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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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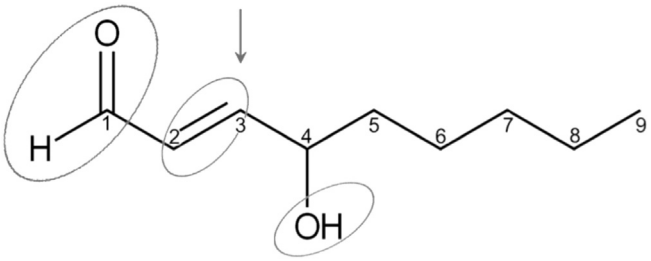


**Fig. 1.** Chemical structure of 4-hydroxy-2,3-trans-nonenal (HNE). Circles indicate the reactive groups of the molecule; the arrow shows the site of nucleophilic attack.

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.

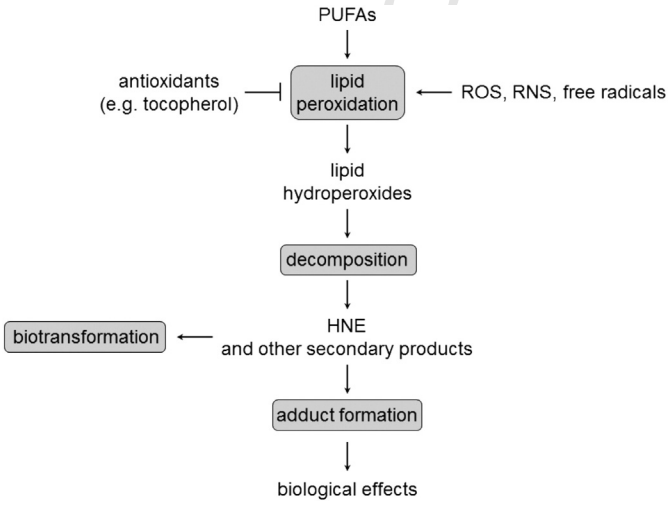


**Fig. 2.** Outline of HNE metabolism. HNE is generated as secondary product of lipid peroxidation. It can be detoxified by various reactions of biotransformation; alternatively, it can form macromolecular adducts.

### 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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components, such as DNA, proteins and other molecules containing nucleophilic thiol or amino groups [6,26]. The C2-C3 double bond is responsible for the Michael addition of thiol or amino compounds at the C3 carbon (Fig. 3). The C1 aldehyde group can react with primary amines and form of Schiff bases. While Schiff base formation is relatively slow and reversible, Michael adducts are stable, thus the formation of the latter is preferred in vivo. The cysteinyl, lysyl and histidyl residues of proteins are the main targets of Michael addition. HNE can also react with lipids containing amino groups (e.g. phosphatidyl ethanolamine, phosphatidyl serine, sphingosine) and with nucleic acids, preferably with the guanin base of DNA (Fig. 3). HNE-DNA adduct formation and the consequent mutagenicity occur in two independent pathways: i, direct interaction of HNE with two nitrogen atoms in guanine moieties, which yields four isomeric propano adducts [27], and ii, oxidation of HNE to 2,3-epoxy-4-hydroxy-nonanal [28] and a consecutive formation of exocyclic etheno adducts of guanine, adenine or cytosine moieties [29,30]. The different genotoxicity of HNE in various organs – beside the differences in tissue level of HNE and intensity of DNA repair mechanisms – can be attributed to the tissue- or cell-specific predominance of one of the two pathways, e.g. the latter one is dominant in hepatocytes [31]. (See Fig. 4.)

Protein-HNE adduct formation can lead to alterations in the normal functioning and modified activity of various proteins (for reviews, see [32–34]. Because of its double reactivity (Michael addition and Schiff bases)), HNE can contribute to protein cross-linking and induce a carbonyl stress.

## 2. HNE in signaling

Only a few plausible effects can be outlined among the confusingly pleiotropic actions of HNE in cell signaling. Antioxidant, heat shock and ER stress responses are activated by HNE and these responses can be integrated into a unified scheme. The three adaptive pathways serve not only the disposal of HNE and the prevention of its toxic effects, but also the negative regulation of proteostasis and stimulation of protein folding. These latter mechanisms help the cell to enter the lists against adduct formation and misfolding.

### 2.1. The Keap1–Nrf2–ARE pathway

Exogenously added HNE has been shown to interact with practically any signaling pathways in cells (for an extensive list of these interactions see [35]), leading to pathological responses. These effects are due to the covalent interactions of HNE with key proteins of signal transduction pathways; there are no experimental evidences for classic, ligand-type interactions. The main target of HNE as a major endogenous electrophilic compound is the Keap1 (Kelch ECH associating protein 1)–Nrf2 (nuclear factor erythroid 2-related factor 2)–ARE (antioxidant response element) pathway. This pathway senses prooxidant effects and organizes the cellular response against oxidant or electrophile stress. The extremely cysteine-rich Keap1 under stress-free conditions binds Nrf2 and directs it towards ubiquitylation and proteasomal degradation. Cysteine residues of Keap1 are sensitive to electrophilic attacks; while electrophiles in high concentrations form adducts almost completely with cysteinyl thiols, in low concentrations they react with a specific subset of thiols [36,37]. It has been reported that Keap1 directly recognizes alkenals (including HNE), NO and $Zn^{2+}$ by three distinct sensors composed by cysteines and basic amino acids [38]. Phylogenetic analyses showed that the alkenal sensor is the most ancient one.

Independently from the nature of the electrophilic stimuli, it seems that the downstream events are the same; adduct formation or oxidation of cysteine residues of Keap1 compromises its potential to recruit the ubiquitin ligase complex, thus Nrf2 can accumulate. The stabilized and accumulated Nrf2, a basic leucine zipper transcription factor, translocates to the nucleus, binds to AREs and regulates target genes. The proteins coded by these genes can be divided into different functional groups.

NADPH generation is controlled by Nrf2 via glucose-6-phosphate dehydrogenase, phosphogluconate dehydrogenase, malic enzyme 1 and isocitrate dehydrogenase 1 expression. NADPH is used by the glutathione and thioredoxin systems as an electron donor. The expression of enzymes of glutathione synthesis, regeneration and utilization (e.g. glutamate–cysteine ligase, glutathione reductase, glutathione-S-transferases and glutathione peroxidase) are also regulated by Nrf2, similarly to those of the thioredoxin system (thioredoxin 1, thioredoxin reductase 1 and peroxiredoxin 1). Finally, the induction of NAD(P)H

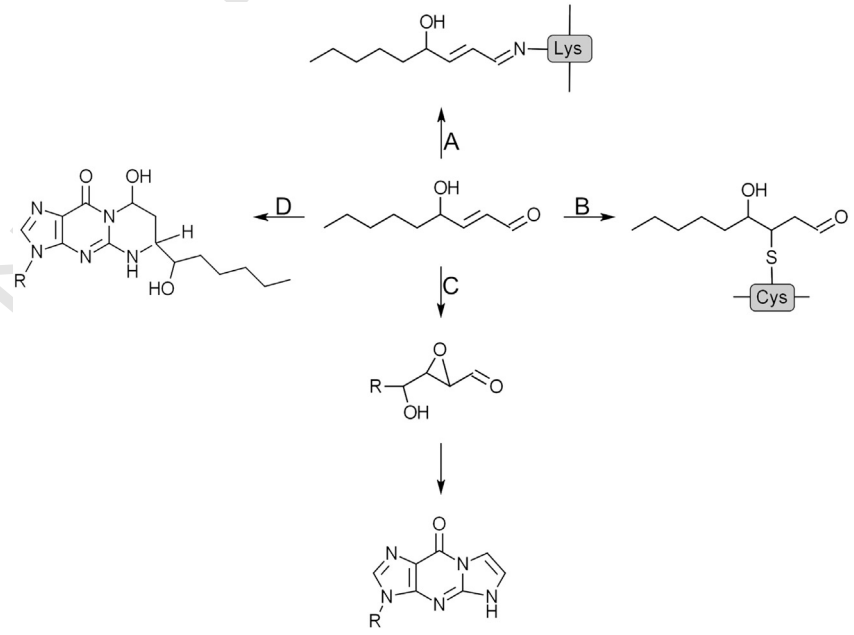


**Fig. 3.** Protein and DNA adducts of HNE. Reaction between C1 aldehyde group and primary amines results in Schiff base formation (A). The C2–C3 double bond of HNE can react with cysteinyl, lysyl and histidyl residues of proteins yielding Michael adducts (B). HNE oxidized to an epoxide reacts with different bases in DNA forming etheno adducts (C). HNE can also form propano adducts with guanine bases of DNA (D).

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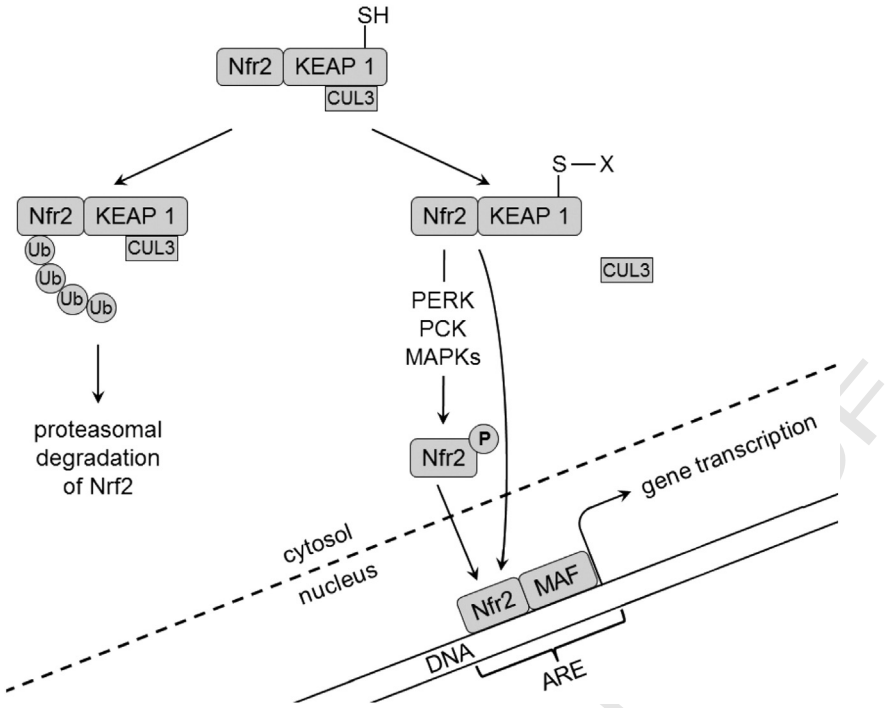


**Fig. 4.** The Keap1–Nrf2–ARE pathway of electrophilic signaling. Under basal conditions, Keap1 binds Nrf2 and promotes its ubiquitylation by Cul3 ubiquitin ligase. Upon electrophilic exposure, electrophiles (e.g. HNE) react with thiol groups of Keap1, which results in the dissociation of Cul3 (Cul3 dissociation model) or in a partial detachment of Nrf2 (hinge and latch model). In both cases Nrf2 escapes ubiquitylation, accumulates, translocates into the nucleus, binds to antioxidant response elements (AREs) and increases the expression of Nrf2 target genes. Phosphorylation of Nrf2 by protein kinases (including PKC, MAPKs and the ER stress kinase PERK) also promotes the dissociation of the Keap1–Nrf2 complex.

quinone oxidoreductase 1, heme oxygenase-1, UDP-glucuronosyltransferases and multidrug-resistance associated proteins completes the antioxidant effects [39]. The final outcomes of the signaling pathway are a reinforced antioxidant defense and a redox shift towards the more reducing conditions.

Beside this simplified mechanism, Keap1 and Nrf2 are also targets of protein kinases and phosphatases; many of them are also redox-sensitive. Recent findings show that the PI3K pathway activates Nrf2 [40]. The complexity of the upstream regulation of Nrf2 is evidenced by its huge interactome [41,42].

Recent observations suggest that the Keap1–Nrf2–ARE pathway is much more than a signaling system for electrophilic or oxidative stress; it might have a crucial function in the healthy cells too. Some of its signals (e.g. NO) are produced as a second messenger upon various physiological situations. Moreover, ARE-responsive proteins include NADPH generating enzymes, which have prominent role in the intermediary metabolism. These considerations raise the possibility that Keap1–Nrf2 signaling plays a more general role in redox signaling [36,43].

### 2.2. Endoplasmic reticulum stress — the unfolded protein response

Accumulation of unfolded or misfolded proteins in the ER lumen results in ER stress, which provokes an adaptation mechanism called the unfolded protein response (UPR). The UPR moderates protein translation and induces ER chaperones to restore protein folding and luminal homeostasis, i.e. the normal macromolecular crowding, redox conditions and $Ca^{2+}$ concentration [44]. HNE and its effect were firstly described in rat liver microsomes derived from the ER [2,45–47]; thus, it is not surprising that HNE can interact with the machinery of protein folding, leading to ER stress. Indeed, it has been reported that HNE reacts with the key players of ER folding, protein disulfide isomerase [48,49], and Grp78 [48,50]. The ER stress sensor PERK kinase was activated upon HNE exposure in rat aortic smooth muscle cells [48]. Exogenous HNE provokes ER stress by a mechanism independent from ROS formation or glutathione depletion in endothelial cells [51]. The role of ROS as a possible mediator of HNE-dependent ER stress was also excluded by another study performed in PC12 cells [52].

An important crosstalk between the UPR and the Nrf2 pathway has also been described. It was observed that Nrf2 is a substrate for PERK ER kinase, which is activated in ER stress [53]. Upon phosphorylation the interaction between Keap1 and Nrf2 is weaker and the complex dissociates. Thus, HNE-provoked ER stress amplifies the electrophilic signaling pathway. Interestingly, in de-differentiated cells, a constitutive (ER stress independent) PERK-Nrf2 signaling was observed, which protects de-differentiated cells from chemotherapy by increased antioxidant defense and drug efflux [54].

### 2.3. The heat shock response

Heat shock response is an adaptive mechanism, which confers resistance to various stress conditions caused by heat, electrophiles, xenobiotics etc. by initiating a transcriptional program primarily regulated by heat shock factor 1 (HSF1). HSF1 upon stress conditions stimulates the expression of various heat shock proteins (HSPs). Similarly to ER chaperones, their cytosolic counterparts HSP70 and HSP90 are also candidates for HNE-dependent modifications [55,56]. Although the exact mechanism is unknown, it can be supposed that modified HSPs lose their repressor functions on HSF1 activation. Thus, HNE can induce heat shock response by an indirect mechanism: binding to HSP70 results in the release of HSF1 from an inactive cytosolic complex and in the increased transcription of the genes of heat shock proteins [33]. In accordance with this mechanism, HSF1 via HSP70 induction prevents the cell from HNE-induced apoptosis [57], while the HSP inhibitor geldanamycin sensitizes the cells towards HNE-dependent cell death

[58]. Heat shock response activators are candidates in the therapy of protein conformational diseases; many of the candidate compounds are electrophiles and activators of the Nrf2 pathway too [59,60].

### 2.4. HNE signaling and proteostasis

Beside redox/antioxidant regulation, the Keap1–Nrf2–ARE pathway is an important regulator of proteostasis. The autophagy substrate p62 interacts with the Nrf2-binding site on Keap1, consequently deficient autophagy results in the accumulation of p62, stabilization of Nrf2 and transcriptional activation of Nrf2 target genes [61]. On the other hand, p62 has been shown to be an ARE-responsive gene product [62], thus p62 creates a positive feedback loop in Nrf2 signaling. Nrf2 dependent mechanisms are also present in the crosstalk between proteasomal and autophagic proteolysis. Increased autophagy was observed in mutant mice with proteasomal dysfunction, which was stimulated by the Keap1–Nrf2 pathway [63]. Nrf2 activation is required for the increased level of the proteasomal regulator Pa28αβ and for maximal proteolytic capacity of proteasomes [64]. Thus, electrophiles and other Nrf2 activators can regulate stress-induced proteasomal activity and removal of damaged/misfolded proteins [65]. Since HNE-dependent ER stress and the consequent activation of UPR are well documented (see above), the activation of ER associated degradation (ERAD) – a proteasomal pathway – and ER stress dependent autophagy is not surprising [65]. Moreover, HNE can also directly interact with the apparatus of translation; e.g. adduct formation with eukaryotic elongation factor 2 results in declined protein synthesis [66].

## 3. HNE in cell life and death decisions

As a potent protein-, lipid- and DNA-damaging agent, which triggers ROS generation and directly depletes the antioxidant capacity of the cells, HNE can be expected to cause profound changes in fundamental cellular processes. Similarly to other insults, excessive lipid peroxidation or HNE treatment is also managed by the cells in three ways. The primary response aims adaptation by eliminating the damaged molecules and preventing any further aggravation and more serious consequences. Cell cycle arrest (quiescence or senescence) and activation of autophagy fit nicely into this strategy. A short-lasting mild or moderate challenge (i.e. low concentrations of HNE) can be survived this way. If the compensatory attempts fail and the cellular intactness is in jeopardy, programmed cell death still provides a chance to maintain the integrity of the tissue and of the whole organism. However, the energy-requiring, active process of apoptosis can be accomplished only if the cell has enough time and still possesses its basic metabolic features. More severe conditions, when the cell is quickly paralyzed by an overwhelming destruction (i.e. high concentrations of HNE), lead to necrosis [67] and a more pronounced and expanded tissue loss usually combined with inflammation. Although an increase in the level of HNE clearly reduces the chance of adaptation in favor of apoptosis or necrosis, the exact HNE doses determining one or the other cell response cannot be uniformly defined as they vary according to the cell types, duration and several environmental factors.

Lipid peroxidation is accelerated in oxidative stress and it is a source of further ROS generation, itself. Therefore, the effects of HNE on autophagy, cell proliferation and apoptosis are often indirect and hard to distinguish from those of other ROS- and stress-activated signaling mechanisms. This chapter focuses on the observations that convincingly suggest a direct interaction of HNE with the key components of these cellular processes.

### 3.1. Effect of HNE on autophagy

Besides proteasome-dependent proteolysis, autophagy is a major physiological mechanism to degrade intracellular proteins in eukaryotic cells. Autophagy plays an important role in differentiation and normal growth control, and its enhancement is essential for the survival during starvation. Macro- and microautophagy sequestrate complete regions of the cytosol including organelles, while in chaperone-mediated autophagy contributes to the cellular protein quality-control as it selectively removes damaged cytosolic proteins one by one [68]. The proteins sequestrated by autophagy are degraded in the lysosomes [69], and hence turn into valuable endogenous nutrient sources. Accordingly, the process is stimulated in energy deficient states by AMP-activated protein kinase and inhibited during the wealth of nutrients by (insulin)-Akt-mTOR signaling [70]. The ER can also generate signals to enhance autophagy, in accordance to its function as a nutrient sensor in the cells [71]. There is ample evidence that accumulation of ROS-mediated damages in macromolecules and organelles plays a central role in aging. Elimination of damaged cellular components through autophagy is a major determinant of longevity, and the repeatedly demonstrated anti-aging effect of caloric restriction can be at least partly attributed to an enhanced autophagic activity [72,73].

The role of chaperone-mediated autophagy in the removal of HNE-modified proteins was demonstrated in transgenic mice overexpressing LAMP2A receptor. The livers of these animals accumulate fewer damaged proteins compared to age-matched wild-type controls due to an enhanced chaperone-mediated autophagy [74]. Activation of autophagy in oxidative stress can be considered as an antioxidant defense mechanism concerning the protective role it plays by eliminating damaged, dysfunctional proteins and organelles [75,76]. Stimulation of autophagy seems to be a pro-survival mechanism in cells undergoing excessive lipid peroxidation. HNE and other lipid peroxidation-derived aldehydes caused a remarkable increase in the number of autophagosomes in cultured rat aortic smooth-muscle cells. Enhanced autophagy largely contributed to the elimination of damaged proteins, and also prevented cell death [77]. The ER as the organelle specified to protein synthesis, maturation and quality control [78] is also involved in HNE-induced autophagy. Luminal accumulation of damaged polypeptides is the key trigger to the ER stress, which in turn is an important source of signals stimulating autophagy [79]. The contribution of the ER stress to HNE-enhanced autophagy was indeed demonstrated in rat aortic smooth-muscle cells [48]. Sublethal concentration of HNE was also shown to stimulate protective autophagy in differentiated SH-SY5Y neuroblastoma cells. Although caspase-3 activation was also observed in the HNE-treated cells, apoptotic cell death intensified only when autophagy had been attenuated through inhibition of glycolysis [80].

A complex and differential regulation of autophagy by HNE during myocardial ischemia and reperfusion has been suggested by a recent study, in which the effect of endogenous HNE was attenuated by overexpression of aldehyde dehydrogenase 2 (ALDH2). ALDH2, one of the major enzymes involved in neutralization of HNE reduced the tissue damage in both ischemia and reperfusion; however its protective effect was due to promotion or inhibition of autophagy in the two phases, respectively. The results indicate that AMP-activated protein kinase and Akt-mTOR signaling is compromised by HNE through interference with upstream regulators, such as LKB1 and PTEN [81]. It can be also concluded that HNE-induced autophagy, albeit protective against apoptosis, has its own deleterious consequences especially in the myocardium. Suppression of HNE-stimulated autophagy in ALDH2-transfected mice has also been reported to ameliorate doxorubicin-induced myocardial dysfunction [82].

Intracellular proteins severely damaged by MDA and HNE may become undegradable due to their aberrant covalent modifications and their deposition is potentially cytotoxic. Lipofuscin of human retinal pigment epithelium was shown to contain injured mitochondrial proteins, which indicates the role of autophagy in the formation of such granules [83]. Further analysis revealed that MDA and HNE interfere with lysosomal protease activities in these cells both directly and through modifications of their substrate peptides [84]. The lysosomal dysfunction results in increased lipofuscinogenesis and reduced autophagy activity in vitro [85].



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### 3.2. Effect of HNE on cell cycle and proliferation

Protein (Ser/Thr) phosphorylations catalyzed by various cyclin:cyclin-dependent kinase (CDK) dimers are key events at the checkpoints in the eukaryotic cell cycle. For instance, the restriction point is passed when retinoblastoma protein (pRb) is hyperphosphorylated by cyclin:CDK dimers accumulating as a result of mitogenic gene expression. The concomitant liberation (and activation) of members of the E2F family of transcription factors prepare the now committed cell to enter the S phase (DNA replication) [86]. CDK activities are controlled by positively and negatively acting phosphorylations and can be halted by the association of CDK inhibitors, such as p21 or p16 [87]. The latter mechanism contributes to the anti-proliferative action of p53 family transcription factors [88], which in turn is activated by various stress conditions, oncogenic insult and severe DNA-damage [89].

#### 3.2.1. Anti-proliferative effects

An inverse relationship was found between cell proliferation and lipid peroxidation in various cell types, i.e. it is generally observed that rapid proliferation is accompanied by low level of lipid peroxidation in different tissues including tumors [90]. The phenomenon is at least partly due to low level of peroxidizable fatty acids in intensively proliferating cells. Enrichment with arachidonic acid renders tumor cells more susceptible to oxidative stress and to cell cycle arrest through lipid peroxidation [91,92]. These findings shed light on the potential role of HNE in the modulation of cell cycle control [93]. HNE was found to reduce the proliferative capacity of K562 human erythroleukemic and HL-60 human promyelocytic cells [94]. Not only the S phase progression was inhibited, but a concomitant granulocytic differentiation was also initiated in HNE-treated HL-60 cells [95]. Diversion from proliferation towards differentiation implies the modulation of master regulators of these processes. Indeed, the expression of proto-oncogen c-myc and c-myb transcription factors is transiently suppressed in HL-60 cells after HNE treatment despite unaltered N-ras expression and cAMP levels [96,97]. A remarkable decrease in the c-myc mRNA level was also demonstrated in K562 cells after the addition of HNE at low (1–3 μM) concentration [98]. Further investigation revealed that HNE affects cell cycle control around the restriction point by modifying the expression of several genes. It was found to down-regulate D1, D2, and A cyclin expression [99], as well as to induce p21 and reduce E2F4 expression, which leads to a lowered pRb phosphorylation [100]. Although p21 is the major mediator of p53-induced anti-proliferative effects, its observed HNE-dependent induction must involve other, yet-unidentified transcription factors in HL-60 cells, which are known to be p53-deficient [101]. The profound alterations in gene expression shift the ratio of DNA-bound activating “free” E2F and suppressing E2F–pRb complexes towards the latter [100]. In line with these observations, phenotypic transformation and immortalization was found in HLE B-3 and CCL-75 adherent cells upon transfection with HNE-metabolizing glutathione S-transferase isozymes [102]. The complex pattern of alterations in gene expression included the induction of TGFβ, c-myc, CDK2, PKCβII and ERK1/2 as well as the down-regulation of p53, p21, p16, TGFα, and c-jun [102,103]. HNE was also reported to inhibit the proliferation of SK-N-BE neuroblastoma cells through an increased expression of p53 family proteins and the consequent up-regulation of p21 and down-regulation of cyclin D2, p53 target proteins [104].

#### 3.2.2. Proliferative effects

It is noteworthy that positive effects of HNE on cell proliferation have also been reported in a few studies. Activation of JNK (but not ERK) isoforms through direct interaction by HNE leading to an increase in c-jun (but not c-fos) mRNA levels and a biphasic increase in AP-1 DNA binding was reported in primary human hepatic stellate cells [105]. In this study, these effects were related to the stimulation of procollagen type I gene expression and synthesis rather than to the enhancement of cell proliferation. In fact, HNE has been reported to reduce the platelet-derived growth factor (PDGF)-induced proliferation through a lowered receptor tyrosine phosphorylation in this cell type [106]. Stimulation of AP-1 DNA binding activity by HNE was also found in rat aortic smooth muscle cells. However, in these cells, somewhat controversially, the enhanced cell growth was attributed to the activation of ERK1 and ERK2 and a consequent induction of c-fos and c-jun protein expression [107]. The anti-proliferative effect of aldehyde dehydrogenase 3A1 (ALDH3A1), an effective consumer of HNE was shown in primary human corneal epithelial cells and in NCTC-2544 human keratinocyte cell line. However, this phenomenon might not have been directly related to the elimination of HNE and was more likely due to a signaling protein activity of ALDH3A1 involved in mitosis rather than its catalytic function [108]. A striking difference between the effects of HNE on cell proliferation in young and old smooth muscle cells indicates the age-dependence and complexity of the signaling involved. Interestingly the increase in ERK signaling activity, cyclin D1 expression and cell growth was more pronounced while the ROS-mediated cytotoxicity was less obvious in young compared to aged smooth muscle cells treated with low concentrations 0.1 μM of HNE for 36 h [109].

### 3.3. HNE-induced apoptotic cell death

Apoptosis, the major type of programmed cell death is an ATP-dependent and meticulously regulated process to eliminate disposable and/or incurable cells. The primary cause of apoptosis in physiological conditions is the lack of sufficient survival stimuli, but it can be triggered also by severe stress (e.g. oxidative or organelle stress), DNA-damage, excessive mitogenic signal (oncogenic insult) or by stimulation of plasma membrane death receptors (e.g. FAS or TNF receptor) by exogenous ligands (e.g. FAS ligand or TNFα) [110]. Apoptotic caspases, central executors of the program, can be irreversibly activated upon limited proteolysis of their zymogens. Cells are protected against premature or inadequate caspase activation by inhibitors of apoptosis (IAPs), i.e. proteins blocking the active sites of caspases. Initiator procaspases (2, 8, 9 and 10) can be auto-activated within certain multiprotein complexes, such as apoptotosome, death inducing signaling complex or PIDDosome [110]. These are assembled upon the release of cytochrome c from the mitochondria, binding of death ligand to its receptor or p53-mediated gene expression, respectively. The release of pro-apoptotic factors from the mitochondria (e.g. cytochrome c, IAP antagonists, endo-DNAse) is a key event in apoptosis. The membrane pore can be formed by pro-apoptotic multidomain members (Bax, Bak) of the Bcl-2 protein family, which are normally restrained by the anti-apoptotic multidomain members (e.g. Bcl-2, Bcl-XL) [111]. Pore formation and thence apoptosis is promoted by the BH3-only members (e.g. Bad, Bid, Bim, Puma, Noxa) of the Bcl-2 family, which are particulate pro-apoptotic factors forwarding various triggers of apoptosis. Bad is kept phosphorylated and inactive by PKB/Akt, and initiates pore formation in the absence of survival signal. Bid is truncated and activated upon exogenous death signals through the death inducing signaling complex. Induction of Bim is part of the ER stress response, while Puma and Noxa are induced by p53 [111]. The complex control of apoptosis is affected by ROS and by various reactive products of lipid peroxidation in multiple ways. Here we are summarizing the major mechanisms, in which HNE is involved directly; for a more comprehensive overview of the topic see Dalleau et al. [112].

Oxidative stress affects caspase activation and function in multiple ways. Although the maintenance of a certain antioxidant capacity is required for appropriate proteolytic activity of caspases, moderate glutathione depletion seems to play an important role in procaspase cleavage [113]. Two initiator (8 and 9) and the major effector (3) caspases were found to be activated directly by glutathione depletion in HNE treated human T-cell leukemia Jurkat cells. The underlying glutathione depletion was due to oxidation by HNE rather than Fas-mediated glutathione release across the plasma membrane [114]. HNE treatment



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caused oxidative stress and glutathione depletion through deregulation of mitochondrial functions and induction of cytochrome P4502E1, which led to an enhanced apoptosis in PC12 rat phaeochromocytoma cells [115]. Stimulated expression of glutathione S-transferase A4-4, a key enzyme of glutathione synthesis in these cells [115] can be considered as a defense mechanism since the protective effect of this enzyme against HNE-induced apoptosis was revealed in human osteoarthritic chondrocytes [116]. The role of glutathione depletion was further supported by the observation that PC12 cells can be protected from HNE-induced cytotoxicity through an increased intracellular glutathione level [117]. These findings do not reveal any direct interaction between HNE and pro-caspase proteins, yet they strongly support the involvement of cellular redox state-linked signaling pathways in HNE-induced caspase activation. In line with this, activation of the stress kinases JNK and p38 MAPK and simultaneous down-regulation of ERK activity were demonstrated to play a primary role in the HNE-dependent apoptosis induction in 3 T3 mouse fibroblasts [118]. The normal functioning of the ER, especially the luminal oxidative folding is largely affected by disturbances in the cellular redox state and it is connected to glutathione homeostasis in particular [119,120]. It is therefore likely that the ER stress also contributes to HNE-induced caspase activation. Development of an ER stress in HNE-treated cells has been discussed in relation to autophagy [48]. Several other studies support the ER stressor action of HNE in various cell types [51,52] and it has also been shown to be a link in HNE-induced, redox-mediated apoptosis [121]. In addition, the aggravation of the ER stress-induced cardiac dysfunction in ALDH2 knockout mice can be attributed to a similar mechanism [122].

Interference of HNE with the survival signal has been found in Jurkat cells [123], in human osteoarthritic chondrocytes [116] and in MG63 human osteosarcoma cells [124]. A decrease in the amount of active phosphorylated Akt, which leads to apoptosis induction thorough an increased Bax and decreased Bcl-2 protein level, likely contributes to HNE-induced cytotoxicity. However, Akt dephosphorylation and inactivation was found to be caspase-3-dependent in HNE-treated Jurkat cells, which contradicts its primary role and also strongly questions its HNE specificity. It still might play a positive feedback role enhancing the HNE-induced primary caspase activation. According to the proposed mechanism, caspases down-regulate Src, and hence decrease the inhibitory Tyr-phophorylation of protein phosphatase 2A (PP2A), which in turn dephosphorylates Akt for inactivation [123].

Activation of p53 has been mentioned as a mechanism leading to cell cycle arrest. This transcription factor is known to act as central guardian of genomic integrity, and as such, it can also stimulate programmed cell death after a severe damage. Accordingly, induction of p53 family gene expression in HNE-treated SK-N-BE neuroblastoma cells not only hindered proliferation but also increased the number of apoptotic cells [104]. It should be noted, that p53 activation does not appear to be a key factor in HNE-induced apoptosis. For example, the pro-apoptotic effect of HNE in RAW 264.7 murine macrophage cells has been shown to be dependent on cytochrome c release but not p53 accumulation [125].

## 4. HNE in the pathogenesis of human diseases

Oxidative/electrophilic stress and increased lipid peroxidation are important factors in the pathogenesis and progression of several human diseases. Specification of these pathologies has been the topic of numerous excellent recent reviews [35,112,126]. Here we focus on diseases of high incidence, in which the previously described alterations in signaling and pathophysiology can be demonstrated.

### *4.1. HNE and myocardial diseases*

Heart is the organ characterized by the highest oxygen uptake and consumption in the body due to its constant pumping activity [127]. Its energy utilization mainly depends on oxidative phosphorylation by the myocardial mitochondria. Accordingly, the human ventricular myocyte contains about 7000 mitochondria, occupying approximately 25% of the cytoplasmic volume [128,129]. The high myocardial oxidative capacity is a constant source of ROS generation and secondary HNE production [130]. While free radicals are short lived, HNE can persist and travel from the site of their origin [6]. Under normal conditions, cardiac HNE is neutralized by aldehyde dehydrogenases (ALDHs), glutathione S-transferases and aldose reductase [35,131]. However, various pathologic conditions, such as myocardial ischemia reperfusion, heart failure, doxorubicin toxicity and diabetes can overwhelm the metabolic capacity leading to increased HNE formation and consequential myocardial dysfunction [130].

Accordingly myocardial HNE accumulation and toxicity has been implicated in several cardiac diseases. It has been demonstrated that oxidative stress is elevated in failing human myocardium [132]. HNE-modified protein expression was 5-fold elevated in patients with dilated cardiomyopathy compared to controls, and carvedilol, a beta-blocker with intrinsic antioxidant capacity, reduced HNE levels by 40%, with functional amelioration of heart failure symptoms [132]. Comparison of 8 patients with chronic heart failure (CHF) with 8 age matched patients revealed that patients with CHF and low ejection fraction had significantly higher unsaturated aldehyde, including plasma HNE levels when compared to healthy controls [133]. Total aldehyde concentration was inversely correlated with + dP/dt left ventricular pressure rise, a well-established indicator of global left ventricular contractility, and cardiac output [133]. In a similar but larger scale study, the blood and plasma levels of protein bound HNE products (HNE-P) were assessed in 61 heart failure (HF) and 71 control patients [134]. All classes of circulating fatty acids and potential HNE-P precursors n − 6 PUFAs, specifically linoleic acid were also quantified. It was shown that while the circulating levels of HNE-P were similar between heart failure and control patients, HF patients had significantly decreased levels of HNE-P precursor linoleic acid [134]. In addition, a strong association between HNE-P, linoleic acid and HDL-cholesterol was found and it was suggested that relative HNE-P increase is associated with HDL-cholesterol decrease in HF patients. HNE-P levels in HF patients were found to positively correlate with New York Heart Association (NYHA) symptom class level [134].

The role of HNE has also been implicated in myocardial ischemia and reperfusion injury. This assumption was tested in isolated perfused hearts from normotensive and spontaneously hypertensive rats with cardiac hypertrophy and signs of heart failure, which were subjected to 30 min global ischemia followed by another 30 min of reperfusion [135]. Generation and release of HNE were demonstrated post-ischemic reperfusion from myocardial effluent in both animal groups. In addition, maximum concentration of HNE in the perfusate correlated with the highest incidence of ventricular fibrillation and maximum contractile dysfunction in spontaneously hypertensive rats animals [135]. The effect of ischemia reperfusion on myocardial HNE generation was studied in a rat heart transplantation model [136]. Excised hearts were first subjected to 30, 240, 480 min of cold ischemia. Subsequently they were transplanted into the recipient animal, connected to the abdominal aorta and vena cava and reperfused for 240 min. Immunohistochemical staining revealed that cold ischemia did not increase myocardial HNE protein adduct formation. In contrast, transplantation and reperfusion markedly enhanced HNE protein adduct generation by 6-fold, independent of preceding ischemic time [136]. Mitochondrial isoform aldehyde dehydrogenase 2 (ALDH2) was recently identified as an enzyme whose activation by phosphorylation reduced myocardial infarct size by 60% in a rodent model of myocardial ischemia [137]. It was postulated that ALDH2 mediated cardioprotection was likely mediated by the elimination of cytotoxic aldehydes particularly HNE. Indeed, pharmacologic activation of ALDH2 led to an in vitro 34% reduction of HNE levels and 60% in vivo reduction in infarct size [137]. The effect of both ALDH2 overexpression and knockout on myocardial ischemia and HNE protein content was further investigated [81]. ALDH2



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overexpression significantly attenuated myocardial infarct size, and prevented the decrease in left ventricular fractional shortening thus left ventricular dysfunction following IR when compared to control animals. In controls HNE protein adduct formation was significantly increased during ischemia and stayed elevated during reperfusion [81]. ALDH2 overexpression depressed HNE rise both during ischemia and reperfusion, while ALDH2 knockout increased HNE protein adduct formation during both circumstances. In vitro exogenous HNE treatment significantly compromised cardiomyocyte mechanical function, which in turn was attenuated by ALDH2 overexpression, providing direct evidence to HNE toxicity. The effects of chronic pharmacologic ALDH2 activation have been investigated recently in a post-infarction heart failure rat model [138]. Male Wistar rats were subjected to myocardial infarction surgery via the ligation of left anterior descending artery. Heart failure ensured approximately 4 weeks after coronary artery ligation, at this time baseline myocardial parameters were determined, and animals were randomly assigned to chronic Alda-1 treatment, a pharmacologic activator of ALDH2 enzyme. 6 weeks later the animals were analyzed and sacrificed. Alda-1 treatment of HF animals significantly improved left ventricular ejection fraction and reversed pathological ventricular remodeling of animal hearts. In the ALDH2 activated HF animals HNE protein adduct levels decreased to sham operated control animal levels [138]. From these experiments one can conclude, that HNE accumulation plays a key role in the pathogenesis of both myocardial ischemia reperfusion injury and heart failure, while its removal by ALDH2 enzyme activation is a promising target for pharmaceutical intervention.

### 4.2. HNE and cancer

Although the cytopathological effects of HNE have been discovered more than three decades ago [2,139,140], the role of HNE during carcinogenesis and cancer progression is still debated.

Numerous HNE-induced DNA modifications were described, and found to be potentially mutagenic [141–143]. The pathogenic role of these DNA lesions is strongly supported by the observation that HNE-DNA adducts are preferentially formed at the third base of codon 249 (−GAGGC/A-) in the most frequently mutated gene in human cancers, the p53 [144]. Nevertheless, the greater reactivity of HNE to proteins compared to DNA gave rise to the assumption that modulation of proteins involved in DNA repair may contribute to the cytotoxic and carcinogenic effects of HNE. Indeed, HNE was shown to hinder nucleotide excision repair of DNA damage induced by benzo[a]pyrene diol epoxide (BPDE), as well as DNA damage induced by UV light irradiation in human colon and lung epithelial cells [145]. These results strongly suggest that HNE damages not only the DNA molecule itself but also the DNA repair mechanisms and contributes to human carcinogenesis.

Initial studies found low level of HNE in tumor tissues compared with healthy tissues, which was explained by rapid and efficient oxidative and conjugative pathways eliminating HNE metabolites from tumor cells [146] and low rate of lipid peroxidation in hepatoma cells [147]. Low levels of HNE were also associated with a decrease in the synthesis and expression of the antiproliferative cytokine, transforming growth factor beta1 (TGF-β1), which repression of TGFβ1 in turn has been shown to correlate with an increase in carcinogenesis progression in human malignant colon tumors [148,149]. Some recent studies have reported controversial observations in several types of human cancers [150–153]. Moreover, other results showed that HNE-protein adduct formation might be implicated in different precarcinogenic stages of hepatitis [154]. The discrepancy of these findings can be explained with the heterogeneity of HNE formation and metabolism in various tumor cells. Firstly, the membrane compositions showed different cholesterol/polyunsaturated fatty acid ratios, which determine different tendencies to HNE formation [155]. Secondly, certain tumor cells can reveal a higher expression of detoxification enzymes and antioxidant proteins allowing more efficient and rapid HNE metabolism and excretion [156]. The α,β-unsaturated aldehydes produced as a result of cellular membrane lipid peroxidation were found to have a dose-dependent promoter activating effect on glutathione S-transferase, the key HNE-metabolizing enzyme, in rat hepatoma cells [157].

As a cancer therapy, anticancer drugs and radiotherapy can induce oxidative stress and trigger cancer cells to apoptosis, however some cells escape the apoptosis through the adaptation to intrinsic oxidative stress, which confers drug resistance. The central role of Nrf2 in the metabolic regulation in cancer cells were highlighted in recent studies [158, 159]. In malignant cells Nrf2 activation provides energetic adaptability and growth advantage; hence increase cancer chemoresistance [160]. Since HNE has direct influence on Keap1–Nrf2–ARE pathway, future studies will be necessary to distinguish physiologic and pathologic roles of HNE, with particular attention to the pro-oxidant anticancer agents and the drug-resistant mechanisms, which could be modulated to obtain a better response to cancer therapy.

### 4.3. HNE and neurodegenerative diseases

The sensibility of a living tissue towards oxidative stress has been greatly attributed to its susceptibility to lipid peroxidation, which in turn largely depends on its PUFA levels. While low PUFA levels can provide an increased resistance towards oxidative stress, as in the case of cancer cells, certain cell types including neurons possess PUFA-rich membrane compartments containing high levels of the HNE-precursor omega-6 fatty acids. Combined with the high abundance of metal ions participating in redox transitions and intense oxygen consumption, brain tissue becomes a prime subject of free radicals and HNE-related degenerative disorders [161,162].

#### 4.3.1. Huntington's disease

The genetic background of Huntington's disease is well defined, and aggregation of the polyglutamine containing mutant huntingtin protein in the striatum and the cerebral cortex [163] has been extensively investigated. The disease manifests as a late onset neuromotor disorder that has a decade long progress from increasing chorea-like involuntary movements to the final stage akinesia. In exploring the pathology of Huntington's on the subcellular level, oxidative stress related scenarios have been examined. The findings, in connection with energy metabolism and mitochondrial dysfunction [164], oxidative damage in the central nervous system [165] and in peripheral blood [166], pointed to oxidative stress as a common denominator. Although the trigger has yet to be found, oxidative damage is generally suggested to be an important part of the pathophysiology of Huntington's disease. In a comprehensive review by Stack et al., several oxidative modifications of proteins and DNA were identified, and even preventive antioxidant Q10 and creatine treatment was proposed [167]. Evidence of lipid peroxidation was also found in Huntington's brain tissue in the form of elevated MDA and HNE levels. Furthermore, HNE was found to colocalize with huntingtin inclusions [168]. Inhibition of proteasomal function by HNE-dependent modifications [169] can lead to accelerated accumulation of aggregates. Protein degradation machinery plays an essential role in eliminating folding incompetent proteins. It has also been suggested that the decrease in superoxide dismutase levels and the altered energy metabolism found in Huntington's effected tissue samples can indirectly effect lipid peroxidation and HNE abundance [170].

#### 4.3.2. Parkinson's disease

Most commonly known for the symptoms bradykinesia and resting tremors (shaking palsy), Parkinson's disease (PD) is the second most abundant neurodegenerative disease. PD presents with the occurrence of Lewy bodies found in the putamen and substantia nigra of the brain as the histological hallmarks of the disease. A major component of Lewy bodies is the mitochondrial and synaptic vesicle formation related protein: α-synuclein (α-syn). Oxidation and nitration of α-syn has been



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shown to impact aggregate formation capacity [171] while oxidative modifications by ROS also impair the autophagic machinery, resulting in decreased α-syn degradation [172]. Lipid peroxidation also leads to the emergence of α-syn derivatives. HNE-α-syn has a greatly increased oligomerization potential; consequently this adduct formation is suspected to serve as a trigger for aggregation [171]. The involvement of this process in the pathological progress was fortified by the finding that Lewy bodies stain positive for HNE [173,174]. It has been reported that different electrophiles can initiate the formation of α-syn oligomers with distinct biochemical, morphological and functional properties [175]. It can be supposed that different oligomers affect the autophagic machinery differently. HNE promotes the formation of seeding-capable oligomers, which distinguished themselves by a cell-to-cell transfer ability [176].

Besides the direct α-syn relation, HNE was also found in connection with dopamine transport. The binding to the dopamine transporter and inhibiting dopamine uptake further contributes to the loss of dopamine dependent and dopamine secreting neurons [170,177], resulting in further progression of PD.

#### *4.3.3. Alzheimer's disease*

Alzheimer's disease (AD) is the most common and most extensively studied neurodegenerative disorder with about 1000 studies published annually. The related mental pathology from mild cognitive impairment (MCI) to severe late stage Alzheimer's disease is being described in increasing details. At the cellular level, the pathomechanism of AD is attributed to the impaired processing of amyloid precursor protein by gamma secretases leading to the accumulation of aggregation prone and ROS generating amyloid beta (aβ) peptide. The broad range of studies approach Alzheimer's as a conformational disease [178], a neurotransmission disorder [179], a response to inflammatory signals [180], and even a metabolic syndrome [181].

Increasing evidence has been collected by various groups demonstrating that besides – and in connection with – the well-known senile plaque pathology, increased oxidative stress is common in the central nervous system in patients with AD [182,183]. Since early in vitro studies confirmed the production of hydrogen peroxide and lipid peroxide by increased aβ levels [184], the presence of various lipid peroxidation products has been reported including MDA, F2-isoprostanes [182,185] and HNE [186]. For the last two decades, studies have confirmed the elevated HNE levels in AD, both in animal models [187] and in patients [188,189]. HNE has been shown to be a member of the amyloid cascade, and contributes to AD pathology as an effector for aβ-induced free radicals [190–192]. The subsequent oxidative modifications affect a wide variety of proteins leading to structural and functional alterations in AD, both at the intracellular and synaptic membrane level [193,194], including enzymes involved in the elimination of aβ itself that can even lead to a disease spiral phenomenon [195]. Proteomic analysis of late stage AD samples has shown that while HNE can directly affect interneuronal communication via the modification of key proteins such as collapsin response mediator protein 2 [194] and glial glutamate transporter (GLT-1) [196], its targets are often key enzymes of energy metabolism: aconitase, aldolase, enolase, and ATP synthase [197], as well as enzymes involved in antioxidant defense: peroxiredoxins, superoxide dismutase, and heme oxygenase [162]. Corollary to the dysfunction of these enzymes, the defenses of neuronal tissue against oxidative damage are further weakened as a result of HNE.

Besides the protein modifications, another reported scenario of HNE causing impaired energy metabolism in AD is dihydrolipoic acid (DHLA) consumption via direct adduct formation. In HNE treated brain tissue, both the overall level and enzymatic activity of lipoamide dehydrogenase (LADH) was found to be decreased as a result of ROS/HNE modifications that led to diminished DHLA production. The combined effect of decreased DHLA synthesis and HNE-lipoic acid conjugate formation leads to a depleted ATP pool [189].

Due to its multiple targets and undeniable effects, lipid peroxidation and HNE adduct formation should attract increased attention and lead to further investigations in the field of neurodegenerative disorders.

## 5. Concluding remarks

HNE emerged 34 years ago as a deleterious, cytotoxic product of lipid peroxidation. During the time elapsed countless pathological effects have been attributed to HNE toxicity. However, the intensive research in the field also revealed less destructive and more specific effects of the molecule. Recent observations on the role of HNE in signaling have shed light on adaptive cytoprotective responses too. It became evident that activation of HNE sensors prepare the cells for antioxidant defense, stimulate the elimination of damaged cellular components or even serve the protection of the organism by inducing apoptosis in severely injured cells [112,198]. Although excessive HNE formation is obviously a pathogenic factor, activation of these protective mechanisms deserves a great scientific interest because it might reveal new molecular targets of medical significance [36,199]. Further studies on HNE metabolism and signaling can contribute to the better understanding of cardiovascular and neurodegenerative diseases. Moreover, HNE research can largely promote the development of new medical interventions, e.g. the exploration and improvement of electrophile therapeutics.



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