Age- and genotype-related neurophysiologic reactivity to oxidative stress in healthy adults

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Abstract

The epsilon4 allele of the apolipoprotein E gene (ApoE), as well as aging increase the risk of Alzheimer’s and vascular diseases. Electroencephalogram (EEG) reactivity to hyperventilation (HV) depends on hypocapnia-induced cerebral vasoconstriction, which may be impaired in subjects with subclinical cerebrovascular disease. Quantitative EEG at rest and under 3-minute HV was examined in 125 healthy subjects divided into younger (age range 28–50) and older (age range 51–82) cohorts and stratified by ApoE genotype. The younger ApoE-epsilon4 carriers had excessive EEG reactivity to HV characterized by the manifestation of high-voltage delta, theta activity and sharp waves, and larger HV-induced changes in EEG relative powers than in the younger ApoE-epsilon4 noncarriers. EEG reactivity to HV decreased with aging, and in the ApoE-epsilon4 carriers the decrease was more pronounced than in the ApoE-epsilon4 noncarriers. The older ApoE-epsilon4 carriers had smaller HV-induced changes in EEG relative powers than the older ApoE-epsilon4 noncarriers. A marked decline of EEG reactivity to HV in the older ApoE-epsilon4 carriers suggests the possible impact of vascular factors on the pathogenesis of ApoE-induced Alzheimer disease.

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Keywords: EEG; Apolipoprotein E; Hyperventilation; Hypocapnia; Oxidative stress; Alzheimer’s disease; Cerebrovascular disease; Aging

1. Introduction

Alzheimer’s disease (AD) is a progressive degenerative dementia of late life with a complex etiology resulting from genetic and environmental factors (Ertekin-Taner, 2007). Mutations in amyloid precursor protein, presenilin 1, and presenilin 2 genes are causative factors for familial AD (Goate et al., 1991; Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995). A common polymorphism in apolipoprotein E (ApoE) located on chromosome 19 has been established as the most common genetic risk factor for AD in Caucasian ethnic groups including the Russian population (Farrer et al., 1997; Korovaitseva et al., 1997; Rogaev, 1999; Saunders et al., 1993; Schmechel et al., 1993).

The ε4 allele of the ApoE gene is strongly associated with AD and is, at the same time, a risk factor for vascular diseases (Rogaev, 1999; Saunders et al., 1993; Schneider et al., 2005). ApoE is a major apolipoprotein in the brain, mediating the transport and clearance of lipids and amyloid-β (Aβ) peptide. The ApoE ε4 allele is
related to Aβ depositions in the brain—a cardinal neuropathological feature of AD—as well as to serum lipid profiles, particularly cholesterol, atherosclerosis, and increased thickness of large arteries (Eichner et al., 2002). The ApoE ε4 allele increases the odds of chronic cerebral infarction detected at autopsy in older persons (Schneider et al., 2005).

AD pathogenesis may start many years, and even decades, before the development of AD symptoms (Arai et al., 1999; Braak and Braak, 1997; Ghebremedhin et al., 1998; Reiman et al., 2004). Quantitative analysis of electroencephalogram (EEG) has predictive value in estimating future AD development in normal elderly subjects (Prichep et al., 2006; Van der Hiele et al., 2008). EEG parameters were reported to be associated with ApoE genotype in patients with AD and mild cognitive impairment (MCI), which is considered to be a prodromic stage of AD (Babiloni et al., 2006; Jelic et al., 1997; Pomareeva et al., 2008). A magnetoencephalography study demonstrated ApoE-related differences in young healthy adults (Filbey et al., 2006).

We previously found that cognitively normal relatives of AD patients carrying the ApoE ε4 allele in their third and fourth decades of life have abnormal EEG reactivity to hyperventilation (HV) characterized by the manifestation of synchronous high-voltage delta and theta activity and sharp waves (Pomareeva et al., 2008). HV exerts multiple effects on the brain, mediated by the physiological reflex response to hypocapnia. The reflex is controlled at least in part by cholinergic mechanisms of the ventral medulla and basal forebrain (Nattie, 1999; Shao and Feldman, 2009), and implies influence on ventilation, cerebral circulation, and arousal (Battaglia, 2002; Daulatzai, 2010; Millhorn and Eldridge, 1986). Carbon dioxide is an important component of acid-base and free radical chain reactions, and various physiological effects of HV are related to oxidative stress (Dean et al., 2004; Veselá and Wilhelm, 2002). EEG changes under HV are due to hypocapnia-induced cerebral vasoconstriction, respiratory alkalosis, and enhanced neuronal excitability in widely distributed networks, and the differences in EEG reactivity to HV depend both on nervous and vascular factors (Mäkiranta, 2004; Sparing et al., 2007; Zenkov, 2002).

EEG reactivity to HV may be impaired in subjects with subclinical cerebrovascular disease as well as in AD-related pathology, including alterations in brain cholinergic systems (Silvestrini et al., 2006; Xie et al., 2006), that were found to be associated with the ApoE ε4 allele (Arai et al., 1999; Cohen et al., 2006).

Aging is the strongest known risk factor for AD and vascular pathology, particularly in ApoE ε4 allele carriers. However, the aging effect of EEG reactivity to HV in relation to ApoE genotype has not been investigated.

The aim of this study was to determine whether the changes of EEG reactivity to HV in normal aging depend on the ApoE genotype.

2. Methods

2.1. Participants

The enrolled cohort included 125 healthy individuals (31 men and 94 women, age range 28–81 years). All subjects were of Russian origin from Moscow and the Moscow region. They underwent neurological examination and cognitive screening. The recruited subjects were free of dementia and other medical, psychiatric, and neurological conditions, including cerebrovascular diseases, hypertension, epilepsy, and endogenous disorders. Exclusion criteria included a history of neurological and psychiatric diseases and any kind of memory impairment. Subjects were evaluated with the Clinical Dementia Rating scale (CDR) (Hughes et al., 1982), and only Clinical Dementia Rating scale 0 cases were included in the study.

Informed written consent was obtained from all participants included in the study. The experimental protocol of this study was approved by the local Ethics Committee.

All subjects were divided into subgroups according to ApoE polymorphism. The ApoE ε4+ subgroups consisted of subjects with at least 1 ApoE ε4 allele and the ApoE ε4− subgroups included the subjects with ε3/ε3 genotype.

As our previous studies showed, the frequency of ε4 ApoE genotype in Russians, and in the Moscow population specifically, is relatively low (approximately 0.12) (Borinskaia et al., 2007; Rogaev, 1999). In follow-up ApoE genotyping of a cohort of nondemented individuals we recruited the relatively equal number of subjects with ApoE ε4− and ApoE ε4+ genotypes, including 60 subjects with ε4+ genotype (14 men, 46 women, mean age 49.7 ± 1.5) and 65 subjects with ε3/ε3-genotype (17 men, 48 women, mean age 50.9 ± 1.6). Subjects with ε2 ApoE allele were excluded from the study.

The participants were divided into cohorts: younger and older than 50 years of age. All of the ApoE ε4− subjects had the ε3/ε3 genotype. Thirty-four of the 36 younger ApoE ε4+ subjects had the ε4/ε3 genotype and 2 had the ε4/ε4+ genotype. All of the 24 older ApoE ε4+ subjects had ε3/ε4 genotype. The demographic characteristics of participants are presented in Table 1.

There was no difference in age, sex, level of education, or smoking prevalence between the younger ApoE ε4− and ApoE ε4+ subjects as well as between the older ApoE ε4− and ApoE ε4+ individuals.

2.2. Procedure

During the experiments, the subjects sat comfortably in a chair. They were asked to close their eyes and to relax during the recording. The technician watched the subject’s vigilance state continuously by monitoring the EEG and observing the subject. The first period was 3 minutes of resting. After that, the 3-minute HV period
was introduced by an experimenter. Under HV, the depth of breathing increased to approximately 2 times that of the resting period; the frequency of ventilation was maintained at 18 – 20 per minute. The effectiveness of HV was verified by measuring the end-tidal CO₂, which was reduced during HV to about 28 mm Hg. Before the start of each experimental session, the subjects practiced for several minutes and adjusted themselves to the breathing method. The time between the breathing practice period and the first resting EEG recording was at least 15 minutes or longer. This minimal interval was sufficient to return to baseline.

2.3. EEG recording

The registration and evaluation of EEG has been carried out in accordance with the International Pharmaco-EEG Society (IPEG) guidelines (Versavel et al., 1995). EEGs were recorded during resting and during 3 minutes of HV. EEG was recorded on Nihon Kohden 4217 G EEG using the time constant of 0.3 seconds, and the high frequency cut-off was 45 Hz. The 16 Ag/AgCl electrodes were placed according to the international 10–20 system at O2, O1, P4, P3, C4, C3, F4, F3, Fp2, Fp1, T6, T5, T4, T3, F8, and F7 positions. Linked ears served as the reference. Electrode impedance did not exceed 10 kΩ. During the recording, 180 seconds of EEG in resting conditions and 120 seconds of EEG under HV (second and third minutes under HV) were simultaneously sampled at 256 Hz per channel and stored on a computer for further analysis off-line. The EEG was reviewed visually for artifacts. Periods of artifact were eliminated from subsequent analysis. After the elimination of artifacts, the last segments of EEG under HV and at rest, each one at a duration of 60 seconds, were selected for further analysis.

2.3. Data analysis

The EEG data were gathered under 2 different conditions: resting with eyes closed and HV with eyes closed. The details of the spectral analysis procedures have been previously described (Ponomareva et al., 2008).

2.4. Genetic analysis

Venous blood samples were drawn and DNA was isolated from leukocytes by the phenol-chloroform method. Apolipoprotein E genotyping was performed by polymerase chain reaction and subsequent HgaII-DNA restriction analysis in polyacrilamide gel (Farrer et al., 1997; Rogaev, 1999).

2.5. Statistical analysis

EEG parameters from each group were tested for the normal distribution by the Wilk-Shapiro test, and in no cases were the data skewed. The significance of the differences between the log-transformed EEG parameters was estimated using analysis of variance with ApoE (e4+ vs. e4−) or age cohort (older vs. younger) as the between-subjects factor, and condition (HV vs. resting) as a repeated measures factor. The significance of the differences between the groups (e4+ versus e4−) in the
number of subjects with synchronous high-voltage delta and theta activity and sharp waves, revealed by visual inspection of the HV EEG recordings, were estimated using the Fisher exact test as described previously (Ponomareva et al., 2008). The Pearson correlation coefficient was calculated between EEG relative powers and age of subjects in the ApoE ε4− and ApoE ε4+ groups.

Demographic scores of the ApoE ε4+ younger, ApoE ε4− younger, ApoE ε4+ older, and ApoE ε4− older individuals were compared with analysis of variance in cases of normal distribution (age, height, education) or Mann-Whitney U test (smoking prevalence).

Pearson correlations were conducted between EEG relative powers and demographic variables (age, height, education) in the ApoE ε4− and ApoE ε4+ groups. Spearman rank correlation was applied to compute the correlation between EEG relative power and smoking prevalence.

Significance levels were set at $P \leq 0.01$ to allow for multiple testing, and values of $P < 0.05$ are reported as trends.

3. Results

3.1. ApoE genotype-related differences in EEG in younger individuals

Resting EEG parameters did not differ significantly between ApoE ε4− and ApoE ε4+ subjects in the younger cohorts (Supplementary Fig. A). Visual inspection of the resting EEG recordings revealed no abnormality.

Fig. 2. Electroencephalography (EEG) under hyperventilation (HV) of healthy subjects: 45 years old with apolipoprotein E (ApoE) ε3/ε4 genotype (a), 39 years old with ApoE ε3/ε3 genotype (b), 59 years old with ApoE ε3/ε4 genotype (c), and 58 years old with ApoE ε3/ε3 genotype (d).
Under HV in younger subjects, the presence of ε4 allele was associated with the manifestation of synchronous high-voltage delta and theta activity and sharp waves, pronounced decrease in alpha and increase in delta and theta relative power (Fig. 1, 2). Visual inspection of EEG recordings demonstrated that, under HV, 17 out of 36 (47.2%) of ApoE ε4/ε11001 younger subjects had synchronous high-voltage delta and theta activity and sharp waves, which appeared at the second and third minutes of the loading (Fig. 2a). Such dynamics was observed only in 6 out of 33 (18.2%) ApoE ε4/ε11002 younger subjects. In ApoE ε4/ε11002 younger group, the changes in delta [F(1,32) = 18.78; P < 0.0001], alpha [F(1,32) = 12.16; P = 0.001] and beta2 [F(1,32) = 10.82; P = 0.002] relative powers were less statistically robust, and the changes of theta relative power did not reach a significant level (Fig. 1).

In the younger ApoE ε4+ group under HV, a sharp increase in delta [F(1,34) = 51.33; P < 0.00001] and theta [F(1,34) = 13.11; P = 0.0009] relative powers and the decrease in alpha [F(1,34) = 40.82; P < 0.00001], beta1 [F(1,34) = 24.72; P < 0.00001], and beta2 [F(1,34) = 36.48; P < 0.00001] relative powers were observed. In ApoE ε4− younger group, the changes in delta [F(1,32) = 18.78; P = 0.0001], alpha [F(1,32) = 12.16; P = 0.001] and beta2 [F(1,32) = 10.82; P = 0.002] relative powers were less statistically robust, and the changes of theta relative power did not reach a significant level (Fig. 1).

Under HV ApoE ε4+ younger subjects had significantly lower beta2 relative power [F(1,67) = 9.26; P = 0.003] than ApoE ε4− younger individuals. The summary values of delta and theta relative powers under HV in the ApoE ε4+ younger subjects were significantly higher [F(1,67) = 8.54; P = 0.005] and the summary values of alpha, beta1,
and beta2 relative powers were significantly lower \([F(1,67) = 6.48; P = 0.01]\) than in the ApoE e4+ younger subjects. The ApoE e4+ younger subjects showed a tendency for higher delta \([F(1,67) = 4.27; P = 0.04]\) and theta \([F(1,67) = 4.45; P = 0.04]\) relative powers and lower alpha \([F(1,67) = 4.21; P = 0.04]\) relative power under HV as compared with the younger ApoE e4− subjects (Fig. 1a).

There was a tendency for more pronounced shifts under HV in alpha relative power in ApoE e4− versus younger ApoE e4− subjects \([F(1,67) = 4.90; P = 0.03]\) (Fig. 1b).

No significant correlation has been found between EEG relative powers on the one hand and height, education, and smoking prevalence on the other hand in the ApoE e4− and the ApoE e4+ younger individuals.

### 3.2. Age-related differences in EEG in ApoE e4+ and ApoE e4− individuals

At resting ApoE e4− as well as in ApoE e4+ older subjects as compared with the younger individuals with the same genotype had an increase in beta1 relative power (Table 2).

The older ApoE e4+ subjects showed a greater decrease in EEG relative activity on HV than the older ApoE e4− subjects. Under HV only 3 out of 24 (12.5%) ApoE e4+ older subjects had paroxysmal high amplitude slow waves activity. In the majority of ApoE e4+ older subjects EEG reactivity to HV was low, the increase in slow-wave activity was not observed (Fig. 2c). Paroxysmal slowing under HV was revealed in 2 out of 32 (6.3%) ApoE e4− older subjects (Fig. 2d). In the majority of ApoE e4− older individuals HV induced a moderate increase in slow-wave activity. The differences in the frequency of paroxysmal high amplitude slowing under HV between younger (47.2%) and older (12.5%) ApoE e4+ subjects was significant (\(P = 0.005\), Fisher exact test). The differences in the frequency of paroxysmal high amplitude slowing under HV between younger (18.2%) and older (6.3%) ApoE e4− subjects have not reached a statistically significant level.

The differences in EEG relative power under HV between older and younger subjects with ApoE e4+ genotype were more pronounced than between older and younger subjects with ApoE e4− genotype (Table 2). Under HV the older ApoE e4+ subjects, as compared with the younger subjects with the same genotype, had significantly lower delta relative powers and higher alpha, beta1, and beta2 relative powers. HV-induced shifts of delta and alpha powers were smaller in older ApoE e4+ subjects as compared with the younger individuals with the same genotype (Table 2). The older ApoE e4− individuals showed only a tendency for higher beta1 relative power under HV \([F(1,63) = 4.04; P = 0.04]\) and for smaller HV-induced shift of alpha relative power \([F(1,63) = 5.88; P = 0.02]\) as compared to the younger ApoE e4− subjects.

The relative power of delta activity showed a negative correlation with age in ApoE e4+ (\(r = -0.54; P < 0.00001\)), but not in ApoE e4− subjects. The values of alpha, beta1, and beta2 relative powers were significantly positively correlated with age in ApoE e4+ subjects only (\(r = 0.43, P < 0.001; r = 0.4, P = 0.001; r = 0.34, P = 0.008\), for alpha, beta1, and beta2, respectively) (Fig. 3).

### 3.3. ApoE genotype-related differences in EEG in older individuals

Resting EEG parameters did not differ significantly between ApoE e4− and ApoE e4+ subjects in the older cohorts (Supplementary Fig. B). Visual inspection of the resting EEG recordings revealed no abnormality.

The difference in the frequency of paroxysmal activity between the ApoE e4+ (12.5%) and the ApoE e4− (6.3%) older individuals was not significant.

In older ApoE e4+ persons only the increase in delta \([F(1,23) = 7.9, P = 0.01]\) and decrease in beta2 \([F(1,23) = 8.95, P = 0.007]\) relative powers under HV were significant (Fig. 4b). In older ApoE e4− subjects HV induced a significant increase in delta \([F(1,31) = 31.52, P < 0.000001]\) and a decrease in beta1 \([F(1,31) = 44.97, P < 0.000001]\), beta2 \([F(1,31) = 49.95, P < 0.000001]\) relative powers.

Under HV ApoE e4+ older subjects had significantly lower delta relative power than ApoE e4− older individuals \([F(1,54) = 6.98, P = 0.01]\) (Fig. 4a). The ApoE e4+ older subjects showed a tendency for a less pronounced shift under HV in beta1 relative power than the ApoE e4− older subjects \([F(1,54) = 4.49, P = 0.04]\) (Fig. 4b).

No significant correlation has been found between EEG relative powers on the one hand and height, education, and smoking prevalence on the other hand in the older ApoE e4− and in the older ApoE e4+ individuals.

Table 2

<table>
<thead>
<tr>
<th>ApoE genotype</th>
<th>delta</th>
<th>theta</th>
<th>alpha</th>
<th>beta1</th>
<th>beta2</th>
<th>delta HV baseline</th>
<th>beta1 HV baseline</th>
<th>beta2 HV baseline</th>
</tr>
</thead>
<tbody>
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<td>baseline</td>
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<tr>
<td>ApoE e4+</td>
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<td>baseline</td>
</tr>
</tbody>
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Key: —, not significant; ApoE, apolipoprotein E; EEG, electroencephalogram; HV, hyperventilation; HV− baseline, hyperventilation minus baseline.
4. Discussion

The main results of the present study indicate that EEG reactivity to HV differs in ApoE ε4/ε4 and ApoE ε4/ε1 subjects in an age-dependent manner. The younger ApoE ε4/ε1 persons had the excessive reactivity of EEG to the HV characterized by high incidence of the paroxysmal bilateral high amplitude slow-wave and sharp-wave activity, while in ApoE ε4/ε4 subjects HV usually induced only a moderate increase in EEG amplitude and diffuse slowing. Under HV ApoE ε4/ε1 younger subjects had significantly higher delta and theta relative powers and lower alpha and beta2 relative powers than ApoE ε4/ε4 younger individuals.

In ApoE ε4/ε4 subjects EEG reactivity to HV decreased with aging to a greater extent than in ApoE ε4/ε4 subjects. The relative power of delta activity showed a negative correlation with age in ApoE ε4/ε4, but not in ApoE ε4/ε4 subjects. The values of alpha, beta1, and beta2 relative powers were significantly positively correlated with age in ApoE ε4/ε4 subjects only. In the older ApoE ε4 carriers HV-induced EEG slowing was not pronounced; the increase in delta and theta relative powers and the decrease in alpha and beta relative powers were smaller than in middle-aged ApoE ε4 carriers. Under HV the older ApoE ε4 carriers had lower delta relative power, as compared with the older ε4 noncarriers.

Complex mechanisms underlying HV-induced changes in EEG are related to the effects of hypocapnia on cerebral blood flow and neuronal excitability. HV may induce respiratory alkalosis, hypohypocapnia, and subsequent vasoconstriction and possibly also hypoxia in the brain (Dager et al., 1995; Kennealy et al., 1986; Mäkiranta et al., 2004; Van der Worp et al., 1991). Vasoconstriction may play an important role in enhancing cortical excitability. The study of regional cerebral blood flow (rCBF) with single photon emission computed tomography and functional magnetic resonance imaging (fMRI) directly demonstrated a close correlation between HV-induced EEG slowing and cerebral hypoperfusion (Jibiki et al., 1992; Mäkiranta et al., 2004). It was shown that the changes in cortical excitability may also be related to alkalosis and a reduction of extracellular calcium (Chesler and Kaila, 1992).
The paroxysmal bilateral high amplitude slow-wave and sharp-wave activity observed under HV in younger ApoE ε4 allele carriers is closely related to epileptic oscillations (Gullapalli and Fountain, 2003; Steriade et al., 1990; Zelnkov, 2002) and can result from a number of factors related to the ApoE ε4+ genotype: an increase in the intracellular level of resting calcium and calcium response to the stimulation of N-methyl D-aspartate (NMDA) glutamate receptors (Qiu et al., 2003), higher susceptibility to oxidative stress (Beal, 1992; Beisiengel et al., 1997; Fokin et al., 1989), and accumulation of Aβ (LaFerla, 1995; Palop et al., 2007.) We found similar EEG dysfunction previously in middle-aged relatives of AD patients (Ponomareva et al., 2003), and particularly in middle-aged AD relatives carrying the ApoE ε4 allele (Ponomareva et al., 2008).

More pronounced reduction of EEG reactivity to HV in the older ApoE ε4+, than in the older ApoE ε4− persons may be related to the complex effect of ApoE ε4 allele on neuronal excitability and sensitivity to CO₂ and/or the changes of cerebrovascular reactivity to hypocapnia in aging.

Recent findings in animal models of AD show that Aβ-induced neuronal network hyperexcitability may cause inhibitory compensatory responses, associated with enhanced synaptic inhibition and alterations in several calcium- and activity-regulated proteins in granule cells including calbindin, Fos, and Arc (Palop and Mucke, 2009; Palop et al., 2007). These compensatory inhibitory mechanisms may also interfere with normal neuronal and synaptic functions required for learning and memory (Palop and Mucke, 2009). Similar inhibitory processes may underlie the decrease of excitability in older ApoE ε4+ subjects. Differential effects of the ApoE genotype on brain function across the lifespan were also recently found in fMRI study of brain activation during encoding memory task. Increased brain activation during the task in young ε4− carriers was shown to be disproportionately reduced with advancing age (Filippini et al., 2011). The authors hypothesized that increased activity in younger ε4− carriers may lead to greater Aβ deposition, which in turn may negatively modulate neuronal activity later in life (Wei et al., 2010).

The changes may affect the respiratory cholinergic mechanisms and respiratory regulation and may alter the physiological reflex response to hypocapnia. Alterations in radioligand binding for muscarinic receptors have been identified in clinically normal ApoE ε4+ subjects (Cohen et al., 2006; Eckelman, 2006).

Cerebrovascular CO₂ reactivity declines significantly with increasing age even in healthy subjects and the changes may alter EEG reactivity to HV, which was relatively mild in ApoE ε4− subjects. The presence of ApoE ε4+ allele was shown to be associated with endothelial dysfunction as a consequence of cerebral amyloid angiopathy, atherosclerosis, and increased thickness of arteries, that may alter the cerebral vasoconstrictive response to hypocapnia (Illarioškin, 2003; Saunders et al., 1993; Schneider et al., 2005). The CO₂/NO axis is a cardinal pathway in the autoregulation of cerebral blood flow (Lavi et al., 2006). The isoform-dependent effect of ApoE on the release of endothelial NO was demonstrated (Sacre et al., 2003). This factor may modify vascular and, hence, EEG response to HV in subjects with different ApoE genotypes. Further studies with Doppler ultrasonography and bold MRI are needed to confirm the dependence on ApoE genotype of impaired cerebral CO₂ vasoreactivity in clinically healthy elderly subjects.

The cerebrovascular responsiveness to CO₂ had a significant effect on ventilatory control in humans. Reduced cerebrovascular reactivity causes a rise of [H⁺] at the level of the central chemoreceptor, enhancing ventilatory responsiveness to CO₂, and may increase the propensity for the apnea that occurs during sleep following a transient ventilatory overshoot (Xie et al., 2006). Reduced cerebrovascular reactivity in the older ApoE ε4+ persons may explain the association of the ApoE ε4 allele with increased risk of

![Fig. 4. Apolipoprotein E (ApoE) genotype related electroencephalogram (EEG) characteristics in older healthy subjects under hyperventilation (HV).](Image)
sleep apnea, particularly in elderly subjects found in the study of Kadotani et al. (2001).

Impaired cerebrovascular reactivity through long-term hypoxemia may irreversibly damage vulnerable areas of the brain, such as the hippocampus, and may negatively affect cognitive functions in ApoE ε4+ elderly persons. The link between cognitive decline and cerebrovascular reactivity was previously demonstrated in AD (Silvestrini et al., 2006). The authors interpreted their results as evidence of pathogenic involvement of vascular factors in cognitive decline in AD patients. The role of vascular factors in AD development is confirmed by the protective effect on the risk of AD of anti-hypertensive medications, particularly angiotensin-converting enzyme inhibitors (Shah et al., 2009).

In conclusion, we found age-dependent alterations of EEG reactivity to HV associated with the ApoE ε4 allele. In younger ApoE ε4+ individuals the excessive reactivity of EEG to HV was characterized by the manifestation of synchronous high-voltage delta, theta activity and sharp waves, and a large decrease in alpha and an increase in delta and theta relative powers. EEG reactivity to HV decreased with aging, and in the ApoE ε4+ subjects the decrease was more pronounced than in the ApoE ε4− subjects. The older ApoE ε4 carriers had smaller delta relative power under HV than the older ApoE ε4 noncarriers. The marked decline of EEG reactivity to HV in older ApoE ε4 carriers may be mediated by the alterations of neuronal and cerebrovascular reactivity to hypoxia. The results suggest the possible impact of vascular factors on the pathogenesis of ApoE-induced AD.

Disclosure statement

The authors disclose no conflicts of interest.

Informed written consent was obtained from all participants included in the study. The experimental protocol of this study was approved by the local Ethics Committee.

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Appendix A. Supplementary data


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