.

Care should be taken by scientists not to overlook the non-enzymatic metabolites of n-3 PUFA, which could have be as equally bioactives as their well-known enzymatic metabolite counterparts. Isoprostanoids production is very sensitive to the environment (diet and oxidative status) and may play advantageous or disadvantageous roles in many diseases, where oxidative status is highly related to the severity of the diseases such as cardiovascular, neurodegenerative, pulmonary, development, metabolic diseases and cancer.

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