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Review

Functional fluxolipidomics of polyunsaturated fatty acids and oxygenated metabolites in the blood vessel compartment

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ABSTRACT

Synthesis of bioactive oxygenated metabolites of polyunsaturated fatty acids and their degradation or transformation products are made through multiple enzyme processes. The kinetics of the enzymes responsible for the different steps are known to be quite diverse, although not precisely determined. The location of the metabolites biosynthesis is diverse as well. Also, the biological effects of the primary and secondary products, and their biological life span are often completely different. Consequently, phenotypes of cells in response to these bioactive lipid mediators must then depend on their concentrations at a given time. This demands a fluxolipidomics approach that can be defined as a mediator lipidomics, with all measurements done as a function of time and biological compartments. This review points out what is known, even qualitatively, in the blood vascular compartment for arachidonic acid metabolites and number of other metabolites from polyunsaturated fatty acids of nutritional value. The functional consequences are especially taken into consideration.

Contents

1. Introduction

Polyunsaturated fatty acids (PUFA) are mainly esterified at the *sn*-2 position in glycerophospholipids of animal cell membranes, and may be released by phospholipases, especially phospholipases A_2 in response to cell activation. Some of these PUFA may be then quickly oxygenated by cell oxygenases to provide very potent lipid mediators that could lose or change their biological activity following specific metabolic pathways. The kinetics of PUFA release will depend on the phospholipases involved, and the metabolic fate of the resulting non-esterified PUFA will undergo concurrent oxygenation at different rates and re-acylation, with preferred routes according to the nature of the PUFA. Similarly, the degradation pathways depend on the different oxygenated products, with even generation of new active mediators instead of inactive products. Measuring the largest possible number of metabolites as a function of time, in an attempt to determine fluxes for each of them, will allow better approaching the phenotype of a biological system, with a global view if the measurements are made in different biological compartments. This lipidomics approach, associated with fluxes determination, justifies the name of fluxolipidomics, as in other

Abbreviations: AdA, adrenic acid; ALA, alpha-linolenic acid; ArA, arachidonic acid; COX, cyclooxygenase; Cyp, cytochrome P_{450}; DAG, diacyl-glycerol; DHA, docosahexaenoic acid; DGLA, dihomo-gammalinolenic acid; EET, epoxy-eicosatrienoate; EPA, eicosapentaenoic acid; EPE, eicosapentaenoate; GPx, glutathione peroxidase; HDoHE, hydroxyl-docosahexaenoate; H(p)ETE, hydro(pero)xyl-eicosatetraenoate; HETrE, hydroxy-eicosatrienoate; HODE, hydroxyl-octadecadienoate; HOTE, hydroxyl-octadecatrienoate; LA, linoleic acid; LOX, lipoxygenase; LT, leukotriene; PMN, polymorphonuclear neutrophil; PG, prostaglandin; PLA, phospholipase A; PLC, phospholipase C; Tx, thromboxane.

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approaches lipidomics may be focused on a specific class of lipids giving the names of mediator lipidomics and structure lipidomics. Special attention will be paid in this review to those lipid mediators produced in blood platelets, endothelial cells and leukocytes that play important roles in the athero-thrombosis regulation, and which are close to cell compartments.

This review will focus on these aspects, with qualitative considerations for the enzyme kinetics that are not known yet in detail.

2. PUFA relevant for cell functions

The most abundant PUFA in animal cells are presented in Fig. 1. The major PUFA is arachidonic acid (ArA or 20:4n-6), except in the brain and retina where the major one is docosahexaenoic acid (DHA or 22:6n-3) [1]. However, the PUFA content of most tissues changes in response to environment, notably the remodeling of phospholipid composition by nutrition [2]. The brain may be an exception because of the blood–brain barrier that exerts selective crossing of PUFA, which likely explains its high enrichment in DHA [3].

In addition to ArA, the other PUFA of interest within the n-6/omega-6 family are linoleic acid (LA or 18:2n-6), the most abundant PUFA in plant oils, dihomo-gamma-linolenic acid (DGLA or 20:3n-6), the immediate precursor of ArA, and docosatetraenoic/adrenic acid (AdA or 22:4n-6), the elongation product of ArA. Within the n-3/omega-3 family fatty acids, the essential precursor alpha-linolenic acid (ALA or 18:3n-3), found in some plant oils, and eicosapentaenoic (EPA or 20:5n-3) as well as docosapentaenoic (DPA or 22:5n-3) acids are the main PUFA of marine origin with DHA. They are the major n-3 PUFA of biological interest (Fig. 1). As shown in this figure, other PUFA intermediates belong to both families, but their oxygenation metabolism and the biological action of their metabolites have not been investigated in detail. They will not be discussed in the frame of this review.

3. Arachidonic acid as a reference PUFA

The main classes of oxygenated PUFA, such as prostanoids, leukotrienes and other oxygenase products, have arachidonic acid (ArA) as the reference precursor [4]. Fig. 2 shows as a general scheme for the main active metabolites and their stable degradation products, all relevant to the blood and vascular cells compartment. Also, ArA is a major PUFA of the peripheral tissues in mammals, including the blood vessel compartment, where its conversion into oxygenated products is of relevance for cell function. Fig. 3 points out some biological functions of relevant primary and secondary metabolites with a special emphasis to antagonistic and synergistic functions.

First, ArA must be released from membrane phospholipids in response to cell activation by extracellular messengers. The main phospholipase involved is the cytosolic phospholipase A_2 ($cPLA_2$) which requires micromolar concentrations of cytosolic calcium ions [5]. This concentration can be reached either by calcium entry from the extracellular space or by release from endoplasmic reticulum [6]. In the latter case, inositol trisphosphate (IP_3) may be the triggering agent, which establishes a link between the cleavage of phosphatidylinositol-4,5-bisphosphate (PIP_2) by phospholipase C (PLC), the primary event, and the activation of $cPLA_2$. The other cleavage product is diacylglycerol (DAG), mainly 1-palmitoyl,2-arachidonoyl-glycerol, which is generated prior to the activation of $cPLA_2$. Then, the release of ArA from phospholipids (mainly phosphatidyl-choline and -ethanolamine) by $cPLA_2$ may parallel that from ArA-containing DAG by DAG lipase [7], although with different kinetics. However, in terms of quantities, ArA released by $cPLA_2$ is likely higher than that from PIP_2 through the PLC/DAG lipase cascade.

Once released, ArA will be either oxygenated by cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome P_{450} (Cyp) monooxygenases, depending on the cell equipment, or re-acylated into membrane phospholipids by re-esterifying the lysophospholipids produced by the primary cleavage [8].

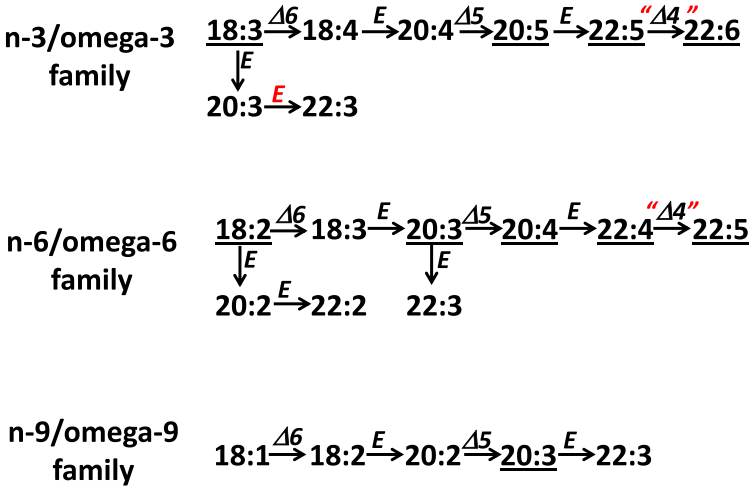

Fig. 1. Biogenesis of the most frequent polyunsaturated fatty acids (PUFA). These PUFA belong to the three n-3/omega-3, n-6/omega-6 and n-9/omega-9 families. *E* indicates an elongase, and Δ a desaturase, followed by the carbon number of the new double bond issued from the desaturation. However, *Δ4* has quotation marks because it means *Δ4* desaturation instead of *Δ4* desaturase in one step. It must be taken as a more complex step than the other desaturation (*e.g.* *Δ5* and *Δ6*). Indeed *Δ4* desaturation includes first a further elongation, followed by *Δ6* action, and finally beta-oxidation [105]. PUFA undergoing oxygenation metabolism and addressed in this review are underlined. They are: 18:3n-3: alpha-linolenic acid (ALA, 9,12,15-octadecatrienoic acid); 20:5n-3: eicosapentaenoic acid (EPA, 5,8,11,14,17-eicosapentaenoic acid); 22:5n-3: docosapentaenoic acid (DPAn-3, 7,10,13,16,19-docosapentaenoic acid); 22:6n-3: docosahexaenoic acid (DHA, 4,7,10,13,16,19-docosahexaenoic acid); 18:2n-6: linoleic acid (LA, 9,12-octadecadienoic acid); 20:3n-6: dihomo-gamma-linolenic acid (DGLA, 8,11,14-eicosatrienoic acid); 20:4n-6: arachidonic acid (ArA, 5,8,11,14-eicosatetraenoic acid); 22:4n-6: adrenic acid (AdA, 7,10,13,16-docosatetraenoic acid); 22:5n-6: docosapentaenoic acid (DPAn-6, 4,7,10,13,16-docosapentaenoic acid); 20:3n-9: Mead acid (5,8,11-eicosatrienoic acid).