Sleep Deprivation and Epilepsy

Beth A. Malow, M.D., M.S.

Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee

> A patient with epilepsy should "spend the day awake and the night asleep. If this habit be disturbed, it is not so good . . . worse of all when he sleeps neither night nor day." —Hippocrates (1)

This review summarizes the data for and against sleep deprivation as a facilitator of epileptic seizures and interictal epileptiform discharges. Much of these data are derived from clinical studies; however, basic science investigations are greatly needed to determine the influence of sleep deprivation on seizure susceptibility and neuronal function. Study of the effects of sleep deprivation on epilepsy may create a window of opportunity that could help decipher how seizures are triggered and facilitated, potentially providing an avenue for future interventions.

Introduction

Sleep is a highly sought-after commodity in our fast-paced society, with sleep loss more potent than alcohol in causing sedation (2). Sleep deprivation has been associated with a variety of physiologic effects, ranging from impaired appetite suppression (3) to altered learning and memory (4). Might sleep deprivation also affect seizure control in patients with epilepsy?

A series of articles in the 1960s and 1970s suggested that sleep deprivation was a promoter of epileptic seizures and a facilitator of interictal epileptiform discharges. Forty years later, clinical research studies are critically examining these assumptions. Meanwhile, basic science investigations of the effects of sleep deprivation on memory and neuronal excitability, at both the behavioral and cellular levels, have heightened our interest in the impact of sleep deprivation on hippocampal function. This review presents the evidence for and against sleep deprivation as a trigger for epileptic seizures and interictal activity.

Address correspondence to Beth A. Malow, M.D., M.S., Vanderbilt University Medical Center, 2100 Pierce Avenue, Room 352, Nashville, Tennessee 37212, U.S.A. E-mail: beth.malow@vanderbilt.edu

Epilepsy Currents, Vol. 4, No. 5 (September/October) 2004 pp. 193–195
Blackwell Publishing, Inc.

Case Series: Does Sleep Deprivation Alone or in Combination with Other Factors Promote Epileptic Seizures?

In 1962, Janz (5) reported that in patients with generalized tonic–clonic seizures, sleep deprivation, along with alcohol consumption, was a known precipitant of epileptic seizures, particularly seizures on awakening. Cases from the 1960s and 1970s focused on military personnel. In one series, pilots had their first, single generalized tonic–clonic seizure in the setting of sleep deprivation, work-related stress, missed meals, and in one case, heavy alcohol use (6,7). The majority of these individuals had evidence of generalized spike-and-wave activity on EEGs. In another series, soldiers were sleep deprived for prolonged periods (many for >48 hours), and the majority had ingested alcohol the night before their seizures (8). In a study of "stress convulsions," provoking factors included lack of sleep but also emotional, somatic, and intellectual stress, abuse of alcohol, and abuse of drugs (9).

Similar results were found in a patient survey in which precipitants that might trigger or exacerbate seizures were cited, although alcohol intake was not noted (10). Stress, fatigue, and sleep deprivation were commonly reported precipitants—often coexisting in the same individuals. Sleep deprivation was noted as a precipitant in 28% of patients with idiopathic generalized epilepsy and in 27% of patients with temporal lobe epilepsy. A relation was found between relative sleep deprivation and occurrence of temporal lobe seizures in patients who kept written daily diaries of the duration of night sleep and dates of seizures (11).

Because sleep deprivation rarely occurs in a vacuum but rather in association with physical or emotional stress and substance abuse, it is difficult to tease out the relative contribution of sleep deprivation. In a study of 84 patients with medically refractory partial epilepsy who were undergoing inpatient monitoring, patients were assigned in consecutive blocks to either sleep deprivation every other night or to normal sleep (12). Seizures per day for complex partial, secondarily generalized, and combined complex partial and secondarily generalized were calculated from admission until end of protocol and did not differ significantly between the sleep-deprived and normal sleep groups. The sleep deprivation and normal sleep subjects did not differ in age, sex, seizure localization, or percentage dosage reduction in antiepileptic drugs from baseline at days 1 to 3 of monitoring. The data suggest that for patients with partial epilepsy, monitored in an inpatient setting relatively free of the stresses of everyday life, sleep deprivation does not affect seizure

frequency. This is a group effect, however, and individual patients may be prone to the effects of sleep deprivation on seizure frequency to a greater extent than others. Furthermore, chronic sleep deprivation may worsen seizure frequency. For example, sleep disorders, such as obstructive sleep apnea, may disrupt sleep and lead to chronic sleep loss. In several retrospective and prospective case series, treatment of obstructive sleep apnea has been associated with improvement in seizure control even when medications are not altered (13–16).

Interictal Spiking and Sleep Deprivation

In parallel with case series that show that sleep deprivation may activate seizures, EEG studies also have implicated sleep deprivation in the promotion of interictal epileptiform discharges (IEDs) (17,18). Ordering an EEG, after sleep deprivation, for suspected seizures has become a widespread but inconsistent practice (19). As non–rapid eye movement (NREM) sleep is a powerful activator of IEDs (20,21), the question has arisen as to whether sleep deprivation facilitates IEDs simply because sleep-deprived patients are more likely to fall asleep during EEG procedures or because the study provides an additional chance to demonstrate IEDs not previously recorded. A critical review of the literature, with emphasis on method, established that sleep deprivation facilitates IEDs, even apart from its effects on sleep (22). Exactly how sleep deprivation might activate epileptic regions, however, is unclear. Further support for the theory that sleep deprivation activates IEDs came from a study documenting increased occurrence of IEDs during sleep deprivation in patients whose routine EEGs did not show IEDs (23). Most of the patients had discharges recorded after sleep deprivation, with activation rates not significantly different in wakefulness as compared with sleep. Therefore the majority of evidence supports the hypothesis that sleep deprivation activates IEDs.

Basic Science Investigations of Sleep Deprivation: Does Sleep Deprivation Affect Neuronal Excitability?

How can the effects of sleep deprivation and its presumed lowering of seizure threshold be explained on a neuronal level? The largest body of literature concerning the effects of sleep deprivation on neuronal function pertains to aspects of learning and memory. McDermott et al. (24) recently reported on behavioral and membrane excitability effects of sleep deprivation in hippocampal neurons. They exposed rats to 72 hours of sleep deprivation (primarily rapid-eye-movement or REM-deprived sleep) and documented impaired performance on a hippocampus-dependent spatial learning task but not on an amygdala-dependent task. They also showed that sleep deprivation reduced membrane excitability. After 72 hours of REM-sleep deprivation, CA1 pyramidal neurons, but not dentate granule cells, had a lower membrane input resistance and decreased action potentials in response to depolarizing current. Sleep deprivation also inhibited long-term potentiation in both CA1 pyramidal neurons and dentate granule cells. A strength of this study was that the investigators attempted to differentiate the effects of sleep deprivation from the effects associated with nonspecific stress by using various platforms to promote sleep deprivation or immobilization stress. One cannot generalize findings from this study, whose focus was on learning and memory, to the impact of sleep deprivation on epilepsy. Such a study would require analysis of measures of epileptogenicity in an animal model of epilepsy, although the work of McDermott et al. can provide useful methodological approaches for inducing specific forms of sleep deprivation.

To date, basic science studies of the effects of sleep deprivation on epilepsy have been largely observational—at the level of the organism rather than the neuron. Sleep deprivation increased susceptibility to kindled and penicillin-induced seizure events in cats, during both waking and sleep (25). In a genetic model of absence epilepsy, rats were deprived of sleep for 12 hours by shaking of their cages whenever EEG-detected sleep occurred. During the first 4 hours of the sleep-deprivation period, an increase in the number of spike–wave discharges was found, whereas in the following hours, epileptic activity returned to baseline values (26). Limitations of these investigations are that sleep deprivation has not been separated from nonspecific stress. Other investigations focusing on REM sleep have supported the construct that REM sleep and its components (e.g., hippocampal theta rhythm) suppress seizure activity, whereas REM sleep deprivation facilitates seizures (27–29). If this construct is correct, then increasing the duration of REM sleep should suppress seizure activity. Seizure susceptibility in rats, as measured by the threshold current required to elicit after-discharges in the amygdala, has been shown to decrease relative to the duration of carbachol-induced REM sleep (27).

Effects of Sleep Deprivation on Epilepsy: Future Directions for Research

A growing interest is expressed in research on the effects of sleep deprivation in every aspect of medical care; epilepsy is not an exception. In animal models of epilepsy, methods can be applied to promote sleep deprivation, independent of nonspecific stress, and both the behavioral as well as the cellular aspects can be studied.

Clinical investigations can complement basic science studies in furthering an understanding of how sleep deprivation influences epilepsy. A variety of experimental paradigms can be considered, including assessment of the impact of chronic sleep deprivation on epilepsy resulting from insufficient sleep as well as from common sleep disorders that disrupt sleep, such as obstructive sleep apnea. These investigations may help pinpoint

when seizures more commonly occur after sleep deprivation. For example, are post–sleep-deprivation seizures taking place in the day during times of drowsiness (suggesting a sleep-state–related facilitation of seizures) or during full alertness (suggesting altered neuronal excitability), or are they occurring at night during transitions in and out of sleep (suggesting that sleep-related transitions promote seizure activity)? Research on how sleep deprivation triggers or facilitates seizure may provide insight into effective clinical interventions.

References

1. Lloyd GER. Hippocrates, the Sacred Disease, Aphorisms, and Prognosis. In: Lloyd GER, ed. Hippocratic writings. Boston: Penguin, 1983:237–251, 206–236, 170–185.
2. Roehrs T, Burduvali E, Bonahoom A, Drake C, Roth T. Ethanol and sleep loss: a "dose" comparison of impairing effects. Sleep 2003;26:981–985.
3. Mullington JM, Chan JL, Van Dongen HPA, Szuba MP, Samaras J, Price NJ, Meier-Ewert HK, Dinges DF, Mantzoros CS. Sleep loss reduces diurnal rhythm amplitude of leptin in healthy men. J Neuroendocrinol 2003;15:851–854.
4. Maquest P. The role of sleep in learning and memory. Science 2001;294:1048–1051.
5. Janz D. The grand mal epilepsies and the sleeping-waking cycle. Epilepsia 1962;3:69–109.
6. Bennett DR. Sleep deprivation and major motor convulsions. Neurology 1963;13:953–958.
7. Bennett DR. Sleep deprivation, neurological and EEG effects. Aerospace Med 1964; 35:888–890.
8. Gunderson C, Dunne P, Feyer T. Sleep deprivation seizures. Neurology 1973;23:678–686.
9. Friis ML, Lund M. Stress convulsions. Arch Neurol 1974;31:155–159.
10. Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 2000;41:1534–1539.
11. Rajna P, Veres J. Correlations between night sleep duration and seizure frequency in temporal lobe epilepsy. Epilepsia 1993;34:574–579.
12. Malow BA, Passaro E, Milling C, Minecan DN, Levy K. Sleep deprivation does not affect seizure frequency during inpatient video-EEG monitoring. Neurology 2002;59:1371–1374.
13. Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. Neurology 1994;44:2060–2064.
14. Vaughn BV, D'Cruz OF, Beach R, Messenheimer JA. Improvement of epileptic seizure control with treatment of obstructive sleep apnoea. Seizure 1996;5:73–78.
15. Malow BA, Fromes GA, Aldrich MS. Usefulness of polysomnography in epilepsy patients. Neurology 1997;48:1389–1394.
16. Malow BA, Weatherwax KJ, Chervin RD, Hoban TF, Marzec ML, Martin C, Binns LA. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. Sleep Med 2003;4:509–515.
17. Mattson RH, Pratt KL, Calverley JR. Electroencephalograms of epileptics following sleep deprivation. Arch Neurol 1965;13:310–315.
18. Pratt KL, Mattson RH, Weikers NJ, Williams R. EEG activation of epileptics following sleep deprivation: a prospective study of 114 cases. EEG Clin Neurophysiol 1968;24:11–15.
19. Glick TH. The sleep-deprived electroencephalogram: evidence and practice. Arch Neurol 2002;59:1235–1239.
20. Sammaritano M, Gigli GL, Gotman J. Interictal spiking during wakefulness and sleep and the localization of foci in temporal lobe epilepsy. Neurology 1991;41:290–297.
21. Malow BA, Lin X, Kushwaha R, Aldrich MS. Interictal spiking increases with sleep depth in temporal lobe epilepsy. Epilepsia 1998;39:1309–1316.
22. Ellingson R, Wilken K, Bennett D. Efficacy of sleep deprivation as an activation procedure in epilepsy patients. J Clin Neurophysiol 1984;1:83–101.
23. Fountain NB, Kim JS, Lee SI. Sleep deprivation activates epileptiform discharges independent of the activating effects of sleep. J Clin Neurophysiol 1998;15:69–75.
24. McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC. Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 2003;23:9687–9695.
25. Shouse MN. Sleep deprivation increases susceptibility to kindled and penicillin seizure events during all waking and sleep states in cats. Sleep 1988;11:162–171.
26. Drinkenburg WHIM, Coenen AML, Vossen JMH, vanLuijtelaar ELJM. Sleep deprivation and spike-wave discharges in epileptic rats. Sleep 1995;18:252–256.
27. Kumar P, Raju TR. Seizure susceptibility decreases with enhancement of rapid eye movement sleep. Brain Res 2001;922:299–304.
28. Shouse M, Siegel J, Wu M, Szymusiak R, Morrison A. Mechanism of seizure suppression during rapid-eye movement (REM) sleep in cats. Brain Res 1989;505:271–282.
29. Miller J, Turner G, Gray B. Anticonvulsant effects of the experimental induction of hippocampal theta activity. Epilepsy Res 1994;18:195–204.