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Biochemical and Biophysical Research Communications 338 (2005) 668–676
BBRC
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Review

Lipid peroxidation: Mechanisms, inhibition, and biological effects ☆

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Received 16 July 2005
Available online 19 August 2005

Abstract

In the last 50 years, lipid peroxidation has been the subject of extensive studies from the viewpoints of mechanisms, dynamics, product analysis, involvement in diseases, inhibition, and biological signaling. Lipids are oxidized by three distinct mechanisms; enzymatic oxidation, non-enzymatic, free radical-mediated oxidation, and non-enzymatic, non-radical oxidation. Each oxidation mechanism yields specific products. The oxidation of linoleates and cholesterol is discussed in some detail. The relative susceptibilities of lipids to oxidation depend on the reaction milieu as well as their inherent structure. Lipid hydroperoxides are formed as the major primary products, however they are substrates for various enzymes and they also undergo various secondary reactions. Phospholipid hydroperoxides, for example, are reduced to the corresponding hydroxides by selenoproteins in vivo. Various kinds of antioxidants with different functions inhibit lipid peroxidation and the deleterious effects caused by the lipid peroxidation products. Furthermore, the biological role of lipid peroxidation products has recently received a great deal of attention, but its physiological significance must be demonstrated in future studies.

Keywords: Lipid peroxidation; Antioxidant; HODE; Linoleic acid; Cholesterol; Oxysterols; Vitamin E

Lipid peroxidation has been the subject of extensive studies for several decades, and its mechanisms, dynamics, and products are now fairly well established. It was first studied in relation to the oxidative deterioration of foods. In 1955, the oxygenase enzyme was discovered by Hayaishi et al. [1] and Mason et al. [2] independently, and since then lipid peroxidation by lipoxygenases and cyclooxygenases has been studied extensively. Lipid oxidation by cytochrome P450 has also been studied and is well documented. The free radical-mediated peroxidation of lipids has received a great deal of attention in connection with oxidative stress in vivo. The oxidation hypothesis for atherosclerosis [3] has stimulated extensive studies on the oxidative modification of low density lipoprotein (LDL). Researchers have also focused their attention on lipid peroxidation by non-enzymatic, non-radical mechanisms. Singlet oxygen and ozone are examples of molecules that induce such oxidation. More recently, the role of lipid peroxidation products as cellular regulators and signaling messengers has been a growing subject. In this article, the oxidation of lipids, particularly polyunsaturated fatty acids (PUFA) and cholesterol, and their inhibition will be briefly reviewed, aiming specifically at elucidating the effects of milieu.

Mechanisms and dynamics of lipid peroxidation

Both PUFA and cholesterol are oxidized by enzymatic and non-enzymatic pathways. The oxidation of arachidonates by lipoxygenases and cyclooxygenases has been studied extensively [4], however, in this article, linoleates are considered as the model substrate, since they are the most abundant PUFA in vivo and their oxidation proceeds by a straightforward mechanism to give much simpler products

☆ *Abbreviations:* DPPP, diphenylpyrenylphosphine; HNE, 4-hydroxynonenal; H(P)ODE, hydro(pero)xyoctadecadienoate; IsoF, isofuran; IsoP, isoprostane; KCh, ketocholesterol; LDL, low density lipoprotein; O(O)HCh, hydro(pero)xycholesterol; PUFA, polyunsaturated fatty acid; NP, neuroprostane; TOH, tocopherol.

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0006-291X/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2005.08.072

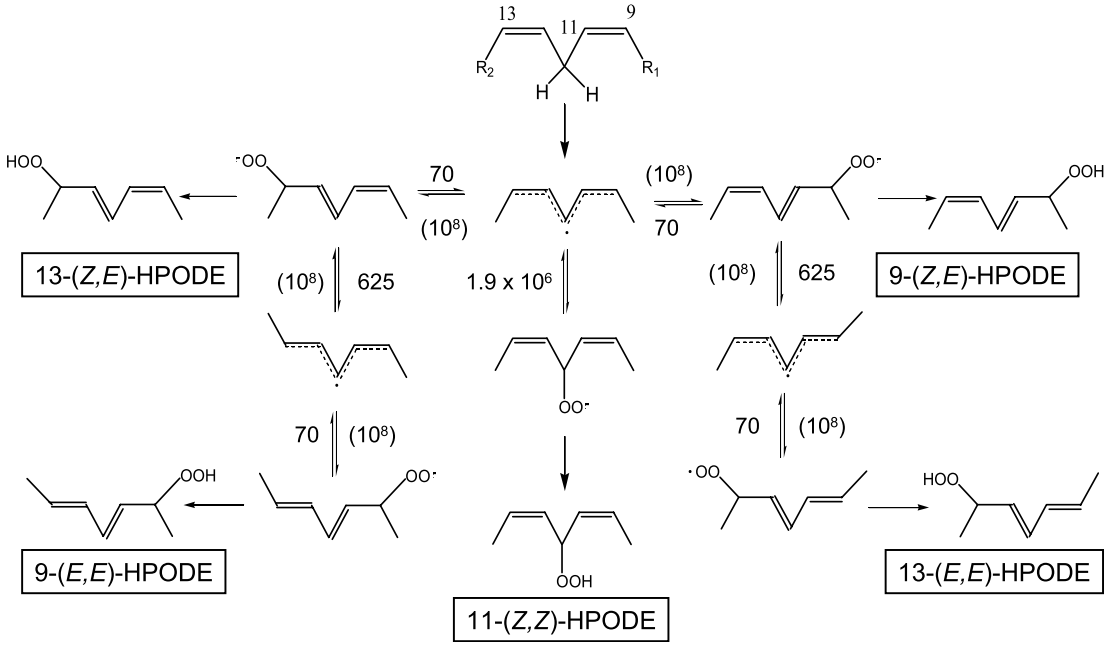
than arachidonates and more highly unsaturated fatty acids such as docosahexaenoates. The characteristics and specific products of the oxidation of linoleates by different mechanisms are given in Table 1. The oxidation of linoleate by lipoxygenase proceeds catalytically to give regio-, stereo-, and enantio-specific hydroperoxy octadecadienoates (HPODEs). The specificity depends on the type of enzyme, substrate, and reaction milieu. Additionally, the enantiospecificity varies considerably, which decreases with the type of substrate in the order of free linoleic acid > methyl linoleate > phospholipids > cholesteryl esters, and with the milieu, aqueous solution > lipoproteins > plasma [5,6]. Lipoxygenases undergo suicide inactivation [7] to liberate iron, which induces free radical-mediated lipid peroxidation, resulting in a decrease in specificity.

The free radical-mediated peroxidation of PUFA proceeds by five elementary reactions: (1) hydrogen atom transfer from PUFA to the chain initiating radical or chain carrying peroxyl radicals to give a pentadienyl carbon-centered lipid radical, (2) reaction of the lipid radical with molecular oxygen to give a lipid peroxyl radical, (3) fragmentation of the lipid peroxyl radical to give oxygen and a lipid radical (a reverse reaction of the above reaction (2)), (4) rearrangement of the peroxyl radical, and (5) cyclization of the peroxyl radical [8]. Reaction (5) is important only for PUFA having more than three double bonds, and it does not take place during the oxidation of linoleates. The reaction steps for linoleate oxidation are shown in Scheme 1 (modified based on [9]). The pathway and dynamics are determined primarily by thermochemistry. It has been confirmed that the oxidation of linoleic acid and its esters in an organic solution gives four isomeric conjugated diene hydroperoxides quantitatively. A typical example of the oxidation of methyl linoleate in an organic solution induced by an azo initiator is given in Scheme 2, and it can be noted that the amounts of oxygen consumption, substrate consumption, and formation of conjugated diene, peroxide, and HPODE are in good agreement [10].

Cholesterol oxidation products, commonly referred to as oxysterols, have received increasing attention as diagnostic biomarker of oxidative stress, as intermediates in bile acid biosynthesis, and messengers for cell signaling and cholesterol transport [11]. Cholesterol is oxidized by both enzymatic and non-enzymatic mechanisms (Scheme

Table 1
Lipid peroxidation (products from linoleate)

Type	Characteristics	Isomers of HPODE		
		Regio	Stereo	Enantio
Enzymatic (15-LOX)	Specific catalytic	13	cis, trans	*S*
Non-enzymatic, free radical chain oxidation ($LO_2^{\cdot}$)	Random chain reaction	9.13	cis, trans, trans, trans 9-ct = 13-ct, 9-tt = 13-tt	*R* = *S* (racemic)
Non-enzymatic, non-radical oxidation ($^1O_2$)	Random stoichiometric	9, 10, 12, 13	cis, trans	



Scheme 1. Reaction pathways of the peroxidation of linoleate.