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Forum Review

Protein Oxidation and Lipid Peroxidation in Brain of Subjects with Alzheimer's Disease: Insights into Mechanism of Neurodegeneration from Redox Proteomics

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ABSTRACT

Alzheimer's disease (AD), the leading cause of dementia, involves regionalized neuronal death, synaptic loss, and an accumulation of intraneuronal, neurofibrillary tangles and extracellular senile plaques. Although the initiating causes leading to AD are unknown, a number of previous studies reported the role of oxidative stress in AD brain. Postmortem analysis of AD brain showed elevated markers of oxidative stress including protein nitrotyrosine, carbonyls in proteins, lipid oxidation products, and oxidized DNA bases. In this review, we focus our attention on the role of protein oxidation and lipid peroxidation in the pathogenesis of AD. Particular attention is given to the current knowledge about the redox proteomics identification of oxidatively modified proteins in AD brain. *Antioxid. Redox Signal.* 8, 2021–2037.

INTRODUCTION

Alzheimer's disease (AD), the leading cause of dementia, involves regionalized neuronal death, synaptic loss and an accumulation of intraneuronal, neurofibrillary tangles and extracellular senile plaques (103). Currently, about 4 million Americans have Alzheimer's disease, and thousands of people die of Alzheimer's disease every year. The number of Americans with Alzheimer's disease is expected to increase to 14 million by 2050, unless a cure or preventive measures can be found. To date, despite intensive efforts, the mechanism(s) responsible for AD remain elusive, and this incomplete understanding of disease pathogenesis has greatly affected the development of accurate animal and cellular models, and thereby retarded the development of therapeutic modalities.

Several independent hypotheses have been proposed to link the pathologic lesions and neuronal cytopathology with, among others, apolipoprotein E genotype (120, 195), hyperphosphorylation of cytoskeletal proteins, and amyloid-β metabolism (81, 183). However, none of these hypothesis alone is sufficient to explain the diversity of biochemical and pathologic abnormalities of AD, which involve a multitude of cellular and biochemical changes (87, 94, 134, 180, 215). A number of previous studies reported the role of oxidative stress in AD brain (33, 36, 134). Amyloid β-peptide (1–42), [Aβ(1–42)], a main component of senile plaques, has been reported to play a central role in oxidative stress in AD and also in the development and progression of AD (26, 32, 33, 143, 148).

Aβ40 and Aβ42 are produced from amyloid precursor protein (APP), a transmembrane protein, by the action of β- and γ-secretases. Aβ is present in soluble form, aggregated form, oligomeric form, protofibrils (PF), and fibrils. Oligomers, PF, and amyloid-derived diffusible ligands (ADDLs) are believed to generate the potent toxicity of Aβ (2, 60, 108, 163, 230). Previous studies from our laboratory demonstrated the important role of methionine at residue 35 in Aβ-induced oxidative stress and toxicity both *in vitro* and *in vivo* (29, 35, 201, 218, 219, 228).

Oxidative stress occurs because of an imbalance in the oxidant and antioxidant levels. Oxidants can damage virtually all

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biologic molecules: DNA, RNA, cholesterol, lipids, carbohydrates, proteins, and antioxidants. In AD brain, the levels of the antioxidants were found to be decreased, with an associated increase in protein oxidation (protein carbonyl and 3-nitrotyrosine), lipid peroxidation, DNA oxidation, advanced glycation end products, and reactive oxygen species (ROS) formation, among other indices, strongly suggesting a role for oxidative stress in the pathogenesis of AD (27, 36, 46, 125, 134, 197–199, 208, 209). Further, the use of vitamin E in cell culture diminishes Aβ (1–42)–induced toxicity, further consistent with a role of oxidative damage in AD pathology (22, 31, 227). In addition, Aβ(1–42) can bind to receptors on neuronal and glial cells [*e.g.*, the α7-nicotinic acetylcholine receptor, neurotrophin p75 receptor, the *N*-methyl-D-aspartate receptor, the receptor for advanced glycation end products (RAGE) (220, 222), and others], forming calcium and potassium channels in cell membranes (11, 61, 64), decreasing glucose transport across brain endothelial cells (19), and activating the release of chemokines (66) and cytokines (1). In the present review, we discuss protein oxidation and lipid peroxidation in AD brain.

PROTEIN OXIDATION

ROS and RNS attack proteins, leading to the formation of protein carbonyls and 3-nitrotyrosine (3-NT). Hence, the levels of protein carbonyls and 3-NT reflect the level of total protein oxidation in a cell.

Protein carbonyls

Protein carbonyls may be generated by backbone fragmentation, hydrogen atom abstraction at alpha carbons, or attack on several amino acid side-chains (Lys, Arg, Pro, Thr, etc.), and by the formation of Michael adducts between Lys, His, and Cys residues and reactive alkenals, which are products of lipid peroxidation (see later). Protein carbonyls are also produced by glycation/glycoxidation of Lys amino groups, forming advance glycation end products (AGEs) (18, 39, 51, 52, 201). A number of reactions of protein radicals can give rise to other radicals, which can cause damage to other biomolecules. Protein carbonylation leads to oxidation of side-chains, backbone fragmentation, formation of new reactive species (peroxides, DOPA), release of further radicals, and occurrence of chain reactions. Most protein damage is irreparable and could lead to a wide range of downstream functional consequences, such as dimerization or aggregation; unfolding or conformational changes to expose more hydrophobic residues to an aqueous environment; loss of structural or functional activity; alterations in cellular handling/turnover; effects on gene regulation and expression; and modulation of cell signaling, induction of apoptosis and necrosis, etc., indicating that protein oxidation has physiologic and pathologic significance (39). Thus, identification of carbonylated proteins should be followed by functional assessment of the protein, whether it is enzyme or structural protein. These functional studies may identify metabolic or structural defects caused by oxidative modification. Certain oxidation products of proteins, such as oxidation of Cys to cystine, and Met residues to methionine sulfoxide, can be repaired by enzymes like glutathione reductase and methionine sulfoxide (68, 155). The majority of the oxidized proteins are catabolized by proteosomal and lysosomal pathways, but some materials appear to be poorly degraded and accumulate within the cell (58, 76). The accumulation of such damaged material may contribute to a range of human pathologies.

Protein carbonyls are chemically stable compared with the other products of oxidative stress (*e.g.*, F_2 isoprostanes), which are readily generated during sample storage, processing, and analysis, and hence protein carbonyls are general and widely used markers to determine the extent of oxidative modification both in *in vivo* and *in vitro* conditions (18, 39, 51, 52, 201, 225). Several sensitive assays were developed for the detection of oxidatively modified proteins (52, 119).

A number of oxidatively modified proteins have been detected in AD brain and plasma (28, 43, 44, 46, 51, 54, 205, 206, 209). By using redox proteomics (53), our laboratory first identified the specific targets of carbonylation and nitration in AD inferior parietal lobule (IPL). After this study, a number of other targets of oxidation have been reported from our laboratory in different brain regions, and this later study also showed that oxidatively modified proteins are prone to inactivation (205).

More recently, with a redox proteomics approach, we reported specific carbonylation of the following proteins: alpha enolase, ubiquitin carboxyl terminal hydrolase L-1 (UCHL-1), dihydropyrimidinase-related protein 2, heat-shock cognate 71, creatine kinase BB, peptidyl prolyl-*cis,trans*-isomerase 1 (Pin1), glutamine synthase, triosephosphate isomerase, ATP synthase alpha chain, and carbonic anhydrase 2 (43, 44, 46, 205, 206, 209). These data support the notion that protein carbonylation perturbs energy metabolism, pH regulation, and mitochondrial functions. These proteins are discussed in detail later.

Protein nitration

Tyrosine nitration is another marker of protein oxidation, and numerous studies support the notion that nitrative stress also contributes to neurodegeneration in AD (46, 54, 197, 209, 213). Reactive nitrogen species (RNS) generated within a physiologically relevant concentration by Ca^{2+}-activated constitutive nitric oxide synthase (NOS) are not toxic; rather, RNS so generated are relatively specific in their cellular targets (112). In addition, NOS activities are modulated by phosphorylation and protein–protein interactions. Recently, several studies suggested that protein nitration could be a cellular signaling mechanism and is often a reversible and selective process, similar to protein phosphorylation (13, 109). In addition, proteins that are nitrated are more prone to proteosomal degradation than are their counterparts (75). In AD brain, increased levels of nitrated proteins compared with those of control were found, and ubiquitin carboxyl-terminal hydrolase L-1 (UCH L-1), one of the components of the proteasomal pathway, was identified as an oxidized protein in the IPL and hippocampus of AD, further suggesting a role for nitration in protein accumulation (46, 209).

RNS could be produced via the overexpression of inducible and neuron-specific nitric oxide synthase (NOS: iNOS and

nNOS, respectively) leading to increased levels of NO. AD brain has been reported to show mitochondrial abnormalities (15), which could lead to leakage of $O_2^{-\bullet}$. These two radicals [NO and $O_2^{-\bullet}$] react at diffusion-controlled rates to produce peroxynitrite, an extremely strong oxidant that can cause oxidative damage to proteins, lipids, and carbohydrates and might be involved in the deterioration observed in AD. The amino acids cysteine, methionine, phenylalanine, and tyrosine are particularly susceptible to nitration.

Tyrosine residues in a protein play an important role in redox cell signaling and oxidative inflammatory injury, because nitration has been shown to alter protein function, including modulation of catalytic activity, cell signaling, and cytoskeletal organization (190). Tyr is a site of phosphorylation, a prominent regulation function. Addition of nitrite to the protein at the 3 position of tyrosine residues sterically hinders the phosphorylation of the tyrosine OH moiety and also may change the structure of proteins, thereby rendering a protein dysfunctional, and decreased tyrosine phosphorylation could lead to cell death (39, 112). Nitration of proteins may lead to irreversible damage to the proteins and also affect the energy status of neurons by inactivating key enzymes (13, 96, 109). This widespread occurrence of oxidative alterations not only decreases or eliminates the normal functions of these macromolecules but also may activate an inflammatory response (the complement cascade, cytokines, acute-phase reactants, and proteases) in the AD brain (66, 143).

As noted, in AD brain and CSF, increased levels of nitrated proteins have been found, implying a role for RNS in AD pathology (46, 84, 197, 209). Increased levels of 3-NT immunoreactivity in neurons from AD brain when compared with aged matched controls were observed (197), and dityrosine and 3-NT levels were reported to be elevated in the hippocampus, IPL, and neocortical regions of the AD brain and in ventricular cerebrospinal fluid (VF) (197, 213). The increased 3-NT residues and free adducts in CSF of AD subjects probably reflect increased leakage of mitochondrial electron equivalents, protein nitrating agents, with resultant and increased protein nitration in brain tissue. More recent work demonstrates that $ONOO^-$ can induce α-synuclein oligomerization through covalent 3,3′-dityrosine cross-linking and may facilitate the misfolding and deposition of selected proteins through nitrosative and/or oxidative modification. Horiguchi *et al*. (91) demonstrated the presence of nitrated tau in pretangles, tangles, and tau inclusions in AD brain. The expression of nitration was robust in pretangles of early AD cases compared with those of more advanced cases, suggesting that tau nitration may be an early event in AD.

Redox proteomics

Proteomics involves the systematic study of proteins to provide a comprehensive view of the structure, function, and regulation of a given cell, tissue, or organism. The term *proteomics* was coined as an analogy to genomics, but proteomics is very much different from genomics. One organism will have radically different expression in different parts of its body and in different stages of development. Because the expression of proteins is often altered in disease conditions, proteomics can serve as a sensitive technique to gain insight into a host of biologic processes and phenotyes of both normal and diseased cells.

Previously an immunoprecipitation technique was used to identify a selective target of protein oxidation, but this technique requires a thorough knowledge of the identified protein and the availability of the antibody for the oxidatively modified protein (4, 207). Further, the oxidation of proteins could also induce structural changes that can interfere with the precipitation process. Redox proteomics represents a much more convenient way to identify a large number of proteins in a sample at one time (53). However, a disadvantage of using proteomic analysis for the identification of oxidatively modified proteins is that carbonylated or nitrated abundant proteins with a low "specific carbonyl/nitration content" will appear prominent on immunoblots, whereas proteins present at low levels but with a high specific carbonyl content may be missed. Further, less abundant proteins require that they be purified, most conveniently by immunoprecipitation. Sultana *et al.* (207) showed oxidative inactivation of MRP-1 and GST protein in AD brain by using the immunoprecipitation approach, and others also used this technique to demonstrate the effect of oxidation on the protein function in other models of AD (90, 192, 221). Several targets of protein nitration in AD brain have been identified by using redox proteomics (46, 209).

With a redox proteomics approach, we reported specific nitration of α-enolase, γ-enolase, L-lactate dehydrogenase, triosephosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATP synthase α chain, voltage-dependent anion channel protein 1, and carbonic anhydrase 2 in AD brain (46, 209). These data support the notion that nitration of specific proteins perturbs energy metabolism, pH regulation, and mitochondrial functions, which could be one of the mechanisms for the onset and progression of AD.

Proteomics methods include separation of proteins by two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) or HPLC (30), surface chromatography by adsorbing proteins to activated surfaces (surface-enhanced or matrix-assisted laser desorption–ionization, protein chip array technology) (216), peptide ionization procedures for analysis of proteins from gels or protein chips by mass spectroscopy, and finally, bioinformatics interrogation of databases for protein identification.

2D gel electrophoresis separates a mixture of proteins into single detectable protein spots based on two physicochemical properties [*i.e*., isoelectric point (IEF) and molecular migration (Mr)]. The 2D protein map permits comparison and matching between different sets of samples to identify isoforms, splice variants, mutants, and posttranslationally modified species for statistical analysis (212). 2D gel electrophoresis gives high reproducibility and resolution, and each protein spot on the gel mostly represents a single protein in a sample (205). In addition to those noted earlier, the main limitations of this technique include solubilization of membrane proteins; the inability to detect low-abundance proteins and proteins of high and low pI, proteins of high molecular weight, or very low molecular weight; and the insensitivity to proteins of high lysine and arginine content

(28, 30, 85, 184). However, our laboratory and many others are trying to overcome these issues by using chaotropic agents, such as urea and thiourea, coupled with nonionic detergents to solubilize and prevent the precipitation of proteins during first and second dimension. The use of immobilized pH IEF strips improves the reproducibility between the samples and also eliminates the typical cathodic drift associated with previously used tube gels (69). Further, the use of narrow-range IEF strips enables the investigator to separate proteins over a wide range of pH, even with a unit pH difference of one. However, the IEF strip pH range normally used (*i.e.*, 3–10) limits the identification of highly basic proteins. The identification of low-abundance proteins in a given sample is a limitation, as noted earlier, one that is important when a protein of this group may be involved in the pathogenesis of a disease. However, immunoprecipitation or other concentration-enhancing methods can sometime overcome these limitations.

The 2D gels are visualized by classic detection methods, including Coomassie blue, silver staining, and fluorescent dyes, such as SYPRO Ruby (150). These images were used to identify main proteins with altered expression, oxidation, and so on, by using specially programmed software depending on the kind of stain used. Once the proteins spots are chosen, they are excised, digested in-gel with trypsin or other appropriate protease, and subjected to mass spectrometry analysis (98, 204). The data obtained from mass spectrometry allow the identification of the protein. Databases are available for theoretical digests of all known proteins; thus matching the peptide mass data obtained from biologic samples to this database of theoretically digested proteins can successfully identify the proteins. This process, known as peptide mass fingerprinting, must account for several factors, such as molecular weight, pI, and the probability that a single peptide appears in the whole database, for the identification of a protein. Many search engines are available to perform this matching process (Table 1). Further, the protein identification can be confirmed by immunoprecipitation (28, 30). Initially proteomics was used only for protein-expression profiling; with advances in technology, proteomics has been used to analyze posttranslational modifications and protein–protein interactions as well (28, 30, 53). In our laboratory, we derivatized brain samples with dinitrophenyl hydrazine (DNPH) to identify oxidatively modified proteins (Fig. 1) (43, 44, 205).

REDOX PROTEOMICS STUDIES IN ALZHEIMER'S DISEASE

Redox proteomics in AD

AD has been investigated with proteomics (28, 56, 100, 122, 124, 208). Our laboratory used a redox proteomics approach for the first time in AD brain to identify specifically oxidized proteins; this has provided new insights into potential mechanisms of AD and other diseases (28, 43, 44, 46, 205, 206, 209).

Protein expression analysis in AD

The expression analysis of proteins potentially can aid in better understanding of the pathways involved in the pathogenesis of AD, and thereby help in delineating a mechanism of progression of AD. A 2D-PAGE study detected 350 silver-stained proteins in the plasma of six control cases, five AD cases, and three non-AD dementias, of which 73 spots were identified by sequencing or immunostaining, including the AD-related proteins apoE, tau, and presenilin-2 (41, 231). Additionally, Schonberger *et al.* (189) showed a significant regional difference in the expression of proteins in the AD brain compared with the age-matched control by using 2D PAGE and N-terminal sequencing. Lubec *et al*. (128) and others (189) have carried out an extensive protein-expression analysis in AD brain. Several other studies used CSF to identify proteins with altered expression, such as proapolipoprotein, apolipoprotein E, β_2 microglobulin, retinol-binding protein, transthyretin, α-1 antitrypsin, cell-cycle progression 8 protein, and ubiquitin, which could reflect the biochemical changes occurring in the brain (41, 231). However, CSF has a relatively high abundance of certain proteins like IgG and albumin, which could interfere with analysis, and hence their removal is a must to analyze such samples. These studies showed that in AD, complex interrelated mechanisms are at work and demonstrated the utility of proteomics to gain insight into the disease mechanisms in AD.

OXIDATIVELY MODIFIED PROTEINS IN AD BRAIN

Redox proteomics was used for the detection and identification of carbonylated and nitrated proteins in AD brain by our laboratory and others (28, 43, 44, 46, 47, 110, 205, 206,

Table 1. Mass Spectrometry Search Engines for Peptide Mass Fingerprinting

Search engine	*URL*
Mascot	http://www.matrixscience.com
MOWSE	http://www.hgmp.mrc.ac.uk/Bioinformatics/Webapp/mowse
Profound	http://prowl.rockefeller.edu/profound_bin/WebProFound.exe
MS-fit	http://prospector.ucsf.edu/ucsfhtml4.0/msfit.htm
Peptident	http://ca.expasy.org/tools/peptident.html
Mass Search	http://cbrg.inf.ethz.ch
Peptide Search	http://www.mann.emblheidelberg.de
ExPASy	http://www.expasy.ch/tools

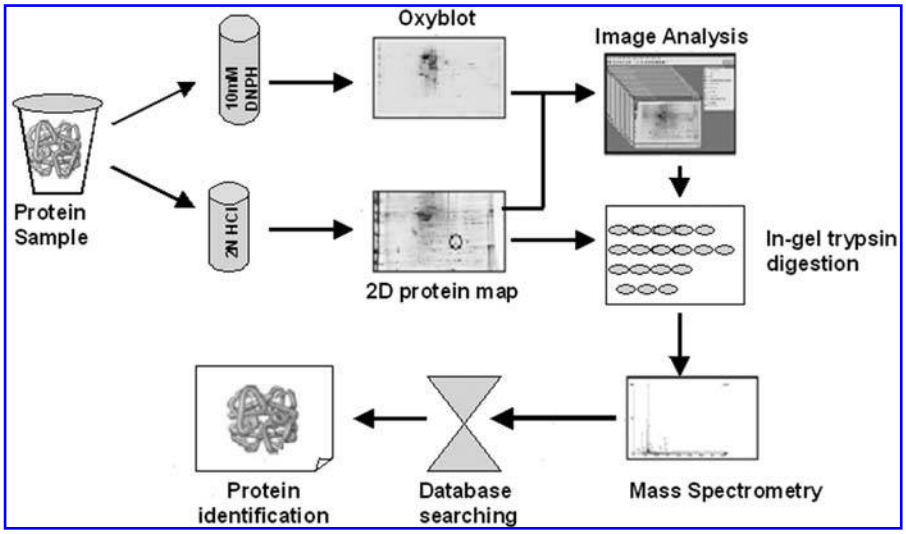


FIG. 1. Protocol for the identification of oxidized proteins by redox proteomics used in our laboratory.

208, 209). Redox proteomics has the potential of detecting disease markers and identifying potential targets for drug therapy in AD (28, 30, 208). With redox proteomics, several specific targets of protein oxidation and nitration in AD brain were identified: creatine kinase (CK), α-enolase, triosephosphate isomerase (TPI), phosphoglycerate mutase 1 (PGM1), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), voltage-dependent anion channel protein 1 (VDAC1), γ-soluble *N*-ethylmaleimide-sensitive factor attachment protein (SNAP), glutamine synthase (GS), ubiquitin carboxy hydrolase L-1 (UCHL1), neuropolypeptide h3, dihydropyrimidinase-related protein 2 (DRP2), β-actin, peptidyl prolyl-*cis,trans*-isomerase (PIN1), and carbonic anhydrase II (CA2) were identified as potentially involved in different cellular functions. These proteins may play an important role in neurodegeneration (Table 2) (43, 44, 46, 205, 206, 209). In this review, we discuss their potential link to AD pathology.

ENERGY DYSFUNCTION

Altered energy metabolism has been reported in AD brain (70, 145, 217). Positron emission tomography (PET) studies also show a pattern consistent with the reduced cerebral glucose utilization in AD brain (93, 177). These biochemical alterations are consistent with the identification of CK, ENO1, TPI, GAPDH, PGM1, and α-ATPase as oxidized proteins with redox proteomics, because each of these proteins is involved directly or indirectly in ATP production (5, 43, 44, 46, 205, 209). The oxidative modification of these enzymes likely leads to their inactivation (83, 170). For example, CK, enolase, PGM1, GAPDH, and ATPase activities are reportedly diminished in AD brain (5, 83, 205). Because glucose is the main source of energy for the normal functions of brain, decreased ATP levels would lead to impaired ion-motive ATPases to maintain potential gradients, operate pumps, and

TABLE 2. OXIDATIVELY MODIFIED PROTEINS IDENTIFIED IN AD BRAIN USING REDOX PROTEOMICS

Protein functions	*Oxidized proteins*	*References*
Energy-related enzymes	CK, Enolase, TPI, PGM1, LDH, GAPDH	2, 43, 44, 45, 205, 208
Neurotransmitter-related proteins	EAAT2, GS	26, 44, 116
Proteasome-related proteins	UCHL1,HSC	71, 43, 44
Cholinergic system	Neuropolypeptide h3	46
pH regulation-protein	CA2 II	205
Structural proteins	DRP2, β-actin	43, 205
Cell cycle, tau phosphorylation	Pin 1	205, 206
Synaptic abnormalities and LTP	Gamma-SNAP	205
Mitochondrial abnormalities	ATP synthase alpha chain, VDAC-1	208

CK, creatine kinase BB, TPI, triose phosphate isomerase; PGM1, phosphoglycerate mutase 1; LDH, lactate dehydrogenase; EATT2, excitatory amino acid transporter 2; GS, glutamine synthase; UCHL1, ubiquitin carboxy-terminal hydrolase L-1; HSC 71, heat-shock cognate 71; DRP2, dihydropyrimidinase-related protein 2; Pin1, peptidyl-prolyl-*cis,trans*-isomerase; gamma-SNAP, gamma-soluble NSF-attachment protein; VDAC, voltage-dependent anion channel protein.

maintain membrane lipid asymmetry, and so on. Such changes could also lead to exposure of phosphatidylserine to the outer membrane leaflet, a signal for apoptosis (147). Moreover, ATP shortage can also induce hypothermia, causing abnormal tau phosphorylation through differential inhibition of kinase and phosphatase (167).

EXCITOTOXICITY

Glutamine synthase plays an important role in regulation of neuronal pH, and loss of its activity could lead to accumulation of ammonia, providing a possible mechanism for neuronal degeneration (39). GS regulates the levels of glutamate in cells by the glutamate–glutamine cycle, and the oxidation of this protein in AD brain contributes to the glutamate dysregulation in AD brains (118). Such deregulation leads to an influx of Ca^{2+} and activation of NMDA and AMPA receptors that are ultimately responsible and cause neuronal excitotoxic death (138, 139). Further, the identification of GS as an oxidatively dysfunctional protein supports previous studies showing the diminished activity of GS in AD (3, 34, 83). The excitatory amino acid transporter, EAAT2 and GS are two proteins involved in the regulation of the extraneuronal levels of glutamate and neurotransmission. Hence, the oxidative dysfunction of GS, which leads to structural alterations of this protein and a reduced activity (3, 34, 39, 43, 92), could be detrimental to neurons.

A previous study identified the glutamate transporter EAAT2 as oxidatively modified by the lipid peroxidation product, HNE, in AD brain (116). Aβ(1–42) has been shown to lead to oxidative modification of EAAT2 (116).

PROTEOSOMAL DYSFUNCTION

The ubiquitin–proteasome pathway was found to be dysfunctional in AD brain and could be involved in the pathogenesis of AD (46, 47, 205). Ubiquitin carboxyl terminal hydrolase L1 (UCH-L1) is a part of ubiquitin–proteasome systems and is involved in the degradation of damaged, excess, or altered proteins that could lead to synaptic degeneration in AD brain (46, 47, 82). UCHL-1 activity was found to be decreased in AD brain (205), consistent with the observed increased protein ubiquitinylation, decreased proteasome activity, and accumulation of damaged proteins in AD brains (28). Similarly, the activities of the 26S proteasome, ubiquitin-activating enzyme (E1), and ubiquitin-conjugating enzyme are reversibly depressed under conditions of oxidative stress (104, 193). By using redox proteomics, we identified UCH-L1 protein as carbonylated in AD brain (43, 205), consistent with protein-function impairment that could lead to protein aggregates in AD brains. In addition, some recent *in vitro* studies showed that HNE, a lipid peroxidation product, decreased the activity of recombinant UCH-L1 (95, 164, 194), suggesting that oxidative modification of UCH-L1 inactivates its hydrolase activity. Our proteomics result identifying UCH-L1 as an oxidative modified protein in AD (43, 205) was recently confirmed by others (47). Taken together, these different lines of evidence support a role for dysfunction of the ubiquitin–proteasome pathway in the pathogenesis of AD.

LIPID ABNORMALITIES AND CHOLINERGIC ALTERATIONS

Previous studies reported decreased activity of choline acetyl transferase (ChAT) in AD brain (57), and ChAT has also been found to be HNE-modified in synaptosomes treated with Aβ(1–42) (36). ChAT is regulated in part by neuropolypeptide h3 (NPH3), a phosphatidyloethanolamine-binding protein (PEBP) or cholinergic neurostimulating peptide. PEBP may play an important role in maintaining phospholipid asymmetry, a process that is important to normal mitochondrial and plasma membranes function (45, 147). Therefore, oxidative modification of NPH3 (or PEBP) possibly leads to functional abnormalities, thereby causing impaired cholinergic properties, mitochondria function, and apoptosis in AD. Further, Aβ(1–42) or HNE, which is formed by Aβ(1–42), leads to loss of synaptosomal membrane lipid bilayer asymmetry (45, 147).

NEURITIC ABNORMALITIES

One of the characteristic features of AD is synaptic loss. A number of studies reported β-actin (ACT)- and dihydropyrimidinase-related proteins 2 (DRP2) as downregulated and oxidatively modified in AD brain (43, 44, 46, 49, 128). Both of these proteins are critical to neuroplasticity for memory consolidation (114). β-Actin is involved in maintenance of cytoskeleton network integrity and is concentrated in dendritic spines in adult brain, where it can produce rapid change in their shape that might be involved in memory function (99). DRP2 also plays an important function in maintaining interneuronal communication, neuronal repair, and in axonal outgrowth (79, 102). In addition, DRP2 interacts with collapsin and regulates dendritic length. Based on the functions of these proteins, it is evident that oxidation of these proteins could lead to loss of membrane integrity, activation of cellular events that may lead to apoptosis, loss of interneuronal connections, neuronal repair, and shortened dendritic lengths as observed in AD (49), eventually leading to memory impairment and synapse loss, clearly important for AD.

TAU HYPERPHOSPHORYLATION AND CELL CYCLE

One of the pathologic hallmarks of AD is the presence of intraneuronal tangles. The main protein component of neurofibrillary tangles (NFTs) is hyperphosphorylated tau (9, 24, 55, 67, 72, 74). The hyperphosphorylation of tau protein leads to impaired ability to stabilize microtubules, eventually leading to disruption of the axonal cytoskeleton. The phosphorylation–dephosphorylation of tau protein is regulated in part by peptidyl prolyl-*cis,trans*-isomerase (Pin). Pin1 is a chaperone enzyme that recognizes phosphorylated Ser-Pro and phosphorylated Thr-Pro motifs in proteins, and alters the conformation of proteins from cis to trans between a given amino acid and a proline (191). Pin1 is crucial for cell growth and is required for proper progression through the cell cycle in dividing cells (127). Pin1 has been shown to colocalize with phosphorylated tau and also shows an inverse relation to the expression of tau

in AD brains (89, 111, 176, 205, 206). Further, Pin1 is found to be oxidatively dysfunctional in AD brain (205, 206). The oxidative modification of Pin1 could lead to structural modifications and thereby affect the properties of its targeted proteins, such as tau. Pin1 is also involved in keeping neurons from entering the cell cycle. In AD, postmitotic neurons become trapped, resulting in apoptosis (199, 232). Oxidatively modified Pin1 conceivably could be related to the observation of elevated cell-cycle proteins in AD brain (157).

Consistent with this notion, a recent study showed that Pin1 could restore the function of tau protein in an AD model (121, 157), suggesting oxidative alteration of Pin1 could be one of the initial events that trigger tangle formation and oxidative damage in AD brains. Further studies are required to understand the role of Pin1 in the disease progression.

SYNAPTIC ABNORMALITIES AND LTP

Previous studies have shown that synaptic pathology is central to the pathogenesis of AD (186), and relations among synaptic alterations, amyloid deposits, cytoskeletal abnormalities, and cognitive deficits in individuals with AD reportedly exist (138). By using redox proteomics, we identified soluble *N*-ethylmaleimide–sensitive factor (NSF) attachment protein (γ-SNAP) as an oxidized protein in AD brain (205). γ-SNAP is a member of SNAPs that plays an important role in vesicular transport for neurotransmitter release, hormone secretion, and mitochondrial integrity. The function of SNAPs was reported to be altered in AD brain (16, 202); hence, oxidation may lead to an altered neurotransmission system and impaired learning and memory in AD (140, 186, 206).

pH MAINTENANCE

The activity of carbonic anhydrase 2 (CA2) is decreased in AD brain (144, 170, 206). CA2 regulates cellular pH, CO_2, and HCO_3^- transport, and maintains H_2O and electrolyte balance (196) by reversible hydration of CO_2 in normal cells. CA2 was identified as one of the oxidized protein that likely explains the diminished activity observed in AD brain (205), and the deficiency of CA2 activity might lead to loss of a major buffering system in brain and could also lead to cognitive defects varying from disabilities to severe mental retardation (196, 198). The change in buffering system in the brain could consequently lead to protein aggregation, which is more pronounced in AD brain, and, because the pH could be altered, to altered mitochondrial production of ATP.

MITOCHONDRIAL ABNORMALITIES

Many links have been found between mitochondrial abnormalities and AD over the years (10, 86, 130). Postmortem assessment of human brain homogenates has consistently demonstrated defects in mitochondrial enzyme activities, and several other studies indicate that Aβ decreases the activity of mitochondrial respiratory chain complexes (20, 71, 86, 126, 149, 210). A recent study from our laboratory identified the voltage-dependent anion channel (VDAC) as a nitrated protein in AD brain (209). VDAC is an outer-pore component of the mitochondrial permeability transition pore (MPTP) that plays an essential role in movement of metabolites like ATP in and out of mitochondria by passive diffusion, synaptic communication, and in the early stages of apoptosis. Identification of VDAC1 protein as a nitrated protein in AD suggests an alteration in the function of the MPTP, leading to mitochondrial depolarization and altered signal-transduction pathways, which could be crucial in synaptic transmission and plasticity. Moreover, alterations in the MPTP could lead to apoptotic processes. Further, VDAC1-deficient mice were reported to show deficits in learning behavior and synaptic plasticity (223). Moreover, dysfunction of mitochondria recently has been described to alter the APP metabolism, enhancing the intraneuronal accumulation of amyloid β-peptide and enhancing neuronal vulnerability (25).

LIPID PEROXIDATION IN AD

Lipid peroxidation

Accumulating evidence indicates that reactive oxygen species–mediated reactions, particularly of neuronal lipids, are extensive in AD brain areas directly involved in the disease processes (48). In recent years, numerous investigations have pointed to the functional importance of oxidative imbalance as a crucial event in mediating AD pathogenesis. The availability of specific and sensitive markers to monitor *in vivo* oxidative stress, in combination with studies performed in living patients with clinical diagnosis of AD, are helping to elucidate these issues (153).

Lipid peroxidation is one of the major sources of free radical–mediated injury that directly damages membranes and generates a number of secondary products. In particular, markers of lipid peroxidation have been found to be elevated in brain tissues and body fluids in several neurodegenerative diseases, and the role of lipid peroxidation has been extensively discussed in the context of the pathogenesis of AD, Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and prion disease (6, 12, 97, 107).

It has been widely demonstrated that a direct link exists between the etiologic disease-causing agent, amyloid β-peptide, and lipid peroxidation processes occurring in the brain and the cerebrospinal fluid, which might lead to a deeper understanding of Alzheimer's pathology (32, 33, 36, 174).

Brain is subject to lipid peroxidation because of its high oxygen utilization, low level of antioxidants, and high level of polyunsaturated fatty acids (PUFAs), the substrate for lipid peroxidation. This complex process of lipid peroxidation involves the interaction of oxygen-derived free radicals with polyunsaturated fatty acids and finally results in a variety of highly reactive electrophilic aldehydes that are capable of easily attaching covalently to proteins by forming adducts with cysteine, lysine, or histidine residues. Among the aldehydes formed, malondialdehyde (MDA), 4-hydroxynonenal (HNE), and acrolein represent the major products of lipid peroxidation (Fig. 2) (63, 123, 175). In addition, lipid hydroperoxyl radicals undergo endocyclization to produce fatty acids es-

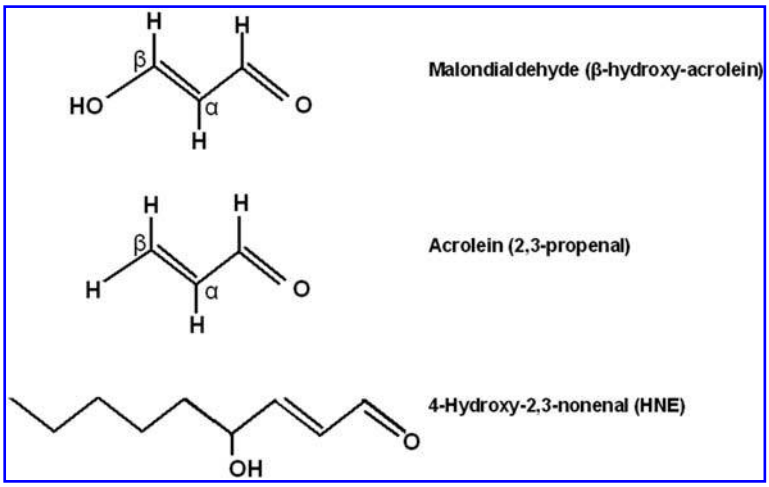


FIG. 2. Products of lipid peroxidation.

ters; two classes of these cyclized fatty acids are isoprostanes and neuroprostanes (Fig. 3) (154, 156). F_2-isoprostanes (F_2-IsoPs) are the stable products of free radical damage to arachidonic acid (AA), and 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 liberate free iso- and neuroprostanes that are detectable in body fluids (181).

Peroxidation of membrane lipids can have numerous effects, including increased membrane rigidity, decreased activity of membrane-bound enzymes (*e.g.*, sodium pumps), altered activity of membrane receptors, and altered permeability (8, 229). In addition to effects on phospholipids, radicals can also directly attack membrane proteins and induce lipid–lipid, lipid–protein, and protein–protein cross-linking, all of which obviously have effects on membrane function (65).

Biochemistry of lipid peroxidation

Lipid peroxidation refers to the oxidative degradation of lipids. It is the process whereby free radicals abstract an H atom from the lipids in cell membranes, resulting in cell damage. This process proceeds by a free radical chain-reaction mechanism consisting of five steps (scheme 1) (161):

Step 1: initiation, in which the free radical attacks a methylene group in the PUFAs, leading to a rearrangement of the double bonds to the conjugated diene form, and simultaneously producing a carbon-centered alkyl radical.

Step 2: the alkyl radical reacts with molecular oxygen to give rise to a peroxyl radical.

Step 3: propagation, in which the peroxyl radical, in its turn, starts a self-perpetuating chain reaction in which most of the membrane lipids are converted to a variety of hydroperoxides and cyclic peroxides. The hydroperoxides can be further degraded to hydrocarbons, alcohols, ether, epoxides, and aldehydes. Of these products, malondialdehyde and 4-hydroxynonenal have the additional ability to inactivate phospholipids, proteins, and DNA by bringing about binding to or cross-linking between these molecules (62).

Step 4: termination, in which the chain reaction is stopped by interactions between the radicals themselves, or step 5 between the radicals and antioxidants, giving rise to nonradical products or unreactive radicals.

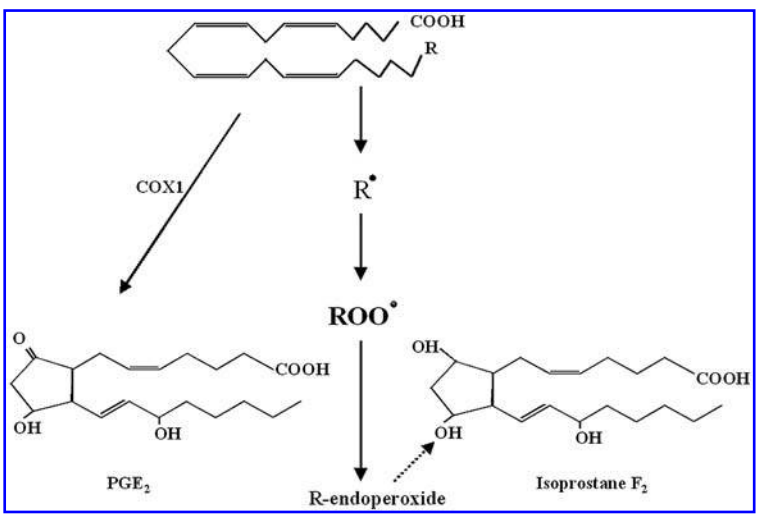
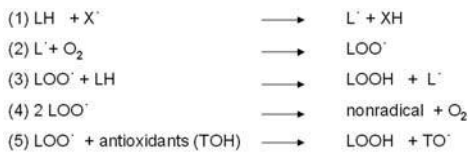


FIG. 3. Formation of F_2 isoprostanes.



Chain-breaking antioxidants such as vitamin E and vitamin C prevent the propagation of lipid peroxidation at the early stages of free radical attack (17, 59). For this reason, many experimental studies have been undertaken to test the possibility of a therapeutic use of free radical scavengers and antioxidants against free radical–mediated toxicity.

ROLE OF APOE

Apolipoprotein E (ApoE), a major lipoprotein in brain, is a lipid and cholesterol transport protein that is synthesized within the CNS (113). ApoE polymorphism is one of the major factors that influences progression and age at onset of AD. Of the three human ApoE isoforms (E2, E3, and E4), the dosage of ApoE4 increases the risk and reduces the age at onset for familial and sporadic AD (50).

ApoE is a 34-kDa very low-density lipoprotein that functions in the periphery as a mediator of lipoprotein metabolism and lipid clearance through binding of ApoE-containing lipoprotein particles to the low-density lipoprotein receptor–related protein (178, 224). In the CNS, ApoE is synthesized and secreted primarily by astrocytes and microglia, and its importance is underscored by the low abundance of other apolipoproteins (160). Additionally, it has been shown to play a pivotal role in the redistribution of lipid and cholesterol during membrane repair and in maintaining synaptic plasticity, especially after neuronal injury (77).

How do the three ApoE (E2, E3, and E4) alleles and their encoded protein isoforms alter the risk of developing AD? A number of hypotheses have been proposed to explain the isoform-specific association of ApoE and AD (115), including differential isoform-specific neurotrophic (88) and neurotoxic properties (214), antioxidative activity (146), and amyloidogenic effects (129). The latter hypothesis is supported by postmortem neuropathologic findings from several laboratories, which have consistently demonstrated increased amyloid burden in ApoE4 carriers (179). A dominant hypothesis is that ApoE binds to amyloid-β, the major component of the senile plaques, and thereby acts as a "pathologic chaperone" to reduce the solubility and stabilize the β-pleated structure of amyloid fibrils (226).

Another hypothesis, based on the isoform-specific differences in the binding of ApoE to the microtubule-associated protein tau, proposes a differential ApoE isoform contribution to AD cytoskeletal pathology by affecting phosphorylation of this protein and thereby NFT formation and microtubule stabilization (203).

The immunohistochemical localization of ApoE to senile plaques and tangles (158) in the AD brain provided one of the first clues that ApoE may be involved. This association has now been replicated in numerous subsequent studies, leading to the general hypothesis that ApoE plays a significant role in the disease (42, 80, 179, 187, 203). Consistent with the concept that in the absence of ApoE, Aβ would accumulate in the brain (182), results from our laboratory and others have shown that increased markers of protein and lipid peroxidation correlate with ApoE allele-specific interaction with Aβ (48, 117, 142, 188). These findings are particularly relevant to Alzheimer's pathology where Aβ is overproduced, oxidative damage is evident and for which ApoE is a risk factor.

Lipid peroxidation in AD brain

Numerous studies have demonstrated increased lipid peroxidation in the brain of patients with AD compared with age-matched controls (14, 32, 33, 36, 125, 136, 151, 152). These data include quantification of fission and endocyclized products such as HNE, acrolein, MDA, isoprostanes, and neuroprostanes. Immunohistochemical and biochemical studies have localized the majority of lipid peroxidation products to neurons. As lipid peroxidation can be detected not only in brain tissue but also in body fluids, it might serve as a useful marker of disease progression and as a monitor of therapeutic efficacy.

TBARS

Thiobarbituric acid-reactive substances (TBARS) measure the concentration of malondialdehyde (MDA), an end product of the oxidation and decomposition of polyunsaturated fatty acids containing three or more double bonds. This method has been criticized for its lack of specificity, sensitivity, and reproducibility, but it is one of the easiest and most frequently used methods.

MDA reacts with TBA to form the MDA–TBA adduct. This adduct is most commonly quantified by using a spectrophotometric assay (166). The reasons for concern include possible interferences present in biologic samples (carbohydrates, pyrimidines, and hemoglobin), the heating condition during the assay, the presence of iron in the reagents used for analysis, rapid metabolism of MDA, and the fact that MDA represents <1% of lipid peroxides (166). Thus, it is not recommended to be used as a sole index of lipid peroxidation (23). Some investigators are now measuring MDA directly, by using high-performance liquid chromatography (HPLC) to separate MDA from other interfering chromogens, thus improving specificity (78). However, this approach does not overcome all the limitations of the MDA and may explain the diversity in TBARS levels in different brain regions in AD.

HNE

Lipid peroxidation causes structural membrane damage and produces diffusible secondary bioactive aldehydes, including HNE, MDA and acrolein, all of which are increased in several brain regions of late-stage AD patients (116, 125, 136). Numerous findings support an important role of HNE in development of AD. Thus, a significant increase of free HNE in CSF, amygdala, hippocampus, and parahippocampal gyrus was detected in brain of AD patients when compared with control subjects (136). Moreover, an elevated level of protein-bound HNE in brain from subjects with mild cognitive impairment (MCI) was observed (38). Arguably, MCI is

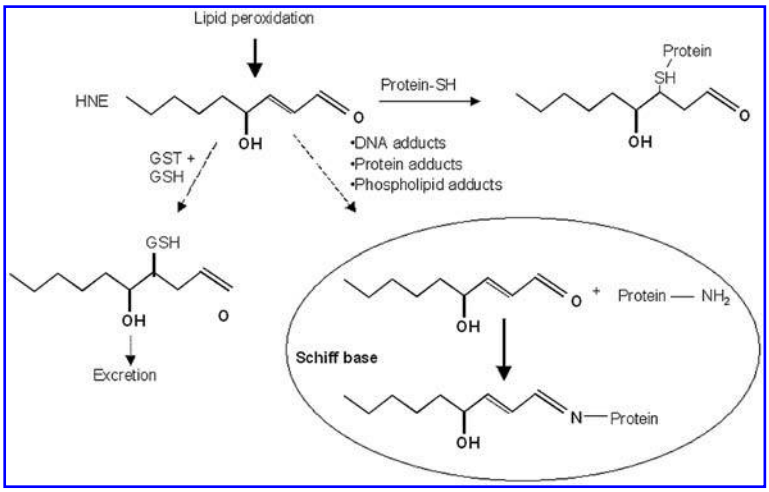


FIG. 4. Toxicity and metabolism of 4-hydroxynonenal (HNE).

the earliest form of AD (38), so lipid peroxidation likely is an early event in AD progression.

Immunohistochemical studies have demonstrated the presence of HNE in amyloid deposits (185), in NFT, and non–NFT-containing neurons in the hippocampus and in the hippocampus and temporal cortex in association with the APOE4 allele of apolipoprotein E in AD (7). HNE reacts with proteins, forming stable covalent adducts to histidine, lysine, and cysteine residues through Michael addition (38). HNE can inhibit synthesis of DNA, RNA, and proteins and alter the activity of glycolytic, degradative, and transport proteins (Fig. 4) (38,62). HNE mediates amyloid β-peptide–induced oxidative damage in cultured hippocampal neurons by impairing ion-motive ATPase activity, causing an increase in intracellular calcium and neuronal death (132). HNE impairs glucose and glutamate transport in rat neocortical synaptosomes (105), inhibits glucose transport in cultured hippocampal neurons, and impairs glutamate transport in cortical astrocytes (116). HNE disrupts coupling of muscarinic cholinergic receptors and metabotropic glutamate receptors to phospholipase C–linked GTP-binding proteins in cultured rat cerebrocortical neurons (19). The administration of HNE into the basal forebrain of rats damaged cholinergic neurons, decreased choline acetyltransferase activity, and impaired visuospatial memory (165). This suggests that HNE may play a role in the dysfunction and degeneration of cholinergic neuronal circuits in AD (211).

As noted earlier, increasing evidence links mitochondrial dysfunction to the pathology of AD (141). HNE induces apoptosis in cultured PC12 cells and primary rat hippocampal neurons (200). HNE increases neuronal death and exacerbates mitochondrial oxygen free radical formation induced by Aβ or glutamate (133). HNE causes the microtubule-associated protein tau to become resistant to dephosphorylation, which may contribute to neurofibrillary degeneration in AD. HNE also inhibits neurite outgrowth, disrupts neuronal microtubules, and modifies cellular tubulin, which may contribute to the cytoskeletal alterations that occur in AD (159).

Glutathione transferases are enzymes that inactivate the toxic products of oxygen metabolism, including HNE (131). A significant decrease of glutathione transferase activity and of other antioxidative enzymes was described in amygdala, hippocampus, and inferior parietal lobule in patients with AD (125). This could lead to more pronounced effects of HNE in these brain regions. Moreover, GST and the multidrug-resistant protein 1 (MRP-1), which effluxes the GSH-HNE conjugate from cells, were both highly modified by HNE in AD brain compared with controls (207). This oxidative modification may be related to the decreased activity of GST and may account for the elevated levels of HNE in AD.

Acrolein, the most reactive α,β-unsaturated aldehyde product of lipid peroxidation, could be rapidly incorporated into proteins, generating a carbonyls or modifying DNA basis with the formation of exocyclic adducts (137). Acrolein is neurotoxic in a time- and concentration-dependent manner and more toxic than HNE at 5 μ*M* concentration for hippocampal tissue cultures (125). Acrolein may inactivate the reductase responsible for reducing vitamin E radicals, and together with depletion of glutathione, this could lead to further lipid peroxidation. Acrolein preferentially reacts with lysine residues that are prominent components of tau (73) and are present in NFTs and dystrophic neurites surrounding SP (senile plaque) in AD (40). Studies from our laboratory showed that acrolein inhibits NADH-linked mitochondrial enzyme activity (168). We have also reported that at very low concentration, acrolein can structurally change transmembrane and cytoskeletal proteins (169). Thus, not only HNE but also acrolein is likely to be a factor in AD pathogenesis.

BRAIN PHOSPHOLIPIDS

Unlike other body membranes, neuronal membranes contain a very high percentage of long-chain polyunsaturated fatty acids because they are used to construct complex structures needed for high rates of signal transfer and data processing.

Polyunsaturated fatty acids are sometimes called essential fatty acids because they cannot be synthesized by the body and therefore must be provided by the diet. Only two precursors exist for dietary essential PUFAs: α-linolenic acid and linoleic acid. In theory, these 18-carbon PUFAs can be con-

verted to form predominantly 20- and 22-carbon long-chain PUFAs with four or more double bonds.

However, the CNS is unique compared with other tissues because it cannot directly use α-linolenic or linoleic acids, only their long-chain PUFA derivatives, which are mainly docosahexaenoic acid (DHA) and arachidonic acid (AA). Long-chain PUFAs are the building material of the CNS and also are required for the normal behavior of cell-signaling systems, which determine how neurons function.

Phospholipid metabolism has been shown to be abnormal in AD brain cortex, as indicated by a depletion of phospholipids in AD brain: tissue levels of the two major phospholipid classes, phosphatidylcholine and phosphatydilethanolamine, were 10–12% lower in parietal and frontal cortex of AD patients than in brains of control subjects (162, 171).

One consequence of abnormal phospholipid metabolism could be enhanced amyloid deposition. Amyloid deposition in AD brains requires abnormal processing of APP. Defective membrane metabolism could expose the APP transmembrane domain to proteolytic cleavage, thus leading to increased amyloid β-peptide release.

ISOPROSTANES

As noted earlier, isoprostanes are prostaglandin-like compounds formed *in vivo* from the free-radical–catalyzed peroxidation of arachidonic acid, independent of the cyclooxygenase enzyme. F_2-Isoprostanes (F_2-IsoPs), one group of nonenzymatic lipid peroxidation products derived from arachidonic acid, are especially useful as *in vivo* biomarkers of lipid peroxidation. F_2-IsoP concentration is selectively increased in diseased regions of brain from patients who died of advanced AD, in which pathologic changes include amyloid β-peptide deposition, NFT formation, and extensive neuron death (152). Broad agreement exists that increased CSF levels of F_2-IsoPs also are present in patients with early AD. It has been recently shown that subjects with MCI (mild cognitive impairment) have plasma, urine, and CSF levels of F_2-IsoPs higher than those of healthy subjects (172). This evidence clearly indicates that oxidative imbalance and subsequent oxidative stress are early events in AD evolution (37, 38, 106) and are probably secondary to other mechanisms specific to AD, but not present in other neurodegenerative diseases (135, 173). It has been suggested that measurement of isoprostanes may identify a subgroup of patients with MCI with increased lipid peroxidation who are at increased risk to progress to symptomatic AD (135).

F_2-isoPs are also of interest as they have been directly demonstrated to accelerate Aβ generation and aggregation (21), so these moieties could plausibly lie upstream of amyloidogenesis. Studies of Tg2576 plaque-forming transgenic mice showed that brain, plasma, and urine levels of the isoprostane, 8,12-iso-iP $F_2\alpha$, increase during aging, beginning at a point when cerebral amyloidosis of transgenic human Aβ is incipient (174). The attraction of urinary isoPs is that they might serve as noninvasively acquired biomarkers, which could guide the selection of patients and dosing for trials of antioxidants as well as the timing of dosing. This may prove particularly useful in a disease, such as AD, in which the rate of progression varies markedly between individuals.

Increased levels of TBARS and MDA in the brains of persons with MCI were reported (106). In addition, data from our laboratory have shown in brain obtained at short postmortem intervals that the levels of HNE are elevated in amnestic MCI hippocampus and inferior parietal lobules compared with those of control brain (38). Thus, increased levels of HNE in MCI brain implicate lipid peroxidation as an early event in AD pathophysiology and also suggest that the pharmacologic intervention to prevent lipid peroxidation at the MCI stage or earlier may be a promising therapeutic strategy to delay or prevent progression to AD.

CONCLUSIONS

This review has summarized many of the studies of protein oxidation and lipid peroxidation in AD brain. Protein oxidation and lipid peroxidation have several important downstream consequences that are detrimental to neurons and clearly are important in AD. Moreover, given the findings that protein (37) and lipid (38, 106, 135) oxidative damage occur in brain of subjects with amnestic MCI, we suggest that oxidative damage is an early event in the progression of AD and not simply a consequence of this dementing disorder. Accordingly, therapeutic strategies designed to modulate the protein oxidation and lipid peroxidation early in the course of the disease, if not before the onset of MCI, may be promising to slow or possibly prevent AD.

ACKNOWLEDGMENTS

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ABBREVIATIONS

2D-PAGE, two-dimensional polyacrylamide gel electrophoresis; 3-NT, 3-nitrotyrosine; Aβ(1–42), amyloid beta-peptide (1–42); AA, arachidonic acid; AD, Alzheimer's disease; ADDLs, amyloid-derived diffusible ligands; AGEs, advance glycation end products; ALS, amyotrophic lateral sclerosis; APOE, apolipoprotein E; APP, amyloid precursor protein; ChAT, choline acetyl transferase; CK, creatine kinase BB; CSF, cerebrospinal fluid; DHA, docosahexanoic acid; DNPH, dinitrophenyl hydrazine; DRP2, dihydropyrimidinase-related protein 2; F_2 IsoP, F_2 isoprostanes; F_4-NP, F_4-neuroprostanes; γ-SNAP, gamma-soluble NSF-attachment proteins; GS, glutamine synthase; GST, glutathione S-transferase; HNE, 4-hydroxynonenal; HPLC, high-performance liquid chromatography; HSC 71, heat-shock cognate 71; IEF, isoelectric point; iNOS, inducible nitric oxide synthase; IPL, inferior parietal lobule; LDH, lactate dehydrogenase; LTP, long-term potentiation; MCI, mild cognitive impairment; MDA, malondialdehyde; MPTP, mitochondrial permeability transition pore; Mr, molecular migration; MRP-1, multidrug-resistance protein-1; NFT,

neurofibrillary tangle; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; $O_2^{-\bullet}$, superoxide; $ONOO^-$, peroxynitrite; PD, Parkinson disease; PEBP, phosphatidylethanolamine binding protein; PET, positron emission tomography; PF, protofibrils; PGM1, phosphoglycerate mutase 1; Pin1, peptidyl-prolyl-*cis,trans*-isomerase; PUFA, polyunsaturated fatty acids; RAGE, receptor for advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; SP, senile plaque; TBARs, thiobarbituric acid–reactive substances; TPI, triose phosphate isomerase; UCHL-1, ubiquitin carboxy-terminal hydrolase L-1; VDAC, voltage-dependent anion channel protein; VF, ventricular cerebrospinal fluid.

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