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Review

On the role of 4-hydroxynonenal in health and disease

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The authors and Valeria Mile dedicate this article to the pioneer of HNE research, Angelo Benedetti on the occasion of his 70th birthday.

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ABSTRACT

Polyunsaturated fatty acids are susceptible to peroxidation and they yield various degradation products, including the main α,β-unsaturated hydroxyalkenal, 4-hydroxy-2,3-trans-nonenal (HNE) in oxidative stress. Due to its high reactivity, HNE interacts with various macromolecules of the cell, and this general toxicity clearly contributes to a wide variety of pathological conditions. In addition, growing evidence suggests a more specific function of HNE in electrophilic signaling as a second messenger of oxidative/electrophilic stress. It can induce antioxidant defense mechanisms to restrain its own production and to enhance the cellular protection against oxidative stress. Moreover, HNE-mediated signaling can largely influence the fate of the cell through modulating major cellular processes, such as autophagy, proliferation and apoptosis. This review focuses on the molecular mechanisms underlying the signaling and regulatory functions of HNE. The role of HNE in the pathophysiology of cancer, cardiovascular and neurodegenerative diseases is also discussed.

1. Synthesis and breakdown of HNE

4-Hydroxy-2,3-*trans*-nonenal (4-hydroxynonenal, HNE) is an α,β-unsaturated hydroxyalkenal. The molecule is highly reactive due to its three functional groups: an aldehyde, a double bond (alkene) between carbon C2 and C3, and a secondary alcohol at carbon C4 (Fig. 1). Carbon C1 and C3 are electrophilic sites and carbon C1 is also a redox center. The compound was first described in autooxidized polyunsaturated fatty acids (PUFAs) and triglycerides [1]. The first report on the formation of HNE in a biological system was published Benedetti et al. in Biochim. Biophys. Acta in 1980 [2]. This pioneer work investigated the pathological effects of NADPH-Fe induced lipid peroxidation in liver microsomes, including the defective activity of glucose-6-phosphatase, and identified HNE as the underlying toxic intermediate.

1.1. HNE formation

Lipid peroxidation is a general term, which refers to different mechanisms and can be classified as enzymatic, non-enzymatic non-radical and non-enzymatic free-radical mediated peroxidation [3]. Free-radical non-enzymatic peroxidation of PUFAs is the dominant pathway in oxidative stress induced by radiation, heat, free radicals, xenobiotics, metal ions or reactive oxygen or nitrogen species (ROS or RNS). Hydroxyl radical (OH·), the most powerful initiator of lipid peroxidation can be generated from hydrogen peroxide via the Fenton– and Haber–Weiss reactions, in the presence of free iron or copper ions. Lipid peroxidation can be initiated by a hydroxyl-radical-mediated removal of an H• radical from a lipid (LH), which yields a lipid radical (L•). In the propagation phase, L• reacts with oxygen and forms a lipoperoxyl radical (LOO•). Lipoperoxyl radical in turn reacts with another PUFA to yield a new L• and a lipid hydroperoxyde (LOOH). Thus, one hydroxyl radical can generate a high number of lipid hydroperoxydes until the chain reaction is terminated by a chain-breaking antioxidant (e.g. tocopherol).

Lipid hydroperoxydes are regarded as primary products of lipid peroxidation (Fig. 2). However, these compounds are unstable: they can be

Abbreviations: AD, Alzheimer's disease; ALDH, aldehyde dehydrogenase; AMI, acute myocardial infarction; ARE, antioxidant response element; CDK, cyclin-dependent kinase; CHF, chronic heart failure; DHLA, dihydrolipoic acid; ER, endoplasmic reticulum; GSH, glutathione; HL-60, human promyelocytic cell line; HNE, 4-hydroxy-2,3-trans-nonenal; Keap1, Kelch ECH associating protein 1; PC12, rat phaeochromocytoma cell line; pRb, retinoblastoma protein; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; UPR, unfolded protein response

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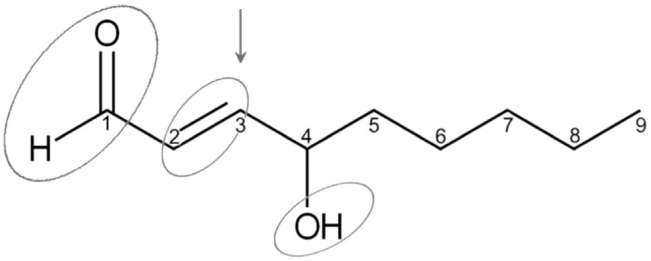

Fig. 1. Chemical structure of 4-hydroxy-2,3-trans-nonenal (HNE). Circles indicate the reactive groups of the molecule; the arrow shows the site of nucleophilic attack.

transformed into peroxyl and alkoxyl (LO·) radicals and can be decomposed to secondary products. Alkoxyl radicals are especially prone to β-scission, which results in the formation of short-chain products, including HNE (Fig. 2). Among the end products of lipid peroxidation other reactive aldehydes, such as malondialdehyde (MDA) are also present; for more detailed description of the biosynthetic pathways we refer to recent excellent reviews [4,5].

The secondary products of lipid peroxidation are reactive, yet relatively stable compounds, they can travel remarkable distances from the site of synthesis. HNE, for instance can reach well measurable concentrations in the tissues and in the blood, thus it can be regarded as a biomarker of the oxidative stress. Its physiological concentration is in the submicromolar range (<0.1 μM), while in oxidative stress, even micromolar levels can be observed [6].

1.2. Biotransformation of HNE

In situ lipid peroxidation is not the only source of HNE as it can also be taken up with the food [7]. Thus, HNE is both a xeno- and an endobiotic substrate for biotransformation. The metabolism of HNE (and other secondary lipid peroxidation products) is rapid and effective, involving all phases of biotransformation. Since the molecule already possesses functional groups suitable for conjugation, the phases I and II of biotransformation can be reversed. It should be noted that the relative contribution of various pathways to HNE biotransformation markedly differs in different species and tissues (see e.g.[8]), which can be in the background of variable toxicity of HNE.

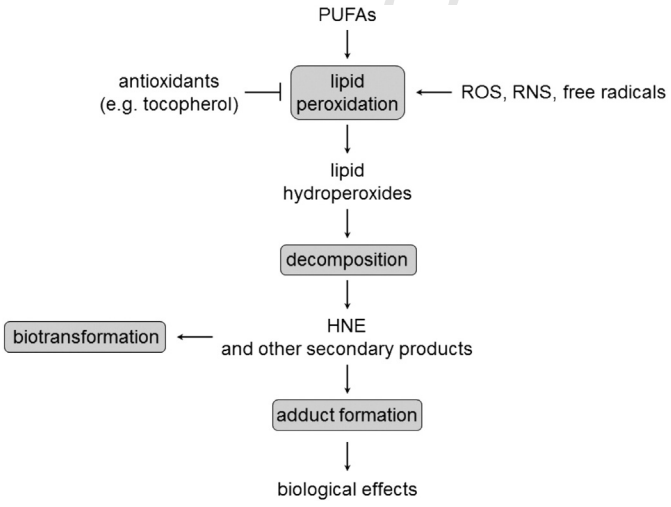

Fig. 2. Outline of HNE metabolism. HNE is generated as secondary product of lipid peroxidation. It can be detoxified by various reactions of biotransformation; alternatively, it can form macromolecular adducts.

1.2.1. Phase I reactions

The aldehyde group is a substrate for oxidoreductases, and it can be reduced to an alcoholic hydroxyl or oxidized to a carboxylic group. The participating enzymes are aldose reductase and aldehyde dehydrogenase; they form 1,4-dihydroxynonene and 4-hydroxynonenoate, respectively [9,10]. The latter product can undergo a consecutive β-oxidation. Several cytochrome P450 isozymes have been also shown to catalyze both the oxidation [11] and the reduction [12] of the aldehyde group. Cytochome P450s of the CYP4A family are also involved in the oxidative metabolism of HNE, by catalyzing the ω- and ω-1 oxidation of 4-hydroxynonenoate [13,14]. Ketogenic diet upregulates ω- and ω-1 hydroxyation of 4-hydroxynonenoate in rat liver via the induction of CYP4A isozymes [14]. The hydroxyl group of carbon C4 and the double bond between C2 and C3 are also subjects of oxidation or reduction, respectively.

1.2.2. Phase II reactions

The carbon-carbon double bond of HNE reacts with nucleophilic thiol groups, including that of the tripeptide glutathione (GSH). Michael addition leads to the formation of GSH conjugates. This spontaneous reaction can be highly accelerated by glutathione-*S*-transferases. The conjugation reaction is present in most cells and tissues.

The glutathione conjugation can be followed by oxidoreductions described above; and thence the glutathione conjugates of 1,4-dihydroxynonane and 4-hydroxynonanate are formed. Aldose reductase has a low micromolar K_M towards the glutathione conjugate of HNE, thus this metabolic pathways seems to be dominant in vivo [15].

It should be noted that the glutathione conjugates of HNE are not inactive product, but potential signal molecules. Mitogenic effect of HNE has been reported to be mediated by the glutathione conjugate reduced by aldose reductase in rat aortic smooth muscle cells [16]. These compounds were also shown to mediate the inflammatory effect of oxidative or glucotoxic stress in adipocytes [17,18]. Inhibition of aldose reductase prevented systemic inflammation and cardiomyopathy upon endotoxin treatment [19].

The oxidized acidic derivatives can be further metabolized by cytochrome P4504A, yielding ω-hydroxylated metabolites. The mercapturic acid derivatives of these products are present in the urine and can serve as biomarkers of in vivo lipid peroxidation (for a review see [20]). Glutathione and mercapturic acid conjugates of HNE, 1,4-dihydroxynonane and 4-hydroxynonanate are secreted also into the bile.

Cysteine can be also a conjugation partner for HNE. In a recent study increased extracellular formation of HNE-cysteine conjugate was observed in colon cells with a mutation of the adenomatous polyposis coli gene; the reaction – together with the upregulation of aldehyde dehydrogenases, glutathione transferase and cystine transporter – confers higher resistance towards HNE in mutant cells [21].

1.2.3. Phase III reactions

MRP1 and MRP2 multidrug resistance proteins have been shown to transport glutathione conjugates of HNE and to protect the cell from HNE toxicity [22,23]. Another ATP dependent, but non-ABC transporter, RLIP76 (Ral-interacting GTPase activating protein, also known as Ral-binding protein 1) has high transport activity towards glutathione conjugates of HNE; this protein accounts for the majority of the transport [24,25]. Indeed, overexpression of RLIP76 abolished the mitogenic effects of HNE and its glutathione conjugates observed in rat aortic smooth muscle cells, while its downregulation promoted the mitogenic effects [14].

1.3. Adduct formation

HNE accumulation and toxicity are counteracted by an efficient and rapid biotransformation. Yet, in spite of these protective efforts, HNE is present in the cells at measurable concentrations, and gives rise to undesired events. HNE is able to react readily with various cellular

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