To Not Sleep, Perchance to Seize

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Sleep Deprivation Exacerbates Seizures and Diminishes GABAergic Tonic Inhibition

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Patients with epilepsy report that sleep deprivation is a common trigger for breakthrough seizures. The basic mechanism of this phenomenon is unknown. In the Kv1.1<sup>−/−</sup> mouse model of epilepsy, daily sleep deprivation indeed exacerbated seizures though these effects were lost after the third day. Sleep deprivation also accelerated mortality in ~52% of Kv1.1<sup>−/−</sup> mice, not observed in controls. Voltage-clamp experiments on the day after recovery from sleep deprivation showed reductions in GABAergic tonic inhibition in dentate granule cells in epileptic Kv1.1<sup>−/−</sup> mice. Our results suggest that sleep deprivation is detrimental to seizures and survival, possibly due to reductions in GABAergic tonic inhibition.

Commentary

Sleep and seizures have a well-recognized bidirectional relationship that is discussed widely in the literature—seizures affect sleep quantity and quality, and sleep disruption, especially sleep deprivation, enhances seizure likelihood. Indeed, sleep deprivation is associated with increased seizure probability in nearly all forms of epilepsy. Clinicians routinely advise patients that not getting enough sleep may lead to breakthrough seizures, with the presumption that sufficient sleep is a modifiable risk factor that is, at least to some degree, under an individual’s control. Yet, controversy persists about the validity of this clinical dictum, with uncertainty as to whether the presumed causal relationship between sleep deprivation, increased interictal discharges, and seizure provocation is supported by data. Clinical studies have shown a spectrum of outcomes—some conclude that sleep deprivation is a seizure trigger, while others have not suggested a causal relationship. The only available randomized controlled study, performed on adults with epilepsy admitted to an epilepsy monitoring unit, failed to show that sleep deprivation increased or exacerbated seizures.

From a mechanistic perspective, sleep deprivation increased cortical excitability in focal and generalized epilepsies in patients, as shown using transcranial magnetic stimulation. The relationship between sleep deprivation and seizure occurrence has also been shown in animal models, but few studies have investigated the underlying mechanisms. If such mechanisms could be elucidated, targeted therapies might be feasible.

Against this background, Konduru and colleagues examined the effect of sleep deprivation in a genetic animal model of temporal lobe epilepsy, the Kv1.1 knockout mouse (Kv1.1<sup>−/−</sup>). These mice harbor a mutation in the alpha subunit of the voltage-gated delayed rectifier potassium channel K<em>cna1</em>, making them prone to spontaneous seizure generation as well as to sudden unexpected death (thus of relevance to understanding SUDEP, sudden unexpected death in epilepsy). These mutant mice also have disrupted sleep at baseline. In this study, the authors reduced sleep time in adult Kv1.1<sup>−/−</sup> mice even further by keeping them awake (with “gentle” handling) 4 hours per day during a period of time when they ordinarily sleep, for 5 days in a row. EEG recordings showed that these sleep-deprived mice had significantly more electrographic seizures on the second, third, and fourth days of sleep deprivation, but this effect wore off and their seizure counts were not different from controls (Kv1.1<sup>−/−</sup> mice without sleep deprivation) on the fifth day of sleep deprivation and returned to baseline levels after sleep deprivation was stopped. Furthermore, there was a dramatic increase in seizure-associated deaths in sleep-deprived Kv1.1 null mice (52% mortality) compared with Kv1.1 null mice that were not sleep deprived (0% mortality). Thus, in this model, modest sleep deprivation was associated with a transiently higher seizure frequency and a greater risk of seizure-related mortality.

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The authors then explored possible mechanisms by which sleep deprivation caused increased seizures. They performed whole-cell voltage-clamp recordings of dentate gyrus (DG) neurons in hippocampal slices of Kv1.1^−/− mice that were sleep deprived compared with those not sleep deprived. The hypothesis was that gamma-aminobutyric acid (GABA) currents would be reduced in sleep-deprived mutants in the DG, a sub-region of hippocampus that is responsible for gating signal flow through the hippocampus. GABA, the most prevalent inhibitory neurotransmitter in the brain, is intimately involved in both sleep regulation and in the excitation/inhibition balance that governs neuronal excitability. Both major types of GABA currents were evaluated: phasic and tonic. Phasic GABA currents are mediated by presynaptic release of GABA onto postsynaptic GABA-A receptors, while tonic GABA currents are mediated by ambient GABA diffusing throughout the extracellular space onto extrasynaptic GABA-A receptors. In the DG, tonic GABAergic inhibition is primarily mediated via GABA-A receptors containing the specific subunits, alpha-4 and delta. The authors speculated that decreased tonic inhibition could facilitate seizures by allowing greater excitation (reduced inhibition) in hippocampal circuits and their connections.

Konduru and colleagues found that miniature GABA-mediated inhibitory postsynaptic currents (IPSCs) in hippocampal dentate gyrus neurons from sleep-deprived Kv1.1 knockout mice were reduced (both current magnitude and density) compared with nonsleep-deprived mutants. This reduction in tonic GABAergic inhibition may contribute to increased excitability already present in Kv1.1 null mice, leading to increased seizures as well as increased risk of SUDEP. By contrast, phasic inhibition did not differ between the two groups. Notably, in wild-type mice, no differences in tonic GABA current were seen in sleep-deprived mice compared with nonsleep-deprived controls, suggesting that reduced tonic GABAergic inhibition is not a universal explanation for the effects of sleep deprivation-increased seizures. Clearly, it is crucial to evaluate other epilepsy models as well.

These results suggest that sleep deprivation in Kv1.1 null mice is associated with increased electrophysiological seizure occurrence and that a reduction of tonic GABAergic inhibition may comprise part of the mechanism. Obviously there are many potential additional or alternative contributors to the altered circuit excitability in Kv1.1 null mice, with and without sleep deprivation, including other aspects of GABAergic function (e.g., receptor subunit type and expression (GABA-A, GABA-B), neurotransmitter synthesis, abundance, uptake, and degradation). It is not clear why tonic GABA current is higher at baseline in nonsleep-deprived Kv1.1^−/− mice; perhaps it is a protective or compensatory mechanism for the seizure-induced sleep disruption already present in the mutants. Moreover, it is not known why tonic GABA current is reduced (to the levels seen in Kv1.1^+/+ mice) as a result of sleep deprivation, but both total tonic current and tonic current density are similar in sleep-deprived null mice and wild-type mice with or without sleep deprivation. Furthermore, mechanisms related to increased excitatory neurotransmission need to be investigated.

The Kv1.1 null mouse is an appropriate model to begin to sort out the mechanisms of sleep deprivation-induced seizures, because of its well-established abnormalities in sleep integrity and circadian rhythms and its predisposition to SUDEP. In this and other epilepsy models, a sleep dose-response relationship needs to be evaluated, and other brain regions involved in sleep regulation should be assessed. Reasons for the transient nature of the sleep deprivation-induced seizure worsening also remain unclear. Finally, it is possible that GABA receptors (or specific receptor subunits) might be differentially targetable in different types of epilepsy. Sleep-regulating GABAergic drugs such as benzodiazepines, neurosteroids, and others, currently used clinically to regulate sleep, might affect the tonic GABA system and inform future drug development. Overall, the findings of Konduru and colleagues raise the possibility that treatments aimed at restoring tonic GABA function might ameliorate the consequences of sleep deprivation in epilepsy, beyond simply advising that patients “get more sleep.”

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