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Oxidative stress in blood in Alzheimer's disease and mild cognitive impairment: A meta-analysis

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ABSTRACT

Abnormal oxidative stress is an established feature of Alzheimer's disease, but clinical trials aiming to reduce oxidative stress have not yet proven an effective therapy for dementia patients. The purpose of this review is to systematically analyze available data describing markers of oxidative stress and antioxidants in blood from subjects with Alzheimer's disease or those with mild cognitive impairment to highlight potential interactions between peripheral redox changes and central nervous system pathology and contribute to the design of future clinical study. PubMed, SCOPUS and Web of Science were systematically queried to collect studies which have evaluated markers of oxidative stress, levels of antioxidants, copper, transferrin and ceruloplasmin levels in blood from subjects with Alzheimer's disease and matched controls. After application of quality measures, results were aggregated in a random effects analysis. We found that markers of lipid peroxidation are elevated in blood in Alzheimer's disease and in mild cognitive impairment, copper metabolism is dysregulated and total antioxidant capacity is decreased. While surprisingly none of the major antioxidative enzymes are significantly decreased, non-enzymatic antioxidants in blood (particularly uric acid, vitamins A, E and C, α- and β-carotene) are significantly decreased. There is significant oxidative damage in peripheral blood early in the process of neurodegeneration. We propose that clinical studies assessing cognitive outcomes after antioxidant therapy tailor interventions to individual patients' deficiencies and confirm an improvement in an appropriate serological marker of oxidative stress. This strategy may be most effectively applied in a clinical trial of primary prevention.

Introduction

Cellular oxidative processes are critical to life, but unconstrained, generation of oxidative species is toxic and is thought to contribute to many diseases and is central to our understanding of the process of aging. Every cell has elaborate mechanisms to control reactive oxidative species and to cope with stress produced from these toxins. Abnormal levels of oxidative stress have been reported in Alzheimer's disease in both the brain and the blood stream. The changes in Alzheimer's disease which produce a pro-oxidative imbalance have been attributed to decreased antioxidant defenses, toxicity related to amyloid-β and/or altered metal metabolism (both in the brain and in blood). The purpose of this review is to highlight the evidence of aberrant redox balance in blood in subjects with Alzheimer's disease and those who will subsequently develop Alzheimer's disease and discuss strategies for future therapeutic study. Fig. 1 serves as a brief review of the basic biochemical pathways which will be discussed in the course of this article.

Methods

Data search was completed on 1 August 2012. Studies were identified from systematic searching of PubMed, ISI Web of Science, and Scopus databases, supplemented by searches of Google Scholar and the reference lists from all included studies and major relevant review papers. Databases were queried with a molecule name keyword (such as "superoxide dismutase"), one or more tissue keywords (such as "serum" or "plasma") and "Alzheimer's disease". Case–control studies with human subjects were considered for inclusion. Data

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Table 1
Circulating oxidative changes in Alzheimer's disease and mild cognitive impairment.

Oxidative markers	Subject group	% Change (vs age-matched controls)	Effect size Hedge's g (95% confidence interval)	Total N (AD/control) (MCI/control)	Number of studies included/number excluded
Malondialdehyde/TBARS	AD	24% ↑**	0.79 (0.41–1.16)	1165/1152	27 studies/1 excluded
(in plasma/serum)	MCI	29% ↑	0.46 (0.10–0.82)	77/54	2 studies
Protein carbonylation	AD	N.S., 4.3% ↑	0.22 (−0.13 to 0.58)	334/329	9 studies/4 excluded
(in plasma/serum)	MCI	36% ↑	1.11 (0.57–1.65)	34/28	1 study
Oxidized LDL	AD	55% ↑**	1.47 (0.15–2.78)	122/80	5 studies
(in plasma/serum)	MCI	No data			
Uric acid	AD	↓ 25%	−0.59 (−1.26 to −0.09)	453/447	10 studies/4 excluded
(in plasma/serum)	MCI	Inconsistent	−0.73 (−2.70 to 1.24)	49/80	2 studies
Vitamin E (α-tocopherol)	AD	↓ 20%**	−0.80 (−1.11 to −0.49)	703/691	20 studies
(in plasma/serum)	MCI	N.S., ↓7.4%	−0.45 (−1.00 to 0.10)	142/117	3 studies
Vitamin C (ascorbic acid)	AD	↓ 40%**	−1.05 (−1.53 to −0.58)	460/471	11 studies
(in plasma/serum)	MCI	↓ 52%	−1.97 (−2.53 to −1.40)	25/56	1 study
Vitamin A (retinol)	AD	↓ 22%**	−0.77 (−1.09 to −0.45)	388/334	9 studies
(in plasma/serum)	MCI	↓ 12%	−1.09 (−1.59 to −0.58)	25/56	1 study
α-Carotene	AD	↓ 46%**	−0.63 (−1.03 to −0.22)	284/249	6 studies
(in plasma/serum)	MCI	↓ 52%	−0.62 (−1.10 to 0.14)	25/56	1 study
β-Carotene	AD	↓ 25%	−0.41 (−0.78 to −0.05)	423/477	9 studies
(in plasma/serum)	MCI	No change	−0.03 (−0.50 to 0.44)	25/56	1 study
Total antioxidant capacity	AD	↓ 16%**	−0.85 (−1.29 to −0.41)	1088/1067	22 studies/2 excluded
(in plasma/serum)	MCI	N.S., ↓ 2.7%	−0.15 (−0.41 to 0.12)	204/181	2 studies
Superoxide dismutase	AD	No change	0.03 (−0.75 to 0.81)	383/339	11 studies
(in plasma/serum)	MCI	50% ↓**	−1.43 (−1.87 to −0.99)	40/71	2 studies
Glutathione peroxidase	AD	N.S., ↓ 15%	−0.40 (−0.1.18 to 0.37)	282/258	9 studies
(in plasma/serum)	MCI	Inconsistent	−0.86 (−1.28 to −0.45)	40/71	2 studies
Copper	AD	5.8% ↑	0.30 (0.09–0.51)	1167/1397	24 studies/8 excluded
(in plasma/serum)	MCI	6.0% ↑	0.35 (0.07–0.63)	90/119	2 studies
Ceruloplasmin (Cp)	AD	N.S., 2% ↑	0.08 (−0.26 to 0.41)	647/942	15 studies/1 excluded
(in plasma/serum)	MCI	No change	0.17 (−0.12 to 0.47)	100/116	2 studies
Cp oxidase activity	AD	↓ 13%	−0.49 (−0.98 to 0.00)	163/154	4 studies/1 excluded
(in plasma/serum)	MCI	No data			
Transferrin	AD	N.S., ↓ 4%	−0.14 (−0.36 to 0.09)	479/780	12 studies/2 excluded
(in plasma/serum)	MCI	No change	−0.14 (−2.72 to 0.15)	83/100	1 study
Malondialdehyde/TBARS	AD	Inconsistent	1.58 (0.31–2.84)	288/290	8 studies
(in erythrocytes)	MCI	47% ↑	2.57 (1.91–3.06)	15/15	1 study
Superoxide dismutase	AD	Inconsistent	0.24 (−0.36 to 0.85)	639/590	19 studies
(in erythrocytes)	MCI	33% ↓*	−2.14 (−2.72 to −1.56)	25/56	1 study
Glutathione peroxidase	AD	No change	−0.01 (−0.30 to 0.32)	570/520	13 studies
(in erythrocytes)	MCI	No change	0.06 (−0.18 to 0.29)	186/119	4 studies
Glutathione reductase	AD	No change	−0.15 (−1.12 to 0.82)	241/247	6 studies
(in erythrocytes)	MCI	No change	−0.20 (−0.86 to 0.47)	152/91	3 studies
Catalase	AD	No change	0.02 (−0.78 to 0.82)	238/271	7 studies
(in erythrocytes)	MCI	No change	0.18 (−0.33 to 0.70)	33/26	1 study
8-hydroxyguanosine	AD	58% ↑*	1.25 (0.59–1.91)	196/200	6 studies
(in lymphocytes)	MCI	>100% ↑	1.50 (0.68–2.33)	15/15	1 study

AD = Alzheimer's disease, MCI = mild cognitive impairment, LDL = low density lipoprotein. N.S. = not significant.
* $p < 0.01$.
** $p < 0.0001$.

was extracted and compiled as summary statistics (N, mean and SD); for studies reporting non-parametric summary data, mean and standard deviation were estimated by established methods (see supplement). Several studies reported on multiple groups of Alzheimer's disease patients at varying stages of the disease — in these cases only the group with the earliest stage of Alzheimer's disease was included in meta-analysis. Basic quality measures were applied; all included studies were approximately age and sex matched (discussed in supplement 1). Effect size was determined by Hedge's G (an effect size of 1 is equal to an increase equivalent to 1 standard deviation) and studies were merged using a random-effects analysis. Results were interpreted as significant when alpha <0.05. Publication bias was assessed by funnel plot and when present was corrected by trim and fill analysis. Heterogeneity was assessed by the Q test and I^2 tests and datasets were considered heterogeneous when both tests reached significance. Figures were generated using MIX 1.7. Detailed listing of excluded citations, rationale for exclusion criteria, reporting of heterogeneity, and corrections applied for biases are included in the supplemental sections.

Evidence of oxidative damage in blood in Alzheimer's disease

Damage to circulating lipids, proteins and nucleic acids

Twenty-seven studies reporting malondialdehyde levels were included in this meta-analysis including 1098 subjects with Alzheimer's disease and 1094 controls; malondialdehyde levels were significantly elevated in Alzheimer's disease plasma/serum, effect size 0.79 (95% CI 0.45–1.14, $p < 0.0001$) (Table 1) — approximately a 25% increase (Ahlskog et al., 1995; Aybeck et al., 2007; Bourdel-Marchasson et al., 2001; Casado et al., 2008; Ceballos-Picot et al., 1996; Cito et al., in press; Cristalli et al., 2012; Dixit et al., 2011; Fernandes et al., 1999; Galbusera et al., 2004; Haines et al., 1991; Helmer et al., 2003; Jeandel et al., 1989; Kalman et al., 1994, 1999; Martin-Aragon et al., 2009; McGrath et al., 1998; Ozcankaya and Delibas, 2002; Polidori et al., 2004; Polidori and Mecocci, 2002; Puertas et al., 2012; Sekler et al., 2008; Serra et al., 2001, 2009; Sinem et al., 2010; Torres et al., 2011; Zafrilla et al., 2006) Only two studies evaluated malondialdehyde levels in subjects with mild cognitive impairment (MCI), both showed a