Available online at www.sciencedirect.com
ScienceDirect
Pharmacology & Therapeutics 115 (2007) 400–409
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: R.M. Wadsworth

Chlorinated lipids and fatty acids: An emerging role in pathology

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Abstract

Although the existence of halogenated lipids in lower organisms has been known for many years, it is only since the 1990s that interest in their occurrence in mammalian systems has developed. Chlorinated (and other halogenated) lipids can arise from oxidation by hypohalous acids, such as HOCl, which are products of the phagocytic enzyme myeloperoxidase and are generated during inflammation. The major species of chlorinated lipids investigated to date are chlorinated sterols, fatty acid and phospholipid chlorohydrins, and α-chloro fatty aldehydes. While all of these chlorinated lipids have been shown to be produced in model systems from lipoproteins to cells subjected to oxidative stress, as yet only α-chloro fatty aldehydes, such as 2-chlorohexadecanal, have been detected in clinical samples or animal models of disease. α-Chloro fatty aldehydes and chlorohydrins have been found to have a number of potentially pro-inflammatory effects ranging from toxicity to inhibition of nitric oxide synthesis and upregulation of vascular adhesion molecules. Thus evidence is building for a role of chlorinated lipids in inflammatory disease, although much more research is required to establish the contributions of specific compounds in different disease pathologies. Preventing chlorinated lipid formation and indeed other HOCl-induced damage, via the inhibition of myeloperoxidase, is an area of growing interest and may lead in the future to antimyeloperoxidase-based antiinflammatory therapy. However, other chlorinated lipids, such as punaglandins, have beneficial effects that could offer novel therapies for cancer.

Keywords: Chlorohydrin; Chlorohexadecanal; Inflammation; Myeloperoxidase

Contents

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0163-7258/$ - see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.pharmthera.2007.06.002

1. Introduction: the existence of chlorinated lipids in biology

Naturally occurring organohalogen compounds are widespread in biology, and reports of chlorinated fatty acids and lipids go back to at least the 1970s (Gribble, 2003). A halogenating enzyme, chloroperoxidase, was identified in the fungus *Caldariomyces fumago* in 1959 (Shaw and Hager, 1959), and until 10 years ago it was thought that haloperoxidases, which catalyse the oxidation of chloride, bromide or iodide by hydrogen peroxide, were responsible for the production of biological organohalides (van Pee & Patallo, 2006). The majority of haloperoxidases in terrestrial organisms are iron-haem enzymes, but vanadium-containing haloperoxidases are common in marine algae, and nonmetal-containing haloperoxidases are also known (Butler, 1999). However, recently a more regiospecific family of enzymes, the flavin halogenases, has been discovered, and these enzymes are now thought to be more likely candidates for synthesis of the wide variety of halogenated compounds, at least in bacteria (van Pee & Patallo, 2006). Halogenated metabolites are particularly common in marine organisms (Gribble, 2003), and this also applies to the occurrence of halogenated fatty acids and lipids, which has been reviewed by Dembitsky and Srebnik (2002). For example, a family of fatty acid chlorohydrins has been identified in jellyfish (White & Hager, 1977), while dichlorinated and tetrachlorinated fatty acids have also been found in lipids of several species of fish and marine invertebrates (Bjorn et al., 1998). However, halogenated lipids do also occur naturally in terrestrial organisms, such as plants and fungi (Dembitsky & Srebnik, 2002).

In contrast, halogenated compounds are considerably rarer in mammals (Gribble, 2003), although several haloperoxidases are known, including myeloperoxidase, eosinophil peroxidase, lactoperoxidase, and thyroperoxidase (Arnhold et al., 2003; Ruf & Carayon, 2006). All of these, except thyroperoxidase, are involved in antimicrobial defense by the production of hypohalous acids and other reactive halogenated compounds. The formation of halogenated lipids in mammalian systems is not thought to be a normal physiological process but instead is associated with adverse conditions, such as infection and inflammation, and is currently regarded as an undesirable and damaging process. Although both myeloperoxidase and eosinophil peroxidase can catalyse the oxidation of small anions other than chloride, as described in the next section, many studies on halogenation in inflammation and tissue damage have focused on chlorination of biomolecules.

Consequently, this review will concentrate on chlorinated lipids: it will explore the types of chlorinated lipids that can be produced by these enzymes and consider their formation in comparison to chlorination of other biomolecules. The main methods that have been used for their analysis in biological systems and evidence for their existence in vivo will be described. The review will also discuss the possible contributions of chlorinated lipids to the pathology of inflammatory diseases, such as atherosclerosis, and will consider the potential of therapeutic approaches based on an understanding of these aspects.

2. Myeloperoxidase as a halogenating system

2.1. Substrates and products of myeloperoxidase

Although some chlorinated products occur naturally in animals, in mammals the majority of chlorinated lipids are thought to be produced by oxidative damage during inflammatory processes via the action of the halogenating enzymes myeloperoxidase and eosinophil peroxidase. Myeloperoxidase occurs in the azurophilic granules of phagocytes and is especially abundant in neutrophils, where it comprises ~ 5% of cellular protein (Klebanoff, 1999). The closely related eosinophil peroxidase is found only in eosinophils and has different substrate specificity to myeloperoxidase; the main difference being that it is essentially unable to oxidize chloride (Senthilmohan & Kettle, 2006). Both these enzymes are members of the haem peroxidase family and use hydrogen peroxide (H_2O_2) to oxidize halides (X^-) to hypohalous acids (HOX), and pseudohalides, such as thiocyanate (SCN^-) to hypothiocyanite ($OSCN^-$), as well as oxidizing other small anions or organic molecules (Arnhold et al., 2003; Senthilmohan & Kettle, 2006). Initially it was presumed that the oxidants were released from the enzyme and that the free hypohalous acids were responsible for subsequent oxidation reactions, but there is evidence that at least some such reactions proceed via enzyme-bound HOCl (Marquez & Dunford, 1994).

For some years it was assumed that chloride was the physiological substrate for myeloperoxidase, largely because its concentration in plasma is at least 1000-fold higher than the concentrations of the other substrates. However, it was subsequently shown that the relative specificity constant for chloride as a substrate of myeloperoxidase is much lower than either bromide or thiocyanate and that even in the presence of 100 mM Cl^- and 100 μM thiocyanate, approximately half the hydrogen peroxide utilized by myeloperoxidase was channeled into formation of hypothiocyanite (van Dalen et al., 1997). More recently, it has been shown that with concentrations of bromide (100 μM) and chloride (140 mM) that occur in plasma, oxidation of bromide to hypobromous acid accounts for ~ 1 quarter of the hydrogen peroxide utilization at pH 7.4. Thus, it was suggested that bromide may also be an important substrate at physiological pH, although these reactions were carried out in the absence of thiocyanate (Senthilmohan & Kettle, 2006). The situation in vivo is further complicated by the fact that HOCl is capable of oxidizing thiocyanate to hypothiocyanite; as hypothiocyanite is rather less reactive and damaging than HOCl, this means that it is effectively acting as a redox buffer and limiting the lifetime of the more powerful oxidant (Ashby et al., 2004). It is also important to remember that HOCl produced by this reaction is in equilibrium with molecular chlorine, which can also chlorinate biomolecules (Hazen et al., 1996). Moreover, myeloperoxidase can oxidize nitric oxide (NO) via a nitrosonium cation to nitrite (NO_2^-) (Podrez et al., 2000), itself a substrate that can be oxidized to nitrogen dioxide (NO_2) (van der Vliet et al., 1997), which is capable of nitrating proteins and other biomolecules (Zhang et al., 2002). Thus, it is important to realize that HOCl is only one physiological product of myeloperoxidase and that the balance of oxidants formed during inflammation will depend on where this occurs and the