Cortical excitability and sleep deprivation: a transcranial magnetic stimulation study

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Abstract
The objective was to assess the changes in cortical excitability after sleep deprivation in normal subjects. Sleep deprivation activates EEG epileptiform activity in an unknown way. Transcranial magnetic stimulation (TMS) can inform on the excitability of the primary motor cortex. Eight healthy subjects (four men and four women) were studied. Transcranial magnetic stimulation (single and paired) was performed by a focal coil over the primary motor cortex, at the “hot spot” for the right first dorsal interosseous muscle. The following motor evoked potential features were measured: (a) active and resting threshold to stimulation; (b) duration of the silent period; (c) amount of intracortical inhibition on paired TMS at the interstimulus intervals of 2 and 3 ms and amount of facilitation at interstimulus intervals of 14 and 16 ms. The whole TMS session was repeated after a sleep deprivation of at least 24 hours. After the sleep deprivation, the threshold to stimulation (in the active and resting muscle), as well as the silent period, did not change significantly. By contrast, the paired stimulus study showed a significant (p<0.05) reduction in both intracortical inhibition and facilitation. Thus, TMS showed that sleep deprivation is associated with changes in inhibition-facilitation balance in the primary motor cortex of normal subjects. These changes might have a link with the background factors of the “activating” effects of sleep deprivation.

Keywords: sleep deprivation; cortical excitability; transcranial magnetic stimulation

Sleep deprivation is a powerful activator of seizures in nearly all types of epilepsy. It is also the best method for provoking EEG epileptiform abnormalities, or enhancing those induced by intermittent light stimulation and hyperventilation. Few workers attributed the epileptic activation to drowsiness alone, and most concluded that sleep deprivation has a specific activating effect on its own. However, its intrinsic mechanisms are still obscure. In animals, sleep deprivation results in a lowering of the thresholds to electroshock convulsions and for kindling to occur. This could relate to a change in the balance between excitatory and inhibitory neurotransmitters.

Transcranial magnetic stimulation (TMS) is a safe probe of neuronal excitability of the primary motor cortex. Several variables contribute to assessment, of which the threshold to stimulation and the silent period may be assessed by the single pulse technique. Then, the paired pulse method allows measurement of the so called intracortical (corticocortical) inhibition and facilitation curve. This describes the effects that a weak (submotor threshold) conditioning magnetic shock induces on a test stimulus set to produce a motor evoked potential (MEP) of 0.5–1 mV. Intracortical inhibition and facilitation are thought to reflect the excitability of separate populations of interneurons intrinsic to cortical area 4. Thus, we used these TMS methods to detect possible changes in the cortical physiology of normal subjects induced by a sleep deprivation of at least 24 hours.

Subjects and methods
Eight healthy volunteers (four men and four women, mean age 28.7 (SD 4.2) years; range 25 to 36 years) were studied. All gave their informed consent. The local ethics committee approved the experimental procedures. Awake subjects sat in a comfortable chair with their eyes open. Two monophasic electromagnetic stimulators (Magstim 200, Magstim Co, Whitland, Dyfed, UK) were used coupled with a Bistim device. The TMS was performed with a “figure of eight” or “butterfly” coil, delivering focal pulses over the left primary motor cortex, at the “hot spot” for the right first dorsal interosseous muscle. Motor evoked potentials (MEPs) were recorded from this muscle via surface Ag-AgCl cup electrodes (diameter=9 mm). A Viking 4 machine (Nicolet Biomedical, Madison, WI, USA) amplified (0.1–5 mV/cm) and filtered (20–5000 Hz) the signal, then stored it on hard disks. The sampling rate for digitisation was 25 kHz. Firstly, the following variables were determined with a single stimulator: (1) relaxed threshold (RT), defined as the minimum stimulator intensity that evoked at least 50% of responses with an amplitude of 50 µV or more (sensitivity 0.1 mV/division,
Comparison of the inhibitory and facilitatory effects of sleep deprivation on inhibitory (3 ms) and facilitatory (16 ms) interstimulus intervals. Each tracing represents the average of eight control (upper tracing) and eight experimental (lower tracing) motor evoked potentials. A significant reduction of both inhibition (p = 0.025) and facilitation (p = 0.019) after sleep deprivation was found. Black column = before sleep deprivation (SD); grey column = after SD; bars = standard deviation. (B) Effects of sleep deprivation on the single ISIs of the inhibition and facilitation curve. Squares = before SD; diamonds = after SD; bars = standard deviation. (C) Typical example (subject 3) of the effects of sleep deprivation on inhibitory (3 ms) and facilitatory (16 ms) interstimulus intervals. Each tracing represents the average of eight control (upper tracing) and eight experimental (lower tracing) motor evoked potentials.

Results

In all subjects, the average score on the Stanford sleepiness scale was equal to 1 before, and equal to 3.5 after the sleep deprivation. In other words, somnolent subjects were still sufficiently alert and able to follow the instructions during the experiments.
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and perhaps obscure, pathophysiology, yet cortex, as the conditioning pulses are too weak agonists were attributed a similar effect, antagonists. The first (1–5 ms) phase, inhibition, the silent period to alterations of the primary motor cortex remained unaltered. Changes in TMS, however, did not affect the motor threshold or the silent period. Motor threshold most likely reflects axon membrane excitability, because drugs acting on voltage and frequency dependent sodium and calcium channels modulate it. Thus we assume that sleep deprivation had no direct effect on the membrane of the nerve cells presynaptic to the corticospinal neuron; these largely represent the primary excitation site of TMS. The silent period has a more complex, and perhaps obscure, pathophysiology, yet sleep deprivation seemed to alter none of its many putative generators. The sensitive variable was the intracortical inhibition and facilitation curve, both phases of which were depressed. The first (1–5 ms) phase, inhibition, is thought to rely on a different interneuron circuit from the second one (7–16 ms)—that is, facilitation. Both arise from the cerebral cortex, as the conditioning pulses are too weak to activate the corticospinal tract. Some authors made inferences to the transmitters implied in these phenomena. Antiepileptic GABAergic drugs were able to reduce facilitation, and, to some extent, enhance inhibition. NMDA-receptor antagonists and dopamine agonists were attributed a similar effect, whereas the reverse was true for dopamine antagonists. On this basis, paired pulse TMS was proposed as an assay of both excitability and pharmacology of the interneuronal circuitry in the primary motor cortex. In general, most of the conditions studied showed an inverse correlation between inhibition and facilitation. If the second decreased, the first increased, and vice versa. A partial exception to this rule might be the effects of vigabatrin, a typical GABAergic drug that reduced facilitation without affecting inhibition, or the serotonergic 5HT1D agonist zolmitriptan, which reduced inhibition leaving facilitation unaffected. In general, the intimate pharmacological nature of the paired pulse effects seems to need further study. In our present findings, however, loss of inhibition was unexpectedly coupled with reduction of facilitation. The coexistence of such apparently opposing phenomena is difficult to interpret. In theory, proepileptogenic and antiepileptogenic effects would seem to cancel each other. To us, it may be more useful to note that sleep deprivation was associated with a general hypoactivity of cortical area 4 interneurons, reflected by the flattening of the paired pulse curve. Besides, excess excitation, and defective but also excessive inhibition, interact in a very complex manner to predispose the cortex to epileptiform discharges. Thus, we cannot exclude the possibility that our findings might be compatible with an “activating” net effect within the cortex.

As our method explored the primary motor cortex, the relevance of our data to those epileptiform activities which might affect the brain with a different topography may be questioned. Yet, area 4 excitability was found altered in various epileptic syndromes, not only generalised but also partial (for example, with the temporal lobe epilepsy). The data suggest that intracortical inhibition is related to a more severe EEG and clinical picture. Thus, area 4 physiology—in the epilepsy field—proved sensitive to phenomena that exceed its boundaries.

In conclusion, TMS disclosed some subtle changes in normal cortical physiology, which may serve as a model for studying the “activating” effects of sleep deprivation in patients with epilepsy.

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