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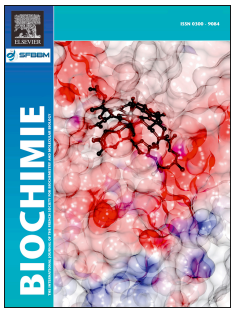

Bioactive metabolites of docosahexaenoic acid

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Title: **Bioactive metabolites of docosahexaenoic acid**

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Abstract

Docosahexaenoic acid (DHA) is an essential fatty acid that is recognized as a beneficial dietary constituent and as a source of the anti-inflammatory specialized proresolving mediators (SPM): resolvins, protectins and maresins. Apart from SPMs, other metabolites of DHA also exert potent biological effects. This article summarizes current knowledge on the metabolic pathways involved in generation of DHA metabolites. Over 70 biologically active metabolites have been described, but are often discussed separately within specific research areas. This review follows DHA metabolism and attempts to integrate the diverse DHA metabolites emphasizing those with identified biological effects. DHA metabolites could be divided into DHA-derived SPMs, DHA epoxides, electrophilic oxo-derivatives (EFOX) of DHA, neuroprostanes, ethanolamines, acylglycerols, docosahexaenoyl amides of amino acids or neurotransmitters, and branched DHA esters of hydroxy fatty acids. These bioactive metabolites have pleiotropic effects that include augmenting energy expenditure, stimulating lipid catabolism, modulating the immune response, helping to resolve inflammation, and promoting wound healing and tissue regeneration. As a result they have been shown to exert many beneficial actions: neuroprotection, anti-hypertension, anti-hyperalgesia, anti-arrhythmia, anti-tumorigenesis etc. Given the chemical structure of DHA, the number and geometry of double bonds, and the panel of enzymes metabolizing DHA, it is also likely that novel bioactive derivatives will be identified in the future.

Keywords: DHA; specialized proresolving mediators; FAHFA; DHEA; N-acyl amides; omega-3 PUFA;

1. Introduction

Naturally occurring long-chain omega-3 polyunsaturated fatty acids (omega-3), namely eicosapentaenoic acid (EPA; 20:5 ω-3) and docosahexaenoic acid (DHA; 22:6 ω-3), have many beneficial metabolic effects, including prevention of cardiovascular diseases [1], amelioration of non-alcoholic fatty liver disease [2], or lowering hypertriacylglycerolemia [3]. They exert anti-inflammatory and hypolipidemic effects (reviewed in [4]), while increasing catabolism of lipids via a PPARα-mediated mechanism [4-6]. Although negative effects of omega-3 PUFA on prostate cancer risk [7] and prevention of cardiovascular diseases [8] were published these findings were later revised [9-11]. The discrepancies probably reflect multiple variables that could complicate the outcome of these studies (reviewed in [4]) and suggest that omega-3 dose and context (medication, disease) have to be considered. Patients who could potentially benefit from omega-3 supplementation are often premedicated with over-the-counter nonsteroidal anti-inflammatory drugs, pain relievers, statins or other drugs which could interact with lipid metabolism and eicosanoid/docosanoid production and neutralize the potential of omega-3. In addition there is information suggesting that genetic variants can explain some of the individual variability in therapeutic potential of omega-3 supplementation [12, 13] Despite the occasionally divergent findings, omega-3 are generally considered as food supplements with positive properties.

The beneficial effects of DHA are mediated by the fatty acid itself (PPARα ligand [14, 15]) as well as by its bioactive metabolites – the specialized proresolving mediators (SPM) and other DHA derivatives. Although DHA triggers signaling through the Free fatty acid receptor 4 (FFAR4, also known as G protein-coupled receptor 120; GPR120)[16-18], recent studies have shown that FFAR4 is not required for the anti-inflammatory and insulin sensitizing effects of omega-3 [19-21] supporting existence of additional DHA receptors. The DHA metabolites have a wide range of actions acting simultaneously at different levels and sites. They activate various cell surface receptors (GPR32 , GPR110, N-formyl peptide receptor 2; cannabinoid receptor 1 & 2; transient receptor potential channels; etc.)[22-25], and they also act as ligands to nuclear receptors PPARα/γ [26, 27].

2. Enzymes metabolizing DHA