

## Mini-review

# Structure-function relationships of non-cyclic dioxygenase products from polyunsaturated fatty acids: Poxyttrins as a class of bioactive derivatives



Michel Lagarde\*, Evelyne Véricel, Miao Liu, Ping Chen, Michel Guichardant

Université de Lyon, UMR Inserm 1060, INSA-Lyon, IMBL, Villeurbanne, France

## ARTICLE INFO

## Article history:

Received 22 April 2014

Accepted 4 September 2014

Available online 16 September 2014

## Keywords:

Blood cells

Lipoxygenases

Cyclo-oxygenases

Prostanoids

Leukotrienes

## ABSTRACT

More and more attention is paid to omega-3 fatty acids because of their potential activities in preventing cardiovascular events. In this brief review, we focus on the lipoxygenase end-metabolites of two relevant nutrients belonging to the omega-3 family fatty acids: alpha-linolenic and docosahexaenoic acids, the latter being a prominent component of brain lipids. Dihydroxylated derivatives are described as well as their inhibitory effects on platelet aggregation and cyclooxygenase activities. We point out that only the dihydroxylated products with the *trans,cis,trans/E,Z,E* conjugated triene geometry exhibit those inhibitory activities. These properties being found with other polyunsaturated fatty acid oxygenated products sharing the same *E,Z,E* molecular motif, they have been collectively named poxyttrins. From alpha-linolenic and docosahexaenoic acids, poxyttrins are linotrins and protectin DX, respectively.

© 2014 Elsevier B.V. and Société française de biochimie et biologie Moléculaire (SFBBM). All rights reserved.

## 1. Introduction

Most polyunsaturated fatty acids (PUFA) of the omega-6 and -3 families are considered having essential functions, and they derive from the indispensable precursors linoleic (18:2 $\omega$ 6) and alpha-linolenic (18:3 $\omega$ 3) acids in humans. They can be metabolized into longer and highly unsaturated fatty acid derivatives by a series of desaturases and elongases [1]. All the PUFA have at least two methylene-interrupted double-bonds, which is the required molecular motif, called 1,4-*cis,cis/Z,Z*-pentadiene, to be oxygenated by lipoxygenases or by non-enzyme peroxidation [2].

Lipoxygenases have been first described in plants, and 18:2 $\omega$ 6 is a well-known substrate of soybean lipoxygenase to produce 13-hydroperoxy-octadecadienoic acid (13-HpODE), and considered to be a better substrate than arachidonic acid (20:4 $\omega$ 6) [3]. Then, animal lipoxygenases have been reported to mainly oxygenate 20:4 $\omega$ 6 at carbon 5, 12 and 15 giving 5-, 12- and 15-hydroperoxy-eicosa-tetraenoic acids (HpETE), respectively, that are reduced into the corresponding alcohols (HETE) by glutathione peroxidase (GPx), usually the cytosolic isoform (GPx-1) [4]. The stereochemistry of those products is usually *S* when lipoxygenases are the catalysts, whereas racemic (*R/S*) products are issued from non-enzyme peroxidation [5]. In some cases, the product of one

lipoxygenase may be further oxygenated by a second one, e.g. 5(*S*)-HETE may be further converted into 5(*S*),12(*S*)-diHETE by 12-lipoxygenase or *vice versa*. In addition, 15-lipoxygenase may act twice, first producing 15(*S*)-HETE, and second at position 8, making a double lipoxygenase product: 8(*S*),15(*S*)-diHETE [6]. In terms of double-bond geometry, the mono-oxygenated products are *E,Z* conjugated dienes with the oxygenation closest to the *E* double-bond, and the double oxygenated products are *E,Z,E* conjugated trienes with the oxygenation adjacent to the *E* double-bonds. Thus, the double lipoxygenase end-product 5(*S*),12(*S*)-*E,Z,E*-diHETE, sometimes called leukotriene B<sub>x</sub>, is a stereo-chemical and geometric isomer of leukotriene B<sub>4</sub> (5(*S*),12(*R*)-*Z,E,E*-diHETE) [7,8].

## 2. Lipoxygenation of docosahexaenoic acid into protectins

Docosahexaenoic acid (DHA) is a major PUFA of the omega-3 family. It is the main PUFA in structural lipids in the brain and retina where it plays important roles in brain development, learning ability and visual acuity [9]. As a main nutrient from marine glycerolipids, DHA is known as well for its protective effects against athero-thrombosis and inflammation [10]. It is not a substrate of cyclooxygenases but inhibits them by competing with arachidonic acid [11]. In contrast, it is a fairly good substrate of lipoxygenases leading to the end-products hydroxyl-docosa-hexaenoic acids (HDoHE): 4- and 7-HDoHE through 5-lipoxygenase [12,13], 11- and 14-HDoHE through 12-/ $\omega$ 9-lipoxygenase [14] and 17-HDoHE

\* Corresponding author.

E-mail address: [michel.lagarde@insa-lyon.fr](mailto:michel.lagarde@insa-lyon.fr) (M. Lagarde).

through 15- $\omega$ 6-lipoxygenase [15]. In addition to those mono-oxygenations, DHA may undergo a double oxygenation by 15- $\omega$ 6-lipoxygenase. The end-product is 10(*S*),17(*S*)-dihydroxy-4*Z*,7*Z*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid [16]. This product has been named protectin DX (PDX) to differentiate it from protectin D1 (PD1), also called neuroprotectin D1 (NPD1) because of its occurrence in the brain where it exerts neuroprotective activities [17]. PD1 (10(*R*),17(*S*)-dihydroxy-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-docosahexaenoic acid) differs from PDX both by the stereochemistry of carbon 10 (*R* instead of *S*) and the conjugated triene geometry (*E,E,Z* instead of *E,Z,E*) [18].

Like all the other *E,Z,E* conjugated trienes (named poxytrins<sup>®</sup>, Fig. 1) tested, including the other double lipoxygenation end-products 8*S*,15*S*-diHETE from 20:4 $\omega$ 6, 10(*S*),17(*S*)-di-OH-22:3 from 22:3 $\omega$ 6 and 7(*S*),14(*S*)-di-OH-22:6, the latter being a geometric and stereo-isomer of maresin 1 [19], PDX inhibits human blood platelet aggregation induced by both collagen and thromboxane. As collagen induces platelet aggregation via a cascade which includes the release of endogenous arachidonic acid from membrane phospholipids, its oxygenation into thromboxane  $A_2$  and its response to the latter, the oxygenated metabolism of arachidonic acid was investigated. It appeared that PDX does not alter the release of arachidonic acid but its oxygenation through cyclooxygenase-1, the only isoform within blood platelets [20]. However, further studies have shown that cyclooxygenase-2 is inhibited as well by PDX, with even more potency compared to cyclooxygenase-1 [21]. PDX also inhibits thromboxane  $A_2$ -induced aggregation (using the stable analog U46619 as an agonist) as it has been shown previously with inhibitors such as monohydroxy derivatives of PUFA and leukotriene B<sub>x</sub> but not leukotriene B<sub>4</sub> [22]. This means that PDX inhibits both the generation of thromboxane and its aggregatory effect. Of note, the inhibitory power towards collagen and 20:4 $\omega$ 6 was similar, suggesting that PDX is not active against the phospholipase  $A_2$ -induced release of endogenous 20:4 $\omega$ 6. In all aggregation tests, it appeared that, in contrast to *E,Z,E* derivatives, the non *E,Z,E* ones tested (*E,E,Z* and *E,E,E*) are devoid of inhibitory effect [20]. This is in agreement with a previous paper reporting that PD1 (*E,E,Z* motif) is a weak inhibitor of ADP-induced platelet aggregation [23].

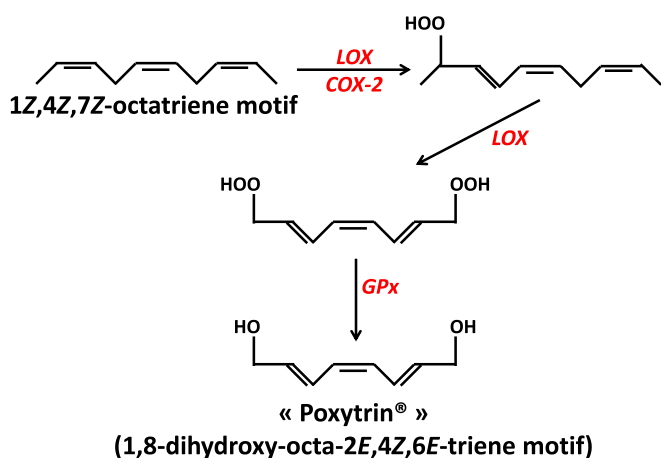
Very recent data, obtained in a completely different biological system, have shown that PDX, but not PD1, can improve insulin

sensitivity in skeletal muscle of obese diabetic mice [24]. However, this specific effect could not be attributed solely to the *E,Z,E* motif as 8(*S*),15(*S*)-diHETE (with the *E,Z,E* geometry) was inactive [24]. This is another example of biological effect of PDX after other recent data showing that PDX (called PD1 isomer and even PD1 in most part of the text [18]) specifically inhibits the replication of the influenza virus, and improves severe influenza states [25].

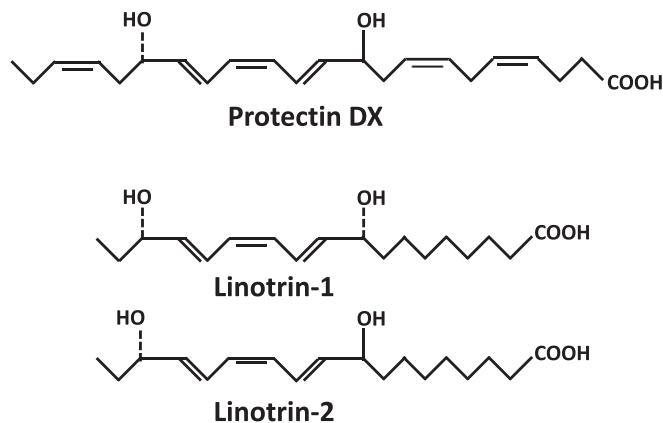
### 3. Lipoxygenation of alpha-linolenic acid into linotriens

Although alpha-linolenic acid (18:3 $\omega$ 3, ALA) is known to exert protective effects against atherothrombogenesis [26], it is known to hardly accumulate in human blood and tissues. Also, its conversion into long-chain omega-3 derivatives such as eicosapentaenoic acid (20:5 $\omega$ 3, EPA) and DHA is weak [27], preventing to consider it could mainly act through the long-chain derivatives. Finally, ALA is believed to be efficiently beta-oxidized [28], but this does not explain the majority of its metabolic fate. ALA has the structural basis for being a substrate of 15- $\omega$ 6-lipoxygenase as well as 18:2 $\omega$ 6, which explains part of its metabolic behavior, yet its lipoxygenation has been scarcely studied [29,30], and the chemical characterization of the end-products in these studies was not completed. In addition, no biological activities were proposed to the oxygenated products from ALA.

The conversion of ALA by soybean lipoxygenase has been more thoroughly investigated, in conditions similar to those used to study the conversion of DHA to PDX. Substantial amount of 13(*S*)-hydroxy-9*Z*,11*E*,15*Z*-octadecatrienoic acid (13(*S*)-HOTE) was obtained, and characterized by mass spectrometry after reduction of the hydroperoxide intermediate by NaBH<sub>4</sub>. In addition, four conjugated triene end-products have been found after reduction, and characterized by UV, mass spectrometry, and NMR. They are 9(*R*),16(*S*)-dihydroxy-10*E*,12*E*,14*E*-, 9(*S*),16(*S*)-dihydroxy-10*E*,12*E*,14*E*-, 9(*S*),16(*S*)-dihydroxy-10*E*,12*Z*,14*E*-, and 9(*R*),16(*S*)-dihydroxy-10*E*,12*Z*,14*E*-octadecatrienoic acids. The two latter ones have the *E,Z,E* conjugated triene feature of poxytrins (Fig. 2), and were found to inhibit human blood platelet aggregation induced by collagen, whereas the two former ones are all-trans (*E,E,E*) products which are not active upon platelets [31]. The two poxytrins derived from ALA have been named “linotriens<sup>®</sup>”. Interestingly, linotrin 9(*R*),16(*S*) (linotrin-1) appeared slightly more potent to inhibit platelet aggregation than linotrin 9(*S*),16(*S*) (linotrin-2) (Fig. 2). They both inhibited the two cyclooxygenase isoforms COX-1 and COX-2, in their pure form, with the same highest activity for linotrin-1. In addition, the latter inhibited



**Fig. 1.** Biosynthesis of poxytrins. PUFA that possess at least three double-bonds with the 1,2,4,7,7-octatriene motif may be oxygenated twice by lipoxygenases (LOX) or first by cyclooxygenase-2 (COX-2) in an aborted cyclooxygenation process. When COX-2 is acetylated by aspirin, the stereochemistry of the oxygenated carbon is *R* instead of *S* in normal oxygenations. Then, the hydroperoxide intermediates are reduced by glutathione peroxidase (GPx) to provide the 1,8-dihydroxy-octa-2*E*,4*Z*,6*E*-triene motif of poxytrins. It is not known whether GPx acts on the dihydroperoxide (as shown in the figure), or sequentially on the first one, then on the second one after the second lipoxygenation, or both ways.



**Fig. 2.** Chemical structures of three poxytrins. They are protectin DX (10(*S*),17(*S*)-dihydroxy-4*Z*,7*Z*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid) from DHA, and linotriens-1 & -2 (9(*R*),16(*S*)- & 9(*S*),16(*S*)-dihydroxy-10*E*,12*Z*,14*E*-octadecatrienoic acids, respectively) from ALA.

Download English Version:

<https://daneshyari.com/en/article/1952097>

Download Persian Version:

<https://daneshyari.com/article/1952097>

[Daneshyari.com](https://daneshyari.com)