Untangling a Web: Basic Mechanisms of the Complex Interactions Between Sleep, Circadian Rhythms, and Epilepsy

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Abstract
Seizures have sleep–wake and circadian patterns in various epilepsies and, in turn, disrupt sleep and circadian rhythms. The resultant sleep deprivation (SD) is an exacerbating factor for seizures that sets up a vicious cycle that can potentially lead to disease progression and even to epilepsy-related mortality. A variety of cellular or network electrophysiological changes and changes in expression of clock-controlled genes or other transcription factors underlie sleep–wake and circadian distribution of seizures, as well as the disruptions seen in both. A broad understanding of these mechanisms may help in designing better treatments to prevent SD-induced seizure exacerbation, disrupt the vicious cycle of disease progression, and reduce epilepsy-related mortality.

Keywords
epilepsy, seizures, neuronal excitability, sleep and circadian

Introduction
Epilepsy is a chronic disorder with recurrent seizures that are often unpredictable. About 35% of patients are intractable to currently available drugs and continue to have breakthrough seizures of varying frequency. Seizures are often associated with sleep–wake states and have circadian or multidien patterns. In turn, seizures themselves cause disruptions in sleep and circadian rhythms. These disruptions may exacerbate epilepsy as evidenced by sleep deprivation (SD) being a common trigger for seizures and SD-enhancing interictal spikes on electroencephalogram (EEG). Thus, sleep or circadian rhythms and epilepsy have a complex bidirectional relationship, potentially setting up a vicious cycle leading to disease progression and even to mortality (Figure 1).

Understanding the basic mechanisms of the relationship between sleep, circadian rhythms, and epilepsy has treatment implications. In this review, we first examine how basic cellular or neuronal network physiology mediates sleep or circadian rhythms. Next, we evaluate mechanisms underlying the dependence of seizures on sleep or circadian rhythms, followed by mechanisms of sleep or circadian rhythm disruptions in epilepsy. Finally, we highlight the data on the possible mechanisms of seizure exacerbation by SD in epilepsy.

Sleep–Wake and Circadian Changes in Neuronal or Network Activity in Health

The sleep–wake cycle is regulated by an interaction of 2 oscillatory processes, namely, circadian and homeostatic mechanisms. Circadian rhythms are endogenous rhythms with a period of approximately 24 hours that are entrainable and self-sustainable, persisting in the absence of time cues and regulated by the suprachiasmatic nucleus via a transcriptional–translational feedback loop of clock genes. Sleep–wake cycle is a critical example of a circadian rhythm, though many physiological functions in the body have a circadian rhythm. Homeostatic regulation is dependent on prior sleep debt where drive to sleep or sleep pressure increases with time awake. Sleep serves to homeostatically regulate neuronal or network activity where...
Excitability and synaptic strength increase during wakefulness and decrease during sleep. According to the synaptic homeostasis hypothesis, neuronal excitability increases during wake and restores to baseline during subsequent sleep, although later work found that neuronal firing rate homeostasis is indeed gated by sleep–wake states, but sleep rather inhibited this homeostasis. Other work showed that neurons in hippocampus or cortex display distinct firing patterns during different vigilance states. During wake, neurons have a net elevated firing rate whereas during nonrapid eye movement (NREM) sleep, net neuronal population firing is reduced and concentrated in sharp-wave ripple events that decline across the night. During rapid eye movement (REM) sleep, there is a decrease in net population firing rates in cortex or hippocampus. Moreover, there is a divergence of hippocampal and neocortical neuronal firing, especially between low-firing and high-firing neurons during different sleep states. During NREM sleep, there is a narrowing in the spread of firing rate distributions between high- and low-firing neurons along with a decrease in interneuron firing rates. During REM sleep, there is a marked decrease in net hippocampal firing rates, a widening of spread between high- and low-firing neurons, as well as increased interneuron activity. Neuronal firing rate changes also occur during stage transitions. A net decrease in neuronal firing rates during sleep leads to net weakening of synaptic strength, especially of excitatory synapses, and a net increase in firing rates in wake leads to net synaptic strengthening in a normal brain, which supports the synaptic homeostasis hypothesis. In addition, neuronal excitability is subject to circadian influences as demonstrated by variations in the size of transcranial magnetic stimulation (TMS)-evoked EEG potentials at different times of the day. Furthermore, many ion channels are shown to have rhythmic expression and activity under circadian regulation, including T- and L-type Ca channels, voltage-gated K channels, and cGMP-gated ion channels. Membrane excitability also has a circadian rhythmicity where, for example, in the suprachiasmatic nucleus, potassium currents peak in the evening to silence clock neurons. Finally, several neurotransmitters that regulate neuronal or membrane excitability also have circadian variation in their expression. In an epileptic brain, this normal physiology may be altered, leading to changes in excitability during different vigilance states or in a circadian manner.

Mechanisms Underlying Dependence of Seizures or Interictal Activity on Sleep–Wake States

In an epileptic brain, both seizures and interictal epileptiform discharges (IEDs) can vary with vigilance states. Studies from intracranial EEG demonstrated that compared to REM sleep,
focal IEDs are 1.11 times higher in wakefulness, 1.75 times higher in stage 1, 1.69 times higher in stage 2, and 2.46 times higher in stage 3 of NREM sleep. Interictal epileptiform discharges are more widespread in NREM sleep, whereas they are suppressed but better localized in REM sleep. Mechanistically, the higher occurrence of epileptiform discharges in sleep, especially slow wave or stage 3 NREM sleep, is mediated by high-amplitude and very low-frequency slow waves in the 0.5 to 1 Hz range. The high-amplitude slow waves have “up” states and “down” states (the up slope and the down slope of a slow wave), and both interictal spikes and high-frequency oscillations occur during the transition from “up” to “down” states. This was also shown in vivo local field potential recordings from the cortex and in vitro recordings of brain slices in animal models. Using invasive EEG, human studies showed that intrinsic excitability progressively increases during wake and is balanced during sleep with a gradual decline in excitability of cortical tissue as measured by the size of evoked potentials. Such excitability is also shown to have a circadian pattern by actively tracking excitability of brain networks using a fully implantable monitoring system in dogs. In epilepsy, the IEDs during sleep likely lead to synaptic strengthening and loss of the normal homeostatic weakening of synaptic strength during sleep. Along with synaptic weakening during sleep, NREM delta power also normally diminishes across the night. In epilepsy, however, NREM delta power remains high with loss of nocturnal decline, and in parallel, the normal synaptic downscaling during sleep is “hijacked” or lost.

Moreover, in epilepsy, sleep either activates or uncovers epileptic networks. In the absence of other generalized epilepsies, thalamocortical networks undergo a shift from the working mode during awake to burst-firing mode during NREM sleep. Earlier studies indicated that the degree of synchrony within the thalamic network that involves the reticular and thalamic relay neurons played a crucial role in determining how normal sleep activity such as sleep spindles turns on and off. Mechanistically, the higher occurrence of epileptiform discharges in sleep, especially slow wave or stage 3 NREM sleep, is mediated by high-amplitude and very low-frequency slow waves in the 0.5 to 1 Hz range. The high-amplitude slow waves have “up” states and “down” states (the up slope and the down slope of a slow wave), and both interictal spikes and high-frequency oscillations occur during the transition from “up” to “down” states. This was also shown in vivo local field potential recordings from the cortex and in vitro recordings of brain slices in animal models. Using invasive EEG, human studies showed that intrinsic excitability progressively increases during wake and is balanced during sleep with a gradual decline in excitability of cortical tissue as measured by the size of evoked potentials. Such excitability is also shown to have a circadian pattern by actively tracking excitability of brain networks using a fully implantable monitoring system in dogs. In epilepsy, the IEDs during sleep likely lead to synaptic strengthening and loss of the normal homeostatic weakening of synaptic strength during sleep. Along with synaptic weakening during sleep, NREM delta power also normally diminishes across the night. In epilepsy, however, NREM delta power remains high with loss of nocturnal decline, and in parallel, the normal synaptic downscaling during sleep is “hijacked” or lost.

Mechanisms Underlying a Circadian Pattern for Seizures or Interictal Discharges

Similar to sleep–wake pattern of seizures and IEDs presented above, both have a temporal association with circadian rhythm. The presence of circadian patterns in epilepsy has been recognized for centuries now, and seizures were classified initially as diurnal, nocturnal, or diffuse. Interictal epileptiform discharges peak during sleep, regardless of the topographic location of electrodes, but seizures occur with different circadian patterns depending on the ictal network or epilepsy type. Both seizures and IEDs can also have multidiurnal rhythms lasting days or weeks. Circadian pattern of seizures or interictal phenomena are demonstrated in animal models of limbic epilepsy as well as generalized epilepsy. The principal mechanism of circadian variation in neuronal excitability may involve genes that regulate circadian rhythms, that is, clock-controlled genes. BMAL1 and CLOCK and their transcription factors BMAL1-CLOCK contribute to circadian variation in neuronal excitability through modulation of other downstream transcription factors that are causally involved in epilepsy, namely, DBP, TEF, and HLF. In a conditional knockout mouse model, deletion of CLOCK in pyramidal neurons resulted in increased spikes and seizures during rodent sleep time. Similarly, lack of BMAL1 in hippocampus reduced seizure threshold and abolished circadian variation of electrically induced seizures. Lack of PAR bZip transcription factors (DBP, TEF, and HLF), which are downstream of clock genes, similarly subjected mice to epilepsy and a circadian pattern of seizures. Mechanistic target of rapamycin (mTOR) signaling has also been implicated, as it is under the control of circadian timing system and associated with clock-controlled genes such as PER1. Mutations in other regulatory proteins (such as GATOR1) that bind to and suppress mTOR pathway have been implicated in nocturnal frontal lobe epilepsy where seizures occur exclusively during sleep. Several other transcription factors that govern the circadian clock were also implicated in the circadian pattern of seizures, including EGR-1 and EGR-2, STAT-3, SP-1, XBP1, SREBP1, PAM, and Oligophrenin-140. Lastly, circadian dynamics of the hippocampal transcriptome and proteome are also altered in experimental TLE where oscillation of transcripts of core clock genes and downstream transcription factors are dysregulated.
including lifestyle issues, medications, primary sleep disorders, and reduced melatonin issues contribute to sleep disturbances.40 Data from animal models, however, revealed other factors such as enhanced expression of orexin in the lateral hypothalamus.47 Orexin is a wake-promoting hormone and orexin antagonists improve both NREM and REM sleep. Interestingly, orexin antagonists reduced seizure severity and duration in pentylentetrazol and in Kv1.1−/− mouse models but also improved sleep in these models.48 In the Dravet syndrome mouse model, reduced action potential firing due to decreased NaV currents in GABAergic interneurons of reticular nucleus of thalamus contributed to sleep disruptions.55

Factors associated with circadian rhythm disturbances have focused on clock-controlled genes and associated transcription factors as discussed above. Disrupted rest activity rhythms in diurnal or circadian conditions have been associated with diminished oscillation of CLOCK and PER1 as well as an epigenetic regulator of clock genes, Sirtuin1 in the hypothalamus.46 Enhancing Sirtuin1 function restored the disrupted circadian rhythms in aging and neurodegenerative disorder models by restoring normal oscillation of clock-controlled genes.44 Whether enhancing Sirt1 function restores sleep and circadian rhythms and offers beneficial effects for epilepsy is an avenue to explore.

**Mechanisms of SD-Associated Seizure Exacerbation**

Sleep deprivation is a common trigger for seizures and is often employed during EEG recordings for confirmation of diagnosis of epilepsy. As opposed to IEDs, there is a controversy on whether SD exacerbates seizures in humans.49 In the Kv1.1−/− mouse model, SD indeed exacerbated seizure frequency but also hastened mortality.50 In the same model, sleep progressively declined prior to mortality,51 suggesting that SD may be a factor in causing disease progression and is relevant for epilepsy-related mortality.

The mechanisms of SD-associated seizure exacerbation are not well understood. Sleep deprivation is known to enhance cortical excitability in humans with juvenile myoclonic epilepsy as demonstrated by decreased intracortical inhibition and increased intracortical facilitation in TMS studies.52 Diminished adenosine tone was seen in the CA-1 region of hippocampus, or altered expression of adenosine receptors has been reported. Adenosine is an inhibitory neurotransmitter and reduced adenosine tone increases excitability.53 Although no studies examined effects of SD on excitatory and inhibitory transmission or the excitation–inhibition balance, in the Kv1.1−/− mouse model, SD reduced GABAergic tonic but not phasic inhibition in dentate granular cells.50 Diminished tonic currents in normal C57/BL6 mice also occurred with SD in the dentate gyrus in addition to associated reduction in α-5 and δ-subunit containing GABA_A receptors in the hippocampus.54 While other studies have shown that the same subunits diminish in the dentate or CA-1 in TLE, surprisingly, tonic currents were preserved in mouse models of TLE.55 Diminished tonic currents in dentate or hippocampus may be one mechanism that SD triggers breakthrough seizures at least in TLE.

**Conclusions and Future Directions**

In summary, the relationship between sleep and epilepsy is complex and bidirectional. Further work is needed for a deeper understanding of how cellular or network excitability varies with vigilance states and precise molecular mechanisms of sleep and circadian rhythms alterations in epilepsy syndromes. Specifically, the role of hypothalamus in driving network excitability changes, possibly with simultaneous extracellular/microelectrode recordings in hypothalamus and cortex or hippocampus is also warranted. Further work is also needed in understanding cellular and molecular mechanisms of SD-induced increases in excitability in rodent models. Better understanding could lead to breakthroughs in treatment of epilepsy, in designing chronotherapy for epilepsy where drugs or neuromodulation are delivered at an individual’s circadian or multidien peak of IEDs or seizures, as well as to develop therapies against SD-induced seizure exacerbation. Finally, future studies could examine whether disrupting the vicious cycle of sleep and epilepsy can be protective against disease progression in epilepsy or to prevent epilepsy-related mortality.

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