Sleep and Breathing (2019) 23:889–892
https://doi.org/10.1007/s11325-018-1761-0

The effect of continuous positive airway pressure (CPAP) treatment on serum levels of proBDNF and mature BDNF in patients with obstructive sleep apnea

Yoshito Mizoguchi[1] · Jun-ichi Oyama[2] · Yoshiomi Imamura[1] · Koichi Node[2] · Akira Monji[1]

Received: 6 August 2018 / Revised: 17 November 2018 / Accepted: 20 November 2018 / Published online: 29 November 2018

To the Editor,

Obstructive sleep apnea (OSA) is caused by repetitive intermittent hypoxia and re-oxygenation during sleep and has been associated with an increased risk of many adverse health outcomes, including cognitive impairment, cardiovascular events, stroke, and depression. OSA is effectively treated by continuous positive airway pressure (CPAP) therapy [1], which protects pharyngeal airway to improve oxygenation during sleep. CPAP therapy can normalize sleep parameters of OSA and also ameliorate depressive symptoms. However, mechanisms underlying the effect of CPAP therapy on improvements of sleep parameters and/or depressive symptoms remain to be unclear.

Brain-derived neurotrophic factor (BDNF), one of neurotrophins, has various important roles in the brain. In addition to its neurotrophic actions, mature BDNF plays important roles in the regulation of glucose and lipid metabolism or the energy homeostasis in peripheral organs [2]. Accumulating evidence shows that serum BDNF levels are decreased in psychiatric and metabolic disorders, including sleep disorders, depression, obesity, type 2 diabetes mellitus, and cardiovascular diseases [2, 3]. Moreover, proBDNF is converted to mature BDNF by proteases, such as matrix metalloproteinases and/or plasmin. Interaction of mature BDNF with TrkB receptors promotes cell survival, while binding of proBDNF to p75 neurotrophin receptor induces apoptosis, suggesting that proBDNF and mature BDNF induce complete opposite biological responses [3]. Thus, further works to measure both mature BDNF and proBDNF will be needed to elucidate the functional roles of BDNF on psychiatric and metabolic disorders [3].

To our knowledge, only one study has measured the change of BDNF signaling during CPAP therapy in OSA patients [4]. This is the first report to focus on the relationships among sleep parameters, depressive symptoms, and BDNF signaling in OSA patients during CPAP therapy, suggesting that baseline mature BDNF levels might predict the amelioration of SpO_2% after the CPAP therapy.

The result was obtained from a prospective trial with consecutive enrollment of patients who were recruited from July 1, 2012, to June 30, 2014. We recruited patients who were suffered from OSA to take home sleep test using the LS-100 device. Subsequently, we had selected patients suffering from moderate/severe OSA, whose apnea–hypopnea index (AHI) > 15, using full-night polysomnography (PSG). We had treated patients who presented AHI > 20 by CPAP therapy for 3 months. We scored sleep stages and respiratory parameters in reference to the standard criteria of the American Academy of Sleep Medicine. Although we enrolled 95 patients with suspected OSA and 29 patients who received CPAP therapy for 3 months, we evaluated 19 patients who presented both Geriatric Depression Scale (GDS), a 15-item self-rating depression screening scale, and serum samples before and after CPAP therapy in this study. None of CPAP compliant patients was previously prescribed or using antidepressant drug therapy over the course of this study. This study was approved by the Institutional Review Board of Human Research at Saga University, and we obtained written informed consents from all participants. We measured serum levels of proBDNF and mature BDNF by the human proBDNF and BDNF ELISA Kits (Adipo Bioscience, Santa Clara, CA, USA). Measurements were performed according to the manufacturer's instructions and based on our experiences as previously reported. We used the Statistical Package for the Social Sciences (SPSS) software for statistical analyses. Statistical significance was determined

✉ Yoshito Mizoguchi
ymizo@cc.saga-u.ac.jp

[1] Department of Psychiatry, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

[2] Department of Cardiovascular Medicine, Saga University, Saga, Japan

by Student's paired *t* test when one group was compared before and after CPAP therapy. Pearson correlation coefficients were calculated to assess the associations of mature BDNF and proBDNF with other variables collected. Multiple linear regression analysis was used to verify the relationship of mature BDNF levels with another variable controlling for age. Unstandardized and standard regression coefficients (beta) and standard errors (SEs) were calculated. Statistical significance was set at p value of less than .05

Although CPAP therapy did not affect BMI and blood test results, CPAP therapy significantly reduced both systolic blood pressure (SBP) and diastolic blood pressure (DBP). Following 3 months of CPAP therapy, depressive symptoms assessed by GDS did not significantly change (from 3.7 to 4.0), while all sleep parameters except TST significantly improved. These suggest that CPAP therapy could improve sleep parameters but not depressive symptoms in patients with OSA in our sample. In this study, serum levels of proBDNF did not reach the minimum concentration (0.78 ng/mL) measurable by the ELISA kit. After 3 months of CPAP therapy, serum concentrations of mature BDNF significantly decreased from 14.45 ± 3.85 to 7.16 ± 2.34 ng/mL. On the other hand, serum levels of proBDNF did not significantly change after 3 months of CPAP therapy in OSA patients (Fig. 1, Table 1). In addition, we found a significant correlation between baseline concentration of mature BDNF and SpO_2 ave% after 3 months of CPAP therapy ($r = -0.592$, $p = 0.011$), although we did not find any correlation between the baseline mature BDNF and all sleep parameters except SpO_2 ave% after 3 months of CPAP therapy.

Staats et al. have reported that serum concentrations of mature BDNF significantly decreased (from 18.0 to 4.1 ng/mL) after one night of CPAP therapy [4]. Following 3 months of CPAP therapy, serum concentrations of mature BDNF increased again though they were still significantly lower than baseline levels [4]. We also observed that serum concentrations of mature BDNF significantly decreased (from 14.5 to 7.2 ng/mL) after 3 months of CPAP therapy, suggesting that CPAP therapy could decrease circulating BDNF levels in OSA patients. As shown in the table, the effect size of CPAP therapy on mature BDNF was almost as important as on the AHI. It was interesting because accumulating evidence shows that serum BDNF levels are decreased in many psychiatric and metabolic disorders [2, 3]. Takashio et al. reported that plasma BDNF levels were significantly lower in patients suffered from heart failure (HF) compared with those without HF [5]. In their study, they observed that plasma BDNF levels increased after the treatment of HF [5]. In addition, it was also shown that physical exercise increases circulating BDNF levels in patients with obesity

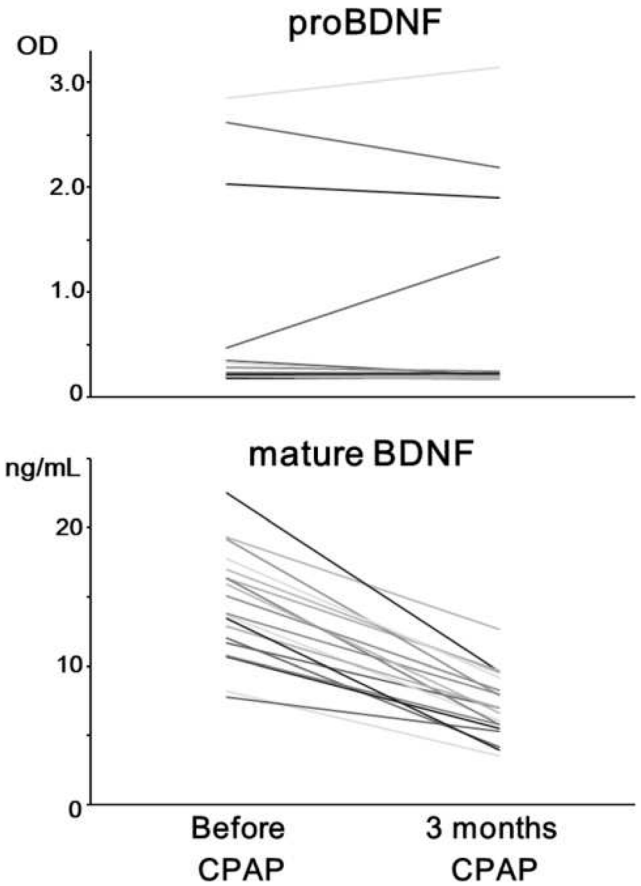

Fig. 1 Serum levels of proBDNF and mature BDNF in OSA patients before and after the CPAP therapy

or type 2 diabetes [2]. Thus, intervention to increase the concentration of mature BDNF is shown to have beneficial effects on both psychiatric and metabolic disorders. Circulating BDNF can be produced by both the central and peripheral neurons and by vascular endothelial, skeletal muscle and immune cells. In addition, BDNF levels in human serum are useful to estimate the amount of BDNF stored in platelets. Although we have not addressed the exact mechanism of the effect of CPAP therapy on serum BDNF levels in patients with OSA, it might be related to modulation of production or storage systems by CPAP therapy. In our sample, we did not find any correlation between the baseline mature BDNF and all sleep parameters except SpO_2 ave%. Although we could not find any references suggesting the possible mechanism underlying the higher mature BDNF in the beginning and the lower average SpO_2 after 3 months CPAP, it might be useful for further study. We also observed that serum levels of proBDNF did not change after 3 months of CPAP therapy and suggest that CPAP therapy might not affect the conversion from proBDNF to mature BDNF in OSA patients. A randomized controlled trial of

Table 1 Characteristics and sleep parameters of OSA patients before and after the CPAP therapy

	Before CPAP	3 months CPAP	*p*	Cohen's *d*
Sex	M15/F4			
Age (years)	60.7 ± 11.6			
BMI (kg/m^2)	28.1 ± 4.1	28.5 ± 4.2	n.s.	0.08
SBP (mmHg)	132 ± 3.6	126 ± 3.7	$p < 0.05$	0.34
DBP (mmHg)	76 ± 2.8	72 ± 2.5	$p < 0.05$	0.36
Plt	21.4 ± 5.4	21.9 ± 5.3	n.s.	0.11
Glu	107.1 ± 24.9	100.8 ± 15.5	n.s.	0.31
HbA1c	5.7 ± 0.5	5.7 ± 0.3	n.s.	0.03
T-Cho	207.1 ± 35.6	196.0 ± 33.3	n.s.	0.22
TG	177.3 ± 101.1	205.3 ± 144.8	n.s.	0.23
AST	27.4 ± 12.2	24.9 ± 11.0	n.s.	0.21
ALT	30.2 ± 16.0	27.6 ± 18.8	n.s.	0.15
GDS	3.6 ± 3.5	4.0 ± 4.1	n.s.	0.06
proBDNF (O.D.)	0.60 ± 0.86	0.61 ± 0.87	n.s.	0.01
Mature BDNF (ng/mL)	14.45 ± 3.85	7.16 ± 2.34	$p < 0.001$	2.29
Sleep parameters				
TST (min)	407.2 ± 63.9	426.1 ± 66.0	n.s.	0.29
Sleep efficiency	76.3 ± 10.6	83.1 ± 10.0	$p < 0.05$	0.66
AHI	47.0 ± 18.5	7.3 ± 9.3	$p < 0.001$	2.71
ODI	40.9 ± 18.9	6.9 ± 8.1	$p < 0.001$	2.23
SpO_2 ave (%)	93.1 ± 3.2	96.1 ± 1.2	$p < 0.001$	1.30
SpO_2 mini (%)	78.8 ± 7.4	89.2 ± 2.4	$p < 0.001$	1.89
ESS	8.7 ± 3.9	6.4 ± 4.8	$p < 0.01$	0.54
JESS	10.7 ± 4.6	7.9 ± 5.6	$p < 0.01$	0.55
Coexisting condition, *n*				
DM	2			
HT	13			
DL	7			
Medication, *n*				
CCB	11			
ACEi/ARB	8			
Anti-arrhythmia	1			
Antiplatelet	1			
Statin	4			
Other anti-DL drug	2			
Anti-hyperuricemic drug	4			
Antidiabetic drug	0			
No medication	4			

BMI body mass index, *SBP* systolic blood pressure, DBP diastolic blood pressure

Sleep parameters: *ODI* oxygen desaturation index, *ESS* Epworth Sleepiness Scale, JESS Japanese version of the Epworth Sleepiness Scale

Coexisting condition: DM diabetes mellitus, *HT* hypertension, DL dyslipidemia

Medication: *CCB* Ca channel blocker, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor antagonist

CPAP vs sham-CPAP would be desirable. Although major limitations of this study include small sample size, this is the first report to focus on the relationships among sleep parameters, depressive symptoms, and both proBDNF and mature BDNF levels in OSA patients before and after the CPAP therapy.

Funding This study was supported by grants from the Japan Agency for Medical Research and Development (AMED) (to Y.M and A.M) and the Japan Society for the Promotion of Science—KAKENHI ((C) to Y.M and A.M).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Institutional Review Board of Human Research at Saga University and with the 1964 Helsinki declaration.

Informed consent We obtained written informed consent from all individual participants in the study.

References

1. Ning Y, Zhang TS, Wen WW, Li K, Yang YX, Qin YW, Zhang HN, du YH, Li LY, Yang S, Yang YY, Zhu MM, Jiao XL, Zhang Y, Zhang M, Wei YX (2018) Effects of continuous positive airway pressure on cardiovascular biomarkers in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. Sleep Breath. https://doi.org/10.1007/s11325-018-1662-2
2. Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA (2009) Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. Exp Physiol 94:1153–1160
3. Mizoguchi Y, Monji A (2017) Microglial intracellular Ca^{2+} signaling in synaptic development and its alterations in neurodevelopmental disorders. Front Cell Neurosci 11:69
4. Staats R, Stoll P, Zingler D, Virchow JC, Lommatzsch M (2005) Regulation of brain-derived neurotrophic factor (BDNF) during sleep apnoea treatment. Thorax 60:688–692
5. Takashio S, Sugiyama S, Yamamuro M, Takahama H, Hayashi T, Sugano Y, Izumiya Y, Hokimoto S, Minamino N, Yasuda S, Anzai T, Ogawa H (2015) Significance of low plasma levels of brain-derived neurotrophic factor in patients with heart failure. Am J Cardiol 116:243–249