Transcranial Magnetic Stimulation and Sleep Deprivation as Experimental Tools: When Sleep Deprivation Is Too Exciting

Sleep Deprivation Increases Cortical Excitability in Epilepsy: Syndrome-Specific Effects. Badawy RA, Curatolo JM, Newton M, Berkovic SF, Macdonell RA. *Neurology* 2006;67(6):1018–1022. OBJECTIVE: To use transcranial magnetic stimulation (TMS) to investigate the hypothesis that sleep deprivation increases cortical excitability in people with epilepsy. METHODS: We performed paired pulse TMS stimulation, using a number of interstimulus intervals (ISIs) on each hemisphere of 30 patients with untreated newly diagnosed epilepsy (15 idiopathic generalized epilepsy [IGE] and 15 focal epilepsy) and on the dominant hemisphere of 13 healthy control subjects, before and after sleep deprivation. RESULTS: Both hemispheres in patients with IGE and the hemisphere ipsilateral to the EEG seizure focus in those with focal epilepsy showed an increase in cortical excitability following sleep deprivation at a number of ISIs. This change in excitability was most prominent in the patients with IGE. Although there were minor changes after sleep deprivation in control subjects and the contralateral hemisphere in the focal epilepsy group seen at the 250-millisecond ISI, it was less than that in the other groups. CONCLUSIONS: Sleep deprivation increases cortical excitability in epilepsy; the pattern of change is syndrome dependent.

Effects of Sleep Deprivation on Cortical Excitability in Patients Affected by Juvenile Myoclonic Epilepsy: A Combined Transcranial Magnetic Stimulation and EEG Study. Manganotti P, Bongiovanni LG, Fuggetta G, Zanette G, Fiaschi A. *J Neurol Neurosurg Psychiatry* 2006;77(1):56–60. OBJECTIVE: To investigate the effect of sleep deprivation on corticospinal excitability in patients affected by juvenile myoclonic epilepsy (JME) using different transcranial magnetic stimulation (TMS) parameters. METHODS: Ten patients with JME and 10 normal subjects underwent partial sleep deprivation. Motor threshold (MT), motor evoked potential amplitude (MEP), and silent period (SP) were recorded from the thenar eminence (TE) muscles. Short latency intracortical inhibition (SICI) and short latency intracortical facilitation (SICF) were studied using paired magnetic stimulation. TMS was performed before and after sleep deprivation; EEG and TMS were performed simultaneously. RESULTS: In patients with JME, sleep deprivation induced a significant decrease in SICI and an increase in SICF, which was associated with increased paroxysmal activity. A significant decrease in the MT was observed. No significant changes in any TMS parameters were noted in normal subjects after sleep deprivation. The F wave was unchanged by sleep deprivation in both control subjects and in patients with JME. CONCLUSIONS: In patients with JME, sleep deprivation produces increases in corticospinal excitability in motor areas as measured by different TMS parameters.

COMMENTARY

Sleep deprivation is increasingly recognized as an important seizure precipitant, and its relationship to epilepsy was reviewed previously in *Epilepsy Currents* (1). In a prospective survey of 400 patients with epilepsy, Frucht and colleagues found that 62% reported at least one seizure precipitant (2). Stress was the most commonly reported precipitant and occurred in 30% of patients. However, sleep deprivation was the second most common precipitant overall, reported by 18% of patients. Sleep deprivation was reported as a seizure precipitant most frequently in those with idiopathic generalized epilepsies. Others have reported that sleep deprivation is a precipitant in 77% of patients with juvenile myoclonic epilepsy (JME) (3). Thus, sleep deprivation is more than a casual precipitant and has a differentially strong influence on patients with JME.

The studies by Badawy et al. and Manganotti et al. used transcranial magnetic stimulation (TMS) to examine the state of excitability of the motor system. The great value of TMS is that it can noninvasively examine excitability in an awake, intact person; it is applied to the scalp and stimulates a specified area of cortex. The motor response is quantified by measuring the EMG response from the thenar muscles. The state of inhibition can be measured using principles of experimental neurophysiology. A consistent-amplitude, reproducible response can be measured after each stimulus if sufficient time is allowed to elapse between stimulations. Neuronal excitation is followed immediately by inhibition, either from an intrinsic neuronal afterhyperpolarization or because the neuron receives GABAergic inhibitory input. If a second stimulation is delivered during the period when the neuron is inhibited, then there is a decreased response. Paired-pulse inhibition paradigms use the second response to measure the duration and strength of the inhibition. If the response to the second stimulus is as strong as to the first stimulus, then inhibition is impaired.

It is surprising that impaired inhibition was demonstrated so clearly and easily in these experiments, as it has been the subject of such intense scrutiny and controversy in the experimental epilepsy world. Both TMS studies reviewed here reported evidence of impaired inhibition in epilepsy and found the second pulse to be affected at an interpulse interval that potentially

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could result from impaired GABAergic inhibition. However, it is important to note that these TMS experiments only measure the final output of the system and that the simple observation of impaired inhibition on paired-pulse stimulation cannot be taken as direct evidence of impairment of GABAergic interneurons. Instead, it is merely the demonstration of an imbalance of excess excitation and impaired inhibition, possibly representing a final common pathway. If the investigators had given patients a benzodiazepine, it could have revealed whether GABAergic inhibition was specifically affected. The finding of impaired inhibition in epilepsy may seem like a small accomplishment because it has previously been demonstrated in animal models and has been an intense focus of animal research. However, the TMS studies reviewed here are some of the first studies to demonstrate impaired inhibition in humans and particularly in patients with JME.

An important aspect of the study by Badawy et al. is the inclusion of patients with focal epilepsy, for whom the investigators found the same impairment of inhibition as seen in patients with JME, but it appeared only in the hemisphere containing the seizure focus. Thus, the findings may be broadly applicable to epilepsy. It is possible that hyperexcitability represents a general phenomenon in epilepsy, part of the complex milieu needed for epilepsy to occur. However, why would hyperexcitability be present only in the neocortex of one hemisphere?

The findings support some aspects of the known pathophysiology of JME. Although there is no consistent, single pathophysiologic or genetic defect in JME, the most commonly reported mutations affect GABA neurotransmission (e.g., *GABRA1*, encoding the $GABA_A$ $\alpha 1$ subunit), chloride channels (e.g., *CLCN2*), and potassium channels (e.g., *KCNQ3*), among others (4). The fact that the TMS studies support a seemingly consistent defect of inhibition in localization-related and generalized epilepsies suggests that there is indeed a final common pathway of expression, even if there are many different systems affected to arrive there.

Sleep deprivation provides unique insights into epilepsy, but its role in epilepsy also provides insights into the basic biology of sleep deprivation. Sleep deprivation in an animal model can impair neurogenesis (5). It seems reasonable that if sleep deprivation impairs GABAergic inhibition, then it could allow excitatory neurotransmission to go unchecked and contribute to excitotoxicity, at least at the level of the individual neuron. Although speculative, the theory illustrates how this type of active experimental manipulation in human epilepsy can lead to insights about the basic biology of neuronal function.

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