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Review Article

Novel molecular approaches for improving enzymatic and nonenzymatic detoxification of 4-hydroxynonenal: toward the discovery of a novel class of bioactive compounds

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ABSTRACT

4-Hydroxy-*trans*-2-nonenal (HNE), an α,β-unsaturated aldehyde generated endogenously by the radical-mediated peroxidation of ω-6 polyunsaturated fatty acids, is a bioactive molecule acting in several physiopathological mechanisms and most of its activity is due to the covalent modification of biomolecules. Although at low and physiological levels HNE acts as an endogenous signaling molecule, a growing bulk of evidence indicates that at high and toxic concentrations, HNE is involved in the onset and propagation of several human diseases. To get more conclusive evidence of HNE as a pathogenetic factor, a pharmacological tool able to inhibit the HNE-induced cellular response is required. Such compound is currently not available, although several molecular strategies have so far been reported with the aim of inhibiting HNE formation or catalyzing its removal. Although most of these are not selective, such strategies have been found to induce several biological responses and would merit further investigation. In this review the various strategies are reported and discussed together with their limits and potentials.

Contents

Abbreviations: HNE, 4-hydroxy-*trans*-2-nonenal; ALE, advanced lipoxidation end product; AGE, advanced glycation end product; FFA, free fatty acid; RCS, reactive carbonyl species; NAC, *N*-acetylcysteine; HHE, 4-hydroxyhexenal; AG, aminoguanidine; PYR, pyridoxamine; HY, hydralazine; GO, glyoxal; MGO, methylglyoxal; MDA, malondialdehyde; L-CAR, carnosine; His-DHN, His–1,4-dihydroxynonane; D-CAR, d-carnosine; ALDH, aldehyde dehydrogenase; Alda-1, ALDH2 activator 1

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Chemical reactivity and biological functions of 4-hydroxy-*trans*-2-nonenal: an introduction

Reactivity of 4-hydroxy-trans-2-nonenal

4-Hydroxy-*trans*-2-nonenal (HNE)[1] is an α,β-unsaturated aldehyde generated endogenously by the radical-mediated peroxidation

of ω-6 polyunsaturated fatty acids. HNE is a reactive carbonyl species able to form covalent adducts with nucleophilic biological targets, including proteins, DNA, and phospholipids [1]. The unique reactivity of this molecule can be explained by considering its marked electrophilicity, which is due to both the carbonyl group and the conjugated double bond, which generate two electrophilic centers: the carbonyl carbon atom and the β-carbon atom, both of which can condense with suitable nucleophilic moieties. Notably, the reactivity of the β-carbon atom is here enhanced by the electron-donor effect of the vicinal γ-hydroxyl function. [2,3].

Therefore, HNE can give covalent adducts with the protein nucleophilic side chains, namely, the cysteine thiol group, the lysine ε amino group, and the histidine imidazole ring. Although all these reactions mainly involve the β-carbon atom, yielding the corresponding Michael adducts, they occur with slightly different mechanisms, which can partly explain the different reactivities of the mentioned residues and which deserves some basic considerations [4].

Among the cited nucleophilic moieties, the thiol function is the most reactive; the anionic thiolate is its reactive form and thus the reactivity of the cysteine residues increases with the acidity of their thiol group. The thiol group can react with the carbonyl carbon atom, giving a reversible thioacetal adduct, and with the β-carbon atom, giving the corresponding Michael adduct (Fig. 1). Although the former is kinetically favored, the greater stability of the latter renders it the only adduct detectable at the equilibrium [5].

Similar to cysteines, the reaction between HNE and the lysine ε amino group can involve the carbonyl carbon group, giving a reversible Schiff base, and the β-carbon atom, giving the corresponding Michael adduct (Fig. 1). Because the neutral ε amino group is the reactive form, the lysine reactivity largely depends on its basicity. Indeed, strongly basic lysines ($pk \gg 10$) exclusively exist in their protonated state and as such they can yield neither Schiff bases nor Michael adducts, whereas less basic ε amino groups can condense with HNE, giving Schiff bases and/or the corresponding Michael adducts depending on the nucleophilicity as well as on the surrounding protein environment. Of note, lysines endowed with a poorly basic ε amino group and embedded in a hydrophobic environment tend to yield stable and detectable Schiff bases (regardless of their ability to give also the Michael adducts). Such lysines lose the selectivity for α,β-unsaturated aldehydes and can also trap exogenous or physiological carbonyl compounds [6].

The histidine imidazole ring is finally the least reactive moiety and indeed it cannot give Michael addition alone at physiological pH (Fig. 1) as confirmed by several synthetic studies (see for example [7]). This means that the environment surrounding a reactive histidine should be able to catalyze the addition by enhancing the basicity of the imidazole ring and/or the electrophilicity of the approaching HNE molecule (Fig. 2). The latter can occur when the carbonyl oxygen atom interacts with a positively charged residue, which polarizes the carbonyl group thus enhancing the reactivity of the β-carbon atom. A second mechanism to potentiate the HNE reactivity can involve the condensation of its

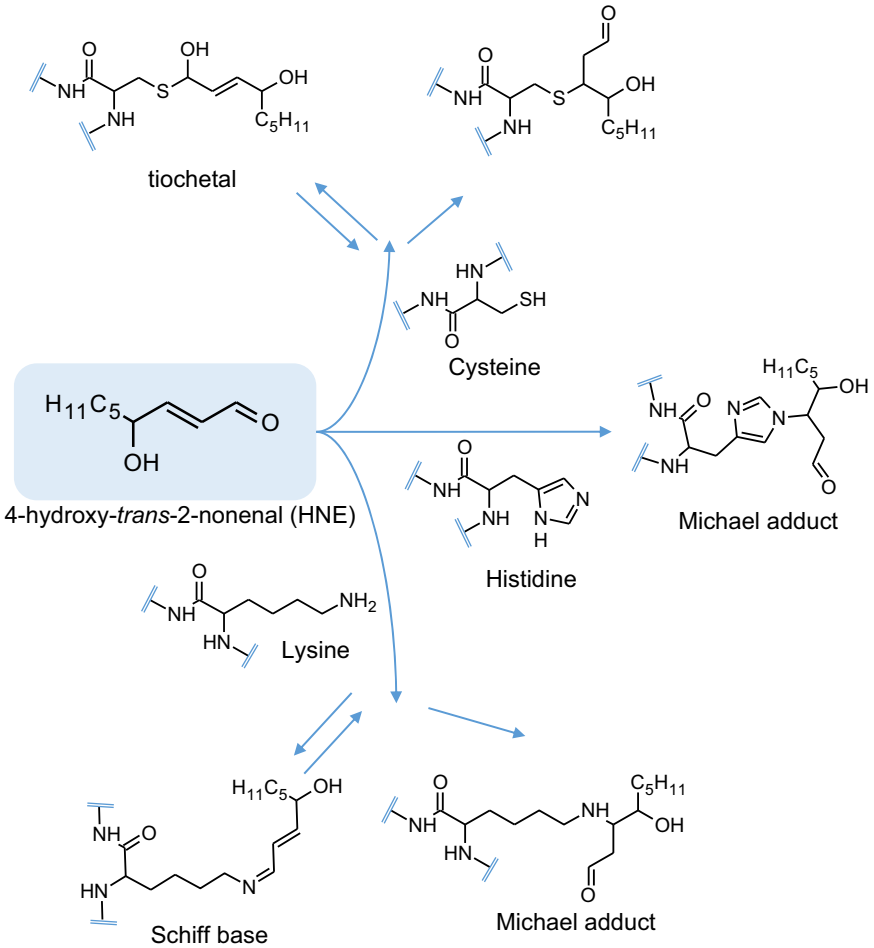

Fig. 1. Major adducts arising from the reaction between HNE and the nucleophilic residues cysteine, lysine, and histidine.