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Review

Molecular bases of the treatment of Alzheimer's disease with antioxidants: prevention of oxidative stress

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Abstract

Alzheimers's disease is associated with a systemic oxidative stress situation which can be followed in vivo by determining biomarkers such as plasma lipoperoxides and TBARS levels and the oxidation degree of glutathione in red blood cells. It has been observed that Alzheimer's patients show an increased level of plasma TBARS, which indicates a higher free radical oxidation of plasma unsaturated phospholipids, and an increased oxidation of red blood cells glutathione, which indicates oxidative stress in peripheral cells. This latter, glutathione oxidation, was found to correlate statistically with the cognitive status of the patients. Treatment with vitamin E resulted in an improved cognitive performance only of those patients in which the tocopherol acted as an antioxidant, according to blood indicative markers of oxidative stress. Indeed, the effect of vitamin E on Alzheimer's disease patients showed considerable variations both in its antioxidant function and in its capacity to improve cognitive functions. An important conclusion from the reported results is that epidemiological or clinical studies that aim to test the effect of antioxidant supplementation on given functions should include the determination of the antioxidant status of the patients by the measurement of blood markers of oxidative stress.

Abbreviations: AIDS, acquired Immuno-deficiency syndrome; SH, reduced glutathione; GSSG, oxidized glutathione; O_2^-, superoxide radical

Keywords: Alzheimer's disease; Oxidative stress; Oxidized glutathione; Mini-mental state examinations

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1. The mitochondrial theory of ageing. Importance in age-associated diseases

Ageing is characterised by a progressive accumulation of changes with time, which are responsible for an increased probability of disease and death. More than a hundred theories and hypotheses have been published to explain ageing (for a reviews, see Medvedev, 1990). Probably the today most accepted theory is the free radical theory of ageing which was postulated by Harman (1956). The original theory advanced that oxygen free radicals are responsible of the cell and tissue damage associated with ageing. The free radical theory of ageing was further refined by Miquel and co-workers in what was called the mitochondrial-free-radical hypothesis of ageing (Miquel et al., 1980). These authors postulated that mitochondria were the key organelles in the generation of free radicals and reactive oxygen species in ageing, and that the same organelles were also essential targets of the damage caused by the reactive oxygen species. An important feature of this theory is that it is fertile in the sense that it has room for intervention to modify the rate and the conditions of ageing. The possibility of intervention, at least as a concept, is open for aiming both to a prevention of the generation of free radicals in a given condition, and to an increased antioxidant capacity by supplementation with antioxidants to minimise cellular damage. Many antioxidants have shown beneficial effects in different biological systems, in which they were able to prevent age-associated damage in cultured cells, to lower the incidence of age-associated diseases and to increase lifespan (Beckman and Ames, 1998). Of the various antioxidants utilized in experimental studies, great attention has been paid to antioxidant vitamins, particularly vitamin E, and to natural extracts rich in flavonoids, such as the ones obtained from *Ginkgo biloba* leaves. Quite recently the role of oestrogens, and phytoestrogens has been underlined.

Free radicals have been considered involved in the pathophysiology of many diseases (Ozben, 1998; Halliwell and Gutteridge, 1999). Both mitochondrial and

cytosolic oxidative stress have been considered to explain the molecular mechanisms underlying pathophysiological situation. In some cases, as in ischemia-reperfusion, the same situation was explained by either cytosolic or mitochondrial mechanisms (Parks et al., 1982; McCord, 1985; González-Flecha et al., 1993). Cytosolic mechanisms of oxidative stress appear involved in diabetes and in AIDS, whereas AIDS also shows mitochondrial oxidative stress. In diabetes, cytosolic oxidative stress is triggered by the transformation of xanthine dehydrogenase in xanthine oxidase, that is an active source of cytosolic superoxide radicals (McCord, 1985; Desco et al., 2002). In AIDS, cytosolic oxidative stress is due to the absence of cystathionase, a critical enzyme for the maintenance of normal glutathione levels (Martin et al., 2001). Moreover, AIDS treatment with antiretroviral agents causes mitochondrial oxidative stress (De la Asuncion et al., 1998). Thus, it is clear that preventing or at least minimising oxidative stress is an important strategy in the treatment of several diseases. In this review we shall deal with the importance of antioxidant treatments in neurological diseases and in particular in Alzheimer's disease.

2. Oxidative stress, antioxidants and Alzheimer's disease

The fact that there is a brain and a systemic oxidative stress in Alzheimer's disease has been recognised in the last decade. In 1991, Floyd, Stadtman and co-workers (Smith et al., 1991) reported an excess brain protein oxidation associated to enzyme dysfunction in the brain of patients with Alzheimer's disease. Smith and Perry reported that oxidative stress is indeed involved in the pathogenesis of this disease and suggested that the cellular characteristics of Alzheimer's disease are either cause or effect of oxidative stress (Smith et al., 1996, 1997). Concerning the mechanistics aspects, it has been recognized that β-amyloid aggregates lead to peptide fragmentation and free radical generation (Hensley et al., 1994) and that there is an active iron accumulation in Alzheimer's disease (Smith et al., 1997), both conditions are synergistic for the generation of oxidising free radicals. Moreover, St. George-Hyslop (2000) reviewed evidence showing that the damage caused by the β amyloid peptide originates from inside cells and from the extracellular space, both being relevant to the development of Alzheimer's disease.

In a highly relevant contribution in the context of the present review, Cecchi et al. (1999) showed that oxidative stress in Alzheimer's disease can be also detected in peripheral cells and not only in neuronal cells. Therefore, evidence has largely accumulated showing that oxidative stress is a key event in the onset and development of Alzheimer's disease.

Three recent and important studies have dealt with the concept that vitamin E intake is effective in the prevention and treatment of Alzheimer's disease. Sano et al. (1997) reported the results of a controlled trial showing that vitamin E, at a dose of 2000 IU/day, is effective in the treatment of Alzheimer's disease. This key paper showed for the first time that vitamin E could be a treatment and not just a mechanism for prevention of Alzheimer's disease (Fig. 1). Moreover, two major papers appeared in JAMA in 2002 in which the role of the dietary intake of antioxidants

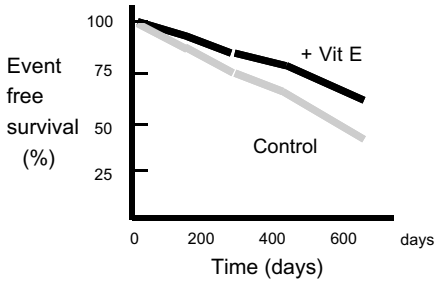

Fig. 1. Vitamin E (2000 IU/day) decreases unpleasant events in Alzheimer's disease. Modified from "The Alzheimer's Disease Comparative Study" (Sano et al., 1997).

and the risk of Alzheimer's disease were investigated (Morris et al., 2002; Engelhart et al., 2002). Both studies concluded that an increased intake of vitamin E lowers the risk of Alzheimer's disease.

3. Vitamin E, oxidative stress and Alzheimer's disease

In the question of the relationships between oxidative stress, vitamin E and Alzheimer's disease there are two important main concepts. First, whether systemic oxidative stress occurs in Alzheimer's disease patients, and in second place, if decreasing oxidative stress by oral administration of vitamin E improves the clinical condition, i.e., the cognitive function of Alzheimer's disease patients. A critical point is to determine if the improvement in antioxidant redox status directly correlates with the improvement in cognitive function. Pioneering work by the group of Azzi (reviewed in Azzi et al., 2002) had shown that vitamin E has several cellular functions apart from its antioxidant function. Therefore, the eventual beneficial effects of vitamin E on Alzheimer's disease could be due not to its antioxidant properties, but rather to other functions related to cell signalling.

4. Glutathione redox status, oxidative stress and Alzheimer's disease

Glutathione redox status, properly represented by the GSSG/GSH ratio constitutes a reliable index of oxidative stress in all types of tissues, cells and organelles. For instance, the oxidation of mitochondrial glutathione in the development of ageing (García de la Asunción et al., 1996) and of apoptosis (Esteve et al., 1999) correlates with the oxidative damage to mitochondrial DNA. Moreover, the GSSG/GSH ratio in red blood cells has proven to be a useful indicator of oxidative stress in several physiological and patho-physiological situations (Asensi et al., 1999). Oxidation of blood glutathione correlates with the increased lactate levels observed in exhaustive exercise (Sastre et al., 1992).

The GSSG/GSH ratio in Alzheimer's disease patients, indicating oxidative stress in peripheral cells, was found significantly increased as compared with their age-matched controls (Fig. 2). Moreover, glutathione oxidation and the cognitive function (assessed by several methods but we only report here results obtained with the mini-mental state examination test) were significantly correlated in patients treated with vitamin E (Fig. 3). Thus, it appears that systemic oxidative stress is a useful indicator of Alzheimer's disease. Vitamin E is effective in improving the cognitive performance in Alzheimer's disease patients (Fig. 3; Sano et al., 1997), but it show large individual variations. Plasma lipid peroxidation, determined as malondialdehyde-thiobarbiturate adduct by high performance liquid chromatography, behaved similarly to the GSSG/GSH as indicator of oxidative stress in these patients; Alzheimer's disease patients had a higher level of plasma malondialdehyde and an increased oxidation of blood glutathione when compared with their age matched controls. A six months treatment with vitamin E significantly improved the cognitive performance of Alzheimer's disease patients and also ameliorated peripheral cell oxidative stress, as determined by blood glutathione redox ratio. However, the response to vitamin E showed significant interindividual variations. Not all patients responded equally to vitamin E, some patients did not show significant reductions of the glutathione redox ratio or significant increases of cognitive performance.

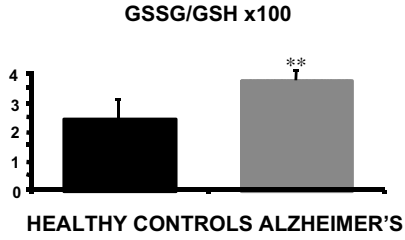

Fig. 2. Glutathione redox status as GSSG/GSH contents ratio in red blood cells in Alzheimer's disease patients. Values are GSSG/GSH×100 and bars and lines indicate means and SEM. $^{**}p < 0.05$, $n = 14$ in each group.

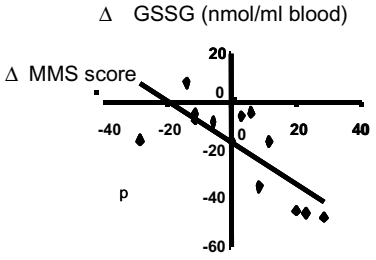

Fig. 3. Relationship between the improvement of the oxidative stress in red blood cells (ΔGSSG) and the improvement of cognitive function (ΔMMSE score) in Alzheimers's disease patients after 6 months of vitamin E treatment.

A possible explanation for this difference is that the absorption of vitamin E also shows great individual variations (Roxborough et al., 2000). Thus, the same dose of vitamin E will not result in a similar antioxidant effect in vivo in all treated patients. These results strongly suggest the idea that the beneficial effect of vitamin E in cognition in Alzheimer's disease patients is related to its antioxidant properties and not to other roles of this vitamin in cell signalling. One of most important conclusions of the considered evidence is, after considering the high variation of the human response to vitamin E intake, that the clinical and epidemiological studies aimed to assess the effect of antioxidants in given functions (i.e., the incidence of cardiovascular diseases after supplementation with vitamin E) should be accompanied by the determination of the oxidant-antioxidant status of the patients using markers of blood oxidative stress such as plasma malonaldehyde, plasma vitamin E and red blood cells GSSG/GSH ratio, as remarked recently by Halliwell (2000).

5. Concluding remarks

The results summarised here show indicate that the cognitive function in Alzheimer's disease patients is inversely correlated with systemic oxidative stress. They also confirm the idea that vitamin E can be considered as an effective treatment of Alzheimer's disease. The effect of vitamin E on Alzheimer's disease patients shows considerable variations both in its antioxidant function and in its capacity to improve cognitive functions. An important conclusion of the summarised evidence is that the level of peripheral oxidative stress markers should be determined in clinical studies aimed to test the effect of antioxidants on given functions.

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