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Review Article

Self-regulatory role of 4-hydroxynonenal in signaling for stress-induced programmed cell death

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ABSTRACT

Within the last two decades, 4-hydroxynonenal has emerged as an important second messenger involved in the regulation of various cellular processes. Our recent studies suggest that HNE can induce apoptosis in various cells through the death receptor Fas (CD95)-mediated extrinsic pathway as well as through the p53-dependent intrinsic pathway. Interestingly, through its interaction with the nuclear protein Daxx, HNE can self-limit its apoptotic role by translocating Daxx to cytoplasm where it binds to Fas and inhibits Fas-mediated apoptosis. In this paper, after briefly describing recent studies on various biological activities of HNE, based on its interactions with Fas, Daxx, and p53, we speculate on possible mechanisms through which HNE may affect a multitude of cellular processes and draw a parallel between signaling roles of H_2O_2 and HNE.

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Introduction

Initially thought to be merely a toxic end product of lipid peroxidation, 4-hydroxynonenal (HNE) has now emerged as an important signaling small molecule which is involved in signaling for cell cycle control and the regulation of expression of a multitude of genes, the products of which regulate a variety of cellular processes. Earlier studies on the effects of HNE on DNA, RNA, and protein synthesis, chemotaxis, and effector proteins such as phospholipase C and adenylate cyclase

Abbreviations: HNE, 4-hydroxynonenal; RalBP1, Ral-binding protein1; Daxx, death-associated protein; HSF1, heat shock factor 1; HSP, heat shock proteins; GST, glutathione *S*-transferases, ASK1, apoptosis signaling kinase 1; JNK, c-jun N-terminal kinase.

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(reviewed in [1]) received little attention and even the earlier reports demonstrating its role in signaling for apoptosis were met with skepticism but in recent years its role on regulation of various signaling pathways is firmly established. The list of studies demonstrating its role in signaling for apoptosis, regulation of gene expression, proliferation, transformation, and its interactions with signaling components in membranes, cytoplasm, and nucleus is consistently growing. Similar to H_2O_2, a major physiologic initiator of signaling processes, HNE is a small molecule, has a relatively short life, is diffusible, and its intracellular concentrations are tightly regulated by enzymes that are induced rapidly under stress conditions that increase its intracellular levels. Formation of HNE is proportional to ROS produced as a result of internal (e.g., metabolic) or external (e.g., UV, chemicals) stress and in recent years credible evidence has accumulated which suggests that at least a part of ROS-induced signaling may be transduced via HNE and that it can be regulated by limiting its intracellular concentration [2–4]. These studies have opened a new area in the field of ROS-induced signaling focusing on the regulatory roles of the enzymes involved in the formation and metabolism of HNE. Recent studies in this area have shown that enzymes such as glutathione *S*-transferases (GSTs), aldehyde dehydrogenases, aldose reductase, glutathione peroxidase, and RalBP1 (Ral-binding protein 1) that are among the major determinants of intracellular levels of HNE can modulate stress-induced signaling for programmed cell death [2–10]. Some of these studies [11–14] seem to have major clinical implications particularly in regard to cancer chemotherapy [11,12], inhibition of tumor growth [13], and sepsis [14] as discussed briefly later in this review.

Recent studies suggest that HNE can induce signaling for apoptosis via multiple pathways, which seem to converge on the activation of JNK and caspase3 [15,16]. Furthermore, there is credible evidence that HNE plays an important role in membrane receptor-mediated signaling and that it can directly interact with transcription factors and transcription repressors. These multiple actions of HNE are consistent with its role in regulation of the expression of numerous genes and modulation of various signaling processes.

Initial pioneering studies on HNE and signaling were covered by Esterbauer in his comprehensive review [1]. A number of recent reviews covering studies on the role of HNE in the modulation of signaling processes are also available [2–4,17–24]. Most of these reviews have focused on the role of HNE in inducing apoptosis, regulation of the expression of genes, and its interactions with target proteins including the components of various signaling cascades. In this review, against a backdrop of relatively recent studies showing the role of HNE in regulation of various cellular processes, we discuss the mechanisms of HNE-induced apoptosis through the extrinsic and intrinsic pathways, its self-regulatory role in this process, its interactions with Fas (CD95), p53, and Daxx, and speculate on probable mechanisms through which HNE affects such a multitude of cellular processes.

4-HNE and signaling

Some of the reported effects of HNE including cell cycle signaling, cell proliferation, transformation, chemotaxis, regulation of gene expression, its interactions with membrane receptors, transcription factors, transcription repressors, and its role in signaling for programmed cell death are listed in Table 1 [25–76]. In recent years, studies in our laboratory have focused on the mechanisms of HNE-induced signaling and its regulation by enzymes which determine the intracellular concentration of HNE. These studies indicate an important role of HNE in signaling for apoptosis induced by stressors including H_2O_2, UV, heat, and oxidant chemicals such as naphthalene or doxorubicin and that apoptosis induced by these agents can be inhibited in cells transfected with enzymes that limit the intracellular concentrations of HNE [7–9,47,77]. For example, the overexpression of GSTA4-4 or GST5.8, which detoxify HNE, inhibits apoptosis induced by xanthine/xanthine oxidase, H_2O_2, UV, and doxorubicin [9]. Furthermore, these studies indicate that

Table 1
4-HNE as signaling molecule

Model system	Observed effect(s); Ref. given in parentheses
Jurkat cells	Facilitates cytosolic export of Daxx and its binding to Fas to self-limit Fas-mediated apoptosis [16]
Colon carcinoma RKO cells	Attenuation of HSF-1, induction and stabilization of BCLxL [25]
Human lens epithelial cells	Fas-mediated DISC-independent apoptosis [15]
Vascular smooth muscle cells	Mitogenic response [13]
Rat epithelial type II cells	Induction of γ-GGT via EpRE/Nrf2 [26]
Vascular cells and atherosclerotic lesions	Desensitization of platelet derived growth factor receptor beta [27]
In vitro and In vivo	Inhibition of thioredoxin and thioredoxin reductase [28]
Caco-2 human adenocarcinoma cells	Antiproliferative effects [29]
Human osteosarcoma cells	Proliferation, differentiation, and apoptosis [30]
K562, HL60, HLE B-3	Role in stress-mediated signaling for apoptosis transformation, proliferation, differentiation [3,4,31,32]
Rat hepatocytes	Apoptotic signaling through PKC delta [33]
Rat hepatocytes	Alteration in gene expression [34]
PC12 cells	Adaptive response and enhancement of cell tolerance through induction of thioredoxin reductase via activation of Nrf-2 [35]
HLE B-3 cells	Profound changes in gene expression on depletion of 4-HNE [36]
Pulmonary epithelial cells	Increase in heme oxygenase-1 through activation of the ERK pathway [37]
Nerve cells	Modulation of stress-activated protein kinase pathways [38]
Human fetal liver hematopoietic stem cells	Inhibition of cell proliferation and alteration of differentiation pathways [39]
Human cell lines of varying origin	Modulation of signaling kinases [2]
Macrophages	Inducer of COX-2 [40–42]
Rat pancreatic stellate cells	Activation of the activator protein-1 and mitogen-activated protein kinases [43]
Human neuroblastoma cells	Regulation of glycogen synthase kinase 3 beta [44]
Human lens epithelial cells	HNE depletion leads to phenotypic transformation of adherent cells [45]
Colorectal carcinoma, HL60, HLE B-3 cells	Induction of apoptosis [46–48]
Dentate granule cells	Modulation of voltage gated Ca^{2+} current [49]
Human hepatic stellate cells	Profibrogenic stimulus. Interaction with JNK isoforms [50]
Human erythroleukemic cells	Role in UVA-mediated signaling for apoptosis [9]
Cells of varying origin	Triggers multistep signal transduction for suppression of cellular functions [20]
Hepatic stellate cells	Direct interaction with JNK isoforms [51]
Jurkat cells	Down regulation of Akt kinase [52]
Neurons	NGF withdrawal-induced neuronal apoptosis [53]
Chlamydia pneumoniae	Inhibition of IKK/I kappa B-mediated signaling [54]
HBE1 cells	Induction of glutamate cysteine ligase through JNK [55]
Human lung fibroblasts	Activation of epidermal growth factor receptor-linked extracellular signal kinase p44/42 pathway [56]
Retinal pigment epithelial cells	Induction of vascular endothelial growth factor [57]
Macrophages	Activation of PKC beta isoforms [58]
K562 cells	Role in adaptive response of cells to heat and oxidative stress [7]
Vascular smooth muscle cells	Prevents NO production [59]
Vascular smooth muscle cells	NF-kappaB activation and formation of isoprostane [60]
PC12 cells	Activation of JNK pathway [61]
Neurons	Inhibits constitutive and inducible activity of NF-Kappa B [62]
Hepatic stellate cells	Reduces tyrosine phosphorylation [63]
Human epidermoid carcinoma A431 cells	Triggers an epidermal growth factor receptor for growth inhibition [64]
Rat hepatocytes	Regulation of PKC beta isozymes [65]
HeLa cells	Affects expression of c-fos proto-oncogene and proliferation [66]