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Potential cognitive decline linked to angiotensin-converting enzyme gene but not hypertension: Evidence from cognitive event-related potentials

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HIGHLIGHTS

- The ACE D/D genotype may be related to cognitive decline independently of the effect of hypertension by means of ERPs.
- There was no association between hypertension and cognitive ERPs.
- Decreased amplitude and prolonged latency of P300 in healthy subjects with the ACE D/D genotype may reflect subtle cognitive impairment.

ABSTRACT

Objectives: The aims of the present study were to investigate the effect of hypertension and angiotensin-converting enzyme (ACE) genotypes on cognitive event-related potentials (ERPs), and whether the impact of ACE genotypes on P300 is related to the influence of hypertension.
Methods: Using the Cognitive Abilities Screening Instrument (CASI), we recruited 97 mentally healthy middle-aged and older adults. Medical histories were collected, and blood pressure, ACE insertion/deletion polymorphisms and ERPs in an auditory oddball task were measured for all participants.
Results: When the participants were stratified according to the presence or absence of hypertension, there were no differences in CASI score, percentage of ACE genotypes and ERPs. The subjects with the D/D homozygote displayed lower amplitude and longer latency of P300, although there were no differences in CASI score and the percentage of hypertension.
Conclusions: The subjects with the D/D genotype tended to have decreased amplitude and prolonged latency of P300 ERPs which reflected subtle cognitive impairment. There were no associations between hypertension, CASI score and P300 measurements.
Significance: Using ERPs, potential cognitive decline was linked to ACE genotypes, independently of the effect of hypertension.

1. Introduction

Increasing evidence suggests a connection between cognitive impairment and cardiovascular risk factors such as diabetes, hypertension and dyslipidemia (Daviglus et al., 2011; Etgen et al., 2011). In the elderly, only diabetes has been more consistently associated with cognitive decline, and other risk factors have revealed mixed results (Kerola et al., 2011). Control of hypertension has been linked to beneficial effects in terms of cognition in cross-sectional and prospective follow-up studies, however such results remain controversial (Birns and Kalra, 2009; Duron and Hanon, 2010; Elias et al., 2012; Chang-Quan et al., 2011). The interaction between environmental and genetic vascular factors has

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been reported to explain these findings (Lopez et al., 2013; Wolf, 2012).

Angiotensin-converting enzyme (ACE), a component of the Renin–Angiotensin system, plays an important role in blood pressure regulation (Reid, 1992), and an increase in plasma ACE activity may increase blood pressure. Circulating ACE levels vary considerably by individual and are highly genetically determined (Cambien et al., 1992). Previous studies have reported that an insertion/deletion (I/D) (indel) polymorphism of the ACE gene located on chromosome 17q23 (Rigat et al., 1992) is associated with circulating ACE plasma activity (Gerholm-Larsen et al., 2000). Nevertheless, the association between the ACE gene and hypertension has yet to be firmly established (Lin et al., 2004; Konoshita, 2011). The ACE gene is also regarded to be a plausible biological candidate susceptibility gene for Alzheimer's disease through degrading the toxic peptide β-amyloid (Hemming and Selkoe, 2005; Hu et al., 2001), a pathologic hallmark of Alzheimer's disease (1998). However, studies on the relationship between ACE I/D polymorphisms and cognitive decline have reported conflicting results (Bartres-Faz et al., 2000; Hajjar et al., 2010; Liu et al., 2011; Richard et al., 2000; Visscher et al., 2003; Amouyel et al., 1996; Stewart et al., 2004).

Cognitive event-related potentials (ERPs) are one of the most informative and dynamic methods of monitoring cognitive processes, especially in the temporal domain (Duncan et al., 2009; Katada et al., 2004). In particular, P300 has been widely used to study dementia and aging (Hogan et al., 2006; Juckel et al., 2008; Lai et al., 2010; Golob et al., 2007). P300 is a positive shift that occurs approximately 300 ms after the onset of stimulus, particularly when a subject detects an informative task-relevant stimulus (Polich, 2007; Sutton et al., 1965). Several studies have investigated the effect of hypertension on P300, however the nature of this relationship remains unclear (Mecklinger et al., 2006; Qureshi and Babbar, 2007; Cicconetti et al., 2000, 2004, 2001, 2007; Tandon and Joon, 1997). Furthermore, these studies did not explore the potential role of genetic factors. To the best of our knowledge, the associations between hypertension, ACE polymorphisms, and cognitive ERPs have not previously been reported. In this study, we aimed to examine the influence of hypertension and ACE polymorphisms on neurological alterations of higher brain functions, and to determine whether the effect of ACE genotypes on P300 is related to the influence of hypertension.

2. Methods

2.1. Subjects

Using a Chinese version of the Cognitive Abilities Screening Instrument (CASI) (Liu et al., 1994; Teng et al., 1994), 97 mentally healthy middle-aged and older adults (range 60–81 years; 52.6% male; Taiwanese Chinese), were recruited from the Kaohsiung Medical University Hospital and the general community. The CASI includes 25 test items which are divided into nine cognitive domains in terms of attention, mental manipulation, orientation, short-term memory, long-term memory, language ability, constructional praxis, category fluency, and abstraction and judgment. The maximum score is 100, with higher scores indicating better ability. The participants also received a comprehensive medical evaluation including history, physical examination, blood chemistry, and cognitive assessment. Resting blood pressure was also measured. All of the participants were right-handed (Oldfield, 1971) and underwent assessments for hypertension, ACE polymorphisms and ERP measurements in the morning (between 9 AM to 11 AM) after signing informed consent. None of the participants consumed alcohol, caffeine, nicotine or took any cognitive enhancing medications before the day of testing. This study was approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUH-IRB-950376). All subjects were volunteers and signed informed consent before participating in the study.

2.2. Hypertension

The criteria for hypertension included a history of diagnosed essential hypertension (without clinical manifestations of vascular incidents or secondary disorders) and a sitting blood pressure of more than 140/90 mmHg on at least two occasions or the use of antihypertensive medications.

2.3. Angiotensin-converting enzyme genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a QIAmp blood kit (QIAGEN). Detection of the indel polymorphisms of the human ACE gene was performed as described previously (Rigat et al., 1990). To confirm the genotype assignments, and in particular the D/I vs. D/D genotype, we performed a second analysis as described by Lindpaintner et al. (Lindpaintner et al., 1995).

2.4. Event-related potentials measurements

The subjects were tested while sitting in a comfortable chair with neck support in a sound-attenuated room with dim lighting. They were asked to keep their eyes open and fixed on a spot in front of them to avoid eye movement. First, the binaural audiometric thresholds were determined at 1000 Hz for each subject. All stimuli were presented over headphones at 80 dB SPL (each 20 ms in duration). The auditory stimuli consisted of 1000 Hz pure tone bursts as standard stimuli, and 2000 Hz pure tone bursts as target stimuli using an "oddball" paradigm. The inter-stimulus intervals were delivered at a variable time interval between 1 and 2 s. The probability of each sound category was 85% for the standard and 15% for the target. Thus, there were 50 target trials in each block. The two sound types were presented randomly in a stimulus sequence. The subjects were requested to press a button using their right thumb as quickly as possible when they detected the target sound. The experiment consisted of two blocks, with 325 trials in each block.

Behavioral data included reaction time and accuracy measurements. Reaction time was measured relative to the target onset for correct trials, and accuracy was measured as the percentage of correct responses out of all responses to the target tones.

Electro-encephalography (EEG) was recorded using Ag/AgCl electrodes placed at 21 scalp locations (FP1,FPz, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, Oz, O2) based on the 10–20 system, all of which were referenced to linked earlobes. The electrode impedance was kept below 5 kΩ. The EEG was amplified (band pass, 0.01–40 Hz; NeuroScan) and continuous EEG recordings were stored for further off-line analysis at a sampling rate of 256 Hz. The averaging epoch was 1024 ms, including 200 ms of pre-stimulus baseline.

Individual trials with eye blink artifacts (more than 100 μV of peak-to-peak amplitude), target trials for which the reaction time was more than 1 s, and non-target trials with a response were all excluded from the averaging. Separate ERP averages were made for each trial type, and peak amplitudes were measured relative to a 200 ms baseline preceding the stimulus onset. The P300 component was defined as the maximum positivity between 250 and 500 ms.