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Review

Functional lipidomics of oxidized products from polyunsaturated fatty acids

M. Guichardant, P. Chen, M. Liu, C. Calzada, R. Colas, E. Véricel, M. Lagarde*

Université de Lyon, UMR 1060/CarMeN, INSERM, IMBL, INSA-Lyon, Univ-Lyon 1, INRA, 20 Ave A. Einstein, 69621 Villeurbanne, France

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ABSTRACT

Because of their high degree of unsaturation, polyunsaturated fatty acids (PUFA) in mammals, with mainly 18, 20 and 22 carbons, can easily be autooxidized, and converted into many oxidized derivatives and degradation products. This short review reports on some of those relevant to the evaluation of oxidative stress *in situ*. In addition, the enzyme-dependent oxygenation by both dioxygenases and monooxygenases is briefly reviewed by functional and/or metabolic categories, pointing out the structure variety and the analytical approaches.

Contents

1. Introduction

Polyunsaturated fatty acids (PUFA) of nutritional interest are highly susceptible to oxidative stress, which leads to lipid peroxidation with degradation products from primary hydroperoxides. Besides non-enzymatic lipid peroxidation, enzyme-induced peroxidation, e.g. cyclooxygenases and lipoxygenases, is a process that leads to hydroperoxides specifically transformed into a series of more stable metabolites called eicosanoids, docosanoids and even octadecanoids from C20, C22 and C18 PUFA, respectively.

Functional lipidomics may be seen as targeted lipidomics addressed to classes of lipids associated with specific types of function or biological system, e.g. eicosanoids in the vascular bed. This contrasts with the measurement of a limited number of markers associated with a physiological or pathophysiological situation. In this short review, the analysis of oxidized products from PUFA will be discussed in relation with their biological relevance.

2. Autooxidation of PUFA

It is well known that the autooxidation of PUFA leads to many metabolites that have been used as markers of the process (Catalá, 2009). The mostly used one is malondialdehyde (MDA), which can also be produced through the cleavage of prostaglandin (PG) H_2, releasing equimolecular amount of 12-hydroxy-heptadecatrienoic acid (HHT) (Hecker et al., 1987), making MDA an index of cyclooxygenase pathway as well. In addition to be a global index of lipid peroxidation, it can derive from non-lipid precursors such as carbohydrates, amino acids and DNA (Janero, 1990). Despite this lack of specificity, the advantage of its measurement in urine for instance is to provide an integrative and non-invasive assessment of overall oxidative stress in the body (Guichardant et al., 1994).

In contrast to this lack of specificity, products such as isoprostanes and neuroprostanes are quite specific, perhaps too much as they represent the peroxidation of only two precursors, i.e. arachidonic acid (ARA) and docosahexaenoic acid (DHA), respectively (Roberts and Fessel, 2004). In addition, they are quite numerous with 64 different isoprostane isomers (Morrow and Roberts, 1997). Among them, at least two isoprostanes exert biological activities. 8-Iso-$PGF_{2\alpha}$ and 8-Iso-PGE_2 exhibit vasoconstricting

* Corresponding author. Tel.: +33 472438240.
E-mail address: michel.lagarde@insa-lyon.fr (M. Lagarde).

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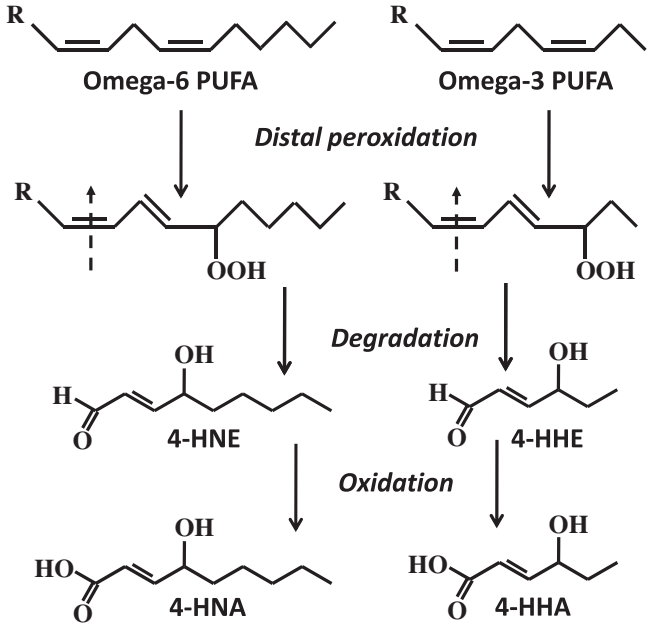

Fig. 1. Distal peroxidation and subsequent degradation by cleavage of the cis (Z) double bond of the conjugated diene leading to a hydroxyl-alkenal. 4-Hydroxy-2E-nonenal (4HNE) and 4-hydroxy-2E-hexenal (4-HHE) derives from omega-6 and omega-3 PUFA, respectively. Further oxidation of the hydroxyl-alkenal leads to corresponding carboxylic acids, 4-hydroxy-2E-nonenoic (4-HNA) and 4-hydroxy-2E-hexenoic (4-HHA) acids.

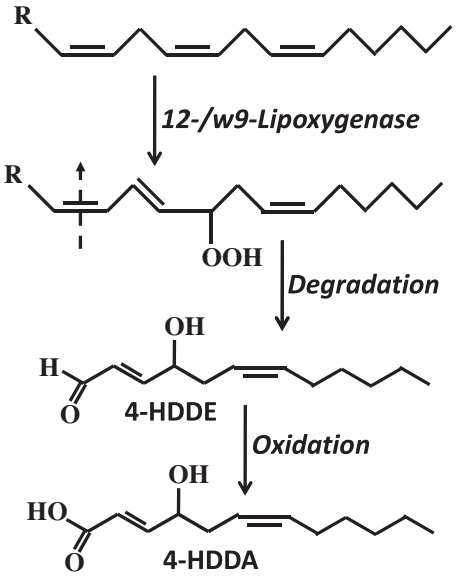

Fig. 2. 12-Lipoxygenation of an omega-6 polyunsaturated fatty acid (PUFA), such as arachidonic acid, and subsequent degradation/cleavage leading to 4-hydroxy-2E-dodecadienal (4-HDDE), further oxidized into 4-hydroxy-2E-dodecadienoic acid (4-HDDA).

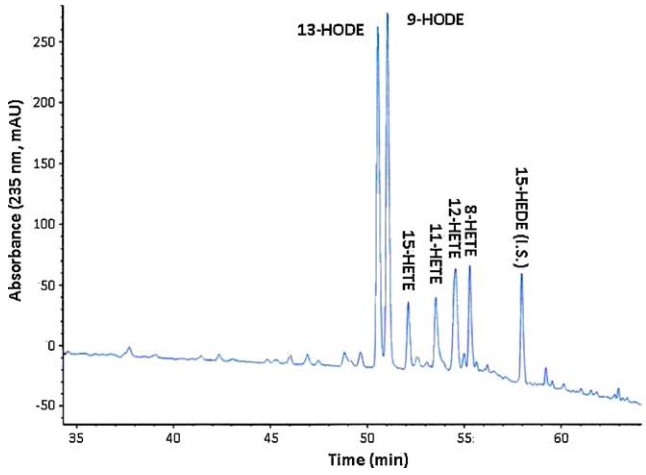

Fig. 3. Reverse phase HPLC profile of monohydroxy-derivatives of linoleic (HODEs) and arachidonic (HETEs) acids of biological relevance, with detection at 235 nm. Sensitivity can be evaluated from the less represented metabolite, 15-HETE, as the signal corresponds to around 10 pmol.

effects (Fukunaga et al., 1993), with the latter also affecting platelet aggregation (Lahaie et al., 1998; Longmire et al., 1994). On the other hand, neuroprostanes could be sensitive biomarkers of brain injury in response to oxidative stress, and then be relevant to neurodegenerative diseases (Montine et al., 2004).

We have been interested in hydroxy-alkenals that may be issued from the whole series of omega-3 or omega-6 PUFA, in contrast to isoprostanes and neuroprostanes that are products of ARA and DHA only. In that case, 4-hydroxy-hexenal (4-HHE) and 4-hydroxy-nonenal (4-HNE) are indices of omega-3 and omega-6 peroxidation (or distal peroxidation in the esterified fatty chain), respectively (Guichardant et al., 2006; Bacot et al., 2007) (Fig. 1). It can however be argued that hydroxy-alkenals are reactive enough to make covalent adducts with protein residues (on thiol and amine groups) as well as with amino-phospholipids and other bio-amines (Jürgens et al., 1990; Guichardant et al., 1998). Therefore, the measurement of 4-HHE and 4-HNE only represents the remaining free molecules. Yet, this argument is also valid for chemically stable isoprostanes, and neuroprostanes, that are very likely (although not reported) to be beta-oxidized as described for prostaglandins, and then found partly in urine as dinor and tetranor derivatives (Diczfalusy, 1994). The advantage of measuring hydroxy-alkenals is the possibility to include in the same run of analysis the measurement of other homologues such as 4-hydroxy-dodecadienal (Fig. 2) derived from the 12-lipoxygenase product of ARA, 12-HpETE (Bacot et al., 2007). These molecules have been measured in blood plasma (Calzada et al., 2010), and a non-invasive measurement of their acidic metabolites (Fig. 1), 4-hydroxy-hexaenoic/nonenoic acids in urine is a possible alternative (Guichardant et al., 2006). In terms of biological effects, recent results show their cytotoxic activity (Pillon et al., 2010).

Hydroperoxy derivatives of PUFA can also be reduced into their stable counterparts by glutathione-dependent peroxidase (Foster and Sumar, 1997), namely hydroxy derivatives, and then escape the spontaneous cleavage into hydroxy-alkenals. In that case, the various hydroxy-eicosatetraenoic acids (HETEs) from ARA and hydroxy-octadecadienoic acids (HODEs) from linoleic acid can easily be measured (Fig. 3). As an example of clinical investigation, 9- and 13-HODE have been found as the main hydroxy derivatives present in LDL, and are significantly increased in LDL from type 2 diabetic patients compared to control LDL (Colas et al., 2010). However, it should be noted that HETEs and HODEs may also derive from the action of lipoxygenases/glutathione peroxidase, making these markers as indices of both autooxidation and enzyme-dependent oxygenation. The only difference between autooxidation product and lipoxygenase-derived products is the R/S racemic configuration in the former and the S configuration in the latter. The biological function of HETEs and HODEs has been thoroughly reviewed (Spector et al., 1988).

3. Dioxygenase-dependent oxygenated products

The main dioxygenases involved in oxygenation of PUFA are cyclooxygenases and lipoxygenases.