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Relationship between brain-derived neurotrophic factor and cognitive function of obstructive sleep apnea/hypopnea syndrome patients

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ABSTRACT

Objective: To determine the relationship between the blood serum brain-derived neurotrophic factor (BDNF) level and cognitive function deterioration in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS), and to explore the possible mechanism of cognitive impairment. **Methods:** Twenty-eight male OSAHS patients and 14 normal males (as controls) were enrolled in the study. Polysomnography and the Montreal cognitive assessment (MoCA) were conducted. The blood serum BDNF levels were measured using ELISA. **Results:** The OSAHS group had significantly decreased blood serum BDNF levels compared with the control group ($t = -10.912$, $P = 0.000$). The blood serum BDNF level of the subjects was significantly positively associated with the MoCA score ($r = 0.544$, $P = 0.000$), significantly negatively associated with the apnea-hypopnea index (AHI) and shallow sleep (S1+S2) (AHI: $r = -0.607$, $P = 0.000$; S1+S2: $r = -0.768$, $P = 0.000$), and significantly positively associated with the lowest SaO_2 (LSO), slow wave sleep (S3+S4), and rapid eye movement sleep (REM) (LSO: $r = 0.566$, $P = 0.000$; S3+S4: $r = 0.778$, $P = 0.000$; REM: $r = 0.575$, $P = 0.000$). **Conclusions:** OSAHS patients have significantly decreased blood serum BDNF levels compared with the control. Nocturnal hypoxia as well as the deprivation of slow wave sleep and REM may lead to the decreased serum BDNF level of OSAHS patients. This decreased blood serum BDNF level may contribute to the cognitive impairment in OSAHS.

1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common, serious disease characterized by complete or partial upper airway closure during sleep that results in periodic nocturnal oxyhemoglobin desaturation and sleep fragmentation. OSAHS commonly affects the cardiovascular, nervous, and endocrine systems, among others. Cognitive impairment is the major complication of the nervous system in OSAHS. Studies showed that this condition can cause adult dementia[1]. Sleep fragmentation, repetitive nocturnal hypoxemia, and daytime sleepiness are suggested to contribute to the cognitive deficit in OSAHS[2]. However, although some researchers believe that this hypothesis can be proven by further experiments[3], how these factors affect cognition is unclear.

Brain-derived neurotrophic factor (BDNF) is a protein produced by brain tissues. BDNF is the most abundant and widely distributed member of the neurotrophic factor family[4]. A number of studies proved the importance of BDNF in the differentiation, development, growth, and regeneration of the nervous system[5,6]. BDNF is also suggested to be closely associated with cognition. Li *et al*[7] reported that age-related cognitive decline (ARCD) patients have significantly decreased serum blood BDNF

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levels compared with healthy people. Caccamo *et al*[8,9] found that BDNF is correlated with cognitive impairment in Alzheimer's disease (AD) and type 2 diabetes mellitus (DM) patients. Several studies have demonstrated the relationship of BDNF with cognitive impairment in OSAHS, but the results are inconsistent. Wang *et al* reported that OSAHS children with cognitive impairment whose blood serum BDNF levels were significantly decreased compared with the control group[10]. Another study on adult OSAHS patients with cognitive deficit carried out by Hu *et al* had similar results[11]. Staats *et al* suggested that there is no significant difference in serum and plasma BDNF level between OSAHS patients and control group[12]. In the present study, we hypothesized that the serum BDNF level of OSAHS patients changed compared with healthy people and it related with their cognitive function. Thus, we determined the blood serum BDNF levels of middle-aged OSAHS men as well as explored the relationship of their cognitive deficit with sleep fragmentation and hypoxia/hypopnea to offer new clues to the mechanism of cognitive impairment in OSAHS patients.

2. Materials and methods

2.1. Subjects

From February 2011 to October 2011, 28 Han Chinese OSAHS male patients and 14 healthy volunteers aged 40-49 years were recruited to participate in this controlled, randomized, open-labeled study at the First Affiliated Hospital of Hunan Normal University. The inclusion criteria for OSAHS patients were as follows: newly diagnosed OSAHS by polysomnography according to standard criteria[13], apnea-hypopnea index (AHI) $\geqslant$5 without any previous therapy, and educational attainment higher than middle school. The exclusion criteria were as follows: history of chronic obstructive pulmonary disease, cardiovascular disease, hematological disorders, nephritic disease, nervous system diseases and injury, as well as diseases of the endocrine system; abnormal hepatic function; history of taking hormones, sedatives, and antipsychotics, as well as excessive drinking (>80 g/d); and concurrent oncologic diseases.

The control group comprised individuals who were proved to be healthy and OSAHS free by polysomnography (PSG) and medical examination.

This study was approved by the Ethics Committee of Hunan Normal University. Written informed consent was obtained from all participants before the start of the study.

2.2. Treatments

2.2.1. PSG

OSAHS was diagnosed using PSG. OSAHS was defined based on the American Association of Sleep Disorder standards. Within 24 h before PSG, the subjects were not allowed to take sedatives as well as drink alcohol, tea, and coffee. They were put to sleep for 7.5 h from 10:30 pm to 6:00 am. The main indicators of PSG included AHI, lowest SaO_2 (LSO), duration of sleep stage Ⅰ (S1) (%), sleep stage Ⅱ (S2) (%), sleep stage Ⅲ (S3) (%), sleep stage Ⅳ (S4) (%), and rapid eye movement sleep (REM) (%). The PSG results were examined and approved by the same doctor in the sleep center.

2.2.2. Cognitive function

Cognitive function was evaluated using the Montreal cognitive assessment (MoCA) that evaluates executive function, naming, attention, calculation, language, abstraction, memory, and orientation. The total MoCA score is 30. A total MoCA score <26 indicates cognitive impairment, whereas a score $\geqslant$26 indicates normal cognitive function. If the schooling length of the subject was less than 12 years, 1 point was added to the total score to adjust for educational bias[14]. The PSG lasted for 10 min.

2.2.3. Serum sample collection and BDNF measurement

From 6:30 am to 7:00 am, 3 mL of blood was collected from the cubital veins before breakfast on the morning after PSG monitoring. Blood was allowed to coagulate for 10-20 min at room temperature and centrifuged for about 20 min (3 000 rpm). Serum was collected and stored in a refrigerator at -80 ℃. BDNF was measured using an enzyme-linked immunosorbent assay kit purchased from R&D.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 17.0 for Windows. For continuous variables, all values were expressed as mean±standard deviation. The means between two groups were compared using the *t* test. Pearson correlation coefficient analysis was performed for variable correlation. The statistical significance level was set at two-sided $\alpha = 0.05$.

3. Results

Twenty-eight male OSAHS patients aged 40-49 years [average = (44.93±2.98) years] participated in this study. All subjects had educational attainments higher than middle school, with an average length of education of (14.43±1.99) years. The maximal, minimal, and average body mass indices (BMI) were 34.80, 21.71, and (28.69±3.70) kg/m^2. Fourteen healthy male volunteers aged 40-49 years [average = (44.79±2.58) years] were included in the study. All volunteers had educational attainments higher than middle school, with an average length of education of (14.43±1.99) years. The maximal, minimal, and average BMIs were 33.10, 23.38, and (27.42±2.80) kg/m^2, respectively. No significant difference was found in the age, schooling length, and BMI

between the OSAHS and control groups (Table 1). These results indicated that the study groups had comparable baseline data.

The OSAHS group had significantly higher AHI than the control group (Table 2). LSO was significantly decreased, and shallow sleep (S1+S2) was significantly extended in the OSAHS group. Slow wave sleep (S3+S4) and REM were also significantly reduced.

Table 1

Baseline socio-demographic characteristics of the OSAHS and control groups.

Characters	OSAHS group(n=28)	Control group(n=14)	t	P
Age (years)	44.93±2.98	44.79±2.58	0.153	0.879
Length of schooling (years)	14.43±1.99	14.21±1.76	0.341	0.735
BMI (kg/m^2)	28.69±3.70	27.42±2.80	1.124	0.268

Table 2

Conditions of sleep and respiration of the OSAHS and control groups (mean±SD).

Indexes	OSAHS group(n=28)	Control group(n=14)	t	P
AHI (times/h)	49.63±28.56	2.27±1.21	8.757*	0.000
LSO (%)	67.92±12.66	89.64±5.95	−7.556	0.000
S1+S2 (%)	76.75±6.33	25.96±6.82	23.899	0.000
S3+S4 (%)	10.24±2.84	37.36±12.76	−7.859*	0.000
REM (%)	5.78±2.71	22.02±5.51	−10.411	0.000

Note: *t' value.

Table 3 shows that the OSAHS group had significantly decreased total MoCA scores as well as scores of executive function, calculation, abstraction, and memory compared with the control group ($P < 0.05$).

The mean serum BDNF level of the OSAHS group was (5.01±0.61) ng/mL, whereas that of the control group was (7.27±0.68) ng/mL. The serum BDNF level of the OSAHS patients were significantly decreased compared with the control group ($t = -10.912$, $P = 0.000$).

Table 3

Cognitive function of the OSAHS and control groups (mean±SD).

Cognitive function	OSAHS group (n = 28)	Control group (n = 14)	t	P
Total MoCA score	24.04±1.75	28.57±1.09	−8.835	0.000**
Executive function	3.39±0.92	4.86±0.36	−7.375	0.000**
Naming	2.79±0.42	2.86±0.53	−0.475	0.637
Attention	2.39±0.49	2.57±0.51	−1.085	0.284
Calculation	2.54±0.51	2.86±0.36	−2.355	0.024*
Language	2.54±0.74	2.71±0.47	−0.817	0.419
Abstraction	1.61±0.50	2.14±0.36	−3.965	0.000**
Memory	3.14±0.76	4.50±0.52	−6.027	0.000**
Orientation	5.57±0.50	5.79±0.43	−1.444	0.159

Note: *$P < 0.05$, **$P < 0.01$.

Table 4 shows that the total MoCA score of the subjects was significantly positively associated with the blood serum BDNF level ($r = 0.544$, $P = 0.000$) (Table 4). The scores of executive function ($r = 0.550$, $P = 0.000$), abstraction ($r = 0.408$, $P = 0.007$), and memory ($r = 0.509$, $P = 0.001$) were also significantly positively associated with the blood serum BDNF level. The serum BDNF level had no significant difference from the age, BMI, and schooling length.

Table 5 shows that the serum BDNF level had no correlation with the age, BMI, and schooling length. The serum BDNF level was significantly negatively correlated with the AHI and S1+S2, but significantly positively correlated with the LSO, S3+S4, and REM.

Table 4

Correlation of the MoCA score with the age, BMI, schooling length, and blood serum BDNF level.

Indexes	Age	BMI	Schooling length	BDNF (ng/mL)
Total MoCA score	−0.307	−0.274	0.113	0.544**
Executive function	−0.295	−0.243	0.197	0.550**
Naming	−0.219	−0.138	0.140	0.176
Attention	−0.040	−0.302	0.184	0.047
Calculation	−0.289	−0.010	0.152	0.162
Language	−0.090	−0.176	−0.025	0.039
Abstraction	0.238	−0.087	−0.307	0.408**
Memory	−0.088	−0.063	−0.064	0.509**
Orientation	0.095	−0.211	−0.163	0.047

Note: All values in the table are expressed as r. Pearson correlation coefficient analysis was performed to analyze the relationship of the MoCA score with the age, BMI, schooling length, and blood serum BDNF level. *$P < 0.05$, **$P < 0.01$.

Table 5

Correlation analysis of the serum BDNF level with the age, BMI, schooling length, and sleep structure.

Indexes	r	P
Age	0.072	0.653
BMI	−0.020	0.900
Length of schooling	−0.010	0.952
AHI (times/h)	−0.607**	0.000
LSO (%)	0.566**	0.000
S1+S2 (%)	−0.768**	0.000
S3+S4 (%)	0.778**	0.000
REM (%)	0.575**	0.000

4. Discussion

The mechanism of cognitive impairment in OSAHS patients is unclear. Animal experiments showed that BDNF mRNA expression in the hippocampus especially in the CA2 and CA3 areas are closely associated with learning and memory[15]. BDNF and its receptor are involved in long-term potentiation by regulating the cholinergic system of the basal forebrain, synaptic transmission, and synaptic plasticity, as well as by affecting learning and memory[16]. Researchers

argued that reduced BDNF production in the cortex and hippocampus can lead learning and memory degradation[17].

Compared with the control group, the AHI of the OSAHS group was significantly higher, the LSO was significantly decreased, shallow sleep (S1+S2) was significantly extended, and both slow wave sleep (S3+S4) and REM were significantly reduced. These results suggested that the OSAHS patients had nocturnal hypoxemia and sleep disturbance. The OSAHS patients had poorer cognitive function than the control group. Their executive function, calculation, memory, and abstraction were also significantly decreased compared with the control group. These results well agreed with previous results[18,19].

The serum BDNF level of the subjects was detected using ELISA. Considering cognitive function and serum BDNF level were influenced by sex, age, education degree, other diseases and so on, abovementioned factors were controlled for subjects in this study. The OSAHS patients had significantly decreased serum BDNF levels compared with the controls. This finding suggested that the synthesis and release of BDNF in the OSAHS patients were inhibited. This result was similar to that obtained by Wang *et al*[10]. Further analysis on the relationship between cognitive function and the serum BDNF level was performed. The serum BDNF level was significantly positively correlated with the total MoCA score as well as the scores of executive function, memory, and abstraction. Thus, a higher serum BDNF level corresponded to better cognitive function, executive function, memory, and abstraction. These results are consistent with those obtained by previous researchers[20]. Although references on the correlation between BDNF and OSAHS are limited, the close correlation between BDNF and cognition was proved in several studies on cognitive deficit in AD, ARCD, and type 2 DM. It is reported that the serum and cerebrospinal fluid BDNF levels of AD patients are significantly decreased compared with controls, and decrease with age in healthy individuals[21,22]. McLay *et al*[23] used a Morris water maze to test the memory and learning ability of rats. They found that aged rats have poorer memories and learning abilities than younger rats, and the cognitive function of rats is negatively correlated with the neuron density and BDNF gene expressed in the hippocampus. Other studies suggested that the serum and plasma BDNF levels of type 2 DM patients are lower than those of healthy people, and this variety is correlated with their cognitive degradation. Researchers suggested that adequate blood BDNF concentrations can stop cognitive impairment[24-27]. Based on previous studies and the present one, we supposed that the decrease in serum BDNF is one of the biochemical mechanisms of cognitive deficit in OSAHS patients.

To determine the reason for the declined serum BDNF level of OSAHS patients, we analyzed the relationship between the serum BDNF level and sleep structure of the subjects. We found that the serum BDNF level was closely negatively correlated with the time percentages of stages 1 and 2 sleeps, but closely positively correlated with the time percentages of stage 3 and 4 sleep, as well as with REM. A longer time of shallow sleep or shorter time of slow wave sleep corresponded to lower serum BDNF levels. Thus, extending shallow sleep or shortening deep sleep and REM sleep may lead to declined serum BDNF levels in OSAHS patients. Hiroyoshi *et al*[28-30] reported that the cerebellar and brainstem BDNF levels of rats decline after 6 h of REM sleep deprivation. They suggested that a shortened REM time explains the reduction in BDNF secretion and release. Ugo *et al*[30] proved that the synthesis and release of BDNF occur in the brain during the period of slow wave sleep. After exogenous BDNF is injected into the cerebral hemispheres of rats, the animals can more deeply sleep than untreated rats. They believed that BDNF is important in slow wave sleep and both conditions regulate each other. Based on our study, we suggest that the decreased serum BDNF levels of OSAHS patients is due to a sleep structural disorder, particularly, significantly shortened slow wave and REM sleep, which lead to cognitive dysfunction.

Nocturnal hypoxemia and the serum BDNF level were correlated. We found that the serum BDNF level was significantly negatively correlated with the AHI, but significantly positively correlated with the LSO. Thus, a higher severity of apnea/hyponea in OSAHS patients resulted in lower serum BDNF levels. This finding suggested that the serum BDNF level of OSAHS patients was closely related to the severity of nocturnal hypoxemia. Samantha *et al*[31] found that intermittent hypercapnic hypoxia upregulated apoptotic promoters and downregulated apoptotic inhibitors in the developing hippocampus of a piglet. Based on our findings, we speculate that nocturnal hypoxemia can promote neuronal apoptosis in the cerebral regions that are closely related with cognition, resulting in lower-than-normal levels of BDNF and its receptor.

In conclusion, the decrease in the serum BDNF levels of OSAHS patients is probably one of the mechanisms that lead to cognitive impairment as a result of nocturnal hypoxemia as well as deprived slow wave sleep and REM.

Conflict of interest statement

We declare that we have no conflict of interest.

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