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## 4-hydroxynonenal in the pathogenesis and progression of human diseases

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### Abstract

Metastable aldehydes produced by lipid peroxidation act as 'toxic second messengers' that extend the injurious potential of free radicals. 4-hydroxy 2-nonenal (HNE), a highly toxic and most abundant stable end product of lipid peroxidation, has been implicated in the tissue damage, dysfunction, injury associated with aging and other pathological states such as cancer, Alzheimer, diabetes, cardiovascular and inflammatory complications. Further, HNE has been considered as a oxidative stress marker and it act as a secondary signaling molecule to regulates a number of cell signaling pathways. Biological activity of HNE depends on its intracellular concentration, which can differentially modulate cell death, growth and differentiation. Therefore, the mechanisms responsible for maintaining the intracellular levels of HNE are most important, not only in the defense against oxidative stress but also in the pathophysiology of a number of disease processes. In this review, we discuss the significance of HNE in mediating various disease processes and how regulation of its metabolism could be therapeutically effective.

### Keywords

4-hydroxy 2-nonenal; oxidative stress; cancer; cataract; Alzheimer

## 1. INTRODUCTION

Free radicals such as superoxide anion and hydroxyl radicals have been suggested to stimulate tissue injury related to several disease states and the degenerative processes of senescence. However, the mechanism (s) of free radical-induced injury remains poorly understood [1, 2]. Due to their high reactivity, the toxicity of free radicals is limited to the site of their generation [3]. The injury may be extended by the metastable products of free radical reactions, such as aldehydes which can act as “toxic second messengers” [4]. One of the most abundant and cytotoxic lipid -derived aldehyde is 4-hydroxy 2-nonenal (HNE). The HNE is formed by the oxidation of  $\omega$ -6 polyunsaturated fatty acids [5; Figure-1]. During autoxidation, fatty acids form alkoxy radicals [6] that undergo beta-scission leading to the formation of several saturated and unsaturated oxo-compounds of which HNE is one of the most reactive and under some conditions represents 95 % of the generated aldehydes [7]. Currently, HNE is considered an important marker of oxidative stress, a possible contributory agent to several diseases such as Alzheimer and a stimulant of prominent pathobiochemical pathways such as inflammation, indicating a potential contribution of the

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aldehyde to the pathogenesis of several chronic diseases [8–10]. The biological occurrence of this molecule appears within the range of 0.1–1  $\mu\text{M}$  [5]. Steady-state concentration of HNE can easily reach 5  $\mu\text{M}$  to 5  $\text{mM}$  or more within membranes during various pathological conditions [11, 12]. HNE has been shown to have high toxicity to mammalian cells, can inactivate various enzymes and also inhibit DNA and protein synthesis [13].

## 2. BIOCHEMICAL PROPERTIES OF HNE

HNE is a tremendously reactive [14–16] and is considered to be the most toxic aldehyde because of the presence of  $\alpha$ ,  $\beta$ -double bond at C-2 position, carbonyl group at C-1 and hydroxyl group at C-4 position [17, 18]. This aldehyde can readily react with molecules containing thiol and amino groups (Figure-2). Amino acids such as cysteine, histidine and lysine are the primary reactants with HNE [18–19]. Because of the presence of C=C double bond, HNE can react with nucleophiles, such as cysteine or glutathione and form Michael adducts [20, 21], also known as primary reaction. However, primary reaction velocity is greatly enhanced if the reaction is catalysed by enzyme glutathione-S-transferases (GSTs) [22, 23]. Once this primary reaction occurs leading to free rotation at C2–C3 bond secondary reaction takes place which involves the carbonyl and the hydroxyl groups in which primary amines may alternatively react with the carbonyl group to form Schiff bases [18]. Interestingly, thiol or amino groups react primarily at C-3 position and secondarily at the carbonyl C-1 due to a partial positive charge at C-3 because of the presence of C=C double bond and carbonyl group (C=O) [18]. Hydroxyl group at C-4 also offers inductive effect which further increases the partial positive charge [18, 24].

HNE is an extraordinary lipid aldehyde generated during peroxidation of unsaturated fatty acyl residues esterified in phospholipids [25–27]. It has been considered that degradation of hydroperoxides leads to the formation of aldehydic products such as HNE, malonaldehyde (MDA) etc. Spiteller et al. reported that decomposition of 13-hydroperoxy-9, 11-octadecadienoic acid (13-HPODE) generates these aldehydic products [27]. These toxic lipid aldehydes (HNE and MDA) could be generated by the oxidation of linoleic acid and arachidonic acid in vitro [28, 29]. Furthermore, metals-mediated generation of ROS via Fenton-like reactions in the cell membrane also produces hydroxyl radicals which accelerate lipid peroxidation. Metals also participate in the formation of lipid peroxidation end-products, such as HNE. In addition, the peroxidation of fatty acids, particularly arachidonic acid, leads to the formation of a number of cytotoxic aldehydes including HNE [30, 31]. There are three main pathways associated with the metabolism of HNE: The HNE could be reduced to DHN by aldose reductase (AR) or oxidized to HNA by ALDH1. Also, HNE could conjugate with proteins, and more readily with glutathione (GSH) catalyzed by the glutathione S-transferases (GSTs) such as hGSTA4-4 and hGST5.8 to form GS-HNE [32–34]. The GS-HNE could be reduced by AR to GS-DHN [35]. Both GS-HNE and GS-DHN are actively transported out by multidrug resistance associated protein (MRP) and Ral-binding protein (RLIP76). Recent studies indicate that RLIP76 is responsible for significant (70%) transport of the GS-conjugates of HNE in cultured cells [36].

## 3. BIOLOGICAL FUNCTIONS OF HNE

HNE exerts physiologically beneficial effects depending on its intracellular concentration [13]. Lower intracellular concentrations (< 2  $\mu\text{M}$ ) of HNE seems to be beneficial to cells as they promote cell survival and proliferation [37, 38]. Higher concentrations of HNE (10 to 60  $\mu\text{M}$ ) have genotoxic effects since they lead to sister chromatid exchange [41], micronuclei formation and DNA fragmentation [39–42]. At concentrations > 100  $\mu\text{M}$ , HNE and related aldehydes cause lethal toxicity, and at these concentrations, inhibition of glycolytic enzymes, mitochondrial respiration, DNA and protein synthesis also occurs [42].

Low concentrations of HNE have been shown to disturb cellular calcium homeostasis [43]. Thus, the observations that large amounts of lipid aldehydes accumulate under pathological conditions, and that they affect cellular metabolism at relatively low concentrations, certainly substantiate the view that these aldehydes act as 'toxic second messengers'. Further, HNE at micromolar concentrations has consistently been shown to up-regulate the expression of transcription factors such as Nuclear Factor-Kappa B (NF- $\kappa$ B) which regulate the expression of a variety of genes involved in cell proliferation and differentiation the activation of protein kinase C (PKC), mitogen activated protein kinase (MAPK) [44, 35, 36], and while at higher concentrations HNE has been shown to inhibit the formation of NF- $\kappa$ B [45]. Higher concentration of HNE increases AP1 and other apoptotic related proteins. Poli et al [22] have demonstrated that inhibitors of PKC can significantly prevent HNE-induced AP-1 nuclear binding. Since HNE can react with proteins and enzymes, resulting in their modification and inactivation. Out of several major toxic effects of HNE produced during oxidative stress also cause damage to cellular components such as proteins and DNAs. However, several studies have demonstrated that HNE at nontoxic levels can potently activate stress response pathways such as MAPK and nuclear translocation of a redox-sensitive transcriptional factor, Nrf2 [46]. HNE also increases the expression and synthesis of the main fibrogenic cytokine, the transforming growth factor  $\beta$ 1 (TGF  $\beta$ 1), by macrophages. Besides up-regulation of the inflammatory and TGF  $\beta$  1, HNE has recently been reported to induce the expression and synthesis of monocyte chemotactic protein-1 (MCP1), which plays a major role in atherosclerosis [47, 48]. Further, recent studies demonstrate that GS-conjugates of HNE could play a key role in the inflammatory signaling [49, 50; Figure-3]. HNE and GS-HNE but not AR-catalyzed reduced form of GS-HNE, GS-DHN, has been shown to cause cell death or growth via activation of PKC, MAPK and NF-KB in colon cancer cells, vascular smooth muscle cells and macrophages. These studies suggest that GS-conjugates of HNE could act as oxidative stress-induced signaling intermediates that could increase or decrease the inflammation based on their concentration as well as type of cells where they generated and acted upon.

#### 4. INVOLVEMENT OF HNE IN DISEASE PROCESSES

The involvement of lipid peroxidation product HNE has been demonstrated in important neurodegenerative diseases such as Alzheimer's disease (AD) [51], Parkinson's disease (PD) [52], multiple sclerosis [53] and other diseases such as cancer [54], diabetes [55], inflammatory complications [56], atherosclerosis [57], osteoporosis [58], cataract and age-related macular degeneration [59–61]. A number of studies have identified increased HNE and HNE-modified proteins in human diseases.

#### 5. NEURODEGENERATIVE DISEASES

AD is a neurodegenerative condition in which nerve tissue in the brain breaks down which gradually reduces the ability to learn, think, and memorize [62]. Recent studies have established the relationship between oxidative stress-generated toxic aldehydes and possible causes of AD [63, 64]. HNE was found to be neurotoxic since elevated levels of HNE have been reported in the brain tissues and ventricular fluid of AD patients which is correlated with increased neuronal apoptosis [65–67]. Further, beta-amyloid was found to be positive for HNE and its modification could contribute to the toxicity associated with the amyloid deposits [68]. Antibodies against HNE-histidine were found to be reactive with neurofibrillary tangles and beta-amyloid core of senile plaques [69]. HNE at concentrations less than 10  $\mu$ M has been shown to impair Na<sup>+</sup>/K<sup>+</sup>-ATPase activity, covalent modification of the glucose transporter GLUT3 which impairs glucose transport, increase in neuronal vulnerability that leads to excitotoxicity and impairs mitochondrial function in neurons and synaptosomes of AD patients [71, 72]. Further, HNE by directly binding to GTP-binding

protein G<sub>q11</sub> has been shown to impair coupling of muscarinic cholinergic receptors to G<sub>q11</sub> in cortical neuron cultures which is significantly related to AD [73]. Parkinson disease (PD) is another age-related neurodegenerative disease clinically characterized by tremors at rest, muscular rigidity, bradycinesia and dementia [74]. Increased levels of HNE and HNE-protein adducts have been found in neurons of PD patients [68, 75, 76]. Castellani et al have shown that HNE is present in Lewy bodies in PD. A number of antioxidants including glutathione that alter the intracellular concentrations of HNE have been shown to prevent AD and PD [77].

## 6. CANCER

HNE is considered to contribute to the mutagenic and carcinogenic effects associated with oxidative stress-induced lipid peroxidation [78–81]. HNE and or its related bioactive metabolites can damage DNA, leading to formation of pro-mutagenic lesions in inflammation-driven cancers [82]. Several studies have shown that formation of protein-HNE adducts in renal and colon cancer cells and tissues are related to growth and progression of kidney and colon cancers [83–86]. Increased HNE or protein-HNE levels were observed in renal proximal tubules in a rat model of renal adenocarcinoma [87]. Further, increased HNE has been shown to be associated with hepatocarcinogenesis initiation in long-evans cinnamon (LEC) rats and these studies indicate that protein modification by HNE could be a potential mechanism of cellular disturbances leading to liver cancer initiation [88, 89]. Normal plasma concentration of HNE was found to be 0.65  $\mu$ M in healthy human subjects [90, 91]. Our recent studies indicate that AR catalyzed reduced form of GS-HNE; GS-DHN could mediate carcinogenic signals in human colon cancer cells [92–94]. Further, inhibition of AR that effectively reduces HNE and GS-HNE (K<sub>m</sub> 10–30  $\mu$ M) has been shown to prevent colon cancer growth and metastasis [95]. Overexpression of GSTs that conjugate HNE to GS-HNE has been shown to protect cells from UV induced cytotoxicity in K562 leukemia cells [96]. Recent studies also indicate that the RLIP76, a protein that transports and maintains the cellular levels of HNE, GS-HNE and GS-DHN could be used to regulate the tumorigenesis process [97].

## 7. CATARACT AND AMD

Cataractogenesis is a multi-factorial process in which progressive loss of light transmission by the lens is associated with profound changes in its structure, physiology and metabolism [98–101]. Overwhelming experimental evidence supports the view that oxidative stress plays a central role in cataract formation [102]. Although the lens is exposed to low oxygen tension (<30 mm Hg), and is rich in antioxidants such as glutathione (GSH), constant exposure to light imposes continuous oxidative stress [103]. Moreover, the concentration of H<sub>2</sub>O<sub>2</sub>, which causes lipid peroxidation and generates HNE, has been shown to be increased in patients with cataracts [104, 105]. Further, HNE has been shown to induce lens opacification and increased formation of protein-HNE adducts in cell membranes of epithelial cells [104, 106]. Downstream of protein-HNE adducts intercalate cell membranes and cause membrane fluidity changes that leads to calcium influx and activation of caspases inducing apoptosis that contributes to cataractogenesis [107, 108]. Therefore, the strategies that decrease the intracellular concentrations of HNE could be anti-cataractogenic. Indeed, we have recently shown that ablation of ALDH1 by ALDH1-specific siRNA resulted in increased lens opacification in rat lenses accompanied by increased formation of HNE-protein adducts [106]. Moreover, metal chelation up-regulates ALDH1 thereby increases HNE-detoxification and oxidation-associated toxicity [60]. Further, over-expression of GST has been shown to prevent cytotoxic effects of HNE in ocular cells [107–109]. In age-related macular degeneration (AMD), the retina is particularly susceptible to oxidative stress because of its high concentration of easily oxidized PUFAs and the presence of retinal

pigments that generate ROS when exposed to light. Lipid peroxidation- derived lipid aldehydes such as HNE and malondialdehyde have been shown to be significantly increased in the retina of AMD eyes as well as in patient's plasma [110, 111].

## 8. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Smoking and environmental pollutants such as air pollutants and industrial dust, are main risk factors for COPD, a fifth leading cause of death worldwide [112, 113]. Cigarette smoke is one of the major sources of ROS [114]. The inflammatory response to cigarette smoke is augmented due to increased release of ROS in neutrophils and macrophages. Indeed, increased oxidative stress and elevated levels of protein-HNE adducts has been observed in the lungs of COPD patients [112]. Furthermore, exposure of cigarette smoke to mice has been shown to increase HNE adducts in alveolar macrophages and bronchiole epithelial cells indicating involvement of HNE in cigarette smoke –induced COPD [113].

## 9. ALCOHOLIC LIVER DISEASE (ALD)

Alcoholic liver disease (ALD) is one of the major cause of death in United States and is linked with period and magnitude of alcohol consumed [115]. More than 90% of individuals consuming alcohol on a daily basis develop fatty liver (steatosis). Recent studies indicate that HNE and other lipid peroxidation products react with cellular proteins and the aldehyde-modified proteins serve as a biomarker for alcohol-induced oxidative stress [116]. Moreover, several reports have identified HNE- or MDA-conjugated proteins in liver [117, 118]. These reports demonstrate that despite the highly effective antioxidant systems, the chronic alcohol ingestion generates a pro-oxidative environment in the liver resulting in lipid peroxidation and the covalent modification of hepatic proteins which are linked to the pathophysiology of ALD [116].

## 10. INFLAMMATORY DISEASES

Increased formation of HNE and protein-HNE has been shown in many inflammatory diseases, such as endotoxemia, ischaemia-reperfusion injury [120], atherosclerosis [121], and rheumatoid arthritis [122]. Recent studies indicate that glutathione-conjugate of HNE induces vascular smooth muscle cell proliferation as well as death depending on its intracellular concentrations [36, 109, 123]. These studies indicate that GS-aldehyde conjugates could act as cellular signaling intermediates. Further, a recent study by Spite et al indicates that GS-HNE is a more potent inducer of inflammation than nonconjugated HNE [124]. Infact, GS-HNE has been shown to directly activate human neutrophils to generate superoxide anions, which in turn may facilitate HNE generation in a feedback cycle. In isolated neutrophils from mice, GS-HNE increases the cell surface expression of the CD11b/CD18 which could increase neutrophil influx into the peritoneal cavity [125]. Further, HNE and GS-HNE, but not GS-DHN has been shown to activate NF-kB in macrophages, indicating that GS-DHN formed by the reduction of GS-HNE by AR could be a novel signaling intermediate [126].

Most of the recent studies indicate that HNE and HNE-protein adducts could act as biomarkers for a number of human diseases since their formation is significantly enhanced in most of the human pathologies [127–129]. Recent studies indicate that regulation of proteins that maintain the cellular homeostasis of HNE could alter fate of these pathologies and serve as potential therapeutic targets [130]. Additional studies are required to clearly investigate how these enzymes/proteins regulate the formation of this important molecule, HNE, and disease progression [131]. Additionally, further, studies are necessary to understand how GS-HNE metabolites could act as signaling intermediates by regulating



various transcription factors that express inflammatory markers and initiate inflammatory pathologies.

## CONCLUSIONS and FUTURE PERSPECTIVES

Recent studies indicate without doubt that lipid aldehydes and glutathione-lipid aldehydes can act as signaling intermediates or toxic messengers of oxidative stress. Increased formation HNE and its protein adducts have been observed in number disease processes in humans. HNE has been shown to alter the cellular redox homeostasis responsible for cell growth, death and differentiation. Further, recent studies indicate that glutathiolation of HNE regulates its toxic effects. Despite multiple studies showing the connection between oxidative stress-generated lipid aldehydes (specifically HNE) and pathological consequences leading to a number of disease processes, the mechanisms by which varying concentrations of HNE detects cells fate towards death or growth is not clearly known. It is still not clear, how HNE and its glutathione conjugates regulate activation of redox transcription factors such as NF- $\kappa$ B and AP1? Moreover the role of HNE and its glutathione conjugates in regulation of innate and adoptive immune responses is not known. This is an important area, which needs to be investigated to understand the role of lipid aldehydes in the pathophysiology of inflammatory disorders. Investigations on how HNE regulates inflammasome activation will provide clues to identify the possible mechanism by which HNE mediates innate immune response. Regulation of enzyme activities of GST, AR and ALDH1 which are involved in the metabolism of HNE and maintaining the in situ concentration of HNE, could also control the pathophysiology of disease progression.

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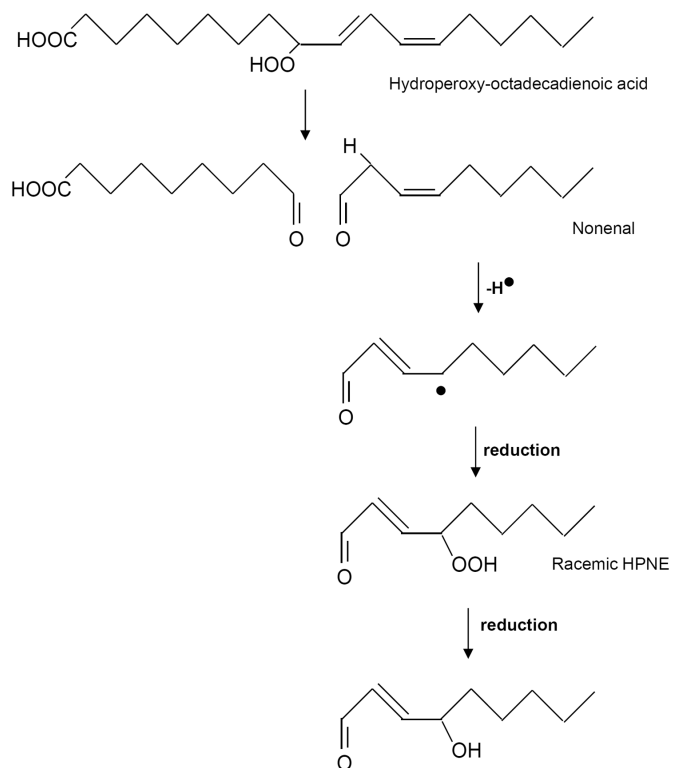
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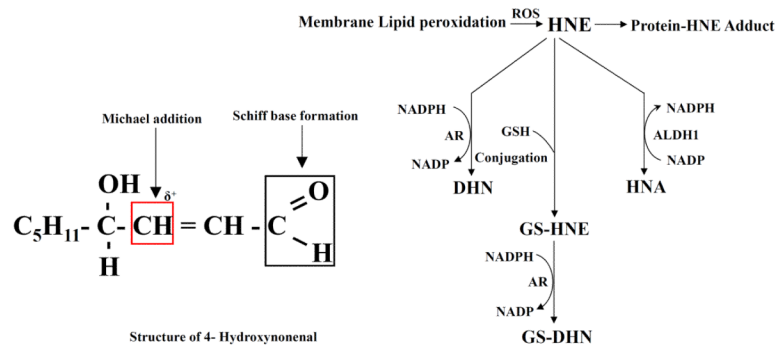
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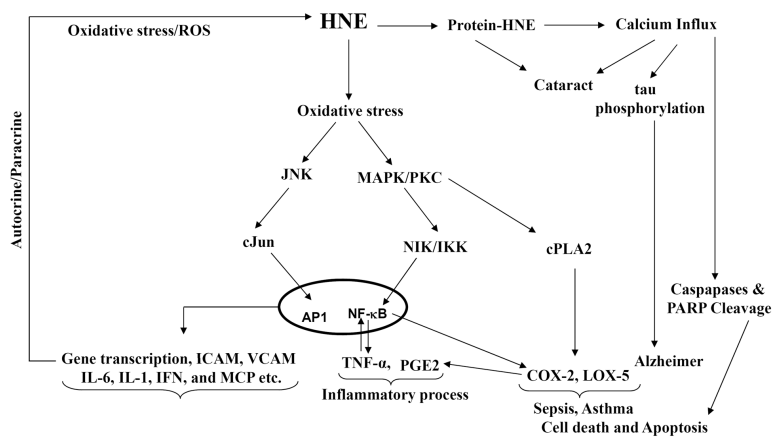




**Fig.1.**  
Formation of HNE from linoleic acid.



**Fig.2.**  
HNE and its metabolism.



**Fig.3.**  
Role of HNE in human diseases.