Oxidatively modified, mitochondria-relevant brain proteins in subjects with Alzheimer disease and mild cognitive impairment

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Abstract Alzheimer disease (AD) is an age-related neurodegenerative disorder, characterized histopathologically by the presence of senile plaques (SP), neurofibrillary tangles and synapse loss in selected brain regions. Positron emission tomography (PET) studies of glucose metabolism revealed decreased energetics in brain of subjects with AD and arguably its earliest form, mild cognitive impairment (MCI), and this decrease correlated with brain structural studies using MRI. The main component of senile plaques is amyloid beta-peptide (Aβ), a 40–42 amino acid peptide that as oligomers is capable of inducing oxidative stress under both in vitro and in vivo conditions and is neurotoxic. In the mitochondria isolated from AD brain, Aβ oligomers that correlated with the reported increased oxidative stress markers in AD have been reported. The markers of oxidative stress have been localized in the brain regions of AD and MCI that show pathological hallmarks of this disease, suggesting the possible role of Aβ in the initiation of the free-radical mediated process and consequently to the build up oxidative stress and AD pathogenesis. Using redox proteomics our laboratory found a number of oxidatively modified brain proteins that are directly in or are associated with the mitochondrial proteome, consistent with a possible involvement of the mitochondrial targeted oxidatively modified proteins in AD progression or pathogenesis. The precise mechanistic link between mitochondrial oxidative damage and role of oligomeric Aβ has not been explicated. In this review, we discuss the role of the oxidation of mitochondria-relevant brain proteins to the pathogenesis and progression of AD.

Keywords Oxidative stress · Alzheimer’s disease · Mitochondria · MCI

Introduction

Alzheimer’s disease (AD) is an age-related neurodegenerative disorder, characterized clinically by the impairment of cognitive functions and behavioral alterations (Katzman and Saitoh 1991; Salmon et al. 2002). AD is histopathologically characterized by the presence of senile plaques (SP), neurofibrillary tangles and synapse loss in selected brain regions that are responsible for learning, memory processing, and executive functioning. The main component of senile plaques is amyloid beta-peptide (Aβ), a 40–42 amino acid peptide that is derived by proteolytic cleavage of amyloid precursor protein (APP) by the action of beta- and gamma-secretases, and SP are extra cellular in localization (Zhang and Xu 2007).

Role of Aβ(1-42) in oxidative stress in brain of subject with AD and MCI

A number of in vitro and in vivo studies showed that Aβ(1-42) is a neurotoxic peptide that exists in various forms, e.g., soluble (monomers, oligomers, and protofibrils) and insoluble (fibrils) forms. Recent studies suggest that the small
oligomers of Aβ are the actual toxic species of this peptide rather than Aβ fibrils (Drake et al. 2003; Lambert et al. 2001; Oda et al. 1995; Walsh et al. 1999). The most concrete evidence suggesting the role of Aβ in AD pathogenesis comes from the genetic observations from familial Alzheimer disease [FAD] (Hardy and Selkoe 2002) that showed that mutations of the genes of amyloid precursor protein (Goate et al. 1991), presenilin-1 and presenilin-2 (Cruts et al. 1998) leads to increased accumulation of fibrillar Aβ in the brain (Hardy and Selkoe 2002; Saida 2003) of FAD subjects.

Oxidative stress in AD brain is manifested by elevated lipid peroxidation (Buttfield et al. 2001; Butterfield and Lauderback 2002; Montine et al. 2002; Sayre et al. 1997), protein oxidation (Butterfield and Stadtman 1997; Good et al. 1996; Hensley et al. 1995; Smith et al. 1997), advanced glycation end products (Vitek et al. 1994), and oxidation of nucleic acids (Gabbita et al. 1998; Lovell and Markesbery 2001; Mecocci et al. 1994; Nunomura et al. 1999, 2001). Further, the markers of oxidative stress have been localized to the regions of the AD brain that have pathological hallmarks of this dementing disorder (Hensley et al. 1995), consistent with a role of Aβ in the initiation of the free radical mediated process and consequently to the build up oxidative stress and AD pathogenesis.

In addition to the observation of increased levels of oxidative stress in AD brain, studies from our laboratory and other have shown increase levels of oxidative stress in brain of subjects with mild cognitive impairment brain (MCI), a transition stage between AD and normal aging, that shows neuropsychological hallmarks similar to AD such as temporal lobe atrophy, low CSF Aβ levels (Chertkow et al. 2001), but different cognitive effects, e.g., mild current memory loss without dementia or significant impairment of other cognitive functions (Morris and Cummings 2005; Petersen et al. 1999). Like AD, brain from MCI subjects also showed increased levels of oxidative stress markers for protein oxidation [indexed by protein carbonyls and 3-nitrotyrosine (3-NT)], lipid peroxidation [indexed by protein bound-4-hydroxy-2-nonenal (HNE), isoprostanes, and neuroprostanates], and nucleic acid oxidation [indexed by 2,6-diamino-4-hydroxy-5-formamidopyrimidine (fapy-guanine), 8-hydroxyadenine, 4,6-diamino-5-formamidopyrimidine (fapyadenine) and 5-hydroxycytosine] (Bader Lange et al. 2008; Butterfield et al. 2006a, b; Keller et al. 2005; Markesbery et al. 2005; Migliore et al. 2005; Wang et al. 2006; Williams et al. 2006). Our laboratory is the first to show that protein-bound HNE levels, and 3-NT are elevated in the MCI brain compared to control IPL and hippocampus (Butterfield et al. 2006a, 2007a; Keller et al. 2005). These results suggest the accumulation of oxidative stress markers (Butterfield et al. 2006b; Ding et al. 2006; Keller et al. 2005) in MCI brain, and are consistent with the notion that oxidative stress could be an early event in the progression of MCI to AD.

A number of studies provided evidence of increased oxidative stress in AD pathogenesis, which could initiate from mitochondria, cytoplasm, and also outside the cells (Butterfield and Lauderback 2002; Cross et al. 1987; Markesbery 1997; Smith et al. 1995). Mitochondria use a major part of oxygen in the electron transport system, during which superoxide radicals are produced, one-five percent of which leak out from mitochondria. Superoxide radicals, in turn, can lead to increased production of highly reactive hydroxyl radicals, peroxynitrite, etc., that can contribute to oxidation of proteins, lipids, carbohydrates and nucleic acids (Butterfield and Stadtman 1997).

Recent studies showed the presence of Aβ(1-42) monomers and oligomers in the mitochondrial membranes isolated from the AD brain and brain of animal models of AD (Caspersen et al. 2005; Crouch et al. 2007; Manczak et al. 2006), which suggest possible alterations in mitochondrial structure and function as one of the mechanism(s) of AD pathogenesis.

Previous studies from our laboratory and others have shown that Aβ has a critical methionine residue at position 35, which is believed to be associated with the toxicity of Aβ peptide (Boyd-Kimball et al. 2004, 2005; Butterfield and Boyd-Kimball 2005; Clementi et al. 2006; Crouch et al. 2006; Kanski et al. 2002; Murray et al. 2005). The substitution of Met by norleucine diminishes the toxic effect of the Aβ that clearly documented the importance of Aβ peptide in AD pathogenesis (Butterfield and Kanski 2002; Kanski et al. 2002).

Identification of oxidatively modified brain proteins in subjects with AD and MCI

Our laboratory is the first to use redox proteomics approaches to identify oxidatively modified proteins in brain of subjects with AD and MCI. Employing redox proteomics we identified a large number of oxidatively modified proteins in AD and MCI brain that play key roles in various cellular functions. Many of the proteomics-identified brain proteins belong to energy metabolism pathways. Oxidative modification of the proteins alters conformation and function of proteins (Lauderback et al. 2001a; Subramaniam et al. 1997). Previous studies in AD brain showed that HNE modification of the glutamate transporter (Glt-1 or EAAT), glutathione-S-transferase (GST), and multi-drug resistant protein (MRP-1) (Lauderback et al. 2001a; Sultana and Butterfield 2004) leads to decrease function of these proteins and consequently lead to excitotoxic cell death owing to the decrease clearance of glutamate or increased...