Suppression of Motor Evoked Potential and H–reflex during Cataplexy in Narcolepsy

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Objectives: To investigate the electrophysiologic mechanism of cataplexy, the authors measured motor evoked potential (MEP) and H-reflex during asymptomatic, cataplectic and post-cataplectic periods in a narcolepsy patient.

Methods: For MEP recording, transcranial magnetic stimulation (TMS) was applied to the right and left hemispheres using a Magstim 200 stimulator and a figure of 8-shaped coil. MEP amplitudes in resting state were measured at stimulus intensities of 120 and 150% of resting motor threshold (rMT). H-reflex was elicited by electrical stimuli on a tibial nerve.

Results: rMT at baseline was 43% in the right and 39% in the left hemisphere. Mean MEP amplitude at baseline was 1.15 mV at a stimulation intensity of 120% rMT and 1.77 mV at 150% rMT. During a cataplectic episode, MEP amplitude abruptly decreased to 0.15 mV at 120% rMT and 0.18 mV at 150% rMT when the patient began to feel facial weakness and experience difficulty talking; subsequently no MEP was evoked during loss of whole body muscle tone. H-reflexes were well elicited during asymptomatic periods (mean amplitude: 2.55 mV at 10.0 mA) whereas H-reflex amplitude abruptly decreased and then disappeared after a cataplectic attack started.

Conclusion: Suppression of both MEP and H-reflex during cataplexy indicates that postsynaptic spinal motor neuron inhibition is the main pathomechanism underlying cataplexy.

Key Words: Narcolepsy, Cataplexy, Transcranial magnetic stimulation, Motor evoked potential, H-reflex

1. Introduction

Cataplexy is the most devastating symptom in narcolepsy patients, and it is characterized by a sudden generalized or focal loss of muscle tone and is usually triggered by strong emotions such as laughter, anger or excitement.¹ Cataplexy is often explained as the occurrence of the physiological phenomenon of rapid eye movement (REM) sleep atonia at an inappropriate moment.² REM sleep atonia is thought to be effected through the inhibition of the cell bodies of alpha motor neurons in the spinal cord by descending influences, a mechanism referred to as “postsynaptic inhibition”.³ This is evidenced clinically by the absence of tendon jerks and by electrophysiologically diminished H-reflexes and F-responses.⁴,⁵ The results of MEP studies in REM sleep are controversial, and in particular, one MEP study during cataplexy showed MEP persistence during cataplexy, which suggested that increased motor cortex excitability overcame spinal inhibition. However, no other MEP study has been reported during cataplexy. In addition, the mechanism of cataplexy remains obscure, based in part on a failure to explain why cataplexy should be triggered by states like laughter, which are not normally associated with REM sleep.

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To investigate the electrophysiological mechanism of cataplexy, we measured motor evoked potentials (MEPs) using transcranial magnetic stimulation (TMS) and H-reflexes by electrical stimulation during asymptomatic periods, cataplectic episodes, and post-cataplectic periods.

2. Methods

An 18-year-old high-school student had suffered from excessive daytime sleepiness (EDS) and frequent episodes of sudden loss of muscle tone triggered by emotional changes. He had experienced daily episodes of transient weakness of face and both shoulders for 1-3 minutes over the previous year, and these cataplectic attacks frequently gradually worsened to involve both legs to the extent of causing him to fall during full-blown cataplexy. There was no blunting of sensorium and he maintained a full awareness of his environment during cataplectic attacks. The described symptoms usually developed when the subject had a strong pleasant feeling. The patient showed short sleep latency (2.5 min) and short REM sleep latency (1.5 min) in overnight polysomnography, and a short mean sleep latency (2.2 min) and five sleep-onset REM periods out of five daytime nap trials in the Multiple Sleep Latency Test. The patient had been treated with modafinil and clomipramine, but he had discontinued these medications one month prior to this presentation due to unsatisfactory efficacy and an expected move to our hospital. Since clomipramine was discontinued, his cataplectic attacks have occurred more frequently and lasted longer. Moreover, although the patient tried to control emotional changes, cataplectic attacks occurred daily to varying degrees.

Informed consent was obtained from the patient after explaining the study protocol and the recording MEP and H-reflex methods used. The Institutional Review Board at the Samsung Medical Center authorized the informed consent form and the study protocol.

Generalized cataplectic spells were easily induced by watching a comical program on TV. MEPS and H-reflexes were recorded during pre-cataplectic asymptomatic periods, cataplectic spells, and post-cataplectic periods.

2.1. MEP recording

Resting motor threshold (rMT) and motor evoked potentials (MEP) were obtained during asymptomatic periods. The patient was seated in an armchair with his head fixed in a plastic foam headrest. TMS was applied to the right and left hemispheres using a Magstim 200 stimulator (Magstim Co., Whitland, Dyfed, UK) with an 8-shaped coil (external diameter of each loop 9 cm).

Surface EMG was recorded from the first dorsal interosseus (FDI) muscle using surface EMG electrodes placed in a belly-tendon montage. EMG raw signals were amplified and bandpass-filtered (20 Hz to 10 kHz). An auditory feedback EMG signal was produced to ensure complete voluntary relaxation of a target muscle. Placement of the magnetic coil over the motor cortex was performed after locating and marking an optimal scalp site in terms of producing MEPs in the FDI muscle with current induced in the brain from posterior to anterior, approximately perpendicular to the assumed line of the central sulcus.

rMT was defined as the lowest stimulator output intensity capable of inducing MEPs of at least 50 μV peak-to-peak amplitude in FDI muscles in the relaxed state during 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 in resting FDI muscles were measured at stimulus intensities of 120 and 150% of rMT. A total of eight stimuli were delivered during each session. Average values were calculated at these two intensities.

To obtain MEP amplitudes during cataplectic spells, a technician waited for the patient to laugh out loud. Two
long cataplectic episodes of approximately 8 and 6 min durations were induced for MEP study. Multiple MEPs were recorded by repeated TMS stimulations every 15 sec during whole cataplexy periods (from initial decrease in facial muscle tone to progression to whole body hypotonia). Stimulation intensities were determined as 120% and 150% of rMT at baseline for each episode.

2.2. H-reflex recording

H-reflex was elicited by stimulating the tibial nerve using an AgCl cathode in the popliteal fossa and a 40 mm diameter anode placed over the patella. Optimum sites for nerve stimulation were first located using a hand-held electrode using the criterion that soleus Ia afferents could be stimulated selectively at low stimulus intensities. The stimulus used was a 1 ms square pulse delivered by a custom-built constant current stimulator. Maximal M wave (Mmax) and the maximal H reflex amplitudes were measured during rest. The subject sat in a comfortable chair, and electrical stimuli were first applied to identify optimal stimulation sites, after which stimulus intensities necessary to elicit Mmax were determined.

Stimuli were applied 15 times every two seconds to obtain 15 H-reflexes during the asymptomatic baseline period and then repeatedly throughout cataplectic and post-cataplectic periods using a Viking IV EMG apparatus (Nicolet Medical) with a 20-10,000 Hz bandwidth and a 100 ms post-stimulus acquisition period. Recorded H-reflexes were stored automatically on a floppy diskette.

One long cataplectic spell of 4 min duration was provoked for H-reflex study and H-reflexes were recorded by repeated stimulations during the pre-cataplectic baseline period, the whole period of cataplexy (from initial facial muscle tone decrease to whole body hypotonia) and the post-cataplectic period.

3. Results

3.1. MEP

rMT at baseline was 43% in the right and 39% in the left hemisphere. Mean MEP amplitudes during the asymptomatic baseline period were 1.15 mV for stimulation at 120% rMT intensity and 1.77 mV for 150% rMT intensity.

Before, during and after the cataplectic attacks, which lasted for 6 min and 8 min, TMS was applied repetitively every 15 seconds. Mean MEP amplitude abruptly decreased from 1.15 mV to 0.15 mV at stimulation of 120% rMT intensity and from 1.77 mV to 0.18 mV at stimulation of 150% rMT intensity at the beginning of a cataplectic episode when the patient felt facial weakness and experienced difficulty talking. No MEP was recorded after whole body muscle tone had been lost.

When the patient started to recover from a cataplectic attack and could talk, but with slurred speech, MEPs were recorded at low amplitude (four rows from the bottom in Fig. 1F) (mean MEP amplitude was 0.71 mV and ranged from 0.35 to 1.36 mV), and then increased quickly. When cataplexy ended and the patient had recovered near normal muscular strength and speech, mean MEP amplitude increased to 1.11 mV (Fig. 1G).

3.2. H-reflex

Mean H-reflex amplitude during the asymptomatic baseline period was 2.55 mV. After a cataplectic spell started, H-reflex amplitude decreased abruptly and then stopped. At the end of a cataplectic spell, small H-reflexes were evoked, but these increased to the normal amplitude level after the patient had recovered fully. After a cataplectic attack is over, H-reflexes of very high amplitude (6.62 mV) were recorded, which subsequently gradually decreased to 3.26 mV. Overall the mean amplitudes of H-reflexes was 4.60 mV during the immediate post-cataplectic period.
Figure 1. Motor evoked potential recordings during a cataplectic attack. During the asymptomatic baseline period, motor evoked potentials (MEP) were well recorded and were of mean amplitude 1.77 mV by stimulation at 150% rMT intensity (A). When the patient started to experience articulation difficulties and motor weakness in all four extremities, MEP amplitudes abruptly decreased, and subsequently no MEPs with occasional diminutive MEPs were recorded during full blown cataplexy (C-E). When our patient recovered but with slurred speech after a cataplectic episode, low amplitude MEPs were recorded (lower four rows in f), and MEP amplitudes subsequently increased (G). However, MEP amplitudes during the immediate post-cataplectic period were smaller than those of asymptomatic baseline period.

4. Discussion

The present study shows that the amplitudes of MEP and H-reflexes decreased at the beginning of a cataplectic attack and ceased during full-blown generalized cataplexy.

One previous report has been issued on motor-evoked responses to TMS during human cataplexy, and in this study it was found that MEP amplitudes and motor thresholds were not remarkably changed during cataplexy versus the asymptomatic period. It was suggested that the preservation of muscle responses during cataplexy is probably due to enhanced cortical excitability to TMS, which might compensate for the postsynaptic spinal inhibition of muscle tone. However, the durations of individual cataplectic attacks were not described in detail, and it is known that if a single cataplectic spell is short that MEP testing by TMS is not feasible. As was observed in the present study, MEPs may be evoked during the initial and terminal periods of cataplexy when spinal motor neurons are not completely shut down. In our patient, a slight MEP reduction was observed during the early period of cataplexy (first row in Fig. 1B).

Our results do not agree with those of this previous report. During the initial period when the patient felt dysarthria and mild muscle weakness, MEPs were recordable but their amplitudes much lower and were subsequently abolished during full-blown generalized cataplexy. The same phenomenon was observed in H-reflex study of our patient.

Thus our results suggest that; 1) The mechanism of atonia during cataplexy involves an inhibition of spinal motor neurons, which is the common pathway for MEP and H-reflex, and 2) that spinal motor neuron inhibition rapidly develops, but not in an all-or-none fashion. We also observed a short MEP recovery period. During the recovery phase from cataplectic spell, MEPs were recorded
in small amplitudes (2\textsuperscript{nd} to 4\textsuperscript{th} rows from bottom in Fig. 1F). In practice, narcolepsy patients are frequently observed to stand slowly after a cataplectic attack.

Several studies have suggested presynaptic involvement during cataplexy. MEP and H-reflex studies in healthy volunteers demonstrated that laughter caused mean MEP areas to increase by 60% and mean H-reflex amplitude to decrease by 33\%.\textsuperscript{7} This pattern demonstrates that postsynaptic inhibition is not the sole cause of motor inhibition during laughter, the strongest trigger of cataplexy. Our previous brain SPECT studies in narcolepsy patients with cataplexy showed reduced CBF during the asymptomatic period and increased CBF during a cataplectic attack in bilateral premotor cortices, which contain negative motor areas.\textsuperscript{8,9} These findings suggest presynaptic involvement during a cataplectic spell.

Reported MEP responses during REM sleep are discordant in the literatures. An early study reported that response amplitudes to TMS are depressed during slow wave sleep (SWS) and enhanced or similar during REM sleep,\textsuperscript{10} whereas reduced motor responses to magnetic stimulation and increased rMTs during REM sleep awakenings were demonstrated in other studies.\textsuperscript{11,12} In another study, amplitudes of muscle responses during REM sleep were extremely variable, and for example ranged in the trapezius from -100\% to +473\% versus wakefulness during the magnetic stimulation of human brain during phasic and tonic REM sleep.\textsuperscript{13} In this study, it was suggested that responses to TMS during REM sleep may be preserved, with decreased or increased amplitude, because of a fluctuating cortical excitability and/or spinal inhibition during REM sleep in humans. Thus, motor physiology during REM sleep appears to be more complex and variable than that of cataplexy. However, maintaining REM sleep without arousals during TMS is a critical issue in these studies. If a patient has arousals during TMS, motor response is greatly changed. Cortical excitability during REM sleep awakening is also variable, a significant increase in intracortical facilitation at 10 and 15 ms interstimulus intervals was reported by one study,\textsuperscript{14} whereas an increase in motor threshold of
>10% was observed in other. Increased cortical excitability during REM sleep has been suggested to be due to prominent brain activities during REM sleep, which are not found during cataplexy. One brain SPECT study demonstrated significantly increased CBF in the occipital lobe during REM sleep as compared to that during cataplectic attack, which suggested the absence of dreaming during a cataplectic attack. However, H-reflexes were found to be reduced or absent during REM sleep and cataplexy (our result). These observations indicate that cortical excitability may differ in REM sleep and cataplexy, although spinal motor neuron inhibition occurs during both. Furthermore, increased CBF in negative motor areas during cataplexy versus REM sleep supports that motor inhibition is more predominant during cataplexy.

The present study demonstrates a rapid decrease with subsequent abolishment of MEP and H-reflex during a cataplectic attack, which suggests that brainstem inhibition of spinal motor neurons is a predominant mechanism of cataplexy. However, we were unable to find evidence of increased cortical excitability during cataplexy.

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REFERENCES