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Review

Functional and pathological roles of the 12- and 15-lipoxygenases

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ABSTRACT

The 12/15-lipoxygenase enzymes react with fatty acids producing active lipid metabolites that are involved in a number of significant disease states. The latter include type 1 and type 2 diabetes (and associated complications), cardiovascular disease, hypertension, renal disease, and the neurological conditions Alzheimer's disease and Parkinson's disease. A number of elegant studies over the last thirty years have contributed to unraveling the role that lipoxygenases play in chronic inflammation. The development of animal models with targeted gene deletions has led to a better understanding of the role that lipoxygenases play in various conditions. Selective inhibitors of the different lipoxygenase isoforms are an active area of investigation, and will be both an important research tool and a promising therapeutic target for treating a wide spectrum of human diseases.

Contents

Abbreviations: AD, Alzheimer's disease; AIF, apoptosis-inducing factor; AA, arachidonic acid; CAM, cellular adhesion molecule; CDC, cinnamyl-3,4-dihydroxy-α-cyanocinnamate; COX, cyclooxygenase; EPA, eicosapentaenoic acid; ESI, electrospray ionization; ELISA, enzyme-linked immunosorbent assay; GC/MS, gas chromatography-mass spectrometry; HPETE, hydroperoxyeicosatetraenoic; HETE, hydroxyeicosatetraenoic acid; HODE, hydroxyoctadecadienoic acid; HPODE, hydroperoxyoctadecadienoic acid; LT, leukotrienes; LRP, lipoprotein receptor-related protein; LXA4, lipoxin A4; LOX, lipoxygenase; 12-LOX, 12-lipoxygenase; 15-LOX, 15-lipoxygenase; LC, liquid chromatography; MS/MS, tandom mass spectrometry; mitogen-activated protein kinase, MAPK; NO, nitric oxide; NDGA, nordihydroguaiaretic acid; PD, Parkinson's disease; PPAR, peroxisome proliferators-activated receptor; PC, phosphatidylcoline; PE, phosphatidylethanolamine; PUFA, polyunsaturated fatty acid; PD1, protectin D1; PKC, protein kinase C; RAS, renin-angiotensin system; RvD1, resolvin D1; TxA_2, thromboxane; TLR4, Toll-like receptor 4.

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1. Introduction

Twenty carbon fatty acids serve a variety of important physiological functions in humans, from providing cellular membrane structure to serving as substrates from which a number of important cell signaling molecules and secondary messengers are derived [1]. In particular, arachidonic acid serves as one major precursor for a number of molecules termed eicosanoids that have significant roles in human diseases, including types 1 and 2 diabetes and atherosclerosis, as well as the neurological diseases Parkinson's disease (PD) and Alzheimer's disease (AD) [2–4]. The following review will focus on the 12- and 15-lipoxygenase enzymes (12-LOX, 15-LOX), their products, and the varied effects of those products in human metabolic, vascular, and neurological diseases.

Arachidonic acid (AA) is released from the cell membrane by phospholipases, such as phospholipase A1, in response to various cytokines, peptides, and growth factors that become active under inflammatory conditions [5,6]. There are three families of enzymes involved in the oxidative metabolism of AA. These include the lipoxygenases, which produce leukotrienes (LT), hydroperoxyeicosatetraenoic acids (HPETEs), hydroxyeicosatetraenoic acids (HETEs), and hydroxyoctadecadienoic acids (HODEs); the cyclooxygenases (COX-1 and COX-2) which produce prostaglandins including G_2 and H_2 as well as thromboxanes; and cytochrome P-450 monooxygenases which produce epoxides and HETEs [6,7]. Of note, prostaglandin H_2 is further metabolized to prostaglandins D_2, $F_{2\alpha}$, and I_2 (prostacyclin), as well as to thromboxane (TxA_2) [8].

Lipoxygenases (LOXs) are found in both plants and in animals. The mouse has seven different ALOX genes (note that the LOX genes are termed by convention "ALOX", for arachidonic acid lipoxygenase), while humans have five known genes [7]. The different LOX enzymes are named for the numbered carbon where they oxygenate their polyunsaturated fatty acid (PUFA) substrates, with the use of stereoisomer nomenclature (*S* and *R*) as appropriate (e.g., 12*S*-LOX and 12*R*-LOX) [7]. As shown in Table 1, the human LOX enzymes include 5-LOX (which produces LTs), 12-LOX (with platelet-type and leukocyte-type forms), and 15-LOX (which is further separated into the reticulocyte or leukocyte-type, 15-LOX-1, and the epidermis-type, 15-LOX-2) [9,10]. The human leukocyte-type 12-LOX and the human reticulocyte-type 15-LOX-1 can form similar products from common substrates and are often referred to in the literature as 12/15-LOXs [6,10]. Furthermore, there is significant species-specific variation in the products formed by the different 12- and 15-LOX isoforms. Mice do not express 15-LOX and only express the leukocyte-derived 12-LOX [11]. Rabbits express both reticulocyte-derived 15-LOX and leukocyte-derived 12-LOX [12]. These differences often make it difficult to translate data obtained in different animal models of disease to their human counterparts. This may, for instance, explain conflicting data on the effects of different 12- and 15-LOX isoforms on vascular function and on atherosclerosis [13].

In humans, 12/15-LOXs act upon AA to create a number of important lipid mediators (Fig. 1). These include 12- and 15HPETEs and 12- and 15HETEs [7]. The 15-LOX-1 enzyme also produces 13-*S*-hydroxyoctadecadienoic acid (HODE) from linoleic acid [14]. These lipid products have a variety of functions in human tissues. For example, 12(S)-HETE and 15(S)-HPETE are involved in monocyte binding in the vasculature, by stimulating protein kinase C (PKC) and various cellular adhesion molecules (CAMs) [6,15]. Some products, including 13HPODE, are pro-inflammatory and act via various transcription factors including NF-κB [16]. HETEs are also involved in cell growth, acting through various mitogen-activated protein kinases (MAPKs) [17].

A number of interesting anti-inflammatory molecules have also been identified that are derived from AA or $\omega - 3$ fatty acids, including the lipoxins (for "lipoxygenase interaction products"), resolvins, and protectins [18,19] (Fig. 1). The lipoxins are synthesized from AA by 5-, 12-, and 15-LOX, as well as by COX-2 in the presence of aspirin [18]. These molecules are involved in actively limiting and resolving the inflammatory response. In particular, lipoxins derived from the 15-LOX product 15HETE (termed lipoxin A4 and B4) have been shown to stimulate vasodilation and inhibit neutrophil function [20]. The resolvins are derived from the omega-3 PUFAs docosahexanoic acid (the D-series resolvins) and eicosapentaenoic acid (the E-series resolvins), and their synthesis can involve aspirin and COX-2 (resolvin E1), as well as 5-LOX (resolvin E1) and 15-LOX (D-series resolvins) [19]. E-series resolvins are involved in granulocyte function and clearance, and reduce the release of various pro-inflammatory cytokines [19]. Synthesis of the protectins also involves the action of 15-LOX [19]. These agents appear to be involved in airway/mucosal injury in human asthma, and may also be protective after ischemic renal injury [21,22].

An interesting class of 12- and 15-LOX-derived lipid products is the esterified eicosanoids formed by direct enzymatic oxidation of membrane phospholipids. First evidence for formation of these

Table 1
Lipoxygenase isoforms in humans. (From Entrez Gene, through the National Center for Biotechnology Information). Humans have five different lipoxygenase (LOX) genes, termed by convention "ALOX" for arachidonic acid lipoxygenase. 5-LOX predominantly produces leukotrienes (LTs), while 12- and 15-LOX predominantly produce the eicosanoids hydroperoxyeicosatetraenoic acid (HPETE) and hydroxyeicosatetraenoic acid (HETE). All LOX genes are located on chromosome 17.

Gene name	Abbreviation	Alternative nomenclature	Predominant enzyme products
Arachidonate 12-lipoxygenase	ALOX12	12S-LOX platelet-type lipoxygenase 12	12(S)-HPETE 12(S)-HETE
Arachidonate 12-lipoxygenase, 12R type	ALOX12B	12R-LOX, epidermis-type lipoxygenase 12	12(R)-HPETE 12(R)-HETE
Arachidonate 15-lipoxygenase	ALOX15	15-LOX-1	15(S)-HPETE, 15HETE
Arachidonate 15-lipoxygenase, type B	ALOX15B	15-LOX-2; 15-LOX-B	15(S)-HPETE, 15HETE
Arachidonate lipoxygenase 3	ALOXE3	eLOX3, epidermis-type lipoxygenase 3	Epoxyalcohols (hepoxilins), from 12(R)-HPETE