Chapter 7

The Protective Role of Vitamin E in Vascular Amyloid β-Mediated Damage

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Abstract: Amyloid β peptide (Aβ) accumulation produces the senile plaques in the brain parenchyma characteristic of Alzheimer's Disease (AD) and the vascular deposits of Cerebral Amyloid Angiopathy (CAA). Oxidative stress is directly involved in Aβ-mediated cytotoxicity and antioxidants have been reported as cytoprotective in AD and CAA. Vitamin E has antioxidant and hydrophobic properties that render this molecule as the main antioxidant present in biological membranes, preventing lipid peroxidation, carbonyl formation and inducing intracellular modulation of cell signalling pathways. Accordingly, vascular damage produced by Aβ and prooxidant agents can be decreased or prevented by vitamin E. The protective effect of vitamin E against Aβ cytotoxicity in vascular cells in comparison to the neuronal system is reviewed in this chapter.

Key words: Amyloid β-peptide, Cerebral Amyloid Angiopathy, vitamin E, vascular cells, antioxidants, oxidative stress.

1. VASCULAR AMYLOIDOSIS

The different systemic diseases generally termed *amyloidosis* are all characterized by the misfolding of proteins into β-pleated sheet-rich structures that in turn leads to the aggregation and fibrillogenesis of the proteins, triggering pathological processes in the tissues. The most representative pathologies affecting the brain vessels are those produced by the aggregation of cystatin C (hereditary cerebral hemorraghe with amyloidosis of the Icelandic type; HCHWA-I), transthyretin (familial

transthyretin amyloidosis; TTR), gelsolin (familial amyloidosis of the Finnish type; FAF), prion protein (Gerstmann-Sträussler-Scheinker syndrome; GSS), ABri (familial British dementia; FBD), ADan (familial Dannish dementia) and the amyloid β-peptide (Alzheimer disease and cerebral amyloid angiopathy; AD and CAA).

2. CEREBRAL AMYLOID ANGIOPATHY

CAA is present in most cases of AD and it is characterized by the deposition of amyloid β-peptide (Aβ) in the media and adventitia of both leptomeningeal arteries and intracortical arterioles and capillaries (Figure 1), and less frequently in veins (Vinters *et al.*, 1988; Calhoun *et al.*, 1999). These vascular deposits are mostly composed by $A\beta_{1-40}$ wild type (Castaño *et al.*, 1996) and produce degeneration of vascular smooth muscle cells (VSMCs) from the media (Wisniewski and Wegiel, 1994; Zhang *et al.*, 1998) and endothelial cells from the intima (Wisniewski *et al.*, 1992; Kalaria, 1997). A variant of CAA with an early onset of the disease is hereditary cerebral haemorrhage with amyloidosis of the Dutch type (HCHWA-D). HCHWA-D is caused by Aβ-encoding gene point mutation which produces substitution of Glu→Gln at the position 22 (Levy *et al.*, 1990) resulting in a peptide with increased ability to form amyloid fibrils (Wisniewski *et al.*, 1991). Although HCHWA-D patients show diffuse amyloid deposition in the brain parenchyma, the main hallmarks of AD (mature senile plaques and neurofibrillary tangles) are not observed (Timmers *et al.*, 1990; Maat-Schieman *et al.*, 1994). In both CAA and HCHWA-D, the vascular amyloid deposits contain extracellular matrix molecules and other common components of senile plaques from the neuropil of AD patients (Snow *et al.*, 1988; Verbeek *et al.*, 1998; Mesulam *et al.*, 1992; Van Duinen *et al.*, 1995). Significantly, as in senile plaques (Vehmas et al., 2003), the vascular deposits show the presence of reactive glia (Uchihara et al., 1997).

3. ORIGIN OF VASCULAR Aβ

The amyloid precursor protein (APP) is present in VSMCs, pericytes and endothelial cells (Schmechel *et al.*, 1988; Shoji *et al.*, 1990; Tagliavini et al., 1990; Wisniewski and Wegiel, 1994), but the origin of vascular Aβ deposits

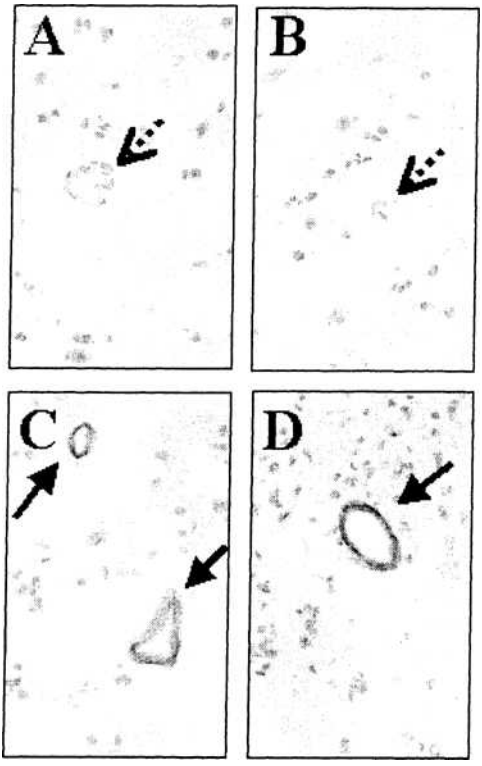

Figure 1. Amyloid deposits identified by Congo red staining in brain samples from the frontal cortex of control (A,B) and AD patients (C,D) with AD in the VI stage. Arrows show the blood vessels. The samples from AD patients show that most of the blood vessels are Congo red-positive.

is controversial (Weller *et al.*, 1998). VSMCs are able to produce Aβ (Frackowiak *et al.*, 1995), which has been identified even in intracellular compartments of VSMCs (Mazur-Kolecka *et al.*, 1995; Wisniewski *et al.*, 2000). Nevertheless, transgenic mice overexpressing neuronal mutated APP (Dutch-Iowa-Swedish mutations) also develop CAA (Davis *et al.*, 2004), indicating that neuronal Aβ is deposited in the vessels. It could be due to the flux from the neuronal Aβ drainage, but the contribution of VSMCs to the vascular Aβ deposits could be also relevant by producing seeds for the fibrillation of the Aβ coming from the neurons. It could be due to the flux from the neuronal Aβ drainage, but the contribution of VSMCs to the vascular Aβ deposits has been demonstrated in cell cultures (Frakcowiak *et al.*, 2004) and human brain vessel cultures (Mazur-Kolecka *et al.*, 2004). Moreover, if neurons were the producers of all the vascular Aβ, a gradient of

immature Aβ deposits should be shown from the parenchyma to the vessels and it does not occur in arteries or small arterioles, where Aβ deposits have been found. Nevertheless, such a gradient is shown in the proximity of veins, probably corresponding to the clearance of neuronal Aβ. These findings suggest that the vascular Aβ is produced by both type of cells, neurons and VSMCs, and that VSMCs play a key role in the Aβ secretion.

4. Aβ EFFECTS ON THE VESSELS

CAA is characterized by the degeneration of VSMCs and endothelial cells (Miyakawa *et al*, 1997; Kalaria, 1997). Aβ deposits are present in the tunica media of large vessels at early stages of AD. VSMCs close to Aβ deposits have swollen nuclei and express the proliferating cell nuclear antigen. When the amyloidosis is at advanced stages, the tunica media is replaced by amyloid deposits and VSMCs degenerate becoming scarce (Wisniewscki *et al.*, 2000). Thus, it has been reported that there is an increase in the number of apoptotic VSMCs and endothelial cells in AD (De la Monte *et al.*, 2000). A direct toxic effect of Aβ on VSMCs *in vitro* has been also demonstrated (Davis and Van Nostrand, 1996; Muñoz *et al.*, 2002).

At the functional level, Aβ enhances the vessel contraction (Crawford *et al.*, 1998; Suo *et al.*, 2000) and decreases the endothelium-dependent vasodilatation (Thomas *et al.*, 1997) despite the increased nitric oxide (NO) production by AD endothelial cells (Grammas *et al.*, 2000). The lack of vasodilatatory properties of NO may be due to the sequestration of NO in a pro-oxidant environment to produce peroxynitrite, a powerful oxidant produced from the reaction of superoxide anion ($O_2^{\cdot-}$) and NO. There is also evidence of endothelial cell degeneration in CAA (Miyakawa *et al.*, 1997), which produces blood vessel damage and increased permeability of the blood-brain barrier (Wisniewski *et al.*, 2000).

5. OXIDATIVE STRESS IN THE ETIOLOGY OF AD

Oxidative stress could be involved in the development of AD since it has been demonstrated that the expression and activity of BACE, the proposed β-secretase for APP, is increased by oxidative stress (Tamagno *et al.*, 2002), and that oxidative stress enhances the production of Aβ (Frederikse *et al.*,

1996). Moreover, homocysteine, a well-known risk factor for atherogenic damage and vascular disease, has been also proposed as a risk factor for AD (Seshadri *et al.*, 2002), and the deleterious effect of homocysteine on blood vessels may be mediated by oxidative stress (Perna *et al.*, 2003). Thus the putative role of homocysteine in the development of AD could be related to a pro-oxidant activity yielding to an increase in the production of Aβ, and/or because homocysteine increases Aβ-induced cytotoxicity (Mok *et al.*, 2002).

6. OXIDATIVE STRESS IN Aβ-MEDIATED CYTOTOXICITY

The existence of a specific receptor mediating the cytotoxicity induced by Aβ has been proposed, but none of the putative candidates can explain all the cytotoxic effects observed. There is an increased amount of experimental and histopathological evidence suggesting that oxidative stress plays a key role in Aβ-mediated cytotoxicity (Behl *et al.* 1994; Miranda *et al.*, 2000; Muñoz *et al.*, 2002).

Aβ generates hydrogen peroxide (H_2O_2) through metal ion reduction (Huang *et al.*, 1999) and is able to increase the free radical generation by metals such as iron, copper and zinc (Bondy *et al.*, 1998), which are highly concentrated within the core and periphery of Aβ deposits (Lovell *et al.*, 1998). The oxidative damage of proteins generates an increase in carbonyl groups (Stadtman, 1990). Carbonyl residues and protein nitration in AD brain may come from the action of peroxynitrites (Smith *et al.*, 1997). Proteins can also be modified by non-enzymatic reaction with monosaccarides, such as the Maillard reaction, when irreversible advanced glycation end products (AGEs) are formed, concomitant with hydroxyl radical ($HO^{\cdot}$) generation (Münch *et al.*, 1997a). It has been demonstrated *in vitro* that Aβ induces lipoperoxidation of membranes (Koppal *et al.*, 1998, Mark *et al.*, 1997) leading to the disruption of the physiological signalling pathways (Kelly *et al.*, 1996). Moreover, it impairs the function of membrane-regulatory proteins, including cation transport ATPases (Mark *et al.*, 1995). The impairment of ATPase function means that the intracellular calcium cannot be pumped out. The progressive cytoplasmic accumulation of calcium and the oxidative damage on mitochondria and nucleic acid (Gabbita *et al.*, 1998; Nunomura *et al.*, 1999) trigger cellular apoptotic mechanisms. Therefore, extracellular Aβ produces a cascade of ROS which induces intracellular damage (Figure 2).

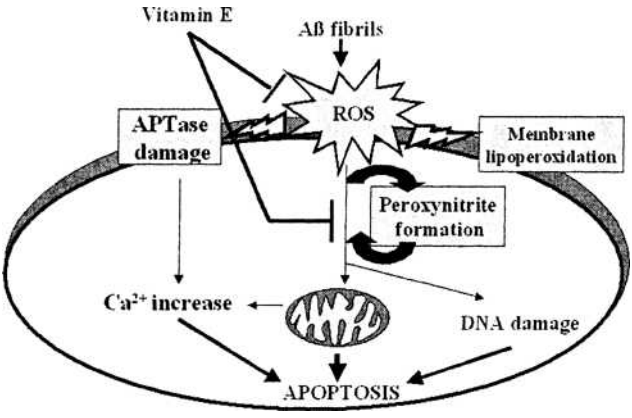

Figure 2. Aβ produces oxidative damage leading to the cell death. Reactive oxygen species (ROS) induce peroxidation with damage to both membrane lipid and protein. This event disrupts cell homeostasis. The intracellular ROS cascade is increased by the formation of peroxynitrites. Mitochondrial oxidative damage is triggering apoptotic pathways by the release of cytochrome C and the enhancement of intracellular calcium, which even activates endonucleases. Vitamin E can prevent the cell death by inhibiting the damage from extracellular ROS in the membrane and in the intracellular ROS cascade.

7. INTRACELLULAR SIGNALLING PATHWAYS INVOLVED IN THE OXIDATIVE DAMAGE

The mitogen-activated protein kinase (MAPK) pathways are involved in the deleterious effect of Aβ, but the specific role of the extracellular signal-regulated kinase (ERK), c-Jun NH_2-terminal protein kinase (JNK) and p38/RK/MpK2/CSBP kinases in the Aβ toxicity is controversial (Zhu *et al.*, 2002).

Low levels of radical/reactive oxygen species (ROS) play an important role in normal cell proliferation (Burdon, 1995; Benhar *et al.*, 2002) and regulate cellular signalling by the activation of MAPKs leading to induction of gene expression to protect cells. But at high concentrations, these agents activate ERK2 and JNK and ICE/Ced-3 caspase pathway inducing apoptosis

(Kong et al., 1998). Other authors propose that low concentrations of H_2O_2 activates phosphatidylinositol-3-kinase (PI-3K) giving an increase in the cell survival by the activation of c-AMP response element binding protein (CREB) throughout the action of ERK1/2 and Akt/PKB pathways, while high concentrations of H_2O_2 are proapoptotic throughout the activation of JNK/c-jun cascade in cortical neurons (Crossthwaite et al., 2002). In cardiac myocytes two of the MAPK pathways, JNK and p38 are reported as proapoptotic, whereas ERK pathway is considered antiapoptotic (Aikawa et al., 1997; Turner et al., 1998).

Regarding Aβ, it triggers the JNK/c-jun cascade (Figure 3) producing cell death and increasing the expression of proapoptotic molecules in neurons (Okazawa and Estus, 2002). Therefore, the inhibition of JNK protects PC12 cells against Aβ-mediated cytotoxicity (Troy *et al.*, 2001). The involvement of JNK and p38 pathways in AD has been also demonstrated in an animal model. Thus, both MAPK pathways are activated in the cerebral cortex of a double transgenic mice for mutant APP (Swedish mutations) and mutated presenilin-1 (P264L), which produces a dramatic increase in the production and the consequent aggregation of Aβ (Savage *et al.*, 2002). All these results show that firstly the activation of MAPK pathways rendering apoptosis or protection depends on cell type and the concentration of the prooxidant agent. Secondly, the specific role of ERK1/2 in oxidative stress/AD/CAA is the most controversial but JNK and p38 appears to be directly involved in the cell damage.

On the other hand, oxidative stress produces the activation of redox-sensitive transcription factors, such as nuclear factor-κβ (NF-κβ) (Piette *et al.*, 1997) and activator protein-1 (AP-1) (Lo *et al.*, 1996; Vollgraf *et al.*, 1999) triggering apoptosis or inducing the protection of the cells (Bossy-Wetzel et al., 1997). AP-1 is a protein complex containing Jun and Fos proteins or Jun dimers (Gass and Herdegen, 1995), and the activation of the migration to the nucleus of AP-1 and NF-κβ is mainly controlled by JNK and p38 pathways (Behrens *et al.*, 1999). These mechanisms have been demonstrated to occur under the effect of Aβ in neurons (Kaltschmidt *et al.*, 1997; Mattson *et al.*, 1997), and in vascular cells with different pro-oxidant insults (Yin *et al.*, 2002; Wang *et al.*, 2002; Robbesyn *et al.*, 2003)

8. INTRACELLULAR ANTIOXIDANT DEFENCES

The cellular mechanism of protection against oxidative stress is constituted by different intacellular enzymes, mainly catalase, superoxide

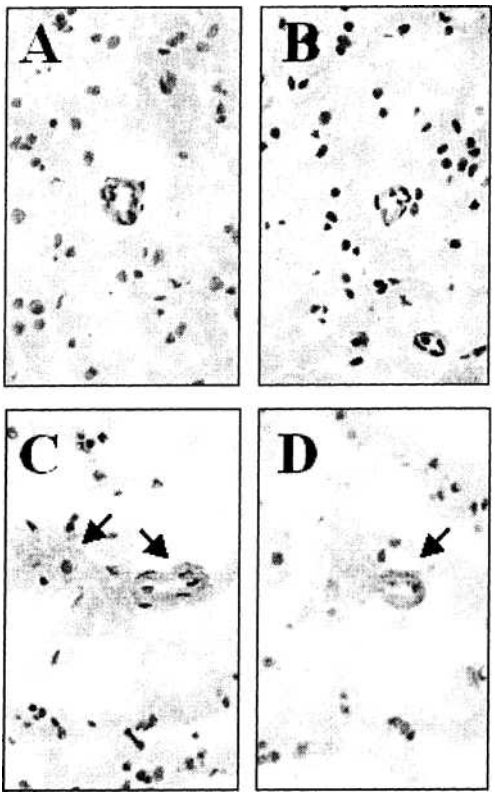

Figure 3. c-jun activation identified by immunohistochemical staining with peroxidase in brain samples from the frontal cortex of control (A, B) and AD patients (C, D) with AD in the VI stage. Asterisks indicate the presence of vessels. Arrows show the positive areas for c-jun activation into the vessels and the brain parenchyma. Positive areas for c-jun correlate with AD brain vessels and their periphery in all the samples analysed from AD patients.

dismutase (SOD), thioredoxin, the peroxiredoxins and the enzymes related to the glutathione (GSH) pathway. GSH is a tripeptide formed by glutamate, glycine and cysteine, and its antioxidant properties depends on the thiol group of the molecule. GSH-peroxidase is considered one of the most important enzymes involved in the hydrolysis of peroxides in the brain. Furthermore, different neuronal cell lines showed resistance against Aβ-mediated cytotoxicity which was directly proportional to the levels of GSH-peroxidase (Calderón *et al.*, 1999). The relevance of the protective role of antioxidants in the vasculature was first evidenced by the observation that Aß-induced endothelial damage is prevented by the enzyme SOD (Thomas *et al.*, 1996; 1997; Crawford *et al.*, 1997). These results are in agreement

with a direct effect of $O_2^{\cdot-}$ in Aβ-mediated cytotoxicity in vascular cells, as it was demonstrated by the measurement of the dihydroethidium fluorescence, an indicator of ROS, in VSMCs and endothelial cells challenged by Aβ (Muñoz *et al.*, 2002).

9. PROTECTION BY ANTIOXIDANT MOLECULES

Antioxidants such as vitamin E, 17β-estradiol or melatonin have demonstrated protective properties on neuronal cells against the Aβ-mediated cytotoxicity (Behl, 2000; 2002; Behl *et al.*, 1992; 1997; Mattson and Goodman, 1995; Pappolla *et al.*, 1997; Bonnefont *et al.*, 1998), (see also Chapter 3). Vitamin E can protect VSMCs and endothelial cells against alcohol, which may induce oxidative stress (Altura and Gebrewold, 1996), and against Aβ-mediated cytotoxicity (Muñoz *et al.*, 2002). Vitamin C, which shares anti-oxidant properties (Podmore *et al.*, 1998), prevents β-amyloid-induced intracellular calcium increase and cell death in PC12 cells (Yallampalli *et al.*, 1998). However other authors have not found any protection with antioxidants such as vitamin E, trolox (a hydrosoluble form of vitamin E), vitamin C or N-acetyl-L-cysteine (NAC) on neuronal cells (Lockhart *et al.*, 1994; Pike *et al.*, 1997). This lack of protection could be due to the experimental procedures. The steroidal hormone 17β-estradiol has also been proposed to play a key role in the prevention or retardation of AD related pathologies, since women treated with estrogen replacement therapy showed a lower prevalence of AD (Tang *et al.*, 1996; Kawas *et al.*, 1997) due to the pleiotropic effects of 17β-estradiol (Behl, 2002).

10. PROTECTION BY VITAMIN E

Vitamin E was discovered by Evans and Bishop in 1922. Vitamin E is a term which includes a group of tocopherols and tocotrienols, both having four isomers (alpha, beta, gamma and delta). The alpha-tocopherol is the most active in humans because of the high affinity of the tocopherol transporter protein (TTP) for this molecule (Hosomi *et al.*, 1997). The relevance of this transporter is shown when there are mutations in the TTP gene. It produces a reduction of alpha-tocopherol in plasma and tissues yielding to ataxia with vitamin E deficiency (Ben Hamida *et al.*, 1993). When considering the vitamin E distribution in brain, there are no specific areas of the brain or spinal cord that are richer in vitamin E than others, however, the uptake of vitamin E is considerably high in the cerebellum (Vatassery, 1992).

Due to the antioxidant and hydrophobic characteristics of vitamin E, it is the main antioxidant present in biological membranes (Perly *et al.*, 1985), preventing lipid peroxidation (Halliwell and Gutteridge, 1984) by trapping the peroxyl radicals (Naiki *et al.*, 1998). Vitamin E has protective properties on neuronal cells against the Aβ-mediated cytotoxicity (Behl *et al.*, 1992). These neuronal protective properties have been demonstrated even in synaptosomas challenged with Aβ (Koppal *et al.*, 1998). Regarding the role of vitamin E on blood vessels (Figure 4), it has been reported that alpha-tocopherol can protect VSMCs and endothelial cells against alcohol (Altura and Gebrewold, 1996) and against Aβ-mediated cytotoxicity even when both types of cells were challenged with the Dutch variant of Aβ, which is more toxic for vascular cells than the wild type Aβ (Muñoz *et al.*, 2002).

The protective effect of vitamin E against oxidative stress is not just due to the free radical scavenging activity of the molecule but also due to the modulation of signalling pathways. In fact, vitamin E has been reported to protect against oxidative stress by decreasing JNK activity and increasing the ERK activity in cardiac myocytes (Qin *et al.*, 2003), and inhibiting caspase-3 activation in vascular endothelial cells (Uemura *et al.*, 2002).

Moreover, in HeLa cells, pretreatment with free radical scavengers NAC, GSH or vitamin E, inhibited JNK pathway activation by prooxidant agents (Kong *et al.*, 1998). Furthermore, the protective roles of vitamin E could also be related to other intracellular effects such as the activation of PP2A, the inhibition of alpha-PKC in VSMCs (Ricciarelli *et al.*, 1998), the inhibition of the production of eicosanoids (Pratico *et al.*, 1998; Jialial *et al.*, 2001; Lee *et al.*, 1999) or the inhibition of inducible NO synthase (iNOS) (Badger *et al.*, 2000; Guan *et al.*, 1998) which leads to a decrease in the protein peroxynitration. On the other hand, vitamin E protects neurons and vascular cells against oxidative cell death *in vitro* by the activation of NF-κß (Behl, 2000; Li-Weber *et al.*, 2002). Alpha-tocopherol also induces the expression of connective tissue growth factor (CTGF) in VSMCs in a PKC-independent pathway (Villacorta *et al.*, 2003) and increases the synthesis of alpha-tropomyosin in VSMCs (Aratri *et al.*, 1999), suggesting an improvement in the VSMC function in the vessels. Moreover, vitamin E can be a vasodilatatory agent since thrombin-mediated PKC activation and endothelin secretion are inhibited by alpha-tocopherol in endothelial cells (Martin-Nizard *et al.*, 1998). A clinical trial confirmed the positive role of vitamin E in preventing AD in ageing people (Sano *et al.*, 1997). There are also reports suggesting that use of high vitamin E and vitamin C supplements may decrease the risk of AD (Morris *et al.*, 1998). Other studies suggest that vitamin E could be also protective in vascular disease (*reviewed by*

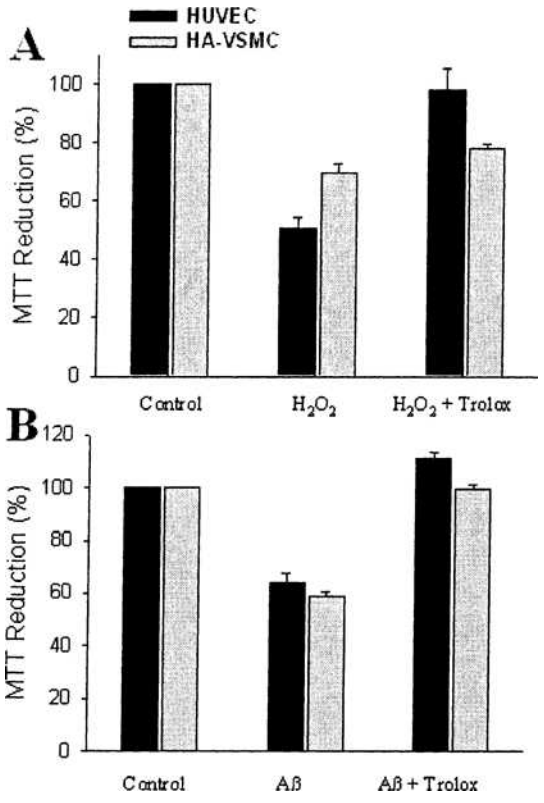

Figure 4. The water-soluble analogue of Vitamin E (Trolox) protects human umbilical vein endothelial cells (HUVEC) and human aortic vascular smooth muscle cells (HA-VSMC) from H_2O_2 and Dutch $A\beta_{1-40}$ fibrils cytotoxicity. Representative experiments were performed in quadruplicate. Cells were challenged with 4 μM H_2O_2 in HUVEC and 50 μM H_2O_2 in HA-VSMCs (A), and 0.25 μM Aβ in HUVEC and 0.125 μM Aβ in HA-VSMCs (B). For the protection studies, cells were treated with 500 μM Trolox. Cell viability was evaluated by MTT reduction after 24h of incubation. Control cells were assumed to have 100% of viability.

Steinberg, 1995; Gotto, 2003). In addition, there are experimental data demonstrating that treatment with antioxidants such as idebenone and alpha-tocopherol prevents learning and memory deficits caused by Aβ in rats (Yamada *et al.*, 1999). Furthermore, decreasing serum levels of vitamin E were associated with poor memory performance in older people (Perkins *et al.*, 1999), however this effect was not found in rats (Ichitani *et al.*, 1992).

11. CONCLUSIONS

Oxidative stress is directly involved in Aβ-mediated cytotoxicity. Thus, free radical scavengers and antioxidants are considered key pharmacological tools against AD and CAA. Vascular damage produced by Aβ and prooxidant agents can also be decreased or avoid by vitamin E. These findings suggest that vitamin E is a good biological cytoprotective agent, but more work is needed to elucidate all the intracellular mechanism triggered by vitamin E and the changes in the expression of specific protective genes such antiapoptotic molecules. Moreover, considering that Aβ production has been related directly with oxidative stress, vitamin E could prevent the triggering of AD by decreasing the production of Aβ in vascular cells.

ACKNOWLEDGEMENTS

We acknowledge Dr. Elena Hidalgo and Dr. Miguel A. Valverde for the very fruitful critical suggestions on the manuscript. This work was supported by grants from FIS (Ministerio de Sanidad, Spain; grant nº 01-1029; and Red HERACLES) and Fundación Domingo Martínez. We also thank the Banc de Teixits Neurologics, Universitat de Barcelona-Hospital Clínic for providing brain samples.

Abbreviations: AD, Alzheimer's disease; AGEs, advanced glycation end products; AP-1, activator protein-1; APP, amyloid precursor protein; Aß, amyloid ß-peptide; CAA, cerebral amyloid angiopathy; CREB, c-AMP response element binding protein; CTGF, connective tissue growth factor; ERK, extracellular signal-regulated kinase; GSH, glutathione; HCHWA-D, hereditary cerebral haemorrhage with amyloidosis of the Dutch type; iNOS, inducible NO synthase; JNK, c-Jun NH_2-terminal protein kinase; MPAKs, mitogen-activated protein kinases; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NAC, N-acetyl-L-cysteine; NF-κβ, nuclear factor-κβ; NO, nitric oxide; PI-3K, phosphatidylinositol-3-kinase; ROS, radical oxygen species; SOD, superoxide dismutase; TTP, tocopherol transporter protein; VSMCs, vascular smooth muscle cells.

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