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Abnormal recovery function of somatosensory evoked potentials in patients with primary insomnia

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ABSTRACT

Neurobiological correlates underlying insomnia are poorly understood. The hyperarousal of the central nervous system indicates that cortical excitability may be abnormal in patients with insomnia. The purpose of the present study was to investigate changes in cortical excitability by examining the recovery function of median nerve somatosensory evoked potentials (SEPs) in patients with primary insomia (PI). We studied the recovery function of median nerve SEPs in 12 medication-naive PI patients and in 12 age- and sex-matched healthy subjects. SEPs in response to single stimulus and paired stimuli at interstimulus intervals (ISIs) of 20, 60, 100 and 150 ms were recorded. The recovery function of the cortical components of frontal P20 and parietal N20 showed significantly reduced suppression in PI patients as compared to healthy controls. In conclusion, this is the first study investigating changes in cortical excitability in PI patients by examining the recovery function of median nerve SEPs. The present study suggests that cortical excitability is increased in PI patients. Dysfunction of inhibitory GABAergic interneurons of the cerebral cortex might contribute to the increased cortical excitability in PI patients.

1. Introduction

Insomnia is considered to be the most common sleep disorder. Occasional episodes of insomnia symptoms are reported in half of all adults, while primary insomnia (PI) affects 3–5% of the adult population (Ohayon, 2002; Riemann et al., 2010). Despite its wide prevalence and broad medical impact, little is known about the neurobiological correlates underlying insomnia.

The hyperarousal perspective of insomnia has gained widespread attention as an integrative approach to the pathophysiology of insomnia (Riemann et al., 2010). Previous studies suggested that insomnia is primarily a disorder of central nervous system hyperarousal. First of all, although patients with insomnia complain of daytime fatigue as well as significantly less nocturnal sleep, they do not show increased sleepiness as compared to normal sleepers. On the contrary, they are significantly more alert than normal sleepers, as shown by their longer sleep latencies compared to controls in the multiple sleep latency test (MSLT) (Stepanski et al., 1988; Edinger et al., 2001). The results of the MSLT reflected a state of hypervigilance in patients with insomnia. Secondly, patients with insomnia exhibit elevated levels of electroencephalographic (EEG) beta frequency (15–40 Hz) activity during both sleep and wake (Perlis et al., 2001). Since cortical electrophysiological signals in the beta band have been hypothesised to be a main feature of coherent cortical processing of sensory information, an EEG power increase in this frequency range could be interpreted as a sign of cortical hyperactivity in patients with insomnia (Başar-Eroglu et al., 1996; Jefferys et al., 1996). Finally, positron emission tomography (PET) has been used to assess cerebral glucose metabolism in patients with insomnia (Nofzinger et al., 2004). Compared to healthy controls, patients with insomnia exhibited an overall increase in whole-brain metabolism during both waking and non-rapid eye movement sleep states. The PET findings indicated a whole-brain hyperactivity in patients with insomnia. Taken together, these findings indicated that cortical excitability may be abnormal in patients with insomnia.

The recovery function of the cortical components of somatosensory evoked potentials (SEPs) is believed to reflect the cortical excitability (Ugawa et al., 1996). It is known that when SEPs are obtained by two paired electrical shocks at specified interstimulus intervals (ISIs), the SEP amplitude evoked by the second stimulus is smaller than that one recorded from a single stimulus. The longer the ISI, the higher the amplitude of the SEP evoked by the second stimulus, until a complete amplitude recovery is observed (Shagass and Schwartz, 1964; Meyer-Hardting et al., 1983; Emori et al., 1991; Romani et al., 1995). This paired stimulation technique has been applied to study the cortical excitability in patients with various psychiatric and neurological disorders (Shagass and Schwartz, 1963, 1964; Ugawa et al., 1987; Kanda et al., 1989;

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Nakashima et al., 1992; Frasson et al., 2001; Valeriani et al., 2005; Mochizuki et al., 2006). In the present study, we investigated alterations of cortical excitability in patients with PI by examining the recovery function of median nerve SEPs.

2. Methods

2.1. Subjects

We studied the recovery function of median nerve SEPs in 12 medication-naive PI outpatients from our institution and in 12 age- and sex-matched healthy controls. The study was approved by our Institutional Review Board (IRB) and written informed consent was obtained from each subject.

Subjects retained for a screening visit were interviewed and examined by two sleep neurologists. The interview included the administration of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959), Hamilton Depression Rating Scale (HAMD, 24-item version) (Hamilton, 1960) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Subjects showing any polysomnographic (PSG) evidence of other sleep disorders, such as the sleep apnoea syndrome (i.e., thermistor monitored apnoea–hypopnoea index >5) (American Academy of Sleep Medicine, 1999) and periodic leg movements (i.e., periodic leg movement index >10) (American Sleep Disorders Association, 1993), were excluded from the study.

Inclusion criteria for PI patients were as follows: PSQI higher than 5; actual PI according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition, DSM-IV) criteria for PI; absence of other psychiatric diseases as evidenced by the MINI; absence of PSG evidence of other sleep disorders; and no history of psychopharmacological treatment for insomnia.

Inclusion criteria for healthy controls were as follows: PSQI lower than 5; absence of psychiatric diseases as evidenced by the MINI; and absence of PSG evidence of sleep disorders.

Exclusion criteria for both groups were as follows: evidence of neurological or other physical diseases such as respiratory, cardiac, renal, hepatic and endocrinal diseases as assessed by clinical history, physical examination or routine laboratory tests performed during the screening visit; any medication that might affect sleep or regional cerebral function within 14 days; irregular sleep schedules associated with shift work, frequent travel or personal preference (as indicated by a weekly variation >3 h in bedtime or wake time, or time in bed duration <5.5 or >10 h per night).

2.2. SEP recording procedure

For SEP recording, subjects were instructed to lie supine on an examination couch in a relaxed and comfortable position in a quiet and semi-darkened room, and to stay awake but keep their eyes closed. The left median nerve was stimulated at the wrist at an intensity fixed at about 1.2 times the motor threshold (stimulus duration: 0.2 ms, stimulus rate: 1 Hz). SEPs were recorded using an Neuropack M1 MEB-9200 EP/EMG measuring system (Nihon Kohden Corporation, Tokyo, Japan). Recording electrodes were placed over the ipsilateral Erb point, the spinous process of the sixth cervical vertebra (Cv6), the parietal C4' (2 cm posterior to the C4 placement of the International 10-20 System) and frontal F4 scalp regions contralateral to the stimulation side. All of these recording electrodes were referred to the right earlobe. The ground electrode was placed over the forearm. The analysis time was 100 ms, with a sampling rate of 20 kHz. The amplifier band-pass was 5–2000 Hz. We identified the following SEP components: the N9 potential was recorded at the Erb point; the N13 potential was recorded at Cv6; the P14, N20 and P25 potentials were recorded over the parietal region contralateral to the stimulation side; and the P14, N18, P20 and N30 potentials were recorded over the contralateral frontal region.

2.3. SEP recovery function

The recovery function of the SEP was studied using a paired stimulation technique. Paired stimuli of equal intensity were administered at ISIs of 20, 60, 100 and 150 ms.

Table 1
Demographic and clinical characteristics of the subjects.

Variable	PI patients	Controls	*p*-value
	Mean (S.D.)	Mean (S.D.)	
Cases	12	12	
Male/Female	5/7	5/7	1.00[#]
Age	38.33 (9.99)	41.91 (10.2)	0.48[*]
PSQI	13.75 (3.44)	2.25 (1.14)	0.00[*]
HAMA	6.50 (2.39)	3.50 (2.61)	0.01[*]
HAMD	7.25 (2.77)	4.92 (1.31)	0.02[*]

Notes. PSQI: Pittsburgh Sleep Quality Index. HAMA: Hamilton Anxiety Rating Scale. HAMD: Hamilton Depression Rating Scale. [#]: The *p* value was obtained using a Pearson x^2 two-tailed test. [*]: The *p* value was obtained by an independent-samples *t*-test.

Table 2
Mean amplitudes (μV) of SEP components in the single stimulus condition.

Components	N9	N13	N18	P20	N30	N20	P25
Controls							
Mean	6.62	3.40	1.35	1.78	4.79	3.18	4.99
S.D.	2.74	0.87	0.64	0.95	2.90	0.94	3.00
Patients							
Mean	5.63	3.11	1.32	1.23	3.17	2.63	4.41
S.D.	3.22	0.61	0.61	0.94	1.41	0.60	2.05

SEP recording to a single stimulus was used as the control condition. The sequence of these trials was randomised among the subjects. The time interval between two successive pairs was set at more than 5 s. At least 300 sweeps were averaged for each trial until clean, artefact-free and reliable responses were obtained. To ascertain reproducibility of results, SEPs of each condition (single stimulus, and paired stimuli at ISIs of 20, 60, 100 and 150 ms) were recorded at least twice, one trial after another trial. Then we obtained the average SEP time series of each condition used for subtraction. Thereafter, SEPs evoked by the test stimulus (T-SEPs) were obtained by subtracting SEPs evoked by a single stimulus alone (S-SEPs) from those elicited with paired stimuli (P-SEPs). Amplitudes of all SEP components (N9, N13, N18, frontal P20 and N30, parietal N20 and P25) were measured from the preceding peak (peak-to-peak) to prevent the impact of a baseline shift on the results. We measured amplitudes of each component in the subtracted SEP waveform and then calculated the relative amplitude ratios of T-SEPs to that of the corresponding S-SEPs at different ISIs. The value of ratio ≥1 means that there is no suppression.

2.4. Statistical analysis

The statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Statistical comparisons of the demographic data and clinical characteristics between the two groups were performed using an independent-samples *t*-test. For amplitudes and latencies of SEPs obtained by single stimulus, an independent-samples *t*-test was performed. For recovery function obtained by paired stimuli, a repeated measures analysis of variance (ANOVA) was performed with ISI as the within-subjects factor and group defined as the between-subjects factor. Results were considered statistically significant at a level of $p<0.05$.

3. Results

3.1. Demographic and clinical characteristics

The PSQI ($t=10.99, p=0.00$), HAMA ($t=2.93, p=0.01$) and HAMD ($t=2.64, p=0.02$) scores of PI patients were significantly higher than those of healthy controls. The demographic and clinical characteristics of the subjects are summarised in Table 1.

3.2. Single-pulse SEPs

In the single stimulus condition, there were no significant differences in the amplitudes and latencies between PI patients and healthy controls ($p>0.05$). Mean amplitudes and latencies of the SEPs obtained in the single stimulus condition are shown in Tables 2 and 3.

3.3. SEP recovery function

In healthy controls, the frontal P20 and N30, parietal N20 and P25 component' amplitudes of the test response were suppressed (ratios<1.0) at all ISIs of 20, 60, 100 and 150 ms with respect to those of the control response. The N9 and N13 component amplitudes of the

Table 3
Mean latencies (ms) of SEP components in the single stimulus condition.

Components	N9	N13	N18	P20	N30	N20	P25
Controls							
Mean	8.81	12.05	15.97	19.56	28.58	17.95	23.52
S.D.	0.68	0.75	0.95	1.19	3.25	1.03	2.52
Patients							
Mean	8.96	12.43	16.20	19.79	26.68	18.10	23.54
S.D.	0.58	0.84	1.33	2.18	2.96	0.96	2.17