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Original Article

Altered cortical excitability in patients with untreated obstructive sleep apnea syndrome

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ABSTRACT

Objective: To investigate cortical excitability in patients with obstructive sleep apnea syndrome (OSAS) during wakefulness.
Methods: The authors recruited 45 untreated severe OSAS (all males, mean age 47.2 years, mean apnea–hypopnea index = 44.6 h^{-1}) patients and 44 age-matched healthy male volunteers (mean apnea–hypopnea index = 3.4 h^{-1}). The TMS parameters measured were resting motor threshold (RMT), motor evoked potential (MEP) amplitude, cortical silent period (CSP), and short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). These parameters were measured in the morning (9–10 am) more than 2 h after arising and the parameters of patients and controls were compared. The Epworth Sleepiness Scale (ESS) and the Stanford Sleepiness Scale (SSS) were also measured before the TMS study.
Results: OSAS patients had a significantly higher RMT and a longer CSP duration (*t*-test, $p < 0.001$) compared to healthy volunteers. No significant difference was observed between MEP amplitudes at any stimulus intensity or between the SICI (2, 3, 5 ms) and ICF (10, 15, 20 ms) values of OSAS patients and healthy volunteers ($p > 0.05$).
Conclusions: This TMS-based study suggests that untreated severe OSAS patients have imbalanced cortical excitabilities that enhanced inhibition or decreased brain excitability when awake during the day.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is an insidious condition characterized by repetitive upper airway closures during sleep and includes a constellation of symptoms, but more commonly, excessive daytime somnolence and cognitive deficits. Neurocognitive problems, such as impairments in memory, attention, and visuoconstructive abilities, frequently accompany OSAS [1]. The main contributory factors are presumed to be sleep fragmentation and intermittent nocturnal hypoxemia during sleep apnea. Alterations of event-related potentials paralleling cognitive impairment have been reported in patients with OSAS [2,3], which suggests alterations in cortical associative areas. Furthermore, it is also likely that alterations in motor cortical excitability also occur.

Transcranial magnetic stimulation (TMS) is a non-invasive method that can be used to study the physiology of the human brain. Using different stimulation protocols, TMS can excite or inhibit the brain, and this allows *in vivo* functional evaluations of excitatory and inhibitory intracortical circuits. However, little study has been conducted on sleep apnea. In a preliminary study, a prolongation of MEP latencies in the hand muscles of patients with OSAS was observed [4]. The authors suggested a widespread defect in the conductivity or excitability of the cortico-motor system. Unfortunately, no explanation was presented that supported this suggestion. Furthermore, this conduction/excitability defect was not reproduced in two recent studies [5,6], in which it was found that motor cortical excitability is altered in OSAS patients during daytime and even during apneas. However, interpretations based on these studies are limited by patient numbers and the number of TMS parameters used [5,6].

Accordingly, the aim of this study was to investigate cortical excitability in OSAS patients during wakefulness in a large number of patients using various parameters of TMS. To achieve this, we measured cortical excitability using single- and paired-pulse TMS and assessed excessive daytime sleepiness in severe OSAS patients and in age- and gender-matched healthy volunteers.

2. Methods

2.1. OSAS patients and healthy volunteers

Forty-five male patients with severe OSAS and 44 age-matched male healthy volunteers were included. Patients were recruited from the Samsung Medical Center Sleep Center located in South Korea. Inclusion criteria were as follows: (1) male; (2) age >18

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but <55 years; and (3) an apnea–hypopnea index >30 h^{-1}. Healthy volunteers were recruited by advertising in a local community. Each candidate completed a detailed clinical interview and a sleep questionnaire, and underwent overnight polysomnography. Healthy volunteer candidates with evidence of OSAS (an apnea–hypopnea index of >5 h^{-1}) or with a history suggesting other sleep disorders were excluded. The exclusion criteria applied to all study subjects were (1) a mean daily sleep time of <7 h; (2) an abnormal sleep-wake rhythm; (3) other sleep disorders such as insomnia, narcolepsy, chronic sleep deficiency, periodic limb movement disorder, or restless legs syndrome; (4) hypertension, diabetes, heart, or respiratory diseases; (5) a history of cerebrovascular disease; (6) other neurological (neurodegenerative diseases, epilepsy, head injury) or psychiatric diseases (psychosis, current depression); and (7) alcohol or illicit drug abuse or the current intake of psychoactive medications. Informed consent was obtained from all study subjects and the institutional review board of our hospital authorized the study protocol.

2.2. Overnight polysomnography

The day before sleep studies, patients were asked not to drink alcohol or caffeinated beverages. Sleep studies were recorded using a Somnologica or RemLogic (Embla, Broomfield, CO, USA). Overnight polysomnography was performed using a six-channel electroencephalogram (EEG, F_3/A_2; F_4/A_1; C_3/A_2; C_4/A_1; O_1/A_2; O_2/A_1), a four-channel electrooculogram (EOG), an electromyogram (EMG; of submental, intercostal, and anterior tibialis muscles), and an electrocardiogram with surface electrodes. A thermistor (for monitoring nasal airflow), a nasal air pressure monitor, an oximeter (for measuring oxygen saturation), piezoelectric bands (for determining thoracic and abdominal wall motion), and a body position sensor were also attached to patients. Patients were recorded on videotape using an infrared video camera and were continuously observed by a polysomnography technician. Patients went to bed at 11:00 PM and were awakened at 7:00 AM. Sleep architecture was scored in 30-s epochs, and sleep staging was interpreted according to the standard criteria described by Rechtschaffen and Kales [7].

The AHI is the number of both apneas and hypopneas per hour of sleep. Obstructive apnea was defined as a reduction in airflow of >90% lasting at least 10 s, during which there was evidence of a persistent respiratory effort; central apneas consisted of a complete cessation of airflow for 10 s or more with an absence of respiratory effort. Hypopneas consisted of $\geqslant$30% reduction in airflow, were 10 s or more in duration and were accompanied with a 4% desaturation in blood O_2 saturation [8].

2.3. Assessment of excessive daytime sleepiness (EDS)

Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS), which is a simple self-administered questionnaire with eight-item, four point scales that evaluate daytime somnolence among patients suffering from sleep-awake disorders [9], and the Stanford Sleepiness Scale, which is a quick way to assess how alert one is feeling. Objective sleepiness was evaluated using the Multiple Sleep Latency Test (MSLT) [10]. In brief, the MSLT consists of a series of 25-min naps at 2-h intervals in the morning and afternoon. Patients are asked to try to sleep in a dark room. The means of individual latencies to sleep onset from light-off was calculated for five nap trials. Final diagnoses of OSAS were based on overnight polysomnography findings and on associated clinical symptoms.

2.4. Transcranial magnetic stimulation (TMS)

Motor evoked potentials were recorded using surface electromyography (EMG) electrodes placed over the first dorsal interosseus (FDI) muscle in a belly-tendon montage. EMG raw signals were amplified and bandpass-filtered (10 Hz–20 kHz). An auditory feedback EMG signal was produced to ensure complete voluntary relaxation of FDI muscle. TMS was delivered through a focal figure-of-eight shaped magnetic coil (70 mm internal diameter) connected to two Magstim 200 magnetic stimulators via a BiStim-module (Magstim, Whitland, South West Wales, UK). Subjects were seated in an armchair with heads fixed in a plastic foam headrest. Placement of the coil over the motor cortex was performed by finding and marking a scalp site that was optimal in terms of producing MEPs in FDI muscle with the induced brain current flowing from posterior to anterior, approximately perpendicular to the assumed line of the central sulcus.

2.5. TMS parameters of motor cortex excitability

- *Resting motor threshold (RMT)* was defined as the lowest stimulator output intensity capable of inducing MEPs of at least 50-μV peak-to-peak amplitude in FDI muscle in the relaxed state in at least 4 of 8 consecutive trials. A step width of 1% of maximum stimulator output was used to determine motor thresholds.
- *Peak-to-peak MEP amplitudes* were measured in resting FDI at stimulus intensities of 120%, 140%, and 150% of the RMT. TMS stimuli were delivered randomly 5 s apart with eight stimuli at each stimulus intensity, and average MEP amplitudes were calculated at each intensity.
- *Cortical silent period (CSP)* was measured using eight trials at stimulus intensities of 120%, 140%, and 150% of RMT in moderately active FDI (at approximately 30% of maximum voluntary contraction) [11]. TMS stimuli were delivered randomly 5 s apart also with eight stimuli at each stimulus intensity. CSP duration was defined in the individual trials from the time of the first turning point of the stimulus-induced MEP to the first recurrence of rectified voluntary EMG activity. Time of the first turning point was determined by the EMG machine. CSP offset time was determined by a single blinded investigator (EY Joo). Average CSP duration was calculated for all stimulus intensities [12].
- *Short-Interval Intracortical Inhibition (SICI)* was obtained at short interstimulus intervals (ISIs) of 2, 3, and 5 ms and *Intracortical Facilitation (ICF)* at longer interstimulus intervals of 10, 15, and 20 ms using a previously described protocol [13,14]. The conditioning stimulus was set at 80% of RMT, at which level no changes of spinal cord excitability were induced [13]. The intensity of the following suprathreshold test stimulus was adjusted to produce MEPs of approximately 1.5 mV peak-to-peak amplitude at rest for all baseline and effect measurements. Eight trials of single control test stimuli and eight-paired stimuli of each ISI were recorded and delivered 5 s apart in a random order generated by a computer program. The average of eight trials was used to define amplitudes of peak-to-peak MEPs. Conditioned response was defined as the mean amplitude of conditioned responses belonging to the ISI and was expressed as percentage of the mean amplitude of the unconditioned test responses.

TMS parameters were obtained for the dominant hemispheres of OSAS patients and healthy volunteers using identical protocols.

2.6. Statistical analysis

Differences between the TMS parameters of OSAS patients and age- and sex-matched normal controls were compared using the independent *t*-test. The parametric *t*-test was used to compare