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Review Article

Lipid peroxidation triggers neurodegeneration: A redox proteomics view into the Alzheimer disease brain

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ABSTRACT

Lipid peroxidation involves a cascade of reactions in which production of free radicals occurs selectively in the lipid components of cellular membranes. Polyunsaturated fatty acids easily undergo lipid peroxidation chain reactions, which, in turn, lead to the formation of highly reactive electrophilic aldehydes. Among these, the most abundant aldehydes are 4-hydroxy-2-nonenal (HNE) and malondialdehyde, while acrolein is the most reactive. Proteins are susceptible to posttranslational modifications caused by aldehydes binding covalently to specific amino acid residues, in a process called Michael adduction, and these types of protein adducts, if not efficiently removed, may be, and generally are, dangerous for cellular homeostasis. In the present review, we focused the discussion on the selective proteins that are identified, by redox proteomics, as selective targets of HNE modification during the progression and pathogenesis of Alzheimer disease (AD). By comparing results obtained at different stages of the AD, it may be possible to identify key biochemical pathways involved and ideally identify therapeutic targets to prevent, delay, or treat AD.

Contents

Lipid peroxidation and neurodegeneration

One of the major targets of the lipid peroxidation process is the central nervous system (CNS). Indeed, the brain is highly sensitive to oxidative stress because this 1300-g organ consumes about 20–30% of inspired oxygen, contains high levels of polyunsaturated fatty acids (PUFAs), is an ideal target for free radical attack, and high levels of redox transition metals. The latter play a crucial role in initiation/propagation of the cascade of reactions that start with the abstraction of an electron from the conjugate double bond system of fatty acid acyl chain. This process leads to the formation of a variety of free radical species, commonly

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grouped as reactive oxygen species (ROS), with slightly different reactivity. Altogether, ROS are highly unstable and easily react with all macromolecules such as proteins, nucleic acids, and lipids. These events are further exacerbated in the brain by the relative inability of neuronal cells to neutralize free radicals due to the paucity of both enzymatic and nonantioxidants.

Lipid peroxidation is one of the major sources of free radical-mediated injury that directly damages neuronal membranes and yields a number of secondary products responsible for extensive cellular damage. Free radical attack to PUFAs leads to the formation of highly reactive electrophilic aldehydes, including malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), the most abundant products, and acrolein, the most reactive (Fig. 1) [1–3]. In addition to aldehyde formation, lipid hydroperoxyl radicals undergo endocyclization to produce fatty acid esters; two classes of these cyclized fatty acids are ispoprostanes and neuroprostanes (Fig. 1) [4,5].

Peroxidation of arachidonic acid (AA) leads to the formation F_2-isoprostanes (F_2-IsoPs), while F_4-neuroprostanes (F_4-NPs) are the stable product of free radical damage to docosahexanoic acid (DHA). Once formed, F_2-NPs and F_4-NPs can undergo hydrolysis to free iso- and neuroprostanes that can be measured in body fluids [6], and F_2-NPs and F_4-NPs can undergo nonenzymatically additional conversions to form isochetals and neurochetals both of which are dangerous to cells [7,8]

However, cells also are endowed with lipid antioxidants, especially lipid-soluble vitamins and glutathione, glutathione *S*-transferases, one isoform of glutathione peroxidase, and beta-alanyl-L-histidine, which can quench lipid oxidants including HNE. In addition, albumin and apolipoproteins in plasma can bind and buffer HNE. However, a specific repair process of lipid peroxidation does not exist as it does for proteins and DNA and this may explain why moderate levels of lipid peroxidation could have physiological significance for cell signaling and membrane remodeling [9].

Peroxidation of membrane lipids affects a variety of functions resulting in increased membrane rigidity, decreased activity of membrane-bound enzymes (e.g., sodium pump), impairment of membrane receptors, and altered permeability [10,11]. In addition to damage to phospholipids, radicals also can directly attack membrane proteins and induce lipid–protein and protein–protein crosslinking, all of which contribute to altered membrane integrity [12]. It is reasonable to hypothesize that perturbation of all the above-noted functions displayed by PUFAs and its metabolites, together with modification of proteins, affects neuronal homeostasis, thus contributing to brain dysfunction.

The role of free radical-mediated oxidative damage in the pathogenesis of neurodegenerative disorders has been firmly established [13–17]. In particular, markers of lipid peroxidation have been found to be elevated in brain tissues and body fluids in several neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and Down syndrome (DS) [17–21]. In agreement with these findings, several reports have documented increased levels of reactive products of lipid peroxidation in diseased regions of brain [17,22,23], but generally not in regions uninvolved in the disease [17]. This review focuses on the role of lipid peroxidation in brain of subjects at various stages of AD.

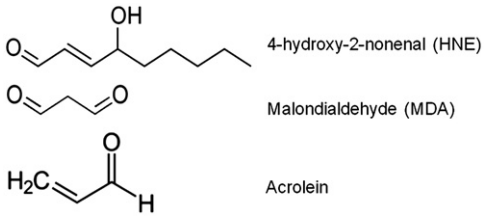

Fig. 1. Chemical structure of 4-hydroxy-2-nonenal (HNE), malondialdehyde (MDA), and acrolein.

The chemistry of lipid peroxidation: Focus on HNE

Lipid peroxidation involves a cascade of reactions which cause the degradation of lipids commonly described as a 5-step sequence (Fig. 2).

Step 1: **Initiation**, in which the free radical (hydroxyl $HO^{\bullet}$, alkoxyl $RO^{\bullet}$, peroxyl $ROO^{\bullet}$, and possibly $HO_2^{\bullet}$ but not H_2O_2 or O_2^{-}) abstracts an allylic H from a methylene group in the acyl chain of phospholipids, followed by rearrangement of the double bonds to the conjugated diene form, and simultaneously producing a carbon-centered alkyl radical.
Step 2: A peroxyl radical is produced when the alkyl radical reacts with paramagnetic molecular oxygen.
Step 3: **Propagation**, in which the peroxyl radical abstracts another allylic H atom to initiate a self-perpetuating chain reaction that ultimately leads to a variety of cyclic peroxides and hydroperoxides. These latter can be further degraded to hydrocarbons, alcohols, ether, epoxides, and aldehydes. Among these by-products, MDA, HNE, and acrolein can cause irreversible modification of phospholipids, proteins, and DNA [24].
Step 4: **Termination**, by which different types of radicals react with each other leading to formation of stable products; or
Step 5: Termination, by which reactions between the radicals and antioxidants give rise to nonradical products or unreactive radicals. Both exogenous and endogenous antioxidants such as vitamin E and vitamin C prevent the propagation of lipid peroxidation at the early stages of free radical attack [25,26]. Vitamin E (α-tocopherol) is a "chain-breaking" antioxidant; when the allylic hydrogen is abstracted in step 1, and α-tocopherol radical forms (step 5), the tocopherol radical can be reverted back to vitamin E by the vitamin C (ascorbic acid) and glutathione. The protective effects exerted by antioxidant toward HNE and other toxic aldehydes have been investigated by many groups to test the possibility of a therapeutic use of free radical scavengers and antioxidants against lipid peroxidation-mediated toxicity. In addition to small molecules, antioxidant enzymes such as heme oxygenase-1 (HO-1), catalase, superoxide dismutase, peroxiredoxin, and

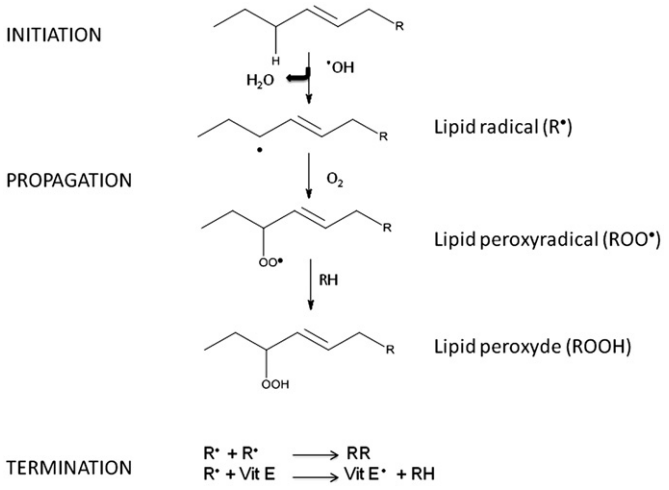

Fig. 2. Lipid peroxidation process.

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