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Differences in BDNF Serum Levels in Patients with Alzheimer's Disease and Mild Cognitive Impairment

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Abstract

Objectives: A great deal of research has been conducted into the possible involvement of neurotrophins such as brain-derived neurotrophic factor (BDNF) in the pathogenesis of Alzheimer's disease (AD). We hypothesized that lower BDNF serum levels may be associated with cognitive decline. To test this hypothesis, we examined the differences in the serum BDNF levels in patients with AD and mild cognitive impairment (MCI) and normal controls.

Method: We enrolled 56 subjects with AD, 29 subjects with MCI, and 24 healthy control subjects in the study. A total of 109 subjects agreed to blood sampling to evaluate serum BDNF levels. Serum levels of BDNF were measured using an enzyme-linked immunosorbent assay (ELISA) method.

Results: The MCI group had higher BDNF levels as compared to the AD group (p=0.027). However, there were no significant differences between either the AD group or the MCI group and the control group. A significant correlation was observed between MMSE-K score and serum BDNF level. However, BDNF serum concentrations did not significantly correlate with age or level of education in the AD, MCI, and control groups.

Conclusion: Our data suggest that BDNF serum levels are increased in subjects with MCI, supporting the hypothesis of an upregulation of BDNF in preclinical stages. BDNF levels might be involved in the pathophysiology of cognitive decline in elderly people.

Keywords: Alzheimer's disease; Mild cognitive impairment; Brain-derived neurotrophic factor

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive decline with loss of memory, speech, and executive function. The neuropathological features of AD include the formation of neuritic plaques due to the deposition of beta-amyloid protein and the formation of neurofibrillary tangles in the brain. Mild cognitive impairment (MCI) represents a transitional state between normal aging and dementia [1], although not all patients in the MCI group automatically convert to AD [2].

Recently, a great deal of research has been conducted into the possible involvement of neurotrophins such as brain-derived neurotrophic factor (BDNF) in either the pathogenesis of AD or the course of the disease [3]. In animal models, BDNF is highly expressed and widely distributed throughout the central nervous system, especially in the hippocampus and cerebral cortex [4,5], and it is important in the survival and function of the hippocampus and cortex [6-8]. In addition, BDNF is critical for synaptic plasticity and memory processing in the adult brain [9,10]. BDNF has been demonstrated to transit the blood–brain barrier (BBB) in both directions [11,12]. Thus, BDNF serum levels may represent an important reserve pool for the brain.

Some studies have reported reduced serum levels of BDNF in patients with MCI [13] and AD [14,15] in comparison to healthy controls and patients with other forms of dementia. Higher serum BDNF levels were associated with better neuropsychological function in healthy older adults [16]. On the other hand, some studies have shown increased BDNF serum concentrations in patients with early stages of AD as compared to those with more severe stages of AD and age-matched healthy controls [17]. BDNF polymorphism could be a risk factor for disease progression in AD. In several postmortem analyses, decreased levels of BDNF mRNA or protein could be demonstrated in the hippocampus and cortex in subjects with AD [18,19].

BDNF represents a potential neuroprotective agent useful in preventing neurodegeneration, as clearly demonstrated in animal models [20,21]. In humans, however, the association of BDNF serum levels with the rate of cognitive decline is still unclear.

Given the substantial neuroprotective effects of BDNF in animal models of AD and the potential of BDNF to transit the BBB, we hypothesized that lower BDNF serum levels may be associated with cognitive decline. To test this hypothesis, we examined BDNF serum levels in patients with AD and MCI and normal controls. Researchers thus far have focused mostly on patients with various neurodegenerative diseases such as AD, vascular dementia, lewy body disease, but we selected AD patient group to investigate the mechanism and roles of BDNF in a homogenous group. Preclinical stage of AD have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI [22]. However, in this study preclinical stage of AD was included in the normal group.

Method

Subjects

We enrolled 56 subjects with AD, 29 subjects with MCI, and 24

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healthy control subjects from the psychiatric department of the Ilsanpaik hospital between October 2013 and September 2014. Patients in all three groups underwent physical, neurological, and psychiatric examinations. All subjects provided informed consent prior to participation. The study protocol was approved by the Institutional Review Board (IRB) of Ilsanpaik hospital.

A dementia screening test was performed using the Korean version of the Mini-Mental State Examination (MMSE-K), and the Clinical Dementia Rating scale (CDR), and for probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [23]. Inclusion criteria for MCI used the Petersen guidelines: i) complaint of defective memory only (amnestic MCI) or memory plus another cognitive domain (multidomain MCI), ii) normal activities of daily living, iii) normal general cognitive function, iv) abnormal memory function for age, and v) absence of dementia.

Patients with a history or the current presence of major physical illness such as uncontrolled diabetes, obstructive pulmonary disease, cardiovascular disease, comorbidity of primary psychiatric or neurologic disorders including major depressive disorder, Parkinson's disease, and cerebral stroke, and alcohol or substance abuse were excluded from the study. A total of 109 subjects agreed to blood sampling to evaluate serum BDNF levels and were free of treatments at time of blood collection.

Measurement of BDNF serum concentration

Peripheral venous blood of the fasted study subjects was sampled into serum tubes between 8:00 and 9:00 am in order to take into account a possible circadian rhythm. To minimize the source of platelets, serum was centrifuged within 30 min after sampling and stored at -18°C until further analysis.

Serum levels of BDNF were measured using an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. All samples and standards were measured in duplicate, and the means of the duplicates were used for statistical analyses. All samples from a given patient were analyzed in the same microtiter plate to minimize run-to-run variability.

Statistical analysis

Chi-square tests and/or analyses of variance (ANOVAs) were conducted to assess the demographic and clinical data. Comparisons among the experimental groups on continuous variables were performed using univariate ANOVAs followed, when appropriate, by post-hoc testing. Dependent variable is serum BDNF level. Independent variables are AD, MCI, control groups.

The level of statistical significance was set at $p<0.05$. Pearson's correlation analyses were performed ($p<0.05$) to assess correlations between MMSE-K scores and serum BDNF levels.

Results

Demographic and clinical data

Clinical and demographic data of the AD, MCI, and control groups are shown in Table 1. A chi-square analysis revealed that there was no significant difference in gender distribution among the groups ($x^2=4.052$, df=2, $p>0.05$). As compared to the control group, subjects in the AD group were significantly older ($p<0.01$) but there were no significant age differences between either the AD group ($p>0.05$) or the control group ($p>0.05$) and the MCI group. Educational level was significantly higher in the control group than in the AD group ($p<0.05$) and the MCI group ($p<0.05$).

The mean MMSE-K score of the AD group was significantly lower than that for the other groups ($p<0.01$), but there was no significant difference in MMSE-K scores between the MCI group and the control group ($p>0.05$). In addition, the mean Clinical Dementia Rating (CDR) score of the AD group was significantly higher than that for the other groups ($p<0.01$), but there was no significant difference in CDR scores between the MCI group and the control group ($p>0.05$).

BDNF serum levels in AD, MCI, and control groups

BDNF serum levels in the AD, MCI, and control groups are shown in Figure 1. Among these groups, there was a significant difference in serum BDNF levels (df=2,106, F=3.594, p=0.031). Post-hoc comparisons revealed that the MCI group (22378.69 ± 5776.09 pg/ml) had higher BDNF levels as compared to the AD group (18504.41 ± 5969.77 pg/ml) (p=0.027). However, there were no significant differences between either the AD group (p=0.792) or the MCI group (p=0.678), and the control group (20244.54 ± 7756.14 pg/ml).

Variables	AD group (N=56)	MCI group (N=29)	Control group (N=24)
Gender (M/F)	19/37	5/24	10/14
Age (mean ± SD) (years)	77.21 ± 6.76	73.66 ± 6.82	70.54 ± 5.83
Education (mean ± SD) (years)	6.41 ± 3.87	6.41 ± 3.94	9.25 ± 3.83
MMSE-K score (mean ± SD)	15.38 ± 5.49	24.55 ± 2.01	26.96 ± 1.60
CDR score (mean ± SD)	1.12 ± 0.71	0.50 ± 0.13	0.15 ± 0.23

Table 1: Demographics and clinical parameters of AD, MCI, and control groups
Data are the mean ± standard deviation. AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating

There was no significant difference in gender distribution among the groups. As compared to the control group, subjects in the AD group were significantly older. Education level was significantly higher in the control group than in the AD group and the MCI group. The mean MMSE-K score of the AD group was significantly lower than that for the other groups. In addition, the mean Clinical Dementia Rating (CDR) score of the AD group was significantly higher than that for the other groups

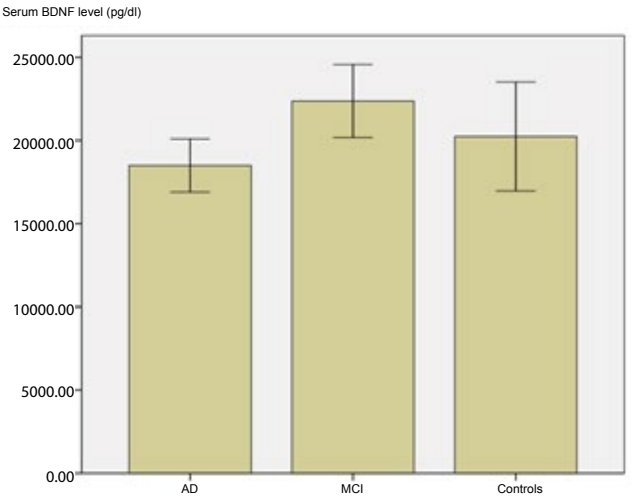

Figure 1: Brain-derived neurotrophic factor (BDNF) serum levels in Alzheimer's disease group (AD), mild cognitive impairment group (MCI), and healthy control group (Controls). Standard deviation indicated by error bars. AD, Alzheimer's disease; MCI, mild cognitive impairment. *Values are presented in pg/dl.

The Mini-Mental State Examination score (Korea) and serum BDNF concentration

A positive correlation was observed between MMSE-K score and serum BDNF level (Figure 2). However, BDNF serum concentrations did not significantly correlate with age (r=-0.128, n=109, p=0.092, 1-tailed) or level of education (r=-0.010, n=109, p=0.457, 1-tailed) in the AD, MCI, and control groups.

Discussion

BDNF plays a key role in modulating synaptic transmission and plasticity in the brain, which is important in the processes of learning and memory [19]. According to experimental data, BDNF protects against beta-amyloid induced neurotoxicity [20] and may contribute to increased Aβ degradation.

There is experimental evidence that BDNF can cross the BBB [21]. In addition, an animal study found a positive correlation between serum and cortical BDNF levels [24]. According to these results, BDNF changes within the CNS might be paralleled by changes in BDNF serum levels.

According to our study, the serum BDNF levels of MCI subjects were increased, but the increases were not statistically significant. The results of this study were slightly different from the hypothesis 'lower BDNF serum levels may be associated with cognitive decline'; the BDNF level was not in NC>MCI>AD order but showed higher BDNF level in MCI than in controls. These findings are similar to previous data in humans showing increased BDNF serum levels in preclinical stages of Alzheimer's disease [14]. Another study showed significantly increased BDNF serum concentrations in patients with MCI compared to healthy controls [25]. The increase in BDNF may reflect a compensatory repair mechanism in early neurodegeneration and could also be neuroprotective by contributing to the degradation of beta-amyloid. Some studies have demonstrated that BDNF may contribute to increased beta-amyloid degradation by promoting the expression of somatostatin [26,27]. Somatostatin increases the activity in primary cortical neurons of neprilysin, which is the key in vivo enzyme in the degradation of beta-amyloid [28]. In addition, BDNF is capable of inactivating glycogen synthase kinase 3 beta (GSK-3β) [29], which is involved in hyperphosphorylation of the tau protein [30]. An increase in BDNF serum levels might also be linked to an exacerbated inflammatory response of blood cells, although no signs of systemic inflammation have been previously observed in subjects with AD [31-33]. On the contrary, some studies have reported reduced serum levels of BDNF in patients with mild cognitive impairment [10].

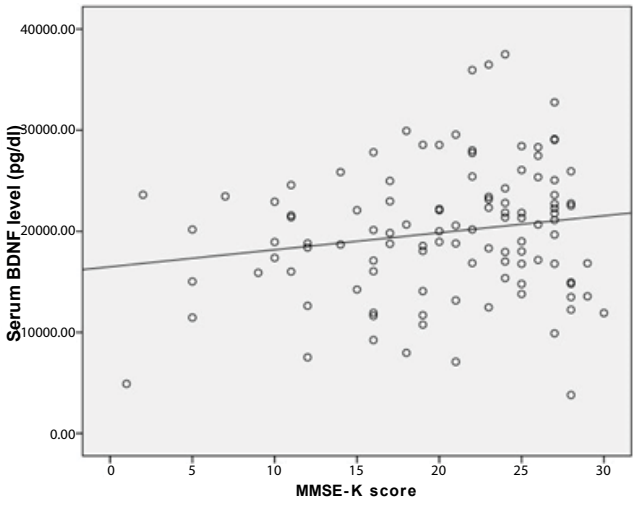

Figure 2: Correlation between BDNF serum concentration and MMSE score (r=0.172, n=109, p=0.037, 1-tailed). Pearson's correlation analyses.

In the group with AD, we found a statistically nonsignificant decrease of mean BDNF serum concentration in comparison to aged healthy controls. The reduction was statistically meaningful, however, in comparison to subjects in the MCI group. In line with our data, a growing body of evidence implicates BDNF in the pathophysiological changes that ultimately lead to the clinical expression of AD in humans. Post-mortem studies have demonstrated a significant reduction in BDNF mRNA expression and protein levels in several brain regions such as hippocampus and cortex in subjects with AD [34]. A significantly lower BDNF level in patients with AD has been shows compensatory repair mechanism of MCI patients compared to those with controls. Decreased serum concentration of BDNF has also been consistently described in patients with AD [12,35-37]. Serum BDNF levels have been found to be statistically nonsignificantly lower in AD patients than those in a matched group with vascular dementia and controls, and the levels correlate with scores on the MMSE-K [11]. In view of the neuroprotective effects of BDNF in general, the demonstrated decrease in BDNF in AD may contribute to the development of this neurodegenerative disease due to a lack of neurotrophic support. In opposition to these findings, Angelucci et al. found that serum BDNF levels were significantly increased in patients with AD when compared to control subjects [25]. Moreover, this increase in BDNF in the AD group was not dependent on treatment with acetylcholinesterase inhibitors or antidepressant drugs.

Komulainen et al. analyzed data from 1389 healthy older adults participating in the Dose–Responses to Exercise Training Study and found decreased levels of plasma BDNF significantly associated with poorer Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery scores [37,38]. Gunstad et al. recruited 35 healthy older adults and found that higher BDNF serum levels were associated with better performance on the MMSE and the short form of the Boston Naming Test [39]. In addition, Laske et al. demonstrated a positive association between BDNF serum levels and MMSE scores in 30 subjects with AD, with symptoms ranging from mild to severe dementia. This study also confirmed a significant correlation between MMSE-K and BDNF concentration [14]. In contrast, other studies failed to demonstrate a significant association between BDNF serum levels and MMSE scores in patients with MCI or AD [11,12,25]. The reasons for these discrepancies are not known, probably reflecting differences in patient recruitment and the stage of the disease. In more recent studies, the Val66Met, polymorphism in the brain-derived neurotrophic factor gene, BDNF, located at 11p13, has been associated with a wide range of cognitive functions. Meta-analysis included 23 publications containing 31 independent samples comprised of 7095 individuals. The meta-analysis did not establish significant genetic associations between the Val66Met polymorphism and any of the phenotypes that were included [40].

There are several limitations to this study. The first, it had a relatively small study population and was cross-sectional in design. The second, the fact that AD patients were significantly older and had less education than controls is a possible limitation to the interpretation of our data. The third, we didn't categorize the MCI patients into subtype groups such as the MCI phenotype (amnestic MCI vs non-amnestic

MCI) and the number of cognitive domains affected (single-domain MCI vs multiple-domain MCI). The fourth, the stage of AD patients was relatively mild.

Conclusion

Our data suggest that BDNF serum levels are increased in subjects with MCI, supporting the hypothesis of an up regulation of BDNF in preclinical stages, and that BDNF serum levels are decreased in AD in contrast to MCI. This result may reflect a lack of trophic support and thus contribute to progressive degeneration. Our data also suggest that the role of BDNF as a candidate marker for clinical diagnosis and therapeutic monitoring in MCI and AD should be evaluated. Additional studies are necessary to establish the role of BDNF as a biomarker in MCI and AD. Large clinical and epidemiological cohorts will be required to ascertain the role of BDNF in different stages of neurocognitive disorder and to proof the hypothesis that BDNF is upregulated as repair mechanism to neurodegeneration.

Conflict of Interest

None

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