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Review

Reactive electrophilic oxylipins: Pattern recognition and signalling

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ABSTRACT

Oxidized lipids in plants comprise a variety of reactive electrophiles that contain an α,β-unsaturated carbonyl group. While some of these compounds are formed enzymatically, many of them are formed by non-enzymatic pathways. In addition to their chemical reactivity/toxicity low levels of these compounds are also biologically active. Despite their structural diversity and biosynthetic origin, common biological activities such as induction of defense genes, activation of detoxification responses and growth inhibition have been documented. However, reactive electrophilic oxylipins are poorly defined as a class of compounds but have at least two properties in common, i.e., lipophilicity and thiol-reactivity. Thiol-reactivity is a property of reactive oxylipins (RES) shared by reactive oxygen and nitrogen species (ROS and RNS) and enables these agents to modify proteins *in vivo*. Thiol-modification is assumed to represent a key mechanism involved in signal transduction. A metaanalysis of proteomic studies reveals that RES oxylipins, ROS and RNS apparently chemically modify a similar set of highly sensitive proteins, virtually all of which are targets for thioredoxins. Moreover, most of these proteins are redox-regulated, i.e., post-translational thiol-modification alters the activity or function of these proteins. On the transcriptome level, effects of RES oxylipins and ROS on gene induction substantially overlap but are clearly different. Besides electrophilicity other structural properties such as target affinity apparently determine target selectivity and biological activity. In this context, different signalling mechanisms and signal transduction components identified in plants and non-plant organisms as well as putative functions of RES oxylipins are discussed.

Contents

Abbreviations: GSH, glutathione; KOTE, oxo-octadecatrienoic acid; LOOH, lipid hydroperoxides; MDA, malondialdehyde; JA, jasmonic acid; OPDA, 12-oxo phytodienoic acid; RES, reactive electrophilic species; RNS, reactive nitrogen species; ROS, reactive oxygen species; Nrf2-Keap1, nuclear factor erythroid 2 P45-related factor; PPARγ, peroxisome proliferator-activated receptor γ.

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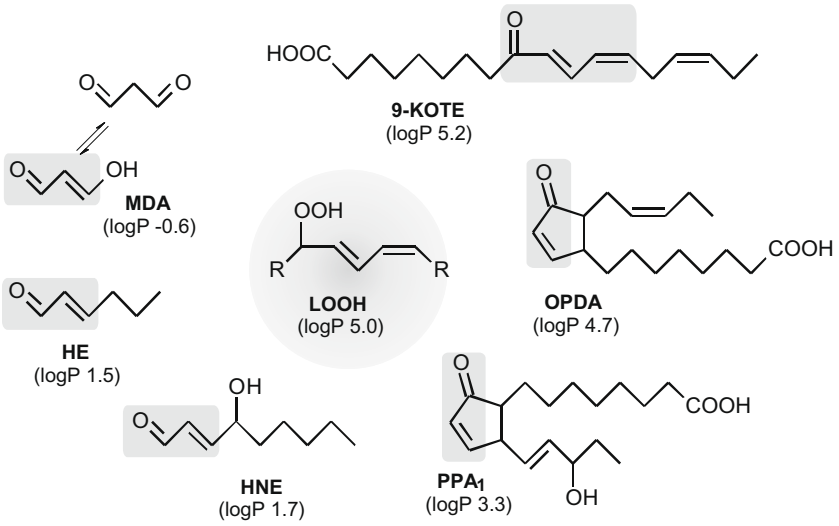

Fig. 1. Representative reactive electrophilic species (RES). Oxylipins shown are fatty acid hydroperoxides (LOOH), malondialdehyde (MDA), 2*E*-hexenal (HE), 4-hydroxy-2*E*-nonenal, A_1-phytoprostanes (PPA_1), 12-oxo-phytodienoic acid (OPDA) and 9-oxo-octadecatrienoic acid (9-KOTE). Lipophilicity of the oxylipins is indicated by their log*P* value (see text for details).

1. Fatty acid derived reactive electrophilic species (RES)

Non-enzymatic as well as enzymatic oxygenation of polyunsaturated fatty acids produces an array of substances, many of which can be classified as chemically reactive electrophilic species (Almeras et al., 2003). Reactive electrophiles may react with nucleophiles in cellular targets such as proteins and nucleic acids. Hence, RES have the inherent potential to initiate severe adverse biological effects including general toxicity and mutagenicity. However, low levels of RES are found ubiquitously in all higher organisms and are naturally present even in unstressed cells and tissues (Mueller, 2004).

For systematic and functional reasons, in this review reactive electrophilic oxylipins are classified as compounds that display significant chemical reactivity and covalently bind to nucleophiles such as thiols and amines. According to this classification, fatty acid derived hydroperoxides, α,β-unsaturated epoxides and α,β-unsaturated aldehydes and ketones are denoted as RES. The focus will be especially on thiol-reactive oxylipins comprising the chemical reactive α,β-unsaturated carbonyl moiety (some representative examples are shown in Fig. 1). As outlined below, reactivity of these compounds with protein thiols is at least equal or higher than H_2O_2, which is discussed as a key feature qualifying them as potential intracellular signals. Significantly weaker electrophiles such as saturated ketones and aldehydes (i.e., jasmonic acid, jasmone and hexanal) are not classified as RES.

A variety of RES oxylipins are synthesized in plants mainly from the polyunsaturated fatty acids linolenic acid (18:3), linoleic acids (18:2) and hexadecatrienoic acid (16:3). In the enzymatic pathways, lipoxygenases catalyze the entry reaction and form fatty acid hydroperoxides (LOOH) in esterified form in membranes and in free form. LOOH are reactive RES oxylipins that can be metabolized through three major RES-generating pathways (Feussner and Wasternack, 2002; Mosblech et al., 2009): (1) via the allene oxide synthase or jasmonate pathway jasmonates are formed. This pathway comprises two RES oxylipins: a short lived allene oxide and the cyclopentenone intermediates 12-oxo-phytodienoic acid (OPDA, Fig. 1) and dinor-OPDA. In *Arabidopsis thaliana*, OPDA/dinor-OPDA synthesis may take place on both esterified membrane fatty acids and free fatty acids. (2) Reduction or dismutation of LOOH yields the hydroxy fatty acids and reactive oxo-fatty acids including 9-oxo-octadecatrienoic acid (9-KOTE, Fig. 1). (3) Alternatively, free fatty acid hydroperoxides can be fragmented by hydroperoxide lyase into two fragments. Cleavage of 9- and 13-hydroperoxides from C18 fatty acids yield hexanal and 9-oxo-nonanoate as well as two RES: 3*Z*-hexenal (rapidly isomerized to 2*E*-hexenal, Fig. 1) and 12-oxo-9*Z*-dodecenoate (rapidly isomerized to 12-oxo-10*E*-dodecenoate) as first products. Under basal conditions only low amounts of free RES oxylipins accumulate. However, both pathways can be rapidly activated by wounding and a variety of biotic and abiotic stress conditions leading to a transient over-accumulation of free RES oxylipins. For further reading, excellent reviews on this topic are available (Mosblech et al., 2009; Wasternack, 2007).

In addition, similar to the enzymatic RES oxylipin formation, non-enzymatic, free radical-catalyzed reactions take place under basal and – more dramatically – under severe oxidative stress conditions. Here, several fatty acid LOOHs (including the enzymatically formed species) first accumulate in membrane lipids where also the subsequent steps take place: (1) reduction or dismutation of LOOH yields a series of hydroxy- and oxo-fatty acids (i.e., 9-KOTE, Fig. 1) including those compounds formed enzymatically. (2) Under free radical catalysis, however, LOOH may be further oxidized to a great variety of acyclic and cyclic oxylipins, one of which is A_1-phytoprostane (Fig. 1). (3) Under free radical catalysis, LOOH and their oxidation products can be fragmented to give rise to a myriad of products including the products formed by hydroperoxide lyase (see above) and additional RES oxylipins such as malondialdehyde (MDA, Fig. 1) and 4-hydroxy-2*E*-nonenal (Fig. 1). Non-enzymatic oxidation takes place in membranes *in situ* from which RES oxylipins can be released through lipases or fragmentation. It is out of the scope of this review to describe the mechanisms of formation which is reviewed elsewhere extensively (Frankel, 2005; Mueller, 2004).

Notably, non-enzymatically and enzymatically synthesized RES oxylipins are typically formed simultaneously under a variety of biotic and abiotic stress conditions. Usually, analytical, genetic and functional studies focus on single products or a class of compounds such as MDA (Weber et al., 2004), jasmonates and volatile aldehydes (Chehab et al., 2008) or phytoprostanes (Thoma et al., 2004) thereby underestimating the total amount of RES oxylipins accumulating under a certain condition. As outlined below, RES oxylipins may be recognized as a pattern of reactive electrophiles with largely overlapping biological activities. Hence, a much larger