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Apolipoprotein E genotype, vitamin E, and Alzheimer's disease prevention

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Summary

Alzheimer's disease (AD) is a multi-causal neurodegenerative disorder and the most common form of dementia in the elderly. Although extensively investigated, the exact underlying molecular and cellular mechanisms of AD remain to be fully elucidated. Amongst other factors, AD may be associated with increased oxidative stress and chronic inflammation. Although dietary antioxidants, in particular vitamin E, have been related to a reduction of AD risk, data from clinical studies are still contradictory. Aside from increasing age, one key risk factor for sporadic AD is the apolipoprotein E4 genotype. As major component of lipoproteins the apolipoprotein E (apoE) is of crucial importance in the distribution of cholesterol and lipids within the brain and thus, involved in neuronal membrane repair mechanisms. However, apoE4 has been associated with several altered cellular features including an impaired neuronal repair function and a higher neuronal vulnerability towards oxidative insults leading to an increased AD risk. In this context, the role of antioxidant supplementation as a primary prevention strategy for subjects at high risk including carriers of the *apoε4* allele, is discussed.

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder of the elderly and the most frequent cause of dementia during aging in Western countries. Every year 250,000 new AD patients are confirmed in Germany. Prevalence of AD increases with age from 0.4% at <65 years of age to 10% at >65 years of age. Only a small percentage of the AD cases exhibits a familial trait with an early disease onset (<65 years of age), more than 90% of the patients develop a sporadic form (Laws et al., 2003). The progressive disorder is characterised by massive neuronal loss in specific brain regions important for cognition and memory such as the hippocampus and parts of the cortex. Histopathological hallmarks of the AD are extracellular depositions containing amyloid β (Aβ) peptides and intracellular neurofibrillary tangles (NFT) of the hyperphosphorylated tau protein. A profile of cellular abnormalities occurs in AD including oxidative stress, mitochondrial dysfunction and impaired regulation of cellular calcium homeostasis (Mattson, 2000). Furthermore, AD brains exhibit profound loss of synapses, microglial activation and inflammatory processes (Pratico and Trojanowski, 2000; Selkoe, 2002).

The amyloid precursor protein (APP) is considered to play a central role in the AD pathology corroborated by the fact that autosomal dominant inherited forms of the Alzheimer's dementia are mainly caused by mutations of three genes including *APP* and *presenilines-1/2* (*PS-1* and *PS-2*), which are involved in APP processing. The transmembrane glycoprotein APP comprises a large extracellular C-terminal domain, a membrane-spanning domain and an intracellular N-terminus (Gralle and Ferreira, 2007). Major consequences for AD pathology arise from the amyloid β sequence, which is located partly in the extracellular and the trans-membrane domain of APP.

Proteolytic activity of enzymes called β- and γ-secretase (see Fig. 1) contributes to the release of the toxic Aβ fragment whereas α-secretase cleavage hinders Aβ production (Haass et al., 1992). The secreted Aβ peptides are hydrophobic and form insoluble fibrils that aggregate and accumulate in the extracellular matrix as amyloid plaques. The main Aβ species consist of 40 to 42 amino acids with the 42 amino acid form being deposited first (Iwatsubo et al., 1994).

Amyloid plaques are supposed to produce reactive oxygen species and thereby injuring surrounding neuronal membranes and initiating neurite degeneration (Hensley et al., 1995). The association of amyloid plaques with astrocytes and activated microglia induce cytokine production and inflammatory processes (Selkoe, 1999). Thus, occurrence of amyloid plaques is accompanied by chronic inflammatory burden which may in turn contribute to neuronal degeneration.

Apolipoprotein E

Apolipoprotein E (apoE) is one of the different classes of apolipoproteins in the body and is a main regulator of cholesterol transport.

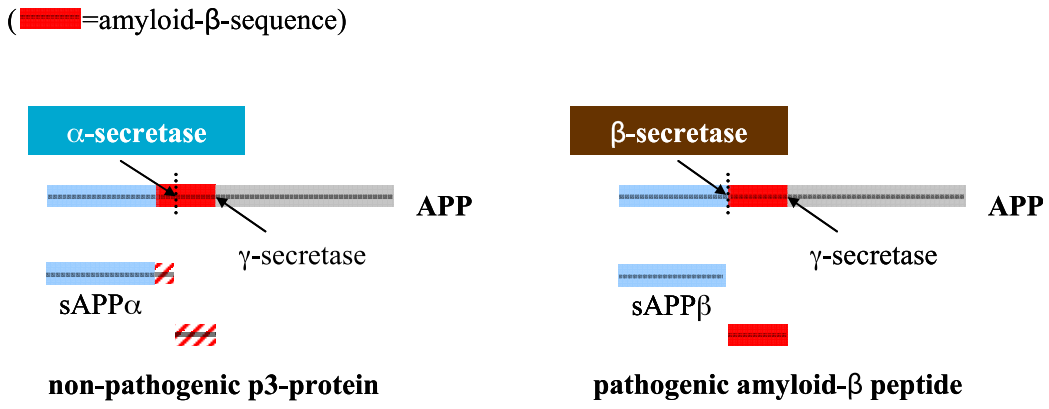


Fig. 1: Scheme of the alternative cleavage pathways of the transmembrane protein amyloid precursor protein (APP) by either α-secretase (non-amyloidogenic) or β-secretase (amyloidogenic).

Several tissues synthesize apoE and of these, the liver and the brain are major sites of apoE expression. Moreover, besides apoJ, apoE is the major apolipoprotein in the brain suggesting its primary role in the central nervous system. ApoE is considered to distribute cholesterol from astrocytes to neurons based on the fact that astrocytes are the main source of apoE and cholesterol in the brain whereas neurons express receptors to endocytose apoE and cholesterol from lipoproteins (LAWS et al., 2003). Nevertheless, a part of activated microglia and many neurons have been shown to express apoE in response to injury (XU et al., 2006) suggesting that apoE may play a pivotal role in inflammatory and repair processes in the brain.

The apoE gene is subjected to numerous single nucleotide polymorphisms and the common polymorphism gives rise to three apoE genotypes, apoE2, apoE3 and apoE4. From these arise three homozygous (E2/2, E3/3, E4/4) and three heterozygous (E2/3, E3/4, E2/4) phenotypes with different distribution throughout population and different susceptibility towards AD progression. ApoE allelic distribution varies worldwide, but the *apoε3* allele is always the most abundant. In a selected German population allelic distribution was reported to be 8.1% for *ε2*, 78.2% for *ε3* and 13.6% for *ε4* (SINGH et al., 2006).

Tab. 1: ApoE genotype frequency in the general population (USA) and in AD-patients (according to RABER et al., 2004).

apoE genotype	population	AD
ε2/ε2	1 %	0.1 %
ε2/ε3	12 %	4 %
ε3/ε3	60 %	35 %
ε3/ε4	21 %	42 %
ε4/ε4	2 %	16 %

The frequency of individual phenotypes is shifted in AD patients compared to general population, whereby frequency of the E3/4 phenotype increases to 42% (from 21% in general) and of the E4/4 genotype to 16% (from 2% in general) (RABER et al., 2004). Thus, *apoε4* allelic frequency has been reported to increase from approximately 14% in the control population to around 40% in the AD population (POIRIER et al., 1993) and age of disease onset is decreased in association with apoE4 (LOCKE et al., 1995). In addition, there is also an apparent gene dosage effect according to the number of the *apoε4* alleles. Thus, the risk for AD rises from 20% when no *apoε4* allele is present to 90% when two copies of the *apoε4* allele are present in 42 families with late onset AD (CORDER et al., 1993). On the other side, it has been shown that the *apoε2* allele is associated with a delayed age of onset, and in addition, the *ε2* allele is under-represented in AD compared to control population (POIRIER et al., 1993). From these findings it was proposed that the *ε4* allele increases AD risk whereas the *ε2* allele of the apoE gene has a protective effect against the development of AD.

The apoE protein contains 299 amino acids and has a mass of approximately 34 kDa. The primary structure of the three common isoforms varies at two sites of the protein: 112 and 158. ApoE2 has two cystein and apoE4 two arginine residues at these positions whereas apoE3 has a cystein at position 112 and an arginine residue at position 158. In apoE2, cystein at position 158 results in less effective binding to the LDL receptor family and type III hyperlipoproteinaemia, a lipid disorder characterised by increased plasma level of triglycerides and cholesterol (MAHLEY et al., 2006). In apoE4, the arginine residue at position 112 causes a domain interaction which is associated with reduced protein stability and different lipoprotein preferences compared to apoE3 and E2. Due to the conformational difference, apoE4 favours to bind to large lower-density lipoproteins, VLDL and LDL, whereas apoE3 and E2 prefer smaller, cholesterol-rich particles, HDL (HATTERS et al., 2006). This contributes to differences in lipoprotein metabolism and thus, total cholesterol and LDL cholesterol levels are elevated in *apoε4* carriers. Due to higher remnant catabolism, the LDL receptors were supposed to be down regulated thereby increasing LDL level in *apoε4* carriers (MAHLEY and RALL, 2000). On that account, apoE4 was associated with an increased risk for cardiovascular disease but more evident seems to be the involvement of apoE4 in neurodegenerative processes.

ApoE and neurodegeneration

Several cellular features in the brain seem to be altered in the apoE4 as compared to the apoE3 genotype (see Fig. 2). Due to the limited ability of neurons to regenerate, the maintenance of synaptic function is of crucial importance. Specific brain areas such as the hippocampus are able to induce formation of presynaptic extensions, and this process of compensatory synaptogenesis is accompanied by increased apoE expression. Thus, synaptic repair is a key function of apoE and it has been reported to be impaired in *apoε4* carriers (POIRIER, 1994).

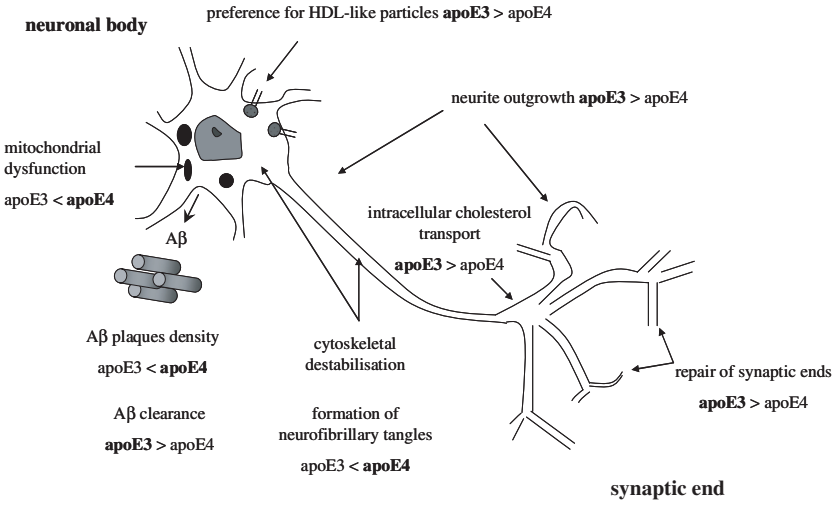


Fig. 2: Role of apoE3 and apoE4 in neuronal functions.

In the cerebrospinal fluid cholesterol and lipids are transported in small high-density lipoprotein-like particles (LADU et al., 2000) and thereby can be delivered to sites of injury for repair of cells and synaptic ends. As the preference of apoE4 is lower for high-density than for low-density lipoproteins and apoE4 containing lipoprotein remnant catabolism is increased in relation to apoE3, insufficient neuronal uptake and intracellular cholesterol transfer may be likely to account for impaired neuronal membrane repair in the apoE4 genotype. In this regard apoE4 compared to apoE3 has been shown to inhibit neurite outgrowth (BELLOSTA et al., 1995; HOLTZMAN et al., 1995). Further information on the impact of the apoE genotype are gained from transgenic mouse models, where apoE4 has been reported to be associated with a smaller number of presynaptic ends, a higher plaque density and increased degree of tau phosphorylation. Moreover, memory, cognitive performance and synaptic plasticity are impaired in the apoE4 genotype (RABER et al., 2000; MAHLEY et al., 2006).

As mentioned above, the production and accumulation of amyloid β are major cornerstones in the pathogenesis of AD. In this context, decreased clearance and increased deposition of Aβ in the apoE4 genotype contribute to the detrimental impact of apoE4 compared to apoE3 in AD progression. Furthermore, the apoE4 isoform has been shown to enhance Aβ production *in vitro* and this effect has been attributed to mediation through the domain interaction caused by the arginine residue at position 112 (YE et al., 2005). In transgenic mice with human apoE3 or apoE4 replacing murine apoE in the mouse genome it has been demonstrated that alpha-secretase expression is decreased in apoE4 compared to apoE3 mice (Fig. 3) suggesting a shift from the non-amyloidogenic to the amyloidogenic cleavage pathway in relation to the apoE genotype (HUEBBE et al., 2007b).

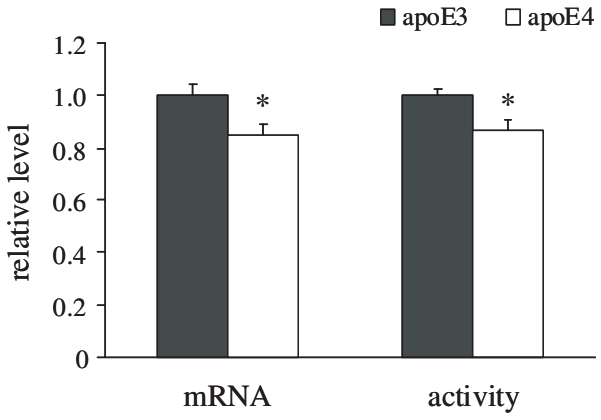


Fig. 3: Relative mRNA and activity level of non-amyloidogenic α-secretase in the brain of apoE3 and apoE4 transgenic mice. * indicates a significant ($p<0.05$) apoE4 genotype dependent effect compared to apoE3. (According to HUEBBE et al., 2007b).

Besides all, cognitive impairment and functional brain abnormalities related to apoE4 have been found also in non-demented subjects (BAXTER et al., 2003; CASELLI et al., 2004; REIMAN et al., 2004) suggesting a global effect of the apoE genotype on brain function prior to the onset of AD symptoms. Thus, mitochondrial dysfunction associated with AD has been observed to be more pronounced in apoE4 subjects (GIBSON et al., 2000) and disruption of mitochondrial regulation of energy and glucose metabolism in neurons has been shown in both healthy and demented *apoε4* carriers (SMALL et al., 1995). Due to the lower apoE4 protein stability, increased formation of apoE4 fragments has been supposed to interact with the cytoskeletal components and to induce formation of neurofibrillary tangles (HUANG et al., 2001). Mitochondrial and cytoskeletal alterations caused by apoE4 fragments are assumed to be key mechanisms for the Aβ-independent neuropathology involving apoE4 (MAHLEY et al., 2006).

While many aspects of the apoE4-AD association have been discussed lately, one of the first putative mechanisms was supposed to be the apoE allele-specific antioxidant activity. The apoE4 isoform has been shown to protect neuronal cells *in vitro* against oxidative insults to a lesser extent than apoE3 (Fig. 4), whereas apoE2 exhibited most protection (MIYATA and SMITH, 1996; HUEBBE et al., 2007a). Moreover, in stably transfected macrophages the apoE4 relative to the apoE3 genotype increases the production of superoxides, a prominent member of reactive oxygen species (JOFRE-MONSENY et al., 2007a).

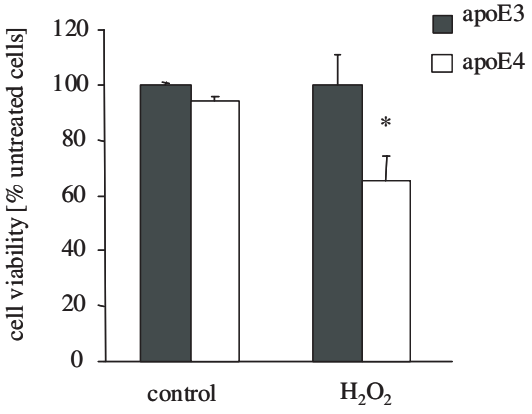
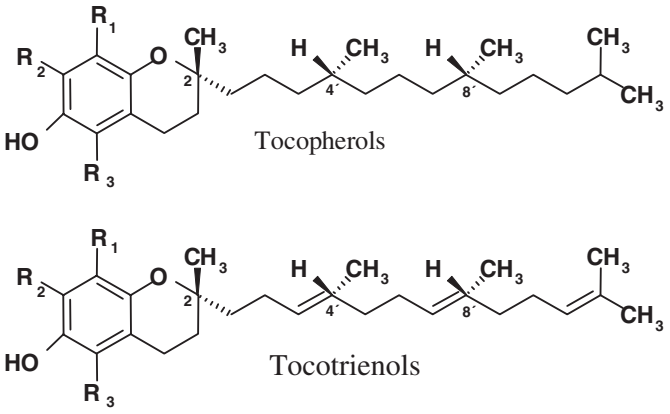


Fig. 4: Effect of apoE3 and apoE4 conditioned media on neuronal cell viability following hydrogen peroxide challenge. * indicates a significant difference between apoE3- and apoE4-cultured cells. (According to HUEBBE et al., 2007a).

Oxidative stress is linked to inflammatory processes and increased innate immune activity in the brain. Importantly, activation of immune response including production of pro-inflammatory cytokines is higher in apoE4-macrophages (JOFRE-MONSENY et al., 2007b) and apoE4-microglia (MAEZAWA et al., 2006a) compared to the apoE3 genotype. Neurotoxicity mediated by activated microglia, cells mediating the innate immune response in the brain similar to macrophages, is more pronounced in apoE4 than apoE3 transgenic mice (MAEZAWA et al., 2006b). Moreover, production of anti-inflammatory mediators such as interleukin-10 is lower in the apoE4 compared to the apoE3 genotype (JOFRE-MONSENY et al., 2007b).

Vitamin E

As alterations in the oxidant/antioxidant balance are considered a primary feature of AD the lower antioxidant activity of apoE4 may be associated with a higher requirement of dietary antioxidants in *apoε4* carriers (DREON and PEROUTKAL, 2001). In this regard, vitamin E is of particular interest since it is the major lipid soluble antioxidant in the human body. Vitamin E is the most effective chain-breaking antioxidant in biological membranes, where it contributes to membrane stabilisation and protection of functional molecules and cellular structures against damage from free radicals (MEYDANI, 1995). Furthermore, vitamin E is especially suitable to improve antioxidant status in the brain by easily crossing the blood-brain-barrier. Vitamin E is a generic term used to describe at least four forms of (α-, γ-, β-, δ-) tocopherols and tocotrienols (Fig. 5), which exhibit the biological functions in varying activity (RIMBACH et al., 2002). Compared to the other tocopherols α-tocopherol is preferentially incorporated into lipoproteins and secreted into the plasma facilitated by the α-tocopherol transfer protein (α-TTP) (BRIGELIUS-FLOHE and TRABER, 1999). Furthermore, hepatic degradation of vitamin E to the corresponding



	R_1	R_2	R_3
α-	CH_3	CH_3	CH_3
β-	CH_3	H	CH_3
γ-	H	CH_3	CH_3
δ-	H	H	CH_3

Fig. 5: Molecular structure of vitamin E stereoisomers.

water-soluble hydroxychromans is shifted to favour of non-α-vitamin E forms (SONTAG and PARKER, 2002). However, *in vitro*, in contrast to α-tocopherol, γ-tocopherol is suggested to act as a trap for membrane-soluble electrophilic reactive nitrogen species (CHRISTEN et al., 1997). Furthermore, tocotrienols are supposed to posses neuroprotective properties at a much lower concentration than α-tocopherol and may exhibit cholesterol lowering properties *in vitro* and *in vivo* (PACKER et al., 2001).

A number of cell culture and animal studies using models of neurodegeneration have suggested a protective role for vitamin E in the reduction of oxidative damage, glycation and amyloid beta toxicity (USUKI et al., 2001). The symptoms of vitamin E deficiency in alpha-tocopherol transfer protein (α-TTP) knock-out mice include neurological impairment, ataxia and dysfunctional reflexes accompanied by increased oxidative damage in the brain tissue. Vitamin E supplementation has been shown to decrease oxidative damage and prevent neurodegeneration in TTP knock out mice (YOKOTA et al., 2001). In our own studies pre-incubation of neuronal cells with different vitamin E forms exhibited significant protection against peroxide-induced cell death (Fig. 6).

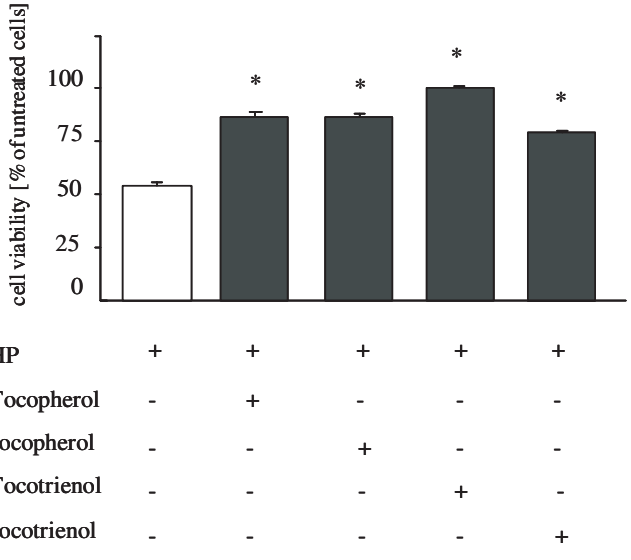


Fig. 6: Protective effects of a pre-incubation of neuronal cells with different vitamin E forms against peroxide induced cell death (*tert* butyl hydroperoxide, tBHP). *indicates significant ($p<0.001$) effects of a vitamin E pre-treatment on neuronal viability (according to HUEBBE et al., 2007a).

Evidence of a role for vitamin E in protecting against the onset of AD and its progression in humans is based largely on epidemiological data, where lower plasma, brain and cerebrospinal fluid (CSF) vitamin E levels were detected in AD patients relative to matched control groups (TOHGI et al., 1994; GRUNDMAN and DELANEY, 2002; RINALDI et al., 2003). Morris and co-workers observed a lower rate of development of AD in individuals who regularly consumed vitamin E supplements relative to the non-supplement users in a 4 year prospective study of non-AD elderly participants at baseline (MORRIS et al., 2002). Additionally, *in vitro* studies support a potential role for vitamin E in AD prevention (HALKS-MILLER et al., 1986; BEHL et al., 1992; LUCHSINGER and MAYEUX, 2004; HUEBBE et al., 2007a). However, only one clinical trial in subjects with established AD suggested that a high dose vitamin E supplementation (2000 IU/d) delayed disease progression (SANO et al., 1997). On the other hand, there have been several contradictory clinical studies showing no benefit from vitamin E supplementation (1000-2000 IU/d) in AD patients (KLATTE et al., 2003; FILLENBAUM et al., 2005; PETERSEN et al., 2005).

Albeit the discussion whether high dietary vitamin E intake is beneficial or not, the molecular mechanisms of potential protective effects remain poorly understood. Whereas beneficial effects of vitamin E may be partly attributable to its antioxidant activity, thereby reducing oxidative modification within the neuronal cell, it is likely that vitamin E also mediates its biological role through non-antioxidant molecular targets in the brain tissue. The first observations of a cell signalling role for vitamin E were made in 1991 by Azzi and co-workers (BOSCOBOINIK et al., 1991) who demonstrated that vitamin E inhibited protein kinase C activity and cell proliferation in cultured cells.

Advances in microarray technology have allowed us to investigate genes differentially expressed in various tissues including liver (BARELLA et al., 2004; RIMBACH et al., 2004), testes (ROTA et al., 2004), prostate (SILER et al., 2004), cortex (GOHIL et al., 2003), hippocampus (ROTA et al., 2005) and total brain homogenates (ROY et al., 2002) in response to vitamin E deficiency thereby offering the possibility of more insight into the molecular functions of vitamin E. In this context, several AD related genes have been identified to be regulated by dietary alpha-tocopherol. In particular, vitamin E strongly affected a number of genes that were associated with hormone activities and hormone metabolism, nerve growth factor, apoptosis, dopaminergic neurotransmission, and clearance of amyloid beta (Aβ) and advanced glycated end products (AGE) (ROTA et al., 2005). These data demonstrate that vitamin E *in vivo* may affect the expression of an array of genes encoding for proteins directly or indirectly involved in the prevention of AD pathogenesis.

ApoE genotype and dietary vitamin E

As the complexity of pathological cellular features contributes to the lack of therapeutic success and the prevention of AD is being more and more of primary importance the identification of subjects at high AD risk is required most. Accordingly, the apoE genotype as well as lifestyle and dietary factors have been discussed as determinants of AD disease risk. It is of considerable interest if one's risk for AD may be reduced by preventive strategies similar to those that reduce the risk of cardiovascular disease (MATTSON, 2004). Interestingly, it has been shown that the apoE4 genotype enhances adverse effects of cigarette smoking on cardiovascular disease risk (HUMPHRIES et al., 2001) and that *apoε4* carriers benefit to a certain extent from dietary antioxidant supplementation as far as inflammatory gene expression is concerned (MAJEWICZ et al., 2005).

Recent studies suggest that vitamin E metabolism is different in apoE4 to non-apoE4 subjects (PROTEGGENTE et al., 2006) indicating a lower peripheral α-tocopherol concentration in *apoε4* carriers due to increased retention of vitamin E in plasma (LODGE et al., 2004). Furthermore, in our own studies lower α-tocopherol concentrations were evident in tissues of apoE4 compared to apoE3 mice with the highest difference in the lung, whereas plasma α-tocopherol tended to be higher in the apoE4 as compared to the apoE3 genotype. We hypothesize that the vitamin E uptake from circulating low-density and high-density lipoproteins via lipoprotein receptors is affected by the apoE genotype (JOFRE-MONSENY, 2007). Mas and co-workers (2006) proposed that the apoE4 genotype is associated with a functional vitamin E deficiency in the brain due to an impaired delivery of this antioxidant to the neuronal tissue (MAS et al., 2006).

In consequence, the benefit of a dietary vitamin E supplementation may partly depend on the apoE genotype. In a prospective study, Morris and co-workers observed a positive association of vitamin E and the lower risk of AD only among individuals who were non *apoε4* carriers (MORRIS et al., 2002). On that account, supplementation of *apoε4* carriers with vitamin E as suggested by DREON and PEROUTKAL (2001) to reduce the risk for AD is still an open issue. Furthermore, systematic investigations on the peripheral vitamin E metabolism in relation to the apoE genotype are needed.

Acknowledgments

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