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Nutritional approaches to combat oxidative stress in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) brains are characterized by extensive oxidative stress. Additionally, large depositions of amyloid β-peptide (Aβ) are observed, and many researchers opine that Aβ is central to the pathogenesis of AD. Our laboratory combined these two observations in a comprehensive model for neurodegeneration in AD brains centered around Aβ-induced oxidative stress. Given the oxidative stress in AD and its potentially important role in neurodegeneration, considerable research has been conducted on the use of antioxidants to slow or reverse the pathology and course of AD. One source of antioxidants is the diet. This review examines the literature of the effects of endogenous and exogenous, nutritionally-derived antioxidants in relation to AD. In particular, studies of glutathione and other SH-containing antioxidants, vitamins, and polyphenolic compounds and their use in AD and modulation of Aβ-induced oxidative stress and neurotoxicity are reviewed.

Keywords: Alzheimer's disease; Antioxidants; Glutathione; Polyphenols; Vitamins; Oxidative stress; Amyloid beta-peptide; Cellular response genes

1. Introduction

Alzheimer's disease (AD), the major dementing disorder of the elderly, has millions of victims worldwide. Amyloid β-peptide (Aβ), a 40–42 amino acid peptide, accumulates in the AD brain, and many researchers now believe that this peptide is central to the pathogenesis of this disorder [1]. In addition, the AD brain is under intense oxidative stress that is manifested by lipid peroxidation, free radical formation, protein oxidation, nitrotyrosine, advanced glycation end-products, and DNA/RNA oxidation [2–5]. Our laboratory has united these two observations into the Aβ-associated free radical oxidative stress model for neurodegeneration in AD brain [3,6,7]. Aβ in mechanisms that likely involve the single methionine at residue 35 [7–11], causes protein oxidation, lipid peroxidation, free radical formation, DNA oxidation, and neuronal cell death, in ways that are inhibited by free radical antioxidants [3–5,12–15]. In particular, the antioxidants vitamin E, melatonin, epigallocatechin gallate, N-acetylcysteine, α-lipoic acid, various flavones, estrogen and phytoestrogen, and polyphenols, such as curcumin, Ginkgo baloba extract, etc., among others, are protective against amyloid β-peptide-induced oxidative stress and neurotoxicity or oxidative modification produced by lipid peroxidation products caused by Aβ [12,13,17–28]. Aβ-induced oxidative stress and neurotoxicity has recently been reviewed [3–5].

The brain is particularly vulnerable to oxidative damage due to the high utilization of inspired oxygen, the large amount of easily oxidizable polyunsaturated fatty acids, the abundance of redox-active transition metal ions, and the relative dearth of antioxidant defense systems. Free radicals are produced from a number of sources, among which are enzymatic, mitochondrial, and redox metal ion-derived sources [29]. Aging, the major risk factor for AD [30], leads to loss of free radical scavenging ability by endogenous mechanisms [29]. Hence, the normal balance between free

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radical generation and free radical scavenging is disrupted with aging and other oxidative stress conditions [31].

Since oxidative stress may underlie some, if not all, aspects of AD neurodegeneration, and since Aβ appears central to the disease [3], considerable research has been aimed at reducing the effects of oxidative stress by use of free radical scavengers. Among the latter are those derived

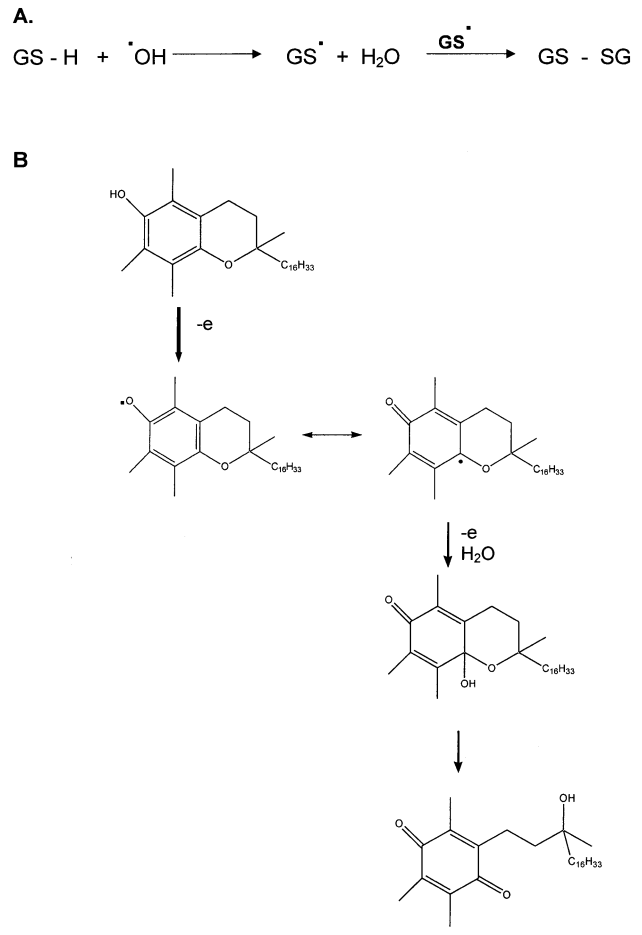

Fig. 1. (A). Scavenging of free radicals by glutathione to form oxidized glutathione. (B). Trapping of free radicals by vitamin E.

Table 2
Relative vitamin levels in aging and dementia

Reference	Study Population	Method	Results
[204]	AD	Plasma	Decreased Vit. E, retinol
[136]	AD Vascular dementia (VaD) PD with dementia (PDm)	Plasma	Decreased Vit. A in AD, VaD Vit. C in AD, VaD, PDm Vit. E in AD, VaD
[205]	AD	Plasma	Decreased Vit. A, E, C
[206]	AD, VaD	Plasma	Decreased Vit. A, E, β-carotene in AD Decreased Vit. E, β-carotene in VaD
[207]	AD	Serum	No change α-carotene, Decreased Vit. A, β-carotene
[135]	AD	Plasma	Decreased Vit. C
[208]	AD, VaD	Plasma	Decreased Vit. C, E Increased β-carotene in VaD
[209]	AD, dementia	Plasma	Decreased Thiamine
[210]	AD	Cerebrospinal fluid	Decreased Vit. B_{12}

studies reporting correlations among dietary carotenoids, vitamin E, and vitamin C and cognitive decline in aging [34]. The review of nine different studies had varying results. Most researchers showed no association with nutritional changes and increased dementia. Nourhashemi et al. [42] reviewed seven studies on the relationship between vitamin status and cognitive skills in elderly patients, revealing a correlation between low vitamin C, vitamin B_{12}, riboflavin, folic acid, niacin, thiamine, β-carotene, vitamin B_6 levels and decreased performance on cognitive tests.

An increase in these vitamins also showed a correlation with improved cognitive performance. Chandra investigated whether an optimum intake of all essential micronutrients would improve cognitive function in the elderly [43]. Healthy elderly where given a cocktail of vitamins and trace elements (vitamins A, E, C, D, B_{12}, B_6, β-carotene, thiamine, riboflavin, niacin, folate, iron, zinc, copper, selenium, iodine, calcium, and magnesium). The supplemented group showed a significant improvement in all cognitive tests except long-term memory recall. Thus, some studies show that nutritional deficiencies may be a contributing factor in the decline of cognitive function in old age and dementia.

Vitamin E, a phenolic compound, acts as an antioxidant by scavenging free radicals via the phenolic H-atom as shown in Fig. 1B. As discussed below, these reactions of vitamin E, vitamin C, and glutathione may be linked by various recycling pathways, thereby increasing efficency of these moieties against oxidative stress.

As noted, in AD there is evidence of subclinical deficiency in levels of vitamim E, C, folate, and GSH. Hence, dietary sources of these and other molecules that inhibit oxidative stress may be an important approach in delaying progression of and treating AD.

2.3. Polyphenols

Polyphenols are natural substances ubiquitously present in fruits and vegetables, as well as, beverages obtained from plants such as tea, red wine and olive oil. Flavonoids compose the largest group of polyphenols. Their skeletal structure consists of an aromatic ring condensed to a heterocyclic ring, attached to a second aromatic ring. Flavonoids are mainly divided into: anthocyanins, glycosylated derivative of anthocyanidin, present in colorful flowers and fruits, and anthoxantins, colorless compounds further divided in several categories including flavones, flavans, flavonols, flavanols, and isoflavones (Fig. 2). The remarkable antioxidant activity of these compounds is conferred by the numerous phenolic hydroxyl groups on the aromatic ring. The rapid

donation of a hydrogen atom to lipid peroxyl radical results in the formation of the polyphenol phenoxyl radical ($PP^{\cdot}$) according to the reaction

$$ROO^{\cdot} + PPH \rightarrow ROOH + PP^{\cdot}$$

that can be stabilized by further donation of another hydrogen or by reacting with another radical. In addition, flavonoids present efficient iron chelating activity, for which the 3-OH is important [44].

The physiological effects of flavonoids are particularly significant in those pathologies where the oxidative stress hypothesis is accepted and supported by experimental data, such as AD. *In vitro*, flavonoids are capable of scavenging superoxide anions [45] and hydroxyl radicals [46].

Once ingested, these compounds are capable of elevating the redox and antioxidant level [47]. In red blood cells, polyphenols enhance cell resistance to oxidative insult [48], as well as inhibit LDL oxidation in plasma [49]. The importance of these molecules in protecting cells from oxidative stress goes beyond the simple radical oxygen species (ROS) scavenging properties. In a recent study on neuronal cells [50], three different mechanisms of protection have been identified: Flavonoids can prevent cell death after glutamate injury by scavenging radicals, maintaining the correct glutathione levels and inhibiting Ca^{2+} influx, which represents the last step in the cell death cascade. These properties, together with anti-inflammatory properties attributed to some polyphenols [51], renders this class of compounds suitable for application where oxidative stress, together with inflammation and antioxidant defense depletion take place, such as AD.

2.4. Heme oxygenase as a target for cytoprotective strategies

Many approaches have been undertaken to understand AD, but the heterogeneity of the etiologic factors makes it difficult to define the clinically most important factor determining the onset and progression of the disease [52]. How-

of agents is the safe induction of the heat shock response as a means to reduce organ pathology in diverse clinical conditions, such as ischemia-reperfusion, sepsis, and neurodegenerative insult. Notably, recent reports have demonstrated important interactions between the heat shock response and NFκB pathway [63]. For example, induction of heat shock response by thermal or nonthermal stimuli inhibited activation of the NFκB pathway in various *in vitro* and *in vivo* models [64]. Additionally, some pharmacological inhibitors of NFκB, each having distinct mechanism of inhibition, are able to induce the heat shock response [65].

These evidences, together with the findings that Aβ causes oxidative damage to and neurotoxicity of neurons [3,7], vitamin E blocks these effects in vitro [12,13,66,67], the glutamate transporter, Glt-1, is oxidatively modified in AD brain with increased opportunity for excitotoxic mechanisms to lead to oxidative stress and neurodegeneration [40], all indicate that excess formation of free radicals exists in AD brain [3]. Consequently, such free radicals may be influenced by antioxidants, which can thus modify the intensity of inflammatory reactions and degenerative damage.

Spices and herbs often contain phenolic substances with potent antioxidative and chemopreventive properties [68].

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vanilin and ferulic acid [73] or, through a peroxyl linkage at the 3′ position of the curcumin phenolic ring, coupling products which generate, via intramolecular Diels-Alder reaction, non radical stable compounds [74].

Curcumin contains two electrophilic α,β-unsaturated carbonyl groups, which can react with nucleophiles such as glutathione [75]. By virtue of its Michael reaction acceptor function and its electrophilic characteristics, curcumin and several other polyphenolic compunds have been recently demonstrated to induce the activities of Phase I and Phase II detox system [76,77], e.g., inhibition of COX-1 and COX-2 enzymes [78] and stimulation of glutathione-S-transferase [79]. In addition to its ability to scavenge carcinogenic free radicals [71,80], curcumin also interferes with cell growth through inhibition of protein kinases. Although the exact mechanisms by which curcumin promotes these effects remains to be elucidated, the antioxidant properties of this yellow pigment appear to be an essential component underlying its pleiotropic biological activities. Of particular interest is the ability of curcumin to inhibit lipid peroxidation and effectively to intercept and neutralize ROS (superoxide, peroxyl, hydroxyl radicals) [81] and NO-based free radicals (nitric oxide and peroxynitrite) [82]. In this regard, curcumin has been demonstrated to be several times more potent than vitamin E [83].

The hydroxycinnamate, ferulic acid, is found in many fruits and vegetables such as the tomato [84]. Tomato consumption

glutathione. Improved behavior and diminished markers of oxidative stress were reported for aged rats fed a diet supplemented with LA [110–112]. Recently, α-lipoic acid was administered to AD patients [113]. The non-randomized study gave 600 mg of lipoic acid daily for 337 days to AD and other dementia patients. The treatment led to a stabilization of cognitive functions in the study group as demonstrated by constant scores in two neuropsychological tests

altered in Alzheimer's disease [120]. Several studies have been done to determine the effects of thiamine supplementation on Alzheimer's disease with varying results. Blass et al. [121] noted a significant improvement in cognitive ratings in AD patients who took 3 g per day of oral thiamine for three months. Nolan and collegues saw no difference in mini-mental state scores after twelve months of 3 g per day oral thiamine in AD patients [122]. In contrast, Meador et al. [123] noted mild beneficial effect in dementia of Alzheimer patients after 3 to 8 g/day of thiamine was administered orally. A derivative of thiamine, fursultiamine was taken by AD patients, at an oral dose of 100 mg/day for twelve weeks. Mildly impaired Alzheimer's patients showed cognitive improvement [124]. Thiamine supplementation, possibly through its involvement with cholinergic neurons, may have possible therapeutic implications for AD.

3.2.4. Vitamin C

Humans lack the enzyme L-gulono-γ-lactone oxidase which is necessary for biosynthesis of vitamin C, ascorbate, and therefore must obtain ascorbate from dietary sources. Ascorbate is a water-soluble antioxidant present primarily as a monovalent anion at physiological pH. Ascorbate functions as an antioxidant by giving up to two electrons. Ascorbate can lose one electron to form the semidehydroascorbate, the ascorbyl radical, a relatively stable resonance-stabilized radical of low reactivity [125] (Fig. 5). The loss of a second electron results in the formation of dehydroascorbate. Ascorbate and ascorbyl radical have low reduction potentials putting these species on the lower end of the "pecking order" and they can therefore react with stronger oxidizing species such as hydroxyl radical, superoxide, etc. [126].

Ascorbate plays an important role with the lipophilic antioxidant vitamin E in protecting the membrane from oxidative stress. Ascorbate soluble in the aqueous phase can regenerate vitamin E which is present in the membrane. Ascorbate can reduce the tocopheryl radical, formed when vitamin E scavenges a lipid radical within the membrane. The hydroxyl group of vitamin E has been shown to be at the membrane-water interface, in close proximity to the water-soluble ascorbate [126] (Fig. 6). The tocopherol radical formed from the lipid radical can then be recycled back to tocopherol by ascorbate.

An important aspect of the antioxidant capability of ascorbate is the ability of oxidized ascorbate to be recycled back to the reduced ascorbate. Glutathione is important in the recycling of ascorbate by direct chemical reduction [127] and by glutathione-dependent enzymes [128,129]. Recently, dehydroascorbate reductase activity has been found to be present in brain cytosol and the enzyme was found to be present in several brain regions including the cerebellum and hippocampus [130]. This enzyme uses glutathione as an electron donor to restore ascorbate to a reduced state from dehydroascorbate [130]. Other enzymes that function to reduce dehydroascorbate to ascorbate are the NADPH-dependent enzymes 3α-hydroxysteroid dehydrogenase [129] and thioredoxin reductase [131]. Additionally, thioredoxin reductase has been shown to reduce the ascorbyl radical to ascorbate [132].

However, an important aspect of ascorbate chemistry is the pro-oxidant behavior of ascorbate *in vitro.* Ascorbate has long been known to participate in Fenton chemistry by reducing Fe(III) or Cu(II), yielding Fe(II) or Cu(I) and the ascorbyl radical. Fe(II) or Cu(I) can then catalyze the Fenton reaction with H_2O_2, resulting in production of hydroxyl radical [133]. Consequently, one must consider the possibility that long-term megadoses of vitamin C may cause oxidation in a living system.

Plasma ascorbate levels have been found to be decreased in AD patients as compared to control patients, in levels corresponding to dementia [134–136]. More interestingly, CSF levels of ascorbate were found to be decreased in AD patients as compared to control subjects which may h6D

Fig. 6. Role of vitamin C, GSH, and lipoic acid as antioxidants.

vitamin E and C, suggesting that vitamin C should be given concurrently with vitamin E in AD patients.

3.2.5. Vitamin E

In neuronal cultures, the lipophilic antioxidant vitamin E inhibits A -induced lipid peroxidation, protein oxidation, free radical formation, and cell death [12,13,16,67,139]. Lowered levels of vitamin E are observed in AD cerebrospinal uid (CSF), a nding that was inversely correlated with levels of lipid peroxidation [140]. This latter observation is consistent with the increased lipid peroxidation reported for AD [2,3] and caused by A[40,141].

Vitamin E alone or vitamin E and vitamin C in combination were given to AD patients [138], with the results being that CSF levels of vitamin E were increased. In the combination study, decreased susceptibility of lipoproteins to oxidation was found, consistent with the notions that vitamin C is able to regenerate the tocopheroxyl radical back to vitamin E, thus increasing antioxidant activity.

Moderately advanced AD patients were subjected to a clinical trial of high dose (2000 I.U.) vitamin E [142]. Delayed entry into nursing homes was found in the population of patients who received this high dose regimen. Although the progression of AD seemed to be slowed in these moderately advanced AD patients on high dose vitamin E, others have criticized this study as not directly showing ef cacy of vitamin E [143]. However, based in part on the known oxidative stress in AD brain, the NIH is currently funding a multi-center clinical trial of high dose vitamin E in patients with the earliest sign of clincial memory loss, so-called mild cognitive impairment. The hypothesis is that early intervention with the antioxidant vitamin E will show more ef cacy than with late-stage patients, and that vitamin E will signi cantly retard progression of this oxidative stress-related dementing disorder [144,145].

3.3. Polyphenols

Flavonoids from four different sources will be reviewed with respect to experimental data from in vitro and in vivo studies and clinical trials in AD.

3.3.1. Red wine

In the 1970s, studies [146] showing a correlation between a Mediterranean diet and low incidence of coronary and ischemic heart disease, raised public interest as to the effects of beverages such as red wine protecting against health problems and aging. Among the many phenolic compounds of wine, one that deserves to be mentioned is resveratrol. This polyphenol is produced by the grape in response to a mycelium infection and confers high resistance to its attack. Higher concentrations of resveratrol are found in red wines, especially in cabernet sauvignon grapes of Bordeaux.

The mechanism of antioxidant action of this natural compound has been extensively investigated [147], demonstrating that the para-hydroxyl group of trans-resveratrol is necessary for ef cient scavenging activity. The bene cial effect has been tested in several studies. Frankel et al. [148] found that a 10 M phenol-containing wine inhibited low density lipoprotein (LDL) oxidation more ef ciently than vitamin E. In PC12 cells, resveratrol showed a protective effect against oxidative insult [149]. Others demonstrated that administration of resveratrol in rats protected the brain against excitotoxic damage [150] and in hippocampal neurons against nitric oxide-related toxicity [151].

The effects of red wine consumption in age-related dementia and AD were evaluated by several investigations. A French study [152] on a community of persons 65 years of age and older, whose only consumption of alcoholic beverages was represented by red wine in the amount considered

moderate (3 to 4 glasses per day), analyzed the incidence of dementia and AD compared to non-drinkers. After adjusting for age, sex, education and other factors, the study showed an inverse relationship between moderate wine drinking and AD incidence, suggesting that wine concumption may slow or prevent dementia. The same French investigators reported an epidemiological study on the effects of dietary wine flavonoids in preventing dementia in elderly. After a 5-year study on the dietary habits of 1,367 subjects, the authors concluded that the risk of developing dementia is lower for those subjects having a diet rich in flavonoids [153]. Taken together with the findings that resveratrol inhibits the oxidative and neurotoxic properties of Aβ [154], these results support a potentially beneficial effect of red wine in ameliorating the onset and symptoms of disorders associated with age, due to the powerful antioxidant effect of polyphenols.

3.3.2. Ginkgo biloba

Modern scientific studies on the biological activity of extracts from dried ginkgo biloba leaves started 20 years ago, even though the beneficial effects of these natural substances were known for 5000 years in traditional Chinese medicine. The ginkgo extracts that are currently used for medicinal purposes contain 24% flavonoids and 6% terpenoids. The antioxidant effects of flavonoids combined with the anti-inflammatory properties of the terpenoids bilobalide and ginkgolides A, B, C, M and J, terpenoids antagonists of platelet-activating factor (PAF), make these natural extracts plausible to use in Alzheimer's disease, characterized by both oxidative damage [3,155] and inflammation [156].

Extensive studies on Ginkgo extracts showed their ability to protect brain neurons from oxidative stress [157], to

[174,175] did not report any signi

[189]. This finding highlights the important role of curcumin as a heat shock response inducer and cytoprotectant, and substantiates the notion that many of the biological actions of curcumin, including inhibition of cell proliferation [190], antioxidant potential [87] and modulation of inflammatory response [69], can be ascribed to overexpression of HO-1 [191–193]. Curcumin is a potent inducer of HO-1 in vascular endothelial cells, and tin protophorphyrin IX, an inhibitor of HO activity, abolished curcumin-mediated cytoprotection against oxidative stress [194].

In astroglial cells the role of caffeic acid phenethyl ester (CAPE), an active component of propolis, recently was demonstrated to be a novel HO-1 inducer [195]. This study also provides experimental evidence that both CAPE- and

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