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4-hydroxynonenal-mediated signaling and aging

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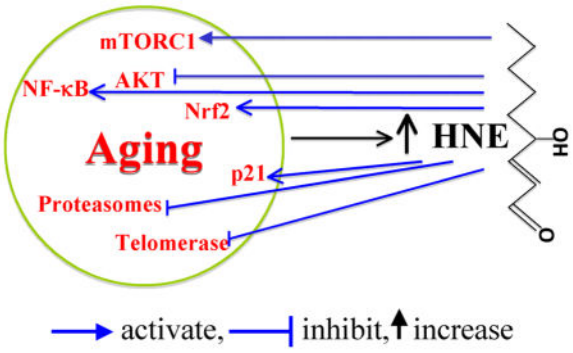
Abstract

4-Hydroxy-2-nonenal (HNE), one of the major α, β-unsaturated aldehydes produced during lipid peroxidation, is a potent messenger in mediating signaling pathways. Lipid peroxidation and HNE production appear to increase with aging. Although the cause and effect relation remains arguable, aging is associated with significant changes in diverse signaling events, characterized by enhanced or diminished responses of specific signaling pathways. In this review we will discuss how HNE may contribute to aging-related alterations of signaling pathways.

Graphical abstract



Keywords

4-Hydroxynoneal; HNE; aging; redox signaling; oxidative stress

Introduction

4-hydroxy-2-nonenal (HNE) is a major α, β-unsaturated aldehyde derived from the decomposition of peroxidation products of omega-6 polyunsaturated fatty acids; i.e., arachidonic acid and linoleic acid [1–5]. As a consequence of the natural occurrence of lipid peroxidation in aerobic biologic systems, HNE is present, at low concentrations, in almost all cells and tissue fluids under physiological condition. A marked increase of HNE

concentration is usually observed during oxidative stress. By forming adducts with proteins, nucleic acids, and lipids, HNE causes dysfunction of targeted biological molecules and is implicated in various diseases, including Alzheimer disease [6–8], cancers [9], chronic obstructive pulmonary disease (COPD) [10], and cardiovascular diseases [11], etc. [12, 13]. Therefore, HNE is recognized as one of the key culprits in cell and tissue damage caused by oxidative stress.

In contrast, numerous studies have shown that at physiological or slightly greater concentrations, HNE acts as a potent mediator that regulates a variety of signaling pathways [14, 15] and cellular processes [12]. The signaling effect of HNE originates from its ability to form adducts with proteins involved in signal transduction and gene expression, including receptors, kinases, phosphatases, and transcription factors [16]. Since it was first proposed by Harman that oxidant (free radical) mediated damage of macromolecules causes aging [17], this idea has remained a major theme in aging research, although it has been strongly questioned in terms of its relative contribution to aging per se and is more likely a participant in age-related diseases. Certainly, increased accumulation of oxidatively modified macromolecules and chronic oxidative/elephophilic state in the elderly [18–22] has been well documented, but accumulation of damaged material may not equate with actual injury. Rather, the involvement of oxidants in aging is far more complex than simple accumulation of oxidized macromolecules [23] and more likely involves disruption of redox signaling and oxidative metabolism [21]. Based on a recent proposal for the dynamic regulation of redox homeostasis and maintenance of oxidant/antioxidant balance [24], we suggest that chronic oxidative stress in aging results in an new antioxidant/electrophile steady state and age-adjusted redox homeostasis that is oxidized compared with that of youth. The signaling mechanisms establishing this new more oxidized steady state poorly adjust to additional stress. Fitting the older paradigm of the free radical theory of Harmann, HNE derived from lipid peroxidation and HNE-modified proteins inevitably increase during aging and are frequently used as a marker of aging-related oxidative stress [22]. But, in regard to the newer proposal that redox signaling and homeostasis are abnormal in aging, the potential role of HNE as a signaling mediator in age-related signaling events has not been given much consideration. Therefore, while the involvement of HNE in age-related pathologies has been discussed by many excellent reviews [6–10, 25–28], here we will discuss the role that HNE may play in altering signaling pathways during aging.

Increased HNE concentration in aging

Under physiologic conditions, HNE is present at very low concentration in plasma, in the range of 0.28–0.68 μM [1, 3, 29], but its concentration in cells, where it is produced, is higher (≤ 5 μM) [5]. Under oxidative stress, HNE concentration can be markedly increased as much as by 100 times [3]. Although it has been well recognized that lipid peroxidation increases with aging [30, 31], data on the change in HNE concentration in aging are limited.

Studies on flies and animals suggest that HNE concentrations, either free HNE or as protein adducts, increase during aging. Zheng et al. measured HNE-adduct accumulation in aging in fruit flies using an ELISA method and found that HNE adduct concentrations remained relatively unchanged during the first half of adult life and then significantly increased by

about 2 fold. After reaching a peak, HNE adducts appeared to decrease later in life of flies [32]. The change in HNE in aging in mammals seems more consistent. Using a gas chromatography-mass spectrometry method, Asselin et al. assessed the change of protein-bound HNE in the blood of aging rats (Wistar rats at 7, 15, 22, and 30 weeks of age) and found that the concentration of protein-bound HNE in the blood was significantly increased with aging [33]. In a similar study, Kim et al. showed that HNE adduction to serum proteins was significantly increased by 2–3 fold in old Fischer 344 rats, and free HNE was increased from about 0.3 μM to 0.7 μM (7 months vs 24 months) [34]. The increase of HNE-protein adducts in old animals is supported by others, as observed in the heart of rats (6 months vs 30 months) [35, 36] and bone of mice (6 months vs 25 months) [37].

The change in HNE concentration in aging is less studied in humans. Gil et al. measured HNE and other oxidative stress markers in the blood and plasma of 194 healthy human of ages from 18 to 84 years and found that the concentrations of HNE and other oxidative markers were all increased during aging. Plasma HNE concentration was increased from 68.9 ± 15.0 nmol/L in the young group (up to 30 yr old) to 107.4 ± 27.3 nmol/L in the elderly group (older than 70 yr) [38]. On the other hand, there are many studies on the increased lipid peroxidation with human aging. In these studies, the questionable thiobarbituric acid test, but also the more reliable measurement of protein carbonyls, have been used as indicators of lipid peroxidation. As a principle lipid peroxidation derivative, it is inferred that HNE concentration also increases with aging. Nonetheless, more direct determination of free HNE or its adduct concentration in elderly will help to further understanding the biological effects of HNE in aging.

Aging-related signaling pathways affected by HNE

Aging is characterized by the manifestation of a systematic decline in functions. As a fundamental mechanism underlying most cellular responses and functions, signal transduction also varies in aging. But, whether these changes in signaling are a cause or effect in the aging process remains uncertain. Here we provide several examples to show that HNE may play a potential role in these age-related signaling pathways.

NF-κB signaling

The immune system in the elderly becomes increasingly dysfunctional and the immune response to infectious pathogen and vaccine is blunted [39]. On the other hand, aging is usually accompanied by low-grade chronic inflammation characterized by elevated plasma concentrations of proinflammatory cytokines and acute phase proteins, such as TNFα, IL-6, and C-reactive protein [40–43]. In agreement with this, the expression and activity of the central key player in cytokine regulation and inflammatory response, NF-κB, is increased in cells/tissues from elderly adults [44]. Thus, so-called “inflammaging” is assumed to be the culprit in many age-associated diseases [45, 46].

The NF-κB signaling pathway can either be activated or inhibited by HNE, depending on concentration (Fig. 1). At low concentrations, HNE could activate NF-κB signaling pathway via activating IKK. Amma et al. reported that 0.1–1 μM HNE activated IKK and thus increased NF-κB activity via forming adducts with IKK and IκB in human fibroblast cells

but, 2.5 μM HNE inhibited IKKs [47]. Similarly at low concentration (1μM), HNE activated IKK and increased NF-κB activity in raw 246.7 cells [48] and vascular smooth muscle cells [49, 50]. In contrast, in studies using HNE concentrations higher than 5 μM (in the range of 5–50 μM), IκBα degradation [51] and phosphorylation [52] were prevented, possibly through inhibition of IKKs [53, 54]. As a result, the basal and inducible NF-κB activity was inhibited [55–59]. Conjugation and inhibition of either IKKα [53] or IKKβ [55] was reported. However, there was controversial report that at high concentration (15 μM) HNE increased IKK phosphorylation and activation, and IkBα degradation, and thus increased NF-κB activation in rat prostate endothelial cells [60]. In summary, the ability of HNE to activate NF-κB signaling at concentration as low as that found in the plasma of elderly suggests a potential role of HNE in the age-related increase of NF-κB activity and proinflammatory cytokines.

Nrf2 signaling

Nrf2 is a transcription factor involved in the regulation of a large number of antioxidant and detoxification enzymes, and plays a key role in the adaptation response to oxidative stress and maintenance of cellular redox homeostasis. The regulation of Nrf2 signaling involves multiple signaling molecules including KEAP1, p21, p63, PKCs, MAPKs, etc., as discussed in a recent review [61]. Accumulating evidence suggests that the induction of Nrf2 signaling declines in aging, while its basal activity was increased in some animal tissues in aging [61]. Although being extensively studied, the underlying mechanism of aging-related variation of Nrf2 signaling remains elusive.

Studies have found that HNE can activate Nrf2 signaling at concentrations ≤ 0.3 μM [62–64], through activating multiple signaling pathways including atypical protein kinase C iota (aPKCι) [65], phosphatidylinositol 3-kinase (PI3K) [63], and mitogen activated proteine kinases (MAPKs) [66, 67]. This suggests how HNE may be involved in the increase of basal Nrf2 signaling in the elderly but not in the decline of Nrf2 signaling response to stimuli in aging.

AKT/PKB signaling

AKT, which is also called protein kinase B (PKB), is a central player in processes downstream of activated growth factor receptor signaling such as insulin and epidermal growth factor receptors, and plays important roles in various processes including cell survival, cell growth, apoptosis, protein synthesis, energy metabolism, and oncogenesis [68, 69]. In the canonical pathway, AKT activation occurs sequentially in the order of binding of growth factors to tyrosine kinase receptors, activation of PI3K, and increased phosphatidylinositol (3,4,5)-trisphosphate (PIP3)-AKT activation. All three highly conserved AKT isoforms (AKT1, AKT2 and AKT3) are activated by the same mechanism. In addition, AKT can also be regulated through a redox-dependent mechanism [70]. In this non-canonical pathway, AKT signaling is regulated through oxidative modification of signaling molecules involved in AKT activation, including PI3K, PTEN, and AKT itself (Fig. 2).

AKT plays critical roles in aging-related processes through phosphorylating and regulating the downstream substrates including mammalian target of rapamycin (mTOR) (activation), glycogen synthase kinase beta (GSK3β) (inactivation) and Forkhead box O (FOXO) (inactivation) (Fig. 2), as discussed in a recent review [71]. Accumulating evidence suggests that AKT signaling changes with aging and the variation seems tissue dependent [72]. For example, AKT phosphorylation (at Ser473) and activity were significantly declined in the elderly in mice hippocampus (6 months vs 20 months) [73], skeletal muscle of human [74], but increased the old in rat soleus muscles (6 months vs 33 months) [75] and hypothalamus (6 months vs 24 months) [76].

Many studies have investigated the effect of HNE on AKT in diverse cell models and with a wide range of HNE concentration (Table 1). HNE decreased AKT phosphorylation and activity in a wide concentration range from 5–100 μM in MG63 human osteosarcoma cells [77], 3T3-L1 adipocytes [78], human OA chondrocytes [79] and Jurkat cells [80]. In contrast, increased AKT phosphorylation was observed in vascular smooth muscle cells (1μM) [50], PC12 cells (15 μM) [81], human neuroblastoma IMR-32 cells (10 μM) [82], human corneal epithelial cells (30μM) [83] and retinal pigment epithelial (RPE) cells (0.1–5 μM) [84]. In rat slow-twitch skeletal muscle cells however, HNE did not affect AKT phosphorylation and activity [85]. This evidence indicates that the regulation of HNE on AKT activity is cell dependent. However, it remains unclear what underlies the different regulatory effects of HNE on AKT.

HNE could regulate AKT activity directly through forming adducts. Shearn et al. investigated the regulation of HNE on AKT1 and AKT2 in HePG2 cells and found that both AKT1 and AT2 could form adducts with HNE, and as a result, the activity of AKT1 or AKT2 was inhibited [86][87]. Interestingly total AKT phosphorylation (Ser473) was increased in both cases. There is evidence that the overall effect of HNE on AKT signaling may be an integrated result of activation via canonical pathway (PI3K activation), dephosphorylation by PTEN and PP2A, and HNE conjugation (inhibition) [80, 86, 87] (Fig. 2). The role of AKT3 in this regulation is unknown.

In summary, HNE may affect age-related AKT signaling in a complex manner (Fig. 2). Since most studies on AKT signaling regulation used much higher HNE concentrations than physiological concentration, the exact role of HNE in the change of AKT signaling with aging *in vivo* needs to be further elucidated. Further studies on how HNE affects the AKT signaling initiated by insulin are expected, as recent report that HNE inhibited the response of AKT to insulin and H_2O_2 [86].

mTOR signaling

Mechanistic target of rapamycin (mTOR) has been being extensively studied as a key modulator of aging and aging-related diseases, and its role as a key regulatory nexus of modulating anabolic processes versus catabolic processes and involvement in aging-related processes have been well discussed by many [88, 89]. The signaling network of mTOR is described briefly here. mTOR is a serine/threonine protein kinase of the PI3K-related family that functions in two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Fig. 3) [88], and the former is much more extensively studied than the latter.

Upstream, mTORC1 can be activated by growth factors such as insulin, and environmental nutrients such as amino acids, and oxidative stress, or repressed by AMP-activated protein kinase (AMPK), a key sensor of cellular energy status. Downstream, mTORC1 phosphorylates and regulates a diverse substrates including ribosomal protein S6 kinases (S6K), NF-κB, hypoxia inducible factor 1 alpha (HIF-1α), etc. (Fig. 3), thus promotes cell growth and proliferation, lipid synthesis, and modulates mitochondria function and autophagy [90–92]. In contrast, mTORC2 is less studied, and available evidence suggests it is regulated by growth factors and primarily involved in cytoskeleton assembly and cell size modulation [93, 94]. As feedback regulation, S6K could inhibit mTORC1 pathway through phosphorylating and inhibiting insulin receptor (IRS)/PI3K/AKT signaling and thus benefit longevity processes. On the other hand, mTORC2 could activate AKT pathway and enhance aging. The actual situation is much more complex as interactions occur among signaling networks.

HNE could modulate mTOR-signaling network via acting on several targets. Besides modulating AKT signaling to mTOR as discussed above (Fig. 2), HNE could also regulate mTOR signaling through liver kinase B1 (LKB1)-AMPK-mTORC1 pathway (Table 2, Fig. 3).

LKB1, also called serine/threonine kinase 11, is kinase that phosphorylates and activates AMPK, a central metabolic sensor that regulates lipid, cholesterol and glucose metabolism. Dolinsky et al. first reported that HNE (40 μM) could conjugate with LKB1 and repress its activity, and inhibit its downstream substrate AMPK activity, and thus result in the activation of mTOR/p70S6 kinas pathway in isolated cardiomyocytes [95]. This finding was supported by other studies, which demonstrated that LKB1 was inhibited by HNE in various cell models, including primary mouse cardiomyocytes (20 μM) [96], HEK293T cells (1–40 μM) [97], and rat ventricular cardiomyocytes (10 μM) [98]. In these studies, HNE-LKB1 adducts were detected and total LKB1 decreased, and this was postulated as the mechanism of LKB1 inhibition. HNE inhibition on LKB1 would suppress subsequent AMPK activity, and thus activate mTORC1 signaling. However, this hypothesis is challenged by a recent study, in which LKB1 knockout did not replicate the effect of HNE on mTORC1-S6K-RPS6 signaling [98]. It is suggested that HNE may activate mTORC1 signaling through direct inhibition of AMPK. Although AMPK activity was inhibited by HNE [95, 96, 99, 100], direct evidence of HNE-AMPK1 adducts has not been demonstrated.

Other age-related signaling

The aging process is accompanied by variation in multiple signaling pathways that have been less examined. P21, a protein implicated in cell cycle arrest and senescence [101, 102], was increased by HNE at concentration of as low as 1 μM [103, 104] in p53-dependent- [103, 105] or p53-independent manner [106]. The activity of both 20S proteasome and telomerase declines with aging and are implicated in the aging processes. Both 20S proteasome and telomerase were reportedly inhibited by HNE [107, 108]. It is expected that HNE with its many targets will be shown to alter additional signaling and other enzymatic activities associated with aging as work continues in this field.

Summary and future prospective

HNE concentration (in free or adduct form) increases with aging. Given its modification of multiple signaling molecules and its meditation of a wide range of signaling pathways, HNE is involved in aging-related signaling pathways through multiple entry points. In this article, we discussed the potential contribution of HNE to NF-κB, AKT, Nrf2, and mTOR, four signaling pathways that are implicated in aging processes (Fig. 4). Although not yet specifically examined, other signaling pathways involved in aging, such as that related to growth factor signaling EGFR [109–114], PDGFR [115–117], and others [118], are also mediated by HNE. It is noted that most of the evidence cited here is based on cell models and further evidence with model organisms would help elucidate the role of HNE in aging.

Acknowledgments

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Highlights

- HNE concentration in the plasma and cells/tissues increases with aging
- HNE regulates NF-κB signaling in concentration-dependent manner
- HNE contributes to aging-related decline in Nrf2 signaling response
- HNE causes aging-related variation of AKT signaling via PTEN and others.
- HNE alters aging-related mTORC1 signaling through LKB1, AMPK and others.

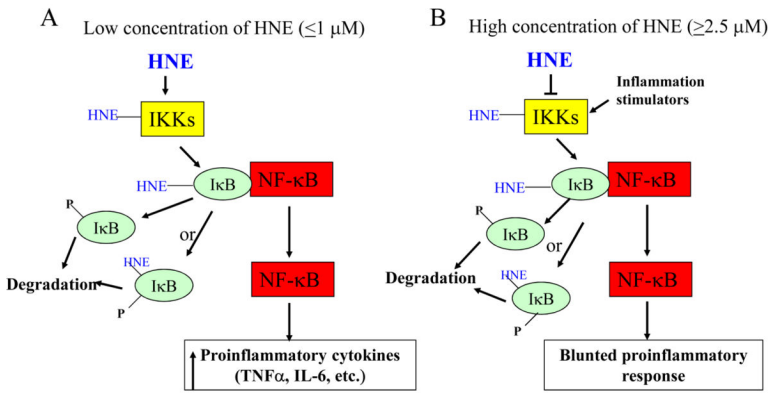

Figure 1.

Regulation of NF-κB signaling by HNE. At low concentration (0.1–1 μM) HNE activates NF-κB signaling through conjugating with IKKs (IKKα and IKKβ) and IκB, and increases the expression of proinflammatory cytokines (A). While at high concentration (2.5–50 μM), HNE inhibits IKKs, resulting in the repression of basal and inducible activity of NF-κB signaling (B).

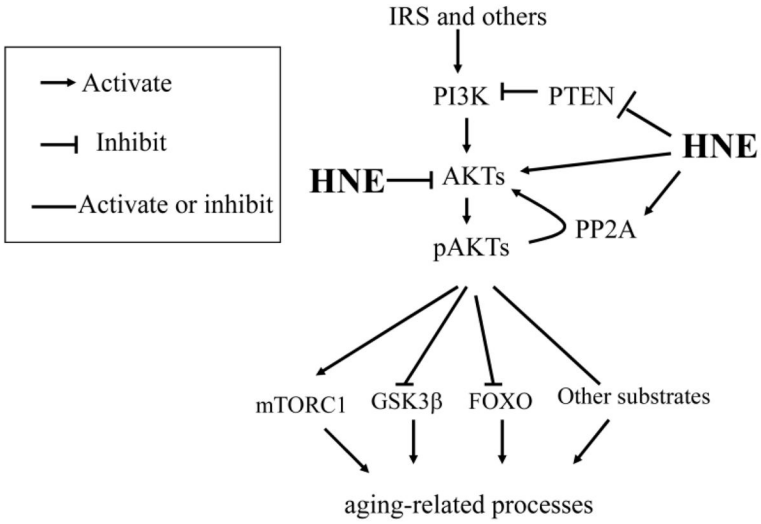

Figure 2.

HNE mediates AKT signaling. HNE could either activate AKT, through inhibiting PTEN and activating PI3K, or inhibiting AKT, through forming an HNE-AKT adduct or activating PP2A, a phosphatase that dephosphorylates pAKT. HNE may interfere with insulin-activated AKT signaling. Thus the final effect of HNE on AKT signaling may vary depending on cell type or other factors. Active AKT regulates the downstream targets involved in aging processes. IRS, insulin receptor substrate; GSK3β, glycogen synthase kinas 3 beta; FOXO, Forkhead box O; PP2A, Protein phosphatase 2.

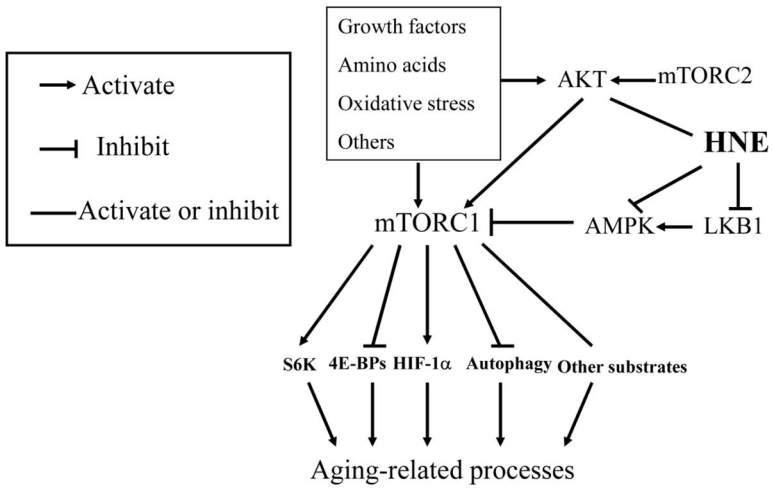

Figure 3.

HNE is involvement in mTOR signaling. HNE could conjugate and inhibit LKB1, thus inhibiting AMPK activity, and subsequently leading to the activation of mTORC1 and regulation of its downstream targets that are involved in aging processes. HNE could also either activate or inhibit mTORC1 through regulating AKT signaling as illustrated in Fig. 2. S6K, ribosome S6 kinase; 4E-BPs, translation initiation factor 4E-binding proteins; HIF-1α, hypoxia inducible factor 1alpha.

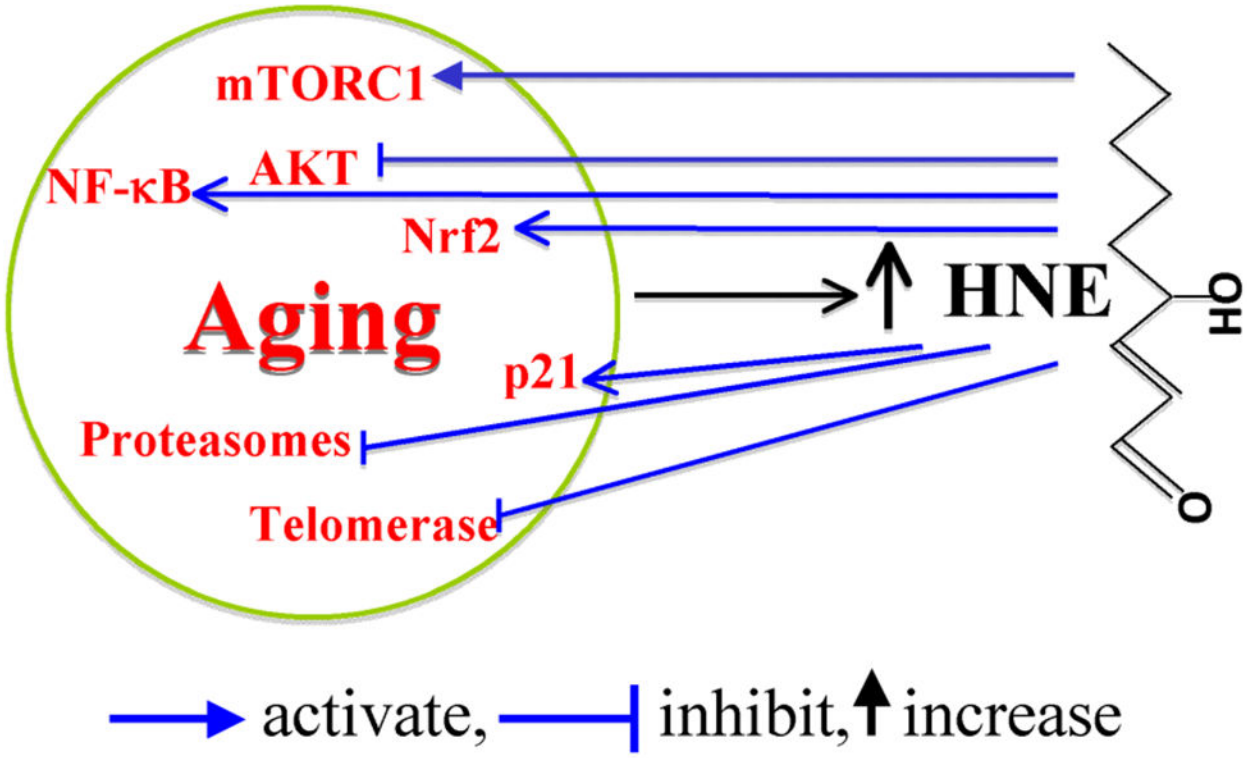

Figure 4.

A summary of HNE involvement in aging-related signaling alteration. HNE may contribute to the aging process through activating or inhibiting aging-related signaling. It should be noted that HNE might have a dual effect on some signaling molecules such as AKT, as discussed in the text.

Table 1

Differential regulation of HNE on AKT signaling

Signaling molecules	HNE concentration (μM)	Effect	Cells	Reference
AKT and PP2A	20 in 10% FBS medium	Decreased AKT phosphorylation and inhibited its activity via activating PP2A	Jurkat cells	[80]
PI3K/AKT	10 in 10% FBS medium	Activated	Human neuroblastoma IMR-32 cells	[82]
AKT	15 in 10% FBS medium	Activated	PC12 cells	[81]
PI3K/AKT	25–100 μM in 0.2% serum free medium	Inhibited	3T3-L1 adipocytes	[78]
PI3K/AKT	1 μM in 10% FBS medium	Activated	Vascular smooth muscle cells	[50]
AKT	30 μM in 2% FBS medium	Inhibited	Human OA chondrocytes	[79]
AKT1 and AKT2	100 μM in serum free medium	Increased AKT2 phosphorylation via inhibiting PTEN, but inhibit its activity via forming AKT-HNE adduct. No effect on AKT1	HepG2 cells	[87]
AKT and PTEN	12.5–100 μM in serum free medium	Increased AKT phosphorylation at Ser473 and thr308, conjugated and decreased PTEN phosphorylation and activity	HepG2 cells and primary rat hepatocyte	[119]
AKT	0.1–5 μM in 10% FBS medium	Increased AKT phosphorylation	Retinal pigment epithelial (RPE) cells	[84]
AKT1	25–100 μM in serum free medium	Inhibited AKT1 phosphorylation but not AKT2, and inhibited AKT activity by forming carbonyl AKT1 adduct	HepG2 cells	[86]
PI3K/AKT	30 μM in 5% FBS medium	Activated	Human corneal epithelial cells	[83]
AKT	5–50 μM in 10% FBS medium	Inhibited AKT activity	MG63 human osteosarcoma cells	[77]
AKT	50 μM in 10% FBS medium	No effect on AKT phosporylation at Ser473	Rat slow-twitch skeletal muscle	[85]

Table 2

Regulation of HNE on mTOR signaling molecules

Signaling molecules	HNE concentration (μM)	Effect	Cells	Reference
LKB1 and AMPK	N/A	Conjugated with LKB1, and inhibited LKB1 and AMPK activity	MCF-7 and RKO cells	[120]
LKP1 and AMPK	40 μM in 10% FBS medium	Conjugated and inhibited LKB1; inhibited AMPK activity	Cardiomyocytes	[95]
AMPK	10–30 μM in 10% FBS medium	Inhibited AMPKα activity via decreasing its phosphorylation at Thr172	Human retinal pigment epithelium cell line ARPE19	[100]
LKB1 and AMPK	20 μM in 10% FBS medium	Decreased total and phosphorylated LKB1, and inhibited AMPK activity	Primary Mouse cardiomyocytes	[96]
LKB1	1–40 μM in 10% FBS medium	Conjugated with LKB1 and inhibited its activity	HEK293T cells	[97]
LKB1	10 μM in 10% FBS medium	Conjugated with LKB1 and inhibited its activity; inhibited AMPK activity, increased mTOR–p70S6K–RPS6 signaling	Rat ventricular cardiomyocytes	[98]
AMPK	10 and 30 μM in 10% FBS medium	Inhibited AMPK activity	3T3-L1 adipocyte	[99]
LKB1	N/A	Increase of HNE-LKB1 adducts	Mouse heart tissue	[121]